NHCs in Organocatalysis: Azolium Enolate Generation and Synthetic Applications

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degree of Doctor of Philosophy

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Abstract

This thesis details investigations into organocatalytic reactions promoted by N-Heterocyclic Carbenes (NHCs) that proceed *via* an assumed azolium enolate intermediate.

Initial research focused on the catalytic asymmetric synthesis of β-lactones *via* an NHC-catalysed formal [2+2] cycloaddition of alkylarylketenes and chloral. This process operated in good yield (typically >70%) and moderate diastereoselectivity (typically ~75:25 *dr*, *anti:syn*) for a range of alkylarylketenes. The enantioselectivity was consistently high for the major *anti* diastereomer (typically >80% *ee*) and minor *syn* diastereomer (typically >70% *ee*). Interestingly, when a ketene bearing a 2-substituent on the aryl ring, or one that included an α-branched alkyl group was used, an exclusive asymmetric chlorination pathway was accessed. This is, to the best of our knowledge, the first use of chloral as an electrophilic chlorination agent. This methodology was found to be applicable to a range of 2-arylsubstituted alkylarylketenes in good yield and enantioselectivity (typically >70% yield and up to 92% *ee*).

The scope of this reaction with respect to the aldehyde moiety was then analysed with 2-nitrobenzaldehyde providing β-lactone products in excellent *dr* (up to 94:6 *syn:anti*) and with good yield and enantioselectivity (typically >60% yield and >80% *ee*). Importantly these β-lactone products were amenable to further derivatisation with transformation to β-amino- and β-hydroxy acids.

Following the identification of an NHC-catalysed chlorination reaction using chloral, the development of a general procedure was undertaken. Following a wide screen of electrophilic chlorination sources, 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone was identified as optimal, operating in excellent yield (up to 97%) but in moderate to poor levels of enantioselectivity (21–61% *ee*).

Efforts to expand the practicality of azolium enolate processes focused on the use of α-aroyloxyaldehydes as bench stable mono-substituted ketene surrogates. A range of differentially substituted α-aroyloxyaldehydes allowed access to δ-lactones *via* the NHC-catalysed [4+2] cycloaddition between azolium enolates and β,γ-unsaturated α-ketoesters. Following initial optimisation the reaction proceeded in exquisite diastereo- and enantiocontrol (typically >95:5 *dr* and >99% *ee*).

Acknowledgements

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Ac	acetyl
app	apparent
ASAP	atmostpheric solids analysis probe
aq	aqueous
Ar	aryl
Bn	benzyl
BINOL	1,1'-bi-2-napthol
Boc	tert-butyloxycarbonyl
br	broad
Cbz	carboxybenzyl
Cy	cyclohexyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
conc	concentrated
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
decomp	decomposition
DMAP	4-dimethylaminopyridine
DSMO	dimethyl sulfoxide
DMF	*N,N*-dimethylformamide
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalent molar quantity
Et_2O	diethylether
ESI+	electrospray ionisation, positive ion
Et	ethyl
g	gram(s)
GC	gas chromatography
h	hour(s)
HOMO	highest occupied molecular orbital
HOAt	1-hydroxy-7-azabenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i-Bu	isobutyl

IPA	isopropanol
i-Pr	isopropyl
KHMDS	potassium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
M	molar (i.e. mol dm^{-3})/mesomeric effect
m	multiplet
min	minute(s)
Me	methyl
Mes	mesityl
MHz	megahertz
mp	melting point
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
ND	not determined
NFSI	*N*-fluorobenzenesulfonimide
NHC	N-heterocyclic carbene
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NSI	nanospray ionisation
Ph	phenyl
ppm	parts per million
PPY	4-pyrrolidinopyridine
PPY*	ferrocene-fused 4-pyrrolidinopyridine
q	quartet
quant	quantitative
quint	quintuplet
rt	ambient (room) temperature
s	singlet
sat	saturated
t	triplet/time
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol
temp	temperature

TBS	*tert*-butyldimethylsilyl
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSQD	trimethylsilyl quinidine
TS	transition state
v	volume
W	weight

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Chapter 1: Introduction

1.0 Organocatalysis

The term "organocatalysis" describes the promotion or acceleration of a chemical reaction through the addition of a substoichiometric quantity of an organic compound that does not contain a metal atom.[1] This definition represents a synthetic paradigm that was conceived in the late 1990's and has arguably become one of the most desired synthetic methods for the creation of enantiomerically enriched products. The last 100 years has seen sporadic reports of reactions catalysed by small organic molecules; it was not until the landmark publication from the group of MacMillan in 2000 that the advent of iminium ion catalysis as a general reaction platform for organocatalysis was formally conceptualised.[2] In this historic paper[3] MacMillan clearly defines the field in three important ways: (i) the term organocatalysis was introduced for the first time allowing future publications to be placed within a chemical descriptor; (ii) the potential benefits of organocatalysis to both academia and industry were highlighted, for example potential reductions in cost and greater synthetic practicality; (iii) most importantly it introduced the concept of a generic mode of activation that allows multiple reaction types from a single catalytic concept. Arguably this allowed organocatalysis to be considered a viable synthetic strategy for the construction of molecular complexity. Following this publication, the field underwent a rapid expansion and led to organocatalysis becoming recognised as a major branch of catalysis in its own right. Much recent development has focused around five main modes of activation: (i) iminium ion catalysis;[4] (ii) enamine catalysis;[5] (iii) phase transfer catalysis;[6] (iv) H-bonding catalysis;[7] (v) Lewis base catalysis.[8] Representative modern asymmetric examples will be discussed below.

1.1 Iminium ion catalysis

Iminium ion catalysis (a subclass of Lewis base catalysis) was the first mode of activation to be fully explored. It was initially rapidly expanded by MacMillan and co-workers with the development of various imidazolidinone catalysts[9] and more recently through the diaryl prolinol derivatives introduced by Jørgensen *et al.*[10] Iminium ion catalysis has provided some of the most diverse reactions types including asymmetric Diels-Alder,[11] Friedel-Crafts[12] and dihydroxylation[13] reactions. These all operate *via* the common mode of reversible iminium ion formation leading to a lowering of the α,β-unsaturated aldehyde LUMO. In a strikingly simple approach the group of MacMillan utilised catalyst **3** in the asymmetric hydride reduction of enals.[14]

This proceeds *via* iminium ion formation followed by stereoselective reduction by Hantzsch ester **2**. The reaction tolerates a range of saturated aldehydes in good yield (typically >70%) and excellent levels of enantioselectivity (typically >90% *ee*) **(Scheme 1)**.
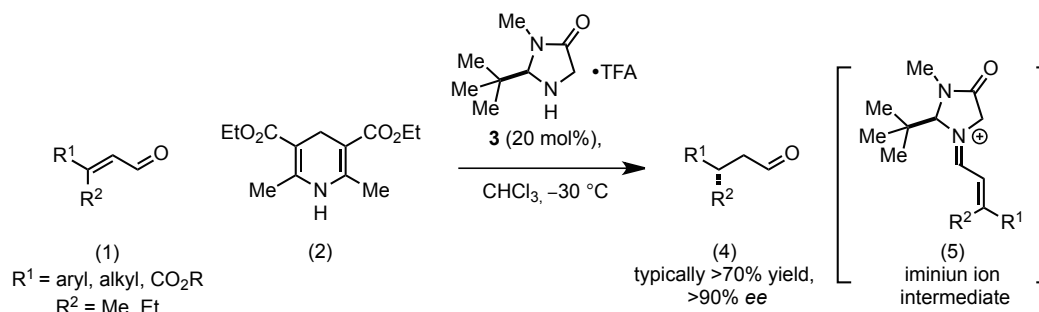
Scheme 1: Iminium catalysed asymmetric hydride reduction of enals.

1.2 Enamine catalysis

The benefits of enamines were reported as early as 1954 by Stork *et al.*,[15] with a later proline catalysed intramolecular aldol reaction published in 1971 independently by Weichert, Sauer and Eder[16] as well as Hajos and Parrish.[17] Despite these foundations, this mode of catalysis lay dormant until the landmark publication of Barbas, Lerner and List in 2000.[18] Following this a wide range of publications focusing on asymmetric enamine catalysis were disclosed, commonly employing either proline,[19] its derivatives, or the imidazolidinones introduced by MacMillan. The stereoselective α-functionalisation of aldehydes and ketones has been an especially active area of enamine catalysis,[20] with the asymmetric fluorination of aldehydes reported in 2005 by the group of MacMillan.[21] Catalyst **8** was found to be efficient for a range of aldehydes producing the valuable α-fluoroaldehyde motif (which were subsequently reduced to the corresponding alcohol **9**) in good yields and excellent enantioselectivities (typically >70% yield and 90% *ee*) **(Scheme 2)**.
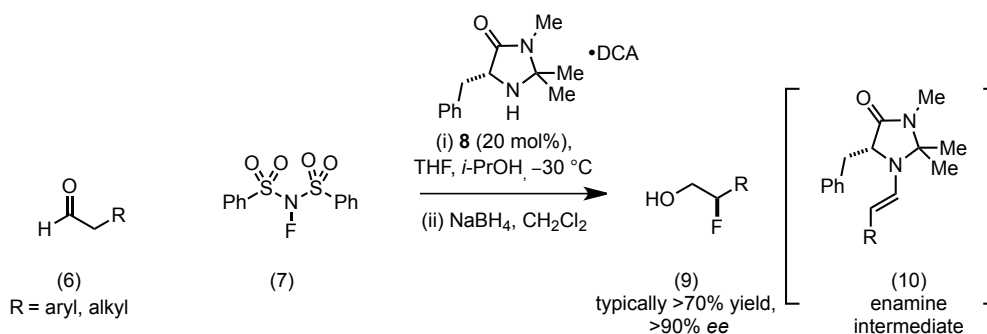
Scheme 2: Asymmetric fluorination of aldehydes *via* enmine catalysis.

1.3 Phase transfer catalysis

Perhaps more than any other mode of activation, phase transfer catalysis, as defined by Starks,[22] has recieved appreciable interest within an industrial chemistry setting. This growth began with the pioneering work of Merck in the 1980's[23] and later spread to the wider academic community with a range of asymmetric organocatalytic strategies. Recent pioneering structure-activity/selectivity relationship studies by the group of Denmark have also sought to quantify the area.[24] One of the major contributors to this area is the group of Maruoka who developed a range of BINOL derived chiral quaternary ammonium salts such as **13**.[25] In a 2005 benchmark publication,[26] catalyst **13** is employed in the benzylation of glycine derived imine **11** (a proving ground for phase transfer catalysts).[27] At the extremely low catalyst loadings of 0.05 mol% and with co-catalytic 18-crown-6, the benzylated product **12** is obtained in an excellent 90% yield and 98% *ee* **(Scheme 3)**.
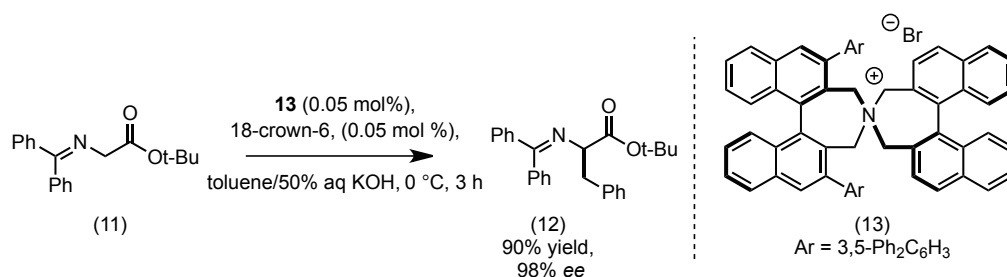
Scheme 3: Asymmetric phase transfer benzylation.

1.4 Hydrogen bonding catalysis

There has been an array of discrete catalyst architectures reported in the last 10 years that can be classified as hydrogen bond donors. These range in the pK_a spectrum from the phosphoric acids initially defined by Terada[28] and Akiyama[29] to the urea[30] and thiourea[31] derivatives of the Jacobsen group. In a recent representative example of the power of hydrogen bonding catalysis, Jacobsen and co-workers report an asymmetric, scalable Strecker synthesis for the preparation of a wide variety of unnatural α-amino acids **(Scheme 4)**.[32] Mechanistically, the thiourea **16** is postulated to facilitate the formation of a catalyst-bound iminium/cyanide ion pair through hydrogen bond interactions.[33] Collapse of this ion pair in the rate determining C–C bond forming event releases the α-aminonitrile **15** and the thiourea catalyst **16**.
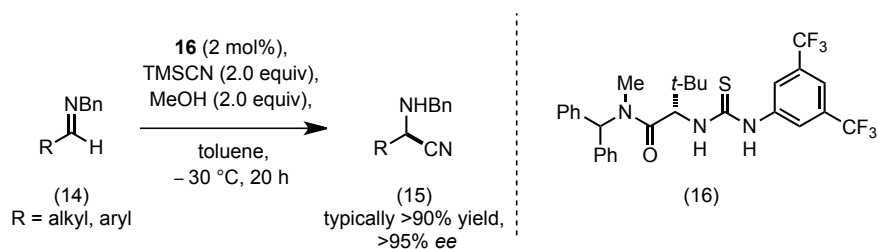
Scheme 4: Asymmetric Strecker reaction *via* H-bonding catalysis.

1.5 Lewis base catalysis

Lewis base catalysis (that includes the previously summarised iminium and enamine catalytic modes) has been the area of greatest appreciable research since the birth of organocatalysis. Defined in its simplest terms by the donation of a pair of electrons,[34] Lewis bases span a broad catalysis landscape[8] from iminium and enamine to ammonium enolate[35] and acyl ammonium manifolds[36] **(Fig 1)**. NHC catalysis is also contained within this mode of activation and will be the basis for the forthcoming review of the literature.
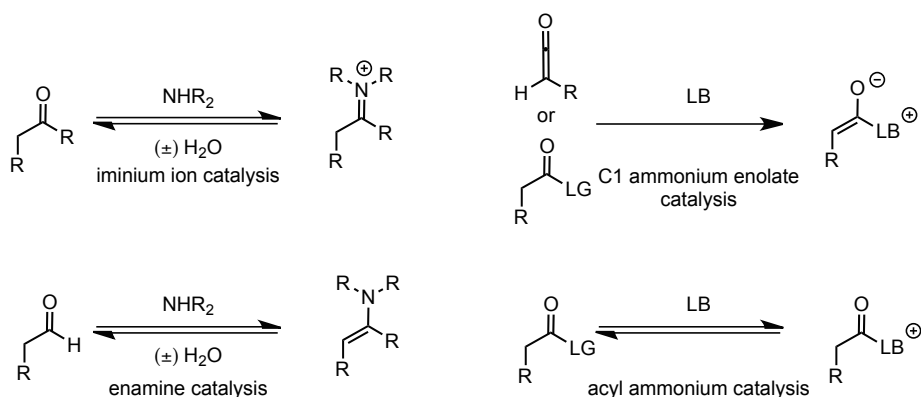
Fig 1: Modes of Lewis base activation.

2.0 N-Heterocyclic Carbenes

Carbenes are neutral compounds featuring a divalent carbon atom with only six valence electrons in two possible ground state spin multiplicities.[37] Singlet carbenes possess a filled and a vacant orbital and show ambiphilic character whereas triplet carbenes contain two singly occupied orbitals and behave as diradicals. NHCs are a specific class of carbene that typically contain two adjacent nitrogen atoms. NHCs typically exhibit greater stability when compared to other classes of carbene which can be simplistically attributed to a "push-pull" stabilisation **(Fig 2)**. This mechanism operates *via* the mesomeric donation of a nitrogen lone pair into the vacant *p* orbital, with a concurrent electron withdrawing effect from the doubly occupied σ orbital to

the electronegative nitrogen substituent. NHCs can also be kinetically stabilised by sterically bulky *N*-substituents that provide shielding of the carbene centre, through which their lifetime, with respect to dimerisation, is extended.
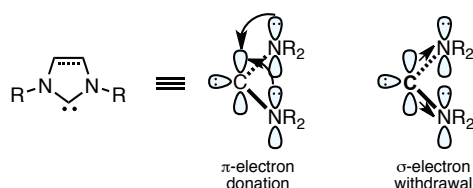
Fig 2: Stabilisation of NHCs.

These factors contributed to the isolation of the first stable crystalline form of an NHC in 1991 by Arduengo *et al.*[38] who employed an imidazolinylidene framework with sterically bulky *N*-adamantyl substituents **(Scheme 5)**. This publication followed the previous 1988 report of Bertrand who isolated the first stable phosphinocarbene.[39] The early pioneering work of Wanzlick and co-workers in the field must also be recognised, as although the isolation of a free NHC was never reported they were actively involved in the preparation of imidazolidin-2-ylidenes as early as the 1960's.[40]
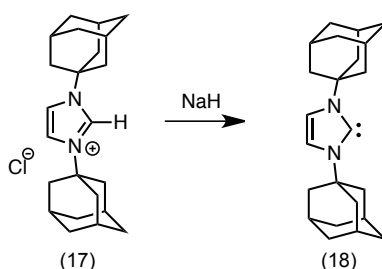
Scheme 5: Preparation of the first stable NHC.

One of the earliest reports of carbene Lewis base catalysis was the 1943 account of Ukai *et al.*[41] where the ability of thiazolium salts to promote the benzoin reaction was demonstrated. These transformations are postulated to occur *via* the catalytic effect of a carbene type intermediate, first proposed by Breslow[42] and based on the initial ideas of Lapworth's similar system[43] that was used to explain the thiamine catalysed benzoin condensation **(Fig 3)**. This function, by which an electron deficient moiety is converted into a nucleophilic 'Umpolung' (reversed polarity)[44] species, is the basis of the reaction pathway induced by the action of an NHC.
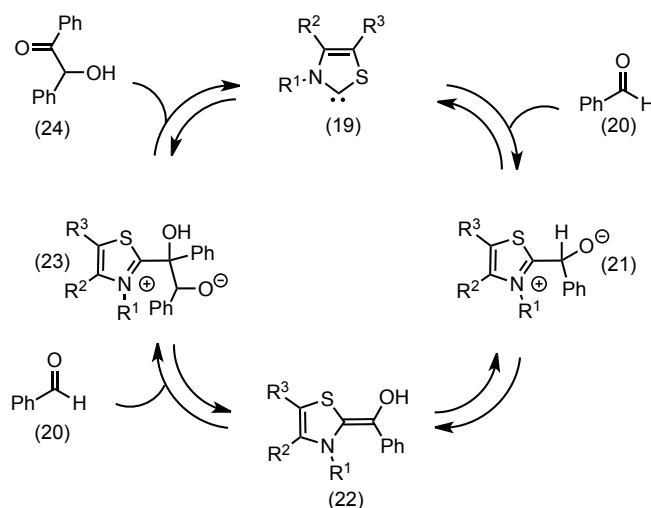
Fig 3: Proposed mechanism for the thiamine catalysed benzoin condensation.

While NHC mediated organocatalysis was founded *via* this 'Umpolung' mode of reaction[45] centred upon thiazolium derived NHCs, recent research has moved away from employing thiazolinylidenes to other catalyst architectures such as imidazolidinylidenes, imidazolinylidenes and triazolinylidines. The acyl anion mode of reactivity, more specifically the benzoin reaction, was the first to be studied in detail. This reaction and the corresponding intramolecular α,β-unsaturated aldehyde variant (Stetter reaction)[46] represent the most heavily investigated use of acyl anion synthons. More recently, other modes of reactivity have been demonstrated that have widened the scope of NHC reactions, allowing access to d^2 (enolate), d^3 (homoenolate) and eletrophilic a^1 synthons **(Fig 4)**.
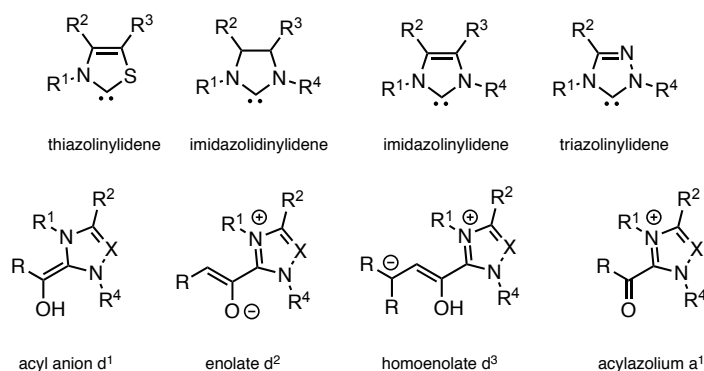
Fig 4: Representative NHC scaffolds and modes of reactivity.

3.0 Modes of NHC induced reactivity

3.1 Generation and reactivity of acyl anion equivalents in asymmetric catalysis

The first reported asymmetric benzoin reaction was by Sheehan and Hunneman[47] in 1966 who employed thiazolium precatalyst **25** to achieve an *ee* of 22%. Although wide ranges of thiazolium architectures were later developed, the levels of enantioselectivity remained low, with the axially chiral precatalyst **26** proving optimal to date.[48] It was not until the introduction of triazolium precatalyst **27–29** by the groups of Enders[49] and Leeper[50] in the later 1990's that the obtained level of enantioinduction reached practical levels (up to 90% *ee*) **(Scheme 6)**.

The current state of the art in the benzoin condensation is the 2009 report from the group of Connon.[51] Crucial is the employment of precatalyst **30**, bearing both a *N*-C$_6$F$_5$ substituent and a free hydroxyl group, the former being vital for good reactivity and the latter for high enantioselectivity. These two important catalyst features combine to provide both the broadest scope of tolerable aldehydes and the highest enantioselectivities to date.
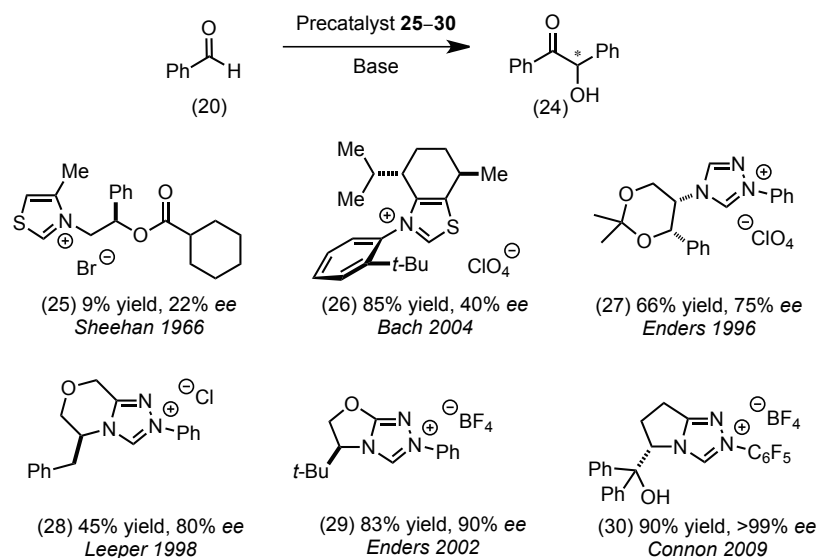
Scheme 6: Development of NHCs in the asymmetric benzoin reaction.

Since the original report by Stetter and co-workers in 1976[52] the application of acyl anion chemistry to the asymmetric Stetter reaction has received much attention.[53] In this reaction process the acyl anion equivalent adds to a Michael acceptor to furnish a new C–C bond. Due to the inherent problem with competing benzoin reaction research initially focussed on the more facile intramolecular Stetter reaction. Enders and co-workers were the first to report the asymmetric Stetter reaction on substrate **31**

utilising precatalyst **33**,[54] with subsequent work detailing a diverse set of NHC precatalysts that have been developed and evaluated on substrate **31**. The group of Miller demonstrated the structurally interesting peptidic thiazolium precatalyst **34**[55] with the current state of the art represented by precatalyst **35** developed within the group of Rovis **(Scheme 7)**.[56]
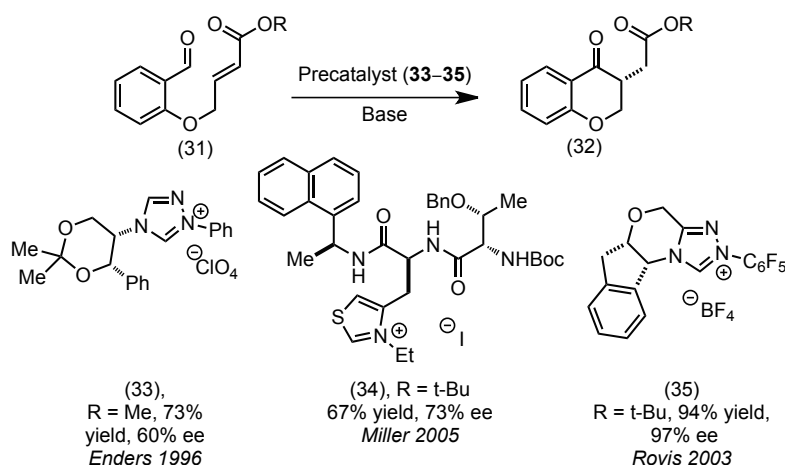
Scheme 7: Development of NHCs for the asymmetric intramolecular Stetter reaction.

The asymmetric intermolecular Stetter reaction, in comparison to the intramolecular variant, has only recently been investigated. Only sporadic reports from the group of Enders[57] were known prior to the recent studies of Rovis *et al.* who, in the current state of the art, generate Stetter products **38** from heteroaryl aldehydes **36** and nitroalkenes **37** in excellent yield and enantioselectivity (up to 98% yield and 90% *ee*).[58] Although this report is a clear advancement in the field, the problems of competing benzoin condensation continue to severely restrict the reaction scope and utility **(Scheme 8)**.
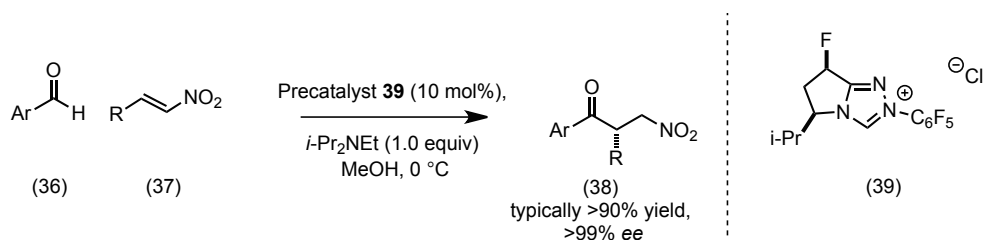
Scheme 8: Current state of the art in asymmetric intermolecular Stetter reaction.

3.2 Generation and reactivity of homoenolate equivalents in asymmetric catalysis

Under specific conditions homoenolates[59] can be generated from the action of a NHC with an enal. Following NHC addition and proton transfer to form the Breslow intermediate **42**, tautomerisation of this species can lead to homoenolate **43 (Fig 5)**.
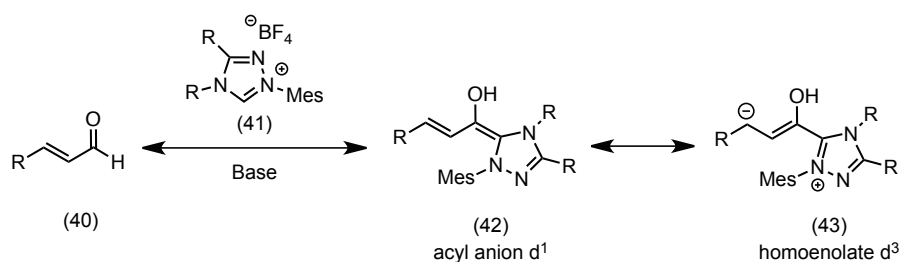
Fig 5: Generation of homoenolates form enals.

The generation and reactivity of homoenolates from enals was independently investigated by the groups of Glorius[60] and Bode[61] in the synthesis of γ-butyrolactones **46**. The former also reported the use of chiral NHC precatalyst **47**, however only low levels of enantioselectivity were obtained (25% *ee*) **(Scheme 9)**.
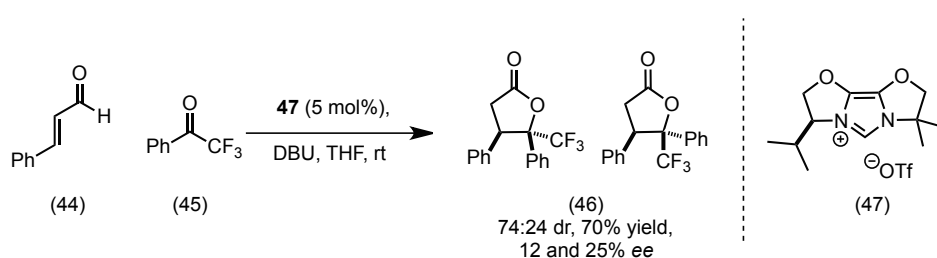
Scheme 9: Synthesis of γ-butyrolactones *via* formal [3+2] cycloadditions of homoenolates with trifluoromethylketones.

In a recent study the group of Scheidt has shown the ability of homoenolates to participate in asymmetric formal [3+2] cycloadditions with nitrones.[62] The reaction employing precatalyst **51** proceeds with excellent levels of diastereo- and enantioselectivity (typically >70% yield and 90% *ee*) for a range of aryl nitrones **49** and alkyl or aryl substituted enals **48 (Scheme 10)**.
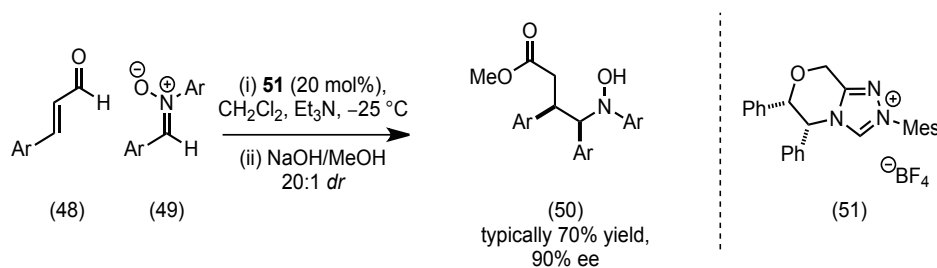
Scheme 10: Asymmetric formal [3+2] cycloadditions of homoenolates with nitrones.

4.0 Generation and reactivity of azolium enolates in asymmetric catalysis

Following extensive investigation into the benzoin and Stetter reactions attention turned to extending the reactive centre from a d^1 to a d^2 synthon, thus formally inducing enolate type reactivity. This mode of reactivity has allowed access to novel structural motifs and has become an especially efficient route to a range of important heterocyclic scaffolds *via* formal [2+2], [4+2] and, to a lesser extent, [3+2] type cycloadditions. Synthetically interesting enantioenriched esters and α-chloroesters have been furnished along with other reaction modes such as intramolecular cyclisations and desymmetrisations, often leading to high levels of molecular complexity. There are three distinct modes of generation for azolium enolates: *via* ketenes, α-functionalised aldehydes and enals that will serve as valid subclasses for the forthcoming section **(Fig 6)**.
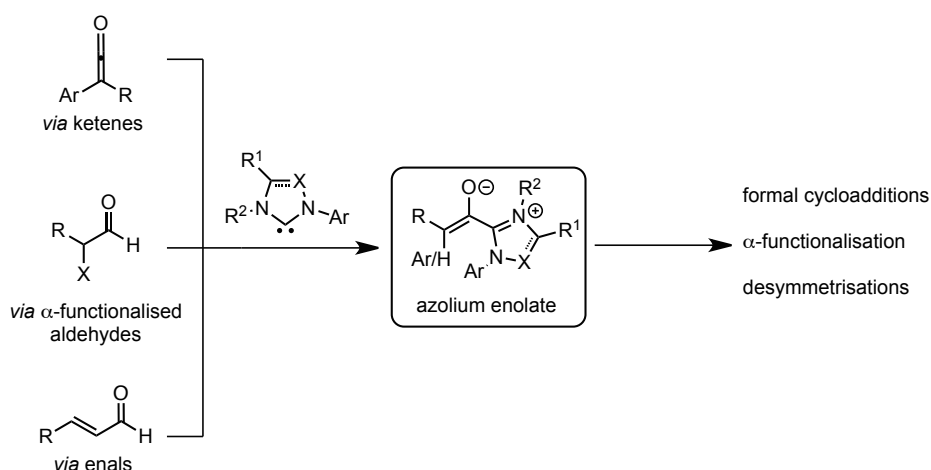
Fig 6: Generation of azolium enolates.

4.1 Generation of azolium enolates *via* ketenes
4.1.1 Ketenes

Ketenes are a class of highly reactive carbonyl containing molecules.[63] A ketene was probably first prepared by Wedekind in 1901 when he treated diphenylacetyl chloride with *n*-Pr$_3$N and noted the formation of the *n*-Pr$_3$N.HCl salt.[64] He did not however, isolate the ketene and thus allowed the first characterisation to be reported by Staudinger.[65] In 1905, inspired by the formation of the stable triphenylmethyl radical by Gomberg,[63] Staudinger was successfully able to isolate diphenylketene **51** *via* the dehalogenation of 2-chlorodiphenylacetyl chloride **52** with zinc. Diphenylketene represents one of the most stable compounds of this class whose behaviours are

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typified by the highly electrophilic C^1 carbon. The highest occupied molecular orbital (HOMO) **54** lies perpendicular to the ketene plane, showing substantial electron density on oxygen and C^2. The lowest occupied molecular orbital (LUMO) **55** shows significant positive charge character at C^1 explaining the observed trend for nucleophilic addition to this carbon **(Fig 7)**.[66]
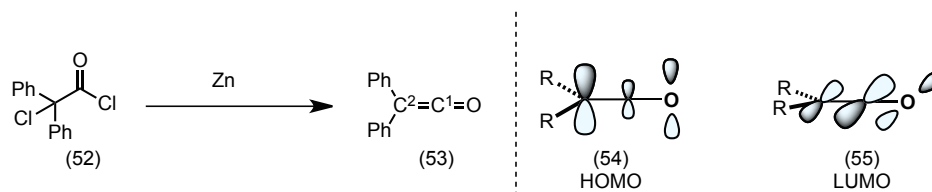
Fig 7: Formation of diphenylketene and HOMO and LUMO representations for diphenylketene.

Although diphenylketene represents one of the most stable disubstituted ketenes, owing to the steric shielding of the C^1 carbon that hinders its dimerisation, a wide range of other more reactive ketenes can be prepared and utilised in synthesis. There are many methods for the formation of ketenes[67] other than that first used by Stuadinger, for example pyrolysis of the parent dimer or acid anhydride. A route to form other less reactive ketenes is *via* the dehydrohalogenation of acyl chlorides, reported by Staudinger in 1911.[68] This method, although generally limited to alkylarylketenes, benefits from the preparative ease of the parent acyl halides and easy removal of the base hydrochloride salt *via* filtration.

Since their discovery ketenes have shown a vast array of different reactivities.[69] The [2+2] cycloaddition however, remains the most characteristic and most investigated reaction type. Staudinger's original 1907 report of the formation of β-lactams from ketenes and imines[70] continues to receive attention and serve as a inspiration for more modern synthetic approaches to these biologically important motifs. A variant of the Staudinger β-lactam synthesis by Fu and co-workers involves the use of electrophilic imines **57**, with Umpolung ketene reactivity generated from addition of a Lewis basic catalyst[71] to form an enolate. In this reversal of reactivity, excellent enantiomeric induction (typically >90% *ee*) can be achieved *via* the use of PPY derivative **59** as a chiral Lewis basic catalyst **(Scheme 11)**.
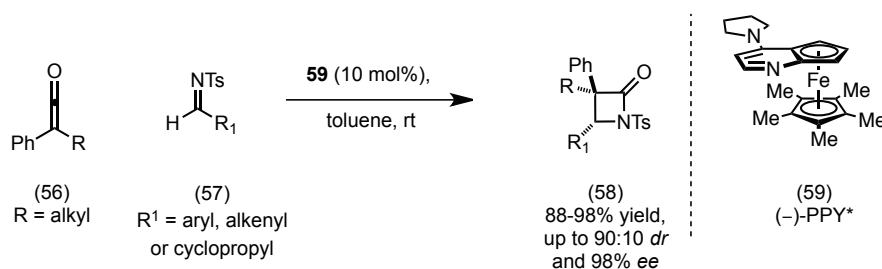
Scheme 11: Asymmetric β-lactam synthesis from ketenes and imines.

Interestingly, in a stereo-complementary report from Fu and co-workers the use of *N*-Tf imines resulted in a switch of diastereoselectivity.[72] In this instance the *anti* β-lactams **62** were formed as the major product with equally high levels of enantioselectivity observed **(Scheme 12)**.

SO$_2$R = Ts: 11:89 *dr; syn* major (98% *ee*)
SO$_2$R = Tf: 97:3 *dr; anti* major (63% *ee*)
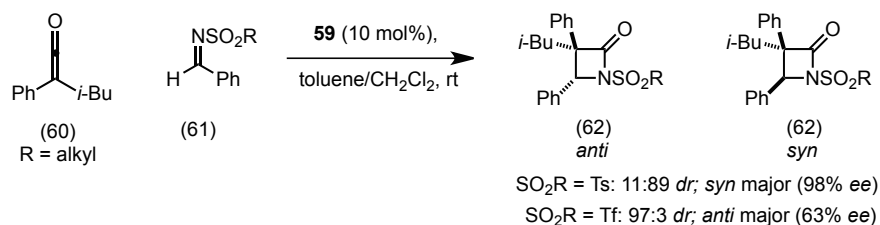
Scheme 12: Switch in diastereoselectivity for the use of *N*-Tf imines when compared to *N*-Ts imines in the asymmetric β-lactam synthesis.

This mode of ketene activation has been heavily investigated in the last ten years, especially in formal [2+2], [4+2] and α-functionalisation reactions.[73] In a series of other excellent reports Fu expands the scope of this reaction mode to encompass a range of formal cycloadditions allowing, amongst others, the synthesis of aza β-lactams,[74] β-lactones[75] and nitroso derived α-hydroxycarboxylic acids.[76] These pioneering studies of Fu employing ketenes as precursors to ammonium enolates functioned as invaluable inspiration for the development of the first studies into the action of ketenes and NHCs.

4.1.2 NHC-catalysed formal [2+2] cycloadditions employing ketenes

There have been many recent publications on formal [2+2] cycloaddion reactions (concurrent with this thesis) and an appropriate selection of which will be discussed in the following section.[77]

The groups of Smith and Ye independently discovered the field of NHC-mediated ketene derived azolium enolate chemistry in 2007. Ye[78] employed (*R*)-pyroglutamic

acid derived precatalyst **66** in the formal [2+2] cycloaddition of unsymmetrical alkylarylketenes and *N*-Boc imines **64** with excellent levels of diastereo- and enantioselectivities (up to 99:1 *dr* and 99% *ee*). The work of Smith[79] employed a similar reaction protocol with diphenylketene and *N*-tosyl imines **68**, the optimum precatalyst being either triazolium **70** or imidazolium precatalyst **71** providing up to 75% *ee* that could be further increased to 99% with recrystallisation **(Scheme 13)**. The enantiocontrol in the reaction employing precatalyst **71** was shown to be relayed from the cyclohexane backbone to the reactive centre *via* the intimacy of the *N*-benzyl substituent.[80] This effect was later fully investigated with a variety of catalyst skeletons and *N*-substituents examined.[81]
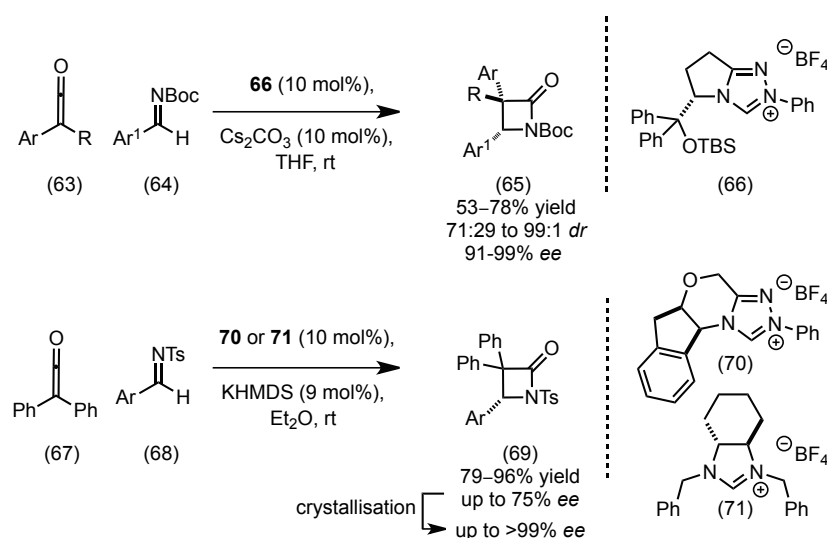
Scheme 13: NHC-catalysed formal [2+2] cycloaddition between ketenes and imines.

A common mechanistic rationale for formal [2+2] cycloaddition is shown in **(Fig 8)**. Attack of NHC **72** on the ketene α-carbon, *anti* to the aryl unit,[82] yields enolate **73** with subsequent addition to imine **64** to produce zwitterionic intermediate **74**. Collapse of this species generates β-lactam **65** and releases NHC **72** back into the catalytic cycle. The origin of enantio-and diasterstereo selectivity was not rationalised in the original work of Ye however it has been recently investigated computationally by Tang and co-workers.[83]
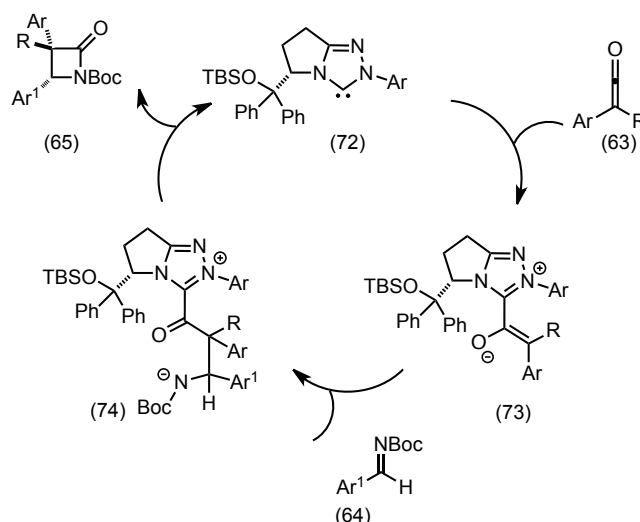
Fig 8: Postulated catalytic cycle for the NHC-catalysed β-lactone synthesis.

The β-lactone functionality can be generated by either the use of 2-oxoaldehydes[84] or trifluoromethylketones.[85] For the synthesis of β-lactones **76** from 2-oxoaldehydes **75**, alkylarylketenes incorporating a 2-substituent on the aryl portion, or an *i*-pr alkyl moiety, were vital for high diastereoselectivity. In this series the *anti* lactones are obtained in good yield (typically >70%) in excellent diastereo- and enantioselectivities (up to >20:1 *dr* and 99% *ee*) **(Scheme 14)**.
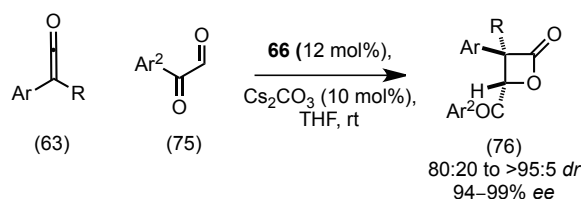
Scheme 14: NHC-catalysed asymmetric β-lactone synthesis from ketenes and oxoaldehydes.

Trifluoromethyl lactones **78** were generated in equally impressive yields and selectivities, (typically >80% yield and up to 23:1 *dr* and 99% *ee*). In this instance the use of an alkylarylketene substituted in the two position, or an *i*-pr alkyl substituent provided no reaction. This is a structural feature consistent with a range of formal [2+2] and [4+2] ketene cycloadditions employing NHCs, where either 2-substitution of the aryl unit, or α-branching on the alkyl substituent, generally results in reduced yields or in some specific cases, a reversal of enantioselectivity (*vide infra*).
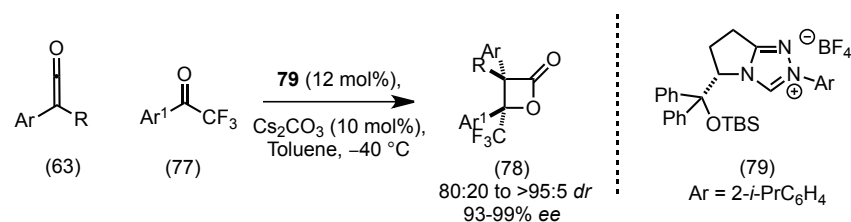
Scheme 15: NHC-catalysed asymmetric β-lactone synthesis from ketenes and trifluoromethyl ketones.

Biologically important spirocyclic oxindoles **81** were generated *via* the formal [2+2] cycloaddition between disubstituted ketenes and isatins **80 (Scheme 15)**.[86] Although the reaction only proceeded in moderate diastereoselectivity (typically 3:1 *dr*, *anti:syn*) the levels of enantioselectivity for the major diastereomer were uniformly outstanding (13 examples of 99% *ee*). A range of alkylarylketenes were tolerated in the process, however 2-substitution on the aryl portion resulted in significantly lower yield. The scope of the isatin *N*-substituent was briefly explored with *N*-Me, *N*-Bn and *N*-Cbz substituents all providing similarly high yields and enantioselectivities, with the moderate diastereoselectivity for the *anti* isomer also retained. The reaction utility was also demonstrated *via* ring opening of the oxindole-β-lactone **81** to generate the corresponding hydroxy ketone **82** with no erosion of enantiointegrity.
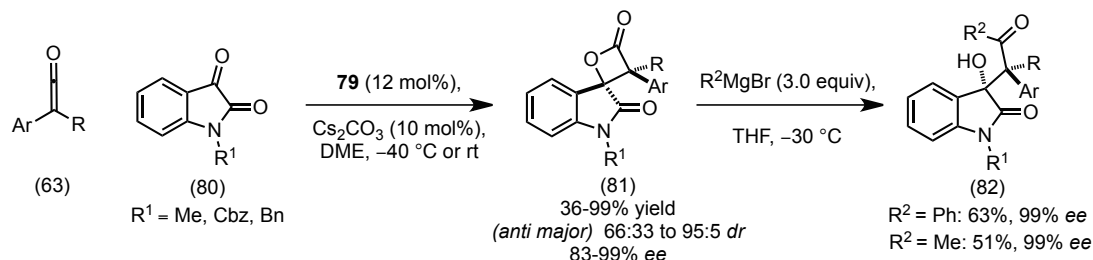
Scheme 16: NHC-catalysed asymmetric spiro-β-lactone synthesis from ketenes and isatins.

Nitrogen electrophiles are also well suited to similar cycloaddition processes, with diazenedicarboxylates **83** and disubstituted ketenes providing access to aza β-lactams **84** with excellent enantioselectivity **(Scheme 17)**.[87] The nature of the *N*-carbonyl group is crucial for control of formal [2+2] *vs* [4+2] reaction processes, with the carboxylates providing [2+2] cycloaddition products with various alkylarylketenes in excellent yields (typically 80–90%) and good to excellent enantioselectivities (typically 80–90% *ee*). Interestingly, employment of a ketene bearing a 2-substituted aryl moiety or one including an α-branch on the alkyl portion resulted in a switch in enantioselectivity to the opposite enantiomer (2-chlorophenylethyl ketene provided

52% yield and 57% *ee*). A limited range of other dialkyl diazenedicarboxylates (dimethyl, di(*i*-propyl), and di(*t*-butyl)) were also shown to be valid coupling partners with the cycloaddition reaction producing similar results.
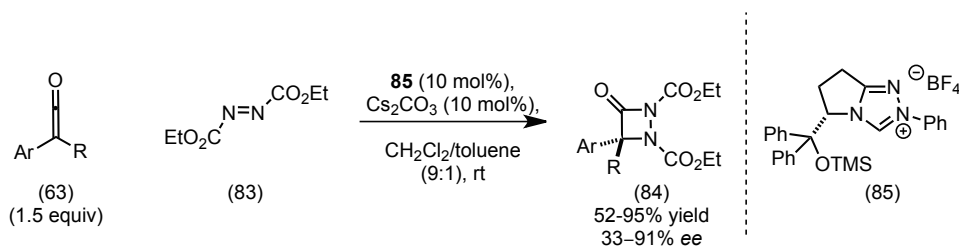
Scheme 17: NHC-catalysed asymmetric aza-β-lactam synthesis from ketenes and diazenedicarboxylates.

Alkylarylketenes have also been employed in dimerisation reactions promoted by precatalyst **87**, forming the unsymmetrical dimer **86** in exclusive regioselectivity and with good to excellent levels of enantiocontrol (46–99% yield and typically >90% *ee*) **(Scheme 18)**.[88] The lactone products served as viable synthetic precursors with reductive ring-opening providing β-keto alcohols in high *dr* (typically >99:1) and with no erosion of enantiointegrity. The enantioselectivity of the reaction was shown to be dependent on the use of precatalysts with a free hydroxyl group (such as **87**) and, as such, a stereochemical model featuring a key hydrogen-bond between the NHC and the ketene was postulated.
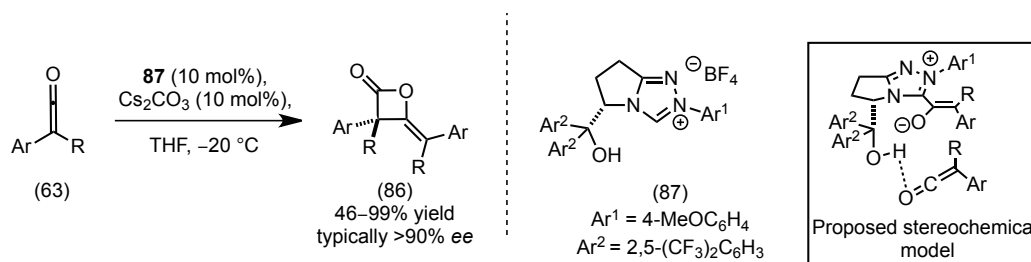
Scheme 18: NHC-catalysed asymmetric ketene dimerisation with postulated stereochemical model.

4.1.3 Formal [4+2] cycloadditions employing ketenes

Prior to the reported formal [2+2] cycloaddition of ketenes and diazenes **(Scheme 17)** the corresponding formal [4+2] cycloaddition was realised *via* the use of *N*-benzoyldiazenes **89 (Scheme 19)**.[89] This reaction proceeds in good yield and excellent enantioselectivity for a wide range of alkylarylketenes (up to 97% yield and 97% *ee*). Control of this dibenzoyldiazene reaction is highly dependent on the catalyst substructure, with the *N*-substituent playing a pivotal role in the level and absolute

sense of configuration at the newly formed stereocentre. Precatalyst **66** and **91** bearing the *N*-phenyl group provided product **88** with the (*S*) absolute configuration at the quaternary centre, whereas *N*-mesityl substituted precatalyst **92** supplied the (*R*)-enantiomer of **90**.
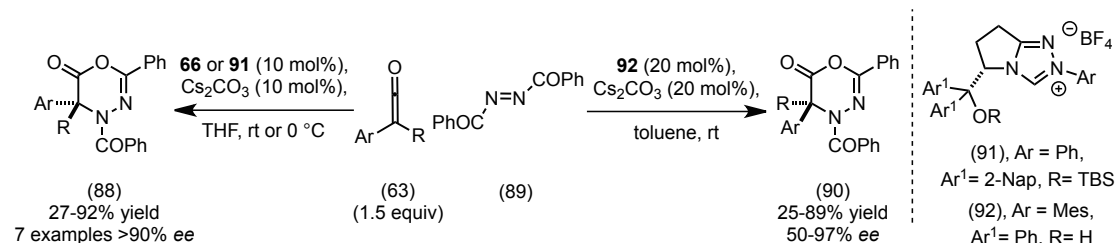
Scheme 19: NHC-catalysed asymmetric [4+2[cycloaddition between ketenes and diazenes.

To account for this difference in selectivity the authors proposed two possible transition states (TS) based on the orientation of the enolate to the triazole framework. Following addition of the NHC to the ketene, the enolate can adopt a conformation whereby maximum orbital overlap can be achieved, with the enolate and triazole portions adopting a coplanar conformation (TS A). This conformation, however, is not available with the mesityl substituted precatalyst **92** due to the larger steric demand or the *N*-aryl substituent, favouring a perpendicular orientation (TS B) that leads to the opposite absolute configuration (**Fig 9**). This provides access to both enantiomers of the product, which was shown to undergo ring opening by MeOH/NaOMe to afford α,α−disubstituted-α−amino acid derivatives.

Coplanar TS A   Perpendicular TS B
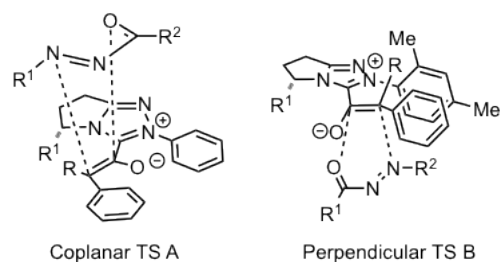
Fig 9: Proposed rationale for the switch in absolute configuration. One methyl group of the mesityl group has been omitted for clarity.

In an interesting extension of the formal [4+2] cycloadditions of ketene derived enolates to a 4π component, unsaturated acyl chlorides **97** were employed as vinylogous dienolate precursors in a [4+2] cycloaddition reaction with ketones **(Scheme 20)**.[90] Reactions with trifluoromethyl ketones **77** provided dihydropyranones **96** in excellent yield (up to 94%) and good enantioselectivity (typically >70% *ee*). Isatins **79** were also effective coupling partners in this methodology leading to

spirocyclic oxindole-dihydropyranones **93** in equally impressive yield (typically >75%) and enantiocontrol (71–95% *ee*). The dihydropyranone products proved amenable to further derivatisation including epoxidation, leading to products with enantioenriched trifluoromethyl bearing stereogenic centres.
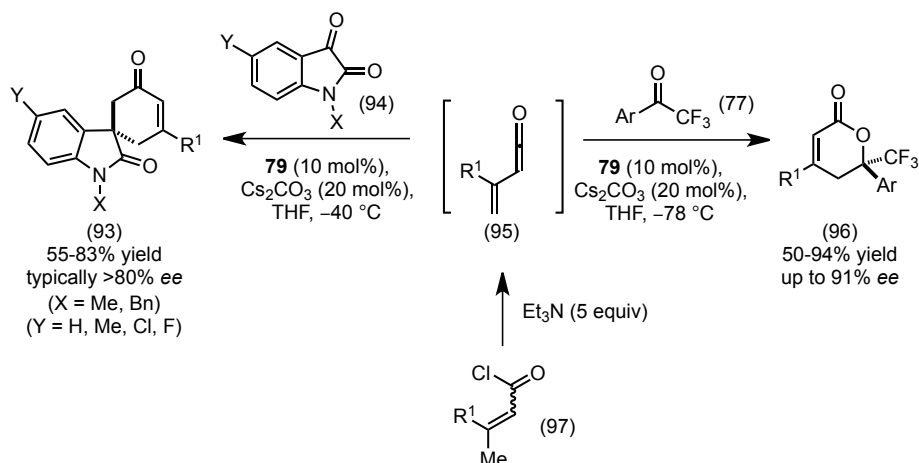
Scheme 20: Asymmetric formal [4+2] cycloaddition reaction employing vinylogous dienolate.

4.2 Generation of azolium enolates from α-functionalised aldehydes

Whilst the addition of an NHC to a ketene allows direct and rapid access to a reactive enolate equivalent, the high sensitivity and limited diversity of the ketene component has led to the development of alternative protocols that allow the *in situ* generation of an azolium enol or enolate intermediate. This mode of generation has been widely utilised as a means to access an acylazolium species **162** from α-functionalised aldehydes **98 (Fig 10)** *via* sequential elimination of a suitable leaving group from the Breslow intermediate **101** to form the azolium enol or enolate species **99**. This can then undergo protonation to form an acylazolium **102** and undergo further redox esterification and amidation processes.[91] There has also been appreciable research into the direct use of the enol or azolium intermediate in a number of different reactions, especially those that asymmetrically forge carbon-carbon bonds. For those reactions that employ the enol or azolium intermediate in catalysis the use of a catalyst bearing a *N*-mesityl substituent is crucial to obtain good reactivity. In a recent and insightful study by the group of Bode[92] the *N*-mesityl substituent is rationalised to increase the rate of formation of Breslow intermediate **101** and accelerate the likely irreversible and rate determining displacement of leaving group to generate azolium enolate **99**. The *N*-mesityl substituent is also postulated to enhance the electron density of the enolate **99** and reduce the unwanted tautomerisation to the acylazolium **102**.
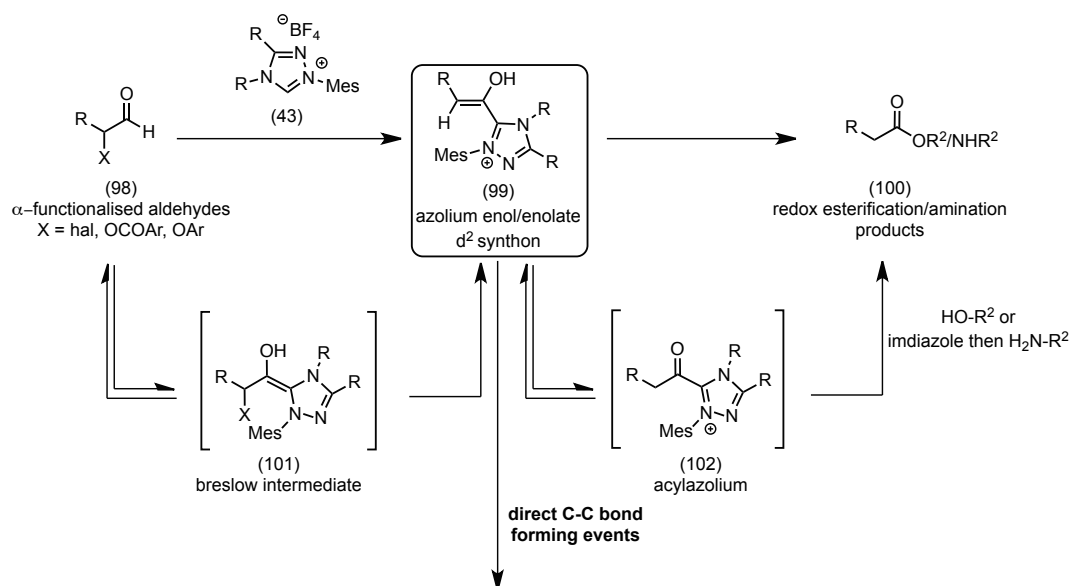
Fig 10: Generation of azolium enolates from α-Functionalised aldehydes.

In 2005 Rovis and co-workers developed a novel strategy to access α-chloroesters *via* the enantioselective protonation of an *in situ* generated α-chloroenolate **107 (Scheme 21)**.[93] The use of a bulky acidic phenol **104** as a buffer negated the problem of background epimerisation of the product and in combination with an excess of an alternative phenolic compound provided access to a range of α-chloroesters **105** in good yields (typically 60–70%) and excellent enantioselectivity (84–93% *ee*). This methodology was later extended to the direct synthesis of α-halo carboxylic acids *via* the use of water as a nucleophile in a biphasic reaction medium.[94] Both asymmetric protonation and deuteration could be achieved in excellent yields and enantioselectivites (up to 95% yield and 95% *ee*). Further pharmaceutical importance was demonstrated by the generation of α-fluoro carboxylic acids with excellent enantiocontrol (up to 96% *ee*) from the redox hydration of α-fluoroenals.
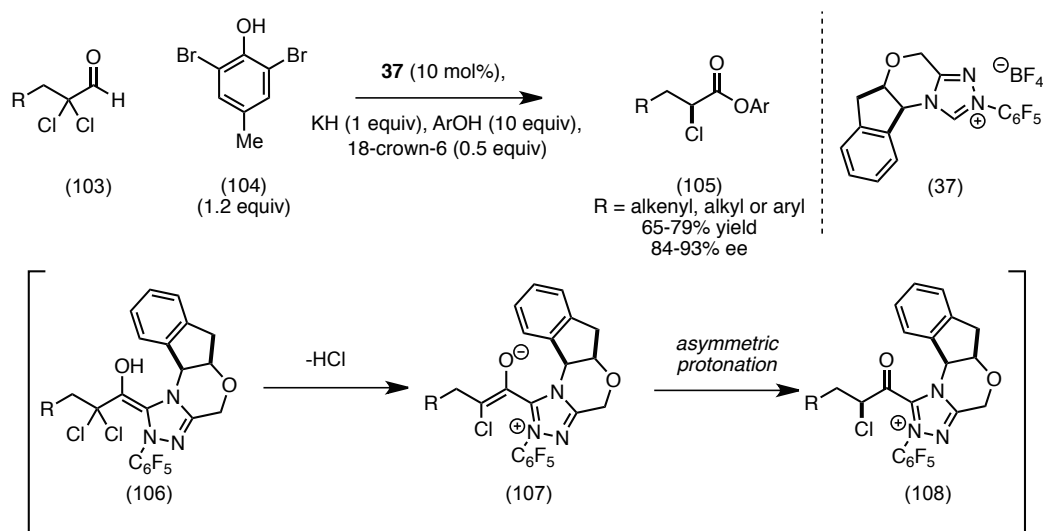
Scheme 21: NHC-catalysed asymmetric synthesis of α-chloro esters.

The use of α-halo aldehydes was extended to racemic α-chloroaldehydes **109** by the group of Bode who showed them to be effective enolate precursors in the [4+2] oxodiene Diels-Alder reaction with enones **110 (Scheme 22)**.[95] Very low catalyst loadings of 0.5 mol% of **122** were used to prepare a range of 3,4,6-trisubstituted dihydropyran-2-ones **111** in excellent yield (up to 98%) and with high diastereo- and enantioselectivity (up to >20:1 *dr* and typically 99% *ee*, respectively). The absolute configuration of the α-chloro stereocentre was not important in the success of the reaction, as identical results were observed using both enantiomers of the aldehyde. During the reaction, complete epimerisation of the starting α-chloroaldehyde occurred after 1.5 h, accounting for this observation.
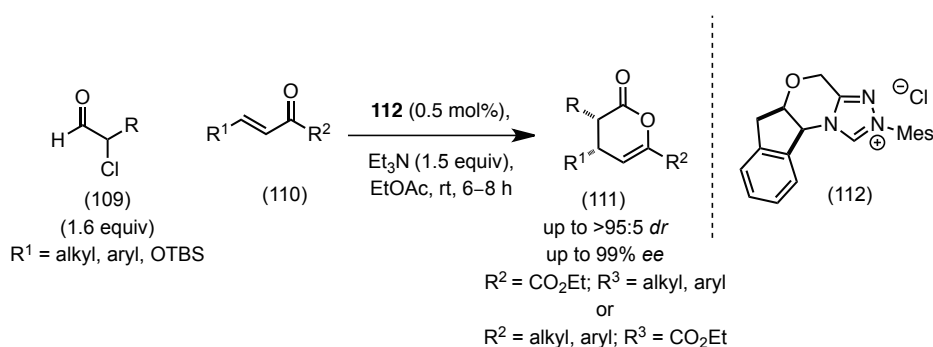
Scheme 22: Synthesis of dihdropyran-2-ones from α-chloro aldehydes.

4.3 Generation of azolium enolates from enals

A second synthetic route for obtaining azolium enolates from aldehydes is the addition of an NHC **41** to an enal **40**. Under specific conditions β-protonation of the homoenolate species **43** leads to the azolium enolate **99 (Fig 11)**. As with those

enolates generated from α-halo aldehydes, the use of an NHC bearing an *N*-mesityl substituent is crucial for control of the reaction mode, in this instance increasing the propensity of tautomerisation of the acyl anion species **42** to access either homoenolate **43** or the desired enolate **99**.
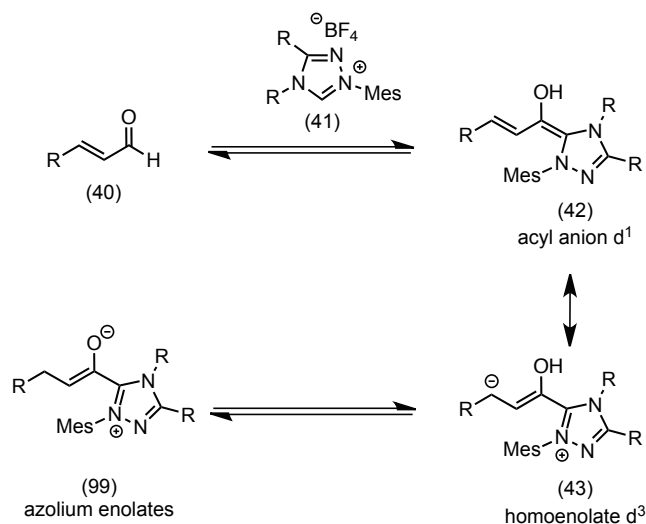
Fig 11: Generation of azolium enolates from from enals.

Recently Bode *et al.* has fully explored and expanded the scope of enal derived enolate equivalents in the formation of a range of substituted dihydropyran-2-ones **115 (Scheme 23)**.[96] Crucial to the control of undesired homoenolate pathways and promotion of the enolate mode of reactivity is the use of a weak amine base such as *N*-methylmorpholine (NMM) or 4-dimethylaminopyridine (DMAP). This facilitates the protonation of the homoenolate from the conjugate acid of the amine base at a faster rate than direct homoenolate C–C bond formation, minimising this potential side reaction. A wide range of electron deficient enones **114** were demonstrated to be good coupling partners with the catalytically formed enolate equivalent, with outstanding levels of diastereo- and enantioselectivity uniformly observed (typically >20:1 *dr* and 99% *ee*) in the formation of heterocyclic products **116–120**. The [4+2] reactivity of enolates derived from enals could also be extended to the use of α,β-unsaturated imines, generating dihydropyridinone products in high diastereo- and enantioselectivity (>20:1 *dr* and typically 99% *ee*).[97]
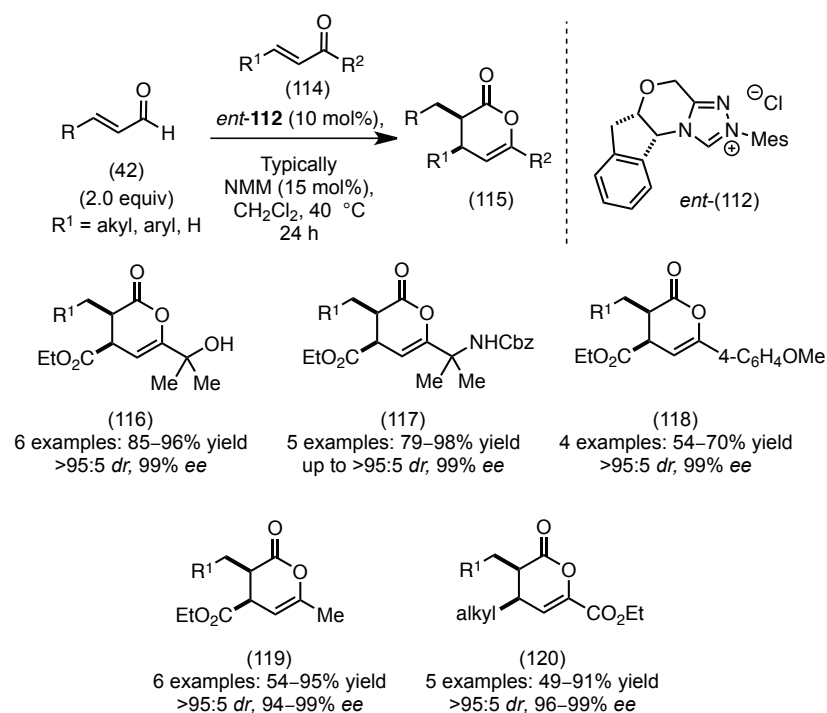
Scheme 23: Synthesis of a range of dihydropyran-2-ones *via* enals.

Scheidt and co-workers have developed an expedient synthesis of β-lactone frameworks and successfully applied it to the synthesis of Bakkenolides *I, J* and *S* **123** **(Scheme 24)**.[98] The key NHC step in this process is a desymmetrisation of **121** to produce the 6,5-carbocyclic core **122** in 69% yield with the key ring junction set with the required *cis*-fused stereochemistry in an exquisite 20:1 *dr* and 98% *ee* from aldehyde. Importantly this reaction could be performed on 5 g scale allowing rapid access to a large quantity of stereochemically pure intermediate that formed the main framework of Bakkenolide *I, J* and *S* natural products.
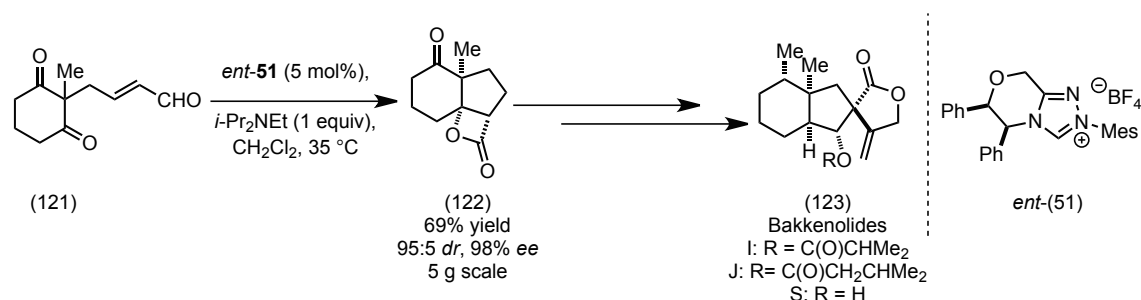
Scheme 24: Synthesis of Bakkenolides I, J and S featuring a key NHC-catalysed desymmetrisation

5.0 Previous work within the Smith group

As previously summarised, the Smith group, independently to the group of Ye, have disclosed some of the first interactions between ketenes and NHCs. Following multiple reports of the NHC-catalysed Staudinger reaction efforts were directed towards other NHC-catalysed processes. The asymmetric esterification of ketenes has been demonstrated, again independently by the groups of Smith[99] and Ye.[100] The methodology developed in the Smith group uses 2-phenylphenol **124** to access esters **125** under the catalytic influence of precatalyst **126**. This process operates in similar yields (65–91%) and enantioselectivities (up to 84% *ee*) to that obtained by Ye and co-workers. **(Scheme 25)**.
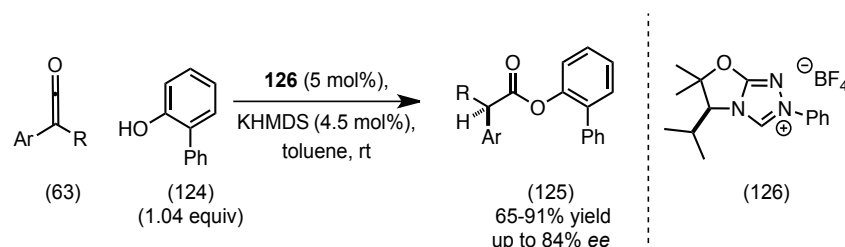
Scheme 25: NHC-catalysed asymmetric esterification.

6.0 Aims and objectives

This thesis will explore the scope of NHC-mediated catalysis, specifically the generation and reactivity of azolium enolates. Studies will be initiated to expand the successful methodology for β-lactam formation to an analogous β-lactone protocol. Research will focus on obtaining good reactivity *via* the identification and optimisation of a reaction procedure. Following this, the development of an enantioselective protocol will be undertaken *via* the synthesis and evaluation of a broad range of different NHC catalyst architectures.

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Chapter 2: Synthesis of Ketenes and Large Scale Preparation of NHC Precatalysts

1.0 Synthesis of alkylarylketenes

To enable detailed investigation into reactions employing azolium enolates generated from NHCs and ketenes, it was imperative from the outset to employ a reliable protocol for the formation of alkylarylketenes. It was found that dehydrohalogenation of the requisite acid chloride could adequately supply a variety of alkylarylketenes in good purity and acceptable yields **(Scheme 26, Table 1)**.
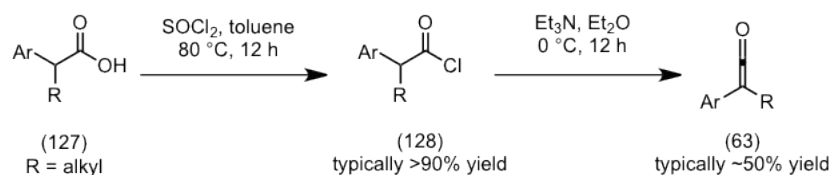
Scheme 26: Synthesis of alkylarylketenes.

Entry	R	Aryl	Yield (%)
1	Me	Ph	45
2	Et	Ph	60
3	*i*-Pr	Ph	50
4	*n*-Bu	Ph	51
5	Et	4-FPh	55
6	Et	4-MePh	52
7	Et	4-MeOPh	48
8	Et	2-MePh	35
9	Et	2-ClPh	52
10	*i*-Pr	Thiophene	59

Table 1: The synthesis of a representative range of alkylarylketenes.

Key to the success of this process is the filtration under inert atmosphere of the $Et_3N.HCl$ generated during the course of the reaction **(Fig 13, picture 2)**. Following this, concentration of the reaction solution and transfer *via* cannula to a Kugelrohr flask, allowed purification by distillation while maintaining the inert atmosphere throughout the procedure **(Fig 13, picture 3)**.
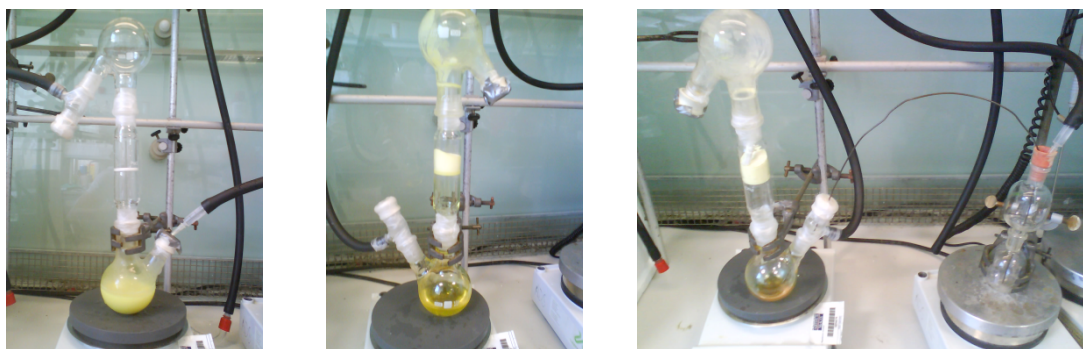
Figure 13: Synthetic procedure for the synthesis of alkylarylketenes.

Importantly, once experienced with the synthetic procedure it could be reliably carried out on multiple occasions resulting in near identical results in terms of yield and purity. Generally, the ketenes can be stored for periods of up to one month when stored at -20 ºC under an argon atmosphere. After this period, however, impurities as a result of hydrolysis can be observed. The limitation of this procedure was the scale, with approximately 2.5 g of ketene typically representing the maximum quantity of a single reaction, irrespective of the quantity of acid chloride used. With a reliable procedure for the synthesis of alkylarylketenes, attention turned to the synthesis of a frequently employed NHC precatalyst.

2.0 Synthesis of NHC precatalyst 66

2.1 Analysis of current synthetic route

A variety of NHC precatalyst architectures have been developed[1] however due to the limited availability and/or expense of purchasing such NHC precatalysts for asymmetric transformations, the synthetic community has yet to fully embrace their use. This is compared to other organocatalytic platforms such as enamine catalysis where the most common catalyst structures, proline and its derivatives, are widely available or readily prepared. This lack of commercial availability is one of the fundamentally limiting aspects to the wider use and uptake of NHC-mediated processes in the chemical community.

