Bifunctional Iminophosphoranes as Catalysts for Enantioselective Prototropic Shifts

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A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (DPhil)

Jonathan Golec

Supervisor: Prof. Darren J. Dixon

Merton College

University of Oxford

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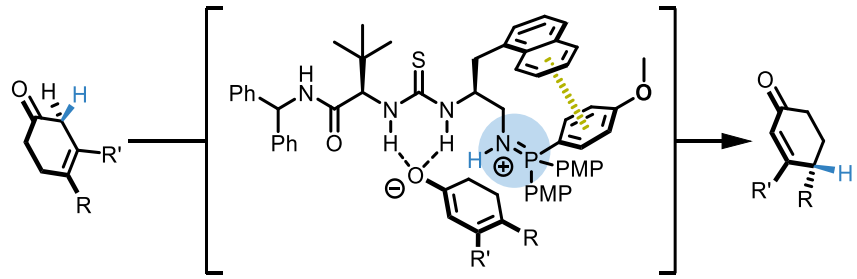
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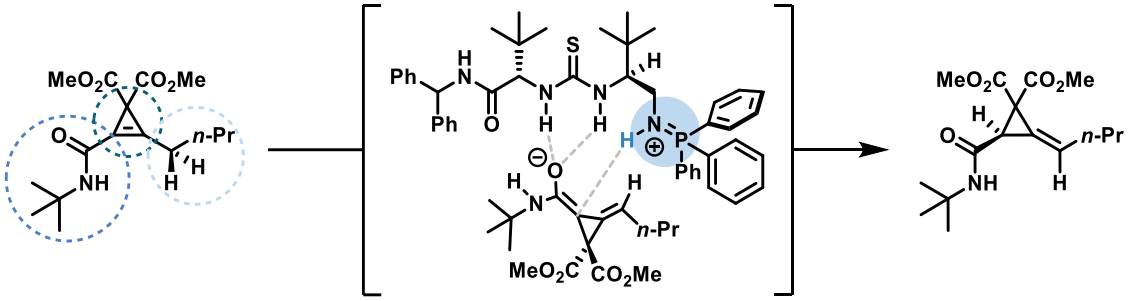
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Abstract

Bifunctional Iminophosphoranes as Catalysts for Enantioselective Prototropic Shifts



This thesis describes investigations into the application of the bifunctional iminophosphorane (BIMP) catalyst previously developed in the Dixon group to new transformations in superbase catalysis. Chapter **2** summarises the development of the enantioselective [1,3]-prototropic shifts of β,γ-unsaturated cyclohexenones into their chiral conjugated counterparts. The reaction proceeds via an initial rapid and reversible deprotonation followed by a rate- and stereo-determining protonation at the γ-position of the extended enolate which occurs in up to 99% ee and up to 99% yield. The reaction was found to be broadly applicable to a range of β,γ-unsaturated cyclohexenones synthesised from Hagemann's ester and, by tuning the catalyst's basicity and hydrogen-bond donor ability, the transformation could be carried out on more challenging substrates synthesised by [Co]-catalysed Diels-Alder reactions. The products were derivatised further while maintaining enantiopurity, we also demonstrated the transformation's relevance to a key building block of (−)-reserpine and (−)-penitrem D. The mechanistic aspects of the reaction were probed by both deuterium labelling experiments as well as computational work in collaboration with Prof. Robert Paton and Dr. Luis Simón.



Adhering to the same theme, chapter **3** describes the development of a novel BIMP catalysed strain release concept to synthesise chiral cyclopropanes. By strategic placement of an electron withdrawing group on a cyclopropene ring, γ-deprotonation occurs readily and the consequential extended enolate protonates asymmetrically at the α-position mirroring the prototropic shift of β,γ-unsaturated cyclohexenones. The reaction occurs rapidly with high levels of selectivity (up to 99% ee) and is applicable to a range of carbonyl species including esters and amides and, by tuning the catalyst scaffold, ketones. By structural modification of the cyclopropene as well as the iminophosphorane the transformation's applicability to the synthesis of pyrethroid-type molecules such as permethrin was demonstrated.

Declarations

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from June 2017 until June 2021, under the supervision of Prof. Darren J. Dixon. All the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.



Jonathan Golec

15th June 2021

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Entertainment outside the lab has mainly been found by hanging out with a group who calls them self 'the Council' (Mix, Rob, Ben and Antoine). We've had some extremely

memorable times (though most are hazy at best) with trips to Jersey (consumption of the breakfast material was observed after 2 min 40 s), the lake district (not sure we're allowed back to the punch bowl), many formals (Temperature is not sophisticated, nor is it piano music) and some mad parties. I'll miss hanging out with you guys, Mix, you're always welcome despite being the world's worst dinner guest and though I do miss living with you all, living without Rob is a whole lot less grim. A thousand years.

Thank you Tiff for all your love and support over the last year or so (and the proof reading) and for letting me win at chess every so often (though judging by your reaction, you didn't actually mean for it to happen). You've made the restrictions so much more bearable, the last year has flown by with you and I'm sure they will continue to do so (as long as you don't keep keeping me up at night with your snoring).

Finally, thank you, Mum, Dad and Alexander, for all your love, support and encouragement during my time at Oxford and everything else you've done for me, hopefully you'll all be as willing to come on trips up to Nottingham as you were to Oxford and we'll have some great times there too.

Abbreviations

Ac	Acetate
MeCN	Acetonitrile
ACP	Alkylidenecyclopropane
app-	Apparent
aq	Aqueous
Ar	Aryl
Bn	Benzyl
BIMP	Bifunctional iminophosphorane
DPPE	1,2-Bis(diphenylphosphino)ethane
br	Broad
br s	Broad singlet
Bu	Butyl
Cat.	Catalyst
CL	Catalyst loading
Cbz	Carboxy benzyl
cm	Centimetre
conc.	Concentrated
J	Coupling constant
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*, *N*′-Dicyclohexylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DKP	Diketopiperazine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DBE	Double bond dissociation energy
ddd	Double doublet of doublets
d	Doublet
dd	Doublet of doublets
dq	Doublet of quartets
dt	Doublet of triplets
ES	ElectroSpray Ionisation
ee	Enantiomeric excess
eq	Equivalent
Et	Ethyl
FCC	Flash column chromatography
FDA	Food and Drug Administration
g	Gram
$t_{1/2}$	Half life
hep	Heptet
Hz	Hertz
h	Hour

HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HOBt	Hydroxybenzotriazole
IR	Infrared
i-	Iso
i-Pr	Isopropyl
IPA	Isopropyl alcohol
K	Kelvin
lit.	Literature value
LHMDS	Lithium bis(trimethylsilyl)amide
m/z	Mass to charge ratio
MHz	Mega hertz
MP	Melting point
MEM	2-Methoxyethoxymethyl ether
Me	Methyl
MVK	Methyl vinyl ketone
μm	micrometre
mg	Milligram
ml	Millilitre
mm	Millimetre
mmol	Millimole
min	Minute(s)
M	Molar concentration
m	Multiplet
Np	Naphthyl
n-	Normal
NMR	Nuclear Magnetic Resonance Spectroscopy
Nu	Nucleophile
o-	*Ortho*-
p-	*Para*-
PMP	*Para*-methoxy phenyl
*p*TSA	*Para*-toluenesulfonic acid
ppm	Parts per million
Ph	Phenyl
Phth	Phthalimide
KHMDS	Potassium bis(trimethylsilyl)amide
Pr	Propyl
q	Quartet
rt	Room temperature
sat.	Saturated
s	Singlet
t-	Tert
Boc	*Tert*-butoxycarbonyl
TBAB	*Tert*-butyl ammonium bromide
TBAF	*Tert*-butyl ammonium fluoride
TBME	*Tert*-butyl methyl ether

TBS	*Tert*-butyl dimethyl silane
THF	Tetrahydrofuran
TMG	1,1,3,3-Tetramethylguanidine
Me_4Phen	3,4,7,8-Tetramethyl-1,10-phenanthroline
TLC	Thin layer chromatography
Tol	Toluene
Ts	Tosyl
TS	Transition state
TBD	Triazabicyclodecene
TMS	Trimethyl silane
TFDA	Trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate
t	Triplet

1. Introduction

1.1 The importance of enantioselective techniques

With very few exceptions, the fundamental processes of biochemistry take place through the interaction of chiral molecules. Stereocentres are regularly incorporated into pharmaceutical agents to improve specificity and potency towards target binding sites, which has led to the development of a plethora of enantioselective methods for the synthesis of small chiral molecules. Often, chiral drug molecules exhibit enantio-dependent properties as a consequence of diastereomeric interactions *in vivo*.[1] Historically, drug molecules were often administered as a racemic mixture of enantiomers or chiral compounds were altogether avoided – the administration of a racemic mixture is inconsequential, provided that the inactive isomer is benign. However, this is not always the case, with "inactive" enantiomers often being responsible for side effects, different metabolic pathways, and possible toxic metabolites.

The most famous example of a drug's stereochemical configuration influencing its performance comes from thalidomide. Thalidomide was administered as a treatment for morning sickness, but led to severe limb malformation in infants, with over 10,000 being exposed to the drug between 1957 and 1961.[2] It was later found that the (*S*)-enantiomer is a teratogen.[3] Research was undertaken to synthesise a single, stable enantiomer, but the drug was later found to racemise *in vivo*.[4]

Thalidomide is an extreme case – often the effects of the undesirable enantiomer are less severe. An often-quoted example of the influence of stereochemical configuration on pharmacodynamics is given in the anticoagulant, warfarin. The (*S*)-(−)-enantiomer (**1**)

has been found to be significantly more potent than its (*R*)-(+)-counterpart (**2**). The two enantiomers are metabolised in different ways leading to a range of metabolites resulting from oxidations occurring at positions **1**, **2**, **3**, **15** and **21** (Figure 1).[5] It transpired that the *R*-(+)-isomer inhibits the enzyme CYP2C9 (one of the major metabolic enzymes of the *S*-(−)-isomer) which consequently leads to increased levels of the active *S*-(−)-enantiomer and increased time for drug clearance.[1]

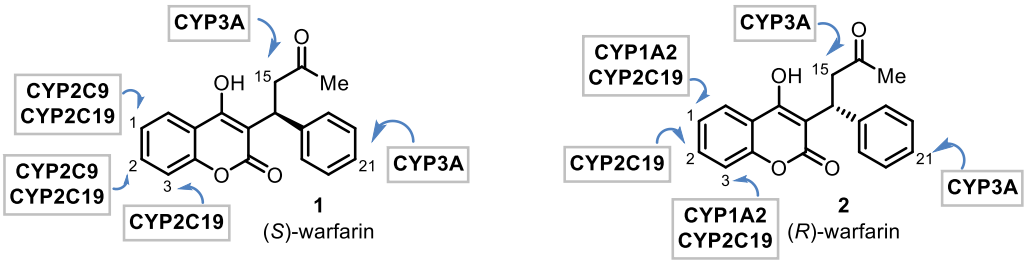


Figure 1: (*S*)-warfarin and (*R*)-warfarin and their different metabolic pathways. Oxidations occur at the assigned positions.[5]

In the wake of thalidomide, to reduce the likelihood of future disasters, the U.S. Food and Drug Administration (FDA) has compelled drug discovery projects to consider stereochemical configuration as early as possible in the drug discovery process so that the pharmacologic activity, pharmacokinetic profile, and toxicology of each individual isomer can be studied. This means that absolute stereochemical configuration must be known for compounds with stereogenic centres early on to ensure that analysis is considered thorough and valid for inclusion in the drug approval application. Consequently, the demand for novel approaches to the enantioselective synthesis of drug molecules is of the utmost importance, both for analysis and regulatory approval.

Historically, methods to achieve the synthesis of single enantiomer compounds have involved the use of chemical chiral resolution or the separation of each enantiomer chromatographically.[6,7] Unfortunately, these techniques result in the loss of 50% of the

starting material, as the undesired enantiomer is removed. To overcome this, chiral auxiliaries such as Evans or Ellman's may be utilised.[8,9] Chiral auxiliaries are covalently bound to the reactive molecule and can influence the stereochemical outcome of a reaction. The auxiliary is then cleaved, providing the product in high enantiomeric excess. Unfortunately, these can be cumbersome to install and remove, adding at least two steps to a synthetic route and significantly decreasing atom economy as stoichiometric amounts of auxiliary are necessarily required.

The effective use of chiral catalysts to generate enantioenriched products is a superior technological approach. Only catalytic amounts of the active molecule are required, which reduces waste and improves the efficiency of a synthetic sequence. Enantioselective catalysis has been defined by Bolm and Gladysz as "the catalytic, selective, and reproducible generation of a given enantiomer of a chiral product from achiral reactants".[10] To achieve this, the catalyst must be chiral and non-racemic, and decrease the activation energy to favour the formation of one of the enantiomers. As such, chirality is transferred from the catalyst to the product – known as asymmetric induction. Enantioselective catalysis has become commonplace in organic synthesis, and in 2001 the Nobel Prize in Chemistry was awarded to Knowles, Noyori and Sharpless for their work on asymmetric hydrogenation and oxidation reactions. These enantioselective methods frequently require the use of chiral transition metal complexes.[11] Such complexes can be highly efficient catalysts, often used with extremely low catalyst loadings, and for a diverse range of enantioselective transformations. Despite the advantages of transition metal catalysed enantioselective transformations, the metals used are often toxic and can be difficult to remove,

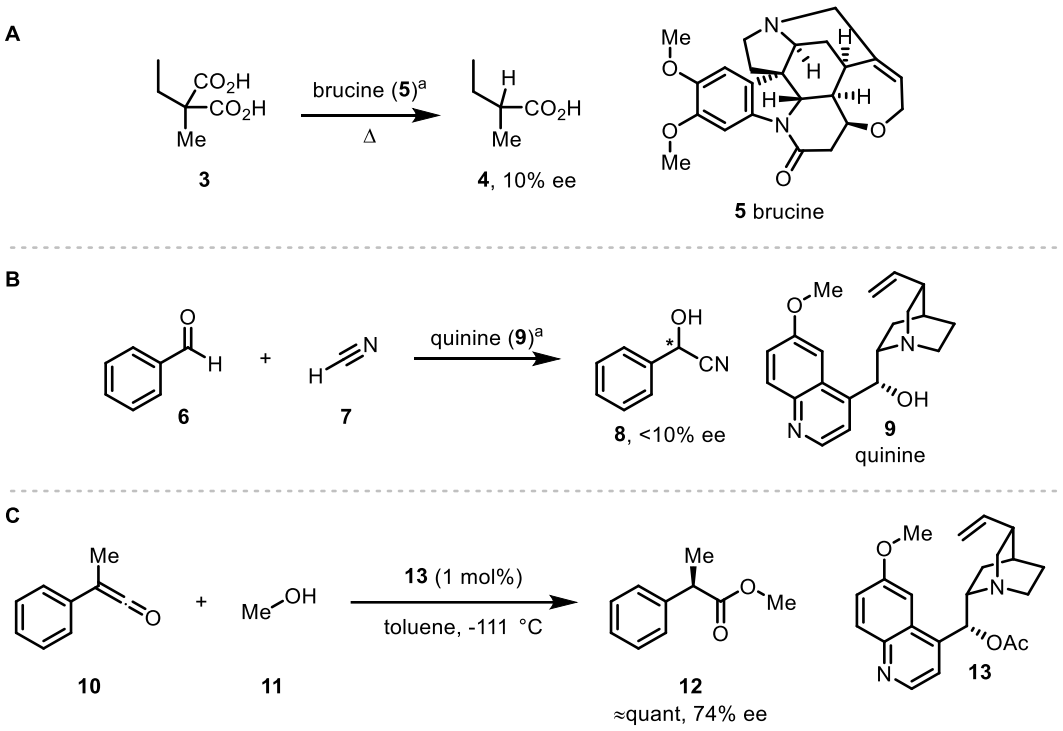
contaminating a final product with residual trace metal. Additionally, many such metals are prohibitively expensive.

To complement transition metal catalysis, small organic molecules have been deployed as chiral catalysts. These molecules, coined ‘organocatalysts’ by MacMillan in 2000, can be readily synthesised, often from commercially available starting materials, and reduce the requirement for the exclusion of air and moisture from a reaction vessel due to their lower sensitivity to air and moisture in comparison with transition metal complexes.[12] These features offer advantages over transition metal catalysis, and allow for the development of new transformations currently unfeasible with metal catalysis, as well as reducing the need for expensive, toxic metals.

Prior to MacMillan’s ‘organocatalyst’ terminology, Langebeck had used ‘organic catalysts’ to describe catalysts lacking metal centres as early as 1949, and throughout the 20th century numerous reports of molecules acting as enantioselective organocatalysts were reported.[13] This chapter briefly follows the emergence of enantioselective organocatalysis, and in particular, the development of Brønsted base / hydrogen bond (H-bond) donor catalysis and their superbasic counterparts. More recent examples of their use are also outlined to demonstrate the field’s continued prominence.

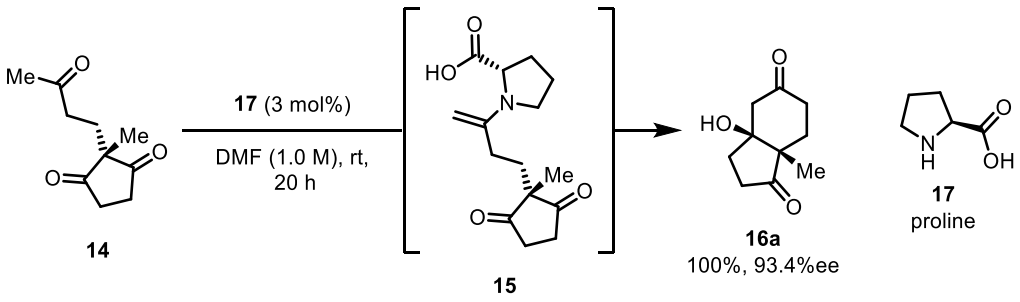
1.2 The emergence of enantioselective organocatalysis

Asymmetric induction by small organic molecules was observed as early as 1904. In an enantioselective decarboxylation of malonic acid (**3**), Marckwald *et al.* used Brucine (**5**) to synthesise the desired chiral acid (**4**) in 10% ee (Scheme 1A).[14,15] It was not until later into the 20th century that small chiral organic molecules would be extensively investigated as viable enantioselective catalysts. Although Marckwald's report of an organocatalysed decarboxylation could be considered a starting point for the field, its results have been found to be somewhat irreproducible.[16] Marckwald's decarboxylation was followed nine years later by the first example of a metal-free enantioselective C–C bond-forming reaction catalysed by an organic molecule.[17] Quinine (**9**), one of the cinchona alkaloids, imparted chirality (<10% ee) in the addition of hydrogen cyanide (**7**) to benzaldehyde (**6**) (Scheme 1B). In 1960, Pracejus used an acylated analogue of quinine (**13**) and applied it to the enantioselective reaction of phenyl(methyl)ketene (**10**) with MeOH (**11**). The reaction proceeded at low temperature, –111 °C, and with very low catalyst loading (1 mol%) (Scheme 1C).[18] It is believed that the reaction occurs by initial base-catalysed addition of MeOH to the ketene, followed by an enantioselective protonation step by the protonated alkaloid catalyst with a high degree of enantiofacial selectivity (74% ee).



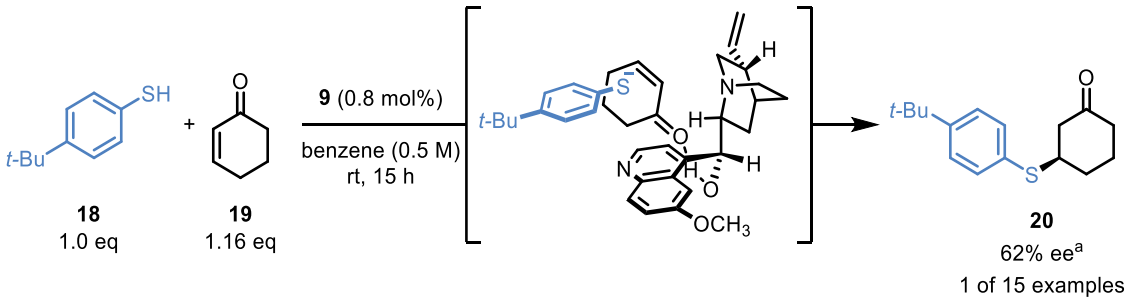
Scheme 1: A) Marckwald's eantioselective decarboxylation of malonic acid – 1904; B) Quinine-catalysed enantioselective addition of hydrogen cyanide to benzaldehyde; C) Pracejus' enantioselective addition of MeOH to phenyl(methyl)ketene.[a]Additional reaction conditions and product yield are not available.

Eleven years later, the Hajos–Parrish–Eder–Sauer–Wiechert reaction was developed. Here, natural-proline (**17**) was deployed as a covalent organocatalyst for the synthesis of cyclohexanones (Scheme 2).[19,20] The reaction proceeds via initial formation of a reactive enamine intermediate (**15**) at the methyl ketone which then undergoes an intramolecular, enantioselective aldol reaction with one of the two pro-chiral ketones residing on the molecule's five-membered ring. The selectivity is believed to arise from hydrogen bonding interactions between the carboxylic acid and ketone. Following the addition, the resulting iminium ion intermediate is hydrolysed, regenerating the proline catalyst.



Scheme 2: The proline-catalysed Hajos-Parrish-Eder-Sauer-Wiechert reaction – 1971.

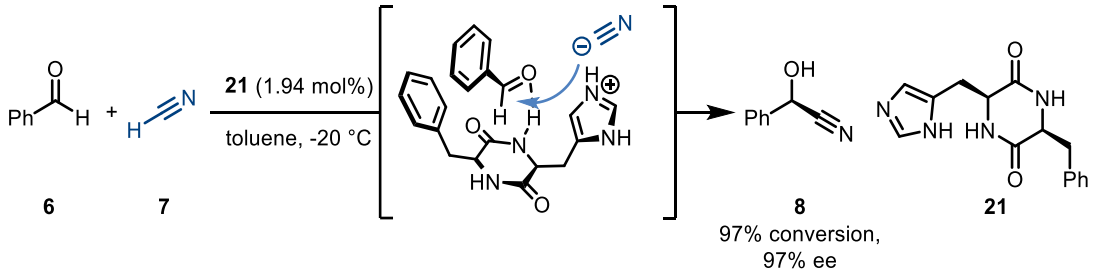
In 1981, the cinchona alkaloids re-emerged as viable catalysts to facilitate the sulfa-Michael addition of aromatic thiols to cyclic α,β-unsaturated ketones in an enantioselective manner (Scheme 3).[21] In the study, Hiemstra and Wynberg demonstrated that the hydroxyl group of the cinchona alkaloid was vital for enantioselectivity and that use of the catalyst's diastereomer was similarly detrimental to the enantio-enrichment of the product. The authors postulated a transition state involving the deprotonated thiol species as well as the free hydroxyl activating and binding the enone. π-π stacking between the aromatic thiols and quinoline's heterocycle were also suggested to contribute to the enantioselectivity.



Scheme 3: Quinine (**9**) catalysed sulfa-Michael addition of aromatic thiols to α,β-unsaturated cyclohexenones – 1981.[a]Yields typically ranged from 80% to 98%.

Up to this point, the organocatalytic species had been directly derived from natural products such as the cinchona alkaloid family. At the same time as Hiemstra and Wynberg's enantioselective Michael addition, Inoue disclosed a novel catalyst scaffold.[22] The new diketopiperazine (DKP) catalyst (**21**) was formed by the condensation of L-phenylalanine and L-histidine and could catalyse the enantioselective addition of hydrogen cyanide (**7**) to benzaldehyde (**6**) in up to 97% ee with just 1.94 mol% of catalyst (Scheme 4). The observed

enantioselectivity was explained using a model in which hydrogen-bonding interactions between the DKP and benzaldehyde pointed the bulky aromatic ring away from the piperazine ring of the DKP, leading to preferential attack of the cyanide to one face of benzaldehyde (Scheme 4).

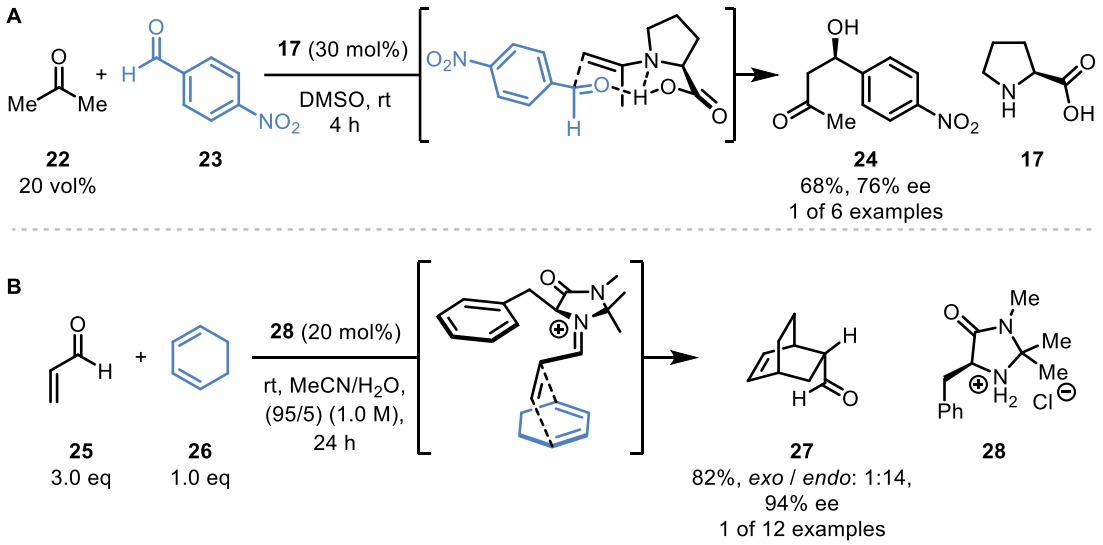


Scheme 4: Inoue's DKP catalyst (**21**) for the enantioselective addition of hydrogen cyanide to benzaldehyde.

It was not until 2000 that the field of organocatalysis came to the forefront of organic synthesis. List *et al.* and MacMillan *et al.* published their landmark works on asymmetric enamine and iminium catalysis in the same year.[12,23] List's work demonstrated the use of proline (**17**) as a catalyst for cross-aldol reactions between ketones (**22**) and non-enolisable aldehydes such as **23**, proposing that the reaction proceeded via initial condensation of proline with the ketone, raising the reactive enolate's HOMO, followed by addition of the enamine to a non-enolisable aldehyde (Scheme 5A).[23] This was expected to occur in a Zimmerman-Traxler-like transition state (TS) with the bulky substituents occupying equatorial positions on the chair-like conformation (Scheme 5A).

MacMillan's work demonstrated the applicability of chiral secondary amines to the asymmetric Diels-Alder reaction between dienes and α,β-unsaturated enals (Scheme 5B).[12] Condensation of the amine (**28**) with the enal (**25**) forming an iminium ion species, increased the enal's reactivity towards the diene (**26**) by lowering the enal's LUMO. The catalyst loading could be decreased to as low as 5 mol% and the transformation was applicable to a range of cyclic (5- and 6-membered rings) as well as acyclic dienes. To explain the

selectivity, the authors proposed that the benzyl group of the amine blocked the *si*-face of the iminium, preventing the cyclohexadiene's approach. This led to a high degree of enantioselectivity.



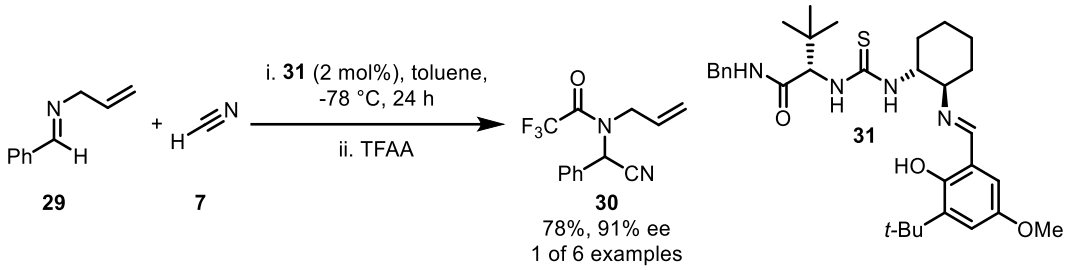
Scheme 5: A) Proline-catalysed addition of ketones to non-enolisable aldehydes by List *et al.*; B) Secondary amine catalysed Diels-Alder reaction by MacMillan *et al.*

The field of organocatalysis has expanded considerably since 2000, and now encompasses several catalytic regimes including covalent, H-bond donor, nucleophilic, superacid and superbase catalysis, among others to perform a rich variety of enantioselective chemical transformations.

1.3 The development of Brønsted base / H-bond donor catalysts

Following the success of covalent organocatalysts such as proline (**17**) in enantioselective transformations, investigations into the use of non-covalent interactions to induce chirality were undertaken. Early examples of H-bond donor catalysis were demonstrated in the ring opening of epoxides with secondary amines by Hine *et al.*, and by a significant rate enhancement of the Diels-Alder reaction of cyclopentadiene with methyl vinyl ketone (MVK) by Kelly.[24,25] More recently, in 1998, Jacobsen identified a Schiff base /

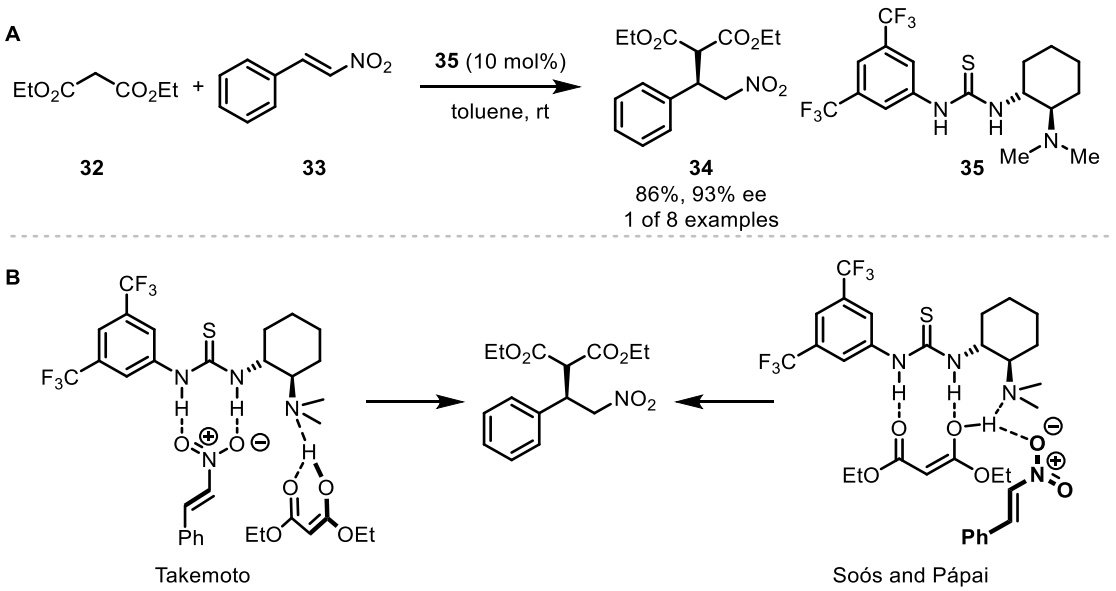
H-bond donor catalyst scaffold for the promotion of a highly enantioselective (up to 91% ee) Strecker reaction of HCN (**7**) with a series of aldimines (**29**) whilst investigating their use as chiral ligands (Scheme 6A).[26] In 2000, Jacobsen applied the same catalyst to the enantioselective addition of HCN to ketimines.[27] Other examples have also been developed including additions of phosphites,[28] silyl-ketene acetals[29] and nitroalkanes to imines.[30] The reaction is thought to occur via H-bond activation of the imine in a 'pull'-type mechanism.



Scheme 6: Jacobsen's Schiff base H-bond donor catalysed enantioselective Strecker reaction.

H-bond donor catalysis has been shown to be efficacious in reactions that do not require activation of a pro-nucleophile. To overcome this limitation in 2003, Takemoto *et al.* developed the first example of a Brønsted base / H-bond donor catalyst (**35**) for the enantioselective Michael-addition of malonate esters (**32**) to nitro-olefins (**33**) (Scheme 7A).[31] The thiourea hydrogen-bond donor was of paramount importance in achieving high levels of enantioselectivity. Replacing the thiourea with an amide decreased the selectivity from 93% ee to 35% ee. This was also detrimental to the yield. Takemoto explained the enantioselectivity through a transition state model in which a strong hydrogen bond interaction formed between the thiourea and nitro-olefin, bringing the two reactants into proximity and in the correct orientation. The model subsequently has been disputed by Soós and Pápai who proposed an alternative model where the key hydrogen bond is positioned differently (Scheme 7B).[32] Takemoto's original proposal placed the

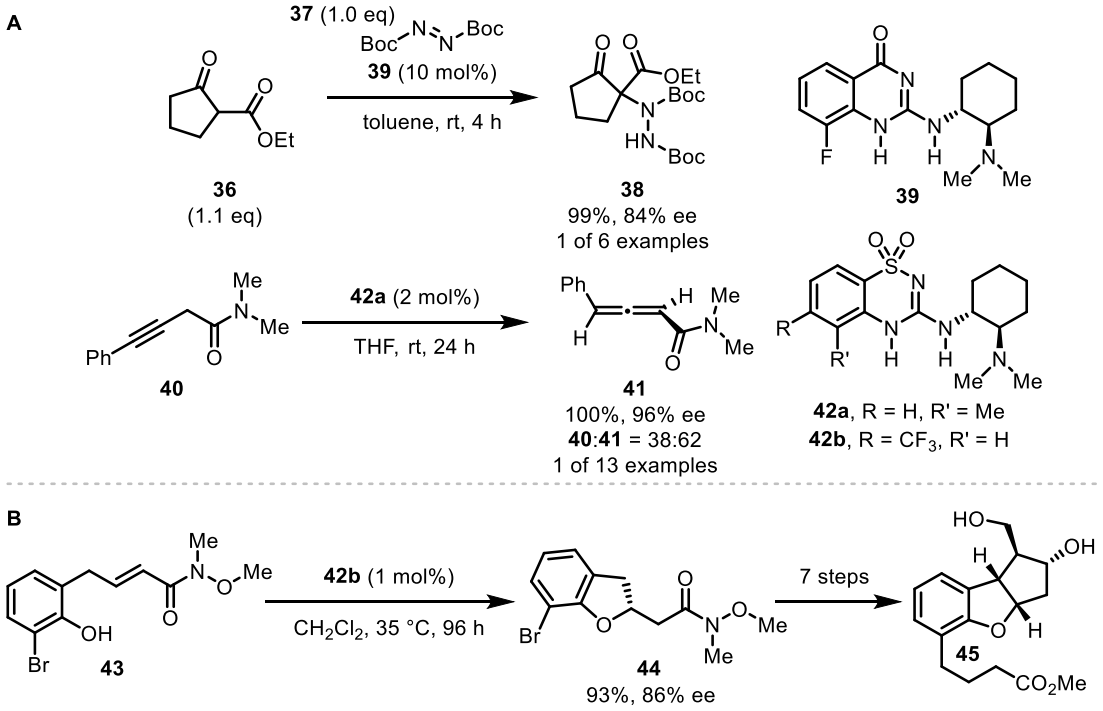
nitro-olefin in the grasp of the thiourea, while the deprotonated malonate remained in close proximity to the protonated amine. Soós and Pápai's alternate model bound the enolate to the thiourea while the nitro-olefin interacted with the protonated amine. Calculations show that Soós and Pápai's model is the more realistic transition state by an energy difference of 2.7 kcal/mol.



Scheme 7: A) Takemoto's Brønsted base / H-bond donor catalysed enantioselective Michael addtion of malonate esters to nitro-olefins; B) Proposed models to explain enantioselectivity.

Takemoto's original bifunctional Brønsted base catalyst has been a focal point for novel catalyst designs, and modification of the H-bond donor scaffold has been the subject of several investigations. In 2011 Takemoto unveiled quinazoline (**39**) and benzothiadiazine (**42**) catalysts for the enantioselective hydrazination of 1,3-dicarbonyl compounds (up to 94% ee), and the enantioselective isomerisation of β,γ-unsaturated alkyne esters and amides (up to 98% ee) (Scheme 8A).[33,34] The benzothiadiazine-based catalysts have also been used in the intramolecular oxa-Michael-addition to α,β-unsaturated amides and α,β-unsaturated Weinreb amides, which proved useful in the synthesis of a key intermediate (**45**) towards the synthesis of beraprost (Scheme 8B).[35,36] The reaction proceeded well

on α,β-unsaturated Weinreb amide **43** providing the desired product (**44**) in 93% yield and 86% ee. A more recent development introduced the squaramide H-bond donor to the scaffold. However, the utility of the catalyst has yet to be established.[37]

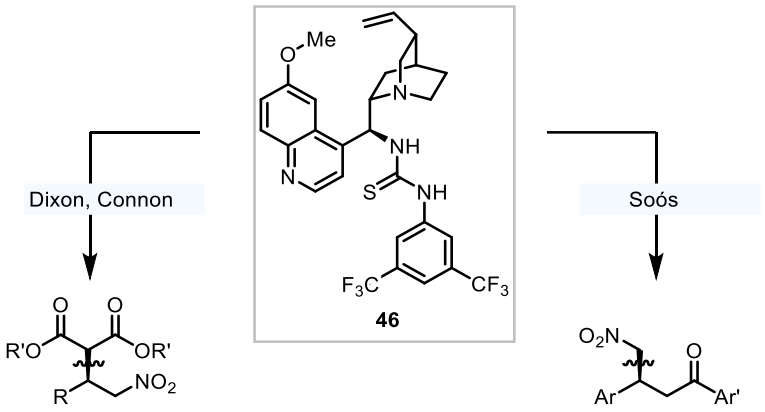


Scheme 8: A) Takemoto's quinazoline (**39**) and benzothiadiazine (**42**) catalysts and their use in the synthesis of enantioenriched α-amino malonates and allenes; B) Use of catalyst **42** in Takemonto's synthesis of a key intermediate of beraprost.

1.4 Further advancements in the field – cinchona alkaloid type catalysts

Following Takemoto's seminal report on Brønsted base / H-bond donor catalysed enantioselective Michael additions, many other research groups joined the field. Although Takemoto's original catalyst performs well, it is somewhat limited by its low basicity making it unsuitable for transformations involving low acidity pro-nucleophiles. New catalytic scaffolds were required to overcome this problem. For instance, a more basic tertiary amine, in the form of the quinuclidine core of the cinchona alkaloids, was found to be an efficient chiral base. The free hydroxyl group associated with these alkaloids could act as a hydrogen bond donor required for enantio-induction, but also to

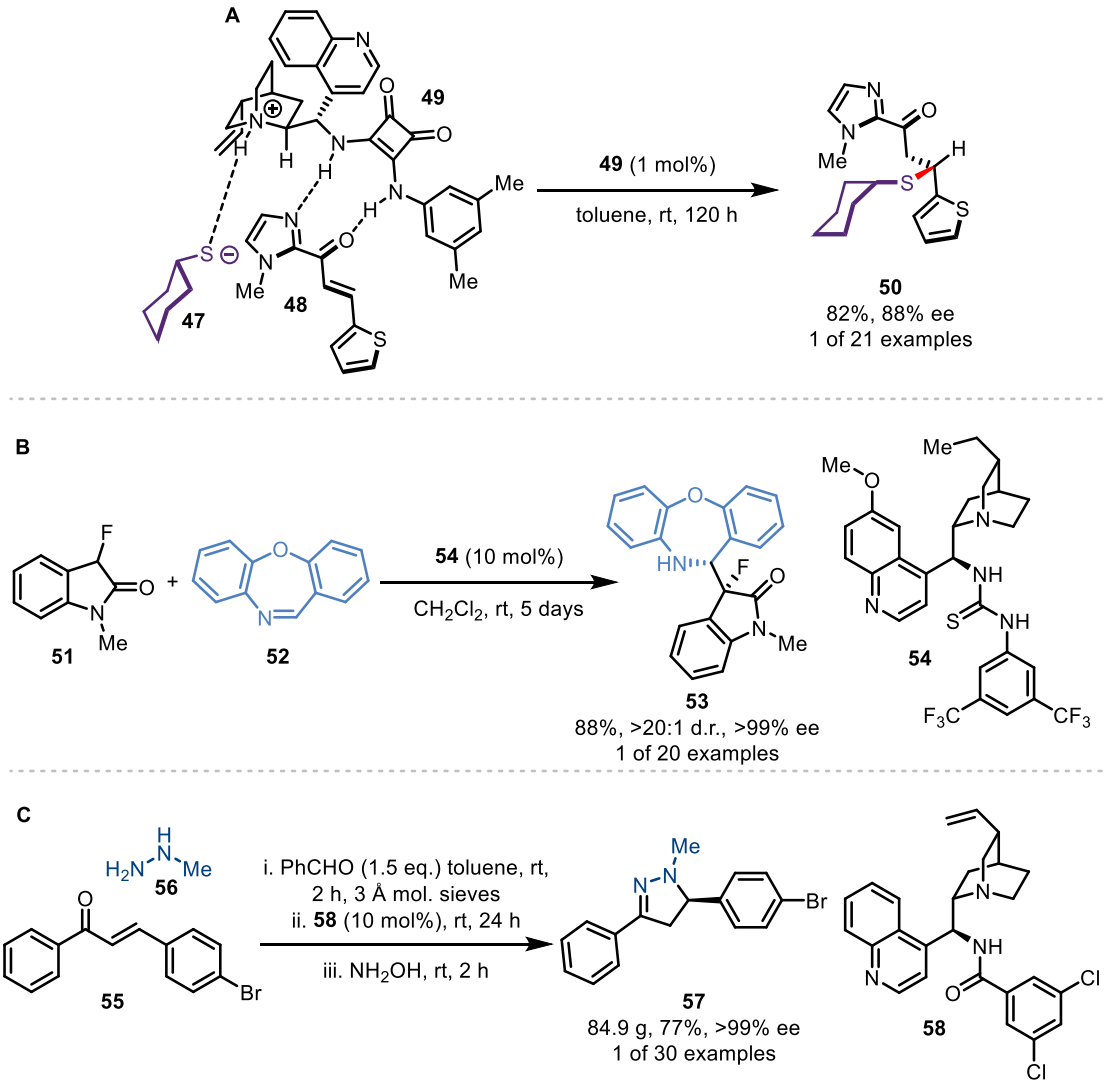
serve as a point of modification to afford a variety of other hydrogen bond donors that might improve utility. Four separate research groups, Chen,[38] Connon,[39] Dixon[40] and Soós[41] reported the use of synthetically modified cinchona catalysts such as **46** in a variety of highly enantioselective Michael additions, involving pro-nucleophilic malonate esters and nitromethane (Scheme 9).



Scheme 9: The use of cinchona alkaloid derived catalysts to perform enantioselective Michael-additions as demonstrated by Chen,[38] Connon,[39] Dixon[40] and Soós[41].

Following the original cluster of reports, these novel cinchona derived Brønsted base / H-bond donor catalysts have been used in many enantioselective transformations. The catalysts are still frequently used, and recent examples include the enantioselective sulfa-Michael addition to α,β-unsaturated 2-acyl imidazoles (**48**) by Singh *et al.* in which a squaramide-derived catalyst (**49**) was employed to form the desired Michael-adducts in excellent enantioselectivity (up to 92% ee) and yield (up to 98%) (Scheme 10A).[42] Du *et al.* also used a cinchona-derived catalyst to carry out the enantioselective Mannich addition of 3-fluorooxindoles (**51**) to dibenzo[*b*,*f*][1,4]oxazepines (**52**) (Scheme 10B).[43] The transformation was effective on 20 substrates, highlighting both the 3-fluorooxindoles' and the dibenzo[*b*,*f*][1,4]oxazepines' structural importance in bio-active molecules such as Maxipost and pharmaceutical agents such as Loxapine. Most recently, work in the Dixon group used a cinchona-based catalyst for the enantioselective Michael

addition of hydrazines (**56**) to β-substituted enones (**55**) to form 2-pyrazolines (**57**) in one pot (Scheme 10C).[44] The reaction could be scaled up to 100 g providing 84.9 g of the final product (77% yield) in >99% ee after a single recrystallisation. To showcase the catalyst's applicability to large scale synthesis, it was demonstrated that most of the catalyst (89%) could be recovered post-reaction.



Scheme 10 A) Enantioselective sulfa-Michael addition to α,β-unsaturated 2-acyl imidazoles and transition state model by Singh *et al.*; B) Enantioselective Mannich reaction of 3-fluorooxindoles to dibenzo[*b*,*f*][1,4]oxazepines by Du *et al.*; C) Enantioselective Michael-addition of hydrazines to β-substituted enones by Dixon *et al.*

1.5 Superbase catalysis

Despite the success of Brønsted base / H-bond donor catalysis, it was believed that the reaction scope and catalyst utility could be improved further by increasing the basicity. This could be achieved by the introduction of superbasic groups. Loosely defined, a superbase includes any compound with a pK_{BH+} greater than that of proton sponge® (**59**) (pK_{BH+} 18.6 in MeCN) (Figure 2).[45] The definition encompasses a variety of basic organic molecules such as guanidines (**61** and **64**),[46] cyclopropenimines (**65**),[47] phosphazenes (**66**)[46] and proazaphosphatranes (**67**)[48] (Figure 2).

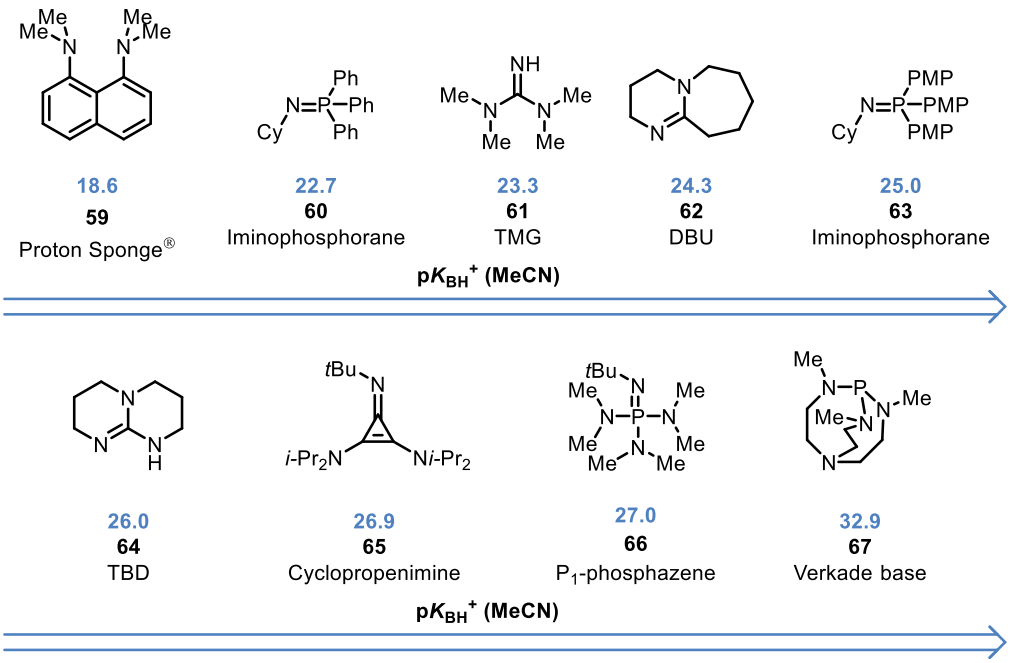
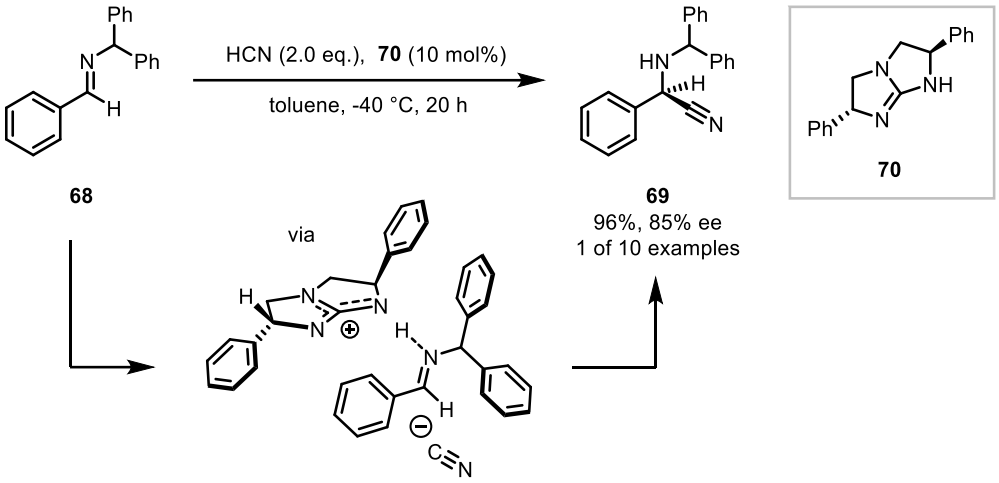


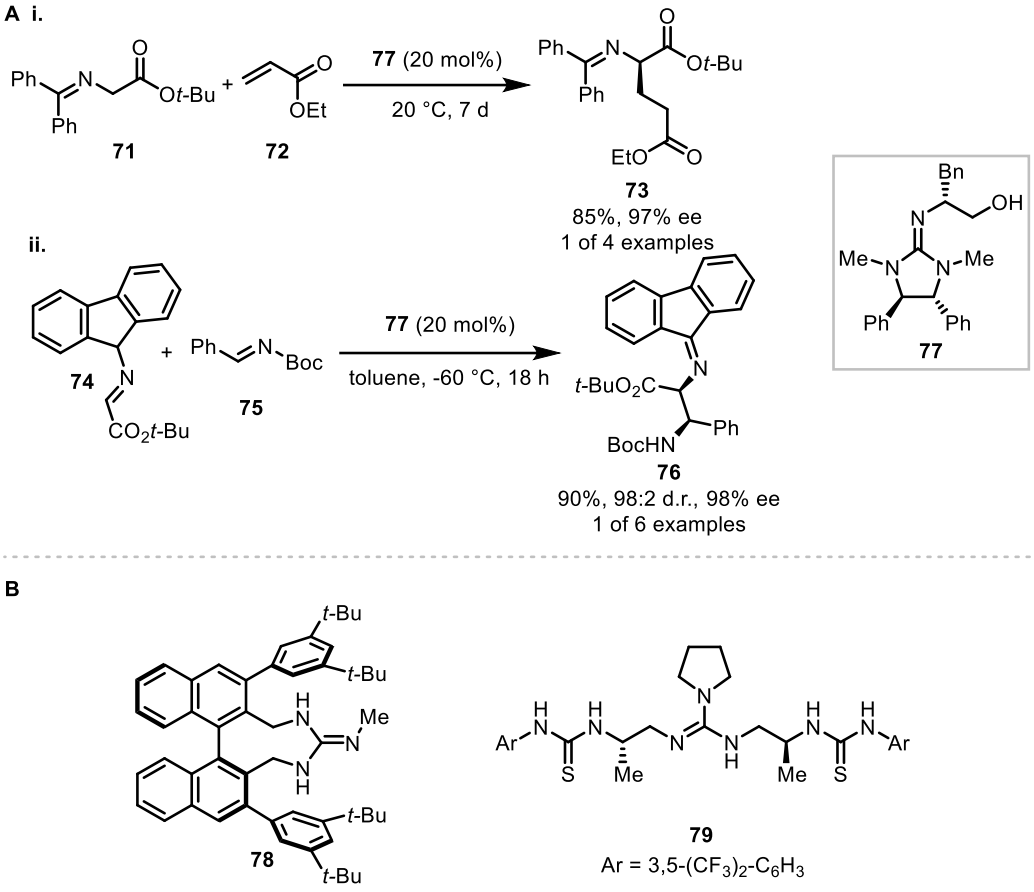
Figure 2: Superbasic moieties in order of increasing basicity from left to right. pK_{BH^+} values are taken in MeCN.

Chiral bicyclic guanidines (**70**) were recorded as powerful asymmetric catalysts for use in the asymmetric Strecker reaction in 1999 by Corey. Twelve years later, Tan *et al.* proposed that the protonated catalyst salt operates as a hydrogen bond donor to guide nucleophilic attack (Scheme 11).[49,50] Around the same time, Tan showed that an analogous bicyclic guanidine catalyst could promote the enantioselective conjugate addition of α-fluoro-β-ketoesters to *N*-alkyl maleimides.[51]



Scheme 11: Corey's chiral guanidine catalyst's use in the asymmetric Strecker reaction and Tan's model.

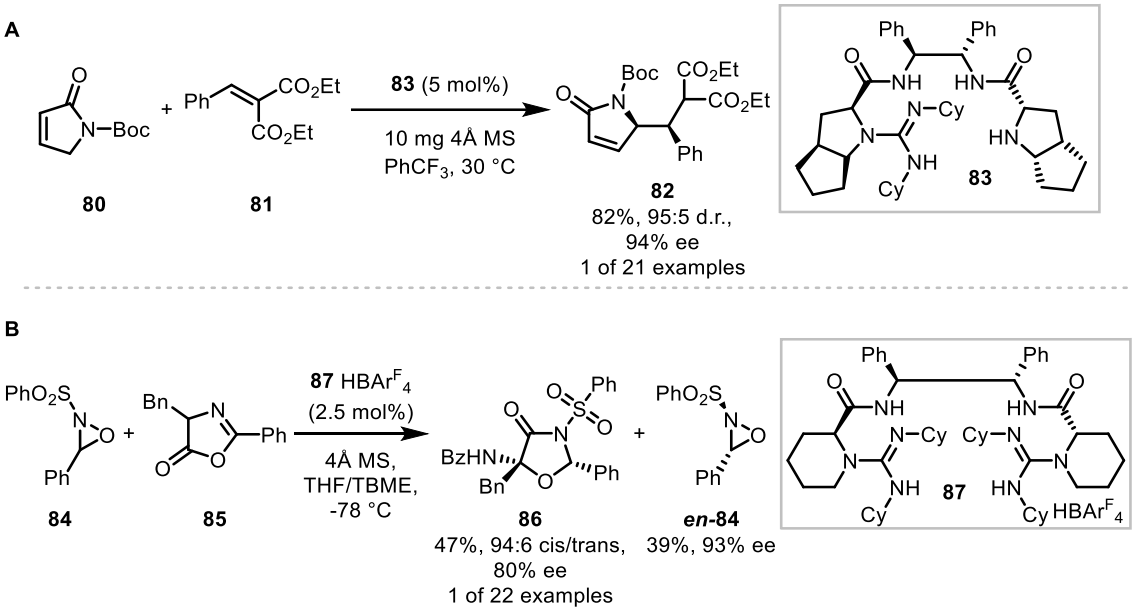
Efforts to attach superbasic moieties to chiral H-bond donor backbones have proved successful and the resultant catalysts have been applied to many reactions. Early progress was made by Ishikawa, who combined a cyclic C_2-symmetric guanidine scaffold with a hydroxyl H-bond donor functionality linked by a chiral tether to the basic site (**77**) (Scheme 12A).[52] The resulting chiral catalyst was capable of catalysing the addition of glycine imines (**71**) to acrylate esters (**72**) in up to 97% ee and high yields (up to 98%) (Scheme 12Ai). Kobayashi successfully applied this catalyst to an asymmetric Mannich-type reaction of fluorenone imines of glycine esters (**74**) (Scheme 12Aii).[53] The catalyst imparted high levels of diastereoselectivity (up to >99:1 syn / anti) as well as excellent enantioselectivity (up to 98% ee). Other variations of the guanidine / H-bond donor structure have been developed and used in the catalysis of a series of challenging reactions. These include Terada's axially-chiral catalyst (**78**), which was used to achieve the 1,4-addition of 1,3-dicarbonyl compounds to nitroalkenes and Nagasawa's double thiourea C_2 symmetric scaffold (**79**) for the Mannich-type reaction of *N*-Boc aldimines with malonates (Scheme 12B).[54,55]



Scheme 12: A) i. Isikawa's chiral H-bond donor guanidine catalyst (**77**) and its use in the asymmetric addition of glycine imines to acrylate esters; ii. Kobayashi's asymmetric Mannich-type reaction of fluorenone imines with catalyst **77**; B) Terada's axially-chiral catalyst **78** and Nagasawa's double thiourea C_2 symmetric catalyst **79**.

Since their development, chiral guanidine catalysts have been used in numerous interesting enantioselective transformations, including the direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams with alkylidene malonates by Feng and Liu (Scheme 13A).[56] Use of the chiral guanidine catalyst **83** provided the enantioenriched adducts in up to 94% ee which could be recrystallised to enantiopurity. The authors showcased the transformation with a selection of electron-rich and electron-poor malonates, varying the β- and alkoxy-substituents, but no attempts were made to vary the nucleophile. Liu and Feng also reported another chiral guanidine catalysed enantioselective transformation in 2013, this time with C_2-symmetric catalyst **87** – a catalyst scaffold they first developed in 2010 for the enantioselective inverse-electron-

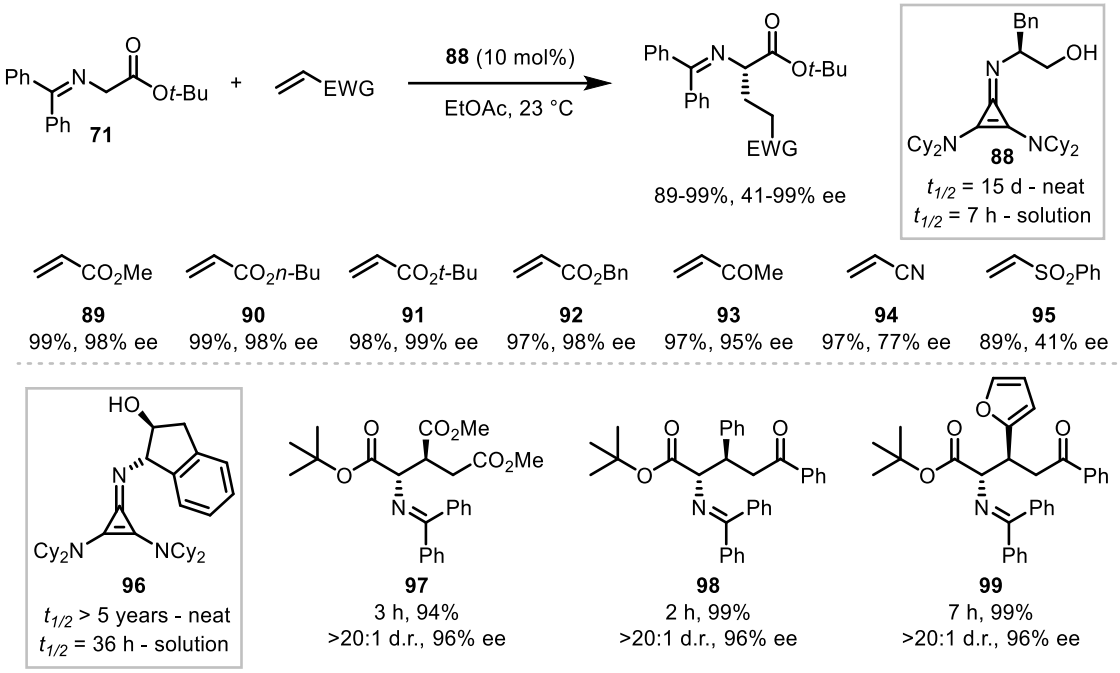
demand hetero-Diels-Alder reaction of chalcones with azlactones (Scheme 13B).[57] Using catalyst **87** as its $HBAr^{F}_{4}$ salt, racemic oxaziridines (**84**) were kinetically resolved by reaction with azlactones (**85**) providing both the enantioenriched oxaziridines (***en*-84**) in up to 99% ee as well as enantioenriched oxazolin-4-ones (**86**).[58] The chiral oxaziridines were then used to derivatise other organic molecules including styrene and an indole. Liu and Feng's reaction is a rare example of triple diastereoselection.[59,60] The reaction involves three chiral components: the racemic oxaziridine, racemic azlactone and the chiral catalyst. All three can exert some control over stereochemical events as the reaction proceeds towards the generation of a single new stereocentre in the product. In the reaction the azlactone is epimerised and reacts preferentially with one enantiomer of the racemic oxaziridine. The reaction's diastereomeric outcome was shown to be independent of the stereochemical configuration of the azlactone (as it is readily epimerised); however, if the enantiomer of the oxaziridine that was mismatched with the catalyst was used, the product's yield (36%) and d.r. (67:33) was significantly reduced while the enantiomeric excess remained high. The importance of the catalyst's H-bond interactions were also demonstrated. Without mono-protonation of the catalyst, racemic product was obtained whereas protonation of both basic moieties resulted in no reaction occurring. Mono-protonation however resulted in highly enantioenriched products leading the authors to speculate a bifunctional species as the active catalyst, where the free-guanidine would activate the azlactone and the guanidinium would preferentially recognise and activate one of the enantiomers of the oxaziridine.



Scheme 13: A) Michael reaction of α,β-unsaturated γ-butyrolactams with alkylidene malonates by Feng and Liu using catalyst **83**; B) Feng and Liu's kinetic resolution of oxaziridines using C_2-symmetric guanidine catalyst **87**.

While guanidines have seen extensive use as superbase catalysts, other basic functionalities such as cyclopropenimines are also highly important. Cyclopropenimines (pK_{BH+} = 26.9) far exceed the basicity of guanidines and are of comparable basicity to P_1 phosphazenes (pK_{BH+} = 27.0) (Figure 2). Attracted by the high basicity of these small, compact molecules, Lambert *et al.* developed a suitable H-bond donor / cyclopropenium scaffold to craft the first chiral cyclopropenimine catalyst (**88**) (Scheme 14).[47] This highly-reactive species was shown to be a useful catalyst in both Michael reactions of glycine imines and Mannich reactions of the same species; catalyst loadings could be as low as 1.0 mol%. Unfortunately, early iterations of the catalyst were found to decompose with a half-life ($t_{1/2}$) of 15 days at room temperature and eight months upon cold storage. Their half-life in solution was just seven hours (Scheme 14). Improvements were made (**96**), with half-lives extended to greater than five years at room temperature and 36 hours in solution, while catalytic activity was retained in the Michael additions of glycine imine **71** to provide Michael adducts **97** to **99** (Scheme 14).[61] Further work by the group led to

the development of higher order cyclopropeniminiums with enhanced basicity, though these have not been applied to enantioselective transformations at this point.[62] Jørgensen *et al.* used the chiral cyclopropeniminium catalyst to enable the enantioselective [3+2] cycloaddition of 2-acyl cycloheptatrienes to azomethine ylides, and demonstrated its advantages over cinchona-alkaloid based catalysts.[63]



Scheme 14: A) Chiral cyclopropenium catalysed Michael-addition of glycine-imines to Michael acceptors; B) Improved catalyst design and application to the synthesis of products **97** – **99**.

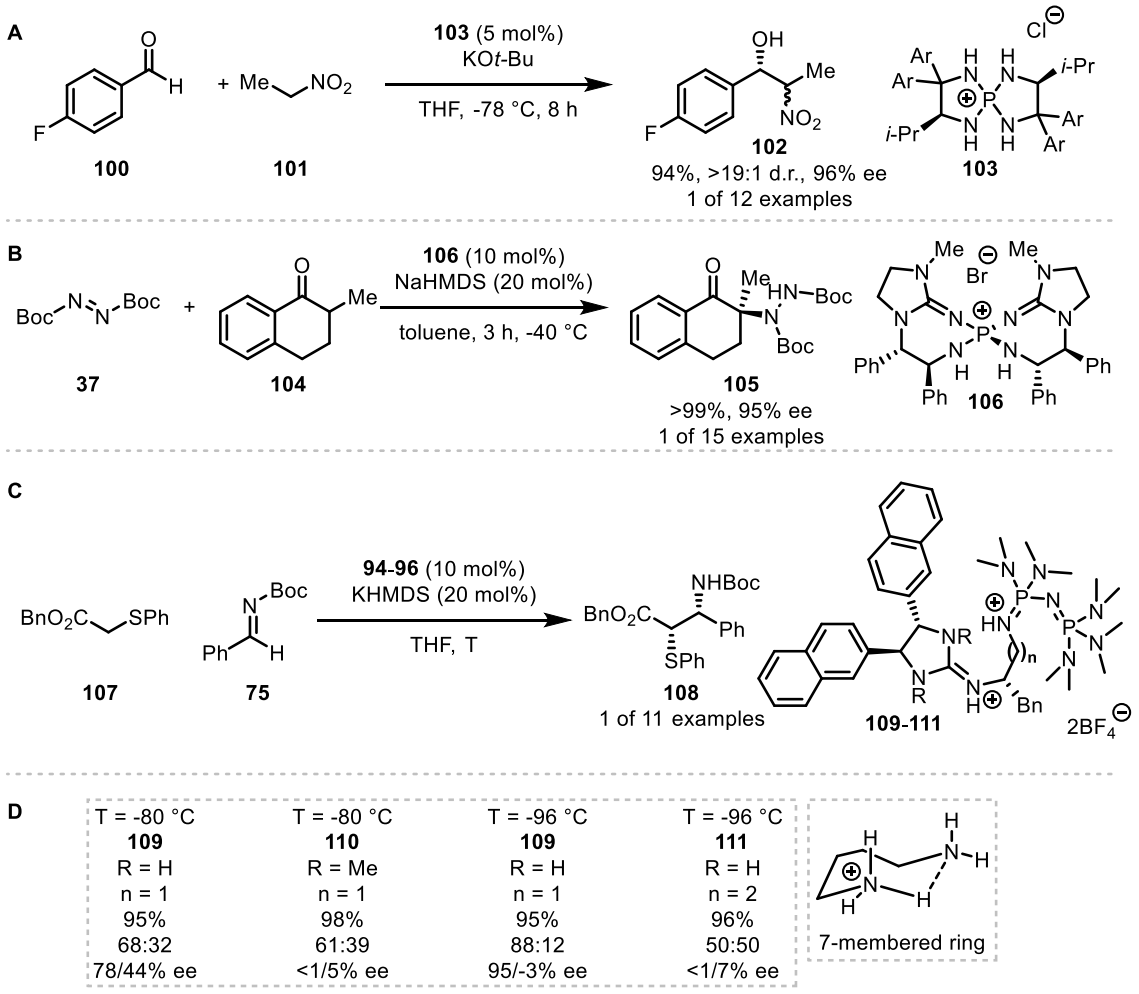
Phosphazenes (**66**), molecules of phosphorus(V) substituted by four nitrogen atoms, were identified in the 1970s and expanded upon into the 80s.[64] Each of the nitrogen atoms can be replaced by an additional phosphazene to give molecules with the highest known non-ionic basicity (pK_{BH+} values can exceed 40).[65] The number of phosphorus atoms present in the base determines the phosphazene order and phosphazenes up to P_7 are known.[66] The high basicity of these structures make them attractive candidates as catalysts for the reactions of high pK_a pro-nucleophiles. Chiral versions of phosphazenes were not reported until 2007 when Ooi *et al.* reported their pioneering cage-like chiral-superbases

(**103**), which are now prominent in enantioselective organocatalysis.[67] Their use in an enantioselective Henry-reaction was described, delivering the desired products (**102**) in consistently high enantioselectivities of up to 99% ee and with excellent diastereomeric ratios (Scheme 15A). Since their conception, the spiro-superbase catalysts have been applied to many asymmetric transformations, including the Payne-type oxidation of *N*-tosyl imines and a selection of Michael additions, as well as a highly enantioselective aldol-reaction with high pK_a ketonic substrates.[68–71]

Terada and Takeda have extended the scope of chiral phosphazene superbase scaffolds by integrating electron rich guanidines into the spirocyclic core of the phosphazene base (**106**) (Scheme 15B) to produce the most basic chiral superbase catalysts known. The high pK_a target 2-methyltetralone (**104**) was deemed too challenging for Ooi's original chiral-phosphazene catalysts, whose attempt at amination of the α-position with **103** resulted in only 18% yield and 57% ee. Terada's guanidine / phosphazene chiral-superbase (**106**), however, elevated the reactivity and selectivity to 99% yield and 98% ee, and the reaction was amenable to a range of substrates.[72,73]

The guanidine-phosphazine combination was modified further by the Terada group, who during 2020 disclosed a new P_2-phosphazene / guanidine superbasic scaffold (**109**).[74] They reasoned that by connecting the two functionalities with a chiral linker, deprotonation of the pro-nucleophile would result in the formation of a rigid 7-membered ring through hydrogen-bond donor / acceptor interactions, creating a tight chiral environment (Scheme 15C). The chiral pocket, combined with the exceedingly high pK_{BH+} of the P_2-phosphazene, enabled the direct Mannich-type reaction of α-phenylthioacetates (**107**), which are exceptionally high pK_a substrates (pK_a of α-

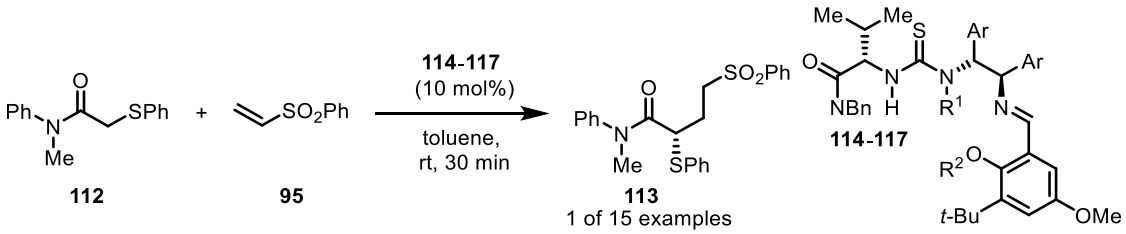
phenylthioacetate = 21.4 in DMSO). The reaction proceeded with excellent yields and levels of enantioselectivity (up to 95% ee), however diastereoselectivity was moderate across a range of substrates. To demonstrate the importance of the 7-membered ring, various catalysts were synthesised with and without the H-bond donor interaction proving that smaller rings and those with no interaction performed with significantly reduced stereoselectivity (Scheme 15C).



