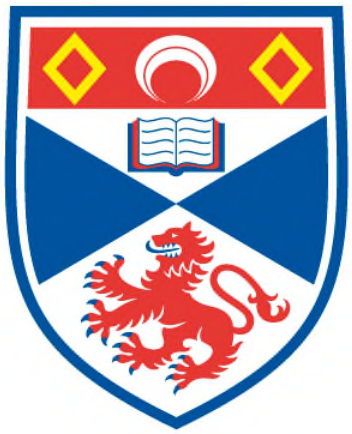
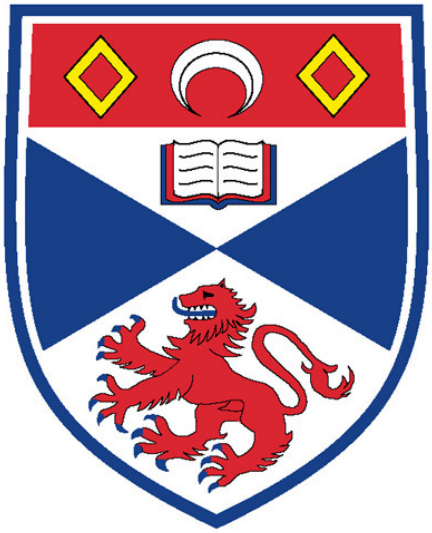
LEWIS BASE-PROMOTED ORGANOCATALYSIS: O- TO C-CARBOXYL TRANSFER REACTIONS

Craig D. Campbell

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



2010



University
of
St Andrews

Lewis base-promoted organocatalysis: O- to C-carboxyl transfer reactions

Craig D. Campbell

2010

Thesis submitted in partial fulfilment for the
degree of Doctor of Philosophy

Declarations

1. Candidate's declarations:

I, Craig Donald Campbell, hereby certify that this thesis, which is approximately 60,000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in September 2006 and as a candidate for the degree of Doctor in July 2007, the higher study for which this is a record was carried out in the University of St Andrews between 2006 and 2010.

Date 25/06/2010 Signature of candidate …… **Craig D. Campbell**

2. Supervisor's declaration:

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of Doctor of Philosophy in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

Date 25/06/2010 Signature of supervisor …… **Andrew D. Smith**

3. Permission for electronic publication:

In submitting this thesis to the University of St Andrews I understand that I am giving permission for it to be made available for use in accordance with the regulations of the University Library for the time being in force, subject to any copyright vested in the work not being affected thereby. I also understand that the title and the abstract will be published, and that a copy of the work may be made and supplied to any bona fide library or research worker, that my thesis will be electronically accessible for personal or research use unless exempt by award of an embargo as requested below, and that the library has the right to migrate my thesis into new electronic forms as required to ensure continued access to the thesis. I have obtained any third-party copyright permissions that may be required in order to allow such access and migration, or have requested the appropriate embargo below.

The following is an agreed request by candidate and supervisor regarding the electronic publication of this thesis:

(iii) Embargo on both all of printed copy and electronic copy for the same fixed period of 5 years on the following grounds:

publication would preclude future publication.

Date 25/06/2010 Signature of candidate …… **Craig D. Campbell**

Signature of supervisor …… **Andrew D. Smith**

Abstract

This work describes the application of a variety of Lewis bases, encompassing predominantly N-heterocyclic carbenes (NHCs), but also the use of imidazoles, aminopyridines, amidines and isothioureas, as effective catalysts in the dearomatisation of heterocyclic carbonates, predominantly the rearrangement of oxazolyl carbonates to their *C*-carboxyazlactone isomers by means of the Steglich rearrangement. This rearrangement reaction has been investigated extensively, with the development of simplified reaction procedures and the invention of domino cascade protocols incorporating this transformation. In an attempt to understand the mechanism of this *O*- to *C*-carboxylation process, a number of interesting observations have been made. Firstly, the class of NHC has an important factor in promoting the rearrangement, with triazolinylidenes being the most effective. Secondly, an interesting chemoselectivity has been delineated using triazolium-derived NHCs, prepared using weak bases (typically Et_3N) or strong metallated bases; both alkyl and aryl oxazolyl carbonates undergo smooth rearrangement with triazolinylidenes derived from strong metallated bases such as KHMDS, while only aryl oxazolyl carbonates undergo rearrangement using Et_3N. Extensive effort has focused towards the development of asymmetric variants of these protocols, primarily towards the design, synthesis and evaluation of chiral NHC precatalysts. To this end, a number of chiral azolium salts have been prepared, encompassing a number of different NHC classes, including C_1- and C_2-imidazolinium salts, C_2-imidazolium salts and a range of triazolium salts. Efforts towards the asymmetric catalysis of the Steglich rearrangement of oxazolyl carbonate substrates have given an optimal 66% *ee*. Similar rearrangements have been demonstrated with the related furanyl heterocyclic substrate class, producing a mixture of α- and γ-carboxybutenolides. In contrast to the analogous oxazolyl carbonates, the regioselectivity of this rearrangement is dependent upon the nature of the Lewis base employed. Amidines and aminopyridines give a mixture of the α- and γ- regioisomers with generally the α-regioisomer being preferred, while a triazolium-derived NHC gives rise to predominantly the thermodynamically more stable γ-carboxybutenolide. Using amidines or aminopyridines, this rearrangement has been shown to proceed *via* an irreversible C-C bond-forming process, but in contrast, the rearrangement using the NHC proceeds *via* an equilibrium process with an optimised regioselectivity of >98:2 for the γ-carboxybutenolide regioisomer over the α-regioisomer. Whilst the asymmetric variant using chiral NHCs has proven unfruitful, rearrangements using a chiral isothiourea have given high levels of regioselectivity towards the α- regioisomer and with excellent levels of enantiodiscrimination (77–95% *ee*).

Acknowledgements

Firstly I would like to thank the most important people in my life, my wife Charmaine, my parents Coreen and Donald and the rest of my family, for the encouragement and constant support they have given me over the years. I am also extremely thankful to all of the scientists I have had the opportunity to work with, particularly my laboratory supervisor Dr Andrew Smith, project colleagues Jennifer Thomson, Caroline Joannesse, Louis Morrill, Drs Carmen Concellón, Nicolas Duguet and Kenneth Ling, and the rest of the Smith group for coping with me singing all of the time. Many thanks also go to Dr Gordon Florence for his valuable advice, Prof. Alexandra Slawin for X-ray crystallography and Prof. Douglas Philp for his help with computational analysis. Further thanks go to the instrumentation technicians, Mrs Melanja Smith, Dr Tomáš Lébl and Mrs Caroline Horsburgh.

Table of Contents

Abbreviations

Ac	acetyl	CH_3CO-
app	apparent	
aq	aqueous	
Ar	aryl	
Bn	benzyl	$C_6H_5CH_2$-
br	broad	
n-Bu	*n*-butyl	$CH_3(CH_2)_3$-
t-Bu	*tert*-butyl	$(CH_3)_3C$-
CAAC	cyclic alkylaminocarbene	
conc	concentrated	
Cy	cyclohexyl	
d	doublet	
D-	*dextro*, right	
DABCO	1,4-diazabicyclo[2.2.2]octane	
DBN	1,5-diazabicyclo[4.2.0]non-5-ene	
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	
DCC	dicyclohexylcarbodiimide	
DCE	1,2-dichloroethane	
decomp	decomposition	
DMAP	4-dimethylaminopyridine	
DMF	*N*,*N*-dimethylformamide	$N(CH_3)_2CHO$
DMPU	*N*,*N*'-dimethylpyrimidin-2-one	
dr	diastereomeric ratio	
ee	enantiomeric excess	
equiv	equivalent molar quantity	
ESI+	electrospray ionisation, positive ion	
ESI-	electrospray ionisation, negative ion	
Et	ethyl	C_2H_5-
g	gram(s)	
GC	gas chromatography	
h	hour(s)	
HMDS	hexamethyldisilazane	
HMPA	hexamethylphosphoric triamide	

HOAt	1-hydroxy-7-azabenzotriazole	
HOBt	1-hydroxybenzotriazole	
HPLC	high performance liquid chromatography	
HRMS	high resolution mass spectrometry	
i-Bu	isobutyl	$(H_3C)_2CHCH_2$-
IMes	*N*,*N'*-dimesitylimidazolinylidene	
IPA	isopropanol	
i-Pr	isopropyl	$(H_3C)_2CH$-
KHMDS	potassium hexamethyldisilazide	
L-	*laevo*-, left	
LDA	lithium diisopropylamide	
LiHMDS	lithium hexamethyldisilazide	
M	molar (i.e. mol dm^{-3})/mesomeric effect	
m	multiplet	
*m*CPBA	*meta*-chloroperbenzoic acid	
min	minute(s)	
Me	methyl	CH_3-
Mes	mesityl	2,4,6-$(H_3C)_3C_6H_2$-
mp	melting point	
Ms	mesyl	CH_3SO_2-
MS	mass spectrometry	
NHC	N-heterocyclic carbene	
NMM	*N*-methylmorpholine	
NMR	nuclear magnetic resonance	
p-An	*para*-anisyl	4-$MeOC_6H_4$-
Ph	phenyl	C_6H_5-
ppm	parts per million	
PPA	polyphosphoric acid	
PPY	4-pyrrolidinopyridine	
PPY*	ferrocene-fused 4-pyrrolidinopyridine	
*p*TSA	*para*-toluenesulfonic acid	
q	quartet	
quant	quantitative	
quint	quintuplet	

[R]	reduction/reducing agent	
rt	ambient (room) temperature	
s	singlet	
sat	saturated	
sept	septuplet	
SIMes	*N*,*N*′-dimesitylimidazolidinylidene	
SM	starting material	
t	triplet/time	
$t_{1/2}$	half-life	
TADMAP	(*S*)-1-(4-(dimethylamino)pyridin-3-yl)-2,2,2-triphenylethyl acetate	
temp	temperature	
Tf	triflyl	CF_3SO_2-
TFA	trifluoroacetic acid	CF_3COOH
ThDP	thiamine diphosphate	
THF	tetrahydrofuran	
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine	
TBS	*tert*-butyldimethylsilyl	Me_2(*t*-Bu)Si-
TMS	trimethylsilyl	Me_3Si-
TOF	time of flight	
v	volume	
wt	weight	

Chapter 1: Introduction

Section 1.1: Organocatalysis

In an effort to maximise the efficiency of organic reactions, specifically, in order to limit the quantities of reagents, reaction time and the purification of the product, catalysis has proven to be an important solution. While traditional catalysis is most commonly effected by acid, base or metals (and metal complexes), biochemical investigations have illuminated numerous biological catalysts which are organic in nature. Enzymes provide a large number of such catalysts, but vitamins have also been discovered to play an integral part in affecting many biochemical transformations and are often referred to as co-catalysts. In the past ten years, with increasing understanding into the modes of action of these biological catalysts, organic chemists have exploited these important motifs in order to develop and utilise simplified "organocatalysts". The term "organocatalysis" describes the promotion or acceleration of a chemical reaction through the addition of a substoichiometric quantity of a metal-free organic compound.[1] The appeal of this type of catalysis, in comparison with metal-catalysed processes, is that it precludes the use of heavy metals, many of which are highly toxic and cumulative poisons. Many metal-catalysed processes also require the use of sensitive ligands (such as phosphines) and/or catalysts. Organocatalysts generally do not suffer such difficulties in either their preparation or their application, and thus, provide a convenient alternative to such strategies. Furthermore, the use of generally mild reaction conditions allows for greater functional group tolerance in such transformations. As such, this field of research has seen a revitalisation of interest with a multitude of reaction types being developed.[2] In broad terms, the field of organocatalysis can be grouped into four main classes, based upon the mode of action of the catalyst: Brønsted acid, Brønsted base, Lewis acid and Lewis base. Representative examples from each of these classes follow.

Section 1.1.1: Brønsted acid catalysis

A Brønsted acid is defined as a substance that can donate a proton to an acceptor, itself termed a Brønsted base. In this area, key hydrogen bond interactions give rise to accelerated reaction rates, whilst also allowing for the development of asymmetric variants. As an illustration, Gong and co-workers have elegantly demonstrated chiral BINOL-derived phosphoric acid **4** as a Brønsted acid catalyst to promote asymmetric Mannich reactions, providing β-aminoketone products **5** with excellent diastereo- and enantioselectivity, *via* proposed transition state **6** (Figure 1).[3]

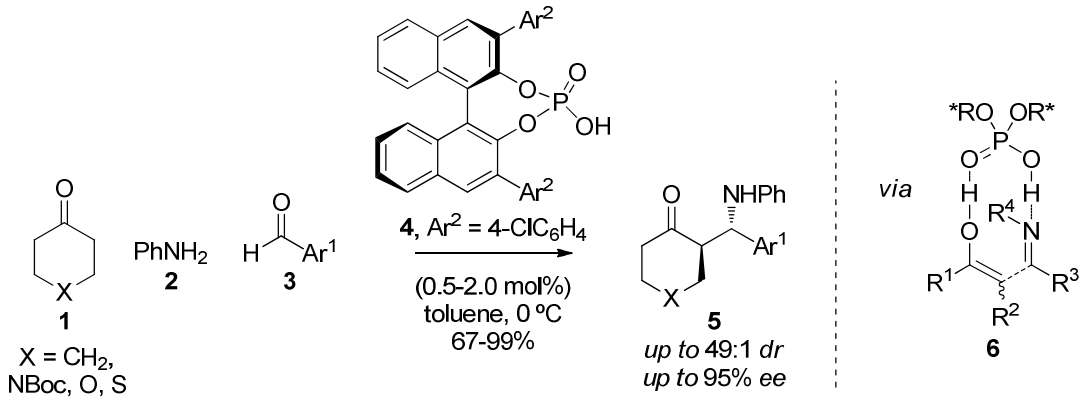


Figure 1: Asymmetric phosphoric acid catalysis

Section 1.1.2: Brønsted base catalysis

An approach to the asymmetric Strecker reaction has been developed by Corey and co-workers using a C_2-symmetric Brønsted base catalyst **9**. It is proposed that the guanidine **9**, pK_{aH} ~13–14,[4] initially increases the nucleophilicity of hydrogen cyanide by aiding in deprotonation to generate the cyanide anion (pK_{aH} 12.9[5]), remaining as a complex with the guanidinium cation. This in turn also activates the imine reagent (acting as a Brønsted acid), delivering the cyanide selectively to the *Si*-face of the imine **7**, giving rise to the aminonitrile product **10** in excellent ee (Figure 2).[6]

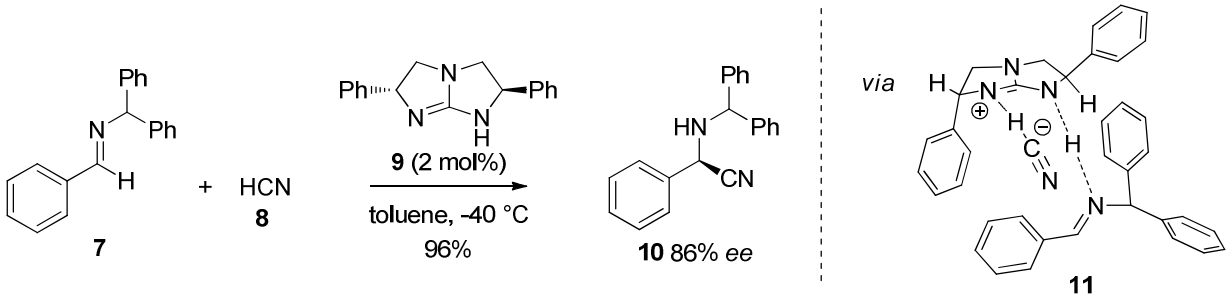


Figure 2: Asymmetric Strecker reaction

Section 1.1.3: Lewis acid catalysis

Lewis acids are defined as substances that can accept a lone pair of electrons from another species, defined as a Lewis base. Phase transfer reagents are an example of Lewis acid organocatalysts, which associate with substrate as ion pairs. Most often these are ammonium or phosphonium[7] species, and a number of such chiral species have been utilised in asymmetric transformations catalytically. A recent example by Maruoka and co-workers employed axially chiral phosphonium salt **14** in asymmetric Mannich reactions of β-ketoesters **12** with azodicarboxylates **13**. The reaction is general and delivers the product in very good to excellent *ee* (Figure 3).[8]

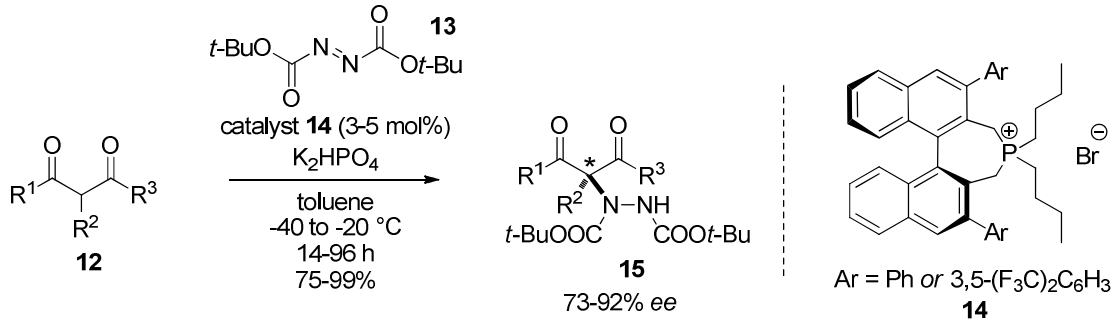


Figure 3: Asymmetric amination

Section 1.1.4: Lewis base catalysis

The most widely applied mode of organocatalysis may be classified as Lewis base catalysis, promoted by a species bearing a lone pair of electrons. The reaction scope is ever expanding and still remains a field of extensive research. Within this area, a range of reactions have been developed, most notably in the fields of aldol reactions, Michael-type additions, esterification, Mannich reactions, Diels-Alder reactions and transfer hydrogenation. The utility of hydrogen bonding to effect asymmetric organocatalysis has been exploited successfully by a number of groups,[9] whilst arguably the most developed area of asymmetric organocatalysis has been demonstrated by MacMillan and co-workers with the use of chiral imidazolidinones as Lewis base organocatalysts. As an illustration, these secondary amine based catalysts react with aldehydes to form reactive electrophilic iminium species. In a given reaction, a stereodirecting unit blocks one face of the iminium intermediate, affording highly enantiomerically enriched products. As an illustration, MacMillan and co-workers have used this methodology to perform domino Friedel-Crafts alkylation–chlorination reactions using secondary amine **19** in conjunction with activated arenes **18** and electrophilic chlorine source **17** (Figure 4). In addition, these chiral imidazolidinones have also been applied in cycloaddition reactions, including Diels-Alder reactions[10] and nitrone [3+2] cycloadditions,[11] and in conjunction with CAN, in SOMO catalysis.[12]

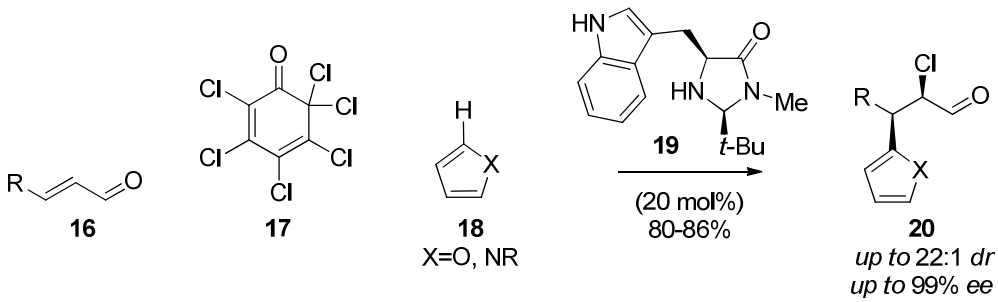


Figure 4: Lewis base promoted domino cascade

Many organocatalysed processes, although highly selective, typically require high catalyst loading (up to 20 mol%), long reaction times (>24 h) and the use of highly polar aprotic solvents such as DMSO or DMF. These problems illustrate some of the challenges of organocatalysis, namely, that there is still considerable scope for optimisation, such as through design of catalysts with greater reactivity.

Section 1.2: Carbenes

Carbenes are neutral, divalent, reactive species bearing a carbon atom with two non-bonding electrons in their valence shell. Most carbenes have a 'bent' structure (bond angles in the range of 100–150º) which imposes sp^2-type hybridisation at the carbon centre. Two possible electronic configurations of a carbene are permitted, the electron-paired singlet state carbene ($2\Sigma m_s + 1 = 1$), or the unpaired triplet state ($2\Sigma m_s + 1 = 3$) (Figure 5).[13]

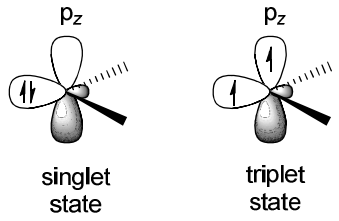


Figure 5: Singlet and triplet carbenes

The difference in spin multiplicity between these two states gives rise to a difference in reactivity: singlet carbenes show ambiphilic activity due to the filled σ-type (or *n*) orbital and unfilled p_z-orbital but, in contrast, the unpaired electrons of triplet carbenes give rise to diradical reactivity.

Given the unusually electron-deficient nature of carbenes, these species are highly reactive and typically exhibit only transient lifetimes, though the stability of these species can be increased by both electronic (inductive and mesomeric) and steric effects. Inductively, σ-electron withdrawing groups lead to an increase in *s* character of the non-bonding σ-orbital, resulting in an increased difference between the σ and p_z orbital energies, thus favouring the spin-paired (i.e. singlet) state. Mesomerically electron donating groups lead to a greater occupation of the p_z orbital, destabilising the triplet state carbene, whilst also stabilising the singlet state. Sterically bulky groups flanking the carbene centre are able to stabilise the carbene, possibly through hyperconjugation or simply by protection from the surrounding environment, due to the large van der Waals radii of the substituents.

Section 1.3: Nature's carbene source: thiamine diphosphate

Thiamine, also known as vitamin B_1, is an important dietary requirement for the conversion of carbohydrates and lipids into energy, and for the maintenance of the digestive system, heart function and nervous system. Thiamine is the precursor to the active coenzyme thiamine diphosphate, ThDP, **22**, which is involved in the action of a number of enzymes, including pyruvate dehydrogenase and decarboxylase, α-ketoglutarate dehydrogenase, branched-chain α-keto acid dehydrogenase and transketolase.[14] The ability of ThDP **22** to facilitate these reactions is due to the properties and reactivity of the thiazolium ring system. The C(2) proton, flanked by the heteroatoms of the ring, is relatively acidic (pK_a ~17),[15] and is readily deprotonated under physiological conditions to generate the conjugate base **25**, a thiazolinylidene carbene (Figure 6). The rate of exchange of this proton in water is rapid, as demonstrated with deuterium labelling studies, with $t_{1/2}$ ~20 min.[16] The active catalyst then facilitates decarboxylation of the requisite substrate in order to generate the well-established "Breslow intermediate", a formal acyl anion equivalent (Figure 6). In conjunction with ThDP **22**, decarboxylase enzymes can perform the (asymmetric) synthesis of a variety of chiral α-hydroxyketones by trapping of the Breslow intermediate with an aldehyde (Figure 6).[17]

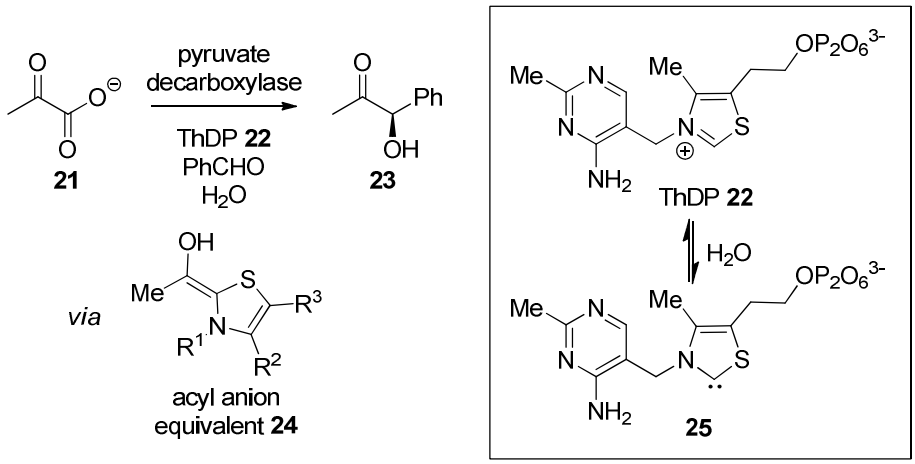


Figure 6: Action of thiamine diphosphate **22**

Section 1.4: N-Heterocyclic carbenes (NHCs)

Similar in nature to the thiazolinylidene carbene **25**, N-heterocyclic carbenes (NHCs) are a specific class of carbene bearing two nitrogen atoms flanking the formally electron deficient carbene centre. Arduengo and co-workers isolated the first stable crystalline NHC **27** by deprotonation of imidazolium salt **26** with NaH and catalytic DMSO (Figure 7).[18]

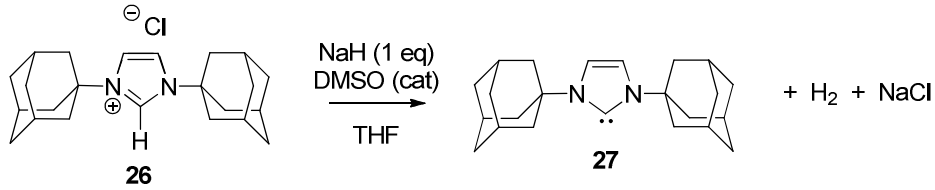


Figure 7: Preparation of stable crystalline carbene **27**

A combination of steric and electronic effects contribute to the stability of carbene **27**, *via* a "push-pull" mechanism: mesomeric electron donation from the lone pairs of the nitrogen atoms into the empty p_z orbital of the carbon atom stabilises the carbene, whilst electron density is withdrawn inductively through the σ-system by the electronegative nitrogen atoms (Figure 8). Furthermore, the introduction of sterically bulky *N*-adamantyl substituents also protects the electron-deficient centre from subsequent reactions such as reprotonation and dimerisation, thus accounting for the enhanced kinetic stability of the NHC.

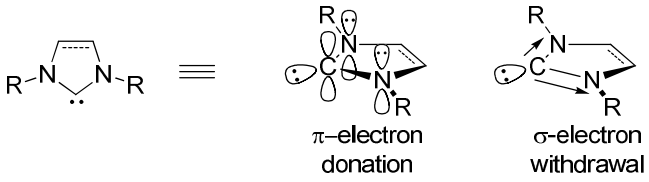


Figure 8: Electronic stabilisation of NHCs

These stabilisation factors have been exploited in the synthesis and application of a wide range of NHCs. By virtue of the singlet (i.e. Lewis basic) nature of NHCs, in addition to the ability to design and vary the N-substituents, these molecules have proven good candidates as ligands for metal-based catalysts and also as Lewis base organocatalysts.

Section 1.5: NHCs as ligands in catalysis

NHCs have played an important part in the development of organometallic chemistry, with considerable focus upon their inclusion as ligands in transition metal-based catalysts. Some of the most well known demonstrations are the ruthenium complexes developed by Grubbs and co-workers[19,20] and then Hoveyda and co-workers[21,22] for the catalysis of olefin metathesis reactions,[23] while Nolan and co-workers have demonstrated a range of noteworthy applications of NHCs as palladium ligands in the catalysis of Buchwald-Hartwig amination and Suzuki-Miyaura cross-coupling.[24] This thesis focuses upon applications of NHCs as organocatalysts, and the remainder of this introduction will exemplify their use as such Lewis basic catalysts.

Section 1.6: N-Heterocyclic carbenes in organocatalysis

Section 1.6.1: Introduction

The ability of N-heterocyclic carbenes (NHCs) to promote a remarkably diverse series of organocatalytic transformations has been identified in recent years, with a series of excellent reviews documenting progress in this area.[25] The aim of this section is two-fold; firstly, to describe the ability of NHCs to generate synthetically useful intermediates and illustrate their reactivity, and secondly, to review the use of NHCs in stereoselective reaction processes. In order to categorise the recent advances in reactivity involving NHC mediated transformations, this chapter will classify reaction processes by the type of intermediate through which C-C, C-H or C-heteroatom bond-forming processes proceed. Within this framework, four main synthetic intermediates are accessed: three nucleophilic species **28–30**, formally resulting in the formation of d^1, d^2 and d^3 synthons[26] (acyl anion, azolium enol or enolate, and azolium homoenolate intermediates, respectively) and an electrophilic a^1 synthon (acylazolium species **31**) (Figure 9).

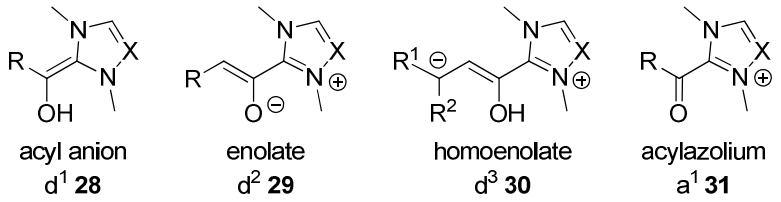


Figure 9: Synthetic intermediates generated with NHCs

In each case, an illustration of an asymmetric variant will be given in order to highlight the significance of the application of chiral NHCs in these transformations. In the event that a reaction proceeds through a number of these intermediates, the reaction will be categorised according to the first asymmetric step in the transformation, with a miscellaneous section covering other reaction types. Of particular note to this thesis is the application of NHCs as acylazolium species, for which a fuller discussion will be described.

Section 1.6.2: Reactivity of NHC derived synthons

Section 1.6.2.1: Generation of acyl anion equivalents (d^1 synthons) from aldehydes

Practically, the simplest and most direct manner to generate acyl anion equivalents is through reaction of an NHC **33** with an aldehyde **32**, generating an enamine species **35**, commonly referred to as a "Breslow intermediate". Subsequent reaction with an electrophile, classically using aldehydes or enones, generates the benzoin[27] and Stetter products **37** and **38** respectively (Figure 10).

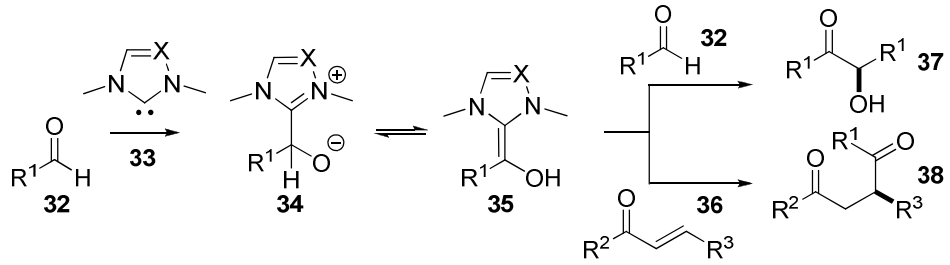
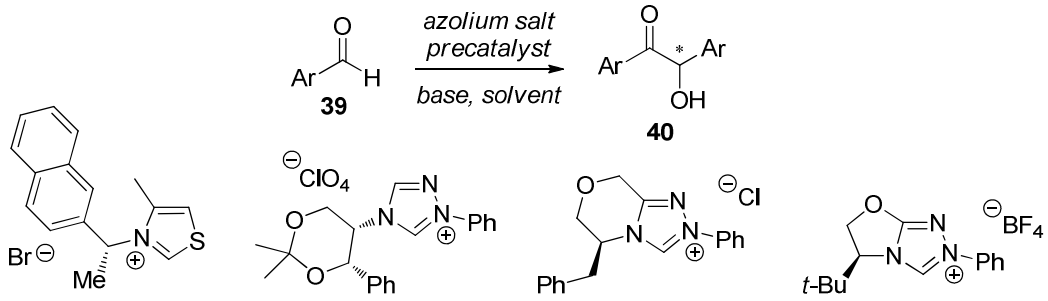


Figure 10: Generation of acyl anion equivalents with NHCs

The same "Breslow intermediate" has been employed from acyl silanes[28] or α-ketoacids,[29] although these processes have yet to be utilised in asymmetric transformations.

A wide range of chiral thiazolium salt precatalysts have been studied in order to perform the benzoin reaction asymmetrically, however, the enantioselectivities obtained for the condensation of benzaldehyde using thiazolium precatalysts are generally poor, with **41** proving optimal on balance of both yield and enantioselectivity.[30] Following studies of triazolium-based NHC catalysts,[31] Enders and co-workers studied chiral triazolium salt precatalysts for the asymmetric benzoin reaction. The NHC derived from **42** provided acyloin products **40** in moderate to good yields and up to 84% *ee*, although the asymmetric benzoin reaction of electron-deficient aldehydes remained a challenge.[32] In 1997, Knight and Leeper developed the bicyclic triazolium salt **43**, derived from L-phenylalanine. Good enantioselectivities (up to 83% *ee*) were obtained for a range of aromatic aldehydes, although the isolated yields were modest, even with high catalyst loadings (30 mol%).[33] In 2002, Enders and co-workers reported triazolium salt **44**, derived from L-*tert*-leucine, as an effective catalyst for the asymmetric benzoin reaction. Excellent enantioselectivities (up to 99% *ee*) were observed for a range of aromatic aldehydes, with electron-rich aldehydes generally giving higher enantioselectivities (but lower yields) than electron-deficient aldehydes (Figure 11).[34,35]



Ar	41 (10 mol%) yield (%)	*ee*	42 (1.25 mol%) yield (%)	*ee*	43 (30 mol%) yield (%)	*ee*	44 (10 mol%) yield (%)	*ee*
Ph	85	40 (*R*)	66	75 (*R*)	45	80 (*S*)	83	90 (*S*)
4-MeC_6H_4	-	-	28	84 (*R*)	38	83 (*S*)	16	93 (*S*)
4-ClC_6H_4	-	-	51	29 (*R*)	11	76 (*S*)	80	64 (*S*)

Figure 11: Chiral azolium precatalysts for the asymmetric benzoin reaction

Suzuki and co-workers recently applied the asymmetric intramolecular benzoin reaction to the synthesis of the homoisoflavonoid (+)-sappanone B **48**.[36] The authors found that triazolium salt precatalyst **46** gave the best results for the cyclisation of ketoaldehyde **45**, with electron-withdrawing *N*-aryl substituents on the NHC important in order to suppress competing aldol pathways. The synthesis of (+)-sappanone B **48** from benzoin product **47** was achieved in two steps by sequential deprotection of the aryl methyl ethers (Figure 12).

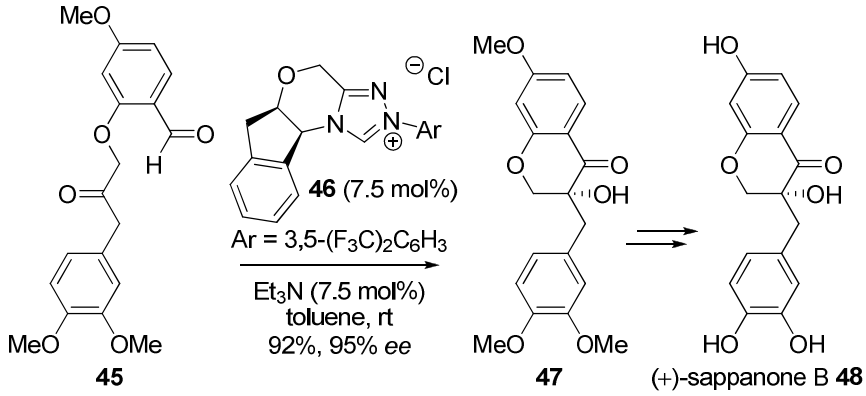


Figure 12: Synthesis of sappanone B using NHC-mediated catalysis

The first asymmetric intramolecular Stetter reactions were reported by Enders and co-workers utilising triazolium salt precatalyst **51**. Treatment of substrates **49** generated 1,4-dicarbonyl compounds **50** in good yield and enantioselectivity.[37] These salicylaldehyde-derived substrates **49** have since become the standard test substrates for the development of new catalysts for the asymmetric intramolecular Stetter reaction. Bach and co-workers have achieved moderate enantioselectivities using axially-chiral thiazolium precatalyst **52**,[30f] whilst Miller and co-workers have developed peptidic thiazolium precatalyst **53**.[38] In 2005, Rovis and co-workers showed that the NHCs derived from triazolium salts **54**–**56** were excellent catalysts for the

asymmetric intramolecular Stetter reaction of a wide range of substrates, giving typically excellent yields and enantioselectivities.[39] The *N*-pentafluorophenyl substituted catalyst **55** currently represents the state of the art in asymmetric Stetter reactions (Figure 13).[40]

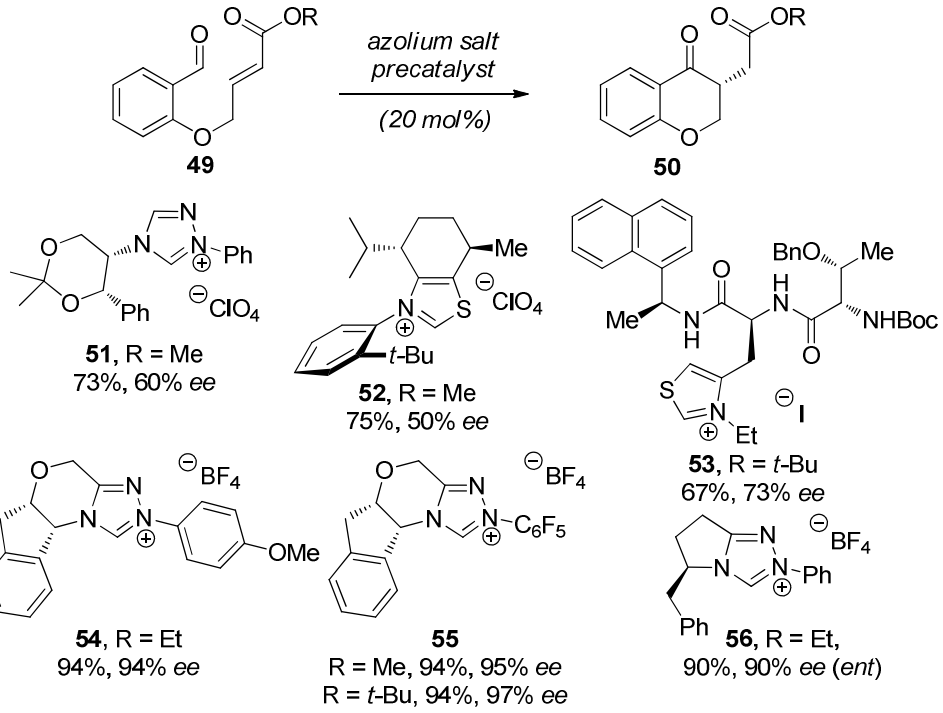


Figure 13: Asymmetric intramolecular Stetter reactions

Rovis and co-workers have also shown that precatalyst **55** is competent with a wide range of Michael acceptors including enals, amides, nitriles, esters, thioesters, vinylphosphonates and vinylphosphine oxides (Figure 14).[39b,41] Further developments have allowed Stetter reactions to be extended to the use of aliphatic aldehydes,[42] the formation of quaternary stereocentres[43] and to intermolecular reactions.[44]

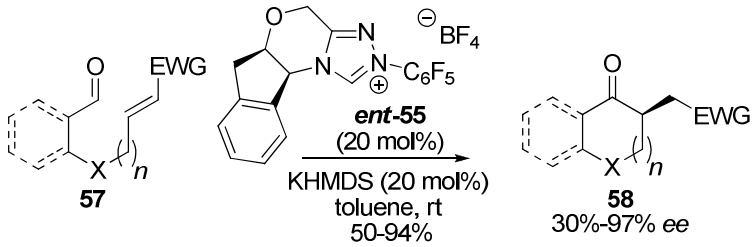


Figure 14: Scope of the asymmetric intramolecular Stetter reaction

Section 1.6.2.2: Generation of homoenolates, enolates and acylazoliums from enals

Treatment of enals with NHCs allows the generation of nucleophilic (homoenolate and enolate) and electrophilic (acylazolium) species. Initial addition of an NHC to an enal **59** generates hydroxyazolium **60**, that can either be oxidised *in situ* to generate α,β-unsaturated acylazolium **66**, or, after proton transfer, generates Breslow-type intermediate **61** which acts as a homoenolate

equivalent **62**. Azolium enol or enolate species can also be accessed through variation of the reaction conditions and electrophilic partner in these reactions; selective β-protonation or tautomerisation of the homoenolate **62** can generate an intermediate **63** with enolate reactivity. Enolate **63** can undergo either protonation or further reaction with an electrophile to generate an acylazolium **64**, with nucleophilic attack giving the desired product **65** and regenerating the NHC (Figure 15).

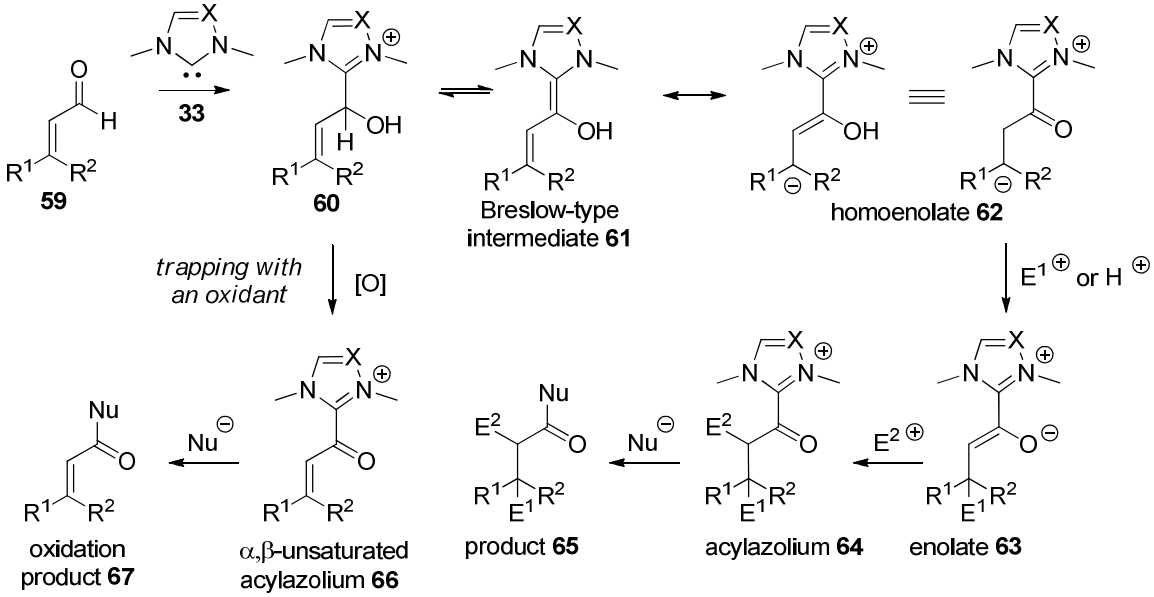


Figure 15: Modes of reactivity of enals with NHCs

Representative examples of the synthetic utility of these reaction processes, all of which have been utilised in asymmetric transformations, are covered below.

Section 1.6.2.2a: Oxidation processes

Scheidt and co-workers have employed cascade oxidation pathways from allylic or propargylic alcohols **68** to afford unsaturated ester products **72**. *In situ* oxidation of an unsaturated alcohol **68** to an enal **69** using MnO_2, followed by NHC addition, affords hydroxyazolium **70** that is oxidised to acylazolium **71** and trapped with an alcohol. The oxidation of the hydroxyazolium intermediate is assumed to occur considerably faster than deprotonation to afford the Breslow-type intermediate **73** in this process, as no homoenolate-derived products are observed under these conditions (Figure 16).[45]

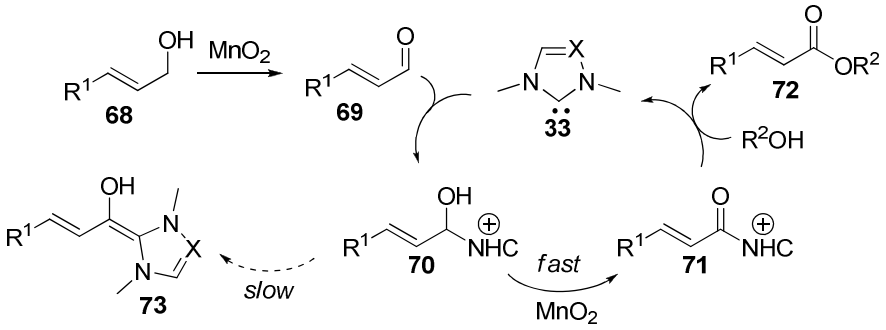


Figure 16: Cascade oxidation pathway by hydroxyazolium trapping

Related oxidation processes have been reported that allow the generation of esters directly from aryl aldehydes[46] and the hydroacylation of α-ketoesters with aldehydes.[47] Scheidt and co-workers have used their *in situ* hydroxyazolium oxidation strategy to allow the desymmetrisation of diol **74** using chiral triazolium salt **76**, giving mono-ester **77** in 80% *ee* (Figure 17).[48]

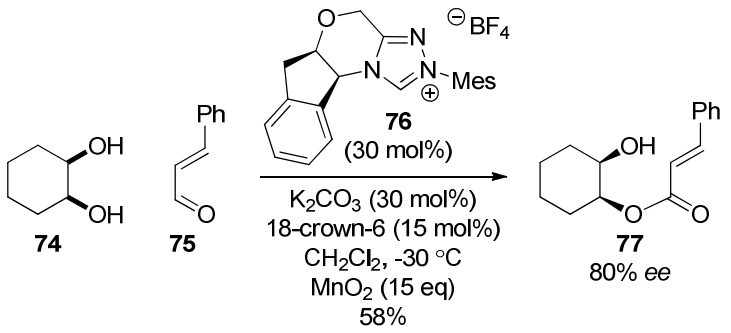


Figure 17: Desymmetrisation *via* oxidation pathway

Section 1.6.2.2b: Homoenolate reactivity

The ability to generate homoenolates from enals was reported independently by Glorius and Burstein,[49] and Bode and co-workers[50] in the preparation of γ-butyrolactones **80** (Figure 18). A sterically demanding NHC catalyst is required to promote reactivity at the d^3 terminus and to prevent competitive benzoin dimerisation. The asymmetric variant has been investigated by Glorius and Burstein, though *ee*s of up to only 25% were obtained.[49] You and co-workers have demonstrated enantioselective γ-lactone formations using glyoxalate **82**, achieving up to 78% *ee* with the NHC derived from chiral triazolium salt **83**, although with low levels of diastereoselectivity (Figure 19).[51]

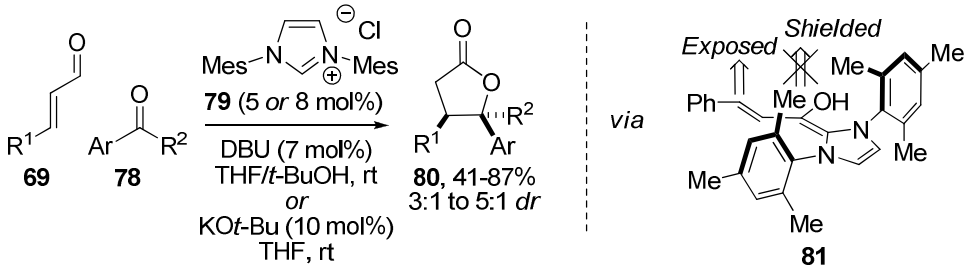


Figure 18: γ-Butyrolactone formation with homoenolates

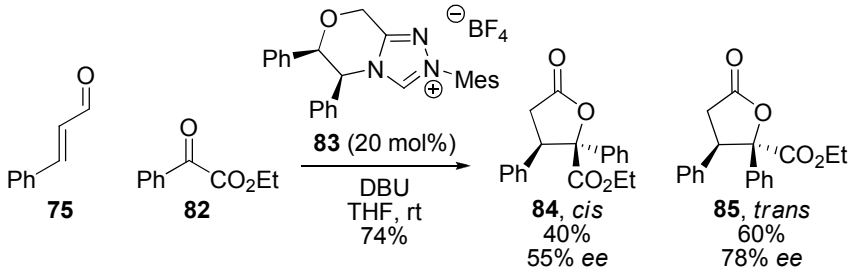


Figure 19: Asymmetric γ-butyrolactone synthesis with glyoxalates

Nair and co-workers have reported a related spiro-γ-lactone formation reaction using cyclic 1,2-diones, including cyclohexane-1,2-dione and substituted isatin derivatives,[52] and have also extended the utility of homoenolates to allow ring annulation with enones.[53] Cyclopentene formation is achieved *via* homoenolate attack upon the enone **86**, generating β-lactone **87** after cyclisation, which undergoes spontaneous decarboxylation to afford the *trans*-substituted cyclopentene products **88** in good to excellent yield (Figure 20).

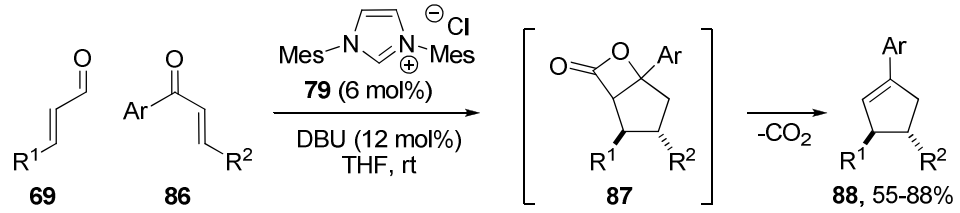


Figure 20: Scope of cyclopentene formation

Bode and co-workers have used NHCs to form *cis*–γ-butyrolactams (such as **96**) from a range of β-alkyl and β-aryl substituted enals and saccharin-derived cyclic sulfonylimines (e.g. **95**),[54] with a single example of an asymmetric variant giving good levels of both diastereo- and enantioselectivity. Scheidt and Chan have shown enals and azomethine imines **91** can generate pyridazinones **92** with high diastereoselectivity,[55] and Scheidt and co-workers have shown that nitrones **93** give rise to enantiomerically enriched γ-amino esters **94** following methanolysis of the oxazinone intermediate (Figure 21).[56]

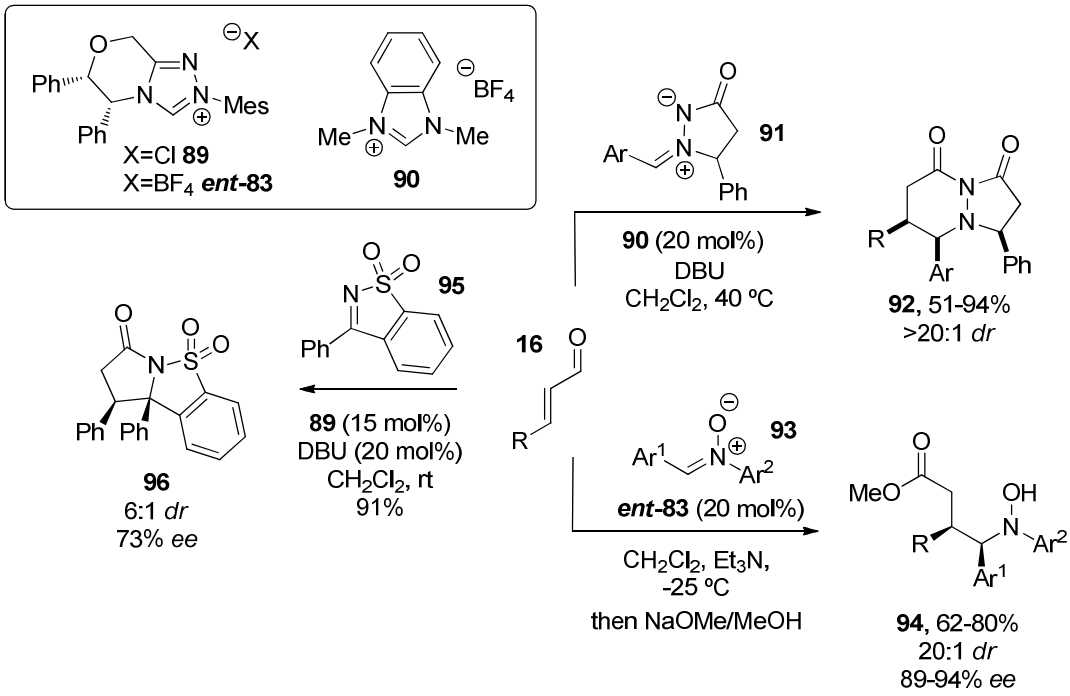


Figure 21: Asymmetric γ-lactamisation and preparation of amino esters

Nair and co-workers have demonstrated NHC-catalysed formation of spirocyclic diketones **99** from enals **97** and substituted dibenzylidene-cyclopentanones **98**. Where chalcones and dibenzylidene cyclohexanones give only cyclopentene products (as a result of β-lactone formation then decarboxylation), cyclopentanones **98** give only the spirocyclic diketone products **99**.[57] Of particular note are the formation of an all-carbon quaternary centre and the excellent level of diastereoselectivity observed in the reaction. An asymmetric variant of this reaction has been demonstrated by Bode and co-workers using chiral imidazolium salt **100**, obtaining the desymmetrised product with good diastereo- and enantioselectivity, though in modest yield (Figure 22).[58]

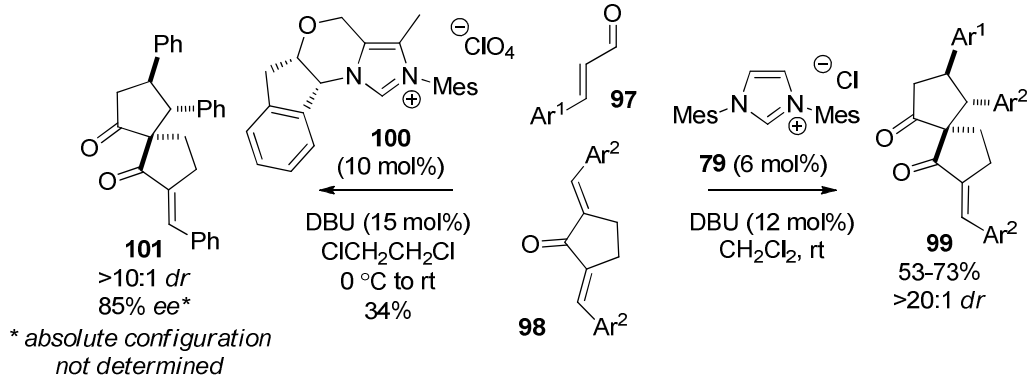


Figure 22: Spirocyclopentanone formation

A formal [3+2] cycloaddition reaction with homoenolates has also been realised with nitrogen-based electrophiles. Scheidt and Chan have shown that pyrazolidinones **104** can be

prepared from enals **27** and acyldiazenes **102**.[59] An example of the asymmetric variant demonstrates excellent levels of enantioselectivity in this reaction (90% *ee*) (Figure 23).

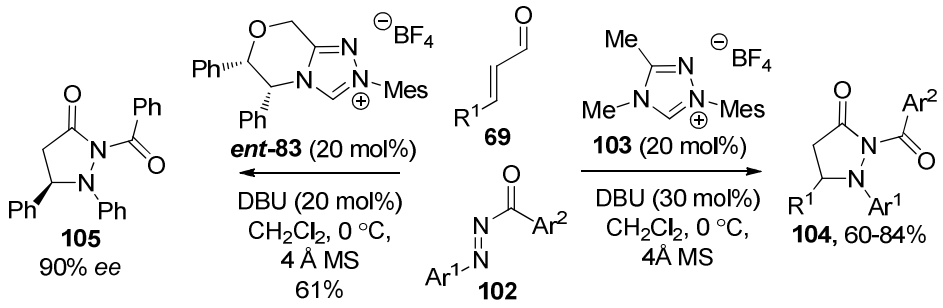


Figure 23: Pyrazolidinone formation

Section 1.6.2.2c: Homoenolate protonation

The β-protonation of homoenolates has been observed by Scheidt and co-workers, resulting in a redox transformation of enals **106** to afford saturated esters **109**. This process is catalysed by the NHC derived from imidazolium salt **107** and utilises phenol as a proton source.[60] A range of primary and secondary alcohols, and phenol itself, are competent nucleophiles with which to trap the acylazolium intermediate **108** generated upon protonation (Figure 24).

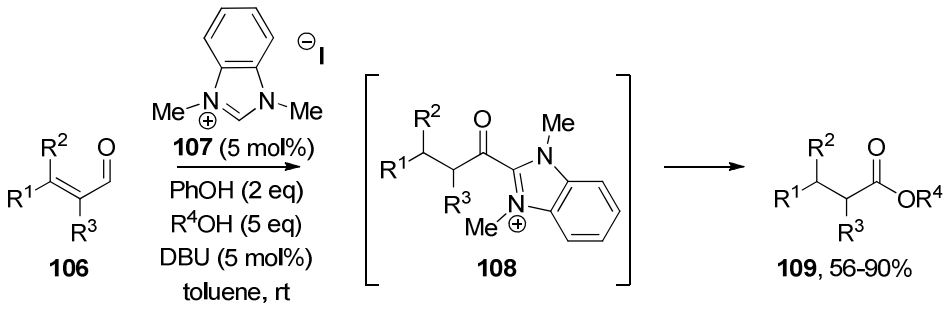
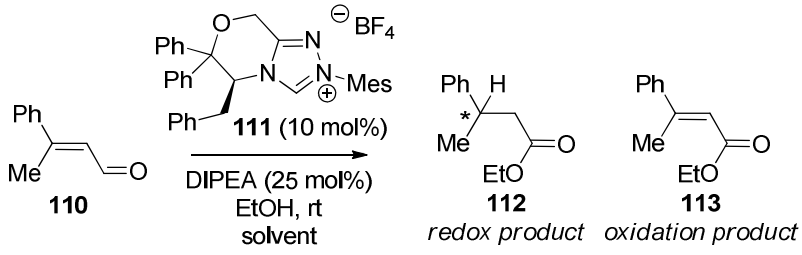


Figure 24: Redox reaction of enals to saturated esters

In addition to the use of homoenolates to access C-C or C-heteroatom bond formation, Scheidt and co-workers have investigated enantioselective homoenolate protonation using chiral triazolium salt **111** as the NHC precatalyst. Moderate but similar levels of enantioselectivity are observed in both polar and non-polar solvents, though a competing *in situ* oxidation process is more pronounced in THF than in toluene (Figure 25).[61]



solvent	redox:oxidation product ratio	% yield (combined)	% *ee*
THF	3:1	58	55
toluene	13:1	81	53

Figure 25: Enantioselective homoenolate protonation *vs* oxidation

NHC-Catalysed homoenolate generation has been applied by Bode and Struble in the formal synthesis of the natural product salinosporamide A.[62] The key step in the synthesis is a late-stage NHC-catalysed intramolecular lactonisation. With an achiral triazolium-derived NHC, a 4:1 diastereomeric ratio of products was obtained in preference for the *undesired* product **116**. To suppress this, chiral triazolium salt ***ent*-76** was employed, giving an approximately 1:1 mixture of desired:undesired diastereomers (Figure 26).

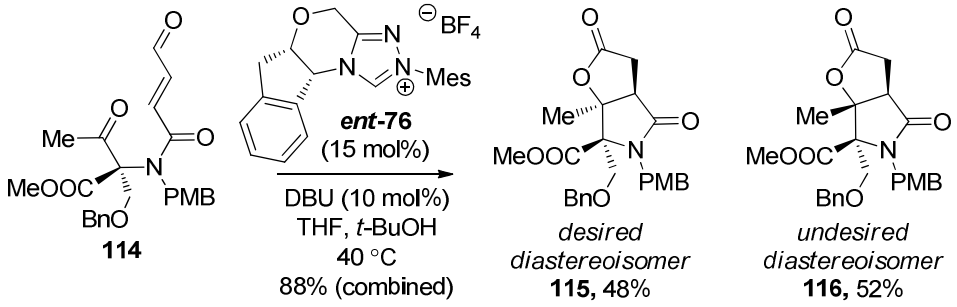


Figure 26: Homoenolate methodology in natural product synthesis

Section 1.6.2.2d: α-Hydroxyenones as homoenolate surrogates

Whilst enals can be used as homoenolate equivalents, these substrates have significant synthetic drawbacks: they suffer from aerobic instability, generally require multi-step synthesis, and competitive benzoin dimerisation is often an issue. Bode and co-workers have addressed these issues by employing air-stable, crystalline α-hydroxyenones **117** as homoenolate surrogates, which can be prepared readily from commercially available 3-hydroxy-3-methylbutanone and the requisite aldehyde in one step.[63] Significantly, these species are unable to participate in benzoin dimerisation. Upon treatment of the α-hydroxyenone **117** with an NHC, the intermediate hydroxyazolium **119** undergoes a retro-benzoin reaction, liberating acetone and the homoenolate equivalent **61** (Figure 27). Interestingly, whilst practical to prepare and handle, the relative reactivity of these α-hydroxyenones is significantly reduced in comparison with their enal

counterparts. Competition experiments show that hydroxyenones are ~5–6 times less reactive than the corresponding enals in cyclopentene formation.

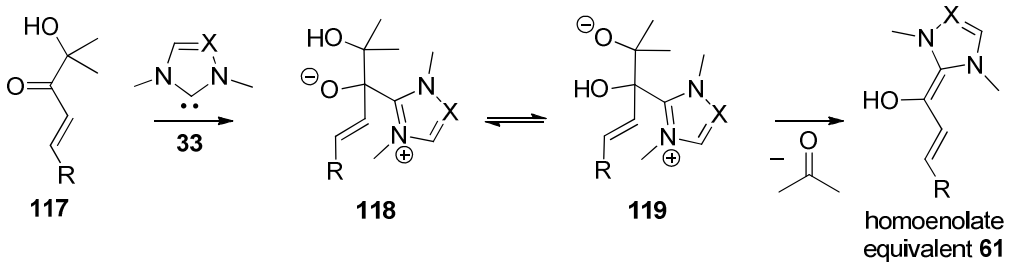


Figure 27: Generation of homoenolate equivalent from α-hydroxyenones

Bode and co-workers have demonstrated the application of such substrates in a number of reactions, including cyclopentene ring formation, amidation and γ-lactamisation.[64] For example, cyclopentene **126** is obtained using enone **125** with good levels of both diastereoselectivity and enantioselectivity but in only moderate yield,[63] and γ-lactamisation with saccharin-derived sulfonylimines **122** has been achieved with moderate to excellent stereocontrol (Figure 28).

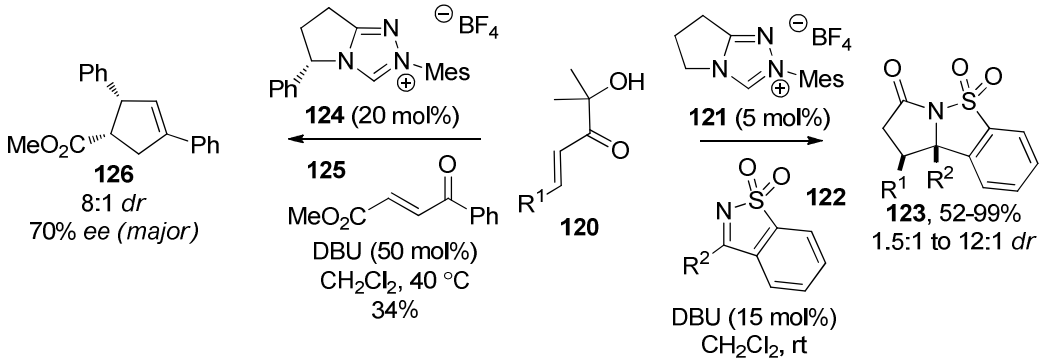


Figure 28: Applications α-hydroxyenones

Section 1.6.2.3: Azolium enolates from ketene activation

Azolium enolates such as **63** can be generated directly through addition of NHCs to symmetrical or unsymmetrical ketenes. For example, we have shown that NHC promoted β-lactam formation from isobutylphenylketene **127** and *N*-tosyl imines **129** proceeds with good yields and moderate levels of diastereoselectivity *via* enolate **131** (Figure 30).[65]

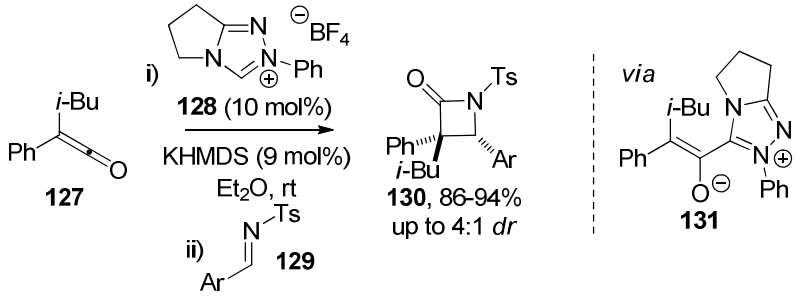


Figure 29: β-Lactam formation promoted by NHCs

Applications of this methodology using chiral NHCs were independently investigated by the Ye and Smith groups for the asymmetric synthesis of β-lactams. Ye and co-workers showed that the pyroglutamic acid derived NHC precatalyst **134** gave good diastereocontrol (up to 99:1 *dr*) and excellent levels of enantiocontrol (up to 99% *ee*) for the preparation of β-lactams **135** using a range of unsymmetrical alkylarylketenes **132** and *N*-Boc imines **133**.[66] We showed that good catalytic activity and good levels of enantioselectivity (up to 74% *ee*) could be observed in the reaction of diphenylketene **136** with *N*-tosyl imines **129** employing the NHCs from either triazolium or imidazolidinium precatalysts **137** or **138**, with crystallisation generating products **139** with excellent *ee* (up to >99% *ee*, Figure 30).[65]

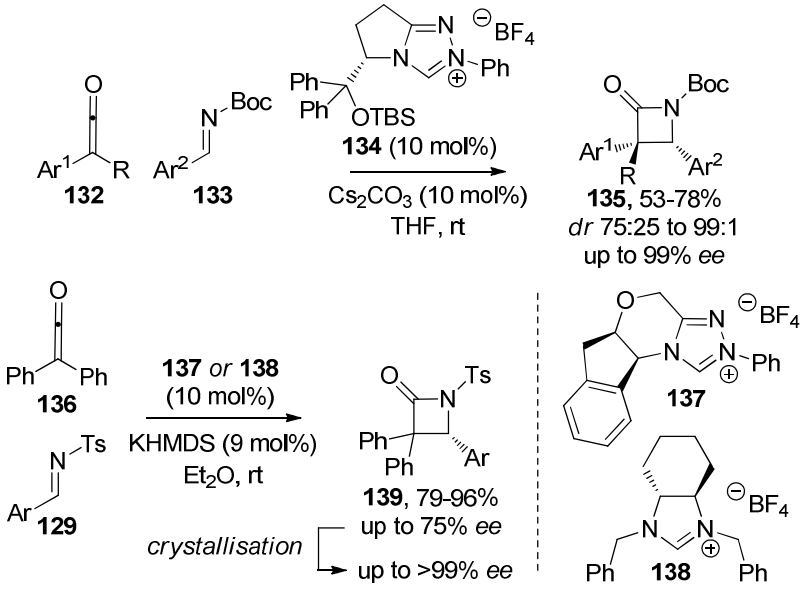


Figure 30: Asymmetric β-lactam synthesis using chiral NHCs

Ye and co-workers have extended this methodology to a range of enantioselective formal [2+2] and [4+2] cycloaddition processes involving unsymmetrical ketenes and a range of electrophiles. All of these processes utilise structurally related NHCs derived from pyroglutamic acid. For example, the formal asymmetric [2+2] reaction of alkylarylketenes **132** with 2-oxoaldehydes **148** generates the corresponding β-lactones **149** with good levels of diastereo- and enantiocontrol;[67] it is notable that a preference for the *anti*-diastereomer is noted in this reaction, in contrast to the *syn*-stereoisomeric preference in the β-lactam series. This chemistry has been extended to encompass trifluoromethylketones **146**[68] and diazenes **142** and **144** as the electrophile; with diazenes, however, both formal [2+2] and [4+2] cycloaddition processes are possible by changing the nature of the N-substituent of the diazene (Figure 31).[69]

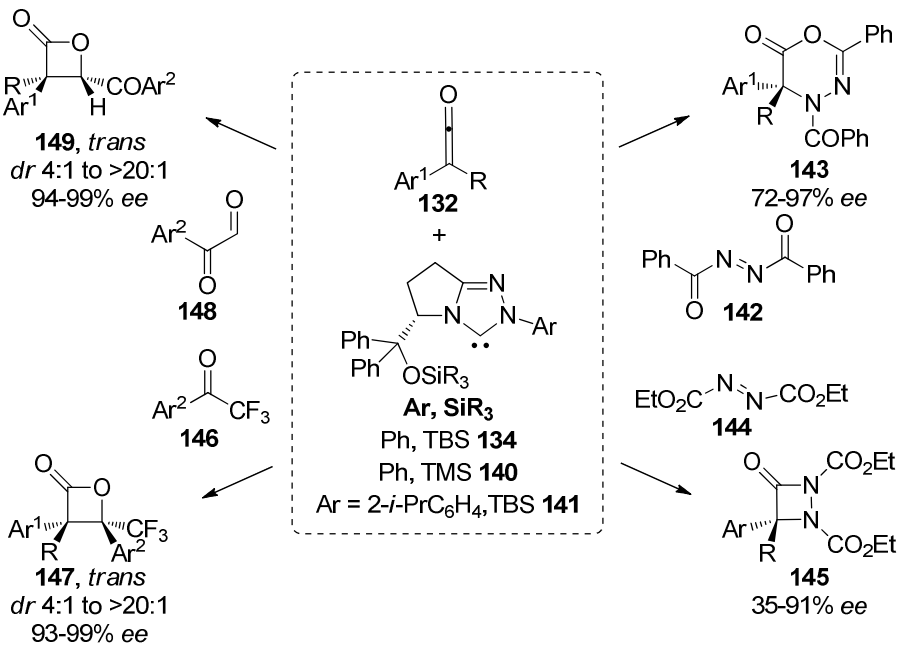


Figure 31: Applications of ketenes in [2+2] and [4+2] cycloadditions

A change in enantioselectivity is observed with variation of the N-substituent of the NHC used to catalyse the [4+2] addition of ketenes and *N*-aryl-*N*-benzoyldiazenes. For example, *N*-phenyl substituted NHC **150** (Ar = Ph) gave (*R*)-**154** in 40% yield and 86% *ee* in the reaction with ethylphenylketene **152** and *N*-phenyl-*N*-benzoyldiazene **153**, whereas *N*-mesityl substituted NHC **151** (Ar = Mes) gave (*S*)-**154** in 76% yield and 96% *ee* (Figure 32).

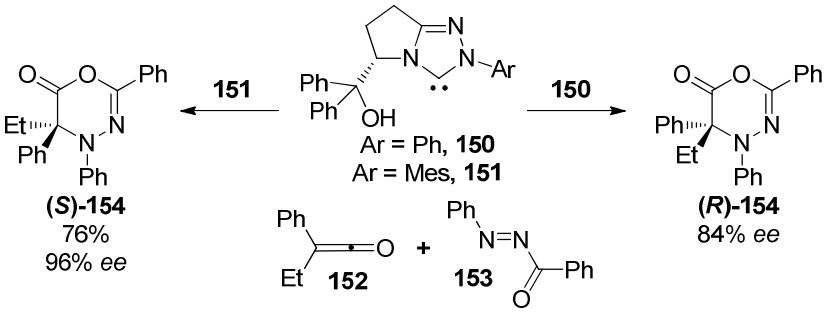


Figure 32: Effect of NHC *N*-aryl substituent on enantioselectivity

Further work by the Ye group has shown that NHCs derived from precatalyst **156** can also promote the asymmetric dimerisation of alkylarylketenes **155** to generate alkylidene β-lactones **157** in good diastereo- and enantioselectivity.[70] The asymmetric [4+2] addition of enones and alkylarylketenes to generate δ-lactones **160** in excellent *ee* has also been accomplished,[71] as has the asymmetric esterification of alkylarylketenes to give esters **162** using benzhydrol **161**, which is assumed to proceed *via* a Lewis-base mediated mechanism (Figure 33).[72]

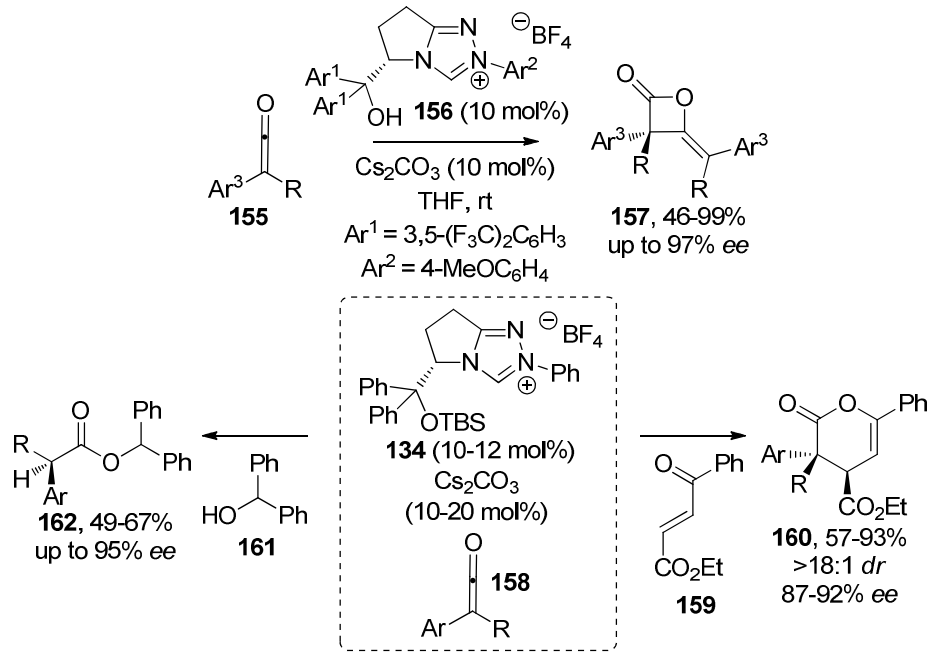


Figure 33: Further applications of ketenes as enolate equivalents

Within the latter area, we have also shown that asymmetric NHC promoted esterifications of alkylarylketenes **158** can also be achieved with 2-phenylphenol **163**, using the oxazolidinone derived triazolium precatalyst **164** (up to 84% *ee*) (Figure 34).[73]

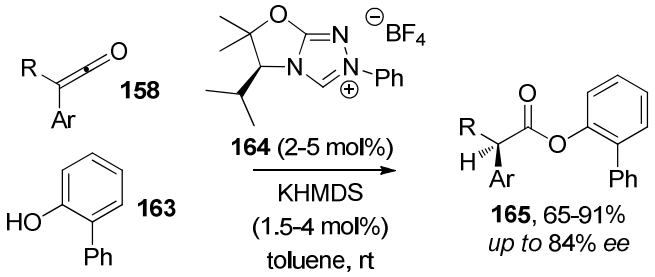


Figure 34: Asymmetric esterification of ketenes with 2-phenylphenol

Section 1.6.2.4: Azolium enolates from α-functionalised aldehydes

Whilst the addition of a NHC to a ketene generates an azolium enolate directly, a number of strategies have been developed that allow asymmetric reactions to proceed *via* an enol or enolate intermediate starting from α-functionalised aldehydes. For example, Rovis and co-workers have shown that chiral azolium enolate species can be generated from α,α-dihaloaldehydes **166**, with enantioselective protonation and subsequent esterification generating α-chloroesters **168** in excellent *ee* (84–93% *ee*). Notably, in this process a bulky acidic phenol **167** is used as a buffer alongside an excess of an alternative phenolic component to minimise product epimerisation. This transformation is thought to proceed *via* an azolium enolate **169** and subsequent

protonation/phenoxide trapping (Figure 35). An extension of this approach allows the synthesis of enantiomerically enriched α-chloroamides (80% *ee*).[74]

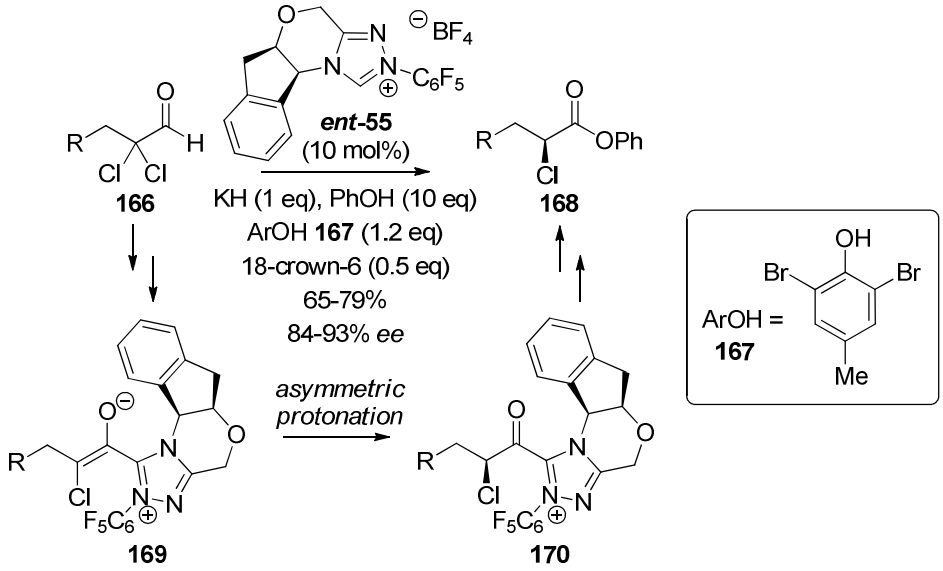


Figure 35: Asymmetric protodehalogenation

Bode and co-workers have used the NHC derived from precatalyst **171** to generate an enolate **172** from a range of enals **69**, with subsequent hetero-Diels-Alder type reaction with an α,β-unsaturated imine **173** generating dihydropyridinones **174** in excellent diastereo- and enantioselectivities (Figure 36).[75] This methodology has recently been applied to the synthesis of 3,4-dihydropyranones in high *ee*, with a stepwise, rather than a concerted, process thought to be operating.[76]

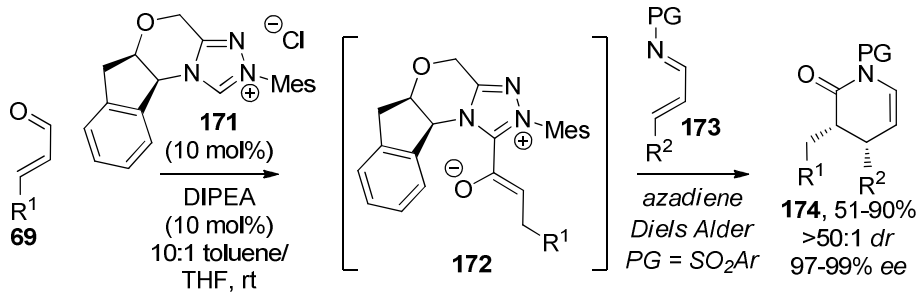


Figure 36: Asymmetric dihydropyridone formation

Further studies by Bode and co-workers have shown that enolate formation from α-chloroaldehydes **175** and subsequent reaction with 4-oxo-enoates or unsaturated α-ketoesters **176** generates dihydropyranones **177** in excellent diastereo- and enantioselectivities, and with impressively low catalyst loadings.[77] This work has been extended to the generation of enolate equivalents from bisulfite adducts of α-haloaldehydes **178** under aqueous conditions (Figure 37).[78]

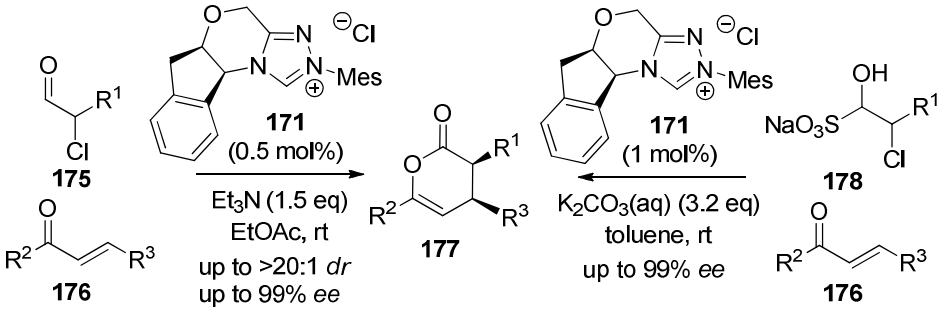


Figure 37: Asymmetric dihydropyranone formation

Formation of the enolate equivalent from enals with the NHC derived from **171**, followed by an intramolecular Michael reaction and *O*-acylation, gives the lactone products **180**. These products are readily opened by either alcohols or amines to generate functionalised cyclopentane derivatives **181** in excellent *ee*. This reaction is equally amenable to enals with both aliphatic and aromatic β-substituents, although the formation of substituted cyclohexanes (from analogous enals) proceeds with reduced enantioselectivity (Figure 38).[79] The same reaction is also promoted by camphor-derived triazolium salts in high *ee*.[80]

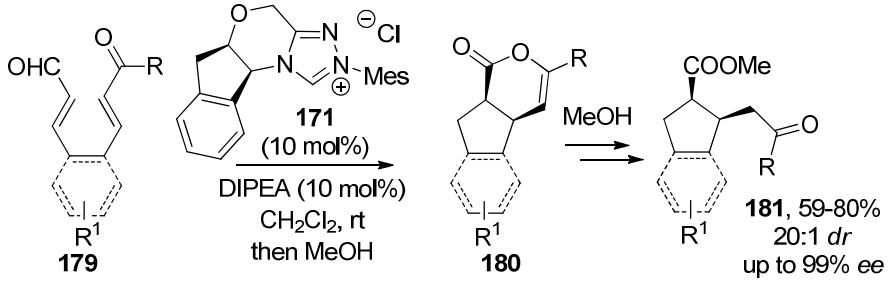


Figure 38: Intramolecular Michael reactions

Scheidt and co-workers have generated functionalised cyclopentenes **184** in high *ee* by desymmetrisation of substrates such as **182** (Figure 39).[81] NHC-Promoted enolate formation from an enal, followed by a desymmetrising aldol event, generates β-lactones **183**, and subsequent loss of CO_2 affords the cyclopentene product **184**; with acyclic diketones, the β-lactones are formed with the R^1 group *anti-* to the tertiary alkoxide, while with cyclic diketones, the β-lactone products have the R^1 group with a *syn*-stereochemical relationship to the alkoxide.[82]

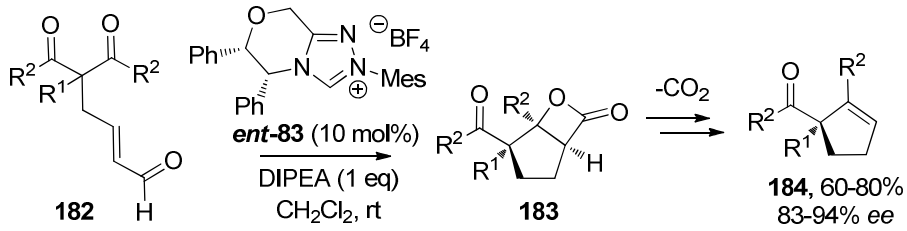


Figure 39: Desymmetrisation of 1,3-diketones

Section 1.6.2.5: Generation of acylazoliums (a^1 synthons)

Section 1.6.2.5a: Transesterification

Acylazolium species can be prepared through a number of discrete reaction pathways. The first catalytic reactions that proceed through such an intermediate were the transesterification processes published independently by the Nolan[83] and Hedrick groups (Figure 40).[84,85] This work has been extended to transesterification with secondary alcohols,[86] and of phosphonate esters.[87] Movassaghi and co-workers have demonstrated that NHCs effectively catalyse the amidation of esters with amino alcohols. An alternative mechanism involving the NHC acting as a Brønsted base has been proposed, resulting in nucleophilic activation of the alcohol for an initial transesterification event, followed by rapid *O*- to *N*-acyl transfer.[88,89]

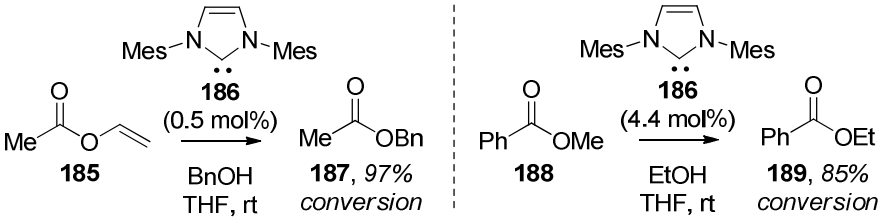


Figure 40: Acyl transfer using NHCs

This concept has been extended to the use of enantiomerically pure NHCs to facilitate asymmetric *O*-acylations. For example, Marouka and co-workers have employed chiral C_2-symmetric imidazolium salt **191** and a hindered enol ester to achieve excellent levels of enantioselectivity (*s* values up to 80) in the kinetic resolutions of alkyl-aryl carbinols **190** (Figure 41).[90] Related work by Suzuki and co-workers has shown that good selectivity (*s* values up to 37) in the kinetic resolution of 2-naphthylethanol can be achieved using a related imidazolium salt as a precatalyst and vinyl acetate as the acyl donor.[91]

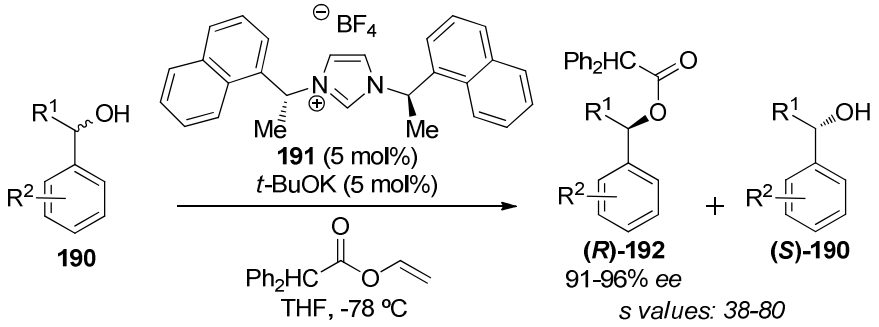


Figure 41: Kinetic resolution of alkyl-aryl alcohols

Section 1.6.2.5b: Enol to acylazolium tautomerisation - Redox transformations

A range of α-functionalised aldehydes generate acylazoliums *via* the corresponding enol intermediate. Presumably, addition of an NHC to an α-haloaldehyde **193** generates the Breslow

species **195**, with elimination of HX affording the enol **196**. Subsequent *in situ* tautomerisation generates the acylazolium species **197** that can be trapped by a nucleophile to afford the product **198** that has formally undergone a redox reaction (Figure 42).

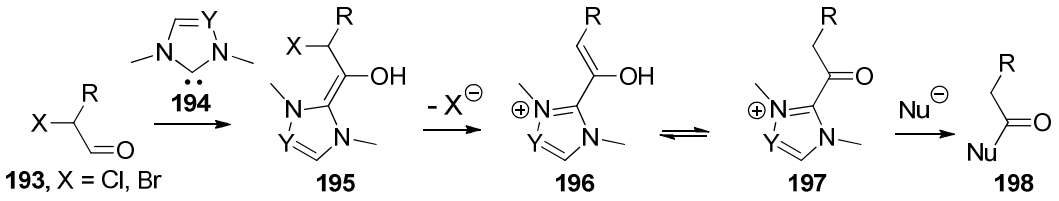


Figure 42: Redox reactions with α-haloaldehydes

This approach has been applied by Rovis and co-workers to the formation of saturated esters from α-haloaldehydes and alcohols. A range of alcohols is tolerated, including isopropanol, cyclohexanol and phenol, and aniline proved a competent nucleophile to prepare anilides (Figure 43).[92]

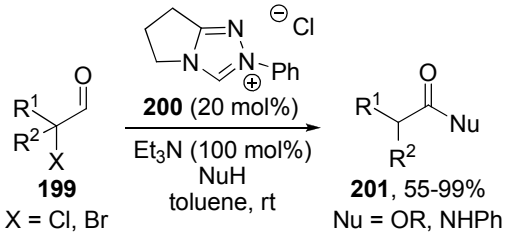


Figure 43: Acyl transfer using α-haloaldehydes

A conceptually similar protocol was reported simultaneously by Bode and co-workers, employing α,β-epoxyaldehydes **202** as acylazolium precursors (Figure 44). With these substrates, good levels of diastereoselectivity for the β-hydroxyester products **204** are obtained resulting from stereoselective protonation of the enol intermediate.[93] A related ring opening reaction catalysed by NHCs was subsequently reported, using chiral formylketocyclopropanes.[94]

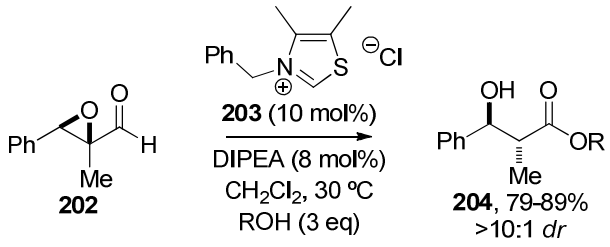


Figure 44: Other representative redox transformation

Related redox transformations allow the conversion of ynals to α,β-unsaturated esters,[95] as well as the ring expansion of formyl β-lactams,[96] oxacycloalkane-2-carboxaldehydes,[97] and 2-acyl-1-formylcyclopropanes.[98] Further developments allow the synthesis of amides from enals,

α-chloro or α,α-dichloroaldehydes, α,β-epoxy or aziridinoaldehydes and formyl-cyclopropanes, but require an additive, such as imidazole, HOAt or HOBt to allow efficient amidation.[99]

As an extension of their redox transformations, Rovis and co-workers have used α-haloaldehyde **205** to generate a chiral acylazolium species with the NHC derived from precatalyst **207**, allowing desymmetrisation of *meso*-diol **206** in good yield and enantioselectivity (Figure 45).[92]

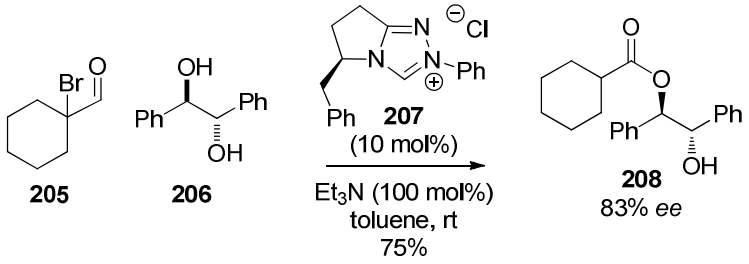


Figure 45: Desymmetrisation using α-haloaldehydes

Section 1.6.2.6: Miscellaneous asymmetric reactions

Bode and He have shown that chalcone-derived (acyclic) α,β-unsaturated sulfonylketimines **209** can act as competent electrophiles with enals **16**, giving highly enantioenriched β-lactam products **210**.[100] The scope and generality of the reaction has been widely examined and a range of enals **16** and sulfonylketimines **209** are tolerated. Notably, alkyl-substituted enals, acrolein and 3,3-dimethylacrolein are all suitable substrates, all giving excellent levels of enantio- and diastereoselectivity, although the acroleins give only moderate yields (45–50%) (Figure 46). Notably, this reaction follows a different pathway to the related work by the same authors using sulfonylaldimines **172**, which give rise to dihydropyridone products **173**.

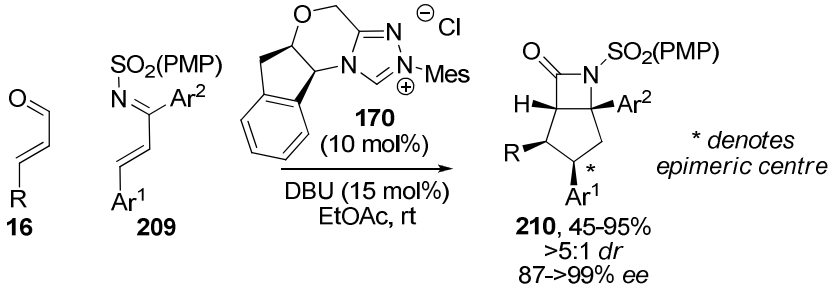


Figure 46: Enantioselective γ-lactamisation

Related work by Nair and co-workers (using enones in place of α,β-unsaturated sulfonylimines (see page 14), generates β-lactones with *trans*-ring substituents, while the β-lactam products **210** possess a *cis*-stereochemical relationship. A mechanistic rationale for the observed *cis*-selectivity has been proposed based on preorganisation of the Breslow-type intermediate and imine through hydrogen bonding **211**, with an aza-benzoin oxy-Cope process proposed. Reaction *via* a boat transition state delivers the observed *cis*-stereochemistry of the product (Figure 47).

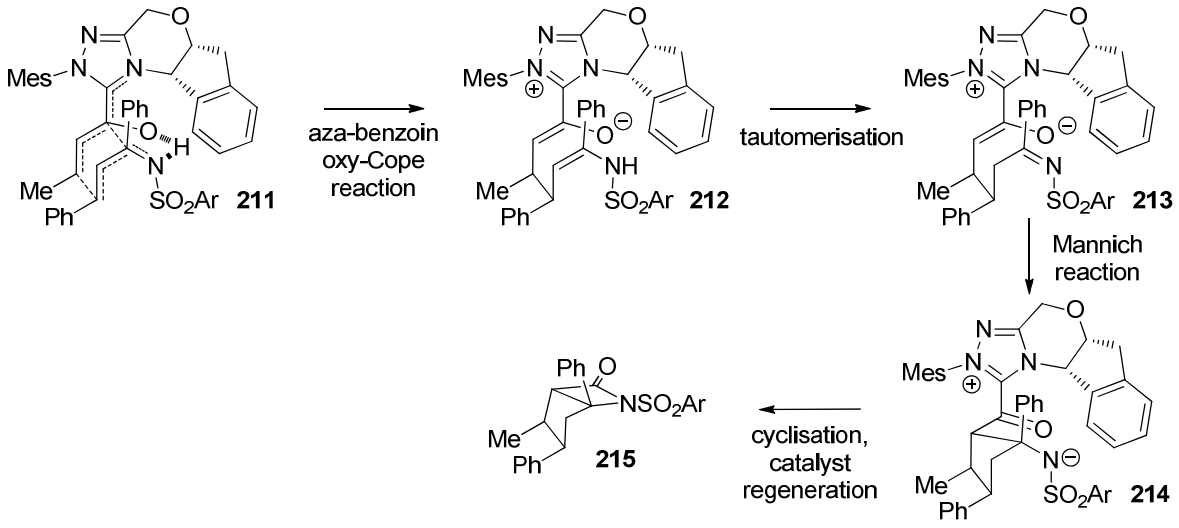


Figure 47: Rationale for enantio- and diastereoselective β-lactam formation

Bode and Kaeobamrung have demonstrated an analogous reaction using α-hydroxyenone **217** as the electrophile.[101] Interestingly, triazolium-derived NHCs give β-lactones **219** and imidazolium-derived NHCs give γ-lactones **218**, both with excellent levels of enantioselectivity. The authors postulate a similar benzoin oxy-Cope mechanism to account for the high level of stereoselectivity in the process. This divergence in behaviour has been attributed to the leaving group ability of the NHC: the triazolinylidene has a significantly lower pK_a than the respective imidazolinylidene, so in the case of the triazolium catalyst, the NHC is a sufficiently good leaving group to afford β-lactones as the major product. In contrast, the intermediate derived from the imidazolium catalyst undergoes preferential alkoxide elimination to afford an acylimidazolium intermediate, which undergoes a retro-aldol–aldol sequence (Figure 48).

