Direct asymmetric catalytic syntheses of alpha,beta-difunctional amino and hydroxy carbonyls via the bifunctional catalytic in-situ generation of chiral enolates

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Direct asymmetric catalytic syntheses of α,β-difunctional amino and hydroxy carbonyls *via* the bifunctional catalytic *in-situ* generation of chiral enolates

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For the degree of Doctor of Philosophy
University of Bath
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Abstract

Chapter one is an introduction to aldol and Mannich reactions – tools used to access natural products containing di-functional amino and hydroxy carbonyl motifs. A discussion of the recent catalytic and asymmetric developments of these reactions is included. In addition the concept of soft enolisation is addressed through examples in the literature. An outline of the project's goals is disclosed which includes the development of new catalytic asymmetric processes encompassing the *in situ* generation and trapping of chiral enolates through soft enolisation.

Chapter two describes the synthetic work carried out. The first part describes the development of a direct catalytic enantioselective synthesis of protected β-hydroxy-α-amino acids. The second part describes the application of the developed asymmetric catalysis to natural product synthesis – vancomycin's AA-6 amino acid. The third part describes the extension of the developed aldol reaction to an asymmetric Mannich variant which delivers protected α,β-diamino acids as products. The fourth and final part describes a direct diastereoselective synthesis of protected α,β-dihydroxy ketones employing similar conditions as developed in previous syntheses.

Chapter three provides detailed experimental procedures.

Acknowledgements

I would like to thank Dr Michael Willis for the opportunity to have worked on such a challenging yet rewarding project. His enthusiasm to assist and guide throughout the four years was greatly appreciated.

May I also thank Dr Matt John for his far away presence for the most part as an industrial supervisor, guidance during the three months placement at GlaxoSmithKline, and for his enthusiasm and ideas during collaborative meetings.

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May I thank all of the above and new members of the group whom assisted in proof reading my thesis.

Finally and most importantly I would like to thank my family for their generous support over the past four years, my loving wife Julie, my parents Bill and Marie, my brother Lawrie and my sister-in-law Reeva, my sister Tash, my grand parents George and Nesta, my mother and father-in-law Evelyne and Jean-Yves, and my brother and sister-in-laws Achille and Myriam together with my nephew and niece Gatien and Amaelle.

Abbreviations

AA	Amino acid
Ac	Acetyl
AIBN	Azobisisobutylonitrile
Ala	Alanine
App.	Apparent
AQN	Anthraquinone
Ar	Aryl
BINOL	1,1′-Bi-2-naphthol
bipy	bipyridine
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOx	Bisoxazoline
Bu	Butyl
c	Cyclo
C	Celsius
CBz	Benzoyl
CI	Chemical ionisation
config.	configuration
Cp	Cyclopentadiene
Cy	Cyclohexyl
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dec	decomposes
DBF	Dibenzofuran
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
de	Diastereomeric excess

DHQD	Dihydroquinidine
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	Dimethoxy ethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
ee	Enantiomeric excess
EI	Electron impact
e.r.	Enantiomeric ratio
ES	electrospray
eq./equiv.	Equivalent
Et	Ethyl
FT	Fourier transform
g	gram
h	hour
HMDS	Hexamethyldisilazane
HPLC	High pressure liquid chromatography
Im	Imidazoyl
IR	Infrared
J	coupling constant
L/lig	Ligand
LA	Lewis acid
Lac	Lactose
LDA	Lithium diisopropylamide
m	multiplet
m	*meta*
M	Metal
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl

MEM	Methoxyethoxymethyl
mg	milligram
min	Minute
mL	milliliter
mp	melting point
MRSA	Methicillin resistant *staphylococcus aureus*
MS	molecular sieves
MTM	Methylthiomethyl
n	*normal*
NBS	*N*-bromo succinamide
NCS	Isothiocyanate
NEP	*N*-Ethylpiperidine
NMI	*N*-Methylimidazole
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	*ortho*
ON	Overnight
Ox	Oxazoline
p	*para*
P	Protecting group
Ph	Phenyl
PHAL	Phthalazine
Pht	Phthalyl
PMB	*p*-Methoxybenzyl
PMP	Pentamethyl piperidine
ppm	part per million
prod	Product
PTC	Phase transfer catalyst

Py	Pyridine
q	quartet
Q	Quaternary ammonium
RT	Room temperature
s	*secondary*
sat.	Saturated
sp.	species
t	triplet
TBAHS	Tetrabutylammonium hydrogen sulfate
TBS	*tert*-Butyldimethylsilyl
t	*tertiary*
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMP	Tetramethyl piperidine
TMS	Trimethylsilyl
Tol	Tolyl
t_R	retention time
Ts	Tosyl
TS	Transition state
VRE	Vancomycin resistant *enterococci*
VRSA	Vancomycin resistant *staphylococcus aureus*
wt.	weight
Y	Yield
*	Chiral

Contents

I Introduction

The work in this thesis describes the development of a new methodology for the generation and trapping of chiral enolates *via* soft enolisation and their use in aldol type processes and Mannich reactions. A vast array of natural products include an α-amino or α-hydroxy carbonyl moiety in addition to either a β-amino or β-hydroxy substituent; functionality reached through either the aldol or Mannich reaction, which has been demonstrated herein for all such analogues. Recent examples of such natural products are illustrated below. In order to access such products synthetically, techniques that can effectively control the stereochemical outcome of the synthetic route are a necessity.

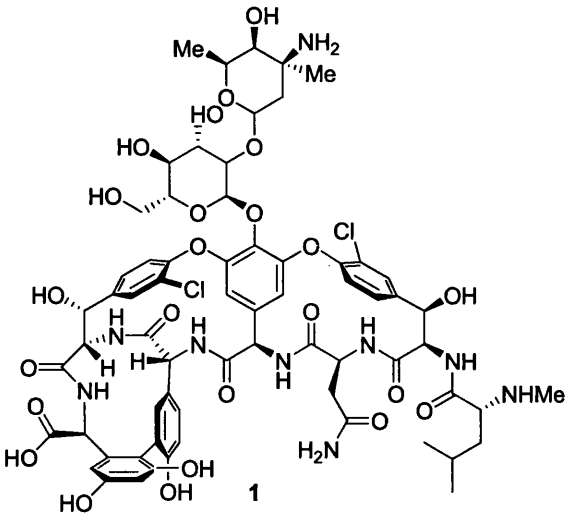
The background of the aldol reaction and issues of stereochemical outcome are briefly described, followed by an inclusion of the development of the Mukaiyama aldol reaction and selected others, which invoke high stereoselectivity. This leads to the further discovery and development of more versatile direct catalysts for the aldol reaction, mainly bimetallic species. The emergence of organocatalysis in the aldol reaction is highlighted. Current asymmetric Darzens reactions and asymmetric Mannich reactions are discussed briefly – two topics of importance within the work described. Finally, the concept of soft enolisation is discussed within an introduction to the proposed work towards an asymmetric catalytic aldol and Mannich reaction. This section is not intended to be a comprehensive review of the aldol and Mannich reaction. Its purpose is to highlight the important features of the processes relevant to the results and discussion section.

I 1 Analogous α,β-(amino and hydroxy) carbonyl motifs in natural products and designed molecules

I 1.1 The α-amino-β-hydroxy carbonyl unit

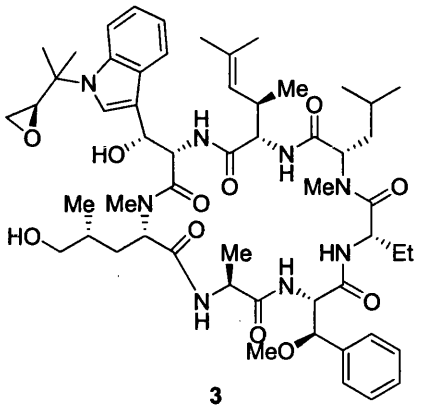
The α-amino-β-hydroxy carbonyl unit is ubiquitous in many naturally occurring molecules. Their biological activities are widespread and include antibiotic and antifungal functions,[1] anti-inflammatory activity,[2] and cellular transport functions.[3] In addition designed molecules have also been implicated in functions such as hypotension.[4] Aryl-substituted variants are an important sub-class; vancomycin **1** (Figure 1),[1] ristocetin A,[1] and biphenomycin A **2** (Figure 1)[5] are cyclic peptides that display significant antibiotic activity. Vancomycin **1** is described in more detail in section (II 2). Ristocetin A is structurally related to vancomycin and exhibits similar antibiotic activity although its clinical use was discontinued owing to fatalities.[6] Biphenomycin **2** is a simpler cyclic tripeptide isolated from the culture broths of *Streptomyces filipinensis* and *S. griseoruuginosus*.[5] This compound exhibits potent activity against Gram-positive bacteria such as *Streptococcus aureus* and *Enterococcus faecalis*. The cyclomarins display significant anti-inflammatory properties.[2] Cyclomarin A **3** is a novel cyclic peptide isolated from the marine bacterium *Streptomyces* sp., which contains four structurally very unusual amino acids (Figure 1). Exochelins are a class of α-amino-β-hydroxy carbonyls that play a crucial role in cellular iron(III) transport of mycobacteria.[3] Exochelin MN **4** (Figure 1) was isolated from culture broths of *M. neoaureum* and can transport iron into *M. leprae* cells which are causative of leprosy.[7]

Figure 1. Examples of β-hydroxy-α-amino acid natural products.



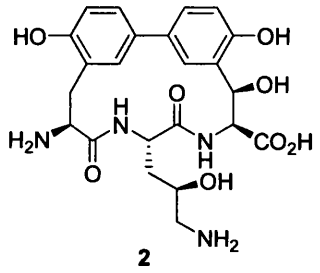
1

Vancomycin



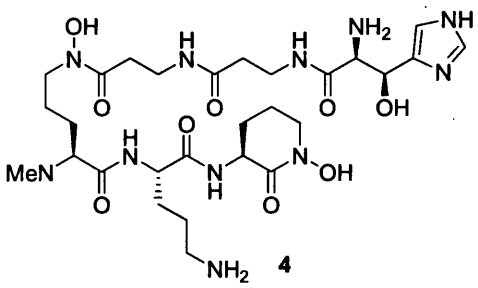
3

Cyclomarin A



2

Biphenomycin A



4

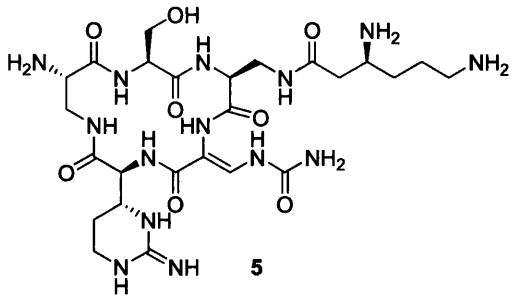
Exochelin MN

I 1.2 The α,β-diamino carbonyl template[8]

The nonproteinogenic α,β-diamino acid motif, which holds valuable biological properties makes it an interesting target for the synthetic chemist. The α,β-diamino carbonyl unit is abundant in nature and many examples show antibiotic activity.[9] The bleomycins, isolated from *Streptomyces verticillus* are peptides containing α,β-diamino acid residues which are clinical antitumor agents used for the treatment of Hodgkin's lymphoma.[10] Also isolated from the same cultures is the amino glycoside antibiotic capreomycin IA **5** (Figure 2) which is used to treat tuberculosis.[11] An

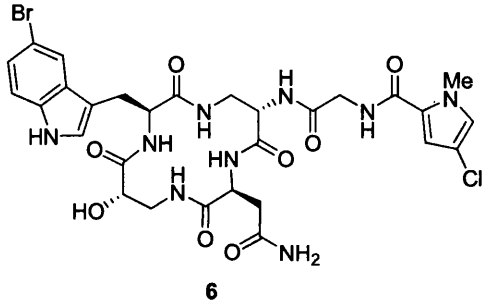
interesting example, discovered through routine screening focused on detecting active antitumor agents, and isolated from marine sponge *Psammocinia* sp. is cyclocinamide A **6** (Figure 2) which is an unusual halogenated hexapeptide containing both 5-bromoindole and 4-chloro-*N*-methylpyrrole fragments.[12]

Figure 2. α,β-diamino acids in natural and designed products.



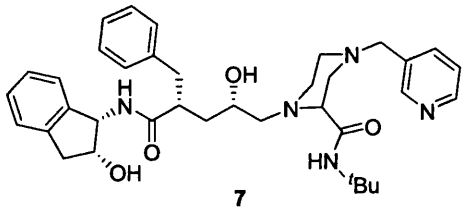
5

Capreomycin IA



6

Cyclocinamide A



7

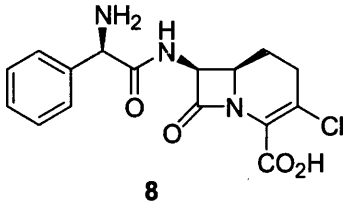
Indinavir (L-735,524, crixivan)

Apart from naturally formed products the α,β-diamino carbonyl template is found in synthetically produced therapeutic drugs such as the 2-carboxypiperazine containing drug indinavir **7** (Figure 2).[13] This drug is an effective HIV protease inhibitor and one of the most important to date to treat the HIV virus.

α,β-Diamino carbonyl compounds in a protected form are useful precursors to α-amino-β-lactam antibiotics. Examples are the carbacephalosporin antibiotics, and one which is currently on the market to treat paediatric ear infections is loracarbef **8** (Figure 3).[14] A final example of a

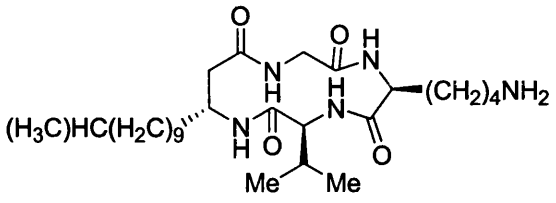
natural product in which a total synthesis utilises a protected α,β-diamino carbonyl precursor is the antifungal cyclic peptide rhodopeptin B5 **9** (Figure 3).[15]

Figure 3. Natural products utilising α,β-diamino carbonyl precursors.



8

Loracarbef



9

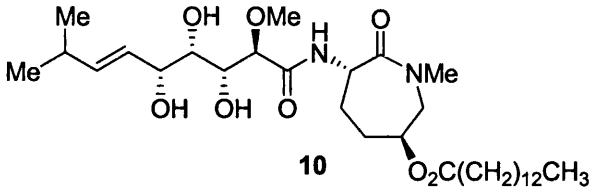
Rhodopeptin B5

I 1.3 The α,β-dihydroxy carbonyl unit

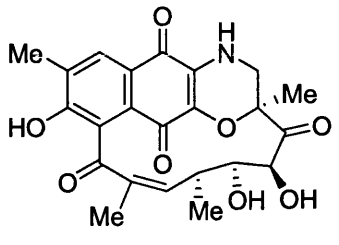
In addition to the α-amino-β-hydroxy carbonyl unit obtained by the aldol reaction, α-hydroxy substituted enolate components can provide access to α,β-dihydroxy carbonyl units which are ubiquitous in natural products. A recent example has been reported by Boeckman, in the enantioselective total synthesis of bengamide B **10** (Figure 4).[16] The natural product, isolated from an Australian halichondrid sponge, shows potential anti-proliferation activity and could be indicated as a therapeutic for drug resistant solid tumours. The side chain last connected to the caprolactam was obtained by two subsequent aldol reactions using α-etherate substituted enolates. Rubransarol A **11** (Figure 4), another example, is a precursor to the antibiotic rubradirin A which interferes with ribosomal functions related to enzymatic peptide chain initiation.[17] Antitumor agent TMC-95A **12** (Figure 4), also a α-amino-β-hydroxy carbonyl species related to biphenomycin (Section I 1.1), contains the α,β-dihydroxy carbonyl moiety.[18] A final example is potassium

aeshynomate **13**, which was identified as a leaf-opening substance in a nyctinastic plant, *Aeshynomene indica* L.[19]

Figure 4. Examples of α,β-dihydroxy carbonyls.

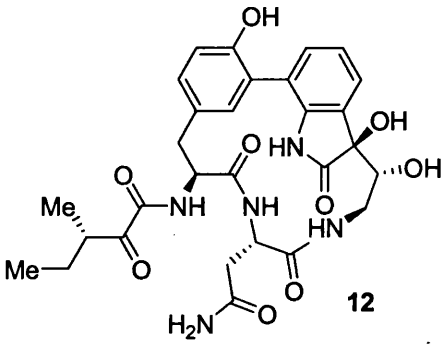


Bengamide B

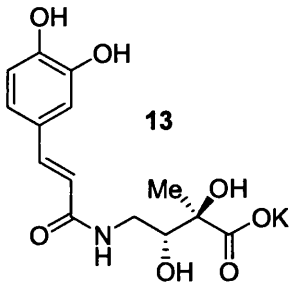


11

Rubransarol A



TMC-95A

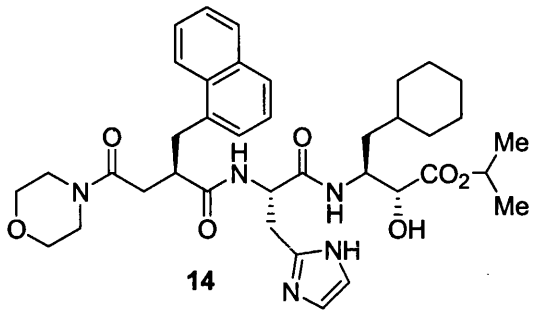


Potassium aeshynomate

I 1.4 The β-amino-α-hydroxy carbonyl template

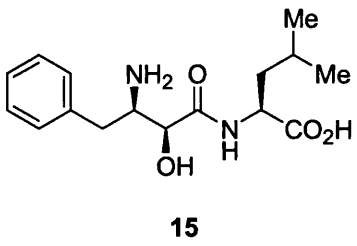
The final member of the di-functional aldol products we will consider is the β-amino-α-hydroxy carbonyl motif. An interesting example is the potent renin inhibitor used in antihypertension therapy, KRI 1314 **14** (Figure 5), which is a tripeptide containing a cyclohexylnorstatine residue.[20] Finally bestatine[21] **15** (Figure 5) a potent aminopeptidase B inhibitor is included as a drug molecule example although there are many others in the literature such as anticancer drugs paclitaxel and taxotère,[22] and the potent HIV protease inhibitor KN1-272.[23]

Figure 5. β-amino-α-hydroxy carbonyls in designed therapeutics.



14

KRI 1314



15

Bestatine

These few examples (Section I 1) illustrate how the β-(hydroxy or amino)-α-(hydroxy or amino) carbonyl motifs feature in numerous natural products and accordingly their synthesis has become important. The specific synthesis of vancomycin is explored later (Section II 2). The aldol and Mannich reactions are excellent methodologies for this purpose and gives direct access to these moieties. In the next section, the background of the aldol reaction will be briefly exposed.

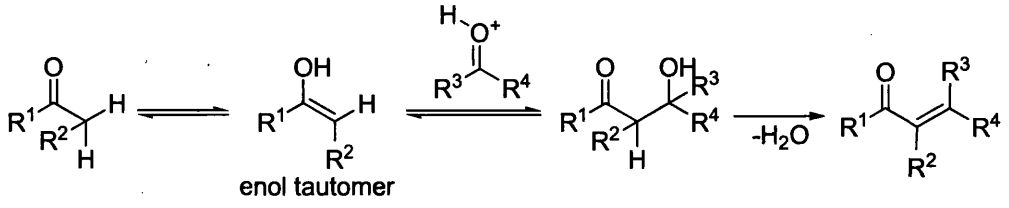
I 2 The aldol reaction

I 2.1 Acid or base catalysis – enol or enolate

The aldol reaction, in which an α-carbon of one aldehyde or ketone adds to a carbonyl carbon of another *via* an enolate or enol, is one of the most important organic reactions. This is because the carbon-carbon bond forming reaction can produce highly functionalised compounds with up to two new adjacent stereocentres simultaneously. The acid-catalysed reaction proceeds *via* an enol tautomer, which then reacts with an acid-activated electrophilic

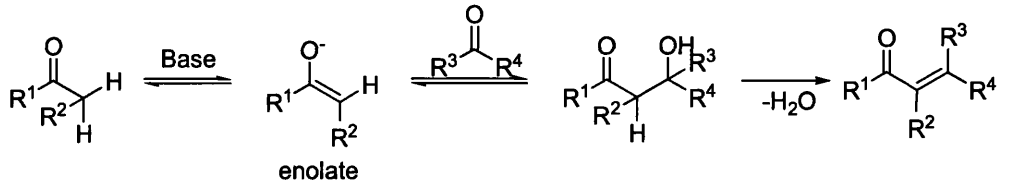
carbonyl (Scheme 1). The product obtained is an α-hydroxy aldehyde or ketone. The retro reaction is also feasible, regenerating starting materials. In addition, the product can undergo further reaction *via* dehydration, forming an α,β-conjugated carbonyl which is irreversible.

Scheme 1. Acid catalysed aldol reaction and dehydration.



The more common base-catalysed reaction proceeds *via* the formation of an enolate (Scheme 2). A base abstracts an α-proton from the carbonyl substrate and this activated nucleophile then adds to an electrophilic carbonyl to form the aldol adduct. As in the acid catalysed process, this reaction is reversible. Moreover, if a second α-deprotonation is possible, this may lead to elimination of water and the production of an enone or enal.

Scheme 2. Base catalysed aldol reaction.

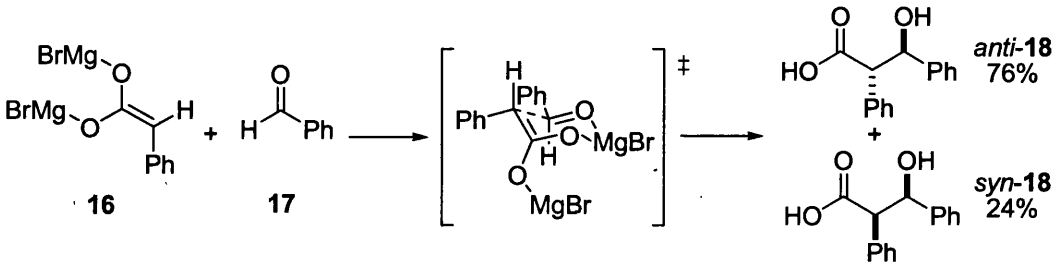


However, the outcome of the reaction can easily be a mixture of different products and starting materials, especially if there is more than one α-proton involved. Not only can chemo- and regioselectivity become issues, in addition, depending on the R-groups involved, different diastereomers and enantiomers can be formed. Therefore, the controlled formation of one product over another has been a quest for many years.

I 2.2 Stereochemical issues of the aldol reaction

To become synthetically useful, the stereochemistry of the products of the aldol reaction must be predictable. One of the first attempts to account for stereochemistry came from Zimmerman and Traxler in 1957.[24] An observation was that the addition reaction of preformed magnesium dianion **16** to benzaldehyde **17** was *anti*-selective (Scheme 3). Consequently, it was proposed that the reaction proceeded *via* a cyclic chair-like 6-membered transition state, a so-called 'Zimmerman-Traxler' transition state, depicted below (Scheme 3). Zimmerman and Traxler suggested that both the oxygen of the aldehyde and one from the carboxylate, chelate to one of the two magnesium cations. In order to minimise steric congestion, the two phenyl-substituents occupy equatorial positions of the 6-membered cycle, and thereby preferentially form *anti*-**18**.

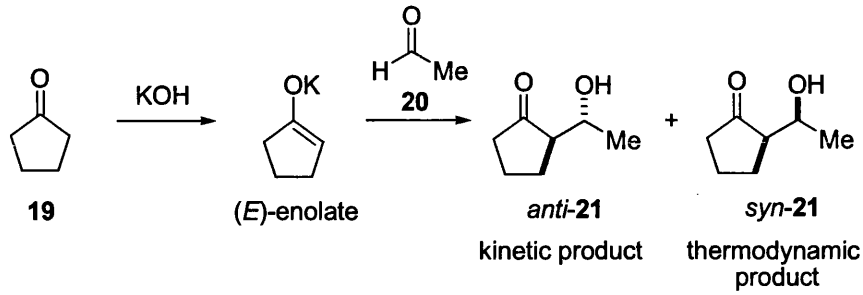
Scheme 3. An early aldol diastereoselectivity model.



Later in 1967, Dubois *et al* exposed kinetic and thermodynamic control in the aldol reaction.[25,26] Solvent and temperature effects on the equilibrium of the products *syn*-**21** and *anti*-**16** were studied (Scheme 4). Dubois *et al* observed that the (*E*)-enolate obtained from cyclopentanone **19** treated with KOH in MeOH, added to acetaldehyde **20** to afford preferentially *syn*-**21** under thermodynamic conditions (4 h at 5 °C). However, under kinetic

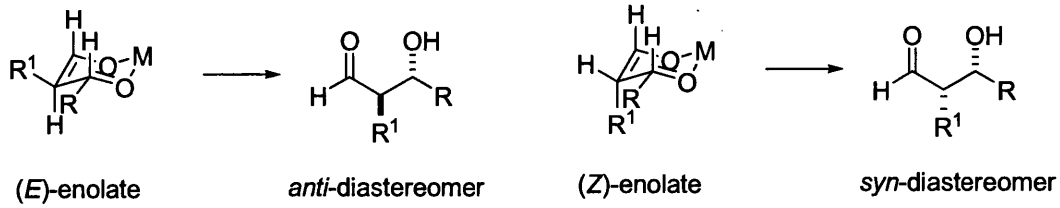
conditions (15 s at -20 °C) the (*E*)-enolate afforded preferentially the opposite *anti*-diastereomer.

Scheme 4. Kinetic and thermodynamic control in the aldol reaction.



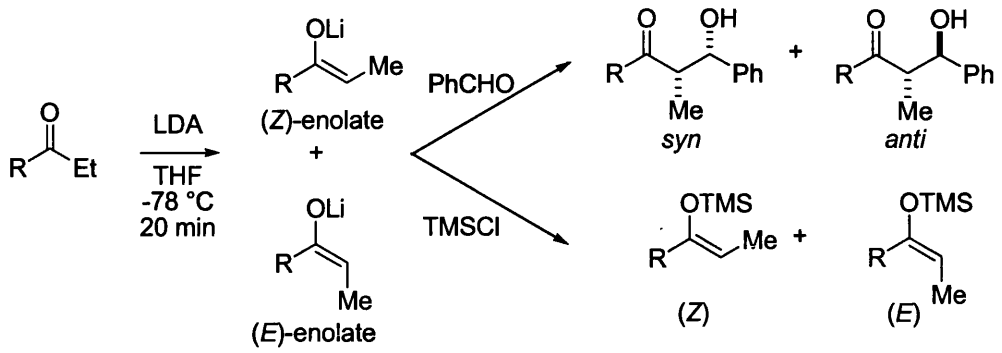
In kinetically controlled aldol processes, the reaction usually proceeds *via* a Zimmerman-Traxler transition state, which is structured around a metal centre. The largest substituent of the electrophile adopts the equatorial position to minimise steric interactions.[27] Consequently, an (*E*)-enolate would normally give access to an *anti*-diastereomer whereas a (*Z*)-enolate would give access to a *syn*-diastereomer (Scheme 5).

Scheme 5. Zimmerman-Traxler transition states of (*E*)- and (*Z*)-enolates and stereochemical outcome.



In 1980, Heathcock studied the diastereoselectivity of the aldol reaction.[28] The survey correlated the ratio of *syn*- and *anti*-diastereomers afforded from the reactions of preformed lithium enolates with benzaldehyde **17** to the ratio of the starting enolate (Table 1).

Table 1. Correlation between *Z*:*E* and *syn*:*anti*.



Entry	R	*Z*:*E*	*Syn*:*anti*
1	^{t}Bu	> 98:2	> 98:2
2	Mesityl	5:95	8:92
3	MeO	5:95	62:38

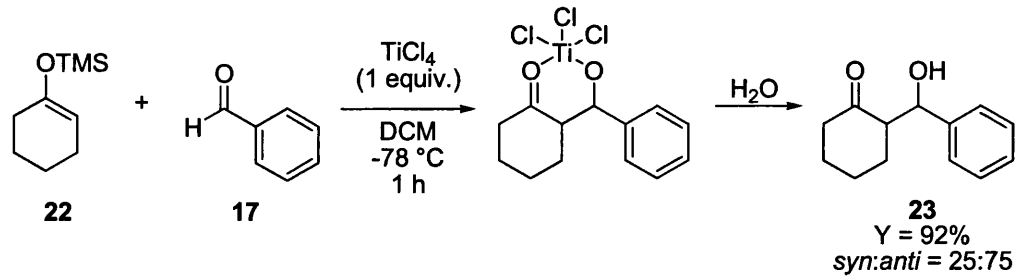
The diastereomeric ratios were determined by trapping the enolate mixtures with TMSCl. Complete kinetic stereoselection was observed for bulky R substituents. Entries 1 and 2 showed a good correlation between the enolate geometry and the stereochemistry of the aldol product. The (*Z*)-enolate provided the *syn*-aldol product (Entry 1) while the (*E*)-enolate provided preferentially the *anti*-aldol product (Entry 2). However, for ketones or esters with smaller substituents, such as a methyl ester (Entry 3), the stereoselectivity either decreased or disappeared. Many examples of aldol reactions support the concept of chair-like transition states but in this case, some other less controlled pathway is taking place. It is evident that the presence of other coordinating sites or the nature of the Lewis acid involved can have a dramatic effect on the nature of the transition state; not only a different closed transition state perhaps even an open one. One fact is certain, the geometry of the enolate whether (*E*) or (*Z*) has a considerable effect on the selectivity of the reaction and its formation must be controlled as much as possible. Small R substituents generally form (*E*)-enolates whereas increasing the substituent's size increases the amount of (*Z*)-enolate. However, a bulky base for example affords predominantly the (*E*)-enolate. To shortcut the

problem of enolate stereochemistry, Mukaiyama ingenuously reported the use of silyl enol ethers as latent enolates. The fixed stereochemistry involved provides useful results and is described below.

I 2.3 The achiral Mukaiyama aldol reaction

In 1974, Teruaki Mukaiyama reported the nucleophilic addition of latent enolates such as enol silanes to aldehydes or ketones activated by a Lewis acid. This was a milestone in the development of the aldol reaction.[29] It was discovered that titanium tetrachloride promoted the reaction of silyl enol ether **22** with benzaldehyde **17**, to yield under kinetic control, the aldol adduct, β-hydroxyketone **23** (92%) after subsequent hydrolysis. A reasonable degree of diastereoselectivity was achieved (*syn:anti* = 25:75) (Scheme 6).

Scheme 6. Mukaiyama aldol reaction.



22 **17** **23**
Y = 92%
syn:anti = 25:75

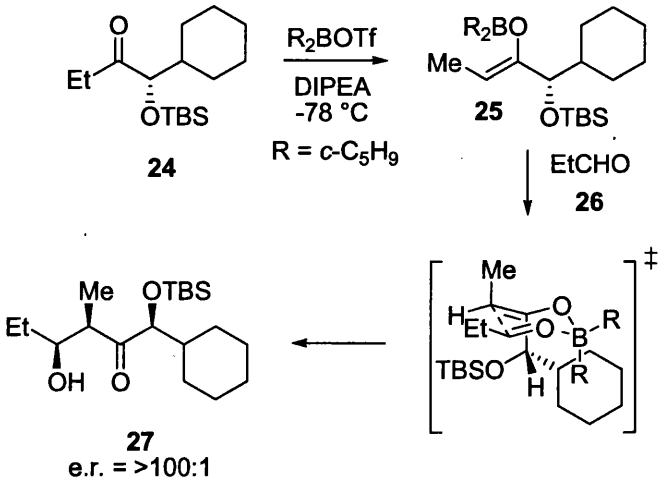
The lewis acid, $TiCl_4$ was found to be optimal and in addition, good yields of up to 80% were attained when only 13 mol% of $TiCl_4$ was employed. This reaction was examined with other aldehydes, such as alkyl aldehydes but higher temperatures were necessary to achieve reaction and diastereoselectivities suffered as a result.

I 3 Stoichiometric chiral component asymmetric aldol reactions

I 3.1 The use of boron enolates

In 1981, the groups of Masamune[30] and Evans[31] concurrently reported extremely stereoselective asymmetric aldol reactions utilising chiral boron enolates. Masamune employed chiral α-silyloxyketones such as **24** and bulky boron Lewis acids to give *syn*-aldols exclusively in the reactions of achiral aldehydes, for example **26** (Scheme 7). This indicated the complete formation of the (*Z*)-boron enolate **25**.

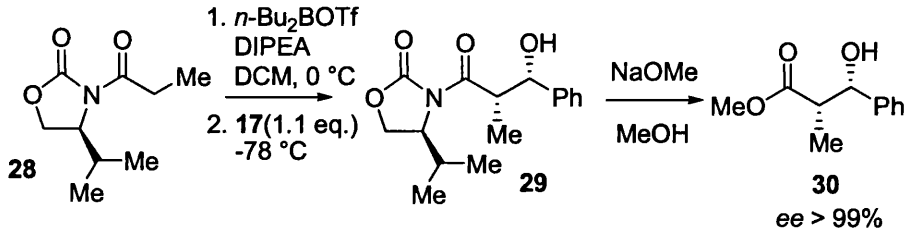
Scheme 7. Masamune's chiral boron enolate.



In the transition state proposed for the reaction the substituents attached to the chiral centre of the enolate are oriented such that steric congestion is minimised. Therefore, the chirality dictates the approach of the enolate with respect to the aldehyde, which is translated into the absolute configuration of the aldol product **27**.

Evans utilised chiral 2-oxazolidinones as in **28** as recyclable chiral auxiliaries for carboxylic acids in aldol reactions *via* boron enolates, which were again *syn*-selective (Scheme 8).[31] The employment of di-*n*-butylboryl triflate gave the (*Z*)-enolate with a diastereomeric ratio *Z*:*E* > 100:1. The *syn*-selection observed was as high as 500:1 depending on the aldehyde. The chiral auxiliary attached aldols, when transformed to their corresponding methyl esters gave optical purities > 99% in all cases. The chiral auxiliaries can easily be prepared from optically active amino alcohols and have been widely used in organic synthesis.

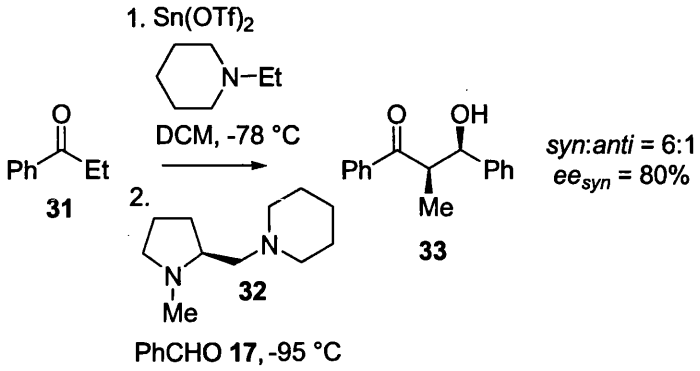
Scheme 8. Evans's chiral oxazolidinone boron enolate.



I 3.2 Chiral diamines in the aldol reaction

Mukaiyama made a further advancement with the asymmetric aldol reaction in 1982 through incorporation of a chiral ligand component.[32] The group reported highly enantioselective reactions of achiral tin(II) enolates, formed from $Sn(OTf)_2$, *N*-ethylpiperidine as a base, and a stoichiometric amount of the chiral diamine **32** acting as the ligand, which added to achiral aldehydes (Scheme 9). This was the first reported example where significant selectivity could be induced through the formation of a metal enolate, which was generated *in situ* from a ketone. For example phenyl ethyl ketone **31** produced *syn*-**33** in 80% *ee*.

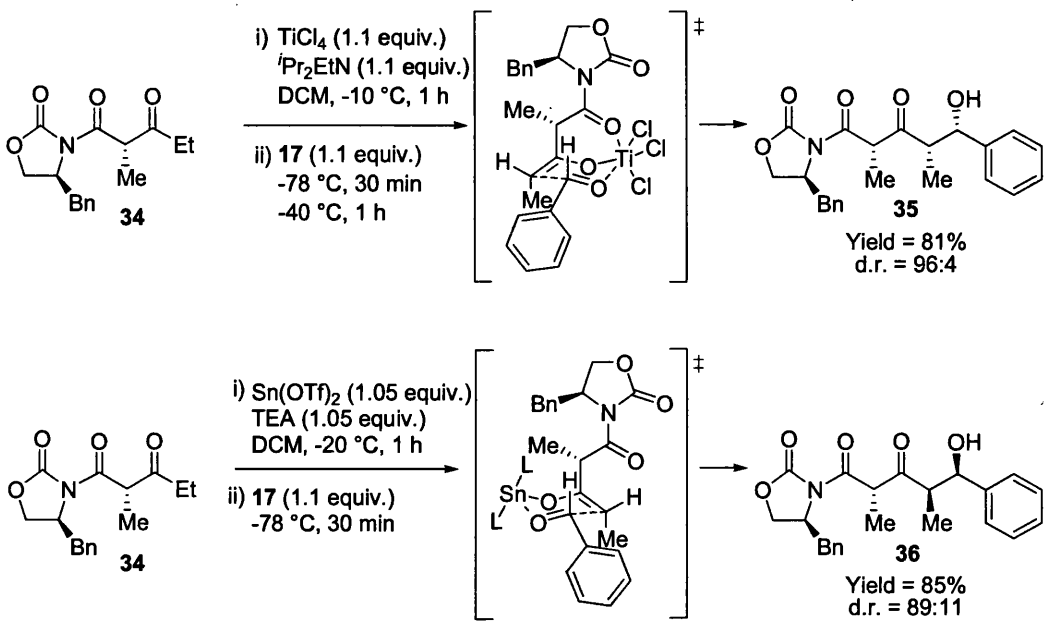
Scheme 9. Asymmetric induction *via* stoichiometric chiral diamines.



I 3.3 Titanium(IV) versus tin(II) enolates

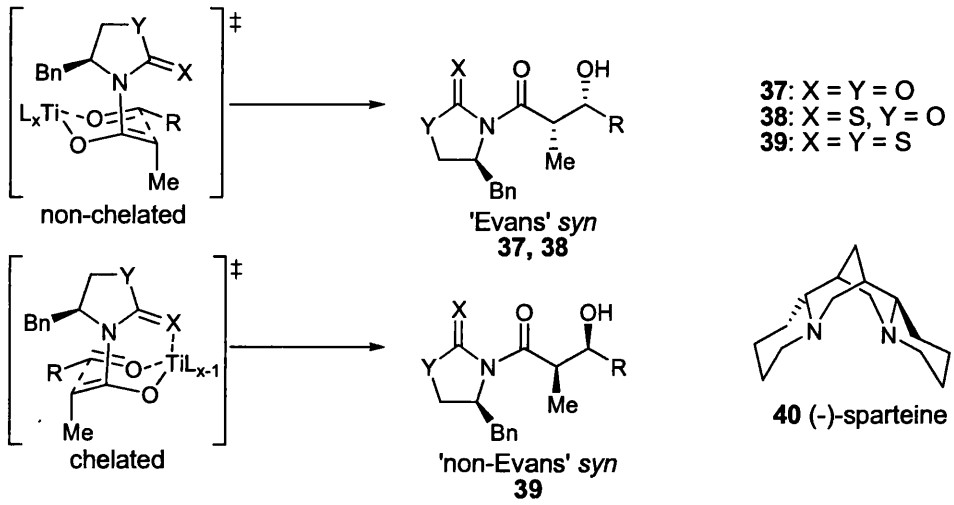
In 1990, the employment of titanium tetrachloride as used in the Mukaiyama aldol reaction described above was also utilised by Evans in aldol reactions with chiral oxazolidinones (Scheme 10).[33] At the same time, Evans disclosed the same reaction could be carried out with tin(II) triflate, although a different stereochemical outcome was observed (Scheme 10).[33] It was proposed that the all-*syn* adduct **35** derived from the Ti(IV) enolate consisted of a transition state whereby the acyl oxazolidinone **34** coordinated to the titanium centre. Conversely, in the Sn(II) case which afforded **36** such coordination did not occur and a non-chelation controlled reaction pathway followed dominated by the methyl bearing stereocentre.

Scheme 10. Ti(IV) versus Sn(II) enolates; opposite *syn*-selectivity.



More recently, Crimmins further investigated Ti(IV) enolates, including the use of different chiral auxiliaries and (-)-sparteine **40** as a weak base.[34] Depending on the auxiliary, *N*-acyl oxazolidinone **37**, oxazolidinethione **38**, or thiazolidinethione **39**, either the 'Evans' or 'non-Evans' *syn*-adducts were produced (Scheme 11).

Scheme 11. Crimmin's asymmetric aldol addition.



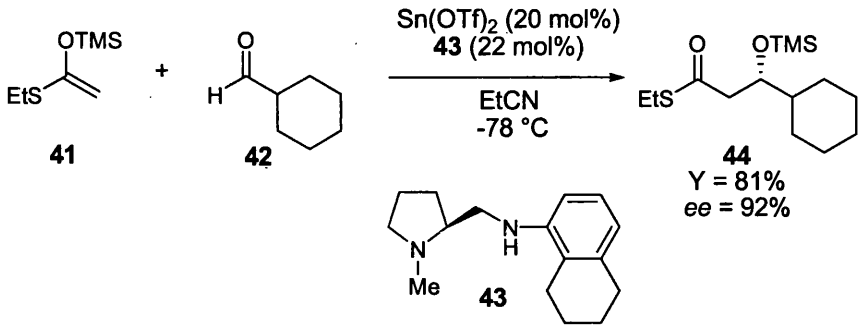
The fact that thiazolidinethiones produce non-Evans *syn*-aldols, can be attributed to a highly ordered chelated transition state. The thiocarbonyl of thiazolidinethiones is more nucleophilic than the oxazolidinone carbonyl or the oxazolidinethione carbonyl, thus has a higher affinity to chelate to the Ti(IV) centre.

I 4 Catalytic asymmetric aldol reactions[35,36,37,38]

I 4.1 The catalytic asymmetric Mukaiyama aldol reaction

A major problem encountered during the development of stereo-controlled versions of the Mukaiyama aldol reaction was that of release of TMSCl as a by-product. TMSCl is able to act as a stereorandom aldol catalyst.[39] However, Mukaiyama, Kobayashi and co-workers developed a system for the reaction of silyl ketene acetals of thioesters with aldehydes.[40,41] Excellent diastereo- and enantioselection was obtained using chiral diamines coordinated to Sn(II) triflate and tributyltin fluoride (Bu_3SnF).[42,43] In the absence of Bu_3SnF products were obtained as racemates, which suggested that a stoichiometric amount of this additive was suppressing the competing trimethylsilyl triflate catalysed reaction.[44] This reaction was developed into a catalytic variant with similar results (Scheme 12), although the aldehyde had to be added very slowly to the prepared catalyst system of $Sn(OTf)_2$ and chiral diamine **43** in propionitrile. Aldol adduct **44** for example, was isolated in 81% yield and 92% *ee*.[45]

Scheme 12. Catalytic asymmetric Mukaiyama aldol reaction.



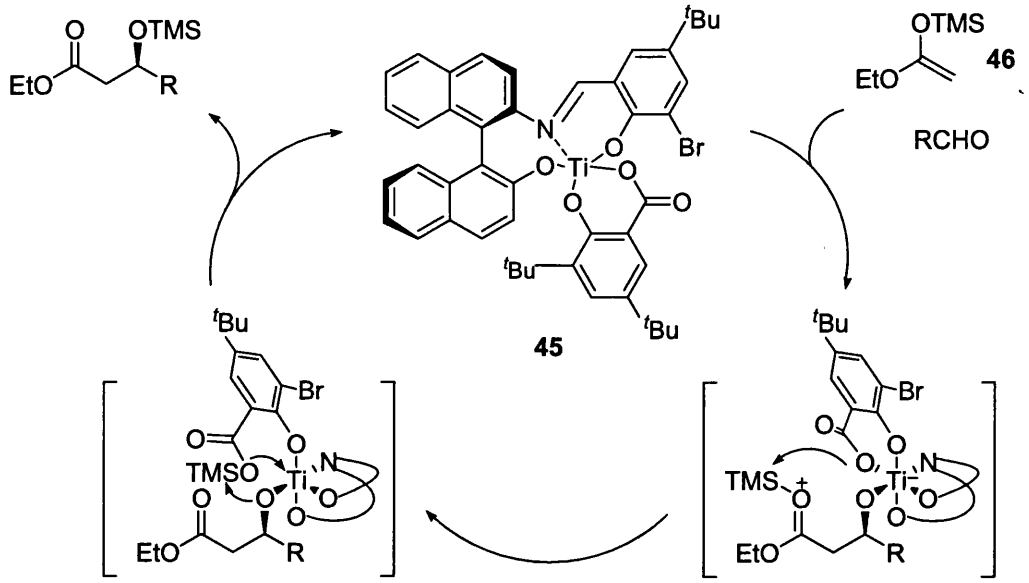
This process was applied to a range of aldehydes which gave good yields and enantioselection. The success was attributed to the coordination of the metal centre by the solvent, increasing the electron density around the tin alkoxide. The reactivity of this metal alkoxide towards silylation was therefore accelerated. The TMSOTf was trapped faster, regenerating the active catalyst, increasing turnover and hence the stereoselectivity of the reaction.

I 4.2 Carreira's Ti(IV) catalyst

Carreira delivered a solution to stereorandom catalysis in the aldol reaction.[46,47,48] The design of the catalysis involved accelerating the silylation of the metal alkoxide species, thereby regenerating the active catalyst more rapidly. A mechanism of intramolecular shuttling of the trimethylsilyl moiety sufficed, which the Ti(IV)-Schiff base complex **45** provided (Scheme 13); the secondary ligand, 3,5-di-*t*-butylsalicyclic acid, acting as the silyl shuttle. The catalyst gave excellent yields for aliphatic and aromatic aldehydes reacting with silyl enol ethers or silyl dienolates. Reactions conducted at -10 °C in diethyl ether with as little as 0.5 mol% of catalyst

afforded yields of up to 99% and high levels of asymmetric induction (88-99% *ee*).

Scheme 13. Carreira's Ti(IV) catalyst.

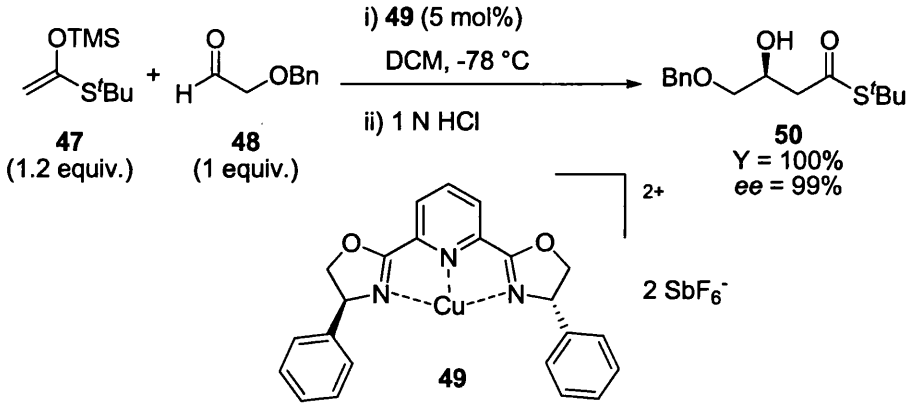


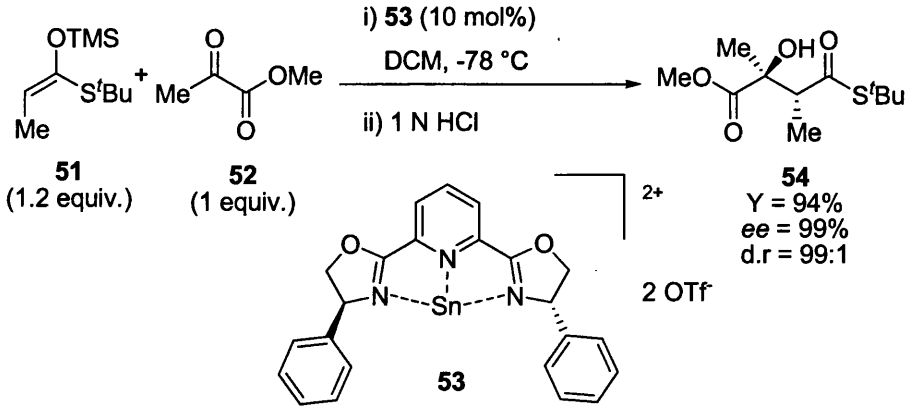
I 4.3 Evans' Cu(II) and Sn(II) catalysts

Evans reported, in 1996 for Cu(II) and shortly after in 1997 for Sn(II), highly efficient enantioselective Mukaiyama aldol reactions with complementary *syn*- and *anti*-selection.[49,50] One of the efficient copper catalysts employed consisted of a tridentate bis(oxazolinyl)pyridine (PyBOx) ligand chelated to copper(II) hexafluoroantimonate **49** (Scheme 14). Five mol% of the catalyst was sufficient for the addition of the silyl ketene acetal **47** (1.2 equiv.) to benzyloxyacetaldehyde **48** (1 equiv.). The *syn*-aldol adduct **50** was obtained in quantitative yield and 99% *ee*. The reaction was found to be general with respect to the silyl ketene acetal but the requirement for a chelating substituent on the aldehyde was critical to catalyst selectivity.

Indeed, bulkier etheric aldehydes gave lower *ee*'s and non-chelating aldehydes led to racemates. In addition, the use of α-substituted silyl ketene acetals afforded preferentially the *syn*-aldol, regardless of the geometry of the nucleophile (diastereoselectivities ranging from 95:5 to 97:3 with *ee*'s > 95%). This was rationalised by the attack of the silyl ketene acetal *via* an open transition state on the *si* face of the chelated aldehyde minimising the number of repulsive gauche interactions.

Scheme 14. Complementary Cu(II)- and Sn(II)-catalysed enantioselective Mukaiyama aldol reactions.





The Sn(II) system offered a complementary extension to glyoxylate and pyruvate esters, both bi-coordinating electrophiles, delivering adducts

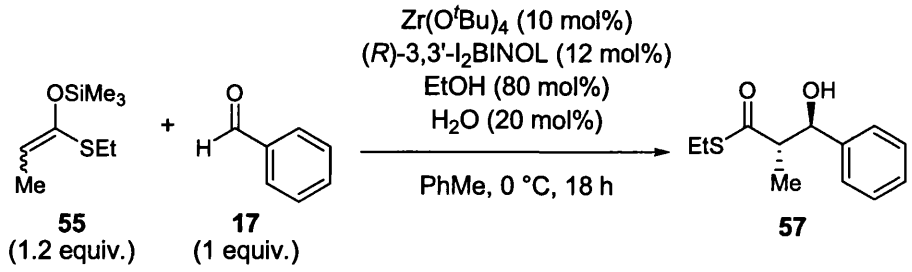
with high *anti*-selectivity. The catalyst composed of a tridentate bis(oxazolinyl)pyridine (PyBOx) ligand chelated to tin(II) triflate **53** (Scheme 14) afforded adducts, for example **54** in up to 99% *ee* and a d.r. of 99:1 (*anti*:*syn*).

I 4.4 Kobayashi's *anti*-selective Zr catalyst

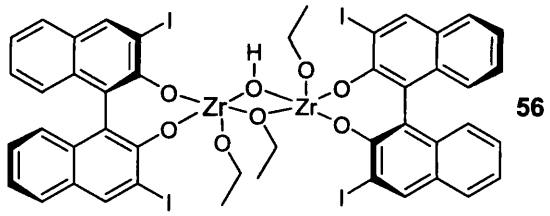
Kobayashi recently reported a highly *anti*-selective catalytic Mukaiyama aldol reaction promoted by a zirconium Lewis acid (Table 2).[51,52] Initially, they developed an effective enantioselective catalytic system, furnishing aldol adducts in good yield and enantioselectivity. The catalyst was formed from zirconium tetra-*tert*-butoxide ($Zr(O^tBu)_4$), (*R*)-3,3'-diiodo-1,1'-binaphthalene-2,2'-diol ((*R*)-3,3'-I_2BINOL) and a primary alcohol to act as a proton source to aid in the regeneration of the catalyst. In addition, it was later discovered that the addition of a small amount of water increased the activity of the catalyst and improved reproducibility. From NMR experiments, the assumption was made that the water was taking part in the formation of the complex **56**, the active catalyst species (Table 2). With this catalyst, *anti*-diastereoselectivity was obtained, regardless of the geometry of the starting silyl ketene acetal (Entries 1 and 2, Table 2). Reactions of mixtures enriched in either the (*E*)- or (*Z*)-silyl ketene acetal **55** (1.2 equiv.) with benzaldehyde **17** (1 equiv.) furnished the aldol adduct **57**. Yields achieved were greater than 63%. The diastereoselectivity attained was in the order of 8:92 in favour of the *anti*-diastereomer with *ee*'s greater than 95%. The catalytic cycle was proposed to proceed *via* activation of the aldehyde by the Lewis acid **58** (Scheme 16). The *anti*-selectivity was postulated to be a result of steric repulsions between the α-alkyl substituent of the nucleophile

and the Lewis acid in an open transition state (Scheme 15). After carbon-carbon bond formation, the ligand is then silylated. The primary alcohol traps the trimethyl silyl species, regenerating the active catalyst and furnishing the α-hydroxy carbonyl.

Table 2. *anti*-Selective Zr catalyst for the Mukaiyama aldol reaction.



Entry	*E*:*Z* ratio	Yield (%)	*Syn*:*anti*	*ee* (%)
1	88:12	63	9:91	95
2	7:93	77	7:93	98



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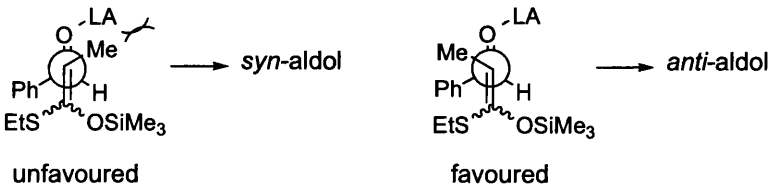
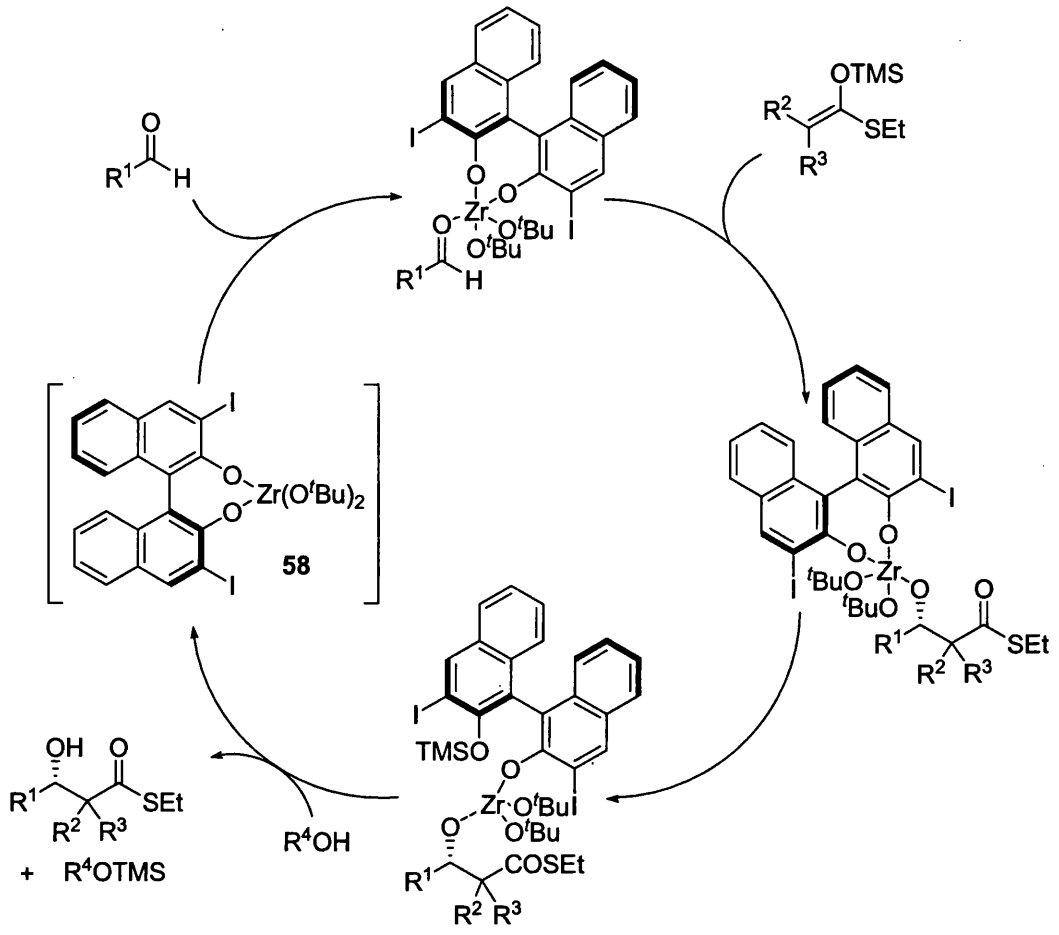
Scheme 15. Kobayashi's *anti*-selectivity model.



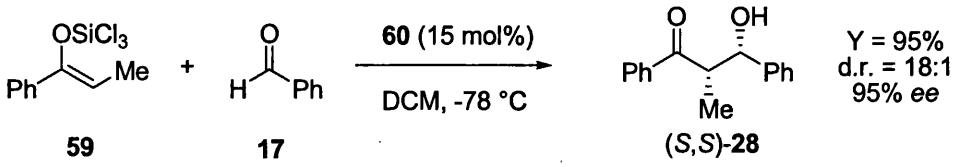
Scheme 16. Kobayashi's proposed catalytic cycle.

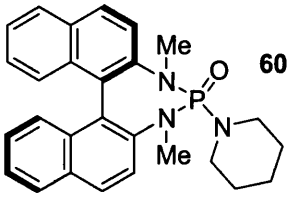


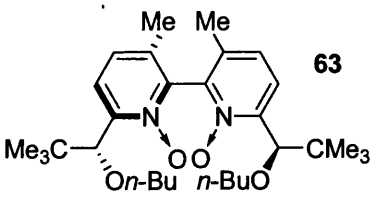
I 4.5 Denmark's Lewis base approach

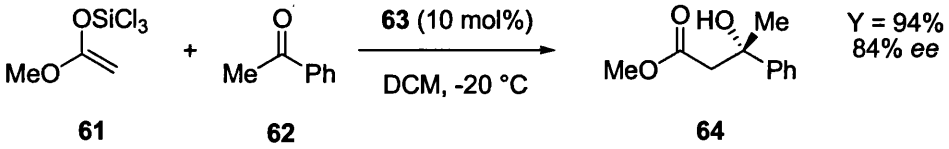
The group of Denmark have developed the use of chiral Lewis bases, which is a conceptually different latent enolate approach than the above-described methodologies. Phosphoramides have been used to efficiently promote the reaction of trichlorosilyl enolates with aldehydes[53] and more recently ketones by employment of bis-*N*-oxide catalysts (Scheme 17).[54] Replacement of chlorine by coordination of the catalyst's oxygen atoms to silicon appears to lead to a cationic silicon enolate intermediate species that subsequently binds to the electrophilic carbonyl to effect aldolisation.

Scheme 17. Phosphoramides and bis-*N*-oxides as chiral Lewis base catalysts.









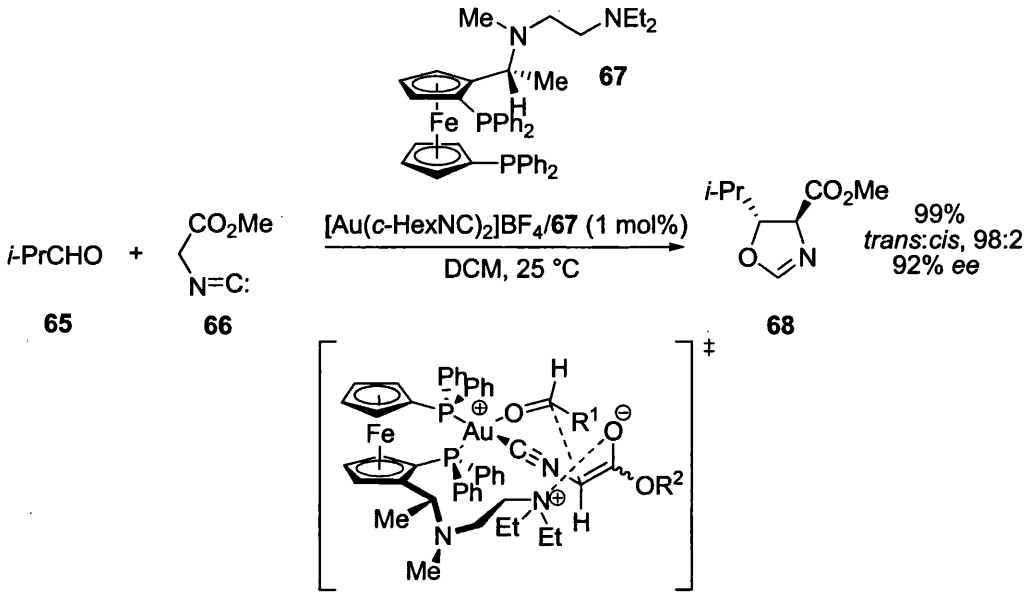
I 5 Direct metallic asymmetric catalysis[36,37,38]

I 5.1 Ito and Hayashi's Au(I) catalyst

All the reactions described so far entail chiral auxiliaries/substrates, preformed enolates, or stoichiometric chiral ligands. Ito and Hayashi reported an early example of a direct catalytic asymmetric aldol reaction in 1986.[55] Chiral ferrocenylphosphine(67)-gold(I) complexes were used to catalyse the reaction of an *iso*cyanoacetate, for example **60**, with achiral aldehydes to produce optically active oxazoline-carboxylates **68** (Scheme 18). These products are useful synthetic intermediates to optically active *β*-hydroxyamino acids. The high efficiency of the gold catalyst, which is employed at loadings as low as 1 mol%, has been attributed to a transition

state that utilises the terminal amino group to deprotonate an α-proton of the *iso*cyanoacetate, coordinated to the gold, thus forming an ion pair. This interaction permits a favourable stereodefined arrangement of the enolate and aldehyde (Scheme 18).

Scheme 18. Gold-catalysed asymmetric aldol reaction.

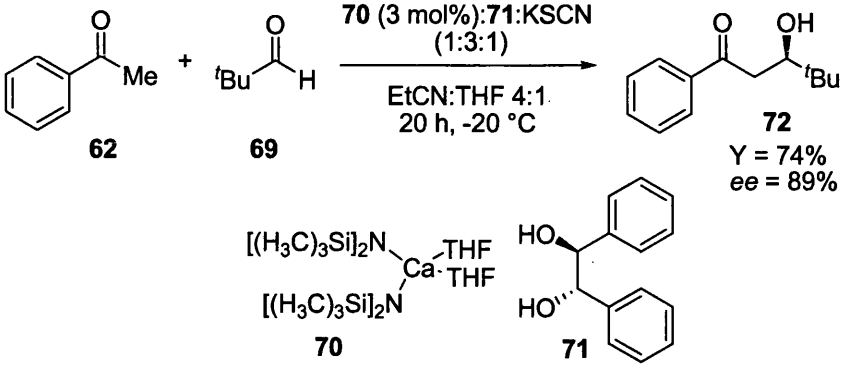


I 5.2 Noyori's calcium (II) catalyst

Several metallic catalysts have recently been developed for the direct asymmetric aldol reaction. Noyori reported a protocol employing a simple diol containing-calcium catalyst that provided reasonable enantioselectivity (Scheme 19).[56] For example, the reaction of acetophenone **62** and pivaldehyde **69** was promoted by the catalyst system composed of $Ca[N\{Si(CH_3)_3\}_2]_2THF_2$ **70**, (*S,S*)-hydrobenzoin **71**, and KSCN, in a respective ratio of (1:3:1), to provide β-hydroxyketone **72** in 74% yield and 89% *ee*. However, a large

excess of ketone, 10 equivalents, was crucial in obtaining the aldol adducts in reasonable yield and with a satisfactory *ee*.

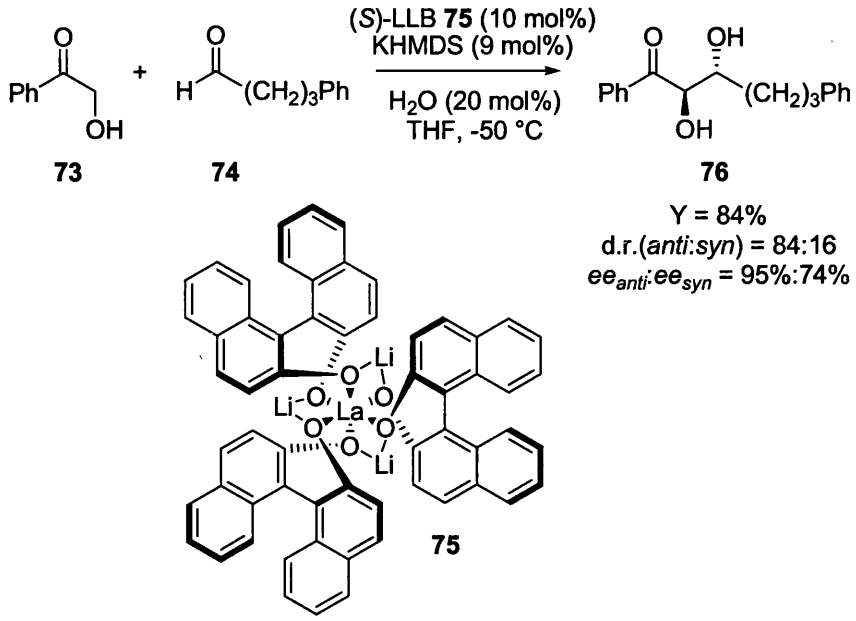
Scheme 19. Noyori's Ca-hydrobenzoin direct asymmetric catalysis.



I 5.3 Shibasaki's LLB catalyst

The design of low molecular weight catalysts that mimic enzymes has been an approach for the development of aldol reactions of unmodified ketones by certain groups. Shibasaki, for example has employed the heterobimetallic complex LaLi3tris(binaphthoxide) (LLB) **75** which is bifunctional in having both Lewis acid and Brønsted basic sites (Scheme 20). The reaction has been conducted with methyl ketones[57] and more recently α-hydroxy ketones[58] with aldehydes. The use of additives $KN(SiMe_3)_2$ and H_2O generating KOH *in-situ* has lead to a much more active heteropolymetallic species reducing reaction times and catalyst loadings. The reaction of α-hydroxy ketones is *anti*-selective, and with 10 mol% LLB, 9 mol% KHMDS, and 20 mol% H_2O, reaction times are approximately 24 h with adducts afforded in up to 95% *ee* (Scheme 20).

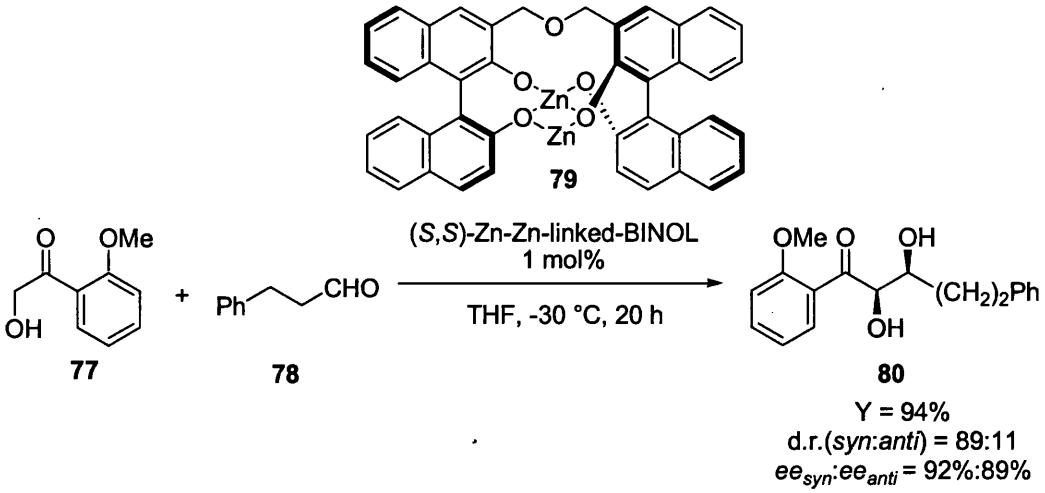
Scheme 20. Shibasaki's direct catalytic asymmetric aldol reaction.



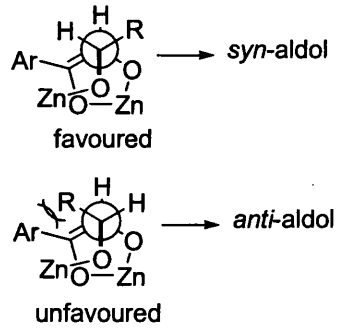
I 5.4 Shibasaki's Et_2Zn/linked BINOL complex

Shibasaki has also reported a practical complementary synthesis of *syn*-1,2-diols using a Zn-Zn–linked-BINOL **79** complex.[59] The reaction of 2-hydroxy-2'-methoxyacetophenone **77** as a starting material proceeds smoothly using as little as 1 mol% of the dinuclear catalyst. High yields, *syn*-selectivity, and high *ee*'s are reported making this one of the most efficient asymmetric aldol catalysts to date (Scheme 21). The *syn*-selectivity is attributed to steric congestion induced from the approach of the aldehyde to the *si* face between the enolate aryl group and aldehyde R-group (Scheme 22).

Scheme 21. Shibasaki's dinuclear zinc *syn*-selective direct catalytic asymmetric aldol reaction.



Scheme 22. Proposed transition state for the dinuclear zinc reaction.

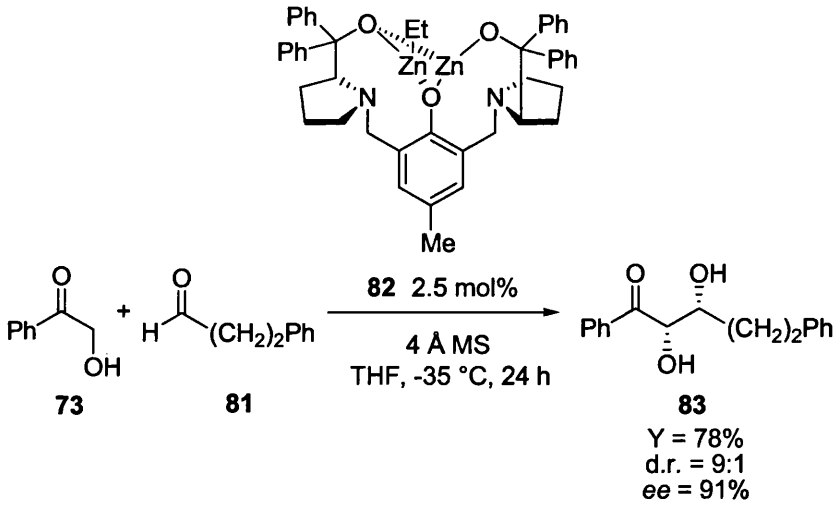


I 5.5 Trost's bimetallic Zn catalysts

In addition to Shibasaki's zinc catalyst, Trost has reported the use of a bimetallic zinc catalyst for the direct asymmetric aldol reaction.[60] The semicrown Zn(II) complex **82** has been designed on the basis of the recognition ability of crown compounds and the behaviour of aldolase II-type enzymes.[61] The complex works very efficiently in the reaction of aryl ketones with aliphatic α-branched aldehydes with loadings as low as 5

mol%. The addition of a weak coordinating agent for zinc, triphenylphosphine sulfide, helped in terms of turnover and *ee*. The reaction was not at all atom economic with employment of an aldehyde:ketone ratio of 1:10. Trost's more recent publication discloses a much more atom economic catalysis and employs α-hydroxyketones as donors.[62] A 1.5:1 ratio of hydroxyketone to aldehyde is used along with a low catalyst loading of 2.5 mol% (Scheme 23). Trost has also developed this reaction for acetone as a donor.[63]

Scheme 23. Trost's dinuclear zinc catalysed direct asymmetric aldol reaction.



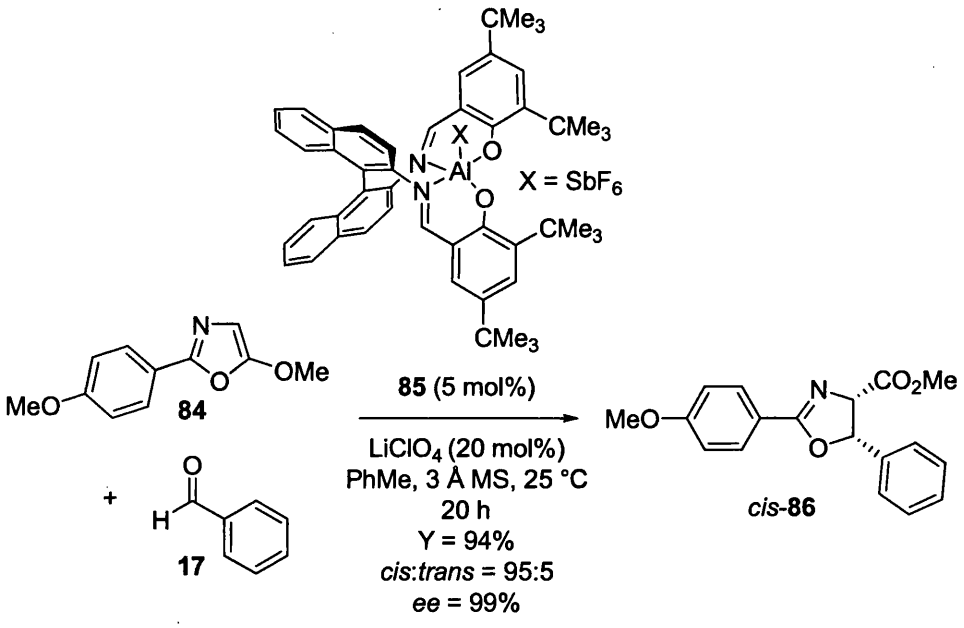
I 5.6 Evans' salen-Al catalyst

Evans has utilised salen-aluminium complex **85** to promote the catalytic synthesis of *cis*-oxazoles, for example **86**, synthetic equivalents of α-amino-β-hydroxy acids (Scheme 24).[64] The reaction of 5-methoxyoxazole **84** (1 equiv.) with benzaldehyde **17** (1.2 equiv.) in the presence of 5 mol% of **85**, 3 Å MS, and 20 mol% of $LiClO_4$ delivered the *cis*-oxazole **86** in a 94% yield, with a

cis:*trans* ratio of 95:5 and an *ee* of 99%. The $LiClO_4$ additive was proposed to promote the breakdown of the aluminium alkoxide aldolate intermediate.

The scope of the aldehyde was studied and extended to a wide range of aromatic compounds. The yields were all higher than 93%, with diastereomeric ratios of the order, 90:10 in favour of the *cis*-oxazole, and *ee*'s were all higher than 91%.

Scheme 24. Salen-Al catalyst for the enantioselective oxazole aldol reaction.

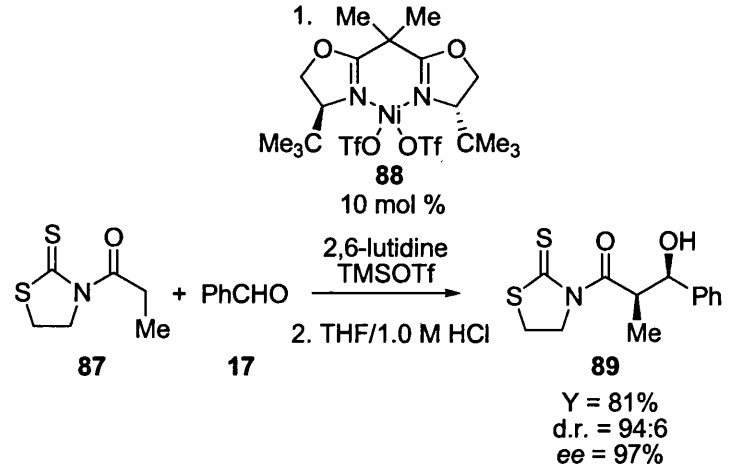


Surprisingly, aliphatic aldehydes were found to be unreactive under the standard reaction conditions. An advantage of the *cis*-product outcome was that epimerisation at the α-centre to *trans*-**86** could be achieved through the treatment of a catalytic amount of DBU (*cis*:*trans* = 5:95, *ee* > 99%).

I 5.7 Evans' Ni(II) bis(oxazoline) catalyst

Evans has recently reported the first example of a direct catalytic asymmetric aldol reaction of simple carboxylic acid derivatives.[65] The Ni(II) bis(oxazoline) **88** as the Lewis acid catalyst promotes the 2,6-lutidine based soft-enolisation of thiazolidinethiones (Scheme 25). On this occasion TMSOTf is used as an additive, but a conceived Mukaiyama pathway was ruled out based on the experimental evidence that when the aldehyde component was excluded from the reaction no silylketene acetal was observed. A role in the catalytic cycle of silylation of the Ni(II) alkoxide intermediate is proposed for TMSOTf hence aiding product decomplexation and eventual catalyst turnover. Very high enantioselectivity was achieved irrespective of the aldehyde component for the major *syn*-diastereomer.

Scheme 25. Ni(II) bis(oxazoline)-catalysed *syn*-aldol reaction.



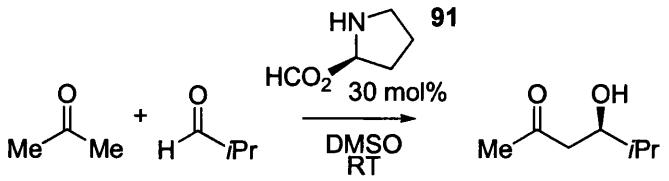
I 6 Asymmetric Organocatalysis[66,67,68]

Catalysis *via* small chiral organic molecules – organocatalysis, has emerged as a prominent field in asymmetric synthesis over the past few years. (*L*)-Proline for example has shown to be an excellent organocatalyst for the aldol reaction and is highlighted in this section along with other examples.

I 6.1 List's proline catalyst

Recently, List and co-workers discovered a novel catalytic reaction that uses a simple optically active amine-based catalyst in the direct aldol addition of acetone **90** and a variety of aldehydes (Scheme 26).[69,70] It has been identified that (*L*)-proline **91** works well as a class I aldolase mimic in this reaction and there is no requirement for any metal intervention. The reaction has the advantages of being direct, water tolerant and conducted at RT.

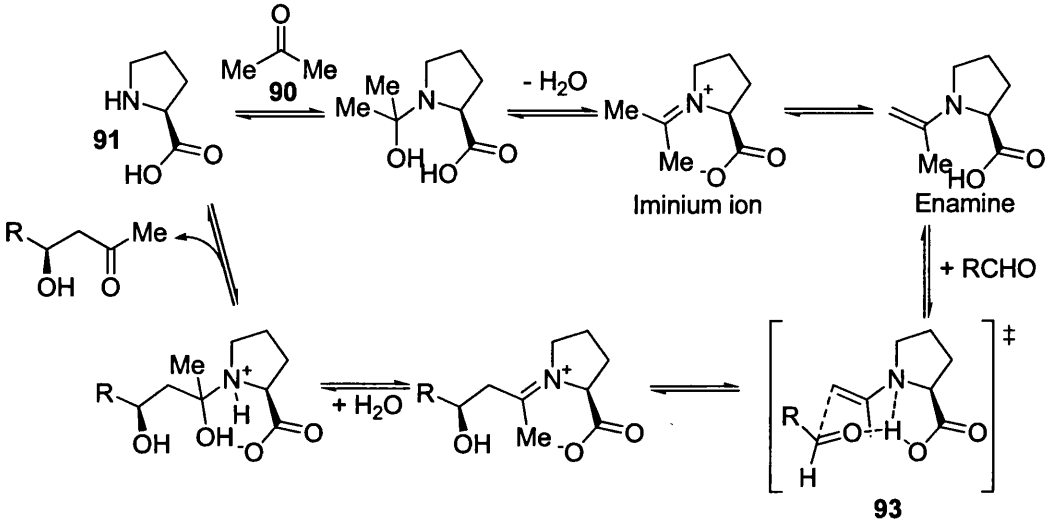
Scheme 26. (*L*)-Proline catalysed aldol reaction.



Under optimised conditions, a 30 mol% loading of (*L*)-proline promotes the reaction, *via* an enamine type mechanism (Scheme 27). The resultant enantioselectivity can be attributed to a metal free Zimmerman-

Traxler transition state **93** comprising a tricyclic hydrogen bonded framework. The drawback of this catalysis is the need for the ketone component to be in high excess – acetone was used as a co-solvent.

Scheme 27. List's proposed enamine mechanism.

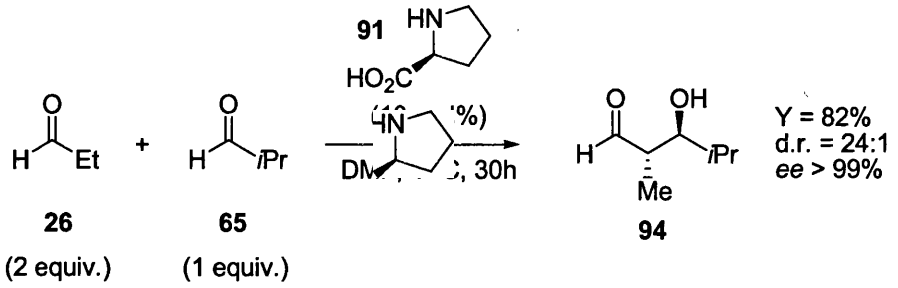


I 6.2 MacMillan's aldehyde cross aldol reaction

The reaction of two aldehydes, one acting as the nucleophilic component and the other acting as the electrophilic partner, which is a difficult process to control, has been successfully achieved through (*L*)-proline organocatalysis. MacMillan and co-workers have realised that under slow addition of the donor aldehyde to a mixture of (*L*)-proline (10 mol%) and the acceptor aldehyde in DMF at 4 °C, cross aldol adducts of up to 99% *ee* can be reached.[71] For example propionaldehyde **26** (2 equiv.) and isobutyraldehyde **65** (1 equiv.) afford *β*-hydroxyaldehyde **94** in 82% yield and 99% *ee* (d.r. = 24:1 in favour of the *anti*-aldol) (Scheme 28). In this process, a respectable excess of the nucleophilic component aldehyde can be

employed. More recently, MacMillan has extended the scope of the acceptor aldehyde to α-thioacetal aldehydes generating adducts in up to 99% *ee*.[72]

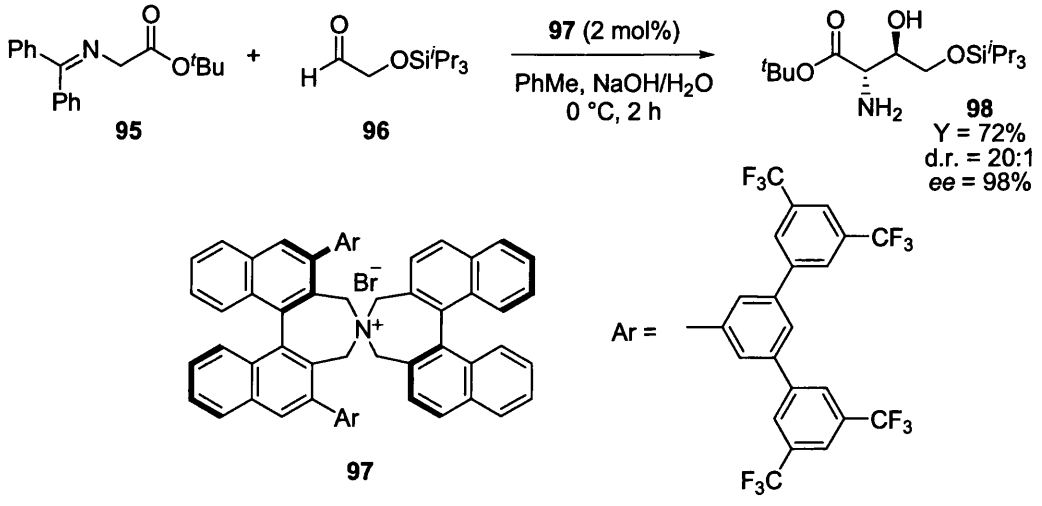
Scheme 28. MacMillan's aldehyde cross aldol reaction.