NHC precatalyst **35**, **66** and **112 (Fig 14)** represent some of the most widely employed NHC scaffolds, with **66**, and its structural analogues, finding particularly prevalent use in formal cycloadditions employing ketenes. Although a scalable synthetic procedure for the highly effective precatalysts **35** and **112** has been

reported,[2] the synthesis of precatalyst **66** within our group has only been reliably carried out to provide ~1 g of material.
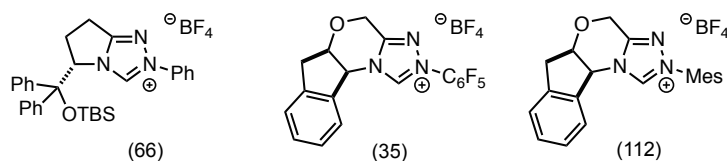
Figure 14: Frequently employed NHC precatalysts.

The synthetic procedure to give **66** was initially carried out according to the literature.[3] Pyroglutamic acid is first converted to the methyl ester **130** by treatment with thionyl chloride in methanol followed by double phenylmagnesium bromide addition to form the tertiary alcohol **131**. TBS protection of the alcohol moiety is carried out to obtain **132** then the lactam is converted to the triazolium scaffold in a one-pot, three-stage process yielding precatalyst **66**. This is achieved through activation of the carbonyl by methylation using trimethyloxonium tetrafluoroborate to form an acetimidate *in situ*, with subsequent phenylhydrazine displacement to afford the amide-derived hydrazone hydrotetrafluoroborate salt. Concentration of the reaction mixture followed by reflux in triethyl orthoformate and methanol precipitates the final NHC precatalyst as the tetrafluoroborate salt **(Scheme 27)**.
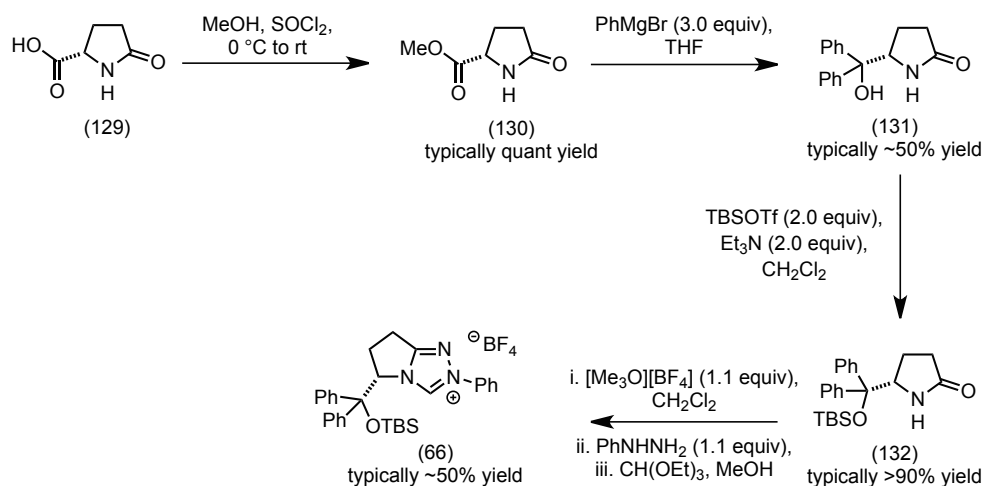
Scheme 27: Previous synthetic route to precatalyst 66.

In our hands there are a number of problems associated with this reported route, especially when applied to large scale synthesis:

- Firstly the methyl ester preparation typically provided a very viscous oil and therefore no direct purification of this material by distillation was normally attempted. The purity of methyl ester **130** was only crudely established by [1]H

NMR spectroscopy and typical mass return exceeded 100% implying significant residual impurities such as $SOCl_2$ or dimethyl sulfite.

- The quality of the methyl ester was found to effect directly the subsequent Grignard addition step, with yields for this stage showing considerable variation.[4] A second factor for the variable yields for the Grignard step was a particularly difficult work up and isolation procedure, particular on scale. This is postulated to be due to the large quantities of magnesium salts formed during the reaction process.

- The TBS protection step, although quoted as high yielding in the literature, provided erratic yields in our hands. This is likely due to difficulties associated with the chromatography of **132**; ideally, no chromatographic purification would be necessary.

- The final three-step procedure is inherently difficult. Typically, if the precatalyst salt **66** does not precipitate from the reaction solution following reflux with triethyl orthoformate, an arduous and often low-yielding isolation procedure had to be undertaken. Although not reported in this course of research, other work in the Smith group has recently found that the hydrazone intermediate can be isolated and partially purified prior to the cyclisation step.[5]

With these problems defined, an improved procedure that allowed the facile synthesis of **66** on large (>10 g) scale was developed. This portion of research was undertaken at the AstraZeneca Process Research and Development department in Macclesfield as part of the CASE award programme.

2.2 Large scale synthesis of methyl ester 130

The first stage of this project was to ascertain the purity of the material obtained from the current methanol and thionyl chloride method for preparation of methyl ester **130**. Following the literature procedure on a 50 g scale of (*S*)-pyroglutamic acid, treatment with 1.1 equivalents of thionyl chloride provided >120% mass return of a thick pale yellow oil. ^{1}H NMR spectroscopic analysis in a variety of solvents indicated the presence of significant residual solvent but also other unidentified organic impurities. At this point it was found that the crude methyl ester could be purified by washing with saturated aqueous $NaHCO_3$. Significant material, however, is lost due to

hydrolysis, giving only an isolated yield of 40%. Other methods such as the use of catalytic quantities of concentrated hydrochloric acid[6] or thionyl chloride[7] were attempted according to the literature. These procedures incorporated the aqueous NaHCO$_3$ wash and again, yields of 40% and 44% were obtained, respectively. Purification by distillation of the crude methyl ester product was found to be effective on small scale; however due to the viscosity of the material at this stage, Kugelrohr distillation of large quantities (>50 g) was not envisaged as a long term practical solution **(Scheme 28)**.
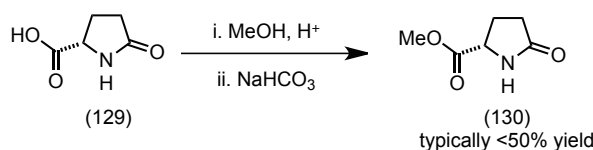
Scheme 28: Low yielding routes to methyl ester 130

A practical and scalable solution to this problem was found by the use of solid Amberlyst^{TM} 15 acidic resin. An approximate 40% weight/weight quantity in 400 mL of methanol at reflux for 24 h delivered analytically pure methyl ester as a highly mobile colourless oil in 97% yield. Importantly, this reaction was readily conducted on a 100 g scale with >100 g of the methyl ester returned with no requirement for purification. This reaction was carried out in a 1 L jacketed CLR (Controlled Laboratory Reactor) that allowed increased ease of procedure; in practice, however, this reaction could also be conducted in standard laboratory glassware **(Scheme 29)**.
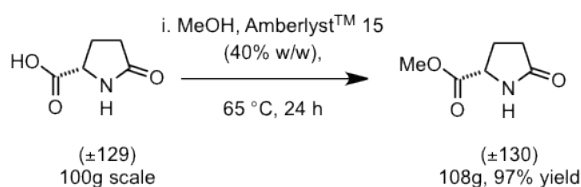
Scheme 29: Successfully developed synthesis of methyl ester 130

2.3 Large scale synthesis of alcohol 131

Although it was predicted that the use of purified methyl ester **130** in the subsequent Grignard addition reaction would improve the yield of this step, the problems associated with the work up remained. To this end the use of phenyllithium was explored and found to be an effective substitute with an improved work up on a laboratory scale.[8] On a large scale (typically 50 g of methyl ester) it was found that the use of commercial phenyllithium, (1.8 M in dibutyl ether) generated an effective solvent composition to allow direct precipitation of the alcohol product from the

reaction medium, following NH$_4$Cl (aq) quench. The alcohol product **131** could then be directly obtained *via* filtration and typically proceeded in up to 61% yield following a recrystallisation.
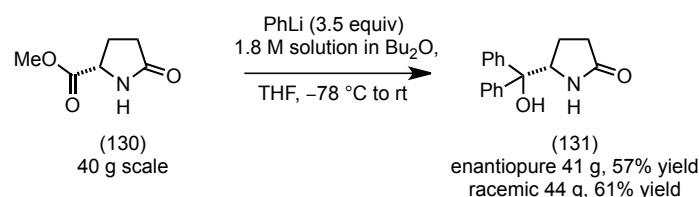
Scheme 30: Successfully developed synthesis of alcohol 131

2.4 Large scale TBS protection of alcohol 131

The TBS protection of alcohol **131** was attempted on large scale following the typical reaction conditions employing TBSOTf and Et$_3$N. In this instance, reaction on a 40 g scale failed to provide any conversion to the TBS protected alcohol. Significant problems were encountered with the solubility of alcohol **131** in the CH$_2$Cl$_2$ reaction solvent, with this only becoming apparent when >1 L of reaction solvent are required. The reaction mixture could be made homogeneous upon addition of additional TBS triflate, however this had no apparent effect on the reaction course and alcohol **131** was recovered in near quantitative yield **(Scheme 31)**.
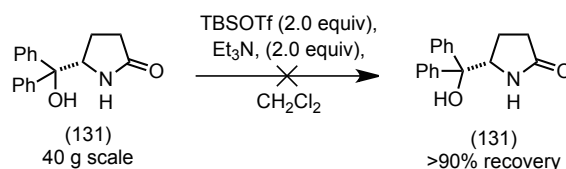
Scheme 31: Unsuccessful TBS protection of alcohol 131

The TBS protection could be carried out effectively by using the reaction conditions employed by Enders *et al.*[3b] employing the combination of TBS triflate and 2,6-lutidine. This gave the product in 59% yield without the need for silica chromatography.[9] This is lower than the typically reported yields for this procedure, which are generally quoted as >90%, however the use of standard silica chromatography on >100g of crude product greatly inhibits the synthetic practicality of this approach.
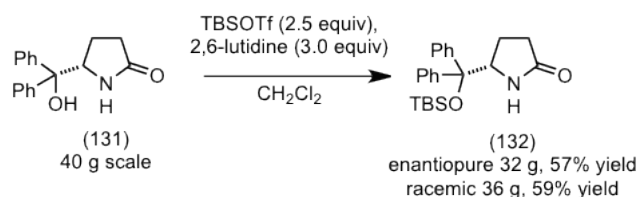
Scheme 32: Successfully developed TBS protection of alcohol 131

2.5 Large scale three-step triazolium heterocycle construction

The final three stages were conducted in keeping with the literature and as previously carried out within our own research group. On a 20 g scale for both the racemic and enantiopure TBS protected alcohol **132**, triazolium precatalyst **66** was obtained in an average 60% yield following recrystallisation from methanol **(Scheme 33)**.[10]
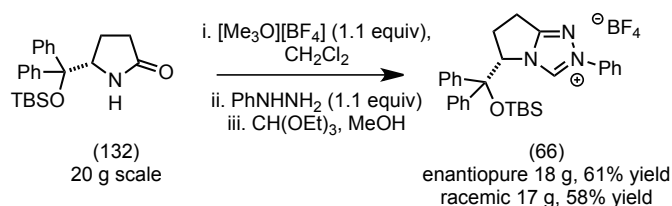
Scheme 33: Final three step synthesis of NHC precatalyst 66.

3.0 Summary

Overall, the developed precatalyst synthesis provided ~20 g of both the racemic and the enantiopure (*S*)-precatalyst **66**. Importantly, this scaled-up procedure provided solutions to a number of the practical issues associated with the literature and moreover it is very unlikely that the previously employed route **(Scheme 27)** could have provided comparable quantities of material.

With both racemic and enantiopure precatalysts **66** synthesised on such large scale, the standard quantities employed in future organocatalytic processes could be increased. This allowed both an increase in reaction practicality and accuracy, while allowing access to a greater quantity of material upon which derivatisation studies could be conducted.

4.0 References and Notes

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3. (a) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2007**, *10*, 277; (b) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367.
4. Yields were typically 50% however on scale (15 g of methyl ester) the yields fluctuated to as low as 18%.
5. Specifically, it has been shown that washing related hydrazone intermediates with EtOAc can provide a material that performs more reliably in the final cyclisation step than the crude material.
6. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
7. Doyle, M., P.; Winchester, W., R.; Protopopova, M., N.; Kazala, A. P.; Westrum, L. J. *Org. Synth.* **1996**, *73*, 13.
8. The use of phenyllithium was initially suggested and then experimentally validated prior to the research at AstraZeneca by Dr K. Ling and Mr S. Leckie
9. It was found that following work up and partial concentration of the organic phase the TBS protected alcohol precipitated in good purity that could be improved *via* simple filtration through a plug of silica. Further material could be obtained from manipulation of the organic portion. Full details are provided in the experimental information.
10. To ensure the minimum quantity of methanol was used to solubilise the crude hydrazone methanol was added drop-wise to a refluxing suspension of thiethylorthoformate until dissolution. The quantity of methanol was reduced to a minimum as to facilitate the precipitation of the triazolium salt.

Chapter 3: Chemo- and Enantiodivergent NHC-Catalysed Reactions of Alkylarylketenes and Chloral

1.0 Introduction

Previous work within the Smith group had shown that NHCs are efficient Lewis base catalysts for the formal [2+2] cycloaddition reaction between disubstituted ketenes and imines, enabling access to a range of enantioenriched β-lactams.[1] Following this proof of concept, the expansion of this methodology to the analogous formal [2+2] cycloaddition between disubstituted ketenes and aldehydes, generating β-lactones, was investigated.

The β-lactone moiety has a long and distinguished history in synthetic chemistry, serving as a versatile starting material in both complex[2] and small molecule synthesis.[2b,3] Although less biologically prevalent than the analogous β-lactam motif, the β-lactone moiety features in the core structure of a range of natural products with notable pharmacological properties.[4] A number of synthetic methods have been used to prepare these versatile scaffolds in enantioenriched form, ranging from substrate[5] and chiral auxiliary[6] controlled processes to catalytic asymmetric methods.[7] The Lewis base catalysed formal [2+2] cycloaddition between aldehydes and ketenes to generate β-lactones is well documented.[8] As early as 1982 Wynberg and Staring reported the efficient synthesis of β-lactone **135** from parent ketene and chloral, elegantly demonstrating the synthetic utility of this approach by the derivatisation of **135** to (*S*)-acid **136 (Scheme 34)**.[9]
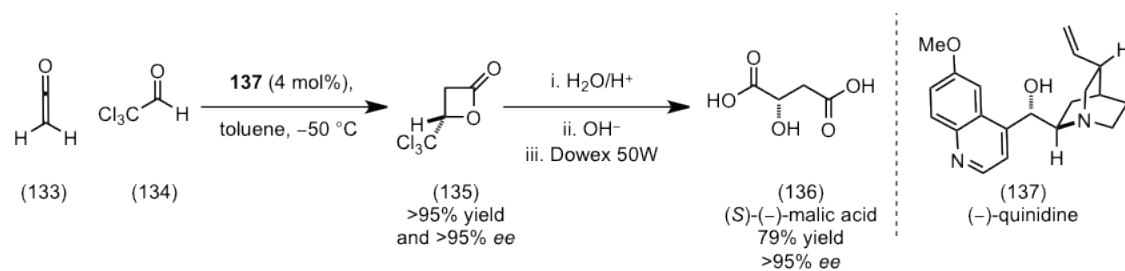
Scheme 34: Wynberg's pioneering Lewis base catalysed formal [2+2] cycloaddition.

Romo *et al.* have expanded the scope and practicality of the Wynberg approach by the use of mono-substituted ketenes, generated *in situ*.[10] The use of less reactive dichlorinated aldehydes **139** was also demonstrated, with the utility of the β-lactone products **140** showcased *via* a range of derivatisation strategies, including conversion to the β-hydroxy ester **141 (Scheme 35)**.
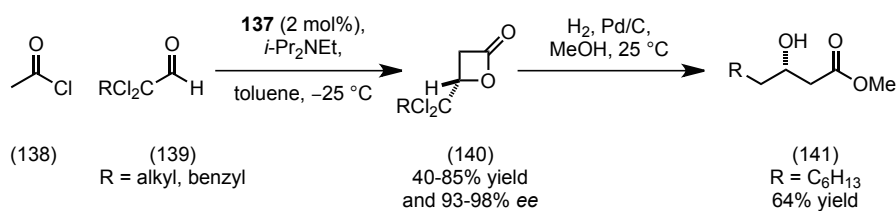
Scheme 35: Development of the original Wynberg process by Romo *et al.*

Further utility of the parent Wynberg lactone **135** was demonstrated by the group of Romo. In this report the use of trichloromethyl-β-lactone **135** as an amino acid synthon is outlined.[11] This strategy proceeds *via* ring opening to provide an enantioenriched trichloromethylcarbinol, followed by conversion to the α-azido acid as developed by Corey.[12] This procedure is known to proceed with inversion of configuration at the carbinol centre, thus providing the masked amino acid motif in enantiomerically pure form from either enantiomer of the commercially available lactone **135**. Romo and co-workers later exemplified this efficient methodology in the synthesis of Schulzeines B and C **145**.[13]
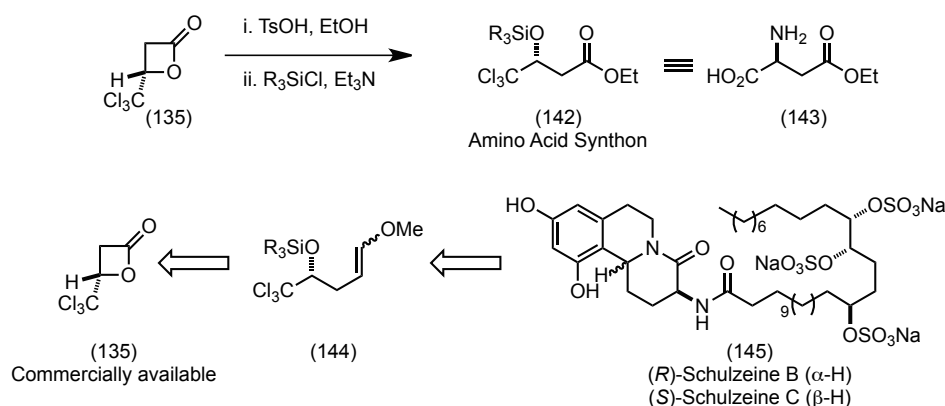
Scheme 36: The use of trichloromethyl-β-lactone 135 as an amino acid synthon.

Although Wynberg's original synthesis stands as an elegant early example of organocatalysis where the utility of the parent trichloromethyl-β-lactone has been demonstrated, extension to the α,α-disubstituted lactone motif *via* the use of disubstituted ketenes has not been realised.

2.0 Project aim

This project will seek to expand the original report of Wynberg to reactions of disubstituted ketenes and chloral, *via* the development of an NHC-catalysed formal [2+2] cycloaddition process. The amenity of the β-lactone products to derivatisation, most importantly to the amino acid motif, will be investigated.

3.0 NHC-catalysed asymmetric β-lactone synthesis

3.1 Preliminary investigations

Initial investigations into the feasibility of this approach began by employing precatalyst **66**, whose general structure had proved effective in a wide range of similar processes **(Chapter 1: 4.1.2)**. Employing triazolium salt **66** at a prototypical precatalyst loading of 10 mol% in combination with 9 mol% KHMDS as the base,[14] the formal [2+2] cycloaddition process was investigated with ketene **146** (1.0 equiv) and chloral (1.0 equiv) at 0 °C. Pleasingly, the desired separable β-lactone products were obtained in 89% combined yield as a 72:28 (*anti:syn*) diastereoisomeric ratio of products **147** and **148**. The enantiomeric excess of both products was determined by chiral HPLC by comparison with genuine racemic standards prepared in analogous fashion from racemic precatalyst **66**. The major *anti* lactone **147** was formed in an excellent 92% *ee* with the minor *syn* product **148** formed in slightly lower 84% *ee* **(Scheme 37)**.
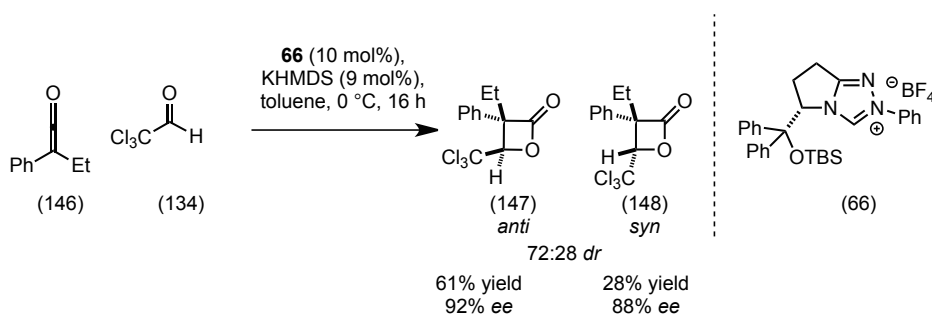
Scheme 37: Initial reaction screen.

The relative configurations within **147** and **148** were established by X-ray crystallography, with the *anti* configured product found to be the major diastereomer (*vide infra*). Following this unambiguous assignment the relative configurations could also be assigned *via* the characteristic ¹H NMR resonances for the lactone C(4) and ethyl protons **(Fig 15 and 16)**. Specifically, the lactone C(4) proton for the *anti* diastereomer **147** has a resonance at higher chemical shift (ppm) than the corresponding *syn* **148** C(4) lactone proton. Typically he two diastereotopic CH$_2$ ethyl protons for the *anti* lactones are observed at distinct chemical shift, whereas the corresponding ethyl protons for the *syn* diastereomer are not typically resolved.
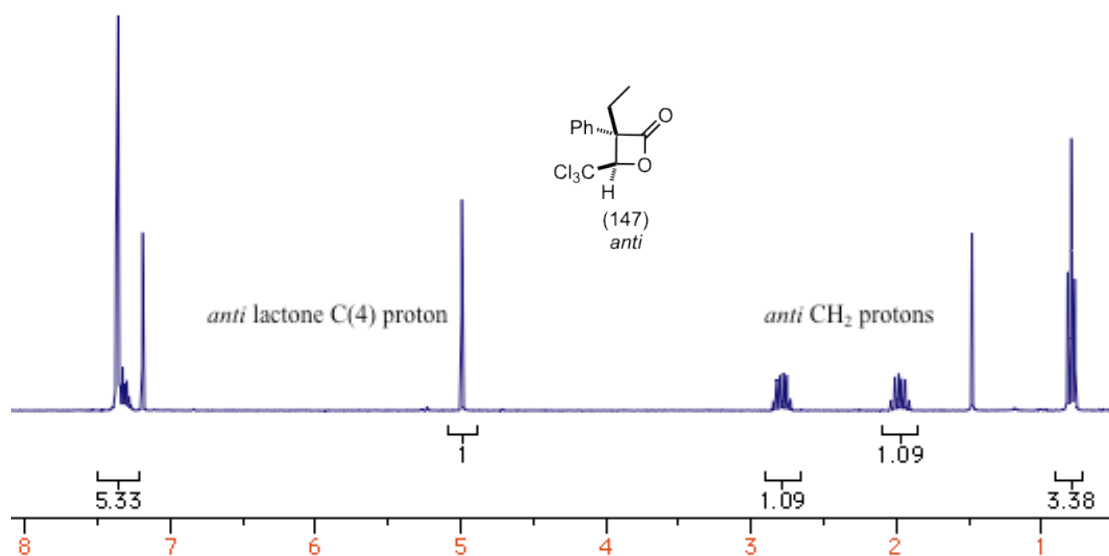
Figure 15: Characteristic *anti* ^{1}H NMR proton resonances.
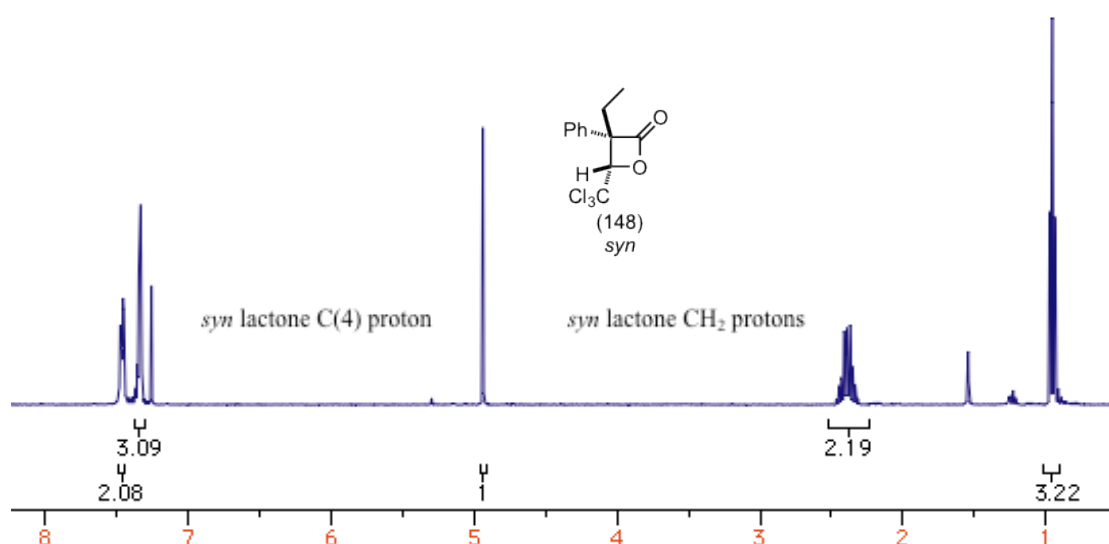
Figure 16: Characteristic *syn* ^{1}H NMR proton resonances.

In all further examples, the diastereoselectivity was defined *via* analysis of the characteristic C(4) proton shift by ^{1}H NMR spectroscopy and comparison with the authenticated diastereomers of **147** and **148**.

3.2 Optimisation of NHC catalyst architecture

Following this promising initial result a representative range of both chiral triazolium and imidazolinium NHC precatalysts was screened under identical conditions **(Scheme 38, Table 2)**. Precatalyst **70**[15] provided slightly reduced yield (76%), but improved *dr* (83:17), and almost identical enantiomeric excess [16] (*anti* 91% *ee*, *syn*

84% *ee*) **(Table 2, Entry 2)**. To investigate the effects of the *N*-aryl moiety of the triazolium-derived NHC, other differentially *N*-substituted aminoindanol derived precatalysts, **112**[15] and **35**,[17] were then screened. *N*-Mesityl substituted precatalyst **112**, know to function effectively for other NHC modes of action,[18] was considerably less effective than the *N*-phenyl substituted precatalyst, proceeding in lower yield (43%), diastereomeric ratio (70:30 *dr*), and low (≤10% *ee*) enantioselectivities **(Table 2, Entry 3)**. The *N*-pentafluorophenyl substituted precatalyst **35**, known to favour acyl anion processes,[18] failed to provide any lactone product, possibly due to preferential addition to chloral **(Table 2, Entry 4)**. Triazolium precatalyst **126** proceeded to give the desired product in similar *dr* to **70** but with substantially lower yields (12% and 22%) and enantioselectivities (10% and 39% *ee*) **(Table 2, Entry 5)**. Imidazolinium precatalyst **71**, effective in the β-lactam methodology, provided reduced *dr* (63:37) and yield (54%) while providing only slightly enantioenriched *anti* product (17% *ee*) and essentially racemic *syn* product (<5% *ee*) **(Table 2, Entry 6)**.
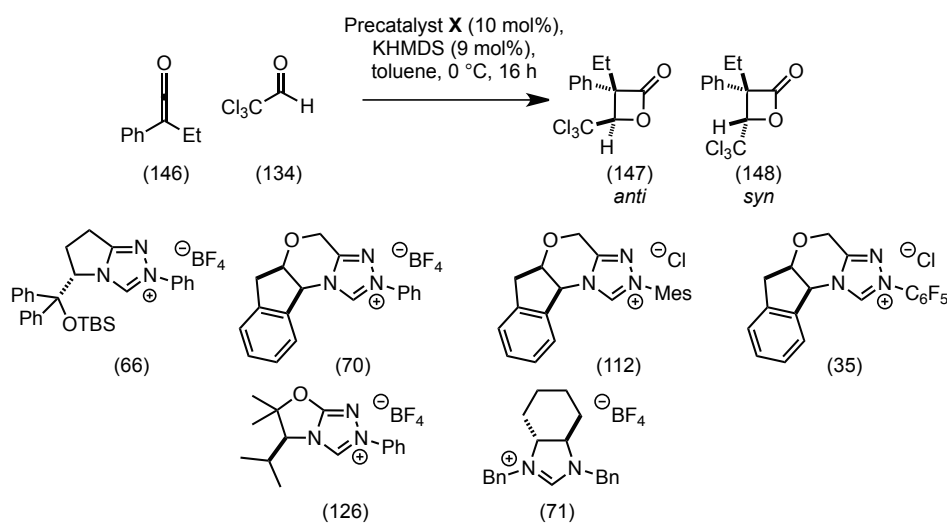
Scheme 38: Initial precatalyst screen.

Entry	Precatalyst	*dr*[a] (*anti*:*syn*)	Yield (%)[b] (*anti*:*syn*)	*ee* (%)[c] (*anti*:*syn*)
1	**66**	72:28	61, 28	92, 88
2	**70**	83:17	59, 17	91 (*ent*), 84 (*ent*)
3	**112**	70:30	31, 12	10, 7
4	**35**	–,–	NR	–,–
5	**126**	77:23	12, 22	10, 39 (*ent*)
6	**71**	63:37	34, 20	17, <5

[a] Calculated by inspection of the crude reaction mixture using ¹H NMR spectroscopy [b] Combined isolated yield of single diastereomer. [c] % *ee* determined by HLPC analysis on a chiral stationary phase.

Table 2: Initial precatalyst screen.

3.3 Optimisation of reaction conditions

Precatalyst **66** was chosen for further optimisation due to its comparable results to **70**, the most effective precatalyst screened, combined with its availability in gram quantities in both enantiopure and racemic form.[19] The effects of base and temperature were then analysed **(Scheme 39 Table 3)**. Cs_2CO_3, a frequently employed alternative to KHMDS, was tested under the reaction conditions and found to provide incomplete conversion on multiple attempts, even at elevated reaction temperatures **(Table 3, Entry 1)**. At rt only 50% conversion was obtained in 69:31 *dr*, providing low isolated yield (16% *anti*) but in excellent enantiomeric excess (94% *ee*). Lowering of the reaction temperature when employing KHMDS as the base provided incomplete lactone formation with considerable ketene dimerisation at either −25 °C or −78 °C **(Table 3, Entry 2 & 3)**. In the absence of precatalyst **66**, it was found that KHMDS proved proficient in promoting the (racemic) background reaction, proceeding in good conversion but low *dr* (53:46) **(Table 3 Entry 4)**. Similar such observations have been reported by Wilhelm, where KHMDS has been shown to promote formal [2+2] cycloadditions of ketenes with imines or carbonyls.[20]
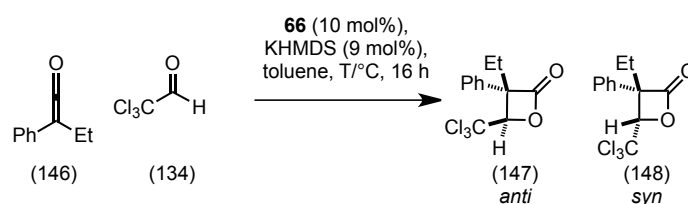
Scheme 39: Temperature screen employing optimal precatalyst 66.

Entry	Temp (°C)	Conversion (%)[a]	dr[a] (syn:anti)	Yield (%)[b] (syn:anti)	ee (%)[c] (syn:anti)
1[d]	rt	50	69:31	16, −	94 , −
2	−25	50	74:26	−,−	−,−
3	−78 to rt	50	85:15	−,−	−,−
4[e]	rt	>75	53:46		

[a] Calculated by inspection of the crude reaction mixture using ^{1}H NMR spectroscopy [b] Isolated yield of single diastereomer. [c] % *ee* determined by HLPC analysis on a chiral stationary phase. [d] 9 mol% Cs_2CO_3 used as the base. [e] Reaction performed in the absence of precatalyst **66**.

Table 3: Temperature screen employing optimal precatalyst 66.

3.4 Substrate scope

Following the identification of optimum conditions for this methodology, a range of disubstituted ketenes were tested to establish the reaction scope. Firstly, a range of alkylphenyl ketenes bearing different alkyl substitution were prepared and evaluated in this protocol **(Scheme 40)**. Reducing the length of the alkyl side chain, from ethyl to methyl, resulted in a excellent isolated yield, an increase in *dr* to 88:12 (*anti*:*syn*), and with a slight decrease in enantiomeric excess (82% and 78% *ee*, respectively). Conversely, an increase in the alkyl chain length (to *n*-butyl) decreased the *dr* to 69:31, giving the combined lactones in 75% yield, with an *ee* of 88% for the major *anti* diastereomer **154**. The enantiomeric excess for the minor *syn* diastereomer could not be determined *via* chiral HPLC analysis or derivatisation methods.[21] Finally, a further increase in the steric demand of the alkyl portion to an *i*-butyl group reduced the *dr* to a lower level (42:58 *dr*), in this case, slightly in favour of the *syn* diastereomer. The yield for this example was good (85%), as was the *ee* for the major *syn* diastereomer **155** (84% *ee*). Unfortunately the enantiomeric excess for the minor *anti* diastereomer could not be determined by chiral HPLC or derivatisation methods.[21]

(150) *anti*   (151) *syn*

(152)
95% yield[a]
88:12 *dr*[b]
anti 82% *ee*[c]
syn 78% *ee*[c]

(153)
89% yield[d]
72:28 *dr*[b]
anti 92% *ee*[c]
syn 88% *ee*[c]

(154)
75% yield[a]
69:31 *dr*[b]
anti 88% *ee*[c]
syn % ee ND

(155)
85% yield[a]
42:58 *dr*[b]
anti % *ee* ND
syn 84% *ee*[c]
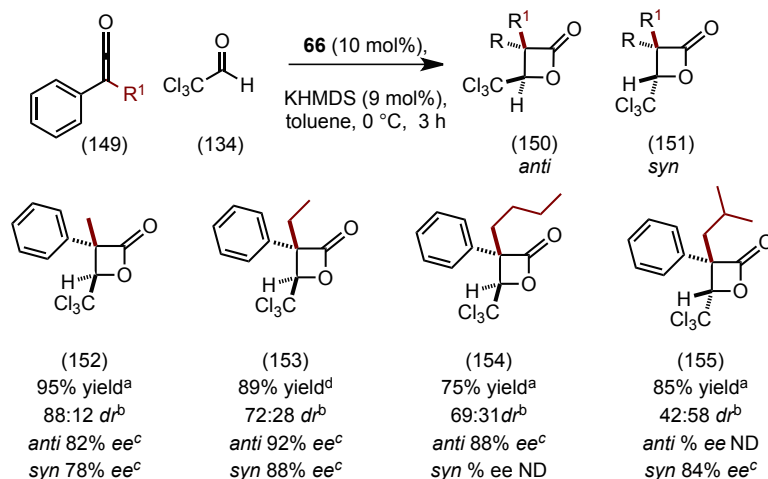
[a] Combined isolated yield of combined diastereomers [b] Calculated by inspection of the crude reaction mixture using ^{1}H NMR [c] % *ee* determined by HLPC analysis on a chiral stationary phase. [d] Isolated yield of single diastereomers.

Scheme 40: Scope of the reaction with respect to the alkyl substituent.

Substitution on the aryl portion of the ketene was next evaluated by screening a range of electron rich substituted alkylarylketenes **(Scheme 41)**. Employment of a 4-tolyl group as the aryl substituent was well tolerated with results consistent with those observed for the parent ethylphenylketene (**159**: 69% yield, 73:27 *dr*, 88% *ee anti*, 76% *ee syn*). Reducing the alkyl chain to a methyl group whilst maintaining the 4-tolyl group gave the expected increase in *dr* to 88:12, and proceeded in good yield and enantioselectivities (**160**: 69% yield, 82% *ee anti*, 76% *ee syn*). Finally, 4-methoxyphenylethylketene provided equally good results as those previously obtained for the tolyl substituted ketenes (**161**: 70% yield, 75:25 *dr*, 88% *ee anti*, 84% *ee syn*).
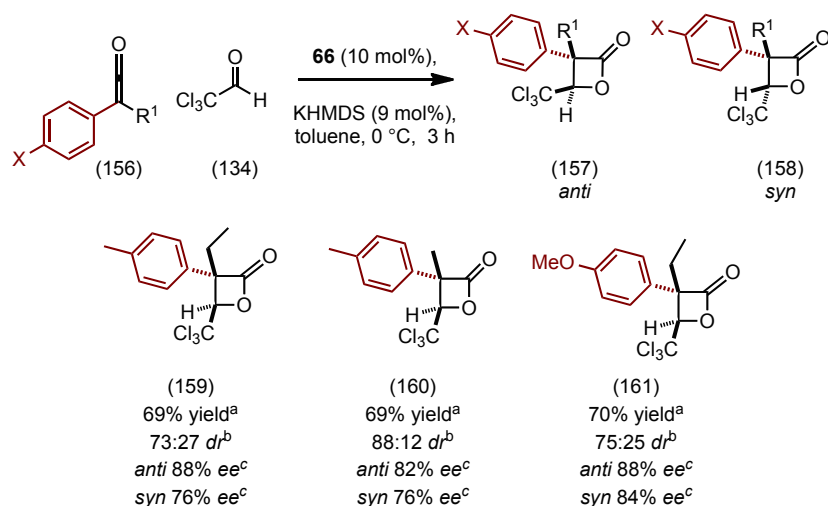
[a] Combined isolated yield of single diastereomers [b] Calculated by inspection of the crude reaction mixture using ^{1}H NMR spectroscopy [c] % *ee* determined by HLPC analysis on a chiral stationary phase.

Scheme 41: Scope of the reaction with respect electron donating groups on the aryl substituent.

Electron deficient aryl substituted ketenes were then selected to test further the substrate scope **(Scheme 42)**. Initially, 4-fluorophenylketene was examined with the reaction proceeding in only moderate conversion. In this case, ketene dimerisation functioned as the predominant pathway under standard reactions conditions. It was found that dropwise addition of the ketene to the reaction over 0.5 h, to minimise the potential for the competing ketene dimerisation process, was sufficiently effective to allow good conversions to β-lactone products **165**. The 4-fluorophenyl moiety led to improved enantioselectivities (94% and 97% *ee* respectively) while maintaining the good yield and diastereoselectivity (73% yield, 69:31 *dr*). Changing to a 4-chloro or 4-bromophenyl substituent had minimal effect, with both well tolerated in the reaction process, providing results similar to those with the parent ethylphenylketene.

(162)   (134)
66 (10 mol%),
KHMDS (9 mol%),
toluene, 0 °C, 3 h
(163) *anti*   (164) *syn*

(165)
73% yield[a]
69:31 dr[b]
anti 94% ee[c]
syn 97% ee[c]

(166)
88% yield[a]
74:26 dr[b]
anti 92% ee[c]
syn 84% ee[c]

(167)
79% yield[a]
75:25 dr[b]
anti 90% ee[c]
syn 82% ee[c]
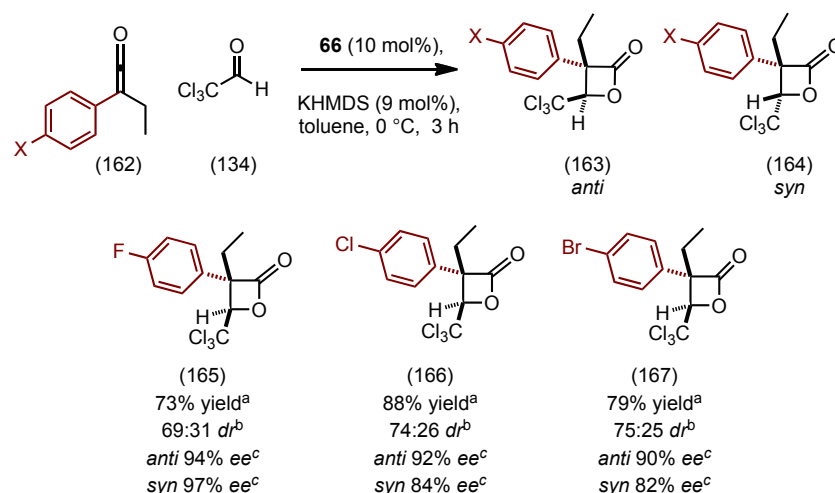
Ketenes added dropwise as a solution over 0.5 h [a] Combined isolated yield of single diastereomers [b] Calculated by inspection of the crude reaction mixture using ^{1}H NMR spectroscopy [c] % *ee* determined by HLPC analysis on a chiral stationary phase.

Scheme 42: Scope of the reaction with respect electron withdrawing groups on the aryl substituent.

3.5 Preparative scale synthesis of lactones 147 and 148

To demonstrate the synthetic utility of this process, a multi-gram scale reaction of ethylphenylketene and chloral was carried out with a reduced catalyst loading of 2.5 mol% of **66 (Scheme 43)**. As with the use of the electron deficient aryl substituted ketenes, the ketene was added dropwise to prevent any competing dimerisation. The reaction proceeded with improved results compared to the standard scale with over 3 g of separable lactone product isolated (80% combined yield). The enantioselectivity was increased to 94% *ee* for the *anti* diastereomer **147** and 92% *ee* for the *syn* **148**, which could each be further increased to enantiopurity with a single recrystallisation.

(146)   (134)
66 (2.5 mol%),
KHMDS (2.0 mol%),
toluene, 0 °C, 3 h
(147) *anti*   (148) *syn*
74:26 dr
2.4 g   0.96 g
94% ee   92% ee
recrystallisation   80% combined yield
>99% ee
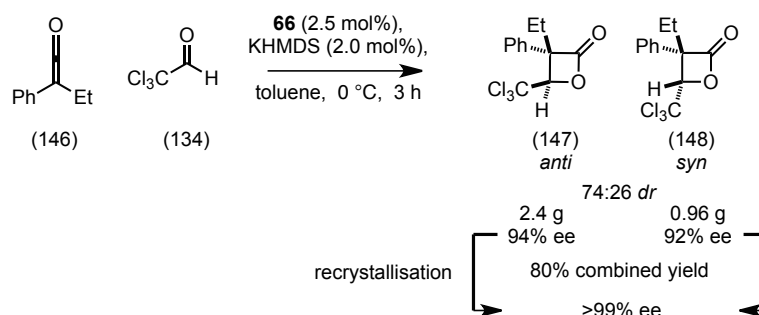
Scheme 43: Preparative scale β-lactone formation.

3.6 Absolute configurations of lactone products

With material of >99% *ee* obtained, the absolute configurations of the lactone products were unambiguously identified by X-ray crystallographic analysis. The *anti* lactone **147** was found to have the (3*S*,4*R*) configuration, while the *syn* **148** was proven to be (3*S*,4*S*) **(Fig 17)**.
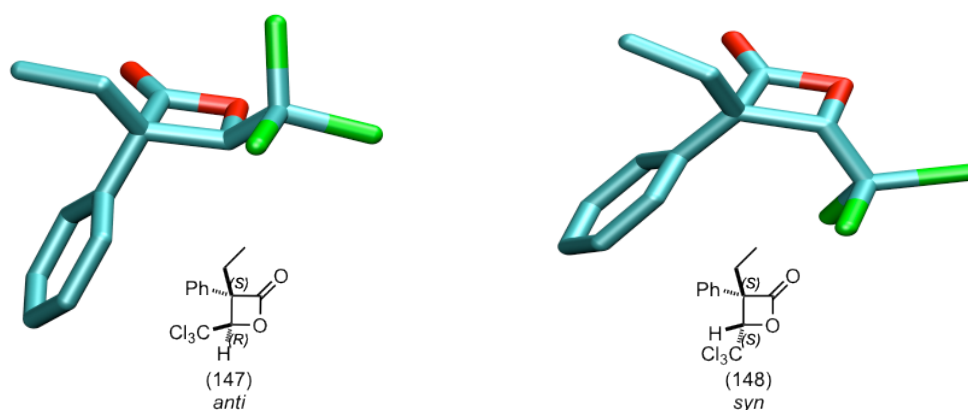
Figure 17: X-ray crystallographic representations of *anti* and *syn* lactones showing relative and absolute configuration.

3.7 Derivatisation studies

Following the initial choice of chloral as the aldehyde component, it was envisaged that facile derivatisation could provide acess to amino acid-type motifs. To this end, a range of ring-opening strategies was undertaken, initially using simple alcohols (MeOH, EtOH and BnOH) under acidic or basic reaction conditions. On all occasions this failed to provide any ring-opened product with the starting material returned in all cases. Next, a more proficient nucleophile, azide, was employed as it had previously been shown to open effectively benzaldehyde derived β-lactones by the group of Fu.[22] Under both open flask and sealed tube conditions at 65 °C for 24 h, no ring opening was observed using sodium azide, returning the lactone in all cases. It is postulated that addition of nucleophiles to the C(4) carbon is severely hindered by both the trichloromethyl group and the adjacent quaternary centre, thus preventing ring opening. Addition to the carbonyl was next investigated with attempted tandem ring opening and trichloromethyl group hydrolysis by aqueous KOH. Accordingly, lactone **147** was heated to 65 °C in a sealed tube for 12h in a mixture of KOH/THF, resulting in a complex mixture of products. More mild KOH ring opening conditions were also

screened but resulted in inefficient ring opening. In a solitary example of lactone utility, it was found that lactone **147** could be reduced with 3.5 equivalents of DIBAL to afford the diol **168** in 42% yield. However, a reduction in enantiomeric excess to 84% *ee* (from 92% *ee* for the lactone) was observed, this is attributed to the potential error in chiral HPLC analysis. Given the difficulties in lactone ring opening, especially with azide (to allow access the desired amino acid motif), no further strategies were investigated.
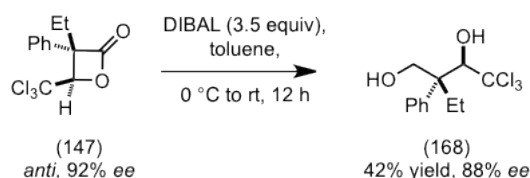
Scheme 44: DIBAL reduction of lactone 147 to furnish diol 168.

3.8 Mechanistic proposal

We postulate this NHC-mediated process is initiated through NHC addition of *in situ* generated NHC **169** to ketene **146**, preferentially *anti* to the aryl unit,[23] to generate azolium enolate intermediate **170**. Subsequent concerted, but asynchronous,[24] formal [2+2] cycloaddition with chloral provides zwitterionic intermediate **171**. Collapse of this intermediate results in concurrent catalyst regeneration and lactone formation **(Fig 18)**.
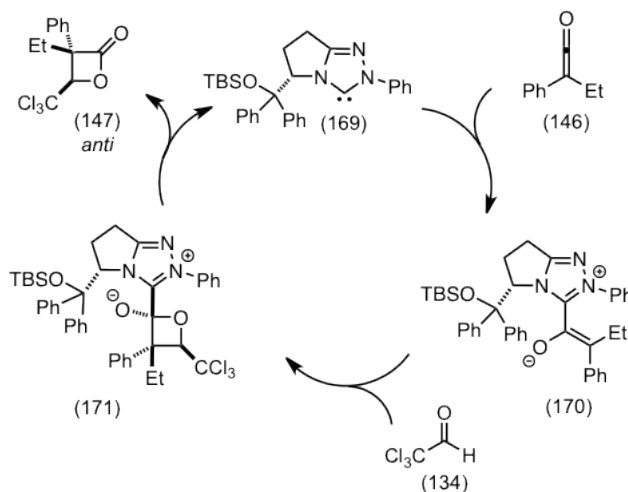
Figure 18: Postulated catalytic cycle.

This mechanism is in accordance with the mechanism postulated by Ye for the corresponding synthesis of β-lactones from 2-oxoaldehydes.[25] We assume that as no benzoin products have been detected in these reactions that this possible competitive mechanistic pathway is not in operation. Although NHC addition to the reactive

chloral aldehyde is likely, it is assumed that this is reversible. Any subsequent benzoin step originating from a Breslow type intermediate is also presumed to be either slow or reversible under the reaction conditions. Basic mechanistic investigations such as addition of stoichiometric amounts of the NHC to either chloral or ketene, then *in situ* analysis by ^{1}H NMR spectroscopy, were undertaken. Under no conditions did these studies show any conclusive evidence for either an NHC-chloral adduct, or the anticipated enolate from NHC addition to the ketene, and no further analysis was attempted. In a rudimentary reaction to probe whether the reaction may be proceeding *via* an initial but reversible ketene dimerisation, ketene dimer **172** was prepared according to the literature[7h] and employed as a ketene surrogate in the standard protocol **(Scheme 45)**. No lactone product was isolated with the ketene dimer starting material recovered unchanged from the reaction mixture.
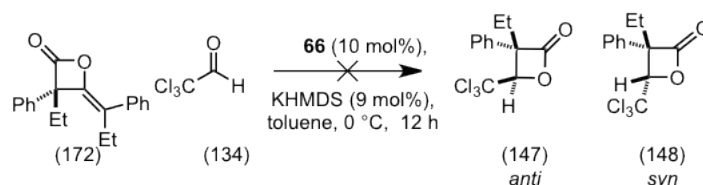
Scheme 45: Use of the ketene dimer 172 as a potential ketene surrogate.

3.9 Stereochemical considerations

For a full rationale of the observed diastereo- and enantioselectivity of this reaction a series of factors must be taken into consideration. First is the selective formation of an (*E*)-enolate following NHC addition to the ketene. Following this, an explanation of the facial reactivity of this enolate, either *Re* or *Si,* must be accounted for in order to explain the configuration at the C(3) centre. Finally, a model that rationalises the diastereoselectivity and is able to account for the observed trends (higher *dr* for methyl substituted ketenes, lower for butyl) is required.

Our stereochemical model begins with the assumed addition of the NHC *anti* to the more sterically demanding aryl unit of the ketene. This reasoning is based on the location of the ketene LUMO **(Chapter 1: 4.1.1)**, which lies in the plane of the ketene. Nucleophilic attack must proceed directly past either the alkyl or more sterically demanding aryl substituent, with the former being the more dominant pathway **(Fig 19)**. This is supported by computational calculations on the addition of chiral alcohols to ketenes from the group of Houk, as well as enolate trapping studies by Tidwell and co-workers.[23]
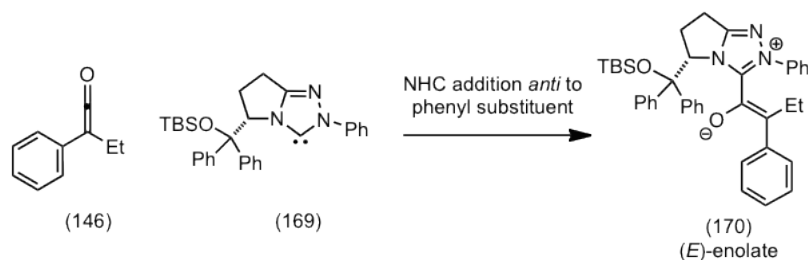
Fig 19: Proposed geometry of azolium enolate.

Following the formation of the azolium enolate **170**, we postulate that the enolate is orientated approximately perpendicular to the triazolium ring, to minimise any steric interactions with the *N*-substituent **(Fig 20)**. A co-planar orientation has been proposed by Ye and co-workers for a similar system[87] **(Fig 9)**, however we suggest that the steric interactions between the enolate and the *N*-Ph group favor a more perpendicular orientation. This conformation has previously been proposed by research from Smith and co-workers,[26] and is supported by computational calculations from the group of Bode,[27] who investigated the orientation of the azolium enolate generated from the addition of an NHC to an enal. We, in agreement with Bode, postulate the enolate to orientate with the oxy-anion directed towards the large stereodirecting group to minimise steric interactions between the enolate and the large stereodirecting unit. Assuming this is the most favourable orientation of the azolium enolate, two clear approaches to different faces of the ketene are available. One approach is past the *N*-substituent, with reaction from the *Re* face of the enolate. The alternative, passing the stereodirecting group, would render reaction to the opposing *Si* face of the enolate **(Fig 20)**.
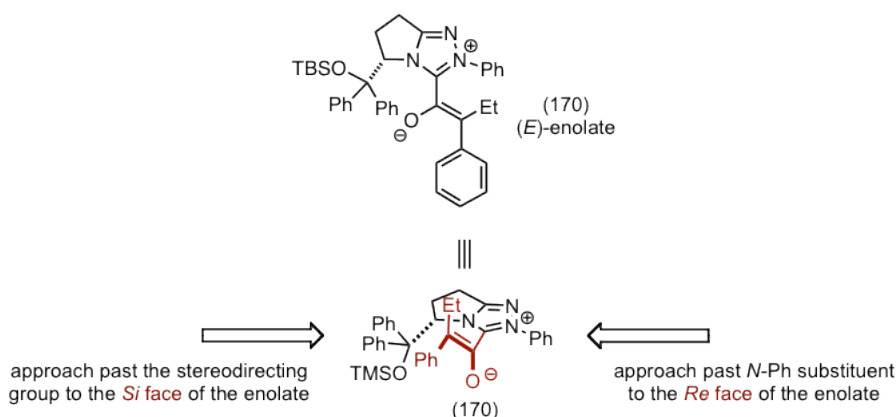
Fig 20: Differing approaches defining the facial selectivity of azolium enolate 170.

Due to the considerable size of the stereodirecting group we propose the approach of chloral past the *N*-phenyl substituent **(Fig 21)**. In this regard approach past the *N*-substituent, and subsequent reactivity from the *Re* face of the enolate, would

provide the observed (*S*)-configuration at the lactone C(3) position. The diastereoselectivity from this selective approach would be defined by the facial addition to either the *Re* or *Si* face of chloral. Addition to the *Re* face of chloral would provide the *anti* diastereomer with the observed (3*S*,4*R*) configuration **(Fig 21)**.
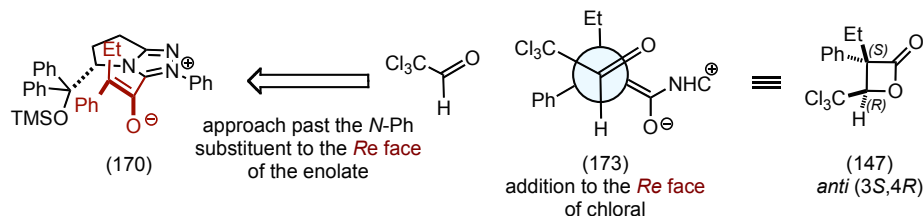
Fig 21: Rationale for the observed configuration at C(3).

The preference for addition to the *Re* face of chloral over the *Si* face in a ratio of 72:28 for the use of ethylphenylketene may be explained by a combination of steric and electrostatic arguments. Firstly it is assumed that arrangement is staggered about the two prochiral faces to minimise steric interactions, with the bulky CCl$_3$ group orientated away from the NHC skeleton on steric grounds. This is also in agreement with a concerted but asynchronous [2+2] cycloaddition process, with the build up of electron density on the forming chloral oxy-anion orientated towards the forming acylazolium in the transition state **(Fig 22)**. With the CCl$_3$ group placed opposite the NHC skeleton there are two possible orientations for the approaching carbonyl, one with the C=O dipole aligned with the azolium enolate oxy-anion or one with dipoles opposed. We propose that in order to reduce the overall dipole moment of the pre-transition state assembly the C=O bond preferentially directs away from the azolium enolate oxygen, thus favouring addition to the *Re* face, generating the *anti* β-lactone **(Fig 22)**.
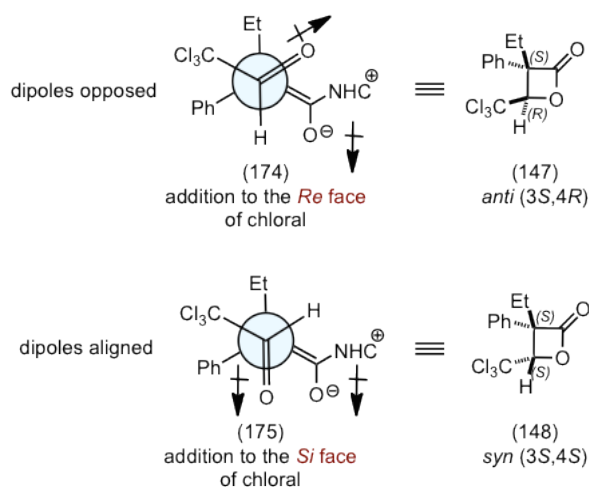
Fig 22: Rationale for the observed diastereoselectivity.

The observed increase in diastereoselctivity with the use of methylphenylketene (88:12, *anti, syn*) and the corresponding decrease for the use of butylphenylketene (69:31, *anti, syn*) may be explained *via* the steric interactions between the alkyl substituent on the azolium enolate and the CCl₃ group **(Fig 23)**. A decrease in the steric size of the alkyl substituent will decrease any steric interaction with the CCl₃ group and favour the pre-transition state assembly shown above where the dipoles are opposed **(Fig 22)**. Increasing the steric demand of the alkyl substituent will result in greater steric clash with the CCl₃ group. To minimise this clash it is proposed that chloral now approaches from the *Si* face, positioning the CCl₃ group opposite the alkyl substituent while maintaining the proximity requirements of a concerted but asynchronous cycloaddition. This pre-transition state assembly would lead to the *syn* β-lactone, as predicted, this assembly is an increasingly favored as the size of the alkyl group increases **(Fig 23)**.
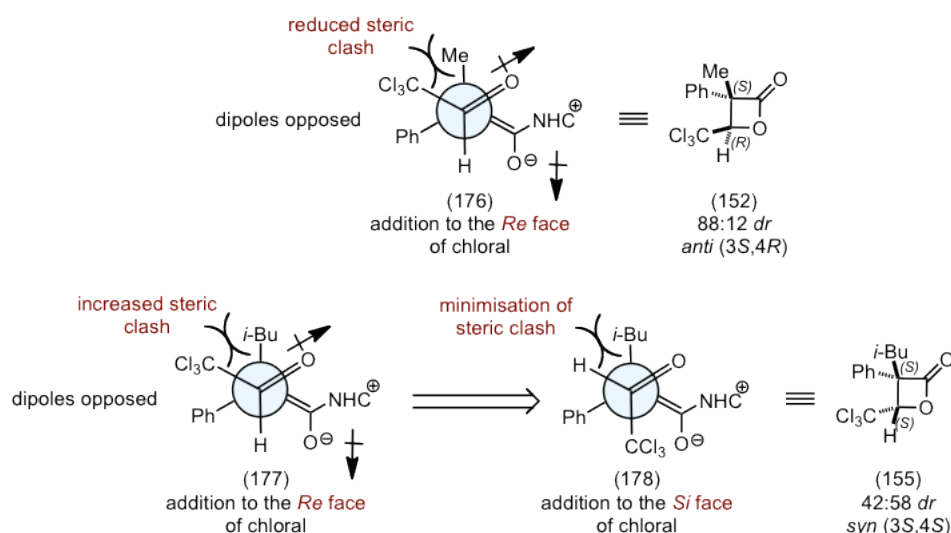
Fig 23: Rationale for the observed trend in diastereoselectivity.

4.0 Unexpected chlorination pathway

4.1 Initial reaction discovery

It is known that the use of ketenes substituted in the two position, or containing α-branching on the alkyl portion, normally leads to no reaction in NHC-catalysed formal cycloadditions of ketenes.[7h,28] In certain rare cases, partial reactivity is retained,[29] or a change in absolute configuration for the product is observed.[30] For example in the formal [2+2] cycloaddition between ketenes and diazenedicarboxylates **83** by the group of Ye,[30b] the use of 2-chlorophenylketene

resulted in a proposed switch in product configuration. The reaction also proceeds with reduced yield and enantioselectivity (52% yield, 57% *ee*) when compared to other ketenes (typically >90% yield and >90% *ee*) **(Scheme 46)**.
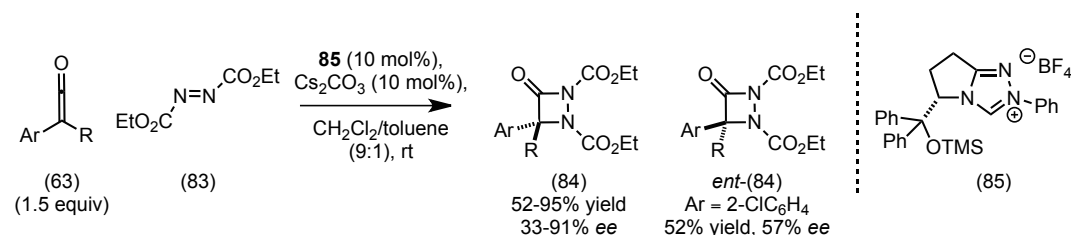
Scheme 46: Switch in absolute configuration for the NHC-catalysed synthesis of aza-β-lactams.

In an isolated case also reported by Ye *et al*, 2-chlorophenyl substitution,[25] or α-branching on the alkyl portion of the ketene, is vital to achieve good selectivity for the formal [2+2] cycloaddition between ketenes and oxoaldehydes with no reported examples employing other alkylarylketenes **(Scheme 47)**. No reasoning for this was postulated and in all the reports to date no specific reasoning for the effect of the 2-substituent or α-branching has been proposed.
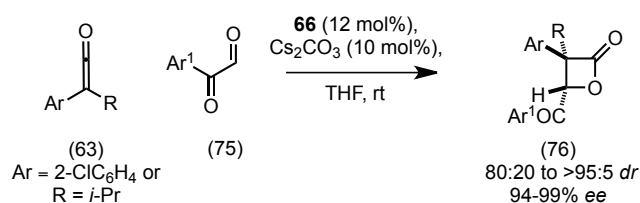
Scheme 47: Synthesis of β-lactones requiring of 2-aryl substitution or α-branching on the ketene.

With such a large quantity of literature detailing the effects of 2-substitution on the aryl group of the ketene, we were intrigued to discover what effect this would have in our developed methodology. To this end, 2-chlorophenylethylketene was prepared and tested under the optimised reaction conditions **(Scheme 48)**. No lactone product was observed by ^{1}H NMR spectroscopic analysis, instead the reaction proceeded cleanly to give α-chloroester **180** as the sole product in 73% yield and 62% *ee*. α-Chloroester **180** is believed to be the result of formal chlorination of the ketene by means of chloral acting as a electrophilic chlorinating agent.
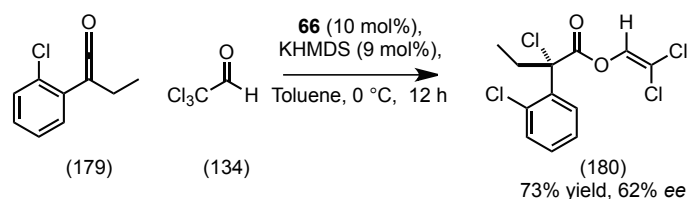
Scheme 48: Unexpected chlorination product from 2-chlorophenylethylketene.

4.2 Mechanistic proposal

This surprising result is, to the best of our knowledge, the first example of chloral acting as an electrophilic chlorinating reagent. We postulate this unexpected reaction mechanism to proceed to through an analogous initial process to the lactonisation cycle, by addition of the NHC **169** to the ketene **179** to generate azolium enolate **170**. This enolate may then abstract a chlorine atom from chloral **134**,[31] forming a new α-chloro stereocentre and a second enolate species **183**. These species may combine to displace the NHC catalyst, generating α-chloroester **180**, and complete the catalytic cycle **(Fig 24)**.
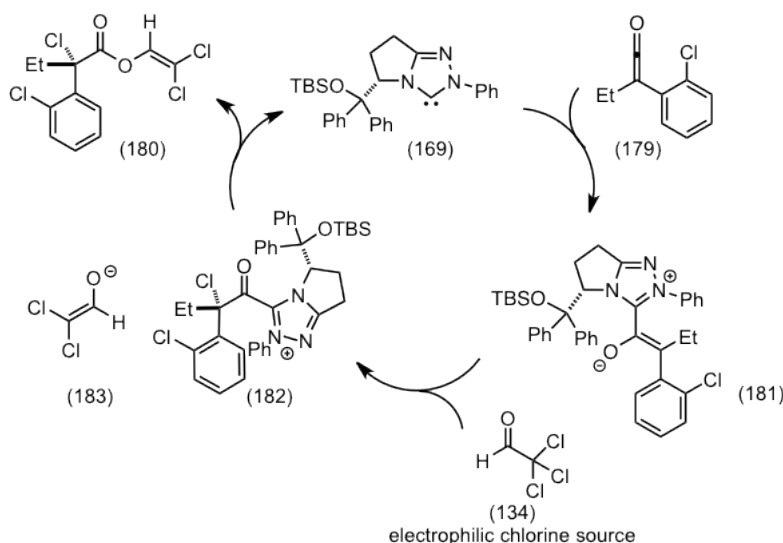
Fig 24: Postulated catalytic cycle for the formation of chlorinated product 180.

4.3 Substrate scope

To probe whether this was a general reaction, a further range of 2-tolyl substituted ketenes were prepared **(Scheme 49)**. Three 2-tolylalkyl ketenes with methyl, ethyl and butyl groups were screened under the developed reaction conditions. In all cases, moderate to good reactivity was observed, forming exclusively the chlorinated product. Methyl-2-tolylketene proceeded in 52% yield and 80% *ee*, a significant improvement on the initial 62% *ee* achieved with 2-chlorophenylethylketene. Ethyl-2-tolylketene also proceeded in high *ee* (82%) and in increased yield (71% yield) compared to the methyl analogue **186**. Finally, butyl-2-tolylketene provided a good isolated yield of the chlorinated product **188**, however the enantioselectivity could not be determined *via* HPLC analysis.

(184) (134) (185)

(186)
52% yield
80% ee[a]

(187)
71% yield
82% ee[a]

(188)
71% yield
% ee ND[a]
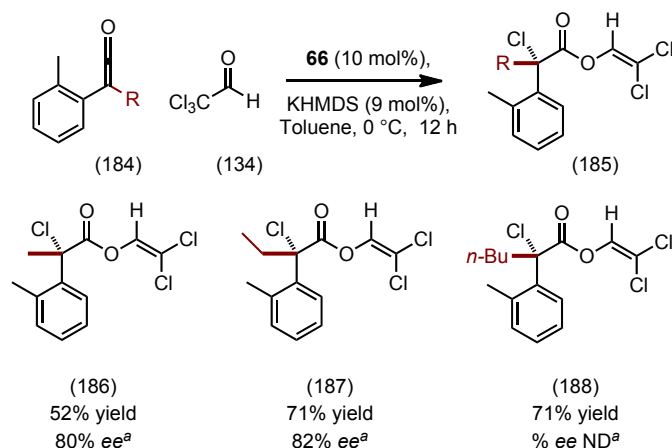
[a] % *ee* determined by HLPC analysis on a chiral stationary phase.

Scheme 49: Scope of the reaction with respect alkyl chain length on 2-tolylalkyl substituted ketenes.

Maintaining this range of alkyl groups, switching the aryl substituent to 1-naphthyl also provided good isolated yields of exclusively chlorinated products **(Scheme 50)**. Methyl-1-naphthylketene proceeded in 63% yield and 84% *ee* **(191)**, similar to the levels of enantioselectivity observed with the 2-tolyl substituent. Employing ethyl-1-naphthylketene, however, provided an excellent level of enantioselectivity (92% *ee*) with good isolated yield (80%) **(192)**. Finally butyl-1-naphthylketene was screened with similar yield (84%) and in excellent enantiomeric excess (90% *ee*) **(193)**.

(189) (134) (190)

(191)
63% yield
84% ee[a]

(192)
80% yield
92% ee[a]

(193)
84% yield
90% ee [a]
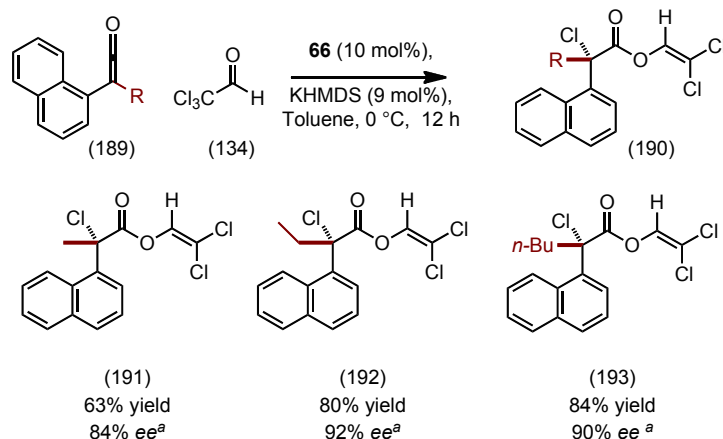
[a] % *ee* determined by HLPC analysis on a chiral stationary phase.

Scheme 50: Scope of the reaction with respect alkyl chain length on 1-naphthylalkyl substituted ketenes.

At this stage it was clear that a 2-substituent on the phenyl ring was effectively switching the reaction course to provide exclusively the chlorinated product. As α-branching on the ketene substituent has previously been shown to effect NHC-catalysed formal cycloadditions in a similar manner to 2-substitution, *i*-propylphenylketene was prepared and evaluated in this reaction **(Scheme 51)**. In accordance with the use of 2-substitution on the aryl substituent, the use of an *i*-propyl alkyl group also provided exclusively chlorinated ester **195**, in 86% yield and 88% *ee*.
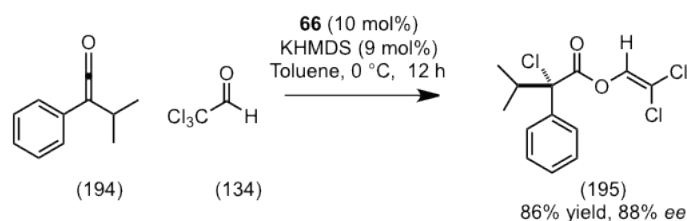
Scheme 51: Chlorination reaction employing isopropylphenylketene 194.

4.4 Preparative scale synthesis of chlorinated product 196

Following the demonstration of substrate scope, the utility of the chlorination process was demonstrated by preparative scale formation of chlorinated product **192**. The formation of chlorinated product **192** proceeded in 86% yield and with 94% *ee* to provide 1.1 g of the chloroester. Importantly, at this increased scale only 2.5 mol% of precatalyst **66** was employed **(Scheme 52)**.
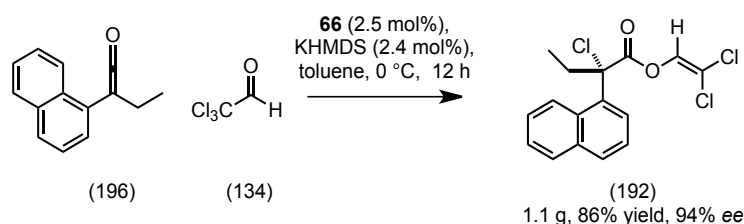
Scheme 52: Preparative scale chlorination reaction.

4.5 Determination of the absolute configuration

X-ray crystallographic methods could not be directly utilised to provide details of the absolute configuration of the products as all α-chloroester products were liquids. To determine conclusively the absolute configuration of the chlorination reaction, a two-step procedure to form the amide **197** was undertaken. Following the precedent of Fu,[32] the ester **192** (92% *ee*) was initially treated with bromine then subjected to (*S*)-α-methylbenzylamine in THF to provide the amide product **197** in 90% yield as a

single diastereomer after purification. This compound was sufficiently crystalline to allow unambiguous X-ray crystallographic determination of the absolute configuration, giving the (*S,S*)-configured product.
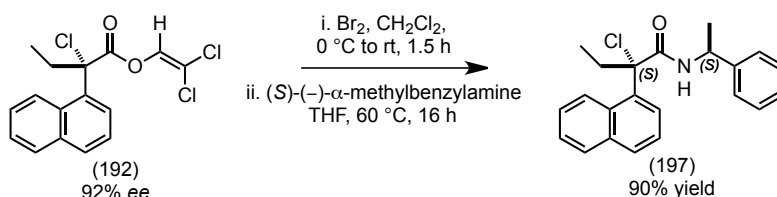
Scheme 53: Derivatisation of chlorinated product 192 to allow X-ray crystallographic analysis.
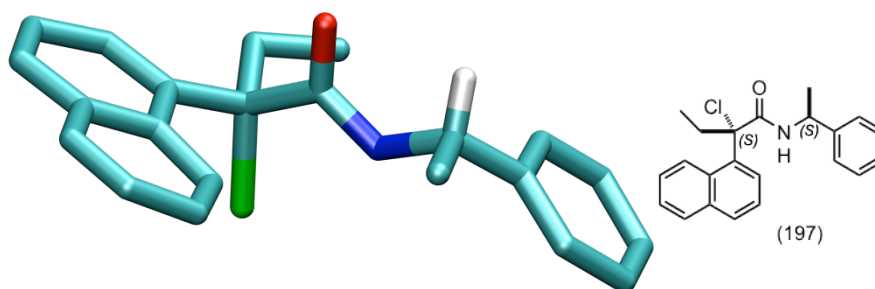
Figure 25: X-ray crystallographic representations 197-(*S,S*).

The determination of the absolute configuration for the chlorination pathway as (*S*) implies reaction from the opposite *Si* face of an assumed (*E*)-enolate to that observed for the β-lactone process. The configuration of (*S*) at the ketene derived stereocentre for both products is the result of a change in Cahn-Ingold-Prelog priority[33] caused by the presence of a chlorine atom in the latter ester product. In the lactone formation the absolute configuration was explained *via* reaction from the *Re* face of the enolate, with chloral approach past the *N*-phenyl substituent. Therefore any rationale for the absolute configuration employing a similar azolium enolate orientation would be required to explain reaction of the azolium enolate, for the opposite *Si* face, with chloral approach past the stereodirecting group.

4.6 Chemoselectivity and stereochemical considerations

Two important questions are raised by the identification that the chlorination reaction is both chemo- and enantiodivergent. Firstly, an explanation for the switch in reactivity to provide exclusively the chlorination product is required. Secondly, this proposal must also account for the observed switch in facial reactivity of the azolium enolate from *Re* to *Si*.

The rationale for both these questions begins by assuming an (*E*)-geometry for the azolium enolate **198** generated from NHC addition to a ketene bearing a 2-substituted aryl group. With this initial geometry fixed we next assume that the azolium enolate orientates with the oxy-anion approximately directed towards the stereodirecting group, as proposed previously **(Fig 26)**.
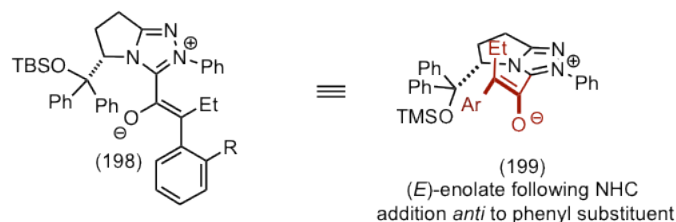
Fig 26: Azolium enolate geometry consistent with the previous model.