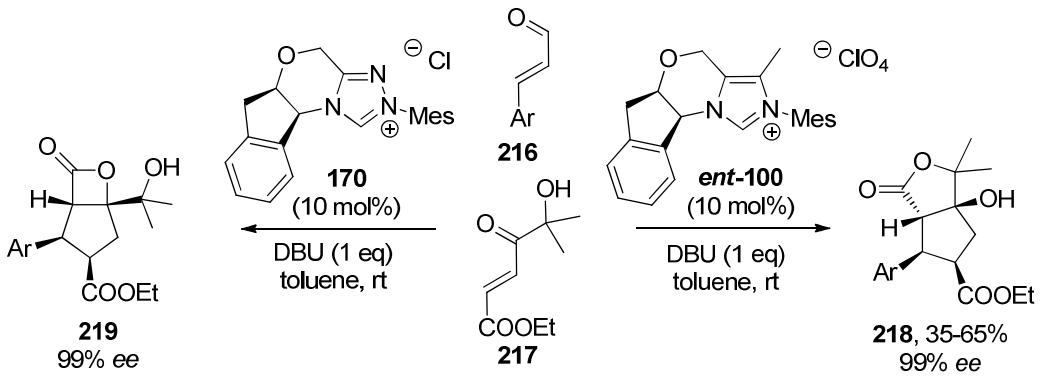


Figure 48: Divergence between triazolium- and imidazolium-derived NHCs in lactone formation with hydroxyenones

Recent developments by Lupton and co-workers have shown alternative uses for NHCs in organocatalysis through trapping of α,β-unsaturated azolium intermediates.[102] Treatment of enol esters **220** with an imidazolium-derived NHC gives pyranones **221** in good yield.

Mechanistically, it is proposed that nucleophilic addition of the NHC to the enol ester generates an α,β-unsaturated azolium intermediate and enolate, which recombine in a conjugate manner to afford pyranones **221**. An enantioselective variant of this reaction has been demonstrated using chiral triazolium salt **55** as the NHC precatalyst, obtaining the product in good yield and 50% *ee* (Figure 49). The intermolecular version of this reaction has also been achieved with TMS enol ethers and α,β-unsaturated acyl fluorides, but not yet in an enantioselective fashion.

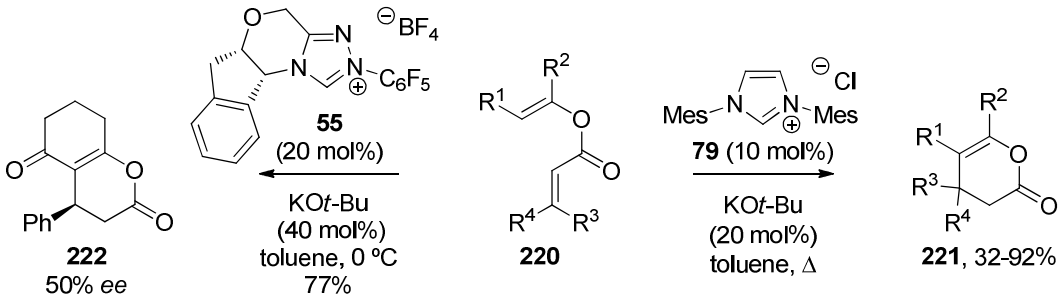


Figure 49: Pyranone formation

Section 1.7: Steglich rearrangement

While many developments have been made in NHC-mediated organocatalysis, their ability to mimic classical Lewis bases, such as the aminopyridine DMAP (4-dimethylaminopyridine), have been relatively less investigated. This thesis sets out to exploit this reactivity, with the goal of extending the substrate scope due to their increased reactivity in comparison with the traditional aminopyridines.

This thesis focuses on the transformation first described by Steglich and Höfle, the rearrangement of oxazolyl esters and carbonates **223** to their *C*-acylazlactone isomers **226** and **227**. This reaction, known as the Steglich rearrangement, was shown to be catalysed by the aminopyridines DMAP **224** and PPY (4-pyrrolidinopyridine) **225**.[103] Variation of the steric and electronic properties of the substrates was investigated, whereby generally the α-carboxyazlactone product **227** is obtained in preference over the γ-carboxyazlactone product **226**. Regioselectivity in this process can be altered by choice of the R^1 and R^2 substituents: if R^1 is highly electron-withdrawing (i.e. CF_3 or 4-$O_2NC_6H_4$), this overrides the general preference for α-carboxylation, thereby giving the γ-carboxyazlactone **226**; furthermore, attempts to perform the rearrangement of the highly sterically encumbered substrate **223** with R^2 = *t*-Bu give rise to the γ-carboxyazlactone **226**, possibly due to the reduced steric interactions in this product in comparison to the α-carboxyazlactone, which would bear vicinal quaternary stereocentres.

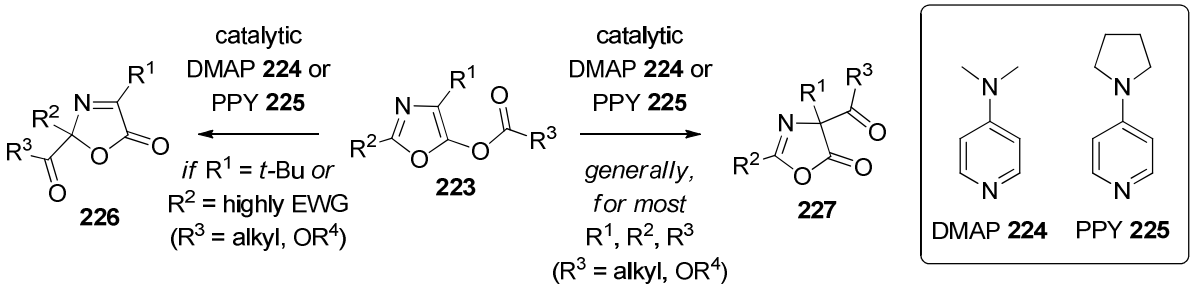


Figure 50: Dearomatisation of oxazolyl esters/carbonates – the Steglich rearrangement

This transformation allows for the catalytic formation of a new quaternary centre, a particular challenge in organic synthesis.[104] The products of the reaction, in particular the *C*-carboxyazlactones, are masked forms of quaternary amino acids, biologically important products.[105] Quaternary amino acids are generally unnatural amino acids, playing a key role in higher order protein structure by giving unique folding to polypeptide structures (such as the Aib-Pro β-turn), and the amino acids have increased chemical and metabolic stability compared to natural amino acids. The azlactone products can be treated with a range of nucleophiles[106,107,108] to give access to highly functionalised products (Figure 51) which can be further elaborated as required.

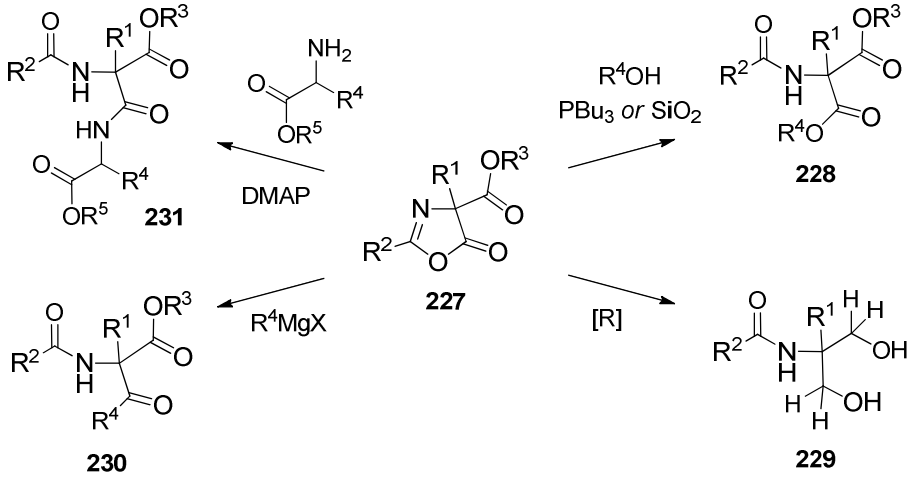


Figure 51: Illustration of product derivatisation

Whilst this transformation has proven highly valuable, there are several drawbacks to the reaction. Reaction times often extend from several hours to days, and the regioselectivity of the reaction is dependent upon both the steric and electronic properties of the 2- and 4- substituents of the oxazolyl framework **223**.

Mechanistically, it has been proposed that both DMAP **224** and PPY **225** act as nucleophilic (Lewis basic) catalysts by attack at the carbonyl of **223**, generating an acyl transfer agent **233** and an aromatic dienolate anion **232** (Figure 52). This dienolate **232** can undergo addition to the

acyl transfer reagent **233** to yield the rearranged isomer **227** (or **226**) with regeneration of the DMAP catalyst **224**.

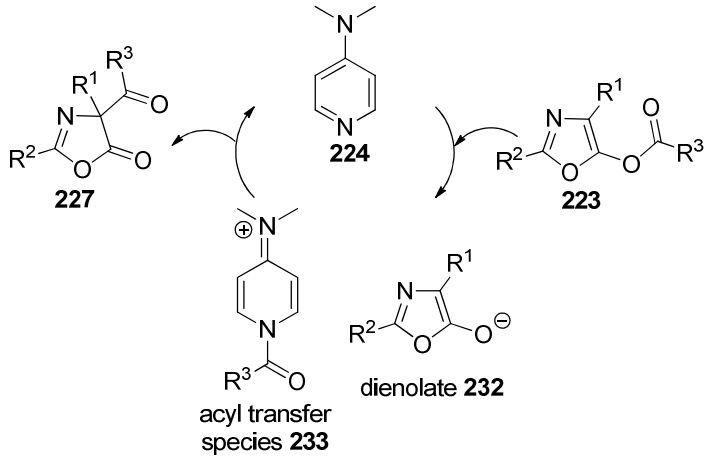


Figure 52: Catalytic cycle of the Steglich rearrangement

As this rearrangement gives rise to the formation of a new stereocentre, there has been significant interest in effecting this transformation asymmetrically, with several publications detailing such efforts.[109] Fu and co-workers published the first enantioselective Steglich rearrangement using a planar-chiral catalyst PPY* **235**, a ferrocene-fused PPY analogue (Figure 53).[106] This catalyst promoted the enantioselective rearrangement of a number of oxazolyl carbonates **234** at low catalyst loadings (typically >2 mol%), but the reaction requires the use of a polar solvent (*tert*-amyl alcohol) and a relatively long reaction time of >6 h. The synthesis of the catalyst **235** also requires numerous steps, including a late-stage resolution to facilitate its preparation in enantiomerically pure form. Importantly, α-branched substitution at C(4) is also not tolerated.

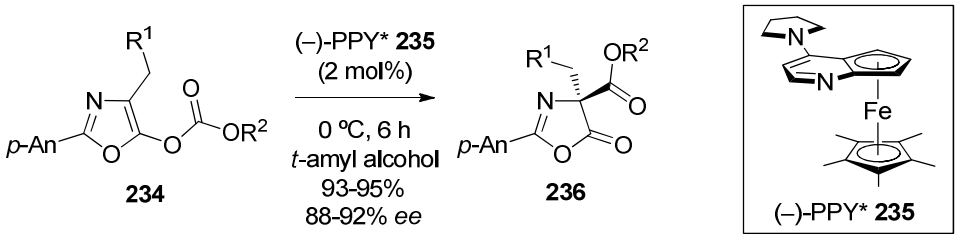


Figure 53: Enantioselective Steglich rearrangement using PPY* (Fu)

Subsequently, Vedejs and co-workers have introduced two new chiral Lewis basic catalysts to perform the Steglich rearrangement enantioselectively. The first is a related aminopyridine TADMAP **238**, based upon the structural core of DMAP but with a proximal stereocentre.[107] The catalytic activity and level of asymmetric induction of **238** is comparable to that published by Fu and co-workers for similar rearrangements (Figure 54). These studies extended the range of

successful rearrangement substrates described by Fu and co-workers, although reaction times remain long, a polar solvent is still required, and α-branched alkyl carbonates are not tolerated.

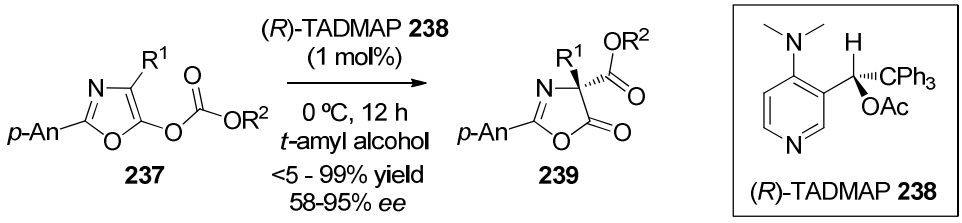


Figure 54: Enantioselective Steglich rearrangement using aminopyridine TADMAP (Vedejs)

The second was the chiral phosphine-based catalyst **240**. Similarly to the results of Fu, the phosphine promoted rearrangement of C(4)-alkyl substituted oxazolyl carbonate substrates **234** in good yield and up to excellent levels of asymmetry, but again, α-branched substituents are not tolerated.

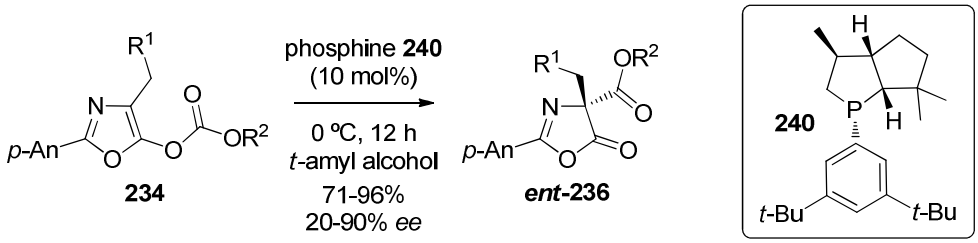
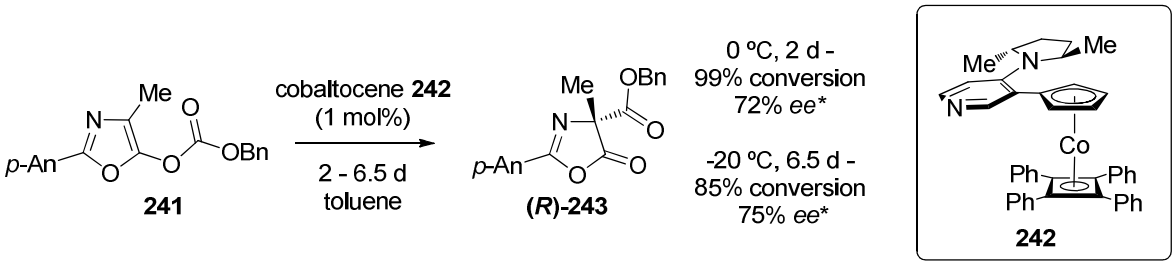


Figure 55: Chiral phosphine-promoted asymmetric Steglich rearrangement

A recent publication by Richards and co-workers utilised chiral relay technology to induce enantioselectivity (Figure 56), with low catalyst loadings of cobaltocene **242** and the use of the non-polar solvent toluene.[108] Extensive reaction times were still necessary and cryogenic incubation at -20 ºC was required to induce higher enantioselectivity, at the expense of decreased product conversion.



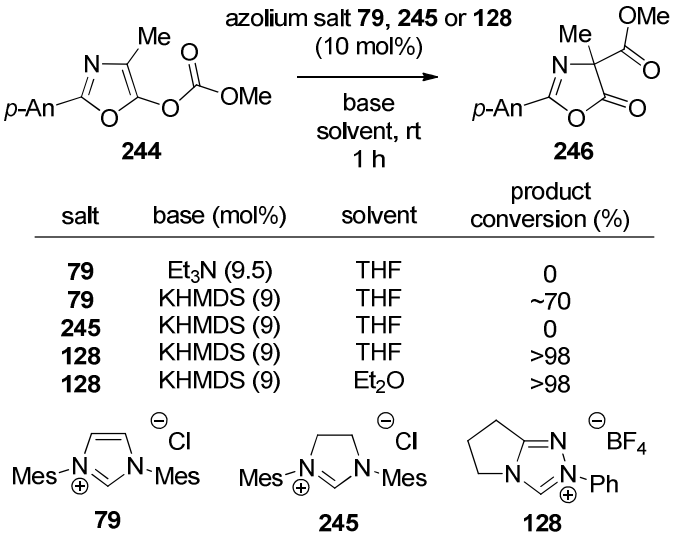
** Determined by methanolysis of the product and analysis by chiral HPLC. Assumed retention of configuration.*

Figure 56: Chiral relay effect to effect enantioselective Steglich rearrangement (Richards)

Section 1.8: Previous work in the Smith group

Preliminary work within the Smith group has utilised achiral NHCs as efficient catalysts to effect the Steglich rearrangement of oxazolyl carbonates.[110] Initial investigation of model substrate **224**

using the NHCs derived from imidazolium salts **79** and **245** showed limited success at effecting the Steglich rearrangement (Figure 57). A vast improvement in the protocol was made by using triazolium salt precatalyst **128** and KHMDS as the base to generate the active NHC; using Et_3N as the base, no product conversion was observed.



salt	base (mol%)	solvent	product conversion (%)
79	Et_3N (9.5)	THF	0
79	KHMDS (9)	THF	~70
245	KHMDS (9)	THF	0
128	KHMDS (9)	THF	>98
128	KHMDS (9)	Et_2O	>98

Figure 57: Initial previous studies of the Steglich rearrangement using NHCs

The generality of this rearrangement protocol was demonstrated by variation of the carbonate functionality with a number of unbranched oxazolyl carbonate substrates, giving the products in generally very good isolated yield (Figure 58).

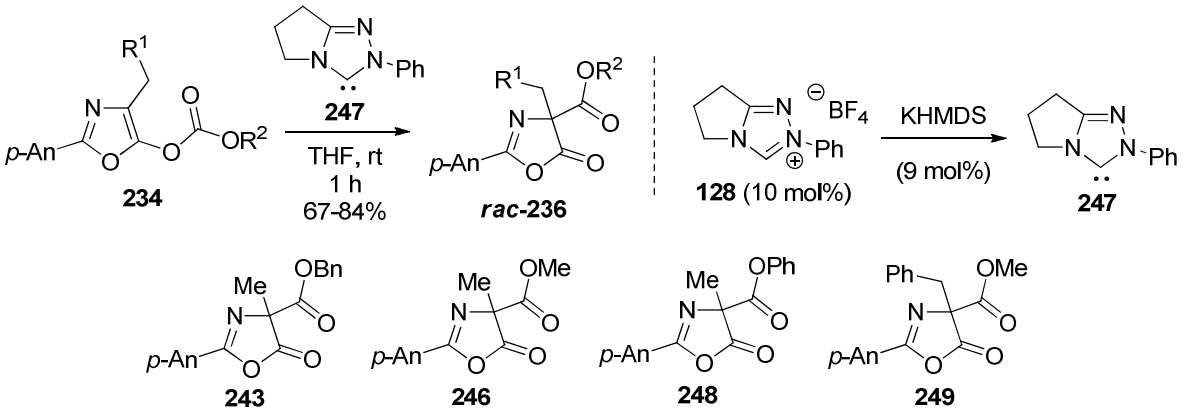


Figure 58: Demonstration of the effectiveness of the NHC in catalysis of the Steglich rearrangement

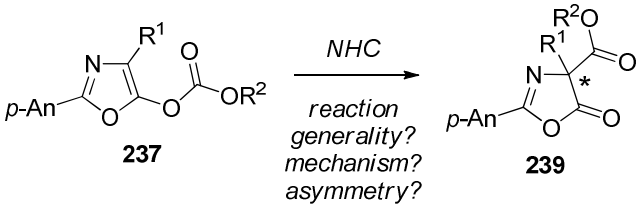
Mechanistically, a similar catalytic cycle to that for DMAP **224** is proposed, supported by studies using crossover experiments. These studies have also shown that the C-C bond formation is irreversible with the rearrangement of oxazolyl carbonates, but full determination of the catalytic cycle was still required.

Section 1.9: Aims and objectives

This work set out to further investigate the use of NHCs as Lewis basic catalysts and efficient carboxyl transfer reagents to effect the Steglich rearrangement.

The first aim of the research was to probe the reactivity of both catalyst and substrate in order to afford an extension to the substrate scope of the rearrangement, with the potential to promote the rearrangement of α-branched substrates. Further to this, a fuller investigation of the mechanism of the rearrangement was sought.

With an understanding of the rearrangement, the enantioselective variant of the Steglich rearrangement was to be investigated, through the design, synthesis and investigation of chiral NHCs, whilst also exploring the potential of the development of new Lewis bases capable of promoting these reactions.

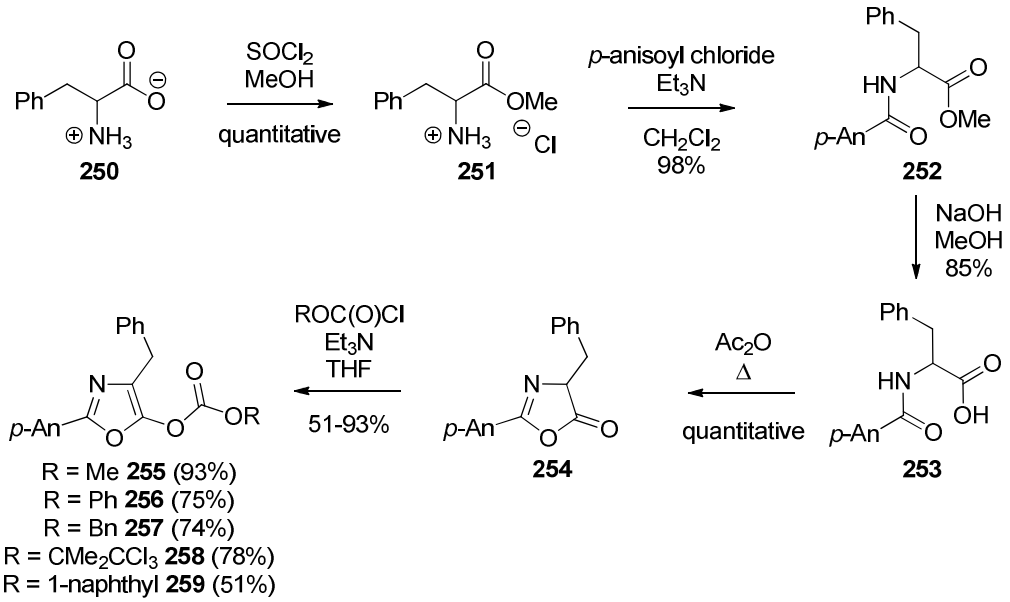


The final aim of this research was to extend the synthetic utility of the Lewis base-promoted rearrangement to other heterocyclic carbonate frameworks.

Chapter 2: Scope and limitations of the Steglich rearrangement

Section 2.1: Preparation of model oxazolyl carbonate substrates

To further extend the scope of the Steglich rearrangement and to gain a greater understanding of the reactivity of the substrates and catalysts, a wide range of oxazolyl carbonate substrates were prepared. The principal substrates chosen for investigation were derivatives of phenylalanine, with differing electronic and steric characteristics, with particular focus on the effect of changing the electronic properties of the carbonate function.[110] The *p*-anisyl aromatic C(2)-substituent was chosen as this was shown to provide highly regioselective α-carboxylation, good levels of stability to the final *C*-carboxyazlactone products, and was also shown to provide the greatest levels of enantioselectivity in the asymmetric rearrangement protocols adopted by Vedejs and Fu. The key intermediate azlactone **254**, the precursor to the carbonate substrates, was ultimately derived from DL-phenylalanine **250** *via* a facile four step procedure in excellent yield (Scheme 1).[106] To investigate the differing effects of the carbonate function, a range of carbonates **255**–**259** was prepared with the respective chloroformate and Et_3N in reproducibly good to excellent yield. Under the reaction conditions, exclusive *O*-carboxylation was observed, with no direct *C*-carboxylation detected spectroscopically.

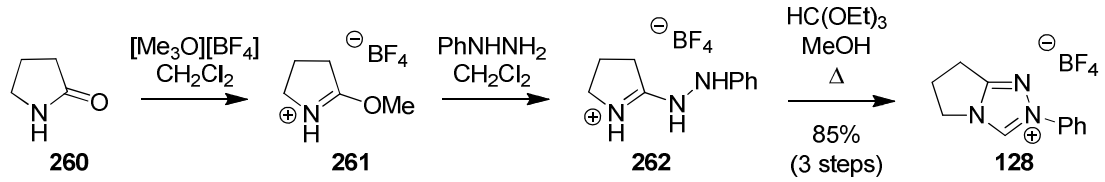


Scheme 1: Conversion of DL-phenylalanine to oxazolyl carbonates

Section 2.2: Synthesis of azolium salt precatalysts

To reaffirm the suitability of NHCs to promote the Steglich rearrangement, triazolium salt **128** was prepared according to literature precedent,[110] *via* a three step protocol from lactam **260** (Scheme 2). This standard protocol, originally described by Rovis and co-workers, began from a key amide substrate: γ-butyrolactam **260** was treated with Meerwein's salt to obtain the methylamidate salt **261** and then treated directly with the requisite arylhydrazine, in this case

phenylhydrazine, to afford the hydrazone hydrotetrafluoroborate salt **262**. Final cyclisation with triethyl orthoformate in methanol at reflux afforded the desired triazolium salt **128** in excellent yield over the three steps.



Scheme 2: Synthesis of the triazolium salt precatalyst

To determine if other NHCs could promote the rearrangement, a selection of azolium salts from a range of precatalyst classes, namely, thiazolium, imidazolium and imidazolinium salts, were prepared and investigated. A simple thiazolium salt **203** was prepared from the commercially available 4,5-dimethylthiazole **263** and benzyl chloride in good yield (Figure 59).

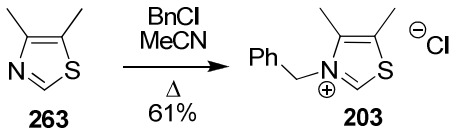


Figure 59: Synthesis of related thiazolium salt **203**

The imidazolium and imidazolinium salts IMes HCl **79** and SIMes HCl **245** are commercially available, but to determine the effect that the counterion of the azolium salt has upon the Steglich rearrangement, the related imidazolium tetrafluoroborate **265** (IMes HBF_4) was prepared. This was prepared from mesitidine **264**, glyoxal, paraformaldehyde and aqueous tetrafluoroboric acid in a one-pot procedure (Figure 60).

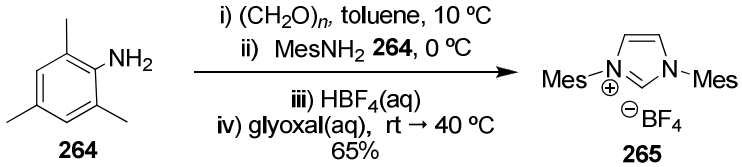


Figure 60: Preparation of IMes HBF_4

Section 2.3: Examination of NHC catalyst classes

With the required substrates and catalysts in hand, a full investigation of the rearrangement protocol was undertaken, with the aim to better understand the behaviours of the catalysts and substrates. It was envisaged that the results of the study would prove useful in identifying the requirements for successful rearrangement, and thus give an insight into understanding the reaction.

Phenylalanine-derived phenyl carbonate **256** was chosen as the model substrate and was investigated, using KHMDS as the base, in order to determine a reactivity profile (Figure 61, Table 1). The triazolium-derived NHC **247** successfully promoted complete rearrangement of the phenylalanine-derived phenyl carbonate **256** to its *C*-carboxyazlactone product **266**. Thiazolium salts **203** and the commercially available **267** were ineffective at promoting rearrangement, but that imidazolium salts **79** and **245** were more effective. It appeared that the nature of the counterion may also play a role, with IMes HBF_4 **265** giving significantly less product conversion than with the related chloride salt **79**. Although these imidazolium-derived NHCs promoted the rearrangement, the reaction mixture was generally contaminated with several side-products, of which the decarboxylated product, azlactone **254**, was identified. These results are in contrast with those described in the original publication (see Figure 57, page 32), in which only the triazolium-derived NHC **247** proved effective in promoting full rearrangement of the alanine-derived methyl carbonate **244**. Imidazolium-derived NHCs promoted only high levels of rearrangement of the (phenylalanine-derived) phenyl carbonate **256**.

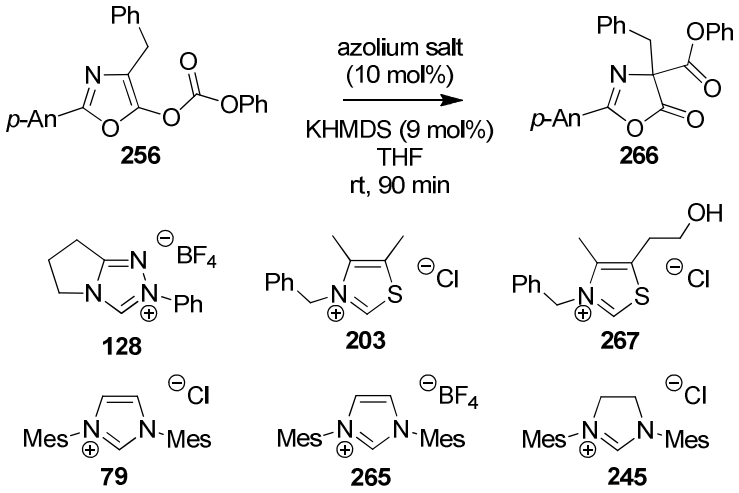


Figure 61: Rearrangement screen with the different azolium salt classes

Precatalyst	Conversion (%) [a]	Isolated yield (%) [b]
128	>98	80
203	11	-
267	<5	-
79	>90	68
265	~40	-
245	>90	-

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Isolated yield of homogeneous product following chromatographic purification

Table 1: Evaluation of NHC catalyst classes

In order to investigate if this difference was due to the nature of the carbonate, the related phenylalanine-derived methyl carbonate **255** was evaluated using a range of azolium-derived NHCs (Figure 62, Table 2). Consistent with the results obtained in the original publication and those with the phenyl carbonate, the triazolium-derived NHC **247** proved highly effective in promoting rearrangement of the methyl carbonate **255**. The imidazolium and imidazolinium salts **79** and **245** also proved much less effective, with only IMes promoting appreciable rearrangement. Intuitively, this striking difference in chemoselectivity between the phenyl and methyl carbonates could be attributed primarily to the difference in electrophilicity of the carbonyls, as the phenyl carbonate would be expected to be more electrophilic than the methyl carbonate. The reactivity difference between different carbonates will be addressed in subsequent discussions throughout the thesis.

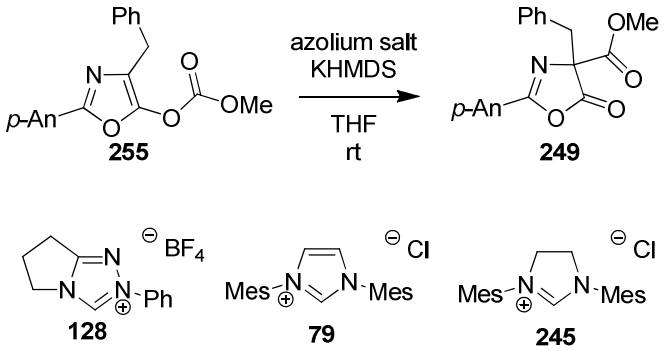


Figure 62: Screening of the methyl carbonate **255**

Precatalyst (mol%)	KHMDS (mol%)	Time (min)	Conversion (%) [a]
128 (10)	9	90	>98 (76) [b]
128 (5)	4.5	90	>98
128 (1)	0.9	90	>98
128 (1)	0.9	5	>98
79 (10)	9	90	~75 (68) [b]
245 (10)	9	90	<5

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Isolated yield of homogeneous product following chromatographic purification

Table 2: Screening of methyl carbonate **255** with NHCs

Section 2.4: Optimisation of the NHC-promoted Steglich rearrangement protocol

Section 2.4.1: Investigation of catalyst loading and *N*-aryl substituent

Returning to the model oxazolyl phenyl carbonate **256**, a range of *N*-aryl substituted triazolium salts[i] was screened in order to ascertain the electronic effect of variation of the *N*-aryl substituent,[ii] whilst also investigating reducing the catalyst loading and reaction time (Figure 63, Table 3). All triazolium salts gave successful rearrangement to *C*-carboxyazlactone **266** at low catalyst loadings (all <10 mol%, though generally effective at <1 mol%), and with complete conversion achieved smoothly in <90 min, irrespective of the electron-donating or withdrawing properties of the different aryl substituent.

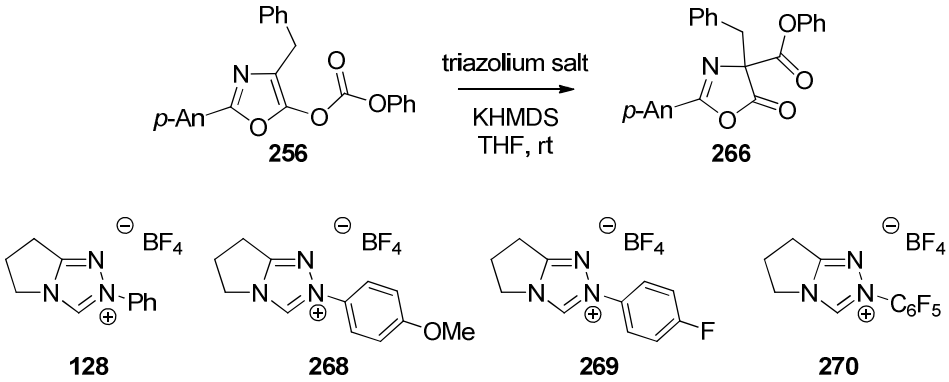


Figure 63: Rearrangement screen with triazolium salts

Precatalyst (mol%)	KHMDS (mol%)	Time (min)	Conversion (%) [a]
128 (10)	9	90	>98 (80) [b]
128 (10)	9	5	>98 (75) [b]
128 (5)	4.5	5	>98
128 (1)	0.9	5	>98 (79) [b]
268 (10)	9	90	>98
268 (1)	0.9	5	>98
269 (10)	9	90	>98
270 (10)	9	90	>98
270 (10)	9	5	>98

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Isolated yield of homogeneous product following chromatographic purification

Table 3: Strong base screen with triazolium salts according to standard protocol with KHMDS in THF

[i] Triazolium salts **268**, **269** and **270** were prepared by other members of the Smith group.
[ii] Several authors have reported that the nature of the *N*-aryl substituent is important in providing the desired reactivity; in many cases, *N*-mesityl substituted triazolium salts provide the desired reactivity whereas the *N*-phenyl substituent provides poor reactivity or leads to by-products.

The related methyl carbonate **255** was examined using several different triazolium salts in order to determine if the nature of the N-substituent was important (Figure 64, Table 4). Triazolium salt **268** also proved highly effective, but changing the *N*-aryl substituent to an electron-deficient pentafluorophenyl moiety (triazolium salt **270**) proved detrimental to the efficacy of the catalyst, only promoting ~65% conversion to *C*-carboxyazlactone **249**.

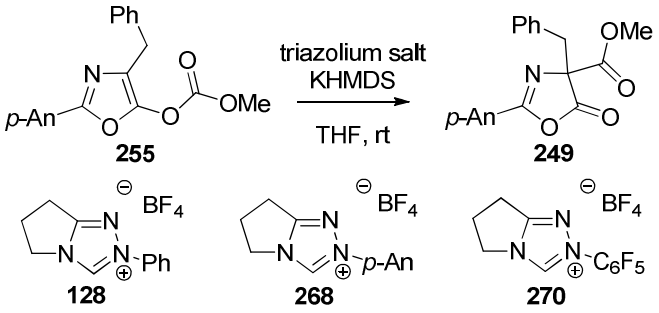


Figure 64: Rearrangement screen with triazolium salts

Precatalyst (mol%)	KHMDS (mol%)	Time (min)	Conversion (%) [a]
128 (10)	9	90	>98 (76) [b]
128 (1)	0.9	5	>98
268 (10)	9	90	>98
268 (1)	0.9	90	>98
270 (10)	9	90	~65

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Isolated yield of homogeneous product following chromatographic purification

Table 4: Comparison of methyl carbonate with different triazolium-derived NHCs

Section 2.4.2: Investigation of NHC concentration

Using the effective triazolium salt **128** as the NHC precursor, an investigation of the NHC concentration was undertaken, in order to assess fully a suitable concentration range with which to perform the rearrangement. Choosing phenylalanine-derived phenyl carbonate **256** as the model substrate, a wide range of concentrations for the reaction was evaluated, following the standard rearrangement protocol developed within the Smith group. Using a precatalyst loading of 10 mol% of triazolium salt **128**, and assuming complete deprotonation using KHMDS, a range of NHC catalyst concentrations from 40 mM to 0.5 mM was examined over the timeframe of 1 h (Figure 65, a Determined by ^{1H} NMR spectroscopic analysis of the crude reaction product

Table 5). The rearrangement of **256** to **266** was shown to be effective at catalyst concentrations greater than 1 mM, but a considerable drop in activity was noted at the lower concentration of 0.5 mM. Therefore, all subsequent operations were performed at an NHC concentration of between 2 and 40 mM.

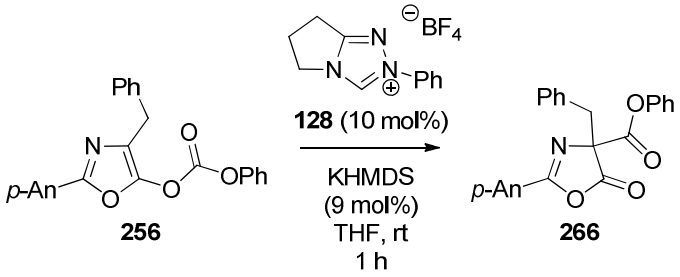


Figure 65: Concentration study for the Steglich rearrangement

Maximum catalyst conc. (mM)	Conversion (%) [a]
40	>98
25	>98
5	>98
1	>98
0.5	15

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

Table 5: Effects of concentration of catalyst on reactivity

Section 2.4.3: Investigation of solvents and alternative strong bases

A range of solvents and strong bases (LiHMDS, *n*-BuLi and NaH) was next evaluated at a range of catalyst loadings, and the reaction progression monitored. Highlighted results of this screen are detailed (Figure 66, Table 6). The rearrangement of the model substrate **256** is highly efficient using a range of strong bases, allowing full rearrangement to occur rapidly (<5 min), even with very low catalyst loadings (<0.5 mol%). A control reaction in dichloromethane confirmed that the active catalytic species was indeed the triazolinylidene **247** and not any potential chlorocarbene generated from deprotonation of the bulk solvent.

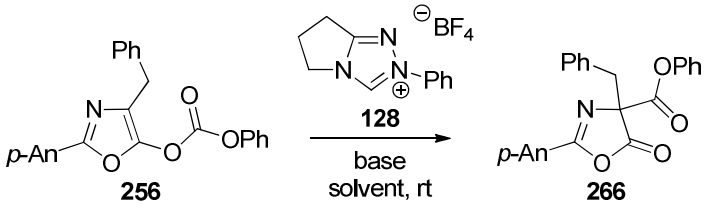


Figure 66: Further screening with a range of solvents and bases

Precatalyst (mol%)	Base (mol%)	Solvent	Time (min)	Conversion (%) [a]
128 (0.5)	KHMDS (0.4)	THF	<5	>98
128 (1)	LiHMDS (0.9)	THF	5	>98
128 (10)	*n*-BuLi (0.9)	THF	5	>98
128 (1)	NaH (9)	THF	5	>98
128 (10)	KHMDS (9)	toluene	60	92
128 (10)	KHMDS (9)	CH_2Cl_2	60	>98
no precatalyst	KHMDS (9)	CH_2Cl_2	60	0

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

Table 6: Results of rearrangement screen with a range of solvents and bases

Section 2.4.4: Scope and limitations

Having developed successful protocols with which to perform the rearrangement, the scope and limitations of the protocol were investigated using the set of phenylalanine-derived carbonates **255**–**259**. Employing typically 1 mol% triazolium salt and KHMDS as the base, all such substrates underwent rapid, complete rearrangement to the desired *C*-carboxyazlactones in reproducibly high isolated yield (75–84%) (Figure 67).

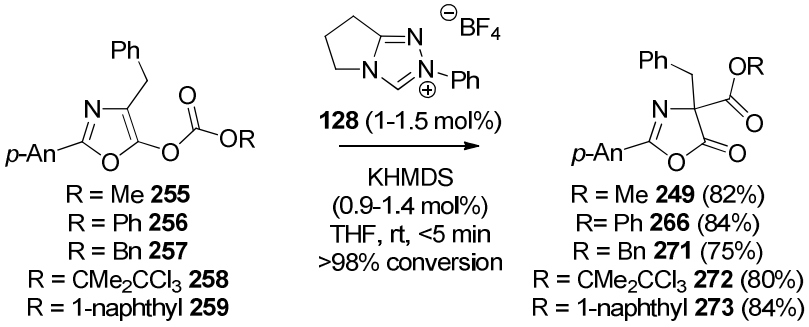
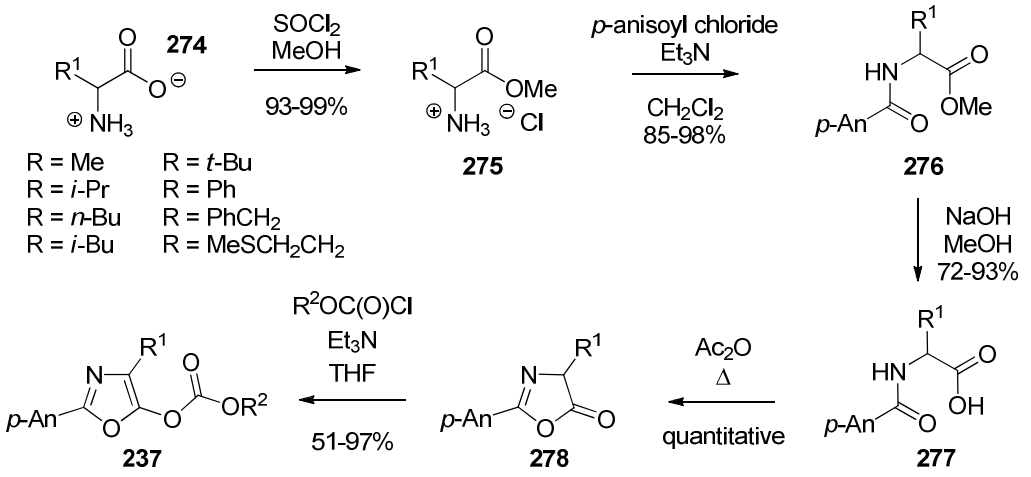


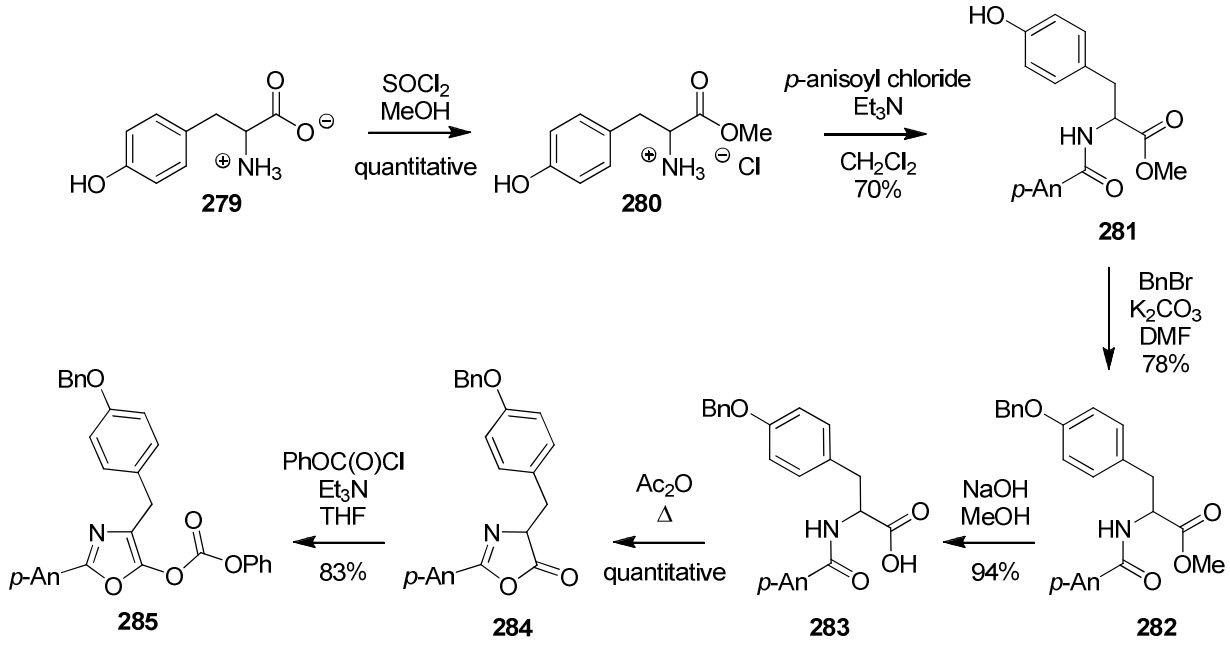
Figure 67: Rearrangement of phenylalanine-derived carbonates

To illustrate the scope and limitations of this NHC-catalysed process, a wide range of oxazolyl carbonate substrates **237** was prepared by variation of the C(4)-substituent. These carbonates were prepared *via* a similar synthetic procedure to that illustrated from phenylalanine, using a number of other commercially available amino acids **274** (Scheme 3). Of particular interest were the derivatives of the more sterically challenging branched amino acids leucine, valine, phenylglycine and *tert*-leucine, known to prove less amenable to rearrangement protocols employing DMAP **224**, the related aminopyridines and chiral phosphine **240**.



Scheme 3: Preparation of a range of other amino acid-derived substrates

Attempts to prepare *O*-protected serine derivatives were unsuccessful due to elimination side-reactions, but phenolic relative **285** was obtained from tyrosine **279** whereby the phenol was *O*-protected (Scheme 4). *O*-Benzylation was achieved by alkylation of the amide intermediate **282** with benzyl bromide in DMF, then converted to the desired phenyl carbonate **285** as described above, in good yield over each step.



Scheme 4: Preparation of the tyrosine-derived substrate

In collaboration with a colleague,[i] all such C(4)-substituted substrates were evaluated in the rearrangement (Figure 68, Table 7). Gratifyingly, all such substrates **237** underwent similarly efficient rearrangement to the *C*-carboxyazlactone, again with typically low catalyst loadings and reaction times (<10 mol%, <1 h). Of particular note is that the sterically challenging branched carbonate substrates **237** (R^1 = *i*-Pr, *i*-Bu, *t*-Bu and Ph) undergo facile rearrangement using

[i] Collaboration with Jennifer Thomson.

triazolium salt **128** but, in contrast to the findings using aminopyridines, only the α-carboxyazlactone product **239** is obtained. These branched substrates, in particular the α-branched valine and *tert*-leucine derived carbonates, have been found to be generally unamenable to rearrangement with other catalysts, and thus the use of triazolium-derived NHCs has provided a significant extension to the reaction scope of oxazolyl carbonate substrates.

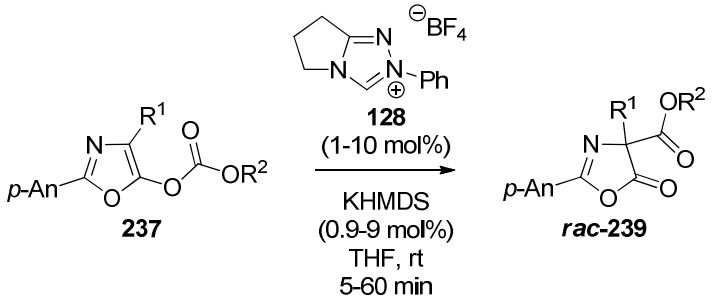


Figure 68: Variation of C(4)-substituent

R^1	R^2	Precatalyst (mol%)	Conversion (%)	Isolated yield (%)
Me	Me	1	>98	84
Me	Ph	1	>98	82
Me	1-naphthyl	1	>98	80
Me	CMe_2CCl_3	1.5	>98	72
Et	Ph	1	>98	75
i-Pr	Ph	1.5	>98	79
n-Bu	Ph	1	>98	74
i-Bu	Ph	1	>98	80
i-Bu	CMe_2CCl_3	1	>98	78
t-Bu	Ph	5	>98	73
Ph	Ph	1.5	>98	81
4-$BnOC_6H_4CH_2$	Ph	1	>98	80
$MeSCH_2CH_2$	Ph	1	>98	82

Table 7: Results of C(4)-variation

Section 2.5: Development of a one-pot protocol

In the rearrangement reaction manifolds, the generation of the NHC is generally achieved by *in situ* deprotonation of the azolium salt with KHMDS over a period of 30 min in order to ensure complete deprotonation. In an effort to further simplify the reaction protocol, generation of the active NHC in the presence of the carbonate substrate was investigated. Cognisant of the recent publication by Wilhelm and co-workers employing KHMDS as a Lewis base catalyst,[111] control reactions showed that KHMDS alone gave little conversion to any products, highlighting the necessity for the NHC as the catalyst. Having established the requirement of the NHC derived

from triazolium salt **128** to effect the catalysis, azolium salt and carbonate were stirred together in a suitable solvent then followed by addition of base (Figure 69, Table 8). Pleasingly, triazolium salts **128**, **268** and **270** all gave clean conversion to the desired *C*-carboxyazlactone product **266**, but imidazolium salts **79** and **245** were also highly effective. Thiazolium salts **203** and **267**, however, were less successful at promoting the rearrangement. These observations further supported the earlier findings, in which the nature of the NHC had a significant bearing on the successful promotion of the rearrangement.

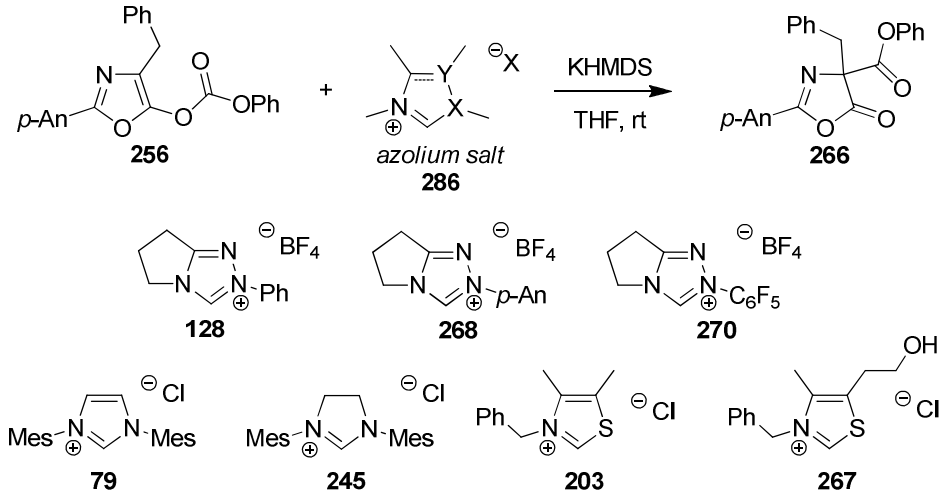


Figure 69: One-pot protocol with phenyl carbonate **256**

Precatalyst (mol%)	KHMDS (mol%)	Time (min)	Conversion (%) [a]
no precatalyst	9	60	<5
128 (10)	9	60	>98 (80) [b]
128 (10)	9	5	>98 (80) [b]
128 (1)	0.9	5	>98
268 (1)	0.9	5	>98
270 (1)	0.9	5	>98
79 (9)	9	60	>95
245 (9)	9	60	>95
203 (9)	9	60	~30
267 (9)	9	60	72

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Isolation of homogenous purified product by chromatography

Table 8: Results of one-pot protocol

To ensure that this one-pot protocol could be applied more generally to other substrates, the same protocol was employed for the rearrangement of other carbonates **237** (Figure 70, Table 9). This alternative procedure proved general, with quantitative conversion achieved at low NHC catalyst loading in <5 min and with consistently very good isolated yield of the *C*-carboxyazlactone products **239**.

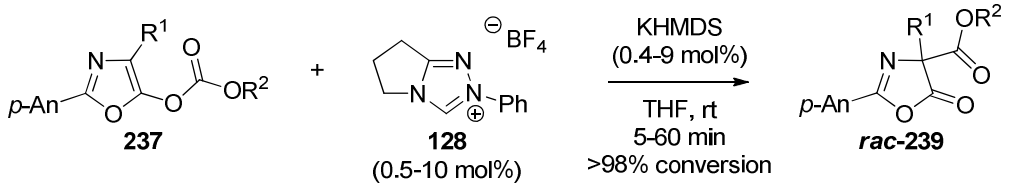


Figure 70: Scope of one-pot protocol

R^1	R^2	Precatalyst (mol%)	Isolated yield (%)
Me	Me	1	72
Me	Ph	1	82
Me	1-naphthyl	1	80
Me	CMe_2CCl_3	1.5	80
Et	Ph	1	78
i-Pr	Ph	1.5	80
n-Bu	Ph	1	78
i-Bu	Ph	1.5	81
i-Bu	CMe_2CCl_3	1	78
t-Bu	Ph	10	70
Ph	Ph	1.5	81
$PhCH_2$	Me	1	82
$PhCH_2$	Ph	0.5	84
$PhCH_2$	Bn	1.5	83
$PhCH_2$	1-naphthyl	1	80
4-$BnOC_6H_4CH_2$	Ph	1	80
$MeSCH_2CH_2$	Ph	1	83

Table 9: Highlighted results of one-pot protocol

As purification of the rearrangement products had previously required chromatographic separation, alternative means to purify the *C*-carboxyazlactone products were investigated. It was envisaged that, with quantitative conversion, the only 'impurities' in the mixture were the presence of ionic species (such as KBF_4 and the azolium salt), the protonated base and potentially the free NHC. To isolate the (organic) product from the impurities, it was proposed that acidic aqueous workup would result in reprotonation of the NHC, to allow the removal of these species by extraction into the aqueous phase. Treatment of the product mixture showed that the product was stable to 1 M HCl(aq) and the residual impurities were indeed removed to the aqueous phase, giving the 'washed' product in comparable isolated yield (82%) to that obtained from chromatographic purification (80%).

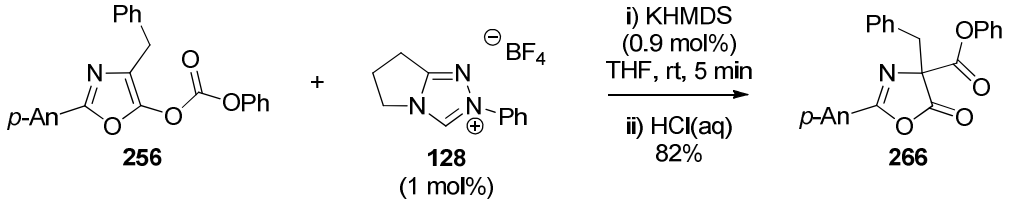


Figure 71: One-pot protocol with purification by workup

Section 2.6: Summary

These investigations demonstrate a range of effective protocols to promote rapid Steglich rearrangement of oxazolyl carbonates to their *C*-carboxyazlactone isomers using low catalyst loadings of NHCs. Furthermore, the triazolium-derived NHC **247** has allowed extension to the substrate scope of the rearrangement, promoting exclusively α-carboxylation with the sterically challenging phenylglycine, valine and *tert*-leucine-derived branched substrates.

Means to simplify the reaction protocol have been investigated, with one-pot reaction procedures and aqueous extraction techniques being employed. These procedures were found to be a highly satisfactory manner with which to perform the reaction, simplifying the reaction procedure and minimising the reaction time.

Investigations have illuminated chemoselectivity between NHC classes in the rearrangement protocols: in conjunction with KHMDS as the base, triazolium salts have proven the most effective at promoting rearrangement, with both imidazolium and thiazolium salts being less effective. The electronic nature of the carbonate functionality appears also to have an effect on chemoselectivity, as the generally less effective imidazolium and thiazolium-derived NHCs appear to be more effective catalysts with phenyl carbonate **256** than with methyl carbonates **244** and **255**. Furthermore, the triazolium *N*-aryl substituent also appears to play a role in the chemoselectivity of the rearrangement, with phenyl and *p*-anisyl substituted triazolium salts performing the rearrangement of both phenyl and methyl carbonate **256** and **255**, but the related pentafluorophenyl substituted triazolium salt is less effective with methyl carbonate **255**. These observations will be reinvestigated in further chapters.

Chapter 3: Rearrangement with weak bases: inclusion in domino cascade protocols

Section 3.1: Rearrangement protocol with weak organic bases

Whilst the aforementioned results illustrate the effectiveness of triazolium-derived NHCs as catalysts to promote the Steglich rearrangement, the results had illuminated a number of interesting chemoselectivities. Firstly, a difference in reactivity between different azolium-based NHCs was observed. Secondly, a difference in reactivity of different carbonate substrates (based on the same core architecture) was observed. Cognisant of the results in the initial publication which showed that weak bases Et_3N and DBU (in conjunction with the optimal triazolium salt **128**) were ineffective in promoting rearrangement of methyl carbonate **244**,[110] the same experiments were investigated using the phenylalanine-derived phenyl carbonate **256**.

Section 3.1.1: Investigations with different azolium salts

With such a distinction in both catalyst and substrate reactivity between the phenyl and methyl carbonates, the possibility that relatively weak bases could be used in order to generate the active NHC, and thus effect the Steglich rearrangement, was re-examined. A wide range of both organic and inorganic weak bases was screened with model oxazolyl phenyl carbonate **256**, of which highlighted results are detailed (Figure 72, Table 10 and Table 11). Using Et_3N as the base (Table 10), a marked difference in reactivity was observed, both in comparison with the results in the initial publication and between the NHC classes. Amongst the triazolium salts, the *N*-phenyl and *N*-*p*-anisyl substituted triazolium salts **128** and **268** again proved most effective, promoting quantitative conversion to the desired *C*-carboxyazlactone **266** in 2 h; the *N*-pentafluorophenyl substituted triazolium salt **270** also promoted quantitative conversion, but requiring a longer reaction time (4 h) to reach completion. These reaction times were considerably longer when compared with the use of KHMDS as the base, whereby the reaction times are generally <5 min. This disparity in reaction rate is likely to be due to difference in pK_a of the two bases. In order to try to explain the difference in reactivity, the pK_a of the triazolium salt was determined. In collaboration with O'Donoghue and Lindsay at the University of Durham, the pK_a of triazolium salt **128** has been determined as 17.7 ± 0.5 (in H_2O).[112] By comparison of this value with that for Et_3N (pK_{aH} 10.9), the active quantity of NHC generated *in situ* is approximately six orders of magnitude lower than for reactions with strong metallated bases.[i] By increasing the stoichiometry of Et_3N to 100 mol%, quantitative conversion to the rearrangement product was achieved with reaction times of <5 min. Addition of 1 equiv of $Et_3N{\cdot}HCl$ was shown to significantly impede the reaction, further supporting this hypothesis.

[i] Assuming full kinetic deprotonation is observed.

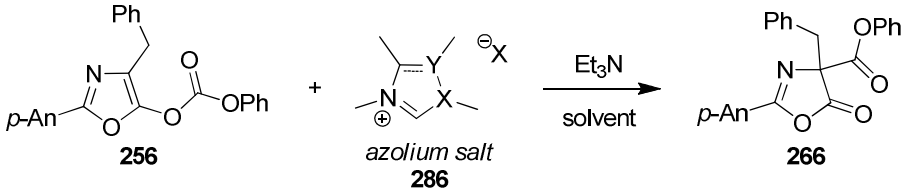


Figure 72: Investigations using Et_3N

Precatalyst (mol%)	Base (mol%)	Solvent	Time	Conversion (%) [a]
128 (1)	Et_3N (0.9)	THF	>24 h	<10
128 (10)	Et_3N (9) + Et_3N·HCl (1 equiv)	THF	2 h	75
			3 h	>98
128 (10)	Et_3N (9)	THF	2 h	>98
128 (10)	Et_3N (100)	THF	<5 min	>98
128 (10)	Et_3N (9)	CH_2Cl_2	2 h	~75
268 (10)	Et_3N (9)	THF	2 h	>98
270 (10)	Et_3N (9)	THF	4 h	>98
79 (10)	Et_3N (9)	THF	>24 h	<10
245 (10)	Et_3N (9)	THF	>24 h	<5
265 (10)	Et_3N (9)	THF	>24 h	<5

[a] Determined by ^1H NMR spectroscopic analysis of the crude reaction product

Table 10: Results of Et_3N-promoted rearrangement with azolium salts

A range of alternative weak Brønsted bases was examined (Figure 73, Table 11), and there appears to be a subtle interplay between the nature of the base and its ability, in conjunction with the NHC precatalyst, to perform the rearrangement: where Et_3N and proton sponge are suitable bases, the use of DABCO, *N*-methylmorpholine and 2,6-lutidine did not afford any rearrangement product; in addition, inorganic carbonates K_2CO_3 and Cs_2CO_3 could also be used to generate the active catalyst in order to promote the rearrangement.

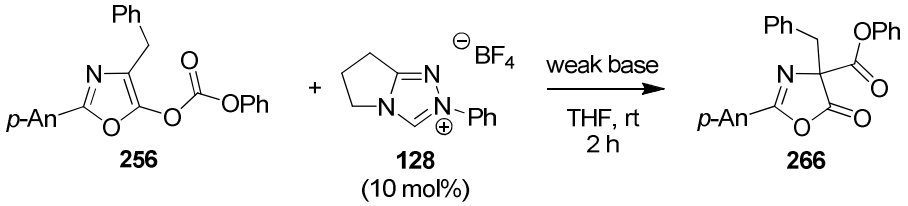


Figure 73: Screen of a range of weak bases

Base (mol%)	Conversion (%)
DBU (9)	>90
DBN (9)	>95
K_2CO_3 (9)	>95
Cs_2CO_3 (9)	>95
proton sponge (9)	>95
DABCO (9)	<5
N-methylmorpholine (9)	<5
2,6-lutidine (9)	<5

Table 11: Results of rearrangement with a range of weak bases

Section 3.1.2: Background reactions with amidines and development of new Lewis bases

Whilst the use of the organic bases DBU and DBN allowed successful Steglich rearrangement of the phenyl carbonate **256**, amidines such as DBU have been used as Lewis bases to facilitate a number of organic transformations. In particular, such amidines have seen application in eliminations,[113] in esterifications,[114] condensations[115] and the formation of trichlorocarbinols.[116] An early example of Lewis basic reactivity was shown in the silylation of a range of alcohols (Figure 74). Activation of the silylation species is generally achieved using imidazole, however Kim and Chang have shown that DBU can also be highly effective.[117]

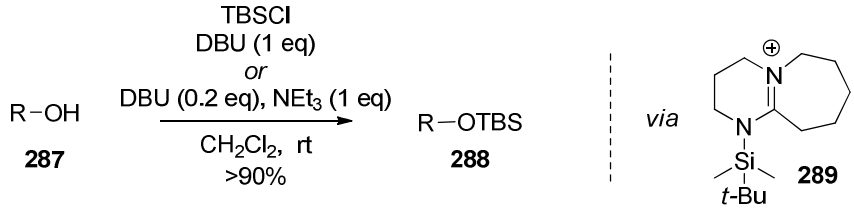


Figure 74: DBU-Catalysed alcohol silylations

A range of other amidine-catalysed reactions are known to allow access to carbon-heteroatom bond formation, such as esterifications with dimethyl carbonate,[118] Baylis-Hillman reactions[119] and cyanoacylation of ketones with acyl cyanides.[120] In the latter case, the reaction is proposed to be promoted *via* formation of an acylamidinium cyanide intermediate **294**, an acyl transfer species. The liberated cyanide allows for formation of the cyanohydrin anion intermediate which is trapped by the acyl transfer species to afford the *O*-acylated cyanohydrin product **297** with regeneration of the amidine catalyst (Figure 75).

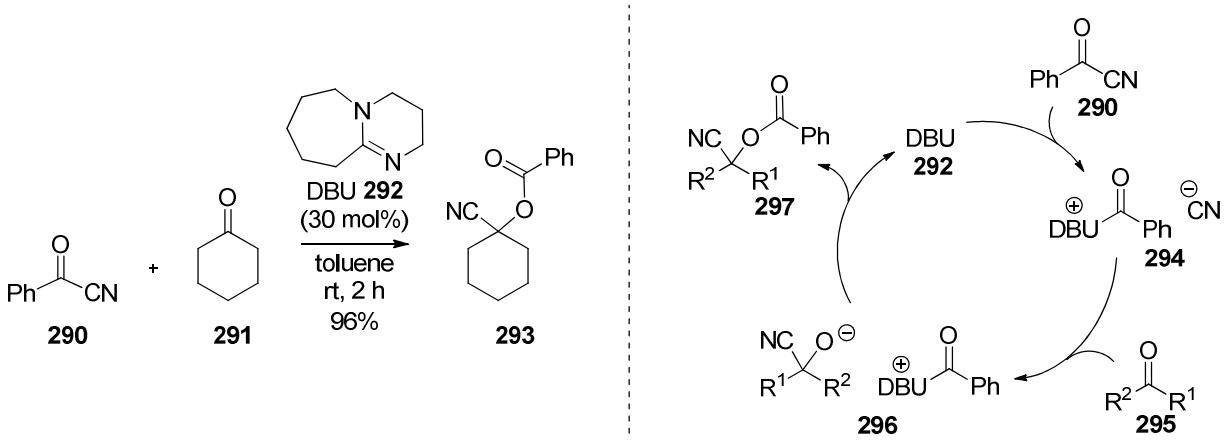


Figure 75: DBU-Catalysed cyanoacylation of ketones with acyl cyanides

Notably, Birman and co-workers have introduced a new class of amidine catalysts for enantioselective acyl transfer based on the 2,3-dihydroimidazo-[1,2-*a*]pyridine (DHIP) framework. These chiral catalysts have proven effective at inducing high levels of enantioselectivity in a number of acyl transfer reactions, notably in kinetic resolution and desymmetrisation of secondary alcohols.[121] In the kinetic resolution of secondary benzylic and allylic alcohols, chiral catalysts **299** (CF_3-PIP) and **300** (Cl-PIQ) were optimal, both giving good selectivity levels in each case (Figure 76).[122]

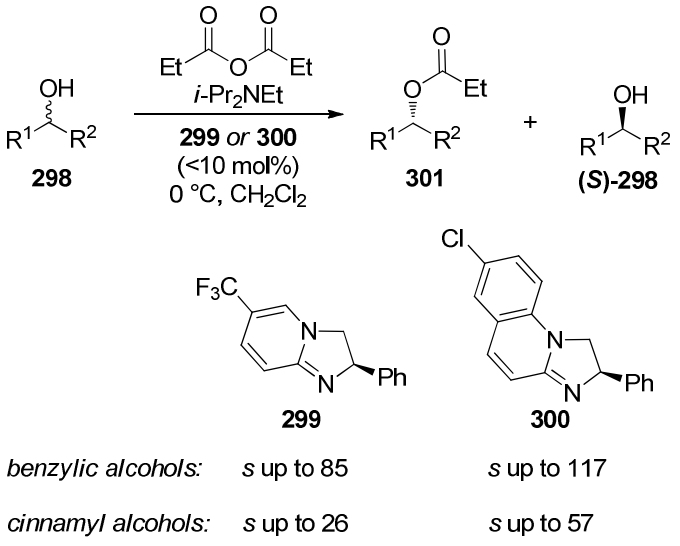


Figure 76: DHIP-Catalysed kinetic resolution of secondary alcohols

In addition to catalysts based on the DHIP architecture, Birman and co-workers have also shown that the commercially available anthelmintic (*S*)-tetramisole and its benzannulated derivative **303** are also highly effective enantioselective acyl transfer catalysts, such as in the kinetic resolution of 1-phenylpropanol **302** (Figure 77).[123]

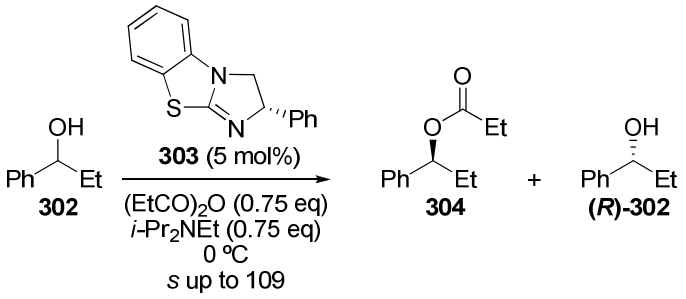


Figure 77: Isothiourea-catalysed kinetic resolution of 1-phenylpropanol

In order to ascertain if such tertiary amines and amidines were indeed able to promote the Steglich rearrangement, background reactions were examined, using the bicyclic amidines DBU **292** and DBN **306**, and the simple tertiary amine base Et_3N as catalysts in the absence of azolium salts (Figure 78, Table 12). The results of this study showed that Et_3N alone was ineffective as a Lewis base in promoting the rearrangement, but the amidines exhibited a marked difference in reactivity. Both amidines gave rise to a mixture of products arising from interaction with the carbonate substrate. A distinct difference in behaviour between the 6:7-fused bicyclic amidine DBU **292** and its 6:5-fused relative DBN **306** was also observed, with successful rearrangement obtained with DBN but not with amidine DBU. In both cases, however, the carbonate substrate was fully consumed, with the remainder of the material identified as the azlactone **254** and diphenyl carbonate **305**.

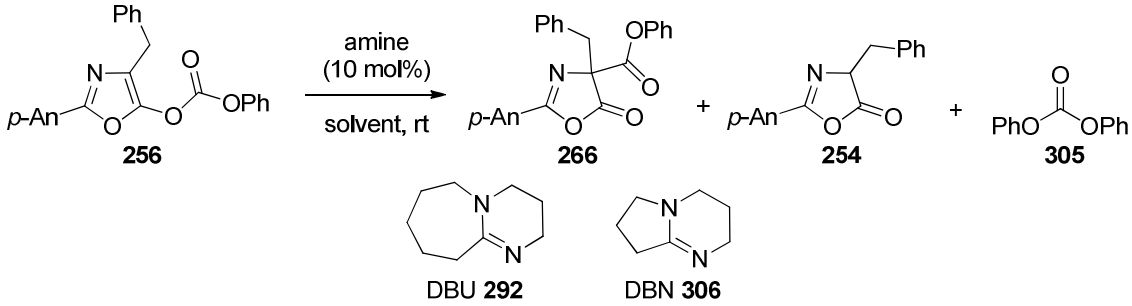


Figure 78: Control experiments with amidine bases and Et_3N

Base (mol%)	Solvent	Time (h)	Conversion to 266 (%)	Conversion to 254 (%)
DBU **291** (9)	THF	4	<5	30
DBN **306** (9)	THF	1	80	20
DBN **306** (9)	CH_2Cl_2	1	90	10
Et_3N (9)	THF	4	0	0

Table 12: Results of control experiments with the weak organic bases

These results indicate that both amidines are exhibiting Lewis basic behaviour, and presumably act in a similar fashion to that of DMAP, through initial addition to the carbonate carbonyl. One means of rationalising the observation of the azlactone and diphenyl carbonate can be made *via*

crossover between two different carboxyamidinium salts **308** and **309**, generated from collapse of the tetrahedral intermediate **307** by two possible pathways (Figure 79). Though this disproportionation reaction accounts for the production of azlactone **254** and diphenyl carbonate **305**, dioxazolyl carbonate **310** would also be expected, but this species has never been detected. Attempts to prepare and isolate this substrate have also failed, suggesting that this product may be unstable and thus cannot be observed in the reaction manifold.

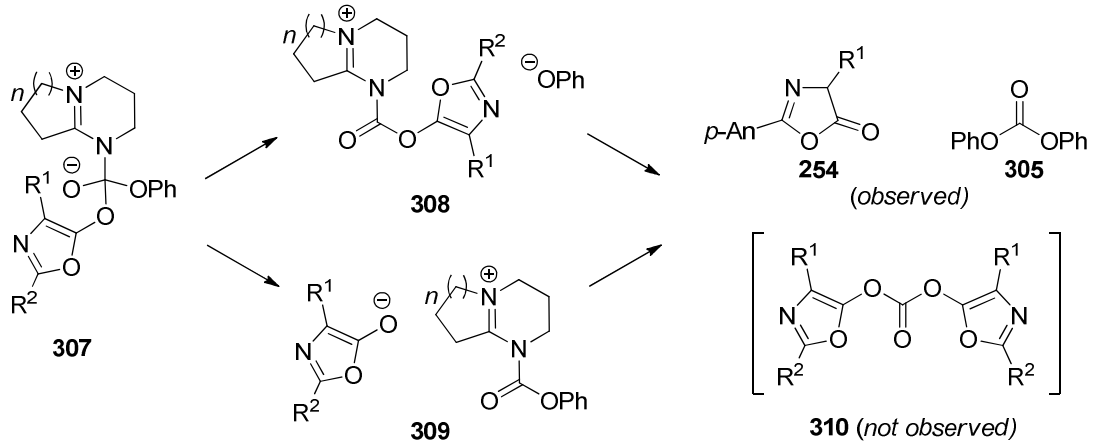


Figure 79: Possible alternative fragmentation pathways leading to disproportionation

Despite this mechanistic ambiguity, further work has being carried out in the Smith group, with the development of a related isothiourea **311** as a Lewis base catalyst which is highly effective in promoting the carboxyl rearrangement.[124] In addition, further work has probed the asymmetric variant of the rearrangement, leading to the development of chiral isothiourea **312** which promotes excellent levels of asymmetry in the rearrangement (up to 94% *ee* at -50 ºC).[125]

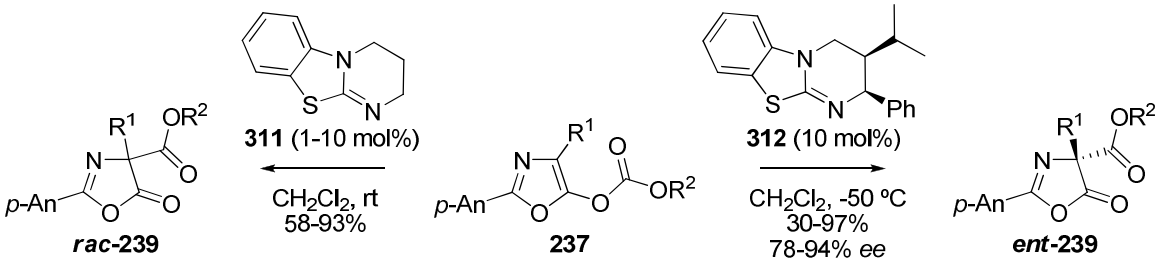
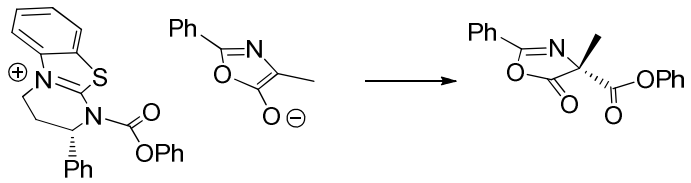


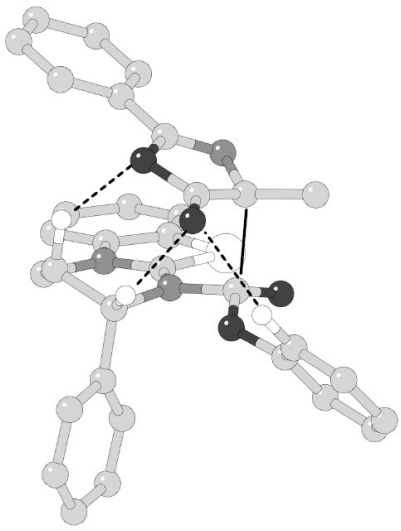
Figure 80: Demonstration of isothiourea-catalysed carboxyl Steglich rearrangements

DFT-Calculations to a high level of theory (B3LYP/6-31G(d,p)) have been performed in order to explain the origin of enantioselectivity in the process. The lowest energy conformation of the presumed carboxyl transfer species, referred to as the *N*-carboxy species, was revealed to orientate the stereodirecting Ph group pseudoaxially, in order to minimise 1,2-strain in this intermediate. The preferred rotameric form of the carboxyl group was found to lie co-planar with the isothiourea motif, and with the C=O "*syn*" to the C=N of the isothiourea moiety. Having controlled the carboxyl transfer geometry, computational analysis of the possible transition states

showed that one possible combination of the dienolate and *N*-carboxy components was significantly lower in energy than the others (by >3.5 kcal mol^{-1}), in agreement with the stereochemical outcome observed experimentally.[125]

Simplified model system:





Ball and stick representation of the lowest energy transition state (B3LYP/6-31G(d,p)) accessed by a simplified *N*-carboxy intermediate and oxazolyl dienolate for the above-illustrated *C*-carboxylation. Dashed lines indicate C-H···O interactions and the solid black line indicates the C-C bond forming. Carbon atoms are light grey, nitrogen and oxygen atoms are dark grey, and hydrogen atoms are white.[i]

Figure 81: DFT Calculations on a simpler related model system, to explain the origin of enantioselectivity with the chiral isothiourea

Whilst these investigations were underway, the asymmetric acyl Steglich rearrangement using tetramisole **314** or benzotetramisole **303** as a catalyst was reported by Gröger and Dietz.[126,127] Whilst successful, this reaction is slow and requires a high catalyst loading (up to 32 mol%), only proceeding to ~80% after two days (Figure 82). Related acyl Steglich rearrangements, however, have proven unsuccessful in our hands.[ii]

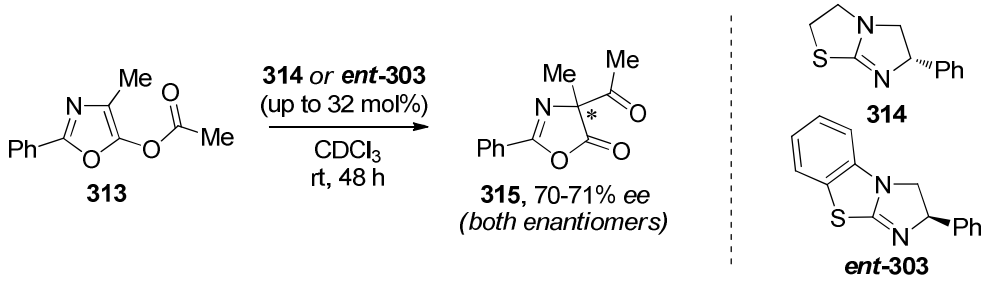


Figure 82: Asymmetric isothiourea-catalysed acyl Steglich rearrangement

Section 3.1.3: Investigation of phenylalanine-derived oxazolyl carbonates

Having observed that Et_3N can be used as a base to promote the rearrangement of carbonate **256**, the generality of the process was investigated with a range of different phenylalanine-derived carbonates (Figure 83, Table 13). With Et_3N as the base, a striking chemoselectivity was observed between different carbonates. Only aryl (phenyl and 1-naphthyl) carbonates underwent the desired rearrangement process, occurring rapidly (<5 min), but all alkyl carbonate substrates

[i] Reproduced with permission, from *Angew. Chem., Int. Ed.* **2009**, *48*, 8914–8918.

[ii] Investigated by Jennifer Thomson and Caroline Joannesse.

failed to provide any of the rearrangement product, even with higher catalyst loadings (20 mol%) and after extended reaction times. In contrast, as described previously, all phenylalanine-derived carbonates **255**–**259** underwent complete rearrangement within 5 min with KHMDS as the base.

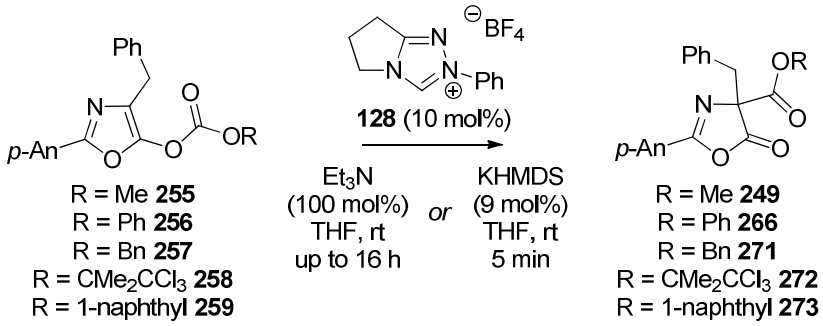


Figure 83: Comparison of rearrangement with KHMDS and Et_3N

R	Base	Time	Conversion (%)
Me	KHMDS	5 min	>98
Me	Et_3N	16 h	<5
Ph	KHMDS	5 min	>98
Ph	Et_3N	5 min	>98
Bn	KHMDS	5 min	>98
Bn	Et_3N	16 h	<5
CMe_2CCl_3	KHMDS	5 min	>98
CMe_2CCl_3	Et_3N	16 h	<5
1-naphthyl	KHMDS	5 min	>98
1-naphthyl	Et_3N	5 h	>98

Table 13: Comparison of aryl and alkyl carbonates using KHMDS and Et_3N

Having delineated that only aryl carbonates undergo the rearrangement process using Et_3N as the base, a range of C(4)-substituted oxazolyl carbonates was examined in the reaction manifold (Figure 84, Table 14). The reaction process proved quite general, with a variety of C(4)-substituted carbonates **316** undergoing successful rearrangement and good isolated yield, including the phenylglycine derivative (R = Ph). Only the α-branched valine derived substrate **316** (R = *i*-Pr) proved unsuccessful.

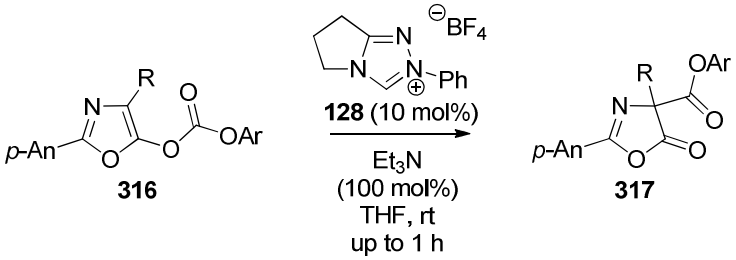


Figure 84: Scope and limitations of the use of Et_3N as the base

R	Ar	Conversion (%)	Isolated yield (%)
Me	Ph	>98	81
Me	1-naphthyl	>98	77
n-Bu	Ph	>98	81
i-Bu	Ph	>95	78
Ph	Ph	>98	72
$PhCH_2$	Ph	>98	82
$PhCH_2$	1-naphthyl	>95	80
CH_2CH_2SMe	Ph	>90	-
4-PhOC(O)O-$C_6H_4CH_2$	Ph	>95	77
i-Pr	Ph	<15	-

Table 14: Scope and limitations of the use of Et_3N as the base

Section 3.2: Development of domino cascade protocols

The development of cascade reaction processes that permit the efficient introduction of molecular complexity from simple starting materials in a single reaction sequence is highly desirable. A number of such so-called 'domino' cascade transformations have been used in synthesis, with several reviews dedicated to this topic.[128]

Section 3.2.1: From azlactones

Having demonstrated the effectiveness of Et_3N as a base to promote the rearrangement of aryl oxazolyl carbonates, investigation of the incorporation of this transformation into a multi-step transformation was carried out. The conversion of azlactone **254** to carbonate **256** can be facilitated using Et_3N as the base, thus, it was proposed that these two steps could be combined into a cascade procedure, obtaining ester **266** directly from the azlactone **254**, in the presence of triazolium salt **128** (Figure 85). The initial findings of this investigation were encouraging: upon treatment of the azlactone **254** with 1 equiv of phenyl chloroformate and 1.2 equiv of Et_3N, 70% conversion of azlactone starting material to the *C*-carboxyazlactone **266** was observed, with the remainder of the mixture present as the azlactone **254** and the carbamate **318**.

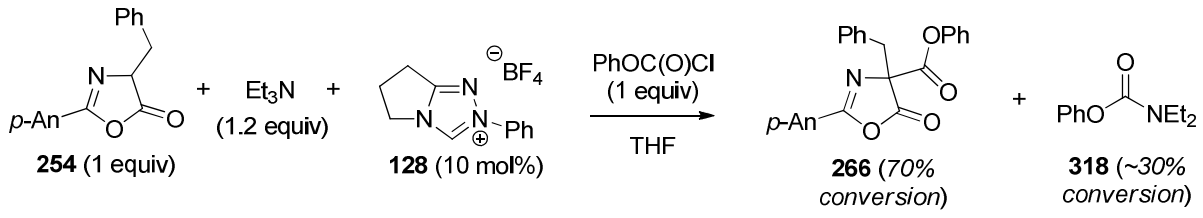


Figure 85: Two-step cascade procedure

The identity of carbamate **318** was confirmed unambiguously by chemical synthesis, through treatment of phenyl chloroformate with solely Et_3N (Figure 86), thus indicating that carbamate formation is a competing pathway to the desired cascade reaction.

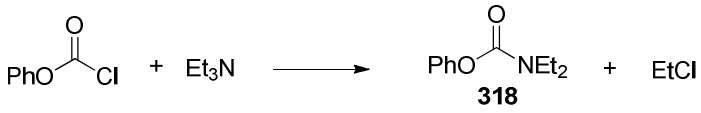


Figure 86: Competing reaction pathway leading to carbamate adduct **318**

Upon closer inspection of the standard formation of the phenyl carbonate substrate **256** from azlactone **254**, formation of the carbamate product **318** is also observed, but is removed upon purification by means of recrystallisation or chromatography. Upon inspection of the literature, it was found that phenyl chloroformate (and a range of other chloroformates) is known to promote dealkylation of tertiary amines,[129] so an alternative base was sought which would not be prone to such reactions. A range of hindered bases, such as Hünig's base, 2,6-lutidine, DABCO and 1,2,2,6,6-pentamethylpiperidine was investigated in the cascade reaction. Unfortunately, neither 2,6-lutidine, DABCO nor 1,2,2,6,6-pentamethylpiperidine were successful in affording the desired *C*-carboxyazlactone product **266**. Hünig's base proved moderately competent in the cascade reaction, but this trialkylamine also led to formation of a similar carbamate product **319** as a result of highly selective dealkylation from the quaternary ammonium intermediate **320** (Figure 87).

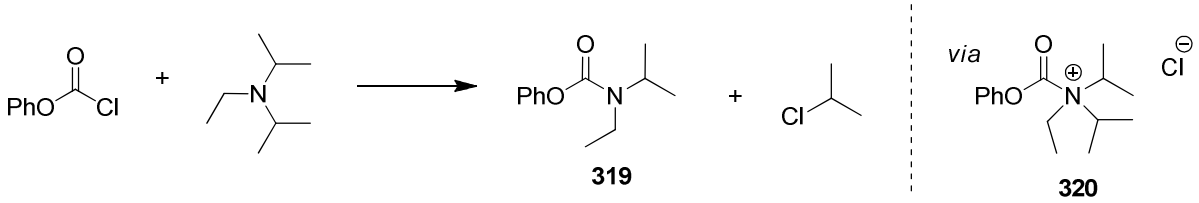
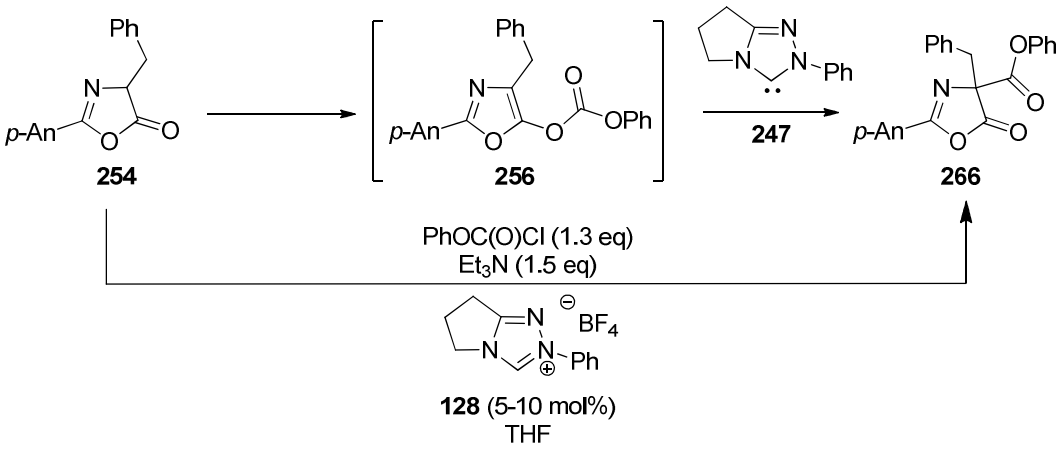


Figure 87: Carbamate adduct obtained with Hünig's base

In light of these results, optimisation of the reaction conditions with Et_3N was investigated. It was found that upon scale-up and by treatment of the azlactone **254** first with 1.3 equiv of phenyl chloroformate and then 1.5 equiv of Et_3N, quantitative conversion to the desired product **266** was achieved and formation of the by-product **317** was minimised. Isolation of the *C*-carboxyazlactone **266** was achieved in better yield to those reactions carried out using either the standard protocol or the one-pot protocol, i.e. 82% *via* the telescoped process, compared to an overall 73–75% by the sequential two step process. To ensure that this process was indeed a cascade reaction, aliquots were taken from the reaction mixture at regular time intervals and analysed spectroscopically. The results indicated that the carbonate intermediate **256** was formed

rapidly, followed by a much slower rearrangement of the carbonate **256** to the desired *C*-carboxyazlactone **266**, consistent with this being a domino cascade.



Scheme 5: Domino cascade analysis showing initial carbonate formation

With a successful protocol in place, the scope and limitations of the procedure were examined. By variation of both the aryl chloroformate and C(4)-substituted azlactone, the reaction proved quite general, affording the *C*-carboxyazlactones **317** in good isolated yield (Figure 88, Table 13). Notably, the branched leucine-derived and phenylglycine-derived azlactones **321** (R = *i*-Bu and Ph, respectively) gave the desired products in excellent yield. This protocol is, however, intolerant of conversion of the α-branched valine-derived azlactone **321** (R = *i*-Pr), and the methylthio-containing substituent in the methionine-derived azlactone **321** (R = $MeSCH_2CH_2$), both returning predominantly the carbonate intermediate **316**. Additionally, attempts to perform the related reactions with alkyl chloroformates gave only formation of the carbonate intermediate **237**. These results support our earlier findings, where the alkyl oxazolyl carbonates **237** underwent no further reaction to the desired *C*-carboxyazlactones when the triazolinylidene was generated from Et_3N.

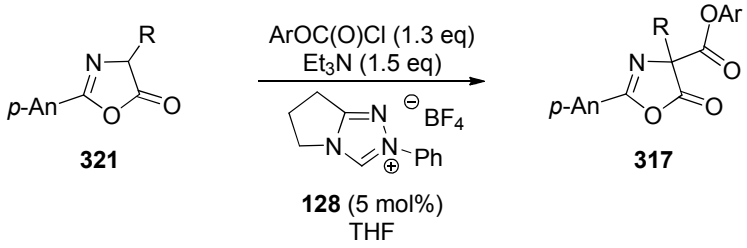


Figure 88: Scope of the domino cascade from azlactones

R	Ar	Conversion (%)	Isolated yield (%)
Me	Ph	>95	81
i-Bu	Ph	>95	85
Ph	Ph	>95	75
$PhCH_2$	Ph	>95	82
$PhCH_2$	1-naphthyl	>95	85
4-$BnOC_6H_4CH_2$	Ph	>95	85
i-Pr	Ph	~15 [a]	-
$MeSCH_2CH_2$	Ph	~10 [a]	-

[a] Remainder present as carbonate intermediate **316**

Table 15: Scope of the domino cascade from azlactones

Section 3.2.2: From *N*-acyl amino acids

With a successful two-step procedure developed, the next extension to the domino cascade was incorporation of the preparation of the azlactone intermediate. We took inspiration from the Dakin West reaction, a known transformation of an amino acid **274** into an amido ketone **325**.[130] This occurs *via* *N*-acylation followed by *O*-activation to a mixed anhydride, followed by intramolecular cyclisation to an azlactone **323** (Figure 89).

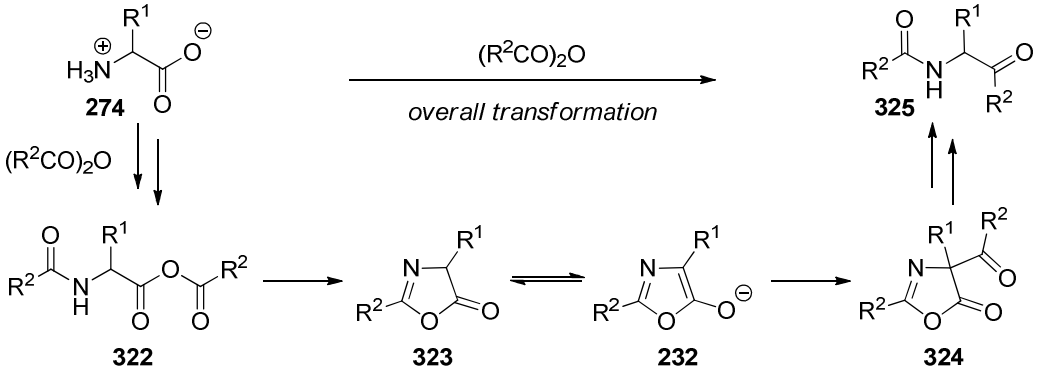


Figure 89: Highlighted mechanism of the Dakin-West reaction

Section 3.2.2.1: Activation/cyclisation using DCC

Fu and co-workers had shown that such azlactone cyclisations could be performed using the carbodiimide DCC, so the possibility of exploiting this transformation, in combination with our developed two-step cascade protocol, was explored. Using *N*-*p*-anisoyl-DL-phenylalanine **253** as a model substrate, attempts were made to induce cyclisation to the azlactone **254** and to promote carbonate formation and rearrangement (Figure 90). The result of this investigation was highly encouraging: upon treatment of *N*-*p*-anisoyl-DL-phenylalanine **253** with DCC, the desired cyclised azlactone product **254** was obtained within 1 h. To remove the dicyclohexylurea by-product from the activation/cyclisation, the mixture was filtered. Filtration of the mixture directly into a mixture of Et_3N and triazolium salt in THF, followed by final addition of phenyl

chloroformate, gave the desired *C*-carboxyazlactone **266** in ~90% conversion (up to 10% remaining as the carbonate intermediate **256**), from which 71% was isolated by chromatography.

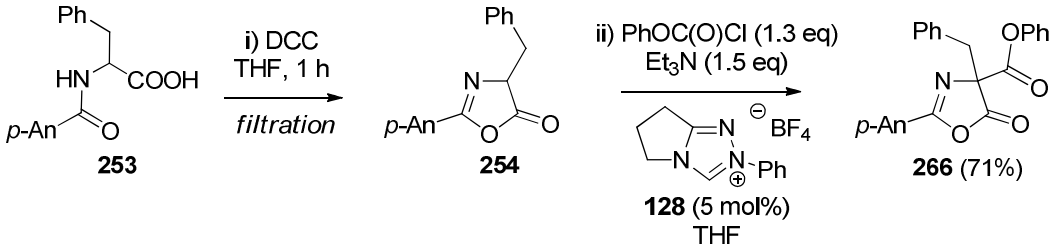


Figure 90: Multi-step domino cascade using DCC activation/cyclisation

With a working protocol in hand, the scope and generality of this procedure was next investigated (Figure 91, Table 16). By varying both the *N*-*p*-anisoyl amino acid **326** and the aryl chloroformate, the protocol proved amenable to afford the *C*-carboxyazlactones **317**, provided that the C(4)-substituent was not α-branched or contained the methylthio functionality. With *N*-*p*-anisoyl-DL-valine (R = *i*-Pr) and methionine (R = $MeSCH_2CH_2$), only the carbonate intermediate **316** was obtained, with no detected rearrangement product. With *N*-*p*-anisoyl-DL-phenylglycine (R = Ph), however, a complex mixture of products was obtained, from which the desired rearrangement product could not be isolated. Upon examination of the DCC cyclisation of *N*-*p*-anisoyl-DL-phenylglycine in isolation, a mixture of products was obtained, and carrying this mixture through the multi-step procedure proved detrimental. This general procedure, however, allowed rapid access to the desired *C*-carboxyazlactone products **317** in very good isolated yield.