I 6.3 Chiral ammonium salts as organocatalysts

Maruoka and co-workers have employed phase transfer catalysis in synthesising β-hydroxy-α-amino acid derivatives.[73] The chiral ammonium salt **97**, derived from binaphthyls, is able to catalyse the reaction of glycine Schiff bases and aldehydes to afford aldol adducts in good yield and in very high *ee* (Scheme 29).

Scheme 29. Phase-transfer organocatalysis.

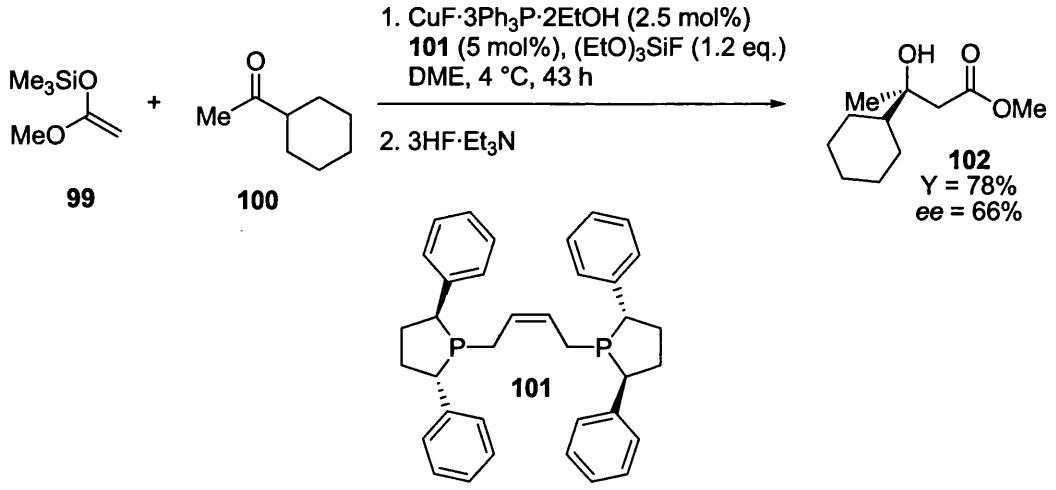


The biphasic catalysis employs only 2 mol% of the phase-transfer catalyst and yields the free β-hydroxy-α-amino moiety under the reaction conditions.

I 7 Most recent developments

The group of Shibasaki has recently developed a process involving new bis(diphenylphospholane) ligands to aid in the Cu(I)-catalysed enantioselective aldol reaction of ketones.[74] The use of ketene trimethylsilyl acetal **99** generates the corresponding copper enolate (the actual nucleophilic species) through a transmetalation between silicon and copper atoms, which facilitates the addition reaction of ketones (Scheme 30).[75] Chiral phosphine ligand **101** generated the most enantioselective Cu(I) catalyst, affording β-hydroxyester **102** in 78% yield and 66% *ee* after 43 h in DME from dialkylketone **100**.

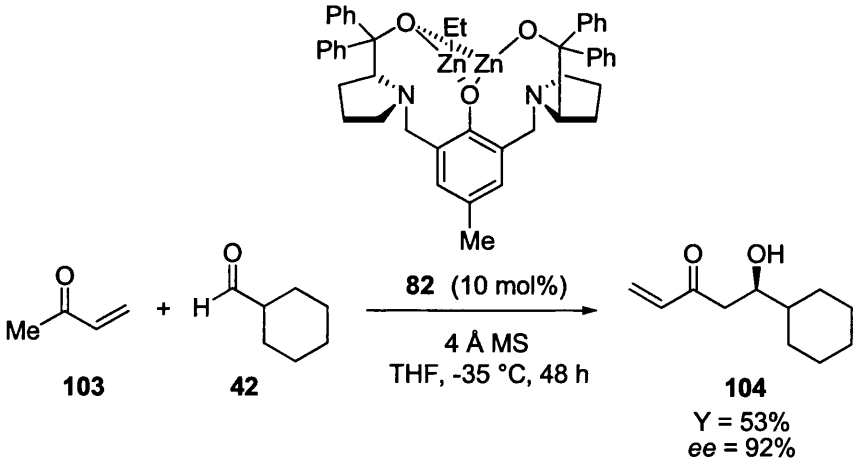
Scheme 30. Shibasaki's new phosphine-Cu(I) enolate addition to ketones.



The Cu(I) catalyst derived from $CuF{\cdot}3Ph_3P{\cdot}2EtOH$ was employed at the low loading of 2.5 mol% and the system required a stoichiometric amount of the additive, $(EtO)_3SiF$, to aid in catalyst turnover. Although *ee* is moderate, this is the most enantioselective reaction to date using aliphatic ketones.

Trost has recently extended the scope of the dinuclear zinc catalyst **82** to include the reaction of methyl vinyl ketone **103** (a highly functionalised nucleophile) with a variety of aldehydes (Scheme 31).[76] This is the first general asymmetric aldol reaction to date of the highly useful bifunctional building block – methyl vinyl ketone, which due to its base instability has had hampered development in aldol processes. Products could be obtained in up to 98% *ee* and yields of up to 74% depending on the aldehyde, solvent and temperature employed.

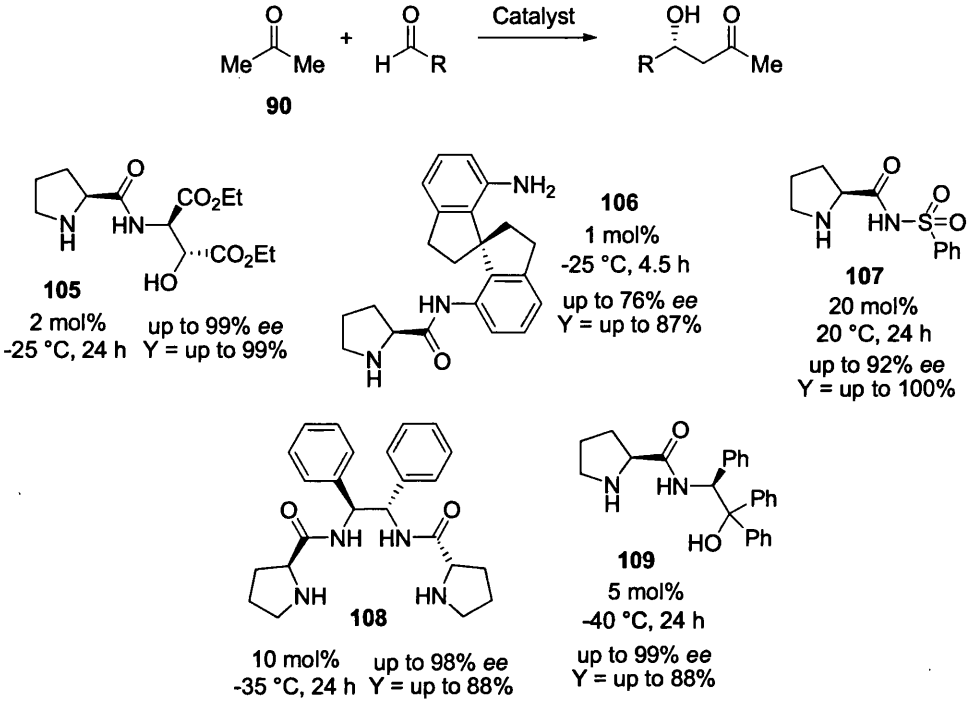
Scheme 31. Trost's use of methyl vinyl ketone as a substrate.



Organocatalysis has developed rapidly very recently, and many groups have seized the opportunity to develop this field especially in the asymmetric aldol reaction. Only in the last year have several novel (*L*)-proline derivatives been synthesised by numerous groups and applied to the

reaction of acetone and various aldehydes with high degrees of enantioselection (Scheme 32).[77,78,79,80,81]

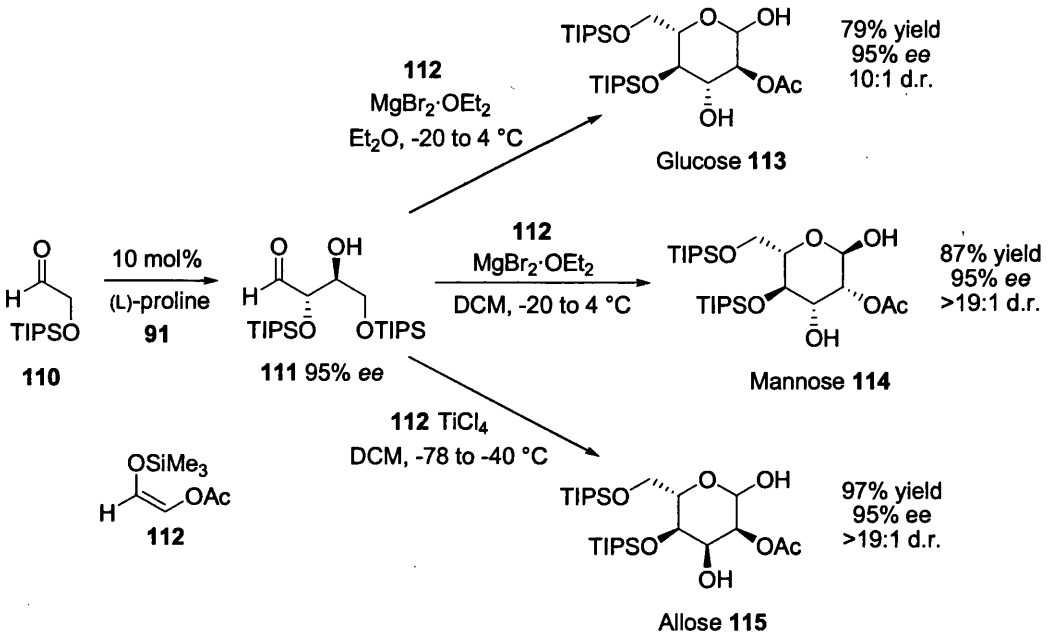
Scheme 32. Derivatised (*L*)-proline catalysts for the acetone/aldehyde aldol reaction.



A final inclusion of an asymmetric organocatalytic process and in particular a utilisation of (*L*)-proline is that of carbohydrate synthesis. The group of MacMillan have devised a two-step synthesis of protected glucose, allose, and mannose stereoisomers from an initial enantioselective self-aldolisation reaction catalysed by 10 mol% (*L*)-proline.[82] The second carbohydrate-forming step involves a Mukaiyama aldol addition-cyclisation reaction catalysed by either $MgBr_2 \cdot OEt_2$ or $TiCl_4$ (Scheme 33). The α-oxyaldehyde dimerisation in step one of the two-step tandem reaction produces adducts in 95% *ee* (*anti:syn* = 4:1) (Scheme 33). Adducts of the first step, β-hydroxy aldehydes, are inert to further enamine addition therefore require alternative mediation to continue the process. The outcome of the

Lewis acid mediated second step including cyclisation i.e. whether a glucose, allose, or mannose derivative is produced is dependent on the Lewis acid and solvent used. Hexoses are produced in up to 97% yield, up to a d.r. of > 19:1, and no loss in *ee* (95%).

Scheme 33. (*L*)-Proline catalysed carbohydrate synthesis.



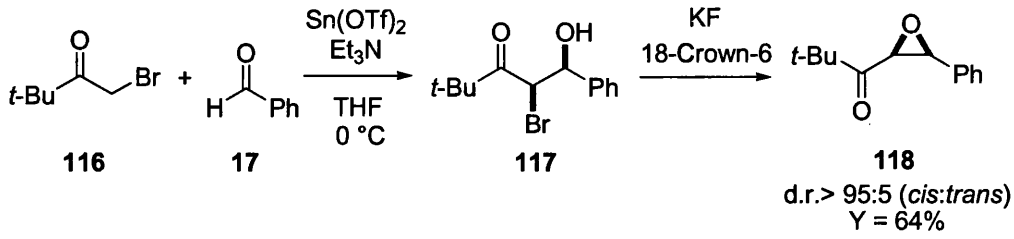
I 8 The asymmetric Darzens reaction[83]

An aldol reaction in which a post aldol cyclisation occurs at the α-centre to bring about epoxide formation – the Darzens reaction, is an interesting modification. A direct asymmetric catalytic process involving metallic species is an attractive methodology to pursue but has remained elusive.

In 1982 Mukaiyama showed that under stoichiometric soft-enolisation conditions *cis*-α,β-epoxyketones could be synthesized *via* a 2-step Darzens route stereoselectively.[84] The cross aldol reaction between α-bromoketone **116** and benzaldehyde **17** is mediated by $Sn(OTf)_2$ and triethylamine. The major

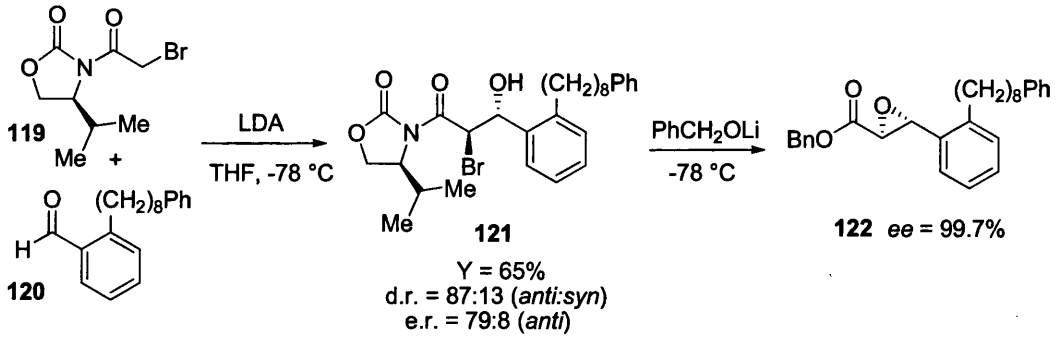
syn-aldol adduct **117** is then treated with KF/dicyclohexyl-18-crown-6 as an HBr captor to allow formation of the correct *cis*-epoxide **118** without epimerisation of the α-centre (Scheme 34).

Scheme 34. Stoichiometric Sn(II)-mediated Darzens reaction of α-bromoketones.



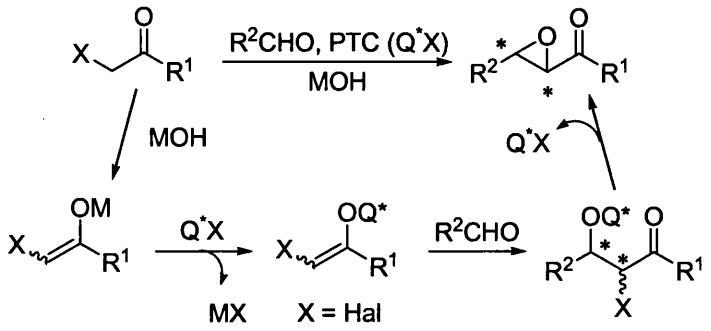
Asymmetric Darzens reactions are scarce. The reaction is dominated by the use of phase transfer catalysis although Pridgen *et al* have employed Evans' chiral oxazolidinone protocol to initially prepare enantioenriched α-halo aldol adducts from various metal enolates.[85] The *anti*-bromohydrins afford stereospecifically *trans*-benzyl-α,β-epoxy esters upon treatment with lithium benzyloxide (Scheme 35). Again, this is a modified two-step procedure of the Darzens reaction.

Scheme 35. Chiral auxiliary controlled Darzens reaction.



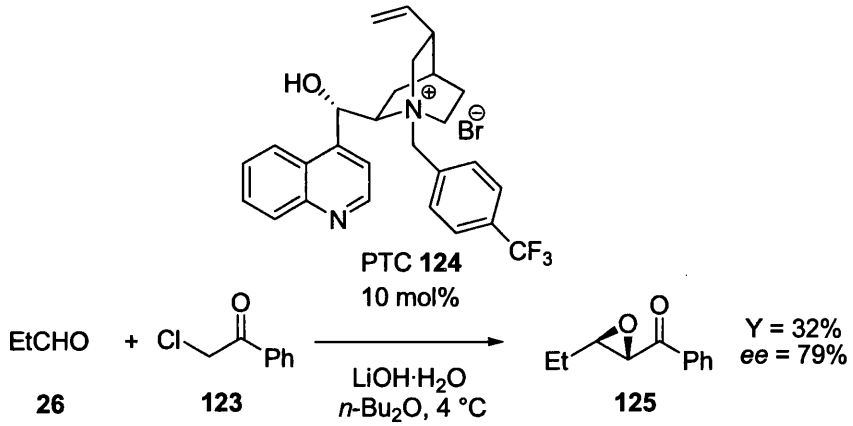
The group of Shiori has made considerable progress in the development of catalytic asymmetric Darzens reactions *via* phase transfer catalysis.[86] A reactive and soluble ammonium halide (QX) can be transformed into a chiral active species in the presence of an inorganic base (MOH), which leads to an effective catalytic cycle (Scheme 36).

Scheme 36. PT catalytic cycle for the asymmetric Darzens reaction.



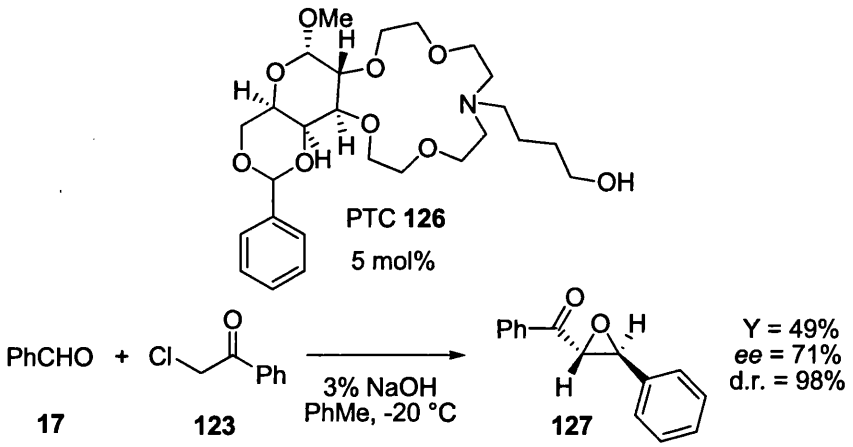
Shiori initially worked on α-chloroketones with various aldehydes and found that *N*-(4-trifluoromethylbenzyl)cinchonium bromide **124** and LiOH worked well as a catalyst system in di-*n*-butyl ether at 4 °C. The reaction of phenacyl chloride **123** with aliphatic aldehydes proceeded smoothly to give the corresponding epoxides with good stereocontrol and yield under the mild conditions (Scheme 37). Mechanistic studies discarded the reasonable assumption that the stereocontrol is derived from the reaction of the aldehyde with the chiral ammonium enolate. Instead, studies showed that stereoselectivity is controlled by a retro-aldol reaction and kinetic resolution.

Scheme 37. Shioiri's phase-transfer-catalysed asymmetric Darzens reaction.



A final example is that of Bakó and co-workers who have described the use of chiral crown ethers derived from D-glucose and D-galactose as effective phase transfer catalysts in the Darzens condensation (Scheme 38).[87]

Scheme 38. 15-Crown-5 PT-catalysed Darzens condensation.



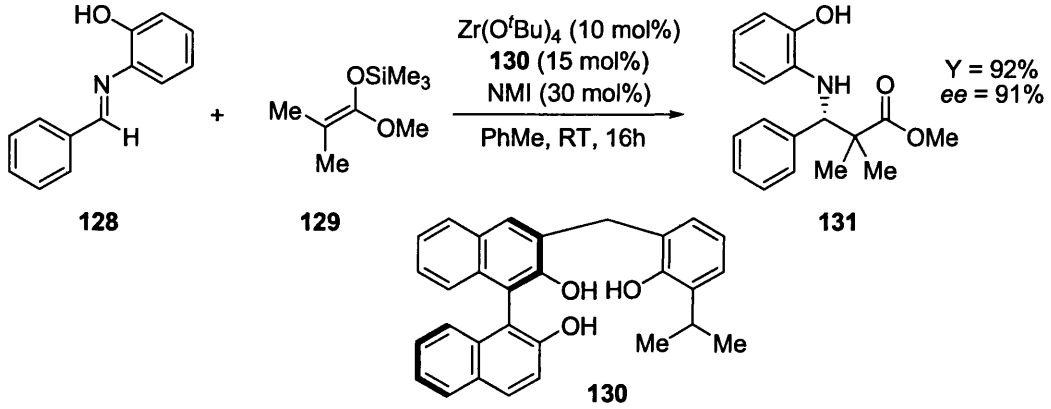
The reaction of phenacyl chloride **123** with benzaldehyde **17** in the presence of 5 mol% chiral crown ether catalyst **126** and 30% NaOH produced α,β-epoxyketone **127** in 71% *ee*. Other nitrogen fragments resulted in much lower *ee*'s especially those without the added hydroxyl side-arm. In all cases the *trans*-diastereomer was obtained in excellent *de* (> 98 %).

I 9 The asymmetric Mannich reaction[88]

The final reaction to mention is the Mannich reaction where an imine electrophile takes the place of the electrophilic carbonyl component in the aldol reaction. The Mannich or imine-aldol reaction has taken similar developmental paths as the aldol reaction in terms of catalytic asymmetric methodologies. Described herein are a few of the latest developments of the asymmetric Mannich reaction – a means to highlight the vast array of catalyses to be found in the current literature for a C-C bond forming reaction that synthetically reaches important products such β-amino acids.

A highly enantioselective example of a latent enolate metal mediated catalysis is that of Kobayashi's zirconium-tridentate BINOL derivative system.[89] The addition of ketene silyl acetals such as **129** to benzaldimines such as **128** proceeded smoothly under the reactions conditions of $Zr(O^tBu)_4$ (10 mol%), ligand **130** (15 mol%), and *N*-methylimidazole (NMI) (20 mol%) in toluene (Scheme 39).

Scheme 39. Kobayashi's zirconium catalysed asymmetric Mannich reaction.

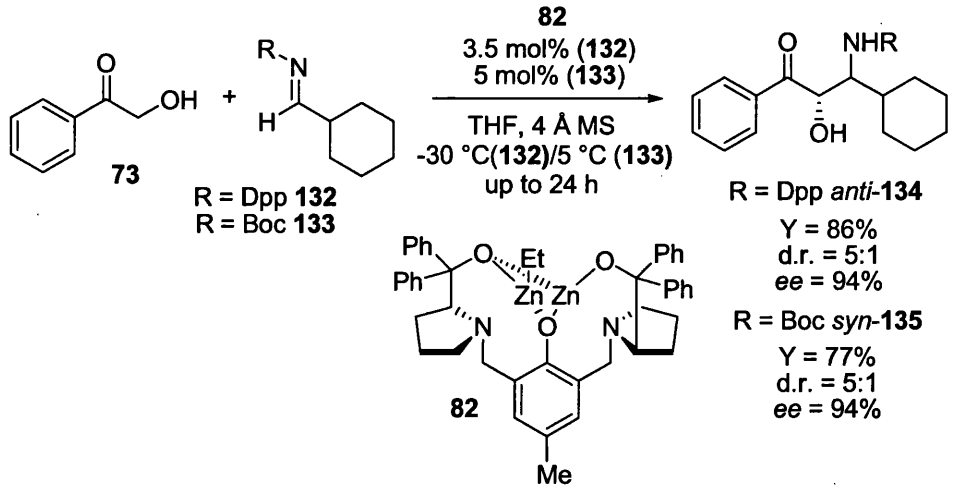


The high design of the BINOL derived ligand stemmed from an assumed 2:1 (*R*)-6,6'-Br_2-BINOL:Zr transition state structure from previous

work on asymmetric Mannich reactions.[90] Tridentate-BINOL derivative **130** has superseded (*R*)-6,6'-Br$_2$-BINOL as a ligand with increased enantioselection and yields across the substrate range. The newly developed catalyst could also be conducted at room temperature with little loss in *ee* (Scheme 39). *N*-methylimidazole is believed to play an important role of dissociating oligomeric Zr-species and regulating the structure of the Zr complex.

A recent example of a direct metal mediated catalyst system comes from the group of Trost.[91] The dinuclear zinc catalyst **82**, already mentioned as an effective catalyst in aldol reactions (Sections I 5.5 and I 7), has been utilised in the Mannich reaction of α-hydroxy ketones with *N*-protected imines. The outcome of the Mannich adducts, whether *anti* or *syn*, could be controlled by the type of *N*-protection incorporated into the starting imine. Diphenylphosphinoyl (Dpp) imines provided access to *anti*-adducts whereas Boc-imines provided *syn*-adducts (Scheme 40).

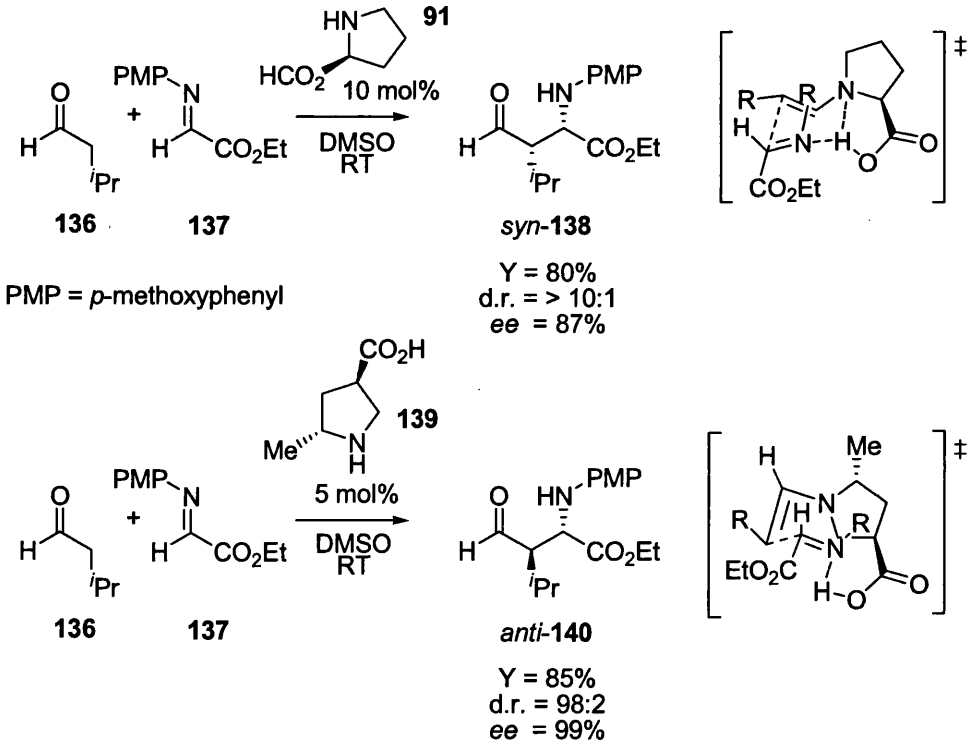
Scheme 40. Trost's dinuclear Zn-catalyst in asymmetric Mannich reactions.



Yields of up to 86%, d.r.'s of up to 6:1 and *ee*'s of up to > 99% have been achieved for a range of aliphatic imines and aryl ketones through employment of as little as 3.5% of catalyst **82** (Scheme 40). Modifications of the ligand were made but did not fulfil any improvement of the original dinuclear zinc catalyst.

Asymmetric organocatalytic methods have emerged as an effective protocol in many reactions as seen in the aldol reaction above (Sections I 6 and I 7). The Mannich reaction has not escaped such developments. The groups of Barbas III, and Tanaka have recently disclosed an *anti*-selective amino acid catalysed Mannich reaction whereas (*L*)-proline is *syn*-selective (Scheme 41).[92,93]

Scheme 41. Amino acid catalysed Mannich reactions.

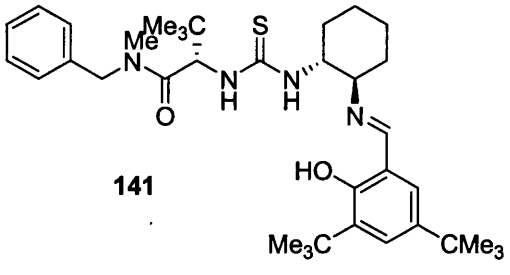


The organocatalyst 5-Methyl-3-pyrrolinecarboxylic acid **139** provides the *anti*-adducts in up to 99% *ee* and 98:2 d.r. for the reaction of aldehydes

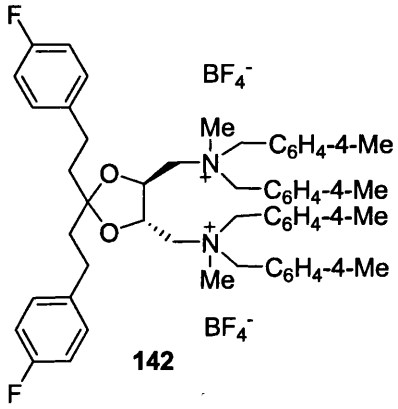
and *p*-methoxyphenyl protected imines. The reason for the opposite stereochemical outcome compared to (*L*)-proline is portrayed in the above proposed transition states for both types of catalysts which react through enamine based mechanisms (Scheme 41). The stereoselective formation of the *anti*-product necessitates a reversal in the facial selectivity of the enamine, which the 5-methyl substituent of **139** facilitates.

To end this section, other organocatalysts have been developed to mediate Mannich reactions. For example Jacobsen and co-workers have developed chiral thiourea catalysts such as **141** (Figure 6) for the reaction of ketene silyl acetals and Boc-protected imines,[94] whereas the group of Shibasaki have developed chiral phase transfer catalysts such as **142** (Figure 6) for the reaction of glycine Schiff bases and various *N*-protected imines.[95]

Figure 6. Chiral organic molecules as catalysts for the asymmetric Mannich reaction.



141



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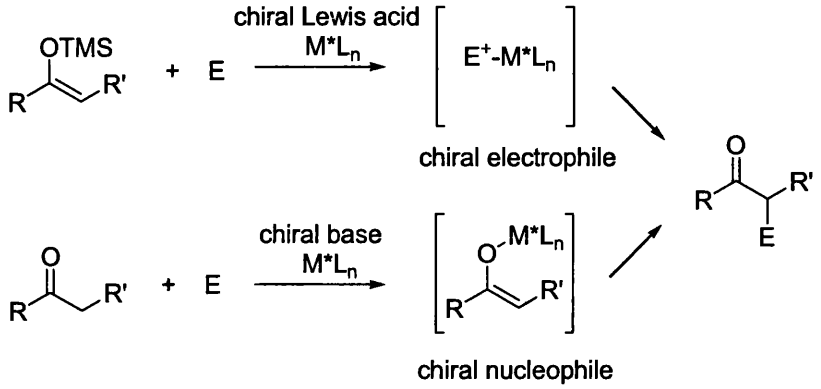
I 10 Outline of the project

Enolate-electrophile bond constructions are among the most efficient and general strategies for the stereoselective formation of carbon-carbon bonds in organic synthesis. The aldol addition reaction and imine variant being the most utilised. Accordingly, there are many examples of diastereoselective aldol/Mannich reactions that employ stoichiometric chiral controllers to ultimately deliver enantiomerically enriched adducts as discussed. Examples of catalytic enantioselective reactions are scarcer; however, several research groups have enjoyed considerable success in developing catalytic enantioselective variants of the Mukaiyama reaction. In such reactions, which employ a latent enolate equivalent, the enantioselectivity originates from the use of a chiral Lewis acid catalyst. The catalyst functions *via* the formation of a transient chiral electrophile (i.e., complexation of the Lewis acid to the carbonyl or imine group) and mediates only the bond-forming process. The formation of the enolate equivalent takes place in a separate operation. A more attractive strategy is to deliver the same bond construction by an aldol/Mannich reaction incorporating enolate generation as an integral part of the catalytic cycle. This results in the catalyst mediating both enolisation and subsequent bond formation. Such reactions proceed *via* the catalytic formation of a chiral nucleophile (Scheme 42). Denmark's enantioselective aldol system (Section I 4.5) which employs chiral base catalysts does not fit well into either of the scenarios described above because the chiral base formed actually originates from a preformed enolate equivalent.

As detailed (Scheme 42) there is a requirement for the use of a 'chiral base' as the asymmetric catalyst; one approach towards obtaining such a base is to exploit 'soft enolisation' conditions produced by the combination of a

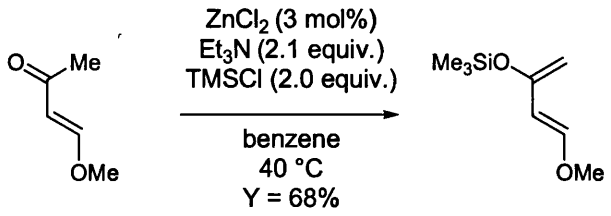
Lewis acid and a weak base. In this process the Lewis acid first coordinates to the carbonyl oxygen for example, thus activating the α-hydrogen atoms to deprotonation. Crucially, by using this protocol a much weaker base than usual can be employed for the deprotonation step.

Scheme 42. Generation of chiral electrophiles and nucleophiles.



The idea of soft enolisation has been seen throughout the introduction section but a few examples are discussed here to address the concept. Danishefsky and co-workers reported an impressive example of the use of soft enolisation.[96] In search of different functionalities and oxidation levels of dienes for the Diels-Alder reaction, 1,3-dialkoxybutadienes were sought after. Pyrolysis of 1,1,3,3-tetramethoxybutane gave unsatisfactory results. However, reaction of **143** with TMSCl in the presence of triethylamine and zinc chloride at 40 °C gave a 68% yield of *trans*-1-methoxy-3-trimethylsilyloxybuta-1,3-diene **144** (Scheme 43). Importantly, in the absence of the zinc chloride Lewis acid, enolisation of **143** did not occur.

Scheme 43. Danishefsky's diene formation.



143 **144**

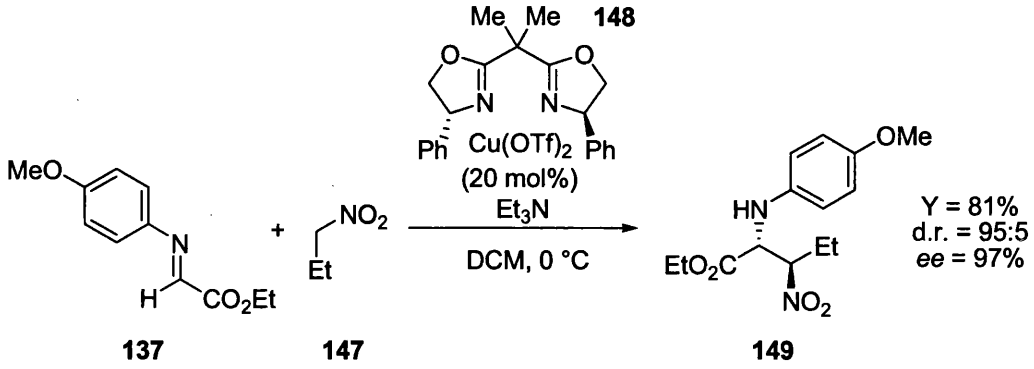
More recently the group of Evans has employed soft enolisation conditions in magnesium halide-catalysed *anti*-aldol reactions of chiral *N*-acyloxazolidinones (Scheme 44).[97] Although the enantioselectivity is derived from the auxiliary, i.e. no chiral catalyst is involved, the reaction is catalytic with respect to the magnesium halide Lewis acid (10 mol %). The weak base used is triethylamine and although TMSCl is used as an additive, the reaction does not proceed *via* a Mukaiyama aldol pathway.

Scheme 44. Soft enolisation portrayed in Evans' magnesium catalysed *anti*-aldol reaction of chiral *N*-acyloxazolidinones.

145 **17** **146**

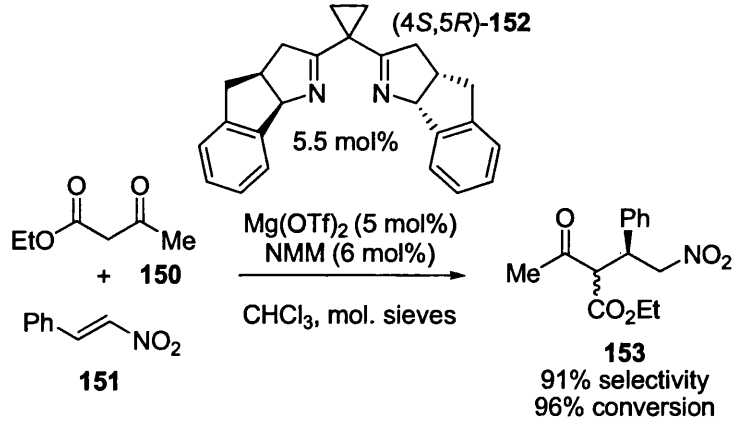
Jørgensen *et al* have applied catalytic enolisation conditions to the nitro-Mannich reaction.[98] The reaction involves the catalytic addition of nitro compounds to imines to give β-nitro-α-amino esters. A Cu(II) bis(oxazoline) **148** catalyst is utilised, and triethylamine as the weak base (Scheme 45).

Scheme 45. Catalytic asymmetric enolisation nitro-Mannich reaction.



The recent work of both Lygo and Corey using phase-transfer-catalysts in enantioselective alkylations[99] can also be rationalised by involving catalytic chiral enolates along with the work of Shibasaki's mixed-metal-BINOL catalysts already mentioned in this section. Ji and Barnes have applied soft enolisation conditions to the enantioselective conjugate addition of β-keto esters to nitroalkenes (Scheme 46).[100]

Scheme 46. Ji and Barnes' nitroalkene conjugate addition.

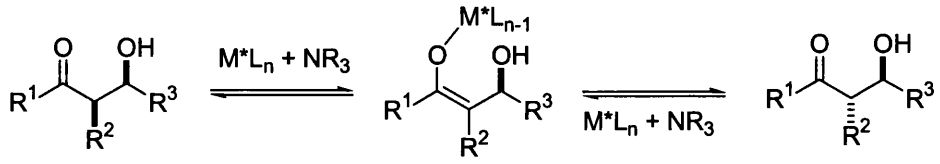


Treatment of 5 mol% of the Lewis acid, obtained by the combination of bis(oxazoline) **152** and $Mg(OTf)_2$, together with *N*-methyl morpholine as a base produced a chiral enolate good enough to undergo selective addition to nitrostyrene. The adducts were furnished in good yield and with good

selectivity at the carbon centre β to the nitro group. Unfortunately, the ester-bearing stereogenic centre was produced without selectivity.

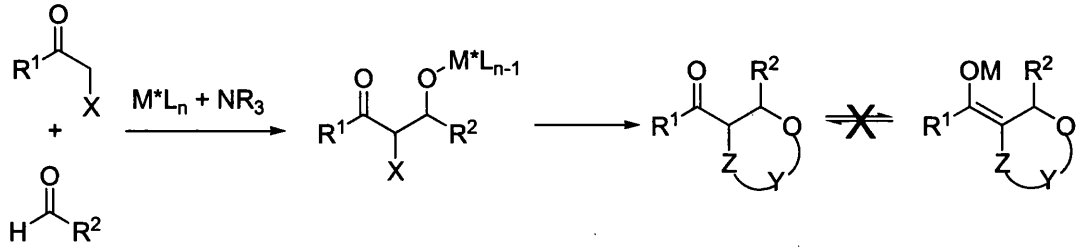
The lack of selectivity at the α-carbon arose because the pK_a of the substrate and product were similar allowing enolisation of the product and subsequently epimerisation (Scheme 47).

Scheme 47. Epimerisation of the α-carbon centre.



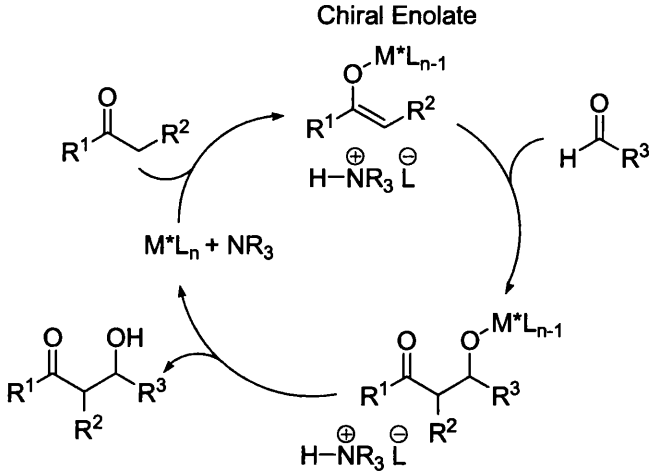
A solution to this problem would be to tune the selectivity of the base so that a small difference in acidity between the substrate and the product α-protons would be sufficient to limit product deprotonation. Usually the difference is too small and an alternative solution is to derivatise the product *in-situ* so that the pK_a of the proton α to the carbonyl group in the product is less acidic. This requires an α-substituent that can be modified post carbon-carbon bond formation; most likely by reaction with the alkoxide oxygen (Scheme 48).[55] Incorporating the newly formed hydroxyl group in a cyclic structure would also reduce the opportunity of product inhibition that could occur with a free β-hydroxy-carbonyl unit.

Scheme 48. Product derivatisation.



The catalytic cycle for an aldol bond construction for example employing an aldehyde and an enolisable carbonyl compound conducted under soft-enolisation conditions is depicted below (Scheme 49). In order for the cycle to be effective several criteria must be achieved; most importantly the 'chiral base' produced by the combination of the Lewis acid and amine base must be capable of facilitating enolisation. Ideally the aldehyde component will be unaffected by these conditions. Finally, the system must be able to turnover. The alkoxide adduct must be able to deprotonate the ammonium salt and thus regenerate the free base. Careful selection of the Lewis acid, base component, and α-substituent on the carbonyl should allow these criteria to be fulfilled.

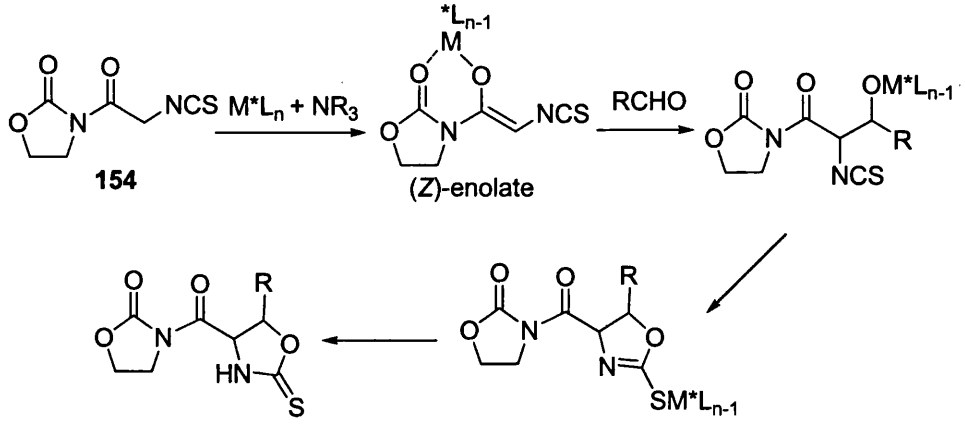
Scheme 49. Catalytic cycle for a chiral enolate aldol addition.



*Iso*thiocyanate substituted *N*-acyl oxazolidinone **154** satisfies many of the required design criteria (Scheme 50). The *iso*thiocyanate significantly

attenuates the pK_a of the substrate, whilst following carbon-carbon bond formation, reaction with the newly generated alkoxide to form an oxazolidinethione is possible.[101] The α-proton present in the final product will have an attenuated pK_a to that of the starting substrate **154**. The basicity of the metal coordinated thiooxazolidinone intermediate should be sufficient to regenerate the free base thus allow the use of catalytic amounts of Lewis acid and base.

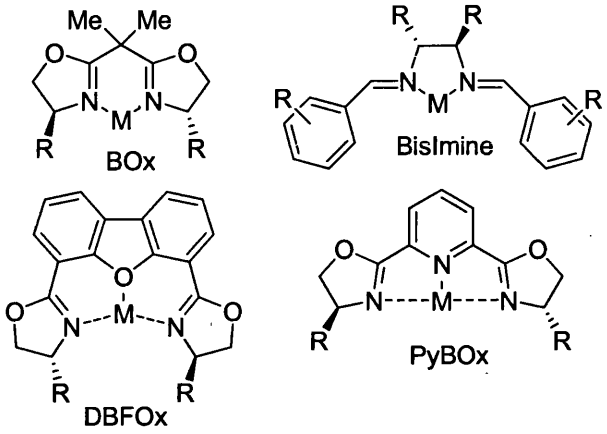
Scheme 50. Proposed *iso*thiocyanatoacetate substituted aldolisation.



One of the key objectives in establishing such a catalytic cycle is that the enolates produced are effective in transferring the chiral information from the catalyst to the incipient bond. *N*-acyloxazolidinones are known to selectively form (*Z*)-enolates.[102] This, together with their bidentate nature results in rigid structurally well-defined enolates. Finally and of crucial importance is that the ultimate products of the catalytic cycle are synthetically useful stereo-defined products. In order to achieve efficient transfer of stereochemical information, incorporation of chiral ligands would be expected to form rigid enolate complexes. This could be achieved by combining the bidentate oxazolidinone substrate **154** with bi- and tridentate chiral ligands. Possible ligand candidates include bisoxazolines (BOx),

dibenzofuran (bis)oxazolines (DBFOx), bisimines and pyridine (bis)oxazolines (PyBOx) (Figure 7).

Figure 7. Potential chiral ligand selections.



Early studies focussed on identifying suitable Lewis acid and base combinations that would effect deprotonation and allow completion of the catalytic cycle. In selecting these combinations, it was essential that the Lewis acid and the amine base did not form an irreversible adduct.

What is described in the following section is an account of the work carried out to establish such an aldol catalysis centred around soft enolisation. The commencement of an achiral system and development to an enantioselective variant are described. The application to a natural product synthesis – one of vancomycin's amino acid fragments is also disclosed. The extension of the developed aldol catalysis is extended to a Mannich variant and other types of direct enolate reactions centred around the formation of analogous α,β-difunctional carbonyl products. Finally, the same soft enolisation approach for the Darzens reaction is explored.

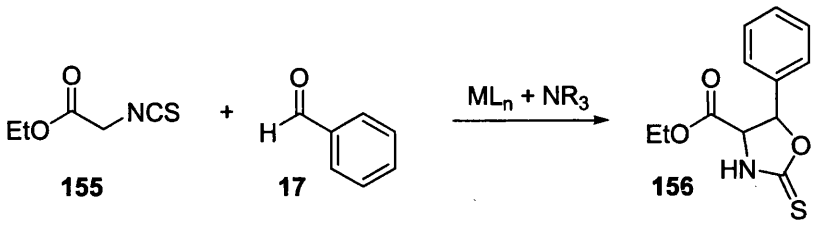
II Results and Discussion

II 1 A direct catalytic enantioselective route to β-hydroxy-α-amino acids

II 1.1 Introduction

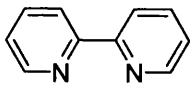
The β-Hydroxy-α-amino acid motif described previously (Section I 1) is highly significant in natural products and biologically active molecules. The attractive route to such a unit by employment of a glycine equivalent in a catalytic soft enolisation aldol process is demonstrated in this section. Herein the development of an achiral diastereoselective process is described followed by the extension of this system to a highly enantioselective variant. Early work within the Willis group carried out by V. J.-D. Piccio on the achiral system focussed on the glycine equivalent, α-isothiocyanate substituted ethyl ester **155** for the initial screening of the soft enolisation catalysis, which is previously proposed and laid-out in Section I (Scheme **51**). This readily available starting material was used to differentiate the pK_a between the substrate and of adducts formed under soft enolisation conditions, which included a cyclisation post aldol addition. Initially benzaldehyde **17** was elected as a non-enolisable electrophile.

Scheme 51. Initial screening for the soft enolisation.



The employment of both these substrates with various weak amine bases and several metal ions with differing counter ions were screened. The solvent, differing promotional additives and other reaction parameters were also included in this initial evaluation. After much effort excellent catalytic conditions were discovered. The optimal combination of Lewis acid and base were found to be $Mg(ClO_4)_2$ (10 mol%) and TEA (20 mol%). A crucial additive, 2,2′-bipyridine **157** (10 mol%) was discovered for this catalysis which acts as an external ligand and accelerates the reaction rate (Figure 8). Interestingly, the group of Watanabe had reported a cross aldol reaction of α,β-unsaturated ketones that were catalysed by a one to one complex of cobaltous acetate with the same achiral ligand 2,2′-bipyridine.[103, 104]

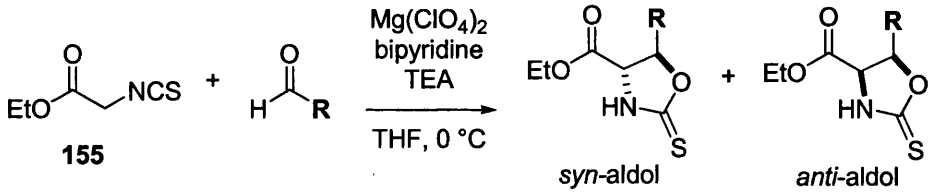
Figure 8. 2,2′-bipyridine.



157

This method was found to be general to a range of aromatic aldehydes and delivered adducts in excellent yields and moderate *syn*-selectivity (Table 3).[105] The need for an external ligand to form an active catalyst was encouraging for the following part of the project which was the development of an asymmetric version of this process utilising enantiomerically enriched ligands.

Table 3. Racemic reaction scope of aromatic aldehydes.[a]



Entry	R	Product	Time (h)	*Syn:Anti*[b]	Yield (%)[c]
1	C_6H_5	**156**	21	65:35	86
2	4-NO_2-C_6H_4	**158**	25	70:30	70
3	4-CN-C_6H_4	**159**	22	75:25	85
4	2-Br-C_6H_4	**160**	23	65:35	84
5	3-Br-C_6H_4	**161**	21	65:35	88
6	4-Br-C_6H_4	**162**	21	70:30	84
7	2,6-diCl-C_6H_3	**163**	25	70:30	49
8	4-MeO-C_6H_4	**164**	23	60:40	67
9	2-Naphthyl	**165**	21	60:40	89

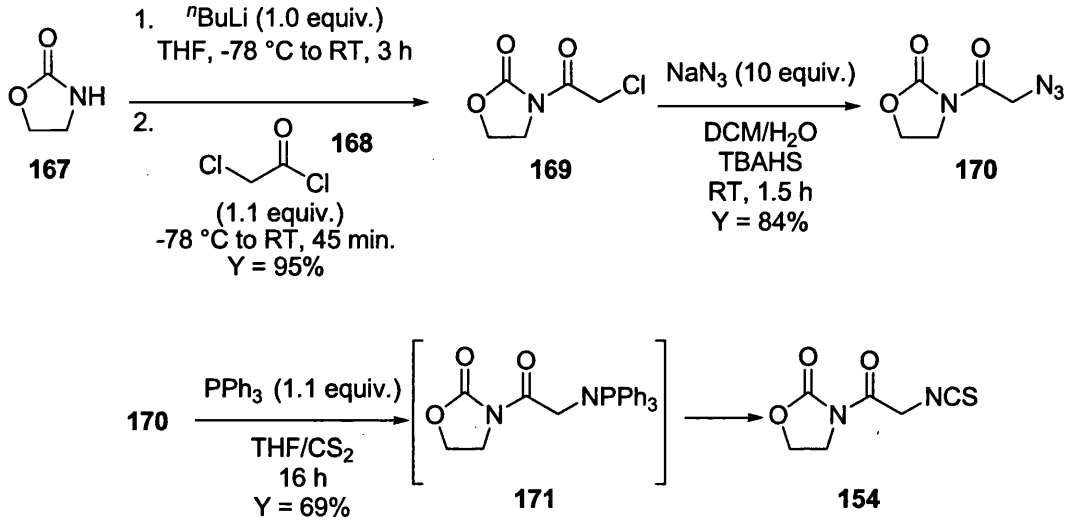
[a] All reactions: ester (1.0 equiv.), **aldehyde** (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%), TEA (20 mol%).
[b] Determined by ^1H NMR.
[c] Combined yield of the isolated diastereomers.

II 1.2 Enantioselective variant

The next phase of events carried out by V. J.-D. Piccio, which involved exchange of bipyridine for a range of enantiomerically pure C_2-symmetric nitrogen-containing ligands, determined that ethyl ester **155** was not a good choice of substrate to bind effectively to the Lewis acid and allow for asymmetric induction. Therefore, a two-point binding nucleophile

oxazolidinone **154** was prepared in the expectation of generating a more ordered enolate and used to develop the asymmetric process (Scheme 52). Its preparation, initially performed by V. J.-D. Piccio, and later improved, followed the procedure for the synthesis of a chiral *iso*thiocyanatoacetyl-oxazolidinone reported by Evans.[106]

Scheme 52. Preparation of oxazolidinone **154**.



To circumvent the difficulties due to low solubility of oxazolidin-2-one **167**, larger amounts of solvent were employed (Section III 2). After addition of *n*-BuLi and chloroacetyl chloride **168**, the chlorocarbamate **169** was isolated in 95% yield. After nucleophilic substitution of NaN_3 the azidocarbamate **170** was obtained in 84% yield. The *iso*thiocyanatocarbamate **154** was furnished in 69% yield through the reaction of azidocarbamate **170** and triphenylphosphine in THF and carbon disulfide *via* phosphoazocarbamate **171**.

A meticulous screening of bases, solvents, chiral ligands and temperatures with benzaldehyde **17**, carried out by V. J.-D. Piccio, created excellent conditions for the asymmetric catalytic aldol reaction.[107] The key

chiral ligands examined in the asymmetric development are presented below (Figure 9) and their selectivities under optimised base and solvent conditions are detailed in Table 4. To aid in the determination of *ee* values of the products, the direct adducts were treated immediately with a solution of magnesium methoxide to yield the corresponding methyl ester derivatives.[106]

Figure 9. C_2-symmetric ligands.

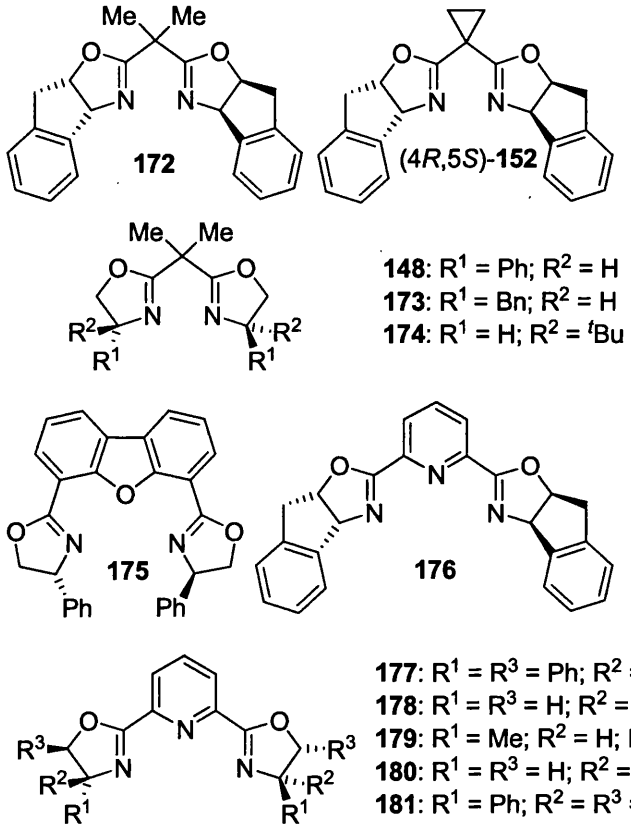
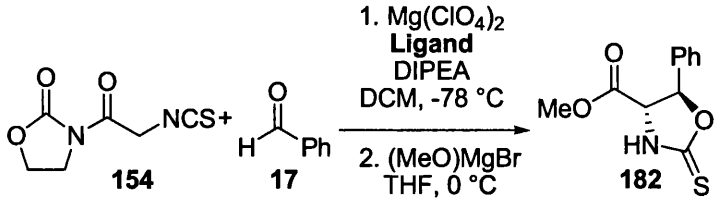


Table 4. Chiral ligand screen.[a]



154 **17** **182**

Entry	Ligand	Time (h)	*Syn*:*anti*[b]	ee_{syn} (%)[c]	Yield (%)[d]
1	**172**	26	80:20	40	69
2	(4*R*,5*S*)-**152**	20	60:40	5	36
3	**148**	22	55:45	12	30
4	**173**	24	55:45	13	43
5	**174**[g]	24	65:35	7	65
6	**175**	19	50:50	16	52
7	**176**	21	60:40	67	70
8	**177**	18	90:10	73	69
9	**178**[g]	22	70:30	45	53
10	**179**	19	80:20	55	71
11	**180**	21	35:65	44[e]	51
12	**181**	20	75:25	83	71
13[f]	**181**	**23**	**80:20**	**90**	**86**

[a] Conditions: isothiocyanate (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and **ligand** (10 mol%).
[b] Determined by ^1H NMR.
[c] Enantiomeric excess determined by chiral HPLC using a Chiracel OD column.
[d] Combined yield of the isolated diastereomers.
[e] Enantiomeric excess corresponds to *anti*-aldol.
[f] 4 Å MS present.
[g] Enantiomeric excess corresponds to opposite enantiomer.

The optimised reaction conditions comprised of $Mg(ClO_4)_2$ (10 mol%), and Hünig's base (20 mol%) as opposed to TEA in the achiral bipyridine system. The use of DCM as a solvent and lower temperatures of -78 °C

offered higher diastereo- and enantioselectivity. Bidentate bis(oxazolines) as ligands generated poorly selective catalysts (entries 1 to 5). The most selective was (4*R*,5*S*)-indBOx, (4*R*,5*S*)-**172** (ee_{syn} = 40%, d.r. = 80:20, entry 1). This was also the case for dibenzofuran bis(oxazoline) (*R*,*R*)-**175** (ee_{syn} = 16%, d.r. = 50:50, entry 6). However, the switch to a pyridine bis(oxazoline) (PyBOx) ligand generated a catalyst that delivered the product with a much improved selectivity (entries 7 to 12). Variation of ligand substituents was used to tune selectivity of the catalyst. Benzyl and *tert*-butyl substituents attached to the PyBOx (entries 9 and 11 respectively) achieved the predominant aldol diastereomer with *ee*'s of 44% and 45% respectively. The highest *ee* attained was from the catalyst composed of phenyl-substituted PyBOx (*R*,*R*)-**181** (entry 12). An *ee* of 83% was observed with this tridentate ligand and a respectable d.r. of 75:25 achieved with the *syn*-aldol predominating. This was the same preferred diastereomeric outcome as in the achiral bipyridine system. As a precaution against degradation of the hygroscopic $Mg(ClO_4)_2$, activated molecular sieves were added to the system and an increase in selectivity to an impressive 90% *ee* was observed (entry 13). The addition of 20 mol% water to the system resulted in a significant reduction in the enantioselectivity of the process (50 to 60% *ee* depending on the exact reaction).

II 1.3 Aldehyde scope

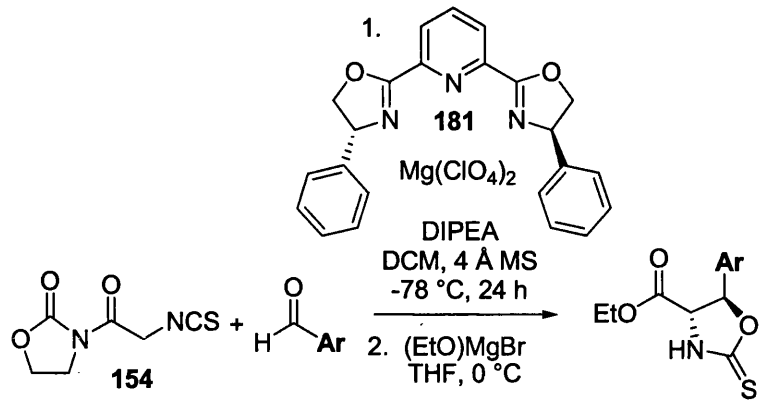
With optimised conditions and the project now fully transferred to the author's hands, the scope of the process was then explored with respect to the aryl aldehyde component (Table 5). To aid in the determination of *ee* values of the products, the direct adducts were this time treated immediately

with a solution of magnesium ethoxide to yield the corresponding ethyl ester derivatives. A wide variety of heteroatom, alkyl, and aryl substituents were readily accommodated in the *para* position of the aldehyde with observed enantioselectivities of up to 94% *ee* (entries 1, 2 and 5 to 9). In all cases the *syn*-aldol adduct was obtained as a major diastereomer with selectivities of up to 91:9 (d.r.) achieved. Substitution in the *meta* position was tolerated well (ee_{syn} = 86%, d.r. = 82:18, entry 3), however the presence of a more hindered *ortho* substituent resulted in a 50:50 ratio of diastereomers, although the *anti*-aldol was generated in 89% *ee* (entry 4).

Moving towards more electron-withdrawing substitution in the *para* position diminished enantioselectivity (entries 10 to 12). These electron deficient examples gave the minor *anti*-diastereomer in higher *ee* than the predominant *syn*-aldol, although diastereoselection was comparable to their electron-rich counterparts (up to 74:26 d.r.) and high yields were still achieved (71 to 79% depending upon the exact example). *p*-Cyanobenzaldehyde with a strongly electron-deficient aryl system showed considerable loss of enantioselectivity as well as diminished diastereoselectivity, although the yield was again very good (71%, entry 12). The last example, 2-naphthaldehyde, was found to be a good substrate with the required aldol adduct obtained in 87% *ee* and a d.r. of 72:28 in favour of the *syn*-aldol (entry 13).

The absolute configuration of the major *syn*-adduct of benzaldehyde was confirmed previously by the Willis group through X-ray crystallography to be (4*S*,5*R*). Another example ***syn*-227** described later (Section II 2) was also confirmed to have (4*S*,5*R*) configuration through X-ray crystallography. The stereochemistry of the other examples described has been assigned by analogy.

Table 5. Aldehyde scope.[a]



Entry	Ar	Product	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)[d]
1	Ph	**156**	79:21	86:72	79
2	4-Me-C_6H_4	**183**	88:12	92:62	88
3	3-Me-C_6H_4	**184**	82:18	85:73	84
4	2-Me-C_6H_4	**185**	50:50	62:89	88
5	4-Et-C_6H_4	**186**	91:9	90:60	95
6	4-MeO-C_6H_4	**164**	85:15	86:53	69
7	4-EtO-C_6H_4	**187**	87:13	93:60	85
8	4-MeS-C_6H_4	**188**	85:15	94:62	64
9	4-Biphenyl	**189**	71:29	85:61	73
10	4-F_3CO-C_6H_4	**190**	74:26	52:63	78
11	4-Br-C_6H_4	**162**	73:27	46:59	79
12	4-CN-C_6H_4	**159**	66:34	3:37	71
13	2-Naphthyl	**165**	72:28	85:71	64

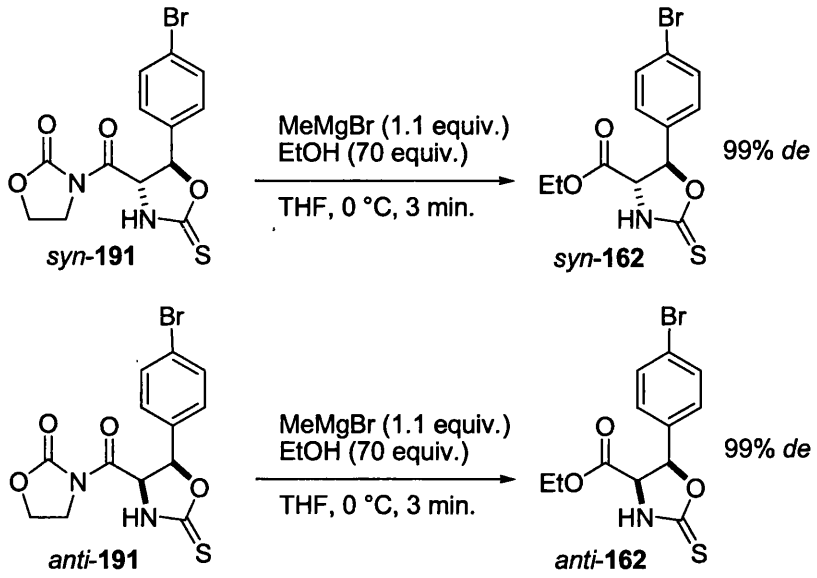
[a] Conditions: isothiocyanate (1.0 equiv.), **aldehyde** (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and ligand (10 mol%), 4 Å MS present.
[b] Determined by ^1H NMR.
[c] Enantiomeric excess determined by chiral HPLC using a Chiracel OD column.
[d] Combined yield of the isolated diastereomers.

II 1.4 Epimerisation and selectivity issues

The fact that for electron-deficient aldehydes, poorer selectivities were observed (the more electron-deficient the aldehyde the lower the *ee* of the major *syn*-aldol), it is plausible that epimerisation was taking place during ethanolysis for such examples. Examination of this process previously by the Willis group, *via* isolation of *syn*-and *anti*-oxazolidinones for benzaldehyde adducts and then subjection to both methanolysis and ethanolysis conditions had shown that no epimerisation at the α-centre was taking place. In addition diastereomeric ratios determined by ^{1}H NMR for both aldol and alkanolysis steps showed no differentiation.

To examine this hypothesis further i.e. with an electron-deficient example, initially formed *syn*- and *anti*-oxazolidinones from 4-bromobenzaldehyde **192** were isolated. Their subjection to ethanolysis conditions confirmed that no epimerisation was taking place in either diastereomer (Scheme 53). This result was also supported by diastereomeric ratios determined by ^{1}H NMR for this example and others, which again showed no differentiation before and after ethanolysis.

Scheme 53. Ethanolysis of *syn*- and *anti*-oxazolidinone **191**.

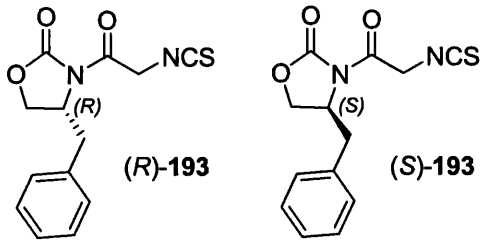


The question remained therefore why the lack of selectivity in electron-deficient systems – could product epimerisation have occurred during the soft enolisation reaction? The isolated 4-bromo *syn*- and *anti*-oxazolidinones **191** were resubjected to the soft enolisation conditions and no apparent epimerisation was observed. An interesting observation was made by the Willis group that the aldol reaction of oxazolidinone **154** and benzaldehyde **17** in the presence of no Lewis acid or ligand produced minimal reaction (39%) in the presence of Hünig's base alone after 22 h at -78 °C. Therefore, a system containing a more activated, electron-deficient aldehyde could undergo a faster background reaction than the Lewis acid catalysed reaction. A reduction in *ee* is expected therefore, especially if coordination of the aldehyde to a Lewis acid species is required. Moreover, aldehydes that are electron-deficient and therefore more electrophilic would have more difficulty coordinating to the Lewis acid. This is believed to be the reason for this trend of lowered enantioselectivity with regards to more electrophilic aldehydes.

II 1.5 Evidence for chelation – stereo-differentiating experiments

The fact that monodentate substrate ethyl ester **155** failed to achieve successful enantioselection whereas bidentate oxazolidinone **154** succeeded suggests the existence of a more ordered enolate chelation. In order to obtain a better understanding mechanistically of the developed asymmetric catalysis for the preparation of protected β-hydroxy-α-amino acids, it was envisaged that double stereo-differentiating experiments where the *iso*thiocyanate substrate contained a chiral fragment as a blocking group would influence the outcome of the reaction and therefore give further insight into chelation events and the enolate involved.[108] Preparation of both (*R*)- and (*S*)-*iso*thiocyanate substrates bearing benzyl substituted oxazolidinone fragments was achieved following the procedure described by Evans (Figure 10).[106]

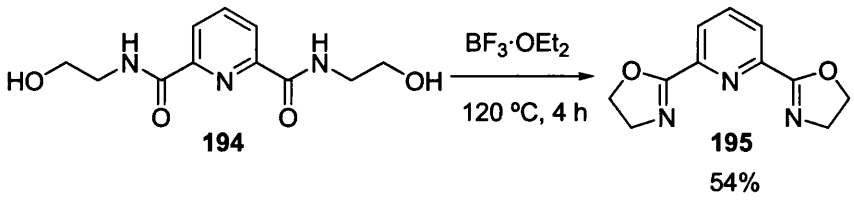
Figure 10. (*R*)- and (*S*)-benzyl-oxazolidinones **193**.



Experiments were performed with *p*-tolualdehyde **196** under the standard reaction conditions (Table 6). The combination of (*S*)-benzyl oxazolidinone (*S*)-**193** and (*R,R*)-Ph-PyBOx **181** (ee_{syn} = 90%, entry 1) generated an enolate that produced a comparable result to the unsubstituted

oxazolidinone **154** (ee_{syn} = 92%, entry 2) – the matched case. On the other hand, the combination of (*R*)-benzyl oxazolidinone (*R*)-**193** and (*R,R*)-Ph-PyBOx **181** gave a slower reaction and therefore lower yielding product of lower *ee* and of the opposite configuration (ee_{syn} = 64%, entry 3) – the unmatched case. In the cases where no PyBOx ligand was employed, similar results followed that of the unmatched case (entry 2) in terms of the major enantiomer produced, *ee*, d.r., and yield (entries 4 and 5). In an attempt to achieve a better understanding of these results an unsubstituted PyBOx ligand **195** (Scheme 54) was synthesised which would allow for a similar coordination behaviour as the chiral PyBOx example. Hydroxy amide **194** was prepared according to the method described by Kumar and subsequently treated with excess boron trifluoride diethyletherate at reflux to attain the cyclised product **195** in 54% yield.[109,110]

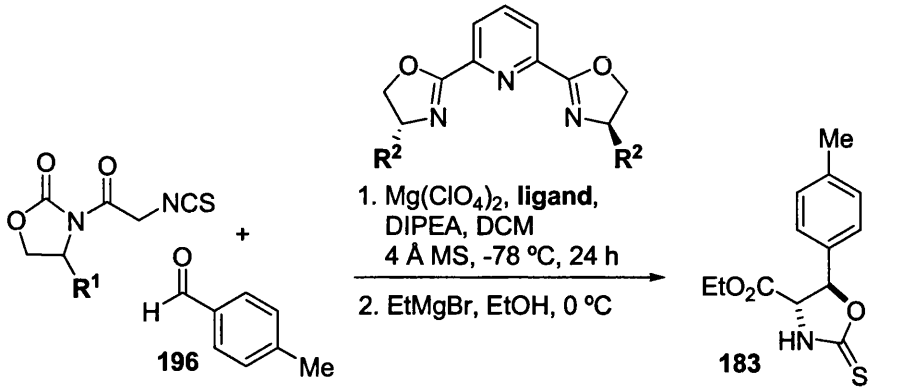
Scheme 54. Synthesis of unsubstituted PyBOx **195**.



This ligand employed with (*S*)-benzyl oxazolidinone (*S*)-**193** and *p*-tolualdehyde **196** achieved a much more selective process (ee_{syn} = 83%, entry 6). In addition the yield improved to 87% and the major diastereomer was assigned (4*S*,5*R*). Although the diastereomeric ratio remained static compared to the non-ligand examples it was important to realise the extent of the ligand effect on enantioselectivity, reaction rate and the 4*S* absolute configuration. The last entry (entry 7) shows the lack of reactivity associated

with a non-Lewis acid promoted system where base alone could mediate the reaction.

Table 6. Double stereo-differentiating reactions.[a]



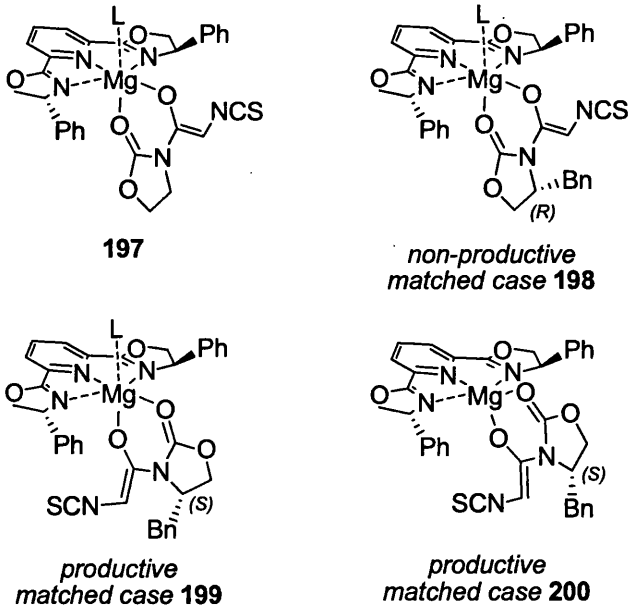
Entry	R^1 (*config.*)	R^2	*Syn:anti*[b]	ee_{syn} (%)[c] (*config.*)	Yield (%)[d]
1	Bn (*S*)	Ph	91:9	90 (4*S*,5*R*)	88
2	H	Ph	88:12	92 (4*S*,5*R*)	88
3	Bn (*R*)	Ph	81:19	64 (4*R*,5*S*)	74
4[e]	Bn (*S*)	-	80:20	68 (4*S*,5*R*)	72
5[e]	Bn (*R*)	-	81:19	67 (4*R*,5*S*)	71
6	Bn (*S*)	H	81:19	83 (4*S*,5*R*)	87
7[f]	Bn (*S*)	-	-	-	0

[a] Conditions: **isothiocyanate** (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and **ligand** (11 mol%), 4 Å MS present.
[b] Diastereomeric ratio determined by ^1H NMR.
[c] Enantiomeric excess determined by chiral HPLC using a Chiracel OD column.
[d] Combined yield of diastereomers.
[e] No ligand used.
[f] No ligand or Lewis acid used.

To explain the aforementioned stereo-differentiating experimental results a working model was postulated for the favoured enolate generated and the product outcome during the catalysis. We had postulated that a six-coordinate Mg(II) species was involved and to account for the absolute

configuration of the major aldol adduct (4*S*,5*R*), the preferentially formed (*Z*)-enolate is hindered by the (4*R*)-phenyl substituent on the chiral ligand (*R*,*R*)-**181** at the *re* face; enolate **197** (Figure 11). The attack from the *si* face of the (*Z*)-enolate to the aldehyde furnishes the 4*S* absolute configuration. The remaining apical octahedral coordination site presumably occupied by the reacting aldehyde would therefore be adjacent to the enolate, the oxygen of which coordinating to the equatorial site in the plane of the PyBOx ligand, and so forms a closed transition state bearing one Mg^{2+} centre. However, the likely distance between the two reacting carbon atoms resulting from such coordination seems too far for this cyclic transition state to occur.

Figure 11. Chelated enolate geometries as working models.



197

non-productive matched case **198**

productive matched case **199**

productive matched case **200**

L = aldehyde or solvent

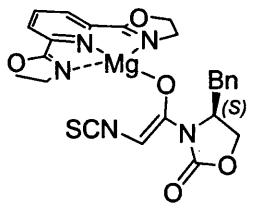
In addition, the same six-coordinate enolate geometry, adapted to (*R*)-benzyl oxazolidinone (*R*)-**193**, enolate **198** (Figure 11) would result in a (4*S*,5*R*) productive matched combination of substrate and ligand. The experimental observation was however that this combination is in fact a

mismatched case. Therefore, it was postulated that the enolate oxygen is coordinating an apical site and that the oxazolidinone carbonyl coordinates in the ligand plane, enolate **199**. This geometry would account for (*S*)-benzyl oxazolidinone (*S*)-**193** as the matched productive case. A five-coordinate trigonal bipyrimidal species is not out of the question as depicted by enolate **200**. This also predicts (*S*)-benzyl oxazolidinone (*S*)-**193** as a matched case although the aldehyde no longer coordinates the same Mg^{2+} centre as the enolate. This outcome is however not a concern due to the fact it supports the more plausible hypothesis of a more complicated bimetallic transition state where the aldehyde is activated by a second Mg^{2+} species.

What has not been explained is the fact that the mismatched combination of (*R*)-benzyl oxazolidinone (*R*)-**193** and (*R,R*)-Ph-PyBOx **181** is still productive of the opposite (4*R*,5*S*) enantiomer although at a slower reaction rate and the benzyl fragments of oxazolidinone **193** do not hinder the generation of productive absolute configuration. The outcome of reactions catalysed by $Mg(ClO_4)_2$ alone seems to be that of Evan's auxiliary control. The opposite absolute configuration is achieved through minimising dipole-dipole interactions between oxazolidinone carbonyl and enolate moieties. In the case of (*R,R*)-Ph-PyBOx **181** and (*S*)-benzyl oxazolidinone (*S*)-**193** (the matched combination) this should not occur because a 'good fit' is achieved and may be overriding to a conformation arising from the minimisation of any dipole-dipole interactions that would result from a non-coordinating oxazolidinone carbonyl. Such dipole-dipole interactions are also minimised through the Mg^{2+} cation, and control of *si* addition from the PyBOx ligand is therefore dominating. The mismatched case on the other hand, due to the steric hindrance of benzyl and phenyl groups, may override a two-point binding enolate and thus the reaction can proceed *via* Evan's auxiliary control. The result from the reaction employing unsubstituted PyBOx ligand **195** seems to be comparative to the ligand omitted Evan's

auxiliary controlled reactions in respect to the absolute configuration in the final product. Although, the reaction is more selective in terms of enantioselectivity than a non-ligand system, where a singly bound oxygen enolate species may be more ordered in this case (Figure 12).

Figure 12. Unsubstituted PyBOx ligand model.

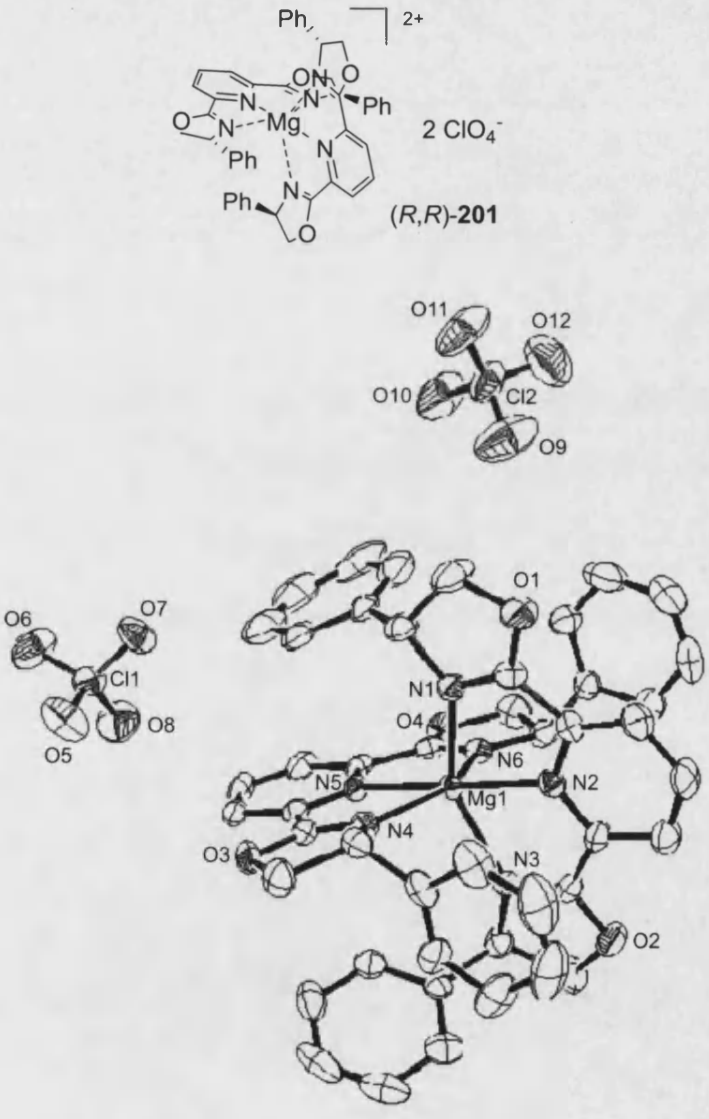


II 1.6 Evidence for chelation – X-ray crystallography experiments

X-ray crystallography would surely bring light to such matters as coordination geometry of the enolate involved. Many attempts failed to produce crystals of the chiral PyBOx ligand and starting materials coordinated to $Mg(ClO_4)_2$ for X-ray crystallography. This was also the case for attempts at crystallising the actual enolate species. However, crystals were gathered from such attempts, of a stable species containing $Mg(ClO_4)_2$ and two (*R,R*)-Ph-PyBOx ligands (Section III 7). The X-ray crystal structure of [Mg((*R,R*)-phenyl-bis(oxazolinyl)pyridine)$_2$]$(ClO_4)_2$ **201** depicted below (Figure 13) is an octahedral species with slight distortions to accommodate the tridentate PyBOx ligand. The opposing phenyl groups from each PyBOx ligand seem to be able to orientate themselves so that minimal steric hindrance occurs even though they are both of (*R*)-configuration. The failure to form crystals of a Mg(II) species containing oxazolidinone **154** chelating

via two carbonyls suggests that such a species is unstable existing as an equilibrium between the free and chelated oxazolidinone. It was envisaged that a temperature dependent ^{1}H NMR study would bring some light to this matter.

