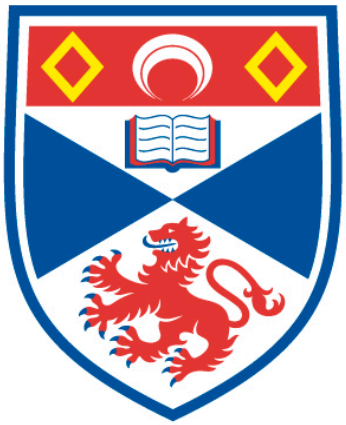
NUCLEOPHILIC HETEROCYCLIC CARBENE CATALYSIS : GENERATION OF AZOLIUM ENOLATES FOR NOVEL ENANTIOSELECTIVE INTER- AND INTRAMOLECULAR FORMAL [4+2] CYCLOADDITIONS

Nassilia Attaba

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



2019

Nucleophilic Heterocyclic Carbene Catalysis: Generation of Azolium Enolates For Novel Enantioselective Inter- and Intramolecular Formal [4+2] Cycloadditions

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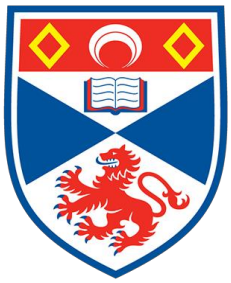

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This thesis is submitted in partial fulfilment for the degree of

Doctor of Philosophy (PhD)

at the University of St Andrews

September 2018

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To my loved ones.

In the loving memory of my grand-father Papy (02/03/1916–23/08/2012).

Point n’est besoin d’espérer pour entreprendre ni de réussir pour persévérer.

Guillaume d’Orange

Acknowledgment

First of all, I would like to thank my supervisor, Prof. Andrew Smith for giving me the opportunity to work in his research group and for his support and advice throughout the years.

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It's been rough, but we made it! Good night and good luck!

Abstract

N-Heterocyclic carbene (NHC)-catalysed processes that utilise azolium enolates intermediates have been used for a broad range of transformations such as enantioselective cycloaddition, protonation, halogenation, Mannich reactions and desymmetrisation processes. One efficient way to quickly build molecular complexity is through cycloadditions such as formal [4+2] cycloadditions. In this context, ketenes, aldehydes, esters, enals and α-halo aldehydes have been used in numerous reactions for the construction of 6-membered rings. Nevertheless, the current limitations include lack of stability from the precursors and unwanted side-reactions. To broaden the synthetic utility of azolium enolates, alternative precursors are necessary This has been addressed in this thesis in novel inter- and intramolecular formal [4+2] cycloadditions using α-aroyloxyaldehydes and enone-acids as bench-stable azolium enolate precursors.

An intermolecular NHC-catalysed [4+2]-hetero-Diels-Alder process using α-aroyloxyaldehydes as azolium enolate precursors and trichloromethyl ketone Michael acceptors was first explored. This methodology led to the formation of *syn*-dihydropyranones in up to 95% yield, >95:5 dr and >99:1 er. A sequential [4+2] cycloaddition/nucleophilic ring-opening with amines or alcohols led to the selective synthesis of either highly functionalised diamides or γ-ester amide derivatives in up to 90% with excellent diastereo- and enantioselectivity. This highlighted the ability of trichloromethyl ketones to act as amide surrogates.

An investigation of using carboxylic acids bearing a pendant enone, referred as enone-acid, led to the first NHC-catalysed formal [4+2] cycloaddition protocol. A range of dihydrobenzofurans were accessed in moderate to high yield, and high to excellent diastereo- and enantioselectivity. This novel methodology could be extended to the synthesis of *syn*-dihydropyranone and *syn*-dihydrochromenone derivatives in moderate to high yield and excellent diastereo- and enantioselectivity.

Publications

The work described in this thesis has formed the basis for the following peer-reviewed publication to date:

Enantioselective NHC-Catalyzed Redox [4+2]-hetero-Diels-Alder Reactions using α,β-Unsaturated Trichloromethyl ketones as Amide Equivalents

Attaba, N.; Taylor, J. E.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2015**, *80*, 9728.

Abbreviations

Å	Ångström(s) (1 x 10^{-10} m)
Ac	Acetyl
AcOH	Acetic Acid
APCI	Atmospheric Pressure Chemical Ionization
app.	Apparent
aq.	Aqueous
Ar	Aromatic
atm	Atmosphere
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
br	Broad
BTM	Benzotetramisole
Bu	Butyl
Bz	Benzoyl
c	Concentration
C	Celsius
cal	Calorie(s)
cat.	Catalytic
CBz	Carboxybenzyl
CDI	1,1'-Carbonyldiimidazole
CI	Chemical ionisaton
cm	Centimetre(s)
conv.	Conversion
CPME	Cyclopentyl methyl ether
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
dec.	Decomposition
DFT	Density functional theory
DIBAL-H	Di-*iso*-butylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethyl sulfoxide
dr	Diasteroisomeric ratio
E	Entgegen (opposite)
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

EDG	Electron donating group
EI	Electron impact
equiv	Equivalent molar quantity
er	Enantiomeric ratio
ES	Electrospray
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
FID	Flame ionization detector
FTMS	Fourier Transform Mass Spectrometry
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HOBt	1-Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
i	Iso
ID	Ionization detector
IPA	Isopropyl alcohol
IR	Infrared
J	Coupling constant
KIE	Kinetic isotope effect
LB	Lewis base
LDA	Lithium diisopropylamide
LG	Leaving group
Lit	Literature
LUMO	Lowest unoccupied molecular orbital
M	Molar (i.e. mol dm^{-3})
m	Multiplet
m	Meta
m/z	Mass / charge
Me	Methyl
MeCN	Acetonitrile
Mes	Mesityl
mg	Milligram(s)
MHz	Megahertz
min	minute(s)

mL	Millilitre(s)
mol	Mole(s)
mp	Melting point
MS	Mass spectrometry/ Molcular sieve
n	Normal
n/a	Non available
NHC	N-heterocyclic carbene
nm	Frequency
NMM	*N*-methylmorpholine
NMR	Nuclear magnetic resonance
NSI	Nanospray ionization
Nuc	Nucleophile
o	Ortho
o/n	Overnight
Ox	Oxidant
p	Para
PG	Protecting group
Ph	Phenyl
PhMe	Toluene
Piv	Pivaloyl
ppm	Parts per million
PPY	4-Pyrrolidinopyridine
Pr	Propyl
precat	Precatalyst
PS	Polymer supported
Py	Pyridine
q	Quartet
quant.	Quantitative
R	Alkyl
R	Rectus (right)
rac	Racemic
Re	Rectus (right); applied to heterotopic prochiral faces
rt	Ambient (room) temperature
s	Singlet
S	Sinister (left)
sat.	Saturated
sept	Septet
Si	Sinister (left); applied to heterotopic prochiral faces
t	Triplet/time

t	Tert
T	Temperature
TBAI	Tetrabutylamonium iodide
TCBC	Trichlorobenzoyl chloride
Tf	Triflyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
tolyl	Methylphenyl
Ts	Tosyl
TS	Transition state
Z	Zusammen (together)
δ	Chemical shift
Δt	Reaction duration
μL	Microlitre(s)
ν_{max}	Frequency
(±)	Racemic

Table of Contents

1- Introduction

The development of asymmetric catalysis in organic chemistry is the result of a high interest in simple, efficient and enantioselective processes to access to complex molecules, mainly in the agrochemical and pharmaceutical industries. Enantioselectivity is extremely important especially in drug discovery as enantiomers have different biological properties. Indeed, one enantiomer can have the desired activity as a drug target whereas the other one could be inactive, antagonistic or worse induce unwanted biological effects potentially leading to dramatic results. One example, in 1960s thalidomide was commercialised as a racemic mixture and prescribed as a sedative and anti-morning sickness to pregnant women (Figure 1). Only one enantiomer was treating those symptoms whilst the other was a teratogen leading to birth defects.

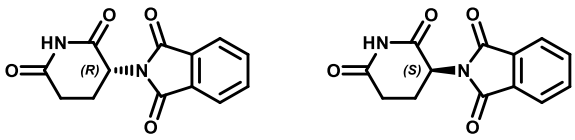
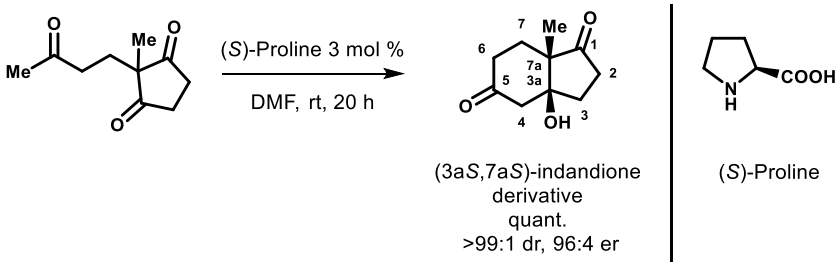


Figure 1: Thalidomide

Other advantages to the selective synthesis of one enantiomer are the reduction of the administered dose and a more precise understanding on the structure-activity relationship. There are two main ways of controlling the geometry of a reaction, the use of chiral auxiliaries and the use of enantioselective catalysts. Chiral auxiliaries such as Evans' oxazolidinones have to be introduced in stoichiometric quantity then removed.[1] Therefore, extra synthetic steps are needed and lead to an expensive process. For many years, catalysis was subdivided in two fields: biocatalysis and metal catalysis. Biocatalysis uses enzymes to catalyse reactions very efficiently with low catalyst loading but can be highly substrate dependant, leading to a narrow substrate scope. Enantioselective metal catalysis usually utlises transition-metal catalysts and the stereoselectivity is induced by chiral ligands. It has been widely developed over the years and acknowledged with several Nobel prices (P. Sabatier in 1912, W. R. Knowles, R. Noyori and K. B. Sharpless in 2001, Y. Chauvin, R. H. Grubbs and R. R. Schrock in 2005, R. F. Heck, E.-I. Negishi, and A. Suzuki in 2010). Although these catalysts are very efficient, their main problems, apart from the potential toxicity and air-sensitivity of the metal centre, can include the cost of the metal between the mining, the waste treatment and the price volatility. A new area of catalysis named organocatalysis has been developed recently. Organocatalysts are small metal-free molecules which can be less moisture and air sensitive, and less expensive.

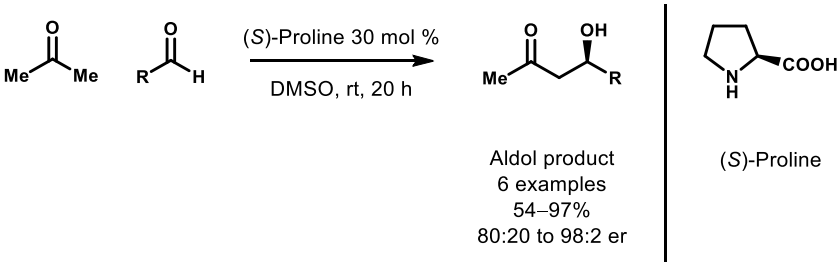
1-1 Organocatalysis:

Organocatalysts can be divided in two main domains depending on the nature of the interaction between the catalyst and the substrate, *ie* non-covalent or covalent interactions. Non-covalent catalysis consists of the formation of a catalyst-substrate complex through hydrogen bonding or ionic interactions. In covalent catalysis, activation proceeds through the formation of a bond between the catalyst and the substrate. This bond is subsequently broken to regenerate the catalyst. The most common catalysts are Lewis bases such as secondary amine-based catalysts (biomolecules and derivatives) and isothioureas, and N-heterocyclic carbenes catalysts. The catalysis proceeds through nucleophilic substitution or addition of the Lewis base to the substrate. The first results in organocatalysis were obtained in an attempt to mimic enzymes. As such, one of the first important discoveries was the intramolecular aldol reaction catalysed by (*S*)-proline leading to an indandione derivative in quantitative yield and excellent stereoselectivity (Scheme 1).[2] This result was independently reported in the 1970s by Hajos and Parrish from Hoffman-La Roche and Eder, Sauer and Wiecher from Schering AG.



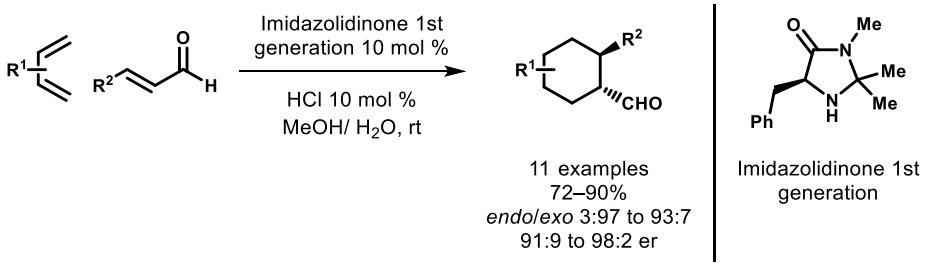
Scheme 1: Hajos-Parrish-Eder-Sauer-Wiecher intramolecular aldolisation.

Thirty years later, in 2000, this reaction was revisited by Barbas and List with the development of an intermolecular version (Scheme 2).[3]. The activation mode of ketones consists of the formation of an enamine intermediate and has been widely developed for amination, nitro-olefin addition and cross aldolisation.[4]



Scheme 2: Intermolecular aldolisation by Barbas and List.

Another milestone from 2000 was the enantioselective Diels-Alder reaction reported by MacMillan (Scheme 3).[5] It consists of the activation of α-β unsaturated aldehydes through the lowering of their LUMO. This methodology has been further explored and extended to α-β unsaturated ketones mainly by MacMillan and Jørgensen, for cycloaddition reactions,[6] Friedel-Craft alkylation,[7] epoxidation,[8] cyclopropanation[9] and conjugate reduction.[10]



Scheme 3: Enantioselective Diels-Alder reaction by MacMillan *et al*.

In the recent years, one of the most versatile classes of organocatalysts used was nucleophilic heterocyclic carbenes (NHC).

1-2 From Carbenes to NHCs

Carbenes are neutral species containing a divalent carbon with 6 valence electrons, 2 of which are unshared. Their existence was first postulated in 1862 and since then, many questions have been raised about their electronic configuration and geometry.[11] Numerous studies including in physical and early computational studies provided some insight into these intriguing species.[12] It was established that carbenes can exist in two different geometries around their divalent carbon, namely linear or bent (Figure 2).

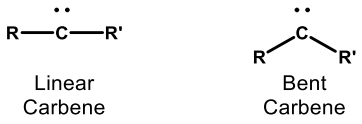


Figure 2: Representation of the different geometries of carbenes.

The differences in geometry are associated with different hybridisations and ground states (Figure 3).[13] Linear carbene geometry implies sp-hybridisation of the divalent carbon with two non-bonding degenerate p orbitals (p_x and p_y). A change of hybridisation from sp to sp^2 breaks the degeneracy of the non-bonding orbitals leading to a p orbital and a lower in energy sp^2 orbital.

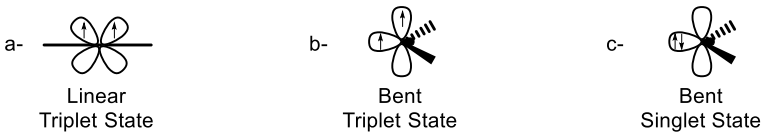


Figure 3: Schematic representation of hybridised orbitals.

Carbenes can exist in singlet or triplet states depending on their electronic configurations. In the linear geometry, each of the unpaired electrons can occupy one of the degenerate p orbitals with parallel spins, leading to a triplet state (Figure 3-a). In the bent geometry, a triplet state is also possible (Figure 3-b). In this, one of the electrons occupies the non-bonding p orbital and the other one the sp^2 orbital with a parallel spin orientation. Another relevant alternative for the bent geometry has both electrons in the same sp^2 non-bonding orbital with anti-parallel spins, giving a singlet state and a different energy gap between the two non-bonding orbitals (Figure 3-c). The difference of energy between the p and sp^2 orbitals can be affected by the α-substituents of the carbon.

Nucleophilic Heterocyclic Carbenes (NHCs) are a specific type of carbene containing heteroatoms α- to the divalent carbon, with at least one of them being a nitrogen atom. They are often cyclic and the most common ring size contains 5 atoms (Figure 4-a).[14] The lone pairs on the heteroatoms neighbouring the carbene centre can donate into the carbon-centred p orbital leading to an increased energy gap between the non-bonding orbitals of the divalent carbon.[13,14] Therefore, NHCs adopt preferentially a singlet state with bent geometry and have an empty p orbital orthogonal to the plane of the ring. For these reasons, they exhibit moderate π-acidity but are also strong σ-donors and Brønsted bases. As free carbenes are often unstable, NHCs are synthesised and stored as their precursor equivalents (Figure 4-b). The free carbene can subsequently be generated *in situ* by deprotonation with a base.

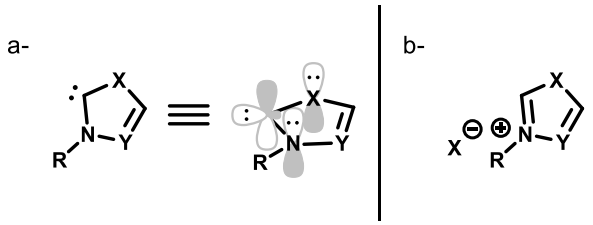


Figure 4: Schematic representation of a- NHC and b- their salt equivalents.

There are three main classes of 5-membered heterocyclic NHCs depending on the nature of X and Y: thiazolium, imidazolium and triazolium (Figure 5).

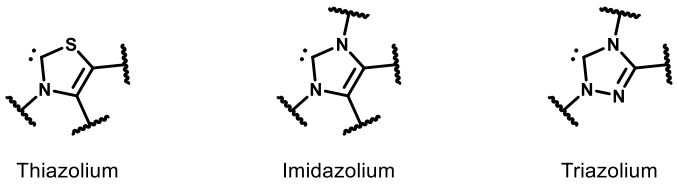
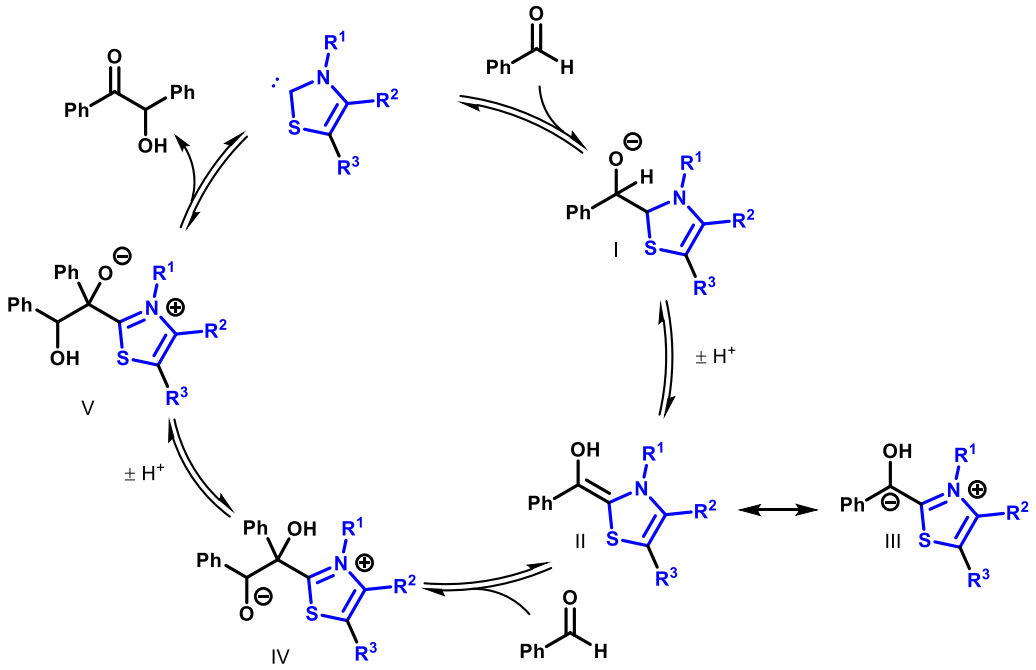


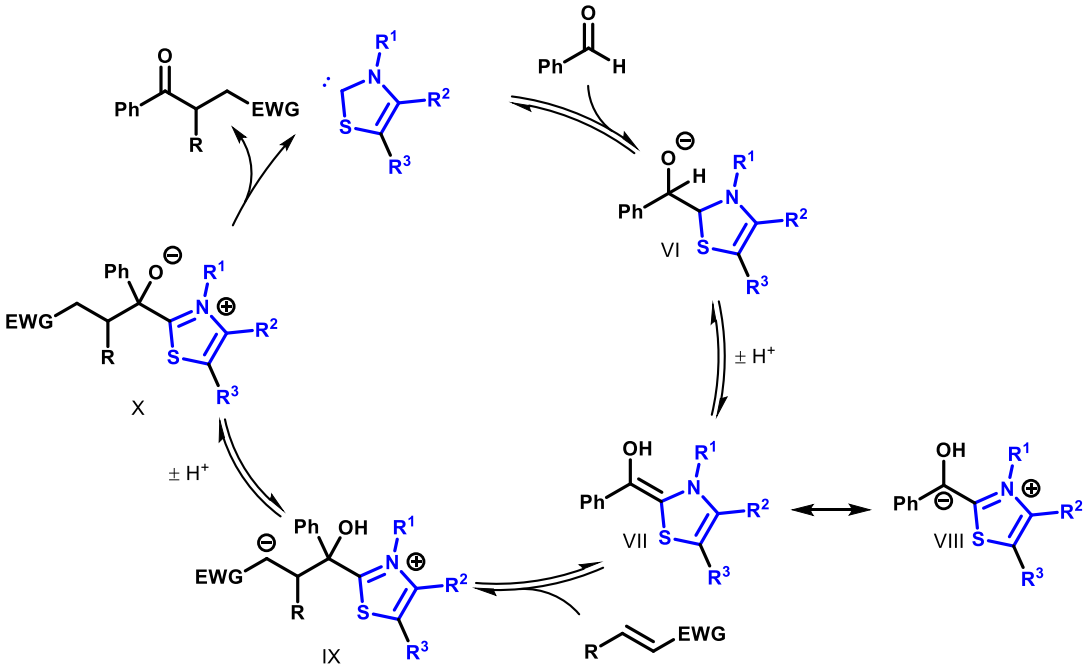
Figure 5: Three main classes of NHCs.

NHCs are well known as ligands for metal complexes[14a] for use in processes such as metathesis[15] and cross-coupling[16] reactions but are also employed as organocatalysts.[17] They have been known as organocatalysts for sixty years for their use in the benzoin condensation reported by Ukai in 1943.[14b,18] The current mechanism was postulated by Breslow in 1958, with one of the key steps being the formation of an enaminol **II** known as the Breslow intermediate (Scheme 4).[19] This acyl anion equivalent presents a reverse polarity or umpolung with the electrophilic carbon from the aldehyde acting as a nucleophile in the Breslow intermediate.[20] Enaminol **II** can add to benzaldehyde to form a new C-C bond. The 1,2-addition product, namely benzoin, is eliminated with regeneration of the catalyst.



Scheme 4: Benzoin reaction mechanism as postulated by Breslow.

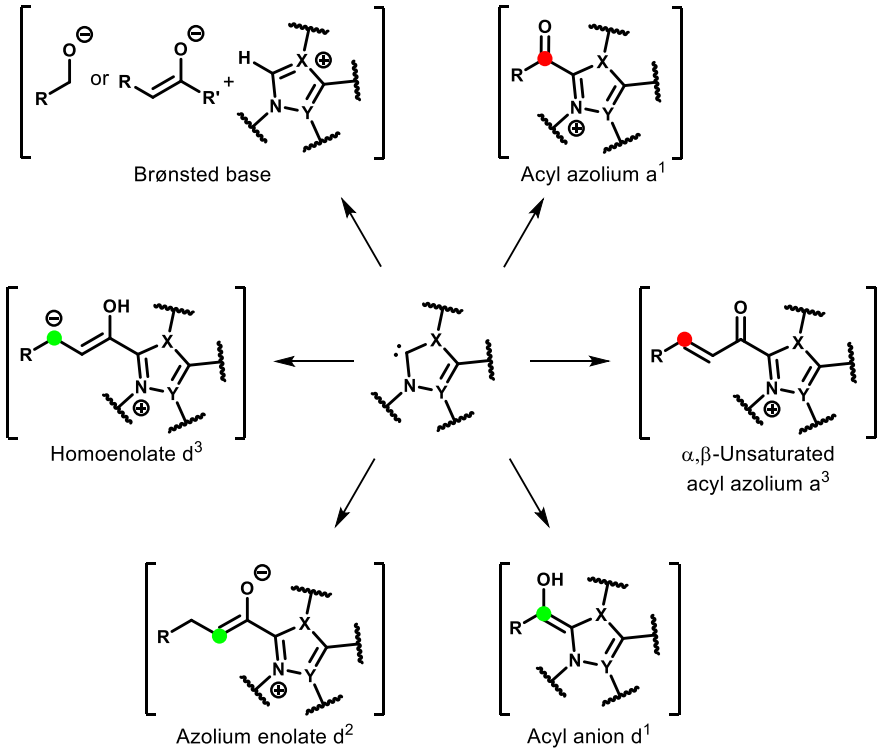
Similarly, the Stetter reaction is an extension of the benzoin reaction to include 1,4-addition to Michael acceptors, facilitating the formation of 1,4-diketones, 4-ketoesters and 4-ketonitriles.[21] The postulated mechanism goes through the Breslow intermediate **VII** (Scheme 5). Thanks to its reverse polarity, enaminol **VII** can react with a Michael acceptor. Although the desired 1,4-addition competes with the 1,2-addition, the final product of the Stetter reaction is more stable than from the benzoin condensation, therefore the overall reaction is favoured and irreversible.



Scheme 5: Postulated mechanism of the Stetter reaction.

Aldehydes are highly reactive towards self-benzoin reactions and easily undergo condensation. This reason slowed down a lot progress regarding the Stetter reaction and more generally NHC-catalysed reactions. This explains why the use of NHCs in organocatalysis has been quite late with the expansion of the field mainly over the last two decades. Indeed, they were found to be versatile organocatalysts that can be used as Brønsted bases to form alkoxides or enolates or as Lewis bases (Scheme 6).[14]

They can therefore be used in a broad range of organocatalysed processes, thanks to the wide variety of intermediates that can be generated through their unique reactivity. Following their addition to an ester or an aldehyde derivative, a series of different intermediates can be generated, which can either have an increased electrophilicity or nucleophilicity on one of the adjoining carbons. Intermediates which are electrophilic can be described as an acceptor a^n at C(n), where the descriptor 'a' refers to acceptor and 'n' to the number of carbons away from the NHC moiety (highlighted in red on Scheme 6).[22] Therefore, acyl azoliums are classified as a^1 as they develop a more electrophilic character on C(1). Similarly, α,β-unsaturated acyl azoliums are described as a^3. The intermediates presenting an increased nucleophilicity at C(n) are referred as donor d^n (highlighted in green on Scheme 6).[22] Acyl anions present a nucleophilic C(1) which was previously the electrophilic carbon of the carbonyl group and are therefore d^1. This type of polarity inversion is called an umpolung as mentioned earlier for the mechanisms of the benzoin and Stetter reactions. This concept was first introduced by Wittig *et al.* in 1951 and brought to popular attention by Seebach and Corey in 1965.[20,23] Similarly, azolium enolates are d^2 species (nucleophilic at C(2)) and homoenolates are d^3 (nucleophilic at C(3)).

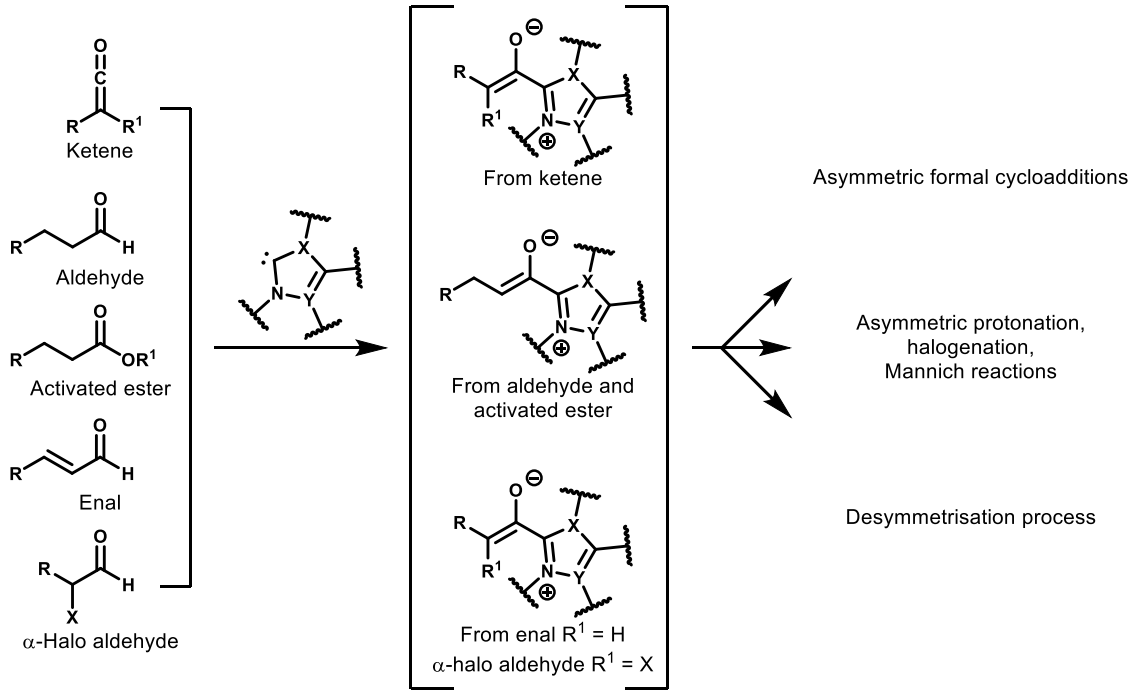


Scheme 6: Generation of intermediates using NHCs as catalysts.

Many reports have been published on each of these intermediates. This thesis will not cover the use of acyl anions,[24] homoenolates,[25] acyl azoliums,[26] α,β- unsaturated acyl azoliums[27] or the use of NHCs as Brønsted bases,[17,28] and will instead focus on the generation and applications of azolium enolates in organocatalysis.

1-3 Azolium enolate precursors

Azolium enolates are an important class of synthetic intermediates. They are classified as d^2, which means that they exhibit nucleophilic character at C(2). They can be generated from ketenes, aldehydes, activated esters, and α-functionalised aldehydes (enals and α-halo aldehydes), and undergo a wide range of reactions including formal cycloadditions, protonation, halogenation, Mannich reactions and desymmetrisation processes (Scheme 7).[18b]

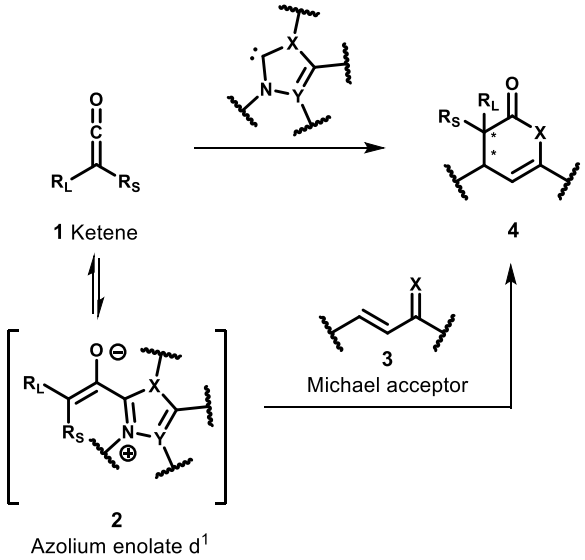


Scheme 7: Azolium enolates: generation and reactivity.

This introduction will focus on the use of azolium enolates in formal [4+2] cycloadditions leading to versatile motifs relevant to agrochemical and pharmaceutical industries and present a selection of existing methodologies. For a full report on the generation and reactivity of azolium enolates, several comprehensive recent reviews have been published.[14,18]

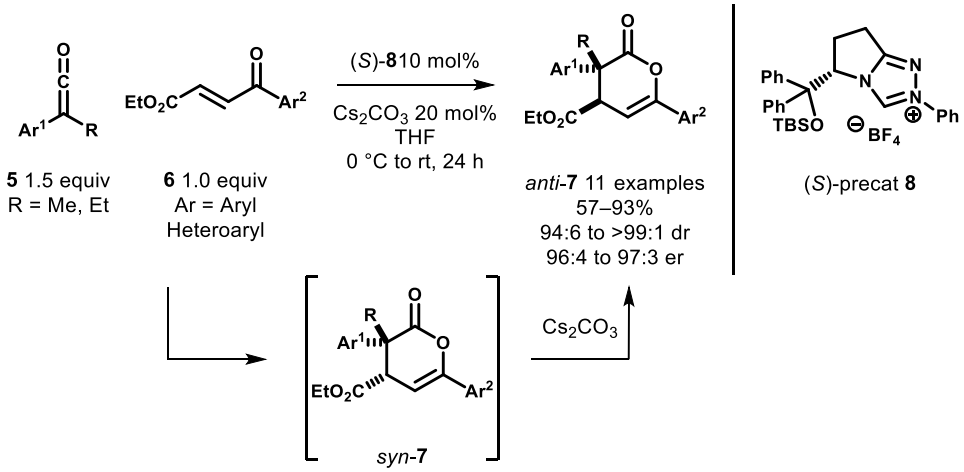
1-3-1 Ketenes as azolium enolate precursors in NHC-catalysed formal [4+2] cycloaddition

An azolium enolate can be generated by addition of an NHC-catalyst to a ketene **1** (Scheme 8). The obtained azolium enolate **2** is assumed to adopt an (*Z*)-geometry where the largest substituent avoids eclipsing interactions with the catalyst. Upon reaction with Michael acceptor **3**, a ring-closed product like **4** can be obtained.



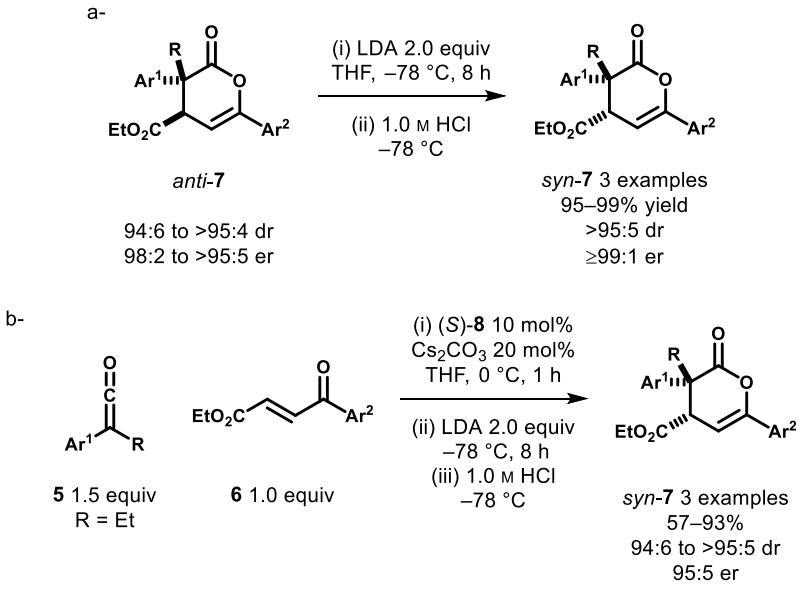
Scheme 8: Azolium enolates from ketenes in formal [4+2] cycloadditions.

The first paper reporting NHC-catalysed formal [4+2] cycloadditions using ketenes was published by Ye and co-workers in 2008.[29] Disubstituted alkylarylketenes **5** and α,β-unsaturated γ-arylketoesters **6** generated *anti*-dihydropyranones **7** with α-quaternary-β-tertiary stereocentres in moderate to high yield and excellent diastereo- and enantiocontrol (Scheme 9). The high diastereoselectivity was the results of *in situ* epimerisation of *syn*-dihydropyranones **7** into their *anti*-isomers.



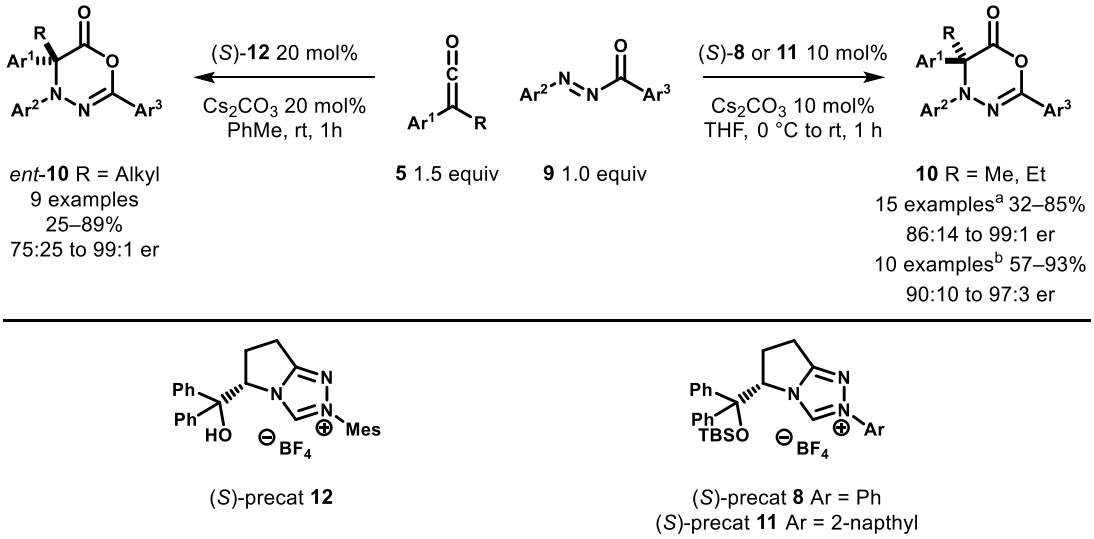
Scheme 9: NHC-catalysed formal [4+2] cycloaddition of disubstituted alkylarylketenes **5** with α,β-unsaturated γ-ketoesters **6**.

To extend the synthetic utility of this process, the generation of *syn*-dihydropyranones **7** was investigated. Epimerisation of *anti*-**7** by deprotonation using LDA and kinetic protonation mediated by aqueous HCl at –78 °C led to *syn*-**7** in excellent yield, dr and er (Scheme 10-a). This process could also be carried out *via* a one-pot reaction, to afford *syn*-**7** in 71–80% yield, 94:6 to >95:5 dr and 95:5 er (Scheme 10-b).



Scheme 10: Epimerisation to *syn*-**7** a- from isolated *anti*-**7** and b-in a pot-pot process from the corresponding disubstituted alkylarylketene **5** and α,β-unsaturated γ-arylketoesters **6**.

In 2009, the same group reported the NHC-catalysed formal [4+2] cycloaddition of disubstituted alkylarylketenes **5** with *N*-benzoyldiazenes **9** affording 1,3,4-oxadiazin-6-ones **10** (Scheme 11).[30] Precatalysts **8** and **11** led to the formation of the desired products **10** in low to high yield and high to excellent enantioselectivity (Scheme 11, right arrow). Interestingly, the authors also demonstrated that the *N*-substituent on the catalyst influenced the stereochemical outcome of the reaction. Indeed, the opposite enantiomer of the product *ent*-**10** was obtained in low to excellent yield and moderate to excellent enantiocontrol with a *N*-mesityl substituted precatalyst **12** at higher concentration (Scheme 11, left arrow).



Scheme 11: NHC-catalysed formal [4+2] cycloaddition of disubstituted alkylarylketenes **5** with *N*-benzoyldiazenes **9** using precatalysts (*S*)-**8**, (*S*)-**11** and (*S*)-**12**.

(a) Results obtained when using precatalyst (*S*)-**8**; (b) Results obtained when using precatalyst (*S*)-**11**.

To explain this switch of enantioselectivity, two different transition states were proposed (Figure 6). X-Ray crystallographic analysis of the precatalysts showed the *N*-substituent and the triazole ring to be coplanar in (*S*)-**8**, and orthogonal in (*S*)-**12**. In the transition states, the same geometry was assumed. The enolate was expected to be coplanar with the triazole ring of (*S*)-8 in **TS1**, and oriented to avoid steric interactions between R^1 and the *N*-phenyl group. In **TS2**, the enolate is proposed to be orthogonal to the triazole ring and therefore parallel to the mesityl group from (*S*)-**12**, with the aromatic substituent Ar^1 from the enolate facing the mesityl group which could possibly facilitate π-π stabilising interactions. The diazene would approach the top (*Re*) face of the enolate in **TS1** as the bottom (*Si*) face is blocked by the stereodirecting group R' in the catalyst. In **TS2**, the back (*Re*) of the enolate is blocked by the mesityl group, favouring the diazene to approach from the front (*Si*). In both cases, the diazene is orientated to maximise dipole opposition between its carbonyl and the oxyanion

of the enolate. Reverse enantioselectivity was observed with a bulky group on ketene **5** (Ar^1 = 2-ClC_6H_4, 1-naphthlyl or R = *i*Pr) when using precatalyst (*S*)-**8**. This was assumed to be due to a change in the transition state geometry from planar to orthogonal as in **TS₂** due to steric hindrance.

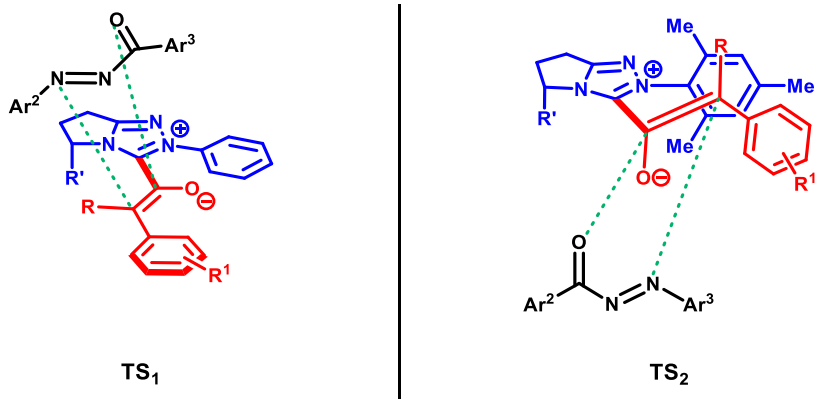
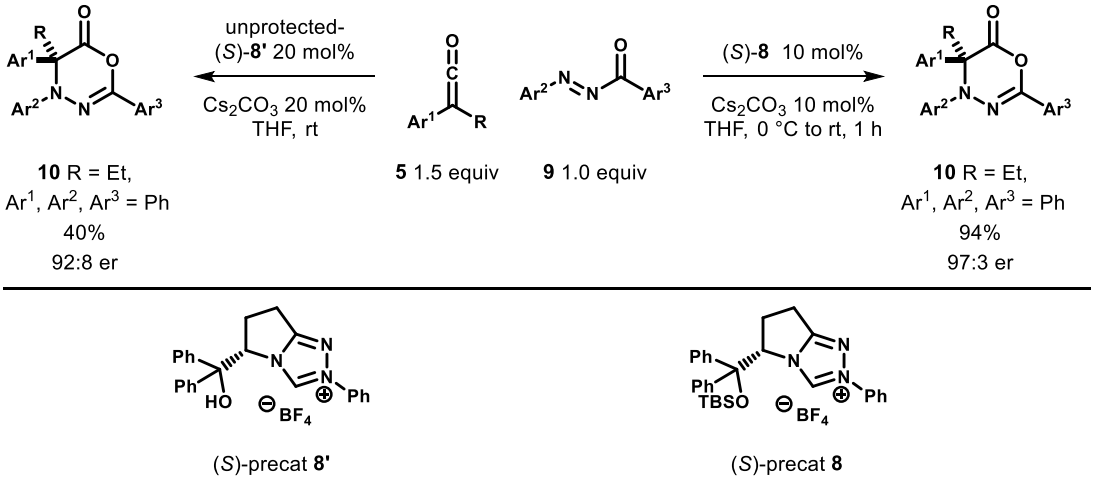


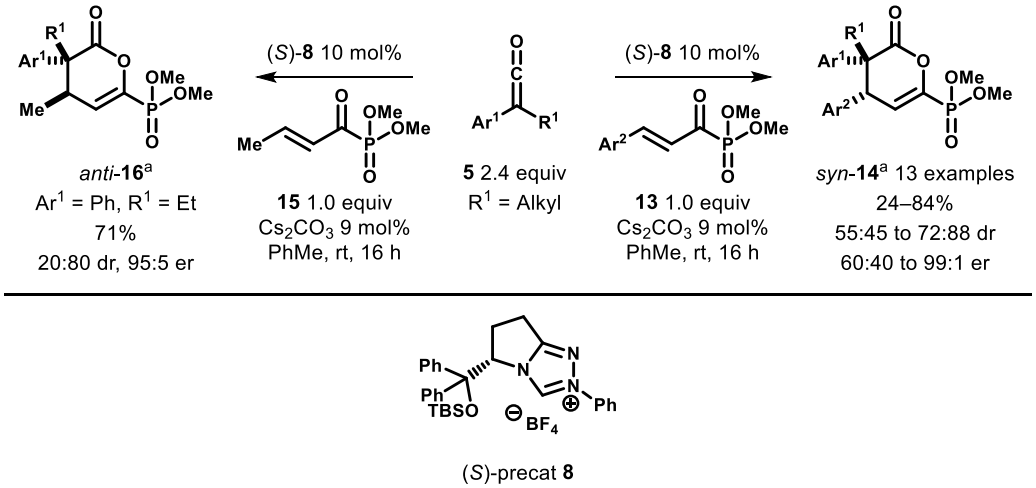
Figure 6: Schematic representation of transition states **TS₁** and **TS₂**.

The TBS-deprotected version of (*S*)-**8**, namely (*S*)-**8'**, led to lower yield and er despite using an increased 20 mol% catalyst loading (Scheme 12). Despite these interesting results, the influence on stereoselectivity of the presence of a free hydroxy group in precatalysts (*S*)-**8'** and (*S*)-**12** was not further discussed in the paper.



Scheme 12: Comparison between TBS-protected (*S*)-**8** and unprotected (*S*)-**8'**.

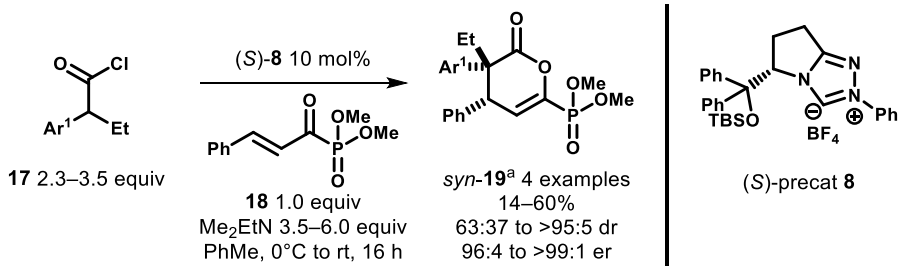
In 2013, the Smith group published the use of disubstituted alkylarylketenes **5** as azolium enolate precursors in formal [4+2] cycloaddition with β,γ-unsaturated α-ketophosphonates **13** and **15** (Scheme 13).[31] The use of γ-aryl-β,γ-unsaturated α-ketophosphonate **13** led to the formation of *syn*-dihydropyranones **14** in good to high yield, moderate diastereoselectivity and moderate to excellent enantioselectivity using precatalyst **8** (Scheme 13, right arrow). When γ-methyl-β,γ-unsaturated α-ketophosphonate **15** was utilised the major product obtained was the *anti*-diastereoisomer **16** (Scheme 13, left arrow).



Scheme 13: NHC-catalysed formal [4+2] cycloaddition of disubstituted alkylarylketenes **5** with γ-aryl-β,γ-unsaturated α-ketophosphonates **13** and with γ-methyl-β,γ-unsaturated α-ketophosphonate **15**.

(a) Isolated yield of both diastereoisomers; dr *syn*/*anti*; er from the major diastereoisomer.

In situ generation of ketenes **5** from the corresponding arylacetyl chlorides **17** was also demonstrated leading to *syn*-**19** with improved overall yields and stereoselectivity (Scheme 14).



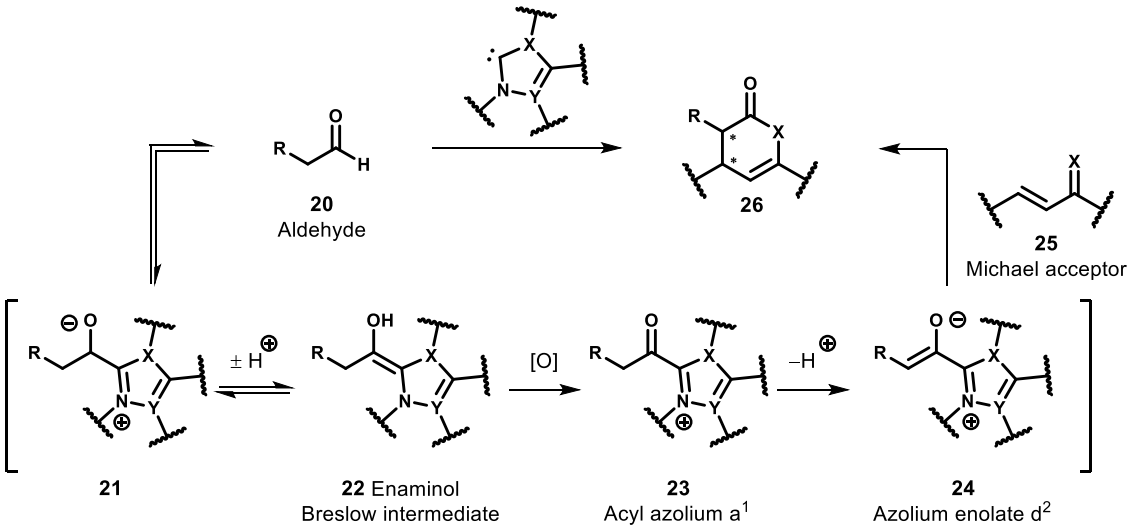
Scheme 14: NHC-catalysed formal [4+2] cycloaddition with *in situ* generation of arylethylketenes **5**.

(a) Isolated yield of both diastereoisomers over two-step reaction; dr *syn*/*anti*; er from the major *syn*-diastereoisomer **19**.

To date the scope of ketenes in NHC-catalysed [4+2] cycloadditions is limited to disubstituted arylalkylketenes. Ketenes are traditionally difficult to synthesise and are, in general, not bench stable. Therefore, alternative methods to access azolium enolates have been developed.

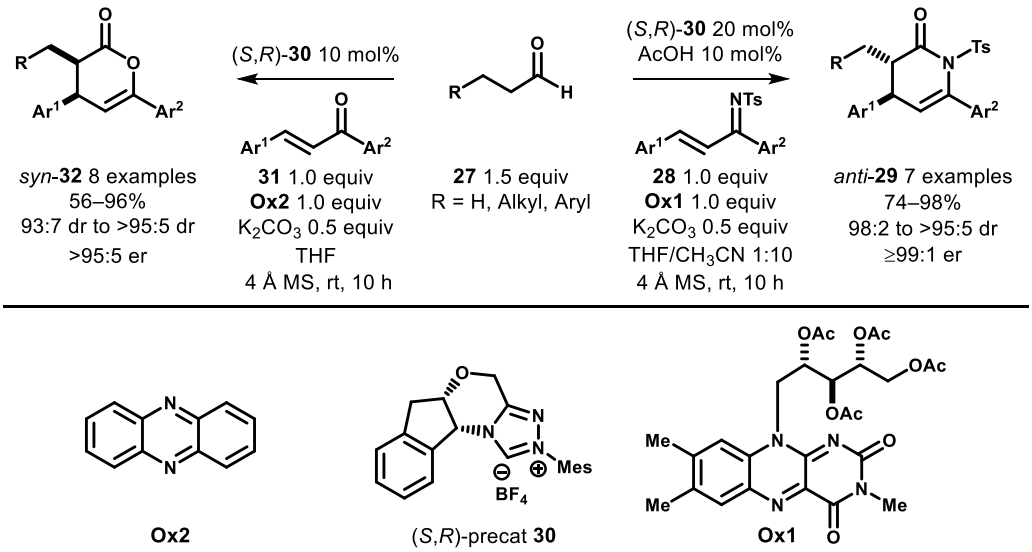
1-3-2 Aldehydes as azolium enolate precursors in NHC-catalysed formal [4+2] cycloaddition

Aldehydes are easily accessible and relatively stable starting materials that act as azolium enolate precursors. The formation of azolium enolates from aldehydes follows a different pathway to that from ketenes (Scheme 15). Addition of the NHC-catalyst to aldehyde **20** leads to an NHC-aldehyde adduct **21**. Proton transfer gives Breslow intermediate **22**.[19] This enaminol **22** is oxidised by an external oxidant to generate acyl azolium **23** before deprotonation to give the desired azolium enolate **24** that can react further in a formal [4+2] cycloadditions fashion with Michael acceptor **25** to afford the desired product **26**.



Scheme 15: Azolium enolates from aldehydes in formal [4+2] cycloadditions.

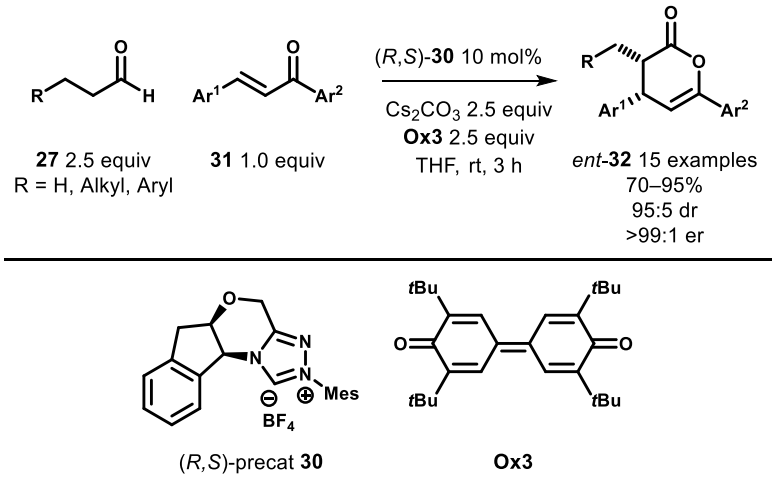
A seminal paper published by Rovis *et al.* in 2012, reported the use of aldehydes **27** in formal [4+2] cycloadditions (Scheme 16).[32] The desired *anti*-dihydropyridinones **29** were obtained when using tosyl-protected α,β-unsaturated ketimines **28** as Michael acceptors (Scheme 16, right arrow) and *syn*-dihydropyranones **32** when α-β-unsaturated ketones **31** were utilised (Scheme 16, left arrow). The optimal conditions for the synthesis of dihydropyridinones **29** from aldehydes **27** and ketimines **28** used one equivalent of oxidant **Ox1**. Catalytic acetic acid was necessary to avoid irreversible 1,2- or 1,4-addition of the free carbene to ketimines **28**, while using a mixture of THF/CH_3CN as solvent increased the solubility of the inorganic base. The desired *anti*-dihydropyridinones **29** were obtained in high yield excellent dr and er, and tolerated the inclusion of electron withdrawing or donating groups on either aryl substituents of ketimine **28**. The synthesis of dihydropyranones **32** using α,β-unsaturated ketones **31** proceeded in THF with phenazine as oxidant **Ox2** (Scheme 16, left arrow). In this case, *syn*-dihydropyranones **32** were afforded in moderate to high yield and excellent diastereo- and enantiocontrol. No explanation of the reversal in diastereoselectivity was provided by the authors.



Scheme 16: NHC-catalysed formal [4+2] cycloaddition of aldehydes **27** with tosyl-protected α,β-unsaturated ketimines **28** and with α-β-unsaturated ketones **31** by Rovis *et al*.

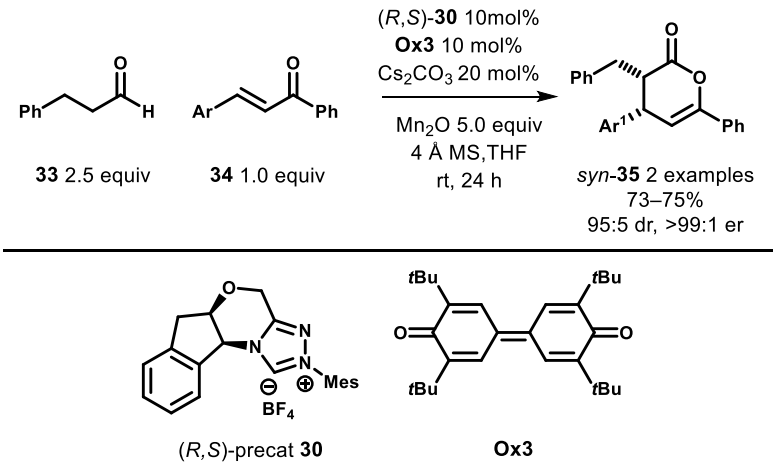
In 2013, Chi *et al.* published independently the synthesis of *syn*-dihydropyranones *ent*-**32** using α-β-unsaturated ketones **31** as Michael acceptors (Scheme 17).[33] This system required an excess of oxidant **Ox3** and an excess of aldehyde **27** (2.5 equiv) to overcome unwanted hydrolysis of the acyl azolium intermediate. The desired *syn*-dihydropyranones **32** were obtained in high yield and excellent diastereo- and enantioselectivity. The use of electron-donating and electron-withdrawing groups in either or both reagents gave good

results, but no reaction was observed with bulky aldehydes (α-aryl or α,α'-disubstituted) or with alkyl substituted enones.



Scheme 17: NHC-catalysed formal [4+2] cycloaddition of aldehydes **27** α-β-unsaturated ketones **31** by Chi *et al.*

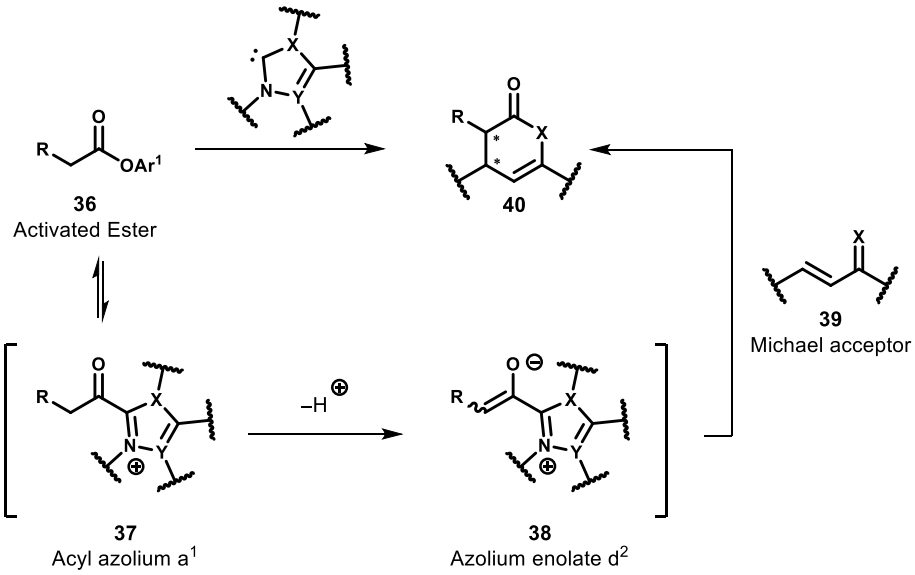
The main drawback to the approach of using aldehydes as azolium enolate precursors is the requirement for an external oxidant that can be very expensive (£38.41 for 0.1 mmol, £96.02 per reaction for **Ox3** from Sigma-Aldrich). Therefore, Chi *et al.* developed a catalytic version of this system using 10 mol% of oxidant **Ox3** with 5.0 equivalents of MnO_2 as a co-oxidant (Scheme 18). Using MnO_2 as the sole oxidant gave only trace amounts of the desired product **35**, which is consistent with MnO_2 being only involved in the regeneration of oxidant **Ox3**.



Scheme 18: NHC-catalysed formal [4+2] of aldehydes **32** with α,β-unsaturated ketones **34** with catalytic use of **Ox3**.

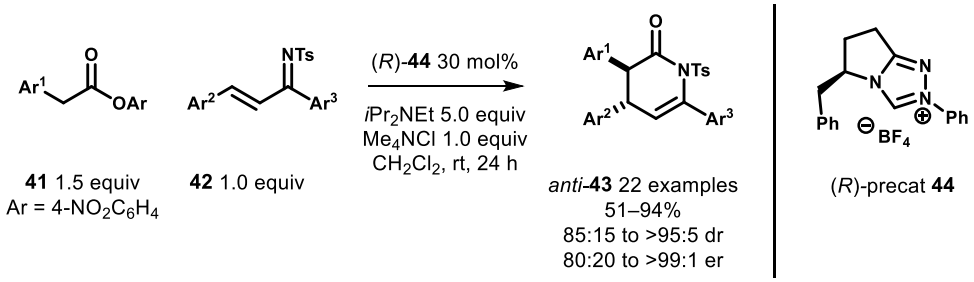
1-3-3 Activated esters as azolium enolate precursors in NHC-catalysed formal [4+2] cycloadditions

The generation of an azolium enolate **38** from an activated ester **36** does not require the use of external oxidants and proceeds *via* an acyl azolium **37** which is then deprotonated (Scheme 19). Formal [4+2] reaction with Michael acceptor **39** leads to the desired ring-closed product **40**.



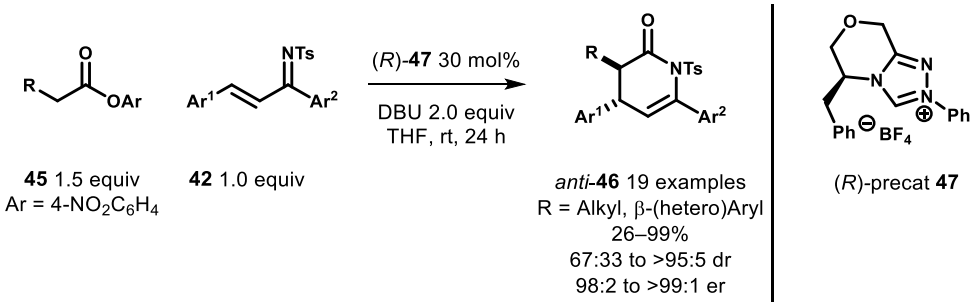
Scheme 19: Azolium enolates from activated esters in formal [4+2] cycloadditions.

In 2012, Chi *et al.* proposed arylacetic esters **41** as an alternative to the use of ketenes (Scheme 20).[34] Esters **41** bear an electron deficient leaving group, 4-nitrophenol. The NHC-catalysed formal [4+2] cycloaddition of esters **41** with *N*-tosyl protected α,β-unsaturated ketimines **42** led to the formation of dihydropyridinones **43** in good to excellent yield and dr, and good to excellent er. This methodology was limited to arylacetic esters and aryl-substituted ketimines, required tetramethylamonium chloride as an additive and high 30 mol% precatalyst **44** loading.