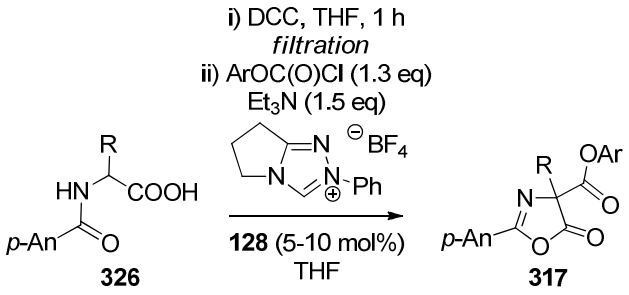


Figure 91: Domino cascade protocol using *N*-acyl amino acids and DCC

R	Ar	Isolated yield (%)
Me	Ph	69
n-Bu	Ph	73
i-Bu	Ph	85
$PhCH_2$	Ph	71
$PhCH_2$	1-naphthyl	80
4-$BnOC_6H_4CH_2$	Ph	84
i-Pr	Ph	- [a]
$MeSCH_2CH_2$	Ph	- [a]
Ph	Ph	- [b]

[a] Only carbonate intermediate **316** obtained
[b] Complex mixture obtained

Table 16: Domino cascade protocol using *N*-acyl amino acids and DCC

Section 3.2.2.2: Activation/cyclisation using aryl chloroformates

Whilst satisfactory, this reaction protocol required two separate manipulations, so we next sought to explore a single reaction vessel domino cascade. As such, the use of chloroformates with Et_3N as both the activating agent[131] *and* the azlactone carboxylation agent, was investigated. Firstly, the formation of the carbonate substrate directly from *N*-acyl amino acids was explored. Again using *N*-*p*-anisoyl-DL-phenylglycine as the model substrate, a selection of chloroformates (methyl, benzyl and phenyl) was investigated (Figure 92). Only phenyl chloroformate proved competent in promoting cyclisation to the azlactone intermediate **254**. Neither benzyl nor methyl chloroformate afforded cyclisation to the azlactone intermediate, giving only the mixed anhydride intermediate **327**, presumably due to the leaving group capacity of aryloxide *vs* alkoxide.

Upon addition of an excess of phenyl chloroformate and Et_3N, the azlactone **254** underwent further carboxylation, but, unlike in the Dakin-West reaction, only *O*-carboxylation (to the carbonate **256**) was obtained, nearly instantaneously. It was noted that 2 equivalents of chloroformate were insufficient to provide consistently quantitative conversion to the carbonate substrate, but increasing to 3 equivalents gave smooth quantitative conversion to the desired carbonate, with the formation of diphenyl carbonate **305** as a by-product. This can be explained as cyclisation to the azlactone liberates phenoxide, which is then consumed stoichiometrically by an equivalent of phenyl chloroformate.

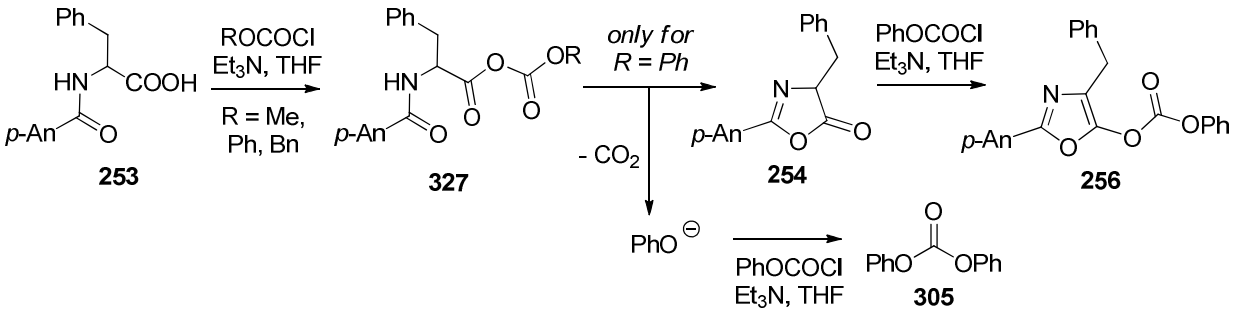


Figure 92: Activation/cyclisation using chloroformates

With a means to preparing carbonates in a single manipulation, the possibility of extending the reaction cascade to incorporate an *O*- to *C*-carboxyl transfer step using a suitable Lewis base was investigated. The Lewis bases DMAP, isothiourea **311** and triazolium salt **128** were examined as suitable candidates with which to attempt the domino cascade (Figure 93). Isothiourea **311** was surprisingly unable to provide the desired *C*-carboxyazlactone **266**, but pleasingly, DMAP and triazolium salt **128** gave good levels of conversion (>85%) the desired *C*-carboxyazlactone **266** with catalytic levels of Lewis base. The *O*- to *C*-carboxyl transfer step proved relatively slow in comparison with the formation of the oxazolyl carbonate intermediate, as the reaction may be retarded by the presence of the $Et_3N{\cdot}HCl$ by-product.

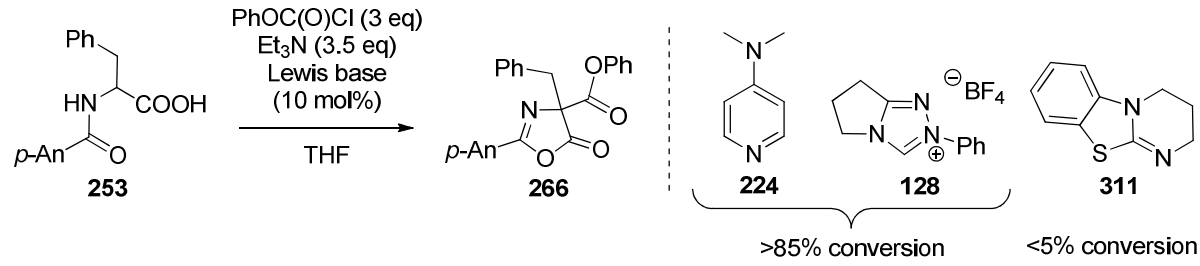


Figure 93: Multi-step domino cascade using phenyl chloroformate

With a successful protocol in place, the scope and limitations of this process were investigated (Figure 94). The procedure was found to be amenable to a range of primary alkyl substituted *N*-acyl amino acids and with either phenyl or 1-naphthyl chloroformate, affording the desired *C*-carboxyazlactone products **317** in typically 5–60 min and good isolated yield (70–84%). Derivatives of the branched amino acids leucine, valine and phenylglycine were all less competent with this procedure, giving rise to <60% conversion to the desired *C*-carboxyazlactone. The methionine derivative also proved incompatible, affording only the carbonate intermediate **316**.

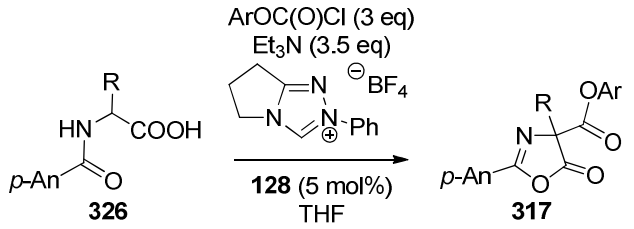


Figure 94: Multi-step single manipulation cascade from *N*-acyl amino acids

R	Ar	Isolated yield (%)
Me	Ph	78
Me	1-naphthyl	70
n-Bu	Ph	78
$PhCH_2$	Ph	71
$PhCH_2$	1-naphthyl	70
4-$BnOC_6H_4CH_2$	Ph	84
i-Pr	Ph	- [a]
i-Bu	Ph	- [b]
$MeSCH_2CH_2$	Ph	- [a]
Ph	Ph	- [b]

[a] Only carbonate intermediate **316** present
[b] Complex mixture obtained

Table 17: Domino cascade protocol using aryl chloroformates

Furthermore, the unprotected *N*-acyl tyrosine derivative **328** (obtained by hydrolysis of ester **281**), was competent in the reaction manifold (Figure 95). By increasing the stoichiometry of aryl chloroformate, the protected *C*-carboxyazlactones **329** and **330** were obtained in very good isolated yield.

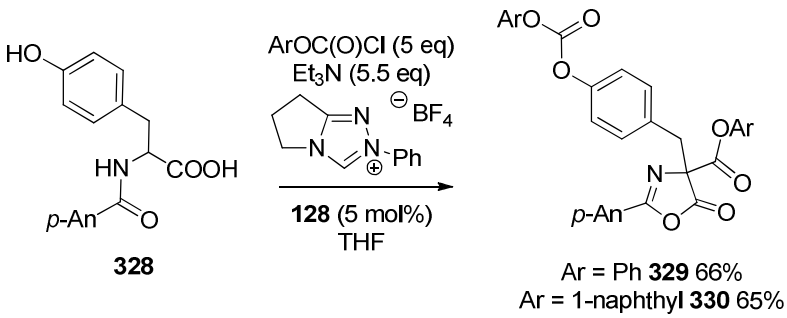


Figure 95: Multi-step domino cascade using the unprotected *N*-acyl tyrosine

From this result, a further chemoselectivity was observed in the reaction, namely, that the NHC only promoted rearrangement of the oxazolyl carbonate and not of the phenolic carbonate. Endeavours to investigate possible Fries rearrangement of diphenyl carbonate **305** however, showed that no such rearrangement reaction was possible using the triazolium-derived NHC.

Section 3.3: Conclusions

The scope and limitations of the use of strong metallated base with various NHC classes illuminated some interesting differences in reactivity. This was further explored using weak bases to generate the active NHC, and this protocol was found to be highly chemoselective: only aryl oxazolyl carbonates underwent the desired *C*-carboxylation, where alkyl carbonates appeared inert.

This, however, proved to be useful, as it allowed the Steglich rearrangement transformation to be incorporated into domino cascade protocols. Azlactones can be transformed to their *C*-carboxyazlactone products in one step, or the azlactone precursor, the *N*-acyl amino acid, can be activated and cyclised to its azlactone, and taken through one of two avenues.

These multi-step protocols represent a synthetic advantage over the more traditional methods of preparation as they give rapid access to the desired product, using low catalyst loadings and minimal volume of solvent.

Chapter 4: Mechanistic investigations

Section 4.1: Mechanistic investigations

Throughout the investigations into the NHC-catalysed Steglich rearrangement process, a number of interesting selectivities have been discovered. Firstly, triazolium salts appear to be the best precatalyst candidates for the reaction when a strong metallated base (such as KHMDS) is used. Secondly, there is a striking difference in the reactivity of triazolium-derived NHCs generated using weak bases, promoting the Steglich rearrangements only with aryl oxazolyl carbonates and no rearrangement with alkyl oxazolyl carbonates. With such differences in reactivity, we questioned if these processes all proceeded *via* a similar mechanism, and probed this through crossover experiments.

With a mechanism for the NHC-catalysed Steglich reaction proposed similar to that previously established using DMAP, namely through generation of a carboxyazolium species, attempts to isolate and characterise this proposed intermediate were made. Unfortunately, deprotonation of the triazolium salt **128** with KHMDS and treatment with phenyl chloroformate gave a mixture of products, from which the proposed carboxyazolium species could never be isolated nor identified in solution. Furthermore, identification of the proposed reaction intermediates *in situ*, in particular the hypothesised carboxyl transfer species, proved somewhat difficult to perform spectroscopically, even with low catalyst loadings, high dilution and cooling of the reaction.

Section 4.1.1: Crossover experiments using KHMDS as the base

Whilst not being able to identify or isolate the intermediate carboxyl transfer species directly, the *behaviour* of the presumed carboxyl transfer species was probed by examination of the product distributions arising from crossover experiments between different substrates. Based upon our proposed catalytic cycle (Figure 96), the triazolinylidene catalyst **247** first attacks the electrophilic carbonate carbonyl to form the tetrahedral intermediate **332**. This intermediate then collapses to afford the carboxyl transfer species **333** and azlactone dienolate **232** as an ion pair, which then recombine to deliver the desired rearranged product **334**, again, presumably *via* a tetrahedral intermediate.

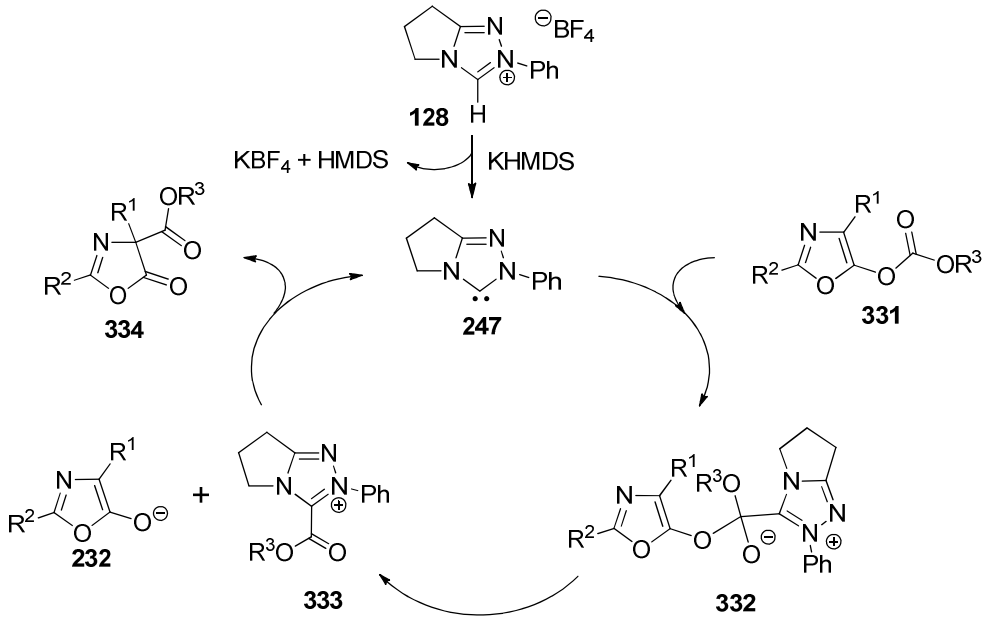


Figure 96: Proposed catalytic cycle

Section 4.1.1.1: Using optimal triazolium-derived NHC

The most effective NHC catalyst in the Steglich rearrangement is that derived from triazolium salt **128** with KHMDS as the base, a combination that promotes rearrangement of all oxazolyl substrates irrespective of carbonate substituents. This set of conditions was used as a reference point for all of the subsequent investigations, with the hope that comparisons would help to explain the chemoselectivities with the less successful protocols. As such, phenylalanine-derived phenyl carbonate **256** and alanine-derived methyl carbonate **244** were chosen as suitable candidates for the initial crossover reactions, as all potential crossover products had previously been prepared, isolated and characterised and, importantly, could be identified spectroscopically.[i] Under the optimised reaction conditions, treatment of a 50:50 mixture of carbonates **256** and **244** gave a near statistical mixture of all four potential rearrangement products (22:28:27:23 ratio of **248**:**246**:**266**:**249**) (Figure 97) upon ^{1}H NMR spectroscopic analysis of the crude reaction product. The observation of crossover products indicates that there is at least one intermolecular step in the reaction manifold, and that any such ion pair intermediates may be held together relatively weakly in solution, allowing appreciable crossover. Within the group, other studies have shown that resubjecting mixtures of the isolated rearrangement products **246** and **266** to the reaction conditions, only **246** and **266** are returned, with no crossover to the recombination products **248** or **249**. This indicates that the C-C bond-forming step in this process is irreversible.

[i] All further crossover experiments were also chosen as each individual possible recombination product had also been isolated and fully characterised.

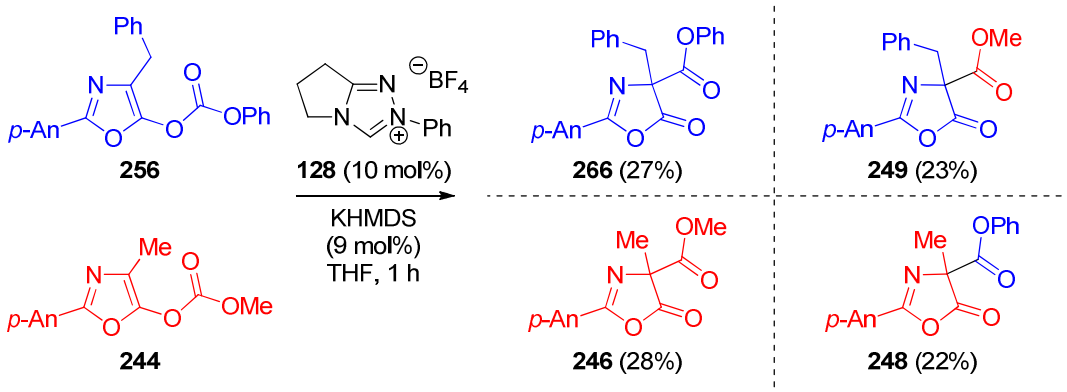


Figure 97: Crossover using optimal triazolinylidene catalyst

At this point, the only indication of the mechanism is that an intermolecular step is involved in the mechanism. Cognisant of the relatively reactive nature of phenyl carbonate **256**, a related crossover experiment with two less reactive carbonate substrates was investigated, to enable identification of any potential intermediates in the reaction prior to the reaction reaching completion. By investigating two alkyl carbonates, trichlorodimethylethyl carbonate **258** and methyl carbonate **244**, under the same reaction conditions, similarly consistent crossover was observed to those with the phenyl and methyl carbonates discussed above. In order to allow identification of any potential intermediates, the rate of rearrangement was impeded by employing low catalyst loading (1 mol%) and at high dilution (~2 mM for the active NHC **247**) (Figure 98). In this case, a mixture of the four possible carbonates was obtained after only 5 min (6–7% of both crossover carbonates); after 30 min a mixture of all four carbonates (~80% of the total mixture) *and* all four rearrangement products (~20% of the total mixture), in approximately equal proportions was obtained. This near statistical mixture of the carbonates indicates that an initial *O*-transcarboxylation process is occurring, presumably through recombination of the postulated carboxyl transfer agent and dienolate on oxygen, and that this is a relatively fast and reversible process, with a subsequent slower *C*-carboxylation step. Though an *O*-transcarboxylation step is occurring, the nature of the final transformation (from the dienolate **232** and carboxyazolium intermediate **333**) to the *C*-carboxyazlactone product **334** cannot be investigated, as the crossover step has already occurred in the manifold (Figure 104).

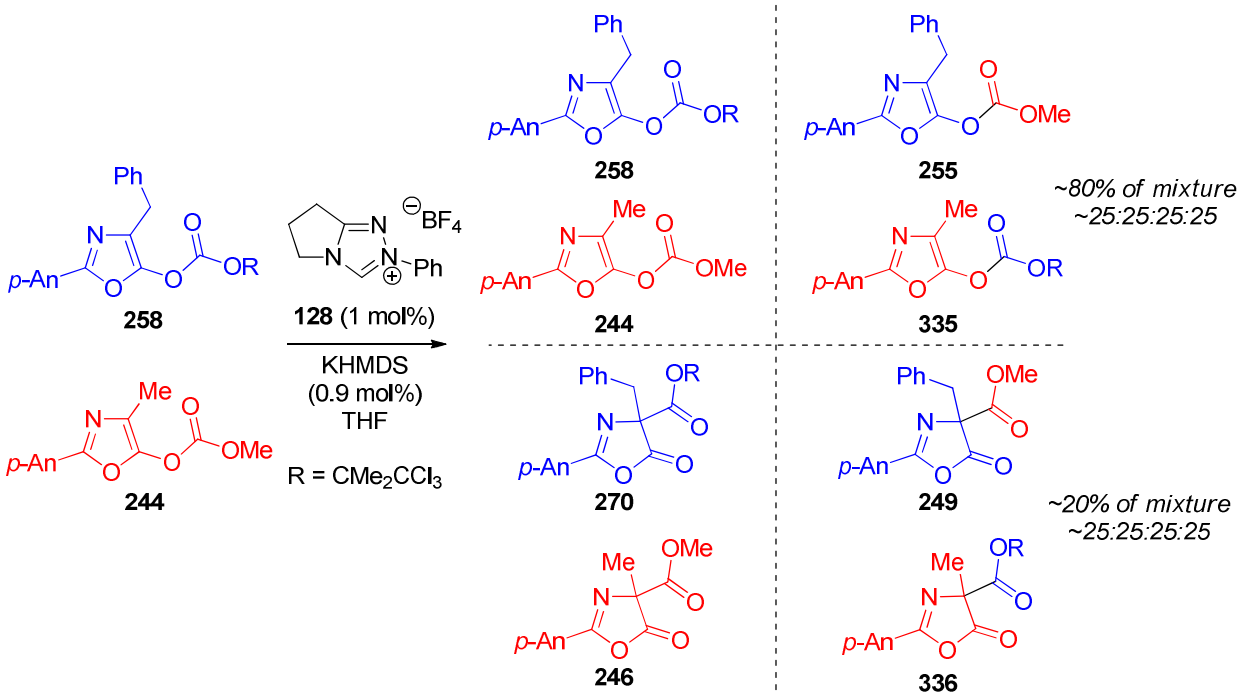


Figure 98: Impeded crossover reaction

Section 4.1.1.2: Using imidazolium-derived NHCs

In light of the observation that thiazolium and imidazolium-derived NHCs were considerably less effective in promoting the Steglich rearrangement (Chapter 2), similar crossover experiments with imidazolium salts IMes HCl and SIMes HCl were investigated, to ascertain why these NHCs were ineffective (Figure 99). Very different results were obtained with the imidazolium-derived NHCs: complete crossover to a statistical mixture of all four carbonate substrates (as can be suggested with the triazolinylidene from an *O*-transcarboxylation process), but *no* rearrangement, was observed, even after an extended reaction time. This indicates that the NHCs are indeed highly Lewis basic in character, but that the nature of the carboxyl transfer species between the different catalyst classes has a dominant effect upon the viability of the *C*-carboxylation event, giving rise to this chemoselectivity. Whilst similar mechanisms could be invoked to explain the reactions, Zipse and co-workers have shown that Brønsted basicity (i.e. pK_a) does not correlate directly to Lewis basicity in a related Lewis base-promoted reaction, the Baylis-Hillman reaction. The authors note that methyl cation affinity, rather than proton affinity, can be used to better correlate catalyst reactivity.[132] To date, no such methyl cation affinity data for NHCs have been determined, but the nature of the carboxyl transfer species between these different classes could be sufficiently different as to observe this difference in behaviour.

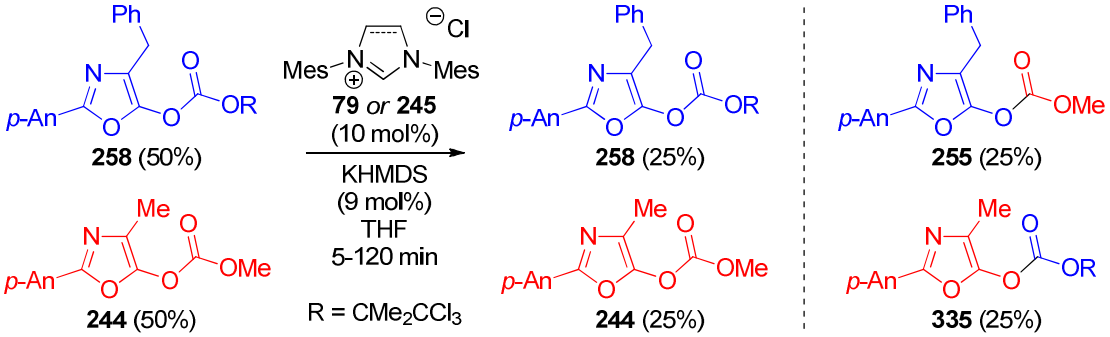


Figure 99: Imidazolinylidene crossover reaction, giving only *O*-transcarboxylation

Section 4.1.2: Crossover experiments using Et_3N as the base

Cognisant of the results obtained in crossover studies using strong metallated bases KHMDS, related experiments employing Et_3N were investigated. In order to propose explanations for the observed chemoselectivity with Et_3N, comparative crossover reactions were first carried out using an imidazolium and triazolium salt, using Et_3N as the base. Having shown that aryl carbonates are amenable to rearrangement with Et_3N as the base, a crossover reaction between a reactive phenyl carbonate **256** and an apparently unreactive methyl carbonate **244** was investigated (Figure 100). In this case, triazolium salt **128** and Et_3N gave exclusively the rearrangement product **266** and returned carbonate **244**, consistent with the chemoselectivity observed in the previous reactions. No *O*-transcarboxylation processes were observed.

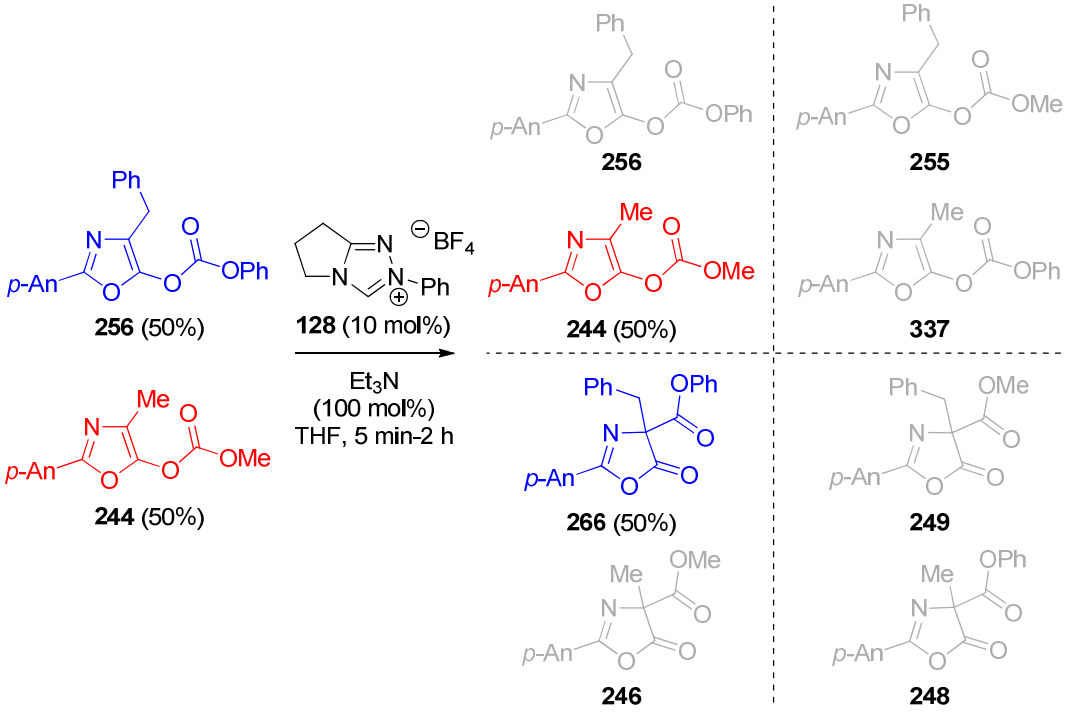


Figure 100: Chemoselectivity in crossover with Et_3N

Having observed exclusive reactivity with only the phenyl carbonate substrate, a crossover reaction between two aryl carbonates was investigated (Figure 101). Treatment of a 50:50 mixture of phenyl carbonate **256** and 1-naphthyl carbonate **338** gave, under the standard conditions, a near statistical mixture of the four possible rearrangement products **266**:**339**:**272**:**248** (23:22:27:26 ratio). Upon adjustment of the reaction conditions in order to impede the reaction rate,[i] a mixture of all eight possible products was observed, again consistent with a reversible *O*-carboxylation process followed by a presumably slower *C*-carboxylation event.

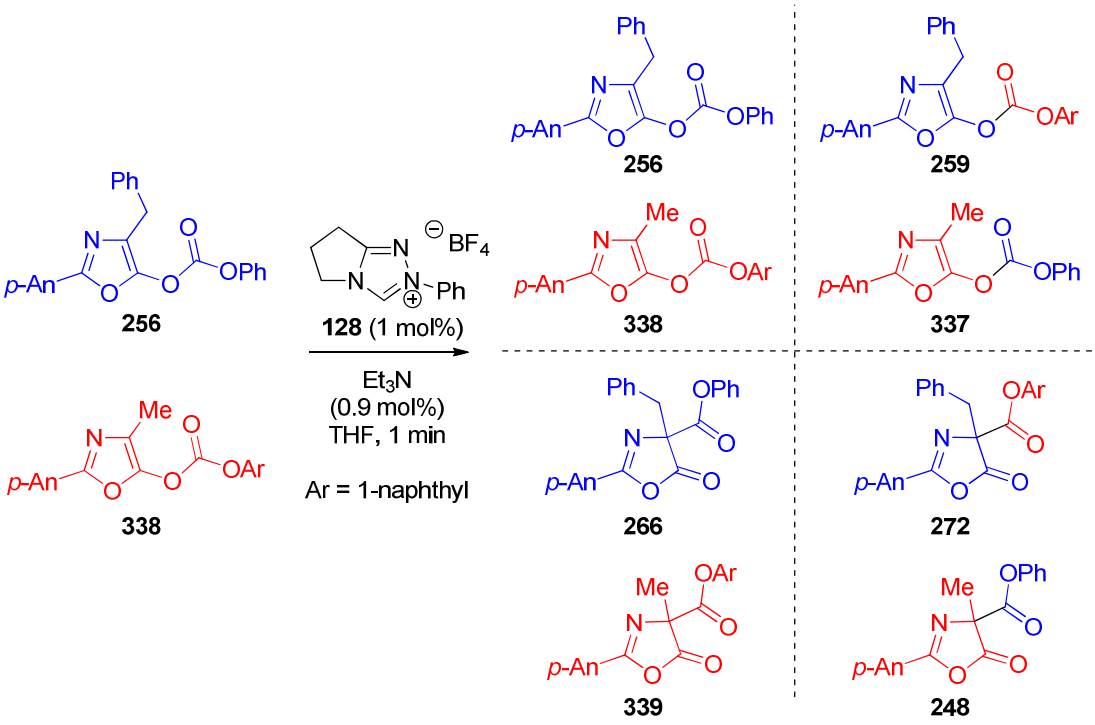


Figure 101: Crossover with two aryl carbonates using Et_3N

Finally, two unreactive alkyl carbonate substrates, trichlorodimethylethyl carbonate **258** and methyl carbonate **244**, were investigated in crossover reactions. Both imidazolium and triazolium salt were evaluated as NHC precatalysts, in order to ascrtain if there were any differences in their behaviour (Figure 102). Using stoichiometric Et_3N as the base, neither SIMes HCl nor triazolium salt **128** promoted any carboxyl transfer processes, returning exclusively the starting carbonates even after extended reaction times (up to 16 h). For the imidazolinium salt, the considerably larger difference in pK_a/pK_{aH} between the imidazolinium salt and Et_3N could account for the poor reactivity, as a considerably lower concentration of active NHC would be generated than in the corresponding reaction using KHMDS (where *O*-transcarboxylation was

[i] A low catalyst loading of 1 mol%, 0.9 mol% Et_3N and at a maximum theoretical NHC **247** concentration of ~2 mM was used.

observed). With the triazolium salt, however, this further confirms that there is a marked chemoselectivity difference between NHCs generated with different bases.

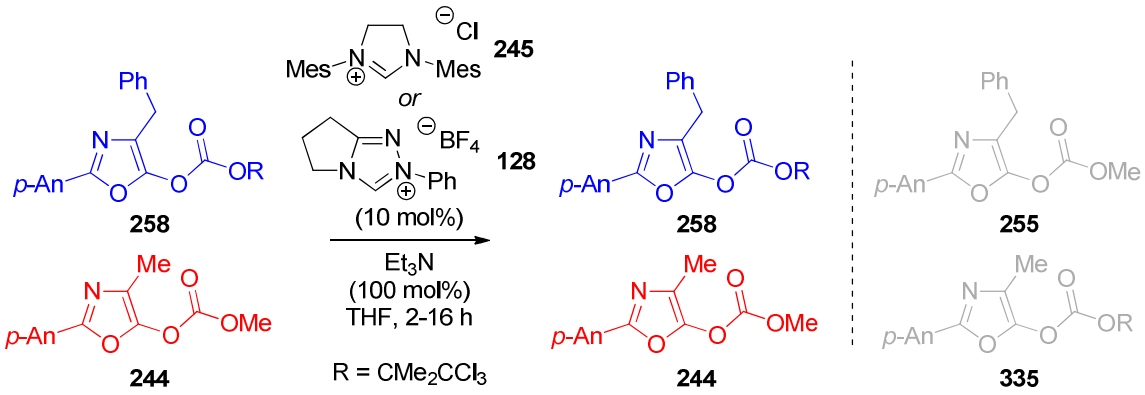


Figure 102: Crossover of alkyl carbonates with NHCs generated using Et_3N

In order to underpin the nature of the final *C*-carboxylation step using Et_3N as the base, a 50:50 mixture of phenylalanine-derived phenyl ester **266** and alanine-derived 1-naphthyl carbonate substrate **338** was subjected to the reaction conditions (Figure 103). From this crossover reaction, unsurprisingly, only the two rearrangement products **266** and **339** were returned, indicating that the final C-C bond-forming step in the reaction is irreversible, consistent with the findings using KHMDS.

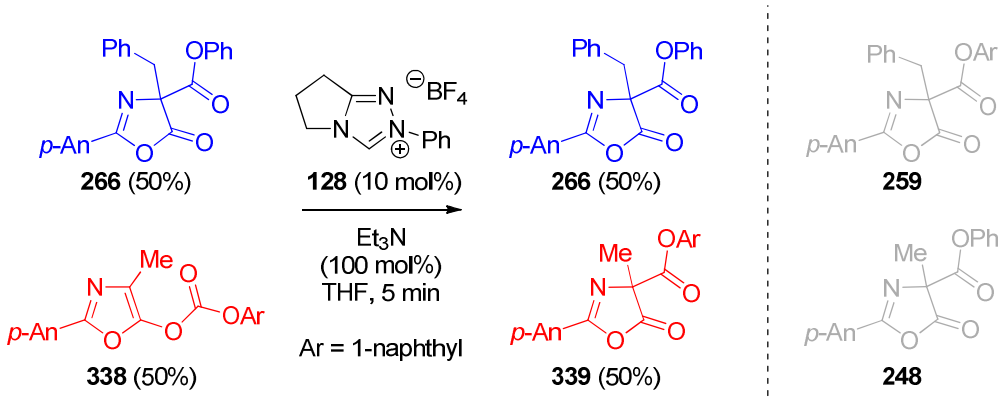


Figure 103: Irreversible C-C bond formation from crossover reaction

Section 4.1.3: Exploration of the chemoselectivity

Taken together, these crossover experiments further support the findings that triazolinylidene NHCs generated from both KHMDS and Et_3N proceed through a similar mechanistic pathway, *via* an initial *O*-transcarboxylation event followed by a slower *C*-carboxylation process in which the C-C bond formation is irreversible (Figure 104).

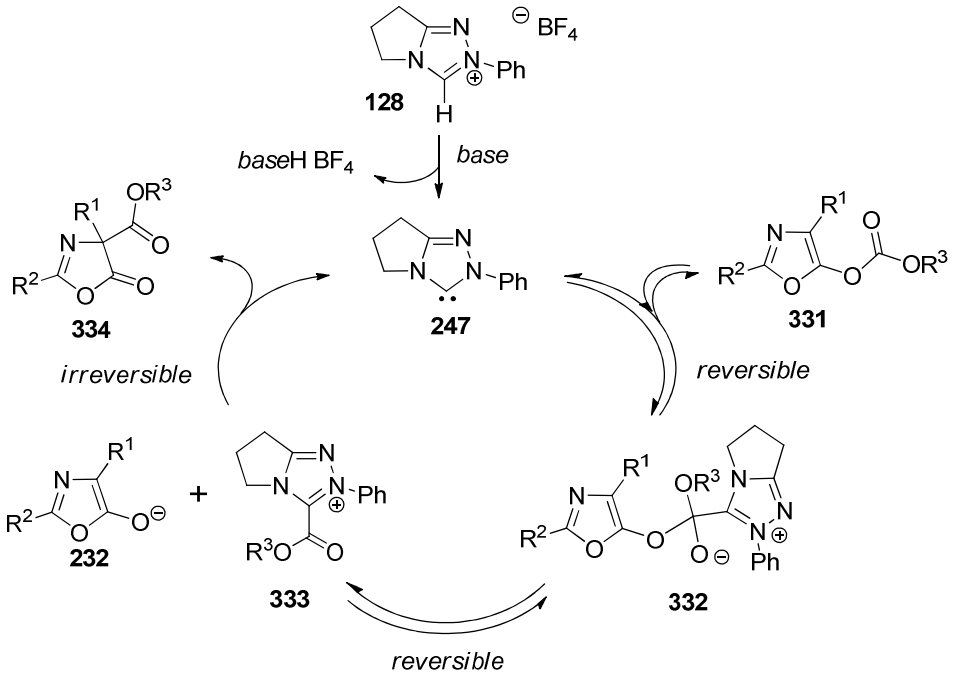


Figure 104: Completed catalytic cycle for triazolinylidene-promoted Steglich rearrangement

This mechanistic proposal does not, however, account for the difference in chemoselectivity in the process using Et_3N as the base. The results of these crossover studies allow a number of potential explanations for the chemoselectivity to be proposed. Firstly, the nature of the NHC generated with a metallated base and with Et_3N could be significantly different, as to alter the Lewis basicity of the NHC species due to the presence (or absence) of a related counterion. In reactions using KHMDS to generate the NHC, the by-product KBF_4 is produced, whereas when using Et_3N as the base, the counterion is the Et_3NH^+ cation. The interplay between the NHC and the counterion (the ammonium or K^+ cation) could play a role in the chemoselectivity of the rearrangement process, or simply, that the cation could play a role in activation of the substrate.

Having shown that doping of $Et_3N{\cdot}HCl$ to a reaction impeded the carboxyl transfer process (see Table 10, page 50), the related effect with KBF_4 was examined (Figure 105). Doping of 1 equiv of KBF_4 to the reaction mixture containing phenyl carbonate **256** resulted in a significant rate enhancement, giving >95% conversion to the *C*-carboxyazlactone **266** after 60 min, as opposed to requiring 120 min. However, the related experiment using methyl carbonate **255** gave no rearrangement product, consistent with the chemoselectivity of this process not being affected by the presence of KBF_4.

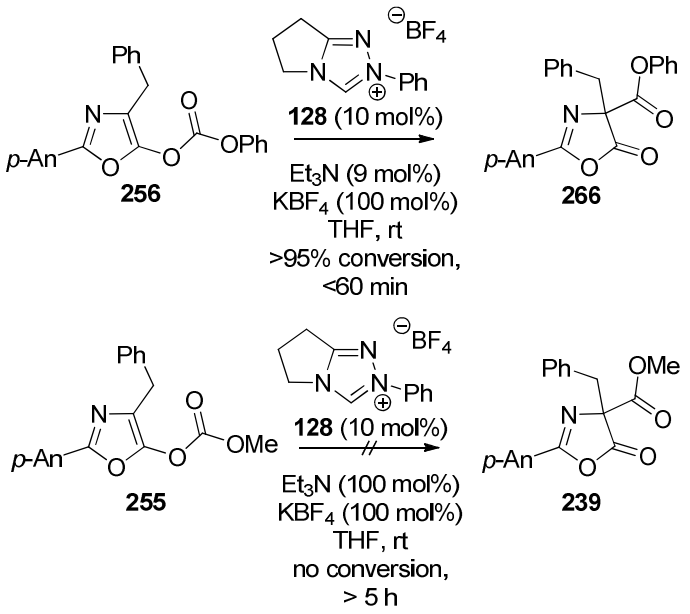


Figure 105: Effect of addition of KBF_4

In order to examine if the presence of KBF_4 affected the *O*-transcarboxylation process, a related crossover experiment of phenyl carbonate **256** and methyl carbonate **244** was carried out in the presence of 1 equiv KBF_4 (Figure 106). This crossover experiment also returned the same product distribution to that in the absence of KBF_4, promoting the rearrangement of exclusively the phenyl carbonate. Thus, the K^+ cation could be acting as a cooperative Lewis acid catalyst in the reaction manifold, enhancing the electrophilicity of the carbonate carbonyl, but not affecting the chemoselectivity of the process.

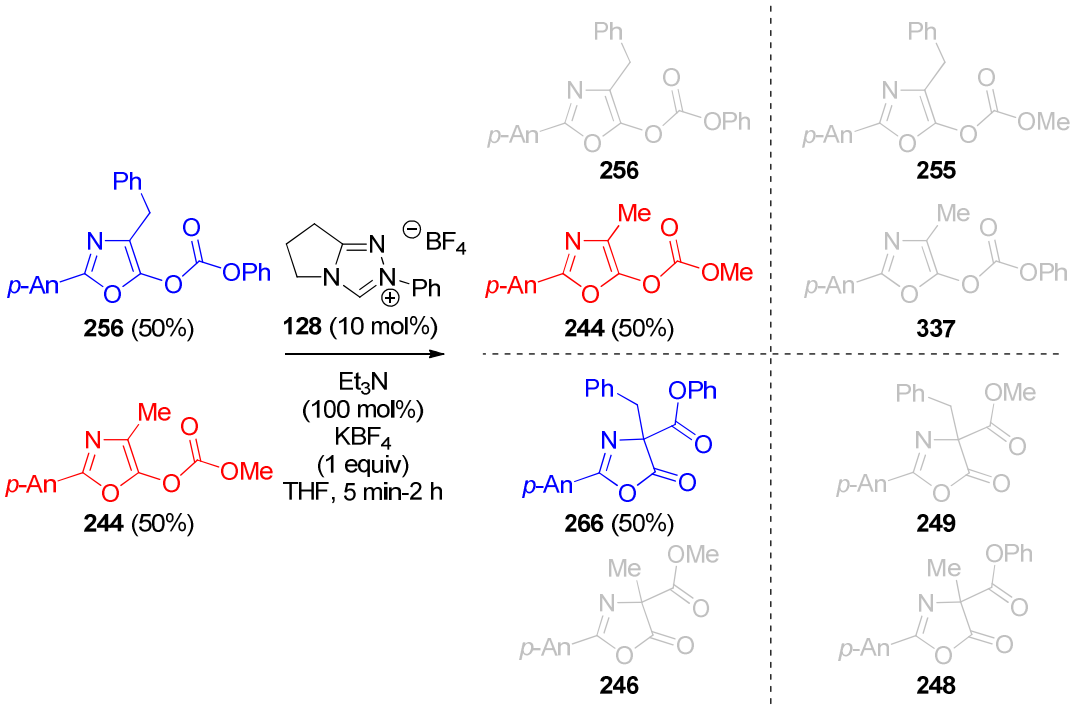
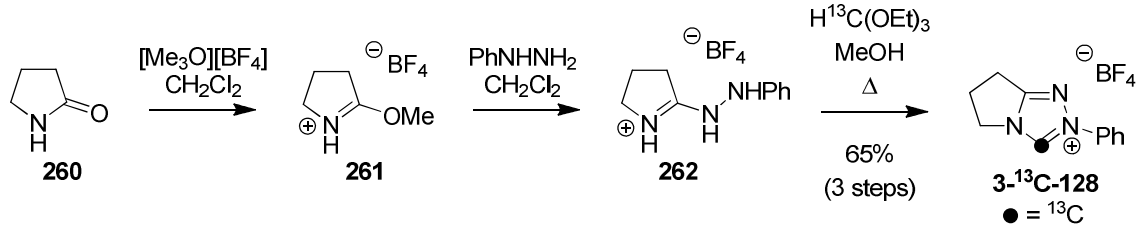


Figure 106: Chemoselectivity in crossover with Et_3N

In order to better understand the differences in reactivity, delineation of the exact nature of the generated NHC was attempted. As Alder and co-workers have shown that imidazolium-derived NHCs form complexes with alkali metal cations,[133] a related complexation event may also be present in the generation of the NHC **247** using KHMDS. Alder had shown that the presence of such "free" or complexed NHCs can be detected spectroscopically, so related experiments were performed with the triazolium salt **128**. To allow rapid analysis of the substrate by ^{13}C NMR spectroscopy, the ^{13}C-labelled triazolium salt **3-^{13}C-128** was prepared from lactam **260** and >99% isotopically enriched triethyl orthoformate (Scheme 6), with complete ^{13}C incorporation at C(3) of the triazolium salt **128**.[i]



Scheme 6: Preparation of the isotopically enriched triazolium salt **3-^{13}C-128**

There have been only very limited investigations into the nature of such "free" triazolinylidenes, though Enders and co-workers have isolated NHC **341** by pyrolysis of methanol adduct **340**, which has a characteristic free carbene chemical shift of δ_C ~215 ppm.[134]

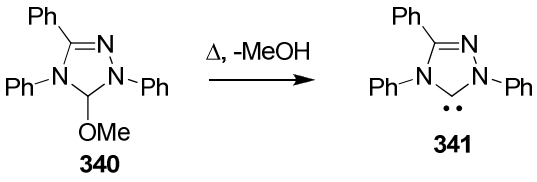


Figure 107: Preparation of the free triazolinylidene **341**

Upon inspection of a mixture of triazolium salt **3-^{13}C-128** in THF which had been treated with KO*t*-Bu and catalytic NaH, an apparent single product, δ_C ~227 ppm, was obtained. Upon treatment of the same triazolium salt **3-^{13}C-128** with 1 equiv of KHMDS, however, a number of ^{13}C-labelled species were identified, all with chemical shifts in the expected range for free NHCs and NHC complexes (δ_C >200 ppm). In this reaction manifold, solid precipitate was deposited over time, suggesting that the species in solution were only sparingly soluble, and thus the analysis was a reflection of only the species present in solution. Nonetheless, this observation tentatively suggests that KHMDS promotes the formation of both complexed and free NHC in solution.

[i] Incorporation determined spectroscopically by ^{1}H and ^{13}C NMR techniques.

In order to ascertain the nature of the NHC derived using Et_3N, similar experiments were performed, but no detectable traces of any NHC species were observed. This could be due to the difference in pK_a of the two species, so neat Et_3N was employed as the solvent, but only the isotopically enriched triazolium salt **128** was identified in solution.

Though attempts to rationalise the chemoselectivity by these means have proven inconclusive, a number of other postulated processes could account for the difference in chemoselectivity.

If the difference in electrophilicity of the aryl and alkyl carbonate substrates was responsible for the chemoselectivity, the active species would still be generated in all cases, even if only in small quantities. As no crossover is observed after even extended reaction times, this proposal can be excluded. An alternative explanation is that the nature of the ion pair in the different reactions is important. The metallated dienolate may be responsible for the enhanced reactivity in reactions using KHMDS, whereas with Et_3N, the conjugate acid cation may H-bond to the dienolate, thus changing its chemical behaviour. In order to investgate if the generated by-products have a bearing on the chemoselectivity, in collaboration with Prof. S. Nolan at the University of St Andrews, means to generate the free NHC **247** (in the absence of such by-products) is being investigated, with subsequent evaluation of this NHC in this rearrangement process.

Section 4.2: Summary

A thorough investigation of the mechanism of the Steglich rearrangement has been undertaken in order to rationalise the behaviour of both substrate and catalyst in the reaction manifold.

While all metallated base-derived NHCs behave as Lewis bases, the nature of the carboxyazolium intermediate appears important in promoting rearrangement. Carboxytriazolium intermediates promote rapid and reversible *O*-carboxylation but also promote the desired *C*-carboxylation. The related imidazolium-derived carboxyazolium intermediates, however, promote rapid *O*-carboxylation but only promote appreciable levels of *C*-carboxylation with aryl oxazolyl carbonates.

Et_3N-Derived NHCs are considerably less reactive than those obtained using strong metallated bases, but aryl oxazolyl carbonates are successfully rearranged using a triazolium salt and Et_3N as the base. The chemoselectivity in the process was further confirmed through crossover experiments.

A possible explanation for this chemoselectivity could be the subtle difference in the nature of the NHC or the carboxyazolium intermediate, as the related counterion could affect the properties of the species in the reaction pathway. For example, Movassaghi and co-workers have shown that NHCs can form complexes with protic solvents to form azolium alkoxides which are held together by H-bonding interactions.[135] In reactions where Et_3N has been used to generate

the active NHC, this could give rise to a similar NHC···H-NEt_3^+ complex, though attempts to identify such species have proven unfruitful.

Chapter 5: NHC-Catalysed asymmetric Steglich rearrangement

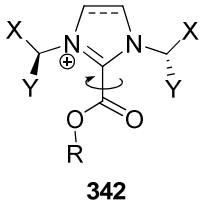
Section 5.1: Synthesis of chiral azolium salt precatalysts

Having fully evaluated the scope and limitations of the Steglich rearrangement with achiral NHCs, the asymmetric variant was next examined. To investigate the asymmetric Steglich rearrangement, a library of enantiomerically pure azolium salts as precursors to the desired chiral NHC catalysts was compiled.

Section 5.1.1: Chiral imidazolium salts

Section 5.1.1.1: C_2-Symmetric imidazolium salts

The first set of chiral NHC precatalysts chosen for preparation were the imidazolium salts, as the inherent C_2-symmetry of the imidazolium core was appealing. Even if predicted to be less effective than triazolium-derived NHCs, the C_2-symmetry would restrict the number of reactive conformations of the proposed carboxyazolium cation **342** and may prove to be good candidates for asymmetric induction (Figure 108).



342

Figure 108: Proposed conformational restriction of the carboxyl moiety about a C_2-axis

Choosing the α-methylbenzyl stereodirecting unit, the C_2-symmetric imidazolium salt **344** was prepared from the commercially available (*S*)-α-methylbenzylamine **343**, paraformaldehyde, glyoxal and aqueous tetrafluoroboric acid as a source of the required counterion in a one-pot procedure (Figure 109).

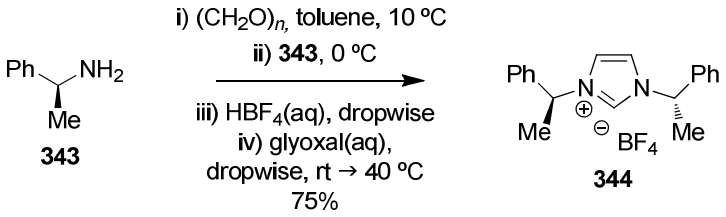
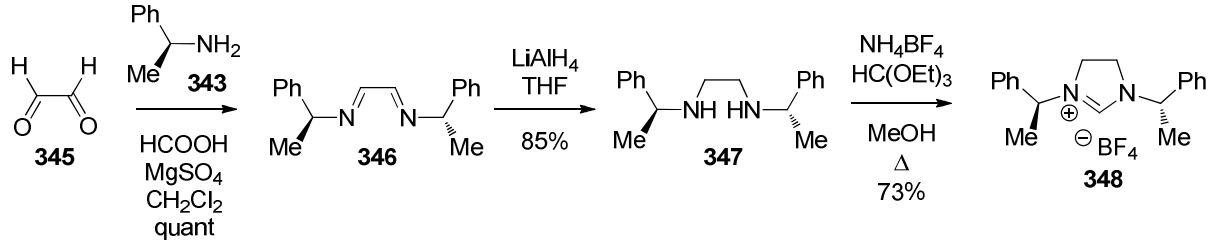


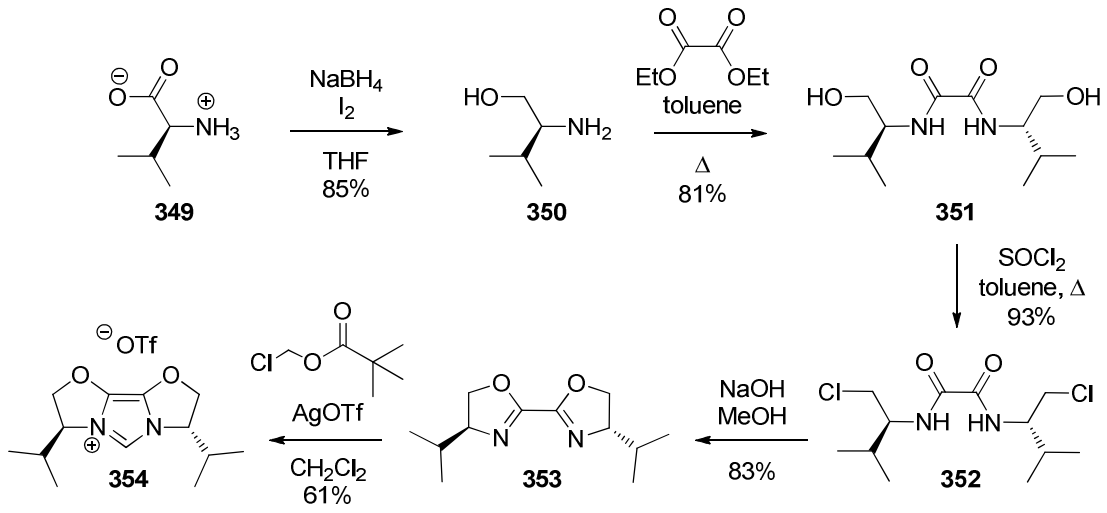
Figure 109: Preparation of imidazolium salt **344**

The related imidazolinium salt **348** was prepared in three steps from (*S*)-α-methylbenzylamine **343** and glyoxal **345**. Condensation gave diimine **346** in quantitative crude yield, which was reduced with lithium aluminium hydride to afford the diamine **347**, then cyclised using triethyl orthoformate and ammonium tetrafluoroborate in methanol to afford the imidazolinium salt **348** in good yield over the two steps (Scheme 7).



Scheme 7: Preparation of imidazolinium salt **348**

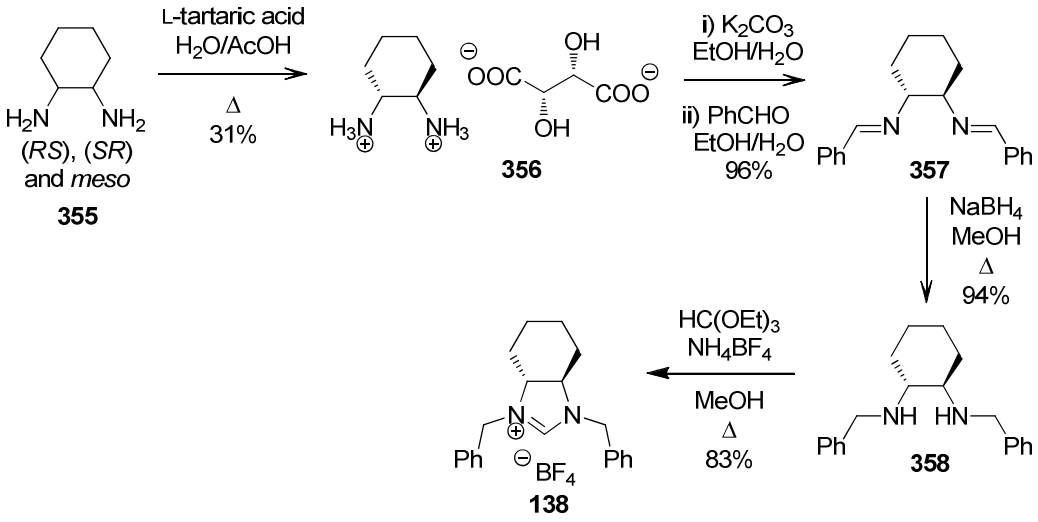
A third imidazolium-based catalyst series was synthesised based upon the Bisox ligand **353** scaffold (Scheme 8). By formation of an imidazolium salt between the two oxazoline rings, tricyclic C_2-symmetric imidazolium salt IBox HOTf **354** was synthesised. Edwards and co-workers had reported a three step protocol for conversion of (*S*)-valinol **350** to the desired Bisox ligand **353**.[136] Access to (*S*)-valinol **350** was achieved by reduction of (*S*)-valine **349** using sodium borohydride and iodine.[137] Formation of diamide **351** was achieved using diethyl oxalate, followed by conversion of diol **351** to dichloride **352** using thionyl chloride, with final ring closure to the bisoxazoline **353** using sodium hydroxide. Pleasingly, this process was achieved smoothly in very good yield (63% over the three steps). Cyclisation to the imidazolium salt **354** was effected according to literature precedent[138] using chloromethyl pivalate and silver triflate in good yield.



Scheme 8: Preparation of IBox HOTf precatalyst **354**

A fourth NHC precatalyst class was based upon the cyclohexanediamine scaffold, by conversion of enantiopure (*R*,*R*)-1,2-*trans*-diaminocyclohexane to the imidazolinium salt **359** (Scheme 9). This was achieved *via* an initial resolution of a mixture of the three possible 1,2-diaminocyclohexane stereoisomers using L-tartaric acid, affording the (*R*,*R*)-diamine as the L-tartrate salt **356**,[139] which was then converted to its dibenzylidene dimine **357**, reduced to its dibenzylamine **358**, then cyclised with triethyl orthoformate and ammonium tetrafluoroborate

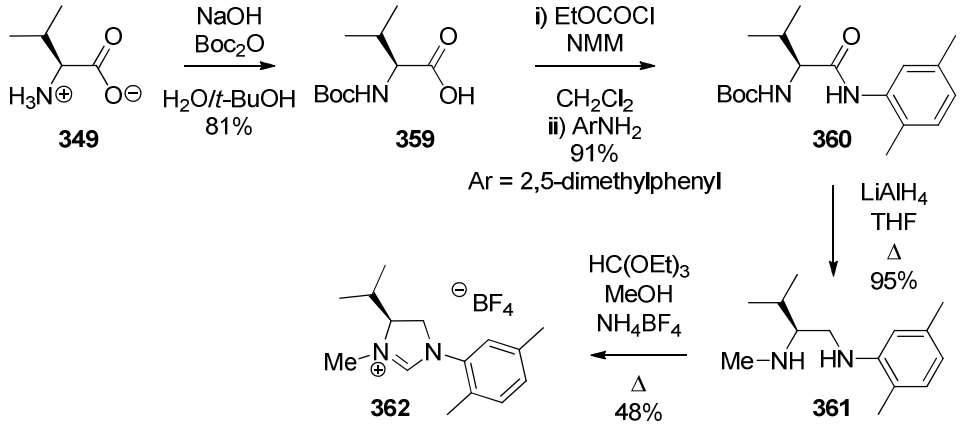
promoted cyclisation to the desired imidazolinium salt **138** in very good yield. The dibenzyl derivative was chosen as the stereodirecting cyclohexyl unit would be somewhat remote from the carboxyazolium moiety, and we envisaged that the conformationally flexible *N*-benzyl groups could exhibit a chiral relay effect, a transmission or amplification of chiral information within that substrate close to the point of the reaction through conformational restraints.[140,141,142,143]



Scheme 9: Preparation of imidazolinium salt **138**

Section 5.1.1.2: C_1-Symmetric imidazolium salts

To complement the set of C_2-symmetric salts, a range of bespoke chiral imidazolinium salts were prepared from the chiral pool of amino acids.[144] As an illustration of this methodology, several routes were investigated as there were a number of points of diversification. The first strategy illustrated preparation of a 'mixed' *N*-alkyl, *N*′-aryl substituted imidazolinium salt **362**. Initial Boc protection of L-valine was achieved under Schotten-Baumann type conditions in good yield, followed by amide coupling *via* the mixed anhydride and trapping with the requisite aniline, in this case, 2,5-dimethylaniline. Boc-protected amide **360** was fully reduced to the desired diamine intermediate **361** by treatment with excess $LiAlH_4$ at reflux in THF, affording the *N*-aryl, *N*′-methyl diamine in excellent yield, which was pleasingly cyclised to the desired imidazolinium salt **362** with triethyl orthoformate and ammonium tetrafluoroborate in moderate yield.



Scheme 10: Preparation of C_1-symmetric catalyst

A particular problem found with peptide-type coupling is that of racemisation of the sensitive α-position. To attempt to ascertain the stereochemical integrity of the transformations in the synthesis, enantiomerically pure (*S*)-α-methylbenzylamine was employed as a diastereomeric marker. The synthetic route was carried out using both enantiomerically pure L-valine and racemic DL-valine, with only enantiomerically pure (*S*)-α-methylbenzylamine as the amide coupling partner (Figure 110). ^{1}H NMR Spectroscopic analysis indicated a 50:50 mixture of diastereomers in the preparation using DL-valine, but only one diastereomer was detected in the amide coupling with enantiomerically pure L-valine, so stereochemical integrity was assured during the amide coupling step.

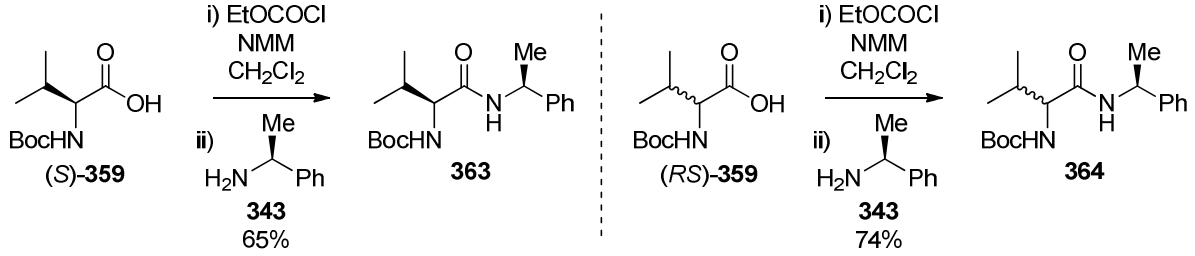
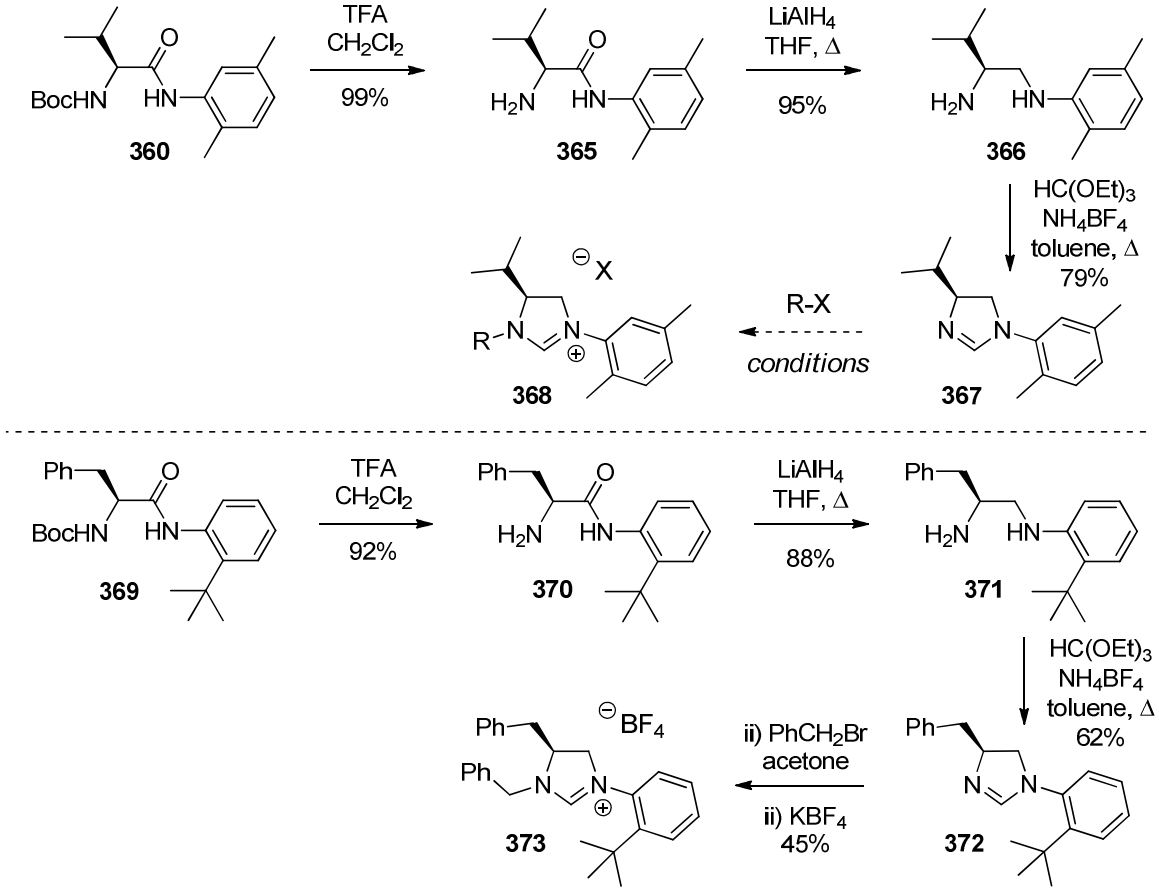


Figure 110: Use of a stereochemical marker

To ascertain if racemisation was occurring in the reduction step, both the single diastereomer and the mixed diastereomeric product were both subjected to $LiAlH_4$ reduction. Surprisingly, it appeared that the alkylamine-derived products **363** and **364** were ill-suited to the reduction, even under considerably more forcing conditions with large excesses (>10 equiv) of reducing agents $LiAlH_4$ or BH_3·THF at reflux for 7 days. This may be attributable to the difference in electrophilicity between the alkylamides and arylamides, but the exact nature of these processes is unclear; Voight and co-workers note that such reductions of (Boc-amino) and amino amides are often unreliable and give low to moderate yields of secondary amines.[145] This has been attributed to incomplete reactions, difficulty in the cleavage of the B–N bond following

reduction with borane, and side-reactions, particularly leading to significant amounts of cyclic ureas when using $LiAlH_4$.

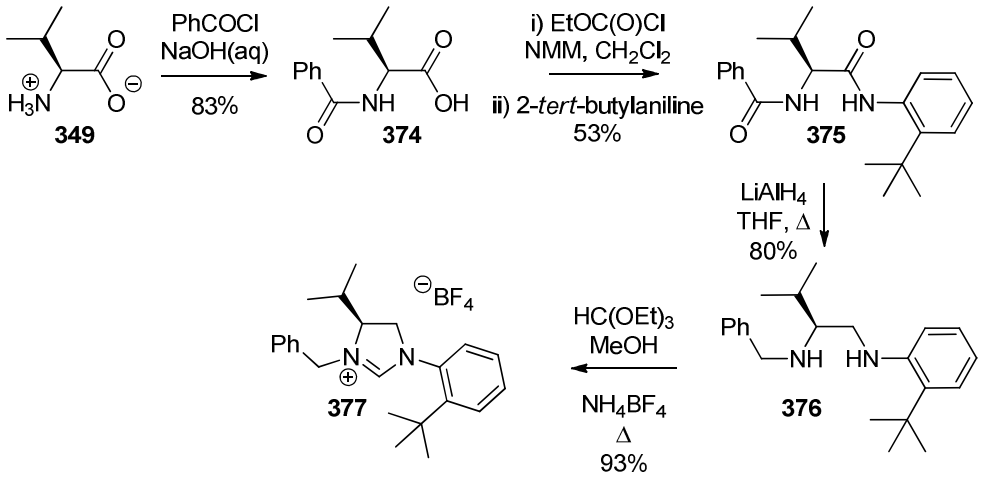
It was envisaged that a library of *N*-alkyl, *N*′-aryl substituted imidazolinium salts could be prepared *via* alkylation of imidazolines (Scheme 11). The chiral imidazoline, or amidine, **367** was prepared by deprotection of the carbamate functionality of the previously prepared amide **360** using TFA, followed by full reduction of the amino amide **365** with $LiAlH_4$ to afford the diamine **366** in excellent yield and purity. The diamine **366** was converted to the desired amidine **367** using triethyl orthoformate and NH_4BF_4 as a source of acid, in very good yield. It was noted at this juncture that this amidine intermediate, whilst key in attempting to prepare a number of imidazolinium salts, could in fact act as a Lewis base catalyst in its own right. Completing the synthetic strategy, alkylation was attempted using benzyl bromide followed by anion exchange to afford the desired imidazolinium salt **368**. Whilst partially successful, purification proved difficult due to the polar nature of the by-products, however, alkylation of the analogous phenylalanine-derived amidine **372** proved highly successful in obtaining the purified product **373**, as demonstrated by a colleague in the group.[i]



Scheme 11: Preparation of chiral amidines and alkylation to imidazolinium salts

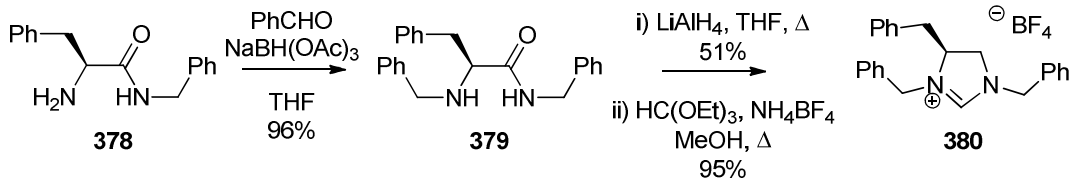
[i] Demonstrated by Eddy Kallström, MChem Masters thesis 2009, University of St Andrews.

With a benzyl substituted phenylalanine-derived imidazolinium salt in hand, the related imidazolinium salt **377** with the isopropyl stereodirecting group was prepared *via* acylation of L-valine (Scheme 12). Under Schotten-Bauman conditions, *N*-benzoylvaline **374** was prepared in good yield, which was then transformed to the diamide *via* the mixed anhydride and treatment with the relevant aniline. Reduction of the diamide **375** with $LiAlH_4$ or BH_3 (generated *in situ* from $NaBH_4$ and I_2) gave, after extended reaction times (>7 days) with a large excess of reducing agent, a mixture of reduction products. Nonetheless, an acceptable yield (80%) of the desired diamine **376** was obtained following chromatographic purification, which was transformed to the desired imidazolinium salt **377** under the established protocols using triethyl orthoformate and ammonium tetrafluoroborate in excellent yield.



Scheme 12: Preparation of the chiral imidazolinium salt **377**

Cognisant of the reports of Voight and the difficulties experienced in our hands, an alternative route to preparing such substituted imidazolinium salts was sought, particularly as a dialkyl substituted imidazolinium salt had yet to have been prepared readily. In collaboration with a colleague,[i] a method to prepare such dialkyl-substituted imidazolinium salts was developed by reductive amination of phenylalanine-derived amino amide **378** using benzaldehyde and $NaBH(OAc)_3$, followed by reduction of the alkylated amide **379** and final cyclisation using triethyl orthoformate and NH_4BF_4 in excellent yield (Scheme 13).



Scheme 13: Synthesis of the dialkyl substituted imidazolinium salt **380** (prepared by Eddy Kallström)

[i] Prepared by Eddy Kallström using the phenylalanine-derived substrate, MChem Masters thesis 2009, University of St Andrews. Attempts to repeat this strategy with the analogous valine derivative proved unsuccessful.

Section 5.1.2: Chiral triazolium salts

Cognisant of the improved reactivity observed in the Steglich rearrangement employing triazolium-derived NHCs in the racemic series, a diverse library of chiral triazolium salts were designed and prepared. Such triazolium salt scaffolds were generally prepared according to the one-pot transformation from the requisite lactam, pioneered by Leeper and co-workers[33] and reinvestigated by Rovis and co-workers[146,147] To evaluate fully the potential of chiral triazolium-derived NHCs in the asymmetric Steglich rearrangement, a range of potential scaffolds were identified (Figure 111). The closest relative to the achiral triazolium salt precatalyst, the most successful NHC architecture (see Chapters 2–4), was that based upon structure **381**, derived from chiral pyrrolidones of the form **384**. Maintaining a 5:5-bicyclic scaffold, incorporation of an oxygen atom was envisaged to perturb the electronic properties of the NHC ring system (i.e. scaffolds of the form **382**), which could be derived from oxazolidinones **385**. Finally, variation of the ring size was identified, with 6:5-fused ring systems **383** chosen as the target, ultimately derived from morpholinones **386**.

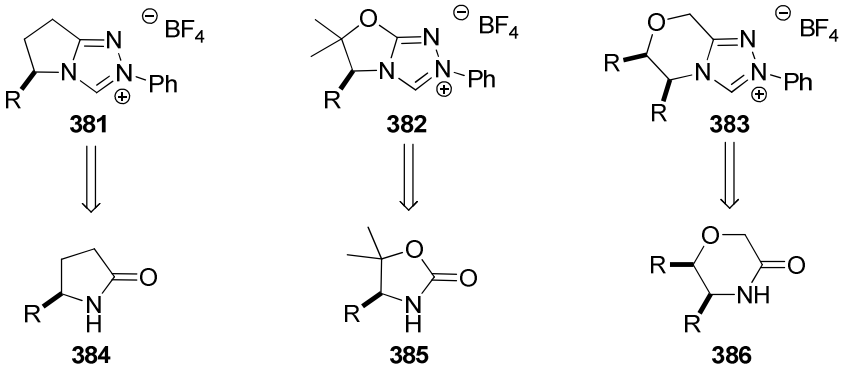
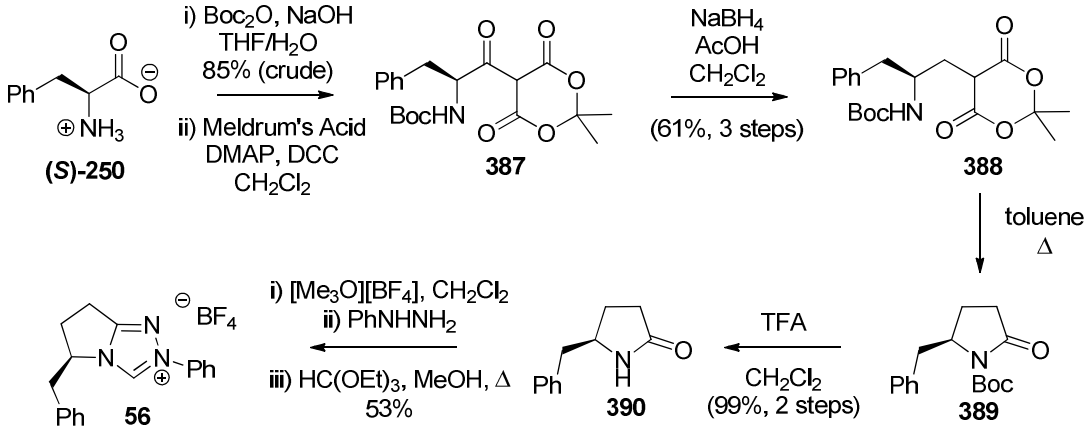


Figure 111: Set of lactam, oxazolidinone and morpholinone-derived triazolium salts

A range of such triazolium salts was prepared following procedures described in the literature or from common precursors in the literature, derivatives of materials from the chiral pool. Whilst many of these desired salts have been prepared previously in the literature, explicit preparative methods of both the intermediates and product triazolium salts were often not given, so our initial aim was to develop successful synthetic procedures in order to prepare these precatalysts.

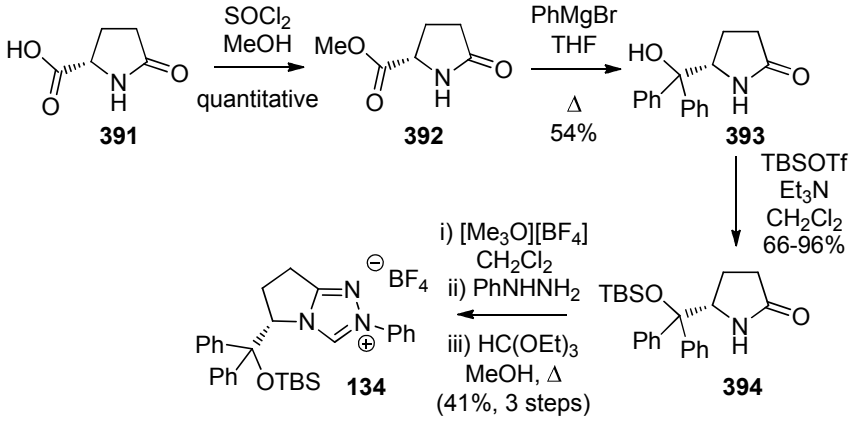
The first chiral triazolium salt **56**, bearing the identical bicyclic architecture to the achiral triazolium salt **128**, was prepared following literature precedent from L-phenylalanine (Scheme 14).[147] Treatment of L-phenylalanine with Boc_2O under Schotten-Bauman type conditions afforded the *N*-Boc amino acid. The crude protected amino acid was treated with DCC and Meldrum's acid to afford the ketomalonate product **387**, which was again carried through crude to the next step. Reduction with sodium borohydride gave the coupled malonate

derivative **388** by full reduction of the keto-functionality, in good yield after purification. Pyrolysis of this malonate derivative in toluene at reflux gave the desired Boc-protected lactam **389**, which was then deprotected with trifluoroacetic acid to obtain pyrrolidinone **390** in quantitative yield over the two steps. Following the standard protocol for transformation of lactams to triazolium salts, namely, through conversion to the methyl imino ether with trimethyloxonium tetrafluoroborate, the amino hydrazone with phenylhydrazine and cyclisation with triethyl orthoformate, the desired triazolium salt **56** was obtained in good yield.



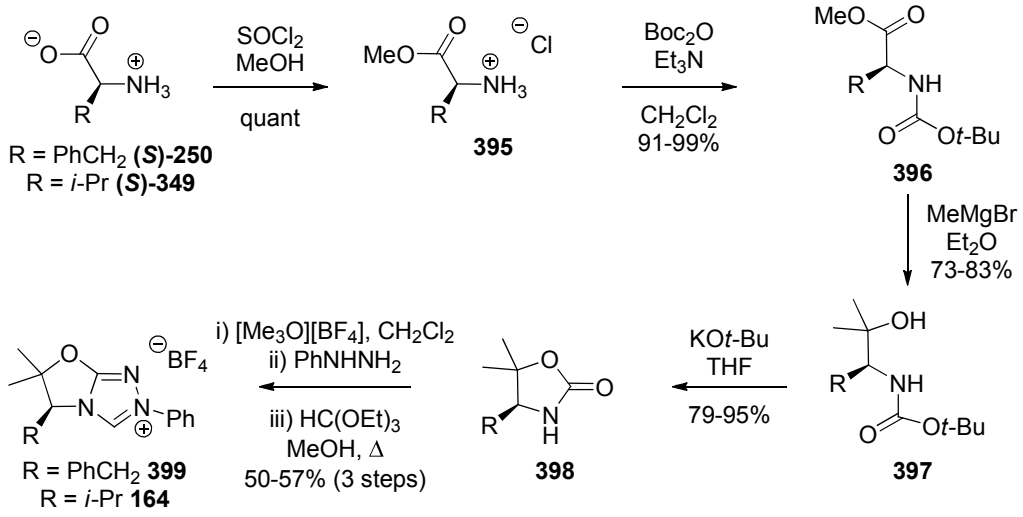
Scheme 14: Preparation of the 5:5-fused bicyclic catalyst **56**

Another triazolium salt based on this 5:5-fused scaffold was prepared starting from commercially available (*S*)-pyroglutamic acid **391** (Scheme 15). Treatment of the pyroglutamic acid **392** with thionyl chloride in methanol afforded the methyl pyroglutamate **392** in quantitative yield, which was treated with excess phenylmagnesium bromide to afford the tertiary alcohol **393** in good yield. Though successful, further developments in the group have led to the use of phenyllithium as the organometallic reagent, generated *in situ* from bromobenzene and *n*-BuLi, which considerably simplifies the purification step. Silyl protection was achieved by treatment of the alcohol **393** with excess *tert*-butyldimethylsilyl triflate and Et_3N in several portions in generally good isolated yield. The lactam **394** was then transformed into the desired triazolium salt **134** according to the literature procedure, using the standard conditions *via* the imino ether and imino hydrazone salts.



Scheme 15: Synthesis of the pyroglutamic acid-derived triazolium salt

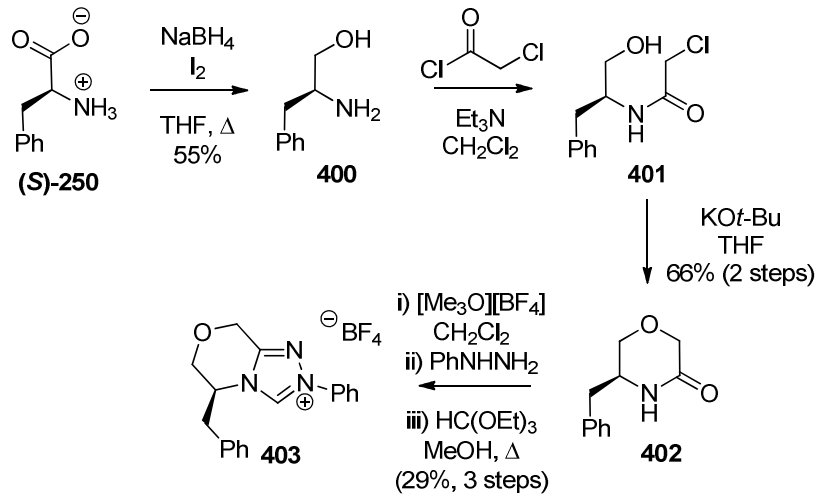
The related oxazolidinone-derived triazolium salts were next prepared from the known SuperQuat auxiliaries **385**, prepared from the requisite amino acids L-phenylalanine and L-valine (Scheme 16).[148] The amino acids were first converted to their methyl ester hydrochlorides **395** then Boc-protected in good yield. Treatment of the esters **396** with methylmagnesium bromide afforded the tertiary alcohols **397** in good yield, which were then cyclised to the desired oxazolidinones **398** with KO*t*-Bu in excellent yield. With the key oxazolidinones in hand, the standard three-step protocol afforded the desired triazolium salts **164** and **399** in good yield over the three steps.



Scheme 16: Synthesis of oxazolidinone-derived triazolium salts

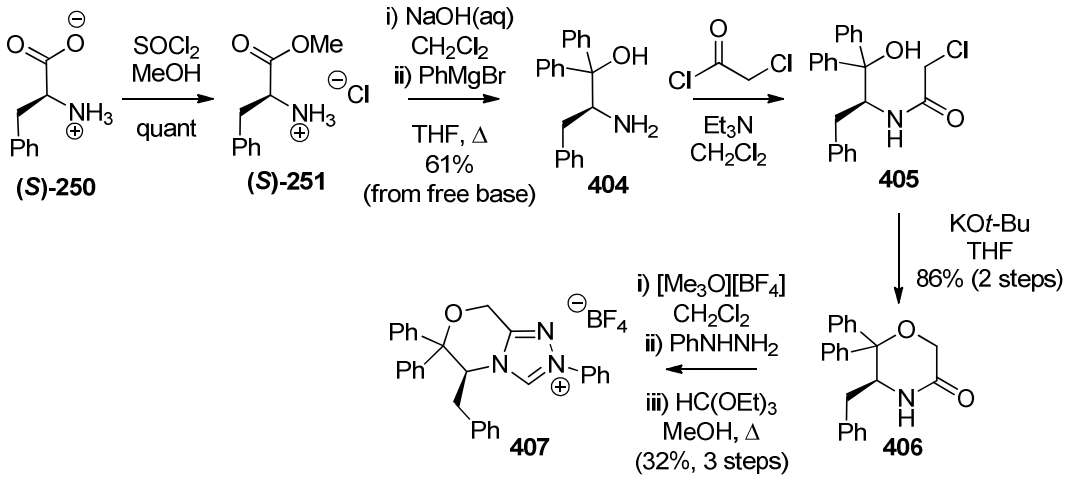
To complement the set of 5:5-fused bicyclic triazolium salts, a number of 5:6-fused bicyclic salts were prepared based on the morpholinone architecture. The first of such morpholinone-derived triazolium salts was the phenylalanine-derived salt **403** (Scheme 17). The desired 1,2-aminoalcohol **400**, the precursor to the morpholinone, was prepared by borane reduction of L-phenylalanine to phenylalaninol **400** using sodium borohydride and iodine. The desired

morpholin-3-one **402** was obtained by a two-step sequential protocol, firstly through amide coupling with chloroacetyl chloride, then intramolecular cyclisation with KO*t*-Bu in good isolated yield over the two steps. With the desired lactam in hand, transformation to the desired triazolium salt **403** was achieved using the standard conditions in moderate yield.



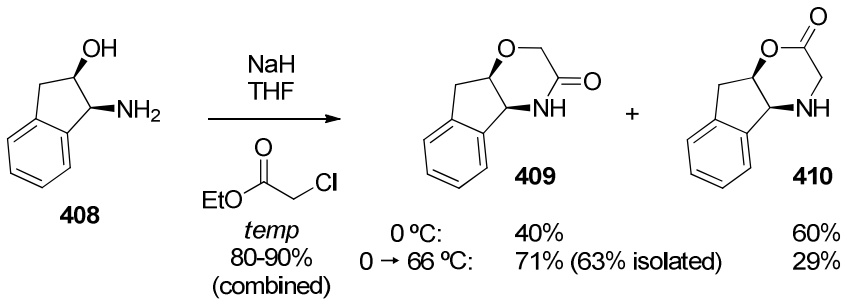
Scheme 17: Preparation of the 6:5-fused bicyclic catalyst

In order to increase the effect of the stereodirecting group, the *gem*-diphenyl substituted triazolium salt **407** was prepared (Scheme 18). It was believed that the presence of the phenyl groups in the constrained ring may restrict the degrees of freedom about the stereodirecting benzyl group, thereby enforcing orientation further towards the active site of the generated NHC.[149] The desired substituted morpholinone intermediate **406** was again prepared from L-phenylalanine, with first conversion to its methyl ester hydrochloride **251**. Treatment of the ester hydrochloride with excess phenylmagnesium bromide gave irreproducible isolated yields of the desired amino alcohol **404**, but conversion to the phenylalanine methyl ester free base and treatment with phenylmagnesium bromide gave more reliable isolated yields of the desired product **404**. Following the same two step procedure as for phenylalaninol, the desired morpholinone **406** was obtained in excellent yield. Final transformation to the desired triazolium salt **407** was achieved by the standard three-step protocol in moderate yield.



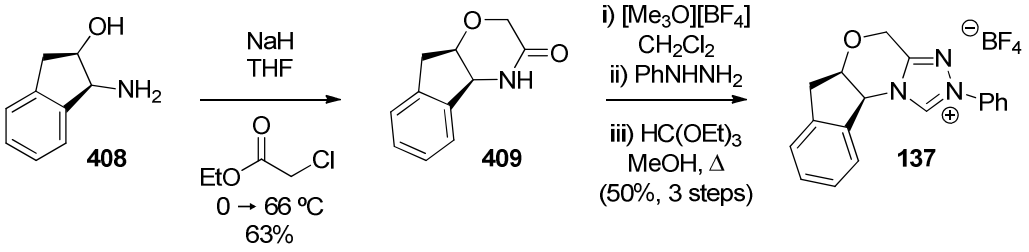
Scheme 18: Preparation of the more sterically constrained 6:5-fused bicyclic catalyst

The chiral NHC precatalyst **137** developed by Rovis looked attractive to access potential asymmetric Steglich rearrangements, having been demonstrated to effect asymmetric Stetter reactions with high enantioselectivity.[146] Starting from commercially available aminoindanol **408**, the conversion to morpholin-3-one derivative **409** was investigated. Surprisingly, the two step sequential process using either chloroacetyl chloride or bromoacetyl bromide gave a complex mixture of products. Variation of the conditions and with a range of potential dielectrophiles gave mixtures of the desired morpholinone **409** and its regioisomeric product **410**. Where the usual two-step protocol proceeds *via* amidation followed by alkoxide-promoted S_N2 ring closure, inversion of the reaction sequence was optimal in promoting successful morpholinone formation. The initial amidation process, however, was a significant competing pathway. The optimal conditions were found using ethyl chloroacetate with the anion of the aminoindanol **408**, at elevated temperature (66 ºC). This improved the ratio of 3-morpholinone:2-morpholinone to 71:29, from which the desired morpholinone product **409** was isolated in good yield (63%) (Scheme 19).



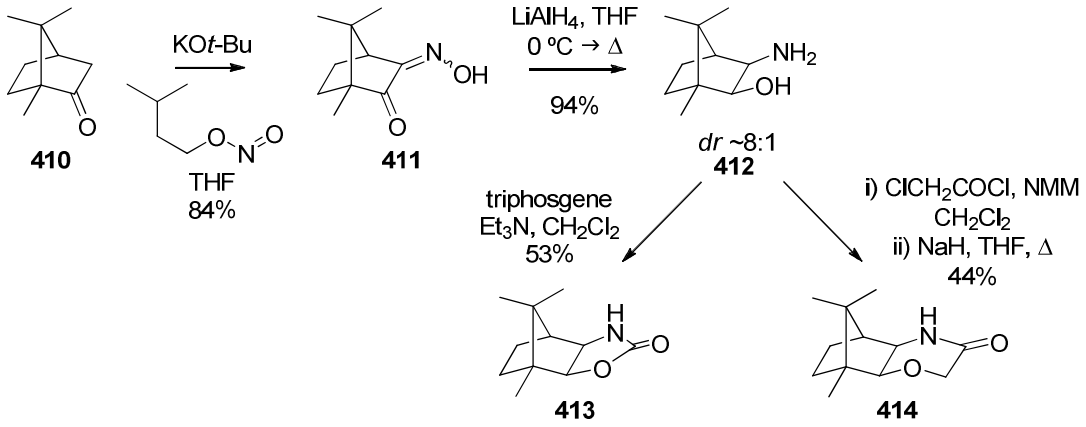
Scheme 19: Selectivity issue with formation of the desired 3-morpholinone **409**

Following the standard protocol for conversion of lactam to triazolium salt, the desired aminoindanol-derived triazolium salt **137** was obtained in good yield over three steps (Scheme 20).



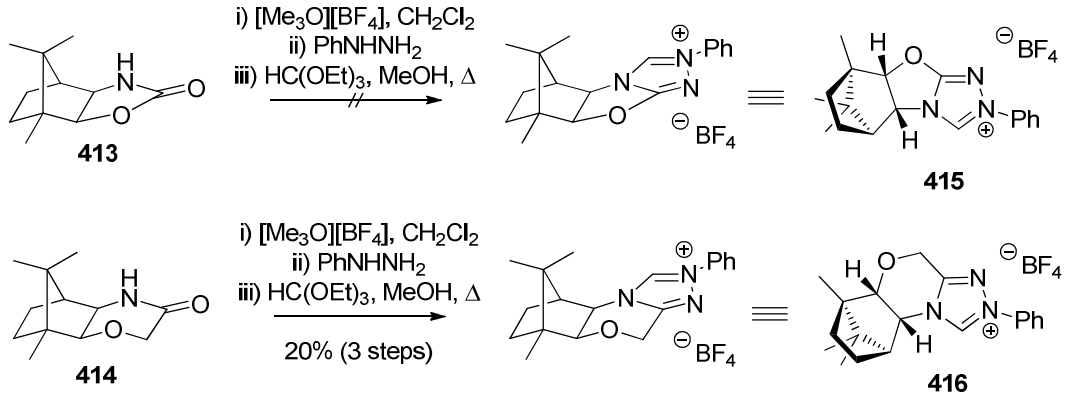
Scheme 20: Preparation of the precatalyst **137**

Finally, oxazolidinone **413** and morpholinone **414** targets were prepared from the terpene D-camphor **410** (Scheme 21). α-Oximation was achieved *via* treatment of the camphor enolate with *i*-amyl nitrite, giving as a mixture of *E*- and *Z*- diastereomeric oximes **411** in excellent yield. Both the oxime and ketone functionalities were reduced with $LiAlH_4$ to afford the *syn*-1,2-aminoalcohol **412** in excellent yield and high *dr* (~8:1). The amino alcohol **412** was diversified *via* treatment with triphosgene to afford the oxazolidinone **413**, and using chloroacetyl chloride followed by intramolecular cyclisation to the morpholinone analogue **414**, both in moderate yield.



Scheme 21: Preparation of the camphor-derived oxazolidinone **413** and morpholinone **414**

With the key intermediates in hand, preparation of the desired triazolium salts *via* the three-step procedure was investigated (Scheme 22). The morpholinone **414** underwent successful transformation to the desired triazolium salt **416** in moderate yield, however, reaction with the camphor-derived oxazolidinone **413** gave a complex mixture of products.



Scheme 22: Preparation of the camphor-derived precatalyst **416**

Section 5.2: Enantioselective Steglich rearrangements

Section 5.2.1: Investigations with model phenyl carbonate

To evaluate the potential of performing the Steglich rearrangement asymmetrically using chiral NHCs, phenylalanine-derived phenyl carbonate **256** was chosen as the model substrate. This carbonate had proven to be one of the most readily rearranged substrates and the product *ee* could be determined readily by chiral HPLC.[i] The set of standard conditions developed in the achiral series, namely 10 mol% of azolium precatalyst, 9 mol% KHMDS as the base and THF as the solvent, were used and reactions were carried out at ambient temperature.

Section 5.2.1.1: Imidazolium-derived NHCs

Studies using the imidazolium-derived NHC were not encouraging (Figure 112, Table 18). C_2-Symmetric imidazolium salts **344**, **348**, **354** and **138** as NHC precursors gave either low conversion to the desired product **266** (in the case with azolium salt **354**), or quantitative conversion but low enantioselectivities of <5% *ee*. Evaluation of the C_1-symmetric imidazolinium NHC precatalysts **362**, **377** and **380** also showed that these were unsuitable candidates, giving low conversion to the desired rearrangement product or with low levels of enantiomeric enrichment (<5% *ee*).

[i] Chiral HPLC analysis used to determine all enantioselectivities, using a CHIRALPAK AD or OD-H column.

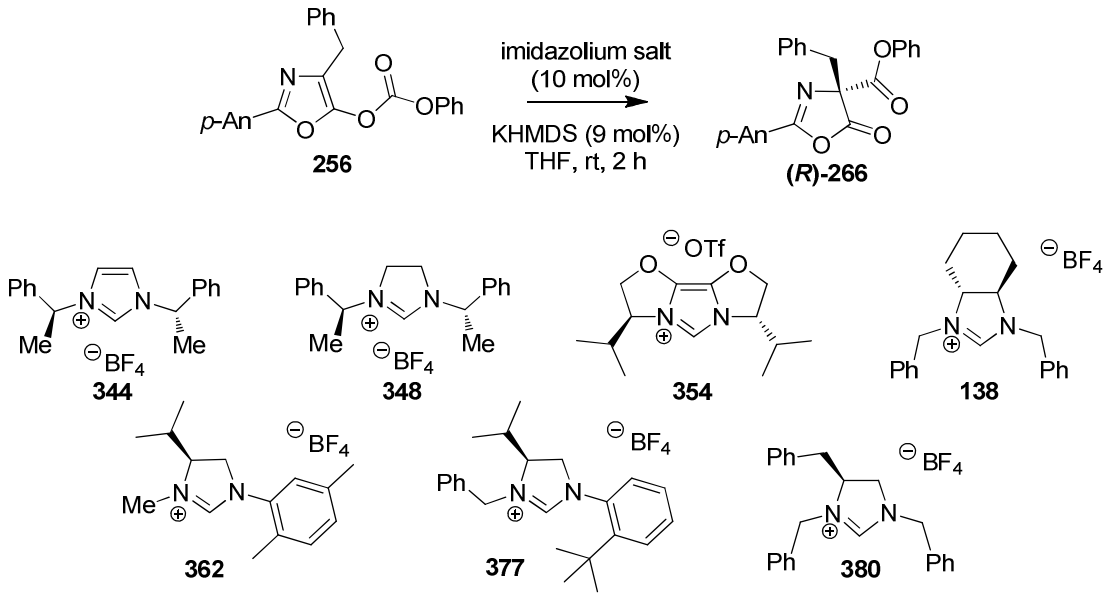


Figure 112: Asymmetric Steglich rearrangement with chiral diazolium salt-derived NHCs

Imidazolium salt	Conversion (%) [a]	*ee* of (*R*)-266 (%) [b]
344	70	<5
348	>98	<5
354	<5	-
138	65	11
362	75	<5
377	~20	-
380	~65	<5

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Small samples of purified material isolated by silica chromatography in order to determine *ee* by chiral HPLC.

Table 18: Imidazolium-derived NHCs in the asymmetric Steglich rearrangement

The apparent low reactivity of these imidazolium-derived NHCs would not be expected due to steric effects, as the achiral relatives IMes and SIMes both promoted high levels of conversion to the desired *C*-carboxyazlactone product **266**. With many of these chiral imidazolium-derived NHCs bearing less sterically demanding N-substituents than those of the achiral IMes and SIMes NHCs, the reduced reactivity could be due to carboxyazolium and dienolate recombination to reform the carbonate substrate **256**. This would be consistent with the observations noted using SIMes in crossover experiments. Similar such studies, however, have not been undertaken using these chiral imidazolium-derived NHCs.

Section 5.2.1.2: Triazolium-derived NHCs

Having determined an enhanced reactivity profile of triazolium-derived NHCs in the achiral series, the asymmetric Steglich rearrangement using chiral triazolium-derived NHCs was next

investigated, beginning with the 5:5-fused bicyclic triazolium salts **56**, **134**, **399** and **164** (Figure 113, Table 19).