Scheme 15: A) Enantioselective Henry-reaction with phosphazene catalyst **103** by Ooi *et al.*; B) Terada and Takeda's azidation of 2-methyltetralone (**104**) using catalyst **106**; C) Mannich-type reaction of α-phenylthioacetates using catalyst **109** by Terada *et al.*; D) Variation of **109**'s ring size and hydrogen bond donors and the effect on reactivity.

Another recent contribution to the field by Terada in 2020 showcased the use of derivatives of Jacobsen's Schiff base catalyst (**114**-**117**) in conjunction with NaO*t*-Bu

(Scheme 16).[75] The enantioselective Michael addition of poorly-acidic α-thioacetamides (**112**) to vinyl sulfones (**95**) was investigated and, following optimisation, the reaction could achieve enantioselectivities of up to 98% ee with consistently high yields. The importance of the three H-bond donor units was also investigated through methylation of the individual sites which confirmed the importance of the phenolic proton in the C–C bond forming reaction (Scheme 16).



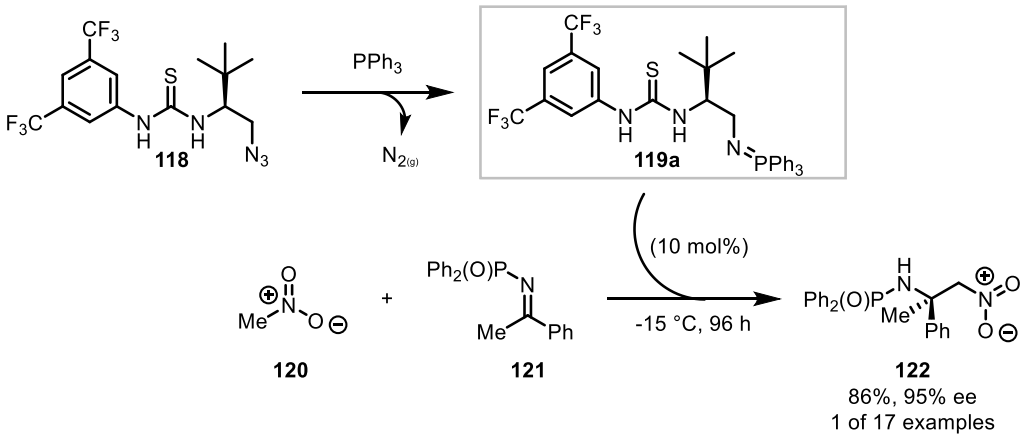
NaO*t*-Bu (20 mol%)	NaO*t*-Bu (20 mol%)	NaO*t*-Bu (20 mol%)	NaO*t*-Bu (10 mol%)
114	**115**	**116**	**117**
R^1 = H	R^1 = Me	R^1 = Me	R^1 = H
R^2 = H	R^2 = H	R^2 = H	R^2 = Me
Ar = 1-nap	Ar = Ph	Ar = 1-nap	Ar = Ph
98%, 95% ee	99%, 80% ee	92%, 96% ee	99%, <1% ee

Scheme 16: Terada's enantioselective Michael addition of α-thioacetamides to vinyl sulfones.

1.6 The Bifunctional Iminophosphorane (BIMP)

Inspired by the success of chiral phosphazene superbases, Dixon *et al.* investigated chiral-superbasic catalysis based on triaryliminophosphorane functionality (**119**).[76] Their aim was to develop a superbasic catalyst, that by late stage introduction of the superbasic element would be straightforward to synthesise, leading to the development of the bifunctional iminophosphorane catalyst (BIMP). This could be achieved via the Staudinger reaction, allowing – in most cases – the superbasic iminophosphorane to be formed '*in situ*' over 24 h (Scheme 17). '*In situ*' synthesis would also prevent decomposition of the potentially sensitive iminophosphorane and allow the catalyst's basic character to be tuned to suit individual reactions. Not only did the BIMP catalyst

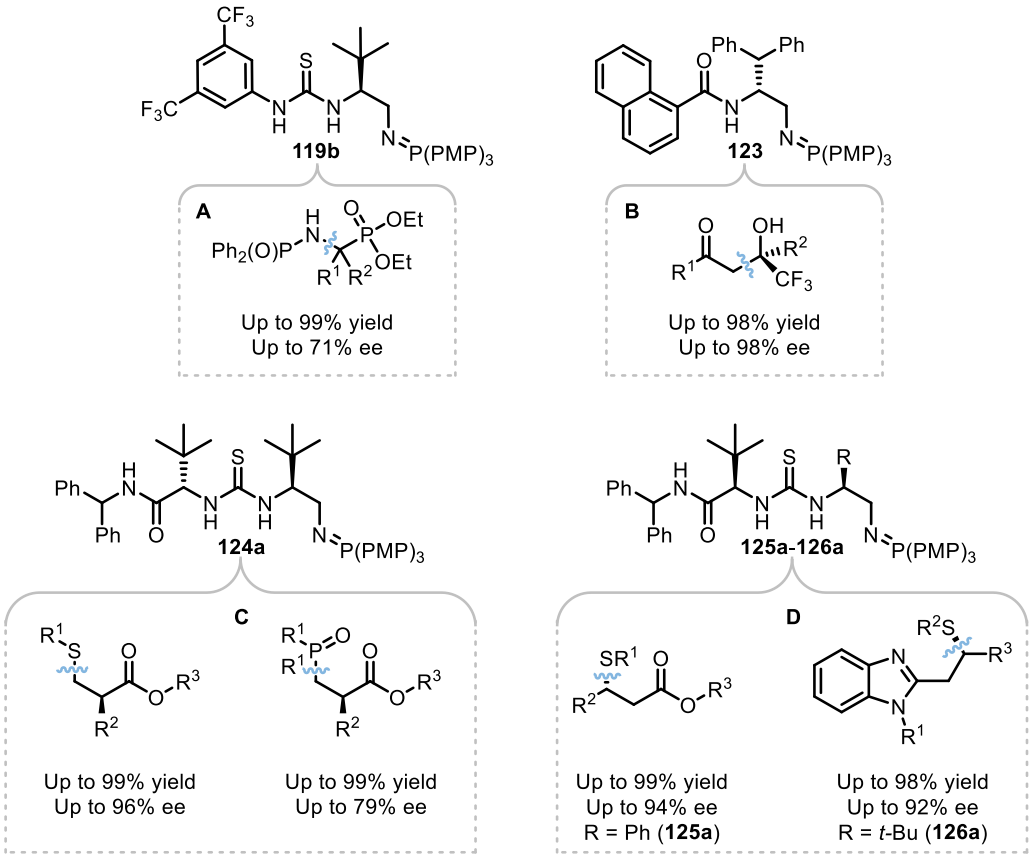
offer enhanced and tunable basicity, straightforward synthesis from amino acids permitted the introduction of a hydrogen bond donor unit, which could be tuned by the addition of different isocyanates or isothiocyanates. Following the development of the BIMP catalyst, studies were undertaken to investigate the iminophosphorane's pK_{BH+} with respect to other superbasic moieties. Investigations found that P(PMP)$_3$ derived iminophosphoranes (**63**) are of comparable basicity to that of DBU (**62**) (pK_{BH+} = 24.34 in MeCN) with a basicity of approximately 25.0 pK_{BH+} units as determined by NMR – significantly higher than tertiary amine bases such as triethylamine (pK_{BH+} = 18.82 in MeCN), though lower than P$_1$-phosphazenes (**66**) (Figure 2).[77] The tunable basic properties of the iminophosphorane were also investigated; a PPh$_3$-derived iminophosphorane (**60**) was found to be far less basic, exhibiting a pK_{BH+} of 22.7 and thereby demonstrating the effect of the electron-donating *para*-methoxy groups in enhancing basicity.[78]



Scheme 17: BIMP-catalysed nitro-Mannich reaction to ketimines by Dixon *et al*.[77]

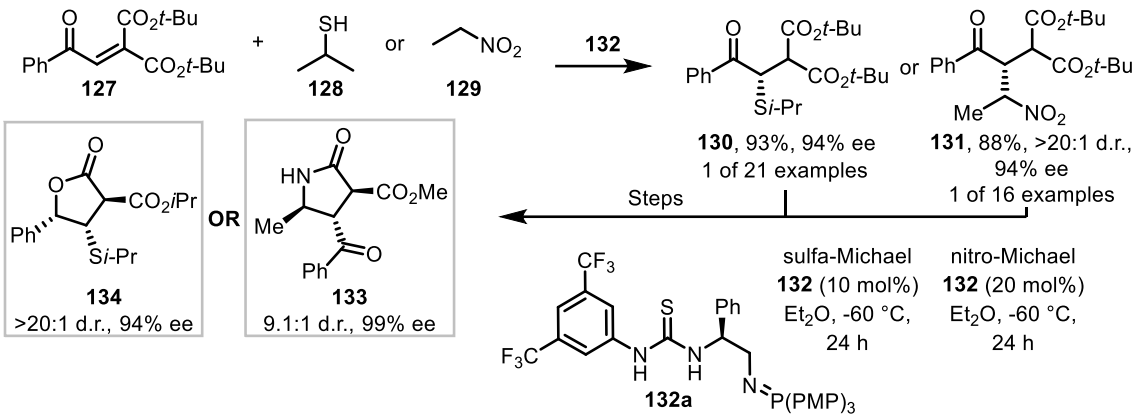
Since the BIMP catalyst's creation in 2013 it has been deployed in many enantioselective transformations and various catalyst scaffolds have been developed. The preliminary report disclosed a highly enantioselective method to accomplish the nitro-Mannich reaction of ketimines, showcasing the superbasic catalyst's ability to activate high pK_a

nucleophiles as well as poorly-reactive electrophiles, while achieving enantioselectivities of up to 95% ee (Scheme 17).[77] The 1st generation catalysts have been found to be useful in enantioselective phospha-Mannich reactions and most recently in an aldol reaction (Scheme 18A and B).[79,80] Following the development of 1st generation catalysts, the BIMP was evolved into a novel scaffold by introducing a 2nd stereocentre (**124a**-**126a**) (Scheme 18C and D).[81] The 2nd generation catalysts offered diastereomeric tunability and were found to catalyse the asymmetric addition of thiols to low electrophilicity Michael acceptors such as acrylates, crotonates and benzimidazoles (Scheme 18C and D).[81–83] Additions to acrylates not only provided the Michael-adducts in excellent yields and enantioselectivity, but also demonstrated the use of the catalyst for asymmetric protonation.[84,85] The Dixon group has also achieved the enantioselective Michael addition of phosphine oxides to acrylates, though reactivity and selectivity were highly substrate dependent (Scheme 18C).[86]



Scheme 18: Enantioselective BIMP-catalysed transformations.

The use of BIMP catalysts has become increasingly widespread over the last decade. Recently, Johnson *et al.* reported that the BIMPs (**132a**) would catalyse the sulfa-Michael addition to enone diesters in a highly enantioselective transformation (up to 97% ee) (Scheme 19).[87] The adducts could be lactonised over two steps to provide substituted lactones (**134**) with excellent levels of diastereo- and enantioselectivity. The chiral catalysts were also found to catalyse the enantioselective addition of nitroalkanes to the same Michael acceptors, which could later be cyclised to create enantioenriched substituted lactams (**133**) (Scheme 19).[88] Previous work in the group also demonstrated the catalyst's failure to carry out the intramolecular Michael-addition of dithianes to cyclohexadienes.[89] Though few iminophosphoranes were trialled, the authors suggested that the BIMP's basicity was too low to carry out the transformation efficiently.

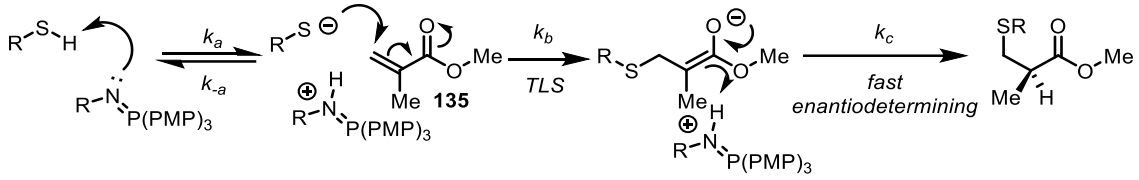


Scheme 19: Sulfa- and nitro-Michael additions to enone diesters followed by lactonisation and lactamisation by Johnson *et al*.[87,88]

1.7 BIMP catalysis and enantioselective protonations

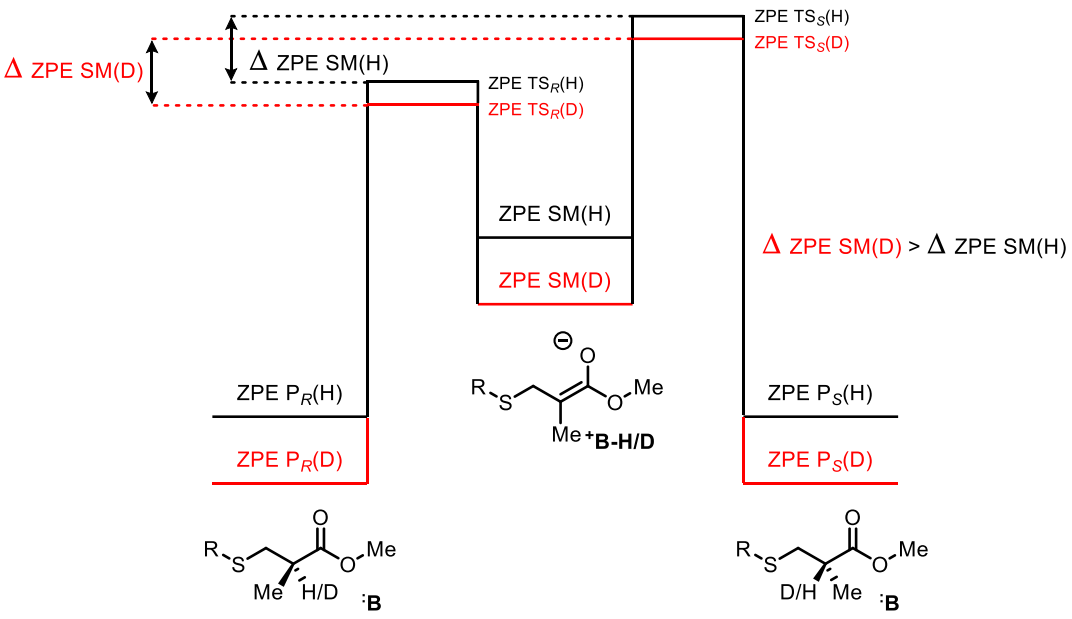
Of the currently investigated BIMP-catalysed enantioselective transformations, two examples achieve enantioselectivity via an asymmetric protonation step following a Michael addition. Both the sulfa- and phospha-Michael additions to acrylates require protonation of the enolate intermediate formed upon addition to the β-positions, and hence chirality is transferred at the α-position from the catalyst (Scheme 18C).[81,86] During 2013, an unpublished study into the kinetic isotope effect (KIE) was undertaken to investigate the mechanism of the enantioselective sulfa-Michael addition to α-substituted α,β-unsaturated esters (**135**).[90] A deuterated thiol was synthesised by stirring 1-propanethiol in D_2O, and was then subjected to the enantioselective sulfa-Michael addition with 1st generation BIMP catalyst **119b** and the reaction was monitored over time by ^1H NMR analysis. The initial rate of reaction was found to be greater with the deuterated propanethiol than with propanethiol. An explanation for this inverse KIE was offered, wherein it was suggested that the turnover limiting step (TLS) was addition to the Michael acceptor, as opposed to the protonation of the enolate (Scheme 20). The TLS was preceded by a fast and reversible deprotonation of the thiol by the Brønsted basic catalyst in which the deuterium would prefer to be on the highest frequency oscillator

(the strongest bond), hence deprotonation to form an N–D bond would be more favourable than deprotonation to form an N–H bond and so *K* for deuterated thiols would be greater than that for unlabelled thiols.



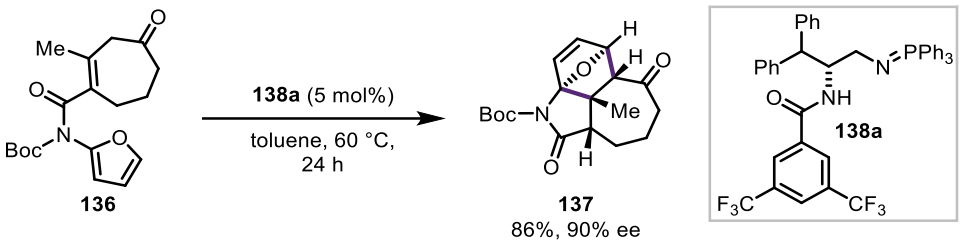
Scheme 20: Postulated mechanism for the BIMP-catalysed enantioselective sulfa-Michael addition to methyl methacrylate (**135**).

Another interesting phenomenon was that an increase in selectivity from 72% ee to 81% ee was observed with the deuterated thiol. This was explained by assuming that the enantiodetermining step was rapid and irreversible protonation of the enolate with selectivity originating from the barriers to each enantiomer in which formation of the *R*-isomer dominates due to its lower energy transition state. Hence, with a deuterium-labelled substrate there is a greater energy barrier to form the *S*-isomer as a consequence of the deuterium-labelled substrate's reduced zero-point energy (ZPE) (Scheme 21). Alternatively, it has been argued that the shorter N–D bond length compared to the N–H bond length of the iminophosphorane amplifies the repulsive and attractive interactions between the catalyst and the substrates.[78] The shorter N−D bond creates a tighter transition structure favouring protonation of the *si* face to give the (*R*)-enantiomer while the decreased bond length exaggerates any unfavourable steric interactions making protonation of the *re* face increasingly unfavourable leading to an increase in energetic discrimination between the two diastereomeric transition states. This results in a higher enantioselectivity. Similarly exchange of the thiourea protons is likely to occur improving the hydrogen bond ability of the catalyst and improving the reaction outcome.



Scheme 21: Energy level diagram for the enantioselective sulfa-Michael addition with protonated and deuterated thiol.

The BIMP has also been revealed to be an excellent catalyst for intramolecular proton shifts, which are another mode of asymmetric protonation. During 2017 the total synthesis of (−)-himalensine A was completed in the Dixon group.[91] Key to the construction of the tricyclic core (**137**) was a BIMP-catalysed [1,3]-prototropic shift followed by an intramolecular Diels-Alder furan reaction (Scheme 22). The reaction proceeded well with the desired complex scaffold (**137**) being obtained in 90% ee using a triphenyl phosphine derived iminophosphorane (**138a**).



Scheme 22: BIMP-catalysed enantioselective 1,3-prototropic shift and intramolecular furan Diels-Alder reaction to furnish the tricyclic core of (−)-himalensine A by Dixon *et al.*

1.8 DPhil aims and objectives

The one-off example of a BIMP catalysed enantioselective prototropic shift used in the synthesis of (−)-himalensine A required a very specific, activated substrate with little scope for further substrate examples. As of yet, the asymmetric intramolecular reprotonation has not been applied to the synthesis of other, more synthetically useful substrates with the BIMP-catalyst. These initial studies into BIMP-catalysed asymmetric protonation provide the foundations for further investigations into this transformation and throughout this DPhil, we aimed to carry out detailed investigations into asymmetric prototropic shifts. In doing so a new method to create complex, chiral molecular scaffolds from simple building blocks would be developed.

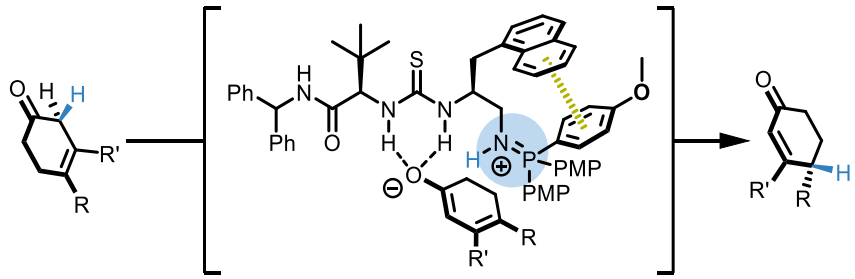
The aim of the first project (Chapter **2.**) was to develop an enantioselective prototropic shift of β,γ-unsaturated cyclohexenones into their common, conjugated, counterparts and, if feasible, combine the prototropic shift with an intramolecular Michael addition reaction. Conjugation with the ketone would provide the driving force for the reaction to occur and reprotonation would set a stereogenic centre at the γ-position. The tethered nucleophile would then be poised to attack the newly formed enone to form a fused ring system. If successful, the mechanistic pathway of the reaction would be investigated using a series of deuterium labelling studies and the enantioenriched products would be further derivatised.

The second project (Chapter **3.**) aimed to build upon the key concepts of the enantioselective prototropic shift of β,γ-unsaturated cyclohexenones developed in chapter **2.** and apply them to the synthesis of small rings, specifically, cyclopropanes. Rather than use conjugation as a driving force we aimed to develop a novel

deconjugative, enantioselective transformation that relied on the release of the ring strain present in small carbocycles. To achieve this, appropriate substrates needed to be synthesised and a catalyst capable of highly enantioselective α-protonation would need to be discovered.

2. Investigations Into the BIMP-catalysed Enantioselective Prototropic Shift of β,γ-Unsaturated Cyclohexenones

2.1 Chapter overview



Scheme 23: A BIMP-catalysed enantioselective prototropic shift of β,γ-unsataurated cyclohexenones.

This chapter describes the development of the BIMP-catalysed prototropic shift of β,γ-unsaturated cyclohexenones to provide their enantioenriched conjugated counterparts. α,β-Unsaturated cyclohexenones are synthetically relevant, finding use in a variety of total syntheses and have often been created through transformations such as Robinson annulations or the desymmetrisation of cyclohexadienones.[92] The method discussed in this chapter offers a simplistic approach to their synthesis through the use of a superbasic BIMP catalyst providing the enones in yields of up to 99% and enantiomeric excess of up to 99% ee. To overcome challenging reactivity, the modularity and tuneability of the

BIMP catalyst was investigated and used to broaden the reaction scope. Importantly, the substrates could be synthesised with ease through two separate methods. Additionally, detailed computational studies were carried out by Prof. Robert Paton and Dr. Luis Simón which were complemented by deuterium labelling studies to investigate the mechanistic aspects of the transformation as well as the origin of enantioselectivity. Previously disclosed methods for this reaction were limited by substrate scope, reaction times and the requirement for additives and low temperatures.[93] We aimed to overcome these problems and our efforts and achievements are detailed in the following chapter.

2.2 Introduction

2.2.1 α,β-Unsaturated cyclohexenones and organocatalytic asymmetric approaches to their construction

The cyclohexenone structure is contained within many important, naturally occurring and bioactive molecules, and can be exploited in pathways towards their synthesis.[94–99] α,β-Unsaturated cyclohexenones have multiple reactive sites making them particularly useful in organic synthesis. Their ability to undergo Michael additions, [2+2] cycloadditions and Diels-Alder reactions,[100] as well as their potential for functionalisation at both the carbonyl carbon and the enolisable α-atom makes them ideal intermediates in the creation of complex molecular skeletons, such as those found in natural products.[101,102] The crocusatin (**139**) and kanshone families (**140**) provide examples of natural products comprising the α,β-unsaturated cyclohexenone system (Figure 3).[95,96] Examples where these multifunctional 6-membered carbocycles act as intermediates in the synthesis of complex natural products include the syntheses of (−)-reserpine (**142**) by Stork *et al.* and (−)-penitrem D (**143**) by Smith *et al.* (Figure 3).[98,99] In both syntheses, a small, chiral

cyclohexenone is used as an important, early-stage building block to control the stereochemical outcome of the proceeding reactions (see section **2.9.2**). Use of this strategy led to the completion of impressive total syntheses of the two complex natural products.

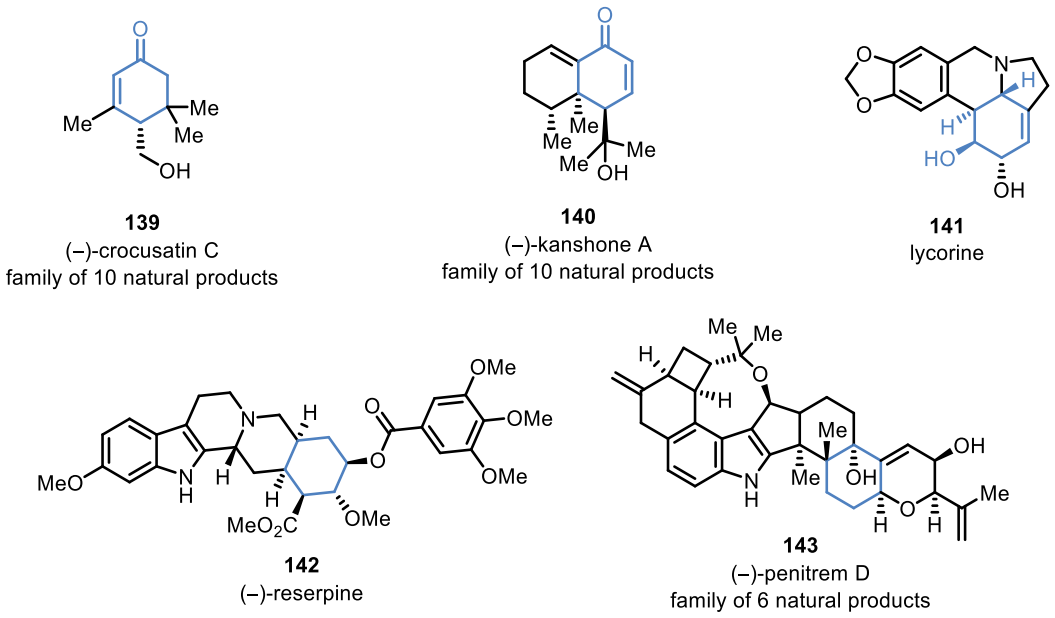
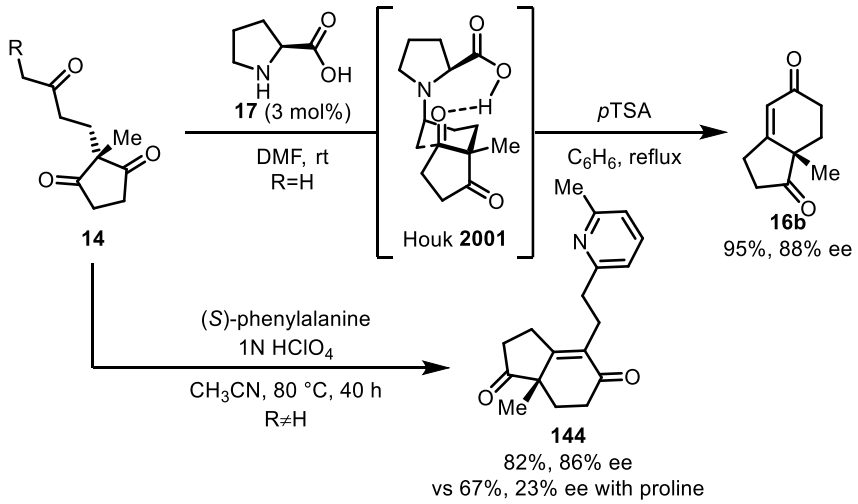


Figure 3: Natural products incorporating or synthesised from α,β-unsaturated cyclohexenones

The cyclohexenone ring contains three sp^3 hybridised carbon atoms each of which may be stereogenic and each one requiring different chemistry for its derivatisation. Numerous organocatalytic methods have been developed to construct chiral derivatives in an enantioselective fashion; hence, with many different organocatalysts to choose from including proline catalysts, chiral Brønsted bases, chiral phosphoric acids and primary amines, a broad range of structurally diverse carbocycles can be obtained.[92] This section provides a brief overview of some of the many ways chiral cyclohexenones may be constructed using enantioselective organocatalysis.

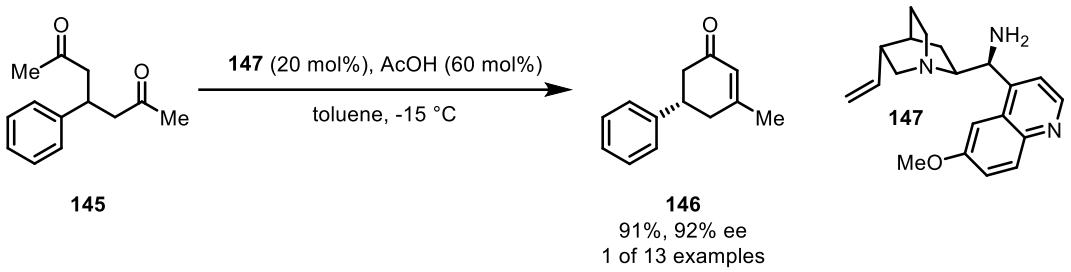
As early as the 1970s, enamine catalysis has played a major role in the synthesis of chiral cyclohexenones and, in particular, fused bicyclic variants. The first example of this was

the Hajos–Parrish–Eder–Sauer–Wiechert reaction in which (S)-proline (**17**) mediates enamine formation and a consequential intramolecular aldol reaction of a tri-ketone (**14**) to produce the desired bicycle (**16b**) following treatment with *p*TSA (Scheme 24).[19] The mechanism was confirmed by List *et al.* through oxygen labelling experiments and Houk proposed a model for the transformation in 2001, in which the intramolecular reaction proceeds via a chair transition state stabilised by H-bond interactions between the carboxylic acid and ketone (Scheme 24).[103–105] Further work in the field identified (S)-phenylalanine as a superior catalyst in reactions involving non-methyl ketones and similar reports have surfaced including the use of β-amino acids as chiral primary amine catalysts (Scheme 24).[106,107] In 2000, Akiyama *et al.* established a new method of triketone desymmetrisation using a chiral phosphoric acid catalyst. Activation of the ketone by H-bond donation from the chiral catalyst resulted in tautomerisation to the enol, which could carry out the desired intramolecular annulation enantioselectively to desymmetrise the *meso*-1,3-dicarbonyl.[108]



Scheme 24: The Hajos–Parrish–Eder–Sauer–Wiechert reaction and model provided by Houk to provide **16b**. Further investigations demonstrated the use of (S)-phenylalanine to provide enantioenriched α-substituted enones (**140**).

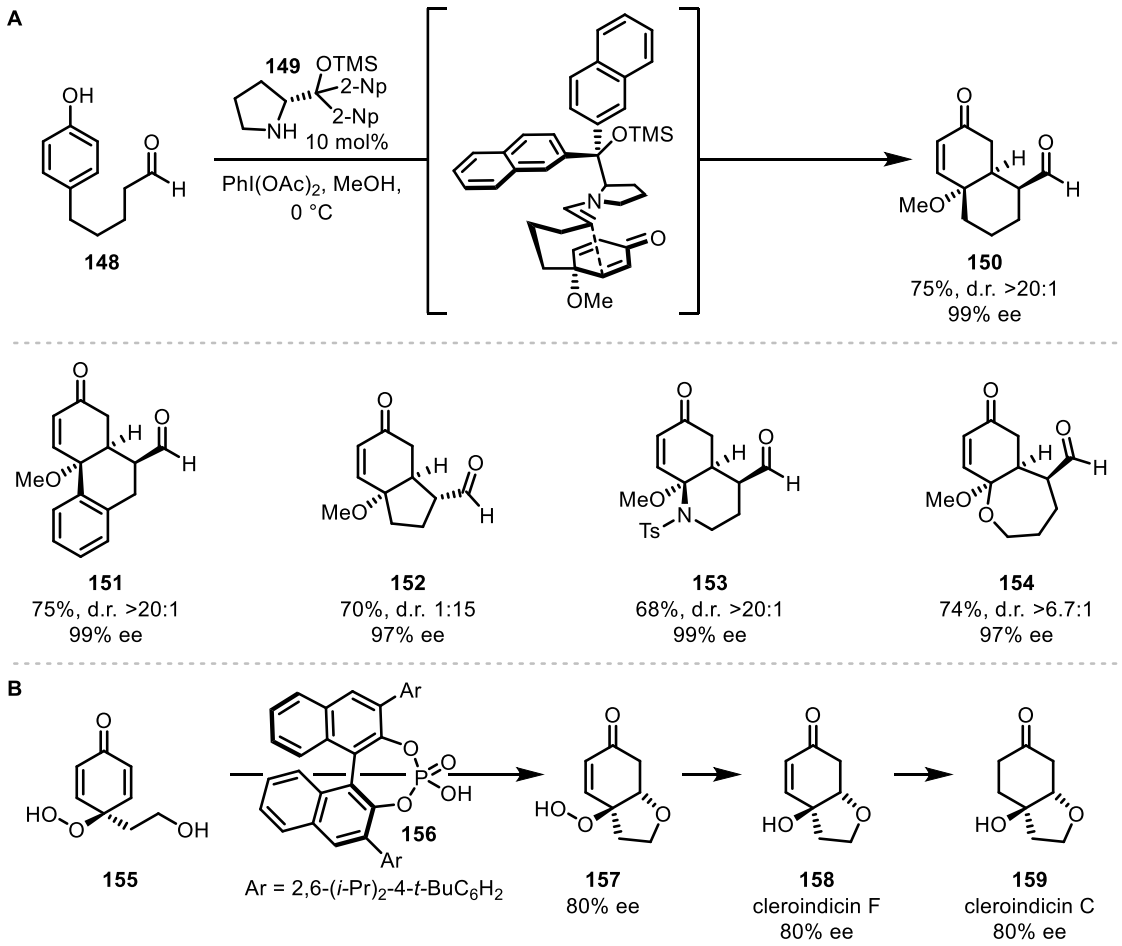
In 2008, List *et al.* demonstrated the use of cinchona derived primary amine catalysts such as **147** to carry out an enantioselective desymmetrising annulation of diones (**145**).[109] The reaction proceeded with enantioselectivities of up to 94%, a marked improvement on previous literature reports where proline was only able to provide moderate levels of enantiocontrol.[110] The authors proposed a model in which the imine is deprotonated by the basic quinuclidine moiety which in turn acts as a hydrogen bond donor group guiding the aldol reaction to provide the observed enantiocontrol.



Scheme 25: Enantioselective desymmetrising annulation of diones using primary amine catalyst **143** by List *et al.*

Intramolecular Michael additions provide another noteworthy method for the enantioselective construction of cyclohexenones. This approach frequently involves the desymmetrisation of 4-substituted cyclohexadienones. Many catalytic methods have been applied to this reaction, allowing a range of enantioenriched cyclohexenone derivatives to be constructed. A particularly interesting example of this desymmetrisation was carried out by Gaunt *et al*. The authors utilised a secondary amine catalyst (**149**) to carry out a 'one-pot' dearomatisation of substituted phenols (**148**). The ensuing desymmetrisation of the resulting dienone provided the desired bicycles in yields of up to 84% and enantioselectivities of up to 99% ee (Scheme 26A).[111] Other methods have involved the use of both chiral Brønsted bases and acids. You *et al.* showed that the chiral phosphoric acid **156** catalysed the oxy-Michael addition of ethylene glycol derived cyclohexadieneones (**155**) in an enantioselective fashion. The utility of this reaction was

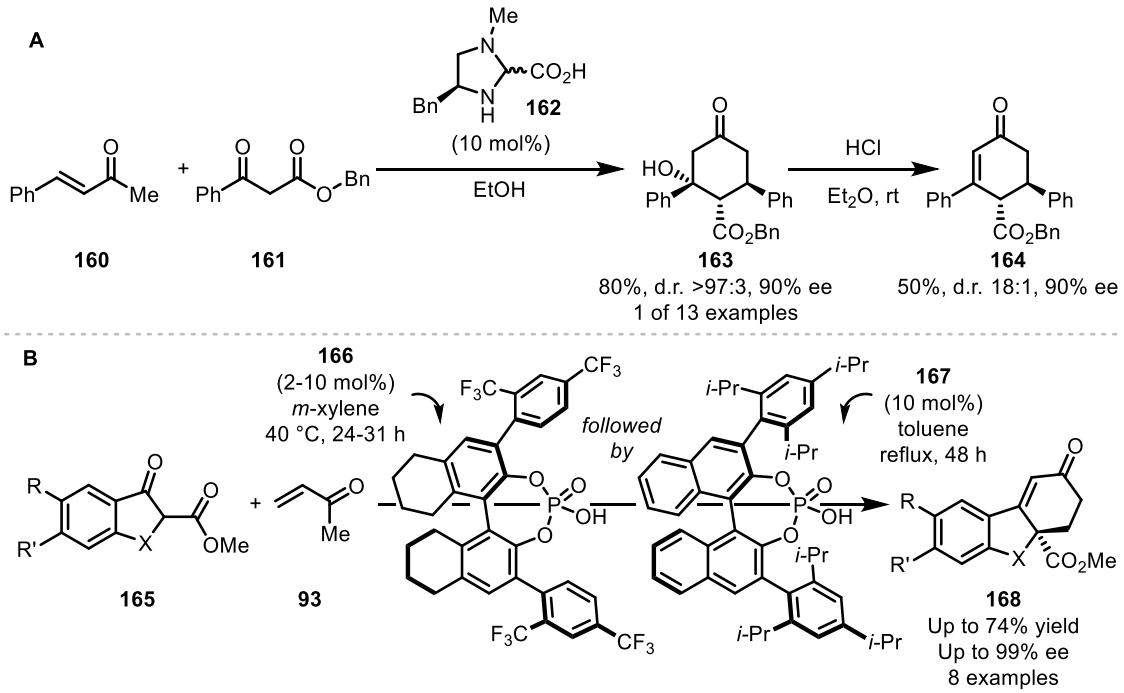
demonstrated in the synthesis of members of the cleroindicin family of natural products, C (**159**) and F (**158**) (Scheme 26B).[112] The cleroindicin family of natural products derive from the *Clerodendrum* genus of plants located in tropical locations about Asia and Africa and have been found to have medically relevant properties.[113] In 2009 Pettus *et al.* synthesised all the known chiral members of the family from 2,4-dihydroxybenzaldehyde.[114]



Scheme 26: A) Gaunt's dearomatisation, desymmetrisation strategy towards the enantioselective synthesis of cyclohexenones; B) You's use of chiral phosphoric acids to catalyse the enantioselective desymmetrisation of cyclohexadienones and its application to the total synthesis of members of the cleroindicin family of natural products.

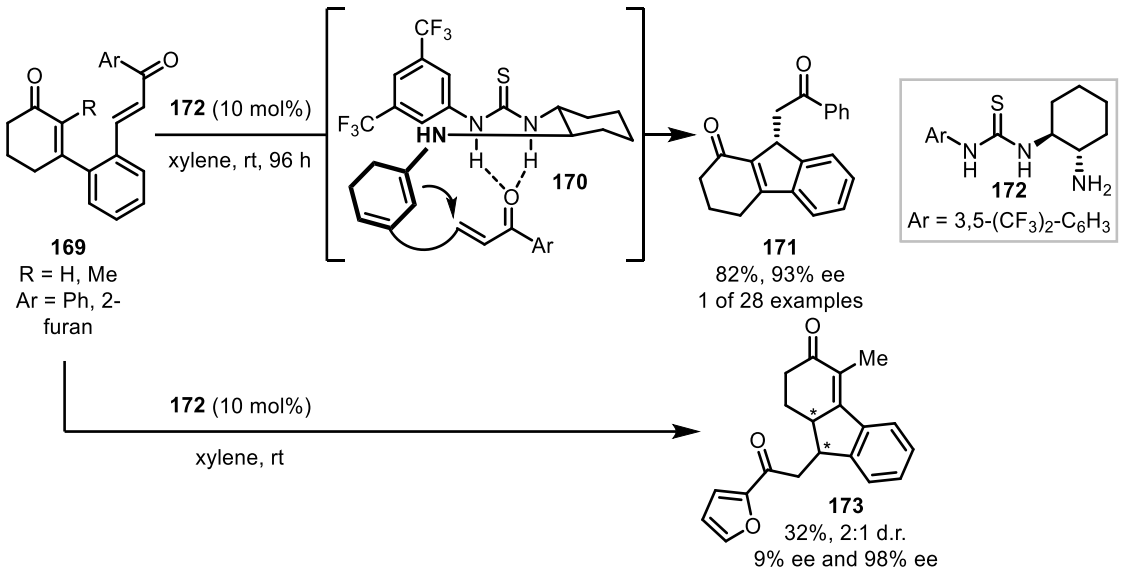
The organocatalytic methods described so far have all involved the use of tethered nucleophiles, most likely facilitating enantiocontrol and reducing side reactions through the rapidity of the intramolecular addition. However, it has been thoroughly demonstrated

that with the appropriate catalytic system, intermolecular reactions can give high levels of both chemo- and enantioselectivity in the synthesis of chiral cyclohexenones. In 2004, Jørgensen *et al.* described the use of an imidazoline catalyst (**162**) to drive the domino aldol-Michael reaction of a β-keto ester (**161**) and α,β-unsaturated ketone (**160**) towards a highly substituted cyclohexanone product (**163**) (Scheme 27A).[115] The cyclohexanone product was dehydrated by the addition of HCl to provide an enantioenriched cyclohexenone (**164**) in high enantiomeric excess and good yield. In a similar manner, Akiyama *et al.* used chiral phosphoric acids (**166** and **167**) to concomitantly activate α,β-unsaturated ketones (**93**) and indanones (**165**) whilst bringing them into close proximity and fusing them together to create complex cyclohexenone scaffolds from simple starting materials in excellent yields (up to 74%) and enantioselectivities (up to 99% ee) (Scheme 27B).[116]



Scheme 27: A) Imidazoline catalyst **162** and its use in the domino aldol-Michael reaction of a β-keto esters and α,β-unsaturated ketones to form highly substituted cyclohexanone by Jørgensen *et al.*; B) Chiral phosphoric acid catalysed Michael addition to form cyclohexenones by Akiyama *et al.* X = CH_2 or O.

The examples described above represent a small number of the available methods to create complex cyclohexanone scaffolds via intramolecular reactions. Less commonly, a pre-formed cyclohexenone scaffold may be derivatised enantioselectively to introduce asymmetric centres. This approach has been employed by Ghorai *et al.* to provide highly enantioenriched Rauhut−Currier adducts (**171**) (Scheme 28).[117] The reaction proceeds via the formation of an extended enamine (**170**) and consequential H-bond directed intramolecular Michael addition to a tethered chalcone at the β-position to furnish the [6-5] fused ring system (Scheme 28). The reaction performed remarkably well on a variety of substrates; however, methylation of the cyclohexenone's sp^2 α-position (R = Me) led to addition at the γ-position of the cyclohexenone (**173**). The product was obtained in low yield however the minor diastereomer had formed in 98% ee.



Scheme 28: Primary amine catalysed route to enantioenriched Rauhut−Currier adducts from cyclohexenones by Ghorai *et al.*

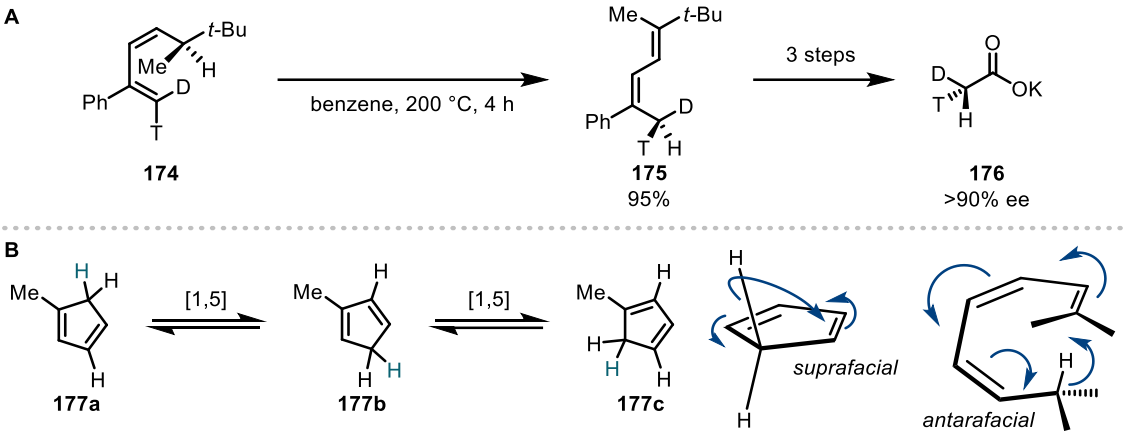
An important yet underdeveloped method for the synthesis of α,β-unsaturated cyclohexenones is the isomerisation of their β,γ-unsaturated counterparts which allows direct modification of the cyclohexenone scaffold. This elegant pathway provides access

to a remote stereocentre in a single step from simple starting materials and the potential for an extremely atom economical transformation. We wished to investigate the potential for a superbase catalysed enantioselective prototropic shift of β,γ-unsaturated cyclohexenones that would be applicable to a broad range of substrates. The following sections provide key background and insights into prototropic shifts and will prove useful in the development of such a transformation.

2.2.2 Prototropy – a brief overview

The migration of a proton from one location on a molecule to a different one on the same molecule is called prototropy. One of the most common examples of this phenomenon is the tautomerisation of carbonyl compounds into their enol form. Here, an α-proton is shifted to the oxygen or *vice versa*. Carbonyl compounds predominantly exist as carbonyls rather than enols. However, structural effects and reaction conditions, for example pH, can influence the equilibrium considerably. Prototropic shifts may occur under thermodynamic conditions; molecules changing to more stable, often increasingly conjugated forms, provide a good example. For instance, in 1999 Mulzer *et al.* demonstrated that upon heating to 200 °C, compound **174** would undergo a thermodynamically favoured [1,5]-prototropic shift (Scheme 29A).[118] They realised that by increasing the steric bulk about the sp^3 carbon at which the shift was occurring, the reaction would proceed in a stereoselective manner to form it's chiral-methyl counterpart **175** in 95% yield. After a further 3 steps, the molecule could be converted to chiral acetic acid (**176**), with H, D and T at the α-position in >90% ee. In a similar manner, methyl cyclopentadiene's (**177**) protons undergo [1,5]-prototropic shifts about their rings even at low temperature; the increase in speed in comparison with the previous example is attributed to the relative proximity of the participating carbons, in contrast to those of **174**

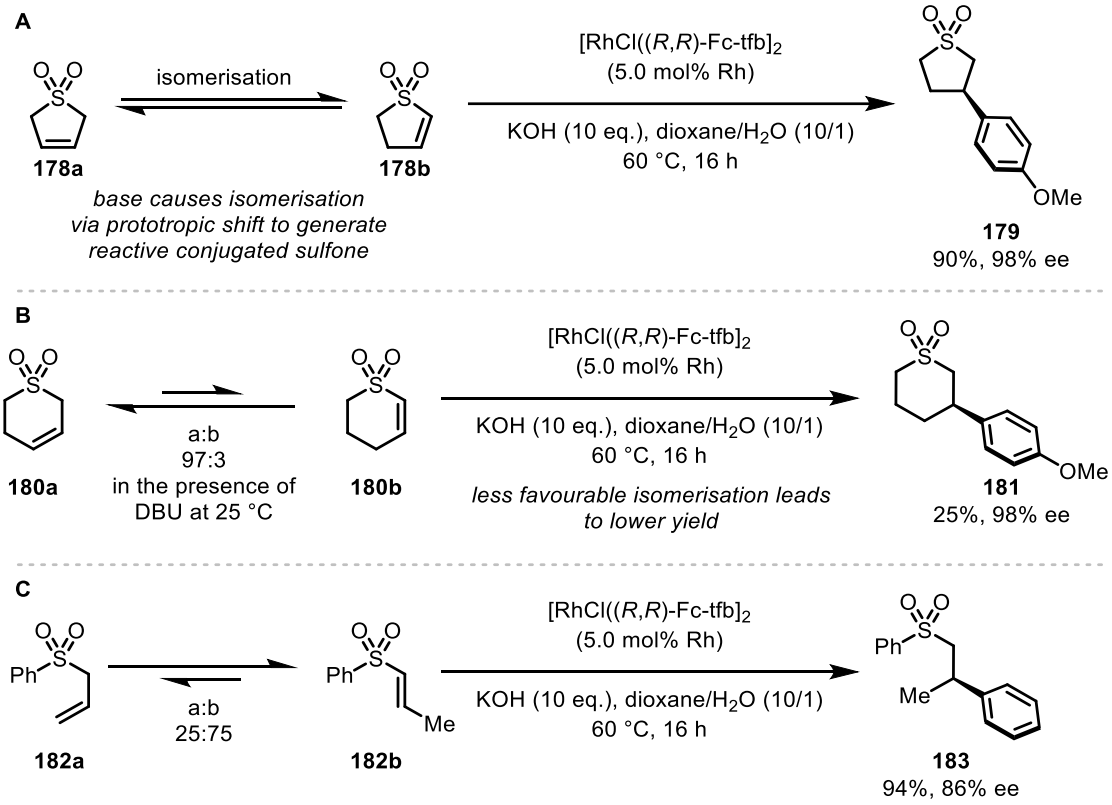
(Scheme 29B). In both cases, the uncatalysed shifts are allowed by the Woodward-Hoffmann rules and must occur in a suprafacial manner. If the π-system was enlarged so that a [1,7]-shift could occur, we would expect the transformation to be antarafacial (Scheme 29B).



Scheme 29: A) Mulzer's synthesis of chiral acetic acid featuring a [1,5]-prototropic shift; B) [1,5]-prototropic shift of cyclopentadiene occurring in a suprafacial manner according to the Woodward-Hoffmann rules and a [1,7]-prototropic shift occurring in an antarafacial manner.

Small basic molecules can be used as shuttles to carry the protons from position to position on a range of "acidic" molecules.[119] In 2015, Hayashi *et al.* investigated rhodium-catalysed asymmetric arylation of cyclic allyl sulfones.[120] These 5-membered cyclic allyl sulfones equilibrate under basic conditions, e.g. in the presence of KOH, to a ratio of 60:40−50:50 (**178a**:**178b**) of their isomeric forms (Scheme 30A). By adding base to the reaction mixture, and assuming that the isomerisation occurs faster than the arylation, the authors believed that the two isomers could be interconverted *in situ* and the more reactive conjugated isomer would react to produce the desired enantioenriched products. This turned out to be the case. The reaction was trialled on both 6-membered rings (**180**) and acyclic substrates (**182**). It performed poorly on 6-membered rings. The authors suggested that this was a consequence of the equilibrium lying too far over towards the deconjugated species. With DBU the observed ratio was 97:3 (**180a:180b**)

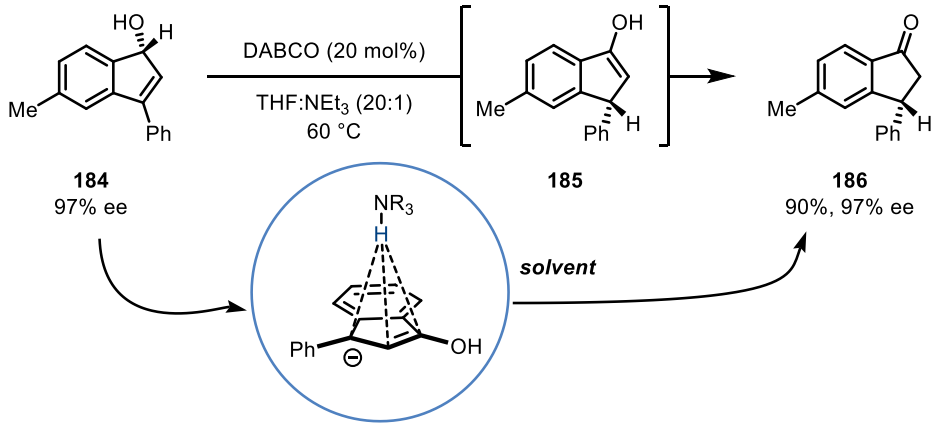
(Scheme 30B) and under the standard reaction conditions the product **181** was only obtained in 25% yield. With acyclic substrates, the equilibrium was far more favourable (25:75 of **182a**:**182b**) and the product (**183**) could be obtained in 94% yield and 86% ee (Scheme 30C).



Scheme 30: Hayashi *et al.* demonstrate the importance of a prototropic shift of β,γ-unsaturated sulfones in an asymmetric rhodium catalysed arylation

More recently, Paton *et al.* carried out computational studies on stereospecific prototropic shifts of indenols (**184**).[121] Earlier computational studies concluded that the isomerisation proceeds through a series of suprafacial [1,5]-prototropic shifts that require exceedingly high activation energy and favour a racemic product. Experimental labelling data, on the other hand, pointed towards an intramolecular stereospecific [1,3]-prototropic shift.[122,123] The researchers proposed as an alternative mechanism a [1,3]-prototropic shift catalysed by DABCO (Scheme 31). Upon deprotonation of the indenol,

a long-lived contact ion pair would be formed between the negatively charged ring and the positively charged conjugate acid of DABCO. The formation of the ion pair would allow chirality transfer from the initial position to the final resting place and its separation would require an unfavourable 10 kcal/mol. The computed energy barrier was found to be 15 kcal/mol lower than that of those involving [1,5]-shifts which would be disruptive to aromaticity of the indenol ring strongly favouring the 'proton-slide' mechanism.

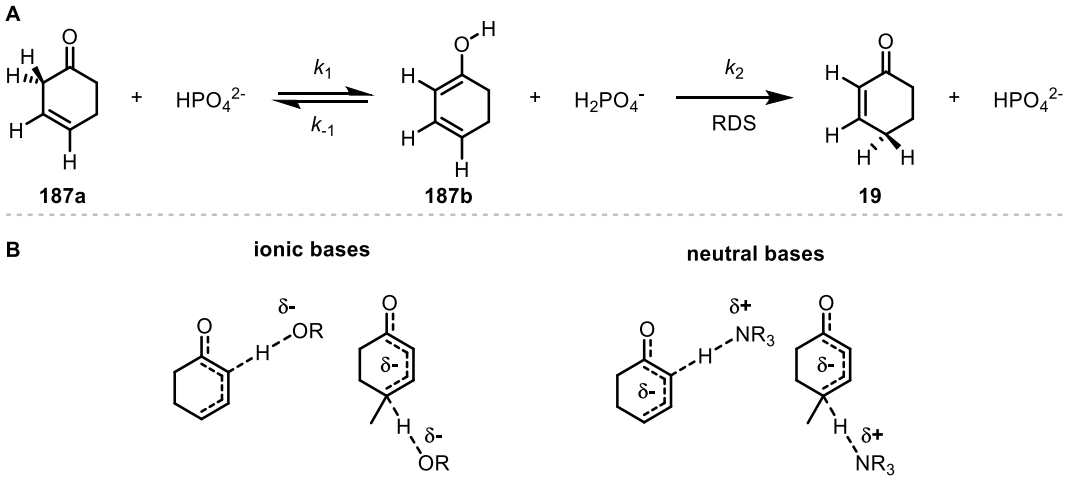


Scheme 31: Computational studies by Paton *et al.* have shown that the stereoretentive base catalysed prototropic shift of indenoles proceeds via a [1,3]-mechanism as a 'proton slide'.

2.2.3 The kinetics of base catalysed 1,3-prototropic shifts of β,γ-unsaturated cyclohexenones

It is generally accepted that the turnover limiting step in the base catalysed isomerisation of β,γ-unsaturated cyclohexenones is protonation at the γ-position of the extended enolate. This was proven by Whalen who investigated the differences between neutral and ionic bases on the rates of base catalysed isomerization. Whalen showed that isomerisation of **187** with $HPO_4^{2-}(H_2O)$ and $DPO_4^{2-}(D_2O)$ resulted in a normal KIE (k_{HPO42-}/ k_{DPO42-}) of 7.7, indicative of a pre-equilibrium followed by turn over limiting γ-protonation (Scheme 32A).[124] The reaction is generally observed to proceed faster with neutral bases (such as 3-quinuclidinol or triethylamine) compared to anionic bases (such

as potassium carbonate or hydroxides) for species of approximately the same pK_{BH+}. Whalen attributed the effect to charge build up in the transition states. In a transition state involving a charged base, such as hydroxide, the α-proton is removed, and negative charge builds up on the substrate (Scheme 32B). This leads to an unfavourable electrostatic interaction between the base and substrate in the transition structure. A similar effect may be postulated for the reprotonation of the γ-position. In contrast, a neutral base, such as triethylamine, develops a positive charge in the transition state while the substrate becomes negatively charged. The electrostatic interactions between the pair are now more favourable including the reprotonation step.



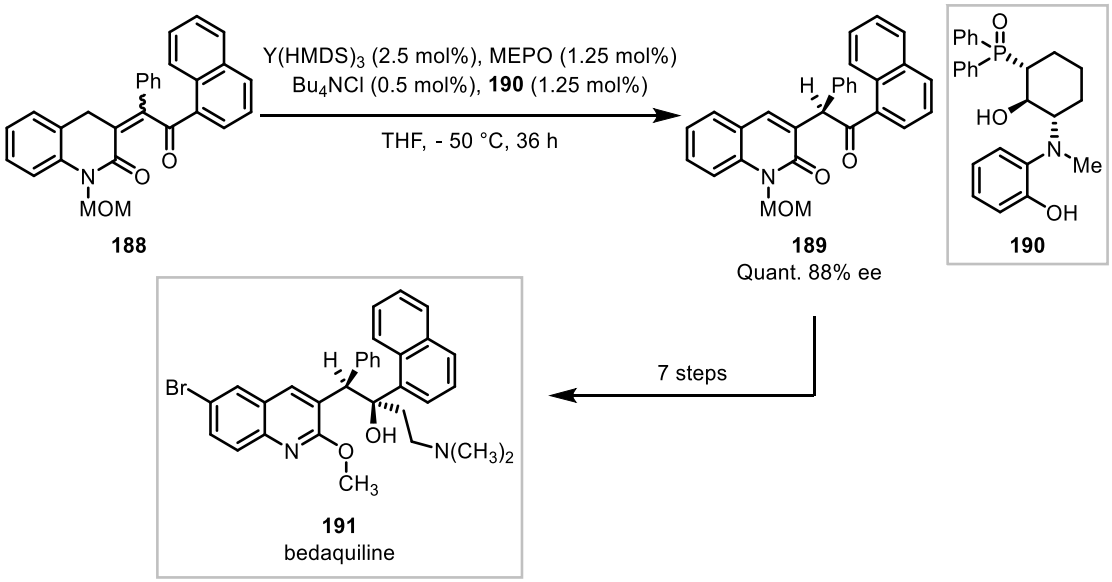
Scheme 32: A) Mechanism for the base catalysed isomerisation of β,γ-unsaturated cyclohexenone **187**; B) Electrostatic considerations for base catalysed deprotonations of β,γ-unsaturated cyclohexenones.

Based on the results from Whalen's study we expected that tunability of the basic functionality of the BIMP catalyst would be a requirement for high levels of reactivity across diverse substrate classes. If the basicity was too high, the catalyst would be unable to protonate the extended enolate thereby decreasing the overall reaction rate whereas, if the basicity was not sufficient, deprotonation of the deconjugated substrate would become problematic. This concept is common to all base catalysed reactions as the catalyst itself operates within a narrow pK_a window. If the pK_a of the substrate is too high

the equilibrium of deprotonation will be too far to the protonated starting material, reducing the overall reaction rate. However, if the pK_a of the substrate is too low then protonation of the catalyst will occur irreversibly and the overall rate of reaction will be retarded as proton transfer from the protonated catalyst to the substrate becomes limiting/problematic. Further problems may arise from the pK_a of any acidic protons in the product, for instance the α-proton of an α-substituted Michael-adduct. If the α-proton is too acidic then scrambling of the stereogenic centre will occur and therefore erode the enantiomeric excess of the product. These factors must be taken into consideration when designing and optimising a new superbase-catalysed reaction.

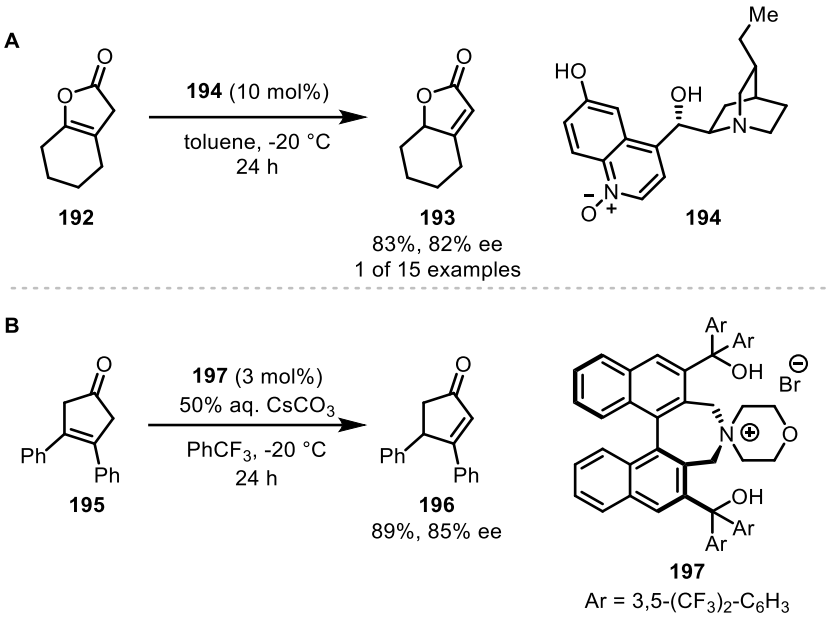
2.2.4 Previous examples of enantioselective catalysed prototropic shifts

Reports of enantioselective prototropic shifts are scarce. In 2010, Shibasaki and Kanai used a chiral yttrium catalyst to promote an enantioselective prototropic shift on quinolinone **188** to generate its chiral conjugated counterpart **189** (Scheme 33).[125] They proposed a mechanism, supported by ESI-MS data, where the chiral ligands (**190**) surrounding the yttrium core function as the basic moiety required for the deprotonation and enantioselective re-protonation step. Having used the method to furnish the key stereocentre, the group went on to complete the first asymmetric synthesis of bedaquiline (**191**), a drug used for multidrug resistant tuberculosis.



Scheme 33: Shibasaki and Kanai's Yttrium catalysed enantioselective prototropic shift in the synthesis of bedaquiline.

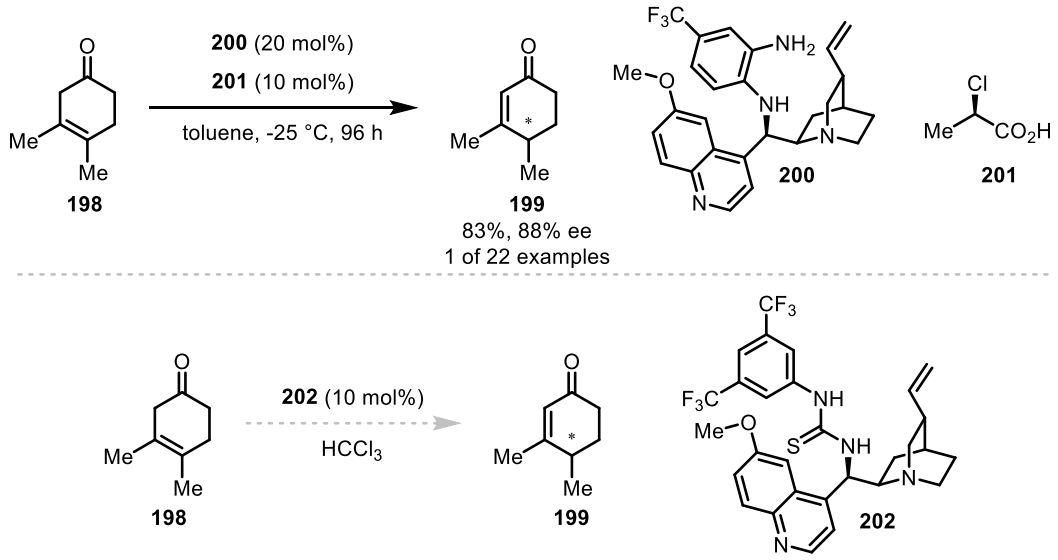
In 2012, Deng *et al.* established a synthetic route to enantioenriched chiral butenolides from their deconjugated double bond isomers (**192**) (Scheme 34A).[126] They used a chiral Brønsted base catalyst (**194**) to promote a 1,3-prototropic shift proceeding through an achiral furan intermediate. A range of cinchona alkaloid scaffolds was tested for potential scaffolds for the chiral catalyst. Catalyst **194** gave the best results (up to 90% ee and 95% yield) and impressively, the catalyst loading could be reduced to 0.5 mol%. Kinetic isotope effects pointed to γ-reprotonation as the rate-determining step. The majority of examples concerned alkyl-substituted substrates where the transformations were rapid and selective, independent of the position of substitution, α, β or γ. In 2015, Maruoka *et al.* reported a standalone example of an enantioselective prototropic shift of β,γ-unsaturated cyclopentenones (**195**) using axial chiral phase transfer catalyst **197**. The conjugated ketone (**196**) was obtained in 89% yield and 85% ee (Scheme 34B).[127]



Scheme 34: A) Enantioselective 1,3-prototropic of butenolides catalysed by cinchona alkaloid catalyst **194** by Deng *et al.*; B) Enantioselective 1,3-prototropic of a symmetrical cyclopentenone (**195**) using enantioselective phase transfer catalysis by Maruoka *et al.*

Further studies by Deng *et al.* found that chiral diamine catalyst **200** could be employed as a mediator of a similar transformation of β,γ-unsaturated cyclohexenones (Scheme 35).[93] This approach utilises concepts discussed by Janda *et al.* with monoclonal antibody enamine catalysts but in Deng's case the enamine catalyst (**200**) is able to transfer its chirality to the conjugated product.[128] The group first attempted to carry out this transformation using chiral Brønsted base catalysis with catalyst **202**.[126] Unfortunately, the low acidity of the ketone's α-proton made this mode of catalysis ineffective and chiral diamine iminium catalysis was found to be better. The quinidine derived catalyst **200** was ideal for reactivity and selectivity, providing the desired α,β-unsaturated enones in high yield (up to 85%) and enantioselectivity (up to 90% ee). However, the reaction was limited to alkyl substitutions at the β- and γ-positions and required long reaction times (average 85 h). Chiral acid additives (**201**) and low temperatures were also required. Despite these limitations, the group was able to deploy their methodology in a key step in the synthesis of (−)-isoacanthodoral to furnish the

desired natural product in 18% overall yield. Following Deng's publication, other research groups have applied the method to install key stereogenic centres in the total syntheses of several natural products including (−)-crinipellin A and B and as part of a synthetic strategy towards (−)-daphlongamine H.[129,130]



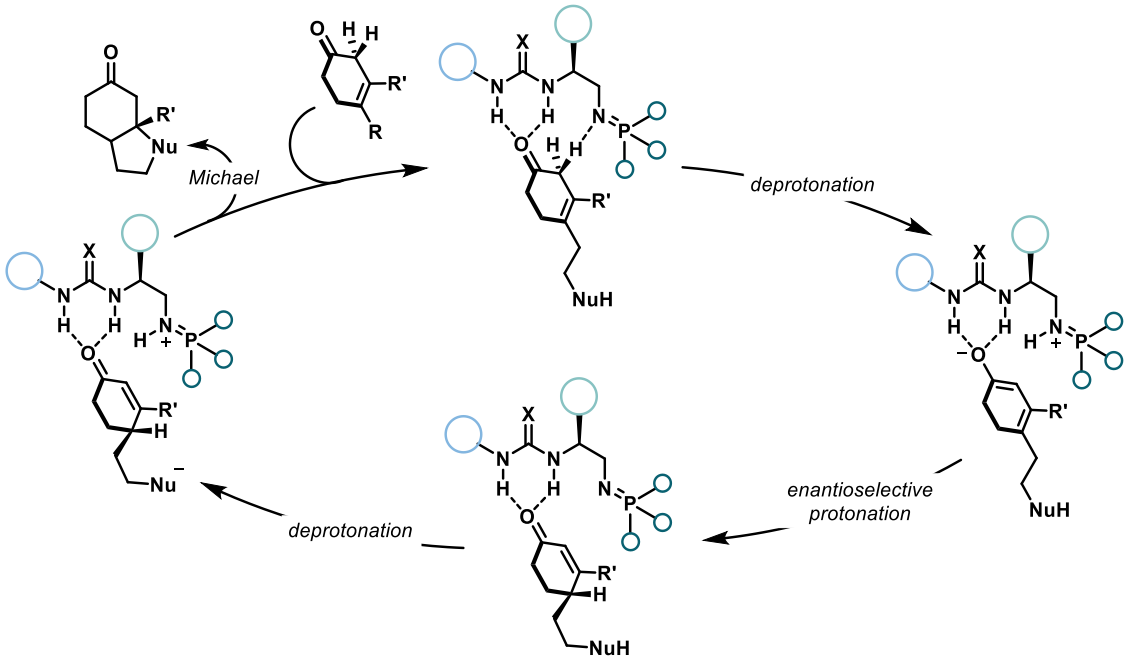
Scheme 35: Primary amine catalysed enantioselective 1,3-prototropic shift of β,γ-unsaturated cyclohexenones as described by Deng *et al.*

2.3 Initial studies

2.3.1 Proposal for the development of a BIMP-catalysed [1,3]-prototropic shift Michael addition cascade sequence

The limitations of Deng's method offered an opportunity for improvement on the original reaction. The idea of a superbase catalysed prototropic shift and how it could be applied to the synthesis of more complex, substituted cyclohexanones was explored. We envisioned the enantioselective synthesis of fused bicycles which, in principle, could be formed by an intramolecular Michael addition following the initial enantioselective prototropic shift. A β,γ-unsaturated cyclohexenone with a pro-nucleophile tethered to the γ-position was likely to undergo this transformation in a favourable 5- or 6-exo-trig

fashion. The idea is set out in Scheme 36 where the superbasic BIMP catalyses both the [1,3]-prototropic shift (thus controlling the stereochemical outcome) and activates the pro-nucleophile for a concomitant ring closing Michael-addition reaction. Such a transformation would in principle allow the formation of a range of bond forming reactions including C–C, C–O, C–N and C–S depending on the nature of the nucleophile.