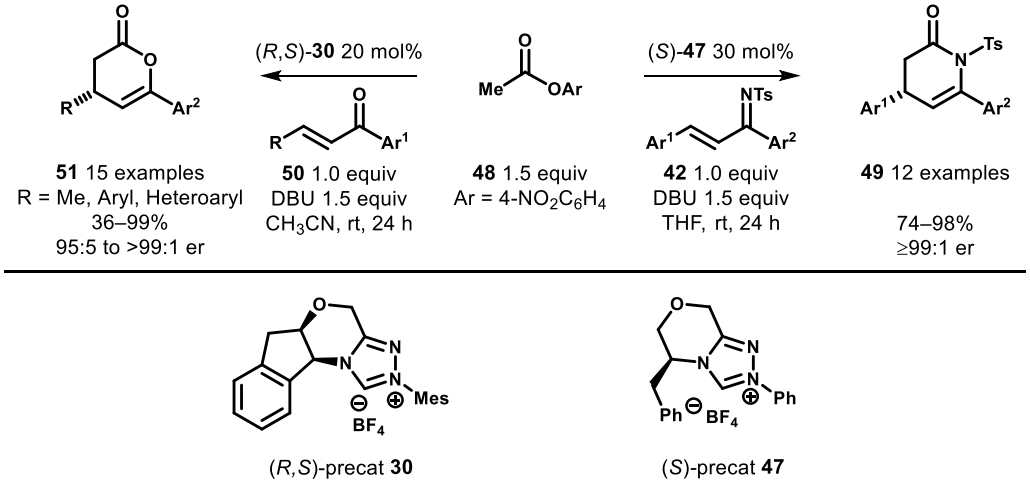
Scheme 20: NHC-catalysed formal [4+2] cycloaddition of arylacetic ester **41** with tosyl-protected α,β-unsaturated ketimines **42**.

In 2013, further studies on the use of alkylacetic esters **45** were published by the same group (Scheme 21).[35] The tuning of the strength of the base and the careful choice of the NHC precatalyst were key for the generation of azolium enolates from **45**. The base was indeed changed to DBU (2.0 equiv) and morpholine derived triazolium precatalyst **47** was used. The desired dihydropyridinones **46** were obtained in poor to quantitative yield, in low to excellent dr and excellent er.



Scheme 21: NHC-catalysed formal [4+2] cycloaddition of alkyl acetic ester **45** with tosyl-protected α,β-unsaturated ketimines **42**.

The use of 4-nitrophenyl acetate **48** was also demonstrated with both tosyl-protected α,β-unsaturated ketimines **42** and α,β-unsaturated ketones **50** (Scheme 22).[36] The desired dihydropyridinones **49** were obtained in excellent yield and enantioselectivity using 30 mol% precatalyst **47** but appeared to be limited to aryl-substituted ketimines (Scheme 22, right arrow). Dihydropyranones **51** were afforded in moderate to quantitative yield, and good to excellent enantioselectivity utilising precatalyst **30** in a lower 20 mol% loading. (Scheme 22, left arrow).



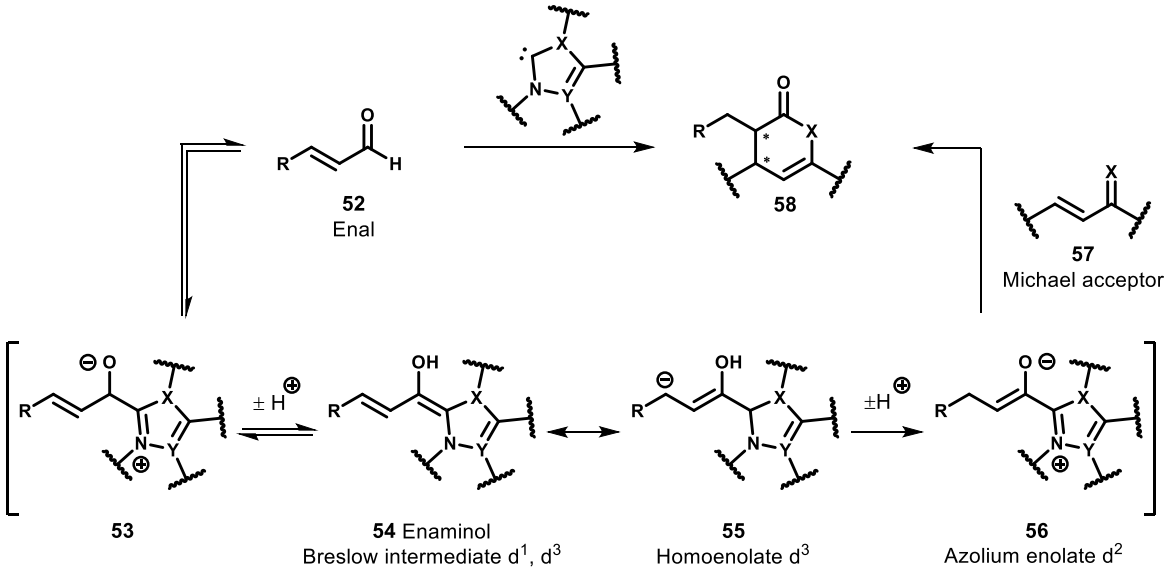
Scheme 22: NHC-catalysed formal [4+2] cycloaddition of 4-nitrophenyl acetate **48** with tosyl-protected α,β-unsaturated ketimines **42** and and α,β-unsaturated ketones **50**.

1-3-4 α-Functionalised aldehydes as azolium enolate precursors in NHC-catalysed formal [4+2] cycloaddition

Enals and α-halo aldehydes are two types of α-functionalised aldehydes that can behave as azolium enolate precursors. Using these precursors, the formation of the azolium enolate occurs *via* oxidation of the aldehyde and reduction of the carbon backbone.

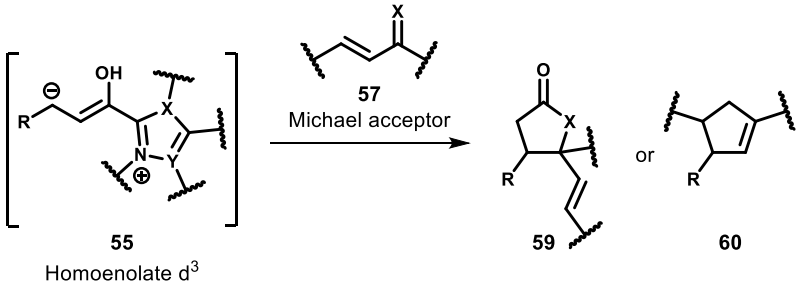
Enals:

Starting with enal **52**, the first step corresponds to the addition of the free carbene onto the carbonyl functionality (Scheme 23). Proton transfer leads to Breslow intermediate **54** that can undergo both d^1 and d^3 reactivity. A β-protonation of its homoenolate resonance form **55** leads to the desired azolium enolate **56** that can react with Michael acceptor **57** to afford the desired 6-membered ring product **58**.



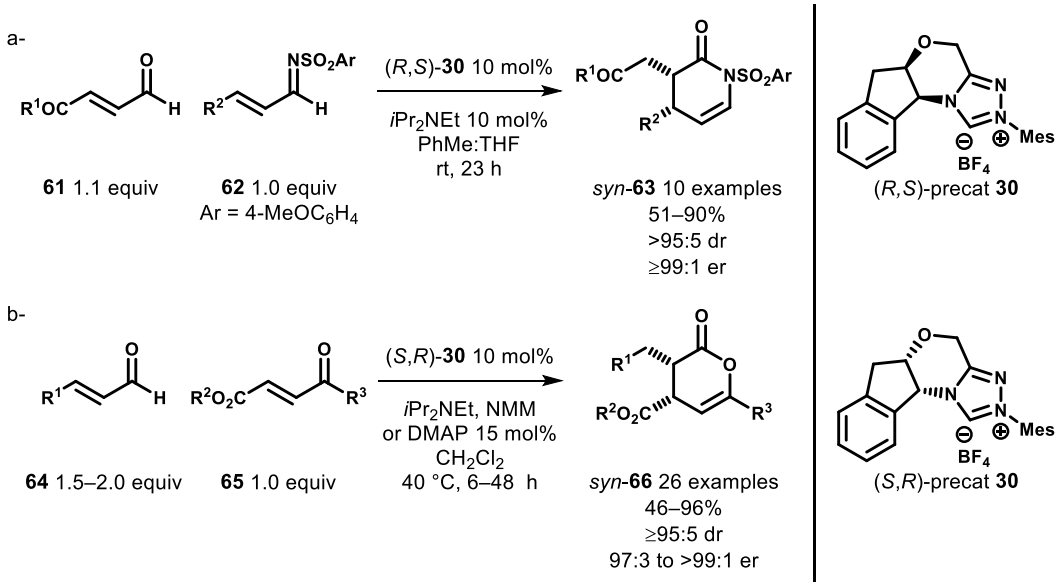
Scheme 23: Azolium enolates from enals in formal [4+2] cycloadditions.

Due to the high reactivity of homoenolate **55** formal [3+2] cycloadditions with Michael acceptor **57** can take place, leading to the formation of 5-membered rings **59** or **60** (Scheme 24).[37] To promote the formal [4+2] cycloaddition, reaction conditions favouring the azolium enolate pathway must be found.



Scheme 24: Unwanted side-reaction through homoenolate **55**.

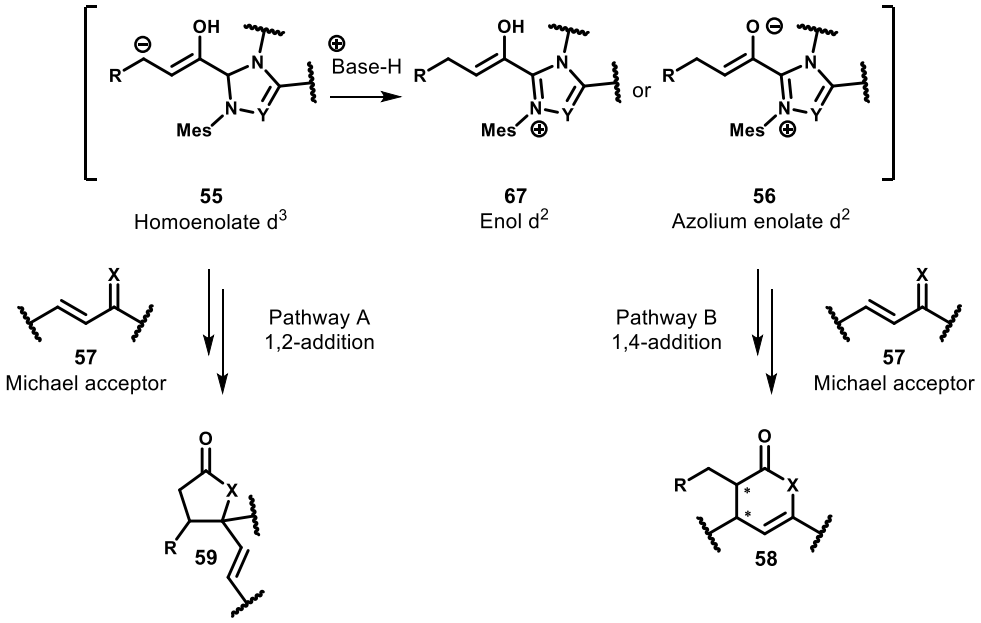
In 2006, Bode, and *et al.* reported the first example of NHC-catalysed formal [4+2] cycloaddition of α,β-unsaturated ketoenals **61** with *N*-sulfonyl aldimines **62** leading to the formation of the desired *syn*-dihydropyridinones **63** in moderate to excellent yield and excellent diastereo- and enantiocontrol (Scheme 25-a).[38] In 2010, the same group published the use of simple β-alkyl or aryl substituted enals **64** as azolium enolate precursors in combination with a variety of α,β-unsaturated γ-ketoesters **65** bearing different functionalities on the ketone moiety (R^3 = Me, 4-$MeOC_6H_4$, CO_2Et, $(CH_3)_2C(OH)$, $(CH_3)_2C(NHCbz)$) to afford the corresponding *syn*-dihydropyranone derivatives **66** in moderate to excellent yield and excellent diastereo- and enantioselectivity (Scheme 25-b).[39]



Scheme 25: NHC-catalysed formal [4+2] reaction of enals with: a- α,β-unsaturated aldimines **62**; b- α,β-unsaturated γ-ketoesters **65**.

Other than solvent and temperature, three factors influenced the reaction toward the exclusive generation of the azolium enolate over the homoenolate. Firstly, the nature of the NHC-catalyst as well as its *N*-substituent was important. In the first report, screening of catalysts showed that the presence of the *N*-mesityl group was required for any reaction to proceed. The use of an *N*-mesityl substituted imidazolium catalyst did not lead to the β-protonation of the homoenolate intermediate (Pathway A), whereas reactions catalysed by *N*-mesityl substituted triazolium gave the desired dihydropyridinones **63** (Pathway B) as the major product (Table 1, Entries 1 and 2). The second factor was the strength of the base used to activate the precatalyst, and more precisely the strength of its conjugate acid was an influential parameter. Bode *et al.* postulated the conjugate acid to be the species involved in the β-protonation of the homoenolate, thus generating the desired azolium enolate (Pathway B). Through optimisation, they observed that weak amine bases gave the best

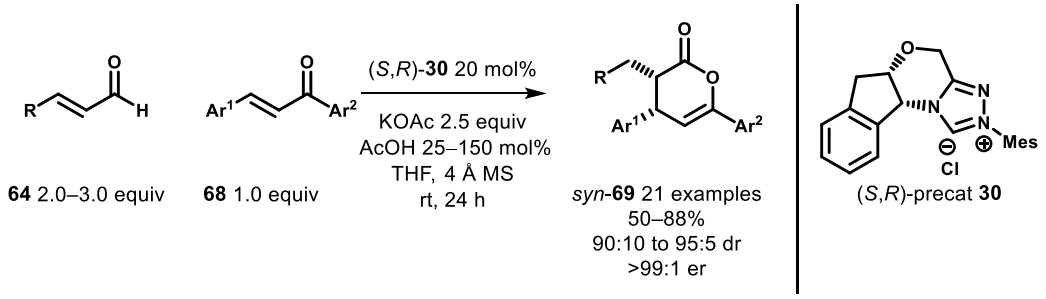
results. For example, in the achiral version of the reaction the use of 10 mol% of DBU in PhMe at rt gave a 90:10 ratio between the desired *syn*-dihydropyridinone **63** and the unwanted γ-lactone **59** whereas the use of 10 mol% of *i*Pr$_2$NEt in the same reaction conditions gave an improved 95:5 ratio (Table 1, Entries 2 and 3). The third factor was the electronic characteristics of the starting materials. The generation of *syn*-dihydropyridinones **63** was limited to the electron deficient β,γ-unsaturated γ-ketonenals **61**. This showed a requirement for the enal to have an electron withdrawing substituent to be more electrophilic and therefore more reactive toward the addition of the catalyst. Concerning the formation of *syn*-dihydropyranones **66**, the ratio between the 6-membered and 5-membered ring products was influenced by the substituent on the γ-ketoester **65**. Indeed, reaction of enals **64** with enones **65** containing aliphatic, alicyclic or electron-rich aryl α-substituents (R^3 = EDG) led exclusively to the desired *syn*-dihydropyranones **66** (Pathway B), whereas with electron-poor aromatic group (R^3 = EWG), cyclopentenes **60** were obtained as the major product (Pathway A).



Entry	Catalyst	Base	58:59
1	Y = CH	DBU	<10:90
2	Y = N	DBU	88:12
3	Y = N	*i*Pr$_2$NEt	>95:5

Table 1: Influence of the base and catalyst on the **58**:**59** ratio.

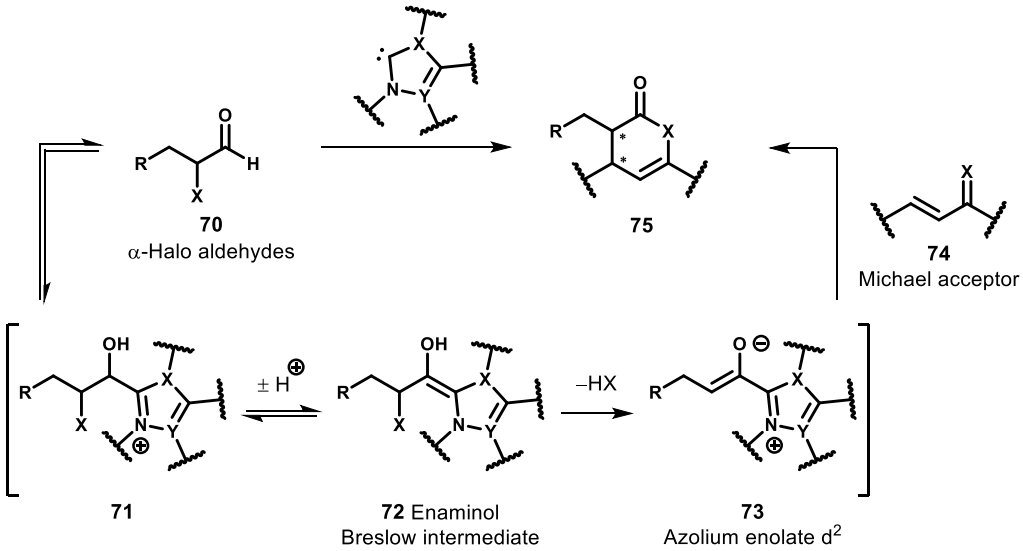
In 2013, Chi *et al.* reported a method based on the addition of external acid for the formal [4+2] cycloaddition of enals **64** and α,β-unsaturated ketones **68** (Scheme 26).[40] The process used relatively high loading of precatalyst **30**, stoichiometric quantities of base to activate the precatalyst, and between 25 and 150 mol% of acetic acid, leading to 80:20 to 95:5 ratio between desired *syn*-dihydropyranones **69** and undesired cyclopentene **60**. Bulky substituents on enal **64** favoured the azolium enolate pathway. For example, when enal **64** was substituted by R = 2-BrC_6H_4, the ratio between the 6-membered and the 5-membered ring was 95:5 (**69**:**60**) whereas for R = 4-BrC_6H_4 the ratio decreased to 85:15 (**69**:**60**) in favour to undesired **60**. The same trend was observed between R = 2-$MeOC_6H_4$ (95:5, **69**:**60**) and R = 4-$MeOC_6H_4$ (90:10, **69**:**60**).



Scheme 26: NHC-catalysed formal [4+2] cycloaddition with enals **64** with α,β-unsaturated ketones **68** using external acid.

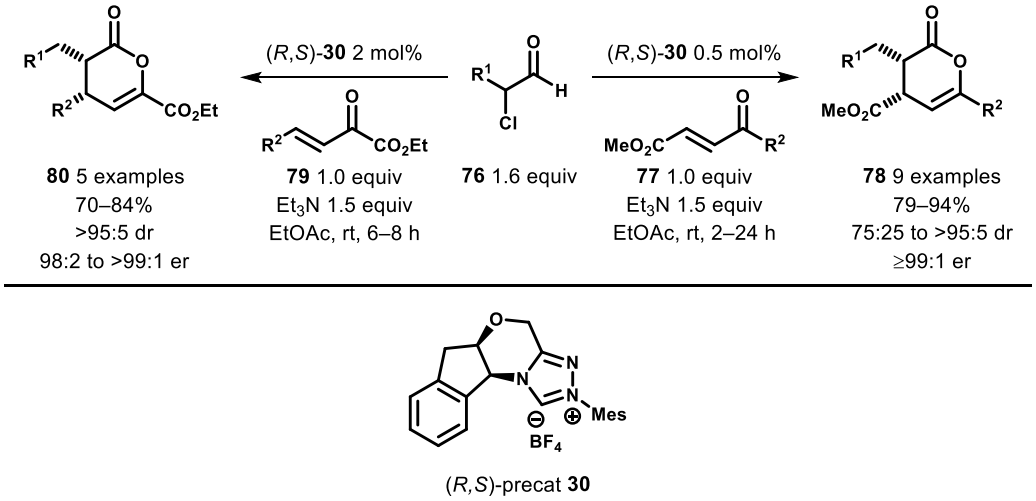
α-Halo aldehydes:

The generation of azolium enolate **73** from α-halo aldehyde **70** proceeds through addition of the NHC-catalyst to aldehyde **70** to form **71**, followed by elimination of the halogen and deprotonation of Breslow intermediate **72** (Scheme 27). The subsequent formal [4+2] cycloaddition with Michael acceptor **74** provides ring-closed product **75**.



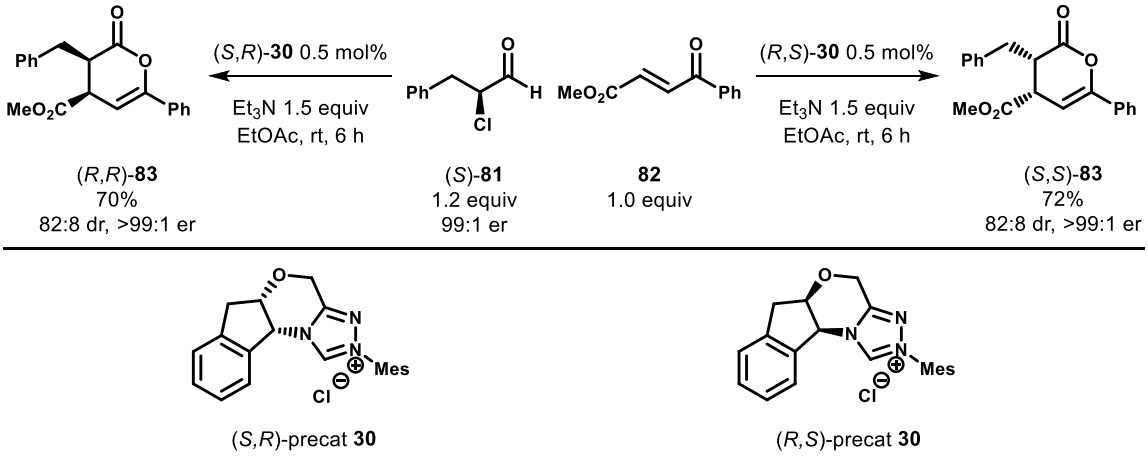
Scheme 27: Azolium enolates from α-halo aldehydes in formal [4+2] cycloadditions

In 2006, Bode *et al.* described the use of α-chloro aldehydes **76** in NHC-catalysed formal [4+2] cycloadditions with enones **77** and **79** (Scheme 28).[41] The desired *syn*-dihydropyranones **78** were all obtained in high to excellent yield, diastereo- and enantiocontrol with enones **77**, using only 0.5 mol% of precatalyst **30** (Scheme 28, right arrow). A drop in diastereoselectivity was observed with arylketones (R^2 = Ar) due to epimerisation of the *syn*-product **78** under the reaction conditions. With β,γ-unsaturated α-ketoesters **79**, the precatalyst loading had to be increased from 0.5 mol% to a still low 2 mol% to obtain higher yield and enantioselectivity for **80** (Scheme 28, left arrow).



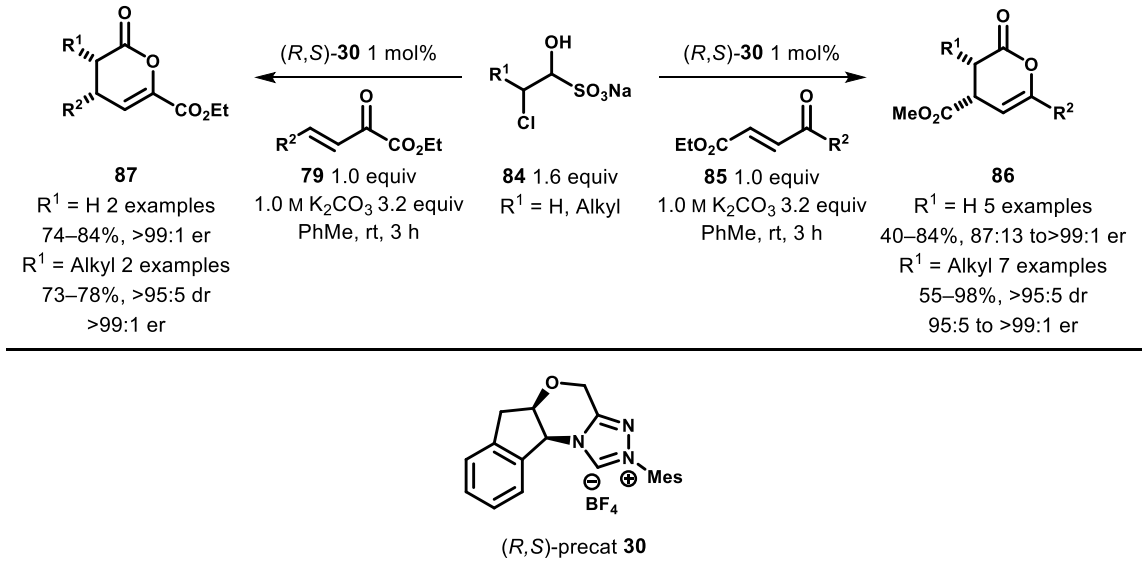
Scheme 28: NHC-catalysed formal [4+2] cycloaddition of α-chloro aldehydes **76** with α,β-unsaturated γ-ketoesters **77** and with γ-substituted β,γ-unsaturated α-ketoesters **79**.

The importance of the stereochemistry of the α-carbon on the aldehyde starting material was also studied (Scheme 29). To this end, two reactions were performed, using enantioenriched α-chloroaldehyde **81** with enone **82**, each one catalysed by a different enantiomer of precatalyst **30** (Scheme 29). The desired *syn*-dihydropyranones **83** were obtained in high yield and excellent diastereo- and enantiocontrol, and presented opposite absolute configuration. When the reactions were stopped before completion, the remaining α-chloroaldehyde **81** was found to have racemised. This is consistent with the loss of stereochemical information in the starting α-chloro aldehydes with the stereochemistry of the precatalyst determining the stereochemical outcome of the reaction.



Scheme 29: Test of the influence of the stereochemistry of the α-carbon of α-chloroaldehyde **81**.

Although α-chloro aldehydes showed promising results, they are sensitive to moisture and oxygen and therefore too unstable to be easily used as enolate precursors. To overcome their instability, Bode *et al.* developed their bisulfite salts equivalents **84**, obtained by simple addition of aqueous sodium bisulfite salt to the corresponding α-chloroaldehydes.[42] The NHC-catalysed [4+2] cycloadditions were performed in a biphasic system to enable the regeneration *in situ* of α-chloroaldehydes and gave dihydropyranones **86** and **87** in moderate to high yield, excellent diastereoselectivity and very good to excellent enantioselectivity (Scheme 30).

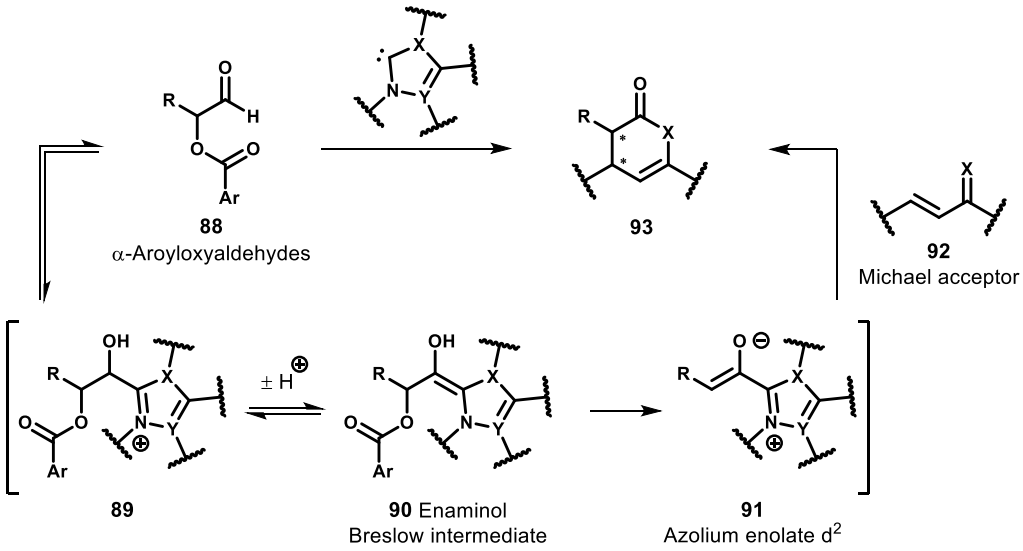


(*R,S*)-precat **30**

Scheme 30: NHC-catalysed formal [4+2] cycloaddition with bisulfite salt **84** and unsaturated γ-ketoesters **85** and with γ-substituted β,γ-unsaturated α-ketoesters **79**.

α-Aroyloxyaldehydes:

In order to circumvent the lack of stability of α-chloro aldehydes, the Smith group developed a bench stable alternative which are the α-aroyloxyaldehydes **88** (Scheme 31).[43] Azolium enolates **91** can be accessed in similar way than for α-halo aldehydes and can used with Michael acceptors **92** in a range of NHC-catalysed formal [4+2] cycloadditions and will be discussed in more details in chapter 2.[44, 45,46]

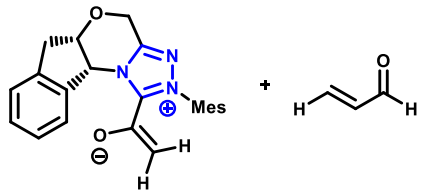


Scheme 31 Azolium enolates from α-aroyloxyaldehydes in formal [4+2] cycloadditions

1-4 N-Mesityl substituted aminoindane based triazolium precatalyst

Among NHC precatalysts previously presented, one has received particular interests over the past decade, *N*-mesityl substituted aminoindane-based triazolium precatalyst **30**.[47] The use of precatalyst **30** was first reported in 2006 by Bode *et al.* for the generation of azolium enolates from β,γ-unsaturated ketoenals with in the formal [4+2] cycloaddition with *N*-sulfonyl protected aldimine (Section 1-3-4, Scheme 25-a)[38] and since then has been used in numerous methodologies.[14] The structure of this precatalyst contains a triazolium ring, a *N*-mesityl moiety and an aminoindole core. These three components have a role in the high diastereo- and enantiocontrol observed in the outcome of a formal [4+2] cycloaddition catalysed by the free carbene from **30**.

In 2012, Bode, Kozlowski *et al*. published computational studies that rationalised the origin of this stereoselectivity and deciphers the pathway of the formal [4+2] cycloadditions.[48] The model system used acetaldehyde enolate **94**, obtained from acetaldehyde and (*S*,*R*)-**30**, and acrolein **95** (Figure 7).



94 Acetaldehyde enolate **95** Acrolein

Figure 7: Model system used in computational studies by Bode, Kozlowski *et al*.

Their investigations showed the reaction to be an asynchronous *endo*-hetero-Diels–Alder process. Computation demonstrated the enolate to be coplanar to the triazole ring and orthogonal to the mesityl group (Figure 8-a). The formation of the (*Z*)-enolate to avoid steric clash leads to two different conformations. With the oxyanion pointing toward the electron rich mesityl group possibly resulting in repulsive interactions, conformation A is disfavoured (highlighted in red in Figure 8-a). In conformation B, the hydrogen on C(2) of the enolate is directed towards the mesityl group (highlighted in green in Figure 8-b). Calculations showed this led to stabilising CH–π interactions and helped to lock the enolate in this conformation. In the most favourable computed transition states, the aminoindole core blocks one face (drawn here as the bottom face on Figure 8-b) of the enolate which results in the diene, namely enone **95**, approaching the enolate from the opposite face. Furthermore, this approach is endocyclic to avoid interaction with the mesityl, with maximised dipole oppositions between the oxyanion of the enolate and the carbonyl of the enone. An additional secondary interaction between the lone pair of the oxyanion and the π* orbital of the carbonyl was observed (highlighted in brown in Figure 8-b). These results are consistent with the diastereochemical outcome of the reactions using enals as azolium enolate precursors with the predominant formation of the *syn* products (R^1, R^2, $R^3 \neq H$; Section 1-3-4, Scheme 25-b).

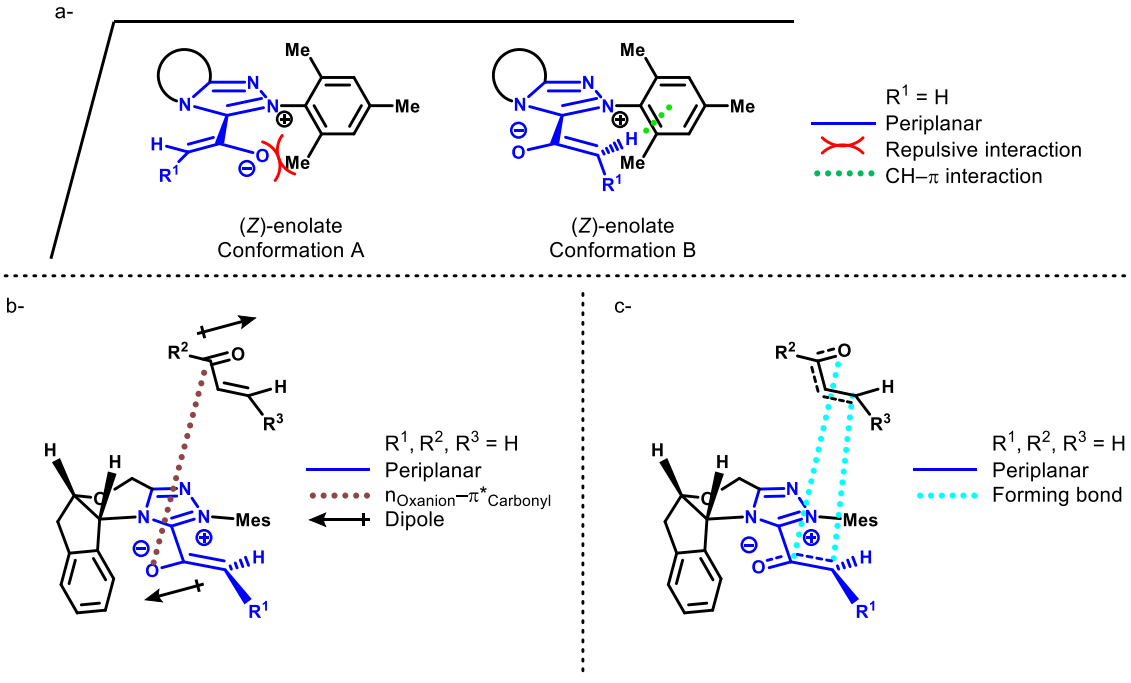
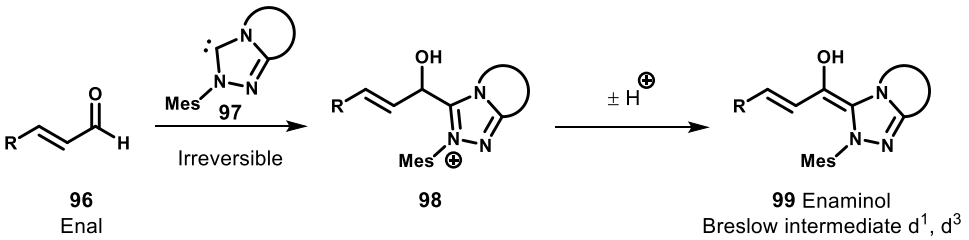


Figure 8: Proposed pre-transition state assembly following computational studies from Bode, Kozlowski *et al*.

Bode and Mahatthananchai published that year a comparative study on the use *N*-aryl substituted triazolium precatalysts for the generation of azolium enolate from enals to investigate the effects of the *N*-substituent on reactions outcome.[49] The investigations demonstrated that in this case the formation of Breslow intermediate **99** was favoured when sterically hindered *N*-mesityl triazolium precatalyst was used. Indeed, the presence of the *N*-mesityl substituent led to an irreversible addition of the free carbene onto enal **96** to form a sterically hindered adduct **98** and therefore to the rapid formation of Breslow intermediate **99**.[50]



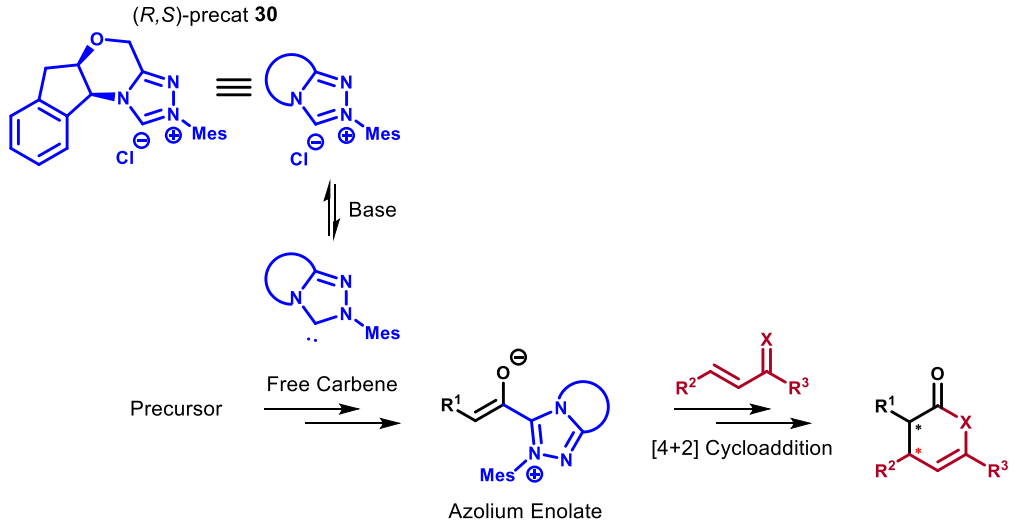
Scheme 32: Irreversible addition of *N*-mesityl triazolium precatalyst onto enal **96**.

Precatalyst **30** is a powerful carbene precursor, especially in reaction involving the formation of a Breslow intermediate. It can generate azolium enolates from diverse precursors and lead to good to excellent stereocontrol due to electronic and steric interactions with both the donor and acceptor participating in the reaction This makes it one of the most efficient NHC precatalyst involved in formal [4+2] cycloadditions, and therefore an interesting subject of study.

1-5 Aim and Objectives

To conclude, the generation of azolium enolates has received much attention but suffers from drawbacks. They can be difficult to access, lack stability, have limited scopes and unwanted side-reactions, as well as requiring external additives such as oxidants. Therefore, alternative classes of azolium enolates need to be investigated to try to expand their synthetic utility.

The aim of this thesis is the use of alternative species that could generate azolium enolates in combination with precatalyst **30** and be utilised in formal [4+2] cycloaddition methodologies (Scheme 33). In this perspective, the progenitors need to meet several demands such as being bench-stable and easily accessible in gram-scale from cheap starting materials, to present synthetic utility as azolium enolate precursors. Chapter 2 will describe the use of α-aroyloxyaldehydes as azolium enolate precursors in formal [4+2] cycloadditions with trichloromethyl ketones. Chapter 3 will describe the development of a novel methodology using carboxylic acid as azolium enolate precursors in intramolecular [4+2] cycloaddition.

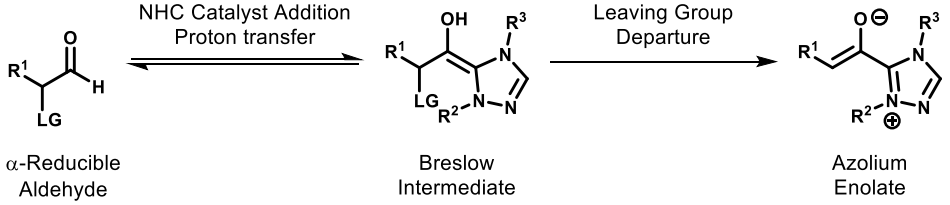


Scheme 33: Alternative azolium enolate precursors generated in combination with precatalyst **30** in [4+2] cycloaddition.

2- α-Aroyloxyaldehydes as Azolium Enolate Precursors in [4+2] Cycloadditions with Trichloromethyl Ketones

2-1 Development of alternative α-reducible aldehyde as azolium enolate precursors in the Smith group

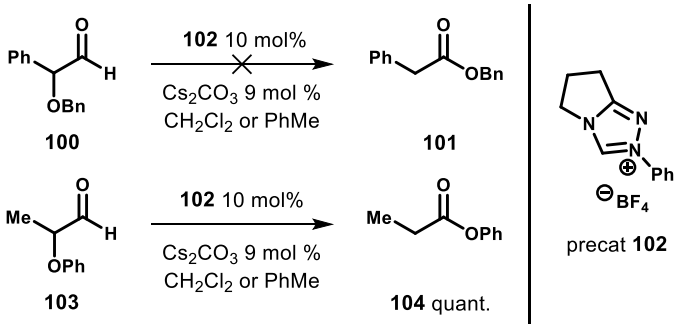
Previous studies in the Smith group in the context of NHC-catalysed redox reactions considered alternative α-functionalised aldehydes as starting materials for acyl azolium and enolate reactions. Two main characteristics were considered: this new class had to be easily accessible and stable, and the α-functional group had to be a good leaving group (Scheme 34).



Scheme 34: Generation of azolium enolate from α-reducible aldehydes.

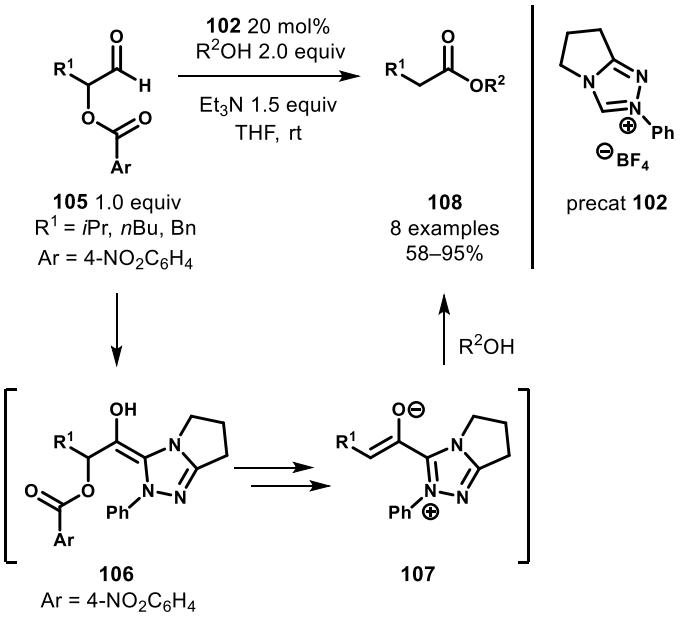
2-1-1 Development of α-reducible α-aroyloxyaldehydes

First, α-oxyaldehydes were examined in the context of redox esterifications.[43] The intramolecular reactions were performed with achiral precatalyst **102** (10 mol%) and a catalytic amount of Cs_2CO_3 (9 mol%) in CH_2Cl_2 or PhMe (Scheme 35). No reaction was observed with α-benzyloxyaldehyde **100** whereas α-phenoxyaldehyde **103** gave the desired ester **104** quantitatively. While this showed proof-of-concept, the absence of a general synthetic pathway giving access to α-substituted α-phenoxyaldehydes rendered these unsuitable alternatives.



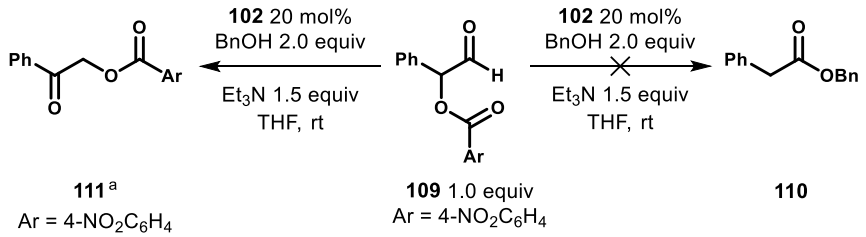
Scheme 35: α-Oxyaldehydes **100** and **103** as alternative α-functionalised aldehydes in NHC-catalysed intramolecular redox esterification.

Subsequently, α-aroyloxyaldehydes were investigated as they contain a carboxyl moiety that can act as a leaving group. Initially, promising results were achieved, and optimisation led to the design of bench stable α-aroyloxyaldehydes **105** containing a 4-nitrobenzoyl substituent (Scheme 36). The intermolecular esterification with **105** occurred through the formation of enaminol **106** followed by azolium enolate **107**, leading to product **108** with good to high yield. The reaction tolerated α-aroyloxyaldehydes presenting linear, β-branched and α-alkyl substituents and a range of alcohols such as benzyl alcohol, methanol, ethanol, allyl alcohol and furfuryl alcohol.



Scheme 36: NHC-catalysed redox oxidation of α-aroyloxyaldehydes **105** containing a 4-nitrobenzoyl group.

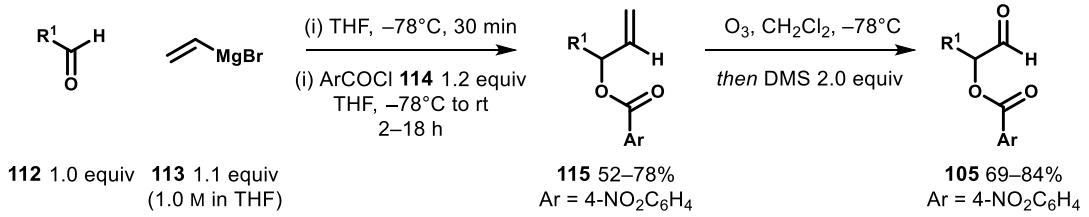
Interestingly, the use of α-aryl α-aroyloxyaldehyde **109** did not lead to the desired ester **110** but to product **111** (Scheme 37). Under the same reaction conditions but in the absence of catalyst **102**, **111** was also obtained and isolated in quantitative yield consistent with this being the result of a base-promoted rearrangement of α-aroyloxyaldehyde **109**. This highlighted the limitation of this type of azolium enolate precursor.



Scheme 37: Limit of the scope for NHC-catalysed intermolecular redox esterification.

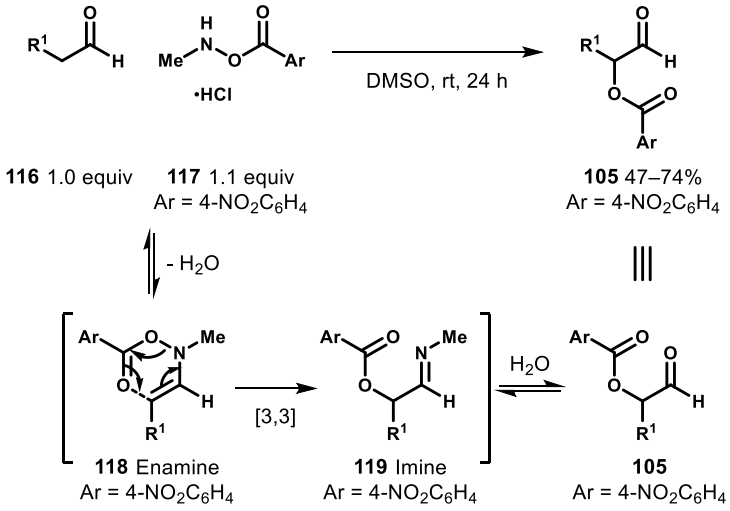
(a) **111** isolated in quantitative yield in the absence of precatalyst **102**.

To be a suitable alternative class of azolium enolate precursors, α-aroyloxyaldehydes **105** need to be easily accessible. First, a range of α-aroyloxyaldehydes **105** were synthesised following a two-step process developed in the Smith group (Scheme 38).[43] A Grignard reaction followed by an *O*-benzylation using 4-nitrobenzoyl chloride **114** led to **115** in moderate to high yield. Ozonolysis gave the desired α-aroyloxyaldehyde **105** in high yield.



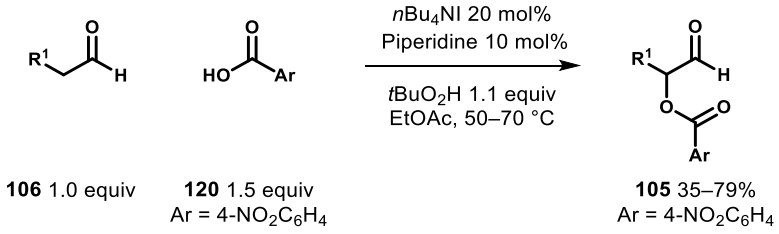
Scheme 38: Two-steps synthesis of α-aroyloxyaldehydes **105** developed Smith *et al*.

A major drawback of this strategy was the ozonolysis step as it demands high dilution of the reaction mixture which is impractical on a large scale. Therefore, two other synthetic pathways were chosen. Using a procedure adapted from Tomkinson *et al.*, α-aroyloxyaldehydes **105** could be obtained in 47–74% yield, through the α-acylation of aldehyde **116** using *N*-methyl-*O*-(4-nitrobenzoyl)hydroxylamine hydrochloride **117** (Scheme 39).[51,52] This one-step reaction is assumed to proceed *via* a [3,3] sigmatropic rearrangement followed by hydrolysis to give the desired product **105**.



Scheme 39: Synthesis of α-aroyloxyaldehyde **105** adapted from Tomkinson *et al.*

A methodology developed by Ishihara *et al.* was then examined and adapted.[53] It successfully gave access in one step and in gram-scale to a variety of α-aroyloxy aldehydes **105** (Scheme 40).[44] The reaction proceeds *via* the direct α-oxylation of the requisite aldehyde **116** with 4-nitrobenzoic acid **120** using tetrabutylammonium iodide (nBu$_4$NI) as a precatalyst, piperidine as a co-catalyst and *tert*-butyl hydroperoxide as the oxidant. Ishihara's group tried to elucidate the mechanism without success.[54] The precise role of piperidine in the reaction is also unknown but was shown to reduce side-reactions.

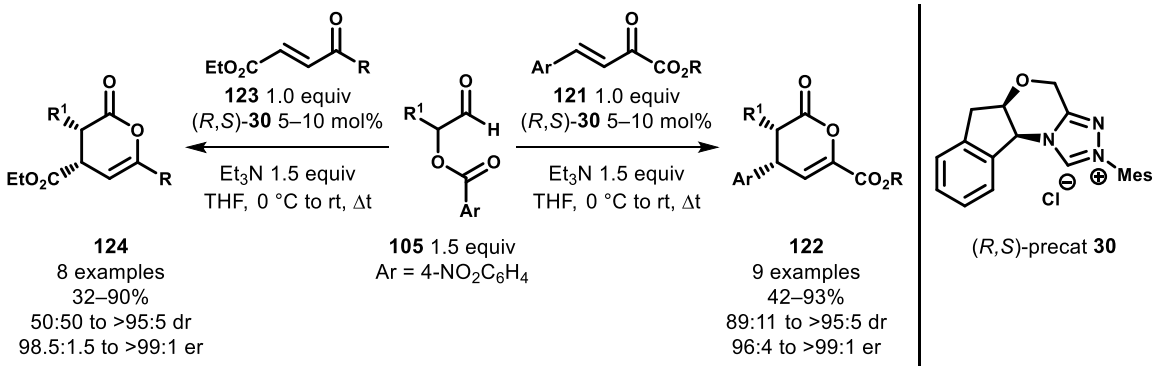


Scheme 40: Synthesis of α-aroyloxyaldehyde **105** adapted from Ishihara *et al.*

To conclude, α-aroyloxyaldehydes **105** contain a good leaving group, namely the 4-nitrobenzoyl substituent, are accessible from cheap and commercially available starting materials, can be synthesised in gram-scale from two different procedures and are bench stable. Consequently, they are a suitable alternative class of α-reducible aldehydes to be used as precursors for azolium enolates.

2-1-2 Use of α-aroyloxyaldehydes as azolium enolate precursors in [4+2] cycloadditions

A range of Michael acceptors has been probed with α-aroyloxyaldehydes as azolium enolate precursors in [4+2] cycloaddition methodologies.[44,45] With β,γ-unsaturated α-ketoesters **121**, *syn*-dihydropyranones **122** were obtained in modest to high yield and high to excellent dr and excellent er (Scheme 41).[45] The desired *syn*-dihydropyranones **124** were obtained with α,β-unsaturated γ-ketoesters **123** as Michael acceptors in moderate to excellent yield, modest to high dr and excellent enantioselectivity.[45]



124
8 examples
32–90%
50:50 to >95:5 dr
98.5:1.5 to >99:1 er

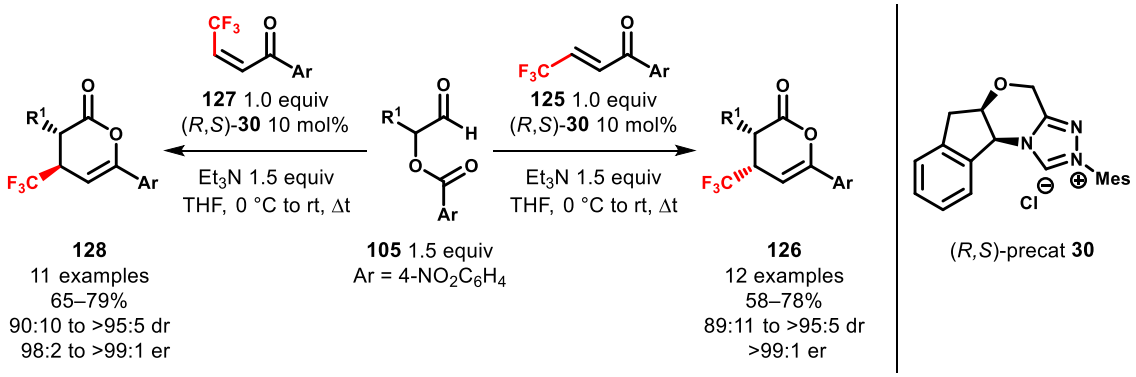
105 1.5 equiv
Ar = 4-$NO_2C_6H_4$

122
9 examples
42–93%
89:11 to >95:5 dr
96:4 to >99:1 er

(*R,S*)-precat **30**

Scheme 41: α-Aroyloxyaldehydes **105** as azolium enolate precursors with β,γ-unsaturated α-ketoesters **121** and α,β-unsaturated γ-ketoesters **124** in NHC-catalysed [4+2] cycloaddition.

The methodology was also applied to trifluoromethyl enones (Scheme 42).[44] These are of particular interest due to the presence of the trifluoromethyl moiety in a range of compounds with a pharmacologic profile.[55] First, the use of (*E*)-β-trifluoromethyl enones **125** led to the formation of the desired *syn*-product **126** in good yield, high dr and excellent er. Changing the Michael acceptor for (*Z*)-β-trifluoromethyl enones **127** gave *anti*-dihydropyranones **128** in good yield, high dr and excellent er. It proved the reaction to be stereospecific with retention of the stereogeometry of the Michael acceptor. In other words, (*E*)-enones **125** gave selectively access to *syn*-product **126** while (*Z*)-enones **127** led selectively to *anti*-**128**.



128
11 examples
65–79%
90:10 to >95:5 dr
98:2 to >99:1 er

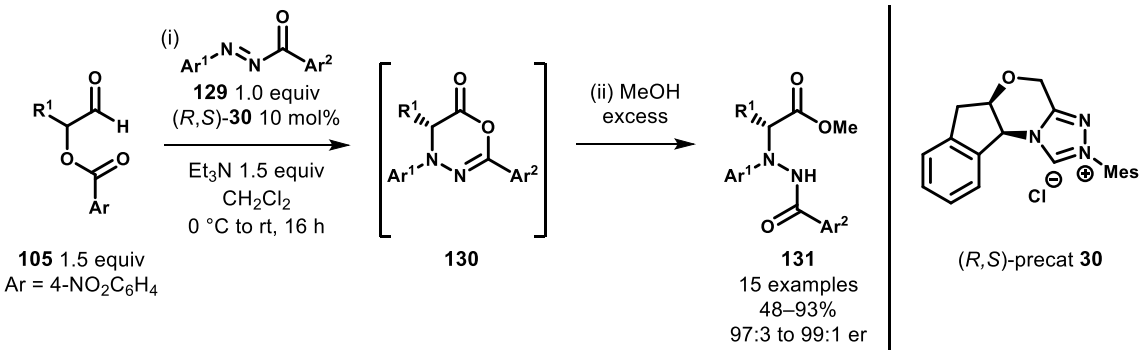
105 1.5 equiv
Ar = 4-$NO_2C_6H_4$

126
12 examples
58–78%
89:11 to >95:5 dr
>99:1 er

(*R,S*)-precat **30**

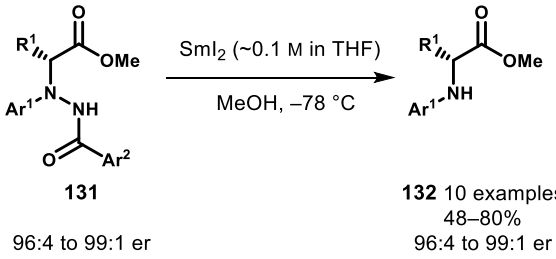
Scheme 42: α-Aroyloxyaldehydes **105** as azolium enolate precursors with (*E*)- and (*Z*)-β-trifluoromethyl enones **125** and **127** in NHC-catalysed [4+2] cycloaddition.

In 2013, another report presented the α-amination of α-aroyloxyaldehydes **105** in a one-pot formal NHC-catalysed [4+2] cycloaddition/ring-opening with *N*-aryl-*N*-aroyldiazenes **129** (Scheme 43).[46] The desired α-hydrazino esters **131** were obtained on moderate to high yield and excellent er.



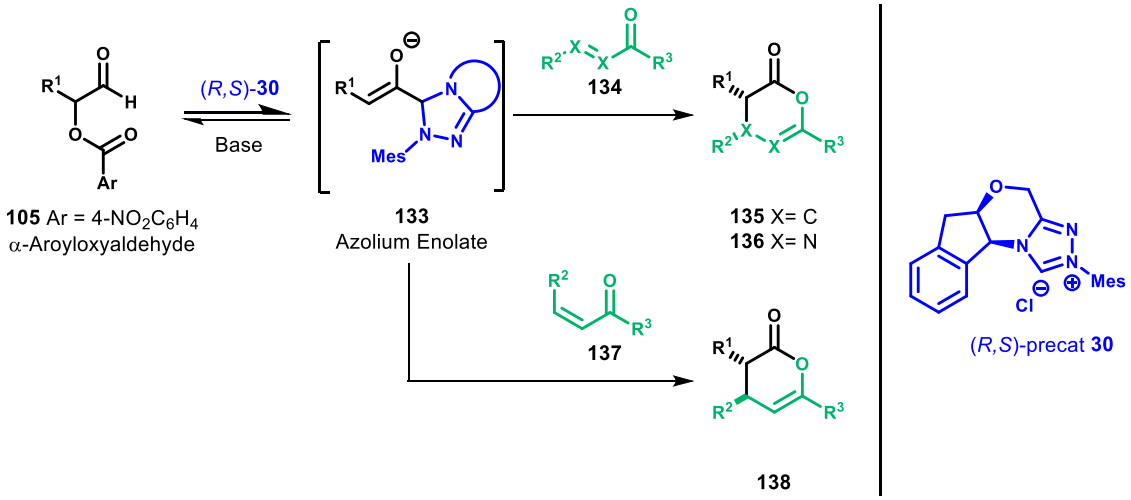
Scheme 43: Aroyloxyaldehydes **105** as azolium enolate precursors with *N*-aryl-*N*-aroyldiazenes **129** in NHC-catalysed [4+2] cycloaddition/ring-opening.

The SmI_2-mediated N–N bond cleavage of α-hydrazino esters **131** proceeded to enantioenriched *N*-aryl amino esters **132** without erosion of er (Scheme 44). These amino esters **132** present a synthetic interest as the α-amino carbonyl moiety is present in amino acids.[46]



Scheme 44: SmI_2-mediated N–N bond cleavage of α-hydrazino esters **131** to enantioenriched *N*-aryl amino ester **132**.

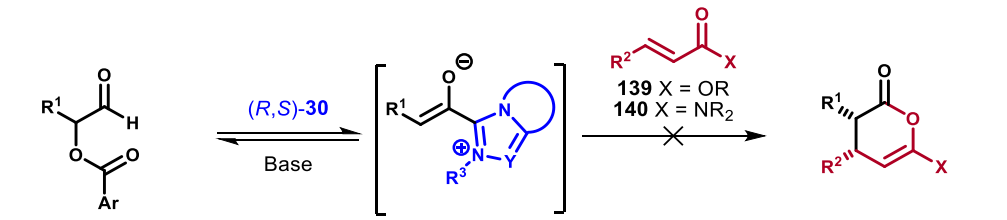
To summarise, α-aroyloxyaldehydes **105** have been investigated as alternative azolium enolate precursors **133** for use in [4+2] cycloaddition reactions with a range of electron deficient Michael acceptors **134**, **136** and **137** (Scheme 45).[43–46]



Scheme 45: α-Aroyloxyaldehydes as azolium enolate precursors in [4+2] cycloadditions.

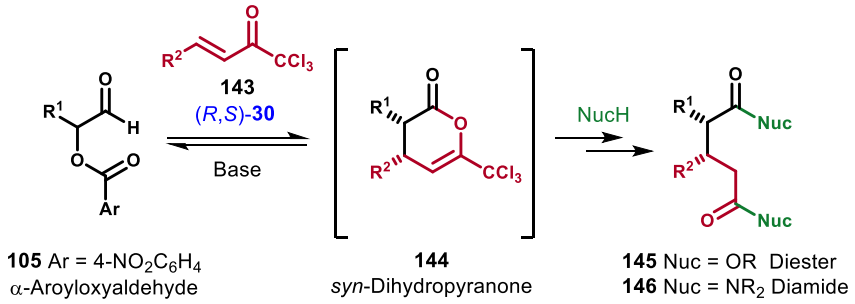
2-2 Aim of the project and postulated mechanism

As described previously, many reports utilise electron deficient enones in [4+2] cycloadditions with azolium enolates while the use of α,β-unsaturated esters **139** and amides **140** has not been explored due to their moderate electrophilicity (Scheme 46).



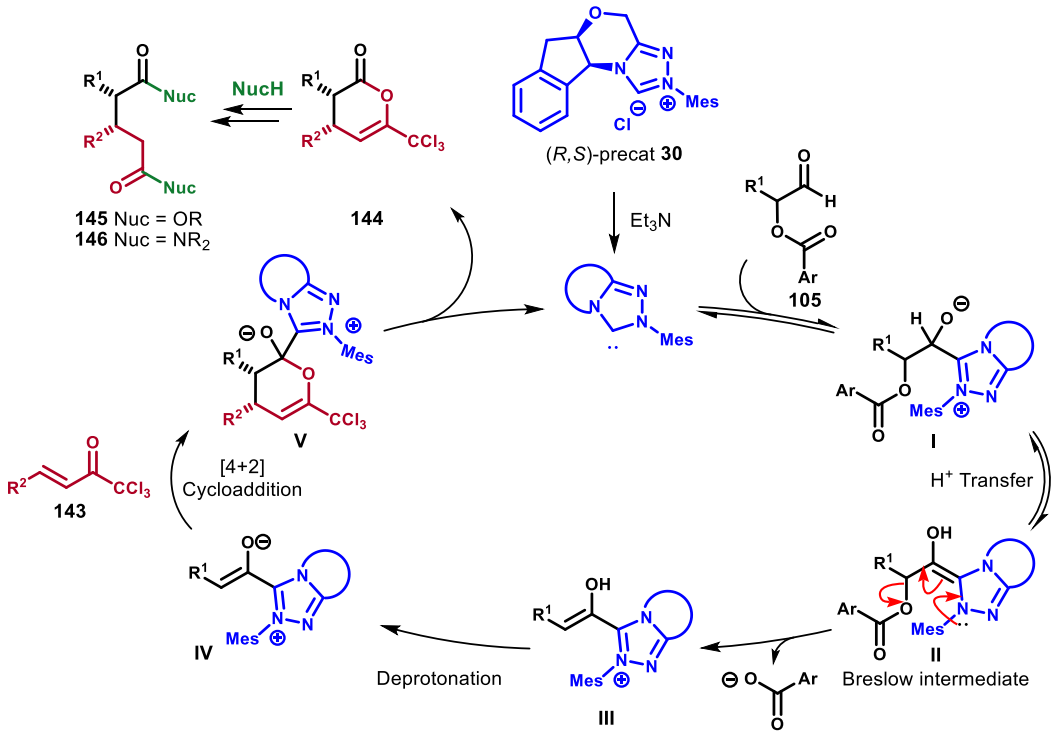
Scheme 46: Lack of reactivity of α,β-unsaturated esters and amides in NHC-catalysed [4+2] cycloaddition with azolium enolates.