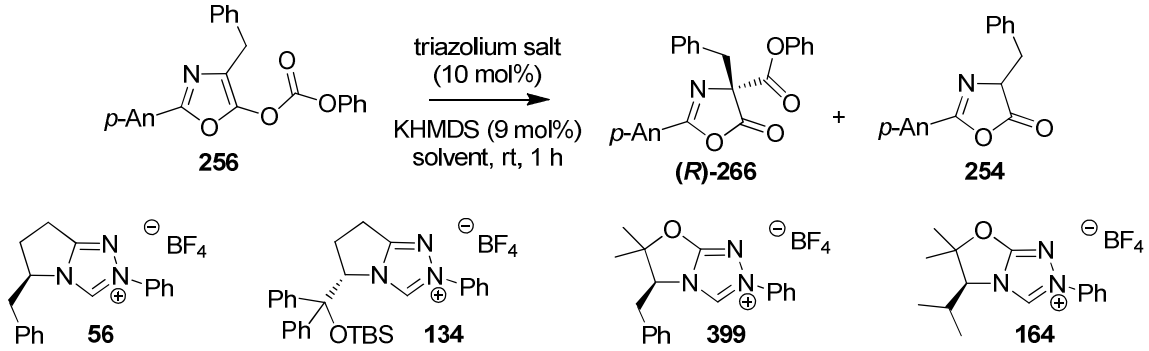


Figure 113: 5:5-Fused bicyclic triazolium-derived NHCs in the asymmetric Steglich rearrangement

Triazolium salt	Solvent	Conversion (*R*)-266:254 (%) [a]	*ee* of (*R*)-266 (%)
56	THF	~70:30	<5
56	toluene	~55:45	<5
134	THF	>98:<2	20 (*ent*)
134	toluene	95:5	20 (*ent*)
399	THF	>98:<2	<5
399	toluene	>98:<2	34
164	THF	>98:<2	16
164	toluene	88:12	31

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

Table 19: 5:5-Fused bicyclic triazolium-derived NHCs in the asymmetric Steglich rearrangement

Using the standard conditions in THF, these triazolium-derived NHC catalysts proved effective in promoting efficient rearrangement, generally obtaining the desired *C*-carboxyazlactone **266** in >98% conversion within 1 h. The least effective precatalyst was the pyrrolidinone-derived triazolium salt **56**, affording a ~70:30 mixture of desired product **266** to the decarboxylated product, azlactone **254**.[i] The levels of enantioenrichment, however, were modest (≤20% *ee*). By repeating the reactions using toluene as the solvent, the competing formation of azlactone **254** was more pronounced, though the phenylalanine-derived precatalyst **399** suffered no such loss in product formation. The change of solvent to toluene also generally resulted in an increase in the enantioselectivity of the process, with the phenylalanine-derived precatalyst **399** proving optimal also in terms of enantioselectivity (34% *ee*).

The range of morpholinone-derived NHC-precatalysts[ii] was evaluated under similar conditions (Figure 114, Table 20). Similar trends of reactivity and enantioselectivity were obtained with

[i] Similar proportions of diphenyl carbonate **305** are also assumed, though precise measurement was not possible spectroscopically.
[ii] Triazolium salt ***ent*-170** was kindly donated by Prof. Jeffrey Bode.

these morpholinone-derived triazolium salts, in comparison with 5:5-fused bicyclic triazolium salts. All of these triazolium-derived NHCs proved highly effective catalysts in THF, obtaining exclusively the desired *C*-carboxyazlactone product **266**, though as effectively racemic products in all cases. By changing the solvent to toluene, competing decarboxylation was observed in most cases, though this was minimal (<10%). The only catalyst which gave a significant, though small, increase in enantioselectivity was that derived from triazolium salt **416** (<5% → 20% *ee*).

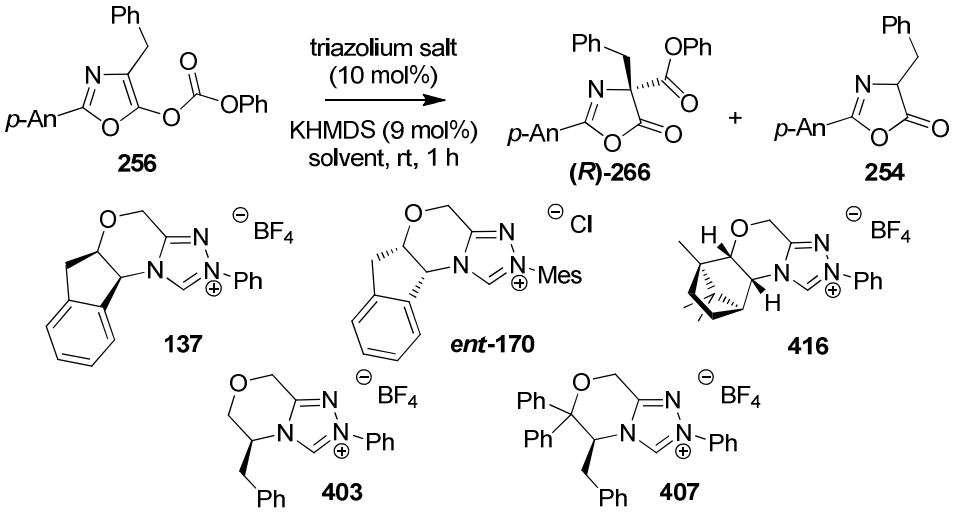


Figure 114: Morpholinone-derived NHCs as catalysts for the asymmetric Steglich rearrangement

Triazolium salt	Solvent	Conversion (*R*)-266:254 (%) [a]	*ee* of (*R*)-266 (%)
137	THF	>98:<2	<5
137	toluene	>98<:2	<5
***ent*-170**	THF	>98:<2	<5 (*ent*)
***ent*-170**	toluene	>95:<5	<5 (*ent*)
416	THF	>98:<2	<5 (*ent*)
416	toluene	95:5	20 (*ent*)
403	THF	>98:<2	<5
403	toluene	88:12	<5
407	THF	>98:<2	<5
407	toluene	90:10	6

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

Table 20: 6:5-Fused bicyclic triazolium-derived NHCs in the asymmetric Steglich rearrangement

Having obtained relatively low levels of enantioselectivity with all NHC catalysts, other variables were next investigated to try to improve the enantioselectivity. Since the aminoindanol-derived catalysts, both known to effect excellent levels of enantioselectivity in Stetter reactions, proved ineffective at promoting asymmetry in the rearrangement reaction under the conditions evaluated, these triazolium salts were chosen for initial optimisation (Figure 115, Table 21). Variation of the base which generated the NHC appeared to have little effect on the *ee*

of the product, returning essentially racemic products, so the catalyst loading, solvent and reaction temperature were varied. Under a wide variety of conditions, with only some selected as an illustration, the aminoindanol-derived NHCs suffered from at least one of several drawbacks: at temperatures of ≥0 ºC, complete rearrangement was observed within 1 h but the products were essentially racemic; lowering of the reaction temperature did improve the enantioselectivity, but this was modest (≤20% *ee*), and at the detriment of requiring extended reaction times (up to 16 h) to effect complete rearrangement. Furthermore, at low temperature, significant proportions of the decarboxylated azlactone precursor **254** were returned (up to 20%), even with strict exclusion of air and moisture from the reaction manifold, presumably as a result of competing decarboxylation. Variation of the *N*-aryl moiety from phenyl to the more hindered mesityl substituent also appeared detrimental to the reaction in terms of both reactivity and enantioselectivity, however, the role of the different counterion cannot be excluded.

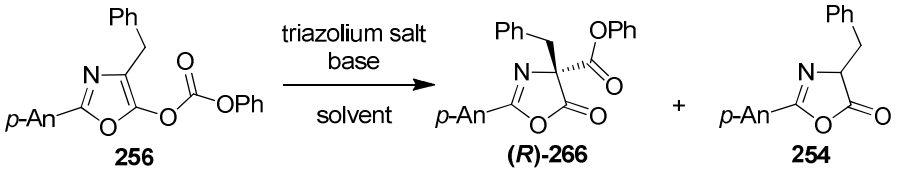
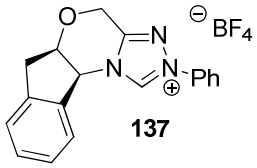
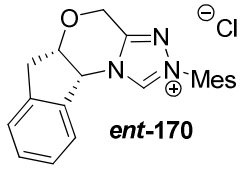


Figure 115: Optimisation studies using aminoindanol-derived triazolium salts

Precatalyst	Precatalyst loading (mol%)	Base (mol%)	Solvent	Temp (ºC)	Conversion (*R*)-266:254 (%) [a]	ee (%)
 **137**	10	KHMDS (9)		0	>98:<2	<5
	10	KHMDS (9)		-78 to rt	~90:10	12
	5	KHMDS (4.5)		-78 to rt	~90:10	12
	1	KHMDS (0.9)	THF	-78 to rt	~85:15	13
	10	*n*-BuLi (9)		-78 to rt	~90:10	9
	10	LiHMDS (9)		-78 to rt	~90:10	10
	10	Et_3N (9)		rt	~90:10	11
	5	KHMDS (4.5)		rt	>98:<2	<5
	5	KHMDS (4.5)	toluene	-78 to rt	~85:15	20
	50	KHMDS (45)		-78 to rt	~95:5	<5
 ***ent*-170**	10	KHMDS (9)	THF	-78 to rt	~85:15	8 (*ent*)
	10	Et_3N (9)	THF	rt	~85:15	5 (*ent*)
	5	KHMDS (4.5)	toluene	-78 to rt	~80:20	11 (*ent*)

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

Table 21: Optimisation studies using aminoindanol-derived triazolium salts

The reduced reactivity of the mesityl-substituted NHC (in comparison with the phenyl-substituted NHC) may be due to the increased steric parameter introduced, but there may

also be differences in electronic properties between these systems. Nolan and co-workers have obtained X-ray crystal structures of NHC-Pt complexes and examined the tilt angles θ between different *N*-aryl ring substituents and the central azolium core (Figure 116).[150] From the X-ray crystallographic data, a significant tilt angle is observed the *N*-phenyl substituted NHC of **419**, with an average of 50.9º observed, presumably as a balance between the steric repulsion in the complex and with the orbital overlap of the aromatic substituents with the central azolium core. In the *N*-mesityl substituted NHCs of complexes **417** and **418**, the steric encumbrance introduced by the N-substituents enforces the aromatic rings significantly out of conjugation with the triazolium ring, to nearly an orthogonal orientation ($\theta > 74º$). This loss of orbital overlap could have a significant impact on the electronic properties of the NHC. Whilst these observations have been made in the solid state and with related NHCs, these data may provide an explanation for the significant differences in behaviour between the differentially substituted NHCs observed in the Steglich rearrangement and also other NHC-catalysed processes.

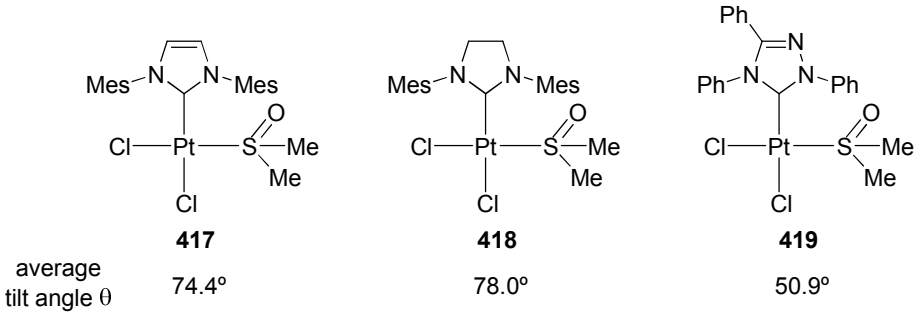


Figure 116: Tilt angles between different *N*-aryl substituents

Section 5.2.2: Optimisations of the conditions

Having identified the oxazolidinone-derived NHCs as the best candidates for the asymmetric Steglich rearrangement, the process was optimised using these catalysts. In collaboration with a colleague,[i] an extensive screen of solvents, concentration, base and temperature was performed, for which highlighted data is described below (Figure 117, Table 22). The results of the extensive efforts showed that toluene was the best solvent with which to promote the rearrangement with highest levels of enantioselectivity. Lowering the temperature to -20 or -30 ºC improved the enantioselectivity of the process up to 50% *ee*, but at the detriment of formation of the decarboxylated by-product **254**, and thus compromising the yield of the desired product. Further lowering of the reaction temperature resulted in inhibition of the rearrangement process, with no conversion of carbonate **254** being observed. Of note is that weak bases such as inorganic carbonates and Et_3N could be employed in order to promote the rearrangement of the

[i] Collaboration with Dr Carmen Concellón.

phenyl carbonate, consistent with the results obtained in the racemic series, but with no significant impact on the enantioselectivity of the process.

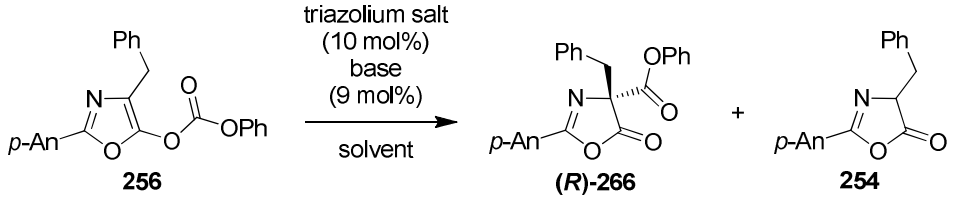
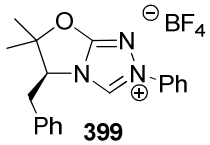
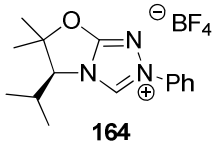


Figure 117: Optimisation using oxazolidinone-derived triazolium salts

Precatalyst	Base	Solvent	Temp (ºC)	Time (h)	Conversion (*R*)-266:254 (%) [a]	*ee* (%)
 **399**	KHMDS	PhCl	rt	1	>98:2	13
	KHMDS	Et_2O	rt	1	>98:2	27
	KHMDS	toluene	rt	1	>98:2	34
	KHMDS	toluene	-20	16	74:17 [b]	46
	KHMDS	toluene	-30	16	0:0 [b]	-
	Et_3N	CH_2Cl_2	rt	4	90:10	22
 **164**	KHMDS	PhCl	rt	1	>98:2	8
	KHMDS	toluene	rt	1	88:12	31
	KHMDS	toluene	-30	16	63:37	50
	Cs_2CO_3	THF	rt	1	80:20	25
	Cs_2CO_3	toluene	rt	1	75:25	5
	NaHMDS	toluene	rt	1	70:30	33
	LiHMDS	toluene	rt	1	>98:2	39
	n-BuLi	toluene	rt	1	0:0 [b]	-

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Remainder present as unreacted carbonate **256**

Table 22: Optimisation using oxazolidinone-derived triazolium salts

Section 5.2.3: Scope and generality of the asymmetric Steglich rearrangement

Using the optimised conditions, the scope and generality of the asymmetric process was explored. Upon reflection of all the data, the rearrangement was investigated using the three most effective NHC catalysts, the most reactive catalyst derived from triazolium salt **403**, and the oxazolidinone-derived triazolium salts **399** and **164** which gave the greatest levels of enantioselectivity. To establish if the results obtained from the model screen were representative, a range of reactive aryl carbonates and other carbonates was examined.

Using the most reactive morpholinone-derived triazolium salt **403**, the reactive ethylglycine-derived phenyl carbonate (R^1 = Et, R^2 = Ph) was chosen, and to complement the series, two of the most challenging substrates to undergo rearrangement, a methyl carbonate

(R^1 = Me, R^2 = Me) and trichlorodimethylethyl carbonate (R^1 = *i*-Bu, R^2 = CMe_2CCl_3), were examined (Figure 118, Table 23). All substrates underwent complete consumption, returning >90% *C*-carboxyazlactone **239** in all cases (the remaining material was present as the decarboxylated azlactone **276** and diphenyl carbonate **305**). Very good isolated yields of the product were obtained, but the levels of enantioenrichment were again low (up to 31% *ee*).

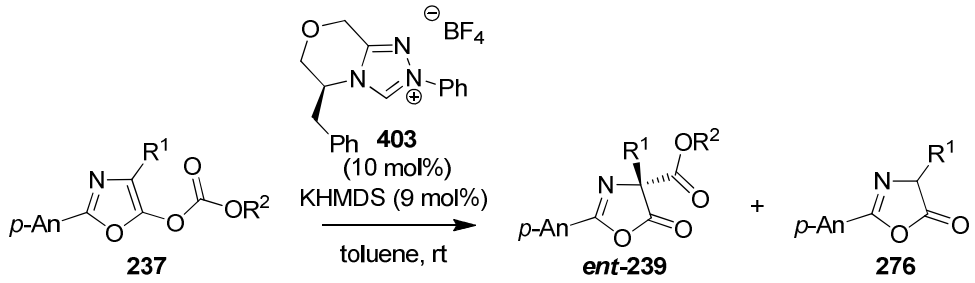


Figure 118: Scope of the asymmetric Steglich rearrangement using the reactive triazolium salt

R^1	R^2	Conversion *ent*-239:276 (%) [a]	Isolated yield (%)	*ee* (%)
$PhCH_2$	Ph	95:5	72	<5
Et	Ph	~90:10	70	<5
Me	Me	>95:5	70	31%
i-Bu	CMe_2CCl_3	>95:5	85	5%

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

Table 23: Scope of the asymmetric Steglich rearrangement with the reactive triazolium salt

Having observed good reactivity but only modest levels of enantioselectivity with the morpholinone-derived triazolium salt **403**, the oxazolidinone-derived triazolium salts **399** and **164** were more extensively investigated with a range of aryl and alkyl oxazolyl carbonates (Figure 119, Table 24). Consistent with our previous observations with achiral NHCs, aryl oxazolyl carbonates proved most amenable to rearrangement with these oxazolidinone-derived NHCs, giving good levels of reactivity in all cases with both oxazolidinone-derived NHCs. Within 1 h, all aryl carbonates underwent complete conversion to the desired aryl ester products **239**, with the exception of the phenylalanine-derived carbonates which gave a small proportion (up to 12%) of azlactone **276**. Methyl and benzyl carbonates proved reasonably amenable to rearrangement with these NHCs, with the exception of the alanine derivative (R^1 = R^2 = Me) which gave low conversions to the product (<23%). The hindered alkyl carbonates (R^2 = CMe_2CCl_3) gave modest conversions (40%) to the rearrangement products. There appeared to be no discernible trend in terms of the enantioselectivity of the process, as a wide range of enantioselectivities was obtained, ranging from <5–66% *ee*. The nature of the alkyl or aryl carbonate moiety appeared not to have a consistent bearing on the level of enantioselectivity observed: for example, the leucine-derived trichlorodimethylethyl product was obtained in

66% *ee*, the highest level for any substrate, whilst the analogous phenylalanine-derived product was obtained in only 8% *ee*.[i]

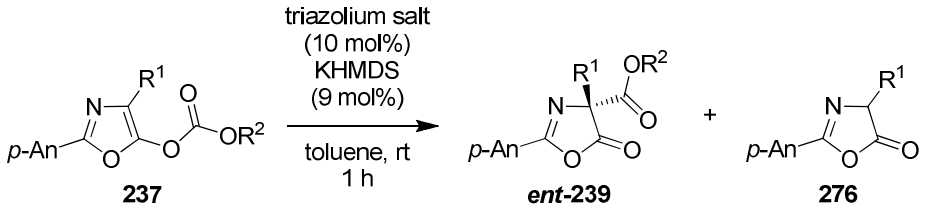
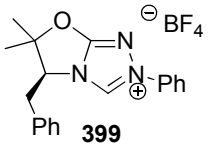
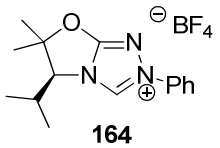


Figure 119: Scope of the asymmetric Steglich rearrangement using the oxazolidinone-derived NHCs

Precatalyst	R^1	R^2	Conversion *ent*-239:276 (%) [a]	*ee* (%)
 **399**	$PhCH_2$	Ph	>98:2	34
	Me	Ph	>98:2	42
	Et	Ph	>98:2	22
	4-$BnOC_6H_4CH_2$	Ph	>98:2	8
	Me	Me	23:0	48
	$PhCH_2$	Me	>90:0	<24 [b]
	$PhCH_2$	CMe_2CCl_3	40:0 [c]	8 [d]
	i-Bu	CMe_2CCl_3	40:0 [c]	66
 **164**	$PhCH_2$	Ph	88:12	31
	$PhCH_2$	1-naphthyl	95:5	<5
	$PhCH_2$	Me	50:0	<37 [b]
	$PhCH_2$	Bn	>98:2	25
	Me	Ph	>98:2	19
	Me	Me	0:0	-

[a] Remainder of material present as unreacted carbonate
[b] Small quantity of co-eluting impurity in HPLC trace
[c] Reaction time was extended to 16 h
[d] *ee* Determined by ^{1}H NMR spectroscopic analysis following derivatisation with (*S*)-α-methylbenzylamine, to amide **553** (see Experimental section)

Table 24: Substrate screen with oxazolidinone-derived triazolium salts

This wide range of *ee* values suggests that the nature of the transition state may be complex, with a number of factors important in delivering high levels of enantioselectivity. Many NHC-catalysed processes occur *via* highly organised transition states (*e.g.* see Introduction, Section 1.6), but in the Steglich rearrangement, the level of enantioselectivity in the process is dependent on the organisation of both the carboxyazolium and the dienolate components. As such, it would appear that the nature of the solvent affects the level of enantioselectivity, with

[i] The 8% *ee* of the product was determined by ^{1}H NMR spectroscopic analysis following derivatisation with (*S*)-α-methylbenzylamine, assuming no loss in stereochemical integrity in the derivatisation step. See experimental section for further details.

non-polar solvents (e.g. toluene) promoting greater levels of enantioselectivity than polar solvents (e.g. THF). If the proposed ionic intermediates are formed, non-polar solvents promote tighter binding of the ion pair and could potentially form a more organised transition state in order to promote higher levels of asymmetry in the process. Cognisant of the computational analysis performed with the related chiral isothiourea (page 55), we showed that the stereochemical outcome of the transformation is reliant upon a combination of factors, including carboxyl orientation (i.e. lying co-planar with the core heterocycle of the Lewis base), facial selectivity due to the stereodirecting unit and finally, docking of the dienolate. Whilst similar DFT calculations have yet to be investigated with our chiral carboxyazolium species, a number of plausible combinations of these intermediates may have relatively similar energetic profiles, leading to formation of a mixture of both enantiomers of the *C*-carboxyazlactone product.

Section 5.2.4: Mechanistic studies

In order to ensure that the products of the rearrangement were configurationally stable, isolated samples of rearrangement products **266** of 50% and 20% *ee* (in separate experiments) were retreated under the reaction conditions, using the triazolium salt **164** and **137**, respectively (Figure 120). Reactions with both chiral NHCs returned the *C*-carboxyazlactone products **266** unchanged, indicating that the rearrangement product **266** was indeed configurationally stable, and thus, the observed low enantioselectivities are a reflection of the enantiodiscrimination in the transition state and not *via* a racemisation process.

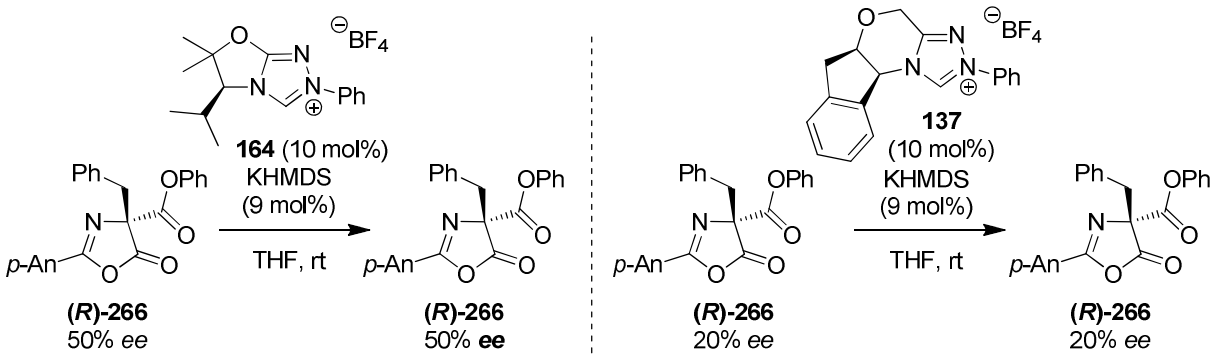


Figure 120: Configurational stability of the *C*-carboxyazlactone products

In order to explain the relative lack of reactivity observed with certain substrates and to probe the mechanism of this asymmetric transformation, crossover experiments were investigated. A mixture of two relatively unreactive substrates **258** and **244**, a trichlorodimethylethyl and methyl carbonate, respectively, were treated with the NHC derived from chiral triazolium salt **399** to investigate the nature of the NHC in the reaction manifold (Figure 121). No *C*-carboxyazlactone products were observed in either THF or toluene, but significant (~15%) crossover to the carbonates **255** and **335** was observed in THF (35:35:15:15 product ratio); a small amount (~2%)

of crossover was observed in toluene. These results suggest that the chiral NHC is still acting as a Lewis base, but may be less reactive than the achiral NHC derived from **128**, as crossover is incomplete even after 2 h (cf. complete crossover after 1 h with the achiral triazolium salt).

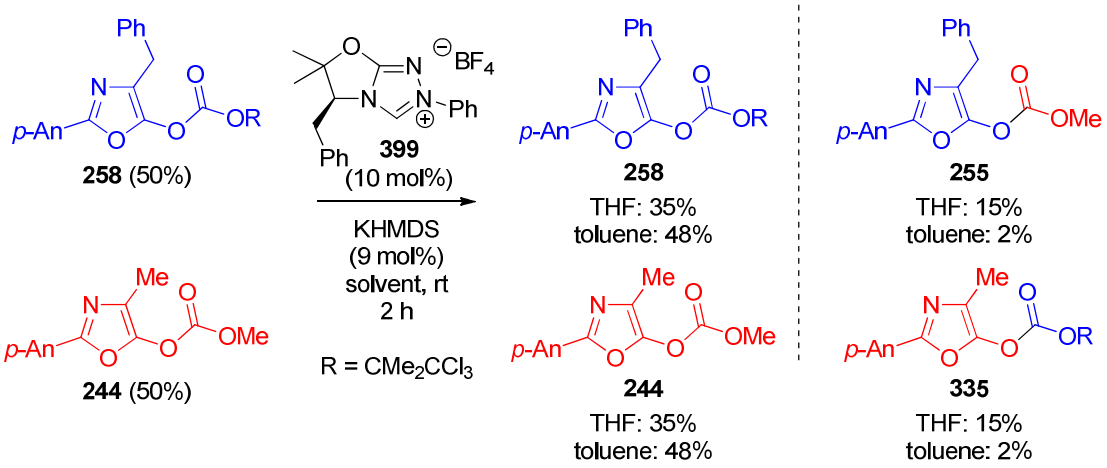


Figure 121: Crossover reaction with chiral oxazolidinone-derived triazolium salt and less reactive substrates

As a direct comparison, the chiral triazolium salt that promoted facile rearrangement of all substrates, morpholinone-derived triazolium salt **403**, was examined with these substrates **258** and **244** in toluene (Figure 122). In this case, full rearrangement to the *C*-carboxyazlactone products **270**:**246**:**249**:**336** was obtained within 1 h, with ~13–14% crossover (36:37:14:13 ratio of products) being observed.

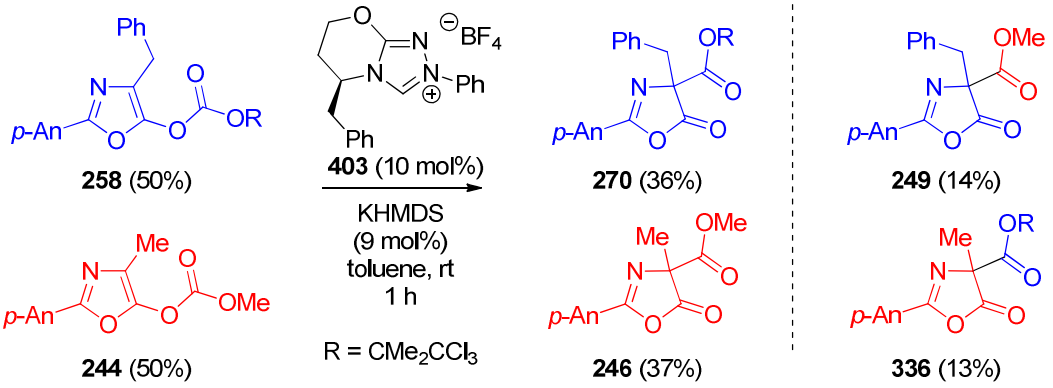


Figure 122: Crossover reaction with reactive triazolium salt and reactive substrates

Returning to the oxazolidinone-derived triazolium salt **399**, the effect of performing a similar crossover experiment between two more reactive (aryl) carbonate substrates was next examined (Figure 123). After 1 h, a mixture of the eight possible products was obtained as a ~70:30 mixture of *C*-carboxyazlactone:carbonate products, with each product in an approximately equimolar proportion. This further supported the previous findings of the greater reactivity of aryl carbonates in the reaction manifold, and whilst the *C*-carboxylation was still incomplete,

complete scrambling of the substrates could be assumed, as a statistical mixture of carbonates was returned.

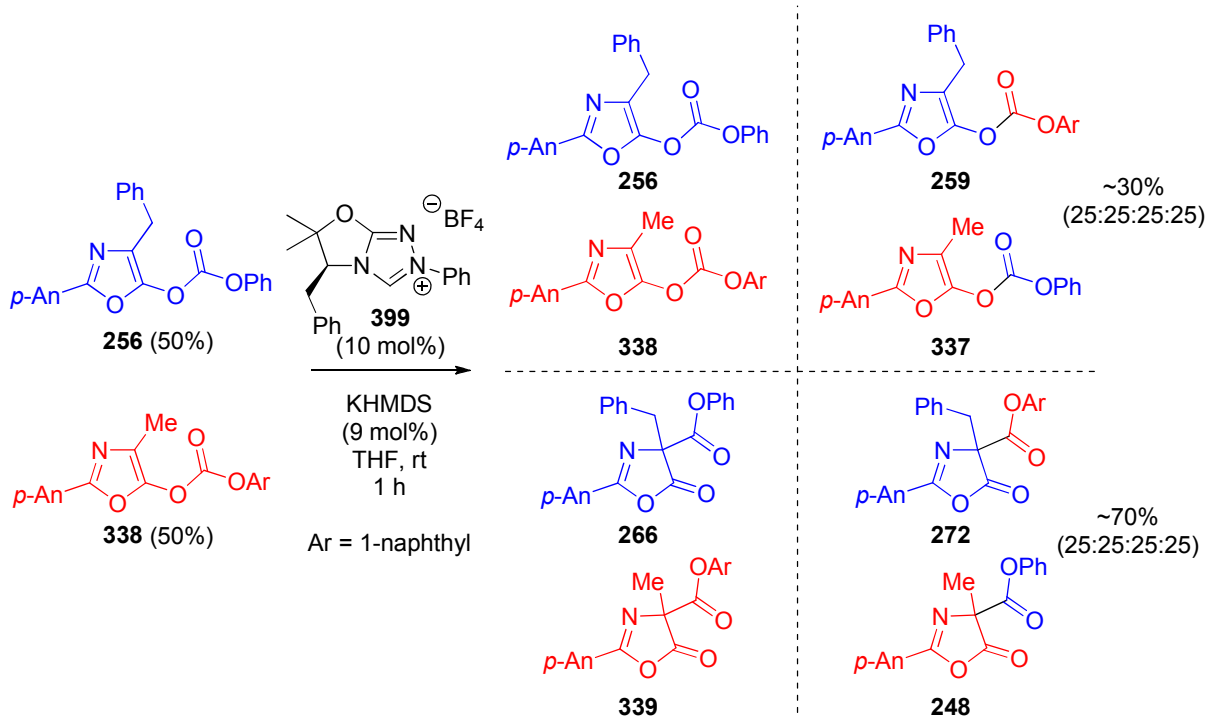


Figure 123: Crossover reaction with chiral oxazolidinone-derived triazolium salt with reactive substrates

Taken together, the results of these crossover experiments help support the hypothesis that the asymmetric variant of the rearrangement using chiral NHCs is likely to proceed *via* a similar mechanistic pathway to that with the achiral triazolium-derived NHC, i.e. that an intermolecular step is present, with a presumed carboxyazolium and dienolate being formed. The findings suggest that this process is kinetically slower than with the achiral triazolium-derived NHC, with both *O*-transcarboxylation and *C*-carboxylation steps requiring considerably longer to achieve conversion. It also appears that the proposed ion pair intermediate is held more tightly in toluene than in THF, as lower levels of crossover products were identified.

Section 5.3: Enantioselective domino cascade reactions

Having investigated the enantioselective Steglich rearrangement with NHCs in the single-step protocol, the asymmetric variant of the domino cascade reactions was pursued. Our attention was focused on the multi-step protocol from *N*-acyl amino acids, as this was deemed to be of greater synthetic significance than the other cascade procedures (Figure 124, Table 25). A number of chiral azolium salts were evaluated in the domino reaction manifold and it was found that most reactions gave rise only to the carbonate intermediate **256**. Of the azolium salts investigated, the C_2-symmetric azolium salt **138** and bicyclic triazolium salts **56** and **403** promoted successful

rearrangement. Though good isolated yields were obtained, the level of asymmetric induction in the process was modest (up to 14% *ee*).

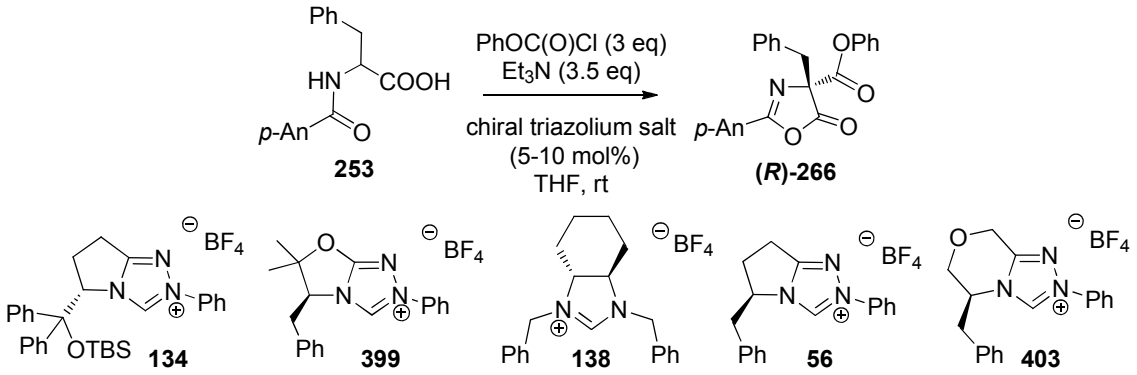


Figure 124: Selected asymmetric domino cascade investigations

Azolium salt	Yield (%)	*ee* (%)
134	- [a]	-
399	- [a]	-
138	60	10
56	85	14
403	70	<5

[a] Only carbonate **256** was obtained

Table 25: Selected results of the asymmetric domino cascade

Section 5.4: Summary

A wide range of chiral azolium salts has been prepared and evaluated in the asymmetric variant of the established Steglich rearrangement using NHCs. Azolium salts of various classes have been prepared, and the results of the investigations have confirmed the findings in the racemic series. Aryl carbonates have proven to undergo more facile rearrangement than other carbonates, though the nature of the carbonate moiety does not appear to have a significant bearing on the level of enantioselectivity in the reaction. The enantioselectivity of the process can be increased by the choice of a non-polar solvent, with toluene giving optimal results, though a wide range of enantioselectivities has been obtained, up to 66% *ee* with the optimal NHC catalyst **399**, derived from SuperQuat. Crossover studies have shown that the reactions proceed *via* a similar process to those with the achiral triazolium salt **128**, and for reactions carried out in toluene, the presumed ion pair intermediate appears to be held more tightly than in the more polar solvent THF. Finally, the asymmetric variant of the domino cascade protocol from *N*-acyl amino acids has been investigated briefly, affording the product in good yield but in low *ee*.

Chapter 6: Furanyl carbonates: synthetic methodology and rearrangement

Section 6.1: Investigation of furanyl carbonate rearrangements

Section 6.1.1: Background

Having demonstrated the efficacy of NHCs as Lewis bases to promote *O*- to *C*-carboxyl transfer in the Steglich rearrangement, the furanyl carbonate substrate class was chosen as a suitable alternative for study. For direct comparison to the rearrangement of oxazolyl carbonates, the key furanyl carbonate architecture **420** would be functionalised at C(3) and C(5). It was envisaged that the rearrangement of such substrates may give rise to two possible regioisomeric products, the α-carboxybutenolide **421** arising from carboxyl migration to C(3), or the γ-carboxybutenolide product **422** from carboxyl migration to C(5) (Figure 125). With a range of Lewis bases shown to promote rearrangement of related oxazolyl carbonates, the possibility of regio- and enantio-selective rearrangements, dependent upon the choice of Lewis base used, was investigated.

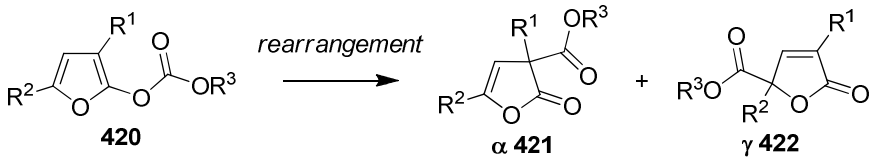


Figure 125: Furanyl carbonate template anticipated to give rise to two regioisomeric products

The butenolide moiety is a privileged structure, present in a wide variety of biologically active natural products.[151] Functionalisation of butenolides has been demonstrated by reaction of a furanyl dienolate with an appropriate electrophile. Alkylations, vinylogous Mukaiyama aldol condensations, vinylogous Mukaiyama-Michael reactions and vinylogous Mukaiyama-Mannich reactions have all been explored, generally observing high levels of selectivity for *γ*-functionalisation.[152] The majority of this methodology, however, demonstrates the preparation of tertiary centres, though MacMillan and co-workers have illustrated an organocatalytic strategy for the preparation of a single example of a quaternary-functionalised butenolide in good yield and excellent *dr* and *ee* using chiral imidazolidinone **424** as a catalyst (Figure 126).[152i]

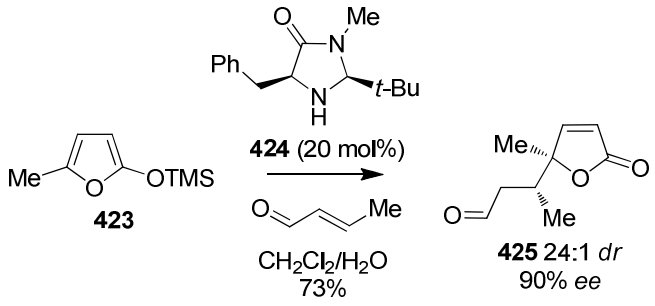


Figure 126: Quaternary γ-functionalisation of siloxyfuran

Buchwald and Hyde have also shown that quaternary-functionalised butenolides **429** can be prepared from the parent butenolide **426** through Pd-mediated cross-coupling (Figure 127).[153] The authors propose that the formal dienolate must be generated *in situ*, and the choice of solvent in the reaction is critical, as a number of by-products are generated if *t*-amyl alcohol is not present, attributed to solvent stabilisation of the dienolate intermediate. The authors also show that generally poly-substituted butenolide substrates are most effective, with mono-substituted substrates often giving rise to complex mixtures as the dienolates are unstable in the reaction manifold. In all successful cases however, only γ-arylation is observed.

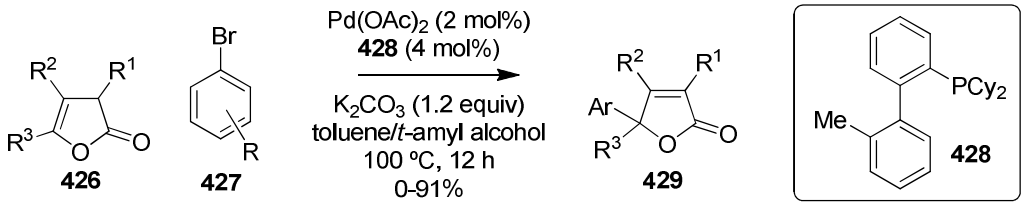


Figure 127: Arylation of butenolides

Vedejs and co-workers have investigated the enantioselective rearrangement of a series of 5-aryl-3-methylfuranyl carbonates **430** using the chiral aminopyridine TADMAP **238** (Figure 128).[107] In these cases, whilst very high level of enantioselectivity is achieved, a mixture of both regioisomers is observed, with the relative proportions dependent on the choice of solvent, but more crucially, upon the electronic perturbations imposed upon the dienolate (Table 26). For example, the 5-phenyl substituted furanyl carbonate underwent successful rearrangement to a 60:40 mixture of α-carboxybutenolide product **431** and γ-carboxybutenolide product **432**, respectively. A number of alternative aryl substituted carbonates also underwent successful rearrangement, with γ-electron-donating aromatic substituents disfavouring γ-functionalisation, giving predominantly the α-carboxybutenolide product **431** (up to 92:8 mixture of products). However, the mesomerically electron-withdrawing 4-cyanophenyl substituent favoured predominantly γ-functionalisation, giving a 20:80 mixture of α-carboxy:γ-carboxy products **431**:**432** respectively.

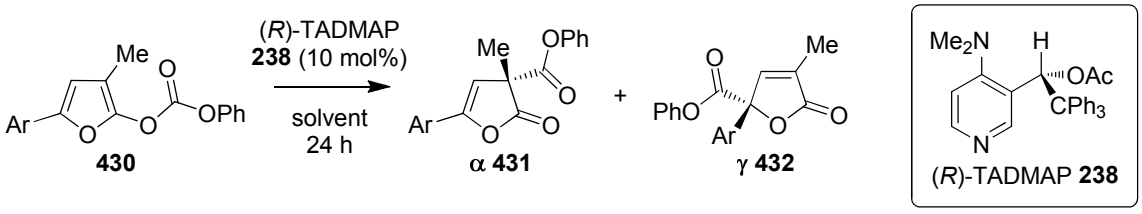


Figure 128: TADMAP-Promoted rearrangement of 5-aryl-3-methylfuranyl carbonates (Vedejs)

Ar	Solvent	Ratio of α:γ products	ee_{major} (%)
Ph	CH_2Cl_2	60:40	91
4-$MeOC_6H_4$	CH_2Cl_2	83:17	82
4-$MeOC_6H_4$	THF	91:9	90
4-$MeOC_6H_4$	toluene	92:8	83
4-$MeOC_6H_4$	*t*-amyl alcohol	86:14	91
4-NCC_6H_4	CH_2Cl_2	20:80	63
4-NCC_6H_4	THF	20:80	74
4-NCC_6H_4	toluene	20:80	83
4-NCC_6H_4	*t*-amyl alcohol	20:80	50

Table 26: Results of TADMAP-promoted furanyl rearrangements (Vedejs)

Section 6.2: Investigations of a model furanyl carbonate

Section 6.2.1: Synthesis *via* keto-acid

Commercially available 2-methyl-4-oxo-4-phenylbutyric acid **433** was chosen as a suitable starting material and was utilised to obtain the furanyl carbonate **435**, directly comparable with that of Vedejs (Figure 129). Treatment of keto-acid **433** with acetic acid and acetic anhydride at 100 ºC gave a ~35:65 mixture of 3*H* and 5*H*- butenolides **434** respectively in quantitative conversion. Treatment of this mixture with LDA yielded the dienolate and subsequent addition of phenyl chloroformate gave the desired carbonate **435** in good yield, which was used to investigate the heterocyclic rearrangement. In an effort to develop a more facile procedure to prepare the desired carbonate under similar conditions as found with azlactones, the mixture of butenolides **434** was treated with Et_3N followed by phenyl chloroformate and this also afforded the desired carbonate in comparable yield, though an excess of chloroformate and Et_3N was required due to partial consumption of phenyl chloroformate and Et_3N due to competing dealkylation (see page 58).

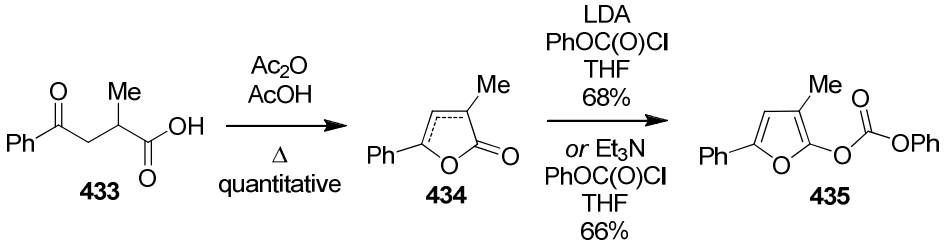


Figure 129: Synthesis of model furanyl carbonate substrate

Section 6.2.2: Rearrangement of model furanyl carbonate

With the model substrate **435** in hand, the regioselectivity of the rearrangement with different classes of Lewis base was investigated.

Section 6.2.2.1: Using aminopyridines

The 'classical' aminopyridines DMAP **224** and PPY **225** were first evaluated to allow direct comparison with the results of Vedejs and to examine the effectiveness of these Lewis bases (Figure 130, Table 27). These catalysts successfully promoted the carboxyl transfer reaction to afford a mixture of *C*-carboxybutenolide products **436** and **437** respectively, with a bias towards formation of the α-regioisomer: a 60:40 mixture of α:γ-regioisomeric products was obtained using DMAP and a 51:49 ratio using PPY. These results are consistent with the findings of Vedejs using the chiral aminopyridine TADMAP, which provided a similar 60:40 mixture of α:γ-regioisomeric products.[107] PPY also provided a significant proportion of the butenolide **438** as a result of decarboxylation; at low catalyst loading (0.5 mol%) with DMAP, a similar effect was noted, but without affecting the ratio of α:γ regioisomers. As noted in the rearrangement of oxazolyl carbonates, where decarboxylation is observed, diphenyl carbonate **305** is also returned, but only one butenolide, the 5*H*-butenolide **438**, was also recovered.

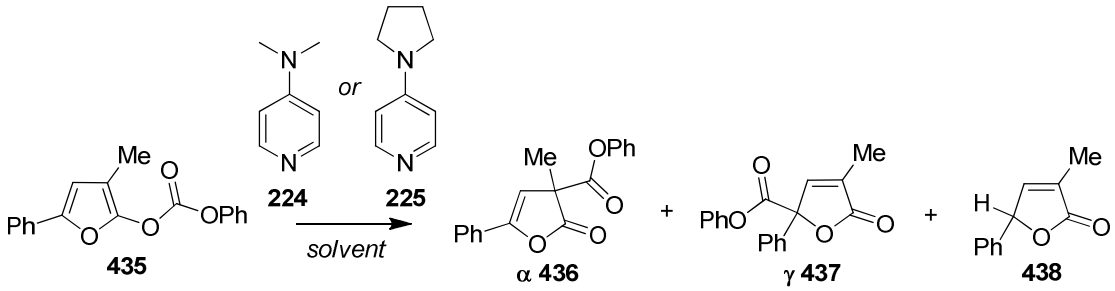


Figure 130: Aminopyridine-catalysed furanyl rearrangement

Catalyst	mol%	Solvent	Conversion (%) [a]	Ratio of α:γ products [b]	Decarboxylation (%) [b]
DMAP	10	THF	>98	60:40	0
DMAP	10	CH_2Cl_2	>98	60:40	0
DMAP	0.5	THF	>98	57:43	16
PPY	10	THF	>98	51:49	23

[a] Conversion determined by consumption of carbonate **435**
[b] Values determined by ^{1}H NMR spectroscopic analysis of crude reaction product

Table 27: Results of aminopyridine-catalysed carboxyl transfer

Section 6.2.2.2: Using amidines

The rearrangement of model substrate **435** was next examined using 'amidine' Lewis bases which have been shown to induce carboxyl transfer in the related Steglich rearrangement.[103,124] *N*-Methylimidazole, DBN and isothiourea **311** were chosen to represent the set of different

amidine classes and were examined in this reaction manifold (Figure 131, Table 28). Unlike the Steglich rearrangement of oxazolyl phenyl carbonate **256**, DBN proved the least effective catalyst with the furanyl carbonate, returning only a small proportion (4%) of the γ-carboxybutenolide **437**, but giving predominantly the decarboxylated product **438** and unreacted furanyl carbonate **435**. *N*-Methylimidazole **439** proved more competent, giving an ~50:50 ratio of α:γ products, though with significant amounts (27%) of the decarboxylated product **438**. Isothiourea **311** also gave a similar mixture of the rearrangement products and significant amounts of decarboxylated product **438**. At lower catalyst loading of the isothiourea (0.5 mol%), the reaction was considerably slower, but returned similar ratios of α:γ regioisomers.

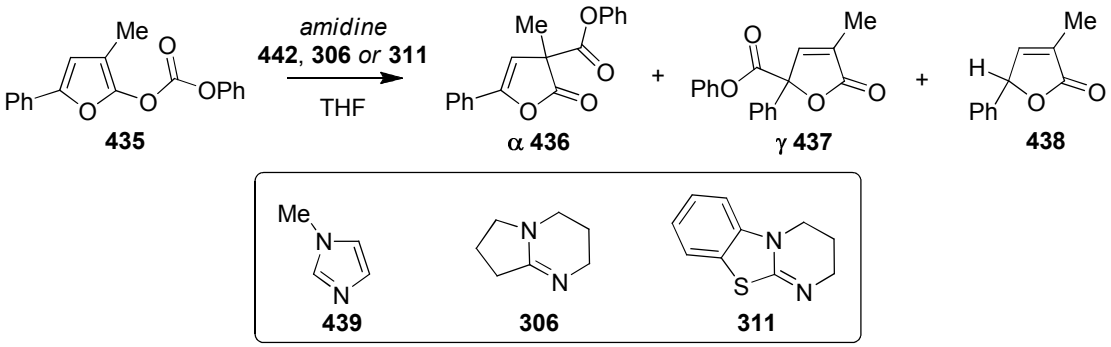


Figure 131: Amidine-catalysed furanyl rearrangement

Catalyst	mol%	Conversion (%) [a]	Ratio of α:γ products [b]	Decarboxylation (%) [b]
NMI **439**	10	>98	49:51	27
DBN **306**	10	82	0:100	78
isothiourea **311**	10	>98	58:42	38
isothiourea **311**	0.5	15	56:44	6

[a] Conversion determined by consumption of carbonate **435**
[b] Values determined by ^{1}H NMR spectroscopic analysis of crude reaction product

Table 28: Results of amidine-catalysed carboxyl transfer

Section 6.2.2.3: Using NHCs

Finally, the NHC catalysed rearrangement of the model furanyl substrate was investigated (Figure 132, Table 29). With 10 mol% of azolium salt and 9 mol% of KHMDS as the base, the rearrangement was highly effective with triazolium salt NHC precatalysts. In each case, a 16:84 ratio of α:γ regioisomers **436**:**437** respectively was obtained with the rearrangement occurring rapidly (<5 min) and with no change in product ratio after extended reaction times. With either triazolium salt **128** and Et_3N, or imidazolium- or imidazolinium-derived NHCs generated using KHMDS, no reaction was observed. These results contrast those found with the majority of the

other Lewis bases where the rearrangement has been effective: the NHCs show a complete change in selectivity towards preferential formation of the γ-regioisomer, not the α-regioisomer.

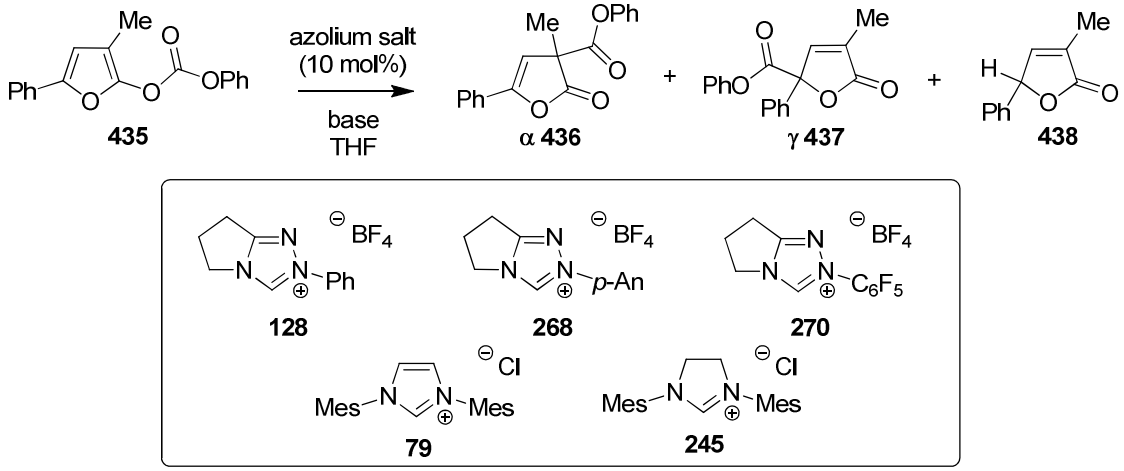


Figure 132: NHC-Catalysed furanyl rearrangement

Precatalyst (mol%)	Base (mol%)	Conversion (%) [a]	Ratio of α:γ products [b]	Decarboxylation (%) [b]
128	KHMDS (9)	>98	16:84	0
128	Et_3N (100)	<5	-	-
268	KHMDS (9)	>98	16:84	0
270	KHMDS (9)	>98	16:84	0
79	KHMDS (9)	<5	-	-
245	KHMDS (9)	<5	-	-

[a] Conversion determined by consumption of carbonate **435**
[b] Values determined by ^{1}H NMR spectroscopic analysis of crude reaction product

Table 29: Results of NHC-catalysed carboxyl transfer

Section 6.2.2.4: Investigation of the regioselectivity: probing thermodynamic *vs* kinetic control

To evaluate the effectiveness of NHCs in this rearrangement, a range of NHC catalyst loadings (0.5–25 mol%) was investigated (Figure 133, Table 30). Operating at similar concentrations to those for the Steglich rearrangement (i.e. ~5–20 mM concentration of **128**), the reaction was shown to be highly efficient, giving quantitative conversion to carboxybutenolide products within 1 h. The ratio of regioisomeric products appeared to be dependent on the catalyst loading. At higher catalyst loadings from 5–25 mol% (5–20 mM concentration of **128**), a consistent 16:84 ratio of α:γ-carboxy products **436**:**437** was obtained. By lowering the NHC catalyst loading to 0.9 mol% (8 mM concentration), the reaction still progressed rapidly to completion (<5 min), but the ratio of α:γ-carboxy products increased from 16:84 to 4:96. Further lowering of the catalyst loading to 0.5 mol% and sampling the reaction immediately allowed the reaction progression to be examined before the carbonate starting material was fully consumed. In this case, at 92%

consumption of carbonate **435**, the reaction had proceeded to afford exclusively the γ-carboxy product **437**. On further sampling after 5 min, quantitative conversion of carbonate **435** to *C*-carboxybutenolides **436** and **437** was obtained, giving nearly exclusively the γ-regioisomer (<2:98 ratio of α:γ-carboxy products). This ratio, however, decayed slightly to 6:94 after 1 h.

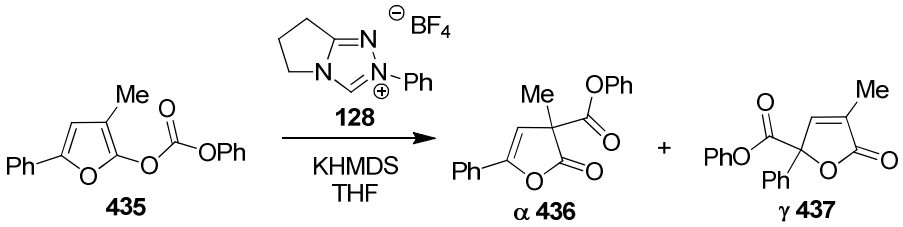


Figure 133: Carboxyl rearrangement of furanyl carbonate **435**

Precatalyst (mol%)	KHMDS (mol%)	Temp (ºC)	Conversion (%) [a]	Ratio of α:γ products [b]	Isolated yield of α:γ products (%) [c]
25	24	rt	>98	16:84	-
10	9	rt	>98	16:84	6:72
5	4.5	rt	>98	16:84	5:70
2	1.8	rt	>98	10:90	-
1	0.9	rt	>98	4:96	0:85
1	0.9	0	>98	<4:>96	-
0.5	0.45	rt	92 [d]	0:100	-
0.5	0.45	rt	>98	<2:>98	-

[a] Conversion determined by consumption of carbonate **435**
[b] Values determined by ^{1}H NMR spectroscopic analysis of crude reaction product
[c] Isolated yield of individual regioisomers following chromatography
[d] Sampling the reaction mixture immediately

Table 30: Results of screening at different catalyst loadings

Section 6.2.2.5: Exploration of the mechanism

From the screen of Lewis bases, two effective catalysts were identified, namely DMAP and the NHC derived from triazolium salt **128**. These two catalysts also promote complementary regioselective rearrangement: with DMAP, a mixture of both α:γ-carboxy products is obtained but with a small preferential bias towards the α-regioisomer; with the NHC, the γ-carboxy product predominates, with considerably higher regioselectivity. The change in ratio of products with both NHC catalyst loading/concentration and reaction time suggested that there may be some interconversion of the two regioisomeric products, potentially promoted by the NHC. To investigate this potential interconversion, individual regioisomers were isolated then retreated under the reaction conditions with the two most effective catalysts, DMAP and NHC **247**, and also the isothiourea **311**. With DMAP or isothiourea **311**, both of the individual

C-carboxybutenolide products **436** and **437** were stable to treatment, returning only the initial *C*-carboxybutenolide even after an extended reaction time of 5 h (Figure 134).

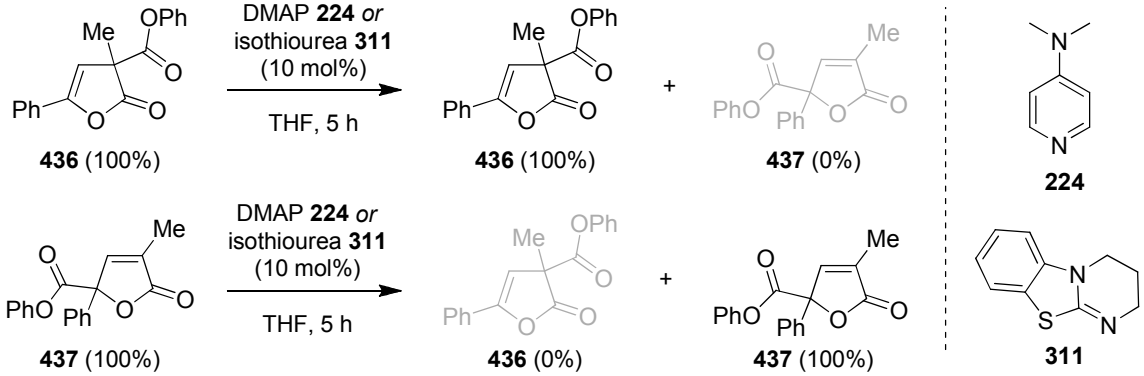


Figure 134: Results of resubjection of individual regioisomers with DMAP and isothiourea

With the NHC, however, contrasting results were obtained (Figure 135): upon treatment of the α-carboxy product **436** with the NHC, a mixture of carboxybutenolide products was obtained, with a significant regioisomeric exchange to the γ-carboxy product **437** being observed (17:83 ratio). Treatment of the pure γ-carboxy regioisomer **437** with the NHC also delivered a mixture of α- and γ- regioisomeric products in a 14:86 ratio. These ratios are (with experimental error) the same as was observed in the original investigations with the NHC using higher catalyst loading.

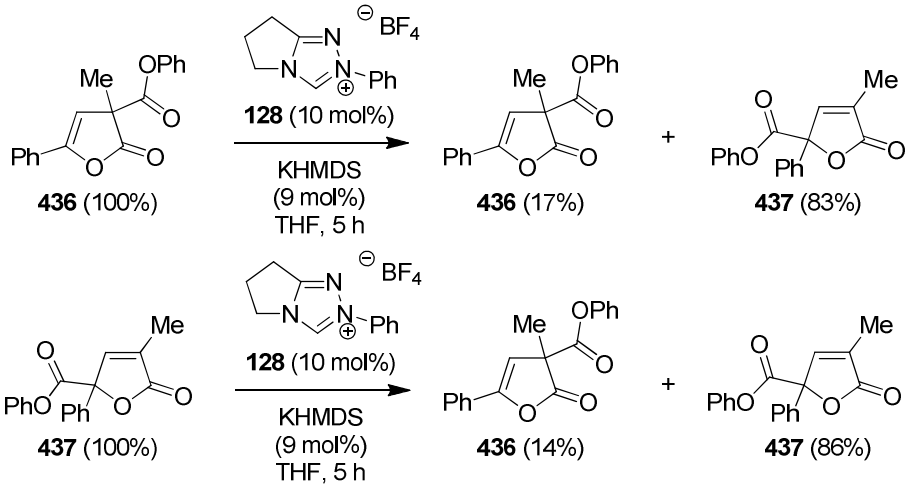


Figure 135: NHC-Promoted interconversion of regioisomers

These findings suggest that the NHC has a dual role in this reaction manifold, whereas the aminopyridine DMAP and isothiourea **331** appear to play a part only in the initial carboxyl transfer reaction. The NHC appears to promote *O*- to *C*-carboxyl transfer, but, in contrast to observations in the Steglich rearrangement, the interconversion of the products is also promoted by the active NHC. It appears that, with DMAP and isothiourea **311**, the product ratio obtained is a reflection of the kinetic products of the transfer process, in both cases with a slight preference

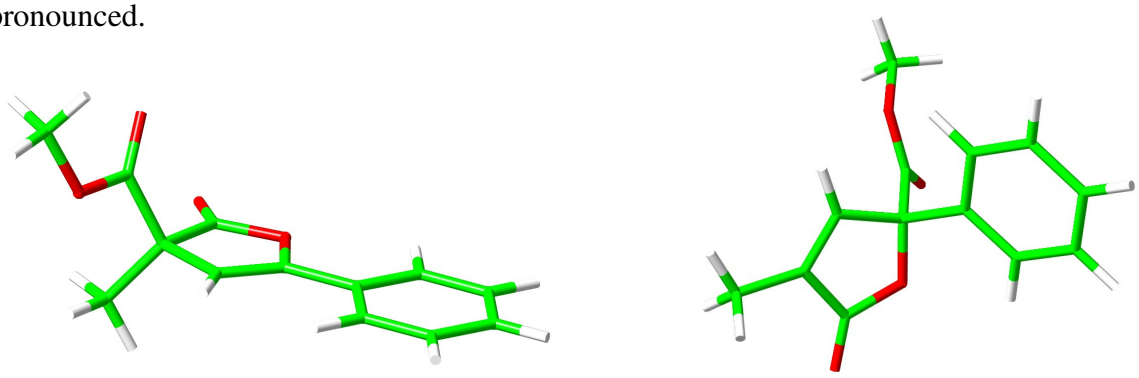
for α-carboxylation. With the NHC however, the kinetically formed product appears to be the γ-carboxybutenolide, as this is the initially formed product in the reaction manifold. As the NHC facilitates product interconversion, it appears that the γ-carboxybutenolide is also the thermodynamically more stable product, as this was the predominant product obtained with high catalyst loading and upon extended reaction times, consistently obtained in a 14:86 regioisomeric ratio.

Section 6.2.2.6: Preliminary computational modelling and crossover studies

To rationalise the interesting selectivities observed between these different bases, several issues had to be addressed: firstly, to determine if the observed ratio of products is a reflection of their relative thermodynamic stabilities; secondly, to understand the divergent behaviour in the regioisomeric ratio obtained with the different Lewis bases.

Section 6.2.2.6a: Product stability computational analysis

In collaboration with Prof. Philp at the University of St Andrews, preliminary computational analysis was performed. Using the B3LYP/6-31G(d,p) level of theory, energy minimisation of α/γ-regioisomeric products was performed and the relative stabilities computed (Figure 136).[i] The results of these calculations show that the energy difference between the two regioisomeric products is marginal, with the γ-regioisomeric product **436** being slightly more stable than the α-regioisomeric product **437** (by 0.07 kcal mol^{1}). The results of this calculation suggest that the calculations performed may require further refinement in order to obtain a more accurate rationale in comparison to the experimental findings, where the energy difference is more pronounced.



α-*regioisomer* **436** γ-*regioisomer* **437**

Figure 136: DFT Calculated energy minimisation of the dearomatised products from the model furanyl carbonate

Section 6.2.2.6b: Crossover experiments

As a prerequisite to the computational analysis, further experimentation was required to help confirm that a similar mechanism to that of the Steglich rearrangement was operating in this

[i] To simplify the calculations, the methyl ester, not the phenyl ester, regioisomeric products were examined.

system. Initial studies were carried out to confirm that the reaction was not auto-catalytic with respect to the dienolate (generated upon addition/elimination of the Lewis base to the carbonate substrate). This was investigated by preparation of a catalytic quantity (10 mol%) of the equivalent potassium dienolate **442** (prepared *via* treatment of the butenolide mixture with KHMDS) and treatment with the furanyl carbonate substrate (Figure 137). Upon treatment of the carbonate substrate **435** with the potassium dienolate **442**, no rearrangement was observed, consistent with the reaction not being autocatalytic with respect to the dienolate.

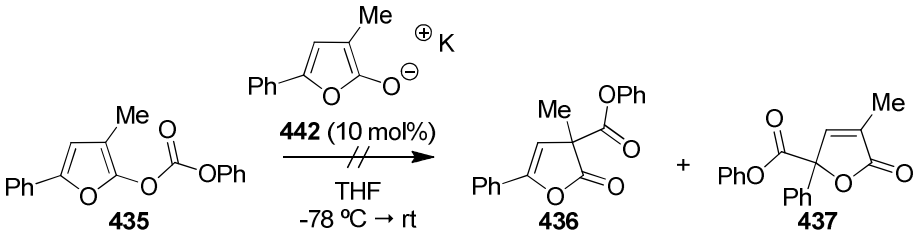


Figure 137: No autocatalytic pathway with furanyl carbonates

Having established that the Lewis base was involved in the key C-C bond-forming event(s), crossover experiments were performed. A 50:50 mixture of oxazolyl and furanyl carbonates was treated with both DMAP and NHC **247** (in separate experiments). The possible products from this crossover reaction were six *C*-carboxy products: two carboxyazlactones and four carboxybutenolides, four carbonate substrates and two decarboxylated products. From the crossover reaction with DMAP, a mixture of the six *C*-carboxy products was obtained with a small proportion (10%) of the decarboxylated butenolide product (Figure 138). The combined ratio of the carboxybutenolide α:γ-regioisomers reflects the approximate ratio observed with just the model substrate: with the model substrate **435**, a ratio of 60:40 α:γ-regioisomers was obtained with DMAP; in the crossover reaction, the summed percentages of the α-regioisomers (**436**+**443**) to the summed percentage of the γ-regioisomers (**437**+**444**) gave a similar ~60:40 ratio of products. This observed crossover helped support the hypothesis that an intermolecular step must also be present in the rearrangement of the furanyl carbonate substrates.

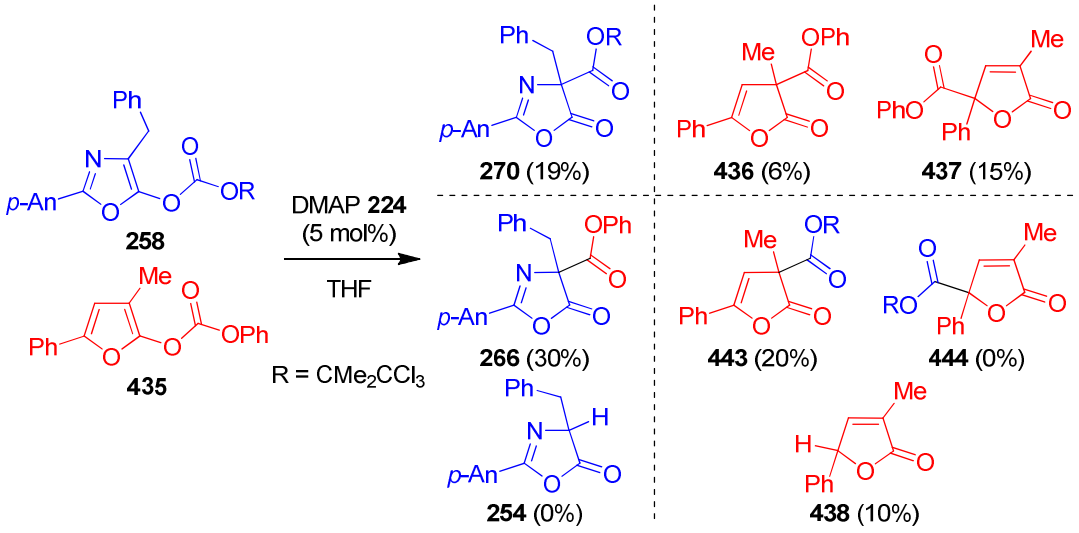


Figure 138: Crossover reaction using DMAP

The same experiment was repeated using the triazolium-derived NHC (generated using KHMDS) (Figure 139). In this case, similar levels of crossover were observed, and of the possible *C*-carboxybutenolide products, essentially only the γ-regioisomers were obtained, again reflecting the kinetic formation of the γ-regioisomer over the α-regioisomer.

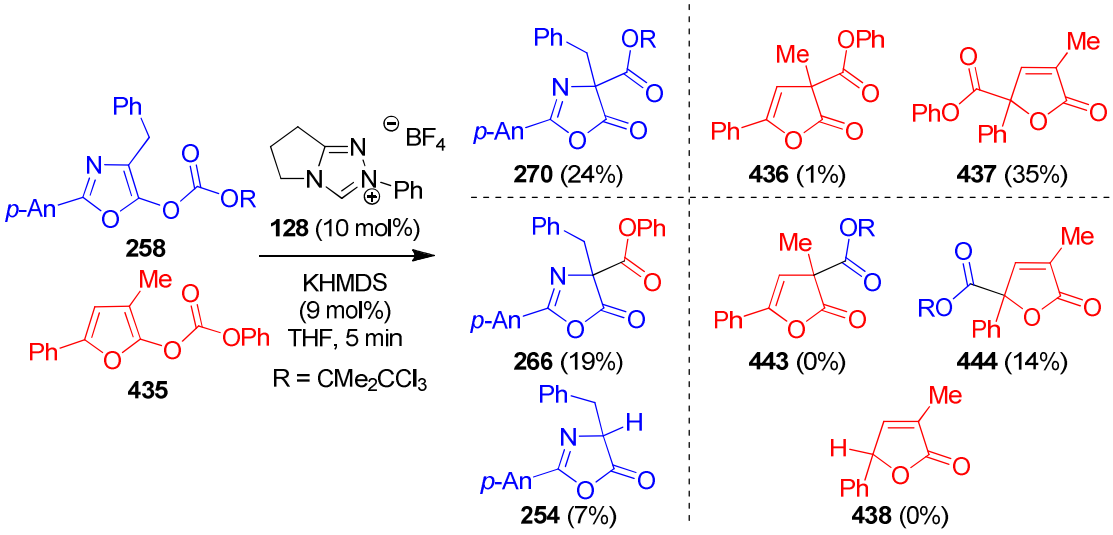


Figure 139: Crossover reaction using NHC

Whilst not definitive, these data support the proposed mechanism of the transformation proceeding *via* a carboxyl transfer intermediate with both DMAP and the NHC, but with a reversible final carboxylation step only with the NHC (Figure 140).

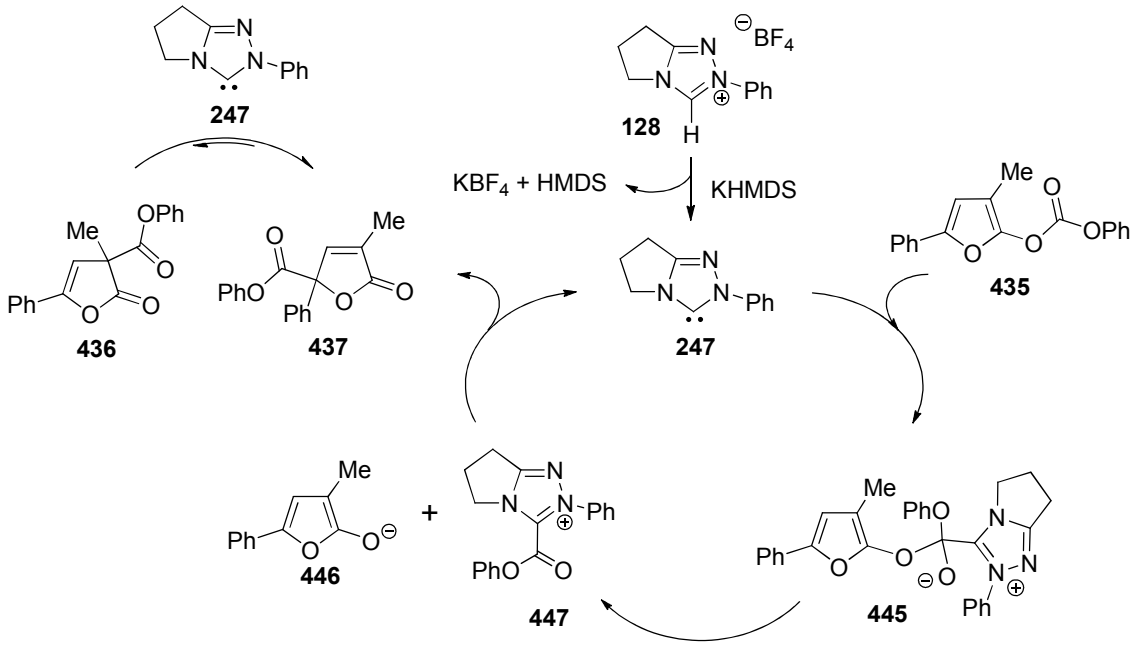
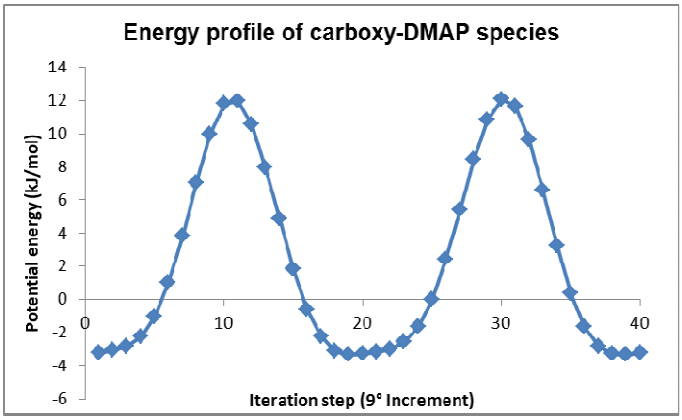


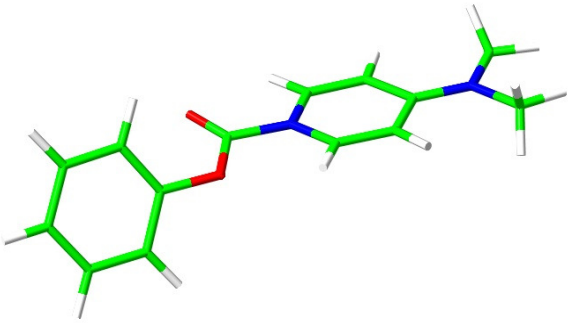
Figure 140: Proposed catalytic cycle using model furanyl carbonate **435**

Finally, in order to ascertain if the K^+ counterion generated in the reaction manifold plays a role in affecting the regioselectivity, the same crossover experiment with the NHC was repeated in the presence of a large excess of a K^+ cation source. In this case, KPF_6 (5 equiv) was used, but the same ratio of products was obtained within experimental error, therefore, the role of the K^+ was discounted.

Section 6.2.2.6c: Towards transition state analysis

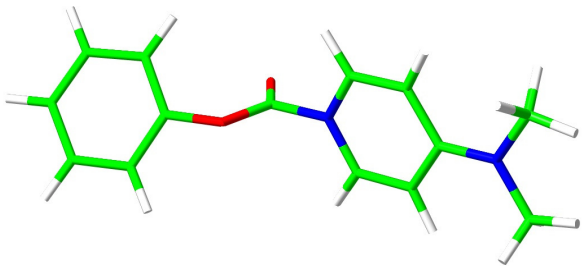
To rationalise the product distributions observed with the different Lewis bases, comparison of the relative transition state energies for the key C-C bond-forming steps were sought. In order to determine such transition states, DFT calculations were performed on both the carboxyl transfer species and the dienolate components. Firstly, the energy-minimised structures of the carboxyl transfer species were computed. The structures of both the carboxy-DMAP and carboxyazolium species were minimised, then the rotation about the carbonyl was investigated in order to determine the global minimum and maximum energies. For both carboxyl species, the energies were calculated in 9° increments. The lowest energy conformation of the carboxy-DMAP species was determined as **448**, having the carbonyl aligned co-planar to the aminopyridine ring system; the global maximum energy (species **449**) is obtained when the carbonyl is placed orthogonally to the aminopyridine ring (Figure 141). These calculations are in agreement with the *ab initio* calculations of Vedejs for the related TADMAP-derived carboxyl transfer species.[107]





Global minimum **448**

(*Iterations 19 and 39,* ∠C-N-C=O ≈ 0º)



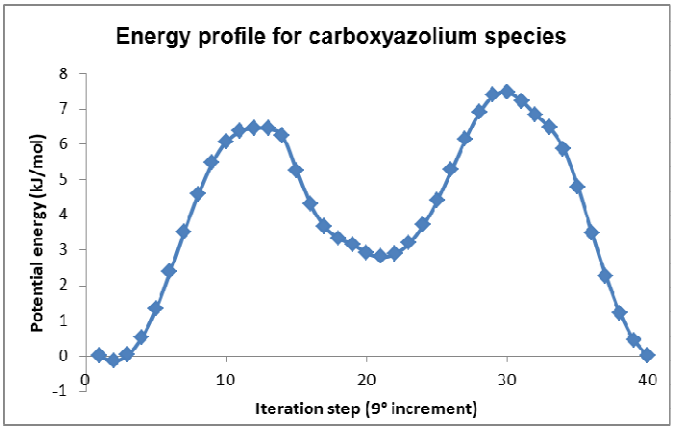
Global maximum **449**

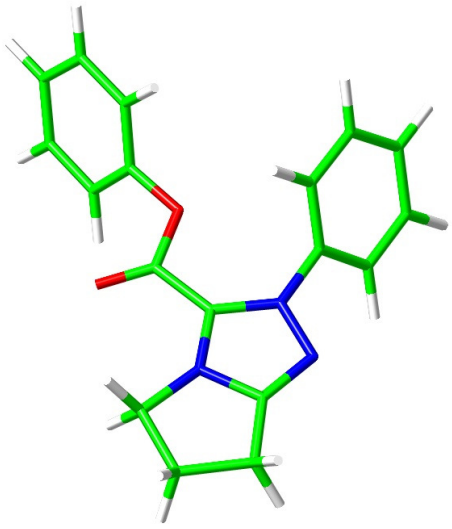
(*Iterations 10 and 30,* ∠C-N-C=O ≈ 90º)

Figure 141: DFT Calculations of the energy profile of the carboxy-DMAP species, and selected molecular representations

For the carboxyazolium species, an asymmetric energy profile is obtained, with two minima and two maxima (Figure 142). As was found with the carboxy-DMAP species, both minima are found with the carbonyl and the central azolium ring lying co-planar, with the global minimum **453** being ~3 kJ mol^{-1} more stable than the local minimum **450**. Interestingly, in the global minimum conformer **451**, the *N*-phenyl substituent of the triazolium ring is found to exhibit a tilt angle θ of 60° in relation to the central triazolium ring, similar to the observations of Nolan from X-ray crystallographic data for a related triazolium-derived NHC-Pt complex (see page 97).[150] Consistent with the findings for the carboxy-DMAP species, the maxima are observed with the carbonyl approximately orthogonal to the central ring system (species **452** and **453**).

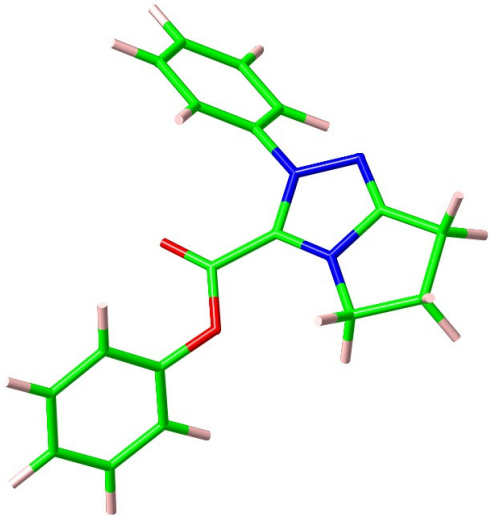
Next, the nature of the dienolate species was investigated. The dienolate structure **446** was minimised, which led to the anticipated planar heterocyclic species, for which the HOMO was determined. The results of this calculation indicated that there is indeed considerable electron density located at both the C(3)- and C(5)-positions, thus giving rise to a mixture of α- and γ-carboxybutenolide products, but the experimentally observed ratio of products cannot be rationalised from these data alone.





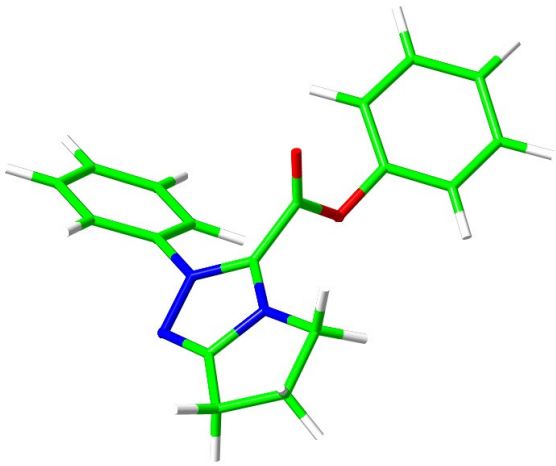
Local minimum **450** *(Iteration 20)*

(∠N-C-C=O ≈ 180º)



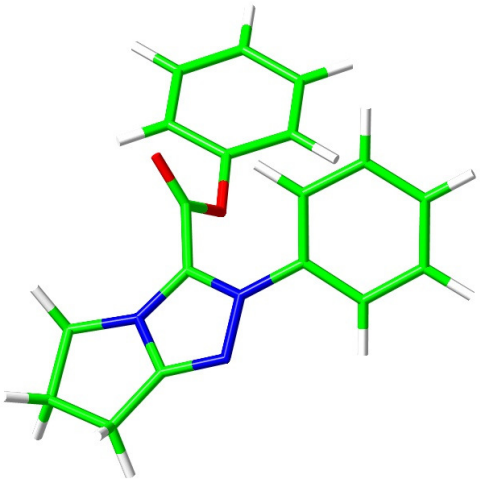
Global minimum **451** *(Iteration 40)*

(∠N-C-C=O ≈ 0º)



Local maximum **452** *(Iteration 14)*

(∠N-C-C=O ≈ 126º)



Global maximum **453** *(Iteration 30)*

(∠N-C-C=O ≈ 270º)

Figure 142: DFT Calculations of the energy profile of the carboxyazolium species, and selected molecular representations

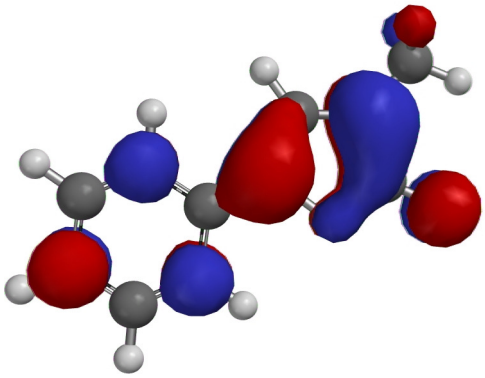
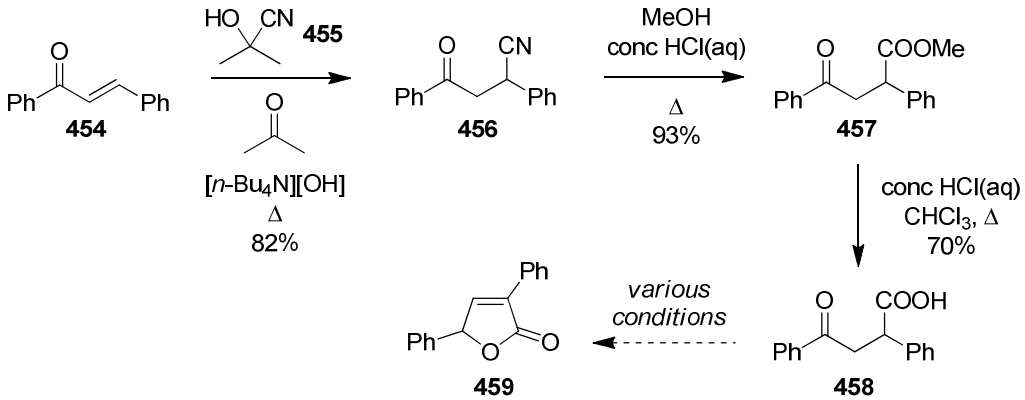


Figure 143: DFT-Calculated HOMO for the furanyl dienolate **446**

With these data, DFT calculations are underway through combination of the two individual components, to determine the relative transition state energies for the transformations with both DMAP and the NHC. It is hoped that the results of these pending computations will account for the observed differences in the kinetic product formation with the different Lewis bases.

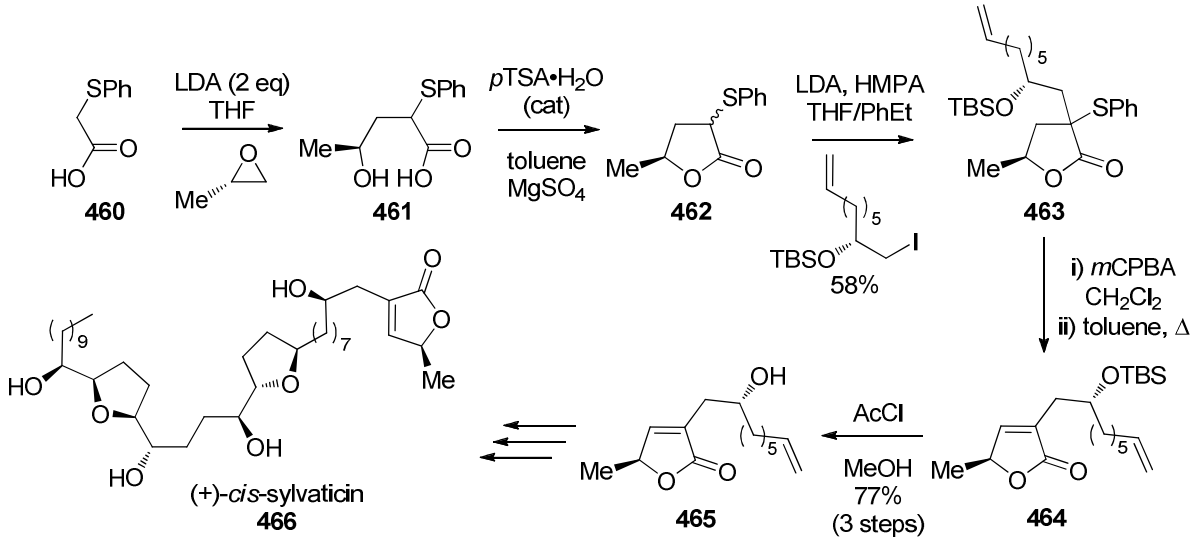
Section 6.3: Preparation of 3-alkyl-5-arylfuranyl carbonates

In order to investigate the generality of this rearrangement process, a range of 3-alkyl-5-phenylfuranyl carbonate substrates was prepared. It was envisaged that the key to the synthetic routes would be construction of the butenolides, the direct precursor to the furanyl carbonates. These butenolides could be prepared *via* related keto-acid intermediates, and a number of routes were explored. Surprisingly, many of these routes proved synthetically problematic, with the keto-acid intermediate not undergoing cyclisation to the desired butenolide. As an illustration, chalcone **454** was successfully converted to the keto-acid intermediate **458** by initial conjugate cyanide addition using acetone cyanohydrin **455**[154] followed by a two-step hydrolysis in good overall yield (Scheme 23). Attempts to induce cyclisation of the keto-acid to the butenolide **459**, however, were unsuccessful using a number of methods, including Ac_2O, $POCl_3$, PPA, DCC and a range of chloroformates.



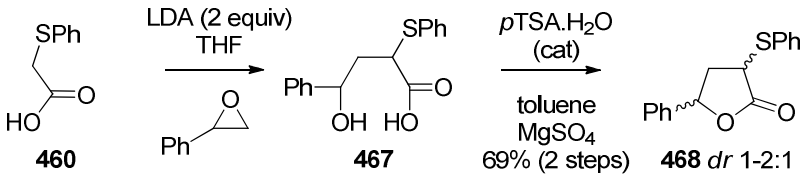
Scheme 23: Installation of the carboxylic acid moiety and attempted cyclisation to butenolide **458**

To circumvent this potential cyclisation problem, the desired lactone core structure had to be installed at an earlier juncture in the synthesis. A number of approaches to preparation of the butenolides were investigated, but the most applicable route was that developed by Lee and co-workers[155] *via* formation of (phenylthio)butyrolactones of the type **462**. As a recent example of this process in the synthesis of (+)-*cis*-sylvaticin **466**, Donohoe and co-workers[156] had shown that such lactones could be alkylated followed by oxidation/thermolysis to afford the desired butenolide architecture (Scheme 24).



Scheme 24: Synthetic strategy demonstrated by Donohoe

In order to investigate the scope and generality of the furanyl carbonate rearrangement with other related substrates, we initially chose to maintain a C(5)-phenyl moiety and to vary the C(3)-alkyl substituent. Following a similar strategy to that employed by Donohoe, using (racemic) styrene oxide in place of propylene oxide in the initial alkylation step gave the desired (phenylthio)butyrolactone intermediate **468** in good yield and as a mixture of diastereomers (*dr* 1–2:1) (Scheme 25). No regioisomeric products were observed as a result of ring opening at the more hindered secondary centre.



Scheme 25: Preparation of the (phenylthio)butyrolactone

With the parent butyrolactone **468** in hand, the alkylation step was next investigated (Figure 144). Donohoe had used HMPA as a co-solvent in order to achieve alkylation, and other related work by a number of others all used a similar strategy, all using iodides as the alkylation partner. In order to circumvent the use of the highly toxic and carcinogenic HMPA – which had

to be employed at superstoichiometric quantities – several alternative strategies were investigated. In the absence of any Li^+ complexation agent, treatment of the enolate with either methyl iodide or benzyl bromide did not provide any of the desired alkylated product. Addition of TMEDA resulted in low levels of alkylation also, but DMPU, a common non-toxic substitute for HMPA, proved highly successful in delivering the desired alkylated products **469** and **470** in good yield and with high levels of diastereoselectivity for the *syn*-product (>12:1 *dr*).

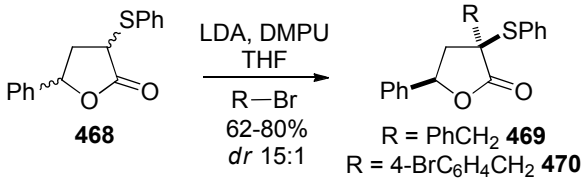


Figure 144: Investigation of the alkylation of the butyrolactone

The assignment of the relative configuration of the major diastereomer was determined by NOESY experiments, and the assignment was further supported following X-ray crystallographic analysis of the major diastereomer of **469** (Figure 145).

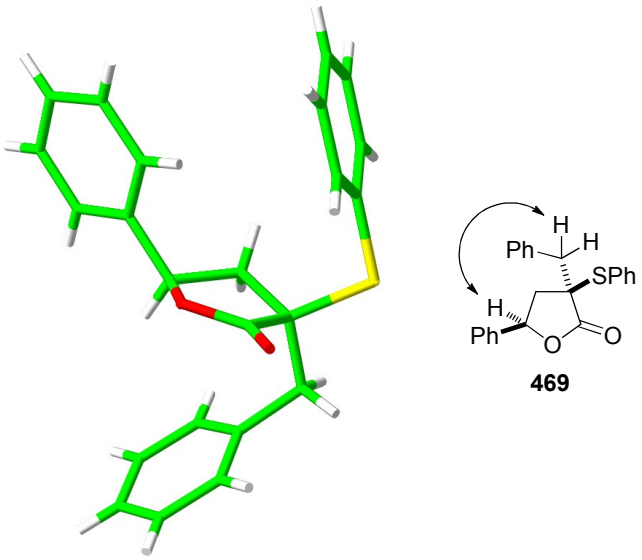


Figure 145: Representation of the X-ray crystal structure of the major diastereomer, and NOESY correlation

Following alkylation, treatment of the diastereomeric mixtures **469** and **470** with *m*CPBA provided the desired sulfoxide intermediates as a mixture of diastereomers, which underwent thermal elimination in toluene at reflux to afford the desired butenolide products **471** and **472** as a mixture of regioisomers in good yield (Figure 146). The isomerisation process, not observed in related C(5)-alkyl substituted butenolides, may be occurring *via* tautomerisation to the aromatic hydroxyfuran heterocycle. This may be due to the enhanced acidity of the (benzylic) proton at C(5), resulting in the formation of an extended conjugated aromatic framework.

With the desired butenolides in hand, conversion to the furanyl carbonates **473** and **474** was achieved in good yield (58–60%) using Et_3N as the base (Figure 146). The use of LDA was also

attempted using butenolide mixture **471**, though poor conversion (~5%) to the desired carbonate was obtained.

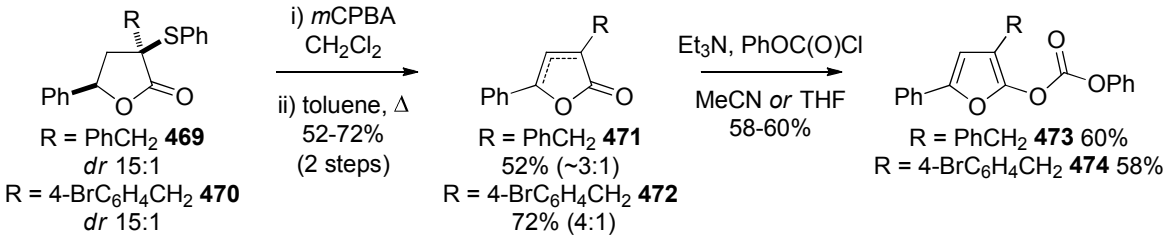


Figure 146: Thermolysis and *O*-carboxylation to 3-alkyl-5-phenylfuranyl carbonates

With a successful means of preparing such substrates, related analogues with different electronic properties were investigated. Cognisant of the findings of Vedejs, electronic perturbations of the 5-aryl moiety were investigated to observe the impact on the regioselectivity of the rearrangement. The 4-methoxyphenyl substituted carbonate could not be readily accessed as 4-methoxystyrene oxide is not commercially available, however, the commercially available 4-fluorostyrene oxide was transformed successfully to the desired carbonate **479** *via* a similar synthetic route (overall 20% yield) (Figure 147).