At this point the model for the chlorination reaction deviates from that proposed for the formation of β-lactone products. We propose that the presence of a 2-substituent on the aryl group of the azolium enolate forces the aryl group to adopt a non-planar orientation with respect to the enolate. This twisted orientation would necessitate directing the 2-substituent either towards the *N*-phenyl group or the large stereodirecting group **(Fig 27)**.
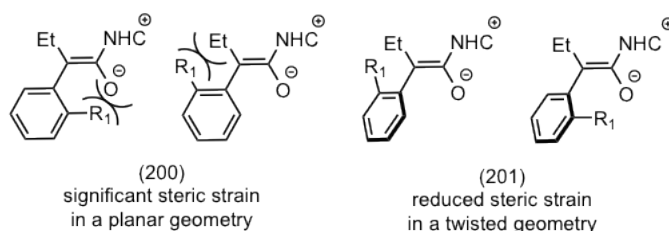
Fig 27: Rationale for a twisted enolate geometry when 2-substitued aryl groups are employed.

Using this model, we proposed that the 2-substituent will orient towards the *N*-phenyl substituent as to avoid the large stereodirecting group. With the 2-substituent directed towards the *N*-phenyl substituent, the previously favoured approach to the *Re* face of the enolate is now effectively blocked. This rationale explains the reaction of the azolium enolate from the *Si* face, with approach of chloral past the stereodirecting group accounting for the enantiodivergent nature of this process **(Fig 28)**. It is also proposed that to allow reaction from the *Si* face a twist in enolate geometry from the approximately perpendicular orientation **(Fig 20)** is required to eleviate some of the steric interactions with chloral approaching past the stereodirecting unit. A similar argument is employed for the use of a α-branched group. In this case, either its own steric effect, or a steric clash induced *via* a twisting of the accompanying phenyl

group, results in approach past the *N*-phenyl substituent to the *Re* face of the azolium enolate being disfavoured.[34]
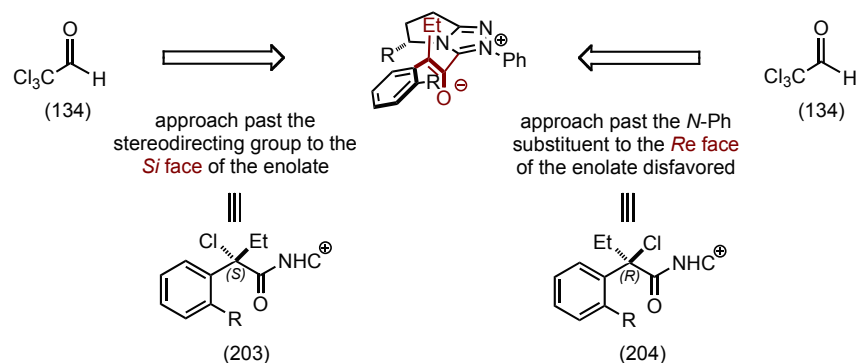
Fig 28: Rationale for the change in facial reactivity of the azolium enolate when 2-substituted aryl groups are used.

The switch in chemoselectivity observed for the reaction with chloral is rationalised by the consideration of the hybridisation of the electrophile in both mechanistic pathways. For the lactonisation to occur the azolium enolate must add to the π^* orbital of the sp^2 hybridised carbonyl at approximately 107° **(206)**.[35] In comparison, addition in the chlorination pathway must occur to the C–Cl σ^* orbital, with an antiperiplanar orientation of the C–Cl σ^* orbital and the C=O π^* orbital **(205) (Fig 29)**.
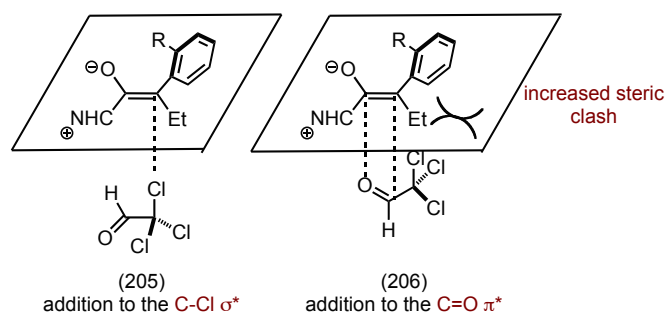
Fig 29: Rationale for the change in chemoselectivity

It is this difference in hybridisation of the electrophile that is proposed to account for the difference in reactivity. Specifically the geometrical requirements for the addition to the carbonyl of chloral, followed by lactonisation in a concerted but asynchronous manner, cannot be met with this orientation of the azolium enolate. Thus reactivity from the *Si* face of the enolate proceeds with addition to the sp^3 hybridised CCl$_3$ centre to furnish the (*S*)-configuration at the chlorinated-centre.

The proposed twist of aryl substituent, and subsequent disfavoured approach, may be employed to account for the consistently low reactivity observed for ketenes bearing

2-substituted aryl groups in most cycloaddition processes. In our case it is the unexpected dual reactivity of chloral that is postulated to allow reactivity from the *Si* face of the azolium enolate, past the large stereodirecting group.

5.0 Further 2-substituted examples

5.1 The use of 2-anisylethylketene

To test further the limits of this methodology, particularly with respect to where the crossover may lie between the lactonisation and chlorination pathways, 2-anisylethylketene was prepared **(Scheme 54)**. This ketene has not previously been reported in NHC-catalysed formal cycloaddition reactions.[36] We predict that it may provide a different reactivity profile when compared to other 2-substituted ketenes, due to a more conformationally flexible 2-methoxy group. This proposal was verified by the use of 2-anisylethylketene under standard reaction conditions, which produced an approximate 66:33 ratio of lactonisation **209** to chlorination products. The chlorinated product **210** was isolated in 11% yield, however the enantiomeric excess could not be determined *via* HPLC analysis. Analysis of the crude ^{1}H NMR spectrum indicated the lactone **209** had been formed as a single diastereomer and was subsequently isolated in 48% yield and with >99% *ee*.
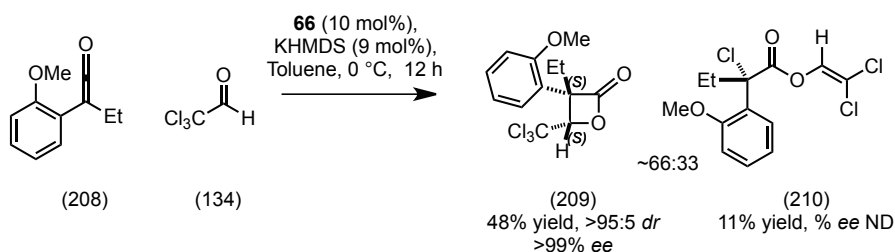
Scheme 54: Use of 2-anisylethylketene in the reaction procedure.

This lactone **209** product was confirmed as the *syn* diastereomer *via* X-ray crystallographic analysis which also identified the absolute configuration to be (3*S*,4*S*) **(Fig 30)**.
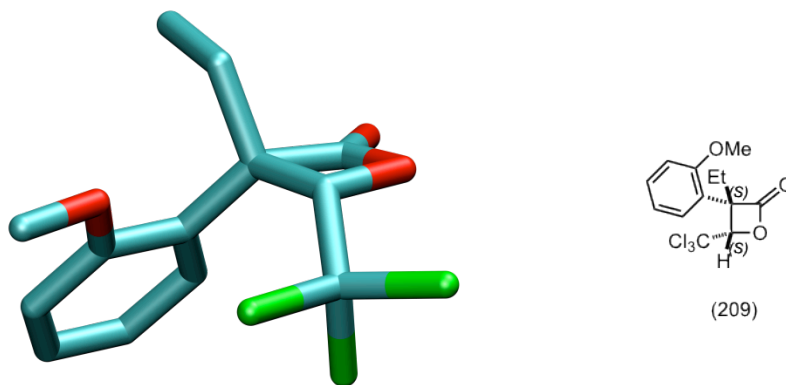
Figure 30: X-ray crystollgraphic representation showing the absolute configuration of the β-lactone 209.

The competitive formation of both the β-lactone and the chlorination product validates the proposal that a 2-substituent with increased flexibility could alter the product ratio. The formation of the β-lactone could be rationalised by the increased flexibility of the 2-methoxy substituent allowing approach past the *N*-phenyl substituent to the *Re* face of the enolate. Approach to the *Re* face accounts for the configuration obtained at the C(3) centre, while the opposite diastereoselectivity (preferentially *syn*) compared to the preferentially *anti* diastereomer is not instantly apprent. To account for the high diastereoselectivity (preferentially *syn*), addition to the *Si* face of chloral **211** must be preferred over addition to the *Re* face **210**, assuming the same orienentation of the enolate with respect to the NHC **(Fig 31)**. At this time, a full rationale for the preference cannot be provided.
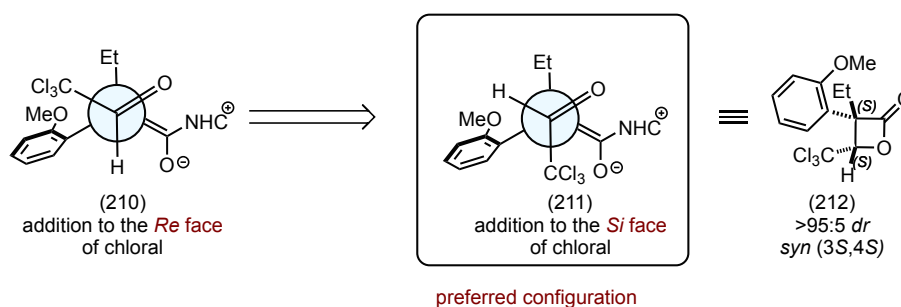
Fig 31: Proposed rationale for the observed configuration of the lactone product obtained from 2-anisylethylketene.

5.2 The use *i*-propyl-3-thiophenylketene

A second ketene that could potentially provide dual reactivity was *i*-propyl-3-thiophenylketene.[35] As with 2-anisylethylketene, this ketene has not previously been reported in NHC-catalysed formal cycloaddition reactions. It could provide a different reactivity profile when compared to other α-branched alkyl substituted ketenes due to a less sterically demanding aryl unit. In this case the use of *i*-propyl-3-thoipheneketene in the reaction protocol proceeded to give predominantly chlorination, with an approximate 75:25 ratio of chlorination to lactonisation (16:84 *anti:syn* ratio of lactone diastereomers). The chlorinated product **215** was isolated in 32% yield and in 78% *ee*; however, due to difficulties associated with the purification of the two lactone diastereomers **214** the enantioselectivities could not be determined **(Fig 55)**.[37]
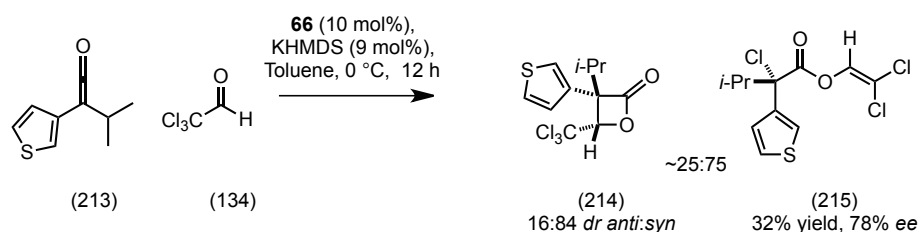
Scheme 55: The use of *i*-propyl-3-thiophenylketene in the reaction protocol.

It is inferred by the increased ratio of chlorination to lactonisation that the combination of a thiophene and an *i*-propyl substituent disfavour the lactonisation process to a greater degree than a 2-anisyl group. Although, as predicted, the thiophene substituent still results in a greater proportion of lactonisation than a phenyl and an *i*-propyl substituent, presumably due to the reduced steric demand of thiophene compared to the phenyl moiety.

The preferentially *syn* diastereoselectivity can be explained *via* the proposal to account for reduced *dr* obtained with butylphenylketene. In this rationale the increased steric demand of the *i*-propyl substituent results in addition to the *Si* face of chloral as to minimise steric interactions between the bulky CCl$_3$ group and the *i*-propyl substituent of the azolium enolate **(Fig 32)**.
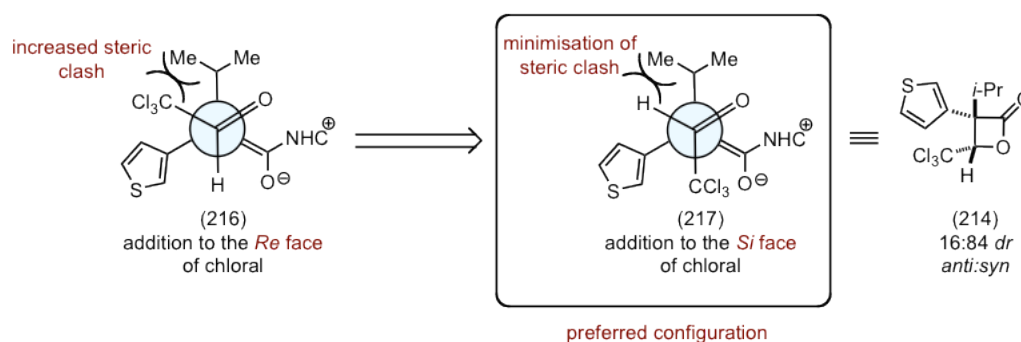
Fig 32: Rationale for the observed diastereoselectivity with *i*-propyl-3-thiophenyl ketene

6.0 Summary

This chapter has reported the identification and development of a novel chemo- and enantiodivergent reaction manifold. The first strategy to be developed was the NHC-catalysed formal [2+2] cycloaddition between disubstituted ketenes and chloral. This proceeded for a range of alkylarylketenes in good yield (55-95%), with moderate to good diastereoselectivities (up to 88:12 *dr*) and in good to excellent levels of enantioselectivity (up to 97% *ee*). This reaction was highly amenable to scale with >3 g prepared from a single reaction using the low precatalyst loading of 2.5 mol%. The synthetic utility remained limited, with the desired derivatisation to amino acid-type motifs were not realised due to the difficulties encountered with various lactone ring opening strategies. Reduction methods with DIBAL, however, delivered the alcohol products, which could potentially be derivatised to the desired amino acid targets if desired.

A second and intriguing novel chlorination reaction pathway was also discovered when 2-chlorophenylethylketene was used. This reaction was found to be general, and provide exclusively chlorination products for a range of ketenes either substituted in the two position of the aryl ring, or bearing an α-branched alkyl chain. In most cases no lactone products could be detected spectroscopically with only chlorinated esters isolated in good to excellent yield (52-86%), and moderate to excellent enantioselectivity (up to 94% *ee*). This novel chlorination methodology was also amenable to preparative scale with >1 g isolated using the low precatalyst loading of 2.5 mol%. This methodology still has significant scope for improvement, especially with regard to the following:

- Further study is needed into the scope of the reaction with respect to the aldehyde component. Further work will aim to develop a NHC promoted lactonisation methodology suitable for less reactive aldehydes other than

chloral, that may allow significant improvements in utility *via* ring opening derivatisation strategies.

- Investigation into the possibility of developing a more general asymmetric halogenation methodology in order to extend the scope of the reaction beyond the necessity for either a 2-substituted aryl group or α-branching on the alkyl substituent.

- Whilst the use of isolable ketenes allows efficient access to highly reactive azolium enolates, they are limited with respect to the available substitution pattern, as well as reaction scale and practicality. The use of a suitable ketene surrogate, such as an α-functionalised aldehyde, could address some of these problems.

These highlighted limitations will be addressed in the subsequent chapters of this thesis.

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37. The major *syn* diastereomer for the lactone product could be partially isolated in small quantities to allow characterisation (see experimental information). The specific rotation of this compound was found to be +213.

Chapter 4: NHC-Catalysed Asymmetric β-Lactone Formation from Alkylarylketenes and Benzaldehydes

1.0 Project aim

(Chapter 3) demonstrated the efficient NHC-catalysed synthesis of β-lactones from disubstituted ketenes and chloral. Although proceeding in excellent yield and enantioselectivity, the diastereoselectivities obtained were modest, typically ~75:25 *anti*:*syn*, and thus represented significant scope for improvement. Equally, the use of anhydrous chloral as a highly reactive aldehyde substrate limited both the scope and the practicality of the procedure. To overcome these limitations expansion of the NHC-catalysed formal [2+2] cycloaddition to less reactive benzaldehyde derivatives was investigated.

2.0 Introduction

Following the seminal publication of Wynberg and Staring,[1] the use of cinchona type derivatives as Lewis bases in asymmetric β-lactone synthesis has been expanded through the reports of Romo,[2] Nelson[3] and Calter.[4] Crucially Romo and co-workers improved the utility of the original Wynberg process *via* the replacement of the parent dimeric ketene gas with *in situ* generation of parent ketene by dehydrohalogention of acetyl chloride. This work also expanded the scope of the aldehyde component to other activated aldehydes and functions in good yield and excellent enantioselectivity (93-98% *ee*) **(Scheme 56)**.
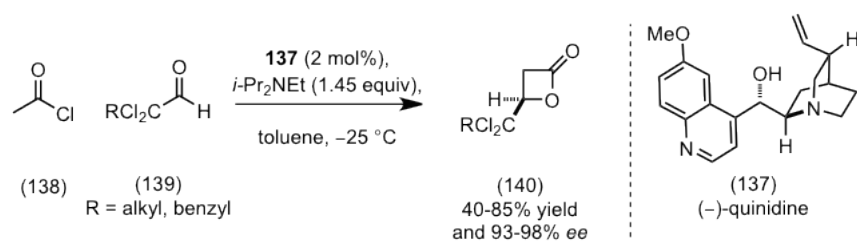
Scheme 56: Use of in-situ generated ketene in the Wynberg β-lactone process.

In an elegant extension to the Wynberg procedure catalysed by either silylated quinine or quinidine **221**, the group of Nelson utilised a wide range of aldehydes in partnership with *in situ* generated unsubstituted and monomethylketene. Unactivated aryl and alkyl (both linear and branched) aldehydes provide good yield (typically >75%) and excellent diastereo- and enantioselectivity (typically >20:1 *dr* and ≥99% *ee*). Importantly this extension to the previous reports allows the preparation of 3,4-disubstituted β-lactones **(Scheme 57)**.
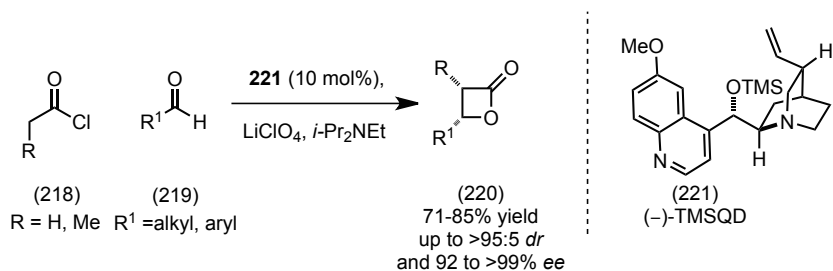
Scheme 57: Extension of the Wynberg β-lactone synthesis to mono-substituted ketenes.

Calter and co-workers have employed the same cinchona alkaloid derivative **221** but achieved the synthesis of *anti* β-lactones by the use of a scandium(III) trifluoromethanesulfonate Lewis acid co-catalyst. This switch in diastereoselectivity is explained *via* an antiperiplanar open transition state compared to the closed transition state proposed by Nelson to rationalise the *syn* selectivity in their process (**Scheme 58**.
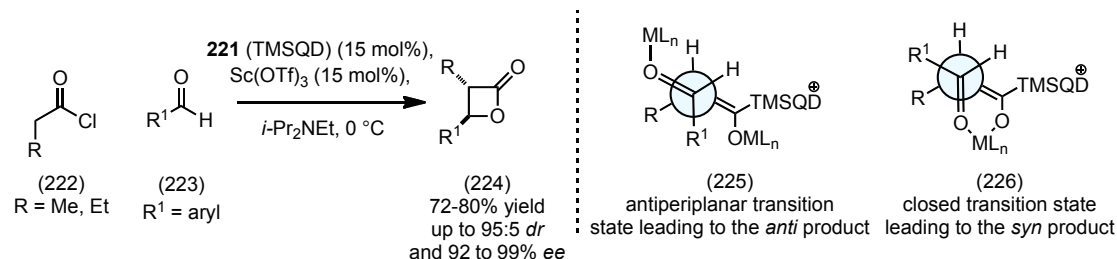
Scheme 58: Synthesis of *anti* β-lactones with proposed transition states.

These methods provide efficient and rapid access to a range of β-lactones with mono-substitution in the α-position, owing to the use of mono-substituted ketenes. Reactions employing disubstituted ketenes are more limited, with recent reports from the group of Fu,[5] Ye[6] and Kerrigan.[7] Fu reports the efficient synthesis of β-lactones from dialkyl ketenes and benzaldehydes under the catalytic influence of the well documented planar chiral PPY derivative **59** in good yield (48-92%) and excellent enantioselectivity (up to 91% *ee*).[8] However the diastereoselectivity was typically moderate (up to 4.5:1 *dr syn*:*anti*) and alkylarylketenes were not tolerated in this process **(Scheme 59)**.
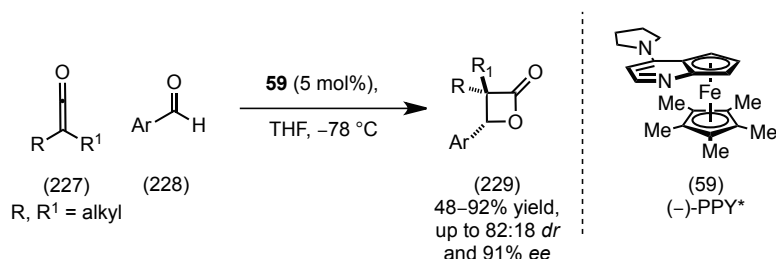
Scheme 59: Synthesis of α,α-disubstituted β-lactones

As previously summarised **(Chapter 1, 4.1.2))** Ye has employed NHCs to catalyse the formal [2+2] cycloaddition between alkylarylketenes and highly reactive 2-oxo-aldehydes or trifluoromethylketones. Notably the reported methodology for 2-oxo-aldehydes failed for the cycloaddition of 2-chlorophenylethylketene and the less reactive 4-chlorobenzaldehyde. The current state of the art was reported by the group of Kerrigan (during the course of our own investigations) who showed the viability of a chiral C_2-symmetric diphosphine **232** catalysed the formal [2+2] cycloaddition between alkylarylketenes and various benzaldehyde derivatives **(Scheme 60)**. *anti* β-Lactones were obtained in good yield (typically >60%) and in excellent diastereo- and enantiocontrol (typically >90:10 *dr* and up to 99% *ee*). In this report optimum diastereocontrol is obtained when less sterically demanding alkyl groups are employed: with methyl or ethyl groups, the lactones are obtained in typically >90:10 *dr*; the use of a butyl group gave significantly reduced *dr* to 53:47 (*anti*:*syn*). Kerrigan and co-workers postulate addition of the phosphine to the aldehyde to generate a phosphonium alkoxide as the first step in the catalytic cycle. This is in contrast to other mechanistic propositions (such as that of Ye *et al*.) who favour addition to the ketene as the initial step.
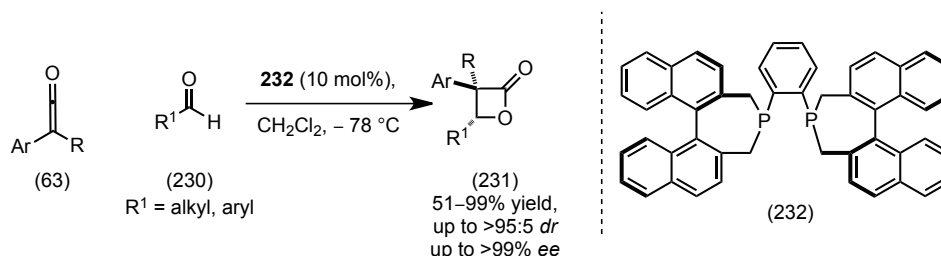
Scheme 60: Diphosphine catalysed asymmetric β-lactone synthesis from disubstituted ketenes.

3.0 NHC-catalysed asymmetric β-lactone formation

3.1 Initial investigations

Aware of the ability of NHCs to promote asymmetric benzoin reactions of benzaldehydes[9,10] and ketene dimerisation processes,[11] we set out to minimise these at the onset of the investigation. Initial studies employed ethylphenylketene and triazolium precatalyst **66** with a range of benzaldehydes **(Scheme 61, Table 4)**. While benzaldehyde gave no β-lactone product (giving only ketene dimer) **(Table 4, Entry 1)**, promising reactivity was observed with electron deficient benzaldehydes, employing dropwise ketene addition to minimise ketene dimerisation. At 0 °C, benzaldehydes incorporating 4-substituted inductively or mesomerically electron

withdrawing groups (4-trifluoromethyl- or 4-nitrobenzaldehyde respectively) gave good yields of β-lactones, with moderate preferential *anti* diastereoselectivity and promising levels of enantioselectivity for the minor *syn* diastereomer **(Table 4, Entry 2 & 3)**. Improved enantiocontrol was achieved at the detriment of product yield at −78 ºC using 4-nitrobenzaldehyde **(Table 4, Entry 4 & 5)**, with ketene dimerisation product and starting aldehyde the major reaction components after 12 h. Interestingly, *syn* diastereoselectivity (89:11 *syn*:*anti*) and high *ee* were observed using 2-nitrobenzaldehyde **(Table 4, Entry 6)**.
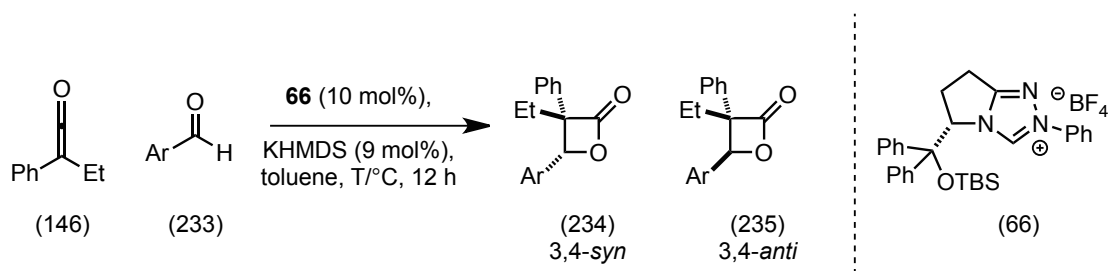
Scheme 61: Initial investigations of benzaldehyde derivatives.

Entry	Ar	Temp (ºC)	dr[a] (*syn*:*anti*)	Yield (%)[b] (*syn*:*anti*)	ee (%)[c] (*syn*:*anti*)
1[d]	Ph	0	––	––	––
2[e]	4-CF$_3$C$_6$H$_4$	0	30:70	27, 55	80, 38
3[f]	4-NO$_2$C$_6$H$_4$	0	40:60	30, 50	81, 14
4[f]	4-NO$_2$C$_6$H$_4$	−78 to rt	40:60	7, 34	97, 54
5[f]	4-NO$_2$C$_6$H$_4$	−78	23:77	–, 27	–, 76
6[g]	2-NO$_2$C$_6$H$_4$	0	89:11	86, –	94, –

Unless stated ketene added dropwise as a solution in toluene. [a] Calculated by inspection of the crude reaction mixture using ^{1}H NMR spectroscopy [b] Isolated yield of single diastereomer. [c] % *ee* determined by HLPC analysis on a chiral stationary phase. [d] Ketene added in a single portion. [e] 1.5 equiv of aldehyde. [f] 1.5 equiv of ketene. [g] 1.2 equiv of aldehyde.

Table 4: Initial investigations of benzaldehyde derivatives.

3.2 Assignment of the configuration of 236 and 238.

The diastereoselectivity and the absolute configuration for the β-lactone **236** derived from 4-nitrobenzaldehyde was assigned by derivatisation to known hydroxy acid **237**.[7] In this instance the absolute configuration of **237** was found to be (*R,R*) *via* comparison of the specific rotation $[\alpha]_D^{20}$ −46 (*c* 0.05, EtOAc, 76% *ee*) [literature $[\alpha]_D^{20}$ −48 (*c* 0.32, EtOAc), 87% *ee* (2*R*,3*R*)] **(Scheme 62)**. The diastereoselectivity for 4-trifluorobenzaldehyde derived lactone was assigned in analogy to **236** *via* ^{1}H NMR spectroscopic analysis of the characteristic shift for the lactone C(4)H.
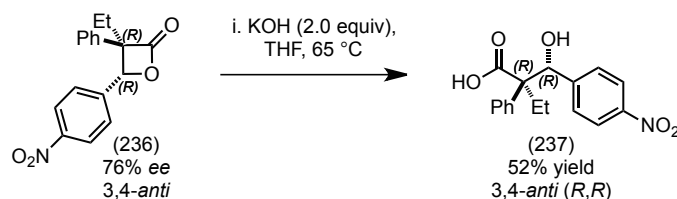
Scheme 62: Determination of the absolute configuration of lactone 236.

The *syn* diastereoselectivity observed using 2-nitrobenzaldehyde was initially assigned *via* ^{1}H nuclear Overhauser effect (nOe analysis). A clear signal enhancement was observed for the ethyl CH$_2$CH$_3$ protons under irradiation of the signal corresponding to proton A (C(4)H$_a$), confirming their relative relationship as *syn*.
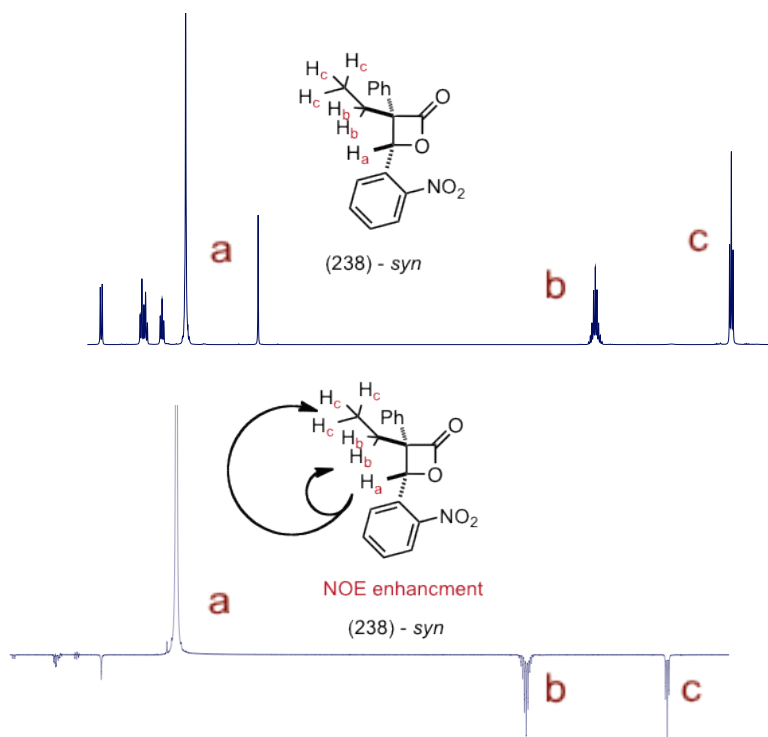
Fig 33: Assignment of the relative configuration of lactone 238 by ^{1}H NMR nOe analysis.

3.3 Optimisation of reaction conditions

Further optimisation of this process was achieved through lowering of the reaction temperature, with consistently high levels of diastereo- and enantioselectivity observed **(Scheme 63, Table 5)**. Interestingly, lowering the reaction temperature below −50 ºC had a detrimental effect on product *ee*, whilst maintaining good diastereoselectivity **(Table 5, Entry 4)**. This was postulated to be due to a competitive KHMDS-catalysed racemic pathway at this temperature, as the use of KHMDS to promote formal [2+2] cycloadditions of ketenes with imines or carbonyls has been previously reported by the group of Wilhelm.[12] This was independently confirmed by a control reaction in the absence of precatalyst **66 (Table 5, Entry 5)**. Attempted removal of HMDS from the reaction mixture prior to the addition of ketene and aldehyde, *via* concentration *in vacuo* following a presumed deprotonation event, led to reduced yield (45%) and enantioselectivity (95:5 *dr*, 64% *ee*) **(Table 5, Entry 6)**.
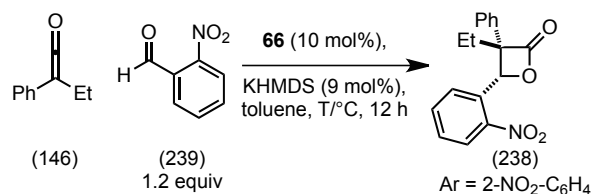
Scheme 63: Optimisation of reaction conditions.

Entry	Ar	Temp (ºC)	*dr*[a] (*syn*:*anti*)	Yield (%)[b] (*syn*:*anti*)	*ee* (%)[c] (*syn*:*anti*)
1[d]	2-NO$_2$C$_6$H$_4$	−15	91:9	66, –	95, –
2[d]	2-NO$_2$C$_6$H$_4$	−25	92:8	77, –	97, –
3[d]	2-NO$_2$C$_6$H$_4$	−50	93:7	83, –	93, –
4[d]	2-NO$_2$C$_6$H$_4$	−78	94:6	86, –	82, –
5[e][f]	2-NO$_2$C$_6$H$_4$	−78	89:11	–,–	–, –
6[g]	2-NO$_2$C$_6$H$_4$	−78	95:5	45, –	64, –

Unless stated, ketene added dropwise as a solution in toluene. [a] Calculated by inspection of the crude reaction mixture by ^{1}H NMR spectroscopy [b] Isolated yield of single diastereomer. [c] % *ee* determined by HLPC analysis on a chiral stationary phase. [d] 1.2 equiv of aldehyde. [e] Reaction carried out in the absence of precatalyst **66**. [f] Crude conversion estimated to be >75%. [g] Attempted removal of HMDS prior to the ketene addition.

Table 5: Optimisation of reaction conditions.

3.4 Expansion of the protocol to a range of 2-substitued benzaldehyde derivatives

Aiming to expand the methodology, a range of 2-halosubstituted benzaldehydes were also screened under these optimised conditions giving the corresponding β-lactones with poor diastereo- but good enantiocontrol **(Scheme 64, Table 6)**. The 2-halosubstituted β-lactone diastereomers proved challenging to separate from both the ketene dimer and/or any residual aldehyde. Purification and characterisation was achieved by derivatisation to the corresponding benzylated β-hydroxy **244–246** acids to allow determination of enantioselectivity.[13] Unfortunately, due to the essentially 50:50 mixture of the diastereomer and the inability to separate them chromographically, the enantioselectivities could not be conclusively assigned to either the *syn* or *anti* β-lactones and have been arbitrarily assigned. The requirement for an electron withdrawing substituent was further confirmed by using 2-tolylbenzaldehyde. In this instance, only ketene dimer and the starting aldehyde were obtained **(Table 6, Entry 4)**.
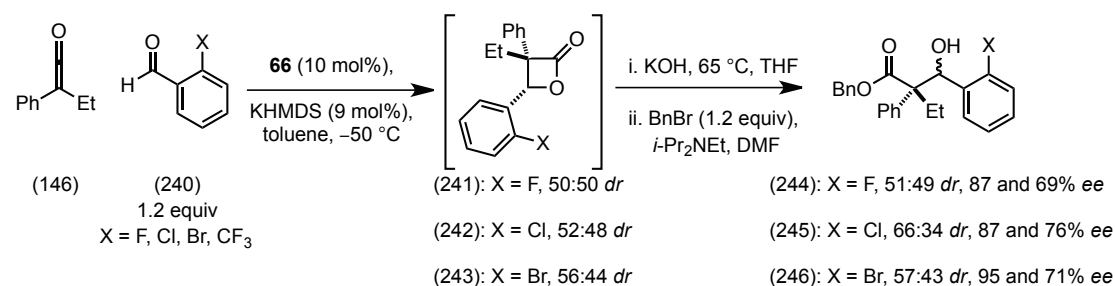
Scheme 64: Expansion of the protocol to a range of 2-substituted benzaldehyde derivatives.

Entry	X	dr[a][b]	Yield (%)[c]	ee (%)[d] (syn:anti)[b]
1	F	50:50	29	87, 69
2	Cl	52:48	36	87, 76
3	Br	56:48	25	95, 71
4	CH₃	–, –	–	–, –

Unless stated, ketene added dropwise as a solution in toluene. [a] Calculated by inspection of the crude reaction mixture by ^{1}H NMR spectroscopy. [b] Diastereoselectivity was not assigned [c] Isolated yield of combined diastereomer following ring opening derivatisation (3 steps). [d] % *ee* determined by HLPC analysis on a chiral stationary phase on the corresponding ring opened derivatised product.

Table 6: Expansion of the protocol to a range of 2-substituted benzaldehyde derivatives.

It is interesting to note that the 2-nitro group is key for high diastereoselectivity and that the major diastereomer obtained is the opposite to that for either 4-substituted benzaldehydes or the β-lactones derived from chloral **(Chapter 3)**. The diastereoselectivity is also the reverse of that obtained by the phosphine catalysis of Kerrigan *et al*. who obtained similar levels of diastereoselectivty (~90:10 *dr*), but the *anti* diastereomer is preferred. In one isolated example in the work of Kerrigan when 2-chlorobenzaldehyde is used, the β-lactone formed in high yield but with reduced diastereoselectivity 75:25 *dr* (*anti*:*syn*); the enantioselectivity of this reaction was not reported.

3.5 Analysis of the substrate scope with respect to the alkyl substituent

With 2-nitrobenzaldehyde identified as giving optimal diastereo- and enantiocontrol in this process, the scope and limitations of the lactonisation process were defined by screening a range of disubstituted ketenes **(Scheme 65)**. In all cases, the enantioselectivity was evaluated by chiral HPLC analysis compared to genuine racemic samples prepared in an analogous fashion from racemic precatalyst **66**. Variation of the alkyl chain in a series of alkylphenylketenes showed that incorporation of a methyl substituent gave poor *dr* whilst maintaining high *ee* **242**. Ethyl **238** and *n*-butyl **243** substitution gave β-lactones in high *dr* and *ee*, while *i*-butyl substitution leads to high *dr* but poor *ee* **244**. This trend in diastereoselectivity is directly opposite to that obtained by the use of chloral. In that series **(Chapter 3)** the use of a methyl group in the alkyl position improved the diastereoselectivity from 72:28 for ethylphenylketene to 87:13 for methylphenylketene, whilst lowering the enantioselectivity from 92% to 82% *ee*, respectively.
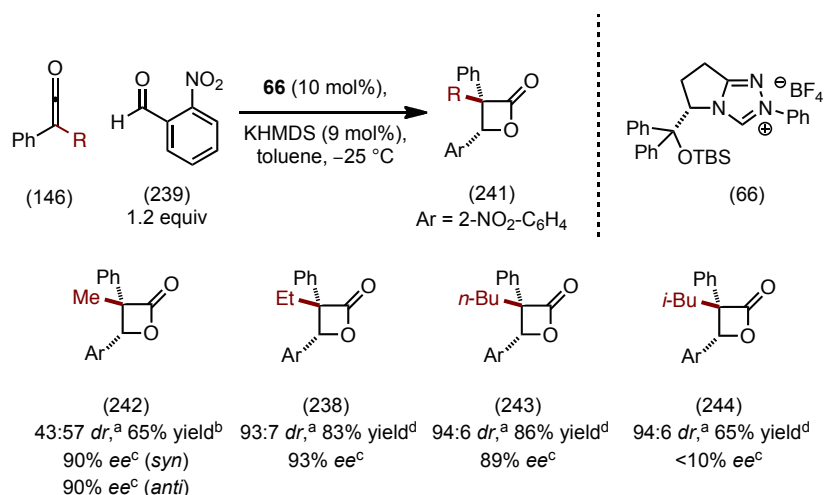
For all reactions, ketene was added dropwise as a solution in toluene. [a] Calculated by inspection of the crude reaction mixture by ^{1}H NMR spectroscopy. [b] Isolated yield of mixture of diastereomer. [c] % *ee* determined by HLPC analysis on a chiral stationary phase. [d] Isolated yield of single diastereomer.

Scheme 65: Scope of the reaction with respect to the alkyl substituent.

3.6 Analysis of the substrate scope with respect to the aryl substituent

Variation of the aryl unit within a series of ethylarylketenes was also investigated, with both electron withdrawing and donating substituents providing β-lactones with high *dr* and *ee* **(Scheme 66)**. Further substrate variation showed that *i*-propyl-3-thiophenylketene gave β-lactone **252** with poor *dr* although high *ee* for the *anti* diastereomer. In line with the previous result **(Scheme 65)**, the use of a methyl unit, this time in combination with a 4-chlorophenyl moiety, provided poor diastereoselectivity but high enantioselectivity **248**. Consistent with the previous findings of Ye,[6a] and that of **(Chapter 3)**, the employment of ethyl-2-tolylketene with 2-nitrobenzaldehyde gave no β-lactone products, returning only starting aldehyde and a mixture of both ketene dimerisation and formal hydrolysis products.
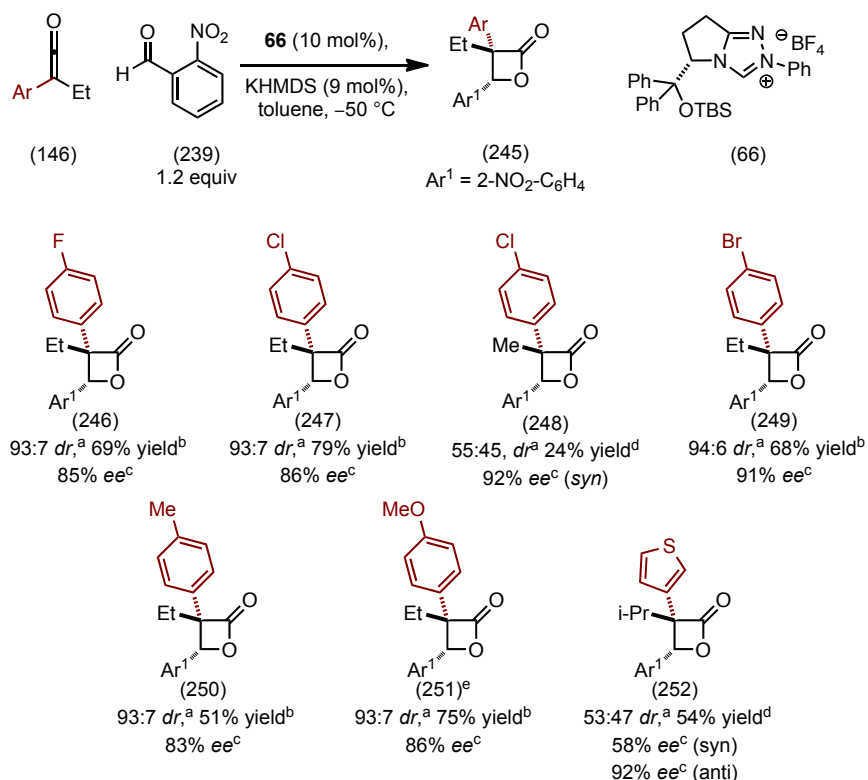
For all reactions, the ketene was added dropwise as a solution in toluene. [a] Calculated by inspection of the crude reaction mixture by ^{1}H NMR spectroscopy. [b] Isolated yield of single diastereomer. [c] % *ee* determined by HLPC analysis on a chiral stationary phase. [d] Isolated yield of combined diastereomer. [e] 1.2 equiv of ketene and 1.0 equiv of aldehyde used.

Scheme 66: Scope of the reaction with respect to the aryl substituent.

3.7 Mechanistic proposal

As previously noted the observed trend in diastereoselectivity using NHC-mediated catalysis in this process (reduced *dr* for methylaryl ketenes) is opposite to that using phosphine catalysis (high *dr* for methylaryl ketenes, reduced *dr* for *n*-butylaryl ketenes).[14] Kerrigan favours Lewis base addition to the aldehyde as the initial step in the phosphine-catalysed system to give **253**. This is followed by addition to the ketene, *anti* to the sterically large aryl group,[15] before cyclisation to produce the β-lactone products and regeneration of the phosphine catalyst **(Fig 34)**.
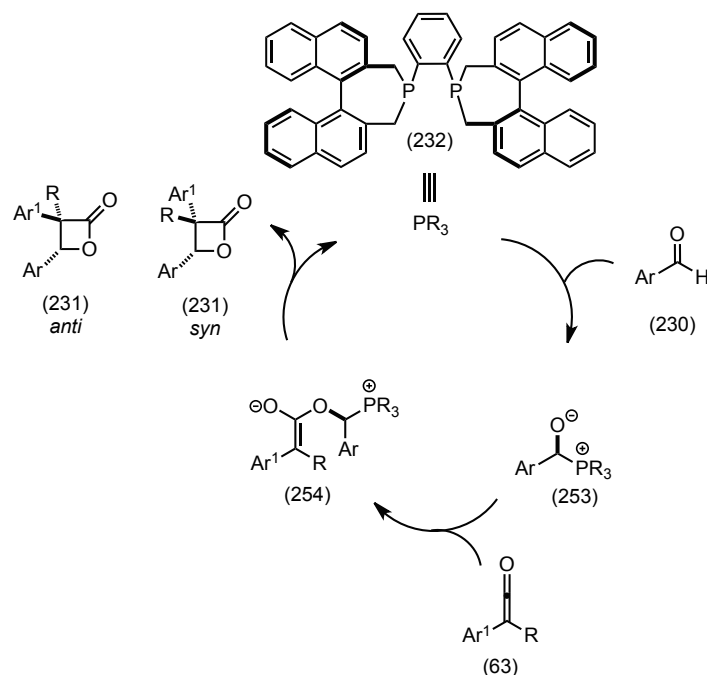
Fig 34: Mechanistic proposal from Kerrigan for the diphosphine catalysed β-lactone formation.

In the NHC-mediated process, initiation through NHC addition to the ketene is postulated. As previously summarised for the use of chloral **(Chapter 3, 3.8)**, addition of *in situ* generated NHC **169** to ketene **146**, preferentially *anti* to the aryl unit, generates azolium enolate intermediate **170**. Subsequent concerted, but asynchronous, formal [2+2] cycloaddition with 2-nitrobenzaldehyde yields zwitterionic intermediate **255**, with subsequent catalyst regeneration and lactone formation.
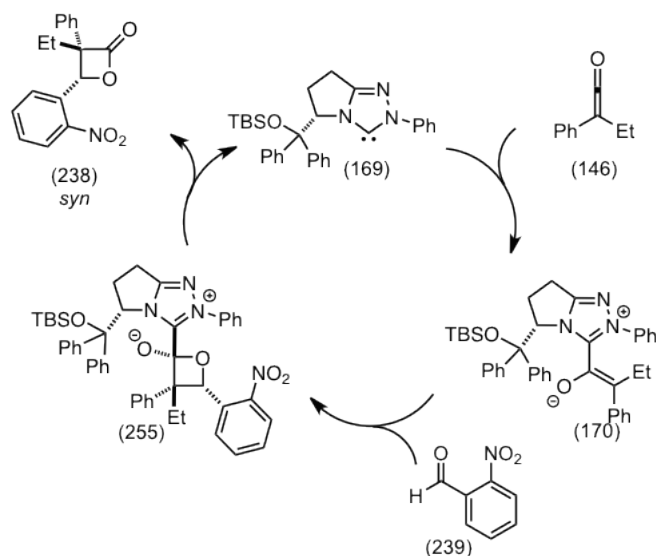
Fig 35: Mechanistic proposal for the NHC-catalysed β-lactone formation.

To confirm that a competing but reversible benzoin reaction is not in operation, synthesis of benzoin product **256** was attempted, but was found to be unsuccessful. Under the benzoin conditions developed by Connon *et al*. that have proved optimal for a range of aromatic aldehydes,[16] no benzoin product could be obtained. Further analysis of the literature identified that no known NHC-catalysed benzoin condensation for aldehyde **239** has been reported. It is inferred from this information that the benzoin condensation of 2-nitrobenzaldehyde is not a likely mechanistic pathway under the conditions employed.
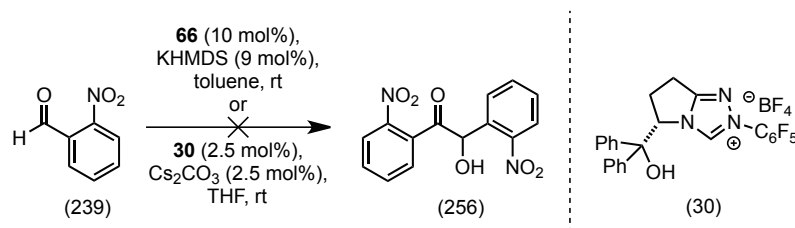
Scheme 67: Attempted benzoin condensation of 2-nitrobenzaldehyde.

3.8 Determination of the absolute configuration.

The absolute and relative configuration of **238** was proven by X-ray crystallography and found to be (3*S*,4*R*),[17] with all other configurations assigned by analogy.[18] Importantly, the absolute sense of induction at the ketene derived stereogenic centre is the same as that for β-lactones obtained *via* the use of chloral. The importance difference between the systems is the *syn* diastereoselectivty observed for the use of 2-nitrobenzaldehyde, compared to the *anti* selectivity for the chloral series.
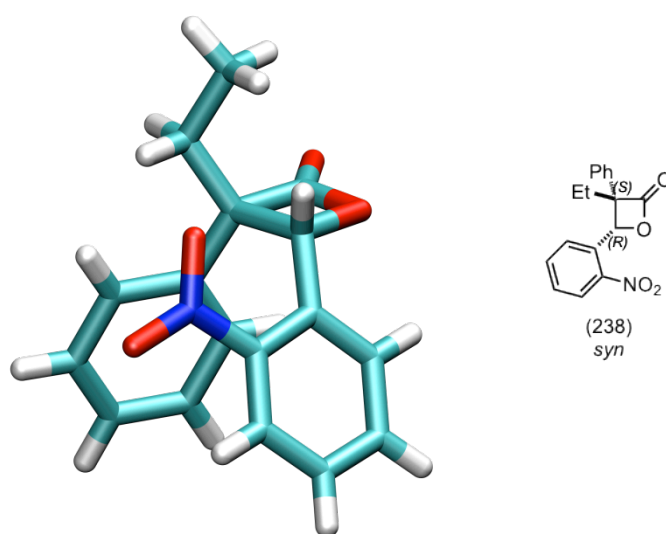
Fig 36: X-ray crystallographic representation of lactone 238 showing the absolute configuration.

3.9 Stereochemical considerations

The rationale for the observed (3*S*,4*R*) absolute configuration is initially concurrent with that proposed for the use of chloral in **(Chapter 3, 3.9)** We propose an identical enolate geometry and orientation with respect to the trazolium ring, as well as the same direction of approach past the *N*-phenyl substituent. Addition to the *Re* face of the azolium enolate in this manner would account for the same sense of induction at the C(3) position of both lactone products **(Fig 37)**.
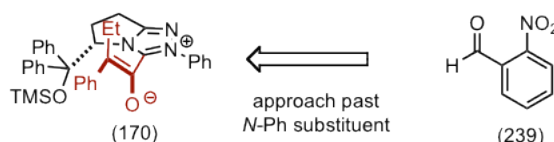
Fig 37: postulated approach of 2-nitrobenzaldehyde past *N*-phenyl substituent.

The difference in diastereoselectivity between the two systems is postulated to be due to addition to the *Si* face of 2-nitrobenzaldehyde, compared to addition to the *Re* face of chloral in the previous series. Importantly, the obtained levels of diastereoselectivity for the 2-nitrobenzaldehyde process are significantly greater than the chloral series, although as previously shown, they are highly dependent on the presence of the 2-nitro functionality. Moreover, the trend in diastereoselectivity with respect to the alkyl chain length is reversed for the two series. Greater diastereoselectivity is observed for the use of more sterically demanding alkyl groups in the 2-nitrobenzaldehyde series. Conversely, the use of these groups in the chloral series greatly diminished the *dr* **(Fig 38)**. Combining these observations it is possible to postulate a working stereochemical rationale for the observed trend in diastereoselectivity.
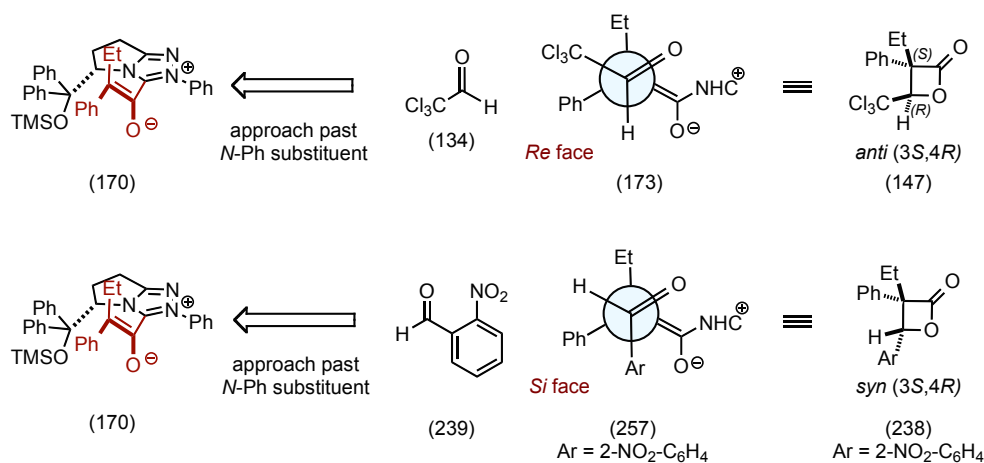
Fig 38: Differing facial approaches of 2-nitrobenzaldehyde and chloral.

The first consideration is that of the conformation of 2-nitrobenzaldehyde. We postulate that due to the steric clash between the formyl group and the 2-nitro substituent that the formyl group will be orientated out of the plane of the benzene ring. Evidence for this distortion is provided by X-ray crystallographic data of the solid state structure of 2-nitrobenzaldehyde reported by Coppens and Schmidt[19] **(Fig 39)**. In this report they quantify the angle of rotation from the plane of the ring as 27 and 31° for the nitro- and the aldehyde group, respectively. This rotation has also been recently analysed in the gas phase by computational methods by González *et al*. who were in agreement with the approximate 30° angle of distortion.[20]
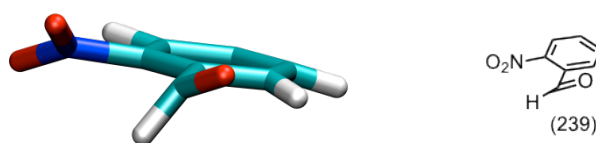
Fig 39: X-ray crystallographic representation of 2-nitrobenzaldehyde.

Although solid phase structural characteristics may not be indicative of solution phase conformation, by invoking this twisted geometry the preferential addition to the *Si* face of 2-nitrobenzaldehyde can be rationalised. Simplistically *via* the minimisation of steric interactions with the sp^3 hybridised alkyl substituent on the azolium enolate. In this model the twisted geometry of 2-nitrobenzaldehyde forces it to orientate preferenatially *anti* to the enolate alkyl substituent with the 2-nitro group directed away from the aryl group of the enolate. Also maintained is the assumed spacial arrangement of the developing oxy-anion, crucial for a concerted but asynchronous cycloaddition process **(Fig 40)**. This is consistant with the model proposed for the poor diastereoselectivity observed for the use of butylphenylketene in the chloral β-lactone series **(Chapter 3)**.
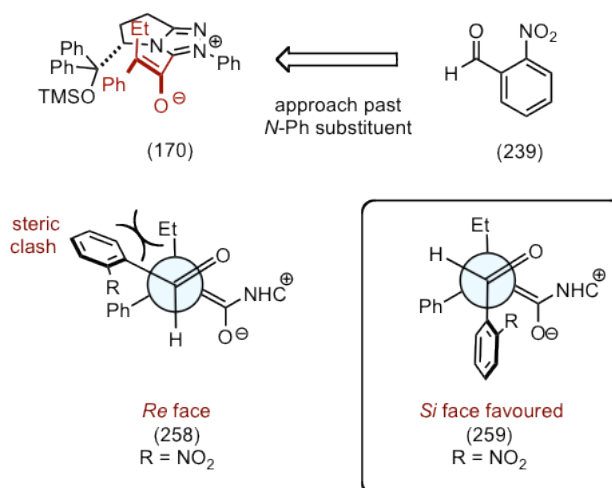
Fig 40: Proposal for the observed *syn* diastereoselectivity

This model is also consistent with the trend in diastereoselectivity observed for the use of 2-nitrobenzaldehyde. The decrease in *dr* associated with the use of a methyl group on the ketene can be attributed to a decrease in the steric clash between the methyl group of the azolium enolate and the 2-nitrobenzaldehyde. Competitive *Re/Si* facial approach giving an approximate 50:50 *dr*. Consistent with this model, an increase in the size of the alkyl group on the azolium enolate leads to an improvement in diastereoselectivity: with *i*-butylphenylketene, high *dr* is indeed obtained (94:6 *dr*, *syn*:*anti*). Simplistically, a large alkyl substituent on the azolium enolate reinforces the steric clash with the 2-nitrobenzaldehyde, further disfavouring addition to the *Re* face of aldehyde **(Fig 41)**.
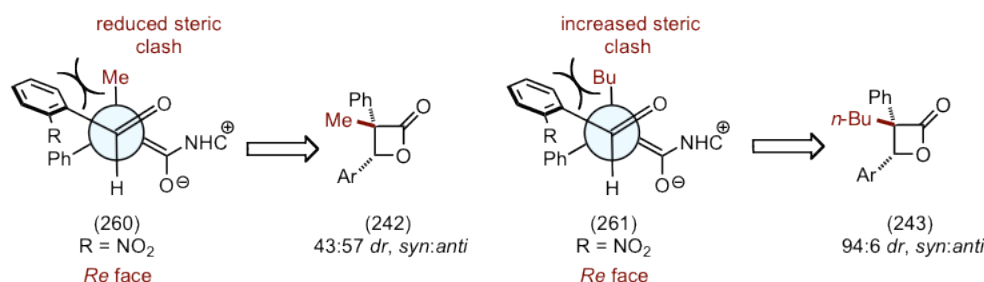
Fig 41: Rationale for the observed trend in diastereoselectivity.

Although no direct X-ray crystallographic or computational evidence could be obtained for the solution or solid state conformations of other 2-substituted benzaldehydes, it is proposed that a twisting of the aldehyde geometry, as seen in 2-nitrobenzaldehyde, is not present, resulting in low levels of diastereoselectivity. It is reasoned that planar orientation of the aldehyde carbonyl with respect to the benzene ring is inadequate to provide significant differentiation between a *Re* and *Si* face approach, leading to poor diastereoselectivity.

3.10 Synthetic utility

3.10.1 Preparative scale synthesis of β-lactone 238

To demonstrate the synthetic utility of this process, under optimised conditions, this reaction was carried out on a preparative scale **(Scheme 68)**. Low NHC loadings (2 mol%), provided >2.5g of lactone **238** as a single diastereomer and in high *ee* (83% yield, 95% *ee*) that was recrystallised to enantiopurity. As with the scale in the β-lactone methodology from chloral, the limitation of this process is the quantity of ketene employed. In practise the yields for the synthesis of disubstituted ketenes begin to fall sharply on scales above 5 g of acid chloride, with the formation of ~2.5 g of ketene product being the approximate limit in our hands under the method employed.
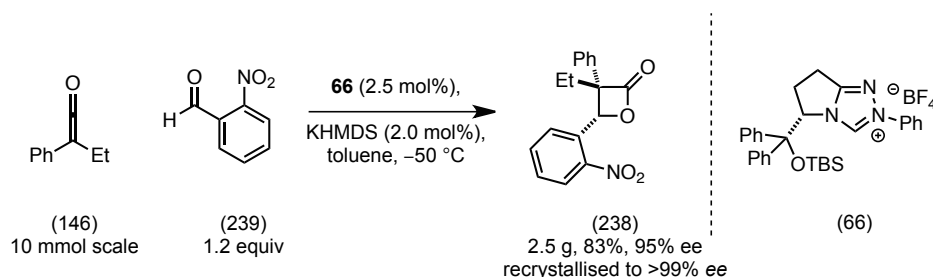
Scheme 68: Preparative scale synthesis of β-lactone 238.

3.10.2 Ring opening of β-lactone 238 with sodium azide

It was previously shown **(Chapter 3)** that the ring opening of β-lactones derived from ketenes and chloral was not possible using sodium azide under standard conditions. As representative of this series of β-lactones, functionalisation of **238** was achieved through ring opening with either azide or hydroxide. Following facile opening with azide, a Staudinger reduction could be carried out to provide the α,α-disubstituted β-amino acid **263**, however purification from residual triphenylphosphine oxide proved difficult. In an effort to bypass the parent amino acid, the crude product from the Staudinger reduction was treated under a range of conditions to affect methyl ester formation. However, neither the combination of thionyl chloride/methanol, acetyl chloride/methanol or acidic Dowex resin and methanol provided any reasonable amount of the methyl ester **264**. It is assumed that the acid catalysed methanolysis failed due to the sterically encumbered α,α-disubstituted acid, prohibiting addition to the carbonyl moiety.
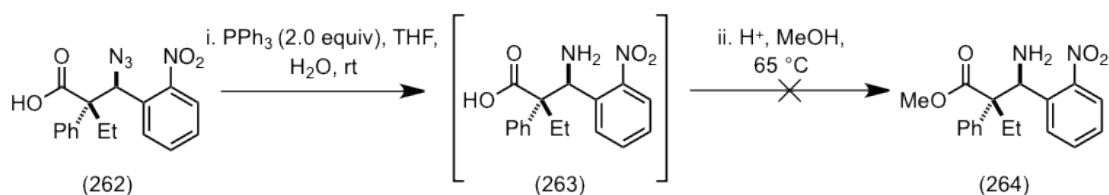
Scheme 69: Two step azide reduction and methanoloysis

Attempts to directly acquire the methyl ester *via* ring opening with sodium methoxide also failed. Hydrogenation of the azide in the presence of di-*t*-butyl dicarbonate in an attempt to directly procure the *N*-Boc protected acid was also unsuccessful. In general, hydrogenation of the azide product did not proceed as cleanly as the Staudinger reduction. This is postulated to be due to a competing nitro group reduction process. Fortuitously, following overnight reflux in methanol with 1.0 equiv of SOCl$_2$, the crude reaction mixture obtained from Staudinger reduction could be triturated with CHCl$_3$ to provide the α,α-disubstituted β-amino acid **236** in 74% yield and >99% *ee*. It is assumed that the trituration step is responsible for the increase in enantiopurity from 95% to >99% *ee*. In all cases, the *ee* was established *via* derivatisation to the benzylated and dibenzylated products **265** and **266 (Scheme 70)**.
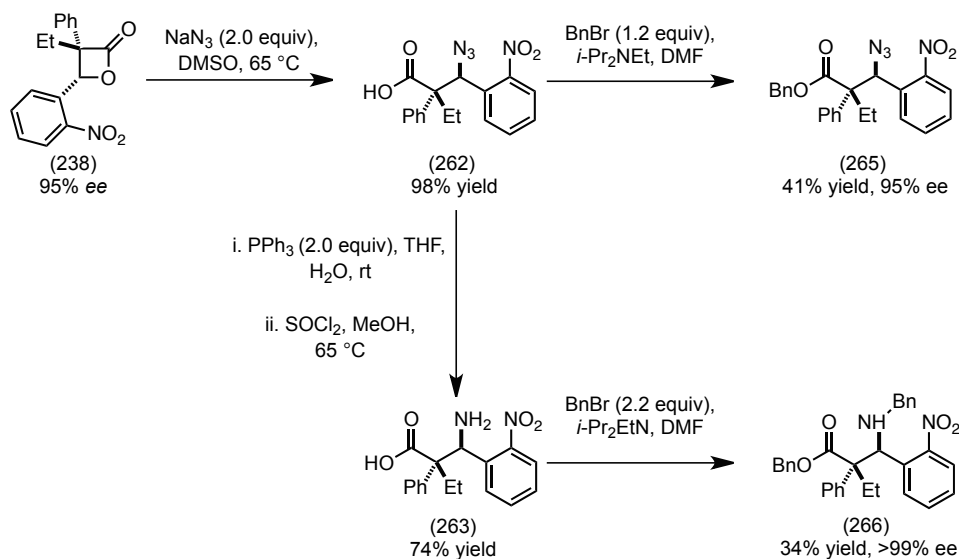
Scheme 70: Successful two step derivatisation of β-lactone 238 to β-amino acid 263.

It was expected that the ring opening with azide would proceed with inversion of configuration at the C(4) position *via* an S$_N$2 process.[21] This was confirmed by an X-ray crystal structure of racemic β-azido ester **265** showing an *anti* configuration with respect to the aryl groups at C(3)-C(4).
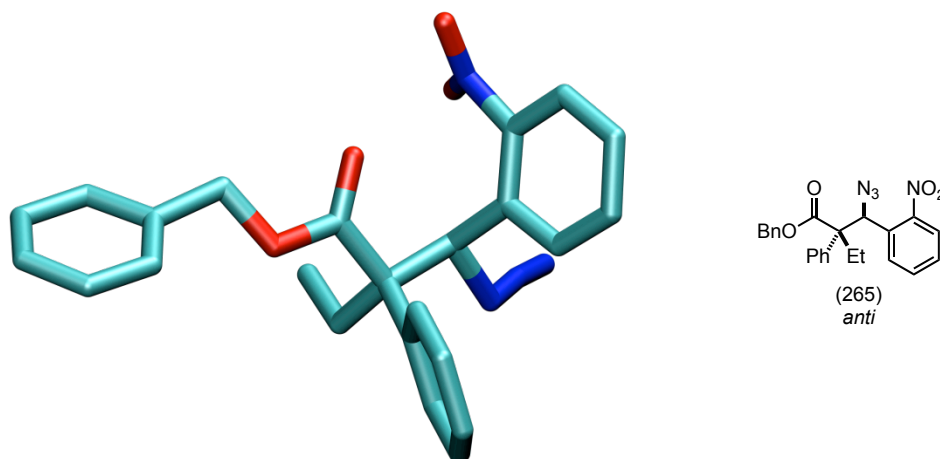
Figure 42: X-ray crystallographic representation of (±) azide 265 showing anti relative configuration.

3.10.3 Hydroxide ring opening of β-lactone 238.

The ring-opened α,α-disubstituted β-hydroxy acid product was obtained simply through treatment of lactone **238** with 1 M aqueous KOH, following the procedure of Kerrigan,[7] in good yield and *ee* (96%). The enantiomeric excess of the derivatised product **267** was determined by chiral HPLC *via* conversion to the benzyl ester **268**. The relative *syn* configuration is assumed to have been retained, as expected from addition to the C(2) carbonyl.
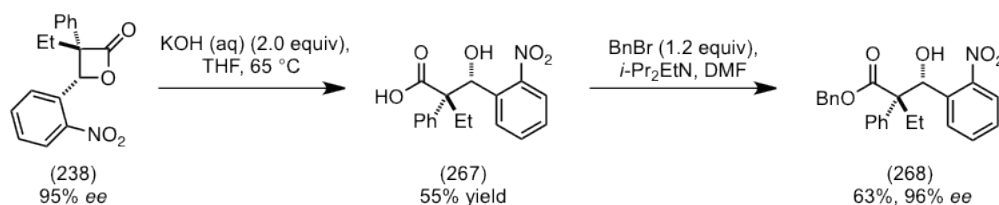
Scheme 71: Hydroxide ring opening of β-lactone 238, followed by carboxylate alkylation.

4.0 Summary

In summary, a highly efficient and scalable methodology for the stereocontrolled formation of β-lactones from ketenes and bezaldehydes, catalysed by chiral NHCs has been evaluated. The optimised reaction proceeds in excellent levels of enantio- and diastereoselectivity with 2-nitrobenzaldehyde, and expands the scope of the formal [2+2] cycloaddition between ketenes and aldehydes. Notably, no competing benzoin reaction or significant ketene dimerisation products were observed under the reaction conditions, with the lactone product being readily transformed to synthetically useful α,α-disubstituted β-hydroxy- and β-amino acid building blocks. This project has

made significant progress in solving the issues associated with the chloral project **(Chapter 3)**, specifically the improvements in *dr* and aldehyde scope. However this process is still limited by the use of isolated ketenes as azolium enolate precursors and the requirement for 2-nitrobenzaldehyde to obtain high diastereoselectivity.

5.0 References and notes

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10.   Specifically, precatalyst **66** is known to function poorly in the benzoin reaction of benzaldehyde see Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, 19, 1367-1371.

11.   Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Adv. Synth. Catal.* **2008**, *350*, 2715-2718.

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13.   The NHC-catalysed reactions proceed in high conversion. The low yields are due to poor isolation in the subsequent unoptimised KOH ring opening reactions.

14.   Specifically, high *anti dr* is obtained for methylarylketenes (>90:10) and low *anti dr* obtained for *n*-butylarylketenes (53:47) *(see reference 7)*.

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17.   Lactone **238** was recystallised to enantiopurity proir to the collection of the crystallographic data.

18.   Crystallographic data for **238** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 854302.

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Chapter 5: Catalytic Asymmetric Halogenation of Alkylarylketenes

1.0 Project aim

As described in **(Chapter 3)**, a novel chlorination process had been identified from the reaction of chloral and alkylarylketenes bearing either a 2-substitued aryl group or an α-branched alkyl substituent. This proceeded in excellent yield and enantioselectivity (up to 94% *ee*), however it was fundamentally limited by the relatively small substrate scope with respect to the ketene. This project will aim to develop a general NHC-catalysed asymmetric halogenation protocol for alkylarylketenes.

2.0 Introduction

Stereogenic halogenated centres have become increasingly important in both synthetic and medicinal chemistry. They serve as important chemical handles by which further stereocontrolled functionalisation can occur. Recently the incorporation of halogen atoms (most noticeably fluorine) has found increasing use in medicinal and materials chemistry.

Within the field of asymmetric halogenations the predominating strategy is the generation of a chiral enolate or enolate equivilent that may react in a stereocontrolled manner with an electrophilic halogenation source.[1] This broad approach can be further broken down into sub-categories for the specific formation of a reactive enolate or enolate equivalent: (i) the coordination of a chiral Lewis acid followed by deprotonation; (ii) the ionic pairing of an asymmetric phase-transfer catalyst with the enolate oxygen; (iii) the formation of a chiral enamine by the addition of a chiral secondary amine to an aldehyde or a ketone containing a α-proton; (iv) the addition of a chiral Lewis base to a ketene to directly form a zwitterionic chiral enolate. Of particular interest to this thesis are those methods that employ Lewis basic organocatalysts, of which some of the recent advances will be discussed in further detail below in a brief overview of the area.

2.1 Halogenation of β-ketoesters

β-Ketoesters are one of the most studied substrates in asymmetric halogenation reactions due to the facile formation of six-membered chelates with oxophilic chiral Lewis acids, rigidifying the transition state to provide facial discrimination and thus allowing enantioselective halogenation. The first of these processes to be reported was by the group of Togni[2] who employed titanium-TADDOL complexes **272** and

273 to achieve the unprecedented catalytic asymmetric fluorination, and subsequently chlorination,[3] of β-ketoesters in up to 90% *ee* **(Scheme 72)**. The use of such Lewis acids in asymmetric halogenation subsequently received attention from a number of groups including Sodeoka,[4] Cahard[5] and Jørgensen.[6]
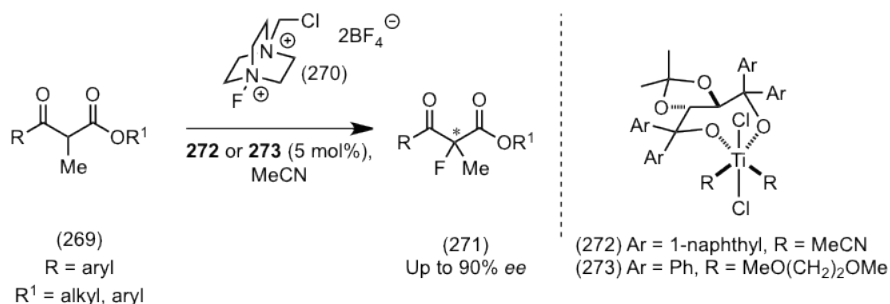
Scheme 72: Halogenation of β-ketoesters.

2.2 Organocatalytic halogenation of aldehydes

The advent of organocatalysis has led to a proliferation of asymmetric halogenation reactions and allowed facile access to new structural motifs, for example stereogenic α-halo carbonyl compounds.[7] In 2004 the groups of MacMillan[8] and Jørgensen[9] reported the asymmetric chlorination of aldehydes. This was rapidly followed by the groups of Enders[10] and Barbas,[11] independently extending this methodology to the asymmetric fluorination of aldehydes.[12] The chlorination strategy employed by MacMillan and co-workers utilised the imidazolidinone catalyst **280** and chlorinating agent **275** to provide a range of α-functionalised aldehydes in excellent yield and enantioselectivity **(Scheme 73)**. This method accessed enantioenriched α-chloro intermediates that were readily transformed to a diverse set of products such as epoxides, α-hydroxy acids and amino acids.[13]
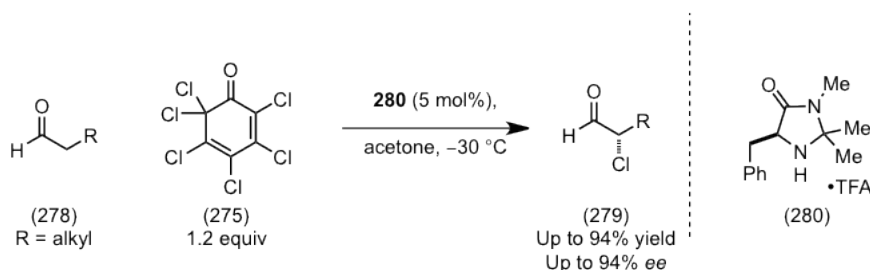
Scheme 73: Asymmetic halogenation of aldehydes.

2.3 Synthesis of α-halo esters

As previously described, Rovis *et al*. have elegantly accessed α-halogenated esters from the corresponding α,α-dichloroaldehydes **(Chapter 1, Scheme 21)**. The group

of Lectka has extensively studied an alternative approach to α-halo esters *via* the use of mono-substituted ketenes.[1a] In these reports acyl halides are treated with a chiral Lewis base catalyst (such as benzoylquinine **230**) and a Brønsted base to generate a chiral ammonium enolate *in situ* that can be asymmetrically halogenated in excellent yields and enantioselectivities **(Scheme 74)**.[14,15] This method was applicable to both chlorination and bromination and later extended to fluorination, however this required the addition of a suitable transition metal co-catalyst to increase enolate nucleophilicity.[16]
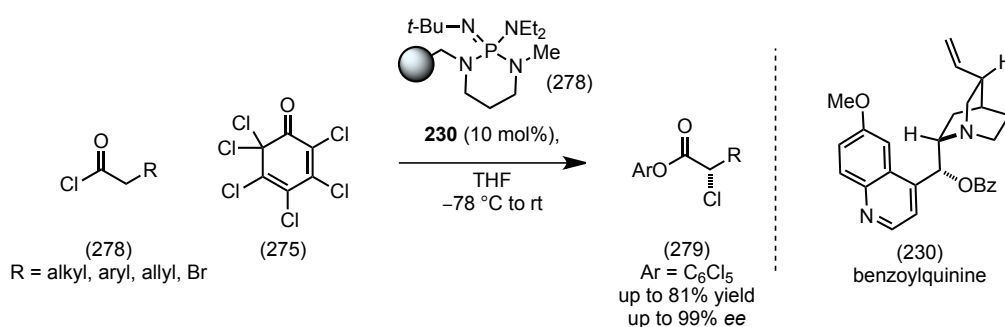
Scheme 74: Synthesis of α-halo esters.