Therefore, the development of the first NHC-catalysed methodology employing α,β-unsaturated amide and ester surrogates in [4+2] cycloadditions with azolium enolates was of interest.[56] α,β-Unsaturated trichloromethyl ketones **143** are an interesting class of Michael acceptors where the CCl_3 group is known to be a good leaving group.[57] The first aim of this project was to develop a highly stereodefined synthetic route to *syn*-dihydropyranones **144** from α,β-unsaturated trichloromethyl ketones **143**, using α-aroyloxyaldehydes **105** as azolium enolate precursors (Scheme 47). The second is to investigate the ability of **143** to act as amide and ester surrogates.



Scheme 47: NHC-catalysed [4+2] cycloaddition with α-aroyloxyaldehyde **105** and trichloromethyl ketones **143** as amide and ester surrogates.

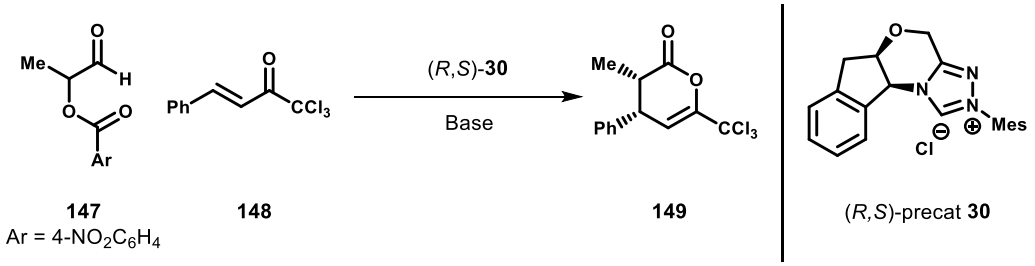
The postulated mechanism is believed to proceed *via* the addition of free triazolium catalyst **30** to α-reducible α-aroyloxyaldehyde **105** to form adduct **I** (Scheme 48). A proton transfer leads to the formation of enaminol **II**, which is known as the Breslow intermediate.[19] Rapid elimination of 4-nitrobenzoate gives **III**, which upon deprotonation forms azolium enolate **IV**. Subsequent [4+2] cycloaddition with trichloromethyl ketone **143** leads to adduct **V**. Following computational works from Bode *et al.* this step is presumably an asynchronous *endo*-hetero-Diels–Alder. [48,49,58] **V** then collapses to release the free NHC catalyst along with the desired dihydropyranones **144**. Based on previous work in the Smith group, the major diastereoisomer was assumed to be *syn*-**144**.[44,45] Finally, ring-opening and subsequent displacement of the CCl_3 group through either aminolysis or alcoholysis by the requisite nucleophile gives highly functionalised diester **145** or diamide **146**.



Scheme 48: Postulated mechanism.

2-3 Reaction optimisation

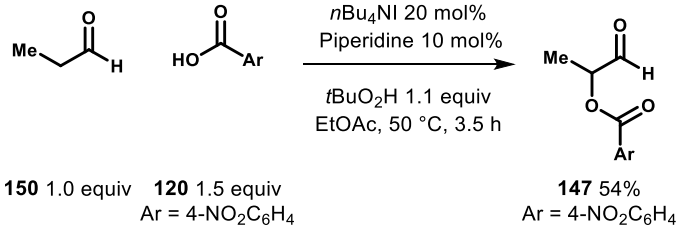
The optimisation focussed on the NHC-catalysed [4+2] cycloaddition step as both the diastereo- and enantiocontrol are set at this stage. For the development of the model system, α-aroyloxyaldehyde **147** and trichloromethyl ketone **148** were selected (Scheme 49).



Scheme 49: Selected α-aroyloxyaldehyde **147** and trichloromethyl ketone **148** for the model system.

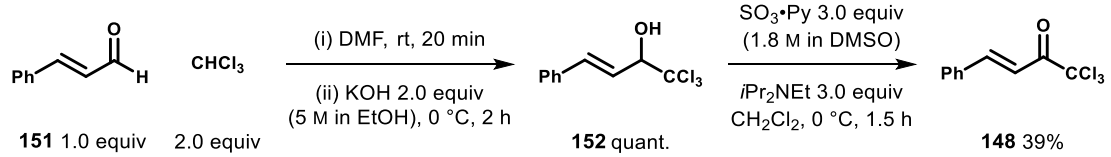
2-3-1 Synthesis of the starting material for the model system

The synthesis of the parent α-aroyloxyaldehyde **147** used the one-step process adapted from the Ishihara group (Scheme 50).[53] The desired α-aroyloxyaldehyde **147** was obtained in moderate 54% yield due to a moderate stability on silica, but was successfully isolated on a multi-gram scale.



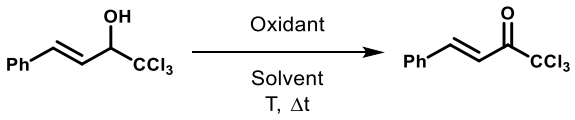
Scheme 50: Synthesis of α-aroyloxyaldehyde **147**.

Following previous work in the Smith group, parent trichloromethyl ketone ((*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one) **148** was synthesised from *trans*-cinnamaldehyde **151** in two steps (Scheme 51). Trichloromethylation as described by Zheng *et al*. led to trichloromethyl alcohol **152** in quantitative yield that was used without further purification.[59] Parikh-Doering oxidation, gave access to the desired trichloromethyl ketone **148** in 39% yield.[60]



Scheme 51: First synthesis of trichloromethyl ketone **148**.

Although trichloromethyl ketone **148** could be generated on gram-scale, the yield of the Parikh-Doering oxidation was disappointingly low, possibly to be due to decomposition of trichloromethyl alcohol **152** *in situ*. Therefore, several alternative oxidation processes were examined in an attempt to improve the yield of the reaction (Table 2). Initially, a different version of the Parikh-Doering oxidation was tested (Table 2, Entry 2). The base was changed for Et_3N and introduced in higher quantity (7.0 equiv) but **148** was obtained in a lower 18% yield after a longer reaction time due to greater degradation.[60,61] Jones' oxidation was investigated next (Table 2, Entry 3).[62] Both addition of trichloromethyl alcohol **152** to the oxidant and portionwise addition of the oxidant to **152** led to its rapid degradation according to ^1H NMR analysis of the reaction mixtures. Swern oxidation gave **148** in 41% yield (Table 2, Entry 4).[63,64] The use of MnO_2 as an oxidant was then investigated (Table 2, Entry 6 and 7).[65] First, MnO_2 (10 equiv) was used without any pre-treatment giving **148** in an encouraging 39% yield (Table 2, Entry 6). A 48% yield was obtained by using reactivated MnO_2 as oxidant with a 72 h reaction time at rt. Reactivation was achieved by washing MnO_2 with distilled water and drying the filter cake in an oven at 130 °C for 3 h (Table 2, Entry 7). Whilst it required extended reaction time, no distilled or anhydrous reagents or solvent were required. **148** could be isolated in gram-scale by simple filtration of the oxidant and concentration under reduced pressure without any further purification. For these reasons, this oxidation was chosen as optimal.



152 148

	Oxidation Conditions					Results
Entry	**Oxidant**		**Solvent**	**T**	**Δt**	**Isolated Yield**
1[a]	SO_3·Py DMSO *i*Pr_2NEt	3.0 equiv 2.4 equiv 3.0 equiv	CH_2Cl_2	0 °C	1.5 h	39%
2[b]	SO_3·Py DMSO Et_3N	3.0 equiv 9.6 equiv 7.0 equiv	CH_2Cl_2	0 °C to rt	16 h	18%
3[c]	CrO_3 H_2SO_4 H_2O	1.5 equiv	Acetone	0 °C	1 h	–
4[d]	$(COCl)_2$ DMSO Et_3N	1.5 equiv 2.0 equiv 5.0 equiv	CH_2Cl_2	–78 °C to rt	15 min	41%
6	MnO_2	10 equiv	CH_2Cl_2	rt	72 h	39%
7[e]	MnO_2	10 equiv	CH_2Cl_2	rt	72 h	48%

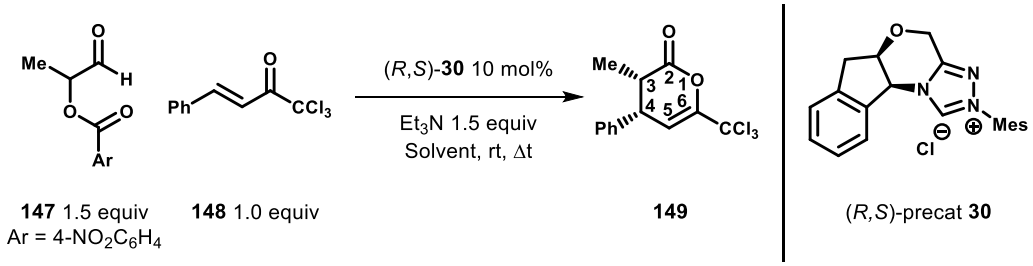
Table 2: Oxidation screening.

(a) SO_3·Py 1.8 M in DMSO; (b) SO_3·Py 4.4 M in DMSO; (c) Reaction stirred at 0 °C for 6 h then warmed up to rt overnight; Bench grade acetone; (d) DMSO and Et_3N distilled prior to use; (e) Reactivated MnO_2: wash with distilled H_2O and dried in the oven at 130 °C for 3 h. Coupling constant $^3J_{HH}$=15.6 confirms **148** to be the (*E*)-isomer.

2-3-2 Catalysis and optimisation

The reactions were performed on a 0.20 mmol scale, followed by TLC analysis and stopped after full consumption of trichloromethyl ketone **148**. The enantioselectivity of the process was evaluated by chiral HPLC analysis. The traces were compared with an authentic racemic one prepared using (±)-**30**. The assignment of diastereoisomers was based upon previous work in the Smith group (Section 2-1-2) [44,45]. The relative and absolute configurations were secured by X-ray crystallography on derived product **202** (Section 2-6-2, Figure 9).

The influence of the solvent was investigated first (Table 3). Four anhydrous solvents were tested: THF, Et_2O, PhMe and CH_2Cl_2 leading to the desired *syn*-dihydropyranone **149** in similar and excellent dr and er. In THF, **149** was obtained in 57% yield after 5 h (Table 3, Entry 1). The use of either Et_2O or PhMe led to **149** in 55% yield after 1.5 h (Table 3, Entries 2 and 3). Finally, in CH_2Cl_2 **149** was obtained after only 1 h in a higher 67% yield (Table 3, Entry 4). Consequently, CH_2Cl_2 was selected as the solvent for this reaction.

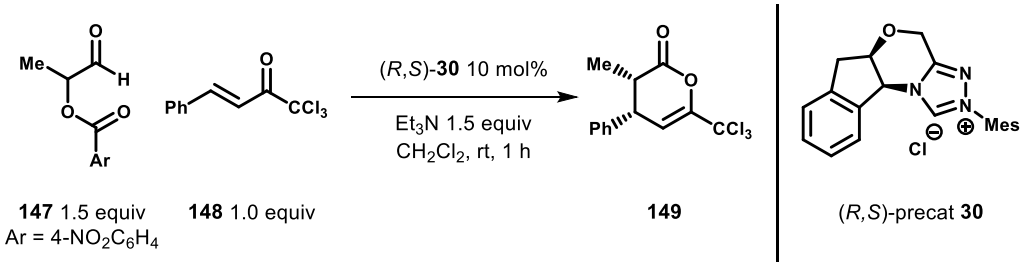


	Reaction Condition		Results		
Entry	**Solvent**	**Δt**	**dr**	**Isolated Yield**	**er**
1	THF	5 h	>95:5	57%	>99:1
2	Et_2O	1.5 h	>95:5	55%	>99:1
3	PhMe	1.5 h	>95:5	55%	>99:1
4	CH_2Cl_2	1 h	>95:5	67%	>99:1

Table 3: Solvent screening

The dr was determined by ^1H NMR spectroscopic analysis of the crude reactions by comparison of the integration for C(5)*H* between the major product (*syn*-**149**) and the minor one (*anti*-**149**). The er was obtained by chiral HPLC analysis. The relative and absolute configuration of the products was later confirmed by X-ray crystallographic analysis of diamide **202**, with all other products assigned by analogy (Section 2-6-2, Figure 9).

Next, the concentration of the α-aroyloxyaldehyde **147** was studied (Table 4). This factor did not influence the diastereo- or the enantioselectivity since 95:5 dr and >99:1 er were obtained in all cases. As stated previously, **149** was obtained in 67% yield at 0.01 M (Table 4, Entry 1) and 66% yield at 0.02 M (Table 4, Entry 2), whereas it dramatically decreased to 44% at 0.04 M (Table 4, Entry 3) and 39% at 0.09 M (Table 4, Entry 4). Since full consumption of trichloromethyl ketone **148** was observed in each case, the drop in the yield observed at 0.04 and 0.09 M could be due to a decomposition of either trichloromethyl ketone **148** or product **149**. For practicality the initial concentration of 0.01 M for **147** was utilised.



147 1.5 equiv
Ar = 4-$NO_2C_6H_4$

148 1.0 equiv

149

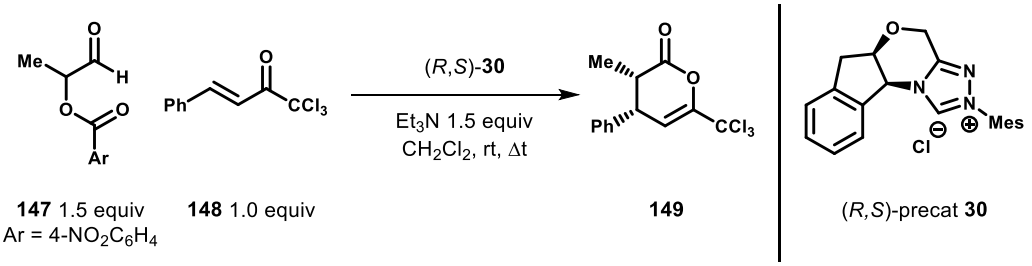
(*R*,*S*)-precat **30**

	Reaction Concentration	**Results**		
Entry	**[147]**	**dr**	**Isolated Yield**	**er**
1	0.01 M	>95:5	67%	>99:1
2	0.02 M	>95:5	66%	>99:1
3	0.04 M	>95:5	44%	>99:1
4	0.09 M	>95:5	39%	>99:1

Table 4: Concentration screening.

The dr were determined by ^{1}H NMR spectroscopic analysis of the crude reactions.

Finally, the amount of precatalyst **30** used in this process was varied (Table 5). When the catalyst loading was decreased to 5 mol%, the reaction required only 3.5 h to pleasingly give similar results (Table 5, Entry 2). Indeed, **149** presented >95:5 dr and >99:1 er and was isolated in 66% yield. Further decreasing to 2 and 1 mol% led to complex mixtures according to ^{1}H NMR spectroscopic analysis of the crude reaction mixtures (Table 5, Entry 3 and 4). Finally, the reaction was scaled up from 0.20 mmol to 1.20 mmol. Pleasingly, **149** was obtained without compromising the stereocontrol of the process in >95:5 dr, >99:1 er and in an increased 84% yield as a larger scale facilitated isolation (Table 5, Entry 5).



147 1.5 equiv
Ar = 4-$NO_2C_6H_4$

148 1.0 equiv

149

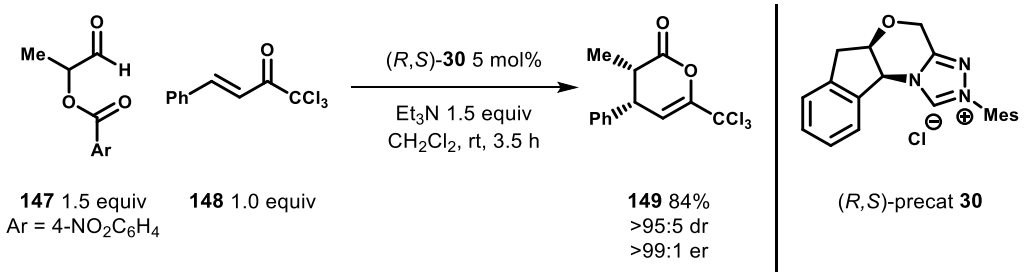
(*R,S*)-precat **30**

	Reaction Condition		Results		
Entry	**(*R,S*)-30**	**Δt**	**dr**	**Isolated Yield**	**er**
1	10 mol%	1 h	>95:5	67%	>99:1
2	5 mol%	3.5 h	>95:5	66%	>99:1
3	2 mol%	24 h	–	–	–
4	1 mol%	24 h	–	–	–
5[a]	5 mol%	3.5 h	>95:5	84%	>99:1

Table 5: (*R,S*)-precatalyst **30** loading.

The dr were determined by ^{1}H NMR spectroscopic analysis of the crude reactions. (a) Reaction on a 1.20 mmol scale.

The optimised reaction conditions required the use of 1.5 equivalents of α-aroyloxyaldehyde **147**, 1.0 equivalent of trichloromethyl ketone **148** and 1.5 equivalents Et_3N in presence of 5 mol% of precatalyst **30** (Scheme 52).



147 1.5 equiv
Ar = 4-$NO_2C_6H_4$

148 1.0 equiv

149 84%
>95:5 dr
>99:1 er

(*R,S*)-precat **30**

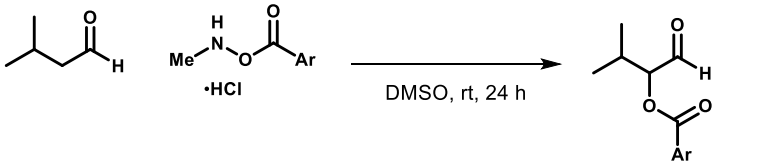
Scheme 52: Optimised reaction conditions.

Although the isolation of the desired *syn*-dihydropyranone **149** was increased on a 1.20 mmol scale, the generality of this process and the limit of the scope was established on a standard 0.20 mmol scale for economic reasons.

2-4 Synthesis of starting materials

2-4-1 Synthesis of α-aroyloxyaldehydes

A range of α-aroyloxyaldehydes were synthesised within the group using two different methods, in both cases starting from their corresponding aldehydes (Section 2-1-1).[51,53] The synthesis of α-aroyloxyaldehyde **154** was done in-house following an adapted procedure from Tomkinson *et al.* (Scheme 53).[51]



Scheme 53: Synthesis of α-aroyloxyaldehyde **154** using an adapted procedure from Tomkinson *et al*.

N-Methyl-*O*-(4-nitrobenzoyl)hydroxylamine hydrochloride **117** and α-aroyloxyaldehyde **154** were synthesised in-house by Dr J. J. Douglas.

Using the already described procedure adapted from Ishihara *et al*., α-aroyloxyaldehydes **155**–**159** were obtained in moderate yield due to their instability on silica but in gram-scale (Table 6).[53]

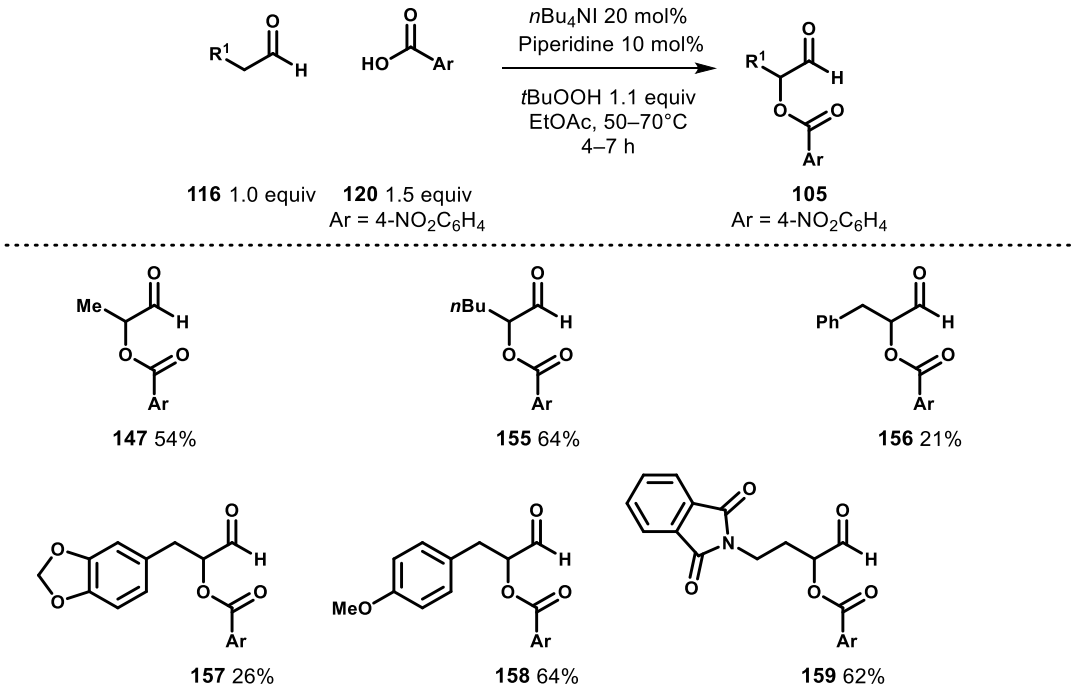
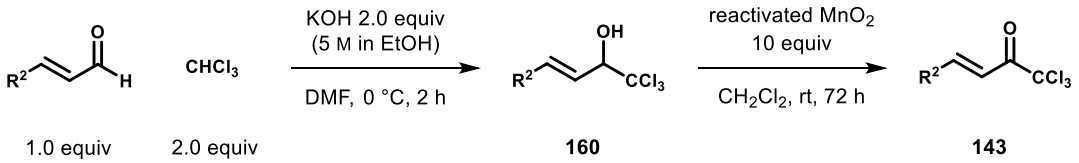


Table 6: Synthesis of a range α-aroyloxyaldehydes using and adapted procedure from Ishihara *et al.*

α-Aroyloxyaldehydes **157–159** were synthesised in-house by Dr J. E. Taylor and Dr D. S. D. Daniels.[46]

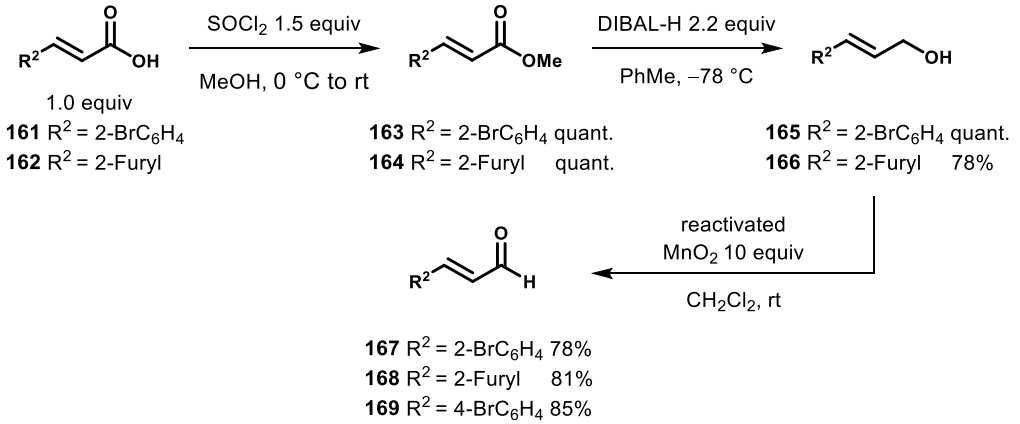
2-4-2 Synthesis of trichloromethyl ketones

Following the methodology developed for the synthesis of parent trichloromethyl ketone **148**, the synthesis of a range of trichloromethyl ketones was examined (Scheme 54).



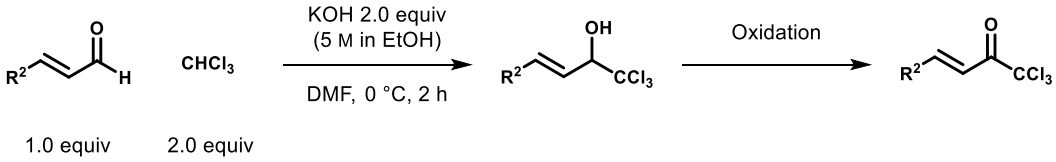
Scheme 54: Planned synthesis of a range of trichloromethyl ketones.

Where the required aldehydes were not commercially available, they were synthesised through a step-wise procedure starting from their corresponding carboxylic acid or allylic alcohol (Scheme 55). Esterification of carboxylic acid **161** and **162** led to methyl ester **163** and **164** in quantitative yield.[66] Reduction using DIBAL-H (2.2 equiv) gave allylic alcohol **165** in quantitative yield and **166** in 78% yield.[66] Finally, MnO_2 mediated oxidation led to the desired aldehydes **167**–**169** in high yield.[65]



Scheme 55: Synthesis of aldehydes **167–169**.

The synthesis of a range of trichloromethyl ketones was attempted (Table 7). The trichloromethylation step led to the desired trichloromethyl alcohols **170–174** in high yield (up to 95%). While products **148** and **171** obtained in 48% and 68% respectively *via* MnO_2 oxidation (Table 7, Entries 1 and 2), the final MnO_2 mediated oxidation on crude trichloromethyl alcohols **172** and **173** was found out to be unsuccessful. Trichloromethyl ketone **177** was obtained in quantitative yield by switching the final step back to a Parikh-Doering oxidation (Table 7, Entry 6).

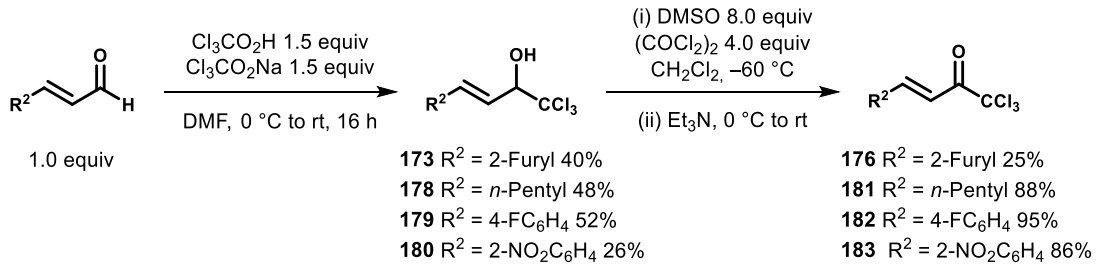


		Trichloromethylation		Oxidation		
Entry	**R^2**	**Product**	**Yield**	**Oxidant**	**Product**	**Yield**
1	Ph	**152**	quant.	MnO_2	**148**	48%
2	4-$MeOC_6H_4$	**170**	71%	MnO_2	**171**	68%
3	2-BrC_6H_4	**172**	95%	MnO_2	**175**	–
4	2-Furyl	**173**	87%	MnO_2	**176**	–
5[a]	4-BrC_6H_4	**174**	93%	SO_3·Py Et_3N	**177**	quant.

Table 7: Trichloromethylation and oxidation steps for the synthesis of trichloromethyl ketones.

(a) Parikh-Doering oxidation: SO_3·Py (3.0 equiv) 1.8 M in dist. DMSO, dist. Et_3N (3.0 equiv), CH_2Cl_2, 0 °C, 16 h *then* SO_3·Py (3.0 equiv), 0 °C to rt, 48 h.

These results were first thought to be due to the final oxidation being substrate dependant. Parallel work with trichloromethyl ketones in the Smith group faced the same problems. It was found to be caused by polymerisation during the trichloromethylation step leading to poor yield of trichloromethyl alcohols. This issue was solved by changing the synthesis of the trichloromethylation step to a procedure established by Corey *et al*. followed by Swern oxidation.[63,67] A range of trichloromethyl ketones was synthesised in our group by trichloromethylation of the corresponding aldehydes (Scheme 56).[68] The *in situ* generation of CCl_3 anion from trichloroacetic acid and sodium trichloroacetate led to trichloromethyl alcohols **173** and **178–180** in 26–52% yield after purification by column chromatography. Swern oxidation gave the desired trichloromethyl ketones **176** and **181–183** in low to moderate overall yield but in gram-scale.



Scheme 56: Successful synthesis of trichloromethyl ketones.[a]

(a) Trichloromethyl alcohols and ketones synthesised by Dr L. C. M. Morrill and D. G. Stark.[68]

2-5 α-Aroyloxyaldehydes as azolium enolate precursors in NHC-catalysed [4+2] cycloaddition with trichloromethyl ketones

With a range of both α-aroyloxyaldehydes and trichloromethyl ketones in hand, the scope of this NHC-catalysed [4+2] cycloaddition methodology was examined (Table 8). The reaction using *n*-pentyl substituted trichloromethyl ketone **181** required a higher 10 mol% precatalyst **30** loading to give **184** in excellent >95:5 dr and >99:1 er. However, it was necessary to stop the reaction after 26 h and before full conversion to reduce the formation of unknown side-products from decomposition of trichloromethyl ketone **181**. Although ^{1}H NMR spectroscopic analysis of the crude product presented a 67% yield (using 1,3,5-trichlorobenzene as an internal standard in CD_2Cl_2), product **184** was isolated in a disappointingly low 26% yield due to product decomposition on silica. When the sterically hindered isopropyl-substituted α-aroyloxy aldehyde **154** was used as an azolium enolate precursor it was completely unreactive. When **154** was used in combination with *N*-aryl-*N*-aroyldiazene **129** as Michael acceptor it successfully led to the desired α-hydrazino ester **131** in 61% yield and 99:1 er (Section 2-1-2,Scheme 43).[45] This lack of reactivity was postulated not only to be due to the formation of a sterically hindered and therefore less reactive azolium enolate but also a generally lower reactivity of trichloromethyl ketones **143** compared with *N*-aryl-*N*-aroyldiazenes **129**. Using **148** (R^2 = Ph) and **156** (R^1 = $PhCH_2$), **186** was formed in high 81% yield, >95:5 dr and >99:1 er. 4-Substituted aryl groups containing electron-donating and electron-withdrawing groups were also successfully included on C(4) giving **187** and **188** respectively, both in high yields and excellent stereoselectivities (>95:5 dr and >99:1 er). With benzo[*d*]dioxol, 4-methoxybenzyl substituted and phthalamide protected α-aroyloxyaldehydes, **189**, **190** and **191** were obtained with moderate yields, and lower dr compared with most of the examples. Product **189** was obtained as a 85:15 mixture of *syn*:*anti* diastereoisomers and isolated as single diastereoisomer. Disappointingly, the er could not be determined either with chiral HPLC or GC analysis. Dihydropyranone **190**

(R^2 = 4-$MeOC_6H_4$) was formed in 90:10 dr and >99:1 er. Phthalamide protected product **191** (R^2 = $PhthN(CH_2)_2$) was obtained as a 65:35 mixture of diastereoisomers, and isolated in an inseparable 90:10 mixture of diastereoisomers, both presenting excellent >99:1 er.

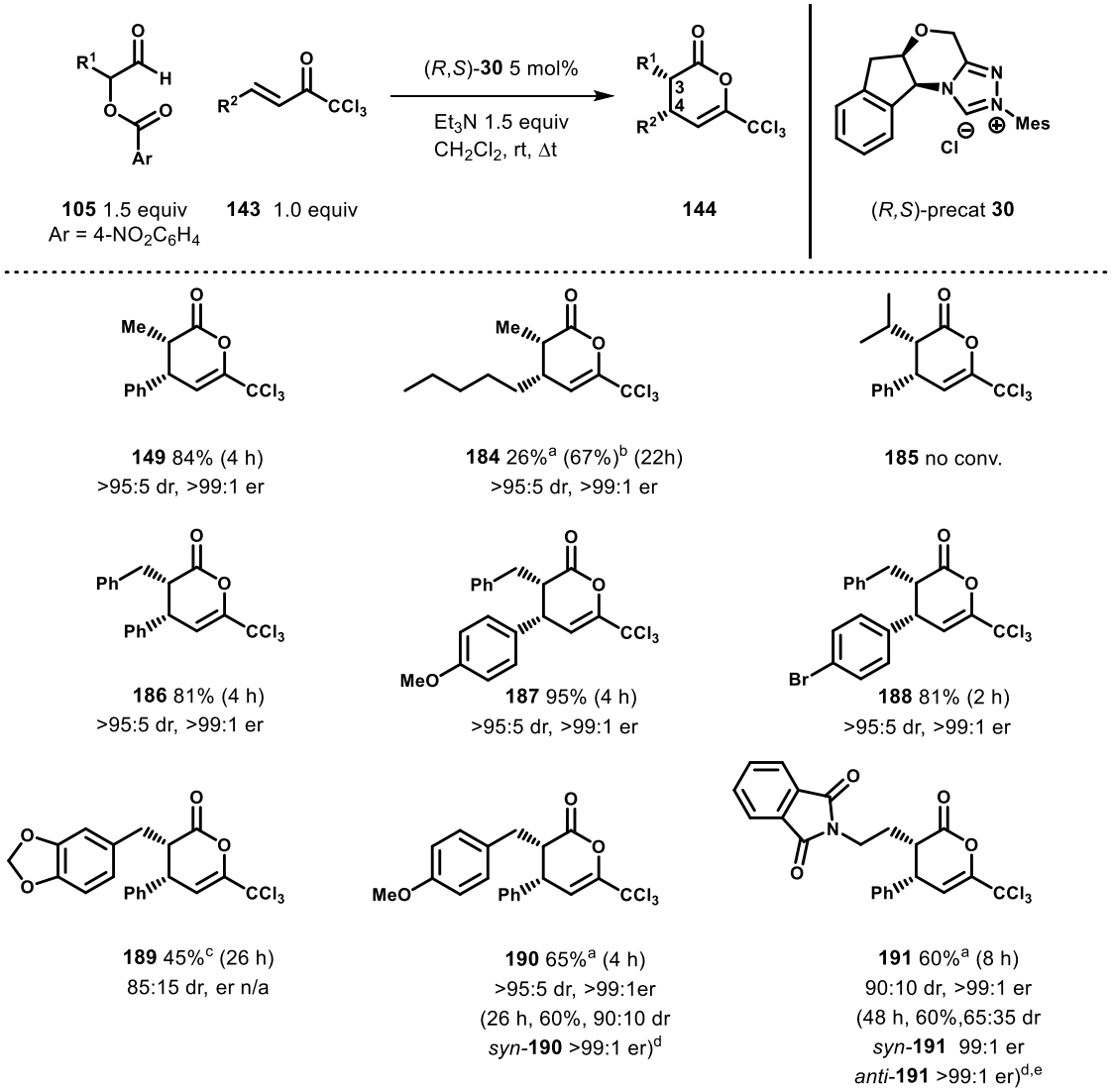
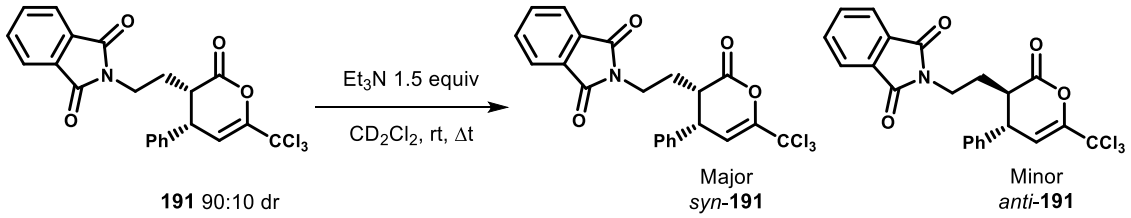


Table 8: [4+2] Cycloaddition: scope of substrates.

The dr was determined by ^{1}H NMR spectroscopic analysis of the crude reaction. Isolated yield following column chromatography. (a) Use of 10 mol% precatalyst **30**; (b) Yield determined by ^{1}H NMR spectroscopic analysis of the crude reaction in the presence of 1,3,5-trichlorobenzene in $CDCl_2$ as internal standard; (c) The er could not be determined with either HPLC or GC analysis; (d) Use of 5 mol% precatalyst **30** loading; (e) **191** isolated as an inseparable 90:10 mixture of diastereoisomers.

The observed reduction in dr could be due to steric factors, with the insertion of sterically demanding groups modifying the geometry of the enolate or due to epimerisation of the *syn*-dihydropyranone on C(3) leading to the formation of the *anti*-products. To test the latter hypothesis, an isolated fraction of **191** (R^2 = $PhthN(CH_2)_2$, 90:10 dr, >99:1 er) was dissolved

in CD_2Cl_2 with Et_3N (1.5 equiv). The dr was monitored by ^1H NMR analysis of the reaction mixture over 72 h by comparison of integration of C(5)*H* for both diastereoisomers (Table 9). The ratio between the major and minor diastereoisomers decreased from 90:10 dr (Table 9, Entry 1) to 78:22 dr after 23 h (Table 9, Entry 4) and 67:33 dr after 72 h (Table 9, Entry 5), showing that base-promoted epimerisation occurs over time. The epimerisation seems to be a slow process; therefore, the drop of dr was observed only in reactions that required reaction time longer than 24 h. The enantioselectivity was not compromised as both *syn*-**191** and *anti*-**191** presented >99:1 er at t = 0 and t = 72 h.



	Epimerisation	**dr**	
Entry	**Δt**	***syn*-191**	***anti*-191**
1	0	90	10
2	1 h	85	15
3	5 h	82	18
4	23 h	78	22
5	72 h	67	33

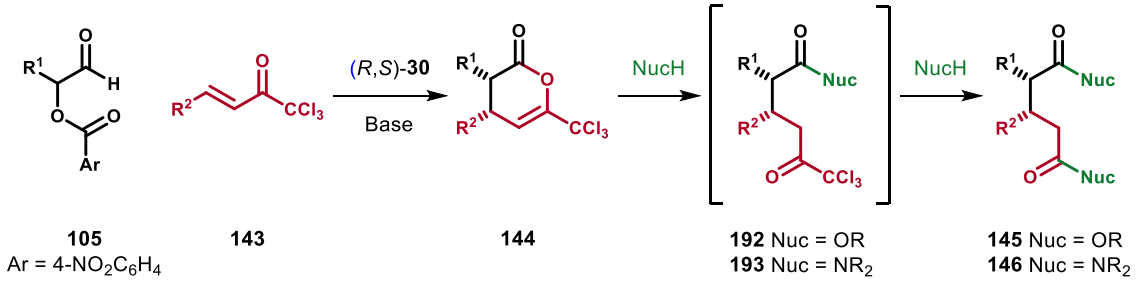
Table 9: Base-promoted epimerisation

The dr was monitored by ^1H NMR spectroscopic analysis over 72 h by comparison of integration of C(5)*H* for both diastereoisomers of **191**.

Products **190** (R^2 = 4-$MeOC_6H_4$) and **191** (R^2 = $PhthN(CH_2)_2$) were synthesised again with an increased 10 mol% loading of precatalyst **30** to reduce the cycloaddition reaction time (Table 8). Although the yield was equivalent, the diastereoselectivity improved significantly. Dihydropyranone **190** was formed in a >95:5 dr and isolated as a single diastereoisomer, while **191** was formed in a 90:10 dr and isolated as a 97:3 mixture of diastereoisomers.

2-6 Sequential [4+2] Cycloaddition/two-step nucleophilic sequence

Having successfully synthesised a variety of *syn*-dihydropyranones, the viability of α,β-unsaturated trichloromethyl ketones **143** as ester and amide surrogates was investigated next with the development of either a one-pot or a sequential [4+2] cycloaddition/ring-opening/alcoholysis or aminolysis process was examined (Scheme 57). After formation of *syn*-dihydropyranone **144**, addition of the requisite nucleophile to the reaction mixture would lead either to ketoester **192** or ketoamide **193** and the following displacement of the CCl_3 moiety by alcoholysis or aminolysis would lead to diester **145** or diamide **146**.

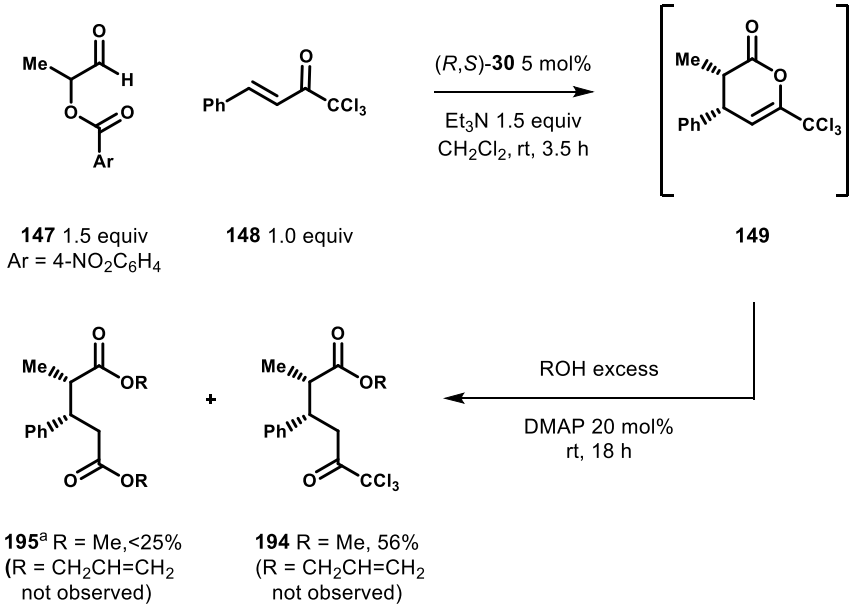


105 Ar = 4-$NO_2C_6H_4$ | **143** | **144** | **192** Nuc = OR, **193** Nuc = NR_2 | **145** Nuc = OR, **146** Nuc = NR_2

Scheme 57: Trichloromethyl ketones as ester and amide surrogates.

2-6-1 Two-step nucleophilic reaction with alcohols

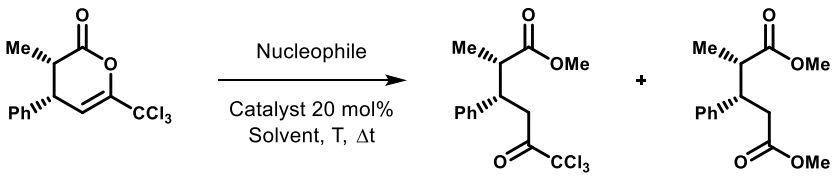
The reaction was initially tested on parent donor **147** (R^1 = Me) and acceptor **148** (R^2 = Ph) with initial [4+2] cycloaddition followed by the addition of methanol in large excess and catalytic DMAP (20 mol%) (Scheme 58). Surprisingly, a mixture of ketoester **194** and diester **195** was formed. Diester **195** was obtained as a minor product and could not be isolated as a pure fraction, whereas ketoester **194** was isolated in 56% yield. However, the relative configuration of diester **195** could be confirmed by comparison with ^{1}H NMR spectroscopic analysis from literature.[69] The reaction was also conducted with allylic alcohol without any success as a mixture of unknown side-products and unreacted dihydropyranone **149** was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.



Scheme 58: One-pot [4+2] cycloaddition/ring-opening/methanolysis.

(a) Could not be cleanly isolated.

To improve these results a range of ring-opening/methanolysis conditions were tried on isolated *syn*-dihydropyranone **149** (Table 10). The results discussed below are based on ^{1}H NMR spectroscopic analysis of the crude reaction mixtures after full consumption of **149**. First, an excess of MeOH in presence of catalytic DMAP (20 mol%) was investigated at rt, 50 °C and 70 °C (Table 10, Entry 1–3). The ratio between ketoester **194** and diester **195** at rt was 63:37 in favour of ketoester **194** (Table 10, Entry 1). At both 50 °C and 70 °C a 75:25 mixture of **194**:**195** was obtained (Table 10, Entry 2 and 3). This slight difference could be due to the observed partial evaporation of methanol overnight at rt, thus concentrating the reaction mixture and slightly favouring conversion of **194** to **195**. Using PPY as a catalyst at rt led to a 71:29 mixture of **194**:**195** (Table 10, Entry 4). Finally, a solution of NaOMe in methanol (0.5 M, 2.5 equiv) was utilised at rt (Table 10, Entry 5). However, the desired diester **195** was observed alongside a range of unknown side-products in the ^{1}H NMR spectroscopic analysis of the crude reaction mixture, showing that NaOMe was too reactive to be a suitable alternative.



149
>95:5 dr, >99:1

194

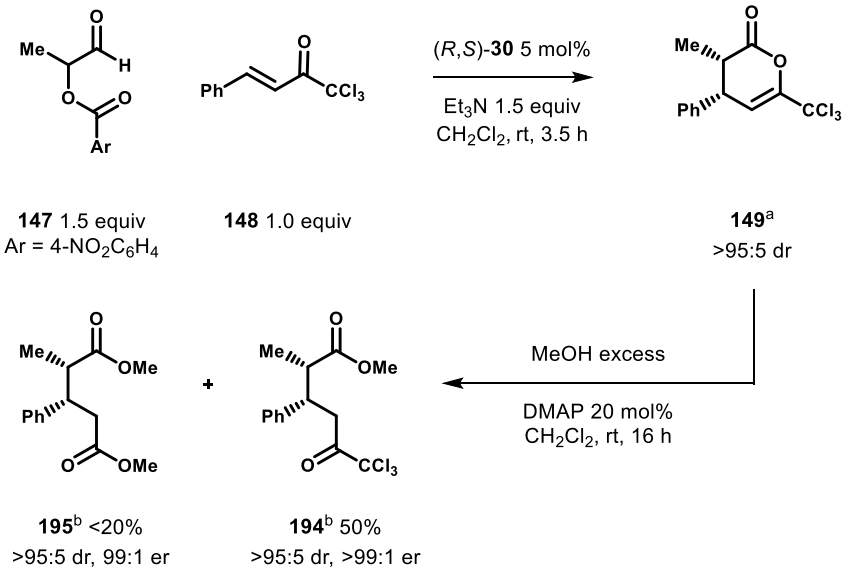
195

	Reaction conditions				Results[a]	
Entry	**Nucleophile**	**Catalyst**	**T**	**Δt**	**194**	**195**
1	MeOH	DMAP	rt	18 h	63	37
2	MeOH	DMAP	50 °C	18 h	75	25
3	MeOH	DMAP	70 °C	18 h	75	25
4	MeOH	PPY	rt	18 h	71	29
5	NaOMe MeOH	–	rt	23 h	–	n/a

Table 10: Conditions screened for the ring-opening of **149**.

Reactions performed on a 0.10 mmol scale. (a) Results based on ^{1}H NMR spectroscopic analysis of crude reaction mixtures. Full consumption of **149** was observed.

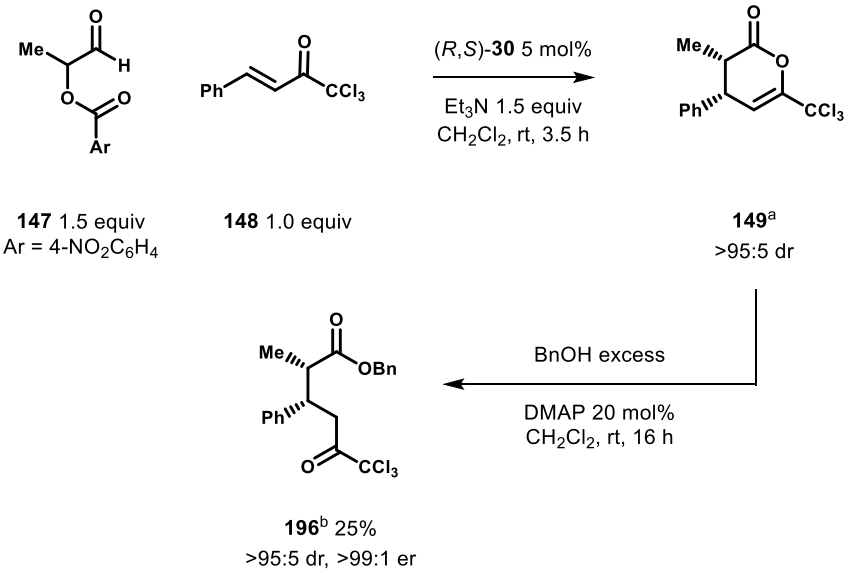
Having ketoester **194** as the major product indicates that displacement of the CCl_3 group is difficult to achieve. Consequently, focus was redirected on the synthesis of ketoester **194**. A sequential approach was chosen with a work-up after the [4+2] cycloaddition step to remove undesired by-products. Ring-opening with methanol catalysed with 20 mol% DMAP at rt enabled the isolation of ketoester **194** in 50% yield with >95:5 dr and >99:1 er (Scheme 59). Diester **195** could be isolated (with minor impurities) with >95:5 dr and 99:1 er.



Scheme 59: Sequential [4+2] cycloaddition/ring-opening/methanolysis.

The dr was determined by ^1H NMR spectroscopic analysis of the crude reactions. (a) Work up: dilution in EtOAc, wash with H_2O, $NaHSO_4$ aq. 40% and brine. No further purification; (b) Isolated yield.

The use of benzyl alcohol as the nucleophile led to the sole formation of the ketoester **196** in 25% yield and excellent >95:5 dr and >99:1 er (Scheme 60). The purification of ketoester **196** required removal of excess BnOH by Kugelrohr distillation of the crude reaction mixture, possibly leading to product decomposition which could explain the low yield despite full conversion of *syn*-dihydropyranone **149**.



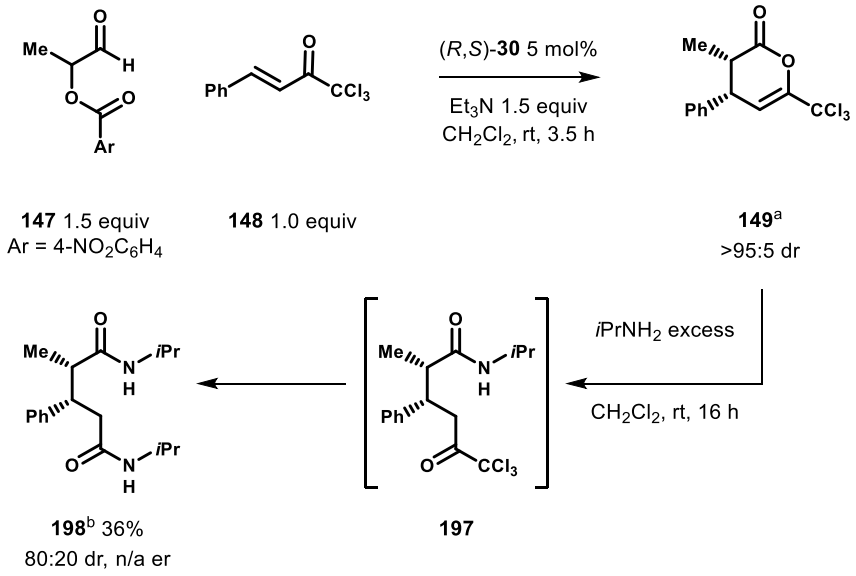
Scheme 60: Sequential [4+2] cycloaddition/ring-opening/alcoholysis with benzylic alcohol.

The dr was determined by ^{1}H NMR spectroscopic analysis of the crude reactions. (a) Crude **149** obtained after work up. No further purification; (b) Isolated yield after Kugelrohr distillation and column chromatography.

Next the project focussed on the development of a sequential [4+2] cycloaddition/ring-opening/aminolysis process to assess the synthetic utility of trichloromethyl ketones as amide surrogates.

2-6-2 Two-step nucleophilic reaction with amines

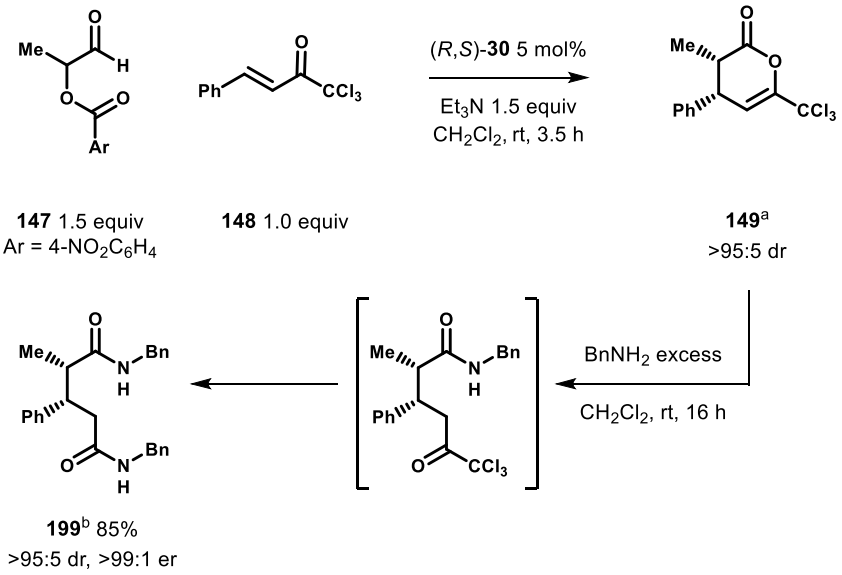
Amines present increased nucleophilicity compared to alcohols. This should favour their double additions onto the dihydropyranones. Sequential [4+2] cycloaddition and ring-opening with isopropyl amine was investigated first (Scheme 61). Diamide **198** was isolated in 36% without the need of any additional catalyst, such as DMAP. Intermediate ketoamide **197** was not observed in the ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Pleasingly, purification did not require column chromatography as a simple trituration with Et_2O was successful after work up. However, it was not possible to determine the enantioselectivity by chiral HPLC or GC analyses. The ^{1}H NMR spectroscopic analysis of the crude reaction showed a lower than expected 80:20 dr which could be due to epimerisation promoted by the nucleophile.



Scheme 61: Sequential [4+2] cycloaddition/ring-opening/aminolysis with isopropylamine.

The dr was determined by ^{1}H NMR spectroscopic analysis of the crude reactions. (a) Crude **149** obtained after work up. No further purification; (b) Isolated yield after trituration in Et_2O. The er could not be determined.

Nevertheless, these initial results were encouraging. The sequential approach was next conducted using benzylamine as the nucleophile (Scheme 62). After the [4+2] cycloaddition and a simple work up, **149** was ring-opened and the CCl_3 group was successfully displaced using an excess of $BnNH_2$ in CH_2Cl_2 for 16 h at rt. Once again, no trace of ketoamide was observed in the ^1H NMR spectroscopic analysis of the crude reaction mixture. The desired diamide **199** was formed in >95:5 dr and isolated after a simple trituration in Et_2O in high 85% yield and excellent >99:1 er. Enantiocontrol was assessed before and after trituration in Et_2O to ascertain if improvement of stereoselectivity had been achieved and the same >99:1 er was obtained in both cases.



Scheme 62: Sequential [4+2] cycloaddition/ring-opening/aminolysis with benzylamine.

The dr was determined by ^1H NMR spectroscopic analysis of the crude reactions. (a) Crude **149** obtained after work up. No further purification; (b) Isolated yield after trituration in Et_2O; >99:1 er obtained before and after trituration in Et_2O.

Building upon this result, the scope of the reaction was investigated using benzylamine as a nucleophile in a chromatography-free sequential procedure. The scope of the acceptors was examined first (Table 11). Electron withdrawing and electron donating aryl groups were well tolerated. Indeed, **201** (R^2 = 4-FC_6H_4) was formed in 95:5 dr, and isolated in high 90% yield and >99:1 er. Diamide **202** (R^2 = 4-$MeOC_6H_4$) presented excellent diastereo- and enantiocontrol and was obtained in a lower but still high 75% yield. Pleasingly, 2-substituted nitrophenyl acceptor **183** gave **203** in 68% yield, 90:10 dr and >99:1 er. 2-Furyl incorporation was also successful leading to **204** in 75% yield with excellent diastereo- and enantioselectivity. The use of *n*-pentyl substituted acceptor **181** in the sequential process required 10 mol% of precatalyst **30** and gave **205** with > 95:5 dr, >99:1 er but did not show any improvement in yield compared with the isolated and unstable *syn*-dihydropyranone **184** (Section 2-5, Table 8, 26% yield). Pleasingly, this two-step nucleophilic process did not show any erosion in diastereo- and enantiocontrol with the *syn*-dihydropyranones **149** and **184** and their corresponding diamides **199** and **205** exhibiting the same dr and er.

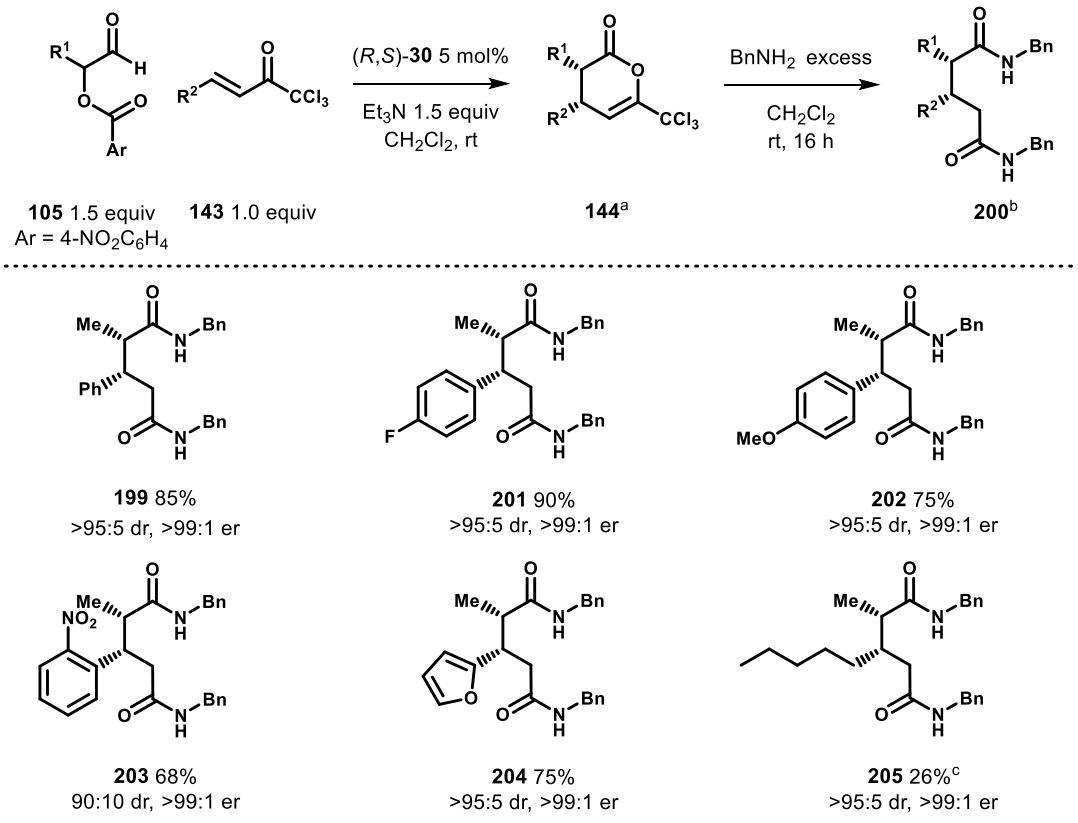


Table 11: Sequential [4+2] cycloaddition/ring-opening/aminolysis with benzylamine: scope of acceptors.

The dr was determined by crude ^{1}H NMR spectroscopic analysis of the crude reactions. (a) Crude obtained after work up. No further purification; (b) Isolated yield after trituration in Et_2O; (c) Use of 10 mol% precatalyst **30** loading.

Variation of the substituents on the α-aroyloxy aldehyde donor was examined next (Table 12). Whereas the corresponding *syn*-dihydropyranone could not be isolated, butyl substituted diamide **206** was pleasingly formed in 89% yield with excellent dr and er using 10 mol% precatalyst **30** loading in THF. Similar 48% yield and 80:20 dr were obtained for **207** (benzo[*d*]dioxol) compared with the corresponding *syn*-dihydropyranone **186**, but disappointingly the er could not be determined. Variation of both donor and acceptor was investigated next. Diamide **208** containing both an electron donating group (R^1 = 4-$MeOC_6H_4CH_2$ on C(2)) and electron withdrawing group (R^2 = 4-FC_6H_4 on C(3)) was obtained in 60% yield with excellent diastereo- and enantiocontrol. The incorporation of a 2-furyl substituent on C(3) in the presence of an extended alkyl chain on C(2) led to **209** in >95:5 dr, >99:1 er and a lower 39% yield.

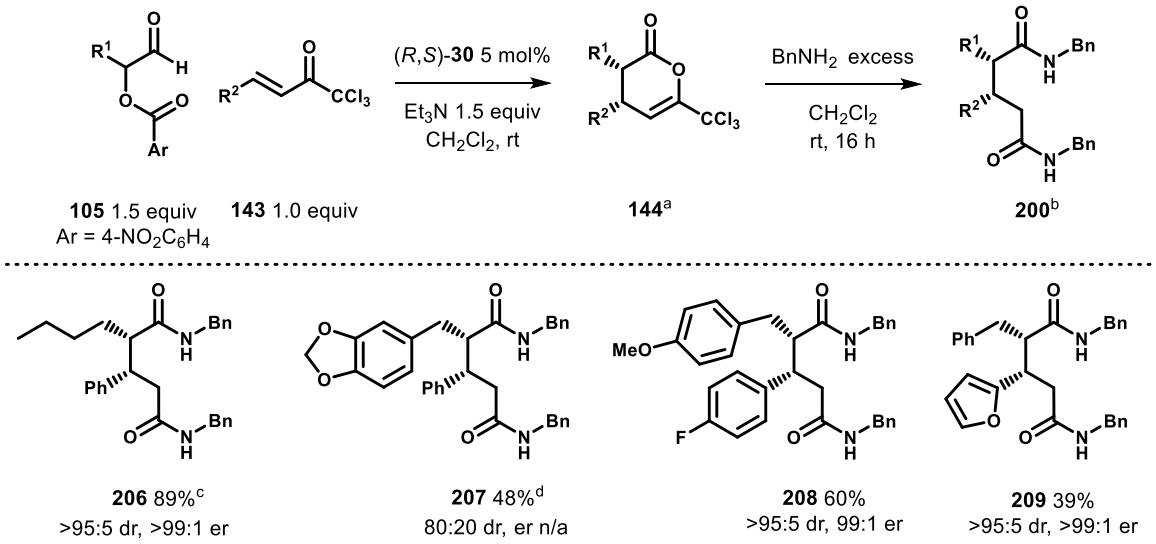


Table 12: Sequential [4+2] cycloaddition/ring-opening/aminolysis with benzylamine: variation of acceptor and donor.

The dr was determined by crude ^{1}H NMR spectroscopic analysis of the crude reaction. (a) Crude obtained after work up. No further purification; (b) Isolated yield after trituration in Et_2O; (c) [4+2] cycloaddition in anhydrous THF with 10 mol% precatalyst **30**; (d) The er could not be determined either with HPLC or GC analysis.

X-Ray crystallography analysis of diamide **202** confirmed the absolute configuration to be(2*S*,3*S*) (Figure 9). The configuration of all other products was assigned by analogy.