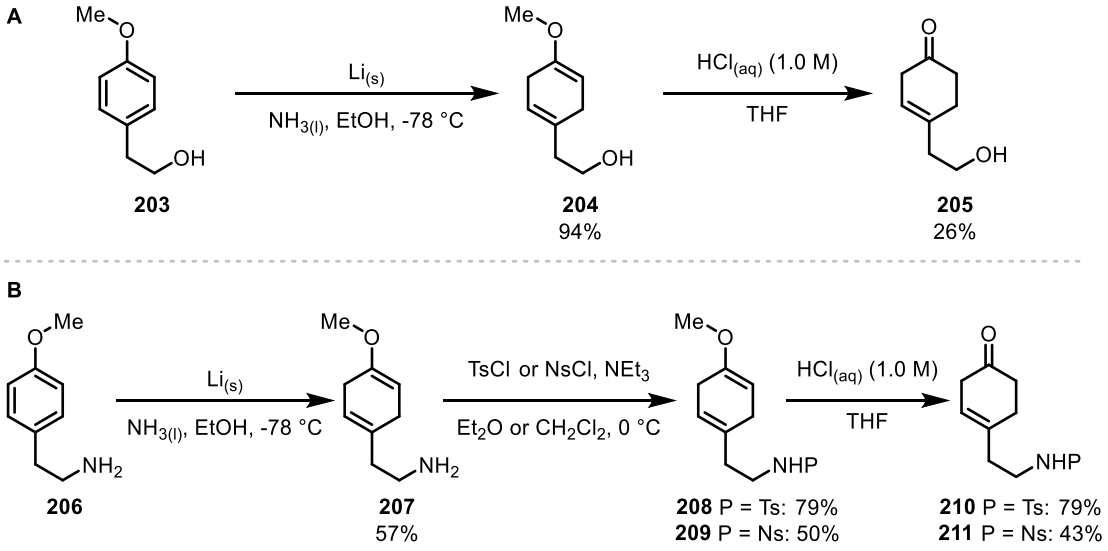
Scheme 36: Concept for a prototropic shift cascade intramolecular Michael addition.

2.3.2 Synthesis of γ-substituted β,γ-unsaturated cyclohexenones containing oxy- and aza-nucleophiles

To investigate the possibility of prototropic shift Michael-cascade reaction, the relevant substrates were synthesized. γ-Substituted β,γ-unsaturated cyclohexenones were obtained through the Birch reduction of *para*-substituted anisoles to give dienes that were converted to the cyclohexenones on hydrolysis of the resultant enol ether (Scheme 37). The Birch reduction of anisole **203** gave the diene **204** in high yield (94%) which on acid catalysed deprotection gave the β,γ-unsaturated cyclohexanone **205** in 26% yield. The

product contained a tethered hydroxyl group primed for intramolecular addition to the enone (Scheme 37A).

The same sequence when applied to anisole **206** led to a complex mixture of products at the hydrolysis stage. This problem was thought to be a consequence of the acid catalysed reaction of the free amine with the unmasked ketone and was exacerbated by the lability of the internal double bond. To overcome this tosyl (**210**) and nosyl (**211**) protected substrates were prepared which had reduced propensity to undergo reaction with the ketone whilst maintaining the amine pro-nucleophile tether (Scheme 37B). The tosyl protected substrate (**210**) was prepared in 35% overall yield while the nosyl version (**211**) was prepared in a usable 12% yield from the starting anisole.

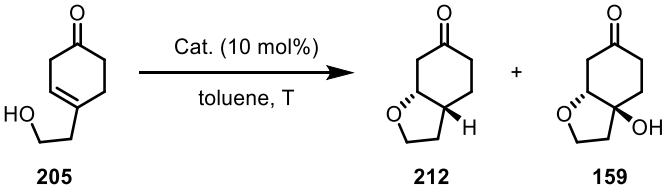


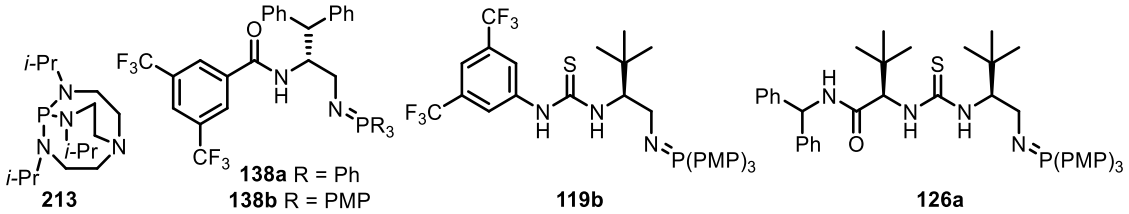
Scheme 37: Synthesis of substrates **205**, **210** and **211** via Birch reduction followed by acid catalysed deprotection.

2.3.3 Application of chiral superbase catalysts to the [1,3]-prototropic shift intramolecular Michael cascade sequence

Firstly, Verkade superbase (**213**) was used to test the feasibility of the desired [1,3]-prototropic shift Michael cascade. With substrate **205**, featuring the alcohol pro-

nucleophile, the reaction proceeded as hoped and provided the bicyclic ether (**212**) in 44% yield (Table 1, Entry 1) after 24 h. Having shown the sequence to be feasible, Verkade superbase was replaced with BIMP catalysts to probe for enantiocontrol. 1st generation BIMPs **138a** and **138b**, incorporating a single stereocentre with different iminophosphorane basicity, were unable to impart any significant reactivity even after extended time periods (Table 1, entries 2 and 3). The 2nd generation catalyst **126a** offered little improvement, though **212** could be isolated in 5% yield after prolonged heating at 60 °C for four days (Table 1, entry 5). A small quantity of an interesting side product (**159**) was also isolated from the mixture. Spectral data identified it as the natural product cleroindicin C (**159**), a consequence of molecular oxygen in the reaction mixture and its addition to the γ-position of the extended enolate.



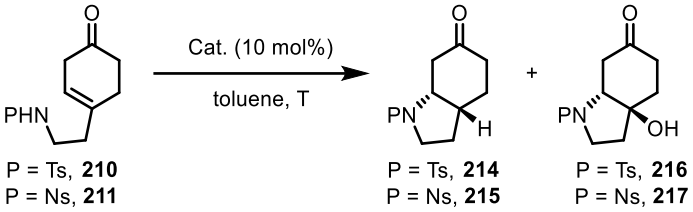


entry	*catalyst*	*conc / M*	*temp / °C*	*time / days*	*yield **212** / %*	*yield **159** / %*
1[a]	**213**	0.1	rt	1	44	0
2	**138a**	0.1	rt	4	0	14
3	**138b**	0.1	rt	4	0	3
4	**126a**	0.1	rt	4	0	6
5	**126a**	0.05	60	4	5	5
6	**126a**	0.05	rt	5	0	11

Table 1: Condition screen for the BIMP-catalysed prototropic shift / Michael cascade reaction of **205**. [a]Reaction carried out in THF. [b]Stereochemistry is undefined for products **212** and **159**.

Initial tests with substrate **205** were not promising. Accordingly, we tested sulfonamide substrates **210** and **211** in the analogous reaction to see whether they would offer any improvement in reactivity. When the *p*-toluenesulfonamide substrate (**210**) was reacted in the presence of a catalytic amount of Verkade base (10 mol%), its reactivity was similar to its alcohol counterpart (**205**) and the bicycle **214** was obtained in 63% yield after 24 h (Table 2, entry 1). Next, we trialled BIMP catalysts in the reaction. Once again however, the catalysts performed relatively poorly. Catalyst **119b** promoted no reactivity even after 43 h at 60 °C (Table 2, entry 2). To counter the insufficient reactivity both catalyst and temperature were varied. Changing the catalyst to **126a** offered no improvement on the outcome of the reaction and the best yield was 13% with disappointing selectivity (7%

ee) after 5 days at room temperature (Table 2, entries 3 and 4). Further variation of the catalyst to **138b** failed to improve the reaction outcome and no product was obtained after 41 h at room temperature (Table 2, entry 5). To try and increase the yield, the reaction was warmed to 50 °C and a higher concentration of 0.5 M was also investigated (Table 2, entries 6 and 7). Unfortunately, neither set of conditions were able to improve the outcome. Finally, *N*-Ns substrate **211** was subjected to the prototropic shift reaction conditions. Disappointingly, **211** also failed to perform well in the reaction with both Verkade base (**213**) and BIMP catalyst **119b** (Table 2, entries 8 and 9). The substrate's poor solubility in THF may have hampered reactivity and the high N–H acidity could have irreversibly protonated and hence deactivated the catalysts.



P = Ts, **210**
P = Ns, **211**

P = Ts, **214**
P = Ns, **215**

P = Ts, **216**
P = Ns, **217**

entry	*substrate*	*catalyst*	*conc / M*	*time / h*	*T / °C*	*yield* ***214/215*** */ %*	*ee* ***214/215*** */ %*	*yield* ***216/217*** */ %*
1[a]	**210**	**213**	0.1	24	rt	63	0	0
2	**210**	**119b**	0.1	43	60	0	N/A	0
3	**210**	**126a**	0.1	41	rt	3[b]	4	13
4	**210**	**126a**	0.1	120	rt	13[b]	7	9
5	**210**	**138b**	0.1	41	rt	0	N/A	0
6[a]	**210**	**138b**	0.1	96	50	3	4	13
7	**210**	**138b**	0.5	41	rt	6[b]	6	8
8[a]	**211**	**213**	0.1	17	rt	<10	0	0
9[a]	**211**	**119b**	0.1	24	rt	2[c]	N/A	0

Table 2: Conditions screen for the BIMP-catalysed prototropic shift/Michael cascade reaction of **210** and **211**. [a]Reaction carried out in THF. [b]NMR yield. [c]Conversion to product. [d]Stereochemistry is undefined for products **214**, **215**, **216** and **217**.

2.4 Investigations into substrates derived from Hagemann's ester

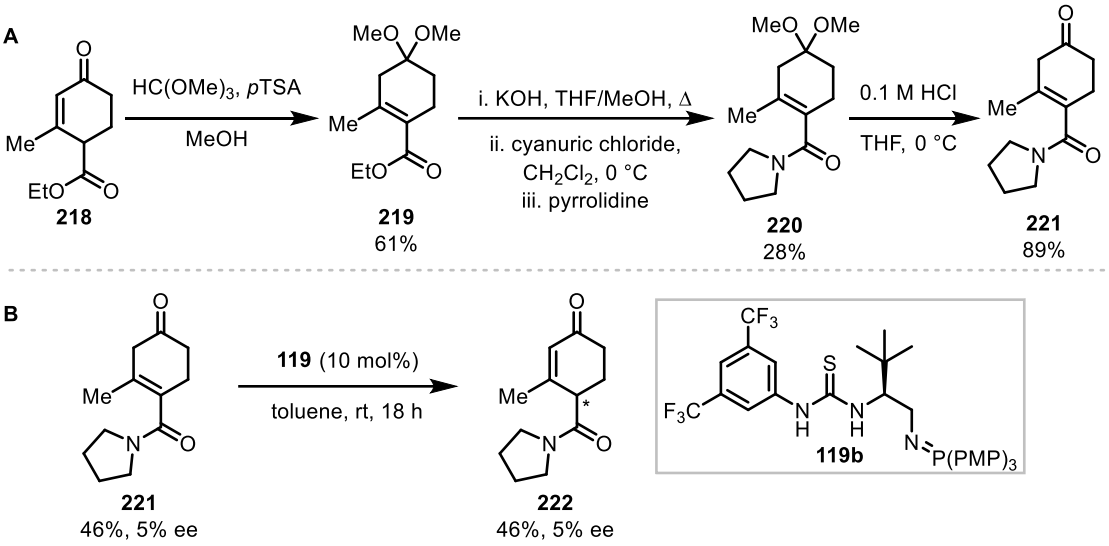
2.4.1 Improving β,γ-cyclohexenone susceptibility to 1,3-protropic shift by enhancing α-hydrogen acidity

Verkade base (**213**) (pK_{BH^+} = 33.6 in MeCN)[45] had consistently outperformed the less basic BIMP catalysts in the prototropic shift-Michael cascade reactions; it was surmised that increasing the α-proton's acidity might therefore improve reactivity. The structure of substrate **136** used in the synthesis of (−)-himalensine A was considered and it was noted that the substrate contained an acidity-enhancing amide group at the substrate's γ-

position.[91] To test this, a pyrrolidine amide functionality was introduced into the system, in the hope that it would provide a significant boost in the acidity of the α-position.

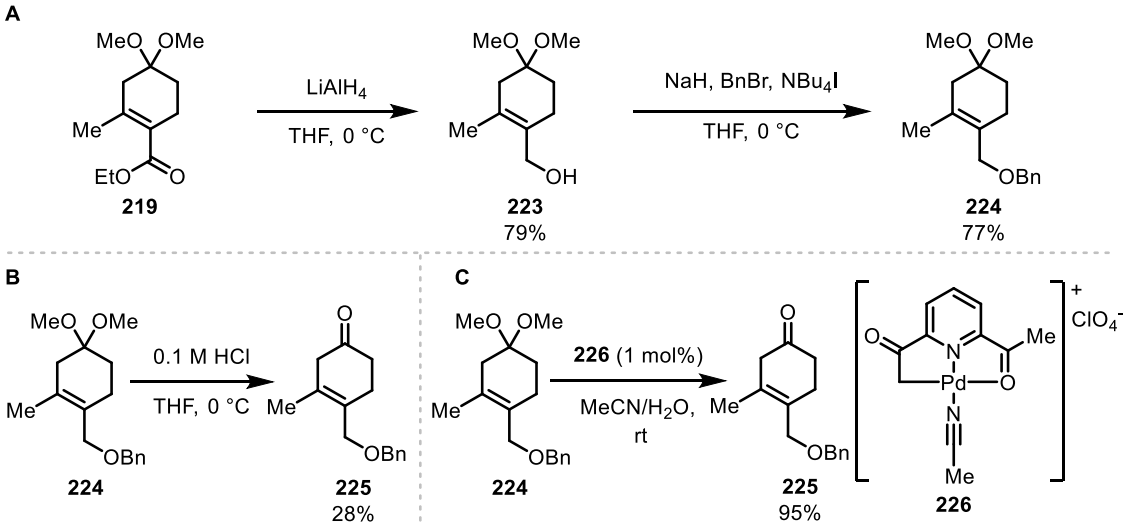
2.4.2 The synthesis of Hagemann's ester derived β,γ-unsaturated cyclohexenone substrates with enhanced α-proton acidity

Hagemann's ester (**218**) offered a commercially available package of all the elements required to provide β,γ-unsaturated cyclohexenones with more acidic α-protons: an unsaturated cyclohexenone substituted with an acidity enhancing carbonyl moiety at the γ-position.[131] To synthesise the required substrate, Hagemann's ester's ketone was protected with trimethyl orthoformate in the presence of a catalytic amount of *p*TSA, followed by a basic work-up which simultaneously shifted the double bond into conjugation with the ethyl ester in 61% yield (Scheme 38A).[132] From previous studies it had been shown that hydrolysis of the conjugated ester (**219**) to provide a carboxylic acid had been unsuccessful due to decomposition which prevented its isolation. Thus, a new route was devised to convert **219** into an amide (**221**) over three steps. The new route required the synthesis of a potassium-carboxylate salt which was achieved by hydrolysis of the **219**'s ester with aqueous KOH. The stable potassium salt was then reacted with cyanuric chloride providing the desired acid chloride, which underwent rapid reaction with pyrrolidine. Mild acid hydrolysis of the of the dimethyl ketal provided the desired β,γ-unsaturated ketone (**221**) in 89% yield. Gratifyingly, this new substrate underwent the [1,3]-prototropic shift in toluene at room temperature with catalyst **119b** over 18 h. The desired enone (**222**) was formed in 46% yield and 5% ee (Scheme 38B).



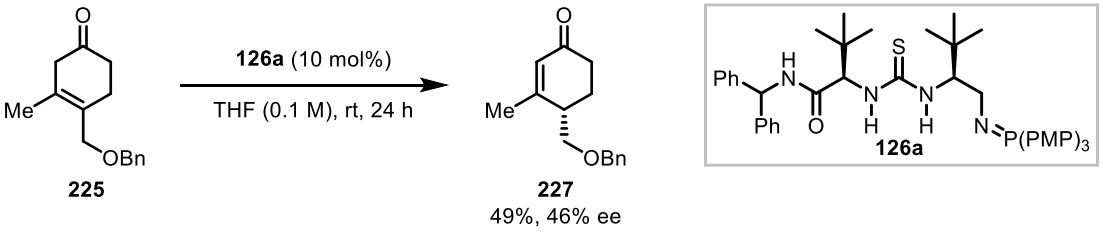
Scheme 38: A) Synthesis of substrate **221** from Hagemann's ester; B) BIMP-catalysed enantioselective prototropic shift of substrate **221**.

Following this successful test reaction, it was identified that Hagemann's ester could provide other substrates where a heteroatom might influence α-proton acidity (**225**). Hence, **219** was reduced with $LiAlH_4$ and benzylated giving ether **224** in 61% yield over two steps (Scheme 39A). Ketal hydrolysis provided the new β,γ-unsaturated cyclohexenone **225**, albeit in poor yield (28%) (Scheme 39B); re-conjugation of the double bond under acid conditions accounted for the low yield. This problem was overcome using Vicente's palladium-based pincer complex (**226**), developed for the rapid (ca. 5 min) deprotection of acid sensitive acetals.[133] The palladium catalyst (**226**) was readily synthesised according to the Vicente group's procedure and used to deprotect **224** to give the desired β,γ-unsaturated enone **225** in 95% yield (Scheme 39C).[134] Using this approach substrate **225** was easily prepared in gram quantities.



Scheme 39: A) Synthesis of **224** from Hagemann's ester; B) Acid catalysed deprotection of **224**; C) Deprotection of **224** using catalyst **226** developed by Vicente *et al.*

With gram quantities of ether **225** in hand, the substrate was subjected to the BIMP-catalysed prototropic shift with 2nd generation catalyst **126a** (Scheme 40). After 24 h the conjugated product (**227**) was isolated in good yield of 49% and optimisable 46% ee. This was a significant improvement in enantioselectivity in comparison with amide **221**, and gave the prospect, after conditions and catalyst optimisation, of a good route to readily derivatised chiral cyclohexenones.

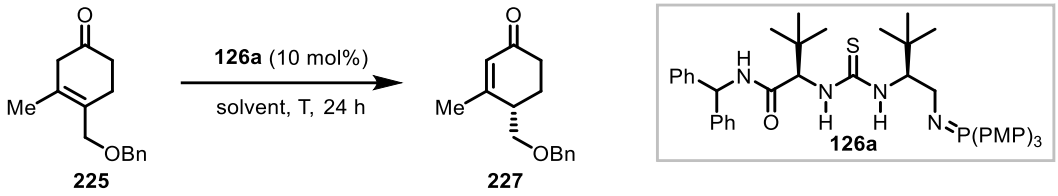


Scheme 40: BIMP-catalysed prototropic shift of substrate **225**.

2.4.3 Optimisation of reaction conditions

There are multiple approaches towards optimising a catalytic enantioselective reaction. For instance, one approach is to optimise the catalyst for reactivity and enantioselectivity before investigating the optimal reaction conditions such as solvent and temperature. In

our case, the catalyst was already providing a significant amount of product and the selectivity was good for an initial test reaction. For this reason, we initially decided to investigate the reaction conditions with catalyst **126a** (10 mol%) which had provided **227** in 49% yield and 46% ee after 24 h in THF (0.1 M) at room temperature (Table 3, entry 1). Reaction conditions optimisation was taken from this base point. Increasing and decreasing the temperature from room temperature, was found to significantly improve the ee. Reactions conducted at 0 °C and at 40 °C raised the selectivity to 61% ee and 69% ee respectively (Table 3, entries 2 and 3). In contrast, reduction of the temperature was found to have a detrimental effect on the yield in the same time period (24% yield), although raising the temperature benefitted it (93% yield). Next, concentration was changed. Lowering the concentration from 0.1 M to 0.05 M considerably increased the selectivity (72% ee) at the expense of reaction rate and ultimately yield (21%) (Table 3, entry 4). Increasing the concentration to 0.2 M surprisingly had a similar though less pronounced effect (52% yield, 61% ee) (Table 3, entry 5). Mindful that in previous BIMP studies solvent had been shown to play a major role in selectivity and reaction progress, different solvents were then trialled in the reaction.[81] Carrying out the reaction in TBME provided the conjugated enone **227** in 93% yield and 69% ee (Table 3, entry 6); an early promising result. Changing the solvent to Et_2O improved the outcome further still and **227** was isolated in near quantitative yield of 97% and in an impressive 85% ee (Table 3, entry 7).



entry	*solvent*	*temp / °C*	*conc / M*	*yield / %*	*ee / %*
1	THF	rt	0.10	49	46
2	THF	0	0.10	24	61
3	THF	40	0.10	93	69
4	THF	rt	0.050	21	72
5	THF	rt	0.20	52	61
6	TBME	rt	0.10	93	69
7	Et_2O	rt	0.10	97	85

Table 3: Temperature, concentration and solvent screen for the BIMP-catalysed enantioselective prototropic shift of model substrate **225**.

2.4.4 Catalyst screen

Having laid the foundations for a superbase catalysed enantioselective prototropic shift, a library of BIMP catalysts was then screened under the optimised reaction conditions in the hope of achieving an excellent level of enantioselectivity (Figure 4). Firstly, BIMP catalyst (**138a**) used in the synthesis of (−)-himalensine A was tested.[91] Surprisingly, both $N{=}PPh_3$ and $N{=}P(PMP)_3$ iminophosphoranes (**138a** and **138b** respectively) imparted only low levels of enantiocontrol of 1% and -7% respectively, and only small amounts of the product were obtained. Similarly, 1st generation catalyst **123**, with its weaker amide hydrogen bond donor group, gave poor results (27%, 1% ee). The thiourea based catalyst (**119b**) (53%, -14% ee) was also unsatisfactory despite its reportedly superior 3,5-[bis(trifluoromethyl)phenyl]thiourea hydrogen bond unit.[135]

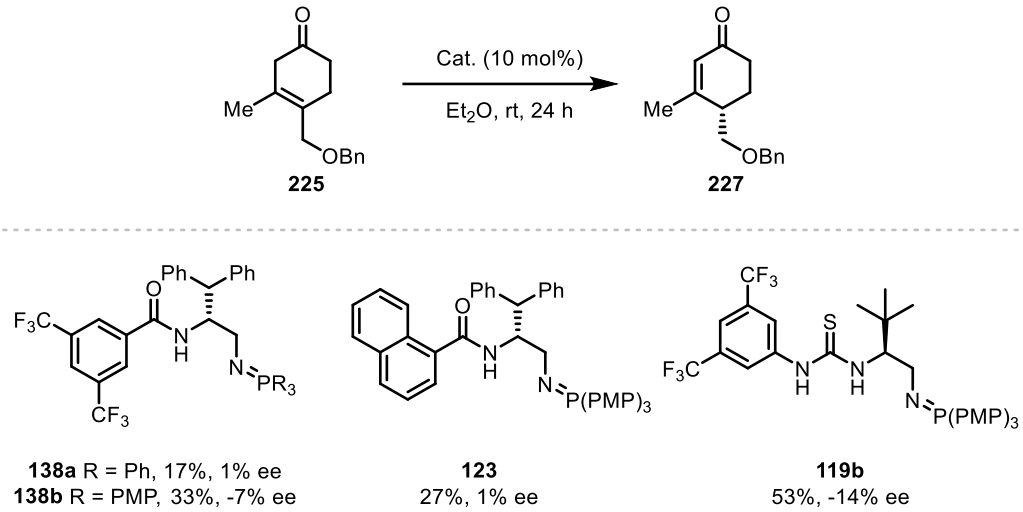


Figure 4: 1st generation catalyst screen for the enantioselective prototropic shift of β,γ-unsaturated cyclohexenones.

Since 1st generation catalysts appeared to perform poorly, the 2nd generation catalysts were examined more thoroughly (Figure 5). Inversion of configuration of stereocentre **a** to give the opposite diastereomer of **126a**, **124a**, proved detrimental to both reaction yield (67%) and selectivity (18% ee) and further modification of the same stereocentre's substituent to give **228** inhibited catalytic activity (19% yield) and selectivity (10% ee). Clearly, catalyst structure was playing a major role in reactivity and enantiocontrol and so the *cis*-configured catalyst scaffold was re-examined, in particular the modification of the substituent of stereocentre **b**. Replacement of the *tert*-butyl group with a phenyl ring (**125a**) retained the excellent reactivity observed with **126a** and provided **227** in 83% yield and impressive 93% ee. Further alteration to stereocentre **b** by the introduction of a naphthylmethyl group (**229a**) improved the selectivity further, with almost complete enantiocontrol (97% ee) after 24 h. Upon scale up to 2.6 mmol from 0.065 mmol the product could be obtained in 90% yield and 99% ee.

It was recognised that a free amine could be formed by the catalyst's potential *in-situ* reactivity with substrate **225** via an aza-Wittig reaction. To check that the free amine was not responsible for catalytic activity, a control experiment was carried out. Amine **229b**,

formed by reduction of the catalyst precursor azide (urea version), was exposed to substrate **225**. Pleasingly the amine failed to provide any product, confirming that the reaction was indeed, superbase catalysed (Figure 5).

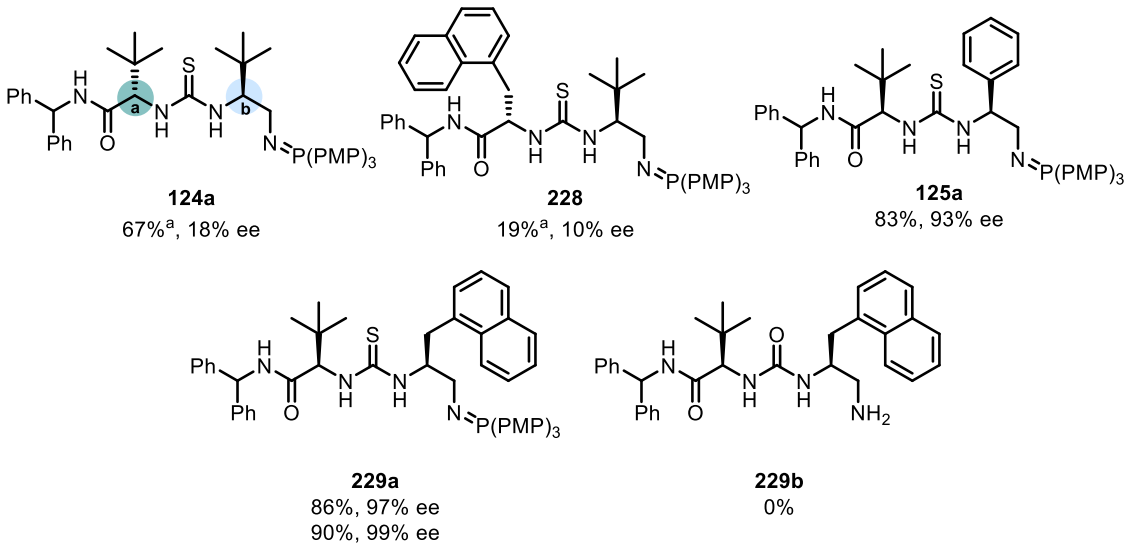


Figure 5: 2nd generation catalyst screen for the enantioselective prototropic shift of β,γ-unsaturated cyclohexenones. [a]NMR yield.

2.5 Reaction scope – ethers and esters derived from Hagemann's ester

2.5.1 Ethers and esters derived from Hagemann's ester

Having optimised the reaction for our model substrate **221**, the applicability to a wider variety of ethers was then investigated. A convenient way to rapidly synthesise a library of substrates was via the previous route beginning from Hagemann's ester (**218**). The previously prepared alcohol (**223**) was used as a nucleophile to synthesise an assortment of ethers. The ketone deprotection with catalyst **226** liberated the β,γ-unsaturated enones (Figure 6). This high yielding method was employed to introduce a range of ethers including methyl (**230**), allyl (**231** and **232**), propargyl (**233**) and a silyl ether (**234**) that was employed in section **2.9.1** for further scaffold elaboration.

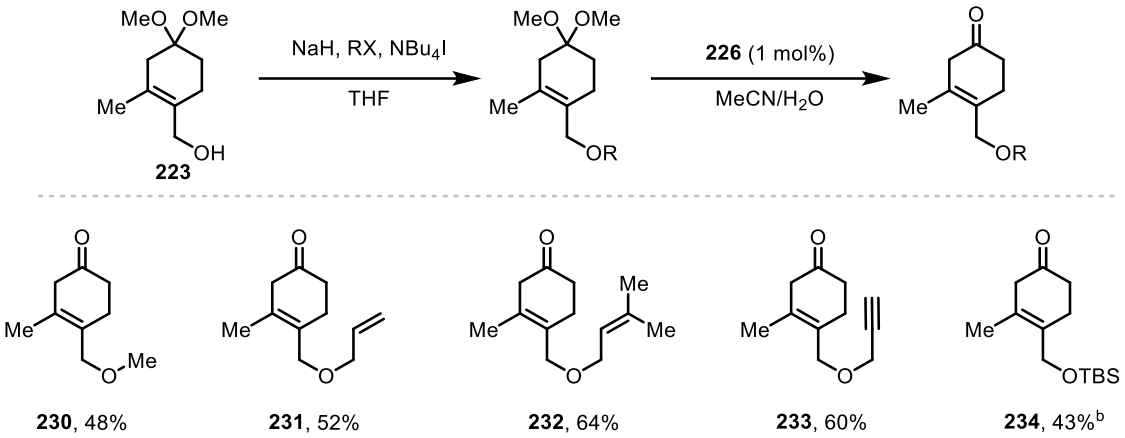


Figure 6: Synthesis of substrates for the BIMP-catalysed prototropic shift.[a]Yield over two steps.[b]Step 1: TBSCl, NEt_3, CH_2Cl_2.[c]Extra equivalents of **226** were added in some cases (see experimental section).

Each of the newly synthesised substrates was subjected to the prototropic shift reaction conditions (Figure 7). Pleasingly methyl ether substrate **230** performed well, albeit with a slightly depreciated yield of 58%, possibly due to the product's volatility. Despite this, the enone (**235**) was obtained in excellent enantiomeric excess of 96% ee, a promising result as the scope of the reaction was initially explored. Excitingly, allyl ethers, **231** and **232** also underwent the isomerisation in high yields of 80% and 85% respectively with almost complete enantiocontrol in both cases (98% ee and 99% ee respectively). Similarly, propargyl substrate **233** performed extremely well, and the desired α,β-unsaturated ketone (**238**) was obtained in an excellent yield of 96% and impressive 99% ee which could be reproduced upon scale up to 200 mg.

While ethers proved to be well-behaved substrates, an unsubstituted hydroxyl substrate derived directly from **223** provided a point of interest. Upon subjection to the reaction conditions, the double bond moved smoothly around the ring, and the product (**239**) was isolated in 67% yield and 85% ee. The moderate decrease in reactivity and selectivity was attributed to the free hydroxyl interfering with the hydrogen bonding abilities of the catalyst and an increased likelihood of background protonation. To avoid this problem,

the hydroxyl proton was replaced with a TBS group (**234**) which could be removed at a later stage to reveal the alcohol. Satisfyingly, the substrate performed remarkably well under the prototropic shift conditions despite the considerable increase in steric bulk around the ether (82%, 99% ee). Scale up to 1.5 g provided the chiral α,β-unsaturated compound (**240**) with complete enantiocontrol and excellent yield (90%, 99% ee).

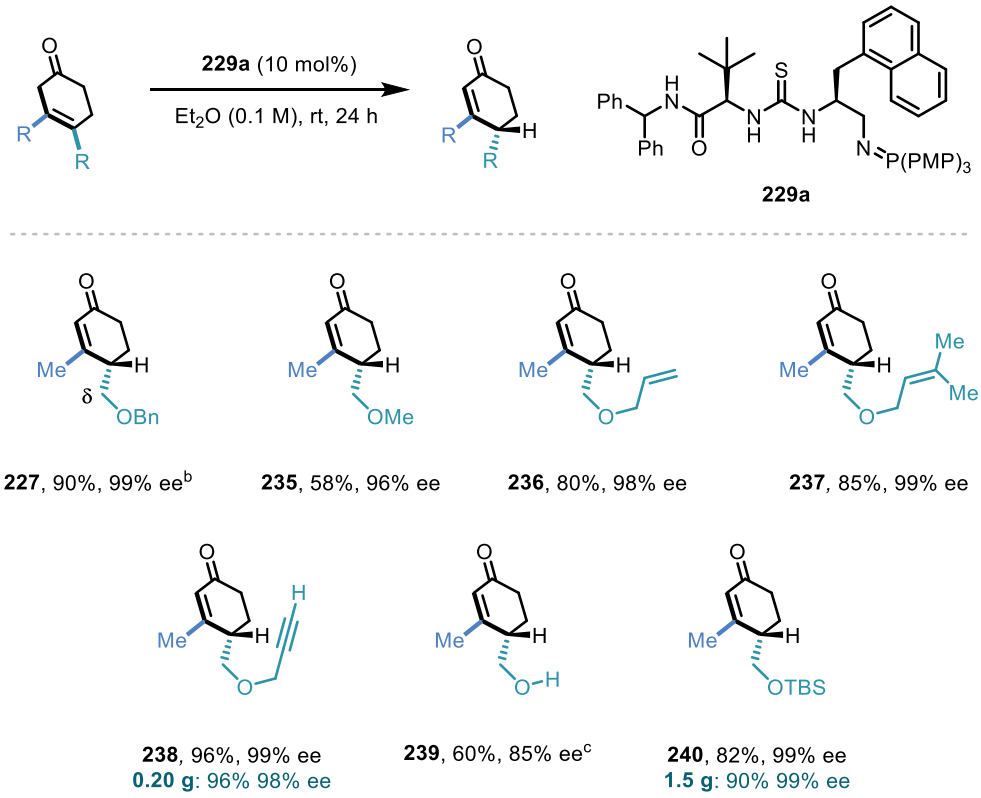
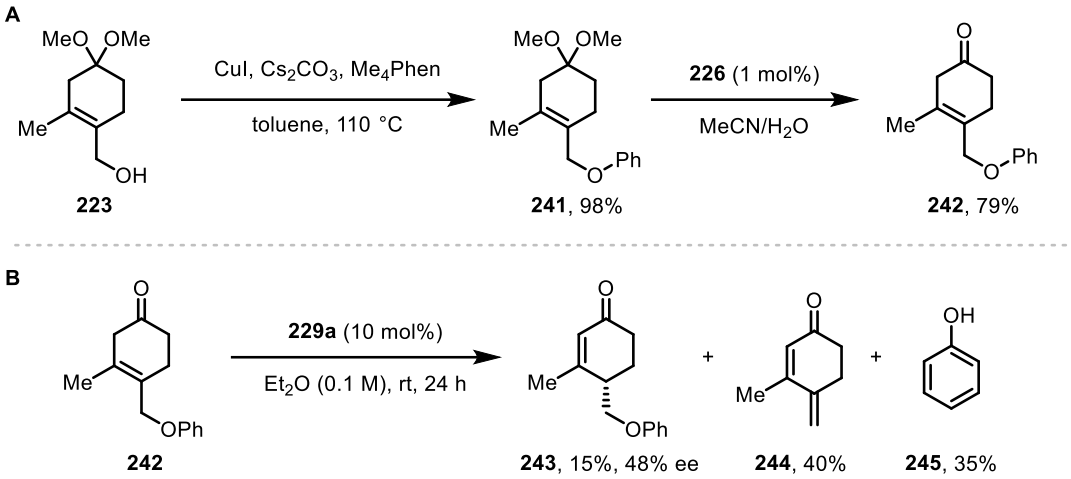


Figure 7: Primary substrate scope for the BIMP-catalysed enantioselective prototropic shift of β,γ-unsaturated cyclohexenones.

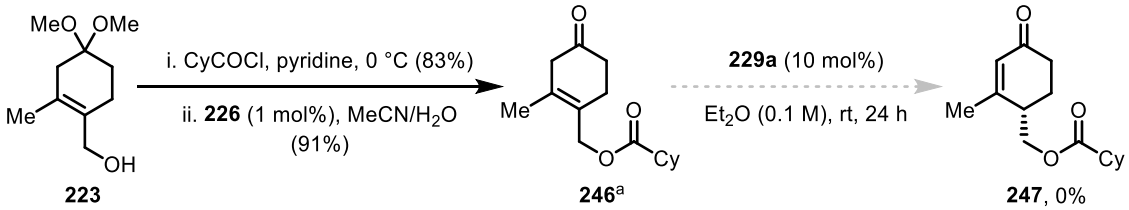
Phenyl ether substrates offer the attractive possibility of cyclisation of the aryl group onto the enone to generate [6,5]-fused ring systems post-prototropic shift. An Ullmann coupling on **223** gave the aryl ether **241** in good yield (98%), and the usual deprotection method provided the desired enone **242** in 79% yield (Scheme 41A).[136] Subjecting **242** to the prototropic shift reaction conditions led to a complex mixture of products from which the desired conjugated enone (**243**) could only be obtained in 15 % yield and 48

% ee (Scheme 41B). This was a consequence of the competing elimination of phenol (**245**) (detected by NMR) and hence less selective protonation of the γ-position.



Scheme 41: A) Synthesis of phenyl ether **242**; B) Phenyl ether **242**'s performance in the enantioselective prototropic shift reation. *Compounds **243**-**245** were partially characterised

The free alcohol (**223**) could also be readily acylated by stirring with the desired acyl chloride in pyridine (Scheme 42B). The acylated product was obtained in excellent yield (83%) and deprotected accordingly to give **246** in 91% yield (decomposition was observed on silica gel during attempted flash column chromatography but an aqueous work up delivered the desired substrate without the need for purification). Substrate **246** was subjected to the prototropic shift but disappointingly decomposed to a complex mixture of products during the reaction, as a consequence of elimination.

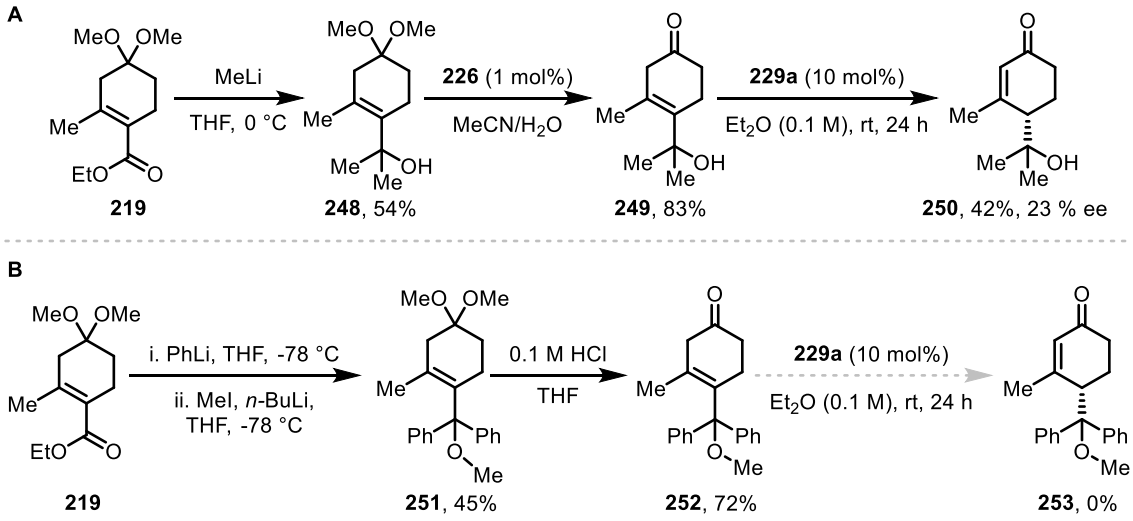


Scheme 42: Synthesis and reactivity of substrate **246**.[a]Compound **246** was partially characterised.

Inspired by the tetrahydrocannabinol structure,[137] in particular the structure's quaternary ether affixed to a cyclohexyl ring, [1,3]-prototropic shift substrates carrying both

dimethyl and diphenyl moieties at the δ-position (defined in Figure 7) were prepared. Ester **219** was treated with either methyl lithium or phenyl lithium (Scheme 43). The double addition of methyl lithium afforded the desired product (**248**) in good yield of 54%. After addition of phenyl lithium to **219**, the resulting alcohol was methylated and **251** was obtained in 45% overall yield. Both ketals could be deprotected to give their respective ketones in excellent yield, however palladium catalyst **226** was found to be unreactive with **251**, and acid catalysed deprotection was necessary to reveal the ketone (**252**) (Scheme 43A and B, respectively).

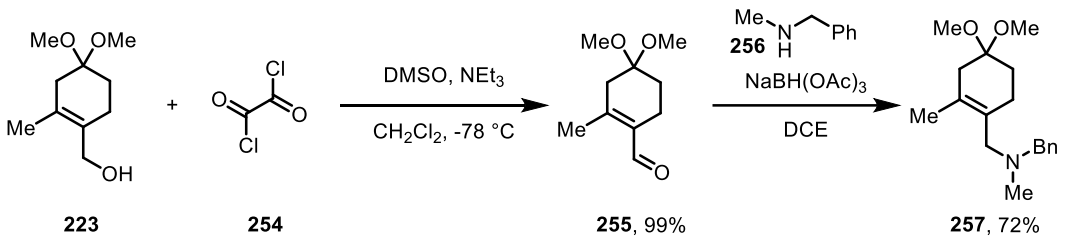
The BIMP catalyst **229a** promoted the prototropic shift on the dimethyl alcohol compound **249**. However, the conjugated product (**250**) could only be isolated in moderate yield of 42%, and a significant loss of enantiocontrol (23% ee) was observed, possibly as a consequence of hindered protonation at the γ-position combined with background reprotonation and hydrogen bond interference as observed with product **239**. The reactivity issue was even more pronounced with compound **252** as the α,β-unsaturated cyclohexenone (**253**) failed to form.



Scheme 43: A) Synthesis of compound **249** and its performance in the prototropic shift; B) Synthesis of compound **252** and its performance in the prototropic shift. *Compounds **248**-**252** were partially characterised.

2.5.2 Amines synthesised from Hagemann's ester

Initially we planned to synthesise amine substrates by converting the primary hydroxyl group into an aldehyde via Swern oxidation, then carrying out reductive aminations on the aldehyde (Scheme 44). The Swern oxidation proceeded well, and the desired aldehyde (**255**) was obtained in excellent yield (99%). Reductive amination of the product with amine **256** and $NaBH(OAc)_3$ progressed smoothly to amine **257**, in good yield of 72%. Deprotection of **257** with catalyst **226** failed to provide any product, likely due to coordination of the substrate's amino functionality with the catalyst. Acid hydrolysis was tried, however, following removal of the acetal in 0.1 M $HCl_{(aq)}$, the product decomposed quickly, which was attributed to the basicity of the free amine. Despite some success this route was abandoned in favour of an alternate known procedure.[132]

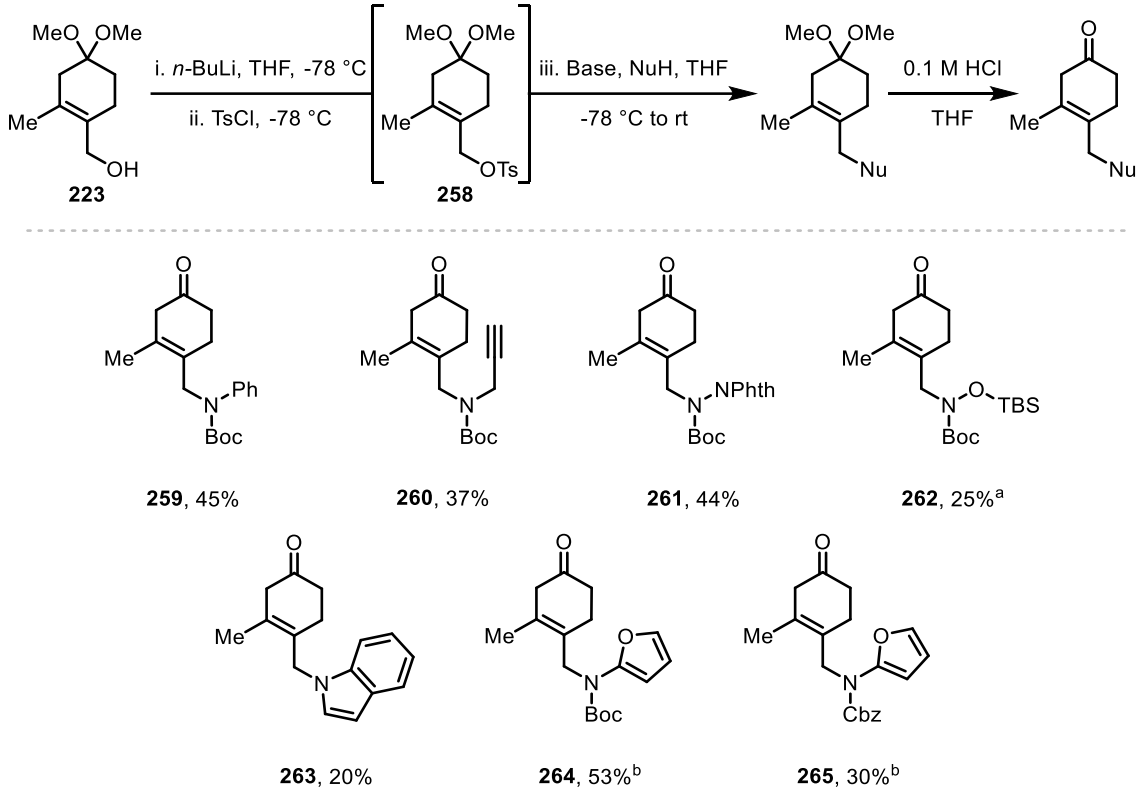


223 **254** **255**, 99% **257**, 72%

Scheme 44: Swern oxidation of compound **223** and reductive amination of aldehyde **255** to provide amine **257**.*Compounds **255** and **257** were partially characterised.

The direct synthesis of protected secondary amines from **223** offered a better prospect. A modified version of a scheme reported by colleagues was used: [132] tosylation of **223**'s hydroxyl group at –78 °C followed by *in situ* addition of a deprotonated, protected secondary amine would provide access to the substrates (Scheme 45). Application of this method led to a range of nitrogen-based substrates that included the *N*-Boc aniline (**259**) (in 50% yield), the *N*-Boc propargyl (**260**) (in 44% yield), the amino furan derivatives **264** and **265** and the indole **263**. Other pro-nucleophiles such as thiols and pyrroles were

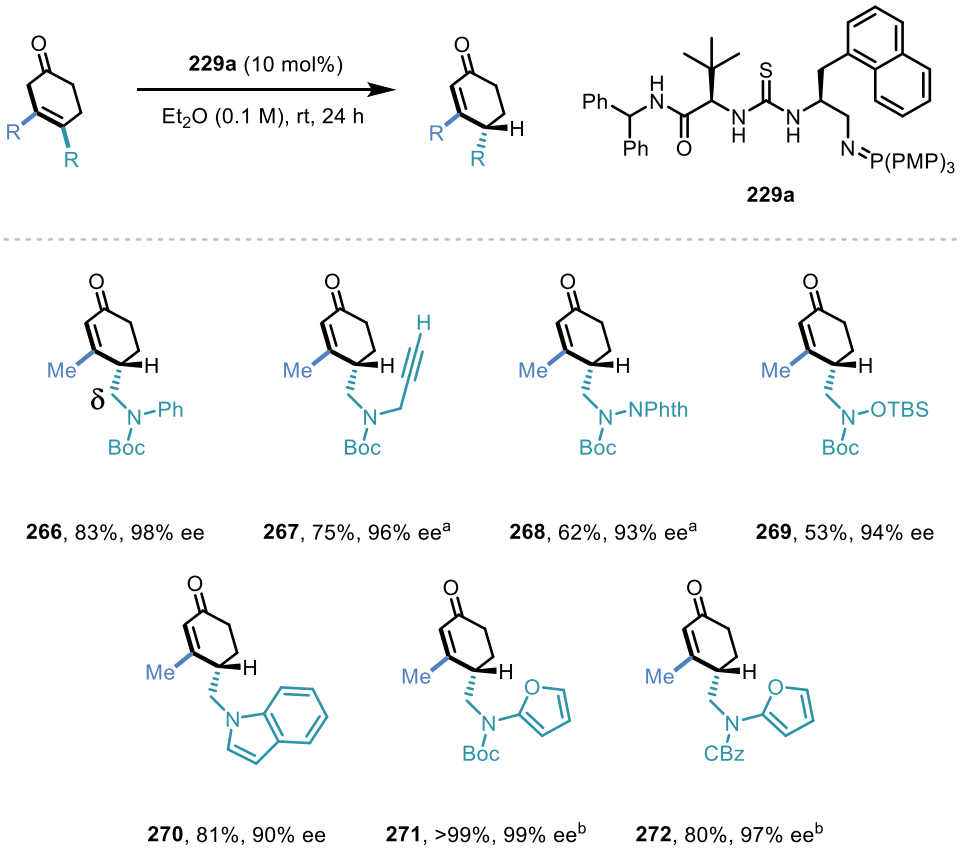
added to **258**, however, decomposition of the final products to complex mixtures was observed.



Scheme 45: Synthesis of substrates via tosylation and in-situ nucleophilic addition.[a]**226** (1.0 mol%), MeCN/H_2O. [b]Substrates originally synthesised in this project by Eve Carter based on previous studies by John Ward.[132,138]

N-Boc substrates **259** and **260** were subjected to the prototropic shift conditions with catalyst **229a** (Scheme 46) and both were found to undergo the isomerisation in high yield (83% and 75%, respectively) and with excellent levels of enantiocontrol (98 and 96% ee, respectively). The hydrazine based substate **261** and hydroxylamine-based substrate **262** underwent the prototropic shift in marginally lower yields (62% and 53%, respectively). Despite this, both α,β-unsaturated enones (**268** and **269**) could be obtained in excellent enantiomeric excess (93% and 94% respectively). The indole substrate **263** performed particularly well and the conjugated product (**270**) was obtained in 80% yield and with 90% ee. The two amido-furan substrates, **264** and **265** have structural similarity to intermediates used in the synthesis of (−)-himalensine A and, after the prototropic shift,

it was envisaged that the enantioenriched products could undergo an intramolecular Diels-Alder to create complex tricyclic scaffolds (Scheme 22).[91] This investigation is described in greater detail in section **2.9.1**. Both substrates performed well in the prototropic shift in terms of yield *and* selectivity with product **271** being obtained in 99% ee and quantitative yield.

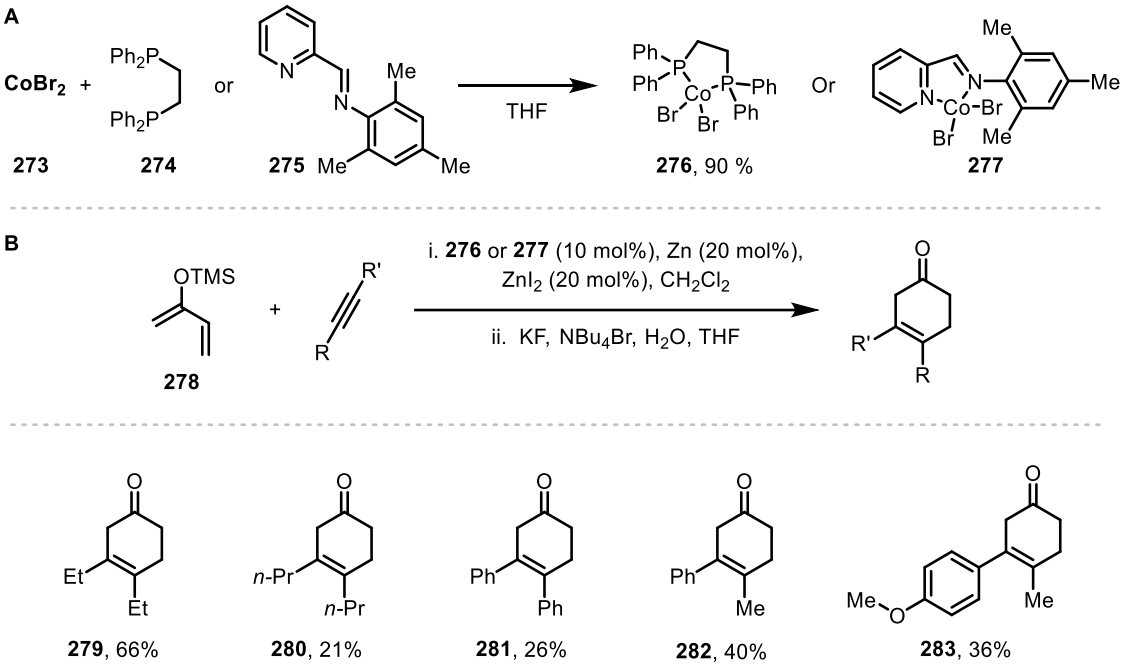


Scheme 46: Secondary scope of the BIMP-catalysed prototropic shift showcasing a range of amino functionalities.[a]48 h.[b]Original reaction was carried out by Eve Carter; the result depicted is a repeat.[138]

2.5.3 Further scope expansion

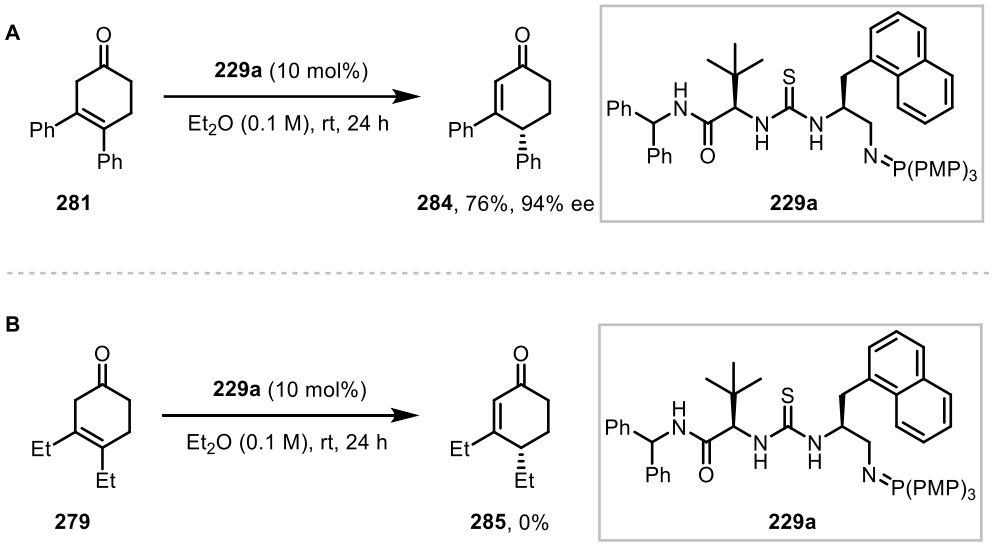
While the Hagemann's ester (**218**) had provided a good range of substrates, it imposed a heteroatom at the δ-position (Scheme 46) and allowed no scope for variation at the β-position. A Diels-Alder reaction, developed in the Hilt group offered a straightforward way of accessing a variety of new substrates (Scheme 47A).[139] The Diels-Alder reaction between alkynes and 2-(trimethylsiloxy)-1,3-butadiene (**278**) employs two different

Co(II) catalysts (**276** and **277**) that dictate the substitution pattern of the product β,γ-unsaturated cyclohexenone. The catalysts were obtained as green powders by stirring $CoBr_2$ (**273**) with the desired ligand in THF. With the two catalysts in hand, the substrate library was expanded (Scheme 47B). Nine substrates were synthesised. Symmetrical alkynes 3-hexyne and 4-octyne could be used to add alkyl substituents at the β- and γ-positions providing products **279** and **280** in 66 % and 21% yield, respectively. Likewise, diphenylacetylene could be used as a substrate, though the desired β,γ-unsaturated cyclohexenone (**281**) was only obtained in low yield of 26% following recrystallisation. Perhaps the observed low conversion was as a result of steric clash in the formation of the product. Two points of interest were variation of the electronic properties of the enone as well improving structural diversity at the β-position. Using py-imine catalyst **277** to control the Diels-Alder's regioselectivity, **282** and **283** were synthesised in good yield (40% and 36% respectively), ready for use in the prototropic shift.



Scheme 47: A) Synthesis of two [Co] catalysts **276** and **277**; B) Synthesis of substrates **279-283** via a [Co]-catalysed Diels-Alder reaction.[139]

Pleasingly, bis-aryl substrate **281** underwent the prototropic shift in a high yield of 76% and a high level of enantioselectivity (94% ee) despite its drastically modified steric and electronic properties compared to other substrates (Scheme 48). Substrates **279** and **280** were tested under the optimised reaction conditions. Disappointingly, catalyst **229a** was unable to impart the same levels of activity observed with previous substrates and the desired α,β-unsaturated cyclohexenone was not obtained. To overcome this, mechanistic investigations were initiated in the hope of finding out why catalyst **229a** performed poorly with substrate **279**.



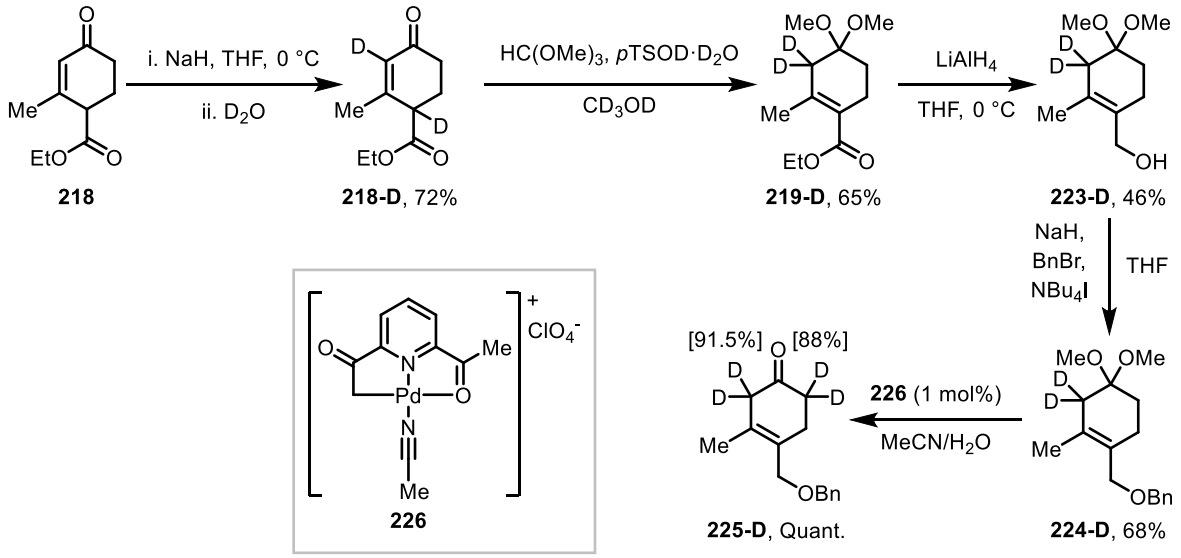
Scheme 48: A) Enantioselective BIMP-catalysed prototropic shift of substrate **281**; B) Poor reactivity of substrate **279** with catayst **229a**.

2.6 Deuterium labelling studies

2.6.1 Synthesis of a deuterium labelled substrate

To gain a mechanistic insight into the BIMP-catalysed prototropic shift a deuterium labelled substrate was synthesised and investigated. The substrate was synthesised in the usual manner (Scheme 39), however, Hagemann's ester (**218**) required deuteration prior to the process. Deuterium could be incorporated via deprotonation of **218**'s γ-position with sodium

hydride followed by addition of D_2O. This process was repeated twice to maximise deuterium incorporation. Subsequently, the ketone was protected in CD_3OD with trimethyl orthoformate using catalytic *p*TsOD·D_2O to provide **219-D**. Labelled compound **219-D** could be taken on through the steps outlined previously in Scheme 39 and the desired deuterated substrate **225-D** was obtained in quantitative yield after deprotection (Scheme 49).

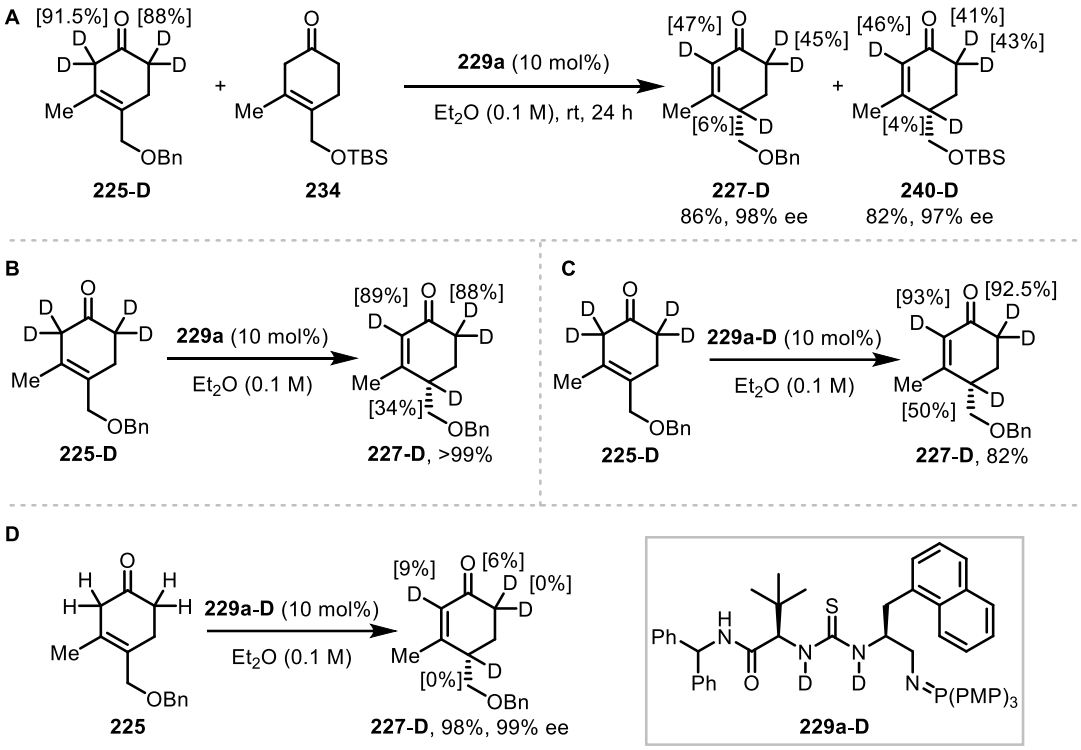


Scheme 49: Synthesis of a deuterium labelled substrate.