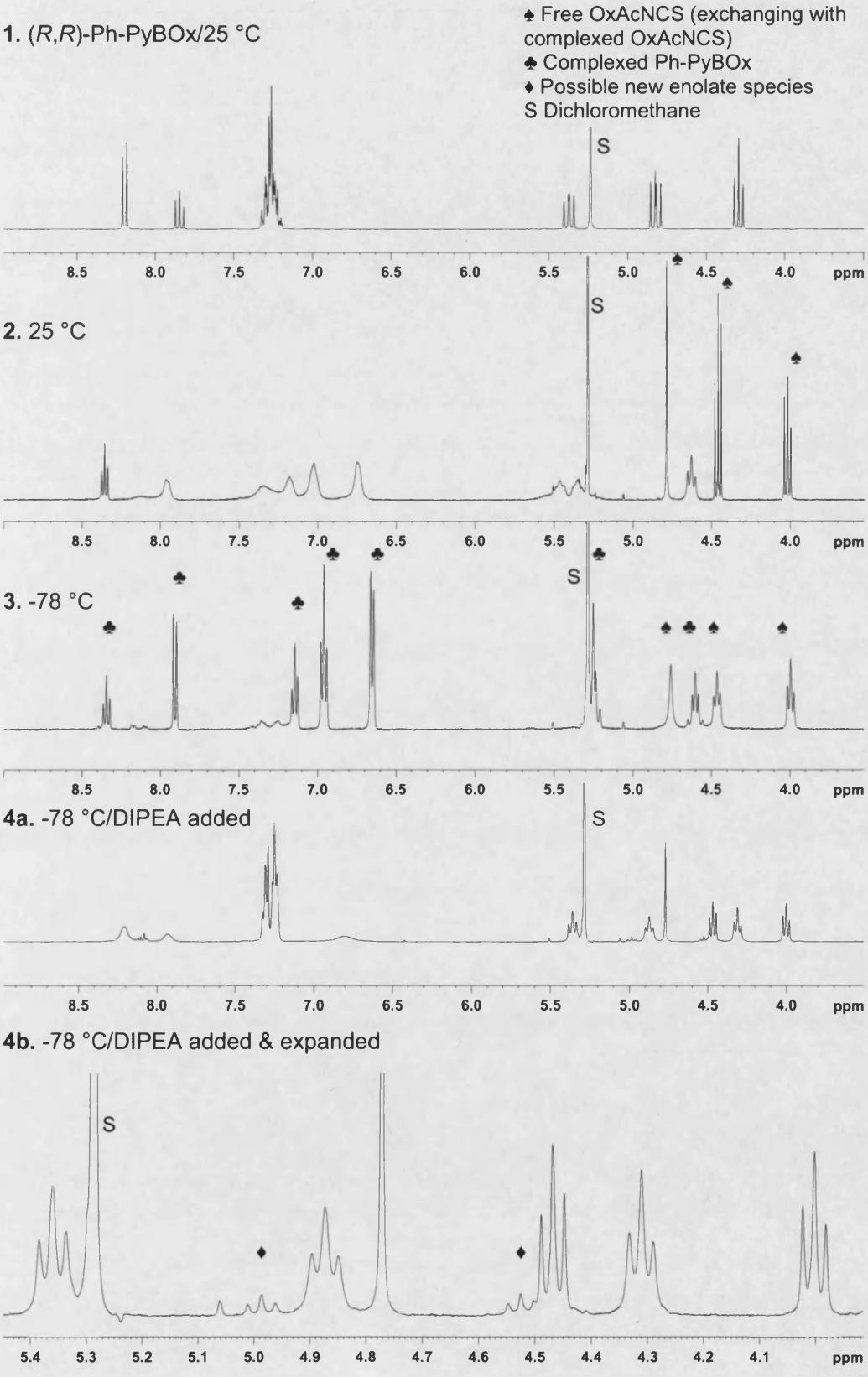
Figure 13. X-ray crystal structure of [Mg((*R,R*)-phenyl-bis(oxazolinyl)pyridine)$_2$]$(ClO_4)_2$ **201**.



II 1.7 Evidence for chelation – temperature dependent ^{1}H NMR study

^{1}H NMR spectroscopy is a tool that has previously been used to provide evidence for the structure of catalysts complexed to substrates.[111] Low temperature ^{1}H NMR was used to study our catalyst system of $Mg(ClO_4)_2$ and (*R,R*)-Ph-PyBOx **181** combined with the substrate oxazolidinone **154**. Molar equivalents of each material were stirred in deuteriodichloromethane at room temperature and then transferred to an NMR tube. At room temperature (Figure 14, 2) there is a transition between free and complexed (*R,R*)-Ph-PyBOx due to two separate ligand species signals (compare ^{1}H NMR spectrum of (*R,R*)-Ph-PyBOx, Figure 14, 1). The oxazolidinone substrate **154** (referred to as OxAcNCS, Figure 14) is observed as a free species at room temperature possibly exchanging very rapidly with a complexed species. At lower temperature (-78 °C) the PyBOx ligand is now fully complexed although there is still no separation between a free or complexed oxazolidinone species, which would signify the low stability of such a complex (Figure 14, 3). At a temperature of -78 °C a molar equivalent of DIPEA was added (Figure 14, 4a) and as a result, although not conclusive, the proton spectrum shows a separate oxazolidinone species forming – possibly an enolate species, although the enolate proton chemical shift range is too congested to specify (Figure 14, 4b).

Figure 14. Temperature dependent ^{1}H NMR study.

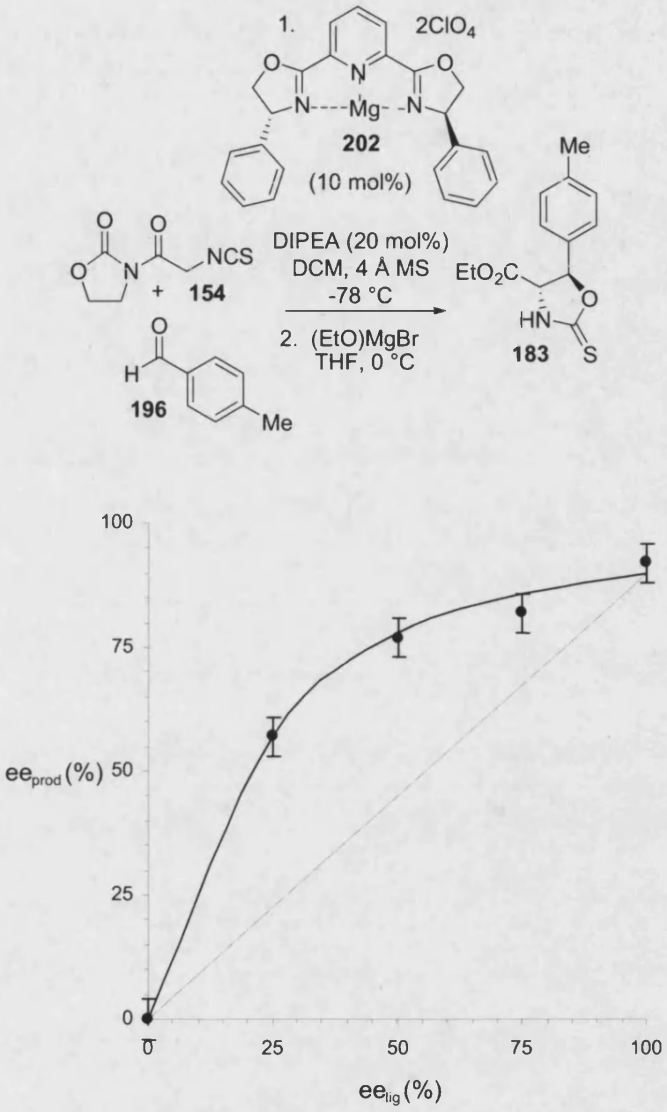


II 1.8 Nonlinear effects

Nonlinear effects can provide useful insight into both the behaviour of enantioselective catalyst systems and the mechanisms of the processes they mediate.[112] Consequently, experiments were performed to determine if nonlinear effects were operative in the Mg(II) PyBOx-catalysed aldol reaction under investigation. Indeed, when the aldol reaction was conducted with the catalyst [Mg(Ph-PyBOx)]$(ClO_4)_2$ **202** (10 mol%) with ligand of reduced enantiomeric excess a strong positive nonlinear effect was observed (Figure 15). For example, employment of a catalyst of 25% *ee* afforded the aldol adduct in 57% *ee*, and a catalyst of 50% *ee* afforded the aldol adduct in 77% *ee*.

To rationalise this significant nonlinear effect it is postulated that either (i) the transition state is of a bimetallic nature i.e. two chiral units are involved in the stereochemical rate-determining step of the reaction, one Mg-(*R*,*R*)-Ph-PyBOx coordinated to the bidentate enolate and another Mg-(*R*,*R*)-Ph-PyBOx coordinated to the reacting aldehyde or (ii) formation of a stable [Mg((*S*,*S*)-Ph-PyBOx)((*R*,*R*)-Ph-PyBOx)]$(ClO_4)_2$ 2:1 ligand:metal complex serves as a catalytically inactive reservoir for the minor (*R*,*R*)-Ph-PyBOx ligand, consequently enriching the enantiomeric excess of the remaining Mg-(*R*,*R*)-Ph-PyBOx catalyst. The fact that a more hindered 2:1 ligand:metal complex of (*R*,*R*)-Ph-PyBOx and $Mg(ClO_4)_2$ has been isolated through crystallisation suggests the latter reasoning plausible. Conversely, a bimetallic catalyst is a likely outcome through these findings and other experiments performed including stereo-differentiation and working model postulation. Time has precluded a conclusive rationale for the above described (+)-nonlinear effect.

Figure 15. Nonlinear effect in the Mg(II)-PyBOx catalysed aldol reaction.



II 1.9 Conclusion

In summary, a simple catalyst system assembled from an enantiomerically pure tridentate ligand, a Lewis acidic metal, and an amine base, efficiently generates a chiral glycine enolate derived from oxazolidinone **154**. The preferentially formed (*Z*)-enolate undergoes

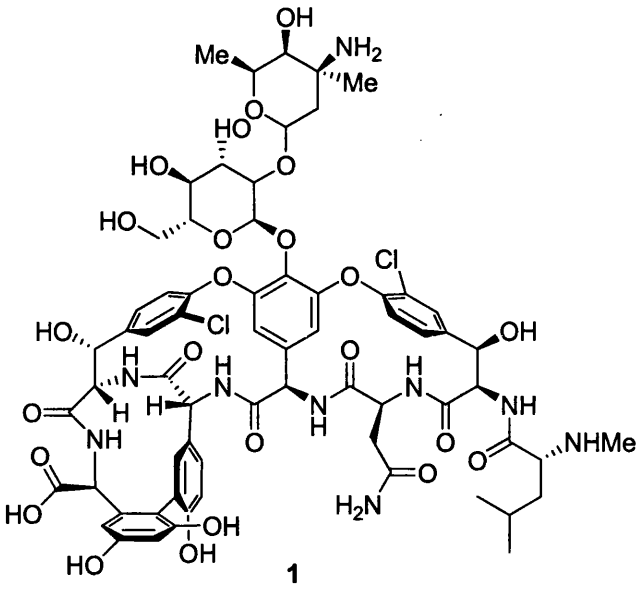
enantioselective addition to a range of aryl aldehydes to provide protected aryl β-hydroxy-α-amino acids in good yields with high enantioselectivities. Importantly, all of the catalyst components are commercially available and reactions are simple to perform. The catalysis has been probed mechanistically through stereo-differentiating experiments, X-ray crystallography, temperature dependent NMR studies, and nonlinear effect studies. Although time has precluded any concrete conclusion, evidence leans towards a complex bimetallic catalysis where both enolate and aldehyde are coordinated to separate chiral Lewis acids in the transition state.

II 2 Synthesis of a building block for the total synthesis of vancomycin – AA6

II 2.1 Introduction

Vancomycin **1** (Figure 16) is referred to as an antibiotic of last resort towards the highly drug resistant *staphylococcus aureum* bacterium – the so called 'hospital superbug' responsible for MRSA. Vancomycin belongs to the glycopeptide family of antibiotics and was discovered as the first member in 1956 from an Indonesian soil sample as a product from the *streptomyces orientalis* bacterium. Since then the family has grown to thousands of members, particularly after determination of its crystal structure and mechanism of action.[113] Vancomycin's potency against all gram-positive bacteria is derived from its capability of being able to inhibit cell wall biosynthesis by inhibiting a crucial amide-based cross linking event during cell wall assembly. This has the effect of weakening the target bacterium's cell wall causing the cell to lyse. The cross linking event involves the docking of the D-Ala-D-Ala dipeptide terminus of a peptidoglycan precursor to a transpeptidase enzyme; vancomycin also has this D-Ala-D-Ala recognition site and through five strong hydrogen bonds can thus block the enzymes mode of action.

Figure 16. Structure of vancomycin.



1

Vancomycin

It has been reported that even such a potent antibiotic as vancomycin can become less effective towards certain strains of bacteria. Both vancomycin-resistant *enterococci* (VRE) which causes a rare form of meningitis and vancomycin-resistant *staphylococcus aureus* (VRSA) bacteria have been described.[114,115] These bacteria have become resistant *via* a mutation which causes a change in the D-Ala-D-Ala dipeptide terminus of adjoining peptidoglycan chains. The terminus has become a D-Ala-D-Lac amino acid series which offers the possibility of only four hydrogen bonds.[116] New antibiotics have come onto the market to combat such strains but they are not without severe side effects. So the search continues to find an all conquering antibiotic for the so called 'superbugs' of today and their mutations of tomorrow and with many libraries of antibiotic derivatives already in place we are one step closer to achieving this goal. Because of its already observed potency, vancomycin's core framework has become an important target for derivative synthesis and thus easy, rapid, and convergent synthetic

methodology of such an entity has become a necessity for efficient screening of the drugs of tomorrow for diseases such as MRSA.

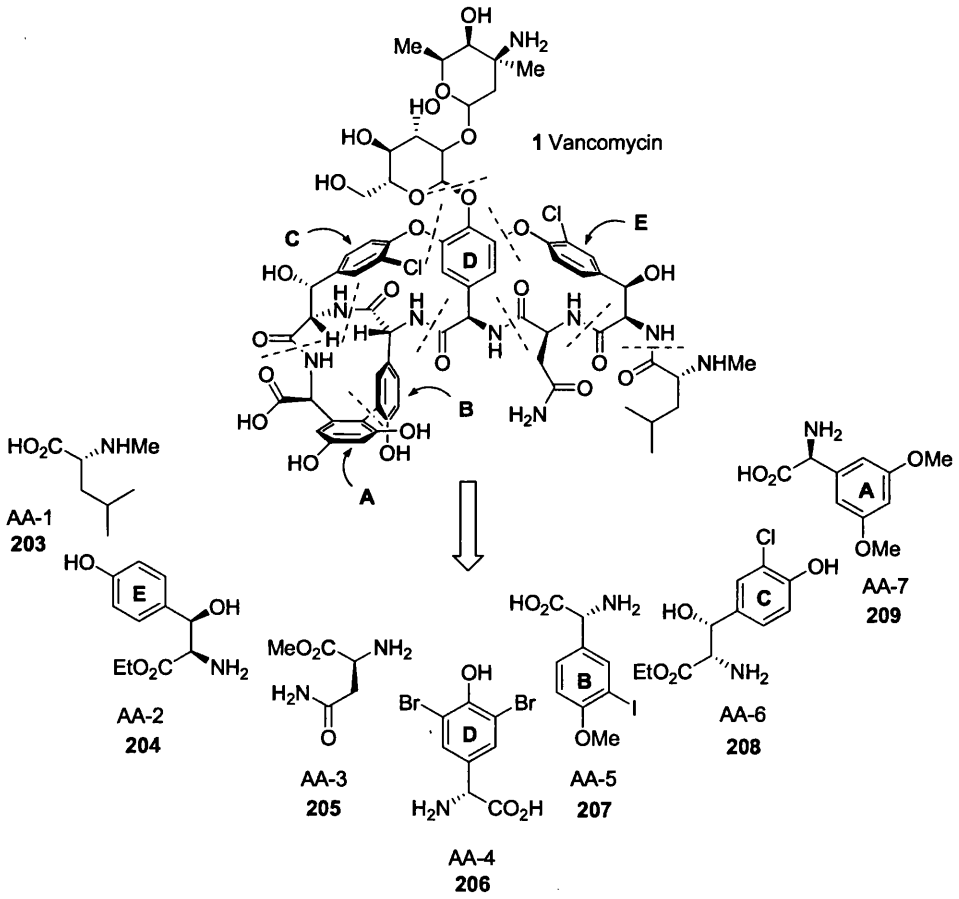
II 2.2 Retrosynthetic issues of vancomycin

All glycopeptide antibiotics are structurally highly related and fall into one of the sub-categories: vancomycins, ritocetins, teicoplanins, and avoparcins. Their core structure consists of a cyclic polypeptide framework with a variety of substituents giving the molecule its characteristics. Vancomycin for example comprises amino, hydroxy, amido, carboxylic, phenolic, and chloro functionality. Vancomycin has a strained heptapeptide framework or aglycon and another disaccharide-containing segment made up of an L-vancosamine unit linked to a D-glucose unit through an α-glycoside bond. The aglycon is fused to the L-vancosamine section *via* a phenolic β-glycoside linkage. The heptapeptide aglycon unit can be broken down retrosynthetically to its seven base amino acids (AA 1-7). There are five aromatic components (A-E) and eight stereocentres within these seven amino acids and they make up the three macrocycles of the heptapeptide; in addition the structure therefore inherently contains three sites of atropisomerism (Scheme 55).[117,118]

The amino acid building blocks themselves present a formidable challenge to the synthetic chemist due to the stereochemistry and functionality involved. Amino acids AA-4, 5, and 7 (**206**, **207**, and **209** respectively) are examples of aryl glycines, AA-2 and 6 (**204**, and **208**) are β-hydroxytyrosine derivatives, AA-1 **203** is a protected *N*-methyl leucine and AA-3 **205** is an asparagine derivative. Both Evans and Nicolaou have completed the total synthesis.[119,120] The syntheses differ overly in their build-up of the three macrocycles AB, C-*O*-D and D-*O*-E. Evans commenced with

the AB macrocycle, followed by the C-*O*-D and D-*O*-E aryl ether linkages. Nicolaou on the other hand found success by beginning with the C-*O*-D macrocycle and to append AB and D-*O*-E units accordingly. Once these appendages were complete, further functional group interconversions were necessary.

Scheme 55. 'Amino acid' building blocks of vancomycin.



One key aspect of the total structure of vancomycin is that of atropisomerism. The three macrocycles must be constructed in their specific conformations due to the fact that rotation about the C-O and C-C bonds within the macrocycles is in fact an energetic barrier. Evans more convincingly introduces this selectivity *via* a nucleophilic aromatic substitution of a fluoro species as a 5:1 ratio in favour of the correct

atropisomer. Nicolaou on the other hand settles for a lack of selectivity with regards to the correct atropisomer utilising a triazene driven copper mediated reaction.

Returning to the seven amino acid building blocks, any synthetic route that may be envisaged must be facile and efficient in providing the degree of stereoselectivity required that is inherent in these sub-structures.

The asymmetric catalysis methodology that was described previously (Section II 1) has potential for such a synthesis of one of these key building blocks of vancomycin. The same stereochemical information portrayed in the enantioselective aldol reaction is inherent in the amino acid AA-6 **208**, a β-hydroxytyrosine derivative. The synthesis of AA-6 **208** incorporating this methodology as the key step is described in due course after briefly examining previous enantioselective syntheses of AA-6 **208**.

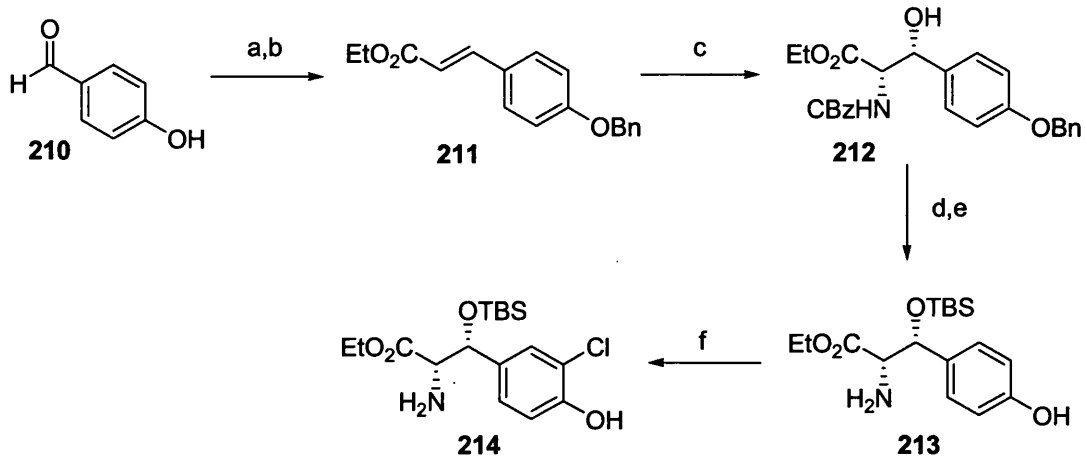
II 2.3 Previous asymmetric syntheses of vancomycin's building block AA-6

Described in the four part report on the total synthesis of vancomycin, Nicolaou targets a Sharpless asymmetric aminohydroxylation step as key to AA-6's synthesis.[117] The synthesis is carried out over six linear steps starting from the commercially available 4-hydroxy benzaldehyde **210** (Scheme 56). The overall synthesis generates AA-6 in 31% and the key enantioselective step delivers the correct enantiomer in 87% *ee* but in a poor yield of 45%.

4-hydroxy benzaldehyde **210** is first benzylated before a Horner-Wadsworth-Emmons reaction with $(EtO)_2(O)PCH_2CO_2Et$ to yield *trans*-α,β-unsaturated ester **211**. This sets up the Sharpless asymmetric aminohydroxylation to give **212** in 45% yield and 87% *ee*. The low yield is attributed to a regioselectivity issue governed by the type of ligand

incorporation, PHAL or AQN but Nicolaou omits any description of the actual regioselectivity observed. Subsequent protection/deprotection steps to furnish the free amino ester **213** swiftly follow this step. To finish the synthesis reaction of **213** with SO_2Cl_2 provides the 3-chloro adduct **214** in 80% yield.

Scheme 56. Nicolaou's synthesis of AA-6.

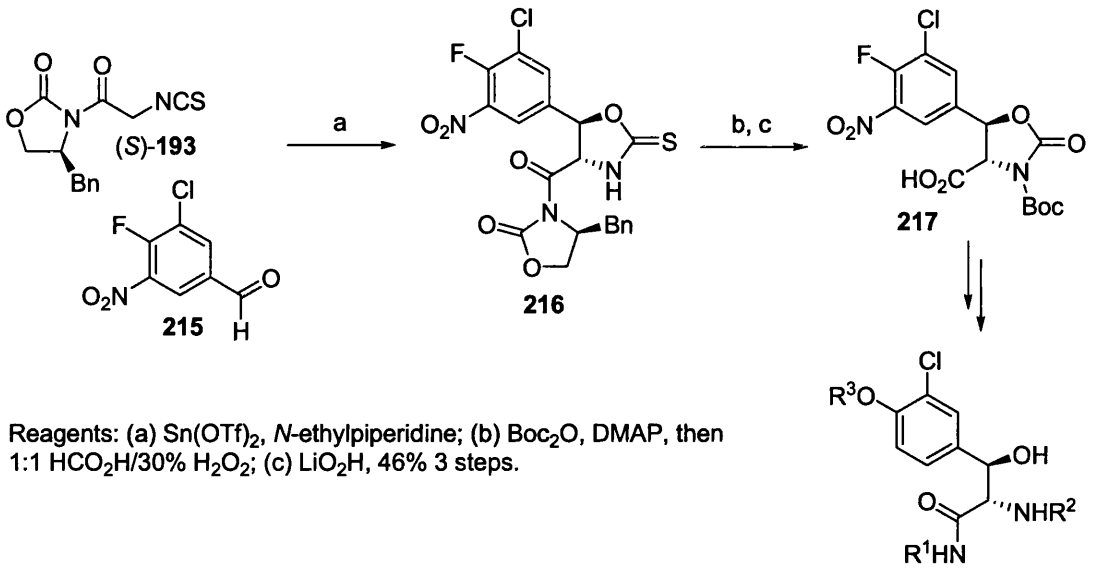


Reagents: (a) BnBr, K_2CO_3, KI, 98%; (b) $(EtO)_2(O)PCH_2CO_2Et$, KOH, 95%; (c) NaOH, NH_2CO_2Bn, *t*BuOCl, (DHQD)AQN, $K_2[OsO_2(OH)_4]$, *n*PrOH:H_2O (1:1), 45% (87% *ee*); (d) TBSOTf, 2,6-lutidine, 98%; (e) H_2, $Pd(OH)_2/C$, 95%; (f) SO_2Cl_2, Et_2O, 80%.

In the Evans's synthesis of vancomycin the Evans auxiliary is called upon to build the AA-6 sub-unit (Scheme 57).[119] A chiral glycine derivative (*S*)-**193** involving the oxazolidinone auxiliary is partnered with aldehyde **215** in a tin(II) triflate mediated aldol condensation. A 95:5 diastereoselectivity in favour of the desired *syn*-aldol was attained. The AB macrocycle is then duly developed before further manipulation has taken place on the AA-6 portion. Later in the synthesis of the AB macrocycle, the oxazolidinone is ring opened with Li_2CO_3 in MeOH and even further along the synthesis, after the C-*O*-D

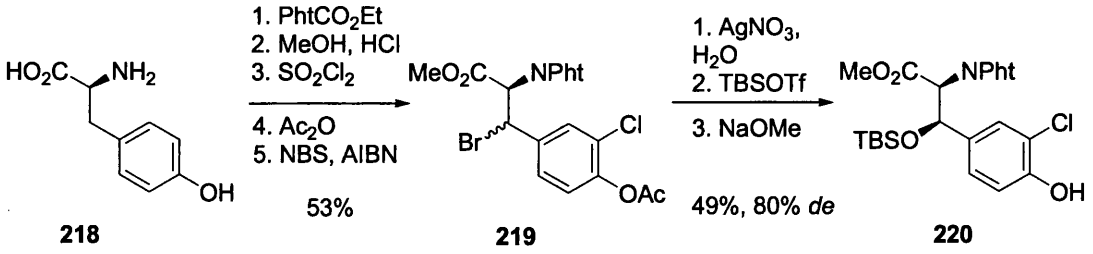
linkage step which employs the aryl fluoride functionality, the nitro group is removed with Zn^0, HOAc, and EtOH.

Scheme 57. Evans's construction of the AA-6 portion.



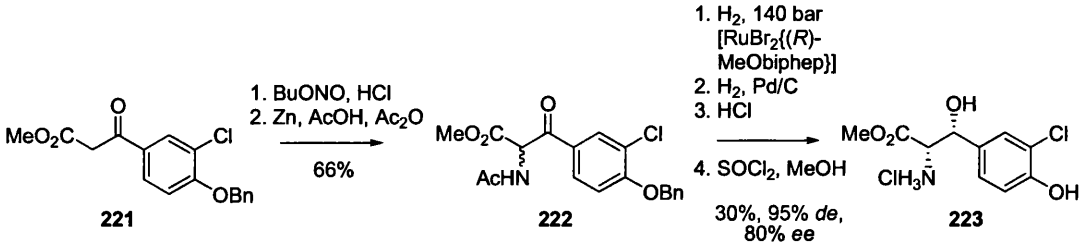
Rama Rao *et al* have also synthesised a protected form of AA-6 starting from a chiral tyrosine amino acid. The inherent (*S*)-stereocentre of the amino acid was used as a platform to introduce the second stereocentre *via* a silver nitrate promoted displacement of epimeric *β*-bromo intermediate **219** (Scheme 58).[113]

Scheme 58. Synthesis of AA-6 from (*S*)-tyrosine.



One final mention to synthetic methods of AA-6 is that of the Genêt's group in which asymmetric catalytic hydrogenation takes centre stage. Genêt commences from the aryl-β-ketoester **221** and after two steps the racemic α-ketoamide **222** is treated with an optically active ruthenium catalyst under 140 bar of hydrogen to incorporate the correct configuration at both stereocentres (Scheme 59).[113]

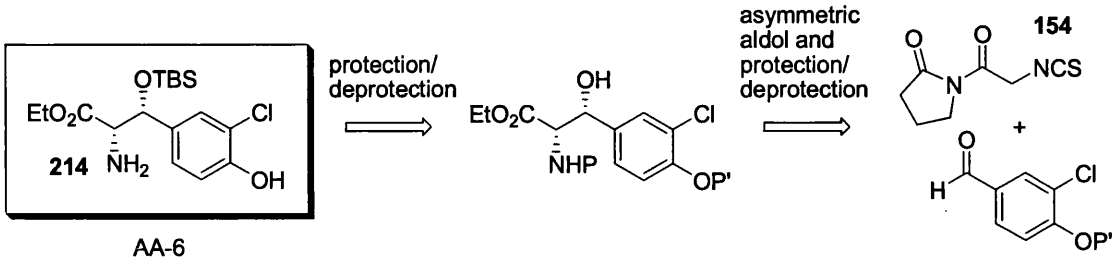
Scheme 59. Synthesis of AA-6 by asymmetric catalytic hydrogenation.



II 2.4 A direct catalytic enantioselective synthesis of AA-6

The handful of syntheses just described are the few in the literature that bias any enantioselective route to the β-hydroxy-α-amino acid AA-6 to date. Others either give poor diastereoselectivities or generate the *anti*-adduct as a major product rather than the desired *syn*-aldol.[113] The desire for high enantio- as well as diastereo-control means that finding an effective strategy is difficult. The direct catalytic enantioselective route to protected *syn*-β-hydroxy-α-amino acids as previously described (Section II 1) qualifies as such a route due to the fact that the key asymmetric step is early in the synthesis and quickly and directly gives a protected form of AA-6. All one has to do after the key C-C bond formation is to deprotect the necessary functionality. A retrosynthetic view is given in Scheme 60.

Scheme 60. Retrosynthetic analysis of AA-6.



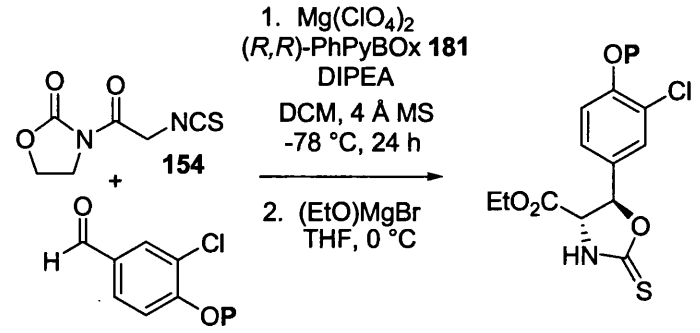
As seen previously (Section II 1) the combination of a tridentate PyBOx ligand, magnesium perchlorate and Hünig's base allows the catalytic generation of a chiral glycine-enolate that undergoes a highly enantioselective addition to a range of aryl aldehydes.

II 2.5 The key enantioselective step: in search of a protected aldehyde

It was now time to extend this aldehyde range to an appropriate aldehyde that contained the correct 3-chloro and 4-hydroxyl substitution pattern in order to reach the final amino acid of vancomycin. 3-Chloro-4-hydroxy benzaldehyde is commercially available and was tested in the standard reaction (Section II 1) but the free hydroxyl moiety suppressed any reactivity. Therefore, a range of protected aldehydes at the 4-hydroxyl position were prepared and screened under the normal reaction conditions. The procedure also included the second step removal of the oxazolidinone for the ethyl ester derivative for ease of HPLC analysis. It was evident from the examples chosen that those, which had a more electron-rich aryl system, fared better (Table 7). The protecting groups examined were TBS (entry 2), MEM (entry 3), MTM (entry 4) and finally PMB (entry 5) respectively. Although encouraging results were obtained with the middle three entries it was not until the PMB group was explored that the true nature of an electron

rich system was realised. In fact, an excellent diastereoselectivity and enantioselectivity was observed with this example, 93:7 d.r. and 95% *ee*. This was the best result to date and for a structure with such implications towards natural product synthesis beckoning (this was a good day).

Table 7. Screening of 3-chloro-4-hydroxy benzaldehydes.[a]

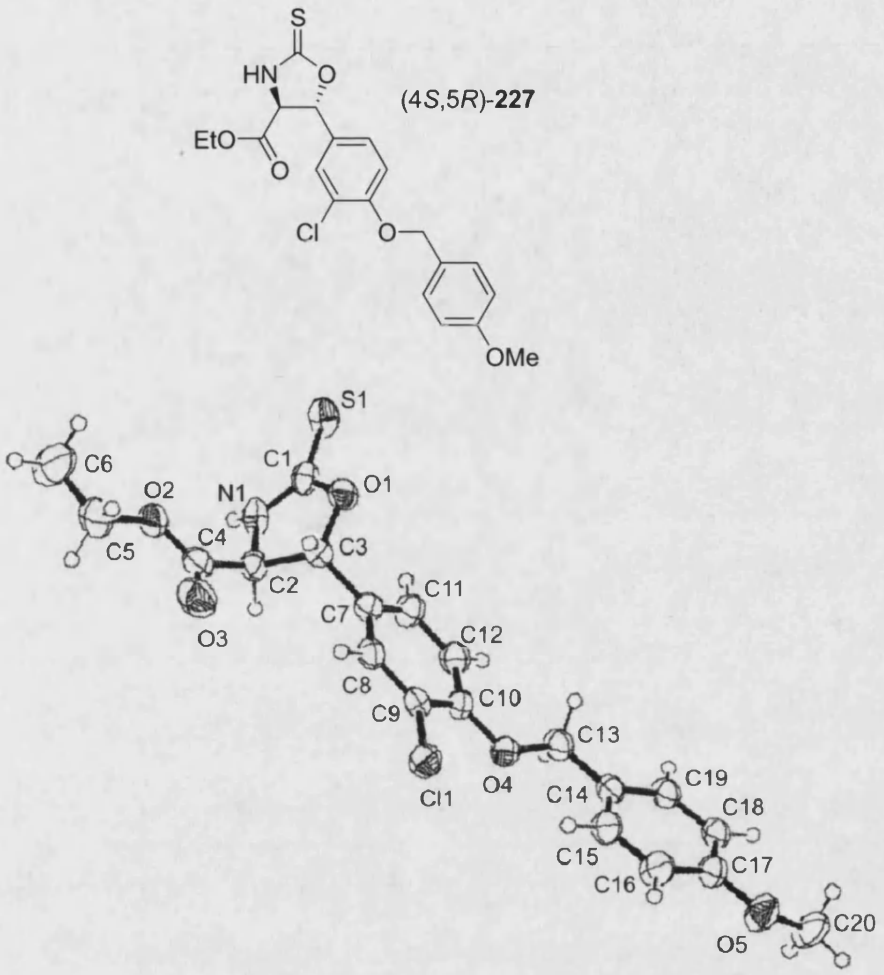


Entry	P	Product	*Syn:anti*[b]	Yield (%)	ee_{syn} (%)[c]
1	H	-	-	0	-
2	TBS	**224**	75:25	80	74
3	MEM	**225**	77:23	79	72
4	MTM	**226**	93:7	63	82
5	**PMB**	**227**	**93:7**	**77**	**95**

[a] All reactions: isothiocyanate (1.0 equiv.), **aldehyde** (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%),DIPEA (20 mol%) and ligand (11 mol%).
[b] Diastereomeric ratio determined by ^1H NMR.
[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.

The absolute configuration of the *syn*-**227** aldol adduct was confirmed by X-ray crystallography (Appendix A) as being (4*S*,5*R*) as required for AA-6 (Figure 17).

Figure 17. Oxazolidinethione (4*S*,5*R*)-**227** and X-Ray crystal structure.

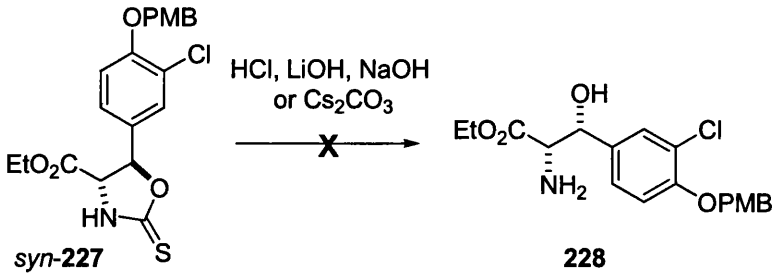


II 2.6 The racemic route: a lesson in deprotection/ protection chemistry

Now that a successful aldehyde candidate had been found for the key enantioselective step in the synthesis of AA-6 all that was required in order to reach the target molecule were a few deprotection and protection steps. Already a synthetic method was established to exchange the oxazolidinone for an ester appendage, which was required for the synthesis of AA-6 (Table

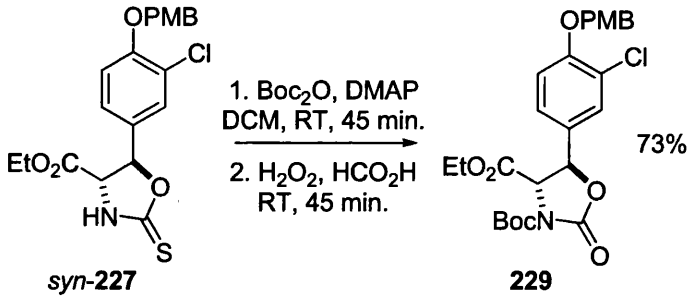
7). The following description of events proceeded with the chosen *syn*-aldol adduct **227** as a racemate (see Section III 11) in order to examine the feasibility of onward syntheses. In turn, it was necessary to deprotect the oxazolidinethione ring. Attempts at doing this directly failed in both acidic and basic media – reactions gave complex reaction mixtures (Scheme 61).

Scheme 61. Direct oxazolidinethione deprotection.



It was deemed necessary to first *N*-protect and then transform the oxazolidinethione into oxazolidinone **229** *via* a peroxide oxidation.[121] This methodology was successfully achieved in one pot (Scheme 62) employing Boc_2O and H_2O_2/HCO_2H as reagents. The oxazolidinone functionality later proved to be easier to ring open.

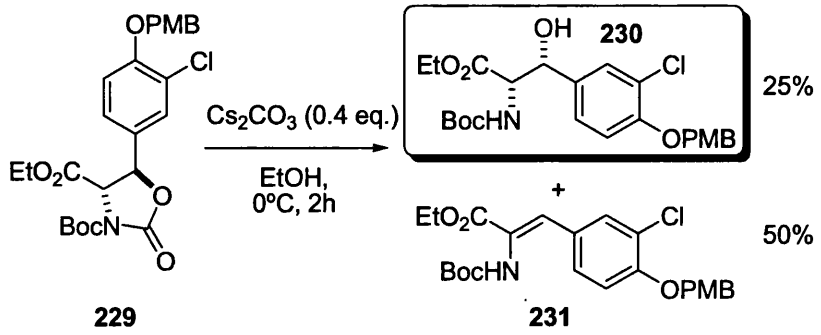
Scheme 62. Manipulation of the oxazolidinethione ring.



Protection of the nitrogen as the *N*-Boc species and displacement of sulfur for oxygen gave a much more accessible ring towards deprotection. Treatment of **229** with a catalytic amount of Cs_2CO_3 in ethanol gave a 25%

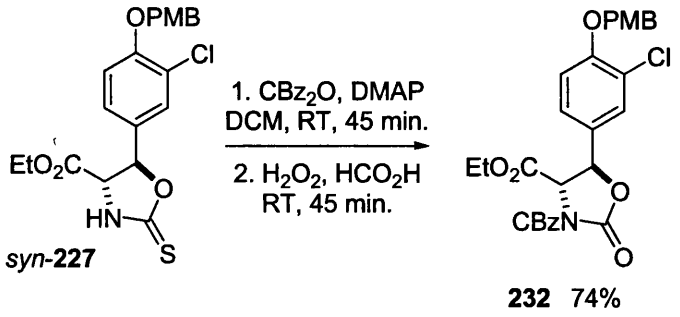
yield of the desired ring opened material although this chemistry was far from optimal. The major drawback with this reaction was that of a major elimination side reaction (Scheme 63). The (Z)-configuration was assigned by analogy to the methyl ester analogue **237** *via* NOESY experiment (appendix F) – see later (Scheme 67).

Scheme 63. Ring opening of the oxazolidinone functionality.



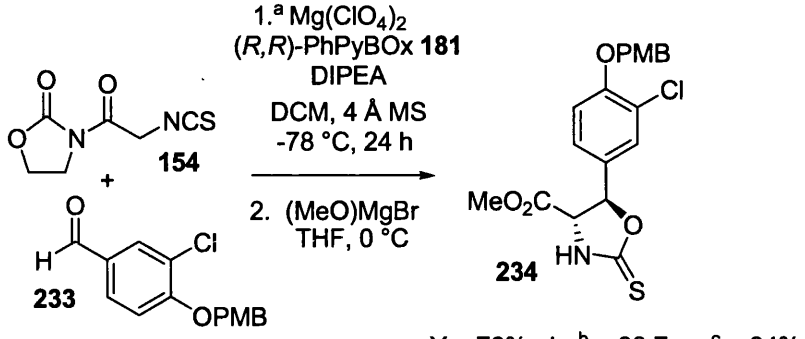
As an aside, it was envisaged that by replacing the Boc for a CBz *N*-protecting group on the oxazolidinethione ring the number of steps could be reduced in the synthesis of AA-6 by allowing a double PMB and CBz deprotection step *via* hydrogenation. The *N*-CBz protected adduct was obtained in 74% yield (Scheme 64). On treatment with cesium carbonate in ethanol a complicated mixture of products was observed; again the elimination product predominated, but also the CBz group was removed and further transesterification occurred. Therefore this route was terminated.

Scheme 64. Synthesis of a CBz protected oxazolidinone.



Returning to the original problem, this was eventually remedied through the exploration of various solvents. If the afore mentioned reaction was carried out in methanol the outcome was, as a major product, the desired deprotected oxazolidinone rather than the elimination side-product. In fact, a different problem now arose. Due to the utilisation of the ethyl ester a mixture of methyl and ethyl transesterification products were attained when the reaction was conducted in methanol. Therefore the initial oxazolidinone formed directly from the asymmetric aldol addition was necessarily transformed to the corresponding methyl ester **234** *via* reaction with (MeO)MgBr in THF with very similar results as in the preparation of ethyl ester analogue **227** (Scheme 65).

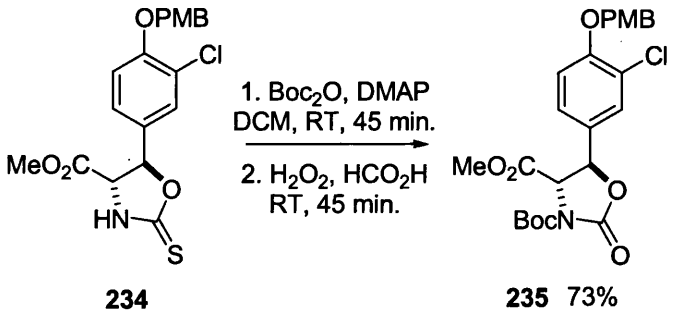
Scheme 65. Synthesis of the methyl ester oxazolidinethione analogue.



[a] Reaction conditions: isothiocyanate (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and ligand (11 mol%).
[b] Diastereomeric ratio determined by ^1H NMR.
[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.

With the methyl ester analogue in hand the same procedure of *N*-Boc protection and sulfur displacing oxidation again utilising racemic material (see Section III 11) could now be carried out. This reaction gave similar results to the ethyl ester giving a high yield (73%) for the one-pot process (Scheme 66).

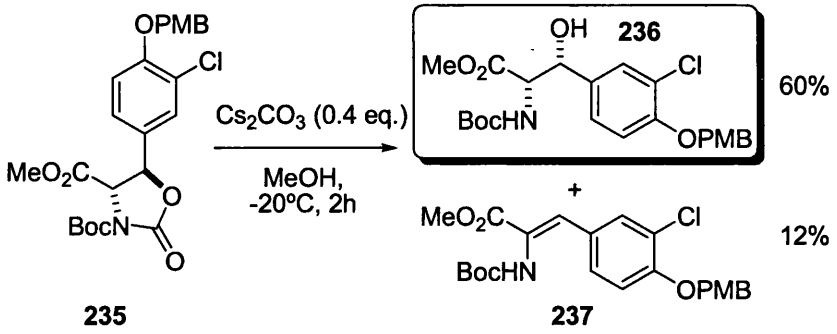
Scheme 66. Manipulation of the oxazolidinethione ring (methyl ester).



The key step of ring opening the oxazolidinone was then performed under careful conditions and produced the desired hydroxy-carbamate **236**

successfully in 60% yield unavoidably giving a small amount of the elimination by-product **237** (Scheme 67).

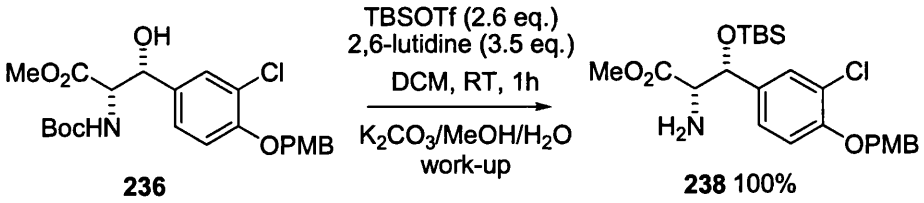
Scheme 67. Ring opening of the oxazolidinone functionality (methyl ester **235**).



With this ring-opened material in hand, the scene was set to embark on the final deprotection chemistry. It was decided to remove the PMB group last, therefore it was necessary to deprotect the *N*-Boc moiety. Finally to give a direct comparison to Nicolaou's AA-6 compound **214**, the protection of the free hydroxyl as a TBS ether was necessary.

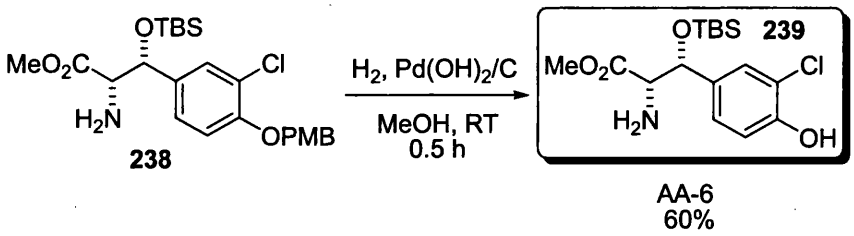
It was envisioned that these last two steps could be incorporated into one single reaction step by the use of the reagent TBSOTf. This reagent, commonplace in the literature as a silylating agent, has also been used to deprotect *N*-Boc groups in the presence of 2,6-lutidine.[122] Utilisation of 2.6 equivalents of TBSOTf and excess 2,6-lutidine was enough to complete both the hydroxyl protection and *N*-Boc deprotection. On basic work-up employing a solution of K_2CO_3 in MeOH/water, any remaining base labile *N*-CO_2TBS species was cleaved to give the free amino alcohol in quantitative yield (Scheme 68). Without a basic work-up only 44% yield of the desired compound is achieved under the described reaction conditions.

Scheme 68. One-pot double TBS protection and *N*-Boc deprotection.



The final step of the racemic synthesis was to cleave the PMB group to furnish the free *o*-chloro phenol. In the literature it has been demonstrated that *o*-Cl-OBn protected phenols can be cleaved utilising classical palladium based hydrogenation.[123] Pearlman's catalyst, 20% $Pd(OH)_2$ on carbon was employed as the palladium source and treatment with hydrogen under vigorous stirring accomplished the de-*p*-methoxybenzylation. Yields of 60% were achieved, after column chromatography, of the desired AA-6 analogue **239** (Scheme 69). Reassuringly in this reaction only one product was observed and the Cl-group and more hindered benzyl fragment of the compound were left intact.

Scheme 69. De-*p*-methoxybenzylation employing $Pd(OH)_2/C$ and H_2.

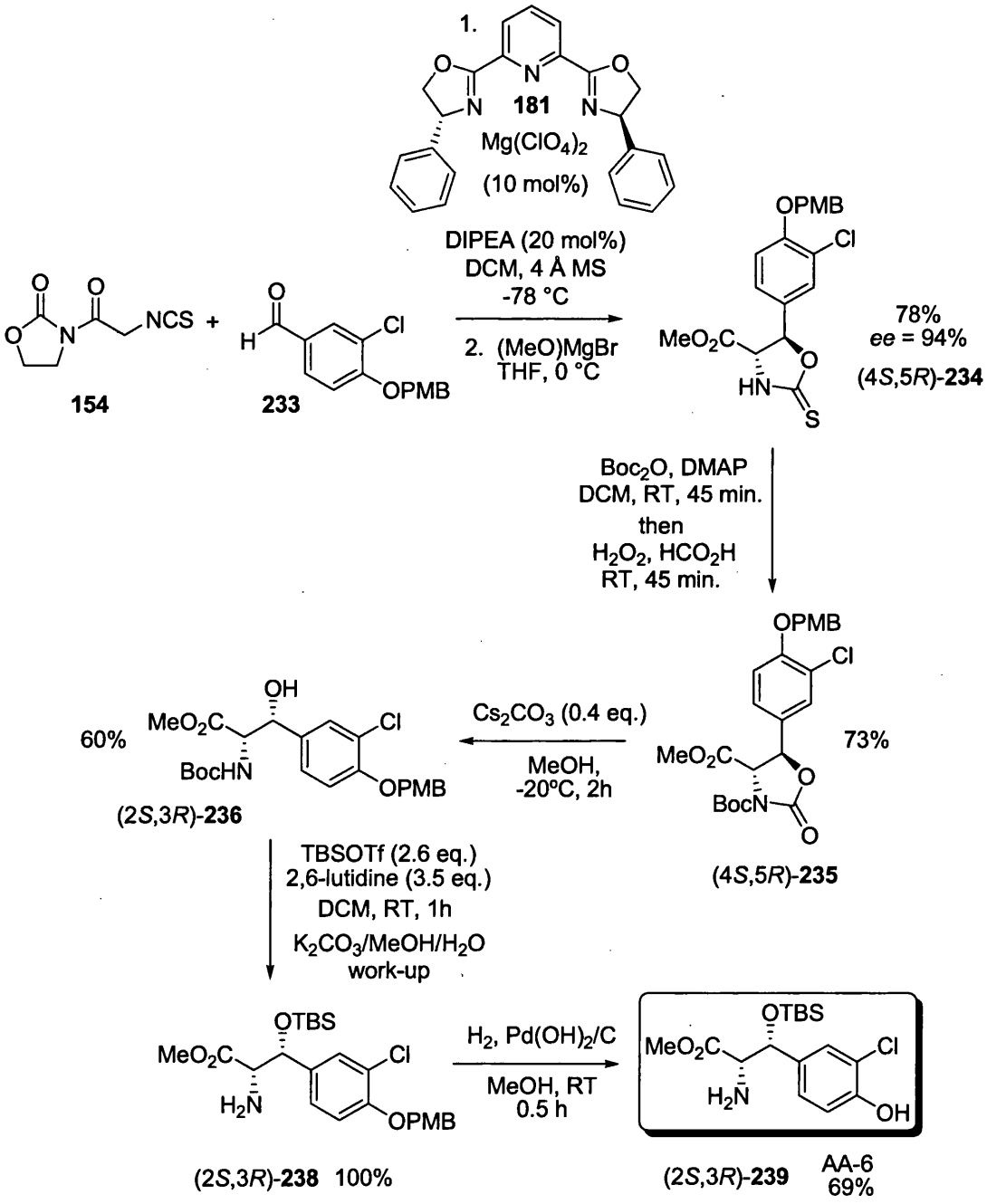


II 2.7 The asymmetric route to AA-6

Now that the chemistry and synthetic route to the AA-6 analogue had been proven, the synthesis could be taken through with asymmetric material from the initial key enantioselective aldol reaction. This was subsequently achieved with similar results to the racemic synthesis over all steps. The final

hydrogenation step was improved slightly generating the final product (4*S*,5*R*)-**239** in 69% yield. The overall scheme of synthetic events is provided below (Scheme 70).

Scheme 70. Asymmetric synthesis of AA-6 methyl ester analogue.



The overall yield for this asymmetric synthesis was 23% over 6 steps commencing from the enantioselective key aldol step. The ethyl ester adduct *syn*-**227** was shown to have the correct configuration true to AA-6 through X-ray crystallography and later steps of the synthesis with methyl ester derivatives **234, 235, 236, 238,** and **239** generated no apparent epimerisation products. The final AA-6 analogue **239** gave polarimetry parameters of the same sign ($[\alpha]_D^{20}$ = -11.0 (c = 1.0, DCM)) to the final ethyl ester **214** ($[\alpha]_D^{22}$ = -17.9 (c = 0.98, EtOAc)) as in Nicolaou's AA-6 synthesis.

II 2.8 Conclusion

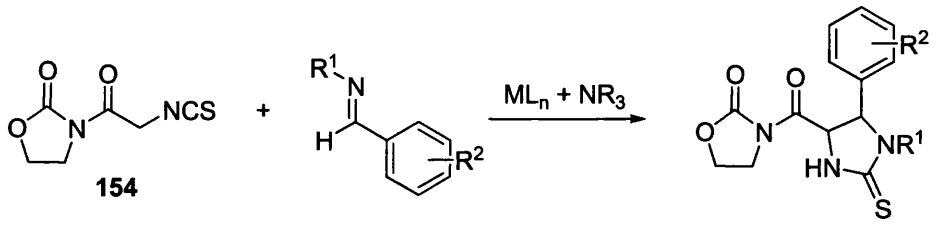
What must be noted in this section is the fact that, although further protection and deprotection steps were found to be necessary in this formal synthesis of vancomycin's AA-6 building block, the elementary idea of the application of a direct catalytic enantioselective route with a high degree of stereoselectivity to such a target has been accomplished. The asymmetric key steps in syntheses of AA-6 to date have been limited in the degree of enantioselectivity achieved. Nicolaou's very impressive synthesis although very short (32% in 6 steps) encompasses a low yielding (45%) asymmetric aminohydroxylation that achieves a respectable 87% *ee*. The asymmetric synthesis described in this section allows for a high yielding diastereoselectivity (93:7 d.r.) and excellent enantioselectivity (94-95% *ee*) and incorporates this stereochemistry early on. A key problem encountered was the difficulty in deprotecting the oxazolidinethione moiety directly and therefore further manipulation was deemed necessary. With starting materials in hand, the *iso*thiocyanate **154** and aldehyde **233** were taken through to the methyl ester analogue of AA-6 in 6 steps and an overall yield of 23%.

II 3 A direct catalytic enantioselective route to α,β-diamino acids

II 3.1 Introduction

A key aspect of the project was to further develop and expand the scope of electrophiles utilised in the bifunctional enantioselective catalysis already developed for aryl aldehydes. The addition of oxazolidinone **154** to imines proved attractive due to the fact that products of such a Mannich type reaction would deliver protected α,β-diamino acids in the form of cyclic thioureas. This type of Mannich reaction with post addition cyclisation of the *iso*thiocyanate substituent has been reported by Volkmann.[124] The protected α,β-diamino acid moiety has important potential applications, including the formation of β-lactams, scaffolds for some of the most important antibiotics.[125] The formation of an imidazolidinethione should prevent the epimerisation at the α-carbon. The proposed reaction is illustrated below (Scheme 71).

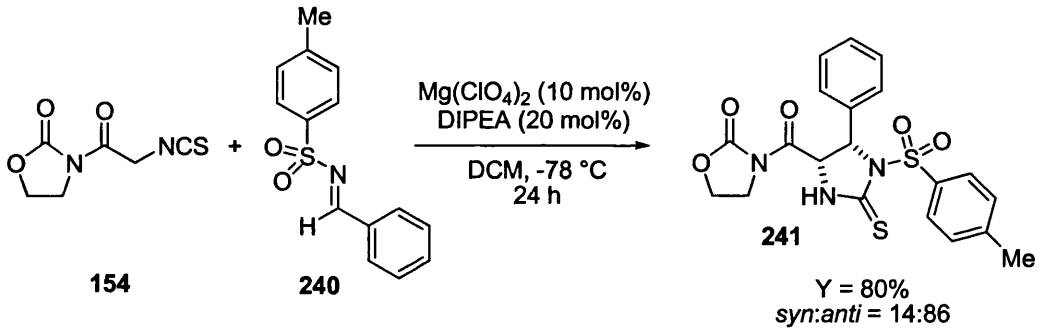
Scheme 71. Proposed Mannich reaction.



The transition from *iso*thiocyanato ethyl ester **155** to oxazolidinone **154** in the achiral catalytic aldol reaction showed increases in reactivity. The former substrate depended more on the bipyridine complexed Mg catalyst for maximised yields. Therefore, exploration of a catalytic Mannich reaction

commenced with oxazolidinone **154**. The imine partner, *N*-tosylimine **240** was selected as an activated imine source due to literature precedent of readily undergoing imine-aldol reactions.[126,127] It was soon realised that *N*-tosylimine **240** utilising similar catalytic conditions; $Mg(ClO_4)_2$ (10 mol%) and DIPEA (20 mol%) readily underwent the addition reaction in DCM at -78 °C employing two equivalents of tosylimine (Scheme 72). It was a surprise to observe that the reaction was in fact *anti*-selective and delivered the adduct in high yield. The next stage of development addressed the application of this catalysed reaction to an enantioselective reaction employing C_2-symmetric ligands as in the asymmetric aldol reaction.

Scheme 72. Achiral Mannich reaction.



II 3.2 Asymmetric induction

The C_2-symmetric ligands elected for the asymmetric induction screen are presented below (Figure 18). Again a range of bidentate bis(oxazolines) were examined (entries 1 to 4, Table 8) and all produced the predominant *anti*-imidazolidinethione adducts in relatively poor *ee*. The highest enantioselectivity was achieved by (4*R*)-benzyl substituted bis(oxazoline) **242** (ee_{anti} = 39%, entry 3). A vast array of tridentate pyridine bis(oxazolines) (PyBOx) ligands were also examined in the screen. All of these ligands

produced the imidazolidinethione adducts in high yield and *anti*-selectivities of up to 86:13 (entries 6 to 11). The (4*S*)-benzyl substituted PyBOx **178** gave the poorest enantioselectivity of this ligand type (ee_{anti} = 8%, entry 8). The successfully employed (4*R*)-phenyl substituted PyBOx **181** with regards to the asymmetric aldol reaction (Sections II 1 and II 2) delivered the *anti*-product in only 45% *ee* (entry 11). The highest enantioselectivity from a PyBOx ligand was achieved by employing (4*R*)-*iso*propyl PyBOx **244** (ee_{anti} = 70%, entry 7). The last ligand variety explored was the tridentate dibenzofuran bis(oxazoline) (DBFOx) that comprises a central oxygen coordinating atom.

Figure 18. C_2-symmetric ligands.

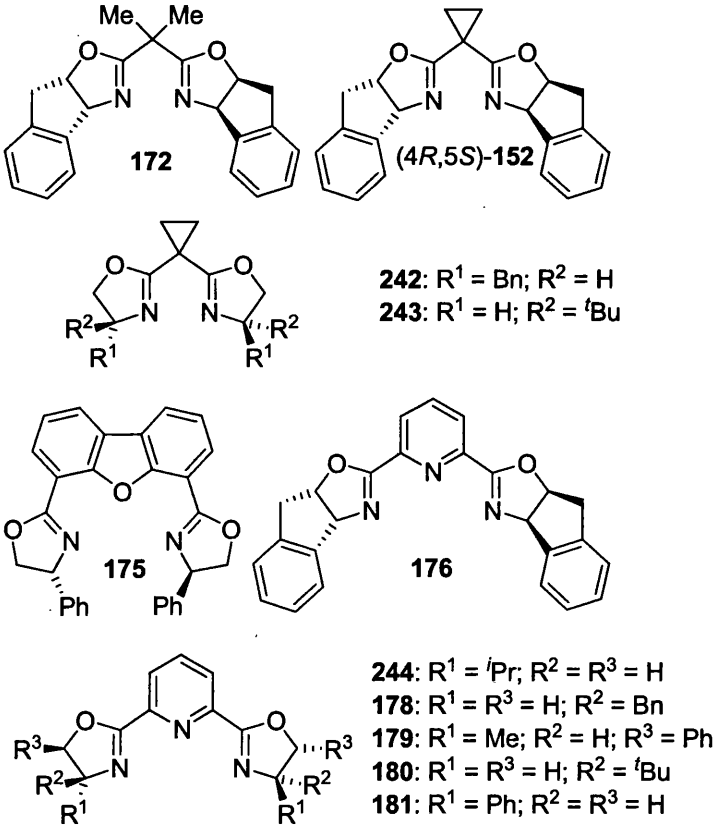
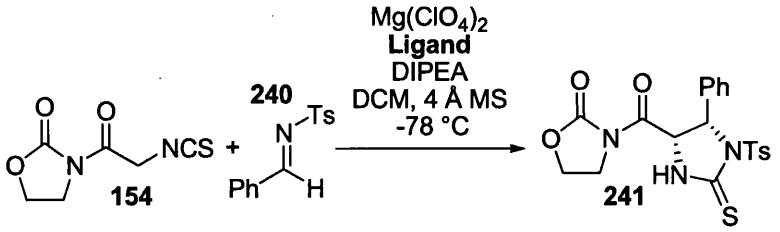


Table 8. C_2-symmetric ligand screen for the asymmetric Mannich reaction.[a]



Entry	Ligand	Time (h)	*Syn:anti*[b]	Yield (%)[c]	ee_{anti} (%)[d]
1	**172**	24	25:75	82	10
2	**152**	24	20:80	100	4
3	**242**	24	33:67	97	39
4	**243**[e]	24	40:60	83	4
5	**175**	24	13:87	94	96
6	**176**	24	22:78	100	63
7	**244**	24	14:86	100	70
8	**178**[e]	24	31:69	100	8
9	**179**[e]	24	39:61	82	19
10	**180**[e]	24	20:80	100	43
11	**181**	24	37:63	100	45

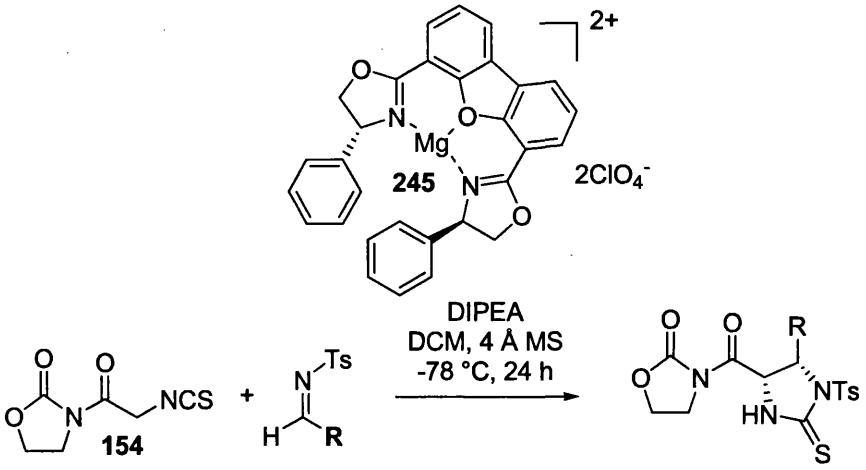
[a]Conditions: isothiocyanate (1.0 equiv.), tosylimine (2.0 equiv.), $Mg(ClO_4)_2$ (10 mol %), DIPEA (20 mol %) and **ligand** (11 mol %).
[b] Diastereomeric ratio determined by ^1H NMR.
[c] Isolated yield of both diastereomers.
[d] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.
[e] Enantiomeric excess corresponds to opposite enantiomer.

This ligand, (*R,R*)-Ph-DBFOx (*R,R*)-**175**, gave poor selectivity in the aldol reaction but the switch from aldehyde to a tosylimine electrophile furnished the *anti*-imidazolidinethione adduct in high yield and with an *ee* of 96% (entry 5). In addition the highest d.r. was achieved with this ligand (*syn:anti* = 13:87).

II 3.3 Tosylimine scope

Now that a highly selective ligand had been discovered, which invoked high enantioselection and diastereoselection, it was time to explore the scope of the tosylimine component (Table 9). To aid in the determination of *ee* values of certain products, the direct adducts were treated with a solution of magnesium ethoxide to yield the more soluble corresponding ethyl ester derivatives (entries 11 to 14) (Section III 17). As with the asymmetric aldol reaction, a wide variety of substitution on the aryl imine was readily accommodated. Both electron rich and electron poor substitution in the *para* and *meta* positions delivered adducts in high *ee*, for example the *anti*-adducts from 4-bromo tosylimine **247** (ee_{anti} = 98%, d.r. = 83:17, entry 3), 4-cyano tosylimine **258** (ee_{anti} = 99%, d.r. = 67:33, entry 14) and 3-methyl tosylimine **249** (ee_{anti} = 99%, d.r. = 86:14, entry 5). This degree of electrophile scope, employing electron-rich and poor systems, is in contrast to that of the comparable aldol reaction. The reaction could also be applied to a wide range of tosylimines other than aryl species such as heterocyclic, alkenyl, and alkyl imines with a high degree of enantioselection, for example where R = cyclohexyl **251** (ee_{anti} = 99%, d.r. = 67:33, entry 7), R = (*E*)-cinnamyl **254** (ee_{anti} = 97%, d.r. = 78:22, entry 9) and R = thiophenyl **255** (ee_{anti} = 90%, d.r. = 50:50, entry 11). This was not achieved in the aldol variant. One last example, where R = *n*-pentyl **252** (entry 8) although produced in lower yield and diastereoselectivity was furnished in 84% *ee*.

Table 9. Tosylimine scope of the asymmetric Mannich reaction.[a]



Entry	R	Product	*Anti:syn*[b]	Yield (%)[c]	ee_{anti} (%)[d]
1	Ph	**241**	87:13	94	96
2	2-Naphthyl	**246**	93:7	100	98
3	4-Br-C_6H_4	**247**	83:17	86	98
4	4-F-C_6H_4	**248**	75:25	98	93
5	3-Me-C_6H_4	**249**	86:14	91	99
6	4-^{t}Bu-C_6H_4	**250**	82:18	96	99
7	Cy	**251**	67:33	98	99
8	C_5H_{11}	**252**	67:33	40	84
9	(*E*)-cinnamyl	**253**	78:22	97	97
10	2-furyl	**254**	50:50	92	-[e,f]
11	2-thiophenyl	**255**	50:50	94	90[e]
12	4-Me-C_6H_4	**256**	83:17	96	99[e]
13	4-MeO-C_6H_4	**257**	76:24	86	97[e]
14	4-CN-C_6H_4	**258**	67:33	85	99[e]

[a]Conditions: isothiocyanate (1.0 equiv.), **tosylimine** (2.0 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and (*R,R*)-Ph-DBFOx **175** (11 mol%).
[b] Diastereomeric ratio determined by ^{1}H NMR.
[c] Isolated yield corresponds to combined diastereomers.
[d] *ee* determined by chiral HPLC on a Chiralcel OD column.
[e] *ee* corresponds to the derivatised ethyl ester.
[f] Enantiomers could not be separated by Chiral HPLC.

II 3.4 Absolute configuration – Xray crystallography experiments

The absolute configuration of the major *anti*-adducts was confirmed by X-ray crystallography of two of the above examples; benzyl and cyclohexyl adducts, *anti*-**241**, and *anti*-**251** respectively to be (4*S*,5*S*) (Figures 21 and 22). The other examples reported have been assigned by analogy. The same (4*S*)-configuration is observed in the product as in the asymmetric aldol reaction which implies the same *si* face attack from the enolate species to the electrophilic component albeit with a different C_2-symmetric ligand. The fact that the *anti*-diastereomer of (5*S*)-configuration, is formed preferentially, is believed to be due to the nature of the tosylimines coordination to the Lewis acid. The steric hindrance due to the much larger spatial occupancy of the *N*-tosyl group compared to that of an aldehyde is responsible for a change in orientation of the coordinating electrophile i.e. the metal would lie *cis* to the R-group of the imine, and lie *trans* to the R-group of an aldehyde (Figure 20). This difference in orientation would transfer to the transition state and therefore inherently determine the diastereomeric outcome of the reaction.

Figure 20. Coordination of tosylimines and aldehydes to Mg.

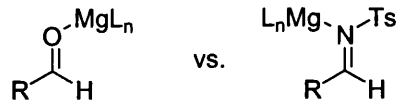
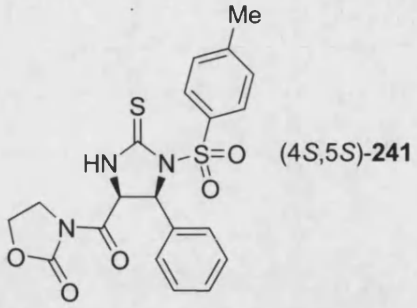


Figure 21. Imidazolidinethione (4*S*,5*S*)-**241** and X-ray crystal structure.



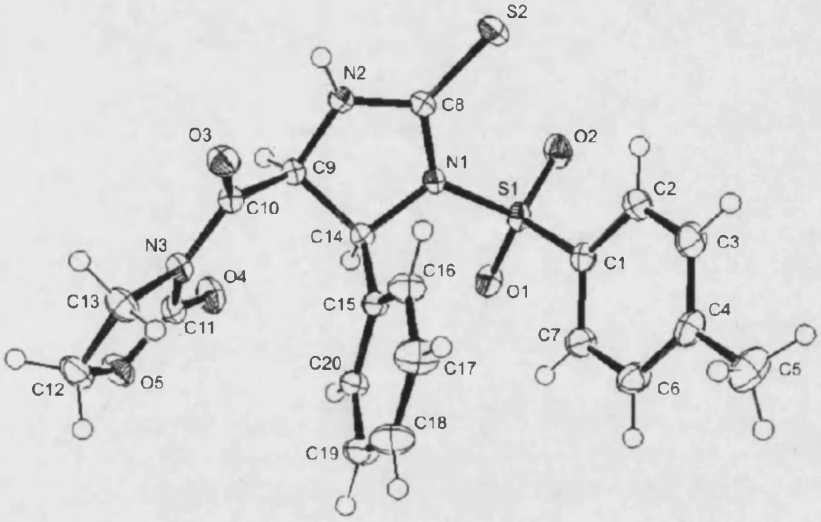
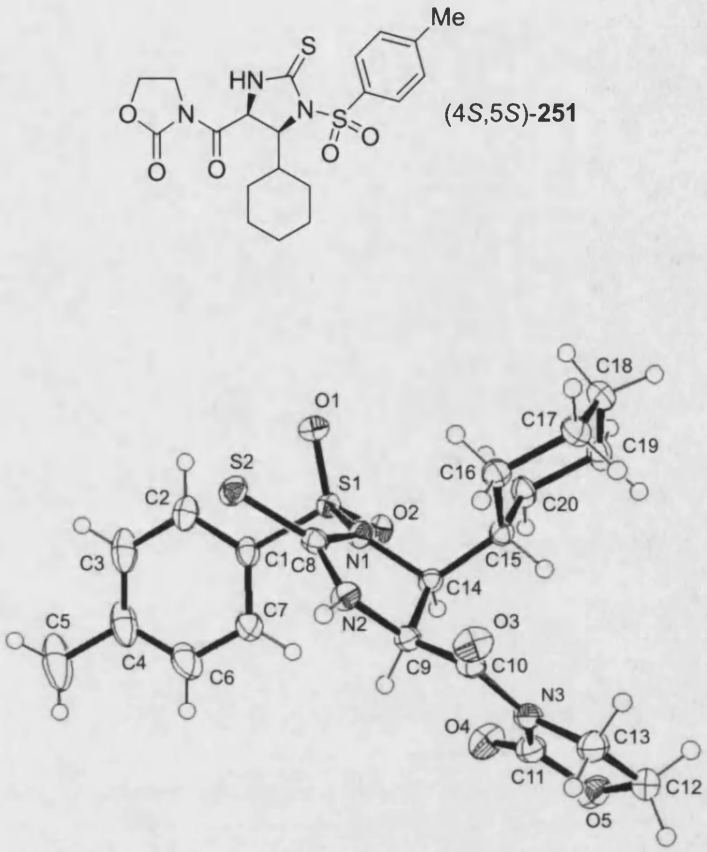


Figure 22. Imidazolidinethione (4*S*,5*S*)-**251** and X-ray crystal structure.



II 3.5 Conclusion

The extension of an asymmetric catalytic aldol process involving soft enolisation to reach other electrophiles in particular tosylimines (a Mannich variant) has been accomplished. The discovery of (*R*,*R*)-Ph-DBFOx **175** as an effective enantioselective ligand for the reaction of tosylimines with oxazolidinone **154** was crucial in this development. The other commercially available catalyst components remained the same, the Lewis acid, $Mg(ClO_4)_2$ and amine base, DIPEA. The characteristics of this imine-aldol reaction out perform those of the aldol reaction in that higher enantioselectivity is reached (up to 99%) over a broader range of electrophiles including those

with alkyl substitution. The observed *anti*-selectivity, which is unusual in such an addition, is the reverse of the aldol process and has been achieved in ratios of up to 93:7 for the 2-naphthyl analogue **246**. Time constraints have not allowed any probing of the mechanism although it is believed to be similar to the aldol process aforementioned (Section II 1) with the tosylimine adopting a different orientation of coordination to the Mg centre.

II 4 A direct catalytic and diastereoselective route to protected α,β-dihydroxyketones

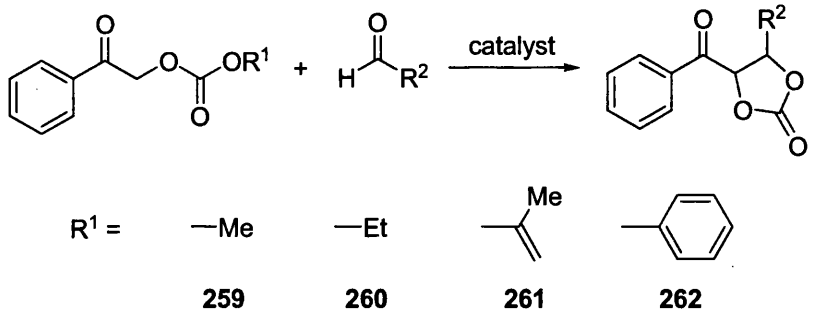
II 4.1 Introduction

To supplement the direct catalytic asymmetric synthesis of β-hydroxy-α-amino and α,β-diamino moieties it was envisaged that employment of an α-oxygenated carbonyl in our system would add to aldehydes to yield α,β-dihydroxy adducts. This third class of functionality is ubiquitous in a variety of natural products and biologically active molecules and examples of such are described in section (I 1).

Accordingly, there are a number of methods available to prepare this structural motif[128] but one of the most attractive strategies is the use of an α-oxygenated enolate addition to an aldehyde which features a single step formation of both a carbon-carbon bond and two hydroxyl stereocentres. Direct catalytic examples that deliver high diastereoselectivity and enantioselectivity are rare and present a formidable challenge.

One problem that was envisioned in applying our catalytic system to the synthesis of poly-hydroxylated adducts was the possibility of product inhibition due to binding between an alkoxy intermediate and Lewis acid. To limit this an α-carbonate substituent was chosen that should allow *in situ* protection of the newly formed hydroxyl group *via* carbonate transfer (Scheme 73). This strategy of incorporating the newly formed hydroxyl group in a cyclic structure follows suit to that of the *iso*thiocyanate variant of the proposed reaction.

Scheme 73. Direct catalytic aldol route to protected 1,2-diols.

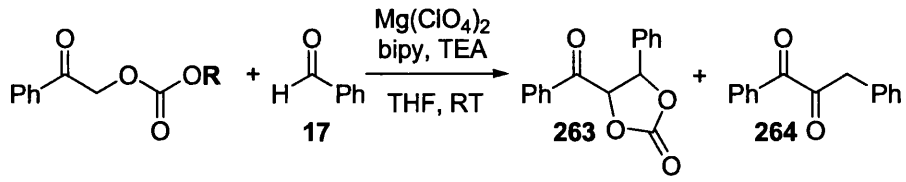


259 **260** **261** **262**

II 4.2 Initial studies

A selection of phenyl ketones with various α-carbonate substituents; methyl **259**, ethyl **260**, *i*-propenyl **261** and phenyl **262** were prepared from phenacyl alcohol and the corresponding chloroformate for initial study (Section III 18).[129] The choice of an aryl ketone was believed to be a good starting point. The increased acidity of α-protons compared to that of ester/amide analogues would allow for more facile deprotonation since the reactivity was unclear for these substrates in a soft-enolisation system. Benzaldehyde **17** was elected as the initial electrophilic component due to its non-enolisable nature. Catalyst conditions employed in the enolisation of α-isothiocyanate substituted esters for the synthesis of protected β-hydroxy-α-amino acids, previously developed in our group, were investigated in this reaction. The catalyst components of this system were $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%), and triethylamine (20 mol%). The α-carbonates were initially reacted with sub-stoichiometric (50 mol%) loadings of Lewis acid component and a stoichiometric amount of tertiary amine base in order to gain insight into the reactivity of the addition reaction (Table 10).

Table 10. α-Carbonate variation.[a]

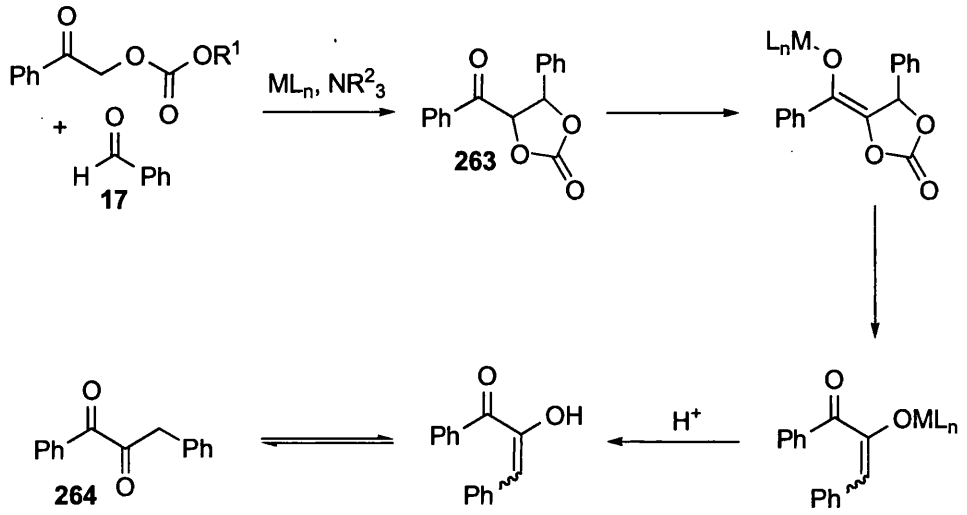


Entry	R	Time (h)	Yield **263** (%)[b]	Yield **264** (%)[b]
1	Ethyl	48	49	12
2	Methyl	48	62	23
3	Phenyl	48	38	50
4	*i*-Propenyl	48	50	50

[a] All reactions: carbonate (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (50 mol%), bipy (50 mol%), TEA (100 mol%).
[b] Conversion measured by ^1H NMR.

Under conditions of high Lewis acid loading the cyclic carbonate product **263** was found to be unstable and readily underwent elimination to generate a 1,2-dicarbonyl by-product **264**. The use of methyl carbonate **259** (entry 2) gave greater conversion to the cyclic carbonate than ethyl carbonate **260** (entry 1) and *i*-propenyl carbonate **261** (entry 4) reacted fastest under the high Lewis acid loading. The phenyl carbonate **262** (entry 3) proved to be unstable under the reaction conditions and was soon discarded from the investigation. The elimination that occurs is depicted in scheme 74 and was later found to be easily controlled under conditions of lower Lewis acid loading.

Scheme 74. Generation of 1,2-dicarbonyl by-product.

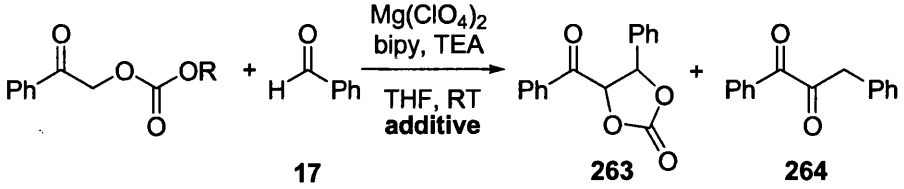


II 4.3 Employment of additives

Under lower loadings of the Lewis acid magnesium perchlorate (10 mol%) the generation of 1,2-dicarbonyl **264** had completely diminished (Table 11) but yields of the desired cyclic carbonate **263** were low (entry 1) even after extended reaction times. In order to increase yields the addition of 4 Å MS was found to be beneficial with methyl carbonate **259** (entry 3). The reason for this was initially believed to be due to removal of methanol introduced into the system, which could potentially deactivate the Lewis acid. It was later observed that *i*-propenyl carbonate **261** which generates acetone rather than an alcohol into the system also gave an increased yield with the addition of 4 Å MS (entry 7). The more obvious reason for this increased reactivity lies in the hygroscopic nature of $Mg(ClO_4)_2$, in that weighing and charging was not carried out in an anhydrous atmosphere and 4 Å MS act to activate the Lewis acid catalyst. The exclusion of either bipyridine or 4 Å MS resulted in minimal reaction (entries 1 and 2). In order to achieve greater yields and turnover of the catalyst an alcohol could also act as a proton source and thus *i*-PrOH (entry 4) and 2,2,2-trifluoroethanol

(entry 5) were examined in the system.[130] These additives gave no beneficial turnover of catalyst.

Table 11. Effects of additives.[a]



Entry	R	Additive[d]	Time (h)	Yield **263** (%)[b]	Yield **264** (%)[b]
1	Methyl	-	96	13	0
2[c]	Methyl	4 Å MS	72	16	0
3	Methyl	4 Å MS	48	57	0
4	Methyl	4 Å MS, ^{i}PrOH	48	51	0
5	Methyl	4 Å MS, CF_3CH_2OH	48	52	0
6	^{i}Propenyl	-	48	16	0
7	^{i}Propenyl	4 Å MS	48	62	0

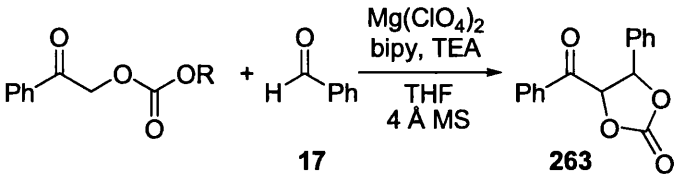
[a] All reactions: carbonate (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), bipy (10 mol%), TEA (100 mol%).
[b] Conversion measured by ^{1}H NMR.
[c] No bipy employed.
[d] ^{i}PrOH and CF_3CH_2OH (1.0equiv.), 4 Å MS (200 mg/mmol of carbonate).

II 4.4 Other preliminary variables

At this point in the development of the α-carbonate addition, it was deemed necessary to investigate such variables as equivalents of reagents, temperature, and solvent systems. Under the conditions of $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) in THF at RT the excesses of tertiary amine base, aldehyde and carbonate were examined to see whether the reaction could be driven to completion (Table 12).

TEA (200 mol%, entry 2), aldehyde (2.2 equivalents, entry 3), and carbonate (2.0 equiv., entry 4) were employed but none of these conditions enhanced reaction efficiency. The effect of temperature was also briefly examined. At attenuated reaction temperatures (entry 6) the reaction started to become a complex mixture of products and lowering the temperature to 0 °C inhibited the reactivity of the catalyst (entry 7).

Table 12. Effect of reagent stoichiometry and temperature.[a]



17 263

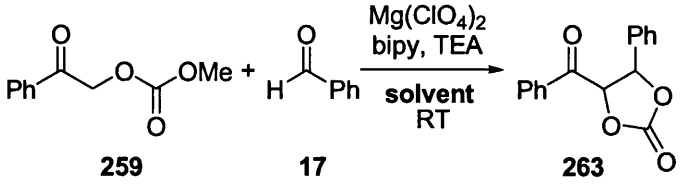
Entry	R	Time (h)	T (°C)	Yield **263** (%)[b]
1	Methyl	48	RT	57
2[c]	Methyl	48	RT	56
3[d]	Methyl	48	RT	47
4[e]	Methyl	48	RT	50
5[f]	^{i}Propenyl	48	RT	16
6[f]	^{i}Propenyl	48	35	22
7[f]	^{i}Propenyl	48	0	0

[a] All reactions: carbonate (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), bipy (10 mol%), TEA (100 mol%), 4 Å MS (200 mg/mmol of carbonate).
[b] Conversion measured by ^{1}H NMR.
[c] TEA (200 mol%).
[d] Aldehyde (2.2 equiv.).
[e] Carbonate (2.0 equiv.).
[f] No 4 Å MS used.

The effects of several solvents were also examined in this reaction (Table 13). In changing the solvent, a reduction in the difference in pK_a between the substrate coordinated to Mg^{2+} and tertiary amine base may be

achieved therefore increasing the rate of enolisation. It is also possible that a change in solvent could accelerate the turnover of catalyst. The polarity of the solvent could affect stabilisation of any transition state involved and/or products generated which would alter rates of forward/retro aldol reactions.