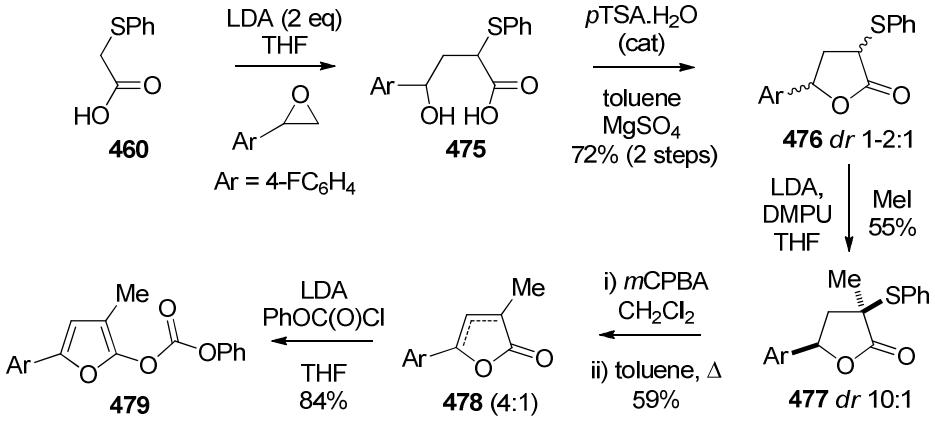


Figure 147: Preparation of related 4-fluorophenyl substituted furanyl carbonate

Section 6.4: Rearrangement of 3-alkyl-5-arylfuranyl carbonates

With a range of furanyl carbonates in hand, the rearrangement of the 3-alkyl-5-arylfuranyl substrates was firstly investigated, using DMAP and the NHC derived from triazolium salt **128** as catalysts (Figure 148, Table 31). The results of these rearrangements have shown a number of trends. Firstly, all 3-alkyl-5-phenylfuranyl carbonate substrates **480** (Ar = Ph) undergo rapid rearrangement to provide a mixture of α- and γ- regioisomers, with the major regioisomer dependent on the choice of Lewis base. With DMAP, a mixture of both regioisomers is obtained with a slight preference for the α-regioisomer **481** in each case (53–64:47–36 ratio). In contrast, at 9 mol% NHC catalyst loading, a mixture of regioisomers is also obtained, but in which the

γ-regioisomer **482** predominates (10–19:90–81 ratio). Using low NHC catalyst loadings and short reaction times, both the methyl and benzyl substituted carbonate indicate initial (presumably kinetically favoured) γ-carboxylation, giving >96% regioselectivity for the γ-carboxybutenolide **482**. Upon variation of the electronic properties of the 5-aryl substituent to the 4-fluorophenyl moiety, the α-carboxybutenolide product **481** is the predominant regioisomer with DMAP (71:29 ratio). With the NHC, however, the γ-regioisomer **482** again predominates (12:88 ratio).

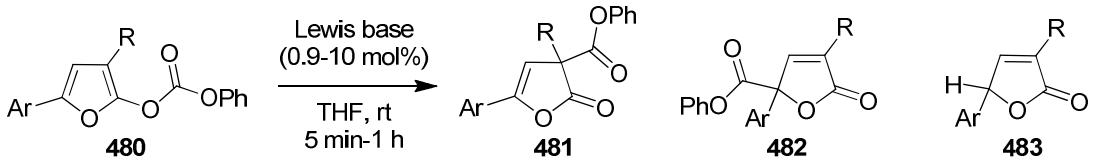


Figure 148: Examination of different furanyl carbonates with Lewis bases

R	Ar	Catalyst (mol%)	Ratio of α:γ products [a]	Decarboxylation (%) [a]	Yield of major product (%)
Me	Ph	DMAP (10)	60:40	0	60 (α)
Me	Ph	NHC (9)	16:84	0	72 (γ)
Me	Ph	NHC (0.9)	<2:98	0	85 (γ)
$PhCH_2$	Ph	DMAP (10)	64:36	2	45 (α)
$PhCH_2$	Ph	NHC (9)	19:81	3	67 (γ)
$PhCH_2$	Ph	NHC (0.9)	4:96	5	67 (γ)
4-$BrC_6H_4CH_2$	Ph	DMAP (10)	53:47	0	43 (α)
4-$BrC_6H_4CH_2$	Ph	NHC (9)	10:90	0	80 (γ) [b]
Me	4-FC_6H_4	DMAP (10)	71:29	6	52 (α)
Me	4-FC_6H_4	NHC (9)	12:88	3	67 (γ)

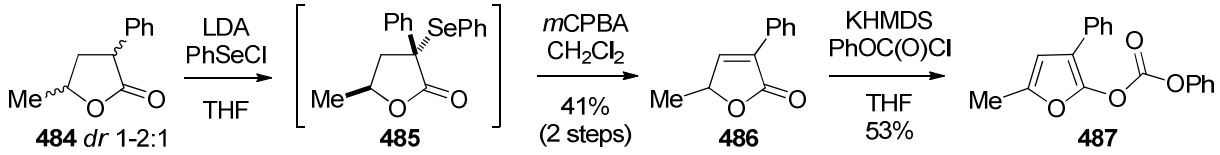
[a] Values determined by ^{1}H NMR spectroscopic analysis of crude reaction product
[b] Product contaminated with 5% **483** as a result of partial decomposition on silica

Table 31: Collated results of furanyl carbonate rearrangements

Section 6.5: Preparation and evaluation of isomeric furanyl carbonate

To probe further the steric and electronic requirements of the furanyl rearrangement, the isomeric 5-methyl-3-phenylfuranyl carbonate **487** was prepared, whereby the C(3)- and C(5)-substituents were switched in comparison with the model substrate **435**. This isomeric furanyl carbonate was prepared *via* a strategy related to that employed with (phenylthio)acetic acid, but instead beginning with phenylacetic acid (Scheme 26). Following related protocols, multi-gram quantities of the desired butyrolactone **484** were obtained *via* epoxide opening,

followed by dehydration.[i] Having experienced some minor difficulties in phenylthiolation and the subsequent oxidation/elimination with this substrate, phenylselenation was chosen as an alternative.[208] Upon treatment of the butyrolactone **484** with LDA and phenylselenyl chloride, the selenated lactone **485** was obtained and immediately treated with *m*CPBA to afford the desired butenolide **486**, exclusively as the 5*H*-isomer, in 41% yield over the two steps. With the desired butenolide **486** in hand, formation of the desired isomeric carbonate **487** was investigated. Treatment with Et_3N and phenyl chloroformate gave no conversion to the desired carbonate, but pleasingly, treatment with KHMDS and phenyl chloroformate afforded the desired isomeric carbonate **487** in good yield. The structure of the carbonate product **487** was confirmed by X-ray crystallographic analysis (Figure 149).



Scheme 26: Preparation of the isomeric 5-methyl-3-phenylfuranyl carbonate

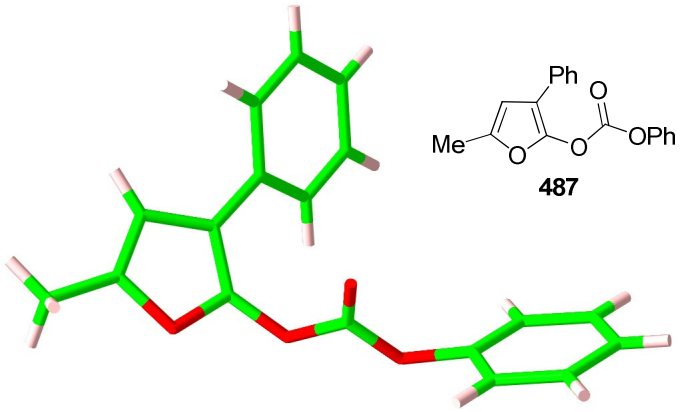


Figure 149: Representation of the X-ray crystal structure of carbonate **487**

Prior to investigation of the isomeric substrate **487** in the Lewis base promoted rearrangement, DFT calculations were performed on the related dienolate in order to predict regioselectivity in the rearrangement. The results of the calculations showed that HOMO of the isomeric dienolate was similar to that of the model dienolate, i.e., that both C(3)- and C(5)-functionalisation would be anticipated (Figure 150).

[i] Kindly donated by Louis Morrill.

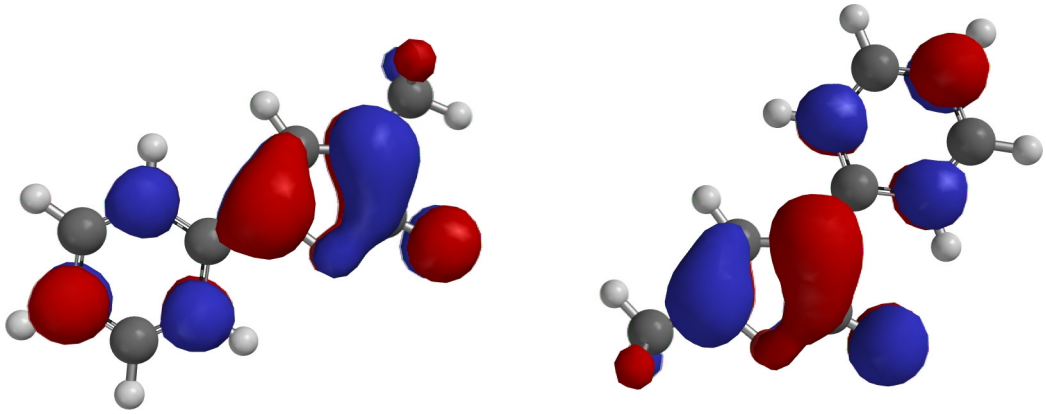


Figure 150: Comparison of the HOMO of the isomeric furanyl carbonates

Whilst the electronic distributions in the HOMO of the two dienolates were similar, the ground-state energies of the α- and γ-carboxybutenolide regioisomers **488** and **489**, respectively, were markedly different (Figure 151). In this case, the γ-carboxybutenolide regioisomer **489** was determined to be considerably more stable than the α-carboxybutenolide regioisomer **488** (by 12.7 kcal mol^{-1}), which according to Boltzmann distribution calculations would be expected to afford nearly exclusively the γ-carboxybutenolide regioisomer **489** at equilibrium.

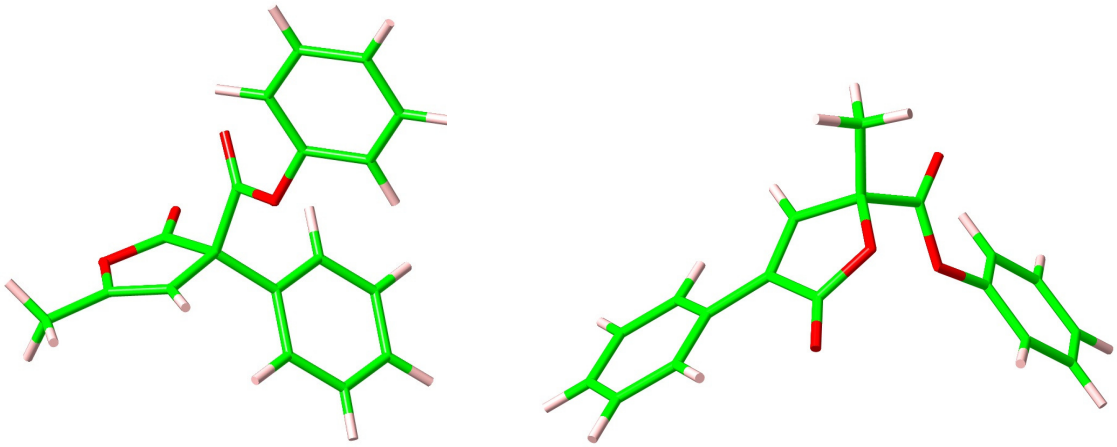


Figure 151: DFT Calculated ground state energy minimisation of the dearomatised products from the isomeric furanyl carbonate

Finally, the rearrangement of the isomeric carbonate **487** was investigated (Figure 152). Preliminary current investigations indicate that γ-carboxylation is favoured with both DMAP and the NHC, with the NHC promoting exclusive γ-carboxylation. These ratios have been assigned by spectroscopic examination of the crude reaction product,[i] as attempts to isolate the individual regioisomers by chromatography proved unsuccessful due to complete decomposition on silica. These tentative assignments, however, appear to confirm the predictions of the DFT studies,

[i] By comparison of the indicative resonances, namely, the C=C*H* and the CH_3 in the α-carboxy regioisomer, and the CH_3 in the γ-carboxy regioisomer.

namely, that both C(3) and C(5)-carboxylation are possible pathways, but the significantly thermodynamically favoured product is the γ-carboxy regioisomer **489**.

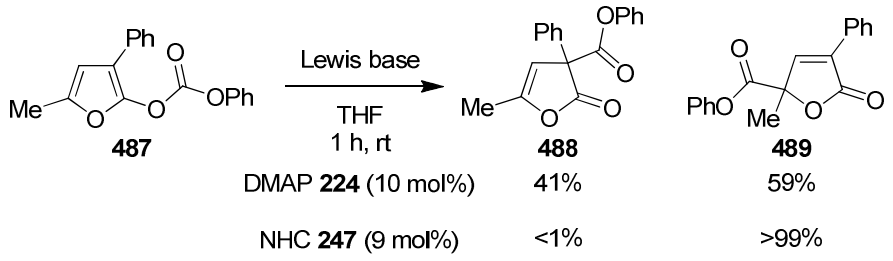


Figure 152: Rearrangement of isomeric furanyl carbonate

Section 6.6: Enantioselective furanyl carbonate rearrangements

Having evaluated the regioselective rearrangement of furanyl carbonates in the racemic series, the asymmetric variant was then investigated. Using model furanyl carbonate **435**, a range of chiral NHC precatalysts was evaluated (Figure 153). Surprisingly, none of the NHCs derived from triazolium salts **56**, **134**, **399**, **403**, **137** or **416** promoted rearrangement to either of the desired *C*-carboxybutenolides, returning predominantly furanyl carbonate **435** in each case (and, in certain instances, decarboxylated butenolide **438**). Whilst unexpected, the observed 'lack' of reactivity with imidazolium derived NHCs in both the furanyl and oxazolyl carbonate systems suggests that the *C*-carboxylation process may be similarly disfavoured with these chiral NHCs.

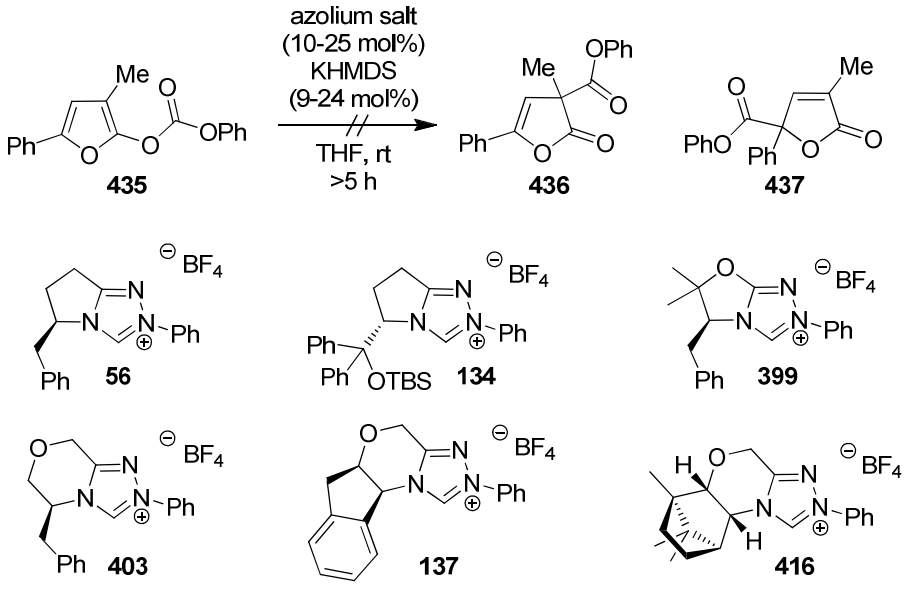


Figure 153: Attempted enantioselective furanyl carbonate rearrangement using chiral NHCs

Whilst these results were discouraging, the chiral isothiourea **312** was evaluated (Figure 154). This catalyst was chosen as it was shown to give excellent levels of both reactivity and enantioselectivity in the related Steglich rearrangement.[125] Pleasingly, this catalyst did indeed promote carboxyl transfer. Only the α-carboxybutenolide rearrangement product **436** and the

decarboxylated product **438** were obtained as an ~80:20 mixture. Following purification, the enantioenriched α-carboxybutenolide product **436** was obtained in good yield and excellent *ee* (70%, 95% *ee*).

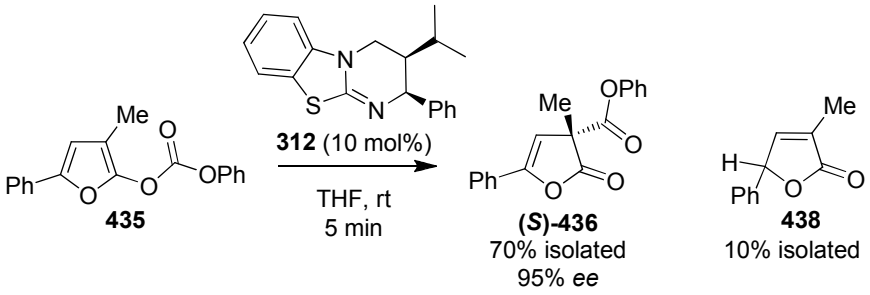


Figure 154: Enantioselective furanyl carbonate rearrangement using chiral isothiourea **312**

The absolute configuration of this product was determined by preparation of the enantioenriched product by the method of Vedejs,[107] as no specific rotation data was given for the product in the literature. Using (*S*)-TADMAP **238**,[i] an authentic sample of the α-carboxybutenolide (*R*)-**436** was obtained, allowing assignment of the (*S*)-configuration of the major enantiomer of our enantioenriched product. This was encouraging as this indicated that catalyst **312** gave the same sense of induction to that observed in the related Steglich rearrangement.[125] The related substituted carbonates **480** were also examined in the reaction manifold (Figure 155, Table 32). Similar results were obtained, with these substrates giving rapid rearrangement to predominantly the α-regioisomer **481**, with either the γ-regioisomer **482** or the decarboxylated product **483** as the only other minor product. In all cases, the α-regioisomer **481** was obtained in good isolated yield and with excellent levels of enantioselectivity (77–95% *ee*) at ambient temperature, with absolute configuration assigned by analogy. The *ee* of the minor γ-regioisomer **482** was not determined, as the chromatographic method required to separate the α- and γ-regioisomers promoted partial decomposition of the γ-regioisomeric product.

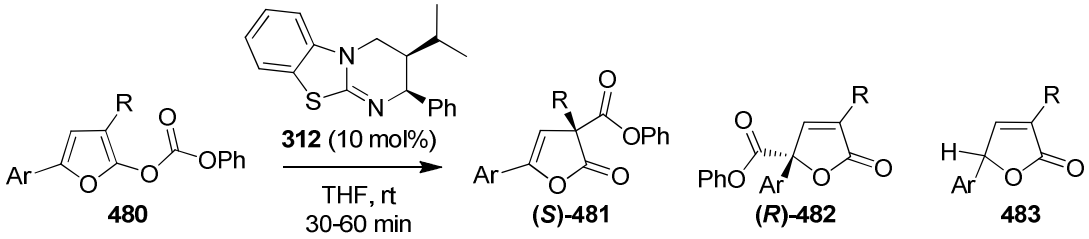


Figure 155: Enantioselective furanyl carbonate rearrangements using chiral isothiourea **312**

[i] Kindly donated by Prof. Edwin Vedejs.

R	Ar	Ratio of α:γ products [b]	Decarboxylation (%) [b]	Yield of α product (%)	*ee* (%)
Me	Ph	100:0	20	70	95
$PhCH_2$	Ph	100:0	22	66	95
4-BrC_6H_4	Ph	69:31	0	65	87
Me	4-FC_6H_4	80:20	8	72	77

[a] Conversion determined by consumption of carbonate **480**
[b] Values determined by ^{1}H NMR spectroscopic analysis of crude reaction product

Table 32: Results of asymmetric isothiourea-catalysed carboxyl transfer

Computational analysis is currently underway to establish the origin of the asymmetry in the rearrangement of the furanyl carbonate substrates. Since similar DFT analysis has already been performed to establish the origin of asymmetry for the related Steglich rearrangement using this catalyst,[125] giving the same sense of stereochemical induction in both cases, a similar transition state model could be invoked (see page 55).

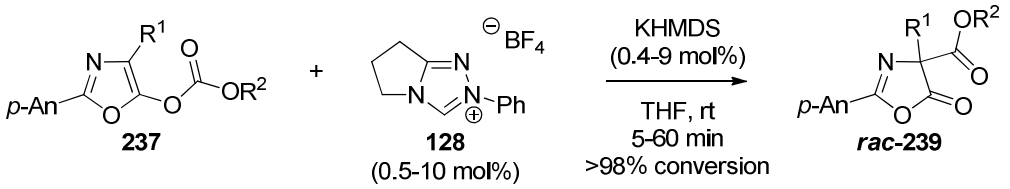
Section 6.7: Summary

The furanyl carbonate substrate class has proven highly amenable to Lewis base-promoted rearrangement to the *C*-carboxybutenolide isomers, with the proportion of the regioisomer governed by several factors. Firstly, the choice of Lewis base determines the ratio of products, with a triazolium-derived NHC giving preferential γ-carboxylation and aminopyridines and isothioureas generally favouring α-carboxylation. Investigation of the mechanism of the transformation has illuminated a difference between the use of DMAP and the NHC: the final C-C bond-forming step in the reaction is irreversible with DMAP but reversible with the NHC, thus, the product ratio obtained with the NHC is initially a reflection of the kinetically formed product, but leads to the thermodynamically derived product distribution. Computational analysis supports the findings that the γ-carboxybutenolide products are indeed the thermodynamically favoured product. The asymmetric variant of the rearrangement has been investigated with chiral NHCs and an isothiourea. Whilst chiral NHCs have proven unsuccessful, chiral isothiourea **312** has proven highly competent, giving predominantly the α-regioisomeric carboxybutenolide product in excellent *ee* (77–95%).

Chapter 7: Conclusions and further work

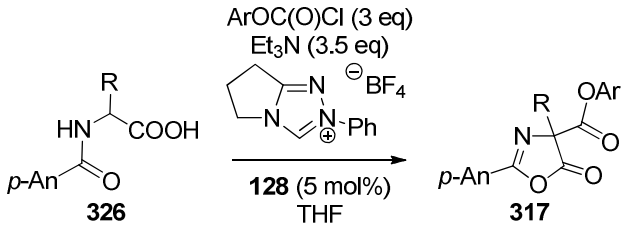
Section 7.1: Conclusions

This work demonstrates an extensive investigation of the Steglich rearrangement of oxazolyl carbonates to their *C*-carboxyazlactone isomers using NHCs as Lewis bases. These catalysts have permitted extension to the substrate scope for such rearrangement, allowing the rearrangement to challenging α-branched substrates.

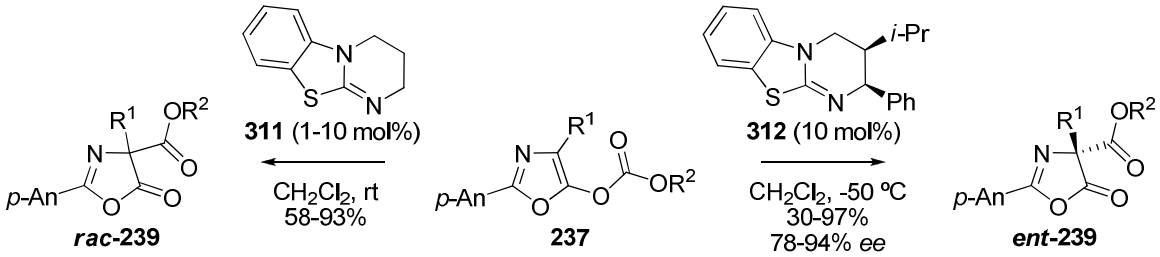


Mechanistic studies using crossover experiments have helped propose a mechanism similar to that identified using aminopyridines, through generation of a carboxyl transfer species, which has been supported by crossover studies. From this work, the NHC promotes rapid reversible *O*-carboxylation, with the rate determining step being the final C-C bond formation to give the carboxyazlactone products.

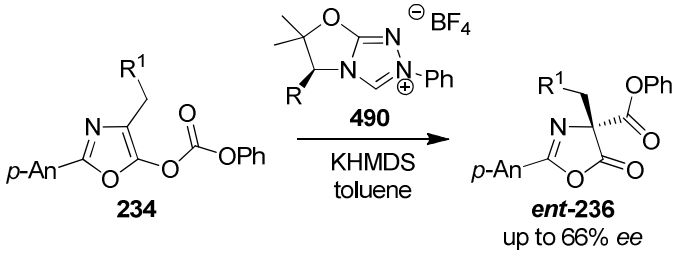
A number of chemoselectivities have been identified using NHCs, whereby triazolium-derived NHCs perform the rearrangement most successfully. Imidazolium-derived NHCs promote rapid reversible *O*-carboxylation, but do not efficiently promote the final *C*-carboxylation step. The reactivity profiles of different substrates, dependent on the electrophilicity of the carbonate carbonyl, have been identified. Aryl oxazolyl carbonates have proven most amenable to rearrangement, where even the weak organic base Et_3N can be used to generate the active triazolinylidene catalyst. The exact nature of the NHC in these reaction manifolds could not be fully delineated, but the use of Et_3N as the base has allowed us to incorporate the Steglich rearrangement into multi-step domino cascade protocols. This has allowed rapid access to such *C*-carboxyazlactone products by significantly reducing the number of individual steps.



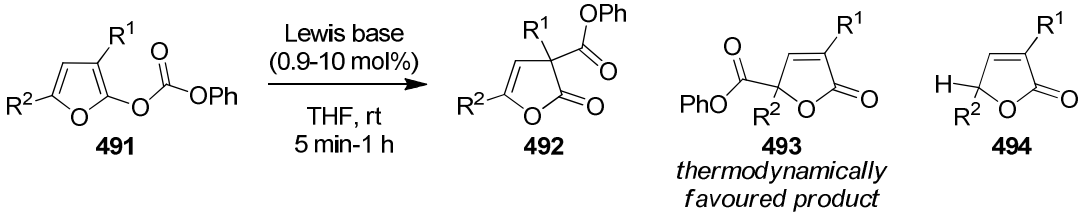
Through our investigations we have discovered that amidines such as DBU and DBN interact with oxazolyl carbonates, with DBN promoting the Steglich rearrangement catalytically, without the need for azolium salts. This has led to the development of isothioureas, a new class of efficient Lewis base with which to promote the Steglich rearrangement.



A range of different classes of chiral NHC precatalysts have been successfully prepared and evaluated in the asymmetric variant of the Steglich rearrangement, with modest levels of enantioselectivity of up to 66% *ee*.

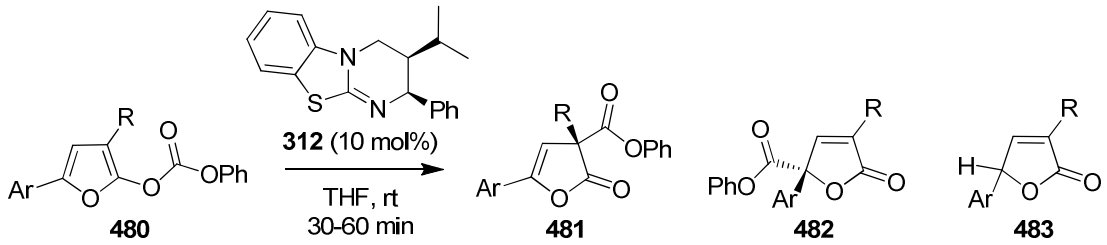


An extension to the systems suitable for carboxyl rearrangement has been established. Methodology has been developed to prepare furanyl carbonates by a range of methods, and related rearrangement reactions have been performed with a variety of Lewis bases. Investigations with a model furanyl carbonate have shown that mixtures of regioisomers are obtained. The regioselectivity of the rearrangement is dependent on the nature of the Lewis base: NHCs promote kinetic γ-carboxylation, but isothioureas and aminopyridines give a small preference for formation of the α-regioisomer. In contrast with the results obtained using NHCs in the rearrangement of oxazolyl carbonates, the final C-C bond-forming step in the related furanyl carbonate rearrangement is reversible, so the ratio of products using high catalyst loadings and/or extended reaction times is a reflection of the relative thermodynamic stability of the products. Computational studies support the findings that the γ-carboxybutenolide products, the major regioisomer obtained with NHCs, are indeed the thermodynamically more stable products.



The asymmetric variant of the rearrangement has been investigated, but chiral NHCs have proven incompetent in the reaction manifold. Chiral isothiourea **312** has, however, proven highly

effective in promoting α-regioisomer formation with excellent levels of enantioselectivity (77–95% *ee*) at ambient temperature.



Section 7.2: Further work

In order to delineate the difference in chemoselectivity of the KHMDS and Et_3N-derived NHC in the Steglich rearrangement, further investigations are needed in order to establish the exact nature of the triazolium-derived NHC.

Differences in regioselectivity in the rearrangement of furanyl carbonates have been identified using different Lewis bases. Therefore a range oxazolyl carbonate substrates bearing different steric and electronic C(2)-substituents could be investigated to see what effect this has on the regioselectivity of the process (Figure 156).

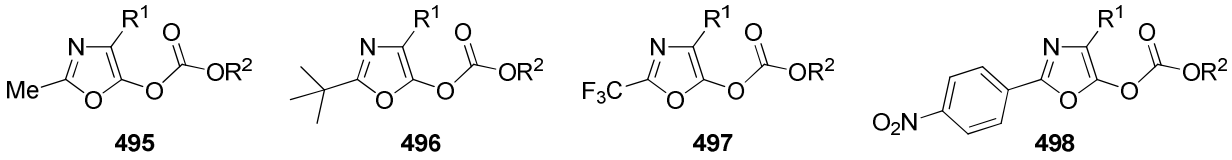


Figure 156: Possible C(2)-substituted oxazolyl carbonates to investigate regioselectivity

The use of chiral azolium salt to effect the asymmetric Steglich rearrangement have had only limited success. A range of NHC types could be further explored, such as the *N*-alkyl substituted derivatives such as **499** or the recently described cyclic alkylaminocarbene (CAAC) **500** developed by Bertrand and co-workers[157] which possesses stereocentres directly adjacent to the Lewis basic centre (Figure 157).

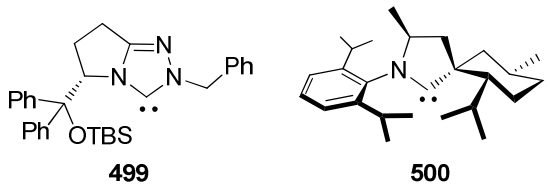


Figure 157: Potential alternative chiral NHCs

A computational analysis of the intermediates and transition state(s) along the reaction coordinate, with particular focus on the final C-C bond-forming step, should be undertaken in order to ascertain the origin of the asymmetric induction. This insight may allow targeted design

of NHC scaffolds, rather than screening of an entire library. This approach may allow identification of new NHC candidates in order to improve the enantioselectivity of the process.

Further investigations should be explored into the extension and application of rearrangements of furanyl carbonates. Rearrangement of carbonate **487**, or relatives of such with greater stability, needs to be repeated in order to confirm the findings in the initial study. Further investigations of the thermodynamic *versus* kinetic parameters of furanyl rearrangements should be undertaken with carbonates bearing substituents with different electronic behaviour. Examples of such are the mesomerically electron-withdrawing and electron-donating 4-cyano- and 4-methoxyphenyl containing carbonates **501** and **502**, and carbonate **503** bearing an inductively withdrawing trifluoromethyl group. Furthermore, there is need for development of methodology to prepare the dialkyl- and diaryl-substituted furanyl carbonates **504** and **505** (Figure 158).

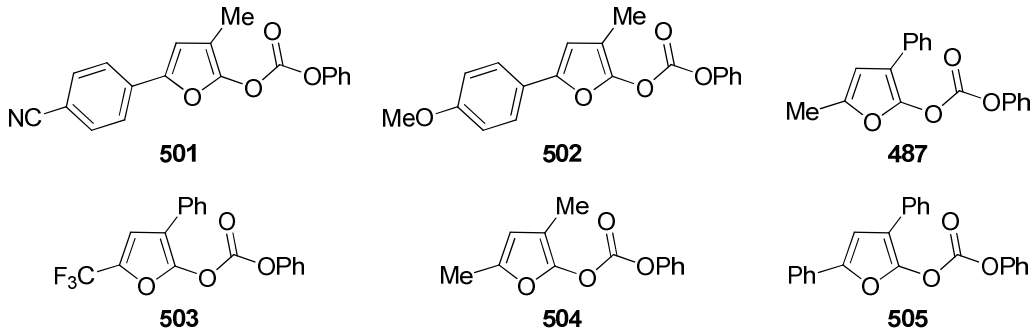
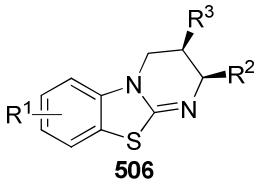


Figure 158: Potential furanyl carbonates for investigation

Finally, a more extensive screen of chiral isothioureas of the type **506** should be undertaken in order to optimise both regioselectivity and enantioselectivity in the asymmetric rearrangement manifolds.



Chapter 8: Experimental details

General information

^{1}H NMR Spectra were recorded using a Bruker Avance 400 spectrometer and Bruker Avance 300 spectrometer at 400 MHz and 300 MHz respectively, using residual protonated solvent as a reference for internal lock. The chemical shift information (δ_H) for each resonance signal are given in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ_H TMS = 0.00 ppm, or to residual (protonated) solvent. The number of protons (*n*) for a reported resonance signal are indicated by *n*H from their integral value and their multiplicity is reported with their coupling constants (*J*) quoted in Hz. Coupling constants are determined by analysis using iNMR® and Topspin®.

^{13}C NMR Spectra were recorded using a Bruker Avance 300 and Bruker Avance 400 spectrometer using the PENDANT sequence at 75.5 MHz and 100 MHz respectively with internal deuterated solvent lock. The chemical shift information (δ_C) for each resonance signal is given in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ_C TMS = 0.00 ppm, or to the relevant solvent.

^{19}F NMR Spectra were recorded using a Bruker Avance 400 spectrometer at 282 MHz. The chemical shift information (δ_F) for each resonance signal are given in units of parts per million (ppm) relative to trichlorofluoromethane ($CFCl_3$) where δ_F = 0.00.

Mass spectrometric (*m/z*) data were acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI), either at the University of St Andrews Mass Spectrometry facility ([A] quoted) or at the EPSRC National Mass Spectrometry Service Centre, Swansea ($[A]^+$ or $[A]^-$ quoted). At the University of St Andrews, low and high resolution ESI MS was carried out on a Micromass LCT spectrometer and low and high resolution EI and CI MS was carried out on a Micromass GCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, low resolution ESI MS was carried out on a Waters Micromass ZQ4000 spectrometer and low resolution EI and CI MS was carried out on a Micromass Quattro II spectrometer. High resolution ESI and ESI MS was carried out on a Finnigan MAT 900 XLT or a Finnigan MAT 95 XP; a Thermofisher LTQ Orbitrap XL spectrometer was also used to obtain high resolution ESI MS for accurate mass determination but also provided fragmentation data for the characterisation of samples. Values are quoted as a ratio of mass to charge in Daltons.

Melting points were determined using an Electrothermal 9100 melting point apparatus and are uncorrected.

Optical rotations were determined using a PerkinElmer Model 341 Polarimeter, at 20.0 ºC using a Na/Hal lamp tuned to 589 nm.

Chiral HPLC was performed on either a Varian ProStar or Gilson apparatus, using a CHIRALPAK OD-H, AD-H or AS-H silica column, 0.46 cm $\phi \times$ 25 cm, using hexane and isopropanol as eluents.

Analytical thin layer chromatography (tlc) was carried out on pre-coated 0.20 mm Machery-Nagel Polygram SIL G/UV_{254} silica plates. Visualisation was carried out by absorption of ultraviolet light or thermal decomposition after dipping in either an ethanolic solution of phosphomolybdic acid or an aqueous solution of potassium permanganate/sodium hydroxide.

Chromatography was performed using Merck Ltd. silica gel 40–63 μm, eluting with solvents supplied under a positive pressure of compressed air.

Anhydrous solvents were obtained under the following conditions:

Dry dichloromethane was distilled from calcium hydride in a recycling still; dry THF was distilled from sodium in a recycling still using benzophenone ketyl as an indicator; dry diethyl ether was distilled from sodium in a recycling still using benzophenone ketyl as an indicator.

From January 2007, anhydrous solvents were obtained from the MBraun SPS-800 solvent purification system.

Chemicals were purchased from Acros UK, Sigma-Aldrich UK, Alfa Aeasar UK, Fisher UK or Merck. Brine refers to a saturated aqueous solution of sodium chloride.

Reactions involving moisture sensitive reagents were performed under an atmosphere of N_2 or Ar using standard vacuum line techniques and with freshly distilled solvents. All glassware was flame-dried and allowed to cool under vacuum.

For known compounds, where certain elements of analytical data are not described in the literature, these data have been reported in this thesis and are marked §.

General Procedures:

When more than one procedure has been followed, an example procedure is described as an illustration.

Conversion of amino acids to their azlactone:

General procedure A (Methyl ester hydrochloride formation)

Thionyl chloride (1.5 equiv) was carefully added dropwise to a stirred suspension of amino acid (1 equiv) in MeOH at 0 ºC. The reaction mixture was then allowed to warm to ambient temperature and stirred for 16 h, after which time the solvent was removed *in vacuo*. Trituration with Et_2O may be used for further purification if necessary.

General procedure B (Amidation)

Et_3N (2.35 equiv) was added to a stirred suspension of amino acid methyl ester hydrochloride (1 equiv) in CH_2Cl_2 at 0 ºC. A solution of *p*-anisoyl chloride (0.98 equiv) in CH_2Cl_2 was added dropwise to the solution and the reaction mixture stirred at ambient temperature over 16 h. The solution was washed with 1 M HCl(aq), sat $NaHCO_3$(aq), brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General procedure C (Ester deprotection)

To a solution of crude *N*-(*p*-anisoyl)amino acid methyl ester (1 equiv) in MeOH was added 2 M NaOH(aq) (1.16 equiv). The solution was stirred for 1 h then the mixture was concentrated *in vacuo* and 1 M HCl(aq) added until pH <2. Upon acidification, a colourless precipitate of the product was formed. Filtration of the mixture followed by azeotropic removal of H_2O by addition of toluene and concentration *in vacuo* gave the desired *N*-(*p*-anisoyl)amino acid product.

General procedure D (*Azlactone cyclisation*)

A mixture of *N*-(*p*-anisoyl)amino acid (1 equiv) in Ac_2O was heated at 65 ºC for 1 h then concentrated *in vacuo* to afford the title compound.

General procedure E (Formation of oxazolyl carbonates with triethylamine)

Based upon a procedure by Fu and co-workers, Et_3N (1.1–1.5 equiv) was added to a stirred solution of the desired azlactone (1 equiv) in THF at 0 ºC, followed by addition of the desired chloroformate (1.06 equiv). The mixture was stirred at 0 °C for 30 min before warming to ambient temperature and stirring over 16 h. The resulting solution was poured into H_2O and the aqueous phase extracted with Et_2O (× 3). The organic extracts were combined, washed with

0.1 M HCl(aq), sat $NaHCO_3$(aq) solution, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by recrystallisation or silica chromatography gave the desired product.

Procedures for Steglich rearrangement and related furanyl carbonate rearrangement:

General procedure F (*Standard protocol*)

To a mixture of azolium salt (*x* mol%) in solvent (typically THF, ~1 mL per 100 mg of carbonate) was added a solution of base in solvent (0.9*x* mol%). The mixture was stirred for 20 min then a solution of carbonate (1 equiv) in solvent (typically THF, ~1 mL per 100 mg of carbonate) was added *via* cannula. The mixture was stirred for *y* min then concentrated *in vacuo* and, if necessary, the residue was purified by silica chromatography.

General procedure G (*Low temperature*)

To a mixture of azolium salt (*x* mol%) in THF or toluene (~1 mL per 100 mg of carbonate) was added a solution of base in solvent (0.9*x* mol%). The mixture was stirred for 20 min then cooled to -78 ºC and a cooled (-78 ºC) solution of carbonate (1 equiv) in THF or toluene (~1 mL per 100 mg of carbonate) was added *via* cannula. The mixture was stirred for 16 h at -78 ºC then concentrated *in vacuo*, and, if necessary, the residue was purified by silica chromatography.

General procedure H (*One-pot*)

To a mixture of azolium salt (*x* mol%) and carbonate (1 equiv) in THF or toluene (~1 mL per 100 mg of carbonate) was added a solution of base in solvent (0.9*x* mol%). The mixture was stirred for *y* min then concentrated *in vacuo* and, if necessary, the residue was purified by silica chromatography.

For crossover experiments, 0.5 equiv of both carbonate substrates were combined in the relevant solvent, and following the aforementioned general procedure H, a sample of the product mixture was concentrated *in vacuo* then examined spectroscopically to determine the product distributions.

General procedure I (*Purification by extraction*)

To a mixture of triazolium salt (*x* mol%) in THF (~1 mL per 100 mg of carbonate) was added a solution of base in solvent (0.9*x* mol%). The mixture was stirred for 20 min then a solution of carbonate (1 equiv) in THF (~1 mL per 100 mg of carbonate) was added *via* cannula. The mixture was stirred for *y* min then quenched with 1 M HCl(aq), extracted with Et_2O (× 3) and, if necessary, the residue was purified by silica chromatography.

General procedure J (*Two-step domino cascade*)

To a mixture of azlactone (1 equiv) and triazolium salt (5 mol%) in THF (~1 mL per 100 mg of azlactone) was added Et_3N (1.5 equiv) followed by the requisite aryl chloroformate (1.3 equiv). The mixture was stirred at ambient temperature, then $Et_3N{\cdot}HCl$ was removed by filtration and the filtrate concentrated *in vacuo*. Purification by silica chromatography (EtOAc/petrol, Et_2O/petrol or CH_2Cl_2/petrol) gave the desired product.

General procedure K (*Multi-step domino cascade with DCC*)

A mixture of *N*-(*p*-anisoyl) amino acid (1 equiv) and DCC (1.01 equiv) were stirred in THF for 2 h then filtered (to remove dicyclohexylurea), followed by addition of triazolium salt **128** (5 mol%), Et_3N (1.5 equiv) and then phenyl chloroformate (1.3 equiv). The mixture was stirred at ambient temperature, then $Et_3N{\cdot}HCl$ was removed by filtration and the filtrate concentrated *in vacuo*. Purification by silica chromatography (Et_2O/petrol) gave the desired product.

General procedure L (Alternative multi-step domino cascade protocol using aryl chloroformates)

To a mixture of *N*-(*p*-anisoyl) amino acid (1 equiv) and triazolium salt **128** (5–10 mol%) in THF was added Et_3N (3.5 equiv) followed by phenyl chloroformate (3 equiv), with significant exotherm and effervescence observed. The mixture was stirred at ambient temperature, then $Et_3N{\cdot}HCl$ was removed by filtration and the filtrate concentrated *in vacuo*. Purification by silica chromatography (Et_2O/petrol or CH_2Cl_2/petrol) gave the desired product.

General procedure M (*General Lewis base-promoted rearrangement*)

To a solution of carbonate (1 equiv) in solvent (~1 mL per 100 mg of carbonate) was added the requisite Lewis base (aminopyridine, amidine or isothiourea) (*x* mol%). The mixture was stirred for 5 min to 16 h, then concentrated *in vacuo*, and the residue purified by silica chromatography if necessary.

For crossover experiments, 0.5 equiv of both carbonate substrates were combined in the relevant solvent, and following the aforementioned general procedure M, a sample of the product mixture was concentrated *in vacuo* then examined spectroscopically to determine the product distributions.

General procedure N (Amide coupling via mixed anhydride)

To a cooled (0 ºC) mixture of carboxylic acid (1 equiv) in CH_2Cl_2 was added *N*-methylmorpholine (1.15 equiv) over 5 min, followed by dropwise addition of ethyl

chloroformate (1 equiv) over 15 min. Finally, amine (1 equiv) was added over 15–20 min then the mixture was allowed to warm to ambient temperature slowly over 16 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (× 3). The organic fractions were combined and washed sequencially with 4% $NaHCO_3$(aq) and 1 M HCl(aq), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was then triturated with ice-cold pentane to obtain the purified product.

General procedure O (Reduction of amino amides)

To a mixture of amino amide (1 equiv) in THF was carefully added $LiAlH_4$ (3 equiv of a 2.0 M solution in THF) at ambient temperature, with notable effervescence. The mixture was then heated at reflux (80–85 ºC) for 18–34 h, then the mixture was cooled in an ice bath, and H_2O (*x* mL for *x* g of $LiAlH_4$ used) was added carefully, followed by 15% KOH(aq) (*x* mL for *x* g of $LiAlH_4$ used) and more H_2O (3*x* mL for *x* g of $LiAlH_4$ used). The mixture was stirred rapidly for 5 min, then excess $MgSO_4$ added to the mixture and the mixture stirred rapidly for 4–6 h. The mixture was then filtered through celite, eluting with Et_2O, then the filtrate concentrated *in vacuo* to afford the crude product.

General procedure P (Reduction of N-Boc-amino amides)

To a mixture of *N*-Boc-amino amide (1 equiv) in THF was carefully added $LiAlH_4$ (6 equiv of a 2.0 M solution in THF) at ambient temperature, with notable effervescence. The mixture was then heated at reflux (80–85 ºC) for 18–34 h, then the mixture was cooled in an ice bath, and H_2O (*x* mL for *x* g of $LiAlH_4$ used) was added carefully, followed by 15% KOH(aq) (*x* mL for *x* g of $LiAlH_4$ used) and more H_2O (3*x* mL for *x* g of $LiAlH_4$ used). The mixture was stirred rapidly for 5 min, then excess $MgSO_4$ was added to the mixture and the mixture stirred rapidly for 4–6 h. The mixture was then filtered through celite, eluting with Et_2O, then the filtrate concentrated *in vacuo* to afford the crude product.

General procedure Q (Boc deprotection)

To a mixture of carbamate (1 equiv) in CH_2Cl_2 was added TFA (~2 mL per g of carbamate) and the mixture stirred at ambient temperature for 16 h. The mixture was then concentrated *in vacuo*, followed by extraction from 1 M NaOH(aq) with CH_2Cl_2 (× 3). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated to afford the desired amino amide.

Preparation of furanyl carbonates via butenolides from (phenylthio)acetic acid

General procedure R (Preparation of the butyrolactone)

To a solution of diisopropylamine (2.21 equiv) in THF at 0 °C was added *n*-BuLi (2.5 M in hexanes, 2.21 equiv). After 15 min, the solution of LDA was cooled to -78 ºC and the

(phenylthio)acetic acid (1 equiv) was added as a solution in THF. After 1 h, the requisite epoxide (1.20 equiv) was added in one portion and the mixture allowed to warm to ambient temperature over 16 h. The reaction mixture was quenched with 2 M NaOH(aq) and extracted with Et_2O (× 3). The aqueous layer was acidified with 10 M HCl(aq) and extracted with Et_2O (× 3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatographic purification (100% CH_2Cl_2) gave the desired product as a mixture of diastereomers, ~1–2:1 *dr*. The product was used without further purification.

General procedure S (Alkylation of the butyrolactone)

To a solution of diisopropylamine (1.3 equiv) in THF at 0 °C was added *n*-BuLi (2.5 M in hexanes, 1.3 equiv). After 15 min, the solution of LDA was cooled to -78 ºC and a solution of the requisite lactone (1 equiv) in THF was added over 15 min. After 30 min, a solution of the requisite halide* (1 equiv) in DMPU was added in one portion and the mixture allowed to warm to ambient temperature over 16 h. The reaction was quenched with sat NH_4Cl(aq) and extracted with Et_2O. The combined organic extracts were washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatographic purification (20% Et_2O:petrol) gave the desired product as a mixture of diastereomers, generally >9:1 *dr* in favour of the *syn*-diastereomer.

* If using a reactive alkyl halide, such as benzyl bromide, only DMPU is required to promote the alkylation. If not activated, Finklestein catalysis should be employed using NaI (0.2–1 equiv).

General procedure T (Oxidation/thermolysis to the butenolide)

To a solution of lactone (1 equiv) in either CH_2Cl_2 or $CHCl_3$ at 0 °C was added *m*CPBA (70% purity, 1 equiv) [NB. For large scale reactions the *m*CPBA was added portionwise to prevent overoxidation to the sulfone]. After 1 h, sat $NaHCO_3$(aq) (excess) was added and the solution was extracted with EtOAc. The combined organic extracts were washed with brine and dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude sulfoxide. The crude sulfoxide was dissolved in toluene and heated at reflux for 16 h, then the mixture was concentrated *in vacuo*. Chromatographic purification (10% → 20% Et_2O:petrol) gave the butenolide, generally as a mixture of tautomers.

General procedure U (*Preparation of the carbonate)*

To a cooled (0 ºC) solution of butenolide (mixture of tautomers) in THF was added Et_3N (2 equiv) followed by dropwise addition of phenyl chloroformate (2 equiv) The mixture was warmed to ambient temperature over 16 h, then quenched with sat NH_4Cl(aq) and extracted with Et_2O. The organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude carbonate product. Chromatographic purification (10% Et_2O:petrol) gave the desired carbonate product.

General Procedure V (Resubjection of rearrangement products)

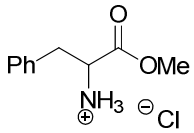
With NHC:

To a mixture of *C*-carboxybutenolide (either the α- or γ-regioisomer) (1 equiv) and triazolium salt **128** (10 mol%) in THF (~1 mL $mmol^{-1}$) was added KHMDS (0.5 M solution in toluene, 9 mol%) and the mixture stirred for 5 h. After this time, the mixture was concentrated *in vacuo* then analysed spectroscopically to determine the product distribution.

With DMAP:

To a solution of *C*-carboxybutenolide (either the α- or γ-regioisomer) (1 equiv) in THF (~1 mL $mmol^{-1}$) was added DMAP (9 mol%) and the mixture stirred for 5 h. After this time, the mixture was concentrated *in vacuo* then analysed spectroscopically to determine the product distribution.

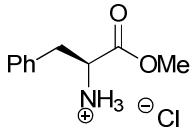
DL-Phenylalanine methyl ester hydrochloride 251



251

To a stirred suspension of DL-phenylalanine **250** (12.5 g, 75.7 mmol) in MeOH (125 mL) at 0 ºC was added thionyl chloride (8.30 mL, 114mmol) dropwise. The mixture was allowed to warm to ambient temperature and stirred for 16 h. The mixture was concentrated *in vacuo* to afford the crude product as a pale yellow solid which was triturated with Et_2O (250 mL) to afford the product as a colourless solid (16.3 g, quantitative). **mp** 158–161 ℃, lit.[158] 161–162 ºC; δ_H (300 MHz, D_2O) 7.45–7.37 (3H, m, Ar*H*), 7.31–7.27 (2H, m, Ar*H*), 4.42 (1H, ABX, J_{XB} 7.4, J_{XA} 5.2, C*H*), 3.82 (3H, s, CH_3), 3.34 (1H, ABX, J_{AB} 14.6, J_{AX} 5.2, PhCH_AH$_B$) and 3.21 (1H, ABX, J_{BA} 14.6, J_{BX} 7.4, PhCH$_A$$H_B$). Spectroscopic data are in accordance with the literature.[159]

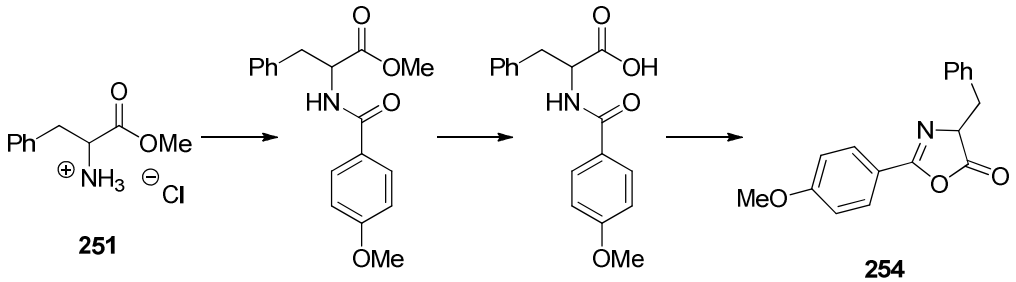
L-Phenylalanine methyl ester hydrochloride (*S*)-251



(*S*)-251

Following the above procedure using L-phenylalanine **(*S*)-250**, the enantiomerically pure product was obtained in quantitative yield; **mp** 159–160 °C, lit.[160] 158–162 °C; $[\alpha]_D^{20}$ +19.5 (*c* 1.0, MeOH), lit.[161] +18.1 (*c* 2.0, MeOH). Data are in accordance with the literature.

4-Benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole 254



251 **252** **253** **254**

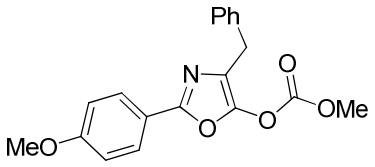
Following general procedure B, DL-phenylalanine methyl ester hydrochloride **251** (13.7 g, 63.6 mmol), CH_2Cl_2 (140 mL), Et_3N (20.8 mL, 149.4 mmol) and *p*-anisoyl chloride (10.6 g, 62.4 mmol) in CH_2Cl_2 (17 mL) gave the amido ester product **252** as a pale cream solid (19.5 g, 98%). δ_H (300 MHz, $CDCl_3$) 7.72–7.66 (2H, m, MeOAr*H*–3,5), 7.33–7.20 (3H, m, Ph*H*), 7.16–7.11 (2H, m, Ph*H*), 6.95–6.89 (2H, m, MeOAr*H*-2,6), 6.50 (1H, br d, *J* 7.5, N*H*), 5.11 (1H, dt,

J 7.5, 5.7, C*H*NH), 3.85 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.28 (1H, ABX, J_{AB} 13.8, J_{AX} 5.7, CH_AH$_B$Ph) and 3.21 (1H, ABX, J_{BA} 13.8, J_{BX} 5.5, CH$_A$$H_B$Ph).

Following general procedure C, *N*-*p*-anisoyl-DL-phenylalanine methyl ester **252** (19.51 g, 62.3 mmol), MeOH (125 mL) and 2 M NaOH(aq) (38 mL) gave the acid product **253** as a colourless solid (15.9 g, 85%). **mp**[§] 109–112 ºC (glassy); δ_H (300 MHz, $CDCl_3$) 7.51 (1H, d, *J* 8.6, MeOAr*H*-3,5), 7.08–6.92 (5H, m, Ph*H*), 6.72 (2H, d, *J* 8.6, MeOAr*H*-2,6), 4.59 (1H, ABX, J_{XB} 4.9, J_{XA} 4.1, NHC*H*(Bn)COOH), 3.60 (3H, s, OCH_3), 3.10 (1H, ABX, J_{AB} 13.4, J_{AX} 4.1, CH_AH$_B$Ph) and 2.91 (1H, ABX, J_{BA} 13.4, J_{BX} 4.9, PhCH$_A$$H_B$). Spectroscopic data are in accordance with the literature.[106]

Following general procedure D, *N*-*p*-anisoyl-DL-phenylalanine **253** (5.00 g, 16.7 mmol) and Ac_2O (8.5 mL) gave the title compound as a pale yellow solid (4.70 g, quantitative). **mp**[§] 114–115 ºC; δ_H (300 MHz, $CDCl_3$) 7.81–7.67 (2H, m, MeOAr*H*-3,5), 7.22–7.10 (5H, m, Ph*H*), 6.89–6.84 (2H, m, MeOAr*H*-2,6), 4.59 (1H, ABX, J_{XB} 6.7, J_{XA} 5.0, C*H*NHR), 3.79 (3H, s, ArOCH_3), 3.28 (1H, ABX, J_{AB} 13.9, J_{AX} 5.0, CH_AH$_B$Ph) and 3.10 (1H, ABX, J_{BA} 13.9, J_{BX} 6.7, CH$_A$$H_B$Ph). Spectroscopic data are in accordance with the literature.[106]

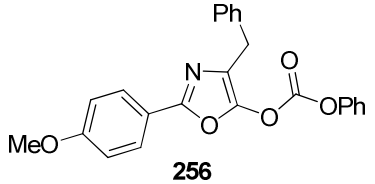
4-Benzyl-2-(4-methoxyphenyl)oxazolyl methyl carbonate 255



255

Following general procedure E, Et_3N (4.46 mL, 32.1 mmol), azlactone **254** (5.64 g, 20.0 mmol), THF (100 mL) and methyl chloroformate (2.33 mL, 30.1 mmol) gave, after crystallisation (Et_2O/petrol), the title compound as a colourless solid (6.31 g, 93%). **mp** 58–60 ºC, lit.[162] 58–60 ºC; δ_H (300 MHz, $CDCl_3$) 7.83–7.78 (2H, m, MeOAr*H*-3,5), 7.24–7.12 (5H, m, Ph*H*), 6.88–6.83 (2H, m, MeOAr*H*-2,6), 3.80 (3H, s, COOCH_3), 3.79 (2H, s, CH_2Ph) and 3.77 (3H, s, ArOCH_3). Spectroscopic data are in accordance with the literature.[162]

4-Benzyl-2-(4-methoxyphenyl)oxazol-5-yl phenyl carbonate 256

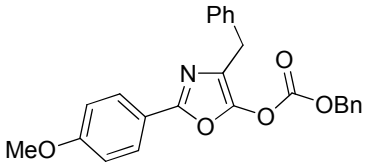


256

Following general procedure E, Et_3N (3.72 mL, 26.7 mmol), azlactone **254** (4.70 g, 16.7 mmol), THF (70 mL) and phenyl chloroformate (3.14 mL, 25.1 mmol) gave, after recrystallisation

(Et_2O/petrol), the product as a colourless solid (5.03 g, 75%). **mp**[§] 93–94 °C; **δ_H** (300 MHz, $CDCl_3$) 7.96–7.91 (2H, m, MeOAr*H*-3,5), 7.47–7.18 (10H, m, Ph*H*), 6.99–6.94 (2H, m, MeOAr*H*-2,6), 3.96 (2H, s, CH_2Ph) and 3.87 (3H, s, ArOCH_3). Spectroscopic data are in accordance with the literature.[106]

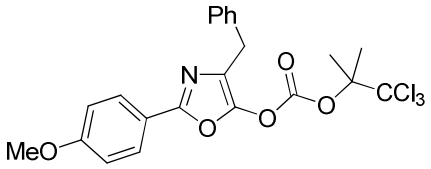
Benzyl 4-benzyl-2-(4-methoxyphenyl)-oxazol-5-yl carbonate 257



257

Following the general procedure E, Et_3N (0.540 mL, 3.91 mmol), azlactone **254** (1.00 g, 3.55 mmol), THF (25 mL) and benzyl chloroformate (0.890 mL, 3.76 mmol) gave, after chromatographic purification (25% Et_2O:petrol), the product as a yellow oil (1.10 g, 74%). **δ_H** (300 MHz, $CDCl_3$) 7.87 (2H, d, *J* 9.0, MeOAr*H*-3,5), 7.41–7.39 (5H, m, Ph*H*), 7.27–7.25 (5H, m, OCH_2Ph*H*), 6.92 (2H, d, *J* 9.0, MeOAr*H*-2,6), 5.21 (2H, s, OCH_2Ph), 3.85 (3H, s, OCH_3) and 3.85 (2H, s, CH_2Ph). Spectroscopic data are in accordance with the literature.[107]

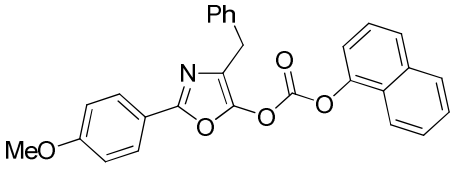
4-Benzyl-2-(4-methoxyphenyl)-oxazol-5-yl 1,1,1-trichloro-2-methylpropan-2-yl carbonate 258



258

Following general procedure B, Et_3N (3.91 mmol, 0.540 mL), azlactone **254** (1.00 g, 3.55 mmol), THF (30 mL) and 1,1,1-trichloro-2-methylpropan-2-yl chloroformate (900 mg, 3.76 mmol) gave, after chromatographic purification (25% Et_2O:petrol), the product as a colourless solid (1.34 g, 78%). **mp** 62–64 °C, lit.[124] 62–64 °C; **δ_H** (300 MHz, $CDCl_3$) 7.89 (2H, d, *J* 9.0, MeOAr*H*-3,5), 7.31–7.29 (5H, m, Ar*H*), 6.93 (2H, d, *J* 9.0, MeOAr*H*-2,6), 3.88 (2H, s, CH_2), 3.85 (3H, s, OCH_3) and 1.92 (6H, s, 2 × CH_3). Data are in accordance with the literature.[124]

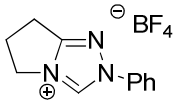
4-Benzyl-2-(4-methoxyphenyl)oxazol-5-yl naphthalen-1-yl carbonate 259



259

Following general procedure E, Et_3N (0.594 mL, 4.27 mmol), azlactone **254** (1.00 g, 3.56 mmol), CH_2Cl_2 (10 mL) and 1-naphthyl chloroformate (0.660 mL, 4.09 mmol), gave the crude product as a yellow oil. Crystallisation (Et_2O:hexane) gave the product as a colourless solid (828 mg, 51%). **mp** 86–88 ºC; δ_H (400 MHz, $CDCl_3$) 7.95–7.89 (4H, m, MeOAr*H*-3,5 and Nap*H*), 7.80 (1H, d, *J* 8.3, Nap*H*), 7.57 (2H, dt, 6.7, 3.0, Ar*H*), 7.49 (1H, t, *J* 8.0, Ar*H*), 7.39–7.31 (5H, m, Ar*H*), 7.27–7.24 (1H, m, Ar*H*), 6.95 (2H, d, *J* 8.8, MeOAr*H*-2,6), 3.97 (2H, s, PhCH_2) and 3.85 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 161.7 (MeOAr*C*-1), 155.7 (Ar*C*), 150.2 (Ar*C*), 146.6 (Ar*C*), 145.9 (Ar*C*), 137.6 (Ar*C*), 134.8 (Ar*C*), 129.1 (Ar*C*H), 128.8 (Ar*C*H), 128.3 (Ar*C*H), 128.0 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (Ar*C*H), 127.1 (Ar*C*H), 126.9 (Ar*C*H), 126.1 (Ar*C*), 125.4 (Ar*C*H), 123.5 (Ar*C*), 120.9 (Ar*C*H), 119.9 (Ar*C*), 117.3 (Ar*C*H), 114.4 (Ar*C*H), 55.6 (O*C*H_3) and 31.9 (*C*H_2); ***m/z*** MS (ESI+) 469 (100, $[M+NH_4]^+$), HRMS (ESI+) $C_{28}H_{25}N_2O_5^+$ ($[M+NH_4]^+$) requires 469.1758, found 469.1758 (+0.0 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3052 (Ar C-H), 3027, 2970, 2913, 2835, 1792 (C=O), 1667 (Ar C=C), 1617 (C=N), 1603 (Ar C=C), 1459, 1502, 1455, 1434, 1393, 1307, 1258 (C-O), 1213 (C-O) and 1180 (C-O).

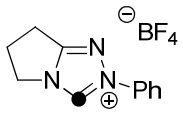
2-Phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolium tetrafluoroborate 128



128

Trimethyloxonium tetrafluoroborate (2.96 g, 20.0 mmol) was added to a solution of pyrrolidin-2-one (1.40 mL, 18.1 mmol) in CH_2Cl_2 (120 mL) and the mixture was stirred at ambient temperature for 16 h. Phenylhydrazine (1.80 mL, 18.1 mmol) was added and stirred for 2 d before concentration *in vacuo*. The residue was dissolved in MeOH (10 mL) and triethyl orthoformate (40 mL) and heated at reflux (100 ºC) for 16 h. The resultant solid was filtered and recrystallised from MeOH to afford the title compound as a golden-orange solid (4.22 g, 85%). **mp** 154–156 ºC, lit.[110] 154–156 ºC; δ_H (300 MHz, d_6-DMSO) 10.71 (1H, s, C*H*), 7.91–7.85 (2H, m, Ph*H*-2,6), 7.73–7.60 (3H, m, Ph*H*-3,4), 4.41 (2H, t, *J* 7.4, NCH_2), 3.21 (2H, t, *J* 7.4, CCH_2) and 2.75 (2H, tt, *J* 7.4, $CH_2CH_2CH_2$). Data are in accordance with the literature.[110]

3-^{13}C-2-Phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazolium tetrafluoroborate 3-^{13}C-128

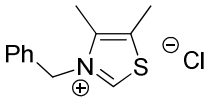


3-^{13}C-128

● = ^{13}C

Trimethyloxonium tetrafluoroborate (814 mg, 5.50 mmol) was added to a solution of pyrrolidin-2-one (0.415 mL, 5.36 mmol) in CH_2Cl_2 (120 mL) and the mixture was stirred at ambient temperature for 16 h. Phenylhydrazine (0.547 mL, 5.50 mmol) was added and stirred for 2 d before concentration *in vacuo*. The residue was dissolved in MeOH (10 mL) and triethyl $^{13}C_1$-orthoformate (2.00 g, 13.4 mmol) and heated at reflux (100 ºC) for 16 h. Precipitation was induced by addition of Et_2O (3 drops) and cooling to 0 ºC in an ice-bath. The resultant solid was filtered and triturated with cold (-78 ºC) EtOAc (5 mL) to afford the title compound as a pink-orange solid (1.24 g, 82%). **mp** 154–156 ºC; **δ_H** (300 MHz, d_6-DMSO) 10.71 (1H, d, *J* 160, ^{13}C*H*), 7.91–7.85 (2H, m, Ph*H*-2,6), 7.73–7.60 (3H, m, Ph*H*-3,4), 4.41 (2H, t, *J* 7.4, NCH_2), 3.21 (2H, t, *J* 7.4, CCH_2) and 2.75 (2H, tt, *J* 7.4, $CH_2CH_2CH_2$). Data are in accordance with the unlabelled product **128**.

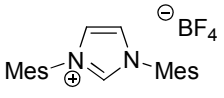
3-Benzyl-4,5-dimethylthiazolium chloride 203



203

To a solution of 4,5-dimethylthiazole (2.30 g, 20.3 mmol) in acetonitrile (10 mL) was added benzyl chloride (2.57 g, 20.3 mmol) dropwise over 10 min. The solution was heated at reflux (85 ºC) for 24 h. The mixture was allowed to cool to ambient temperature then precipitation of the product was induced with gentle scraping with a spatula. The precipitate was collected by filtration and washed with cold CH_3CN (10 mL). The product was dried *in vacuo* for 24 h, to afford the product as a colourless solid (2.97 g, 61%). **mp** 55–56 ºC, lit.[163] 56–58 ºC; **δ_H** (400 MHz, $CDCl_3$) 11.88 (1H, s, SC*H*N), 7.37–7.32 (5H, m, Ph*H*), 6.13 (2H, s, CH_2Ph), 2.48 (3H, s, CH_3-4) and 2.36 (3H, s, CH_3-5). Data are in accordance with the literature.[163]

Bis(2,4,6-trimethylphenyl)imidazolium tetrafluoroborate 265

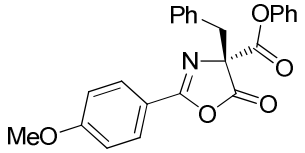


265

To a solution of mesitidine (1.40 mL, 10.0 mmol) in toluene (20 mL) was added paraformaldehyde (300 mg, 10.0 mmol) with vigorous stirring and cooling to 10 ºC. After

30 min, further mesitidine (1.40 mL, 10.0 mmol) was added at 0 ºC, then HBF_4(aq) (1.25 mL of a 40% w/v solution, 10.0 mmol) was added dropwise, stirred at ambient temperature for 30 min then heated to 40 ºC for 12 h. Addition of Et_2O (10 mL) resulted in precipitation of an oily substance from which the liquor was decanted. The oily substance was triturated exhaustively with Et_2O and hexane to afford the product as a brown/grey solid (2.57 g, 65%). **mp**[§] 240–243 ºC; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.80 (1H, t, *J* 1.5, NC*H*N), 7.53 (2H, d, *J* 1.5, NC*H*C*H*N), 6.97 (4H, s, Ar*H*-3,5), 2.30 (6H, s, 4-CH_3Ar) and 2.05 (12H, s, 2,6-(CH_3)$_2$Ar); $\boldsymbol{\delta_C}$[§] (100 MHz, $CDCl_3$) 141.2 (NAr*C*-1), 137.0 (N*C*HN), 134.0 (Ar*C*(CH$_3$)-2), 130.5 (Ar*C*(CH$_3$)-4), 129.7 (Ar*C*H-3,5), 125.2 (N*C*H*C*HN), 21.1 (4-*C*H$_3$Ar) and 17.1 (2,6-(*C*H$_3$)$_2$Ar); **IR**[§] ν_{max} (KBr) /cm^{-1} 3118 (C-H), 2944 (C-H), 2863 (C-H), 1625 (C=C/C=N), 1530 (C=C/C=N stretch), 1455 (C-H), 1377 (C-H) and 1221 (C-N). Data are in accordance with the literature.[164]

(*R*)- and (*RS*)-Phenyl 4-benzyl-5-oxo-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylate 266



(*R*)-266

All procedures F-M were employed to afford the title compound.

Following general procedure F, KHMDS (13.5 μL, 6.75 μmol), triazolium salt **128** (2.05 mg, 7.50 μmol), THF (3 mL) and oxazolyl carbonate **256** (300 mg, 0.750 mmol) gave, after chromatographic purification (20% Et_2O:petrol), the title compound as a colourless oil (241 mg, 80%). $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.92–7.87 (2H, m, MeOAr*H*-2,6), 7.43–7.37 (2H, m, Ph*H*), 7.30–7.19 (6H, m, Ph*H*), 7.15–7.10 (2H, m, Ph*H*), 6.98–6.94 (2H, m, MeOAr*H*-2,6), 3.88 (3H, s, ArOCH_3), 3.75 (1H, ABd, *J* 13.7, CH_AH$_B$Ph) and 3.61 (1H, ABd, *J* 13.7, CH$_A$$H_B$Ph). Spectroscopic data are in accordance with the literature.[107]

Enantiomeric excesses were determined by HPLC with Chiralcel OD-H column (5% *i*-PrOH:hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 13.8 min and t_R(*S*) 18.9 min.

Catalyst screening studies

To evaluate the efficacy of all NHCs in the Steglich rearrangement protocol, the following procedure was employed.

Following general procedure F or H, KHMDS (0.45-9 mol%), azolium salt precatalyst (0.5-10 mol%), THF (1 mL) and oxazolyl carbonate **256** (100 mg, 0.249 mmol) were used, and samples taken after specified times, concentrated *in vacuo* and inspected spectroscopically

(^{1}H NMR); in cases where isolated yields are stated, chromatographic purification (20% Et_2O:petrol) gave the title compound as a colourless oil.

Results of screen with achiral azolium salts via *preformation of NHC* in situ*:*

All reactions were carried out according to general procedure F above, at 10 mol% precatalyst loading in THF (1 mL, 0.249 mM concentration of carbonate substrate **256**) after 1 h.

Precatalyst	Conversion (%) [a]	Isolated yield (%)
128	>98	80
203	11	-
267	<5	-
79	>90	68
265	~40	-
245	>90	-

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

Results of screen with achiral azolium salts via *one-pot protocol:*

All reactions were carried out according to general procedure H, at *x* mol% precatalyst loading in THF (1 mL, 0.249 mM concentration of carbonate substrate **256**).

Precatalyst (mol%)	KHMDS (mol%)	Time (min)	Conversion (%) [a]
no precatalyst	9	60	<5
128 (10)	9	60	>98 (80) [b]
128 (10)	9	5	>98 (80) [b]
128 (1)	0.9	5	>98
268 (1)	0.9	5	>98
270 (1)	0.9	5	>98
79 (9)	9	60	>95
245 (9)	9	60	>95
203 (9)	9	60	~30
267 (9)	9	60	72

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Isolation of homogenous purified product by chromatography

Results of screen with achiral azolium salts using triethylamine as the base

All reactions were carried out according to general procedure F above, at *x* mol% precatalyst loading and Et_3N as the base at the stated molar equivalence, in the relevant solvent (1 mL, 0.249 mM concentration of carbonate substrate **256**).

Precatalyst (mol%)	Base (mol%)	Solvent	Time	Conversion (%) [a]
128 (1)	Et_3N (0.9)	THF	>24 h	<10
128 (10)	Et_3N (9) + Et_3N·HCl (1 equiv)	THF	2 h	75
			3 h	>98
128 (10)	Et_3N (9)	THF	2 h	>98
128 (10)	Et_3N (100)	THF	<5 min	>98
128 (10)	Et_3N (9)	CH_2Cl_2	2 h	~75
268 (10)	Et_3N (9)	THF	2 h	>98
270 (10)	Et_3N (9)	THF	4 h	>98
79 (10)	Et_3N (9)	THF	>24 h	<10
245 (10)	Et_3N (9)	THF	>24 h	<5
265 (10)	Et_3N (9)	THF	>24 h	<5

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

Results of screen with chiral diazolium salts via *preformation of NHC* in situ*:*

All reactions were carried out according to general procedure F above, at 10 mol% precatalyst loading in THF (1 mL, 0.249 mM concentration of carbonate substrate) after 1 h. Conversions were determined spectroscopically, and enantiomeric excesses were determined following chromatographic purification (20% Et_2O:petrol).

Chiral diazolium precatalyst	Conversion (%) [a]	*ee* of (*R*)-266 (%)
344	70	<5
348	>98	<5
354	<5	-
138	65	11
362	75	<5
377	~20	-
380	~65	<5

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

Results of screen with chiral triazolium salts via *preformation of NHC* in situ*:*

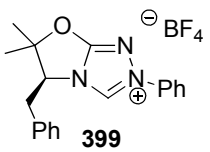
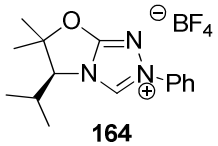
All reactions were carried out according to general procedure F above, at 10 mol% precatalyst loading in either THF of toluene (1 mL, 0.249 mM concentration of carbonate substrate **256**). Conversions were determined spectroscopically, and enantiomeric excesses were determined following chromatographic purification (20% Et_2O:petrol).

Chiral triazolium salt	Solvent	Conversion (*R*)-266:254 (%) [a]	*ee* of (*R*)-266 (%)
56	THF	~70:30	<5
56	toluene	~55:45	<5
134	THF	>98:<2	20 (*ent*)
134	toluene	95:5	20 (*ent*)
399	THF	>98:<2	<5
399	toluene	>98:<2	34
164	THF	>98:<2	16
164	toluene	88:12	31
137	THF	>98:<2	<5
137	toluene	>98<:2	<5
***ent*-170**	THF	>98:<2	<5 (*ent*)
***ent*-170**	toluene	>95:<5	<5 (*ent*)
416	THF	>98:<2	<5 (*ent*)
416	toluene	95:5	20 (*ent*)
403	THF	>98:<2	<5
403	toluene	88:12	<5
407	THF	>98:<2	<5
407	toluene	90:10	6

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product

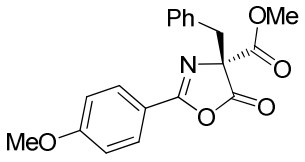
Optimisation of asymmetric Steglich rearrangement using chiral oxazolidinone-derived triazolium salts

All reactions were carried out according to general procedure F above, at 10 mol% precatalyst loading, with the relevant base and solvent stated (1 mL solvent, 0.249 mM concentration of carbonate substrate **256**), and at the temperature stated. Conversions were determined spectroscopically, and enantiomeric excesses were determined following chromatographic purification (20% Et_2O:petrol).

Precatalyst	Base	Solvent	Temp (ºC)	Time (h)	Conversion (*R*)-266:254 (%) [a]	*ee* (%)
 **399**	KHMDS	PhCl	rt	1	>98:2	13
	KHMDS	Et_2O	rt	1	>98:2	27
	KHMDS	toluene	rt	1	>98:2	34
	KHMDS	toluene	-20	16	74:17 [b]	46
	KHMDS	toluene	-30	16	0:0 [b]	-
	Et_3N	CH_2Cl_2	rt	4	90:10	22
 **164**	KHMDS	PhCl	rt	1	>98:2	8
	KHMDS	toluene	rt	1	88:12	31
	KHMDS	toluene	-30	16	63:37	50
	Cs_2CO_3	THF	rt	1	80:20	25
	Cs_2CO_3	toluene	rt	1	75:25	5
	NaHMDS	toluene	rt	1	70:30	33
	LiHMDS	toluene	rt	1	>98:2	39
	n-BuLi	toluene	rt	1	0:0 [b]	-

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Remainder present as unreacted carbonate **256**

(*R*)- and (*RS*)-Methyl 4-benzyl-5-oxo-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylate 249


(*R*)-249

Procedures F-I were employed to afford the title compound.

Following general procedure F, KHMDS (90.0 μL of a 0.5 M solution in toluene, 0.0450 mmol), triazolium salt **128** (13.7 mg, 50.0 μmol), THF (2 mL) and carbonate **255** (170 mg, 0.500 mmol) gave, after chromatographic purification (15% Et_2O:petrol), the title compound as a colourless oil (129 mg, 76%). δ_H (300 MHz, $CDCl_3$) 7.85–7.80 (2H, m, MeOAr*H*-3,5), 7.20–7.14 (5H, m, Ph*H*), 6.94–6.89 (2H, m, MeOAr*H*-2,6), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.63 (1H, ABd, *J* 13.7, CH_AH$_B$Ph) and 3.48 (1H, ABd, *J* 13.7, CH$_A$$H_B$Ph). Spectroscopic data are in accordance with the literature.[110]

Enantiomeric excesses were determined by HPLC with Chiralcel OD-H column (2% *i*-PrOH:hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 15.7 min and t_R(*S*) 19.9 min.

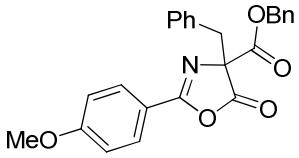
Results of screen with achiral azolium salts via *preformation of NHC* in situ:

All reactions were carried out according to general procedure F above, at *x* mol% precatalyst loading in THF (0.249 mM concentration of carbonate substrate).

Precatalyst (mol%)	KHMDS (mol%)	Time (min)	Conversion (%) [a]
128 (10)	9	90	>98 (76) [b]
128 (5)	4.5	90	>98
128 (1)	0.9	90	>98
128 (1)	0.9	5	>98
79 (10)	9	90	~75 (68) [b]
245 (10)	9	90	<5

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product
[b] Isolated yield of homogeneous product following chromatographic purification

Benzyl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 271

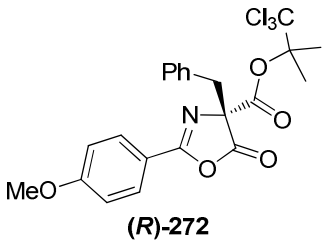


271

Procedures F and H were employed to afford the title compound.

Following general procedure F, KHMDS (36.0 μL of a 0.5 M solution in toluene, 18.0 μmol), triazolium salt **128** (5.46 mg, 20.0 μmol), THF (2 mL) and carbonate **257** (82.0 mg, 0.200 mmol) gave, after chromatographic purification (15% Et_2O:petrol), the title compound as a colourless oil (150 mg, 75%). δ_H (300 MHz, $CDCl_3$) 7.82 (2H, d, *J* 9.0, MeOAr*H*-3,5), 7.35–7.31 (5H, m, Ph*H*), 7.20–7.14 (5H, m, Ph*H*), 6.91 (2H, d, *J* 9.0, MeOAr*H*-2,6), 5.30 (1H, ABd, *J* 12.4, PhCH_AH$_B$O), 5.24 (1H, ABd, *J* 12.4, PhCH$_A$$H_B$O) 3.85 (3H, s, OC$H_3$), 3.64 (1H, ABd, *J* 13.8, PhCH_AH$_B$) and 3.50 (1H, ABd, *J* 13.8, PhCH$_A$$H_B$). Spectroscopic data are in accordance with the literature.[107]

(*R*)- and (*RS*)-1,1,1-Trichloro-2-methylpropan-2-yl 4-benzyl-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 272



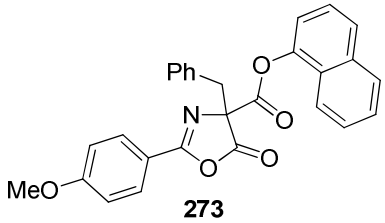
(*R*)-272

Procedures F and H were employed to afford the title compound.

Following the general procedure F, oxazolyl carbonate **258** (200 mg, 0.413 mmol), THF (2 mL), triazolium salt **128** (11.3 mg, 41.3 μmol) and KHMDS (74.4 μL of a 0.5 M in toluene, 37.2 μmol) gave, after 1 h and chromatographic purification (20% Et_2O:petrol), the product as a colourless oil (168 mg, 84%). δ_H (300 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.8, MeOAr*H*-3,5), 7.23–7.18 (5H, m, Ph*H*), 6.89 (2H, d, *J* 8.8, MeOAr*H*-2,6), 3.86 (3H, s, OCH_3), 3.59 (1H, ABd, *J* 13.6, CH_AH$_B$), 3.48 (1H, ABd, *J* 13.6, CH$_A$$H_B$), 1.95 (3H, s, C$H_3$) and 1.91 (3H, s, C$H_3$). Spectroscopic data are in accordance with the literature.[125]

Enantiomeric excess for reaction was determined by derivatisation (see below). Absolute configuration assigned by analogy with the absolute configuration of related products.

Naphthalen-1-yl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 273



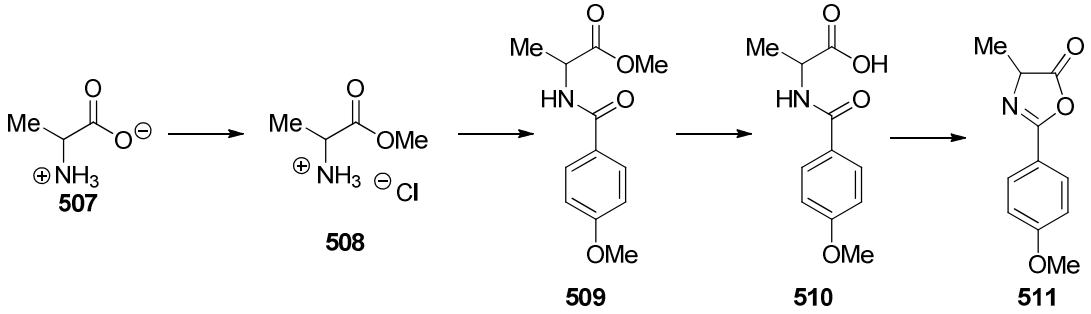
273

Procedures F, H, J and M were employed to afford the title compound.

Following general procedure M, *N*-*p*-anisoyl-DL-phenylalanine **253** (200 mg, 0.668 mmol), 1-naphthyl chloroformate (0.325 mL, 2.00 mmol), Et_3N (0.325 mL, 2.34 mmol), triazolium salt **128** (9.12 mg, 33.4 μmol) and THF (2 mL), gave, after chromatographic purification (20% EtOAc:petrol), the product as a colourless oil (232 mg, 70%). δ_H (400 MHz, $CDCl_3$) 7.96–7.90 (1H, m, MeOAr*H*-3,5), 7.88–7.83 (2H, m, Nap*H*), 7.76 (1H, br d, *J* 8.1, Ar*H*), 7.54–7.48 (2H, m, Ar*H*), 7.45 (1H, t, *J* 8.2, Ar*H*), 7.33–7.17 (6H, m, Ar*H*), 6.97–6.63 (2H, m, MeOAr*H*-2,6), 3.86 (3H, s, OCH_3), 3.81 (1H, ABd, *J* 13.7, PhCH_AH$_B$) and 3.68 (1H, ABd, *J* 13.7, PhCH$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 174.0 (*C*-2), 164.6 (MeOAr*C*-1), 163.7 (*C*OOAr), 163.5 (Ar*C*), 151.9 (Ar*C*), 146.0 (Ar*C*), 134.6 (Ar*C*), 132.8 (Ar*C*), 130.5 (Ar*C*H), 130.3 (Ar*C*H), 128.4 (Ar*C*H), 128.0 (Ar*C*H), 127.7 (Ar*C*H), 126.9 (Ar*C*H), 126.8 (Ar*C*H), 126.7 (Ar*C*H), 126.3 (Ar*C*H), 125.2

(Ar*C*H), 121.0 (Ar*C*H), 117.1 (Ar*C*), 114.3 (MeOAr*C*-2,6), 77.9 (*C*-4), 55.6 (O*C*H_3) and 40.1 (*C*H_2); ***m/z*** MS (ESI+) 451 (42, $[M+H]^+$), 407 (100, $[M+MeOH-Ph]^+$); HRMS (ESI+) $C_{23}H_{22}O_2N$ ($[M+H]^+$) requires 344.1645, found 344.1647 (+0.4 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3063, 3033, 2965, 2937, 2841, 1822 (C=O), 1770 (C=O), 1645 (C=N), 1606 (Ar C=C), 1575, 1512, 1495 (Ar C=C), 1442, 1426, 1390, 1307, 1263 (C-O), 1212 (C-O) and 1173 (C-O).

2-(4-Methoxyphenyl)-4-methyloxazalone 511



Following general procedure A, thionyl chloride (30.7 mL, 0.421 mol), DL-alanine **507** (25.0 g, 0.281 mol) and MeOH (500 mL) gave, after trituration with Et_2O, DL-alanine methyl ester hydrochloride **508** as a colourless solid (39.2 g, quantitative). **mp** 159–161 ºC, lit.[165] 155–158 ºC; δ_H (300 MHz, CD_3OD) 4.13 (1H, q, *J* 7.2, C*H*CH_3), 3.84 (3H, s, OCH_3) and 1.55 (3H, d, *J* 7.2, CH_3). Data data are in accordance with the literature.[108,165]

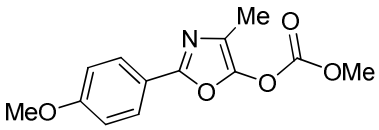
Following general procedure B, Et_3N (91.0 mL, 0.653 mol), DL-alanine methyl ester hydrochloride **508** (38.8 g, 0.278 mol), CH_2Cl_2 (550 mL), *p*-anisoyl chloride (36.9 mL, 0.273 mol) and CH_2Cl_2 (100 mL) gave, after recrystallisation (CH_2Cl_2/Et_2O), amide **509** as a colourless solid (60.1 g, 91%). **mp**[§] 107–108 ºC; δ_H (300 MHz, $CDCl_3$) 7.79–7.74 (2H, m, MeOAr*H*-3,5), 6.94–6.89 (2H, m, MeOAr*H*-2,6), 6.65 (1H, br s, N*H*), 4.78 (1H, quin, *J* 7.2, C*H*CH_3), 3.84 (3H, s, OCH_3), 3.78 (3H, s, OCH_3) and 1.51 (3H, d, *J* 7.2, CHCH_3). Spectroscopic data are in accordance with the literature.[107]

Following general procedure C, 2 M NaOH(aq) (120 mL), *N*-*p*-anisoyl-DL-alanine methyl ester **509** (40.0 g, 0.169 mol) and MeOH (360 mL) gave, after purification, *N*-*p*-anisoyl-DL-alanine **510** as a colourless solid (35.0 g, 93%). **mp** 176–178 ºC, lit.[106] 169–170 ºC; δ_H (300 MHz, d_6-DMSO) 8.55 (1H, br d, *J* 7.2, N*H*), 7.89–7.84 (2H, m, MeOAr*H*-3,5), 7.02–6.97 (2H, m, MeOAr*H*-2,6), 4.45–4.34 (1H, m, C*H*CH_3), 3.80 (3H, s, ArOCH_3) and 1.37 (3H, d, *J* 7.3, CHCH_3). Data are in accordance with the literature.[106]

Ac_2O (90 mL) was added to *N*-*p*-anisoyl-DL-alanine **510** (10.0 g, 0.447 mol) and the resultant solution heated to 65 ºC for 1 h before concentration *in vacuo* to give azlactone **511** as a colourless solid (9.09 g, 99%) which was used without further purification. **mp** 91–94 ºC, lit.[106] 95–97 ºC; δ_H (300 MHz, $CDCl_3$) 7.97–7.91 (2H, m, MeOAr*H*-3,5), 7.02–6.97 (2H, m,

MeOAr*H*-2,6), 4.45 (1H, q, *J* 7.6, NC*H*CH_3), 3.91 (3H, s, ArOCH_3) and 1.60 (3H, d, *J* 7.6, CHCH_3). Data are in accordance with the literature.[106]

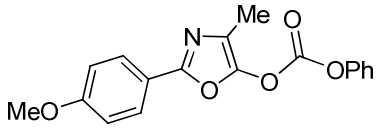
2-(4-Methoxyphenyl)-4-methyloxazol-5-yl methyl carbonate 244



244

Following general procedure E, Et_3N (1.32 mL, 9.50 mmol), azlactone **511** (1.50 g, 7.31 mmol), THF (15 mL) and methyl chloroformate (2.10 mL, 27.2 mmol) gave, after recrystallisation (Et_2O/petrol), the product as a colourless solid (1.64 g, 84%). **mp** 57–58 ºC, lit.[106] 60–61 ºC; δ_H (300 MHz, $CDCl_3$) 7.90–7.86 (2H, m, MeOAr*H*-3,5), 6.97–6.92 (2H, m, MeOAr*H*-2,6), 3.98 (3H, s, OCH_3), 3.85 (3H, s, OCH_3) and 2.13 (3H, s, CH_3). Data are in accordance with the literature.[106]

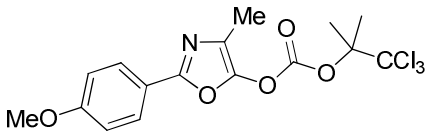
2-(4-Methoxyphenyl)-4-methyloxazol-5-yl phenyl carbonate 337



337

Following general procedure E, Et_3N (1.32 mL, 9.50 mmol), azlactone **511** (1.50 g, 7.31 mmol), THF (15 mL) and phenyl chloroformate (1.05 mL, 8.41 mmol) gave, after recrystallisation (Et_2O/hexane), the product as a colourless solid (1.80 g, 5.53 mmol, 76%). **mp**[§] 98–100 ºC; δ_H (300 MHz, $CDCl_3$) 7.94–7.89 (2H, m, MeOAr*H*-3,5), 7.48–7.42 (2H, m, OPh*H*-3,5), 7.36–7.29 (3H, m, OPh*H*-2,4), 6.98–6.94 (2H, m, MeOAr*H*-2,6), 3.86 (3H, s, OCH_3) and 2.20 (3H, s, CH_3). Spectroscopic data are in accordance with the literature.[107]

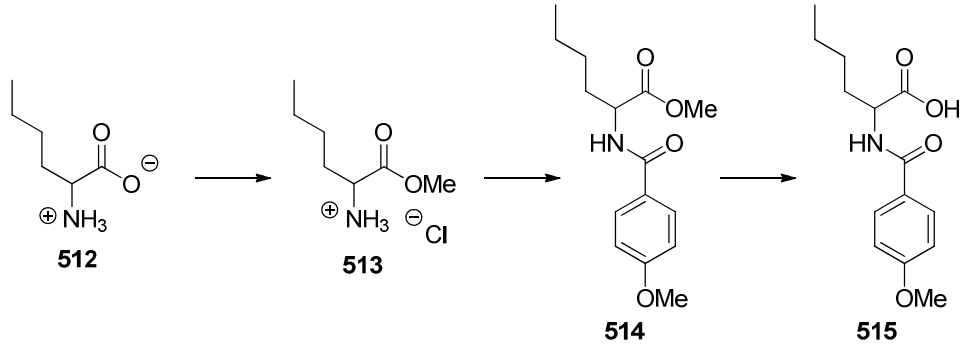
(1,1,1-Trichloro-2-methylpropan-2-yl) 2-(4-methoxyphenyl)-4-methyloxazol-5-yl carbonate 335



335

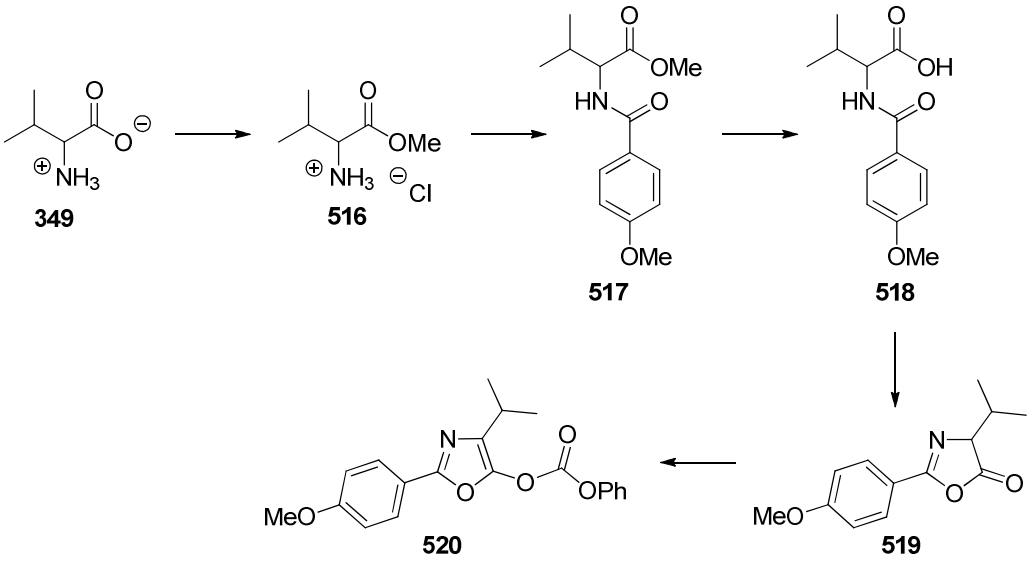
Following general procedure E, Et_3N (1.46 mL, 9.52 mmol), azlactone **511** (1.50 g, 7.32 mmol), THF (15 mL) and 2,2,2-trichloro-1,1-dimethylethyl chloroformate (1.86 g, 7.76 mmol) gave, after recrystallisation (Et_2O/petrol), the product as a colourless solid (2.16 g, 72%). **mp** 97–98 ºC, lit.[108] 97–101 ºC; δ_H (400 MHz, $CDCl_3$) 7.90–7.86 (2H, m, MeOAr*H*-3,5), 6.96–6.90 (2H, m, MeOAr*H*-2,6), 3.86 (3H, s, OCH_3), 2.14 (3H, s, CH_3) and 2.02 (6H, s, C(CH_3)$_2$CCl_3). Data are in accordance with the literature.[108]

2-(4-Methoxybenzamido)hexanoic acid 515



Following general procedure A, DL-norleucine **512** (15.0 g, 115 mmol), MeOH (150 mL) and thionyl chloride (12.5 mL, 172 mmol) gave the crude methyl ester hydrochloride **513** as a pale yellow oil (20.8 g, quantitative). Without further purification, following general procedure B, ester hydrochloride **513** (20.5 g, 113 mmol), CH_2Cl_2 (150 mL), Et_3N (36.3 mL, 261 mmol) and *p*-anisoyl chloride (14.8 mL, 109 mmol) in CH_2Cl_2 (30 mL) gave, after purification, the desired crude amide **514** as a colourless solid (26.7 g, 87%), which was used immediately without further purification. Following general procedure C, amide **514** (25.7 g, 91.8 mmol), MeOH (300 mL) and 2 M NaOH(aq) (68.9 mL) gave, after acidification, a suspension. Precipitation was induced upon scratching and the product was collected by filtration then dried azeotropically with toluene (100 mL × 5), giving acid **515** as a colourless solid (23.1 g, 87%). **mp** 135–138 ºC; $\boldsymbol{\delta_H}$ (400 MHz, d_6-DMSO) 12.51 (1H, br s, COO*H*), 8.41 (1H, d, *J* 7.7, CON*H*), 7.91–7.86 (2H, m, MeOAr*H*-3,5), 7.04–6.96 (2H, m, MeOAr*H*-2,6), 4.38–4.29 (1H, m, C*H*COOH), 3.79 (3H, s, OCH_3), 1.87–1.66 (2H, m, CHCH_2), 1.44–1.20 (4H, m, CH_2CH_2) and 0.85 (3H, t, *J* 7.0, CH_3); $\boldsymbol{\delta_C}$ (100 MHz, d_6-DMSO) 174.1 (*C*OOH), 166.0 (*C*ONH), 161.7 (MeOAr*C*-1), 129.4 (MeOAr*C*H-3,5), 126.3 (MeOAr*C*-4), 113.4 (MeOAr*C*H-2,6), 55.4 (O*C*H_3), 52.6 (*C*HN), 30.4 (*C*H_2), 28.1 (*C*H_2), 21.8 (*C*H_2CH$_3$) and 13.9 (*C*H_3); ***m/z*** MS (ESI+) 294 (35, $[M+MeOH+H]^+$), 266 (100, $[M+H]^+$), 248 (40, $[M–OH]^+$) and 135 (40, $ArC{\equiv}O^+$); HRMS (ESI+) $C_{14}H_{20}NO_4$ ($[M+H]^+$), requires 266.1388, found 266.1392 (-1.6 ppm); **IR** ν_{max} (KBr)/cm^{-1} 3373 (br, OH), 2923 (CH), 2963 (CH), 2348, 1721 (C=O), 1704 (C=O), 1615 (Ar C=C), 1575, 1539, 1506, 1456, 1417, 1309 and 1256 (C-O).