2.6.2 Labelling studies

To investigate whether proton transfer was taking place intra- or intermolecularly, a crossover experiment involving a substrate labelled at the α-positions and an unlabelled substrate, was designed. Unlabelled substrate **234** was selected owing to its separability from the labelled substrate (**225-D**) and the conjugated product (**227-D**) as well as its similar structural and reactivity profile (Scheme 50A). The substrates, in an equimolar ratio, were subjected to the catalytic enantioselective reaction conditions with catalyst **229a** and the reaction was allowed to proceed for 24 h. When the reaction had reached completion the two products were separated by column chromatography. It was found that deuterium was

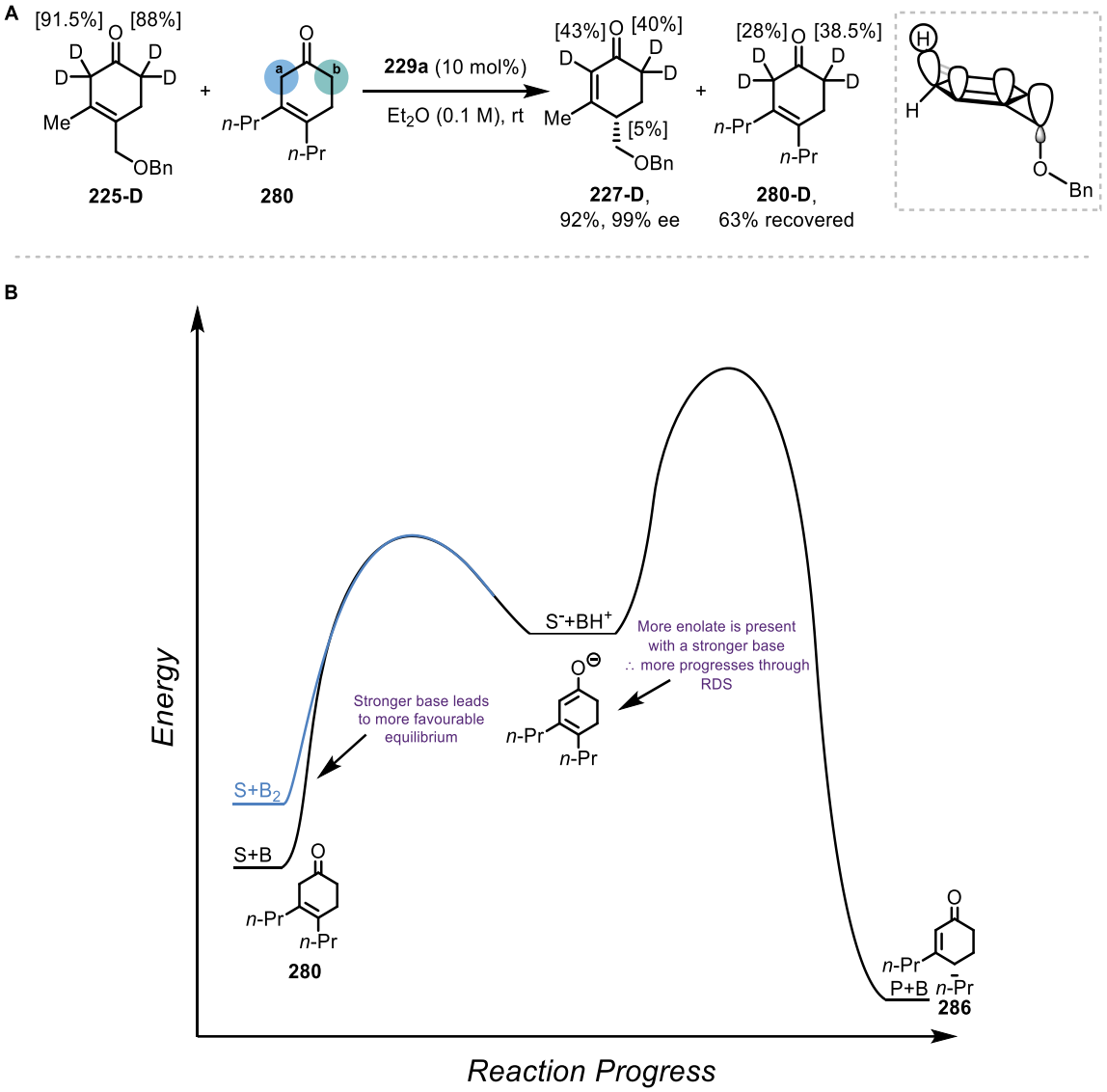
incorporated at each individual α-position of the products and quantitative NMR revealed approximately 50% incorporation at each α-position (see experimental section). This outcome suggested a rapid and reversible pre-equilibrium in which the BIMP catalyst deprotonates the substrate and replaces the proton / deuterium at one of the four α-positions. This observation is in keeping with previous studies.[124] Interestingly, only low levels of deuterium incorporation were found at the γ-positions in **227-D** and **240-D**, suggesting a turnover limiting reprotonation step in keeping with mechanistic studies described by Whalen *et al.* (Scheme 50A).[124] In a separate experiment, with no unlabelled substrate present in the reaction mixture, the levels of deuterium incorporation at the γ-position were increased, demonstrating that the proton source is majorly the α-position of the β,γ-unsaturated cyclohexenones (Scheme 50B). Deuteration of the catalyst (**229a-D**) by repeated cycles of solvation of the azide precursor in deuterated methanol followed by concentration *in vacuo*, also led to increased deuterium incorporation in the final product (Scheme 50C). This suggested that, at some point in the reaction, protons could be removed from the catalyst's urea or thiourea moieties. In a similar experiment, deuterated catalyst **229a-D** was used in conjunction with unlabelled substrate **225**. The product was found to have low levels of deuterium incorporation at the α-positions. However, no deuteration was observed at the γ-positions providing further evidence that proton-exchange from the catalyst can occur (Scheme 50D).



Scheme 50: A) Crossover experiment between deuterated compound **225-D** and substrate **234**; B) Enantioselective prototropic shift of deuterium labelled substrate **225-D** with catalyst **229a;** C) Enantioselective prototropic shift of deuterium labelled substrate **225-D** with catalyst **229a-D**; D) Enantioselective prototropic shift of unlabelled substrate **225** with catalyst **229a-D**.

To provide insight into the poor reactivity of bis-alkyl substrates such as **279** and **280**, another crossover experiment was performed with deuterated substrate **225-D** and unlabelled substrate **280** (Scheme 51A). The reaction was allowed to proceed until **225-D** was completely consumed. Upon isolation of the starting material (**280-D**), unlike in previous experiments, far lower levels of deuteration at α-position **a** were observed though the α-protons at position **b** showed similar levels of deuterium incorporation to that of **227-D** (Scheme 51A). The low level of deuterium incorporation at position **a** is a consequence of a reduction in acidity compared to the α-positions of substrate **225**. The π-bonding orbital and $\sigma^*_{c\text{-}o}$ of substrate **225** are likely to exhibit some overlap, this would improve hyperconjugation of the α-position and result in improved conjugate base (enolate) stability as well as increased charged density at the γ-position favouring γ-protonation, bis-alkyl substrate **280** would not experience these effects (Scheme 51A). It was therefore expected

that a stronger base would be required to remove the α-proton of **280** and would shift the equilibrium between the protonated and deprotonated species towards the enolate so that at any one time, more enolate would be present in the system improving the likelihood of transition through the turnover limiting step towards the conjugated product by increasing the overall ground state energy of the starting materials. This can be visualised by a reaction coordinate diagram as depicted in Scheme 51B. Unfortunately, the product **286** was not isolated from the reaction mixture and so it is unknown as to whether it contains a closer ratio of deuterium to that of **225-D**.



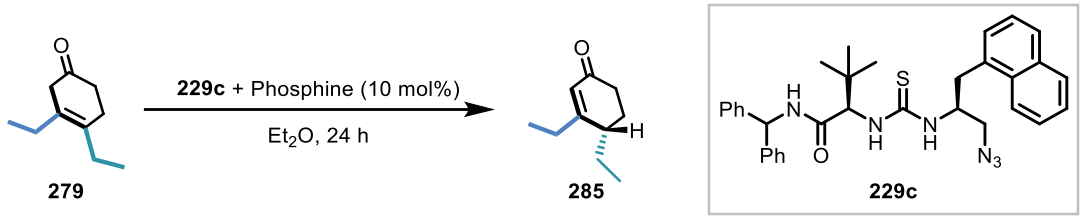
Scheme 51: A) Crossover experiment between deuterated substrate **225-D** and substrate **280**; B) Reaction coordinate diagram for the prototropic shift of substrate **276** with two bases of varying strength. S = Substrate; B = Base; B_2 = Stronger base; BH^+ = Protonated form of B or B_2; P = Product.

2.7 Reaction scope – substrates synthesised via Diels-Alder reaction

2.7.1 Re-optimisation of the reaction conditions

The deuterium labelling studies indicated that the prototropic shift reaction of bis-alkyl substrates such as **279** and **280** might benefit from catalysts with enhanced basicity. It has been shown that variation of the phosphine on BIMP catalysts has a significant effect on their basicity and that the prototropic shift's turnover limiting step is basicity

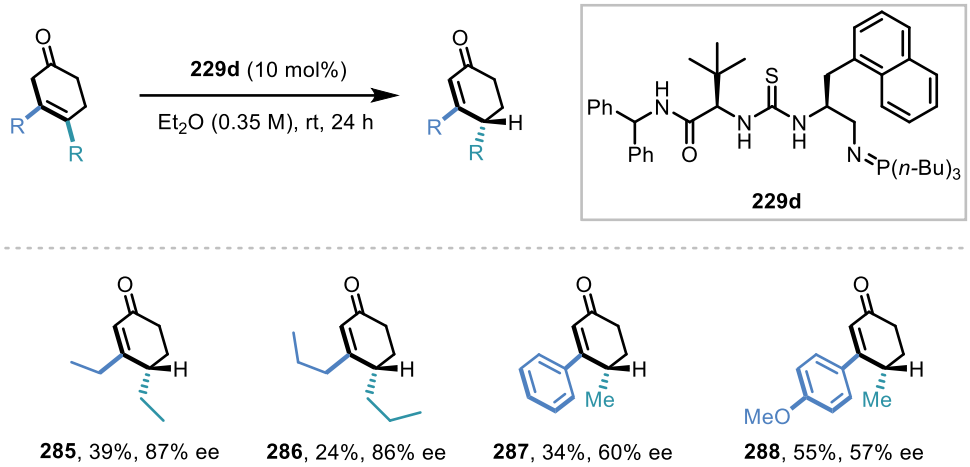
dependent.[77,124] If the iminophosphorane's basicity is too high, the proton will not be returned to the substrate, but if it is too low, then the α-proton will not be removed. As expected, the less basic iminophosphorane derived from triphenyl phosphine provided no increase in reaction rate and no product was obtained (Table 4, entry 2). Identical results were obtained with tris(4-chlorophenyl)phosphine and tris(4-trifluoromethylphenyl)phosphine (Table 4, entries 3 and 4). Dimethyl phenyl phosphine provided trace amounts of the isomeric product **285** in good enantiomeric excess demonstrating the importance of the chiral scaffold in the stereochemical outcome (Table 4, entry 5). The yield, however, was still poor. Tributyl phosphine was found to improve the yield (20%) under the standard reaction conditions whilst maintaining high levels of enantioselectivity (87% ee) (Table 4, entry 6). By using this same catalyst (**229c** + P(*n*-Bu)$_3$ = **229d**) at higher concentration, the desired α,β-unsaturated cyclohexenone **285** was obtained in 39% yield and 87% ee (Table 4, entry 7).



entry	*phosphine*	*temp / °C*	*conc / M*	*yield / %*	*ee / %*
1	$P(PMP)_3$	rt	0.10	0	N/A
2	PPh_3	rt	0.10	0	N/A
3	$P(p\text{-}ClC_6H_4)_3$	rt	0.10	0	N/A
4	$P(p\text{-}CF_3C_6H_4)_3$	rt	0.10	0	N/A
5	$PPhMe_2$	rt	0.10	trace	88
6	$P(n\text{-}Bu)_3$	rt	0.10	20	87
7	$P(n\text{-}Bu)_3$	rt	0.35	39	87

Table 4: Iminophosphorane screen for the prototropic shift of substrate **279**.

Having made good progress with the new iminophosphorane catalyst **229d** on one stubborn substrate (**279**), other products of the [Co]-catalysed Diels-Alder were trialled in the reaction, many of which had failed to perform with catalyst **229a**. The β,γ-dipropyl substrate **280** that was unresponsive to catalyst **229a** now gave the prototropic shift product in low yield of 24% and 86% ee (Scheme 52). The electronically modified substrates **282** and **283** that feature aromatic rings at the β-positions responded to the new catalyst to give reasonable yields (34% and 57%, respectively) of conjugated cyclohexenone and moderate levels of enantioselectivity (60% ee and 57%, ee respectively). While progress had been made with the new catalyst, there was clearly much scope for improvement.



Scheme 52: Reaction scope using catalyst **229d**.

2.7.2 Further catalyst development

In looking for clues on how to improve the new iminophosphorane catalyst, the ^{31}P NMR spectra of catalyst **229d** was carefully examined. The ^{31}P NMR spectrum of **229d** in C_6D_6 showed a significant broadening of the iminophosphorane peak at 29.99 ppm, suggesting some sort of interaction and exchange, possibly partial deprotonation of the catalyst's acidic thiourea motif forming a zwitterionic species (Figure 8A). Previous research in the group has shown zwitterion formation is plausible if the basicity of the iminophosphorane high enough to deprotonate the H-bond donor unit however, aggregates of the catalyst may also play a role in reducing catalytic activity.[78] The 1st generation catalysts (containing a 3,5-[bis(trifluoromethyl)phenyl]thiourea moiety) are known to dimerise on crystallisation and preliminary calculations suggested that a rapid equilibrium should exist between the monomer and dimer in solution. Within the dimeric species, interactions between the thiourea and iminophosphorane occur reducing the catalyst's ability to deprotonate while the monomer is thought to exist with the iminophosphorane preferentially protonated. To explore the possibility of zwitterion formation, the thiourea (pK_a = 21.1) was replaced with its less acidic counterpart, the urea (pK_a = 26.9). The new

urea-based scaffold was used in conjunction with the tributyl phosphine derived iminophosphorane (**229e**) and its ^{31}P NMR spectrum was studied.[140] **229e**'s ^{31}P NMR spectrum (C_6D_6) showed a much sharper iminophosphorane peak at 26.57 ppm than that of **229d**'s, the likely consequence of reduced interactions (either deprotonation and zwitterion formation or dimerization of the active catalyst) with the urea moiety (Figure 8B). To confirm that the iminophosphorane was indeed being formed in both cases, 10 equivalents of AcOH were added. Formation of the iminophosphorane salt was observed in both cases with the peak shifting to ≈ 57 ppm, confirming an identical iminophosphorane had been formed with each catalyst (Figure 8C and D).

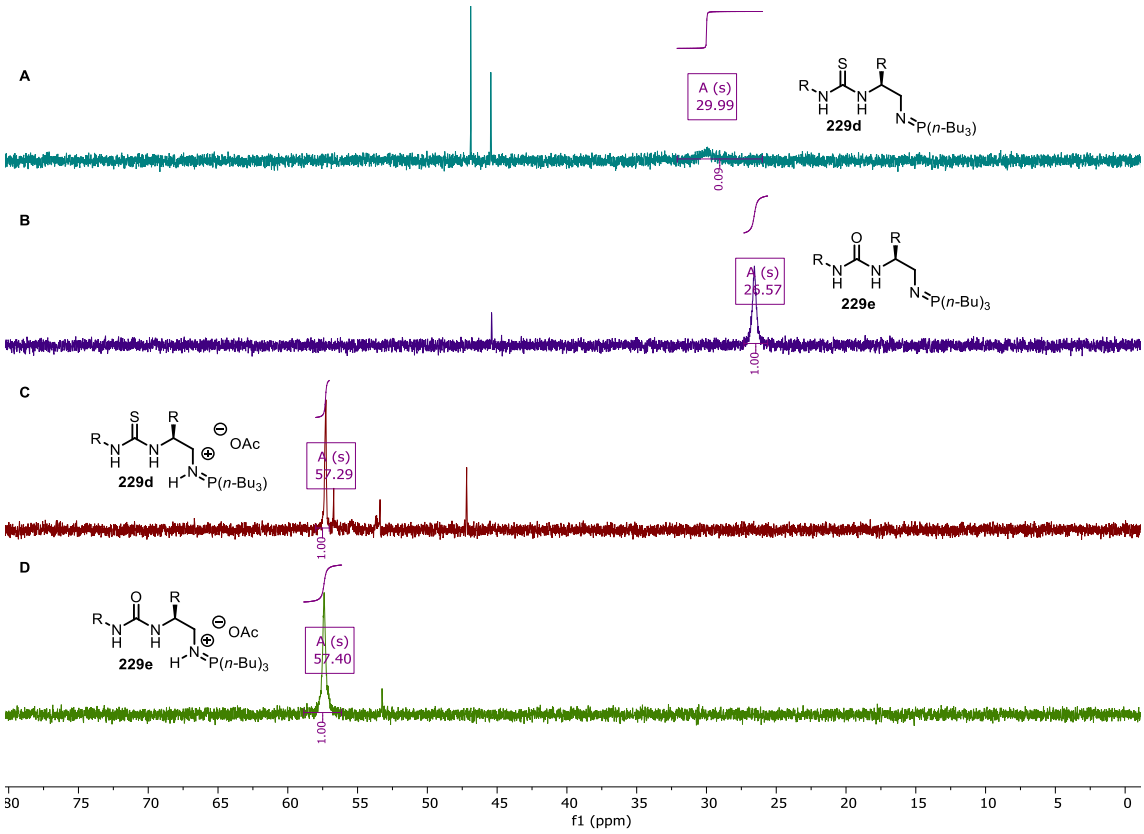
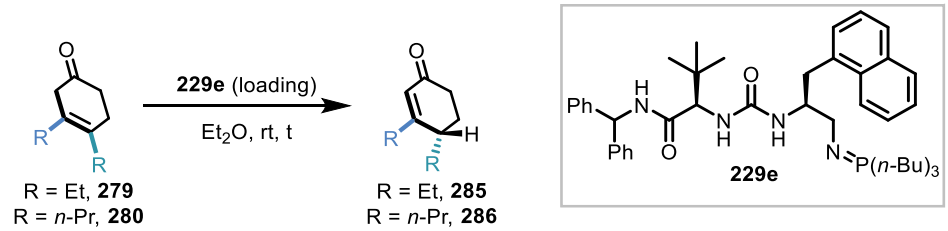


Figure 8: ^{31}P NMR spectra of: A) Catalyst **229d**; B) Catalyst **229e**; C) Protonated catalyst **229d**; D) Protonated catalyst **229e** in C_6D_6.

The new urea-based catalyst (**229e**) was tested under the original reaction conditions, and found to significantly outperform the previous catalyst (**229d**) with the product now being obtained in 45% yield and impressive 98% ee (Table 5, entry 1) as opposed to 20% yield and 87% ee with catalyst **229d** (Table 4, entry 6). Increasing the concentration to 0.20 M improved things further and the cyclohexenone (**285**) was now obtained in 65% yield and 97% ee (Table 5, entry 2). Further increasing the concentration to 0.40 M offered no advantage, and although the enantiomeric excess remained the same (97% ee), the yield was lower (32%) (Table 5, entry 3). Raising the temperature to 40 °C had a similar effect (45%, 98% ee) (Table 5, entry 4). Substrate **280** was trialled under the best conditions (Table 5, entry 2) which significantly depreciated the yield though the enantioselectivity remained consistent (39%, 97% ee) (Table 5, entry 6). The conditions were to re-optimised on the new substrate. It was beneficial to increase the catalyst loading to 15 mol% whilst keeping the concentration at 0.20 M, resulting in 50% yield and 97% ee (Table 5, entry 8). Repeating the reaction with substrate **279** showed that the conditions could be applied to both substrates (Table 5, entries 8 and 5).

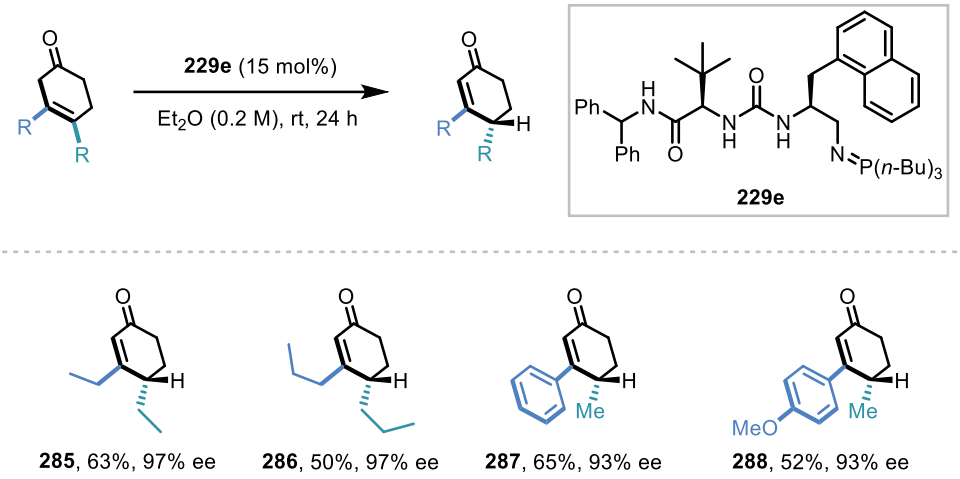


entry	*R*	*loading / mol%*	*Temp / °C*	*time / h*	*conc / M*	*yield / %*	*ee / %*
1	Et	10	rt	24	0.10	45	98
2	Et	10	rt	24	0.20	65	98
3	Et	10	rt	24	0.40	32	97
4	Et	10	40	24	0.20	45	98
5	Et	15	rt	24	0.15	63	97
6	Pr	10	rt	24	0.20	39	97
7	Pr	10	rt	48	0.35	42	91
8	Pr	15	rt	24	0.20	50	97
9	Pr	20	rt	24	0.20	36	97
10	Et	20	rt	24	0.20	63	97

Table 5: Conditions screen for the BIMP-catalysed enantioselective prototropic shift of substrates **279** and **280**.

2.7.3 Further scope expansion

The improved reaction conditions (Table 5, entry 8) and new catalyst (**229e**) were tested on substrates **282** and **283**. The results were pleasing (Scheme 53). Substrate **282**, incorporating a β-phenyl group behaved well under the new conditions and the desired cyclohexenone (**287**) was obtained in 63% yield and impressive 95% ee, a great improvement on the previous best 34% yield and 60% ee with catalyst **229d** (Scheme 52). Likewise, **283** incorporating a *para*-methoxy group on the aromatic ring performed acceptably well providing **288** in 52% yield and 93% ee.



Scheme 53: Substrate scope using catalyst **229e**.

To compare the urea catalyst (**229e**) to its previous thiourea iteration (**229d**), each BIMP was applied to substrate **225** for a period of 2 h. Interestingly, the α,β-unsaturated cyclohexenone could be obtained in 86% yield and 97% ee after the short period of time with catalyst **225e**. To compare, **225** was subjected to identical conditions with catalyst **229a** over the same time period. After the shortened duration of time, enone **227** was only obtained in 57% yield. This result is as expected, the increased basicity of the iminophosphorane shifts the rapid reversible equilibrium towards the deprotonated enolate. This means the probability of transitioning through the turnover limiting step to product is increased and more product is formed in a shorter time span.

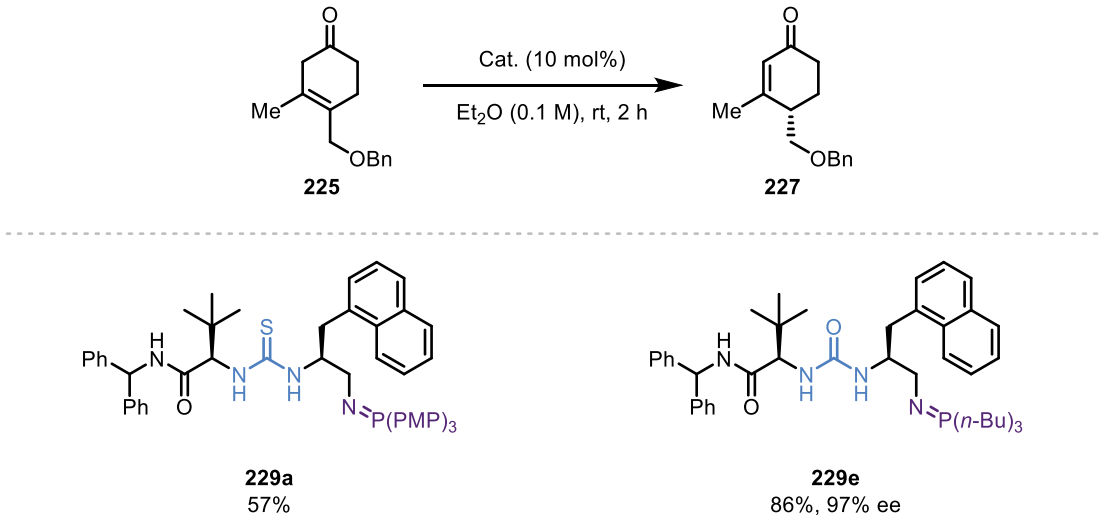


Figure 9: Rate comparison for the enantioselective prototropic shift of substrate **225** with catalyst **229a** and **229e**.

2.8 Computational studies

The work in this section was carried out by Professor Robert Paton and Dr. Luis Simón and has been included for completeness. Further details can be found in the published work.[141]

Having developed a highly enantioselective BIMP-catalysed [1,3]-prototropic shift of β,γ-unsaturated cyclohexenones, the finer details of the reaction mechanism still remained unknown. In particular, an explanation for the stereochemical outcome of the reaction in terms of transition state models was required. To achieve this goal, computational studies were carried by Professor Robert Paton and Dr. Luis Simón. Firstly, their study provided a detailed analysis of the reaction mechanism depicted in Figure 10 with a Gibbs energy profile of substrate **225** in the presence of catalyst **229a**. It was shown that the energy of the transition state (TS) for γ-protonation is highest, identifying this process as the rate- and enantiodetermining step. This is in keeping with our labelling studies carried out in section **2.6**. A model for the transition state shows that the BIMP catalyst grasps the substrate at the oxygen atom with dual H-bonding interactions from both of the thiourea's N-H protons. Protonation then occurs irreversibly, going on to form the (*S*)-enantiomer which is favoured

by 2.2 kcal/mol. This is equivalent to a computed 95% ee. The computations also predicted that the catalyst:dienolate ion-pair may reversibly dissociate prior to the irreversible protonation, and that reversible deprotonation of the α-position is likely to occur. This is consistent with the data obtained via labelling studies in section **2.6**.

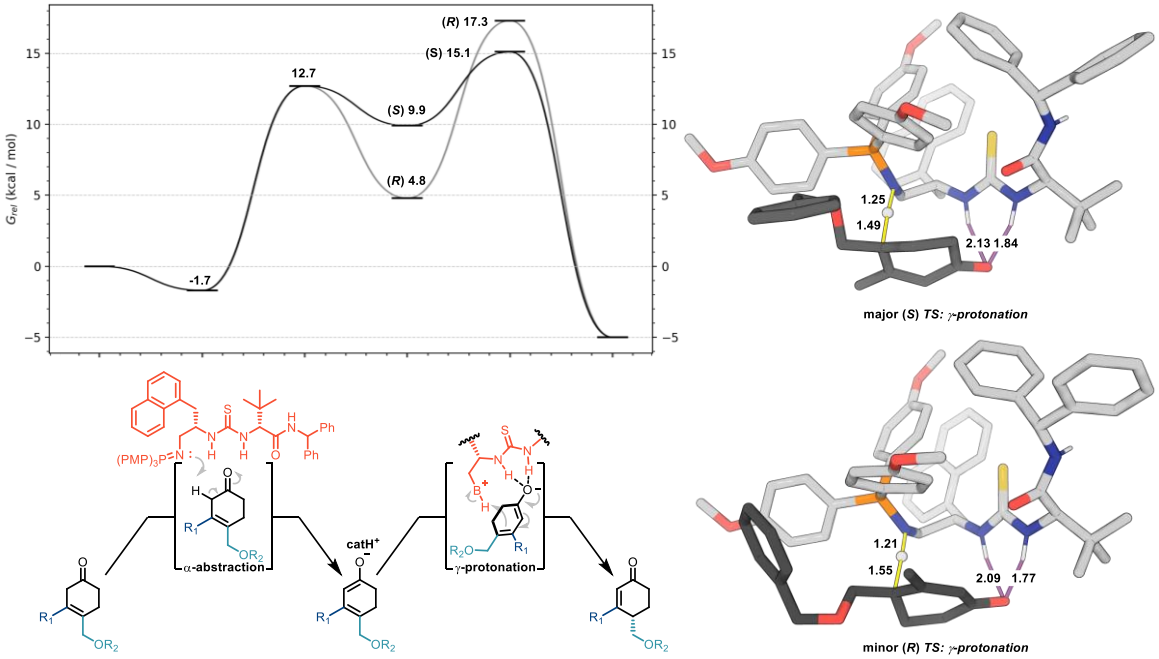


Figure 10: A) Gibbs energy profile for the BIMP-catalysed [1,3]-prototropic shift of substrate **225**; B) Transition structures for enantioselective protonation of the extended enolate of **225** with BIMP catalyst **229a**.[a]The most stable major and minor transition structures in the enantiodetermining step are shown (bond lengths in Å).

Interestingly, Paton and Simón showed that intramolecular dispersion interactions occur between the naphthyl ring and one of the PMP groups favouring the conformation in Figure 10. The benzhydryl group is also oriented to avoid steric clash with the proximal iminophosphorane. Despite this favourable interaction between the naphthyl and PMP groups, it was shown that the main contributor to the enantioselectivity was the conformation of the substrate. The (*S*)-TS has lower levels of torsional and 1,3-allylic strain ($A^{1,3}$-strain) whereas the (*R*)-TS has greater eclipsing interactions in the ring (Figure 11). The orientation of the alkoxy group in this conformation also raises its $A^{1,3}$-strain, and both of these lead to a computed substrate distortion energy that is 1.6 kcal/mol greater than that of the (*S*)-TS.

This may also provide an explanation as to why replacing the $P(PMP)_3$ phosphine with $P(n\text{-}Bu)_3$ (**229e**) has little effect on enantioselectivity.

As well as the cyclohexenone ring's conformation playing an important role in the outcome, computational studies suggest that the γ-substituent is also important, adopting different conformations to avoid clash with the P-substituents. This would suggest that a flexible γ-substituent is likely to be favourable, which may also explain the slight reduction in selectivity with substrates **282** and **283** which feature γ-methyl groups and provide conjugated products in 93% ee. The findings also show that the β-substituent is not vital for enantioselectivity though its omittance reduces allylic strain in the TS, hence Paton and Simón computed a reduced $\Delta\Delta G^{\ddagger}$ of 1.9 kcal/mol (92% ee) for substrate **289** (substrate **289** will be covered in more detail in section **2.9.2**).

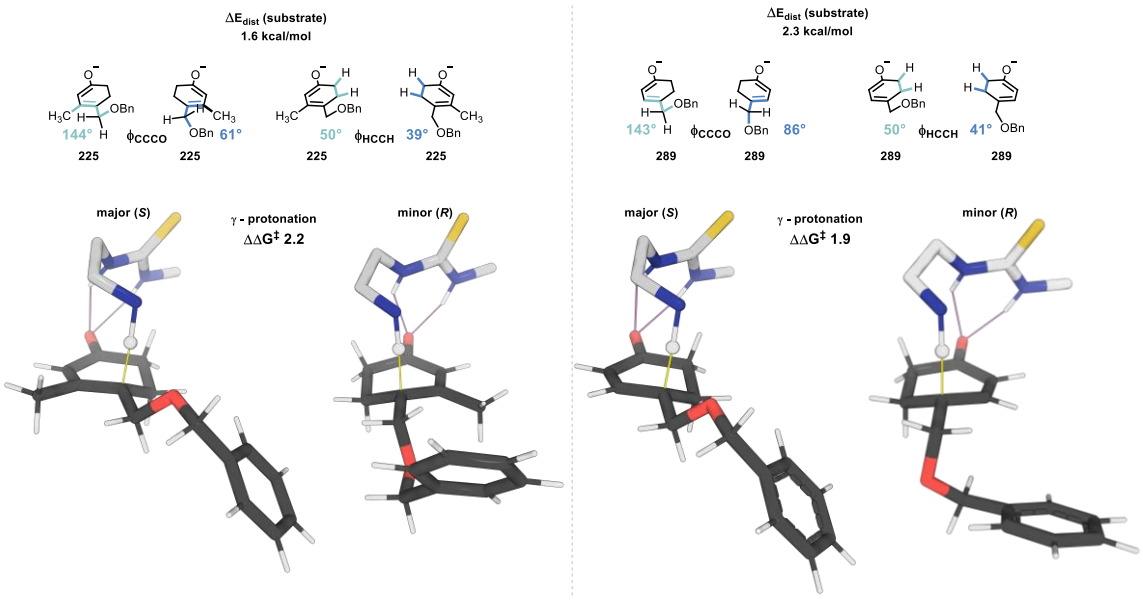
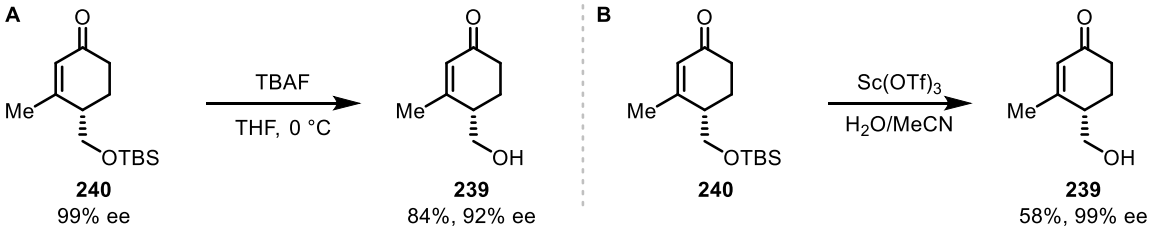


Figure 11: Enantioselectivity of the [1,3]-prototropic shift is controlled by the distortion energy of substrate **225** and **289**.

2.9 Derivatisation and synthesis of (−)-reserpine and (−)-penitrem D precursor

2.9.1 Derivatisation of enantioenriched cyclohexenones

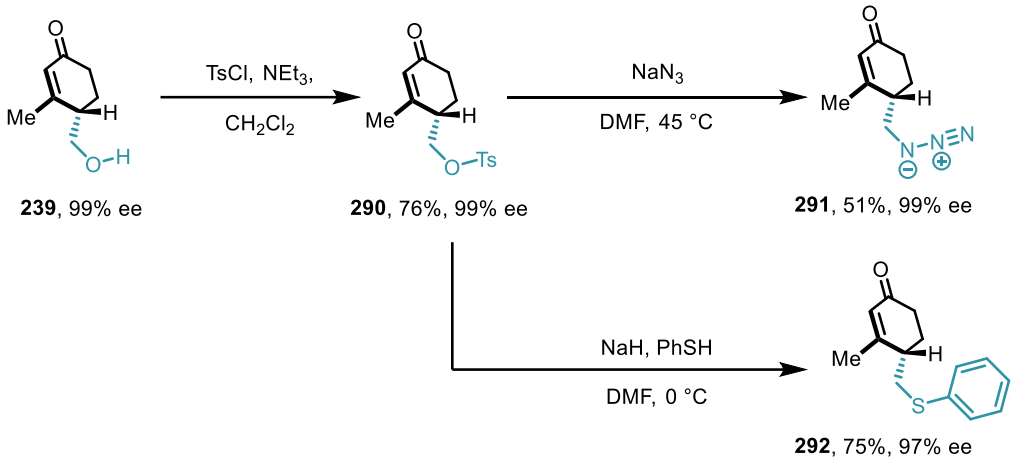
After a thorough investigation into the mechanism and origin of enantioselectivity, the synthetic utility of the products was then showcased. The alcohol **239** presents itself as an ideal substrate for derivatisation and elaboration into 'drug-like' molecules and natural products. Our plan was to convert TBS protected product **240**, that had been prepared by means of a BIMP-catalysed [1,3]-prototropic shift (see section **2.5.1**) in high yield (90%) and optical purity (99% ee), into alcohol **239**. TBAF deprotection removed the TBS protecting group in good yield (84%) but caused a high degree of racemisation, leading to 92% ee in the product (**239**) compared to 99% ee in the starting material (**240**). This was thought to be a consequence of TBAF's Brønsted basicity affecting γ-position integrity. Following a procedure by Oriyama *et al.* that uses a catalytic amount of $Sc(OTf)_3$, the TBS group could be removed to provide the optically pure alcohol (**239**) in moderate yield of 58%.[142]



Scheme 54: A) Deprotection of substrate **240** using TBAF; B) Deprotection of substrate **240** using catalytic $Sc(OTf)_3$.

With a significant amount of enantiopure **239** in hand, its derivatisation possibilities were examined (Scheme 55). Tosylation of the free hydroxyl afforded, in high yield and without loss of enantiopurity (99% ee), **290** that was expected to be an extremely versatile intermediate in the preparation of a diverse range of molecules. **290** underwent slow

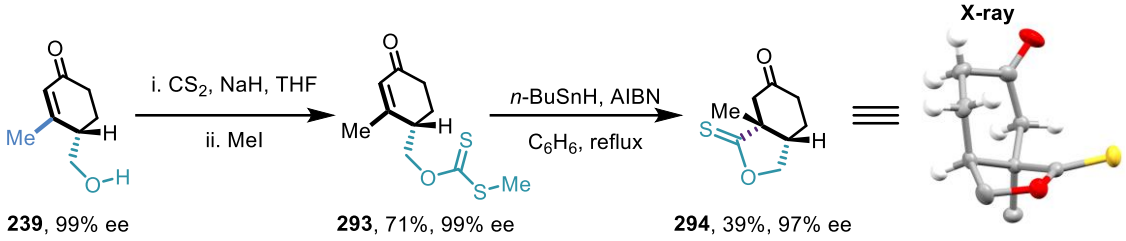
decomposition if left at room temperature; however, storage at –20 °C prevented this allowing its convenient use in a medley of nucleophilic substitution reactions. As examples of common elaborations of tosylates, **290** was converted into an azide and a sulfide. Addition of sodium azide to **290** at 45 °C rapidly provided **291** in 99% ee though in moderate, but un-optimised yield of 51%. Addition of sodium thiophenolate (formed by addition of sodium hydride to thiophenol) to **290** afforded the sulfide **292** with minimal loss of enantiopurity (97% ee) and in excellent yield (75%).



Scheme 55: Derivatisation of enantioenriched α,β-unsaturated cyclohexenone **239**.

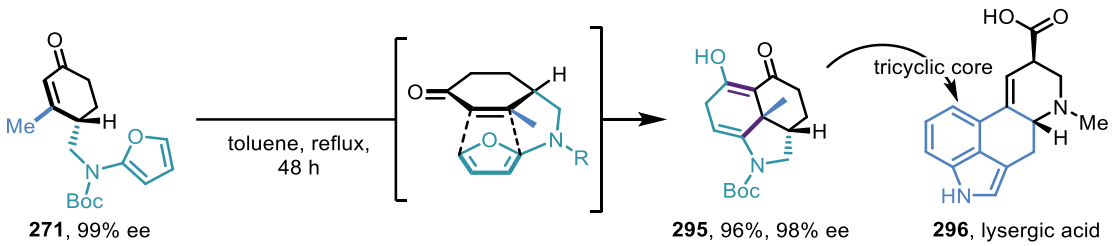
The enantioenriched cyclohexenone systems were prone to undergo cyclisations to provide interesting [6-5]-fused ring systems via one or two electron processes. To explore this idea, the free hydroxyl group of **239** was smoothly transformed into enantiopure xanthate ester **293** (99% ee) through addition to CS_2 followed by methyl iodide (Scheme 56). In the presence of a radical initiator such as AIBN and a propagator (*e.g. n*-BuSnH), favourable 5-exo-trig cyclisations are known to occur between the carbon of xanthate esters and proximal enone systems.[143] In the case of **293**, a reaction of this nature would lead to the formation of a bicyclic thionolactone. Under the reaction conditions, the cyclisation worked well on our system and the enantioenriched fused bicycle (**294**) was obtained in modest yield of 39%

and in an impressive 97% ee. This product was recrystallised to >99% ee and an X-ray crystal structure was obtained to provide confirmation of absolute stereochemical configuration.



Scheme 56: Synthesis of thionolactone **294** from xanthate **293** and single-crystal X-ray structure of **294** confirming the absolute stereochemical configuration.

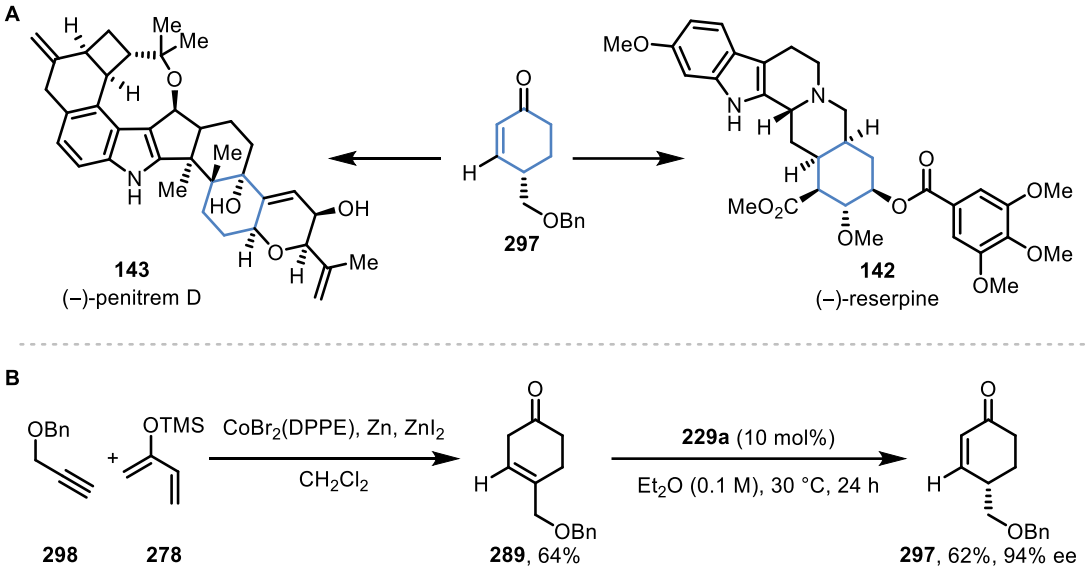
To complete one of the goals mentioned in section **2.5.2**, the intramolecular furan Diels-Alder reaction of **271** to create a complex tricyclic scaffold of the type present in natural products such as lysergic acid (**296**), was investigated (Scheme 57).[76] Previous work in the group had demonstrated that the reaction could be carried out by prolonged heating of the cyclohexenone in toluene and later on, a similar transformation was used to forge the tricyclic core of (−)-himalensine A.[91,132,138] After careful distillation of the toluene and re-purification of the enone (**271**), the cyclisation progressed to afford the complex cyclic scaffold (**295**) in almost quantitative yield and an impressive ee of 98% (Scheme 57).



Scheme 57: Intramolecular Diels-Alder reaction of **271** to provide tricyclic compound **295** analogous to lysergic acid's core.*Initial studies into this transformation were carried out by John Ward and later Eve Carter, the example depicted is an improved repeat.[132,138]

2.9.2 Synthesis of a key building block in the synthesis of (−)-reserpine and (−)-penitrem D

Although the synthetic relevance of the products had been demonstrated through derivatisation, the transformation's use in total synthesis had yet to be established. To prove the BIMP catalysed enantioselective prototropic shift's applicability to total synthesis, the construction of a key intermediate was undertaken. A brief survey of natural products incorporating similar motifs to our enantioenriched enones revealed that, both (−)-reserpine (**142**) and (−)-penitrem D (**143**)**,** with their complex frameworks, could be targeted (Scheme 58A). (−)-Reserpine has been previously synthesised by Stork *et al.* in 2005, and (−)-penitrem D by Smith *et al*.[98,99] In both cases, compound **297** contributes significantly to the introduction of stereochemical information contained within the complex molecular targets. α,β-Unsaturated enone **297** has previously been prepared in five steps from dihydroresorcinol methylether[144] and in nine steps from (−)-(*R*)-pantolactone and propenoyl chloride.[145] We recognised that the synthesis of **297** could be reduced to two steps using the Hilt group's Cobalt-catalysed Diels-Alder reaction followed by our enantioselective prototropic shift.[139] The preliminary Diels-Alder reaction progressed in a good yield of 64%, providing us with a substrate primed for use in the enantioselective prototropic shift (Scheme 58B). Pleasingly, the new substrate (**289**) performed well under catalytic prototropic shift conditions using catalyst **229a** at the slightly raised temperature of 30 °C for improved enantioselectivity, and the target building block could be obtained in 62% yield and 94% ee (Scheme 58B).



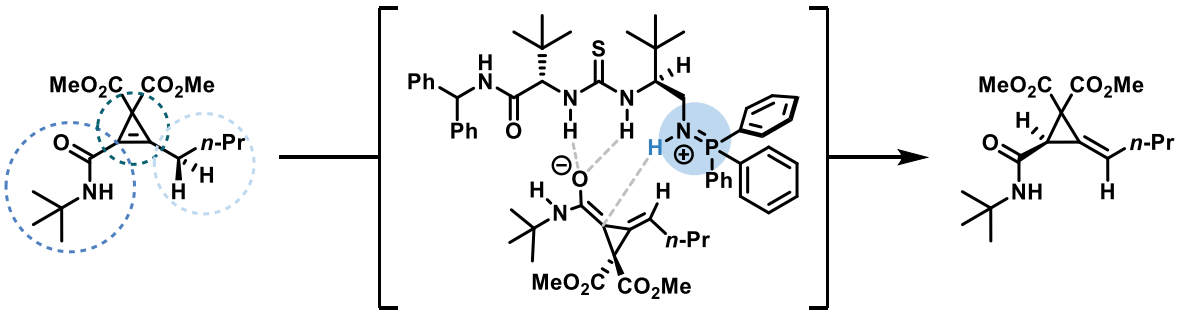
Scheme 58: A) Smith's synthesis of (−)-penitrem D (**143**) and Stork's synthesis of (−)-reserpine (**142**) using compound **297** as a key building block; B) Synthesis of compound **297** via [Co]-catalysed Diels-Alder and BIMP-catalysed enantioselective prototropic shift.

2.10 Conclusions and further work

In conclusion, the development of a synthetically relevant enantioselective prototropic shift has been achieved using bifunctional iminophosphorane catalysis.[141] The methodology overcomes problems associated with previous methods, resulting in a diverse range of enantioenriched products which have been shown to be primed for further downstream derivatisation. To complement the technique, detailed computational and deuterium labelling studies were carried out. In future work, problems encountered, but not resolved, during the project could be overcome. Section **2.3.1** outlined the initial studies into a prototropic shift Michael cascade reaction, however, the reaction failed to progress with the current BIMP catalysts. Applying the knowledge gained throughout the project to the tethered nucleophile substrates may lead to the development of such a reaction. By investigating and fine-tuning the reaction conditions and basicity of the catalyst, substrates prone to elimination may also find use in the reaction broadening the reaction scope and allowing access to more elaborate cyclohexenone derivatives.

3. The Development of a Strain Relieving Enantioselective Cyclopropene Deconjugation

3.1 Chapter overview



Scheme 59: A BIMP-catalysed enantioselective deconjugation of cyclopropenes.

This chapter describes the development of a novel synthetic approach towards enantioenriched cyclopropanes. The method relies on the relief of the high levels of strain energy present in cyclopropene rings by deconjugating their internal double bond. The reaction proceeds smoothly producing alkylidenecyclopropanes (ACPs) with extremely high levels of enantiocontrol (up to 99% ee) and is also high yielding (up to >99%) within a short time frame.[146] By tuning the basicity of the iminophosphorane, a transformation amenable to the synthesis of a range of cyclopropene structures was accomplished, independent of the electron withdrawing carbonyl functionality. By modifying the BIMP catalyst's scaffold, reactive ketone-bearing cyclopropenes could be used in the reaction and finally, the method was applied to the synthesis of a notable pyrethroid insecticide and multiple insecticide cores.

3.2 Introduction

3.2.1 Biological and medicinal importance of cyclopropanes

The smallest possible carbocycles, cyclopropanes and cyclopropenes, are of high importance to synthetic organic chemistry. Cyclopropane rings have been incorporated into pharmaceuticals since the 1960s, for example in the monoamine oxidase (MAO) inhibitor tranylcypromine (**299**) which is used as a treatment for depression (Figure 12A).[147] Tranylcypromine is administered as a racemic mixture despite the differing bio-activity of the two enantiomers.[148]

The cyclopropane ring, with its unique structure, provides a very interesting platform for medicinal chemists.[149] The planarity of the cyclopropane carbons, the necessarily eclipsed C–H bonds, the unusual hybridisation character and the high bond strengths leads to valuable pharmacokinetic properties.[150–153] For example, the planarity of the ring can reduce lipophilicity making it a suitable bioisostere of the phenyl group, while the eclipsing protons, or equivalent substituents, disrupt stacking leading to poorer crystal packing that can improve aqueous solubility.[154] The cyclopropane ring's C−H bond (106 kcal/mol) is comparatively stronger than those of the methyl group in ethane (101 kcal/mol) and is less susceptible to metabolic oxidation and thus can improve the pharmacokinetic properties of drug candidates.[151] An example of how the introduction of the cyclopropyl group can alter pharmacokinetic properties is given by the adenosine A_{2B} receptor antagonist **300**. The adenosine A_{2B} receptor plays a pivotal role in the release of inflammatory mediators from mast cells and airway epithelial cells and antagonists are expected to be effective in the treatment of asthma. Eastwood *et al.* demonstrated that the replacement of **300**'s acetamide

with a cyclopropylamide (**301**) improved potency, increased half-life ($t_{1/2}$) and led to an overall improvement in the compound's pharmacokinetic profile.[155]

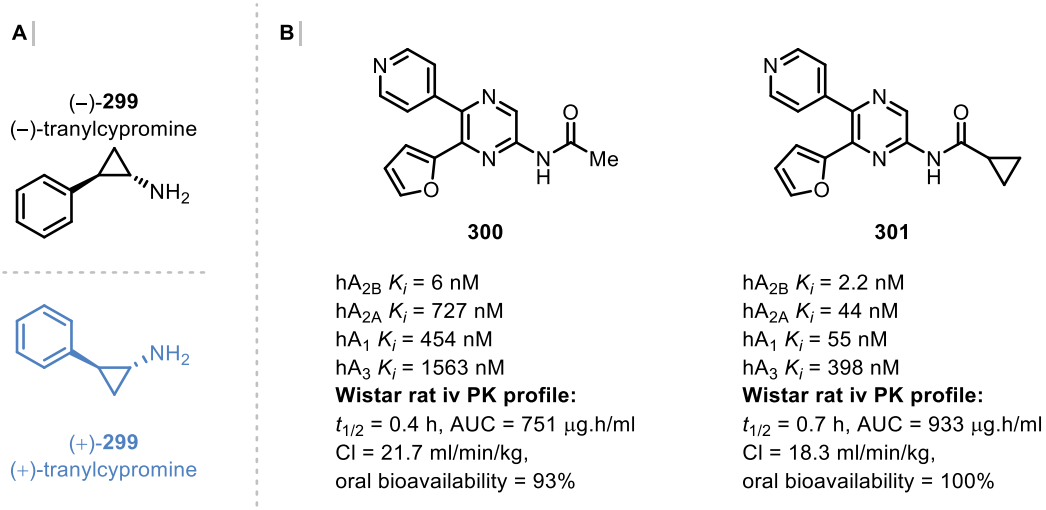


Figure 12: A) The enantiomers of tranylcypromine, a monoamine oxidase inhibitor first approved for use in the USA in 1961; B) Modification of pharmacokinetic properties by the replacement of a methyl group with a cyclopropane.

In addition to their clear utility in the pharmaceutical industry, cyclopropanes are prominent in agrochemicals. Cyclopropane containing pyrethrins, a class of compounds obtained from the plant *Chrysanthemum cinerariifolium*, have been used as insecticides for thousands of years. They kill insects by delaying the closure of voltage-gated sodium channels which are present in the nerve cells.[156] The low absorption by mammals as well as low mammalian nerve sensitivity, reduces the toxic effects of these compounds in comparison with those experienced by insects, thus achieving a safety margin. Unfortunately, they can be toxic to some aquatic organisms.[156–158]

Cyclopropane containing pyrethroids (synthetic pyrethrin derivatives) may carry up to three stereocentres and hence exist as multiple enantiomers and diastereomers.[159] Not all the enantiomers and diastereomers of these compounds are potent insecticides, for example, only the (*R*,*R*) and (*S*,*R*)-enantiomers of permethrin (**302**) exhibit insecticidal activity (Figure 13).[159] Not only can they lack the desired potency, but they can also be

more toxic to other species and degrade more slowly in the environment.[160] Therefore, it is clear that cost-effective methods for their enantioselective syntheses are required.

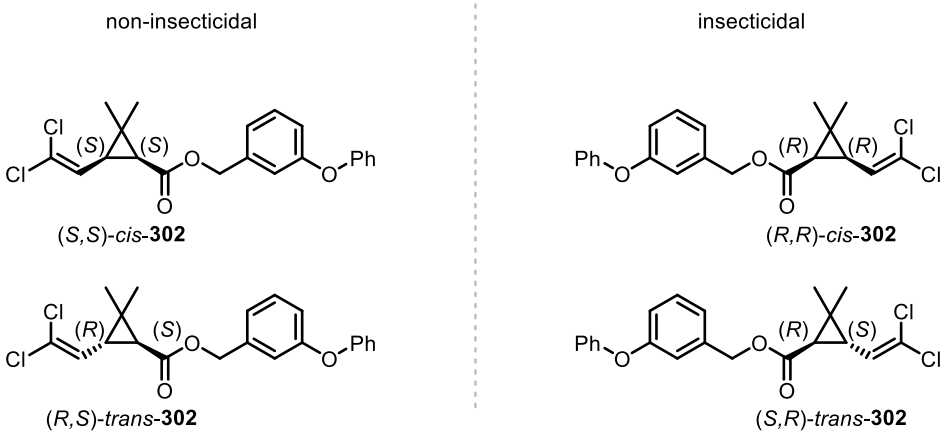
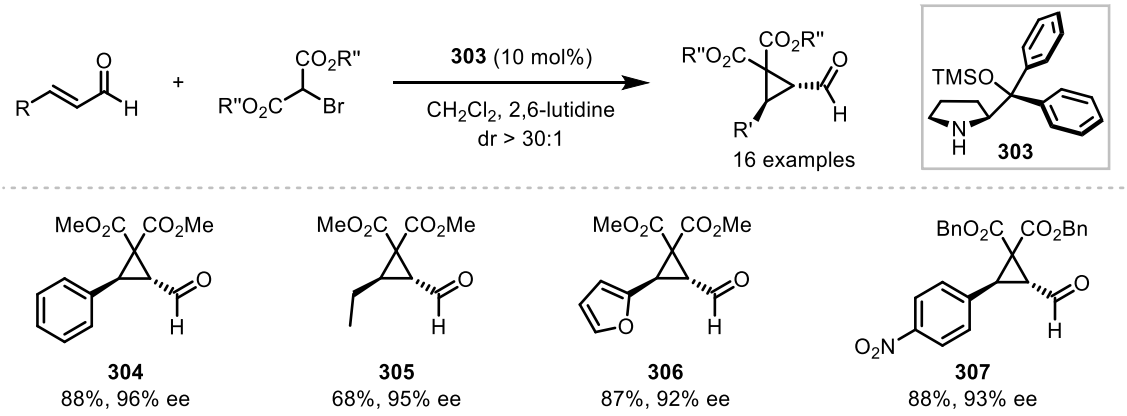


Figure 13: Differences in the insecticidal properties between the enantiomers of the permethrin diastereomers.

3.2.2 Organocatalytic methods for the synthesis of chiral cyclopropanes

Organocatalytic methods to synthesise optically active cyclopropanes are uncommon and few directly modify the carbon skeleton. Many of these methods exploit Michael additions that form reactive enolates that can close the cyclopropane ring in an enantioselective fashion. This strategy was successfully executed by Wang *et al.* in 2007, where a cascade Michael-alkylation process utilising iminium-enamine catalysis was used to create chiral cyclopropylaldehydes (**304 - 307**) with high levels of enantioenrichment of up to 98% ee and, generally, as single diastereomers (Scheme 60).[161] The authors described unintended cyclopropane ring opening during the reaction, though they were able to overcome this by tuning the base. In 2019 Takikawa *et al.* applied the method developed by Wang to their synthesis of salinipostin A, a marine cyclic enol-phosphotriester isolated from *Salinispora sp*, a genus of bacteria belonging to the *Micromonosporaceae* family.[162] Having set the stereocentre using Wang's approach, the cyclopropane's ring strain could be manipulated and the ring could be opened to introduce a new hydroxyl group whilst maintaining the stereochemical information. A similar method, with the same catalyst, was used by Rios *et*

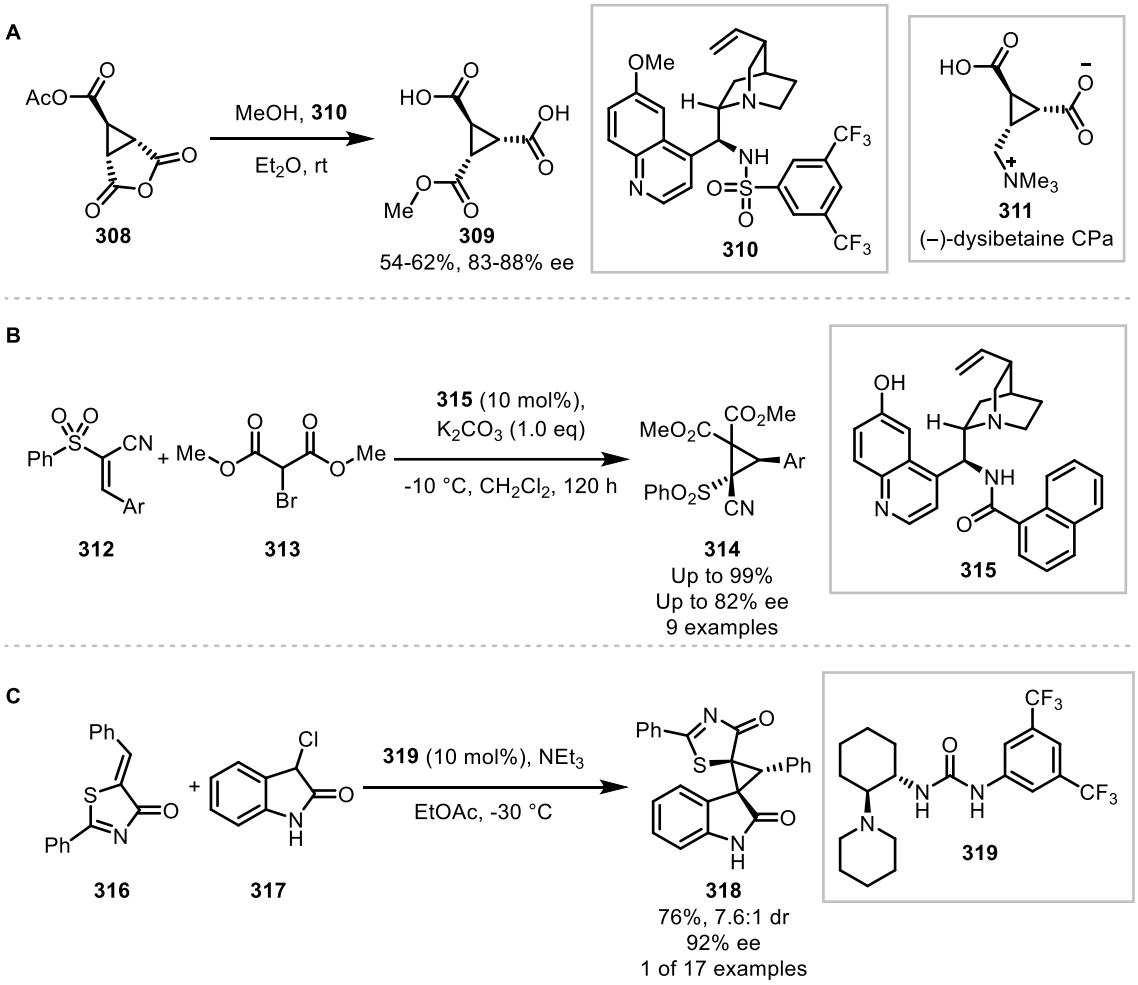
al. in 2016. They showed that acidic benzyl chlorides could be used as nucleophiles for the Michael-alkylation cascade and in doing so were able to generate three stereocentres about the ring in a single step in up to 99% yield and 99% ee.[163]



Scheme 60: Cascade Michael-alkylation process utilising iminium-enamine catalysis to create chiral cyclopropylaldehydes reported by Wang *et al.*

Brønsted base catalysis has also played an important role in the construction of chiral cyclopropanes. The first example was reported by Oikawa *et al.* in 2013 as part of their enantioselective total synthesis of (−)-dysibetaine CPa (**311**) (Scheme 61A).[164] In this desymmetrisation approach, a [3,5]-fused anhydride ring (**308**) was synthesised and a bifunctional quinine-sulfonamide catalyst (**310**) was used to catalyse an asymmetric methanol mediated anhydride ring opening in 83-88% ee. Subsequently, Cobb reported the use of catalyst **315** to accomplish an enantioselective Michael addition to conjugated cyanosulfones and subsequent intramolecular alkylation to furnish highly substituted cyclopropane scaffolds in enantiomeric excesses of up to 96% following recrystallisation (Scheme 61B).[165] The authors converted their enantioenriched cyclopropanes into δ^3-amino acid precursors and 3-azabicyclo[3.1.0]hexane systems present in a variety of natural products. A modification of Takemoto's catalyst (**319**) has been used by the Sheng group to synthesise highly functionalised spiro-thiazolone cyclopropane-oxindoles (**318**) via a

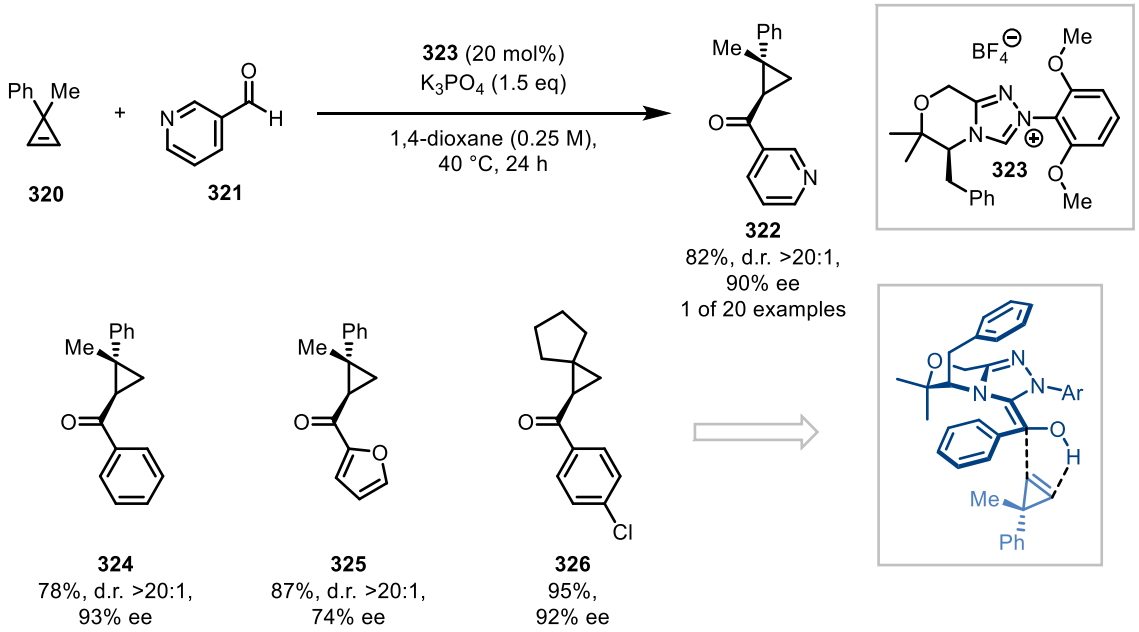
Michael addition and cascade intramolecular alkylation.[166] The complex scaffolds were obtained in high enantioselectivities (Scheme 61C).



Scheme 61: A) Oikawa's Brønsted base catalysed anhydride desymmetrisation to form the chiral cyclopropane core of (−)-dysibetaine CPa (**311**); B) Cobb's enantioseletive Michael-cascade to form highly substituted cyclopropane derivatives; C) Sheng's synthesis of highly functionalised spiro-thiazolone–cyclopropane-oxindoles using catalyst **319**.

Glorius *et al.* showed that skeletal enantioselective carbonylation of a symmetrical cyclopropene can be achieved by *N*-heterocyclic carbene (NHC) catalysis (Scheme 62).[167] Carbonylation of the double bond was realised with almost complete diastereoselectivity and enantioselectivity of up to 96% ee and tolerated a variety of cyclopropenes and aldehydes. The authors proposed a model using dominant Breslow intermediates calculated by Houk

and Yates in which the *E*-geometry dominates, to explain the asymmetric induction and rationalise the design of their new catalyst scaffold (**323**) (Scheme 62).[168,169]



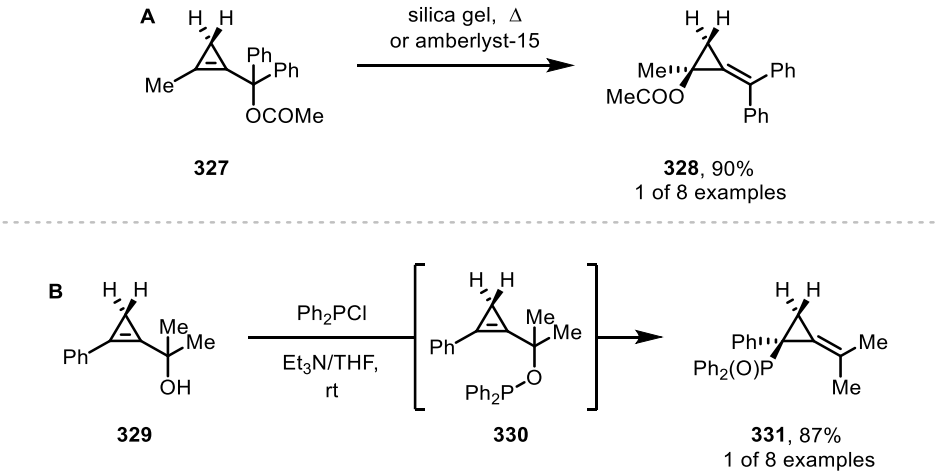
Scheme 62: NHC-catalysed enantioselective carbonylation of cyclopropenes by Glorius *et al.*

3.2.3 Previous work and project aims

The majority of the few enantioselective organocatalytic approaches to the construction of cyclopropanes available require multiple, specific reagents which can be limiting to the reaction scope. From the outset of the project, the development of an enabling methodology for the synthesis of enantioenriched cyclopropanes using the superbasic BIMP catalytic platform that would be applicable to a broad range of substrates was of key importance.

In chapter two, a molecule's propensity to conjugate was successfully exploited in our enantioselective BIMP-catalysed [1,3]-prototropic shifts of β,γ-unsaturated cyclohexenones. Theoretically, a similar type of enantioselective prototropic shift could be used to access chiral methylene / alkylidenecyclopropanes which can be readily reduced to their cyclopropane counterparts.[146,170–173] Previous studies have

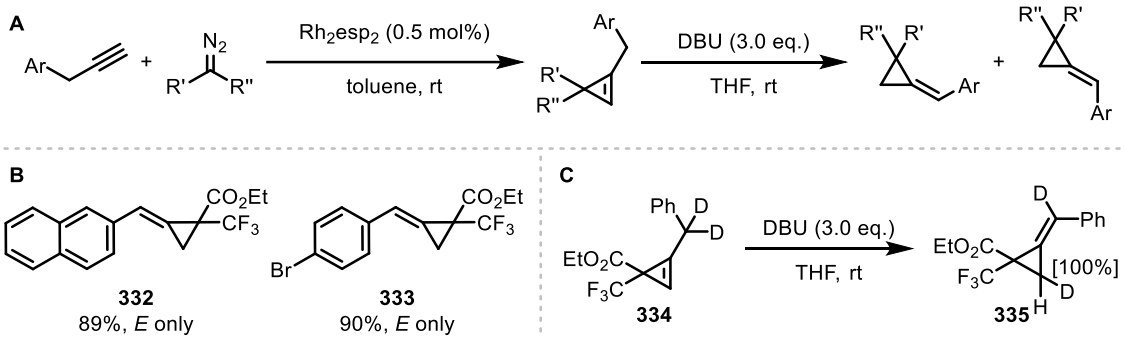
demonstrated the lability of the cyclopropene double bond due to its heightened strain energy in comparison with the product alkylidene cyclopropanes (10.3 kcal/mol).[174] In 2007 Marek *et al.* showed that cyclopropenes could rapidly undergo [3,3]- and [2,3]-sigmatropic rearrangements to provide heteroatom-substituted alkylidene cyclopropanes (Scheme 63).[175] The reaction occurred with both cyclopropenyl acetates (**327**) ([3,3]) and cyclopropenyldiphenylphosphinites (**330**) ([2,3]). In the case of cyclopropenyl acetates, the reaction proceeded upon filtration through silica gel, heating in CH_2Cl_2 or by the addition of amberlyst® 15. While for cyclopropenyldiphenylphosphinites the reaction proceeded upon formation of the substrate.



Scheme 63: [3,3]- and [2,3]-sigmatropic rearrangements od cyclopropenes.

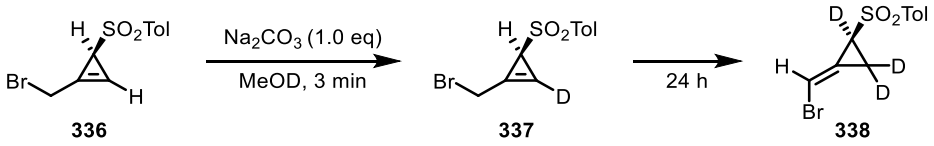
More relevant to our work on prototropic shifts, Shi *et al.* have demonstrated the use of super-stoichiometric DBU (**62**) to mediate a double bond isomerisation of aryl cyclopropenes (Scheme 64B).[146,176] In this case, the movement of the double bond is driven by conjugation with the aromatic group in much the same way as the [1,3]-prototropic shift of β,γ-cyclohexenones. Examples omitting the aromatic ring failed to react. The authors reported excellent yields of up to 96% on a range of substrates with remarkable *E/Z*-selectivity. The substrates could be synthesised by the carbene addition

to terminal aryl-alkynes (Scheme 64A) and the mechanistic pathway was explored through deuterium labelling studies which confirmed migration of the benzylic deuterium to the cyclopropane ring (Scheme 64C).



Scheme 64: A) Synthesis of cyclopropenes followed by DBU (**62**) mediated conjugation; B) Scope examples; C) Deuterium labelling studies.*10 examples.