Although the impressive advancements in organocatalytic asymmetric halogenation reactions provide α-halo carbonyl products in excellent yield and enantioselectivities, they are generally restricted to the production of secondary halides. Outside the use of β-keto esters as substrates, asymmetric catalytic methodology to access tertiary halide centres is considerably less well documented. One excellent report to date from the group of Fu has employed disubstituted ketenes as azolium enolate precursors in the asymmetric halogenation reaction catalysed by planar-chiral PPY derivative **59**.[17] The reaction was applicable to a range of disubstitued ketenes and produced α-chloro esters **282**, amenable to a range of further derivatisations, in excellent yields and with good to excellent levels of stereocontrol (up to 90% yield and 95% *ee*) **(Scheme 75)**.
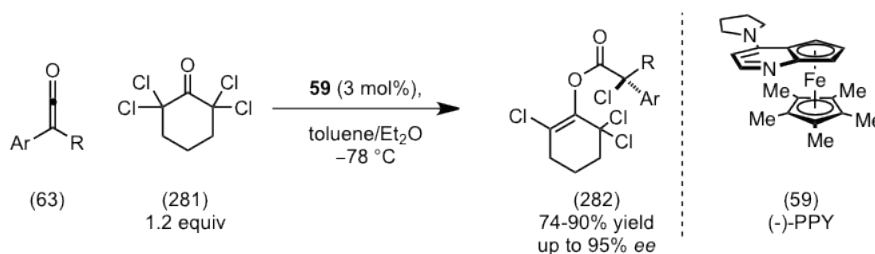
Scheme 75: Synthesis of asymmetric tertiary halide centres.

Inspired by the work of Lectka and Fu, and in an effort to expand the highly substrate specific asymmetric chlorination reaction discovered in **(Chapter 2)**, a generalised reaction protocol for the NHC-catalysed asymmetric halogenation of disubstituted ketenes was investigated.

3.0 Asymmetric chlorination of disubstituted ketenes

3.1 Chlorination of with 2,2,6,6-tetrachlorocyclohexanone

Initial studies into the viability of an NHC-catalysed asymmetric halogenation methodology began by employing chlorination reagent 2,2,6,6-tetrachlorocyclohexanone **281**. Chlorination was chosen as the primary target due the relative availability of electrophilic sources of chlorine and specifically chlorine source **281** as this was shown to provide the highest enantioselectivities in the work of Fu *et al.*[17] Ethylphenylketene, the standard ketene used to screen reactions conditions, was employed with a representative range of triazolium and imidazolium precatalyst scaffolds in toluene, using either KHMDS or Cs_2CO_3 as the base with which to generate the active NHC *in situ* at room temperature **(Scheme 76)**. Disappointingly the majority of precatalysts tested returned no ester product **283**, returning the chlorination agent **281** and the acid hydrolysis product from the ketene. Precatalyst **66**, which was found to be optimal in the previously described β-lactone methodology, was also screened under identical conditions, giving ~50% conversion to **283** by ^{1}H NMR spectroscopy that was isolated in 47% yield **(Table 7, Entry 5)**.
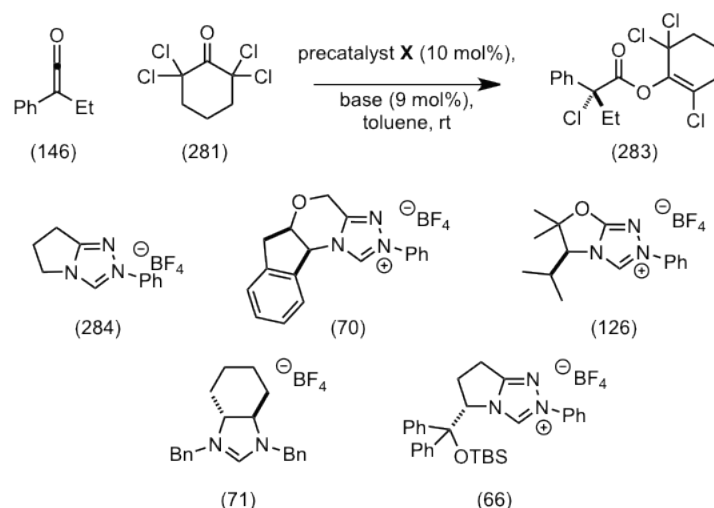
Scheme 76: Catalyst screen for the use of 2,2,6,6-tetrachlorocyclohexanone 281.

Entry	Precatalyst	Base	Yield (%)[a]	ee (%)[b]
1	**284**	KHMDS	–	–
2	**70**	KHMDS	–	–
3	**126**	KHMDS	–	–
4	**71**	KHMDS	–	–
5	66	Cs_2CO_3	47	<5
6[c]	66	Cs_2CO_3	35	<5

[a] Isolated yield of ester **283**. [b] Determined by GC analysis of the corresponding methyl ester **292**.

[c] Reaction performed at –40 °C followed by warming to rt.

Table 7: Catalyst screen for the use of 2,2,6,6-tetrachlorocyclohexanone 281.

Due to the failure of the reaction employing achiral precatalyst **284** to provide an authentic racemic sample of **283**,[18] it was converted to known methyl ester **285** *via* the two step procedure reported by Fu **(Scheme 77)**.[17] The enantiomeric excess of **285** was determined by chiral GC analysis and disappointingly was found to be essentially racemic. Further reduction of the reaction temperature to –40 °C for 3 h followed by warming to rt over 12 h provided no appreciable increase in yield or enantioselectivity (35% yield and <5 % *ee*) **(Table 7, Entry 6)**.
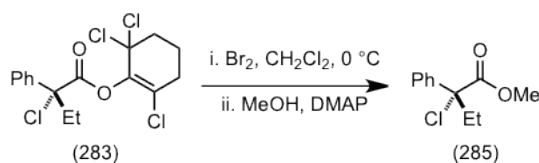
Scheme 77: Transesterification of 283 to allow determination of the enantioselectivity.

3.2 Chlorination with NCS

Due to the low reactivity of **281** in the initial protocol, *N*-chlorosuccinimide (NCS) was screened as a potentially more facile chlorinating reagent. Pleasingly, good conversions to a proposed succinimide adduct **287** were observed (by ^{1}H NMR spectroscopic analysis of the crude reaction mixture) for a range of precatalysts **(Scheme 78)**. The proposed chloro-amides proved sensitive to silica chromatography so unambiguous structural assignment could not be made. To resovle this problem the crude reaction mixture was directly submitted to methanolysis (MeOH, DMAP) to yield the methyl ester products in moderate yield over the two steps. The enantioselectivity was evaluated by chiral GC and found to be low in all cases **(Table 8)**. To investigate the reasonable reactivity but consistently low levels of enantioselectivity for the procedure employing *N*-chlorosuccinimide, a background

reaction in the absence of the azolium salt was conducted. It was found that KHMDS alone (1 equiv) was not able to promote the chlorination reaction, however Cs_2CO_3 (1 equiv) did provide efficient conversion to the succinimide adduct **287**. Throughout these studies a sub-stoichiometric quantity of base was employed to minimise any background reaction, however base catalysed, or other feasible background reactions, cannot be completely ruled out in many of these cases.
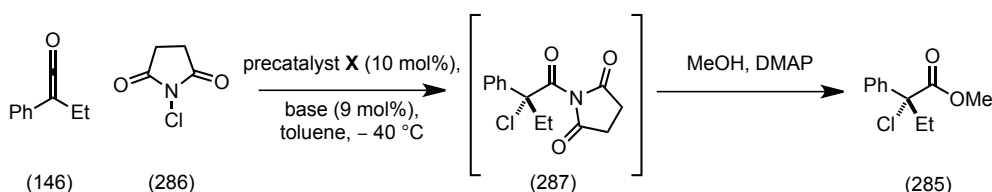
Scheme 78: Catalyst screen for the use of NCS.

Entry	Precatalyst	Base	Yield (%)[a]	*ee* (%)[b]
1	**284**	KHMDS	–	–
2	**70**	KHMDS	39	<5
3	**126**	KHMDS	39	11
4	**71**	KHMDS	15	<5
5	**66**	Cs_2CO_3	28	<5

[a] Isolated yield of the methyl ester **292** (over two steps). [b] Determined by chiral GC analysis of the corresponding methyl ester **292**.

Table 8: Catalyst screen for the use of NCS.

3.3 Chlorination with hexachloroacetone

With improvements made in reactivity but with still consistently low levels of enantioselectivity, hexachloroacetone was next evaluated as a chlorination reagent. Under the reaction conditions employed for NCS, hexachloroacetone provided good conversions and on this occasion moderate to good yields of isolable ester **289** **(Scheme 79)**. The enantioselectivites obtained using precatalysts **126**, **71**, **66**, were determined *via* derivatisation to the corresponding methyl esters **285**, were equally low as with the previous chlorination reagents. The use of aminoindanol derived precatalyst **70** however provided the first promising enantioselectivity of 29% *ee* **(Table 9, Entry 2)**. In control experiments both KHMDS and Cs_2CO_3 (1 equivalent) were found to be unable to promote the background chlorination reaction.
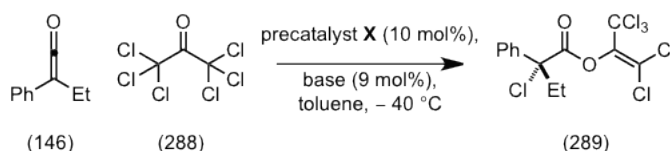
Scheme 79: Catalyst screen for the use of hexachloroacetone.

Entry	Precatalyst	Base	Yield (%)[a]	*ee* (%)[b]
1	**284**	KHMDS	44	–
2	**70**	KHMDS	47	29 (*ent*)
3	**126**	KHMDS	67	<5
4	**71**	KHMDS	72	8
5	**66**	Cs$_2$CO$_3$	37	<5

[a] Isolated yield of **296**. [b] Determined by GC analysis of the corresponding methyl ester **285**.

Table 9: Catalyst screen for the use of hexachloroacetone.

3.4 Chlorination with 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone

3.4.1 Catalyst screen

Next the chlorinating reagent was changed to 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone **275** that has previously been reported for similar organocatalytic systems of the groups of Lectka[14] and MacMillan.[8] Pleasingly all chiral NHC precatalysts screened provided good to excellent isolated yields of α-chloro perchlorophenyl ester **290** with precatalyst **66** returning the most promising *ee* of 57% **(Scheme 80, Table 10)**. In keeping with the previously variable enantioselectivities, precatalysts **70** and **71** resulted in little to no enantioselectivity whereas **126** provided 22% *ee*. Finally *N*-mesityl precatalyst **112** was screened. In this instance, ester **290** was isolated in 72% yield but with no enantioselectivity **(Table 10, Entry 6)**.
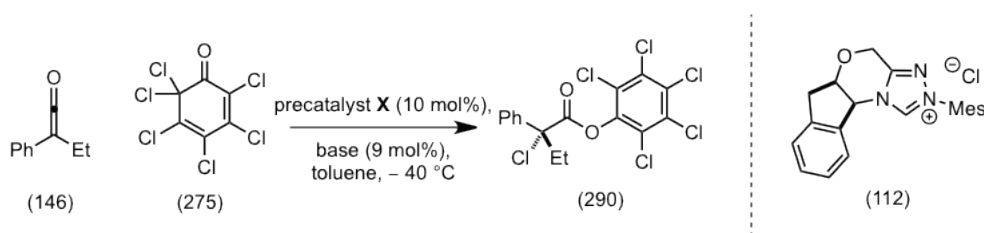
Scheme 80: Catalyst screen for the use of 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone 275.

Entry	Precatalyst	Base	Yield (%)[a]	ee (%)[b]
1	**284**	KHMDS	65	–
2	**70**	KHMDS	89	6
3	**126**	KHMDS	43	22
4	**71**	KHMDS	77	<5
5	**66**	Cs$_2$CO$_3$	92	57
6	**112**	KHMDS	72	<5
7[c]	**66**	Cs$_2$CO$_3$	90	61
8[d]	**66**	Cs$_2$CO$_3$	86	53

[a] Isolated yield of perchlorophenyl ester **290**. [b] Determined by GC analysis of the corresponding methyl ester **285**. [c] 1.1 equiv of ketene was used. [d] The reaction was warmed from −60 °C to rt over 12 h

Table 10: Catalyst screen for the use of 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone 275.

In further optimisation of **(Table 10, Entry 5)**, 1.1 equivalents of ketene were used to ensure full consumption of the chlorinating reagent **275**, as **290** was often difficult to separate from the product **290**. These conditions proved optimal as lowering the reaction temperature to −60 °C suppressed reactivity, whilst slow warming from −60 °C to room temperature gave slightly diminished enantioselectivity **(Table 10 Entry 8)**.

3.4.2 Assignment of absolute configuration

X-ray crystallographic analysis of racemic compound **290** provided unambiguous structural identification while comparison of the specific rotation and GC retention times of the methyl ester **285** from **(Table 10, Entry 7)** with the literature[17] confirmed the absolute configuration as (*R*) **(Scheme 81)**.
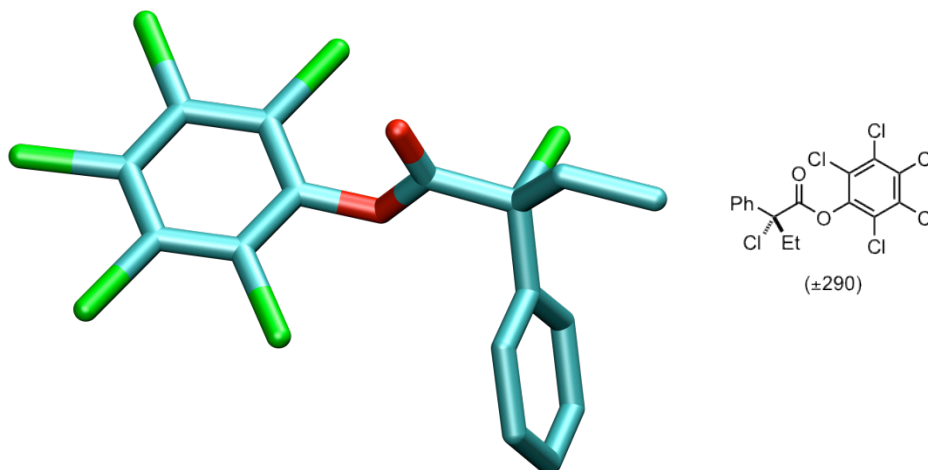
Fig 43: X-ray crystallographic representation of (±)-290.
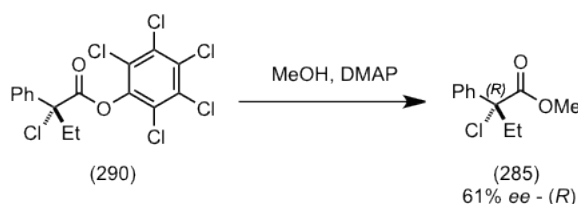
Scheme 81: Determination of the absolute configuration of 297.

3.4.3 Analysis of quinoline derived chlorinating reagent 291

The increased reactivity of the chlorination reagent **275** is in line with the electrophilicities reported by Mayr and co-workers[19] who calculate **275** to be a 10^4 to 10^5- fold more electrophilic than **291**. To validate further the need for a strong electrophile to achieve good yields, chlorination reagent **291** was prepared from 8-hydroxyquinoline[20] and tested in this system, failing to provide any conversion to the desired product, even at rt **(Scheme 82)**.
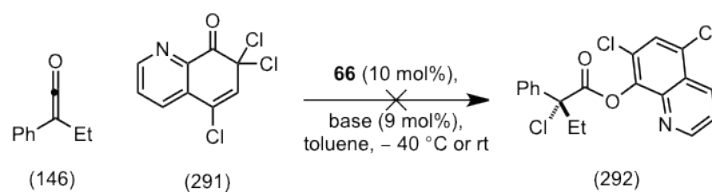
Scheme 82: Analysis of quinoline derived chlorinating reagent 291.

3.4.4 Analysis of substrate scope

With an optimised procedure functioning in high yield, albeit with moderate enantioselectivity, extension of the alkyl chain to an *n*-butyl substituent was undertaken. The reaction proceeded in similar yield, however the enantioselectivity was reduced to 34% *ee* **(Scheme 83)**.
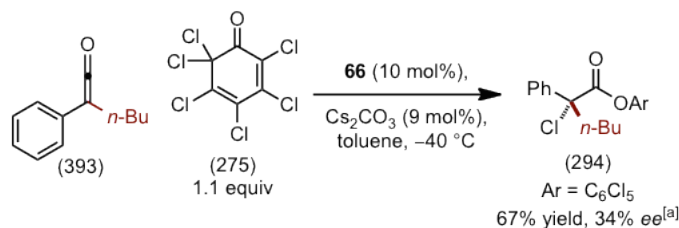
[a] Determined by ^{1}H NMR spectroscopic analysis of the (*S*)-α-methylbenzylamide

Scheme 83: Use of an *n*-butyl alkyl substituent.

In general the ester products proved challenging to separate by chiral HPLC so alternative methods were used to determine product enantioselectivity. In the absence of literature chiral GC conditions for the methyl ester derivatives other than **285**, it

was found that amidation with (*S*)-α-methylbenzylamine provided clean conversion to a diastereomeric mixture of amides **297** that could be analysed by ^{1}H NMR spectroscopy. The amides proved sensitive to further purification with a tendency to undergo elimination, however ^{1}H NMR spectroscopic analysis of the crude reaction product provided a sufficiently accurate means to assess the enantiomeric excess of chlorinated esters *via* determination of the diastereomeric ratio of derivatives **297** **(Scheme 84)**.
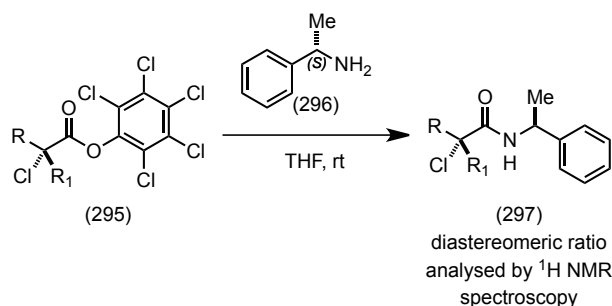
Scheme 84: Method for the determination of the enantioselectivity *via* derivatisation.

This method was validated on ester **285** *via* comparison with the enantioselectivity determined by chiral GC, with minimal variance observed **(Scheme 85)**.[21]
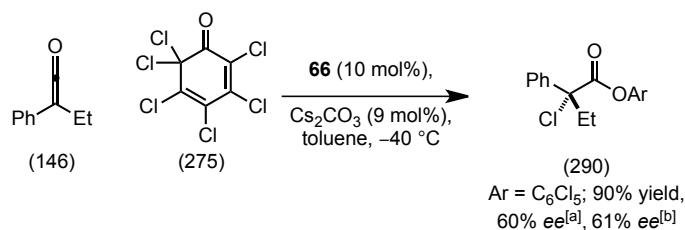
[a] Determined by ^{1}H NMR spectroscopic analysis of the (*S*)-α-methylbenzylamide [b] Determined by chiral GC analysis of the corresponding methyl ester **285**

Scheme 85: Determination of the enantioselectivity *via* two separate methods.

Substitution on the aryl portion of the ketene was investigated with both electron donating and withdrawing groups in the 4-position providing good to excellent yields and moderate levels of enantiocontrol (44 to 48% *ee*) **(Scheme 86)**. Finally a 2-substituent on the aryl portion, previously shown to either reduce greatly or alter reactivity, was well tolerated in this case proceeding in 91% yield, however with diminished enantioselectivity (26% *ee*). In an attempt to rationalise the moderate levels of enantioselectivity in this reaction the background reaction in the absence of precatalyst **66** was evaluated. In this instance employing 1.0 equiv of Cs$_2$CO$_3$ at rt resulted in smooth conversion to the chlorinated product highlighting the trade-off between necessarily high electrophilicity of the chlorinating reagent and the

consequence of competing racemic background pathways.

(63)   (275)
1.1 equiv

66 (10 mol%),
Cs$_2$CO$_3$ (9 mol%),
toluene, –40 °C

(298)
Ar = C$_6$Cl$_5$

(299)
88% yield[a],
48% ee[b]

(300)
76% yield,
44% ee [b]

(301)
91% yield,
44% ee [b]

(302)
97% yield,
26% ee [b]
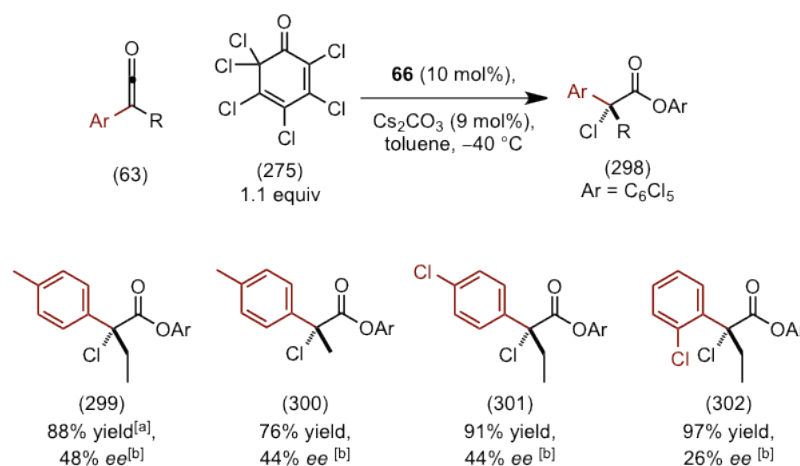
[a] 1.5 equiv of ketene and 25 mol% of **66** were used [b] Determined by ^{1}H NMR spectroscopic analysis of the (*S*)-α-methylbenzylamide.

Scheme 86: Analysis of the substrate scope with respect to the aryl substituent.

3.4.5 Mechanistic proposal

Two notable mechanistic postulates exist for this reaction that differ fundamentally in the role of the NHC. As previously rationalised, attack of the NHC *anti* to the phenyl group can lead to azolium enolate species **170**. Subsequent stereoselective chlorination renders the α-chloroazolium **304** that undergoes nucleophilic attack from the previously liberated perchlorophenolate anion to release the NHC catalyst and form α-chloroester **290**.
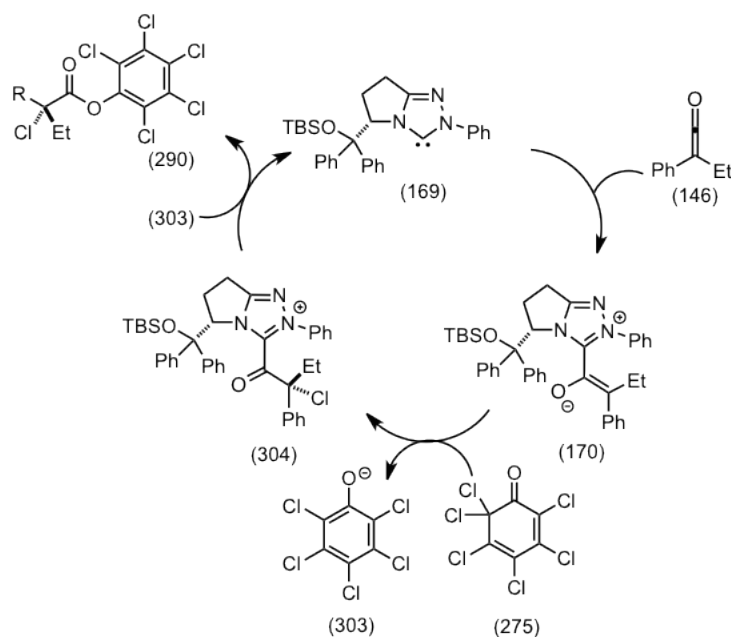
Fig 44: Postulated mechanism *via* initial addition of the NHC to the ketene.

In addition to this stepwise azolium enolate pathway a concerted process may be in

operation. This reaction mechanism featuring a six-membered transition state **304** involving Cl agent **275** was considered by Lectka and co-workers in analogous reseach.[14] However following computation analysis it was deemed unlikely due to the requirement for a highly bent μ-Cl anionic interaction **306** that was disfavoured when compared to a linear arrangement of the C-Cl-C motif **305**.
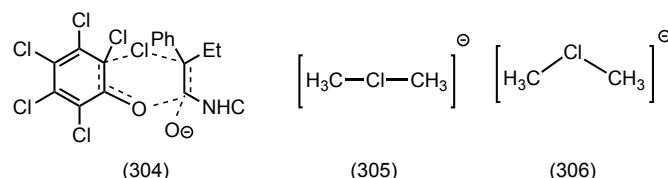
Fig 45: Postulated concerted process *via* the bent μ-Cl anionic interaction 306.

A second plausible reaction mechanism involves the initial formation of a chlorinated NHC following abstraction of a Cl atom from **275** by the NHC. Addition of the perchlorophenol to the ketene could then produce prochiral enolate **308**. This enolate could then be chlorinated by **307** in a stereoselective fashion to yield the final ester **290** and regenerate the NHC. This mechanistic postulate was proposed by Fu, in conjuction with the azolium enolate mechanism above.[17]
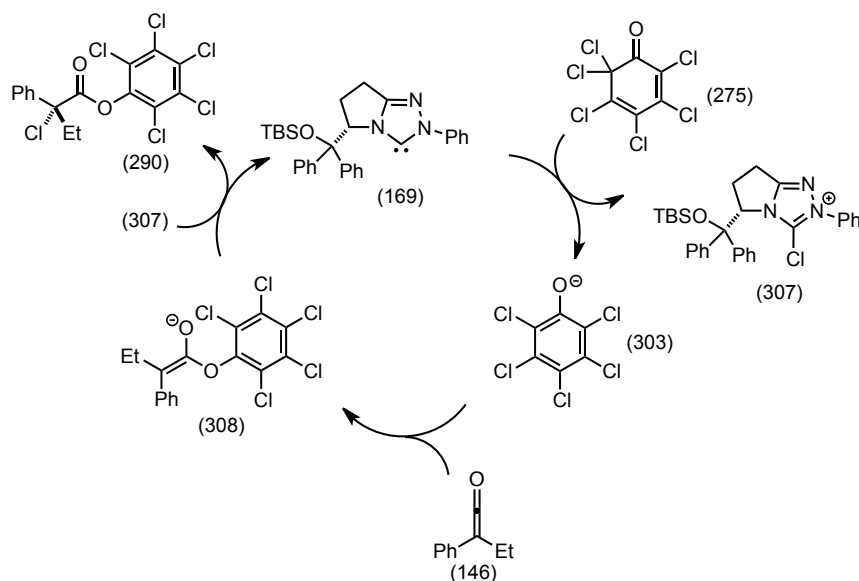
Fig 46: Postulated mechanism for *via* initial chlorination of the NHC.

At this stage our investigations have not provided any clear evidence that would rule out either mechanistic pathway. However, if consistent with the initial stages of previous mechanistic rationales **(Chapter 3, 3.8)**, addition to the ketene as the initial step in this pathway would be favoured.

3.4.6 Stereochemical considerations.

Given the ambiguity regarding the mechanistic pathway, and the low levels of observed enantioselectivity, defining an unambiguous rationale for the observed (*R*) absolute configuration is challenging. Some limited evidence may be taken from the observation that both the chlorination reaction described here and the β-lactone formation **(Chapter 3 and 4)** proceed with the same sense of induction at the ketene centre. This sense of induction is that obtained *via* addition from the *Re* face of the enolate, assuming that it adopts the orientation proposed in **(Chapter 3, 3.9)**. It is therefore postulated that addition from the *Re* face of the enolate is favoured, with the chlorinating reagent **275** approaching past the *N*-aryl substituent rather than the bulky stereodirecting unit **(Fig 47)**.
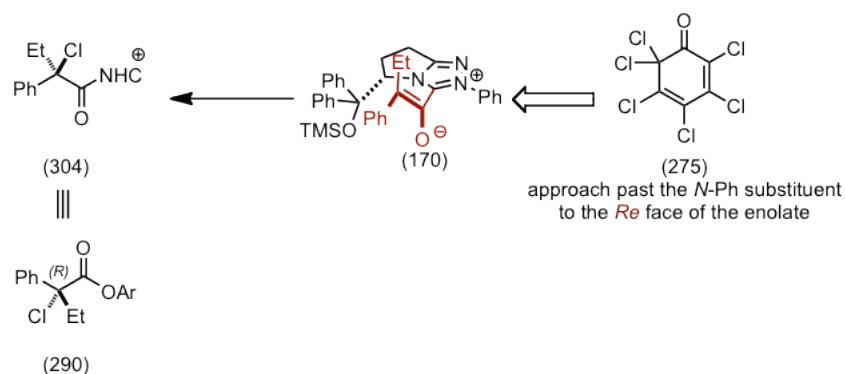
Fig 47: Rationale for the absolute configuration.

The explanation for the modest levels of enantioselectivity observed for the chlorination reaction when compared to the β-lactone formation is not immediately clear. It could be due to a more facile racemic background reaction or the different steric demand placed upon the system for the use of chlorination reagent **285**.

4.0 Extension to the asymmetric bromination of ketenes.

4.1 Use of NBS and brominating reagent 311.

With a viable, but modest, enantioselective method for the asymmetric chlorination of ketenes established, attempts were made to expand the process to bromination. Lectka *et al*. have previously shown their methodology developed for chlorination could be applicable to bromination, although significant investigation was required to optimise this process.[21] With this in mind initial studies applied the previously developed

conditions to bromination reagents **310** and **311**. *N*-Bromosuccinamide (NBS) was selected due to its commercial nature but provided no promising conversion. Given the likely inherent problems with product stability, as previously found with the NCS series, coupled with literature precedent for its ineffectiveness in a similar system,[23] further evaluation of its use was not attempted. Tribromoquinolinone **311**,[22a] structurally related to **291**, was next selected for evaluation. It was however limited by its poor solubility at rt in a range of representative solvents employed in NHC reactions (toluene, THF, CH_2Cl_2) and no promising conversion was seen, even at rt **(Scheme 87)**.
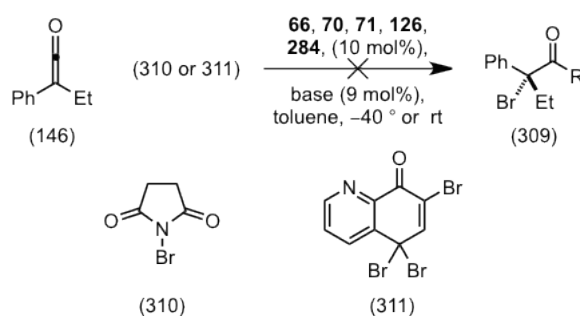
Scheme 87: Attempted bromination with NBS or brominating reagent 311.

4.2 Use of polybrominated *p*-quinone brominating reagent.

Finally polybrominated *p*-quinone **312**, prepared from commercially available tribromophenol, which has been utilised by the group of Letcka, was tested.[22] Pleasingly, under the optimum reaction conditions developed for the chlorination with **285**, tribromophenolic esters were obtained in synthetically useful yields but generally low enantioselectivites. The reaction proved especially facile under the catalytic influence of **66** with an isolated 92% yield and a moderate *ee* of 46%. As with some previously utilised halogenation reagents there is an efficient background reaction in the absence of precatalyst with either KHMDS or Cs_2CO_3.
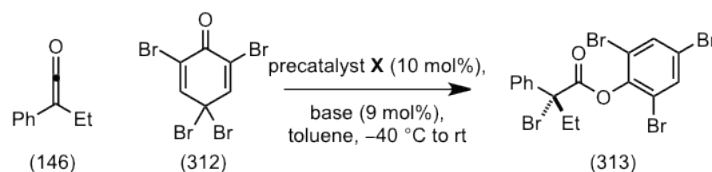
Scheme 88: Catalyst screen for the use of brominating reagent 312.

Entry	Precatalyst	Base	Yield (%)[a]	*ee* (%)[b]
1	**284**	KHMDS	–	N/A
2	**71**	KHMDS	55	12
3	**70**	KHMDS	61	<10
4	**126**	KHMDS	54	<10
5	**66**	Cs$_2$CO$_3$	92	46

[a] Isolated yield of ester **313**. [b] Determined by chiral HPLC analysis [c]

Table 11: Catalyst screen for the use of brominating reagent 312.

5.0 Asymmetric fluorination of ketenes.

The report of Lectka *et al*. provides evidence for the difficulties associated with extension of azolium enolate methodologies to fluorination.[16] In the previously mentioned study a catalytic, enantioselective, 'dual activation' strategy was necessary to obtain a range of products in both high yield and enantiomeric excess. Specifically a transition metal co-catalyst was required to increase enolate nucleophilicity **(Scheme 89)**. Feasibly, the enolate generated from an NHC could have higher nucleophilicity than the cinchona alkaloid derived ketene enolate employed by Lectka, thus removing the need for a transition metal co-catalyst.
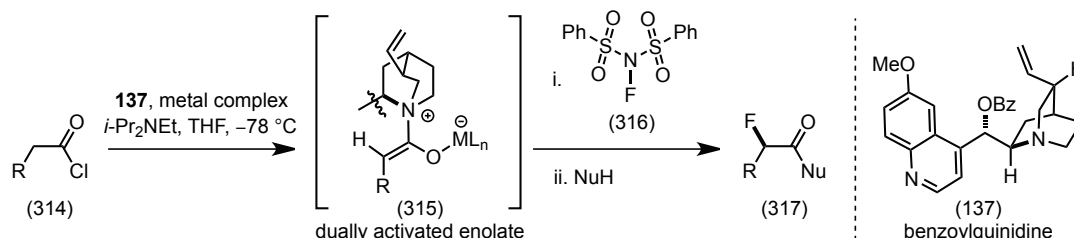
Scheme 89: Duel activation strategy for the asymmetric fluorination.

Unfortunately, under a range of conditions, employing various NHC precatalysts, no reaction was observed **(Scheme 90)**. In all cases only phenylbutyric acid, from ketene hydrolysis, and unreacted *N*-fluorobenzenesulfonimide (NFSI) (observed by ^{19}F NMR spectroscopy) were obtained. We inferred from this, and as suggested by Leckta, that the azolium enolates produced from NHCs or cinchona alkaloid derivatives are insufficiently nucleophilic to afford fluorination *via* the use of standard fluorination agents, such as NFSI. Further investigations into the effectiveness of Lewis acidic additives was not undertaken as they were not believed to be compatible with such Lewis basic ligands for complexation. Subsequently the group of Scheidt has shown the viability of co-operative catalysis between NHCs and Lewis acids.[24]
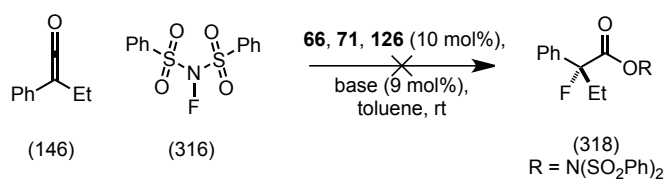
Scheme 90: Failed NHC-catalysed asymmetric fluorination.

6.0 Summary

It has been demonstrated that NHCs are viable Lewis base catalysts for the α-chlorination and α-bromination of disubstituted ketenes. A range of chlorination agents were screened with **275** proving optimal, giving excellent yields of tertiary α-chloro esters in one step. Chiral NHC precatalyst **66** shows promising levels of enantioselectivity (up to 61% *ee*).

The corresponding bromination reaction could also be readily achieved, however the enantioselectivity was low to moderate, with a maximum achievement of 46% *ee*.

Finally further extension to a synthetically attractive fluorination methodology was unsuccessful. In line with previous reports it is assumed that the azolium enolate lacks sufficient nucleophilicity to react with fluorination reagents such as NFSI.

7.0 References and notes

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14. France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245-4255.
15. Interestingly, in this protocol the enolate could be formed *via* two distinct mechanistic pathways depending on the choice of conditions. The enolate can be formed either directly from the addition of the catalyst to an *in situ* generated ketene or alternatively, deprotonation of an acylated catalyst species would also provide the required enolate.
16. Paull, D. H.; Scerba, M. T.; Alden-Danforth, E.; Widger, L. R.; Lectka, T. *J. Am. Chem. Soc.* **2008**, *130*, 17260-17261.
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18. At this stage the synthesis of the racemic precatalyst **66** had not been undertaken.
19. Duan, X.-H.; Mayr, H. *Org. Lett.* **2010**, *12*, 2238-2241.
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21. Care was taken to ensure all derivatisation reactions ran to compleation. Under these conditions we assume no kinetic resolution effect to be in operation that might lead to one diastereomer in preference.
22. (a) Dogo-Isonagie, C.; Bekele, T.; France, S.; Wolfer, J.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *J. Org. Chem.* **2006**, *71*, 8946-8949; (b) Dogo-Isonagie, C.; Bekele, T.; France, S.; Wolfer, J.; Weatherwax, A.; Taggi, A. E.; Paull, D. H.; Dudding, T.; Lectka, T. *Eur. J. Org. Chem.* **2007**, *2007*, 1091-1100.

23.   Specifically Lectka found that the use of NCS in his procedure (*see reference 22a*) provided only trace quantities of product and thus was not evaluated further.

24.   (a) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345-5347; (b) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nature. Chem.* **2010**, *2*, 766-771.

Chapter 6: α-Aroyloxyaldehydes as Bench Stable Mono-Substituted Ketene Surrogates

1.0 Project aim

As highlighted in **(Chapters 3 & 4)**, the use of isolable alkylarylketenes limits the available substitution pattern for NHC derived azolium enolates. One method by which the more reactive non-isolable mono-substituted ketene motif has been accessed is *via in-situ* dehydrohalogention of the requisite acid chloride.

To date, this method has not been demonstrated in the presence of NHCs, being primarily limited to the use of Cinchona type Lewis bases. The generation of mono-substituted azolium enolates of this type within the area of NHC catalysis has recently been investigated *via* the use of enals or α-functionalised aldehydes as mono-substituted ketene surrogates, as reviewed in **(Chapter 1)**.

The goal of this project was to explore and optimise the ability of α-aroyloxyaldehydes to function as efficient azolium enolate precursors. Key to this research is the greater utility associated with α-aroyloxyaldehydes when compared to ketenes due to their increased stability. It was also envisioned that a wider substrate scope could be accessed, with the previous azolium enolate research **(Chapters 3 & 4)** being limited by the prerequisite for the alkylaryl substitution pattern.

2.0 Introduction

As previously outlined in **(Chapter 1, Fig 10)**, the treatment of a suitably α-functionalised aldehyde with an NHC can lead to azolium enolate species **99** *via* elimination from the Breslow intermediate **101**. Initial pioneering work in this field focused on the protonation of enolate **99** to generate an activated acylazolium **102** that could undergo redox esterification and amidation reactions **(Fig 48)**.
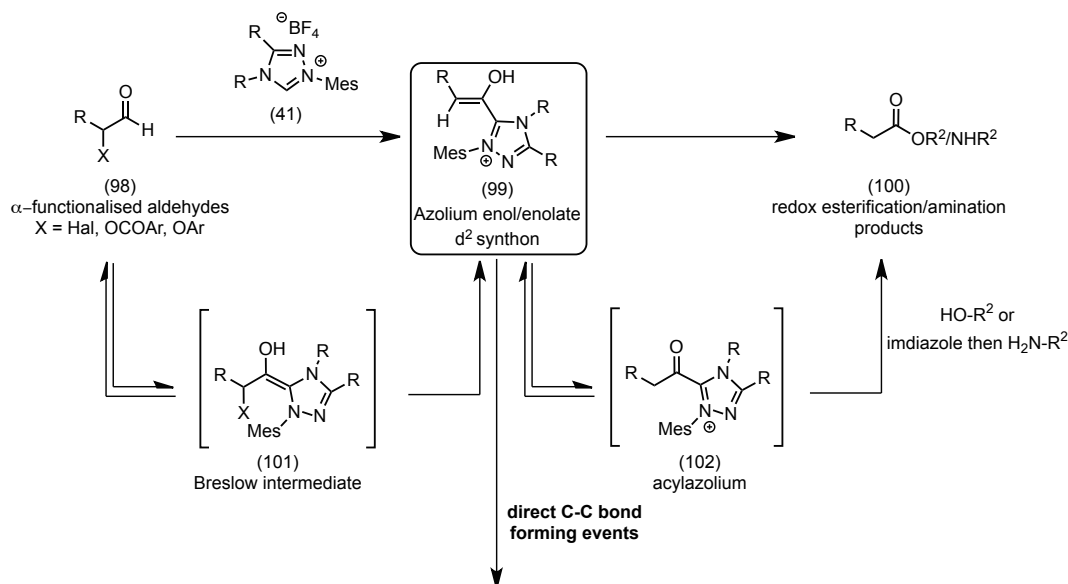
Fig 48: Generation of azolium enolates from α-functionalised aldehydes.

2.1 The use of α-functionalised aldehydes as precursors for acylazolium ions

The first reports in this field were by Rovis and co-workers who employed secondary and tertiary α-halo aldehydes to provide various ester products **320**,[1] and that by Bode *et al.* who utilised epoxy aldehydes for the generation of *anti* β-hydroxy esters[2] **325** **(Scheme 91)**.
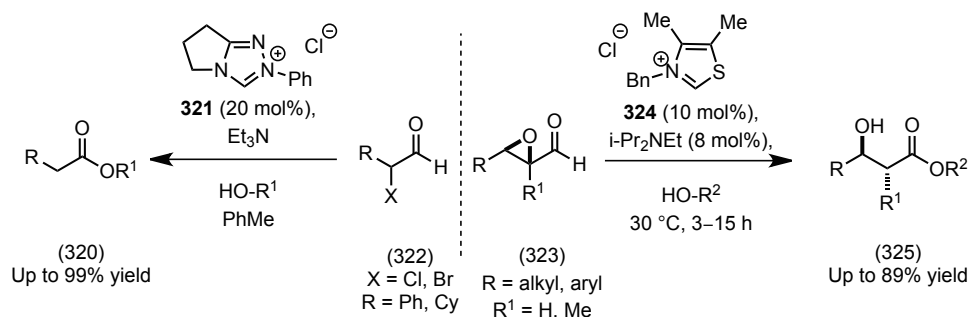
Scheme 91: Redox esterification generation of an acylazolium.

Although these processes allowed rapid and atom economical entry into carboxylate motifs, the extension to amide bond formation remained a significant challenge. Only isolated reports from the groups of Rovis[2] and Scheidt,[3] who employed aniline and vinylogous imides respectively, managed to overcome the inherent problem of competing imine formation during any attempted internal redox amidation process. A second difficulty associated with the redox amination processes is the slow reaction of an amine with an acylazolium compared to reaction with alcohols. Specifically the rate of collapse of the tetrahedral intermediate **329** formed from addition of an amine

to an acyl azolium is significantly slower than the corresponding intermediate **327** formed from addition of an alcohol to an acylazolium **(Fig 49)**.[4]
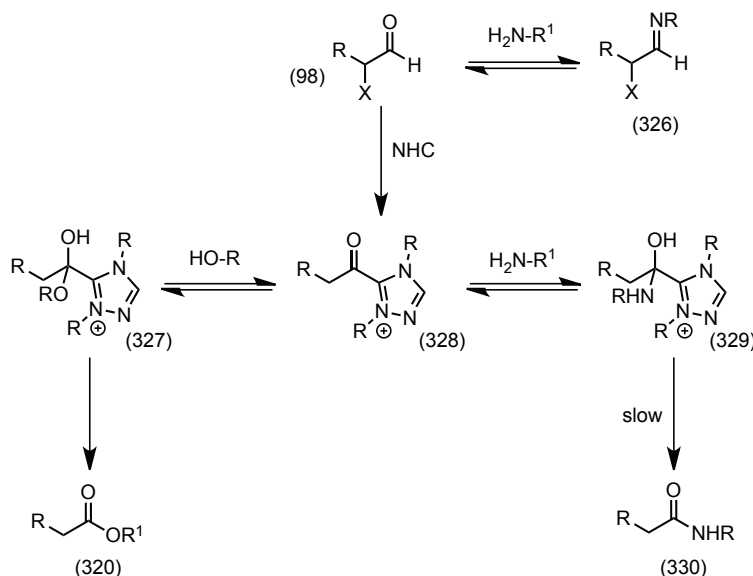
Fig 49: NHC-catalysed esterification and amidation.

An elegant solution to this problem was reported independently by the groups of Bode[5] and Rovis[6] in 2007. Bode *et al.* utilised imidazole as an additive to form rapidly and preferentially an acyl imidazole species **336** that can be intercepted with a range of primary and secondary amines to afford a range amides **344 (Scheme 92)**. The method was also compatible with the use of other acylazolium precursors such as α-chloro aldehydes and enals.
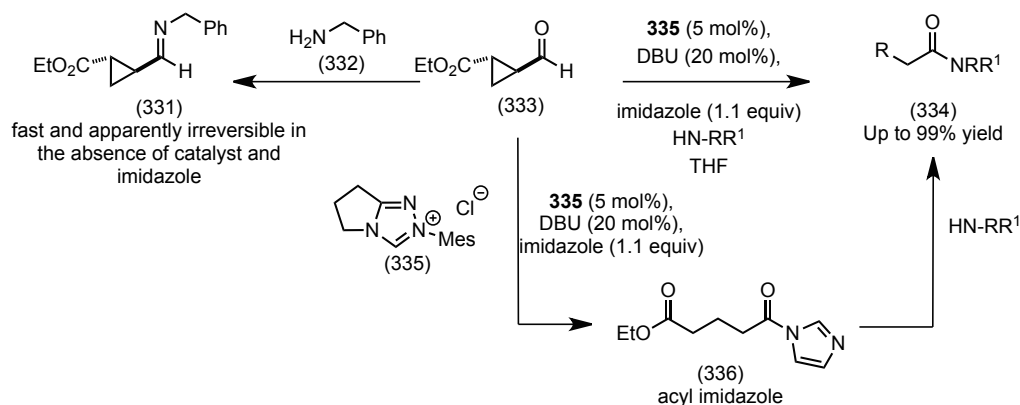
Scheme 92: The use of imidazole as an additive in the redox amidation of cyclopropyl aldehydes.

Rovis *et al.* have employed a similar strategy using 1-hydroxy-7-azabenzotriazole (HOAt) **341** as a co-catalyst, shuttling the acyl azolium through to an activated carboxylate **342** that undergoes nucleophilic attack by an amine to afford the amide products **339 (Scheme 93)**. Although these advancements provide redox amidation

products they are limited by the requirement of an additive and the relative instability of the α-functionalised aldehydes employed.
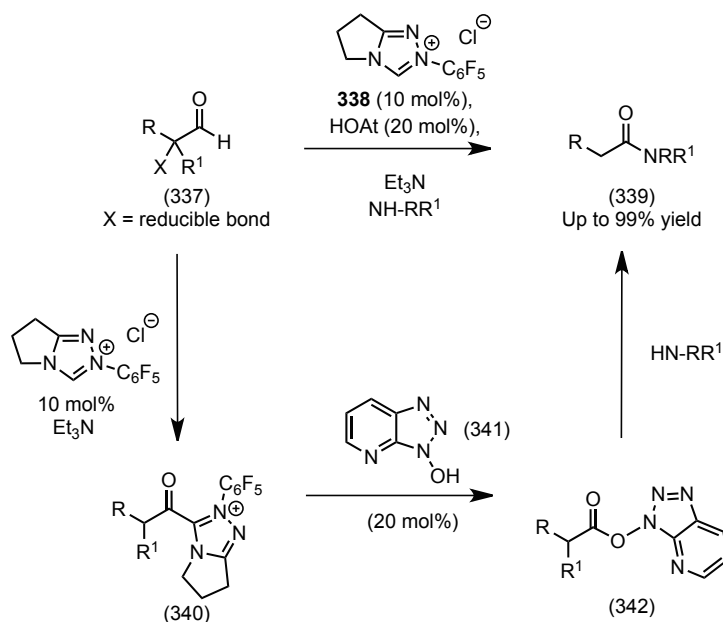
Scheme 93: Development of a redox amination process.

The current state of the art in redox aminations is the methodology developed by Bode and co-workers.[4] In this report, crystalline α'-hydroxyenones **343** serve as surrogates for α-functionalised aldehydes that eliminate the possibility for competing imine formation. The reaction mechanism proceeds *via* addition of the NHC to the enone, followed by retro benzoin reaction to release acetone and generate the conjugated Breslow intermediate. β-Protonation of this homoenolate species leads to the active acylazolium **346**, itself only a slow acylating agent for amines, but which is readily converted to the activated carboxylate by addition of co-catalytic 1,2,4-triazole **347**. This species functions as a highly reactive amine acylating agent that allows the formation of a range of primary and secondary amides, as well as chemoselective amide formation from amino-alcohols **(Scheme 94)**.
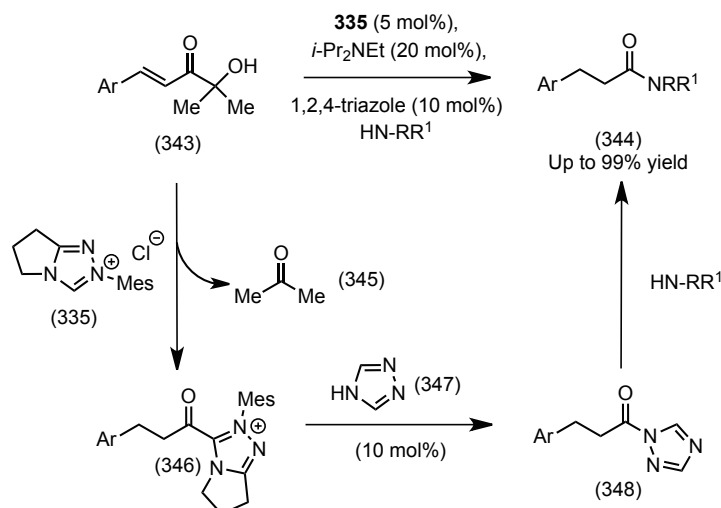
Scheme 94: The use of α'-hydroxyenones as redox amination precursors.

2.2 The use of α-functionalised aldehydes as precursors for azolium enolates

Along with ketenes and enals, α-functionalised aldehydes provide access to reactive azolium enolates for a range of asymmetric carbon-carbon bond forming reactions **(Fig 50)**.
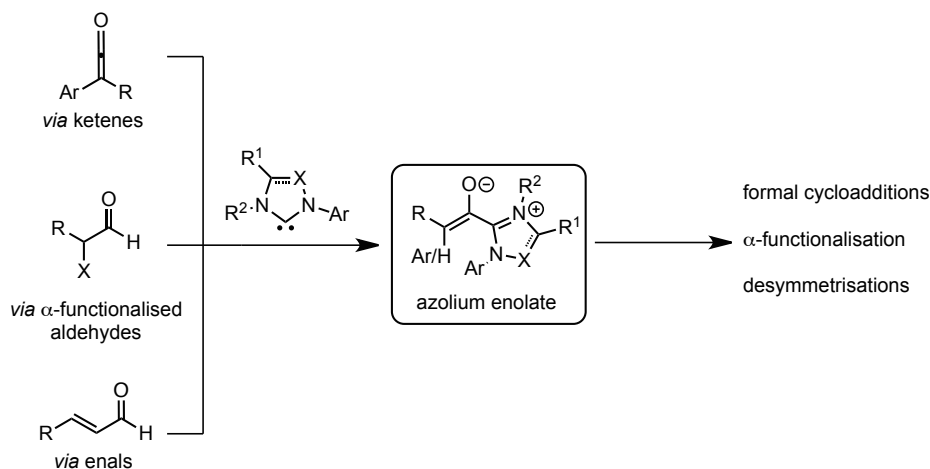
Fig 50: Generation of azolium enolates.

The use of ketenes and enals was reviewed in the introduction **(Chapter 1, 4.2 & 4.3)** and will not be further elaborated upon in this section. However a selected range of examples of α-functionalised aldehyde reactivity will be discussed below.

In an extension to the initial report of the use of α-chloroaldehydes from Bode and co-workers summarised in the introduction, a 2008 report of Bode *et al.* documents the use of α-chloroaldehyde bisulfite adducts **349** as effective azolium enolate precursors.[7] Under biphasic reaction conditions the protocol was effective for a range

of substituted β,γ-unsaturated α-ketoesters **350** in a [4+2] hetero Diels-Alder reactions proceeding in good yield (40–90%) and outstanding diastereo- and enantioselectivitiess (>95:5 *dr* and typically >99% *ee*). These precursors provide greater stability than the α-functionalised aldehydes and importantly represent a novel solution to the enantioselective addition of a acetate equivalent *via* the use of commercially available aldehyde surrogate **349** (R = H) **(Scheme 95)**.
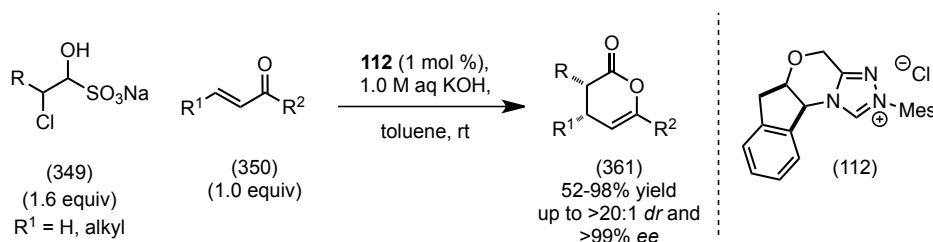
Scheme 95: The use of α-chloroaldehyde bisulfite salts as bench stable α-functionalised aldehydes.

α-Chloroaldehydes were also employed by the group of Kobayashi who aimed to expand the methodology to the synthesis of *trans* stereoisomers of nitrogen substituted dihydropyran-2-ones from the NHC-catalysed cycloaddition of α,β-disubstituted enones **363** and 2-chloropropanal **362 (Scheme 96)**.[8] This methodology proceeds in high enantioselectivity (up to 98% *ee*) for a limited range of nitrogen containing acceptors. Contrary to the predicted stereochemical outcome the *syn* isomer predominates, leading the authors to propose a stepwise, rather than a concerted process.
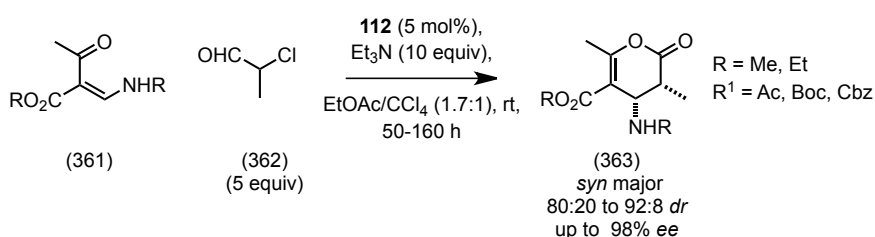
Scheme 96: Synthesis of dihydropyran-2-ones from 2-chloropropanal.

In 2009 the group of Scheidt showed that α-aryloxyacetaldehydes **364** are competent enolate equivalents in the NHC-catalysed Mannich reaction with imines **365 (Scheme 97)**.[9] The reaction was applicable to a range of aryl imines with *in situ* generation of the corresponding amides **366** in good yields (56-75%) and with excellent enantiocontrol (typically >90% *ee*), however only the parent unsubstituted α-aryloxyacetaldehyde was demonstrated. Other products such as the carboxylic acid, methyl ester or 1,3-aminoalcohol could also be obtained by correct choice of

additional reagent following consumption of the starting material (MeOH/aq. NaOH, sodium methoxide or LiBH$_4$ respectively) **(Scheme 97)**. The general utility of this methodology is reduced by the availability of the precursors, with the number of readily prepared α-aryloxyacetaldehydes limited.
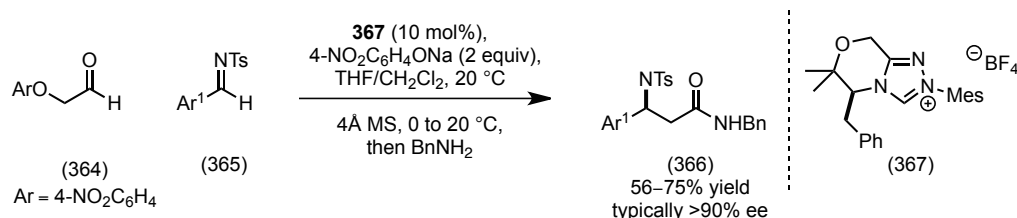
Scheme 97: Use of α-aryloxyacetaldehydes as enolate equivalents.

The aryloxy leaving group is key to the postulated mechanistic rational in what the authors describe as "rebound-activation". The cycle begins with initial NHC addition and tautomerisation to the Breslow intermediate **368**, followed by elimination of aryloxy anion **370** to form the azolium enolate **369**. Subsequent C-C bond formation provides intermediate **371** with acylation of this species by aryloxy anion **370** providing the ester **372** and regenerating the NHC. Transamidation of this ester *in situ* provided the amide products **(Fig 51)**.
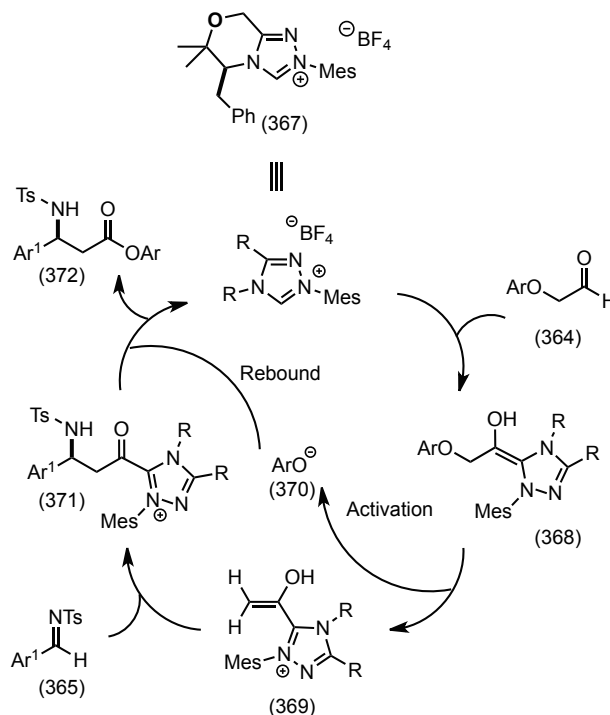
Fig 51: Mechanistic rationale for the use of α-aryloxyacetaldehydes.

3.0 Previous work within the group

Previous work in this area from within our group aimed to develop an alternative bench stable α-functionalised aldehyde that would provide further ease of procedure compared to the frequently employed, but sensitive α-haloaldehydes.[10] α-Aroyloxyaldehydes were found to be adequate leaving groups in this methodology, and subsequently selected as efficient redox precursors due to their prolonged stability and general ease of synthesis. They can be readily prepared in one-step form the corresponding aldehyde utilising an α-oxidation reagent developed by Tomkinson,[11] itself readily prepared on >50 g scale (*vide infra*). A range of ester products could be accessed and employment of phenol followed by addition of benzylamine to the crude reaction mixture allowed a redox amidation process to be realised.

α-Aroyloxyaldehydes were shown to be competent precursors for C–C bond forming reactions with an isolated preliminary result employing β,γ-unsaturated α-ketoester **375** in a [4+2] cycloaddition in a promising yield (54%) and *dr* (69:31). In this report *N*-mesityl NHC precatalyst **335** was found to be a uniquely reactive catalyst architecture. As summarised in **(Chapter 1, 4.2)** there is a general requirement for the use of *N*-mesityl NHCs for reactions involving α-functionalised aldehydes.
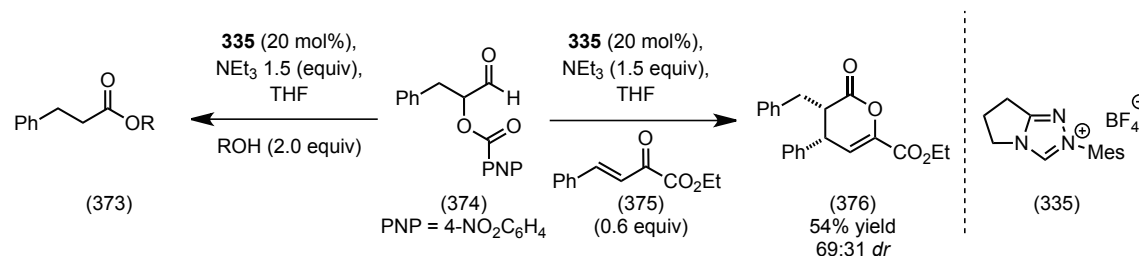
Scheme 98: Development of α-aroyloxyaldehydes as efficient acylazolium precursors.

4.0 Development of α-aroyloxyaldehyde 374 as a bench stable ketene surrogate

4.1 Synthesis of α-aroyloxyaldehyde 374

Studies began by ensuring the literature procedure[10] for the synthesis of α-aroyloxyaldehyde **374** was sufficiently robust to provide material for an optimisation project. Although proceeding in relatively poor overall yield (approximately 25% for the three steps) scaling up of the reported procedure could conveniently provide a 1 g quantity of the necessary α-aroyloxyaldehyde.
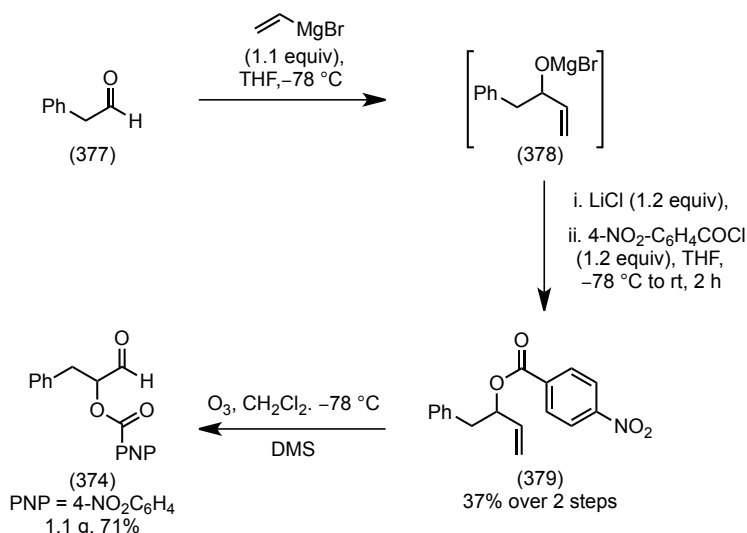
Scheme 99: Synthesis of α-aroyloxyaldehyde 374.

4.2 Synthesis of α-ketoester 381

With sufficient quantities of the α-aroyloxyaldehyde **374** in hand, studies were directed towards the optimisation of the cycloaddition reaction. It has been reported in similar [4+2] processes employing α-ketoester substrates such as **381** that the ester portion can play a key role in the diastereoselectivity,[12] specifically that a methyl ester was optimal for high diastereoselectivity. Accordingly methyl ester **381** was prepared from the parent potassium salt **(Scheme 100)**[13,14] and tested under a range of reaction conditions.
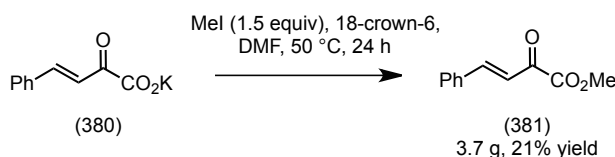
Scheme 100: Synthesis of α-keteoester 381.

4.3 Optimisation of conditions for the use of α-aroyloxyaldehyde 374

Employing 20 mol% achiral precatalyst **335**, 1.0 equiv α-ketoester **381**, 1.5 equiv of α-aroyloxyaldehyde **374** and 1.5 equiv of Et₃N, the reaction gave both promising yield and an improved *dr* when compared to the previously reported reaction with ethyl ester **375 (Scheme 101)**. When chiral precatalyst **112** was used under identical reaction conditions the *dr* increased further and there was a small but appreciable increase in isolated yield **(Table 12, Entry 2)**. The enantiomeric excess of **382** was established *via* chiral HPLC and found to be exquisite (>99% *ee*). This is consistent with the reported use of this catalyst in a similar system utilising α-chloro aldehydes

as azolium enolate precursors.[7,15] This catalyst was employed due the necessity for an *N*-mesityl substituent and its success in related literature processes. Attempts to lower both the catalyst loading and the number of equivalents of **374 (Table 12, Entry 3)** led to reduced conversions and lower *dr*. Under these conditions the *dr* could be improved up to >99:1 by lowering of the reaction temperature, however at the detriment of reduced product conversions **(Table 12, Entry 4 & 5)**.
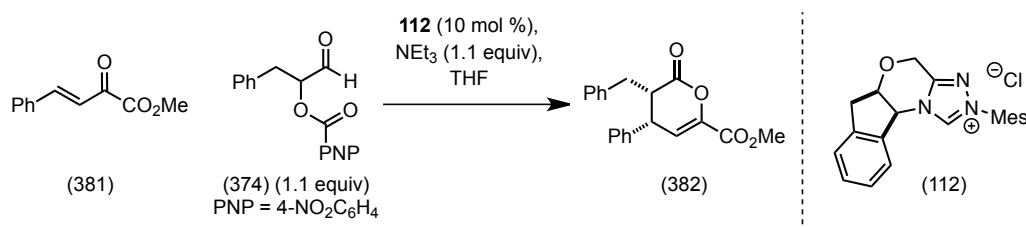
Scheme 101: Optimisation of reaction conditions for use if benzyl substituted α-aroyloxyaldehyde

Entry	Precatalyst, (mol%)	Temperature (°C)	Time (h)	Conversion (%)[a]	*dr*[a]	Yield (%)[b]	*ee* (%)[c]
1[d]	**335**, 20	rt	16	>80	84:16	37	NA
2[d]	**112**, 20	rt	5	>90	92:8	50	>99%
3	**112**, 10	rt	12	85	84:16	–	–
4	**112**, 10	0	12	65	97:3	–	–
5	**112**, 10	−78	12	45	>99:1	–	–

[a] Calculated by inspection of the crude reaction mixture using ^{1}H NMR spectroscopy. [b] Isolated yield of single diastereomer. [c] *ee* % determined by HLPC analysis on a chiral stationary phase. [d] 1.5 equiv of aldehyde and 1.5 equiv of Et$_3$N.

Table 12: Optimisation of reaction conditions for use if benzyl substituted α-aroyloxyaldehyde 374.

Literature examples typically require at least 1.5 equivalents of the α-functionalised aldehyde for good yields in azolium enolate reactions,[7,15] so this stoichometry was employed for the remainder of the optimisation. Employing these conditions the catalyst loading could be lowered to 10 mol% with excellent conversion and *dr* **(Table 13, Entry 1)**. Pleasingly, under these conditions, lowering the reaction temperature and allowing slow warming to rt overnight provided both excellent conversions and improved diastereoselectivity (98:2 *dr*). As anticipated, the lactone product, isolated in excellent yield, retained the high degree of enantioselectivity

(>99% *ee*) **(Table 13, Entry 2)**. A single diastereoisomeric product could be obtained by maintaining a reaction temperature of 0 °C, however this had a detrimental effect on conversion **(Table 13, Entry 3)**. It has been reported that EtOAc could provide a rate enhancement in similar reactions *via* the precipitation of $Et_3N.HCl$ from the reaction solution.[15] In this case employing EtOAc as the reaction solvent under identical conditions to provided no significant increase in reaction rate and no further optimisation of solvent was undertaken.
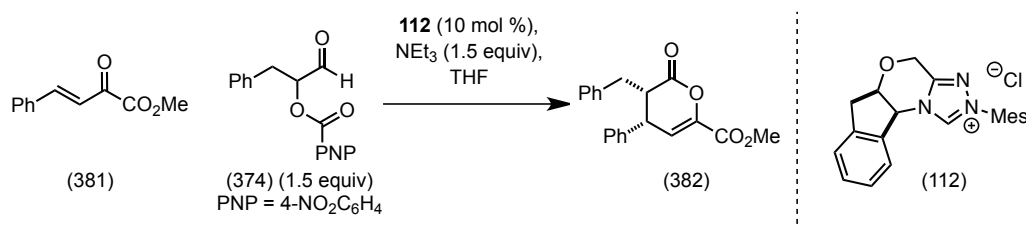
Scheme 102: Effect of temperature whilst employing 1.5 equiv of α-aroyloxyaldehyde 374.

Entry	Temperature (°C)	Time (h)	Conversion (%)[a]	dr[a]	Yield (%)[b]	ee (%)[c]
1	rt	12	>90	85:15	–	–
2	0 to rt	12	>90	98:2	93	>99
3	0	12	60	>95:5	–	–

[a] Calculated by inspection of the crude reaction mixture using ^{1}H NMR spectroscopy. [b] Isolated yield of single diastereomer. [c] *ee* % determined by HLPC analysis on a chiral stationary phase.

Table 13: Effect of temperature whilst employing 1.5 equiv of α-aroyloxyaldehyde 374.

4.4 Assignment of relative and absolute configuration

In all cases both the relative and absolute configurations were assigned in analogy to the literature.[15] As we rationalise the reaction proceeding *via* an identical enolate species, it is presumed that the reaction employing the α-ketoester substrate **381** will proceed *via* the same mechanistic course as proposed by Bode *et al.* for the isomeric α-β-unsaturated ketones **383**, thus resulting in a identical stereochemical outcome **(Scheme 103)**.
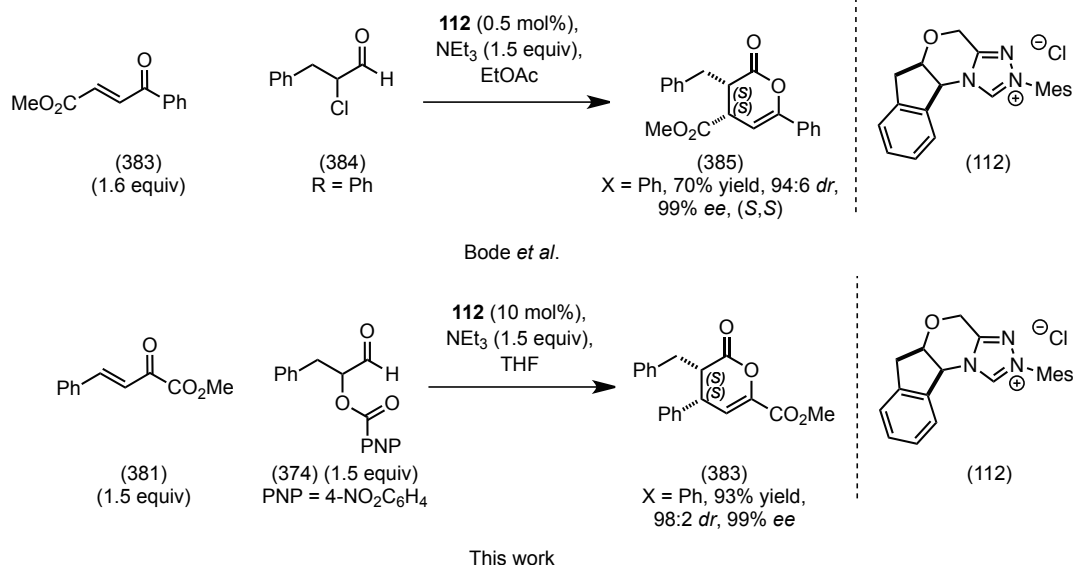
Scheme 103: Assignment of the relative and absolute configuration by analogy.

The stereochemistry was further verified by the use of oxodiene **386** as a substrate in our developed methodology from α-aroyloxyaldehyde **374**. Accordingly, under the developed reaction conditions, **387** was isolated in 79% yield using precatalyst **112**. The specific rotation of this substrate was then compared to the literature[8] [**387** $[\alpha]_D^{20}$ +173 (*c* 1.05, CHCl$_3$) literature value +107 (*c* 1.82, CHCl$_3$, 99% *ee*)], identifying **387** as (3*S*,4*S*).
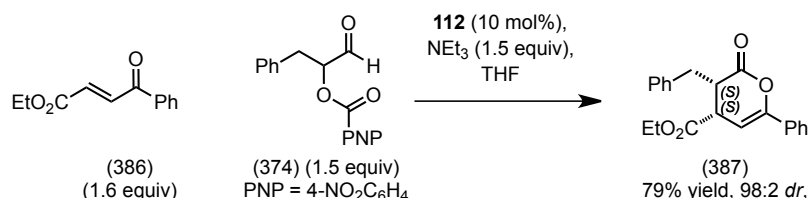
Scheme 104: Synthesis of literature compound 387 from α-aroyloxyaldehyde 374.

4.5 Effect of catalyst loading

Previous literature has shown that precatalyst **112** is effective at low catalyst loadings (as low as 0.5 mol%) when employing α-chloroaldehydes[15] as azolium enolate precursors. The efficiency of α-aroyloxyaldehydes **112** at low catalyst loadings was investigated by the use of 1 mol% of **112**, initially at rt. The reaction was found to be complete after an extended reaction time of 48 h, though with diastereoselectivity 76:24. The enantioexcess for the major diastereomer remained exquisite (99%), as did the *ee* of the minor (>99% *ee*) **(Scheme 104)**.
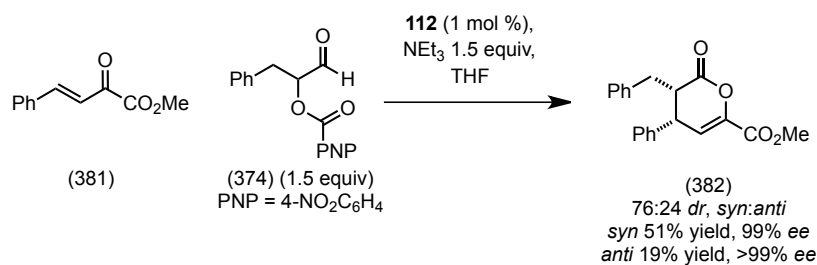
Scheme 104: Reaction performed with 1 mol% of precatalyst 112.

4.6 Investigations into the epimerisation and isomerisation of lactone 382

As previous reactions employing precatalyst **112** had proceeded with excellent diastereoselectivity, it was postulated that the moderate diastereocontrol in this case could be due to a base or NHC mediated epimerisation of the major *syn* diastereomer to the *anti* product. To test this hypothesis, an isolated sample of the diastereo- and enantiomerically pure *syn* lactone **382** was resubjected to various reaction conditions.

Initially, the effect of the NHC catalyst was evaluated by resubjecting *syn* lactone **382** to 15 mol% precatalyst **112** and 15 mol% Et$_3$N for 65 h. Under these conditions epimerisation of the *syn* to the *anti* lactone was observed with a reduction in the *dr* from >95:5 to 89:11 **(Table 14, Entry 1)**. There was also a significant quantity of isomerised lactone **388** (41:59 *dr*), in which the olefinic double bond has isomerised out of conjugation with the ester. A smaller amount of isomerisation to lactone **389** was also observed, as the result of the isomerisation of the double bond into conjugation with the lactone carbonyl. To examine the effect of Et$_3$N on this process, 15 mol% of base was used in the absence of precatalyst **112 (Table 14, Entry 2)**. It was found that both the amount of epimerisation and isomerisation were greatly reduced, suggesting an enhanced propensity of the NHC to facilitate the proton transfer process when compared to Et$_3$N. It was shown that by employing 1.0 equivalent of Et$_3$N, an increased percentage of isomerisation of the parent lactone could be seen **(Table 14, Entry 3)**, with further reaction times favouring increased isomerisation to **389 (Table 14, Entry 4)**. It is therefore postulated that the free NHC is the main facilitator of epimerisation, with Et$_3$N favouring isomerisation, with longer reaction times leading to the formation of the presumably thermodynamically favoured lactone **389**. Due to the inherent difficulties in isolation of the various products from the reaction mixtures, more detailed analysis of these processes, along with clarification of enantioselectivity, was not undertaken.[15]
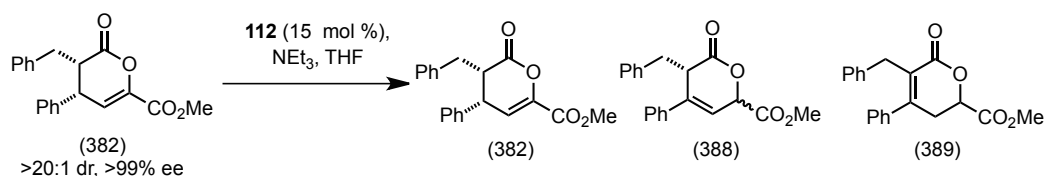
Scheme 106: Stability of lactone 382 to the reaction conditions.