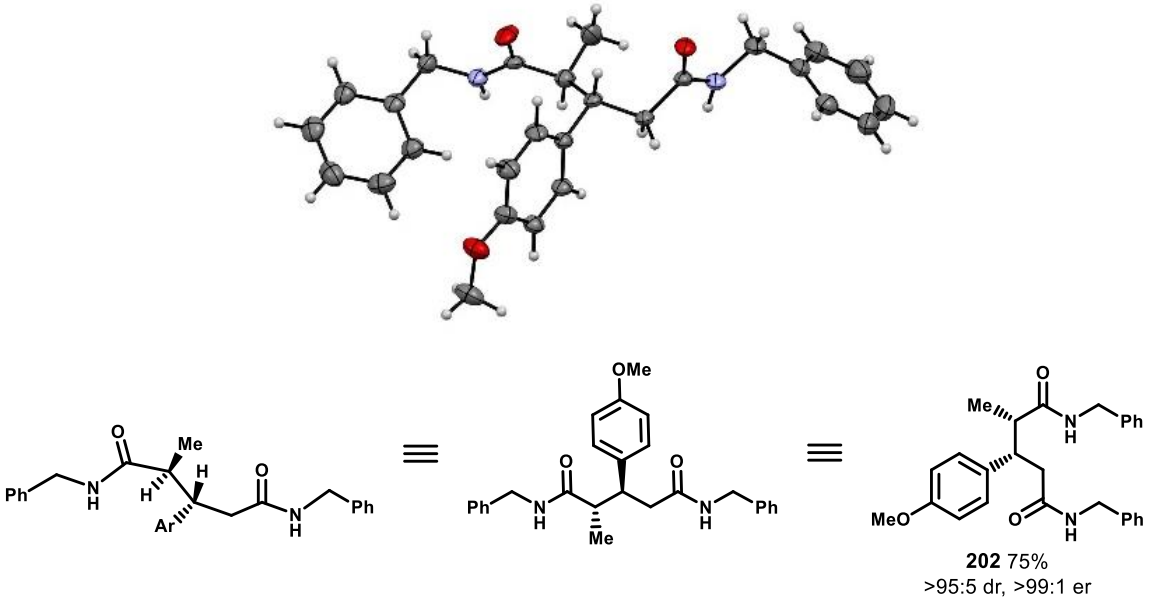


Figure 9: Molecular representation of the X-ray crystal structure of diamide **202**.

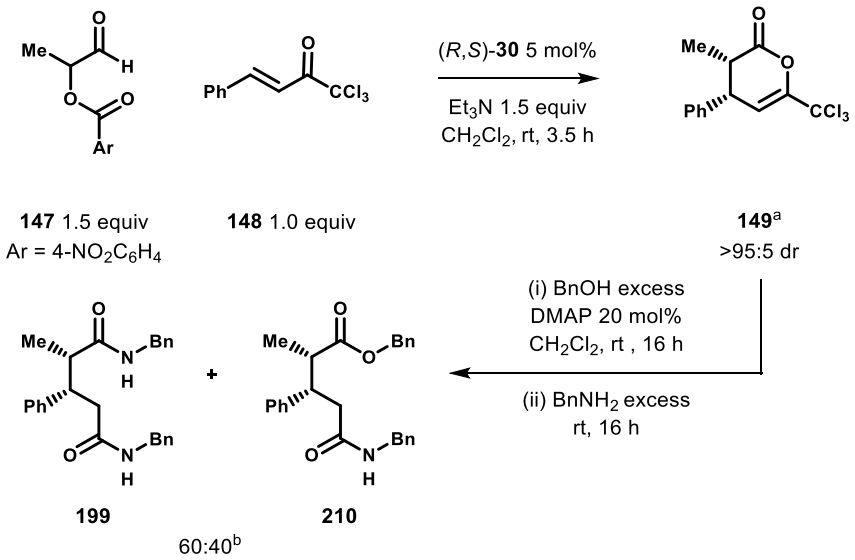
The relative and absolute configuration of the products was assigned by X-ray crystallographic analysis of diamide **202**, with all other products assigned by analogy. Data for **202** have been deposited with the CambridgeCrystallographic Data Centre as supplementary publication CCDC 1410758.

A chromatography free and short sequential [4+2] cycloaddition between azolium enolates generated from α-aroyloxyaldehydes and trichloromethyl ketones was successfully developed to access highly functionalised diamides. It proved the ability of trichloromethyl ketones to act as amide surrogates. Next the possibility of a combined ring-opening with alcohol and aminolysis of the CCl_3 group to synthesise a bifunctional product was investigated.

2-6-3 γ-Ester amide synthesis

Based upon the results obtained while investigating trichloromethyl ketones as ester and amide surrogates, a selective sequential nucleophilic ring-opening using benzyl alcohol and CCl_3 displacement with benzylamine was proposed. This would give access to bifunctional *γ*-ester amide **210** in a three-step sequence.

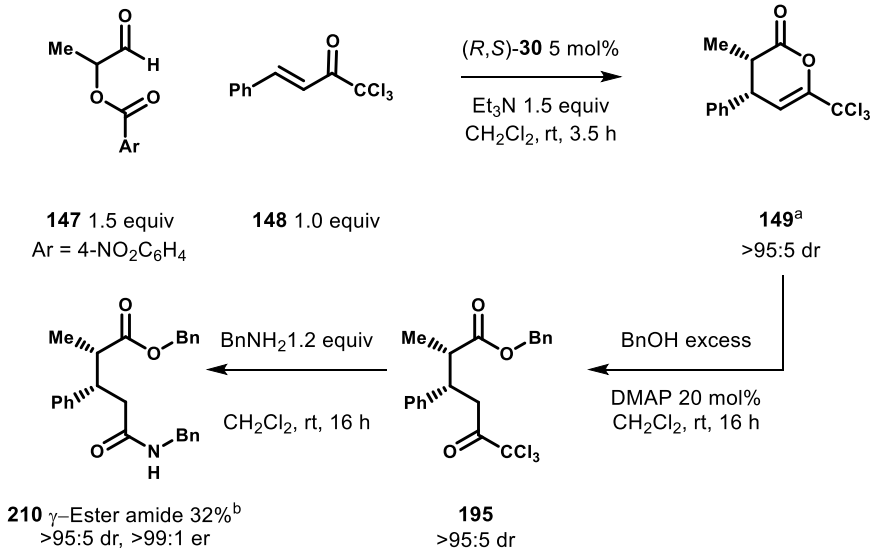
Firstly, a one-pot process from the crude *syn*-dihydropyranone **149** was attempted with benzyl alcohol and benzylamine in large excess (Scheme 63). This formed the desired *γ*-ester amide **210** along with diamide **199** in a 40:60 mixture according to ^{1}H NMR spectroscopic analysis of the crude reaction mixture.



Scheme 63: Sequential [4+2] cycloaddition/ring-opening with benzyl alcohol and CCl_3 displacement using excess benzylamine.

The dr was determined by ^{1}H NMR spectroscopic analysis of the crude reaction. (a) Crude **149** obtained after work up. No further purification; (b) Ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction.

This result could be consistent with incomplete ring-opening of *syn*-dihydropyranone **149** by the alcohol. The ring-opening step was therefore left for a longer 24 h reaction time and the remaining benzyl alcohol was removed by Kugelrohr distillation, before aminolysis using just 1.2 equivalents of benzyl amine. Pleasingly, this 3-step sequence gave access to highly functionalised and stereodefined γ-ester amide **210** in >95:5 dr and >99:1 er albeit in modest 32% yield after column chromatography (Scheme 64).



Scheme 64: Three steps synthetic route to highly functionalised and stereodefined γ-ester amide **210**.

The dr was determined by ^{1}H NMR spectroscopic analysis of the crude reaction. (a) Crude **149** obtained after work up. No further purification; (b) Isolated yield after column chromatography.

2-7 Proposed stereochemical model

To rationalise the stereochemical outcome of the reaction, a pre-transition state assembly is proposed (Figure 10). This is based on computational studies from Bode, Kozlowski *et al.* on related [4+2] cycloadditions between enals and enones as described previously (Section 1-4).[58a] Their studies showed the reaction to be a concerted but asynchronous *endo*-hetero-Diels–Alder process. First, the enolate moiety is assumed to adopt a (*Z*)-geometry with the enolate coplanar to the triazolium ring and perpendicular to the mesityl group (Figure 10-a).[58a] Two conformations are possible. In conformation A, the oxyanion points toward the mesityl group, which would be unfavoured due to the resulting repulsive interactions (highlighted in red on Figure 10-a). Conformation B is characterised by the hydrogen on C(2) of the enolate pointing towards the mesityl group. This could lead to a stabilising CH–π interaction and therefore contribute to the stereocontrol of the reaction by "locking" the enolate in this conformation (highlighted in green on Figure 10-b). The indane blocks the enone to approach from the top (*Re*) face of the enolate. Therefore, the enone approaches from the available bottom (*Si*) of the enolate in an *endo* fashion to avoid steric interactions between R^2 and the mesityl group (Figure 10-c). This is consistent with the diastereocontrol observed for this process. A secondary interaction might be present between the lone pain of oxyanion from the enolate and the π* orbital of the carbonyl of the enone (highlighted in brown on Figure 10-b). These would favour the formation of the *syn* product.

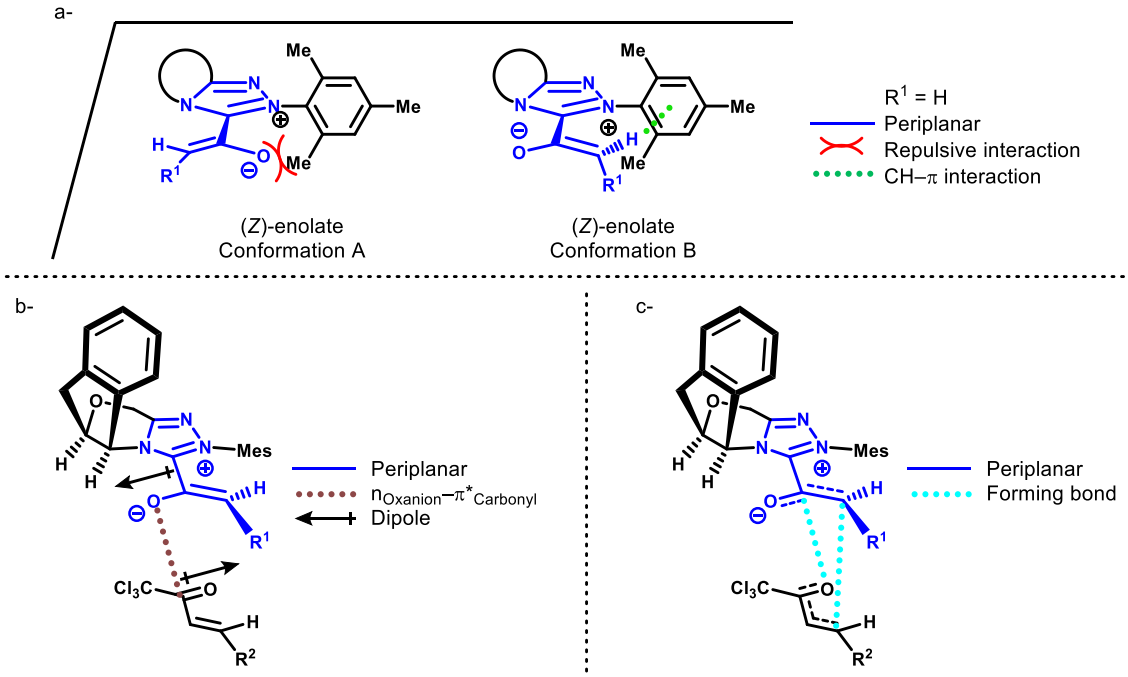
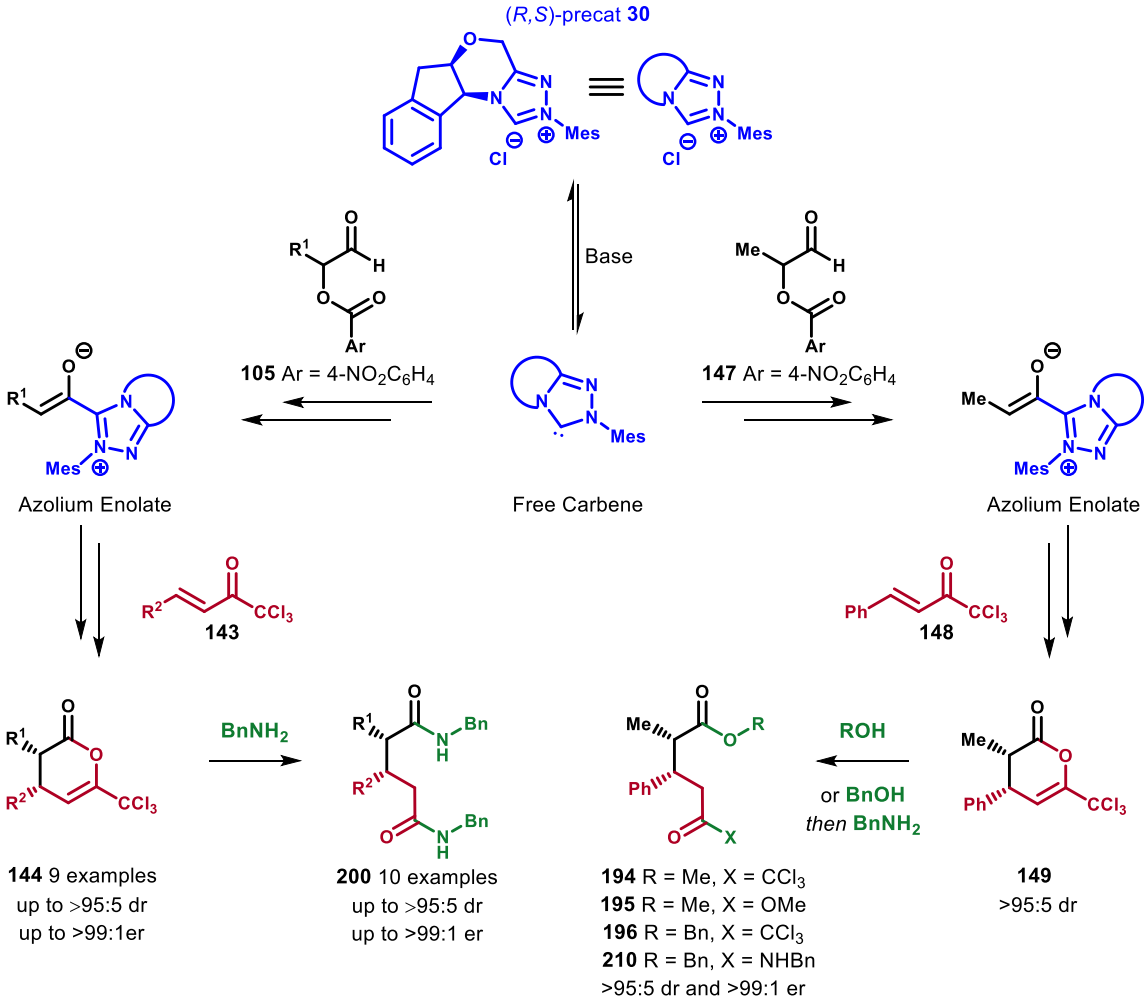


Figure 10: Proposed pre-transition state assembly.

2-8 Conclusions

This work presents a novel and short NHC-catalysed synthetic route to stereodefined and highly functionalised diamides **200** *via syn*-dihydropyranones **144** from α,β-unsaturated trichloromethyl ketones **143**, and generating azolium enolate from α-aroyloxyaldehydes **105** using precatalyst **30** (Scheme 65). Although α,β-unsaturated amides are not reactive enough to be used in this type of process, trichloromethyl ketones **143** have been shown to act as amide surrogates. Sequential cycloaddition/nucleophilic addition gives access to diamides **200** *via* ring-opening and subsequent displacement of the CCl_3 group by the amine. Pleasingly, both *syn*-dihydropyranones **144** and diamides **200** were obtained in up to >95:5 dr and >99:1 er with good to high yield. Ring-opening with methanol and benzyl alcohol gave access to ketoesters **194** and **196** as a major compound instead of the expected diester, the nucleophilic substitution of the CCl_3 group being difficult to realise in this process. However, it enabled the possibility to obtain a highly functionalised and stereodefined γ-ester amide **210** through two sequential nucleophilic reactions from *syn*-dihydropyranone **149**. Indeed, after formation of ketoester **196**, the more nucleophilic benzylamine can displace the CCl_3 group, giving the desired bifunctional γ-ester amide **210**.



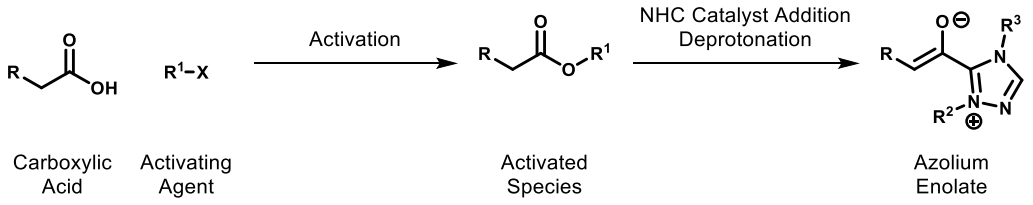
Scheme 65: Summary: NHC-catalysed [4+2] cycloaddition and sequential NHC-catalysed [4+2] cycloaddition/ring-opening process using α-aroyloxyaldehydes and α,β-unsaturated trichloromethyl ketone

3- Carboxylic Acids as Azolium Enolate Precursors in Intramolecular Formal [4+2] Cycloadditions

3-1 Generation of 5-membered ring tethers: Synthesis of 2,3-disubstituted 2,3-dihydrobenzofuran derivatives

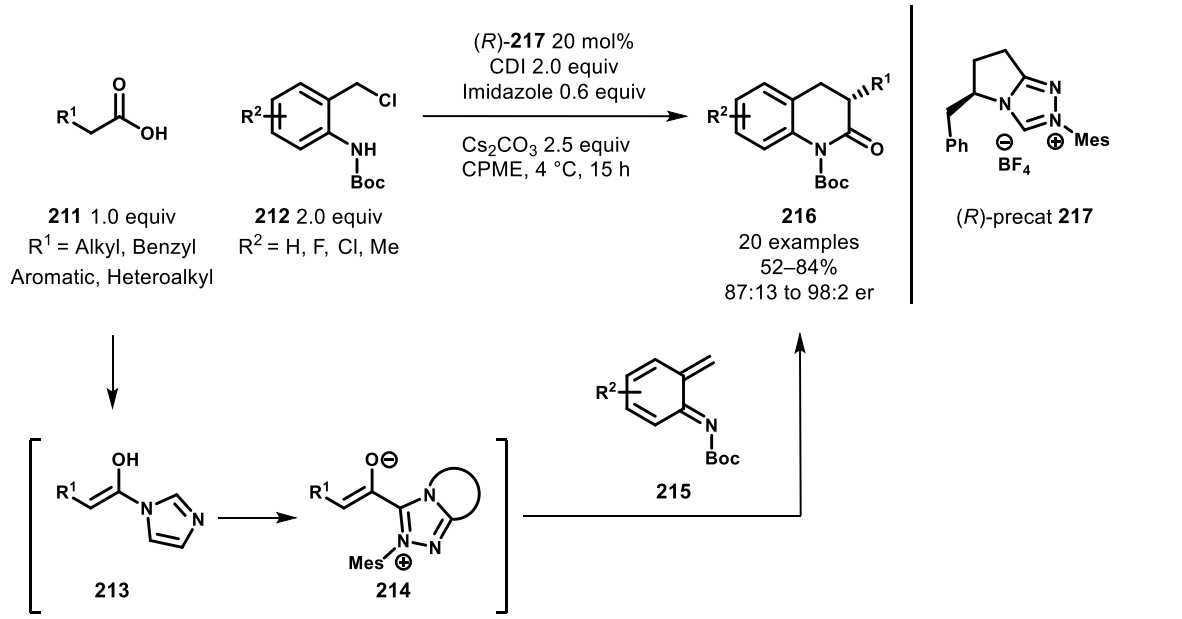
3-1-1 Introduction

One of the challenges in this field is to find a stable, readily available and inexpensive azolium enolate precursor. The enolate progenitor must also show selectivity for the formation of azolium enolates. In this regard, carboxylic acids would be an ideal alternative. While carboxylic acids have been extensively used in Lewis base catalysis using isothiourea-, cinchona alkaloid- and DMAP-derived catalysts for the generation of C1 ammonium enolates through *in situ* "activation" usually *via* formation of a mixed anhydride or related derivative, this concept remains underexplored in NHC-catalysed processes.[70] Indeed, one of the difficulties to overcome is the generation of a carboxylic acid equivalent *in situ* without any side-reactions resulting in deactivation of the reagents (Scheme 66).



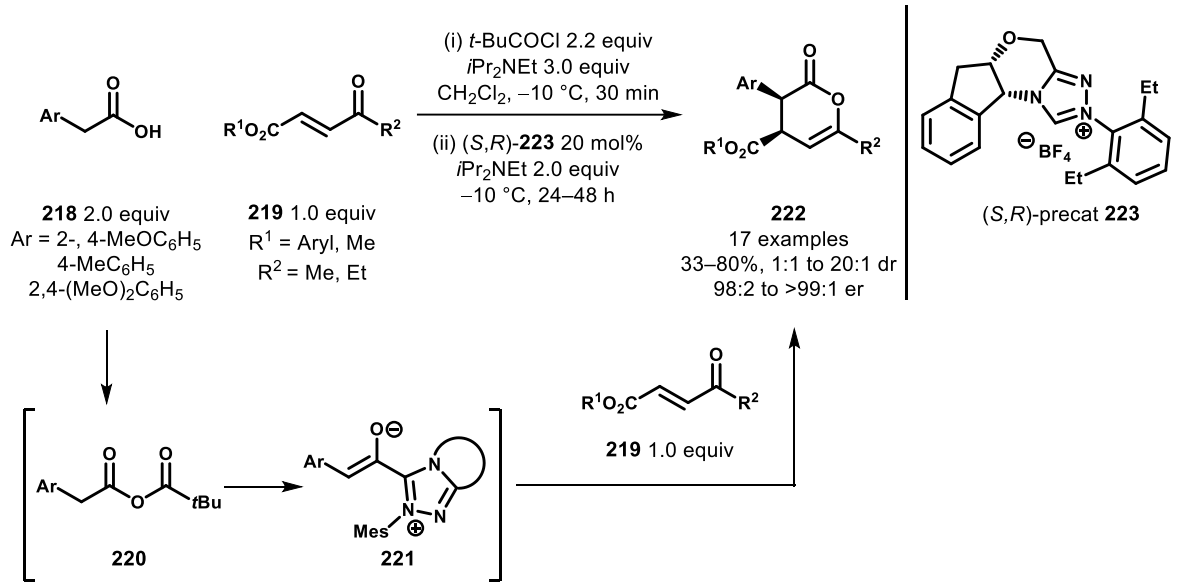
Scheme 66: Carboxylic acid as azolium enolate precursors with triazolium catalyst.

The use of carboxylic acids to generate azolium enolate intermediates for use in intermolecular formal [4+2] cycloadditions has been reported by a few groups. A seminal article published in 2014 by Scheidt *et al*. demonstrated the use of carboxylic acids **211** toward the synthesis of dihydroquinolones **216** in up to 98:2 er (Scheme 67).[71] The reaction proceeded through *in situ* transformation of carboxylic acid **211** with 1,1-carbonyldiimidazole (CDI) to form the corresponding acyl imidazole **213** as a viable azolium enolate precursor when used in combination with free catalyst obtained from **217** (20 mol%). A formal [4+2] cycloaddition with aza-*o*-quinone methide **215** also generated *in situ* from *t*-butyl carbamate protected 2-aminobenzyl chloride **212** gave the desired product **216** in 52–84% yield. The reaction showed improved yield in the presence of substoichiometric imidazole (0.6 equiv) to neutralise HCl and therefore preventing it from deactivating both the free catalyst and the reagents.



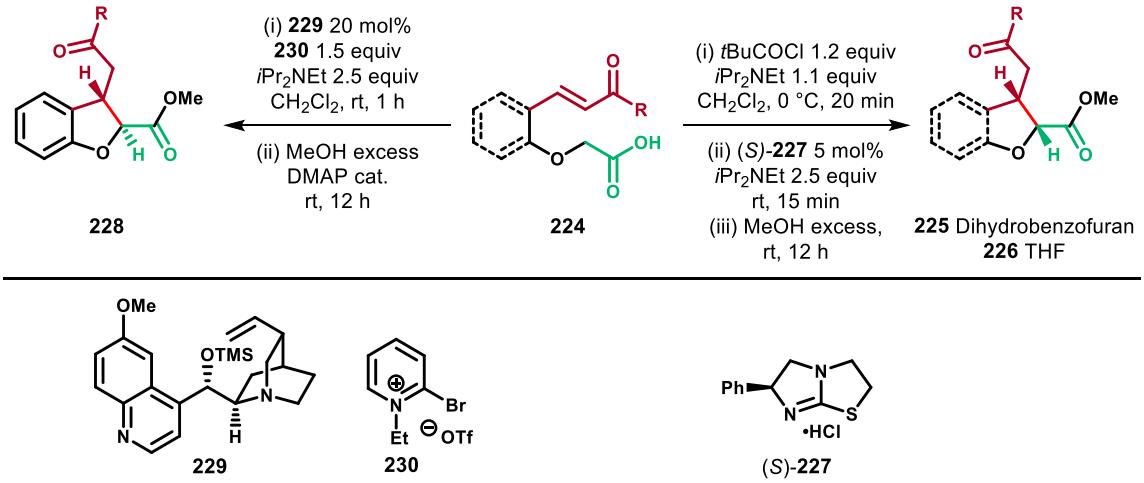
Scheme 67: NHC-catalysed formal [4+2] cycloaddition of carboxylic acids **211** with *t*-butyl carbamate protected 2-aminobenzyl chloride **212**.

In 2015, Ye *et al.* reported the synthesis of *syn*-dihydropyranones **223** in up to >20:1 dr and >99:1 er, starting from 2-aryl carboxylic acids **218** bearing electron donating groups (-OMe, -Me) and unsaturated ketoesters **219** (Scheme 68).[72] The *in situ* generation of more reactive mixed anhydride **220** derived from the carboxylic acid was achieved using pivaloyl chloride (*t*BuCOCl) and *i*Pr$_2$NEt. The mixed anhydride was intercepted by the free NHC catalyst **223** (20 mol%) to form the desired azolium enolate intermediate **221**. Upon reaction with enone **219**, it led to the formation of *syn*-dihydropyranone **222**.



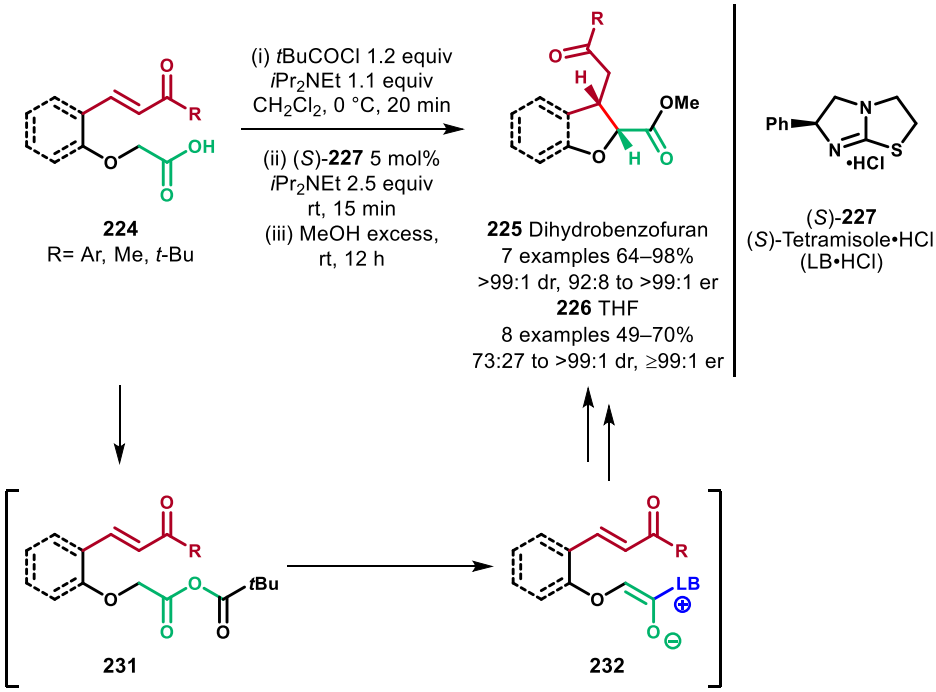
Scheme 68: NHC-catalysed formal [4+2] cycloaddition of arylacetic acids **218** with unsaturated α,β-unsaturated γ-ketoesters **219**.

To the best of our knowledge, no report has been published on NHC-catalysed intramolecular formal [4+2] cycloadditions using carboxylic acid as azolium enolate precursors. The Smith group has previously reported the use of carboxylic acids bearing a pendant enone, known as enone-acids, for intramolecular formal [4+2] cycloadditions catalysed by different types of Lewis base. Studies included isothiourea- and cinchona alkaloid-catalysed reactions where selective choice of the catalyst gave preferential access to either the *cis*- or *trans*-diastereoisomers of the product (Scheme 69).[73]



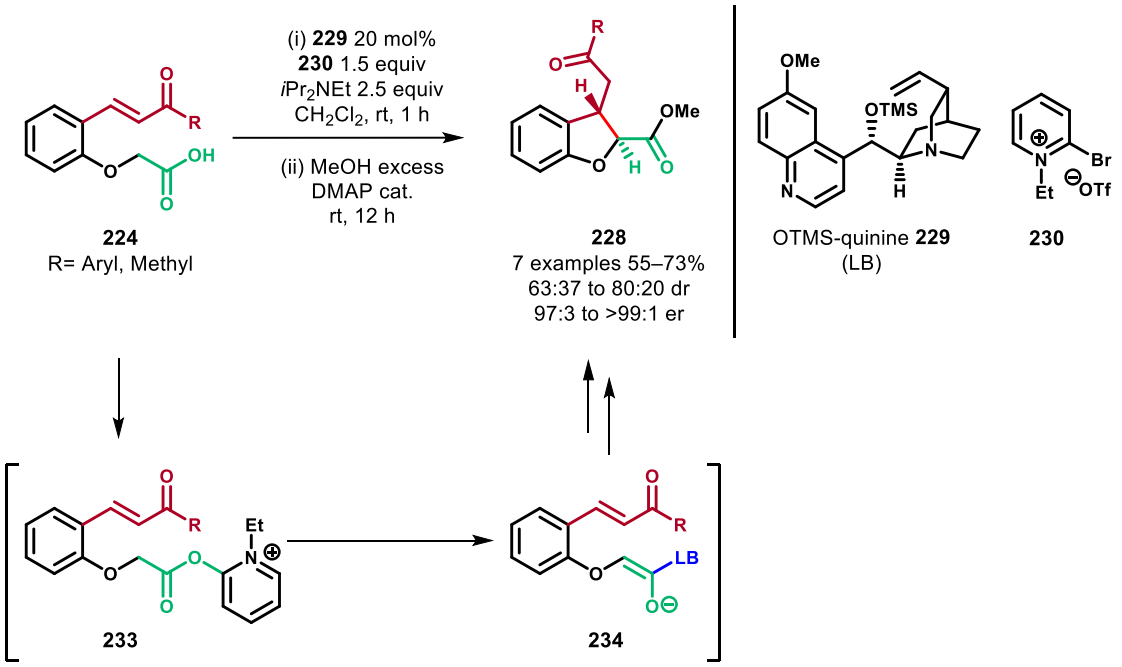
Scheme 69: Cinchona alkaloid- and isothiourea-catalysed intramolecular formal [4+2] cycloaddition starting from enone-acids **224**.

The isothiourea-catalysed process to form *cis*-**225** and *trans*-**226**, required *in situ* formation of the reactive mixed anhydride **231** from enone-acid **224** using pivaloyl chloride (Scheme 70). The anhydride can undergo nucleophilic attack by the Lewis base catalyst (*S*)-tetramisole **227** (5 mol%) leading to C1 ammonium-enolate **232**. Intramolecular formal [4+2] cycloaddition followed by DMAP-catalysed ring-opening with methanol gave **225** in good yield with excellent enantio- and diastereocontrol and **226** in moderate to high dr and yield, and excellent er.



Scheme 70: Isothiourea-catalysed intramolecular formal [4+2] cycloaddition starting from enone-acids **224**.

In the cinchona alkaloid-catalysed formation of *trans*-**228**, Mukaiyama reagent derivative **230** was utilised to form ester **233** (Scheme 71). In this case "activation" and catalysis reagents were introduced all at once. The final *trans*-dihydrobenzofurans **228** were obtained in moderate dr, moderate to good yield and high er.



Scheme 71: Cinchona alkaloid-catalysed intramolecular formal [4+2] cycloaddition starting from enone-acids **224**.

These two methodologies required different "activating" agents showing the "activation" to be catalyst and not substrate specific. The observed divergence in diastereocontrol is postulated to be the result of the different pre-transition state assemblies (Figure 11). In the isothiourea-catalysed process, a non-bonding 1,5-S···O interaction is postulated to lock the enolate moiety in a conformation where the oxyanion is *syn* to the sulphur of the catalyst (Figure 11-a).[74] The directing phenyl group blocks the bottom (*Si*) face of the adduct forcing the enone moiety to approach from the top (*Re*) face with the carbonyl oriented to maximise the dipole opposition with the oxyanion. These lead to the *cis*-product. The pretransition-state assembly postulated in the cinchona alkaloid-catalysed methodology has the directing groups of the catalyst blocking the bottom (*Re*) face (Figure 11-b). This favours a top (*Si*) face approach of the enone moiety onto the enolate one. The *trans*-conformation of the major final products is assumed to be the results of minimised interaction between the enone and the ethylene bridge of the catalyst.

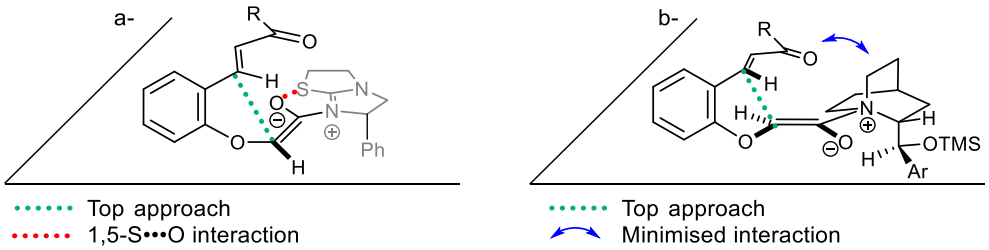
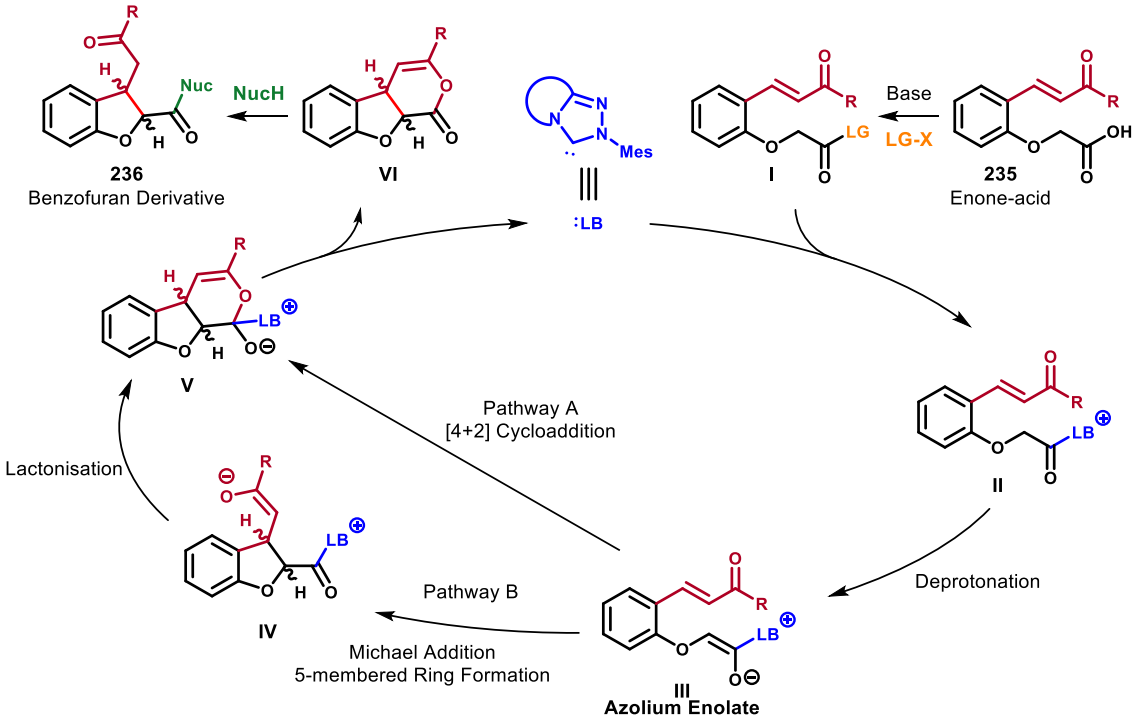


Figure 11: Postulated pre-transition state assemblies obtained using a- (*S*)-tetramisole **227** and b- OTMS-quinine **229**.

Whether being the *cis* or the more predominant *trans*-diastereoisomer, the 2,3-disubstituted 2,3-dihydrobenzofuran scaffold is present in many natural and synthetic products covering with a versatile pharmacology profile.[75] This motif is therefore an interesting target.

3-1-2 Aim of the project and Postulated mechanism:

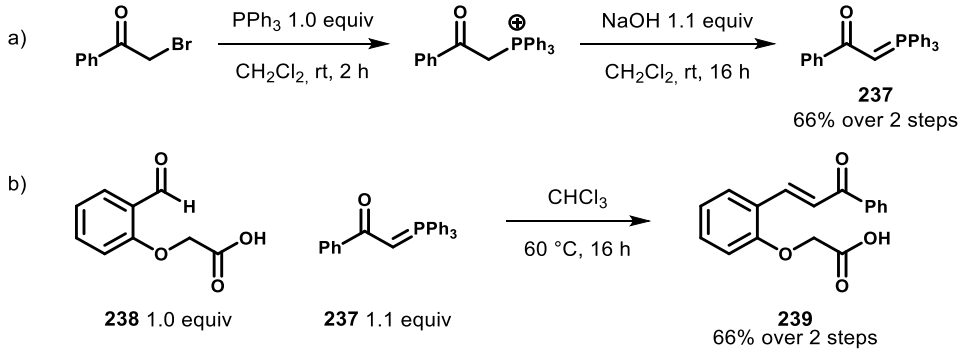
Based on these previous works, the aim of this project was to use for the first time enone-acids in NHC-catalysed intramolecular formal [4+2] cycloaddition (Scheme 72). One of the main problems considered in this project was to find an optimal reagent leading to **I** and being compatible with the catalyst to form acyl azolium **II**. After deprotonation to form azolium enolate **III**, the mechanism was postulated to follow a formal [4+2] cycloaddition pathway based on the computational work of Bode, Kozlowski *et al* (Pathway A).[48] An alternative representation would be a stepwise one (Pathway B) consisting of a Michael addition (5-*exo*-trig) followed by a lactonisation (6-*exo*-trig).[71,73] In both cases, the cycloaddition leads to the formation of adduct **V** that collapses to release the free catalyst alongside with annulation product **VI**. Previous experience has shown that dihydropyranobenzofuran **VI** cannot be isolated as it is not stable on silica.[73] Therefore, the last step consists of a ring-opening of the dihydropyranone moiety by a nucleophile to form the desired 2,3-disubstituted 2,3-dihydrobenzofuran product **236**.



Scheme 72: Postulated mechanism for the NHC-catalysed synthesis of dihydrobenzofuran derivatives.

3-1-3 Reaction optimisation:

Enone-acid **239** was chosen for the development of a model system. The synthesis was straightforward and consisted of a Wittig reaction between 2-formylphenoxyacetic acid **238** and phosphorane **237** (Scheme 73). [73,76]

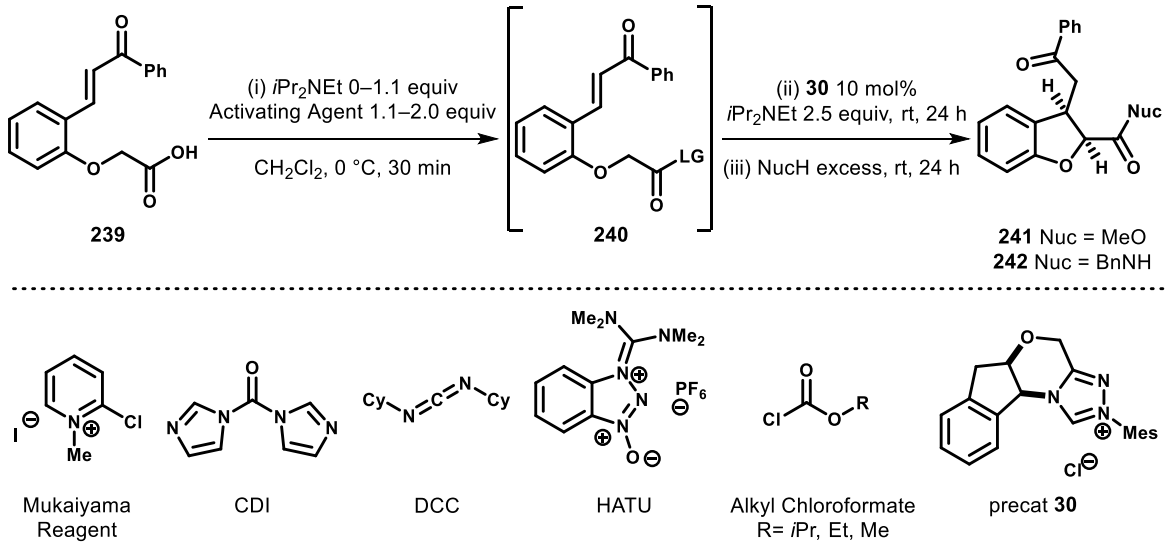


Scheme 73: Synthesis of parent enone-acid **239**.

The initial optimisation focussed on identifying the correct reagent for the "activation" step and its compatibility with NHC-catalysis (Table 13). The following reactions were performed on a 0.20 mmol scale under anhydrous conditions. Based on work with isothiourea catalyst **227** (Scheme 70),[73] the first step consisted of the addition of the "activating" agent (1.1 equiv) and *i*Pr$_2$NEt (1.1 equiv) to a solution of enone-acid **239** in CH_2Cl_2 and leading to **240**. The reaction was stirred at 0 ºC for 30 min then warmed to rt. Precatalyst **30** (10 mol%) was added with additional *i*Pr$_2$NEt (2.5 equiv) and the reaction mixture was stirred for 24 h before ring-opening with methanol (excess).

The use of pivaloyl chloride led to the formation of **241** as a minor product (<5% isolated yield) among unknown side-products. EDCI or a combination of EDCI and HOBt did not provide the desired products but rather the degradation of the starting material and at best the formation of the corresponding enone-methyl ester. Mukaiyama reagent led to the formation of **241** in 80:20 dr (*cis*:*trans*) which was isolated in about 18% yield alongside unknown side-products (Table 13, Entry 1). A similar dr was obtained using CDI and DCC, with **241** isolated in lower 9 and 10% yield respectively (Table 13, Entry 2 and 3), whereas HATU led to **241** in an improved >95:5 dr and low 14% yield (Table 13, Entry 4).

Although these reactions were not conclusive, they led to the formation of enough racemic sample of **241** to generate racemic standards for HPLC analysis. Next isopropyl chloroformate (1.0 M in PhMe) was tested with (*R*,*S*)-precatalyst **30** to assess the enantioselectivity of the reaction (Table 13, Entry 5). The conversion of enone-acid **239** was met with moderate success with a 46:54 ratio **239**:**241** according to ^{1}H NMR analysis of the crude reaction mixture. Nevertheless, it led to an encouraging 38% yield and 91:9 er of the major enantiomer identified as (2*S*,3*R*)-**241** by comparison with literature HPLC analysis and specific rotation values.[73] To facilitate isolation of the final product, methanol was replaced by benzylamine in the ring-opening step, allowing a chromatography-free procedure with a simple trituration in Et_2O; unfortunately further investigation showed this trituration process led to reproducibility issues (Table 13, Entry 6). Using a larger excess of isopropyl chloroformate (2.0 equiv) gave **242** in an improved 67% yield and excellent >95:5 dr and >99:1 er (Table 13, Entry 7). Disappointingly, inconsistencies in the results rose while investigating the system further (base, drying agent, equivalents). This indicated that isopropyl chloroformate was not a reliable activating agent for this system. Another range of chloroformates were therefore tested including primary alkyl chloroformates. Primary alkyl chloroformates are theoretically less inclined to degradation as decarboxylation would lead to primary carbocations which are less stable and therefore disfavoured.[77] When using ethyl chloroformate, **242** was obtained in >95:5 dr and isolated in moderate 45% yield and 97:3 er (Table 13, Entry 8). Activation of the enone-acid **239** with methyl chloroformate provided **242** in >95:5 dr, 96:4 er but in a lower 37% yield (Table 13, Entry 9).

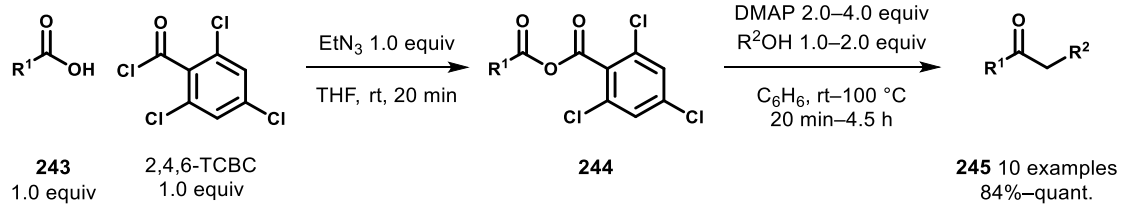


	Activation		Catalysis	Ring-Opening	Results: 241 or 242		
Entry	**Activating Agent**	**Equivalents**	**Catalyst**	**NucH**	**dr (*cis*:*trans*)**[a]	**Isolated Yield**[b]	**er**
1	Mukaiyama reagent	1.1 equiv	(±)-**30**	MeOH	80:20	18%	–
2	CDI	1.1 equiv	(±)-**30**	MeOH	80:20	9%	–
3	DCC[c]	1.1 equiv	(±)-**30**	MeOH	80:20	10%	–
4	HATU	1.1 equiv	(±)-**30**	MeOH	>95:5	14%	–
5	Isopropyl Chloroformate	1.1 equiv	(*R*,*S*)-**30**	MeOH	89:11	38%	91:9
6	Isopropyl chloroformate	1.1 equiv	(*R*,*S*)-**30**	$BnNH_2$	>95:5	39%[d]	86:14
7	Isopropyl chloroformate	2.0 equiv	(*R*,*S*)-**30**	$BnNH_2$	>95:5	67%	>99:1
8	Ethyl chloroformate	2.0 equiv	(*R*,*S*)-**30**	$BnNH_2$[e]	>95:5	45%	97:3
9	Methyl chloroformate	2.0 equiv	(*R*,*S*)-**30**	$BnNH_2$[e]	>95:5	37%	96:4

Table 13: Activating agents screening.

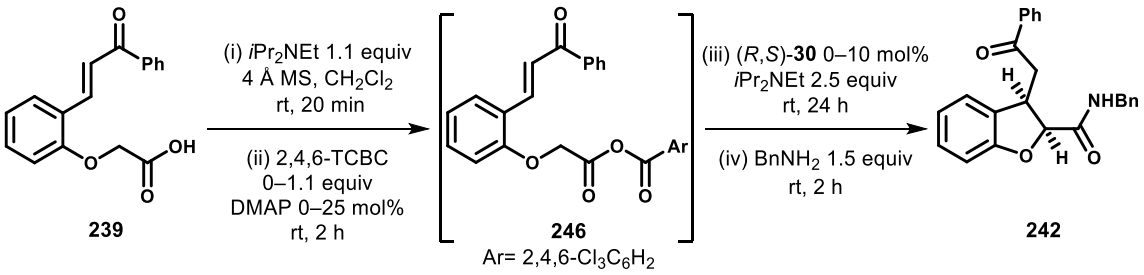
(a) Determined by ^1H NMR spectroscopic analysis of the crude reaction; (b) Isolated yield following column chromatography; (c) DCC used in step (i) without *i*Pr_2NEt; (d) Isolated yield following trituration in Et_2O of the crude reaction mixture; (e) $BnNH_2$ 1.5 equiv.

Moving away from chloroformates, the use of 2,4,6-trichlorobenzoyl chloride (2,4,6-TCBC) known as the Yamaguchi reagent was explored next. Its utility for the formation of mixed anhydrides *en route* to esters was initially reported by Yamaguchi *et al*. in 1979 (Scheme 74).[78]



Scheme 74: Esterification of carboxylic acid using 2,4,6-trichlorobenzoyl chloride developed by Yamaguchi *et al*.

The combination of 2,4,6-TCBC, *i*Pr$_2$NEt, and catalytic DMAP gave **242** with >95:5 dr 36% yield and 66:34 er (Table 14, Entry 1). When the reaction was performed in the absence of precatalyst **30**, the desired *cis*-**242** was isolated in 94:6 dr and 43% yield, consistent with a racemic background reaction catalysed by DMAP (Table 14, Entry 2). The use of 2,4,6-TCBC without DMAP formed the desired mixed anhydride which, after NHC-catalysed cycloaddition and ring-opening, led to the formation of **242** in >95:5 dr and was isolated in 61% yield and >99:1 er (Table 14, Entry 3). Having the best results in terms of yield and diastereo- and enantioselectivity, the use of the Yamaguchi reagent was deemed to be optimum for this system.

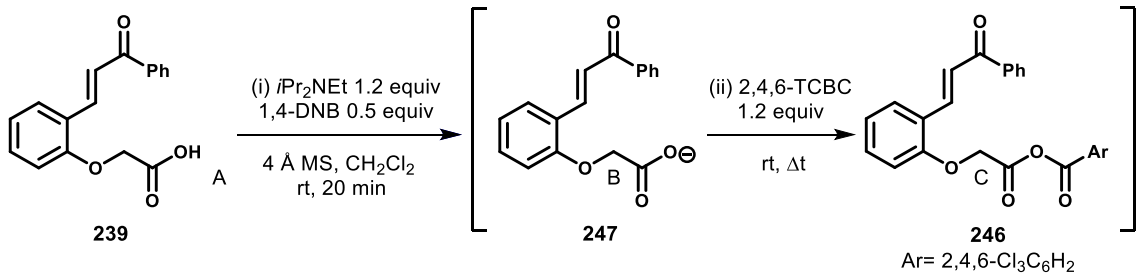


	Catalysts		Results			
Entry	**DMAP**	(*R*,*S*)-**30**	**dr (*cis*:*trans*)**[a]	**NMR Yield**[b]	**Isolated Yield**[c]	**er**
1	25 mol%	10 mol%	>95:5	54%	36%	66:34
2	25 mol%	–	94:6	44%	43% (94:6 dr)	50:50
3	–	10 mol%	>95:5	79%	61%	>99:1

Table 14: Screening with 2,4,6-trichlorobenzoyl chloride.

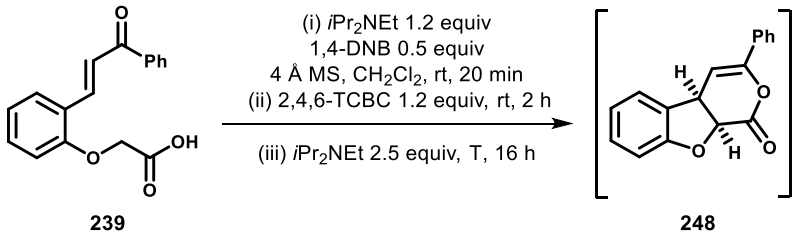
(a) Determined by ^{1}H NMR spectroscopic analysis of the crude reaction; (b) NMR yield determined by ^{1}H NMR spectroscopic analysis of the crude reaction using 1,4-dinitrobenzene as the internal standard; (c) Isolated yield following column chromatography.

The activation being difficult to follow by TLC analysis, this step was studied closer through ^{1}H NMR experiments in presence of 1,4-dinitrobenzene (1.4-DNB, 0.5 equiv) as an internal standard over 6 h (Scheme 75). The focus was on the singlet signal for the CH_2 group in each of the different species. In the enone-acid **239** it corresponds to peak A at 4.83 ppm, after deprotonation of the carboxylic acid moiety (Step (i)) the CH_2 signal shifts to B at 4.59 ppm. In the mixed anhydride **246** the CH_2 peak C was observed at 4.94 ppm. It showed equivalent formation (around 80%) of the desired mixed anhydride between 1 and 6 h. This seems to indicate that the activation step is an equilibrium. A 2 h reaction time was seemingly the best compromise between maximising mixed anhydride **246** concentration and reducing reaction time.



Scheme 75: Model reaction for the ^{1}H NMR spectroscopic analysis of the activation step.

Next, the influence of the nucleophile used in the ring-opening step was investigated using methanol, benzylamine, diethylamine, piperidine and morpholine. The desired products were obtained in moderate to good yields, good enantio- and diastereoselectivities, with morpholine giving the best results. Nevertheless, further experiments to improve both the dr and er (base screening, ring-opening conditions etc.) proved the system to be sensitive to temperature changes as a rise by a few degrees of the room temperature generated a base-promoted racemic background reaction, leading to decreased diastereo- and enantioselectivities (at 30 °C, **242** obtained in 55% yield, 91:7 dr and 89:11 er). Indeed, at rt in the absence of precatalyst **30**, dihydropyranone **248** was formed in 82:18 dr and 42% yield according to ^{1}H NMR spectroscopic analysis of the crude reaction. When the reaction was repeated at 0 °C, the background racemic reaction was reduced and **248** was observed in >95:5 dr and ≈ 20% NMR yield over 16 h (Table 15).



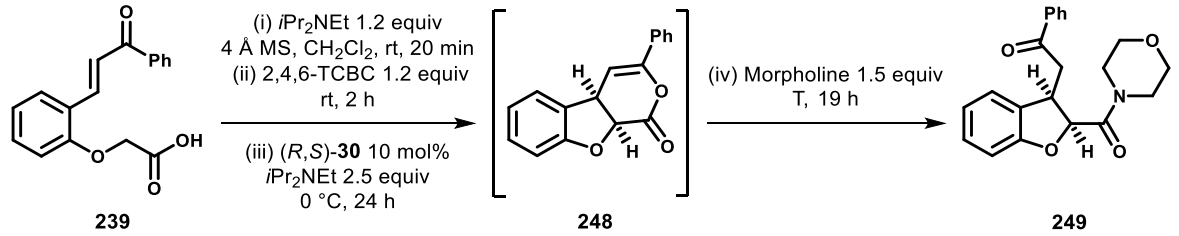
239 **248**

	Cycloaddition	**Results**	
Entry	**T**	**NMR Yield**[a]	**dr**[b]
1	rt	42%	82:18
2	0 °C	20%	>95:5

Table 15: Background reaction.

(a) NMR yield of product **248** determined by ^{1}H NMR spectroscopic analysis of the crude reaction using 1,4-dinitrobenzene as the internal standard; (b) Determined by ^{1}H NMR spectroscopic analysis of the crude reaction.

Next, the influence of the temperature on the one-pot NHC-catalysed [4+2] cycloaddition/ring opening was investigated (Table 16). Product **249** was obtained in >95:5 dr, 95:5 er and 73% yield when the ring-opening step was left for 19 h at 0 ºC (Table 16, Entry 1). Decreasing the temperature further to –10 °C led to identical yield and dr, and similar 93:7 er (Table 16, Entry 2).

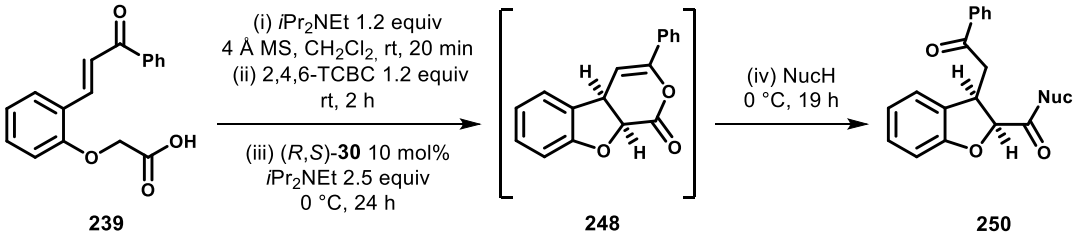


	Ring-opening		Results		
Entry	**Reaction time**	**T**	**dr (*cis*:*trans*)[a]**	**Isolated Yield[b]**	**er**
1	19 h	0 °C	>95:5	73% (96:4 dr)	95:5
2	19 h	–10 °C	>95:5	73% (94:6 dr)	93:7

Table 16: Influence of the temperature of the ring-opening step.

(a) Determined by ^{1}H NMR spectroscopic analysis of the crude reaction; (b) Isolated yield following column chromatography.

Finally, after screening many conditions and observing irreproducible results, optimal reaction conditions for this model system were established (Scheme 76). Enone-acid **239** was deprotonated by distilled *i*Pr$_2$NEt in anhydrous CH_2Cl_2 over 4 Å molecular sieves. The reactive mixed anhydride was formed using distilled 2,4,6-TCBC at rt. Cyclised product **248** was obtained at 0 ºC and ring-opening by a nucleophile such as morpholine at 0 ºC led to the final product **250**.



Scheme 76: Model system.

3-1-4 Nucleophile scope

The scope of this transformation was firstly assessed by varying the nucleophile to promote ring-opening of the dihydropyranone after formal [4+2] cycloaddition. Following the standard conditions, employing both catalysis and ring-opening at 0 °C, a range of nucleophiles were tried to form isolable products (Table 17). Ring-opening with morpholine (1.5 equiv) gave **249** in excellent >95:5 dr, 95:5 er and 73% yield. Using piperidine or benzylamine (1.5 equiv) as a nucleophile gave amides **251** and **242** in good yields and excellent selectivity. Utilising a larger excess of Et_2NH (5.0 equiv) was required to obtain **252** in 94:6 dr, 69% yield (95:5 dr) and 93:7 er. Finally, 10 equivalents of MeOH with catalytic DMAP led to the formation of methyl ester **241** in 95:5 dr, isolated in 60% yield with 96:4 er and >95:5 dr. The results obtained for dihydrobenzofuran ester **241** are lower than in the isothiourea-catalysed process.

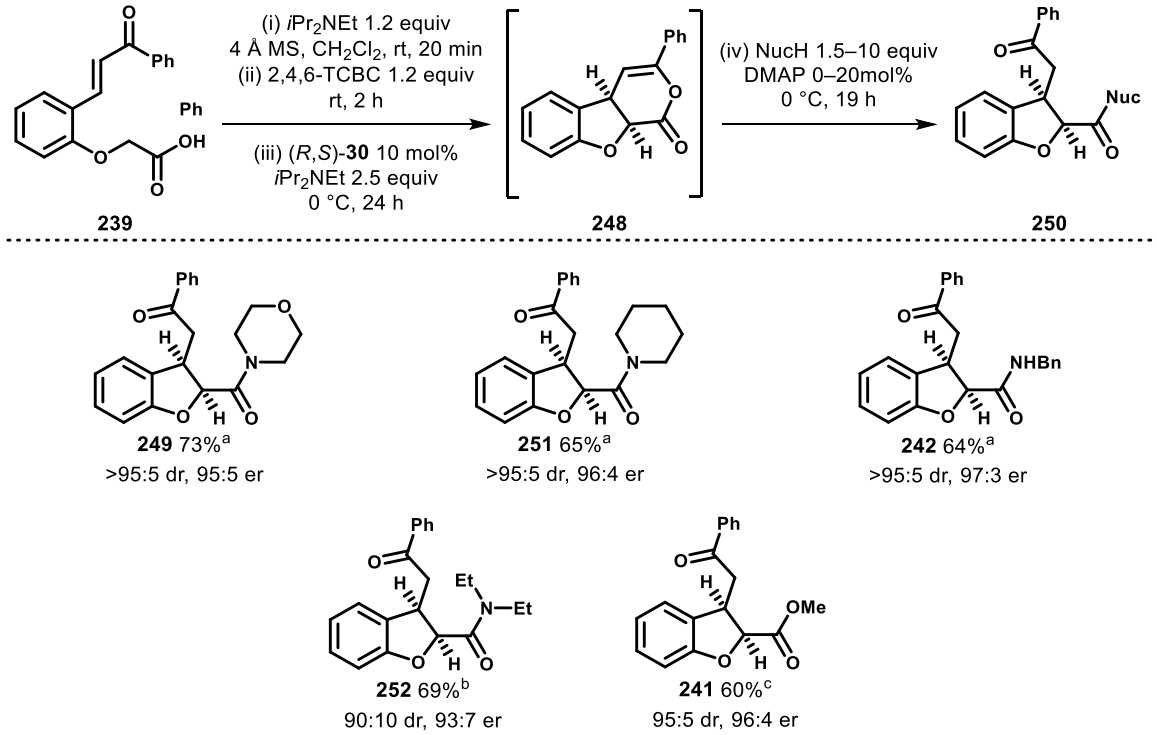
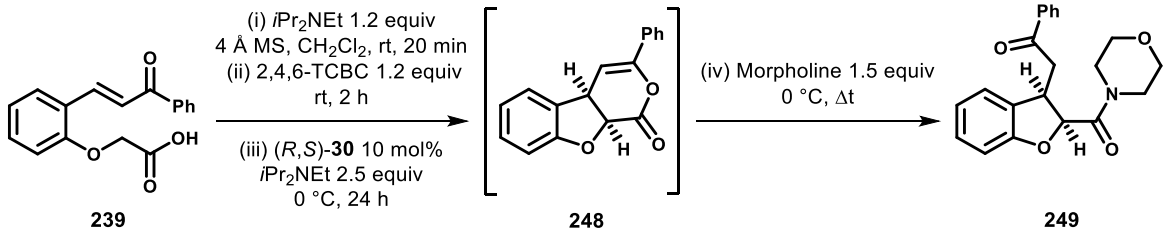


Table 17: Nucleophile scope.

(a) NucH (1.5 equiv); (b) Et_2NH (5.0 equiv); **252** isolated as a 95:5 mixture of diastereoisomers; (c) MeOH (10 equiv), DMAP (20 mol%); **241** isolated in >95:5 dr.

As morpholine gave the best results, it was chosen as the optimal nucleophile to examine the scope of enone-acids for this one-pot methodology. To shorten the overall reaction time of this intramolecular NHC-catalysed process, the ring-opening time was examined (Table 18). Similar dr and er were obtained overall and **249** could be isolated in high 94% yield after 4 h of reaction time for the ring-opening.



	Ring-opening	Results		
Entry	**Reaction time**	**dr (*cis*:*trans*)**[a]	**Isolated Yield**[b]	**er**
1	19 h	>95:5	73% (96:4 dr)	95:5
2	6 h	>95:5	80% (96:4 dr)	97:3
3	4 h	>95:5	94% (96:4 dr)	97:3
4	2 h	>95:5	85% (97:3 dr)	97:3

Table 18: Ring-opening reaction time.

(a) Determined by ^{1}H NMR spectroscopic analysis of the crude reaction; (b) Isolated yield following column chromatography.

Upon these results, ring-opening with morpholine (1.5 equiv) at 0 °C for 4 h was chosen for the investigation of the enone-acid scope.

3-1-5 Enone-acid scope

The synthesis of a range of enone-acids was carried out following the same procedure previously described (Scheme 73). The required Wittig reagent was synthesised except when commercially available or already synthesised in-house (**258** R = Me), then used in a Wittig reaction with 2-formylphenoxyacetic acid **238** (Table 19).