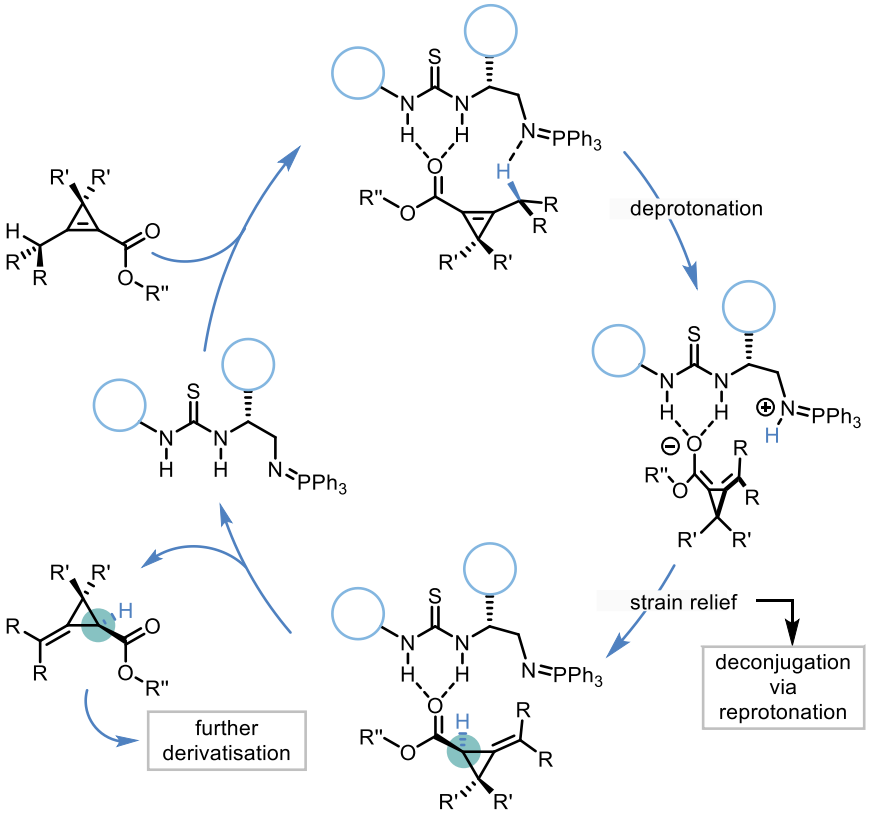
A similar transformation can also be carried out on 2-bromomethyl-2-cyclopropenyl 4-tolyl sulfones (**336**).[177] Na_2CO_3 moves the proton from the external to the internal position relieving strain. The enantiopurity of the cyclopropene is also maintained in the reaction despite deuterium labelling studies suggesting that exchange can occur α- to the sulfone. When enantioenriched **336** (91% ee) is reacted in the presence of 1.0 eq of Na_2CO_3 and MeOH, the final product **338** is obtained in 89% ee indicating stereoretentive H / D exchange at the carbon α- to the tosyl group.



Scheme 65: Deuterium labelling studies demonstrating the isomerisation of **336** using Na_2CO_3 as a base.

The transformations described in Scheme 64 and Scheme 65 have the potential to be carried out enantioselectively with a pro-chiral substrate and a suitable chiral catalyst, although this type of transformation remains unreported at the time of writing. A reaction driven by conjugation, however, may be scope limiting and investigations into different

concepts in cyclopropane chemistry are of high importance. A deconjugative transformation was postulated driven by strain relief as opposed to the stability of a conjugated double bond. A reasonable assumption was made, if the γ-position of a conjugated cyclopropene was sufficiently acidic, then, in the presence of a base, it would likely undergo isomerisation to the exo-position (Scheme 66). If the base was chiral, such a reaction would not only alleviate ring strain, but concomitantly generate an optically active stereogenic carbon α- to the electron withdrawing group and on the cyclopropane. This would potentially allow for a range of electron withdrawing groups to be explored. Extensive investigations into the strain energy of cyclopropene rings, and their cyclopropane counterparts, has been carried out. The studies outlined in the next section gave us confidence that our conceptual enantioselective transformation was feasible.

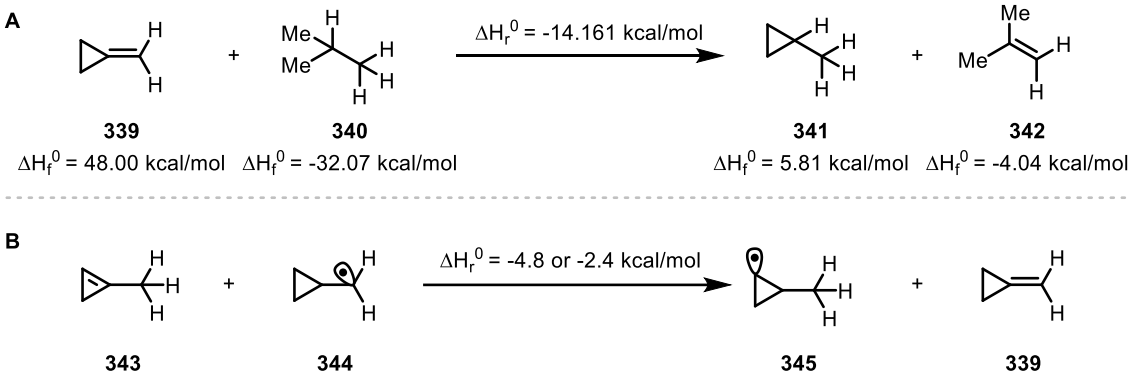


Scheme 66: Concept for a BIMP-catalysed deconjugation of cyclopropenes

3.2.4 Origins of heightened strain energy in cyclopropane and cyclopropene

The origins of the elevated levels of strain energy that allows for the transformations described in section **3.2.3.1** has been the subject of many investigations. In 1968, Wiberg and Fenoglio investigated the heats of formation of methylenecyclopropane (**339**) and 1-methylcyclopropene (**343**).[174] They discovered that the introduction of each trigonal centre to the ring resulted in an increase in strain energy of 12-14 kcal/mol. This is in line with the ≈ 14 kcal/mol calculated to be attributable to the strain relief of methylenecyclopropane when the experimental heats of formation of methylenecyclopropane (**339**),[174] 1-methylcyclopropane (**343**),[178] isobutylene (**342**)[179] and isobutane (**340**)[179] are applied to the isodesmic equation below (Scheme 67A). Wiberg and Fenoglio's view that strain energy is a consequence of angular strain, that increases with each new sp^2 carbon introduced onto the ring, was widely accepted until 1997, when Borden offered a new explanation.[180] Although introduction of each trigonal centre does increase angular strain, it is not nearly enough to account for the 12-14 kcal/mol each additional centre introduces. Borden suggested that the additional strain energy could be accounted for by the strength of the cyclopropane C–H bonds. Wiberg and Fenoglio found that the experimental heats of formation of methylenecyclopropane (**339**) and 1-methylcyclopropene (**343**) differed by 10.2 kcal/mol, while Borden's calculations suggested between 11.2 and 12.7 kcal/mol, in close agreement with the experimental value.[174,180] Methylenecyclopropane (**339**) and 1-methylcyclopropene (**343**) are structural isomers of one another that provide identical compounds upon hydrogenation. The difference between their heats of formation should therefore be equivalent to the difference between their heats of hydrogenation which is calculated to

be 11-13 kcal/mol.[180] Borden used the isodesmic reaction in Scheme 67B to show that the π-bond dissociation energy accounted for less than half of the value of the difference in the heats of formation between **343** and **339** (11-13 kcal/mol vs 4.8 or 2.4 kcal/mol). Because the π-BDE is not the main contributor, the difference must arise from the difference from the C–H bond strengths which is equal to the difference in the heats of formation of the 2-methylcyclopropyl radical and the cyclopropylmethyl radical. Borden calculated this difference to be 7.9 and 8.8 kcal/mol at the ROHF and CASPT2N levels of theory respectively which is equivalent to the difference in the BDE of a secondary and a primary C–H bond in methylcyclopropane. Hence the authors suggested that the heat of formation for methylene cyclopropane is significantly lower than 1-methyl cyclopropene because of methylene cyclopropane's strong secondary C–H bond.



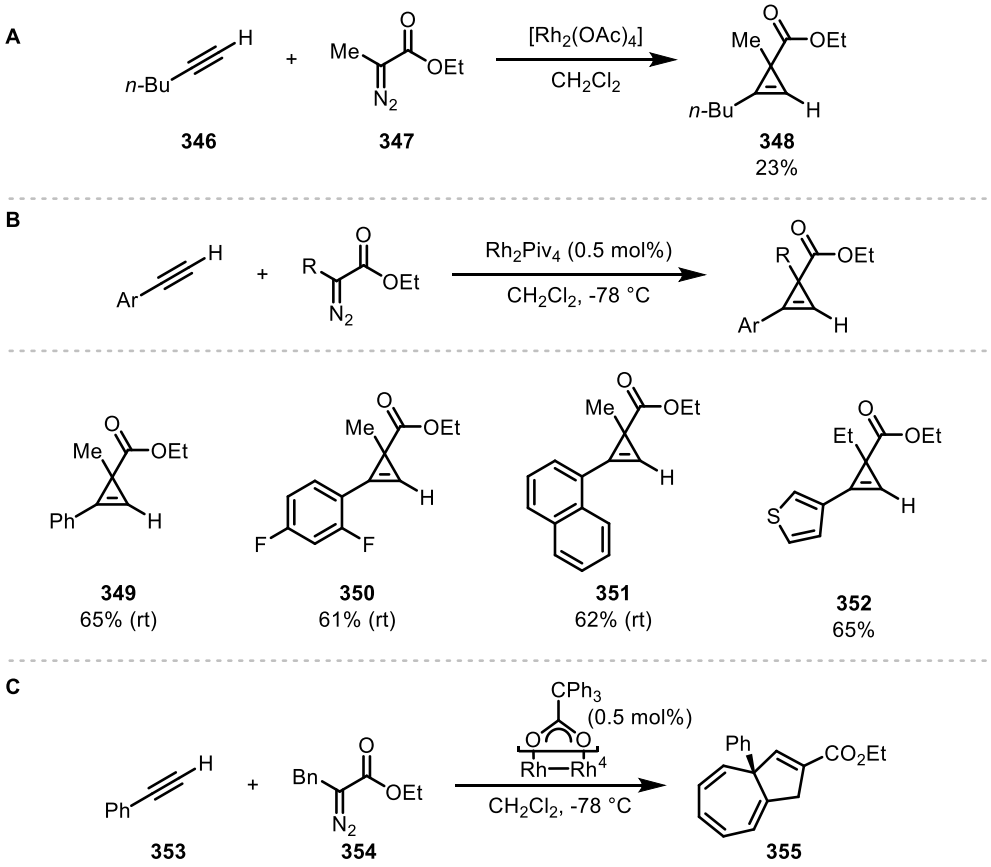
Scheme 67: A) Increase in strain energy for the introduction of a trigonal centre to a cyclopropane; B) π-BDE of methylcyclopropane.

3.2.5 Synthesis of cyclopropenes

Confident that the difference in strain energy between methylcyclopropene and methylene cyclopropene could be exploited to drive a deconjugation event, methods to synthesise the cyclopropene substrates were required.

Commonly, diazo-compounds have been applied to the synthesis of cyclopropenes. Their use was reported as early as 1956 by D'jakonov *et al.* in the reaction of 1-phenylpropyne

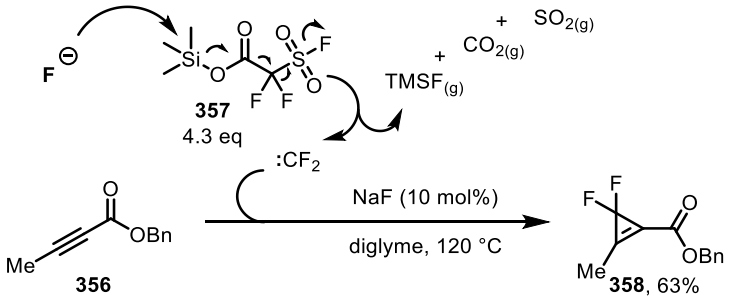
and ethyl diazoacetate (**347**), generating a 3-cyclopropene carboxylate compound using a copper catalyst to form the carbenoid.[181] Building on this early publication, carbenoid chemistry using diazo-compounds has become a widespread technique for the synthesis of cyclopropenes. Often, this chemistry makes use of rhodium catalysts due to their high reactivity with diazo-species and hence low catalyst loadings.[182] Rh_2(carboxylate)$_4$ catalysts were found to be poor cyclopropenation reagents if the desired carbenoid contained β-hydrogens. Previous studies have demonstrated that these kinds of carbenoids have a tendency to undergo β-hydride elimination to produce α,β-unsaturated esters.[183] However, Müller and Padwa independently demonstrated that α-diazopropionate (**347**) will react with 1-hexyne (**346**) in the presence of $Rh_2(OAc)_4$ to generate the predicted cyclopropene (**348**) (Scheme 68A).[184,185] In 2007, Fox *et al* established a method to overcome these limitations by varying the ligands on rhodium.[186] Increasing the steric bulk about the rhodium centre was found to increase the yield of the cyclopropene (Scheme 68B). However, increasing the steric bulk by too great an extent favoured the formation of azulenes (**355**) (Scheme 68C). In total, 16 examples of cyclopropenation were reported in moderate to good yields.



Scheme 68: A) Müller's cyclopropenation of 1-hexyne (**346**) using $Rh_2(OAc)_4$; B) Cyclopropenation of a series of alkynes by Fox *et al*. (16 examples); C) Increasing the steric bulk around rhodium leads to the formation of azulenes.

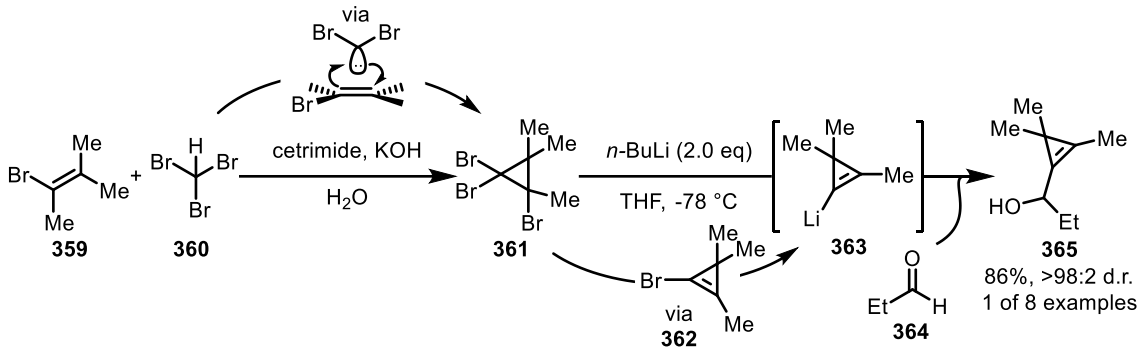
Another approach to the synthesis of cyclopropenes, involves the generation of difluoro-carbenes and their subsequent [1+2] addition to alkynes. Numerous complementary reagents are capable of $:CF_2$ generation, for example, trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA) and (triphenylphosphonio)difluoromethanide.[187,188] In the case of TFDA (**357**), the difluorocarbene is generated in a highly entropically favourable manner. Addition of TFDA (**357**) to a catalytic amount of NaF liberates $CO_{2(g)}$, $SO_{2(g)}$ and TMS-$F_{(g)}$ while simultaneously regenerating a fluoride ion and one equivalent of $:CF_2$ (Scheme 69). If this is carried out in the presence of an alkyne (e.g. **356**), the two species will undergo [1,2]-addition to generate the difluorocyclopropene (**358**). In 2020 Cossy *et al.* demonstrated the difluorocarbene addition using TFDA (**356**) to alkyne esters (**356**).[189] The reaction generally proceeded in high yield on a range of

substrates however required large excess of TFDA (**357**). Similarly, thermal decomposition of sodium bromodifluoroacetate lead to generation of $CO_{2(g)}$, NaBr and the desired difluorocarbene which may go on to react with an alkyne in a similar fashion.[190]



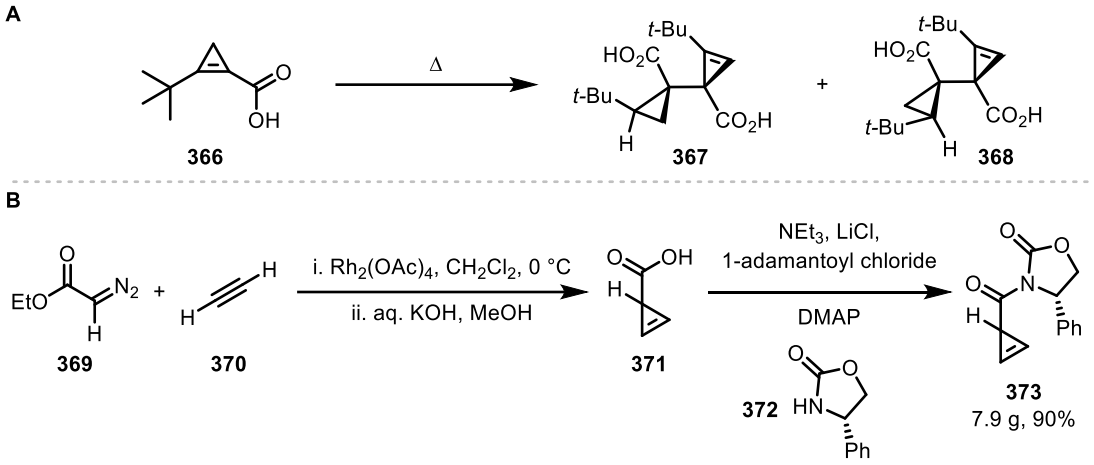
Scheme 69: Use of TFDA (**357**) in the presence of NaF to generate difluorocarbenes and their subsequent reaction with **356** to provide difluorocyclopropene **358**.

An alternative approach, described by Baird *et al.* in 1986, involves the synthesis of trihalocyclopropanes (**361**) and allows for more variation at the sp^3 centre of the cyclopropene.[191] Tribromocyclopropanes can be generated by reaction of bromoform with KOH to form a dibromocarbene and subsequent [1+2] addition to a vinyl bromide (**359**), in the presence of a phase transfer reagent such as cetrimide ($N(CH_3)_3(CH_2(CH_2)_{12}CH_3)Br$) (Scheme 70). Addition of two equivalents of a strong base, such as *n*-BuLi or MeLi, to the tribromocyclopropane (**361**) initially facilitates elimination, which is followed by a second lithium-halogen exchange to generate a reactive lithium cyclopropene (**363**). Garratt *et al.* and Marek *et al.* have shown that the lithiated cyclopropene (**363**) can undergo nucleophilic addition to a variety of electrophiles including silyl chlorides and aldehydes (**364**) allowing for facile derivatisation of the cyclopropene at the terminal position.[192,193]



Scheme 70: Synthesis of a tribromo cyclopropane (**361**) followed by elimination, lithium halogen exchange and addition to propionaldehyde by Marek *et al*.

Synthesis of less substituted cyclopropenes at the internal sp^3 centre is challenging owing to the final product's instability following isolation. Numerous reports have shown that on standing, cyclopropenes that are unsubstituted at the bridging carbon have a tendency to dimerise and polymerise (Scheme 71A).[194–197] These intermolecular reactions have been found to occur at temperatures as low as –60 °C.[198,199] The stability of the molecule is improved as substituents are added to the ring's sp^3 carbon, however, even mono-substituted rings are still susceptible to decomposition at elevated temperatures.[200] Fox *et al.* were able to design a multi-step but scalable synthesis to a stable cyclopropene derivative (**373**) from ethyl 2-diazoacetate (**369**) and ethyne gas (**370**) amenable to scale up to 7.9 grams (Scheme 71).[201] These compounds were demonstrated to be highly reactive dienophiles in Diels-Alder reactions and hence useful in diastereoselective synthesis.

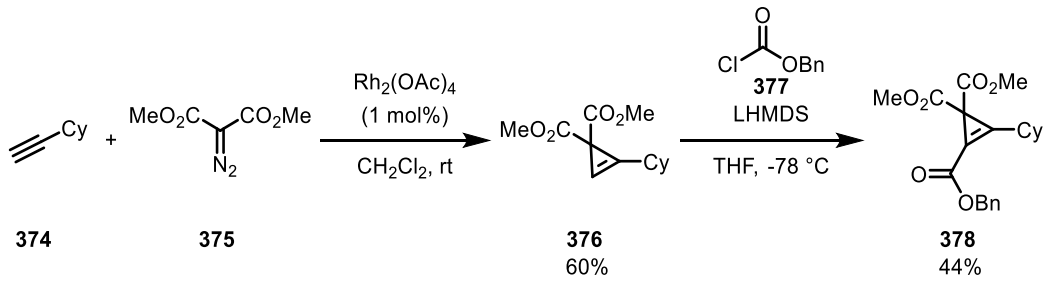


Scheme 71: A) Dimerisation of **366** as described by Baird *et al.;* B) Synthesis of a stable mono-substituted cyclopropene by Fox *et al*.

3.3 Results and discussion

3.3.1 Substrate synthesis and reaction optimisation

Armed with some knowledge of synthetic routes to cyclopropenes and factors affecting their stability, a suitable model substrate for our proposed enantioselective deconjugation reaction was prepared. Terminal cyclopropenes may be deprotonated at the sp^2 carbon using a strong base, for example MeLi, *n*-BuLi or LHMDS, and prior research has demonstrated that the resulting anion can be added to electrophiles such as TMSCl.[202] We reasoned that, treatment of a cyclopropene anion with chloroformate esters could potentially lead to conjugated cyclopropenes in the form of α,β-unsaturated esters. Accordingly, a suitable terminal cyclopropene (**376**) was synthesised in 60% yield via the rhodium-catalysed addition of dimethyl diazomalonate (**375**) to cyclohexylacetylene (**374**). Addition of terminal cyclopropene **376** to benzyl chlorofomate (**377**) in the presence of LHMDS at –78 °C proceeded smoothly and pleasingly to the desired conjugated cyclopropene (**378**) which was obtained in 44% yield.



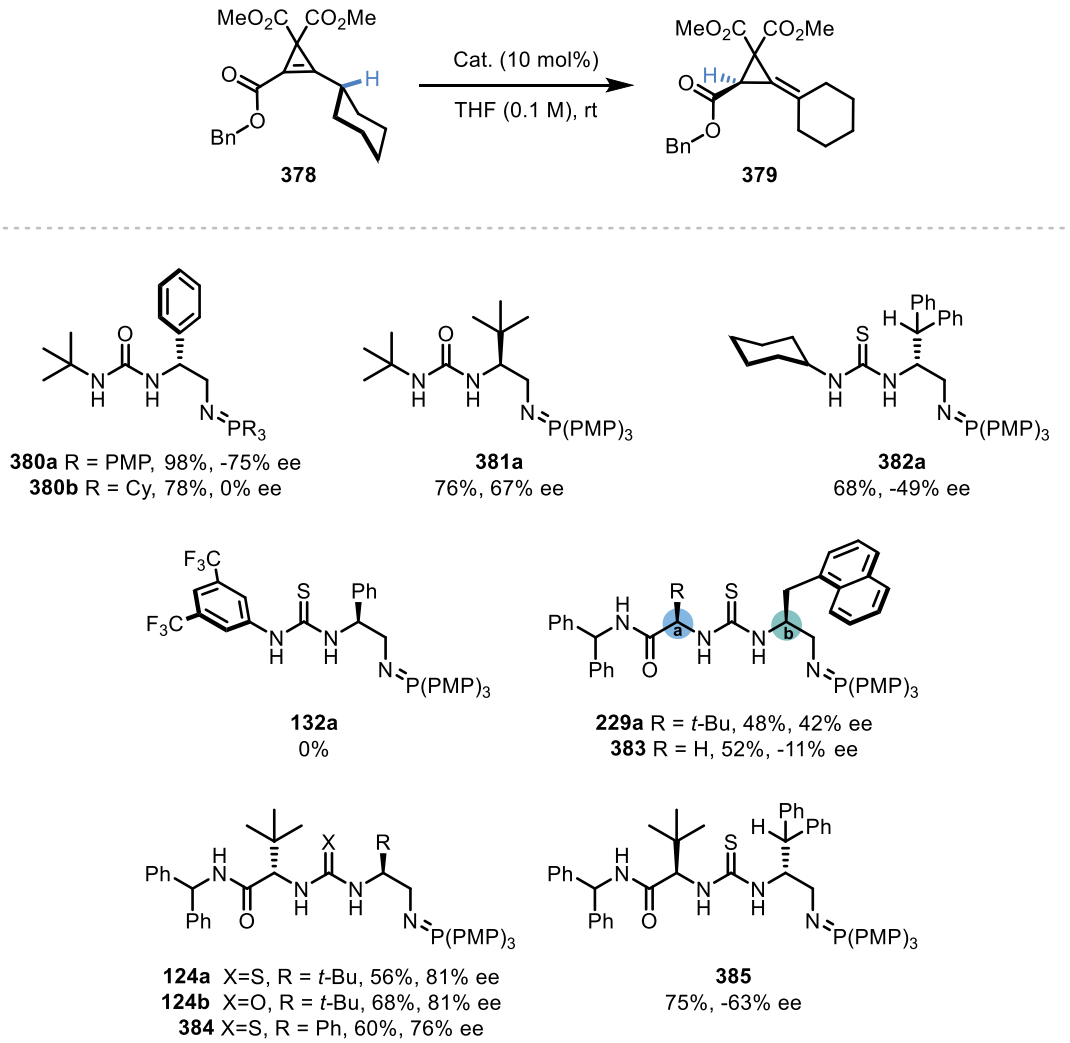
374 **375** **376** 60% **378** 44%

Scheme 72: Synthesis of model substrate **378**.

Conjugated cyclopropene **378** was investigated for reactivity with a range of BIMP catalysts (Scheme 73). THF was chosen as the solvent to improve catalyst solubility and the reactions were carried out at room temperature for convenience. The 1st generation BIMP catalyst **380a** performed the deconjugation remarkably well providing – on the first attempt – the chiral alkylidendecyclopropane (ACP) in 98% yield and −75% ee. Variation of the iminophosphorane, using tricyclohexyl phosphine (catalyst **380b**) however, led to complete loss of enantiocontrol. Although investigations were not carried out into this particular catalyst structure, this result was thought to be due to racemisation of the product ACP. Other 1st generation catalysts (**381a**, **382a** and **132a**) were also trialled however no improvement in enantioselectivity was observed. Notably, catalyst **132a** containing a 3,5-[bis(trifluoromethyl)phenyl]thiourea moiety failed to provide any product. This could be due to zwitterion formation of the catalyst resulting in reduced basicity.[78]

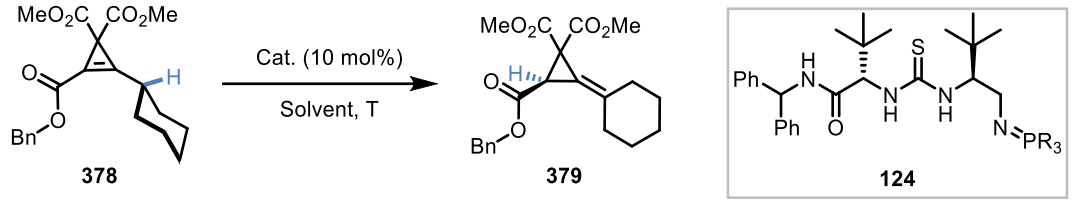
Encouraged by our initial result with 1st generation catalyst **380a**, a range of 2nd generation catalysts were investigated to hopefully improve the enantioselectivity. Catalyst **229a**, which had proven to be highly efficient in the enantioselective prototropic shift of β,γ-unsaturated cyclohexenones, only provided the desired product in 48% yield with low levels of selectivity (42% ee). Removing the substituent at stereocentre **a** (**383**) led to a significant reduction in enantioselectivity (11% ee). Catalyst **124a** provided the

desired product in 56% yield and 81% ee, poorer yield but a similar enantioselectivity to that obtained with **380a**. Changing the hydrogen bond donor group to a urea had little effect on reactivity and selectivity (**124b**). Considering the success of catalyst **380a**, a 2nd generation catalyst (**384**) was synthesised incorporating a phenyl group at stereocentre **b** (see experimental section for further detail). Disappointingly, the new catalyst offered no improvement on **380a** or **124a**. The product was obtained in 76% ee. Equally, benzhydryl catalyst **385** was unable to improve the selectivity.



Scheme 73: Catalyst screen for the enantioselective deconjugation of model substrate **378**.

Next, the impact on enantioselectivity of varying the reaction conditions was explored using our best catalyst (**124a**, 81% ee). Raising the temperature to 50 °C had little effect on enantioselectivity (78% ee) however changing the solvent to Et_2O and diluting the reaction to 0.05 M provided a moderate elevation to 84% ee (Table 6, entries 2 and 3). Reducing the temperature to –22 °C had no observable effect (Table 6, entry 4). Noting the high speed of the reaction, we anticipated that the specific basicity of the iminophosphorane could be lowered without detracting from the conversion, whilst also preventing potential racemisation of the product. This hypothesis was supported, and the ACP could be obtained in 99% yield and 97% ee with catalyst **124c** (Table 6, entry 5).



378 **379** **124**

entry	*phosphine*	*solvent*	*temp / °C*	*conc / M*	*time / h*	*yield / %*	*ee / %*
1	$P(PMP)_3$	THF	rt	0.1	4	56	81
2	$P(PMP)_3$	THF	50	0.1	2	60	78
3	$P(PMP)_3$	Et_2O	rt	0.05	2	76	84
4	$P(PMP)_3$	Et_2O	-22	0.05	23	>99	84
5	PPh_3 (**124c**)	Et_2O	rt	0.05	4	99	97

Table 6: Conditions screen for the enantioselective deconjugation of cyclopropenes with catalyst **124**.

3.3.2 Substrate scope – esters

Using the optimised conditions (Table 6, entry 5), the reaction scope was explored. For this purpose, a series of terminal cyclopropenes was prepared utilising the previously described reaction sequence.

Subjecting the *n*-pentyl substrate **386** to the optimised reaction conditions gave the deconjugated product **387** with lower levels of enantioselectivity (88% ee) than had been seen with the cyclohexyl substrate **378**, while the yield remained high (95%). Interestingly compound **387** was selectively formed as the *Z*-isomer using BIMP **124c** with a d.r. of >20:1 (*Z*/*E*). It was expected that the lower levels of enantioselectivity were attributed to product racemisation. To test this hypothesis, the reaction was performed on a larger scale and aliquots of the reaction mixture were taken and analysed at intermittent time points. The reaction turned out to be complete by the first time point at 30 min and **387** was obtained with an enantioselectivity of 96% ee (Figure 14). In line with the hypothesis, aliquots taken over 48 h showed a steady decrease in enantiomeric excess over the period and at 26 h 87.3 % ee was observed, as observed with our previous result. This suggested that the BIMP catalyst was able to deprotonate at the α-position of the ester product, leading to racemisation. No change in d.r. was observed suggesting the reaction was not fully reversible.

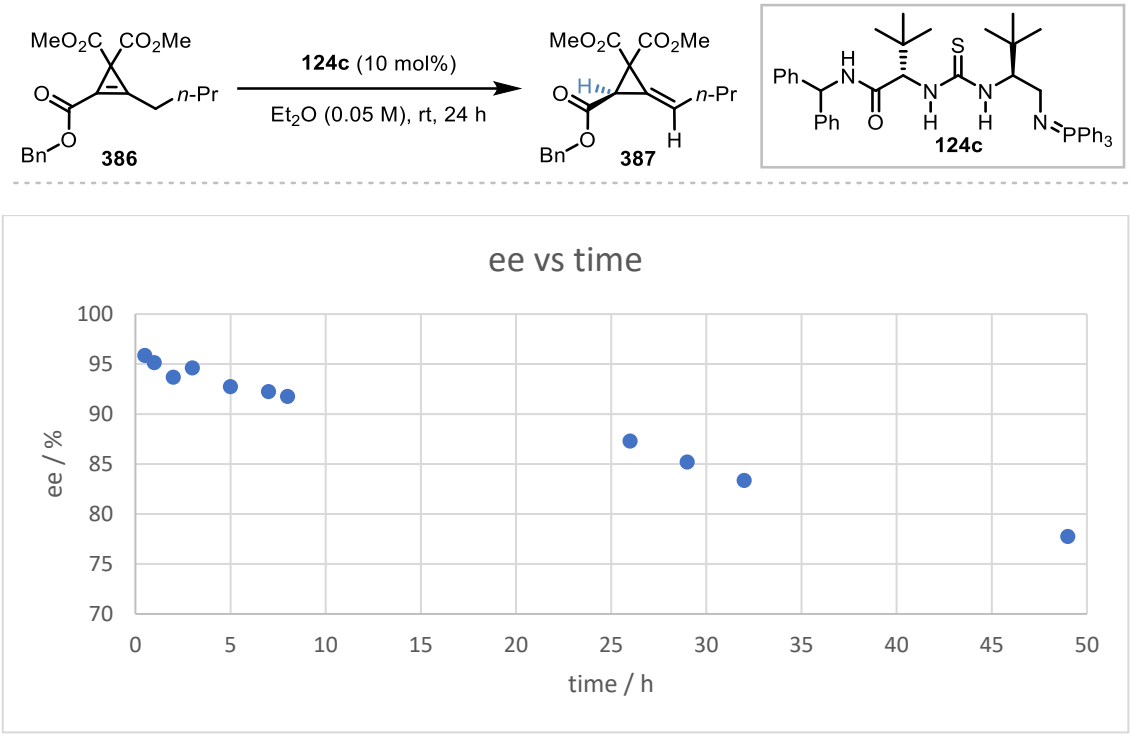
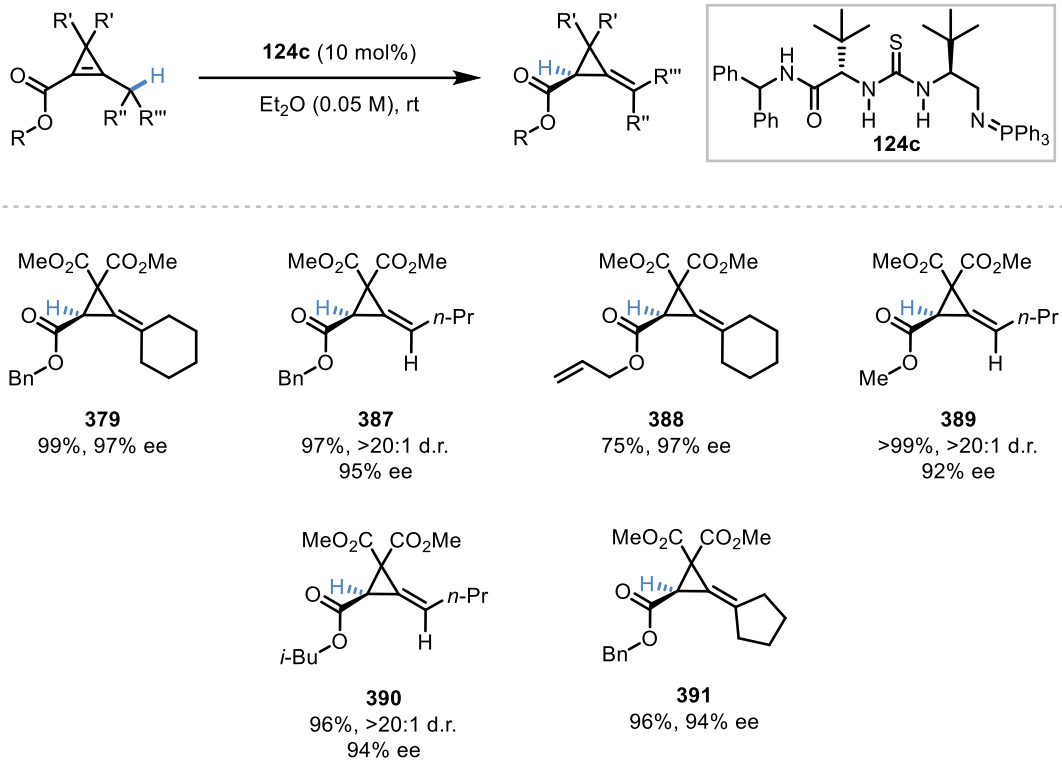


Figure 14: Plot of ee vs time for the BIMP-catalysed enantioselective deconjugation of compound **386**.

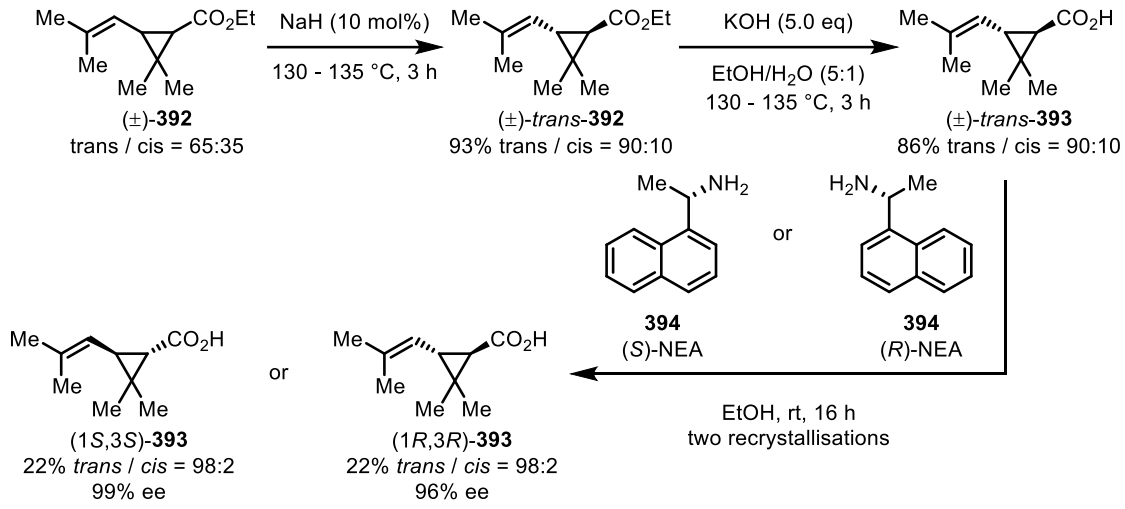
Equipped with this knowledge, it was applied to our reaction scope. TLC analysis was employed to determine accurate and specific end-points for each substrate to minimise racemisation (Scheme 74). Using this new approach, **387** was obtained in 97% yield and 95% ee as a single diastereomer. More substrates were investigated, and the ester group could be successfully varied: the equivalent allyl ester underwent the reaction to provide cyclopropane **388** in 75% yield and 97% ee, methyl ester and *iso*-butyl ester also performed well under the reaction conditions. The products, **389** and **390**, were obtained in excellent yield (>99% and 96% respectively) and with excellent levels of selectivity for the *Z*-isomer (>20:1 d.r.) and (*R*)-enantiomer (92% and 94% ee respectively). The catalyst also tolerated ring size variation. Product **391**, incorporating a cyclopentyl ring, could be obtained in 96% yield and 94% ee.



Scheme 74: Reaction scope for the BIMP-catalysed enantioselective deconjugation with esters.

3.3.3 Enantioselective synthesis of pyrethrins and pyrethroids

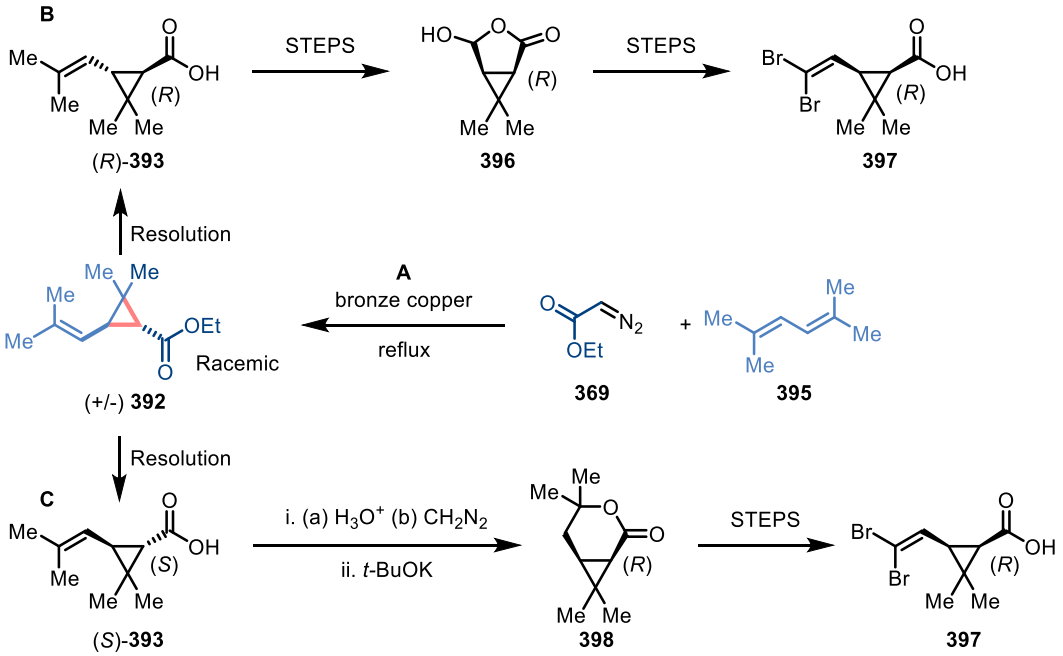
While pyrethrins can be extracted directly from the dried flowers of *Tanacetum cinerariaefolium*, which are cultivated in parts of East Africa, Tazmania and southern China, the extract, pyrethrum, consists of six esters, pyrethrin I, pyrethrin II, cinerin I, cinerin II, jasmolin I, and jasmolin II that are inseparable from one another.[203] Tanabe and Matsuo recently reported the chiral total syntheses of all six variants from racemic ethyl chrysanthemate (**392**) via optical resolution of the *trans*-acid (**393**) and investigated the independent insecticidal properties of the individual compounds (Scheme 75).[204]



Scheme 75: Tanabe and Matsuo's total synthesis of all six pyrethrins.

Since LaForge and Barthel's elucidation of the structures of pyrethrins I and II in 1944 and the establishment of their absolute configurations in the 1950s, numerous structural modifications to the scaffold have been made.[205–207] This has resulted in a sub-set of derivatives known as pyrethroids which, as of 2020, account for 25% of global sales of insecticides.[159] These pyrethroids generally have enhanced stability and insecticidal properties along with reduced mammalian toxicity over their pyrethrin progenitors. Versatile and efficient syntheses of these structural families is therefore an important goal for the agrochemical industry.[203] Few pyrethroids are used as a single enantiomer despite the well-documented effect of their stereochemical configuration on agrochemical performance. Deltamethrin, a widely used pyrethroid, whose greatest activity is exhibited by the *cis*-(1*R*,3*S*) is notably used as a single enantiomer.[208] Owing to its value as a potent insecticide, several methods have been developed to synthesise the core cyclopropane ring enantioselectively.[208] At an industrial scale, chrysanthemic acid is synthesised as a racemate using a procedure developed in 1945 by Harper *et al*. Addition of α-diazo ester **369** to 2,5-dimethylhexa-2,4-diene (**389**) using a copper-bronze catalyst provides the *cis* and *trans* isomers which are then separated (Scheme 76A).[209] The *trans*

racemic mixture is then resolved using ((1*R*,2*R*)-1-(4-nitro-phenyl)-2-dimethylaminopropanediol) to provide the synthetically useful (*R*)-*trans* isomer ((*R*)-**393**) which can be converted into deltamethrinic acid (**397**) via lactonisation and epimerisation (Scheme 76B).[210–213] The (1*S*)-*trans*-chrysanthemic acid ((*S*)-**393**) is also utilised by converting it into deltamethrinic acid (**397**) via conversion into a lactone followed by epimerisation at the ester forming the *cis*-fused [6,3]-ring (**398**) (Scheme 76C).[210–213] A ring-opening elimination forms a chrysanthemic acid derivative that may undergo ozonolysis to yield the aldehyde. The aldehyde is then subjected to tetrabromomethane and triphenylphosphine to afford enantiopure deltamethrinic acid (**397**).



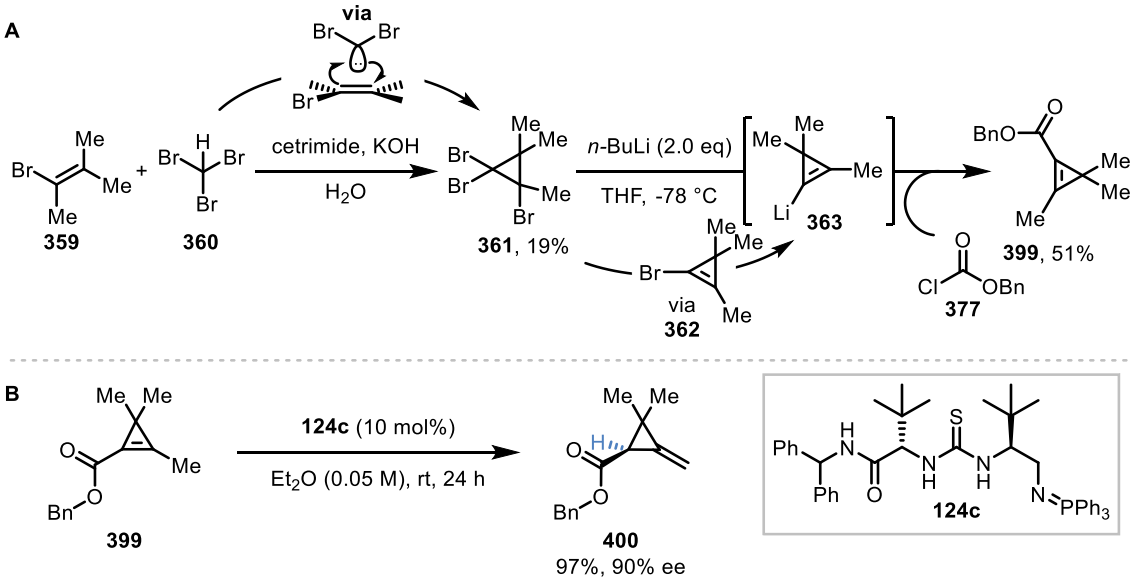
Scheme 76: Industrial process for the synthesis of (*R*)-*cis*-deltamethrinic acid (**391**) from achiral starting materials.

Despite the large number of publications on the synthesis of pyrethrin and pyrethroid insecticides, there are few examples where enantioselective catalysis has been applied.[208] Having developed a highly enantio- and diastereoselective method for the synthesis of ACPs our plan was to apply the transformation to the synthesis of single

enantiomers and diastereomers of various pyrethrin / pyrethroid insecticides. This would potentially enable the properties of individual isomers to be studied more thoroughly without the need for laborious separations of enantiomers and diastereomers.

3.3.4 Synthesis of permethrin

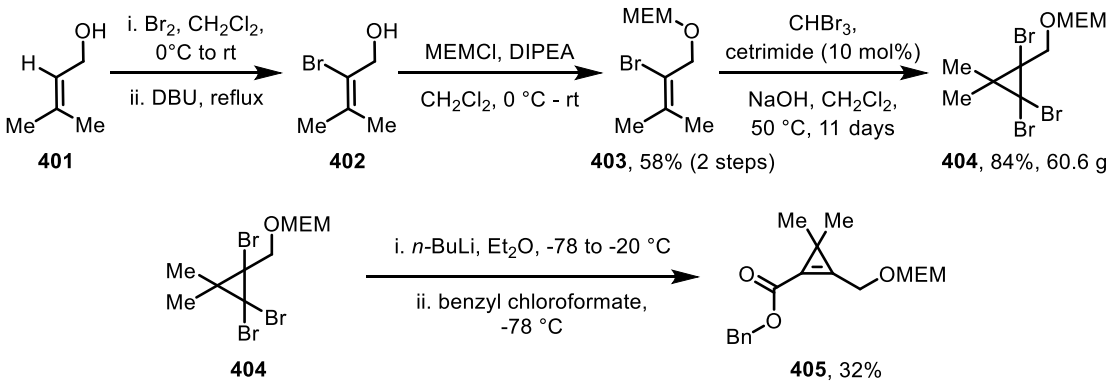
In order to synthesise cyclopropene building blocks amenable to transformation into pyrethroids, the development of a new route was required. Addition of a dibromocarbene to vinyl bromide **359** afforded tribromo cyclopropane **361**. Treatment of **361** with *n*-BuLi at –78 and allowing the reaction to warm to –20 °C, followed by low temperature addition of the lithiated cyclopropene to benzyl chloroformate (**377**), provided the α,β-unsaturated ester **399** in 51% yield (Scheme 77A). The cyclopropene ester (**399**) was then subjected to the optimised enantioselective strain-relieving deconjugation to give the methylene cyclopropane (**400**) with excellent enantiocontrol (90% ee) (Scheme 77B).



Scheme 77: A) Synthesis of dimethyl substrate **399**; B) Enantioselective deconjugation of substrate **399**.

This promising result prompted the search for an expedient route to cyclopropenes that could be directly converted into pyrethroids. Such substrates would have to contain the

gem-dimethyl structure as well as an appropriately linked substituent in the γ-position to allow access to the external alkene commonly found in the structures of pyrethrins/pyrethroids. To form the external alkene, the final deconjugation could result in an enol ether which could be readily transformed into an aldehyde and then the alkene via a Wittig reaction. The required aldehyde precursor was prepared as described in Scheme 78. Addition of bromine to allyl alcohol **401** followed by elimination afforded the allylic alcohol **402** which was protected without prior purification with MEMCl / DIPEA. The overall yield for the sequence was 58%. (Scheme 78). Treatment of the protected vinyl bromide (**403**) with bromoform in the presence of NaOH and cetrimide gave the tribromocyclopropane (**404**) after 11 days at 50 °C. This route was very amenable to scale up and 60.6 g of the final tribromocyclopropane **404** was isolated. Addition of the tribromocyclopropane to benzyl chloroformate (**377**) provided model substrate **405** in 32% yield.

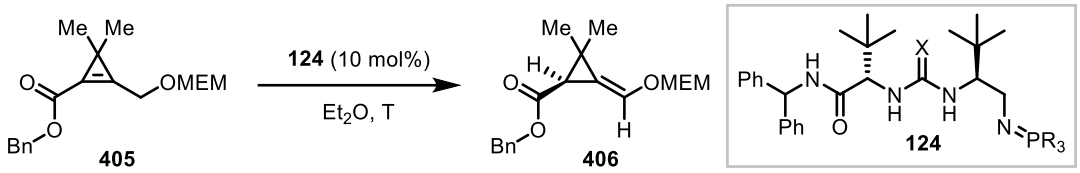


Scheme 78: Synthesis of model substrate **405** for the development of a new enantioselective route to the pyrethrin / pyrethroid structure.

The attempt to perform the enantioselective deconjugation of substrate **405** with catalyst **124c** gave a disappointing outcome; only 17% (by NMR) of the substrate (**405**) was converted to enol ether (**406**) after 24 h at room temperature. Increasing the temperature to 40 °C failed to improve the outcome (Table 8, entry 1). Considering the electronically

modified structure of substrate **405**, the γ-position was thought to be less acidic than that of our previous substrates therefore more basic catalysts were investigated. However, the $P(PMP)_3$ derived 2nd generation BIMP **124a** did not significantly speed up the reaction (59% conversion after 54 h) and the diastereoselectivity was found to be poor (76:24) (Table 8, entry 2). Despite the low diastereoselectivity, the major diastereomer was obtained in 70% ee. Increasing the basicity still further with the P(*n*-Bu)$_3$-derived iminophosphorane and urea hydrogen bond donor group provided the deconjugated product within an hour (Table 8, entry 3). Unfortunately, the product was now racemic and the diastereoselectivity had switched (11:89 d.r.). In this case the minor diastereomer was obtained in 60% ee. In an attempt to enhance stereoselectivity the temperature was lowered to –20 °C (Table 8, entry 4). After 12 h only 25% of the starting material had been converted to the product and both the diastereo- and enantioselectivity were inadequate (11:89 d.r., both diastereomers were found to be racemic). Since temperature variations appeared to be ineffective at improving enantio- and diastereoselectivity the effect of concentration change was explored. With $P(PMP)_3$ derived catalyst **124a** at 0.2 M the reaction was found to proceed rapidly, however the diastereoselectivity switched and both diastereomers were found to have low levels of enantiomeric enrichment (Table 8, entry 5). Further modifications were made to the catalyst. Noting the high reactivity of the urea-based catalyst scaffold the problem was clearly not entirely due to the increased basicity of the iminophosphorane. To test this, the $P(PMP)_3$ iminophosphorane catalyst (**124b**) was trialled and the reaction proceeded to completion within 2 h with moderate diastereoselectivity (64:36 d.r.) and enantioselectivity for the major diastereomer (75% ee) (Table 8, entry 6).

Next, more BIMP catalysts based on the chiral-urea scaffold were investigated. Electron poor iminophosphoranes gave rise to a low reaction rate however, the diastereoselectivity and enantioselectivity for the major enantiomer were good (Table 8, entries 8 and 9). Electron rich superbase catalysts were expected to do better, however, despite this the *p*-tolyl derived iminophosphorane only imparted low levels of reactivity (Table 8, entry 10). In contrast, the sterically encumbered bis-*tert*-butyl analogue promoted complete reaction within an hour with a diastereoselectivity of 98:2 (Table 8, entry 11). Furthermore, a moderate increase in the enantioenrichment of the major diastereomer (80% ee) was observed, which could be further increased to 87% ee by lowering the temperature to –20 °C (Table 8, entry 12). Curious about the effect of the hydrogen bond donor group in the urea-based catalyst, the same iminophosphorane with the thiourea hydrogen-bond donor was trialled (Table 8, entry 13). Once again, the reaction proceeded rapidly (100% conversion to product within 1 h) with excellent diastereoselectivity (>20:1 d.r.) and the major diastereomer was obtained in 98% ee.



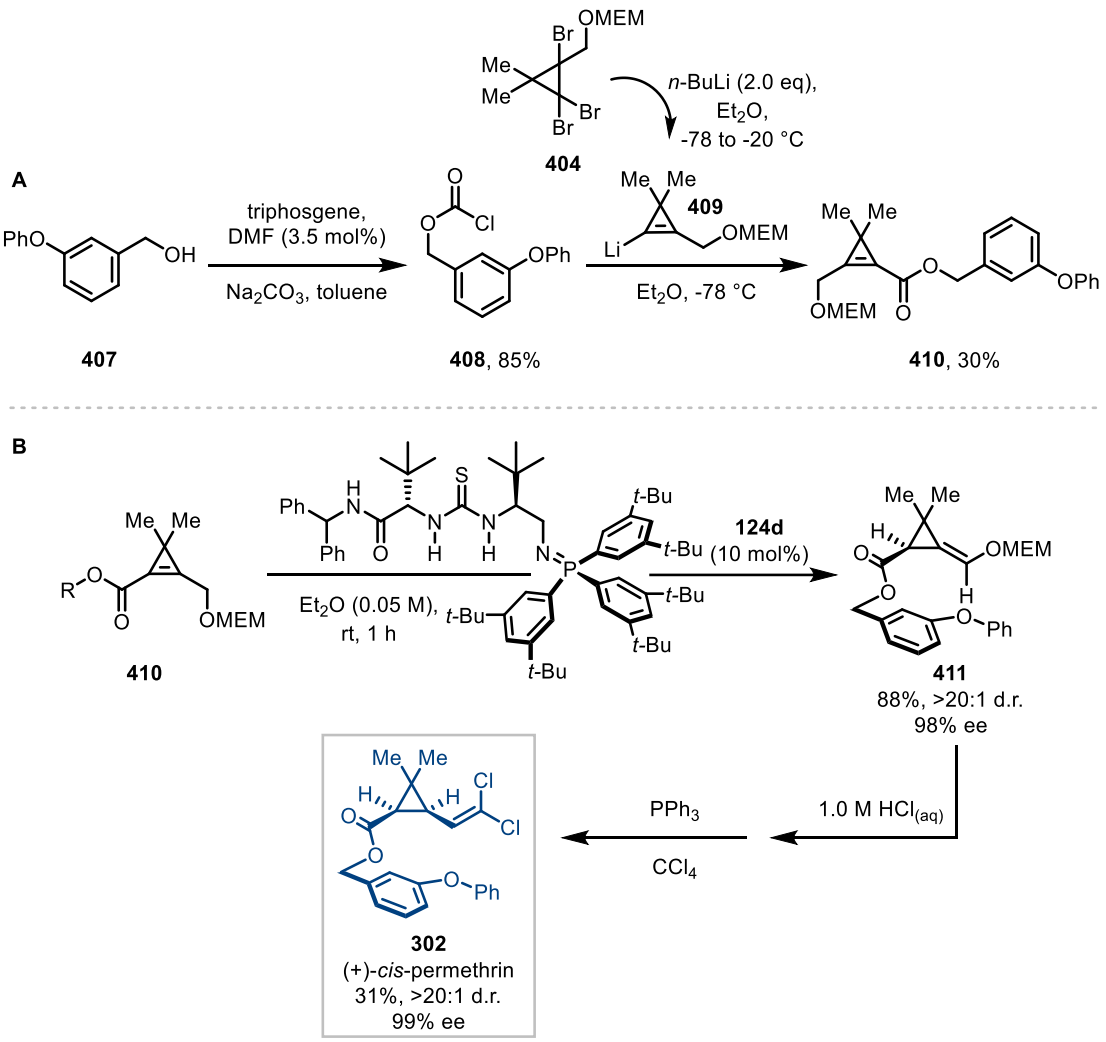
entry	*X*	*phosphine*	*T / °C*	*conc / M*	*time / h*	*conversion / %*	*d.r. (Z/E)*	*ee maj / %*	*ee min / %*
1	S	PPh_3	rt to 40	0.05	24	17	N/D	N/D	N/D
2	S	$P(PMP)_3$	rt	0.05	54	59	76:24	70	5
3	O	$P(n\text{-}Bu)_3$	rt	0.05	1.0	88[a]	11:89	0	60
4	O	$P(n\text{-}Bu)_3$	-78 to -20	0.05	24	25	12:88	0	0
5	S	$P(PMP)_3$	rt	0.2	2.0	100	16:84	4	32
6	O	$P(PMP)_3$	rt	0.05	2.0	100	64:36	75	6
7	O	PPh_3	rt	0.05	24	12	90:10	88	19
8	O	$PPh_2(p\text{-}CF_3C_6H_4)$	rt	0.05	24	4	90:10	87	6
9	O	$PPh_2(p\text{-}CNC_6H_4)$	rt	0.05	24	30	>20:1	87	12
10	O	$P\ (p\text{-}MeC_6H_4)_3$	rt	0.05	24	18	74:26	84	4
11	O	$P((m\text{-}t\text{-}Bu)_2C_6H_3)_3$	rt	0.05	0.75	100	>20:1	80	32
12	O	$P((m\text{-}t\text{-}Bu)_2C_6H_3)_3$	-20	0.05	34	100	>20:1	87	30
13	S	$P((m\text{-}t\text{-}Bu)_2C_6H_3)_3$	rt	0.05	1.0	100	>20:1	98	56

Table 7: Phosphines and conditions screen for the enantioselective deconjugation of compound **400**.[a]Isolated yield

Excited by the efficiency of the thiourea based catalyst **124d** (thiourea analogue of scaffold **124** bearing a $P((m\text{-}t\text{-}Bu)_2C_6H_3)_3$ derived iminophosphorane) it was deployed as the catalyst in a route to permethrin (**302**) (Scheme 79). The substrate **410** for the key enantioselective deconjugation reaction was prepared according to Scheme 79A. The requisite chloroformate (**408**) was prepared in high yield (85%) by the addition of triphosgene to commercially available alcohol (**407**) in the presence of a catalytic

quantity of DMF. Addition of the lithiated tribromocyclopropane (**409**) to the freshly synthesised chloroformate (**408**) afforded the required cyclopropene precursor to permethrin in 30% yield.

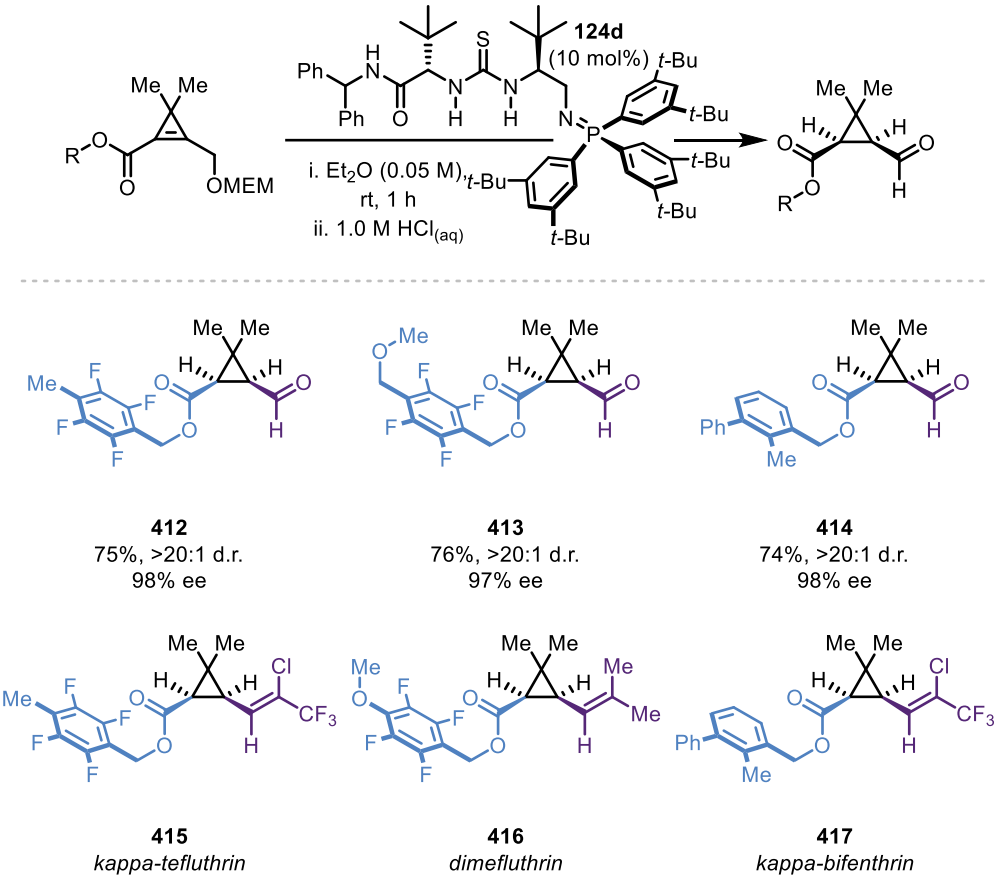
Catalyst **124d** performed well in the deconjugative step converting the cyclopropene (**410**) to the desired enol ether (**411**) as a single diastereomer in 88% yield and 98% ee (Scheme 79B). The reaction was improved by replacing acetic acid with 1.0 M HCl(aq) to quench the BIMP catalyst and hydrolyse the MEM protecting group at the same time. The desired aldehyde formed in >20:1 d.r. which, following an aqueous work up, could be taken on without further purification. By subjecting the aldehyde to CCl_4 in the presence of PPh_3 (+)-*cis*-permethrin (**302**) was obtained in 31% yield and 99% ee over two steps and synthesised in 6 steps overall (longest linear sequence). To confirm the diastereomeric configuration, the sample's NMR data was compared to a literature report which verified that the *cis*-diastereomer had been preferentially formed.[214] This suggested that reprotonation of the enol occurred kinetically on the least hindered face to form the *cis*-configured aldehyde. The result was used to assign the absolute stereochemical configuration of the chiral ACPs by comparison of the literature value for optical rotation, which was found to be a close match to that published in the literature: Optical rotation of isolated **302**: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +1.81 (*c* 1.43, CH_2Cl_2); Literature value: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +2.6 (*c* 1.5, CH_2Cl_2) (>99.95% diastereomeric purity, 99.7% ee).[214]



Scheme 79: Enantioselective synthesis of (+)-*cis*-permethrin (**302**) utilising a BIMP-catalysed enantioselective deconjugation. R = $CH_2C_6H_4$(*m*-OPh)

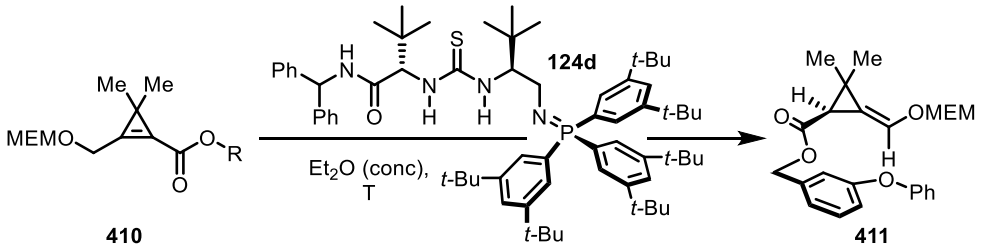
Excited by our successful synthesis of (+)-*cis*-permethrin (**302**) our investigations were expanded to the cores of other relevant pyrethroids. The precursors could be synthesised by addition of tribromocyclopropane **404** to the relevant chloroformates following the same procedure used to synthesise substrate **410**. All three substrates performed well under the optimised reaction conditions which rapidly transformed them into their enol ether counterparts. Addition of 1.0 M $HCl_{(aq)}$ following the BIMP catalysed step led to the formation of the *cis*-configured aldehydes and in each case the product was formed in >20:1 d.r. and almost complete enantiopurity. Products **412**, **413** and **414** represent the

cores of kappa-tefluthrin (**415**), dimefluthrin (**416**) and kappa-bifenthrin (**417**) respectively and could feasibly be transformed into them via Wittig reactions.[215]



Scheme 80: Synthesis of enantioenriched insecticide aldehyde-precursors.

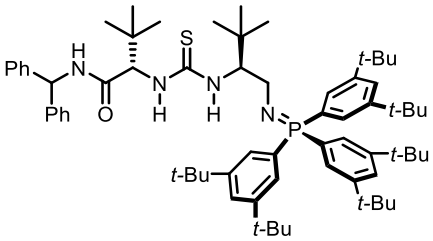
In an effort to improve the sequence further, the high catalyst loading (CL) of 10 mol% was reduced. Halving the loading did not have any bearing on the reaction performance and, after 24 h, 99% conversion to product was observed with a d.r. of >20:1 (Table 8, entry 1). Unfortunately, reducing the loading to 2.5 mol% resulted in only 50% conversion after 24 h and d.r. of >20:1 (Table 8, entry 2); increasing the concentration to 0.1 M made no difference (Table 8, entry 3). As might have been expected, decreasing the catalytic loading to 1 mol% made matters worse and increasing the concentration made no difference to the conversion (Table 8, entry 4 and 5).



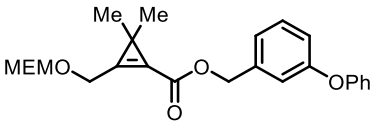
entry	*CL / mol%*	*T / °C*	*conc / M*	*time / h*	*conversion / %*	*d.r.*	*ee maj /%*
1	5.0	rt	0.05	24	100	>20:1	99
2	2.5	rt	0.05	24	50	>20:1	98
3	2.5	rt	0.1	24	50	>20:1	98
4	1.0	rt	0.1	24	16	>20:1	N/D
5	1.0	rt	0.5	24	18	>20:1	N/D

Table 8: Investigation into catalyst loading in the enantioselective deconjugation of substrate **410**. R = $CH_2C_6H_4$(*m*-OPh).

Surprisingly, increasing the concentration at both 2.5 mol% and 1 mol% loading failed to improve the rate of reaction as might have been expected and thus the possible causes were investigated. It was possible that the catalyst was decomposing under the reaction conditions and the discovery of the degradation pathway was of paramount importance to improving the reaction outcome if this was the case. The *m*/*z* peak corresponding to the active BIMP catalyst ($[M+H^+]$ = 1051.7) in low-resolution mass spectra (ESI) of the reaction mixtures in Table 8, entries 3, 4 and 5 could not be located. Interestingly, each spectrum showed *m/z* = 1463.8 corresponding to an adduct between the catalyst and the substrate (Exact Mass: 1462.92) which could occur by Michael addition of the iminophosphorane or the thiourea to the cyclopropene.