Table 13. Solvent screening.[a]



Entry	**Solvent**	Time (h)	Yield **263** (%)[b]
1	THF	48	13
2	DCM	48	1
3	Toluene	48	1
4	MeCN	48	0
5	DME	48	14
6	1,4-Dioxane	48	13

[a] All reactions: carbonate (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), bipy (10 mol%), TEA (100 mol%).
[b] Conversion measured by ^1H NMR.

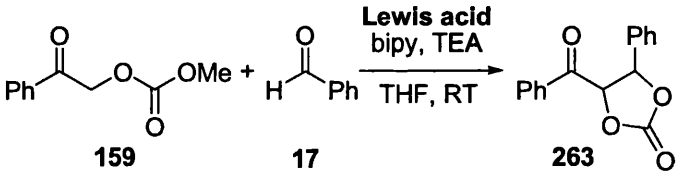
The reaction carried out in acetonitrile (entry 4) gave no reaction and can be attributed to the solvents polarity and strong coordination to the magnesium cation. Less polar solvents like toluene (entry 3) and DCM (entry 2) gave minimal reaction. Etheric solvents like DME (entry 5), 1,4-dioxane (entry 6), and THF (entry 1) provide some solvating function and gave the best results. THF was elected for further studies of this soft-enolisation catalysis.

II 4.5 Lewis acid screening

Although magnesium has been a focal point of the project, it was deemed necessary to screen at least some of the well-known Lewis acids employed in catalyses in combination with an amine base. Varying the metal centre of the catalyst would allow insight into Lewis acid activity for the system under investigation.

Commercially available triflate salts of various metals were utilised (Table 14). Sn(II) and Cu(II) triflates (entries 3 and 4 respectively) produced no reaction whereas Zn(II) and Sc(III) triflates resulted in complex reaction mixtures. The use of Mg(II) triflate produced minimal reaction compared to its perchlorate counterpart (entry 2).

Table 14. Lewis acid screening.[a]



Entry	**Lewis acid**	Time (h)	Yield **263** (%)[b]
1	$Mg(ClO_4)_2$	48	62
2	$Mg(OTf)_2$	48	35
3	$Sn(OTf)_2$	48	0
4	$Cu(OTf)_2$	48	0
5[c]	$Zn(OTf)_2$	48	-
6[c]	$Sc(OTf)_3$	48	-

[a] All reactions: carbonate (1.0 equiv.), aldehyde (1.1 equiv.), **Lewis acid** (50 mol%), bipy (50 mol%), TEA (100 mol%).
[b] Conversion measured by ^1H NMR.
[c] Complex reaction mixture resulted.

From the few metal Lewis acids examined $Mg(ClO_4)_2$ offered the most active catalyst component and was therefore employed in the following screening of tertiary amine bases.

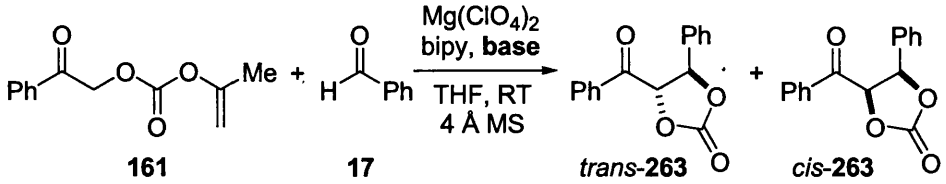
II 4.6 Base screening

In an attempt to increase the yield of the catalytic addition reaction a number of non-nucleophilic bases were screened. It is essential that the Lewis acid and amine base combination do not form an irreversible adduct. Thus bases deemed suitable were elected having a pK_a in water of approximately 5 to 12 (Table 15).[131] Bases having a pK_a below 7 for example bipyridine (entry 1) and diethylaniline (entry 2) gave no reaction; a stronger base was required in order for the ketone to be deprotonated. The fact that bipyridine employed at a stoichiometric loading was unable to carry out the deprotonation heeds well for the function of bipyridine being that of an external ligand. Bases having a pK_a value of 11.0 and above gave little or no reaction. Quinuclidine (entry 8) and DBU (entry 10) afforded no reaction and this may be attributed to an irreversible Lewis acid base complex formation. DIPEA produced the cyclic carbonate in very low yield and poor selectivity (27%, entry 9).

The screening of amine bases allowed the selectivity of the soft-enolisation and addition to be examined. In all cases the *syn*-aldol adduct leading to the *trans*-cyclic carbonate was the major diastereomer and it was in the pK_a range of 7.4 to 10.8 that the diastereoselectivity and yield of the catalysis became fruitful. Although DABCO (entry 4) and NEP (entry 5) afforded the cyclic carbonates as a 15:1 mixture of diastereomers the yields were particularly lower (31% and 45% respectively) than when TEA (62%, entry 6) was employed as the base. This is quite a surprising result since the

pK_a's of both DABCO and NEP lie between the pK_a range of NMM and TEA. NMM (entry 3) having a pK_a of 7.4 furnished the cyclic carbonate adduct in 74% yield – the highest yield achieved so far. This positive result was dampened somewhat by the low diastereoselectivity attained of 7:1 in favour of the *syn*-aldol.

Table 15. Screening of amine bases.[a]



161 **17** *trans*-**263** *cis*-**263**

Entry	**Base**	pK_a[d]	Time (h)	*Syn*:*Anti*[b]	Yield **263** (%)[c]
1	2,2'-Bipyridine	4.5	48	-	0
2	*N*,*N*-Diethylaniline	6.5	48	-	0
3	*N*-Methylmorpholine	7.4	48	7:1	74
4	DABCO	8.8	48	15:1	31
5	*N*-Ethylpiperidine	10.5	48	15:1	45
6	Triethylamine	10.8	48	13:1	62
7	Tri-*n*-butylamine	10.9	48	9:1	42
8	Quinuclidine	11.0	48	-	0
9	di-*i*-propylethylamine	11.4	48	2:1	27
10[e]	DBU	12	48	-	0

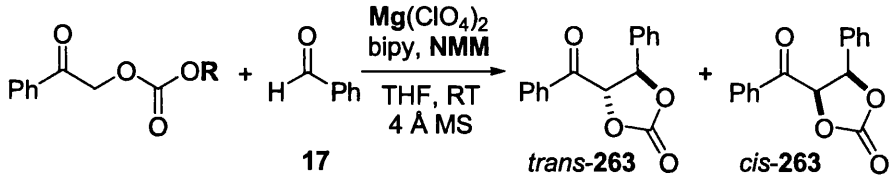
[a] All reactions: carbonate (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), bipy (10 mol%), **base** (100 mol%), 4 Å MS (200 mg/mmol of carbonate).
[b] dr measured by ^{1}H NMR.
[c] Conversion measured by ^{1}H NMR.
[d] pK_a of protonated nitrogen in H_2O at RT.[131]
[e] pK_a of protonated nitrogen in DMSO at RT.[131]

The choice of carbonate for this study in the selection of amine base was later examined and will be described in the next sub-section. The choice between *i*-propenyl **161** and methyl **159** carbonates for further development was yet to be decided since similar results were gathered for these substrates.

II 4.7 Further optimisation

The initial focus of the use of *i*-propenyl carbonate **161** was to avoid the introduction of an alcohol into the system, which could potentially deactivate the Lewis acid. However, reaction of methyl carbonate **159** in combination with $Mg(ClO_4)_2$ employed at 20 mol% and NMM (Table 16) delivered the cyclic carbonate in almost identical conversion and an isolated yield of 72% along with an increased diastereoselectivity (10:1, entry 4). The utilisation of Mg at 20 mol% increased turnover and therefore yield of the reaction without the occurrence of 1,2-dicarbonyl by-product formation observed earlier. The use of 20 mol% Lewis acid also allowed the reaction time to be reduced to 24 hours. The yield could be further increased to 91% by raising the equivalents of carbonate from 1.0 to 2.0 (entry 5). A 50 mol% loading of NMM was found to be optimal with lower loadings resulting in reduced yields (entries 5 and 6).

Table 16. Final optimisation.[a]



Entry	R	Mg (mol%)	NMM (mol%)	Time (h)	*Syn:Anti*[b]	Yield **263** (%)[c]
1	*i*-Propenyl	10	100	48	7:1	74
2	*i*-Propenyl	20	100	24	7:1	81
3[d]	*i*-Propenyl	20	100	24	-	4
4	Methyl	20	100	24	10:1	72[e]
5[f]	Methyl	20	50	24	10:1	91[e]
6	Methyl	20	20	24	11:1	78
7	Methyl	0	50	24	-	0
8	Methyl	20	0	24	-	0
9[g]	Methyl	20	50	24	11:1	17

[a] All reactions: carbonate (1.0 equiv.), aldehyde (1.1 equiv.), bipy (as Mg), 4 Å MS (200 mg/mmol of carbonate).
[b] dr measured by ^{1}H NMR.
[c] Conversion measured by ^{1}H NMR.
[d] $Mg(OTf)_2$.
[e] Isolated yield.
[f] 2.0 equivalents of carbonate.
[g] No bipy used.

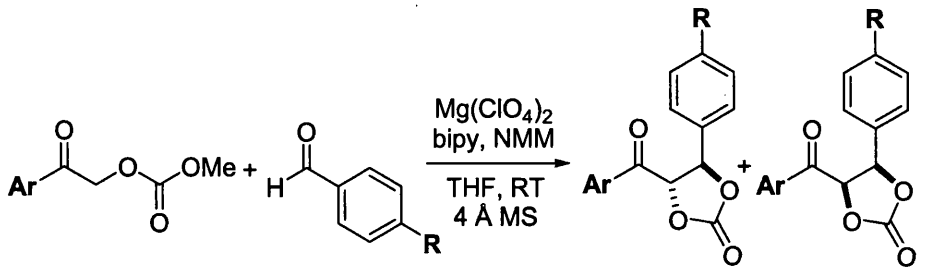
To conclude the optimisation process, $Mg(OTf)_2$ was also re-examined and produced minimal reaction (entry 3). It was established that both Lewis acid (entry 7) and amine base (entry 8) were necessary in order to achieve reaction and finally that bipyridine plays an important role as an external ligand and accelerates the reaction rate (entry 9).

II 4.8 Ketone and aldehyde variation

With optimised conditions in hand, the scope of aldehydes that could be successfully employed in the reaction was investigated (Table 17). The catalyst system generated from $Mg(ClO_4)_2$ (20 mol%), bipyridine (20 mol%) and NMM (50 mol%) was used to promote the addition of carbonate **159** (2.0 equiv.) to a range of aromatic aldehydes (1.0 equiv.). All reactions were conducted at RT in THF in the presence of 4 Å molecular sieves. The benzaldehyde derived adduct was obtained in 91% yield as a 10:1 mixture of diastereomers (entry 1). Electron rich aldehydes such as *p*-tolualdehyde (97%, 16:1, entry 2) and *p*-anisaldehyde (86%, 11:1, entry 3) also performed well, albeit after longer reaction times. Conversely, electron poor aldehydes gave quicker reaction times with *p*-trifluoromethyl- and *p*-cyanobenzaldehyde furnishing the cyclic carbonate adducts in 65% and 76% respectively (entries 4 and 5).

The phenyl ketone portions were then changed to the corresponding 2-naphthyl analogues (Section III 18) and the same trends broadly followed although less of an excess of carbonate **274** could be employed effectively. The benzaldehyde derived adduct was delivered in 79% as an 8:1 mixture of diastereomers (entry 6). *p*-Anisaldehyde (72%, 14:1, entry 8) delivered the required adduct in increased diastereoselectivity to the phenyl counterpart. This was also the case for electron poor aldehydes for example *p*-cyanobenzaldehyde (69%, 16:1, entry 10).

Table 17. Ketone and aldehyde scope.[a]



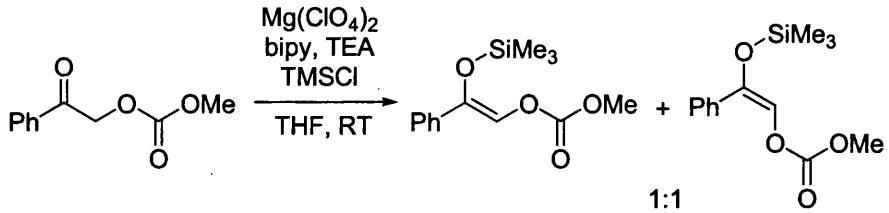
Entry	Ar	R	Product	Time (h)	*Syn:Anti*[b]	Yield (%)[c]
1	Ph	H	**263**	24	10:1	91
2	Ph	Me	**265**	48	16:1	97
3	Ph	OMe	**266**	48	11:1	86
4	Ph	CF_3	**267**	24	9:1	65
5	Ph	CN	**268**	18	9:1	76
6[d]	2-Naphthyl	H	**269**	24	8:1	79
7[d]	2-Naphthyl	Me	**270**	48	8:1	75
8[d]	2-Naphthyl	OMe	**271**	48	14:1	72
9[e]	2-Naphthyl	CF_3	**272**	24	15:1	97
10[e]	2-Naphthyl	CN	**273**	18	16:1	69

[a] All reactions: carbonate (2.0 equiv.), aldehyde (1.0 equiv.), $Mg(ClO_4)_2$ (20 mol%), bipy (20 mol%), NMM (50 mol%), 4 Å MS (200 mg/mmol of carbonate).
[b] dr measured by ^1H NMR.
[c] Isolated yields of combined diastereomers.
[d] Carbonate (1.0 equiv.).
[e] Carbonate (1.5 equiv.).

II 4.9 Diastereoselectivity issues

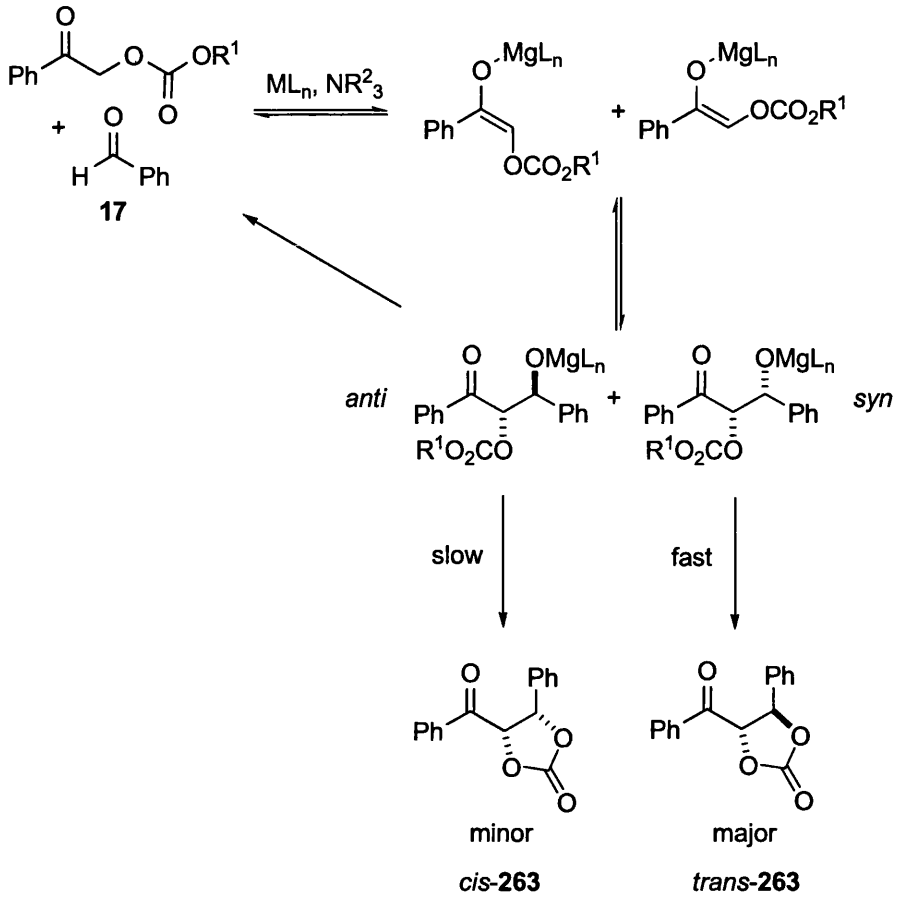
In all examples that have been studied, the *trans*-cyclic carbonate has been isolated as the major diastereomer and selectivities of up to 16:1 have been achieved. An investigation into how these useful levels of diastereoselection arise has been conducted. The trapping of enolates produced under the catalytic conditions has been carried out using TMSCl. From ^{1}H NMR experiment The ratio of *E*:Z silyl enol ethers formed was found to be 1:1 (Scheme 75). Hence, an initial unselective aldol addition is believed to occur. This is then followed by a rapid cyclisation of the *syn*-aldol adduct to give the *trans*-cyclic carbonate. Cyclisation of the *anti*-aldol intermediate (which would provide the *cis*-carbonate) is slow and preferentially reverts to starting materials (Scheme 76). This has been shown experimentally by preparative isolation of the initial *anti*-aldol adduct (Section III 20) and resubjection to the reaction conditions. Isolation of the *syn*-aldol adduct was not possible due to the rapid cyclisation step. Isolated *cis* and *trans*-cyclic carbonates have also been resubjected to the reaction conditions and have shown no signs of epimerisation.

Scheme 75. Trapping of enolates with TMSCl.



159 (*Z*)-**275** (*E*)-**275**

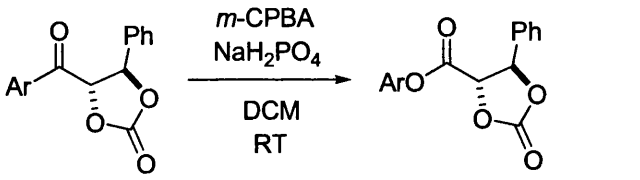
Scheme 76. Origin of diastereoselectivity.



II 4.10 Synthetic utility

α,β-Dihydroxylated ketones are established intermediates in organic synthesis and specifically for the above direct catalytic route comprise electron rich analogues. The inclusion of an aromatic ketone substituent allows the amenable synthesis of aryl esters. Baeyer-Villager oxidation of both phenyl and 2-naphthyl adducts was found to be straightforward when phosphate buffered *m*-CPBA was employed (Scheme 77).

Scheme 77. Baeyer-Villiger oxidations.



Ar = 2-Naphthyl **277**, 87%
Ar = Ph **276**, 67%

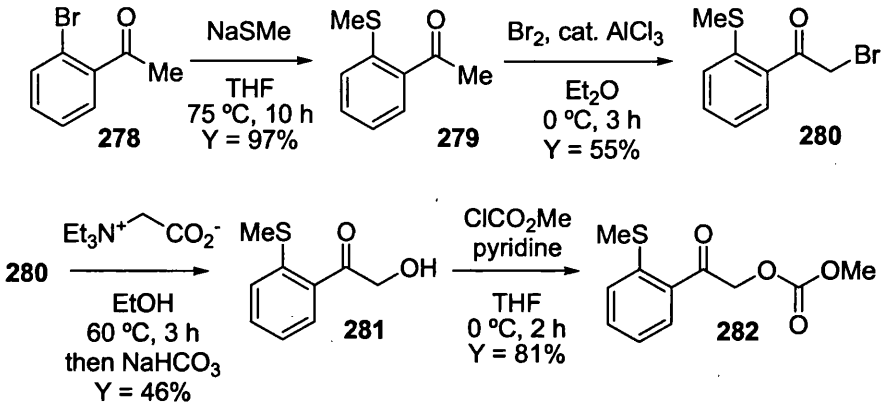
The oxidation of phenyl ketone *trans*-**263** produced the aryl ester *trans*-**276** as the major product and in reasonable yield (67%) although as an 8:1 mixture of regioisomers. 2-Naphthyl ketone *trans*-**269** delivered the corresponding aryl ester *trans*-**277** in high yield (87%) without the complication of regioisomer formation.

II 4.11 Enantioselective variant

The next stage of development was to examine the replacement of bipyridine with a chiral ligand. The need for a ligand to generate an active catalyst was encouraging for this part of the project and it was hoped a chiral ligand would allow for asymmetric induction. Although chiral bipyridines were not commercially available and the few synthetic routes already reported were lengthy, the success of pyridine (bis)oxazolines in the *iso*thiocyanate additions reported earlier was deemed a good starting point.[132,133,134] As well as the phenyl ketone **259** a two-point binding substrate was also considered in this investigation. This would allow a more rigid, structurally defined enolate, which may be required to furnish a more efficient asymmetric process. An *o*-SMe moiety on the phenyl ketone was selected to provide the bidentate binding in the enolate and the synthesis of such a substrate is demonstrated in scheme 78. The α-carbonate **282** was reached through the same chemistry as in other α-carbonate preparations

once the *o*-SMe group had been incorporated (Section III 18). This was accomplished through direct displacement of 2′-bromoacetophenone **278** with NaSMe. Acetophenone **279** was then α-brominated with the addition of bromine and a catalytic amount of $AlCl_3$. The α-bromo species **280** was treated with betaine followed by basic work-up to give α-hydroxy ketone **281** and finally reacted with methyl chloroformate to furnish the corresponding α-carbonate **282** in 81% yield.

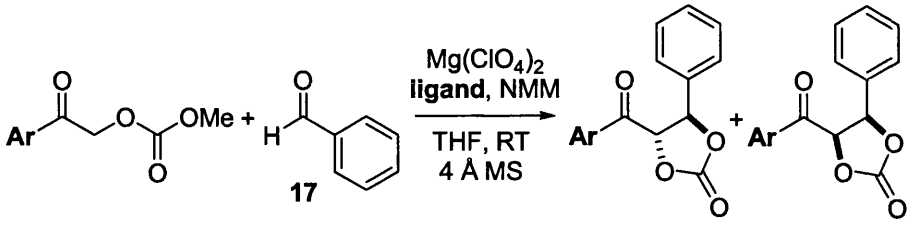
Scheme 78. Preparation of bidentate α-carbonate.



With this new starting material in hand, the asymmetric catalysis was investigated. The *o*-SMe phenyl ketone **282** was first subjected to the original conditions employing $Mg(ClO_4)_2$ (20 mol%), bipyridine (20 mol%), NMM (50 mol%) in THF with 4Å MS at RT in order to gain insight into the reactivity of this species. An 8:1 mixture of diastereomers in favour of the *trans*-product was achieved and a yield of 75% of the *trans*-carbonate **283** was attained (Table 18, entry 2). The bipyridine ligand was then exchanged for (*R,R*)-PhPyBOx **181** and experiments were conducted utilising bidentate carbonate **282** and the original methyl carbonate **259** (entries 3 and 4). Surprisingly the yields were very low (7% conversion in both cases) and *ee* values were not gathered. Another ligand (4*R*,5*R*)-4-Me-5-PhPyBOx **179** was also examined but this gave no improvement (entries 5 and 6). The solvent was changed to

DCM and the same results were obtained (entries 7 and 8). Finally another ligand type was tried and (4*R*,5*S*)-indBOx **152** gave the same levels of reaction in both carbonate cases (entries 9 and 10).

Table 18. Screening of chiral ligands.[a,e]



Entry	Ar	Ligand	Time (h)	*Syn*:*Anti*[b]	Yield **263**/ **283** (%)[c]
1	Ph	2,2'-bipy	24	10:1	91[f]
2	2-MeS-C_6H_4	2,2'-bipy	24	8:1	75[f,g]
3	Ph	(*R*,*R*)-PhPyBOx	24	-	7
4	2-MeS-C_6H_4	(*R*,*R*)-PhPyBOx	24	-	7
5	Ph	(4*R*,5*R*)-4-Me-5-PhPyBOx	24	-	6
6	2-MeS-C_6H_4	(4*R*,5*R*)-4-Me-5-PhPyBOx	24	-	6
7[d]	Ph	(*R*,*R*)-PhPyBOx	24	-	7
8[d]	2-MeS-C_6H_4	(*R*,*R*)-PhPyBOx	24	-	7
9	Ph	(4*R*,5*S*)-indBOx	24	-	8
10	2-MeS-C_6H_4	(4*R*,5*S*)-indBOx	24	-	7

[a] All reactions: carbonate (2.0 equiv.), aldehyde (1.0 equiv.), $Mg(ClO_4)_2$ (20 mol%), **ligand** (20 mol%), NMM (50 mol%), 4 Å MS (200 mg/mmol of carbonate).
[b] dr measured by ^1H NMR.
[c] Conversion measured by ^1H NMR.
[d] DCM used.
[e] ees were not recorded.
[f] Isolated yield. [g]of *trans*-carbonate only.

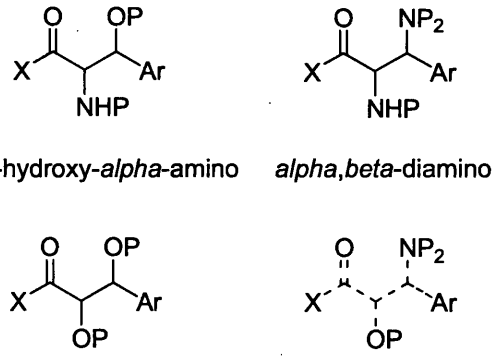
Unfortunately, time precluded a full screening of ligands including those having a bipyridine core in order to achieve a successful

enantioselective catalysis. From these initial results, it is clear that some ligand types have a dramatic effect on reactivity. Whether or not bulk is the major factor is a topic for further study.

II 4.12 β-Amino-α-hydroxy-ketones

As part of future work, it was envisaged that to complete the set of four amino/hydroxy analogues, the final β-amino-α-hydroxy carbonyl (highlighted in Figure 23) could be reached if tosylimines were employed in the α-carbonate addition. As with *iso*thiocyanatocarbamates, this was possible and the exchange of aldehyde for imine gave a reversal in the selectivity of the reaction products.

Figure 23. The four amino/hydroxy analogous set.

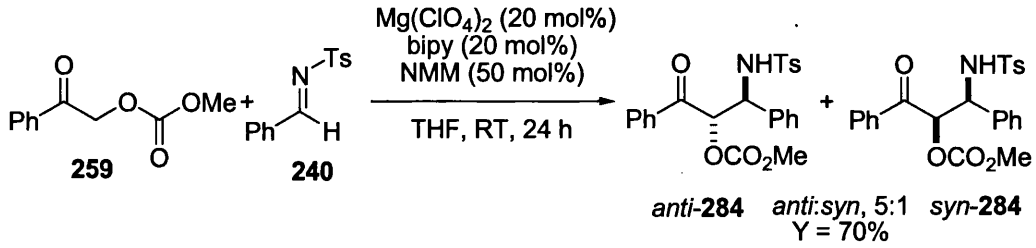


beta-hydroxy-*alpha*-amino *alpha*,*beta*-diamino

alpha,*beta*-dihydroxy *beta*-amino-*alpha*-hydroxy

Reaction of methyl carbonate **259** with tosylimine **240** delivered the Mannich adduct without cyclisation under the conditions of $Mg(ClO_4)_2$ (20 mol%), bipy (20 mol%), NMM (50 mol%) in THF and in the presence of 4 Å MS at RT (Scheme 79). As with the *iso*thiocyanatocarbamate-imine additions, *anti*-selectivity was observed.

Scheme 79. α-Carbonate Mannich reaction.

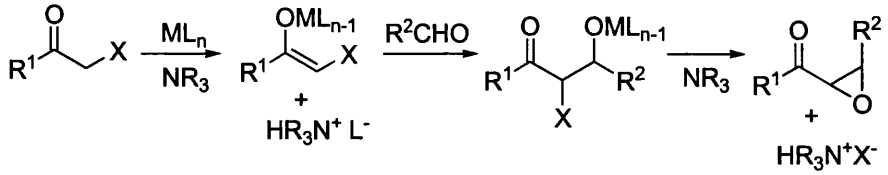


A respectable yield (70%) and diastereoselectivity in favour of the *anti*-aldol was achieved (5:1). The reversal of diastereoselectivity in this reaction as with the addition of *iso*thiocyanatocarbamates to tosylimines (Section II 3), compared to aldehydes, can again be explained in terms of steric hindrance of the much larger spatial occupancy of the *N*-tosyl group forfeiting a different orientation in the coordination of substrate to Lewis acid and eventual opposite diastereomeric outcome. The reason that no cyclisation had occurred can be assumed on steric grounds. Formation of a *cis*-cyclised product is unfavoured and is therefore a very slow step. Again, time constraints have precluded any further investigation of scope and optimisation of this reaction.

II 4.13 In search of a Darzens reaction

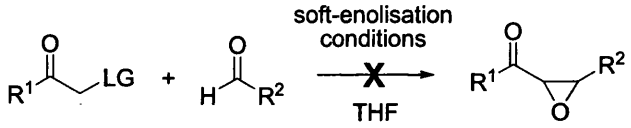
Much time has been spent preparing substrates for a catalytic Darzens variant of the previously described reactions (Section III 23). In the Darzens process as illustrated in scheme 80, it is necessary to have a stoichiometric amount of amine base and for this process, the difference in pK_a between the substrate and product is expected to be large enough to prohibit product epimerisation.

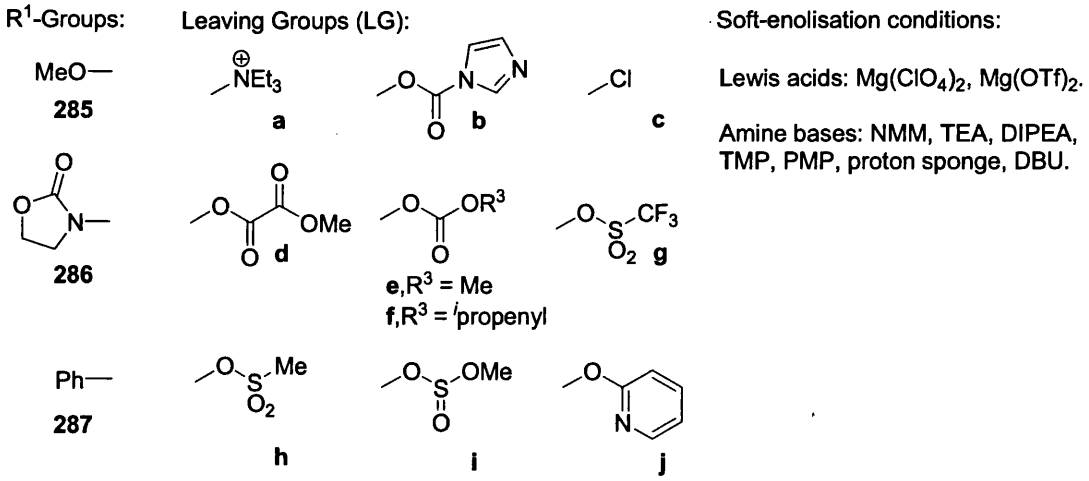
Scheme 80. Potential catalytic Darzens reaction.



A large number of α-substituted substrates were prepared in order to screen for a possible Darzens closure (Scheme 81). Up until now, only 5-*exo*-trig ring closures were observed. In order for a Darzens reaction to proceed, a 3-*exo*-tet ring closure would need to occur.

Scheme 81. Substrate variation for the Darzens reaction.





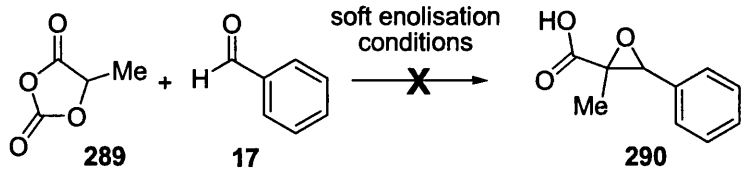
Unfortunately, no combination of substrate employed with aryl aldehydes delivered epoxide products under various Lewis acid and amine base conditions. Certain substrates did bring about reaction with benzaldehydes, acting in a 5-*exo*-trig fashion, as in α-methyl carbonate **259** described previously (Section II 4) and the *O*-imidazoyl substrate **287b**, delivering cyclic carbonate species. Oxazolidinone **286f** and methyl ester

285e analogues of such α-substituents did not achieve reaction – the pK_a of α-protons is believed to be too low in these examples. α-Triflate **287g** reacted with amine bases such as TEA to form a quaternary nitrogen salt whereas bulkier amines such as DBU gave no reaction. The quaternary nitrogen salts formed in these reactions were also investigated, in hope that *via* an *N*-ylide the catalysis would proceed. Under solvating conditions (THF was replaced with acetonitrile), these substrates again failed to show reactivity. α-Chloro phenyl ketone **287c** provided limited conversion to initial aldol adducts even at stoichiometric levels of Lewis acid (Section III 24). All other substrates including α-mesylate **287h**, and α-oxalate **286d** and **287d** gave no reaction, which is surprising considering some of these examples have attenuated α-proton acidity.

In the case of phenacyl methyl oxalate **287d**, it was believed that the responsible factor for lack of reactivity lied in the oxalate moiety. The oxalate portion could act as a bidentate ligand to the Lewis acid rendering the metal centre inactive. It was envisaged that incorporation of an *o*-SMe group in the phenyl ring would allow a stronger binding site at the necessary carbonyl for the catalysis to proceed. Unfortunately, the prepared substrate **288** (Section III 23) again showed no reactivity.

An interesting last example examined for this reaction was that of cyclic anhydride **289**, which would hopefully lead to the generation of glycidic acids under soft enolisation conditions (Scheme 82). Again, this substrate failed to give the desired products and was found to be unstable under the reaction conditions.

Scheme 82. Plausible glycidic acid synthesis.



II 4.14 Conclusion

The α,β-dihydroxy unit is an important class of functionality to the organic chemist. There are numerous examples of this motif in biologically active synthetic targets and their synthesis is attractive. Protected α,β-dihydroxy ketones have been accessed through the development of a direct catalytic aldol route, combining strategies of soft enolisation and post aldol cyclisation, to prohibit product epimerisation and allow turnover of the catalytic species. The optimised catalyst components comprise of $Mg(ClO_4)_2$, bipyridine, *N*-methylmorpholine and 4 Å MS and all are commercially available. A wide range of aromatic aldehydes can be employed in the catalysis and excellent yields and high levels of diastereoselectivity have been achieved. The origins of the high diastereoselectivity have been investigated and evidence points to an initial unselective enolate formation. The selectivity results from a slow *anti*-aldol cyclisation step and relatively fast *syn*-aldol cyclisation step. The products of the reaction have been further utilised synthetically and the synthesis of ester analogues has been successfully demonstrated. The extension of this system to an enantioselective synthesis of α,β-dihydroxy ketones has been examined albeit with no success although much work needs to be done evaluating ligands further. Synthesis of protected α-hydroxy-β-amino compounds has been accomplished through the same catalysis which concludes the set of four amino/hydroxy analogous targets: β-hydroxy-α-amino, α,β-diamino, α-

hydroxy-β-amino, and α,β-dihydroxy moieties. To this end, an investigation of a Darzens type reaction under catalytic soft enolisation conditions has been conducted but no successful substrates and conditions could be found.

III Experimental

III 1 General information

All reactions were performed under an inert atmosphere of nitrogen, in oven or flame dried glassware unless otherwise stated. Nitrogen was passed through a Drierite®-filled drying-tube before use.

The solvents used in the reactions were distilled prior to use from the relevant drying agent. Toluene, *n*-hexane, diethyl ether and THF were distilled from sodium metal. DCM, chloroform, and acetonitrile were distilled from calcium hydride. Light petroleum refers to petroleum spirit (bp 40-60 °C).

Analytical thin layer chromatography was carried out using precoated aluminium-backed silica plates (Merck Kieselgel $60F_{254}$). Plates were visualised under ultraviolet light (254 nm) or by staining with $KMnO_4$. Flash column chromatography was carried out using Merck Kieselgel 60H silica. Pressure was applied at the column head *via* hand bellows.

Melting points were determined using a Büchi 535 melting point apparatus and are reported uncorrected. Infrared measurements were carried out as liquid films on NaCl discs or as a KBr disc using a Perkin-Elmer 1600 series FTIR spectrometer with internal calibration in the range 4000-500 cm^{-1}. Mass spectrometry was carried out on a Micromass Quattro II and Finnegan MAT 95XP by the EPSRC mass spectrometry service at the University of Wales, Swansea. Elemental analysis was performed on an Exeter Analytical CE440 Elemental Analyser at the University of Bath.

^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance experiments were carried out using a Bruker AC-300 MHz or AC-400 MHz NMR spectrometer. Chemical shifts were reported in parts per million from tetramethylsilane for

^{1}H and ^{13}C experiments. The residual solvent peak was used as an internal standard. The multiplicities of the spectra are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Sometimes apparent multiplicities (app.) were observed. Coupling constants (*J*) are given in Hz.

Optical rotations were performed on an Optical Activity LTD: AA-10 automatic polarimeter.

Analytical high performance liquid chromatography was carried out using Thermo Separation Products (TSP) spectra SERIES P200, using the Chiralcel® OD00CE-IJ033 column. The loading loop was 20 μL. The eluant employed was an isocratic mixture of *n*-hexane and IPA (80:20 respectively) at a flow of 1 $mL.min^{-1}$. A TSP spectra SERIES UV100 detector was fitted to the outlet of the column and indicated the absorption at 254 nm, r = 0.0005. Retention times are reported in minutes. The enantiomeric excess was calculated from the integration of the absorption peaks at 254 nm.

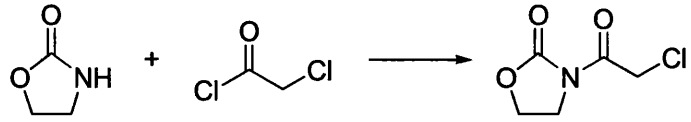
All chemicals were purchased from Acros, Aldrich, Alfa Aesar or Strem chemical companies and were used after distillation for liquids but without further purification for solids.

2,6-Bis-[(4′*R*)-4′-phenyloxazolin-2′-yl]-pyridine **181**,[135] 4,6-dibenzofurandiyl-2,2′-bis[4-(*R*)-phenyl-1,3-oxazoline] **175**,[136] pyridine-2,6-dicarboxylic acid bis-[(2-hydroxy-ethyl)-amide] **194**,[109] 4-benzyl-3-(2-*iso*thiocyanatoacetyl)oxazolidin-2-one **193**,[106] *N*-tosylbenzaldimines,[137] *N*-tosyl-2-naphthaldimine **309**,[137] (furan-2-yl)-*N*-tosylmethanimine **322**,[138] (thiophen-2-yl)-*N*-tosylmethanimine **324**,[139] cyclohexyl-*N*-tosylmethanimine **314**,[140] *N*-tosylhexan-1-imine **315**,[140] (*E*)-3-phenyl-*N*-tosylprop-2-en-1-imine **313**,[137] 2-hydroxy-1-(naphthalen-2-yl)ethanone **327**,[141] 2-bromo-1-(2′-(methylthio)phenyl)ethanone **280**,[142] 5-methyl-[1,3]dioxolane-2,4-dione **289**,[143] trifluoromethanesulfonic acid 2-oxo-2-phenyl-ethyl ester **287g**,[144] methanesulfonic acid 2-oxo-2-phenyl-ethyl ester **287h**,[137] and 1-phenyl-2-

(pyridin-2-yloxy)ethanone **287j**[145] were prepared as described in the literature.

III 2 Preparation of 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154

Preparation of 3-(2-chloroacetyl)-oxazolidin-2-one 169



167 **168** **169**

A solution of *n*-BuLi (2.5 M in *n*-hexane, 8.00 mL, 20.0 mmol) was added drop-wise to a solution of oxazolidine-2-one **167** (1.74 g, 20.0 mmol) in dry THF (300 mL) at -78 °C and the reaction was stirred for an additional 15 min. The temperature was allowed to reach RT for 2.5 h and then the mixture was cooled to -78 °C for 15 min. Chloroacetyl chloride **168** (1.75 mL, 22.0 mmol) was added slowly to the reaction mixture. After 15 min, the light yellow solution was warmed to RT for a further 30 min. The reaction was quenched with saturated aqueous ammonium chloride solution (10 mL). The mixture was concentrated under reduced pressure, taken up in water (10 mL) and extracted with DCM (3 × 40 mL). The organic portions were dried ($MgSO_4$) and concentrated under reduced pressure. The *chlorocarbamate* **169** (3.14 g, 96%) was obtained as a white solid. An analytical sample was prepared by recrystallisation from DCM; mp 61 °C (DCM); R_f(SiO_2, DCM) 0.19; ν_{max}(KBr)/cm^{-1} 2966 (CH), 2928 (CH), 1782 (C=O), 1720 (C=O); δ_H(400 MHz; $CDCl_3$) 4.74 (2H, s, CH_2Cl), 4.51 (2H, t, J = 8.0, OCH_2), 4.09 (2H, t, J = 8.0,

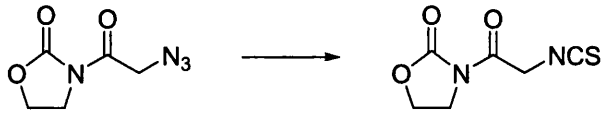
NCH_2); δ_C(100 MHz; $CDCl_3$) 165.7, 152.9, 62.7, 43.3, 42.5; HRMS (ES+): $C_5H_6{}^{35}ClNO_3$, M^+ requires 163.0036. Found 163.0038.

Preparation of 3-(2-azidoacetyl)-oxazolidin-2-one 170

169 **170**

A solution of sodium azide (6.50 g, 100 mmol) in water (20 mL) was added to a solution of *chlorocarbamate* **169** (3.14 g, 19.2 mmol) in DCM (20 mL). The biphasic system was stirred vigorously and tetrabutylammonium hydrogen sulfate (0.68 g, 2.00 mmol) was added. After 1.5 h at RT, the organic layer was separated and concentrated under reduced pressure. The residue was filtered through silica using DCM as the mobile phase. After concentration, the *azidocarbamate* **170** (2.70 g, 83%) was obtained as a colourless oil; R_f(SiO_2, DCM) 0.18; ν_{max}(neat)/cm^{-1} 2926 (CH), 2210 (N_3), 1786 (C=O), 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 4.52 (2H, t, J = 8.1, OCH_2), 4.51 (2H, s, CH_2N_3), 4.09 (2H, t, J = 8.1, NCH_2); δ_C(100 MHz; $CDCl_3$) 167.5, 153.0, 62.9, 52.3, 42.1.

Preparation of 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154

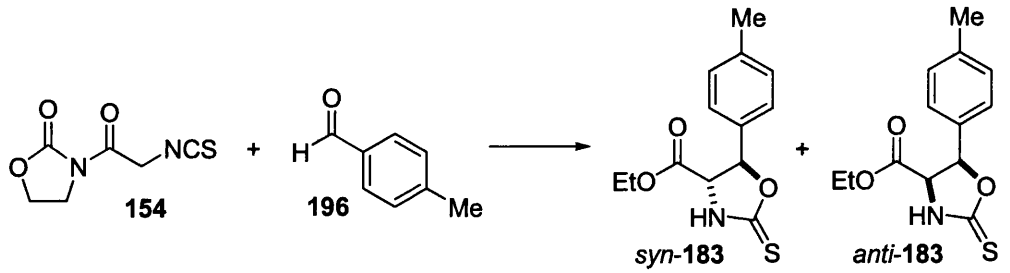


170 **154**

Triphenylphosphine (3.32 g, 12.7 mmol) was added to a solution of the *azidocarbamate* **170** (1.96 g, 11.5 mmol) in CS_2 (15 mL) and THF (15 mL) in a 500 mL round bottom flask fitted with a condenser. After evolution of nitrogen, the solution gently self-refluxed and was left overnight. After

concentration under reduced pressure, the residue was purified by flash chromatography (SiO_2, DCM) to yield the *isothiocyanate* **154** (1.49 g, 69%), as a white solid which was recrystallised from DCM-*n*-hexane; mp 99 °C (DCM-*n*-hexane); R_f(SiO_2, DCM) 0.26; ν_{max}(KBr)/cm^{-1} 2928 (CH), 2064 (NCS), 1786 (C=O), 1721 (C=O); δ_H(400 MHz; $CDCl_3$) 4.85 (2H, s, CH_2NCS), 4.54 (2H, t, J = 8.1, OCH_2), 4.11 (2H, t, J = 8.1, NCH_2); δ_C(100 MHz; $CDCl_3$) 165.7, 153.4, 140.0, 63.6, 49.6, 42.8; HRMS (ES+): $C_6H_6N_2O_3S$, M^+ requires 186.0099. Found 186.0099.

III 3 Preparation of (4*S**,5*R**)-2-thioxo-5-*p*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *syn*-183 and (4*R**,5*R**)-2-thioxo-5-*p*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *anti*-183; to serve as a typical experimental procedure for the racemic preparation of derivatised adducts of aromatic aldehydes and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154

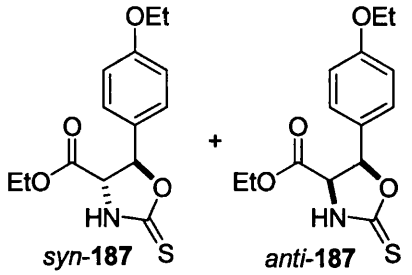


A mixture of $Mg(ClO_4)_2$ (15 mg, 0.07 mmol), 2,2′-bipyridine (12 mg, 0.08 mmol) and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one **154** (128 mg, 0.69 mmol) was stirred in dry THF (15 mL) with activated powdered 4 Å MS (200 mg) under nitrogen at 0 °C. After 15 min, *p*-tolualdehyde **196** (90 μL, 0.76 mmol) and triethylamine (20 μL, 0.14 mmol) were added and the mixture was stirred for a further 3 h. The reaction was quenched with saturated

aqueous ammonium chloride (5 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in dry THF (15 mL) and cooled to 0 °C. A solution of methyl magnesium bromide (3 M in diethyl ether, 0.30 mL, 0.89 mmol) was added to ethanol (3.3 mL) at 0 °C and subsequently added to the previous solution *via* cannula transfer. After 3 min. the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (5 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1 M, 10 mL) and DCM (10 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide the title compounds, in order of elution, *oxazolidinethione syn*-**183** (140 mg, 75%), as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.43; ν_{max}(neat)/cm^{-1} 3176 (NH), 2983 (CH), 1736 (C=O), 1491 (NHC=S), 1162 (CO), 1095 (CO); δ_H(300 MHz; $CDCl_3$) 7.83 (1H, s, NH), 7.22-7.31 (4H, m, ArH), 5.93 (1H, d, J = 6.0, ArCH), 4.47 (1H, d, J = 6.0, EtO(C=O)CH), 4.25-4.40 (2H, m, CH_2CH_3), 2.38 (3H, s, $ArCH_3$), 1.35 (3H, t, J = 7.2, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 188.5, 167.5, 139.2, 133.3, 129.3, 125.2, 85.3, 64.1, 62.5, 20.8, 13.6; HRMS (ES+): $C_{13}H_{16}NO_3S$, $[M+H]^+$ requires 266.0845. Found 266.0842. $C_{13}H_{15}NO_3S$ requires C, 58.9; H, 5.70; N, 5.28%. Found C, 59.0; H, 5.63; N, 5.09%; and *oxazolidinethione anti*-**183** (19 mg, 12%), as a white solid; mp 137 °C (DCM:EtOAc, 98:2); R_f(SiO_2, DCM:EtOAc, 98:2) 0.22; ν_{max}(KBr)/cm^{-1} 3253 (NH), 2922 (CH), 1738 (C=O), 1472 (NHC=S), 1163 (CO), 1087 (CO); δ_H(300 MHz; $CDCl_3$) 7.18-7.22 (5H, m, ArH & NH), 6.05 (1H, d, J = 9.9, ArCH), 4.87 (1H, d, J = 9.9, EtO(C=O)CH), 3.67-3.86 (2H, m, CH_2CH_3), 2.35 (3H, s, $ArCH_3$), 0.85 (3H, t, J = 7.2, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.6, 166.5,

139.3, 129.7, 128.7, 126.1, 84.9, 62.2, 61.6, 20.8, 13.0; HRMS (ES+): $C_{13}H_{16}NO_3S$, $[M+H]^+$ requires 266.0845. Found 266.0844.

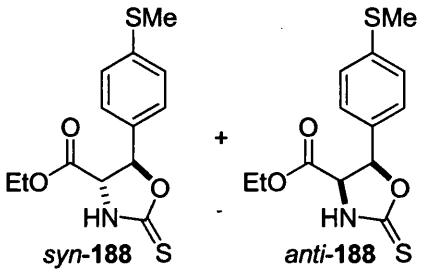
Preparation of (4*S,5*R**)-5-(4-ethoxy-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-187 and (4*R**,5*R**)-5-(4-ethoxy-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-187**



The reaction was carried out according to the experimental procedure above (Section III 3) with 4-ethoxybenzaldehyde **291** (106 μL, 0.76 mmol) and provided, in order of elution, *oxazolidinethione syn*-**187** (145 mg, 72%), as a pale yellow solid; mp 66 °C (DCM:EtOAc, 98:2) R_f(SiO_2, DCM:EtOAc, 98:2) 0.28; ν_{max}(KBr)/cm^{-1} 3313 (NH), 2985 (CH), 1731 (C=O), 1469 (NHC=S), 1155 (CO), 1020 (CO); δ_H(300 MHz; $CDCl_3$) 7.65 (1H, s, NH), 7.32 (2H, d, *J* = 9.0, ArH), 6.93 (2H, d, *J* = 9.0, ArH), 5.90 (1H, d, *J* = 6.2, ArCH), 4.48 (1H, d, *J* = 6.0, EtO(C=O)CH), 4.25-4.40 (2H, m, (C=O)OC*H*$_2$CH$_3$), 4.05 (2H, q, *J* = 6.9, OC*H*$_2$CH$_3$), 1.43 (3H, t, *J* = 6.9, OCH$_2$C*H*$_3$), 1.34 (3H, t, *J* = 7.2, (C=O)OCH$_2$C*H*$_3$); δ_C(100 MHz; $CDCl_3$) 189.0, 168.0, 160.0, 128.4, 127.5, 115.0, 86.9, 64.5, 63.6, 62.9, 14.7, 14.1; HRMS (ES+): $C_{14}H_{18}NO_4S$, $[M+H]^+$ requires 296.0951. Found 296.0956; and *oxazolidinethione anti*-**187** (15 mg, 8%), as a white solid; mp 100 °C (DCM:EtOAc, 98:2); R_f(SiO_2, DCM:EtOAc, 98:2) 0.17; ν_{max}(KBr)/cm^{-1} 3168 (NH), 2977 (CH), 1730 (C=O), 1515 (NHC=S), 1161 (CO), 1085 (CO); δ_H(300 MHz; $CDCl_3$) 7.48 (1H, s, NH), 7.22 (2H, d, *J* = 9.0, ArH), 6.86 (2H, d, *J* = 9.0, ArH), 6.03 (1H, d, *J* = 9.8, ArCH), 4.87 (1H, d, *J* = 9.8, EtO(C=O)CH), 4.01 (2H, q, *J* = 7.2, OC*H*$_2$CH$_3$), 3.65-3.90 (2H, m, (C=O)OC*H*$_2$CH$_3$), 1.40 (3H, t, *J* = 6.9, OCH$_2$C*H*$_3$), 0.88 (3H, t, *J* = 7.2,

(C=O)OCH$_2$C*H*$_3$); *δ*c(100 MHz; CDCl$_3$) 190.0, 167.1, 160.0, 128.2, 125.1, 114.5, 85.3, 63.6, 62.7, 62.2, 14.7, 13.6; *m/z* (EI+) 295 (37%, M$^+$); HRMS (ES+): $C_{14}H_{18}NO_4S$, $[M+H]^+$ requires 296.0951. Found 296.0955.

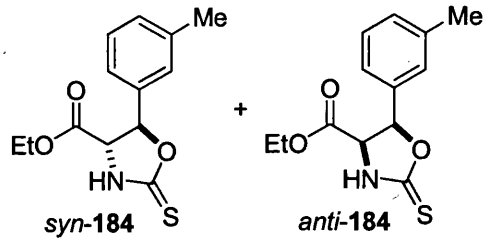
Preparation of (4*S,5*R**)-5-(4-methylsulfanyl-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-188 and (4*R**,5*R**)-5-(4-methylsulfanyl-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-188**



The reaction was carried out according to the experimental procedure above (Section III 3) with 4-(methylthio)benzaldehyde **292** (101 μL, 0.76 mmol) and provided, in order of elution, *oxazolidinethione syn*-**188** (100 mg, 49%), as a yellow solid; mp 75 °C (DCM:EtOAc, 98:2) R_f(SiO$_2$, DCM:EtOAc, 98:2) 0.33; ν_{max}(KBr)/cm^{-1} 3299 (NH), 2980 (CH), 1736 (C=O), 1489 (NHC=S), 1169 (CO), 1088 (CO); δ_H(300 MHz; CDCl$_3$) 7.56 (1H, s, NH), 7.27-7.35 (4H, m, ArH), 5.92 (1H, d, *J* = 6.3, ArCH), 4.45 (1H, d, *J* = 6.3, EtO(C=O)CH), 4.25-4.40 (2H, m, C*H*$_2$CH$_3$), 2.50 (3H, s, SCH$_3$), 1.35 (3H, t, *J* = 7.2, CH$_2$C*H*$_3$); *δ*c(100 MHz; CDCl$_3$) 188.4, 167.3, 140.4, 132.7, 126.2, 125.7, 85.0, 64.0, 62.5, 15.0, 13.6; *m/z* (EI+) 297 (57%, M$^+$), 151 (51%, C_8H_7OS); HRMS (ES+): $C_{13}H_{16}NO_3S_2$, $[M+H]^+$ requires 298.0566. Found 298.0564. $C_{13}H_{15}NO_3S_2$ requires C, 52.5; H, 5.08; N, 4.71%. Found C, 52.1; H, 5.07; N, 4.78%; and *oxazolidinethione anti*-**188** (11 mg, 5%), as a white solid; mp 132 °C (DCM:EtOAc, 98:2); R_f(SiO$_2$, DCM:EtOAc, 98:2) 0.18; ν_{max}(KBr)/cm^{-1} 3151 (NH), 2982 (CH), 1739 (C=O), 1475 (NHC=S), 1172 (CO), 1093 (CO); δ_H(300 MHz; CDCl$_3$) 7.23 (4H, m, ArH), 7.19 (1H, s, NH), 6.04 (1H, d, *J* = 9.8, ArCH), 4.88 (1H, d, *J* = 9.8, EtO(C=O)CH), 3.70-3.90 (2H, m,

CH_2CH_3), 2.48 (3H, s, SCH_3), 0.88 (3H, t, J = 7.2, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.4, 166.4, 140.6, 129.2, 126.6, 125.5, 84.5, 62.1, 61.7, 29.2, 14.9, 13.1; HRMS (ES+): $C_{13}H_{16}NO_3S_2$, $[M+H]^+$ requires 298.0566. Found 298.0569.

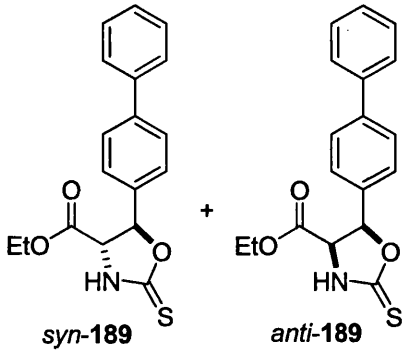
Preparation of (4*S,5*R**)-2-thioxo-5-*m*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *syn*-184 and (4*R**,5*R**)-2-thioxo-5-*m*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *anti*-184**



The reaction was carried out according to the experimental procedure above (Section III 3) with *m*-tolualdehyde **293** (90 μL, 0.76 mmol) and provided, in order of elution, *oxazolidinethione syn*-**184** (115 mg, 63%), as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.45; ν_{max}(neat)/cm^{-1} 3182 (NH), 2982 (CH), 1736 (C=O), 1488 (NHC=S), 1168 (CO), 1094 (CO); δ_H(300 MHz; $CDCl_3$) 7.39 (1H, s, NH), 7.18-7.35 (4H, m, ArH), 5.94 (1H, d, J = 6.0, ArCH), 4.46 (1H, d, J = 6.0, EtO(C=O)CH), 4.25-4.40 (2H, m, CH_2CH_3), 2.38 (3H, s, $ArCH_3$), 1.35 (3H, t, J = 7.2, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 188.5, 167.5, 138.6, 136.3, 129.8, 128.6, 125.7, 122.3, 85.3, 64.1, 62.5, 20.9, 13.6; HRMS (ES+): $C_{13}H_{16}NO_3S$, $[M+H]^+$ requires 266.0845. Found 266.0847; $C_{13}H_{15}NO_3S$ requires C, 58.8; H, 5.70; N, 5.28%. Found C, 58.8; H, 5.71; N, 5.41% and *oxazolidinethione anti*-**184** (23 mg, 13%), as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.29; ν_{max}(neat)/cm^{-1} 3147 (NH), 2983 (CH), 1741 (C=O), 1491 (NHC=S), 1163 (CO), 1092 (CO); δ_H(300 MHz; $CDCl_3$) 7.72 (1H, s, NH), 7.10-7.30 (4H, m, ArH), 6.05 (1H, d, J = 9.8, ArCH), 4.90 (1H, d, J = 9.8, EtO(C=O)CH), 3.65-3.85 (2H, m, CH_2CH_3), 2.34 (3H, s, $ArCH_3$), 0.83 (3H, t, J = 7.2, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 190.1, 167.2,

138.4, 133.1, 130.4, 128.5, 127.2, 123.9, 85.4, 62.8, 62.1, 21.3, 13.4; HRMS (ES+): $C_{13}H_{16}NO_3S$, $[M+H]^+$ requires 266.0845. Found 266.0846.

Preparation of (4*S,5*R**)-5-biphenyl-4-yl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-189 and (4*R**,5*R**)-5-biphenyl-4-yl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-189**

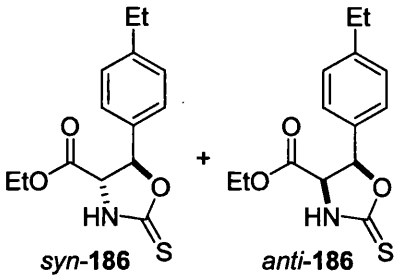


syn-**189** *anti*-**189**

The reaction was carried out according to the experimental procedure above (Section III 3) with biphenyl-4-carboxaldehyde **294** (138 mg, 0.76 mmol) and provided, in order of elution, *oxazolidinethione syn*-**189** (118 mg, 52%), as a pale yellow solid; mp 145 °C (DCM:EtOAc, 98:2) R_f(SiO_2, DCM:EtOAc, 98:2) 0.37; ν_{max}(KBr)/cm^{-1} 3252 (NH), 2978 (CH), 1738 (C=O), 1485 (NHC=S), 1161 (CO), 1087 (CO); δ_H(300 MHz; $CDCl_3$) 7.75 (1H, s, NH), 7.65 (2H, m, ArH), 7.58 (2H, m, ArH), 7.37-7.50 (5H, m, ArH), 6.02 (1H, d, J = 6.2, ArCH), 4.53 (1H, d, J = 6.2, EtO(C=O)CH), 4.30-4.40 (2H, m, CH_2CH_3), 1.37 (3H, t, J = 7.2, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 188.5, 167.5, 142.1, 139.6, 135.2, 128.4, 127.4, 127.3, 126.7, 125.7, 85.0, 64.1, 62.6, 13.7; HRMS (ES+): $C_{18}H_{18}NO_3S$, $[M+H]^+$ requires 328.1002. Found 328.0998. $C_{18}H_{17}NO_3S$ requires C, 66.0; H, 5.23; N, 4.28%. Found C, 65.7; H, 5.14; N, 4.47%; and *oxazolidinethione anti*-**189** (32 mg, 14%), as a white solid; mp 183 °C (DCM:EtOAc, 98:2); R_f(SiO_2, DCM:EtOAc, 98:2) 0.21; ν_{max}(KBr)/cm^{-1} 3154 (NH), 2985 (CH), 1735 (C=O), 1486 (NHC=S), 1172 (CO), 1083 (CO); δ_H(300 MHz; $CDCl_3$) 7.55-7.62 (4H, m, ArH), 7.38-7.45 (5H, m, ArH), 7.16 (1H, s, NH), 6.13 (1H, d, J = 9.5, ArCH), 4.92 (1H, d, J = 9.5,

EtO(C=O)CH), 3.70-3.90 (2H, m, CH_2CH_3), 0.83 (3H, t, J = 7.2, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.6, 166.5, 142.2, 139.6, 131.6, 128.4, 127.4, 126.8, 126.7, 126.6, 84.6, 62.2, 61.7, 13.0; HRMS (ES+): $C_{18}H_{18}NO_3S$, $[M+H]^+$ requires 328.1002. Found 328.1005.

Preparation of (4*S,5*R**)-5-(4-ethyl-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-186 and (4*R**,5*R**)-5-(4-ethyl-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-186**

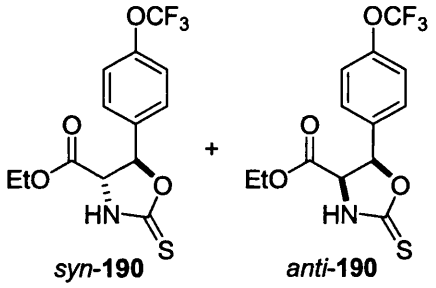


syn-**186** *anti*-**186**

The reaction was carried out according to the experimental procedure above (Section III 3) with 4-ethylbenzaldehyde **295** (104 μL, 0.76 mmol) and provided, in order of elution, *oxazolidinethione syn*-**186** (155 mg, 80%), as a white solid; mp 74 °C (DCM:EtOAc, 98:2) R_f(SiO_2, DCM:EtOAc, 98:2) 0.39; ν_{max}(KBr)/cm^{-1} 3315 (NH), 2967 (CH), 1739 (C=O), 1492 (NHC=S), 1214 (CO), 1165 (CO); δ_H(300 MHz; $CDCl_3$) 7.46 (1H, s, NH), 7.32 (2H, d, J = 8.4, ArH), 7.26 (2H, d, J = 8.4, ArH), 5.94 (1H, d, J = 6.0, ArCH), 4.47 (1H, d, J = 6.0, EtO(C=O)CH), 4.25-4.40 (2H, m, (C=O)OCH_2CH_3), 2.67 (2H, q, J = 7.8, CH_2CH_3), 1.35 (3H, t, J = 7.2, (C=O)OCH_2CH_3), 1.24 (3H, t, J = 7.8, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.0, 168.0, 146.0, 134.0, 128.7, 125.8, 85.8, 64.5, 63.0, 28.6, 15.5, 14.1; HRMS (ES+): $C_{14}H_{18}NO_3S$, $[M+H]^+$ requires 280.1002. Found 280.0999. $C_{14}H_{17}NO_3S$ requires C, 60.2; H, 6.13; N, 5.01%. Found C, 60.1; H, 6.20; N, 4.94%; and *oxazolidinethione anti*-**186** (10 mg, 5%), as a white solid; mp 120 °C (DCM:EtOAc, 98:2); R_f(SiO_2, DCM:EtOAc, 98:2) 0.23; ν_{max}(KBr)/cm^{-1} 3163 (NH), 2974 (CH), 1736 (C=O), 1486 (NHC=S), 1163 (CO), 1088 (CO);

δ_H(300 MHz; $CDCl_3$) 7.20-7.26 (4H, m, ArH), 7.08 (1H, s, NH), 6.05 (1H, d, J = 9.5, ArCH), 4.86 (1H, d, J = 9.5, EtO(C=O)CH), 3.67-3.83 (2H, m, (C=O)OC$H_2$$CH_3$), 2.64 (2H, q, J = 7.5, C$H_2$$CH_3$), 1.20 (3H, t, J = 7.5, CH_2CH_3), 0.81 (3H, t, J = 7.2, (C=O)OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 190.1, 167.0, 146.2, 130.5, 128.1, 126.7, 85.4, 62.6, 62.1, 28.7, 15.6, 13.4; HRMS (ES+): $C_{14}H_{18}NO_3S$, $[M+H]^+$ requires 280.1002. Found 280.0998.

Preparation of (4*S,5*R**)-2-thioxo-5-(4-trifluoromethoxy-phenyl)-oxazolidine-4-carboxylic acid ethyl ester *syn*-190 and (4*R**,5*R**)-2-thioxo-5-(4-trifluoromethoxy-phenyl)-oxazolidine-4-carboxylic acid ethyl ester *anti*-190**

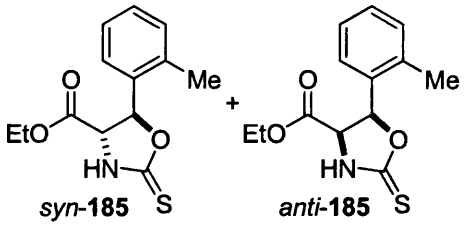


syn-**190** *anti*-**190**

The reaction was carried out according to the experimental procedure above (Section III 3) with 4-(trifluoromethoxy)benzaldehyde **296** (108 μL, 0.76 mmol) and provided, in order of elution, *oxazolidinethione syn*-**190** (128 mg, 56%), as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.37; ν_{max}(neat)/cm^{-1} 3183 (NH), 2986 (CH), 1740 (C=O), 1510 (NHC=S), 1371 (CF_3), 1210 (CO), 1152 (CO); δ_H(300 MHz; $CDCl_3$) 7.47 (2H, d, J = 8.1, ArH), 7.42 (1H, s, NH), 7.29 (2H, d, J = 8.1, ArH), 5.99 (1H, d, J = 6.3, ArCH), 4.44 (1H, d, J = 6.3, EtO(C=O)CH), 4.25-4.40 (2H, m, (C=O)OC$H_2$$CH_3$), 1.36 (3H, t, J = 7.2, (C=O)OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 188.7, 167.7, 150.0, 135.4, 127.3, 121.7, 120.4 (q, $^1J_{CF}$ = 258.5), 84.6, 64.5, 63.2, 14.1; HRMS (ES+): $C_{13}H_{13}F_3NO_4S$, $[M+H]^+$ requires 336.0512. Found 336.0509. $C_{13}H_{12}F_3NO_4S$ requires C, 46.6; H, 3.61; N, 4.18%. Found C, 46.3; H, 3.67; N, 4.11%; and *oxazolidinethione anti*-**190** (50 mg,

22%), as a white solid; mp 112 °C (DCM:EtOAc, 98:2); R_f(SiO_2, DCM:EtOAc, 98:2) 0.22; ν_{max}(KBr)/cm^{-1} 3158 (NH), 2995 (CH), 1736 (C=O), 1494 (NHC=S), 1380 (CF_3), 1152 (CO), 1082 (CO); δ_H(300 MHz; $CDCl_3$) 7.35-7.40 (3H, m, NH & ArH), 7.23-7.26 (2H, m, ArH), 6.10 (1H, d, J = 9.6, ArCH), 4.91 (1H, d, J = 9.6, EtO(C=O)CH), 3.72-3.82 (2H, m, (C=O)OC$H_2$$CH_3$), 0.83 (3H, t, J = 7.2, (C=O)OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.8, 166.8, 150.1, 132.0, 128.5, 121.2, 120.3 (q, $^1J_{CF}$ = 258.0), 84.2, 62.6, 62.4, 13.4; HRMS (ES+): $C_{13}H_{13}F_3NO_4S$, $[M+H]^+$ requires 336.0512. Found 316.0514.

Preparation of (4*S,5*R**)-2-thioxo-5-*o*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *syn*-185 and (4*R**,5*R**)-2-thioxo-5-*o*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *anti*-185**

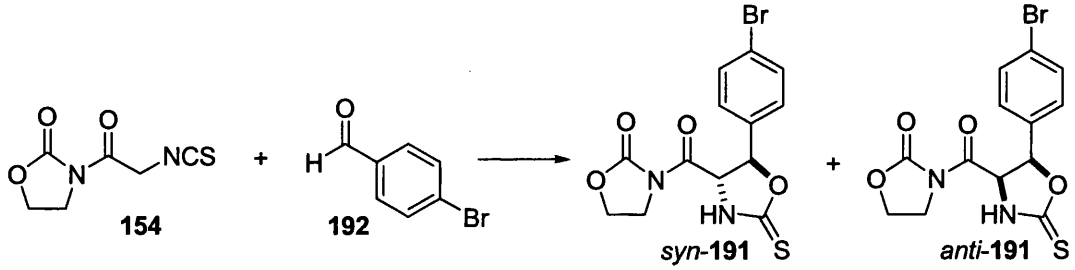


syn-**185** *anti*-**185**

The reaction was carried out according to the experimental procedure above (Section III 3) with *o*-tolualdehyde **297** (88 μL, 0.76 mmol) and provided, in order of elution, *oxazolidinethione syn*-**185** (92 mg, 50%), as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.23; ν_{max}(neat)/cm^{-1} 3184 (NH), 2985 (CH), 1740 (C=O), 1510 (NHC=S), 1210 (CO), 1152 (CO); δ_H(400 MHz; $CDCl_3$) 7.69 (1H, s, NH), 7.21-7.34 (4H, m, ArH), 6.23 (1H, d, J = 4.0, ArCH), 4.44 (1H, d, J = 4.0, EtO(C=O)CH), 4.25-4.40 (2H, m, (C=O)OC$H_2$$CH_3$), 2.42 (3H, s, Ar$CH_3$), 1.35 (3H, t, J = 8.0, (C=O)OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.2, 168.1, 135.1, 134.7, 131.2, 129.5, 126.9, 125.7, 83.5, 64.0, 63.0, 19.1, 14.1; HRMS (ES+): $C_{13}H_{16}NO_3S$, $[M+H]^+$ requires 266.0845. Found 266.0844; and *oxazolidinethione anti*-**185** (65 mg, 35%), as a white solid; R_f(SiO_2, DCM:EtOAc, 98:2) 0.14; ν_{max}(KBr)/cm^{-1} 3158 (NH), 2995 (CH), 1738 (C=O), 1495 (NHC=S), 1152 (CO), 1082 (CO);

δ_H(400 MHz; $CDCl_3$) 7.38 (1H, m, ArH), 7.17-7.27 (4H, m, NH & ArH), 6.31 (1H, d, J = 10.0, ArCH), 4.87 (1H, d, J = 10.0, EtO(C=O)CH), 3.58-3.66 (1H, m, (C=O)OC$H_A$$H_B$$CH_3$), 3.72-3.80 (1H, m, (C=O)OC$H_A$$H_B$$CH_3$), 2.36 (3H, s, $ArCH_3$), 0.79 (3H, t, J = 8.0, (C=O)OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 190.3, 167.2, 135.1, 131.5, 130.2, 129.4, 126.5, 125.9, 82.8, 62.2, 61.6, 19.2, 13.4; HRMS (ES+): $C_{13}H_{16}NO_3S$, $[M+H]^+$ requires 266.0845. Found 266.0839.

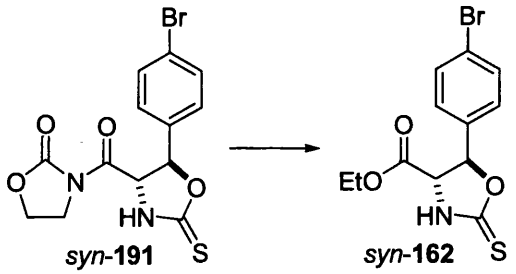
Preparation of 3-(4*S,5*R**)-[5-(4-bromo-phenyl)-2-thioxo-oxazolidine-4-carbonyl]-oxazolidin-2-one *syn*-191 and 3-(4*R**,5*R**)-[5-(4-bromo-phenyl)-2-thioxo-oxazolidine-4-carbonyl]-oxazolidin-2-one *anti*-191**



A mixture of $Mg(ClO_4)_2$ (120 mg, 0.54 mmol), 2,2′-bipyridine (85 mg, 0.54 mmol) and 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one **154** (1.00 g, 5.37 mmol) in dry THF (20 mL) was stirred for 15 min. under nitrogen at 0 °C. Triethylamine (150 μL, 1.07 mmol) was added and 5 min. later followed by 4-bromobenzaldehyde **192** (1.09 g, 5.91 mmol). After 3 h the reaction was deemed complete (TLC) and quenched with sat. aqueous ammonium chloride solution (20 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 40 mL). The organic portions were combined and washed with $CuSO_4$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 90:10) to provide, in order of elution, *oxazolidinethione syn*-**191** (840 mg, 42%), as white crystals; mp 177 °C (DCM-*n*-hexane); R_f(SiO_2, DCM:EtOAc, 98:2) 0.08; ν_{max}(KBr)/cm^{-1} 3309 (NH), 1792

(C=O), 1683 (C=O), 1485 (NHC=S), 1193 (CO); δ_H(300 MHz; DMSO) 10.53 (1H, s, NH), 7.66 (2H, d, J = 8.6, ArH), 7.33 (2H, d, J = 8.6, ArH), 6.08 (1H, d, J = 2.7, ArCH), 5.42 (1H, d, J = 2.7, N(C=O)CH), 4.46 (2H, t, OCH_2), 3.95 (2H, t, NCH_2); δ_C(75 MHz; DMSO) 189.4, 168.5, 154.1, 137.7, 132.0, 128.9, 122.6, 83.9, 63.8, 63.3, 43.0; HRMS (EI+): $C_{13}H_{11}{}^{79}BrN_2O_4S$, $[M]^+$ requires 369.9617. Found 369.9617. $C_{13}H_{11}BrN_2O_4S$ requires C, 42.0; H, 2.99; N, 7.55%. Found C, 41.9; H, 2.94; N, 7.46%; and *oxazolidinethione anti*-**191** (222 mg, 11%), as white crystals; mp 189 °C (DCM); R_f(SiO_2, DCM:EtOAc, 90:10) 0.06; ν_{max}(KBr)/cm^{-1} 3340 (NH), 2913 (CH), 1773 (C=O), 1674 (C=O), 1503 (NHC=S), 1174 (CO); δ_H(300 MHz; DMSO) 10.57 (1H, s, NH), 7.63 (2H, d, J = 8.3, ArH), 7.09 (2H, d, J = 8.3, ArH), 6.25 (1H, d, J = 10.1, ArCH), 5.87 (1H, d, J = 10.1, N(C=O)CH), 4.27 (1H, m, OCH_AH_B), 3.94 (1H, m, OCH_AH_B), 3.72 (1H, m, NCH_CH_D), 3.10 (1H, m, NCH_CH_D); δ_C(75 MHz; DMSO) 188.8, 167.3, 153.3, 133.9, 131.7, 129.4, 123.1, 83.4, 63.7, 62.8, 42.5; HRMS (EI+): $C_{13}H_{11}{}^{79}BrN_2O_4S$, $[M]^+$ requires 369.9617. Found 369.9617.

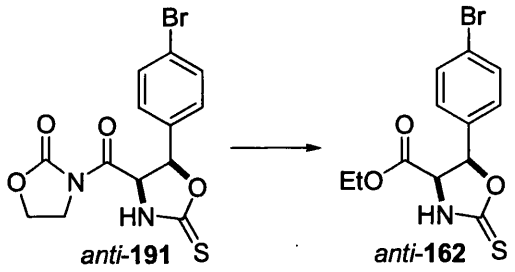
Preparation of (4*S,5*R**)-2-thioxo-5-(4-bromo-phenyl)-oxazolidine-4-carboxylic acid ethyl ester *syn*-162**



A solution of methyl magnesium bromide (3 M in ether, 0.15 mL, 0.39 mmol) was added to ethanol (2.5 mL) at 0 °C and subsequently added *via* cannula transfer to a suspension of the oxazolidinethione *syn*-**191** (130 mg, 0.35 mmol, *de* = 99%) dissolved in dry THF (7.5 mL) cooled to 0 °C. 3 min. later the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (7.5

mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1 M, 7.5 mL) and DCM (15 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide oxazolidinethione *syn*-**162** (92 mg, 80%, *de* = 99%) as white crystals; mp 112 °C (DCM-light petroleum (bp 40-60 °C)); R_f(SiO_2, DCM:EtOAc, 98:2) 0.23; ν_{max}(KBr)/cm^{-1} 3424 (NH), 2935 (CH), 1750 (C=O), 1596 (Ar), 1490 (NHC=S), 1174 (CO); δ_H(400 MHz; $CDCl_3$) 7.95 (1H, s, NH), 7.58-7.55 (2H, m, ArH), 7.31-7.26 (2H, m, ArH), 5.93 (1H, d, *J* = 6.2, ArCH), 4.43 (1H, d, *J* = 6.2, (C=O)CH), 4.39-4.27 (2H, m, CH_2), 1.35 (3H, t, *J* = 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 188.4, 167.5, 135.6, 132.2, 127.2, 123.6, 84.8, 64.5, 63.2, 14.2; HRMS (EI+): $C_{12}H_{12}{}^{79}BrNO_3S$, $[M]^+$ requires 328.9721. Found 328.9733; $C_{12}H_{12}BrNO_3S$ requires C, 43.7; H, 3.65; N, 4.2%. Found: C, 43.6; H, 3.6; N, 4.3%.

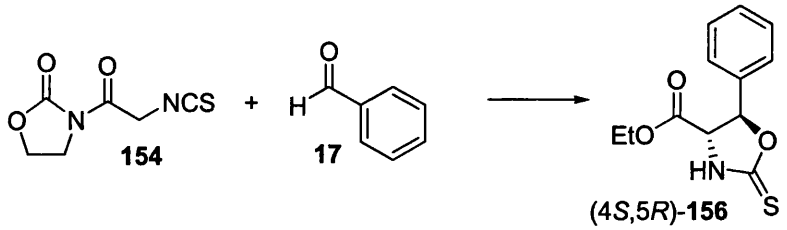
Preparation of (4*R,5*R**)-2-thioxo-5-(4-bromo-phenyl)-oxazolidine-4-carboxylic acid ethyl ester *anti*-162**



A solution of methyl magnesium bromide (3 M in ether, 0.11 mL, 0.29 mmol) was added to ethanol (1.9 mL) at 0 °C and subsequently added *via* cannula transfer to a suspension of the oxazolidinethione *anti*-**191** (98 mg, 0.26 mmol, *de* = 99%) dissolved in dry THF (5.5 mL) cooled to 0 °C. 3 min. later the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (5.5

mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1 M, 5.5 mL) and DCM (10 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide oxazolidinethione *anti*-**162** (67 mg, 78%, *de* = 99%) as white crystals; mp 122 °C (DCM-light petroleum (bp 40-60 °C)); R_f(SiO_2, DCM:EtOAc, 98:2) 0.11; ν_{max}(DCM, 0.05 M)/cm^{-1} 3424 (NH), 2935 (CH), 1749 (C=O), 1595 (Ar), 1492 (NHC=S); δ_H(400 MHz; $CDCl_3$) 7.58 (1H, s, NH), 7.53-7.50 (2H, m, ArH), 7.23-7.18 (2H, m, ArH), 6.04 (1H, d, *J* = 9.8, ArCH), 4.90 (1H, d, *J* = 9.8, (C=O)CH), 3.85 (1H, dq, *J* = 10.8, 7.2, CH_AH_B), 3.74 (1H, dq, *J* = 10.8, 7.2, CH_AH_B), 0.89 (3H, t, *J* = 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 189.8, 166.9, 132.4, 132.0, 128.6, 124.2, 84.7, 62.9, 62.7, 14.0; HRMS (ES+): $C_{12}H_{12}{}^{79}BrNO_3S$, $[M]^+$ requires 328.9721. Found 328.9707.

III 4 Asymmetric preparation of (4*S*,5*R*)-5-phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-156; to serve as a typical experimental procedure for the asymmetric preparation of derivatised adducts of aromatic aldehydes and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154



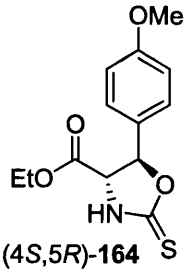
A mixture of $Mg(ClO_4)_2$ (15 mg, 0.07 mmol), 2,6-bis((*R*)-4,5-dihydro-4-phenyl-2-oxazolyl)pyridine **181** (28 mg, 0.08 mmol) and 3-(2-

*iso*thiocyanatoacetyl)-oxazolidin-2-one **154** (128 mg, 0.69 mmol) was stirred for 1 h in dry DCM (15 mL) with activated powdered 4 Å MS (200 mg) under nitrogen at RT. The temperature was then lowered to -78 °C. After 15 min, benzaldehyde **17** (77 μL, 0.76 mmol) and di*iso*propylethylamine (24 μL, 0.14 mmol) were added and the mixture was stirred for a further 24 h at -78 °C. The reaction was quenched with saturated aqueous ammonium chloride (5 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in dry THF (15 mL) and cooled to 0 °C. A solution of methyl magnesium bromide (3 M in diethyl ether, 0.30 mL, 0.89 mmol) was added to ethanol (3.3 mL) at 0 °C and subsequently added to the previous solution *via* cannula transfer. After 3 min. the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (5 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1 M, 10 mL) and DCM (10 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide, in order of elution, the title compound and *anti*-diastereomer (137 mg, 79%), *syn*:*anti* = 79:21, ee_{syn} = 86%, $[\alpha]_D^{21}$ = +44.0 (*c* = 1.0, DCM), ee_{anti} = 72%; oxazolidinethione *syn*-**156** (108 mg, 62%), as white crystals; mp 107 °C (EtOAc-light petroleum (bp 40-60 °C)); R_f(SiO_2, $CHCl_3$:EtOAc, 75:25) 0.53; ν_{max}(KBr)/cm^{-1} 3426 (NH), 2952 (CH), 1748 (C=O), 1486 (NHC=S), 1177 (CO); δ_H(400 MHz; $CDCl_3$) 7.94 (1H, s, NH), 7.46-7.38 (5H, m, ArH), 5.98 (1H, d, *J* = 6.1, ArCH), 4.49 (1H, d, *J* = 6.1, EtO(C=O)CH), 4.40-4.26 (2H, m, CH_2), 1.40 (3H, t, *J* = 7.0, CH_3); δ_C(100 MHz; $CDCl_3$) 189.9, 168.2, 137.0, 129.7, 129.3, 125.9, 85.9, 64.9, 63.4, 14.5; and oxazolidinethione *anti*-**156** (29 mg, 17%), as white crystals; mp 114 °C (EtOAc-light petroleum (bp 40-60 °C)); R_f(SiO_2, $CHCl_3$:EtOAc, 75:25) 0.38;

ν_{max}($CHCl_3$, 0.05 M)/cm^{-1} 3426 (NH), 2964 (CH), 1749 (C=O), 1486 (NHC=S), 1176 (CO); δ_H(400 MHz; $CDCl_3$) 7.59 (1H, s, NH), 7.42-7.20 (5H, m, ArH), 6.09 (1H, d, J = 9.8, ArCH), 4.91 (1H, d, J = 9.8, EtO(C=O)CH), 3.80 (1H, dq, J = 10.7, 7.2, CH_AH_B), 3.67 (1H, dq, J = 10.7, 7.2, CH_AH_B), 0.82 (3H, t, J = 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 190.0, 167.3, 133.4, 129.9, 128.8, 126.9, 85.5, 63.0, 62.5, 13.9.

The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 9.0 min. and t_{R2} = 10.8 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the same conditions; t_{R1} = 13.9 min. and t_{R2} = 39.9 min.