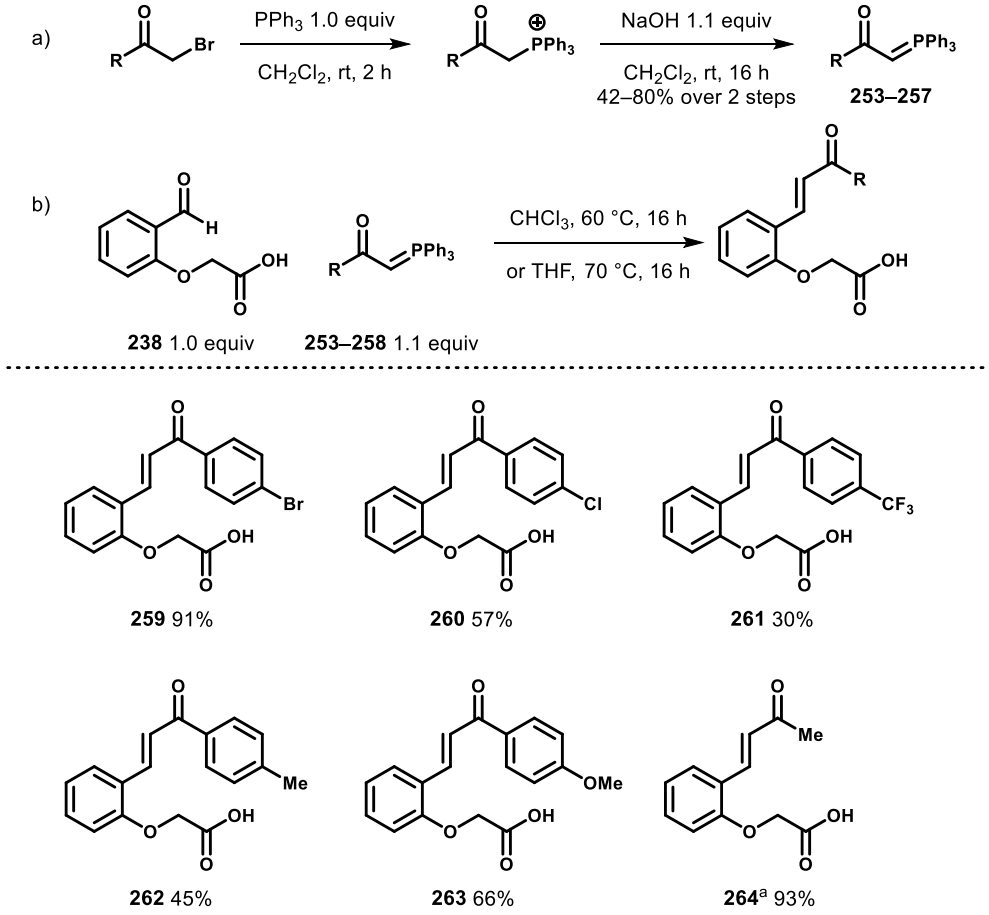


Table 19: Synthesis of enone-acids.

(a) From commercially available phosphorane **258**.

With the ring-opening reaction shortened to 4 h, the scope of enone-acids was examined starting with the influence of electron withdrawing groups on the enone fragment (Table 20). Dihydrobenzofuran derivative **265** (R = 4-BrC_6H_4) was obtained in excellent 72% yield, >95:5 dr and 97:3 er. Product **266** (R = 4-ClC_6H_4) was afforded in excellent 74% yield and >95:5 dr and 93:7 er. Similarly, **267** (R = 4-$F_3CC_6H_4$) was formed in >95:5 dr and 93:7 er but in lower 55% yield. These results seem consistent with the presence of the more electron withdrawing R = 4-$F_3CC_6H_4$ leading to a more reactive enone-acid. It could result in the formation of unwanted side-products observed by ^{1}H NMR spectroscopic analysis due to unwanted side-reactions and/or degradation, leading to a lower isolated yield.

A drop in yield, diastereo- and enantiocontrol was observed when electron donating aromatic groups were present. When enone-acid **262** (R = 4-MeC_6H_4) was used, **268** was formed in 90:10 dr and isolated as an inseparable 91:9 mixture of diastereoisomers in 54% yield with 83:17 er for the major *cis*-product and 56:44 er for the minor *trans*-product. Product **269** bearing R = 4-MeOC_6H_4 was obtained in a lower 84:16 dr in a 51% yield of an inseparable 92:8 mixture of diastereoisomers. Lower enantiocontrol was also observed as *cis*-**269** presented 83:17 er and *trans*-**269** 58:42 er. Of note, the yield and stereocontrol obtained for **269** decreased over time when the reaction was repeated using the same batch of starting material (92:8 dr, 83:17 er versus 39%, 86:14 dr and 71:29 er 4 weeks later). Finally, when the aromatic ring was replaced with a methyl group, product **270** was formed in only a small quantity (<10% by ^{1}H NMR analysis of the crude reaction) even when increasing the precatalyst **30** loading to 20 mol% and could not be isolated.

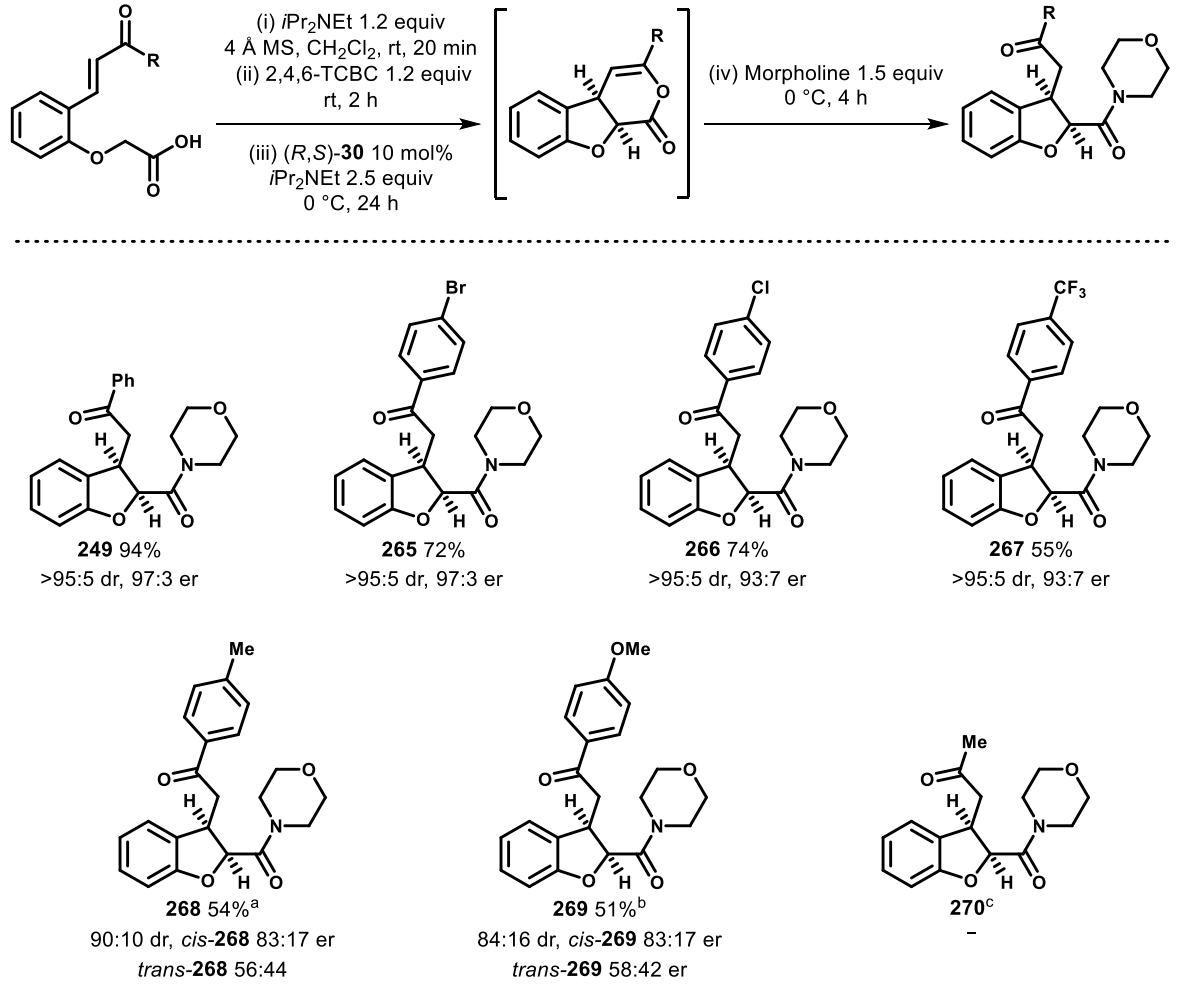


Table 20: Enone-acid scope.

(a) Isolated as a 91:9 mixture of diastereoisomers; (b) Isolated as a 92:8 mixture of diastereoisomers containing grease (c) Use of 20 mol% precatalyst **30** loading; **270** could not be isolated.

3-1-6 Proposed stereochemical model

Similarly to the previous chapter (Section 1-4), a pre-transition state assembly is proposed based on literature precedents not only on intramolecular processes,[79] but also the computational studies on intermolecular [4+2] *endo*-hetero-Diels–Alder from Bode, Kozlowski *et al*. (Figure 12).[48]

Whether the pathway is a concerted or a stepwise one, the enantiocontrol obtained is consistent with the enolate adopting a (*Z*)-geometry and being periplanar to the triazolium ring and orthogonal to the mesityl group. Having the hydrogen on C(2) of the enolate pointing towards the mesityl group, possibly stabilised a CH–π interaction (highlighted in green on Figure 12-a). This would help lock the conformation of the enolate with the top (*Re*) face of the enolate moiety is blocked by the indane group.

The enone-moiety preferentially approaches from the bottom (*Si*) face of the enolate in an endocyclic fashion to avoid steric clash with both the indane and the mesityl functional groups of the catalyst. The stereocontrol could be enhanced by further possible electronic interactions, namely the $n_{Oxanion}$–$\pi^*_{Carbonyl}$ that guides the approach of the enone moiety (highlighted in brown on Figure 12-b). These steric and electronic interactions would lead to the preferred formation of the *cis*-product (Figure 12-c).

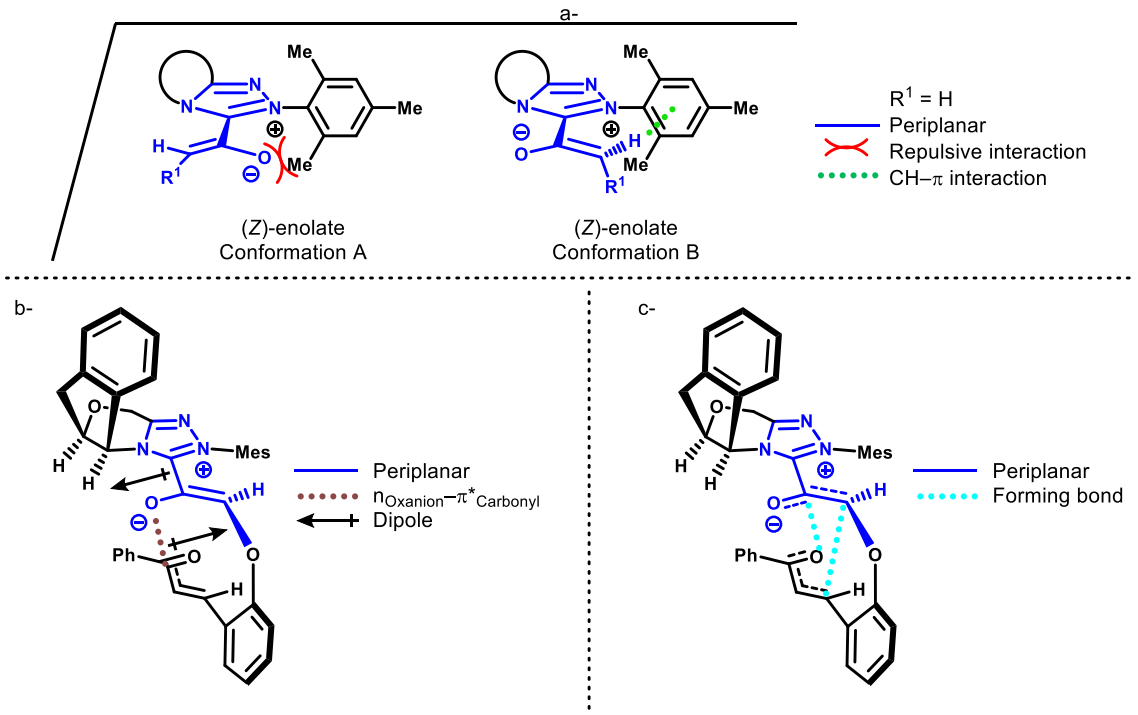
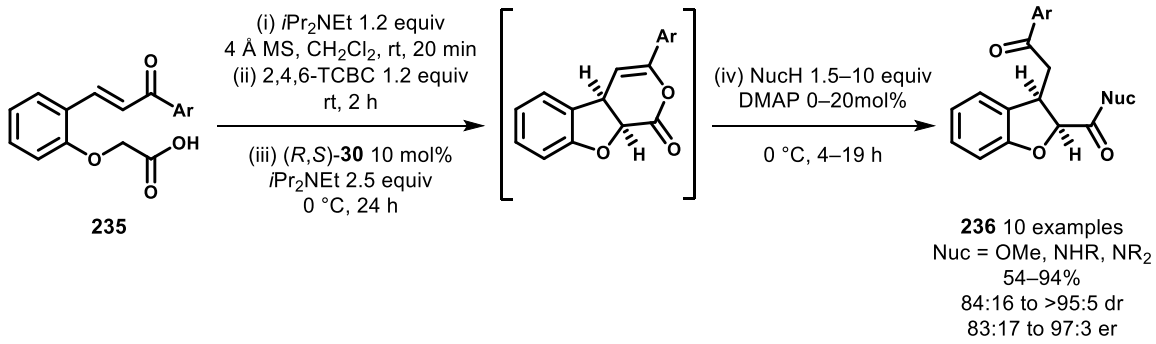


Figure 12: Proposed pretransition state assembly

3-1-7 Summary: NHC-catalysed synthesis of 2,3-disubstituted 2,3-dihydrobenzofuran derivatives

The generation of azolium enolates from enone-acids for the first intramolecular synthesis of dihydrobenzofuran derivatives catalysed by NHC was developed after extensive screening. Products with a preferential *cis*- configuration are generated as when using isothiourea catalysis (Scheme 77).[73] The nucleophile scope gave the desired products in good to excellent yield, diastereo- and enantioselectivity. Finally, results from the enone-acid scope showed that an aromatic substituent on the enone moiety of the starting material was necessary to enable the isolation of the desired dihydrobenzofuran derivatives. Enone-acid **239** (R=Ph) led to the best results in terms of yield, diastereo- and enantiocontrol. Electron withdrawing groups upon the enone were well tolerated but the insertion of electron donating groups led to a significant decrease in yield, diastereo- and enantioselectivity, especially with the 4-$MeOC_6H_4$ substituent.

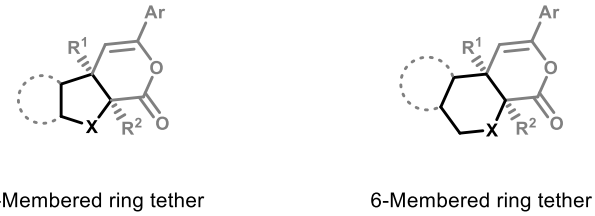


Scheme 77: First NHC-catalysed intramolecular synthesis of dihydrobenzofuran derivatives **236** *via* the generation of azolium enolates from enone-acids **235**.

Next, the viability of this methodology was assessed using alternative enone-acids to generate either quaternary stereocentres, or to prepare alternative carbo- and heterocycles.

3-2 Investigation of the generality of the methodology for the generation of 5- and 6-membered ring tethers

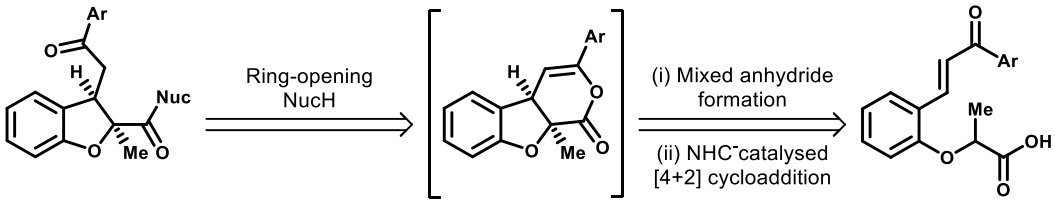
Having developed a successful process toward the formation of 2,3-disubstituted 2,3-dihydrobenzofuran derivatives, the generality of this method was evaluated by testing it not only for the formation of 5-membered ring tethers, but also for the generation of 6-membered ring ones (Scheme 78).



Scheme 78: Schematic representation of 5- and 6-membered ring tether products.

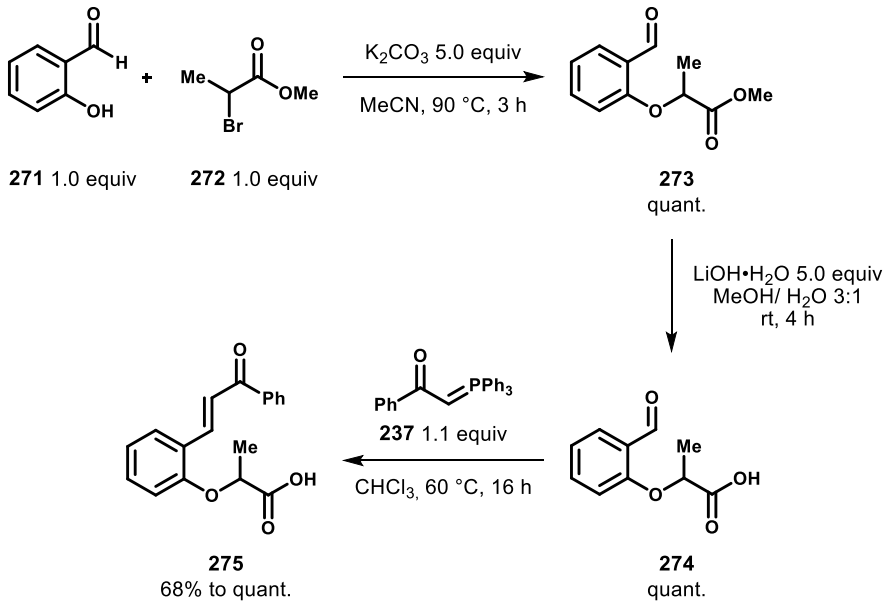
3-2-1 Extension to different 5-membered ring tethers: NHC-catalysed synthesis of dihydrobenzofuran derivatives containing a highly substituted centre

The dihydrobenzofuran derivatives obtained thus far contain two consecutive stereocentres, at C(2) and C(3). The complexity of this motif could be further increased by generating a highly substituted stereocentre at C(2) through the insertion of a substituent, such as a methyl group, on the carbon α- to the carboxylic acid in the starting material (Scheme 79).



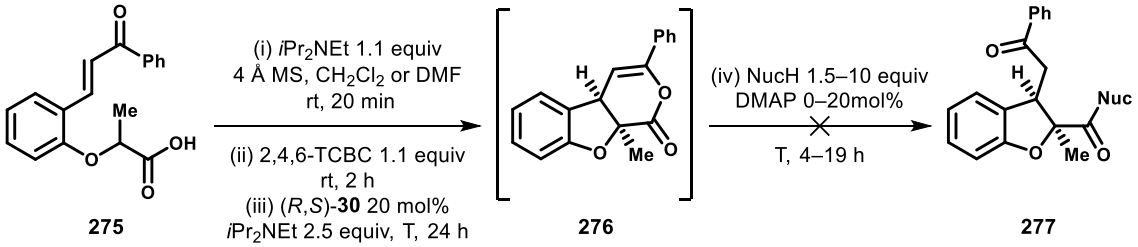
Scheme 79: Retrosynthetic rational for the generation of benzofuran derivatives with a highly substituted centre.

The synthesis of (*E*)-2-(2-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy)propanoic acid **275** was realised in 3 chromatography-free steps, starting from salicylic aldehyde **271**. Following a procedure adapted from Kowalewska and Kwiecień, the alkylation of **271** with methyl 2-bromopropionate gave **272** in quantitative yield.[80] Ester hydrolysis led to the corresponding carboxylic acid **274** in up to quantitative yield. Subsequent Wittig reaction with phosphorane **237** generated the desired enone-acid **275**. The reaction was repeated a number of time and gave **275** in 68% to quantitative yield.



Scheme 80: Synthesis of enone-acid **275** with a methyl group on the acid chain.

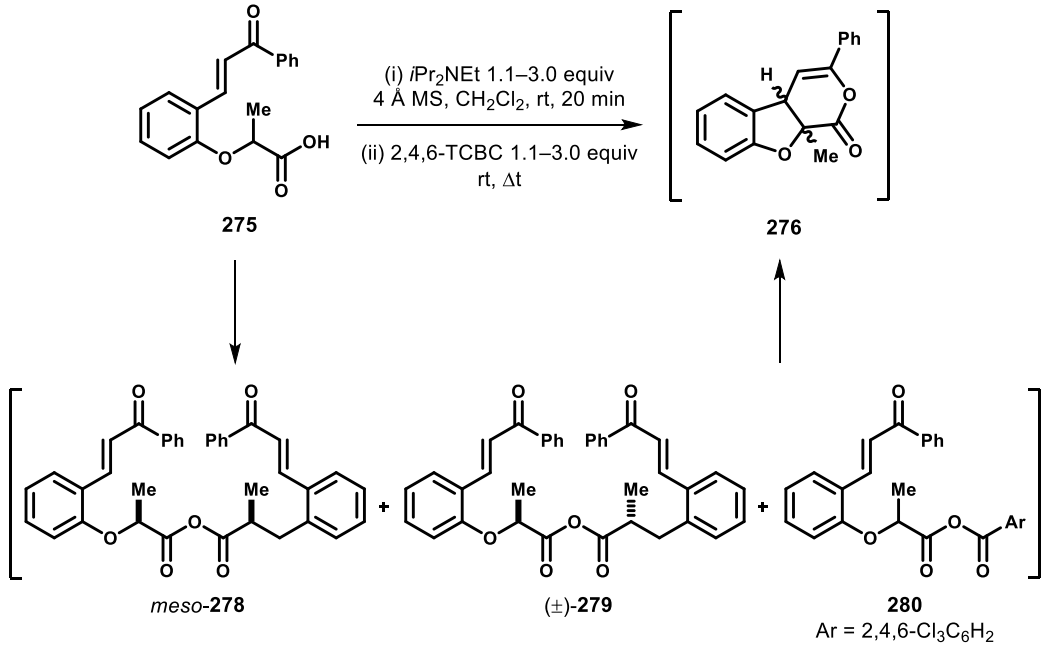
Enone-acid **275** was tested in the catalytic system developed for the synthesis of 2,3-disubstituted 2,3-dihydrobenzofuran derivatives (Section 3-1-3, Scheme 76). The generation of the mixed anhydride was tested using *i*Pr$_2$NEt and 2,4,6-TCBC and catalysis was attempted using a higher 20 mol% precatalyst **30** loading. (Scheme 81). The reaction was first carried out with the catalysis and the ring-opening at 0 °C. ^{1}H NMR spectroscopic analysis of the crude material showed a complex mixture and attempted purification did not lead to the isolation of the desired product but only side-products. Variations of the temperature to rt and 40 °C, the solvent to DMF and the nucleophile used in the ring-opening step were not beneficial.



Scheme 81: Variation of the temperature and solvent for the generation of a highly substituted stereocentre

In an effort to get a better understanding of this system, the formation of the mixed anhydride was monitored by ^{1}H NMR analysis over time and using either 1.1, 2.0 or 3.0 equivalents of *i*Pr$_2$NEt and 2,4,6-TCBC (Scheme 82). Three starting-material-derived species were tentatively assigned based on distinct chemical shifts. A quartet at 4.66 pm (α-proton to the carboxylic acid) and a doublet at 1.66 ppm (CH_3) was identified as the desired mixed anhydride **280**. The two remaining species presented overlapping quartets at 4.93 ppm and

two doublets at 1.71 and 1.64 ppm corresponding to both the *meso*- and *rac*-homoanhydride **278** and **279**. Homoanhydrides **278** and **279** approximatively remained in a 1:1 ratio across the reactions and overall the reaction times, as may be expected due to the starting enone-acid **275** being racemic. Both diastereoisomers of ring-closed product **276** (relative configuration not assigned) were observed as the main products and in 68:32 dr. The rate of formation of the ring-closed product was observed to be greater in the presence of higher equivalents of *i*Pr_2NEt and 2,4,6-TCBC.

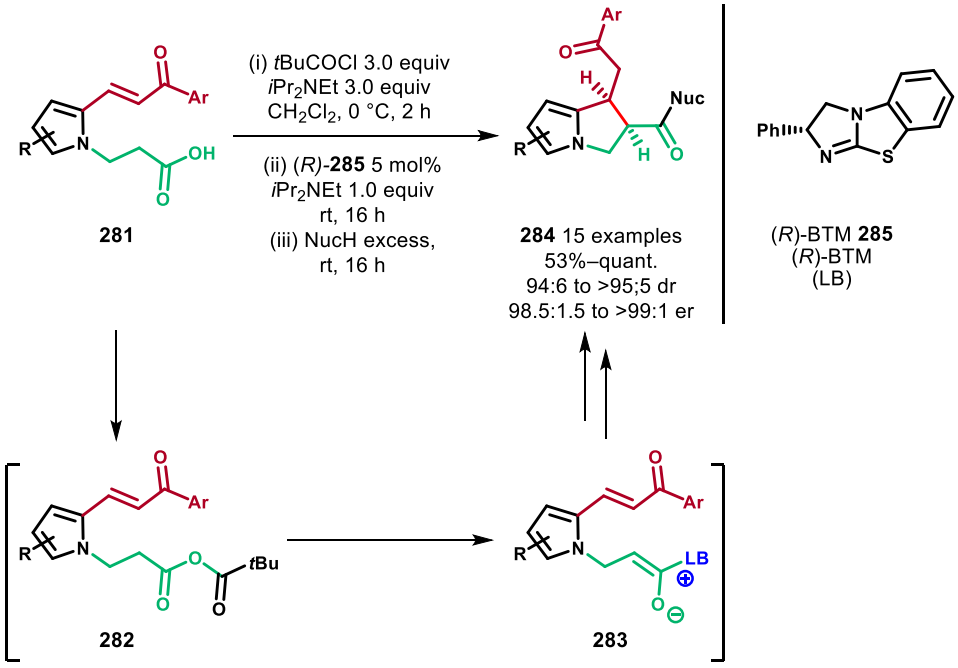


Scheme 82: ^{1}H NMR analysis of the generation of anhydrides from enone-acid **275**.

These observations are consistent with a base-promoted cycloaddition and suggest that formation of the desired enolate, the formal [4+2] cycloaddition of this type of enone-acid is feasible. Increasing the equivalents of 2,4,6-TCBC seems to enable the formation of the different anhydride species quicker than when using only 1.1 equivalents. For an enantioselective version of this reaction, the NHC-catalysed formal [4+2] cycloaddition needs to outcompete the base-promoted cyclisation. This may be achieved by varying solvent, temperature, base or investigating the addition of precatalyst **30** during the formation of the mixed anhydride.

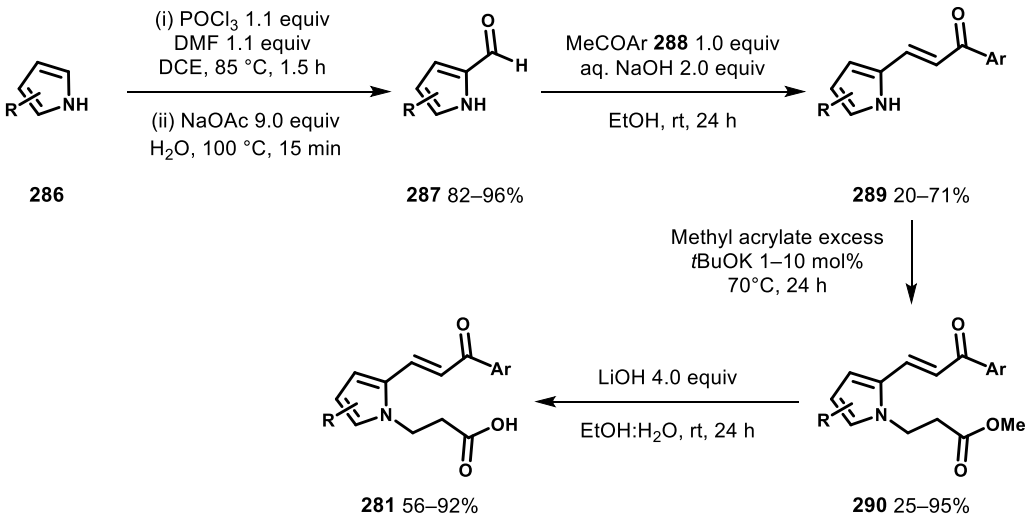
3-2-2 Extension to different 5-membered ring tethers: Attempted NHC-catalysed synthesis of pyrrolyzines derivatives

5,5-Bicyclic pyrrolizines are alkaloids with a nitrogen atom at the bridgehead. This motif is present in many natural products with diverse biological activities and is therefore a target of interest in the development of organocatalytic processes.[81] Previous work in the Smith group focused on the synthesis of chiral 5,5-biyclic pyrrolizines using the corresponding pyrrole-derived enone-acids **281** (Scheme 83).[82] Enone-acid **281** reacted with pivaloyl chloride and *i*Pr$_2$NEt to form mixed anhydride **282**. Intramolecular cyclisation was catalysed by (*R*)-BTM **285** (5 mol%). The ring-opening proceeded in the presence of excess nucleophile to give the desired 2,3-disubstituted 2,3-dihydropyrrolizine amide or ester products **284** in excellent dr and er and in 53% to quantitative yield.



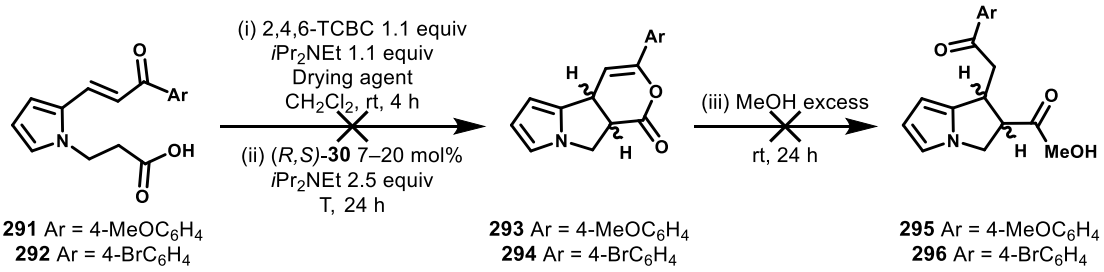
Scheme 83: Isothiourea-catalysed intramolecular formal [4+2] cycloaddition toward the synthesis of 5,5-bicyclic pyrrolizines derivatives **284**.

In this paper, pyrrole-derived enone-acids **281** were obtained in a 4-step synthesis from the corresponding pyrrole **286** in up to 56% overall yield on a multi-gram scale (Scheme 84).[82] Pyrrole 2-carboxaldehyde **287** were obtained *via* a Vilsmeier-Haack formylation of the requisite pyrrole. An aldol condensation between pyrrole 2-carboxaldehyde **287** and ketone **288** gave pyrrole-enone **289**. The next step consisted of an *N*-alkylation with methyl acrylate, followed by ester hydrolysis to provide the desired enone-acids **281**.



Scheme 84: Synthesis of pyrrole-derived enone-acid **281**.

The aim of this project was to investigate if NHC precatalyst **30** could give access to the same type of products **284**. The synthesis of pyrrolizine derivatives was attempted starting from already available in-house pyrrole-derived enone-acids **291** and **292** (Table 21). The reaction was first tried using enone-acid **291** at rt with 20 mol% precatalyst **30** loading (Table 21, Entry 1). A complex mixture was observed by ^{1}H NMR analysis of the crude reaction mixture. Enone-acid **292** was tried next with a slightly different procedure, with *i*Pr$_2$NEt added portionwise in the catalysis step (Table 21, Entry 2). Observation of the changes in the reaction mixture during the catalysis and ^{1}H NMR analysis of the crude reaction mixtures seems to indicate that side-reactions started as soon as the free carbene was generated. Therefore, the catalysis was tried with slow addition of a solution of 0.04 M of precatalyst **30** in CH_2Cl_2 (increased dilution of the catalyst), but disappointingly after adding 0.35 mL (7 mol%), similar results were observed (Table 21, Entry 3). The reaction was then attempted at –10 °C and provided a complex reaction containing methyl ester derivative of the starting material (Table 21, Entry 4). The reaction was tried with $MgSO_4$ instead of molecular sieves and without any drying agent, but similar results were obtained (Table 21, Entries 5 and 6).



	Activation		Catalysis	
Entry	**Ar**[a]	**Drying agent**	**T**	**Catalyst loading**
1	4-$MeOC_6H_4$	4 Å MS	rt	20 mol%
2[b]	4-BrC_6H_4	4 Å MS	rt	20 mol%
3	4-$MeOC_6H_4$	4 Å MS	rt	7 mol%[c]
4	4-$MeOC_6H_4$	4 Å MS	−10 ºC	20 mol%
5	4-$MeOC_6H_4$	$MgSO_4$[d]	−10 ºC	20 mol%
6	4-$MeOC_6H_4$	–	−10 ºC	20 mol%

Table 21: Attempted synthesis of 5,5-bicyclic pyrrolizines **295** and **296**.

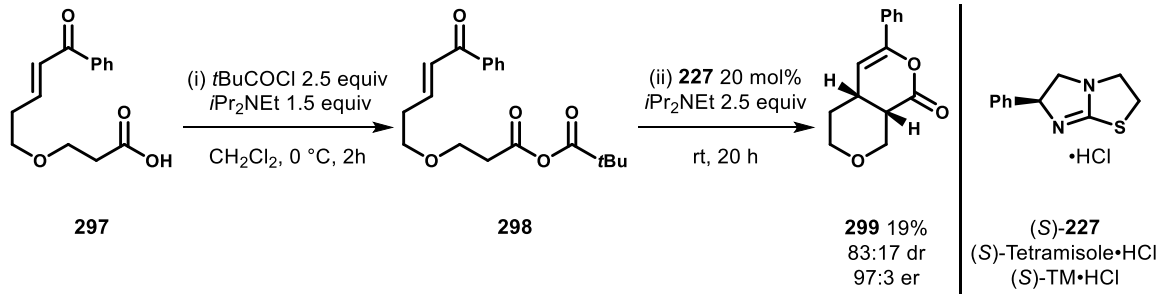
(a) Synthesised by Dr D. G. Stark in-house; (b) After addition of precatalyst **30**, *i*Pr_2NEt was added portionwise (1.1 equiv. *then* 1.4 equiv); (c) Addition of 0.35 mL of 0.04 M precatalyst **30** in CH_2Cl_2; (d) Dried in the oven for several hours.

Several sets of conditions were tried but were not meet with any success. Indeed, complex mixtures devoid of the desired products, and containing enone-acid derivatives at best, were obtained. The side-reactions seem to happen upon deprotonation of the precatalyst **30** to form its free carbene equivalent, making it impossible to obtain the desired chiral 5,5-bicyclic pyrrolizines.

Following these results, the generation of 6-membered ring tethers through NHC-catalysed intramolecular formal [4+2] cycloaddition was investigated next.

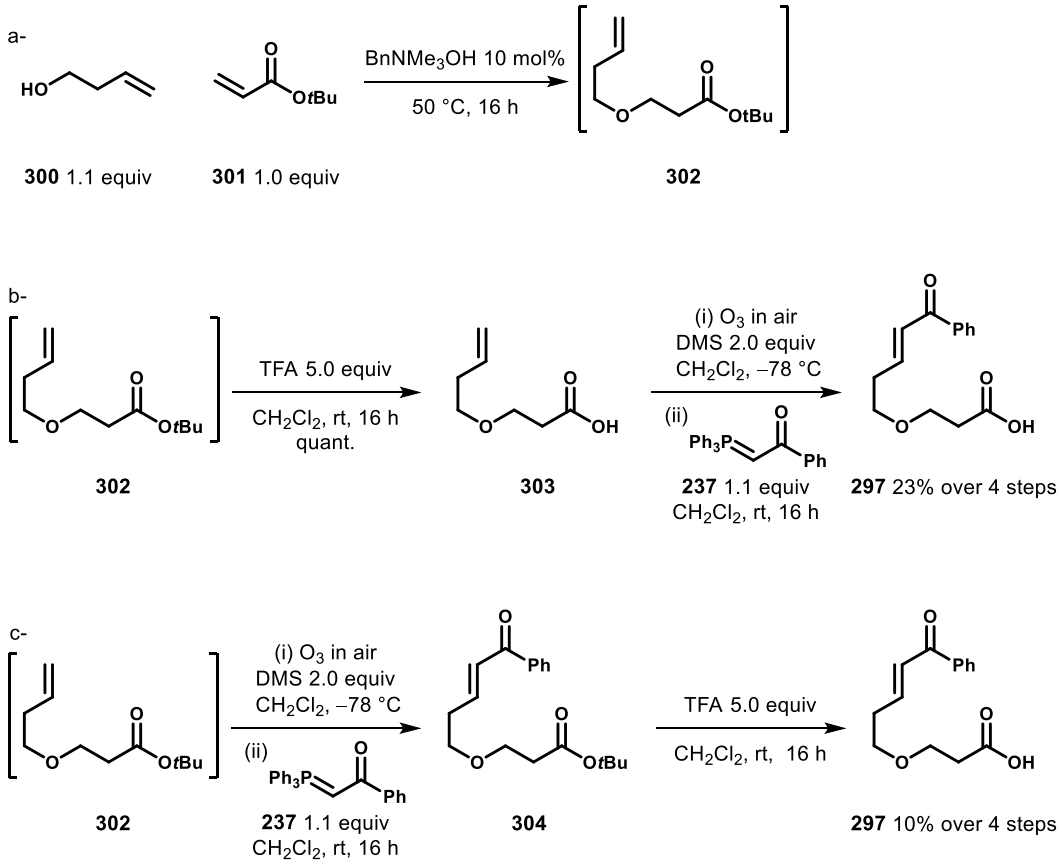
3-2-3 Extension to 6-membered ring tethers: Synthesis of a tetrahydropyran derivative

A few reports have been published on organocatalytic intramolecular formal [4+2] cycloadditions for the generation of 6-membered ring tethers.[83] Therefore, the viability of the model system developed for the synthesis of 2,3-disubstituted 2,3-dihydrobenzofurans (Section 3-1-3, Scheme 76) was tested toward the formation of 6-membered rings. Initial studies have been done the Smith group on enone-acid **297** in an isothiourea-catalysed process (Scheme 85).[84] Upon deprotonation of **297** by *i*PrNEt$_2$ and reaction with pivaloyl chloride, mixed anhydride **298** was formed. The intramolecular formal [4+2] cycloaddition using (*S*)-**227** (20 mol%) gave the desired tetrahydropyran derivative **299** that could be isolated in low 19% yield, moderate 83:17 dr and high 97:3 er. X-Ray crystallography analysis of **299** confirmed the absolute configuration to be (4a*R*,8a*S*).



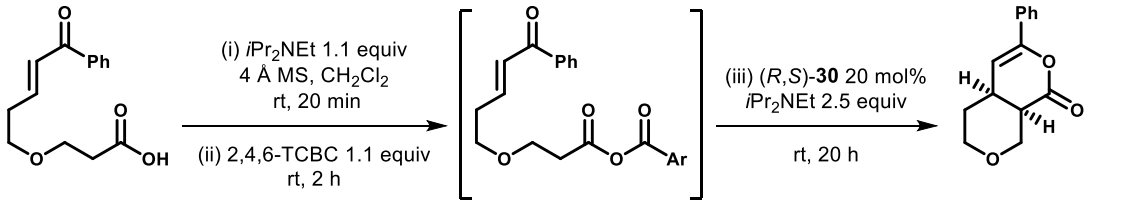
Scheme 85: Isothiourea-catalysed [4+2] cycloaddition toward the synthesis of dihydropyranones derivative **299**.

The synthesis of the starting material was adapted from a procedure developed in the Smith group (Scheme 86). The first step consists in *O*-alkylation of 3-buten-1-ol **300** with *tert*-butyl acrylate **301** (Scheme 86-a). Ester hydrolysis using TFA led to **302** and was followed by ozonolysis and Wittig reaction to give the desired enone-acid **297** as an oil in about 23% yield over 4 steps but alongside impurities (Scheme 86-b). No further purification of **297** was possible due to its instability on silica. A modified pathway was tried from alkene-acid **302** (Scheme 86-c). Ozonolysis and Wittig reaction with phosphorane **237** led to **304**, which was hydrolysed to give **297** in 10% yield over 4 steps. The desired enone-acid was obtained in high purity after aqueous work up.



Scheme 86: Synthesis of enone-acid **297**.

With the starting material in hand, the model reaction was performed. After unsuccessful results when the reaction was tried with 5 and 10 mol% precatalyst **30** loadings, even at higher temperature, the reaction was tested with 20 mol% precatalyst **30** at rt. The desired *cis*-tetrahydropyran derivative **299** was afforded in 50% yield and >99:1 er and identified as (4a*S*,8a*R*)-**299** by comparison with HPLC analysis (Scheme 87).

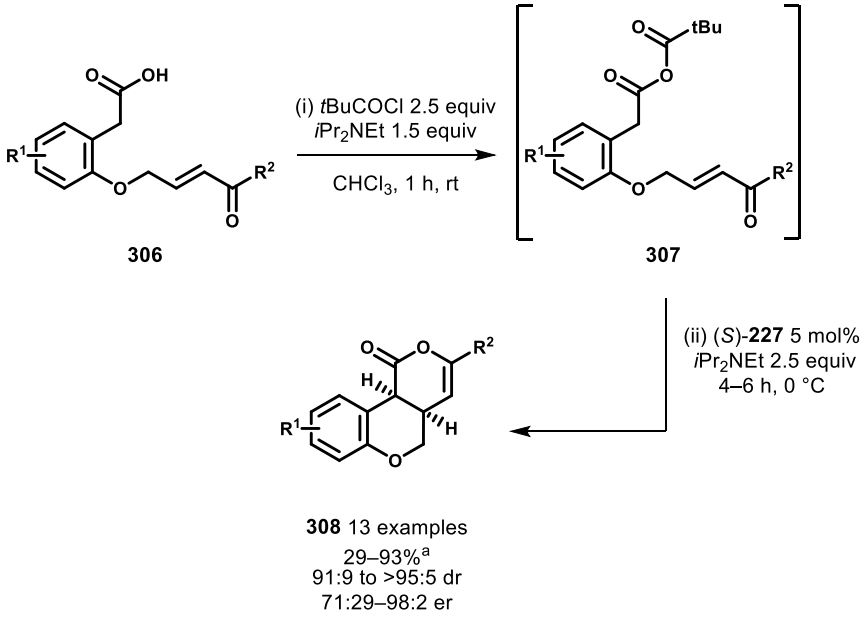


Scheme 87: First NHC-catalysed intramolecular synthesis of dihydropyranone derivative **299** *via* the generation of azolium enolate from enone-acid **297**.

(a) Determined on ^{1}H NMR spectroscopic analysis on the crude reaction; Isolated yield following column chromatography.

3-2-4 Extension to 6-membered ring tethers: Synthesis of a chromenone derivative

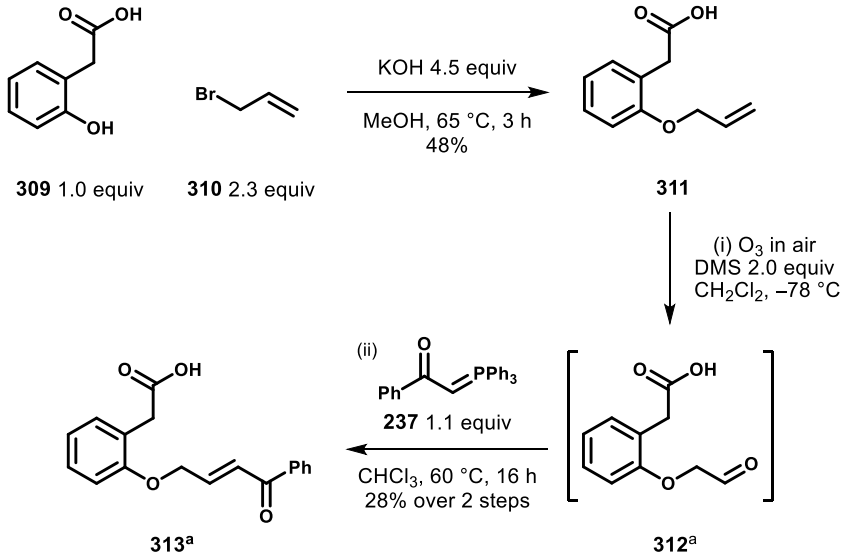
A recent paper by the Smith group reported the first synthesis of chromenone derivatives **308** through an intramolecular formal [4+2] cycloaddition from enone-acids **306** and catalysed by isothiourea catalyst (*S*)-**227** (Scheme 88).[83c] The desired products were obtained in low to excellent yield of both diastereoisomers and in 91:9 to > 95:5 dr and moderate to excellent er. To avoid product epimerisation, the reaction mixture had to be quenched with 1 M HCl at 0 °C.



Scheme 88: Isothiourea-catalysed [4+2] cycloaddition toward the synthesis of dihydrochromenone derivatives **308**.

(a) Combined isolated yield of diastereoisomers.

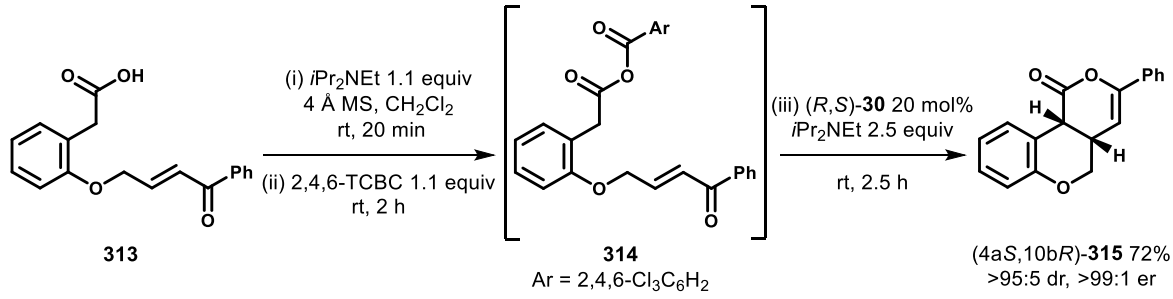
Enone-acid **313** (R^1 = H, R^2 = Ph) was chosen to examine if the developed NHC-catalysed methodology could be applied to the synthesis of chromenone. Enone-acid **313** was synthesised in 3 steps from 2-hydrophenylacetic acid **309** (Scheme 89).[83c] Alkylation of **309** with allyl bromide **310** led to **311** in 48% yield in a chromatography-free procedure. Ozonolysis and Wittig reaction led to the desired enone-acid **313** in 28% yield over 2 steps.



Scheme 89: Synthesis of enone-acid **313**.

(a) Synthesised by R. M. Neyyappadath.

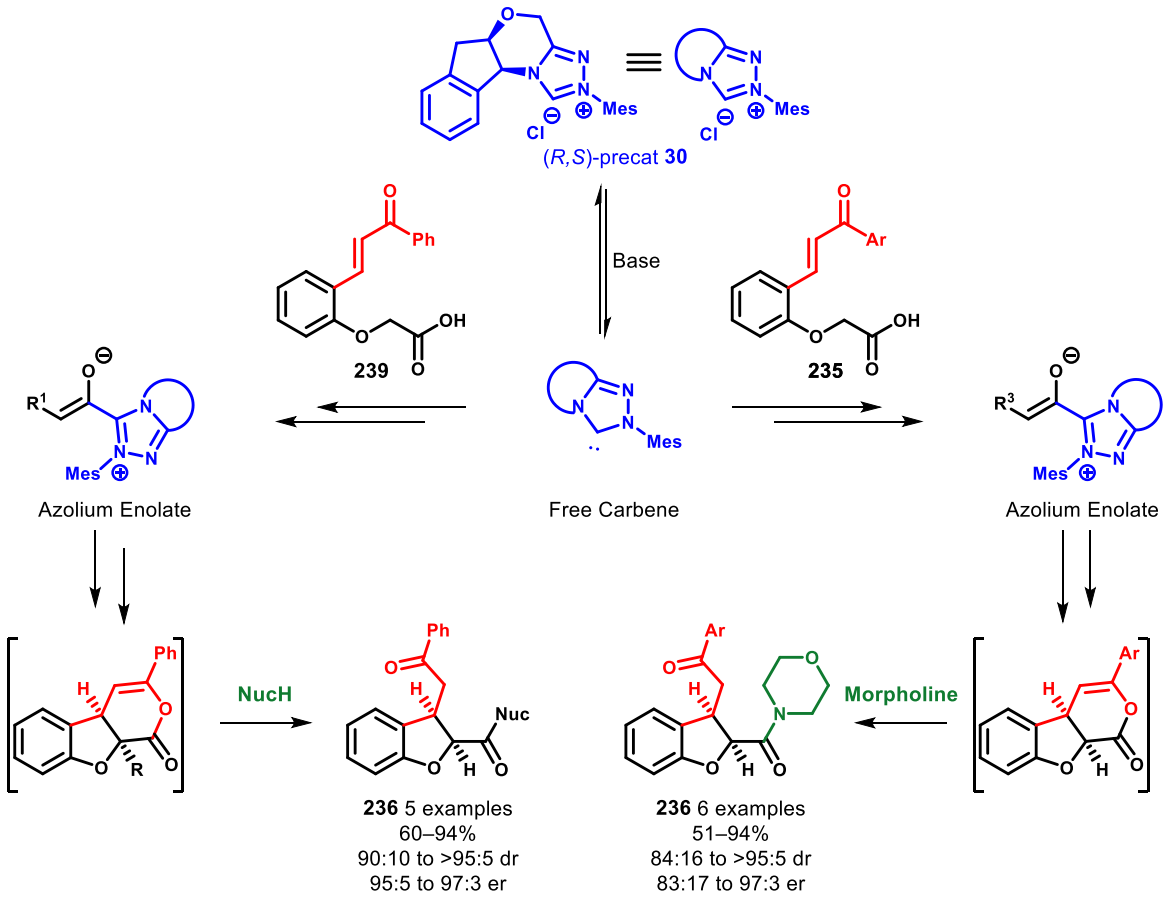
The reaction was tested in the system developed for the NHC-catalysed synthesis of dihydrobenzofurans (Section 3-1-3, Scheme 76) using an increased 20 mol% precatalyst **30** loading (Scheme 90). The reaction was performed at rt and did not require any work up as the reaction mixture was simply concentrated under reduced pressure and purified by column chromatography. The desired dihydrochromenone derivative **315** was obtained in 72% yield, >95:5 dr and >99:1 er and identified as (4a*S*,10b*R*)-**315** by comparison with literature HPLC analysis and specific rotation values.[83c] This is a promising proof of concept that the enantio and diastereoselective formation of dihydrochromenone derivatives can be catalysed by NHC precatalyst **30** as well as isothiourea **227**.



Scheme 90: First NHC-catalysed intramolecular synthesis of dihydrochromenone derivative **315** *via* the generation of azolium enolates from enone-acids **313**.

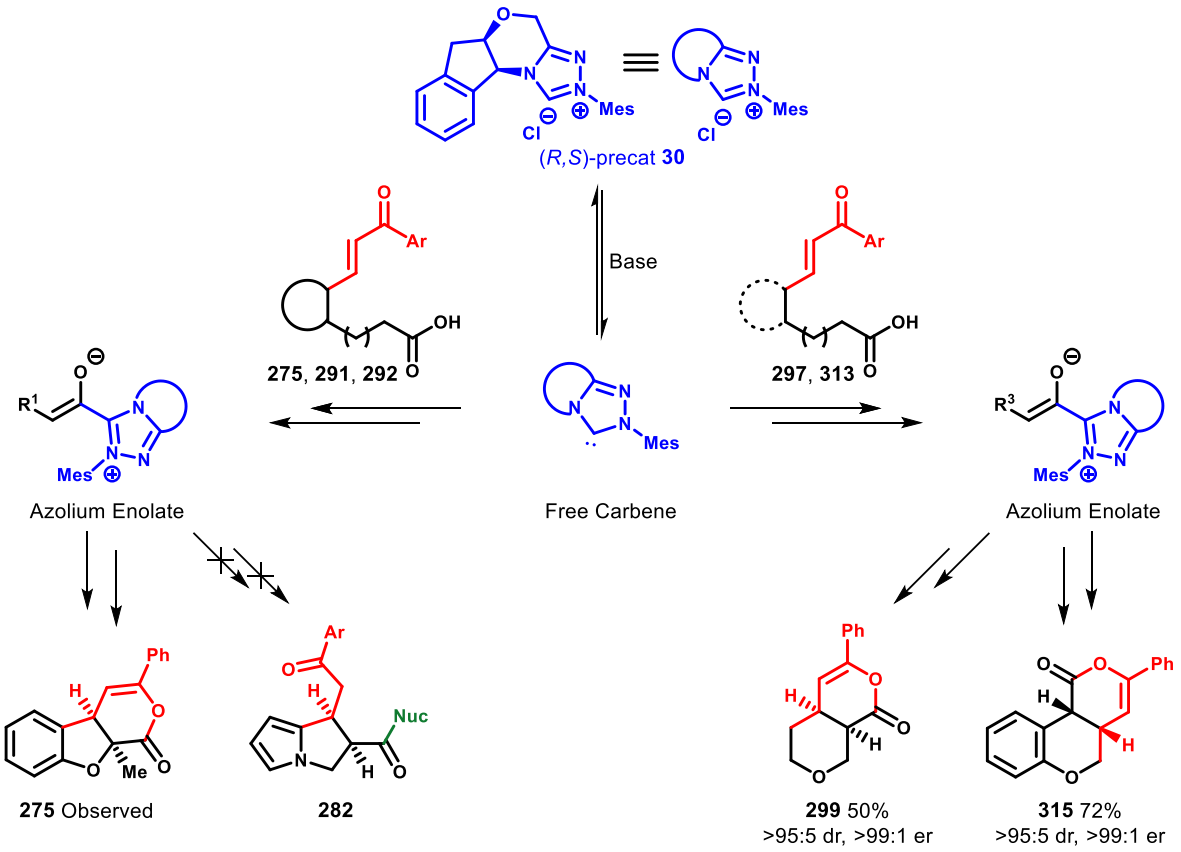
3-3 Conclusions

In this chapter, an NHC-catalysed intramolecular formal [4+2] cycloaddition methodology through the generation of azolium enolate from carboxylic acids toward the formation of 5-membered rings was developed. It successfully generated of 2,3-disubstituted 2,3-dihydrobenzofurans **236**.



Scheme 91: NHC-catalysed intramolecular formal [4+2] cycloaddition through the generation of azolium enolate from carboxylic acids toward the formation of dihydrobenzofuran derivatives.

This system was tested with different types of enone-acids for proof-of concept. For the generation of different 5-membered ring tethers, the use of enone-acid **275** is promising and will require more investigations while pyrrole-derived enone-acids **281** did not show any reactivity toward the synthesis of the desired products **284**. The generation of 6-membered ring tethers such as dihydropyranone and dihydrochromenone derivatives **299** and **315** was successful. Dihydropyranone derivative **299** was obtained in good yield and excellent diastereo- and enantiocontrol. Chromenone derivative **315** was afforded in high yield and excellent diastereo-and enantioselectivity.



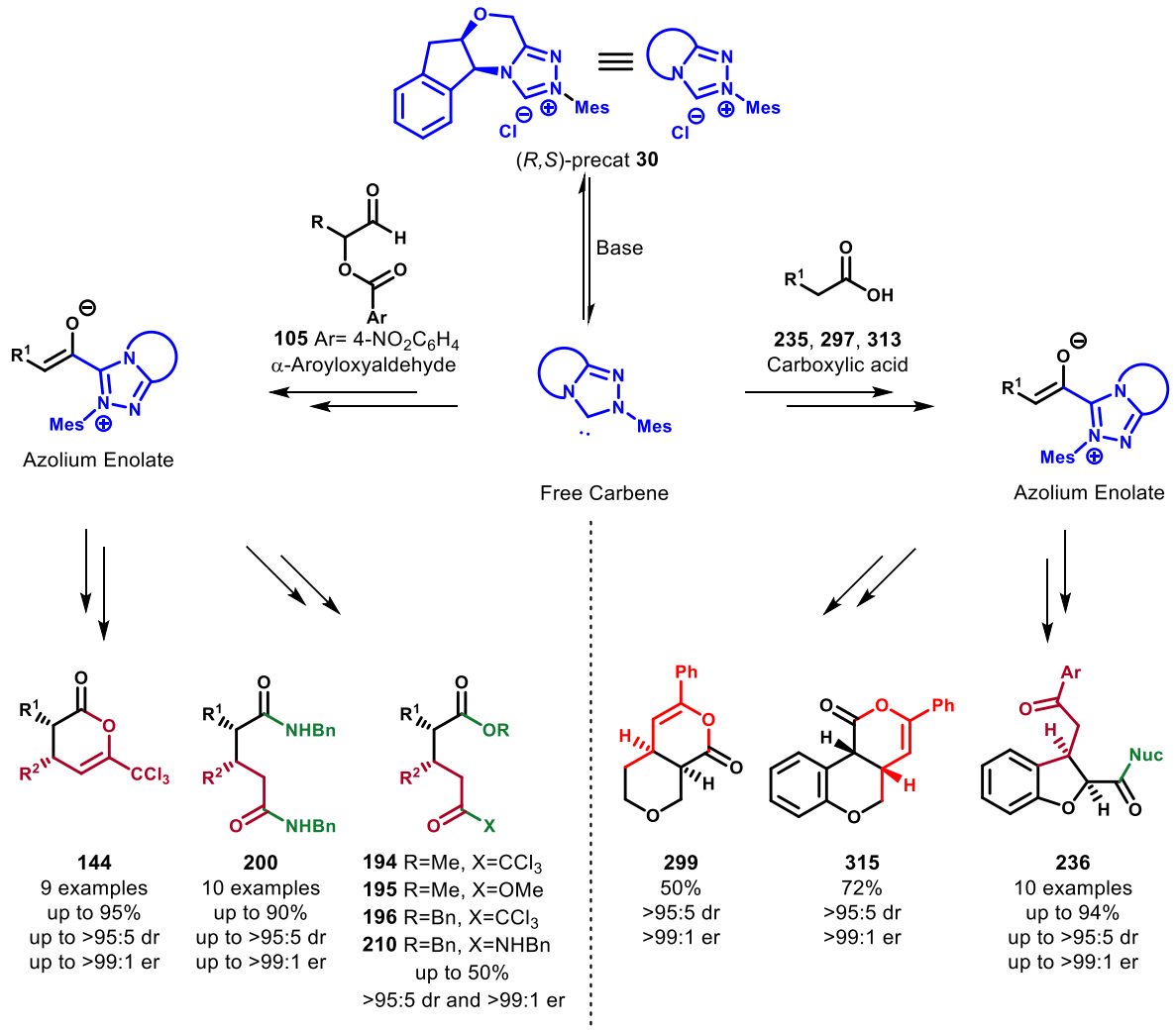
Scheme 92: NHC-catalysed intramolecular formal [4+2] cycloaddition through the generation of azolium enolate from carboxylic acids toward the generation of 5- and 6-membered ring tethers.

Conclusions

Azolium enolates are useful and versatile synthetic tools. Nevertheless, their precursors can present a lack of stability or unwanted reaction pathways. One of the most powerful NHC precatalysts used in this context is *N*-mesityl substituted aminoindane based triazolium precatalyst **30**. This thesis has described the use of bench stable alternative azolium enolate precursors in novel NHC-catalysed formal [4+2] cycloadditions employing *N*-mesityl substituted aminoindane based triazolium precatalyst **30** (Scheme 93).

The synthetic utility of α-aroyloxyaldehydes **105** as azolium enolate precursors has been extended to *endo*-hetero-Diel–Alder reactions with α,β-unsaturated trichloromethyl ketones **143** for the synthesis of *syn*-dihydropyranones **144** in 26 to 95% yield with excellent diastereo- and enantiocontrol. A chromatography-free sequential [4+2] hetero-Diel–Alder/ring-opening/aminolysis with benzylamine led to diamides **200** in up to 90% yield and excellent diastereo- and enantioselectivity, showing the ability of trichloromethyl ketones **143** to act as amides surrogates. Ketoesters **194** and **196** could also be synthesised in up to 50% yield and excellent stereoselectivity, allowing the synthesis of a bifunctional compound **210** in 32% over three steps from the corresponding α-aroyloxyaldehyde in excellent diastereo- and enantioselectivity.

In order to broaden the synthetic utility of azolium enolates, the search for a stable, available and inexpensive precursors led to the development of the first intramolecular NHC-catalysed formal [4+2] cycloaddition of enone-acids. A one-pot cycloaddition/nucleophilic ring-opening led to the synthesis of 2,3-disubstituted 2,3-dihydrobenzofurans derivatives **236** in up to 94% yield with good to excellent diastereo- and enantiocontrol. The methodology could not be extended to the formation of pyrrolizine derivatives but proved successful for the generation of 6-membered ring products such as pyranone and chromenone derivatives **299** and **315** in good to high yield and with excellent diastereo- and enantioselectivity.



Scheme 93: Summary.

Preliminary results were obtained on the formation of sterically hindered benzofuran derivatives bearing a quaternary centre and is a potential area to develop this methodology further.

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4- Experimental details

All reactions involving moisture sensitive reagents were performed under inert atmosphere (nitrogen or argon) using standard vacuum line techniques and freshly dried solvents. All glassware was flame dried and allowed to cool under vacuum. Anhydrous diethyl ether (Et_2O), tetrahydrofuran (THF), toluene (PhMe), and dichloromethane (CH_2Cl_2) were obtained from a solvent purification system (MBraun, SPS-800). All other solvents and commercial reagents were usedas received without further purification unless otherwise stated. Petrol is defined as petroleum ether 40−60 °C. Room temperature (rt) refers to 20–25 °C. Temperatures of 0 °C, −10 °C and –78 °C were obtained using ice/water, ice/water/salt baths and CO_2(s)/acetone baths, respectively. Temperatures of 0 °C to –78 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reaction involving heating were performed using DrySyn blocks and a contact thermocouple.

Under reduced pressure refers to the use of either a Büchi Rotavapor R-200 with a Büchi V-491 heating bath and Büchi V-800 vacuum controller, a Büchi Rotavapor R-210 with a Büchi V-491 heating bath and Büchi V-850 vacuum controller, a Heidolph Laborota 4001 with vacuum controller, an IKA RV10 rotary evaporator with a IKA HB10 heating bath and ILMVAC vacuum controller, or an IKA RV10 rotary evaporator with a IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL601 Recirculating Coolers filled with ethylene glycol and set to –5 °C.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm) and/or staining with either aqueous $KMnO_4$ solution, ethanolic phosphomolybdic acid, or ethanolic Vanillin solution followed by heating. Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated. Automated chromatography was performed on a Biotage Isolera Four running Biotage OS578 with a UV/Vis detector using the method stated and cartridges filled with Kieselgel 60 silica.

Melting points were recorded on an Electrothermal 9100 melting point apparatus, (dec) refers to decomposition.

Optical rotations were measured on a PerkinElmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained on a Shimadzu HPLC consisting of a DGU-20A5 degasser, LX-20AT liquid chromatograph, SIL-20AHT autosampler, CMB-20A column oven with

variable temperature setting (25−40 °C). Separation was achieved using Chiralcel OD-H and OJ-H columns or Chiralpak AD-H, AS-H, IA and IB columns. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra.