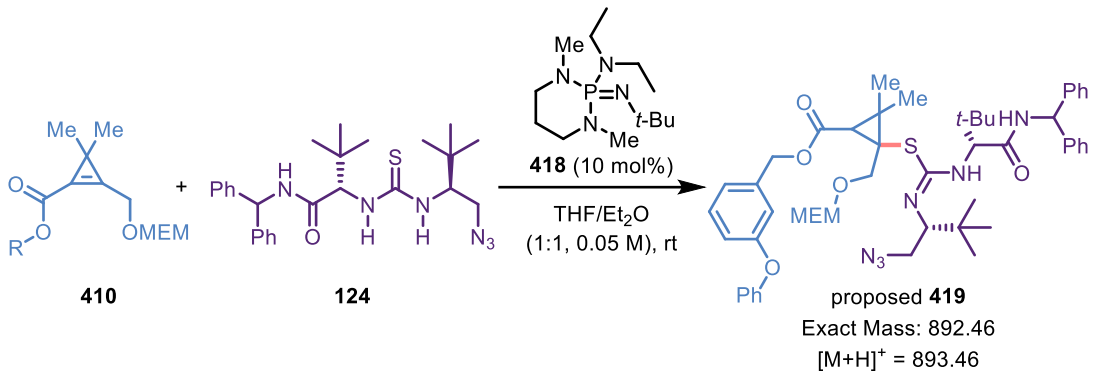
124d
Exact Mass: 1050.73
$[M+H]^+$ = 1051.73



410
Exact Mass: 412.19
$[M+H]^+$ = 413.20

Figure 15: Exact mass for compounds **124d** and **410**.

To establish which of the BIMP's functionalities was reacting with the substrate, the azide precursor (**124**) of the BIMP catalyst was added to substrate **410** in the presence of a catalytic amount of BEMP (**418**). After stirring the reaction overnight in a mixture of THF and Et_2O, low-resolution mass spectrometry confirmed the presence of an adduct between **124** and **410** (*m/z* = 893.4) however, the product (**419**) could not be cleanly isolated (Scheme 81).

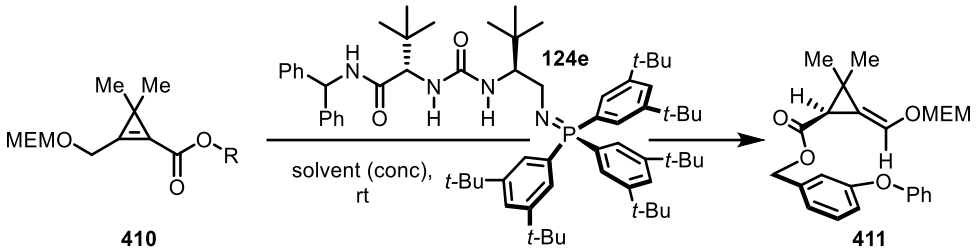


Scheme 81: Addition of azide **124** to substrate **410** using a catalytic amount of BEMP (**418**). R = $CH_2C_6H_4$(*m*-OPh).

This was strong evidence that the catalyst was becoming poisoned during the reaction by addition to the cyclopropene substrate through the thiourea, most likely through the sulfur atom. We speculated that a urea would be less nucleophilic and hence less prone to Michael addition reactions as a consequence of the lower nucleophilicity of oxygen compared to sulfur. Thus, urea derived catalyst **124e** was tested in the reaction. It was

unlikely that the adduct was the catalytic species as the reactions at low catalyst loading had not progressed and the enantioselectivities with other substrates were consistent.

The BIMP-catalysed enantioselective deconjugation was repeated with 1.0 mol% of urea catalyst (**124e**) and substrate **410**. As predicted, the reaction performed much better and 100% conversion was observed after 52 h (Table 9, entry 1). Despite the markedly improved conversion, the product was only obtained in 80% ee, possibly as a consequence of the poorer hydrogen bond donor ability of the urea compared to the thiourea. Similar results were obtained when the loading was reduced to 0.5 mol% and the concentration raised to 0.2 M albeit with a slightly lower conversion and a moderate improvement in enantioselectivity (Table 9, entry 2). To try and improve the optical purity of the product, experiments were performed with different solvents. TBME and CPME both gave 100% conversion after 24 h and a slight boost in ee to 85% ee and 88% ee respectively (Table 9, entries 3 and 4). Use of toluene led to further improvement in selectivity and the product was obtained in 91% ee (Table 9, entry 5) while benzene offered no improvement (Table 9, entry 6). Following the success of toluene, a range of similar solvents was investigated. Full conversion after 24 h was obtained in mesitylene after 24 h, however the ee was only 87% (Table 9, entry 7). *m*-Xylene and benzotrifluoride were poor solvents for the reaction and only low levels of conversion was observed after 24 h (Table 9, entries 8 and 9). *Tert*-Butylbenzene performed similarly to toluene and the substrate was completely converted to product over 24 h and in 90% ee (Table 9, entry 10). Raising the temperature with toluene as the solvent was found to be detrimental and enantioselectivity was reduced to 85% ee. Decreasing the temperature to 0 °C raised the selectivity to 94% ee but slowed the reaction so that only 43% conversion was observed in the same time frame.



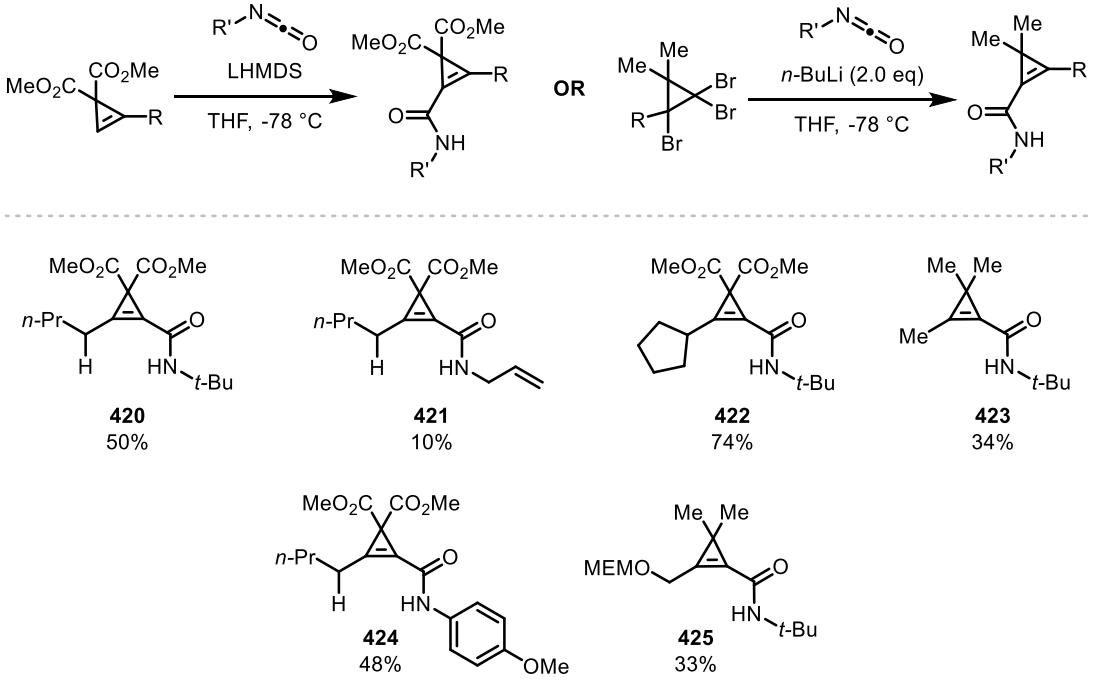
entry	*mol%*	*solvent*	*T / °C*	*conc / M*	*time / h*	*conversion / %*	*d.r.*	*ee / %*
1	1.0	Et_2O	rt	0.05	52	100	>20:1	80
2	0.5	Et_2O	rt	0.2	52	85	>20:1	84
3	1.0	TBME	rt	0.05	24	100	>20:1	85
4	1.0	CPME	rt	0.05	24	100	>20:1	88
5	1.0	toluene	rt	0.05	24	100	>20:1	91
6	1.0	benzene	rt	0.05	24	100	>20:1	86
7	1.0	mesitylene	rt	0.05	24	100	>20:1	87
8	1.0	*m*-xylene	rt	0.05	24	45	>20:1	89
9	1.0	benzotrifluoride	rt	0.05	24	23	>20:1	79
10	1.0	*t-b*utylbenzene	rt	0.05	24	100	>20:1	90
11	1.0	toluene	50	0.05	24	100	>20:1	85
12	1.0	toluene	0	0.05	24	43	>20:1	94

Table 9: Investigation into catalyst loading in the enantioselective deconjugation of substrate **410** with **124e**. R = $CH_2C_6H_4$(*m*-OPh)

Given the promising results obtained so far, investigations will continue in order to improve the conversion, rate and the stereoselectivity of this powerful reaction, to allow a scaled-up reaction to be carried out in future work.

3.3.5 Reaction scope - amides and a phosphine oxide

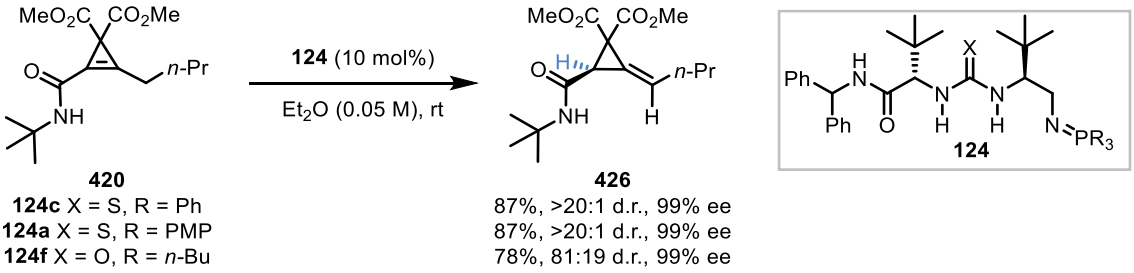
Following the investigation of cyclopropene substrates bearing an ester group, substrates bearing amides were then investigated. Synthesis of amide-bearing substrates was achieved in a manner similar to that of the α,β-unsaturated esters in section **3.3.1**. Replacement of the chloroformates with isocyanates provided secondary α,β-unsaturated amides **420-425**, in yields ranging from 10% to 74%.



Scheme 82: Synthesis of amide-bearing substrates.

Amide **420** was trialled in the deconjugation reaction with three catalyst variations. Although we initially expected a stronger basic moiety than that of **124c** to be required for high conversion to product, to our surprise, all three catalysts rapidly provided the desired deconjugated amides in high d.r. (Scheme 83). The enantiocontrol was similarly high; in each case the product was obtained in >95% ee despite the additional acidic hydrogen present in the secondary amide with its potential for background reprotonation. Catalyst **124c** was used for further scope expansion. Noting that the diastereomer

obtained under the enantioselective reaction conditions was yet undefined, NOESY experiments were employed to determine the E/Z isomer displaying a cross-peak between the amidic N-H and the alkene's C–H supporting the proposed *Z*- stereochemical configuration (see Experimental section for further detail).



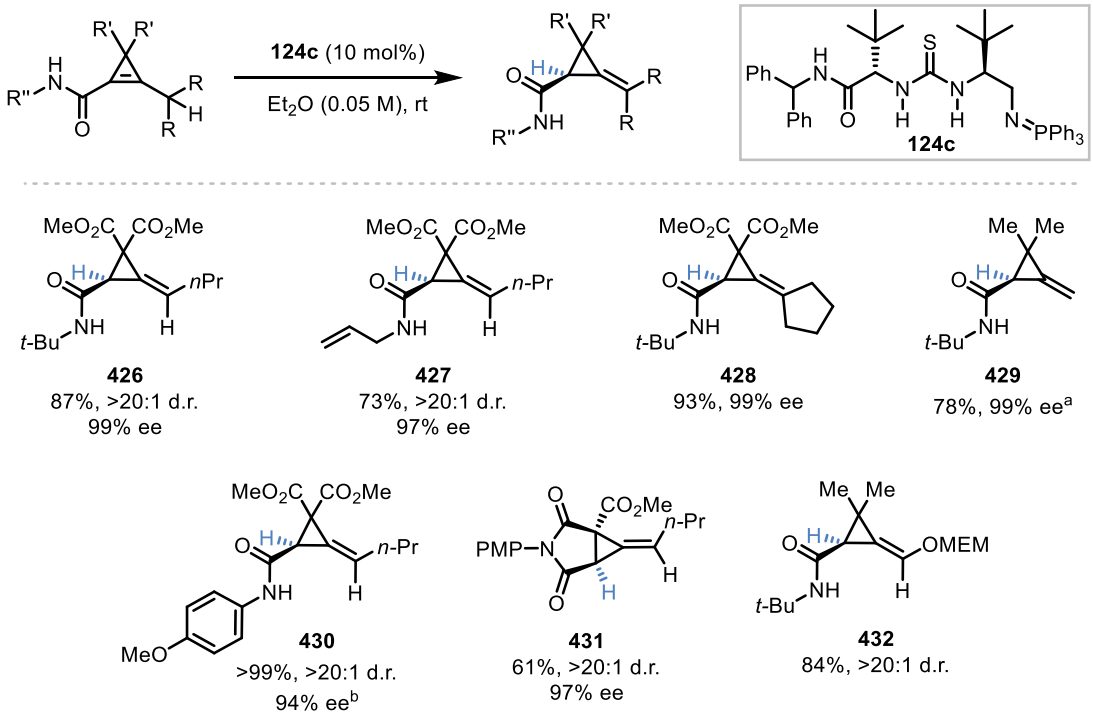
420
124c X = S, R = Ph
124a X = S, R = PMP
124f X = O, R = *n*-Bu

426
87%, >20:1 d.r., 99% ee
87%, >20:1 d.r., 99% ee
78%, 81:19 d.r., 99% ee

Scheme 83: Enantioselective deconjugation of amide **408** with iterations of **124**.

Variation of the amide from *tert*-butyl amide **420** to allyl amide **421** had no effect on reactivity or selectivity and the final alkylidenecyclopropane (**427**) could be obtained in 73% yield and 97% ee. The deconjugated cyclopentyl-bearing product **428** was obtained in 93% yield and with complete enantiocontrol (99% ee) showing that additional steric bulk about the γ-proton was tolerated. *Gem*-dimethyl amide **423** was trialled in the reaction, this time with catalyst **124d**. The catalyst gave remarkable control in the deconjugation of the amide and product **429** was obtained in 73% yield and 99% ee. Amide **424** was found to be poorly soluble in Et_2O and so THF was used as the solvent instead. Fortunately, it made no difference to the desired reaction outcome and the ACP (**430**) was isolated in quantitative yield as a single diastereomer in 94% ee. Interestingly, when this reaction was carried out in Et_2O and left to stand for 24 h, the product was found to have cyclised to the [3,5]-fused bicyclic compound **431** in 97% ee. It is probable that the BIMP had catalysed the intramolecular lactamisation. Structurally related compounds were investigated as CCR2 antagonists by Merck, Sharp & Dohme (MSD).[216] Finally, substrate **425**, featuring the OMEM group from the synthesis of

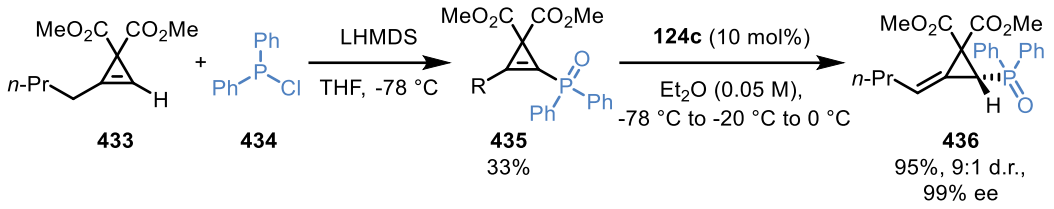
permethrin, underwent the deconjugation with catalyst **124c** and the product (**432**) was obtained in 84% yield as a single diastereomer. Unfortunately, an accurate value for the ee for compound **432** has not been obtained at the time of writing.



Scheme 84: Reaction scope for the BIMP-catalysed enantioselective deconjugation of amide bearing substrates. [a]Catalyst **124d** was used. [b]Reaction carried out in THF.

As a final point of interest, the use of a phosphine oxide electron withdrawing group was investigated for reactivity and selectivity under the deconjugative conditions. The desired substrate was readily synthesised by the addition of terminal cyclopropene **433** to chlorodiphenylphosphine (**434**) in the presence of LHMDS resulting in the phosphine, which oxidised to provide the phosphine oxide during the aqueous work-up (Scheme 85). With the new substrate in hand, we tested it in the BIMP catalysed reaction. Initially, the reaction was carried out at –78 °C as racemisation of the final product was a concern however, the reaction failed to progress and so was warmed to –20 °C. Unfortunately, conversion to product was still slow and so the temperature was raised further to 0 °C and left to react for 1 h. Now reactivity was observed, and the desired ACP (**436**) was

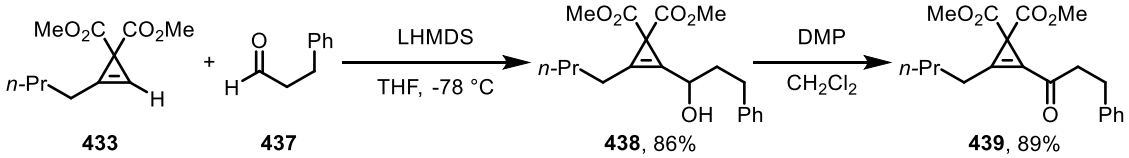
obtained in excellent yield (95%), high diastereoselectivity (9:1 d.r.) and with complete enantiocontrol (99% ee).



Scheme 85: Synthesis and reactivity of phosphine oxide substrate **435**. R = *n*-Bu.

3.3.6 Optimisation of reaction conditions - ketones

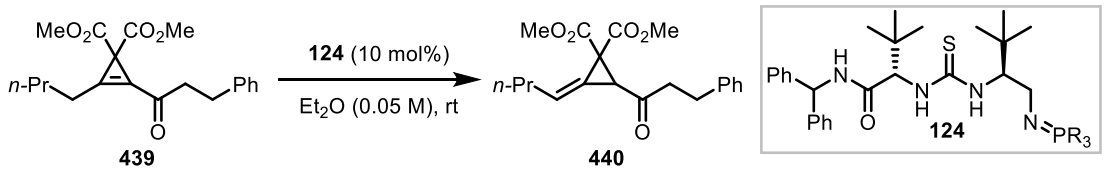
Following the success with esters, amides and a standalone example of a phosphine oxide, the compatibility of other electron withdrawing groups under the reaction conditions was investigated, allowing further expansion into new chemical space.



Scheme 86: Synthesis of substrate **439**.

Ketone **439** was prepared by addition of cyclopropene **433** to aldehyde **437** in the presence of LHMDS (86% yield) followed by oxidation with DMP (89% yield) (Scheme 86). It rapidly (complete in 15 min) underwent the deconjugation reaction when subjected to the conditions described in section **3.3.1**. NMR data revealed a single E/Z isomer had been formed and the product (**440**) was isolated in 84% yield. Unfortunately, the catalyst was unable to control the enantioselectivity of the ketone as it had for previous substrates and the product was only obtained in 20% ee. In order to overcome this problem, the basicity of the catalyst was reduced by varying the iminophosphorane. Four iminophosphoranes were tested. An iminophosphorane featuring a single *p*-CF_3 accelerated reaction completion to within 5 minutes but the isolated product was obtained

in just 4% ee (Table 10, entry 2). Similarly, a single *p*-C≡N group on the phosphine gave fast reaction and little enantiocontrol (4% ee after 10 minutes) (Table 10, entry 3). Introduction of an additional *p*-CF_3 group in the catalyst gave rapid reaction but resulted in the preferential formation of the opposite enantiomer in 10% ee (Table 10, entry 4). Introduction of a third *p*-CF3 group slowed the reaction somewhat but indeed resulted in a better enantiomeric excess (20%) (Table 10, entry 5).

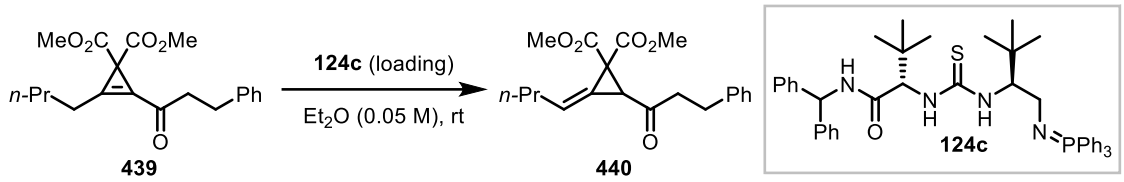


entry	*phosphine*	*time / min*	*yield / %*	*d.r. (Z:E)*	*ee (Z) / %*
1	PPh_3	15	84	>20:1	20
2	$PPh_2((p\text{-}CF_3)C_6H_4)$	10	90	>20:1	4
3	$PPh_2((p\text{-}CN)C_6H_4)$	10	78	>20:1	4
4	$PPh((p\text{-}CF_3)C_6H_4)_2$	10	85	N/D	-10
5	$P((p\text{-}CF_3)C_6H_4)_3$	43	84	N/D	-20

Table 10: Phosphine screen for the enantioselective deconjugation of ketone **439**.

In 2011, Gröger and Berkessel showed that the selectivity in an enamine catalysed aldol reaction could be improved by lowering the catalyst loading.[217] It was believed that the reaction was likely to be under thermodynamic control at high catalyst loadings (5.0 mol%) and kinetic control at low loadings (0.5 mol%). Since our reaction proceeded so rapidly at 10 mol% catalytic loading, a similar trend with respect to catalyst loading was expected, and thus investigated by lowering the catalyst loading to 0.5 mol%. Loadings this low could be achieved by making a stock solution of the active BIMP catalyst from which aliquots were taken and added to the substrate solution. Once confirmed as complete by TLC, reactions were filtered through a silica plug for analysis. Our initial

result (Table 11, entry 2) showed completion of the reaction within 40 minutes however the enantioselectivity remained poor at 22% ee. By taking TLC samples every two minutes, completion was observed after 20 min with 0.5 mol% catalyst loading (Table 11, entry 3). (TLC plates were developed by UV lamp observation followed by $KMnO_4$ staining) Armed with this knowledge, the experiment was repeated and worked up at the earlier time point of 20 min (Table 11, entry 4). Despite the reduced reaction time, the outcome remained the same with the desired deconjugated ketone (**440**) being obtained in 23% ee. The catalyst loading was lowered further to 0.1 mol% (entry 5) however, the reaction took far longer to complete (180 min) and the product was again obtained in 23% ee.

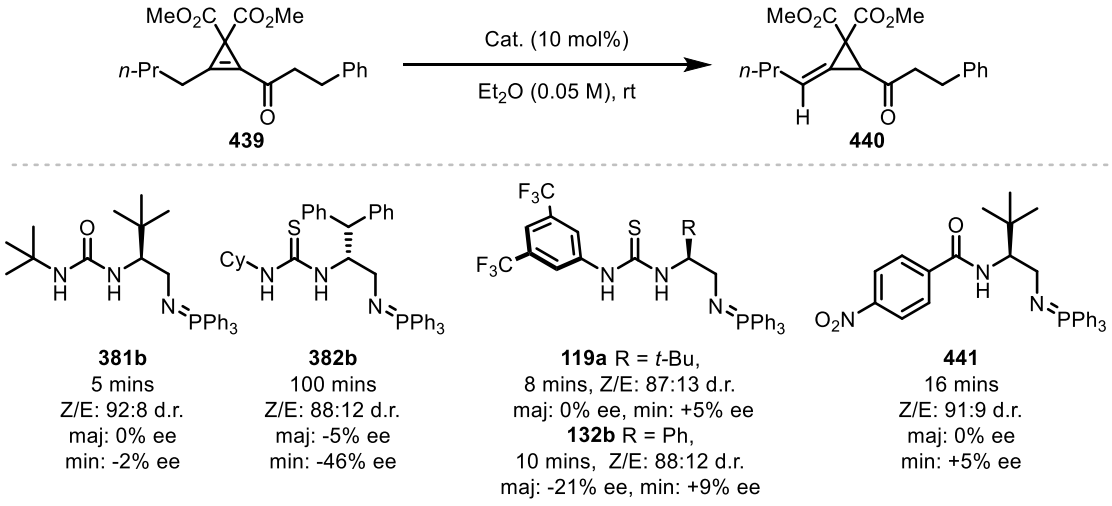


entry	*CL / mol%*	*time / min*[a]	*ee (Z) / %*
1	10	15	20
2	0.5	40	22
3	0.5	42	22
4	0.5	20	23
5	0.1	180	23

Table 11: Investigations into the catalyst loading for the enantioselective deconjugation of substrate **439**. [a]Time to 100% consumption of starting material as observed by TLC.

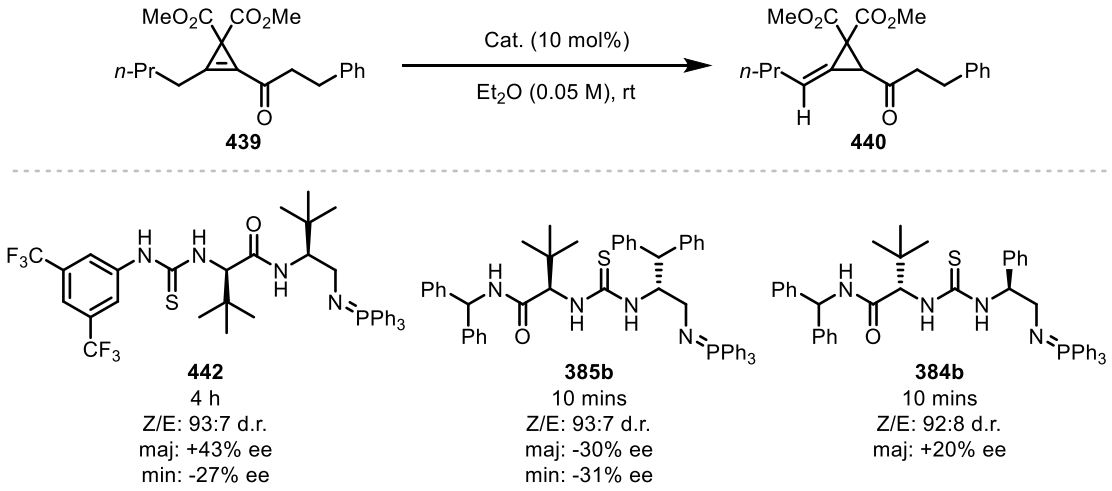
Disappointed that no significant levels of enantioselectivity with catalyst **124c** could be accessed, the effect of other catalyst scaffolds on substrate **439** was investigated (Scheme 87) by screening a library of 1st generation BIMP catalysts. Catalyst **381b**, whose scaffold

had performed well with our ester derived substrates with $P(PMP)_3$ as the phosphine (**381a**) (Scheme 73), affected complete reaction in 5 min, but without significant levels of enantioselectivity. Catalyst **382b**, containing a thiourea H-bond donor, was a less effective catalyst than **381b**, the reaction taking 100 minutes to reach completion; similarly low levels of enantioselectivity were observed for the major E/Z isomer (5% ee) while the minor isomer was obtained in 46% ee. The H-bond donor was modified further and this time catalyst **119a** containing a 3,5-[bis(trifluoromethyl)phenyl] moiety – to increase the thiourea's H-bond donor capabilities – was used. The reaction was rapid (ca. 8 min to completion), however, the major isomer was found to be racemic, and the minor isomer was only obtained in 5% ee. Upon changing the substituent at the stereocentre of catalyst **119a** to feature a phenyl group (**132b**), a slight boost in selectivity was detected and the major and minor isomers were provided in 21% ee and 9% ee respectively. As a final point of investigation into the 1st generation catalysts the H-bond donor was switched to an amide (**441**) though this did not improve the outcome and the major isomer was found to be racemic.



Scheme 87: Enantioselective deconjugation of substrate **439** with 1st generation BIMP catalysts. [a]Time to 100% consumption of starting material as observed by TLC.

Following limited success with 1st generation catalysts, the suitability of 2nd generation scaffolds was probed (Scheme 88). Catalyst **442**, notable for the increased distance between the hydrogen bond donor and the iminophosphorane, was initially investigated. Despite an increased reaction time, this catalyst provided the product's major diastereomer in 43% ee and its minor diastereomer in 27% ee, a significant improvement from our original catalyst scaffold (**124c**) and the 1st generation catalysts (Scheme 87). 2nd generation catalysts **385b** and **384b** provided the major isomer of **440** in -30% ee and 20% ee respectively and catalyst **385b** gave a similar level of selectivity in the minor isomer that was obtained in -31% ee.

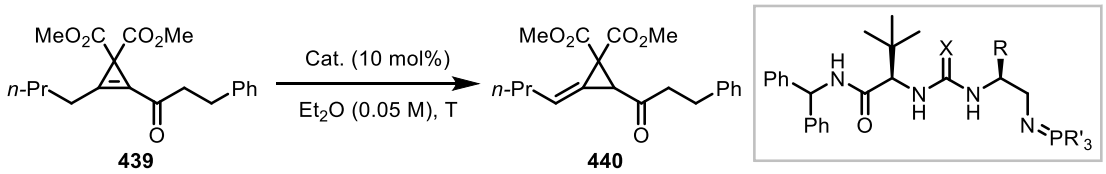


Scheme 88: Enantioselective deconjugation of substrate **439** with 2nd generation BIMP catalysts. [a]Time to 100% consumption of starting material as observed by TLC.

Following the moderate success with *trans*-2nd generation catalyst scaffolds, the reactivity of their *cis*-diastereomers was naturally of interest. Initially, the catalyst used in the enantioselective prototropic shift of β,γ-unsaturated cyclohexenones was trialled (catalyst scaffold **229**), and pleasingly provided the major E/Z isomer in 39% ee and the minor in 46% ee after 3 h (Table 12, entry 1). The use of catalysts with electron poor phosphines (Table 12, entries 2 and 3) led to a deterioration of enantioselectivity in the major product isomer (28% ee and 24% ee after 7.5 h with PPh_2(*p*-CNC_6H_4) and PPh_2(*p*-

$CF_3C_6H_4$) respectively), however, promisingly, the selectivity for the minor isomer was increased to 50% ee and 60% ee (Table 12, entries 2 and 3). Switching the naphthylmethyl group for a phenyl group (**125**) led to a reduction in the selectivity to 31% ee (Table 12, entry 4). By changing the substituent at stereocentre **b** to a benzyl group (**443**) enantioselectivity was enhanced in both the major and minor isomers after 1.5 h (48% ee and 57% ee respectively) (Table 12, entry 5). A further modification, incorporating a cyclohexyl group (**444**) at the same stereocentre, led to a further increase to 55% ee of the major isomer (Table 12, entry 6). It appeared that increasing the steric bulk around the iminophosphorane's proximal stereocentre correlated with an improvement in enantioselectivity and thus, catalyst scaffold **126** used previously in the sulfa-Michael addition to benzimidazoles, would be expected to offer an uplift in selectivity on this system.[83] To investigate this theory, the corresponding azide was synthesised (see experimental section) and catalyst scaffold **126** was trialled in the reaction. Considering the reaction rates already seen with *cis*-2nd generation catalysts (**125**, **443** and **444**), the reaction was allowed to progress over 2 h (Table 12, entry 7). Unexpectedly, the major diastereomer of the product was found to be racemic while the minor diastereomer was obtained in 31% ee. It appeared that racemisation was occurring following formation of the deconjugated ketone as had been observed with esters. To counter this effect, the reaction was quenched after 5 min (Table 12, entry 8) and now the enantiomeric excess of the major isomer was increased to 24% ee and the minor isomer's appeared to >99% ee. Reducing the reaction time to 30 s (Table 12, entry 9) enhanced enantioselectivity still further and the major isomer was now obtained in 65% ee. The high reaction rate meant that a lower temperature could be tolerated. Cooling the reaction to –78 °C, and allowing the reaction to progress over the course of an hour, provided the

uplift in selectivity required. The β,γ-unsaturated ketone was obtained in 93% yield (by NMR) and 94% ee (Table 12, entry 10). Repeating the reaction and allowing it to proceed for 2 h produced the desired alkylidenecyclopropane (**440**) in 99% yield and 93% ee as a single diastereomer (Table 12, entry 11). Finally, NOESY experiments were used to investigate the double bond geometry; a cross-peak was observed between the alkene's C–H and the ketone's α-CH_2 proton, supporting the molecule's *Z*- stereochemical configuration.

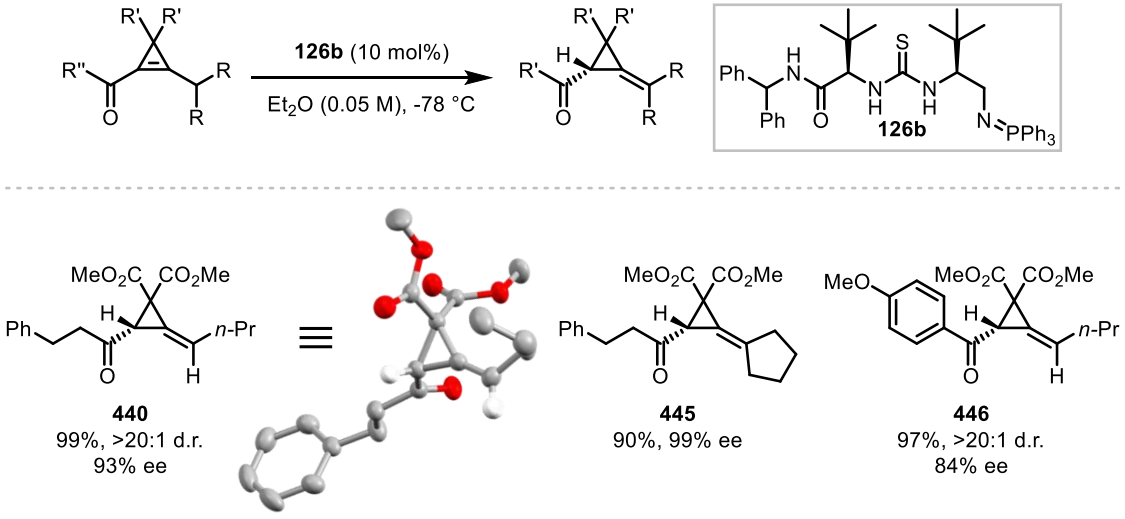


entry	*R*	*phosphine*	*temp / °C*	*time / min*[a]	*Z/E (d.r.)*	*ee maj (Z)/%*	*ee min (E)/%*
1	CH_2(1-Np)	PPh_3	rt	180	76:24	+39	+46
2	CH_2(1-Np)	PPh_2(*p*-CNC_6H_4)	rt	450	83:17	+28	+50
3	CH_2(1-Np)	PPh_2(*p*-$CF_3C_6H_4$)	rt	250	81:19	+24	+60
4	Ph (**125**)	PPh_3	rt	180	92:8	+31	+33
5	Bn (**443**)	PPh_3	rt	90	76:24	+48	+57
6	Cy (**444**)	PPh_3	rt	90	87:13	+55	N/D
7	*t*-Bu (**126b**)	PPh_3	rt	120	20:1	0	+31
8	*t*-Bu	PPh_3	rt	5	20:1	+24	>+99
9	*t*-Bu	PPh_3	rt	0.5	>20:1	+65	>+99
10	*t*-Bu	PPh_3	-78	60[b]	>20:1	+94	N/D
11	*t*-Bu	PPh_3	-78	120[c]	>20:1	+93	N/D

Table 12: Catalyst, phosphine and conditions screen for the enantioselective deconjugation of substrate **439**. [a]Time to 100% consumption of starting material as observed by TLC. [b]93% NMR yield. [c]99% yield.

3.3.7 Reaction scope - ketones

With our re-optimised reaction conditions that were applicable to more reactive ketone cyclopropenes, more substrates were investigated to assess the scope with catalyst **126b**. Replacement of the *n*-Bu group (**439**) with a cyclopentyl ring led to an improvement in enantioselectivity (99% ee) and the product (**445**) was obtained in 90% yield. Similarly, modification of the electronic properties of the ketone was well tolerated and product **446** featuring a PMP ketone was obtained in 97% yield and 84% ee, with complete diastereocontrol. Finally a single-crystal X-ray structure was obtained for compound **440** confirming the absolute stereochemistry. Interestingly, the stereochemistry was found to be opposite to that obtained when esters and amides were used in the reaction suggesting an alternate mechanism.

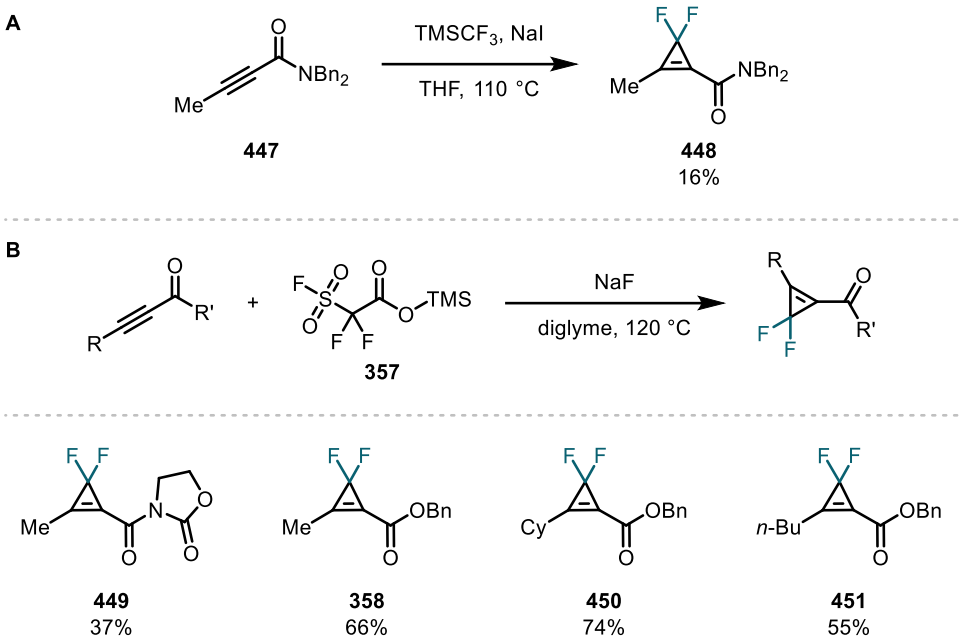


Scheme 89: Reaction scope for the BIMP-catalysed enantioselective deconjugation with ketones and single-crystal X-ray structure of compound **440**.

3.3.8 Difluorocyclopropenes

As a final point of interest, the applicability of difluorocyclopropenes in the reaction was investigated to provide a new method to synthesise difluorocyclopropanes in an enantioselective manner. Addition of difluorocarbenes to alkynes was a feasible way to form

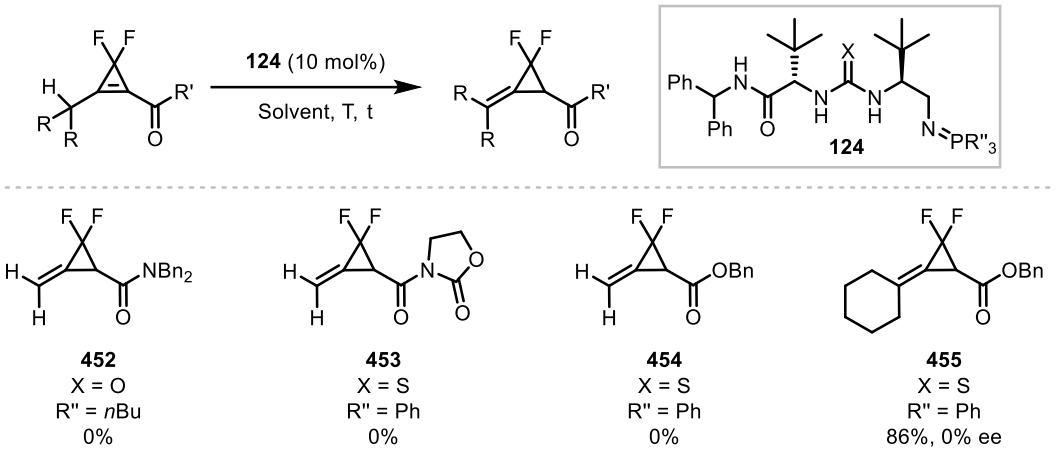
the desired difluorocyclopropenes (Scheme 69). This could be achieved using $TMSCF_3$ in the presence of sodium iodide at high temperature (Scheme 69A) or through the dropwise addition of TFDA (**357**) to a solution of the alkyne and catalytic sodium fluoride at 120 °C (Scheme 69B). A range of substrates were synthesised using these methods.



Scheme 90: A) Synthesis of difluorocyclopropene **448** using $TMSCF_3$; B) Synthesis of difluorocyclopropene **449**-**451** using TFDA (**357**).

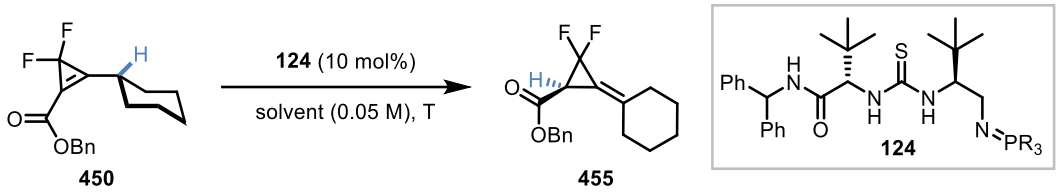
Each substrate was subjected to our optimised reaction conditions with catalyst scaffold **124**. No reactivity was observed with substrates **448**, **449** and **358**. **448** failed to react even with the more basic P(*n*-Bu)$_3$ derived iminophosphorane. Substrate **450** which featured a cyclohexyl group as well as the benzyl ester was smoothly converted to the deconjugated product in 86% yield. Unfortunately, the product was not obtained with any level of enantioselectivity. It is worth noting that substrates **358** and **450** are identical with the exception of their Me and cyclohexyl groups. The difference in reactivity could therefore be attributed to the difference in stability of their external double bonds, with the more substituted product **455** being the more stable and energetically favourable to form under the

reaction conditions. Research by Wiberg has also shown fluorine substituents stabilise the cyclopropene which could hamper reactivity.[218]



Scheme 91: BIMP-catalysed deconjugation of difluorocyclopropenes.

Undeterred by the lack of selectivity, the effect of the catalyst's basicity on the deconjugation with substrate **450** and a range of phosphines were screened with BIMP scaffold **124**. Disappointingly iminophosphoranes derived from phosphines P(*p*-$CF_3C_6H_4)_3$, P(*p*-$FC_6H_4)_3$ and P(*p*-$ClC_6H_4)_3$ (Table 13, entries 1 to 3) performed poorly under the reaction conditions providing only trace amounts of product although P(*p*-$CF_3C_6H_4)_3$ provided the product in 60% ee (Table 13, entry 1). Reactivity was improved with PPh_2(*p*-$CF_3C_6H_4$) and PPh_2(*p*-ClC_6H_4) and the product could be obtained in 82% and 87% NMR yield respectively (Table 13, entries 4 and 5). Product was obtained in 61% ee with PPh_2(*p*-$CF_3C_6H_4$) though phosphine PPh_2(*p*-ClC_6H_4) led to a decrease to 30% ee. PPh_2(*p*-CNC_6H_4) featuring a single *p*-C≡N group provided an improvement in enantioselectivity (69% ee) although the yield was only 3% (Table 13, entry 6). Decreasing the temperature to –78 °C and allowing it to warm to –20 °C was found to be detrimental to the yield (58%) however enantioselectivity was improved (33% ee) with PPh_3 (Table 13, entry 7).

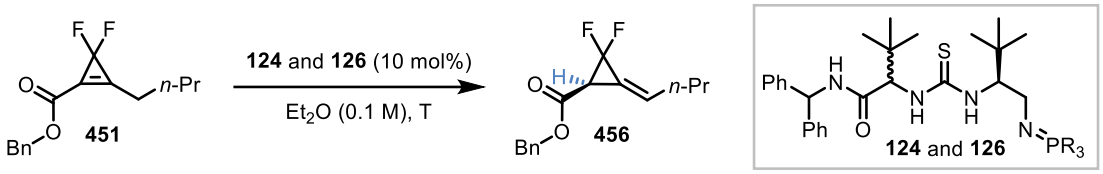


entry	*solvent*	*phosphine*	*temp / °C*	*yield / %*	*ee maj (Z) / %*
1	Et_2O	P(*p*-$CF_3C_6H_4$)$_3$	rt	trace	60
2	Et_2O	P(*p*-FC_6H_4)$_3$	rt	trace	N/D
3	Et_2O	P(*p*-ClC_6H_4)$_3$	rt	trace	N/D
4	Et_2O	PPh_2(*p*-$CF_3C_6H_4$)	rt	82[a]	61
5	Et_2O	PPh_2(*p*-ClC_6H_4)	rt	87[a]	30
6	Et_2O	PPh_2(*p*-CNC_6H_4)	rt	3	69
7	Et_2O	PPh_3	-78 to -20	58	33

Table 13: Conditions screen for the enantioselective deconjugation of **450**.[a]NMR yield.

The deconjugation with difluorocyclopropenes proved tougher to control than with previously investigated substrates. Having had limited success with **450** substrate **451** was trialled to see if the less bulky *n*-Pr group offered any improvement to the reactivity. Unfortunately, catalyst scaffold **124** with PPh_3 only provided the product in 43% yield after 25 h in 2% ee, and with PPh_2(*p*-CNC_6H_4) no reaction was observed (Table 14, entries 1 and 2). PPh_2(*p*-$CF_3C_6H_4$) and PPh(*p*-$CF_3C_6H_4$)$_2$ gave similar reactivity to PPh_3 and the diastereoselectivity was consistent however the ee was low (10% ee) (Table 14, entries 3 and 4). Catalyst scaffold **126** was also trialled in the reaction and gave higher levels of conversion to product with a range of phosphines however the diastereoselectivity was generally poor and enantioselectivity was extremely low (Table 14, entries 5 to 8). It was noted that product formation tended to occur rapidly within the first hour of the reaction, as determined by TLC analysis, however, the reactions never

appeared to reach completion. This suggests that either an equilibrium was being reached or that the catalyst was decomposing. The equilibrium may be explained by the *gem*-difluorocyclopropene's partial aromatic character, hence, the enhanced stability provided by the *gem*-difluoro group makes deconjugation less favourable.[173] It appears however that additional substituents in the γ-position improves the desired reactivity as the stability of the double bond is increased. A similar effect was demonstrated by Shi *et al.* who improved the stability of the alkylidene cyclopropane through aromatic conjugation as discussed in section **3.2.3**.[176] Other studies have shown that an alkylidene cyclopropane bearing a *gem*-difluoro group is likely to undergo isomerisation to the cyclopropene.[219] Further research will need to be undertaken to improve the outcome of this reaction.



entry	*Cat.*	*phosphine*	*temp / °C*	*time / h*	*yield / %*	*d.r.*	*ee (maj) / %*
1	**124**	PPh_3	rt	25	43	N/D	2
2	**124**	$PPh_2(p\text{-}CNC_6H_4)$	rt	26	0	N/D	N/D
3	**124**	$PPh_2(p\text{-}CF_3C_6H_4)$	rt	24	46[a]	87:13	10
4	**124**	$PPh(p\text{-}CF_3C_6H_4)_2$	rt	24	36[a]	88:12	N/D
5	**126**	$P((m\text{-}t\text{-}Bu)_2C_6H_3)_3$	rt	19	83[a]	50:50	3
6	**126**	$PPh_2(p\text{-}CF_3C_6H_4)$	rt	19	74[a]	71:29	13
7	**126**	$PPh(p\text{-}CNC_6H_4)_2$	rt	19	78[a]	56:44	8
8	**126**	$PPh(p\text{-}CF_3C_6H_4)_2$	rt	19	66[a]	86:14	8

Table 14: Conditions screen for the enantioselective deconjugation of **451**.[a]Conversion to **456**.

3.4 Conclusions and further work

To conclude, the applicability of the BIMP catalyst family towards the synthesis of highly enantio- and diastereoenriched cyclopropanes has been established. The reaction proceeds via a strain-relieving deconjugation of pro-chiral α,β-unsaturated carbonyl compounds to form the methylene cyclopropane generating a new stereocentre α- to the carbonyl. A range of carbonyl motifs were demonstrated to be applicable in the reaction including esters, ketones and amides and structural modifications could be made to the cyclopropene ring. Excitingly modification of the ring and re-optimisation of the BIMP catalyst allowed the synthesis of pyrethroid insecticides and their cores. Further work on

the cyclopropene deconjugation is currently ongoing. It is hoped that this strategy will be applicable to other small rings such as cyclobutenes.

4. Final remarks and future endeavours

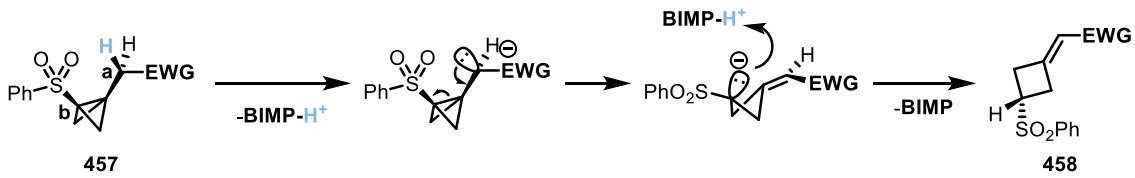
Over the course of this DPhil, two new BIMP-catalysed transformations have been developed.

In chapter **2** BIMP catalysis was shown to perform extremely well in the enantioselective [1,3]-prototropic shift of β,γ-unsaturated cyclohexenones providing the desired conjugated counterparts in up to 99% yield and 99% ee. The limitations of this transformation were addressed during the project and by tuning the iminophosphorane a method has been developed for the synthesis of a broad range of enantioenriched cyclohexenones. The enantioenriched products could be derivatised further. This transformation was investigated by in depth labelling studies as well as computational modelling providing an insight into the reaction mechanism.

The concepts and ideas that were tackled in the [1,3]-prototropic shift of β,γ-unsaturated cyclohexenones were then applied to a brand new project in chapter **3**. Here the BIMP catalyst was used to carry out a strain relieving deconjugation of cyclopropenes to form their alkylidenecyclopropane counterparts whilst concomitantly generating a new stereocentre. By careful modification of the BIMP catalyst the method was applied to a number of carbonyl-types including esters, amides and ketones and the products could be obtained in up to 99% yield and 99% ee. To further supplement the work the transformation was applied to the synthesis of (+)-*cis*-permethrin which could be obtained as a single diastereomer in 99% ee.

The application of the BIMP to a strain relieving deconjugation opens a new dimension in BIMP catalysis and it is hoped that future work will pursue the concept of strain relief. The direction of the work will, in some respects, follow similar lines to that of the cyclopropene deconjugation, with the intention of designing and developing novel methods for the synthesis of important small, chiral molecules. Preliminary studies have already been undertaken into the strain relieving enantioselective deconjugation of cyclobutenes and the initial results showed promise, though further work will be required to discover the correct chiral-catalyst as well as optimise the reaction conditions for a broad reaction scope.

To further build upon the exploitation of strain, within the realm of organocatalysis, investigations into the reactions of bicylobutanes and propellanes could be undertaken. The highly strained internal σ-bonds of these species are susceptible to the addition of nucleophiles and, with the placement of a suitable electron-withdrawing group, could be applicable to prototropic-shift type reactions such as that outlined in Scheme 92.



Scheme 92: Concept for a BIMP catalysed enantioselective strain release of bicyclobutanes.

The progress made on bifunctional iminophosphorane catalysis, during this DPhil, has furthered understanding of the catalyst class itself and thoroughly demonstrated its tunability building upon previous work in the group. Not only this but the catalyst's applicability to enantioselective prototropic shifts has been successfully demonstrated. Future investigations into BIMP-catalysis will likely uncover new, exciting areas of research as well as a greater range of catalyst-designs and transformations.

5. Experimental

5.1 General experimental

5.1.2 Atmosphere

All reactions were carried out under an atmosphere of Ar or N_2 unless otherwise stated.

5.1.3 Solvents

Moisture sensitive reactions were carried out using solvents obtained from the MBRAUN-SPS solvent purification system (CH_2Cl_2, THF, pentane, toluene, DMF, Et_2O) and often dried over 3Å molecular sieves. Reactions that were not deemed moisture sensitive were carried out using solvents taken from Winchester bottles. For reactions sensitive to oxygen solvents were degassed with Ar.

5.1.4 Catalysts

Some BIMP catalysts and precursors were kindly provided by other group members who had previously synthesised them.

5.1.5 Chromatography

TLCs were carried out using Merck aluminium backed DC60 F254 plates (particle size 0.2 mm). UV light was used to visualise spots which were often stained with $KMnO_4$, vanillin or ninhydrin depending on the compound. Flash column chromatography was carried out using Sigma Aldrich silica gel 60 Å (particle size 43-60 μm) with the indicated solvent system.

5.1.6 Spectroscopy

Proton (^{1}H), carbon (^{13}C), phosphorus (^{31}P) and (^{19}F) spectra were recorded on Bruker DPX200 (200 MHz) Bruker AVG400 (400/101 MHz), Bruker AVH400 (400/101 MHz), Bruker AVF400 (400/101 MHz), Bruker AVC500 (500/126 MHz), Bruker AVB500 (500/126 MHz), Bruker AVX500 (500/126 MHz), Bruker NEO600 (600/151) and Bruker AV600 (600/151) NMR spectrometers. Spectra were referenced with respect to the residual solvent peak ($CHCl_3$: δ_H 7.26, δ_C 77.16 ppm; C_6D_5H: δ_H 7.16, δ_C 128.06 ppm; CD_3COCD_2H: δ_H 2.05, δ_C 29.84 ppm; CD_2HCN: δ_H 1.94, δ_C 1.32 ppm; $C_6D_4HCD_3$: δ_H 7.09, δ_C 125.13 ppm; CHD_2OD: δ_H 3.31, δ_C 49). Peak assignments were made based on chemical shifts, integrations, coupling constants, 2-D COSY and HSQC, HMBC and NOESY. Peak multiplicities are described as singlet (s), doublet (d), triplet (t), pentet (p), or a combination e.g. doublet of doublets, or as a multiplet over a peak range. Some peaks are described as broad (b). Coupling constants are reported to the nearest 0.5 Hz and ^{13}C chemical shifts are given to the nearest 0.1 ppm.

5.1.7 Mass spectrometry

High-resolution mass spectra (ESI) were recorded using a Bruker μTOF mass spectrometer.

5.1.8 Melting points

Melting points (MP) were obtained using a Leica Galen III Hot-stage melting point apparatus and microscope and on a Kofler hot block and are reported uncorrected.

5.1.9 Infrared

Infrared spectra (IR) were recorded using a Bruker Tensor 27 FT-IR spectrometer as a film or powder sample. Selected maximum absorbances were reported in ν_{max} (cm^{-1}).

5.1.10 X-Ray

Single crystal X-Ray diffraction data were collected using an Enraf-Nonius KCCD diffractometer or an Oxford Diffraction SuperNova diffractometer at 150 K. Crystal structures were solved with SIR92 and refined with CRYSTALS by Dr. Heyao Shi (University of Oxford), Dr. Amber L. Thompson and Dr. Kirsten E. Christensen (University of Oxford Chemical Crystallography department).

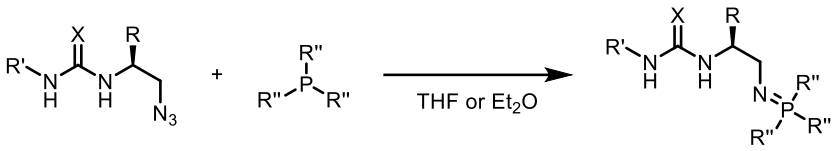
5.1.11 Compound naming

Compound names are those generated by ChemDraw software following the IUPAC nomenclature.

5.2 Synthesis of active BIMP catalysts

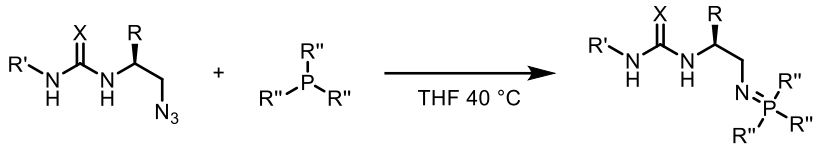
5.2.1 General procedures

General procedure I for *in situ* generation of active BIMP catalysts



To a mass spectrometry vial was weighed the desired azide (1.00 eq) and the desired phosphine (1.00 eq). The vial was placed under an atmosphere of Ar and Et_2O or THF (0.2M) was added. The cap was replaced and sealed with parafilm® and the mixture was stirred for 18 – 24 h. The volatiles were removed under reduced pressure or under a constant stream of Ar and the crude iminophosphorane was used without further purification.

General procedure II for *in situ* generation of active BIMP catalysts with electron poor phosphines



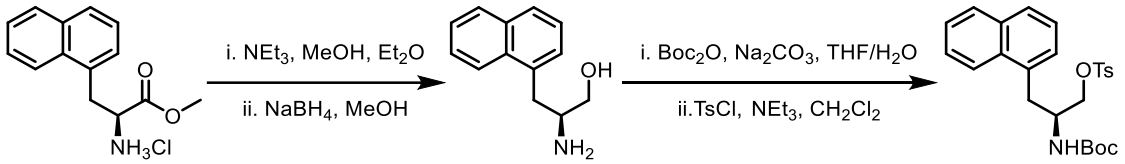
To a mass spectrometry vial was weighed the desired azide (1.00 eq) and the desired phosphine (1.50 – 2.00 eq). The vial was placed under an atmosphere of Ar and THF (0.20 M) was added. The cap was replaced and sealed with parafilm® and the mixture was stirred at 40 °C for 18 – 24 h. The volatiles were removed under reduced pressure or under a constant stream of Ar and the crude iminophosphorane was used without further purification.

5.3 Synthesis of BIMP azide precursors

5.3.1 Synthesis of protected amino azides

5.3.1.1 Synthesis and characterisation of E1

(S)-2-amino-3-(naphthalen-1-yl)propan-1-ol (E1)



a) According to a literature procedure,[220] methyl (*S*)-2-amino-3-(naphthalen-1-yl)propanoate hydrochloride (2.00 g, 6.34 mmol, 1.00 eq) was stirred in MeOH as a slurry. NEt_3 (1 ml) was added followed by Et_2O (35 ml). The mixture was stirred at −10 °C for 1 h at which point the mixture was filtered and washed with Et_2O (30 ml). The filtrate was concentrated *in vacuo* and then placed under an Ar atmosphere. MeOH (18 ml) was added and the solution was cooled to 0 °C. To the stirred solution was added $NaBH_4$ (0.600 g, 15.9 mmol, 2.50 eq) and the reaction mixture was allowed to warm to room temperature overnight. H_2O (30 ml) was added and the aqueous layer was extracted with EtOAc (3 x 30 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo* and taken on without further purification. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = – 47 (*c* 0.21, $CHCl_3$).

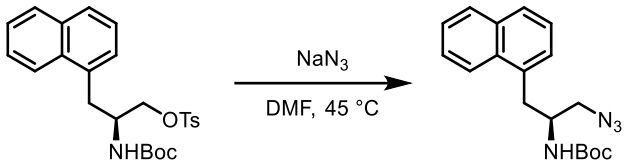
b) To a stirred solution of the crude product obtained in step **a** (1.13 g, 5.61 mmol, 1.00 eq) in a 4/1 mixture of THF/H_2O (14 ml) at 0 °C was added Na_2CO_3 (1.33 g, 12.6 mmol, 2.24 eq) and Boc_2O (1.35 g, 6.18 mmol, 1.10 eq). The reaction was allowed to warm to room temperature overnight at which point H_2O was added (30 ml) and the solution brought to pH 2 by the addition of 0.1 M HCl. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 ml). The combined organic phases were washed with brine, dried over

$MgSO_4$, filtered, and concentrated *in vacuo*. The crude compound, a white solid, was taken on without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 8.19 (d, *J* = 8.5 Hz, 1H, ArH), 7.94 – 7.82 (m, 1H, ArH), 7.75 (dt, *J* = 8.0, 1.0 Hz, 1H¸ ArH), 7.59 – 7.51 (m, 1H, ArH), 7.51 – 7.44 (m, 1H, ArH), 7.44 – 7.32 (m, 2H¸ ArH), 4.94 (bs, 1H, NH), 4.09 – 3.98 (m, 1H, CHNH), 3.76 – 3.49 (bm, 2H, CH_2OH), 3.46 – 3.17 (bm, 2H, CH_2Ar), 2.50 (bs, 1H, OH), 1.42 (bs, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 156.3 (C=O), 134.32 (ArC), 134.1 (ArC), 132.3 (ArC), 128.9 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 126.4 (ArCH), 125.8 (ArCH), 125.6 (ArCH), 124.0 (ArCH), 79.8 (OC(CH_3)$_3$), 64.3 (CH_2OH), 53.2 (CHNH), 34.8 (CH_2Ar), 28.5 (C(CH_3)$_3$).

c) To a stirred solution of the crude product obtained in step **b** (1.28 g, 6.35 mmol, 1.00 eq) in CH_2Cl_2 (21 ml) at 0 °C was added NEt_3 (1.06 ml, 7.62 mmol, 1.20 eq) followed by tosyl chloride (1.33 g, 6.99 mmol, 1.10 eq). The reaction was allowed to warm to room temperature overnight until completion was observed by TLC analysis at which point H_2O (30 ml) was added. The aqueous phase was extracted with EtOAc (3 x 30 ml), washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 85/15 to 8/2) to provide the title compound (**E1**) as an unstable white solid (foam) which was quickly taken on to the next step.

5.3.1.2 Synthesis and characterisation of E2

tert-butyl (S)-(1-azido-3-(naphthalen-1-yl)propan-2-yl)carbamate (E2)

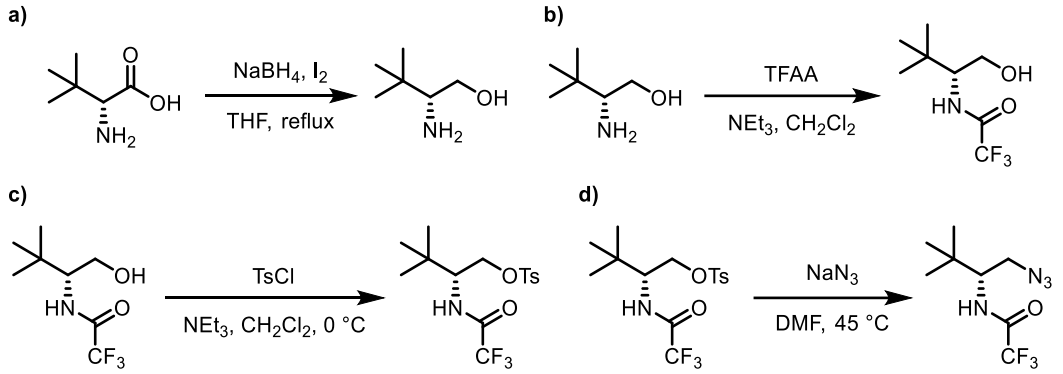


d) According to a literature procedure,[78] sodium azide (1.50 g, 23.1 mmol, 5.00 eq) was added to a stirred solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(naphthalen-1-yl)propyl 4-methylbenzenesulfonate (**E1**) (2.10 g, 4.61 mmol, 1.00 eq) in DMF (23 ml) behind a blast shield. The reaction was warmed to 45 °C and stirred until deemed complete by TLC analysis. H_2O (30 ml) was added, and the aqueous layer was extracted with EtOAc (3 x 30 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* behind a blast shield. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 8/2) to provide the title compound (**E2**) as a white solid in 65% yield (0.975 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 8.17 (d, *J* = 8.5 Hz, 1H, ArH), 7.87 (dd, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.77 (d, *J* = 8.0 Hz, 1H, ArH), 7.57 (t, *J* = 7.5 Hz, 1H, ArH), 7.50 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, ArH), 7.42 (dd, *J* = 8.0, 7.0 Hz, 1H, ArH), 7.35 (d, *J* = 7.0 Hz, 1H, ArH), 4.80 (d, *J* = 8.5 Hz, 1H, NH), 4.21 – 4.03 (m, 1H, CHNH), 3.43 (m, 2H, one of CH_AH_BAr and one of $CH_AH_BN_3$), 3.33 (dd, *J* = 12.5, 4.0 Hz, 1H, one of $CH_AH_BN_3$), 3.20 (dd, *J* = 14.0, 9.0 Hz, 1H, one of CH_AH_BAr), 1.44 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 155.3 (C=O), 134.1 (ArC), 133.6 (ArC), 132.2 (ArC), 129.0 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 126.6 (ArCH), 125.9 (ArCH), 125.6 (ArCH), 123.9 (ArCH), 79.9 ($OC(CH_3)_3$), 53.3 (CH_2N_3), 50.8 (CHNH), 35.6 (CH_2Ar), 28.5 ($OC(CH_3)_3$); **IR** (powder) ν_{max}/cm^{-1}: 3361 (N-H), 2093 (N=N=N), 1687 (C=O); **HRMS** (ES+) exact mass calculated

for $[M+Na]^+$ ($C_{18}H_{22}N_4NaO_2^+$) requires *m/z* 349.1635, found *m/z* 349.1634; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +5.2 (*c* 0.47, $CHCl_3$).

5.3.1.3 Synthesis and characterisation of E3

(R)-N-(1-azido-3,3-dimethylbutan-2-yl)-2,2,2-trifluoroacetamide (E3)



a) According to a literature procedure,[221] a solution of I_2 (9.67g, 38.1 mmol, 1.00 eq) in THF (22.4 ml) was added to a stirred solution of D-*tert*-leucine (5.00 g, 38.1 mmol, 1.00 eq) and $NaBH_4$ (3.46 g, 91.5 mmol, 2.40 eq) in THF (95.3 ml) at 0 °C. The resulting solution was warmed to ambient temperature over 15 min and then refluxed overnight. The solution was then cooled to 0 °C and MeOH was added until the solution turned colourless. The solution was then stirred for a further 30 min at which point the volatiles were removed *in vacuo*. The resulting paste was dissolved in 20% aq KOH and stirred for 3 h. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude amino-alcohol which was taken on to the next step without further purification.

b) According to a literature procedure,[221] Tf_2O (5.56 ml, 40.0 mmol, 1.05 eq) was added over 40 min to a stirred solution of the crude product obtained in step **a** and triethylamine (6.38 ml, 45.7 mmol, 1.20 eq) in CH_2Cl_2 (127 ml). The reaction was stirred for 2 h at which point H_2O (100 ml) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4,

filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 8/2 to 6/4) to provide the product as a white solid in 55% yield (4.45 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 6.52 (bs, 1H, N<u>H</u>), 3.92 – 3.82 (m, 2H, C<u>H</u>C(CH_3)$_3$ and one of C<u>H</u>$_A$H$_B$OH), 3.75 – 3.66 (m, 1H, one of CH$_A$<u>H</u>$_B$OH), 1.95 (s, 1H, O<u>H</u>), 0.98 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 158.3 (<u>C</u>=O), 117.6 (<u>C</u>F_3), 61.7 (<u>C</u>H_2OH), 59.7 (<u>C</u>HCH$_2$), 34.2 (<u>C</u>(CH_3)$_3$), 26.9 (C(<u>C</u>H$_3$)$_3$); **^{19}F NMR** (377 MHz, $CDCl_3$) δ(ppm): -75.7 (C<u>F</u>$_3$); **IR** (powder) ν_{max}/cm^{-1}: 3401 (O-H), 3233 (N-H), 2972 (C-H), 1700 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_8F_3H_{14}NNaO_2^+$) requires *m/z* 236.0716, found *m/z* 236.0719; **MP**: 96 – 98 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = +6.4 (*c* 0.39, $CHCl_3$).

c) According to a literature procedure,[221] the crude product obtained in step **b** was dissolved in CH_2Cl_2 (35 ml) and triethylamine (35 ml). The solution was cooled to 0 °C and TsCl (4.41 g, 23.1 mmol, 1.10 eq) was added. The reaction was stirred at 0 °C overnight at which point H_2O (100 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was taken on without further purification.