Preparation of (4*S*,5*R*)-5-(4-methoxyphenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-164



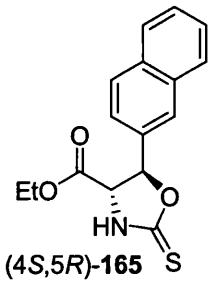
(4*S*,5*R*)-**164**

The reaction was carried out according to the experimental procedure above (Section III 4) with 4-methoxybenzaldehyde (92 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (133 mg, 69%), *syn*:*anti* = 85:15, ee_{syn} = 86%, $[\alpha]_D^{21}$ = +49.0 (c = 1.0, DCM), ee_{anti} = 53%; the oxazolidinethione *syn*-**164** (109 mg, 56%) as white crystals; mp 80 °C (DCM-light petroleum (bp 40-60 °C)); R_f(SiO_2, DCM:EtOAc, 98:2) 0.19; ν_{max}(KBr)/cm^{-1} 3426 (NH), 2815 (CH), 1748 (C=O), 1614 (Ar), 1517 (Ar), 1486 (NHC=S), 1171 (CO), 1032 (CO); δ_H(400 MHz; $CDCl_3$) 7.71 (1H, s, NH), 7.34-7.32 (2H, m, ArH), 6.96-6.92 (2H, m, ArH), 5.90 (1H, d, J = 6.2, ArCH), 4.47 (1H, d, J = 6.2,

EtO(C=O)CH), 4.37-4.25 (2H, m, CH_2), 3.82 (1H, s, OCH_3), 1.34 (3H, t, J = 7.0, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 188.7, 167.7, 160.4, 128.5, 127.3, 114.4, 85.8, 64.4, 62.9, 55.4, 14.2; and oxazolidinethione *anti*-**164** (9 mg, 5%) as white crystals; mp 87 °C (DCM-light petroleum (bp 40-60 °C)); R_f(SiO_2, DCM:EtOAc, 98:2) 0.11; ν_{max}(KBr)/cm^{-1} 3425 (NH), 2859 (CH), 1747 (C=O), 1614 (Ar), 1517 (Ar), 1487 (NHC=S), 1171 (CO), 1032 (CO); δ_H(400 MHz; $CDCl_3$) 7.51 (1H, s, NH), 7.25-7.21 (2H, m, ArH), 6.90-6.86 (2H, m, ArH), 6.04 (1H, d, J = 9.8, ArCH), 4.86 (1H, d, J = 9.8, EtO(C=O)CH), 3.84 (1H, dq, J = 10.6, 7.2, CH_AH_B), 3.80 (3H, s, OCH_3), 3.73 (1H, dq, J 10.6, 7.2, CH_AH_B), 0.88 (3H, t, J = 7.2, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.9, 167.1, 160.7, 128.3, 125.4, 114.1, 85.5, 63.0, 62.5, 55.7, 14.0.

The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 12.0 min. and t_{R2} = 13.3 min. The enantiomers of the *anti*-diastereomer were separated analytically using the same conditions; t_{R1} = 15.9 min. and t_{R2} = 45.9 min.

Preparation of (4*S*,5*R*)-5-(2-naphthyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-165



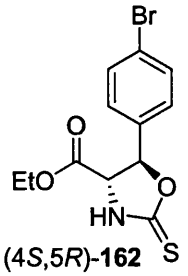
(4*S*,5*R*)-**165**

The reaction was carried out according to the experimental procedure above (Section III 4) with 2-naphthaldehyde (119 mg, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (133 mg, 64%, *syn*:*anti* = 72:28), ee_{syn} = 85%, $[\alpha]_D^{21}$ = +46.0 (c = 1.0, DCM), ee_{anti} = 71%;

oxazolidinethione *syn*-**165** (96 mg, 46%) as white crystals; 145 °C (DCM-light petroleum (bp 40-60 °C)); R_f(SiO_2, DCM:EtOAc, 98:2) 0.21; ν_{max}(KBr)/cm^{-1} 3426 (NH), 2957 (CH), 1749 (C=O), 1582 (Ar), 1487 (NHC=S), 1180 (CO); δ_H(400 MHz; $CDCl_3$) 7.92-7.85 (5H, m, ArH & NH), 7.55-7.53 (2H, m, ArH), 7.48-7.46 (1H, m, ArH), 6.14 (1H, d, *J* = 6.2, ArCH), 4.56 (1H, d, *J* = 6.2, EtO(C=O)CH), 4.42-4.29 (2H, m, CH_2), 1.38 (3H, t, *J* = 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 189.1, 168.1, 134.1, 133.8, 133.1, 129.7, 128.5, 128.0, 127.3, 127.1, 125.6, 122.6, 86.1, 64.9, 63.4, 14.6; and oxazolidinethione *anti*-**165** (37 mg, 18%) as white crystals; mp 169 °C (DCM-light petroleum (bp 40-60 °C)); R_f(SiO_2, DCM:EtOAc, 98:2) 0.11; ν_{max}(KBr)/cm^{-1} 3425 (NH), 2913 (CH), 1748 (C=O), 1603 (Ar), 1489 (NHC=S), 1175 (CO); δ_H(400 MHz; $CDCl_3$) 7.86-7.83 (4H, m, ArH), 7.55-7.50 (3H, m, ArH & NH), 7.39-7.36 (1H, m, ArH), 6.26 (1H, d, *J* = 9.8, ArCH), 4.97 (1H, d, *J* = 9.8, EtO(C=O)CH), 3.64 (1H, dq, *J* = 10.7, 7.2, CH_AH_B), 3.48 (1H, dq, *J* = 10.7, 7.2, CH_AH_B), 0.55 (3H, t, *J* = 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 189.7, 166.7, 133.5, 132.5, 130.3, 128.4, 128.1, 127.6, 126.9, 126.7, 126.4, 123.3, 85.4, 62.8, 62.2, 13.4; *m/z* (EI) 301 (68%, M^+), 256 (8%, M – C_2H_5O), 43 (57%, CHNO), 29 (77%, C_2H_5); (Found: M^+, 301.0763. $C_{16}H_{15}NO_3S$ requires *M*, 301.0773).

The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 11.8 min. and t_{R2} = 14.0 min. The enantiomers of the *anti*-diastereomer were separated analytically using the same conditions; t_{R1} = 15.3 min. and t_{R2} = 53.2 min.

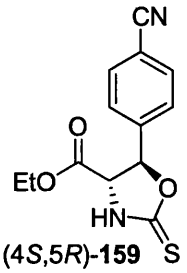
Preparation of (4*S*,5*R*)-5-(4-bromophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-162



(4*S*,5*R*)-**162**

The reaction was carried out according to the experimental procedure above (Section III 4) with 4-bromobenzaldehyde **192** (141 mg, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (180 mg, 79%), *syn*:*anti* = 73:27, ee_{syn} = 46%, $[\alpha]_D^{21}$ = +11.0 (*c* = 1.0, DCM), ee_{anti} = 59%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 10.2 min. and t_{R2} = 11.8 min. The enantiomers of the *anti*-diastereomer were separated analytically using the same conditions; t_{R1} = 14.3 min. and t_{R2} = 49.2 min.

Preparation of (4*S*,5*R*)-5-(4-cyanophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-159

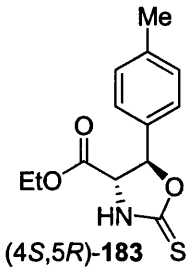


(4*S*,5*R*)-**159**

The reaction was carried out according to the experimental procedure above (Section III 4) with 4-cyanobenzaldehyde (100 mg, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (135 mg, 71%), *syn*:*anti* = 66:34, ee_{syn} = 3%, ee_{anti} = 37%; oxazolidinethione *syn*-**159** (91 mg, 47%) as white crystals; mp 132 °C (DCM-light petroleum (bp 40-60 °C)); R_f(SiO_2, DCM:EtOAc, 98:2) 0.09; ν_{max}(KBr)/cm^{-1} 3425 (NH), 2946 (CH), 2233 (CN), 1750 (C=O), 1613 (Ar), 1488 (NHC=S), 1171 (CO); δ_H(400 MHz; $CDCl_3$) 8.09 (1H, s, NH), 7.75-7.54 (4H, m, ArH), 6.03 (1H, d, *J* = 6.1, ArCH), 4.44 (1H, d, *J* = 6.1, (C=O)CH), 4.41-4.29 (2H, m, CH_2), 1.37 (3H, t, *J* = 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 188.2, 167.2, 141.6, 132.8, 126.1, 117.9, 113.4, 84.0, 64.4, 63.4, 14.2; *m*/*z* (EI) 276 (57%, M^+), 69 (32%, C_3H_3NO), 29 (39%, C_2H_5); (Found: M^+, 276.0567. $C_{13}H_{12}N_2O_3S$ requires *M*, 276.0569) (Found: C, 56.6; H, 4.4; N, 10.2. $C_{13}H_{12}N_2O_3S$ requires C, 56.5; H, 4.38; N, 10.1%); and oxazolidinethione *anti*-**159** (29 mg, 15%) as white crystals; mp 169 °C (DCM-light petroleum (bp 40-60 °C)); R_f(SiO_2, DCM:EtOAc, 98:2) 0.06; ν_{max}(KBr)/cm^{-1} 3423 (NH), 2950 (CH), 2233 (CN), 1749 (C=O), 1485 (NHC=S); δ_H(400 MHz; $CDCl_3$) 7.72-7.46 (4H, m, ArH), 7.36 (1H, s, NH), 6.12 (1H, d, *J* = 9.8, ArCH), 4.94 (1H, d, *J* = 9.8, (C=O)CH), 3.85 (1H, dq, *J* = 10.7, 7.1, CH_AH_B), 3.72 (1H, dq, *J* = 10.7, 7.1, CH_AH_B), 0.88 (3H, t, *J* = 7.1, CH_3); δ_C(100 MHz; $CDCl_3$-CD_3OD, 67:33) 189.7, 167.0, 138.9, 132.2, 127.5, 118.0, 113.1, 83.7, 63.0, 62.1, 13.6; HRMS (ES+): (Found: M^+, 276.0570. $C_{13}H_{12}N_2O_3S$ requires *M*, 276.0569).

The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 19.7 min. and t_{R2} = 21.2 min. The enantiomers of the *anti*-diastereomer were separated analytically using the same conditions; t_{R1} = 23.0 min. and t_{R2} = 64.9 min.

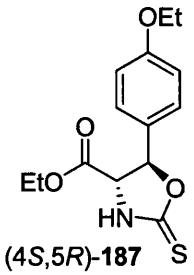
Preparation of (4*S*,5*R*)-2-thioxo-5-*p*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *syn*-183



(4*S*,5*R*)-**183**

The reaction was carried out according to the experimental procedure above (Section III 4) with *p*-tolualdehyde **196** (90 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (161 mg, 88%), *syn*:*anti* = 88:12, ee_{syn} = 92%, $[\alpha]_D^{21}$ = +32.0 (*c* = 1.0, DCM), ee_{anti} = 62%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 9.0 min. and t_{R2} = 9.9 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the same conditions; t_{R1} = 12.3 min. and t_{R2} = 38.2 min.

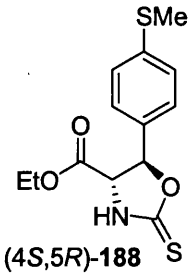
Preparation of (4*S*,5*R*)-5-(4-ethoxy-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-187



(4*S*,5*R*)-**187**

The reaction was carried out according to the experimental procedure above (Section III 4) with 4-ethoxybenzaldehyde (106 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (174 mg, 85%), *syn*:*anti* = 87:13, ee_{syn} = 93%, $[\alpha]_D^{21}$ = +46.0 (*c* = 1.0, DCM), ee_{anti} = 62%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 20.0 min. and t_{R2} = 21.6 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the same conditions; t_{R1} = 26.9 min. and t_{R2} = 79.2 min.

Preparation of (4*S*,5*R*)-5-(4-methylsulfanyl-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-188

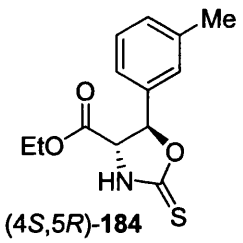


(4*S*,5*R*)-**188**

The reaction was carried out according to the experimental procedure above (Section III 4) with 4-(methylthio)benzaldehyde (101 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (131

mg, 64%), *syn*:*anti* = 85:15, ee_{syn} = 94%, $[\alpha]_D^{21}$ = +40.0 (*c* = 1.0, DCM), ee_{anti} = 62%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 13.1 min. and t_{R2} = 14.5 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the same conditions; t_{R1} = 16.1 min. and t_{R2} = 48.9 min.

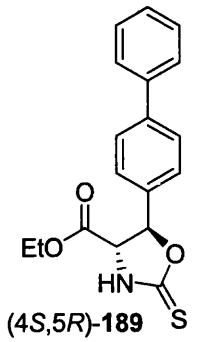
Preparation of (4*S*,5*R*)-2-thioxo-5-*m*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *syn*-184



(4*S*,5*R*)-**184**

The reaction was carried out according to the experimental procedure above (Section III 4) with *m*-tolualdehyde (90 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (152 mg, 84%), *syn*:*anti* = 82:18, ee_{syn} = 85%, $[\alpha]_D^{21}$ = +25.0 (*c* = 1.0, DCM), ee_{anti} = 73%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 8.2 min. and t_{R2} = 9.7 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the same conditions; t_{R1} = 11.6 min. and t_{R2} = 36.8 min.

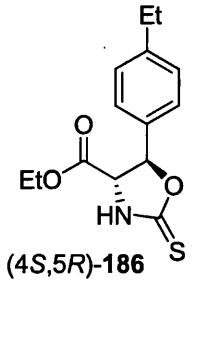
Preparation of (4*S*,5*R*)-5-biphenyl-4-yl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-189



(4*S*,5*R*)-**189**

The reaction was carried out according to the experimental procedure above (Section III 4) with biphenyl-4-carboxaldehyde (138 mg, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (164 mg, 73%), *syn*:*anti* = 71:29, ee_{syn} = 85%, $[\alpha]_D^{21}$ = +26.0 (*c* = 1.0, DCM), ee_{anti} = 61%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 14.7 min. and t_{R2} = 16.5 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the same conditions; t_{R1} = 17.0 min. and t_{R2} = 52.9 min.

Preparation of (4*S*,5*R*)-5-(4-ethyl-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-186

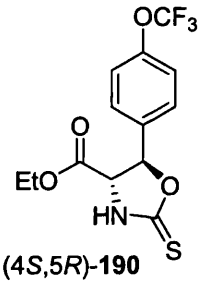


(4*S*,5*R*)-**186**

The reaction was carried out according to the experimental procedure above (Section III 4) with 4-ethylbenzaldehyde (104 μL, 0.76 mmol) to provide, in

order of elution, the title compound and *anti*-diastereomer (181 mg, 95%), *syn*:*anti* = 91:9, ee_{syn} = 90%, $[\alpha]_D^{21}$ = +34.0 (*c* = 1.0, DCM), ee_{anti} = 66%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 7.4 min. and t_{R2} = 9.6 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the same conditions; t_{R1} = 11.4 min. and t_{R2} = 36.6 min.

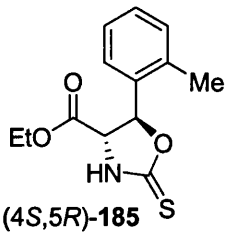
Preparation of (4*S*,5*R*)-2-thioxo-5-(4-trifluoromethoxy-phenyl)-oxazolidine-4-carboxylic acid ethyl ester *syn*-190



(4*S*,5*R*)-**190**

The reaction was carried out according to the experimental procedure above (Section III 4) with 4-(trifluoromethoxy)benzaldehyde (108 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (180 mg, 78%), *syn*:*anti* = 74:26, ee_{syn} = 52%, $[\alpha]_D^{21}$ = +5.0 (*c* = 1.0, DCM), ee_{anti} = 63%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 7.7 min. and t_{R2} = 8.9 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the same conditions; t_{R1} = 11.3 min. and t_{R2} = 36.1 min.

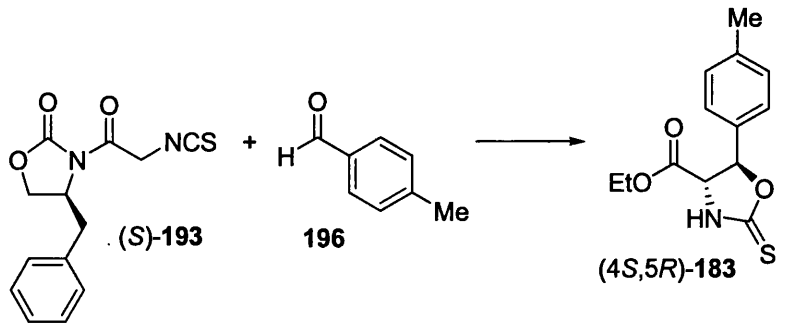
Preparation of (4*S*,5*R*)-2-thioxo-5-*o*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *syn*-185



(4*S*,5*R*)-**185**

The reaction was carried out according to the experimental procedure above (Section III 4) with *o*-tolualdehyde (88 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (162 mg, 88%), *syn*:*anti* = 50:50, ee_{syn} = 62%, $[\alpha]_D^{21}$ = +12.5 (*c* = 3.0, DCM), ee_{anti} = 89%, $[\alpha]_D^{21}$ = +163.8 (*c* = 1.0, DCM). Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 9.7 min. and t_{R2} = 11.7 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the same conditions; t_{R1} = 14.9 min. and t_{R2} = 42.8 min.

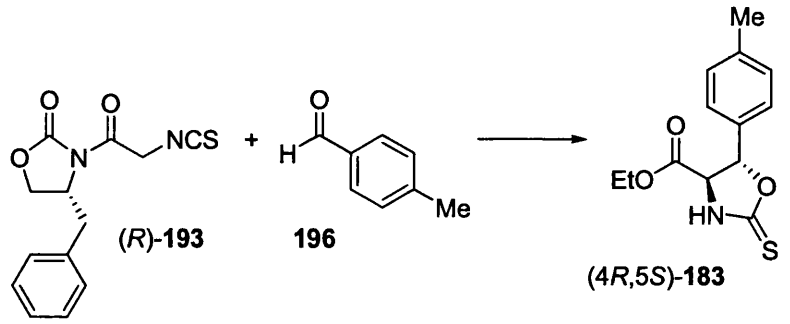
III 5 Preparation of (4*S*,5*R*)-2-thioxo-5-*p*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *syn*-183 employing (*S*)-4-benzyl-3-(2-*iso*thiocyanatoacetyl)oxazolidin-2-one 193



(*S*)-**193** **196** (4*S*,5*R*)-**183**

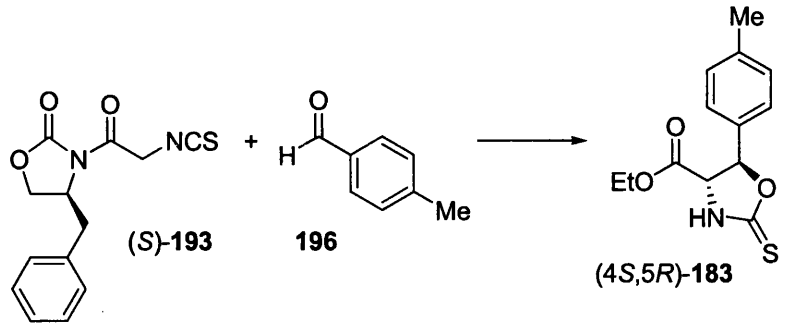
The reaction was carried out according to the experimental procedure above (Section III 4) with (*S*)-4-benzyl-3-(2-*iso*thiocyanatoacetyl)oxazolidin-2-one[106] **193** and *p*-tolualdehyde **196** (90 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (161 mg, 88%), *syn*:*anti* = 91:9, ee_{syn} = 90%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 9.0 min. and t_{R2} = 9.9 min.

Preparation of (4*R*,5*S*)-2-thioxo-5-*p*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *syn*-183 employing (*R*)-4-benzyl-3-(2-*iso*thiocyanatoacetyl)oxazolidin-2-one 193



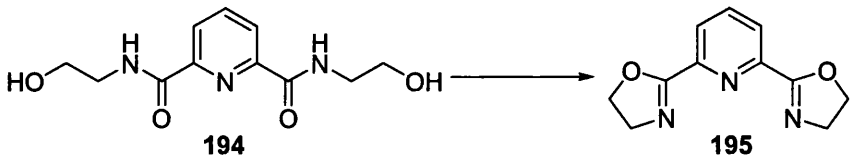
The reaction was carried out according to the experimental procedure above (Section III 4) with (*R*)-4-benzyl-3-(2-*iso*thiocyanatoacetyl)oxazolidin-2-one[106] **193** and *p*-tolualdehyde **196** (90 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (137 mg, 75%), *syn*:*anti* = 81:19, ee_{syn} = 64%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 9.0 min. and t_{R2} = 9.9 min.

Preparation of (4*S*,5*R*)-2-thioxo-5-*p*-tolyl-oxazolidine-4-carboxylic acid ethyl ester *syn*-183 employing (*S*)-4-benzyl-3-(2-*iso*thiocyanatoacetyl)oxazolidin-2-one 193 and 2,6-bis-(4,5-dihydro-oxazol-2-yl)-pyridine 195 as a ligand



The reaction was carried out according to the experimental procedure above (Section III 4) with (*S*)-4-benzyl-3-(2-*iso*thiocyanatoacetyl)oxazolidin-2-one[106] **193**, 2,6-bis-(4,5-dihydro-oxazol-2-yl)-pyridine **195** (17 mg, 0.08 mmol) and *p*-tolualdehyde **196** (90 μL, 0.76 mmol) to provide, in order of elution, the title compound and *anti*-diastereomer (160 mg, 87%), *syn*:*anti* = 81:19, ee_{syn} = 83%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 9.0 min. and t_{R2} = 9.9 min.

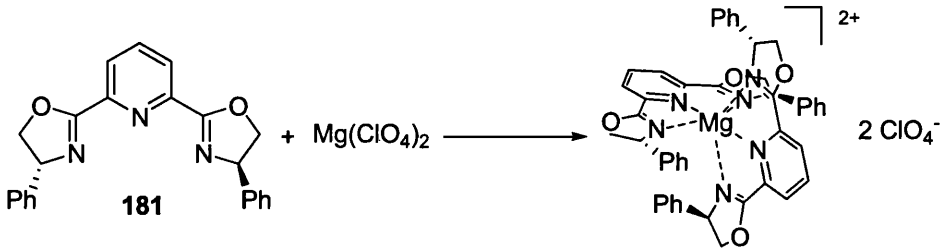
III 6 Preparation of 2,6-bis-(4,5-dihydro-oxazol-2-yl)-pyridine 195



Pyridine-2,6-dicarboxylic acid bis-[(2-hydroxy-ethyl)-amide] **194** (1.63 g, 3.95 mmol) as prepared by Kumar *et al*[109] was stirred in boron trifluoride diethyl-

etherate (15 mL) for 4 h at 120 °C under a nitrogen atmosphere. The reaction mixture was cooled to ambient temperature and diluted with DCM (75 mL), then poured into chilled 2 M sodium hydroxide (75 mL). The organic layer was then concentrated under reduced pressure to yield the *pyridinebisoxazoline* **195** as a white solid (760 mg, 54%). An analytical sample of the title compound was prepared by recrystallisation from dimethylsulfoxide; mp 185 °C dec. (DMSO); ν_{max}(KBr)/cm^{-1} 2874 (CH), 1660 (C=N), 1569 (C=N); δ_H(300 MHz; $CDCl_3$) 8.17 (2H, d, J = 5.7, ArH), 7.88 (1H, t, J = 5.7, ArH), 4.54 (4H, t, J = 7.2, CH_2CH_2), 4.12 (4H, t, J = 7.2, CH_2CH_2); δ_C(75 MHz; $CDCl_3$) 163.8, 147.2, 137.8, 125.9, 68.7, 55.5; HRMS (ES+): $C_{11}H_{12}N_3O_2$, $[M+H]^+$ requires 218.0924. Found 218.0924; $C_{11}H_{11}N_3O_2$ requires C, 60.8; H, 5.10; N, 19.34%. Found C, 60.5; H, 5.12; N, 19.2%.

III 7 Preparation of [Mg((*R*,*R*)-phenyl-bis(oxazolinyl)pyridine)$_2$](ClO$_4$)$_2$ 201



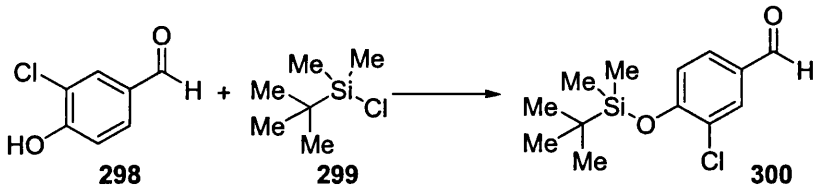
201

A mixture of $Mg(ClO_4)_2$ (137 mg, 0.62 mmol) and 2,6-bis((*R*)-4,5-dihydro-4-phenyl-2-oxazolyl)pyridine **181** (250 mg, 0.68 mmol) was stirred for 8 h in dry acetonitrile (50 mL) under a nitrogen atmosphere at reflux. The reaction mixture was then cooled to ambient temperature and concentrated under reduced pressure to furnish a pale pink foam. The foam was dissolved up in DCM (25 mL), filtered through a sintered funnel and chilled for several days

to afford the title compound as transparent lilac prisms. The crystals were stored under DCM until subjection to X-ray crystallography (Appendix B).

III 8 Preparation of *O*-protected analogues of 3-chloro-4-hydroxybenzaldehyde

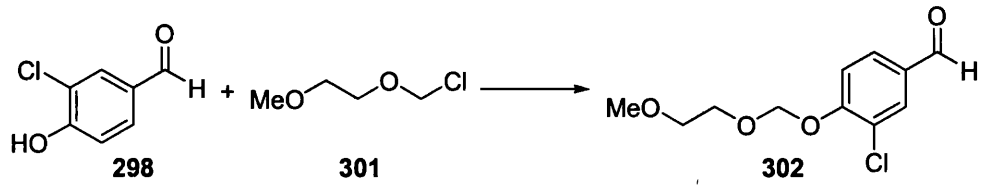
Preparation of 4-(*tert*-butyl-dimethyl-silanyloxy)-3-chloro-benzaldehyde 300



298 299 300

3-Chloro-4-hydroxybenzaldehyde **298** (2.0 g, 12.8 mmol) was stirred in dry DMF (5 mL) under a nitrogen atmosphere at 0 °C. To the solution was added *t*-butyldimethylsilyl chloride **299** (2.02 g, 13.4 mmol) and imidazole (0.91 g, 13.4 mmol) portion-wise and the mixture was allowed to stir for 2 h to reach RT. The mixture was then diluted with light petroleum (bp 40-60 °C) and washed twice with water. The organic phase was filtered through a short plug of neutral alumina and concentrated under reduced pressure to provide the aldehyde[146] **300** as a pale yellow oil (2.78 g, 80%); δ_H(300 MHz; $CDCl_3$) 9.83 (1H, s, CHO), 7.90 (1H, d, J = 2.2, ArH), 7.68 (1H, dd, J = 8.2, 2.2, ArH), 6.99 (1H, d, J = 8.2, ArH), 1.04 (9H, s, $C(CH_3)_3$), 0.28 (6H, s, $Si(CH_3)_2$); δ_C(100 MHz; $CDCl_3$) 190.2, 157.5, 132.3, 131.3, 130.1, 127.3, 121.0, 25.9, 18.8, -3.9.

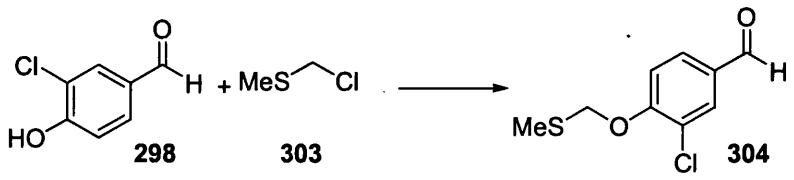
Preparation of 3-chloro-4-(2-methoxy-ethoxymethoxy)-benzaldehyde 302



298 301 302

3-Chloro-4-hydroxybenzaldehyde **298** (2.0 g, 12.8 mmol) was stirred in dry DCM (50 mL) under a nitrogen atmosphere at 0 °C. To the suspension was added 2-methoxyethoxymethyl chloride **301** (1.60 mL, 14.0 mmol) and di*iso*propylethylamine (2.45 mL, 14.0 mmol) portion-wise and the mixture was allowed to stir for 2 h to reach RT. The mixture was then quenched with saturated aqueous ammonium chloride (5 mL) and diluted with DCM. The organic phase was separated and washed twice with water. The extract was filtered through a short plug of neutral alumina and concentrated under reduced pressure to provide the aldehyde[147] **302** as a pale yellow oil (2.50 g, 80%); δ_H(400 MHz; $CDCl_3$) 9.87 (1H, s, CHO), 7.92 (1H, s, ArH), 7.75 (1H, d, *J* = 8.0, ArH), 7.36 (1H, d, *J* = 8.0, ArH), 5.44 (2H, s, OCH_2O), 3.88 (2H, t, *J* = 4.0, OCH_2CH_2O), 3.56 (2H, t, *J* = 4.0, OCH_2CH_2O), 3.37 (3H, s, OCH_3).

Preparation of 3-chloro-4-methylsulfanylmethoxy-benzaldehyde 304

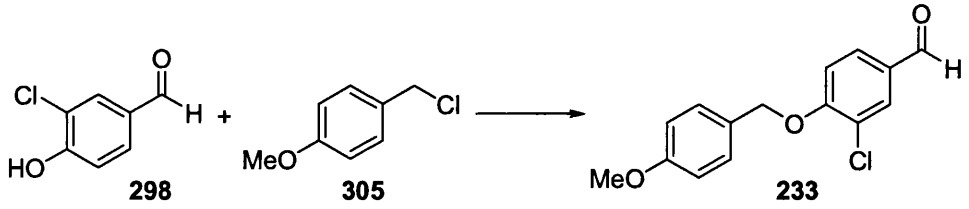


298 303 304

3-Chloro-4-hydroxybenzaldehyde **298** (2.0 g, 12.8 mmol) was stirred in dry DMF (10 mL) under a nitrogen atmosphere at RT. To the solution was added chloromethyl methyl sulfide **303** (1.18 mL, 14.0 mmol) and anhydrous potassium carbonate (1.94 g, 14.0 mmol) portion-wise and the mixture was allowed to stir for 16 h at RT. The mixture was then diluted with DCM and

washed twice with water. The extract was filtered through a short plug of neutral alumina and concentrated under reduced pressure to provide the *aldehyde* **304** as a pale yellow oil (2.35 g, 85%); ν_{max}(neat)/cm^{-1} 2923 (CH), 1700 (C=O), 1227 (CO), 1054 (CO); δ_H(300 MHz; $CDCl_3$) 9.83 (1H, s, CHO), 7.88 (1H, s, ArH), 7.73 (1H, d, J = 9.0, ArH), 7.08 (1H, d, J = 9.0, ArH), 5.29 (2H, s, SCH_2O), 2.26 (3H, s, SCH_3); δ_C(75 MHz; $CDCl_3$) 189.8, 157.2, 131.4, 130.9, 130.0, 125.0, 114.7, 73.4, 14.7; HRMS (ES+): $C_9H_{13}{}^{35}ClNO_2S$, $[M+NH_4]^+$ requires 234.0350. Found 234.0352.

Preparation of 4-(4-methoxybenzyloxy)-3-chlorobenzaldehyde 233

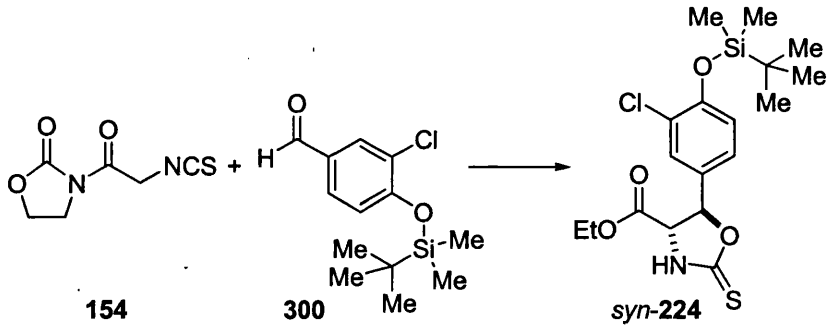


3-Chloro-4-hydroxybenzaldehyde **298** (2.0 g, 12.8 mmol) was stirred in dry DMF (10 mL) under a nitrogen atmosphere at RT. To the solution was added *p*-methoxybenzyl chloride **305** (1.90 mL, 14.0 mmol), and anhydrous potassium carbonate (1.94 g, 14.0 mmol) portion-wise and the mixture was allowed to stir for 16 h at RT. The mixture was then diluted with water and the precipitate formed was filtered through a sinter funnel and washed with water and dried. The crude product was purified by recrystallisation from DCM-*n*-hexane to provide the *aldehyde* **233** as a white crystalline solid (3.0 g, 85%); mp 102-103 °C (DCM-*n*-hexane); ν_{max}(KBr)/cm^{-1} 1688 (C=O), 1273 (CO), 1249 (CO), 1193 (CO), 1175 (CO); δ_H(300 MHz; $CDCl_3$) 9.84 (1H, s, CHO), 7.93 (1H, d, J = 3.0, ArH), 7.74 (1H, dd, J = 6.0, 3.0, ArH), 7.39 (2H, d, J = 7.5, ArH), 7.09 (1H, d, J = 6.0, ArH), 6.94 (2H, d, J = 7.5, ArH), 5.18 (2H, s, OCH_2O), 3.82 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 189.9, 159.8, 159.2, 131.4, 130.5, 130.4, 129.0, 127.5, 124.4, 114.3, 113.3, 71.0, 55.4; HRMS (ES+): $C_{15}H_{17}{}^{35}ClNO_3$, $[M+NH_4]^+$

requires 294.0891. Found 294.0889; $C_{15}H_{13}ClO_3$ requires C, 65.1; H, 4.74%. Found C, 64.6; H, 4.68%.

III 9 Racemic preparation of derivatised *syn*-oxazolidinethione aldol adducts of *O*-protected 3-chloro-4-hydroxybenzaldehydes and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154

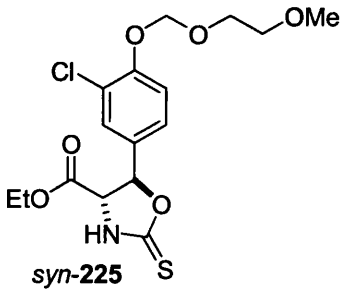
Preparation of (4*S,5*R**)-5-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-chloro-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester 224**



The reaction was carried out according to the experimental procedure above (Section III 3) with 4-(*tert*-butyl-dimethyl-silanyloxy)-3-chloro-benzaldehyde **300** (206 mg, 0.76 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide the title compound ***syn*-224** (180 mg, 63%) as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.30; ν_{max}(neat)/cm^{-1} 3290 (NH), 1746 (C=O), 1506 (NHC=S), 1173 (CO); δ_H(300 MHz; $CDCl_3$) 7.40 (1H, d, J = 2.3, ArH), 7.32 (1H, s, NH), 7.18 (1H, dd, J = 8.4, 2.3, ArH), 6.97 (1H, d, J = 8.4, ArH), 5.87 (1H, d, J = 6.2, ArCH), 4.44 (1H, d, J = 6.2, EtO(C=O)CH), 4.25-4.40 (2H, m, (C=O)OCH_2CH_3), 1.35 (3H, t, J = 7.1, (C=O)OCH_2CH_3), 1.03 (9H, s, $C(CH_3)_3$), 0.23 (6H, s, $Si(CH_3)_2$); δ_C(100 MHz;

$CDCl_3$) 189.2, 168.1, 153.2, 130.7, 128.4, 126.9, 125.6, 121.6, 85.3, 64.8, 63.5, 26.0, 18.8, 14.5, -3.9; HRMS (ES+): $C_{18}H_{27}{}^{35}ClNO_4SSi$, $[M+H]^+$ requires 416.1113. Found 416.1106. and *oxazolidinethione anti-***224** (11 mg, 4%), as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.18; δ_H(300 MHz; $CDCl_3$) 7.69 (1H, s, NH), 7.31 (1H, d, J = 2.3, ArH), 7.10 (1H, dd, J = 8.4, 2.3, ArH), 6.88 (1H, d, J = 8.4, ArH), 5.99 (1H, d, J = 9.7, ArCH), 4.87 (1H, d, J = 9.7, EtO(C=O)CH), 3.83 (2H, m, (C=O)OCH_2CH$_3$), 1.02 (9H, s, C(CH$_3$)$_3$), 0.94 (3H, t, J = 7.1, (C=O)OCH$_2$CH_3), 0.21 (6H, s, Si(CH$_3$)$_2$); HRMS (ES+): $C_{18}H_{27}{}^{35}ClNO_4SSi$, $[M+H]^+$ requires 416.1113. Found 416.1109.

Preparation of (4*S,5*R**)-5-[3-chloro-4-(2-methoxy-ethoxymethoxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester 225**

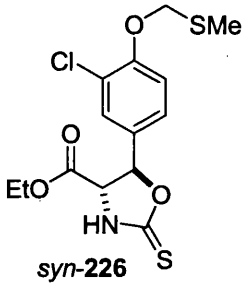


*syn-***225**

The reaction was carried out according to the experimental procedure above (Section III 3) with 3-chloro-4-(2-methoxy-ethoxymethoxy)-benzaldehyde **302** (186 mg, 0.76 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 95:5) to provide the title compound *syn-***225** (174 mg, 65%) as a pale yellow oil; R_f(SiO_2, DCM:EtOAc, 95:5) 0.13; ν_{max}(neat)/cm^{-1} 3404 (NH), 2934 (CH), 1734 (C=O), 1506 (NHC=S), 1188 (CO); δ_H(400 MHz; $CDCl_3$) 7.44 (1H, m, ArH), 7.39 (1H, s, NH), 7.24-7.30 (2H, m, ArH), 5.88 (1H, d, J = 6.0, ArCH), 5.37 (2H, s, OCH_2O), 4.44 (1H, d, J = 6.0, EtO(C=O)CH), 4.25-4.40 (2H, m, (C=O)OCH_2CH$_3$), 3.87 (2H, t, J = 4.0, CH_2CH$_2$), 3.56 (2H, t, J = 4.0, CH$_2$CH_2), 3.38 (3H, s, OCH$_3$), 1.36 (3H, t, J = 6.8, (C=O)OCH$_2$CH_3); δ_C(100 MHz; $CDCl_3$) 188.7, 167.6, 153.8, 131.0, 127.8, 125.4,

124.3, 116.6, 94.0, 84.7, 71.4, 68.2, 64.3, 63.1, 59.0, 14.1; HRMS (ES+): $C_{16}H_{24}{}^{35}ClN_2O_6S$, $[M+NH_4]^+$ requires 407.1038. Found 407.1037. and *oxazolidinethione anti*-**225** (37 mg, 14%), as a colourless oil; δ_H(400 MHz; $CDCl_3$) 7.86 (1H, s, NH), 7.35 (1H, s, ArH), 7.17-7.24 (2H, m, ArH), 6.02 (1H, d, *J* = 8.0, ArCH), 5.35 (2H, s, OCH_2O), 4.90 (1H, d, *J* = 8.0, EtO(C=O)CH), 3.77-3.93 (4H, m, OCH_2CH_2O & $(C=O)OCH_2CH_3$), 3.55 (2H, t, *J* = 4.0, OCH_2CH_2O), 3.37 (3H, s, OCH_3), 0.92 (3H, t, *J* = 6.0, $(C=O)OCH_2CH_3$).

Preparation of (4*S,5*R**)-5-(3-chloro-4-methylsulfanylmethoxy-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester 226**

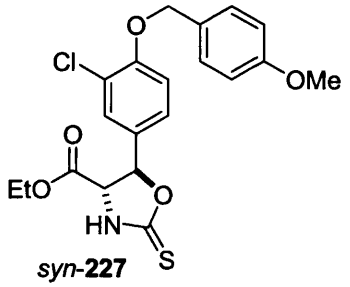


syn-**226**

The reaction was carried out according to the experimental procedure above (Section III 3) with 3-chloro-4-methylsulfanylmethoxy-benzaldehyde **304** (165 mg, 0.76 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 95:5) to provide the title compound *syn*-**226** (148 mg, 59%) as a yellow oil; ν_{max}(neat)/cm^{-1} 3319 (NH), 2980 (CH), 2922 (CH), 1740 (C=O), 1497 (NHC=S), 1225 (CO), 1177 (CO); δ_H(300 MHz; $CDCl_3$) 7.50 (1H, s, NH), 7.46 (1H, d, *J* = 2.3, ArH), 7.30 (1H, dd, *J* = 8.6, 2.3, ArH), 7.04 (1H, d, *J* = 8.6, ArH), 5.90 (1H, d, *J* = 6.0, ArCH), 5.27 (2H, s, SCH_2O), 4.45 (1H, d, *J* = 6.0, EtO(C=O)CH), 4.25-4.40 (2H, m, $(C=O)OCH_2CH_3$), 2.29 (3H, s, SCH_3), 1.36 (3H, t, *J* = 6.9, $(C=O)OCH_2CH_3$); δ_C(75 MHz; $CDCl_3$) 189.1, 168.1, 153.6, 131.3, 128.5, 125.5, 125.4, 116.4, 85.0, 73.9, 64.8, 63.5, 15.0, 14.5; HRMS (ES+): $C_{14}H_{17}{}^{35}ClNO_4S_2$, $[M+H]^+$ requires 362.0282. Found 362.0284. and *oxazolidinethione anti*-**226** (10 mg, 4%), as a yellow oil; ν_{max}(neat)/cm^{-1} 3161

(NH), 2989 (CH), 1734 (C=O), 1506 (NHC=S), 1226 (CO), 1184 (CO); δ_H(300 MHz; $CDCl_3$) 7.51 (1H, s, NH), 7.36 (1H, d, J = 2.4, ArH), 7.20 (1H, dd, J = 8.4, 2.4, ArH), 6.99 (1H, d, J = 8.4, ArH), 6.02 (1H, d, J = 9.8, ArCH), 5.25 (2H, s, SCH_2O), 4.89 (1H, d, J = 9.8, EtO(C=O)CH), 3.75-3.94 (2H, m, (C=O)OCH_2CH_3), 2.26 (3H, s, SCH_3), 0.92 (3H, t, J = 7.2, (C=O)OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.7, 166.8, 153.3, 128.9, 127.4, 125.9, 124.5, 115.7, 84.1, 73.6, 62.6, 62.4, 14.5, 13.6; HRMS (ES+): $C_{14}H_{17}{}^{35}ClNO_4S_2$, $[M+H]^+$ requires 362.0282. Found 362.0288.

Preparation of (4*S,5*R**)-5-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester 227**



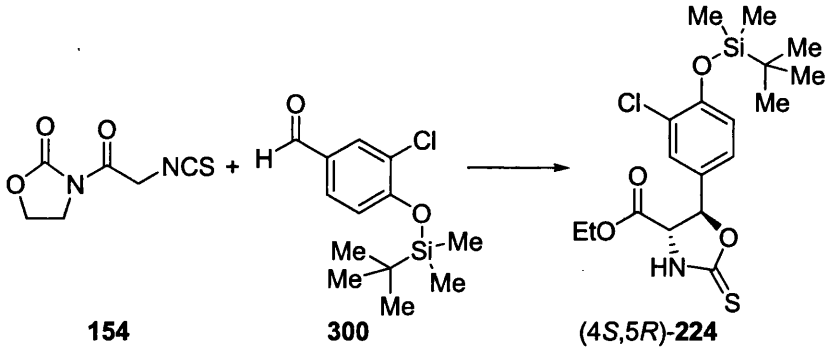
syn-**227**

The reaction was carried out according to the experimental procedure above (Section III 3) with 4-(4-methoxybenzyloxy)-3-chlorobenzaldehyde **233** (210 mg, 0.76 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide the title compound *syn*-**227** (186 mg, 64%) as a white foam; R_f(SiO_2, DCM:EtOAc, 98:2) 0.37; ν_{max}(KBr)/cm^{-1} 3376 (NH), 1739 (C=O), 1515 (NHC=S), 1245 (CO), 1172 (CO); δ_H(300 MHz; $CDCl_3$) 7.55 (1H, s, NH), 7.43 (1H, m, ArH), 7.37 (2H, m, ArH), 7.24 (1H, m, ArH), 7.00 (1H, m, ArH), 6.92 (2H, m, ArH), 5.87 (1H, d, J = 6.5, ArCH), 5.11 (2H, s, $ArCH_2OAr$), 4.43 (1H, d, J = 6.5, EtO(C=O)CH), 4.27-4.38 (2H, m, (C=O)OCH_2CH_3), 3.82 (3H, s, OCH_3), 1.35 (3H, t, J = 7.2, (C=O)OCH_2CH_3); δ_C(75 MHz; $CDCl_3$) 188.7, 167.7, 159.6, 155.1, 129.8, 128.9, 127.9 × 2, 125.4, 124.0, 114.3, 114.1, 84.8, 70.8, 64.4, 63.1, 55.3, 14.1; HRMS (ES+):

$C_{20}H_{21}{}^{35}ClNO_5S$, $[M+H]^+$ requires 422.0823. Found 422.0827. $C_{20}H_{20}{}^{35}ClNO_5S$ requires C, 56.9; H, 4.78; N, 3.32%. Found C, 56.8; H, 4.89; N, 3.26%. and *oxazolidinethione anti*-**227** (37 mg, 13%), as a white solid; mp 112 °C (DCM-EtOAc); ν_{max}(neat)/cm^{-1} 3156 (NH), 1736 (C=O), 1516 (NHC=S), 1250 (CO), 1179 (CO); δ_H(300 MHz; $CDCl_3$) 7.32-7.37 (3H, m, ArH), 7.15 (1H, dd, *J* = 8.7, 2.1, ArH), 7.04 (1H, s, NH), 6.89-6.97 (3H, m, ArH), 5.98 (1H, d, *J* = 9.5, ArCH), 5.10 (2H, s, $ArCH_2O$), 4.85 (1H, d, *J* = 9.5, EtO(C=O)CH), 3.68-3.90 (2H, m, (C=O)O*C*H_2CH_3), 3.81 (3H, s, OCH_3), 0.89 (3H, t, *J* = 7.2, (C=O)OCH_2C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 189.7, 166.7, 159.6, 155.1, 128.8 × 2, 127.9, 126.3, 126.1, 123.5, 114.0, 113.9, 84.2, 70.7, 62.5, 62.3, 55.3, 13.6; $C_{20}H_{20}{}^{35}ClNO_5S$ requires C, 56.9; H, 4.78; N, 3.32%. Found C, 56.9; H, 4.81; N, 3.30%.

III 10 Asymmetric preparation of derivatised *syn*-oxazolidinethione aldol adducts of *O*-protected 3-chloro-4-hydroxybenzaldehydes and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154

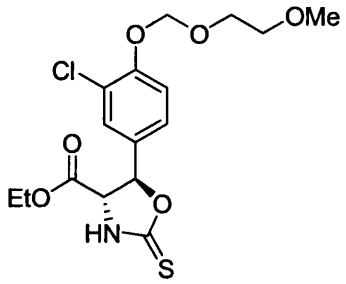
Preparation of (4*S*,5*R*)-5-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-chloro-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester 224



154 **300** (4*S*,5*R*)-**224**

The reaction was carried out according to the experimental procedure above (Section III 4) with 4-(*tert*-butyl-dimethyl-silanyloxy)-3-chloro-benzaldehyde **300** (206 mg, 0.76 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide, in order of elution, the title compound and *anti*-diastereomer (228 mg, 79%), *syn:anti* = 75:25, ee_{syn} = 72%, $[\alpha]_D^{21}$ = +17.9 (*c* = 6.0, DCM). Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 24.7 min. and t_{R2} = 31.8 min.

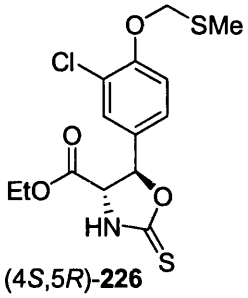
Preparation of (4*S*,5*R*)-5-[3-chloro-4-(2-methoxy-ethoxymethoxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester 225



(4*S*,5*R*)-**225**

The reaction was carried out according to the experimental procedure above (Section III 4) with 3-chloro-4-(2-methoxy-ethoxymethoxy)-benzaldehyde **302** (186 mg, 0.76 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 95:5) to provide, in order of elution, the title compound and *anti*-diastereomer (211 mg, 79%), *syn:anti* = 77:23, ee_{syn} = 74%, $[\alpha]_D^{21}$ = +15.2 (*c* = 2.0, DCM). Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 51.5 min. and t_{R2} = 63.8 min.

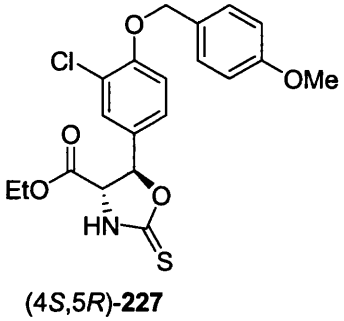
Preparation of (4*S*,5*R*)-5-(3-chloro-4-methylsulfanylmethoxy-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester 226



(4*S*,5*R*)-**226**

The reaction was carried out according to the experimental procedure above (Section III 4) with 3-chloro-4-methylsulfanylmethoxy-benzaldehyde **304** (165 mg, 0.76 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 95:5) to provide, in order of elution, the title compound and *anti*-diastereomer (158 mg, 63%), *syn*:*anti* = 93:7, ee_{syn} = 82%, $[\alpha]_D^{21}$ = +92.0 (*c* = 0.5, DCM). Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 19.7 min. and t_{R2} = 22.6 min.

Preparation of (4*S*,5*R*)-5-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester 227



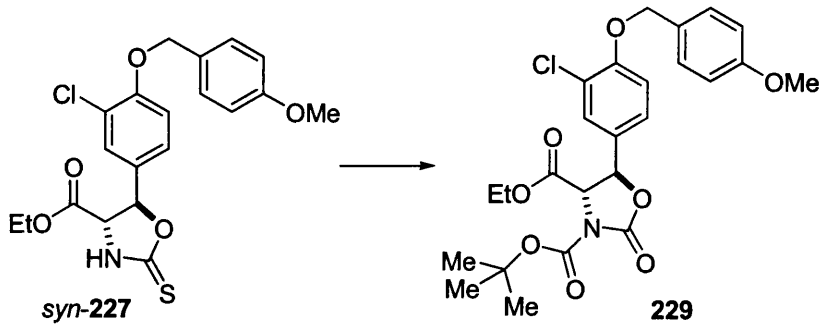
(4*S*,5*R*)-**227**

The reaction was carried out according to the experimental procedure above (Section III 4) with 4-(4-methoxybenzyloxy)-3-chlorobenzaldehyde **233** (210

mg, 0.76 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide, in order of elution, the title compound and *anti*-diastereomer (223 mg, 77%), *syn*:*anti* = 93:7, ee_{syn} = 95%, $[\alpha]_D^{21}$ = +24.0 (c = 1.0, DCM), ee_{anti} = 71%. Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 28.8 min. and t_{R2} = 31.3 min. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 22.8 min. and t_{R2} = 55.4 min. A single crystal of the *syn*-*oxazolidinethione* ***syn*-227** was grown for X-ray crystallography from ^{i}PrOH-*n*-hexane as a colourless needle (Appendix A) over several days at RT; mp 114-115 °C (^{i}PrOH-*n*-hexane).

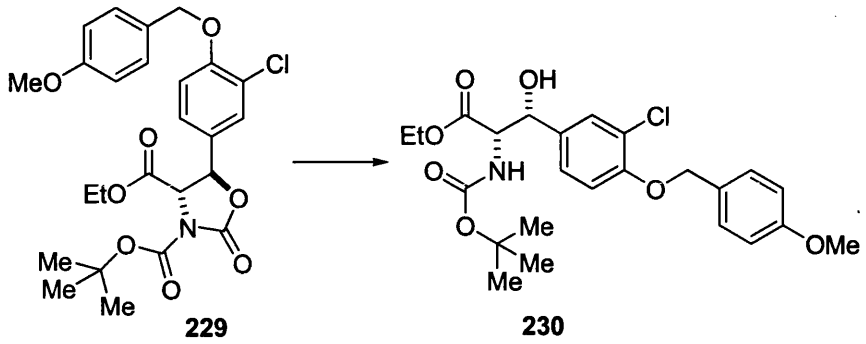
III 11 Racemic preparation of (2*S**,3*R**)-2-amino-3-(*tert*-butyl-dimethyl-silanyloxy)-3-(3-chloro-4-hydroxy-phenyl)-propionic acid methyl ester 239; analogue of AA-6, a vancomycin building block

Preparation of (4*S,5*R**)-5-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-oxo-oxazolidine-3, 4-dicarboxylic acid 3-*tert*-butyl ester 4-ethyl ester 229**



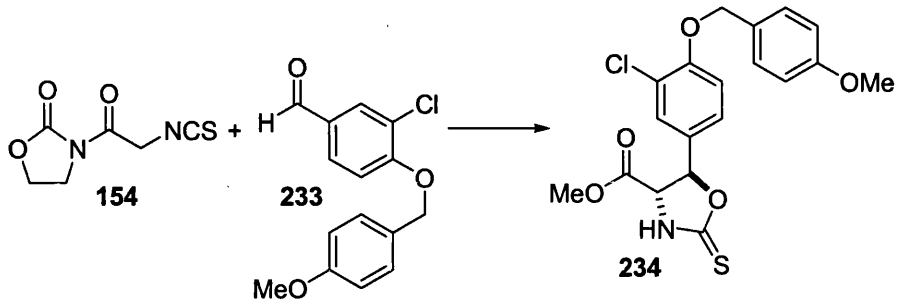
(4*S**,5*R**)-5-[3-Chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester **227** (370 mg, 0.88 mmol) was stirred in dry DCM (10 mL) under a nitrogen atmosphere at RT. To this solution was added di-*tert*-butyl dicarbonate (211 mg, 0.96 mmol) followed by 4-dimethylaminopyridine (5 mg, 0.04 mmol). The mixture effervesced and was allowed to stir for 45 min. The mixture was then cooled to 0 °C and 30 wt.% hydrogen peroxide (3.5 mL) was added portion-wise followed by formic acid (3.5 mL). The mixture was allowed to stir for 45 min. after which time the reaction was deemed complete. The reaction was quenched by the addition of the mixture to 1 M aqueous K_2CO_3 (75 mL). The organic layer was separated and the aqueous layer washed with DCM. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide *oxazolidinone syn*-**229** (324 mg, 73%), as a white foam; ν_{max}(KBr)/cm^{-1} 3451 (NH), 2982 (CH), 1829 (C=O), 1750 (C=O), 1247 (CO), 1060 (CO); δ_H(300 MHz; $CDCl_3$) 7.34-7.41 (3H, m, ArH), 7.20 (1H, dd, *J* = 8.7, 2.4, ArH), 7.00 (1H, d, *J* = 8.7, ArH), 6.92 (2H, d, *J* = 8.7, ArH), 5.27 (1H, d, *J* = 4.5, ArCH), 5.11 (2H, s, OCH_2Ar), 4.57 (1H, d, *J* = 4.5, EtO(C=O)CH), 4.26-4.42 (2H, m, CH_2CH_3), 3.82 (3H, s, OCH_3), 1.51 (9H, s, $C(CH_3)_3$), 1.34 (3H, t, *J* = 7.2, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 168.3, 159.6, 155.0, 150.5, 148.4, 130.2, 128.9, 128.0, 127.3, 124.6, 124.2, 114.3, 114.1, 85.0, 75.2, 70.8, 63.7, 62.7, 55.3, 27.8, 14.2; HRMS (ES+): $C_{25}H_{32}{}^{35}ClN_2O_8$, $[M+NH_4]^+$ requires 523.1842. Found 523.1844.

Preparation of (2*S,3*R**)-2-*tert*-butoxycarbonylamino-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-3-hydroxy-propionic acid ethyl ester 230**



(4*S**,5*R**)-5-[3-Chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-oxo-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-ethyl ester **229** (225 mg, 0.45 mmol) was stirred in dry EtOH (7 mL) under a nitrogen atmosphere at 0 °C. To this solution was added cesium carbonate (59 mg, 0.18 mmol). The mixture was allowed to stir for 2 h after which time the reaction was deemed complete. The mixture was then concentrated under reduced pressure. The residue was taken up in EtOAc and washed with water and brine and dried (Na_2SO_4). After filtration the solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2 then 90:10 and 0:100) to provide *hydroxycarbamate syn*-**230** (52 mg, 25%), as a white solid; mp 104-105 °C (DCM-EtOAc); ν_{max}(KBr)/cm^{-1} 3405 (OH), 2978 (CH), 1746 (C=O), 1671 (C=O), 1252 (CO), 1059 (CO); δ_H(300 MHz; $CDCl_3$) 7.43 (1H, d, *J* = 3.0, ArH), 7.38 (2H, d, *J* = 9.0, ArH), 7.18 (1H, dd, *J* = 9.0, 3.0, ArH), 6.93 (3H, m, ArH), 5.29 (1H, d, *J* = 9.0, ArCH), 5.13 (1H, t, *J* = 3.0, NH), 5.08 (2H, s, OCH_2Ar), 4.46 (1H, d, *J* = 9.0, EtO(C=O)CH), 4.16-4.26 (2H, m, CH_2CH_3), 3.82 (3H, s, OCH_3), 2.68 (1H, s, OH), 1.37 (9H, s, $(CH_3)_3$), 1.25 (3H, t, *J* = 9.0, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 170.8, 159.7, 155.9, 154.2, 133.5, 129.0, 128.6, 128.4, 125.6, 123.5, 114.2 × 2, 80.5, 73.5, 71.0, 62.0, 57.7, 55.5, 28.3, 14.3; HRMS (ES+): $C_{24}H_{31}{}^{35}ClNO_7$, $[M+H]^+$ requires 480.1784. Found 480.1782; $C_{24}H_{30}ClNO_7$ requires C, 60.1; H, 6.30; N, 2.92%. Found C, 60.5; H, 6.26; N, 2.76%.

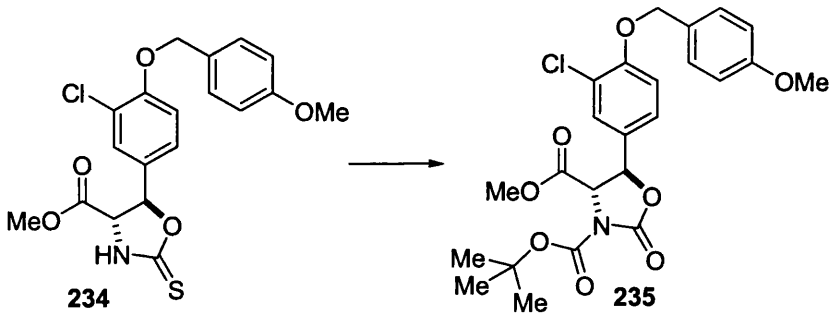
Preparation of (4*S,5*R**)-5-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid methyl ester 234**



A mixture of $Mg(ClO_4)_2$ (360 mg, 1.6 mmol) and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one **154** (3.0 g, 16.1 mmol) was stirred in dry DCM (120 mL) under nitrogen at 0 °C. After 15 min, 4-(4-methoxybenzyloxy)-3-chlorobenzaldehyde **233** (4.90 g, 17.7 mmol) and di*iso*propylethylamine (561 μL, 3.2 mmol) were added and the mixture was stirred for a further 3 h. The reaction was quenched with saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resultant foam was dissolved in dry THF (120 mL) and cooled to 0 °C. A solution of methyl magnesium bromide (3 M in diethyl ether, 6.9 mL, 20.9 mmol) was added to methanol (46 mL) at 0 °C and subsequently added to the previous solution *via* cannula transfer. After 3 min. of vigorous stirring the reaction was quenched by addition of an aqueous pH 7 phosphate buffer. The mixture was concentrated under reduced pressure, taken up in aqueous 1 M HCl and extracted with DCM. The organic layer was separated and the aqueous layer extracted further with DCM. The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide the title compound *syn*-**234** (4.9 g, 75%) as a white solid; mp 192-193 °C (DCM-

EtOAc); ν_{max}(KBr)/cm^{-1} 3177 (NH), 1741 (C=O), 1511 (NHC=S), 1246 (CO), 1173 (CO); δ_H(300 MHz; $CDCl_3$) 7.44 (1H, d, J = 3.0, ArH), 7.38 (2H, d, J = 9.0, ArH), 7.24 (1H, dd, J = 9.0, 3.0, ArH), 7.00 (1H, d, J = 9.0, ArH), 6.92 (2H, m, ArH), 5.88 (1H, d, J = 6.0, ArCH), 5.11 (2H, s, $ArCH_2OAr$), 4.45 (1H, d, J = 6.0, MeO(C=O)CH), 3.88 (3H, s, (C=O)OCH_3), 3.82 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 188.9, 168.3, 159.8, 155.4, 129.9, 129.0, 128.1, 128.0, 125.5, 124.4, 114.5, 114.3, 85.0, 71.0, 64.4, 55.5, 53.8; HRMS (ES+): $C_{19}H_{19}{}^{35}ClNO_5S$, $[M+H]^+$ requires 408.0667. Found 408.0665; $C_{19}H_{18}ClNO_5S$ requires C, 55.9; H, 4.45; N, 3.43%. Found C, 55.7; H, 4.47; N, 3.40%.

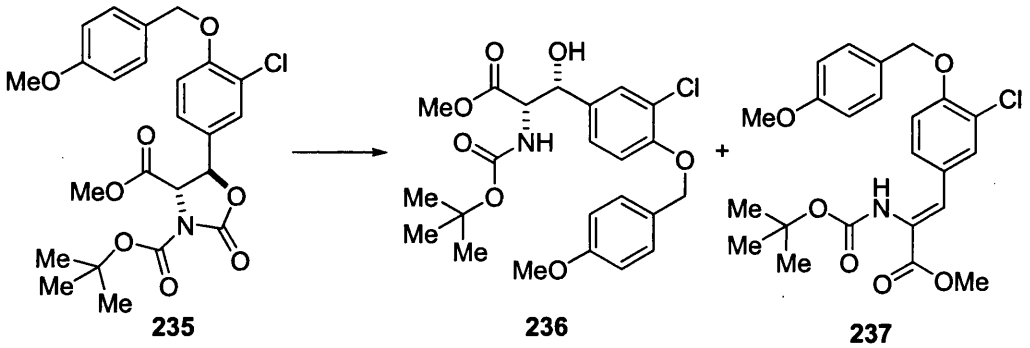
Preparation of (4*S,5*R**)-5-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-oxo-oxazolidine-3, 4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester 235**



(4*S**,5*R**)-5-[3-Chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid methyl ester **234** (4.175 g, 10.24 mmol) was stirred in dry DCM (120 mL) under a nitrogen atmosphere at RT. To this solution was added di-*tert*-butyl dicarbonate (2.46 g, 11.26 mmol) followed by 4-dimethylaminopyridine (63 mg, 0.52 mmol). The mixture effervesced and was allowed to stir 1 h. The mixture was then cooled to 0 °C and 30 wt.% hydrogen peroxide (39 mL) was added portion-wise followed by formic acid (39 mL). The mixture was allowed to stir for 1 h after which time the reaction was deemed complete. The reaction was quenched by the addition of the mixture to 1 M aqueous K_2CO_3 (750 mL). The organic layer was separated

and the aqueous layer washed with DCM. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide *oxazolidinone syn*-**235** (3.68 g, 73%), as a white foam; ν_{max}(KBr)/cm^{-1} 2980 (NH), 1829 (C=O), 1756 (C=O), 1250 (CO), 1061 (CO); δ_H(300 MHz; $CDCl_3$) 7.34-7.41 (3H, m, ArH), 7.19 (1H, dd, *J* = 8.7, 2.4, ArH), 7.00 (1H, d, *J* = 8.4, ArH), 6.92 (2H, d, *J* = 8.7, ArH), 5.28 (1H, d, *J* = 4.5, ArCH), 5.10 (2H, s, OCH_2Ar), 4.60 (1H, d, *J* = 4.5, MeO(C=O)CH), 3.87 (3H, s, (C=O)OCH_3), 3.81 (3H, s, OCH_3), 1.50 (9H, s, $C(CH_3)_3$); δ_C(75 MHz; $CDCl_3$) 168.9, 159.7, 155.1, 150.6, 148.5, 130.1, 129.0, 128.0, 127.4, 124.8, 124.2, 114.4, 114.2, 85.2, 75.2, 70.9, 63.7, 55.4, 53.5, 27.9; HRMS (ES+): $C_{24}H_{30}{}^{35}ClN_2O_8$, $[M+NH_4]^+$ requires 509.1685. Found 509.1684; $C_{24}H_{26}ClNO_8$ requires C, 58.6; H, 5.33; N, 2.85%. Found C, 58.4; H, 5.35; N, 2.72%.

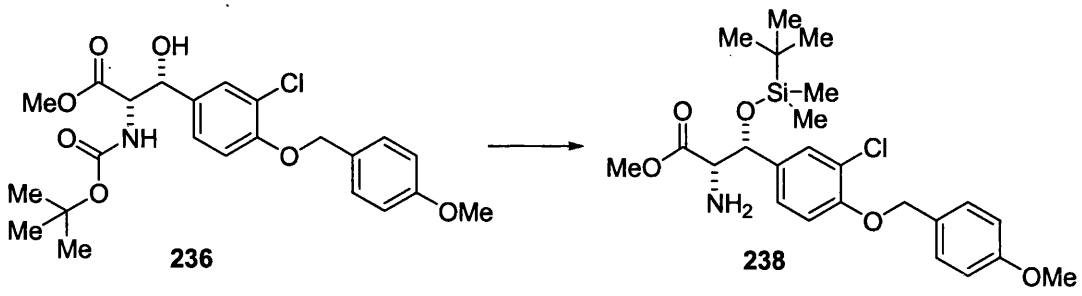
Preparation of (2*S,3*R**)-2-*tert*-butoxycarbonylamino-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-3-hydroxy-propionic acid methyl ester 236**



(4*S**,5*R**)-5-[3-Chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-oxo-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester **235** (3.29 g, 6.69 mmol) was stirred in dry MeOH (100 mL) under a nitrogen atmosphere at -20 °C. To this solution was added cesium carbonate (0.87 g, 2.67 mmol). The mixture was allowed to stir for 2 h after which time the reaction was deemed complete. The mixture was then concentrated under reduced pressure. The residue was taken up in EtOAc and washed with water and brine and dried

(Na_2SO_4). After filtration the solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2 then 90:10 and 0:100) to provide, in order of elution, *(Z)-enamide* **237** (by-product) (370 mg, 12%), as a white solid; 113-114 °C (DCM-EtOAc); ν_{max}(KBr)/cm^{-1} 2944 (CH), 1705 (C=O), 1250 (CO), 1160 (CO); δ_H(300 MHz; $CDCl_3$) 7.63 (1H, d, *J* = 2.4, ArH), 7.37 (3H, d, *J* = 8.7, ArH), 7.20 (1H, s, C=CH), 6.90-6.95 (3H, m, ArH), 6.26 (1H, s, NH), 5.11 (2H, s, OCH_2Ar), 3.84 (3H, s, $(C=O)OCH_3$), 3.82 (3H, s, OCH_3), 1.42 (9H, s, $(CH_3)_3$); δ_C(75 MHz; $CDCl_3$) 166.5, 160.0, 155.2, 153.0, 131.8, 130.5, 129.6, 129.5, 128.5, 128.2, 123.6, 114.4, 113.7, 81.5, 71.0, 55.7, 53.1, 28.6; *m/z* (EI+) 447 (7%, M^+); $C_{23}H_{26}ClNO_6$ requires C, 61.6; H, 5.85; N, 3.13%. Found C, 61.3; H, 5.85; N, 3.04%. Assignment of (*E*)-configuration was accomplished through NOESY experiment, coupling was observed between NH, 6.26 ppm and ArH, 7.63 ppm (Appendix F); and *hydroxycarbamate syn-* **236** (1.87 g, 60%), as a white solid; mp 108-109 °C (DCM-EtOAc); ν_{max}(KBr)/cm^{-1} 3403 (OH), 2978 (CH), 1751 (C=O), 1670 (C=O), 1253 (CO), 1060 (CO); δ_H(300 MHz; $CDCl_3$) 7.42 (1H, m, ArH), 7.37 (2H, d, *J* = 8.7, ArH), 7.17 (1H, m, ArH), 6.90-6.94 (3H, m, ArH), 5.30 (1H, d, *J* = 8.4, ArCH), 5.16 (1H, s, NH), 5.07 (2H, s, OCH_2Ar), 4.48 (1H, d, *J* = 8.4, MeO(C=O)CH), 3.81 (3H, s, $(C=O)OCH_3$), 3.76 (3H, s, OCH_3), 2.66 (1H, s, OH), 1.35 (9H, s, $(CH_3)_3$); δ_C(75 MHz; $CDCl_3$) 169.6, 157.8, 154.0, 152.3, 131.7, 127.2, 126.8, 126.4, 123.8, 121.6, 112.4, 112.3, 78.7, 71.4, 69.1, 57.7, 53.7, 51.1, 26.5; HRMS (ES+): $C_{23}H_{29}{}^{35}ClNO_7$, $[M+H]^+$ requires 466.1627. Found 466.1630; $C_{23}H_{28}ClNO_7$ requires C, 59.3; H, 6.06; N, 3.01%. Found C, 59.3; H, 6.05; N, 3.13%.

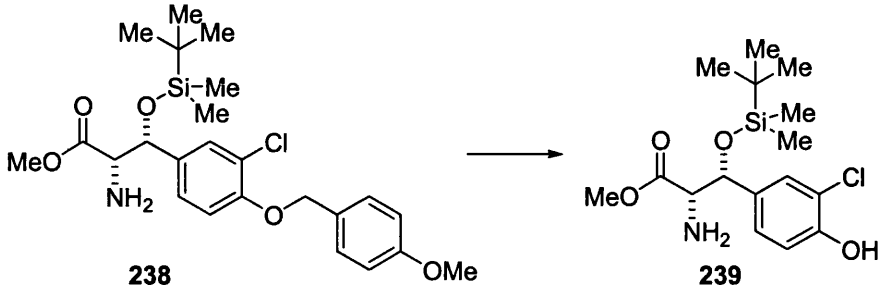
Preparation of (2*S,3*R**)-2-amino-3-(*tert*-butyl-dimethyl-silanyloxy)-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-propionic acid methyl ester 238**



(2*S**,3*R**)-2-*tert*-Butoxycarbonylamino-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-3-hydroxy-propionic acid methyl ester **236** (392 mg, 0.84 mmol) was stirred in dry DCM (25 mL) under a nitrogen atmosphere at 0 °C. To this solution was added drop-wise, 2,6-lutidine (0.87 g, 2.67 mmol), followed by *tert*-butyldimethylsilyl triflate (502 μL, 2.19 mmol). The mixture was allowed to warm to RT over 1 h after which time the reaction was deemed complete. The mixture was then concentrated under reduced pressure and the residue taken up in MeOH (6 mL) and treated with aqueous K_2CO_3 (117 mg, 0.84 mmol in 2 mL H_2O). After 1 h DCM was added and the organic extract was washed with brine. The extract was then concentrated *in vacuo* and the resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 1:1) to provide the title compound, *syn-amino-TBS ether* **238** (402 mg, 100%), as a colourless oil; ν_{max}(KBr)/cm^{-1} 3391 (NH), 3325 (NH), 2952 (CH), 2857 (CH), 1746 (C=O), 1250 (CO), 1059 (CO); δ_H(300 MHz; DMSO) 7.36-7.41 (3H, m, ArH), 7.16-7.26 (2H, m, ArH), 6.96 (2H, d, *J* = 9.0, ArH), 5.09 (2H, s, OCH_2Ar), 5.00 (1H, d, *J* = 3.0, ArCH), 3.76 (3H, s, OCH_3), 3.61 (3H, s, $(C=O)OCH_3$), 3.39 (1H, d, *J* = 3.0, MeO(C=O)CH), 1.56 (2H, s, NH_2), 0.83 (9H, s, $(SiCH_3)_3$), -0.04 (3H, s, $SiCH_3$), -0.21 (3H, s, $SiCH_3$); δ_C(75 MHz; $CDCl_3$) 171.3, 159.9, 155.7, 135.5, 129.3, 128.9, 128.6, 125.8, 123.4, 114.4, 114.1, 74.4, 71.2, 60.8, 55.7, 52.5, 26.1, 18.5, -4.2, -5.1; HRMS (ES+): $C_{24}H_{35}{}^{35}ClNO_5Si$,

$[M+H]^+$ requires 480.1968. Found 480.1969; $C_{24}H_{34}ClNO_5Si$ requires C, 60.0; H, 7.14; N, 2.92%. Found C, 59.6; H, 7.27; N, 2.65%.

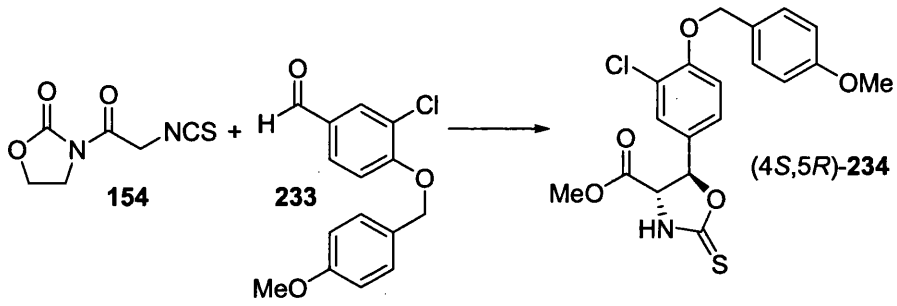
Preparation of (2*S,3*R**)-2-amino-3-(*tert*-butyl-dimethyl-silanyloxy)-3-(3-chloro-4-hydroxy-phenyl)-propionic acid methyl ester 239**



(2*S**,3*R**)-2-Amino-3-(*tert*-butyl-dimethyl-silanyloxy)-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-propionic acid methyl ester **238** (160 mg, 0.33 mmol) was stirred in dry MeOH (4 mL) with 20% $Pd(OH)_2$ on carbon (12 mg) under a hydrogen atmosphere at RT. The mixture was stirred for 30 min. after which time the reaction was deemed complete. After a nitrogen purge the mixture was filtered through celite and then concentrated under reduced pressure. The resultant white solid was purified by flash chromatography (SiO_2, DCM:EtOAc, 1:1) to provide the title compound, *phenol* **239** (72 mg, 60%), as a white solid; mp 116 °C (DCM-EtOAc); ν_{max}(KBr)/cm^{-1} 3352 (NH), 3283 (NH), 2954 (CH), 2857 (CH), 1734 (C=O), 1292 (SiC), 1257 (CO), 1084 (CO); δ_H(400 MHz; DMSO) 10.07 (1H, s, ArOH), 7.29 (1H, d, *J* = 2.0, ArH), 7.08 (1H, dd, *J* = 8.4, 2.0, ArH), 6.89 (1H, d, *J* = 8.4, ArH), 4.93 (1H, d, *J* = 3.2, ArCH), 3.61 (3H, s, (C=O)OCH_3), 3.37 (1H, d, *J* = 3.2, MeO(C=O)CH), 1.56 (2H, s, NH_2), 0.83 (9H, s, $SiC(CH_3)_3$), -0.04 (3H, s, $SiCH_3$), -0.20 (3H, s, $SiCH_3$); δ_C(75 MHz; $CDCl_3$) 173.9, 151.9, 133.9, 127.2, 125.8, 120.7, 117.1, 74.4, 62.0, 52.7, 26.1, 18.5, -4.2, -5.2; HRMS (ES+): $C_{16}H_{27}{}^{35}ClNO_4Si$, $[M+H]^+$ requires 360.1392. Found 360.1391; $C_{16}H_{26}ClNO_4Si$ requires C, 53.3; H, 7.28; N, 3.89%. Found C, 53.0; H, 7.24; N, 3.82%.

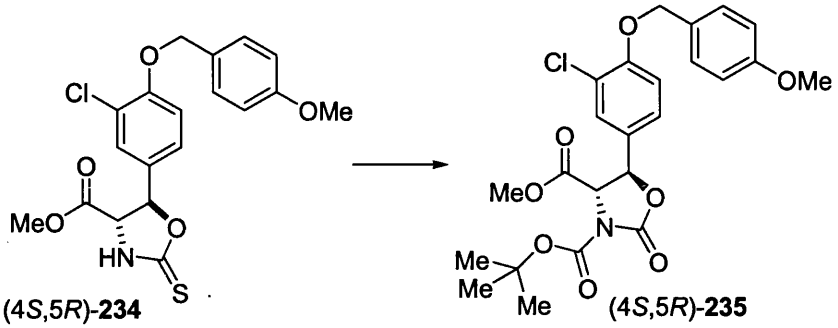
III 12 Asymmetric preparation of (2*S*,3*R*)-2-amino-3-(*tert*-butyl-dimethyl-silanyloxy)-3-(3-chloro-4-hydroxy-phenyl)-propionic acid methyl ester 239; analogue of AA-6 building block of vancomycin

Preparation of (4*S*,5*R*)-5-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid methyl ester 234



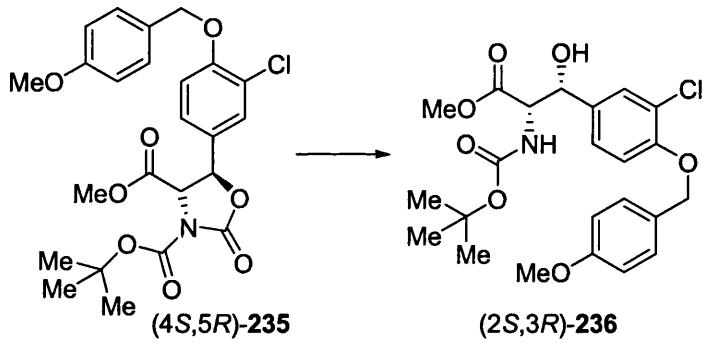
The reaction was carried out according to the experimental procedure above (Section III 4) with 4-(4-methoxybenzyloxy)-3-chlorobenzaldehyde **233** (210 mg, 0.76 mmol) and MeOH (5 mL). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 95:5) to provide, in order of elution, the title compound and *anti*-diastereomer (220 mg, 78%), *syn*:*anti* = 93:7, ee_{syn} = 94%, $[\alpha]_D^{20}$ = +25.0 (c = 1.0, DCM). Data identical to that reported earlier. The enantiomers of the *syn*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 37.7 min. and t_{R2} = 40.8 min.

Preparation of (4*S*,5*R*)-5-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-oxo-oxazolidine-3, 4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester 235



The reaction was carried out according to the experimental procedure above (Section III 10) with (4*S*,5*R*)-5-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid methyl ester **234** (370 mg, 0.91 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide *syn-oxazolidinone syn*-**235** (323 mg, 72%), $[\alpha]_D^{21}$ = +52.0 (*c* = 1.0, DCM). Data identical to that reported earlier.

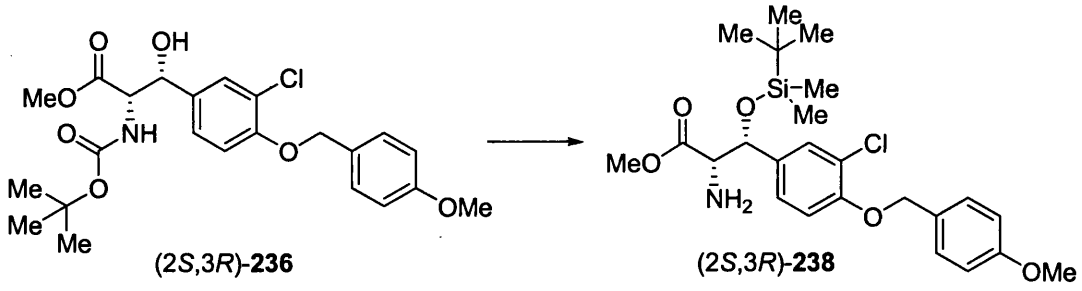
Preparation of (2*S*,3*R*)-2-*tert*-butoxycarbonylamino-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-3-hydroxy-propionic acid methyl ester 236



The reaction was carried out according to the experimental procedure above (Section III 10) with (4*S*,5*R*)-5-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-oxo-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester **235** (235 mg, 0.48 mmol). The resultant residue was purified by flash

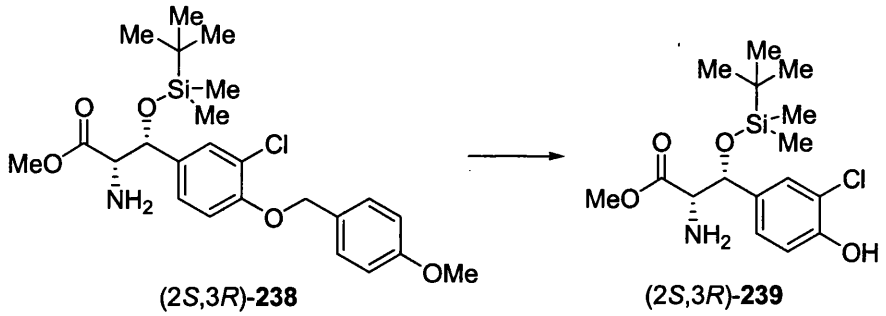
chromatography (SiO_2, DCM:EtOAc, 95:5 then 0:100) to provide *hydroxycarbamate syn*-**236** (130 mg, 60%) as a white solid, $[\alpha]_D^{21}$ = -11.0 (*c* = 1.0, DCM). Data identical to that reported earlier.

Preparation of (2*S*,3*R*)-2-amino-3-(*tert*-butyl-dimethyl-silanyloxy)-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-propionic acid methyl ester 238



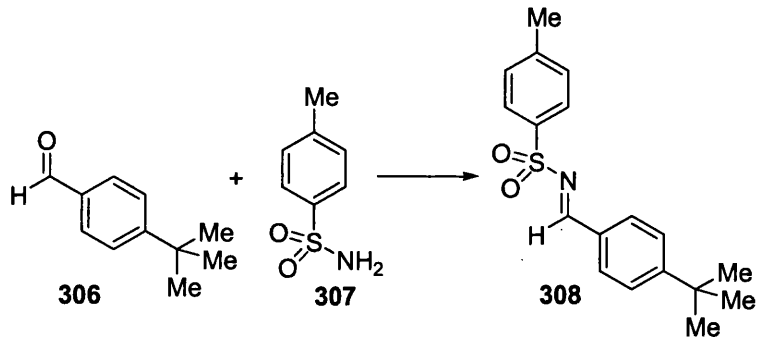
The reaction was carried out according to the experimental procedure above (Section III 10) with (2*S*,3*R*)-2-*tert*-butoxycarbonylamino-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-3-hydroxy-propionic acid methyl ester **236** (114 mg, 0.25 mmol). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 1:1) to provide the title compound, *amino-TBS ether syn*-**238** (117 mg, 100%) as a white solid, $[\alpha]_D^{21}$ = -23.0 (*c* = 1.0, DCM). Data identical to that reported earlier.

Preparation of (2*S*,3*R*)-2-amino-3-(*tert*-butyl-dimethyl-silanyloxy)-3-(3-chloro-4-hydroxy-phenyl)-propionic acid methyl ester 239



The reaction was carried out according to the experimental procedure above (Section III 10) with (2*S*,3*R*)-2-amino-3-(*tert*-butyl-dimethyl-silanyloxy)-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-propionic acid methyl ester **238** (33 mg, 0.07 mmol), MeOH (1 mL) and 20% $Pd(OH)_2$ on carbon (3 mg). The resultant residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 1:1) to provide the title compound, *phenol syn*-**239** (17 mg, 69%) as a white solid, $[\alpha]_D^{20}$ = -30.0 (*c* = 1.0, DCM). Data identical to that reported earlier.