GC analyses were obtained on a Shimadzu GC consisting of a Shimadzu AOC-20i auto injector and a Shimadzu GC-2025 gas chromatograph. Analysis was performed using Shimadzu GCsolution v2.41 software and separation was achieved using the column described.

Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wavenumbers (ν_{max}) reported in cm^{-1}.

^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ NMR spectra were acquired on either a Bruker AV300 with a BBFO probe (^{1}H 300 MHz; $^{13}C\{^{1}H\}$ 75 MHz; $^{19}F\{^{1}H\}$ 282 MHz), a Bruker AV400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz; $^{19}F\{^{1}H\}$ 377 MHz), a Bruker AVII 400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz; $^{19}F\{^{1}H\}$ 376 MHz), a Bruker AVIII-HD 500 with a SmartProbe BBFO+ probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz, $^{19}F\{^{1}H\}$ 470 MHz), a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz, $^{19}F\{^{1}H\}$ 470 MHz), or a Bruker AVIII-HD 700 with a CryoProbe Prodigy TCI probe (^{1}H 700 MHz, $^{13}C\{^{1}H\}$ 176 MHz, ^{19}F 659 MHz) in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples thereof. The abbreviation Ar denotes aromatic, br denotes broad and app denotes apparent. NMR peak assignments were confirmed using 2D ^{1}H correlated spectroscopy (COSY), 2D ^{1}H nuclear Overhauser effect spectroscopy (NOESY), 2D ^{1}H-^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D ^{1}H-^{13}C heteronuclear single quantum coherence (HSQC) where necessary.

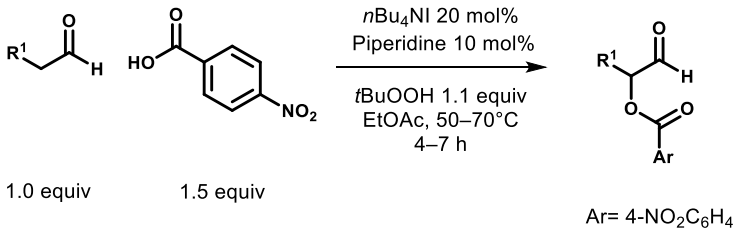
Mass spectrometry (*m/z*) data were acquired by either electrospray ionisation (ESI), chemical ionisation (CI), electron impact (EI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionization (APCI) or nanospray ionisation (NSI) at the EPSRC UK National Mass Spectrometry Facility at Swansea University ($[A]^{+}$ or $[A]^{-}$ quoted).

NHC precatalyst **30** was synthesized according to literature procedure[47]and authentic racemic samples were prepared using (±)-**30**.

4-1 Experimental for chapter 2: α-Aroyloxyaldehydes as azolium enolate precursors in intermolecular [4+2] cycloadditions with trichloromethyl ketones

4-1-1 General Procedures for chapter 2

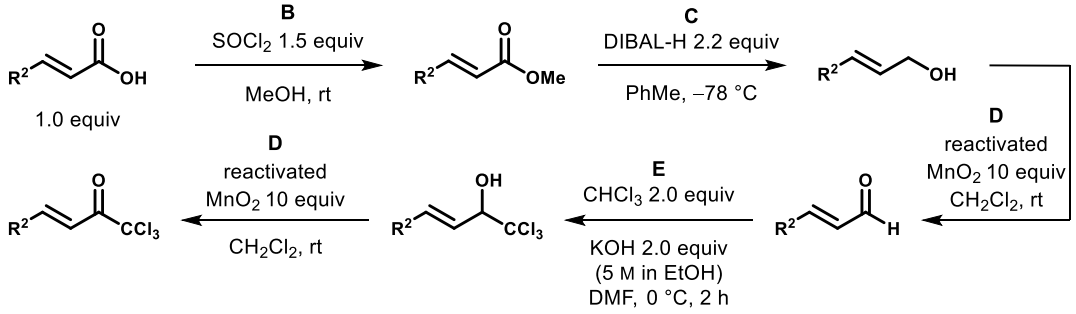
Synthesis of α-aroyloxyaldehydes



General procedure A: Direct α-aroyloxylation of aldehydes with 4-nitrobenzoic acid

From an adapted procedure of Ishihara *et al.*,[1] the required aldehyde (1.0 equiv), 4-nitrobenzoic acid (1.5 equiv), *n*Bu$_4$NI (20 mol%) and piperidine (10 mol%) were dissolved in EtOAc (0.2 M). *t*BuOOH (ca. 5.5 M in decane, 1.1 equiv) was added and the reaction mixture was heated at the temperature stated. The reaction mixture was cooled to rt before being quenched with Na_2SO_4 and with EtOAc (× 2). The organic layer was washed with saturated $NaHCO_3$ (× 2) and brine (× 2) before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product that was purified by flash silica column chromatography to give the desired product.

Synthesis of trichloromethyl ketones



General procedure B: Methyl ester formation

From an adapted procedure of Jørgensen *et al.*,[2] the required acrylic acid (1.0 equiv) was dissolved in MeOH (0.5 M). $SOCl_2$ (1.5 equiv) was added at 0 ºC and the reaction was stirred at 0 ºC for 30 min, then allowed to warm up to rt o/n. The reaction mixture was concentred under reduced pressure to give the crude product which was used without further purification.

General procedure C: DIBAL-H reduction

From an adapted procedure of Jørgensen *et al*.,[2] the required methyl ester (1.0 equiv) was dissolved in PhMe (0.3 M). DIBAL–H (2.2 equiv) was added dropwise at –78 ºC. The reaction mixture was stirred at –78 ºC for 3 h. MeOH was added and the reaction was further stirred for 1 h before adding a saturated La Rochelle salt solution. The mixture was stirred for 1 h at –78 ºC, then warm to rt before being filtered on celite. The resulting mixture was washed with brine (2 ×). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product which was used without further purification.

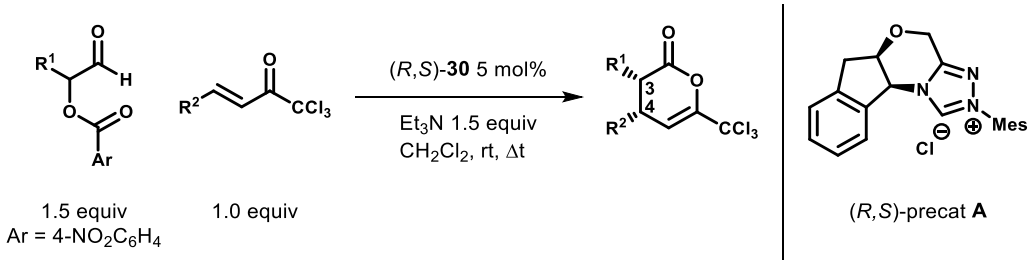
General procedure D: MnO_2 oxidation of allylic alcohol

From an adapted procedure of Patil and Singh,[3] the required allylic alcohol (1.0 equiv) was dissolved in CH_2Cl_2 (0.5 M). Pre-activated MnO_2 (10 equiv) was added stepwise and the reaction was stirred at rt until complete by TLC analysis. The mixture was filtered on celite and concentrated under reduced pressure to give the crude product.

General procedure E: Trichloromethylation of aldehyde

Following the procedure by Zhao *et al*.,[4] the required aldehyde (1.0 equiv) was added to a solution of chloroform (2.0 equiv) in DMF (1.47 M) at rt. The reaction mixture was stirred at rt for 20 min then cooled to 0 ºC before a solution of KOH (2.0 equiv) in EtOH (6 M) was added dropwise. The reaction was stirred at the temperature stated until complete by TLC analysis. The reaction mixture was acidified with 1 M HCl and extracted with EtOAc (× 2). The organic phase was washed successively with water (× 2) and brine (× 3) before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product.

NHC-catalysed redox [4+2] hetero-Diels-Alder reaction of α-aroyloxyaldehydes with α,β-unsaturated trichloromethyl ketones

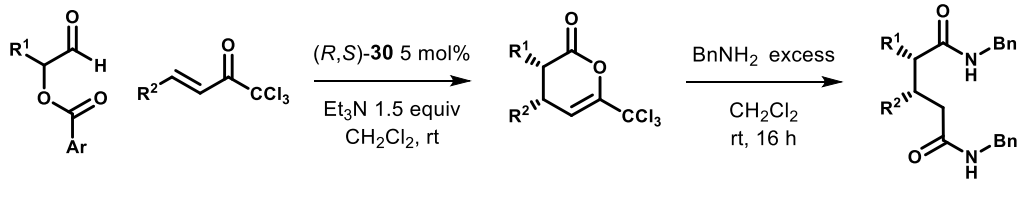


General procedure F: Synthesis of *syn*-dihydropyranone derivatives

The required α-aroyloxyaldehyde (0.30 mmol, 1.5 equiv), the appropriate trichloromethyl ketone (0.20 mmol, 1.0 equiv) and NHC precatalyst **30** (0.010 mmol, 5 mol% or 0.020 mmol, 10 mol%) were dissolved in anhydrous CH_2Cl_2 (2.7 mL). Et_3N (0.30 mmol, 1.5 equiv) was added and the reaction mixture was stirred at rt until complete by TLC analysis. The mixture was diluted in EtOAc (10 mL) and washed with sodium bisulfite aq. 40% (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product that was purified by flash silica column chromatography to give the desired *syn*-dihydropyranone.

Authentic racemic samples were prepared in an analogous fashion using (±)-**30**. The diastereoisomeric ratio was determined by crude ^{1}H NMR analysis through comparison of the integration for the C(5)*H* signal of the two diastereoisomers.

NHC-catalysed redox [4+2] hetero-Diels-Alder reaction followed by ring-opening and aminolysis



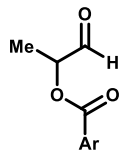
General Procedure G: Synthesis of highly functionalised diamides

The required α-aroyloxyaldehyde (0.30 mmol, 1.5 equiv), the required trichloromethyl ketone (0.20 mmol, 1.0 equiv) and NHC precatalyst **30** (0.010 mmol, 5 mol% or 0.020 mmol, 10 mol%) were dissolved in anhydrous CH_2Cl_2 (2.7 mL). Et_3N (0.30 mmol, 1.5 equiv) was added and the reaction mixture was stirred at rt until complete by TLC analysis. The mixture was diluted in EtOAc (10 mL) and washed with water (10 mL × 2), sodium bisulfite aq. 40% (10 mL × 2) and brine (10 mL × 2). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude *syn*-dihydropyranone product. The crude was dissolved in anhydrous CH_2Cl_2 (6.6 mL) and benzylamine (60 mmol, 300 equiv, 6.6 mL) was added. The reaction mixture was stirred at rt for 16 h before being diluted in EtOAc (20 mL) and wash with 1 M HCl (20 mL × 3), sat. aq. $NaHCO_3$ (20 mL × 3) and brine (20 mL × 3). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product that was triturated in Et_2O then dispersed in $CHCl_3$ and concentrated under reduced pressure to give the desired diamide without any further purification.

Authentic racemic samples were prepared in an analogous fashion using (±)-**30**. The diastereoisomeric ratio was determined by crude ^{1}H NMR analysis through comparison of the integration for the C(2)*H* signal of the two diastereoisomers.

4-1-2 Synthesis of α-aroyloxyaldehydes

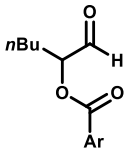
1-Oxopropan-2-yl 4-nitrobenzoate 147



Ar = 4-$NO_2C_6H_4$

Following general procedure **A**, propionaldehyde (1.6 mL, 20 mmol), 4-nitrobenzoic acid (5.0 g, 30 mmol), *n*Bu_4NI (1.5 g, 4.0 mmol) and piperidine (200 μL, 1.0 mmol) in EtOAc (100 mL) and *t*BuOOH (*ca.* 5.5 M in decane, 4.0 mL, 22 mmol) at 50 ºC for 5 h gave an orange oil that was purified by flash silica chromatography (80:20 to 60:40 Petrol: EtOAc) to give the title compound (2.4 g, 54%) as a beige solid with data in accordance with literature.[5] mp 74–76 °C {lit. mp 78–80 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.59 (3H, d, *J* 7.2, C*H*$_3$), 5.39 (1H, q, *J* 7.2, C*H*CH_3), 8.24–8.37 (4H, m, 4-NO_2Ar*H* × 4), 9.67 (1H, s, C*H*=O).

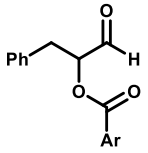
Oxohexan-2-yl 4-nitrobenzoate 155



Ar = 4-$NO_2C_6H_4$

Following general procedure **A**, hexanal (1.23 mL, 10.0 mmol), 4-nitrobenzoic acid (2.50 g, 15.0 mmol), *n*Bu_4NI (0.740 g, 2.00 mmol) and piperidine (100 μL, 1.00 mmol) in EtOAc (50 mL) and *t*BuOOH (*ca.* 5.5 M in decane, 2.0 mL, 11.0 mmol) at 80 ºC for 7 h gave a brown oil that was purified by flash silica chromatography (90:10 to 80:20 Petrol : EtOAc) to give the title compound (1.42 g, 64%) as a yellow oil with data in accordance with literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.95 (3H, t, *J* 7.2, C*H*$_3$), 1.37–1.45 (2H, m, *n*BuC*H*$_2$), 1.45–1.54 (2H, m, *n*BuC*H*$_2$), 1.93 (2H, ddd, *J* 15.5, 14.6, 8.5, *n*BuC*H*$_2$), 5.31 (1H, dd, *J* 8.3, 4.7, C*H*(*n*Bu)), 8.25–8.35 (4H, m, 4-NO_2Ar*H* × 4), 9.64 (1H, d, *J* 0.5, C*H*=O).

1-Oxo-3-phenylpropan-2-yl 4-nitrobenzoate 156

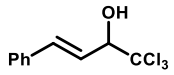


Ar = 4-$NO_2C_6H_4$

Following general procedure **A**, 3-phenylpropanal (1.32 mL, 10.0 mmol), 4-nitrobenzoic acid (2.50 g, 15.0 mmol), *n*Bu_4NI (0.740 g, 2.00 mmol) and piperidine (100 μL, 1.00 mmol) in EtOAc (50 mL) and *t*BuOOH (*ca.* 5.5 M in decane, 2.0 mL, 11.0 mmol) at 50 ºC for 7 h gave a orange oil that was purified by flash silica chromatography (90:10 to 85:15 Petrol ether : EtOAc) and triturated with Et_2O to give the title compound (0.620 g, 21%) as a yellow oil with data in accordance with literature.[5] mp 91–93 ºC, {Lit.[5] mp 85–86 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.22 (1H, dd, *J* 14.5, 8.4, C*H*^{A}H^B), 3.35 (1H, dd, *J* 14.5, 5.0, CH^A*H*^{B}), 5.52 (1H, dd, *J* 8.3, 5.0, C*H*CH_2), 7.27–7.38 (4H, m, Ar*H*), 8.15–8.23 (2H, m, 4-NO_2Ar*H* × 2), 8.26–8.35 (2H, m, 4-NO_2Ar*H* × 2), 9.68 (1H, s, C*H*=O).

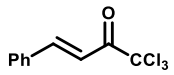
4-1-3 Synthesis of trichloromethyl ketones

(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-ol 152



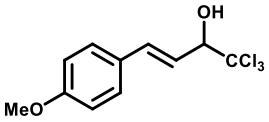
Following general procedure **D**, chloroform (4.0 mL, 50 mmol), *trans*-cinnamaldehyde (3.0 mL, 25 mmol), KOH (2.8 g, 50 mmol), EtOH (9.0 mL) in DMF (17 mL) at 0 ºC for 2 h gave the title compound as a crude brown oil (5.5 g, quant.), which was used without further purification with data in accordance with literature.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.77 (1H, dd, *J* 6.1, 1.3, C(2)*H*), 6.37 (1H, dd, *J* 15.9, 6.1, C(3)*H*), 6.91 (1H, d, *J* 16.2, C(4)*H*), 7.29–7.39 (3H, m, Ar*H*), 7.42–7.48 (2H, m, Ar*H*).

(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-one 148



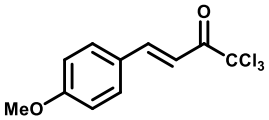
Following general procedure **E**, (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-ol **152** (2.50 g, 10.0 mmol) and re-activated MnO_2 (10.4 g, 100 mmol) in CH_2Cl_2 (20 mL) at rt for 72 h gave a crude brown oil that was purified by flash column chromatography (Petrol ether) to give the title compound (1.20 g, 48%) as a white solid with data in accordance with literature.[4] mp 57–59 ºC {Lit.[4] 59 ºC}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.34 (1H, d, *J* 15.6, C(3)*H*), 7.41–7.52 (3H, m, Ar*H*), 7.61–7.70 (2H, m, Ar*H*), 8.01 (1H, d, *J* 15.6, C(4)*H*).

1,1,1-Trichloro-4-(4-methoxyphenyl)but-3-en-2-ol 170



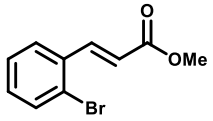
Following general procedure **E**, chloroform (2.4 mL, 30 mmol), 4-methoxycinnamaldehyde (2.4 g, 15 mmol), KOH (1.7 g, 30 mmol), EtOH (5.4 mL) in DMF (10 mL) at 0 ºC for 2 h gave the title compound (4.0 g, 71%) as a crude brown oil, which was used without further purification with data in accordance with literature.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.82 (3H, s, OCH_3), 4.74 (1H, dd, *J* 6.3, 1.2, C(2)*H*), 6.22 (1H, dd, *J* 15.8, 6.3, C(3)*H*), 6.84 (1H, d, *J* 15.8, C(4)*H*), 6.86–6.91 (2H, m, Ar*H*), 7.36–7.42 (2H, m, Ar*H*).

(*E*)-1,1,1-Trichloro-4-(4-methoxyphenyl)but-3-en-2-one 171



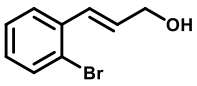
Following general procedure **E:** (*E*)-1,1,1-trichloro-4-(4-methoxyphenyl)but-3-en-2-ol **170** (1.1 g, 3.9 mmol) and MnO_2 (3.4 g, 39 mmol) in CH_2Cl_2 (10 mL) o/n at rt gave the title compound (728 mg, 67%) as a crude brown solid, which was used without further purification with data consistent with literature.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.87 (3H, s, OCH_3), 6.92–6.99 (2H, m, Ar*H*), 7.21 (1H, d, *J* 15.6, C(3)*H*), 7.58–7.65 (2H, m, Ar*H*), 7.97 (1H, d, *J* 15.5, C(4)*H*).

(*E*)-Methyl 3-(2-bromophenyl)acrylate 163



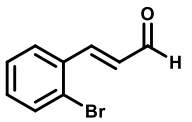
Following general procedure **B**, 2-bromocinnamic acid (2.0 g, 8.8 mmol) and $SOCl_2$ (0.96 mL, 13.2 mmol) in MeOH (17.6 mL) gave the title compound (2.1 g, quant.) as a crude lightly yellow oil, which was used without further purification. ^{1}H NMR (400 MHz, d_6-DMSO) δ_H: 3.75 (3H, s, C*H*$_3$), 6.69 (1H, d, *J* 15.9, C(2)*H*), 7.37 (1H, app td, *J* 7.7, 1.7, Ar*H*), 7.41–7.48 (1H, m, Ar*H*), 7.72 (1H, dd, *J* 8.0, 1.2, Ar*H*), 7.89 (1H, d, *J* 15.9, C(3)*H*), 7.94 (1H, dd, *J* 7.8, 1.7, Ar*H*); ^{13}C {^{1}H} (75 MHz, d_6-DMSO) δ_C: 51.7 (O*C*H$_3$), 121.0 (*C*(2)), 124.7 (ArC), 128.3 (Ar*C*(H)), 128.4(Ar*C*(H)), 132.1 (Ar*C*(H)), 133.2 (Ar*C*(H)), 141.9 (*C*(3)), 166.2 (*C*(1)).

(E)-3-(2-Bromophenyl)prop-2-en-1-ol 165



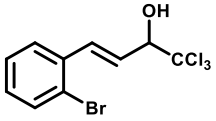
Following general procedure **C**, (*E*)-methyl 3-(2-bromophenyl)acrylate **163** (2.1 g, 8.8 mmol) and DIBAL–H (1.2 M in PhMe, 16 mL, 19 mmol) in PhMe (28 mL) gave the title compound (1.9 g, quant.) as a crude orange oil, which was used without further purification with data in concordance with literature.[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.37 (2H, br s, C*H*$_2$OH), 6.31 (1H, dt, *J* 15.8, 5.6, C(2)*H*), 6.96 (1H, br d, *J* 15.8, C(3)*H*), 7.11 (1H, td, *J* 7.7, 1.7, Ar*H*), 7.23–7.31 (1H, m, Ar*H*), 7.54 (2H, td, *J* 8.1, 1.4, Ar*H*).

(*E*)-3-(2-bromophenyl)acrylaldehyde 167



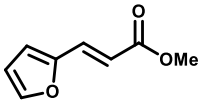
Following general procedure **D**, (*E*)-3-(2-bromophenyl)prop-2-en-1-ol **165** (500 mg, 2.35 mmol) and re-activated MnO_2 (2.05 g, 23.5 mmol) in CH_2Cl_2 (10 mL) for 2 h at rt gave the title compound (387 mg, 78%) as a crude brown solid which was used without further purification with data in accordance with literature.[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.68 (1H, dd, *J* 15.9, 7.7, C(2)*H*), 7.30 (1H, dd, *J* 7.8, 1.7, Ar*H*), 7.34–7.42 (1H, m, Ar*H*), 7.63–7.71 (3H, m, Ar*H*), 7.91 (1H, d, *J* 15.9, Ar*H*), 9.78 (1H, d, *J* 7.7, C(3)*H*).

(*E*)-4-(2-Bromophenyl)-1,1,1-trichlorobut-3-en-2-ol 172



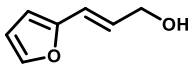
Following general procedure **E**, chloroform (293 μL, 3.7 mmol), (*E*)-3-(2-bromophenyl)acrylaldehyde **114** (387 mg, 1.8 mmol), KOH (205 mg, 3.7 mmol), EtOH (660 μL) in DMF (1.3 mL) at 0 °C for 2 h gave a crude brown solid (575 mg, 95%) which was used without further purification with data in accordance with literature.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.82 (1H, d, *J* 6.1, C*H*), 6.31 (1H, dd, *J* 15.8, 6.1, HC=C*H*), 7.17 (2H, td, *J* 7.7, 1.7, Ar*H*), 7.52–7.60 (3H, m, Ar*H* and *H*C=CH).

Methyl (*E*)-3-(furan-2-yl)acrylate 164



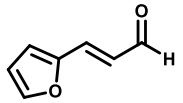
Following general procedure **B**, 3-(2-furyl) acrylic acid (5.0 g, 36 mmol) and $SOCl_2$ (3.9 mL, 54 mmol) in MeOH (72 mL) gave the title compound (5.6 g, quant.) as a crude brown oil, which was used without further purification with data in accordance with literature.[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.78 (3H, s, CH_3), 6.31 (1H, d, *J* 15.7, C(2)*H*), 6.46 (1H, *br* s, furyl-C(4)*H*), 6.61 (1H, d, *J* 2.9, furyl-C(3)*H*), 7.35–7.53 (2H, m, C(3)*H* and furyl-C(5)*H*).

(*E*)-3-(Furan-2-yl)prop-2-en-1-ol 166



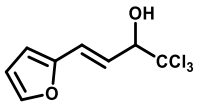
Following general procedure **C**, (*E*)-methyl 3-(furan-2-yl)acrylate **164** (5.6 g, 36 mmol) was DIBAL–H (1.2 M in PhMe, 66 mL) in PhMe (115 mL) gave the title compound (3.5 g, 78%) as an orange oil, which was used without further purification with data in accordance with literature.[10] ^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 4.29 (2H, d, *J* 5.0, CH_2), 6.24 (1H, d, *J* 3.3, furyl-C(3)*H*), 6.29 (1H, dt, *J* 15.9, 5.5, C(2)*H*), 6.36 (1H, dd, *J* 3.3, 1.8, furyl-C(4)*H*), 6.44 (1H, dt, *J* 15.9, 1.4, C(3)*H*), 7.34 (1H, d, *J* 1.7, furyl-C(5)*H*).

(*E*)-3-(Furan-2-yl)acrylaldehyde 168



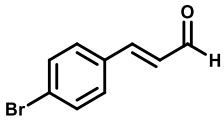
Following general procedure **D**, (*E*)-3-(furan-2-yl)prop-2-en-1-ol **166** (1.0 g, 8.1 mmol) and re-activated MnO_2 (7.0 g, 81 mmol) in CH_2Cl_2 (34 mL) o/n at rt gave the title compound (0.80 g, 81%) as a crude brown solid which was used without further purification with data in accordance with literature.[11] ^{1}H NMR(300 MHz, $CDCl_3$) δ_H: 6.60 (1H, dd, *J* 3.5, 1.8, C(2)*H*), 6.61–6.70 (1H, m, furyl-C(4)*H*), 6.84 (1H, d, *J* 3.5, furyl-C(3)*H*), 7.32 (1H, d, *J* 4.0, furyl-C(5)*H*), 7.6–7.66 (2H, m, C(3)*H*), 9.69 (1H, d, *J* 7.9, C*H*O).

(*E*)-1,1,1-Trichloro-4-(furan-2-yl)but-3-en-2-ol 173



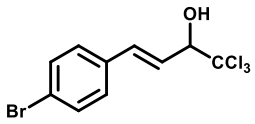
Following general procedure **E**, chloroform (530 μL, 6.6 mmol), (*E*)-3-(furan-2-yl)acrylaldehyde **109** (400 mg, 3.3 mmol), KOH (370 mg, 6.6 mmol), EtOH (1.1 mL) in DMF (2.2 mL) at 0 °C for 2.5 h gave a crude brown oil (686 mg, 87%), which was used without further purification with data in accordance with literature;[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.74 (1H, dd, *J* 5.8, 1.1, C(1)*H*), 6.32 (1H, dd, *J* 15.7, 5.8, C(2)*H*), 6.37 (1H, d, *J* 3.3, furyl-C(4)*H*), 6.41 (1H, dd, *J* 3.3, 1.8, furyl-C(3)*H*), 6.71 (1H, dd, *J* 15.7, 1.3, C(3)*H*), 7.40 (1H, d, *J* 1.5, furyl-C(5)*H*).

(*E*)-3-(4-Bromophenyl)acrylaldehyde 169



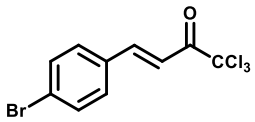
Following general procedure **D**, (*E*)-3-(4-bromophenyl)prop-2-en-1-ol (491 mg, 2.3 mmol) and re-activated MnO_2 (2.0 g, 23 mmol) in CH_2Cl_2 (9.8 mL) for 3.5 h at rt gave the title compound (413 mg, 85%) as a brown solid which was used without further purification with data in accordance with literature.[13] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.70 (1H, dd, *J* 16.0, 7.6, C(2)*H*), 7.43–7.38 (2H, m, Ar*H*), 7.48–7.43 (1H, m, C(3)*H*), 7.62–7.54 (2H, m, Ar*H*), 9.71 (1H, d, *J* 7.6, C*H*O).

(*E*)-4-(4-Bromophenyl)-1,1,1-trichlorobut-3-en-2-ol 174



Following general procedure **E**, $CHCl_3$ (293 μL, 3.66 mmol), (*E*)-3-(4-bromophenyl)acrylaldehyde **169** (387 mg, 1.83 mmol), KOH (205 mg, 3.66 mmol), EtOH (660 μL) in DMF (1.3 mL) at 0 ºC for 2 h gave the title compound (562 mg, 93%) as a brown oil, which was used without further purification.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.76 (1H, dd, *J* 5.9, 1.3, C(1)*H*), 6.37 (1H, dd, *J* 15.9, 5.9, C(2)*H*), 6.85 (1H, br d, C(3)*H*), 7.27–7.35 (2H, m, Ar*H*), 7.43–7.52 (2H, m, Ar*H*).

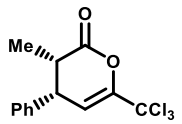
(*E*)-(4-Bromophenyl)-1,1,1-trichlorobut-3-en-2-one 177



Following the procedure described by Evans *et al.*,[14] ((*E*)-4-(4-bromophenyl)-1,1,1-trichlorobut-3-en-2-ol **167** (562 mg, 1.7 mmol, 1.0 equiv) and distilled Et_3N (711 μL, 5.1 mmol, 3.0 equiv) were dissolved in anhydrous CH_2Cl_2 (13.5 mL). A solution of sulfur trioxide pyridine complex (812 mg, 5.10 mmol, 3.0 equiv) in distilled DMSO (2.7 mL) was added dropwise at 0 ºC. The reaction mixture was stirred at 0 ºC for 26 h before adding sulfur trioxide pyridine complex (812 mg, 5.10 mmol, 3.0 equiv). The reaction mixture was stirred at rt for 48 h before being diluted in water (10 mL), extracted with Et_2O (2 × 20) and washed successively with saturated $CuSO_4$ (20 mL), saturated $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under pressure to give the title compound (583 mg, quant.) as a crude brown solid which was used without further purification with data in accordance with literature.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.32 (1H, d, *J* 15.7, C(2)*H*), 7.48–7.65 (4H, m, Ar*H*), 7.93 (1H, d, *J* 15.6, C(3)*H*).

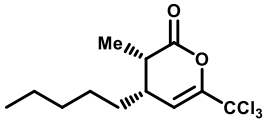
4-1-4 Synthesis of *syn*-dihydropyranones derivatives (Table 8)

(3*S*,4*S*)-3-Methyl-4-phenyl-6-(trichloromethyl)-3,4-dihydro-pyran-2-one 149



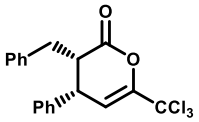
Following General Procedure **F**, 1-oxopropan-2-yl 4-nitrobenzoate **147** (402 mg, 1.80 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (300 mg, 1.20 mmol), NHC precatalyst **30** (22.1 mg, 0.060 mmol) and Et_3N (251 μL, 1.80 mmol) in anhydrous CH_2Cl_2 (16.2 mL) at rt for 3.5 h gave a crude brown solid (>95:5 *syn*:*anti* dr) that was purified by flash silica column chromatography (90:10 Hexane : EtOAc) to give the title compound (307 mg, 84%) as a white solid. mp 142–145 °C; $[\alpha]_D^{20}$ +237.5 (*c* 0.41, CH_2Cl_2); Chiral HPLC AD-H (95:5 hexane : IPA, flow rate 1.0 mL·min^{-1}, 220 nm, 30 °C) t_R major: 5.9 min, t_R minor: 7.1 min, >99:1 er; ν_{max} (film) cm^{-1} 1776 (C=O), 1674 (C=C), 1601 (Ar C=C), 1493 (Ar C=C), 1454 (Ar C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.06 (3H, d, *J* 6.9, C*H*$_3$), 3.08 (1H, p, *J* 6.9, C(3)*H*), 3.75 (1H, t, *J* 6.8, C(4)*H*), 6.42 (1H, d, *J* 6.5, C(5)*H*), 7.04–7.14 (2H, m, C(4)ArC*H*), 7.28–7.39 (3H, m, C(4)ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.1 (*C*H$_3$), 38.2 (*C*(3)), 42.4 (*C*(4)), 90.1 (*C*Cl$_3$), 108.0 (*C*(5)), 128.1 (C(4)Ar*C*H), 128.3 (C(4)Ar*C*H), 129.2 (C(4)Ar*C*H), 135.8 (C(4)Ar*C*(1)), 149.5 (*C*(6)), 168.6 (*C*(2)); *m/z* (APCI$^+$) 307 [(M(^{35}Cl$_2$, ^{37}Cl)+H]$^+$, 100%), 305 [(M(^{35}Cl$_3$)+H]$^+$, 98%); HRMS (APCI$^+$) $C_{13}H_{12}{}^{35}Cl_3O_2$ [M+H]$^+$ found 304.9903 requires 304.9897 (+1.5 ppm).

(3*S*,4*S*)-3-Methyl-4-pentyl-6-(trichloromethyl)-3,4-dihydro-pyran-2-one 184



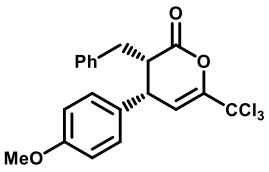
Following General Procedure **F**, 1-oxopropan-2-yl 4-nitrobenzoate **147** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichlorononon-3-en-2-one **181** (49 mg, 0.20 mmol), NHC precatalyst **30** (7.4 mg, 0.020 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 22 h gave a crude brown solid (>95:5 *syn*:*anti* dr) that was purified by flash silica column chromatography (95:5 Hexane: EtOAc) to give the title compound (15 mg, 26%) as a yellow oil. $[\alpha]_D^{20}$ +8.9 (*c* 0.44, $CHCl_3$); Chiral GC analysis Restek Rt-bDEXcst (length: 30 m, thickness: 0.250 mm, film thickness 0.25 μm) carrier gas: He, linear velocity: 20.0 $cm \cdot s^{-1}$, temperature: 160 °C t_R minor: 105.3 min, t_R major: 106.9 min, >99:1 er; ν_{max} (film) cm^{-1} 1782 (C=O), 1668 (C=C), 1458 (Ar C=C); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 0.88 (3H, t, *J* 6.9, C*H*$_3$), 1.26 (3H, d, *J* 7.0, C(3)C*H*$_3$), 1.27–1.40 (7H, m, C(4)C*H*^{A}H^B and $CH_3(CH_2)_3$), 1.50–1.55 (1H, m, C(4)CH^A*H*^{B}), 2.53–2.64 (1H, m, C(4)*H*), 2.81 (1H, app p, *J* 7.0, C(3)*H*), 6.18 (1H, d, *J* 5.8, C(5)*H*); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 11.3 (C(3)*C*H$_3$), 14.0 (*C*H$_3$), 22.4 (CH$_3$*C*H$_2$), 26.0 (CH$_3$(CH$_2$)$_2$*C*H$_2$), 28.8 (C(4)*C*H$_2$), 31.8 (CH$_3$CH$_2$*C*H$_2$), 35.3 (*C*(4)), 36.9 (*C*(3)), 90.1 (*C*Cl$_3$), 109.2 (*C*(5)), 148.4 (*C*(6)), 169.9 (*C*(2)); *m/z* (APCI$^+$) 319 ([M($^{35}Cl_2$,^{37}Cl)+H$_3$O]$^+$, 62%), 317 ([M($^{35}Cl_3$)+H$_3$O]$^+$, 65%), 303 ([M(^{35}Cl,$^{37}Cl_2$)+H]$^+$, 30%), 301 ([M($^{35}Cl_2$,^{37}Cl)+H]$^+$, 95%), 299 ([M($^{35}Cl_3$)+H]$^+$, 100%); HRMS (APCI$^+$) $C_{12}H_{17}{}^{35}Cl_3O_2{}^+$ [M+H]$^+$ found 299.0366 requires 299.0367 (–0.3 ppm).

(3*S*,4*S*)-3-Benzyl-4-phenyl-6-(trichloromethyl)-3,4-dihydro-pyran-2-one 186



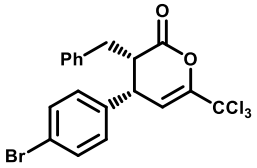
Following General Procedure **F**, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate **156** (90 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (50 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 4 h gave a brown oil (>95:5 *syn*:*anti* dr) that was purified by column chromatography (90:10 Petrol : EtOAc) to give the title compound (62 mg, 81%) as a lightly red oil. $[\alpha]_D^{20}$ +167.7 (*c* 0.43, CH_2Cl_2); Chiral HPLC AS-H (99:1 hexane : IPA, flow rate 0.5 mL·min^{-1}, 211 nm, 30 °C) t_R minor: 16.6 min, t_R major: 19.2 min, >99:1 er; ν_{max} (film) cm^{-1} 1780 (C=O), 1670 (C=C), 1603 (Ar C=C), 1495 (Ar C=C), 1454 (Ar C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.37–2.44 (1H, m, C(3)C*H*^{A}H^B), 3.23–3.32 (2H, m, C(3)CH^A*H*^{B} and C(3)*H*), 3.65–3.70 (1H, m, C(4)*H*), 6.37 (1H, d, *J* 6.8, C(5)*H*), 7.03–7.05 (2H, m, Ar*H*), 7.10–7.13 (2H, m, Ar*H*), 7.24–7.39 (6H, m, Ar*H*); ^{13}C{^{1}H} (101 MHz, $CDCl_3$) δ_C: 32.0 (*C*H$_2$), 39.9 (*C*(4)), 44.8 (*C*(3)), 90.1 (*C*Cl$_3$), 108.6 (*C*(5)), 126.8 (Ar*C*H), 128.3 (Ar*C*H × 2), 128.4 (Ar*C*H), 128.7 (Ar*C*H × 2), 128.9 (Ar*C*H × 2), 129.3 (Ar*C*H × 2), 135.9 (C(3)Ar*C*(1)), 137.8 (C(2)CH$_2$Ar*C*(1)), 149.1 (*C*(6)), 167.8 (*C*(2)); *m/z* (APCI)$^+$ 381 ([M(^{35}Cl$_3$)+H]$^+$, 100%); HRMS $C_{19}H_{16}O_2{}^{35}Cl_3$ [M+H]$^+$ found 381.0204 requires 381.0210 (–1.7 ppm).

(3*S*,4*S*)-3-Benzyl-4-(4-methoxyphenyl)-6-(trichloromethyl)-3,4-dihydro-pyran-2-one 187



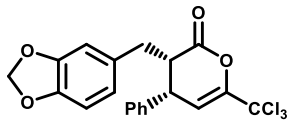
Following General Procedure **F**, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate **156** (270 mg, 0.90 mmol), (*E*)-1,1,1-trichloro-4-(4-methoxyphenyl)but-3-en-2-one **171** (168 mg, 0.60 mmol), NHC precatalyst **30** (11.1 mg, 0.030 mmol) and Et_3N (126 μL, 0.90 mmol) in anhydrous CH_2Cl_2 (8.2 mL) at rt for 3 h gave a brown oil (>95:5 *syn*:*anti* dr) that was purified by column chromatography (90:10 Petrol : EtOAc) to give the title compound (229 mg, 93%) as a white solid. mp 109–111 °C; $[\alpha]_D^{20}$ +369.6 (*c* 0.575, CH_2Cl_2); Chiral HPLC AD-H (98:2 hexane : IPA, flow rate 1.0 mL·min^{-1}, 220 nm, 30 °C) t_R minor: 11.2 min, t_R major: 12.6 min, >99:1 er; ν_{max} (film) cm^{-1} 1778 (C=O), 1609 (C=C), 1512 (Ar C=C), 1252 (PhO–CH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (1H, dd, *J* 15.8, 10.6, C(3)C*H*^{A}H^B), 3.23–3.30 (2H, m, C(3)CH^A*H*^{B} and C(3)*H*), 3.62 (1H, app t, *J* 6.7, C(4)*H*), 3.82 (3H, s, C*H*$_3$), 6.35 (1H, d, *J* 6.8, C(5)*H*), 6.87–6.97 (4H, m, C(4)Ar*H*), 7.10–7.14 (2H, m, Ar*H*), 7.24–7.28 (1H, m, Ar*H*), 7.30–7.35 (2H, m, Ar*H*); ^{13}C{^{1}H} (126 MHz, $CDCl_3$) δ_C: 32.0 (*C*H$_2$), 39.1 (*C*(4)), 45.0 (*C*(3)), 55.3 (*C*H$_3$O), 90.1 (*C*Cl$_3$), 108.9 (*C*(5)), 114.6 (C(4)Ar*C*H), 126.8 (C(3)CH$_2$Ar*C*H), 127.6 (C(4)Ar*C*(1)), 128.7 (C(3)CH$_2$Ar*C*H), 129.0 (C(3)CH$_2$Ar*C*H), 129.4 (C(4)Ar*C*H), 137.9 (C(3)CH$_2$Ar*C*), 148.8 (*C*(6)), 159.6 (C(4)Ar*C*(4)), 168.0 (*C*(2)); *m/z* (APCI)$^+$ 411 ([M(^{35}Cl$_3$)+H]$^+$, 100%), 303 ([M(^{35}Cl$_3$)–4-OMeC$_6$H$_4$]$^+$, 70%); HRMS $C_{20}H_{17}{}^{35}Cl_3O_3$ [M+H]$^+$ found 411.0313 requires 411.0316 (–0.7 ppm).

(3*S*,4*S*)-3-Benzyl-4-(4-bromophenyl)-6-(trichloromethyl)-3,4-dihydro-pyran-2-one 188



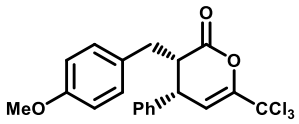
Following General Procedure **F**, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate **156** (90 mg, 0.30 mmol), (*E*)-4-(4-bromophenyl)-1,1,1-trichlorobut-3-en-2-one **177** (70 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 1.5 h gave a brown oil (>95:5 *syn*:*anti* dr) that was purified by column chromatography (90:10 Petrol : EtOAc) to give the title compound (60 mg, 95% pure, 55%) as a yellow oil. $[\alpha]_D^{20}$ +71.4 (*c* 0.29, CH_2Cl_2); Chiral HPLC OD-H (97:3 hexane : IPA, flow rate 1.0 mL·min^{-1}, 220 nm, 30 °C) t_R major: 10.3 min, t_R minor: 11.7 min, >99:1 er; ν_{max} (film) cm^{-1} 1780 (C=O), 1661 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.34–2.41 (1H, m, C(3)C*H*^{A}H^B), 3.26–3.33 (2H, m, C(3)CH^A*H*^{B} and C(3)*H*), 3.64 (1H, app t, *J* 6.7, C(4)*H*), 6.33 (1H, d, *J* 6.8, C(5)*H*), 6.88–6.90 (2H, m, C(4)ArC(2,6)*H*), 7.08–7.12 (2H, m, C(3)Ar*H*), 7.24–7.35 (3H, m, C(3)Ar*H*), 7.48–7.50 (2H, m, C(4)ArC(3,5)*H*); ^{13}C{^{1}H}(101 MHz, $CDCl_3$) δ_C: 32.0 (*C*H$_2$), 39.2 (*C*(4)), 44.4 (*C*(3)), 90.2 (*C*Cl$_3$), 108.0 (*C*(5)), 123.0 (C(4)Ar*C*(1)), 127.0 (C(3)CH$_2$Ar*C*H), 128.8 (C(3)CH$_2$Ar*C*H), 128.9 (C(3)CH$_2$Ar*C*H), 129.9 (C(4)Ar*C*(2,6)), 132.4 (C(4)Ar*C*(3,5)), 135.1 (C(4)Ar*C*(4)), 137.8 (C(3)CH$_2$Ar*C*), 146.6 (*C*(6)), 167.7 (*C*(2)); *m/z* (APCI$^+$) 463 ([M(^{35}Cl,^{37}Cl$_2$,^{79}Br)+H]$^+$, 60%), 461 ([M(^{35}Cl$_2$,^{37}Cl,^{79}Br)+H]$^+$, 100%), 458 ([M(^{35}Cl$_3$,^{79}Br)+H]$^+$, 50%); HRMS $C_{19}H_{15}O_2{}^{79}Br^{35}Cl_3$ [M+H]$^+$ found 458.9312, requires 458.9316 (–0.8 ppm).

(3*S*,4*S*)-(-3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-phenyl-6-(trichloromethyl)-3,4-dihydro-pyran-2-one 189



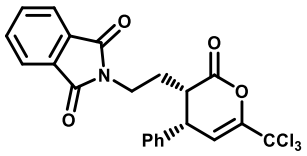
Following General Procedure **F**, 1-(benzo[*d*][1,3]dioxol-5-yl)-3-oxopropan-2-yl 4-nitrobenzoate **157** (103 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (50 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 26 h gave a brown oil (85:15 *syn*:*anti* dr) that was purified by column chromatography (95:5 Petrol : EtOAc) to give the title compound (38 mg, 45%) as a white solid. mp 145–147 °C; $[\alpha]_D^{20}$ +230.4 (*c* 0.51, CH_2Cl_2); er could not be determined by either chiral HPLC or GC; ν_{max} (film) cm^{-1} 1780 (C=O), 1504, 1489 and 1445 (Ar C=C), 1246 (C-O); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.33 (1H, dd, *J* 14.5, 9.1, C(3)C*H*^{A}H^B), 3.15 (1H, dd, *J* 14.5, 5.3, C(3)CH^A*H*^{B}), 3.18–3.22 (1H, m, C(3)*H*), 3.71 (1H, app t, *J* 6.7, C(4)*H*), 5.95 (1H, d, *J* 1.4, OC*H*^{A}H^{B}O), 5.96 (1H, d, *J* 1.4, OCH^A*H*^{B}O), 6.37 (1H, d, *J* 6.8, C(5)*H*), 6.53 (1H, dd, *J* 7.9, 1.5, C(3)CH_2ArC(6)*H*), 6.61 (1H, *app* d, *J* 1.6, C(3)CH_2ArC(4)*H*), 6.75 (1H, d, *J* 7.9, C(3)CH_2ArC(7)*H*), 7.05–7.07 (2H, m, C(4)ArC(3,5)*H*), 7.32–7.39 (3H, m, C(4)ArC(2,4,6)*H*); $^{13}C\{^1H\}$ (126 MHz, $CDCl_3$) δ_C: 31.8 (C(4)*C*H_2), 39.9 (*C*(4)), 45.1 (*C*(3)), 90.1 (*C*Cl_3), 101.0 (O*C*H_2O), 108.4 (C(3)CH_2Ar*C*(7)), 108.6 (*C*(5)), 109.1 (C(3)CH_2Ar*C*(4)), 122.0 (C(3)CH_2Ar*C*(6)), 128.3 (C(4)Ar*C*H), 128.4 (C(4)Ar*C*H), 129.3 (C(4)Ar*C*H), 131.4 (C(3)CH_2Ar*C*(5)), 135.9 (C(4)Ar*C*(1)), 146.4 (C(3)CH_2Ar*C*(3a)), 147.8 (C(3)CH_2Ar*C*(7a)), 149.0 (*C*(6)), 167.8 (*C*(2)); *m/z* (NSI^+) 481 ([M($^{35}Cl_2$,^{37}Cl)+MeOH+Na]$^+$, 65%), 479 ([M($^{35}Cl_3$)+MeOH+Na]$^+$, 67%), 449 ([M($^{35}Cl_2$, ^{37}Cl)+Na]$^+$, 50%), 447 ([M($^{35}Cl_3$) +Na]$^+$, 52%), 444 ([M($^{35}Cl_2$,^{37}Cl)+NH_4]$^+$, 31%), 442 ([M($^{35}Cl_3$)+NH_4]$^+$, 34%), 429 ([M(^{35}Cl, $^{37}Cl_2$)+H]$^+$, 30%), 427 ([M($^{35}Cl_2$, ^{37}Cl)+H]$^+$, 94%), 425 [M($^{35}Cl_3$)+H]$^+$, 100%); HRMS(NSI^+) $C_{20}H_{16}O_4{}^{35}Cl_3$ [M+H]$^+$ found 425.0107 requires 425.0109 (–0.4 ppm).

(3*S*,4*S*)-3-(4-Methoxybenzyl)-4-phenyl-6-(trichloromethyl)-3,4-dihydro-pyran-2-one 190



Following General Procedure **F**, 1-(4-methoxyphenyl)-3-oxopropan-2-yl 4-nitrobenzoate **158** (99 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (50 mg, 0.20 mmol), NHC precatalyst **30** (7.4 mg, 0.020 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 26 h gave a brown oil (>95:5 *syn*:*anti* dr) that was purified by column chromatography (95:5 Petrol : EtOAc) to give the title compound (53 mg, 65%) as a yellow oil. $[\alpha]_D^{20}$ +300.0 (*c* 0.81, $CHCl_3$); Chiral HPLC AD-H (99:1 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) t_R minor: 18.5 min, t_R major: 20.7 min, >99:1 er; ν_{max} (film) cm^{-1} 1780 (C=O), 1612 (C=C), 1514 (Ar C=C), 1456, 1250 (Ph–O–CH_3); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.35 (1H, dd, *J* 14.4, 9.1, C(3)C*H*^{A}H^B), 3.15–3.27 (2H, m, C(3)CH^A*H*^{B} and C(3)*H*), 3.68 (1H, app t, *J* 6.8, C(4)*H*), 3.81 (3H, s, C*H*$_3$O), 6.36 (1H, d, *J* 6.7, C(5)*H*), 6.85 (2H, dd, *J* 9.1, 2.5, C(3)CH$_2$ArC(3,5)*H*), 6.99–7.08 (4H, m, C(3)CH$_2$ArC(2,6)*H* and C(4)ArC(3,5)*H*), 7.31–7.39 (3H, m, C(4)ArC(2,4,6)*H*); ^{13}C{^{1}H} (126 MHz, $CDCl_3$) δ_C: 31.1 (C(3)*C*H$_2$), 39.9 (*C*(4)), 45.0 (*C*(3)), 55.3 (O*C*H$_3$), 90.1 (*C*Cl$_3$), 108.6 (*C*(5)), 114.0 (C(3)CH$_2$Ar*C*(3,5)), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 129.2 (Ar*C*H), 129.7(Ar*C*H), 129.7 (Ar*C*H), 129.9 (Ar*C*H), 136.0 (C(4)Ar*C*(1)), 149.1 (*C*(6)), 158.4 (C(3)CH$_2$Ar*C*(4)), 167.9 (*C*(2)); *m/z* (NSI$^+$) 462 ([M(^{35}Cl$_2$, ^{37}Cl)+MeOH+NH$_4$]$^+$, 51%), 460 ([M(^{35}Cl$_3$)+MeOH+NH$_4$]$^+$, 52%), 445 ([M(^{35}Cl$_2$, ^{37}Cl)+MeOH+H]$^+$, 65%), 443 ([M(^{35}Cl$_3$)+MeOH+H]$^+$, 67%), 432 ([M(^{35}Cl,^{37}Cl$_2$)+NH$_4$]$^+$, 30%), 430 ([M(^{35}Cl$_2$,^{37}Cl)+NH$_4$]$^+$, 97%), 428 ([M(^{35}Cl$_3$)+NH$_4$]$^+$, 100%), 411 ([M(^{35}Cl$_2$,^{37}Cl)+H]$^+$, 43%); HRMS (NSI$^+$) $C_{20}H_{18}O_3Cl_3$ [M+H]$^+$ found 411.0321 requires 411.0316 (+1.2 ppm).

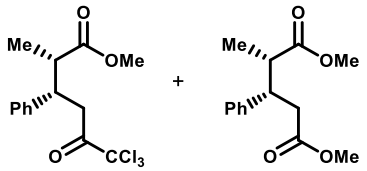
2-(2-((3*S*,4*S*)-2-Oxo-4-phenyl-6-(trichloromethyl)-3,4-dihydro-pyran-3-yl)ethyl)iso-indoline-1,3-dione 191



Following General Procedure **F**, 4-(1,3-dioxoisoindolin-2-yl)-1-oxobutan-2-yl 4-nitrobenzoate **159** (115 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (50 mg, 0.20 mmol), NHC precatalyst **30** (7.4 mg, 0.020 mmol, 10 mol%) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 7 h gave a brown solid (90:10 *syn*:*anti* dr) that was purified by column chromatography (90:10 Petrol : EtOAc) to give the title compound (55 mg, 60%) as a white solid. mp 132 °C (*dec*); $[\alpha]_D^{20}$ +271.2 (*c* 0.16, $CHCl_3$); Chiral HPLC OD-H (97:3 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) t_R minor: 34.3 min, t_R major: 42.2 min, >99:1 er; ν_{max} (film) cm^{-1} 1772 and 1701 (C=O isoxindole), 1701 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.50–1.60 (1H, m, C(3)C*H*^{A}H^B), 2.06–2.16 (1H, m, C(3)CH^A*H*^{B}), 2.95 (1H, q, *J* 7.0, C(3)*H*), 3.76–3.85 (1H, m, C(3)CH$_2$C*H*^{A}H^B), 3.85–3.92 (1H, m, C(3)CH$_2$CH^A*H*^{B}), 4.00 (1H, app t, *J* 7.0, C(4)*H*), 6.42 (1H, d, *J* 6.9, C(5)*H*), 7.12–7.16 (2H, m, Ar*H*), 7.29–7.38 (3H, m, Ar*H*), 7.70–7.75 (2H, m, C(3)(CH$_2$)$_2$Ar(2,5)*H*), 7.83–7.88 (2H, m, C(3)(CH$_2$)$_2$Ar(3,4)*H*); ^{13}C{^{1}H} (101 MHz, $CDCl_3$) δ_C: 26.3 (*C*H$_2$), 35.6(*C*H$_2$), 40.7 (*C*(3)), 40.9 (*C*(4)), 90.0 (*C*Cl$_3$), 108.1 (*C*(5)), 123.4 (Ar*C*H × 2), 128.0 (Ar*C*H × 2), 128.5 (Ar*C*H), 129.4 (Ar*C*H × 2), 132.0 (NPhthAr*C*), 134.1 (Ar*C*H), 135.7 (NPhthAr*C*), 149.3 (C(3)Ar*C*(1)), 167.5 (*C*(2)), 168.4 (C=O × 2); *m/z* (NSI)$^+$ 951 ([2M(^{35}Cl$_2$,^{37}Cl)+Na]$^+$, 100%), 949 ([2M(^{35}Cl$_3$)+Na]$^+$, 85%), 486 ([M(^{35}Cl$_3$)+Na]$^+$, 85%); HRMS $C_{22}H_{16}O_4N_1{}^{35}Cl_3Na$ [M+Na]$^+$ found 486.0041 requires 486.0037 (+0.8 ppm).

4-1-5 Sequential [4+2] cycloaddition/ring opening with alcohols (Scheme 59 and Scheme 60)

(2S,3S)-Methyl 6,6,6-trichloro-2-methyl-5-oxo-3-phenylhexanoate 194 and (2S,3S)-Dimethyl 2-methyl-3-phenylpentanedioate 195



194 **195**

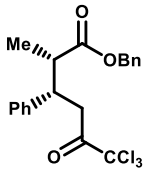
1-Oxopropan-2-yl 4-nitrobenzoate **147** (0.30 mmol, 67 mg, 1.5 equiv), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (0.20 mmol, 50 mg, 1.0 equiv) and NHC precatalyst **30** (0.010 mmol, 3.7 mg, 5 mol%) were dissolved in anhydrous CH_2Cl_2 (2.7 mL). Et_3N (0.30 mmol, 42 μL, 1.5 equiv) was added and the reaction mixture was stirred at rt for 3.5 h. The mixture was diluted in EtOAc (10 mL) and washed with water (10 mL × 2), sodium bisulfte aq. 40% (10 mL × 2) and brine (10 mL × 2). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude orange solid (>95:5 *syn*:*anti* dr). The crude was dissolved in anhydrous CH_2Cl_2 (2.4 mL) with MeOH (60 mmol, 2.4 mL, 300 equiv) and DMAP (0.04 mmol, 5.0 mg, 20 mol%). The reaction mixture was stirred over 16 h before being concentrated under reduced pressure to give a crude orange oil (>95:5 dr) that was purified by flash silica column chromatography (98:2 to 90:10 Hexane: EtOAc) to give:

194 (35 mg, 50%) as a colourless oil. $[\alpha]_D^{20}$ –17.3 (*c* 1.60, $CHCl_3$); Chiral HPLC AD-H (99:1 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) t_R minor: 8.0 min, t_R major: 9.7 min, >99:1 er; ν_{max} (film) cm^{-1} 1734 (C=O), 1456, 1198, 1167; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.23 (3H, d, *J* 7.0, C(2)C*H*$_3$), 2.86 (1H, p, *J* 7.0, C(2)*H*), 3.49 (2H, dd, *J* 6.9, 2.7, C(4)*H*$_2$), 3.52 (3H, s, C(1)OC*H*$_3$), 3.54–3.62 (1H, m, C(3)*H*), 7.17–7.24 (3H, m, Ar*H*), 7.24–7.31 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.8 (C(2)*C*H$_3$), 36.8 (*C*(4)), 44.0 (*C*(3)), 44.7 (*C*(2)), 51.6 (C(1)O*C*H$_3$), 96.2 (*C*(6)), 127.3 (Ar*C*H), 128.1 (Ar*C*H × 2), 128.4 (Ar*C*H × 2), 140.3 (C(3)Ar*C*(1)), 174.9 (*C*(1)), 188.7 (*C*(5)); *m/z* (APCI$^+$) 356 ([M(^{35}Cl$_2$,^{37}Cl)+NH$_4$]$^+$, 34%), 354 ([M(^{35}Cl$_3$)+ NH$_4$]$^+$, 34%), 341 ([M(^{35}Cl,^{37}Cl$_2$)+H]$^+$, 34%), 339 ([M(^{35}Cl$_2$,^{37}Cl)+H]$^+$, 99%), 337 ([M(^{35}Cl$_3$)+H]$^+$, 100%); HRMS (APCI$^+$) $C_{14}H_{15}O_3{}^{35}Cl_3$ [M+H]$^+$ found 337.0164 requires 337.0164 (–0.1 ppm).

195 (10 mg, 20%, 85% pure) as a yellow oil.[15,16] $[\alpha]_D^{20}$ +0.46 (*c* 0.44, $CHCl_3$); Chiral HPLC AD-H (99:1 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) major diastereoisomer:

t_R minor: 13.8 min, t_R major: 15.1 min, 99:1 er, minor diastereoisomer: t_R minor: 12.3 min, t_R major: 13.0 min, >99:1 er; ν_{max} (film) cm^{-1} 1734 (C=O), 1456, 1453, 1258, 1198, 1161; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.18 (3H, d, *J* 7.0, C(2)CH_3), 2.69 (1H, dd, *J* 15.7, 9.7, C(4)H^AH^B), 2.74–2.87 (2H, m, C(4)H^AH^B and C(2)*H*), 3.41–3.48 (1H, m, C(3)*H*), 3.50 (3H, s, C(1)OCH_3), 3.54 (3H, s, C(5)OCH_3), 7.14–7.23 (3H, m, Ar*H*), 7.24–7.30 (2H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 14.4 (C(2)CH_3), 37.0 (*C*(4)), 44.5 (*C*(3)), 45.1 (*C*(2)), 51.5 (C(1)OCH_3), 51.6 (*C*(5)OCH_3), 126.9 (C(3)Ar*C*H), 127.8 (C(3)Ar*C*H × 2), 128.3 (C(3)Ar*C*H × 2), 141.3 (C(3)Ar*C*(1)), 172.4 *C*(5), 175.2 *C*(2); *m/z* (NSI^+) 251 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{14}H_{19}O_4$ $[M+H]^+$ found 251.1279 requires 251.1278 (+0.5 ppm).

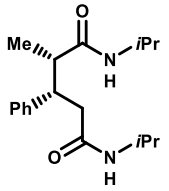
(2*S*,3*S*)-Benzyl 6,6,6-trichloro-2-methyl-5-oxo-3-phenylhexanoate 196



1-Oxopropan-2-yl 4-nitrobenzoate **147** (0.30 mmol, 67 mg, 1.5 equiv), **(***E***)**-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (0.20 mmol, 50 mg, 1.0 equiv) and NHC precatalyst **30** (0.010 mmol, 3.7 mg, 5 mol% or 0.020 mmol, 10 mol%) were dissolved in anhydrous CH_2Cl_2 (2.7 mL). Et_3N (0.30 mmol, 42 µL, 1.5 equiv) was added and the reaction mixture was stirred at rt for 3 h 30. The mixture was diluted in EtOAc (10 mL) and washed with water (10 mL × 2), sodium bisulfite 40% (10 mL × 2), and brine (10 mL × 2). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude orange solid (> 95:5 *syn*:*anti* dr). The crude was dissolved in anhydrous CH_2Cl_2 (6.6 mL) with BnOH (60 mmol, 6.6 mL, 300 equiv) and DMAP (0.04 mmol, 5 mg, 20 mol%). The reaction mixture was stirred over 16 h then diluted in EtOAC and wash with water (20 mL × 2) and brine (20 mL × 2). The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure before distilling off BnOH on Kugelrohr to give a crude orange oil (>95:5 *syn*:*anti* dr) that was purified Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, hexane : EtOAc (100:0 1 CV, 100:0 to 90:10 10 CV, 90:10 10 CV)] to give the title compound (20 mg, 95% pure, 25% yield) as a yellow oil. $[\alpha]_D^{20}$ –30.1 (*c* 1.07, $CHCl_3$); Chiral HPLC AD-H (95:5 hexane : IPA, flow rate 1 mL.min^{-1}, 211 nm, 30 ºC) t_R minor: 6.2 min, t_R major: 7.8 min, 98:2 er; ν_{max} (film) cm^{-1} 1732 (C=O), 1454, 1259, 1159; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.26 (3H, d, *J* 7.0, C(2)C*H*$_3$), 2.91 (1H, quint, *J* 7.0, C(2)*H*), 3.35–3.53 (2H, m, C(4)*H*$_2$), 3.55–3.63 (1H, m, C(3)*H*), 4.89–5.02 (2H, m, OC*H*$_2$), 7.14–7.19 (4H, m, C(3)Ar*H* × 2 and CH_2Ar*H* × 2), 7.20–7.27 (3H, m, C(3)Ar*H* × 3), 7.31–7.34 (3H, m, CH_2Ar*H* × 3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 15.0 (C(2)*C*H$_3$), 37.0 (*C*(4)), 44.1 (*C*(3)), 44.7 (*C*(2)), 66.4 (O*C*H$_2$), 96.2 (*C*(6)), 127.3 (Ar*C*H), 128.2 (Ar*C*H × 2), 128.2 (Ar*C*H), 128.3 (Ar*C*H × 2), 128.4 (Ar*C*H × 2), 128.5 (Ar*C*H × 2), 135.6 (OCH$_2$Ar*C*), 140.1 (C(3)Ar*C*), 174.2 (*C*(1)), 188.6 (*C*(5)); *m/z* (NSI$^+$) 434 ([M(^{35}Cl$_,$ ^{37}Cl$_2$)+H]$^+$, 30%), 432 ([M(^{35}Cl$_2$, ^{37}Cl)+H]$^+$, 97%), 430 ([M(^{35}Cl$_3$)+H]$^+$, 100%); HRMS (NSI$^+$) $C_{20}H_{20}O_3{}^{35}Cl_3$ [M+H]$^+$ found 413.0475 requires 412.0473 (+0.6 ppm).