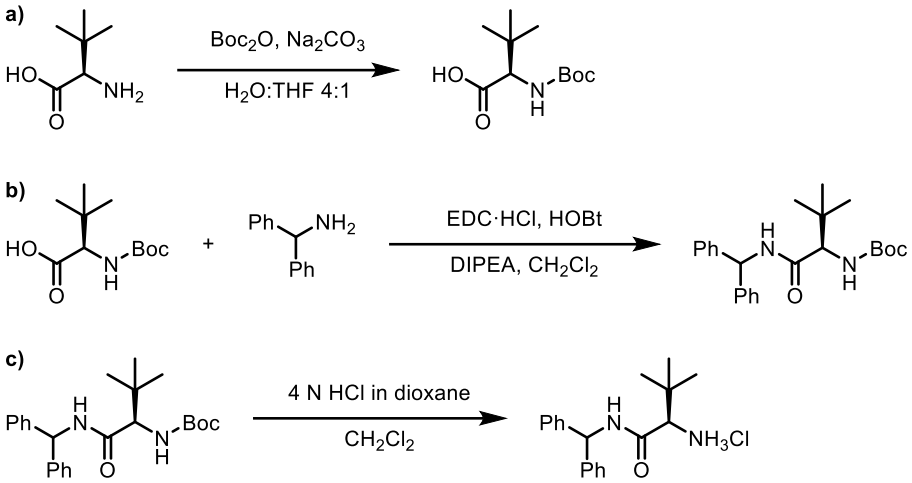
d) According to a literature procedure,[221] the crude product obtained in step **c** (6.64 g, 18.1 mmol, 1.00 eq) was dissolved in DMF (60 ml). Sodium azide (2.35 g, 36.2 mmol, 2.00 eq) was added and the reaction was warmed to 45 °C behind a blast shield. The reaction was stirred at 45 °C overnight at which point H_2O (100 ml) was added. The aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude

product was purified by silica gel column chromatography (pentane/EtOAc = 9/1) to provide the title compound (**E3**) as a white solid in 43% yield (1.86 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 6.27 (bs, 1H, N<u>H</u>), 4.04 – 3.93 (m, 1H, C<u>H</u>NH), 3.63 (dd, *J* = 13.0, 4.0 Hz, 1H, one of C<u>H</u>$_A$H$_B$N$_3$), 3.40 (dd, *J* = 13.0, 8.0 Hz, 1H, one of CH$_A$<u>H</u>$_B$N$_3$), 0.98 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 160.5 – 155.3 (m, <u>C</u>=O), 118.4 – 113.6 (m, <u>C</u>F$_3$), 57.3 (<u>C</u>HNH), 51.2 (C<u>H</u>$_2$N$_3$), 34.3 (<u>C</u>(CH$_3$)$_3$), 26.6 (C(<u>C</u>H$_3$)$_3$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ(ppm): -75.8 (C<u>F</u>$_3$); **IR** (powder) ν_{max}/cm^{-1}: 3283 (N-H), 2971 (C-H), 2092 (N=N=N), 1712 (C=O); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = +46.0 (*c* 1.06, $CHCl_3$). Data are consistent with that published in the literature.[221]

5.3.2 Synthesis of iso(thio)cyanates

5.3.2.1 Synthesis and characterisation of E4

(R)-2-amino-N-benzhydryl-3,3-dimethylbutanamide hydrochloride (E4)



a) According to a literature procedure,[222] D-*tert*-leucine (3.00 g, 22.9 mmol, 1.00 eq), Boc_2O (5.99 g, 27.5 mmol, 1.20 eq) and Na_2CO_3 (4.85 g, 45.7 mmol, 2.00 eq) were stirred overnight in THF (11.4 ml) and H_2O (45.7 ml). The solution was brought to pH 2 by careful addition of HCl (10% aq solution). The aqueous phase was extracted with EtOAc (3 x 50 ml). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product which was taken on without further purification (5.21 g).

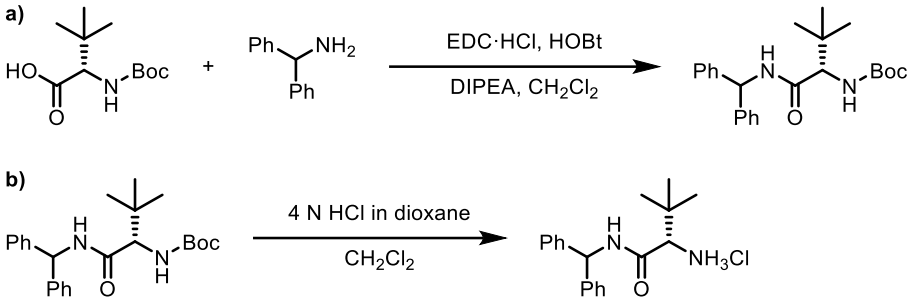
b) According to a literature procedure,[78] DIPEA (4.36 ml, 5.88 mmol, 1.50 eq) and benzhydrylamine (4.27 ml, 24.8 mmol, 1.10 eq) were added sequentially to a stirred solution of EDC hydrochloride (4.75 g, 24.8 mmol, 1.10 eq) and HOBt (3.34 g, 24.8 mmol, 1.10 eq) in CH_2Cl_2 (133 ml) under a N_2 atmosphere at room temperature. *N*-boc-D-*tert*-leucine (5.21 g, 22.5 mmol, 1.00 eq) was added in one portion and the resulting solution stirred for 20 h. The solution was diluted with Et_2O (200 ml) and washed with HCl (0.5 N, 2 x 100 ml). The aqueous phase was extracted with Et_2O (3 x 100 ml) and

the combined organic phases were washed with sat. aq. $NaHCO_3$ (100 ml) and brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product (7.82 g); this was taken on without further purification.

c) According to a literature procedure,[78] 4 N HCl in 1,4-dioxane (47.3 ml, 89.3 mmol, 9.60 eq) was added to a vigorously stirred solution of the crude product obtained in step **b** in CH_2Cl_2 (49.3 ml) under a N_2 atmosphere at room temperature over a period of 5 min. The resulting solution was stirred overnight and concentrated under a stream of N_2. The resulting precipitate was washed with Et_2O and filtered to afford the product crude product (6.35 g). The crude product (**E4**) was taken on without further purification.

5.3.2.2 Synthesis and characterisation of E5

(S)-2-amino-N-benzhydryl-3,3-dimethylbutanamide hydrochloride (E5)

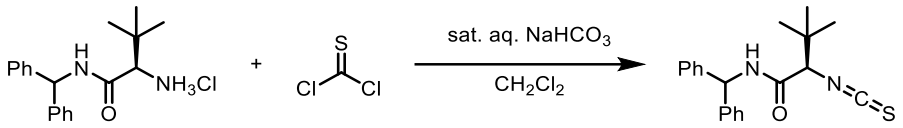


a) According to a literature procedure,[78] DIPEA (11.4 ml, 65.3 mmol, 1.50 eq) and benzhydrylamine (8.21 ml, 47.6 mmol, 1.10 eq) were added sequentially to a stirred solution of EDC hydrochloride (9.12 g, 47.6 mmol, 1.10 eq) and HOBt (6.43 g, 47.6 mmol, 1.10 eq) in CH_2Cl_2 (254 ml) at ambient temperature. *N*-boc-L-*tert*-leucine (10 g, 43.2 mmol, 1.00 eq) was added in one portion and the resulting solution stirred for 20 h. The solution was diluted with Et_2O (200 ml) and washed with HCl (0.5 N, 2 x 200 ml). The aqueous phase was extracted with Et_2O (3 x 200 ml) and the combined organic phases were washed with sat. aq. $NaHCO_3$ (200 ml), brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product which was taken on without further purification.

b) According to a literature procedure,[78] 4 N HCl in 1,4-dioxane (104 ml, 415 mmol, 9.60 eq) was added to a vigorously stirred solution of the crude product obtained in step **a** in CH_2Cl_2 (108 ml) under a N_2 atmosphere at room temperature over a period of 5 min. The resulting solution was stirred overnight and concentrated under a stream of N_2 to afford the product crude product (**E5**) (12.0 g). The crude product was taken on without further purification.

5.3.2.3 Synthesis and characterisation of E6

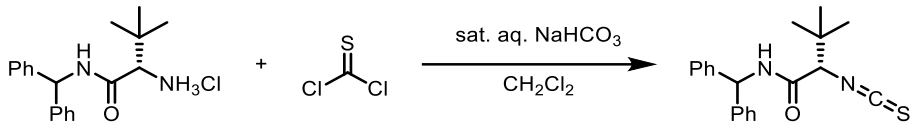
(R)-N-benzhydryl-2-isothiocyanato-3,3-dimethylbutanamide (E6)



According to a literature procedure,[78] sat. aq. $NaHCO_3$ (90 ml) was added to a vigorously stirred solution of (*R*)-2-amino-N-benzhydryl-3,3-dimethylbutanamide hydrochloride (**E4**) (3.00 g, 9.01 mmol, 1.00 eq) in CH_2Cl_2 (90 ml) under a N_2 atmosphere at 0 °C and the biphasic mixture was stirred for 20 min. Stirring was stopped and thiophosgene (0.69 ml, 9.01 mmol, 1.00 eq) added to the organic layer. Vigorous stirring was recommenced immediately after addition and the mixture allowed to warm to room temperature over 30 min. Stirring was stopped, and the organic phase was extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$. The volatiles were removed *in vacuo* to give the crude product (**E6**) as a yellow solid (2.57 g) which was taken on without further purification (84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.32 – 7.19 (m, 6H, ArH), 7.19 – 7.11 (m, 4H, ArH), 6.54 (d, *J* = 8.0 Hz, 1H, NH), 6.17 (d, *J* = 8.0 Hz, 1H, $CHPh_2$), 4.00 (s, 1H, CHC(=O)), 0.99 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 165.5 (C(=O)), 140.9 (ArC), 140.6 (ArC), 137.3 (N=C=S), 128.8 (ArCH), 128.8 (ArCH), 127.8 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.3 (ArCH), 71.0 (CHC(=O)), 57.3 ($CH(Ph)_2$), 37.1 ($CH(CH_3)_3$), 26.8 ($CH(CH_3)_3$); **IR** (powder) ν_{max}/cm^{-1}: 3295 (N-H), 2980, 2971, 2889 (C-H), 1659 (C=O); $[\alpha]_D^{26}$ = –41.8 (*c* 1.06, $CHCl_3$). Data are consistent with that published in the literature.[78]

5.3.2.4 Synthesis and characterisation of E7

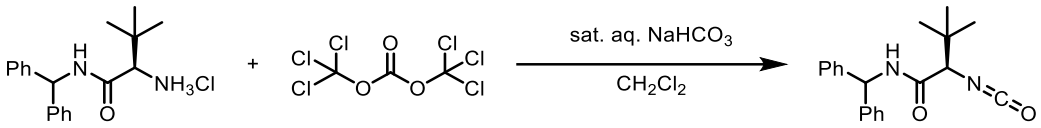
(S)-N-benzhydryl-2-isothiocyanato-3,3-dimethylbutanamide (E7)



According to a literature procedure,[78] sat. aq. $NaHCO_3$ (60 ml) was added to a vigorously stirred solution of (*S*)-2-amino-N-benzhydryl-3,3-dimethylbutanamide hydrochloride (**E3**) (2.00 g, 6.01 mmol, 1.00 eq) in CH_2Cl_2 (60 ml) under a N_2 atmosphere at 0 °C and the biphasic mixture was stirred for 20 min. Stirring was stopped and thiophosgene (0.46 ml, 6.01 mmol, 1.00 eq) added to the organic layer. Vigorous stirring was recommenced immediately after addition and the mixture allowed to warm to room temperature over 30 min. Stirring was stopped, and the organic phase was extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$. The volatiles were removed *in vacuo* to give the crude product (**E7**) as a yellow solid (1.81 g) which was taken on without further purification (89%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.48 – 7.22 (m, 10H, ArH), 6.65 (d, *J* = 8.0 Hz, 1H, NH), 6.28 (d, *J* = 8.0 Hz, 1H, CH(Ph)$_2$), 4.11 (s, 1H, CHC(=O)), 1.10 (s, 10H, ArH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.5 (C(=O)), 140.9 (ArC), 140.6 (ArC), 137.3 (N=C=S), 128.9 (ArCH), 128.8 (ArCH), 127.8 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.3 (ArCH), 71.0 (CHC(=O)), 57.3 (CH(Ph)$_2$), 37.1 (CH(CH$_3$)$_3$), 26.8 (CH(CH$_3$)$_3$); **IR** (powder) ν_{max}/cm^{-1}: 3294 (NH), 3029, 2957 (C-H), 1658 (NHC=O); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = +42.9 (*c* 0.97, $CHCl_3$). Data are consistent with that published in the literature.[81]

5.3.2.5 Synthesis and characterisation of E8

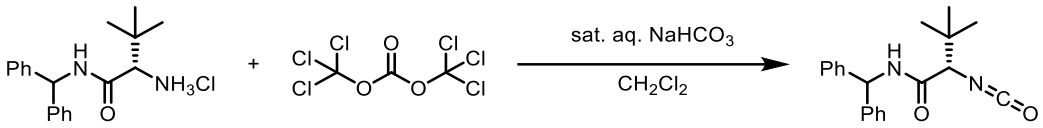
(R)-N-benzhydryl-2-isocyanato-3,3-dimethylbutanamide (E8)



To a stirred solution of (*R*)-2-amino-N-benzhydryl-3,3-dimethylbutanamide hydrochloride (**E4**) (2.00 g, 6.01 mmol, 3.00 eq) in CH_2Cl_2 (33.4 ml) at 0 °C was added sat. aq. $NaHCO_3$. The reaction was stirred for 20 min at which point triphosgene (595 mg, 2.00 mmol, 1.00 eq) was added and the reaction was warmed to room temperature. Upon completion of the reaction the phases were separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 30 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (**E8**) as a white solid in 66% yield (1.27 g) which was taken on without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.37 – 7.05 (m, 10H, ArH), 6.53 (bd, *J* = 8.0 Hz, 1H, NH), 6.18 (d, *J* = 8.0 Hz, 1H, CHNH), 3.71 (s, 1H, CHN=C=O), 0.95 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 167.7 (NHC(=O)), 141.1 (cyclised product)*, 141.0 (cyclised product), 128.9 (cyclised product), 127.8 (ArCH), 127.6 (N=C=O), 127.5 (ArCH), 68.7 (CHN=C=O), 57.4 (CHNH), 36.3 (C(CH_3)$_3$), 26.8 (C(CH_3)$_3$); **IR** (powder) ν_{max}/cm^{-1}: 3659 (N-H), 1651 (N=C=O), 1651 (NHC=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{22}N_2NaO_2^+$) requires *m/z* 345.1574, found *m/z* 345.1574; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +2.6 (*c* 1.06, $CHCl_3$). Data are consistent with that published in the literature.[82] *Minor peaks are a consequence of cyclisation of the amide onto the isocyanate: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 9H, ArH), 7.21 (s, 1H, ArH), 7.16 (s, 1H, NH), 3.68 (d, *J* = 1.5 Hz, 1H, CH(*t*-Bu)), 0.98 (s, 9H, C(CH_3)$_3$).

5.3.2.6 Synthesis and characterisation of E9

(S)-N-benzhydryl-2-isocyanato-3,3-dimethylbutanamide (E9)

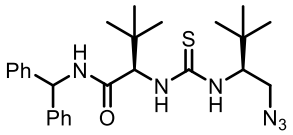


To a stirred solution of (*S*)-2-amino-N-benzhydryl-3,3-dimethylbutanamide hydrochloride (**E3**) (2.00 g, 6.01 mmol, 3.00 eq) in CH_2Cl_2 (33.4 ml) at 0 °C was added sat. aq. $NaHCO_3$. The reaction was stirred for 20 min at which point triphosgene (595 mg, 2.00 mmol, 1.00 eq) was added and the reaction was warmed to room temperature. Upon completion of the reaction the phases were separated and the aqueous layer was washed with CH_2Cl_2 (3 x 30 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the title compound (**E9**) as a white solid in 86% yield (1.67 g) which was taken on without further purification.**^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.34 – 6.98 (m, 10H, Ar<u>H</u>), 6.53 (d, *J* = 8.0 Hz, 1H, N<u>H</u>), 6.18 (d, *J* = 8.0 Hz, 1H, C<u>H</u>NH), 3.72 (s, 1H, C<u>H</u>N=C=O), 0.95 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 167.7 (NH<u>C</u>(=O)), 141.1 (cyclised product), 141.1 (cyclised produc)), 128.9 (cyclised product), 127.8 (Ar<u>C</u>H), 127.6 (N=<u>C</u>=O), 127.5 (Ar<u>C</u>H), 68.7 (<u>C</u>HN=C=O), 57.4 (<u>C</u>HNH), 36.3 (<u>C</u>(CH$_3$)$_3$), 26.8 (C(<u>C</u>H$_3$)$_3$); **IR** (powder) ν_{max}/cm^{-1}: 3299 (N-<u>H</u>), 2990, 2886 (C-H), 1651 (NHC=O); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –14.6 (*c* 1.13, $CHCl_3$). Data are consistent with that published in the literature.[141] *Minor peaks are a consequence of cyclisation of the amide onto the isocyanate, see page 161.

5.3.3 Addition of amino-azides to iso(thio)cyanates to for BIMP azide precursors

5.3.3.1 Synthesis and characterisation of E10

(R)-2-(3-((S)-1-azido-3,3-dimethylbutan-2-yl)thioureido)-N-benzhydryl-3,3-dimethylbutanamide (E10)

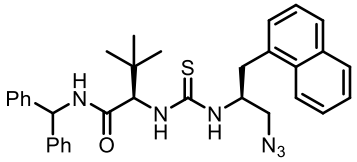


According to a literature procedure,[78] TFA (0.83 ml (1 ml/mmol)) was added to *tert*-butyl (*S*)-(1-azido-3,3-dimethylbutan-2-yl)carbamate (200 mg, 0.83 mmol, 1.00 eq). The reaction was stirred at 0 °C and allowed to warm to ambient temperature over 2 h. The reaction was then concentrated under a stream of N_2 and diluted with Et_2O (4.15 ml (5 ml/mmol)) and H_2O (2.5 ml (3 ml/mmol)). NaOH pellets were added with stirring and the biphasic mixture was brought to pH 14. The phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 20 ml), washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* behind a blast shield (care must be taken as the amine is volatile). 0.71 mmol of amino azide was obtained. The amine was then diluted with THF (2.4 ml) and (*R*)-N-benzhydryl-2-isothiocyanato-3,3-dimethylbutanamide (**E6**) (264 mg, 0.78 mmol, 1.10 eq) was added. Once reaction completion was observed by TLC analysis the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (pentane/Et_2O = 6/4) to provide the title compound (**E10**) as a white solid in 70% yield (280 mg). **^{1}H NMR** (600 MHz, Methanol-d_4) δ(ppm): 7.39 – 7.22 (m, 10H, Ar<u>H</u>), 6.21 (s, 1H, C<u>H</u>Ph_2), 5.06 (s, 1H, C(=O)C<u>H</u>$(CH_3)_3$), 4.68 (d, *J* = 6.5 Hz, 1H, C<u>H</u>CH_2N_3), 3.57 (dd, *J* = 13.0, 4.0 Hz, 1H, one of C<u>H_A</u>H_BN_3), 3.39 – 3.29 (m, 1H, one

of $CH_A\underline{H_B}N_3$), 1.03 (s, 9H, one of $C(C\underline{H_3})_3$), 1.02 (s, 9H, one of $C(C\underline{H_3})_3$); **^{13}C NMR** (151 MHz, Methanol-d_4) δ 186.0 ($\underline{C}$=S), 172.5 ($\underline{C}$=O), 143.0 (Ar$\underline{C}$), 142.7 (Ar$\underline{C}$), 129.5 (Ar$\underline{C}$H), 129.3 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$H), 128.4 (Ar$\underline{C}$H), 128.1 (Ar$\underline{C}$H), 66.5 (C(=O)$\underline{C}$HC$(CH_3)_3$), 62.9 ($\underline{C}HCH_2N_3$), 58.2 ($Ph_2\underline{C}HNH$), 53.0 ($CH\underline{C}H_2N_3$), 35.9 (C(=O)CH$\underline{C}(CH_3)_3$ or NHCH$\underline{C}(CH_3)_3$), 35.7 (C(=O)CH$\underline{C}(CH_3)_3$ or NHCH$\underline{C}(CH_3)_3$), 27.3 ((C(=O)CHC($\underline{C}H_3)_3$ or NHCHC($\underline{C}H_3)_3$)), 27.2 ((C(=O)CHC($\underline{C}H_3)_3$ or NHCHC($\underline{C}H_3)_3$)); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = +5.9 (*c* 1.12, $CHCl_3$). Data are consistent with that published in the literature.[82]

5.3.3.2 Synthesis and characterisation of 229

(R)-2-(3-((S)-1-azido-3-(naphthalen-1-yl)propan-2-yl)thioureido)-N-benzhydryl-3,3-dimethylbutanamide (229)

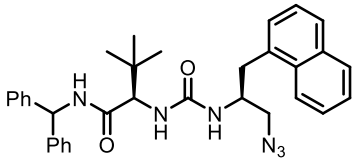


According to a literature procedure,[78] TFA (3 ml (1 ml/mmol)) was added to (*S*)-1-azido-3-(naphthalen-1-yl)propan-2-amine (**E2**) (975 mg, 2.99 mmol, 1.00 eq). The reaction was stirred at 0 °C and allowed to warm to ambient temperature over 2 h. The reaction was then concentrated under a stream of N_2 and diluted with Et_2O (15 ml) and H_2O (9 ml). NaOH pellets were added with stirring and the biphasic mixture was brought to pH 14. The phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 30 ml), washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* behind a blast shield. The amine was then diluted with THF (10.3 ml) and (*R*)-*N*-benzhydryl-2-isothiocyanato-3,3-dimethylbutanamide (**E6**) (1.11 g, 3.29 mmol, 1.10 eq) was added. Once reaction completion was observed by TLC analysis the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (pentane/Et_2O = 7/3 to 6/4) to provide the title compound (**229**) as a white solid in 85% yield (1.44 g). **^{1}H NMR** (400 MHz, Methanol-d_4) δ(ppm): 8.39 (dd, *J* = 8.5, 1.0 Hz, 1H, ArC<u>H</u>), 7.90 – 7.82 (m, 1H, ArC<u>H</u>), 7.76 (dd, *J* = 6.5, 2.5 Hz, 1H, ArC<u>H</u>), 7.54 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, ArC<u>H</u>), 7.48 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, ArC<u>H</u>), 7.44 – 7.36 (m, 2H, ArC<u>H</u>), 7.34 – 7.16 (m, 10H, ArC<u>H</u>), 6.19 (t, *J* = 4.0 Hz, 1H, C<u>H</u>(Ph)$_2$), 5.10 – 5.00 (m, 1H, C<u>H</u>(CH$_2$)$_2$), 4.96 (s, 1H, C<u>H</u>C(CH$_3$)$_3$), 3.55 – 3.39 (m, 2H, one of C<u>H$_A$</u>H$_B$Ar and one of C<u>H$_A$</u>H$_B$N$_3$), 3.39 – 3.17 (m, 2H, one of CH$_A$<u>H$_B$</u>Ar and one of CH$_A$<u>H$_B$</u>N$_3$ and solvent

residue peak), 0.97 (s, 9H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, Methanol-d_4) δ(ppm): 183.2 (<u>C</u>=S), 171.2 (<u>C</u>=O), 141.7 (Ar<u>C</u>), 141.3 (Ar<u>C</u>), 134.1 (Ar<u>C</u>), 133.7 (Ar<u>C</u>), 133.3 (Ar<u>C</u>), 128.4 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 125.3 (Ar<u>C</u>H), 125.0 (Ar<u>C</u>H), 123.9 (Ar<u>C</u>H), 65.1 (<u>C</u>HC(=O)), 56.8 (<u>C</u>H(Ph)$_2$), 53.7 (<u>C</u>H(CH$_2$)$_2$), 53.1 (<u>C</u>H$_2$N$_3$), 34.7 (<u>C</u>H$_2$Ar), 34.4 (<u>C</u>(CH$_3$)$_3$), 26.0 (C(<u>C</u>H$_3$)$_3$); **IR** (powder) ν_{max}/cm^{-1}: 3287 (N-H), 2101 (N=N=N), 1644 (C=O); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{33}H_{36}N_6NaOS^+$) requires *m/z* 587.2564, found *m/z* 587.2564; **MP**: 92-93 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +65.0 (*c* 0.15, $CHCl_3$).

5.3.3.3 Synthesis and characterisation of E11

(R)-2-(3-((S)-1-azido-3-(naphthalen-1-yl)propan-2-yl)ureido)-N-benzhydryl-3,3-dimethylbutanamide (E11)

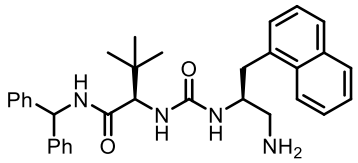


According to a literature procedure,[78] TFA (1.2 ml (1 ml/mmol)) was added to (*S*)-1-azido-3-(naphthalen-1-yl)propan-2-amine (**E2**) (389 mg, 1.19 mmol, 1.00 eq). The reaction was stirred at 0 °C and allowed to warm to ambient temperature over 2h. The reaction was then concentrated under a stream of N_2 and diluted with Et_2O (6 ml) and H_2O (3.6 ml). NaOH pellets were added with stirring and the biphasic mixture was brought to pH 14. The phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 30 ml), washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* behind a blast shield. The amine was then diluted with THF (3.8 ml) and (*R*)-N-benzhydryl-2-isocyanato-3,3-dimethylbutanamide (**E8**) (387 mg, 1.20 mmol, 1.10 eq) was added. Once reaction completion was observed by TLC analysis the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (pentane/Et_2O = 7/3 to 6/4) to provide the title compound (**E11**) as a white solid. **^{1}H NMR** (500 MHz, Methanol-d_4) δ(ppm): 8.19 (d, *J* = 8.5 Hz, 1H, Ar<u>H</u>), 7.85 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar<u>H</u>), 7.74 (dd, *J* = 7.0, 2.5 Hz, 1H, Ar<u>H</u>), 7.53 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1H, Ar<u>H</u>), 7.47 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar<u>H</u>), 7.40 – 7.34 (m, 2H, Ar<u>H</u>), 7.34 – 7.16 (m, 11H, Ar<u>H</u> and N<u>H</u>), 6.16 (s, 1H, C<u>H</u>(Ph)$_2$), 4.59 (s, 1H, N<u>H</u>), 4.25 (tt, *J* = 7.0, 5.0 Hz, 1H, C<u>H</u>CH$_2$N$_3$), 4.07 (s, 1H, C<u>H</u>C(=O)), 3.42 – 3.36 (m, 2H, C<u>H$_2$</u>N$_3$), 3.36 – 3.27 (m, 1H, one of C<u>H$_A$</u>H$_B$CHCH$_2$N$_3$ and solvent residue peak), 3.21 (dd, *J* = 14.0, 7.5 Hz, 1H,

one of $CH_A\underline{H_B}CHCH_2N_3$), 0.86 (s, 9H, $C(C\underline{H_3})_3$); **^{13}C NMR** (126 MHz, Methanol-d_4) δ(ppm): 172.9 ($CH\underline{C}(=O)$), 159.7 ($NH\underline{C}(=O)NH$), 143.0 (Ar<u>C</u>), 142.8 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 135.3 (Ar<u>C</u>), 133.5 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 129.4 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 124.9 (Ar<u>C</u>H), 62.3 ($\underline{C}HC(=O)$), 58.1 ($\underline{C}H(Ph)_2$), 55.6 ($\underline{C}H_2N_3$), 51.7 ($\underline{C}HCH_2N_3$), 36.8 ($\underline{C}H_2CHCH_2N_3$), 35.6 ($\underline{C}(CH_3)_3$), 27.1 ($C(\underline{C}H_3)_3$); **IR** (powder) ν_{max}/cm^{-1}: 3659 (N-H), 2100 (N=N=N), 1629 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{33}H_{36}N_6NaO_2^+$) requires *m/z* 571.2792, found *m/z* 571.2784; **MP**: 107-108 ˚C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +29.2 (*c* 0.59, $CHCl_3$).

5.3.3.4 Synthesis and characterisation of 229b

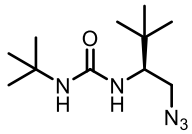
(R)-2-(3-((S)-1-amino-3-(naphthalen-1-yl)propan-2-yl)ureido)-N-benzhydryl-3,3-dimethylbutanamide amide (229b)



To a suspension of Pd/C (≈100 mg/mmol) (10 mg) in MeOH (2 ml) was added azide **E11** (50 mg, 0.096 mmol). The reaction was stirred under an atmosphere of H_2 until deemed complete by TLC (pentane/Et_2O = 7/3). The reaction mixture was filtered through celite, and the crude product was obtained in 98% yield. The crude product was taken on without further purification. **^{1}H NMR** (400 MHz, Methanol-d_4) δ(ppm): 8.22 (d, *J* = 8.5 Hz, 1H, ArH), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.72 (dd, *J* = 6.5, 3.0 Hz, 1H, ArH), 7.53 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, ArH), 7.46 (ddd, *J* = 8.0, 6.5, 1.0 Hz, 1H, ArH), 7.39 – 7.17 (m, 12H, ArH), 6.17 (s, 1H, CHPh$_2$), 4.12 (qd, *J* = 7.5, 4.0 Hz, 1H, CHCH$_2$NH$_2$), 4.04 (s, 1H, CHC(=O)), 3.21 (tp, *J* = 14.0, 7.5 Hz, 2H, CHCH$_2$NH$_2$), 2.79 (dd, *J* = 13.0, 4.0 Hz, 1H, CH$_A$H$_B$CHCH$_2$NH$_2$), 2.59 (dd, *J* = 13.0, 8.5 Hz, 1H, CH$_A$H$_B$CHCH$_2$NH$_2$), 0.87 (s, 9H, C(CH$_3$)$_3$); **^{13}C NMR** (101 MHz, Methanol-d_4) δ(ppm): 173.2 (CHC(=O)), 160.3 (NHC(=O)NH), 143.0 (ArC), 142.8 (ArC), 135.7 (ArC), 135.5 (ArC), 133.6 (ArC), 129.8 (ArC), 129.5 (ArCH), 129.4 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 127.1 (ArCH), 126.6 (ArCH), 126.4 (ArCH), 125.1 (ArCH), 62.6 (CHC(=O)), 58.1 (CH(Ph)$_2$), 54.1 (CHCH$_2$NH$_2$), 46.6 (CH$_2$CHCH$_2$NH$_2$), 37.7 (CH$_2$CHCH$_2$NH$_2$), 35.4 (C(CH$_3$)$_3$), 27.2 (C(CH$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1}: 3297 (N-H), 3060, 2873 (C-H), 1635, 1557 (C=O); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{33}H_{39}N_4O_2^+$) requires *m/z* 523.3066, found *m/z* 523.3065; **MP**: 116 – 118 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = +17.3 (*c* 0.3, $CHCl_3$).

5.3.3.5 Synthesis and characterisation of E12

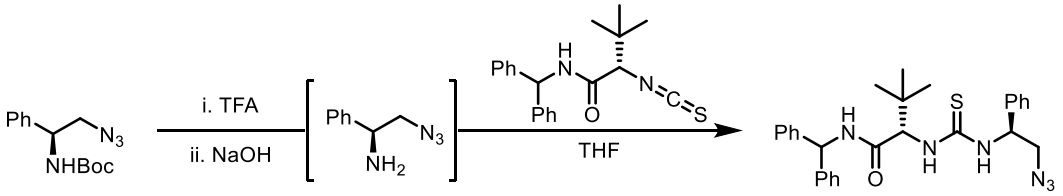
(S)-1-(1-azido-3,3-dimethylbutan-2-yl)-3-(tert-butyl)urea (E12)



According to a literature procedure,[78] TFA (0.83 ml (1 ml/mmol)) was added to *tert*-butyl (*S*)-(1-azido-3,3-dimethylbutan-2-yl)carbamate (200 mg, 0.83 mmol, 1.00 eq). The reaction was stirred at 0 °C and allowed to warm to ambient temperature over 2h. The reaction was then concentrated under a stream of N_2 and diluted with Et_2O (4.15 ml (5 ml/mmol)) and H_2O (2.5 ml (3 ml/mmol)). NaOH pellets were added with stirring and the biphasic mixture was brought to pH 14. The phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 20 ml), washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* behind a blast shield. 0.54 mmol of amino azide was obtained. The amine was then diluted with THF (1.2 ml) and *tert*-butyl isocyante (67.5 µl, 0.590 mmol, 1.10 eq) was added. Once reaction completion was observed by TLC analysis the reaction mixture was concentrated *in vacuo* and purified trituration with pentane to provide the title compound (**E12**) as a white solid in 53% yield (106 mg). **^{1}H NMR** (400 MHz, Methanol-d_4) δ(ppm): 5.77 (d, *J* = 10.5 Hz, 1H, CHN<u>H</u>), 3.69 – 3.59 (m, 1H, C<u>H</u>CH_2), 3.37 (dd, *J* = 12.5, 3.5 Hz, 1H, one of C<u>H</u>$_A$H$_B$), 3.17 (dd, *J* = 12.5, 9.0 Hz, 1H, one of CH$_A$H$_B$), 1.31 (s, 9H, NC(C<u>H</u>$_3$)$_3$), 0.92 (s, 9H, CHC(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (101 MHz, Methanol-d_4) δ(ppm): 160.2 (<u>C</u>=O), 58.7 (<u>C</u>HCH_2), 53.4 (CH<u>C</u>H_2), 50.8 (N<u>C</u>$(CH_3)_3$), 35.2 (CH<u>C</u>$(CH_3)_3$), 29.9 (NC(<u>C</u>H$_3$)$_3$), 27.0 (CHC(<u>C</u>H$_3$)$_3$); **IR** (powder) ν_{max}/cm^{-1}: 3340 (N-H), 2966 (C-H), 2087 (N=N=N), 1633 (C=O); **HRMS** (ES+) exact mass calculated for [M+Na$^+$] ($C_{11}H_{23}N_5NaO^+$) requires *m/z* 264.1795, found *m/z* 264.1796; **MP**: Thermal decomposition was observed at >140 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –33.3 (*c* 0.53, $CHCl_3$).

5.3.3.6 Synthesis and characterisation of E13

(S)-2-(3-((S)-2-azido-1-phenylethyl)thioureido)-N-benzhydryl-3,3-dimethylbutanamide (E13)

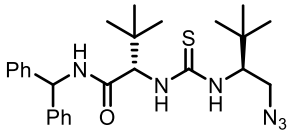


According to a literature procedure,[78] TFA (0.83 ml (1 ml/mmol)) was added to *tert*-butyl (*S*)-(2-azido-1-phenylethyl)carbamate (218 mg, 0.830 mmol, 1.00 eq). The reaction was stirred at 0 °C and allowed to warm to ambient temperature over 2h. The reaction was then concentrated under a stream of N_2 and diluted with Et_2O (4.15 ml (5 ml/mmol)) and H_2O (2.5 ml (3 ml/mmol)). NaOH pellets were added with stirring and the biphasic mixture was brought to pH 14. The phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 20 ml), washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* behind a blast shield. 0.74 mmol of amino azide was obtained. The amine was then diluted with THF (2.5 ml) and (*S*)-N-benzhydryl-2-isothiocyanato-3,3-dimethylbutanamide (**E7**) (264 mg, 0.820 mmol, 1.10 eq) was added. Once reaction completion was observed by TLC analysis the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (pentane/Et_2O = 8/2 to 6/4) to provide the title compound (**E13**) as a white solid in 85% yield (316 mg).**^{1}H NMR** (400 MHz, Methanol-d_4) δ(ppm): 7.50 – 7.04 (m, 15H, Ar<u>H</u>), 6.15 (s, 1H, C<u>H</u>Ph_2), 5.78 (bs, 1H, C<u>H</u>CH_2), 4.96 (s, 1H, C<u>H</u>$C(CH_3)_3$), 3.68 (d, *J* = 1.5 Hz, 1H, one of C<u>H_A</u>H_B), 3.66 (d, *J* = 1.5 Hz, 1H, one of CH_A<u>H_B</u>), 0.99 (bs, 9H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** (151 MHz, Methanol-d_4) δ(ppm): 184.8 (<u>C</u>=S), 172.6 (<u>C</u>=O), 142.9 (Ar<u>C</u>), 142.6 (Ar<u>C</u>), 140.7 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H),

128.5 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 66.7 (<u>C</u>HC(=O)), 58.8 (<u>C</u>HCH$_2$N$_3$), 58.3 (<u>C</u>HPh$_2$), 56.4 (<u>C</u>H$_2$N$_3$), 35.7 (<u>C</u>(CH$_3$)$_3$), 27.3 (C(<u>C</u>H$_3$)$_3$); **IR** (powder) ν_{max}/cm^{-1}: 3281 (N-H), 2990, 2889 (C-H), 2100 (N=N=N), 1649 (C=O); **HRMS** (ES+) exact mass calculated for [M+H$^+$] ($C_{28}H_{32}N_6OS^+$) requires *m/z* 501.2431, found *m/z* 501.2429; **MP**: 84 – 86 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –78.0 (*c* 0.96, CHCl$_3$).

5.3.3.7 Synthesis and characterisation of E14

(S)-2-(3-((S)-1-azido-3,3-dimethylbutan-2-yl)thioureido)-N-benzhydryl-3,3-dimethylbutanamide (E14)

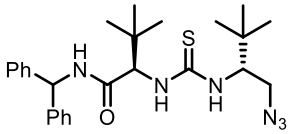


According to a literature procedure,[78] TFA (0.83 ml (1 ml/mmol)) was added to *tert*-butyl (*S*)-(1-azido-3,3-dimethylbutan-2-yl)carbamate (200 mg, 0.830 mmol, 1.00 eq). The reaction was stirred at 0 °C and allowed to warm to ambient temperature over 2h. The reaction was then concentrated under a stream of N_2 and diluted with Et_2O (4.15 ml (5 ml/mmol)) and H_2O (2.5 ml (3 ml/mmol)). NaOH pellets were added with stirring and the biphasic mixture was brought to pH 14. The phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 20 ml), washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* behind a blast shield (care must be taken as the amine is volatile). 0.790 mmol of amino azide was obtained. The amine was then diluted with THF (2.8 ml) and (*S*)-N-benzhydryl-2-isothiocyanato-3,3-dimethylbutanamide (**E7**) (292 mg, 0.86 mmol, 1.10 eq) was added. Once reaction completion was observed by TLC analysis the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (pentane/Et_2O = 6/4) to provide the title compound (**E14**) as a white solid in 73% yield (290 mg). **^{1}H NMR** (400 MHz, Methanol-*d*$_4$) δ (ppm): 7.43 – 7.16 (m, 10H, Ar<u>H</u>), 6.20 (s, 1H, $Ph_2C\underline{H}NH$), 5.05 (s, 1H, $C(=O)C\underline{H}(CH_3)_3$), 4.69 (dd, *J* = 8.0, 4.0 Hz, 1H, $C\underline{H}CH_2N_3$), 3.55 (dd, *J* = 13.0, 4.0 Hz, 1H, $CHCH_A\underline{H_B}N_3$), 1.04 (s, 9H, one of $C(=O)CHC(C\underline{H_3})_3$ or $NHCHC(C\underline{H_3})_3$), 1.01 (s, 1H, one of $C(=O)CHC(C\underline{H_3})_3$ or $NHCHC(C\underline{H_3})_3$) ($CHCH_A\underline{H_B}N_3$ is beneath the solvent peak); **^{13}C NMR** (100 MHz, Methanol-*d*$_4$) δ (ppm) 186.0 (<u>C</u>=S), 172.8 (<u>C</u>=O), 143.0 (Ar<u>C</u>), 142.7 (Ar<u>C</u>), 129.6

(Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 66.6 (C(=O)<u>C</u>HC(CH_3)$_3$), 63.3 (<u>C</u>HCH_2N_3), 58.3 (Ph_2<u>C</u>HNH), 52.9 (CH<u>C</u>H_2N_3), 35.6, 35.6 (C(=O)CH<u>C</u>(CH_3)$_3$ and NHCH<u>C</u>(CH_3)$_3$), 27.3, 27.2 (C(=O)CHC(<u>C</u>H_3)$_3$ and NHCHC(<u>C</u>H_3)$_3$); **MP**: 204-206; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –76.8 (*c* 0.56, $CHCl_3$). Data are consistent with that published in the literature.[81]

5.3.3.8 Synthesis and characterisation of E15

(R)-2-(3-((R)-1-azido-3,3-dimethylbutan-2-yl)thioureido)-N-benzhydryl-3,3-dimethylbutanamide (E15)

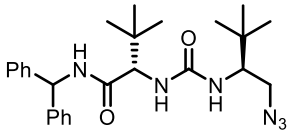


According to a literature procedure,[78,221] (*R*)-N-(1-azido-3,3-dimethylbutan-2-yl)-2,2,2-trifluoroacetamide (**E3**) (800 mg, 3.40 mmol, 1.00 eq) was dissolve in a mixture of MeOH (8.9 ml) and H_2O (4.5 ml). NaOH (1.63 g, 40.8 mmol, 12.0 eq) was added portionwise and the reaction mixture was stirred for 20 h. The aqueous phase was extracted with Et_2O and TFA (3.4 ml) was added. The solvent was removed *in vacuo*. Et_2O (17 ml) and H_2O (10.2 ml) were added. The mixture was basified to pH 14 by addition of NaOH pellets. The aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* behind a blast shield (care must be taken as the amine is volatile). 3.16 mmol of amino azide was obtained. The amine was then diluted with THF (10.5 ml) and (*R*)-N-benzhydryl-2-isothiocyanato-3,3-dimethylbutanamide (**E6**) (1.18 g, 3.48 mmol, 1.10 eq) was added. Once reaction completion was observed by TLC analysis the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (pentane/Et_2O = 9/1 to 8/2 to 6/4) to provide an off-white solid which was triturated with Et_2O. The title compound (**E15**) was obtained as a white solid as in 64% yield (1.05 g). **^{1}H NMR** (600 MHz, Methanol-d_4) δ(ppm): 7.36 – 7.32 (m, 2H, Ar$\underline{H}$), 7.32 – 7.25 (m, 7H, Ar$\underline{H}$), 7.24 – 7.19 (m, 1H, Ar$\underline{H}$), 6.18 (s, 1H, $Ph_2C\underline{H}NH$), 5.03 (s, 1H, C(=O)C$\underline{H}(CH_3)_3$), 4.67 (dd, *J* = 8.0, 4.0 Hz, 1H, C$\underline{H}CH_2N_3$), 3.53 (dd, *J* = 13.0, 4.0 Hz, 1H, CHC$\underline{H_A}H_BN_3$), 1.02 (s, 9H, one of C(=O)CHC(C$\underline{H_3}$)$_3$ or NHCHC(C$\underline{H_3}$)$_3$), 0.99

(s, 9H, one of C(=O)CHC(C$\underline{H}_3$)$_3$ or NHCHC(C$\underline{H}_3$)$_3$). (CHCH$_A\underline{H}_B$N$_3$ is beneath the solvent peak); **^{13}C NMR** (151 MHz, Methanol-d_4) δ(ppm): 186.0 ($\underline{C}$=S), 172.8 ($\underline{C}$=O), 143.0 (Ar$\underline{C}$), 142.7 (Ar$\underline{C}$), 129.6 (Ar$\underline{C}$H), 129.3 (Ar$\underline{C}$H), 129.3 (Ar$\underline{C}$H), 128.6 (Ar$\underline{C}$H), 128.5 (Ar$\underline{C}$H), 128.0 (Ar$\underline{C}$H), 66.6 (C(=O)$\underline{C}$HC(CH$_3$)$_3$), 63.4 ($\underline{C}$HCH$_2$N$_3$), 58.3 (Ph$_2\underline{C}$HNH), 52.9 (CH$\underline{C}$H$_2$N$_3$), 35.6 (one of C(=O)CH$\underline{C}$(CH$_3$)$_3$ or NHCH$\underline{C}$(CH$_3$)$_3$), 35.6 (one of C(=O)CH$\underline{C}$(CH$_3$)$_3$ or NHCH$\underline{C}$(CH$_3$)$_3$), 27.3 (one of C(=O)CHC($\underline{C}$H$_3$)$_3$ or NHCHC($\underline{C}$H$_3$)$_3$), 27.2 (one of C(=O)CHC($\underline{C}$H$_3$)$_3$ or NHCHC($\underline{C}$H$_3$)$_3$); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = +91.4 (*c* 0.99, CHCl$_3$). Data are consistent with that published in the literature.[81]

5.3.3.9 Synthesis and characterisation of E16

(S)-2-(3-((S)-1-azido-3,3-dimethylbutan-2-yl)ureido)-N-benzhydryl-3,3-dimethylbutanamide (E16)

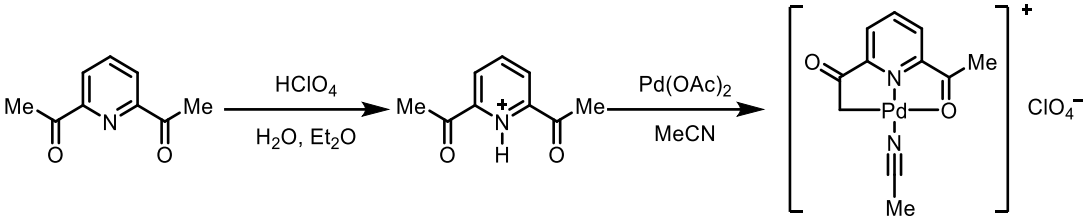


According to a literature procedure,[78] TFA (0.83 ml (1ml/mmol)) was added to *tert*-butyl (*S*)-(1-azido-3,3-dimethylbutan-2-yl)carbamate (200 mg, 0.830 mmol, 1.00 eq). The reaction was stirred at 0 °C and allowed to warm to ambient temperature over 2h. The reaction was then concentrated under a stream of N_2 and diluted with Et_2O (4.15 ml (5 ml/mmol)) and H_2O (2.5 ml (3 ml/mmol)). NaOH pellets were added with stirring and the biphasic mixture was brought to pH 14. The phases were partitioned, and the aqueous phase was extracted with Et_2O (2 x 20 ml), washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* behind a blast shield (care must be taken as the amine is volatile). 0.69 mmol of amino azide was obtained. The amine was then diluted with THF (2.4 ml) and (*S*)-N-benzhydryl-2-isocyanato-3,3-dimethylbutanamide (**E9**) (245 mg, 0.760 mmol, 1.10 eq) was added. Once reaction completion was observed by TLC analysis the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (pentane/Et_2O = 1/1) to provide an off-white solid which was triturated with pentane/Et_2O. The title compound (**E16**) was obtained as a white solid as in 39% yield (150 mg). **^{1}H NMR** (600 MHz, Methanol-d_4) δ(ppm): 7.38 – 7.22 (m, 10H, Ar<u>H</u>), 6.20 (s, 1H, C<u>H</u>Ph_2), 4.21 (s, 1H, C<u>H</u>C(=O)), 3.75 (dd, *J* = 9.5, 3.5 Hz, 1H, C<u>H</u>CH_2N_3), 3.45 (dd, *J* = 13.0, 3.5 Hz, 1H, one of C<u>H_A</u>H_BN_3), 3.22 (dd, *J* = 12.5, 9.5 1H, one of CH_A<u>H_B</u>N_3), 1.01 (s, 9H, one of C(C<u>H_3</u>)$_3$), 0.95 (s, 9H, one of C(CH_3)$_3$); **^{13}C NMR** (151 MHz, Methanol-d_4) δ(ppm): 173.3 (NH<u>C</u>(=O)NH), 160.5 (CH<u>C</u>(=O)), 143.0 (Ar<u>C</u>),

142.9 (Ar<u>C</u>), 129.6 (Ar<u>C</u>H), 129.4 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 62.6 (C(=O)<u>C</u>HC(CH_3)$_3$), 59.6 (<u>C</u>HCH_2N_3), 58.1 (<u>C</u>HPh_2), 53.3 (CH<u>C</u>H_2N_3), 35.4 (one of C(=O)CH<u>C</u>(CH_3)$_3$ or NHCH<u>C</u>(CH_3)$_3$), 35.3 (one of C(=O)CH<u>C</u>(CH_3)$_3$ or NHCH<u>C</u>(CH_3)$_3$), 27.1 ((one of C(=O)CHC(<u>C</u>H_3)$_3$ or NHCHC(<u>C</u>H_3)$_3$), 27.0 ((one of C(=O)CHC(<u>C</u>H_3)$_3$ or NHCHC(<u>C</u>H_3)$_3$); **IR** (powder) ν_{max}/cm^{-1}: 3304 (N-H), 2960 (C-H), 2093 1630 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H^+]^+$ ($C_{26}H_{37}N_6O_2^+$) requires *m/z* 465.2973, found *m/z* 465.2973; **MP**: 206 – 207 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –23.5 (*c* 0.3, $CHCl_3$).

5.4 Synthesis of metal catalysts

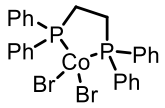
5.4.1 Synthesis of Palladium pincer complex 226



a) According to a literature procedure,[134] 48-50% aq. $HClO_4$ (3.6 g, 17.9 mmol, 1.5 eq) was slowly added to a solution of 1,1'-(pyridine-2,6-diyl)bis(ethan-1-one) (1.95 g, 12.0 mmol, 1.00 eq) in Et_2O (40 ml). The reaction mixture was stirred for 2 h. The precipitate was filtered, washed with Et_2O and recrystallised from acetone/Et_2O to provide the desired salt in 52% yield (1.64 g).

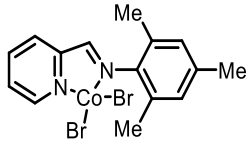
b) The salt obtained in step **a** (894 mg, 3.39 mmol, 1.00 eq) was then stirred in acetonitrile (40 ml) with $Pd(OAc)_2$ (762 mg, 3.39 mmol, 1.00 eq) for 2 h. The reaction mixture was concentrated to dryness. Acetone was added and the mixture concentrated again, this was repeated two more times. The resulting mixture was dissolved in acetonitrile (2 ml) and Et_2O (10 ml) was added. The suspension was filtered and washed with Et_2O to provide a brown solid in quantitative yield (1.38 g). **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ(ppm): 8.39 (t, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 8.12 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar<u>H</u>), 8.03 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar<u>H</u>), 3.60 (s, 2H, C<u>H</u>$_2$), 2.84 (s, 3H, C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, Acetonitrile-d_3) δ(ppm): 200.0 (<u>C</u>=O-Pd), 197.7 (CH$_2$<u>C</u>=O), 156.9 (Ar<u>C</u>), 156.1 (Ar<u>C</u>), 143.9 (Ar<u>C</u>H), 129.9 (Ar<u>C</u>H), 39.1 (<u>C</u>H$_2$), 28.5 (<u>C</u>H$_3$); **IR** (powder) ν_{max}/cm^{-1}: 2328 (C≡N), 1705, 1637 (C=O), 1595 (C=N), 1074 (Cl-O). Data are consistent with that published in the literature.[134]

5.4.2 Synthesis of Cobalt catalyst 276



According to a literature procedure,[223] $CoBr_2$ (1.00 g, 4.60 mmol, 1.00 eq) and DPPE (1.82 g, 4.60 mmol, 1.00 eq) were stirred overnight in THF (50 ml) under an Ar atmosphere. The green precipitate was filtered and washed with pentane (3 x 10 ml) to provide the title compound as a green solid in 90% yield (2.54 g).

5.4.3 Synthesis of Cobalt catalyst 277



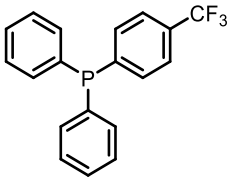
a) According to a literature procedure,[224] formic acid (181 µl, 4.80 mmol, 0.200 eq) was added to a stirred solution of 2-pyridine carboxaldehyde (2.28 ml, 24.0 mmol, 1.00 eq) and 2,4,6-trimethyl aniline (3.36 ml, 24.0 mmol, 1.00 eq) in EtOH (50 ml). The solvent was removed *in vacuo* and the crude reaction mixture was recrystallised from hexane to provide the desired product as yellow crystals in 52% yield (2.8 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 8.72 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, ArH), 8.34 (s, 1H, C(=N)H), 8.28 (dt, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.87 – 7.79 (m, 1H, ArH), 7.39 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, ArH), 6.91 (s, 2H, ArH), 2.30 (s, 3H, *p*-CH_3), 2.15 (s, 6H, 2 x *o*-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 163.6 (C(=N)H and ArCH), 154.7 (ArC), 149.7 (ArC), 148 (ArCH), 136.8 (ArCH), 133.6 (ArC), 128.9 (ArCH), 127.0 (ArCH), 125.3 (ArCH), 121.3 (ArCH), 20.9 (*p*-CH_3), 18.4 (*o*-CH_3); **IR** (powder) ν_{max}/cm^{-1}: 2980, 2912, 2363 (C-H), 1639 (C=N). Data are consistent with that published in the literature.[224]

b) According to a literature procedure,[223] $CoBr_2$ (4.88 g, 22.3 mmol, 1.00 eq) and the product obtained in step **a** (5.0 g, 22.3 mmol, 1.00 eq) were stirred overnight in THF (242 ml) under an Ar atmosphere. The green precipitate was filtered and washed with pentane (3 x 10 ml) and recrystalised from CH_2Cl_2 to provide the title compound (**277**) as a green solid.

5.5 Synthesis of phosphines

5.5.1 Synthesis and characterisation of E17

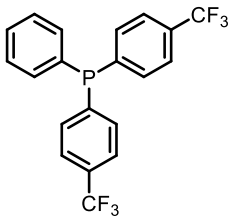
diphenyl(4-(trifluoromethyl)phenyl)phosphane (E17)



According to a literature procedure,[225] *n*-BuLi (2.5 M in hexanes) (0.80 ml, 2.0 mmol, 2.0 eq) was added dropwise over 1 h to a stirred solution of 4-Bromo(trifluoromethyl)benzene (0.28 ml, 2.0 mmol, 2.0 eq) in Et_2O (10 ml) at −78 °C. The resulting solution was stirred for 1 h at −78 °C at which point chlorodiphenylphosphine (0.185 ml, 1.00 mmol, 1.00 eq) in Et_2O (5 ml) was added dropwise over 1 h. The reaction was warmed to room temperature overnight. H_2O (30 ml) was added, and the phases separated. The aqueous phase was extracted with Et_2O (2 x 30 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 98/2) to provide the title compound (**E17**) as a white solid in 60% yield (198 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.62 – 7.52 (m, 2H, Ar<u>H</u>), 7.44 – 7.28 (m, 12H, Ar<u>H</u>); **^{19}F NMR** (377 MHz, $CDCl_3$) δ(ppm): -62.75 (d, J_{PF} = 1.5 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ(ppm): -5.35 (s). Data are consistent with that published in the literature.[226,227]

5.5.2 Synthesis and characterisation of E18

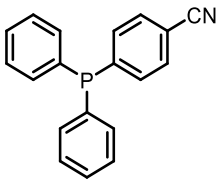
phenylbis(4-(trifluoromethyl)phenyl)phosphane (E18)



According to a modified literature procedure,[225] *n*-BuLi (2.5 M in hexanes) (1.6 ml, 4.0 mmol, 4.0 eq) was added dropwise over 1 h to a stirred solution of 4-Bromo(trifluoromethyl)benzene (0.56 ml, 4.0 mmol, 4.0 eq) in Et_2O (10 ml) at −78 °C. The resulting solution was stirred for 1 h at −78 °C at which point dichlorophenylphosphine (0.14 ml, 1.0 mmol, 1.0 eq) in Et_2O (5 ml) was added dropwise over 1 h. The reaction was warmed to room temperature overnight. H_2O (30 ml) was added and the phases separated. The aqueous phase was extracted with Et_2O (2 x 30 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 98/2) to provide the title compound (**E18**) as a colourless oil in 92% yield (367 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.64 – 7.57 (m, 4H, Ar<u>H</u>), 7.47 – 7.37 (m, 7H, Ar<u>H</u>), 7.36 – 7.28 (m, 2H, Ar<u>H</u>); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 141.6 (d, *J* = 14.0 Hz, Ar<u>C</u>), 134.9 (d, *J* = 10.5 Hz, Ar<u>C</u>), 134.1 (d, *J* = 20.5 Hz, Ar<u>C</u>H), 133.8 (d, *J* = 19.5 Hz, Ar<u>C</u>H), 131.1 (q, *J* = 32.5 Hz, Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.01 (d, *J* = 7.5 Hz, Ar<u>C</u>H), 125.38 (dq, *J* = 7.0, 3.5 Hz, Ar<u>C</u>H), 123.97 (q, *J* = 272.5 Hz, <u>C</u>F_3); **^{19}F NMR** (377 MHz, $CDCl_3$) δ(ppm): -62.87 (d, J_{PF} = 1.5 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ(ppm): -5.63 (s); **IR** (film) ν_{max}/cm^{-1}: 3073, 1606, 1320, 1164, 1121, 1106, 1059, 1016; **HRMS** (ES+) exact mass calculated for $[M+H^+]^+$ ($C_{20}H_{14}F_6P^+$) requires *m/z* 399.0732, found *m/z* 399.0732.

5.5.3 Synthesis and characterisation of E19

4-(diphenylphosphaneyl)benzonitrile (E19)



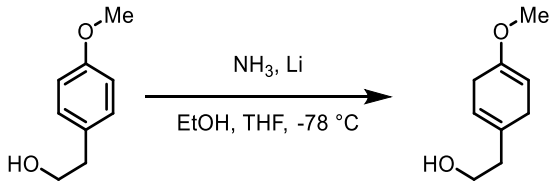
According to a literature procedure,[228] diphenyl phosphine (0.500 ml, 2.87 mmol, 1.00 eq) was added to a stirred suspension of KOH (290 mg, 5.17 mmol, 1.80 eq) in DMSO (14.4 ml). The solution was stirred for 2 h at which point 4-fluorobenzonitrile (348 mg, 2.87 mmol, 1.00 eq) was added. The reaction was stirred for 30 min at which point H_2O was added (20 ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 ml). The combined organic phases were washed with H_2O (3 x 30 ml), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 95/5) to provide a yellow solid which was washed with pentane to provide the title compound (**E19**) as a white solid in 46% yield (369 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.60 – 7.54 (m, 2H, Ar<u>H</u>), 7.42 – 7.28 (m, 12H, Ar<u>H</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 145.26 (d, *J* = 17.0 Hz, Ar<u>C</u>), 135.5 (d, *J* = 10.5 Hz, Ar<u>C</u>), 134.2 (d, *J* = 20.5 Hz, Ar<u>C</u>H), 133.62 (d, *J* = 18.5 Hz, Ar<u>C</u>H), 131.83 (d, *J* = 6.0 Hz, Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 129.00 (d, *J* = 7.5 Hz, Ar<u>C</u>H), 118.9 (Ar<u>C</u>), 112.1 (<u>C</u>≡N); **^{31}P NMR** (162 MHz, $CDCl_3$) δ(ppm): -4.26 (s). Data are consistent with that published in the literature.[229,230]

5.6 The enantioselective prototropic shift cascade reaction of β,γ-unsaturated cyclohexenones

5.6.1 Synthesis of substrates prepared via the Birch reduction of anisoles

5.6.1.1 Synthesis and characterisation of 204

2-(4-methoxycyclohexa-1,4-dien-1-yl)ethan-1-ol (204)

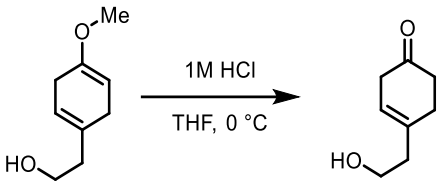


According to a literature procedure,[231] to a three necked flask fitted with a Dewar condenser under N_2 at −78 °C was condensed ammonia (160 ml). EtOH (8 ml) was added followed by 2-(4-methoxyphenyl)ethan-1-ol (4.70 ml, 32.9 mmol, 1.00 eq) and THF (5 ml) followed by EtOH (20 ml). The solution was stirred at −78 °C and Li wire (10.0 eq, 2.30 g, 329 mmol) added portion-wise. The solution turned dark blue and was stirred for 30 min at which point the reaction was allowed to warm to room temperature. The reaction was cooled to 0 °C and quenched with H_2O. The crude mixture was extracted with EtOAc (3 x 30 ml). The organic extracts were pooled and washed with H_2O (30 ml), brine and dried over Na_2SO_4. The mixture was filtered, and the solvent was removed *in vacuo* and the crude mixture purified by silica gel column chromatography (Pentane/Et_2O = 9/1 to 1/1) to provide the title compound (**204**) as a colourless oil with an inseparable impurity in 94% yield (4.78 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 5.47 – 5.41 (m, 1H, C<u>H</u>CH_2COCH_3), 4.56 (m, 1H, C<u>H</u>$COCH_3$), 3.63 (ddd, *J* = 6.5, 5.5 Hz, 2H, C<u>H_2</u>OH), 3.48 (s, 3H, C<u>H_3</u>), 2.69 (bs, 4H, 2 x C<u>H_2</u>CH), 2.21 (t, *J* = 6.5 Hz, 2H, C<u>H_2</u>CH_2OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 152.9 (<u>C</u>OCH_3), 131.9 (<u>C</u>CH_2CH_2OH), 120.4 (<u>C</u>HCH_2CO),

90.3 (<u>C</u>HCOCH$_3$), 60.3 (<u>C</u>H$_2$OH), 53.9 (<u>C</u>H$_3$), 39.8 (<u>C</u>H$_2$CH$_2$OH), 29.2 (2 x <u>C</u>H$_2$CH). Data are consistent with that published in the literature.[231]

5.6.1.2 Synthesis and characterisation of 205

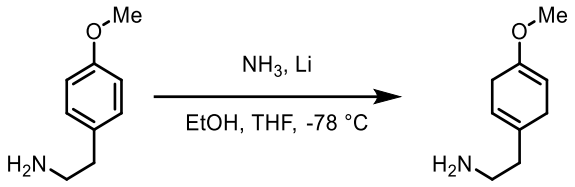
4-(2-hydroxyethyl)cyclohex-3-en-1-one (205)



To a stirred solution of 2-(4-methoxycyclohexa-1,4-dien-1-yl)ethan-1-ol (**204**) (1.65 g, 10.7 mmol, 1.00 eq) in THF (22.8 ml) at 0 °C was added 1.0 M HCL (10 ml) dropwise. The reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous layer extracted with EtOAc (3 x 30 ml). The organic extracts were pooled and washed with H_2O (30 ml), brine and then dried over Na_2SO_4. The mixture was filtered and purified by silica gel column chromatography (Pentane/EtOAc = 7/3 to 2/3 to 0/1). The pure fractions were detected by use of $AgNO_3$ coated TLC plates to provide the title compound (**205**) as a colourless oil in 26% yield (0.386 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 5.56 (tt, *J* = 3.5, 1.0 Hz, 1H, C<u>H</u>CH$_2$C(=O)), 3.73 (t, *J* = 6.5 Hz, 2H, C<u>H$_2$</u>OH), 2.87 (dp, *J* = 3.5, 2.0 Hz, 2H, CHC<u>H$_2$</u>C(=O)), 2.53 – 2.47 (m, 2H, CH$_2$C<u>H$_2$</u>C(=O)), 2.44 (dq, *J* = 7.0, 4.5, 3.0 Hz, 2H, , C<u>H$_2$</u>CH$_2$C(=O)), 2.34 (td, *J* = 6.5, 1.5 Hz, 2H, C<u>H$_2$</u>CH$_2$OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 210.76 (<u>C</u>=O), 135.46 (<u>C</u>=CH), 120.59 (C=<u>C</u>H), 60.52 (<u>C</u>H$_2$OH), 40.22 (<u>C</u>H$_2$CH$_2$OH), 39.72 (CH<u>C</u>H$_2$C(=O)), 38.66 (CH$_2$<u>C</u>H$_2$C(=O)), 28.61 (<u>C</u>H$_2$CH$_2$C(=O)); **IR** (film) ν_{max}/cm^{-1}: 3391 (O-H), 2931, 2890 (C-H), 1708 (C=O), 1045 (C-O).

5.6.1.3 Synthesis and characterisation of 207

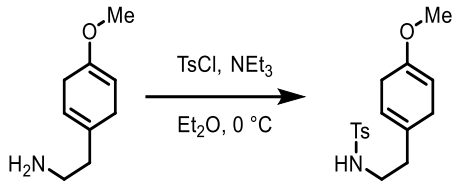
2-(4-methoxycyclohexa-1,4-dien-1-yl)ethan-1-amine (207)



According to a literature procedure,[232] to a three necked flask fitted with a Dewar condenser under N_2 at −78 °C was condensed NH_3 (31 ml). EtOH (24 ml) was added followed by 2-(4-methoxyphenyl)ethan-1-amine (5.00 ml, 34.1 mmol, 1.00 eq). Li (1.74 g, 250 mmol, 7.34 eq) was added followed by THF (15 ml). The reaction was stirred for 15 min at which point the reaction was allowed to warm to ambient temperature and the NH_3 allowed to evaporate. The reaction was quenched with EtOH and extracted with EtOAc (3 x 30 ml). The organic layers were pooled, washed with H_2O (30 ml), brine and dried over Na_2SO_4. The mixture was filtered and concentrated *in vacuo* to provide the title compound (**207**) as a yellow oil in 57% yield (2.98 g) which was taken on without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 5.43 (p, *J* = 1.5 Hz, 1H, $\underline{C}HCH_2CO$), 4.61 (t, *J* = 2.0 Hz, 1H, $\underline{C}HCO$), 3.54 (s, 3H, $C\underline{H_3}$), 2.78 (t, *J* = 6.5 Hz, 2H, $C\underline{H_2}NH_2$), 2.75 – 2.69 (m, 4H, , $CHC\underline{H_2}CO$ and $C\underline{H_2}CHCO$), 2.13 (t, *J* = 6.7 Hz, 2H, $C\underline{H_2}CH_2NH_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 152.98 ($\underline{C}OCH_3$), 132.86 ($C=\underline{C}CH_2$), 119.33 ($\underline{C}HCH_2CO$), 90.36 ($\underline{C}HCO$), 53.91 ($\underline{C}H_3$), 40.83 ($\underline{C}H_2CH_2NH_2$), 39.88 ($\underline{C}H_2NH_2$), 29.15 ($CH\underline{C}H_2CO$ and $\underline{C}H_2CHCO$); **IR** (film) ν_{max}/cm^{-1}: 3364, 3297 (N-H), 3040, 2929, 2830 (C-H), 1696, 1664 (C=C), 1214 (C-N), 1172 (C-O). Data are consistent with that published in the literature.[232]

5.6.1.4 Synthesis and characterisation of 208

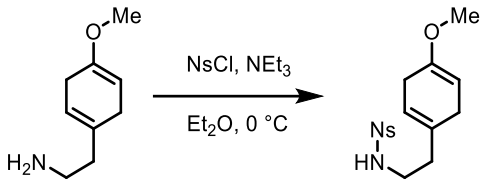
N-(2-(4-methoxycyclohexa-1,4-dien-1-yl)ethyl)-4-methylbenzenesulfonamide (X208X)



2-(4-methoxycyclohexa-1,4-dien-1-yl)ethan-1-amine (**207**) (1.00 g, 6.53 mmol, 1.10 eq) was dissolved in Et_2O (16.5 ml). The solution was cooled to 0 °C and NEt_3 (0.910 ml, 6.53 mmol, 1.10 eq) followed by TsCl (1.13 g, 5.93 mmol, 1.00 eq). The reaction was stirred until completion was observed by TLC (Pentane/EtOAc = 9/1). The reaction mixture was concentrated and extracted with EtOAc (3 x 30 ml). The organic extracts were pooled and washed with H_2O (30 ml), brine and dried over Na_2SO_4. The mixture was filtered, and the solvent was removed *in vacuo*. The crude mixture was purified by silica gel column chromatography (Pentane/EtOAc = 9/1 to 4/1) to provide the title compound (**208**) as a white solid in 79% yield (1.44 g). The product was quickly transferred to the next step due to its rapid decomposition. **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.90 – 7.74 (m, 2H, ArC<u>H</u>), 6.90 – 6.73 (m, 2H, ArC<u>H</u>), 5.06 (dt, *J* = 3.5, 2.0 Hz, 1H, C<u>H</u>CH$_2$CO), 4.73 (t, *J* = 6.0 Hz, 1H, N<u>H</u>), 4.31 (dd, *J* = 4.3, 3.0 Hz, 1H, C<u>H</u>CO), 3.23 (s, 3H, OC<u>H$_3$</u>), 2.89 (td, *J* = 7.0, 6.0 Hz, 2H, C<u>H$_2$</u>NH), 2.68 (tdd, *J* = 7.5, 3.5, 1.5 Hz, 2H, C<u>H$_2$</u>CO), 2.38 (tdd, *J* = 7.8, 3.5, 1.5 Hz, 2H, C<u>H$_2$</u>CHCO), 1.91 (s, 3H, CC<u>H$_3$</u>), 1.88 – 1.81 (m, 2H, C<u>H$_2$</u>CH$_2$NH); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 153.3 (<u>C</u>OMe), 142.8 (Ar<u>C</u>), 138.5 (Ar<u>C</u>), 131.8 (<u>C</u>CH$_2$CH$_2$NH), 129.7 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 120.6 (<u>C</u>HCH$_2$CO), 90.1 (<u>C</u>HCO), 53.6 (O<u>C</u>H$_3$), 41.5 (<u>C</u>H$_2$NH), 36.6 (<u>C</u>H$_2$CH$_2$NH), 29.6 (<u>C</u>H$_2$CO), 29.2 (<u>C</u>H$_2$CHCO), 21.1 (C<u>C</u>H$_3$).