Entry	Time (h)	Ratio 382:388:389[a]		
1[b]	65	50 89:11 dr[a]	30 41:59 dr[a]	20
2[c]	65	92 93:7 dr[a]	8 45:55 dr[a]	0
3[d]	65	48 94:6 dr[a]	37 40:60 dr[a]	15
4[e]	185	27 80:20 dr[a]	14 48:52 dr[a]	59

[a] Analysed by ^{1}H NMR spectroscopy [b] 15 mol% **112** and 15 mol% Et$_3$N were used [c] 15 mol% Et$_3$N was used [d] 1.0 equiv Et$_3$N used [e] Entry 3 was resubjected to a further 120 h under identical conditions to entry 3.

Table 14: Stability of lactone 382 to the reaction conditions.

4.7 Attempted ring opening of lactone 382 with pyrrolidine

Further evidence for the processes operating during the isomerisation was gained during attempted ring opening of **382** using pyrrolidine **(Scheme 107)**. No ring opened product could be observed with complete isomerisation to **389** within 12 h. This is rationalised by the increased basicity of pyrrolidine when compared to Et$_3$N.
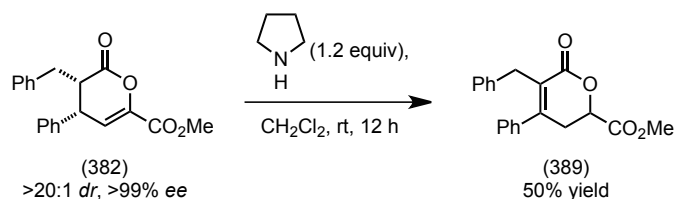
Scheme 107: Isomerisation of lactone 382 *via* treatment with pyrrolidine.

5.0 Synthesis of a range of α-aroyloxyaldehydes

After optimisation of conditions for the formation of lactone **382** in excellent yield (up to 93%), diastereo- and enantioselectivity (up to >98:2 *dr* and >99% *ee*), attention was turned to different α-aroyloxyaldehyde starting materials. The following four substrates **390–393** were selected as representative examples to test the limits of the system with respect to alkyl substitution and branching. Substrates **394** and **395** were not tested as previous investigations had shown them to be either unreactive to NHC redox esterification or prone to rearrangement under the basic reaction conditions required.[17]
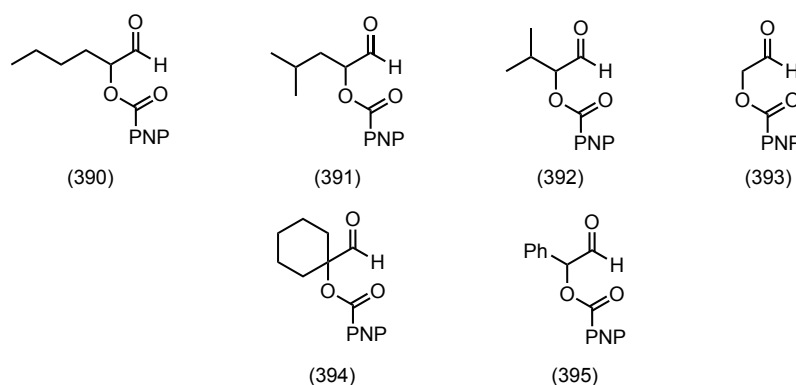
Fig 52: A range of potential α-aroyloxyaldehydes.

5.1 Synthesis of α-aryloxylation reagent 397

The most efficient method to prepare a range of differentially substituted α-aroyloxyaldehydes on scale is to simply treat the requisite commercially available aldehyde precursor with the α-aryloxylation reagent derivative **397,** the general structure of which was initially developed by Tomkinson *et al.* **(Scheme 108).**[11]
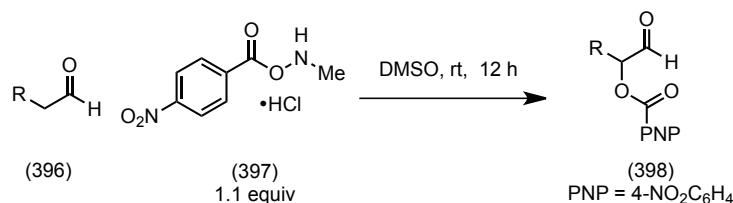
Scheme 108: One step synthesis of α-aroyloxyaldehydes from the requite aldehyde.

This reagent had previously been synthesised and reported in the literature according to **(Scheme 109)** from *N*-methylhydroxylamine hydrochloride.[10] This preparation was carried out on 25 g scale to provide the final reagent in greater than >70 g in a 50% yield over the three steps.
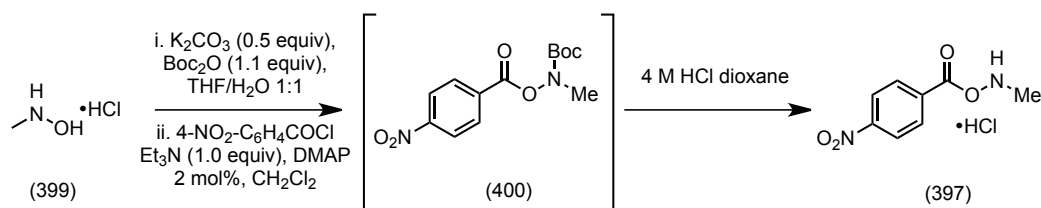
Scheme 109: Synthesis of α-aryloxylation reagent 397.

Accordingly α-aroyloxyaldehydes **390**, **391** and **392** were synthesised *via* the use of reagent **397** or by the multistep method outlined earlier in the synthesis of α-aroyloxyaldehyde **374**.

(390)
1.5 g, 47% yield over two steps
from valeraaldehyde[a]
or
2.4 g, 36% yield from hexanal[b]

(391)
0.94 g, 24% yield over two steps
from *i*-valeraldehyde[a]

(392)
0.92 g, 46% yield over two steps
from *i*-butyraldehyde[a]
or
0.46 g, 74% from *i*-valeraldehyde[b]
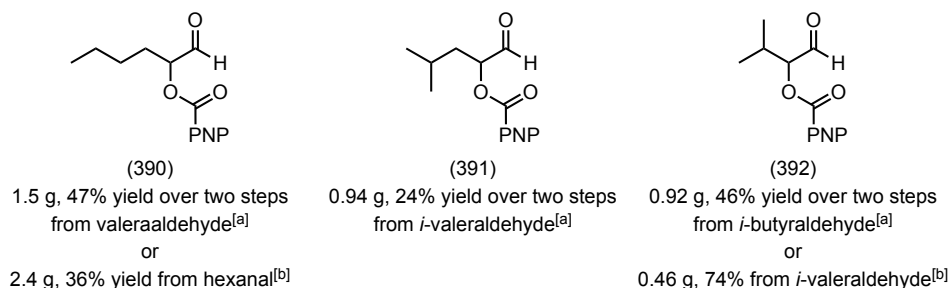
[a] Prepared via the two step Grignard addition, acylation and ozonoloysis protocol. [b] Prepared by the use of α-aryloxylation reagent **397**.

Fig 53: Synthesis of α- aroyloxyaldehyde 390, 391 and 392.

6.0 Use of α-aroyloxyaldehyde 390 in the reaction protocol

n-Butyl substituted α-aroyloxyaldehyde **390** was tested under standard reaction conditions with either achiral precatalyst **335** or the aminoindanol derived precatalyst **112**. The reaction employing precatalyst **355** proceeded in excellent *dr*, albeit with reduced conversion to the lactone **401**. The starting α-ketoester **381** was not fully consumed and there was evidence for isomerisation of lactone **401**, as previously identified with lactone **382 (Table 15, Entry 1)**. Employing precatalyst **112** and closely monitoring the reaction by TLC to minimise the exposure time for the lactone product **401** to the reaction conditions provided **393** in both excellent diastereo- and enantioselectivity and in good isolated yield **(Table 15, Entry 2)**.
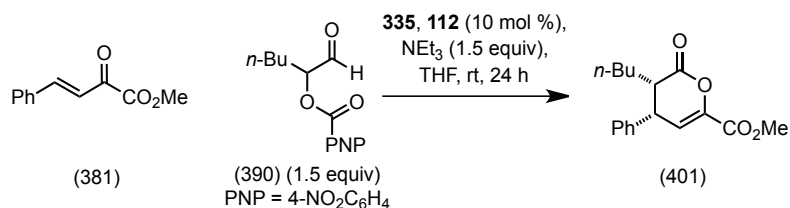
Scheme 110: Use of *n*-butyl α-aroyloxyaldehyde 390 in the reaction protocol.

Entry	Precatalyst	Time (h)	Conversion (%)[a]	dr[a]	Yield (%)[b]	ee (%)[c]
1	**335**	12	75	92:8	40	NA
2	**112**	3	>90	>95:5	63	>99

[a] Calculated by inspection of the crude reaction mixture using ^{1}H NMR spectroscopy. [b] Isolated yield of single diastereomer. [c] *ee* % determined by HLPC analysis on a chiral stationary phase.

Table 15: Use of *n*-butyl α-aroyloxyaldehyde 390 in the reaction protocol.

6.1 Effect of catalyst loading

The effect of catalyst loadings was next investigated, with initial lowering to 1 mol%, pleasingly operating in excellent yield, diastereo- and enantioselectivities **(Table 16, Entry 1)**. Further lowering of the loading to 0.5 mol% resulted in impractically long reaction times, lower *dr* and a poor isolated yield **(Table 16, Entry 2)**.
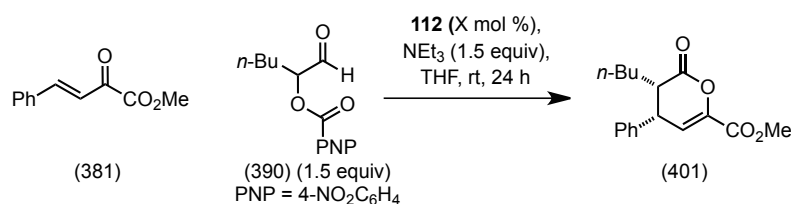
Scheme 111: Effect of catalyst loading.

Entry	Precatalyst (mol%)	Time (h)	Conversion (%)[a]	dr[a]	Yield (%)[b]	ee (%)[c]
1	**112**, 1.0	9	>90	>95:5	69	>99
2	**112**, 0.5	84	<50[d]	95:5	12	>99

[a] Calculated by inspection of the crude reaction mixture using ^{1}H NMR spectroscopy. [b] Isolated yield of single diastereomer. [c] *ee* % determined by HLPC analysis on a chiral stationary phase [d] ^{1}H NMR analysis of the crude also indicated the presence of an isomerised product in approximately a 33:66 ratio with lactone **393**.

Table 16: Effect of catalyst loading.

6.2 Preparative scale reaction using *n*-butyl α-aroyloxyaldehyde 390

Due to the decreased reaction time and lower catalyst loadings associated with α-aroyloxyaldehyde **390**, this substrate was chosen to demonstrate the utility of this reaction process by performing the reaction on increased scale. Lactone **401** was obtained in a moderate yield (41%), with superb diastereo- and enantiocontrol (>95:5 *dr* and >99 % *ee*) **(Scheme 112)**.
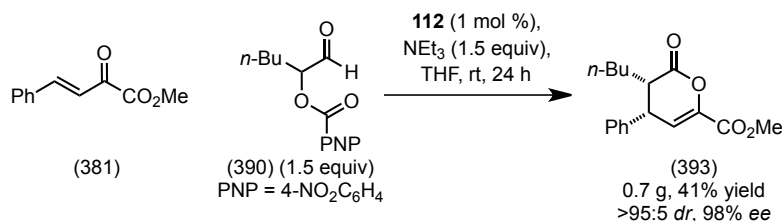
Scheme 112: Preparative scale reaction using α-aroyloxyaldehyde 390.

7.0 Use of α-aroyloxyaldehyde 391 in the reaction protocol

The next aldehyde to be screened was the analogue **391**. Under the established reaction conditions employing achiral precatalyst **355**, lactone **402** was obtained in 33% yield with excellent diastereoselectivity (>95:5 *dr*) **(Table 17, Entry 1)**. The aminoindanol derived precatalyst **112** provided improved conversions and isolated yield (47%) while maintaining the excellent diastereoselectivity (>95:5 *dr*). As with previous examples, the reaction proceeded with outstanding enantioselectivity (>99% *ee*) **(Table 17, Entry 2)**. Prolonging the reaction time led to reduced *dr* and the formation of a proposed isomerisation product **403** in a 72:28 ratio of **394** to **395** with **395** as an approximately 30:70 ratio of diastereomers **(Table, 17, Entry 3)**.[18] Although β-branching was readily tolerated, the reaction was equally susceptible to isomerisation as observed in previous substrates, making purification difficult and leading to reduced isolated yields.
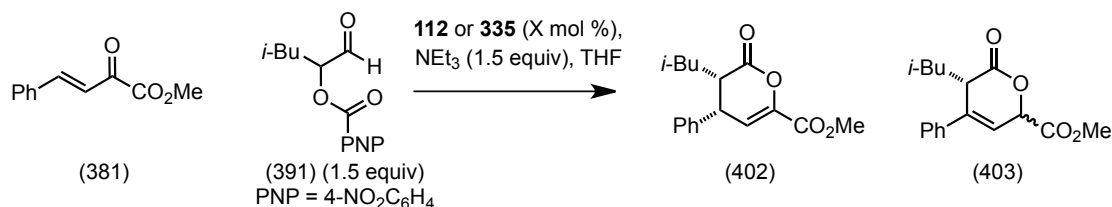
Scheme 113: Use of α-aroyloxyaldehyde 391 in the reaction protocol.

Entry	Precatalyst (mol%)	Time (h)	Conversion (%)[a]	dr[a]	Yield (%)[b]	ee (%)[c]
1	**355**, 20	12	60[d]	>95:5	33	NA
2	**112**, 10	16	>90	>95:5	47	>99
3	**112**, 10	24	>90[e]	96:4	63	>99

[a] Calculated by inspection of the crude reaction mixture using ^{1}H NMR spectroscopy. [b] Isolated yield of a single diastereomer. [c] *ee* % determined by HLPC analysis on a chiral stationary phase. [d] ^{1}H NMR spectroscopic analysis of the crude did not indicate the presence of isomerised product **403** with incomplete consumption of α-ketoester **381**. [e] ^{1}H NMR spectroscopic analysis of the crude indicated approximately 30% of the isomerised lactone **403** with an approximate 30:70 *dr*.

Table 17: Use of α-aroyloxyaldehyde 391 in the reaction protocol.

8.0 Use of α-aroyloxyaldehyde 392 in the reaction protocol

The final α-aroyloxyaldehyde to be screened was the *i*-propyl substituted analogue **392**. In this instance the reaction with achiral NHC precursor **355** proceeded to approximately 50% consumption of the aldehyde after 16 h, giving a 67:33 ratio of lactone **404** (>95:5 *dr*) and the isomerised compound **405** (55:45 *dr*) **(Table 18. Entry 1)**. Use of precatalyst **112** increased the crude product conversion to ~80%, however the ratio of desired lactone **404** (>95:5 *dr*) to the isomerised product **405** (47:53 *dr*) was 47:53 in favor of the isomerisation **(Table 18, Entry 2)**. Owing to the large number of products obtained, including the two starting materials and the desired and isomerised lactones (the latter being a mixture of two diastereomers), no authentic samples could be obtained and no further investigations were conducted.[19]
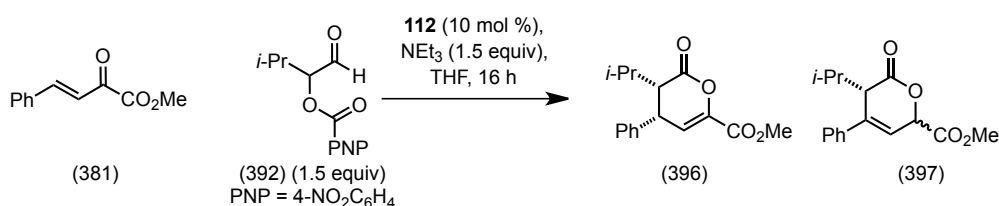
Scheme 114: Use of *i*-propyl α-aroyloxyaldehyde 392 in the reaction protocol.

Entry	Precatalyst (mol%)	Time (h)	Conversion[a] (%)	Ratio 396:397[a]	dr 396[a]	dr 397[a]
1	**355**, 10	18	50	67:33	>95:5	55:45
2	**112**, 10	18	80	47:53	>95:5	47:53

[a] Calculated by inspection of the crude reaction mixture using ¹H NMR

Table 18: Use of *i*-propyl α-aroyloxyaldehyde 392 in the reaction protocol.

9.0 Synthesis of unsubstituted α-aroyloxyaldehyde 393

The development and use of α-aroyloxyaldehyde **393** is an attractive proposal, as it would allow formal access to enantioselective acetate additions. In a similar vein, Bode *et al.* have overcome the safety and practicality issues associated with the formation of α-chloroacetaldehyde by developing commercially available bisulfite salt **406** as a viable precursor **(Fig 54)**.
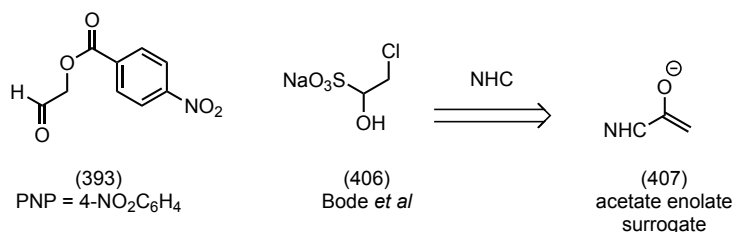
Fig 54: Rationale for the synthesis of unsubstituted α-aroyloxyaldehyde 393.

Initial attempts to employ the α-aroyloxylation agent **397** in combination with acetaldehyde proved unsuccessful with no obvious aldehyde products obtained. The alternative method *via* acylation of allyl alcohol followed by the previously developed ozonoloysis conditions also proved unsuccessful; cleavage of the double bond was noted by ¹H NMR spectroscopic analysis of the crude reaction product, as was formation of an aldehyde, however repeated chromatographic purification gave none of the desired product. Due to the likely inherent instability of **393**, and difficulties involved in purification, no further attempts at either synthesis or isolation were attempted **(Scheme 115)**.
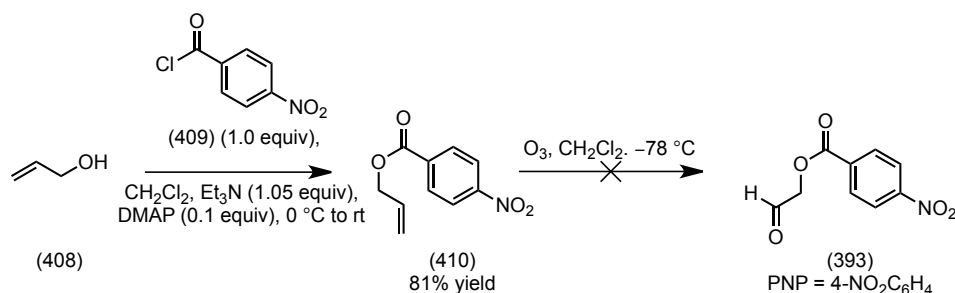
Scheme 115: Attempted synthesis of unsubstituted α-aroyloxyaldehyde 393.

10.0 Mechanistic proposal

In line with other similar process,[1,7,15] our mechanistic proposal begins with NHC addition to aldehyde **374** to form the adduct **413**. Formation of the Breslow-type intermediate **414**, then subsequent elimination of the carboxylate to generates enolate **414**. This then undergoes a [4+2] cycloaddition reaction with α-ketoester **381** to furnish intermediate **417**, which collapses with concurrent formation of lactone **382** and regeneration of the NHC catalyst **(Fig 55)**. A two step Michael addition-lactonisation mechanism is not conclusively ruled out at this stage but has been deemed unlikely by Bode and co-workers for a related system due to the requirement for exclusive reaction from the s-*cis* conformation of the α,β-unsaturated acceptor.[20]
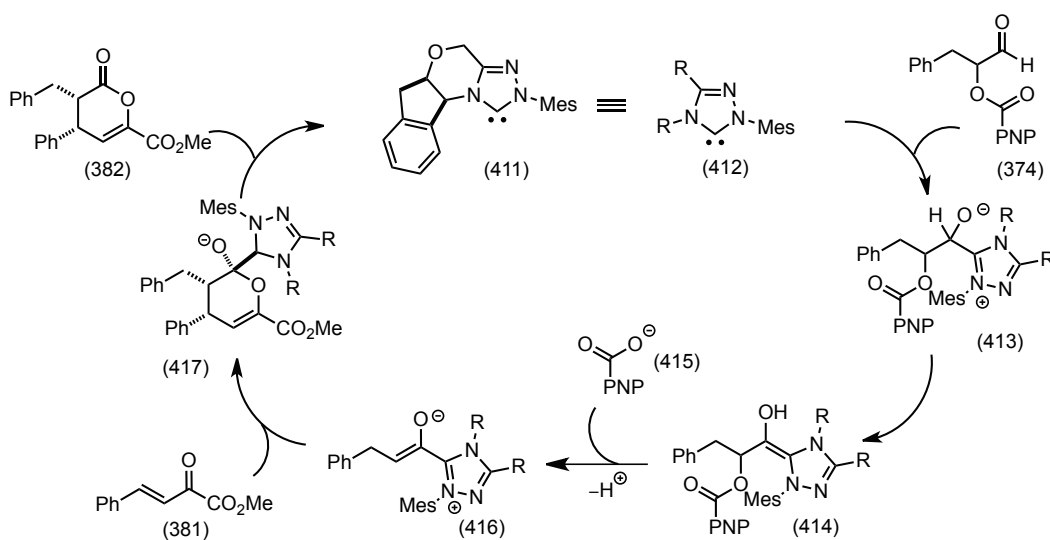
Fig 55: Mechanistic proposal.

11.0 Rationale for the observed absolute configuration

The origin of the enantioselectivity can be explained *via* a similar rationale to that proposed by Bode and co-workers for analogous reactions with enals as azolium enolate precursors.[21] In this postulation the enolate is positioned in an almost perpendicular orientation to the triazolium ring with the *N*-mesityl substituent effectively blocking approach from one face **(Fig 56)**. From this orientation an *endo* selective Diels-Alder reaction (with respect to the orientation of the α,β-unsaturated ketoester and the enolate oxygen) from the (*Z*)-enolate would render the required stereochemical outcome. The conformation of the enolate was supported by computational studies that calculated the perpendicular enolate orientation to be the lowest in energy. It is therefore proposed that this is the operative geometry in the transistion state leading to the observed configuration however this has not been conclusively proven. This perpendicular orentation of the enolate with respect to the triazolium ring was also postulated in the pre-transition state assembly for the NHC-catalysed β-lactone formation **(Chapter 2 & 3)**.
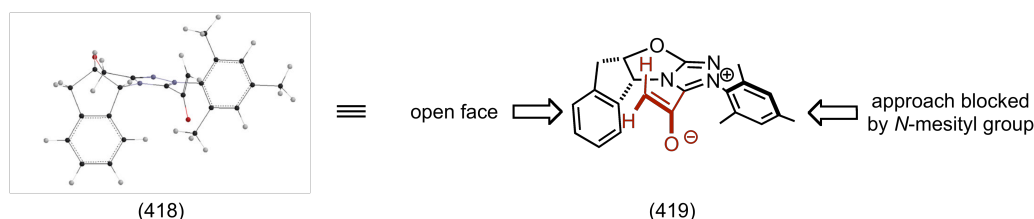
Fig 56: Calculated (HF 6-31G*) structure for the lowest energy enolate accompanied by pictorial representation. The oxygen resides on the same face as the indene ring. Extracted without permission from Bode *et al. Proc. Natl. Acad. Sci.* 2010, *107*, 20661-20665.

12.0 Summary

In conclusion, it has been shown that 4-nitrobenzoyloxyaldehydes are bench stable azolium enolate precursors and serve as effective surrogates for monosubstituted ketenes. Initial [4+2] cycloaddition studies with a limited range of aldehydes have shown the ability of precatalyst **112** to function with outstanding levels of diastereo- and enantioselectivity. The limits of the aldehyde substitution pattern with respect to alkyl branching were established with α-branching poorly tolerated in the reaction. Product stability studies showed that isomerisation and epimerisation are unwanted side reactions of the lactone products. This reaction manifold has improved utility and practicality when compared to the previous work employing isolable alkylarylketenes. Although not directly demonstrated, this protocol may overcome the limitations of

scale placed upon the use of alkyarylketenes by the use of bench stable α-aroyloxyaldehyde. This methodology also allows access to substitution patterns that would be formally obtained by reactive and non-isolable mono-substituted ketenes that require *in situ* formation under strictly anhydrous conditions. This protocol also functions in exquisite diastereo- and enantioselctivity with superior results compared to those obtained for NHC-catalysed formal cycloadditions of alkylarylketenes.

13.0 Refrences and notes

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15. He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088-15089.
16. It is assumed that the C(3) centre remains unaffected during these processes.
17. Specifically **395** undergoes a enolisation of the aldehyde followed by an intramolecular acyl transfer to yield 2-oxo-2-phenylethyl 4-nitrobenzoate (*see reference 9*)
18. As with previous substrates, attempts to isolate and fully characterise the isomerised product proved unsuccessful and it is therefore assigned by analogy.
19. The products were assigned *via* analogy to those previously reported by ^{1}H NMR spectroscopic analysis of the crude and partially purified products.
20. He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418-8420.
21. Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20661-20665.

Chapter 7: Conclusions

Conclusions

This thesis has documented extensive investigations into the generation and reactivity of azolium enolates derived predominatly from alkylarylketenes and NHCs. Various asymmetric methodologies have been developed that further the current literature on formal [2+2] and [4+2] NHC-catalysed cycloadditions of azolium enolates, as well as demonstrating their use for asymmetric halogenation reactions.

Firstly the NHC-catalysed formal [2+2] cycloaddition between alkylarylketenes and chloral has been reported. This methodology has expanded the field of asymmetric α,α-disubstituted β-lactone synthesis operating in good yield, diastereo- and enantioselectivity (up to 95% yield, 88:12 *dr* (*anti:syn*) and 94% *ee*). Although a highly scalable process (up to 3 g scale), limited derivatisation strategies did not allow transformation to the targeted aminoacid type motif and thus the genuine synthetic utility of this process was not realised.
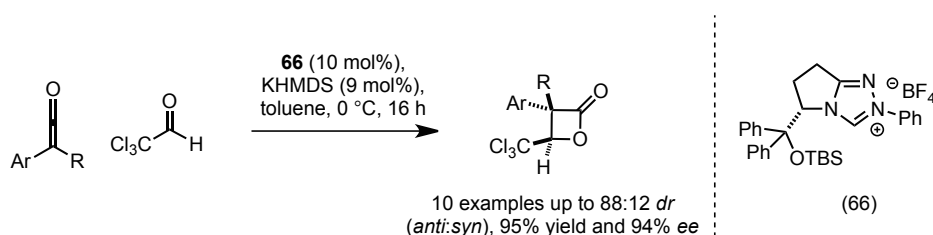
Scheme 116: NHC-catalysed asymmetric β-lactone formation from alkylarylketenes and chloral.

Interestingly, the use of a ketene bearing a 2-substituent on the aryl ring, or one that included an α-branched alkyl group, led to an exclusive chlorination pathway. This is, to the best of our knowledge, the first use of chloral as an electrophilic chlorination agent. This methodology was found to be applicable to a range of 2-arylsubstituted alkylarylketenes in good yield and enantioselectivity (typically >70% yield and 80% *ee*). A rationale for both the chemoselectivity and the observed stereochemical outcome of both lactonisation and chlorination reactions was proposed that is in consistent with the observed trends in stereoselectivity.
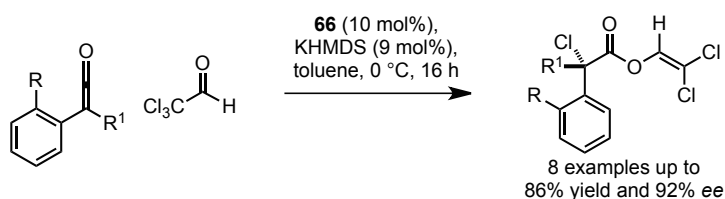
Scheme 117: NHC-catalysed asymmetric chlorination of alkylaryl ketenes with chloral.

A second methodology to access the β-lactone motif was also reported *via* an NHC-catalysed formal [2+2] cycloaddition between alkylarylketenes and benzaldehydes. The optimised reaction proceeds in excellent levels of diastereo- and enantioselectivity with 2-nitrobenzaldehyde (up to 94:6 *dr* (*syn:anti*) and 95% *ee*), and expands the scope of the formal [2+2] cycloaddition between ketenes and aldehydes. Notably, no competing benzoin reaction was observed under the reaction conditions, with the lactone product being readily transformed to synthetically useful α,α-disubstituted β-hydroxy- and β-amino acid building blocks.

66 (10 mol%),
KHMDS (9 mol%),
toluene, −50 °C, 12 h

11 examples up to 94:6 *dr*, *anti:syn*,
83% yield and 94% *ee*
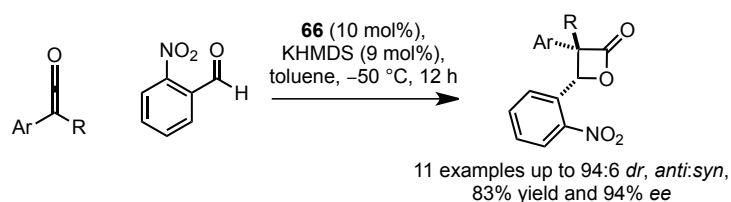
Scheme 118: NHC-catalysed asymmetric β-lactone formation from alkylarylketenes and benzaldehydes.

Building upon the specific asymmetric chlorination reaction discovered with chloral, a general methodology has demonstrated that NHCs are viable Lewis base catalysts for the α-chlorination and α-bromination of alkylarylketenes. A range of halogenating reagents were screened with **275** proving optimal, giving excellent yields of tertiary α-haloesters. Chiral NHC precatalyst **66** shows promising levels of enantioselectivity (up to 61% *ee*) however the typically level of enantiomericexcess was only moderate (typically ~40% *ee*). The corresponding bromination reaction could also be readily achieved, however the enantioselectivity was low to moderate, with a high of 46% *ee*.

66 (10 mol%),
CsCO$_3$ (9 mol%),
toluene, −40 °C, 12 h

(275)

6 examples up to 97% yield
and 61% ee
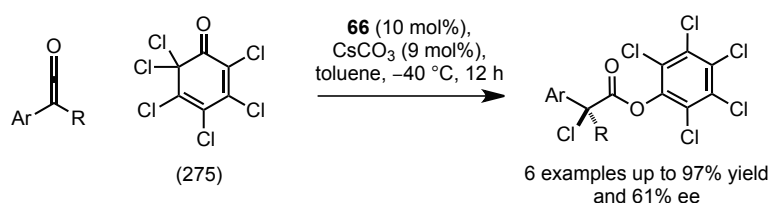
Scheme 119: Catalytic asymmetric halogenation of alkylaryl ketenes.

Efforts to expand the practicality of azolium enolate processes focused on the use of α-aroyloxyaldehydes as bench stable mono-substituted ketene surrogates. A range of differentially substituted α-aroyloxyaldehydes allowed access to δ-lactones *via* an NHC-catalysed [4+2] cycloaddition between azolium enolates and β,γ-unsaturated α-ketoesters. The reaction proceeds with outstanding levels of diastereo- and enantioselectivity (typically >95:5 *dr* and >99% *ee*). Importantly this process has improved utility and practicality when compared to the previous work employing

isolable alkylarylketenes due to the bench stability of α-aroyloxyaldehydes. Although not directly demonstrated, it is envisioned that this protocol would overcome the limitations of scale placed upon the use of alkylarylketenes.
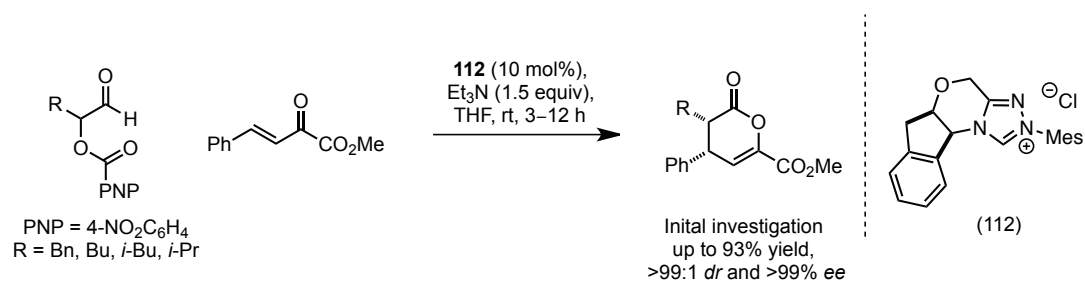
Scheme 120: α-Aroyloxyaldehydes as bench stable mono-substituted ketene surrogates.

Chapter 8: Experimental Information

General experimental information

Reactions involving moisture sensitive reagents were carried out under an argon atmosphere using standard vacuum line techniques in addition to dry solvents. All glassware used was flame dried and cooled under vacuum.

Solvents (THF, CH_2Cl_2, toluene, hexane and Et_2O) were obtained anhydrous and purified by an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40-60 °C. All other solvents were used as supplied without further purification unless stated otherwise.

Unless stated chemicals were purchased from Acros-UK, Sigma-Aldrich, Alfa Aeasar or Fisher.

Potassium bis(trimethylsilyl)amide (KHMDS) was used as a 0.5 M solution in toluene as supplied (Aldrich). Chloral was distilled from CaH_2 before use. The required aldehydes where purified by kugelrohl distillation under reduced pressure prior to use. 2,2,6,6-tetrachlorocyclohexanone (Aldrich) was recrystallised from CH_2Cl_2/pentane.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and −78 °C were obtained using ice/H_2O and CO_2(s)/acetone baths respectively. Temperatures of 0 °C to −50 °C were obtained using an immersion cooler (HAAKE EK 90). Reflux conditions were obtained using an oil bath equipped with a contact thermometer. *In vacuo* refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC_2 vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F_{254} silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution. Flash silica chromatography was performed on Kieselgel 60 silica in the solvent system stated.

^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz, ^{1}H, 75 MHz ^{13}C), a Bruker Avance II 400 (400 MHz, ^{1}H, 376 MHz 19F, 100 MHz ^{13}C) or a Bruker Ultrashield 500 (500 MHz, ^{1}H, 125 MHz ^{13}C) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent as the internal standard. All coupling constants, *J*, are quoted in Hz and reported low to high. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of

doublets, dt (doublet of triplets), dq (doublet of quartets) and td (triplet of doublets). The abbreviation Ar is used to denote aromatic, Ph to denote phenyl, Nap to denote napthyl, Bn to denote benzyl, br to denote broad, and *app* to denote apparent.

Infrared spectra (ν_{max}) were recorded on either a Perkin-Elmer Spectrum GX FT-IR spectrometer using either thin films on NaCl plates, KBr discs or a Shimadzu IRAffinity-1 using a Pike attenuated total reflectance (ATR) accessory.

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected. *Decomp* refers to decomposition.

HPLC analyses were obtained on either a Gilson HPLC consisting of a Gilson 305 pump, Gilson 306 pump, Gilson 811C dynamic mixer, Gilson 805 manometric module, Gilson 401C dilutor, Gilson 213XL sample injector and sample detection was performed with a Gilson 118 UV/vis detector. Or a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatograph, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven which allowed the temperature to be set from 25-40 °C. Separation was achieved using the DACIEL CHIRALPAK or CHIRALCEL column stated. All chiral HPLC traces were compared to the authentic racemic spectrum prepared in analogous fashion.

GC analysis was performed on a Fison 800 gas chromatograph using a CP-Chirasil-Dex CB columnunder the conditions stated.

Mass spectrometry (*m/z*) data were acquired by electrospray ionisation (ESI), electron impact (EI), atmostpheric solids analysis probe (ASAP) or nanospray ionisation (NSI) at the EPSRC National Mass Spectrometry Service Centre, Swansea.

Optical rotations were measured on a Pertin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at rt.

Experimental information for chapter 2

Preparation of acid chlorides

All acid chlorides previously reported in the literature were prepared *via* a slight modification of the method of Smith.[1]

Thionyl chloride (3 equiv) was added to a solution of the corresponding acid (1 equiv) in toluene at room temperature and the reaction mixture was warmed to 80 °C and stirred 12 hours. Solvents were evaporated under reduced pressure and the crude oil purified by Kugelrohr distillation to give the corresponding acid chloride.

(415)-2-(2-Tolyl)hexanoyl chloride

(415)
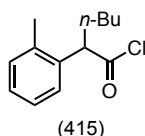
Following the procedure reported by Fu[2] *n*-BuLi 2.5M (46.6 mL, 103 mmol moles, 2.2 equiv) was added dropwise at −78 °C over 15 mins to a solution of 2(2-tolyl)acetic acid (7.00 g, 46.6 mmol, 1.0 equiv) in THF (150 mL). The solution was then warmed to rt and stirred for a further 45 mins before 1-bromobutane (20.0 mL, 186 mmol, 4.0 equiv) was added and the solution stirred overnight at rt. The reaction was quenched *via* carful addition of 5% HCl (75 mL) before extraction with Et_2O (3 × 100 mL) and drying over $MgSO_4$. Filtration and concentration *in vacuo* yielded 8.5 g of crude 2-(2-tolyl)hexanoic acid that was used without further purification.

Thionyl chloride (5.60 mL, 82.3 mmol, 2.0 equiv) was added dropwise to a solution of crude 2-(2-tolyl)hexanoic acid (8.5 g, 41.1 mmol, 1.0 equiv) in toluene 150 mL at 75 °C and stirred overnight. Concentration and kugelrohr distillation 155 – 160 °C (7 mbar) provided the title compound as a pale yellow oil; (8.7 g, 83% yield over 2 steps); ν_{max} (thin film)/cm^{-1} 2958, 1793 (C=O), 1493, 1463, 980, 912 and 740; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.88 (3H, t, *J* 7.1, *n*-Bu*CH*$_3$), 1.20-1.27 (1H, m, *n*-Bu*CH*$_2$), 1.29-1.37 (3H, m, *n*-Bu*CH*$_2$), 1.74-1.83 (1H, m, *n*-Bu *CH*$_2$), 2.12-2.22 (1H, m, *n*-Bu*CH*$_2$), 2.42 (3H, s, Ar*CH*$_3$) 4.24 (1H, *app* t, *J* 7.4, *CH*(Ar)Bu), 7.2-7.24 (4H, m, Ar*H*); ^{13}C NMR (100 mHz CDCl$_3$): δ_C 13.9 (*n*-Bu*CH*$_3$), 19.9 (Ar*CH*$_3$), 22.5 (*n*-Bu*CH*$_2$), 29.3 (*n*-Bu*CH*$_2$), 33.0 (*n*-Bu*CH*$_2$), 59.1 (*CH*(Ar)Bu), 126.8 (Ar*CH*), 127.1 (Ar*CH*), 128.0 (Ar*CH*), 131.0 (Ar*CH*), 134.9 (Ar*C*), 136.7 (Ar*CH*) and 174.9 (*C*=O).

(416)-2-(Naphthalen-2-yl)propanoyl chloride

(416)

Following the procedure reported by Fu:[2] *n*-Buli 2.5M (47.3 mL, 118 mmol moles, 2.2 equiv) was added dropwise at −78 °C over 15 mins to a solution of 1-napthylacetic acid (10.0 g, 57.7 mmoles, 1.0 equiv) in THF (200 mL). The solution was then warmed to rt and stirred for a further 45 mins before methyliodide (5.01 mL, 80.6 mmol, 1.5 equiv) was added and the solution stirred overnight at rt. The reaction was quenched *via* carful addition of 2M HCl (75 mL) before extraction with Et$_2$O (3 × 100 mL) and drying over MgSO$_4$. Filtration and concentration *in vacuo* yielded 6.8 g of crude 2-(naphthalen-2-yl)propanoic acid that was used without further purification. Thionyl chloride (3.70 mL, 51.2 mmol, 1.5 equiv) was added dropwise to a solution of crude 2-(naphthalen-2-yl)propanoic acid (6.8 g, 34.1 mmol, 1.0 equiv) in toluene 50 mL at 75 °C and stirred for 3h. Concentration and kugelrohr distillation 190 – 200 °C (5 mbar) provided the title compound as a pale orange oil; (6.0 g, 47% yield over 2 steps); ν$_{max}$ (thin film)/cm^{-1} 3062, 2985, 1834, 1787 (C=O), 1598, 1512, 918, and 778; ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 1.77 (3H, d, *J* 7.0, C*H$_3$*), 4.92 (1H, q, *J* 7.0, C*H*(Nap)Me), 7.45-7.53 (2H, m, Nap*H*), 7.55-7.64 (2H, m, Nap*H*), 7.87 (1H, d, *J* 7.9, Nap*H*), 7.93 (1H, dd, *J* 8.3, 1.2, Nap*H*) and 8.03 (1H, d, *J* 8.4, Nap*H*); ^{13}C NMR (100 mHz CDCl$_3$): δ$_C$ 18.8 (*C*H$_3$), 53.5 (*C*H(Nap)Me), 122.8 (Nap*C*H), 125.7 (Nap*C*H), 125.9 (Nap*C*H), 126.3 (Nap*C*H), 127.2 (Nap*C*H), 129.2 (Nap*C*H), 129.5 (Nap*C*H), 131.4 (Nap*C*), 134.2 (Nap*C*), 134.4 (Nap*C*) and 176.3 (C=O).

(417)-2-(Naphthalen-2-yl)hexanoyl chloride
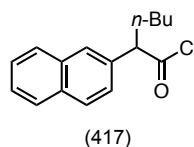
(417)

Following the procedure reported by Fu:[2] *n*-BuLi 2.5M (47.3 mL, 118 mmol moles, 2.2 equiv) was added dropwise at −78 °C over 15 mins to a solution of 1-napthylacetic acid (10.0 g, 57.7 mmol, 1.0 equiv) in THF (200 mL). The solution was then warmed to rt and stirred for a further 45 mins before 1-bromobutane (12.4 mL, 115 mmol, 2.0 equiv) was added and the solution stirred overnight at rt. The reaction

was quenched *via* carful addition of 5% HCl (75 mL) before extraction with Et_2O (3 × 100 mL) and drying over $MgSO_4$. Filtration and concentration *in vacuo* yielded 13.9 g of crude 2-(naphthalen-2-yl)hexanoic acid that was used without further purification. Thionyl chloride (6.30 mL, 86.6 mmol, 1.5 equiv) was added dropwise to a solution of crude 2-(naphthalen-2-yl)hexanoic acid (13.9 g, 57.7 mmol, 1.0 equiv) in toluene 50 mL at 75 °C and stirred for 3 h. Concentration and kugelrohr distillation 200 – 220 °C (5 mbar) provided the title compound as a pale colourless oil; (11.9 g, 79% yield over 2 steps); ν_{max} (thin film)/cm^{-1} 3051, 2958, 1790 (C=O), 1598, 1513, 1466 and 779; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.88 (3H, t, *J* 6.6, *n*-BuC*H*$_3$), 1.26-1.44 (4H, m, *n*-BuC*H*$_2$) 1.94-2.03 (1H, m, *n*-BuC*H*$_2$), 2.31-2.4 (1H, m, *n*-BuC*H*$_2$), 4.78 (1H, *app* t, *J* 7.3, C*H*(Nap)Bu), 7.45-7.55 (3H, m Nap*H*), 7.57-7.61 (1H, m, Nap*H*), 7.86 (1H, d, *J* 7.7 Nap*H*) 7.91 (1H, d, *J* 8.0 Nap*H*) and 8.06 (1H, d, *J* 8.5 Nap*H*); ^{13}C NMR (100 mHz $CDCl_3$): δ_C 14.0 (*n*-BuC*H*$_3$), 22.7 (*n*-BuC*H*$_2$), 29.8 (*n*-BuC*H*$_2$), 33.3 (*n*-BuC*H*$_2$), 58.9 (C*H*(Nap)Bu, 122.8 (NapC*H*), 125.8 (NapC*H*), 126.0 (NapC*H*), 126.2 (NapC*H*), 127.1 (NapC*H*), 129.0 (NapC*H*), 129.4 (NapC*H*), 131.7 (Nap*C*), 132.7 (Nap*C*), 134.3 (Nap*C*) and 175.5 (C=O).

Preparation of ketenes

Representative procedure:

(146)-Ethylphenylketene
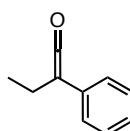
(146)

A flame dried two-neck round bottom flask separated by a sintered adaptor to a second two-neck round bottom flask under an argon atmosphere is charged with strictly anhydrous Et_2O (45 mL), 2-phenylbutanoyl chloride (3.00 g, 16.4 mmol, 1.0 equiv) and cooled to 0 °C. Dropwise addition over 30 min of Et_3N, (2.52 mL, 18.1 mmol, 1.1 equiv) formed a bright yellow solution and a white precipitate that was stirred overnight at 0 °C. The solution was then warmed to rt after which filtration under argon and concentration gave a bright yellow oil; Transfer *via* cannula to a flame dried kugelrohl flask and distillation 80-90 °C (5 mbar) ^{3} gave ethylphenylketene as a light yellow oil; (1.4 g, 60% yield); ^{1}H NMR (300 MHz,

CDCl$_3$) δ_H 1.24 (3H, t, *J* 7.4*,* CH$_2$C*H*$_3$), 2.44 (2H, q, *J* 7.4, C*H*$_2$CH$_3$), 7.02-7.10 (3H, m, Ph*H*-3,4,5) and 7.28-7.35 (2H, m, Ph*H*-2,6).

(418)-Methylphenylketene
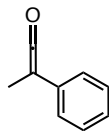
(418)

Following the representative procedure: 2-phenylpropanoyl chloride (4.05g, 24.0 mmol, 1.0 equiv), Et$_3$N (3.34 mL, 24.0 mmol, 1.0 equiv) in Et$_2$O (50 mL) at 0 °C overnight gave, after kugelrohl distillation 60-80 °C (5 mbar) {literature 50 °C, (5 mbar)}[3] a yellow/orange oil; (1.44 g, 45% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 1.92 (3H, s, C*H*$_3$), 6.93-6.95 (2H, m, Ph*H*), 6.97-7.01 (1H, m, Ph*H*) and 7.21-7.25 (2H, m, Ph*H*).

(419)-Butylphenylketene
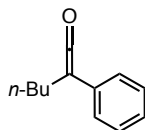
(419)

Following the representative procedure: 2-phenylhexanoyl chloride (3.00 g, 14.2 mmol, 1.0 equiv), Me$_2$EtN (1.70 mL, 15.7 mmol, 1.1 equiv) in Et$_2$O (45 mL) at 0 °C overnight gave, after kugelrohl distillation 110-120 °C (5 mbar) {literature 88 °C (2 mbar)}[4] a yellow/orange oil; (1.26 g, 51% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.87 (3H, *app* t, *J* 7.2, *n*-Bu*H*), 1.30-1.53 (4H, m, *n*-Bu*H*), 2.32 (2H, t, *J* 7.4, *n*-Bu*H*), 6.93-7.01 (3H, m, Ar*H*) and 7.19-7.25 (2H, m, Ar*H*).

(60)-*i*-Butylphenylketene
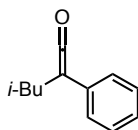
(60)

Following the representative procedure: 4-methyl-2-phenylpentanoyl chloride (3.80 g, 18.0 mmol, 1.0 equiv), Me$_2$EtN (2.15 mL, 20.0 mmol, 1.1 equiv) in Et$_2$O (45 mL) at 0 °C overnight gave, after kugelrohl distillation 110-117 °C (5 mbar) {literature 37-46

°C, (1 mbar)$\}^5$ a yellow/orange oil; (1.75 g, 56% yield); ^{1}H NMR (300 MHz, CDCl$_3$) 0.92 (6H, d, *J* 6.6, *i*-Bu(C*H*$_3$)$_2$), 1.66-1.83 (1H, m, *i*-BuC*H*), 2.19 (2H, d, *J* 7.0, *i*-BuC*H*$_2$), 6.95-7.01, (3H, m, Ph*H*-3,4,5) and 7.17-7.25 (2H, m, Ph*H*-2,6).

(420)-Methyl-4-tolylketene
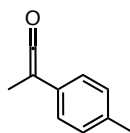
(420)

Following the representative procedure: 2-(4-tolyl)propanoyl chloride (3.16 g, 17.3 mmol, 1.0 equiv), Et$_3$N (2.42 mL, 17.3 mmol, 1.0 equiv) in Et$_2$O (40 mL) at 0 °C overnight gave, after kugelrohl distillation 110 °C (7 mbar) a yellow/orange oil; (1.81 g, 72% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.90 (3H, s, C*H*$_3$), 2.23 (3H, s, ArC*H*$_3$), 6.34 (2H, d, *J* 8.2, Ar*H*) and 7.04 (2H, d, *J* 8.2, Ar*H*).

(421)-Ethyl-4-tolylketene
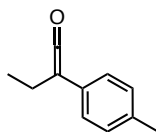
(421)

Following the representative procedure: 2-(4-tolyl)butanoyl chloride (2.16 g, 11.0 mmol, 1.0 equiv), Et$_3$N (1.53 mL, 11.0 mmol, 1.0 equiv) in Et$_2$O (40 mL) at 0 °C overnight gave, after kugelrohl distillation 110-120 °C (7 mbar) {literature 68-72 °C, (0.4 mbar)$\}^6$ a yellow/orange oil; (0.92 g, 52% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.29 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.40 (3H, s, ArC*H*$_3$), 2.50 (2H, q, *J* 7.4, C*H*$_2$CH$_3$), 7.02 (2H, d, *J* 8.1, Ar*H*) and 7.21 (2H, d, *J* 8.1, Ar*H*).

(422)-Ethyl-4-flourophenylketene
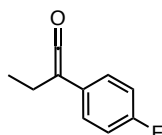
(422)

Following the representative procedure: 2-(4-fluorophenyl)butanoyl chloride (2.70 g, 13.5 mmol, 1.0 equiv), EtMe$_2$N (1.60 mL, 14.8 mmol, 1.1 equiv) in Et$_2$O (40 mL) at 0 °C overnight gave, after kugelrohl distillation 104-110 °C (7 mbar); a yellow/orange

oil; (1.21 g, 55% yield); ν_{max} (thin film)/cm^{-1} 2100; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.13 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.33 (2H, q, *J* 7.4, C*H*$_2$CH$_3$) and 6.87-7.97 (4H, m, Ar*H*); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 12.9 (*C*H$_3$), 17.5 (*C*H$_2$CH$_3$), 41.1 (*C*=C=O), 116.1 (d, *J* 21.7, Ar*C*H-3,5), 125.5 (d, *J* 7.6, Ar*C*H-2,6), 128.5 (d, *J* 3.1, Ar*C*-1), 160.5 (d, *J* 243.4, Ar*C*-4) and 205.7 (C=*C*=O).

(423)-Ethyl-4-chlorophenylketene

(423)
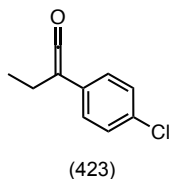
Following the representative procedure: 2-(4-chlorophenyl)butanoyl chloride (763 mg, 3.51 mmol, 1.0 equiv), Et$_3$N (0.49 mL, 3.51 mmol, 1.0 equiv) in Et$_2$O (20 mL) at 0 °C overnight gave, after kugelrohl distillation 125-135 °C (7 mbar); a yellow/orange oil; (368 mg, 56% yield); ν_{max} (thin film)/cm^{-1} 2097; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.34 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.53 (2H, q, *J* 7.4, C*H*$_2$CH$_3$), 7.05-7.09 (2H, m, Ar*H*) and 7.37-7.42 (2H, m, Ar*H*).

(444)-Methyl-4-chlorophenylketene

(444)
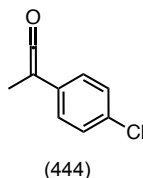
Following the representative procedure: 2-(4-chlorophenyl)propanoyl chloride (2.3 g, 11.3 mmol, 1.0 equiv), Me$_2$EtN (1.35 mL, 12.5 mmol, 1.1 equiv) in Et$_2$O (45 mL) at 0 °C overnight gave, after kugelrohl distillation 118 °C (7 mbar); a yellow/orange oil; (1.0 g, 53% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.91 (3H, s, C*H*$_3$), 6.85 (2H, d, *J* 8.7, Ar*H*) and 7.20 (2H, d, *J* 8.7, Ar*H*).

(424)-Ethyl-4-bromophenylketene

(424)
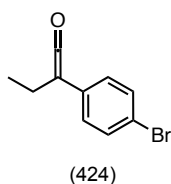
Following the representative procedure: 2-(4-bromophenyl)butanoyl chloride (5.00 g, 19.1 mmol, 1.0 equiv), Et$_2$MeN (2.30 mL, 21.0 mmol, 1.1 equiv) in Et$_2$O (45 mL) at 0 °C overnight gave, after kugelrohl distillation 180 °C (7 mbar); a yellow/orange oil; (1.21 g, 28% yield); ν_{max} (thin film)/cm^{-1} 2100; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.13 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.33 (2H, q, *J* 7.4, C*H*$_2$CH$_3$), 6.87-7.97 and (4H, m, Ar*H*); ^{13}C NMR (75 mHz CDCl$_3$): δ_C 11.7 (*C*H$_3$), 15.9 (*C*H$_2$CH$_3$), 40.7 (*C*=C=O), 116.2 (Ar*C*-4), 124.4 (Ar*C*H), 130.9 (Ar*C*H), and 203.2 (C=*C*=O), Ar*C*-1 could not be resolved.

(425)-Ethyl-4-methoxyphenylketene

(425)
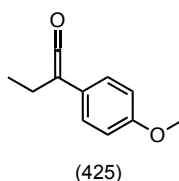
Following the representative procedure: 2-(4-methoxyphenyl)butanoyl chloride (3.00 g, 14.1 mmol, 1.0 equiv), Et$_3$N (3.93 mL, 28.2 mmol, 2.0 equiv) in Et$_2$O (45 mL) at 0 °C overnight gave, after kugelrohl distillation 140-150 °C (3 mbar); a yellow/orange oil; (1.19 g, 48% yield); ν_{max} (thin film)/cm^{-1} 2096; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.21 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.41 (2H, q, *J* 7.4, C*H*$_2$CH$_3$), 3.79 (3H, s, ArC*H*$_3$), 6.86-6.91 (2H, m, Ar*H*-3,5) and 6.95-6.99 (2H, m, Ar*H*-2,6).

(213)-*i*-Propyl-3-thionylketene

(213)
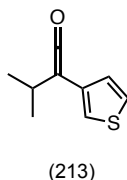
Following the literature procedure of Fu:[7] 3-methyl-2-(thiophen-3-yl)butanoyl chloride (2.27 g, 11.2 mmol, 1.0 equiv), Me$_2$EtN (5.46 mL, 50.4 mmol, 4.5 equiv) in THF (30 mL) at 0 °C for 10 min then rt for 4.5 h gave, after kugelrohl distillation 85-90 °C (3 mbar) {literature 71-73 °C}[7] a yellow/orange oil; (1.09 g, 59% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.25 (6H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 2.77 (1H, sep, *J* 6.7,

C*H*(CH$_3$)$_2$), 6.79-6.82 (2H, m, Ar*H*) and 7.33-7.35 (1H, m, Ar*H*).

(426)-Methyl-2-tolylketene
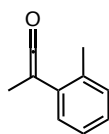
(426)

Following the literature procedure of Fu:[8] 2-(2-tolyl)propanoyl chloride (3.55 g, 19.4 mmol, 1.0 equiv), Me$_2$EtN, added at 0 °C over 5 mins (10.5 mL, 97.2 mmol, 5.0 equiv) in THF (45 mL) then rt overnight gave, after kugelrohl distillation 69 °C (3 mbar) {literature 43 °C, (0.5 mbar)}[8] (997 mg, 35% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 1.97 (3H, s, C*H*$_3$), 2.23 (3H, s, ArC*H*$_3$), 6.95-7.01 (2H, m, Ar*H*), 7.05-7.07 (1H, m, Ar*H*) and 7.10-7.15 (1H, m, Ar*H*).

(427)-Ethyl-2-tolylketene
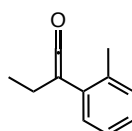
(427)

Following the literature procedure of Fu:[5] 2-(2-tolyl)butanoyl chloride (3.45 g, 17.5 mmol, 1.0 equiv), Me$_2$EtN, added in a single charge (7.60 mL, 70.2 mmol, 4.0 equiv) in THF (40 mL) at 0 °C overnight gave, after kugelrohl distillation 97 °C (3 mbar) {literature 32-33 °C, (0.3 mbar)}[5] (997 mg, 35% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.18 (3H, t, *J* 7.4 CH$_2$C*H*$_3$), 2.32 (3H, s, ArC*H*$_3$), 2.48 (2H, q, *J* 7.4 C*H*$_2$CH$_3$) and 7.07-7.23 (4H, m, Ar*H*).

(428)-Ethyl-2-tolylketene

n-Bu
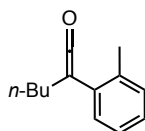
(428)

Following the representative procedure: 2-(2-tolyl)hexanoyl chloride (3.39 g, 15.1 mmol, 1.0 equiv), Me$_2$EtN, added in a single charge (7.40 mL, 68.0 mmol, 4.5 equiv) in THF (45 mL) at 0 °C overnight gave, after kugelrohl distillation 147 °C (3 mbar); (1.56 g, 55% yield); ν_{max} (thin film)/cm^{-1} 2095; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.94

(3H, t, *J* 7.2, *n*-Bu), 1.38-1.55 (4H, m, *n*-Bu), 2.33 (3H, s, ArC*H*$_3$), 2.46 (2H, t, *J* 7.3, *n*-Bu) and 7.09-7.24 (4H, m, Ar*H*); ^{13}C NMR (75 mHz CDCl$_3$): δ$_C$ 13.9 (*n*-Bu*C*H$_3$), 20.9 (Ar*C*H$_3$), 22.4 (*n*-Bu*C*H$_2$), 26.4 (*n*-Bu*C*H$_2$), 30.5 (*n*-Bu*C*H$_2$), 35.7 (*C*=C=O), 125.7 (Ar*C*H), 126.5 (Ar*C*H), 126.7 (Ar*C*H), 130.6 (Ar*C*H), 131.0 (Ar*C*), 135.7 (Ar*C*) and 200.1 (C=*C*=O).

(179)-Ethyl-(2-chlorophenyl)ketene
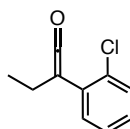
(179)

Following the literature procedure of Ye[7]: 2-(2-chlorophenyl)butanoyl chloride (3.00 g, 13.8 mmol, 1.0 equiv), Me$_2$EtN (5.99 mL, 55.3 mmol, 4.0 equiv) in Et$_2$O (45 mL) at 0 °C overnight gave, after kugelrohl distillation 137 °C (3 mbar) {literature 65-67 °C, (0.2 torr)}[6] (1.32g, 52% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 1.14 (3H, t, *J* 7.4 CH$_2$C*H*$_3$), 2.42 (2H, q, *J* 7.4 C*H*$_2$CH$_3$), 6.94-6.98 (2H, m, Ar*H*), 7.14-7.18 (1H, m, Ar*H*) and 7.24 (1H, dd, *J* 1.3, 8.3 Ar*H*).

(208)-Ethyl-2-methoxyphenylketene
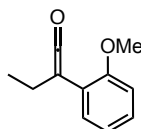
(208)

Following the representative procedure: 2-(2-methoxyphenyl)butanoyl chloride (3.81 g, 17.9 mmol, 1.0 equiv), Me$_2$EtN (7.6 mL, 70.2 mmol, 4.0 equiv) in THF (30 mL) at 0 °C overnight gave, after kugelrohl distillation 140 °C (3 mbar) {literature 60 °C, 0.3 mbar}; a yellow/orange oil; (1.19 g, 48% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 1.15 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.34 (2H, q, *J* 7.4, C*H*$_2$CH$_3$), 3.79 (3H, s, ArC*H*$_3$), 6.69-6.71 (1H, m, Ar*H*), 6.81-6.83 (1H, m, Ar*H*), 6.89 (1H, *app* td, *J* 7.5, 1.2, Ar*H*) and 6.95-6.99 (1H, m, Ar*H*)

(429)-Methyl-2-napthylketene

(429)
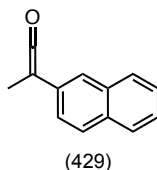
Following the representative procedure: 2-(naphthalen-2-yl)propanoyl chloride (2.79 g, 12.8 mmol, 1.0 equiv), Me_2EtN, added in a single charge (5.50 mL, 51.0 mmol, 4.0 equiv) in THF (25 mL) at 0 °C overnight gave, after kugelrohl distillation 180 °C (3 mbar); (960 mg, 42% yield); ν_{max} (thin film)/cm^{-1} 2099; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 2.22 (3H, s, CH_3), 7.35 (1H, dd, J 7.3 1.1, Nap$H$), 7.46-7.58 (3H, m, Nap$H$), 7.73 (1H, d, J 8.2, Nap$H$), 7.89 (1H, dd, J 6.8, 2.6, Nap$H$) and 8.04-8.07 (1H, m, Nap$H$); ^{13}C NMR (100 mHz CDCl$_3$): δ_C 12.4 (CH$_3$), 29.3 (C=C=O), 124.2 (NapCH), 124.7 (NapCH), 125.9 (NapCH), 126.0 (NapCH), 126.1 (NapCH), 126.8 (NapCH), 129.0 (NapCH), 130.0 (NapC), 131.1 (NapC), 134.2 (NapC) and 200.3 (C=C=O).

(196)-Ethyl-2-napthylketene

(196)
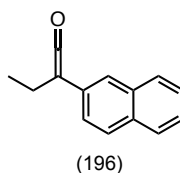
Following the literature procedure of Fu:[9] 2-(naphthalen-2-yl)butanoyl chloride (8.80 g, 37.8 mmol, 1.0 equiv), Me_2EtN, (16.0 mL, 148 mmol, 4.0 equiv) in THF (50 mL) at 0 °C overnight gave, after kugelrohl distillation 175 °C (3 mbar) {literature 80 °C, (0.2 torr)}[9] (3.04 g, 41% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.25 (3H, t, J 7.4, CH$_2$CH_3), 2.63 (2H, q, J 7.4, CH_2CH$_3$), 7.41-7.60 (4H, m, Nap$H$), 7.77 (1H, d, J 8.0, Nap$H$) 7.88-7.91 (1H, m, Nap$H$) and 8.08-8.12 (1H, m, Nap$H$).

(430)-Butyl-2-napthylketene

(430)
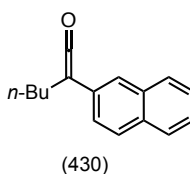
Following the representative procedure: 2-(naphthalen-2-yl)hexanoyl chloride (6.04 g, 23.0 mmol, 1.0 equiv), Me_2EtN, added in a single charge (10.0 mL, 92.6 mmol, 4.0

equiv) in THF (30 mL) at 0 °C overnight gave, after kugelrohl distillation 198 °C (3 mbar); (2.78 g, 54% yield); ν_{max} (thin film)/cm^{-1} 2098; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.96 (3H, t, *J* 7.2, *n*-Bu), 1.44-1.60 (4H, m, *n*-Bu), 2.61 (2H, t, *J* 7.3, *n*-Bu), 7.42-7.61 (4H, m, Nap*H*), 7.78 (1H, d, *J* 7.9, Nap*H*), 7.90 (1H, dd, *J* 7.4, 2.1, Nap*H*) and 8.11-8.14 (1H, m, Nap*H*) ^{13}C NMR (100 mHz CDCl$_3$): δ_C 13.9 (*n*-Bu*C*H$_3$), 22.4 (*n*-Bu*C*H$_2$), 27.1 (*n*-Bu*C*H$_2$), 30.7 (*n*-Bu*C*H$_2$), 34.2 (*C*=C=O), 124.6 (Nap*C*H), 125.8 (Nap*C*H), 126.0 (Nap*C*H), 126.2 (Nap*C*H), 126.3 (Nap*C*H), 127.1 (Nap*C*H), 128.9 (Nap*C*H and Nap*C*), 131.9 (Nap*C*), 134.3 (Nap*C*) and 199.4 (C=*C*=O).

(194)-*i*-Propylphenylketene

(194)
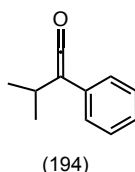
Following the representative procedure: 3-methyl-2-phenylbutanoyl chloride (3.65 g, 18.6 mmol) and Me$_2$EtN (9.02 mL, 83.5 mmol, 4.5 equiv) in THF at rt overnight gave after Kugelrohr distillation 87-92 °C (5 mbar) {literature 90-94 °C (2 mbar)} [10] (1.48 g, 50%); δ_H (300 MHz, CDCl$_3$) 1.23 (6H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 2.83 (1H, sept, *J* 6.7, C*H*(CH$_3$)$_2$), 7.05-7.10 (3H, m, Ar*H*) and 7.28-7.34 (2H, m, Ar*H*)

Synthesis of precatalyst 66

The following series of reactions were carried out at AstraZeneca Process Research and Development facility in Macclesfield. All anhydrous solvents and chemicals were purchased from Aldrich and used without further purification. ^{1}H nuclear magnetic resonance (NMR) spectra were acquired on a Bruker Avance II 400 (400 MHz, ^{1}H) and room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and –78 °C were obtained using ice/H$_2$O and CO$_2$(s)/acetone baths respectively. (±)-(**66**) was prepared in an identical manner to that reported for (*S*)-(**66**)

(130)-(*S*)-Methyl 5-oxopyrrolidine-2-carboxylate
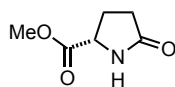
(130)

Following the procedure of O'Leary;[11] Amberlyst 15 wet resin (40 g, 40% w/w) was added to a solution of (*S*)-pyroglutamic acid (100 g, 7.74 mol) in methanol (400 ml). The mixture was refluxed for 24 h, cooled, filtered and concentrated *in vacuo* to provide the product as a yellow oil with no purification necessary; (108 g, 97%); Data in accordance with the literature;[11] ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 2.24-2.48 (4H, m, C*H*$_2$), 3.77 (3H, s, OC*H*$_3$), 4.20-4.28 (1H, m, C*H*) and 6.86 (1H, br s, N*H*).

(131)-(*S*)-5-(Hydroxydiphenylmethyl)pyrrolidin-2-one
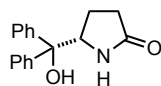
(131)

A solution of **130** (46.0 g, 0.32 moles, 1.0 equiv) in anhydrous THF (500 mL) in a 2 L four neck round bottom flask equipped with an overhead stirrer under a nitrogen atmosphere was cooled to −78 °C. Phenyllithium as a 1.8 M in Bu$_2$O (625 mL, 1.23 mol, 3.5 equiv) was added *via* cannula over 1 h as to maintain the reaction temperature below −50 °C. The solution was then allowed to warm to rt over 12 h before cooling to 0 °C. Saturated NH$_4$Cl(aq) (250 mL) was added dropwise, maintaining the reaction temperature <10 °C before a more rapid second addition of saturated NH$_4$Cl(aq) (250 mL). Following the second addition a thick white slurry formed that was directly filtered and dried in a vacuum oven to provide crude **131**. Partial concentration of the organic filtrate and precipitation on standing for 12 h provided a second crop of crude **131**.[12] The combined crude was heated to near reflux in EtOAc (500 mL) before the addition of the minimum quantity of methanol to allow dissolution (50 mL). The solution was cooled to 50 °C and held for 0.5 h at which point **131** crystallised. The slurry was further cooled to 25 °C before filtration provided **131** as a colourless solid[13]; (41.2 g, 57% yield); mp 174-176 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H Data in accordance with the literature.[14] 1.82-1.91 (1H, m, C*H*$_2$), 1.98-2.05 (1H, m, CH$_2$), 2.12-2.20 (1H, m, C*H*$_2$), 2.22-2.31 (1H, m, C*H*$_2$), 4.61-4.62, (1H, m, C*H*), 7.19-7.24 (2H, m, Ph*H*), 7.26-7.30 (2H, m, Ph*H*), 7.35-7.38 (2H, m, Ph*H*), 7.45-7.48 (2H, m, Ph*H*) and 7.48-7.51 (2H, m, Ph*H*)

(132)-(*S*)-5-(((*t*-Butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidin-2-one
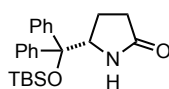
(132)

Following the procedure of Enders:[14] Tert-butyldimethylsilyl triflate (84.8 mL, 0.369 mol, 2.5 equiv) and 2,6-lutidine (51.3 mL, 0.443 mol, 3.0 equiv) were added dropwise to a solution of **131** (39.5 g, 0.148 mol, 1.0 equiv) in CH_2Cl_2 (1 L) at 0 °C. After being stirred overnight at room temperature, the reaction mixture was quenched with 5% aqueous HCl (200 mL). The aqueous layer was extracted (CH_2Cl_2, 3 × 100 mL) and the organics combined, dried (Na_2SO_4) before concentration *in vacuo* to yield crude **132** as a colourless solid. The solid was then washed with hexane, dissolved in EtOAc and loaded onto a 10 cm diameter sinter filter packed with 5 cm of silica. This was eluted with a 1:1 mixture of petrol:EtOAc collecting the first 1 L, concentration in vacuo yielded pure **132** as a colourless solid; (32.4 g, 57%); mp 150-152 °C; $[\alpha]_D^{20}$ −46 (*c* 1.00, CHCl₃) {literature value[14] −65 (*c* 1.01, CHCl₃)}; ^1H NMR (400 MHz, CDCl₃) δ_H −0.39 (3H, s, SiC*H₃*), −0.34 (SiC*H₃*), 0.95 (9H, s, Si*t*-Bu*H*), 0.97-1.09 (1H, m, C*H₂*), 1.82-1.90 (1H, m, C*H₂*), 2.06-2.21 (2H, m, C*H₂*), 4.64 (1H, dd, *J* 8.5, 3.1, CH), 5.80 (1H, br s, N*H*) and 7.30-7.36 (10H, m, Ph*H*). Data in accordance with the literature.[14]

(66)-(*S*)-5-(((*t*-Butyldimethylsilyl)oxy)diphenylmethyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate
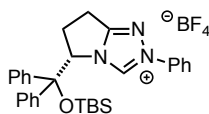
(66)

To an oven dried 250 mL four neck round bottom flask under nitrogen was added **132** (20 g, 52.4 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (50 mL). To this solution was added trimethyloxonium tetrafluoroborate (8.49 g, 57.7 mmol, 1.1 equiv) and the solution stirred for 6 h[15] after which NMR indicated the absence of starting material. Phenylhydrazine (5.70 mL, 57.7 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 12 h. The solution was concentrated *in vacuo* to a pale yellow foam that was used in the next step without further purification. The crude was suspended in triethylorthoformate (50 mL) heated to 80 °C and the minimum quantity of

methanol was added to facilitate dissolution. The solution was heated for 6 h[16] before cooling to rt overnight. The precipitated precatalyst **66** was filtered and washed with Et$_2$O and cold EtOAc to provide crude **66**. This was then recrystallised in methanol (~150 mL) to provide (*S*)-**66** as a dark yellow/brown solid; (18.3 g, 61%); mp 182-186 °C {literature value[17] 210-220} °C; $[\alpha]_D^{20}$ −123 (*c* 1.00, MeCN) {literature value[17] −112 (*c* 0.5, MeCN)}; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H −0.35 (3H, s, SiC*H*$_3$), −0.32 (SiC*H*$_3$), 0.94 (9H, s, Si*t*-Bu*H*), 1.61-1.70 (1H, m, C*H*$_2$), 2.74-2.81 (1H, m, C*H*$_2$), 2.86-2.93 (1H, m, C*H*$_2$), 3.15-3.26 (1H, m, C*H*$_2$), 6.12 (1H, dd, *J* 8.9, 1.2, C*H*), 7.14 (2H, br s, NPh*H*-2,6), 7.34 (2H, t, *J* 7.4, Ph*H*), 7.40-7.47 (4H, m, Ph*H*), 7.51, 7.57 (5H, m, Ph*H*), 7.67-7.71 (2H, m, Ph*H*), and 9.08 (1H, s, NC*H*N). Data in accordance with the literature.[14]

Experimental information for chapter 3

General experimental procedures

General procedure (1): Lactonisation and chlorination at 0 °C.

To a flame dried Schlenk flask under an argon atmosphere was added NHC precatalyst (0.10 mmol), base (0.09 mmol) and toluene (6 mL) and the mixture stirred for 15 min. The mixture was then cooled to 0 °C in an ice/H$_2$O bath followed by addition of a 0 °C solution of the requisite ketene (1.00 mmol) in toluene (12 mL), immediately followed by chloral (1.00 mmol). Toluene (2 mL) was added to wash residual reactants into solution and the reaction was stirred for the stated time at 0 °C before opening the flask to the air for 30 min and concentration *in vacuo*. The resulting crude residue with the stated diastereomeric ratio was purified by flash silica chromatography (Et$_2$O :petrol) to provide either the isolated *anti* or *syn* diastereomer as stated.

General procedure (2): Lactonisation and chlorination at 0 °C with dropwise ketene addition.

To a flame dried Schlenk flask under an argon atmosphere was added NHC precatalyst (0.10 mmol), base (0.09 mmol) and toluene (6 mL) and the mixture stirred

for 15 min. The mixture was then cooled to 0 °C in an ice/H$_2$O bath followed by addition of chloral (1.00 mmol). A 0 °C solution of the requisite ketene (1.00 mmol) in toluene (12 mL) was subsequently added over 0.5 h. The reaction was stirred for an additional 3 h at 0 °C before opening the flask to the air for 0.5 h and concentration *in vacuo*. The resulting crude residue with the stated diastereomeric ratio was purified by flash silica chromatography (Et$_2$O :petrol) to provide either the isolated *anti* or *syn* diastereomer as stated.