4-Isopropyl-2-(4-methoxyphenyl)oxazol-5-yl phenyl carbonate 520



Following general procedure A, DL-valine **349** (10.0 g, 0.855 mol), thionyl chloride (9.35 mL, 0.128 mol) and MeOH (150 mL) gave ester hydrochloride **516** as a colourless solid (14.2 g, 99%) which was used without further purification. **mp** 108–110 ºC, lit.[168] 112–114 ºC; δ_H (300 MHz, $CDCl_3$) 8.85 (3H, br s, NH_3^+), 4.04–3.92 (1H, m, C*H*NH_2), 3.83 (3H, s, OCH_3), 2.52–2.38 (1H, m, C*H*$(CH_3)_2$) and 1.12 (6H, dd, *J* 7.0, 2.9, $CH(CH_3)_2$). Data are in accordance with the literature.[168]

Following general procedure B, Et_3N (24.4 mL, 176 mmol), DL-valine methyl ester hydrochloride **516** (14.2 g, 84.9 mmol), CH_2Cl_2 (320 mL), *p*-anisoyl chloride (11.3 mL, 83.3 mmol) and CH_2Cl_2 (25 mL) gave amide **517** as a pale yellow solid (19.8 g, 86%). **mp**[§] 81–83 ºC; δ_H (300 MHz, $CDCl_3$) 7.80–7.75 (2H, m, MeOAr*H*-3,5), 6.96–6.91 (2H, m, MeOAr*H*-2,6), 6.55 (1H, br d, *J* 8.6, N*H*), 4.77 (1H, ABX, J_{XA} 8.6, J_{XB} 4.9, C*H*NH), 3.85 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 2.32–2.20 (1H, m, C*H*$(CH_3)_2$) and 1.02–0.96 (6H, m, $CH(CH_3)_2$). Spectroscopic data are in accordance with the literature.[107]

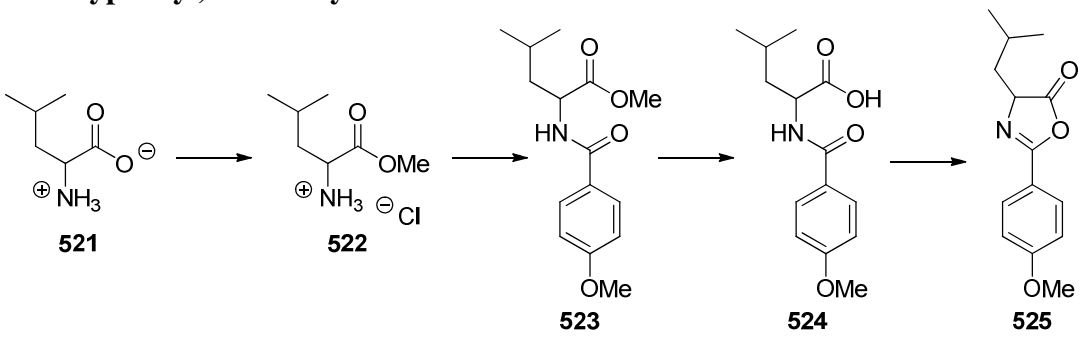
Following general procedure C, 2 M NaOH(aq) (50 mL), *N*-*p*-anisoyl-DL-valine methyl ester **517** (17.0 g, 63.9 mmol) and MeOH (150 mL) gave *N*-*p*-anisoyl-DL-valine **518** as a colourless solid (11.7 g, 72%). **mp** 150–152 ºC, lit.[166] 165–169 ºC; δ_H (300 MHz, $CDCl_3$) 7.81–7.75 (2H, m, MeOAr*H*-3,5), 6.97–6.91 (2H, m, MeOAr*H*-3,5), 6.56 (1H, br d, *J* 8.4, N*H*), 4.77 (1H, ABX, J_{XA} 8.4, J_{XB} 4.9, C*H*NH), 3.85 (3H, s, ArOCH_3), 2.42–2.29 (1H, m, C*H*$(CH_3)_2$), 1.05 (3H, d, *J* 7.1, $CH(CH_3)_2$) and 1.03 (3H, d, *J* 7.1, $CH(CH_3)_2$). Data are in accordance with the literature.[166]

Following general procedure D, Ac_2O (10 mL) and *N*-*p*-anisoyl-DL-valine **518** (4.36 g, 17.4 mmol) gave the product **519** as a pale yellow solid (4.06 g, 99%). **mp** 45–47 ºC, lit.[107] 45–

47 ºC; **δ_H** (300 MHz, $CDCl_3$) 7.96–7.91 (2H, m, MeOAr*H*-3,5), 6.98–6.93 (2H, m, MeOAr*H*-2,6), 4.24 (1H, d, *J* 4.5, NC*H*), 3.86 (3H, s, OCH_3), 2.42–2.28 (1H, m, C*H*(CH_3)$_2$), 1.12 (3H, d, *J* 6.9, CH(CH_3)$_2$) and 0.99 (3H, d, *J* 6.9, CH(CH_3)$_2$). Data are in accordance with the literature.[107]

Following general procedure E, Et_3N (1.67 mL, 12.0 mmol), azlactone **519** (2.00 g, 8.57 mmol), THF (25 mL) and phenyl chloroformate (1.40 mL, 11.1 mmol) gave, after chromatographic purification (10% Et_2O:petrol), carbonate **520** as a colourless oil (2.73 g, 90%). **δ_H** (300 MHz, $CDCl_3$) 7.85–7.81 (2H, m, MeOAr*H*-3,5), 7.39–7.32 (2H, m, Ph*H*), 7.26–7.18 (3H, m, Ph*H*), 6.88–6.83 (2H, m, MeOAr*H*-2,6), 3.76 (3H, s, OCH_3), 2.86 (1H, sept, *J* 6.7, C*H*(CH_3)$_2$) and 1.24 (6H, d, *J* 6.7, CH(CH_3)$_2$). Spectroscopic data are in accordance with the literature.[110]

2-(4-Methoxyphenyl)-4-isobutyloxazalone 525



Following general procedure A, thionyl chloride (16.7 mL, 22.9 mmol), DL-leucine **521** (20.0 g, 15.2 mmol) and MeOH (270 mL) gave ester hydrochloride **522** as a colourless solid (27.4 g, 99%). **mp** 146–147 ºC, lit.[167] 148–150 ºC; **δ_H** (300 MHz, $CDCl_3$) 8.82 (3H, br s, NH_3^+), 4.15–4.03 (1H, m, C*H*NH_2), 3.80 (3H, s, OCH_3), 2.02–1.74 (3H, m, CH_2 and C*H*(CH_3)$_2$) and 0.97 (6H, d, *J* 6.1, CH(CH_3)$_2$). Data are in accordance with the literature.[167]

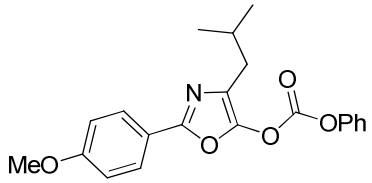
Following general procedure B, Et_3N (24.4 mL, 176 mmol), DL-leucine methyl ester hydrochloride **522** (13.6 g, 74.7 mmol), CH_2Cl_2 (280 mL), *p*-anisoyl chloride (9.92 mL, 73.3 mmol) and CH_2Cl_2 (20 mL) gave the crude amide **523** as a colourless solid (20.8 g, 99%) which was used immediately without further purification. **δ_H** (300 MHz, $CDCl_3$) 7.78–7.73 (2H, m, MeOAr*H*-3,5), 6.93–6.88 (2H, m, MeOAr*H*-2,6), 6.58 (1H, br d, *J* 8.2, N*H*), 4.89–4.80 (1H, m, C*H*NH), 3.84 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 1.80–1.58 (3H, m, CH_2 and C*H*(CH_3)$_2$) and 0.97 (6H, d, *J* 6.0, CH(CH_3)$_2$). Spectroscopic data are in accordance with the literature.[106]

Following general procedure C, 2 M NaOH(aq) (35 mL), *N*-*p*-anisoyl-DL-leucine methyl ester **523** (15.0 g, 53.7 mmol) and MeOH (100 mL) gave *N*-*p*-anisoyl-DL-leucine **524** as a colourless solid (14.3 g, 85%). **mp** 133–135 ºC, lit.[168] 133–136 ºC; **δ_H** (300 MHz, $CDCl_3$) 9.77 (1H, br s, COO*H*), 7.77–7.71 (2H, m, MeOAr*H*-3,5), 6.91–6.84 (2H, m, MeOAr*H*-2,6), 6.78 (1H, br d,

J 8.0, N*H*), 4.84–4.75 (1H, m, *CH*NH), 3.81 (3H, s, OCH_3), 1.85–1.62 (3H, m, CH_2 and CH(CH_3)$_2$) and 0.95 (6H, d, *J* 5.9, CH(CH_3)$_2$). Data are in accordance with the literature.[106,168]

Following general procedure D, Ac_2O (8 mL) was added to *N*-*p*-anisoyl-DL-leucine **524** (5.00 g, 18.8 mmol) and the resultant solution stirred and heated to 65 ºC for 1 h before concentration *in vacuo* to give the title product **525** as a yellow oil that solidified on standing (4.67 g, quant). **mp** 66–67 ºC, lit.[106] 66–67 ºC; δ_H (300 MHz, $CDCl_3$) 7.95–7.90 (2H, m, MeOAr*H*-3,5), 6.99–6.94 (2H, m, MeOAr*H*-2,6), 4.38 (2H, ABX, J_{XA} 8.9, J_{XB} 5.7, C*H*CH_2R), 3.88 (3H, s, OCH_3), 2.11–1.97 (1H, m, CH_AH$_B$CH(CH_3)$_2$), 1.86–1.76 (1H, m, CH$_A$$H_B$CH(C$H_3$)$_2$), 1.71–1.61 (1H, m, C$H$(C$H_3$)$_2$) and 1.03–0.98 (6H, m, CH(CH_3)$_2$). Data are in accordance with the literature.[106]

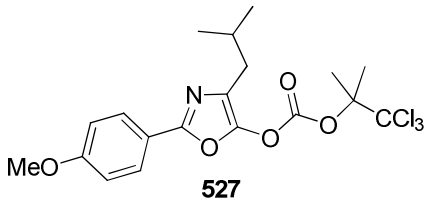
4-Isobutyl-2-(4-methoxyphenyl)oxazol-5-yl phenyl carbonate 526



526

Following general procedure E, Et_3N (0.930 mL, 6.67 mmol), azlactone **525** (1.50 g, 6.07 mmol), phenyl chloroformate (0.800 mL, 6.43 mmol) and THF (20 mL) gave, after chromatographic purification (20% Et_2O:petrol), the product as a colourless oil (1.94 g, 87%). δ_H (300 MHz, $CDCl_3$) 7.94–7.89 (2H, m, MeOAr*H*-3,5), 7.48–7.41 (2H, m, Ph*H*), 7.34–7.27 (3H, m, Ph*H*), 6.97–6.92 (2H, m, MeOAr*H*-2,6), 3.86 (3H, s, OCH_3), 2.40 (2H, d, *J* 6.9, CH_2), 2.09 (1H, sept, *J* 6.9, CH(CH_3)$_2$) and 0.99 (6H, d, *J* 6.9, CH(CH_3)$_2$). Spectroscopic data are in accordance with the literature.[110]

4-Isobutyl-2-(4-methoxyphenyl)-oxazol-5-yl 1,1,1-trichloro-2-methylpropan-2-yl carbonate 527

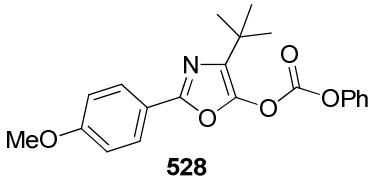


527

Following general procedure E, Et_3N (0.610 mL, 4.40 mmol), azlactone **525** (1.00 g, 4.04 mmol), THF (30 mL) and 1,1,1-trichloro-2-methylpropan-2-yl chloroformate (1.02 g, 4.24 mmol), gave, after chromatographic purification (25% Et_2O:petrol), the product as a colourless solid (1.27 g, 70%). **mp** 68–70 °C, lit.[124] 68-70 ºC; δ_H (300 MHz, $CDCl_3$) 7.89 (2H, d, *J* 9.0, MeOAr*H*-3,5), 6.93 (2H, d, *J* 9.0, MeOAr*H*-2,6), 3.85 (3H, s, OCH_3), 2.34 (2H, d, *J* 6.9,

C*H*$_2$), 2.05 (1H, sept, *J* 6.9, C*H*), 2.01 (6H, s, C(C*H*$_3$)$_2$CCl$_3$) and 0.96 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$). Data are in accordance with the literature.[124]

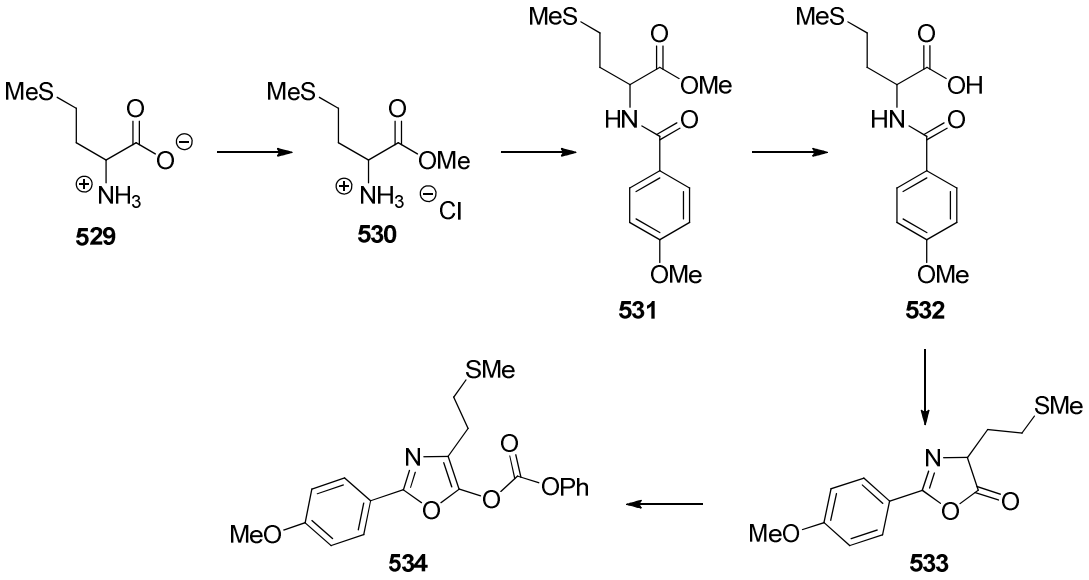
4-*tert*-Butyl-2-(4-methoxyphenyl)oxazol-5-yl phenyl carbonate 528



528

Following general procedure E, Et_3N (0.619 mL, 4.45 mmol), 2-(4-methoxyphenyl)-4-*tert*-butyloxazalone[i] (1.00 g, 4.05 mmol), THF (10 mL) and phenyl chloroformate (0.538 mL, 4.29 mmol) gave, after chromatographic purification (10% Et_2O:petrol), the product as a pale yellow oil (1.34 g, 90%). δ_H (300 MHz, $CDCl_3$) 7.86–7.81 (2H, m, MeOAr*H*-3,5), 7.40–7.33 (2H, m, Ph*H*), 7.27–7.18 (3H, m, Ph*H*), 6.89–6.84 (2H, m, MeOAr*H*-2,6), 3.78 (3H, s, OC*H*$_3$) and 1.29 (9H, s, C(C*H*$_3$)$_3$). Spectroscopic data are in accordance with the literature.[110]

2-(4-Methoxyphenyl)-4-(2′-(methylthio)ethyl)oxazol-5-yl phenyl carbonate 534

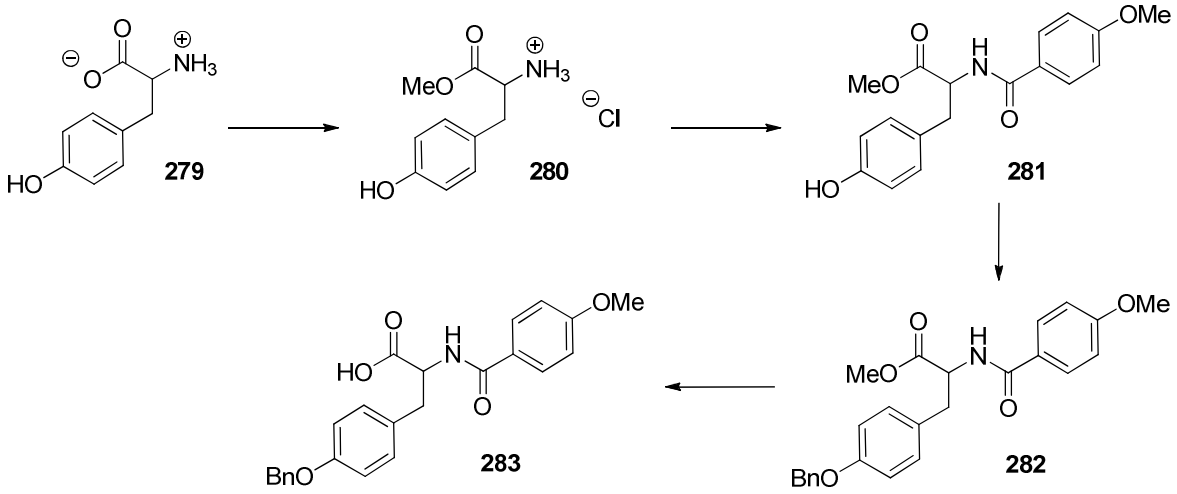


A solution of DL-methionine **529** (20.0 g, 134 mmol) in MeOH (440 mL) was cooled to 0 ºC and thionyl chloride (20.0 mL, 275 mmol) was added dropwise over 45 min. The mixture was allowed to warm to ambient temperature over 16 h then concentrated *in vacuo* to afford the crude methyl ester hydrochloride **530** as a pale yellow oil which solidified on standing (20.8 g, quantitative) which was used without further purification. Following general procedure B, ester hydrochloride **530** (10.0 g, 50.1 mmol), CH_2Cl_2 (100 mL), Et_3N (16.4 mL, 118 mmol) and *p*-anisoyl chloride (6.66 mL, 49.0 mmol) in CH_2Cl_2 (10 mL) gave the desired crude amide **531** as a colourless solid (12.7 g, 87%), which was used without immdediately without further

[i] Kindly donated by Jennifer Thomson.

purification. Following general procedure C, amide **531** (10.0 g, 33.6 mmol), MeOH (67 mL) and 2 M NaOH(aq) (20 mL) gave the purified acid **532** as a colourless solid (8.38 g, 88%). **mp** 131–133 ºC, lit.[106] 122–123 ºC; δ_H (400 MHz, d_6-DMSO) 12.51 (1H, br s, COO*H*), 8.41 (1H, d, *J* 7.7, CON*H*), 7.91–7.86 (2H, m, MeOAr*H*-3,5), 7.04–6.96 (2H, m, MeOAr*H*-2,6), 4.38–4.29 (1H, m, C*H*COOH), 3.79 (3H, s, OCH_3), 1.87–1.66 (2H, m, CHCH_2), 1.44–1.20 (4H, m, CH_2CH_2) and 0.85 (3H, t, *J* 7.0, CH_3). Spectroscopic data are in accordance with the literature.[106]
According to general procedure D, *N*-*p*-anisoyl-DL-methionine **532** (4.00 g, 14.1 mmol) and Ac_2O (8 mL) gave the azlactone product **533** as a yellow semi-solid (3.75 g, 99%) which was used without further purification. δ_H (400 MHz, $CDCl_3$) 7.95–7.92 (2H, m, MeOAr*H*-3,5), 6.99–6.96 (2H, m, MeOAr*H*-2,6), 4.56 (1H, dd, *J* 7.2, 5.8, NC*H*), 3.87 (3H, s, OCH_3), 2.72 (2H, t, *J* 7.1, MeSCH_2), 2.33–2.25 (1H, m, CHCH_AH$_B$), 2.17–2.08 (1H, m, CHCH_AH$_B$) and 2.11 (3H, s, SCH_3). Spectroscopic data are in accordance with the literature.[106]
According to general procedure E, Et_3N (1.31 mL, 9.43 mmol), azlactone **533** (2.00 g, 7.54 mmol), phenyl chloroformate (0.979 mL, 8.67 mmol) and THF (20 mL) gave, after purification by recrystallisation (Et_2O/hexane), carbonate **534** as a colourless solid (2.81 g, 97%). **mp** 64–65 ºC; δ_H (400 MHz, $CDCl_3$) 7.91–7.88 (2H, m, MeOAr*H*-3,5), 7.45–7.40 (2H, m, Ph*H*), 7.31–7.27 (3H, m, Ph*H*), 6.96–6.92 (2H, m, MeOAr*H*-2,6), 3.83 (3H, s, OCH_3), 2.89–2.81 (4H, m, CH_2CH_2SMe) and 2.15 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 161.4 (MeOAr*C*-1), 155.4 (*C*=N), 150.7 (OPh*C*-1), 150.1 (O*C*(O)O), 145.6 (*C*-5), 129.7 (MeOAr*C*H-3,5), 127.6 (OPh*C*H-3,5), 126.8 (OPh*C*H-4), 122.7 (*C*-4), 120.5 (OPh*C*H-2,6), 119.7 (MeOAr*C*-4), 114.1 (MeOAr*C*H-2,6), 55.3 (O*C*H_3), 32.3 (S*C*H_2), 25.3 (*C*H_2) and 15.5 (S*C*H_3); ***m/z*** MS (ESI+) 385 (50, $[M]^+$), 265 (100, $[M–COOPh+H]^+$) and 264 (85, $[M–COOPh]^+$); HRMS (ESI+) $C_{20}H_{19}NO_5S$ ($[M]^+$) requires 385.0978, found 385.0973 (-1.4 ppm); **IR** ν_{max} (KBr)/cm^{-1} 3337, 2948 (C-H), 1723 (C=O), 1634 (C=C), 1605 (Ar C=C), 1505 (C=N), 1261 (C-S) and 1164 (C-O).

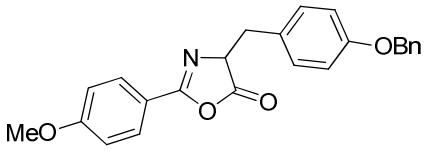
_N_-(4-Methoxybenzoyl)-_O_-benzyl-DL-tyrosine 283



Following general procedure A, DL-tyrosine **279** (30.0 g, 166 mmol), MeOH (350 mL) and thionyl chloride (48.0 mL, 662 mmol) gave the crude methyl ester hydrochloride **280** as a pale cream solid (39.1 g, quantitative). Without further purification, following general procedure B, ester hydrochloride **280** (38.0 g, 164 mmol), CH_2Cl_2 (400 mL), Et_3N (53.6 mL, 385 mmol) and *p*-anisoyl chloride (21.8 mL, 161 mmol) in CH_2Cl_2 (40 mL) gave the crude amide product **281** as a colourless solid (38.0 g, 70%). Without further purification, a suspension of crude amide **281** (5.00 g, 15.2 mmol) and K_2CO_3 (2.31 g, 16.7 mmol) in DMF (40 mL) were stirred for 30 min then benzyl bromide (1.91 mL, 16.0 mmol) was added. The suspension was stirred for 16 h then H_2O (50 mL) was added to induce precipitation. The colourless precipitate was collected by filtration and washed exhaustively with H_2O then dried azeotropically with toluene (50 mL × 5) to afford the product **282** as a colourless solid (6.00 g, 78%), which was used without further purification. To a solution of benzyl ether **282** (4.00 g, 9.54 mmol) in THF (40 mL) was added 2 M NaOH(aq) (5.70 mL) and the mixture stirred for 1 h then concentrated to ~6 mL *in vacuo*, then 2 M HCl(aq) was added to pH <3, inducing precipitation of the product on scratching. The product was collected by filtration then dried azeotropically with toluene (50 mL × 5), giving the title product **283** as a colourless solid (3.62 g, 94%). **mp** 140–142 ºC; $\boldsymbol{\delta_H}$ (300 MHz, CD_3OD) 7.62–7.58 (2H, m, MeOAr*H*-3,5), 7.28–7.13 (5H, m, Ph*H*), 7.07–7.04 (2H, m, BnOAr*H*-3,5), 6.83–6.80 (2H, m, MeOAr*H*-2,6), 6.77–6.74 (2H, m, BnOAr*H*-2,6), 4.86 (2H, s, PhCH_2), 4.83 (3H, s, OCH_3), 4.68 (1H, ABX, J_{XA} 9.0, J_{XB} 5.0, C*H*COOH), 3.14 (1H, ABX, J_{AB} 14.0, J_{AX} 5.0, ArCH_AH$_B$) and 2.94 (1H, ABX, J_{BA} 14.0, J_{BX} 9.0, ArCH$_A$$H_B$); $\boldsymbol{\delta_C}$ (75 MHz, $CDCl_3$) 175.2 (*C*OOH), 169.5 (*C*ONH), 163.9 (MeOAr*C*-1), 159.0 (BnOAr*C*-1), 138.7 (CH_2Ph*C*-1), 131.2 (Ar*C*H), 130.9 (MeOAr*C*-4), 130.2 (Ar*C*H), 129.4 (Ar*C*H), 128.7 (Ar*C*H), 128.5 (Ar*C*H), 127.3 (BnOAr*C*-4), 115.8 (MeOAr*C*H-2,6), 114.6 (BnOAr*C*H-2,6), 70.9 (Ph–*C*H_2O), 55.8 (O*C*H_3) and

37.4 (BnOAr–CH_2); ***m/z*** MS (ESI-) 404 (100, $[M–H]^-$); HRMS (ESI-) $C_{24}H_{22}NO_5^-$ ([M–H]) requires 404.1496, found 404.1498 (-0.5 ppm); **IR** ν_{max} (KBr)/cm^{-1} 3332 (OH), 3062 (CH), 3035 (CH), 2927 (CH), 1734 (C=O), 1632 (C=O), 1608, 1527, 1505 and 1255 (C-O).

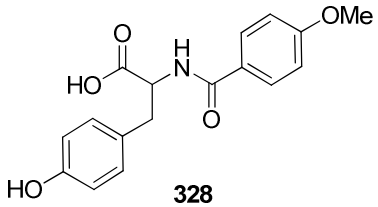
4-(4-Benzyloxyphenyl)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole 284



284

A mixture of *N*-*p*-anisoyl-*O*-benzyl-DL-tyrosine **283** (2.50 g, 6.17 mmol) and Ac_2O (5.00 mL, 52.9 mmol) were heated at 80 ºC for 1 h before concentration *in vacuo*. The remaining AcOH/Ac_2O was removed azeotropically with toluene (20 mL × 5) to afford the azlactone **284** (2.39 g, quantitative) as a colourless solid and was used without further purification. **mp** 118–119 ºC; δ_H (400 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.8, MeOAr*H*-3,5), 7.41–7.28 (5H, m, Ph*H*), 7.18 (2H, d, *J* 8.5, BnOAr*H*-3,5), 6.94 (2H, d, *J* 8.8, MeOAr*H*-2,6), 6.86 (2H, d, *J* 8.5, BnOAr*H*-2,6), 5.00 (2H, s, PhCH_2O), 4.62 (1H, ABX, J_{XA} 6.3, J_{XB} 4.9, *H*-4), 3.86 (3H, s, OCH_3), 3.30 (1H, ABX, J_{BA} 14.0, J_{BX} 4.9, $ArCH_AH_B$) and 3.13 (1H, ABX, J_{AB} 14.0, J_{AX} 6.3, $ArCH_AH_B$); δ_C (100 MHz, $CDCl_3$) 178.0 (*C*=O), 163.2 (Ar*C*-O), 161.4 (Ar*C*-O), 158.0 (N=*C*), 137.1 (Ph*C*), 130.8 (MeOAr*C*H-3,5), 129.9 (Ar*C*H), 128.7 (Ar*C*H), 128.0 (Ar*C*H), 127.8 (MeOAr*C*-4), 127.6 (Ar*C*H), 118.2 (BnOAr*C*-4), 114.8 (MeOAr*C*H-2,6), 114.3 (BnOAr*C*H-2,6), 70.0 (OCH_2), 66.8 (*C*H-N), 55.6 (OCH_3) and 36.7 (CH_2); ***m/z*** MS (CI+) 388 (28, $[M+H]^+$) and 255 (100); HRMS (CI+) $C_{24}H_{22}NO_4$ ($[M+H]^+$) requires 388.1543, found 388.1549 (-1.5 ppm); **IR** ν_{max} (KBr)/cm^{-1} 3059 (CH), 3014 (CH), 2917 (CH), 2860 (CH), 2841 (CH), 1814 (C=O), 1654 (C=N), 1609, 1512, 1332, and 1247 (C-O).

***N*-(4-Methoxybenzoyl)-DL-tyrosine 328**

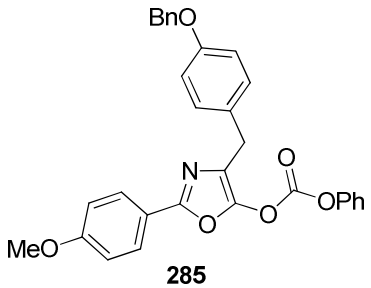


328

Following general procedure C, methyl ester **281** (5.00 g, 15.2 mmol), MeOH (30 mL) and 2 M NaOH(aq) (17.1 mL, 34.2 mmol) gave the product as a colourless solid (4.20 g, 88%). **mp** 152–154 ºC; δ_H (300 MHz, CD_3OD) 7.74–7.68 (2H, m, MeOAr*H*-3,5), 7.08–7.02 (2H, m, HOAr*H*-3,5), 6.97–6.92 (2H, m, MeOAr*H*-2,6), 6.71–6.63 (2H, m, HOAr*H*-2,6), 4.72 (1H, ABX, J_{XB} 8.1, J_{XA} 5.1, C*H*COOH), 3.83 (3H, s, OCH_3), 3.21 (1H, ABX, J_{AB} 13.9, J_{AX} 5.1, $ArCH_AH_B$), 3.02 (1H, ABX, J_{BA} 13.9, J_{BX} 8.1, $ArCH_AH_B$); δ_C (75 MHz, d_6-DMSO) 173.7

(*C*OOH), 166.0 (*C*ONH), 161.8 (MeOAr*C*-1), 155.9 (HOAr*C*-1), 130.1 (MeOAr*C*H-3,5), 129.3 (HOAr*C*H-3,5), 128.4 (MeOAr*C*-4), 126.3 (HOAr*C*-4), 115.1 (MeOAr*C*H-2,6), 113.6 (HOAr*C*H-2,6), 55.4 (O*C*H_3), 54.8 (*C*HN) and 35.7 (*C*H_2); ***m/z*** MS (ESI+) 316 (72, $[M+H]^+$), 298 ($[M–H_2O]^+$) and 135 (100, $ArC{\equiv}O^+$); HRMS (CI+) $C_{17}H_{18}NO_5$ ($[M+H]^+$) requires 316.1193, found 316.1185 (+2.5 ppm); **IR** ν_{max} (KBr)/cm^{-1} 3335 (OH), 3019 (CH), 2936 (CH), 1717 (C=O), 1636 (C=O), 1610, 1538, 1507, and 1262 (C-O).

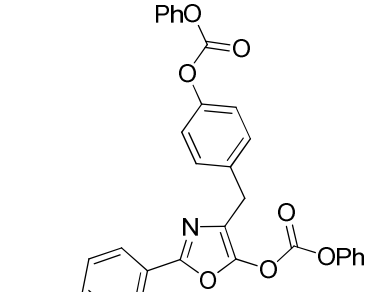
4-((4-Benzyloxy)benzyl)-2-(4-methoxyphenyl)-oxazolyl-5-yl phenyl carbonate 285



285

Following general procedure E, Et_3N (0.395 mL 2.84 mmol,), azlactone **284** (1.00 g, 2.58 mmol), phenyl chloroformate (2.71 mmol, 0.310 mL) and THF (30 mL) gave, after recrystallisation (Et_2O), the product **285** as a colourless solid (1.10 g, 84%). **mp** 116–117 °C; δ_H (400 MHz, $CDCl_3$) 7.96 (2H, d, *J* 9.0, MeOAr*H*-2,6), 7.48–7.30 (10H, m, Ph*H*), 7.27–7.25 (2H, m, BnOAr*H*-2,6), 6.95 (4H, app d, MeOAr*H*-3,5 and BnOAr*H*-3,5), 5.07 (2H, s, CH_2), 3.93 (2H, s, CH_2) and 3.90 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 161.5 (MeOAr*C*-1), 157.7 (*C*=N), 155.5 (BnOAr*C*-1), 150.8 (OPh*C*-1), 150.1 (O*C*(O)O), 145.6 (*C*-5), 137.2 (*C*), 130.1 (Ar*C*H), 129.8 (Ar*C*H), 128.7 (Ar*C*H), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 127.5 (Ar*C*H), 126.9 (Ar*C*H), 123.8 (*C*-4), 120.6 (Ar*C*H), 119.9 (Ar*C*H), 115.0 (MeOAr*C*H-2,6), 114.2 (BnOAr*C*H-2,6), 70.1 (O*C*H_2), 55.5 (O*C*H_3) and 31.1 (*C*H_2); ***m/z*** MS (ESI+) 530 (100, [M+Na]), HRMS (ESI+) $C_{31}H_{25}NO_6Na$ ([M+Na]), requires 530.1580, found 530.1584 (+0.9 ppm); **IR** ν_{max} (KBr)/cm^{-1} 3033 (Ar-H), 2911 (Alk-H), 1800 (C=O), 1613 (Ar C=C) and 1214 (C-O).

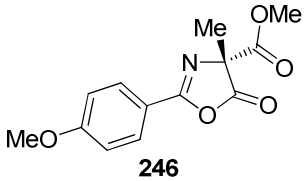
2-(4-Methoxyphenyl)-4-((4-phenoxycarbonyloxy)benzyl)oxazolyl-5-yl phenyl carbonate 535



535

Et_3N (1.94 mL, 14.0 mmol) was added to a solution of *N*-*p*-anisoyl-DL-tyrosine **281** (1.00 g, 3.17 mmol) in THF (20 mL) followed by the addition of phenyl chloroformate (1.50 mL, 13.8 mmol) and stirred for 16 h. The resulting suspension was poured into 1 M HCl(aq) (10 mL) and extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with sat $NaHCO_3$(aq) (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (20% Et_2O:petrol) afforded the product (1.46 g, 86%) as a colourless solid. **mp** 71–74 °C; δ_H (300 MHz, $CDCl_3$) 7.92 (2H, d, *J* 9.0, MeOAr*H*-3,5), 7.45–7.21 (14H, m, Ar*H*), 6.95 (2H, d, *J* 9.0, MeOAr*H*-2,6), 3.93 (2H, s, CH_2) and 3.85 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 161.6 (MeOAr*C*-1), 155.7 (*C*=N), 152.1 (*C*), 151.1 (*C*), 150.8 (*C*), 150.1 (*C*), 149.8 (*C*), 145.8 (*C*-5), 135.7 (*C*), 130.1 (ArCH), 129.9 (ArCH), 129.7 (ArCH), 128.0 (Ar*C*H), 126.4 (Ar*C*H), 126.4 (Ar*C*H), 126.4 (Ar*C*H), 123.0 (*C*-4), 121.0 (Ar*C*H), 120.6 (Ar*C*H), 119.8 (Ar*C*), 114.3 (MeOAr*C*H-2,6), 55.5 (OCH_3) and 31.0 (CH_2); ***m/z*** MS (CI+) 538 (62, [M+H]), 418 (17, [M–COOPh+H]); HRMS (ESI+) $C_{31}H_{23}NO_8Na$ ([M+Na]) requires 560.1321, found 560.1323 (+0.2 ppm); **IR** ν_{max} (KBr)/cm^{-1} 3065 (Ar-H), 2934, 1798 (C=O), 1779 (C=O), 1614 (Ar C=C) and 1235 (C-O).

(*R*)- and (*RS*)-4-Methyl-5-oxo-2-(4-methoxyphenyl)-4,5-dihydro-oxazole-4-carboxylate 246



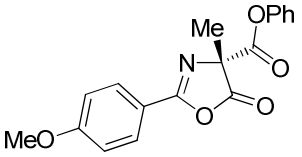
246

Procedures F and H were employed to afford the title compound.

Following general procedure F, carbonate **244** (585 mg, 2.22 mmol), triazolium salt **128** (6.06 mg, 22.2 μmol), KHMDS (40.0 μL, 0.0200 mmol), THF (5 mL) gave, after 5 min and chromatographic purification (30% Et_2O:petrol), the product **246** as a colourless solid (497 mg, 84%). **mp**[§] 58–60 ºC; δ_H (300 MHz, $CDCl_3$) 8.00–7.95 (2H, m, MeOAr*H*-3,5), 7.01–6.96 (2H, m, MeOAr*H*-2,6), 3.89 (3H, s, OCH_3), 3.79 (3H, s, COOCH_3) and 1.77 (3H, s, CH_3). Spectroscopic data are in accordance with the literature.[110]

Enantiomeric excesses were determined by HPLC with Chiralcel OD-H column (2% *i*-PrOH:hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 11.5 min and t_R(*S*) 15.3 min.

(*R*)- and (*RS*)- Phenyl methyl-5-oxo-2-(4-methoxyphenyl)-4,5-dihydro-oxazole-4-carboxylate 248

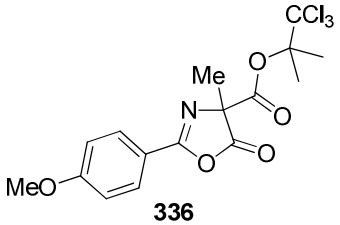


248

Procedures F, G, H, J, K and L were employed to afford the title compound.

Following general procedure H, carbonate **337** (500 mg, 1.54 mmol), KHMDS (27.6 μL, 13.8 μmol), triazolium salt **128** (4.20 mg, 15.4 μmol) and THF (5 mL) gave, after 5 min and chromatographic purification (20% Et_2O:petrol), the product **248** as a colourless oil (410 mg, 82%). δ_H (300 MHz, $CDCl_3$) 7.97–7.92 (2H, m, MeOAr*H*-3,5), 7.34–7.25 (2H, m, Ph*H*-2,6), 7.19–7.13 (1H, m, Ph*H*-4), 7.05–6.99 (2H, m, Ph*H*-3,5), 6.95–6.90 (2H, m, MeOAr*H*-2,6), 3.81 (3H, s, OCH_3) and 1.80 (3H, s, CH_3). Spectroscopic data are in accordance with the literature.[110] Enantiomeric excesses were determined by HPLC with Chiralcel OD-H column (2% *i*-PrOH:hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 14.8 min and t_R(*S*) 18.1 min.

1,1,1-Trichloro-2-methylpropan-2-yl 2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate 336

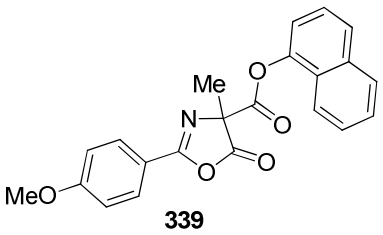


336

Procedure H was employed to afford the title compound.

Following general procedure H, carbonate **335** (200 mg, 0.489 mmol), triazolium salt **128** (6.68 mg, 24.5 μmol), KHMDS (39.2 μL, 19.6 μmol) and THF (2 mL) gave, after 5 min and chromatographic purification (10% Et_2O:petrol), the product **336** as a colourless oil (144 mg, 72%) which partially solidified on standing. δ_H (400 MHz, $CDCl_3$) 7.97–7.92 (2H, m, MeOAr*H*-3,5), 7.00–6.94 (2H, m, MeOAr*H*-2,6), 3.89 (3H, s, OCH_3), 1.93 (3H, s, C(CH_3)$_2$CCl_3), 1.90 (3H, s, C(CH_3)$_2$CCl_3) and 1.75 (3H, s, CH_3). Spectroscopic data are in accordance with the literature.[108]

Naphthalen-1-yl 2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate 339

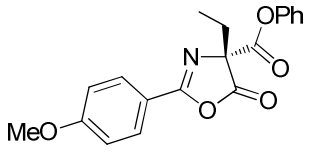


339

Procedures F, J and L were employed to afford the title compound.

Following general procedure L, *N*-*p*-anisoyl-DL-alanine **510** (200 mg, 0.896 mmol), Et_3N (0.436 mL, 3.14 mmol), 1-naphthyl chloroformate (0.436 mL, 2.69 mmol), triazolium salt **128** (12.2 mg, 44.8 μmol) and THF (2 mL) gave, after chromatographic purification (20% Et_2O:petrol) the product **339** as a colourless oil (235 mg, 70%). δ_H (400 MHz, $CDCl_3$) 8.10–8.06 (2H, m, MeOAr*H*-3,5), 7.88–7.83 (2H, m, Nap*H*-5,8), 7.75 (1H, br d, *J* 8.3, Nap*H*-4), 7.52–7.48 (2H, m, Nap*H*-6,7), 7.44 (1H, t, *J* 7.9, Nap*H*-3), 7.28 (1H, dd, *J* 7.6, 1.0, Nap*H*-2), 7.04–7.01 (2H, m, MeOAr*H*-2,6), 3.90 (3H, s, OCH_3) and 1.95 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 175.5 (*C*OOCR_2), 165.0 (*C*OOAr), 164.0 and 163.8 (MeOAr*C*-1 and *C*=N), 146.1 (Nap*C*-1), 134.7 (Nap*C*-4a), 130.5 (MeOAr*C*H-3,5), 128.1 (Nap*C*H-5), 127.0 (Nap*C*H), 126.9 (Nap*C*H), 126.8 (Nap*C*H), 126.4 (Nap*C*-8a), 125.3 (Nap*C*H-3), 121.0 (Nap*C*H-8), 117.9 (Nap*C*H-2), 117.5 (MeOAr*C*-4), 114.6 (MeOAr*C*H-2,6), 73.2 (Me*C*(COOAr)), 55.7 (O*C*H_3) and 20.6 (*C*H_3); ***m/z*** MS (ESI+) 408 (100, $[M+MeOH-H]^+$); HRMS (ESI+) $C_{23}H_{22}NO_6^+$ ($[M+MeOH+H]^+$) requires 408.1442, found 408.1440 (-0.5 ppm); **IR** ν_{max} (thin film) /cm^{-1} 3057, 3009, 2937, 2842, 1826 (C=O), 1772 (C=O), 1645 (C=N), 1608, 1308, 1262 (C-O) and 1221 (C-O).

(*R*)-Phenyl 4-ethyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (*R*)-536



536

Procedure H was employed to afford the title compound.

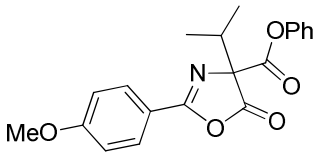
Following general procedure H, 4-ethyl-2-(4-methoxyphenyl)oxazol-5-yl phenyl carbonate[i] (68.0 mg, 0.200 mmol), THF (0.7 mL), triazolium salt **128** (7.88 mg, 20.0 μmol) and KHMDS (36.0 μL, 18.0 μmol) gave, after 60 min and chromatographic purification (20% Et_2O:petrol), product as a colourless oil (47.6 mg, 70%, <5% *ee*). δ_H (400 MHz, $CDCl_3$) 8.04 (2H, d, *J* 9.2,

[i] Kindly donated by Caroline Joannesse.

MeOAr*H*-3,5), 7.40–7.09 (5H, m, Ph*H*), 7.01 (2H, d, *J* 9.2, MeOAr*H*-2,6), 3.90 (3H, s, OCH_3), 2.44 (1H, dq, *J* 14.2, 7.2, CH_AH$_B$), 2.36 (1H, dq, *J* 14.0, 7.2, CH$_A$$H_B$) and 1.01 (3H, t, *J* 7.2, CH_3). Spectroscopic data are in accordance with the literature.[125]

Enantiomeric excess was determined by HPLC with Chiralcel OD-H column (5% *i*-PrOH:hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 9.2 min and t_R(*S*) 11.6 min.

Phenyl 2-(4-methoxyphenyl)-5-oxo-4-isopropyl-4,5-dihydrooxazole-4-carboxylate 537

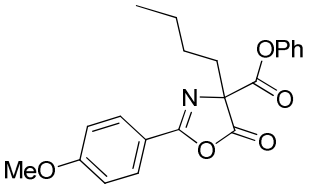


537

Procedure H was employed to afford the title compound.

Following general procedure H, 2-(4-methoxyphenyl)-4-isopropyloxazol-5-yl phenyl carbonate carbonate **520** (100 mg, 0.283 mmol), triazolium salt **128** (7.73 mg, 28.3 μmol), KHMDS (50.9 μL, 25.5 μmol) and THF (1 mL) gave, after 1 h and chromatographic purification (20% Et$_2$O:petrol), product **532** as a colourless oil (79.0 mg, 79%). **δ_H** (300 MHz, CDCl$_3$) 8.05 (2H, d, *J* 9.0, MeOAr*H*-3,5), 7.41–7.11 (5H, m, PhH), 7.01 (2H, d, *J* 9.0, MeOAr*H*-2,6), 3.89 (3H, s, OCH_3), 2.93 (1H, sept, *J* 6.6, C*H*Me$_2$), 1.19 (3H, d, *J* 6.6, CH_3) and 1.08 (3H, d, *J* 6.6, CH_3). Spectroscopic data are in accordance with the literature.[110]

Phenyl 4-butyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 538



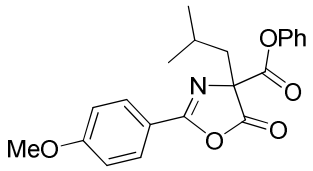
538

Procedure F was employed to afford the title compound.

Following general procedure F, *N*-*p*-anisoyl-DL-norleucine **515** (900 mg, 3.39 mmol), Et$_3$N (1.65 mL, 11.9 mmol), triazolium salt **128** (46.3 mg, 0.170 mmol), THF (9 mL) and phenyl chloroformate (1.14 mL, 10.2 mmol) gave, after chromatographic purification (3% → 20% Et$_2$O:petrol), the title product as a colourless oil (934 mg, 75%). **δ_H** (400 MHz, CDCl$_3$) 8.06–8.02 (2H, m, MeOAr*H*-3,5), 7.69–7.34 (2H, m, Ph*H*-3,5), 7.26–7.22 (1H, m, Ph*H*-4), 7.13–7.10 (2H, m, Ph*H*-2,6), 7.03–6.99 (2H, m, MeOAr*H*-2,6), 3.88 (3H, s, OCH_3), 2.45–2.38 (1H, m, C(4)H_AH$_B$), 2.34–2.28 (1H, m, C(4)H$_A$$H_B$), 1.44–1.35 (3H, m, CH$_3CH_2CH_AH_B$), 1.31–1.21 (1H, m, CH$_3CH_2CH_A$$H_B$) and 0.91 (3H, t, *J* 7.1, CH_3); **δ_C** (100 MHz, CDCl$_3$) 174.5 (*C*OOCR$_2$), 164.8 (*C*OOPh), 163.9 and 163.3 (MeOAr*C*-1 and *C*=N), 150.4 (OPh*C*-1), 130.5 (MeOAr*C*H-3,5),

129.6 (OPh*C*H-3,5), 126.6 (OPh*C*H-4), 121.2 (OPh*C*H-2,6), 117.4 (MeOAr*C*-4), 114.5 (MeOAr*C*H-2,6), 76.8 (*C*-4), 55.7 (OCH_3), 34.3 (CH_2), 25.5 (CH_2), 22.6 (CH_2CH_3) and 13.9 (CH_3); ***m/z*** MS (ESI+) 386 (100, [M+H]), 248 (72, [M–COOPh+H]) and 135 (38, ArC≡O); HRMS (ESI+) $C_{21}H_{22}NO_5$ ([M+H]) requires 368.1489, found 368.1498 (-2.4 ppm); **IR** ν_{max} (thin film)/cm^{-1} 2961, 2934, 2874, 1823 (C=O), 1771 (C=O), 1653 (C=N), 1609, 1513, 1308, 1262 (C-O) and 1173 (C-O).

Phenyl isobutyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 539

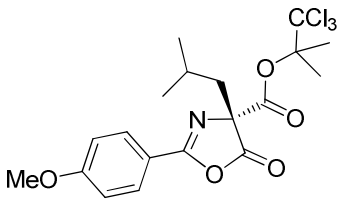


539

Procedure H was employed to afford the title compound.

Following general procedure H, carbonate **526** (200 mg, 0.544 mmol), triazolium salt **128** (1.49 mg, 5.44 μmol), KHMDS (9.60 μL, 4.90 μmol) and THF (2 mL) gave, after 5 min and chromatographic purification (10% Et_2O:petrol), the product as a colourless oil (160 mg, 80%). δ_H (400 MHz, $CDCl_3$) 8.07–8.04 (2H, m, MeOAr*H*-3,5), 7.45–7.09 (5H, m, Ph*H*), 7.05–6.99 (2H, m, MeOAr*H*-2,6), 3.90 (3H, s, OCH_3), 2.48 (1H, ABX, J_{AB} 14.1, J_{AX} 6.0, $CH_AH_BCH(CH_3)_2$), 2.17 (1H, ABX, J_{BA} 14.1, J_{BX} 7.2, $CH_AH_BCH(CH_3)_2$), 1.83 (1H, app sept, *J* 6.6, $CH(CH_3)_2$), 1.01 (3H, d, *J* 6.6, $CH(CH_3)_2$) and 0.97 (3H, d, *J* 6.6, $CH(CH_3)_2$). Spectroscopic data are in accordance with the literature.[107]

(*R*)- and (*RS*)- 1,1,1-Trichloro-2-methylpropan-2-yl 4-isobutyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 540



540

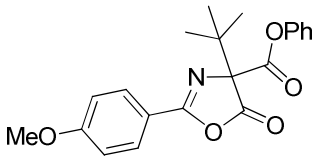
Procedure H was employed to afford the title compound.

Following general procedure H, carbonate **527** (200 mg, 0.444 mmol), chiral triazolium salt **399** (1.75 mg, 4.44 μmol), KHMDS (8.00 μL, 4.00 μmol) and THF (2 mL) gave, after 6 h and chromatographic purification (10% Et_2O:petrol), the enantioenriched product (*R*)-**540** as a colourless solid (160 mg, 80%). **mp** 64–66 °C, lit.[124] 68–70 ºC (for racemate); $[\alpha]_D^{20}$ +40.4 (*c* 0.2, $CHCl_3$), lit.[125] +60.6 (*c* 0.6, $CHCl_3$, 91.2% *ee*); δ_H (300 MHz, $CDCl_3$) 7.96 (2H, d, *J* 9.0,

MeOAr*H*-3,5), 6.97 (2H, d, *J* 9.0, MeOAr*H*-2,6), 3.87 (3H, s, OCH_3), 2.36 (1H, ABX, J_{AB} 14.4, J_{AX} 5.7, CH*H*), 2.03 (1H, ABX, J_{BA} 14.4, J_{BX} 7.5, CH_AH_B), 1.90 (3H, s, CH_3), 1.87 (3H, s, CH_3), 1.71 (1H, sept, *J* 6.6, C*H*), 0.94 (3H, d, *J* 6.6, CH_3) and 0.89 (3H, d, *J* 6.6, CH_3). Data are in accordance with the literature.[124,125]

Enantiomeric excesses were determined by HPLC with Chiralcel OD-H column (1% *i*-PrOH:hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 5.8 min and t_R(*S*) 6.9 min.

Phenyl 4-*tert*-Butyl-5-oxo-2-(4-methoxyphenyl)-4,5-dihydro-oxazole-4-carboxylate 541

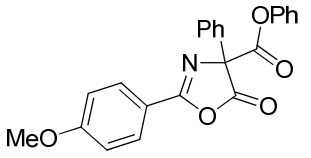


541

Procedure H was employed to afford the title compound.

Following general procedure H, carbonate **528** (200 mg, 0.544 mmol), triazolium salt **128** (14.9 mg, 54.4 μmol), KHMDS (96.0 μL, 49.0 μmol) and THF (2 mL) gave, after 1 h and chromatographic purification (20% Et_2O:petrol), the title product as a colourless oil (140 mg, 70%) which partially solidified on standing. δ_H (300 MHz, $CDCl_3$) 8.08–8.03 (2H, m, MeOAr*H*-3,5), 7.40–7.33 (2H, m, Ph*H*), 7.26–7.22 (1H, m, Ph*H*-4), 7.13–7.08 (2H, m, Ph*H*), 7.03–6.98 (2H, m, MeOAr*H*-2,6), 3.89 (3H, s, OCH_3) and 1.29 (9H, s, C(CH_3)$_3$). Spectroscopic data are in accordance with the literature.[110]

Phenyl 2-(4-methoxyphenyl)-5-oxo-4-phenyl-4,5-dihydrooxazole-4-carboxylate 542



542

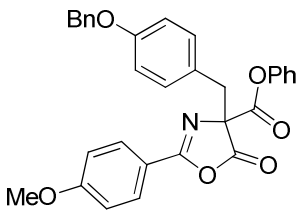
Procedures H and J were employed to afford the title compound.

Following general procedure J, 2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one[i] (200 mg, 0.748 mmol), triazolium salt **128** (10.0 mg, 37.4 μmol), THF (2 mL), Et_3N (0.135 mL, 0.972 mmol) and phenyl chloroformate (93.0 μL, 0.823 mmol) gave, after chromatographic purification (20% Et_2O:petrol), the product as a colourless oil (217 mg, 75%). δ_H (400 MHz, $CDCl_3$) 8.15–8.12 (2H, m, MeOAr*H*-3,5), 7.86–7.84 (2H, m, Ph*H*), 7.49–7.42 (3H, m, Ph*H*), 7.38–7.33 (2H, m, Ph*H*), 7.23 (1H, tt, *J* 7.4, 1.4, Ph*H*-4), 7.11–7.09 (2H, m, Ph*H*-2,6), 7.05–7.02 (2H, m, MeOAr*H*-2,6) and 3.90 (3H, s, OCH_3). Spectroscopic data are in accordance with the

[i] Kindly donated by Jennifer Thomson.

literature.[110]

Phenyl 4-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 543

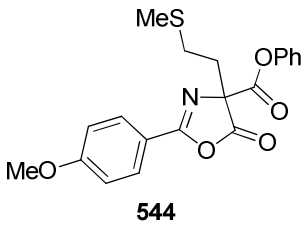


543

Procedure F, H, J, K and L have been employed to afford the title compound.

Following general procedure K, amido-acid **283** (200 mg, 0.493 mmol), DCC (103 mg, 0.498 mmol), triazolium salt **128** (7.04 mg, 25.8 μmol), THF (2 mL), Et_3N (104 μL, 0.747 mmol) and phenyl chloroformate (72.0 μL, 0.641 mmol) gave, after chromatographic purification (20% Et_2O:petrol), the product as a colourless oil (210 mg, 84%); $\boldsymbol{\delta_H}$ (300 MHz, $CDCl_3$) 7.84–7.78 (2H, m, MeOAr*H*-3,5), 7.33–7.21 (7H, m, Ar*H*), 7.20–7.14 (1H, m, Ar*H*), 7.14–7.07 (2H, m, Ar*H*), 7.04–7.00 (2H, m, Ar*H*), 6.89–6.84 (2H, m, MeOAr*H*-2,6), 6.77–6.71 (2H, m, BnOAr*H*-2,6), 4.89 (2H, s, PhCH_2), 3.78 (3H, s, OCH_3), 3.59 (1H, ABd, *J* 13.8, BnOArCH_AH$_B$) and 3.47 (1H, ABd, *J* 13.8, BnOArCH_AH$_B$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.8 (*C*OOCR$_2$), 164.7 (*C*OOPh), 163.8 and 163.3 (MeOAr*C*-1 and *C*=N), 158.4 (BnOAr*C*-1), 150.4 (OPh*C*-1), 137.0 (CH$_2$Ph*C*-1), 131.8 (Ar*C*H), 130.4 (Ar*C*H), 129.7 (Ar*C*H), 128.7 (Ar*C*H), 128.1 (Ar*C*H), 127.6 (Ar*C*H), 126.7 (Ar*C*H), 125.2 (MeOAr*C*-4), 121.3 (Ar*C*H), 117.4 (BnOAr*C*-4), 114.8 (OAr*C*H-2,6), 114.5 (OAr*C*H-2,6), 77.8 (*C*-3), 70.0 (O*C*H$_2$), 55.7 (O*C*H$_3$) and 39.7 (BnOAr–*C*H$_2$); ***m/z*** MS (ESI+) 508 (10, $[M+H]^+$), 135 (38, ArC≡O$^+$) and 95 (100); HRMS (ESI+) $C_{31}H_{26}NO_6$ ($[M+H]^+$) requires 508.1763, found 508.1760 (+0.6 ppm); **IR** ν_{max} (thin film)/cm^{-1} 3064 (CH), 3035 (CH), 2935 (CH), 2841 (CH), 1823 (C=O), 1766 (C=O), 1647, 1609, 1512, 1493, 1325, 1307 and 1262 (C-O).

Phenyl 2-(4-methoxyphenyl)-4-(2-(methylthio)ethyl)-5-oxo-4,5-dihydrooxazole-4-phenyl carboxylate 544



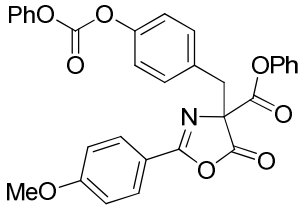
544

Procedures F and H were employed to afford the title compound.

Following general procedure H, KHMDS (9.34 μL, 4.67 μmol), triazolium salt **128** (1.42 mg, 5.19 μmol), carbonate **534** (200 mg, 0.519 mmol) and THF (2 mL) gave, after chromatographic

purification (20% Et_2O:petrol), the product (166 mg, 83%) as a pearlescent oil. **δ_H** (300 MHz, CD_2Cl_2) 8.05–8.00 (2H, m, MeOAr*H*-3,5), 7.43–7.36 (2H, m, Ph*H*), 7.30–7.26 (1H, m, Ph*H*), 7.11–7.07 (2H, m, Ph*H*), 7.05–7.00 (2H, m, MeOAr*H*-2,6), 3.88 (3H, s, OCH_3), 2.75–2.50 (4H, m, CH_2CH_2SMe) and 2.08 (3H, s, SCH_3); **δ_C** (75 MHz, CD_2Cl_2) 175.0 (*C*OOR$_2$), 165.4 (*C*OOPh), 164.7 (Ar*C*), 164.5 (Ar*C*), 151.1 (OPh*C*-1), 131.1 (Ar*C*H), 130.4 (Ar*C*H), 127.4 (Ar*C*H), 121.8 (OPh*C*H-2,6), 118.1 (MeOAr*C*-4), 115.1 (MeOAr*C*H-2,6), 76.3 (N-*C*), 56.4 (O*C*H$_3$), 34.3 (MeS*C*H$_2$), 29.1 (S*C*H$_3$) and 15.7 (*C*H$_2$); ***m/z*** MS (ESI+) 386 (100, [M+H]); HRMS (ESI+) $C_{20}H_{20}NO_5S$ ([M+H]) requires 386.1062, found 386.1055 (-1.8 ppm); **IR** ν_{max} (KBr)/cm^{-1} 2921 (C-H), 2849 (C-H), 1820 (C=O), 1767 (C=O), 1641 (C=C), 1607 (Ar C=C), 1509 (Ar C=C), 1457 (C-H), 1262 (C-N), 1187 (C-O) and 1173 (C-O).

Phenyl 2-(4-methoxyphenyl)-5-oxo-4-(4-phenoxycarbonyloxy)benzyl-4,5-dihydrooxazole-4-carboxylate 329

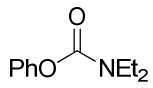


329

Procedures F and L were employed to afford the title compound.

Following a stoichiometric modification to general procedure L, *N-p*-anisoyl-DL-tyrosine **328** (250 mg, 0.793 mmol), Et_3N (661 µL, 4.76 mmol), triazolium salt **128** (10.8 mg, 0.0397 mmol), THF (2.5 mL) and phenyl chloroformate (493 µL, 4.36 mmol) gave, after chromatographic purification (20% Et_2O:petrol), the product as a colourless oil (281 mg, 66%). **δ_H** (300 MHz, $CDCl_3$) 7.91–7.86 (2H, m, MeOAr*H*-3,5), 7.43–7.32 (5H, m, Ar*H*), 7.32–7.27 (2H, m, Ar*H*), 7.26–7.22 (3H, m, Ar*H*), *7*.21–7.08 (4H, m, Ar*H*), 6.97–6.92 (2H, m, MeOAr*H*-2,6), 3.86 (3H, s, OCH_3), 3.74 (1H, ABd, *J* 13.8, ArCH_AH$_B$) and 3.59 (1H, ABd, *J* 13.8, ArCH$_a$$H_B$); **$\delta_C$** (75 MHz, $CDCl_3$) 173.8 (*C*OOCR$_2$), 164.6 (*C*OOPh), 164.0 and 163.6 (MeOAr*C*-1 and *C*=N), 152.0 (Ar*C*), 151.2 (Ar*C*), 150.7 (Ar*C*), 150.5 (Ar*C*), 132.0 (Ar*C*H), 131.3 (Ar*C*H), 130.5 (Ar*C*H), 129.8 (Ar*C*H), 126.8 (Ar*C*H), 126.6 (MeOAr*C*-4), 121.4 (Ar*C*H), 121.2 (Ar*C*H), 121.1 (Ar*C*H), 121.0 (Ar*C*H), 117.2 (PhOC(O)OAr*C*-4), 114.6 (OAr*C*H-2,6), 77.6 (*C*-3), 55.8 (O*C*H$_3$) and 39.7 (*C*H$_2$); ***m/z*** MS (ESI+) 538 (100, [M+H]$^+$); HRMS (ESI+) $C_{31}H_{24}NO_8$ ([M+H]) requires 538.1501, found 538.1502 (-0.2 ppm); **IR** ν_{max} (thin film)/cm^{-1} 2934 (CH), 2824 (CH), 2360 (CH), 1823 (C=O), 1773 (C=O), 1771 (C=O), 1646 (C=N), 1608, 1513, 1493, 1259, 1236 (C-O), 1185, 1161, 980, 841, 742 and 687.

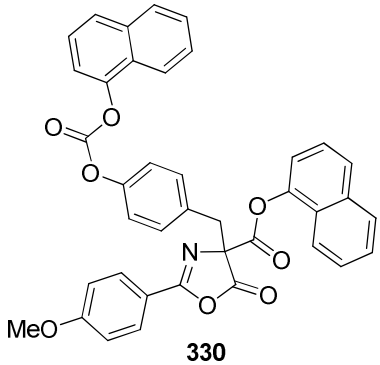
Phenyl diethylcarbamate 318



318

To a solution of Et_3N (0.750 mL, 5.34 mmol) in THF (20 mL) at 0 ºC was added phenyl chloroformate (0.650 mL, 5.14 mmol) and the resultant solution was warmed to ambient temperature over 16 h. H_2O (10 mL) was added and the aqueous layer extracted with Et_2O (10 mL × 3). The organic extracts were combined and washed successively with 0.1 M HCl(aq), sat $NaHCO_3$(aq) (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (10% Et_2O:petrol) afforded carbamate **318** as a pale yellow oil (672 mg, 68%). δ_H (400 MHz, $CDCl_3$) 7.36–7.19 (2H, m, Ph*H*-3,5), 7.12–7.08 (1H, m, Ph*H*-4), 7.06–7.02 (2H, m, Ph*H*-2,6), 3.43–3.24 (4H, m, CH_2CH$_3$) and 1.23–1.06 (6H, m, CH$_2$CH_3). Spectroscopic data are in accordance with the literature.[169]

Naphthalen-1-yl 2-(4-methoxyphenyl)-4-(4-((naphthalen-1-yloxy)carbonyloxy)benzyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 330



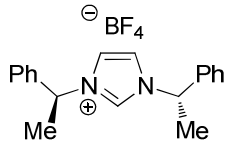
330

Procedure L was employed to afford the title compound.

Following a stoichiometric modification to general procedure L, *N*-*p*-anisoyl-DL-tyrosine **328** (284 mg, 0.900 mmol), 1-naphthyl chloroformate (0.801 mL, 4.95 mmol), Et_3N (0.750 mL, 5.40 mmol), triazolium salt **128** (12.3 mg, 0.045 mmol) and THF (3 mL), gave, after chromatographic purification (20% EtOAc:petrol), the product as a colourless oil (402 mg, 70%). δ_H (300 MHz, $CDCl_3$) 8.09–8.06 (1H, m, Ar*H*), 7.94–7.88 (2H, m, MeOAr*H*-3,5), 7.83–7.78 (2H, m, Ar*H*), 7.63–7.41 (10H, m, Ar*H*) 7.34–7.26 (3H, m, Ar*H*), 7.00–6.95 (2H, m, MeOAr*H*-2,6), 3.88 (1H, ABd, *J* 13.8, ArCH_AH$_B$), 3.87 (3H, s, OCH_3) and 3.74 (1H, ABd, *J* 13.7, ArCH_AH$_B$); δ_C (75 MHz, $CDCl_3$) 174.0 (*C*OOCR$_2$), 164.6 (MeOAr*C*-1), 163.9 (*C*OOAr), 163.8 (Ar*C*), 151.9 (Ar*C*), 150.7 (Ar*C*), 146.8, (Ar*C*), 134.7 (Ar*C*), 131.9 (Ar*C*H), 131.2 (Ar*C*), 130.4 (Ar*C*H), 128.14 (Ar*C*H), 128.07 (Ar*C*H), 127.1 (Ar*C*H), 126.9 (Ar*C*H), 126.8 (Ar*C*H), 126.6 (Ar*C*H), 126.5 (Ar*C*H), 126.5 (Ar*C*), 126.4 (Ar*C*), 125.4 (Ar*C*H), 125.3 (Ar*C*H), 112.0

(Ar*C*H), 120.9 (Ar*C*H), 117.9 (Ar*C*H), 117.5 (Ar*C*), 117.1 (Ar*C*), 114.5 (MeOAr*C*-2,6), 77.7 (*C*-N), 55.6 (O*C*H_3) and 39.4 (Ar–*C*H_2); ***m/z*** MS (CI+) 638.2 (100, $[M+H]^+$); HRMS (ESI+) $C_{39}H_{28}O_8N^+$ ($[M+H]^+$) requires 638.1809, found 638.1807 (-0.4 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3058, 3011, 2937, 2841, 1822 (C=O), 1776 (C=O), 1742 (C=O), 1654 (C=N), 1605 (Ar C=C), 1574, 1508, 1495 (Ar C=C), 1442, 1391, 1302, 1263 (C-O), 1229 (C-O), 1202 (C-O) and 1154 (C-O).

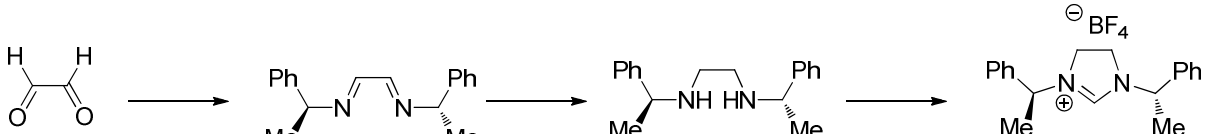
N^1,N^2-Bis((*S*)-1-phenylethyl)imidazolium tetrafluoroborate 344



344

To a solution of (*S*)-α-methylbenzylamine (1.21 g, 10.0 mmol) in toluene (20 mL) was added paraformaldehyde (300 mg, 10.0 mmol) with vigorous stirring and cooling to 10 ºC. After 30 min, further (*S*)-α-methylbenzylamine (1.21 g, 10.0 mmol) was added at 0 ºC, to which was then added HBF_4(aq) (1.25 mL of an ~8 M solution, 10.0 mmol) dropwise. After stirring for 15 min, the ice-bath was removed and aqueous glyoxal (1.45 mL of a 40% w/v solution, 10.0 mmol) was added dropwise. The mixture was stirred for 30 min at ambient temperature then heated to 40 ºC for 12 h. Et_2O (10 mL) and H_2O (10 mL) were added and the mixture extracted with Et_2O (10 mL × 2). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a viscous brown oil. Exhaustive trituration with Et_2O followed by heating to 50 ºC *in vacuo* for 12 h gave the title compound as a viscous orange oil (2.73 g, 75%). $[\alpha]_D^{20}$ § +7.8 (*c* 0.5, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 11.04 (1H, s, NC*H*N), 7.32–7.28 (2H, m, Ph*H*), 7.26 (2H, s, NC*H*C), 7.24–7.20 (3H, m, Ph*H*), 5.92 (2H, q, *J* 7.2, C*H*CH_3) and 1.91 (6H, d, *J* 7.2, CH_3). Spectroscopic data are in accordance with the literature.[170]

N^1,N^2-Bis((*S*)-1-phenylethyl)imidazolinium tetrafluoroborate 348



345 **346** **347** **348**

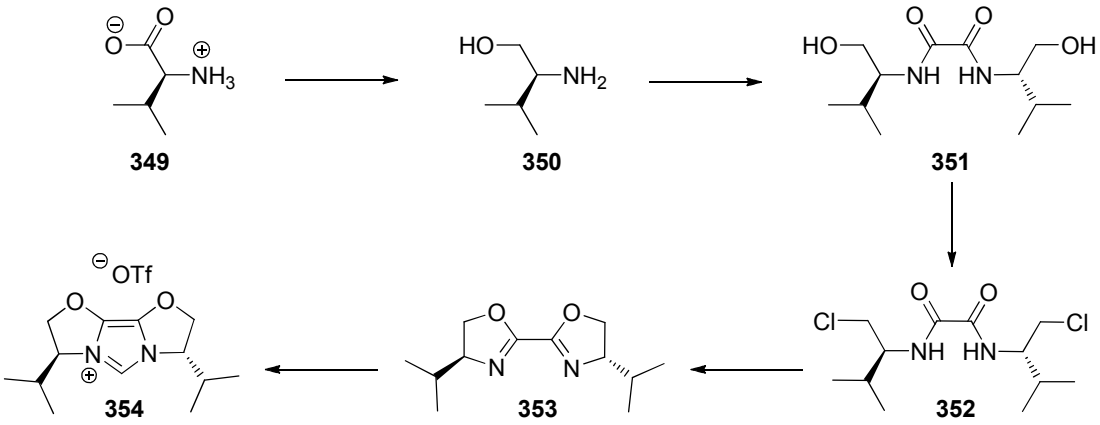
A mixture of aqueous glyoxal (1.13 mL of a 40% w/v solution, 7.80 mmol), (*S*)-α-methylbenzylamine (2.06 mL, 16.0 mmol), $MgSO_4$ (4.00 g, 33.2 mmol) and formic acid (1 drop) was stirred for 15 min at ambient temperature. The suspension was filtered over celite and the filtrate concentrated *in vacuo*, redissolved in hexane (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the imine product **346** as an orange oil (2.04 g, 99%). $[\alpha]_D^{20}$ -114.1 (*c* 0.2, $CHCl_3$), lit.[171] -113.9 (*c* 0.72, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.97 (2H, N=C*H*),

7.35–7.10 (10H, m, Ar*H*), 4.32 (2H, q, *J* 6.7, C*H*(CH_3)Ph) and 1.41 (6H, d, *J* 6.7, CH_3). Data are in accordance with the literature.[171]

To a stirred solution of diimine **346** (1.10 g, 4.16 mmol) in THF (6 mL) was added a solution of lithium aluminium hydride (3.12 mL of a 2.0 M solution, 6.24 mmol) in THF at 0 ºC. The mixture was warmed to ambient temperature over 16 h, then recooled to 0 ºC and ice-cold H_2O added carefully until gas evolution ceased. An aqueous solution of KOH (3 mL of a 3 M solution) was added then the mixture was extracted with EtOAc (10 mL × 3). The organics were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the diamine product **347** as an orange oil (890 mg, 80%). $[\alpha]_D^{20}$ -70.0 (*c* 0.5, $CHCl_3$), lit.[172] -69.4 (*c* 1.1, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.39–7.09 (10H, m, Ph*H*), 3.67 (2H, q, *J* 6.7, C*H*(CH_3)Ph), 2.50 (2H, br s, N*H*) and 1.36 (6H, d, *J* 6.7, CH_3). Data are in accordance with the literature.[172]

To a solution of diamine **347** (500 mg, 1.87 mmol) in MeOH (5 mL) was added triethyl orthoformate (0.78 mL, 4.69 mmol) and NH_4BF_4 (218 mg, 2.08 mmol). The mixture was heated at reflux (100 ºC) for 90 min, the mixture cooled to ambient temperature then Et_2O added (5 mL), forming an oily precipitate. Exhaustive trituration (Et_2O) gave the title compound **348** as an orange/yellow oil (500 mg, 73%). $[\alpha]_D^{20}$ +23.0 (*c* 0.5, $CHCl_3$), lit.[173] +23, (*c* 0.51, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.42 (1H, s, NC*H*N), 7.28–7.42 (10H, m, Ph*H*), 4.94 (2H, q, *J* 6.9, PhC*H*CH_3), 3.62–3.76 (4H, m, NCH_2) and 1.73 (6H, d, *J* 6.9, CH_3); δ_C[§] (100 MHz, $CDCl_3$) 154.6 (N*C*HN), 137.5 (Ph*C*-1), 129.3 (Ph*C*H-2,6), 129.2 (Ph*C*H-4), 127.0 (Ph*C*H-3,5), 58.2 (N*C*HMePh), 46.3 (CH_2) and 18.9 (CH_3). Data are in accordance with the literature.[173]

(3*S*,7*S*)-3,7-Diisopropyl-2,3,7,8-tetrahydroimidazo[4,3-*b*:5,1-*b*']bis(oxazole)-4-ium trifluoromethanesulfonate 354



To a suspension of sodium borohydride (6.92 g, 183 mmol) in THF (200 mL) was added L-valine (8.90 g, 76.0 mmol) in one portion. The mixture was cooled to 0 ºC before addition of a solution of iodine (19.3 g, 76.0 mmol) in THF (50 mL) dropwise over 30 min. Once hydrogen gas evolution ceased, the mixture was heated at reflux (80 ºC) for 18 h then cooled to ambient

temperature. MeOH was added cautiously until the mixture became clear and was stirred for a further 30 min, upon which time the mixture was concentrated *in vacuo* to afford a colourless paste, which was redissolved in 20% KOH(aq) with stirring over 4 h. The mixture was extracted with CH_2Cl_2 (150 mL × 3), the organics combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a colourless semi-solid. Purification by distillation (117–120 ºC /57 mm) afforded (*S*)-valinol **350** as a colourless oil (6.66 g, 85%). $[\alpha]_D^{20}$ +17.1 (*c* 0.5, EtOH), lit.[174] +17.0 (*c* 10.0, EtOH); δ_H (300 MHz, $CDCl_3$) 3.60 (1H, ABX, J_{AB} 12.0, J_{AX} 1.9, OCH_AH$_B$), 3.26 (1H, ABX, J_{BA} 12.0, J_{BX} 11.0, OCH$_A$$H_B$), 2.56–2.47 (1H, m, C*H*NH$_2$), 2.21 (2H, br s, NH_2), 1.52 (1H, *J* 6.9, C*H*(CH$_3$)$_2$) and 0.85 (6H, d, *J* 6.9, CH(CH_3)$_2$). Data are in accordance with the literature.[174,175]

To a solution of (*S*)-valinol **350** (1.00 g, 9.69 mmol) in toluene (35 mL) was added diethyl oxalate (0.64 mL, 4.73 mmol) and the mixture heated at reflux (110 ºC) for 5 h. The mixture was then cooled to ambient temperature and hexane (35 mL) was added, forming a colourless precipitate of the product. Trituration with hexane (20 mL) gave the purified diamide **351** as a colourless solid (1.00 g, 81%). **mp** 171–174 ºC, lit.[176] 172–174 ºC; $[\alpha]_D^{20}$ -28.4 (*c* 0.5, MeOH), lit.[176] -27.7 (*c* 1.5, MeOH); δ_H (300 MHz, d_6-DMSO) 8.13 (2H, d, *J* 9.5, N*H*), 4.64 (2H, br s, O*H*), 3.41–3.57 (6H, m, CH_2 and NC*H*), 1.82 (2H, sept d, *J* 6.9, 6.7, C*H*Me$_2$), 0.85 (6H, d, *J* 6.5, CH_3) and 0.82 (6H, d, *J* 6.4, CH_3). Data are in accordance with the literature.[176]

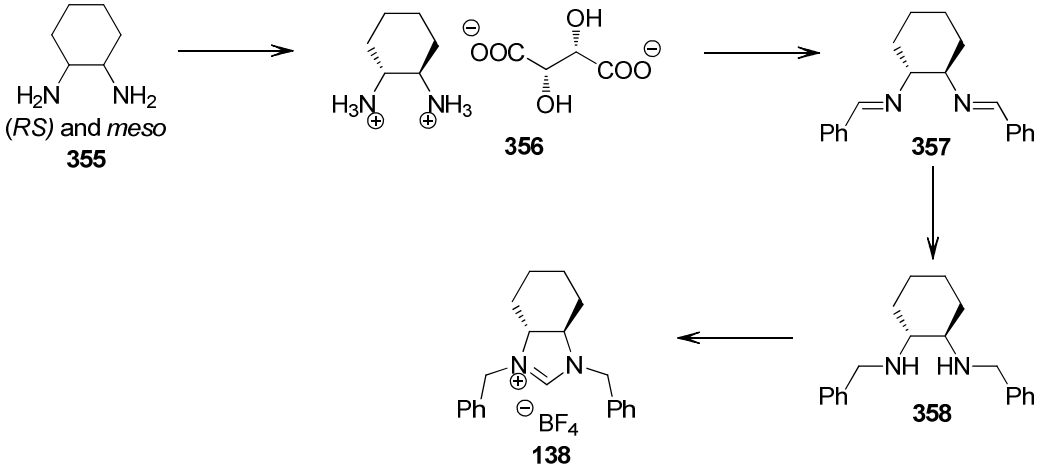
To a suspension of bis(hydroxymethyl)oxalamide **351** (900 mg, 3.46 mmol) in toluene (15 mL) was added thionyl chloride (0.560 mL, 7.64 mmol) and the mixture was heated to 90 ºC for 4 h. The mixture was cooled to ambient temperature then poured onto ice-cold 20% KOH(aq) (7.4 mL) and extracted with CH_2Cl_2 (20 mL × 3). The organics were combined, washed with sat $NaHCO_3$(aq) (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the dichloride **352** as a colourless solid (960 mg, 93%). **mp** 130–132 ºC, lit.[177] 131–132 ºC; $[\alpha]_D^{20}$ -71.0 (*c* 0.5, $CHCl_3$), lit.[177] -68.8 (*c* 2, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.56 (2H, d, *J* 9.0, N*H*), 4.33–4.21 (2H, m, C*H*N), 3.72 (2H, ABX, J_{AB} 11.1, J_{AX} 4.2, CH_AH$_B$Cl), 3.63 (2H, ABX, J_{BA} 11.1, J_{BX} 4.2, CH$_A$$H_B$Cl), 1.62–1.54 (6H, m, C*H*Me$_2$), 0.99 (6H, d, *J* 6.3, CH_3) and 0.96 (6H, d, *J* 6.4, CH_3). Data are in accordance with the literature.[177]

A mixture of dichloride **352** (957 mg, 3.22 mmol) and KOH (452 mg, 8.05 mmol) in MeOH (30 mL) was heated at reflux (70 ºC) for 3 h, with KCl precipitation occurring throughout. The mixture was cooled to ambient temperature, poured into H_2O (40 mL) and extracted with CH_2Cl_2 (20 mL × 3). The organics were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the bisoxazoline **353** as a pale yellow oil which solidified on

standing to a pale cream solid (601 mg, 83%). **mp** 58–60 ºC, lit.[178] 50 ºC; $[\alpha]_D^{20}$ -157.9 (*c* 0.53, $CHCl_3$), lit.[178] -158.8 (*c* 0.97, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.44–4.30 (2H, m, H_A-5), 4.11–3.97 (4H, m, *H*-4 and H_B-5), 1.79 (2H, sept d, *J* 6.7, 1.6, C*H*$(CH_3)_2$), 0.92 (6H, d, *J* 6.7, CH_3) and 0.84 (6H, d, *J* 6.7, CH_3). Data are in accordance with the literature.[178]

To a suspension of silver(I) triflate (415 mg, 1.62 mmol) in CH_2Cl_2 (5 mL) was added chloromethyl pivalate (243 mg, 1.62 mmol) and the resulting suspension stirred for 45 min. The supernatant was transferred to the bisoxazoline **353** (250 mg, 1.12 mmol) and the mixture stirred at 40 ºC in the dark in a sealed Schlenk tube for 24 h. After cooling to ambient temperature, the reaction was quenched with MeOH (5 mL) and the mixture was concentrated *in vacuo* to afford a brown oil. Chromatographic purification (5% MeOH:CH_2Cl_2) and subsequent recrystallisation from CH_2Cl_2/Et_2O gave the title compound **354** as a colourless solid (264 mg, 61%). $[\alpha]_D^{20}$ +54.6 (*c* 0.5, CH_2Cl_2), lit.[179] +55.0 (*c* 1.0, CH_2Cl_2); **mp**[§] 155–157 ºC; δ_H (400 MHz, $CDCl_3$) 8.73 (1H, s, NC*H*N), 5.07 (2H, dd, *J* 9.0, 7.9, CH_2O), 4.98–4.93 (2H, m, C*H*CH_2O), 4.83 (2H, dd, *J* 9.0 and 4.1, CH_2O), 2.35–2.31 (2H, m, C*H*CH_3), 1.03 (6H, d, *J* 6.9, CH_3), 0.99 (6H, d, *J* 6.9, CH_3); δ_C (100 MHz, $CDCl_3$) 125.6 (N*C*O), 120.6 (q, *J* 321, *C*F_3), 116.3 (N*C*HN), 79.1 (*C*H_2), 63.9 (*C*HCH_2), 31.1 (*C*HCH_3), 17.6 (*C*H_3) and 16.7 (*C*H_3); ^{19}F NMR (273 MHz, $CDCl_3$) -78.6 (CF_3). Data are in accordance with the literature.[179]

(3a*R*,7a*R*)-1,3-Dibenzyl-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazolium tetrafluoroborate 138



Following the procedure described by Jacobsen,[139] a solution of L-tartaric acid (50.0 g, 0.333 mol) in H_2O (133 mL) was prepared, to which was added a mixture of (*RS*)-, (*SR*)- and *meso*-1,2-diaminocyclohexane **355** (80.0 mL, 0.650 mol). The addition was made at a rate such that the reaction temperature was maintained at 70 ± 2 ºC, then glacial acetic acid (33.0 mL, 0.583 mol) was added at such a rate that the reaction temperature was maintained at 90 ± 2 ºC. A colourless precipitate formed upon addition of the acid, then the slurry was stirred vigorously as

the mixture was cooled to ambient temperature. The mixture was cooled further in an ice bath for 2 h and the precipitate collected by filtration. The wet filter cake was washed with ice-cold H_2O (33 mL) then MeOH (5 × 33 mL) and dried *in vacuo* to afford the resolved product **356** compound as a colourless solid (52.7 g, 31%). $[\alpha]_D^{20}$ +12.1 (*c* 0.5, H_2O), lit.[180] +12.5 (*c* 4, H_2O); **mp** 270 ºC decomp, lit.[180] 273 ºC decomp; δ_H (400 MHz, CD_3OD) 4.20 (s, 2H, C*H*(OH), 3.30–3.17 (2H, m, ^+H_3NCH), 2.08–1.97 (2H, m, $^+H_3NCHCH_AH_B$), 1.78–1.60 (2H, m, $^+H_3NCHCH_AH_B$), 1.47–1.31 (2H, m, $CH_2CH_AH_B$) and 1.33–1.13 (2H, m, $CH_2CH_AH_B$). Data are in accordance with the literature.[180,181]

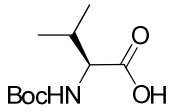
A mixture of (1*R*, 2*R*)-*trans*-cyclohexane-1,2-diammonium (*S*)-tartrate **356** (1.00 g, 3.77 mmol), K_2CO_3 (1.05 g, 7.58 mmol) and H_2O (5 mL) were stirred until complete dissolution occurred, to which was then added EtOH (20 mL). The mixture was heated at reflux (80 ºC) and a solution of benzaldehyde (0.77 mL, 7.58 mmol) in EtOH (8 mL) was added over 30 min. The mixture was heated at reflux for a further 2 h, then, when the solution had cooled to ambient temperature, H_2O (5 mL) was added and the mixture cooled to 0 ºC for 3 h. The mixture was concentrated *in vacuo* to afford the crude diimine. The residue was redissolved in CH_2Cl_2 (15 mL), washed with H_2O (10 mL × 2) and brine (10 mL × 2), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the diimine **357** as a pale cream solid (1.05 g, 96%). **mp** 133–135 ºC, lit.[182] 134–135 ºC; $[\alpha]_D^{20}$ -261.4, lit.[183] -263 (*c* 0.19, CH_3OH); δ_H (400 MHz, $CDCl_3$) 8.20 (2H, s, PhC*H*=N), 7.61 (4H, dd, *J* 7.6 and 2.1, Ph*H*-2,6), 7.36–7.28 (6H, m, Ph*H*-3,4), 3.42–3.35 (2H, m, CH=NC*H*), 3.36–3.41 (2H, m, *H*-1), 1.89–1.63 (6H, m, *H*-3, 3' and 4) and 1.45–1.57 (2H, m, *H*-4'). Data are in accordance with the literature.[182,183]

To a solution of (1*R*,2*R*)-bis(benzylidene)cyclohexyl-1,2-diimine **357** (1.05 g, 3.62 mmol) in MeOH (8 mL) was added $NaBH_4$ (287 mg, 7.59 mmol) portionwise over 30 min. The solution was heated at reflux for 15 min then cooled to ambient temperature. H_2O (8 mL) was added and the mixture extracted with CH_2Cl_2 (10 mL × 2). The organics were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the diamine **358** as a colourless oil (1.00 g, 94%). $[\alpha]_D^{20}$ -69.2 (*c* 0.5, $CHCl_3$), lit.[184] -68 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.31–7.10 (10H, m, Ph*H*), 3.82 (2H, ABd, *J* 13.2, CH_AH_BPh), 3.58 (2H, ABd, *J* 13.2, CH_AH_BPh), 3.41–3.36 (2H, m, *H*-1,2), 1.78 (2H, br s, N*H*), 1.89–1.63 (6H, m, $H_{A,B}$-3,6, H_A-4, and H_A-5) and 1.57–1.45 (2H, m, H_B-4,5). Data are in accordance with the literature.[184,185]

A mixture of (1*R*, 2*R*)-dibenzylcyclohexyl-1,2-diamine **358** (500 mg, 1.70 mmol), triethyl orthoformate (0.70 mL, 4.25 mmol), MeOH (5 mL) and NH_4BF_4 (180 mg, 1.72 mmol) were heated at 110 ºC for 5 h. Hexane (15 mL) was added to the mixture to precipitate the product as a

colourless solid. Recrystallisation from CH_2Cl_2 afforded the title compound **138** as a colourless solid (550 mg, 82%). $[\alpha]_D^{20}$ = -66.8 (*c* 0.2, MeOH); **mp** 150–152 ºC; δ_H (400 MHz, $CDCl_3$) 8.58 (1H, s, NC*H*C), 7.32–7.26 (10H, m, Ph*H*), 4.64 (2H, ABd, *J* 15.1, PhCH_AH_B), 4.51 (2H, ABd, *J* 15.1, PhCH_AH_B), 3.41–3.30 (2H, m, *H*-3a,7a), 2.02–1.92 (2H, m, H_A-4,7), 1.72–1.58 (2H, m, H_B-4,7) and 1.33–1.02 (4H, m, *H*-5,6); δ_C (100 MHz, CD_3OD) 161.9 (*C*H-2), 134.8 (Ph*C*-1), 130.1 (Ph*C*H-3,5), 129.7 (Ph*C*H-4), 129.4 (Ph*C*H-2,6), 69.0 (*C*H-3a,7a), 51.5 (Ph–CH_2), 28.5 (CH_2-4) and 24.5 (CH_2-5); **IR** ν_{max} (KBr) ν_{max} /cm^{-1} 3108 (Ar C-H), 3072 (Ar C-H), 1611 (C=N), 1586 (C=N), 1062 (C-N stretch) and 1059 (C-N stretch); ***m/z*** MS (ESI+) 305 (100, [M–BF_4]); HRMS (ESI+) $C_{21}H_{25}N_2$ ([M–BF_4]) requires 305.2018, found 305.2019 (+0.4 ppm).

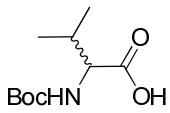
Boc-L-valine (*S*)-359



(*S*)-359

To a solution of L-valine (35.1 g, 300 mmol) in NaOH(aq) (12.0 g in 300 mL) was added *tert*-butanol (200 mL) followed by slow addition of Boc_2O (75.2 g, 360 mmol), with vigorous stirring. The mixture was stirred for 48 h at ambient temperature then the reaction was quenched with 1 M $KHSO_4$(aq) to pH ~1. The mixture was saturated with NaCl, then extracted with Et_2O (300 mL × 3). The combined organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a colourless oil which partially solidified on standing (52.6 g, 81%) which was used without further purification. $[\alpha]_D^{20}$ -5.5 (*c* 1.0, AcOH), lit.[186] -6.3 (*c* 1, AcOH); δ_H (400 MHz, $CDCl_3$) 7.94 (1H, br s, COO*H*), 5.06 (1H, d, *J* 8.9, N*H*CH), 4.28 (1H, dd, *J* 8.9, 4.5, NHC*H*), 2.27–2.19 (1H, m, C*H*Me_2), 1.02 (3H, d, *J* 6.8, CH_3) and 0.96 (3H, d, *J* 6.8, CH_3). Data are in accordance with the literature.[186]

Boc-DL-valine (*RS*)-359

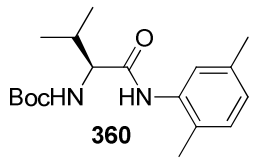


(*RS*)-359

To a solution of DL-valine (7.02 g, 60.0 mmol) in NaOH(aq) (2.40 g in 30 mL) was added *tert*-butanol (40 mL) followed by slow addition of Boc_2O (15.0 g, 68.9 mmol), with vigorous stirring. The mixture was stirred for 48 h at ambient temperature then the reaction was quenched with 1 M $KHSO_4$(aq) to pH ~1. The mixture was saturated with NaCl, then extracted with Et_2O (150 mL × 2). The combined organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product as a colourless oil which partially solidified on standing

(10.9 g, 84%). The product was used without further purification. Spectroscopic data as for *N*-Boc-L-valine.

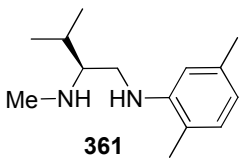
(*S*)-*tert*-Butyl 1-(2,5-dimethylphenylamino)-3-methyl-1-oxobutan-2-ylcarbamate 360



360

A solution of Boc-L-valine **(*S*)-359** (6.74 g, 31.0 mmol) in CH_2Cl_2 (80 mL) was cooled to 0 °C, followed by addition of *N*-methylmorpholine (3.41 mL, 31.0 mmol), then dropwise addition of ethyl chloroformate (2.97 mL, 31.0 mmol) and the mixture was stirred for 20 min. 2,5-Dimethylaniline (3.82 mL, 31.0 mmol) was added slowly, then warmed to ambient temperature over 16 h, then the reaction was quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (100 mL × 3). The organic fractions were combined and washed sequentially with 4% $NaHCO_3$(aq) (100 mL) and 1 M HCl(aq) (100 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was then triturated with ice-cold pentane to obtain the product as a pale green solid (9.01 g, 91%). **mp** 155–156 °C; $[\alpha]_D^{20}$ -54.4 (*c* 1.0, MeOH); δ_H (400 MHz, d_6-DMSO) 9.22 (1H, s, amide N*H*), 7.14 (1H, s, Ar*H*-3), 7.07 (1H, d, *J* 8.0, carbamate N*H*), 6.90–6.88 (1H, m, Ar*H*-6), 6.85 (1H, d, *J* 8.5, Ar*H*-4), 3.93 (1H, t, *J* 8.0, BocNHC*H*), 2.23 (3H, s, ArCH_3-5), 2.12 (3H, s, ArCH_3-2), 2.06–1.95 (1H, m, C*H*Me_2), 1.39 (9H, s, C(CH_3)$_3$), 0.93 (3H, d, *J* 6.8, CH_3) and 0.90 (3H, d, *J* 6.8, CH_3); δ_C (100 MHz, d_6-DMSO) 170.5 (*C*ONHAr), 156.1 (NH*CO*t-Bu), 135.9 (Ar*C*-1), 135.5 (Ar*C*-5), 130.5 (Ar*C*-2), 130.3 (Ar*C*H-3), 126.1 (Ar*C*H-6), 125.8 (Ar*C*-4), 78.4 (O*C*(CH$_3$)$_3$), 60.4 (*C*HCONHAr), 30.5 (*C*HMe_2), 28.4 (OC(*C*H$_3$)$_3$), 20.7 (Ar–*C*H$_3$-5), 19.6 (*C*H$_3$), 18.5 (*C*H$_3$) and 17.5 (Ar–*C*H$_3$-2); ***m/z*** MS (ESI+) 321 (100, $[M+H]^+$), 265 (69, $[M–t\text{-Bu}]^+$), 221 (17, $[M–Boc]^+$); HRMS (ESI+) $C_{18}H_{29}O_3N_2^+$ ($[M+H]^+$) requires 321.2173, found 321.2174 (+0.4 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3316 (NH), 2973, 2963, 1691 (C=O), 1660 (C=O), 1579, 1524, 1491, 1457, 1379, 1368, 1298, 1283, 1247, 1171, 1048, 1024, 887, 814 and 684.

(*S*)-N^1-(2,5-Dimethylphenyl)-$N^{2,3}$-dimethylbutane-1,2-diamine 361

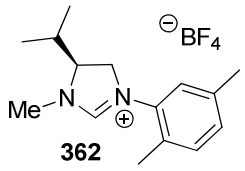


361

Follwing general procedure P, Boc-protected amide **360** (958 mg, 3.00 mmol), $LiAlH_4$ (9.00 mL of a 2 M solution in THF, 18.0 mmol) and THF (10 mL), gave, after workup (0.68 mL H_2O, 0.68 mL KOH(aq) and 2.04 mL H_2O), the diamine **361** as a pink/purple oil (630 mg, 95%). $[\alpha]_D^{20}$

+5.0 (*c* 1.73, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.94 (1H, d, *J* 7.4, Ar*H*-3), 6.48 (1H, br d, *J* 7.4, Ar*H*-4), 6.44 (1H, s, Ar*H*-6), 4.15 (1H, br s, ArN*H*), 3.22 (1H, dt, *J* 11.8, 4.2, $ArNHCH_AH_B$), 2.96 (1H, ddd, *J* 11.8, 7.5, 4.2, $ArNHCH_AH_B$), 2.51 (1H, ddd, *J* 7.5, 6.4, 4.2, MeNHC*H*), 2.41 (3H, s, NCH_3), 2.31 (3H, s, $ArCH_3$-5), 2.12 (3H, s, $ArCH_3$-2), 1.96 (1H, dt, *J* 13.2, 6.8, $CHMe_2$), 1.02 (3H, d, *J* 6.8, $CHCH_3$) and 0.96 (3H, d, *J* 6.8, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 146.9 (NAr*C*-1), 136.8 (NAr*C*-5), 130.0 (NAr*C*-3), 119.5 (NAr*C*-2), 117.3 (NAr*C*-6), 110.9 (NAr*C*-4), 64.2 (MeNH*C*H), 43.3 ($ArNHCH_2$), 33.9 ($NHCH_3$), 29.0 ($CHMe_2$), 21.4 (Ar–CH_3-5), 19.6 ($CHCH_3$), 18.5 ($CHCH_3$) and 17.2 (Ar–CH_3-2); ***m/z*** MS (ESI+) 221 (100, $[M+H]^+$); HRMS (ESI+) $C_{14}H_{25}N_2^+$ ($[M+H]^+$) requires 221.2012, found 221.2017 (+2.1 ppm); **IR** ν_{max} (thin film) /cm^{-1} 3370 (N-H), 3015, 2958, 2927, 2871, 2796, 1615, 1582, 1520, 1455, 1387, 1368, 1313, 1298, 1155, 1137, 1100, 1035, 1001, 840, 792 and 716.