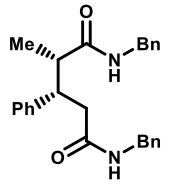
4-1-6 Sequential [4+2] cycloaddition/ring-opening and aminolysis (Scheme 61, Table 11 and Table 12)

(2*S*,3*S*)-*N*^{1},*N*^{5}-Diisopropyl-2-methyl-3-phenylpentanediamide 198



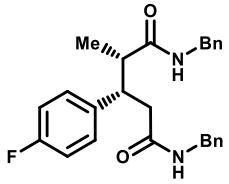
Following General Procedure **G**, 1-oxopropan-2-yl 4-nitrobenzoate **147** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (50 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 3 h 30 gave a crude orange solid (>95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (5.2 mL) with isopropyl amine (5.2 mL, 60 mmol) at rt for 16 h to give a crude orange solid (80:20 dr) that was triturated in Et_2O to give the title compound (22 mg, 36%) as a white solid. mp 226–228 °C; $[\alpha]_D^{20}$ –2.6 (*c* 0.70, $CHCl_3$); er could not be determined; ν_{max} (film) cm^{-1} 3288 (N–H), 1636 (C=O), 1547 (N–C=O), 1454, 1381, 1368, 1269; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.82 (3H, d, *J* 6.5, N^{A}CHC*H*$_3$), 0.94 (3H, d, *J* 6.5, N^{B}CHC*H*$_3$), 0.96–0.99 (3H, m, N^{A}CHC*H*$_3$), 1.02 (3H, d, *J* 6.5, N^{B}CHC*H*$_3$), 1.12–1.16 (3H, m, C(2)C*H*$_3$), 2.37 (1H, dd, *J* 13.5, 8.0, C(4)*H*^{A}H^B), 2.58 (1H, p, *J* 7.0, C(2)*H*), 2.80–2.88 (1H, m, C(4)H^A*H*^{B}), 3.20 (1H, q, *J* 7.7, C(3)*H*), 3.84–4.00 (2H, m, NC*H* ×2), 5.02 (1H, d, *J* 7.5, N^A*H*), 5.70 (1H, d, *J* 7.4, N^B*H*), 7.10–7.32 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 15.9 (C(2)*C*H$_3$), 22.4 (NCH*C*H$_3$), 22.4 (NCH*C*H$_3$), 22.5 (NCH*C*H$_3$), 22.6 (NCH*C*H$_3$), 40.8 (*C*(4) or N*C*H), 40.9 (*C*(4) or N*C*H), 41.1 (*C*(4) or N*C*H), 45.3 (*C*(2)), 46.7 (*C*(3)), 127.0 (Ar*C*H), 128.3 (Ar*C*H × 3), 128.5 (Ar*C*H), 141.3 (Ar*C*), 170.7 (C(5)), 173.1 (C(1)); *m/z* (NSI$^+$) 327 ([M+Na]$^+$, 60%), 305 ([M+H]$^+$, 100%) ; HRMS (NSI$^+$) $C_{19}H_{29}O_2$ [M+H]$^+$ found 305.226 requires 305.2224 (+0.8 ppm).

(2*S*,3*S*)-N^1,N^5-Dibenzyl-2-methyl-3-phenylpentanediamide 199



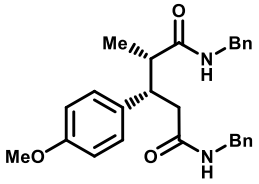
Following General Procedure **G**, 1-oxopropan-2-yl 4-nitrobenzoate **147** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (50 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 3.5 h gave a crude orange solid (>95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude beige solid (dr>95:5) that was triturated in Et_2O to give the title compound (70 mg, 85%) as a white solid. mp 172–174 °C; $[\alpha]_D^{20}$ –8.7 (*c* 0.53, $CHCl_3$); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) t_R minor: 15.3 min, t_R major: 19.1 min, >99:1 er; ν_{max} (film) cm^{-1} 3283 (N–H), 3258 (N–H), 1636 (C=O), 1558 (N–C=O), 1541 (N–C=O), 1495, 1454, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.20 (3H, d, *J* 6.9, C(2)C*H*$_3$), 2.48 (1H, dd, *J* 13.8, 8.6, C(4)*H*^{A}H^B), 2.67 (1H, p, *J* 7.0, C(2)*H*), 2.91 (1H, dd, *J* 13.8, 6.9, C(4)H^A*H*^{B}), 3.36 (1H, q, *J* 7.7, C(3)*H*), 4.14 (1H, dd, *J* 14.7, 5.2, N^{1}C*H*^{A}H^B), 4.24 (1H, dd, *J* 14.9, 5.4, N^{5}C*H*^{A}H^B), 4.31 (1H, dd, *J* 14.7, 6.1, N^{1}CH^A*H*^{B}), 4.38 (1H, dd, *J* 14.8, 6.1, N^{5}CH^A*H*^{B}), 5.58 (1H, br t, *J* 5.0, N^1*H*), 6.10 (1H, br t, *J* 5.0, N^5*H*), 6.87–6.96 (3H, dd, *J* 6.6, 2.8, Ar*H*), 6.97–7.02 (3H, m, Ar*H*), 7.11–7.18 (3H, m, ArH), 7.19–7.26 (8H, m); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 16.0 (C(2)*C*H$_3$), 40.5 (*C*(4)), 43.3 (N*C*H$_2$), 43.4 (N*C*H$_2$), 45.7 (*C*(2)), 46.4 (*C*(3)), 127.1 (Ar*C*H), 127.27 (Ar*C*H), 127.33 (Ar*C*H), 127.5 (Ar*C*H), 127.7 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 137.9 (NCH$_2$Ar*C*(1)), 138.1 (NCH$_2$Ar*C*(1)), 141.3 (C(3)Ar*C*), 171.4 (*C*(5)), 174.0 (*C*(1)); *m/z* (NSI$^+$) 823 ([2M+Na]$^+$, 44%), 423 ([M+Na]$^+$, 42%), 401 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{26}H_{29}O_2N_2$ [M+H]$^+$ found 401.2221 requires 401.2224 (–0.6 ppm).

(2*S*,3*S*)-*N*^{1},*N*^{5}-Dibenzyl-3-(4-fluorophenyl)-2-methylpentanediamide 201



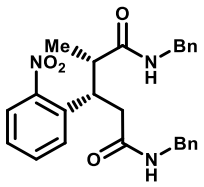
Following General Procedure **G**,1-oxopropan-2-yl 4-nitrobenzoate **147** (67 mg, 0.30 mmol), (E)-1,1,1-trichloro-4-(4-fluorophenyl)but-3-en-2-one **182** (54 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 3 h gave a crude brown oil (>95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude beige solid (>95:5 dr) that was triturated in Et_2O to give the title compound (76 mg, 90%) as a white solid. mp 204–206 °C; $[\alpha]_D^{20}$ –2.5 (*c* 0.52, DMSO); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) t_R minor: 12.8 min, t_R major: 19.1 min, >99:1 er; ν_{max} (film) cm^{-1} 3292 (N–H), 1645 (C=O), 1541 (N–C=O), 1508, 1495, 1456, 1219; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.22 (3H, d, *J* 6.9, C(2)C*H*$_3$), 2.45 (1H, dd, *J* 13.8, 8.7, C(4)*H*^{A}H^B), 2.65 (1H, p, *J* 7.0, C(2)*H*), 2.91 (1H, dd, *J* 13.8, 6.8, C(4)H^A*H*^{B}), 3.38 (1H, q, *J* 8.0, C(3)H), 4.16 (1H, dd, *J* 14.7, 5.1, N^{1}C*H*^{A}H^B), 4.26 (1H, dd, *J* 14.7, 5.3, N^{5}C*H*^{A}H^B), 4.37 (1H, dd, *J* 15.1, 6.8, N^{1}CH^A*H*^{B}), 4.42 (1H, dd, *J* 14.9, 6.4, N^{5}CH^A*H*^{B}), 5.61 (1H, t, *J* 5.5, N^1*H*), 6.01 (1H, t, *J* 5.5, N^5*H*), 6.88–6.94 (1H, m, C(3)ArC(3)*H*), 6.94–6.98 (2H, m, Ar*H* ×1 and C(3)ArC(5)*H*), 7.00–7.06 (2H, m, Ar*H*), 7.09–7.16 (2H, m, C(3)ArC(2,6)*H*), 7.23–7.28 (7H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 16.1 (C(2)*C*H$_3$), 40.7 (*C*(4)), 43.3 (N*C*H$_2$), 43.5 (N*C*H$_2$), 45.7 (*C*(2)), 45.7 (*C*(3)), 115.3 (d, J_{CF} 21.1, C(2)Ar*C*(3,5)), 127.4 (NCH$_2$Ar*C*(4)), 127.5 (NCH$_2$Ar*C*(4)), 127.6 (Ar*C*H × 2), 127.7 (Ar*C*H × 2), 128.6 (Ar*C*H × 4), 129.8 (d, J_{CF} 7.9, C(3)Ar*C*(2,6)), 136.9 (d, J_{CF} 3.1, C(3)Ar*C*(1)), 137.8 (NCH$_2$Ar*C*(1)), 138.0 (NCH$_2$Ar*C*(1)), 161.9 (d, J_{CF} 245.3, C(3)ArC(4)), 171.2 (*C*(5)), 173.8 (*C*(1)); ^{19}F (376 MHz, $CDCl_3$) δ_F: –115.60 (s, C(3)ArC(4)*F*); *m/z* (NSI$^+$) 441 ([M+Na]$^+$, 51%), 419 ([M+H]$^+$, 100%); HRMS (NSI$^+$) [M+H]$^+$ $C_{26}H_{28}O_2N_2F$ found 419.2129 requires 419.2129 (–0.1 ppm).

(2*S*,3*S*)-N^1,N^5-Dibenzyl-3-(4-methoxyphenyl)-2-methylpentanediamide 202



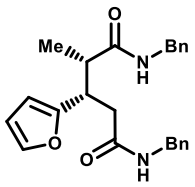
Following General Procedure **G**,1-oxopropan-2-yl 4-nitrobenzoate **147** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-(4-methoxyphenyl)but-3-en-2-one **171** (56 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 22 h gave a crude yellow solid (>95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude light-yellow solid (>95:5 dr) that was triturated in Et_2O to give the title compound (64 mg, 75%) as a white solid. mp 176–178 °C; $[\alpha]_D^{20}$ –12.8 (*c* 0.56, $CHCl_3$); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) t_R minor: 18.1 min, t_R major: 24.8 min, >99:1 er; ν_{max} (film) cm^{-1} 3273 (N–H), 1636 (C=O), 1558 (N–C=O), 1508, 1454, 1429, 1350, 1242; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.22 (3H, d, *J* 6.9, C(2)C*H*$_3$), 2.46 (1H, dd, *J* 13.8, 8.8, C(4)*H*^{A}H^B), 2.64 (1H, p, *J* 6.9, C(2)*H*), 2.91 (1H, dd, *J* 13.8, 6.8, C(4)H^A*H*^{B}), 3.32 (1H, q, *J* 8.0, C(3)*H*), 3.81 (3H, s, OC*H*$_3$), 4.15 (1H, dd, *J* 14.7, 5.1, N^{1}C*H*^{A}H^B), 4.25 (1H, dd, *J* 14.9, 5.3, N^{5}C*H*^{A}H^B), 4.37 (1H, dd, *J* 14.8, 6.4, N^{1}CH^A*H*^{B}), 4.42 (1H, dd, *J* 14.9, 6.3, N^{5}CH^A*H*^{B}), 5.60 (1H, t, *J* 5.5, N^1*H*), 6.08 (1H, t, *J* 5.4, N^5*H*), 6.74–6.82 (2H, m, C(3)ArC(3,5)*H*), 6.91–6.98 (2H, m, Ar*H*), 6.99–7.05 (2H, m, Ar*H*), 7.05–7.11 (2H, m, C(3)ArC(2,6)*H*), 7.21–7.28 (8H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 16.0 (C(2)*C*H$_3$), 40.8 (*C*(4)), 43.3 (N^1*C*H$_2$), 43.4 (N^5*C*H$_2$), 45.6 (*C*(3)), 45.9 (*C*(2)), 55.2 (O*C*H$_3$), 113.9 (C(3)Ar*C*(3,5)), 127.26 (Ar*C*H), 127.33 (Ar*C*H), 127.5 (Ar*C*H), 127.7 (Ar*C*H), 128.5 (Ar*C*H), 129.2 (C(3)Ar*C*(2,6)), 133.2 (C(3)Ar*C*(1)), 137.9 (NCH$_2$Ar*C*(1)), 138.1 (NCH$_2$Ar*C*(1)), 158.6 (C(3)Ar*C*(4)), 171.5 (*C*(5)), 174.1 (*C*(1)); *m/z* (NSI$^+$) 883 ([2M+Na]$^+$, 30%), 453 ([M+Na]$^+$, 58%), 431 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{27}H_{31}O_3N_2$ [M+H]$^+$ found 431.2328 requires 431.2329 (–0.3 ppm).

(2*S*,3*S*)-*N*^{1},*N*^{5}-Dibenzyl-2-methyl-3-(2-nitrophenyl)pentanediamide 203



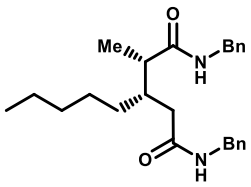
Following General Procedure **G**, 1-oxopropan-2-yl 4-nitrobenzoate **147** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-(2-nitrophenyl)but-3-en-2-one **183** (59 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 2 h gave a crude brown oil (>95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude light yellow solid (approx. 90:10 dr) that was triturated in Et_2O to give the title compound (60 mg, 68%) as a brown solid. mp 176 °C (*dec.*); $[\alpha]_D^{20}$ –2.3 (*c* 0.61, $CHCl_3$); Chiral HPLC AD-H (95:5 hexane : IPA, flow rate 1.5 mL·min^{-1}, 211 nm, 30 °C) t_R major: 63.9 min, t_R minor: 70.9 min, 99:1 er; ν_{max} (film) cm^{-1} 3292 (N–H), 1636 (C=O), 1558 (N–C=O), 1541 (N–C=O), 1522, 1456, 1354; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.21 (3H, d, *J* 6.9, C(2)C*H*$_3$), 2.60 (1H, dd, *J* 15.0, 9.3, C(4)*H*^{A}H^B), 2.80 (1H, p, *J* 7.1, C(2)*H*), 2.87 (1H, dd, *J* 15.0, 5.9, C(4)H^A*H*^{B}), 3.94–4.04 (1H, m, C(3)*H*), 4.21–4.34 (4H, m, NC*H*$_2$ × 2), 6.06 (1H, t, *J* 4.9, N*H*), 6.31 (1H, t, *J* 5.4, N*H*), 6.98–7.08 (4H, m, Ar*H*), 7.18–7.25 (5H, m, Ar*H*), 7.2–7.36 (1H, m, C(3)ArC(5)*H*), 7.36–7.41 (1H, m, C(3)ArC(3)*H*), 7.42–7.49 (1H, m, C(3)ArC(4)*H*), 7.66 (2H, dd, *J* 8.1, 1.2, C(3)ArC(6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 15.1 (C(2)*C*H$_3$), 38.6 (*C*(4)), 43.4 (N*C*H$_2$), 43.5 (N*C*H$_2$), 45.2 (*C*(2)), 124.6 (C(3)Ar*C*(6)), 127.3 (Ar*C*H), 127.4 (Ar*C*H), 127.6 (Ar*C*H), 127.6 (Ar*C*H), 128.6 (Ar*C*H), 132.6 (C(3)Ar*C*(4)), 135.9 (C(3)Ar*C*(1)), 137.9 (NCH$_2$Ar*C*(1)), 138.1 (NCH$_2$Ar*C*(1)), 150.3 (C(3)Ar*C*(2)), 170.4 (*C*(5)), 173.8 (*C*(1)), *C*(3) and C(3)Ar*C*(3) not observed; *m/z* (NSI$^+$) 468 ([M+Na]$^+$, 33%), 446 ([M+H]$^+$, 100%); HRMS (NSI$^+$) found $C_{26}H_{28}O_4N_3$ found 446.2072 requires 446.2074 (–0.5 ppm).

(2*S*,3*S*)-*N*^{1},*N*^{5}-Dibenzyl-3-(furan-2-yl)-2-methylpentanediamide 204



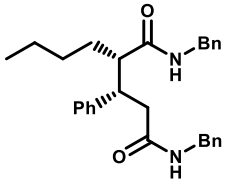
Following General Procedure **G**, 1-oxopropan-2-yl 4-nitrobenzoate **147** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-(furan-2-yl)but-3-en-2-one **176** (48 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 3 h gave a crude brown crystallised oil (95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude beige solid (>95:5 dr) that was triturated in Et_2O to give the title compound (58 mg, 75%) as a beige solid. mp 192–194 °C; $[\alpha]_D^{20}$ –1.4 (*c* 0.50, $CHCl_3$); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) t_R major: 19.8 min, t_R minor: 27.6 min, >99:1 er; ν_{max} (film) cm^{-1} 3279 (N–H), 1645 (C=O), 1562 (N–C=O), 1541 (N–C=O), 1506, 1456; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.19 (3H, d, *J* 7.0, C(2)C*H*$_3$), 2.53 (1H, dd, *J* 13.9, 8.5, C(4)*H*^{A}H^B), 2.71 (1H, p, *J* 7.0, C(2)*H*), 2.80 (1H, dd, *J* 13.9, 6.7, C(4)H^A*H*^{B}), 3.49–3.58 (1H, m, C(3)*H*), 4.25–4.36 (3H, m, N^{1}C*H*$_2$ and N^{5}C*H*^{A}H^B), 4.41 (1H, dd, *J* 14.8, 6.0, N^{5}CH^A*H*^{B}), 5.76 (1H, t, *J* 5.2, N^1*H*), 6.06–6.10 (1H, m, C(3)ArC(5)*H*), 6.15 (1H, t, *J* 4.9, N^5*H*), 6.25 (1H, dd, *J* 3.2, 1.9, C(3)ArC(4)*H*), 7.10–7.18 (4H, m, Ar*H*), 7.22 (1H, dd, *J* 1.8, 0.8, C(3)ArC(3)*H*), 7.23–7.32 (6H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 15.2 (C(2)*C*H$_3$), 38.2 (*C*(4)), 39.8 (*C*(3)), 45.54 (N*C*H$_2$Ph), 45.55 (N*C*H$_2$Ph), 43.9 (*C*(2)), 107.3 (C(3)Ar*C*(5)), 110.3 (C(3)Ar*C*(4)), 127.4 (Ar*C*H), 127.5 (Ar*C*H), 127.7 (Ar*C*H), 127.9 (Ar*C*H), 128.60 (Ar*C*H), 128.61 (Ar*C*H), 138.0 (NCH$_2$Ar*C*(1)), 138.2 (NCH$_2$Ar*C*(1)), 141.4 (C(3)Ar*C*(3)), 154.6 (C(3)Ar*C*(1)), 171.1 (*C*(5)), 173.9 (*C*(1)); *m/z* (NSI$^+$) 413 ([M+Na]$^+$, 41%), 391 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{24}H_{27}O_3N_2$ [M+H]$^+$ found 391.2016 requires 391.2016 (+0.0 ppm).

(2S,3S)-N1,N5-Dibenzyl-2-methyl-3-pentylpentanediamide 205



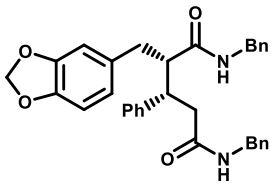
Following General Procedure **G**, 1-oxopropan-2-yl 4-nitrobenzoate **147** (67 mg, 0.30 mmol), (*E*)-1,1,1-trichloronon-3-en-2-one **181** (56 mg, 0.20 mmol), NHC precatalyst **30** (7.4 mg, 0.020 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 24 h gave a crude brown oil (>95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude orange paste (>95:5 dr) that was triturated in Et_2O to give the title compound (21 mg, 26%) as a white solid. mp 168–170°C; $[\alpha]_D^{20}$ +15.0 (*c* 0.40, $CHCl_3$); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 40 °C) t_R minor: 5.3 min, t_R major: 5.8 min, >99:1 er; ν_{max} (film) cm^{-1} 3287 (N–H), 1636 (C=O), 1541 (N–C=O), 1535 (N–C=O), 1454; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.86 (3H, t, *J* 6.8, C*H*$_3$), 1.12 (3H, d, *J* 7.0, C(2)C*H*$_3$), 1.16–1.36 (7H, m, CH$_3$(C*H*$_2$)$_3$ and C(3)C*H*^{A}H^B), 1.43–1.53 (1H, m, C(3)CH^A*H*^{B}), 1.95–2.07 (1H, m, C(3)*H*), 2.22 (1H, dd, *J* 13.9, 6.1, C(4)*H*^{A}H^B), 2.29 (1H, dd, *J* 13.9, 8.0, C(4)H^A*H*^{B}), 2.50–2.59 (1H, m, C(2)*H*), 4.39–4.44 (4H, m, NC*H*$_2$ × 2), 6.14 (1H, t, *J* 4.8, N^5*H*), 6.48 (1H, t, *J* 5.1, N^1*H*), 7.23–7.35 (10H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 14.0 (C(2)*C*H$_3$), 14.1 (*C*H$_3$), 22.6 (CH$_3$*C*H$_2$), 27.3 (CH$_3$(CH$_2$)$_2$*C*H$_2$), 31.1 (C(3)*C*H$_2$), 31.9 (CH$_3$CH$_2$*C*H$_2$), 38.7 (*C*(4)), 40.0 (*C*(3)), 42.1 (*C*(2)), 43.4 (N*C*H$_2$), 43.5 (N*C*H$_2$), 127.4 (Ar*C*H), 127.5 (Ar*C*H), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 128.7 (Ar*C*H), 128.7 (Ar*C*H), 138.4 (NCH$_2$Ar*C*(1)), 138.6 (NCH$_2$Ar*C*(1)), 172.9 (*C*(5)), 174.7 (*C*(1)); *m/z* (NSI$^+$) ([2M+Na]$^+$, 34%), 395 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{25}H_{35}O_2N_2$ [M+H]$^+$ found 395.2690 requires 395.2693.

(2*S*,3*S*)-*N*^{1},*N*^{5}-Dibenzyl-2-butyl-3-phenylpentanediamide 206



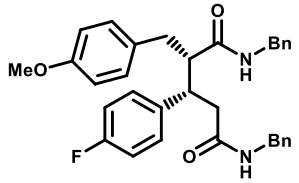
Following General Procedure **G**, 1-oxohexan-2-yl 4-nitrobenzoate **155** (80 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (50 mg, 0.20 mmol), NHC precatalyst **30** (7.4 mg, 0.020 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous THF (2.7 mL) at rt for 3 h gave a crude brown-green oil (>95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude beige solid (>95:5 dr) that was triturated in Et_2O to give the title compound (78 mg, 89%) as a white solid. mp 205–207 °C; $[\alpha]_D^{20}$ –21.6 (*c* 0.63, $CHCl_3$); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) t_R minor: 11.9 min, t_R major: 17.7 min, >99:1 er; ν_{max} (film) cm^{-1} 3279 (N–H), 3252 (N–H), 1636 (C=O), 1558 (N–C=O), 1495, 1454; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.87 (3H, t, *J* 6.9, C*H*$_3$), 1.19–1.34 (4H, m, C(2)CH$_2$(C*H*$_2$)$_2$), 1.52–1.60 (2H, m, C(2)C*H*$_2$), 2.41–2.51 (2H, m, C(2)*H* and C(4)*H*^{A}H^B), 2.89 (1H, dd, *J* 13.8, 7.0, C(4)H^A*H*^{B}), 3.38 (1H, q, *J* 8.0, C(3)*H*), 4.13 (1H, dd, *J* 14.7, 5.1, N^{1}C*H*^{A}H^B), 4.26 (1H, dd, *J* 14.8, 5.4, N^{5}C*H*^{A}H^B), 4.30 (1H, dd, *J* 14.8, 6.2, N^{1}CH^A*H*^{B}), 4.36 (1H, dd, *J* 14.8, 6.1, N^{5}CH^A*H*^{B}), 5.48 (1H, t, *J* 5.3, N^1*H*), 5.96 (1H, t, *J* 5.1, N^5*H*), 6.90–6.95 (2H, m, Ar*H*), 6.98–7.03 (2H, m, Ar*H*), 7.11–7.16 (2H, m, Ar*H*), 7.19–7.26 (9H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 22.7 (*C*H$_2$), 29.8 (*C*H$_2$), 30.2 (C(2)*C*H$_2$), 40.7 (*C*(4)), 43.3(N*C*H$_2$), 43.5 (N*C*H$_2$), 45.3 (*C*(3)), 52.2 (*C*(2)), 127.0 (Ar*C*H), 127.28 (Ar*C*H), 127.32 (Ar*C*H), 127.6 (Ar*C*H × 2), 127.8 (Ar*C*H × 2), 128.3 (Ar*C*H × 2), 128.50 (Ar*C*H × 2), 128.53 (Ar*C*H × 2), 128.6 (Ar*C*H × 2), 138.0 (NCH$_2$Ar*C*), 138.1 (NCH$_2$Ar*C*), 141.4 (C(3)Ar*C*(1)), 171.4 (*C*(5)), 173.2 (C(1)); *m/z* (NSI$^+$) 443 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{29}H_{35}O_2N_2$ [M+H]$^+$ found 443.2692 requires 443.2653 (–0.2 ppm).

(2*S*,3*S*)-2-(Benzo[d][1,3]dioxol-5-ylmethyl)-*N*^{1},*N*^{5}-dibenzyl-3-phenylpentanediamide 207



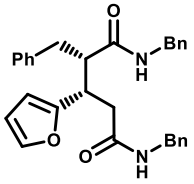
Following General Procedure **G**, 1-(benzo[d][1,3]dioxol-5-yl)-3-oxopropan-2-yl 4-nitrobenzoate **148** (103 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **157** (50 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 27 h gave a crude brown oil (85:15 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude brown solid (80:20 dr) that was triturated in Et_2O to give the title compound (50 mg, 48%) as an off-white solid. mp 198 °C (*dec*); $[\alpha]_D^{20}$ –39.4 (*c* 0.18, $CHCl_3$); er could not be determined; ν_{max} (film) cm^{-1} 3296 (N–H), 1643 (C=O), 1553 (N–C=O), 1499, 1487, 1354; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.57 (1H, dd, *J* 14.0, 8.3, C(4)*H*^{A}H^B), 2.74–2.84 (2H, m, C(2)*H* and C(2)C*H*^{A}H^B), 2.84–2.96 (2H, m, C(2)H^A*H*^{B} and C(4)H^A*H*^{B}), 3.43–3.52 (1H, m, C(3)*H*), 4.01–4.15 (2H, m, NC*H*$_2$), 4.26–4.40 (2H, m, NC*H*$_2$), 5.43 (1H, t, *J* 5.2, N*H*), 5.83 (1H, t, *J* 5.3, *NH*), 5.88–5.94 (2H, m, OC*H*$_2$O), 6.56–6.62 (1H, m, C(2)CH$_2$Ar*H*), 6.62–6.70 (2H, m, C(2)CH$_2$Ar*H*), 6.70–6.75 (2H, m, Ar*H*), 6.99–7.05 (2H, m, Ar*H*), 7.12–7.21 (5H, m, Ar*H*), 7.22–7.25 (6H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 36.2 (C(2)*C*H$_2$), 40.5 (*C*(4)), 43.0 (NCH$_2$), 43.5 (NCH$_2$), 45.2 (*C*(3)), 54.4 (*C*(2)), 100.8 (OCH$_2$O), 109.3 (C(2)CH$_2$Ar*C*H), 121.9 (C(2)CH$_2$Ar*C*H), 127.1 (Ar*C*H × 2), 127.4 (Ar*C*H), 127.5 (Ar*C*H × 2), 127.6 (Ar*C*H × 2), 128.3 (Ar*C*H × 2), 128.4 (Ar*C*H × 2), 128.6 (Ar*C*H × 2), 128.6 (Ar*C*H × 2), 133.1 (C(2)CH$_2$Ar*C*(1)), 137.8 (NCH$_2$Ar*C*(1)), 138.0 (NCH$_2$Ar*C*(1)), 141.2 (C(3)Ar*C*(1)), 146.0 (C(2)CH$_2$Ar*C*(2a or 6a)), 147.6 (C(2)CH$_2$Ar*C*(6a or 2a)), 171.2 (*C*=O), 172.2 (*C*=O); *m/z* (NSI$^+$) 543 ([M+Na]$^+$, 31%), 521 ([M+H]$^+$, 100%); HRMS (NSI)$^+$ $C_{23}H_{33}O_4N_2$ [M+H]$^+$ found 521.2440 requires 521.2435 (+1.0 ppm).

(2*S*,3*S*)-*N*^{1},*N*^{5}-Dibenzyl-3-(4-fluorophenyl)-2-(4-methoxybenzyl)pentanediamide 208



Following General Procedure **G**, 1-(4-methoxyphenyl)-3-oxopropan-2-yl 4-nitrobenzoate **158** (99 mg, 0.30 mmol), (E)-1,1,1-trichloro-4-(4-fluorophenyl)but-3-en-2-one **182** (54 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous CH_2Cl_2 (2.7 mL) at rt for 6 h gave a crude brown oil (>95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude yellow solid (>95:5 dr) that was triturated in Et_2O to give the title compound (61 mg, 60%) as a beige solid. mp 221–223 °C; $[\alpha]_D^{20}$ –23.9 (*c* 0.41, DMSO); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.5 mL·min^{-1}, 211 nm, 40 °C) t_R major: 16.9 min, t_R minor: 21.2 min, 99:1 er; ν_{max} (film) cm^{-1} 3343 (N–H), 3296 (N–H), 1639 (C=O), 1553 (N–C=O), 1454, 1422, 1356; ^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 2.52 (1H, dd, *J* 14.0, 8.5, C(4)*H*^{A}H^B), 2.71–2.78 (1H, m, C(2)*H*), 2.77–2.83 (1H, m, C(2)C*H*^{A}H^B), 2.85–2.93 (2H, m, C(4)H^A*H*^{B} and C(2)CH^A*H*^{B}), 3.48 (1H, q, *J* 8.1, C(3)*H*), 3.79 (3H, s, OC*H*$_3$), 4.00 (1H, dd, *J* 14.8, 5.6, N^{1}C*H*^{A}H^B), 4.12 (1H, dd, *J* 14.9, 6.0, N^{1}C*H*^{A}*H*^{B}), 4.28 (1H, dd, *J* 14.7, 5.5, N^{5}C*H*^{A}H^B), 4.38 (1H, dd, *J* 14.7, 6.0, N^{5}CH^A*H*^{B}), 5.41 (1H, t, *J* 5.6, N^1*H*), 5.78 (1H, t, *J* 5.1, N^5*H*), 6.67–6.71 (2H, m, Ar*H*), 6.75–6.80 (2H, m, Ar*H*), 6.89–6.95 (1H, m, Ar*H*), 7.00–7.03 (1H, m, Ar*H*), 7.03–7.06 (1H, m, Ar*H*), 7.12–7.18 (4H, m, Ar*H*), 7.24–7.28 (6H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 35.7 (C(2)*C*H$_2$), 40.7 (*C*(4)), 43.0 (N^1*C*H$_2$), 43.5 (N^5*C*H$_2$), 44.4 (*C*(3)), 54.4 (*C*(2)), 55.2 (O*C*H$_3$), 113.9 (C(2)CH$_2$Ar*C*(3,5)), 115.3 (d, J_{CF} 21.2, C(3)Ar*C*(3,5)), 127.2 (NCH$_2$Ar*C*(4)), 127.5 (NCH$_2$Ar*C*(4) and N^{1}CH$_2$Ar*C*(2,6)), 127.6 (N^{5}CH$_2$Ar*C*(2,6)), 128.4 (NCH$_2$Ar*C*(3,5)), 128.6 (NCH$_2$Ar*C*(3,5)), 129.87 (C(2)Ar*C*(2,6)), 129.93 (d, J_{CF} 7.8, C(3)Ar*C*(2,6)), 131.1 (C(2)Ar*C*(1)), 137.0 (d, J_{CF} 3.0, C(3)Ar*C*(1)), 137.8 (NCH$_2$Ar*C*), 137.9 (NCH$_2$Ar*C*), 158.2 (C(2)CH$_2$Ar*C*(4)), 161.9 (d, J_{CF} 245.3, C(3)Ar*C*(4)), 170.9 (*C*(5)), 172.2 (*C*(1)); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F: –115.57 (s, C(3)ArC(4)*F*); *m/z* (NSI$^+$) 547 ([M+Na]$^+$, 43%), 523 ([M+H]$^+$, 100%); HRMS (NSI)$^+$ $C_{33}H_{34}O_3N_2F$ [M+H]$^+$ found 524.2554 requires 523.2548 (+1.1 ppm).

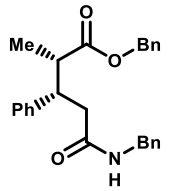
(2*S*,3*S*)-*N*^{1},*N*^{5},2-Tribenzyl-3-(furan-2-yl)pentanediamide 209



Following General Procedure **G**, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate **156** (90 mg, 0.30 mmol), (*E*)-1,1,1-trichloro-4-(furan-2-yl)but-3-en-2-one **176** (48 mg, 0.20 mmol), NHC precatalyst **30** (3.7 mg, 0.010 mmol) and Et_3N (42 μL, 0.30 mmol) in anhydrous THF (2.7 mL) at rt for 4 h gave a crude brown oil (>95:5 *syn*:*anti* dr). The crude was stirred in anhydrous CH_2Cl_2 (6.6 mL) with benzylamine (6.6 mL, 60 mmol) at rt for 16 h to give a crude orange solid (>95:5 dr) that was triturated in Et_2O to give the title compound (36 mg, 39%) as a off-white solid. mp 192–194 °C; $[\alpha]_D^{20}$ –17.3 (*c* 0.48, $CHCl_3$); Chiral HPLC AD-H (80:20 hexane : IPA, flow rate 1.5 mL·min^{-1}, 211 nm, 40 °C) t_R major: 5.6 min, t_R minor: 13.0 min, >99:1 er; ν_{max} (film) cm^{-1} 3275 (N–H), 1638 (C=O), 1560 (N–C=O), 1533, 1495, 1452; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.61 (1H, dd, *J* 14.0, 8.3, C(4)*H*^{A}H^B), 2.83–2.99 (4H, m, C(4)H^A*H*^{B}, C(2)*H*, C(2)C*H*$_2$), 3.59–3.68 (1H, m, C(3)*H*), 4.14 (1H, dd, *J* 14.8, 5.6, N^{1}C*H*^{A}H^B), 4.21 (1H, dd, *J* 14.8, 5.9, N^{1}CH^A*H*^{B}), 4.31–4.42 (2H, m, N^{5}C*H*$_2$), 5.62 (1H, t, *J* 5.5, N^1*H*), 5.98 (1H, t, *J* 5.5, N^5*H*), 6.12–6.17 (1H, m, C(3)ArC(5)*H*), 6.29 (1H, dd, *J* 3.2, 1.9, C(3)ArC(4)*H*), 6.84–6.90 (2H, m, Ar*H*), 7.10–7.17 (4H, m, Ar*H*), 7.17–7.21 (4H, m, Ar*H*), 7.21–7.25 (3H, m, Ar*H*), 7.26–7.33 (3H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 35.8 (C(2)C*H*$_2$), 38.2 (*C*(4)), 38.6 (*C*(3)), 43.3 (N^1*C*H$_2$), 43.6 (N^5*C*H$_2$), 52.1 (*C*(2)), 107.5 (C(3)Ar*C*(4)), 110.4 (C(3)Ar*C*(5)), 126.4 (Ar*C*H), 127.2 (Ar*C*H), 127.4 (Ar*C*H), 127.6 (Ar*C*H × 2), 127.8 (Ar*C*H × 2), 128.4 (Ar*C*H × 2), 128.5 (Ar*C*H × 2), 128.6 (Ar*C*H × 2), 128.9 (Ar*C*H × 2), 137.9 (NCH$_2$Ar*C*(1)), 138.1 (NCH$_2$Ar*C*(1)), 139.3 (C(2)CH$_2$Ar*C*(1)), 141.4 (C(3)Ar*C*(3)), 154.4 (C(3)Ar*C*(1)), 170.9 (*C*(5)), 172.2 (*C*(1)); *m/z* (NSI$^+$) 489 ([M+Na]$^+$, 34%), 467 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{30}H_{31}O_3N_2$ [M+H]$^+$ found 467.2326 requires 467.2329 (–0.7 ppm).

4-1-7 γ-Ester Amide (Scheme 63)

(2*S*,3*S*)-Benzyl 5-(benzylamino)-2-methyl-5-oxo-3-phenylpentanoate 210



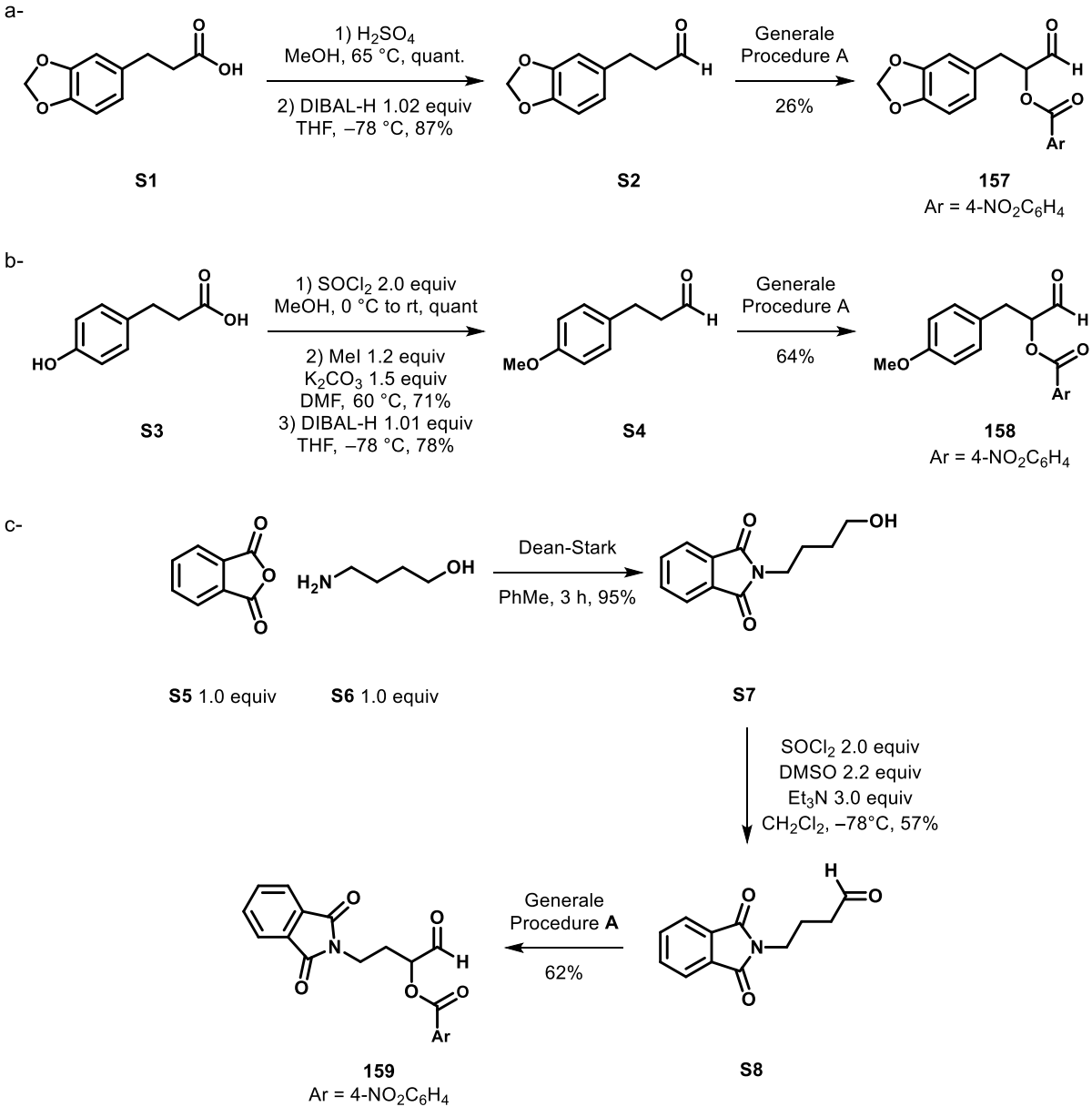
1-Oxopropan-2-yl 4-nitrobenzoate **147** (0.30 mmol, 67 mg, 1.5 equiv), **(***E***)**-1,1,1-trichloro-4-phenylbut-3-en-2-one **148** (0.20 mmol, 50 mg, 1.0 equiv) and NHC precatalyst **30** (0.010 mmol, 3.7 mg, 5 mol%) were dissolved in anhydrous CH_2Cl_2 (2.7 mL). Et_3N (0.30 mmol, 42 μL, 1.5 equiv) was added and the reaction mixture was stirred at rt for 3.5 h. The mixture was diluted in EtOAc (10 mL) and washed with water (10 mL × 2), sodium bisulfite aq. 40% (10 mL × 2), and brine (10 mL × 2). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude orange solid (77 mg, >95:5 dr). The crude was dissolved in anhydrous CH_2Cl_2 (6.6 mL) with BnOH (60 mmol, 6.6 mL, 300 equiv) and DMAP (0.04 mmol, 5 mg, 20 mol%). The reaction mixture was stirred over 16 h then concentrated under reduced pressure and BnOH was removed by Kugelrohr distillation to give a crude orange oil (105 mg, >95:5 dr). The crude was stirred in anhydrous CH_2Cl_2 (2.6 mL) with benzylamine (2.6 mL, 0.24 mmol, 1.2 equiv) at rt for 16 h. The reaction mixture was diluted in EtOAc (20 mL) and wash with 1 M HCl (20 mL × 3), sat. aq. $NaHCO_3$ (20 mL × 3) and brine (20 mL × 3). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude orange oil (105 mg, >95:5 dr) that was purified by Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, hexane : EtOAc (80:20 1 CV, 80:20 to 50:50 15 CV, 50:50 5 CV)] to give the title compound (26 mg, 32%) as a yellow solid. mp 98–100 °C; $[\alpha]_D^{20}$ +6.92 (*c* 0.52, $CHCl_3$); Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.0 mL·min^{-1}, 211 nm, 30 °C) t_R minor: 19.7 min, t_R major: 26.2 min, >99:1 er; ν_{max} (film) cm^{-1} 3319, 3269, 1720 (C(1)=O), 1643 (C(5)=O), 1549 (N–C=O), 1495, 1454, 1256; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.24 (3H, d, *J* 7.0, C(2)CH_3), 2.44 (1H, dd, *J* 14.0, 9.8, C(4)H^AH^B), 2.79 (1H, dd, *J* 14.0, 5.6, C(4)H^AH^B), 2.82–2.92 (1H, m, C(2)*H*), 3.40–3.50 (1H, m, C(3)*H*), 4.18 (1H, dd, *J* 14.8, 5.3, NCH^AH^B), 4.34 (1H, dd, *J* 14.8, 6.2, NCH^AH^B), 4.88 (1H, d, *J* 12.3, OCH^AH^B), 4.93 (1H, d, *J* 12.3, OCH^AH^B), 5.51 (1H, t, *J* 5.1, N*H*), 6.87–6.94 (2H, m, Ar*H*), 7.09–7.17 (4H, m, Ar*H*), 7.18–7.25 (6H, m, Ar*H*), 7.26–7.32 (3H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 15.3 (C(2)CH_3), 40.5 (*C*(4)), 43.4 (NCH_2), 44.8 (*C*(2)), 45.8 (*C*(3)), 66.2 (OCH_2), 127.1 (Ar*C*H), 127.3 (Ar*C*H), 127.5

(Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*H), 128.48 (Ar*C*H), 128.54 (Ar*C*H), 135.7 (OCH_2Ar*C*(1)), 137.9 (NCH_2Ar*C*(1)), 141.1 (C(3)Ar*C*(1)) 170.9 (*C*(5)), 174.6 (*C*(1)); *m/z* (NSI^+) 424 ($[M+Na]^+$, 33%), 402 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{26}H_{28}O_3N_1$ $[M+H]^+$ found 402.2062 requires 402.2064 (–0.4 ppm).

4-1-8 Appendix for chapter 2

Synthesis of α-aroyloxyaldehydes 157 to 159

The synthesis of α-aroyloxyaldehydes **157** to **159** were reported by the Smith group and required the formation of their corresponding aldehydes.[5,15,16] The required aldehyde **S2** was obtained in 87% over 2 steps from the corresponding carboxylic acid **S1** and gave **157** in 26% yield.[5] Aldehyde **S4** was obtained in 55% over 3 steps starting from 3-(4-hydroxyphenyl)propanoic acid **S2** and led to **158** in 64% following generale procedure **A**. desired phthalamide protected α-aroyloxyaldehyde **159** was obtained in 34% over 3 steps from phthalic anhydride **S5** and 4-aminobutan-1-ol **S6**.[16]

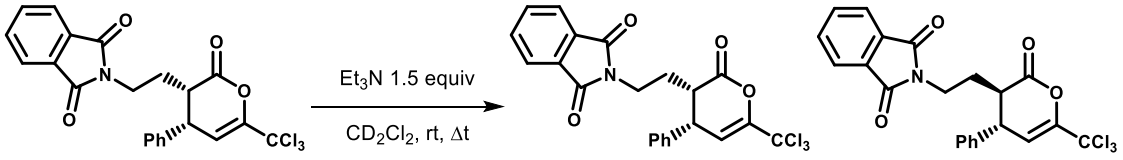


Epimerisation of 191 (Table 9)

2-(2-((3*S*,4*S*)-2-Oxo-4-phenyl-6-(trichloromethyl)-3,4-dihydro-2*H*-pyran-3-yl)ethyl) isoindo-line-1,3-dione **191** (13.2 mg, 0.028 mmol, 1.0 equiv) was dissolved in $CDCl_2$ before adding Et_3N (5.9 µL, 0.42 mmol, 1.5 equiv). The ratio between the two diastereoisomers were monitored using ^1H NMR by comparing the ratio between *syn*-C(5)*H* (δ_H 6.21 (1H, d, *J* 3.7)) and *anti*-C(5)*H* (δ_H 6.45 (1H, d, *J* 6.9)).

HPLC data *syn*-**191**: Chiral HPLC OD-H (97:3 hexane : IPA, flow rate 1.0 $mL \cdot min^{-1}$, 211 nm, 30 °C): t_R (3*R*,4*R*): 34.3 min, t_R (3*S*,4*S*): 42.2 min.

HPLC data *anti*-**191**: Chiral HPLC OD-H (97:3 hexane : IPA, flow rate 1.0 $mL \cdot min^{-1}$, 211 nm, 30 °C): t_R (3*R*,4*S*): 51.3 min, t_R (3*S*,4*R*): 59.2 min.



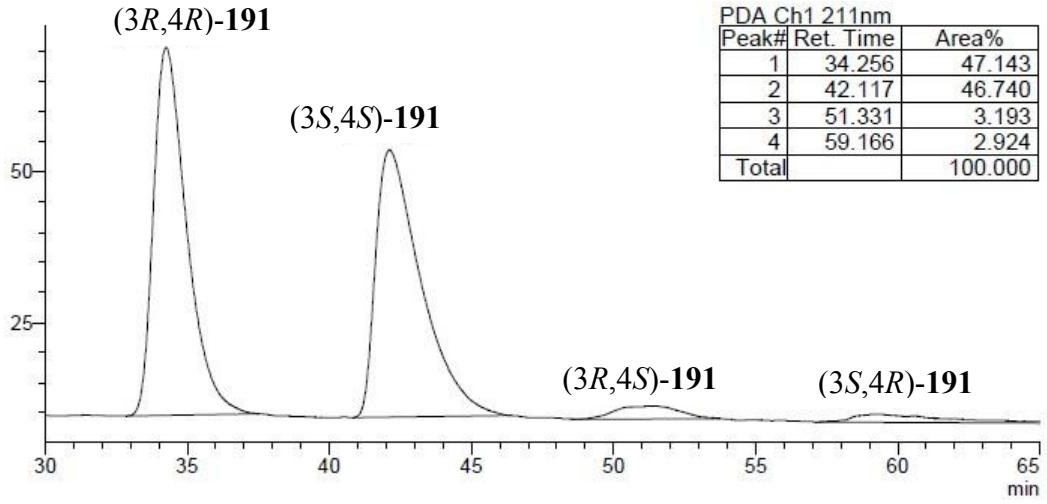
191 90:10 dr

Major *syn*-**191**

Minor *anti*-**191**

	Epimerisation	**dr**		**er**	
Entry	**Δt**	***syn*-191**	***anti*-191**	***syn*-191**	***anti*-191**
1	0	90	10	>99:1	>99:1
2	1 h	85	15	–	–
3	5 h	82	18	–	–
4	23 h	78	22	–	–
5	72 h	67	33	>99:1	>99:1

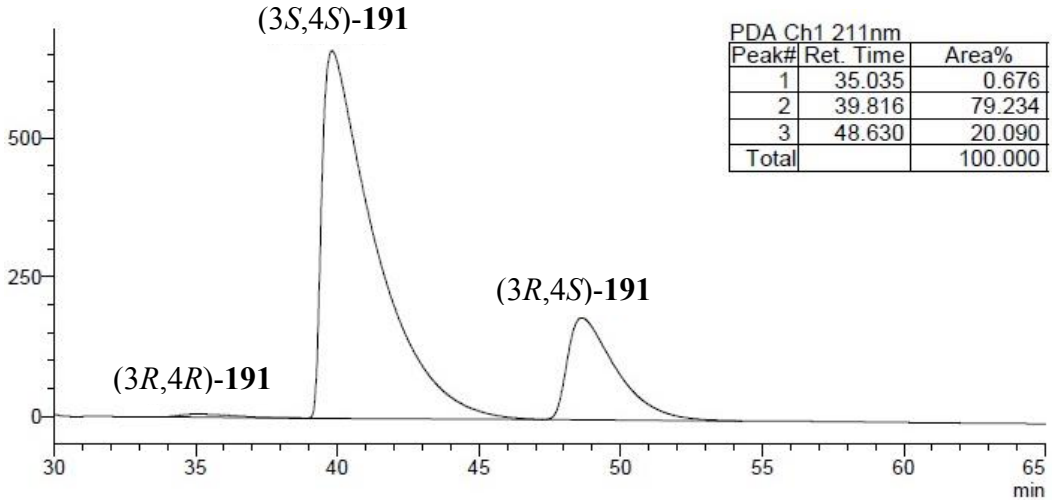
Racemic



PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	34.256	47.143
2	42.117	46.740
3	51.331	3.193
4	59.166	2.924
Total		100.000

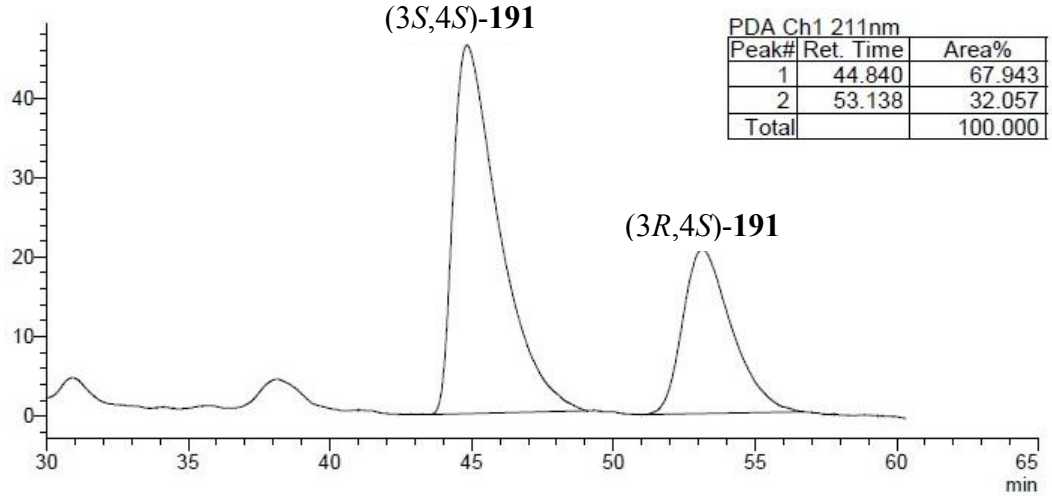
Starting Material (t = 0)



PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	35.035	0.676
2	39.816	79.234
3	48.630	20.090
Total		100.000

After Epimerisation (t = 72 h)



PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	44.840	67.943
2	53.138	32.057
Total		100.000

4-1-9 References for section 4-1

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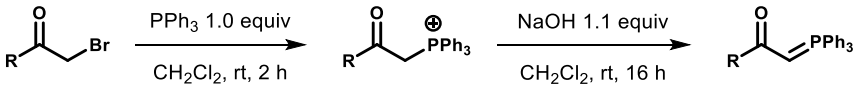
4-2 Experimental for chapter 3: Carboxylic acids as azolium enolate precursors in intramolecular formal [4+2] cycloadditions

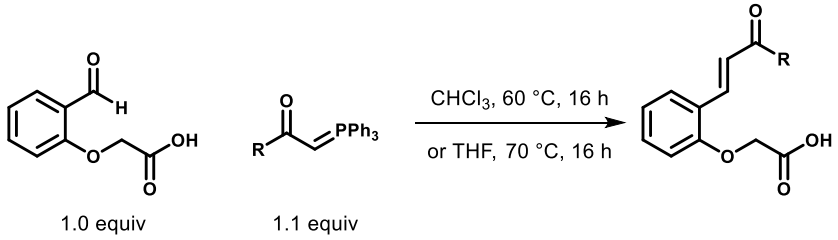
4-2-1 General procedures for chapter 3

General procedure A: Synthesis of phosphoranes



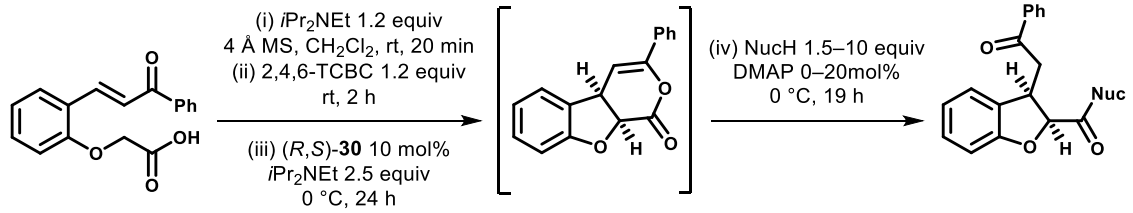
Triphenylphosphine (20 mmol, 1.0 equiv) and the required aromatic acyl bromide (20 mmol, 1.0 equiv) were stirred in CH_2Cl_2 (0.25 M) for 2 h at rt before adding 2 M NaOH (21 mmol, 1.05 equiv) and stirring for another 16 h at rt. The layers were separated and the aqueous was extracted with CH_2Cl_2 (× 3). The combined organic was washed with brine (× 3), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude oil that was precipitated by addition of a few drops of Et_2O. The residual Et_2O was removed under reduced pressure to give a solid that was further purified by recrystallisation in PhMe when required to give the desired phosphorane with data in accordance to literature.

General procedure B: Synthesis of enone-acid



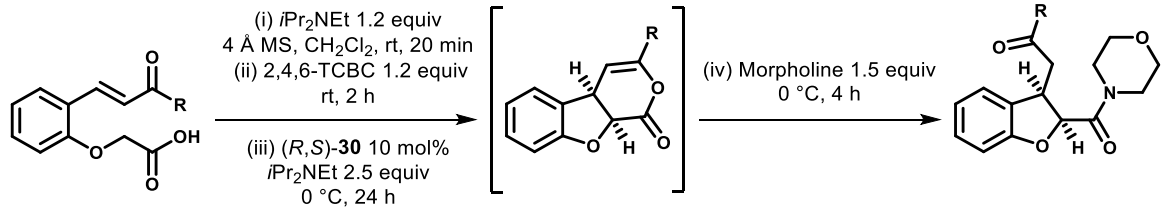
2-(Formylphenoxy) acetic acid (1.0 equiv) and the required phosphorane ylide were heated under reflux in $CHCl_3$ or anhydrous THF overnight. The resulting reaction mixture was concentrated under reduced pressure. The residue was diluted in EtOAc and basified to pH 10 with saturated $NaHCO_3$. The aqueous was washed with EtOAc (× 3) before being acidified to pH 1 with 1 M HCl or pH 5 with 10% citric acid. The aqueous was extracted with EtOAc (× 3). The combined organic was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude solid that was further purified by trituration in Et_2O when required to give the desired enone-acid with data in accordance to literature.

General procedure C: Synthesis of benzofuran derivatives: Nucleophile scope



Enone-acid **239** (0.20 mmol, 1.0 equiv) and distilled *i*Pr$_2$NEt (0.22 mmol, 1.1 equiv) were stirred at rt for 20 min in anhydrous CH_2Cl_2 (3.0 mL) in a Schlenk flask containing 4 Å molecular sieves. Distilled 2,4,6-trichlorobenzoyl chloride (0.22 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 2 h then cooled down to 0 ºC using an immersion cooler. NHC precatalyst **30** (0.02 mmol, 10 mol%) was added, followed with distilled *i*Pr$_2$NEt (0.50 mmol, 2.5 equiv) and the reaction mixture was stirred at 0 ºC using an immersion cooler for 24 h. The appropriate nucleophile (0.30–2.0 mmol, 1.5–10 equiv) and when required DMAP (0.04 mmol, 20 mol%) were added and stirring was carried on at 0 ºC for the required amount of time. The reaction mixture was concentrated under reduced pressure to give the crude product that was purified by flash silica column chromatography to give the desired product.

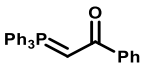
General procedure D: Synthesis of benzofuran derivatives: Enone-acid scope



The appropriate enone-acid (0.20 mmol, 1.0 equiv) and distilled *i*Pr$_2$NEt (0.24 mmol, 1.2 equiv) were stirred at rt for 20 min in anhydrous CH_2Cl_2 (3.0 mL) in a Schlenk flask containing 4 Å molecular sieves. Distilled 2,4,6-trichlorobenzoyl chloride (0.24 mmol, 1.2 equiv) was added and the reaction mixture was stirred at rt for 2 h then cooled down to 0 ºC using an immersion cooler. NHC precatalyst **30** (0.020 mmol, 10 mol%) followed by distilled *i*Pr$_2$NEt (0.50 mmol, 2.5 equiv) were added and the reaction mixture was stirred at 0 ºC using an immersion cooler for 24 h. Morpholine (1.5 equiv, 0.30 mmol) was added and stirring was carried on at 0 ºC for 4 h. The reaction mixture was concentrated under reduced pressure to give the crude product that was purified by flash silica column chromatography to give the desired product.

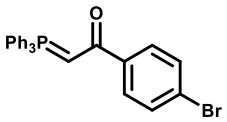
4-2-2 Synthesis of phosphoranes

1-Phenyl-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one 237



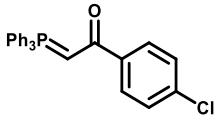
Triphenyl phosphine (25 g, 95 mmol, 1.0 equiv) and 2-bromoacetophenone (18.8 g, 95 mmol, 1.0 equiv) were stirred in CH_2Cl_2 (400 mL) for 2 h at rt. The obtained suspension was filtered. The precipitate was washed with CH_2Cl_2 and dried under high vacuum to give a white solid (27 g, $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$) δ_P: 21.98). The solid was suspended in CH_2Cl (115 mL) before adding 2 M NaOH (50 mL, 100 mmol, 1.05 equiv) to form a biphasic solution that was stirred overnight at rt. The reaction mixture was diluted distilled H_2O and the layers were separated. The aqueous was extracted with CH_2Cl_2 (× 3). The combined organic was washed with brine (× 3), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a slightly yellow crude oil that was precipitated by adding a few drops of Et_2O. The residual Et_2O was removed under reduced pressure to give the title compound (25.3 g, 70%) as a crude white solid with data in accordance with literature.[1] mp 176–178 ºC {Lit.[1] 173–175 ºC}; ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 4.45 (1H, d, *J* 24.6, Ph_3P=C*H*), 7.34–7.41 (3H, m), 7.45–7.54 (6H, m, Ar*H* × 6), 7.54–7.64 (3H, m, Ar*H* × 3), 7.68–7.81 (6H, m, Ar*H* × 6), 7.96–8.02 (2H, m, Ar*H* × 2); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ_P: 16.61.

1-(4-Bromophenyl)-2-(triphenyl-l5-phosphaneylidene)ethan-1-one 253



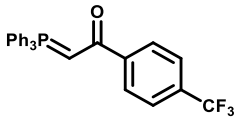
Following general procedure **A**, the title compound was obtained after recrystallisation as an off white solid (6.3 g, 59%) with data in accordance with literature.[2] mp 196–198 ºC {Lit.[2] 199–201 ºC}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 4.38 (1H, d, *J* 23.9, Ph_3P=C*H*), 7.44–7.51 (8H, m, Ar*H* × 8), 7.54–7.60 (3H, m, Ar*H* × 3), 7.67–7.75 (6H, m, Ar*H* × 6), 7.80–7.86 (2H, m, Ar*H* × 2).; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ_P: 16.68.

1-(4-Chlorophenyl)-2-(triphenyl-l5-phosphaneylidene)ethan-1-one 254



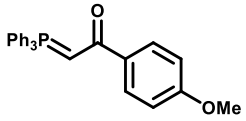
Following general procedure **A**, the title compound was obtained after recrystallisation an off white solid (6.1 g, 74%) with data in accordance with literature.[1] mp 173–175 ºC {Lit.[1] 168–170 ºC}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.38 (1H, d, *J* 24.0, Ph_3P=C*H*), 7.28–7.34 (2H, m,), 7.44–7.52 (6H, m, Ar*H* × 6), 7.54–7.61 (3H, m, Ar*H* × 3), 7.67–7.76 (6H, m, Ar*H* × 6), 7.87–7.94 (2H, m, Ar*H* × 2).^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ_P: 16.67.

1-(4-(Trifluoromethyl)phenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one 255



Triphenyl phosphine (5.63 g, 21.5 mmol, 1.0 equiv) and 2-bromoacetophenone (5.73 g, 95 mmol, 1.0 equiv) were stirred in THF (76 mL) for 4 h at 70 °C. The reaction mixture was concentrated under reduced pressure and the orange oil residue was diluted in CH_2Cl_2 (26 mL) before adding 2 M NaOH (11.3 mL, 22.6 mmol,1.05 equiv) to form a biphasic solution that was stirred overnight at rt. The reaction mixture was diluted distilled H_2O and the layers were separated. The aqueous was extracted with CH_2Cl_2 (× 3). The combined organic was washed with brine (× 3), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a beige solid (9.58 g). After recrystallisation in PhMe, the title compound was obtained as an off white solid (7.66 g, 80%) with data in accordance with literature.[3] mp 186–188 °C {Lit[3] 158–160 ºC}; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 4.62 (1H, d, *J* 23.6, Ph_3P=C*H*), 7.56–7.62 (6H, m, Ar*H* × 6), 7.65–7.73 (11H, m, COArC(3,5)*H* and Ar*H* × 9), 8.07 (2H, d, *J* 8.1, COArC(2,6)*H*); ^{31}P{^{1}H} NMR (202 MHz, d_6-DMSO) δ_P: 15.98 (*P*Ph_3); ^{19}F{^{1}H} NMR (376 MHz, d_6-DMSO) δ_F: –60.86 (C*F*$_3$).

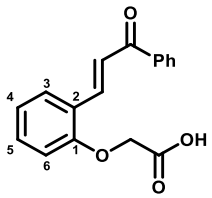
1-(4-Methoxyphenyl)-2-(triphenyl-l5-phosphaneylidene)ethan-1-one 257



Following general procedure **A**, the title compound was obtained as white solid (3.4 g, 42%) with data in accordance with literature.[4] mp 132–134 °C {Lit.[4] 156–158 ºC}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.82 (3H, s, OC*H*$_3$), 4.34 (1H, d, *J* 24.4, Ph_3P=C*H*), 6.82–6.89 (2H, m, COArC(3,5)*H*), 7.42–7.49 (6H, m, Ar*H* × 6), 7.50–7.57 (3H, m, Ar*H* × 3), 7.68–7.77 (6H, m, Ar*H* × 6), 7.92–7.97 (2H, m, COArC(3,5)*H*); ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ_P: 16.56.