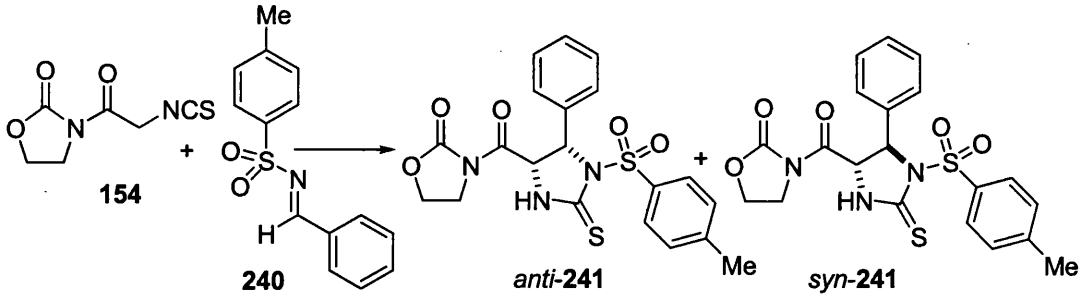
III 13 Preparation of *N*-(4-*tert*-butyl-benzylidene)-4-methyl-benzenesulfonamide 308; to serve as a typical experimental procedure for the preparation of *N*-tosylbenzaldimines employed in the asymmetric Mannich-type reaction



To a refluxing solution of *p*-(*t*-butyl)benzaldehyde **306** (3.0 mL, 17.9 mmol) *p*-toluenesulfonamide **307** (3.07 g, 17.9 mmol) in toluene (50 mL) employing Dean and Stark apparatus was added portion-wise boron trifluoride-diethyl etherate (0.6 mL, 4.7 mmol). The mixture was refluxed for 4 h and then cooled and extracted with aqueous 2 M sodium hydroxide and washed with water. The organic phase was separated, dried over Na_2SO_4 and concentrated to yield a solid which was recrystallised from DCM-light petroleum (bp 40-

60 °C) to provide the title compound as a white solid (4.8 g, 85%); mp 119 °C (DCM-light petroleum (bp 40-60 °C)); ν_{max}(KBr)/cm^{-1} 2968 (CH), 1596 (C=N), 1321 (SO_2), 1156 (SO_2); δ_H(300 MHz; $CDCl_3$) 9.01 (1H, s, (N=C)H), 7.85-7.89 (4H, m, ArH), 7.50 (2H, d, J = 8.7, ArH), 7.33 (2H, d, J = 8.1, ArH), 2.43 (3H, s, $ArCH_3$), 1.33 (9H, s, $C(CH_3)_3$); δ_C(75 MHz; $CDCl_3$) 170.4, 159.7, 144.8, 135.9, 131.7, 130.2, 130.1, 128.4, 126.6, 35.8, 31.4, 22.0; m/z (EI+) 315 (100%, M^+); $C_{18}H_{21}NO_2S$ requires C, 68.5; H, 6.71; N, 4.44%. Found C, 68.5; H, 6.64; N, 4.51%.

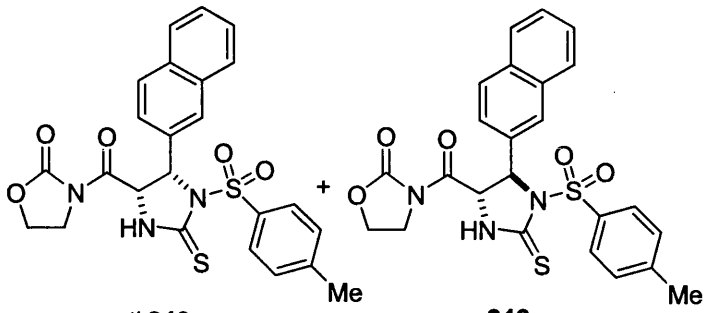
III 14 Preparation of (4*S**,5*S**)-3-[5-phenyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-241 and (4*S**,5*R**)-3-[5-phenyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *syn*-241; to serve as a typical experimental procedure for the racemic preparation of adducts of *N*-tosylimines and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154



A mixture of $Mg(ClO_4)_2$ (15 mg, 0.07 mmol) and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one **154** (128 mg, 0.69 mmol) was stirred for 1 h in dry DCM (15 mL) with activated powdered 4 Å MS (200 mg) under nitrogen at RT. The

temperature was then lowered to -78 °C. After 15 min, *N*-(4-toluenesulfonyl)benzaldimine **240** (358 mg, 1.38 mmol) and di*iso*propylethylamine (24 μL, 0.14 mmol) were added and the mixture was stirred for a further 24 h at -78 °C. The reaction was quenched with saturated aqueous ammonium chloride (5 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 90:10) to provide the title compounds, in order of elution, *imidazolidinethione syn*-**241** (36 mg, 11%), as a white foam; ν_{max}(KBr)/cm^{-1} 3353 (NH), 1777 (C=O), 1699 (C=O), 1491 (NHC=S), 1357 (SO_2), 1164 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.58 (2H, d, *J* = 8.3, ArH), 7.33-7.38 (5H, m, ArH & NH), 7.10-7.15 (3H, m, ArH), 6.34 (1H, d, *J* = 1.2, ArCH), 4.87 (1H, d, *J* = 1.2, N(C=O)CH), 4.50-4.61 (2H, m, OCH_2), 4.04-4.18 (2H, m, NCH_2) 2.37 (3H, s, $ArCH_3$); δ_C(75 MHz; DMSO) 178.7, 167.0, 152.7, 143.4, 140.9, 140.2, 138.5, 134.3, 128.31, 127.8, 127.7, 127.6, 125.7, 124.6, 65.8, 62.3, 60.9, 41.7, 20.0; HRMS (ES+): $C_{20}H_{20}N_3O_5S_2$, $[M+H]^+$ requires 446.0839. Found 446.0830; and *imidazolidinethione anti*-**241** (212 mg, 69%), as white crystals; mp 220-222 °C ($CHCl_3$); ν_{max}(KBr)/cm^{-1} 3338 (NH), 1776 (C=O), 1704 (C=O), 1477 (NHC=S), 1364 (SO_2), 1169 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.42 (2H, d, *J* = 8.3, ArH), 7.25-7.37 (4H, m, ArH & NH), 7.18 (2H, d, *J* = 7.2, ArH), 7.07 (2H, d, *J* = 8.3, ArH), 6.26 (1H, d, *J* = 9.9, ArCH), 5.74 (1H, d, *J* = 9.9, N(C=O)CH), 4.30 (1H, app. dt, *J* = 6.0, 9.2, OCH_AH_B), 3.97 (1H, app. dt, *J* = 6.0, 9.2, OCH_AH_B), 3.75 (1H, m, NCH_CH_D), 3.06 (1H, m, NCH_CH_D) 2.35 (3H, s, $ArCH_3$); δ_C(75 MHz; $CDCl_3$) 179.2, 166.0, 152.7, 144.8, 135.0, 134.9, 129.6, 129.5, 128.7, 128.0, 66.2, 63.1, 62.3, 42.0, 21.6; HRMS (ES+): $C_{20}H_{20}N_3O_5S_2$, $[M+H]^+$ requires 446.0839. Found 446.0841.

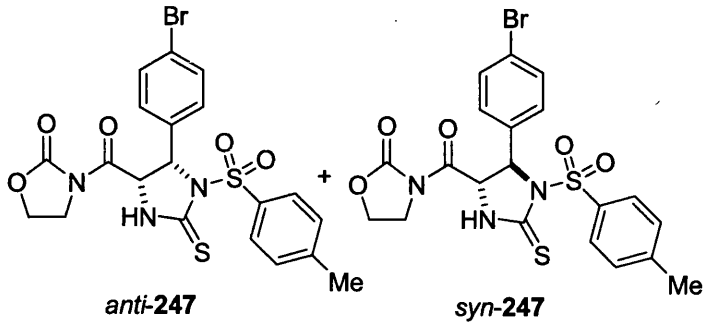
Preparation of (4*S,5*S**)-3-[5-naphthalen-2-yl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-246 and (4*S**,5*R**)-3-[5-naphthalen-2-yl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *syn*-246**



anti-**246** *syn*-**246**

The reaction was carried out according to the experimental procedure above (Section III 14) with 4-methyl-*N*-naphthalen-2-ylmethylene-benzenesulfonamide **309** (427 mg, 1.38 mmol) to provide, in order of elution, *syn-imidazolidinethione syn*-**246** (8 mg, 2%) which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**246** (128 mg, 37%) as a white solid; mp 222-223 °C (DCM-EtOAc); ν_{max}(KBr)/cm^{-1} 3357 (NH), 1770 (C=O), 1699 (C=O), 1476 (NHC=S), 1367 (SO_2), 1168 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.67-7.83 (4H, m, ArH), 7.48-7.57 (2H, m, ArH & NH), 7.38 (2H, d, J = 8.3, ArH), 7.21 (1H, d, J = 9.0, ArH), 6.87 (2H, d, J = 8.3, ArH), 6.42 (1H, d, J = 9.9, ArCH), 5.82 (1H, d, J = 9.9, N(C=O)CH), 4.10-4.23 (1H, m, OCH_AH$_B$), 3.57-3.70 (2H, m, CH_2), 2.76-2.90 (1H, m, NCH$_C$$H_D$), 2.26 (3H, s, $ArCH_3$); δ_C(75 MHz; $CDCl_3$) 179.3, 166.0, 152.8, 144.8, 134.9, 133.4, 132.6, 132.0, 129.3, 128.6, 128.4, 127.7, 127.6, 127.2, 126.8, 124.7, 66.4, 63.0, 62.4, 42.0, 21.5; *m/z* (CI+) 496 (10%, $[M+H]^+$); $C_{24}H_{21}N_3O_5S_2$ requires C, 58.2; H, 4.27; N, 8.48%. Found C, 58.1; H, 4.25; N, 8.63%.

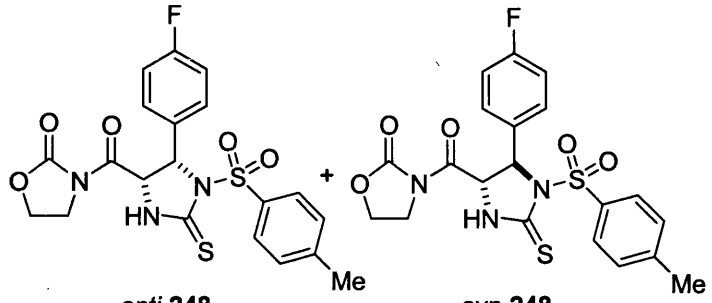
Preparation of (4*S,5*S**)-3-[5-(4-bromo-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-247 and (4*S**,5*R**)-3-[5-(4-bromo-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *syn*-247**



anti-**247** *syn*-**247**

The reaction was carried out according to the experimental procedure above (Section III 14) with *N*-(4-bromo-benzylidene)-4-methyl-benzenesulfonamide **310** (467 mg, 1.38 mmol) to provide, in order of elution, the *syn-imidazolidinethione syn*-**247** (11 mg, 3%) which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**247** (80 mg, 21%) as a white solid; mp 233-235 °C (DCM-EtOAc); ν_{max}(KBr)/cm^{-1} 3341 (NH), 1771 (C=O), 1698 (C=O), 1479 (NHC=S), 1367 (SO_2), 1169 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.50 (2H, d, J = 8.1, ArH), 7.41 (2H, d, J = 8.3, ArH), 7.12 (2H, d, J = 8.1, ArH), 7.07 (2H, d, J = 8.3, ArH), 6.25 (1H, d, J = 9.9, ArCH), 5.70 (1H, d, J = 9.9, N(C=O)CH), 4.34 (1H, app. dt, J = 6.0, 8.1, OCH_AH_B), 4.10 (1H, app. dt, J = 6.0, 8.1, OCH$_A$$H_B$), 3.80 (1H, m, NC$H_CH_D$), 3.22 (1H, m, NCH$_C$$H_D$), 2.39 (3H, s, $ArCH_3$); δ_C(75 MHz; DMSO) 178.8, 166.1, 153.4, 145.0, 135.7, 135.6, 131.9, 129.3, 129.2, 129.1, 122.6, 65.2, 63.7, 62.3, 42.5, 21.5; HRMS (ES+): $C_{20}H_{19}{}^{79}BrN_3O_5S_2$, $[M+H]^+$ requires 523.9944. Found 523.9943; $C_{20}H_{18}BrN_3O_5S_2$ requires C, 45.8; H, 3.46; N, 8.01%. Found C, 45.7; H, 3.46; N, 8.10%.

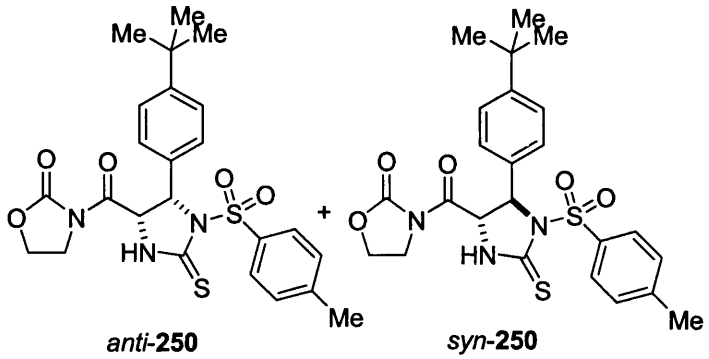
Preparation of (4*S,5*S**)-3-[5-(4-fluoro-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-248 and (4*S**,5*R**)-3-[5-(4-fluoro-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *syn*-248**



anti-**248** *syn*-**248**

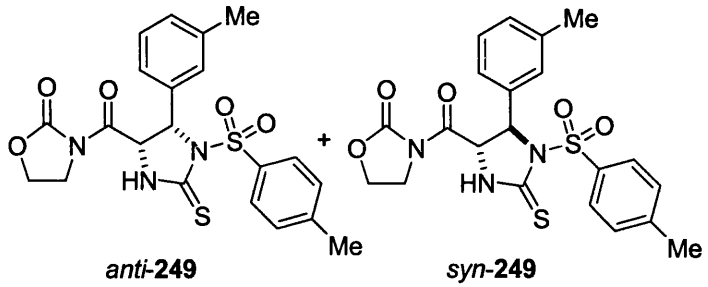
The reaction was carried out according to the experimental procedure above (Section III 14) with *N*-(4-fluoro-benzylidene)-4-methyl-benzenesulfonamide **311** (383 mg, 1.38 mmol) to provide, in order of elution, *syn-imidazolidinethione syn*-**248** which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**248** (35 mg, 10%) as a white solid; mp 238 °C (DCM-EtOAc); ν_{max}(KBr)/cm^{-1} 3334 (NH), 1779 (C=O), 1706 (C=O), 1510 (NHC=S), 1395 (SO_2), 1170 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.48 (2H, d, J = 8.4, ArH), 7.16-7.21 (2H, m, ArH), 7.11 (2H, d, J = 8.1, ArH), 6.94-7.04 (3H, m, ArH & NH), 6.27 (1H, d, J = 9.9, ArCH), 5.72 (1H, d, J = 9.9, N(C=O)CH), 4.35 (1H, app. dt, J = 6.6, 9.3, OCH_AH_B), 4.09 (1H, app. dt, J = 6.6, 9.3, OCH$_A$$H_B$), 3.79-3.89 (1H, m, NC$H_CH_D$), 3.16-3.24 (1H, m, NCH$_C$$H_D$), 2.37 (3H, s, $ArCH_3$); δ_C(75 MHz; DMSO) 179.1, 165.9, 163.1 (d, $^1J_{CF}$ = 250.0), 152.7, 145.1, 135.0, 131.1 (d, $^4J_{CF}$ = 3.3), 130.0 (d, $^3J_{CF}$ = 8.5), 129.4, 128.8, 115.7 (d, $^2J_{CF}$ = 21.7), 65.5, 63.1, 62.3, 42.1, 21.7; HRMS (ES+): $C_{20}H_{19}{}^{19}FN_3O_5S_2$, $[M+H]^+$ requires 464.0745. Found 464.0739; $C_{20}H_{18}FN_3O_5S_2$ requires C, 51.8; H, 3.91; N, 9.07%. Found C, 51.5; H, 4.02; N, 8.89%.

Preparation of (4*S,5*S**)-3-[5-(4-*tert*-butyl-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-250 and (4*S**,5*R**)-3-[5-(4-*tert*-butyl-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *syn*-250**



The reaction was carried out according to the experimental procedure above (Section III 14) with *N*-(4-*tert*-butyl-benzylidene)-4-methyl-benzenesulfonamide **308** (435 mg, 1.38 mmol) to provide, in order of elution, *syn-imidazolidinethione syn*-**250** (17 mg, 5%) which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**250** (132 mg, 38%) as a white foam; ν_{max}(KBr)/cm^{-1} 3340 (NH), 2963 (CH), 1782 (C=O), 1709 (C=O), 1476 (NHC=S), 1394 (SO_2), 1170 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.40 (2H, d, *J* = 8.4, ArH), 7.26 (2H, d, *J* = 8.4, ArH), 7.08 (2H, d, *J* = 8.4, ArH), 7.01 (2H, d, *J* = 8.4, ArH), 6.89 (1H, s, NH), 6.24 (1H, d, *J* = 9.9, ArCH), 5.71 (1H, d, *J* = 9.9, N(C=O)CH), 4.28 (1H, app. dt, *J* = 6.6, 9.0, OC*H*$_A$H$_B$), 3.88 (1H, app. dt, *J* = 6.6, 9.0, OCH$_A$*H*$_B$), 3.67-3.79 (1H, m, NC*H*$_C$H$_D$), 2.92-3.03 (1H, m, NCH$_C$*H*$_D$), 2.34 (3H, s, $ArCH_3$), 1.30 (9H, s, $C(CH_3)_3$); δ_C(75 MHz; $CDCl_3$) 179.6, 166.6, 153.3, 153.0, 145.0, 135.5, 132.3, 129.8, 129.0, 128.1, 125.8, 66.5, 63.4, 62.7, 42.5, 35.2, 31.7, 22.0; HRMS (ES+): $C_{24}H_{28}N_3O_5S_2$, $[M+H]^+$ requires 502.1465. Found 502.1464; $C_{24}H_{27}N_3O_5S_2$ requires C, 57.4; H, 5.43; N, 8.38%. Found C, 57.0; H, 5.46; N, 8.01%.

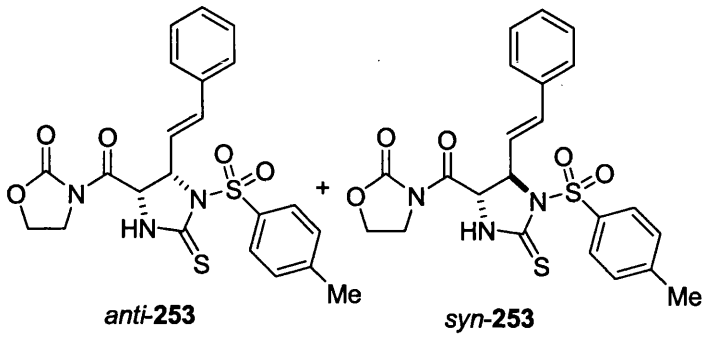
Preparation of (4*S,5*S**)-3-[2-thioxo-1-(toluene-4-sulfonyl)-5-*m*-tolyl-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-249 and (4*S**,5*R**)-3-[2-thioxo-1-(toluene-4-sulfonyl)-5-*m*-tolyl-imidazolidine-4-carbonyl]-oxazolidin-2-one *syn*-249**



anti-**249** *syn*-**249**

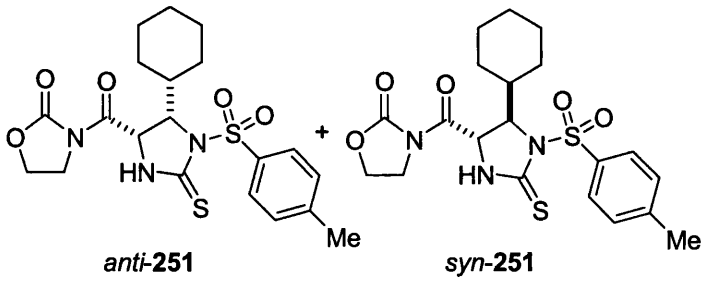
The reaction was carried out according to the experimental procedure above (Section III 14) with 4-methyl-*N*-(3-methyl-benzylidene)-benzenesulfonamide **312** (377 mg, 1.38 mmol) to provide, in order of elution, *syn-imidazolidinethione syn*-**249** which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**249** (101 mg, 31%) as a white foam; ν_{max}(KBr)/cm^{-1} 3334 (NH), 1780 (C=O), 1709 (C=O), 1491 (NHC=S), 1394 (SO_2), 1170 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.45 (2H, d, J = 8.3, ArH), 7.11-7.20 (2H, m, ArH), 7.07 (2H, d, J = 8.3, ArH), 6.95-7.03 (2H, m, ArH), 6.90 (1H, s, NH), 6.21 (1H, d, J = 9.9, ArCH), 5.73 (1H, d, J = 9.9, N(C=O)CH), 4.30 (1H, m, OCH_AH_B), 3.94 (1H, m, OCH$_A$$H_B$), 3.69-3.80 (1H, m, NC$H_CH_D$), 2.99-3.10 (1H, m, NCH$_C$$H_D$), 2.36 (3H, s, $ArCH_3$), 2.22 (3H, s, $ArCH_3$); δ_C(75 MHz; $CDCl_3$) 179.3, 166.1, 152.7, 144.8, 138.5, 135.0, 134.8, 130.2, 129.5, 128.6, 128.4, 125.1, 66.3, 63.1, 62.3, 42.1, 21.6, 21.2; HRMS (ES+): $C_{21}H_{22}N_3O_5S_2$, $[M+H]^+$ requires 460.0995. Found 460.1000; $C_{21}H_{21}N_3O_5S_2$ requires C, 54.9; H, 4.61; N, 9.14%. Found C, 54.6; H, 4.71; N, 8.94%.

Preparation of (4*S,5*S**)-3-[5-styryl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-253 and (4*S**,5*R**)-3-[5-styryl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *syn*-253**



The reaction was carried out according to the experimental procedure above (Section III 14) with 4-methyl-*N*-(3-phenyl-allylidene)-benzenesulfonamide **313** (395 mg, 1.38 mmol) to provide, in order of elution, *syn-imidazolidinethione syn*-**253** (10 mg, 3%) which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**253** (83 mg, 26%) as a white foam; ν_{max}(KBr)/cm^{-1} 3332 (NH), 1782 (C=O), 1706 (C=O), 1477 (NHC=S), 1394 (SO_2), 1169 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.92 (2H, d, *J* = 8.3, ArH), 7.33 (5H, m, ArH), 7.14 (2H, d, *J* = 8.3, ArH), 7.10 (1H, s, NH), 6.83 (1H, d, *J* = 15.0, CH=C*H*Ph), 5.88-6.03 (2H, m, ArCH & C*H*=CHPh), 5.65 (1H, d, *J* = 8.7, N(C=O)CH), 4.41 (1H, app. dt, *J* = 6.6, 9.3, OC*H*$_A$H$_B$), 4.15 (1H, app. dt, *J* = 6.6, 9.3, OCH$_A$*H*$_B$), 3.92-4.01 (1H, m, NC*H*$_C$H$_D$), 3.66-3.75 (1H, m, NCH$_C$*H*$_D$), 2.36 (3H, s, $ArCH_3$); δ_C(75 MHz; $CDCl_3$) 178.7, 166.2, 152.8, 145.0, 137.1, 135.5, 134.9, 129.8, 129.2, 129.0, 127.0, 120.8, 65.4, 63.3, 61.5, 42.4, 21.6; HRMS (ES+): $C_{22}H_{22}N_3O_5S_2$, $[M+H]^+$ requires 472.0995. Found 472.0999; $C_{22}H_{21}N_3O_5S_2$ requires C, 56.0; H, 4.49; N, 8.91%. Found C, 55.7; H, 4.50; N, 8.61%.

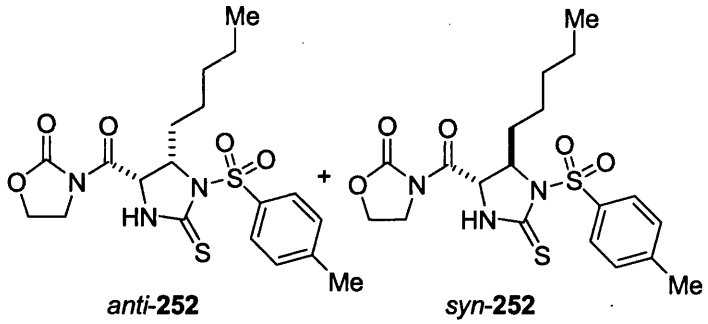
Preparation of (4*S,5*S**)-3-[5-cyclohexyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-251 and (4*S**,5*R**)-3-[5-cyclohexyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *syn*-251**



anti-**251** *syn*-**251**

The reaction was carried out according to the experimental procedure above (Section III 14) with *N*-cyclohexylmethylene-4-methyl-benzenesulfonamide **314** (366 mg, 1.38 mmol) to provide, in order of elution, *syn-imidazolidinethione syn*-**251** which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**251** (61 mg, 19%) as white crystals; mp 239 °C ($CHCl_3$); ν_{max}(KBr)/cm^{-1} 3302 (NH), 2932 (CH), 1771 (C=O), 1712 (C=O), 1517 (NHC=S), 1391 (SO_2), 1167 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.97 (2H, d, J = 8.3, ArH), 7.32 (2H, d, J = 8.3, ArH), 6.75 (1H, s, NH), 5.29 (2H, m, NC*H*CH & N(C=O)CH), 4.50-4.64 (2H, m, OCH_2CH_2), 3.98-4.19 (2H, m, CH_2CH_2N), 2.43 (3H, s, $ArCH_3$), 1.70-1.90 (3H, m, CH & CH_2), 1.40-1.70 (4H, m, CH_2), 1.02-1.24 (4H, m, CH_2); δ_C(75 MHz; $CDCl_3$) 180.0, 166.1, 152.6, 145.0, 135.6, 129.4, 129.1, 68.3, 63.1, 62.2, 42.8, 42.4, 29.4, 27.0, 26.5, 26.4, 25.8, 21.7; HRMS (ES+): $C_{20}H_{26}N_3O_5S_2$, $[M+H]^+$ requires 452.1308. Found 452.1308; $C_{20}H_{25}N_3O_5S_2$ requires C, 53.2; H, 5.58; N, 9.31%. Found C, 52.7; H, 5.47; N, 9.14%.

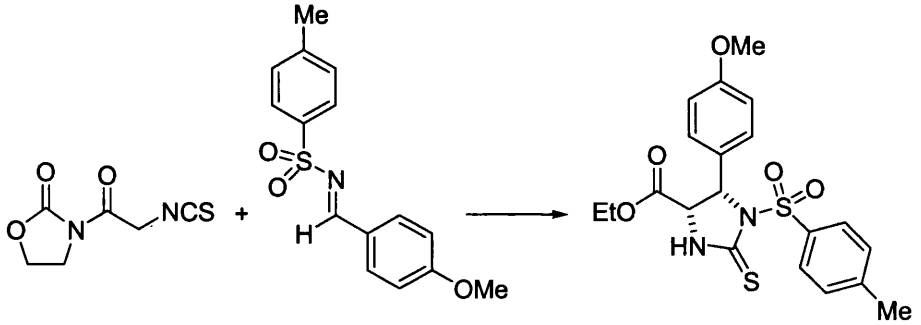
Preparation of (4*S,5*S**)-3-[5-pentyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-252 and (4*S**,5*R**)-3-[5-pentyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *syn*-252**



anti-**252** *syn*-**252**

The reaction was carried out according to the experimental procedure above (Section III 14) with *N*-hexylidene-4-methyl-benzenesulfonamide **315** (350 mg, 1.38 mmol) to provide, in order of elution, the *syn-imidazolidinethione syn*-**252** which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**252** (35 mg, 12%) as white crystals; mp 100-102 °C ($CHCl_3$); ν_{max}(KBr)/cm^{-1} 3369 (NH), 2957 (CH), 1780 (C=O), 1707 (C=O), 1477 (NHC=S), 1394 (SO_2), 1167 (SO_2); δ_H(300 MHz; $CDCl_3$) 8.01 (2H, d, *J* = 8.3, ArH), 7.33 (2H, d, *J* = 8.3, ArH), 6.61 (1H, s, NH), 5.34-5.45 (2H, m, NC*H*CH_2 & N(C=O)CH), 4.56 (2H, t, *J* = 8.1, OC*H*$_2$$CH_2$N), 3.98-4.18 (2H, m, $OCH_2CH_AH_BN$), 2.36 (3H, s, $ArCH_3$), 1.78-1.92 (1H, m, $CHCH_AH_B$), 1.58-1.67 (1H, m, $CHCH_AH_B$), 1.15-1.48 (6H, m, CH_2), 0.86 (3H, t, *J* = 6.6, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 179.6, 166.5, 153.1, 145.5, 135.9, 129.7, 129.5, 64.1, 63.6, 62.3, 42.9, 32.2, 32.1, 23.6, 22.7, 22.1, 14.3; $C_{19}H_{25}N_3O_5S_2$ requires C, 51.9; H, 5.73; N, 9.56%. Found C, 51.4; H, 5.71; N, 9.35%.

III 15 Preparation of (4S*,5S*)-5-(4-methoxy-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-317; to serve as a typical experimental procedure for the racemic preparation of derivatised adducts of *N*-tosylimines and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154

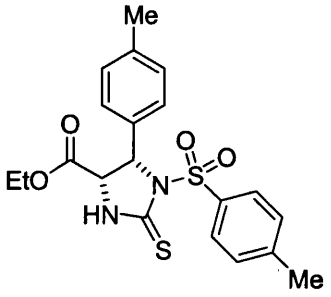


154 **316** ***anti*-317**

A mixture of $Mg(ClO_4)_2$ (15 mg, 0.07 mmol) and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one **154** (128 mg, 0.69 mmol) was stirred for 1 h in dry DCM (15 mL) with activated powdered 4 Å MS (200 mg) under nitrogen at RT. The temperature was then lowered to -78 °C. After 15 min, *N*-(4-methoxy-benzylidene)-4-methyl-benzenesulfonamide **316** (399 mg, 1.38 mmol) and di*iso*propylethylamine (24 μL, 0.14 mmol) were added and the mixture was stirred for a further 24 h at -78 °C. The reaction was quenched with saturated aqueous ammonium chloride (5 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 90:10) to provide, in order of elution, *syn-imidazolidinethione syn*-**257** which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**257** (85 mg, 27%) of which 62 mg, 0.13 mmol was dissolved in dry THF (3 mL) and cooled to 0 °C. A solution of

methyl magnesium bromide (3 M in diethyl ether, 92 μL, 0.28 mmol) was added to ethanol (1.0 mL) at 0 °C and subsequently added to the previous solution *via* cannula transfer. After 40 min. the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (5 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1 M, 10 mL) and DCM (10 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide the title compound *anti*-**317** (28 mg, 51%) as a white foam; ν_{max}(KBr)/cm^{-1} 3347 (NH), 1750 (C=O), 1479 (NHC=S), 1361 (SO_2), 1168 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.39 (2H, d, J = 8.3, ArH), 7.13 (2H, d, J = 8.9, ArH), 7.04 (2H, d, J = 8.3, ArH), 6.92 (1H, s, NH), 6.76 (2H, d, J = 8.9, ArH), 5.90 (1H, d, J = 9.5, ArCH), 4.95 (1H, d, J = 9.5, EtO(C=O)CH), 3.80 (5H, m, CH_2CH_3 & OCH_3), 2.35 (3H, s, $ArCH_3$), 0.87 (3H, t, J = 7.2, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 179.4, 166.1, 160.5, 144.7, 134.8, 129.6, 129.5, 128.6, 126.6, 113.9, 66.3, 62.0, 60.8, 55.4, 21.6, 13.6; HRMS (ES+): $C_{20}H_{23}N_2O_5S_2$, $[M+H]^+$ requires 435.1043. Found 435.1041.

Preparation of (4*S,5*S**)-2-thioxo-1-(toluene-4-sulfonyl)-5-*p*-tolyl-imidazolidine-4-carboxylic acid ethyl ester *anti*-319**

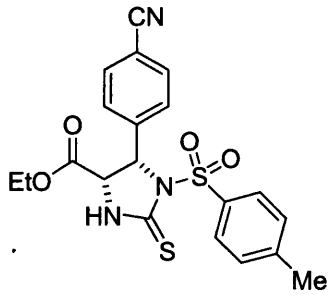


anti-**319**

The reaction was carried out according to the experimental procedure above (Section III 15) with 4-methyl-*N*-(4-methyl-benzylidene)-benzenesulfonamide

318 (377 mg, 1.38 mmol) to provide, in order of elution, *imidazolidinethione syn*-**256** which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**256** (129 mg, 41%) of which 87 mg, 0.19 mmol was dissolved in dry THF (4 mL) and cooled to 0 °C. The reaction was carried out according to the experimental procedure above (Section III 15) with a solution of methyl magnesium bromide (3 M in diethyl ether, 126 μL, 0.38 mmol) added to ethanol (1.4 mL) to provide the title compound *anti*-**319** (48 mg, 60%) as a white foam; ν_{max}(KBr)/cm^{-1} 3355 (NH), 1752 (C=O), 1479 (NHC=S), 1362 (SO_2), 1168 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.37 (2H, d, *J* = 8.7, ArH), 7.00-7.10 (6H, m, ArH), 6.95 (1H, s, NH), 5.89 (1H, d, *J* = 9.5, ArCH), 4.96 (1H, d, *J* = 9.5, EtO(C=O)CH), 3.71-3.86 (2H, m, CH_2CH_3), 2.34 (3H, s, $ArCH_3$), 2.34 (3H, s, $ArCH_3$), 0.83 (3H, t, *J* = 7.2, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 179.9, 166.5. 145.1, 139.9, 135.2, 131.9, 130.0, 129.5, 128.9, 128.5, 66.9, 62.4, 61.2, 22.0, 21.6, 13.9; HRMS (ES+): $C_{20}H_{23}N_2O_4S_2$, $[M+H]^+$ requires 419.1094. Found 419.1097.

Preparation of (4*S,5*S**)-5-(4-cyano-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-321**

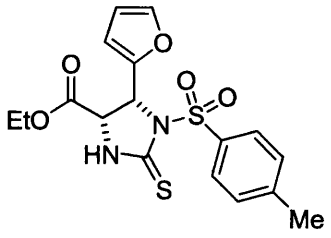


anti-**321**

The reaction was carried out according to the experimental procedure above (Section III 15) with *N*-(4-cyano-benzylidene)-4-methyl-benzenesulfonamide **320** (392 mg, 1.38 mmol) to provide, in order of elution, *imidazolidinethione syn*-**258** which could not be purified from *p*-toluene sulfonamide and

imidazolidinethione anti-**258** (91 mg, 28%) of which 65 mg, 0.14 mmol was dissolved in dry THF (3 mL) and cooled to 0 °C. The reaction was carried out according to the experimental procedure above (Section III 15) with a solution of methyl magnesium bromide (3 M in diethyl ether, 92 μL, 0.28 mmol) added to ethanol (1.0 mL) to provide the title compound *anti*-**321** (24 mg, 40%) as a white solid; mp 172 °C (DCM-*n*-hexane); ν_{max}(KBr)/cm^{-1} 3340 (NH), 2229 (ArCN), 1748 (C=O), 1499 (NHC=S), 1338 (SO_2), 1168 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.58 (2H, d, *J* = 8.4, ArH), 7.47 (2H, d, *J* = 8.4, ArH), 7.36 (2H, d, *J* = 8.4, ArH), 7.11 (2H, d, *J* = 8.4, ArH), 6.69 (1H, s, NH), 5.98 (1H, d, *J* = 9.6, ArCH), 5.00 (1H, d, *J* = 9.6, EtO(C=O)CH), 3.71-3.90 (2H, m, CH_2CH_3), 2.39 (3H, s, $ArCH_3$), 0.88 (3H, t, *J* = 7.2, CH_2CH_3); δ_C(100 MHz; DMSO) 179.3, 167.1, 145.5, 142.3, 135.6, 133.0, 129.7, 129.5, 129.0, 119.1, 112.2, 65.7, 62.0, 61.6, 22.0, 14.2; HRMS (ES+): $C_{20}H_{20}N_3O_4S_2$, $[M+H]^+$ requires 430.0890. Found 430.0895.

Preparation of (4*S,5*S**)-5-furan-2-yl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-323**

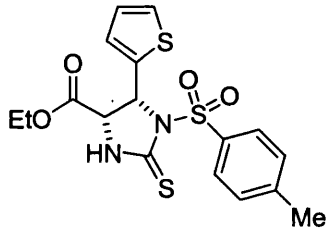


anti-**323**

The reaction was carried out according to the experimental procedure above (Section III 15) with *N*-furan-2-ylmethylene-4-methyl-benzenesulfonamide **322** (344 mg, 1.38 mmol) to provide, in order of elution, *imidazolidinethione syn*-**254** which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**254** (161 mg, 54%) of which 100 mg, 0.23 mmol was dissolved in dry THF (5 mL) and cooled to 0 °C. The reaction was carried out according to the experimental procedure above (Section III 15) with a

solution of methyl magnesium bromide (3 M in diethyl ether, 153 μL, 0.46 mmol) added to ethanol (1.7 mL) to provide the title compound *anti*-**323** (42 mg, 46%) as a yellow oil; ν_{max}(neat)/cm^{-1} 3333 (NH), 1751 (C=O), 1492 (NHC=S), 1365 (SO_2), 1169 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.47 (2H, d, *J* = 8.4, ArH), 7.26 (1H, m, CH=C*H*O), 7.13 (2H, d, *J* = 8.4, ArH), 6.79 (1H, s, NH), 6.51 (1H, d, *J* = 3.2, OC=CH), 6.37 (1H, app. dd, *J* = 3.2, 1.5, CHC*H*=CHO), 6.05 (1H, d, *J* = 9.3, ArCH), 4.90 (1H, d, *J* = 9.3, EtO(C=O)CH), 3.92-4.04 (2H, m, C*H*$_2$CH$_3$), 2.37 (3H, s, ArCH$_3$), 1.02 (3H, t, *J* = 7.2, CH$_2$C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 178.8, 165.6, 147.8, 144.9, 143.2, 134.6, 129.4, 128.8, 111.8, 110.7, 62.3, 59.7, 58.9, 21.7, 13.8; HRMS (ES+): $C_{17}H_{19}N_2O_5S_2$, $[M+H]^+$ requires 395.0730. Found 395.0728.

Preparation of (4*S,5*S**)-5-thiophen-2-yl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-325**

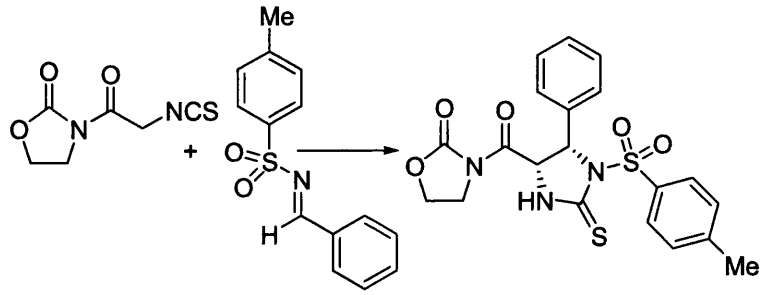


anti-**325**

The reaction was carried out according to the experimental procedure above (Section III 15) with 4-methyl-*N*-thiophen-2-ylmethylene-benzenesulfonamide **324** (366 mg, 1.38 mmol) to provide, in order of elution, *imidazolidinethione syn*-**255** which could not be purified from *p*-toluene sulfonamide and *imidazolidinethione anti*-**255** (56 mg, 18%) of which 47 mg, 0.10 mmol was dissolved in dry THF (2.5 mL) and cooled to 0 °C. The reaction was carried out according to the experimental procedure above (Section III 15) with a solution of methyl magnesium bromide (3 M in diethyl ether, 69 μL, 0.21 mmol) added to ethanol (0.8 mL) to provide the title

compound *anti*-**325** (28 mg, 65%) as a colourless oil; ν_{max}(neat)/cm^{-1} 3332 (NH), 1748 (C=O), 1474 (NHC=S), 1364 (SO_2), 1169 (SO_2); δ_H(300 MHz; $CDCl_3$) 7.41 (2H, d, *J* = 8.4, ArH), 7.25 (1H, d, *J* = 5.1, CH=C*H*S), 7.04-7.09 (3H, m, ArH & SC=CH), 6.92 (1H, app. dd, *J* = 5.1, 3.6, CHC*H*=CHS), 6.85 (1H, s, NH), 6.22 (1H, d, *J* = 8.7, ArCH) 4.96 (1H, d, *J* = 8.7, EtO(C=O)CH), 3.87-3.99 (2H, m, CH_2CH_3), 2.35 (3H, s, $ArCH_3$), 0.94 (3H, t, *J* = 7.2, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 177.7, 164.5, 143.8, 134.8, 133.5, 128.5, 128.0, 127.6, 125.9, 125.7, 61.2, 61.0, 59.8, 20.6, 12.5; HRMS (ES+): $C_{17}H_{19}N_2O_4S_3$, $[M+H]^+$ requires 411.0501. Found 411.0499.

III 16 Preparation of (4*S*,5*S*)-3-[5-phenyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-241; to serve as a typical experimental procedure for the asymmetric preparation of adducts of *N*-tosylimines and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154

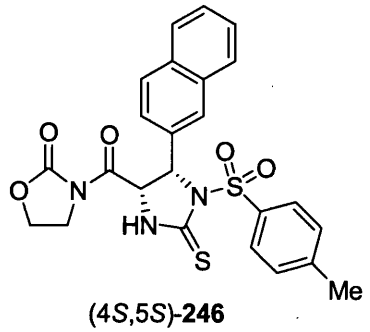


154 **240** (4*S*,5*S*)-**241**

A mixture of $Mg(ClO_4)_2$ (15 mg, 0.07 mmol), (*R*,*R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) **175** (37 mg, 0.08 mmol) and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one **154** (128 mg, 0.69 mmol) was stirred for 1 h in dry DCM (15 mL) with activated powdered 4 Å MS (200 mg) under nitrogen at RT. The temperature was then lowered to -78 °C. After 15 min, *N*-

(4-toluenesulfonyl)benzaldimine **240** (358 mg, 1.38 mmol) and di*iso*propylethylamine (24 μL, 0.14 mmol) were added and the mixture was stirred for a further 24 h at -78 °C. The reaction was quenched with saturated aqueous ammonium chloride (5 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 90:10) to provide the title compound (289 mg, 94%, *anti:syn* = 87:13, ee_{anti} = 96%, $[\alpha]_D^{30}$ = -52.0 (*c* = 0.5, $CHCl_3$)) as colourless crystals. Data identical to that reported earlier. The *syn-imidazolidinethione* could not be purified from *p*-toluene sulfonamide. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 53.8 min. and t_{R2} = 81.0 min. A single crystal of the anti-diastereomer was grown from $CHCl_3$ for X-ray crystallographic experiment (Appendix C).

Preparation of (4*S*,5*S*)-3-[5-naphthalen-2-yl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-246

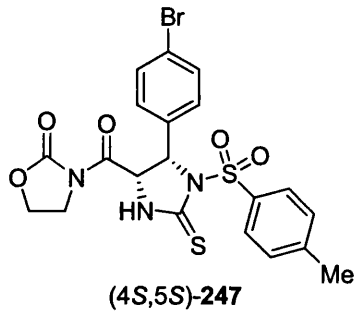


(4*S*,5*S*)-**246**

The reaction was carried out according to the experimental procedure above (Section III 16) with 4-methyl-*N*-naphthalen-2-ylmethylene-benzenesulfonamide **309** (427 mg, 1.38 mmol) to provide the title compound (342 mg, 100%, *anti:syn* = 93:7, ee_{anti} = 98%, $[\alpha]_D^{30}$ = -46.0 (*c* = 0.5, $CHCl_3$)) as a

white solid. Data identical to that reported earlier. The *syn-imidazolidinethione* could not be purified from *p*-toluene sulfonamide. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 59.0 min. and t_{R2} = 113.9 min.

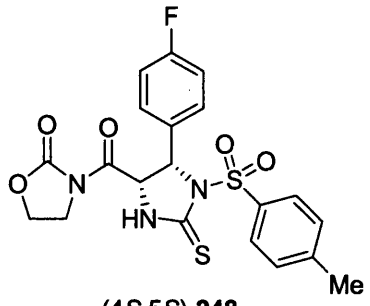
Preparation of (4*S*,5*S*)-3-[5-(4-bromo-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-247



(4*S*,5*S*)-**247**

The reaction was carried out according to the experimental procedure above (Section III 16) with *N*-(4-bromo-benzylidene)-4-methyl-benzenesulfonamide **310** (467 mg, 1.38 mmol) to provide the title compound (312 mg, 86%, *anti*:*syn* = 83:17, ee_{anti} = 98%, $[\alpha]_D^{30}$ = -66.0 (*c* = 0.5, $CHCl_3$)) as a white solid. Data identical to that reported earlier. The *syn-imidazolidinethione* could not be purified from *p*-toluene sulfonamide. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 51.7 min. and t_{R2} = 83.6 min.

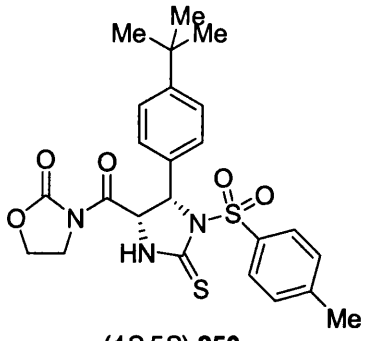
Preparation of (4*S*,5*S*)-3-[5-(4-fluoro-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-248



(4*S*,5*S*)-**248**

The reaction was carried out according to the experimental procedure above (Section III 16) with *N*-(4-fluoro-benzylidene)-4-methyl-benzenesulfonamide **311** (383 mg, 1.38 mmol) to provide the title compound (314 mg, 98%, *anti*:*syn* = 75:25, ee_{anti} = 93%, $[\alpha]_D^{30}$ = -42.0 (*c* = 0.5, $CHCl_3$)) as a white solid. Data identical to that reported earlier. The *syn-imidazolidinethione* could not be purified from *p*-toluene sulfonamide. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 57.0 min. and t_{R2} = 77.7 min.

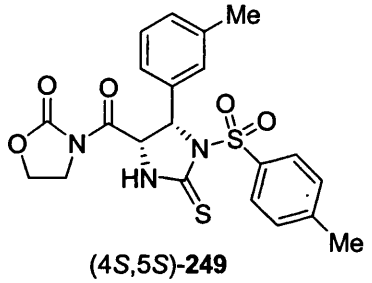
Preparation of (4*S*,5*S*)-3-[5-(4-*tert*-butyl-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-250



(4*S*,5*S*)-**250**

The reaction was carried out according to the experimental procedure above (Section III 16) with *N*-(4-*tert*-butyl-benzylidene)-4-methyl-benzenesulfonamide **308** (435 mg, 1.38 mmol) to provide the title compound (332 mg, 96%, *anti*:*syn* = 82:18, ee_{anti} = 99%, $[\alpha]_D^{30}$ = -60.0 (*c* = 0.5, $CHCl_3$)) as a white foam. Data identical to that reported earlier. The *syn-imidazolidinethione* could not be purified from *p*-toluene sulfonamide. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 31.9 min. and t_{R2} = 51.5 min.

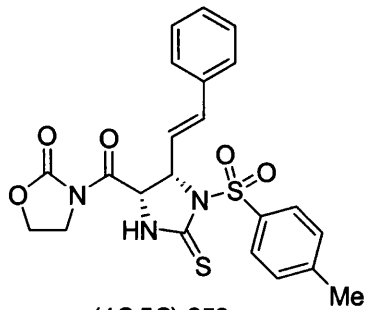
Preparation of (4*S*,5*S*)-3-[2-thioxo-1-(toluene-4-sulfonyl)-5-*m*-tolyl-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-249



(4*S*,5*S*)-**249**

The reaction was carried out according to the experimental procedure above (Section III 16) with 4-methyl-*N*-(3-methyl-benzylidene)-benzenesulfonamide **312** (377 mg, 1.38 mmol) to provide the title compound (290 mg, 91%, *anti*:*syn* = 86:14, ee_{anti} = 99%, $[\alpha]_D^{30}$ = -24.0 (*c* = 0.5, $CHCl_3$)) as a white foam. Data identical to that reported earlier. The *syn-imidazolidinethione* could not be purified from *p*-toluene sulfonamide. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 45.8 min. and t_{R2} = 67.3 min.

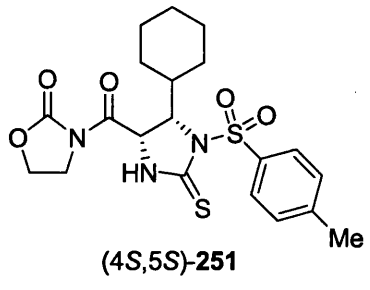
Preparation of (4*S*,5*S*)-3-[5-styryl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-253



(4*S*,5*S*)-**253**

The reaction was carried out according to the experimental procedure above (Section III 16) with 4-methyl-*N*-(3-phenyl-allylidene)-benzenesulfonamide **313** (395 mg, 1.38 mmol) to provide the title compound (314 mg, 97%, *anti*:*syn* = 78:22, ee_{anti} = 97%, $[\alpha]_D^{30}$ = -81.0 (*c* = 0.98, $CHCl_3$)) as a white foam. Data identical to that reported earlier. The *syn-imidazolidinethione* could not be purified from *p*-toluene sulfonamide. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 46.2 min. and t_{R2} = 86.2 min.

Preparation of (4*S*,5*S*)-3-[5-cyclohexyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-251

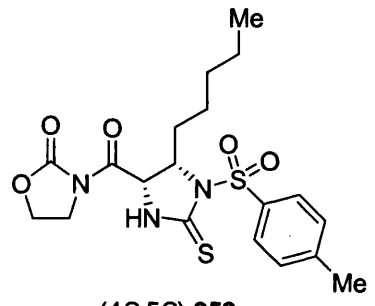


(4*S*,5*S*)-**251**

The reaction was carried out according to the experimental procedure above (Section III 16) with *N*-cyclohexylmethylene-4-methyl-benzenesulfonamide

314 (366 mg, 1.38 mmol) to provide the title compound (306 mg, 98%, *anti*:*syn* = 67:33, ee_{anti} = 99%, $[\alpha]_D^{30}$ = +40.0 (*c* = 0.65, $CHCl_3$)) as white crystals. Data identical to that reported earlier. The *syn-imidazolidinethione* could not be purified from *p*-toluene sulfonamide. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 36.2 min. and t_{R2} = 85.6 min. A single crystal of the *anti*-diastereomer was grown from $CHCl_3$ for X-ray crystallographic experiment (Appendix D).

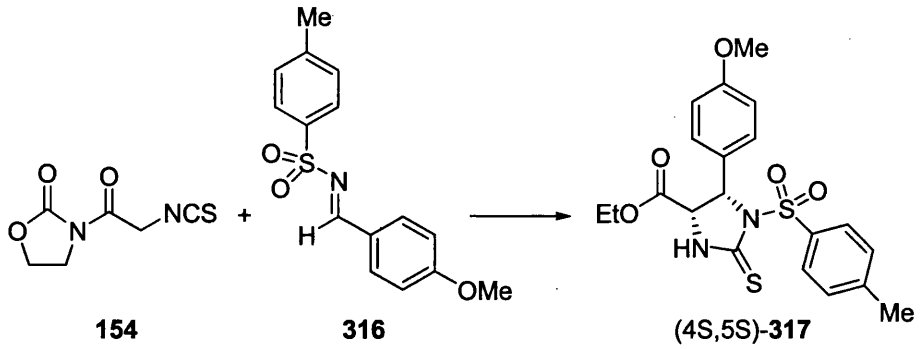
Preparation of (4*S*,5*S*)-3-[5-pentyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one *anti*-252



(4*S*,5*S*)-**252**

The reaction was carried out according to the experimental procedure above (Section III 16) with *N*-hexylidene-4-methyl-benzenesulfonamide **315** (350 mg, 1.38 mmol) to provide the title compound (120 mg, 40%, *anti*:*syn* = 67:33, ee_{anti} = 84%, $[\alpha]_D^{30}$ = +26.1 (*c* = 0.65, $CHCl_3$)) as white crystals. Data identical to that reported earlier. The *syn-imidazolidinethione* could not be purified from *p*-toluene sulfonamide. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 36.0 min. and t_{R2} = 64.1 min.

III 17 Preparation of (4*S*,5*S*)-5-(4-methoxy-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-317; to serve as a typical experimental procedure for the asymmetric preparation of derivatised adducts of *N*-tosylimines and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one 154

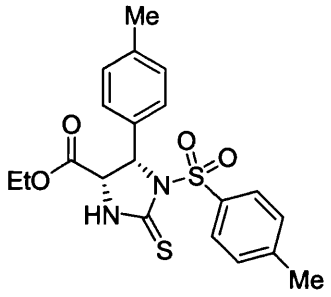


154 **316** (4S,5S)-**317**

A mixture of $Mg(ClO_4)_2$ (15 mg, 0.07 mmol), (*R*,*R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) **175** (37 mg, 0.08 mmol) and 3-(2-*iso*thiocyanatoacetyl)-oxazolidin-2-one **154** (128 mg, 0.69 mmol) was stirred for 1 h in dry DCM (15 mL) with activated powdered 4 Å MS (200 mg) under nitrogen at RT. The temperature was then lowered to -78 °C. After 15 min, *N*-(4-methoxy-benzylidene)-4-methyl-benzenesulfonamide **316** (399 mg, 1.38 mmol) and di*iso*propylethylamine (24 µL, 0.14 mmol) were added and the mixture was stirred for a further 24 h at -78 °C. The reaction was quenched with saturated aqueous ammonium chloride (5 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 90:10) to provide a mixture of *syn* and *anti imidazolidinethiones* (282 mg, 86%, *anti*:*syn* = 76:24) of which 62 mg, 0.13 mmol of *anti-imidazolidinethione* was dissolved in dry THF (3 mL) and cooled

to 0 °C. A solution of methyl magnesium bromide (3 M in diethyl ether, 92 μL, 0.28 mmol) was added to ethanol (1.0 mL) at 0 °C and subsequently added to the previous solution *via* cannula transfer. After 40 min. the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (5 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1 M, 10 mL) and DCM (10 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide the title compound *anti*-**317** (28 mg, 51%, ee_{anti} = 97%, $[\alpha]_D^{30}$ = -36.3 (c = 0.8, $CHCl_3$)) as a white foam. Data identical to that reported earlier. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 19.6 min. and t_{R2} = 29.7 min.

Preparation of (4*S*,5*S*)-2-thioxo-1-(toluene-4-sulfonyl)-5-*p*-tolyl-imidazolidine-4-carboxylic acid ethyl ester *anti*-319

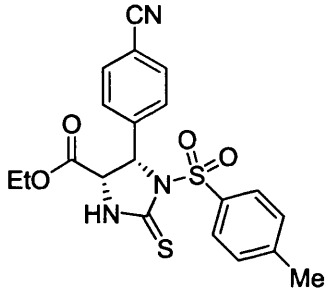


(4*S*,5*S*)-**319**

The reaction was carried out according to the experimental procedure above (Section III 17) with 4-methyl-*N*-(4-methyl-benzylidene)-benzenesulfonamide **318** (377 mg, 1.38 mmol) to provide a mixture of *syn* and *anti* *imidazolidinethiones* (304 mg, 96%, *anti*:*syn* = 83:17) of which 87 mg, 0.19 mmol was dissolved in dry THF (4 mL) and cooled to 0 °C. The reaction was

carried out according to the experimental procedure above (Seaction III 17) with a solution of methyl magnesium bromide (3 M in diethyl ether, 126 μL, 0.38 mmol) added to ethanol (1.4 mL) to provide the title compound *anti*-**319** (48 mg, 60%, ee_{anti} = 99%, $[\alpha]_D^{30}$ = -35.0 (*c* = 0.8, $CHCl_3$)) as a white foam. Data identical to that reported earlier. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 14.8 min. and t_{R2} = 24.2 min.

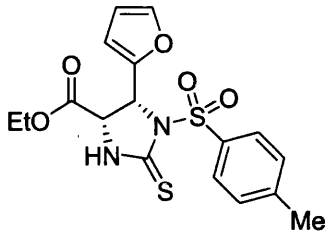
Preparation of (4*S*,5*S*)-5-(4-cyano-phenyl)-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-321



(4*S*,5*S*)-**321**

The reaction was carried out according to the experimental procedure above (Section III 17) with *N*-(4-cyano-benzylidene)-4-methyl-benzenesulfonamide **320** (392 mg, 1.38 mmol) to provide a mixture of *syn* and *anti* *imidazolidinethiones* (280 mg, 85%, *anti*:*syn* = 67:33) of which 65 mg, 0.14 mmol was dissolved in dry THF (3 mL) and cooled to 0 °C. The reaction was carried out according to the experimental procedure above (Section III 17) with a solution of methyl magnesium bromide (3 M in diethyl ether, 92 μL, 0.28 mmol) added to ethanol (1.0 mL) to provide the title compound *anti*-**321** (24 mg, 40%, ee_{anti} = 99%, $[\alpha]_D^{30}$ = -34.3 (*c* = 0.35, $CHCl_3$)) as a white solid. Data identical to that reported earlier. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 32.8 min. and t_{R2} = 41.1 min.

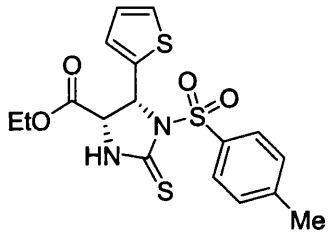
Preparation of (4*S*,5*S*)-5-furan-2-yl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-323



(4*S*,5*S*)-**323**

The reaction was carried out according to the experimental procedure above (Seaction III 17) with *N*-furan-2-ylmethylene-4-methyl-benzenesulfonamide **322** (344 mg, 1.38 mmol) to provide a mixture of *syn* and *anti imidazolidinethiones* (276 mg, 92%, *anti*:*syn* = 50:50) of which 100 mg, 0.46 mmol was dissolved in dry THF (5 mL) and cooled to 0 °C. The reaction was carried out according to the experimental procedure above (Section III 17) with a solution of methyl magnesium bromide (3 M in diethyl ether, 153 μL, 0.46 mmol) added to ethanol (1.7 mL) to provide the title compound *anti*-**323** (42 mg, 46%, ee_{anti} = undetermined, $[\alpha]_D^{30}$ = +7.2 (*c* = 0.97, $CHCl_3$) as a yellow oil. Data identical to that reported earlier. The enantiomers of the *anti*-diastereomer could not be separated analytically by chiral HPLC.

Preparation of (4*S*,5*S*)-5-thiophen-2-yl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-325

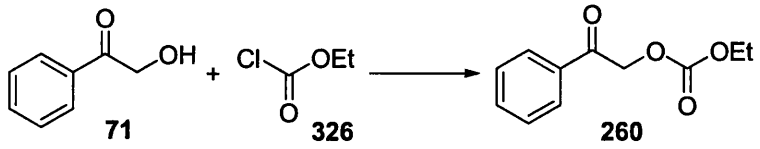


(4*S*,5*S*)-**325**

The reaction was carried out according to the experimental procedure above (Section III 17) with 4-methyl-*N*-thiophen-2-ylmethylene-benzenesulfonamide **324** (366 mg, 1.38 mmol) to provide a mixture of *syn* and *anti imidazolidinethiones* (294 mg, 94%, *anti:syn* = 50:50) of which 47 mg, 0.1 mmol was dissolved in dry THF (2.5 mL) and cooled to 0 °C. The reaction was carried out according to the experimental procedure above (Section III 17) with a solution of methyl magnesium bromide (3 M in diethyl ether, 69 μL, 0.21 mmol) added to ethanol (0.8 mL) to provide the title compound *anti*-**325** (28 mg, 65%, ee_{anti} = 90%, $[\alpha]_D^{30}$ = -24.0 (*c* = 0.5, $CHCl_3$) as a colourless oil. Data identical to that reported earlier. The enantiomers of the *anti*-diastereomer were separated analytically by chiral HPLC using the conditions in the general experimental section; t_{R1} = 20.9 min. and t_{R2} = 25.2 min.

III 18 Preparation of phenacyl and naphthacyl carbonate analogues employed in the direct catalytic aldol addition to aromatic aldehydes

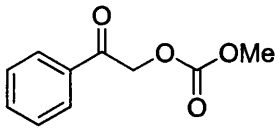
Preparation of carbonic acid ethyl ester 2-oxo-2-phenyl-ethyl ester 260



Ethyl chloroformate **326** (50 mL, 520 mmol) was added drop-wise to a stirred solution of 2-hydroxyacetophenone **71** (7.04 g, 51.7 mmol) in dry pyridine (100 mL) under a nitrogen atmosphere at 0 °C. After 2.5 h at 0 °C the reaction mixture was warmed to 50 °C for a further 30 min. The reaction mixture was

then cooled to ambient temperature and poured into diethyl ether (500 mL) and quenched with cold 1 M H_2SO_4 (500 mL). The organic layer was washed with 1 M H_2SO_4 (2 × 250 mL), saturated $NaHCO_3$ (2 × 250 mL), and brine (2 × 250 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The crude yellow oil (10.28 g) was purified by reduced pressure distillation. The carbonate **260** was obtained as a white crystalline solid (8.80 g, 82%) on cooling; mp 41 °C (lit.,[129] 41-43 °C); bp 104 °C at 0.1 mmHg; R_f(SiO_2, 20% EtOAc in light petroleum (bp 40-60 °C)) 0.39; δ_H(300 MHz; $CDCl_3$) 7.35-7.95 (5H, m, ArH), 5.35 (2H, s, (C=O)CH_2), 4.26 (2H, q, J = 7.2, CH_2CH_3), 1.35 (3H, t, J = 7.2, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 192.2, 155.3, 134.4, 134.4, 129.3, 128.1, 68.9, 65.1, 14.6. Analytical data for this compound is consistent with that in the literature.[129]

Preparation of carbonic acid methyl ester 2-oxo-2-phenyl-ethyl ester 259

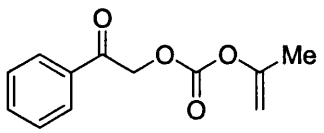


259

Methyl chloroformate (28.4 mL, 367.3 mmol) was added drop-wise to a stirred solution of 2-hydroxyacetophenone **71** (10.0 g, 73.5 mmol) in dry pyridine (100 mL) under a nitrogen atmosphere at 0 °C. After 2 h at 0 °C the reaction was complete. The reaction mixture was then poured into diethyl ether (500 mL) and quenched with cold 1 M H_2SO_4 (500 mL). The organic layer was washed with 1 M H_2SO_4 (2 × 250 mL), saturated $NaHCO_3$ (250 mL), water (250 mL) and brine (250 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The resultant yellow oil was purified by flash column chromatography (SiO_2 (25:1), 10% EtOAc in light petroleum (bp 40-60 °C)) and the carbonate **259** was obtained as a white crystalline solid (11.89 g, 83%); mp 46-47 °C (EtOAc-light

petroleum (bp 40-60 °C)), R_f(SiO_2, 50% EtOAc in light petroleum (bp 40-60 °C)) 0.67; δ_H(300 MHz; $CDCl_3$) 7.92 (2H, d, J = 6.0, ArH), 7.46-7.62 (3H, m, ArH), 5.37 (2H, s, CH_2), 3.87 (3H, s, CH_3). Analytical data for this compound is consistent with that in the literature.[129]

Preparation of carbonic acid *iso*propenyl ester 2-oxo-2-phenyl-ethyl ester 261

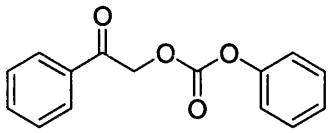


261

*Iso*propenyl chloroformate (3.17 mL, 29.4 mmol) was added drop-wise to a stirred solution of 2-hydroxyacetophenone **71** (2.0 g, 14.7 mmol) in dry pyridine (30 mL) under a nitrogen atmosphere at 0 °C. After 1 h at 0 °C the reaction was complete. The reaction mixture was then poured into diethyl ether (150 mL) and quenched with cold 1 M H_2SO_4 (150 mL). The organic layer was washed with 1 M H_2SO_4 (75 mL), saturated $NaHCO_3$ (2 × 75 mL) and brine (2 × 75 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The resultant yellow oil was purified by flash column chromatography (SiO_2:product, 25:1), 5% EtOAc in light petroleum (bp 40-60 °C)) and recrystallisation from diethyl ether and layered *n*-heptane. The *carbonate* **261** was obtained as a white crystalline solid (1.93 g, 60%); mp 44-45 °C (diethyl ether-*n*-heptane); R_f(SiO_2, 20% EtOAc in light petroleum (bp 40-60 °C)) 0.55; ν_{max}(KBr)/cm^{-1} 1753 (C=O), 1701 (C=O), 1677 (C=C), 1295 (CO), 1204 (CO); δ_H(300 MHz; $CDCl_3$) 7.86-7.95 (2H, m, ArH), 7.56-7.65 (1H, m, ArH), 7.44-7.54 (2H, m, ArH), 5.39 (2H, s, CH_2), 4.88 (1H, s, (H)C*H*=C(CH_3)O), 4.73 (1H, s, (*H*)CH=C(CH_3)O), 2.01 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 191.8, 153.4, 153.1, 134.2, 129.8, 128.6, 127.7, 102.5, 69.2, 19.4; *m/z* (EI+) 220 (9%, M^+), 163 (96%, [M-$CO_2C(CH_3)=CH_2$]$^+$), 105

(100%, PhC≡O$^+$), 77 (89%, Ph$^+$), (CI+) 238 (100%, [M+NH$_4$]$^+$); HRMS (ES+): $C_{12}H_{16}NO_4$, [M+NH$_4$]$^+$ requires 238.1074. Found 238.1068; $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.49%. Found C, 65.40; H, 5.54%.

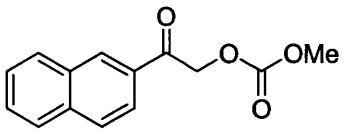
Preparation of carbonic acid 2-oxo-2-phenyl-ethyl ester phenyl ester 262



262

Phenyl chloroformate (3.46 mL, 27.5 mmol) was added drop-wise to a stirred solution of 2-hydroxyacetophenone **71** (2.5 g, 18.4 mmol), triethylamine (3.07 mL, 22.0 mmol in dry THF (120 mL) under a nitrogen atmosphere at 0 °C. After 2.5 h at 0 °C the reaction was deemed complete. The reaction mixture was then poured into EtOAc (200 mL) and water (200 mL). The organic layer was washed with saturated $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The resultant yellow oil was purified by flash column chromatography (SiO_2:product, 25:1), 10% EtOAc in light petroleum (bp 40-60 °C)). The *carbonate* **262** was obtained as a white crystalline solid (2.54 g, 54%) and then recrystallised from diethyl ether and layered light petroleum (bp 40-60 °C); mp 70 °C (EtOAc-light petroleum (bp 40-60 °C)); R_f(SiO_2, 20% EtOAc in light petroleum (bp 40-60 °C)) 0.45; ν_{max}(KBr)/cm^{-1} 1765 (C=O), 1703 (C=O), 1290 (CO), 1255 (CO); δ_H(300 MHz; $CDCl_3$) 7.88-7.95 (2H, m, ArH), 7.57-7.65 (1H, m, ArH), 7.44-7.53 (2H, m, ArH), 7.34-7.42 (2H, m, ArH), 7.21-7.28 (3H, m, ArH), 5.45 (2H, s, CH_2); δ_C(100 MHz; $CDCl_3$) 191.3, 153.6, 151.3, 134.3, 134.0, 129.7, 129.2, 128.0, 126.4, 121.2, 69.5; *m/z* (CI+) 274 (100%, [M+NH$_4$]$^+$); HRMS (ES+): $C_{15}H_{16}NO_4$, [M+NH$_4$]$^+$ requires 274.1074. Found 274.1071; $C_{15}H_{12}O_4$ requires C, 70.3; H, 4.72%. Found C, 70.2; H, 4.78%.

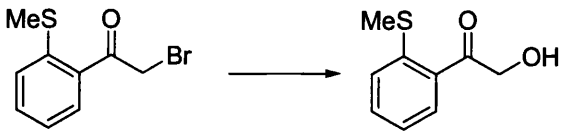
Preparation of carbonic acid methyl ester 2-naphthalen-2-yl-2-oxo-ethyl ester 274



274

Methyl chloroformate (2.07 mL, 26.8 mmol) was added drop-wise to a stirred solution of 2-hydroxy-1-naphthalen-2-yl-ethanone[141] **327** (2.5 g, 13.4 mmol) in dry pyridine (20 mL) under a nitrogen atmosphere at 0 °C. After 1 h at 0 °C the reaction was complete. The reaction mixture was then diluted with EtOAc (100 mL) and quenched with cold 1 M H_2SO_4 (100 mL). The organic layer was washed with 1 M H_2SO_4 (2 × 50 mL), saturated $NaHCO_3$ (50 mL), saturated copper sulfate (25 mL) water (50 mL), and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The *carbonate* **274** was obtained as a yellow solid (3.35 g, 100%); mp 82 °C (EtOAc), R_f(SiO_2, 50% EtOAc in light petroleum (bp 40-60 °C)) 0.81; ν_{max}(KBr)/cm^{-1} 1748 (C=O), 1694 (C=O), 1257 (CO); δ_H(300 MHz; $CDCl_3$) 8.41 (1H, s, ArH), 7.87-7.99 (4H, m, ArH), 7.55-7.66 (2H, m, ArH), 5.51 (2H, s, CH_2), 3.89 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 192.1, 156.0, 136.4, 132.8, 131.7, 130.0, 129.9, 129.4 × 2, 128.3, 127.6, 123.6, 69.19, 55.85; *m/z* (CI+) 262 (100%, $[M+NH_4]^+$); HRMS (ES+): $C_{14}H_{16}NO_4$, $[M+NH_4]^+$ requires 262.1074. Found 262.1073; $C_{14}H_{12}O_4$ requires C, 68.9; H, 4.95%. Found C, 68.9; H, 5.03%.

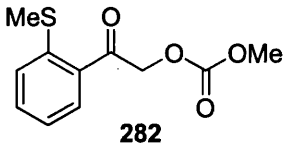
Preparation of 2-hydroxy-1-(2-methylsulfanyl-phenyl)-ethanone 281



280 **281**

2-Bromo-1-(2-(methylthio)phenyl)ethanone[142] **280** (8.86 g, 36.1 mmol) and betaine (5.08 g, 43.4 mmol) were stirred in EtOH (120 mL) under a nitrogen atmosphere at 60 °C. After 3 h, the mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was titrated in EtOAc for 16 h and the resultant solid filtered, taken up in aqueous $NaHCO_3$ and DCM. The biphasic mixture was stirred until the yellow aqueous layer became colourless. The DCM layer was then separated, dried (Na_2SO_4) and concentrated under reduced pressure to provide the title compound, *alcohol* **281** without further purification as a yellow oil (3.02 g, 46%); ν_{max}(neat)/cm^{-1} 3447 (OH), 2919 (CH), 1675 (C=O); δ_H(300 MHz; $CDCl_3$) 7.72 (1H, dd, *J* = 8.0, 1.2, ArH), 7.51-7.57 (1H, m, ArH), 7.37 (1H, d, *J* = 8.0, ArH), 7.19-7.24 (1H, m, ArH), 4.83 (2H, d, *J* = 4.5, C*H*$_2$OH), 3.59 (3H, t, *J* = 4.5, CH$_2$O*H*), 2.47 (3H, s, SCH_3); δ_C(75 MHz; $CDCl_3$) 198.6, 144.0, 133.6, 130.0, 129.8, 125.2, 123.7, 65.9, 15.8; HRMS (ES+): $C_9H_{11}O_2S$, $[M+H]^+$ requires 183.0474. Found 183.0472; $C_9H_{10}O_2S$ requires C, 59.3; H, 5.53%. Found C, 59.4; H, 5.60%.

Preparation of carbonic acid methyl ester 2-(2-methylsulfanyl-phenyl)-2-oxo-ethyl ester 282

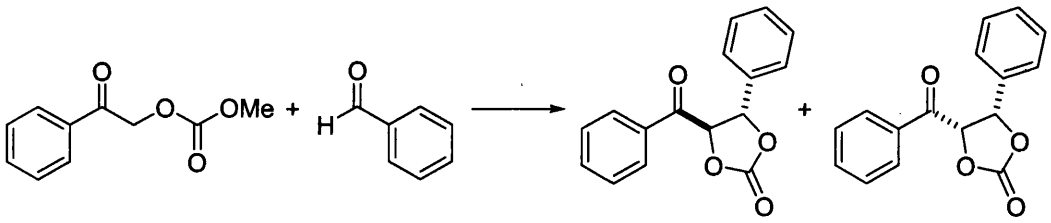


282

Methyl chloroformate (0.32 mL, 4.14 mmol) was added drop-wise to a stirred solution of 2-hydroxy-1-(2-methylsulfanyl-phenyl)-ethanone **281** (377 mg, 2.07 mmol) in dry pyridine (10 mL) under a nitrogen atmosphere at 0 °C. After 2 h at RT the reaction mixture was poured into diethyl ether and quenched with cold 1 M H_2SO_4. The organic layer was washed with 1 M H_2SO_4, saturated $NaHCO_3$ and brine. The organic layer was dried over

anhydrous magnesium sulfate and then concentrated *in vacuo*. The crude yellow oil was purified by flash column chromatography (25% EtOAc in *n*-hexane). The *carbonate* **282** was obtained as an orange crystalline solid (0.40 g, 81%); mp 99 °C (EtOAc-*n*-hexane); ν_{max}(KBr)/cm^{-1} 2959 (CH), 1755 (C=O), 1686 (C=O), 1265 (CO); δ_H(300 MHz; $CDCl_3$) 7.70 (1H, dd, *J* = 7.8, 1.5, ArH), 7.48-7.54 (1H, m, ArH), 7.36 (1H, d, *J* = 7.8, ArH), 7.18-7.23 (1H, m, ArH), 5.30 (2H, s, (C=O)CH_2), 3.85 (3H, s, OCH_3), 2.44 (3H, s, SCH_3); δ_C(75 MHz; $CDCl_3$) 192.5, 155.6, 143.5, 133.2, 131.3, 129.5, 127.7, 123.8, 69.2, 55.5, 16.1; HRMS (ES+): $C_{11}H_{13}O_4S$, $[M+H]^+$ requires 241.0529. Found 241.0526; $C_{11}H_{12}O_4S$ requires C, 55.0; H, 5.03%. Found C, 55.2; H, 5.13%.

III 19 Preparation of (4*R**,5*S**) and (4*R**,5*R**)-4-benzoyl-5-phenyl-[1,3]dioxolan-2-one 263; to serve as a typical experimental procedure for the direct aldol addition of phenacyl and naphthacyl carbonates to aromatic aldehydes

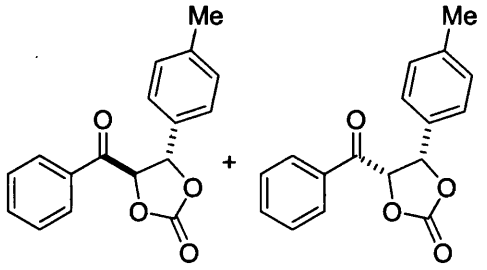


259 **17** *trans*-**263** *cis*-**263**

2,2′-bipyridine (31 mg, 0.2 mmol), 4 Å molecular sieves (200 mg), and magnesium perchlorate (45 mg, 0.2 mmol) were stirred for 30 minutes in dry THF (2.5 mL) under a nitrogen atmosphere at ambient temperature. The suspension formed was then treated with carbonic acid methyl ester 2-oxo-2-phenyl-ethyl ester **259** (388 mg, 2 mmol) in THF (2.5 mL). After 10 minutes benzaldehyde **17** (102 μL, 1 mmol) and *N*-methylmorpholine (55 μL, 0.5

mmol) were added drop-wise. The reaction was monitored by thin layer chromatography. After 24 h the reaction mixture was diluted with EtOAc (2 × 30 mL), filtered through celite and subsequently quenched with a saturated aqueous solution of ammonium chloride (10 mL). The organic layers were washed with a saturated aqueous solution of copper sulfate (10 mL) followed by water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude mixture of diastereomers (*cis*:*trans*, 1:10) was purified by flash column chromatography (SiO_2:product, 50:1) to give an overall yield of 240 mg, 90%. 1:1 DCM:light petroleum (bp 40-60 °C) provided the major diastereomer, *trans*-dioxolan-2-one *trans*-**263** as a white solid (220 mg, 82%); mp 98-99 °C (diethyl ether-light petroleum (bp 40-60 °C)); R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.38; ν_{max}(KBr)/cm^{-1} 1841 (C=O), 1694 (C=O), 1224 (CO), 1163 (CO); δ_H(300 MHz; $CDCl_3$) 7.94 (2H, d, *J* = 7.2, ArH), 7.66 (1H, m, ArH), 7.26-7.52 (7H, m, ArH), 5.95 (1H, d, *J* = 6.3, Ph(C=O)CH), 5.61 (1H, d, *J* = 6.3, PhCH); δ_C(100 MHz; $CDCl_3$) 189.7, 151.8, 134.3, 133.6, 132.0, 128.6, 128.0 × 2, 127.8, 124.6, 80.7, 77.8; *m*/*z* (CI+) 286 (91%, $[M+NH_4]^+$), 242 (100%, $[M-CO_2+NH_4]^+$), 105 (100%, $PhC{\equiv}O^+$); HRMS (ES+): $C_{16}H_{16}NO_4$, $[M+NH_4]^+$ requires 286.1074. Found 286.1071; $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.51%. Found C, 71.9; H, 4.68%. Analytical data for this compound is consistent with that in the literature.[148] 2% EtOAc in DCM provided the minor diastereomer, *cis-dioxolan-2-one cis*-**263** as a white solid (20 mg, 8%); mp 159-160 °C (diethyl ether-*n*-heptane); R_f(SiO_2, DCM) 0.38; ν_{max}(KBr)/cm^{-1} 1815 (C=O), 1682 (C=O), 1225 (CO), 1174 (CO); δ_H(300 MHz; $CDCl_3$) 7.40-7.50 (2H, m, ArH), 7.25-7.35 (2H, m, ArH), 7.05-7.15 (6H, m, ArH), 6.22 (1H, d, *J* = 8.4, Ph(C=O)CH), 6.02 (1H, d, *J* = 8.4, PhCH); δ_C(75 MHz; $CDCl_3$) 191.6, 153.9, 134.6, 134.1, 131.4, 129.7, 128.6, 128.5, 127.9, 126.7, 80.2, 79.1; *m*/*z* (CI+) 286 (100%, $[M+NH_4]^+$), 242 (27%, $[M-CO_2+NH_4]^+$); HRMS (ES+): $C_{16}H_{16}NO_4$, $[M+NH_4]^+$ requires 286.1074. Found 286.1073; $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.51%. Found C, 71.5; H, 4.60%.

Preparation of (4*R,5*S**) and (4*R**,5*R**)-4-benzoyl-5-*p*-tolyl-[1,3]dioxolan-2-one 265**

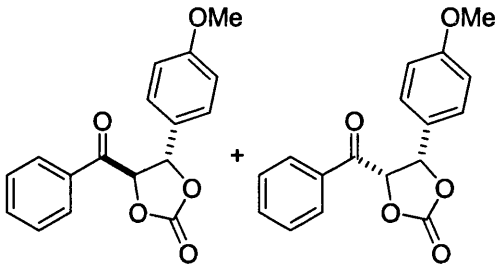


trans-**265** *cis*-**265**

The reaction was carried out according to the experimental procedure above (Section III 19) with *p*-tolualdehyde **196** (118 μL, 1 mmol). The crude mixture of diastereomers (*cis*:*trans*, 1:16) was purified by flash column chromatography (SiO_2:product, 50:1) to give an overall yield of 274 mg, 97%. 1:1 DCM-light petroleum (bp 40-60 °C) provided the major diastereomer, *trans-dioxolan-2-one trans*-**265** as a colourless oil (259 mg, 92%); R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.35; ν_{max}(neat)/cm^{-1} 1814 (C=O), 1691 (C=O), 1225 (CO), 1161 (CO); δ_H(300 MHz; $CDCl_3$) 7.92-7.99 (2H, m, ArH), 7.63-7.70 (1H, m, ArH), 7.47-7.55 (2H, m, ArH), 7.24-7.35 (4H, m, ArH), 5.92 (1H, d, *J* = 6.3, Ph(C=O)CH), 5.59 (1H, d, *J* = 6.3, ArCH), 2.40 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 191.2, 153.2, 140.1, 135.0, 133.4, 132.7, 130.0, 129.4, 129.1, 126.1, 82.0, 79.1, 21.3; *m/z* (CI+) 300 (100%, $[M+NH_4]^+$), 256 (14%, $[M-CO_2+NH_4]^+$), 239 (34%, $[M-CO_2+H]^+$); HRMS (ES+): $C_{17}H_{18}NO_4$, $[M+NH_4]^+$ requires 300.1230. Found 300.1227; $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.00%. Found C, 72.4; H, 5.16%. 1% EtOAc in DCM provided the minor diastereomer, *cis-dioxolan-2-one cis*-**265** as a white solid (14 mg, 5%); mp 133 °C (diethyl ether); R_f(SiO_2, DCM) 0.26; ν_{max}(KBr)/cm^{-1} 1794 (C=O), 1687 (C=O), 1225 (CO), 1172 (CO); δ_H(300 MHz; $CDCl_3$) 7.43-7.51 (3H, m, ArH), 7.27-7.33 (2H, m, ArH), 6.88-6.99 (4H, m, ArH), 6.18 (1H, d, *J* = 8.4, Ph(C=O)CH), 5.98 (1H, d, *J* = 8.4, ArCH), 2.18 (3H, s, $ArCH_3$); δ_C(75 MHz; $CDCl_3$) 191.6, 153.9, 139.8, 134.7,

134.0, 129.2, 128.6, 128.5, 128.0, 126.7, 80.3, 79.4, 21.1; *m/z* (CI+) 300 (85%, $[M+NH_4]^+$), 256 (100%, $[M-CO_2+NH_4]^+$), 105 (32%, $PhC{\equiv}O^+$); HRMS (ES+): $C_{17}H_{18}NO_4$, $[M+NH_4]^+$ requires 300.1230. Found 300.1238.

Preparation of (4*R,5*S**) and (4*R**,5*R**)-4-benzoyl-5-(4-methoxy-phenyl)-[1,3]dioxolan-2-one 266**

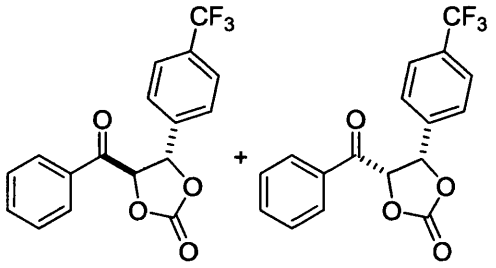


trans-**266** *cis*-**266**

The reaction was carried out according to the experimental procedure above (Section III 19) with *p*-anisaldehyde (244 μL, 2 mmol). The crude mixture of diastereomers (*cis*:*trans*, 1:11) was purified by flash column chromatography (SiO_2:product, 50:1) to give an overall yield of 508 mg, 85%. DCM provided the major diastereomer, *trans-dioxolan-2-one trans*-**266** as a pale yellow oil (508 mg, 85%); R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.18; ν_{max}(neat)/cm^{-1} 1813 (C=O), 1691 (C=O), 1254 (CO), 1224 (CO), 1163 (CO); δ_H(300 MHz; $CDCl_3$) 7.90-7.97 (2H, m, ArH), 7.62-7.70 (1H, m, ArH), 7.46-7.54 (2H, m, ArH), 7.36 (2H, d, *J* = 8.6, ArH), 6.97 (2H, d, *J* = 8.6, ArH), 5.88 (1H, d, *J* = 6.3, Ph(C=O)CH), 5.61 (1H, d, *J* = 6.3, ArCH), 3.84 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 191.2, 160.9, 153.2, 134.9, 133.3, 129.3, 129.1, 127.9, 127.4, 114.8, 81.9, 79.2, 55.4; *m/z* (CI+) 316 (64%, $[M+NH_4]^+$); HRMS (ES+): $C_{17}H_{18}NO_5$, $[M+NH_4]^+$ requires 316.1179. Found 316.1181; $C_{17}H_{14}O_5$ requires C, 68.4; H, 4.73%. Found C, 68.2; H, 4.80%. 2% EtOAc in DCM provided the minor diastereomer, *cis-dioxolan-2-one cis*-**266** as a white solid (7 mg, 1%); mp 104-105 °C (diethyl ether); ν_{max}(KBr)/cm^{-1} 1794 (C=O), 1687 (C=O), 1225 (CO), 1172

(CO); δ_H(300 MHz; $CDCl_3$) 7.46-7.53 (3H, m, ArH), 7.28-7.35 (2H, m, ArH), 7.00 (2H, d, *J* = 8.7, ArH), 6.63 (2H, d, *J* = 8.7, ArH), 6.18 (1H, d, *J* = 8.6, Ph(C=O)CH), 5.97 (1H, d, *J* = 8.6, ArCH), 3.68 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 191.6, 160.5, 149.0, 134.6, 134.1, 128.7, 128.3, 128.0, 123.4, 114.0, 80.1, 79.4, 55.3; *m/z* (CI+) 316 (100%, $[M+NH_4]^+$); HRMS (ES+): $C_{17}H_{18}NO_4$, $[M+NH_4]^+$ requires 316.1179. Found 316.1179.