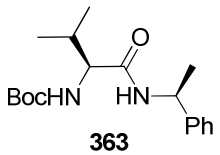
(*S*)-1-(2,5-Dimethylphenyl)-4-isopropyl-3-methyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate 362



362

A mixture of diamine **361** (200 mg, 0.908 mmol), triethyl orthoformate (0.370 mL, 2.27 mmol), MeOH (2.5 mL) and NH_4BF_4 (96.0 mg, 0.916 mmol) were heated at 100 ºC for 6 h, then concentrated *in vacuo*. The mixture was triturated with Et_2O (5 mL × 3) and EtOAc (5 mL). The mixture was redissolved in CH_2Cl_2 then loaded onto a short silica plug (~2 cm depth). The product was eluted with CH_2Cl_2 then increased to 2.5% MeOH:CH_2Cl_2 to afford the product as a green/brown oil (140 mg, 48%). $[\alpha]_D^{20}$ +38.7 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.12 (1H, s, NC*H*N), 7.13 (1H, s, Ar*H*-6), 7.10 (2H, d, *J* 3.3, Ar*H*), 4.50–4.44 (1H, m, (*i*-Pr)CH), 4.33 (1H, app t, *J* 11.7, NCH_AH_B), 3.80 (1H, ABX, J_{BA} 11.1, J_{BX} 7.8, NCH_AH_B), 3.26 (3H, s, NCH_3), 2.33–2.26 (4H, m, NC*H* and $ArCH_3$), 2.26 (3H, s, $ArCH_3$) and 0.97 (6H, app t, *J* 6.5, $CH(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 157.8 (N*C*HN), 137.9 (NAr*C*-1), 134.6 (Ar*C*), 131.7 (Ar*C*H), 130.6 (Ar*C*H), 130.5 (Ar*C*), 126.5 (Ar*C*), 67.0 (N*C*H), 52.0 (NCH_2), 33.1 (NCH_3), 27.0 (Ar–CH_3), 20.7 (Ar–CH_3), 17.8 ($CHCH_3$), 17.4 ($CHMe_2$) and 14.2 ($CHCH_3$); ***m/z*** MS (ESI+) 231 (100, $[M–BF_4]^+$); $C_{15}H_{23}N_2^+$ ($[M–BF_4]^+$) requires 231.1856, found 231.1856 (+0.1 ppm); **IR** ν_{max} (thin film) /cm^{-1} 3636, 3089, 2969, 2880, 1715 (C=N), 1652, 1619, 1576, 1515, 1509, 1464, 1428, 1397, 1377, 1315, 1270, 1215, 1161, 1134, 1058 (br, C-N) 910, 823, 765, 719 and 675.

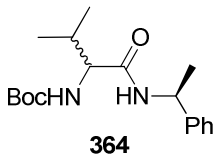
***tert*-Butyl (*S*)-3-methyl-1-oxo-1-((*S*)-1-phenylethylamino)butan-2-ylcarbamate 363**



363

Following general procedure N, Boc-L-valine (673 mg, 3.10 mmol), *N*-methylmorpholine (0.341 mL, 3.10 mmol), ethyl chloroformate (0.295 mL, 3.10 mmol), (*S*)-α-methylbenzylamine (0.400 mL, 3.10 mmol) and CH_2Cl_2 (10 mL) gave, after purification, the product as a colourless solid (648 mg, 65%). **mp** 146 ºC; $[\alpha]_D^{20}$ -80.7 (*c* 1.1, MeOH); δ_H (400 MHz, $CDCl_3$) 7.35–7.29 (4H, m, Ph*H*), 7.20–7.15 (1H, m, Ph*H*-4), 6.20 (1H, br s, amide N*H*), 5.15–5.06 (2H, m, carbamate N*H* and PhC*H*Me), 3.84 (1H, dd, *J* 8.6, 6.3, BocNHC*H*), 2.14–2.06 (1H, m, C*H*(Ph)Me), 1.49 (3H, d, *J* 6.9, PhCHCH_3), 1.43 (9H, s, C(CH_3)$_3$) and 0.91–0.87 (4H, m, CH_3*CH*CH_3). ***m/z*** MS (ESI+) 321 (100, $[M+H]^+$), 265 (46, $[M–t\text{-Bu}]^+$), 221 (14, $[M–Boc]^+$). HRMS (ESI+) $C_{18}H_{29}O_3N_2^+$ ($[M+H]^+$) requires 321.2173, found 321.2174 (+0.4 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3326 (br, N-H), 3313 (N-H), 3255 (N-H), 3071, 2977 (C-H), 1685 and 1646 (C=O), 1527, 1392, 1367, 1299, 1250 (C-O), 1177, 1016, 881, 757 and 698.

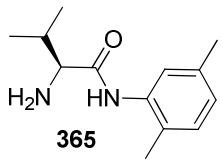
(*S*)-*tert*-Butyl (*RS*)-3-methyl-1-oxo-1-(1-phenylethylamino)butan-2-ylcarbamate 364



364

Following general procedure N, Boc-DL-valine (2.69 g, 12.4 mmol), *N*-methylmorpholine (1.36 mL, 12.4 mmol), ethyl chloroformate (1.20 mL, 12.4 mmol), (*S*)-α-methylbenzylamine (1.60 mL, 12.4 mmol) and CH_2Cl_2 (40 mL) gave, after purification, the product as a colourless solid (2.94 mg, 74%). **mp** 137–139 ºC; δ_H (400 MHz, $CDCl_3$) 7.35–7.23 (4H, m, Ph*H*), 7.28–7.23 (1H, m, Ph*H*-4), 6.31 (1H, br d, *J* 7.8, amide N*H*), 5.11 (2H, app t, *J* 5.5, carbamate N*H* and PhC*H*Me), 3.85 (1H, dd, *J* 8.5, 6.4, BocNHC*H*), 2.16–2.07 (1H, m, C*H*(Ph)Me), 1.49 (3H, d, *J* 6.9, PhCHCH_3), 1.42 (9H, s, C(CH_3)$_3$), 0.97 (3H, d, *J* 6.8, (*R*)-diastereomer CH_3), 0.93–0.88 (4H, m, both diastereomers C*H*CH_3) and 0.87 (3H, d, *J* 6.8, (*S*)-diastereomer CH_3); ***m/z*** MS (ESI+) 321 (100, $[M+H]^+$), 265 (48, $[M–t\text{-Bu}]^+$), 221 (15, $[M–Boc]^+$); HRMS (ESI+) $C_{18}H_{29}O_3N_2^+$ ($[M+H]^+$) requires 321.2173, found 321.2177 (+0.9 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3326 (br, N-H), 3284 (br, N-H), 3079, 2977 (C-H), 2934, 1703, 1686 and 1648 (C=O, mixture of diastereomers), 1553, 1527, 1494, 1451, 1392, 1366, 1302, 1290, 1250 (C-O), 1174, 1016, 878, 761 and 699.

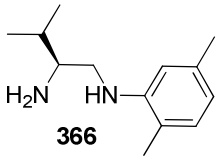
(*S*)-2-Amino-*N*-(2,5-dimethylphenyl)-3-methylbutanamide 365



365

Following general procedure Q, Boc-protected amide **360** (5.00 g, 15.7 mmol), TFA (10 mL) and CH_2Cl_2 (50 mL) gave, after purification, the desired product as a pale green solid (3.45 g, quantitative). The product was used without further purification. **mp** 120 ºC; $[\alpha]_D^{20}$ +3.7 (*c* 1.0, MeOH); δ_H (400 MHz, $CDCl_3$) 9.53 (1H, br s, amide N*H*), 7.96 (1H, s, Ar*H*-6), 7.05 (1H, dd, *J* 7.7, 0.9, Ar*H*-3), 6.85 (1H, dd, *J* 7.6, 3.7, Ar*H*-4), 3.42 (1H, d, *J* 3.5, NH_2CH), 2.48 (1H, sept d, *J* 7.0, 3.5, $CH(CH_3)_2$), 2.33 (3H, s, $ArCH_3$-5), 2.24 (3H, s, $ArCH_3$-2), 1.49 (2H, br s, NH_2), 1.06 (3H, d, *J* 7.0, CH_3) and 0.89 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 172.3 (*C*ONHAr), 136.5 (Ar*C*-5), 135.8 (Ar*C*-1), 130.0 (Ar*C*H-3), 124.9 (Ar*C*H-4) 124.4 (Ar*C*-2), 121.6 (Ar*C*H-6), 60.6 (*C*HCONHAr), 30.7 ($CHMe_2$), 21.2 (Ar–CH_3-5), 19.8 (CH_3), 17.3 (CH_3) and 15.9 (Ar–CH_3-2). ***m/z*** MS (ESI+) 221 (100, $[M+H]^+$), 243 (13, $[M+Na]^+$); HRMS (ESI+) $C_{13}H_{21}ON_2^+$ ($[M+H]^+$) requires 221.1648, found 221.1649 (+0.3 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3375, 3279 (amide N-H), 3047 (Ar C-H), 3022 (Ar C-H), 2987 (N-H), 2986 (N-H), 2955 (N-H), 2924, 2885, 2869, 1644 (C=O) and 1582.

(*S*)-N^1-(2,5-Dimethylphenyl)-3-methylbutane-1,2-diamine 366

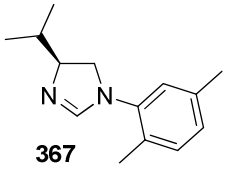


366

Following general procedure O, amido amide **365** (918 mg, 2.78 mmol), $LiAlH_4$ (3.47 mL of a 2 M solution in THF, 6.95 mmol) and THF (6 mL), gave, after workup (0.26 mL H_2O, 0.26 mL KOH(aq) and 0.79 mL H_2O), the product as a pale orange oil (550 mg, 95%). Product was used without further purification. $[\alpha]_D^{20}$ +19.7 (*c* 0.97, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.94 (1H, d, *J* 7.4, Ar*H*-3), 6.48 (1H, d, *J* 7.4, Ar*H*-4), 6.44 (1H, s, Ar*H*-6), 4.06 (1H, br s, ArN*H*), 3.28–3.26 (1H, m, $ArNHCH_AH_B$), 2.87 (1H, ABd, *J* 10.3, $ArNHCH_AH_B$), 2.84–2.78 (1H, m, NH_2CH), 2.30 (3H, s, $ArCH_3$–5), 2.13 (3H, s, $ArCH_3$–2), 1.77–1.65 (1H, m, $CH(CH_3)_2$), 1.23 (2H, br s, NH_2), 1.01 (3H, d, *J* 6.8, $CHCH_3$) and 0.97 (3H, d, *J* 6.8, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 146.5 (NAr*C*-1), 136.6 (NAr*C*-5), 129.9 (NAr*C*H-3), 119.3 (NAr*C*-2), 117.4 (NAr*C*H-6), 110.8 (NAr*C*H-4), 56.1 (NH_2CH), 48.0 ($ArNHCH_2$), 32.7 ($CH(CH_3)_2$), 21.6 ($ArCH_3$–5), 19.4 ($CHCH_3$), 17.9 ($CHCH_3$) and 17.1 ($ArCH_3$–2); ***m/z*** MS (ESI+) 207 (100, $[M+H]^+$); HRMS (ESI+) $C_{13}H_{23}N_2^+$ ($[M+H]^+$) requires 207.1856, found 207.1856 (+0.1 ppm); IR (thin film) ν_{max}

/cm^{-1} 3387 (N-H, broad), 2959, 2932, 1614 (Ar C=C), 1582, 1522 (Ar C=C), 1459, 1377, 1298, 1264, 1169, 1002, 842 and 793.

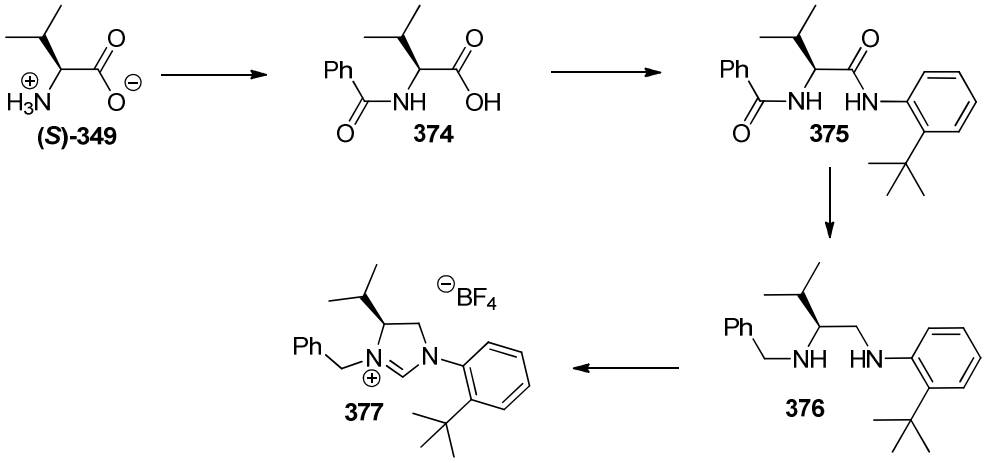
(*S*)-1-(2,5-Dimethylphenyl)-4-isopropyl-4,5-dihydro-1*H*-imidazole 367



367

A mixture of diamine **366** (200 mg, 0.969 mmol), toluene (3 mL), NH_4BF_4 (102 mg, 0.969 mmol) and triethyl orthoformate (0.80 mL) were heated at 90 ºC for 16 h, then cooled to ambient temperature and diluted with Et_2O (10 mL) and washed with 0.1 M NaOH(aq) (3 mL). The organic fraction was dried ($MgSO_4$), filtered and concentrated to obtain the product as a dark orange oil (165 mg, 79%). $\mathbf{[\alpha]_D^{20}}$ -6.0 (*c* 0.4, $CHCl_3$); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.11–7.09 (2H, m, Ar*H*-3 and NC*H*N), 6.99 (1H, d, *J* 7.7, Ar*H*-4), 6.81 (1H, s, Ar*H*-6), 4.02 (1H, dddd, *J* 10.3, 9.0, 6.5, 1.9, NC*H*i-Pr), 3.70 (1H, ABX, J_{AB} 10.3, J_{AX} 9.0, NCH_AH_B), 3.30 (1H, app t, *J* 9.0, NCH_AH_B), 2.30 (3H, s, ArCH_3-5), 2.26 (3H, s, ArCH_3-2), 1.90–1.79 (1H, m, C*H*Me$_2$), 1.04 (3H, d, *J* 6.8, CH_3) and 0.95 (3H, d, *J* 6.8, CH_3); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 153.7 (N*C*HN), 140.2 (Ar*C*-1), 136.7 (Ar*C*-5), 131.4 (Ar*C*H-3), 129.1 (Ar*C*-2), 126.2 (Ar*C*H-4), 123.2 (Ar*C*H-6), 72.7 (*i*-Pr*C*HN), 52.5 (N*C*H$_2$), 33.1 (*C*HMe$_2$), 20.9 (Ar–*C*H$_3$-5), 18.9 (*C*H$_3$), 18.5 (Ar–*C*H$_3$-2) and 18.3 (*C*H$_3$); ***m/z*** MS (ESI+) 217 (100, $[M+H]^+$); HRMS (ESI+) $C_{14}H_{21}N_2^+$ ($[M+H]^+$) requires 217.1699, found 217.1699 (+0.0 ppm); **IR** ν_{max} (thin film) /cm^{-1} 3377, 3070 (Ar CH), 2960, 2926, 2872, 1665 (C=N), 1615, 1584, 1526, 1509, 1463, 1382, 1300, 1275, 1224, 1173, 1139, 1061, 1003, and 794.

(*S*)-1-Benzyl-3-(2-*tert*-butylphenyl)-5-isopropyl-4,5-dihydro-1*H*-imidazolium tetrafluoroborate 377



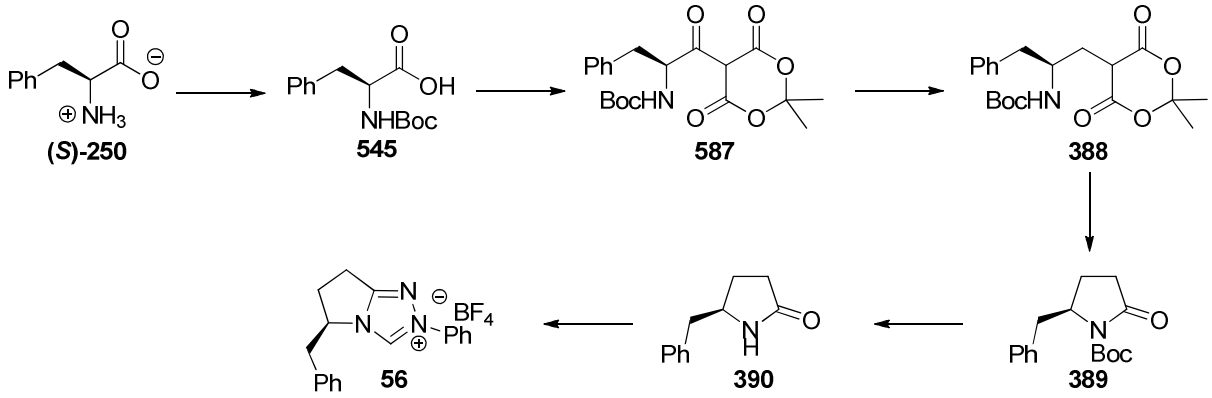
L-Valine (6.57 g, 56.1 mmol) and NaOH (2.34 g) were dissolved in H_2O (17 mL). Et_2O (90 mL) was added, the mixture was cooled to 0 °C and stirred rapidly. Benzoyl chloride (6.58 mL,

56.6 mmol) and a solution of NaOH (2.34 g) in H_2O (6 mL) were added alternatively portionwise over 90 min, then the mixture was warmed to ambient temperature over 16 h. The mixture was then concentrated to half volume *in vacuo* before conc. HCl (5 mL) was added to induce precipitation of the product. The product was collected by filtration and washed with Et_2O (100 mL) and dried, to obtain *N*-benzoylvaline **374** as a colourless solid (10.3 g, 83%), which was used immediately without further purification. A suspension of *N*-benzoylvaline **374** (1.50 g, 6.78 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and *N*-methylmorpholine (0.751 mL, 6.78 mmol) was added before dropwise addition of ethyl chloroformate (0.671 mL, 6.78 mmol). After 20 min, 2-*tert*-butylaniline (1.06 mL, 6.78 mmol) was added to the suspension. The mixture was warmed to ambient temperature over 16 h then quenched with H_2O (30 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and extracted with CH_2Cl_2 (30 mL × 3). The combined organics were washed successively with 4% $NaHCO_3$(aq) (30 mL) and 1 M HCl(aq) (30 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was triturated with pentane (20 mL) to obtain the diamide product **375** as a colourless solid (1.36 g, 53%) which was used without further purification. To a suspension of diamide **375** (1.00 g, 4.06 mmol) in THF (10 mL) was added a solution of $LiAlH_4$ (9.13 mL, 18.3 mmol) and the mixture heated at reflux for 72 h, then quenched at 0 °C with H_2O (0.69 mL), 40% KOH(aq) (0.69 mL) and further H_2O (2.07 mL), before drying with excess $MgSO_4$ and filtration through celite. Following concentration *in vacuo*, chromatographic purification (10% EtOAc:petrol) gave the diamine **376** as a clear colourless oil (790 mg, 60%). $\mathbf{[\alpha]_D^{20}}$ +0.3 (*c* 1.6, $CHCl_3$); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.27–7.22 (4H, m, Ar*H*), 7.20–7.16 (2H, m, Ar*H*), 7.07 (1H, td, *J* 7.6, 1.4, NAr*H*-4), 6.63–6.58 (2H, m, Ar*H*), 4.76 (1H, t, *J* 4.4, ArN*H*), 3.74 (1H, ABd, *J* 12.8, PhCH_AH_B), 3.71 (1H, ABd, *J* 12.8, PhCH_AH_B), 3.20 (1H, dt, *J* 11.5, 4.4, ArNHCH_AH_B), 2.95 (1H, ddd, *J* 11.4, 6.6, 4.4, ArNHCH_AH_B), 2.65 (1H, td, *J* 6.6, 4.0, BnNHC*H*), 2.03–1.91 (1H, m, C*H*$(CH_3)_2$), 1.37 (9H, s, C(CH_3)$_3$), 0.97 (3H, d, *J* 6.8, CH_3) and 0.90 (3H, d, *J* 6.8, CH_3); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 147.1 (NHAr*C*-1), 140.5 (Ph*C*-1), 133.5 (NHAr*C*-2), 128.5 (Ph*C*H), 128.4 (Ph*C*H), 127.2 (Ar*C*H), 127.1 (Ar*C*H), 126.2 (Ar*C*H), 116.5 (NHAr*C*-4), 111.5 (NHAr*C*-6), 61.9 (BnN*C*H), 51.1 (Ph–*C*H_2), 43.3 (ArNH*C*H_2), 34.4 (*C*$(CH_3)_3$), 29.9 (C(*C*H_3)$_3$), 29.3 (*C*H$(CH_3)_2$), 20.0 (*C*H_3) and 18.4 (*C*H_3); ***m/z*** MS (ESI+) 325 (100, $[M+H]^+$); HRMS (ESI+) $C_{22}H_{33}N_2^+$ ($[M+H]^+$) requires 325.2644, found 325.2639 (-1.3 ppm); **IR** ν_{max} (thin film) /cm^{-1} 3425 (br, N-H), 2958, 2930, 1644, 1504, 1443, 1055, 834, 741 and 697.

A mixture of diamine **376** (186 mg, 0.573 mmol), NH_4BF_4 (60.1 mg, 0.573 mmol), triethyl orthoformate (0.23 mL) and MeOH (1.6 mL) were heated at 80 °C for 16 h then concentrated *in vacuo* before dissolution in CH_2Cl_2 and filtration to remove excess NH_4BF_4. The mixture was

concentrated *in vacuo* then chromatographic purification (10% MeOH:CH_2Cl_2) gave the title product as a clear colourless oil (225 mg, 93%). $[\alpha]_D^{20}$ -0.7 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.01 (1H, s, NC*H*N), 7.36 (1H, dd, *J* 8.1, 1.3, ArC*H*-6), 7.27–7.21 (6H, m, ArC*H*), 7.17–7.13 (2H, m, Ar*CH*), 4.87 (1H, ABd, *J* 14.6, PhCH_AH_B), 4.44 (1H, ABd, *J* 14.6, PhCH_AH_B), 4.32–4.26 (1H, m, Me_2CHC*H*), 4.11 (1H, app t, *J* 11.6, ArNCH_AH_B), 3.81 (1H, ABX, J_{BA} 11.6, J_{BX} 9.9, ArNCH_AH_B), 2.34–2.23 (1H, m, C*H*Me_2), 1.21 (9H, s, C(CH_3)$_3$), 0.93 (3H, d, *J* 6.8, CH_3), and 0.80 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 158.8 (N*C*HN), 147.0 (NAr*C*-1), 134.0 (NAr*C*-2), 132.2 (Ph*C*), 130.6 (Ar*C*H), 130.0 (Ar*C*H), 129.5 (Ph*C*H), 129.3 (Ph*C*H), 129.0 (Ar*C*H), 128.8 (Ar*C*H), 128.3 (Ar*C*H), 65.0 (N*C*H(*i*-Pr)), 54.9 (ArN*C*H_2), 50.2 (Ph–*C*H_2), 35.7 (*C*(CH_3)$_3$), 32.0 (C(*C*H_3)$_3$), 26.6 (*C*HMe_2), 18.0 (*C*H_3) and 14.4 (*C*H_3); ***m/z*** MS (ESI+) 335 (100, $[M–BF_4]^+$); HRMS (ESI+) $C_{23}H_{31}N_2^+$ ($[M–BF_4]^+$) requires 335.2487, found 335.2479 (-2.4 ppm); **IR** ν_{max} (thin film) /cm^{-1} 3389, 3069, 2957, 2924, 2850, 1635 (C=N), 1457, 1366, 1259, 1086, 1057, 1036, 753 and 703.

(*R*)-5-Benzyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate 56



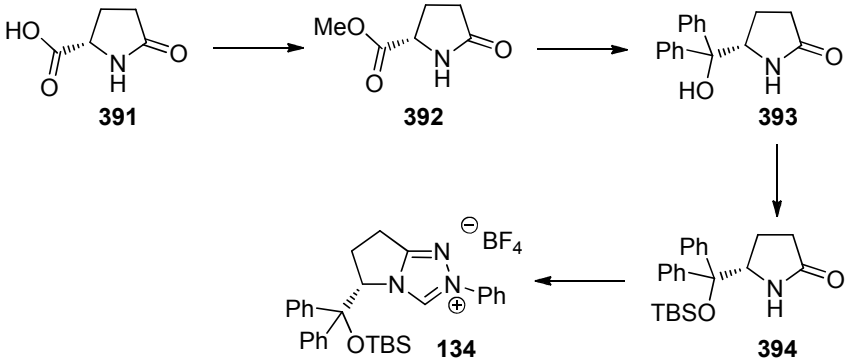
Boc_2O (52.6 g, 0.241 mol) was added dropwise to a stirred solution of L-phenylalanine (34.7 g, 0.210 mol) in 1 M NaOH(aq) (210 mL) and *t*-BuOH (140 mL). The reaction mixture was stirred at ambient temperature for 24 h then acidified to ~pH 1 with 1 M $KHSO_4$(aq) and extracted with Et_2O (250 mL × 3). The organic extracts was combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford Boc-L-phenylalanine **545** as a colourless oil (57.9 g, 85%). $[\alpha]_D^{20}$ +24.0 (*c* 1.03, EtOH), lit.[187] +24.7 (*c* 1.50, EtOH); δ_H (400 MHz, $CDCl_3$) 8.35 (1H, br s, COO*H*), 7.32–7.18 (5H, m, Ph*H*), 4.94 (1H, d, *J* 7.9, N*H*), 4.61 (1H, app q, *J* 6.5, C*H*COOH), 3.21 (1H, ABX, J_{AB} 13.8, J_{AX} 5.4, PhCH_AH_B), 3.09 (1H, ABX, J_{BA} 13.8, J_{BX} 6.5, PhCH_AH_B), 1.42 (6H, s, C(CH_3)$_3$) and 1.28 (3H, s, C(CH_3)$_3$). Data are in accordance with the literature.[187]

To a solution of Boc-L-phenylalanine **545** (15.7 g, 53.2 mmol) in CH_2Cl_2 (200 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (7.61 g, 52.7 mmol) and DMAP (8.78 g, 71.9 mmol). The mixture was cooled to -5 ºC, then a solution of DCC (10.9 g, 52.7 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1 h, after which the mixture was stirred for 20 h at -5 °C. The mixture was warmed to ambient temperature, whereby the precipitate was removed by filtration. The filtrate was then washed with $KHSO_4$(aq) (5% w/v, 100 mL × 4) and brine (100 mL) and dried ($MgSO_4$) at +5 °C (refrigerator) over 18 h. The solution was concentrated *in vacuo* to ~200 mL and the crude product was used immediately without further purification. To the solution of crude ketomalonate **387** (assumed ~53.2 mmol) in CH_2Cl_2 (200 mL) was added glacial AcOH (30 mL) and the mixture cooled to -5 ºC. $NaBH_4$ (4.63 g, 115 mmol) was added portionwise over 3 h at -5 °C, then the reaction mixture was stirred at -5 °C for a further 20 h. The reaction mixture was washed with H_2O (100 mL × 2), brine (100 mL × 2), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a pale yellow oil, and the malonate product **388** was crystallised from Et_2O as a colourless solid (10.2 g, 56% from L-phenylalanine). **mp** 120–121 ºC, lit.[188] 111–113 ºC; $\mathbf{[\alpha]_D^{20}}$ § +4.5 (*c* 1.0, MeOH); $\mathbf{\delta_H}$ (300 MHz, $CDCl_3$) 7.38–7.23 (5H, m, Ph*H*), 4.52–4.49 (1H, m, N*H*), 4.32–4.24 (1H, m, C*H*NH), 3.96 (1H, td, *J* 2.0, 0.5, C*H*C(O)), 2.90 (2H, d, *J* 6.4, PhCH_2), 2.36–2.14 (2H, m, CH_2CHC(O)), 1.82 (3H, s, CH_3), 1.78 (3H, s, CH_3) and 1.40 (9H, s, C(CH_3)$_3$). Data are in agreement with the literature.[188,189]

A solution of malonate derivative **388** (8.76 g, 23.2 mmol) in toluene (100 mL) was heated at 110 ºC for 5 h, then the mixture was concentrated *in vacuo* to afford the crude protected pyrrolidinone product **389** as a brown oil (7.09 g, quantitative yield) which was used immediately without further purification. To a cooled (0 ºC) solution of pyrrolidinone **389** (3.00 g, 10.9 mmol) in CH_2Cl_2 (100 mL) was added TFA (1.86 mL, 24.1 mmol) dropwise. The reaction was allowed to warm to ambient temperature and stirred for 4 h. The reaction was quenched slowly with sat $NaHCO_3$(aq) (100 mL) and extracted with CH_2Cl_2 (50 mL). The combined organic fraction was washed with H_2O (100 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude pyrrolidinone **390** as a yellow solid (1.91 g, quantitative) which was used immediately without further purification. To a solution of pyrrolidinone **390** (1.00 g, 5.71 mmol) in CH_2Cl_2 (40 mL) was added trimethyloxonium tetrafluoroborate (0.930 g, 6.29 mmol) and the reaction stirred for 16 h at ambient temperature. To the solution was added phenylhydrazine (0.620 mL, 6.29 mmol) and stirred for a further 16 h. The mixture was concentrated *in vacuo* then redissolved in MeOH (2 mL) and triethyl orthoformate (20 mL) and heated to 80 ºC for 16 h. The mixture was concentrated *in vacuo* and the product precipitated from EtOAc to give a yellow solid. Recrystallisation from MeOH gave

the title product **56** as a golden crystalline solid (1.03 g, 50%). **mp** 191–192 °C, lit.[146] 195.1 - 196.5 °C; $[\alpha]_D^{20}$ +8.7 (*c* 1.04, MeCN), lit.[146] +9.1 (*c* unspecified, MeCN); δ_H (300 MHz, $CDCl_3$) 10.02 (1H, s, NC*H*N), 7.86–7.80 (2H, m, Ph*H*), 7.60–7.53 (3H, m, Ph*H*), 7.38–7.22 (5H, m, Ph*H*), 5.41–5.32 (1H, m, BnC*H*N), 3.54 (1H, ABX, J_{AB} 13.5, J_{AX} 5.0, PhCH_AH$_B$), 3.23–3.17 (1H, m, CH_AH$_B$-7), 3.15 (1H, ABX, J_{BA} 13.5, J_{BX} 8.8, PhCH$_A$$H_B$), 3.04–2.88 (2H, m, C$H_AH_B$-6 and CH$_A$$H_B$-7) and 2.70–2.59 (1H, m, CH$_A$$H_B$-6); Data are in accordance with the literature.[146]

(*S*)-5-((*tert*-Butyldimethylsilyloxy)diphenylmethyl)-2-phenyl-2,5,6,7-tetrahydropyrrolo [2,1-*c*][1,2,4]triazolium tetrafluoroborate 134



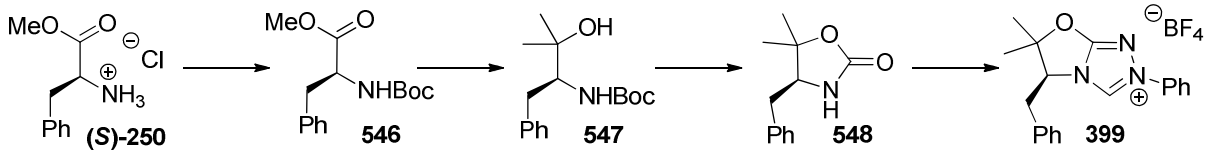
To a solution of (*S*)-pyroglutamic acid (10.0 g, 77.5 mmol) in MeOH (252 mL) at -15 ºC was added thionyl chloride (6.23 mL, 85.7 mmol) dropwise. The mixture was stirred at -15 ºC for 30 min then warmed to ambient temperature before concentration *in vacuo* to afford the crude ester product **392** as a viscous yellow oil (11.1 g, quantitative). The product was used without further purification. To a cooled (-78 ºC) solution of the pyroglutamate **392** (5.00 g, 34.9 mmol) in THF (40 mL) was added phenylmagnesium bromide (40.0 mL of a 3 M solution in Et_2O, 120 mmol) over 30 min. The mixture was warmed to -40 ºC for 15 min then warmed to 0 ºC for 30 min, then the reaction was quenched with 5% HCl(aq) (~30 mL). The product was extracted with CH_2Cl_2 (50 mL × 5). The organic extracts were combined, dried ($MgSO_4$), filtered through celite, concentrated *in vacuo* and the residue was recrystallised from Et_2O to afford the desired tertiary alcohol product **393** as a colourless solid (5.02 g, 54%). **mp** 189–190 ºC, lit.[190] 191–192 ºC; $[\alpha]_D^{20}$ -81.2 (*c* 1.0, $CHCl_3$), lit.[190] -80.8 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.46–7.17 (10H, m, Ph*H*), 4.58 (1H, br s, N*H*), 4.70–4.64 (1H, dd, *J* 8.2, 4.8, NHC*H*), 3.87 (1H, br s, O*H*), 2.36–2.28 (1H, m, C(O)CH_AH$_B$), 2.26–2.17 (1H, m, C(O)CH$_A$$H_B$), 2.12–2.04 (1H, m, C(O)CH$_2$CH_AH$_B$) and 1.95–1.87 (1H, m, C(O)CH$_2$CH$_A$$H_B$). Data are in agreement with the literature.[190]

To a cooled (0 ºC) solution of alcohol **393** (1.50 g, 5.59 mmol) and Et_3N (1.01 mL, 7.29 mmol) in CH_2Cl_2 (30 mL) was added TBSOTf (1.70 mL, 7.29 mmol). The reaction mixture was warmed to ambient temperature over 5 h. Another portion of TBSOTf (0.850 mL, 3.65 mmol)

and Et_3N (0.495 mL, 3.65 mmol) were added and the mixture stirred for 2 h at ambient temperature. The reaction mixture was quenched with H_2O (12 mL) and extracted with CH_2Cl_2 (30 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification (30% EtOAc:petrol) gave the product **394** as a the product as a colourless solid (2.04 g, 96%). **mp**[§] 138–140 ºC; $[\alpha]_D^{20}$ -63.0 (*c* 0.5, $CHCl_3$), lit. –65.0 (*c* 1.01, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.38–7.28 (10H, m, Ph*H*), 5.83 (1H, br s, N*H*), 4.66 (1H, dd, *J* 8.2, 3.3, NHC*H*), 2.19–2.09 (2H, m, $COCH_2$), 1.91–1.80 (1H, m, $COCH_2CH_AH_B$), 1.10–0.89 (1H m, $COCH_2CH_AH_B$), 0.92 (9H, s, $SiC(CH_3)_3$), -0.34 (3H, s, $SiCH_3$) and -0.39 (3H, s, $SiCH_3$). Data are in accordance with the literature.[191]

To a solution of lactam **394** (1.00 g, 2.62 mmol) in CH_2Cl_2 (16 mL) was added trimethyloxonium tetrafluoroborate (426 mg, 2.88 mmol) and the mixture stirred for 16 h. To the solution was added phenylhydrazine (0.258 mL, 2.62 mmol) and stirred for 24 h. The mixture was then concentrated *in vacuo* and the residue redissolved in MeOH (1.18 mL) and triethyl orthoformate (6.35 mL) and heated at reflux (100 ºC) for 16 h. The mixture was cooled to ambient temperature and concentrated *in vacuo* then triturated with Et_2O (~20 mL) to afford the title product **134** as a brown solid (606 mg, 41%). **mp** 208–210 ºC, lit.[192] 210–211 ºC; $[\alpha]_D^{20}$ -108.4 (*c* 0.5, MeCN), lit.[192] -112.4 (*c* 0.5, MeCN); δ_H (300 MHz, $CDCl_3$) 9.07 (1H, s, NC*H*N), 7.73–7.69 (2H, m, Ph*H*), 7.55–7.45 (5H, m, Ph*H*), 7.45–7.35 (4H, m, Ph*H*), 7.00 (2H, t, *J* 7.3, NPh*H*-3,5), 6.95 (2H, app br s, NPh*H*-2,6), 6.11 (1H, d, *J* 8.3, C*H*-5), 3.25–3.14 (1H, m, CH_AH_B-7), 3.00–2.88 (1H, m, CH_AH_B-7), 2.87–2.62 (1H, m, CH_AH_B-6), 1.77–1.65 (1H, m, CH_AH_B-6), 0.96 (9H, s, $Si(CH_3)_3$), -0.32 (3H, s, $SiCH_3$) and -0.35 (3H, s, $SiCH_3$). Data are in accordance with the literature.[192]

(*S*)-5-Benzyl-6,6-dimethyl-2-phenyl-5,6-dihydrooxazolo[2,3-*c*][1,2,4]triazol-2-ium tetrafluoroborate 399



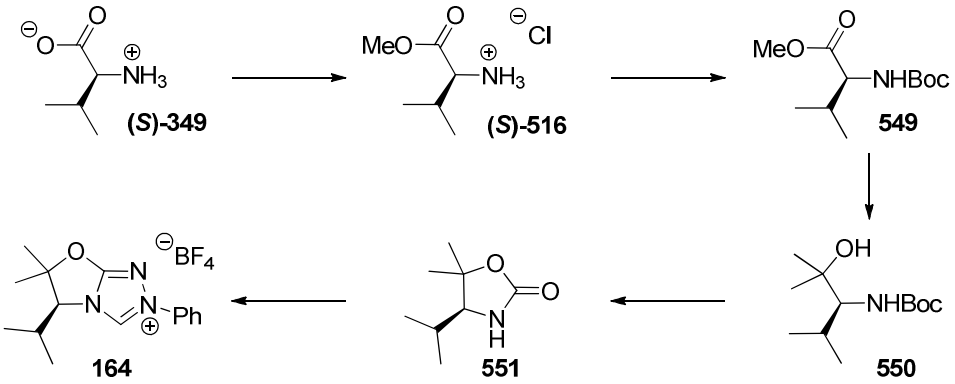
To a suspension of L-phenylalanine methyl ester hydrochloride **(*S*)-250** (20.0 g, 97.2 mmol) in EtOH (60 mL) was added Na_2CO_3 (30.1 g, 284 mmol) and Boc_2O (24.5 g, 112 mmol). The suspension was stirred for 48 h at ambient temperature. The colourless suspension was filtered through celite and the filtrate concentrated *in vacuo* to afford Boc-L-phenylalanine methyl ester **546** as a clear yellow oil (27.2 g, 91%). $[\alpha]_D^{20}$ +49.2 (*c* 1.0, CH_2Cl_2), lit.[193] +46.9 (*c* 3.4, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.06–7.03 (5H, m, Ar*H*), 5.37 (1H, br d, *J* 8.3, N*H*), 4.47 (1H, app q, *J* 7.2, C*H*NH), 3.52 (3H, s, OCH_3), 3.01 (1H, ABX, J_{AB} 13.7, J_{AX} 5.6, $PhCH_AH_B$), 2.90 (1H,

ABX, J_{BA} 13.7, J_{BX} 7.0, $PhCH_AH_B$) and 1.42–1.30 (9H, m, $C(CH_3)_3$). Data are in accordance with the literature.[193]

To a cooled (0 °C) solution of Boc-L-phenylalanine methyl ester **546** (10.0 g, 35.8 mmol) in Et_2O (100 mL) was added methylmagnesium bromide (37.0 mL of a 3.0 M solution in THF, 111 mmol) slowly *via* cannula. The mixture was stirred for 16 h at ambient temperature, quenched with ice-cold H_2O (~30 mL), then filtered through celite. The (partially aqueous) filtrate was extracted with CH_2Cl_2 (50 mL × 2) and the combined organics were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude alcohol product **547** as a pale yellow solid (7.32 g, 73%) which was used immediately without further purification. To a cooled (0 °C) solution of the crude alcohol **547** (5.00 g, 17.9 mmol) in THF (50 mL) was added potassium *tert*-butoxide (2.21 g, 19.7 mmol). The mixture was stirred for 16 h at ambient temperature and then concentrated *in vacuo* to afford a viscous yellow oil. The oil was dissolved in EtOAc (100 mL) and washed with brine (100 mL) and the aqueous phase extracted with EtOAc (20 mL × 2). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a clear yellow oil. Chromatographic purification (25% EtOAc:petrol) gave the oxazolidinone **548** as a yellow oil (3.51 g, 79%); $[\alpha]_D^{20}$ -108.2 (*c* 1.0, $CHCl_3$), lit.[194] -103.5 (*c* 0.6, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.37–7.15 (5H, m, Ar*H*), 4.79 (1H, br s, N*H*), 3.74–3.65 (1H, m, C*H*NH_2), 2.84 (1H, ABX, J_{AB} 13.3, J_{AX} 3.7, $PhCH_AH_B$), 2.67 (1H, ABX, J_{BA} 13.3, J_{BX} 10.8, $PhCH_AH_B$), 1.49 (3H, s, CH_3) and 1.46 (3H, s, CH_3). Data are in accordance with the literature.[194]

To a solution of oxazolidinone **548** (1.86 g, 9.06 mmol) in CH_2Cl_2 (30 mL) was added trimethyloxonium tetrafluoroborate (1.48 g, 10.0 mmol) then the mixture was stirred for 16 h. Phenylhydrazine (0.902 mL, 9.06 mmol) was added and the solution was stirred for a further 24 h. The mixture was concentrated *in vacuo* and the residue dissolved in triethyl orthoformate (20 mL) and MeOH (4 mL) and heated at reflux (100 °C) for 18 h. The resultant precipitate was collected by filtration and washed with cold EtOAc to obtain the purified title product **399** as a light brown solid (2.02 g, 57%). **mp** 178–180 °C, lit.[73] 177–179 °C; $[\alpha]_D^{20}$ -73.0 (*c* 0.5, MeCN), lit.[73] -76.4 (*c* 1.0, MeCN); δ_H (300 MHz, $CDCl_3$) 9.03 (1H, s, NC*H*N), 7.64–7.25 (10H, m, Ar*H*), 5.28 (1H, t, *J* 8.1, CH_2CHN), 3.40 (1H, ABd, *J* 14.0, $PhCH_AH_B$), 3.19 (1H, ABd, *J* 14.0, $PhCH_AH_B$), 1.71 (3H, s, CH_3) and 1.58 (3H, s, CH_3). Data are in accordance with the literature.[73]

(*S*)-6,6-Dimethyl-2-phenyl-5-isopropyl-5,6-dihydrooxazolo[2,3-*c*][1,2,4]triazol-2-ium tetrafluoroborate 164



To a cooled (0 °C) suspension of L-valine (20.0 g, 171 mmol) in MeOH (200 mL) was added thionyl chloride (36.5 mL, 502 mmol) dropwise, after which the reaction was stirred at ambient temperature for 16 h. The reaction mixture was then concentrated *in vacuo* to give a pale yellow solid, which was washed with Et_2O (100 mL) to afford the ester hydrochloride **(*S*)-516** as a colourless solid (28.6 g, quantitative); **mp** 164–165 °C, lit.[195] 169–170 °C; $[\alpha]_D^{20}$ +24.2 (*c* 1.0, MeOH), lit.[196] +22.3 (*c* 2.0, MeOH); δ_H (300 MHz, D_2O) 4.01 (1H, d, *J* 4.7, C*H*NH), 3.83 (3H, s, OCH_3), 2.42–2.25 (1H, m, C*H*Me$_2$), 0.92 (3H, d, *J* 4.4, CH(CH_3)$_A$) and 0.90 (3H, d, CH(CH_3)$_B$). Data are in accordance with the literature.[195,196]

To a suspension of (*S*)-valine methyl ester hydrochloride **(*S*)-516** (20.0 g, 119 mmol) in EtOH (60 mL) was added $NaHCO_3$ (26.1 g, 310 mmol) and Boc_2O (29.6 g, 136 mmol). The mixture was stirred for 48 h at ambient temperature then the colourless suspension was filtered through celite and the filtrate concentrated *in vacuo* to afford the carbamate product **549** as a pale yellow oil (27.5 g, quantitative) which was used without further purification. $[\alpha]_D^{20}$ -4.0 (*c* 0.5, AcOH), lit.[197] -6.3 (*c* 1, AcOH); δ_H (400 MHz, $CDCl_3$) 5.05 (1H, d, *J* 8.7, CHN*H*), 4.17 (1H, ABX, J_{XA} 8.7, J_{XB} 4.8, C*H*NH), 3.68 (3H, s, OCH_3), 2.16–1.98 (1H, m, C*H*Me$_2$), 1.51–1.34 (9H, m OC(CH_3)$_3$), 0.90 (3H, d, *J* 6.9, CH(CH_3)$_A$) and 0.85 (3H, d, *J* 6.9, CH(CH_3)$_B$). Data are in accordance with the literature.[197]

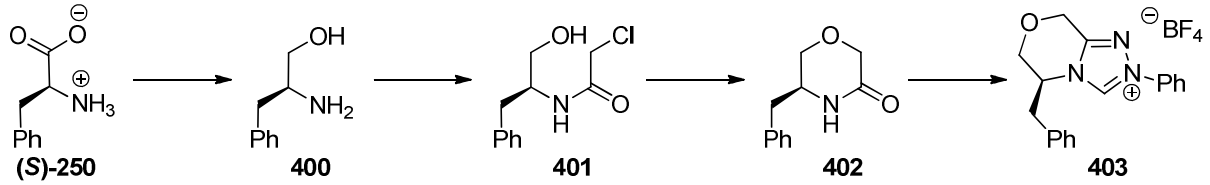
To a cooled (0 °C) solution of Boc-L-valine methyl ester **549** (10.0 g, 43.2 mmol) in Et_2O (100 mL) was added methylmagnesium bromide (46.0 mL of a 3.0 M solution in THF, 138 mmol) dropwise at ambient temperature. The reaction was stirred for 48 h, quenched with ice-cold H_2O (~30 mL) and filtered through celite. The filtrate was extracted with CH_2Cl_2 (50 mL × 2) and the combined organic phase was washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude alcohol **550** as a colourless oil (8.34 g, 83%) which was used without further purification. $[\alpha]_D^{20}$ +11.5 (*c* 1.0, CH_2Cl_2), lit.[198] +9.1

(*c* 0.01, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 4.85 (1H, d, *J* 10.2, CHN*H*), 3.36 (1H, dd, *J* 10.2, 2.7, C*H*NH), 2.12–2.03 (1H, m, C*H*Me_2), 1.43–1.40 (9H, m, OC(CH_3)$_3$), 1.24 (3H, s, C(CH_3)$_A$), 1.20 (3H, s, C(CH_3)$_B$), 0.95 (3H, d, *J* 6.8, CH(CH_3)$_A$) and 0.91 (3H, d, *J* 6.8, CH(CH_3)$_B$). Data are in accordance with the literature.[198]

To a cooled (0 °C) solution of **550** (3.00 g, 13.0 mmol) in THF (60 mL) was added potassium *tert*-butoxide (1.60 g, 14.3 mmol). The solution was warmed to ambient temperature over 16 h and concentrated *in vacuo* then redissolved in EtOAc (50 mL) and washed with 0.5 M HCl (aq) (40 mL) and brine (50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a clear yellow oil. Chromatographic purification (25% EtOAc:petrol) gave the oxazolidinone **551** as a colourless solid (1.94 g, 95%); **mp** 85–87 °C, lit.[194] 87–89 °C; $[\alpha]_D^{20}$ +24.1 (*c* 1.0, $CHCl_3$), lit[194] +21.3 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.06 (1H, s, N*H*), 3.18 (1H, dd, *J* 8.6, 6.7, NHC*H*), 1.88–1.79 (1H, m, C*H*Me_2), 1.49 (3H, s, OC(CH_3)$_A$), 1.38 (3H, s, OC(CH_3)$_B$), 0.99 (3H, d, *J* 6.6, CH(CH_3)$_A$) and 0.92 (3H, d, *J* 6.6, CH(CH_3)$_B$).

To a solution of **551** (1.86 g, 11.8 mmol) in CH_2Cl_2 (50 mL) was added trimethyloxonium tetrafluoroborate (1.93 g, 13.0 mmol) and the mixture was stirred for 16 h. Phenylhydrazine (1.16 mL, 11.8 mmol) was added and the solution was stirred for a further 24 h. The mixture was then concentrated *in vacuo* and the residue dissolved in triethyl orthoformate (28 mL) and MeOH (6 mL) and heated at reflux (100 °C) for 18 h. The solution was concentrated to approximately half volume *in vacuo* and the product precipitated upon addition of Et_2O (~1 mL). The precipitate was collected by filtration and washed with ice-cold EtOAc to afford the title product **164** as a pale brown solid (2.04 g, 50%). **mp** 112–118 °C, lit.[73] 179–180 °C; $[\alpha]_D^{20}$ -5.0 (*c* 1.0, MeCN), lit.[73] -7.0 (*c* 0.5, MeCN); δ_H (300 MHz, d_6-DMSO) 9.54 (1H, s, NC*H*N), 7.99–7.54 (5H, m, Ph*H*), 4.63 (1H, d, *J* 7.5, *i*-PrC*H*N), 2.50–2.35 (1H, m, *i*-PrC*H*), 2.02 (3H, s, C(CH_3)$_A$), 1.82 (3H, s, C(CH_3)$_B$), 1.22 (3H, d, *J* 6.6, CH(CH_3)$_A$) and 1.12 (3H, d, *J* 6.6, CH(CH_3)$_B$). Data are in accordance with the literature.[73]

(*S*)-5-Benzyl-2-phenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium tetrafluoroborate 403



To a mixture of of sodium borohydride (2.60 g, 68.8 mmol) in THF (80 mL) was added L-phenylalanine (5.00 g, 30.2 mmol). The mixture was cooled to 0 °C and a solution of iodine (7.67 g, 30.2 mmol) in THF (20 mL) was added dropwise over 40 min. After gas evolution had ceased, the reaction was heated at reflux (80 °C) for 18 h. When the reaction had cooled to ambient temperature, MeOH was added slowly until the solution became clear and the mixture was stirred for a further 30 min. The mixture was concentrated *in vacuo* to afford a colourless paste, which was redissolved in KOH(aq) (20% w/v, 100 mL) with stirring over 4 h. The mixture was extracted with CH_2Cl_2 (150 mL × 2), the organics layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product as a colourless solid. Recrystallisation from Et_2O gave the product (*S*)-phenylalaninol **400** as a colourless solid (2.49 g, 55%). **mp** 88–90 °C, lit.[199] 86–88 °C; $\mathbf{[\alpha]_D^{20}}$ -22.3 (*c* 1.01, $CHCl_3$), lit.[199] -21.7 (*c* 1.0, $CHCl_3$); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.36–7.18 (5H, m, Ph*H*), 3.66 (1H, ABX, J_{AB} 10.6, J_{AX} 3.9, CH_AH$_B$OH), 3.41 (1H, ABX, J_{BA} 10.6, J_{BX} 7.2, CH$_A$$H_B$OH), 3.18–3.11 (1H, m, C*H*NH_2), 2.82 (1H, ABX, J_{AB} 13.5, J_{AX} 5.2, PhCH_AH$_B$), 2.55 (1H, ABX, J_{BA} 13.5, J_{BX} 8.6, PhCH$_A$$H_B$) and 1.79 (2H, br s, N$H_2$). Data are in accordance with the literature.[199]

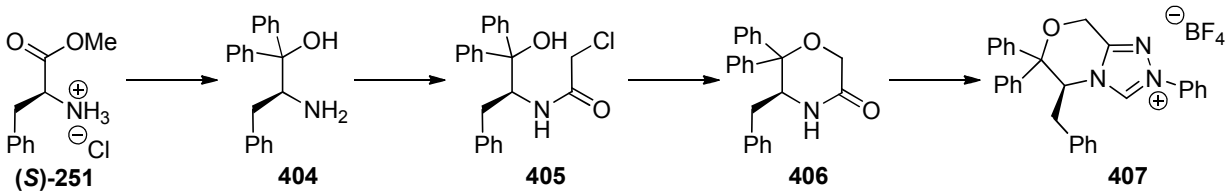
To a cooled (0 ºC) solution of (*S*)-phenylalaninol **400** (500 mg, 3.31 mmol) and Et_3N (1.38 mL, 9.92 mmol) in CH_2Cl_2 (10 mL) was added chloroacetyl chloride (0.28 mL, 3.47 mmol) dropwise. The mixture was warmed to ambient temperature over 16 h then sat $NaHCO_3$(aq) (10 mL) added and the mixture extracted with CH_2Cl_2 (20 mL × 3). The organics were combined and washed with 1 M H_2SO_4(aq) (10 mL), H_2O (10 mL) and brine (10 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude amide intermediate **401** as a brown oil which was used immediately in the subsequent step. The product was redissolved in THF (10 mL) and cooled to 0 ºC before addition of potassium *tert*-butoxide (405 mg, 3.61 mmol). The mixture was warmed to ambient temperature over 90 min then concentrated *in vacuo* then partitioned between EtOAc (10 mL) and brine (10 mL). The aqueous fraction was extracted with EtOAc (10 mL × 2), then the combined organic fractions was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude morpholinone product. Chromatographic purification (40% EtOAc:petrol) gave the morpholinone **402** as a colourless solid (420 mg, 66%). **mp** 85–

87 ºC, lit.[200] 86–87 ºC; $[\alpha]_D^{20}$ +4.2 (*c* 1.0, MeOH), lit.[200] +4.0 (*c* 0.66 MeOH); δ_H (400 MHz, $CDCl_3$) 7.33–7.16 (5H, m, Ph*H*), 5.89 (1H, br s, N*H*), 4.22 (1H, ABd, *J* 17.8, OCH_AH$_B$CO), 4.19 (1H, ABd, *J* 17.8, OCH$_A$$H_B$CO), 3.88 (1H, ABX, J_{AB} 11.5, J_{AX} 3.8, OCH_AH$_B$CH), 3.77 (1H, ddd, *J* 9.2, 5.8, 3.8, NHC*H*), 3.46 (1H, ABX, J_{BA} 11.5, J_{BX} 5.8, OCH$_A$$H_B$CH), 2.85 (1H, ABX, J_{AB} 13.5, J_{AX} 5.8, CH_AH$_B$Ph) and 2.70 (1H, ABX, J_{BA} 13.5, J_{BX} 9.2, CH$_A$$H_B$Ph). Data are in accordance with the literature.[200]

To a solution of lactam **402** (400 mg, 2.09 mmol) in CH_2Cl_2 (12 mL) was added trimethyloxonium tetrafluoroborate (337 mg, 2.28 mmol) and the mixture was stirred for 16 h. To the mixture was then added phenylhydrazine (0.206 mL, 2.09 mmol) and the mixture was stirred for 20 h. The mixture was then concentrated *in vacuo* and redissolved in MeOH (1.5 mL) and triethyl orthoformate (4.5 mL). The mixture was heated at reflux (110 ºC) for 16 h then cooled to ambient temperature, whereby the product had precipitated.[i] The product was collected by filtration and washed with cold (-78 ºC) EtOAc (~5 mL) to afford the title product **403** as a pale peach solid (230 mg, 29%). **mp** 190–195 ºC; $[\alpha]_D^{20}$ -18.1 (*c* 0.8, MeOH); δ_H (400 MHz, d_6-DMSO) 10.91 (1H, s, NC*H*N), 7.90–7.88 (2H, m, Ph*H*), 7.76–7.71 (2H, m, Ph*H*), 7.71–7.65 (1H, m, Ph*H*-4), 7.43–7.40 (2H, m, NPh*H*-2), 7.36–7.32 (3H, m, NPh*H*), 5.23 (1H, ABd, *J* 16.2, OCH_AH$_B$), 5.15 (1H, ABd, *J* 16.2, OCH$_A$$H_B$), 4.85 (1H, app dq, *J* 9.7, 5.9, BnC*H*), 4.01–3.93 (2H, m, OCH_2CHBn), 3.50 (1H, ABX, J_{AB} 13.6, J_{AX} 5.9, PhCH_AH$_B$) and 3.18 (1H, ABX, J_{BA} 13.6, J_{BX} 9.7, PhCH$_A$$H_B$); δ_C (100 MHz, d_6-DMSO) 149.9 (N*C*HN), 135.1 (N=*C*), 134.9 (NAr*C*-1), 134.9 (CH$_2$Ph*C*-1), 130.8 (Ar*C*H-4), 130.4 (Ar*C*H), 129.5 (Ar*C*H), 129.0 (Ar*C*H), 127.5 (Ar*C*H), 120.7 (Ar*C*H), 65.1 (O*C*H$_2$), 61.5 (O*C*H$_2$), 56.3 (N*C*H) and 37.5 (Ph–*C*H$_2$); ***m/z*** MS (ESI+) 292 (100, $[M–BF_4]^+$); HRMS (ESI+) $C_{18}H_{18}ON_3^+$ ($[M–BF_4]^+$) requires 292.1444, found 292.1443 (-0.4 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3337, 3141, 3060 (Ar C-H), 3026, 2987, 2969, 1585 (C=N), 1536, 1497 (Ar C=C), 1469, 1118 (C-O) and 1054 (br).

[i] In the event of no precipitation, the mixture was concentrated *in vacuo*, redissolved in EtOAc (5 mL), then Et_2O (1 drop) was added to induce precipitation).

(*S*)-5-Benzyl-2,6,6-triphenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium tetrafluoroborate 407



Free basification of methyl ester:

A solution of L-phenylalanine methyl ester hydrochloride **(*S*)-251** (5.00 g, 23.2 mmol) was dissolved in Et_2O (25 mL) and NaOH(aq) (25.0 mL of 1 M solution, 25.0 mmol) was added. The product was extracted with Et_2O (25 mL × 2), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the free base as a colourless oil (2.50 g, 60%).

Conversion to the diphenyl alcohol:

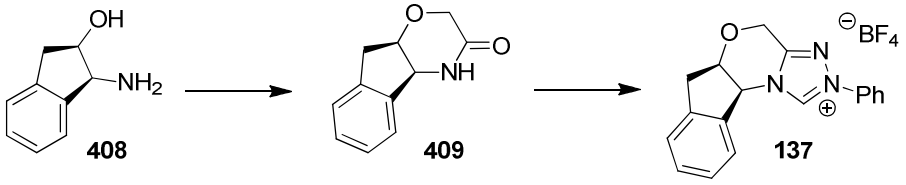
The free base (2.50 g, 13.9 mmol) was dissolved in Et_2O (25 mL). Phenylmagnesium bromide (16.3 mL of a 3.0 M in Et_2O, 48.9 mmol) was added dropwise then the mixture was heated at reflux (60 °C) for 18 h. The reaction was quenched with ice-cold H_2O (60 mL), then extracted with CH_2Cl_2 (50 mL × 2). The organic phases were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a pale yellow solid. Recrystallisation from EtOAc gave the alcohol product **404** as a colourless solid (2.58 g, 61%). **mp** 138–139 °C, lit.[201] 134–136 ºC; $\mathbf{[\alpha]_D^{20}}$ -90.0 (*c* 1.0, $CHCl_3$), lit.[201] -86.0 (*c* 1.53, CH_2Cl_2); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.69–7.66 (2H, m, Ar*H*), 7.65–7.62 (2H, m, Ar*H*), 7.37–7.30 (6H, m, Ar*H*), 7.27–7.20 (5H, m, Ar*H*), 4.21 (1H, ABX, J_{XB} 10.8, J_{XA} 2.5, C*H*NH_2), 2.68 (1H, ABX, J_{AB} 13.9, J_{AX} 2.5, PhCH_AH_B) and 2.49 (1H, ABX, J_{BA} 13.9, J_{BX} 10.8, PhCH_AH_B). Data are in accordance with the literature.[201]

To a cooled (0 ºC) solution of tertiary alcohol **404** (1.00 g, 3.30 mmol) and Hünig's base (0.575 mL, 3.30 mmol) in CH_2Cl_2 (10 mL) was added chloroacetyl chloride (0.262 mL, 3.30 mmol) dropwise. The mixture was warmed to ambient temperature over 16 h then sat $NaHCO_3$(aq) (10 mL) added and the mixture extracted with EtOAc (30 mL × 3). The organics were combined and washed with 1 M H_2SO_4(aq) (10 mL), H_2O (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude amide intermediate **405** as a cream solid which was used immediately without further purification. The product was redissolved in THF (10 mL) and cooled to 0 ºC before addition of potassium *tert*-butoxide (404 mg, 3.60 mmol), and allowed to warm to ambient temperature over 90 min before concentration *in vacuo* and partitioning between EtOAc (10 mL) and brine (10 mL). The aqueous fraction was extracted with EtOAc (15 mL × 2), then the organic fractions were

combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired morpholinone product **406** (970 mg, 86%). **mp** 187–188 ºC; $[\alpha]_D^{20}$ +15.0 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.42–7.21 (13H, m, Ph*H*), 7.11–7.09 (2H, m, Ph*H*), 5.96 (1H, br d, *J* 3.7, N*H*), 4.42–4.36 (2H, m, NHC*H* and OCH_AH$_B$), 3.94 (1H, ABd, *J* 17.2, OCH$_A$$H_B$), 2.73 (1H, ABX, J_{AB} 13.4, J_{AX} 11.2, PhCH_AH$_B$) and 2.42 (1H, ABX, J_{BA} 13.4, J_{BX} 2.7, PhCH$_A$$H_B$); δ_C (75 MHz, $CDCl_3$) 168.3 (N*C*O), 143.3 (OCPh*C*-1), 140.3 (OCPh*C*-1), 137.8 (Ph*C*-1CH$_2$), 129.5, 128.9, 128.5, 127.9, 127.6, 127.2, 126.8, 125.4, 80.1 (Ph$_2$*C*), 63.9 (CO*C*H$_2$), 57.0 (Bn*C*H) and 39.2 (Ph–*C*H$_2$); ***m/z*** MS (ESI+) 344 (100, $[M+H]^+$); HRMS (ESI+) $C_{23}H_{22}O_2N^+$ ($[M+H]^+$) requires 344.1645, found 344.1647 (+0.4 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3175 (NH), 3120, 3060, 6027, 2953, 2917, 2896, 1682 (C=O), 1603 (Ar C=C), 1493, 1448, 1413, 1323 and 1098 (C-O).

To a solution of lactam **406** (0.500 g, 1.46 mmol) in CH_2Cl_2 (5 mL) was added trimethyloxonium tetrafluoroborate (235 mg, 1.57 mmol) and the mixture stirred for 16 h. To the mixture was then added phenylhydrazine (0.143 mL, 1.46 mmol) and the mixture stirred for 20 h. The mixture was then concentrated *in vacuo* and redissolved in MeOH (1 mL) and triethyl orthoformate (4 mL). The mixture was heated at reflux (110 ºC) for 18 h then cooled to ambient temperature and concentrated *in vacuo*. The dark brown oil was redissolved in MeOH:Et_2O (1:20) and was cooled to -78 ºC to induce precipitation. The mixture was filtered rapidly and washed with cold (-78 ºC) Et_2O (5 mL) to afford the title product **407** as a brown solid (250 mg, 32%). **mp** 120 ºC; $[\alpha]_D^{20}$ +3.0 (*c* 0.5, MeOH); δ_H (300 MHz, $CHCl_3$) 9.04 (1H, s, NC*H*N), 7.53–7.30 (6H, m, Ph*H*), 7.36–7.16 (12H, m, Ph*H*), 6.98 (2H, d, *J* 6.7, Ph*H*), 6.19 (1H, ABX, J_{XA} 9.7, J_{XB} 6.0, PhCH$_2$C*H*), 5.34 (1H, ABX, J_{AB} 17.1, J_{AX} 9.7, PhCH_AH$_B$), 4.77 (1H, ABX, J_{BA} 17.1, J_{BX} 6.0, PhCH$_A$$H_B$) and 2.85–2.74 (2H, d, *J* 8.4, OCH$_2$); δ_C (75 MHz, $CHCl_3$) 148.7 (N*C*HN), 140.5 (N-*C*), 137.0 (N-*C*), 134.6 (Ph*C*), 134.4 (Ph*C*), 131.3 (Ph*C*H), 130.6 (Ph*C*H), 130.5 (Ph*C*H), 130.2 (Ph*C*H), 130.1 (Ph*C*H), 130.0 (Ph*C*H), 129.8 (Ph*C*H), 129.21 (Ph*C*H), 129.16 (Ph*C*H-4), 128.4 (Ph*C*H-4), 127.3 (*p*-Ph*C*H), 120.3 (Ph*C*H), 81.8 (*C*Ph$_2$), 60.9 (Bn*C*H), 57.5 (O*C*H$_2$) and 38.1 (Ph–*C*H$_2$); ***m/z*** MS (ESI+) 444 (100, $[M–BF_4]^+$); HRMS (ESI+) $C_{30}H_{26}N_3O^+$ ($[M–BF_4]^+$) requires 444.2070, found 444.2067 (-0.6 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3116, 3059 (Ar CH), 3028, 2920, 1597, 1576 (C=N), 1530, 1496 (Ar C=C), 1450, 1406, 1279, 1259, 1233, 1204, 1158, 1083 (br), 1052, 1031, 972, 758, 719, 703 and 680.

(5a*R*,10b*S*)-2-Phenyl-4,5a,6,10b-tetrahydroindeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]-oxazinium tetrafluoroborate 137

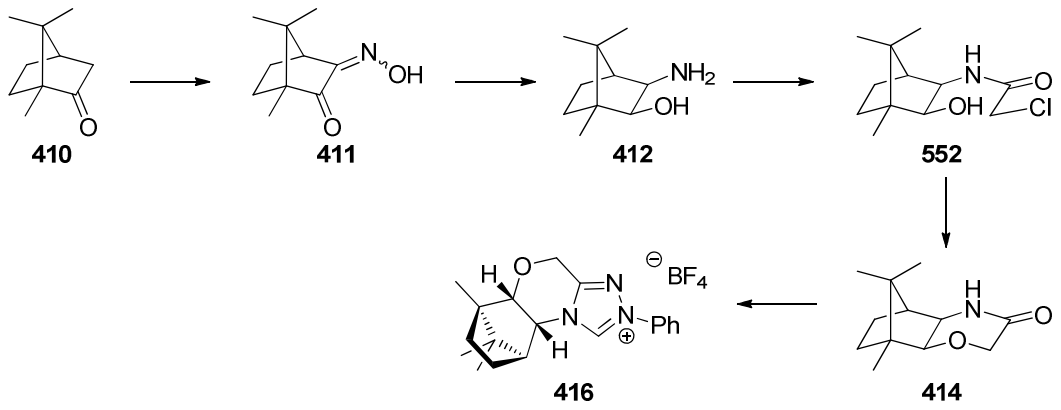


Sodium hydride (60% wt in mineral oil, 273 mg, 6.84 mmol) was suspended in hexane (10 mL) then left to stand for 5 min before removal of the supernatant *via* cannula. This procedure was repeated (× 2), then THF (100 mL) was added. The mixture was cooled to 0 ºC then (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol **408** (500 mg, 3.35 mmol) was added. The mixture was stirred for 15 min then further aminoindanol **408** (500 mg, 3.35 mmol) was added. The mixture was heated to 70 ºC for 40 min then cooled to 0 ºC before ethyl chloroacetate (0.732 mL, 6.84 mmol) was added slowly. The mixture was stirred for 30 min then heated at reflux for 2 h. After cooling to ambient temperature, the solution was washed with brine (20 mL × 2) and the aqueous layers combined and back-extracted with EtOAc (10 mL × 2). The combined organics were dried ($MgSO_4$) with vigorous stirring over 16 h then filtered and concentrated *in vacuo* to afford a pale orange/brown solid. Hexane (30 mL) was added to the crude solid and the heterogeneous mixture heated at reflux for 2 h, cooled to ambient temperature then the hexanes removed by filtration. Final trituration with cold (-78 ºC) EtOAc (10 mL) gave the morpholinone **409** as a colourless solid (799 mg, 63%). **mp**[§] 198–200 ºC decomp; $[\alpha]_D^{20}$ [§] +55.2 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.86 (1H, br d, *J* 4.4, N*H*), 7.39–7.24 (4H, m, Ar*H*), 4.78 (1H, t, *J* 4.4, *H*-4a), 4.54 (1H, t, *J* 4.4, *H*-9a), 4.17 (2H, s, CH_2-2), 3.23 (1H, dd, *J* 17.0 and 4.4, H_A-9) and 3.10 (1H, d, *J* 17.0, H_B-9); δ_C[§] (100 MHz, $CDCl_3$) 169.8 (*C*=O), 140.7 (*C*-8a), 139.2 (*C*-4b), 128.3 (*C*H-8), 127.4 (*C*H-6), 125.1 (*C*H-7), 123.9 (*C*H-5), 76.1 (*C*H-9a), 66.4 (CH_2-2), 58.6 (*C*H-4a) and 37.6 (CH_2-9). **IR**[§] ν_{max} (KBr) /cm^{-1} 3425 (br, H-bonded NH), 3183 (free NH), 2934 (C-H), 2928, 2843, 1641 (C=O), 1462 (C-H), 1372 (C-H) and 1103 (C-O). Spectroscopic data (^{1}H NMR) are in accordance with the literature.[202]

Trimethyloxonium tetrafluoroborate (213 mg, 1.44 mmol) was added to a solution of morpholinone **409** (250 mg, 1.32 mmol) in CH_2Cl_2 (8 mL) and the mixture was stirred at ambient temperature for 16 h. Phenylhydrazine (0.130 mL, 1.32 mmol) was added and stirred for 48 h before concentration *in vacuo*. The residue was dissolved in MeOH (1 mL) and triethyl orthoformate (3 mL) and heated at reflux for 16 h at 100 ºC. The precipitate was filtered and recrystallised from MeOH to afford the title compound **137** as a colourless solid (250 mg, 50%). **mp**[§] 205–207 ºC; $[\alpha]_D^{20}$ +300.4 (*c* 0.5, MeCN), lit.[147] +294.4 (*c* unspecified, MeCN); δ_H

(400 MHz, CD_3OD) 11.10 (1H, s, NC*H*N), 7.93–7.86 (2H, m, *N*Ph*H*-2,6), 7.65–7.55 (3H, m, NPh*H*-3,4), 7.52 (1H, dd, *J* 7.1 and 1.4, *H*-7), 7.33–7.22 (3H, m, *H*-8,9,10), 5.91 (1H, d, *J* 4.0, *H*-10b), 5.13 (1H, ABd, *J* 16.4, H_A-4), 4.97 (1H, ABd, *J* 16.4, H_B-4), 4.89 (1H, app t, *J* 4.3, *H*-5a), 3.36 (1H, ABX, J_{AB} 17.2, J_{AX} 4.9, H_A-6) and 3.17 (1H, obscured AB d, *J* ~17, H_B-6). Data are in accordance with the literature.[147]

(5a*S*,6*R*,9*S*,9a*R*)-6,11,11-Trimethyl-2-phenyl-5a,6,7,8,9,9a-hexahydro-4*H*-6,9-methanobenzo[*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium tetrafluoroborate 416

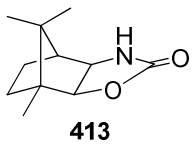


To a cooled (-40 °C) solution of potassium *tert*-butoxide (18.4 g, 103 mmol) in Et_2O (125 mL) was added D-camphor **410** (12.5 g, 82.0 mmol) in Et_2O (40 mL) dropwise over 25 min. Once addition was complete the mixture was stirred at ambient temperature for 1 h, recooled to -40 °C and isoamyl nitrite (22.0 mL, 164 mmol) was added dropwise over 30 min. The bright orange solution was warmed to ambient temperature over 16 h and then extracted with H_2O (50 mL × 3). The combined aqueous phases were acidified to pH 2 with conc. HCl (~8 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed successively with sat $NaHCO_3$(aq) (20 mL), H_2O (20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude oxime **411** as a yellow solid (19.9 g, 84%) as a ~2:1 mixture of *E*/*Z*-diastereomers which was used immediately without further purification. To a cooled (0 °C) solution of oxime **411** (12.1 g, 66.8 mmol) in THF (30 mL) was added $LiAlH_4$ (50.0 mL of a 1 M solution in THF, 100 mmol) dropwise over 30 min. After H_2 evolution had ceased, the solution was heated at reflux (80 °C) for 30 min. The solution was allowed to cool to ambient temperature, diluted with Et_2O (65 mL) and quenched with H_2O (4 mL), NaOH (10% w/v, 4 mL) and H_2O (12 mL). The mixture was filtered through celite and the filtrate was concentrated *in vacuo* to give the crude *syn*-amino alcohol product **412** (~8:1 *dr*) as a colourless solid (10.6 g, 94%) which was used immediately without further purification. To a cooled (0 °C) solution of the amino alcohol **412** (2.30 g, 13.6 mmol) and Et_3N (3.02 mL, 21.7 mmol) in CH_2Cl_2 (60 mL) was added chloroacetyl chloride (1.19 mL, 14.9 mmol) dropwise over 30 min.

The solution was warmed to ambient temperature over 16 h then recooled to 0 °C and a solution of potassium *tert*-butoxide (6.40 g, 57.0 mmol) in isopropanol (50 mL) was added over 30 min. The mixture was allowed to warm to ambient temperature and stirred for 18 h before concentration *in vacuo*. The brown residue was taken up in EtOAc (20 mL) and H_2O (30 mL) added. The product was extracted with EtOAc (20 mL × 3) and the combined organic fraction was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown solid. Chromatographic purification (50% EtOAc:petrol) gave the morpholinone **414** as a pale yellow solid (640 mg, 44%). $[\alpha]_D^{20}$ +96.1 (*c* 1.0, $CHCl_3$), lit.[203] +95.0 (*c* 1.0, $CHCl_3$); **mp**[§] 94–97 °C; δ_H (400 MHz, $CDCl_3$) 5.93 (1H, br s, N*H*), 4.12 (1H, d, *J* 15.4, CH_AH$_B$-2), 3.78 (1H, d, *J* 15.4, CH$_A$$H_B$-2), 3.65 (1H, d, *J* 6.8 C*H*-8a), 3.37 (1H, d, *J* 6.8, C*H*-4a), 1.62–1.54 (4H, m, C*H*-5, CH_2-7 and CH_AH$_B$-6), 1.13 (3H, s, (CH_3)C-8), 1.08–1.02 (1H, m, CH$_A$$H_B$-6), 0.99 (3H, s, C$H_3$) and 0.85 (3H, s, C$H_3$). Data are in accordance with the literature.[203]

To a solution of morpholinone **414** (200 mg, 0.956 mmol) in CH_2Cl_2 (20 mL) was added trimethyloxonium tetrafluoroborate (169 mg, 1.14 mmol) and the mixture was stirred for 16 h at ambient temperature. Phenylhydrazine (94.1 μL, 0.956 mmol) was added and the solution was stirred for 24 h. The mixture was then concentrated *in vacuo* and the residue triturated with Et_2O (10 mL) to give a light brown solid that was dissolved in chlorobenzene (1 mL) and triethyl orthoformate (5 mL) and then heated at reflux (125 °C) for 12 h. The mixture was concentrated *in vacuo* then triturated with Et_2O (10 mL) to afford the title product **416** as a colourless solid (75.9 mg, 20%). $[\alpha]_D^{20}$ +28.8 (*c* 0.5, $CHCl_3$), lit.[203] +29.4 (*c* 1.0, $CHCl_3$); **mp**[§] 191–192 °C; δ_H (300 MHz, $CDCl_3$) 10.28 (1H, s, NC*H*N), 7.91–7.89 (2H, m, Ar*H*), 7.55–7.52 (3H, m, Ar*H*), 5.07 (1H, d, *J* 15.1, C*H*O), 4.67 (1H, d, *J* 15.1, C*H*N), 4.48 (1H, d, *J* 7.0 C*H*), 4.08 (1H, d, *J* 7.0, CH_2), 2.66 (1H, d, *J* 4.5 CH_2), 1.96–1.84 (1H, m, CH_2), 1.68–1.58 (1H, m, CH_2), 1.39–1.24 (1H, m, CH_2), 1.03 (3H, s, CH_3), 0.88 (3H, s, CH_3) and 0.66 (3H, s, CH_3). Data are in accordance with the literature.[203]

(3a*S*,4*S*,7*R*,7a*R*)-7,8,8-Trimethylhexahydro-4,7-methanobenzo[*d*]oxazol-2(3*H*)-one 413

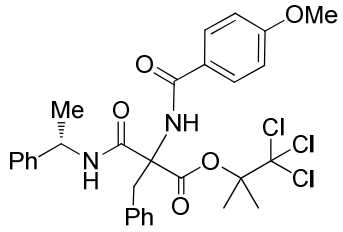


413

To a cooled (0 °C) solution of the crude amino alcohol **412** (see above, p 196) (1.50 g, 8.87 mmol) and Et_3N (2.47 mL, 17.7 mmol) in CH_2Cl_2 (40 mL) was added triphosgene (1.04 g, 3.53 mmol). The mixture was stirred at ambient temperature for 16 h and then washed with NH_4Cl(aq) (30 mL) and brine (30 mL). The combined aqueous phases were combined and

extracted with EtOAc (30 mL × 2). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a brown solid. Chromatographic purification (40% EtOAc:petrol) gave the product **413** as a colourless solid (919 mg, 53%); **mp** 137–138 °C, lit.[204] 138–140 °C; $[\alpha]_D^{20}$ -37.1 (*c* 1.0, CH_2Cl_2), lit.[204] -33 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 6.06 (1H, br s, N*H*), 4.38 (1H, d, *J* 8.1, C*H*-7a), 3.76 (1H, dd, *J* 8.1, 1.1, C*H*-3a), 1.85 (1H, app d, *J* 4.6, C*H*-4), 1.75–1.65 (1H, m, CH_AH_B-6), 1.58–1.53 (1H, m, CH_AH_B-6), 1.08 (3H, s, (CH_3)C-7), 1.03 (3H, s, CH_3), 0.99–0.95 (2H, m, CH_2-5) and 0.89 (3H, s, CH_3). Data are in accordance with the literature.[204]

1,1,1-Trichloro-2-methylpropan-2-yl 2-benzyl-2-(4-methoxybenzamido)-3-oxo-3-(((*S*)-1-phenylethyl)amino)propanoate 553



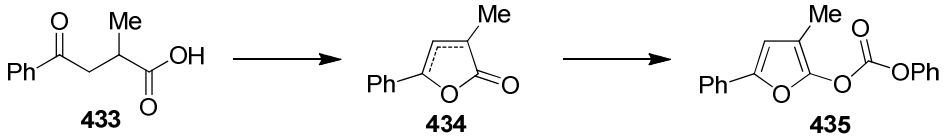
553

To a solution of (racemic) rearrangement product **272** (100 mg, 0.206 mmol) in CH_2Cl_2 (2 mL) was added DMAP (2.52 mg, 20.6 μmol) followed by (*S*)-α-methylbenzylamine (26.6 μL, 0.206 mmol). The mixture was stirred for 16 h then diluted with CH_2Cl_2 (5 mL) and quenched with NH_4Cl(aq) (8 mL). The product was extracted with EtOAc (5 mL × 3) and the organic fractions combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. In the case of the reaction with the racemic *C*-carboxyazlactone, chromatographic purification (30% EtOAc:petrol) gave the product **553** as a pale yellow oil (88.7 mg, 71%) as a 50:50 mixture of diastereomers. δ_H (300 MHz, $CDCl_3$) 7.73 (2H, d, *J* 2.5, MeOArC*H*-3,5), 7.70 (2H, d, *J* 2.5, MeOArC*H*-3,5), 7.58 (1H, s, CON*H*), 7.49 (1H, s, CON*H*), 7.46–7.38 (5H, m, Ph*H*), 7.36–7.25 (9H, m, Ph*H*), 7.17–7.13 (3H, m, Ph*H*), 7.08–7.03 (2H, m, Ph*H*), 6.90–6.95 (4H, m, MeOArC*H*-2,6), 6.79–6.76 (2H, m, Ph*H*), 6.54 (1H, d, *J* 8.0, CON*H*), 6.47 (1H, d, *J* 7.8, CON*H*), 5.22–5.10 (2H, m, PhC*H*(Me)), 4.03 (1H, ABd, *J* 14.1, PhCH_AH_B), 3.95 (1H, ABd, *J* 14.1, PhCH_AH_B), 3.88 (6H, s, OCH_3), 3.54 (1H, ABd, *J* 14.1, PhCH_AH_B), 3.39 (1H, ABd, *J* 14.1, PhCH_AH_B), 2.04 (3H, s, C(CH_3)$_2$CCl_3), 2.02 (3H, s, C(CH_3)$_2$CCl_3), 1.90 (3H, s, C(CH_3)$_2$CCl_3), 1.79 (3H, s, C(CH_3)$_2$CCl_3), 1.65 (3H, d, *J* 7.0, CH(CH_3)) and 1.57 (3H, d, *J* 6.9, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 168.0 (*C*=O), 166.04 (MeOAr*C*-1), 166.00 (MeOAr*C*-1), 164.8 (*C*=O), 164.6 (*C*=O), 162.5 (*C*=O), 142.0 (CH(Me)Ph*C*-1), 141.8 (CH(Me)Ph*C*-1), 134.9 (Ph*C*-1), 134.5 (Ph*C*-1), 130.2 (Ar*C*H), 130.1 (Ar*C*H), 129.1 (Ar*C*H), 128.9 (Ar*C*H), 128.4 (Ar*C*H), 128.2 (Ar*C*H), 128.0 (Ar*C*H), 127.5 (Ar*C*H), 127.2 (Ar*C*H), 126.8 (Ar*C*H), 126.3

(Ar*C*H), 126.2 (MeOAr*C*-4), 113.9 (MeOAr*C*H-2,6), 105.9 (*C*Cl_3), 90.8 (O*C*Me_2), 90.6 (O*C*Me_2), 67.6 (*C*$R_2(CO)_2$), 67.5 (*C*$R_2(CO)_2$), 55.5 (O*C*H_3), 50.1 (Ph*C*H(Me)), 49.8 (Ph*C*H(Me)), 39.2 (Ph–*C*H_2), 39.0 (Ph–*C*H_2), 21.2 (*C*H_3), 21.1 (*C*H_3), 21.0 (*C*H_3) and 20.8 (*C*H_3); ***m/z*** MS (ESI+) 605 (100, ([{$^{35}Cl_3$}M+H]$^+$), 607 (97, [{$^{35}Cl_2{}^{37}Cl$}M+H]$^+$), 609 (30, [{$^{35}Cl^{37}Cl_2$}M+H]$^+$) and 611 (4, ([{$^{37}Cl_3$}M+H]$^+$); HRMS (ESI+) $C_{30}H_{32}Cl_3N_2O_5^+$ ([{$^{35}Cl_3$}M+H]$^+$) expected 605.1371, found 605.1369 (-0.3 ppm); **IR** ν_{max} (thin film) /cm^{-1} 3375, 3087, 3064, 3031, 2975, 2930, 1741 (br d, C=O),1685 (br d, C=O), 1654 (d, C=O), 1607 (Ar C=C), 1522, 1477,1257 (C-O) and 705 (C-Cl).

^{1}H NMR Spectroscopic analysis (400 MHz) of the crude reaction product was used to determine the *ee* of the rearrangement using chiral NHCs.

3-Methyl-5-phenylfuran-2-yl phenyl carbonate 435

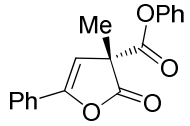


A mixture of 2-methyl-4-oxo-4-phenylbutyric acid **433** (3.00 g, 15.6 mmol), Ac_2O (3.95 mL, 41.8 mmol) and AcOH (5.14 mL, 89.8 mmol) were heated at 100 ºC for 3 h then concentrated *in vacuo* to afford the crude product as a pale yellow oil. Addition of toluene and concentration *in vacuo* (× 3) to remove the remainder of the Ac_2O and AcOH gave the desired 3*H*- and 5*H*-butenolide products **434** (2.72 g, quantitative, 65:35 ratio of tautomers) as a yellow oil which partially solidified on standing. The crude products were sufficiently pure to be used without further purification. Major (3*H*-) tautomer: δ_H (400 MHz, $CDCl_3$) 7.58–7.32 (4H, m, Ph*H*-3,5), 7.31 (1H, m, Ph*H*-4), 5.60 (1H, d, *J* 2.7, C=C*H*), 3.52 (1H, qd, *J* 7.6, 2.7, CH_3CH) and 1.48 (3H, d, *J* 7.6, CH_3); Minor (5*H*-) tautomer: δ_H (400 MHz, $CDCl_3$) 7.65–7.57 (2H, m, Ph*H*-2,6), 7.58–7.32 (3H, m, Ph*H*-3,5 and C=C*H*), 7.17–7.13 (1H, m, Ph*H*-4), 5.91 (1H, quint, *J* 1.9, C*H*Ph) and 2.03 (3H, t, *J* 1.9, CH_3). Data are in accordance with the literature.[27]

To a solution of diisopropylamine (2.87 mL, 20.5 mmol) in THF (25 mL), cooled to 0 ºC, was added *n*-BuLi (7.87 mL of a 2.5 M solution in hexanes, 19.7 mmol). The mixture was stirred for 15 min then cooled to -78 ºC before addition of a solution of the butenolide mixture **434** (2.72 g, 15.6 mmol) in THF (20 mL). The dienolate solution immediately became an intense red colour and was stirred for 30 min at -78 ºC. The dienolate solution was then added dropwise to a solution of phenyl chloroformate (2.55 mL, 20.3 mmol) in THF (15 mL) at -78 ºC then allowed to warm to ambient temperature. The mixture was poured into 0.5 M HCl(aq) (100 mL) and extracted with Et_2O (40 mL × 3). The organics were combined, washed with brine (30 mL),

dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a viscous orange oil. Chromatographic purification (5% Et_2O:petrol) afforded the title product as a colourless solid (2.07 g, 64%). **mp**[§] 96–98 ºC; δ_H (400 MHz, $CDCl_3$) 7.59 (2H, dt, *J* 8.3, 1.5, CPh*H*-2,3), 7.46–7.41 (2H, m, Ph*H*), 7.38–7.34 (2H, m, Ph*H*), 7.32–7.28 (3H, m, Ph*H*), 7.28–7.22 (1H, m, Ph*H*), 6.52 (1H, s, furan*H*-4) and 2.02 (3H, s, CH_3). Spectroscopic data are in accordance with the literature.[107]

(*RS*) and (*S*)-Phenyl 3-methyl-2-oxo-5-phenyl-2,3-dihydrofuran-3-carboxylate 436



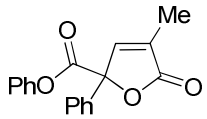
436

Procedures F, H, M and V have been employed to obtain the product.

To a solution of furanyl carbonate **435** (100 mg, 0.340 mmol) in THF (1 mL) was added chiral isothiourea **312** (10.5 mg, 34.0 μmol, 10 mol%). After 60 min, the mixture was concentrated *in vacuo*. Chromatographic purification (20% Et_2O:petrol) gave the product as a colourless oil that solidified on standing (70.1 mg, 70%). **mp**[§] 61 ºC; $[\alpha]_D^{20}$ +65.0 (*c* 0.20, CH_2Cl_2, 95% *ee*). Spectroscopic data are in agreement with the literature.[205]

Chiral HPLC Chiralpak AS-H (5% IPA:hexane, flow rate 1 mL min^{-1}) t_R(*S*) 13.7 min, t_R(*R*) 16.0 min, 95% *ee*. Absolute configuration confirmed by comparitive reaction with (*R*)-TADMAP according to Vedejs.[205] Furanyl carbonate **435** (29.4 mg, 0.100 mmol) and (*R*)-TADMAP **238** (4.37 mg, 10.0 μmol) were dissolved in CH_2Cl_2 (1.0 mL) and allowed to stir for 24 h, then quenched with methyl iodide (0.1 mL) and concentrated *in vacuo*. ^{1}H NMR Spectroscopic analysis of the crude mixture indicated a ~60:40 mixture of α- and γ–carboxybutenolide products **436** and **437**. Chromatographic purification (20% Et_2O:petrol) gave the (major) product **436** as a colourless solid (15.1 mg, 49%, 85% *ee*, (*S*)-absolute configuration for the major enantiomer).

Phenyl 4-methyl-5-oxo-2-phenyl-2,5-dihydrofuran-2-carboxylate 437

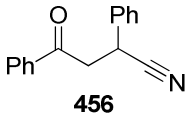


437

Procedures F, H, M and V have been employed to obtain the product.

According to procedure F, to a solution of triazolium salt **128** (1.41 mg, 6.80 μmol) in THF (1 mL) was added KHMDS (12.2 μL of a 0.5 M solution in toluene, 6.12 μmol) and the mixture stirred for 10 min. A solution of furanyl carbonate **435** (200 mg, 0.680 mmol) in THF (1 mL) was added. After 5 min, the mixture was concentrated *in vacuo*. Chromatographic purification (20% Et_2O:petrol) gave the product as a colourless oil (170 mg, 85%). δ_H (400 MHz, $CDCl_3$) 7.58–7.55 (3H, m, OPh*H*-3,5), 7.44–7.39 (3H, m, Ph*H*), 7.34–7.30 (2H, m, Ph*H*), 7.20–7.18 (1H, m, OPh*H*-4), 7.00–6.98 (2H, m, OPh*H*-2,6) and 1.99 (3H, s, CH_3). Data are in accordance with the literature.[205]

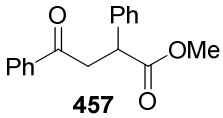
4-Oxo-2,4-diphenylbutyronitrile 456



456

To a slurry of chalcone (2.08 g, 10.00 mmol) in acetone (5 mL) was added acetone cyanohydrin (0.530 g, 6.25 mmol), followed by tetrabutylammonium hydroxide(aq) (0.140 mL of a 40% w/v solution, 6.25 mmol). The mixture was heated at 100 ºC for 2 h then cooled to ambient temperature. H_2O (3 mL) was added to the mixture to induce precipitation of the product. The precipitate was collected by filtration and then washed with H_2O (25 mL), then recrystallised from EtOH (25 mL) as a colourless solid (1.21 g, 82%). **mp** 124–126 ºC, lit.[206] 122–125 ºC; δ_H (400 MHz, $CDCl_3$) 7.88–7.84 (1H, m, C(O)Ph*H*-2,6), 7.65–7.54 (1H, m, C(O)Ph*H*-4), 7.51–7.27 (8H, m, Ph*H*), 4.51 (1H, ABX, J_{XA} 7.9, J_{XB} 6.0, (NC)C*H*Ph), 3.64 (1H, ABX, J_{AB} 18.0, J_{AX} 7.9, PhC(O)CH_AH$_B$) and 3.46 (1H, ABX, J_{BA} 18.0, J_{BX} 6.0, PhC(O)CH$_A$$H_B$). Data are in accordance with the literature.[206]

Methyl 4-oxo-2,4-diphenylbutyrate 457

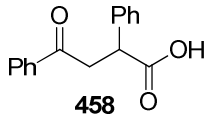


457

To a mixture of 4-oxo-2,4-diphenylbutyronitrile **456** (1.00 g, 4.25 mmol) in methanol (10 mL) was added conc. HCl(aq) (10 mL). The mixture was heated at reflux for 64 h then cooled to

ambient temperature. The mixture was extracted with Et_2O (15 mL × 3) then concentrated *in vacuo* to afford the product as a colourless solid (1.06 g, 93%). Product was used without further purification. **mp** 104–106 ºC, lit.[207] 103–104 ºC; δ_H (400 MHz, $CDCl_3$) 7.92–7.88 (2H, m, C(O)Ph*H*-2,6), 7.53–7.47 (1H, m, C(O)Ph*H*-4), 7.44–7.09 (7H, m, Ph*H*), 4.12 (1H, ABX, J_{XA} 7.9, J_{XB} 6.0, (NC)C*H*Ph), 3.83 (1H, ABX, J_{AB} 18.0, J_{AX} 7.9, PhC(O)CH_AH_B), 3.56 (3H, s, COOCH_3) and 3.27 (1H, ABd, ABX, J_{BA} 18.0, J_{BX} 6.0, PhC(O)CH_AH_B). Data are in accordance with the literature.[207]

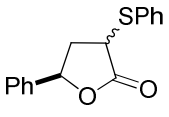
4-Oxo-2,4-diphenylbutyric acid 458



458

A mixture of methyl oxo-butyrate **457** (970 mg, 3.61 mmol), $CHCl_3$ (20 mL) and conc. HCl(aq) (20 mL) was heated at 100 ºC for 72 h. The mixture was concentrated *in vacuo* to remove the $CHCl_3$, and the acid precipitate was collected by filtration. The product was washed with Et_2O (10 mL) and H_2O (10 mL) to afford the product as a colourless solid (681 mg, 70%). **mp** 150–152 ºC, lit.[207] 152–153 ºC; δ_H (400 MHz, $CDCl_3$) 10.45 (1H, br s, COO*H*), 7.91–7.89 (2H, m, C(O)Ph*H*-2,6), 7.48–7.14 (8H, m, Ph*H*), 4.25 (1H, ABX, J_{XA} 8.0, J_{XB} 6.0, (NC)C*H*Ph), 3.87 (1H, ABX, J_{AB} 18.0, J_{AX} 8.0, PhC(O)CH_AH_B) and 3.21 (3H, ABd, ABX, J_{BA} 18.0, J_{BX} 6.0, PhC(O)CH_AH_B). Data are in accordance with the literature.[207]

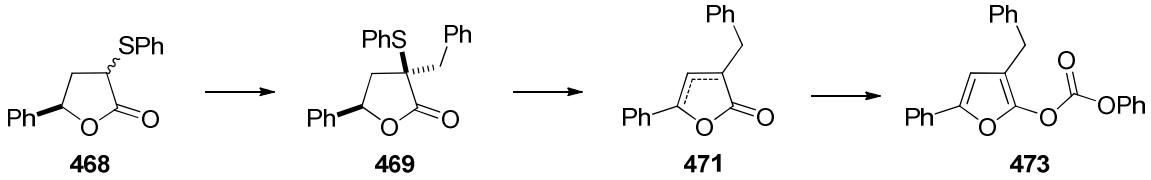
(3*RS*,5*RS*)-5-Phenyl-3-(phenylthio)dihydrofuran-2(3*H*)-one 468



468

Following general procedure R, *n*-BuLi (105 mL, 263 mmol), diisopropylamine (36.6 mL, 261 mmol), THF (380 mL), (phenylthio)acetic acid (20.0 g, 119 mmol) in THF (100 mL) and styrene oxide (16.3 mL, 143 mmol), followed by *p*TSA•H_2O (200 mg, 1.16 mmol) and toluene (200 mL) gave the desired crude lactone **468** as a colourless solid (22.3 g, 69%) as a mixture of diastereomers (~1–2:1 *dr*). Product was treated as an intermediate and was used immediately in subsequent steps.