(147)-*Anti*-(3*S*,4*R*)-3-ethyl-3-phenyl-4-(trichloromethyl)oxetan-2-one and **(148)**-*Syn*-(3*S*,4*R*)-3-ethyl-3-phenyl-4-(trichloromethyl)oxetan-2-one
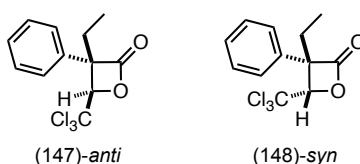
(147)-*anti*   (148)-*syn*

Following general procedure **1**: NHC precatalyst **66** (28.5 mg, 0.05 mmol, 0.10 equiv), KHMDS (0.09 mL, 0.045 mmol, 0.09 equiv), ethylphenylketene **146** (73.0 mg, 0.50 mmol, 1.00 equiv) and chloral (0.05 mL, 0.50 mmol, 1.0 equiv) in toluene (10 mL) at 0 °C for 3 h gave crude product (*dr* 72:28, *anti*:*syn*) that was purified by flash silica chromatography (2% Et$_2$O :petrol) to give:

Anti (eluted first) as a colourless solid; (90 mg, 61% yield); mp 90-92 °C; $[\alpha]_D^{20}$ +38.0 (*c* 0.65, MeOH); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (3*S*,4*R*): 4.7 min, t_R minor (3*R*,4*S*): 8.6 min, 92% *ee*; ν_{max} (KBr)/cm^{-1} 2986, 1829 (C=O), 1493, 1450, 1097, 832, 808 and 758; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.86 (3H, t, *J* 7.4, CH$_2$*CH$_3$*), 2.04 (1H, dq, *J* 14.0, 7.2, C*H$_A$*H$_B$CH$_3$), 2.85 (1H, dq, *J* 14.0, 7.2, CH$_A$*H$_B$*CH$_3$), 5.06 (1H, s, C*H*CCl$_3$), and 7.34-7.41 (1H, m, Ph*H*-4) and 7.42-7.44 (4H, m, Ph*H*); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 8.9 (CH$_2$*C*H$_3$), 24.6 (*C*H$_2$CH$_3$), 69.9 (*C*(Ph)Et), 88.1 (*C*H(CCl$_3$)), 95.6 (*C*Cl$_3$), 126.4 (Ph*C*H), 128.3 (Ar*C*-4)*,* 129.3 (Ph*C*H), 137.0 (Ph*C*-1) and 168.9 (*C*=O); *m/z*: (ESI+) 292.0 (M(^{35}Cl))$^+$ HRMS [M+]: found 291.9817; calcd 291.9819 (–) 0.7 ppm;

Syn (eluted second) as a colourless solid; (41 mg, 28% yield); mp 88-90 °C; $[\alpha]_D^{20}$ +43 (*c* 1.1, MeOH); Chiral HPLC analysis; Chiralcel OJ-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (3*S*,4*S*): 9.9 min, t_R minor (3*R*,4*R*): 12.0 min, 88% *ee*; ν_{max} (KBr)/cm^{-1} 2985, 1840 (C=O), 1497, 1450, 1099, 830 (CCl$_3$), 803 (CCl$_3$), 754

(CCl$_3$); ^{1}H NMR (400 MHz CDCl$_3$): δ$_H$ 0.95 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.32-2.47 (2H, m, C*H$_2$*CH$_3$), 4.94 (1H, s, C*H*CCl$_3$), 7.33-7.35 (3H, m, Ph*H*-3,4,5) and 7.46-7.48 (2H, m, Ph*H*-2,6); ^{13}C NMR (100 MHz CDCl$_3$): δ$_C$ 8.8 (CH$_2$*C*H$_3$), 33.2 (*C*H$_2$CH$_3$), 69.6 (*C*(Ph)Et), 86.9 (*C*H(CCl$_3$)), 95.5 (*C*Cl$_3$), 128.2 (Ph*C*H), 128.4 (Ph*C*-4), 128.3 (Ph*C*H), 131.4 (Ph*C*-1), and 169.2 (*C*=O); *m/z*: (ESI+) 292.0 (M(^{35}Cl))$^+$ HRMS [M+]: found 291.9819; calcd 291.9819 (–/+) 0.0 ppm.

(147)-*Anti*-(3*S*,4*R*)-3-ethyl-3-phenyl-4-(trichloromethyl)oxetan-2-one and **(148)**-*Syn*-(3*S*,4*S*)-3-ethyl-3-phenyl-4-(trichloromethyl)oxetan-2-one: Preparative scale

(147)-*anti*   (148)-*syn*
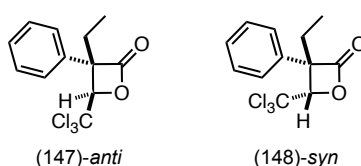
Scheme 43. Following general procedure **2**: NHC precatalyst **66** (214 mg, 0.38 mmol, 0.025 equiv), KHMDS (0.72 mL, 0.36 mmol, 0.024 equiv), ethylphenylketene **146** (2.19 g, 15.0 mmol, 1.00 equiv) and chloral (1.46 mL, 15.0 mmol, 1.0 equiv) in toluene 300 mL at 0 °C for 3 h gave crude product (*dr* 74:26, *anti*:*syn*) that was purified by flash silica chromatography (2% Et$_2$O :petrol)

Anti (eluted first) as a colourless solid; (2.40 g, 54% yield); mp 88-86 °C; $[\alpha]_D^{20}$ +54 (*c* 0.71, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*R*): 4.7 min, t$_R$ minor (3*R*,4*S*): 9.7 min, 94% *ee*;

Syn (eluted second) as a colourless solid; (0.96 g, 22% yield); mp 74-78 °C; $[\alpha]_D^{20}$ +81 (*c* 0.51, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*S*): 8.1 min, t$_R$ minor (3*R*,4*R*): 11.6 min, 92% *ee*;

A portion of *anti* (296 mg, 1.01 mmol) **147** and *syn* (248 mg, 0.845 mmol) **148** were recrystallised from petrol/EtOAc to provide material of >99% *ee* for X-ray crystallographic analysis.

Anti (254 mg, 82% yield); mp 95-96 °C; $[\alpha]_D^{20}$+54 (*c* 0.12, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*R*): 4.7 min, t$_R$ minor (3*R*,4*S*): 8.6 min, >99% *ee*; *Syn* (221, 89% yield); mp 92-94 °C $[\alpha]_D^{20}$ +118 (*c* 0.17, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (3%

IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (3S,4S): 10.0 min, t_R minor (3R,4R): 13.5 min, >99% *ee*;

(152)-*Anti*-(3S,4R)-3-methyl-3-phenyl-4-(trichloromethyl)oxetan-2-one   and   **(152)**-*Syn*-(3S,4S)-3-methyl-3-phenyl-4-(trichloromethyl)oxetan-2-one

(152)-*anti*   (152)-*syn*
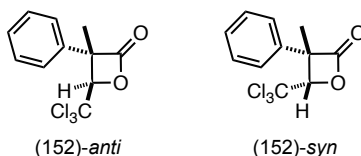
Scheme 40. To a flame dried Schlenk flask under an argon atmosphere was added NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv) and toluene (6 mL) and the mixture stirred for 15 min. The mixture was then cooled to 0 °C in an ice/H$_2$O bath followed by addition of chloral (0.10 mL, 1.00 mmol, 1.0 equiv). A 0 °C solution of the methylphenylketene **418** (132 mg, 1.00 mmol, 1.0 equiv) in toluene (14 mL) was subsequently added dropwise over 0.5 h. The reaction was stirred for an additional 3 h at 0 °C before opening the flask to the air for 30 min. The solution was then passed through a plug of silica, washed with toluene and concentrated *in vacuo* to yield the combined *syn* and *anti* diastereomers (*dr* 88:12, *anti*:*syn*) as a colourless solid; (265 mg, 95% yield):

Anti; mp 68–72 °C; $[\alpha]_D^{20}$ +21 (*c* 0.15, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:Hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (3S,4R): 5.4 min, t_R minor (3R,4S): 11.4 min, 82% *ee*; ν_{max} (KBr)/cm^{-1} 3060, 1846 (C=O), 1266, 1086, 939 and 740; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.89 (3H, s, CH_3), 5.16 (1H, s, CHCCl$_3$) and 7.36-7.46 (5H, m, PhH), ^{13}C NMR (75 MHz CDCl$_3$): δ_C 19.4 (CH$_3$), 65.5 (*C*(Ph)Me), 87.2 (*C*H(CCl$_3$)), 95.6 (*C*Cl$_3$), 125.4 (Ph*C*H), 128.4 (Ph*C*-4), 129.5 (Ph*C*H), 139.5 (*C*Ph-1) and 169.7 (*C*=O); *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS C$_{11}$H$_{13}$O$_2$NCl$_3$ [M+NH$_4$]$^+$: found 296.0006; calcd 296.0003 (−) 1.1 ppm.

Syn; Chiral HPLC analysis; Chiralpak AS-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (3S,4S): 16.6 min, t_R minor (3R,4R): 20.2 min, 78% *ee*; ^{1}H NMR (300 MHz, CDCl$_3$, Characteristic signals) δ_H 2.00 (3H, s, CH_3) and 4.98 (1H, s, CHCCl$_3$); ^{13}C NMR (75 MHz CDCl$_3$, Characteristic signals): δ_C 67.1 (*C*(Ph)Me), 95.34 (*C*Cl$_3$), 128.2(Ph*C*H), 128.3 (Ph*C*H), 128.5 (Ph*C*H-4), 132.8 (Ph*C*-1) and 169.9 (*C*=O).

(154)-*Anti*-(3*S*,4*R*)-3-butyl-3-phenyl-4-(trichloromethyl)oxetan-2-one and **(154)**-*Syn*-(3*S*,4*S*)-3-butyl-3-phenyl-4-(trichloromethyl)oxetan-2-one
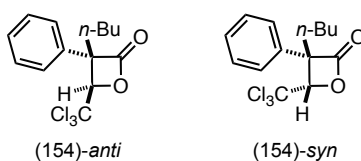
(154)-*anti*　　　　　(154)-*syn*

Scheme 40. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), butylphenylketene **419** (174 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at rt for 3 h gave crude product (*dr* 69:31, *anti*:*syn*) that was purified by flash silica chromatography (2% Et$_2$O :petrol) to give a mixture of *anti* and *syn* (240 mg, 75% yield);

Anti (eluted first) as a colourless solid; mp 58 °C; $[\alpha]_D^{20}$ +42 (*c* 0.45, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*R*): 4.6 min, t$_R$ minor (3*R*,4*S*): 8.9 min, 88% *ee*. ν_{max} (thin film)/cm^{-1} 3055, 1841 (C=O), 1099, 937, 896 and 833; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.80 (3H, t, *J* 7.3, *n*-BuC*H$_3$*), 0.85-0.98 (1H, m, *n*-BuC*H$_2$*), 1.15-1.26 (2H, m, *n*-BuC*H$_2$*), 1.43-1.52 (1H, m, *n*-BuC*H$_2$*), 2.01 (1H, *app* td, *J* 13.2, 4.7, *n*-BuC*H*$_A$H$_B$), 2.73 (1H, ddd, *J* 13.2, 12.2, 4.3, *n*-BuCH$_A$*H*$_B$), 5.03 (1H, s, C*H*CCl$_3$) and 7.36-7.45 (5H, m, Ph*H*); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 13.7 (*n*-Bu*C*H$_3$), 22.8 (*n*-Bu*C*H$_2$), 26.4 (*n*-Bu*C*H$_2$), 31.0 (*n*-Bu*C*H$_A$H$_B$), 69.5 (*C*(Ph)Bu), 88.1 (*C*H(CCl$_3$)), 95.6 (*C*Cl$_3$), 126.2 (Ph*C*H), 128.3 (Ph*C*H-4), 129.2 (Ph*C*H), 137.5 (Ph*C*-1) and 169.0 (*C*=O); *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS C$_{14}$H$_{19}$O$_2$NCl$_3$ [M+NH$_4$]$^+$: found 338.0475; calcd 338.0476 (−) 0.3 ppm.

Syn ^{1}H NMR (400 MHz CDCl$_3$, Characteristic signals): δ_H 4.77 (1H, s, C*H*CCl$_3$) ^{13}C NMR (100 MHz CDCl$_3$, Characteristic signals): δ_C 13.9 (*n*-Bu*C*H$_3$), 22.7 (*n*-Bu*C*H$_2$), 26.4 (*n*-Bu*C*H$_2$), 69.3 (*C*(Ph)Bu), 87.2 (*C*H(CCl$_3$)) and 169.4 (*C*=O).

(155)-*Anti*-(3*S*,4*R*)-3-isobutyl-3-phenyl-4-(trichloromethyl)oxetan-2-one and **(155)**-*Syn*-(3*S*,4*R*)-3-isobutyl-3-phenyl-4-(trichloromethyl)oxetan-2-one

(155)-*anti*   (155)-*syn*

Scheme 40. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.1 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), *i*-butylphenylketene **60** (174 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 3 h gave crude product (*dr* 42:58, *anti*:*syn*) that was purified by flash silica chromatography (1% Et$_2$O :petrol) to give a partially separable mixture of *anti* and *syn* diastereomers (274 mg, 85% yield);

Anti (eluted first) as a colourless solid; mp 86 °C; $[\alpha]_D^{20}$ +13 (*c* 0.3, CHCl$_3$); ν_{max} (KBr)/cm^{-1} 2961, 1834 (C=O), 1492, 1449, 1095, 933, 848, 825, 782, 727 and 701; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.65 (3H, t, *J* 6.7, *i*-Bu(C*H$_3$*)$_2$), 0.96 (3H, t, *J* 6.7, *i*-Bu(C*H$_3$*)$_2$), 1.45-1.51 (1H, m, *i*-BuC*H*), 2.08 (1H, dd, *J* 14.1, 4.3, *i*-BuC*H$_A$*H$_B$), 2.55 (1H, dd, *J* 14.1, 7.9, *i*-BuCH$_A$*H$_B$*), 4.95 (1H, s, C*H*CCl$_3$) and 7.34-7.47 (5H, m, Ph*H*); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 23.2 (*C*H$_3$), 24.6 (*C*H$_3$), 24.8 (*C*H), 39.7 (*C*H$_2$), 69.9, (*C*(Ph)*i*-Bu) 88.2 (*C*H(CCl$_3$)), 95.8 (*C*Cl$_3$), 126.6 (Ph*C*H), 128.6 (Ph*C*H-4), 129.5 (Ph*C*H), 137.9 (*C*Ph-1) and 168.9 (*C*=O); *m/z*: (ASAP) (M(^{35}Cl))$^+$ HRMS C$_{14}$H$_{19}$O$_2$NCl$_3$ [M+NH$_4$]$^+$: found 338.0476; calcd 338.0476 (±) 0.0 ppm.

Syn (eluted second) as a colourless solid: mp 78 °C; $[\alpha]_D^{20}$ +90 (*c* 0.05, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (3% IPA:hexane, flow rate 0.2 mL min^{-1}, 220 nm) t$_R$ major (*S*,*S*): 30.8 min, t$_R$ minor (*S*,*R*): 39.1 min, 84% *ee*; ν_{max} (KBr)/cm^{-1} 2956, 1840 (C=O), 1496, 1450, 1096, 930, 804, 762 and 701; ^{1}H NMR (300 MHz CDCl$_3$): δ_H 0.75 (3H, t, *J* 6.7, *i*-Bu(C*H$_3$*)$_2$), 0.94 (3H, t, *J* 6.7, *i*-Bu(C*H$_3$*)$_2$), 1.57-1.65 (1H, m, *i*-BuC*H*), 2.13 (1H, dd, *J* 14.1, 4.3, *i*-BuC*H$_A$*H$_B$), 2.45 (1H, dd, *J* 14.1, 7.9, *i*-BuCH$_A$*H$_B$*), 4.87 (1H, s, C*H*CCl$_3$), 7.32-7.36 (3H, m, Ph*H*) and 7.47-7.51 (2H, m, Ph*H*); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 23.3 (*C*H$_3$), 24.1 (*C*H$_3$), 25.0 (*C*H), 48.7 (*C*H$_2$), 69.2 (*C*(Ph)*i*-Bu), 87.8 (*C*H(CCl$_3$)), 95.7 (*C*Cl$_3$), 128.4 (Ph*C*H), 128.6 (Ph*C*H-4), 128.9 (Ph*C*H), 131.5 (Ph*C*-1) and 169.4 (*C*=O); *m/z*: (ESI+) (M(^{35}Cl))$^+$ HRMS C$_{14}$H$_{15}$O$_2$Cl$_3$ [M+]: found 320.0130; calcd 320.0132 (–) 0.7 ppm.

(160)-*Anti*-(3*S*,4*R*)-3-methyl-3-(4-tolyl)-4-(trichloromethyl)oxetan-2-one and **(160)**-*Syn*-(3*S*,4*S*)-3-methyl-3-(4-tolyl)-4-(trichloromethyl)oxetan-2-one

(160)-*anti*   (160)-*syn*
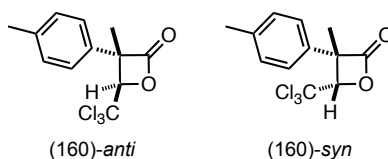
Scheme 41. Following general procedure **1**: NHC precatalyst **66** (23.7 mg, 0.04 mmol, 0.10 equiv), KHMDS (0.08 mL, 0.04 mmol, 0.09 equiv), methyl-4-tolylketene **420** (61 mg, 0.42 mmol, 1.0 equiv) and chloral (0.04 mL, 0.42 mmol, 1.0 equiv) in toluene 20 mL at 0 °C for 3 h gave crude product (*dr* 88:12, *anti*:*syn*) that was purified by flash silica chromatography (2% Et$_2$O :petrol);

Anti (eluted first) as a colourless solid; (83 mg, 57% yield); mp 114-118 °C; $[\alpha]_D^{20}$ +25 (*c* 0.19, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*R*): 5.4 min, t$_R$ minor (3*R*,4*S*): 11.7 min, 82% *ee*; ν_{max} (KBr)/cm^{-1} 3055, 2987, 1846 (C=O), 1515, 1104, 939 and 831; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 1.87 (3H, s, C*H*$_3$), 2.37 (3H, s, ArC*H*$_3$), 5.06 (1H, s, *CH*CCl$_3$), 7.22-7.24 (2H, m, Ar*H*-3,5) and 7.31-7.35 (2H, m, Ar*H*-2,6); ^{13}C NMR (75 MHz CDCl$_3$): δ$_C$ 19.4 (Ar*C*H$_3$), 21.2 (*C*H$_3$), 65.3 (*C*(Ar)Me), 87.5 (*C*H(CCl$_3$)), 95.7 (*C*Cl$_3$), 125.3 (Ar*C*H-2,6), 130.2 (Ar*C*H-3,5), 136.7 (Ar*C*-1), 138.4 (Ar*C*-4) and 169.9 (*C*=O); *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS C$_{12}$H$_{15}$Cl$_3$O$_2$N$_1$ [M+NH$_4$]$^+$: found 310.0163; calcd 310.0166 (+) 1.0 ppm.

Syn (eluted second) as a colourless solid; (15 mg, 12% yield); mp 98-102 °C; $[\alpha]_D^{20}$ +88 (*c* 0.10, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ minor (3*R*,4*R*): 14.9 min, t$_R$ major (3*S*,4*S*): 18.2 min, 76% *ee*; ν_{max} (KBr)/cm^{-1} 3055, 2987, 1849 (C=O), 1517, 1451, 1422, 1086 and 819; ^{1}H NMR (300 MHz CDCl$_3$): δ$_H$ 1.96 (3H, s, C*H*$_3$), 2.34 (3H, s, ArC*H*$_3$), 4.95 (1H, s, *CH*CCl$_3$), 7.14 (2H, d, *J* 7.9, Ar*H*-3,5) and 7.31-7.35 (2H, m, Ar*H*-2,6); ^{13}C NMR (75 MHz CDCl$_3$): δ$_C$ 21.1 (Ar*C*H$_3$), 26.4 (*C*H$_3$), 64.8 (*C*(Ar)Me), 88.0 (*C*H(CCl$_3$)), 95.3 (*C*Cl$_3$), 128.0 (Ar*C*H-2,6), 128.9 (Ar*C*H-3,5), 130.0 (Ar*C*-1), 138.3 (Ar*C*-4) and 170.0 (*C*=O); *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS C$_{12}$H$_{11}$Cl$_3$O$_2$ [M+]: found 291.9819; calcd 291.9817 (−) 0.7 ppm.

(159)-*Anti*-(3*S*,4*R*)-3-ethyl-3-(4-tolyl)-4-(trichloromethyl)oxetan-2-one and **(159)**-*Syn*-(3*S*,4*S*)-3-ethyl-3-(4-tolyl)-4-(trichloromethyl)oxetan-2-one. Preparative scale


(159)-*anti*   (159)-*syn*
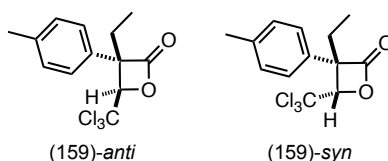
Scheme 41. Following general procedure 1: NHC precatalyst **66** (71.2 mg, 0.13 mmol, 0.25 equiv), KHMDS (0.24 mL, 0.12 mmol, 0.24 equiv), ethyl-4-tolylketene **421** (80 mg, 0.50 mmol, 1.0 equiv) and chloral (0.05 mL, 0.05 mmol, 1.0 equiv) in toluene (10 mL) at 0 °C for 3 h gave crude product (*dr* 73:27, *anti:syn*) that was purified by flash silica chromatography (2% Et_2O :petrol);

Anti (eluted first) as a colourless solid; (84 mg, 54% yield); mp 102-106 °C; $[\alpha]_D^{20}$+42 (*c* 0.19, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (3*S*,4*R*): 4.6 min, t_R minor (3*R*,4*S*): 9.8 min, 88% *ee*; ν_{max} (KBr)/cm^{-1} 2987, 1837 (C=O), 1515, 1252, 1093, 929, 831, 820, 804 and 740; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.86 (3H, s, CH$_2$C*H*$_3$), 2.02 (1H, dq, *J* 13.8, 7.5, C*H*$_A$H$_B$CH$_3$), 2.37 (3H, s, ArC*H*$_3$), 2.83 (1H, dq, *J* 13.8, 7.5, CH$_A$*H*$_B$CH$_3$), 5.03 (1H, s, C*H*CCl$_3$), 7.22-7.24 (2H, m, Ar*H*-3,5) and 7.29-7.32 (2H, m, Ar*H*-2,6); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 8.8 (*C*H$_3$), 21.0 (Ar*C*H$_3$), 24.3 (*C*H$_2$), 69.5 (*C*(Ar)Et), 88.1 (*C*H(CCl$_3$)), 95.5 (*C*Cl$_3$), 126.1 (Ar*C*H-2,6), 129.7 (Ar*C*H-3,5), 133.9 (Ar*C*-1), 138.1 (Ar*C*-4) and 169.0 (*C*=O); *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS C$_{13}$H$_{17}$O$_2$N$_1$Cl$_3$ [M+NH$_4$]$^+$: found 324.0325; calcd 324.0319 (+) 1.7 ppm.

Syn (eluted second) as a colourless solid; (25 mg, 15% yield); mp 132-140 °C; $[\alpha]_D^{20}$ +35 (*c* 0.13, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R minor (3*R*,4*R*): 14.9 min, t_R major (3*S*,4*S*): 18.2 min, 76% *ee*; ν_{max} (CH$_2$Cl$_2$ solution)/cm^{-1} 2979, 1839 (C=O), 1516, 1092, 925, 896, 836 and 819; ^{1}H NMR (300 MHz CDCl$_3$): δ_H 0.88 (3H, s, CH$_2$C*H*$_3$), 2.23-2.36 (2H, m, C*H*$_2$CH$_3$), 2.33 overlapping (3H, s, ArC*H*$_3$), 4.84 (1H, s, C*H*CCl$_3$), 7.06-7.09 (2H, m, Ar*H*-3,5) and 7.31-7.34 (2H, m, Ar*H*-2,6); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 8.8 (*C*H$_3$), 21.2 (Ar*C*H$_3$), 33.1 (*C*H$_2$), 69.4 (*C*(Ar)Et), 86.9 (*C*H(CCl$_3$)), 95.6 (*C*Cl$_3$), 128.2 (Ar*C*-1), 128.4 (Ar*C*H), 128.9 (Ar*C*H), 138.2 (*C*Ar-4) and 169.4 (*C*=O); *m/z*: (ASAP) (M(^{35}Cl)+NH$_4$)$^+$ HRMS C$_{13}$H$_{13}$Cl$_3$O$_2$NH$_4$: found 324.0322; calcd 324.0319 (+) 0.8 ppm.

(161)-*Anti*-(3*S*,4*R*)-3-(4-methoxyphenyl)-3-ethyl-4-(trichloromethyl)oxetan-2-one – and *Syn*-(3*S*,4*S*)-3-(4-methoxyphenyl)-3-ethyl-4-(trichloromethyl)oxetan-2-one
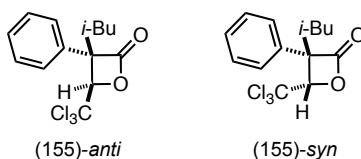

(161)-*anti*   (161)-*syn*

Scheme 41. Following general procedure **1**: NHC precatalyst **66** (57 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-4-methoxyphenylketene **425** (176 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 3 h gave crude product (*dr* 75:25, *anti*:*syn*) that was purified by flash silica chromatography (5% Et$_2$O :petrol)

Anti (eluted first) as a colourless solid; (172 mg, 53% yield); mp 62-64 °C; $[\alpha]_D^{20}$ +48 (*c* 0.50, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (3*S*,4*R*): 4.6 min, t_R minor (3*R*,4*S*): 9.8 min, 88% *ee*; ν_{max} (KBr)/cm^{-1} 3055, 2987, 1836 (C=O), 1514, 1185, 1095, 1033, 951, 929, 896 and 834; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.86 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.00 (1H, dq, *J* 13.8, 7.5, C*H*$_A$H$_B$CH$_3$), 2.82 (1H, dq, *J* 13.8, 7.1, CH$_A$*H*$_B$CH$_3$), 3.83 (3H, s, OC*H*$_3$), 5.02 (1H, s, C*H*CCl$_3$), 6.93-6.96 (2H, m, Ar*H*-3,5) and 7.32-7.35 (2H, m, Ar*H*-2,6); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 8.9 (*C*H$_3$), 24.6 (*C*H$_2$), 55.4, (ArO*C*H$_3$) 69.4 (*C*(Ar)Et), 88.4 (*C*H(CCl$_3$)), 95.7 (*C*Cl$_3$), 114.6 (Ar*C*-1), 127.6 (Ar*C*-3,5), 129.1 (Ar*C*-2,6), 159.5 (Ar*C*-4) and 169.2 (*C*=O); *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS C$_{13}$H$_{17}$O$_3$N$_1$Cl$_3$ [M+NH$_4$]$^+$: found 340.0269; calcd 340.0269 (+) 0.1 ppm.

Syn (eluted second) as a colourless solid; (54 mg, 17% yield); mp 82-84 °C; $[\alpha]_D^{20}$ +90 (*c* 0.50, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (3*S*,4*S*): 16.1 min, t_R minor (3*R*,4*R*): 20.8 min, 84% *ee*; ν_{max} (KBr)/cm^{-1} 2925, 1836 (C=O), 1612, 1516, 1254, 1186, 1093, 1035, 924 and 832; ^{1}H NMR (300 MHz CDCl$_3$): δ_H 0.94 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.28-2.43 (2H, m, C*H*$_2$CH$_3$), 3.81 (3H, s, OC*H*$_3$), 4.90 (1H, s, C*H*(CCl$_3$)), 6.86 (2H, d, *J* 9.0 Ar*H*) and 7.36 (2H, d, *J* 9.0, Ar*H*); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 8.8 (*C*H$_3$), 33.1 (*C*H$_2$), 55.3 (ArO*C*H$_3$), 69.2 (*C*(Ar)Et), 86.9 (*C*H(CCl$_3$)), 95.7 (*C*Cl$_3$), 113.6 (Ar*C*-1), 123.0 (Ar*C*-3,5), 129.9 (Ar*C*-2,6), 159.5 (Ar*C*-4) and 169.5 (*C*=O); *m/z*: (EI+) (M(^{35}Cl))$^+$ HRMS C$_{13}$H$_{13}$O$_3$Cl$_3$ [M+]: found 321.9923; calcd 321.9925 (−) 0.6 ppm.

(165)-*Anti*-(3*S*,4*R*)-3-(4-fluorophenyl)-3-ethyl-4-(trichloromethyl)oxetan-2-one   and

(165)-*Syn*-(3*S*,4*S*)-3-(4-fluorophenyl)-3-ethyl-4-(trichloromethyl)oxetan-2-one and


(165)-*anti*   (165)-*syn*

Scheme 42. Following general procedure **2**: NHC precatalyst **66** (28.0 mg, 0.05 mmol, 0.10 equiv), KHMDS (0.09 mL, 0.05 mmol, 0.09 equiv), ethyl-4-fluorophenylketene **422** (82.1 mg, 0.50 mmol, 1.0 equiv) and chloral (0.05 mL, 0.05 mmol, 1.0 equiv) in toluene (10 mL) at 0 °C for 3 h gave crude product (*dr* 69:31, *anti*:*syn*) that was purified by flash silica chromatography (2% Et$_2$O :petrol)

Anti (eluted first) as a colourless solid; (80 mg, 51% yield); mp 85-86 °C; $[\alpha]_D^{20}$ +58 (*c* 0.5, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (0.5 % IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (3*S*,4*R*): 5.6 min, t_R minor (3*R*,4*S*): 13.4 min, 94% *ee*. ν_{max} (KBr)/cm^{-1} 2979, 2938, 1840 (C=O), 1606, 1514, 1229, 1166, 1098, 912, 840, 829, 820, 798, 759, 660, 643 and 535; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.86 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.01 (1H, dq, *J* 13.8, 7.5, C*H*$_A$H$_B$CH$_3$), 2.86 (1H, dq, *J* 13.8, 7.1, CH$_A$*H*$_B$CH$_3$), 5.03 (1H, s, C*H*CCl$_3$), 7.10-7.18 (2H, m, Ar*H*-3,5) and 7.39-7.44 (2H, m, Ar*H*-2,6); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 8.9 (*C*H$_3$), 24.6 (*C*H$_2$), 69.3 (*C*(Ar)Et), 88.1 (*C*H(CCl$_3$)), 95.4 (*C*Cl$_3$), 116.3 (d, *J* 22.1, Ar*C*H-3,5), 128.2 (d, *J* 8.2, Ar*C*H-2,6), 132.8 (d, *J* 3.3, Ar*C*-1) 162.5 (d, *J* 248.2, Ar*C*-4) and 168.7 (*C*=O); *m/z*: (EI+) (M(^{35}Cl))$^+$ HRMS, C$_{12}$H$_{10}$O$_2$Cl$_3$F$_1$ [M+]: found 309.9724; calcd 309.9725 (–) 0.3 ppm.

Syn (eluted second) as a colourless solid; (35 mg, 22% yield); mp 90-92 °C; $[\alpha]_D^{20}$ +128 (*c* 0.05, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (1% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (3*R*,4*R*): 6.7 min, t_R major (3*S*,4*S*): 8.0 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 2979, 2937, 1840 (C=O), 1606, 1514, 1465, 1229, 1166, 1143, 1098, 1015, 912, 930, 840, 829, 819, 798, 759, 727, 760, 660, 643 and 535; ^{1}H NMR (500 MHz CDCl$_3$): δ_H 0.96 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.32-2.44 (2H, m, C*H*$_2$CH$_3$), 4.93 (1H, s, C*H*CCl$_3$), 7.02-7.08 (2H, m, Ar*H*-3,5) and 7.43-7.48 (2H, m, Ar*H*-2,6); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 8.7 (*C*H$_3$), 33.2 (*C*H$_2$), 68.9 (*C*(Ar)Et), 86.8 (*C*H(CCl$_3$)), 95.4 (*C*Cl$_3$), 115.3 (d, *J* 22.1, Ar*C*H-3,5), 127.2 (d, *J* 3.3, Ar*C*-1), 130.4 (d, *J* 8.2,

ArCH-2,6) 162.5 (d, *J* 248.6, ArC-4) and 169.0 (*C*=O); *m/z*: (EI+) (M(^{35}Cl))$^+$ HRMS C$_{12}$H$_{10}$O$_2$Cl$_3$F$_1$ [M+]: found 309.9723; calcd 309.9725 (−) 0.6 ppm.

(166)-*Anti*-(3*S*,4*R*)-3-(4-chlorophenyl)-3-ethyl-4-(trichloromethyl)oxetan-2-one   and **(166)**-*Syn*-(3*S*,4*S*)-3-(4-chlorophenyl)-3-ethyl-4-(trichloromethyl)oxetan-2-one
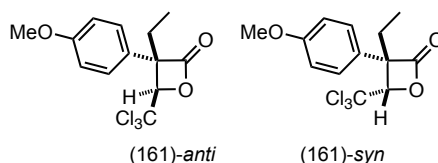

(166)-*anti*   (166)-*syn*

Scheme 42. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-4-chlorophenylketene **423** (181 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 3 h gave crude product (*dr* 74:26, *anti*:*syn*) that was purified by flash silica chromatography (2% Et$_2$O :petrol)

Anti (eluted first) as a colourless solid; (220 mg, 67% yield); mp 78-81 °C; $[\alpha]_D^{20}$+50 (*c* 0.50, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*R*): 5.6 min, t$_R$ minor (3*R*,4*S*): 9.3 min, 92% *ee*; ν_{max} (KBr)/cm^{-1} 2919, 1837 (C=O), 1713, 1494, 1261, 1095, 1016, 831, 804 and 761; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 0.86 (3H, t, *J* 7.2, CH$_2$C*H$_3$*), 2.02 (1H, dq, *J* 14.1, 7.2, C*H$_A$*H$_B$CH$_3$), 2.87 (1H, dq, *J* 14.1, 7.2, CH$_A$*H$_B$*CH$_3$), 5.02 (1H, s, C*H*CCl$_3$) and 7.36-7.44 (4H, m, Ar*H*); ^{13}C NMR (100 MHz CDCl$_3$): δ$_C$ 9.0 (*C*H$_3$), 24.6 (*C*H$_2$), 69.5 (*C*(Ar)Et), 88.0 (*C*H(CCl$_3$)), 95.4 (*C*Cl$_3$), 127.9 (Ar*C*H), 129.6 (Ar*C*H), 134.6 (Ar*C*-4), 135.5 (Ar*C*-1) and 168.6 (*C*=O); *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS C$_{12}$H$_{14}$O$_2$N$_1$Cl$_4$ [M+NH$_4$]$^+$: found 343.9771; calcd 343.9773 (−) 0.6 ppm.

Syn (eluted second) as a colourless solid; (69 mg, 21% yield); mp 118-120 °C; $[\alpha]_D^{20}$+94 (*c* 0.13, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (3% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*S*): 17.1 min, t$_R$ minor (3*R*,4*R*): 20.7 min, 84% *ee*; ν_{max} (KBr)/cm^{-1} 3055, 2986, 1849 (C=O), 1517, 1451, 1422, 1096, 926, 896, 838 and 819; ^{1}H NMR (300 MHz CDCl$_3$): δ$_H$ 0.96 (3H, t, *J* 7.4, CH$_2$C*H$_3$*), 2.34-2.41 (2H, m, C*H$_2$*CH$_3$), 4.94 (1H, s, C*H*CCl$_3$), 7.32-7.36 (2H, m, Ar*H*) and 7.40-7.43 (2H, m, ArH); ^{13}C NMR (100 MHz CDCl$_3$): δ$_C$ 8.7 (*C*H$_3$), 33.1 (*C*H$_2$), 69.0 (*C*(Ar)Et), 86.8 (*C*H(CCl$_3$)), 95.4 (*C*Cl$_3$), 128.5 (Ar*C*H), 129.9 (Ar*C*H), 130.0 (Ar*C*), 134.6

(Ar*C*) and 168.8 (C=O); *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS $C_{12}H_{14}O_2N_1Cl_4$ [M+]: found 343.9769; calcd 343.9773 (−) 1.2 ppm.

(167)-*Anti*-(3*S*,4*R*)-3-(4-bromophenyl)-3-ethyl-4-(trichloromethyl)oxetan-2-one   and
(167)-*Syn*-(3*S*,4*S*)-3-(4-bromophenyl)-3-ethyl-4-(trichloromethyl)oxetan-2-one and
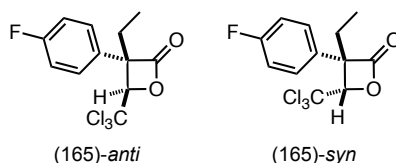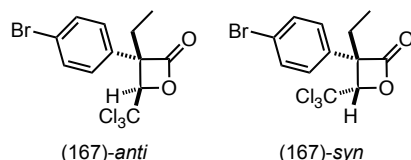

(167)-*anti*   (167)-*syn*

Scheme 42. Following general procedure **2**: NHC precatalyst **66** (28.0 mg, 0.05 mmol, 0.10 equiv), KHMDS (0.09 mL, 0.05 mmol, 0.09 equiv), ethyl-4-bromophrnylketene **424** (113 mg, 0.50 mmol, 1.0 equiv) and chloral (0.05 mL, 0.05 mmol, 1.0 equiv) in toluene (10 mL) at 0 °C for 3 h gave crude product (*dr* 75:25, *anti*:*syn*) that was purified by flash silica chromatography (1% Et$_2$O :petrol)

Anti (eluted first) as a colourless solid; (115 mg, 62% yield); mp 76-78 °C; $[\alpha]_D^{20}$ +31 (*c* 0.25, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*R*): 6.1 min, t$_R$ minor (3*R*,4*S*): 11.6 min, 90% *ee*; ν_{max} (KBr)/cm^{-1} 2971, 1831 (C=O), 1489, 1399, 1261, 1102, 1012, 954, 930, 834, 803, 757, 735, 716, 656 and 526; ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 0.86 (3H, t, *J* 7.4, CH$_2$C*H$_3$*), 2.01 (1H, dq, *J* 14.1, 7.2, C*H*$_A$H$_B$CH$_3$), 2.86 (1H, dq, *J* 14.1, 7.1, CH$_A$*H*$_B$CH$_3$), 5.01 (1H, s, C*H*CCl$_3$), 7.30-7.33 (2H, m, Ar*H*) and 7.56-7.59 (2H, m, Ar*H*); ^{13}C NMR (75 MHz CDCl$_3$): δ$_C$ 7.8 (*C*H$_3$), 23.3 (*C*H$_2$), 68.4 (*C*(Ar)Et), 86.8 (*C*H(CCl$_3$)), 94.2 (*C*Cl$_3$), 121.6 (Ar*C*-4), 127.0 (Ar*C*H), 131.4 (Ar*C*H), 134.9 (Ar*C*-1) and 167.4 (C=O); *m/z*: (EI+) (M(^{35}Cl)(Br^{79}))$^+$ HRMS $C_{12}H_{10}O_2Br_1Cl_3$ [M+]: found 369.8920; calcd 369.8924 (−) 1.2 ppm.

Syn (eluted second) as a colourless solid; (37 mg, 17% yield); mp 110-112 °C; $[\alpha]_D^{20}$ +86 (*c* 0.07, CHCl$_3$); Chiral HPLC analysis; Chiralpak AS-H (1% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*S*): 10.0 min, t$_R$ minor (3*R*,4*R*): 11.2 min, 82% *ee*; ν_{max} (KBr)/cm^{-1} 2968, 1838 (C=O), 1493, 1452, 1399, 1254, 1146, 1099, 1016, 911, 930, 832, 820, 800, 762, 735, 721, 647 and 525; ^{1}H NMR (500 MHz CDCl$_3$): δ$_H$ 0.95 (3H, t, *J* 7.3, CH$_2$C*H$_3$*), 2.34-2.38 (2H, m, C*H$_2$*CH$_3$), 4.93 (1H, s, C*H*(CCl$_3$)), 7.35 (2H, d, *J* 8.2, Ar*H*) and 7.48 (2H, d, *J* 8.2, Ar*H*); ^{13}C NMR (100 MHz CDCl$_3$): δ$_C$ 9.1 (*C*H$_3$), 33.5 (*C*H$_2$), 69.4 (*C*(Ar)Et), 87.2 (*C*H(CCl$_3$)), 95.7

(CCl$_3$), 123.2 (ArC-4), 130.6 (ArCH), 131.0 (ArC-1), 131.9 (ArCH) and 169.2 (C=O); *m/z*: (EI+) (M(^{35}Cl)(Br^{79}))$^+$ HRMS C$_{12}$H$_{10}$O$_2$Br$_1$Cl$_3$ [M+]: found 369.8926; calcd 369.8924 (+) 0.5 ppm.

(168)-(2*S*,3*R*)-4,4,4-Trichloro-2-ethyl-2-phenylbutane-1,3-diol

(168)
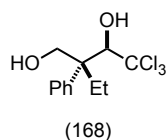
Scheme 44. To a 0 °C solution of **147** (200 mg, 0.68 mmol, 1.0 equiv, 94% *ee*) in dry toluene (10 mL) under an argon atmosphere was added toluene (1M solution in toluene) (2.38 mL, 2.38 mmol, 3.5 equiv) and the solution was warmed slowly to rt over 14 h. The solution was quenched with a solution of Rochelle salt and extracted with Et$_2$O (3×25 mL) before concentration *in vacuo*. This crude product was purified by flash silica chromatography (30% Et$_2$O :petrol) to give **168** as a colorless oil; (86 mg, 42% yield); $[\alpha]_D^{20}$+24 (*c* 0.27, CHCl$_3$); Chiral HPLC analysis; Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (2*R*,3*R*): 11.6 min, t$_R$ minor (2*S*,2*S*): 15.6 min, 84% *ee*; ν_{max} (thin film)/cm^{-1} 3390 (OH), 2926, 1778, 1463, 822 (CCl$_3$) and 764 (CCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.83 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.08-2.32 (2H, m, C*H*$_2$CH$_3$), 4.00 (1H, d, *J* 11.7, C*H*$_A$H$_B$OH), 4.30 (1H, d, *J* 11.7, CH$_A$*H*$_B$OH), 4.63 (1H, s, C*H*(CCl$_3$)OH), 7.16-7.21 (1H, m, Ph*H*-4), 7.25-7.30 (2H, m, Ph*H*-2,6) and 7.35-7.39 (2H, m, Phr*H*-3,5); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 8.7 (CH$_2$*C*H$_3$), 23.6 (*C*H$_2$CH$_3$), 51.3 (*C*(Ph)Et), 67.2 (*C*H$_2$OH), 88.7 (*C*H(OH)CCl$_3$), 102.5 (*C*Cl$_3$), 127.0 (Ph*C*-4), 127.7 (Ph*C*-3,5), 128.5 (Ph*C*-2,6) and 140.8 (P*C*H-1); *m/z*: (ESI +) (M(^{35}Cl))$^+$ HRMS C$_{13}$H$_{13}$O$_3$Cl$_3$ [M+]$^+$: found 330.9829; calcd 330.9832 (−) 0.8 ppm.

(180)-(*S*)-2,2-Dichlorovinyl 2-chloro-2-(2-chlorophenyl)butanoate
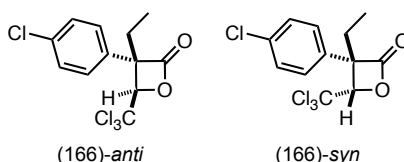

(180)
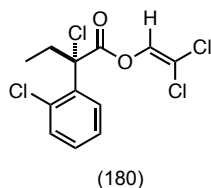
Scheme 48. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-2-

chlorophenylketene **179** (181 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 12 h gave crude product that was purified by flash silica chromatography (2% Et$_2$O :petrol) to give **180** as a colorless oil; (205 mg, 65% yield); $[\alpha]_D^{20}$ +12 (*c* 0.22, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R major (*S*): 7.0min, t_R minor (*R*): 9.7 min, 62% *ee*; ν_{max} (thin film)/cm^{-1} 3094, 2981, 2941, 1771 (C=O), 1469, 1435, 1286, 1197, 1124, 995, 910 and 752; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.87 (3H, t, *J* 7.3 CH$_2$C*H$_3$*), 2.53 (1H, dq, *J* 14.7, 7.3, C*H$_A$*H$_B$CH$_3$), 2.67 (1H, dq, *J* 14.7, 7.3, CH$_A$*H$_B$*CH$_3$), 7.30-7.40 (3H, m, Ar*H*), 7.59 (1H, s, C*H*(CCl$_2$)), and 7.83-7.85 (1H, m, Ar*H*); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 8.5 (*C*H$_3$), 31.7 (*C*H$_2$), 73.8 (*C*(Ar)Et), 114.6 (*C*Cl$_2$), 127.1 (Ar*C*H), 130.1 (Ar*C*H), 130.2 (Ar*C*H), 130.8 (Ar*C*H), 131.7 (Ar*C*-2), 133.4 (*C*H(CCl$_2$)), 135.2 (Ar*C*-1) and 166.1 (*C*=O); *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS C$_{12}$H$_{14}$O$_2$N$_1$Cl$_4$ [M+NH$_4$]$^+$: found 343.9778; calcd 343.9773 (+) 1.4 ppm.

(186)-(*S*)-2,2-Dichlorovinyl 2-chloro-2-(2-tolyl)propanoate
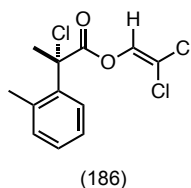

(186)

Scheme 49. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), methyl-2-tolylketene **426** (146 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 12 h gave crude product that was purified by flash silica chromatography (1% Et$_2$O :petrol) to give **186** as a colorless oil; (152 mg, 52% yield); $[\alpha]_D^{20}$ +51 (*c* 0.35, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R minor (*R*): 7.4 min, t_R major (*S*): 8.4 min, 80% *ee*; ν_{max} (thin film)/cm^{-1} 3091, 2977, 1772 (C=O), 1601, 1587, 1489, 1464, 1437, 1283, 1247, 1195, 1135, 1125, 1089, 1026, 992, 906, 863 and 753; ^{1}H NMR (500 MHz, CDCl$_3$) δ_H 2.22 (3H, s, C*H$_3$*), 2.30 (3H, s, ArC*H$_3$*), 7.17-7.19 (1H, m, Ar*H*-6), 7.23-7.28 (2H, m, Ar*H*-4/5), 7.56 (1H, s, C*H*(CCl$_2$)), and 762-7.63 (1H, m, Ar*H*-3); ^{13}C NMR (125 MHz CDCl$_3$): δ_C 20.3 (Ar*C*H$_3$), 29.6 (*C*H$_3$), 68.9 (*C*(Ar)Me), 114.9 (*C*Cl$_2$), 125.7 (Ar*C*H-4/5), 126.2 (Ar*C*H-6), 129.1 (Ar*C*H-4/5), 132.2 (Ar*C*H-3), 133.2 (*C*H(CCl$_2$)), 136.0 (Ar*C*-2), 137.5 (Ar*C*-1) and 167.7 (*C*=O); *m/z*: (EI+)

$(M(^{35}Cl))^+$ HRMS $C_{12}H_{14}O_2N_1Cl_4$ [M+]: found 291.9816; calcd 291.9819 (–) 1.1 ppm.

(187)-(S)-2,2-Dichlorovinyl 2-chloro-2-(2-tolyl)butanoate
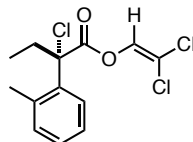

(187)

Scheme 49. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-2-tolylketene **427** (160 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 12 h gave crude product that was purified by flash silica chromatography (1% Et$_2$O :petrol) to give **187** as a colorless oil; (219 mg, 71% yield); $[\alpha]_D^{20}$+130 (*c* 0.05, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (0.5% IPA:hexane, flow rate 0.2 mL min^{-1}, 220 nm) t_R minor (*R*): 33.4 min, t_R major (*S*): 37.2 min, 82% *ee*; ν_{max} (thin film)/cm^{-1} 3093, 2980, 1768 (C=O), 1460, 1286, 1199, 1122, 991, 908, 873, 857, 751 and 737; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 1.02 (3H, t, *J* 7.3, CH$_2$C*H*$_3$), 2.29 (3H, s, ArC*H*$_3$), 2.48-2.65 (2H, m, C*H*$_2$CH$_3$), 7.17-7.19 (1H, m, Ar*H*-6), 7.24-7.27 (2H, m, Ar*H*-4,5), 7.57 (1H, s, C*H*(CCl$_2$)), and 762-7.64 (1H, m, Ar*H*-3); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 8.9 (*C*H$_3$), 20.4 (Ar*C*H$_3$), 33.3 (*C*H$_2$), 74.1 (*C*(Ar)Et), 114.8 (*C*Cl$_2$), 126.1 (Ar*C*H-4/5), 126.6 (Ar*C*H-6), 128.9 (Ar*C*H-4/5), 132.2 (Ar*C*H-3), 133.1 (*C*H(CCl$_2$)), 135.8 (Ar*C*-2), 136.6 (Ar*C*-1) and 167.0 (*C*=O); *m/z*: (CI+) $(M(^{35}Cl))^+$ HRMS $C_{13}H_{17}O_2N_1Cl_3$ [M+NH$_4$]$^+$: found 324.0324; calcd 324.0319 (+) 1.4 ppm.

(188)-(S)-2,2-dichlorovinyl 2-chloro-2-(2-tolyl)hexanoate
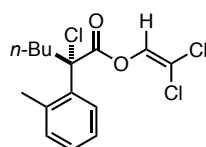
(188)

Scheme 49. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), *n*-butyl-2-tolylketene **428** (188 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 12 h gave crude product that was purified by flash silica

chromatography (0.33% Et$_2$O :petrol) to give **188** as a colorless oil; (219 mg, 72% yield); $[\alpha]_D^{20}$ +55 (*c* 0.95, CHCl$_3$); ν_{max} (thin film)/cm^{-1} 3093, 2961, 2874, 1765 (C=O), 1488, 1461, 1381, 1284, 1196, 1130, 994, 916, 888, 851, 821, 753, 738, 653 and 631; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.93 (3H, t, *J* 7.0, *n*-BuC*H$_3$*), 1.31-1.43 (4H, m, *n*-BuC*H$_2$*), 2.30 (3H, s, ArC*H$_3$*) 2.47-2.55 (2H, m, *n*-Bu*H*), 7.19 (1H, d, *J* 3.4, Ar*H*-6), 7.25-7.28 (2H, m, Ar*H*-4/5), 7.57 (1H, s, C*H*(CCl$_2$)), and 7.63-7.65 (1H, m, Ar*H*-3); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 13.9 (*C*H$_3$), 20.4 (Ar*C*H$_3$), 22.6 (*C*H$_2$), 26.5 (*C*H$_2$), 39.9 (*C*H$_2$), 73.4 (*C*(Ar)Bu), 114.8 (*C*Cl$_2$), 126.1 (Ar*C*H-4/5), 126.5 (Ar*C*H-6), 128.8 (Ar*C*H-4/5), 132.2 (Ar*C*H-3), 133.2 (*C*H(CCl$_2$)), 135.8 (Ar*C*-2), 136.9 (Ar*C*-1) and 167.1 (*C*=O); *m/z*: (EI+) (M(^{35}Cl))$^+$ HRMS C$_{15}$H$_{17}$O$_2$Cl$_3$ [M+]: found 334.0289; calcd 334.2089 (+) 0.1 ppm.

(191)-(*S*)-2,2-Dichlorovinyl 2-chloro-2-(naphthalene-1-yl)propanoate

(191)

Scheme 50. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), methyl-1-napthylketene **429** (182 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 12 h gave crude product that was purified by flash silica chromatography (1% Et$_2$O :petrol) to give **191** as a colorless oil; (207 mg, 63% yield); $[\alpha]_D^{20}$ + 108 (*c* 0.5, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R minor (*R*): 7.5 min, t_R major (*S*): 15.5 min, 84% *ee*; ν_{max} (thin film)/cm^{-1} 3094, 1768 (C=O), 1646, 1513, 1452, 1377, 1214, 1124, 971, 883, 851, 778 and 738; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 2.43 (3H, s, C*H$_3$*), 7.47 (1H, s, C*H*(CCl$_2$)), 7.49-7.53 (3H, m, Nap*H*), and 7.85-7.96 (4H, m, Nap*H*); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 29.9 (*C*H$_3$), 68.8 (*C*(Nap)Me), 115.0 (*C*Cl$_2$), 123.8 (Nap*C*H), 124.3 (Nap*C*H), 124.9 (Nap*C*H), 126.0 (Nap*C*H), 126.9 (Nap*C*H), 129.5 (Nap*C*H), 130.1 (Nap*C*), 130.6 (Nap*C*H), 133.2 (*C*H(CCl$_2$)), 134.3 (Nap*C*), 134.6 (Nap*C*) and 168.3 (*C*=O), *m/z*: (EI+) (M(^{35}Cl))$^+$ HRMS C$_{15}$H$_{11}$O$_2$Cl$_3$ [M+]: found 327.9817; calcd 327.9819 (−) 0.7 ppm.

(192)-(*S*)-2,2-Dichlorovinyl 2-chloro-2-(naphthalene-1-yl)butanoate

(192)

Scheme 50. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-1-napthylketene **196** (196 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 12 h gave crude product that was purified by flash silica chromatography (0.5% Et$_2$O :petrol) to give **192** as a colorless oil; (273 mg, 80% yield); $[\alpha]_D^{20}$ + 96 (*c* 0.75, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (0.5% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t_R minor (*R*): 9.2 min, t_R major (*S*): 10.5 min, 92% *ee*; ν_{max} (thin film)/cm^{-1} 3093, 2981, 1762 (C=O), 1650, 1601, 1512, 1459, 1400, 1345, 1286, 1203, 1124, 986, 804, 775, 652 and 619; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.06 (3H, t, *J* 7.3, CH$_2$C*H*$_3$), 2.73-2.85 (2H, m, C*H*$_2$CH$_3$), 7.47-7.56 (3H, m, Nap*H*), overlapping 7.49 (1H, s, C*H*(CCl$_2$) 7.87-7.92 (3H, m, Nap*H*) and (1H, dd, *J* 3.1, 6.4, Nap*H*); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 9.0 (*C*H$_3$), 33.5 (*C*H$_2$), 74.1 (*C*(Nap)Et), 114.9 (*C*Cl$_2$), 123.5 (Nap*C*H), 124.8 (Nap*C*H), 125.3 (Nap*C*H), 125.8 (Nap*C*H), 126.9 (Nap*C*H), 129.6 (Nap*C*H), 130.1 (Nap*C*), 130.4 (Nap*C*H), 133.1 (*C*H(CCl$_2$)), 133.5 (Nap*C*), 134.3 (Nap*C*) and 167.6 (*C*=O) *m/z*: (CI+) (M(^{35}Cl))$^+$ HRMS C$_{15}$H$_{11}$O$_2$Cl$_3$ [M+NH4]$^+$: found 360.0325; calcd 360.0319 (+) 1.6 ppm.

(192)-(*S*)-2,2-Dichlorovinyl   2-chloro-2-(naphthalene-1-yl)butanoate: Preparative scale

(192)
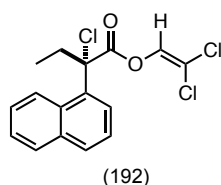
Scheme 52. Following general procedure **1**: NHC precatalyst **66** (51.0 mg, 0.09 mmol, 0.025 equiv), KHMDS (0.17 mL, 0.09 mmol, 0.024 equiv), ethyl-1-napthylketene **196** (702 mg, 3.58 mmol, 1.0 equiv) and chloral (0.35 mL, 3.58 mmol, 1.0 equiv) in toluene (90 mL) at 0 °C for 3 h gave crude product that was purified by flash silica chromatography (0.5% Et$_2$O :petrol) to give **192** as a pale yellow oil;

(1.05 g, 86% yield); $[\alpha]_D^{20}$ + 114 (*c* 0.55, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (0.5% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ minor (*R*): 10.2 min, t$_R$ major (*S*): 12.0 min, 94% *ee*.

(193)-(*S*)-2,2-Dichlorovinyl 2-chloro-2-(naphthalene-1-yl)hexanoate
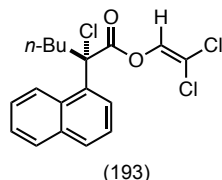
(193)

Scheme 50. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), *n*-butyl-1-napthylketene **430** (224 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 12 h gave crude product that was purified by flash silica chromatography (1% Et$_2$O :petrol) to give **193** as a colorless oil; (311 mg, 84% yield); $[\alpha]_D^{20}$ + 88.5 (*c* 1.0, CHCl$_3$); Chiral HPLC analysis; analysis conducted at AstraZeneca Chiralcel OJ-H (10% ethanol:*i*-hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ minor (*R*): 1.02 min, t$_R$ major (*S*): 1.22 min, 90% *ee*; ν_{max} (thin film)/cm^{-1} 3094, 2960, 2873, 1761 (C=O), 1601, 1513, 1468, 1282, 1199, 1128, 984, 908, 859, 775, 734, 653 and 619; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.92 (3H, t, *J* 7.0, *n*-BuC*H*$_3$), 1.37-1.43 (4H, br m, *n*-BuC*H*$_2$), 2.70-2.77 (2H, br m, *n*-BuC*H*$_2$), 7.47 (1H, s, C*H*(CCl$_2$)), overlapping 7.51-7.54 (3H, m, Nap*H*), 7.88-7.92 (3H, m, Nap*H*) and 7.96-7.99 (1H, m, Nap*H*); ^{13}C NMR (75 MHz CDCl$_3$): δ_C 13.7 (*C*H$_3$), 22.4 (*C*H$_2$), 26.3 (*C*H$_2$), 39.9 (*C*H$_2$), 73.2 (*C*(Nap)Bu), 114.7 (*C*Cl$_2$), 123.3 (Nap*C*H), 124.6 (Nap*C*H), 125.0 (Nap*C*H), 125.6 (Nap*C*H), 126.6 (Nap*C*H), 129.3 (Nap*C*H), 129.9 (Nap*C*), 130.1 (Nap*C*H), 132.9 (*C*H(CCl$_2$)), 133.6 (Nap*C*), 134.1 (Nap*C*) and 167.4 (*C*=O); *m/z*: (EI+) (M(^{35}Cl))$^+$ HRMS C$_{15}$H$_{11}$O$_2$Cl$_3$ [M+]: found 370.0292; calcd 370.0289 (+) 0.9 ppm.

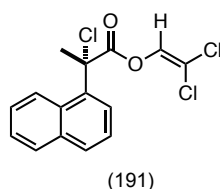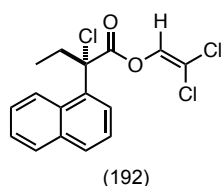**195-(*S*)-2,2-Dichlorovinyl 2-chloro-3-methyl-2-phenylbutanoate**

(195)
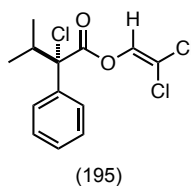
Scheme 51. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), *i*-

propoylphenylketene **194** (160 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 12 h gave crude product that was purified by flash silica chromatography (0.5% Et$_2$O :petrol) to give **195** as a colorless oil; (266 mg, 86% yield); $[\alpha]_D^{20}$ − 6 (*c* 1.0, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (*S*): 5.5 min, t$_R$ minor (*R*): 8.4 min, 88% *ee*; ν$_{max}$ (thin film)/cm^{-1} 3094, 2977, 1755 (C=O), 1494, 1447, 1390, 1282, 1205, 1126, 1008, 867, 764 and 695; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 0.84 (3H, d, *J* 6.5, CH(C*H*$_3$)$_2$), 1.15 (3H, d, *J* 6.5, CH(C*H*$_3$)$_2$), 2.98-3.11 (1H, m, C*H*(CH$_3$)$_2$), 7.31-7.41 (3H, m, Ar*H*-3,4,5), 7.51 (1H, s, C*H*(CCl$_2$)) and 7.63-7.66 (2H, m, Ar*H*-2,6); ^{13}C NMR (75 MHz CDCl$_3$): δ$_C$ 17.0 (*C*H$_3$), 18.8 (*C*H$_3$), 37.1 (*C*H), 80.8 (*C*(Ar)*i*-Pr), 114.3 (*C*Cl$_2$), 126.9 (Ar*C*-2,6), 128.5 (Ar*C*-3,5), 128.7 (Ar*C*-4), 133.2 (*C*H(CCl$_2$)), 137.1 (Ar*C*-1) and 166.0 (*C*=O); *m/z*: (ASAP) (M(^{35}Cl))$^+$ HRMS C$_{13}$H$_{17}$O$_2$NCl$_3$ [M+NH$_4$]$^+$: found 324.0323; calcd 324.0319 (+) 0.9 ppm.

Assignment of the absolute configuration of **192**: (*S*)-2-chloro-2-(naphthalen-1-yl)-*N*-((*S*)-1-phenylethyl)butanamide

(197)
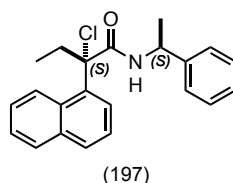
Scheme 53. To a solution of **192** (60.0 mg, 0.17 mmol, 1.0 equiv, 94% *ee*) in CH$_2$Cl$_2$ (3 mL) at 0 °C, was added Br$_2$ (9 μL, 0.17 mmol, 1.0 equiv) and the solution warmed to rt and stirred for 1.5 h. The volatiles were removed *in vacuo* and the crude material dissolved in in THF (3 mL). To this solution was added (*S*)-(−)-α-methylbenzylamine (0.11 mL, 0.87 mmol, 5.0 equiv) and the resulting light blue solution stirred for 16 h at rt. The solution was diluted with EtOAc and washed with 2 × 1M HCl, dried Na$_2$SO$_4$ and concentrated *in vacuo* to give crude material that was purified by flash silica chromatography (5% to 10% Et$_2$O :petrol) to give a **197** as a pale yellow solid; (55 mg, 90% yield); mp 98-100 °C; $[\alpha]_D^{20}$ + 110 (*c* 0.15, CHCl$_3$); ν$_{max}$ (ATR)/cm^{-1} 3298, 2926, 1645 (C=O), 1510, 1450, 1234, 1132, 1022 and 910 ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 0.94 (3H, t, *J* 7.2, CH$_A$H$_B$C*H*$_3$), 1.38 (3H, d, *J* 6.9, C*H*$_3$), 2.67 (1H, dq, *J* 14.3, 7.2, C*H*$_A$H$_B$CH$_3$), 2.76 (1H, dq, *J* 14.3, 7.2, CH$_A$*H*$_B$CH$_3$), 5.16 (1H, *app* quintet, *J* 7.2, C*H*(CH$_3$)Ph), 6.44 (1H, d, *J* 7.8, N*H*), 7.23-7.27 (3H, m, Ph*H*), 7.29-7.33 (2H,

m, Ph*H*), 7.47-7.52 (3H, m, Nap*H*), 7.85-7.91 (3H, m, Nap*H*) and 8.14-8.17 (1H, m, Nap*H*); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 9.4 (CH$_2$*C*H$_3$), 34.3 (*C*H$_3$), 49.9 (*C*H$_2$CH$_3$), 77.2 (*C*(Nap)Et), 125.1 (Ar*C*), 125.2 (Ar*C*), 126.1 (Ar*C*), 126.2 (Ar*C*), 126.5 (Ar*C*), 126.6 (Ar*C*), 126.7 (Ar*C*), 128.9 (Ar*C*), 129.6 (Ar*C*), 130.5 (Ar*C*), 130.8 (Ar*C*), 134.8 (Ar*C*), 136.1 (Ar*C*), 143.1 (Ar*C*) and 169.9 (*C*=O); *m/z*: (ESI+) (M(^{35}Cl))$^+$ HRMS C$_{22}$H$_{23}$ONCl [M+H]$^+$: found 352.1467; calcd 352.1463 (+) 1.2 ppm.

(**209**)-3-Ethyl-3-(2-methoxyphenyl)-4-(trichloromethyl)oxetan-2-one and (**210**)-2,2-Dichlorovinyl 2-chloro-2-(2-mhoxyphenyl)butanoate.

(209)-*syn*   (210)

(~66:33 ratio of 209 to 210)
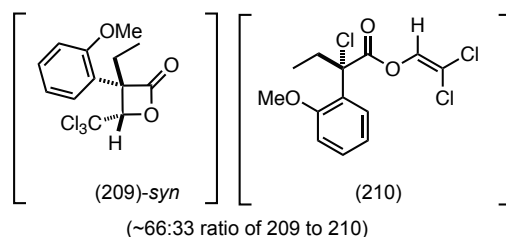
Scheme 54. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-2-methoxyphenylketene **208** (176 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 3 h gave crude product as a ~66:33 mixture of lactone **209** (*dr* >95:5, *syn:anti*) and **210** that was purified by flash silica chromatography (1% Et$_2$O :petrol) **210** as a colorless oil; (37 mg, 11% yield); $[\alpha]_D^{20}$+5 (*c* 0.75, CHCl$_3$); ν_{max} (thin film)/cm^{-1} 3091, 2977, 2940, 1772 (C=O), 1601, 1587, 1489, 1464, 1437, 1247, 1195, 1135, 1089, 1026, 992, 906, 863, 752 and 616; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.87 (3H, t, *J* 7.3, CH$_2$C*H*$_3$), 2.37-2.51 (2H, m, C*H*$_2$CH$_3$), 3.77 (3H, s, ArOC*H*$_3$), 6.87 (1H, dd, *J* 8.2, 7.5, Ar*H*), 7.02 (1H, td, *J* 7.6, 1.1, Ar*H*), 7.34 (1H, ddd, *J* 8.2, 7.5, 1.6, Ar*H*), 7.55 (1H, s, C*H*(CCl$_2$)) and 7.65 (1H, dd, *J* 7.5, 1.6, Ar*H*); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 8.4 (*C*H$_3$), 31.9 (*C*H$_2$), 55.5 (ArO*C*H$_3$), 72.3 (*C*(Ar)Et), 110.1 (Ar*C*H), 113.5 (*C*Cl$_2$), 120.7 (Ar*C*H), 126.7 (Ar*C*-2), 128.4 (Ar*C*H), 130.0 (Ar*C*H), 133.5 (*C*H(CCl$_2$)), 155.2 (Ar*C*-1) and 167.0 (*C*=O); *m/z*: (ESI +) (M(^{35}Cl))$^+$ HRMS C$_{13}$H$_{13}$O$_3$Cl$_3$ [M+]$^+$: found 321.9928; calcd 321.9925 (+) 1.0 ppm.

209 as a colorless solid; (158 mg, 48% yield); mp 76-79 °C; $[\alpha]_D^{20}$ +140 (*c* 0.66, CHCl$_3$); Chiral HPLC analysis; Chiralpak AD-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm) t$_R$ major (3*S*,4*S*): 6.9 min, t$_R$ minor (3*R*,4*R*) 7.8 min >99% ee; ν_{max}

(KBr film)/cm^{-1} 2983, 1832, 1601 (C=O), 1585, 1499, 1464, 1438, 1292, 1256, 1182, 1148, 1088, 1026, 905, 838 and 809; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.87 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.27 (1H, dq, *J* 13.9, 7.0, C*H*$_2$CH$_3$), 3.01 (1H, dq, *J* 13.9, 7.0, C*H*$_2$CH$_3$), 3.76 (3H, s, ArOC*H*$_3$), 4.92 (1H, s, C*H*Cl$_3$) 6.85 (1H, d, *J* 8.3, Ar*H*), 6.9 (1H, *app* t, *J* 7.5, Ar*H*), 7.30 (1H, m, Ar*H*) and 7.58 (1H, d, *J* 7.4, Ar*H*); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 9.1 (*C*H$_3$), 29.8 (*C*H$_2$), 54.5 (ArO*C*H$_3$), 68.4 (*C*(Ar)Et), 87.5 (*C*H(CCl$_3$)), 96.4 (*C*Cl$_3$), 110.9 (Ar*C*H), 118.9 (Ar*C*-1), 120.4 (Ar*C*H), 130.1 (Ar*C*H), 131.4 (Ar*C*H), 156.6 (Ar*C*-2) and 170.4 (*C*=O); *m/z*: (ESI+) (M(^{35}Cl))$^+$ HRMS C$_{13}$H$_{13}$O$_3$Cl$_3$ [M+]$^+$: found 321.9926; calcd 321.9925 (+) 0.4 ppm.

(**215**)-(*S*)-2,2-Dichlorovinyl 2-chloro-3-methyl-2-(thiophen-3-yl)butanoate and (**214**)-3-Isopropyl-3-(thiophen-3-yl)-4-(trichloromethyl)oxetan-2-one

(215)   (214)-*anti*   (214)-*syn*

16:84 *dr, anti:syn*

(~75:25 ratio of 215 to 214)
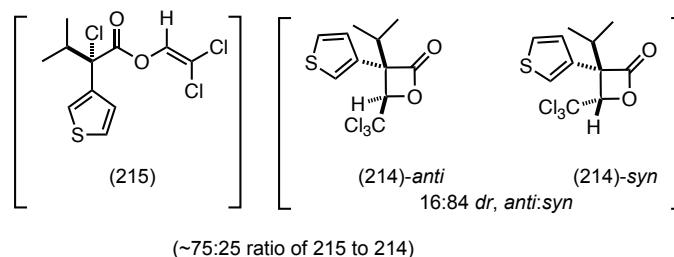
Scheme 55. Following general procedure **1**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), *i*-propyl-3-thioylketene **213** (166 mg, 1.00 mmol, 1.0 equiv) and chloral (0.10 mL, 1.00 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C for 3 h gave crude product as a ~75:25 mixture of **215** and β-lactone **214** (*dr* 84:16, *syn:anti*)) that was purified by flash silica chromatography (1% Et$_2$O :petrol)

215 as a pale yellow oil; (99 mg, 32% yield); $[\alpha]_D^{20}$ –32 (*c* 0.70, CHCl$_3$); Chiral HPLC analysis; Chiralcel OJ-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 254 nm) t$_R$ major (*S*): 5.4 min, t$_R$ minor (*R*): 6.3 min, 78% *ee*; ν$_{max}$ (thin film)/cm^{-1} 3095, 2976, 1777 (C=O), 1650, 1465, 1390, 1280, 1187, 1125, 1007, 849, 770, 686 and 649; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.87 (3H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.10 (3H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 2.97 (1H, sep, *J* 6.6, C*H*(CH$_3$)$_2$), 7.23 (1H, dd, *J* 5.1, 1.3, Ar*H*), 7.33 (1H, dd, *J* 3.1, 5.1, Ar*H*), 7.52 (1H, dd, *J* 3.1, 1.3, Ar*H*) and 7.55 (1H, s, C*H*(CCl$_2$)); ^{13}C NMR (100 MHz CDCl$_3$): δ_C 17.0 (*C*H$_3$), 18.3 (*C*H$_3$), 37.8 (*C*H), 78.5 (*C*(Ar)*i*-Pr), 114.3 (*C*Cl$_2$), 124.7 (Ar*C*H), 126.4 (Ar*C*H), 126.4 (Ar*C*H), 133.2 (*C*H(CCl$_2$)), 138.7

(Ar*C*) and 165.4 (*C*=O); *m/z*: (ASAP) [NH$_4$+] (M(^{35}Cl))$^+$ HRMS C$_{11}$H$_{15}$O$_2$N$_1$Cl$_3$S$_1$ [M+]$^+$: found 329.9890; calcd 329.9884 (+) 1.9 ppm.

214 *Syn* as pale yellow oil;   (8 mg, 3% yield); $[\alpha]_D^{20}$+213 (*c* 0.4, CHCl$_3$); ν$_{max}$ (KBr)/cm^{-1} 2926, 1840 (C=O), 1642, 1464, 1373, 1262, 1097, 937, 867, 833, 789 and 757; ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 1.04 (3H, d, *J* 6.7, CH(C*H$_3$*)$_2$), 1.10 (3H, d, *J* 6.7, CH(C*H$_3$*)$_2$), 2.42 (1H, app quintet, *J* 6.8, C*H*(CH$_3$)$_2$, 4.98 (1H, s, C*H*Cl$_3$), 7.17 (1H, dd, *J* 5.1, 1.3, Ar*H*), 7.30-7.32 (1H, m, Ar*H*) and 7.42 (1H, dd, *J* 2.9, 1.3, Ar*H*); ^{13}C NMR *characteristic signals* (75 MHz CDCl$_3$) δ$_C$ 69.2 (*C*(Ar)*i*-Pr), 84.2 (*C*H(CCl$_3$)), 94.6 (*C*Cl$_3$), 123.9 (Ar*C*H), 124.2 (Ar*C*H), 126.7 (Ar*C*H) and 167.9 (*C*=O); *m/z*: (ESI+) (M(^{35}Cl))$^+$ HRMS C$_{11}$H$_{11}$O$_2$Cl$_3$S [M+NH$_4$]$^+$: found 311.9541; calcd 311.9540 (+) 0.4 ppm.

Experimental information for chapter 4

General experimental procedures

General procedure (1): Reaction Optermisation

To a flame dried Schlenk flask under an argon atmosphere was added NHC-precursor **66** (0.1 equiv), KHMDS (0.09 equiv) and toluene (0.4 relative volumes) and the mixture stirred for 15 min. The solution was then cooled to the required temperature and the requsite aldehyde (1.2 equiv) added followed by the dropwise addition of a solution of the ethylphenylketene (1.0 equiv) in toluene (0.6 relative volumes) over 0.5 h. The solution was stirred for the given period before opening to air for 0.5 h and concentration *in vacuo*. The resulting crude residue was purified by flash silica chromatography to provide the title compound.

General procedure (2): Lactonisation with 2-nitrobenzaldehyde and dropwise ketene addtion at −50 °C

To a flame dried Schlenk flask under an argon atmosphere was added NHC-precursor **66** (0.1 equiv), KHMDS (0.09 equiv) and toluene (0.4 relative volumes) and the mixture stirred for 15 min. The solution was then cooled to −50 °C and 2-nitrobenzaldehyde (1.2 equiv) added followed by the dropwise addition of a solution

of the required ketene (1.0 equiv) in toluene (0.6 relative volumes) over 0.5 h. The solution was stirred for 3 h before opening to air for 0.5 h and concentration *in vacuo*. The resulting crude residue was purified by flash silica chromatography to provide the title compound.

General procedure (3): Benzylation

To a solution of the requisite compound (1.0 equiv) in the required volume of DMF was added benzylbromide (1.2 equiv) and *i*-Pr$_2$NEt (1.2 equiv) and the reaction stirred at rt for 12 h. The reaction was then diluted with Et$_2$O , washed with 2 M HCl and H$_2$O (× 2) before drying (Na$_2$SO$_4$) and concentration *in vacuo* to afford the crude product that was purified by flash silica chromatography to provide the title compound.

(431)-*Anti*-3-Ethyl-3-phenyl-4-(4-(trifluoromethyl)phenyl)oxetan-2-one and **(431)**-*Syn*-3-Ethyl-3-phenyl-4-(4-(trifluoromethyl)phenyl)oxetan-2-one

(431)-*anti*   (431)-*syn*
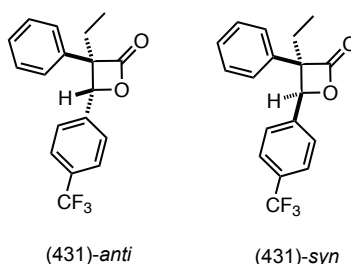
Table 4 Entry 2. Following general procedure **1**: NHC precatalyst **66** (28.5 mg, 0.05 mmol, 0.10 equiv), KHMDS (0.09 mL, 0.045 mmol, 0.09 equiv), ethylphenylketene **146** (73.1 mg, 0.50 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzaldehyde (102 µL, 0.75 mmol, 1.5 equiv) in toluene (10 mL) at 0 °C to rt over 16 h gave crude product (*dr* 72:28, *anti*:*syn*) that was purified by flash silica chromatography (3% Et$_2$O :petrol) to give

Anti (eluted first) as a colourless solid; (88 mg, 55% yield); mp 62 °C; $[\alpha]_D^{20}$ + 3.4 (*c* 0.5, CHCl$_3$); Chiral HPLC analysis Chiralpak AS-H (1% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t$_R$ major: 10.4 min, t$_R$ minor: 21.9 min, 38% *ee*; ν$_{max}$ (KBr)/cm^{-1} 2972, 1827 (C=O), 1621, 1450, 1415, 1324, 1175, 1139, 1101, 1065, 954, 906, 835 and 700; ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 0.69 (3H, t, *J* 7.4, CH$_2$C*H$_3$*), 1.48 (1H, dq, *J* 14.3, 7.2, C*H$_2$*CH$_3$) 1.71 (1H, dq, *J* 7.2, 14.3, C*H$_2$*CH$_3$), 5.72 (1H, s, C*H*(Ar)), 7.38-7.50 (5H, m, Ar*H*), 7.61 (2H, d, *J* 8.2, Ar*H*CF$_3$-3,5) and 7.76 (2H, d, *J* 8.2, Ar*H*CF$_3$-

2,6); ^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ_F –63; ^{13}C NMR (100 MHz, CDCl$_3$) δ_c 8.3 (*C*H$_3$), 27.3 (*C*H$_2$), 68.9 (*C*(Ph)Et), 82.0 (Ar*C*H), 123.9 (d, *J* 272, Ar*C*F$_3$), 125.8 (q, *J* 3.6, *C*ArCF$_3$-2,6), 126.2 (d, *J* 4.3, *C*ArCF$_3$-3,5), 128.1 (Ar*C*), 129.2 (Ar*C*), 129.2 (Ar*C*), 131.0 (q, *J* 32.7, *C*ArCF$_3$-4), 137.1(Ar*C*), 138.9 (Ar*C*) and 171.3 (C=O); *m/z*: (ASAP) HRMS [M+] C$_{18}$H$_{15}$F$_3$O$_2$N$^+$: found 321.1096; calcd 321.1097 (–) 0.3 ppm.