Preparation of (4*R,5*S**) and (4*R**,5*R**)-4-benzoyl-5-(4-trifluoromethyl-phenyl)-[1,3]dioxolan-2-one 267**

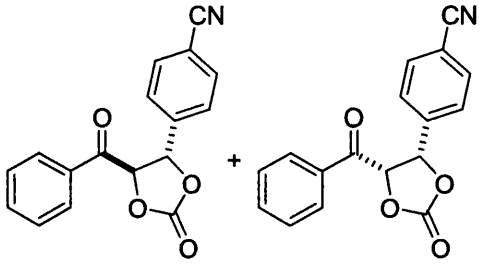


trans-**267** *cis*-**267**

The reaction was carried out according to the experimental procedure above (Section III 19) with 4-(trifluoromethyl)benzaldehyde (137 μL, 1 mmol). The crude mixture of diastereomers (*cis:trans*, 1:8) was purified by flash column chromatography (SiO_2:product, 50:1) to provide an overall yield of 220 mg, 65%. 1:1 DCM-light petroleum (bp 40-60 °C) provided the major diastereomer, *trans-dioxolan-2-one trans*-**267** as a white solid (202 mg, 60%); mp 91-92 °C (DCM-light petroleum (bp 40-60 °C)) R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.34; ν_{max}(KBr)/cm^{-1} 1792 (C=O), 1678 (C=O), 1326 (CF_3), 1233 (CO), 1178 (CO); δ_H(400 MHz; $CDCl_3$) 7.97-8.04 (2H, m, ArH), 7.65-7.77 (3H, m, ArH), 7.50-7.62 (4H, m, ArH), 6.16 (1H, d, *J* = 6.5, Ph(C=O)CH), 5.49 (1H, d, *J* = 6.5, ArCH); δ_C(75 MHz; $CDCl_3$) 191.0, 152.6, 139.7, 135.2, 133.9, 132.0 (q, $^2J_{CF}$ = 32.9), 129.6 × 2, 129.2, 126.4 (q, $^3J_{CF}$ = 3.8), 123.6 (q, $^1J_{CF}$ = 272.4), 81.9, 77.9; δ_F(376 MHz; $CDCl_3$) –62.84; *m/z* (CI+) 354

(48%, $[M+NH_4]^+$), 105 (100%, $PhC{\equiv}O^+$); HRMS (ES+): $C_{17}H_{15}F_3NO_4$, $[M+NH_4]^+$ requires 354.0948. Found 354.0945; $C_{17}H_{11}F_3O_4$ requires C, 60.7; H, 3.30%. Found C, 61.0; H, 3.35%. 1% EtOAc in DCM provided the minor diastereomer, *cis-dioxolan-2-one cis*-**267** as a white solid (18 mg, 5%); mp 152-153 °C (diethyl ether); R_f(SiO_2, DCM) 0.41; ν_{max}(KBr)/cm^{-1} 1799 (C=O), 1686 (C=O), 1324 (CF_3), 1167 (CO), 1069 (CO); δ_H(300 MHz; $CDCl_3$) 7.42-7.54 (3H, m, ArH), 7.25-7.40 (4H, m, ArH), 7.18-7.23 (2H, m, Ar-H), 6.26 (1H, d, J = 8.6, Ph(C=O)CH), 6.06 (1H, d, J = 8.6, ArCH); δ_C(75 MHz; $CDCl_3$) 191.4, 153.5, 135.5, 134.5, 134.4, 131.8 (q, $^2J_{CF}$ = 32.8), 128.9, 127.9, 127.0, 125.5 (q, $^3J_{CF}$ = 3.7), 123.4 (q, $^1J_{CF}$ = 272.3), 79.3, 78.7; *m/z* (CI+) 354 (21%, $[M+NH_4]^+$).

Preparation of (4*R,5*S**) and (4*R**,5*R**)-4-(5-benzoyl-2-oxo-[1,3]dioxolan-4-yl)-benzonitrile 268**

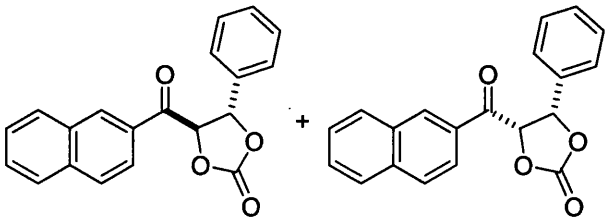


trans-**268** *cis*-**268**

The reaction was carried out according to the experimental procedure above (Section III 19) with 4-cyanobenzaldehyde (144 mg, 1 mmol) in THF (2.5 mL). The crude mixture of diastereomers (*cis*:*trans*, 1:8) was purified by flash column chromatography (SiO_2:product, 50:1) to provide an overall yield of 222 mg, 76%. DCM provided the major diastereomer, *trans-dioxolan-2-one trans*-**268** as a white solid (201 mg, 69%); mp 111 °C (diethyl ether-light petroleum (bp 40-60 °C); R_f(SiO_2, 70% diethyl ether in light petroleum (bp 40-60 °C)) 0.58; ν_{max}(KBr)/cm^{-1} 2229 (C≡N), 1810 (C=O), 1687 (C=O), 1227 (CO), 1177 (CO); δ_H(300 MHz; $CDCl_3$) 8.00-8.03 (2H, m, ArH), 7.68-7.79 (3H, m,

ArH), 7.52-7.60 (4H, m, ArH), 6.18 (1H, d, J = 6.8, Ph(C=O)CH), 5.45 (1H, d, J = 6.8, ArCH); δ_C(75 MHz; $CDCl_3$) 190.9, 152.3, 140.7, 135.3, 133.2, 133.1, 129.6, 129.2, 126.4, 117.9, 113.7, 81.8, 77.6; *m/z* (CI+) 311 (100%, $[M+NH_4]^+$); HRMS (ES+): $C_{17}H_{15}N_2O_4$, $[M+NH_4]^+$ requires 311.1026. Found 311.1027; $C_{17}H_{11}NO_4$ requires C, 69.6; H, 3.78, N, 4.78%. Found C, 69.5; H, 3.86, N, 4.75%. 2% EtOAc in DCM provided the minor diastereomer, *cis-dioxolan-2-one cis*-**268** as a white solid (22 mg, 7%); mp 156-157 °C (diethyl ether-light petroleum (bp 40-60 °C); R_f(SiO_2, DCM) 0.21; ν_{max}(KBr)/cm^{-1} 2232 (C≡N), 1833 (C=O), 1688 (C=O), 1224 (CO), 1162 (CO); δ_H(300 MHz; $CDCl_3$) 7.46-7.59 (3H, m, ArH), 7.40-7.45 (2H, m, ArH), 7.31-7.39 (2H, m, ArH), 7.20-7.25 (2H, m, ArH), 6.29 (1H, d, J = 8.6, Ph(C=O)CH), 6.07 (1H, d, J = 8.6, ArCH); δ_C(75 MHz; $CDCl_3$) 191.1, 153.2, 136.6, 134.8, 134.3, 132.2, 129.0, 127.9, 127.4, 117.7, 113.7, 79.0, 78.4; *m/z* (CI+) 311 (100%, $[M+NH_4]^+$); HRMS (ES+): $C_{17}H_{15}N_2O_4$, $[M+NH_4]^+$ requires 311.1026. Found 311.1030.

Preparation of (4*R,5*S**) and (4*R**,5*R**)-4-(naphthalene-2-carbonyl)-5-phenyl-[1,3]dioxolan-2-one 269**

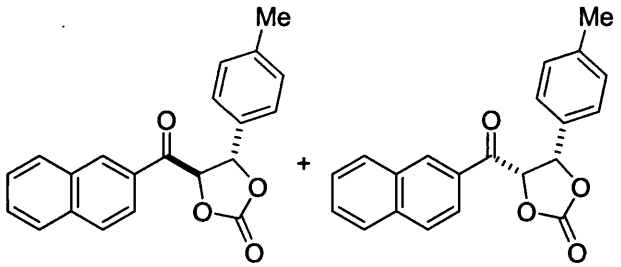


trans-**269** *cis*-**269**

The reaction was carried out according to the experimental procedure above (Section III 19) with benzaldehyde **17** (112 μL, 1.1 mmol). The crude mixture of diastereomers (*cis*:*trans*, 1:7) was purified by flash column chromatography (SiO_2:product, 100:1) to give an overall yield of 252 mg, 79%. 70% DCM in light petroleum (bp 40-60 °C) provided the major diastereomer, *trans-dioxolan-2-one trans*-**269** as a white solid (228 mg, 72%);

mp 127 °C (DCM-light petroleum (bp 40-60 °C); R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.24; ν_{max}(KBr)/cm^{-1} 1818 (C=O), 1680 (C=O), 1148 (CO), 1089 (CO); δ_H(400 MHz; $CDCl_3$) 8.41 (1H, s, ArH), 7.88-8.04 (4H, m, ArH), 7.56-7.69 (3H, m, ArH), 7.47-7.57 (4H, m, ArH), 6.05 (1H, d, *J* = 6.2, Ar(C=O)CH), 5.74 (1H, d, *J* = 6.2, PhCH); δ_C(75 MHz; $CDCl_3$) 191.0, 153.2, 136.3, 135.8, 132.2 × 2, 130.7, 130.0, 129.9, 129.7, 129.4, 129.2, 128.0, 127.4, 126.1, 123.9, 82.2, 79.2; *m/z* (CI+) 336 (71%, $[M+NH_4]^+$), 292 (32%, $[M-CO_2+NH_4]^+$); HRMS (ES+): $C_{20}H_{18}NO_4$, $[M+NH_4]^+$ requires 336.1230. Found 336.1236; $C_{20}H_{14}O_4$ requires C, 75.5; H, 4.43%. Found C, 75.3; H, 4.47%. 2% EtOAc in DCM provided the minor diastereomer, *cis-dioxolan-2-one cis*-**269** as a white solid (24 mg, 7%); mp 138-139 °C (EtOAc-DCM); R_f(SiO_2, DCM) 0.30; ν_{max}(KBr)/cm^{-1} 1805 (C=O), 1688 (C=O), 1177 (CO), 1088 (CO); δ_H(300 MHz; $CDCl_3$) 8.04 (1H, s, ArH), 7.78-7.90 (2H, m, ArH), 7.68-7.74 (1H, m, ArH), 7.52-7.65 (2H, m, ArH), 7.46-7.50 (1H, m, ArH), 7.01-7.14 (5H, m, ArH), 6.37 (1H, d, *J* = 8.4, Ar(C=O)CH), 6.09 (1H, d, *J* = 8.4, PhCH); δ_C(75 MHz; $CDCl_3$) 191.4, 154.0, 135.7, 132.1, 131.9, 131.5, 130.1, 129.7, 129.6, 129.3, 128.8, 128.5, 127.9, 127.2, 126.7, 123.1, 80.4, 79.3; *m/z* (CI+) 336 (53%, $[M+NH_4]^+$), 292 (30%, $[M-CO_2+NH_4]^+$); HRMS (ES+): $C_{17}H_{15}N_2O_4$, $[M+NH_4]^+$ requires 336.1230. Found 336.1233.

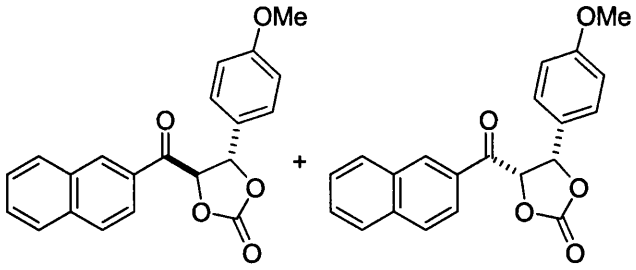
Preparation of (4*R,5*S**) and (4*R**,5*R**)-4-(naphthalene-2-carbonyl)-5-*p*-tolyl-[1,3]dioxolan-2-one 270**



trans-**270** *cis*-**270**

The reaction was carried out according to the experimental procedure above (Section III 19) with *p*-tolualdehyde **196** (130 μL, 1.1 mmol). The crude mixture of diastereomers (*cis:trans*, 1:7) was purified by flash column chromatography (SiO_2:product, 100:1) to give an overall yield of 250 mg, 75%. 70% DCM in light petroleum (bp 40-60 °C) provided the major diastereomer, *trans-dioxolan-2-one trans*-**270** as a white solid (238 mg, 71%); mp 143-144 °C (DCM-light petroleum (bp 40-60 °C); R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.33; ν_{max}(KBr)/cm^{-1} 1805 (C=O), 1682 (C=O), 1172 (CO), 1068 (CO); δ_H(300 MHz; $CDCl_3$) 8.40 (1H, s, ArH), 7.86-8.04 (4H, m, ArH), 7.56-7.70 (2H, m, ArH), 7.27-7.38 (4H, m, ArH), 5.98 (1H, d, J = 6.3, Ar(C=O)CH), 5.73 (1H, d, J = 6.3, ArCH), 2.41 (3H, s, $ArCH_3$); δ_C(75 MHz; $CDCl_3$) 191.0, 153.3, 140.1, 136.3, 132.7, 132.2, 132.1, 130.7, 130.1, 129.9, 129.7, 129.2, 127.9, 127.3, 126.2, 123.9, 82.2, 79.3, 21.3; *m/z* (CI+) 350 (100%, $[M+NH_4]^+$), 306 (41%, $[M-CO_2+NH_4]^+$); HRMS (ES+): $C_{21}H_{20}NO_4$, $[M+NH_4]^+$ requires 350.1387. Found 350.1384; $C_{21}H_{16}O_4$ requires C, 75.8; H, 4.85%. Found C, 75.5; H, 4.85%. 2% EtOAc in DCM provided the minor diastereomer *cis-dioxolan-2-one cis*-**270** as a white solid (12 mg, 4%); mp 125 °C (diethyl ether); R_f(SiO_2, DCM) 0.28; ν_{max}(KBr)/cm^{-1} 1813 (C=O), 1691 (C=O), 1168 (CO), 1090 (CO); δ_H(300 MHz; $CDCl_3$) 8.04 (1H, s, ArH), 7.78-7.90 (2H, m, ArH), 7.68-7.74 (1H, m, ArH), 7.48-7.65 (3H, m, ArH), 6.98 (2H, d, J = 7.8, ArH), 6.83 (2H, d, J = 7.8, ArH), 6.35 (1H, d, J = 8.6, Ar(C=O)CH), 6.06 (1H, d, J = 8.6, ArCH), 2.07 (3H, s, $ArCH_3$); δ_C(75 MHz; $CDCl_3$) 191.6, 154.1, 139.8, 135.7, 132.1, 132.0, 130.1, 129.6, 129.2 × 2, 128.7, 128.5, 127.8, 127.2, 126.6, 123.1, 80.4, 79.5, 21.0; *m/z* (CI+) 350 (46%, $[M+NH_4]^+$), 306 (26%, $[M-CO_2+NH_4]^+$); HRMS (ES+): $C_{21}H_{20}NO_4$, $[M+NH_4]^+$ requires 350.1387. Found 350.1390.

Preparation of (4*R,5*S**) and (4*R**,5*R**)-4-(4-methoxy-phenyl)-5-(naphthalene-2-carbonyl)-[1,3]dioxolan-2-one 271**

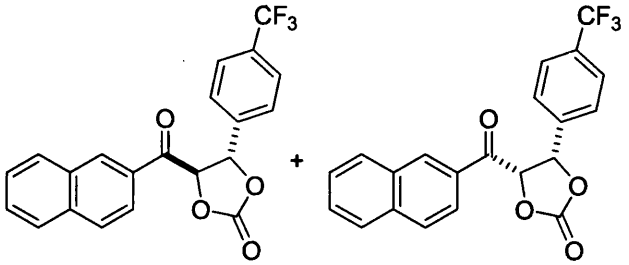


trans-**271** *cis*-**271**

The reaction was carried out according to the experimental procedure above (Section III 19) with *p*-anisaldehyde (134 μL, 1.1 mmol). The crude mixture of diastereomers (*cis*:*trans*, 1:14) was purified by flash column chromatography (SiO_2:product, 100:1) to give an overall yield of 252 mg, 72%. DCM provided the major diastereomer, *trans-dioxolan-2-one trans*-**271** as a pale yellow solid (235 mg, 67%); mp 108 °C (DCM-light petroleum (bp 40-60 °C); R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.18; ν_{max}(KBr)/cm^{-1} 1798 (C=O), 1682 (C=O), 1249 (CO), 1173 (CO), 1066 (CO); δ_H(300 MHz; $CDCl_3$) 8.38 (1H, s, ArH), 7.86-8.04 (4H, m, ArH), 7.56-7.70 (2H, m, ArH), 7.36-7.42 (2H, m, ArH), 6.96-7.02 (2H, m, ArH), 5.93 (1H, d, *J* = 6.9, Ar(C=O)CH), 5.75 (1H, d, *J* = 6.9, ArCH), 3.85 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 191.0, 160.9, 153.3, 136.3, 132.2, 132.1, 130.7, 129.9, 129.7, 129.2, 128.0, 127.9, 127.4 × 2, 123.9, 114.8, 82.1, 79.4, 55.5; *m/z* (CI+) 366 (43%, $[M+NH_4]^+$), 322 (25%, $[M-CO_2+NH_4]^+$); HRMS (ES+): $C_{21}H_{20}NO_5$, $[M+NH_4]^+$ requires 366.1336. Found 366.1337; $C_{21}H_{16}O_5$ requires C, 72.4; H, 4.63%. Found C, 72.0; H, 4.65%. 2% EtOAc in DCM provided the minor diastereomer, *cis-dioxolan-2-one cis*-**271** as a white solid (17 mg, 5%); mp 82-83 °C (diethyl ether); R_f(SiO_2, DCM) 0.22; ν_{max}(KBr)/cm^{-1} 1809 (C=O), 1699 (C=O), 1259 (CO), 1178 (CO), 1096 (CO); δ_H(300 MHz; $CDCl_3$) 8.05 (1H, s, ArH), 7.70-7.90 (3H, m, ArH), 7.50-7.64 (3H, m, ArH), 7.02 (2H, d, *J* = 8.7, ArH), 6.54 (2H, d, *J* = 8.4, ArH), 6.36 (1H, d, *J* =

8.4, Ar(C=O)CH), 6.07 (1H, d, J = 8.4, ArCH), 3.55 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 191.7, 160.4, 154.1, 135.7, 132.0 × 2, 130.1, 129.6, 129.2, 128.7, 128.2, 127.8, 127.2, 123.4, 123.1, 113.9, 80.3, 79.5, 55.1; m/z (CI+) 366 (100%, $[M+NH_4]^+$); HRMS (ES+): $C_{21}H_{20}NO_5$, $[M+NH_4]^+$ requires 366.1336. Found 366.1341.

Preparation of (4*R,5*S**) and (4*R**,5*R**)-4-(naphthalene-2-carbonyl)-5-(4-trifluoromethyl-phenyl)-[1,3]dioxolan-2-one 272**

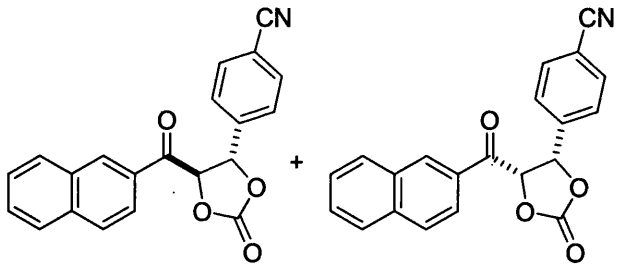


trans-**272** *cis*-**272**

The reaction was carried out according to the experimental procedure above (Section III 19) with 2,2'-bipyridine (63 mg, 0.4 mmol), 4 Å molecular sieves (400 mg) and magnesium perchlorate (89 mg, 0.4 mmol) in dry THF (5 mL). The suspension formed was then treated with carbonic acid methyl ester 2-naphthalen-2-yl-2-oxo-ethyl ester **274** (733 mg, 3.0 mmol) in THF (5 mL). 4-(trifluoromethyl)benzaldehyde (273 μL, 2.0 mmol) and *N*-methylmorpholine (110 μL, 1 mmol) were added drop-wise. The crude mixture of diastereomers (*cis*:*trans*, 1:15) was purified by flash column chromatography (SiO_2:product, 50:1) to give an overall yield of 746 mg, 97%. 70% DCM in light petroleum (bp 40-60 °C) provided the major diastereomer, *trans-dioxolan-2-one trans*-**272** as a white solid (669 mg, 87%); mp 133 °C (DCM-light petroleum (bp 40-60 °C); R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.55; ν_{max}(KBr)/cm^{-1} 1777 (C=O), 1686 (C=O), 1330 (CF_3), 1166 (CO), 1069 (CO); δ_H(300 MHz; $CDCl_3$) 8.50 (1H, s, ArH), 8.01-8.07 (1H, m, ArH), 7.88-7.98 (3H, m, ArH), 7.57-7.77 (6H, m, ArH), 6.22 (1H, d, J = 6.5, Ar(C=O)CH), 5.64 (1H,

d, J = 6.5, ArCH); δ_C(75 MHz; $CDCl_3$) 190.8, 152.7, 139.7, 136.4, 132.4, 132.2, 132.0 (q, $^2J_{CF}$ = 32.9), 130.6, 130.0, 129.8, 129.2, 128.0, 127.5, 126.4 (q, $^3J_{CF}$ = 3.7), 126.3, 123.9 (q, $^1J_{CF}$ = 273.1), 123.7, 82.0, 78.1; m/z (CI+) 404 (76%, $[M+NH_4]^+$); HRMS (ES+): $C_{21}H_{17}F_3NO_4$, $[M+NH_4]^+$ requires 404.1104. Found 404.1100; $C_{21}H_{13}F_3O_4$ requires C, 65.3; H, 3.39%. Found C, 65.4; H, 3.42%. DCM provided the minor diastereomer, *cis-dioxolan-2-one cis*-**272** as a white solid (77 mg, 10%); mp 135 °C (diethyl ether); R_f(SiO_2, DCM) 0.35; ν_{max}(KBr)/cm^{-1} 1819 (C=O), 1701 (C=O), 1328 (CF_3), 1166 (CO), 1070 (CO); δ_H(300 MHz; $CDCl_3$) 8.03 (1H, s, ArH), 7.80-7.90 (2H, m, ArH), 7.70-7.74 (1H, m, ArH), 7.54-7.67 (2H, m, ArH), 7.40-7.45 (1H, m, ArH), 7.29 (2H, d, J = 8.6, ArH), 7.21 (2H, d, J = 8.6, ArH), 6.43 (1H, d, J = 8.4, Ar(C=O)CH), 6.13 (1H, d, J = 8.4, ArCH); δ_C(75 MHz; $CDCl_3$) 191.3, 153.5, 135.8, 135.6, 132.0, 131.9, 131.8 (q, $^2J_{CF}$ = 32.9), 130.1, 129.6, 129.5, 129.1, 127.9, 127.5, 127.0, 125.4 (q, $^3J_{CF}$ = 3.7), 123.3 (q, $^1J_{CF}$ = 272.3), 122.8, 79.4, 78.8; m/z (EI) 386 (100%, M^+), 342 (86%, $[M-CO_2]^+$); HRMS (EI): $C_{21}H_{13}F_3O_4$, M^+ requires 386.0760. Found 386.0758.

Preparation of (4*R,5*S**) and (4*R**,5*R**)-4-[5-(naphthalene-2-carbonyl)-2-oxo-[1,3]dioxolan-4-yl]-benzonitrile 273**

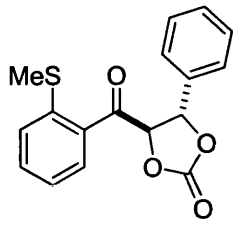


trans-**273** *cis*-**273**

The reaction was carried out according to the experimental procedure above (Section III 19) with 2,2'-bipyridine (63 mg, 0.4 mmol), 4 Å molecular sieves (400 mg) and magnesium perchlorate (89 mg, 0.4 mmol) in dry THF (5 mL). The suspension formed was then treated with carbonic acid methyl ester 2-

naphthalen-2-yl-2-oxo-ethyl ester **274** (733 mg, 3.0 mmol). 4-cyanobenzaldehyde (262 mg, 2.0 mmol) in THF (5 mL) and *N*-methylmorpholine (110 μL, 1.0 mmol) were added drop-wise. The crude mixture of diastereomers (*cis:trans*, 1:16) was purified by flash column chromatography (SiO_2:product, 50:1) to give an overall yield of 467 mg, 68%. DCM provided the major diastereomer, *trans-dioxolan-2-one trans*-**273** as a white foam; mp 147 °C (DCM); R_f(SiO_2, 70% diethyl ether in light petroleum (bp 40-60 °C)) 0.53; ν_{max}(KBr)/cm^{-1} 2229 (C≡N), 1815 (C=O), 1684 (C=O), 1165 (CO), 1087 (CO); δ_H(300 MHz; $CDCl_3$) 8.53 (1H, s, ArH), 7.89-8.07 (4H, m, ArH), 7.76-7.80 (2H, m, ArH), 7.66-7.72 (1H, m, ArH), 7.58-7.66 (3H, m, ArH), 6.25 (1H, d, *J* = 6.9, Ar(C=O)CH), 5.59 (1H, d, *J* = 6.9, ArCH); δ_C(75 MHz; $CDCl_3$) 190.7, 152.4, 140.8, 136.4, 133.1, 132.6, 132.2, 130.6, 130 × 2, 129.3, 128.0, 127.5, 126.4, 123.9, 117.9, 113.8, 82.0, 77.7; *m/z* (CI+) 361 (100%, $[M+NH_4]^+$); HRMS (ES+): $C_{21}H_{17}N_2O_4$, $[M+NH_4]^+$ requires 361.1183. Found 361.1184; $C_{21}H_{13}NO_4$ requires C, 73.4; H, 3.82; N, 4.08%. Found C, 73.1; H, 3.78; N, 4.14%. DCM provided the minor diastereomer, *cis-dioxolan-2-one cis*-**273** as a white solid; mp 175 °C (diethyl ether); R_f(SiO_2, DCM) 0.20; ν_{max}(KBr)/cm^{-1} 2231 (C≡N), 1804 (C=O), 1684 (C=O), 1174 (CO), 1076 (CO); δ_H(300 MHz; $CDCl_3$) 8.08 (1H, s, ArH), 7.82-7.92 (2H, m, ArH), 7.74-7.79 (1H, m, ArH), 7.57-7.70 (2H, m, ArH), 7.44-7.49 (1H, m, ArH), 7.35 (2H, d, *J* = 8.6, ArH), 7.23 (2H, d, *J* = 8.6, ArH), 6.43 (1H, d, *J* = 8.6, Ar(C=O)CH), 6.12 (1H, d, *J* = 8.6, ArCH); δ_C(75 MHz; $CDCl_3$) 190.9, 153.3, 136.8, 135.9, 132.2, 131.9, 131.8, 130.2, 129.8, 129.5, 129.3, 128.0, 127.7, 127.3, 122.7, 117.6, 113.6, 79.1, 78.5; *m/z* (CI+) 361 (100%, $[M+NH_4]^+$); HRMS (ES+): $C_{21}H_{17}N_2O_4$, $[M+NH_4]^+$ requires 361.1183. Found 361.1183.

Preparation of (4*R,5*S**)-4-(2-methylsulfanyl-benzoyl)-5-phenyl-[1,3]dioxolan-2-one 283**



trans-**283**

The reaction was carried out according to the experimental procedure above (Section III 19) with carbonic acid methyl ester 2-(2-methylsulfanyl-phenyl)-2-oxo-ethyl ester **282** (240 mg, 1 mmol). The crude mixture of diastereomers (*cis*:*trans*, 1:8) was purified by flash column chromatography (SiO_2, 75% DCM in light petroleum (bp 40-60 °C)) to provide the major diastereomer, *trans-dioxolan-2-one trans*-**283** as a white solid (235 mg, 75%); mp 131 °C (diethyl ether); ν_{max}(KBr)/cm^{-1} 1813 (C=O), 1689 (C=O), 1152 (CO), 1093 (CO); δ_H(300 MHz; $CDCl_3$) 7.76 (1H, dd, *J* = 8.1, 1.5, ArH), 7.53-7.59 (1H, m, ArH), 7.38-7.49 (6H, m, ArH), 7.19-7.25 (1H, m, ArH), 6.05 (1H, d, *J* = 6.3, Ar(C=O)CH), 5.57 (1H, d, *J* = 6.3, ArCH), 2.49 (3H, t, SCH_3); δ_C(75 MHz; $CDCl_3$) 192.3, 153.5, 145.1, 136.2, 134.2, 131.9, 131.3, 130.2, 129.7, 126.3, 124.3, 82.8, 79.5, 16.5; HRMS (ES+): $C_{17}H_{15}O_4S$, $[M+H]^+$ requires 315.0686. Found 315.0685; $C_{17}H_{14}O_4S$ requires C, 64.9; H, 4.49%. Found C, 64.6; H, 4.52%.

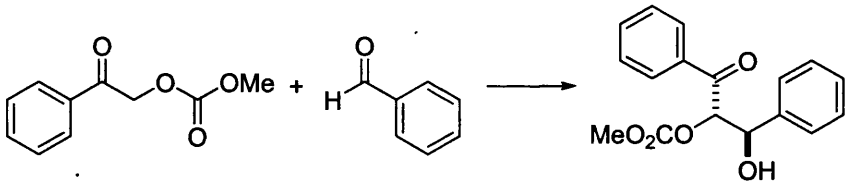
In instances where benzaldehyde **17** and phenacyl carbonates **259**, **260**, **261** and **262** were employed (section II 4.2) with greater loadings of $Mg(ClO_4)_2$ (50 mol%) 1,2-dicarbonyl by-product **264** was also formed in the reactions and characterisation data is given below (a tautomeric mixture was observed in NMR experiments):

1,3-Diphenyl-propane-1,2-dione 264

264 **264a**

R_f(SiO_2, 25% EtOAc in light petroleum (bp 40-60 °C)) 0.56; ν_{max}(neat)/cm^{-1} 1714 (C=O), 1672 (C=O); δ_H (300 MHz; $CDCl_3$) 7.9-7.2 (10 H, m, ArH), 4.2 (2 H, s, CH_2); enol tautomer δ_H (300 MHz; $CDCl_3$) 7.85-7.2 (10 H, m, ArH), 6.4 (1 H, s, PhCH=C); *m/z* (EI+) 224 (100%, M^+), 105 (100%, $PhC{\equiv}O^+$), 77 (44%, Ph^+), (CI+) 242 (100%, $[M+NH_4]^+$). Analytical data for this compound is consistent with that in the literature.[149]

III 20 Preparation of (1*R**,2*R**)-carbonic acid 1-benzoyl-2-hydroxy-2-phenyl-ethyl ester methyl ester *anti*-328



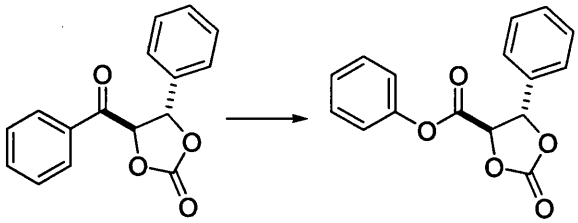
259 **17** **328**

The reaction was carried out according to the experimental procedure above (Section III 19) with benzaldehyde **17**, 1.1 equivalents (224 μL, 2.1 mmol) and trimethylsilyl chloride (252 μL, 2.0 mmol) (which were added in that order). The crude residue of diastereomeric silyl ethers (*syn*:*anti*, 67:33); (*syn*), δ_H(300 MHz; $CDCl_3$) 8.05-7.27 (10H, m, ArH), 6.04 (1H, d, *J* = 5.7, Ph(C=O)CH), 4.85 (1H, d, *J* = 5.7, PhCH), 3.70 (3H, s, OCH_3), -0.07 (9H, s, $OSi(CH_3)_3$); (*anti*), δ_H(300 MHz; $CDCl_3$) 8.0-7.27 (10H, m, ArH), 5.91 (1H, d, *J* = 6.9, Ph(C=O)CH), 5.12 (1H, d, *J* = 6.9, PhCH), 3.67 (3H, s, OCH_3), -0.12 (9H, s, $OSi(CH_3)_3$); was

taken up in toluene (10 mL) and *p*-toluenesulfonic acid mono-hydrate (761 mg, 4 mmol) was added. The mixture was stirred for 48 h at RT and then concentrated and purified by flash column chromatography (SiO_2:product, 50:1) to give an overall yield of the *trans*-dioxolan-2-one *trans*-**263** and the title compound *anti*-**328**, 335 mg, 60%. 90% DCM in light petroleum (bp 40-60 °C) provided the *trans*-dioxolan-2-one *trans*-**263** as a white solid (230 mg, 43%); data identical to that reported earlier. DCM provided the title compound *anti*-**328** as a colourless oil (105 mg, 17%); R_f(SiO_2, DCM) 0.32; ν_{max}(neat)/cm^{-1} 3456 (OH), 1745 (C=O), 1684 (C=O), 1271 (CO); δ_H(300 MHz; $CDCl_3$) 8.00-8.10 (2H, m, ArH), 7.65-7.75 (1H, m, ArH), 7.50-7.60 (2H, m, ArH), 7.20-7.35 (3H, m, ArH), 7.05-7.15 (2H, m, ArH), 5.99 (1H, d, *J* = 2.9, Ph(C=O)CH), 5.67 (1H, dd, *J* = 7.7, 2.9, ArCH), 3.81 (3H, s, OCH_3), 3.63 (1H, d, *J* = 7.7, OH); δ_C(75 MHz; $CDCl_3$) 197.6, 155.3, 134.5, 133.9, 133.3, 129.2, 128.9, 128.9, 128.1, 127.4, 80.4, 75.0, 55.1; HRMS (ES+): $C_{17}H_{20}NO_5$, $[M+NH_4]^+$ requires 318.1336. Found 318.1335.

III 21 Preparation of Baeyer-Villiger oxidation adducts of *trans*-dioxolan-2-ones

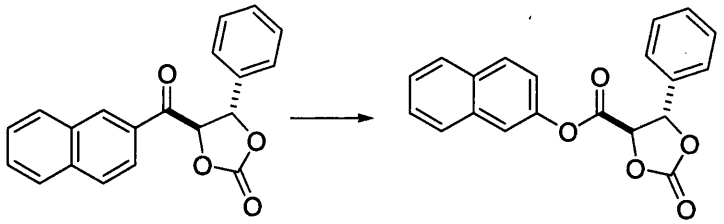
Preparation of (4*R,5*S**)-phenyl 2-oxo-5-phenyl-1, 3-dioxolane-4-carboxylate 276**



trans-**263** *trans*-**276**

To a stirred solution of phenyl ketone *trans*-**263** (134 mg, 0.5 mmol) in DCM (7.5 mL) were added anhydrous NaH_2PO_4 (360 mg, 3 mmol) and *m*-CPBA (345 mg, 2 mmol). The resulting mixture was stirred vigorously at RT for 16 h. The reaction mixture was then diluted with DCM and washed with saturated aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution, water, brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the resultant residue was purified by flash silica-gel column chromatography (70% DCM in light petroleum (bp 40-60 °C)) to afford *phenyl ester* **276** (78 mg, 55%) as a colourless oil. An analytical sample was prepared *via* crystallisation from diethyl ether; mp 75 °C (diethyl ether); R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.50; ν_{max}(neat)/cm^{-1} 1818 (C=O), 1762 (C=O), 1188 (CO), 1080 (CO); δ_H(300 MHz; $CDCl_3$) 7.40-7.54 (7H, m, ArH), 7.28-7.35 (1H, m, ArH), 7.16-7.21 (2H, m, ArH), 5.83 (1H, d, *J* = 5.6, ArCH), 5.15 (1H, d, *J* = 5.6, ArO(C=O)CH); δ_C(75 MHz; $CDCl_3$) 165.4, 152.9, 149.7, 135.3, 130.1, 129.8, 129.5, 126.9, 125.5, 120.9, 80.0, 79.2; *m/z* (CI+) 302 (100%, $[M+NH_4]^+$); HRMS (ES+): $C_{16}H_{16}NO_5$, $[M+NH_4]^+$ requires 302.1023. Found 302.1026.

Preparation of (4*R,5*S**)-naphthalen-2-yl 2-oxo-5-phenyl-1,3-dioxolane-4-carboxylate 277**

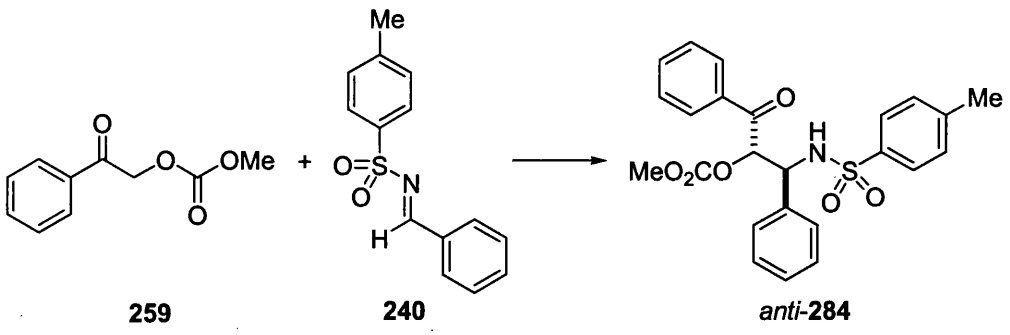


trans-**269** *trans*-**277**

To a stirred solution of *naphthyl ketone trans*-**269** (74 mg, 0.2 mmol) in DCM (3.5 mL), were added anhydrous NaH_2PO_4 (166 mg, 1.38 mmol) and *m*-CPBA (159 mg, 0.9 mmol). The resulting mixture was stirred vigorously at RT for 5

h. The reaction mixture was then diluted with DCM and washed with saturated aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution, water, brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the resultant residue was purified by flash silica-gel column chromatography (70% DCM in light petroleum (bp 40-60 °C)) to afford *naphthyl ester* **277** (67 mg, 87%) as an orange oil; R_f(SiO_2, 30% diethyl ether in light petroleum (bp 40-60 °C)) 0.55; ν_{max}(neat)/cm^{-1} 1792 (C=O), 1762 (C=O), 1193 (CO), 1096 (CO); δ_H(300 MHz; $CDCl_3$) 7.91 (1H, d, *J* = 9.0, ArH), 7.83-7.89 (2H, m, ArH), 7.68 (1H, d, *J* = 2.4, ArH), 7.36-7.48 (7H, m, ArH), 7.29 (1H, dd, *J* = 9.0, 2.4, ArH), 5.88 (1H, d, *J* = 5.7, ArCH), 5.20 (1H, d, *J* = 5.7, ArO(C=O)CH); δ_C(75 MHz; $CDCl_3$) 165.6, 152.9, 147.3, 135.4, 139.6, 131.8, 130.2, 130.0, 129.5, 127.9, 127.8, 127.1, 126.4, 125.6, 119.8, 118.4, 80.0, 79.3; *m/z* (EI+) 334 (100%, $[M]^+$); HRMS (EI): $C_{20}H_{14}O_3$, $[M]^+$ requires 334.0836. Found 334.0833.

III 22 Preparation of (1*R**,2*R**)-carbonic acid 1-benzoyl-2-phenyl-2-(toluene-4-sulfonylamino)-ethyl ester methyl ester 284; to serve as an experimental procedure for the direct Mannich reaction of phenacyl carbonates and *N*-tosylimines

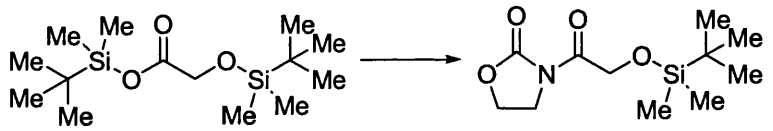


259 **240** ***anti*-284**

2,2'-bipyridine (31 mg, 0.2 mmol), 4 Å molecular sieves (200 mg), and magnesium perchlorate (45 mg, 0.2 mmol) were stirred for 30 min. in dry THF (2.5 mL) under a nitrogen atmosphere at ambient temperature. The suspension formed was then treated with carbonic acid methyl ester 2-oxo-2-phenyl-ethyl ester **259** (194 mg, 1 mmol) in THF (2.5 mL). After 10 min. *N*-(4-toluenesulfonyl)benzaldimine **240** (259 mg, 1 mmol) and *N*-methylmorpholine (55 μL, 0.5 mmol) were added drop-wise. The reaction was monitored by thin-layer chromatography. After 24 h the reaction mixture was diluted with EtOAc (2 × 30 mL), filtered through celite and subsequently quenched with a saturated aqueous solution of ammonium chloride (10 mL). The organic layers were washed with a saturated aqueous solution of copper sulfate (10 mL) followed by water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude mixture of diastereomers (*anti:syn*, 5:1) was purified by flash column chromatography (SiO_2:product, 50:1) to give an overall yield of 314 mg, 70%. 95:5 DCM:EtOAc provided the major diastereomer, *anti-carbonate* **284** as a white solid (141 mg, 31%); mp 185-186 °C ($CHCl_3$); ν_{max}(KBr)/cm^{-1} 3259 (NH), 1760 (C=O), 1702 (C=O), 1278 (CO), 1168 (CO); δ_H(300 MHz; $CDCl_3$) 7.73 (2H, m, ArH), 7.54-7.61 (3H, m, ArH), 7.42 (2H, m, ArH), 7.05-7.14 (5H, m, ArH), 6.94 (2H, m, ArH), 6.11 (1H, d, J = 4.2, Ph(C=O)CH), 5.75 (1H, d, J = 8.4, NH), 5.01 (1H, d, J = 8.4, 4.2, PhCH), 3.75 (3H, s, OCH_3), 2.34 (3H, s, $ArCH_3$); δ_C(75 MHz; $CDCl_3$) 193.6, 155.0, 143.8, 137.5, 135.2, 134.8, 134.4, 129.9, 129.3, 128.8, 127.9, 127.5, 79.6, 58.4, 55.8, 21.9; $C_{24}H_{23}NO_6S$ requires C, 63.5; H, 5.11; N, 3.09%. Found C, 63.2; H, 5.08; N, 3.15%. A single crystal was grown from $CHCl_3$ for X-ray crystallographic experiment (Appendix E).

III 23 Preparation of other acetyl analogues employed as substrates in the direct catalytic aldol addition to aromatic aldehydes

Preparation of 3-[2-(*tert*-butyl-dimethyl-silanyloxy)-acetyl]-oxazolidin-2-one 330

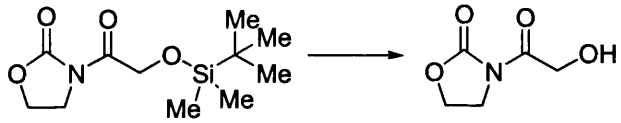


329 **330**

Oxalyl chloride (2.89 mL, 33.1 mmol) was added drop-wise to a stirred solution of *tert*-butyldimethylsilyl *tert*-butyldimethylsilyloxyacetate[150] **329** (8.41 g, 27.6 mmol) and dry DMF (0.1 mL) in dry DCM (35 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was warmed to ambient temperature and after 3 h concentrated *in vacuo*. To the residue was added dry THF (50 mL) and this was stirred under a nitrogen atmosphere at ambient temperature. Meanwhile, 2-oxazolidinone **167** (2.0 g, 23 mmol) was stirred in THF (50 mL) under a nitrogen atmosphere at –78 °C. A 2.32 M solution of *n*-BuLi (9.91 mL, 23 mmol) in *n*-hexane was added drop-wise. Then the prepared solution of (*tert*-butyl-dimethyl-silanyloxy)-acetyl chloride in THF (50 mL) was added drop-wise over 20 min. The reaction mixture was stirred at –78 °C for 30 min. and at ambient temperature for a further 30 min. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (10 mL), volatiles were removed *in vacuo* and water was added. The reaction mixture extracted with EtOAc, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The *oxazolidinone* **330**

was obtained as a colourless oil (4.87 g, 82%). An analytical sample was prepared by recrystallisation from diethyl ether and *n*-heptane obtaining the product as a white crystalline solid; mp 59-60 °C (diethyl ether-*n*-heptane); R_f (SiO_2, 1:1 EtOAc-light petroleum (bp 40-60 °C)) 0.71; ν_{max}(KBr)/cm^{-1} 2926 (CH), 2855 (CH), 1771 (C=O), 1714 (C=O), 1399 (CO), 1297 ($SiCH_3$), 1141 (CO); δ_H(300 MHz; $CDCl_3$) 4.84 (2H, s, CH_2), 4.49 (2H, t, J = 8.1, CH_2O), 4.04 (2H, t, J = 8.1, CH_2N), 0.94 (9H, s, $C(CH_3)_3$), 0.12 (6H, s, $Si(CH_3)_2$); δ_C(75 MHz; $CDCl_3$) 172.2, 154.0, 64.5, 63.5, 42.5, 26.2, 18.8, -5.0; *m/z* (EI+) 259 (15%, M^+), (CI+) 277 (94%, $[M+NH_4]^+$), 260 (100%, $[M+H]^+$), 202 (63%, $[M-^tBu]^+$); HRMS (ES+): $C_{11}H_{25}N_2O_4Si$, $[M+NH_4]^+$ requires 277.1578. Found 277.1583; $C_{11}H_{21}NO_4Si$ requires C, 50.9; H, 8.16; N, 5.40%. Found C, 50.7; H, 8.06; N, 5.34%.

Preparation of 3-(2-hydroxy-acetyl)-oxazolidin-2-one 331

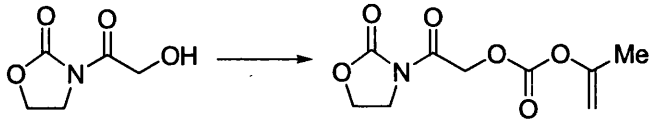


330 **331**

3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-acetyl]-oxazolidin-2-one **330** (4.86 g, 18.7 mmol) was added to a solution of THF (50 mL), and 3:1 HOAc-H_2O (200 mL). The reaction mixture was stirred for 4 h at ambient temperature and then concentrated *in vacuo* to a white solid, which was triturated in dry diethyl ether for 16 h and filtered to provide the *alcohol* **331** as a white solid (2.47 g, 91%). A sample was recrystallised from DCM as colourless needles for analysis; mp 129 °C (DCM); R_f(SiO_2, 1:1 EtOAc- light petroleum (bp 40-60 °C)) 0.17; ν_{max}(KBr)/cm^{-1} 3494 (OH), 1788 (C=O), 1684 (C=O), 1314 (CO), 1221 (CO), 1128 (CO); δ_H(300 MHz; $CDCl_3$) 4.72 (2H, d, J = 5.4, CH_2(C=O)), 4.54 (2H, t, J = 8.1, CH_2O), 4.09 (2H, t, J = 8.1, CH_2N), 3.05 (1H, t, J = 5.4, OH); δ_C(75 MHz; $CDCl_3$) 173.8, 153.6, 63.7, 63.4, 42.4; *m/z* (EI+) 146 (29%, $[M+H]^+$), 128 (100%, $[M-OH]^+$), 87 (82%, $[M-C{=}OCH_2OH+H]^+$); HRMS (ES+): $C_5H_{11}N_2O_4$,

$[M+NH_4]^+$ requires 163.0713. Found 163.0715; $C_5H_7NO_4$ requires C, 41.4; H, 4.86; N, 9.65%. Found C, 41.2; H, 4.86; N, 9.55%.

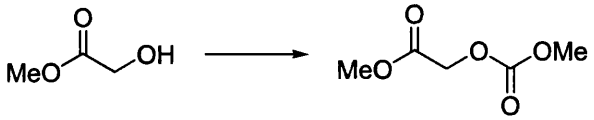
Preparation of carbonic acid *iso*propenyl ester 2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl ester 286f



331 **286f**

*Iso*propenyl chloroformate (1.49 mL, 13.8 mmol) was added drop-wise to a stirred solution of 3-(2-hydroxy-acetyl)-oxazolidin-2-one **331** (1.0 g, 6.9 mmol) in dry DCM (15 mL) and dry pyridine (15 mL) under a nitrogen atmosphere at 0 °C. After 1 h at 0 °C the reaction was deemed complete. The reaction mixture was poured into EtOAc (75 mL) and quenched with cold 1 M H_2SO_4 (75 mL). The organic layer was washed with 1 M H_2SO_4 (75 mL), saturated aqueous copper sulfate (75 mL), water (75 mL), saturated $NaHCO_3$ (75 mL) and brine (75 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The resultant yellow oil was purified by flash column chromatography (SiO_2:product, 20:1), 30% EtOAc in light petroleum (bp 40-60 °C)). The *carbonate* **286f** was obtained as a white crystalline solid (1.43 g, 91%); R_f(SiO_2, 50% EtOAc in light petroleum (bp 40-60 °C)) 0.51; ν_{max}(KBr)/cm^{-1} 1775 (C=O), 1757 (C=O), 1720 (C=O), 1678 (C=C), 1204 (CO); δ_H(300 MHz; $CDCl_3$) 5.25 (2H, s, (C=O)CH_2), 4.87 (1H, d, J = 1.5, (H)C*H*=C(CH_3)O), 4.74 (1H, d, J = 1.5, (*H*)CH=C(CH_3)O), 4.54 (2H, t, J = 8.1, CH_2O), 4.07 (2H, t, J = 8.1, CH_2N), 2.01 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 167.1, 154.0, 153.3, 153.0, 102.6, 66.3, 63.9, 42.3, 19.4; $C_9H_{11}NO_6$ requires C, 47.2; H, 4.84; N, 6.11%. Found C, 47.2; H, 4.85; N, 6.07%.

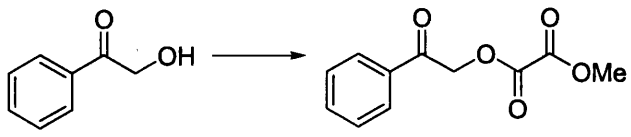
Preparation of methoxycarbonyloxy-acetic acid methyl ester 285e



332 **285e**

Methyl chloroformate (2.11 mL, 27.3 mmol) was added drop-wise to a stirred solution of methyl glycolate **332** (2.46 g, 27.3 mmol) in dry diethyl ether (20 mL) followed by dry pyridine (4.4 mL) under a nitrogen atmosphere at 0 °C. After 1 h at 0 °C the reaction was deemed complete. The reaction mixture was poured into diethyl ether and quenched with cold 1 M HCl. The organic layer was washed with 1 M HCl, saturated aqueous copper sulfate, water, saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The resultant colourless oil was purified by flash column chromatography (SiO_2:product, 20:1), 10% EtOAc in light petroleum (bp 40-60 °C)). The *carbonate* **285e** was obtained as a colourless oil (1.04 g, 26%); R_f(SiO_2, 50% EtOAc in light petroleum (bp 40-60 °C)) 0.67; δ_H(400 MHz; $CDCl_3$) 4.64 (2H, s, CH_2), 3.83 (3H, s, CO_2CH_3), 3.79 (3H, s, OCO_2CH_3); δ_C(100 MHz; $CDCl_3$) 168.0, 155.4, 63.6, 55.7, 52.7; *m/z* (CI+) 166 (100%, $[M+NH_4]^+$), 149 (3%, $[M+H]^+$); HRMS (ES+): $C_5H_{12}NO_5$, $[M+NH_4]^+$ requires 166.0710. Found 166.0714.

Preparation of oxalic acid methyl ester 2-oxo-2-phenyl-ethyl ester 287d

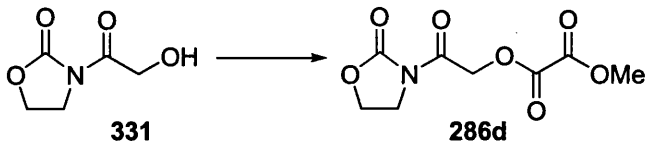


71 **287d**

Methyl chlorooxoacetate (1.77 mL, 19.3 mmol) was added drop-wise to a stirred solution of 2-hydroxyacetophenone **71** (2.5 g, 18.4 mmol), triethylamine (3.07 mL, 22.0 mmol) in dry THF (120 mL) under a nitrogen

atmosphere at 0 °C. After 2 h at 0 °C the reaction was deemed complete. The reaction mixture was poured into EtOAc (200 mL) and water (200 mL). The organic layer was then washed with brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo.* The resultant yellow oil was purified by flash column chromatography (SiO_2:product, 20:1), 15% EtOAc in light petroleum (bp 40-60 °C)). The *oxalate* **287d** was obtained as a very pale yellow crystalline solid (3.65 g, 89%); mp 65-66 °C (EtOAc-light petroleum (bp 40-60 °C)); R_f(SiO_2, 30% EtOAc in light petroleum (bp 40-60 °C)) 0.48; ν_{max}(KBr)/cm^{-1} 1765 (C=O), 1696 (C=O) 1317 (CO), 1210 (CO), 1162 (CO); δ_H(300 MHz; $CDCl_3$) 7.88-7.95 (2H, m, ArH), 7.60-7.68 (1H, m, ArH), 7.47-7.55 (2H, m, ArH), 5.56 (2H, s, CH_2), 3.97 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 190.1, 157.8, 157.1, 134.7, 134.0, 129.4, 128.2, 68.2, 54.2; *m/z* (EI+) 222 (7%, M^+), 163 (100%, $[M-CO_2Me]^+$), 105 (100%, $PhC{\equiv}O^+$), 77 (86%, Ph^+); HRMS (ES+): $C_{11}H_{14}NO_5$, $[M+NH_4]^+$ requires 240.0866. Found 240.0860; $C_{11}H_{10}O_5$ requires C, 59.5; H, 4.54%. Found C, 59.3; H, 4.49%.

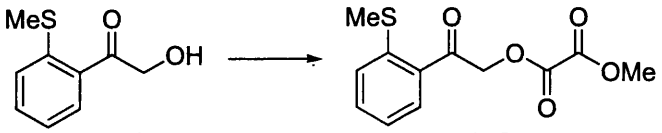
Preparation of oxalic acid methyl ester 2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl ester 286d



Methyl chlorooxoacetate (0.71 mL, 7.7 mmol) was added drop-wise to a stirred solution of 3-(2-hydroxy-acetyl)-oxazolidin-2-one **331** (1.07 g, 7.4 mmol), triethylamine (1.23 mL, 8.8 mmol) in dry THF (50 mL) under a nitrogen atmosphere at 0 °C. After 2 h at 0 °C the reaction was deemed complete. The reaction mixture was poured into EtOAc (75 mL) and water (75 mL). The organic layer was then washed with brine (75 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in*

vacuo to a white foam. The *oxalate* **286d** was obtained without further purification (1.39 g, 81%); mp 102 °C (EtOAc); R_f(SiO_2, 1:1 EtOAc:light petroleum (bp 40-60 °C)) 0.44; ν_{max}(KBr)/cm^{-1} 1791 (C=O), 1754 (C=O) 1704 (C=O); δ_H(300 MHz; $CDCl_3$) 5.40 (2H, s, (C=O)CH_2), 4.55 (2H, t, J = 7.8, OCH_2), 4.06 (2H, t, J = 7.8, NCH_2), 3.96 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 165.6, 157.7, 157.1, 154.0, 65.2, 63.9, 54.3, 42.3; HRMS (ES+): $C_8H_{13}N_2O_7$, $[M+NH_4]^+$ requires 249.0717. Found 249.0721; $C_8H_9NO_7$ requires C, 41.6; H, 3.92; N, 6.06%. Found C, 41.8; H, 4.08; N, 5.80%.

Preparation of oxalic acid methyl ester 2-(2-methylsulfanyl-phenyl)-2-oxo-ethyl ester 288

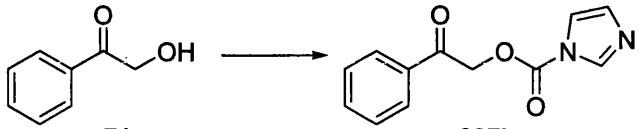


281 **288**

Methyl chlorooxoacetate (0.55 mL, 5.9 mmol) was added drop-wise to a stirred solution of 2-hydroxy-1-(2-methylsulfanyl-phenyl)-ethanone **281** (1.03 g, 5.7 mmol), and triethylamine (0.94 mL, 6.8 mmol) in dry THF (30 mL) under a nitrogen atmosphere at 0 °C. After 2 h at 0 °C the reaction was deemed complete. The reaction mixture was poured into EtOAc (100 mL) and water (100 mL). The organic layer was then washed with brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The *oxalate* **288** was purified by recrystallisation; 1:1 EtOAc:light petroleum (bp 40-60 °C) affording yellow crystals (1.13 g, 75%); mp 100 °C (EtOAc-light petroleum (bp 40-60 °C)); ν_{max}(KBr)/cm^{-1} 1771 (C=O), 1749 (C=O) 1682 (C=O); δ_H(300 MHz; $CDCl_3$) 7.74 (1H, d, J = 9.0, ArH), 7.54 (1H, t, J = 9.0, ArH), 7.38 (1H, d, J = 6.0, ArH), 7.21-7.28 (1H, m, ArH), 5.52 (2H, s, (C=O)CH_2), 3.96 (3H, s, OCH_3), 2.45 (3H, s, SCH_3); δ_C(75 MHz; $CDCl_3$) 190.6, 157.9, 157.1, 144.0, 133.6, 131.2, 129.9, 126.1, 124.1, 68.6, 54.2, 16.3;

HRMS (ES+): $C_{12}H_{16}NO_5S$, $[M+NH_4]^+$ requires 286.0744. Found 286.0747; $C_{12}H_{12}O_5S$ requires C, 53.7; H, 4.51%. Found C, 53.6; H, 4.53%.

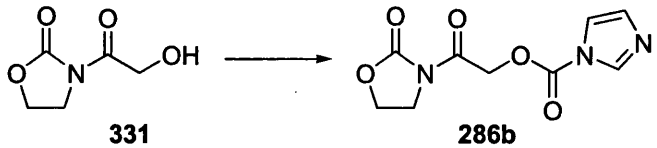
Preparation of imidazole-1-carboxylic acid 2-oxo-2-phenyl-ethyl ester 287b



71 **287b**

To a stirred solution of 2-hydroxyacetophenone **71** (1.0 g, 7.3 mmol) in dry DCM (30 mL) was added 1,1′-carbonyldiimidazole (1.25 g, 7.7 mmol) under a nitrogen atmosphere at 0 °C. After 2 h the reaction mixture was washed with water and concentrated under reduced pressure. The crude *phenyl ketone* **287b** was crystallised from DCM-*n*-hexane to yield a pale orange solid (1.43 g, 85%); δ_H(300 MHz; $CDCl_3$) 8.24 (1H, s, ArH), 7.95 (2H, d, J = 8.1, ArH), 7.67 (1H, m, ArH), 7.51-7.56 (3H, m, ArH), 7.12 (1H, s, ArH), 5.63 (2H, s, (C=O)CH_2); δ_C(75 MHz; $CDCl_3$) 190.7, 148.8, 137.7, 134.8, 133.9, 131.2, 129.5, 128.1, 117.7, 68.9; $C_{12}H_{10}N_2O_3$ requires C, 62.6; H, 4.38; N, 12.17%. Found C, 62.6; H, 4.45; N, 12.1%.

Preparation of imidazole-1-carboxylic acid 2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl ester 286b

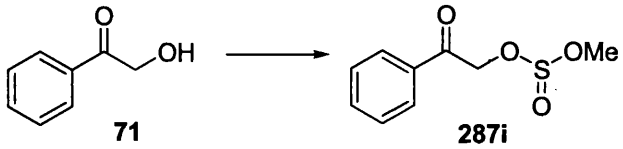


331 **286b**

To a stirred solution of 3-(2-hydroxy-acetyl)-oxazolidin-2-one **331** (1.0 g, 6.9 mmol) in dry DCM (30 mL) was added 1,1′-carbonyldiimidazole (1.12 g, 6.9 mmol) under a nitrogen atmosphere at 0 °C. After 3 h the reaction mixture was washed with water and concentrated under reduced pressure. The

oxazolidinone **286b** was obtained as a white solid and used as in further reactions (1.41 g, 86%); δ_H(400 MHz; $CDCl_3$) 8.20 (1H, s, ImH), 7.48 (1H, s, ImH), 7.11 (1H, m, ImH), 5.49 (2H, s, CH_2), 4.57 (2H, t, J = 8.0, OCH_2CH_2), 4.09 (2H, t, J = 8.0, CH_2CH_2N); δ_C(100 MHz; $CDCl_3$) 165.8, 153.6, 148.4, 137.3, 131.0, 117.3, 65.6, 63.6, 41.9.

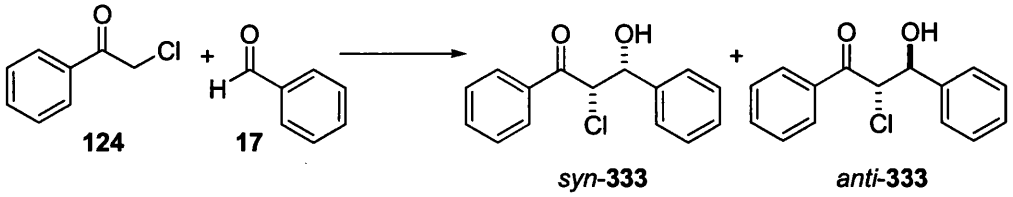
Preparation of sulfurous acid methyl ester 2-oxo-2-phenyl-ethyl ester 287i



Methyl chorosulfinate[151] (4.20 g, 36.7 mmol) was added drop-wise to a stirred solution of 2-hydroxyacetophenone **71** (5.0 g, 36.7 mmol) in dry pyridine (8.3 mL) and diethyl ether (75 mL) under a nitrogen atmosphere at 0 °C. After 1 h at 0 °C the reaction was complete. The reaction mixture was diluted with diethyl ether (150 mL) and quenched with cold 1 M H_2SO_4 (50 mL). The organic layer was washed with 1 M H_2SO_4 (75 mL), saturated $NaHCO_3$ (2 × 75 mL) and brine (2 × 75 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The resultant yellow oil was purified by flash column chromatography (SiO_2:product, 25:1), 100% DCM. The *sulfite* **287i** was obtained as a colourless oil (4.62 g, 59%); ν_{max}(neat)/cm^{-1} 1701 (C=O), 1451 (S=O), 1208 (SO), 1059 (SO); δ_H(300 MHz; $CDCl_3$) 7.90-7.93 (2H, m, ArH), 7.60-7,62 (1H, m, ArH), 7.47-7.52 (2H, m, ArH), 5.24 (2H, s, CH_2), 3.73 (3H, s, OCH_3); δ_C(100 MHz; $CDCl_3$) 192.9, 134.5, 134.4, 129.3, 128.3, 63.7, 49.2.

III 24 Typical experimental procedure for the addition of phenacyl chloride to benzaldehyde

syn-2-Chloro-3-hydroxy-1,3-diphenyl-propan-1-one and _anti_-2-chloro-3-hydroxy-1,3-diphenyl-propan-1-one 333

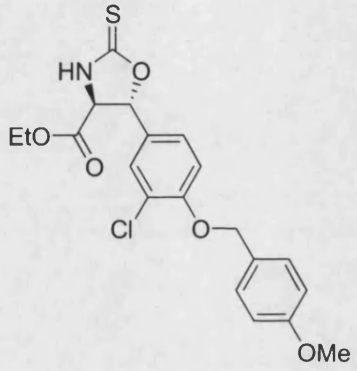


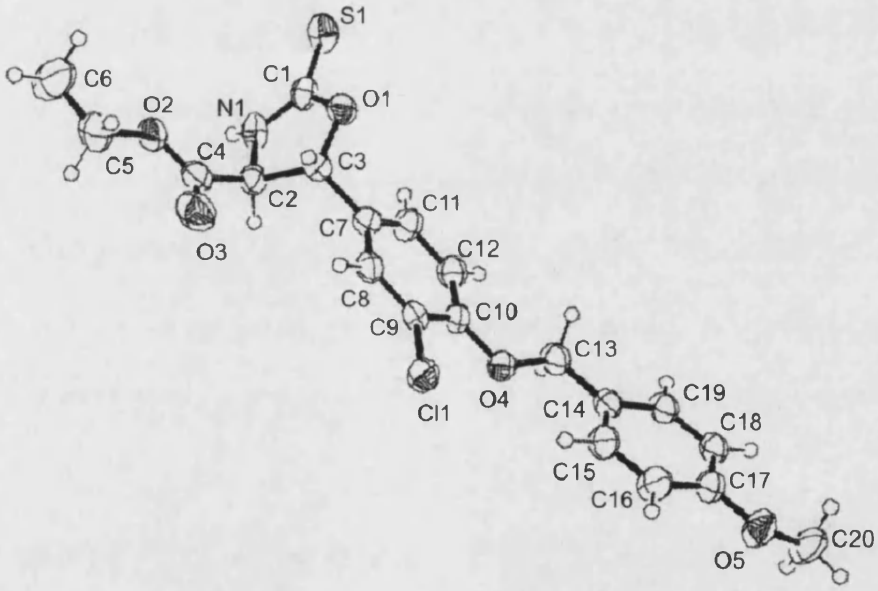
Magnesium perchlorate (322 mg, 1.0 mmol) was stirred for 20 minutes in dry THF (5 mL) under a nitrogen atmosphere at ambient temperature. The solution formed was then treated with 2-chloroacetophenone **124** (155 mg, 1.0 mmol). After 10 min. benzaldehyde **17** (112 μL, 1.1 mmol) and triethylamine (153 μL, 1.1 mmol) were added drop-wise. The reaction was monitored by thin-layer chromatography. After 48 h the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (20 mL) and extracted with diethyl ether (2 × 20 mL). The organic layers were washed with a saturated aqueous solution of copper sulfate (5 mL) followed by water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The pale yellow oil was purified by flash column chromatography (SiO_2:product, 50:1), 10% diethyl ether in light petroleum (bp 40-60 °C) afforded the two aldol diastereomers *syn*- and *anti*-**333** (*syn*:*anti*, 67:33) as colourless oils (0.06 g, 23%); major diastereomer (*syn*-**333**), δ_H(300 MHz; $CDCl_3$) 8.02-7.25 (10 H, m, ArH), 5.23 (1 H, dd, *J* = 8.0, 6.0, C*H*OH), 5.14 (1 H, d, *J* = 8.0, CHCl), 3.31 (1H, d, *J* = 6.0, OH); δ_C(75 MHz; $CDCl_3$) 194.9, 139.5, 135.0, 134.7, 129.5, 129.2, 129.1, 128.9, 127.7, 75.2, 57.9; HRMS (ES+): $C_{15}H_{17}ClNO_2$, $[M+NH_4]^+$ requires

278.0948. Found 278.0947; minor diastereomer (*anti*-**333**), δ_H(300 MHz; $CDCl_3$) 7.89-7.25 (10 H, m, ArH), 5.37 (1 H, dd, *J* = 4.8, 4.0, C*H*OH), 5.27 (1 H, d, *J* = 4.8, CHCl), 3.53 (1H, d, *J* = 4.0, OH); HRMS (ES+): $C_{15}H_{17}ClNO_2$, $[M+NH_4]^+$ requires 278.0948. Found 278.0947. Analytical data for this compound is consistent with that in the literature.[152]

Appendix A

(4*S*,5*R*)-5-[3-Chloro-4-(4-methoxy-benzyloxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester (4*S*,5*R*)-227





Appendix

Table 1. Crystal data and structure refinement for (4*S*,5*R*)-**227**.

Identification code	h04mcw2
Empirical formula	$C_{20}H_{20}ClNO_5S$
Formula weight	421.88
Temperature	150(2) K
Wavelength	0.71070 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 14.3028(3) Å α = 90°
	b = 7.68010(10) Å β = 100.7190(10)°
	c = 18.2410(4) Å γ = 90°
Volume	1968.76(7) $Å^3$
Z	4
Density (calculated)	1.423 mg/m^3
Absorption coefficient	0.332 mm^{-1}
F(000)	880
Crystal size	0.20 x 0.12 x 0.10 mm
Theta range for data collection	3.93 to 27.46°
Index ranges	-18<=h<=18; -9<=k<=9; -23<=l<=23
Reflections collected	41516
Independent reflections	8863 [R(int) = 0.0627]
Reflections observed (>2σ)	6016
Data Completeness	0.992
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8863 / 3 / 515
Goodness-of-fit on F^2	1.024
Final R indices [I>2σ(I)]	R^1 = 0.0529 wR_2 = 0.1250
R indices (all data)	R^1 = 0.0937 wR_2 = 0.1420
Absolute structure parameter	0.01(6)
Largest diff. peak and hole	0.571 and -0.400 $eÅ^{-3}$

Appendix

Notes: 2 molecules in the asymmetric unit. Each molecule involved in 1-dimensional hydrogen-bonding as a consequence of N-H•••S interactions.

Hydrogen bonds with H..A < r(Å) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N1-H1	0.890	2.663	152.20	3.475	S1[-x,y-1/2, -z+2]
N2-H2	0.890	2.407	157.65	3.248	S2[-x+1,y-1/2, -z+1]

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for (4*S*,5*R*)-**227**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Cl(1)	2794(1)	6071(1)	6672(1)	49(1)
Cl(2)	2180(1)	119(1)	8300(1)	57(1)
S(1)	-1059(1)	4027(1)	9793(1)	54(1)
S(2)	6067(1)	728(2)	5317(1)	71(1)
O(1)	155(2)	5442(3)	9067(1)	45(1)
O(2)	2332(2)	4858(3)	10780(1)	52(1)
O(3)	3045(2)	5700(5)	9842(2)	73(1)
O(4)	1280(1)	3929(3)	5934(1)	46(1)
O(5)	909(2)	4986(4)	2489(1)	60(1)
O(6)	4693(2)	2144(4)	5868(2)	68(1)
O(7)	2817(2)	543(5)	4365(2)	84(1)
O(8)	1824(2)	-24(5)	5139(3)	107(1)
O(9)	3812(2)	1743(3)	9147(1)	47(1)
O(10)	4018(2)	1283(4)	12605(1)	63(1)
N(1)	821(2)	3468(4)	9856(2)	45(1)
N(2)	4318(2)	-391(4)	5382(2)	67(1)
C(1)	8(2)	4266(4)	9584(2)	40(1)
C(2)	1620(2)	4054(5)	9546(2)	43(1)
C(3)	1138(2)	5377(5)	8954(2)	42(1)
C(4)	2418(2)	4969(5)	10080(2)	48(1)
C(5)	3125(3)	5768(7)	11290(2)	69(1)
C(6)	2896(3)	5694(10)	12027(3)	99(2)
C(7)	1153(2)	4889(5)	8147(2)	41(1)
C(8)	1887(2)	5546(4)	7832(2)	39(1)
C(9)	1909(2)	5162(5)	7093(2)	38(1)
C(10)	1209(2)	4152(5)	6661(2)	38(1)
C(11)	472(2)	3844(5)	7730(2)	46(1)
C(12)	491(2)	3468(5)	6990(2)	46(1)
C(13)	453(2)	3331(5)	5426(2)	44(1)
C(14)	584(2)	3734(4)	4650(2)	40(1)
C(15)	1366(2)	4658(5)	4502(2)	49(1)
C(16)	1459(2)	5030(6)	3778(2)	55(1)
C(17)	752(2)	4481(5)	3186(2)	46(1)
C(18)	-27(2)	3579(5)	3320(2)	43(1)
C(19)	-111(2)	3208(5)	4047(2)	43(1)
C(20)	371(3)	4125(8)	1854(2)	70(1)
C(21)	4984(3)	801(6)	5511(2)	58(1)
C(22)	3458(3)	65(5)	5633(2)	55(1)

C(23)	3740(3)	1819(5)	6022(2)	57(1)
C(24)	2598(3)	194(5)	5011(2)	56(1)
C(25)	2012(6)	562(14)	3743(4)	219(6)
C(26)	2135(3)	-125(13)	3129(3)	132(3)
C(27)	3784(3)	1795(5)	6868(2)	50(1)
C(28)	3058(3)	1056(5)	7158(2)	49(1)
C(29)	3081(2)	1038(5)	7925(2)	47(1)
C(30)	3849(2)	1819(5)	8408(2)	43(1)
C(31)	4566(2)	2589(5)	8110(2)	51(1)
C(32)	4538(3)	2556(5)	7344(2)	53(1)
C(33)	4622(2)	2360(5)	9666(2)	45(1)
C(34)	4464(2)	2040(5)	10437(2)	42(1)
C(35)	3658(2)	1219(5)	10593(2)	47(1)
C(36)	3533(2)	1012(5)	11318(2)	50(1)
C(37)	4211(2)	1558(5)	11908(2)	47(1)
C(38)	5036(2)	2351(5)	11768(2)	50(1)
C(39)	5152(2)	2570(5)	11038(2)	46(1)
C(40)	4618(3)	2050(8)	13229(2)	70(1)

Appendix

Table 3. Bond lengths [Å] and angles [°] for (4*S*,5*R*)-**227**.

Cl(1)-C(9)	1.743(3)	Cl(2)-C(29)	1.717(4)
S(1)-C(1)	1.651(4)	S(2)-C(21)	1.653(4)
O(1)-C(1)	1.350(4)	O(1)-C(3)	1.459(4)
O(2)-C(4)	1.308(4)	O(2)-C(5)	1.500(4)
O(3)-C(4)	1.205(5)	O(4)-C(10)	1.358(4)
O(4)-C(13)	1.435(4)	O(5)-C(17)	1.386(4)
O(5)-C(20)	1.428(4)	O(6)-C(21)	1.326(5)
O(6)-C(23)	1.464(5)	O(7)-C(24)	1.301(5)
O(7)-C(25)	1.459(5)	O(8)-C(24)	1.185(5)
O(9)-C(30)	1.359(4)	O(9)-C(33)	1.433(4)
O(10)-C(37)	1.366(4)	O(10)-C(40)	1.420(5)
N(1)-C(1)	1.325(4)	N(1)-C(2)	1.438(5)
N(2)-C(21)	1.310(5)	N(2)-C(22)	1.433(5)
C(2)-C(4)	1.527(5)	C(2)-C(3)	1.549(4)
C(3)-C(7)	1.523(4)	C(5)-C(6)	1.443(6)
C(7)-C(11)	1.377(5)	C(7)-C(8)	1.382(5)
C(8)-C(9)	1.386(4)	C(9)-C(10)	1.391(4)
C(10)-C(12)	1.387(5)	C(11)-C(12)	1.385(5)
C(13)-C(14)	1.494(5)	C(14)-C(15)	1.392(5)
C(14)-C(19)	1.398(4)	C(15)-C(16)	1.383(5)
C(16)-C(17)	1.400(5)	C(17)-C(18)	1.372(5)
C(18)-C(19)	1.383(5)	C(22)-C(24)	1.514(5)
C(22)-C(23)	1.541(5)	C(23)-C(27)	1.532(5)
C(25)-C(26)	1.279(7)	C(27)-C(28)	1.373(5)
C(27)-C(32)	1.382(5)	C(28)-C(29)	1.393(5)
C(29)-C(30)	1.408(5)	C(30)-C(31)	1.381(5)
C(31)-C(32)	1.390(5)	C(33)-C(34)	1.486(5)
C(34)-C(35)	1.389(5)	C(34)-C(39)	1.391(5)
C(35)-C(36)	1.376(5)	C(36)-C(37)	1.373(5)
C(37)-C(38)	1.393(5)	C(38)-C(39)	1.382(5)
C(1)-O(1)-C(3)	110.8(2)	C(4)-O(2)-C(5)	112.2(3)
C(10)-O(4)-C(13)	118.0(2)	C(17)-O(5)-C(20)	117.3(3)
C(21)-O(6)-C(23)	110.5(3)	C(24)-O(7)-C(25)	114.7(5)
C(30)-O(9)-C(33)	117.8(3)	C(37)-O(10)-C(40)	119.1(3)
C(1)-N(1)-C(2)	114.5(3)	C(21)-N(2)-C(22)	114.2(3)
N(1)-C(1)-O(1)	109.4(3)	N(1)-C(1)-S(1)	130.3(3)
O(1)-C(1)-S(1)	120.4(2)	N(1)-C(2)-C(4)	116.7(3)
N(1)-C(2)-C(3)	101.3(2)	C(4)-C(2)-C(3)	109.0(3)
O(1)-C(3)-C(7)	109.4(3)	O(1)-C(3)-C(2)	103.8(2)
C(7)-C(3)-C(2)	115.4(3)	O(3)-C(4)-O(2)	126.4(3)
O(3)-C(4)-C(2)	120.2(3)	O(2)-C(4)-C(2)	113.4(3)

C(6)-C(5)-O(2)	106.5(4)	C(11)-C(7)-C(8)	119.8(3)
C(11)-C(7)-C(3)	122.8(3)	C(8)-C(7)-C(3)	117.4(3)
C(7)-C(8)-C(9)	118.9(3)	C(8)-C(9)-C(10)	121.7(3)
C(8)-C(9)-Cl(1)	119.5(2)	C(10)-C(9)-Cl(1)	118.6(2)
O(4)-C(10)-C(12)	124.8(3)	O(4)-C(10)-C(9)	116.6(3)
C(12)-C(10)-C(9)	118.6(3)	C(7)-C(11)-C(12)	121.3(3)
C(11)-C(12)-C(10)	119.6(3)	O(4)-C(13)-C(14)	108.2(3)
C(15)-C(14)-C(19)	118.3(3)	C(15)-C(14)-C(13)	122.4(3)
C(19)-C(14)-C(13)	119.3(3)	C(16)-C(15)-C(14)	121.0(3)
C(15)-C(16)-C(17)	119.4(3)	C(18)-C(17)-O(5)	125.5(3)
C(18)-C(17)-C(16)	120.5(3)	O(5)-C(17)-C(16)	113.9(3)
C(17)-C(18)-C(19)	119.6(3)	C(18)-C(19)-C(14)	121.3(3)
N(2)-C(21)-O(6)	110.4(4)	N(2)-C(21)-S(2)	128.0(3)
O(6)-C(21)-S(2)	121.5(3)	N(2)-C(22)-C(24)	113.7(3)
N(2)-C(22)-C(23)	101.2(3)	C(24)-C(22)-C(23)	113.3(3)
O(6)-C(23)-C(27)	109.3(3)	O(6)-C(23)-C(22)	103.5(3)
C(27)-C(23)-C(22)	114.3(3)	O(8)-C(24)-O(7)	126.7(4)
O(8)-C(24)-C(22)	120.1(4)	O(7)-C(24)-C(22)	113.1(3)
C(26)-C(25)-O(7)	117.4(6)	C(28)-C(27)-C(32)	119.3(3)
C(28)-C(27)-C(23)	120.0(3)	C(32)-C(27)-C(23)	120.6(3)
C(27)-C(28)-C(29)	120.9(3)	C(28)-C(29)-C(30)	119.6(3)
C(28)-C(29)-Cl(2)	121.6(3)	C(30)-C(29)-Cl(2)	118.8(3)
O(9)-C(30)-C(31)	125.2(3)	O(9)-C(30)-C(29)	115.6(3)
C(31)-C(30)-C(29)	119.2(3)	C(30)-C(31)-C(32)	120.2(3)
C(27)-C(32)-C(31)	120.9(4)	O(9)-C(33)-C(34)	109.0(3)
C(35)-C(34)-C(39)	117.7(3)	C(35)-C(34)-C(33)	123.1(3)
C(39)-C(34)-C(33)	119.2(3)	C(36)-C(35)-C(34)	120.6(3)
C(37)-C(36)-C(35)	121.3(3)	O(10)-C(37)-C(36)	116.5(3)
O(10)-C(37)-C(38)	124.2(3)	C(36)-C(37)-C(38)	119.3(3)
C(39)-C(38)-C(37)	119.2(3)	C(38)-C(39)-C(34)	121.9(3)

Appendix

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for (4*S*,5*R*)-**227**. The anisotropic displacement factor exponent takes the form: $-2\,g\pi^2\,[h^2\,a^{*2}\,U11 + ... + 2\,h\,k\,a^*\,b^*\,U12]$.