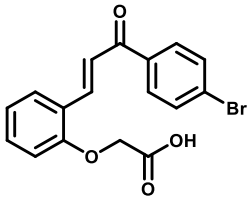
4-2-3 Synthesis of enone-acids

(*E*)-2-(2-(3-Oxo-3-phenylprop-1-en-1-yl)phenoxy)acetic acid 239



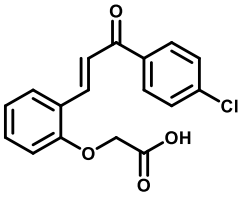
Following general procedure **B** in $CHCl_3$, the title compound was obtained after trituration in Et_2O as beige solid (1.25 g, 4.4 mmol, 88%) with data in accordance with literature.[5] mp 122–124 ºC {Lit.[1] 116–118 ºC}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.81 (2H, s, C*H*$_2$), 6.37 (1H, br s, COO*H*), 6.86 (1H, br d, *J* 8.1, Ar)*H*), 7.07 (1H, td, *J* 7.5, 1.0, Ar*H*), 7.36 (1H, ddd, *J* 8.3, 7.4, 1.7, Ar*H*), 7.42–7.51 (2H, m, COArC(3,5)*H*), 7.49–7.58 (1H, m, COArC(4)*H*), 7.64 (1H, dd, *J* 7.7, 1.7, Ar*H*), 7.95 (1H, d, *J* 15.9, ArC(2)CH=C*H*), 8.04–8.12 (2H, m, ArC(2)C*H*=CH and COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 65.0 (*C*H$_2$), 112.0 (Ar*C*H), 122.1 (Ar*C*H), 124.0 (ArC(2)CH=*C*H), 124.4 (Ar*C*(2)) 128.6 (COAr*C*(3,5)), 128.7 (COAr*C*(2,6)), 131.2 (Ar*C*H), 131.6 (Ar*C*H), 132.8 (COAr*C*(4)), 138.2 (COAr*C*(1)), 140.5 (ArC(2)*C*H=CH), 156.7 (Ar*C*(1)), 173.1 (*C*O$_2$H), 191.4 (*C*OPh).

(*E*)-2-(2-(3-(4-Bromophenyl)-3-oxoprop-1-en-1-yl)phenoxy)acetic acid 259



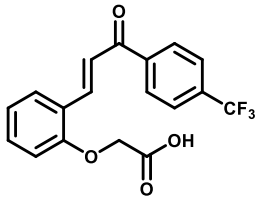
Following general procedure **B** in anhydrous THF, the title compound was obtained after trituration in Et_2O as a yellow solid (325 mg, 0.90 mmol, 30%) with data in accordance with literature.[6] mp 163–165 ºC {Lit.[6] 158–160 ºC}; ^{1}H NMR (500 MHz, *d*$_6$-DMSO) δ_H: 4.85 (2H, s, C*H*$_2$), 7.04–7.09 (2H, m, Ar*H* × 2), 7.43 (1H, ddd, *J* 8.7, 7.4, 1.7, Ar*H*), 7.76–7.79 (2H, m, COArC(3,5)*H*), 7.93 (1H, dd, *J* 7.7, 1.7, Ar*H*), 8.04 (1H, d, *J* 15.7, ArC(2)CH=C*H*), 8.08–8.14 (3H, m, ArC(2)C*H*=CH and COArC(2,6)*H*).

(*E*)-2-(2-(3-(4-Chlorophenyl)-3-oxoprop-1-en-1-yl)phenoxy)acetic acid 260



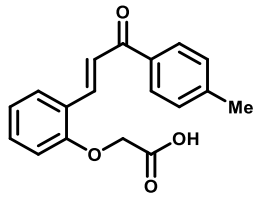
Following general procedure **B** in anhydrous THF, the title compound was obtained after trituration in Et_2O as a shiny yellow solid (723 mg, 2.3 mmol, 57%) with data in accordance with literature.[1] mp 162–164 ºC {Lit.[1] 167–169 ºC}; ^{1}H NMR (500 MHz, *d*$_6$-DMSO) δ_H: 4.86 (2H, s, C*H*$_2$), 7.01–7.11 (2H, m, ArH × 2), 7.43 (1H, ddd, *J* 8.8, 7.5, 1.7, Ar*H*), 7.60–7.66 (2H, m, COArC(3,5)*H*), 7.93 (1H, dd, *J* 7.7, 1.7, Ar*H*), 8.04 (1H, d, *J* 15.7, ArC(2)CH=C*H*), 8.13 (1H, d, *J* 15.7, ArC(2)C*H*=CH), 8.17–8.22 (2H, m, COArC(2,6)*H*).

(*E*)-2-(2-(3-Oxo-3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)phenoxy)acetic acid 261



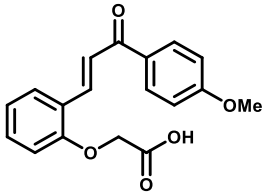
Following general procedure **B** in $CHCl_3$, the title compound was obtained as yellow solid (710 mg, 2.0 mmol, 91%) with data in accordance with literature.[5] mp 169–171 ºC {Lit.[5] 125–130 ºC}; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H: 4.86 (2H, s, C*H*$_2$), 7.03–7.12 (2H, m, Ar*H* × 2), 7.41–7.47 (1H, m, Ar*H*), 7.92–7.96 (3H, m, Ar*H* and COArC(3,5)*H*), 8.07 (1H, d, *J* 15.8, ArC(2)CH=C*H*), 8.16 (1H, d, *J* 15.8, ArC(2)C*H*=CH), 8.31–8.36 (2H, m, COArC(2,6)*H*); ^{19}F{^{1}H} NMR (376 MHz, DMSO) δ_F: –61.49.

(*E*)-2-(2-(3-oxo-3-(p-tolyl)prop-1-en-1-yl)phenoxy)acetic acid 262



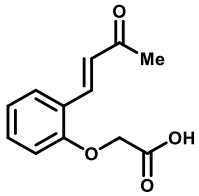
Following general procedure **B** in anhydrous THF, the title compound was obtained as beige solid (475 mg, 1.6 mmol, 45%) with data in accordance with literature.[1,6] mp 128–130 ºC {Lit.[1] 132–134 ºC}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.40 (3H, s, C*H*$_3$), 3.87 (1H, br s, COO*H*), 4.81 (2H, s, C*H*$_2$), 6.86 (1H, d, *J* 8.3, Ar*H*), 7.07 (1H, t, *J* 7.5, Ar*H*), 7.26–7.30 (2H, m, COArC(3,5)*H*), 7.34–7.39 (1H, m, Ar*H*), 7.64 (1H, dd, *J* 7.7, 1.7, Ar*H*), 7.91 (1H, d, *J* 15.8, ArC(2)CH=C*H*), 7.99 (2H, d, *J* 8.0, COArC(2,6)*H*), 8.08 (1H, d, *J* 15.8, ArC(2)C*H*=CH).

(*E*)-2-(2-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)phenoxy)acetic acid 263



Following general procedure **B** in anhydrous THF, the title compound was obtained after recrystallisation in PhMe as a shiny dark beige solid (414 mg, 1.3 mmol, 66%) with data in accordance with literature.[2,5] mp 149–151 ºC {Lit.[5] 140–142 ºC}; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.87 (3H, s, OC*H*$_3$), 4.85 (2H, s, C*H*$_2$), 7.00–7.06 (2H, m, Ar*H* × 2), 7.06–7.10 (2H, m, COArC(3,5)*H*), 7.37–7.46 (1H, m, Ar*H*), 7.90 (1H, dd, *J* 7.7, 1.7, Ar*H*), 7.98 (1H, d, *J* 15.7, ArC(2)C*H*=CH), 8.15 (1H, d, *J* 15.8, ArC(2)CH=C*H*), 8.18–8.20 (2H, m, COArC(2,6)*H*).

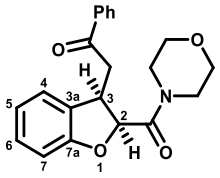
(*E*)-2-(2-(3-Oxobut-1-en-1-yl)phenoxy)acetic acid 264



Following general procedure **B** in $CHCl_3$, the title compound was obtained after recrystallisation in PhMe as a pink solid (414 mg, 1.3 mmol, 66%) with data in accordance with literature.[1] mp 112–114 ºC {Lit.[1] 105–109 ºC}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.40 (3H, s, C*H*$_3$), 4.79 (2H, s, C*H*$_2$), 6.81–6.87 (2H, m, Ar*H* and ArC(2)C*H*=CH), 7.03–7.08 (1H, m, Ar*H*), 7.36 (1H, ddd, *J* 8.3, 7.4, 1.7, Ar*H*), 7.59 (1H, dd, *J* 7.8, 1.7, Ar*H*), 7.95 (1H, d, *J* 16.5, ArC(2)CH=C*H*).

4-2-4 Synthesis of 2,3-disubstituted 2,3-dihydrobenzofuran derivatives: Nucleophile Scope (Table 17)

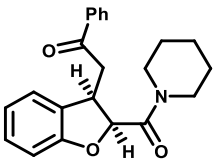
2-((2*S*,3*R*)-2-(Morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)-1-phenylethan-1-one 249



Following general procedure **C**, enone-acid **239** (56 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 μL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 μL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 μL, 0.30 mmol) at 0 ºC for 4 h gave a crude brown oil (272 mg, >95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, CH_2Cl_2 : Et_2O (95:5 5 CV, 95:5 to 80:20 15 CV, 80:20 10 CV)] to give the title compound (66 mg, 94%, >95:5 dr) as a yellow oil. $[\alpha]_D^{20}$ +45.5 (*c* 1.03, $CHCl_3$); Chiral HPLC OD-H (92:8 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R minor: 47.6 min, t_R major: 73.1 min, 97:3 er; ν_{max} (film) cm^{-1}1676 (C=O ketone), 1647 (N–C=O amide I), 1597, 1479, 1458, 1449, 1231 (Ar–O–R), 1113 (R–O–R); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.15 (1H, dd, *J* 18.4, 4.3, C(3)C*H*^{A}H^B), 3.22–3.34 (2H, m, (C*H*^{A}H^B)^1 and (C*H*^{A}H^B)^2), 3.42–3.50 (1H, m, (CH^A*H*^{B})^1), 3.51–3.59 (3H, m, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.65–3.78 (3H, m, C(3)(CH^A*H*^{B}) and (C*H*$_2$)^4), 4.41 (1H, td, *J* 9.1, 4.3, C(3)*H*), 5.68 (1H, d, *J* 8.8, C(2)*H*), 6.86–6.93 (2H, m, Ar*H* × 2), 7.12–7.20 (2H, m, Ar*H* × 2), 7.42–7.49 (2H, m, COArC(3,5)*H*), 7.54–7.61 (1H, m, COArC(4)*H*), 7.90–7.97 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 40.0 (*C*(3)), 40.7 (C(3)*C*H$_2$), 41.9 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 66.1 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^2), 79.9 (*C*(2)), 110.0 (Ar*C*H), 121.3 (Ar*C*H), 124.0 (Ar*C*H), 128.2 (COAr*C*(2,6)), 128.78 (COAr*C*(3,5)), 128.84 (Ar*C*H), 129.1 (*C*(3a)), 133.6 (COAr*C*(4)), 136.3 (COAr*C*(1)), 159.0 (*C*(7a)), 167.0 (C(2)*C*O), 198.2 (*C*OPh); *m/z* (NSI$^+$) 374 ([M + Na]$^+$, 31%), 352 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{21}H_{22}NO_4$ [M+H]$^+$ found 352.1546 requires 352.1543 (+0.8 ppm).

Minor *trans*-diastereoisomer (non-isolated): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.37 (1H, app d, *J* 8.9, C(3)C*H*^{A}H^B), 4.56–4.62 (1H, m, C(3)*H*), 5.15 (1H, d, *J* 5.8, C(2)*H*), 6.81 (1H, app d, *J* 8.0, Ar*H*), 7.36 (1H, app s, Ar*H*), 7.97–7.98 (1H, m, COArC*H*).

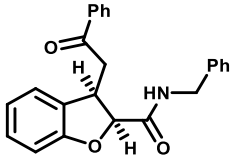
1-Phenyl-2-((2*S*,3*R*)-2-(piperidine-1-carbonyl)-2,3-dihydrobenzofuran-3-yl)ethan-1-one 251



Following general procedure **C**, enone-acid **239** (56 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 μL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 μL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with piperidine (30 μL, 0.30 mmol) at 0 ºC for 19 h gave a crude brown oil (276 mg, >95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL min^{-1}, pentane : EtOAc (95:5 5 CV, 95:5 to 80:20 15 CV, 80:20 10 CV)] to give the title compound (46 mg, 65%, >95:5 dr) as a yellow oil. $[\alpha]_D^{20}$ –18.7 (*c* 1.13, $CHCl_3$); Chiral HPLC OD-H (95:5 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R minor: 25.9 min, t_R major: 64.8 min, 96:4 er; ν_{max} (film) cm^{-1} 1682 (C=O ketone), 1647 (N–C=O amide I), 1597, 1477, 1449, 1242, 1227; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.30–1.40 (1H, m, (C*H*^{A}H^B)^1), 1.43–1.74 (5H, m, (CH^A*H*^{B})^1, (C*H*$_2$)^2 and C*H*$_2$)^3), 2.93 (1H, ddd, *J* 12.8, 8.8, 3.6, (C*H*^{A}H^B)^4), 3.12 (1H, dd, *J* 18.1, 5.6, C(3)C*H*^{A}H^B)), 3.27 (1H, ddd, *J* 13.3, 8.2, 3.2, (C*H*^{A}H^B)^5), 3.48–3.53 (1H, m, (CH^A*H*^{B})^5), 3.57 (1H, dd, *J* 18.1, 8.2, C(3)CH^A*H*^{B}), 3.67 (1H, ddd, *J* 13.0, 6.4, 3.3, (CH^A*H*^{B})^4), 4.41 (1H, td, *J* 8.3, 5.5, C(3)*H*), 5.66 (1H, d, *J* 8.6, C(2)*H*), 6.83–6.93 (2H, m, Ar*H* × 2), 7.11–7.19 (2H, m, Ar*H* × 2), 7.40–7.47 (2H, m, COArC(3,5)*H*), 7.52–7.59 (1H, m, COArC(4)*H*), 7.88–7.94 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 24.4 (*C*H$_2$), 25.4 ((*C*H$_2$)^1), 26.2 (*C*H$_2$), 39.9(*C*(3)), 40.6 (C(3)*C*H$_2$), 42.8 ((*C*H$_2$)^4), 46.6 ((*C*H$_2$)^5), 80.8 (*C*(2)), 110.1 (Ar*C*H), 121.2 (Ar*C*H), 124.3 (Ar*C*H), 128.2 (COAr*C*(2,6)), 128.66 (COAr*C*(3,5)), 128.75 (Ar*C*H), 129.4 (*C*(3a)), 133.4 (COAr*C*(4)), 136.5 (COAr*C*(1)), 158.9 (*C*(7a)), 166.3 (C(2)*C*O), 198.0 (*C*OPh); *m/z* (NSI$^+$) 350 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{24}NO_3$ [M+H]$^+$ found 250.1752 requires 350.1751 (+0.4 ppm).

Minor *trans*-diastereoisomer (non-isolated from the *cis*-**251**): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.35–3.39 (1H, m, C(3)C*H*$_2$ × 1), 4.57–4.63 (1H, m, C(3)*H*), 5.17 (1H, d, *J* 6.0, C(2)*H*), 6.80–6.83 (1H, m, Ar*H*), 7.70–7.77 (2H, m, COAr*H* × 2), 7.95–7.99 (2H, m, COAr*H* × 2).

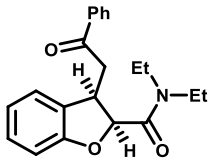
(2*S*,3*R*)-*N*-Benzyl-3-(2-oxo-2-phenylethyl)-2,3-dihydrobenzofuran-2-carboxamide 242



Following general procedure **C**, enone-acid **239** (56 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 μL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 μL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with $BnNH_2$ (33 μL, 0.30 mmol) at 0 ºC for 19 h gave a crude brown oil (234 mg, >95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (95:5 5 CV, 95:5 to 80:20 15 CV, 80:20 20 CV)] to give the title compound (47 mg, 64%, >95:5 dr) as a beige solid. mp 163–165 ºC; $[\alpha]_D^{20}$ –93.9 (*c* 0.99, $CHCl_3$); Chiral HPLC AS-H (90:10 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R major: 16.2 min, t_R major: 28.0 min, 97:3 er; ν_{max} (film) cm^{-1} 3360 (N–H), 1682 (C=O ketone), 1647 (N–C=O amide I), 1595, 1522 (N–H amide II), 1472, 1456, 1362, 1215; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.10 (1H, dd, *J* 17.5, 9.3, C(3)C*H*^{A}H^B), 3.48 (1H, dd, *J* 17.5, 4.6, C(3)CH^A*H*^{B}), 4.40 (1H, dd, *J* 14.7, 5.8, NHC*H*^{A}H^B), 4.48 (1H, td, *J* 9.4, 4.6, C(3)*H*), 4.62 (1H, dd, *J* 14.7, 6.5, NHCH^A*H*^{B}), 5.31 (1H, d, *J* 9.4, C(2)*H*), 6.82–6.91 (2H, m, Ar*H* × 2), 7.10 (1H, br t, *J* 6.4, N*H*), 7.12–7.18 (1H, m, Ar*H*), 7.23 (1H, ddt, *J* 7.5, 1.4, 0.6, Ar*H*), 7.27–7.37 (5H, m, NHCH$_2$Ar*H* × 5), 7.39–7.45 (2H, m, COArC(3,5)*H*), 7.52–7.57 (1H, m, COArC(4)*H*), 7.79–7.83 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 39.5 (*C*(3)), 39.9 (C(3)*C*H$_2$), 43.0 (NH*C*H$_2$), 83.8 (*C*(2)), 109.8 (Ar*C*H), 122.0 (Ar*C*H), 125.8 (Ar*C*H), 127.7 (NHCH$_2$Ar*C*H × 2), 128.0 (COAr*C*(2,6)), 128.1 (Ar*C*H × 2), 128.6 (COAr*C*(3,5)), 128.80 (NHCH$_2$Ar*C*H), 128.83 (NHCH$_2$Ar*C*H and Ar*C*H), 129.7 (*C*(3a)), 133.2 (COAr*C*(4)), 136.8 (COAr*C*(1)), 138.0 (NHCH$_2$Ar*C*(1)), 157.7 (*C*(7a)), 168.9 (C(2)*C*O), 197.5 (*C*OPh); *m/z* (NSI$^+$) 372 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{24}H_{22}NO_3$ [M+H]$^+$ found 372.1596 requires 372.1594 (+0.5 ppm).

Minor *trans*-diastereoisomer (non-isolated from the *cis*-**242**): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.67 (1H, dd, *J* 17.6, 4.8, C(3)C*H*$_2$ × 1), 4.54–4.57 (1H, m, C(3)*H*), 4.92 (1H, d, *J* 6.9, C(2)*H*), 7.46–7.51 (2H, m, COAr*H* × 2), 7.98–8.02 (2H, m, COAr*H* × 2).

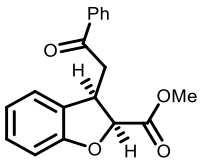
(2*S*,3*R*)-*N*,*N*-Diethyl-3-(2-oxo-2-phenylethyl)-2,3-dihydrobenzofuran-2-carboxamide 252



Following general procedure **C**, enone-acid **249** (56 mg, 0.20 mmol), distilled *i*Pr_2NEt (38 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 μL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr_2NEt (88 μL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with Et_2NH (104 μL, 1.0 mmol) at 0 ºC for 19 h gave a crude dark orange oil (254 mg, 90:10 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (95:5 5 CV, 95:5 to 80:20 15 CV, 80:20 10 CV)] to give the title compound (46 mg, 69%, 95:5 dr) as an orange oil. $[\alpha]_D^{20}$ –1.6 (*c* 0.74, $CHCl_3$); Chiral HPLC OD-H (95:5 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R minor: 17.1 min, t_R major: 34.9 min, 93:7 er; ν_{max} (film) cm^{-1} 1682 (C=O ketone), 1645 (N–C=O amide I), 1597, 1477, 1449, 1238, 1225; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.87 (3H, t, *J* 7.1, N(CH_2CH_3)^1), 1.25 (3H, t, *J* 7.2, N(CH_2CH_3)^2), 2.99 (1H, dq, *J* 13.3, 7.1, N($CH^AH^BCH_3$)^1), 3.10–3.24 (1H, m, N($CH^AH^BCH_3$)^2), 3.20 (1H, dd, *J* 18.6, 4.9, C(3)H^AH^B), 3.43–3.52 (1H, m, N($CH^AH^BCH_3$)^1), 3.53–3.64 (1H, m, N($CH^AH^BCH_3$)^2), 3.71 (1H, dd, *J* 18.6, 8.8, C(3)H^AH^B), 4.42 (1H, td, *J* 8.8, 4.9, C(3)*H*), 5.60 (1H, d, *J* 8.7, C(2)*H*), 6.83–6.92 (2H, m, Ar*H* × 2), 7.12–7.18 (2H, m, Ar*H* × 2), 7.40–7.45 (2H, m, COArC(3,5)*H*), 7.51–7.57 (1H, m, COArC(4)*H*), 7.88–7.93 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 12.7 (N(CH_2CH_3)^1), 14.5 (N(CH_2CH_3)^2), 39.7 (*C*(3)), 40.6 (N(CH_2CH_3)^1), 41.1 (C(3)CH_2), 41.9 (N(CH_2CH_3)^2), 80.6 (*C*(2)), 110.0 (Ar*C*H), 121.1 (Ar*C*H), 124.2 (Ar*C*H), 128.1 (COAr*C*(2,6)), 128.6 (COAr*C*(3,5)), 128.7 (Ar*C*H), 129.4 (*C*(3a)), 133.4 (COAr*C*(4)), 136.4 (COAr*C*(1)), 159.1 (*C*(7a)), 167.2 (C(2)*C*O), 198.1 (*C*OPh); *m/z* (NSI$^+$) 338 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{21}H_{24}NO_3$ [M+H]$^+$ found 338.1472 requires 338.1751 (+0.4 ppm).

Minor *trans*-diastereoisomer (non-isolated from the *cis*-**252**): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.19 (3H, t, *J* 7.1, N(CH_2CH_3)^1), 1.25 (3H, t, *J* 7.1, N(CH_2CH_3)^2), 3.26–3.39 (4H, m, CH_2 × 2), 4.51–4.59 (1H, m, C(3)*H*), 5.13 (1H, d, *J* 6.0, C(2)*H*), 6.81 (1H, m, Ar*H*), 7.71–7.77 (1H, m, COArC(4)*H*), 7.95–7.98 (2H, m, COArC(2,6)*H*).

(2*S*,3*R*)-Methyl 3-(2-oxo-2-phenylethyl)-2,3-dihydrobenzofuran-2-carboxylate 241

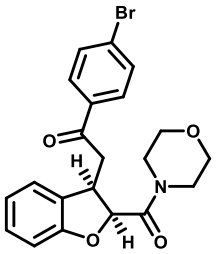


Following general procedure **C**, enone-acid **239** (56 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 μL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 μL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with MeOH (82 μL, 2.0 mmol) and DMAP (4.9 mg, 0.04 mmol, 20 mol%) at 0 ºC for 19 h gave a crude brown oil (199 mg, 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 5 CV, 100:0 to 80:20 15 CV, 80:20 5 CV)] to give the title compound (36 mg, 60%, >95:5 dr) as a limpid oil. $[\alpha]_D^{20}$ –16.7 (*c* 0.76, $CHCl_3$);Chiral HPLC AD-H (90:10 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 30 ºC) t_R minor: 13.3 min, t_R major: 14.5min 96:4 er; ν_{max} (film) cm^{-1} 1749 (C=O ester), 1717, 1684 (C=O ketone), 1653, 1597, 1558, 1506, 1479, 1209; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.30 (1H, dd, *J* 17.9, 6.5, C(3)C*H*^{A}H^B), 3.37 (1H, dd, *J* 17.9, 7.7, C(3)CH^A*H*^{B}), 3.62 (3H, s, OC*H*$_3$), 4.48–4.55 (1H, m, C(3)*H*), 5.39 (1H, d, *J* 9.2, C(2)*H*), 6.86–6.94 (2H, m, Ar*H* × 2), 7.14–7.21 (2H, m, Ar*H* × 2), 7.43–7.50 (2H, m, COArC(3,5)*H*), 7.55–7.60 (1H, m, COArC(4)*H*), 7.90–7.95 (2H, m, COACr(2,6)*H*); ^{13}C{^{1}H} (101 MHz, $CDCl_3$) δc: 40.1 (*C*(3)CH_2 or *C*(3)), 40.2 (*C*(3) *C*(3)CH_2) 52.2 (O*C*H$_3$), 82.6 (*C*(2)), 110.1 (Ar*C*H), 121.5 (Ar*C*H), 124.4 (Ar*C*H), 128.0 (COAr*C*(2,6)), 128.5 (*C*(3a)), 128.7 (COAr*C*(3,5)), 129.0 (Ar*C*H), 133.5 (COAr*C*(4)), 136.5 (COAr*C*(1)), 158.7 (*C*(7 a)), 169.9 (*C*O$_2$CH$_3$), 197.4 (*C*OPh); *m/z* (NSI$^+$) 297 ([M + H]$^+$, 100%); HRMS (NSI$^+$) $C_{18}H_{17}O_4$ [M + H]$^+$ found 297.1124 requires 297.1121 (+0.9 ppm).

Minor *trans*-diastereoisomer (non-isolated from the *cis*-**241**): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.83 (3H, s, OC*H*$_3$), 4.31 (1H, dd, *J* 13.2, 6.6, C(3)*H*), 4.91 (1H, d, *J* 5.8, C(2)*H*), 7.96–8.00 (2H, m, Ar*H* × 2).

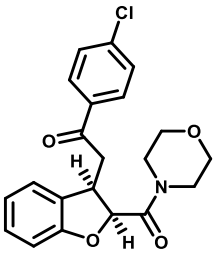
4-2-5 Synthesis of 2,3-disubstituted 2,3-dihydrobenzofuran derivatives: Enone-acid Scope (Table 19)

1-(4-Bromophenyl)-2-((2*S*,3*R*)-2-(morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)ethan-1-one 265



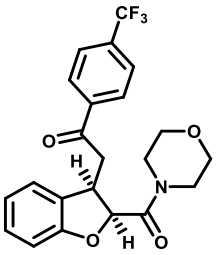
Following general procedure **D**, enone-acid **259** (72 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 μL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 μL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 μL, 0.30 mmol) at 0 ºC for 4 h gave a crude brown oil (227 mg, >95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (62 mg, 72%, >95:5 dr) as a dark orange oil. $[\alpha]_D^{20}$ +25.7 (*c* 0.69, $CHCl_3$); Chiral HPLC AS-H (98:2 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 47.3 min, t_R major: 74.2 min, 97:3 er; ν_{max} (film) cm^{-1} 1680 (C=O ketone), 1647 (N–C=O amide I), 1585, 1479, 1458, 1233, 1113, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.07 (1H, dd, *J* 18.4, 4.2, C(3)C*H*^{A}H^B), 3.25 (1H, ddd, *J* 13.4, 6.8, 3.1, (C*H*^{A}H^B)^1), 3.37 (1H, ddd, *J* 11.4, 6.3, 3.1, (C*H*^{A}H^B)^2), 3.46–3.61 (4H, m, (CH^A*H*^{B})^1, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.66–3.77 (3H, m, C(3)CH^A*H*^{B} and (C*H*$_2$)^4), 4.37 (1H, td, *J* 9.1, 4.2, C(3)*H*), 5.65 (1H, d, *J* 8.6, C(3)*H*), 6.87–6.93 (2H, m, Ar*H* × 2), 7.13–7.20 (2H, m, Ar*H* × 2), 7.58–7.63 (2H, m, COArC(3,5)*H*), 7.77–7.82 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 40.0 (*C*(3)), 40.7 (C(3)*C*H$_2$), 42.0 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 66.2 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^2), 79.8 (*C*(3)), 110.1 (Ar*C*H), 121.4 (Ar*C*H), 124.0 (Ar*C*H), 128.90 (*C*(3a) or COAr*C*(4)), 128.92 (COAr*C*(4) or *C*(3a)), 128.94 (Ar*C*H), 129.6 (COAr*C*(2,6)), 132.1 (COAr*C*(3,5)), 135.0 (COAr*C*(1)), 158.8 (*C*(7a)), 166.9 (C(2)*C*O), 197.3 (*C*OAr); *m/z* (NSI$^+$) 885 ([2M(^{83}Br) + Na]$^+$, 55%), 883 ([2M(^{81}Br) + Na]$^+$, 100%), 881 ([2M(^{79}Br) + Na]$^+$, 47%), 454 ([M(^{81}Br) + Na]$^+$, 60%), 452 ([2M(^{79}Br) + Na]$^+$, 61%); HRMS (NSI$^+$) $C_{21}H_{20}NO_4{}^{79}BrNa$[M+Na]$^+$ found 452.0468 requires 452.0455 (–2.9 ppm).

1-(4-Chlorophenyl)-2-((2*S*,3*R*)-2-(morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)ethan-1-one 266



Following general procedure **D**, enone-acid **260** (63 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 μL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 μL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 μL, 0.30 mmol) at 0 ºC for 4 h gave a crude dark green oil (236 mg, 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (57 mg, 74%, >95:5 dr) as a yellow oil. $[\alpha]_D^{20}$ +19.7 (*c* 0.51, $CHCl_3$); Chiral HPLC AS-H (98:2 hexane : IPA, flow rate 1.00 mL·min^{-1},211 nm, 40 ºC) t_R minor: 39.1 min, t_R minor: 59.6 min, 94:6 er; ν_{max} (film) cm^{-1} 1678 (C=O ketone), 1645 (N–C=O amide I), 1587, 1479, 1460, 1443, 1231, 1113, 1092; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.08 (1H, dd, *J* 18.4, 4.2, C(3)C*H*^{A}H^B), 3.26 (1H, ddd, *J* 13.3, 6.7, 3.1, (C*H*^{A}H^B)^1), 3.37 (1H, ddd, *J* 11.4, 6.3, 3.1, (C*H*^{A}H^B)^2), 3.47–3.51 (1H, m, (CH^A*H*^{B})^1), 3.53–3.62 (3H, m, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.67–3.78 (3H, m, C(3)CH^A*H*^{B} and (C*H*$_2$)^4), 4.37 (1H, td, *J* 9.1, 4.2, C(3)*H*), 5.65 (1H, d, *J* 8.6, C(2)*H*), 6.87–6.94 (2H, m, Ar*H* × 2), 7.13–7.21 (2H, m, Ar*H* × 2), 7.40–7.47 (2H, m, COArC(3,5)*H*), 7.82–7.91 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 40.0 (*C*(3)), 40.7 (C(3)*C*H$_2$), 42.0 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 66.1 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^2), 79.8 (*C*(2)), 110.1 (Ar*C*H), 121.4 (Ar*C*H), 124.0 (Ar*C*H), 128.9 ((Ar*C*H) and *C*(3a)), 129.1 (COAr*C*(3,5)), 129.6 (COAr*C*(2,6)), 134.6 (COAr*C*), 140.1 (COAr*C*), 158.8 (*C*(7a)), 166.9 (C(2)*C*O), 197.1 (*C*OAr); *m/z* (NSI$^+$) 795 ([2M(^{37}Cl) + Na]$^+$, 76%), 793 ([2M(^{35}Cl) + Na]$^+$, 100%), 408 ([M(^{35}Cl) + Na]$^+$, 90%); HRMS (NSI$^+$) $C_{21}H_{20}NO_4{}^{35}ClNa$ [M+Na]$^+$ found 408.0973 requires 408.0964 (–2.2 ppm). Minor *trans*-diastereoisomer (non-isolated from the *cis*-**266**) ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.57–4.63 (1H, m, C(3)*H*), 5.13 (1H, d, *J* 5.9, C(2)*H*), 6.79–6.83 (2H, m, Ar*H* × 2).

2-((2*S*,3*R*)-2-(Morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one 267

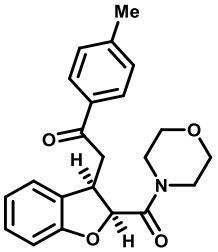


Following general procedure **D**, enone-acid **261** (70 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 µL, 0.30 mmol) at 0 ºC for 4 h gave a crude dark orange oil (70 mg, >95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (46 mg, 55%) as a dark orange oil. $[\alpha]_D^{20}$ +29.0 (*c* 0.50, $CHCl_3$); Chiral HPLC OD-H (92:8 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 35.6 min, t_R major: 46.6 min, 93:7 er; ν_{max} (film) cm^{-1} 1684 (C=O ketone), 1653 (N–C=O amide I), 1479, 1458, 1325, 1234, 1169, 1113, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.12 (1H, dd, *J* 18.5, 4.2, C(3)C*H*^{A}H^B), 3.26 (1H, ddd, *J* 13.4, 6.7, 3.1, (C*H*^{A}H^B)^1), 3.40 (1H, ddd, *J* 11.1, 6.1, 3.1, (C*H*^{A}H^B)^2), 3.49–3.54 (1H, m, (CH^A*H*^{B})^1), 3.55–3.61 (3H, m, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.66–3.80 (2H, m, (C*H*$_2$)^4), 3.81 (1H, dd, *J* 18.5, 9.6, C(3)CH^A*H*^{B}), 4.37 (1H, td, *J* 9.1, 4.2, C(3)*H*), 5.65 (1H, d, *J* 8.5, C(2)*H*), 6.88–6.95 (2H, m, Ar*H* × 2), 7.12–7.23 (2H, m, Ar*H* × 2), 7.72 (2H, d, *J* 8.2, COArC(3,5)*H*), 8.00–8.06 (2H, m, COArC(,5)*H*); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ_F: –63.2; ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 39.9 (*C*(3)), 41.1 (C(3)*C*H$_2$), 42.0 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 66.2 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^2), 79.7 (*C*(2)), 110.2 (Ar*C*H), 121.5 (Ar*C*H), 123.48(1C, q, $^1J_{CF}$ 272.8, *C*F$_3$), 124.0 (Ar*C*H), 125.8 (2C, q, $^3J_{CF}$ 3.5, COAr*C*(3,5)), 128.5 (COAr*C*(2,6)), 128.8 (*C*(3a)), 129.0 (Ar*C*H), 134.8 (1C, q, $^2J_{CF}$ 32.7, COAr*C*(4)), 138.9 (COAr*C*(1)), 158.8 (*C*(7a)), 166.9 (C(2)*C*O), 197.4 (*C*OAr); *m/z* (NSI$^+$) 862 ([2M (^{20}F, ^{19}F$_2$) + Na]$^+$, 28%), 861 ([2M (^{19}F$_3$) + Na]$^+$, 58%), 443 ([M (^{20}F, ^{19}F$_2$) + Na]$^+$, 25%), 442 ([2M (^{19}F$_3$) + Na]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{20}O_4N^{19}F_3$ [M + Na]$^+$ found 442.1237 requires 442.1231(–1.3 ppm).

Minor *trans*-diastereoisomer (non-isolated from the *cis*-**267**): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.07 (1H, app d, *J* 7.6, C(3)C*H*^{A}H^B), 4.54 (1H, app q, *J* 8.4, C(3)*H*), 5.14 (1H, d, *J* 6.0,

C(2)*H*), 6.62–6.71 (1H, m, Ar*H*), 6.78–6.85 (1H, m, Ar*H*), 7.01–7.10 (1H, m, Ar*H*), 8.24 (1H, d, *J* 8.3, Ar*H*).

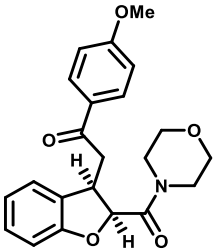
2-((2*S*,3*R*)-2-(Morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)-1-(p-tolyl)ethan-1-one 268



Following general procedure **D**, enone-acid **262** (59 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 μL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 μL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 μL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 μL, 0.30 mmol) at 0 ºC for 4 h gave a crude orange oil (221 mg, 90:10 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, pentane : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (39 mg, 54%, 91:9 dr) as a yellow oil. $[\alpha]_D^{20}$ +31.3 (*c* 0.51, $CHCl_3$); Chiral HPLC OD-H (94:6 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 37.6 min, t_R minor: 62.6 min, 83:17 er; ν_{max} (film) cm^{-1} 1674 (C=O ketone), 1653 (N–C=O amide I), 1607, 1479, 1458, 1234, 1115; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, CH_3), 3.12 (1H, dd, *J* 18.3, 4.3, C(3)CH^AH^B), 3.23–3.35 (2H, m, (CH^AH^B)^1 and (CH^AH^B)^2), 3.46 (1H, ddd, *J* 13.2, 6.7, 3.1, (CH^AH^B)^1), 3.51–3.59 (3H, m, (CH^AH^B)^2 and (CH_2)^3), 3.65–3.74 (3H, m, C(3)CH^AH^B and (CH_2)^4), 4.42 (1H, td, *J* 9.2, 4.2, C(3)*H*), 5.68 (1H, d, *J* 8.8, C(2)*H*), 6.87–6.92 (2H, m, Ar*H* × 2), 7.13–7.20 (2H, m, Ar*H* × 2), 7.21–7.28 (2H, m, COArC(3,5)*H*), 7.81–7.87 (2H, m, COArC(2,6)*H*).; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 21.7 (*C*H$_3$), 40.0 (*C*(3)), 40.6 (C(3)*C*H$_2$), 41.9 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 66.1 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^2), 79.9 (*C*(2)), 110.00 (Ar*C*H), 121.2 (Ar*C*H), 124.0 (Ar*C*H), 128.3 (COAr*C*(2,6)), 128.8 (Ar*C*H), 129.1 (*C*(3a)), 129.4 (COAr*C*(3,5)), 133.8 (COAr*C*(4)), 144.6 (COAr*C*(1)), 159.0 (*C*(7a)), 167.0 (C(2)*C*O), 197.8 (*C*OAr); *m/z* (NSI$^+$) 388 ([M + Na]$^+$, 64%), 366 [M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{24}NO_4$ [M + H]$^+$ found 366.1700 requires 366.1702 (+0.6 ppm).

Minor *trans*-diastereoisomer (non-isolated from the *cis*-**268**): Chiral HPLC OD-H (94:6 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 42.8 t_R major: 57.4 min, 59:41 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.57 (1H, m, C(3)*H*), 5.15 (1H, d, *J* 5.8, C(2)*H*), 6.81 (1H, m, Ar*H*), 7.86 (2H, m, Ar*H* × 2).

1-(4-Methoxyphenyl)-2-((2*S*,3*R*)-2-(morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl)ethan-1-one 269



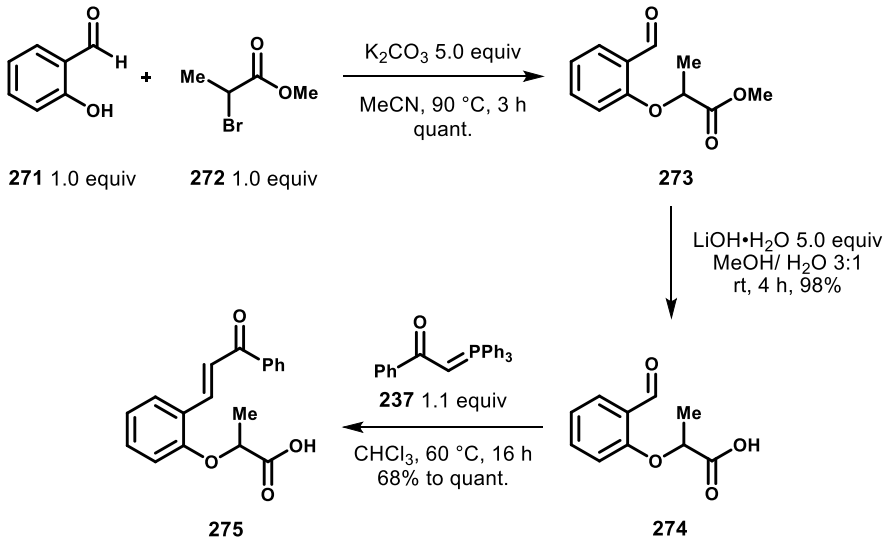
Following general procedure **D**, enone-acid **263** (63 mg, 0.20 mmol), distilled *i*Pr$_2$NEt (38 µL, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst **30** (7.4 mg, 0.02 mmol, 10 mol%) *then* distilled *i*Pr$_2$NEt (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 µL, 0.30 mmol) at 0 ºC for 4 h gave a crude yellow oil (472 mg, 86:14 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, CH_2Cl_2 : EtOAc (100:0 10 CV, 100:0 to 50:50 20 CV, 50:50 15 CV)] to give the title compound (39 mg, 51%, 92:8 dr, contains grease) as a yellow oil. $[\alpha]_D^{20}$ +12.0 (*c* 0.49, $CHCl_3$); Chiral HPLC OD-H (94:6 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 78.1 min, t_R major: 110.2 min, 83:17 er; ν_{max} (film) cm^{-1} 1670 (C=O ketone), 1653 (N–C=O amide I), 1599, 1479, 1458, 1263, 1234, 1171, 1115; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.08 (1H, dd, *J* 18.1, 4.2, C(3)C*H*^{A}H^B), 3.19–3.34 (2H, m, (C*H*^{A}H^B)^1 and (C*H*^{A}H^B)^2), 3.42–3.48 (1H, m, (CH^A*H*^{B})^1), 3.48–3.60 (3H, m, (CH^A*H*^{B})^2 and (C*H*$_2$)^3), 3.59–3.72 (3H, m, C(3)CH^A*H*^{B} and (C*H*$_2$)^4), 3.87 (3H, s, OC*H*$_3$), 4.42 (1H, td, *J* 9.2, 4.2, C(3)*H*), 5.67 (1H, d, *J* 8.8, C(2)*H*), 6.86–6.97 (4H, m, Ar*H* × 2 and COArC(3,5)*H*), 7.11–7.22 (2H, m, Ar*H* × 2), 7.85–7.98 (2H, m, COArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 40.1 (*C*(3)), 40.3 (C(3)*C*H$_2$), 41.9 ((*C*H$_2$)^1), 46.0 ((*C*H$_2$)^3), 55.5 ((O*C*H$_3$)), 66.1 ((*C*H$_2$)^4), 66.5 ((*C*H$_2$)^1), 79.9 (*C*(2)), 110.0 (Ar*C*H), 113.9 (COAr*C*(3,5)), 121.2 (Ar*C*H), 124.4 (Ar*C*H), 128.8 (Ar*C*H), 129.2 (*C*(3a)), 129.4 (COAr*C*(1)), 130.5 (COAr*C*(2,6)), 159.0 (*C*(7a)), 163.9 (COAr*C*(4)), 167.0 (C(2)*C*O), 196.6 (*C*OAr);

m/z (NSI$^+$) 785 ([2M + Na]$^+$, 100%), 404 ([M + Na]$^+$, 77%); HRMS (NSI$^+$) $C_{22}H_{23}NO_3$ [M+Na]$^+$ found 404.168 requires 404.1466 (–0.6 ppm).

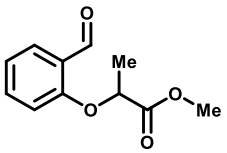
Minor *trans*-diastereoisomer (non-isolated from the *cis*-**269**): Chiral HPLC OD-H (94:6 hexane : IPA, flow rate 1.00 mL·min^{-1}, 211 nm, 40 ºC) t_R major: 88.3 min, t_R minor: 124.0 min, 58:42 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.57 (1H, m, C(3)*H*), 5.16 (1H, d, *J* 5.8, C(2)), 6.78–6.86 (2H, m, Ar*H*).

4-2-6 Extension to different 5-membered ring tethers: NHC-catalysed synthesis of dihydrobenzofuran derivative containing a highly functionalised centre

Synthesis of enone-acid 275



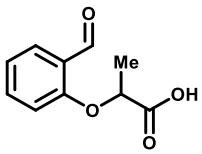
Methyl 2-(2-formylphenoxy)propanoate 273



Following an adapted procedure from Kowalewska and Kwiecień,[7] methyl 2-bromopropionate **272** (2.2 mL, 20.0 mmol, 1.0 equiv) was added to a mixture of salicylic acid **271** (2.1 mL, 20.0 mmol. 1.0 equiv)) and K_2CO_3 (13.8 g, 100 mmol, 5.0 equiv) in MeCN (90 mL). The reaction mixture was heated for 3 h at 90 °C before being diluted in distilled H_2O and extracted with EtOAc (× 3). The organic was washed with brine (× 3), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (4.5 g, quant.) as a crude yellow oil that was used in the next step without further

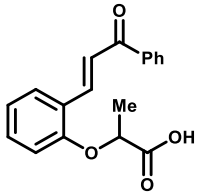
purification. ν_{max} (film) cm^{-1} 1751 (C=O ester), 1686 (C=O aldehyde), 1597, 1481, 1456, 1285, 1207, 1132; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.70 (3H, d, *J* 6.8, C*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 4.89 (1H, q, *J* 6.8, OC*H*(CH$_3$)CO$_2$CH$_3$), 6.80–6.85 (1H, m, ArC*H*), 7.06 (1H, tt, *J* 7.5, 0.9, ArC(3)*H*), 7.50 (1H, ddd, *J* 8.4, 7.3, 1.9, ArC*H*), 7.86 (1H, app dd, *J* 7.7, 1.8, ArC*H*), 10.57 (1H, d, *J* 0.8, C*H*O); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 18.5 (*C*H$_3$), 52.5 (O*C*H$_3$), 73.2 (O*C*H(CH$_3$)CO$_2$CH$_3$), 113.1 (Ar*C*H), 121.7 (Ar*C*(3)H), 125.5 (Ar*C*(2)), 128.5 (Ar*C*H), 135.7 (Ar*C*H), 159.9 (Ar*C*(1)), 171.8 (*C*OCH$_3$), 189.7 (*C*HO); *m/z* (NSI^+) 209 ($[M + H]^+$, 100%); HRMS (NSI^+) $C_{11}H_{13}O_4$ $[M + H]^+$ found 209.0809 requires 209.0808 (+0.3 ppm).

2-(2-Formylphenoxy)propanoic acid 274



Methyl 2-(2-formylphenoxy)propanoate **273** (4.5 g, 20.0 mmol, 1.0 equiv) and LiOH·H$_2$O (4.2 g, 100 mmol, 5.0 equiv) were dissolved in MeOH/distilled H$_2$O (3:1 v/v, 250 mL) and stirred at rt for 3.5 h. MeOH was removed under reduced pressure and the remaining aqueous was acidified to pH 1 with 1M HCl and extracted with EtOAc (× 3). The organic was washed with brine (× 3), dried over MgSO$_4$, filtered and concentrated under reduced pressure to give the title compound (3.8 g, 98%) as a crude orange oil that was used in the next step without further purification. ν_{max} (film) cm^{-1} 3508, 2991, 1732 (C=O carboxylic acid), 1686 (C=O aldehyde), 1599, 1481, 1458, 1286, 1236, 1196; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.76 (3H, d, *J* 6.9, C*H*$_3$), 4.92 (1H, q, *J* 6.9, OC*H*(CH$_3$)CO$_2$H), 6.93 (1H, d, *J* 8.3, Ar*H*), 7.12–7.17 (1H, m, Ar*H*), 7.53–7.60 (1H, m, Ar*H*), 7.83 (1H, dd, *J* 7.7, 1.8, Ar*H*), 10.35 (1H, s, C*H*O); OH underneath the aromatic proton area; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 18.5 (*C*H$_3$), 73.7 (O*C*H(CH$_3$)CO$_2$H), 113.8 (Ar*C*H), 122.3 (Ar*C*H), 125.4 (Ar*C*(2)), 131.3 (Ar*C*H), 136.1 (Ar*C*H), 158.9 (Ar*C*(1)), 174.8 (*C*O$_2$H), 190.8 (*C*HO); *m/z* (NSI^-) 193 ($[M–H]^-$, 100), 387 ($[2M–H]^-$); HRMS (NSI^-) $C_{10}H_9O_4$ $[M–H]^-$ found 193.0507 requires 193.0506 (+0.4 ppm).

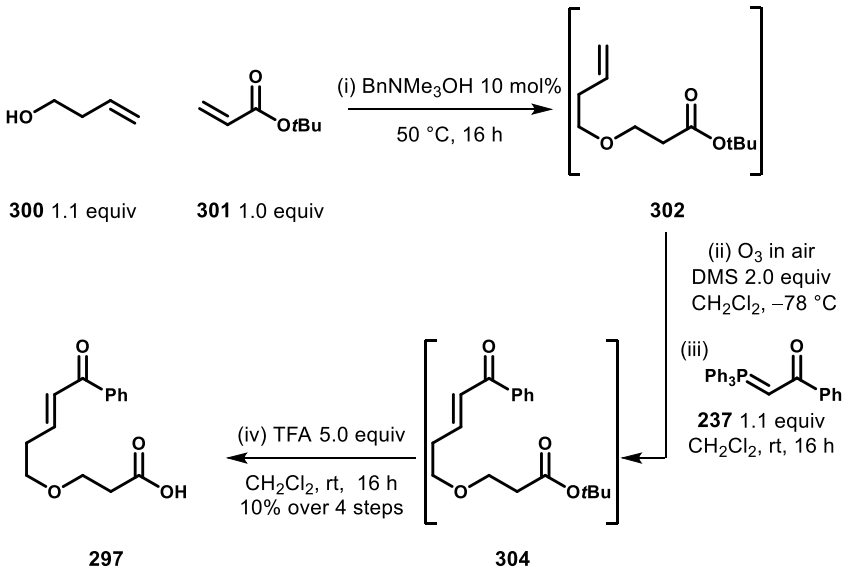
(*E*)-2-(2-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy)propanoic acid 275



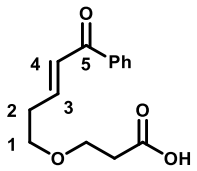
Following general procedure B in $CHCl_3$, the title compound (1.8 g, quant.) was obtained as a crude yellow soild that was used in the next step without further purification. mp 72–74ºC ν_{max} (film) cm ^{1} 1695, 1661, 1587, 1456, 1207;^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.75 (3H, d, *J* 6.8, C*H*$_3$), 4.92 (1H, d, *J* 6.8, OC*H*CH$_3$), 6.84 (1H, d, *J* 8.3, ArC(2)*H*), 7.05 (1H, t, *J* 7.5, ArC(4)*H*), 7.34 (1H, ddd, *J* 8.8, 7.4, 1.7, ArC(3)*H*), 7.48 (2H, t, *J* 7.5, COArC(3,5)*H*), 7.56 (1H, tt, *J* 6.9, 1.2, COArC(4)*H*), 7.66 (1H, dd, *J* 7.7, 1.7, ArC(5)*H*), 7.75 (1H, d, *J* 15.8, COC*H*=CH), 7.99–8.06 (2H, m, COArC(2,6)*H*), 8.13 (1H, d, *J* 15.9, COCH=C*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 18.5 (*C*H$_3$), 72.5 (O*C*HCH$_3$), 112.6 (Ar*C*(2)), 121.9 (Ar*C*(4)), 123.6 (CO*C*H=CH), 124.6 (Ar*C*(6)), 128.6 (COAr*C*(3,5 or 2,6)), 128.7 (COAr*C*(2,6 or 3,5)), 130.4 (Ar*C*(5)), 131.7 (Ar*C*(3)), 132.8 (COAr*C*(4)), 138.4 (COAr*C*(1)), 140.8 (COCH=*C*H), 156.5 (Ar*C*(1)), 177.4 (*C*OOH), 191.6 (*C*OPh); *m/z* (NSI$^-$) 295 ([M–H]$^-$, 100); HRMS (NSI$^-$) $C_{18}H_{15}O_4$ [M–H]$^-$ found 295.0975 requires 295.0976 (–0.3 ppm).

4-2-7 Extension to 6-membered ring tethers: Synthesis of tetrahydropyran derivative 299 (Scheme 87)

Synthesis of enone-acid 297



(*E*)-3-((5-Oxo-5-phenylpent-3-en-1-yl)oxy)propanoic acid 297

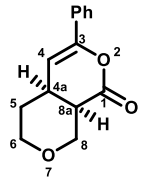


The solution of $BnNMe_2OH$ (Triton B 40%, 3.18 mL, 7.0 mmol, 10 mol%) in MeOH was concentrated under reduced pressure before adding 3-buten-1-ol **300** (66 mL, 77 mmol, 1.1 equiv). The reaction mixture was stirred for 30 min at rt before adding *tert*-butyl acrylate **301** (10.3 mL, 70 mmol, 1.0 equiv). The reaction mixture was stirred at 50 °C for 18 h, cooled to rt and filtered through a pad of celite and silica using CH_2Cl_2 (150 mL). The organic layer was concentrated under reduced pressure to give as a crude light-yellow oil (11.9 g, 77%) that was used in the next step without further purification. The crude (1.8 g, 10 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (290 mL) and cooled to –78°C. A stream of O_3 in air was bubbled through. Upon the change of colour of the reaction mixture to blue, the O_3 stream was stopped and air only was bubbled through for 5 min at –78°C. DMS (1.5 mL. 20 mmol, 2.0 equiv). After 10 min, the reaction mixture was left to slowly warmed to rt. Phosphorane **237** (4.2 g, 11 mmol, 1.1 equiv) was added and the reaction was stirred at rt for 16 h before being basified to pH 10 with saturated $NaHCO_3$. The aqueous was washed

with. The aqueous was acidified to pH 5 with 10% citric acid and extracted with CH_2Cl_2 (× 3). The organic was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude brown oil containing both **304** and phosphorane **237**. The crude oil was dissolved in CH_2Cl_2 (20 mL) before slowly adding TFA (3.8 mL, 50 mmol, 5.0 equiv) and stirring at rt for 17 h. The reaction mixture was concentrated under reduced pressure, diluted in EtOAc and basified to pH 10 using saturated $NaHCO_3$. The aqueous was washed with EtOAc (× 3) then acidified to pH 5 using 10% citric acid and extracted with EtOAc (× 3). The organic was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (317 mg, 10%) as a yellow oil that was used in the next step without further purification. ν_{max} (film) cm^{-1} 2876, 1418, 1668, 1620, 1597, 1287, 1111; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.56–2.64 (4H, m, C*H*$_2$CH$_2$CO$_2$H and C(2)*H*$_2$), 3.63–3.66 (2H, m, OC(1)*H*$_2$), 3.74 (2H, t, *J* 6.3, C*H*$_2$CO$_2$H), 6.94 (1H, m, C(4)*H*), 7.02 (1H, m, C(3)*H*), 7.43–7.48 (2H, m, COArC(3,5)*H*), 7.52–7.58 (1H, m, COArC(4)*H*), 7.90–7.93 (2H, m, COArC(2,6)*H*); ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ_C: 33.0 (*C*(2)), 34.8 (*C*H$_2$CH$_2$CO$_2$H), 66.0 (*C*(1)), 69.3 (*C*H$_2$CO$_2$H), 127.5 (*C*(4)), 128.55 (Ar*C*H × 2), 128.63 (Ar*C*H × 2), 132.8 (Ar*C*(4)H), 137.7 (Ar*C*(1)), 146.0 (*C*(3)), 176.8 (*C*O$_2$H), 190.9 (*C*OPh); *m/z* (APCI$^+$) 249 ([M + H]$^+$, 100%); HRMS (APCI$^+$) $C_{14}H_{16}O_4$ [M + H]$^+$ found 249.1120 requires 249.1121 (–0.5 ppm).

NHC-catalysed intramolecular formal [4+2] addition

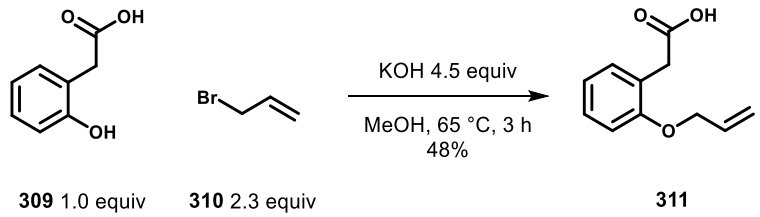
(4a*R*,8a*S*)-3-Phenyl-4a,5,8,8a-tetrahydro-1*H*,6*H*-pyrano[3,4-*c*]pyran-1-one 299



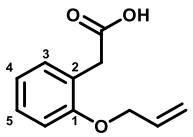
Enone-acid **297** (50 mg, 0.20 mmol, 1.0 equiv) and distilled *i*Pr_2NEt (38 µL, 0.22 mmol, 1.1 equiv) were stirred at rt for 20 min in anhydrous CH_2Cl_2 (3.0 mL) with 4 Å molecular sieves. Distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 2 h. NHC precatalyst **30** (14.7, 0.04 mmol, 20 mol%) and distilled *i*Pr_2NEt (88 µL, 0.50 mmol, 2.5 equiv) were added and the reaction mixture was stirred at rt for 20 h. The reaction mixture was diluted with EtOAc and washed with brine (× 3). The organic was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude brown-green oil (44 mg, >95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, Hexane : EtOAc (95:5 5 CV, 95:5 to 70:30 15 CV, 70:30 10 CV)] to give the title compound (23 mg, 50%) as a yellow oil. $[\alpha]_D^{20}$ +20.0 (*c* 1.0 $CHCl_3$); Chiral HPLC AS-H (95:5 hexane : IPA, flow rate 1 mL·min^{-1}, 211 nm, 40 ºC) t_R minor: 14.6 min, t_R major: 21.1 min, >99:1er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.62 (1H, dtd, *J* 14.5, 10.5, 4.1, C(5)*H*^{A}H^B), 1.76–1.84 (1H, m, C(5)H^A*H*^{B}), 2.63–2.89 (2H, m, C(4a)*H* and C(8a)*H*), 3.50 (1H, td, *J* 11.2, 2.5, C(6)*H*^{A}H^B), 3.61 (1H, dd, *J* 11.8, 3.0, C(8)*H*^{A}H^B), 3.97 (1H, dt, *J* 11.5, 3.7, C(6)H^A*H*^{B}), 4.48–4.60 (1H, m, C(8)H^A*H*^{B}), 5.86 (1H, d, *J* 5.8, C(4)*H*), 7.31–7.44 (3H, m, C(3)Ar*H* including C(3)Ar(4)*H*), 7.59–7.67 (2H, m, C(3)Ar*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 29.6 (*C*(5)), 30.8 (*C*(4a)), 39.6 (*C*(8a)), 65.2 (*C*(8)), 67.1 (*C*(6)), 103.9 (*C*(4)), 124.5 (C(3)Ar*C*H), 128.5 (C(3)Ar*C*H), 129.2 (C(3)Ar*C*(4)), 132.1 (C(3)Ar*C*(1)), 150.2 (*C*(3)), 168.5 (*C*(1)); *m/z* (ESI$^+$) 253 ([M + Na]$^+$, 48%), 271 ([M + Na + H_2O]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{14}O_3Na$ [M +N a]$^+$ found 253.0833 requires 253.0841 (–0.852 ppm).

4-2-8 Extension to 6-membered ring tethers: Synthesis of chromenone derivative 315 (Scheme 90)

Synthesis of alkene acid 311



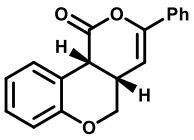
2-(2-(Allyloxy)phenyl)acetic acid 311



Following a procedure adapted from Roe *et al.*,[8] 2-hydroxyphenylacetic acid (40 g, 66 mmol, 1.0 equiv) as added to a solution of KOH (8.4 g, 150 mmol, 2.3 equiv) in MeOH (60 mL). Upon full dissolution, allyl bromide (13 mL, 77 mmol, 1.2 equiv) was added dropwise over 10 min and the resulting reaction mixture was heated to reflux for 2 h. A solution of KOH (8.0 g, 143 mmol, 2.2) in MeOH (40 mL) was added before refluxing the reaction mixture for 1 h then cooled to rt and concentrated under reduced pressure. The residue was dissolved in distilled water and washed with Et_2O (× 3). The aqueous layer was acidified using HCl 6 M to pH 1 and extracted with Et_2O (× 4). The combined organic was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a thick red oil (12.0 g) that was recrystallised in $CHCl_3$ then triturated in Et_2O to give the title compound (6.1 g, 48%) as beige solid that was used in the next step without further purification with data in accordance with literature.[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.70 (2H, s, ArC(2)CH_2), 4.56 (2H, dt, *J* 5.0, 1.6, OCH_2CH=CH$_2$), 5.25 (1H, dq, *J* 10.6, 1.5, OCH$_2$CH=CH^AH^B), 5.41 (1H, dq, *J* 17.3, 1.7, OCH$_2$CH=CH^AH^B), 6.02 (1H, ddt, *J* 17.3, 10.6, 5.0, OCH$_2$C*H*=CH$_2$), 6.86–6.89 (1H, m, ArC(3)*H*), 6.93 (1H, td, *J* 7.5, 1.1, ArC(5)*H*), 7.20 (1H, dd, *J* 7.4, 1.7, ArC(6)*H*), 7.23–7.28 (1H, m, ArC(4)*H*).

NHC-catalysed intramolecular formal [4+2] addition

(4a*S*,10b*R*)-3-Phenyl-4a,10b-dihydropyrano[4,3-c]chromen-1(5*H*)-one 315



Enone-acid **313** (59 mg, 0.20 mmol, 1.0 equiv) and distilled *i*Pr_2NEt (38 µL, 0.22 mmol, 1.1 equiv) were stirred at rt for 20 min in anhydrous CH_2Cl_2 (3.0 mL) with 4 Å molecular sieves. Distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 2 h. NHC precatalyst **30** (14.7, 0.04 mmol, 20 mol%) and distilled *i*Pr_2NEt (88 µL, 0.50 mmol, 2.5 equiv) were added and the reaction mixture was stirred at rt for 2.5 h. The reaction mixture concentrated under reduced pressure to give a crude green oil (201 mg, >95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL·min^{-1}, Hexane : EtOAc (100:0 5 CV, 100:0 to 80:20 15 CV, 80:20 10 CV)] to give the title compound (40 mg, 72%) as a yellow solid. with data in accordance with literature.[9] $[\alpha]_D^{20}$ –147.2 (*c* 1.04, $CHCl_3$);Chiral HPLC AD-H (95:5 hexane : IPA, flow rate 1 mL·min^{-1}, 211 nm, 40 ºC) t_R major: 14.3 min, t_R minor: 19.9 min, >99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.26 (1H, dddd, *J* 8.2, 6.7, 5.0, 3.1, C(4a)*H*), 3.98–4.08 (2H, m, C(5)*H*^{A}H^B and C(10b)*H*), 4.25 (1H, ddd, *J* 11.3, 3.1, 1.2, C(5)H^A*H*^{B}), 5.81 (1H, d, *J* 5.0, C(4)*H*), 6.86 (1H, dd, *J* 8.2, 1.2, C(7)*H*), 6.98 (1H, td, *J* 7.5, 1.3, C(8)*H*), 7.18–7.24 (1H, m, C(9)*H*), 7.30–7.34 (1H, m, C(10)*H*), 7.35–7.40 (3H, m, C(3)ArC(3,4,5)*H*), 7.59–7.65 (2H, m, C(3)ArC(2,6)*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 30.9 (*C*(4a)), 39.9 (*C*(10b)), 65.8 (*C*(5)), 98.6 (*C*(4)), 115.2 (*C*(10a)), 117.2 (*C*(9)), 121.1 (*C*(8)), 124.7 (C(3)Ar*C*(2,6)), 128.5 (C(3)Ar*C*(3,5)), 129.3 (C(3)Ar*C*(4) or *C*(9)), 129.5 (*C*(9) or C(3)Ar*C*(4)), 131.1 (*C*(10)), 131.7 (C(3)Ar*C*(1)), 151.7 (*C*(3)), 153.8 (*C*(6a)), 167.6 (*C*(1)).

References for section 4-2

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