Syn (eluted second) as a colorless solid; (55 mg, 28% yield); mp 104–106 °C; $[\alpha]_D^{20}$ –40 (*c* 0.05, CHCl$_3$); Chiral HPLC analysis Chiralcel OJ-H (5% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t$_R$ major: 20.7 min, t$_R$ minor: 24.9 min, 80% *ee*; ν_{max} (KBr)/cm^{-1} 2972, 1819 (C=O), 1622, 1496, 1450, 1425, 1335, 1255, 1170, 1119, 1072, 1018, 949, 882, 835, 755 and 700; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.07 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.25-2.44 (2H, m, C*H*$_2$CH$_3$) 5.59 (1H, s, C*H*(Ar)), 6.94-6.97 (2H, m, Ar*H*-2,6), 7.09-7.12 (3H, m, Ar*H*-3,4,5) and 7.18 (2H, d, *J* 8.2, ArHCF$_3$-3,5) and 7.42 (2H, d, *J* 8.2, ArCF$_3$-2,6); ^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ_F –63; ^{13}C NMR (100 MHz, CDCl$_3$) δ_c 9.3 (*C*H$_3$), 31.6 (*C*H$_2$), 71.5 (*C*(Ph)Et), 82.0 (*C*HAr), 124.1 (d, *J* 268, Ar*C*F$_3$), 125.1 (q, *J* 3.6, *C*ArCF$_3$-2,6), 127.1 (Ar*C*), 127.4 (Ar*C*), 127.7 (Ar*C*), 128.7 (Ar*C*), 130.8 (q, *J* 32.6, *C*ArCF$_3$-3,5), 134.2 (Ar*C*), 139.3 (*C*Ar) and 171.7 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{18}$H$_{15}$F$_3$O$_2$N$^+$: found 321.1100; calcd 321.1097 (–) 0.6 ppm.

(236)-*Anti*-(3*R*,4*R*)-3-Ethyl-4-(4-nitrophenyl)-3-phenyloxetan-2-one and **(432)**-*Syn*-(3*R*,4*S*)-3-Ethyl-4-(4-nitrophenyl)-3-phenyloxetan-2-one

(236)-*anti*　　　(432)-*syn*

Table 4 Entry 3. Following general procedure **1**: NHC precatalyst **66** (28.5 mg, 0.05 mmol, 0.10 equiv), KHMDS (0.09 mL, 0.045 mmol, 0.09 equiv), ethylphenylketene **46** (73.1 mg, 0.50 mmol, 1.0 equiv) and 4-nitrobenzaldehyde (75.6 mg, 0.50 mmol, 1.0 equiv) in toluene (10 mL) at 0 °C to rt over 16 h gave crude product (*dr* 62:38, *anti*:*syn*) that was purified by flash silica chromatography (20% Et$_2$O :petrol) to give:

Anti (eluted first) as a colourless solid; (74 mg, 50% yield); mp 122-124 °C; $[\alpha]_D^{20}$ −24 (*c* 0.25, CHCl₃); Chiral HPLC analysis Chiralpak AS-H (10% IPA:hexane, flow rate 1.0 mL min⁻¹, 220 nm) t_R major (*R,R*): 20.4 min, t_R minor (*S,S*): 30.0 min, 13% *ee*; ν_{max} (KBr)/cm⁻¹ 2974, 1818 (C=O), 1603, 1514 (NO₂), 1344 (NO₂), 1170, 1105, 956, 904, 858, 759 and 699; ¹H NMR (400 MHz, CDCl₃) δ_H 0.69 (3H, t, *J* 7.4, CH₂C*H*₃), 1.48 (1H, dq, *J* 14.2, 7.2, C*H*₂CH₃) 1.68 (1H, dq, *J* 7.2, 14.2, C*H*₂CH₃), 5.75 (1H, s, C*H*(Ar)), 7.37-7.50 (5H, m, Ar*H*), 7.65-7.68 (2H, m, Ar*H*-NO₂-2,6) and 8.34-8.38 (2H, m, Ar*H*-NO₂-3,5); ¹³C NMR (100 MHz, CDCl₃) δ_c 8.4 (*C*H₃), 27.3 (*C*H₂), 69.3 (*C*(Ph)Et), 81.6 (*C*HAr), 124.1 (*C*ArNO₂-3,5), 126.2 (Ph*C*-2,6), 126.7 (*C*ArNO₂-2,6), 128.3 (Ph*C*-4), 129.3 (Ph*C*-3,5), 136.7(Ph*C*-1), 142.1 (*C*ArNO₂-1), 148.2 (*C*ArNO₂-4) and 170.8 (*C*=O); *m/z*: (ASAP) HRMS [M+] C₁₇H₁₆O₄N⁺: found 298.1070; calcd 298.1074 (−) 1.3 ppm.

Syn (eluted second) as a colourless solid (45 mg, 30% yield); mp 90-92 °C; $[\alpha]_D^{20}$ −14 (*c* 0.55, CHCl₃); Chiral HPLC analysis Chiralcel OJ-H (10% IPA:hexane, flow rate 1.0 mL min⁻¹, 220 nm) t_R major (*R,S*): 36.0 min, t_R minor (*S,R*): 43.8 min, 82% *ee*; ν_{max} (KBr)/cm⁻¹ 2973, 1815 (C=O), 1604, 1516 (NO₂), 1352 (NO₂), 1127, 945, 892, 858, 752 and 699; ¹H NMR (400 MHz, CDCl₃) δ_H 1.08 (3H, t, *J* 7.4, CH₂C*H*₃), 2.27-2.49 (2H, m, C*H*₂CH₃) 5.63 (1H, s, C*H*(Ar)), 6.94-6.97 (2H, m, Ph*H*-2,6), 7.08-7.15 (3H, m, Ar*H*-3,4,5), 7.23-7.26 (2H, m, Ar*H*-NO₂-2,6) and 8.01-8.03 (2H, m, Ar*H*-NO₂-3,5); ¹³C NMR (100 MHz, CDCl₃) δ_c 9.3 (*C*H₃), 31.3 (*C*H₂), 72.2 (*C*(Ph)Et), 81.5 (*C*HAr), 123.3 (*C*ArNO₂-3,5), 126.8 (Ph*C*-2,6), 127.6 (*C*ArNO₂-2,6), 127.8 (Ph*C*-4), 128.7 (Ph*C*-3,5), 133.6 (Ph*C*-1), 142.4 (*C*ArNO₂-1), 147.8 (*C*ArNO₂-4) and 171.2 (*C*=O); *m/z*: (ASAP) HRMS [M+] C₁₇H₁₆O₄N⁺: found 298.1073; calcd 298.1074 (−) 0.3 ppm.

Table 4, Entry 5 *Anti* (76% *ee*, obtained from the reaction at −78 °C with dropwise addition of 1.5 equiv of ethylphenylketene over 0.5 h) derivitised to the corresponding β-hydroxy acid following the procedure of Kerrigan.[18] **236** (80 mg, 0.27 mmol, 1.0 equiv), KOH (0.54 mL, 0.53 mmol, 2.0 equiv), THF (1mL) gave after 3 h **237** as a colourless gum; (45 mg, 52% yield); $[\alpha]_D^{20}$ −46 (*c* 0.05, EtOAc) {literature[18] −47.5 (*c* 0.32, EtOAc), 87% *ee* (*R,R*)} confirming the absolute stereochemistry of **337** to be (*R,R*); ¹H NMR (300 MHz, CDCl₃) δ_H 1.15 (3H, t, *J* 7.4 CH₂C*H*₃), 1.93-2.05 (1H, m,

C*H*$_2$CH$_3$), 2.09-2.01 (1H, m, C*H*$_2$CH$_3$), 5.44 (1H, s, C(OH)*H*), 6.93 (2H, d, *J* 8.8 Ar*H*), 7.03-7.07 (2H, m, Ar*H*), 7.29-7.32 (3H, m, Ar*H*) and 7.95 (2H, d, *J,* 8.8, Ar*H*).

**(238)-**(3*S*,4*R*)-3-Ethyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one
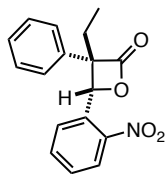
(238)-*syn*

Table 5 Entry 3. Following general procedure **2**: NHC precatalyst **66** (28.5 mg, 0.05 mmol, 0.10 equiv), KHMDS (0.09 mL, 0.045 mmol, 0.09 equiv), ethylphenylketene **146** (73.1 mg, 0.50 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (91 mg, 0.60 mmol, 1.2 equiv) in toluene (10 mL) at –50 °C for 3.5 h gave crude product (*dr* 93:7 *syn*:*anti*) that was purified by flash silica chromatography (5% Et$_2$O :petrol) to give:

Syn as an off white solid[19] (157 mg, 83% yield); mp 58-62 °C [mp of (±) **238** is 86 °C]; $[\alpha]_D^{20}$ –44 (*c* 0.45, CHCl$_3$); Chiral HPLC analysis Chiralcel OJ-H (5% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t$_R$ major: (*S*,*R*) 43.7 min, t$_R$ minor: (*R*,*S*) 51.1 min, 93% *ee*; ν$_{max}$ (KBr)/cm^{-1} 3094, 1768 (C=O), 1646, 1513, 1452, 1377, 1214, 1124, 971, 883, 851, 778 and 738; ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 1.15 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.44-2.59 (2H, m, C*H*$_2$CH$_3$), 6.16 (1H, s, C*H*(Ar)), 6.91-6.98 (5H, m, Ar*H*), 7.20 (1H, *app* t, *J* 7.5, Ar*H*NO$_2$-4), 7.40 (2H, *app* dt, *J* 7.8, 15.7 15.`Ar*H*NO$_2$-5,6) and 7.86 (1H, *app* d, *J* 8.2, Ar*H*NO$_2$-3); ^{13}C NMR (75 MHz, CDCl$_3$) δ$_c$ 9.4 (*C*H$_3$), 29.4 (*C*H$_2$), 72.7 (*C*(Ph)Et), 79.5 (*C*HAr), 124.7 (*C*ArNO$_2$-3), 126.8 (Ph*C*H), 127.8 (Ph*C*H-4), 128.2 (*C*ArNO$_2$-6) 128.5 (Ph*C*H), 129.0 (*C*ArNO$_2$-4), 132.8 (*C*ArNO$_2$-1), 133.8 (Ph*C*-1), 134.1 (*C*ArNO$_2$-5), 146.2 (*C*ArNO$_2$-2) and 172.3 (*C*=O); *m/z*: (EI) HRMS [M+] C$_{17}$H$_{16}$O$_4$N$_1^+$: found 298.1078; calcd 298.1074 (+) 1.4 ppm.

(244)-Benzyl 2-((2-fluorophenyl)(hydroxy)methyl)-2-phenylbutanoate

(241)-50:50 *dr*   (244)-51:49 *dr*
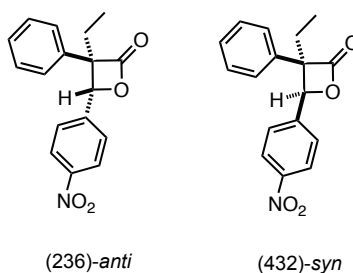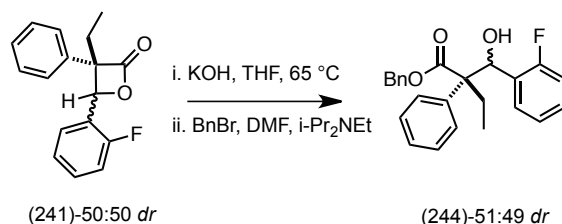
Table 6 Entry 1. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethylphenylketene **146** (146 mg, 1.00 mmol, 1.0 equiv) and 2-fluorobenzaldehyde (126 µL, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 4 h gave the crude product as an inseparable mixture of diastereoisomers (*dr* 51:49). The crude product was dissolved in CH_2Cl_2 washed with 1 M HCl, *dr*ied with Na_2SO_4, concentrated *in vacuo* and used without further purification.

To a solution of the crude lactone product (assume 1.0 mmol) in THF (3 mL) was added KOH (2 mL, 2.00 mmol, 2.0 equiv) and the resulting bi-phasic mixture stirred at 65 °C for 12 h. The solution was cooled to rt, diluted with EtOAc and extracted with $NaHCO_3$. The basic aquous phase was re-acidified with 2 M HCl, extracted with EtOAc (×3), combined, dried with Na_2SO_4 and concentrated *in vacuo* to yield the crude hydroxy acid (119 mg, *dr* 51:49) that was used without further purification.

Following general procedure **3**, (119 mg, assume 0.31mmol, 1.0 mmol), benzylbromide (0.06 mL, 0.37 mmol, 1.2 equiv), *i*-Pr$_2$NEt (0.07 mL, 0.37 mmol, 1.2 equiv) in DMF (2 mL) gave after flash silica chromatography (10% Et$_2$O :petrol) **244** as a colorless oil (112 mg, 51:49 *dr*, 29% yield, based on ketene); Chiral HPLC analysis Chiralpak AD-H (2% IPA:hexane, flow rate 2.0 mL min^{-1}, 220 nm) minor diasteroisomer: t$_R$ minor: 12.9 min, t$_R$ major: 16.3 min, 87% *ee*; major diasteroisomer: t$_R$ minor: 23.2 min, t$_R$ major: 25.6 min, 69% *ee*; ν$_{max}$ (KBr)/cm^{-1} 3535, 2970, 1709 (C=O), 1586, 1491, 1456, 1222, 1124, 758 and 698; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$: 0.80 (3H, t, *J* 7.3, CH$_2$C*H*$_3$), 0.91 (3H, t, *J* 7.3, CH$_2$C*H*$_3$), 1.72-1.97 (3H, m, C*H*$_2$CH$_3$), 2.08 (1H, dq, *J* 14.4, 7.2, C*H*$_2$CH$_3$), 3.72 (1H, d, *J* 3.7, O*H*), 4.07 (1H, d, *J* 5.7, O*H*) 5.10-5.21 (4H, m, OC*H*$_2$Ph), 5.58 (1H, d, *J* 5.7, C*H*OH), 5.73 (1H, d, *J* 3.7, C*H*OH), 5.99 (1H, td, *J* 1.6, 7.6, Ar*H*), 6.60 (1H, td, *J* 0.8, 7.6, Ar*H*), 6.71 (1H, ddd, *J* 10.5, 18.2, 2, , Ar*H*), 6.81-6.88 (3H, m, Ar*H*), 6.92-7.03 (4H, m, Ar*H*) and 7.02-7.29 (18*H*, m, Ar*H*); ^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ$_F$ −117 and −116; ^{13}C NMR (75 MHz,

CDCl$_3$) δ$_c$ 9.3 and 9.4 (2 × rotameric CH_3), 10.1 (CH_3), 25.8 (CH_2CH_3), 26.6 (CH_2CH_3), 60.9 (C(Ph)Et), 61.3 (C(Ph)Et), 67.1 (CH_2Bn), 67.2 (CH_2Bn), 68.5 and 68.5 (2 × rotameric $CHOH$), 72.2 ($CHOH$), 114.3 (d, J 23 CArF-3), 114.9 (d, J, 23 CArF-4), 123.1 (d, J 3 CArF-4), 123.7 (d, J 3), 125.9 (d, J 13 CArF-1), 126.9 (d, J 13 CArF-1), 127.2 (3 × CArH), 128.1 (ArCH), 128.4 (ArCH), 128.5 (ArCH), 128.5 (ArCH), 128.6 (ArCH), 129.0 (ArCH), 129.2 (ArCH), 129.2 (ArCH), 129.3 (ArCH), 130.4 (ArCH), 130.5 (ArCH), 135.2 (PhC-1), 135.4 (PhC-1), 137.1 (CBn-1), 139.0 (CBn-1), 160.1 (d, J 247, CArF-2), 160.2 (d, J 245, CArF-2), 176.1 (C=O) and 176.5 (C=O), (2 ArC could not be resolved); *m/z*: (EI) HRMS [M+NH$_4$] $C_{24}H_{23}O_3FNH_4^+$: found 396.1971; calcd 396.1969 (+) 0.4 ppm.

(245)-Benzyl 2-((2-chlorophenyl)(hydroxy)methyl)-2-phenylbutanoate

(242)-52:48 *dr*   (245)-66:34 *dr*

Table 6, Entry 2. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethylphenylketene (146 mg, 1.00 mmol, 1.0 equiv) and 2-chlorobenzaldehyde (140 μL, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 4 h gave a crude product as a mixture of diastereoisomers (*dr* 52:48). The crude product was dissolved in CH$_2$Cl$_2$, passed through a plug of silca, concentrated *in vacuo* and used without purification.

To a solution of the crude lactone product (assume 1.00 mmol) in THF (3 mL) was added KOH (2 mL, 2.00 mmol, 2.0 equiv) and the resultant bi-phasic mixture stirred at 65 °C for 12 h. The solution was cooled to rt, diluted with EtOAc and extracted with NaHCO$_3$. The basic aquous phase was re-acidified with 2 M HCl, extracted with EtOAc (×3), combined, dried with Na$_2$SO$_4$ and concentrated *in vacuo* to yield the crude hydroxy acid (177 mg, *dr* 67:33) that was used without further purification.

Following general procedure **3**, (177 mg, assume 0.51 mmol, 1.0 mmol), benzylbromide (0.07 mL, 0.61 mmol, 1.2 equiv), *i*-Pr$_2$NEt (0.11 mL, 0.61 mmol, 1.2 equiv) in DMF (2 mL) gave after silica chromatography (5% Et$_2$O :petrol) **245** as a colorless oil (142 mg, *dr* 66:34, 36% yield, based on ketene); Chiral HPLC analysis Chiralpak AD-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) minor

diasteromer: t_R minor: 25.8 min, t_R major: 40.2 min, 87% *ee*; major diasteromer: t_R major: 35.8 min, t_R minor: 66.1 min, 76% *ee*; ν_{max} (KBr)/cm^{-1} 3523, 2940, 1708 (C=O), 1438, 1216, 1123, 1033, 751 and 697; ^{1}H NMR (300 MHz, CDCl$_3$) characteristic data for major diastereoisomer δ_H: 0.96 (3H, t, *J* 7.4, CH$_2$C*H$_3$*), 2.02-2.12 (1H, m, C*H$_2$*CH$_3$), 2.19-2.29 (1H, m, C*H$_2$*CH$_3$), 4.25 (1H, d, *J* 5.6, O*H*), 5.30-5.41 (2H, m, OC*H$_2$*Ph) and 5.94 (1H, d, *J* 5.6, C*H*OH); ^{1}H NMR (300 MHz, CDCl$_3$) characteristic data for minor diastereoisomer δ_H: 1.08 (3H, t, *J* 7.4, CH$_2$C*H$_3$*), 2.02-2.12 (2H, m, C*H$_2$*CH$_3$), 3.82 (1H, d, *J* 3.9, O*H*), 5.30-5.41 (2H, m, OC*H$_2$*Ph), 6.03 (1H, d, *J* 3.9, C*H*OH) and 6.07 (1H, dd *J* 1.6, 8.0, Ar*H*); ^{13}C NMR (75 MHz, CDCl$_3$) δ_c: data for combined diastereoisomers: 10.1 (*C*H$_3$), 10.4 (*C*H$_3$), 26.2 (*C*H$_2$ CH$_3$), 26.4 (*C*H$_2$CH$_3$), 61.7 (*C*(Ph)Et), 67.1 (*C*H$_2$Bn), 67.2 (*C*H$_2$Bn), 72.0 (*C*HOH), 74.7 (*C*HOH), 125.7 (*C*ArH) , 126.5 (Ar*C*H), 127.2 (Ar*C*H), 127.3 (Ar*C*H), 128.0 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (Ar*C*H), 128.7 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 129.2 (Ar*C*H), 129.4 (Ar*C*H), 129.8 (Ar*C*H), 131.1 (Ar*C*H), 133.7 (*C*ArCl), 134.5 (*C*ArCl), 135.1 (*C*ArCl), 135.5 (*C*ArCl), 136.7 (Ph*C*-1), 136.9 (Ph*C*-1), 137.5 (*C*Bn-1), 139.2, (*C*Bn-1), , 176.1 (*C*=O) and 176.3 (*C*=O) (3 Ar*C* could not be resolved); *m/z*: (EI) HRMS [M+NH$_4$] C$_{24}$H$_{23}$O$_3$ClNH$_4$$^+$: found 412.1675; calcd 412.1674 (+) 0.2 ppm.

(246)-Benzyl-2-((2-bromophenyl)(hydroxy)methyl)-2-phenylbutanoate

(243)-56:44 *dr*   (246)-57:44 *dr*

Table 6, Entry 3. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethylphenylketene (146 mg, 1.00 mmol, 1.0 equiv) and 2-bromobenzaldehyde (140 μL, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 4h gave crude product as a mixture of diastereoisomers (*dr* 56:44). The crude product was dissolved in CH$_2$Cl$_2$, passed through a plug of silca, concentrated *in vacuo* and used without purification.

To a solution of the crude lactone product (assume 1.00 mmol) in THF (3 mL) was added KOH (2 mL, 2.00 mmol, 2.0 equiv) and the solution stirred at 65 °C for 12 h. The solution was cooled to rt, diluted with EtOAc and extracted with NaHCO$_3$. The

basic aqueous phase was re-acidified with 2M HCl, extracted with EtOAc (×3), combined, dried with Na_2SO_4 and concentrated *in vacuo* to yield the crude hydroxy acid (110 mg, *dr* 55:45) that was used without further purification.

Following general procedure **3** (110 mg, assume 0.31 mmol, 1.0 mmol), benzylbromide (0.04 mL, 0.38 mmol, 1.2 equiv), *i*-Pr$_2$NEt (0.07 mL, 0.38 mmol, 1.2 equiv) in DMF (2 mL) for 16 h gave after flash silica chromatography (5% Et$_2$O :petrol); **246** as a colorless oil (112 mg, 57:43 *dr*, 25% yield, based on ketene); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) major diastereoisomer: t$_R$ minor: 15.0 min, t$_R$ major: 22.1 min, 95% *ee*; minor diastereoisomer: t$_R$ major: 20.5 min, t$_R$ minor: 47.3 min, 71% *ee*; ν_{max} (KBr)/cm^{-1} 3527, 2940, 1709 (C=O), 1434, 1215, 1126, 1021, 748 and 698; ^{1}H NMR (400 MHz, CDCl$_3$) characteristic data for major diastereoisomer: δ_H: 0.92 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 1.86-2.08 (2H, m, C*H*$_2$CH$_3$), 3.55 (1H, d, *J* 4.0, O*H*), 5.19 (2H, s, OC*H*$_2$Ph), 5.82 (1H, d, *J* 4.0, C*H*OH) and 5.87 (1H, d, *J* 1.7, 8.0, Ar*H*); ^{1}H NMR (400 MHz, CDCl$_3$) characteristic data for minor diastereoisomer: δ_H: 0.76 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 1.86-2.08 (2H, m, C*H*$_2$CH$_3$), 4.08 (1H, d, *J* 5.8, O*H*), 5.22 (2H, *app* q, *J* 12.4, OC*H*$_2$Ph) and 5.74 (1H, d, *J* 5.8, C*H*OH) ^{13}C NMR (75 MHz, CDCl$_3$) data for combined diastereoisomers: δ_c: 10.3 (CH$_3$), 10.4 (CH$_3$), 26.4 (CH$_2$ CH$_3$), 26.5 (CH$_2$ CH$_3$), 61.8 (*C*(Ph)Et), 61.9 (*C*(Ph)Et), 67.0 (CH$_2$Bn), 67.2 (CH$_2$Bn), 74.6 (*C*HOH), 77.2 (*C*HOH), 124.4 (*C*ArBr-2), 125.3 (*C*ArBr-2), 126.2 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (*C*ArH), 127.2 (Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.7 (Ar*C*H), 129.2 (Ar*C*H), 129.2 (Ar*C*H), 129.5 (Ar*C*H), 129.9 (Ar*C*H), 131.4 (Ar*C*H), 132.0 (Ar*C*H), 132.7 (Ar*C*H), 135.0 (Ph*C*-1), 135.5 (Ph*C*-1), 136.7 (*C*Bn-1), 138.4 (*C*Bn-1), 139.1 (*C*ArBr-1), 139.2 (*C*ArBr-1), 176.0 (*C*=O) and 176.1 (*C*=O) (2 Ar*C* could not be resolved); *m/z*: (EI) HRMS [M+NH$_4$] C$_{24}$H$_{23}$O$_3$BrNH$_4^+$: found 456.1166; calcd 456.1169 (−) 0.6 ppm.

(242)-3-Methyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one

(242)-*syn*   (242)-*anti*

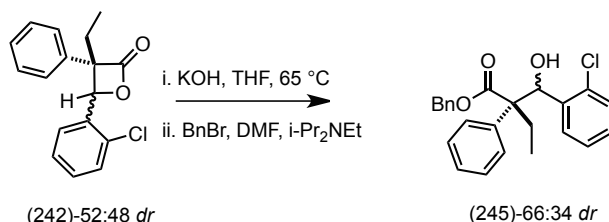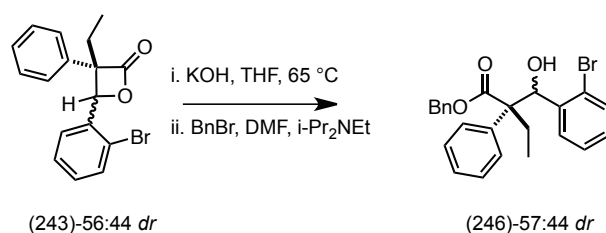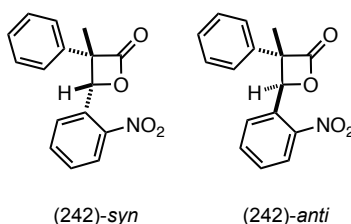**Scheme 65**. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), methylphenylketene **418** (132 mg, 1.00 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 3.5 h gave the crude product (*dr* 43:57 *syn*:*anti*) that was purified by flash silica chromatography (5% Et$_2$O :petrol) to give:

Syn (eluted first) as a colourless solid; (88 mg, 30% yield); mp 68-70 °C; $[\alpha]_D^{20}$ −61 (*c* 0.15, CHCl$_3$); Chiral HPLC analysis Chiralcel OJ-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S,R*): 32.0 min, t_R minor (*R,S*): 36.2 min, 90% *ee*; ν_{max} (KBr)/cm^{-1} 2925, 1834 (C=O), 1527, 1341, 1351 1246, 1133, 945, 911, 866, 790, 745, and 699; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 2.20 (3H, s, C*H*$_3$), 6.22 (1H, s, C*H*(Ar)), 7.00-7.07 (5H, m, Ar*H*), 7.31-7.35 (1H, m, Ar*H*NO$_2$-4) 7.52-7.56 (1H, m, Ar*H*NO$_2$-5/6), 7.61 (1H, d, *J* 7.7, Ar*H*NO$_2$-5/6) and 7.96 (1H, dd, *J* 8.2, 1.2, Ar*H*NO$_2$-3); ^{13}C NMR (75 MHz, CDCl$_3$) δ_c 22.8 (*C*H$_3$), 68.2 (*C*(Ph)Me), 82.4 (*C*HAr), 125.2 (*C*ArNO$_2$-3), 125.9 (Ph*C*H), 128.4 (*C*PhH-4), 128.5 (*C*ArNO$_2$-6), 128.8 (Ph*C*H), 129.5 (*C*ArNO$_2$-4), 133.1 (*C*ArNO$_2$-1), 134.6 (*C*ArNO$_2$-5), 134.7 (*C*PhH-1), 146.6 (*C*ArNO$_2$-2) and 173.4 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{16}$H$_{14}$O$_4$N$^+$: found 284.0912; calcd 284.0917 (−) 1.9 ppm.

Anti (eluted second) as a colourless solid; (103 mg, 35% yield); mp 128–130 °C; $[\alpha]_D^{20}$ − 41 (*c* 0.3, CHCl$_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R major (*S,S*): 22.5 min, t_R minor (*R,R*): 30.4 min, 90% *ee*; ν_{max} (KBr)/cm^{-1} 2982, 1836 (C=O), 1613, 1578, 1526, 1443, 1342, 1125, 1085, 861, 790, 737, 725 and 630; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 1.33 (3H, s, C*H*$_3$), 6.14 (1H, s, C*H*(Ar)), 7.38-7.42 (1H, m, Ar*H*-4), 7.46-7.49 (2H, m, Ar*H*) 7.52-7.54 (2H, m, Ar*H*), 7.60-7.65 (1H, m, Ar*H*NO$_2$-4), 7.83-7.87 (1H, m, Ar*H*NO$_2$-5/6), 7.96 (1H, d, *J* 7.8, Ar*H*NO$_2$-5/6) and 8.24-8.26 (1H, m, Ar*H*NO$_2$-3); ^{13}C NMR (100 MHz, CDCl$_3$) δ_c 15.4 (*C*H$_3$), 65.8 (*C*(Ph)Me), 81.9 (*C*H(Ar)), 125.4 (*C*ArNO$_2$-3), 126.0 (Ph*C*H), 128.2 (*C*PhH-4), 128.4 (*C*ArNO$_2$-6), 129.0 (Ph*C*H), 129.7 (*C*ArNO$_2$-4),

132.2 (CArNO$_2$-1), 134.8 (CArNO$_2$-5), 137.5 (CPhH-1), 146.7 (CArNO$_2$-2) and 172.9 (C=O; *m/z*: (ASAP) HRMS [M+] $C_{16}H_{14}O_4N^+$: found 284.0912; calcd 284.0904 (+) 2.8 ppm.

(248)-(4-Chlorophenyl)-3-methyl-4-(2-nitrophenyl)oxetan-2-one

(248)-*syn*   (248)-*anti*

Scheme 66. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), methyl-4-chlorophenylketene **444** (167 mg, 1.00 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 3.5 h gave crude product (*dr* 55:45 *syn:anti*) that was purified by flash silica chromatography (5% Et$_2$O :petrol) to give **248** *syn* as an off white solid (75 mg, 24% yield); mp 92-94 °C; $[\alpha]_D^{20}$ −49 (*c* 0.15, CHCl$_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R,S*): 15.6 min, t_R major (*S,R*): 18.1 min, 92% *ee*; ν_{max} (KBr)/cm^{-1} 3415, 3110, 1835 (C=O), 1614, 1529, 1494, 1403, 1349, 1243, 1134, 1094, 1012, 945, 943, 916, 838, 747, 731, 644 and 516; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 2.18 (3H, s, CH_3), 6.19 (1H, s, CH(Ar)), 6.96-7.07 (4H, m, *p*-ClArH), 7.36-7.42 (1H, m, ArHNO$_2$-4), 7.56-7.63 (2H, m, ArHNO$_2$-5/6) and 8.01 (1H, dd, *J* 8.0, 0.9, ArHNO$_2$-3); ^{13}C NMR (100 MHz, CDCl$_3$) δ_c 22.5 (CH$_3$), 67.2 (C(PhCl)Me), 81.8(CHAr), 125.0 (CArNO$_2$-3), 128.0 (CArNO$_2$-6), 128.0 (CPhClH), 128.7 (CPhClH), 129.5 (CArNO$_2$-4), 132.3, (CPhClH-4), 133.0 (CArNO$_2$-1), 134.0 (CPhClH-1), 134.4 (CArNO$_2$-5), 146.2 (CArNO$_2$-2) and 172.5 (C=O); *m/z*: (ASAP) HRMS [M+] $C_{16}H_{13}O_4N_1{}^{35}Cl_1^+$: found 318.0526; calcd 318.0528 (−) 0.5 ppm.
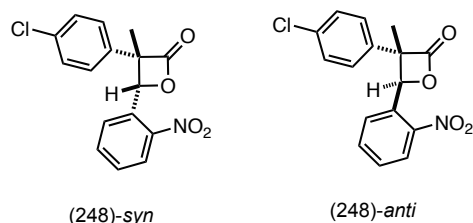
(243)-(3*S*,4*R*)-3-Butyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one

(243)-*syn*

Scheme 65. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), butylphenylketene **419** (174 mg, 1.00 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 3.5 h gave the crude product (*dr* 94:6 *syn*:*anti*) that was purified by flash silica chromatography (5% Et$_2$O :petrol) to give **234** *syn* as an off white solid (240 mg, 74% yield); mp 64-66 °C; $[\alpha]_D^{20}$ −20 (*c* 0.60, CHCl$_3$); ν$_{max}$ (KBr)/cm^{-1} 2958, 1828 (C=O), 1527, 1346, 1117, 918, 790, 744 and 701; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 0.92 (3H, t, *J* 7.3, *n*-BuC*H*$_3$), 1.25-1.34 (1H, m, *n*-Bu*H*), 1.36-1.48 (2H, m, *n*-Bu*H*), 1.67-1.78 (1H, m, *n*-Bu*H*), 2.52-2.59 (2H, m, *n*-Bu*H*), 6.25 (1H, s, C*H*(Ar)), 7.02-7.06 (5H, m, Ar*H*), 7.29 (1H, ddd, *J* 8.3, 7.0, 1.5, Ar*H*NO$_2$-4), 7.44-7.52 (2H, m, Ar*H*NO$_2$-5/6), 7.96 (1H, dd, *J* 8.2, 0.8, Ar*H*NO$_2$-3); ^{1}H NMR (300 MHz, CDCl$_3$) ^{13}C NMR (100 MHz, CDCl$_3$) δ$_c$ 13.8 (*C*H$_3$), 22.9 (*C*H$_2$), 26.9 (*C*H$_2$), 36.1 (*C*H$_2$), 72.4 (*C*(Ph)Bu), 79.7 (*C*HAr), 124.7 (*C*Ar-NO$_2$-3), 126.7 (Ph*C*H), 127.8 (*C*PhH-4), 128.2 (*C*Ar-NO$_2$-6), 128.5 (Ph*C*H), 129.0 (*C*Ar-NO$_2$-4), 132.7 (*C*Ar-NO$_2$-1), 134.0 (Ph*C*-1), 134.0 (*C*Ar-NO$_2$-5), 146.5 (*C*Ar-NO$_2$-2) and 172.1 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{19}$H$_{20}$O$_4$N$_1^+$: found 326.1381; calcd 298.1387 (−) 1.8 ppm.

243 was ring opened with NaN$_3$ and converted to the benzyl ester **433** to allow chiral HPLC analysis:

(433)

A solution of **243** (93 mg, 0.28 mmol, 1.0 equiv) and NaN$_3$ (37 mg, 0.57 mmol, 2.0 equiv) in DMSO (2 mL) was heated to 65 °C for 48 h. After cooling to rt NaHCO$_3$ was added and the solution extracted with Et$_2$O . The aqueous was acidified with 2 M

HCl and extracted three times with Et_2O , washed with water, dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude azide intermediate that was used without further purification. To a solution of the crude azide (assume 0.28 mmol) in DMF (2 mL) was added benzylbromide (0.05 mL, 0.34 mmol, 1.2 equiv) and *i*-Pr_2NEt (0.06 mL, 0.34 mmol, 1.2 equiv) and stirred overnight at rt. The solution was partially concentrated *in vacuo*, diluted with H_2O and extracted with CH_2Cl_2 (×3). The organic phase was then concentrated *in vacuo*, re-diluted with Et_2O and washed with H_2O (×3) and brine. The solution was then dried with Na_2SO_4 and concentrated *in vacuo* to yield the crude product that was purified by flash silica chromatography (5% Et_2O : petrol) to provide **433** as a colorless oil; (31 mg, 24% yield over two steps); $[\alpha]_D^{20}$ +265 (*c* 0.2, MeOH); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor: 4.9 min, t_R major: 6.4 min, 89% *ee*; ν_{max} (thin film)/cm^{-1} 2960, 2104 (N_3), 1732 (C=O), 1533, 1358, 1243, 1207, 1132, 950, 787, 731 and 698; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.76 (3H, t, *J* 7.3, nBuC*H$_3$*), 0.84-0.95 (1H, m, *n*-Bu*H*), 1.11-1.31 (2H, m, *n*-Bu*H*), 1.39-1.44 (1H, m, *n*-Bu*H*), 1.94 (1H, td, *J* 13.0, 3.7 *n*-Bu*H*), 2.45 (1H, td, *J* 12.9, 4.6 *n*-Bu*H*), 4.94 (1H, d, *J* 12.1, BnC*H$_2$*), 5.11 (1H, d, *J* 12.1, BnC*H$_2$*), 6.16 (1H, dd, *J* 1.1, 8.0, Ar*H*NO$_2$), 6.27 (1H, s, C*H*N$_3$), 6.75 (2H, d, *J* 7.5 Ar*H*NO$_2$) 7.03-7.25 (10H, m, Ar*H*) and 7.66 (1H, dd, *J* 1.2, 8.1, Ar*H*NO$_2$), ^{13}C NMR (100 MHz, CDCl$_3$) δ_c 13.9 (*C*H$_3$), 23.2 (*C*H$_2$), 26.8 (*C*H$_2$), 34.8 (*C*H$_2$), 60.1 (*C*(Ph)Bu), 60.6 (*C*H(Ar)N$_3$), 66.9 (*C*H$_2$Bn), 123.8 (*C*ArNO$_2$), 127.6 (Ar*C*H), 127.8 (Ar*C*H), 128.4 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (Ar*C*H), 128.7 (Ar*C*H), 129.0 (Ar*C*H), 130.9 (Ar*C*H), 130.9 (*C*ArNO$_2$-1), 131.6 (*C*ArNO$_2$), 136.2 (*C*ArBn-1), 137.4 (Ph*C*-1), 151.2 (*C*ArNO$_2$-2) and 173.2 (C=O); *m/z*: (EI) HRMS [M+NH$_4$] $C_{26}H_{26}O_4N_4NH_4^+$: found 476.2286; calcd 476.2292 (–) 1.3 ppm.

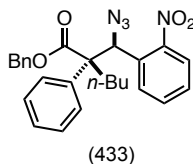**(244)**-(3*S*,4*R*)-3-Isobutyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one

(244)-*syn*

Scheme 65. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), iso-butylphenylketene **60** (167 mg, 1.00 mmol, 1.0 equiv) and 2-nitrobenzaldehyde

(181 mg, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 6 h gave crude product (*dr* 94:6 *syn*:*anti*) that was purified by flash silica chromatography(5% Et$_2$O :petrol) to give **244** *Syn* as an off white solid (95 mg, 30% yield); mp 78-80 °C; $[\alpha]_D^{20}$ 0.0 (*c* 0.3, CHCl$_3$); Chiral HPLC analysis Chiralcel OJ-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm: t_R: 10.6 min, t_R: 12.3 min, <5% *ee*; ν_{max} (KBr)/cm^{-1} 2958, 1819 (C=O), 1613, 1582, 1521, 1448, 1341, 1243, 1118, 974, 904, 788, 842, 706, 642 and 534; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.82 (3H, d, *J* 6.7, *i*-BuC*H*$_3$), 1.06 (3H, d, *J* 6.7, *i*-BuC*H*$_3$), 1.82-1.98 (1H, m, *i*-Bu*H*) 2.44 (1H, dd, *J* 14.6, 6.4, *i*-BuC*H*$_2$), 2.64 (1H, dd, *J* 14.6, 6.4, *i*-BuC*H*$_2$), 6.19 (1H, s, C*H*(Ar)), 7.01-7.07 (5H, m, Ar*H*), 7.26-7.33 (1H, m, Ar*H*NO$_2$-4), 7.43 (2H, d, *J* 3.9, Ar*H*NO$_2$-5,6) and 7.97 (1H, d, *J* 8.1, Ar*H*NO$_2$-3); ^{13}C NMR (100 MHz, CDCl$_3$) δ_c 23.9 (CH$_3$), 23.9 (CH$_3$), 25.5 (CH), 45.3(CH$_2$), 72.3 (*C*(Ph)*i*-Bu), 80.2 (*C*HAr), 124.7 (*C*Ar-NO$_2$-3), 126.8 (Ph*C*H), 127.8 (*C*PhH-4), 128.3 (*C*ArNO$_2$-6), 128.6 (Ph*C*H), 129.1 (*C*ArNO$_2$-4), 132.7 (*C*ArNO$_2$-1), 134.0 (*C*ArNO$_2$-5), 134.4 (Ph*C*-1), 146.9 (*C*ArNO$_2$-2) and 172.1 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{19}$H$_{20}$O$_4$N$_1$$^+$: found 326.1382; calcd 3326.1387 (−) 1.5 ppm
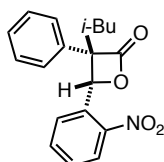
(246)-(3*S*,4*R*)-3-Ethyl-3-(4-fluorophenyl)-4-(2-nitrophenyl)oxetan-2-one

(246)-*syn*

Scheme 65. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-4-flourophenylketene **422** (211 mg, 1.20 mmol, 1.2 equiv) and 2-nitrobenzaldehyde (151 mg, 1.00 mmol, 1.0 equiv) in toluene (10 mL) at −50 °C for 3 h gave crude product (*dr* 93:7 *syn*:*anti*) that was purified by flash silica chromatography (5% Et$_2$O :petrol) to give **246** *syn* as a colourless solid (216 mg, 69% yield); mp 102-104 °C; $[\alpha]_D^{20}$ −19 (*c* 0.85, CHCl$_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R,S*): 11.1 min, t_R major (*S,R*): 12.3 min, 85% *ee*; ν_{max} (KBr)/cm^{-1} 2971, 1831 (C=O), 1614, 1605, 1522, 1319, 1353, 1310, 1299, 1225, 1167, 1144, 1118, 1017, 949, 894, 859, 816, 787, 745, 682, 654, 609, 536 and 506; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 1.14 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.52-

2.67 (2H, m, CH_2CH$_3$), 6.22 (1H, s, CH(Ar)), 6.74-7.78 (2H, m, ArHF-3,5), 7.00-7.04 (2H, m, ArHF-2,6), 7.33-7.37 (1H, m, ArHNO$_2$-4), 7.52 (2H, dd, *J* 1.0, 4.9, ArHNO$_2$-5,6) and 7.99 (1H, d, *J* 8.1, ArHNO$_2$-3); ^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$) δ_F −114; ^{13}C NMR (100 MHz, CDCl$_3$) δ_c 9.3 (*C*H$_3$), 29.5 (*C*H$_2$), 72.3 (*C*(Ar)Et), 79.4 (*C*HAr), 115.5 (d, *J* 21.4 *C*PhF-3,5), 124.8 (*C*Ar-NO$_2$-3), 128.1 (*C*ArNO$_2$-6), 128.6 (d, *J* 8.2 *C*PhF-2,6), 129.2 (*C*ArNO$_2$-4), 129.6 (d *J* 3.1 *C*PhF-1) 132.6 (*C*ArNO$_2$-1), 134.2 (*C*ArNO$_2$-5), 146.5 (*C*ArNO$_2$-2), 162.1 (d, J, 248 *C*PhF-4) and 171.9 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{17}$H$_{15}$F$_1$O$_4$N$_1$$^+$: found 316.0974; calcd 316.0980 (−) 1.8 ppm.

(247)-(3*S*,4*R*)-3-(4-Chlorophenyl)-3-ethyl-4-(2-nitrophenyl)oxetan-2-one
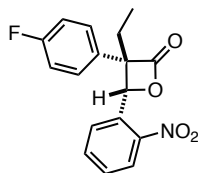

(247)-*syn*

Scheme 65. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-4-chlorophenylketene **423** (181 mg, 1.00 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 3 h h gave the crude product (*dr* 93:7 *syn*:*anti*) that was purified by flash silica chromatography (5% Et$_2$O :petrol) to give **247** *Syn* as an off white solid (262mg, 79% yield); mp 78-80 °C; $[\alpha]_D^{20}$ −15 (*c* 0.5, CHCl$_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t$_R$ minor (*R*,*S*): 22.5 min, t$_R$ major (*S*,*R*): 24.9 min, 86% *ee*; ν_{max} (KBr)/cm^{-1} 2975, 1822 (C=O), 1614, 1525, 1497, 1343, 1250, 1130, 1014, 939, 900, 860, 840, 792, 745, and 685; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.14 (3H, t, *J* 7.4, CH$_2$CH_3), 2.50-2.69 (2H, m, CH_2CH$_3$), 6.23 (1H, s, CH(Ar)), 6.97-7.08 (4H, m, ArClH), 7.34-7.40 (1H, m, ArHNO$_2$-4), 7.51-7.54 (2H, m, ArHNO$_2$-5,6) and 8.00-8.03 (1H, m, ArHNO$_2$-3); ^{13}C NMR (100 MHz, CDCl$_3$) δ_c 9.3 (*C*H$_3$), 29.5 (*C*H$_2$), 72.3 (*C*(Ar)Et), 79.2 (*C*HAr), 124.9 (*C*Ar-NO$_2$-3), 128.1 (*C*ArNO$_2$-6), 128.2 (Ph*C*H), 128.8 (Ph*C*H), 129.4 (*C*ArNO$_2$-4), 132.4 (2×C; (*C*ArNO$_2$-1) and (*C*PhCl-4)), 133.9 (Ph*C*-1), 134.3 (*C*ArNO$_2$-5), 146.5 (*C*ArNO$_2$-2) and 171.6 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{17}$H$_{15}$^{35}Cl$_1$O$_4$N$_1$$^+$: found 332.0681; calcd 332.0684 (−) 0.9 ppm.

(249)-(3*S*,4*R*)-3-(4-Bromophenyl)-3-ethyl-4-(2-nitrophenyl)oxetan-2-one
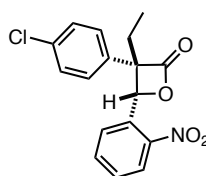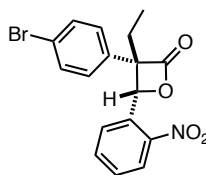

(249)-*syn*

Scheme 65. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-4-bromophenylketene **424** (225 mg, 1.00 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 3 h gave crude product (*dr* 94:6 *syn*:*anti*) that was purified by flash silica chromatography (5% Et$_2$O :petrol) to give **249** *syn* as a pale brown solid (257mg, 68% yield); mp 102-104 °C; $[\alpha]_D^{20}$−14 (*c* 0.5, CHCl$_3$); Chiral HPLC analysis Chiralpak AS-H (5% IPA:hexane, flow rate 0.2 mL min^{-1}, 220 nm) t$_R$ minor (*R*,*S*): 56.8 min, t$_R$ major (*S*,*R*): 61.7 min, 92% *ee*; ν$_{max}$ (KBr)/cm^{-1} 2974, 1821 (C=O), 1613, 1526, 1494, 1342, 1249, 1129, 1077, 1011, 957, 938, 899, 860, 839, 791, 744, 721, 652 and 517; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 1.13 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.49-2.68 (2H, m, C*H*$_2$CH$_3$), 6.21 (1H, s, C*H*(Ar)), 6.79-6.95 (2H, m, ArBr*H*-2,6), 7.18-7.22 (2H, m, ArBr*H*-3,5), 7.34-7.40 (1H, m, Ar*H*NO$_2$-4), 7.50-7.56 (2H, m, Ar*H*NO$_2$-5,6) and 7.99-8.03 (1H, m, Ar*H*NO$_2$-3); ^{13}C NMR (100 MHz, CDCl$_3$) δ$_c$ 9.3 (CH$_3$), 29.5 (CH$_2$), 72.4 (*C*(Ar)Et), 79.2 (CHAr), 122.1 (*C*PhBr-4), 124.9 (*C*Ar-NO$_2$-3), 128.1 (*C*ArNO$_2$-6), 128.5 (*C*PhBrH), 129.4 (*C*ArNO$_2$-4), 131.7 (*C*PhBrH), 132.4 (Ar*C*-1), 132.9 (*C*ArNO$_2$-1), 134.3 (*C*ArNO$_2$-5), 146.6 (*C*ArNO$_2$-2) and 171.6 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{17}$H$_{15}$Br$_1$O$_4$N$_1^{+}$: found 376.0176; calcd 376.0279 (−) 0.8 ppm.

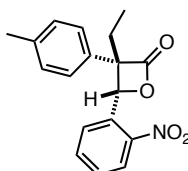**(250)**-(3*S*,4*R*)-3-Ethyl-4-(2-nitrophenyl)-3-(4-tolyl)oxetan-2-one

(250)-*syn*

Scheme 65. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-4-tolylketene

421 (167 mg, 1.00 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 3 h gave the crude product (*dr* 90:10 *syn*:*anti*) that was purified by flash silica chromatography (5% Et$_2$O :petrol) to give **250** *syn* as an off white solid (162 mg, 52% yield); mp 100-102 °C; $[\alpha]_D^{20}$ −39 (*c* 0.25, CHCl$_3$); Chiral HPLC analysis analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t$_R$ minor (*R*,*S*): 9.6 min, t$_R$ major (*S*,*R*): 10.5 min, 83% *ee*; ν_{max} (KBr)/cm^{-1} 2975, 1825 (C=O), 1612, 1526, 1341, 1236, 1134, 1104, 951, 937, 890, 858, 837, 742, 722, 697 and 520; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 1.07 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.07 (3H, s, ArCH$_3$), 2.43-2.61 (2H, m, C*H*$_2$CH$_3$), 6.16 (1H, s, C*H*(Ar)), 6.77-6.85 (4H, m, Ar*H*), 7.24 (1H, ddd, *J* 8.3, 6.8, 1.7, Ar*H*NO$_2$-4), 7.40-7.48 (2H, m, Ar*H*NO$_2$-5,6) and 7.91 (1H, dd, *J* 8.3, 0.9, Ar*H*NO$_2$-3); ^{13}C NMR (75 MHz, CDCl$_3$) δ$_c$ 9.4 (*C*H$_3$), 21.0 (Ar*C*H$_3$, 29.4 (*C*H$_2$), 72.7 (*C*(Ar)Et), 79.5 (*C*HAr), 124.7 (*C*ArNO$_2$-3), 126.6, (Ar*C*H), 128.2 (*C*ArNO$_2$-6), 129.0 (*C*ArNO$_2$-4), 129.2 (Ar*C*H), 130.6 (*C*Ar-1), 132.9 (*C*ArNO$_2$-1), 134.1 (*C*ArNO$_2$-5), 137.5 (*C*PhH-4), 146.5 (*C*ArNO$_2$-2) and 172.3 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{18}$H$_{18}$O$_4$N$_1^+$: found 312.1226; calcd 312.1230 (−) 1.4 ppm.

(251)-(3*S*,4*R*)-3-Ethyl-3-(4-methoxyphenyl)-4-(2-nitrophenyl)oxetan-2-one
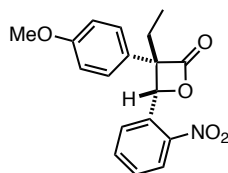

(251)-*syn*

Scheme 65. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), ethyl-4-methoxyphenylketene **425** (211 mg, 1.20 mmol, 1.0 equiv) [1.2 equiv of ketene used to aid purification] and 2-nitrobenzaldehyde (151 mg, 1.00 mmol, 1.2 equiv) in toluene (10 mL) at −50 °C for 3 h gave crude product (*dr* 86:14 *syn*:*anti*) that was purified by flash silica chromatography (10% Et$_2$O :petrol) to give **251** as an off white solid and as a partially separable mixture of diastereoisomers (247 mg, 75% yield); data for major *syn* diastereoisomer; mp 58-64 °C; $[\alpha]_D^{20}$ −57 (*c* 0.25, CHCl$_3$); Chiral HPLC analysis Chiralpak AS-H (10% IPA:hexane, flow rate 0.8 mL min^{-1}, 220 nm) t$_R$ major (*S*, *R*): 18.5 min, t$_R$ minor (*R*,*S*): 20.4 min, 86% *ee*; ν_{max} (KBr)/cm^{-1} 2974,

1828 (C=O), 1612, 1578, 1527, 1465, 1300, 1254, 1185, 1109, 945, 895, 837, 791, 742, 699 and 686 ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.15 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.52-2.66 (2H, m, C*H*$_2$CH$_3$), 3.66 (3H, s, ArOC*H*$_3$), 6.22 (1H, s, C*H*(Ar)), 6.57-6.60 (2H, m, ArMe*H*O-3,5), 6.94 (2H, d, *J* 8.9, Ar*H*MeO-2,6), 7.31-7.35 (1H, m, Ar*H*NO$_2$-4), 7.49-7.56 (2H, m, Ar*H*NO$_2$-5,6) and 7.98 (1H, dd, *J* 8.3, 0.9 Ar*H*NO$_2$-3); ^{13}C NMR (75 MHz, CDCl$_3$) δ_c 9.4 (*C*H$_3$), 29.4 (*C*H$_2$), 55.1 (ArO*C*H$_3$), 72.3 (*C*(Ar)Et), 79.6 (*C*H(Ar)), 113.8 (*C*ArMeO-2,6), 124.8 (*C*ArNO$_2$-3), 125.7 (*C*Ar-1), 128.0 (*C*ArMeO-3,5), 128.2 (*C*ArNO$_2$-6), 129.0 (*C*ArNO$_2$-4), 132.9 (*C*ArNO$_2$-1), 134.1 (*C*ArNO$_2$-5), 146.4 (*C*ArNO$_2$-2), 158.9 (*C*ArMeO-2,6) and 172.4 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{18}$H$_{18}$O$_5$N$_1^+$: found 328.1175; calcd 328.1179 (–) 1.8 ppm.

(252)-3-Isopropyl-4-(2-nitrophenyl)-3-(thiophen-3-yl)oxetan-2-one
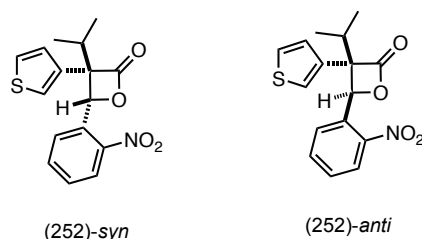

(252)-*syn*   (252)-*anti*

Scheme 252. Following general procedure **2**: NHC precatalyst **66** (57.0 mg, 0.10 mmol, 0.10 equiv), KHMDS (0.18 mL, 0.09 mmol, 0.09 equiv), isopropyl-3-thionylketene **213** (180 mg, 1.00 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (181 mg, 1.20 mmol, 1.2 equiv) in toluene (10 mL) at 0 °C to rt over 12 h gave crude product (*dr* 45:55 *syn*:*anti*) that was purified by flash silica chromatography (3% Et$_2$O :petrol) to give **252** as a predominately separable mixture of diastereoisomers; (147 mg, 46% yield);

minor *Syn* as a pale brown solid (73 mg, 23% yield); mp 114 °C; $[\alpha]_D^{20}$ –24 (*c* 0.15, CHCl$_3$); Chiral HPLC analysis Chiralcel OJ-H (2% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t_R major (*S*,*R*): 44.0 min, t_R minor (*R*,*S*): 49.8 min, 58% *ee*; ν_{max} (KBr)/cm^{-1} 2978, 1825 (C=O), 1613, 1577, 1522, 1342, 1244, 953, 896, 857, 784, 744, 705, 688 and 622; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.95 (3H, d, *J* 6.8, *i*-prC*H*$_3$), 1.45 (3H, d, *J* 6.8, *i*-prC*H*$_3$), 2.87 (1H, sep, *J* 6.8, *i*-pr*H*) 6.37 (1H, s, C*H*(Ar)), 6.55 (1H, dd, *J* 4.9, 1.5, Ar*H*), 6.97-7.01 (2H, m, Ar*H*), 6.97-7.01 (1H, m, Ar*H*NO$_2$-4), 7.50 (2H, d, *J* 3.9, Ar*H*NO$_2$-5,6) and 8.01 (1H, d, *J* 8.1, Ar*H*NO$_2$-3); ^{13}C NMR (100 MHz, CDCl$_3$) δ_c 18.3 (*C*H$_3$), 18.9 (*C*H$_3$), 32.7 (*C*H), 74.4 (*C*(Ar)*i*-Pr), 76.8 (*C*H(Ar)),

122.9 (Ar*C*H), 124.6 (*C*ArNO$_2$-3), 125.1 (*C*ArNO$_2$-4), 126.6 (Ar*C*H), 128.2 (*C*ArNO$_2$-6), 129.0 (Ar*C*H), 133.1 (*C*ArNO$_2$-1), 134.1 (*C*ArNO$_2$-5), 134.9 (*C*Ar-1), 146.5 (*C*ArNO$_2$-2) and 171.1 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{16}$H$_{16}$O$_4$N$_1$S$_1^+$: found 318.0791; calcd 318.0795 (−) 1.1 ppm.

Major *Anti* as an off white solid (38 mg, 12% yield) mp 138-142 °C; $[\alpha]_D^{20}$+40 (*c* 0.1, CHCl$_3$); Chiral HPLC analysis Chiralcel OJ-H (2% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t$_R$ major (*S,S*): 28.8 min, t$_R$ minor (*R,R*): 43.2 min, 92% *ee*; ν$_{max}$ (KBr)/cm^{-1} 2974, 1818 (C=O), 1613, 1535, 1469, 1389, 1344, 1261, 1227, 1192, 1143, 1121, 995, 955, 902, 883, 863, 831, 790, 744, 710, 686 and 638; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 0.40 (3H, d, *J* 6.7, *i*-pr*CH$_3$*), 0.92 (3H, d, *J* 6.8, *i*-pr*CH$_3$*), 2.18 (1H, sep, *J* 6.7, *i*-pr*H*) 6.31 (1H, s, C*H*(Ar)), 7.39 (1H, dd, *J* 5.1, 3.0, Ar*H*), 7.45 (1H, dd, *J* 5.1, 1.3, Ar*H*), 7.63 (1H, *app* td, *J* 7.8, 1.3, Ar*H*), 7.66 (1H, dd, *J* 3.0, 1.3, Ar*H*NO$_2$) 7.79-7.83 (1H, m, Ar*H*NO$_2$), 7.93 (1H, dd, *J* 8.3 1.3, Ar*H*NO$_2$) and 8.21 (1H, dd, *J* 8.2, 1.3, Ar*H*NO$_2$-3); ^{13}C NMR (100 MHz, CDCl$_3$) δ$_c$ 16.7 (*C*H$_3$), 18.1 (*C*H$_3$), 29.2 (*C*H), 71.8 (*C*(Ar)*i*-Pr), 78.9 (*C*H(Ar)), 124.3 (Ar*C*H), 125.4 (*C*ArNO$_2$-3), 125.5 (*C*ArNO$_2$-4), 128.4 (Ar*C*H), 129.7 (*C*ArNO$_2$-6), 130.0 (Ar*C*H), 131.7 (*C*ArNO$_2$-1), 133.7 (*C*Ar-1), 134.1 (*C*ArNO$_2$-5), 148.2 (*C*ArNO$_2$-2) and 171.7 (*C*=O); *m/z*: (ASAP) HRMS [M+] C$_{16}$H$_{16}$O$_4$N$_1$S$_1^+$: found 318.0788; calcd 318.0795 (−) 2.1 ppm.

(238)-(3*S*,4*R*)-3-Ethyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one: Preparative scale

(238)-*syn*

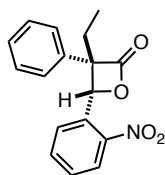**Scheme 68**. Following general procedure **2**: NHC precatalyst **66** (114 mg, 0.2 mmol, 0.02 equiv), KHMDS (0.36 mL, 0.18 mmol, 0.018 equiv), ethylphenylketene **146** (1.47 g, 10.0 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (1.81 g, 12.0 mmol, 1.2 equiv) in toluene (100 mL) at −50 °C for 1 h gave crude product (*dr* 93:7 *syn*:*anti*) that was purified by flash silica chromatography (5% Et$_2$O :petrol) to give **238** *syn* (2.47 g, 83% yield); mp 58-60 °C; $[\alpha]_D^{20}$−46 (*c* 1.0, CHCl$_3$); Chiral HPLC analysis Chiralcel OJ-H (5% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t$_R$ major (*S, R*): 44.4 min, t$_R$ minor (*R,S*): 52.7 min, 95% *ee*; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 1.16 (3H,

t, *J* 7.4, CH$_2$C*H*$_3$), 2.54-2.72 (2H, m, C*H*$_2$CH$_3$), 6.26 (1H, s, C*H*(Ar)), 7.00-7.09 (5H, m, Ar*H*), 7.28-7.34 (1H, m, Ar*H*NO$_2$-4), 7.46-7.55 (2H, m, Ar*H*NO$_2$-5,6) and 7.97 (1H, dd, *J* 8.2 0.9, Ar*H*NO$_2$-3).

Recrystallisation of **238** (95% *ee*)

238 (73.0 mg, 0.25 mmol, 95% *ee*) was recrystallised from petrol and the minimum quantity of EtOAc to facilitate dissolution, cooled slowly to rt and the liquers removed to give **238** *syn* (65.0 mg, 89% yield) mp 56-58 °C; $[\alpha]_D^{20}$ –48 (*c* 0.5, CHCl$_3$); Chiral HPLC analysis Chiralcel OJ-H (5% IPA:hexane, flow rate 0.5 mL min^{-1}, 220 nm) t$_R$ major (*S, R*): 44.0 min, t$_R$ minor (*R,S*): 52.5 min, >99% *ee*;

(263)-(*S*)-2-((*S*)-Amino(2-nitrophenyl)methyl)-2-phenylbutanoic acid

(263)
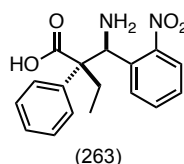
Scheme 70. To a solution of **238** (100 mg, 0.29 mmol, 1.00 equiv) in THF (4 mL) and H$_2$O (1 mL) in a screw top vial was added PPh$_3$ (84 mg, 0.31 mmol, 1.08 equiv) and the mixture vigorously stirred for 6 h. The mixture was then concentrated *in vacuo*, diluted with methanol and cooled to 0 °C in a screw cap vial. SOCl$_2$ (0.06 mL, 0.30 mmol, 1.0 equiv) was added dropwise then the vial heated to 65 °C for 12 h before concentration *in vacuo*. The resulting solid was then triturated with cold CHCl$_3$ to give **263** as an off white solid; (75 mg, 81% yield); mp 188-194 °C (*decomp)*; $[\alpha]_D^{20}$+213 (*c* 0.15 MeOH); ν_{max} (KBr)/cm^{-1} 3417, 2800, 1684 (C=O), 1602, 1531, 1496, 1352, 1220, 1195, 857, 713 and 603; ^{1}H NMR (300 MHz, MeOD$_3$) δ_H 0.55 (3H, t, *J* 7.1, CH$_2$C*H*$_3$), 1.45 (1H, dq, *J* 13.9, 7.0, C*H*$_2$CH$_3$), 1.63 (1H, dq, *J* 13.9, 7.0, C*H*$_2$CH$_3$), 5.53 (1H, s, C*H*NH$_2$), 7.32 (1H, dd, *J* 8.5, 4.1, Ar*H*), 7.37 (4H, m, Ar*H*), 7.66 (1H, t, *J* 7.7, Ar*H*NO$_2$) 7.78 (1H, t, *J* 7.7, Ar*H*NO$_2$) 7.97 (1H, d, *J* 8.1, Ar*H*NO$_2$), and 8.04 (1H, d, *J* 8.1, Ar*H*NO$_2$); ^{13}C NMR (75 MHz, MeOD) δ_c 10.0 (*C*H$_3$), 28.3 (*C*H$_2$), 55.0 (*C*H(Ar)), 60.0 (*C*(Ar)Et), 126.6 (*C*ArNO$_2$), 129.1 (Ph*C*-1), 129.2 (Ph*C*H), 129.7 (*C*ArNO$_2$), 130.2 (Ph*C*H), 130.4 (*C*ArNO$_2$), 131.9 (*C*ArNO$_2$), 134.5 (*C*ArNO$_2$), 137.5 (*C*ArNO$_2$-1), 151.8 (*C*ArNO$_2$-2) and 176.3 (*C*=O); *m/z*: (EI) HRMS [M+] C$_{17}$H$_{17}$O$_4$N$_2^+$: found 313.1186; calcd 313.1194 (–) 2.5 ppm.

(266)-(*S*)-Benzyl 2-((*S*)-(benzylamino)(2-nitrophenyl)methyl)-2-phenylbutanoate

(266)
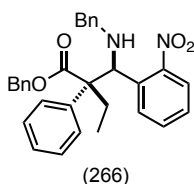
263 derivitised to the di-benzyl compound **266** for chiral HPLC analysis. Following general procedure **3**; **263** (30 mg, 0.10 mmol, 1.0 equiv), benzylbromide (25 µL, 0.21mmol, 2.2 equiv), *i*-Pr$_2$NEt (0.37 µL, 0.19 mmol, 2.2 equiv) in DMF (2 mLs) for 12 h gave after flash silica chromatography (10% Et$_2$O :petrol); **266** as a pale yellow oil (16 mg, 34% yield); $[\alpha]_D^{20}$ +269 (*c* 0.1, CHCl$_3$); Chiral HPLC Chiralcel OD-H (1% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t$_R$ minor (*R,R*): 15.7 min, t$_R$ major (*S,S*): 19.2 min, >99% *ee*; ν$_{max}$ (KBr)/cm^{-1}3031, 1730 (C=O), 1646, 1603, 1529, 1496, 1454, 1357, 1218, 1108, 1029, 856, 739 and 698; ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 0.64 (3H, t, *J* 7.3, CH$_2$C*H*$_3$), 1.82 (1H, dq, *J* 7.1, 13.8, C*H*$_2$CH$_3$), 2.37 (1H, dq, *J* 13.8, 7.1, C*H*$_2$CH$_3$), 3.45 (1H, d, *J* 13.4, BnC*H*$_A$H$_B$), 3.60 (1H, d, *J* 13.4, BnCH$_A$*H*$_B$), 5.01 (1H, d, *J* 12.3, BnC*H*$_A$H$_B$), 5.07 (1H, d, *J*, 12.3, BnCH$_A$*H*$_B$), 5.30 (1H, s, C*H*NHBn), 6.74-6.76 (1H, m, Ar*H*NO$_2$), 6.91 (2H, dd, *J* 8.1, 1.4 Ar*H*NO$_2$), 7.12-7.24 (15H, m, Ar*H*) and 7.64 (1H, dd, *J* 8.1, 1.4, Ar*H*NO$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ$_c$ 9.6 (*C*H$_3$), 28.6 (*C*H$_2$), 51.7 (*C*H$_2$Bn), 58.5 (*C*H(Ar)), 61.5 (*C*(Ar)Et), 66.6 (*C*H$_2$Bn), 123.9 (Ar*C*H), 126.9 (Ar*C*H), 127.2 (Ar*C*H), 127.7 (Ar*C*H), 127.9 (Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*), 130.0 (*C*ArNO$_2$), 131.2 (*C*ArNO$_2$), 135.4 (Ar*C*), 135.5 (Ar*C*), 138.9 (Ar*C*), 140.4 (Ar*C*), 152.5 (*C*ArNO$_2$-2) and 173.7 (*C*=O); (1 Ar*C* could not be resolved); *m/z*: (EI) HRMS [M+] C$_{31}$H$_{31}$O$_4$N$_2$$^+$: found 495.2271; calcd 495.2278 (−) 1.5 ppm.
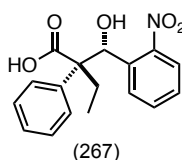
(267)-(*S*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)-2-phenylbutanoic acid

(267)

Scheme 71. To a solution of **238** (200 mg, 0.67 mmol, 1.0 equiv) in THF (4 mL) in a screw cap vial was added 1 M KOH (1.35 mL, 1.35 mmol, 2.0 equiv) and heated to 65 °C for 5 h. The solution was cooled to rt, diluted with NaHCO$_3$ and extracted with Et$_2$O . The aqueous was slowly acidified with 2 M HCl and extracted with EtOAc

(×3). The EtOAc portions were combined, dried Na_2SO_4 and concentrated *in vacuo* to give **267** as an off white solid; (116 mg, 55% yield); mp 140-148 °C; $[\alpha]_D^{20}$ −406 (*c* 0.05 MeOH); ν_{max} (KBr)/cm^{-1} 3438, 1705 (C=O), 1528, 1355, 1223, 1037, 943 and 857; ^{1}H NMR (300 MHz, Me₃OD) δ_H 0.84 (3H, t, *J* 7.4, CH₂C*H*₃), 1.74-1.83 (2H, m, C*H*₂CH₃), 6.14 (1H, s, C*H*OH), 6.38 (1H, dd, *J* 1.2, 8.0, Ar*H*NO₂), 7.05-7.13 (3H, m, Ar*H*), 7.16-7.26 (3H, m, Ar*H*), 7.27-7.34 (1H, m, Ar*H*) and 7.65 (1H, dd, *J* 1.1, 8.1, Ar*H*NO₂); ^{13}C NMR (75 MHz, CDCl₃) δ_c 9.6 (CH₃), 26.7 (CH₂), 63.2 *C*(Ar)Et), 72.1 (*C*H(Ar)), 123.1 (*C*ArNO₂), 127.5 (Ph*C*H), 127.7 (Ar*C*H), 128.5 (Ar*C*H), 129.7 (Ar*C*H), 130.9 (Ar*C*H), 131.3 (Ar*C*H), 132.5 (Ar*C*H), 135.4 (*C*ArNO₂), 149.7 (*C*ArNO₂-2) and 177.7 (*C*=O); *m/z*: (EI) HRMS [M+] $C_{17}H_{16}O_5N^+$: found 314.1029; calcd 314.1034 (−) 1.6 ppm.
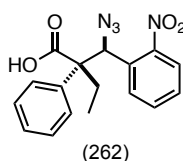
267 Derivatised to the benzylester **268** for chiral HPLC analysis. Following general procedure **3**; **267** (98 mg, 0.31 mmol, 1.0 equiv), benzylbromide (0.05 mL, 0.37 mmol, 1.2 equiv), *i*-Pr₂NEt (0.08 mL, 0.37 mmol, 1.2 equiv) in DMF (2 mL) for 12 h gave after silica chromatography (20% Et₂O :petrol); **268** as a orange oil (79 mg, 63% yield); $[\alpha]_D^{20}$ −807 (*c* 0.3, CHCl₃); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*S, R*): 22.8 min, t_R major (*S,R*): 34.1 min, 96% *ee*; ν_{max} (KBr)/cm^{-1} 3527, 2975, 1714 (C=O), 1607, 1527, 1447, 1355, 1216, 1125, 1039, 990, 912, 856, 785, 738 and 699; ^{1}H NMR (400 MHz, CDCl₃) δ_H 0.74 (3H, t, *J* 7.3, CH₂C*H*₃), 1.61 (1H, dq, *J* 14.3, 7.2, C*H*₂CH₃), 1.86 (1H, dq, *J* 14.5, 7.3, C*H*₂CH₃), 3.81 (1H, d, *J* 4.0, CHO*H*), 5.14 (2H, *app* d, *J* 0.9, BnC*H*₂) 6.12 (1H, d, *J* 4.0, C*H*OH), 6.28 (1H, dd, *J* 8.3, 1.1 Ar*H*NO₂), 6.78-6.80 (2H, m, Ar*H*NO₂), 6.95-6.99 (1H, m, Ar*H*) 7.06-7.10 (2H, m, Ar*H*), 7.14-7.25 (7H, m, Ar*H*) and 7.53 (1H, dd, *J* 1.1, 8.3, Ar*H*NO₂); ^{13}C NMR (75 MHz, CDCl₃) δ_c; 9.2 (CH₃), 26.3 (CH₂), 61.3 (*C*(Ar)Et), 67.2 (*C*H₂Bn), 69.7(*C*H(Ar)OH), 122.9 (Ar*C*H), 127.3 (Ar*C*H), 127.4 (Ar*C*H), 128.3 (Ar*C*H), 128.4(Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 129.3 (Ar*C*H), 131.0 (Ar*C*H), 131.0 (Ar*C*H), 132.5 (Ar*C*), 135.2 (Ar*C*), 136.5 (Ar*C*), 149.8 (*C*ArNO₂-2) and 175.7 (*C*=O); *m/z*: (EI) HRMS [M+H] $C_{24}H_{24}O_5N_1^+$: found 406.1650; calcd 406.1649 (+) 0.2 ppm.

(262)-(*S*)-2-((*S*)-Azido(2-nitrophenyl)methyl)-2-phenylbutanoic acid

(262)

Scheme 70. To a solution of **238** (500 mg, 1.68 mmol, 1.0 equiv) in DMSO (5 mL) in a screw top vial was added sodium azide (219 mg, 3.36 mmol, 2.0 equiv) and the mixture heated to 65 °C for 42 h. The solution was cooled to rt diluted with $NaHCO_3$ (20mL) and extracted with EtOAc (20 mL). The aqueous portion was re-acidified with 2 M HCl (50mL) and extracted with EtOAc (3 × 20 mL). The 3 organic portions were combined, washed with brine (20 mL) and H_2O (20 mL), dried with Na_2SO_4 then concentrated *in vacuo* to give **262** as a light brown solid; (564 mg, 99% yield); mp 156-160 °C; $[\alpha]_D^{20}$ +386 (*c* 0.25, CHCl$_3$); ν_{max} (KBr)/cm^{-1} 2975, 2104 (N$_3$), 1707 (C=O), 1613, 1528, 1360, 1253, 1227, 1141, 1143, 1121, 857, 783, 831, 698, 744 and 677; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 1.10 (3H, t, *J* 7.4, C*H$_2$*CH$_3$), 2.10-2.22 (1H, m, C*H$_2$*CH$_3$) 2.55-2.67 (1H, m, C*H$_2$*CH$_3$) 6.32 (1H, s, C*H*N$_3$), 6.42 (1H, dd, *J* 7.9, 1.2, Ar*H*NO$_2$), 6.92-6.96 (2H, m, Ar*H*NO$_2$), 7.17-7.24 (2H, m, Ar*H*), 7.25-7.28 (1H, m, Ar*H*) 7.30-7.37 (2H, m, Ar*H*) and 7.72 (1H, dd, *J* 8.1, 1.4, Ar*H*NO$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) δ_c 9.4 (*C*H$_3$), 27.5 (*C*H$_2$), 60.5 (*C*(Ar)Et), 60.5 (*C*H(Ar)N$_3$), 123.8 (*C*ArNO$_2$), 127.9 (Ph*C*H), 128.1 (*C*PhH-4), 128.7 (*C*ArNO$_2$), 129.0 (Ph*C*H), 130.4 (Ar*C*), 131.0 (*C*ArNO$_2$), 131.5 (*C*ArNO$_2$), 136.4 (Ar*C*), 151.1 (*C*ArNO$_2$-2) and 178.8 (*C*=O); *m/z*: (EI) HRMS [M+] C$_{17}$H$_{15}$O$_4$N$_4^+$: found 339.1093; calcd 339.1099 (–) 1.7 ppm.