3-Benzyl-5-phenylfuran-2-yl phenyl carbonate 473



468 **469** **471** **473**

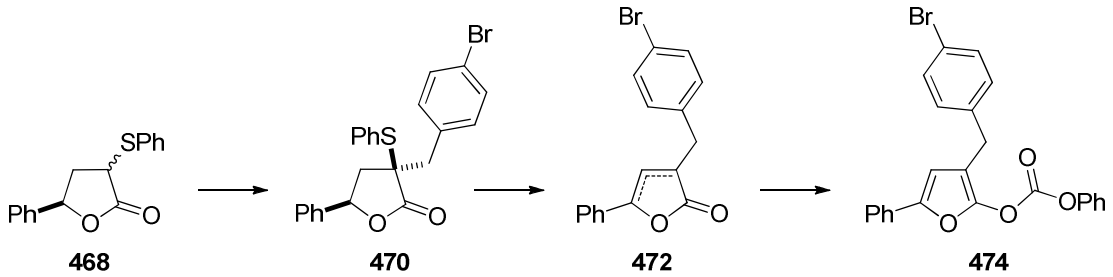
Following general procedure S, *n*-BuLi (11.6 mL, 28.9 mmol), diisopropylamine (3.41 mL, 24.4 mmol), THF (50 mL), lactone **468** (6.00 g, 22.2 mmol) in THF (25 mL) and benzyl bromide (16.3 mL, 143 mmol) in DMPU (13 mL) gave the crude alkylated product **469**. Chromatographic purification (20% → 30% Et_2O:petrol) gave the alkylated lactone **469** as a colourless solid (6.40 g, 80%) as a mixture of diastereomers (15:1 *dr*). **mp** 110–112 ºC; Data for the major diastereomer: δ_H (400 MHz, $CDCl_3$) 7.63 (2H, dt, *J* 8.2, 1.7, Ph*H*), 7.49–7.44 (1H, m, Ph*H*), 7.41–7.31 (7H, m, Ph*H*), 7.22–7.17 (1H, m, Ph*H*), 7.15–7.11 (2H, m, Ph*H*), 6.61–6.58 (2H, m, SPh*H*-2,6), 4.02 (1H, ABX, J_{XB} 8.9, J_{XA} 7.5, OC*H*), 3.47 (2H, ABd, *J* 13.2, PhCH_AH_B), 3.01 (1H, ABd, *J* 13.2, PhCH_AH_B), 2.80 (1H, ABX, J_{AB} 14.1, J_{AX} 7.5, CHCH_AH_B) and 2.33 (1H, dd, J_{BA} 14.1, J_{BX} 8.9, CHCH_AH_B); δ_C (75 MHz, $CDCl_3$) 177.6 (*C*=O), 139.4 (Ph*C*-1), 137.8 (SPh*C*H-3), 135.6 (CH_2Ph*C*-1), 130.6 (SPh*C*-1), 130.5 (CH_2Ph*C*-2), 130.4 (Ar*C*H), 129.8 (Ar*C*H), 129.4 (Ar*C*H), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 128.3 (Ph*C*H-4), 126.0 (SPh*C*H-2), 78.2 (*C*H-5), 58.4 (*C*-3), 43.7 (Ph–*C*H_2) and 40.9 (*C*H_2-4); **IR** ν_{max} (KBr) /cm^{-1} 2978, 1770 (C=O), 1488, 1439, 1172 (C-O), 1070, 980, 752 and 697; Structure confirmed by X-ray crystallographic analysis (see Appendix).

Following general procedure T, benzylated lactone **469** (1.50 g, 4.16 mmol), *m*CPBA (970 mg, 5.30 mmol) and $CHCl_3$ (6 mL), followed by heating in toluene (10 mL) gave the crude butenolide product as a yellow oily solid. Chromatographic purification (10% Et_2O:petrol) gave the desired butenolides **471** as a colourless solid (544 mg, 52%) as a mixture of butenolide tautomers (~3:1). **mp** 68–70 ºC; Data for the major (5*H*-) tautomer: δ_H (400 MHz, $CDCl_3$) 7.48–7.24 (10H, m, Ph*H*), 6.94 (1H, q, *J* 1.9, C*H*=C), 5.90 (1H, q, *J* 1.9, O*C*H), 3.70 (1H, ABd, *J* 1.9, PhCH_AH_B) and 3.69 (1H, ABd, *J* 1.9, PhCH_AH_B); Data for the minor (3*H*-) tautomer: δ_H (400 MHz, $CDCl_3$) 7.68 (1H, t, *J* 2.9, Ph*C*H-4), 7.55–7.51 (2H, m, Ph*H*), 7.48–7.43 (2H, m, Ph*H*), 7.42–7.24 (5H, m, Ph*H*), 5.65 (1H, dd, *J* 8.3, 6.0, C=C*H*), 3.77–3.72 (1H, m, PhCH_AH_B) and 3.20 (1H, ddd, *J* 17.5, 6.0, 3.0, PhCH_AH_B).

Following general procedure U, butenolides **471** (200 mg, 0.800 mmol), Et_3N (0.112 mL, 0.800 mmol), MeCN (2 mL) and phenyl chloroformate (0.100 mL, 0.800 mmol) gave, after chromatographic purification (5% Et_2O:petrol), the carbonate product **473** as a colourless solid (178 mg, 60%). **mp** 95–96 ºC; δ_H (400 MHz, $CDCl_3$) 7.58 (2H, dt, *J* 8.3, 1.5, Ph*H*), 7.45–7.40

(3H, m, Ph*H*), 7.37–7.22 (10H, m, Ph*H*), 6.46 (1H, s, furan*H*-4) and 3.78 (2H, s, PhCH_2); **δ_C** (100 MHz, $CDCl_3$) 151.0 (OPh*C*-1), 150.7 (*C*=O), 147.6 (furan*C*-5), 146.4 (furan*C*-1), 139.2 (CH_2Ph*C*-1), 130.2 (4-Ph*C*-1), 129.8 (Ph*C*H), 129.7 (Ph*C*H), 128.83 (Ph*C*H), 128.76 (Ph*C*H), 128.75 (Ph*C*H), 128.72, (Ph*C*H) 127.6 (Ph*C*H), 126.8 (Ph*C*H), 126.6 (Ph*C*H), 126.5 (Ph*C*H), 123.5 (Ph*C*H), 121.1 (Ph*C*H), 120.8 (Ph*C*H), 108.8 (furan*C*-3), 107.8 (furan*C*H-4) and 30.0 (Ph–*C*H_2); ***m/z*** MS (ESI+) 371 (100, $[M+H]^+$); HRMS (ESI+) $C_{24}H_{19}O_4^+$ ($[M+H]^+$) requires 371.1278, found 371.1279 (+0.3 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3063 (Ar-H), 2924, 2858, 1796 (C=O), 1656 (Ar-H), 1648 (Ar C=C), 1218 (C-O), 1194 (C-O), 1115, 1052 and 760 (furan CH).

3-(4-Bromobenzyl)-5-phenylfuran-2-yl phenyl carbonate 474



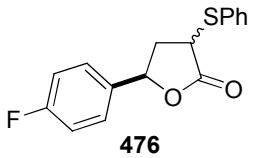
Following general procedure S, *n*-BuLi (5.56 mL, 13.9 mmol), diisopropylamine (1.71 mL, 12.2 mmol), THF (25 mL), lactone **468** (3.00 g, 11.1 mmol) in THF (5 mL) and 4-bromobenzyl bromide (2.78 g, 11.1 mmol) in DMPU (6.7 mL) gave the crude alkylated product. Chromatographic purification (25% Et_2O:petrol) gave the desired alkylated lactone **470** as a colourless solid (3.00 g, 62%) as a mixture of diastereomers (15:1 *dr*). **mp** 126–127 ºC; Data for the major diastereomer: **δ_H** (400 MHz, $CDCl_3$) 7.62–7.59 (2H, m, Ar*H*), 7.51–7.45 (3H, m, Ar*H*), 7.41–7.37 (2H, m, Ar*H*), 7.22–7.15 (5H, m, Ar*H*), 6.69–6.66 (2H, m, Ar*H*), 4.26 (1H, app t, *J* 8.0, OC*H*), 3.39 (1H, ABd, *J* 13.4, ArCH_AH_B), 2.99 (1H, ABd, *J* 13.4, ArCH_AH_B), 2.77 (1H, ABX, J_{AB} 14.2, J_{AX} 7.6, CH_AH_B-4) and 2.35 (1H, ABX, J_{BA} 14.2, J_{BX} 8.6, CH_AH_B-4); **δ_C** (100 MHz, $CDCl_3$) 176.9 (*C*=O), 139.0 (Ph*C*-1), 137.5 (Ar*C*H), 134.3 (BrAr*C*-1), 132.2 (Ar*C*H), 131.9 (Ar*C*H), 130.2 (Ar*C*H), 130.0 (SPh*C*-1), 129.5 (Ar*C*H), 128.62 (Ar*C*H), 128.58 (Ar*C*H), 125.6 (BrAr*C*-4), 77.8 (*C*H-5), 57.5 (*C*-3), 42.7 (Ar–*C*H_2) and 40.4 (*C*H_2-4); ***m/z*** MS (ESI+) 456 (97, $[\{^{79}Br\}M+NH_4]^+$) and 458 (100, $[\{^{81}Br\}M+NH_4]^+$); HRMS (ESI+) $C_{23}H_{19}{}^{79}BrSO_2^+$ ($[\{^{79}Br\}M+NH_4]^+$) requires 456.0627, found 456.0627 (-0.7 ppm); **IR** ν_{max} (KBr) /cm^{-1} 2977, 1769 (C=O), 1488, 1439, 1405, 1326, 1237, 1218, 1164 (C-O), 1072, 1043, 1027, 1012, 984, 752 and 696.

Following general procedure T, lactone **470** (2.70 g, 6.15 mmol), *m*CPBA (1.44 g, 8.36 mmol) and CH_2Cl_2 (8 mL), followed by heating in toluene (10 mL) gave the crude butenolide as a yellow solid. Chromatographic purification (15% Et_2O:petrol) gave the desired butenolides **472**

as a yellow solid (1.46 g, 72%) as a mixture of tautomers (4:1 ratio). **mp** 80–81 ºC**;** Data for major (5*H*-) tautomer: δ_H (400 MHz, $CDCl_3$) 7.49–7.46 (2H, m, Ar*H*), 7.42–7.36 (3H, m, Ar*H*), 7.25–7.23 (2H, m, Ar*H*), 7.15–7.18 (3H, m, Ph*H*), 6.97 (1H, q, *J* 1.7, =C*H*), 5.91 (1H, q, *J* 1.7, OC*H*) and 3.65 (2H, br app d, *J* 1.7, ArCH_2). Product used without further purification.

Following general procedure U, butenolides **472** (448 mg, 1.36 mmol), Et_3N (0.378 mL, 2.72 mmol), THF (3 mL) and phenyl chloroformate (0.341 mL, 2.72 mmol) gave, after chromatographic purification (5% Et_2O:petrol), the carbonate product **474** as a colourless solid (354 mg, 58%). **mp** 92 ºC; δ_H (400 MHz, $CDCl_3$) 7.58–7.56 (2H, m, BrAr*H*-3,5), 7.44–7.40 (4H, m, Ar*H*), 7.37–7.33 (2H, m, Ar*H*), 7.31–7.22 (4H, m, Ar*H*), 7.16–7.13 (2H, m, BrAr*H*-2,6), 6.42 (1H, s, furan*H*-4) and 3.71 (2H, s, CH_2); δ_C (100 MHz, $CDCl_3$) 150.8 (OPh*C*-1), 150.6 (*C*=O), 147.7 (furan*C*-5), 146.4 (furan*C*-2), 138.1 (BrAr*C*-4), 131.7 (Ar*C*H), 130.6 (Ar*C*H), 130.0 (CPh*C*-1), 129.8 (Ar*C*H), 128.8 (Ar*C*H), 127.7 (Ar*C*H), 126.8 (Ar*C*H), 123.5 (Ar*C*H), 120.7 (OPh*C*H-2,6), 120.4 (BrAr*C*-1), 108.2 (furan*C*-3), 107.5 (furan*C*H-4) and 29.5 (*C*H_2); ***m/z*** MS (ESI+) 346 (97, [{^{79}Br}M+NH_4–PhOCO]$^+$), 348 (100, [{^{81}Br}M+NH_4–PhOCO]$^+$); HRMS (ESI+) $C_{17}H_{17}{}^{81}BrNO_2^+$ ([{^{81}Br}M+NH_4–PhOCO]$^+$) requires 348.0417, found 348.0416, (-0.2 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3062 (ArH), 2924, 2858, 1797 (C=O), 1655 (ArH), 1648 (ArH), 1606 (ArH), 1594 (ArH), 1556 (ArH), 1488, 1405, 1216 (C-O), 1194 (C-O), 1114, 1072 (ArC-Br), 1053, 1011, 930 and 760 (furan CH).

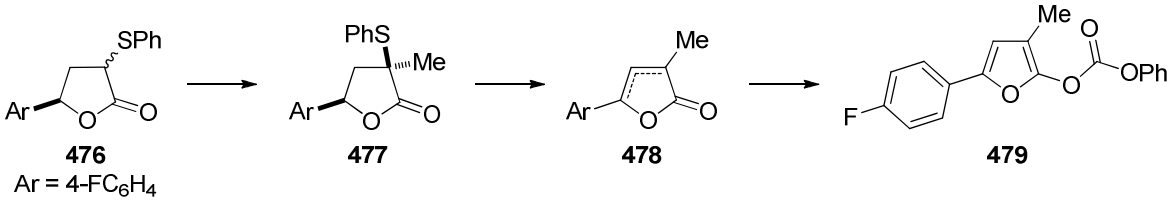
(3*RS*,5*RS*)-5-(4-Fluorophenyl)-3-(phenylthio)dihydrofuran-2(3*H*)-one 476



476

Following general procedure R, *n*-BuLi (15.3 mmol), diisopropylamine (2.17 mL, 15.4 mmol), THF (20mL), (phenylthio)acetic acid (1.18 g, 7.03 mmol) in THF (6 mL) and 4-fluorostyrene oxide (1.00 mL, 8.43 mmol), followed by *p*TSA•H_2O (50.0 mg, 0.290 mmol), toluene (30 mL) and $MgSO_4$ (~5 g) gave the desired product as a colourless solid (1.46 g, 72%) as a mixture of diastereomers (~1–2:1 *dr*). Product was treated as an intermediate and was used immediately in subsequent steps.

5-(4-Fluorophenyl)-3-methylfuran-2-yl phenyl carbonate 479



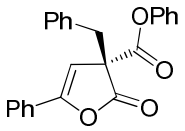
Following general procedure S, *n*-BuLi (4.28 mmol), diisopropylamine (0.510 mL, 3.62 mmol), THF (8 mL), lactone **476** (950 mg, 3.30 mmol) in THF (3 mL) methyl iodide (0.205 mL, 11.1 mmol) in DMPU (2.0 mL), the crude alkylated product was obtained. Chromatographic purification (30% Et_2O:petrol) gave the desired lactone **477** as a colourless solid (545 mg, 55%) as a mixture of diastereomers (10:1 *dr*). **mp** 42–42 ºC. Data for the major diastereomer: δ_H (300 MHz, $CDCl_3$) 7.61–7.57 (2H, m, SPh*H*), 7.47–7.34 (3H, m, Ar*H*), 6.98–6.88 (4H, m, Ar*H*), 5.31 (1H, ABX, J_{XB} 9.0, J_{XA} 7.0, OC*H*), 2.61 (1H, ABX, J_{AB} 13.7, J_{AX} 7.0, CH_AH_B), 2.37 (1H, ABX, J_{BA} 13.7, J_{BX} 9.0, CH_AH_B) and 1.67 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 177.3 (*C*=O), 162.8 (d, *J* 248, *C*-F), 137.2(SPh*C*H-3,5), 134.7 (d, *J* 2.8, FAr*C*-4), 130.5 (SPh*C*H-4), 130.0 (SPh*C*-1), 129.4 (SPh*C*H-2,6), 127.6 (d, *J* 8.3, FAr*C*H-3,5), 115.8 (d, *J* 21.7, FAr*C*H-2,6), 76.7 (*C*H-O), 52.9 (PhS*C*Me), 44.1 (CH_2), and 23.8 (CH_3); δ_F (282 MHz, $CDCl_3$) -113.5 (Ar-*F*); ***m/z*** MS (ESI^+) 320 (100, $[M+NH_4]^+$); HRMS (ESI^+) $C_{17}H_{15}FO_2S^+$ ($[M+NH_4]^+$) requires 320.1115, found 320.1118 (+0.9 ppm); **IR** ν_{max} (KBr) /cm^{-1} 2977, 1769 (C=O), 1488, 1439, 1405, 1326, 1237, 1218, 1164 (C-O), 1072, 1043, 1027, 1012, 984, 752 and 696.

Following general procedure T, the methylated lactone **477** (543 mg, 1.80 mmol), *m*CPBA (488 mg, 1.98 mmol) and $CHCl_3$ (10 mL), gave the crude sulfoxide, which was heated in toluene (10 mL). Chromatographic purification (30% Et_2O:petrol) gave the desired butenolides **478** as a colourless oil (205 mg, 59%) as a mixture of tautomers (4:1); Data for major (5*H*-) tautomer: δ_H (400 MHz, $CDCl_3$) 7.26–7.21 (2H, m, FAr*H*-3,5), 7.11–7.03 (3H, m, FAr*H*-2, C*H*=C), 5.85 (1H, app t, *J* 1.8, OC*H*) and 2.00 (1H, t, *J* 1.8, CH_3); δ_C (75 MHz, $CDCl_3$) 174.6 (*C*=O), 163.6 (d, *J* 238, FAr*C*-1), 148.3 (*C*H=CMe), 131.4 (FAr*C*-4), 130.5 (CH=*C*Me), 128.8 (d, *J* 9, FAr*C*H-3,5), 116.3 (FAr*C*H-2,6), 81.8 (O*C*H) and 11.0 (CH_3); δ_F (282 MHz, $CDCl_3$) -112.6 (Ar-*F*); ***m/z*** MS (ESI+) 193 (100, $[M+H]^+$); HRMS (ESI+) $C_{11}H_{10}O_2F^+$ ($[M+H]^+$) requires 193.0659, found 193.0657 (-0.7 ppm); **IR** ν_{max} (thin film) /cm^{-1} 2924, 2852, 1760 (C=O), 1606 (Ar C=C), 1509 (C=C), 1226 and 1087 (C-F and C-O), 959, 881, 838 and 786.

To a solution of diisopropylamine (0.710 mL, 5.08 mmol) in THF (15 mL), cooled to 0 ºC, was added *n*-BuLi (2.03 mL of a 2.5 M solution in hexanes, 5.08 mmol). The mixture was stirred for 15 min then cooled to -78 ºC before addition of a solution of the butenolides **478** (750 mg, 3.91 mmol) in THF (15 mL). The dienolate solution immediately became an intense red colour

and was stirred for 30 min at -78 ºC. The dienolate solution was then added dropwise to a solution of phenyl chloroformate (0.637 mL, 5.08 mmol) in THF (15 mL) at -78 ºC then allowed to warm to ambient temperature. The mixture was poured into 0.5 M HCl(aq) (100 mL) and extracted with Et_2O (30 mL × 3). The organics were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an orange oil. Chromatographic purification (2.5% EtOAc:petrol) afforded the product **479** as a colourless solid (944 mg, 84%). **mp** 63-65 °C; δ_H (400 MHz, $CDCl_3$) 7.60–7.57 (2H, m, Ar*H*), 7.49–7.44 (2H, m, Ar*H*), 7.35–7.31 (3H, m, Ar*H*), 7.11–7.06 (2H, m, FAr*H*-2), 6.48 (1H, s, furanC*H*-4) and 2.04 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 162.1 (d, *J* 245, FAr*C*-1), 150.9 (furanC-5), 150.6 (OPh*C*-1), 146.2 (*C*=O), 146.2 (furan*C*-2), 129.7 (Ph*C*H), 126.7 (Ph*C*H), 126.6 (d, *J* 3.2, FAr*C*-4), 125.1 (d, *J* 8.4, FAr*C*-3,5), 120.7 (Ph*C*H), 115.7 (d, *J* 20.1, FAr*C*H-2,6), 108.3 (furan*C*-4), 104.8 (furan*C*-3) and 8.6 (*C*H_3); ***m/z*** MS (ESI+) 335 (100, $[M+Na]^+$); HRMS (ESI+) $C_{18}H_{13}O_4NaF^+$ ($[M+Na]^+$) requires 335.0696; found 335.0699 (+1.0 ppm); **IR** ν_{max} (KBr) 3059, 2935 (C-H), 1794 (C=O), 1659 (Ar C=C), 1597, 1561 and 758 (furan CH).

(*RS*)- and (*S*)-Phenyl 3-benzyl-2-oxo-5-phenyl-2,3-dihydrofuran-3-carboxylate 554



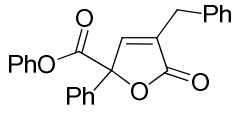
554

Procedures H and M have been applied to afford the product.

Following general procedure M, carbonate **473** (30.0 mg, 81.0 μmol), isothiourea **312** (2.51 mg, 8.10 μmol) and THF (0.5 mL) gave, after purification (10% Et_2O:petrol) the product as a colourless solid (20.0 mg, 67%). **mp** 110–112 ºC; $[\alpha]_D^{20}$ +43.5 (*c* 0.23, CH_2Cl_2, 95% *ee*); δ_H (400 MHz, $CDCl_3$) 7.57–7.51 (2H, m, OPh*H*-3,5), 7.41–7.35 (5H, m, Ar*H*), 7.28–7.23 (6H, m, Ar*H*), 7.08–7.04 (2H, m, OPh*H*-2,6), 5.96 (1H, s, C*H*-4), 3.64 (1H, ABd, *J* 13.6, CH_AH_B) and 3.49 (1H, ABd, *J* 13.6, CH_AH_B); δ_C (100 MHz, $CDCl_3$) 173.1 (*C*-2), 166.4 (*C*OOPh), 154.6 (*C*-5), 150.4 (OPh*C*-1), 134.2 (CH_2Ph*C*-1), 130.4 (Ar*C*H), 130.2 (Ar*C*H), 129.6 (Ar*C*H), 128.9 (Ar*C*H), 128.6 (Ar*C*H), 127.7 (Ar*C*H), 127.6 (Ar*C*), 126.6 (Ar*C*H), 125.3 (OPh*C*H-3,5), 121.3 (OPh*C*H-2,6), 101.8 (*C*H-4), 61.9 (*C*-3) and 40.8 (*C*H_2); ***m/z*** (ESI+) 388 (100, $[M+NH_4]^+$); HRMS (ESI+) $C_{24}H_{22}NO_4^+$ ($[M+NH_4]^+$) requires 388.1543, found 388.1543 (-0.1 ppm); **IR** ν_{max} (thin film) /cm^{-1} 1803 (C=O), 1760 (C=O), 1653 (Ar C=C), 1493, 1449, 1280, 1209, 1187 (C-O), 1159, 1127, 1073, 696, 749 and 688.

Enantiomeric excess was determined by HPLC with Chiralcel AS-H column (5% *i*-PrOH:hexane, flow rate = 1.0 mL min^{-1}), t_R(*S*) 15.8 min and t_R(*R*) 21.6 min, 95% *ee*.

Phenyl 4-benzyl-5-oxo-2-phenyl-2,5-dihydrofuran-2-carboxylate 555

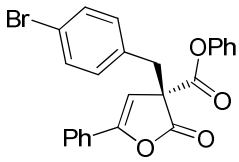


555

Procedures H and M have been applied to afford the product.

According to procedure H, to a solution of triazolium salt **128** (1.47 mg, 5.40 μmol) in THF (2 mL) was added KHMDS (9.72 μL of a 0.5 M solution in toluene, 4.86 μmol) and the mixture stirred for 10 min. Furanyl carbonate **473** (200 mg, 0.540 mmol) was added and, after 5 min, the mixture was concentrated *in vacuo*. Chromatographic purification (20% Et_2O:petrol) gave the product as a colourless oil (134 mg, 67%). δ_H (400 MHz, $CDCl_3$) 7.56–7.53 (2H, m, Ph*H*), 7.46–7.41 (3H, m, Ph*H*), 7.38–7.21 (9H, m, Ph*H* and C*H*-4), 7.01–6.97 (2H, m, OPh*H*-2,6), 3.72 (1H, ABX, J_{AB} 16.9, J_{AX} 1.6, PhCH_AH$_B$) and 3.67 (1H, ABX, J_{BA} 16.9, J_{BX} 1.6, PhCH$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 171.3 (butenolide *C*=O), 166.0 (*C*OOPh), 150.2 (OPh*C*-1), 147.1 (=*C*H), 136.5 (quat *C*), 135.3 (quat *C*), 135.1 (quat *C*), 129.64 (Ph*C*H), 129.64 (Ph*C*H), 129.2 (Ph*C*H), 129.04 (Ph*C*H), 129.04 (Ph*C*H), 127.2 (Ph*C*H), 126.6 (Ph*C*H), 125.9 (Ph*C*H), 121.0 (OPh*C*H-2,6), 87.9 (O-*C*) and 31.9 (*C*H$_2$); ***m/z*** (ESI+) 388 (100, $[M+NH_4]^+$); HRMS (ESI+) $C_{24}H_{22}NO_4^+$ ($[M+NH_4]^+$) requires 388.1543, found 388.1543 (-0.1 ppm); **IR** ν_{max} (thin film) /cm^{-1} 1773 (C=O), 1761 (C=O), 1647 (Ar C=C), 1493, 1451, 1189 (C-O), 1053, 1025, 734 and 676.

(*RS*)- and (*S*)-Phenyl 3-(4-bromobenzyl)-2-oxo-5-phenyl-2,3-dihydrofuran-3-carboxylate 556



556

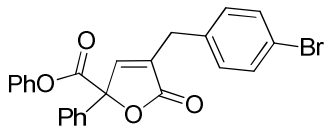
Procedures H and M have been applied to afford the product.

According to general procedure M, carbonate **474** (30.0 mg, 48.2 μmol), isothiourea **312** (1.49 mg, 4.82 μmol) and THF (0.5 mL) gave, after purification (10% Et_2O:petrol), the product as a colourless solid (21.6 mg, 72%). **mp** 151 ºC; $[\alpha]_D^{20}$ +66.0 (*c* 0.2, CH_2Cl_2, 87% *ee*); δ_H (400 MHz, $CDCl_3$) 7.59–7.56 (2H, m, Ph*H*), 7.43–7.37 (7H, m, Ar*H*), 7.29–7.26 (1H, m, OPh*H*-4), 7.16–7.12 (2H, m, BrAr(2,6)*H*), 7.09–7.06 (2H, m, OPh*H*-2,6), 5.94 (1H, s, butenolide C*H*), 3.58 (1H, ABd, *J* 13.7, CH_AH$_B$) and 3.46 (ABd, *J* 13.7, CH$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 172.9 (butenolide *C*=O), 166.3 (*C*OOPh), 155.1 (butenolide *C*-5), 150.5 (OPh*C*-1), 133.3

(BrAr*C*-4), 132.0 (Ar*C*H), 131.8 (Ar*C*H), 130.7 (Ar*C*H-4), 129.8 (Ar*C*H), 129.0 (Ar*C*H), 127.4 (CPh*C*-1), 126.7 (CPh*C*H-4), 125.5 (CPh*C*H-2,6), 122.0 (BrAr*C*-1), 121.3 (BrAr*C*H-2,6), 101.3 (butenolide *C*H-4), 61.7 (butenolide *C*-3) and 39.9 (*C*H_2); ***m/z*** MS (ESI+) 466 (100, [{^{79}Br}M+NH_4]$^+$) and 468 (98, [{^{81}Br}M+H]$^+$); HRMS (ESI+) $C_{24}H_{21}{}^{79}BrNO_4{}^+$ ([{^{79}Br}M+NH_4]$^+$) requires 466.0648, found 466.0641, (-1.6 ppm); **IR** ν_{max} (KBr) /cm^{-1} 3090, 1778 (C=O), 1757 (C=O), 1591 (C=C), 1489, 1421, 1405, 1209, 1188 (C-O), 1056, 1024, 1013, 963, 913, 798, 738 and 689 (C-Br).

Enantiomeric excesses were determined by HPLC with Chiralcel AS-H column (5% *i*-PrOH:hexane, flow rate = 1.0 mL min^{-1}), t_R(*S*) 20.3 min and t_R(*R*) 28.0 min, 87% *ee*.

Phenyl 3-(4-bromobenzyl)-2-oxo-5-phenyl-2,5-dihydrofuran-5-carboxylate 557

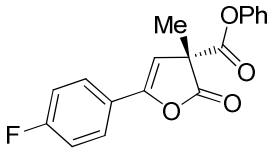


557

Procedures H and M have been applied to afford the product.

Following general procedure H, carbonate **474** (60.2 mg, 0.134 mmol), triazolium salt **128** (3.65 mg, 13.4 μmol), KHMDS (24.2 μL, 12.1 μmol) and THF (1 mL), gave, after chromatographic purification (10% → 20% Et_2O:petrol), the product as a colourless oil (48.0 mg, 80%, contaminated with ~5% butenolide **472**); δ_H (400 MHz, $CDCl_3$) 7.56–7.54 (5H, m, Ph*H*), 7.49–7.43 (2H, m, Ar*H*), 7.38–7.35 (3H, m, Ar*H* and C*H*=C), 7.24–7.20 (1H, m, OPhC*H*-4), 7.14 (2H, app d, *J* 8.4, BrAr*H*-2,6), 7.00–6.98 (2H, m, OPh*H*-2,6), 3.67 (1H, ABX, J_{AB} 16.9, J_{AX} 1.5, CH_AH_B) and 3.62 (1H, ABX, J_{BA} 16.9, J_{BX} 1.5, CH_AH_B); δ_C (100 MHz, $CDCl_3$) 171.1 (butenolide C=O), 165.9 (*C*OOPh), 150.3 (OPh*C*-1), 147.4 (butenolide *C*H-4), 135.5 (quat *C*), 135.0 (quat *C*), 134.7 (quat *C*), 132.2 (BrAr*C*H-3,5), 130.8 (BrAr*C*H-2,6), 129.8 (Ar*C*H), 129.7 (Ar*C*H), 129.3 (Ar*C*H), 126.7 (OPh*C*H-4), 125.9 (Ph*C*H), 121.3 (BrAr*C*-1), 121.0 (OPh*C*H-2,6), 88.0 (butenolide *C*-5) and 31.4 (*C*H_2); **IR** ν_{max} (thin film) /cm^{-1} 3107, 3057, 1804 (C=O), 1760 (C=O), 1652, 1591 (C=C), 1490, 1406, 1281, 1188 (C-O), 1126, 1072, 1013, 94, 833, 755 and 688 (C-Br); ***m/z*** MS (ESI+) 449 (100, [{^{79}Br}M+H]$^+$) and 451 (98, [{^{81}Br}M+H]$^+$); HRMS (ESI+) $C_{24}H_{18}{}^{79}BrO_4{}^+$ ([{^{79}Br}M+H]$^+$) requires 449.0383, found 449.0378, (-1.1 ppm).

(*RS*)- and (*S*)-Phenyl 5-(4-fluorophenyl)-3-methyl-2-oxo-2,3-dihydrofuran-3-carboxylate 558



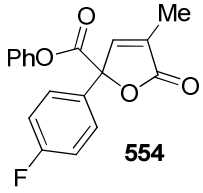
558

Procedures H and M have been applied to afford the product.

Following general procedure M, carbonate **479** (100 mg, 0.320 mmol) and chiral isothiourea **312** (9.89 mg, 32.0 μmol) in THF (1 mL) gave, after 1 h and chromatographic purification (50% CH_2Cl_2:petrol), the product as a colourless solid (72.0 mg, 72%); $\mathbf{[\alpha]_D^{20}}$ +141.5 (*c* 0.2, CH_2Cl_2, 77% *ee*); **mp** 42–44 °C; $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.61–7.57 (2H, m, Ar*H*), 7.31–7.27 (2H, m, Ar*H*), 7.19–7.14 (1H, m, Ar*H*-4), 7.09–7.00 (4H, m, Ar*H*), 5.86 (1H, s, furan*H*-4) and 1.71 (3H, s, CH_3); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 174.2 (butenolide *C*=O), 165.9 (*C*OOPh), 163.9 (d, *J* 250, FAr*C*-1), 153.8 (OPh*C*-1), 150.3 (furan*C*-5), 129.5 (Ph*C*H), 127.4 (d, *J* 9, FAr*C*H-3,5), 126.5 (Ph*C*H), 123.8 (d, *J* 3, FAr*C*-4), 121.1 (Ph*C*H), 116.1 (d, *J* 22, FAr*C*H-2,6), 103.4 (d, *J* 2, C=C*H*), 56.0 (*C*-3) and 20.4 (*C*H_3); ***m/z*** MS (ESI+) 330 (100, $[M+NH_4]^+$); HRMS (ESI+) $C_{18}H_{13}FO_4^+$ ($[M+NH_4]^+$) requires 330.1136, found 330.1139 (+0.9 ppm); **IR** ν_{max} (KBr) 3119, 3073, 2925 (C-H), 2854, 1805 (C=O), 1769, 1741 (C=O), 1653, 1601, 1510.

Enantiomeric excesses determined by chiral HPLC: Chiralpak AS-H (5% IPA:hexane, flow rate 1 mL min^{-1}) t_R(*R*): 12.7 min, t_R(*S*): 17.0 min, 77% *ee*.

Phenyl 2-(4-fluorophenyl)-4-methyl-5-oxo-2,5-dihydrofuran-2-carboxylate 559

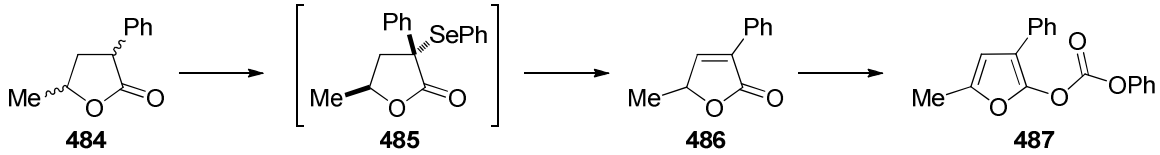


554

Following general procedure H, carbonate **479** (100 mg, 0.320 mmol), triazolium salt **128** (8.75 mg, 32.0 μmol), KHMDS (57.6 μL, 28.8 μmol) and THF (1 mL) gave, after 5 min and chromatographic purification (100% CH_2Cl_2), the product as a colourless oil (67.0 mg, 67%); $\mathbf{\delta_H}$ (400 MHz, $CDCl_3$) 7.54–7.48 (3H, m, C=C*H* and Ar*H*); 7.30–7.25 (2H, m, Ar*H*), 7.18–7.14 (1H, m, Ar*H*-4), 7.08–7.03 (2H, m, Ar*H*), 6.95–6.92 (2H, m, Ar*H*) and 1.95 (3H, s, CH_3); $\mathbf{\delta_C}$ (100 MHz, $CDCl_3$) 171.8 (*C*=O); 166.0 (*C*=O), 163.2 (d, *J* 248.2, FAr*C*-1), 150.2 (OPh*C*-1), 146.2 (*C*=C*H*), 131.2 (Ar*C*), 131.2 (CH=*C*), 129.6 (Ar*C*H), 128.0 (d, *J* 8.3, FAr*C*H-3), 126.6 (Ar*C*H), 120.9 (Ar*C*H), 116.1 (d, *J* 22.2, FAr*C*H-2), 86.9 (O*C*(COOPh)) and 10.8 (*C*H_3); ***m/z*** MS (ESI+) 318 (100, $[M+NH_4]^+$); HRMS (ESI+) $C_{17}H_{20}O_3NS^+$ ($[M+NH_4]^+$) requires 318.1158,

found 318.1161 (+0.8 ppm); **IR** ν_{max} (thin film) 3532, 3084, 2960 (C-H), 1770 (br, 2 × C=O), 1660 (C=C), 1603 and 1509.

5-Methyl-3-phenylfuran-2-yl phenyl carbonate 487



To a cooled (0 ºC) solution of diisopropylamine (0.890 mL, 6.30 mmol) in THF (10 mL) was added *n*-BuLi (2.64 mL of a 2.5 M solution in hexanes, 6.60 mmol). After 20 min at 0 °C, the LDA solution was cooled to -78 °C, and a solution of the butyrolactone **484**[i] (1.06 g, 6.00 mmol) in THF (2 mL) was added. The reaction temperature was maintained at -78 °C for 30 min, and a solution of phenylselenenyl chloride (1.72 g, 9.00 mmol) in THF (5 mL) was added. The resultant mixture was slowly allowed to warm to ambient temperature (over 2 h), diluted with EtOAc (50 mL), washed with NH_4Cl(aq) (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatographic purification (7.5% → 10% Et_2O:petrol) gave the selanyl intermediate **485** as a colourless solid, which was used immediately without characterisation. To a cooled (0 °C) solution of the phenylselanyl intermediate **485** in $CHCl_3$ (10 mL) was added *m*CPBA (70% purity, 2.22 g, 9.00 mmol) portionwise at 0 °C and the mixture was allowed to warm to ambient temperature over 3 h or until TLC indicated the reaction was complete. A further portion of $CHCl_3$ (10mL) was added along with 5% Na_2CO_3(aq) (20 mL). The layers were separated, the organic phase was washed with 5% Na_2CO_3(aq) (20mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatographic purification (25% Et_2O:petrol) gave the butenolide **486** as a colourless solid (418 mg, 40%). **mp** 45–46 °C, lit.[208] 45–46 °C; δ_H (400 MHz, $CDCl_3$) 7.85 (2H, dd, *J* 8.0, 1.6, Ph*H*), 7.54 (1H, d, *J* 1.8, =C*H*), 7.44–7.38 (3H, m, Ph*H*), 5.15 (1H, qd, *J* 6.8, 1.8, OC*H*) and 1.51 (3H, d, *J* 6.8, CH_3). Data are in accordance with the literature.[208]

To a cooled (-78 ºC) solution of butenolide **486** (50.0 mg, 0.287 mmol) in THF (2 mL) was added KHMDS (0.636 mL of a 0.5 M solution in toluene, 0.318 mmol) dropwise and the mixture was stirred for 30 min, turning an intense red/orange colour. Phenyl chloroformate (37.8 μL, 0.301 mmol) was added in one portion and the mixture allowed to warm to ambient temperature over 2 h. The mixture was quenched with sat NH_4Cl(aq) (10 mL) and extracted with Et_2O (10 mL × 3), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a suspension. To the suspension was added petrol (10 mL) and Et_2O (2 mL), and the filtrate was cooled (+5 ºC, refrigerator) for 16 h to afford the recrystallised product **487** as a colourless solid (49.8 mg,

[i] Kindly donated by Louis Morrill.

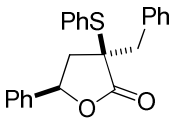
53%). **mp** 72–73 ºC; **δ_H** (300 MHz, $CDCl_3$) 7.57–7.54 (2H, m, Ph*H*), 7.47–7.41 (4H, m, Ph*H*), 7.34–7.27 (4H, m, Ph*H*), 6.33 (br q, *J* 1.0, furan*H*-4) and 2.36 (3H, d, *J* 1.0 Hz, CH_3); **δ_C** (75 MHz, $CDCl_3$) 151.0 (OPh*C*-1), 150.7 (*C*=O), 146.4 (furan*C*-5), 144.3(furan*C*-2), 131.2 (CPh*C*-1), 129.8 (Ph*C*H), 128.9 (OPh*C*-1), 127.0 (Ph*C*H-4), 126.8 (Ph*C*H-4), 126.5 (Ph*C*H), 120.8 (Ph*C*H), 109.0 (furan*C*-3), 106.8 (furan*C*H-4) and 13.7 (*C*H_3); **IR** ν_{max} (KBr) 3050, 2936 (C-H), 1790 (C=O), 1658 (Ar C=C), 1586, 1555 and 1201 (C-O); Structure confirmed by X-ray crystallographic analysis (see Appendix).

NB. MS analysis could not be obtained due to the instability of the carbonate **487**.

Chapter 9: Appendix

X-ray crystallographic data

Crystal data and structure refinement for **469**



469

Identification code	**469** (Reference code: ccas11)	
Empirical formula	C23 H20 O2 S	
Formula weight	360.45	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 11.2854(18) Å	α= 90°.
	b = 16.089(3) Å	β= 90°.
	c = 20.401(3) Å	γ = 90°.
Volume	3704.2(10) $Å^3$	
Z	8	
Density (calculated)	1.293 Mg/m^3	
Absorption coefficient	0.189 mm^{-1}	
F(000)	1520	
Crystal size	0.20 × 0.20 × 0.20 mm^3	
Theta range for data collection	2.42 to 25.34°.	
Index ranges	-13<=h<=13, -19<=k<=19, -24<=l<=24	
Reflections collected	33533	
Independent reflections	3329 [R(int) = 0.0825]	
Completeness to theta = 25.00°	97.9 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.000 and 0.9632	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3329 / 0 / 235	
Goodness-of-fit on F^2	1.175	
Final R indices [I>2sigma(I)]	R1 = 0.0525, wR2 = 0.1846	
R indices (all data)	R1 = 0.0607, wR2 = 0.2161	
Largest diff. peak and hole	0.520 and -0.513 $e.Å^{-3}$	

Table 33: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **469**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6434(1)	3493(1)	985(1)	18(1)
C(2)	5740(2)	2953(1)	657(1)	17(1)
O(2)	4678(1)	2970(1)	709(1)	21(1)
C(3)	6497(2)	2366(1)	239(1)	17(1)
C(4)	7745(2)	2515(1)	502(1)	17(1)
C(5)	7694(2)	3368(2)	838(1)	18(1)
S(3)	5969(1)	1296(1)	309(1)	20(1)
C(6)	6354(2)	1043(2)	1129(1)	24(1)
C(7)	7387(2)	577(2)	1240(2)	35(1)
C(8)	7712(3)	379(2)	1872(2)	51(1)
C(9)	7027(4)	636(2)	2390(2)	62(1)
C(10)	5989(3)	1100(2)	2289(2)	49(1)
C(11)	5651(3)	1299(2)	1651(1)	32(1)
C(12)	6331(2)	2582(2)	-499(1)	18(1)
C(13)	6544(2)	3493(2)	-654(1)	19(1)
C(14)	5600(2)	4048(2)	-664(1)	24(1)
C(15)	5792(2)	4890(2)	-776(1)	27(1)
C(16)	6930(2)	5187(2)	-879(1)	27(1)
C(17)	7871(2)	4634(2)	-875(1)	26(1)
C(18)	7682(2)	3793(2)	-773(1)	22(1)
C(19)	8396(2)	3429(1)	1461(1)	19(1)
C(20)	8016(2)	3048(2)	2036(1)	26(1)
C(21)	8683(2)	3113(2)	2606(1)	31(1)
C(22)	9744(2)	3544(2)	2603(1)	31(1)
C(23)	10139(2)	3907(2)	2031(1)	30(1)
C(24)	9462(2)	3857(2)	1463(1)	22(1)

Table 34: Bond lengths [Å] and angles [°] for **469**

O(1)-C(2)	1.347(3)
O(1)-C(5)	1.468(3)
C(2)-O(2)	1.203(3)
C(2)-C(3)	1.533(3)
C(3)-C(4)	1.526(3)
C(3)-C(12)	1.556(3)
C(3)-S(3)	1.829(2)
C(4)-C(5)	1.535(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(19)	1.501(3)
C(5)-H(5A)	1.0000
S(3)-C(6)	1.775(3)
C(6)-C(11)	1.392(4)
C(6)-C(7)	1.404(4)
C(7)-C(8)	1.378(5)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.373(6)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.404(6)
C(9)-H(9A)	0.9500
C(10)-C(11)	1.392(4)
C(10)-H(10A)	0.9500
C(11)-H(11A)	0.9500
C(12)-C(13)	1.518(3)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.391(4)
C(13)-C(18)	1.393(3)
C(14)-C(15)	1.390(4)
C(14)-H(14A)	0.9500
C(15)-C(16)	1.386(4)
C(15)-H(15A)	0.9500
C(16)-C(17)	1.385(4)
C(16)-H(16A)	0.9500
C(17)-C(18)	1.386(4)
C(17)-H(17A)	0.9500
C(18)-H(18A)	0.9500
C(19)-C(24)	1.387(3)
C(19)-C(20)	1.392(3)
C(20)-C(21)	1.389(4)
C(20)-H(20A)	0.9500
C(21)-C(22)	1.383(4)
C(21)-H(21A)	0.9500
C(22)-C(23)	1.379(4)
C(22)-H(22A)	0.9500
C(23)-C(24)	1.389(4)
C(23)-H(23A)	0.9500
C(24)-H(24A)	0.9500
C(2)-O(1)-C(5)	111.95(17)
O(2)-C(2)-O(1)	121.4(2)
O(2)-C(2)-C(3)	128.1(2)
O(1)-C(2)-C(3)	110.46(18)
C(4)-C(3)-C(2)	102.81(18)
C(4)-C(3)-C(12)	114.66(19)
C(2)-C(3)-C(12)	109.50(18)
C(4)-C(3)-S(3)	114.91(16)

C(2)-C(3)-S(3)	110.79(15)
C(12)-C(3)-S(3)	104.25(15)
C(3)-C(4)-C(5)	105.26(17)
C(3)-C(4)-H(4A)	110.7
C(5)-C(4)-H(4A)	110.7
C(3)-C(4)-H(4B)	110.7
C(5)-C(4)-H(4B)	110.7
H(4A)-C(4)-H(4B)	108.8
O(1)-C(5)-C(19)	109.30(18)
O(1)-C(5)-C(4)	104.46(17)
C(19)-C(5)-C(4)	114.65(19)
O(1)-C(5)-H(5A)	109.4
C(19)-C(5)-H(5A)	109.4
C(4)-C(5)-H(5A)	109.4
C(6)-S(3)-C(3)	102.09(11)
C(11)-C(6)-C(7)	120.5(3)
C(11)-C(6)-S(3)	121.0(2)
C(7)-C(6)-S(3)	118.5(2)
C(8)-C(7)-C(6)	119.7(3)
C(8)-C(7)-H(7A)	120.1
C(6)-C(7)-H(7A)	120.1
C(9)-C(8)-C(7)	120.0(3)
C(9)-C(8)-H(8A)	120.0
C(7)-C(8)-H(8A)	120.0
C(8)-C(9)-C(10)	121.1(3)
C(8)-C(9)-H(9A)	119.4
C(10)-C(9)-H(9A)	119.4
C(11)-C(10)-C(9)	119.2(3)
C(11)-C(10)-H(10A)	120.4
C(9)-C(10)-H(10A)	120.4
C(10)-C(11)-C(6)	119.4(3)
C(10)-C(11)-H(11A)	120.3
C(6)-C(11)-H(11A)	120.3
C(13)-C(12)-C(3)	113.42(19)
C(13)-C(12)-H(12A)	108.9
C(3)-C(12)-H(12A)	108.9
C(13)-C(12)-H(12B)	108.9
C(3)-C(12)-H(12B)	108.9
H(12A)-C(12)-H(12B)	107.7
C(14)-C(13)-C(18)	118.8(2)
C(14)-C(13)-C(12)	120.1(2)
C(18)-C(13)-C(12)	121.1(2)
C(15)-C(14)-C(13)	120.6(2)
C(15)-C(14)-H(14A)	119.7
C(13)-C(14)-H(14A)	119.7
C(16)-C(15)-C(14)	120.4(2)
C(16)-C(15)-H(15A)	119.8
C(14)-C(15)-H(15A)	119.8
C(17)-C(16)-C(15)	119.2(2)
C(17)-C(16)-H(16A)	120.4
C(15)-C(16)-H(16A)	120.4
C(16)-C(17)-C(18)	120.7(2)
C(16)-C(17)-H(17A)	119.7
C(18)-C(17)-H(17A)	119.7
C(17)-C(18)-C(13)	120.4(2)
C(17)-C(18)-H(18A)	119.8
C(13)-C(18)-H(18A)	119.8
C(24)-C(19)-C(20)	119.0(2)
C(24)-C(19)-C(5)	119.5(2)
C(20)-C(19)-C(5)	121.5(2)
C(21)-C(20)-C(19)	120.3(2)

C(21)-C(20)-H(20A)	119.8
C(19)-C(20)-H(20A)	119.8
C(22)-C(21)-C(20)	120.2(2)
C(22)-C(21)-H(21A)	119.9
C(20)-C(21)-H(21A)	119.9
C(21)-C(22)-C(23)	119.7(2)
C(21)-C(22)-H(22A)	120.1
C(23)-C(22)-H(22A)	120.1
C(22)-C(23)-C(24)	120.3(2)
C(22)-C(23)-H(23A)	119.9
C(24)-C(23)-H(23A)	119.9
C(23)-C(24)-C(19)	120.5(2)
C(23)-C(24)-H(24A)	119.8
C(19)-C(24)-H(24A)	119.8

Symmetry transformations used to generate equivalent atoms:

Table 35: Anisotropic displacement parameters ($Å^2 \times 10^3$) for **469**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	13(1)	24(1)	18(1)	-4(1)	-1(1)	1(1)
C(2)	16(1)	22(1)	12(1)	3(1)	-2(1)	1(1)
O(2)	14(1)	28(1)	22(1)	-2(1)	-1(1)	2(1)
C(3)	14(1)	19(1)	19(1)	-1(1)	1(1)	0(1)
C(4)	13(1)	22(1)	17(1)	-1(1)	-1(1)	2(1)
C(5)	12(1)	23(1)	18(1)	0(1)	0(1)	0(1)
S(3)	20(1)	21(1)	19(1)	-1(1)	-1(1)	-2(1)
C(6)	25(1)	23(1)	24(1)	6(1)	-4(1)	-6(1)
C(7)	27(1)	28(1)	49(2)	12(1)	-9(1)	-7(1)
C(8)	48(2)	44(2)	61(2)	25(2)	-29(2)	-13(2)
C(9)	83(3)	57(2)	45(2)	26(2)	-41(2)	-34(2)
C(10)	72(2)	50(2)	24(2)	9(1)	-4(1)	-29(2)
C(11)	37(2)	37(2)	23(1)	4(1)	-2(1)	-10(1)
C(12)	16(1)	23(1)	15(1)	-1(1)	0(1)	0(1)
C(13)	21(1)	25(1)	11(1)	0(1)	-2(1)	-2(1)
C(14)	18(1)	33(1)	21(1)	4(1)	2(1)	3(1)
C(15)	31(1)	23(1)	28(1)	4(1)	2(1)	6(1)
C(16)	39(2)	20(1)	24(1)	1(1)	-1(1)	-4(1)
C(17)	24(1)	31(1)	24(1)	3(1)	-2(1)	-6(1)
C(18)	19(1)	28(1)	18(1)	3(1)	0(1)	2(1)
C(19)	17(1)	21(1)	18(1)	-3(1)	-2(1)	2(1)
C(20)	22(1)	34(2)	22(1)	4(1)	-1(1)	-3(1)
C(21)	34(1)	39(2)	20(1)	7(1)	-3(1)	2(1)
C(22)	30(1)	40(2)	22(1)	-7(1)	-11(1)	4(1)
C(23)	21(1)	38(2)	30(1)	-7(1)	-6(1)	-4(1)
C(24)	20(1)	26(1)	20(1)	-2(1)	0(1)	-1(1)

Table 36: Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **469**

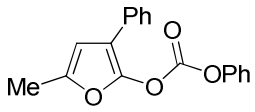
	x	y	z	U(eq)
H(4A)	8329	2518	140	21
H(4B)	7968	2077	820	21
H(5A)	7968	3806	525	21
H(7A)	7860	400	881	42
H(8A)	8410	64	1949	61
H(9A)	7259	499	2824	74
H(10A)	5522	1275	2651	59
H(11A)	4946	1607	1574	39
H(12A)	6884	2240	-762	22
H(12B)	5514	2434	-632	22
H(14A)	4817	3851	-594	29
H(15A)	5140	5263	-782	33
H(16A)	7063	5763	-951	33
H(17A)	8654	4834	-942	32
H(18A)	8333	3418	-784	26
H(20A)	7296	2741	2039	31
H(21A)	8410	2861	2999	37
H(22A)	10199	3589	2993	37
H(23A)	10876	4192	2025	35
H(24A)	9732	4119	1073	26

Table 37: Torsion angles [°] for **469**

C(5)-O(1)-C(2)-O(2)	-178.9(2)
C(5)-O(1)-C(2)-C(3)	0.7(2)
O(2)-C(2)-C(3)-C(4)	-167.2(2)
O(1)-C(2)-C(3)-C(4)	13.2(2)
O(2)-C(2)-C(3)-C(12)	70.5(3)
O(1)-C(2)-C(3)-C(12)	-109.1(2)
O(2)-C(2)-C(3)-S(3)	-43.9(3)
O(1)-C(2)-C(3)-S(3)	136.46(16)
C(2)-C(3)-C(4)-C(5)	-21.0(2)
C(12)-C(3)-C(4)-C(5)	97.8(2)
S(3)-C(3)-C(4)-C(5)	-141.46(16)
C(2)-O(1)-C(5)-C(19)	-137.47(19)
C(2)-O(1)-C(5)-C(4)	-14.3(2)
C(3)-C(4)-C(5)-O(1)	21.8(2)
C(3)-C(4)-C(5)-C(19)	141.44(19)
C(4)-C(3)-S(3)-C(6)	46.54(19)
C(2)-C(3)-S(3)-C(6)	-69.42(18)
C(12)-C(3)-S(3)-C(6)	172.88(15)
C(3)-S(3)-C(6)-C(11)	80.3(2)
C(3)-S(3)-C(6)-C(7)	-99.7(2)
C(11)-C(6)-C(7)-C(8)	-0.6(4)
S(3)-C(6)-C(7)-C(8)	179.4(2)
C(6)-C(7)-C(8)-C(9)	0.0(5)
C(7)-C(8)-C(9)-C(10)	0.2(5)
C(8)-C(9)-C(10)-C(11)	0.1(5)
C(9)-C(10)-C(11)-C(6)	-0.7(4)
C(7)-C(6)-C(11)-C(10)	0.9(4)
S(3)-C(6)-C(11)-C(10)	-179.1(2)
C(4)-C(3)-C(12)-C(13)	-62.1(3)
C(2)-C(3)-C(12)-C(13)	52.8(3)
S(3)-C(3)-C(12)-C(13)	171.42(16)
C(3)-C(12)-C(13)-C(14)	-93.7(3)
C(3)-C(12)-C(13)-C(18)	84.8(3)
C(18)-C(13)-C(14)-C(15)	-1.5(4)
C(12)-C(13)-C(14)-C(15)	177.1(2)
C(13)-C(14)-C(15)-C(16)	0.0(4)
C(14)-C(15)-C(16)-C(17)	0.6(4)
C(15)-C(16)-C(17)-C(18)	0.3(4)
C(16)-C(17)-C(18)-C(13)	-1.9(4)
C(14)-C(13)-C(18)-C(17)	2.4(4)
C(12)-C(13)-C(18)-C(17)	-176.1(2)
O(1)-C(5)-C(19)-C(24)	-137.9(2)
C(4)-C(5)-C(19)-C(24)	105.2(3)
O(1)-C(5)-C(19)-C(20)	43.7(3)
C(4)-C(5)-C(19)-C(20)	-73.2(3)
C(24)-C(19)-C(20)-C(21)	1.5(4)
C(5)-C(19)-C(20)-C(21)	179.9(2)
C(19)-C(20)-C(21)-C(22)	-1.3(4)
C(20)-C(21)-C(22)-C(23)	-0.2(4)
C(21)-C(22)-C(23)-C(24)	1.5(4)
C(22)-C(23)-C(24)-C(19)	-1.3(4)
C(20)-C(19)-C(24)-C(23)	-0.1(4)
C(5)-C(19)-C(24)-C(23)	-178.6(2)

Symmetry transformations used to generate equivalent atoms:

Crystal data and structure refinement for **487**



487

Identification code	**487** (Reference code: ccas12)	
Empirical formula	C18 H14 O4	
Formula weight	294.29	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 5.5181(18) Å	α= 90°.
	b = 16.785(5) Å	β= 92.690(9)°.
	c = 15.844(4) Å	γ = 90°.
Volume	1466.0(8) $Å^3$	
Z	4	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	616	
Crystal size	0.20 × 0.20 × 0.20 mm^3	
Theta range for data collection	2.43 to 25.34°.	
Index ranges	-5<=h<=6, -20<=k<=15, -18<=l<=19	
Reflections collected	9188	
Independent reflections	2645 [R(int) = 0.0527]	
Completeness to theta = 25.00°	98.7 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.000 and 0.944	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2645 / 0 / 201	
Goodness-of-fit on F^2	1.093	
Final R indices [I>2sigma(I)]	R1 = 0.0552, wR2 = 0.1406	
R indices (all data)	R1 = 0.0724, wR2 = 0.1555	
Extinction coefficient	0.018(3)	
Largest diff. peak and hole	0.241 and -0.224 $e.Å^{-3}$	

Table 38: Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **487**. U(eq) is defined as one third of the trace of the orthogonalised U^{ij} tensor

	x	y	z	U(eq)
O(1)	11637(3)	932(1)	10394(1)	47(1)
O(7)	8568(3)	3072(1)	9309(1)	37(1)
O(2)	9136(3)	1969(1)	9972(1)	40(1)
O(6)	11944(3)	2953(1)	10181(1)	41(1)
C(2)	10198(4)	1540(1)	10632(1)	39(1)
C(3)	10050(4)	1605(1)	11477(1)	35(1)
C(4)	11555(4)	967(1)	11801(1)	40(1)
C(5)	12459(5)	573(1)	11149(1)	46(1)
C(6)	10116(4)	2705(1)	9856(1)	34(1)
C(8)	9111(4)	3869(1)	9089(1)	33(1)
C(9)	7462(4)	4439(1)	9301(1)	36(1)
C(10)	7848(4)	5217(1)	9050(1)	38(1)
C(11)	9844(4)	5409(1)	8594(1)	36(1)
C(12)	11446(4)	4820(1)	8385(1)	40(1)
C(13)	11094(4)	4040(1)	8629(1)	40(1)
C(14)	8754(4)	2209(1)	11951(1)	33(1)
C(15)	9720(4)	2466(1)	12735(1)	34(1)
C(16)	8511(4)	3023(1)	13200(1)	39(1)
C(17)	6315(4)	3336(1)	12892(1)	45(1)
C(18)	5346(4)	3087(1)	12112(1)	43(1)
C(19)	6538(4)	2527(1)	11648(1)	39(1)
C(20)	14054(6)	-125(2)	11076(2)	63(1)

Table 39: Bond lengths [Å] and angles [°] for **487**

O(1)-C(2)	1.357(2)
O(1)-C(5)	1.395(2)
O(7)-C(6)	1.339(2)
O(7)-C(8)	1.417(2)
O(2)-C(6)	1.364(2)
O(2)-C(2)	1.378(2)
O(6)-C(6)	1.186(2)
C(2)-C(3)	1.349(3)
C(3)-C(4)	1.435(3)
C(3)-C(14)	1.468(3)
C(4)-C(5)	1.342(3)
C(4)-H(4)	0.9500
C(5)-C(20)	1.473(3)
C(8)-C(9)	1.373(3)
C(8)-C(13)	1.374(3)
C(9)-C(10)	1.385(3)
C(9)-H(9)	0.9500
C(10)-C(11)	1.383(3)
C(10)-H(10)	0.9500
C(11)-C(12)	1.377(3)
C(11)-H(11)	0.9500
C(12)-C(13)	1.381(3)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
C(14)-C(15)	1.397(3)
C(14)-C(19)	1.398(3)
C(15)-C(16)	1.381(3)
C(15)-H(15)	0.9500
C(16)-C(17)	1.389(3)
C(16)-H(16)	0.9500
C(17)-C(18)	1.387(3)
C(17)-H(17)	0.9500
C(18)-C(19)	1.380(3)
C(18)-H(18)	0.9500
C(19)-H(19)	0.9500
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(2)-O(1)-C(5)	104.95(15)
C(6)-O(7)-C(8)	117.27(15)
C(6)-O(2)-C(2)	114.70(16)
C(3)-C(2)-O(1)	113.51(17)
C(3)-C(2)-O(2)	131.89(19)
O(1)-C(2)-O(2)	114.59(16)
C(2)-C(3)-C(4)	103.52(17)
C(2)-C(3)-C(14)	128.08(18)
C(4)-C(3)-C(14)	128.33(18)
C(5)-C(4)-C(3)	108.79(18)
C(5)-C(4)-H(4)	125.6
C(3)-C(4)-H(4)	125.6
C(4)-C(5)-O(1)	109.22(18)
C(4)-C(5)-C(20)	134.22(19)
O(1)-C(5)-C(20)	116.57(18)
O(6)-C(6)-O(7)	128.54(18)
O(6)-C(6)-O(2)	126.45(18)
O(7)-C(6)-O(2)	105.01(17)
C(9)-C(8)-C(13)	122.51(18)

C(9)-C(8)-O(7)	116.59(17)
C(13)-C(8)-O(7)	120.70(17)
C(8)-C(9)-C(10)	118.35(19)
C(8)-C(9)-H(9)	120.8
C(10)-C(9)-H(9)	120.8
C(11)-C(10)-C(9)	120.44(19)
C(11)-C(10)-H(10)	119.8
C(9)-C(10)-H(10)	119.8
C(12)-C(11)-C(10)	119.59(19)
C(12)-C(11)-H(11)	120.2
C(10)-C(11)-H(11)	120.2
C(11)-C(12)-C(13)	120.90(19)
C(11)-C(12)-H(12)	119.5
C(13)-C(12)-H(12)	119.5
C(8)-C(13)-C(12)	118.19(19)
C(8)-C(13)-H(13)	120.9
C(12)-C(13)-H(13)	120.9
C(15)-C(14)-C(19)	118.53(19)
C(15)-C(14)-C(3)	119.59(18)
C(19)-C(14)-C(3)	121.87(18)
C(16)-C(15)-C(14)	120.7(2)
C(16)-C(15)-H(15)	119.7
C(14)-C(15)-H(15)	119.7
C(15)-C(16)-C(17)	120.2(2)
C(15)-C(16)-H(16)	119.9
C(17)-C(16)-H(16)	119.9
C(18)-C(17)-C(16)	119.6(2)
C(18)-C(17)-H(17)	120.2
C(16)-C(17)-H(17)	120.2
C(19)-C(18)-C(17)	120.4(2)
C(19)-C(18)-H(18)	119.8
C(17)-C(18)-H(18)	119.8
C(18)-C(19)-C(14)	120.6(2)
C(18)-C(19)-H(19)	119.7
C(14)-C(19)-H(19)	119.7
C(5)-C(20)-H(20A)	109.5
C(5)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(5)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 40: Anisotropic displacement parameters ($Å^2 \times 10^3$) for **487**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	73(1)	33(1)	34(1)	2(1)	-2(1)	13(1)
O(7)	45(1)	30(1)	36(1)	5(1)	-9(1)	1(1)
O(2)	55(1)	30(1)	34(1)	5(1)	-9(1)	0(1)
O(6)	47(1)	36(1)	39(1)	3(1)	-11(1)	1(1)
C(2)	52(1)	29(1)	34(1)	3(1)	-7(1)	3(1)
C(3)	41(1)	30(1)	35(1)	4(1)	-3(1)	-2(1)
C(4)	52(1)	32(1)	34(1)	7(1)	-5(1)	5(1)
C(5)	68(2)	33(1)	36(1)	7(1)	-2(1)	12(1)
C(6)	46(1)	30(1)	28(1)	0(1)	-2(1)	4(1)
C(8)	40(1)	27(1)	30(1)	2(1)	-6(1)	-1(1)
C(9)	39(1)	38(1)	31(1)	4(1)	3(1)	5(1)
C(10)	44(1)	35(1)	36(1)	1(1)	3(1)	8(1)
C(11)	41(1)	32(1)	35(1)	2(1)	-4(1)	2(1)
C(12)	35(1)	42(1)	42(1)	7(1)	4(1)	4(1)
C(13)	42(1)	37(1)	41(1)	-1(1)	2(1)	10(1)
C(14)	36(1)	30(1)	33(1)	5(1)	-1(1)	-2(1)
C(15)	39(1)	29(1)	35(1)	5(1)	0(1)	-5(1)
C(16)	49(1)	31(1)	36(1)	1(1)	5(1)	-7(1)
C(17)	51(2)	33(1)	51(1)	6(1)	16(1)	1(1)
C(18)	37(1)	42(1)	51(1)	16(1)	5(1)	7(1)
C(19)	39(1)	38(1)	40(1)	9(1)	-2(1)	-3(1)
C(20)	99(2)	47(2)	44(1)	4(1)	-2(1)	28(1)

Table 41: Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **487**

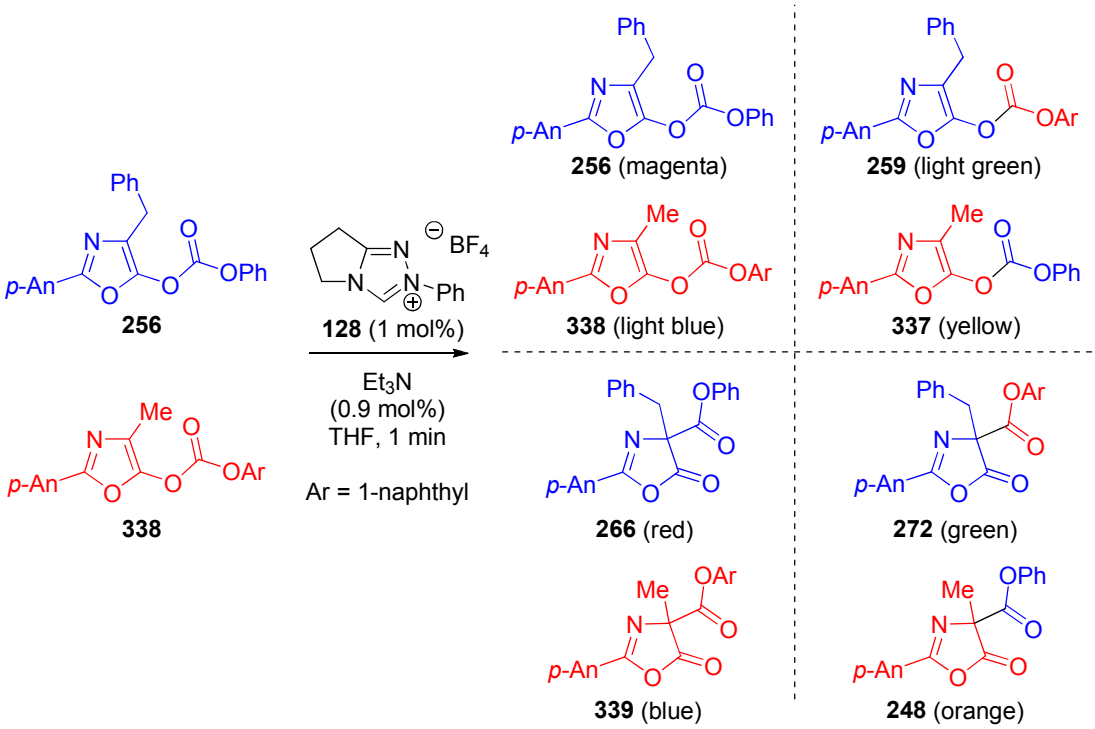
	x	y	z	U(eq)
H(4)	11860	843	12381	47
H(9)	6091	4303	9612	43
H(10)	6736	5622	9193	46
H(11)	10107	5944	8425	43
H(12)	12812	4952	8070	47
H(13)	12193	3633	8481	48
H(15)	11225	2257	12950	41
H(16)	9184	3192	13733	46
H(17)	5482	3718	13213	54
H(18)	3852	3305	11896	52
H(19)	5846	2355	11119	47
H(20A)	15612	44	10863	95
H(20B)	13287	-511	10683	95
H(20C)	14324	-373	11632	95

Table 42: Torsion angles [°] for **487**

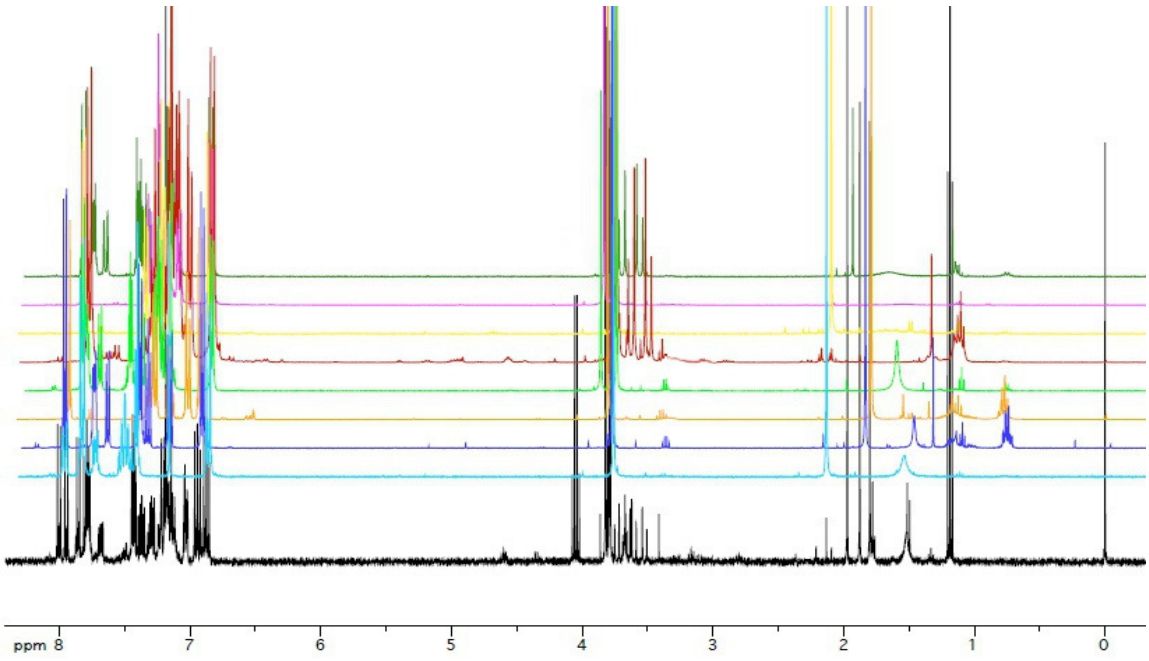
C(5)-O(1)-C(2)-C(3)	0.6(2)
C(5)-O(1)-C(2)-O(2)	-178.57(18)
C(6)-O(2)-C(2)-C(3)	74.9(3)
C(6)-O(2)-C(2)-O(1)	-106.11(19)
O(1)-C(2)-C(3)-C(4)	-0.2(2)
O(2)-C(2)-C(3)-C(4)	178.8(2)
O(1)-C(2)-C(3)-C(14)	177.14(19)
O(2)-C(2)-C(3)-C(14)	-3.8(4)
C(2)-C(3)-C(4)-C(5)	-0.4(3)
C(14)-C(3)-C(4)-C(5)	-177.7(2)
C(3)-C(4)-C(5)-O(1)	0.8(3)
C(3)-C(4)-C(5)-C(20)	-179.1(3)
C(2)-O(1)-C(5)-C(4)	-0.9(3)
C(2)-O(1)-C(5)-C(20)	179.0(2)
C(8)-O(7)-C(6)-O(6)	-1.4(3)
C(8)-O(7)-C(6)-O(2)	178.34(14)
C(2)-O(2)-C(6)-O(6)	11.2(3)
C(2)-O(2)-C(6)-O(7)	-168.49(15)
C(6)-O(7)-C(8)-C(9)	-117.54(19)
C(6)-O(7)-C(8)-C(13)	67.4(2)
C(13)-C(8)-C(9)-C(10)	-1.1(3)
O(7)-C(8)-C(9)-C(10)	-176.02(17)
C(8)-C(9)-C(10)-C(11)	0.3(3)
C(9)-C(10)-C(11)-C(12)	0.3(3)
C(10)-C(11)-C(12)-C(13)	-0.2(3)
C(9)-C(8)-C(13)-C(12)	1.1(3)
O(7)-C(8)-C(13)-C(12)	175.88(18)
C(11)-C(12)-C(13)-C(8)	-0.5(3)
C(2)-C(3)-C(14)-C(15)	-145.5(2)
C(4)-C(3)-C(14)-C(15)	31.2(3)
C(2)-C(3)-C(14)-C(19)	35.8(3)
C(4)-C(3)-C(14)-C(19)	-147.5(2)
C(19)-C(14)-C(15)-C(16)	0.0(3)
C(3)-C(14)-C(15)-C(16)	-178.71(17)
C(14)-C(15)-C(16)-C(17)	-0.2(3)
C(15)-C(16)-C(17)-C(18)	-0.1(3)
C(16)-C(17)-C(18)-C(19)	0.7(3)
C(17)-C(18)-C(19)-C(14)	-0.9(3)
C(15)-C(14)-C(19)-C(18)	0.6(3)
C(3)-C(14)-C(19)-C(18)	179.24(18)

Representative NMR experiment for crossover studies

e.g. Crossover experiment with phenylalanine-derived phenyl carbonate **256** (0.125 mM concentration) and alanine-derived naphthyl carbonate **338** (0.125 mM concentration) following general procedure H, using THF, Et_3N and triazolium salt **128**.



Overlaid ^1H NMR spectra (400 MHz, $CDCl_3$) of the reaction mixture (black) and all possible products (for colour coding, see above figure):



Chapter 10: Bibliography

[1] Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175.
[2] For reviews of organocatalysis see (a) List, B. *Chem. Rev.* **2007**, *107*, 5413–5415; (b) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.
[3] Guo, Q-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790–3791.
[4] Comparison with guanidine, pK_{aH} 13.71, according to Albert, A.; Goldacre, R.; Phillips, J. *J. Chem. Soc.* **1948**, 2240–2249.
[5] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
[6] Corey, E. J.; Grogan, M. J. *Org. Lett*. **1999**, *1*, 157–160.
[7] For a review of phosphonium salt catalysis, see Werner, T. *Adv. Synth. Catal.* **2009**, *351*, 1469–1481.
[8] He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem.* **2008**, *120*, 9608–9610; *Angew. Chem., Int. Ed.* **2008**, *47*, 9466–9468.
[9] For a review of recent developments in asymmetric organocatalysis, see Taylor, M. S. and Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543.
[10] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
[11] Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *121*, 9874–9875.
[12] Beeson, T. D; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582–585.
[13] Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–92.
[14] For reviews see (a) Jordan, F. *Nat. Prod. Rep.* **2003**, *20*, 184–201; (b) Pohl, M.; Lingen, B.; Müller, M. *Chem. Eur. J.* **2002**, *8*, 5289–5295; (c) Schörken, U.; Sprenger, G. A. *Biochim. Biophys. Acta* **1998**, *1385*, 229–243.
[15] Bordwell, F. G.; Satish A. V. *J. Am. Chem. Soc.* **1991**, *113*, 985–990.
[16] Breslow, R. *J. Am. Chem. Soc*. **1957**, *79*, 1762–1763.
[17] (a) Hildebrandt, G.; Klavehn, W. US 1 956 950, **1934**, [*Chem. Abstr.* **1934**, *28*, 40273]; (b) Pohl, M. *Adv. Biochem. Eng. Biotechnol.* **1997**, *58*, 16–43.
[18] Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361–363.
[19] (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041; (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
[20] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
[21] Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
[22] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
[23] For a review, see Vernall, A. J.; Abell, A. D. *Aldrichimica Acta* **2003**, *3*, 93–105.
[24] For these and other applications in organometallic chemistry, see Clavier, H.; Nolan, S. P. *Annu. Rep. Prog. Chem. Sect. B* **2007**, *103*, 193–222.
[25] For recent reviews of the ability of NHCs to catalyse organocatalytic processes see (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655; (b) Marion, N; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000.
[26] Seebach, D. *Angew. Chem.* **1979**, *91*, 259–278; *Angew. Chem., Int. Ed.* **1979**, *18*, 239–258.
[27] Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296–300.
[28] (a) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363–4366; (b) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465–2468; (c) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314–2315.
[29] (a) Stetter, H.; Lorenz, G. *Chem. Ber.* **1985**, *118*, 1115–1125; (b) Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Scheidt, K. A. **2005**, *J. Am. Chem. Soc. 127*, 14675–14680.

[30] (a) Sheehan, J. C.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196–1199; (b) Tagaki, W.; Tamura, Y.; Yano, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478–480; (c) Martím J.; Castells, J.; López-Calahorra, F. *Tetrahedron Lett.* 1993, 34, 521–524; (d) Yamashita, K.; Sasaki, S.-I.; Osaki, T.; Nango, M.; Tsuda, K. *Tetrahedron Lett.* **1995**, *36*, 4817–4820; (e) Knight, R. L.; Leeper, F. *Tetrahedron Lett*. **1997**, *38*, 3611–3614; (f) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025–2035; (g) Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925–2928.
[31] (a) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed.* **1995**, *34*, 1021–1023; (b) Enders, D.; Breuer, K.; Kallfass, U.; Balansiefer, T. *Synthesis* **2003**, *8*, 1292–1295; (c) Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Teles, J. H.; Raabe, G. *Helv. Chim. Acta* **1996**, *79*, 61–83.
[32] Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217–1221.
[33] Knight, R. L.; Leeper, F. J. *J Chem Soc Perkin Trans* **1998**, *1*, 1891–1893.
[34] Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745.
[35] For a computational study on the origin of the enantioselectivity in this reaction, see Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci*. **2004**, *101*, 5770–5775.
[36] Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 2713–2716.
[37] Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, 79, 1899–1902.
[38] Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195–197.
[39] (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299; (b) Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033–2040.
[40] Kerr, M. S.; Rovis, T. *Synlett* **2003**, *12*, 1934–1936.
[41] Cullen, S. C.; Rovis, T. *Org. Lett.* **2008**, *10*, 3141–3144.
[42] Matsumoto, Y.; Tomioka, K. *Tetrahedron Lett.* **2006**, *47*, 5843–5846.
[43] Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877.
[44] Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989–3991.
[45] Maki, E. M.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371–374.
[46] (a) Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003–4006; (b) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727–8730.
[47] (a) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4588–4589; (b) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102–3109.
[48] Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, 65, 3102–3109.
[49] Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205–6208.
[50] Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371.
[51] Li, Y.; Zhuo, Z. A.; He, H.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 1885–1890.
[52] Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507–509.
[53] Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736–8737.
[54] Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266–17267.
[55] Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334–5335.
[56] Phillips, E. M.; Reynolds ,T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416–2417.
[57] Nair, V.; Babu, B. P.; Vellalath, S.; Suresh, E. *Chem. Commun.* **2008**, 747–749.
[58] Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957–960.
[59] Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc* **2008**, *130*, 2740–2741.
[60] Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–908.
[61] (a) Maki, B. E.; Chan, A.; Scheidt, K. A. *Synthesis* **2008**, *8*, 1306–1315; (b) Maki, B. E.; Patterson, E. V.; Cramer, C. J.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 3942–3945.
[62] Struble, J. R.; Bode, J. W. *Tetrahedron* **2009**, *65*, 4957–4967.
[63] Chiang, P. C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714–8718.

[64] Chiang, P. C.; Kim, Y.; Bode, J. W. *Chem. Commun.* **2009**, 4566–4568.
[65] Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108–1113.
[66] Zhang, Y. R.; He, L.; Wu, X.; Shao, P. L.; Ye, S. *Org. Lett.* **2008**, *10*, 277–280.
[67] He, L.; Lv, H.; Zhang, Y.-R.; Ye, S. *J. Org. Chem.* **2008**, *73*, 8101–8103.
[68] Wang, X.-N.; Lv, H.; Huang, X.-L.; Ye, S. *Org. Lett.* **2009**, *11*, 4029–4031.
[69] Huang, X.-L.; Shao, P.-L.; Lv, H.; Ye, S. *J. Org. Chem.* **2009**, *74*, 7585–7587.
[70] Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Adv. Synth. Catal.* **2008**, *350*, 2715–2718.
[71] Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem. Eur. J.* **2008**, *14*, 8473–8476.
[72] Wang, X.-N.; Lv, H.; Huang, X.-L.; Ye, S. *Org. Biomol. Chem.* **2009**, *7*, 346–350.
[73] Concellón, C.; Duguet N.; Smith, A. D. *Adv. Synth. Catal*. **2009**, *351*, 3001–3009.
[74] Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406–16407.
[75] He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420.
[76] Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T.; Ryu, I. *Org. Lett.* **2009**, *11*, 3934–3937.
[77] He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089.
[78] He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817–3820.
[79] Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107–3110.
[80] Li, Y.; Wang, X.-Q.; Zheng, C.; You, S.-L. *Chem. Commun.* **2009**, 5823–5825.
[81] Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098–10099.
[82] Phillips, E. M.; Wadamoto, M.; Scheidt, K. A. *Synthesis* **2009**, 687–690.
[83] Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583–3586.
[84] Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587–3590
[85] For the pioneering stoichiometric transfer of a carboxyl unit from 2-alkoxycarbonyl-imidazolium salts to benzyl alcohol in the presence of DABCO, see Bakhtiar C.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 239–243.
[86] Grasa, G. A.; Guveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *68*, 2812–2819.
[87] Singh, R.; Nolan, S. P. *Chem. Commun.* **2005**, 5456–5458.
[88] Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453–2456.
[89] Schmidt, M. A.; Müller, P.; Movassaghi, M. *Tetrahedron Lett.* **2008**, *49*, 4316–4318.
[90] Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347–1349.
[91] Suzuki, Y.; Yamauchi, K.; Maramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770–2771; Suzuki, Y.; Muramatsu, K.; Yamauchi, K.; Morie, Y.; Sato, M. *Tetrahedron* **2006**, 62, 302–310.
[92] Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519.
[93] Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc* **2004**, *126*, 8126–8127.
[94] Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021–6024.
[95] Zeitler, K. *Org. Lett.* **2006**, *8*, 637–640.
[96] Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, *9*, 3519–3521; Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Chem. Commun.* **2007**, 4788–4790.
[97] Wang, L.; Thai, K.; Gravel, M. *Org. Lett* **2009**, *11*, 891–893.
[98] Li, G.-Q.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2009**, *11*, 1623–1625.
[99] Vora, H.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797; Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799.
[100] He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418–419.
[101] Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677–680.
[102] Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176–14177.
[103] Steglich, W.; Höfle, G. *Tetrahedron Lett.* **1970**, *54*, 4727–4730.

[104] (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 389–401; (b) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688–1690; (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5363–5367.
[105] Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152.
[106] Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.
[107] Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369.
[108] Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769–772.
[109] For a review of all efforts towards the asymmetric rearrangements, see Moyano, A.; El-Hamdouni, N.; Atlamsani, A. *Chem. Eur. J.* **2010**, *16*, 5260–5273.
[110] Thomson, J. E.; Rix, K.; Smith, A. D. *Org. Lett.* **2006**, *8*, 3785–3788.
[111] Tabassum, S.; Sereda, O.; Reddy, P. V. G.; Wilhelm, R. *Org. Biomol. Chem.* **2009**, *7*, 4009–4016.
[112] Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A. C.; Smith, A. D. *Chem. Commun.* **2008**, 3528–3530.
[113] Oediger, H.; Möller, F. *Angew. Chem., Int. Ed.* **1967**, *6*, 76; Otter, B. A.; Taube, A.; Fox, J. J. *J. Org. Chem*. **1971**, *36*, 1251–1255.
[114] Ono, N.; Yamada, T.; Saito, T.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn*. **1978**, *51*, 2401–2404.
[115] Yamanaka, H.; Yokoyama, M.; Sakamoto, T.; Shiraishi, T.; Sagi, M.; Mizugaki, M. *Heterocycles* **1983**, *20*, 1541–1544.
[116] Aggarwal, V. K.; Mereu, A. *J. Org. Chem*. **2000**, *65*, 7211–7212.
[117] Kim, S.; Chang, H. *Bull. Chem. Soc. Jpn*. **1985**, *58*, 3669–3670.
[118] Sheig, W.-C.; Dell, S.; Repic, O. *J. Org. Chem*. **2002**, *67*, 2188–2191.
[119] Aggarwal, V. K.; Mereu, A. *Chem. Commun*. **1999**, 2311–2312.
[120] Zhang, W.; Shi, M. *Org. Biomol. Chem.* **2006**, *4*, 1671–1674.
[121] Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, S.; Kilbane, C. J. *J. Am. Chem. Soc*. **2004**, *126*, 12226–12227.
[122] Birman, V. B.; Jiang, H. *Org. Lett*. **2005**, *7*, 3445–3447; Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron*, **2006**, *62*, 285–294.
[123] Birman, V. B.; Li, X. *Org. Lett*. **2006**, *8*, 1351–1354; Kobayashi, M.; Okamoto, S. *Tetrahedron Lett*. **2006**, *47*, 4347–4350.
[124] Joannesse, C.; Simal, C.; Concellón, C.; Thomson, J. E.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 2900–2907.
[125] Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914–8918.
[126] Dietz, F. R.; Gröger, H. *Synlett* **2008**, 663–666.
[127] Dietz, F. R.; Gröger, H. *Synthesis* **2009**, 4208–4218.
[128] See (a) Tietz, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131–163; (b) Tietze, L. F. *Chem. Ind.* **1995**, 453–457; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (d) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137–165; (e) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206; (f) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306.
[129] Millan, D. S.; Prager, R. H. *Tetrahedron Lett.* **1998**, *39*, 4387–4390.
[130] (a) Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 91–104; (b) Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 745–756.
[131] For a related protocol of activation to a mixed anhydride using methyl chloroformate see Chen, F. M. F.; Slebioda, M.; Benoiton, N. L. *Int. J. Peptide Protein Res.* **1998**, *31*, 330–344.
[132] Wei, Y.; Sastry, G. N.; Zipse, H. *J. Am. Chem. Soc.* **2008**, *130*, 3473–3477.
[133] Alder, R. W.; Blake, M. E.; Bortolotti, C.; Bufali, S.; Butts, C. P.; Linehan, E.; Oliva, J. M.; Orpen, A. G.; Quayle, M. A. *Chem. Commun.* **1999**, 241–242.

[134] Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J. P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed.* **1995**, *34*, 1021–1023.
[135] Schmidt, M. A.; Müller, P.; Movassaghi, M. *Tetrahedron Lett.* **2008**, *49*, 4316–4318.
[136] Stavenger, R. A.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375–3389.
[137] McKennon, M.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568–3571.
[138] Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.
[139] Larrow, F. J.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 1939–1940.
[140] Bull, S. D.; Davies, S. G.; Epstein, S. W.; Ouzman, J. V. A. *Chem. Commun.* **1998**, 659–660; Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech, M. A.; Ouzman, J. V. A. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2321–2330.
[141] Bull, S. D.; Davies, S. G.; Fox, D. J.; Sellers, T. G. R. *Tetrahedron: Asymmetry* **1998**, *9*, 1483–1487.
[142] Bull, S. D.; Davies, S. G.; Fox, D. J.; Garner, A. C.; Sellers, T. G. R. *Pure Appl. Chem.* **1998**, *70*, 1501–1506.
[143] For select examples of "chiral relay" in asymmetric transformations see (a) Watanabe, Y.; Mase, N.; Furue, R.; Toru, T. *Tetrahedron Lett.* **2001**, *42*, 2981–2984; (b) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 2161–2164; (c) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122,* 1802–1803; (d) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael. F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920; (e) Hiroi, K.; Ishii, M. *Tetrahedron Lett*. **2000**, *41*, 7071–7074; (f) Wada, E.; Pei, W.; Kanemasa, S. *Chem. Lett.* **1994**, 2345–2348; (g) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637–1640; (h) Malkov, A. V.; Stoncius, S.; MacDougall, K. N.; Mariani, A.; McGeoch, G. D.; Kocovsky, P. *Tetrahedron* **2006**, *62*, 264–284; (i) Malkov, A. V.; Hand, J. B.; Kocovsky, P. *Chem. Commun.* **2003**, 1948–1949; (j) Maughan, M. A. T.; Davies, I. G.; Claridge, T. D. W.; Courtney, S.; Hay, P.; Davis, B. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 3788–3792.
[144] Duguet, N.; Donaldson, A.; Leckie, S. M.; Kallström, E. A.; Campbell, C. D.; Shapland, P.; Brown, T. B.; Slawin, A. M. Z.; Smith, A. D. *Tetrahedron: Asymm.* **2010**, *21*, 601–616.
[145] Voight, E. A.; Bodenstein, M. S.; Ikemoto N.; Kress, M. H. *Tetrahedron Lett.* **2006**, *47*, 1717–1720.
[146] Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299.
[147] Kerr, M. S.; Read de Alaniz, J.; Rovis, T, *J. Org. Chem.* **2005**, *70*, 5725–5728.
[148] Bull, S. D.; Davies, S. G.; Jones S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 387–398.
[149] For a discussion of the differences between Evans-type chiral auxiliaries and the related *gem*-diphenyl substituted oxazolidinones see Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093–2126.
[150] Fantasia, S.; Petersen, J. L.; Jacobsen, H.; Cavallo, L.; Nolan, S. P. *Organometallics* **2007**, *26,* 5880–5889.
[151] For representative examples see (a) Figadére, B. *Acc. Chem. Res.* **1995**, *28*, 359–365; (b) Tu, L.; Zhao, Y.; Yu, Z.; Cong, Y.; Xu, G.; Peng, L.; Zhang,P.; Cheng, X.; Zhao, Q. *Helv. Chim. Acta* **2008**, *91*, 1578–1587; (c) de Guzman, F. S.; Schmitz, F. J. *J. Nat. Prod.* **1990**, *53*, 926–931; (d) Evidente, A.; Sparapano, L. *J. Nat. Prod.* **1994**, *57*, 1720–1725; (e) Dogné, J.; Supuran, C. T.; Pratico, D. *J. Med. Chem.* **2005**, *48*, 2251–2257; (f) Braña, M. F.; García, M. L.; Lòpez, B.; de Pascual-Teresa, B.; Ramos, A.; Pozuelo, J. M.; Domínguez, M. T. *Org. Biomol. Chem.* **2004**, *2*, 1864–1871.
[152] For illustration of butenolide functionalisation see (a) Jefford, C. W.; Sledeski, A. W.; Boukouvalas, J. *J. Chem. Soc., Chem. Commun.* **1988**, 364–365; (b) Ma, S.; Lu, L.; Lu, P. *J. Org. Chem.* **2005**, *70*, 1063–1065; (c) Jiang, Y.; Shi, Y.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*,

7202–7203; (d) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 8–9; (e) Asaoka, M.; Yanagida, N.; Ishibashi, K.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 4269–4270; (f) Kong, K.; Romo, D. *Org. Lett.* **2006**, *8*, 2909–2912; (g) Kraus, G. A.; Roth, B. *Tetrahedron Lett.* **1977**, *18*, 3129–3132; (h) Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun.* **2004**, 1414–1415; (i) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194; (j) de Oliveira, M. C. F.; Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6995–6997; (k) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319–2322.

[153] Hyde, A. M.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 2663–2666.

[154] US Patent 19960028439P

[155] White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991–4998.

[156] Donohoe, T. J.; Harris, R. M.; Burrows, J.; Parker, J. *J. Am. Chem. Soc.* **2006**, *128*, 13704–13705.

[157] Jazzar, R.; Bourg, J.-B.; Dewhurst, R. D.; Donndieu, B.; Bertrand, G. *J. Org. Chem.* **2007**, *72*, 3492–3499.

[158] White, G. J.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 3177–3178.

[159] Failli, A.; Nelson, V.; Immer, H.; Goetz, M. *Can. J. Chem.* **1973**, *51*, 2769–2775.

[160] *Beil.* **14**, IV, 1555.

[161] Tao, G.-H.; He, L.; Sun, N.; Kou, Y. *Chem. Commun.* **2005**, 3562–3564.

[162] Thomson, J. E.; Campbell, C. D.; Concellón, C.; Duguet, N.; Rix, K.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2008**, *73*, 2784–2791.

[163] Castells, J.; Lopez-Calahorra, F.; Bassedas, M.; Urrios, P. *Synthesis* **1988**, 314–315.

[164] Arduengo, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, 55, 14523–14534.

[165] Barker, A. L.; Skinner, G. S. *J. Am. Chem. Soc.* **1924**, *46*, 40–414.

[166] Davies, J. S.; Hakeem, E. *J. Chem. Soc., Perkin Trans. 2* **1984**,1387–1392.

[167] Commercially available source: Sigma-Aldrich, CAS 7517-19-3.

[168] Benvenuti, S.; Severi, F.; Costantino, L.; Vampa, G.; Melegari, M. *Farmaco* **1998**, *53*, 439–442.

[169] Sibi, M. P.; Chattopadhyay, S.; Dankwardt, J. W.; Snieckus, V. *J. Am. Chem. Soc.* **1985**, *107*, 6312–6315.

[170] Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Chem. Eur. J.* **1996**, *2*, 772–780.

[171] Williamson, C.; Storey, J. M. D.; Harrison, W. T. A**.** *J. Chemical Crystallography* **2006**, *36*, 277–282.

[172] Hulst, R.; de Vries, N. K.; Feringa, E. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699–708.

[173] Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083–2086.

[174] McKennon, M.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568–3571.

[175] Commercially available source: Sigma-Aldrich, CAS 2026-48-4.

[176] Boland, N. A.; Casey, M.; Hynes, S. J.; Matthews, J. W.; Müller-Bunz, H.; Wilkes, P. *Org. Biomol. Chem.* **2004**, *2*, 1995–2002.

[177] Denmark, S. E.; Stavenger, R. A.; Faucher, A. M; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375–3389.

[178] Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232–240.

[179] Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann C. *Chem. Commun.* **2002**, 2704–2705.

[180] Commerically available source: Sigma-Aldrich, CAS 39961-95-0.

[181] Schanz, H.-J.; Linseis, M. A.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 2763–2769.

[182] Denmark, S. E.; Stadler, H.; Dorow, R. L; Kim, J.-H. *J. Org. Chem.* **1991**, *56*, 5063–5079.

[183] Krasik, P.; Alper, H. *Tetrahedron* **1994**, *50*, 4347–4354.

[184] Alexakis, A.; Chauvin, A.-S.; Stouvenel, R.; Vrancken, E.; Mutti, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *8*, 1171–1178.
[185] Watson, I. D. G; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 5160–5167.
[186] Commercially available source: Sigma-Aldrich, CAS 13734-41-3.
[187] Barcelo, G.; Senet, J.-P.; Sennyey, G. *J. Org. Chem.* **1985**, *50*, 3951–3953.
[188] Ullrich, A.; Herrmann, J.; Müller, R.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, 6367–6378.
[189] Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867–12874.
[190] Ostendorf, M.; Dijkink, J.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 115–124.
[191] Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367–1371.
[192] Zhang, Y.-R.; He, L.; Wu, X.; Shao P.-L.; Ye, S. *Org. Lett*. **2008**, *10*, 277–280.
[193] Barfoot, C. W.; Harvey, J. E.; Kenworthy, M. N.; Kilburn, J. P.; Ahmed, M.; Taylor, R. J. K. *Tetrahedron* **2005**, *61*, 3403–3409.
[194] Bull, S. D.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Prasad, S.; Sanganee, H. J. *Synlett* **1998**, 519–521.
[195] Yang, Q.; Wang, X.; Li, Z.; Sun, L.; You, Q.; *Synth. Commun.* **2008**, *38*, 4107–4115.
[196] Tao, T.; He, L.; Sun, N.; Kou, Y. *Chem. Commun.* **2005**, *28*, 3562–3564.
[197] Commercially available source: Sigma-Aldrich, CAS 13734-41-3.
[198] Gibson, S. E.; Mainolfi, N.; Kalindjian, S. B.; Wright, P. T.; White, A. J. P. *Chem. Eur. J.* **2005**, *11*, 69–80.
[199] Cariou, C. A. M.; Kariuki, B. M.; Snaith, J. S. *Org. Biomol. Chem.* **2008**, *6*, 3337–3348.
[200] Hlavacek, J.; Marik, J.; Konvalink, J.; Bennetova, B.; Tykua, R. *Amino Acids* **2004**, *27*, 19–27.
[201] Da, C.-S.; Han, Z.-J.; Ni, M.; Yang, F.; Liu, D.-X.; Zhou, Y.-F.; Wang, R. *Tetrahedron: Asymmetry* **2003**, *14*, 659–665.
[202] Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T.; Ryu, I. *Org. Lett.* **2009**, *11*, 3934–3937.
[203] Li, Y.; Feng, Z.; You, S. *Chem. Commun*. **2008**, 2263–2265.
[204] Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc*. **1991**, *113*, 1299–1308.
[205] Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc*. **2006**, *128*, 925–934.
[206] Iida, H.; Moromizato, T.; Hamana, H.; Matsumoto, K. *Tetrahedron Lett.* **2007**, *48*, 2037–2039.
[207] Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1480–1492.
[208] Pour, M.; Spulák, M.; Balsánek, V.; Kunes, J.; Kubanová, P.; Buchta, V. *Bioorg. Med. Chem.* **2003**, *11*, 2843–2866.