Atom	U11	U22	U33	U23	U13	U12
Cl(1)	39(1)	64(1)	45(1)	-3(1)	7(1)	-6(1)
Cl(2)	45(1)	60(1)	66(1)	-13(1)	6(1)	-8(1)
S(1)	47(1)	56(1)	55(1)	11(1)	2(1)	-10(1)
S(2)	57(1)	73(1)	76(1)	3(1)	-5(1)	-1(1)
O(1)	47(1)	45(1)	45(1)	11(1)	12(1)	9(1)
O(2)	42(1)	62(2)	47(1)	-12(1)	-4(1)	6(1)
O(3)	43(1)	92(2)	82(2)	3(2)	8(1)	-4(2)
O(4)	37(1)	60(2)	37(1)	-11(1)	0(1)	1(1)
O(5)	55(2)	86(2)	38(1)	-9(1)	3(1)	-15(2)
O(6)	86(2)	53(2)	66(2)	-3(1)	21(2)	-16(2)
O(7)	81(2)	124(3)	43(2)	-11(2)	-1(1)	56(2)
O(8)	48(2)	89(3)	184(4)	17(3)	28(2)	-3(2)
O(9)	43(1)	54(1)	40(1)	-7(1)	-2(1)	-6(1)
O(10)	46(1)	93(2)	47(1)	3(1)	2(1)	-11(1)
N(1)	47(2)	42(2)	41(2)	6(1)	-7(1)	-6(1)
N(2)	51(2)	53(2)	87(3)	-14(2)	-9(2)	10(2)
C(1)	47(2)	35(2)	34(2)	-1(1)	-1(1)	-6(2)
C(2)	51(2)	39(2)	37(2)	-2(1)	1(1)	12(2)
C(3)	41(2)	45(2)	39(2)	-1(1)	5(1)	9(2)
C(4)	40(2)	50(2)	51(2)	-6(2)	2(2)	12(2)
C(5)	45(2)	85(3)	68(3)	-25(2)	-11(2)	-3(2)
C(6)	56(3)	167(6)	74(3)	-47(4)	13(2)	-30(3)
C(7)	41(2)	41(2)	38(2)	-3(1)	4(1)	7(2)
C(8)	37(2)	39(2)	37(2)	-4(1)	-3(1)	3(1)
C(9)	29(1)	40(2)	41(2)	4(2)	1(1)	3(1)
C(10)	38(2)	43(2)	32(2)	-3(1)	0(1)	4(2)
C(11)	49(2)	48(2)	41(2)	1(2)	9(1)	-7(2)
C(12)	39(2)	49(2)	46(2)	-5(2)	1(1)	-6(2)
C(13)	36(2)	49(2)	45(2)	-7(2)	0(1)	-1(2)
C(14)	36(2)	40(2)	41(2)	-12(1)	-2(1)	5(1)
C(15)	39(2)	62(2)	43(2)	-13(2)	-1(2)	-8(2)
C(16)	42(2)	74(3)	47(2)	-15(2)	4(2)	-15(2)
C(17)	45(2)	52(2)	39(2)	-5(2)	1(2)	1(2)
C(18)	37(2)	49(2)	39(2)	-11(2)	-4(1)	2(2)
C(19)	35(2)	48(2)	44(2)	-12(2)	-2(1)	0(1)
C(20)	53(2)	120(4)	36(2)	-18(2)	5(2)	-14(3)
C(21)	62(2)	51(2)	55(2)	8(2)	-5(2)	6(2)
C(22)	68(2)	44(2)	51(2)	2(2)	5(2)	-3(2)

Appendix

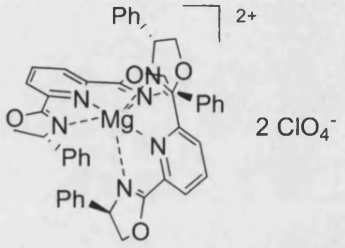
C(23)	68(2)	43(2)	57(2)	6(2)	7(2)	3(2)
C(24)	43(2)	48(2)	74(3)	-11(2)	4(2)	1(2)
C(25)	210(7)	298(11)	98(4)	-127(6)	-106(5)	216(8)
C(26)	60(3)	267(10)	74(3)	-67(5)	24(2)	-48(4)
C(27)	53(2)	48(2)	44(2)	-2(2)	0(2)	8(2)
C(28)	49(2)	42(2)	51(2)	-6(2)	-5(2)	10(2)
C(29)	40(2)	45(2)	52(2)	-7(2)	2(2)	2(2)
C(30)	43(2)	40(2)	43(2)	-3(2)	-1(1)	11(2)
C(31)	44(2)	52(2)	52(2)	-1(2)	-3(2)	-4(2)
C(32)	51(2)	54(2)	51(2)	12(2)	4(2)	6(2)
C(33)	36(2)	46(2)	48(2)	-8(2)	-3(1)	-5(2)
C(34)	35(2)	43(2)	47(2)	-6(2)	2(1)	3(2)
C(35)	37(2)	49(2)	49(2)	-8(2)	-3(1)	4(2)
C(36)	37(2)	55(2)	57(2)	3(2)	5(2)	-3(2)
C(37)	39(2)	55(2)	45(2)	-4(2)	2(1)	0(2)
C(38)	38(2)	58(2)	50(2)	-1(2)	-4(2)	-2(2)
C(39)	34(2)	50(2)	53(2)	-4(2)	4(1)	-3(2)
C(40)	54(2)	104(4)	49(2)	-10(2)	-1(2)	-8(2)

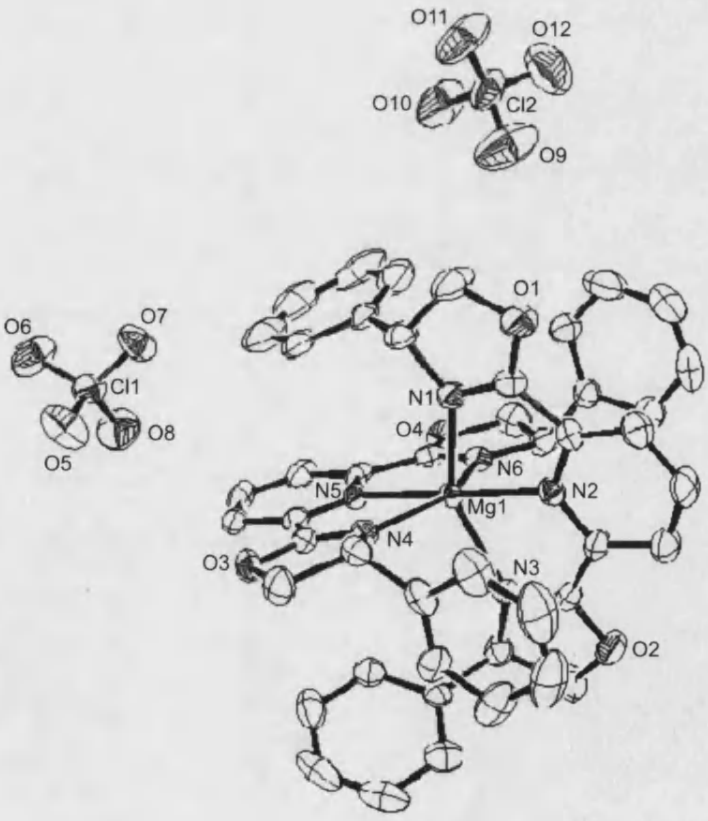
Table 5. Hydrogen coordinates (× 10^4) and isotropic displacement parameters (Å^2 × 10^3) for (4*S*,5*R*)-**227**.

Atom	x	y	z	U(eq)
H(2A)	1886	3061	9296	52
H(3)	1438	6547	9063	50
H(5A)	3739	5177	11284	83
H(5B)	3175	6992	11133	83
H(6A)	3397	6276	12383	148
H(6B)	2848	4476	12175	148
H(6C)	2287	6281	12025	148
H(8)	2368	6249	8118	47
H(11)	-21	3371	7954	55
H(12)	15	2747	6711	55
H(13A)	-122	3924	5531	53
H(13B)	374	2062	5485	53
H(15)	1842	5039	4905	59
H(16)	1997	5653	3682	66
H(18)	-506	3212	2917	52
H(19)	-651	2583	4138	52
H(20A)	545	4596	1399	105
H(20B)	-309	4314	1842	105
H(20C)	508	2874	1887	105
H(22)	3331	-806	6010	66
H(23)	3294	2752	5790	68
H(25A)	1474	-42	3904	263
H(25B)	1819	1789	3641	263
H(26A)	1545	-33	2758	198
H(26B)	2306	-1354	3211	198
H(26C)	2648	486	2946	198
H(28)	2533	552	6832	59
H(31)	5081	3143	8430	61
H(32)	5043	3063	7146	63
H(33A)	4711	3621	9590	54
H(33B)	5202	1743	9585	54
H(35)	3188	797	10195	56
H(36)	2967	481	11412	60
H(38)	5512	2737	12169	60
H(39)	5719	3098	10944	55
H(40A)	4389	1737	13686	106
H(40B)	4608	3319	13173	106
H(40C)	5270	1623	13260	106
H(1)	830(30)	2470(30)	10102(19)	64(12)
H(2)	4330(30)	-1350(30)	5111(18)	60(12)

Appendix B

[Mg((*R*,*R*)-phenyl-bis(oxazolinyl)pyridine)$_2$](ClO$_4$)$_2$ (*R*,*R*)-201





Appendix

Table 1. Crystal data and structure refinement for (*R,R*)-**201**.

Identification code	h04mcw1
Empirical formula	$C_{47}H_{40}Cl_4MgN_6O_{12}$
Formula weight	1046.96
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P212121
Unit cell dimensions	a = 11.5000(1) Å α = 90°
	b = 13.5120(1) Å β = 90°
	c = 30.2080(3) Å γ = 90°
Volume	4693.96(7) Å^3
Z	4
Density (calculated)	1.481 mg/m^3
Absorption coefficient	0.337 mm^{-1}
F(000)	2160
Crystal size	0.40 x 0.40 x 0.40 mm
Theta range for data collection	3.56 to 27.49°
Index ranges	-14<=h<=14; -17<=k<=17; -38<=l<=39
Reflections collected	63575
Independent reflections	10726 [R(int) = 0.0686]
Reflections observed (>2σ)	6984
Data Completeness	0.995
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.90 and 0.88
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10726 / 0 / 651
Goodness-of-fit on F^2	0.990
Final R indices [I>2σ (I)]	R^1 = 0.0476 wR_2 = 0.1029
R indices (all data)	R^1 = 0.0960 wR_2 = 0.1175
Absolute structure parameter	0.00

Largest diff. peak and hole	0.353 and -0.343 eÅ^{-3}

Notes: Asymmetric unit also contains 1 molecule of dichloromethane in which the chlorines are disordered over 2 sites, in a 60:40 ratio.

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters ($Å^2$ × 10^3) for (*R,R*)-**201**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Cl(1)	4446(1)	3763(1)	3872(1)	43(1)
Cl(2)	9304(1)	1487(1)	1296(1)	65(1)
Cl(3)	2237(3)	482(2)	2438(1)	60(1)
Cl(4)	2873(2)	-128(2)	1634(1)	61(1)
Mg(1)	2962(1)	5052(1)	1246(1)	24(1)
O(1)	3581(2)	2406(1)	509(1)	47(1)
O(2)	2234(2)	7497(1)	398(1)	44(1)
O(3)	286(2)	4415(2)	2165(1)	39(1)
O(4)	6085(2)	6030(2)	1847(1)	38(1)
O(5)	4968(2)	3260(2)	3508(1)	61(1)
O(6)	3219(2)	3691(2)	3833(1)	73(1)
O(7)	4768(2)	4772(2)	3879(1)	74(1)
O(8)	4792(3)	3303(2)	4274(1)	81(1)
O(9)	9589(4)	1813(2)	1718(1)	114(1)
O(10)	9083(3)	460(2)	1306(1)	109(1)
O(11)	10223(4)	1674(3)	1009(1)	144(2)
O(12)	8385(4)	2038(2)	1129(1)	121(1)
N(1)	3322(2)	3485(2)	1073(1)	31(1)
N(2)	2825(2)	4955(2)	544(1)	27(1)
N(3)	2454(2)	6566(2)	1011(1)	27(1)
N(4)	1339(2)	4593(2)	1543(1)	29(1)
N(5)	3185(2)	5176(2)	1952(1)	27(1)
N(8)	4726(2)	5579(2)	1349(1)	28(1)
C(1)	3514(3)	2498(2)	1294(1)	40(1)
C(2)	3878(4)	1843(2)	904(1)	72(1)
C(3)	3340(2)	3313(2)	658(1)	33(1)
C(4)	3054(2)	4100(2)	336(1)	31(1)
C(5)	2987(3)	4011(2)	-117(1)	40(1)
C(6)	2666(3)	4838(2)	-360(1)	48(1)
C(7)	2443(3)	5725(2)	-153(1)	43(1)
C(8)	2537(2)	5754(2)	306(1)	31(1)
C(9)	2393(2)	6624(2)	592(1)	30(1)
C(10)	2270(4)	8221(2)	761(1)	56(1)
C(11)	2307(2)	7592(2)	1183(1)	34(1)
C(12)	4361(3)	2619(2)	1673(1)	36(1)
C(13)	5555(3)	2657(3)	1624(1)	59(1)
C(14)	6254(4)	2892(3)	2013(2)	83(2)
C(15)	5659(5)	3058(3)	2410(2)	75(1)

C(16)	4534(5)	2978(3)	2454(1)	72(1)
C(17)	3896(4)	2777(2)	2091(1)	52(1)
C(18)	1263(2)	7654(2)	1488(1)	30(1)
C(19)	204(3)	8057(2)	1364(1)	43(1)
C(20)	-718(3)	8081(3)	1646(2)	59(1)
C(21)	-619(3)	7686(3)	2053(2)	64(1)
C(22)	432(4)	7288(2)	2201(1)	59(1)
C(23)	1382(3)	7284(2)	1914(1)	39(1)
C(24)	229(2)	4162(2)	1384(1)	33(1)
C(25)	-532(3)	4221(3)	1803(1)	44(1)
C(26)	1280(2)	4662(2)	1962(1)	30(1)
C(27)	2302(2)	4975(2)	2222(1)	30(1)
C(28)	2404(3)	5049(2)	2681(1)	37(1)
C(29)	3482(3)	5333(2)	2846(1)	40(1)
C(30)	4399(3)	5539(2)	2571(1)	37(1)
C(31)	4213(2)	5463(2)	2116(1)	28(1)
C(32)	5033(2)	5689(2)	1752(1)	28(1)
C(33)	6666(3)	6130(2)	1416(1)	45(1)
C(34)	5708(2)	5947(2)	1072(1)	33(1)
C(35)	-205(2)	4700(2)	983(1)	36(1)
C(36)	-254(3)	4227(3)	577(1)	60(1)
C(37)	-572(4)	4736(4)	201(1)	80(1)
C(38)	-845(4)	5718(4)	228(1)	79(1)
C(39)	-817(3)	6209(3)	628(1)	60(1)
C(40)	-495(2)	5693(2)	1004(1)	41(1)
C(41)	5979(2)	5234(2)	704(1)	32(1)
C(42)	6460(3)	4315(2)	787(1)	45(1)
C(43)	6625(3)	3643(3)	448(1)	61(1)
C(44)	6308(3)	3872(3)	27(1)	59(1)
C(45)	5839(3)	4780(3)	-67(1)	55(1)
C(46)	5676(3)	5474(2)	269(1)	42(1)
C(47)	1579(3)	58(3)	1962(1)	53(1)
Cl(4A)	2330(4)	45(3)	1484(2)	88(1)
Cl(3A)	1900(5)	834(4)	2405(2)	66(1)

Table 3. Bond lengths [Å] and angles [°] for (*R,R*)-**201**.

Cl(1)-O(8)	1.420(2)	Cl(1)-O(5)	1.425(2)
Cl(2)-O(12)	1.388(3)	Cl(2)-O(11)	1.389(4)
Cl(2)-O(9)	1.390(3)	Cl(2)-O(10)	1.411(3)
Cl(3)-C(47)	1.722(5)	Cl(4)-C(47)	1.806(4)
Mg(1)-N(2)	2.132(2)	Mg(1)-N(5)	2.152(2)
Mg(1)-N(4)	2.160(2)	Mg(1)-N(8)	2.172(2)
Mg(1)-N(1)	2.220(2)	Mg(1)-N(3)	2.244(2)
O(1)-C(3)	1.334(3)	O(1)-C(2)	1.454(4)
O(2)-C(9)	1.329(3)	O(2)-C(10)	1.469(4)
O(3)-C(26)	1.339(3)	O(3)-C(25)	1.467(3)
O(4)-C(32)	1.326(3)	O(4)-C(33)	1.471(3)
N(1)-C(3)	1.276(3)	N(1)-C(1)	1.507(3)
N(2)-C(8)	1.339(3)	N(2)-C(4)	1.343(3)
N(3)-C(9)	1.270(3)	N(3)-C(11)	1.490(3)
N(4)-C(26)	1.272(3)	N(4)-C(24)	1.482(3)
N(5)-C(27)	1.332(3)	N(5)-C(31)	1.340(3)
N(8)-C(32)	1.276(3)	N(8)-C(34)	1.492(3)
C(1)-C(12)	1.512(4)	C(1)-C(2)	1.532(4)
C(3)-C(4)	1.477(4)	C(4)-C(5)	1.375(4)
C(5)-C(6)	1.386(4)	C(6)-C(7)	1.376(4)
C(7)-C(8)	1.390(4)	C(8)-C(9)	1.469(4)
C(10)-C(11)	1.533(4)	C(11)-C(18)	1.515(4)
C(12)-C(13)	1.383(5)	C(12)-C(17)	1.389(4)
C(13)-C(14)	1.458(6)	C(14)-C(15)	1.399(6)
C(15)-C(16)	1.305(6)	C(16)-C(17)	1.347(5)
C(18)-C(19)	1.385(4)	C(18)-C(23)	1.390(4)
C(19)-C(20)	1.360(5)	C(20)-C(21)	1.343(5)
C(21)-C(22)	1.396(6)	C(22)-C(23)	1.393(4)
C(24)-C(35)	1.499(4)	C(24)-C(25)	1.539(4)
C(26)-C(27)	1.476(4)	C(27)-C(28)	1.395(4)
C(28)-C(29)	1.389(4)	C(29)-C(30)	1.372(4)
C(30)-C(31)	1.393(4)	C(31)-C(32)	1.480(4)
C(33)-C(34)	1.534(4)	C(34)-C(41)	1.504(4)
C(35)-C(36)	1.383(4)	C(35)-C(40)	1.384(4)
C(36)-C(37)	1.378(6)	C(37)-C(38)	1.366(6)
C(38)-C(39)	1.379(6)	C(39)-C(40)	1.382(4)
C(41)-C(42)	1.382(4)	C(41)-C(46)	1.398(4)
C(42)-C(43)	1.383(4)	C(43)-C(44)	1.359(5)
C(44)-C(45)	1.370(5)	C(45)-C(46)	1.394(5)
C(47)-Cl(4A)	1.681(5)	C(47)-Cl(3A)	1.740(7)
O(7)-Cl(1)-O(6)	109.19(17)	O(7)-Cl(1)-O(8)	109.61(17)
O(6)-Cl(1)-O(8)	108.65(19)	O(7)-Cl(1)-O(5)	111.24(17)

O(6)-Cl(1)-O(5)	108.73(15)	O(8)-Cl(1)-O(5)	109.38(15)
O(12)-Cl(2)-O(11)	104.8(3)	O(12)-Cl(2)-O(9)	110.0(2)
O(11)-Cl(2)-O(9)	109.7(3)	O(12)-Cl(2)-O(10)	113.5(2)
O(11)-Cl(2)-O(10)	109.3(2)	O(9)-Cl(2)-O(10)	109.52(18)
N(2)-Mg(1)-N(5)	177.23(9)	N(2)-Mg(1)-N(4)	109.32(9)
N(5)-Mg(1)-N(4)	73.45(9)	N(2)-Mg(1)-N(8)	103.40(8)
N(5)-Mg(1)-N(8)	73.83(8)	N(4)-Mg(1)-N(8)	147.28(9)
N(2)-Mg(1)-N(1)	73.78(8)	N(5)-Mg(1)-N(1)	106.61(8)
N(4)-Mg(1)-N(1)	89.16(8)	N(8)-Mg(1)-N(1)	99.93(9)
N(2)-Mg(1)-N(3)	73.79(8)	N(5)-Mg(1)-N(3)	105.88(8)
N(4)-Mg(1)-N(3)	99.67(8)	N(8)-Mg(1)-N(3)	89.38(8)
N(1)-Mg(1)-N(3)	147.51(9)	C(3)-O(1)-C(2)	104.7(2)
C(9)-O(2)-C(10)	105.0(2)	C(26)-O(3)-C(25)	104.5(2)
C(32)-O(4)-C(33)	104.8(2)	C(3)-N(1)-C(1)	105.8(2)
C(3)-N(1)-Mg(1)	114.11(18)	C(1)-N(1)-Mg(1)	140.06(17)
C(8)-N(2)-C(4)	119.4(2)	C(8)-N(2)-Mg(1)	120.29(17)
C(4)-N(2)-Mg(1)	120.30(18)	C(9)-N(3)-C(11)	106.5(2)
C(9)-N(3)-Mg(1)	112.75(18)	C(11)-N(3)-Mg(1)	140.13(16)
C(26)-N(4)-C(24)	107.7(2)	C(26)-N(4)-Mg(1)	115.96(19)
C(24)-N(4)-Mg(1)	136.31(17)	C(27)-N(5)-C(31)	120.3(2)
C(27)-N(5)-Mg(1)	120.09(17)	C(31)-N(5)-Mg(1)	119.65(17)
C(32)-N(8)-C(34)	106.7(2)	C(32)-N(8)-Mg(1)	115.66(17)
C(34)-N(8)-Mg(1)	137.39(16)	N(1)-C(1)-C(12)	109.4(2)
N(1)-C(1)-C(2)	102.2(2)	C(12)-C(1)-C(2)	118.0(3)
O(1)-C(2)-C(1)	105.3(2)	N(1)-C(3)-O(1)	120.0(2)
N(1)-C(3)-C(4)	120.8(2)	O(1)-C(3)-C(4)	119.1(2)
N(2)-C(4)-C(5)	122.0(3)	N(2)-C(4)-C(3)	110.8(2)
C(5)-C(4)-C(3)	127.2(3)	C(4)-C(5)-C(6)	118.1(3)
C(7)-C(6)-C(5)	120.8(3)	C(6)-C(7)-C(8)	117.6(3)
N(2)-C(8)-C(7)	122.2(3)	N(2)-C(8)-C(9)	110.9(2)
C(7)-C(8)-C(9)	126.9(3)	N(3)-C(9)-O(2)	120.1(3)
N(3)-C(9)-C(8)	122.1(2)	O(2)-C(9)-C(8)	117.8(2)
O(2)-C(10)-C(11)	104.6(2)	N(3)-C(11)-C(18)	110.7(2)
N(3)-C(11)-C(10)	103.2(2)	C(18)-C(11)-C(10)	116.9(2)
C(13)-C(12)-C(17)	118.3(3)	C(13)-C(12)-C(1)	124.2(3)
C(17)-C(12)-C(1)	117.3(3)	C(12)-C(13)-C(14)	118.0(4)
C(15)-C(14)-C(13)	117.2(4)	C(16)-C(15)-C(14)	124.0(4)
C(15)-C(16)-C(17)	118.2(4)	C(16)-C(17)-C(12)	124.2(4)
C(19)-C(18)-C(23)	118.5(3)	C(19)-C(18)-C(11)	123.7(2)
C(23)-C(18)-C(11)	117.8(3)	C(20)-C(19)-C(18)	121.7(3)
C(21)-C(20)-C(19)	119.8(3)	C(20)-C(21)-C(22)	121.3(3)
C(23)-C(22)-C(21)	118.7(3)	C(18)-C(23)-C(22)	119.9(3)
N(4)-C(24)-C(35)	110.9(2)	N(4)-C(24)-C(25)	101.8(2)
C(35)-C(24)-C(25)	116.7(2)	O(3)-C(25)-C(24)	104.8(2)
N(4)-C(26)-O(3)	118.9(3)	N(4)-C(26)-C(27)	120.6(2)
O(3)-C(26)-C(27)	120.4(2)	N(5)-C(27)-C(28)	122.1(3)
N(5)-C(27)-C(26)	109.7(2)	C(28)-C(27)-C(26)	128.1(2)

C(29)-C(28)-C(27)	116.8(3)	C(30)-C(29)-C(28)	121.6(3)
C(29)-C(30)-C(31)	117.7(3)	N(5)-C(31)-C(30)	121.5(3)
N(5)-C(31)-C(32)	110.3(2)	C(30)-C(31)-C(32)	128.2(3)
N(8)-C(32)-O(4)	119.9(2)	N(8)-C(32)-C(31)	120.6(2)
O(4)-C(32)-C(31)	119.5(2)	O(4)-C(33)-C(34)	105.0(2)
N(8)-C(34)-C(41)	111.0(2)	N(8)-C(34)-C(33)	102.6(2)
C(41)-C(34)-C(33)	117.0(2)	C(36)-C(35)-C(40)	118.6(3)
C(36)-C(35)-C(24)	120.4(3)	C(40)-C(35)-C(24)	120.9(3)
C(37)-C(36)-C(35)	120.7(4)	C(38)-C(37)-C(36)	119.9(4)
C(37)-C(38)-C(39)	120.8(4)	C(38)-C(39)-C(40)	119.0(4)
C(39)-C(40)-C(35)	121.0(3)	C(42)-C(41)-C(46)	118.6(3)
C(42)-C(41)-C(34)	121.6(3)	C(46)-C(41)-C(34)	119.6(3)
C(41)-C(42)-C(43)	120.7(3)	C(44)-C(43)-C(42)	120.5(3)
C(43)-C(44)-C(45)	120.1(3)	C(44)-C(45)-C(46)	120.4(3)
C(45)-C(46)-C(41)	119.6(3)	Cl(4A)-C(47)-Cl(3)	119.6(3)
Cl(4A)-C(47)-Cl(3A)	123.9(3)	Cl(3)-C(47)-Cl(3A)	20.64(16)
Cl(4A)-C(47)-Cl(4)	26.41(17)	Cl(3)-C(47)-Cl(4)	98.2(2)
Cl(3A)-C(47)-Cl(4)	109.3(3)		

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for (*R,R*)-**201**. The anisotropic displacement factor exponent takes the form: $-2\ g\pi^2\ [h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12]$.

Atom	U11	U22	U33	U23	U13	U12
Cl(2)	119(1)	41(1)	34(1)	2(1)	-15(1)	-6(1)
Cl(3)	50(2)	74(2)	56(1)	4(2)	-6(1)	-20(1)
Cl(4)	65(1)	48(1)	70(2)	-18(1)	24(1)	-12(1)
Mg(1)	26(1)	27(1)	20(1)	0(1)	-1(1)	-1(1)
O(1)	74(2)	33(1)	35(1)	-10(1)	-6(1)	8(1)
O(2)	65(1)	34(1)	33(1)	8(1)	-1(1)	2(1)
O(3)	35(1)	48(1)	34(1)	9(1)	10(1)	-2(1)
O(4)	33(1)	44(1)	37(1)	-1(1)	-10(1)	-6(1)
O(5)	63(2)	79(2)	42(1)	-18(1)	1(1)	15(1)
O(6)	50(2)	99(2)	70(2)	-31(2)	2(1)	-2(1)
O(7)	97(2)	42(1)	84(2)	-6(1)	4(2)	-13(1)
O(8)	145(3)	61(2)	37(1)	-3(1)	-29(2)	23(2)
O(9)	231(4)	71(2)	40(2)	-12(1)	-45(2)	22(2)
O(10)	194(4)	44(2)	90(2)	13(1)	-56(2)	-25(2)
O(11)	230(5)	78(2)	123(3)	-21(2)	95(3)	-15(3)
O(12)	149(3)	89(2)	125(3)	14(2)	-68(3)	17(2)
N(1)	37(1)	28(1)	28(1)	-2(1)	-1(1)	3(1)
N(2)	27(1)	33(1)	22(1)	-3(1)	0(1)	0(1)
N(3)	25(1)	28(1)	30(1)	-2(1)	1(1)	1(1)
N(4)	31(1)	29(1)	27(1)	-2(1)	4(1)	0(1)
N(5)	34(1)	25(1)	22(1)	-2(1)	-3(1)	2(1)
N(8)	26(1)	28(1)	29(1)	-1(1)	-1(1)	-1(1)
C(1)	56(2)	25(2)	38(2)	1(1)	-2(2)	4(1)
C(2)	142(4)	36(2)	39(2)	-7(2)	-19(2)	30(2)
C(3)	35(2)	29(2)	35(2)	-6(1)	-4(1)	-1(1)
C(4)	31(2)	35(2)	28(2)	-2(1)	2(1)	-3(1)
C(5)	46(2)	44(2)	30(2)	-10(1)	-3(1)	-4(2)
C(6)	62(2)	58(2)	22(2)	-4(2)	-5(1)	-1(2)
C(7)	55(2)	46(2)	27(2)	2(1)	-3(1)	1(2)
C(8)	35(2)	35(2)	23(1)	6(1)	-2(1)	0(1)
C(9)	30(2)	31(2)	30(2)	7(1)	-4(1)	-1(1)
C(10)	90(3)	36(2)	43(2)	-1(2)	20(2)	0(2)
C(11)	41(2)	27(1)	36(2)	3(1)	4(1)	-4(1)
C(12)	55(2)	21(1)	31(2)	5(1)	-2(1)	2(1)
C(13)	55(2)	53(2)	69(2)	25(2)	4(2)	1(2)
C(14)	49(2)	48(2)	153(5)	53(3)	-27(3)	-16(2)
C(15)	117(4)	35(2)	72(3)	4(2)	-27(3)	-6(2)
C(16)	127(4)	37(2)	52(2)	-1(2)	-18(3)	18(2)

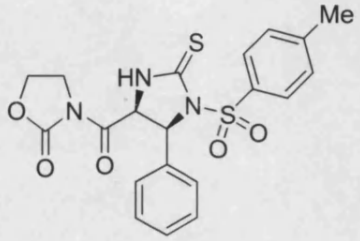
C(17)	92(3)	28(2)	35(2)	5(1)	-4(2)	19(2)
C(18)	34(2)	22(1)	34(2)	-3(1)	4(1)	1(1)
C(19)	45(2)	35(2)	49(2)	-9(2)	-6(2)	2(1)
C(20)	37(2)	49(2)	91(3)	-20(2)	2(2)	7(2)
C(21)	51(2)	44(2)	95(3)	-27(2)	38(2)	-7(2)
C(22)	97(3)	40(2)	41(2)	-5(2)	26(2)	-8(2)
C(23)	50(2)	29(2)	38(2)	-3(1)	4(1)	3(1)
C(24)	28(2)	32(2)	39(2)	-2(1)	3(1)	-5(1)
C(25)	32(2)	54(2)	45(2)	8(2)	5(1)	-9(2)
C(26)	34(2)	25(1)	32(2)	7(1)	8(1)	3(1)
C(27)	38(2)	21(1)	29(1)	3(1)	2(1)	3(1)
C(28)	56(2)	29(2)	26(2)	3(1)	4(1)	8(2)
C(29)	71(2)	29(2)	20(2)	-1(1)	-8(2)	-2(2)
C(30)	57(2)	23(1)	30(2)	-2(1)	-10(1)	0(1)
C(31)	39(2)	18(1)	28(2)	-1(1)	-9(1)	4(1)
C(32)	26(2)	23(1)	36(2)	-1(1)	-9(1)	1(1)
C(33)	34(2)	48(2)	53(2)	0(2)	2(1)	-7(2)
C(34)	29(1)	31(2)	38(2)	6(1)	0(1)	-4(1)
C(35)	23(1)	48(2)	36(2)	-6(1)	4(1)	-11(1)
C(36)	50(2)	81(3)	47(2)	-17(2)	-3(2)	-14(2)
C(37)	76(3)	130(4)	35(2)	-13(2)	-6(2)	-24(3)
C(38)	64(3)	128(4)	46(3)	28(3)	-19(2)	-31(3)
C(39)	50(2)	68(2)	62(2)	21(2)	-20(2)	-15(2)
C(40)	33(2)	51(2)	39(2)	9(2)	-7(1)	-6(2)
C(41)	24(1)	38(2)	36(2)	4(1)	4(1)	-5(1)
C(42)	43(2)	45(2)	48(2)	7(2)	2(2)	7(2)
C(43)	61(2)	48(2)	73(3)	-10(2)	11(2)	17(2)
C(44)	61(2)	61(2)	57(2)	-13(2)	19(2)	-8(2)
C(45)	54(2)	81(3)	30(2)	1(2)	6(1)	-21(2)
C(46)	35(2)	48(2)	42(2)	7(2)	1(1)	-8(2)
C(47)	53(2)	51(2)	56(2)	-15(2)	4(2)	-5(2)
Cl(4A)	120(4)	56(2)	88(3)	-31(2)	59(2)	-40(3)
Cl(3A)	73(4)	69(3)	57(2)	-25(2)	8(2)	-19(2)

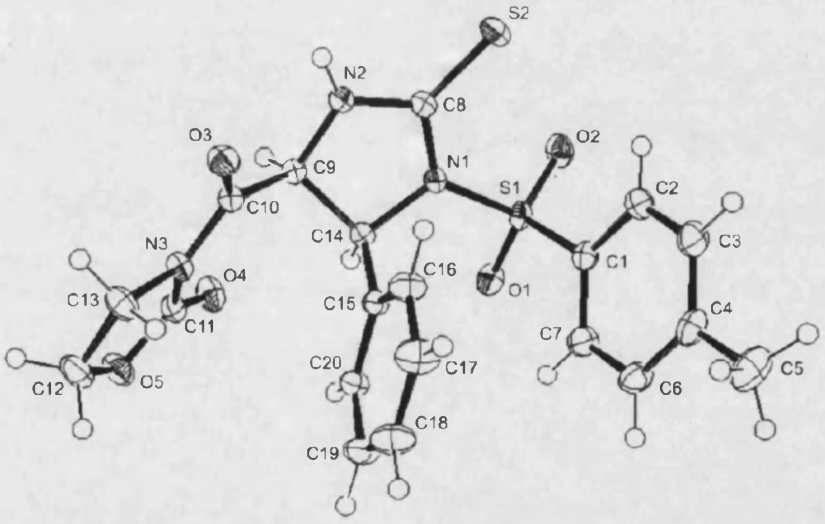
Table 5. Hydrogen coordinates (× 10^4) and isotropic displacement parameters (Å^2 × 10^3) for (*R,R*)-**201**.

Atom	x	y	z	U(eq)
H(2A)	4723	1706	913	87
H(2B)	3453	1206	909	87
H(5)	3155	3401	-260	48
H(6)	2599	4792	-672	57
H(7)	2233	6297	-317	51
H(10A)	1570	8647	757	67
H(10B)	2970	8644	738	67
H(11)	3018	7775	1355	41
H(13)	5910	2533	1345	71
H(14)	7078	2932	1997	100
H(15)	6101	3240	2663	89
H(16)	4175	3060	2735	87
H(17)	3076	2741	2123	62
H(19)	119	8324	1075	52
H(20)	-1429	8375	1556	71
H(21)	-1276	7677	2243	76
H(22)	499	7026	2492	71
H(23)	2108	7027	2011	47
H(24)	358	3451	1307	40
H(25A)	-1108	4763	1777	52
H(25B)	-951	3590	1851	52
H(28)	1768	4912	2872	44
H(29)	3586	5385	3157	48
H(30)	5136	5726	2686	44
H(33A)	7297	5636	1385	54
H(33B)	7000	6801	1381	54
H(34)	5480	6596	939	39
H(36)	-67	3543	558	71
H(37)	-602	4405	-76	96
H(38)	-1056	6068	-33	95
H(39)	-1015	6890	645	72
H(40)	-474	6026	1281	49
H(42)	6679	4144	1081	54
H(43)	6963	3016	510	73
H(44)	6412	3401	-203	71
H(45)	5623	4937	-362	66
H(46)	5361	6107	203	50
H(47A)	1054	558	1830	64
H(47B)	1148	-566	2012	64

Appendix C

(4*S*,5*S*)-3-[5-Phenyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one (4*S*,5*S*)-241





Appendix

Table 1. Crystal data and structure refinement for (4*S*,5*S*)-**241**.

Identification code	k05mcw1
Empirical formula	$C_{21}H_{20}Cl_3N_3O_5S_2$
Formula weight	564.87
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2_1
Unit cell dimensions	a = 9.69500(10) Å $\alpha = 90°$
	b = 9.64000(10) Å $\beta = 93.27°$
	c = 12.98000(10) Å $\gamma = 90°$
Volume	1211.13(2) $Å^3$
Z	2
Calculated density	1.549 mg/m^3
Absorption coefficient	0.590 mm^{-1}
F(000)	580
Crystal size	0.50 x 0.40 x 0.20 mm
Theta range for data collection	3.68 to 35.01°
Limiting indices	-15<=h<=15, -15<=k<=15, -20<=l<=20
Reflections collected / unique	31690 / 10261 [R(int) = 0.0419]
Completeness to theta = 35.01	97.9%
Max. and min. transmission	0.8911 and 0.7568
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10261 / 1 / 349
Goodness-of-fit on F^2	1.036
Final R indices [I>2σ(I)]	$R^1 = 0.0321$, $wR_2 = 0.0818$
R indices (all data)	$R^1 = 0.0338$, $wR_2 = 0.0829$
Absolute structure parameter	0.01(3)
Largest diff. peak and hole	0.386 and -0.497 $eÅ^{-3}$

Appendix

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for (4*S*,5*S*)-**241**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
S(1)	6282(1)	6547(1)	2718(1)	19(1)
S(2)	8167(1)	3510(1)	2816(1)	29(1)
N(1)	5970(1)	5084(1)	3359(1)	19(1)
N(2)	6136(1)	3016(1)	4065(1)	22(1)
N(3)	2502(1)	2854(1)	4841(1)	20(1)
O(1)	5348(1)	7517(1)	3143(1)	24(1)
O(2)	7740(1)	6799(1)	2814(1)	27(1)
O(3)	3945(1)	1356(1)	4129(1)	25(1)
O(4)	2864(1)	5041(1)	5562(1)	28(1)
O(5)	814(1)	3981(1)	5575(1)	30(1)
C(1)	5766(1)	6280(1)	1418(1)	20(1)
C(2)	6650(1)	5615(1)	768(1)	26(1)
C(3)	6192(1)	5377(1)	-252(1)	30(1)
C(4)	4884(1)	5802(1)	-631(1)	26(1)
C(5)	4382(2)	5496(2)	-1728(1)	38(1)
C(6)	4036(1)	6498(2)	33(1)	29(1)
C(7)	4463(1)	6734(1)	1058(1)	26(1)
C(8)	6755(1)	3871(1)	3419(1)	20(1)
C(9)	4912(1)	3598(1)	4503(1)	19(1)
C(10)	3767(1)	2511(1)	4468(1)	19(1)
C(11)	2143(1)	4054(1)	5350(1)	22(1)
C(12)	226(1)	2644(2)	5269(1)	31(1)
C(13)	1338(1)	1889(1)	4705(1)	28(1)
C(14)	4605(1)	4888(1)	3809(1)	18(1)
C(15)	3450(1)	4696(1)	2992(1)	19(1)
C(16)	3557(1)	3766(1)	2181(1)	26(1)
C(17)	2443(1)	3593(2)	1464(1)	35(1)
C(18)	1227(1)	4327(2)	1572(1)	36(1)
C(19)	1118(1)	5249(1)	2375(1)	30(1)
C(20)	2229(1)	5445(1)	3081(1)	23(1)
C(30)	299(7)	9022(6)	1971(5)	38(1)
Cl(1)	1843(3)	9125(2)	2709(2)	37(1)
Cl(2)	560(2)	8091(2)	824(1)	52(1)
Cl(3)	-457(3)	10592(3)	1744(5)	108(1)
C(30A)	80(13)	9230(14)	1854(10)	60(3)
Cl(1A)	1677(6)	9237(5)	2584(4)	55(1)
Cl(2A)	45(9)	7972(3)	862(3)	97(1)
Cl(3A)	-139(5)	10859(4)	1340(2)	74(1)

Table 3. Bond lengths [Å] for (4*S*,5*S*)-**241**.

S(1)-O(2)	1.4330(9)
S(1)-O(1)	1.4332(9)
S(1)-N(1)	1.6740(9)
S(1)-C(1)	1.7513(10)
S(2)-C(8)	1.6527(10)
N(1)-C(8)	1.3946(13)
N(1)-C(14)	1.4881(13)
N(2)-C(8)	1.3421(13)
N(2)-C(9)	1.4570(13)
N(3)-C(10)	1.3843(13)
N(3)-C(11)	1.3868(14)
N(3)-C(13)	1.4656(14)
O(3)-C(10)	1.2138(13)
O(4)-C(11)	1.2029(14)
O(5)-C(11)	1.3392(13)
O(5)-C(12)	1.4545(17)
C(1)-C(2)	1.3925(15)
C(1)-C(7)	1.3932(15)
C(2)-C(3)	1.3910(17)
C(3)-C(4)	1.3958(19)
C(4)-C(6)	1.3960(17)
C(4)-C(5)	1.5077(17)
C(6)-C(7)	1.3883(15)
C(9)-C(10)	1.5254(14)
C(9)-C(14)	1.5544(14)
C(12)-C(13)	1.5226(18)
C(14)-C(15)	1.5087(14)
C(15)-C(16)	1.3916(15)
C(15)-C(20)	1.3970(14)
C(16)-C(17)	1.3946(17)
C(17)-C(18)	1.388(2)
C(18)-C(19)	1.379(2)
C(19)-C(20)	1.3863(16)
C(30)-Cl(3)	1.700(6)
C(30)-Cl(1)	1.733(7)
C(30)-Cl(2)	1.770(5)
C(30A)-Cl(3A)	1.715(13)
C(30A)-Cl(2A)	1.767(14)
C(30A)-Cl(1A)	1.769(14)

Table 4. Bond angles [°] for (4*S*,5*S*)-**241**.

O(2)-S(1)-O(1)	119.87(5)
O(2)-S(1)-N(1)	107.77(5)
O(1)-S(1)-N(1)	102.84(5)
O(2)-S(1)-C(1)	109.52(5)
O(1)-S(1)-C(1)	108.36(5)
N(1)-S(1)-C(1)	107.75(5)
C(8)-N(1)-C(14)	111.48(8)
C(8)-N(1)-S(1)	128.36(7)
C(14)-N(1)-S(1)	119.46(7)
C(8)-N(2)-C(9)	114.21(8)
C(10)-N(3)-C(11)	128.15(9)
C(10)-N(3)-C(13)	119.88(9)
C(11)-N(3)-C(13)	111.97(9)
C(11)-O(5)-C(12)	110.75(9)
C(2)-C(1)-C(7)	121.25(10)
C(2)-C(1)-S(1)	120.02(8)
C(7)-C(1)-S(1)	118.73(8)
C(3)-C(2)-C(1)	118.62(11)
C(2)-C(3)-C(4)	121.38(11)
C(3)-C(4)-C(6)	118.61(10)
C(3)-C(4)-C(5)	120.86(12)
C(6)-C(4)-C(5)	120.51(12)
C(7)-C(6)-C(4)	121.11(11)
C(6)-C(7)-C(1)	119.00(10)
N(2)-C(8)-N(1)	106.74(8)
N(2)-C(8)-S(2)	125.35(8)
N(1)-C(8)-S(2)	127.91(8)
N(2)-C(9)-C(10)	109.30(8)
N(2)-C(9)-C(14)	102.42(7)
C(10)-C(9)-C(14)	114.66(8)
O(3)-C(10)-N(3)	119.55(9)
O(3)-C(10)-C(9)	121.55(9)
N(3)-C(10)-C(9)	118.90(9)
O(4)-C(11)-O(5)	123.09(10)
O(4)-C(11)-N(3)	127.59(10)
O(5)-C(11)-N(3)	109.31(9)
O(5)-C(12)-C(13)	106.13(9)
N(3)-C(13)-C(12)	101.55(10)
N(1)-C(14)-C(15)	112.39(8)
N(1)-C(14)-C(9)	100.60(7)
C(15)-C(14)-C(9)	114.76(8)
C(16)-C(15)-C(20)	119.67(10)
C(16)-C(15)-C(14)	121.77(9)

C(20)-C(15)-C(14)	118.52(9)
C(15)-C(16)-C(17)	119.58(11)
C(18)-C(17)-C(16)	120.10(12)
C(19)-C(18)-C(17)	120.47(11)
C(18)-C(19)-C(20)	119.81(11)
C(19)-C(20)-C(15)	120.35(11)
Cl(3)-C(30)-Cl(1)	113.3(3)
Cl(3)-C(30)-Cl(2)	112.7(4)
Cl(1)-C(30)-Cl(2)	109.5(3)
Cl(3A)-C(30A)-Cl(2A)	110.4(7)
Cl(3A)-C(30A)-Cl(1A)	106.8(8)
Cl(2A)-C(30A)-Cl(1A)	111.9(7)

Table 5. Anisotropic displacement parameters ($Å^2 \times 10^3$) for (4*S*,5*S*)-**241**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$.

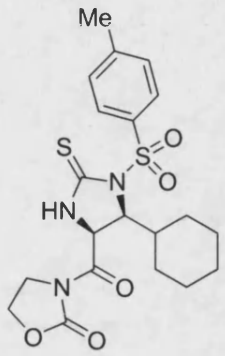
Atom	U11	U22	U33	U23	U13	U12
S(1)	22(1)	19(1)	17(1)	0(1)	2(1)	-3(1)
S(2)	19(1)	33(1)	38(1)	7(1)	11(1)	5(1)
N(1)	17(1)	19(1)	20(1)	4(1)	4(1)	0(1)
N(2)	18(1)	22(1)	28(1)	7(1)	6(1)	3(1)
N(3)	18(1)	21(1)	22(1)	-1(1)	4(1)	-2(1)
O(1)	35(1)	19(1)	20(1)	-1(1)	5(1)	1(1)
O(2)	25(1)	30(1)	27(1)	2(1)	2(1)	-10(1)
O(3)	25(1)	20(1)	31(1)	-1(1)	4(1)	1(1)
O(4)	31(1)	23(1)	30(1)	-6(1)	11(1)	-4(1)
O(5)	22(1)	33(1)	36(1)	-1(1)	11(1)	2(1)
C(1)	24(1)	20(1)	17(1)	0(1)	3(1)	-1(1)
C(2)	26(1)	30(1)	23(1)	0(1)	5(1)	4(1)
C(3)	37(1)	32(1)	21(1)	-3(1)	6(1)	6(1)
C(4)	40(1)	21(1)	18(1)	0(1)	1(1)	1(1)
C(5)	61(1)	33(1)	21(1)	-5(1)	-5(1)	4(1)
C(6)	33(1)	31(1)	22(1)	0(1)	-2(1)	6(1)
C(7)	29(1)	30(1)	20(1)	-2(1)	2(1)	7(1)
C(8)	16(1)	23(1)	22(1)	3(1)	2(1)	1(1)
C(9)	17(1)	20(1)	19(1)	3(1)	2(1)	-1(1)
C(10)	18(1)	21(1)	18(1)	2(1)	2(1)	0(1)
C(11)	22(1)	24(1)	20(1)	2(1)	6(1)	1(1)
C(12)	17(1)	40(1)	34(1)	-1(1)	3(1)	-5(1)
C(13)	20(1)	30(1)	35(1)	-3(1)	4(1)	-7(1)
C(14)	16(1)	19(1)	18(1)	1(1)	3(1)	0(1)
C(15)	17(1)	19(1)	21(1)	1(1)	1(1)	1(1)
C(16)	25(1)	25(1)	29(1)	-6(1)	-3(1)	4(1)
C(17)	33(1)	36(1)	35(1)	-11(1)	-8(1)	2(1)
C(18)	25(1)	40(1)	41(1)	-5(1)	-12(1)	0(1)
C(19)	19(1)	33(1)	38(1)	4(1)	-2(1)	3(1)
C(20)	19(1)	24(1)	27(1)	2(1)	3(1)	2(1)
C(30)	35(2)	33(1)	45(3)	-8(2)	11(2)	-1(1)
Cl(1)	41(1)	35(1)	35(1)	-2(1)	9(1)	-1(1)
Cl(2)	73(1)	53(1)	30(1)	-5(1)	-6(1)	14(1)
Cl(3)	65(1)	54(1)	202(4)	-22(1)	-25(1)	31(1)
C(30A)	40(4)	98(8)	42(3)	18(4)	2(3)	-21(5)
Cl(1A)	58(2)	74(2)	34(1)	8(1)	11(1)	4(1)
Cl(2A)	170(4)	53(1)	60(1)	20(1)	-56(2)	-31(2)
Cl(3A)	91(2)	51(1)	82(1)	6(1)	15(1)	35(1)

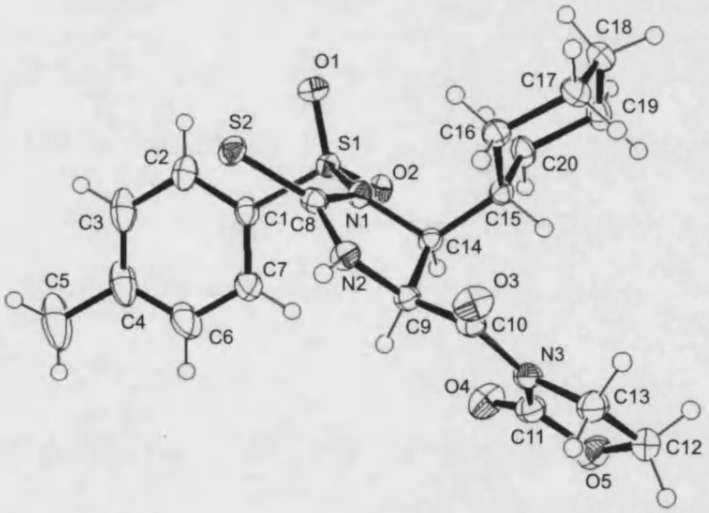
Table 6. Hydrogen coordinates (× 10^4) and isotropic displacement parameters (Å^2 × 10^3) for (4*S*,5*S*)-**241**.

Atom	x	y	z	U(eq)
H(2A)	6410(20)	2160(20)	4140(16)	38(5)
H(2)	7547	5330	1015	31
H(3)	6783	4914	-700	36
H(5A)	3918	4593	-1757	58
H(5B)	5170	5479	-2168	58
H(5C)	3731	6219	-1972	58
H(6)	3153	6816	-220	35
H(7)	3874	7199	1506	31
H(9)	5135	3896	5232	22
H(12A)	-614	2773	4808	37
H(12B)	-24	2111	5883	37
H(13A)	1559	977	5025	33
H(13B)	1058	1754	3966	33
H(14)	4400	5705	4250	21
H(16)	4383	3252	2115	32
H(17)	2515	2973	901	42
H(18)	466	4193	1089	43
H(19)	284	5748	2445	36
H(20)	2159	6092	3627	28
H(30)	-351	8463	2375	45
H(30A)	-681	9034	2322	72

Appendix D

(4*S*,5*S*)-3-[5-Cyclohexyl-2-thioxo-1-(toluene-4-sulfonyl)-imidazolidine-4-carbonyl]-oxazolidin-2-one (4*S*,5*S*)-251





Appendix

Table 1. Crystal data and structure refinement for (4*S*,5*S*)-**251**.

Identification code	k05mcw2
Empirical formula	$C_{20}H_{25}N_3O_5S_2$
Formula weight	451.55
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 2_1 2_1 2_1
Unit cell dimensions	a = 9.63500(10) Å $\alpha = 90°$
	b = 12.01400(10) Å $\beta = 90°$
	c = 18.9670(2) Å $\gamma = 90°$
Volume	2195.52(4) $Å^3$
Z, Calculated density	4, 1.366 mg/m^3
Absorption coefficient	0.279 mm^{-1}
F(000)	952
Crystal size	0.38 x 0.30 x 0.25 mm
Theta range for data collection	4.00 to 30.49°
Limiting indices	-13<=h<=13, -17<=k<=17, -27<=l<=27
Reflections collected / unique	39701 / 6643 [R(int) = 0.0476]
Completeness to theta = 30.49	99.6%
Max. and min. transmission	0.9335 and 0.9014
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6643 / 0 / 276
Goodness-of-fit on F^2	1.031
Final R indices [I>2σ(I)]	R1 = 0.0314, wR2 = 0.0744
R indices (all data)	R1 = 0.0361, wR2 = 0.0768
Absolute structure parameter	-0.01(4)
Largest diff. peak and hole	0.262 and -0.356 $e.Å^{-3}$

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters ($Å^2$ × 10^3) for (4*S*,5*S*)-**251**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
S(1)	5119(1)	-552(1)	9158(1)	20(1)
S(2)	4400(1)	-2178(1)	10551(1)	27(1)
O(1)	6439(1)	-583(1)	9507(1)	26(1)
O(2)	5090(1)	-166(1)	8442(1)	24(1)
O(3)	2443(1)	-4956(1)	8758(1)	33(1)
O(4)	1311(1)	-2268(1)	7484(1)	37(1)
O(5)	745(1)	-3654(1)	6747(1)	35(1)
N(1)	4441(1)	-1823(1)	9124(1)	20(1)
N(2)	2985(1)	-3101(1)	9496(1)	26(1)
N(3)	1664(1)	-4125(1)	7778(1)	24(1)
C(1)	3966(2)	242(1)	9668(1)	26(1)
C(2)	4447(2)	770(1)	10268(1)	32(1)
C(3)	3531(2)	1439(1)	10644(1)	43(1)
C(4)	2174(2)	1572(2)	10433(1)	50(1)
C(5)	1197(4)	2281(2)	10864(1)	85(1)
C(6)	1728(2)	1037(2)	9826(1)	58(1)
C(7)	2620(2)	372(2)	9438(1)	43(1)
C(8)	3931(1)	-2385(1)	9720(1)	22(1)
C(9)	2613(1)	-2964(1)	8759(1)	21(1)
C(10)	2265(1)	-4093(1)	8444(1)	23(1)
C(11)	1253(2)	-3245(1)	7355(1)	27(1)
C(12)	954(2)	-4849(2)	6713(1)	36(1)
C(13)	1286(2)	-5197(1)	7466(1)	32(1)
C(14)	3891(1)	-2331(1)	8459(1)	20(1)
C(15)	4970(1)	-3051(1)	8078(1)	21(1)
C(16)	5715(2)	-3906(1)	8550(1)	26(1)
C(17)	6668(2)	-4640(1)	8102(1)	32(1)
C(18)	7709(2)	-3958(2)	7678(1)	36(1)
C(19)	6999(2)	-3063(1)	7237(1)	32(1)
C(20)	6055(2)	-2339(1)	7699(1)	26(1)

Table 3. Bond lengths [Å] for (4*S*,5*S*)-**251**.

S(1)-O(1)	1.4341(10)
S(1)-O(2)	1.4341(9)
S(1)-N(1)	1.6625(11)
S(1)-C(1)	1.7544(14)
S(2)-C(8)	1.6590(13)
O(3)-C(10)	1.2081(17)
O(4)-C(11)	1.2005(19)
O(5)-C(11)	1.3465(18)
O(5)-C(12)	1.452(2)
N(1)-C(8)	1.4053(16)
N(1)-C(14)	1.4972(16)
N(2)-C(8)	1.3239(18)
N(2)-C(9)	1.4528(17)
N(2)-H(2A)	0.86(2)
N(3)-C(11)	1.3848(19)
N(3)-C(10)	1.3908(18)
N(3)-C(13)	1.4629(18)
C(1)-C(7)	1.378(2)
C(1)-C(2)	1.383(2)
C(2)-C(3)	1.391(2)
C(3)-C(4)	1.376(3)
C(4)-C(6)	1.388(3)
C(4)-C(5)	1.510(3)
C(6)-C(7)	1.385(2)
C(9)-C(10)	1.5195(19)
C(9)-C(14)	1.5547(17)
C(12)-C(13)	1.522(2)
C(14)-C(15)	1.5331(17)
C(15)-C(20)	1.5294(18)
C(15)-C(16)	1.5403(18)
C(16)-C(17)	1.531(2)
C(17)-C(18)	1.524(2)
C(18)-C(19)	1.524(3)
C(19)-C(20)	1.5331(19)

Table 4. Bond angles [°] for (4*S*,5*S*)-**251.**

O(1)-S(1)-O(2)	117.54(6)
O(1)-S(1)-N(1)	110.05(6)
O(2)-S(1)-N(1)	104.65(6)
O(1)-S(1)-C(1)	108.70(7)
O(2)-S(1)-C(1)	109.46(6)
N(1)-S(1)-C(1)	105.79(6)
C(11)-O(5)-C(12)	110.33(12)
C(8)-N(1)-C(14)	110.99(10)
C(8)-N(1)-S(1)	123.15(9)
C(14)-N(1)-S(1)	123.12(8)
C(8)-N(2)-C(9)	113.90(11)
C(8)-N(2)-H(2A)	122.8(14)
C(9)-N(2)-H(2A)	121.5(14)
C(11)-N(3)-C(10)	128.61(12)
C(11)-N(3)-C(13)	111.52(12)
C(10)-N(3)-C(13)	119.70(12)
C(7)-C(1)-C(2)	121.57(14)
C(7)-C(1)-S(1)	118.91(11)
C(2)-C(1)-S(1)	119.42(12)
C(1)-C(2)-C(3)	118.38(17)
C(4)-C(3)-C(2)	121.34(17)
C(3)-C(4)-C(6)	118.83(16)
C(3)-C(4)-C(5)	120.0(2)
C(6)-C(4)-C(5)	121.2(2)
C(7)-C(6)-C(4)	121.07(19)
C(1)-C(7)-C(6)	118.80(17)
N(2)-C(8)-N(1)	107.11(11)
N(2)-C(8)-S(2)	126.14(10)
N(1)-C(8)-S(2)	126.75(10)
N(2)-C(9)-C(10)	109.29(11)
N(2)-C(9)-C(14)	102.21(10)
C(10)-C(9)-C(14)	117.89(11)
O(3)-C(10)-N(3)	118.89(13)
O(3)-C(10)-C(9)	122.83(12)
N(3)-C(10)-C(9)	118.23(12)
O(4)-C(11)-O(5)	123.23(14)
O(4)-C(11)-N(3)	127.98(14)
O(5)-C(11)-N(3)	108.79(13)
O(5)-C(12)-C(13)	105.07(12)
N(3)-C(13)-C(12)	100.94(13)
N(1)-C(14)-C(15)	112.77(10)
N(1)-C(14)-C(9)	99.89(9)
C(15)-C(14)-C(9)	115.74(11)
C(20)-C(15)-C(14)	111.72(11)
C(20)-C(15)-C(16)	109.12(11)
C(14)-C(15)-C(16)	114.69(10)

C(17)-C(16)-C(15)	109.94(11)
C(18)-C(17)-C(16)	112.17(13)
C(19)-C(18)-C(17)	111.92(13)
C(18)-C(19)-C(20)	110.70(12)
C(15)-C(20)-C(19)	110.89(11)

Table 5. Anisotropic displacement parameters ($Å^2 \times 10^3$) for (4*S*,5*S*)-**251**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$.

Atom	U11	U22	U33	U23	U13	U12
S(1)	22(1)	18(1)	19(1)	1(1)	-1(1)	0(1)
S(2)	27(1)	35(1)	18(1)	3(1)	-1(1)	-4(1)
O(1)	23(1)	26(1)	29(1)	5(1)	-4(1)	-2(1)
O(2)	32(1)	21(1)	20(1)	3(1)	1(1)	0(1)
O(3)	36(1)	26(1)	37(1)	8(1)	-6(1)	-2(1)
O(4)	48(1)	28(1)	36(1)	6(1)	-12(1)	-1(1)
O(5)	37(1)	42(1)	26(1)	-1(1)	-7(1)	-3(1)
N(1)	24(1)	20(1)	17(1)	1(1)	2(1)	-3(1)
N(2)	24(1)	34(1)	19(1)	6(1)	1(1)	-8(1)
N(3)	20(1)	23(1)	28(1)	-2(1)	-2(1)	1(1)
C(1)	33(1)	23(1)	21(1)	1(1)	2(1)	7(1)
C(2)	45(1)	25(1)	26(1)	-3(1)	1(1)	1(1)
C(3)	74(1)	28(1)	28(1)	-3(1)	8(1)	11(1)
C(4)	78(1)	43(1)	30(1)	5(1)	11(1)	35(1)
C(5)	125(2)	89(2)	41(1)	4(1)	17(1)	79(2)
C(6)	51(1)	86(2)	37(1)	-3(1)	0(1)	42(1)
C(7)	37(1)	62(1)	29(1)	-9(1)	-4(1)	21(1)
C(8)	20(1)	24(1)	21(1)	4(1)	2(1)	1(1)
C(9)	19(1)	26(1)	19(1)	2(1)	1(1)	-2(1)
C(10)	18(1)	26(1)	26(1)	1(1)	1(1)	-2(1)
C(11)	24(1)	33(1)	25(1)	3(1)	-2(1)	-1(1)
C(12)	30(1)	44(1)	35(1)	-14(1)	-1(1)	3(1)
C(13)	30(1)	27(1)	40(1)	-10(1)	-6(1)	3(1)
C(14)	20(1)	22(1)	18(1)	1(1)	-1(1)	-2(1)
C(15)	20(1)	23(1)	19(1)	-1(1)	1(1)	-2(1)
C(16)	25(1)	30(1)	23(1)	1(1)	-1(1)	4(1)
C(17)	30(1)	35(1)	31(1)	-3(1)	-2(1)	11(1)
C(18)	23(1)	49(1)	36(1)	-14(1)	3(1)	4(1)
C(19)	30(1)	34(1)	31(1)	-9(1)	13(1)	-8(1)
C(20)	27(1)	25(1)	27(1)	-4(1)	9(1)	-5(1)

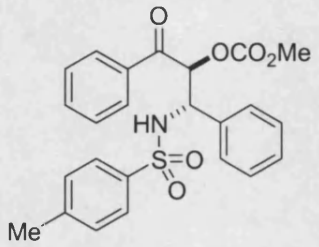
Appendix

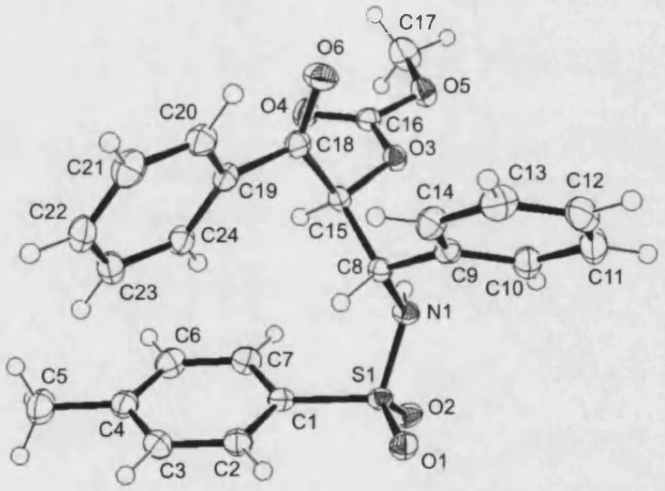
Table 6. Hydrogen coordinates (× 10^4) and isotropic displacement parameters ($Å^2 \times 10^3$) for (4*S*,5*S*)-**251**.

Atom	x	y	z	U(eq)
H(2)	5379	677	10420	39
H(3)	3849	1813	11055	52
H(5A)	1365	2150	11367	127
H(5B)	236	2084	10750	127
H(5C)	1355	3068	10756	127
H(6)	795	1128	9674	69
H(7)	2308	12	9021	51
H(9)	1778	-2472	8726	26
H(12A)	1732	-5034	6393	44
H(12B)	105	-5228	6543	44
H(13A)	468	-5527	7703	39
H(13B)	2068	-5731	7483	39
H(14)	3567	-1728	8135	24
H(15)	4464	-3481	7707	25
H(16A)	6269	-3513	8912	31
H(16B)	5021	-4375	8794	31
H(17A)	7177	-5160	8414	38
H(17B)	6096	-5089	7774	38
H(18A)	8375	-3602	8005	43
H(18B)	8237	-4460	7363	43
H(19A)	6441	-3419	6862	38
H(19B)	7711	-2590	7010	38
H(20A)	6624	-1938	8051	32
H(20B)	5582	-1779	7401	32
H(2A)	2490(20)	-3492(17)	9777(11)	43(5)

Appendix E

(1*R,2*R**)-Carbonic acid 1-benzoyl-2-phenyl-2-(toluene-4-sulfonylamino)-ethyl ester methyl ester *anti*-284**





Appendix

Table 1. Crystal data and structure refinement for *anti*-**284**.

Identification code	k05mcw3
Empirical formula	$C_{24}H_{23}NO_6S$
Formula weight	453.49
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C 2/c
Unit cell dimensions	a = 25.3750(2) Å α = 90°
	b = 10.34100 Å β = 111.2770°
	c = 18.0450(2) Å γ = 90°
Volume	4412.30(7) $Å^3$
Z, Calculated density	8, 1.365 mg/m^3
Absorption coefficient	0.188 mm^{-1}
F(000)	1904
Crystal size	0.45 x 0.35 x 0.35 mm
Theta range for data collection	3.78 to 27.47°
Limiting indices	-32<=h<=32, -13<=k<=13, -23<=l<=23
Reflections collected / unique	35865 / 5011 [R(int) = 0.0334]
Completeness to theta = 27.47	99.2%
Max. and min. transmission	0.9371 and 0.9202
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5011 / 0 / 294
Goodness-of-fit on F^2	1.030
Final R indices [I>2σ(I)]	R1 = 0.0329, wR2 = 0.0862
R indices (all data)	R1 = 0.0352, wR2 = 0.0879
Largest diff. peak and hole	0.382 and -0.501 $e.Å^{-3}$

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for *anti*-**284**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
S	5032(1)	2117(1)	221(1)	19(1)
O(1)	4944(1)	3276(1)	592(1)	26(1)
O(2)	4567(1)	1230(1)	-112(1)	25(1)
O(3)	6461(1)	-278(1)	1483(1)	21(1)
O(4)	6781(1)	-1289(1)	614(1)	28(1)
O(5)	6509(1)	-2354(1)	1509(1)	28(1)
O(6)	7483(1)	822(1)	1964(1)	30(1)
N(1)	5517(1)	1276(1)	877(1)	20(1)
C(1)	5291(1)	2563(1)	-527(1)	20(1)
C(2)	5366(1)	3862(1)	-652(1)	25(1)
C(3)	5561(1)	4223(1)	-1249(1)	28(1)
C(4)	5688(1)	3298(1)	-1719(1)	27(1)
C(5)	5902(1)	3702(2)	-2361(1)	37(1)
C(6)	5618(1)	1995(1)	-1575(1)	29(1)
C(7)	5419(1)	1615(1)	-987(1)	26(1)
C(8)	6081(1)	1848(1)	1286(1)	19(1)
C(9)	6195(1)	2101(1)	2163(1)	21(1)
C(10)	5851(1)	1590(1)	2541(1)	28(1)
C(11)	5965(1)	1853(1)	3342(1)	35(1)
C(12)	6423(1)	2615(1)	3771(1)	34(1)
C(13)	6763(1)	3137(1)	3398(1)	33(1)
C(14)	6646(1)	2894(1)	2594(1)	27(1)
C(15)	6509(1)	933(1)	1129(1)	19(1)
C(16)	6603(1)	-1317(1)	1145(1)	21(1)
C(17)	6618(1)	-3573(1)	1198(1)	39(1)
C(18)	7123(1)	1411(1)	1443(1)	21(1)
C(19)	7252(1)	2609(1)	1079(1)	21(1)
C(20)	7729(1)	3324(1)	1527(1)	26(1)
C(21)	7875(1)	4429(1)	1213(1)	31(1)
C(22)	7556(1)	4819(1)	444(1)	29(1)
C(23)	7081(1)	4119(1)	-4(1)	28(1)
C(24)	6925(1)	3020(1)	312(1)	24(1)

Table 3. Bond lengths [Å] for *anti*-**284**.

S-O(1)	1.4296(8)
S-O(2)	1.4420(8)
S-N(1)	1.6173(10)
S-C(1)	1.7640(11)
O(3)-C(16)	1.3477(13)
O(3)-C(15)	1.4314(13)
O(4)-C(16)	1.1987(14)
O(5)-C(16)	1.3232(14)
O(5)-C(17)	1.4459(15)
O(6)-C(18)	1.2104(14)
N(1)-C(8)	1.4743(14)
C(1)-C(2)	1.3857(16)
C(1)-C(7)	1.3970(16)
C(2)-C(3)	1.3899(17)
C(3)-C(4)	1.3916(18)
C(4)-C(6)	1.3956(19)
C(4)-C(5)	1.5055(17)
C(6)-C(7)	1.3874(18)
C(8)-C(9)	1.5250(15)
C(8)-C(15)	1.5431(15)
C(9)-C(10)	1.3909(17)
C(9)-C(14)	1.3932(17)
C(10)-C(11)	1.3950(18)
C(11)-C(12)	1.384(2)
C(12)-C(13)	1.383(2)
C(13)-C(14)	1.3943(17)
C(15)-C(18)	1.5320(15)
C(18)-C(19)	1.4939(16)
C(19)-C(24)	1.3973(16)
C(19)-C(20)	1.3986(16)
C(20)-C(21)	1.3840(18)
C(21)-C(22)	1.3888(19)
C(22)-C(23)	1.3860(18)
C(23)-C(24)	1.3922(17)

Table 4. Bond angles [°] for *anti*-**284**.

O(1)-S-O(2)	119.05(5)
O(1)-S-N(1)	108.32(5)
O(2)-S-N(1)	104.70(5)
O(1)-S-C(1)	107.70(5)
O(2)-S-C(1)	108.85(5)
N(1)-S-C(1)	107.74(5)
C(16)-O(3)-C(15)	114.54(8)
C(16)-O(5)-C(17)	114.84(9)
C(8)-N(1)-S	119.53(8)
C(2)-C(1)-C(7)	120.60(11)
C(2)-C(1)-S	119.27(9)
C(7)-C(1)-S	120.13(9)
C(1)-C(2)-C(3)	119.63(11)
C(2)-C(3)-C(4)	120.93(12)
C(3)-C(4)-C(6)	118.50(11)
C(3)-C(4)-C(5)	120.41(12)
C(6)-C(4)-C(5)	121.08(12)
C(7)-C(6)-C(4)	121.46(11)
C(6)-C(7)-C(1)	118.86(11)
N(1)-C(8)-C(9)	111.87(9)
N(1)-C(8)-C(15)	106.39(9)
C(9)-C(8)-C(15)	114.48(9)
C(10)-C(9)-C(14)	118.93(11)
C(10)-C(9)-C(8)	121.82(11)
C(14)-C(9)-C(8)	119.23(10)
C(9)-C(10)-C(11)	120.21(12)
C(12)-C(11)-C(10)	120.47(12)
C(13)-C(12)-C(11)	119.70(12)
C(12)-C(13)-C(14)	120.04(13)
C(9)-C(14)-C(13)	120.61(12)
O(3)-C(15)-C(18)	110.92(9)
O(3)-C(15)-C(8)	105.93(8)
C(18)-C(15)-C(8)	115.07(9)
O(4)-C(16)-O(5)	127.16(11)
O(4)-C(16)-O(3)	125.63(11)
O(5)-C(16)-O(3)	107.21(9)
O(6)-C(18)-C(19)	122.26(10)
O(6)-C(18)-C(15)	120.33(10)
C(19)-C(18)-C(15)	117.41(9)
C(24)-C(19)-C(20)	119.35(11)
C(24)-C(19)-C(18)	122.80(10)
C(20)-C(19)-C(18)	117.84(10)
C(21)-C(20)-C(19)	120.27(11)
C(20)-C(21)-C(22)	120.23(11)
C(23)-C(22)-C(21)	119.92(12)
C(22)-C(23)-C(24)	120.30(11)
C(23)-C(24)-C(19)	119.91(11)

Table 5. Anisotropic displacement parameters ($Å^2 \times 10^3$) for *anti*-**284**. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 a*2 U11 + ... + 2 h k a* b* U12].

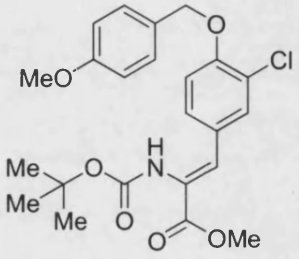
Atom	U11	U22	U33	U23	U13	U12
S	19(1)	15(1)	23(1)	0(1)	7(1)	2(1)
O(1)	33(1)	18(1)	31(1)	-1(1)	17(1)	3(1)
O(2)	18(1)	21(1)	33(1)	-1(1)	6(1)	-1(1)
O(3)	26(1)	17(1)	20(1)	1(1)	11(1)	2(1)
O(4)	33(1)	29(1)	28(1)	-2(1)	18(1)	1(1)
O(5)	42(1)	19(1)	25(1)	2(1)	16(1)	5(1)
O(6)	25(1)	31(1)	29(1)	5(1)	3(1)	2(1)
N(1)	20(1)	15(1)	23(1)	1(1)	5(1)	-1(1)
C(1)	20(1)	20(1)	20(1)	0(1)	6(1)	2(1)
C(2)	30(1)	20(1)	29(1)	1(1)	13(1)	4(1)
C(3)	31(1)	24(1)	32(1)	5(1)	14(1)	2(1)
C(4)	22(1)	36(1)	22(1)	2(1)	7(1)	2(1)
C(5)	34(1)	51(1)	30(1)	3(1)	16(1)	0(1)
C(6)	31(1)	33(1)	26(1)	-8(1)	12(1)	1(1)
C(7)	30(1)	21(1)	27(1)	-4(1)	10(1)	0(1)
C(8)	18(1)	17(1)	20(1)	1(1)	7(1)	-1(1)
C(9)	23(1)	19(1)	21(1)	1(1)	9(1)	5(1)
C(10)	31(1)	28(1)	28(1)	1(1)	14(1)	-1(1)
C(11)	47(1)	34(1)	32(1)	5(1)	25(1)	4(1)
C(12)	49(1)	34(1)	21(1)	-1(1)	14(1)	13(1)
C(13)	33(1)	35(1)	27(1)	-10(1)	8(1)	2(1)
C(14)	28(1)	28(1)	26(1)	-6(1)	12(1)	-2(1)
C(15)	22(1)	19(1)	18(1)	2(1)	8(1)	0(1)
C(16)	20(1)	22(1)	19(1)	-1(1)	6(1)	2(1)
C(17)	64(1)	21(1)	36(1)	-1(1)	23(1)	9(1)
C(18)	22(1)	24(1)	19(1)	-2(1)	8(1)	1(1)
C(19)	20(1)	25(1)	22(1)	-2(1)	10(1)	0(1)
C(20)	22(1)	32(1)	24(1)	-2(1)	7(1)	-2(1)
C(21)	27(1)	32(1)	35(1)	-6(1)	12(1)	-9(1)
C(22)	32(1)	28(1)	35(1)	0(1)	20(1)	-4(1)
C(23)	30(1)	32(1)	25(1)	4(1)	13(1)	-1(1)
C(24)	21(1)	29(1)	22(1)	-1(1)	8(1)	-3(1)

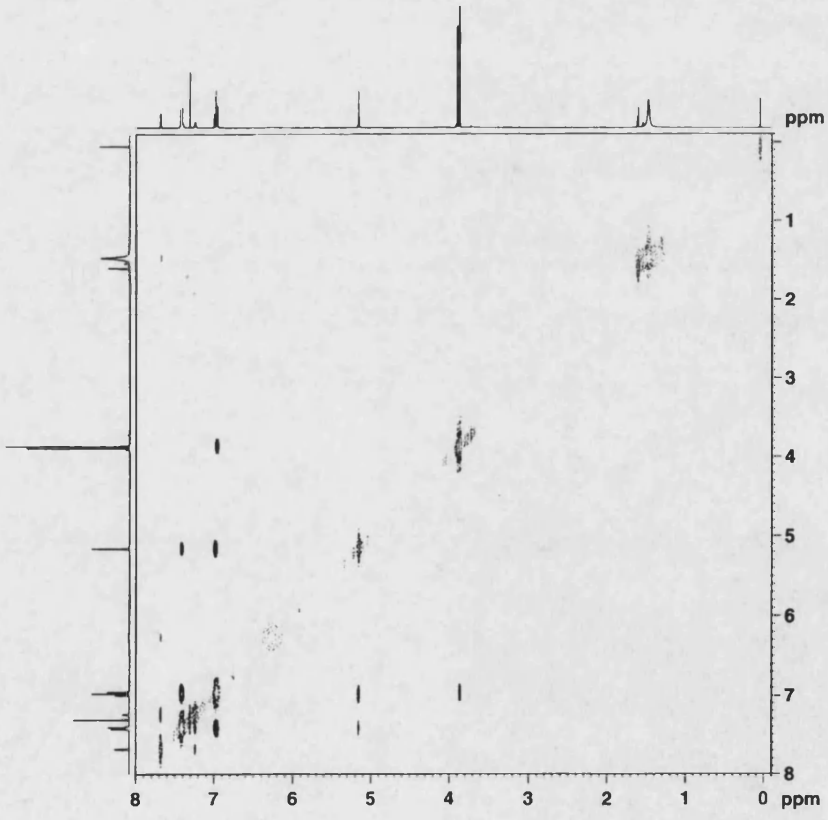
Table 6. Hydrogen coordinates (× 10^4) and isotropic displacement parameters (Å^2 × 10^3) for *anti*-**284**.

Atom	x	y	z	U(eq)
H(1)	5514(6)	498(17)	724(9)	28(4)
H(2)	5285	4501	-330	30
H(3)	5609	5114	-1337	34
H(5A)	5738	4541	-2577	56
H(5B)	5792	3054	-2786	56
H(5C)	6315	3772	-2136	56
H(6)	5708	1354	-1887	35
H(7)	5370	724	-899	31
H(8)	6093	2697	1027	22
H(10)	5539	1059	2252	34
H(11)	5727	1507	3595	42
H(12)	6503	2778	4319	41
H(13)	7077	3662	3690	39
H(14)	6876	3272	2337	32
H(15)	6390	803	542	23
H(17A)	6538	-4285	1500	58
H(17B)	7014	-3609	1246	58
H(17C)	6373	-3650	637	58
H(20)	7954	3051	2049	32
H(21)	8195	4922	1524	37
H(22)	7663	5565	225	35
H(23)	6862	4390	-528	34
H(24)	6597	2549	6	28

Appendix F

NOESY spectrum of (Z)-2-*tert*-butoxycarbonylamino-3-[3-chloro-4-(4-methoxy-benzyloxy)-phenyl]-acrylic acid methyl ester (Z)-237

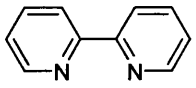




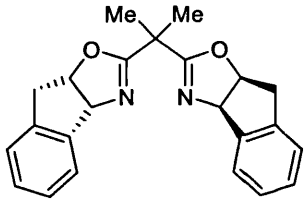
Appendix G

Supply and Synthesis of Ligands

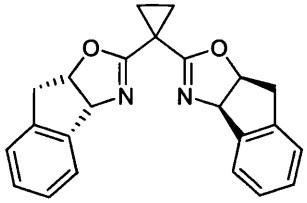
2,2'-Bipyridine **157**: purchased from Aldrich



(3a*R*,8a*S*)-8,8a-Dihydro-2-(2-((3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl)propan-2-yl)-3a*H*-indeno[1,2-*d*]oxazole,[153] (4*R*,5*S*)-**172**: provided by V. J.-D. Piccio

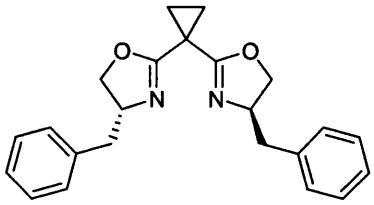


(3a*R*,8a*S*)-8,8a-Dihydro-2-(1-((3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl)cyclopropyl)-3a*H*-indeno[1,2-*d*]oxazole,[154] (4*R*,5*S*)-**152**: provided by V. J.-D. Piccio

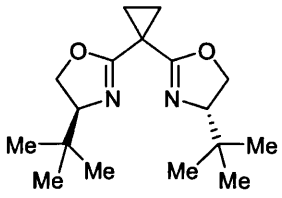


Appendix

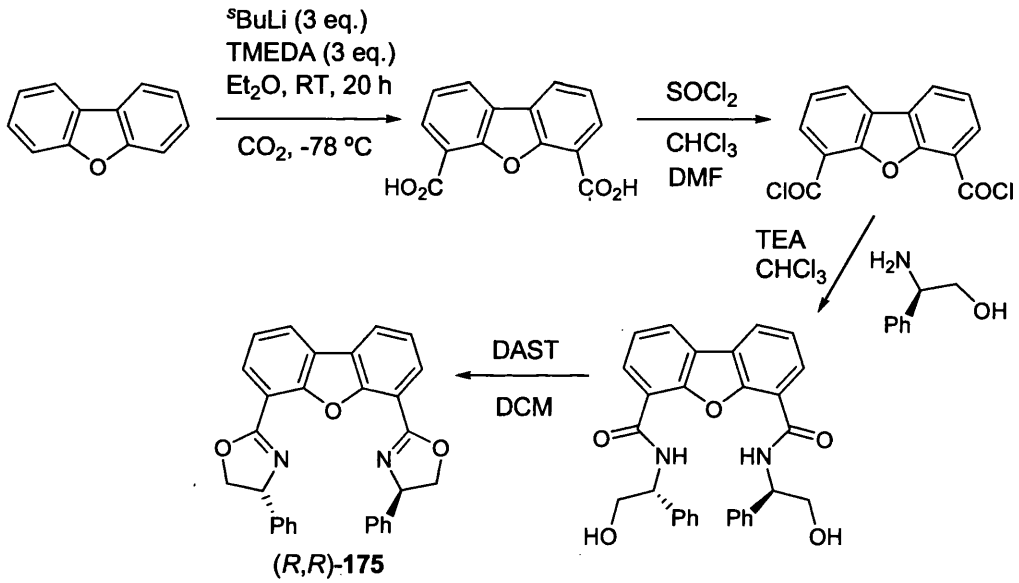
(*R*)-4-Benzyl-2-(1-((*R*)-4-benzyl-4,5-dihydrooxazol-2-yl)cyclopropyl)-4,5-dihydrooxazole, (*R,R*)-**242**: purchased from Aldrich



(*S*)-4-*tert*-Butyl-2-(1-((*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)cyclopropyl)-4,5-dihydrooxazole, (*S,S*)-**243**: purchased from Aldrich

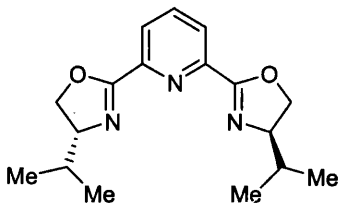


4,6-Dibenzofurandiyl-2,2′-bis[4-(*R*)-phenyl-1,3-oxazoline],[136] (*R,R*)-**175**:

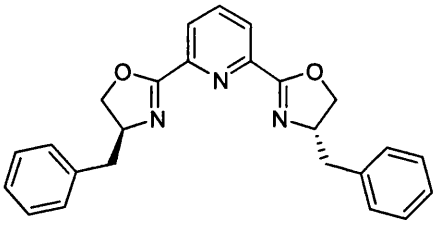


Appendix

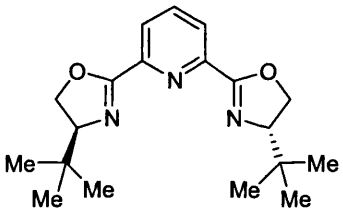
2,6-Bis((*R*)-4,5-dihydro-4-isopropyloxazol-2-yl)pyridine,(*R*,*R*)-**244**: purchased from Aldrich



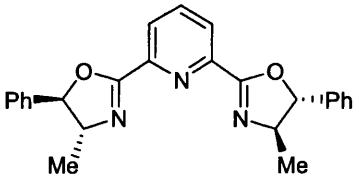
2,6-Bis((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)pyridine,[135] (*S*,*S*)-**178**: provided by V. J.-D. Piccio



2,6-Bis((*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)pyridine,[155] (*S*,*S*)-**180**: provided by V. J.-D. Piccio

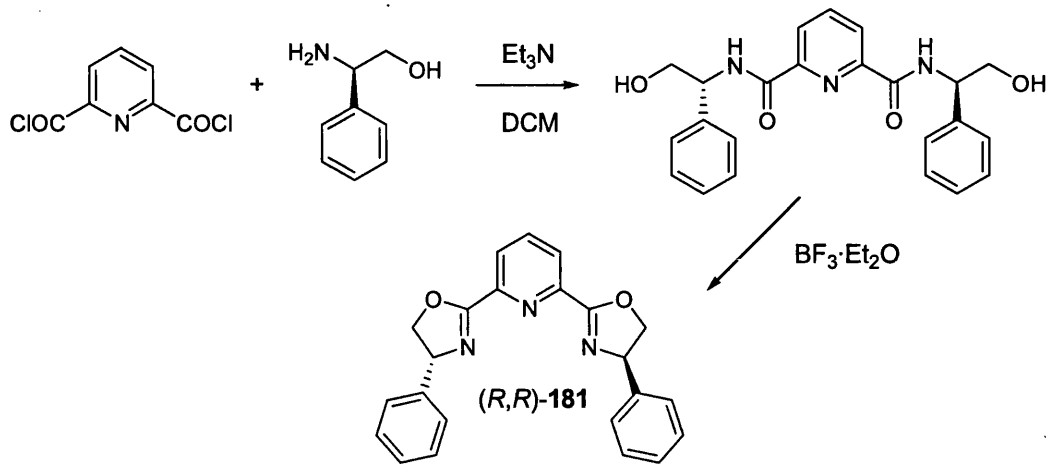


2,6-Bis((4*R*,5*R*)-4,5-dihydro-4-methyl-5-phenyloxazol-2-yl)pyridine, (4*R*,5*S*)-**179**: purchased from Aldrich



Appendix

2,6-Bis-[(4′*R*)-4′-phenyloxazolin-2′-yl]-pyridine,[135] (*R*,*R*)-**181**:



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