262 was derivatised to the benzylester **265** to allow chiral HPLC analysis. Following general procedure **3**: **262** (100 mg, 0.30 mmol, 1.0 equiv), DMF (5 mL), benzylbromide (0.04 mL, 0.36 mmol, 1.2 equiv) and *i*-Pr$_2$NEt (0.06 mL, 0.36 mmol, 1.2 equiv) for 18 h give the crude product that was purified by flash silica chromatography (40% Et$_2$O :petrol) to give **265** as a colorless crystalline solid; (53 mg, 41% yield); mp 128 °C; $[\alpha]_D^{20}$ +376 (*c* 0.25, CHCl$_3$); Chiral HPLC analysis Chiralcel OD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t$_R$ minor (*S,R*): 8.3 min, t$_R$ major (*S,S*): 9.9 min, 95% *ee*; ν_{max} (KBr)/cm^{-1} 3457, 2103 (N$_3$), 1725 (C=O), 1636, 1529, 1357, 1230, 1125, 970, 960, 788, 740 and 700; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.89 (3H, t, *J* 7.4, CH$_2$C*H$_3$*), 1.99-2.11 (1H, m, C*H$_2$*CH$_3$) 2.52 (1H, dq, *J*

14.2, 7.1, CH_2CH_3), 5.04 (2H, *app* q, J 14.5, BnCH_2), 6.21 (1H, m, ArHNO$_2$), 6.30 (1H, s, CHN$_3$), 6.75 (2H, d, J 7.4, ArHNO$_2$), 7.04-7.27 (10H, m, ArH) and 7.67 (1H, dd, J 1.2, 8.1, ArHNO$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) δ_c 9.3 (*C*H$_3$), 27.8 (*C*H$_2$), 60.3 (*C*H(Ar)N$_3$), 60.5(*C*(Ar)Et), 67.0 (*C*H$_2$Bn), 123.8 (*C*ArNO$_2$-3), 127.7 (Ar*C*H), 127.9 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.6 (Ar*C*H), 129.1 (Ar*C*H), 130.9 (*C*ArNO$_2$-1), 130.9 (Ar*C*H), 131.6 (Ar*C*H), 135.2 (ArBn*C*), 137.3 (Ph*C*), 151.1 (*C*ArNO$_2$-2) and 173.2 (*C*=O); *m/z*: (EI) HRMS [M+NH$_4$] C$_{24}$H$_{22}$O$_4$N$_4$NH$_4^+$: found 448.1979; calcd 448.1979 (–) 0.1 ppm.

Experimental information for chapter 5

General experimental procedures

General procedure (1): Halogenation procedure at rt.

To a flame dried Schlenk flask under an argon atmosphere was added NHC precatalyst (0.050 mmol), base (0.045 mmol) and toluene (3 mL) and the mixture stirred for 20 minutes. A solution of the requisite ketene (0.50 mmol) in toluene (6 mL) was added, immediately followed by the requisite chlorinating reagent (0.50 mmol). Toluene (1mL) was added to wash residual solid into solution and the reaction was stirred for 3 h at rt before concentration *in vacuo*. The resulting crude residue was purified by flash silica chromatography to provide the title compound.

General procedure (2): Halogenation procedure at −40 °C.

To a flame dried Schlenk flask under an argon atmosphere was added NHC precatalyst (0.050 mmol), base (0.045 mmol) and toluene (3 mL) and the mixture stirred for 20 minutes. The mixture was then cooled to −40 °C before addition of a −40 °C solution of the requsite ketene (0.50 mmol) in toluene (6 mL), immediately followed by the requisite chlorinating agent (0.50 mmol). Toluene (1mL) was added to wash residual solid into solution and the reaction was stirred for 3 h at −40 °C before opening the flask to the air for 0.5 h and concentration *in vacuo*. The resulting crude residue was purified by flash silica chromatography to provide the title compound.

General procedure (3): Derivatisation to the methyl ester.

Following the procedure of Fu:[20] the requisite α-chloroester (1.0 equiv) was dissolved in methanol (5 mL) and DMAP (3.0 equiv) was added. The resulting solution was stirred at rt for 16h before concentration *in vacuo*. The resulting solid was purified by flash silica chromatography to provide the title compound. Enantioselectivites were determined by chiral gas chromatography as outlined above.
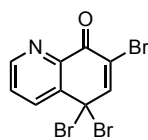
General procedure (4): Dervatisation to (*S,S*) and (*S,R*)−α-methylbenzylamides

To a solution of the requisite pentachlorophenyl α-chloroester (1.0 equiv) in THF (2 mL) was added (*S*)-(−)-α-methlybenzylamine (10-20 equiv) and the mixture stirred at rt for 16 h. The mixture was diluted with EtOAc (2 mL), washed with 2M aq. HCl (2 × 2mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo* to give a mixture of the desired (*S,S*) and (*S,R*)−α-methylbenzylamides and pentachlorophenol.[21] Diastereomeric ratios were determined by integration of the relevant peaks in the crude ^{1}H NMR spectra.

(291)-2,2,4-Trichloronaphthalen-1-(2H)-one

(291)

Scheme 82. **291** was prepared from *via* the literature method of Bartoli *et al.*[22] To a solution of 8-hydroxyquinoline (3.63 g, 25.0 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (125 mL) was slowly added t-butylhypochlorite (11.5 mL, 90.0 mmol, 3.6 equiv) at 0°C. The reaction was stirred at room temperature for 3 hours. The solvent was removed *in vacuo*, 20 mL of Et$_2$O was added to the crude residue to precipatate a solid. The solid was collected by vacuum filtration and washed with cold hexane to afford **291** as a pale solid (3.42 g, 55% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 6.87 (1H, s, C=C*H*), 7.69 (1H, dd, *J* 4.7, 8.1, Ar*H*), 8.13 (1H, dd, *J* 1.5, 8.1, Ar*H*) and 8.89 (1H, dd, *J* 1.5, 4.7, Ar*H*).

(311)-2,4,4-Tribromonaphthalen-1(4H)-one

(311)

Scheme 87. **311** was prepared from *via* the literature method of Bartoli *et al.*[22] A 9/1 glacial acetic acid/distilled H$_2$O solution (400 mL) was added to 8-hydroxyquinoline (2.90 g, 20.0 mmol, 1.0 equiv). The yellow solution was cooled to 0°C in an ice bath and bromine (3.40 mL, 66.0 mmol, 3.3 equiv) was added dropwise over 20 minutes. After 1 hour stirring a precipitate had formed. Ice was added causing further

precipitatation. The solution was carefully extracted with CH_2Cl_2 (3 x 30mL) and the organic layer was washed with a saturated solution of $NaHCO_3$ (3 x 100 mL), H_2O (100 mL) and brine (1 x 100 mL), dried over MgSO4, filtered and trituated with cold CH_2Cl_2 to give **311** as a pale yellow solid (5.11 g, 67% yield); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 7.69 (1H, dd, *J* 8.2, 4.5, Ar*H*), 7.99 (1H, s, C=C*H*), 8.49 (1H, dd, *J* 8.2, 1.6, Ar*H*) and 8.88 (1H, dd, *J* 4.5, 1.6, Ar*H*).

(312)-2,4,4,6-Tetrabromo-2,5-cyclohexadien-1-one

(312)

Scheme 88. **312** was prepared from *via* slight modification to the literature method of Lectka *et al.*[23] To a glacial acetic acid/sodium acetate (13.5 g) solution (250 mL) was added to 2,4,6-tribromophenol (33.1 g, 0.1 mol, 1.0 equiv). The solution was heated to dissolve the 2,4,6-tribromophenol, then cooled to rt. Bromine (5.15 mL, 0.1 mol, 1.0 equiv) in glacial acetic acid (100 mL) was added dropwise over 0.5 h. The reaction was stirred at rt for 0.5 h. The reaction was poured onto ice forming a light yellow precipitate, which was filltered and washed with distilled water. The solid was dissolved in CH_2Cl_2, dried with MgSO$_4$, filtered and concentrated to give (45.6 g, quant). Additional drying was performed on 10 gramm scale as needed using a freeze dryer for 12 h; ^{1}H NMR (300 MHz, C$_6$D$_6$) δ_H 7.41 (1H, s, C=C*H*).

(283)-2,6,6-Trichlorocyclohex-1-en-1-yl 2-chloro-2-phenylbutanoate

(283)

Table 7, Entry 5. Following general procedure **1**: NHC precatalyst **66** (28.5 mg, 0.05 mmol, 0.1 equiv), Cs$_2$CO$_3$ (14.7 mg, 0.045 mmol, 0.09 equiv), ethylphenylketene **146** (73.1 mg, 0.5 mmol, 1.0 equiv) in (6 mL) and **9** (118 mg, 0.05 mmol, 1.0 equiv) in toluene (10 mL) for 16 hours gave a crude product which was purified by flash silica chromatography (alumina, 25% EtOAc/petrol) to give **283** as a colourless oil; (90 mg, 47%) with spectroscopic data in accordance with the literature.[20] $[\alpha]_D^{20}$ 0.0 (*c* 0.4,

CH_2Cl_2); d_H (400 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.2, CH_2CH_3), 1.94-2.01 (2H, m, CH_2), 2.57 (2H, t, *J* 6.2, CH_2) overlapping 2.47-2.59 (1H, m, CH_2), 2.63-2.75 (3H, m, CH_2), 7.32-7.41 (3H, m, Ph*H*-3,4,5) and 7.64-7.69 (2H, m, Ph*H*-2,6).

To a stirred solution of **238** (58 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 0 °C was added bromine (8 μL, 0.15 mmol, 1.0 equiv). The resulting solution was stirred at 0 °C for 2 hours then concentrated *in vacuo* and, following general procedure **3**, treatment with DMAP (55 mg, 0.45 mmol, 3.0 equiv) in MeOH (5 mL) gave a crude product which was purified by flash silica chromatography (silica, 5% EtOAc/petrol) to give **285** as a colourless oil; (23 mg, 72% yield) with spectroscopic data in accordance with the literature:[20] $[\alpha]_D^{20}$ +0.0 (*c* 0.20, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.2, CH_2CH_3), 2.36 (1H, dq, *J* 14.4, 7.2, $CH_AH_BCH_3$), 2.51 (1H, dq, *J* 14.4, 7.2, $CH_AH_BCH_3$), 3.76 (3H, s, OCH_3), 7.30-7.39 (3H, m, Ph*H*-3,4,5), 7.47-7.50 (2H, m, Ph*H*-2,6); GC Analysis: CP-Chirasil-Dex CB column; 100 °C (60 min) 1.0 °C/min to 120 °C; 11.6 psi H_2; t_R major (*R*); 45.2 min, t_R minor (*S*) 46.3 min <5 % *ee*.

(285)-Methyl 2-chloro-2-phenylbutanoate

(285)

Table 8, Entry 3. Following general procedure **2**: NHC precatalyst **126** (17.4 mg, 0.050 mmol, 0.1 equiv), KHMDS (0.5 M in toluene, 0.09 mL, 0.045 mmol, 0.09 equiv), ethylphenylketene **146** (73.1 mg, 0.5 mmol, 1.0 equiv) and NCS (66.8 mg, 0.050 mmol, 1.0 equiv) in toluene (10 mL) for 3 hours at –40 °C before warming to rt gave a crude product. Treatment of the crude mixture with DMAP (183 mg, 1.50 mmol, 3.0 equiv) in MeOH (5 mL) at rt for 16 h gave a crude product which was purified by flash silica chromatography (5% EtOAc/petrol) to give **285** as a colourless oil; (47 mg, 39% yield, *with respect to ketene*) with spectroscopic data identical to that reported above; $[\alpha]_D^{20}$ –2.6 (*c* 0.2, CH_2Cl_2); GC Analysis CP-Chirasil-Dex CB column; 100 °C (60 min) 1.0 °C/min to 120 °C; 11.6 psi H_2; t_R minor (*R*); 41.3 min, t_R major (*S*) 43.7 min 11% *ee*.

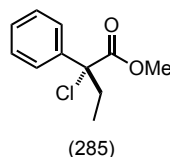**(289)**-Perchloroprop-1-en-2-yl 2-chloro-2-phenylbutanoate

(289)

Table 9, Entry 1. Following general procedure **2**: NHC precatalyst **284** (54.6 mg, 0.20 mmol, 0.1 equiv), KHMDS (0.5 M in toluene, 0.36 mL, 0.18 mmol, 0.09 equiv), ethylphenylketene **146** (292 mg, 2.0 mmol, 1.0 equiv), hexachloroacetone (0.30 mL, 2.00 mmol, 1.0 equiv) and toluene (40 mL) for 3 hours at –40 °C gave a crude product which was purified by flash silica chromatography (2.5% EtOAc/petrol) to give **289** as a colourless oil; (358 mg, 44% yield); ν_{max} (thin film)/cm^{-1}: 2940, 1773 (C=O), 1600 (C=C), 1447, 1162, 1064, 997 and 762; δ_H (400 MHz, CDCl$_3$) 1.03 (3H, t, *J* 7.2, CH$_2$C*H*$_3$), 2.51-2.66 (2H, m, C*H*$_2$CH$_3$), 7.32-7.42 (3H, m, Ar*H*-3,4,5) and 7.60-7.65 (m, 2H, Ar*H*-2,6); δ_C (75 MHz, CDCl$_3$) 8.7 (*C*H$_3$), 34.0 (*C*H$_2$), 74.4 (*C*(Ph)Et), 90.4 (*C*Cl$_3$), 124.6 (*C*Cl$_2$), 127.0 (*C*PhH), 128.3 (*C*PhH), 128.7 (*C*PhH), 136.3 (*C*Ph-1), 142.4 (*C*(Cl$_3$)CCl$_2$) and 166.2 (*C*=O); *m/z* HRMS (CI$^+$), [M+NH$_4$]$^+$, C$_{13}$H$_{10}$O$_2$^{35}Cl$_6$NH$_4$$^+$ requires 425.9155, found 425.9150 (+1.1 ppm): Following general procedure **3**: **289** (50 mg, 012 mmol, 1.0 equiv) and DMAP (45 mg, 0.37 mmol, 3.0 equiv) in MeOH (5 mL) gave a crude product which was purified by flash silica chromatography (silica, 5% EtOAc/petrol) to give **285** as a colourless oil; (26 mg, 89% yield) with spectroscopic data identical to that reported above.
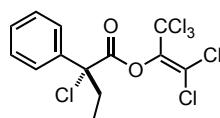
Table 9, Entry 2. Following general procedure **2**: NHC precatalyst **70** (18.9 mg, 0.050 mmol, 0.1 equiv), KHMDS (0.5 M in toluene, 0.090 mL, 0.045 mmol, 0.09 equiv), ethylphenylketene **146** (73.1 mg, 0.50 mmol, 1.0 equiv) in (6 mL) and hexachloroacetone (0.050 mL, 0.050 mmol, 1.0 equiv) in toluene (10 mL) for 3 hours at –40 °C gave a crude product which was purified by flash silica chromatography (2.5% EtOAc/petrol) to give **289** as a colourless oil; (96 mg, 47% yield) with spectroscopic data identical to that reported above; $[\alpha]_D^{20}$ –6.5 (*c* 0.53, CH$_3$Cl).

Following general procedure **3**: **289** (48 mg, 0.12 mmol, 1.0 equiv) and DMAP (43 mg, 0.35 mmol, 3.0 equiv) in MeOH (5 mL) gave a crude product which was purified by flash silica chromatography (silica, 5% EtOAc/petrol) to give **285** as a colourless oil; (25 mg, quantitative yield) with spectroscopic data identical to that reported

above; $[\alpha]_D^{20}$ +3.0 (*c* 0.2, CH$_2$Cl$_2$); GC Analysis CP-Chirasil-Dex CB column; 100 °C (60 min) 1.0 °C/min to 120 °C; 11.6 psi H$_2$; t$_R$ minor (*R*); 44.4 min, t$_R$ major (*S*) 46.0 min 29% *ee*.

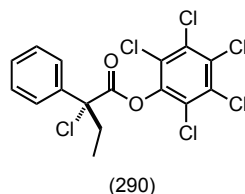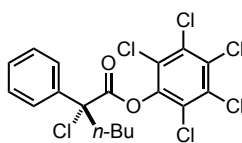**(290)**-Perchlorophenyl 2-chloro-2-phenylbutanoate.

(290)

Table 10, Entry 1. Following general procedure **1**: NHC precatalyst **284** (13.7 mg, 0.050 mmol, 0.1 equiv), KHMDS (0.5 M in toluene, 0.09 mL, 0.045 mmol, 0.09 equiv), ethylphenylketene **146** (80 mg, 0.55 mmol, 1.1 equiv) and **275** (150 mg, 0.50 mmol, 1.0 equiv) in toluene (10 mL) gave a crude product which was purified by flash silica chromatography (petrol) to give **290** as a colourless solid; (146 mg 65% yield); mp 80-84 °C; ν$_{max}$ (KBr disk)/cm^{-1}: 2976, 1773 (C=O), 1386, 1362, 1190, 1183, 1082, 990, 912, 863, 827, 767, 745, 722 and 698; δ$_H$ (400 MHz, CDCl$_3$) 7.67-7.70 (2H, m, Ar*H*), 7.35-7.46 (3H, m, Ar*H*), 2.69 (1H, dq, *J* 14.5, 7.2, C*H*$_A$H$_B$CH$_3$), 2.56 (1H, dq, *J* 14.5 7.3, CH$_A$*H*$_B$CH$_3$) and 1.09 (3H, t, *J* 7.2, CH$_2$C*H*$_3$); δ$_C$ (75 MHz, CDCl$_3$) 9.1 (*C*H$_3$), 34.3 (*C*H$_2$), 74.9 (*C*(Ph)Et), 127.1 (*C*PhH), 127.7 (*C*C$_6$Cl$_5$), 128.6 (*C*PhH), 128.9 (*C*Ph), 132.0 (*C*C$_6$Cl$_5$), 132.2 (*C*C$_6$Cl$_5$), 137.3 (*C*Ph-1), 143.9 (*C*C$_6$Cl$_5$) and 166.7 (C=O); *m/z* HRMS (CI$^+$), [M+NH$_4$]$^+$, C$_{16}$H$_{10}$O$_2$^{35}Cl$_6$NH$_4$$^+$ requires 461.9154, found 461.9150 (+0.8 ppm).

Table 10, Entry 7. Following general procedure **1**: NHC precatalyst **66** (28.5 mg, 0.050 mmol, 0.1 equiv), Cs$_2$CO$_3$ (14.6 mg, 0.045 mmol, 0.09 equiv), ethylphenylketene **146** (80.0 mg, 0.55 mmol, 1.1 equiv) and **275** (150 mg, 0.50 mmol, 1.0 equiv) in toluene (10 mL) for 3 hours at −40 °C gave a crude product which was purified by flash silica chromatography (petrol) to give **290** as a colourless solid; (201 mg 90% yield) with spectroscopic data identical to that reported above; mp 80-86°C; $[\alpha]_D^{20}$+14.8 (*c* 0.50, CHCl$_3$).

Following general procedure **3**: **290** (36 mg, 0.08 mmol, 1.0 equiv) and DMAP (30 mg, 0.24 mmol, 3.0 equiv) in MeOH (5 mL) gave a crude product which was purified by flash silica chromatography (silica, 5% EtOAc/petrol) to give **285** as a colourless

oil; (8.0 mg, 47% yield) with spectroscopic data identical to that reported above: $[\alpha]_D^{20}$ −3.0 (*c* 0.1, CH$_2$Cl$_2$) {literature −23.0 (*c* 0.0005, CH$_2$Cl$_2$, 93% *ee R*)}; GC Analysis CP-Chirasil-Dex CB column; 100 °C (60 min) 1.0 °C/min to 120 °C; 11.6 psi H$_2$; t_R major (*R*); 44.5 min, t_R minor (*S*) 46.1 min (minor) 61 % *ee* {literature CP-Chirasil-Dex CB column; 100 °C (2 min), 1.0 °C/min to 120 °C; 11.6 psi H$_2$; t_R major (*R*); 20.2 min, t_R minor (*S*) 20.5 min 93% *ee*}.

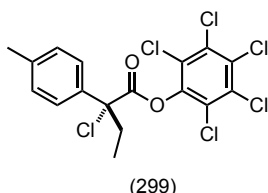**(294)-(*R*)-Perchlorophenyl 2-chloro-2-phenylhexanoate**

(294)

Scheme 83. Following general procedure **2**: NHC precatalyst **66** (28.5 mg, 0.05 mmol, 0.1 equiv), Cs$_2$CO$_3$ (14.6 mg, 0.045 mmol, 0.09 equiv), butylphenylketene **419** (95.8 mg, 0.55 mmol, 1.1 equiv) and **275** (150 mg, 0.50 mmol, 1.0 equiv) in toluene (10 mL) for 3 hours at −40 °C gave a crude product which was purified by flash silica chromatography (petrol) to give **294** as a colourless solid; (158 mg, 67% yield); mp 66-72 °C; $[\alpha]_D^{20}$ +5.9; ν_{max} (KBr disk)/cm^{-1}: 2959, 2933, 1773 (C=O) 1494, 1445, 1385, 1360, 1178, 1133, 1052, 981, 914, 825, 769, 721 and 702; δ_H (400 MHz, CDCl$_3$) 0.93 (3H, t, *J* 7.2, *n*-BuC*H$_3$*), 1.34-1.46 (3H, m, *n*-BuC*H$_2$*), 1.52-1.62 (1H, m, *n*-BuC*H$_2$*), 2.50 (1H, ddd, *J* 14.6, 11.7, 4.1, *n*-BuC*H$_A$*CH$_B$), 2.61 (1H, ddd, *J* 14.6, 10.9, 4.1, *n*-BuCH$_A$C*H$_B$*), 7.34-7.44 (3H, m, Ph*H*-3,4,5) and 7.66-7.69 (2H, m, Ar*H*-2,6); δ_C (75 MHz, CDCl$_3$) 14.0 (*C*H$_3$), 22.7 (*C*H$_2$), 26.7 (*C*H$_2$), 40.8 (*C*H$_2$), 74.3 (*C*(Ph)Et) 127.0 (*C*PhH), 127.8 (*C*C$_6$Cl$_5$), 128.6 (*C*PhH), 129.0 (*C*PhH-4), 132.0 (*C*C$_6$Cl$_5$), 132.2 (*C*C$_6$Cl$_5$), 137.6 (*C*PhH-1), 143.9 (*C*C$_6$Cl$_5$) and 166.7 (*C*=O); *m/z* HRMS (ESI$^+$) [M+NH$_4$]$^+$, C$_{18}$H$_{14}$O$_2^{35}$Cl$_6$NH$_4^+$ requires 489.9459, found 489.9463 (−0.9 ppm).

Following general procedure **4**: **294** (12 mg, 0.03 mmol, 1.0 equiv), (*S*)-α-methylbenzylamine (0.03 mL, 0.30 mmol, 10 equiv), and THF (2 mL) for 16 hours at room temperature gave the crude product as a brown oil. The diastereomeric ratio was determined as 67:33 by integration of the appropriate signals in the ^{1}H NMR of the crude product; δ_H (300 MHz, CDCl$_3$, characteristic signals only) 0.85 (3H, t, *J* 7.1,

diastereomeric *n*-BuC*H*₃), 0.92 (3H, t, *J* 7.1, diastereomeric *n*-BuC*H*₃), 1.48 (3H, d, *J* 6.9, diastereomeric C(Ph)HC*H*₃), 1.53 (3H, d, *J* 6.9, diastereomeric C(Ph)HC*H*₃), 2.32-2.25 (1H, m, *n*-BuC*H*₂), 2.57-2.48 (1H, m, *n*-BuC*H*₂) and 5.01 (1H, *app* quintet, *J* 7.2, PhC*H*(CH₃)N),

(299)-(*R*)-Perchlorophenyl 2-chloro-2-(4-tolyl)butanoate

(299)

Scheme 86. Following general procedure **2**: NHC precatalyst **66** (71.3 mg, 0.13 mmol, 0.25 equiv), Cs₂CO₃ (39.1 mg, 0.120 mmol, 0.24 equiv), ethyl-4-tolylketene **421** (160 mg, 0.75 mmol, 1.5 equiv) and **275** (150 mg, 0.05 mmol, 1.0 equiv) in toluene (10 mL) for 3 hours at −40 °C before warming to rt gave a crude product which was purified by flash silica chromatography (petrol) to give **299** as a colourless solid; (202 mg, 88% yield); mp 66-72 °C; $[\alpha]_D^{20}$ +7.4 (*c* 0.50, CHCl₃); ν_max (KBr disk)/cm⁻¹: 2921, 1784 (C=O), 1511, 1452, 1386, 1362, 1205, 1130, 1067, 1020, 886, 791, 715 and 519; δ_H (400 MHz, CDCl₃) 1.09 (3H, t, *J* 7.3, CH₂C*H*₃), 2.38 (3H, s, ArC*H*₃), 2.53 (1H, dq, *J* 14.5, 7.3, C*H*_AH_BCH₃), 2.67 (1H, dq, *J* 14.5, 7.3, CH_A*H*_BCH₃), 7.22 (2H, d, *J* 8.0 Ph*H*-2,6) and 7.53-7.57 (m, 2H, Ph*H*-3,5); δ_C (75 MHz, CDCl₃) 9.1 (*C*H₃), 21.2 (*C*H₂), 34.3 (Ar*C*H₃), 74.9 (*C*(Ph)Et), 127.0 (*C*ArH), 127.8 (*C*C₆Cl₅), 129.3 (*C*ArH), 132.0 (*C*C₆Cl₅), 132.2 (*C*C₆Cl₅), 134.4 (CAr-4), 138.2 (*C*Ar-1), 144.0 (*C*C₆Cl₅) and 166.8 (*C*=O); *m/z* HRMS (ESI⁺) [M+NH₄]⁺, C₁₇H₁₂O₂³⁵Cl₆NH₄⁺ requires 475.9302, found 476.9307 (−1.0 ppm).

Following general procedure **4**: **299** (45 mg, 0.10 mmol, 1.0 equiv), (*S*)-α-methylbenzylamine (0.1 mL, 1.0 mmol, 10 equiv) and THF (2 mL) for 16 hours at room temperature gave the crude product as a brown oil. The diastereomeric ratio was determined as 74:26 by integration of the appropriate signals in the ¹H NMR of the crude product; δ_H (300 MHz, CDCl₃, characteristic signals only) 0.97 (3H, t, *J* 7.2, di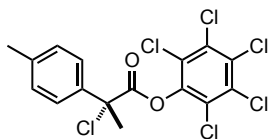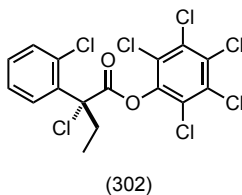astereomeric CH₂C*H*₃), 1.05 (3H, t, *J* 7.2, diastereomeric CH₂C*H*₃), 1.49 (3H, d, *J* 6.9, diastereomeric C(Ph)HC*H*₃), 1.54 (3H, d, *J* 6.9, diastereomeric C(Ph)HC*H*₃), 2.23 (3H, s, ArC*H*₃), 2.17-2.23 (2H, m, C*H*_ACH_BCH₃), 2.44-2.59 (2H, m, CH_AC*H*_BCH₃) and 4.99-5.09 (1H, m, PhC*H*(CH₃)N),

(300)-(*R*)-Perchlorophenyl 2-chloro-2-*p*-tolylpropanoate

(300)

Scheme 86. Following general procedure **2**: NHC precatalyst **66** (28.5 mg, 0.05 mmol, 0.1 equiv), Cs$_2$CO$_3$ (14.6 mg, 0.045 mmol, 0.09 equiv), methyl-4-tolylketene **420** (80.4 mg, 0.55 mmol, 1.1 equiv) and **275** (150 mg, 0.50 mmol, 1.0 equiv) in toluene (10 mL) for 3 hours at –40 °C gave a crude product which was purified by flash silica chromatography (petrol) to give **300** as a colourless solid; (169 mg, 76% yield); mp 66-68 °C; $[\alpha]_D^{20}$ +12.8 (*c* 0.53, CHCl$_3$); ν_{max} (KBr disk)/cm^{-1}: 2922, 1762 (C=O), 1512, 1444, 1382, 1360, 1202, 1185, 1084, 1053, 887, 815, 794, 721 and 518; δ_H (400 MHz, CDCl$_3$) 2.34 (3H, s, C*H*$_3$), 2.39 (3H, s, ArC*H*$_3$), 7.22-7.25 (2H, m, Ar*H*),) and 7.57-7.66 (2H, m, Ar*H*), δ_C (100 MHz, CDCl$_3$) 21.3 (*C*H$_3$), 29.6 (Ar*C*H$_3$), 69.2 (*C*(Ph)Et), 126.7 (*C*ArH), 127.8 (*C*C$_6$Cl$_5$), 129.4 (*C*ArH), 132.1 (*C*C$_6$Cl$_5$), 132.3 (*C*C$_6$Cl$_5$), 136.0 (*C*Ar-4), 139.2 (*C*Ar-1), 144.0 (*C*C$_6$Cl$_5$) and 166.8 (*C*=O); *m/z* HRMS (ESI$^+$), [M+NH$_4$]$^+$, C$_{16}$H$_{14}$O$_2{}^{35}$Cl$_6$NH$_4{}^+$ requires 461.9148, found 461.9150 (–0.5 ppm). Following general procedure **4**: **300** (10 mg, 0.02 mmol, 1.0 equiv), (*S*)-α-methylbenzylamine (0.02 mL, 0.20 mmol, 10 equiv) and THF (2 mL) for 16 hours at room temperature gave the crude product as a brown oil. The diastereomeric ratio was determined as 72:28 by integration of the appropriate signals in the ^{1}H NMR of the crude product; δ_H (300 MHz, CDCl$_3$, characteristic signals only) 1.50 (3H, d, *J* 6.9, diastereomeric CH(Ph)C*H*$_3$), 1.54 (3H, d, *J* 6.9, diastereomeric, CH(Ph)C*H*$_3$), 2.12 (3H, s, diastereomeric, ArC*H*$_3$), 2.14 (3H, diastereomeric, s, ArC*H*$_3$), 2.32 (3H, s, diastereomeric C(Ar)(Cl)C*H*$_3$), 2.36 (3H, s, diastereomeric C(Ar)(Cl)C*H*$_3$) and 5.08-5.14 (m, 1H, PhC*H*(CH$_3$)N).

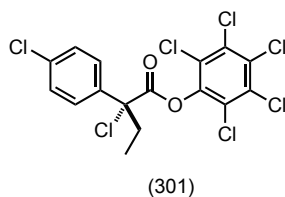**(302)**-(*R*)-Perchlorophenyl 2-chloro-2-(2-chlorophenyl)butanoate

(302)

Scheme 86. Following general procedure **2**: NHC precatalyst **66** (28.5 mg, 0.05 mmol, 0.1 equiv), Cs_2CO_3 (14.6 mg, 0.045 mmol, 0.09 equiv), ethyl-2-chlorophenylketene **179** (99.3 mg, 0.55 mmol, 1.1 equiv) and **275** (150 mg, 0.50 mmol, 1.0 equiv) in toluene (10 mL) for 3 hours at −40 °C gave a crude product which was purified by flash silica chromatography (petrol) to give **302** as a colourless solid; (233 mg, 97% yield); mp 83-85 °C; $[\alpha]_D^{20}$ +3.6 (*c* 0.44, CHCl$_3$); ν_{max} (KBr disk)/cm^{-1}: 2982, 2940, 1781 (C=O), 1465, 1431, 1382, 1359, 1166, 1130, 1066, 988, 910, 822, 764, 754, 718, 726 and 674. δ_H (400 MHz, CDCl$_3$) 0.89 (3H, t, *J* 7.4, CH$_2$C*H*$_3$), 2.65 (1H, dq, *J* 14.8, 7.4, C*H*$_A$H$_B$CH$_3$), 3.11 (3H, dq, *J* 14.8, 7.4, CH$_A$*H*$_B$CH$_3$), 7.32-7.45 (3H, m, Ar*H*) and 7.98-8.01 (1H, m, Ar*H*); δ_C (75 MHz, CDCl$_3$) 8.6 (*C*H$_3$), 31.4 (*C*H$_2$), 75.1 (*C*(Ph)Et), 127.1 (*C*ArH), 128.0 (*C*C$_6$Cl$_5$), 130.3 (*C*ArH), 130.8 (*C*ArH), 131.0 (*C*ArH), 132.0 (*C*Ar-2), 132.0 (*C*C$_6$Cl$_5$), 132.3 (*C*C$_6$Cl$_5$), 134.1 (*C*Ar-1), 143.7 (*C*C$_6$Cl$_5$) and 166.8 (*C*=O); *m/z* HRMS (ESI$^+$), [M+NH$_4$]$^+$, C$_{16}$H$_9$O$_2$^{35}Cl$_7$NH$_4$$^+$ requires 495.8755, found 495.8760 (−1.1 ppm).

Following general procedure **4**: **302** (20 mg, 0.04 mmol, 1.0 equiv), (*S*)-α-methylbenzylamine (0.02 mL, 0.12 mmol, 20 equiv) and THF (2 mL) for 72 hours at reflux gave the crude product as a brown oil. The diastereomeric ratio was determined as 63:37 by integration of the appropriate signals in the ^{1}H NMR of the crude product; δ_H (300 MHz, CDCl$_3$, characteristic signals only) 0.95 (3H, t, *J* 7.2, diastereomeric CH$_2$C*H*$_3$) 1.10 (3H, t, *J* 7.2, diastereomeric CH$_2$C*H*$_3$), 1.55 (3H, d, *J* 4.4, diastereomeric PhCH(C*H*$_3$)N), 1.57 (3H, d, *J* 4.4, diastereomeric PhCH(C*H*$_3$)N) and 5.21-4.12 (1H, m, PhC*H*(CH$_3$)N)
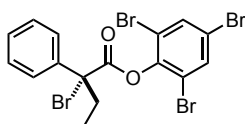
(301)-(*R*)-Perchlorophenyl 2-chloro-2-(4-chlorophenyl)butanoate

(301)

Scheme 86. Following general procedure **2**: NHC precatalyst **66** (28.5 mg, 0.05 mmol, 0.1 equiv), Cs_2CO_3 (14.6 mg, 0.045 mmol, 0.09 equiv), ethyl-4chlorophenylketene **423** (99.3 mg, 0.55 mmol, 1.1 equiv) and **275** (150 mg, 0.50 mmol, 1.0 equiv) in toluene (10 mL) for 3 hours at −40 °C gave a crude product which was purified by flash silica chromatography (petrol) to give **301** as a colourless solid; (218 mg, 91% yield); mp 88-92 °C; $[\alpha]_D^{20}$ +6.2 (*c* 0.53, CHCl$_3$); ν_{max} (KBr disk)/cm^{-1}: 2983, 2942, 1791 (C=O), 1595, 1491, 1390, 1362, 1172, 1099, 1081, 1018, 874, 820, 728, 717 and 517; δ_H (400 MHz, CDCl$_3$) 1.08 (3H, t, *J* 7.2, CH$_2$C*H*$_3$) 2.55 (1H, dq, *J* 14.5, 7.2, C*H*$_A$H$_B$CH$_3$), 2.68 (1H, dq, *J* 14.5, 7.2, CH$_A$*H*$_B$CH$_3$), 7.38-7.43 (2H, m, Ar*H*), and 7.60-7.65 (m, 2H, Ar*H*); δ_C (75 MHz, CDCl$_3$) 8.9 (*C*H$_3$), 34.4 (*C*H$_2$), 74.3 (*C*(Ph)Et), 127.6 (*C*C$_6$Cl$_5$), 128.6 (*C*ArH), 128.7 (*C*ArH), 132.1 (*C*C$_6$Cl$_5$), 132.3 (*C*C$_6$Cl$_5$), 135.1 (*C*Ar), 136.0 (*C*Ar), 143.8 (*C*C$_6$Cl$_5$) and 166.2 (*C*=O); *m/z* HRMS (ESI$^+$) [M]$^+$, C$_{16}$H$_9$O$_2$^{35}Cl$_7$$^+$ requires 477.8417, found 477.8417 (+0.1 ppm); Following general procedure **4**: **301** (8 mg, 0.02 mmol, 1.0 eq), (*S*)-α-methylbenzylamine (0.20 mL, 0.20 mmol, 10 eq) and THF (2 mL) for 16 hours at room temperature gave crude product as a brown oil. The diastereomeric ratio was determined as 72:28 by integration of the appropriate signals in the ^{1}H NMR of the crude product; δ_H (300 MHz, CDCl$_3$, characteristic signals only) 0.88 (3H, t, *J* 7.2, diastereomeric CH$_2$C*H*$_3$), 0.99 (3H, t, *J* 7.2, diastereomeric CH$_2$C*H*$_3$), 1.41 (2H, d, *J* 6.9, diastereomeric PhCH(C*H*$_3$)N), 1.47 (3H, d, *J* 6.9, diastereomeric PhCH(C*H*$_3$)N), 2.14-2.28 (1H, m, C*H*$_A$H$_B$CH$_3$), 2.42-2.56 (1H, m, CH$_A$*H*$_B$CH$_3$) and 5.07-4.97 (1H, m, PhC*H*(CH$_3$)N),

(313)-2,4,6-tribromophenyl 2-bromo-2-phenylbutanoate

(313)

Table 11, Entry 5. To a flame dried Schlenk flask under an argon atmosphere was added NHC precatalyst **66** (28.5 mg, 0.050 mmol, 0.1 equiv), Cs_2CO_3 (14.6 mg, 0.045 mmol, 0.09 equiv) and toluene (3 mL) and the mixture stirred for 20 minutes. The mixture was then cooled to −40 °C in a cryostatic bath before addition of a solution of ethylphenylketene **146** (73.1 mg, 0.55 mmol, 1.1 equiv) in toluene (6 mL) at −40 °C, immediately followed by 2,4,4,6-tetrabromocyclohexa-2,5-dienone **312** (205 mg, 0.50 mmol, 1.0 equiv). Toluene (1mL) was added to wash residual solid into solution and the solution stirred for 3 hours at −40 °C. The solution was allowed to warmed to room temperature over 16 h then concentrated *in vacuo* to give a crude product which was purified by flash silica chromatography (2% EtOAc/petrol) to give **313** as a colourless oil; (257 mg, 92% yield); $[\alpha]_D^{20}$ +11.0 (*c* 0.7, CHCl₃); Chiral HPLC analysis; Chiralcel OJ-H (30% ethanol: *i*-hexane, flow rate 1 mL min⁻¹, 254 nm) t_R 2.5 min, t_R 6.5 min, 44% *ee*; ν_{max} (KBr disk)/cm⁻¹: 3071, 2976, 1762 (C=O), 1560, 1494, 1437, 1373, 1178, 1066, 953, 910, 857, 806, 743 and 694; δ_H (300 MHz, CDCl₃) 1.07 (3H, t, *J* 7.2, CH₂C*H*₃) 2.61-2.78 (2H, m, C*H*₂CH₃), 7.31-7.41 (3H, m, 3, Ph*H*-3,4,5), and 7.71-7.74 (2H, m, Ph*H*-2,6) and 7.66 (2H, br s, C₆*H*₂Br₃); δ_C (75 MHz, CDCl₃) 10.7 (*C*H₃), 35.3 (*C*H₂), 69.3 (*C*(Ph)Et), 118.6 (*C*C₆Br₃), 120.5 (*C*C₆Br₃), 128.6 (*C*PhH), 128.7 (*C*PhH), 129.0 (CPh-4) 135.4 (*C*HC₆Br₃), 137.6 (*C*Ph-1), 145.8 (*C*C₆Br₃-1) and 167.1 (*C*=O); *m/z* HRMS (ESI⁺) [M+NH₄]⁺, C₁₆H₁₆O₂N₁⁷⁹Br₄⁺ requires 569.7906, found 569.7909 (−0.5 ppm).

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Experimental information for chapter 6

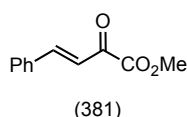**General experimental procedures**

General procedure (1): Synthesis of aroyloxy aldehydes *via* Grignard addition and ozonolysis.

To a stirred solution of the requisite aldehyde (1.0 equiv) in THF (0.5M) at −78 °C was added vinylmagnesium bromide (0.7 M in THF, 1.1 equiv) dropwise and the resulting solution stirred at −78 °C for 0.5 h. Lithium chloride (1.2 equiv) was added followed by 4-nitrobenzoyl chloride (1.2 equiv) portion wise over 5 mins and the mixture stirred at rt for 2 h (until tlc shows complete consumption of the vinyl alcohol). Purification by flash silica chromatography afforded the *O*-4-nitrobenzoyl vinyl alcohol.

A solution of the requisite *O*-4-nitrobenzoyl vinyl alcohol (1.0 equiv) in CH_2Cl_2 (0.025M) at −78 °C was subjected to ozonolysis, followed by addition of dimethyl sulfide (2.0 equiv). The solution was warmed to rt over 2 h then concentrated *in vacuo* and the crude product purified by flash silica chromatography using the solvent system stated.

General procedure (2): Synthesis of dihydropyran-2-ones

To an oven dried vial containing molecular sieves, under an argon atmosphere, was added precatalyst **112** or **335**, the requisite aroyloxy aldehyde (1.5 equiv) (typically as a solution in anhydrous THF), ketoester **381** (1.0 equiv) and anhydrous THF. Triethylamine was added (1.5 equiv) and the reaction stirred at the given temperature for the required period of time. The reaction was then diluted with EtOAc, washed successively with 1 M aq. HCl and saturated $NaHCO_3$, dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude product with the given *dr* that was purified by flash silica chromatography.

(381)-(*E*)-Methyl 2-oxo-4-phenylbut-3-enoate

(381)

Scheme 100. A stirred slurry of potassium (*E*)-2-oxo-4-phenylbut-3-enoate[24] (20 g, 93.3 mmol, 1.0 equiv), 18-crown-6 (493 mg, 1.90 mmol, 0.02 equiv) and methlyiodide (8.72 mL, 140 mmol, 1.5 equiv) in DMF (100 mL) was stirred overnight at rt. An additional 50 mL of DMF was added and the slurry heated to 50 °C for 6 h. The slurry was cooled to rt, diluted with H_2O and extracted twice with EtOAc. The combined organic portions were washed twice with H_2O, twice with $NaHCO_3$, dried with Na_2SO_4 and concentrated *in vacuo* to provide crude **381** as a bright yellow solid. This solid was recrystallised from methanol to provide 2.76 g of **381**. A further 0.95 g of **381** was obtained *via* flash silica chromatography (10% EtOAc:petrol) of the filtrate to provide **381** as a bright yellow solid; combined (3.71 g, 21% yield); mp 56-62 °C, {literature 69-70 °C};[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.94 (3H, s, OC*H*$_3$), 7.38 (1H, d, *J* 16.1, C=C*H*(C(O)CO$_2$Me)), 7.47 (3H, m, Ph*H*-3,4,5), 7.63-7.65 (2H, m, Ph*H*-2,6) and 7.88 (1H, d, *J* 16.1, C=C*H*(Ph)), in accordance with the literature.[23]

(397)-*N*-methyl-O-(4-nitrobenzoyl)hydroxylamine hydrochloride

(397)

Scheme 109. Following the procedure of Tomkinson:[26] potassium carbonate (41.4 g, 0.30 mol, 0.5 equiv) was added to a 0 °C solution of *N*-methylhydroxylamine hydrochloride (50 g, 0.60 mol, 1.0 equiv) in a 1:1 mixture of THF and H_2O (200 ml). A solution of di-tert-butyl dicarbonate (144 g, 0.66 mol, 1.1 equiv) in THF (100 ml) was then added dropwise to the mixture and stirred for 2 h at 0 °C and then warmed to rt for 3 h. The solution was partially concentrated *in vacuo* and extracted (top phase) with CH_2Cl_2 (100 ml) before washing with brine (3 × 50 ml) H_2O and (50 ml). The organic fraction was dried ($MgSO_4$) and concentrated *in vacuo* to yield an pale orange oil that was used without further purification. The crude solution of *N*-Boc-*N*-methyl hydroxylamine, DMAP (2 mol %) and triethylamine (89.0 mL, 0.60 mol, 1.0 equiv) in CH_2Cl_2 (800 ml) was cooled to 0 °C prior to slow addition of 4-nitrobenzoylchloride (72.3 g, 0.60 mol, 1.0 equiv). The reaction mixture was

allowed to warm to rt and stirred for 16 h before washing with brine, $NaHCO_3$ and brine again. The organics were dried with Na_2SO_4 and concentrated *in vacuo* to give a orange solid that was used without further purification.
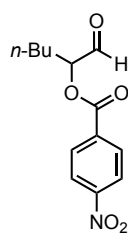
The crude orange solid was broken up and partially dissolved in 4M HCl in dioxane (300 mL) with the reaction exotherm controlled by an ice/H_2O bath. Immediately upon dissolution a colourless solid precipitated from the reaction mixture, additional anhydrous dioxane was added (200 mL) and the slurry was stirred for 1 h until a thick white slurry had formed. The slurry was filtered and washed with Et_2O to provide *N*-methyl-*O*-(4-nitrobenzoyl)hydroxylamine hydrochloride; (71.0 g, 50% yield); mp 135-137 °C *decomp*; ν_{max} (ATR)/cm^{-1} 2340, 1765 (C=O) 1694, 1609, 1537, 1325, 1244, 1059, 1015, 881 and 783 ^{1}H NMR (400 MHz, DMSO) δ_H 2.84 (3H, s, NC*H*$_3$), 8.15 (2H, d, *J* 8.9, ArH-2,6), 8.34 (2H, d, *J* 8.9, ArH-3,5) and 11.48 (1H, br s, N*H*).

(374)-1-Oxo-3-phenylpropan-2-yl 4-nitrobenzoate

(374)

Following general procedure **1**: phenylacetaldehyde (2.92 mL, 25.0 mmol, 1.0 equiv), vinylmagnesium bromide (0.7 M in THF, 39.3 mL, 27.5 mmol, 1.1 equiv), lithium chloride (1.27 g, 30.0 mmol, 1.2 equiv) and 4-nitrobenzoyl chloride (5.60 g, 30.0 mmol, 1.2 equiv) in THF (50 mL) gave, after purification by flash silica chromatography (5% EtOAc:petrol), the title compound as a yellow oil (2.74 g, 37% yield). Ozonolysis of 1-phenylbut-3-en-2-yl 4-nitrobenzoate was carried out on 2 × (765 mg, 2.57 mmol, 1.0 equiv) in CH_2Cl_2 (300 mL) at −78 °C, followed by addition of dimethylsulfide (0.38 mL, 5.1 mmol, 2.0 equiv) gave, after combination and purification by flash silica chromatography (10% EtOAc:petrol), **374** as a sticky white gum; (1.09 g, 71% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 3.25 (1H, dd, *J* 14.5, 8.4, C*H*$_A$H$_B$Ph), 3.38 (1H, dd, *J* 14.5, 5.0, CH$_A$*H*$_B$Ph), 5.55 (1H, dd, *J* 8.4, 5.0, C*H*(Bn)), 7.29-7.34 (5H, m, PhH), 8.21 (2H, d, *J* 9.0, Ar*H*NO$_2$-2,6), 8.33 (2H, d, *J* 9.0, Ar*H*NO$_2$-3,5) and 9.71 (1H, s, C(*H*)=O). In accordance with the literature.[27]

(390)-1-Oxohexan-2-yl 4-nitrobenzoate

(390)
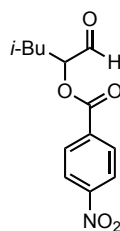
Following general procedure **1**: valeraldehyde (1.60 mL, 15.0 mmol, 1.0 equiv), vinylmagnesium bromide (0.7 M in THF, 23.6 mL, 16.5 mmol, 1.1 equiv) lithium chloride (763 mg, 18.0 mmol, 1.2 equiv) and 4-nitrobenzoyl chloride (3.34 g, 18.0 mmol, 1.2 equiv) in THF (50 mL) gave, after purification by flash silica chromatography (5% EtOAc:petrol), the title compound as a yellow oil (2.4 g, 65% yield). Ozonolysis of hept-1-en-3-yl 4-nitrobenzoate was carried out on $2 \times$ (1.00 g, 3.80 mmol, 1.0 eqiuv) in CH_2Cl_2 (400 mL) at −78 °C, followed by addition of dimethylsulfide (0.56 mL, 7.60 mmol, 2.0 equiv) gave, after combination and purification by flash silica chromatography (10% EtOAc:petrol), **390** as pale yellow oil; (1.46 g, 72% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.98 (3H, t, *J* 7.2, *n*-BuC*H*$_3$), 1.40-1.56 (4H, m, *n*-BuC*H*$_2$), 1.91-2.06 (2H, m, *n*-BuC*H*$_2$), 5.34 (1H, dd, *J* 8.3, 4.8, C*H*(Bu)), 8.28-8.31 (2H, m, Ar*H*NO$_2$-2,6), 8.34-8.38 (2H, m, Ar*H*NO$_2$-3,5) and 9.67 (1H, s, C(*H*)=O). In accordance with the literature.[27]

Following the procedure outlined by Tomkinson:[24] to a stirred solution of hexanal (3.08 mL, 25.0 mmol, 1.0 equiv) in DMSO (50 mL) at rt was added *N*-methyl-*O*-(4-nitrobenzoyl)hydroxylamine hydrochloride (6.4 g, 27.5 mmol, 1.1 equiv) in one portion, and the mixture stirred at rt for 24 h. The mixture was then diluted with EtOAc and washed with brine, then dried, filtered and concentrated *in vacuo* to give a crude product which was purified by slica flash chromatography (5% to 20% EtOAc:petrol) to give **390**; (2.38g, 36% yield) spectroscopic data in accordance with the above described.

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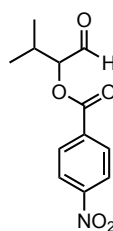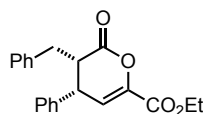**(391)**-4-Methyl-1-oxopentan-2-yl 4-nitrobenzoate

(391)

Following general procedure **1**: *i*-valeraldehyde (1.60 mL, 15.0 mmol, 1.0 equiv), vinylmagnesium bromide (0.7 M in THF, 23.6 mL, 16.5 mmol, 1.1 equiv) lithium chloride (763 mg, 18.0 mmol, 1.2 equiv) and 4-nitrobenzoyl chloride (3.34 g, 18.0 mmol, 1.2 equiv) in THF (50 mL) gave, after purification by flash silica chromatography (5% EtOAc/petrol) gave crude 5-methylhex-1-en-3-yl 4-nitrobenzoate that was taken onto the next step without further purification. Ozonolysis of 5-methylhex-1-en-3-yl 4-nitrobenzoate in CH_2Cl_2 (400 mL) at −78 °C, followed by addition of dimethylsulfide gave, after purification by flash silica chromatography (10% to 20% EtOAc:petrol), **391** as pale yellow oil; (940 mg, 24% yield over two steps); ν_{max} (ATR)/cm^{-1} 2959, 1724 (C=O) 1609, 1525, 1346, 1238, 1101, 1015, 872, 842 and 783; (^{1}H NMR (400 MHz, CDCl$_3$) δ_H 1.01 (3H, d, *J* 6.4, *i*-BuC*H$_3$*), 1.03 (3H, d, *J* 6.4, *i*-BuC*H$_3$*), 1.80-1.90 (3H, m, *i*-BuC*H*/C*H$_2$*), 5.37 (1H, dd, *J* 9.0, 4.6, C*H*(*i*-Bu)), 8.25-8.28 (2H, m, Ar*H*NO$_2$-2,6), 8.31-8.34 (2H, m, Ar*H*NO$_2$-3,5) and 9.63 (1H, s, C(*H*)=O); ^{13}C NMR (100 MHz, CDCl$_3$) 21.7 (*i*-BuC*H$_3$*), 23.2 (*i*-BuC*H$_3$*), 24.8 (*i*-BuC*H*), 37.0 (*i*-BuC*H$_2$*), 78.4 (C*H*(*i*-Bu)), 123.7 (C*A*rHNO$_2$-2,6), 131.0 (C*A*rHNO$_2$-3,5), 134.6 (C*A*r-1), 150.9 (C*A*r-4), 164.3 (C=O ester) and 197.1 (C=O aldehyde); *m/z*: (ASAP) HRMS [M+H]$^+$ C$_{13}$H$_{16}$O$_5$N$^+$: found 266.1024; calcd 266.1023 (+) 0.4 ppm.

(392)-Methyl-1-oxobutan-2-yl 4-nitrobenzoate

(392)

Following general procedure **2**: *i*-butyraldehyde (1.37 mL, 15.0 mmol, 1.0 equiv), vinylmagnesium bromide (0.7 M in THF, 23.6 mL, 16.5 mmol, 1.1 equiv), lithium chloride (763 mg, 18.0 mmol, 1.2 equiv) and 4-nitrobenzoyl chloride (3.34 g, 18.0 mmol, 1.2 equiv) in THF (50 mL) gave a crude oil. Addition of Et$_2$O precipitated a colourless solid that was filtered leaving the filtrate that solidified on standing and was taken on to the next step without further purification. Ozonolysis of 4-methylpent-1-en-3-yl 4-nitrobenzoate was carried out with 2 × (1.00 g, 4.01 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (400 mL) at −78 °C, followed by addition of dimethylsulfide (0.59 mL, 8.02 mmol, 2.0 equiv) gave, after combination and purification by flash silica chromatography; (10% EtOAc:petrol), **392** as a colourless solid (922 mg, 46% yield); mp 46-48 °C {literature 50-52 °C};[27] ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 1.17 (3H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 1.20 (3H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 2.44-2.57 (1H, m, C*H*(CH$_3$)$_2$), 5.22 (1H, dd, *J* 4.5, 0.5, C*H*), 8.32-8.33 (2H, m, Ar*H*NO$_2$-2,6), 8.35-8.39 (2H, m, Ar*H*NO$_2$-3,5) and 9.70 (1H, d, *J* 0.5, C(*H*)=O). In accordance with the literature.[27]

(382)-*Syn*-(±)-Methyl3-benzyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate

(382)

Table 12, Entry 1. Following general procedure **2**: NHC precatalyst **335** (7.0 mg, 0.02 mmol, 0.2 equiv), 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (50 mg, 0.17 mmol, 1.5 equiv), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (21.0 mg, 0.11 mmol, 1.0 equiv), triethylamine (23 μL, 0.17 mmol, 1.5 equiv) and THF (3 mL) for 24 h at rt gave a crude mixture with (*dr* 84:16, *syn*:*anti*). This was purified by flash silica chromatography (10% EtOAc:petrol) to give **382** *Syn* as a colourless solid; (13 mg,

37% yield); mp 105-110 °C; Chiral HPLC analysis Chiralpak AD-H (10% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R 18.0 min, t_R 27.8 min; ν_{max} (KBr)/cm^{-1} 2956, 2925, 1765 (lactone C=O), 1628 (ester C=O), 1664, 1602, 1495, 143, 1316, 1100, 1088, 756, 743, 697 and 539; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 2.33 (1H, dd, *J* 15.8, 10.6, BnC*H*$_A$H$_B$), 3.16-3.23 (2H, m, BnCH$_A$*H*$_B$ and C*H*(Bn)), 3.55 (1H, t, *J* 6.8, C*H*(Ph)), 3.77 (3H, OCH$_3$), 6.58 (1H, d, *J* 6.7, C=C*H*), 6.93-7.00 (4H, m, Ph*H*), and 7.15-7.26 (6H, m, 1 × Ph*H* and 5 × BnAr*H*); ^{13}C NMR (75 MHz, CDCl$_3$) δ_C 32.1(*C*H$_2$Bn), 40.6 (*C*H(Bn)), 44.8 (*C*H(Ph)), 52.7 (O*C*H$_3$), 118.8 (C=*C*H), 126.8 (*C*HArBn-4), 128.4 (*C*HPh-4), 128.4 (*C*ArH), 128.7 (*C*ArH), 128.9 (*C*ArH), 129.2 (*C*ArH), 135.8 (*C*Ph-1), 138.1 (*C*ArBn-1), 141.9 (*C*=CH), 161.0 (*C*=O ester) and 168.5 (*C*=O lactone); *m/z*: (ESI+) HRMS [M+NH$_4$]$^+$ C$_{20}$H$_{22}$O$_4$N$^+$: found 340.1544; calcd 340.1543 (+) 0.2 ppm.

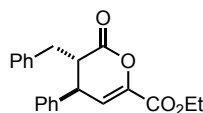***Syn*-(*S*,*S*)-Methyl 3-benzyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate**

Table 12, Entry 2. Following general procedure **2**: NHC precatalyst **112** (3.3 mg, 0.01 mmol, 0.2 equiv), 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (40 mg, 0.13 mmol, 1.5 equiv), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (17.0 mg, 0.09 mmol, 1.0 equiv), triethylamine (19 μL, 0.13 mmol, 1.5 equiv) and THF (2 mL) for 24 h at 0 °C to rt gave a crude mixture with (*dr* 98:2, *syn*:*anti*). This was purified by flash silica chromatography (10% EtOAc:petrol) to give *syn* as a colourless solid; (27 mg, 50% yield); mp 106-107 °C; $[\alpha]_D^{20}$ +398 (c 0.23, CHCl$_3$); Chiral HPLC analysis Chiralpak AD-H (10% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R minor (*R*,*R*) 17.9 min, t_R major (*S*,*S*) 27.8 min >99% *ee*; spectroscopic data in accordance with above.

(382)-*Anti*-(3*S*,4*R*)-methyl-3-benzyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate
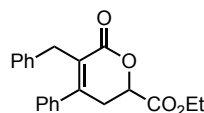

(382)-*anti*

Scheme 104. Following general procedure 1: NHC precatalyst **112** (1.1 mg, 0.003 mmol, 0.01 equiv), 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (135 mg, 0.43 mmol, 1.5 equiv), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (57.0 mg, 0.30 mmol, 1.0 equiv),

triethylamine (63 µL, 0.43 mmol, 1.5 equiv) and THF (4 mL) for 48 h at rt gave a crude mixture with (*dr* 76:24, *syn*:*anti*). This was purified by flash silica chromatography (10% EtOAc:petrol) to give **382** *syn* as a colourless solid; (27 mg, 50% yield, >99% *ee*) spectroscopic data in accordance with above;

382-*Anti* as a colourless solid; (18 mg, 19% yield); $[\alpha]_D^{20}$ +163 (c 0.04, CHCl$_3$); mp 116-118 °C; ν_{max} (ATR)/cm^{-1} 1769 (C=O lactone), 1734 (C=O ester), 1655, 1437, 1283, 1219, 1103 and 991; ^{1}H NMR (400 MHz, CDCl$_3$); 2.79-2.88 (1H, m, CH_2(Bn)). 2.97-3.07 (2H, m, CH_2(Bn) and CH(Bn)), 3.51-3.58 (1H, m, CH(Ph)), 3.81 (3H, m, s OCH_3), 6.46 (1H, d, *J* 5.0, C=CH), 6.93-6.98 (2H, m, PhH), 7.07-7.10 (2H, m, PhH) and 7.21-7.28 (6H, m, PhH); ^{13}C NMR (100 MHz, CDCl$_3$) δ$_C$ 35.7 (CH_2Bn), 41.4 (CH(Bn)), 47.7 (CH(Ph), 52.8 (OCH_3), 116.5 (C=CH), 127.1 (*C*HArBn-4), 127.3 (*C*ArH), 128.0 (*C*HPh-4), 128.8 (*C*ArH), 129.2 (*C*ArH), 129.3 (*C*ArH), 137.3 (*C*Ph-1), 139.2 (*C*ArBn-1), 141.7 (*C*=CH), 160.8 (C=O ester) and 168.0 (C=O lactone); *m/z*: (ESI+) HRMS [M+NH$_4$]$^+$ C$_{20}$H$_{22}$O$_4$N$^+$: found 340.1549; calcd 340.1543 (+) 1.7 ppm.

(389)-Methyl 5-benzyl-6-oxo-4-phenyl-3,6-dihydro-2H-pyran-2-carboxylate


(389)

Scheme 107. To a solution of **382** *syn* (10 mg, 0.03 mmol, 1.0 equiv, >20:1 *dr* and >99% *ee*) in CH$_2$Cl$_2$ (2 mL) was added pyrrolidine (3 µL, 0.04 mL, 1.2 equiv) and the reaction stirred for 16 h. The solution was washed with 1 M HCl, dried (Na$_2$SO$_4$) concentrated *in vacuo* and purified by flash silica chromatography (10% EtOAc:petrol) to give **389** as a colourless oil; (5 mg, 50% yield); ν_{max} (ATR)/cm^{-1}; 1656 (C=O), 1495, 1437, 1361, 1200, 1110 and 1016; ^{1}H NMR (400 MHz, CDCl$_3$); 3.07 (2H, t, *J* 3.7, CH_2), 3.49 (3H, s, OCH_3), 3.62 (1H, d, *J* 14.3, BnCH_AH$_B$), 3.70 (1H, d, *J* 14.4, BnCH$_A$$H_B$), 4.98 (1H, t, *J* 4.9, CH(CO$_2$Et)), 6.91-6.94 (2H, m, PhH), 7.06-7.19 (5H, m, PhH) and 7.32-7.40 (3H, m, PhH); ^{13}C NMR (75 MHz, CDCl$_3$) 33.0 (CH_2Bn), 33.4 (CH_2), 52.8 (OCH_3), 73.6 (*C*H(CO$_2$Me)), 126.2 (*C*PhH-4), 127.4 (*C*PhH), 128.1 (C=C(Bn)), 128.3 (*C*PhH), 128.5 (*C*PhH), 128.9 (*C*PhH), 129.0 (*C*PhH-4), 138.0 (*C*Ph-1), 139.3 (*C*Ph-1), 149.7 (C=C(Ph)), 163.8 (*C*=O lactone) and

170.1 (*C*=O ester); *m/z*: (ESI+) HRMS [M+H]$^+$ C$_{20}$H$_{19}$O$_4$$^+$: found 323.1283; calcd 323.1278 (+) 0.2 ppm.

(393) *syn*-(±)-methyl-3-butyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate
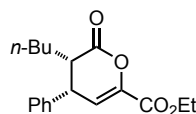
(393)

Table 15, Entry 1. Following general procedure **1**: NHC precatalyst **335** (4.2 mg, 0.01 mmol, 0.1 equiv), 1-oxohexan-2-yl 4-nitrobenzoate (50 mg, 0.19 mmol, 1.5 equiv), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (25.2 mg, 0.13 mmol, 1.0 equiv), triethylamine (28 µL, 0.19 mmol, 1.5 equiv) and THF (3 mL) for 18 h at rt gave a crude mixture with (*dr* 92:8, *syn*:*anti*). This was purified by flash silica chromatography (5% EtOAc:petrol) to give **393** *syn* as a colourless oil; (15 mg, 40% yield); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t$_R$ 16.0 min, t$_R$ 17.4 min; ν_{max} (ATR)/cm^{-1} 2954, 1773 (C=O lactone), 1734 (C=O ester), 1661, 1454, 1437, 1323, 1259, 1045 and 989; ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 0.81 (3H, t, *J* 7.1, *n*-BuC*H$_3$*), 1.08-1.40 (5H, m, *n*-BuC*H$_2$*), 1.60-1.70 (1H, m, *n*-BuC*H$_2$*), 2.79 (1H, d, *J* 6.9, C*H*(*n*-Bu)), 3.79 (1H, t, *J* 6.7, C*H*(Ph)), 3.83 (3H, s, OC*H$_3$*), 6.68 (1H, d, *J* 6.4, C=C*H*), 7.06 (2H, dt, *J* 5.8, 1.8, Ph*H*-2,6) and 7.23-7.29 (3H, m, Ph*H*-3,4,5); ^{13}C NMR (100 MHz, CDCl$_3$) 13.9 (*n*-BuC*H$_3$*), 22.5 (*n*-BuC*H$_2$*), 26.0 (*n*-BuC*H$_2$*), 29.4 (*n*-BuC*H$_2$*), 41.5 (C*H*(Ph)), 43.4 (C*H*(*n*-Bu)), 52.7 (OC*H$_3$*), 118.4 (*C*=CH), 128.1 (*C*PhH-2,6), 128.1 (*C*Ph-4), 129.1 (*C*PhH-3,5), 136.0 (*C*Ph-1), 142.1 (*C*=CH), 161.1 (*C*=O ester) and 168.8 (*C*=O lactone); *m/z*: (ESI+) HRMS [M+NH$_4$]$^+$ C$_{17}$H$_{24}$O$_4$N$^+$: found 306.1702; calcd 306.1700 (+) 0.7 ppm.

(393)-(*S,S*)-methyl-3-butyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate
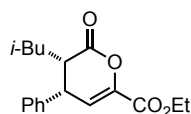
Table 16, Entry 1. Following general procedure **2**: NHC precatalyst **112** (1.2 mg, 0.03 mmol, 0.01 equiv), 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (133 mg, 0.50 mmol, 1.5 equiv), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (63.0 mg, 0.33 mmol, 1.0 equiv), triethylamine (70 µL, 0.50 mmol, 1.5 equiv) and THF (5 mL) for 3 h at rt gave a crude mixture with (*dr* >20:1, *syn*:*anti*). This was purified by flash silica chromatography (5% EtOAc:petrol) to give **393** *syn* as a colourless oil; (66 mg, 69% yield); $[\alpha]_D^{20}$+156 (c 0.15, CHCl$_3$); Chiral HPLC analysis Chiralpak AD-H (5%

IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R,R*) 14.7 min, t_R major (*S,S*) 16.5 min >99% *ee*; spectroscopic data in accordance with above.

(393)-(*S,S*)-methyl-3-butyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate

Scheme 112. Following general procedure **2**: NHC precatalyst **112** (22.0 mg, 0.06 mmol, 0.01 equiv), 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (2.38 g, 8.97 mmol, 1.5 equiv), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (1.14 g, 5.98 mmol, 1.0 equiv), (1.25 mL, 8.97 mmol, 1.5 equiv) and THF (100 mL) for 3 h at rt gave a crude mixture with (*dr* >20:1, *syn:anti*). This was purified by flash silica chromatography (5% EtOAc:petrol) to give **393** *syn* as a pale yellow oil (700 mg, 41% yield); $[\alpha]_D^{20}$ +298 (c 0.28, CHCl$_3$); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R minor (*R,R*) 15.5 min, t_R major (*S,S*) 17.4 min >99% *ee*; spectroscopic data in accordance with above.

**(394)**-*Syn*-(±)-methyl-3-isobutyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate

(394)

Table 17, Entry 1. Following general procedure **2**: NHC precatalyst **335** (16.0 mg, 0.05 mmol, 0.2 equiv), 4-methyl-1-oxopentan-2-yl 4-nitrobenzoate (100 mg, 0.38 mmol, 1.5 equiv), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (48.0 mg, 0.25 mmol, 1.0 equiv), triethylamine (52 μL, 0.38 mmol, 1.5 equiv) and THF (4 mL) for 12 h at rt gave a crude mixture with (*dr* >20:1, *syn:anti*). This was purified by flash silica chromatography (2.5 to 5% EtOAc:petrol) to give **394** *syn* as a colourless solid; (24 mg, 33% yield); mp 84-88 °C; Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t_R 11.9 min, t_R 13.6 min; ν_{max} (KBr)/cm^{-1}; 2959, 1769 (C=O lactone), 1708 (C=O ester), 1661, 1317, 1265, 1094, 1082 and 991; ^{1}H NMR (300 MHz, CDCl$_3$) δ_H 0.83 (3H, d, *J* 6.6, *i*-BuC*H*$_3$), 0.88 (3H, d, *J* 6.6, *i*-BuC*H*$_3$), 1.04 (1H, *app* dt, *J* 7.0, 14.0, *i*-BuC*H*), 1.56 (2H, dt, *J* 13.9, 7.0, *i*-BuC*H*$_A$H$_B$), 1.72 (1H, dd, *J* 14.0, 7.0, *i*-BuC*H*$_A$H$_B$), 2.93 (1H, app q, *J* 6.9, C*H*(*i*-Bu)), 3.77 (1H, t, *J* 6.7, C*H*(Ph)), 3.87 (3H, s, OC*H*$_3$), 6.72 (1H, d, *J* 6.4, C=C*H*), 7.07-7.10 (2H, dt, *J* 1.8, 5.8, Ph*H*-2,6) and 7.27-7.34 (3H, m, Ph*H*-3,4,5); ^{13}C NMR (100 MHz,

CDCl$_3$) δ$_C$ 22.2 (*i*-Bu*C*H$_3$), 22.5 (*i*-Bu*C*H$_3$), 25.2 (*i*-Bu*C*H), 35.2 (*i*-Bu*C*H$_2$), 41.2 (*C*H(*i*-Bu), 41.7 (*C*H(Ph), 52.7 (O*C*H$_3$), 118.4 (C=*C*H), 128.1 (*C*PhH-2,6), 128.1 (*C*Ph-4), 129.1 (*C*PhH-3,5), 136.0 (*C*Ph-1), 142.1 (*C*=CH), 161.1 (*C*=O ester) and 168.9 (*C*=O lactone); *m/z*: (ESI+) HRMS [M+NH$_4$]$^+$ C$_{17}$H$_{24}$O$_4$N$^+$: found 306.1704; calcd 306.1700 (+) 1.4 ppm.

(394)-(*S,S*)- methyl 3-isobutyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate

Table 17, Entry 2. Following general procedure **2**: NHC precatalyst **112** (12.0 mg, 0.03 mmol, 0.10 equiv), 4-methyl-1-oxopentan-2-yl 4-nitrobenzoate (133 mg, 0.50 mmol, 1.5 equiv), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (63.0 mg, 0.33 mmol, 1.0 equiv), triethylamine (70 μL, 0.50 mmol, 1.5 equiv) and THF (5 mL) for 16 h at rt gave a crude mixture with (*dr* >20:1, *syn*:*anti*). This was purified by flash silica chromatography (2.5 to 5% EtOAc:petrol) to give **394** *syn* as a colourless oil; (45 mg, 47% yield); $[\alpha]_D^{20}$ +279 (c 0.14, CHCl$_3$); Chiral HPLC analysis Chiralpak AD-H (5% IPA:hexane, flow rate 1.0 mL min^{-1}, 220 nm) t$_R$ minor (*R,R*) 10.6 min, t$_R$ major (*S,S*) 13.0 min >99% *ee*; spectroscopic data in accordance with above.

(395)-(5*S*)-methyl 5-isobutyl-6-oxo-4-phenyl-5,6-dihydro-2H-pyran-2-carboxylate
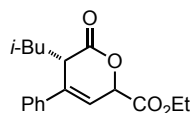
(395)

Scheme 113. Isolated as an inseparable mixture of diastereoisomers (70:30 dr); colourless oil; characteristic ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 0.82 (3H, d, *J* 6.4, *minor-i*-Bu*C*H$_3$), 0.84 (3H, d, *J* 6.6, *major-i*-Bu*C*H$_3$), 0.96 (3H, d, *J* 6.4, *minor-i*-Bu*C*H$_3$), 0.96-0.98 (3H, m, *major-i*-Bu*C*H$_3$), 1.32-1.42 (1H, m, *i*-Bu*C*H$_X$), 1.61-1.80 (1H, m, *i*-Bu*C*H$_X$), 1.82-1.96 (1H, m, *i*-Bu*C*H$_X$), 3.70-3.75 (1H, m, *C*H(*i*-Bu)), 3.84 (4 H, s, *minor*-O*C*H$_3$), 3.85 (3H, s, *major*-O*C*H$_3$), 5.52 (3H, *app* dd, *J* 1.7, 5.1, *major-C*H(CO$_2$Me)), 5.65 (1H, app t, *J* 2.1, *minor-C*H(CO$_2$Me)), 6.20 (1H, *app* t, *J* 4.1, C=C*H*) and 7.37-7.40 (5H, m, Ph*H*),

(396)-(3*S*,4*S*)-methyl-3-isopropyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate
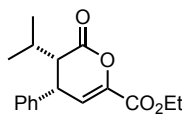
(396)

Table 18, Entry 2. Following general procedure **2**: NHC precatalyst **112** (4.9 mg, 0.013 mmol, 0.10 equiv), 3-methyl-1-oxobutan-2-yl 4-nitrobenzoate (50.0 mg, 0.20 mmol, 1.5 equiv), (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (25.2 mg, 0.13 mmol, 1.0 equiv), triethylamine (28 μL, 0.20 mmol, 1.5 equiv) and THF (3 mL) for 18 h at rt gave a crude mixture with (53:47) ratio of **397** to **396**. **396** isolated in (>95:5 *dr*) as an inseparable mixture with 3-methyl-1-oxobutan-2-yl 4-nitrobenzoate. Characteristic signals ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 0.82 (3H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.01 (3H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.76-1.88 (1H, m, C*H*(CH$_3$)$_2$), 2.54 (1H, dd, *J* 8.7, 6.8, C*H*(*i*-Pr)), 3.78 (3H, s, OMe), 3.85 (1H, t, *J* 6.7, C*H*(Ph)), 6.62 (1H, d, *J* 6.6, C=C*H*), 7.08-7.11 (2H, m, Ph*H*) and 7.23-7.27 (3H, m, Ph*H*).

(387)-(3*S*,4*S*)-ethyl 3-benzyl-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-carboxylate
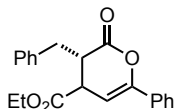
(387)

Scheme 104. Following general procedure **2**; NHC precatalyst **112** (19.5 mg, 0.053 mmol, 0.10 equiv), 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate (238 mg, 0.80 mmol, 1.5 equiv), (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate[28] (108 mg, 0.53 mmol, 1.0 equiv), triethylamine (0.11 mL, 0.80 mmol, 1.5 equiv) and THF (5 mL) for 2 h at rt gave a crude mixture (*dr* 98:2, *syn*:*anti*). This was purified by flash silica chromatography (5 to 10% EtOAc:petrol) to give **387** *syn* as a colourless oil; (140 mg, 79% yield); $[\alpha]_D^{20}$+173 (c 1.05, CH$_3$Cl), {literature[29] +107 (c 1.05, CH$_3$Cl, (3*S*, 4*S*))}; ^{1}H spectroscopic data in accordance with the literature[27] (300 MHz, CDCl$_3$) δ$_H$ 1.29 (4 H, t, *J* 7.1, OCH$_2$C*H*$_3$) 2.77 (1 H, dd, *J* 14.2, 10.2, BnC*H*$_A$H$_B$), 2.98-3.01 (1H, m, C*H*(Bn)), 3.25 (1H, dd, *J* 6.9, 5.9, C*H*(CO$_2$Et)) 3.55 (1H, dd, *J* 14.2, 4.6, BnCH$_A$*H*$_B$), 4.22 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 5.80 (1H, d, *J* 7.0, C=C*H*), 7.16-7.19 (2H, m, Ar*H*), 7.35-7.38 (6H, m, Ar*H*) and 7.60-7.63 (2H, m, Ar*H*).

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12. Partial concentration must be carried out in a fume cupboard due to the large quantities of benzene generated. Full concentration was not attempted due to the high bp of Bu$_2$O

13. A second small crop was obtained *via* further cooling of the filtrate to 0 °C for 12 h.

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15. The trimethyloxonium tetrafluoroborate does not instantly dissolve at this reaction concentraion.

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19. In general all compounds are obtained as colourless solids which slowly turn pale brown on standing. The change in colour has no apprent effect on purity by ^{1}H NMR

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