5.6.1.5 Synthesis and characterisation of 209

N-(2-(4-methoxycyclohexa-1,4-dien-1-yl)ethyl)-4-nitrobenzenesulfonamide (209)

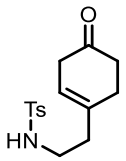


2-(4-methoxycyclohexa-1,4-dien-1-yl)ethan-1-amine (**207**) (500 mg, 3.26 mmol, 1.10 eq) was dissolved in CH_2Cl_2 (14 ml). The solution was cooled to 0 °C and triethylamine (300 µl, 2.97 mmol, 1.00 eq,) followed by NsCl (658 mg, 2.97 mmol, 1.00 eq). The reaction was stirred until completion was observed by TLC. The reaction mixture was concentrated and extracted with CH_2Cl_2 (3 x 30 ml). The organic extracts were pooled and washed with H_2O (30 ml), brine and dried over Na_2SO_4. The mixture was filtered, and the solvent was removed in vacuo. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 1/0 to 90/10) to afford the title compound (**209**) as a white solid in 50% yield (0.553 g). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 8.47 –8.41 (m, 2H, ArH), 8.15 –8.10 (m, 2H, ArH), 6.85 –6.71 (m, 1H, NH), 5.36 (td, J = 3.0, 1.5 Hz, 1H, CHCH$_2$COCH$_3$), 4.55 (t, J = 3.0 Hz, 1H, CHCOCH$_3$), 3.47 (s, 3H, CH$_3$), 3.13 (td, J = 7.0, 6.0 Hz, 2H, CH$_2$NH), 2.65 –2.50 (m, 4H, CHCH$_2$COCH$_3$and CH$_2$CHCOCH$_3$), 2.18 (td, J = 7.0, 1.5 Hz, 2H, CH$_2$CH$_2$NH); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 153.6 (COMe), 151.0 (ArC), 147.9 (ArC), 132.8 (CCH$_2$), 129.3 (ArCH), 125.3 (ArCH), 120.9 (CHCH$_2$CO), 90.8 (CH$_2$CHCO), 54.1 (CH3), 42.4 (CH$_2$NH), 37.4 (CH$_2$CH$_2$NH), CH$_2$CHCO and CHCH$_2$CO are beneath the solvent peak at 30.0 ppm; **IR** (powder) ν_{max}/cm^{-1}: 3299 (N-H), 1699, 1666, 1606 (C=C), 1523, 1348 (N-O), 1327, 1162 (S=O), 1211 (C-O); **HRMS** (ES−) exact

mass calculated for $[M-H^+]^-$ ($C_{15}H_{17}N_2O_3S^-$) requires *m/z* 337.0864, found *m/z* 337.0863.

5.6.1.6 Synthesis and characterisation of 210

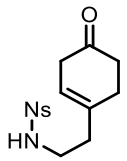
4-methyl-N-(2-(4-oxocyclohex-1-en-1-yl)ethyl)benzenesulfonamide (210)



To a stirred solution of *N*-(2-(4-methoxycyclohexa-1,4-dien-1-yl)ethyl)-4-methylbenzenesulfonamide (**208**) (1.42 g, 4.62 mmol, 1.00 eq) in THF (10 ml) at 0 °C was added 1.0 M HCL (1.8 ml) dropwise. The reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous layer extracted with EtOAc (3 x 30 ml). The organic extracts were pooled and washed with H_2O (30 ml), brine and then dried over Na_2SO_4. The mixture was filtered and purified by silica gel column chromatography (pentane/EtOAc = 7/3 to 60/40) to provide the title compound which was recrystallised from hot IPA to afford the title compound (**210**) as white crystals in 79% yield (1.07 g). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.79 – 7.67 (m, 2H, Ar<u>H</u>), 7.35 – 7.27 (m, 2H, Ar<u>H</u>), 5.43 (m, 1H, C<u>H</u>CH_2), 4.84 (t, *J* = 6.0 Hz, 1H, N<u>H</u>), 3.04 (q, *J* = 6.6 Hz, 2H, C<u>H_2</u>NH), 2.79 (m, 2H, CHC<u>H_2</u>), 2.46 – 2.38 (m, 5H, C<u>H_3</u> and CH_2C<u>H_2</u>C(=O)), 2.23 (m, 4H, CH_2C<u>H_2</u>C(=O), C<u>H_2</u>CH_2NH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 210.2 (<u>C</u>(=O)), 143.7 (Ar<u>C</u>), 136.9 (Ar<u>C</u>), 134.6 (<u>C</u>=CH), 129.9 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 121.3 (C=<u>C</u>H), 40.9 (<u>C</u>H_2NH), 39.6 (CH<u>C</u>H_2), 38.4 (CH_2<u>C</u>H_2C(=O)), 36.8 (<u>C</u>H_2CH_2C(=O)), 28.1 (<u>C</u>H_2CH_2NH), 21.6 (<u>C</u>H_3); **IR** (film) ν_{max}/cm^{-1}: 3255 (N-H), 3103, 3076, 2981, 2944, 2909, 2848 (C-H), 1711 (C=O), 1530, 1352 (N-O), 1309, 1160 (S=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{19}NNaO_3S^+$) requires *m/z* 316.0978, found *m/z* 316.0971; **MP**: 83-84 °C.

5.6.1.7 Synthesis and characterisation of 211

4-nitro-N-(2-(4-oxocyclohex-1-en-1-yl)ethyl)benzenesulfonamide (211)

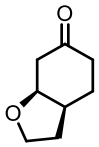


To a stirred solution of N-(2-(4-methoxycyclohexa-1,4-dien-1-yl)ethyl)-4-nitrobenzenesulfonamide (**209**) (500 mg, 1.48 mmol, 1.00 eq) in THF (3 ml) at 0 °C was added 1 M HCL (0.6 ml) dropwise. The reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3 x 30 ml). The organic extracts were pooled and washed with H_2O (30 ml), brine and then dried over Na_2SO_4. The mixture was filtered and recrystallised from hot IPA to afford the title compound (**211**) as white crystals in 43% yield (208 mg). **^{1}H NMR** (500 MHz, DMSO-d_6) δ(ppm): 8.47 –8.35 (m, 2H, Ar<u>H</u>), 8.10 –8.00 (m, 2H, Ar<u>H</u>), 7.99 (t, *J* = 6.0 Hz, 1H, N<u>H</u>), 5.38 (tt, *J* = 3.5, 1.0 Hz, 1H, C<u>H</u>), 2.94 (td, *J* = 7.0, 6.0 Hz, 2H, C<u>H$_2$</u>NH), 2.74 (dt, *J* = 3.5, 2.0 Hz, 2H, CHC<u>H$_2$</u>C(=O)), 2.34 (td, *J* = 6.5, 1.0 Hz, 2H, CH$_2$C<u>H$_2$</u>C(=O)), 2.29 –2.22 (m, 2H, C<u>H$_2$</u>CH$_2$C(=O)), 2.18 –2.11 (m, 2H, C<u>H$_2$</u>CH$_2$N); **^{13}C NMR** (126 MHz, DMSO-d_6) δ(ppm): 209.4 (<u>C</u>=O), 149.5 (Ar<u>C</u>), 146.3 (Ar<u>C</u>), 134.7 (<u>C</u>=CH), 128.0 (Ar<u>C</u>H), 124.6 (Ar<u>C</u>H), 120.2 (C=<u>C</u>H), 41.0 (<u>C</u>H$_2$NH), 39.2 (CH<u>C</u>H$_2$C(=O)), 37.9 (CH$_2$<u>C</u>H$_2$C(=O)), 36.6 (<u>C</u>H$_2$CH$_2$NH), 27.7 (<u>C</u>H2CH2C(=O)); **IR** (powder) ν_{max}/cm^{-1}: 3255 (N-H), 3103, 3076, 2981, 2944, 2909, 2848 (C-H), 1711 (C=O), 1530, 1352 (N-O), 1309, 1160 (S=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}N_2NaO_5S^+$) requires *m/z* 347.0671, found *m/z* 347.0666; **MP**: 104-106 °C.

5.6.2 Synthesis and characterisation of products obtained in the prototropic shift Michael cascade sequence

5.6.2.1 Synthesis and characterisation of 212

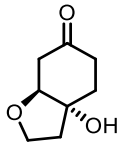
(±)-hexahydrobenzofuran-6(2H)-one (212)



Verkade base (6.4 mg, 0.021 mmol, 0.10 eq) was added to a stirred solution of **205** (30.0 mg, 0.214 mmol, 1.00 eq) in THF (2.4 ml) at room temperature. The reaction was stirred for 13 h at which point the mixture was concentrated under a stream of N_2. The crude reaction mixture was purified by silica gel column chromatography (pentane/EtOAc = 9/1) to provide the title compound (**212**) as a colourless oil in 44% yield (13.2 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 4.19 (dt, *J* = 6.5, 4.5 Hz, 1H, C<u>H</u>O), 3.97 (td, *J* = 8.5, 4.5 Hz, 1H, one of C<u>H</u>$_A$H$_B$O), 3.65 (dt, *J* = 9.0, 8.0 Hz, 1H, CH$_A$<u>H</u>$_B$O), 2.66 (dd, *J* = 16.0, 4.0 Hz, 1H, one of CHC<u>H</u>$_A$H$_B$C(=O)), 2.59 (dd, *J* = 16.0, 4.5 Hz, 1H, one of CHCH$_A$<u>H</u>$_B$C(=O)), 2.51 (h, *J* = 7.0 Hz, 1H, C<u>H</u>CHO), 2.36 (dddd, *J* = 17.0, 8.0, 4.5, 1.0 Hz, 1H, one of CH$_2$C<u>H</u>$_A$CH$_B$C(=O)), 2.29 – 2.17 (m, 2H, one of CH$_2$CH$_A$C<u>H</u>$_B$C(=O) and one of C<u>H</u>$_A$H$_B$CH$_2$O), 1.97 (dddd, *J* = 14.0, 8.0, 5.5, 5.0 Hz, 1H, one of C<u>H</u>$_A$H$_B$CH$_2$C(=O)), 1.73 (m, 2H, one of C<u>H</u>$_A$H$_B$CH$_2$O and one of CH$_A$<u>H</u>$_B$CH$_2$C(=O)); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 210.8 (<u>C</u>(=O)), 77.7 (<u>C</u>HO), 66.9 (<u>C</u>H$_2$O), 43.1 (CH<u>C</u>H$_2$C(=O)), 37.3 (CH$_2$<u>C</u>H$_2$C(=O)), 36.0 (<u>C</u>HCHO), 32.4 (<u>C</u>H$_2$CH$_2$O), 26.2 (<u>C</u>H$_2$CH$_2$C(=O)); **IR** (film) ν_{max}/cm^{-1}: 1713 (C=O), 1084 (C-O).

5.6.2.2 Synthesis and characterisation of 159

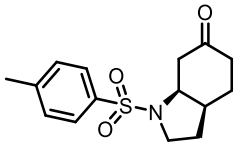
(±)-Cleroindicin C (159)



Compound **159** was isolated as a side-product of the reaction of **205** with superbase catalysts as a result of the addition of molecular oxygen. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 4.02 – 3.96 (m, 2H, one of CH_AH_BOCH and CH_AH_BOCH), 3.91 (td, *J* = 8.8, 7.4 Hz, 1H, one of CH_AH_BOCH), 2.74 (dd, *J* = 16.0, 5.0 Hz, 1H, one of CHCH_AH_BC(=O)), 2.59 (ddd, *J* = 16.0, 5.0, 1.0 Hz, 1H, $CHCH_AH_B$C(=O)), 2.54 – 2.46 (m, 1H, one of $CH_2CH_AH_B$C(=O)), 2.29 (dddd, *J* = 17.5, 9.0, 4.5, 1.0 Hz, 1H, $CH_2CH_AH_B$C(=O)), 2.19 – 2.07 (m, 4H, CH_2CH_2O and CH_2CH_2C(=O)), 1.96 (s, 1H, OH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 209.5 (C(=O)), 83.5 (CHCO), 77.7 (C(OH)), 66.0 (CH_2OC), 42.4 (CHCH_2C(=O)), 40.6 (CH_2C(OH)), 35.0 (CH_2CH_2C(=O)), 33.4 (CH_2CH_2C(=O)); **IR** (film) ν_{max}/cm^{-1}: 3408 (O-H), 1714 (C=O), 1063 (C-O). Data are consistent with that published in the literature.[112]

5.6.2.3 Synthesis and characterisation of 214

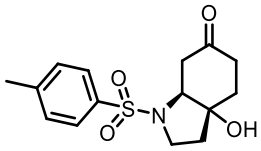
(±)-1-tosyloctahydro-6H-indol-6-one (214)



Verkade base (3.1 mg, 0.010 mmol, 0.10 eq) was added to a stirred solution of **210** (30.0 mg, 0.102 mmol, 1.00 eq) in THF (1.0 ml) at room temperature. The reaction was stirred for 5 h at which point the mixture was concentrated under a stream of N_2. The crude reaction mixture was purified by silica gel column chromatography (pentane/EtOAc = 1/1) to provide the title compound (**214**) as a colourless oil in 63% yield (18.9 mg). [ees were determined by HPLC chiralpak AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 220 nm, t(minor) = 37.9 min, t(major) = 44.5 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.70 (d, *J* = 8.5 Hz, 2H, ArC<u>H</u>), 7.32 (d, *J* = 8.0 Hz, 2H, ArC<u>H</u>), 3.80 (td, *J* = 9.0, 6.0 Hz, 1H, C<u>H</u>N), 3.57 (ddd, *J* = 10.0, 7.5, 3.5 Hz, 1H, one of C<u>H$_A$</u>H$_B$N), 3.14 (td, *J* = 9.5, 7.0 Hz, 1H, one of CH$_A$<u>H$_B$</u>N), 2.86 (ddd, *J* = 15.5, 6.0, 1.0 Hz, 1H, one of CHC<u>H$_A$</u>H$_B$C(=O)), 2.66 (dd, *J* = 15.5, 9.5 Hz, 1H, one of CHCH$_A$<u>H$_B$</u>C(=O)), 2.43 (s, 3H, CH_3), 2.37 (ddd, *J* = 17.0, 7.0, 5.0 Hz, 1H, one of CH_2C<u>H$_A$</u>H$_B$C(=O)), 2.29 – 2.20 (m, 1H, C<u>H</u>CHN), 2.14 (dddd, *J* = 17.0, 9.5, 5.0, 1.0 Hz, 1H, one of CH_2CH$_A$<u>H$_B$</u>C(=O)), 2.02 – 1.94 (m, 1H, one of C<u>H$_A$</u>H$_B$$CH_2$C(=O)), 1.90 (dtd, *J* = 12.5, 7.0, 3.5 Hz, 1H, one of C<u>H$_A$</u>H$_B$$CH_2$N), 1.84 – 1.75 (m, 2H, one of CH$_A$<u>H$_B$</u>CH_2C(=O) and one of CH$_A$<u>H$_B$</u>CH_2N); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 210.05 (<u>C</u>=O), 143.88 (Ar<u>C</u>), 134.06 (Ar<u>C</u>), 129.91 (Ar<u>C</u>H), 127.78 (Ar<u>C</u>H), 58.12 (<u>C</u>HN), 48.46 (<u>C</u>H_2N), 44.88 (CH<u>C</u>H_2C(=O)), 37.27 (<u>C</u>HCHN), 37.14 (CH_2<u>C</u>H_2C(=O)), 29.90 (<u>C</u>$H_2$$CH_2$C(=O)), 24.98 (<u>C</u>$H_2$$CH_2$N), 21.70 (<u>C</u>$H_3$); **IR** (film) ν_{max}/cm^{-1}: 2980, 2927 (C-H), 1716 (C=O), 1340 (S=O), 1160 (C-N); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}NO_3S^+$) requires *m/z* 294.1158, found *m/z* 294.1156.

5.6.2.4 Synthesis and characterisation of 216

(±)-3a-hydroxy-1-tosyloctahydro-6H-indol-6-one (216)

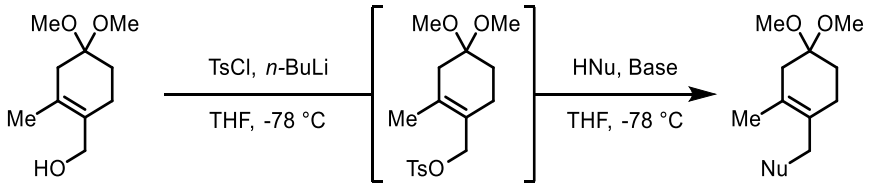


Compound **216** was isolated as a side-product of the reaction of **210** with superbase catalysts as a result of the addition of molecular oxygen. [ees were determined by HPLC chiralpak AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 220 nm t(minor) =37.9 min, t(major) = 44.5 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.81 – 7.68 (m, 2H, Ar<u>H</u>), 7.40 – 7.29 (m, 2H, Ar<u>H</u>), 3.60 (ddd, *J* = 10.0, 8.0, 2.0 Hz, 1H, one of C<u>H</u>$_A$H$_B$N), 3.51 (ddd, *J* = 10.0, 6.0, 1.0 Hz, 1H, C<u>H</u>N), 3.28 (ddd, *J* = 10.8, 9.4, 6.6 Hz, 1H, one of CH$_A$<u>H</u>$_B$N), 2.98 (ddd, *J* = 16.0, 6.0, 1.0 Hz, 1H, one of CHC<u>H</u>$_A$H$_B$C(=O)), 2.48 (dd, *J* = 16.0, 10.0 Hz, 1H, one of CHCH$_A$<u>H</u>$_B$C(=O)), 2.43 (s, 3H, C<u>H</u>$_3$), 2.41 – 2.26 (m, 2H, CH$_2$C<u>H</u>$_2$C(=O)), 2.18 – 2.07 (m, 1H, one of C<u>H</u>$_A$H$_B$CH$_2$N), 2.07 – 2.01 (m, 2H, C<u>H</u>$_2$CH$_2$C(=O)), 1.90 (dddd, *J* = 13.0, 6.5, 2.0, 1.0 Hz, 1H, one of CH$_A$<u>H</u>$_B$CH$_2$N); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 208.87 (<u>C</u>=O), 144.1 (Ar<u>C</u>), 133.3 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 78.9 (<u>C</u>OH), 65.7 (<u>C</u>HN), 47.2 (<u>C</u>H$_2$N), 45.5 (CH<u>C</u>H$_2$C(=O)), 37.5 (<u>C</u>H$_2$CH$_2$N), 35.7 (CH$_2$<u>C</u>H$_2$C(=O)), 33.0 (<u>C</u>H$_2$CH$_2$C(=O)), 21.8 (<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3484 (O-H), 1715 (C=O), 1330 (S=O), 1159 (C-N).

5.7 The eantioselective prototropic shift of β,γ-unsaturated cyclohexenones

5.7.1 General procedures

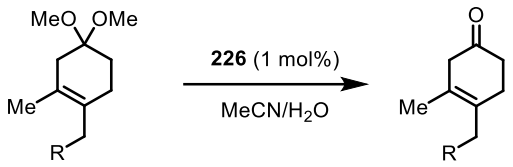
General procedure IV For the addition of nucleophiles to (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (223)



According to a modified literature procedure,[132] *n*-BuLi (1.07 eq, 2.5 M in hexanes) was added to a stirred solution of (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (1.00 eq) in THF (0.54 M) at −78 °C. The reaction was stirred for 15 min at which point a solution of tosyl chloride (1.05 eq) in THF (0.27 M wrt. alcohol) was added. The solution was stirred for a further 30 min at −78 °C. A pre-prepared solution of the desired nucleophile (2.00 eq) and base (2.00 eq) in THF (0.27 M wrt. alcohol) was then added dropwise to the tosylate. The solution was then warmed to 0 °C and stirred until deemed complete by TLC analysis. The reaction mixture was quenched with sat. aq. K_2CO_3 solution and extracted with Et_2O three times. The combined organic phases were washed with H_2O and brine, dried over $MgSO_4$, and filtered. To the organic phase was added solid K_2CO_3 and the solvent was removed under a stream of N_2. The resultant residue was purified by silica gel column chromatography to yield the desired product.

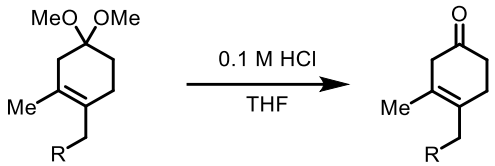
*Compounds synthesised by this method were found to be sensitive to acidic conditions (NMR spectra obtained in $CDCl_3$ often resulted in rapid decomposition) as well as heat (solvent was often removed under a stream of nitrogen rather than *in vacuo*).

General procedure V for the deprotection of acid sensitive substrates



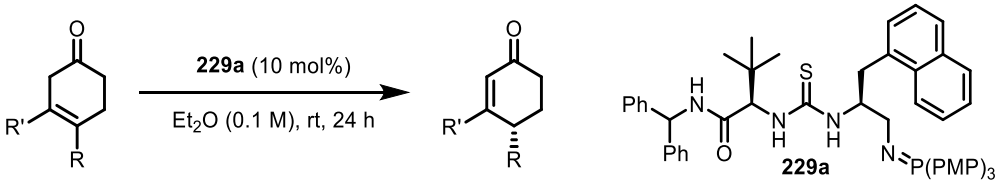
According to a literature procedure,[133,134] **226** (0.01 eq) was added to a stirred solution of the desired protected substrate in wet acetonitrile (0.1 M). The reaction was stirred until deemed complete by TLC analysis and additional catalyst was added if necessary. The reaction mixture was transferred directly onto silica gel and purified by silica gel column chromatography to yield the desired product.

General procedure VI for the deprotection of substrates not sensitive to acid



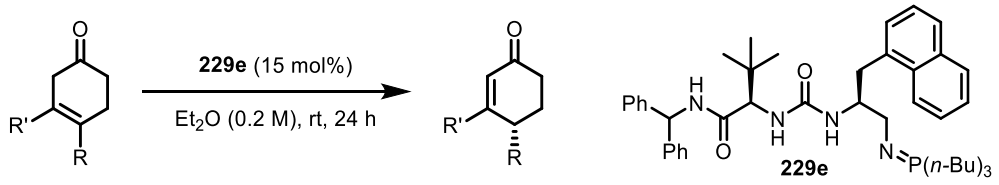
To a stirred solution of the desired protected β,γ-unsaturated substrate in THF (0.14 M) was added an equal volume of 0.1 M HCl. The solution was stirred until deemed complete by TLC analysis at which point the reaction was quenched with sat. aq. K_2CO_3 solution. The aqueous phase was extracted with Et_2O, and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were then purified by silica gel column chromatography to yield the desired products.

General procedure VII for the enantioselective prototropic shift of β,γ-unsaturated cyclohexenones



The BIMP catalyst **229a** (0.100 eq), preformed by general procedure **I**, was concentrated to dryness under a stream of Ar without exposure to air. The desired substrate (1.00 eq) was taken up in Et_2O (0.10 M) under an atmosphere of Ar and transferred to the vial containing the BIMP catalyst. The reaction was stirred for 24 h under Ar at which point the reaction mixture is transferred directly onto silica gel and the products were purified by silica gel column chromatography.

General procedure VIII for the enantioselective prototropic shift of β,γ-unsaturated cyclohexenones

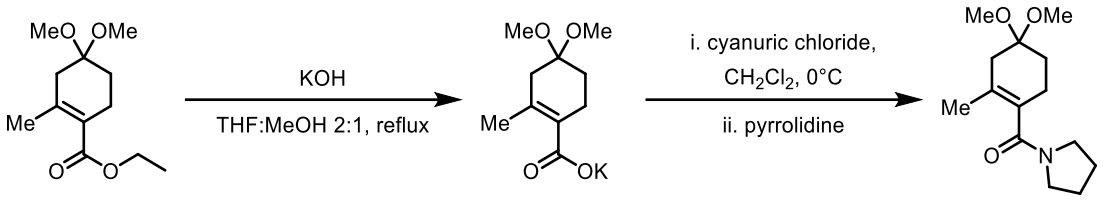


The BIMP catalyst **229e** (0.15 eq), preformed by general procedure **I**, was concentrated to dryness under a stream of Ar without exposure to air. The desired substrate (1.00 eq) was taken up in Et_2O (0.20 M) under an atmosphere of Ar and transferred to the vial containing the BIMP catalyst. The reaction was stirred for 24 h under Ar at which point the reaction mixture was transferred directly onto silica gel and the products were purified by silica gel column chromatography.

5.7.2 Synthesis and characterisation of substrates for use in the enantioselective prototropic shift of β,γ-unsaturated cyclohexenones

5.7.2.1 Synthesis and characterisation of 220

(4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)(pyrrolidin-1-yl)methanone (220)

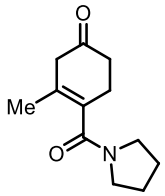


To a stirred solution of ethyl 4,4-dimethoxy-2-methylcyclohex-1-ene-1-carboxylate (**219**, see **5.7.2.3**) (450 mg, 1.97 mmol, 1.00 eq) in MeOH/THF = 1/2 (4.9 ml) was added 2 M aq. KOH (0.99 ml, 1.97 mmol, 1.00 eq). The reaction mixture was refluxed overnight until no organic products were observed in the organic layer by TLC (pentane/EtOAc =9/1) at which point the reaction was allowed to cool to room temperature. The reaction mixture was concentrated and diluted with H_2O (15 ml) and the aqueous phase washed with EtOAc (3 x 15 ml). The aqueous layer was concentrated *in vacuo* with addition of small aliquots of toluene until dry. The crude potassium carboxylate salt (1.00 eq, 386 mg, 2.00 mmol) was dissolved in CH_2Cl_2 (4 ml) and cooled to 0 °C. Cyanuric chloride was added to the solution (371 mg, 2.00 mmol, 1.00 eq). The reaction was removed from the ice bath and stirred for ten minutes. The reaction was then cooled to 0 °C and pyrrolidine (0.82 ml, 10.0 mmol, 5.00 eq) was added. The reaction mixture was stirred and allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 ml) and washed with H_2O (10 ml). The aqueous phase was washed with CH_2Cl_2 (2 x 10 ml) and the organic layers were pooled, washed with H_2O, brine and then dried over Na_2SO_4. The mixture was filtered and concentrated in vacuo to remove solvent and the compound purified by silica gel column chromatography (EtOAc) to afford (4,4-

dimethoxy-2-methylcyclohex-1-en-1-yl)(pyrrolidin-1-yl)methanone (**220**) as a yellow oil in 28% yield (138 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 3.52 – 3.44 (m, 2H, one of $(C\underline{H}_2)_AN(CH_2)_B$), 3.33 – 3.26 (m, 2H, one of $(CH_2)_AN(C\underline{H}_2)_B$), 3.21 (s, 6H, $C(OC\underline{H}_3)_2$), 2.27 – 2.15 (m, 4H, $C\underline{H}_2CH_2C(OCH_3)_2$ and $C\underline{H}_2CCH_3$), 1.88 (m, 6H, $CH_2C\underline{H}_2C(OCH_3)_2$ and $C\underline{H}_2C\underline{H}_2CH_2N$), 1.66 – 1.58 (m, 3H, $CC\underline{H}_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 171.3 ($\underline{C}$=O), 129.4 ($\underline{C}$=CCH_3), 127.3 (C=$\underline{C}CH_3$), 99.7 $\underline{C}(OMe)_2$, 48.0 ($C(O\underline{C}H_3)_2$), 47.1 (one of $(\underline{C}H_2)_AN(CH_2)_B$), 45.0 (one of $(CH_2)_AN(\underline{C}H_2)_B$), 39.0 ($\underline{C}H_2CCH_3$), 28.2 ($CH_2\underline{C}H_2C(OCH_3)_2$), 26.06 (one of $(\underline{C}H_2)_A(CH_2)_BCH_2N$), 24.8 ($\underline{C}H_2CH_2C(OCH_3)_2$), 24.7 (one of $(CH_2)_A(\underline{C}H_2)_BCH_2N$), 20.2 ($C\underline{C}H_3$); **IR** (powder) ν_{max}/cm^{-1}: 2951, 2875, 2825 (C-H), 1612 (C=O), 1128 (C-O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{23}NNaO_3^+$) requires *m/z* 276.1570, found *m/z* 276.1566; **MP**: 82-83 °C.

5.7.2.2 Synthesis and characterisation of 221

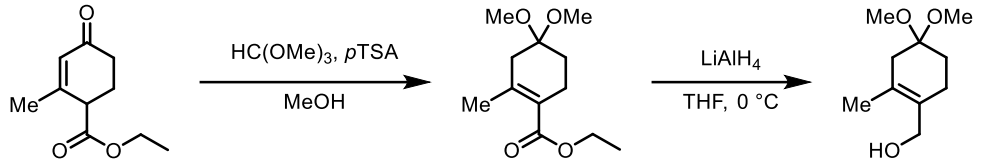
3-methyl-4-(pyrrolidine-1-carbonyl)cyclohex-3-en-1-one (221)



(4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)(pyrrolidin-1-yl)methanone (**220**) (70 mg, 0.28 mmol, 1.0 eq) was deprotected according general procedure **VI**. The crude product (**221**) was deemed clean enough to be used in the prototropic cascade reaction and was obtained in 89% yield with 93% purity by NMR (56 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 3.59 –3.50 (m, 2H, one of $(C\underline{H_2})_AN(CH_2)_B$), 3.37 – 3.27 (m, 2H, one of $(CH_2)_AN(C\underline{H_2})_B$), 2.86 (s, 2H, $C\underline{H_2}CCH_3$), 2.63 (m, 2H, $C\underline{H_2}CH_2C(=O)$), 2.55 (m, 2H, $CH_2C\underline{H_2}C(=O)$), 1.98 –1.89 (m, 4H,$C\underline{H_2}C\underline{H_2}CH_2N$), 1.75 –1.69 (m, 3H, $C\underline{H_3}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 209.0 ($CH_2\underline{C}(=O)$), 170.1 ($N\underline{C}(=O)$), 130.1 ($C=\underline{C}C(=O)$), 129.2 ($\underline{C}=CC(=O)$), 47.22 (one of $(\underline{C}H_2)_AN(CH_2)_B$), 45.3 (one of $(CH_2)_AN(\underline{C}H_2)_B$), 44.5 ($C\underline{C}H_2C(=O)$), 38.3 ($CH_2\underline{C}H_2C(=O)$), 26.6 ($\underline{C}H_2CH_2C(=O)$), 26.1 (one of $(\underline{C}H_2)_A(CH_2)_BCH_2N$), 24.7 (one of $(CH_2)_A(\underline{C}H_2)_BCH_2N$), 20.0 ($\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2971, 2876 (C-H), 1715, 1611 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{18}NO_2^+$) requires *m/z* 208.1332, found *m/z* 208.1330.

5.7.2.3 Synthesis and characterisation of 223

(4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (223)

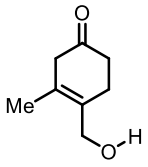


a) To a solution of ethyl-2-methyl-4-oxo-2-cyclohexenecarboxylate (Hagemann's ester, **218**) (10.0 g, 54.9 mmol, 1.00 eq) in MeOH (305 ml) was added trimethyl orthoformate (18.0 ml, 165 mmol, 2.99 eq) followed by *p*TsOH (2.09 g, 11.0 mmol, 0.200 eq). The reaction was stirred overnight at room temperature at which point completion was observed by TLC analysis (Pentane/EtOAc = 95/5). The reaction was quenched with sat. aq. K_2CO_3 (50 ml). The aqueous layer was extracted with EtOAc (3 x 50 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude mixture was purified by silica gel column chromatography (Pentane/EtOAc = 99/1 to 98/2) to afford ethyl 4,4-dimethoxy-2-methylcyclohex-1-ene-1-carboxylate (**219**) as a yellow oil in 61% yield (7.70 g) (The product may also be taken on crude to the next step). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 4.18 (q, *J* = 7.0 Hz, 2H, C$\underline{H_2}$CH$_3$), 3.23 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.43 – 2.29 (m, 4H, C$\underline{H_2}$CH$_2$C(OCH$_3$)$_2$ and C$\underline{H_2}$CCH$_3$), 2.02 (bs, 3H, C$\underline{H_3}$C=C), 1.86 – 1.77 (m, 2H, CH$_2$C$\underline{H_2}$C(OCH$_3$)$_2$), 1.29 (t, *J* = 7.0 Hz, 3H, CH$_2$C$\underline{H_3}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 168.5 (C=O), 142.7 (C=CCH$_3$), 123.9 (C=CCH$_3$), 99.1 (C(OCH$_3$)$_2$), 60.2 (OCH$_2$), 48.1 (OCH$_3$), 42.5 (CH$_2$CCH$_3$), 28.4 (CH$_2$CH$_2$C(OCH$_3$)$_2$), 24.8 (CH$_2$CH$_2$C(OCH$_3$)$_2$), 21.8 (CCH$_3$), 14.5 (CH$_2$CH$_3$). **IR** (film) ν_{max}/cm^{-1}: 2941 (C-H), 1711 (C=O), 1645 (C=C), 1245, 1127 (C-O). **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{20}NaO_4^+$) requires *m/z* 251.1254, found *m/z* 251.1254.

b) To a stirred solution of $LiAlH_4$ (3.00 eq, 1.99 g, 52.6 mmol) in THF (29 ml) at 0 °C was added a solution of ethyl 4,4-dimethoxy-2-methylcyclohex-1-ene-1-carboxylate (**219**) (1.00 eq, 4.00 g, 17.5 mmol) in THF (29 ml). The reaction was stirred at 0 °C and allowed to warm to room temperature over 2 h at which point completion was observed by TLC analysis (Pentane/EtOAc = 95/5). The reaction was diluted with Et_2O (40 ml) and cooled to 0 °C. H_2O (2 ml) was added slowly, followed by 15% aq. NaOH (2 ml) then H_2O (6 ml). The suspension was allowed to warm to room temperature with constant stirring over 15 min. $MgSO_4$ was added and stirred for a further 15 min at which point the suspension was filtered. The solvent was removed *in vacuo* and the crude mixture purified by silica gel column chromatography (Et_2O) to afford (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) as a yellow oil in 79% yield (3.26 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 4.11 (s, 2H, C$\underline{H_2}$OH), 3.21 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.25 – 2.15 (m, 4H, $CH_2C\underline{H_2}C(OCH_3)_2$ and $CC\underline{H_2}C(OCH_3)_2$), 1.86 – 1.76 (m, 2H, C$\underline{H_2}CH_2C(OCH_3)_2$), 1.69 (s, 3H, CC$\underline{H_3}$), 1.57 (bs, 1H, O$\underline{H}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 129.4 ($\underline{C}CH_2OH$), 127.4 ($\underline{C}CH_3$), 99.7 ($\underline{C}(OCH_3)_2$), 62.4 ($\underline{C}H_2OH$), 48.0 (C(O$\underline{C}H_3$)$_2$), 40.8 ($C\underline{C}H_2C(OCH_3)_2$), 28.8 ($\underline{C}H_2CH_2C(OCH_3)_2$), 25.8 ($CH_2\underline{C}H_2C(OCH_3)_2$), 18.8 ($C\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3398 (O-H), 2939, 2915, 2829 (C-H), 1679 (C=C), 1127, 1049 (C-O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{18}NaO_3^+$) requires *m/z* 209.1148, found *m/z* 209.1150.

5.7.2.4 Synthesis and characterisation of E20

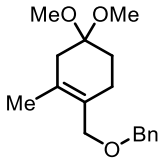
4-(hydroxymethyl)-3-methylcyclohex-3-en-1-one (E20)



The title compound was prepared according to general procedure **V** from (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (100 mg, 0.536 mmol, 1.00 eq) using catalyst **226** (11.0 mg, 0.0286 mmol, 0.05 eq). Upon completion of the reaction as judged by TLC analysis (Et_2O) the reaction mixture was transferred directly to silica gel and purified by silica gel column chromatography (Et_2O) to afford the title compound as a yellow oil in 83% yield (63 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 4.22 (s, 2H, C$\underline{H_2}$OH), 2.83 (s, 2H, CC$\underline{H_2}$C(=O)), 2.57 (m, 2H, $CH_2C\underline{H_2}$C(=O)), 2.51 – 2.46 (m, 2H, C$\underline{H_2}CH_2$C(=O)), 1.75 (s, 3H, C$\underline{H_3}$), 1.46 (s, 1H, O$\underline{H}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 210.6 ($\underline{C}$=O), 130.5 ($CH_3\underline{C}$=C), 128.5 (CH_3C=$\underline{C}$), 62.0 ($\underline{C}H_2$OH), 45.7 (C$\underline{C}H_2$C(=O)), 39.0 ($\underline{C}H_2CH_2$C(=O)), 27.5 ($CH_2\underline{C}H_2$C(=O)), 18.5 ($\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3391 (O-H), 2919, 2857 (C-H), 1709 (C=O), 995 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_8H_{13}O_2^+$) requires *m/z* 141.0910, found *m/z* 141.0911.

5.7.2.5 Synthesis and characterisation of 224

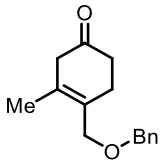
(((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methoxy)methyl)benzene (224)



To a suspension of 60% NaH (0.215 g, 5.37 mmol, 2.00 eq) in THF (3.0 ml) at 0 °C was added a solution of (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (500 mg, 2.69 mmol, 1.00 eq) in THF (3.7 ml). The suspension was stirred for 10 min at which point benzyl bromide (0.48 ml, 4.03 mmol, 1.50 eq) was added followed by TBAI (99.0 mg, 0.270 mmol, 0.100 eq). The reaction was stirred until completion was observed by TLC analysis (Et_2O). The reaction was quenched with sat. aq. NH_4Cl (10 ml) and extracted with EtOAc (3 x 30 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude mixture was purified by silica gel column chromatography (pentane/EtOAc = 9/1) to afford the title compound (**224**) as a yellow oil in 77% yield (575 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.33 – 7.17 (m, 5H, Ar$\underline{H}$), 4.39 (s, 2H, C$\underline{H_2}$Ph), 3.94 (s, 2H, C$\underline{H_2}$OCH$_2$Ph), 3.16 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.18 (td, *J* = 2.0, 1.0 Hz, 2H, CC$\underline{H_2}$C(OCH$_3$)$_2$), 2.13 (ddt, *J* = 6.5, 4.5, 2.0 Hz, 2H, CH$_2$C$\underline{H_2}$C(OCH$_3$)$_2$), 1.77 (t, *J* = 6.5, 2H, (C$\underline{H_2}$CH$_2$C(OCH$_3$)$_2$), 1.66 – 1.56 (m, 3H, CC$\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 138.8 (Ar$\underline{C}$), 128.5 ($\underline{C}$CH$_2$OBn) , 128.5 (Ar$\underline{C}$H), 127.9 (Ar$\underline{C}$H), 127.6 (Ar$\underline{C}$H), 127.0 ($\underline{C}$CH$_3$), 99.7 ($\underline{C}$(OCH$_3$)$_2$), 71.9 ($\underline{C}$H$_2$Ph), 69.3 ($\underline{C}$H$_2$O), 48.0 (O$\underline{C}$H$_3$), 40.9 ($\underline{C}$H$_2$CCH$_3$), 28.7 ($\underline{C}$H$_2$CH$_2$C(OCH$_3$)$_2$), 26.0 (CH$_2\underline{C}$H$_2$C(OCH$_3$)$_2$), 19.1 (C$\underline{C}$H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3030, 2936, 2856, 2827 (C-H), 1095, 1053 (C-O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}NaO_3^+$) requires *m/z* 299.1617, found *m/z* 299.1618.

5.7.2.6 Synthesis and characterisation of 225

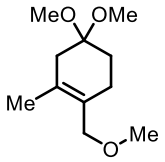
4-((benzyloxy)methyl)-3-methylcyclohex-3-en-1-one (225)



The title compound was prepared according to general procedure **V** from (((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methoxy)methyl)benzene (**224**) (575 mg, 2.08 mmol, 1.00 eq). Upon completion of the reaction as judged by TLC analysis (pentane/Et_2O = 9/1) the reaction mixture was transferred directly to silica gel and purified by silica gel column chromatography (pentane/Et_2O = 95/5) to afford the title compound (**225**) as a yellow oil in 95% yield (457 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.44 – 7.27 (m, 5H, Ar<u>H</u>), 4.50 (s, 2H, C<u>H$_2$</u>Ph), 4.08 (s, 2H, C<u>H$_2$</u>OCH$_2$Ph), 2.84 (s, 2H, CC<u>H$_2$</u>C(=O)), 2.60 – 2.52 (m, 2H, CH$_2$C<u>H$_2$</u>C(=O)), 2.51 – 2.44 (m, 2H, C<u>H$_2$</u>CH$_2$C(=O)), 1.72 (s, 3H, C<u>H$_3$</u>); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 210.6 (<u>C</u>=O), 138.4 (Ar<u>C</u>), 129.6 (CH$_3$<u>C</u>), 128.6 (Ar<u>C</u>H), 128.4 (CH$_3$C=<u>C</u>), 127.9 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 72.4 (<u>C</u>H$_2$Ph), 69.1 (<u>C</u>H$_2$OCH$_2$Ph), 45.7 (C<u>C</u>H$_2$C(=O)), 39.0 (<u>C</u>H$_2$CH$_2$C(=O)), 27.8 (CH$_2$<u>C</u>H$_2$C(=O)), 18.7 (<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 1717 (C=O), 1262 (C-H), 1068; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}NaO_2^+$) requires *m/z* 253.1199, found *m/z* 253.1201.

5.7.2.7 Synthesis and characterisation of E21

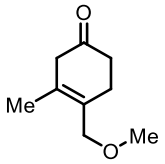
4,4-dimethoxy-1-(methoxymethyl)-2-methylcyclohex-1-ene (E21)



To a solution of (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (200 mg, 1.07 mmol, 1.00 eq) in DMF (1.10 ml) at 0 °C was added 60% NaH (64.4 mg, 1.61 mmol, 1.50 eq). The solution was stirred for 15 min at which point methyl iodide (0.130 ml, 2.15 mmol, 2.00 eq) was added. Additional DMF (0.50 ml) was added to aid solubility. The reaction was stirred overnight, quenched with sat. aq. NH_4Cl (10 ml) and extracted with Et_2O (3 x 10 ml). The combined organic layers were washed with H_2O (3 x 10 ml), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 95/5 to 90/10) to provide the title compound (**E21**) as a colourless oil in 68% yield (145 mg). **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 3.83 (s, 2H, C$\underline{H_2}$O), 3.11 (s, 3H, C$\underline{H_3}$OCH$_2$), 3.08 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.28 – 2.22 (m, 2H, CH$_2$C$\underline{H_2}$C=CCH$_3$), 2.27 – 2.22 (m, 2H, C$\underline{H_2}$CCH$_3$), 1.83 (t, *J* = 6.5, 2H, C$\underline{H_2}$CH$_2$C=CCH$_3$), 1.53 (s, 3H, CC$\underline{H_3}$); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 127.7 (one of $\underline{C}$=C), 127.6 (one of C=$\underline{C}$), 99.8 ($\underline{C}$(OCH$_3$)$_2$), 71.8 ($\underline{C}$H$_2$OCH$_3$), 57.3 (CH$_2$O$\underline{C}$H$_3$), 47.5 (C(O$\underline{C}$H$_3$)$_2$), 40.9 ($\underline{C}$H$_2$CCH$_3$), 29.3 ($\underline{C}$H$_2$CH$_2$C=CCH$_3$), 26.4 (CH$_2$$\underline{C}H_2$C=CCH$_3$), 18.8 (C$\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2921, 2826 (C-H), 1681 (C=C), 1130 (C-O); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{11}H_{20}NaO_3^+$) requires *m/z* 223.1316, found *m/z* 223.1305.

5.7.2.8 Synthesis and characterisation of 230

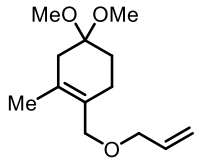
4-(methoxymethyl)-3-methylcyclohex-3-en-1-one (230)



The title compound was prepared according to general procedure **V** from 4,4-dimethoxy-1-(methoxymethyl)-2-methylcyclohex-1-ene (**E21**) (135mg, 0.670 mmol, 1.00 eq). Upon reaction completion as judged by TLC analysis the reaction mixture was diluted with H_2O (20 ml) and extracted with Et_2O (3 x 10 ml). The combined organic layers were washed with H_2O (10 ml), brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 1/1) to obtain the title compound (**230**) as a colourless oil in 71% yield (73.0 mg). **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 3.65 (s, 2H, C$\underline{H_2}$O), 3.01 (s, 3H, C$\underline{H_3}$O), 2.46 (s, 2H, CC$\underline{H_2}$C(=O)), 2.23 – 2.17 (m, 2H, C$\underline{H_2}$CH$_2$C(=O)), 2.17 – 2.11 (m, 2H, CH$_2$C$\underline{H_2}$C(=O)), 1.29 (s, 3H, C$\underline{H_3}$C); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 207.7 ($\underline{C}$=O), 128.9 (one of $\underline{C}$=C), 128.6 (one of C=$\underline{C}$), 71.2 ($\underline{C}$H$_2$O), 57.4 ($\underline{C}$H$_3$O), 45.5 (C$\underline{C}$H$_2$C(=O)), 38.8 (CH$_2\underline{C}$H$_2$C(=O)), 27.6 ($\underline{C}$H$_2$CH$_2$C(=O)), 18.2 (C$\underline{C}$H$_3$); **IR** (film) ν_{max}/cm^{-1}: 2980, 2891, 2818 (C-H), 1717 (C=O), 1083 (C-O); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_9H_{15}O_2^+$) requires *m/z* 155.1066, found *m/z* 155.1067.

5.7.2.9 Synthesis and characterisation of E22

1-((allyloxy)methyl)-4,4-dimethoxy-2-methylcyclohex-1-ene (E22)

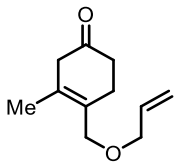


To a solution of (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (100 mg, 0.540 mmol, 1.00 eq) in THF (1.20 ml) at 0 °C was added 60% NaH (23.6 mg, 0.590 mmol, 1.10 eq). The resulting suspension was stirred for 30 min at which point TBAI (10.0 mg, 27 μmol, 0.05 eq) and allyl bromide (51.0 μl, 0.590 mmol, 1.10 eq) were added. The reaction was allowed to warm to room temperature and stirred overnight at which point H_2O (10 ml) was added. The aqueous layer was extracted with EtOAc (3 x 20 ml). The combined extracts were washed with H_2O (20 ml), brine, dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 90/10) to afford the title compound (**E22**) as yellow oil in 53% yield (64.6 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 5.90 (ddt, J = 17.5, 10.5, 5.5 Hz, 1H, C$\underline{H}$=CH_2), 5.24 (dq, J = 17.5, 2.0 Hz, 1H, one of C=C$\underline{H_A}H_B$), 5.10 (dq, J = 10.5, 1.5 Hz, 1H, one of C=C$H_A\underline{H_B}$), 3.95 (s, 2H, C$\underline{H_2}$OCH_2CH), 3.88 (dt, J = 5.5, 1.5 Hz, 2H, OC$\underline{H_2}$CH), 3.15 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.18 (s, 2H, CH_3CC$\underline{H_2}$), 2.10 (ddt, J = 7.0, 4.5, 2.0 Hz, 2H, C$\underline{H_2}$CH_2C(OCH_3)$_2$), 1.74 (t, J = 6.5 Hz, 2H, CH_2C$\underline{H_2}$C(OCH_3)$_2$), 1.65 (s, J = 2.0 Hz, 3H, CC$\underline{H_3}$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 136.7 (C$\underline{H}$=CH_2), 128.3 (C$\underline{C}$$CH_3$), 127.8 (C$\underline{C}$=C$CH_3$), 116.1 (CH=C$\underline{H_2}$), 100.1 (C$\underline{C}$(OC$H_3$)$_2$), 70.9 (C$\underline{H_2}$CH=$CH_2$), 69.7 (C$\underline{H_2}OCH_2$CH=$CH_2$), 47.7 (C(OC$\underline{H_3}$)$_2$), 41.2 (CC$\underline{H_2}$C(OC$H_3$)$_2$), 29.5 (C$H_2C\underline{H_2}$C(OC$H_3$)$_2$), 26.6 (C$\underline{H_2}CH_2$C(OC$H_3$)$_2$), 18.9 (CC$\underline{H_3}$); **IR** (film) ν_{max}/cm^{-1}: 2937, 2828 (C-H), 1647 (C=CH_2), 1095 (C-O); **HRMS** (ES+) exact

mass calculated for $[M+Na]^+$ ($C_{13}H_{22}NaO_3^+$) requires *m/z* 249.1461, found *m/z* 249.1461.

5.7.2.10 Synthesis and characterisation of 231

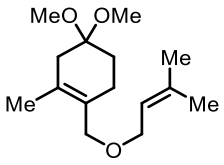
4-((allyloxy)methyl)-3-methylcyclohex-3-en-1-one (231)



The title compound was prepared according to general procedure **V** from 1-((allyloxy)methyl)-4,4-dimethoxy-2-methylcyclohex-1-ene (**E22**) (37 mg, 0.163 mmol, 1.00 eq). Upon completion of the reaction as judged by TLC analysis the reaction mixture was transferred directly to silica gel and purified by silica gel column chromatography (pentane/Et_2O = 9/1) to afford the title compound (**231**) as a colourless oil in 99% yield (25.0 mg). **^{1}H NMR** (400 MHz, Acetone-d_6) δ(ppm): 5.92 (ddt, *J* = 17.5, 10.5, 5.5 Hz, 1H, C<u>H</u>=CH_2), 5.26 (dq, *J* = 17.5, 2.0 Hz, 1H, one of CH=C<u>H$_A$</u>H$_B$), 5.12 (ddt, *J* = 10.5, 2.0, 1.5 Hz, 1H, one of CH=CH_A<u>H$_B$</u>), 4.05 (s, 2H, CH_3C=C<u>CH_2</u>O), 3.94 (dt, *J* = 5.5, 1.5 Hz, 2H, <u>CH_2</u>CH=CH_2), 2.80 (s, 2H, CC<u>H$_2$</u>C(=O)), 2.52 – 2.45 (m, 2H, CH_2C<u>H$_2$</u>C(=O)), 2.42 – 2.36 (m, 2H, C<u>H$_2$</u>CH_2C(=O)), 1.73 (s, 3H, C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, Acetone-d_6) δ(ppm): 209.5 (<u>C</u>=O), 136.5 (<u>C</u>H=CH_2), 129.8 (CH_3<u>C</u>=C), 129.2 (CH_3C=<u>C</u>), 116.4 (CH=<u>C</u>H_2), 71.1 (<u>C</u>H_2CH=CH_2), 69.3 (CH_3C=C<u>C</u>H_2O), 46.0 (C<u>C</u>H_2C(=O)), 39.2 (CH-$_2$<u>C</u>H_2C(=O)), 28.2 (<u>C</u>$H_2$$CH_2$C(=O)),), 18.5 (<u>C</u>$H_3$); **IR** (film) ν_{max}/cm^{-1}: 1717 (C=O), 1671 (C=C), 1072 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{17}O_2^+$) requires *m/z* 181.1223, found *m/z* 181.1224.

5.7.2.11 Synthesis and characterisation of E23

4,4-dimethoxy-2-methyl-1-(((3-methylbut-2-en-1-yl)oxy)methyl)cyclohex-1-ene (E23)

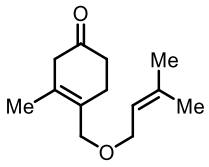


To a stirred solution of (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (500 mg, 2.68 mmol, 1.00 eq) in THF (2.7 ml) at 0 °C was added 60% NaH (118 mg, 2.95 mmol, 1.10 eq). The suspension was stirred for 30 min and allowed to warm to room temperature over a further 30 min. The suspension was cooled back down to 0 °C and 3,3-dimethylallyl bromide (0.310 ml, 2.68 mmol, 1.00 eq) was added dropwise. The reaction was stirred overnight and quenched with sat. aq. NH_4Cl (5 ml). The aqueous phase was extracted with Et_2O (3 x 30 ml) and the organic phases were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**E23**) as a colourless oil in 70% yield (475 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ(ppm): 5.52 (tp, *J* = 6.5, 1.5 Hz, 1H, C$\underline{H}$=C$(CH_3)_2$), 3.96 (s, 2H, C$\underline{H_2}$OCH_2CH=C$(CH_3)_2$), 3.94 (d, *J* = 6.5 Hz, 2H, CH_2OC$\underline{H_2}$CH=C$(CH_3)_2$), 3.09 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.33 – 2.27 (m, 2H, C$\underline{H_2}$CH_2C$(OCH_3)_2$), 2.22 (s, 2H, CC$\underline{H_2}$C$(OCH_3)_2$), 1.85 (t, *J* = 6.5 Hz, 2H, CH_2C$\underline{H_2}$C$(OCH_3)_2$), 1.60 (s, 3H, one of CH=C(C$\underline{H_3}$)$_A$$(CH_3)_B$), 1.57 (s, 3H, C$\underline{H_3}CH_2C(OCH_3)_3$), 1.52 (s, 3H, one of CH=C$(CH_3)_A$(C$\underline{H_3}$)$_B$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 135.3 (C$\underline{}$$(CH_3)_2$), 128.4 (C=C$\underline{}$$(CH_2)$($CH_2$O)), 127.4 (C$\underline{}$=C$(CH_2)$($CH_2$O)), 123.0 (C$\underline{}$H=C), 99.9 (C$\underline{}$$(OCH_3)_2$), 69.4 (C=C$(CH_2)$(C$\underline{H_2}$O)), 66.4 (OC$\underline{H_2}$CH=C), 47.5 (C(OC$\underline{H_3}$)$_2$), 41.0 (CC$\underline{H_2}C(OCH_3)_2$), 29.4 ($CH_2C\underline{H_2}C(OCH_3)_2$), 26.5 (C$\underline{H_2}$$CH_2C(OCH_3)_2$), 25.7 (one of CH=C(C$\underline{H_3}$)$_A$$(CH_3)_B$), 18.9 (C$\underline{H_3}CCH_2C(OCH_3)_2$), 18.0 (one of CH=C$(CH_3)_A$(C$\underline{H_3}$)$_B$); **IR** (film) ν_{max}/cm^{-1}: 2914 (C-H), 1677 (C=C), 1096,

1054 (C-O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{26}NaO_3^+$) requires *m/z* 277.1774, found *m/z* 277.1774.

5.7.2.12 Synthesis and characterisation of 232

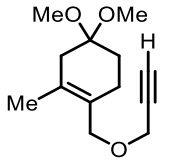
3-methyl-4-(((3-methylbut-2-en-1-yl)oxy)methyl)cyclohex-3-en-1-one (232)



The title compound was prepared according to general procedure **V** from 4,4 dimethoxy-2-methyl-1-(((3-methylbut-2-en-1-yl)oxy)methyl)cyclohex-1-ene (**E23**) (443 mg, 1.74 mmol). The crude product was purified by silica gel column chromatography (pentane/ Et_2O = 85/15) to afford the title compound (**232**) as a colourless oil in 91% yield (331 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 5.32 (tdt, J = 6.5, 3.0, 1.5 Hz, 1H, C$\underline{H}$CH_2O), 4.01 (s, 2H, C$\underline{H_2}$OCH_2CH), 3.93 (d, J = 6.5 Hz, 2H, OC$\underline{H_2}$CH), 2.79 (s, 2H, CC$\underline{H_2}$C(=O)) 2.52 – 2.44 (m, 2H, C$\underline{H_2}$CH_2C(=O)), 2.41 – 2.36 (m, 2H, CH_2C$\underline{H_2}$C(=O)), 1.73 (s, 3H, C$\underline{H_3}$CCH_2C(=O)), 1.72 (d, J = 1.0 Hz, 3H, one of C=C(C$\underline{H_3}$)$_A$(CH_3)$_B$), 1.65 (s, 3H, one of C=C(CH_3)$_A$(C$\underline{H_3}$)$_B$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 209.3 ($\underline{C}$=O), 136.3 ($\underline{C}$(CH_3)$_2$), 129.5 (one of (CH_3)(CH_2)$\underline{C}$=C(CH_2)(CH_2)), 129.5 ((CH_3)(CH_2)C=$\underline{C}$(CH_2)(CH_2)), 122.9 ($CH_2\underline{C}$H=C), 69.0 ($\underline{C}H_2$OCH_2CH), 66.8 (CH_2O$\underline{C}$H$_2$CH), 46.0 (C$\underline{C}$H$_2$C(=O)), 39.2 (CH_2C$\underline{H_2}$C(=O)), 28.3 ($\underline{C}$H$_2$CH_2C(=O)), 25.8 (one of C($\underline{C}$H$_3$)$_A$(CH_3)$_B$), 18.5 ($\underline{C}$H$_3$CCH_2C(=O)), 18.0 (one of C(CH_3)$_A$($\underline{C}$H$_3$)$_B$); **IR** (film) ν_{max}/cm^{-1}: 2970, 2914, 2857 (C-H), 1718 (C=O), 1676 (C=C), 1061 (C-O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{20}NaO_2^+$) requires m/z 231.1356, found m/z 231.1358.

5.7.2.13 Synthesis and characterisation of E24

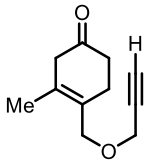
4,4-dimethoxy-2-methyl-1-((prop-2-yn-1-yloxy)methyl)cyclohex-1-ene (E24)



According to a modified literature procedure,[2] 60% NaH (171 mg, 4.30 mmol, 4.00 eq) was added to a stirred solution of (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (200 mg, 1.07 mmol, 1.00 eq) in DMF (6.90 ml) at 0 °C. The solution was stirred for 1 h at which point propargyl bromide (80% in toluene, 0.460 ml, 4.30 mmol, 4.00 eq). The reaction was allowed to warm to room temperature over 12 h at which point H_2O (10 ml) was added. The aqueous layer was extracted with EtOAc (3 x 20 ml). The combined extracts were washed with H_2O (3 x 20 ml), brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 85/15) to afford the title compound (**E24**) as a colourless oil in 78% yield (188 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 4.06 (d, J = 2.5 Hz, 2H, C$\underline{H_2}$C≡C), 4.03 (s, 2H, C$\underline{H_2}$OCH$_2$C≡C), 3.15 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.91 (t, J = 2.5 Hz, 1H, C≡C$\underline{H}$), 2.19 (s, 2H, CC$\underline{H_2}$C(OCH$_3$)$_2$), 2.08 (m, 2H, C$\underline{H_2}$CH$_2$C(OCH$_3$)$_2$), 1.74 (t, J = 6.5 Hz, 2H, CH$_2$C$\underline{H_2}$C(OCH$_3$)$_2$), 1.69 (s, 3H, CC$\underline{H_3}$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 128.7 (C$\underline{C}$CH$_3$), 126.1 (C$\underline{C}$=CCH$_3$), 99.2 (C$\underline{C}$(OCH$_3$)$_2$), 80.4 (C$\underline{C}$≡CH), 74.6 (C≡C$\underline{H}$), 68.1 (C$\underline{H_2}$OCH$_2$C≡C), 55.9 (CH$_2$OC$\underline{H_2}$C≡C), 46.8 (C(OC$\underline{H_3}$)$_2$), 40.3 (C$\underline{C}$H$_2$C(OCH$_3$)$_2$), 28.6 (CH$_2$C$\underline{H_2}$C(OCH$_3$)$_2$), 25.8 (C$\underline{H_2}$CH$_2$C(OCH$_3$)$_2$), 18.0 (C$\underline{C}$H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3252 (C≡C-H), 2940, 2829 (C-H), 2113 (C≡C), 1680 (C=C), 1258, 1131 (C-O); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{13}H_{20}NaO_3^+$) requires *m/z* 247.1305, found *m/z* 247.1304.

5.7.2.14 Synthesis and characterisation of 233

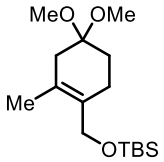
3-methyl-4-((prop-2-yn-1-yloxy)methyl)cyclohex-3-en-1-one (233)



The title compound was prepared according to general procedure **V** from 4,4-dimethoxy-2-methyl-1-((prop-2-yn-1-yloxy)methyl)cyclohex-1-ene (**E24**) (168 mg, 0.75 mmol, 1.00 eq). Upon completion of the reaction as judged by TLC analysis the reaction mixture was transferred directly to silica gel and purified by silica gel column chromatography (pentane/Et_2O = 7/3) to afford the title compound (**233**) as a colourless oil in 77% yield (103 mg). **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 3.82 (s, 2H, C$\underline{H_2}$CCH$_2$), 3.77 (d, *J* = 2.5 Hz, 2H, C$\underline{H_2}$C≡CH), 2.43 (s, 2H, C$\underline{H_2}$CCH$_3$), 2.18 – 2.06 (m, 4H, C$\underline{H_2}$C$\underline{H_2}$C(=O)), 2.02 (t, *J* = 2.5 Hz, 1H, C≡C$\underline{H}$), 1.32 (s, 3H, C$\underline{H_3}$); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 207.4 ($\underline{C}$=O), 130.1 ($\underline{C}$CH$_3$), 127.7 ($\underline{C}$=CCH$_3$), 80.5 ($\underline{C}$≡CH), 74.4 (C≡$\underline{C}$H), 68.2 ($\underline{C}$H$_2$C=CCH$_3$), 56.8 ($\underline{C}$H$_2$C≡CH), 45.5 ($\underline{C}$H$_2$CCH$_3$), 38.7 (CH$_2\underline{C}$H$_2$C(=O)), 27.6 ($\underline{C}$H$_2$CH$_2$C(=O)), 18.3 ($\underline{C}$H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3263 (C≡C-H), 2911, 2852 (C-H), 2113 (C≡C), 1715 (C=O); **HRMS** (APCI+) exact mass calculated for [M+H]$^+$ ($C_{11}H_{15}O_2^+$) requires *m/z* 179.1067, found *m/z* 179.1070.

5.7.2.15 Synthesis and characterisation of E25

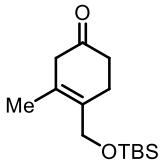
tert-butyl((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methoxy)dimethylsilane (E25)



To a stirred solution of (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (2.00 g, 15.0 mmol, 1.00 eq) and NEt_3 (2.51 ml, 18.0 mmol, 1.20 eq) in CH_2Cl_2 (30 ml) at 0 °C was added a solution of TBSCl (2.49 g, 16.5 mmol, 1.10 eq) in CH_2Cl_2 (20 ml). The solution was stirred overnight and sat. aq. $NaHCO_3$ (30 ml) was added to the reaction and the phases were separated. The aqueous phase was washed with CH_2Cl_2 (2 x 30 ml). The organic extracts were combined, washed with H_2O (30 ml), brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 98/2 to 97/3) to afford the title compound (**E25**) as a white solid in 51% yield (2.31 g). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 4.18 (s, 2H, C$\underline{H_2}$O), 3.14 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.16 (s, 2H, C$\underline{H_2}$C(OCH$_3$)$_2$), 2.14 – 2.10 (m, 2H, C$\underline{H_2}$CCH$_2$O), 1.74 (t, *J* = 6.5 Hz, 2H, CH$_2$C$\underline{H_2}$C(OCH$_3$)$_2$), 1.64 (s, 3H, C=CC$\underline{H_3}$), 0.90 (s, 9H, C(C$\underline{H_3}$)$_3$), 0.07 (s, 6H, Si(C$\underline{H_3}$)$_2$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 130.1 (CH$_3$C=$\underline{C}$), 125.6 (CH$_3\underline{C}$=C), 100.1 ($\underline{C}$(OCH$_3$)$_2$), 63.1 ($\underline{C}$H$_2$O), 47.7 (C(O$\underline{C}$H$_3$)$_2$), 41.2 (C$\underline{C}$H$_2$C(OCH$_3$)$_2$), 29.5 (CH$_2\underline{C}$H$_2$C(OCH$_3$)$_2$), 26.3 (C($\underline{C}$H$_3$)$_3$), 25.9 ($\underline{C}$H$_2$CH$_2$C(OCH$_3$)$_2$), 18.9 ($\underline{C}$(CH$_3$)$_3$), 18.8 (C=C$\underline{C}$H$_3$), -5.1 (Si($\underline{C}$H$_3$)$_2$); **IR** (film) ν_{max}/cm^{-1}: 2929, 2856 (C-H), 1130 (C-O), 1054, 834; **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{16}H_{32}NaO_3Si^+$) requires *m/z* 323.2013, found *m/z* 323.2012; **MP**: 32-33 °C.

5.7.2.16 Synthesis and characterisation of 234

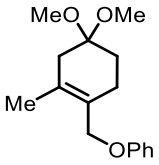
4-(((tert-butyldimethylsilyl)oxy)methyl)-3-methylcyclohex-3-en-1-one (234)



The title compound was prepared according to general procedure **V** from *tert*-butyl((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methoxy)dimethylsilane (**E25**) (2.30 g, 7.65 mmol). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to afford the title compound (**234**) as a colourless oil in 84% yield (1.63 g). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 4.28 (s, 2H, C$\underline{H_2}$O), 2.78 (s, 2H, $CH_3CC\underline{H_2}C(=O)$), 2.55 – 2.48 (m, 2H, C$\underline{H_2}CH_2C(=O)$), 2.42 – 2.36 (m, 2H, $CH_2C\underline{H_2}C(=O)$), 1.72 (s, 3H, C=CC$\underline{H_3}$), 0.91 (s, 9H, C(C$\underline{H_3}$)$_3$), 0.09 (s, 6H, Si(C$\underline{H_3}$)$_2$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 209.4 ($\underline{C}$=O), 131.4 ($\underline{C}$=CCH_3), 127.1 (C=$\underline{C}CH_3$), 62.7 ($\underline{C}H_2O$), 46.0 ($CH_3C\underline{C}H_2C(=O)$), 39.2 ($CH_2\underline{C}H_2C(=O)$), 27.6 ($\underline{C}H_2CH_2C(=O)$), 26.3 (C($\underline{C}H_3$)$_3$), 18.8 ($\underline{C}(CH_3)_3$), 18.4 (C=C$\underline{C}H_3$), -5.1 (Si($\underline{C}H_3$)$_2$); **IR** (film) ν_{max}/cm^{-1}: 2956, 2929, 2887, 2856 (C-H), 1721 (C=O), 1063 (C-O); **HRMS** (APCI+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{27}O_2Si^+$) requires *m/z* 255.1775, found *m/z* 255.1778.

5.7.2.17 Synthesis and characterisation of 241

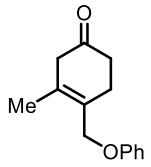
((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methoxy)benzene (241)



According to a literature procedure,[136] a microwave vial was charged with CuI (9.0 mg, 0.047 mmol, 0.050 eq), $CsCO_3$ (459 mg, 1.41 mmol, 1.50 eq), Me_4Phen (22.2 mg, 0.093 mmol, 0.100 eq), **223** (300 mg, 1.41 mmol, 1.50 eq), iodobenzene (106 µl, 0.945 mmol, 1.00 eq) and toluene (0.48 ml). The reaction mixture was stirred at 110 °C overnight. The crude reaction mixture was filtered through celite, concentrated *in vacuo* then purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**241**) in 98% yield (162 mg). **^{1}H NMR** (400 MHz, Methanol-d_4) δ(ppm): 7.33 – 7.19 (m, 2H, Ar<u>H</u>), 6.91 (dtd, *J* = 6.5, 1.5, 1.0 Hz, 3H, Ar<u>H</u>), 4.51 (s, 2H, C<u>H</u>$_2$OPh), 3.21 (s, 6H, C(OC<u>H</u>$_3$)$_2$), 2.27 (bs, 2H, C=CC<u>H</u>$_2$C(OCH$_3$)$_2$), 2.21 (tq, *J* = 6.5, 2.0 Hz, 2H, C<u>H</u>$_2$CCH$_2$O), 1.86 – 1.79 (m, 2H, CH$_2$C<u>H</u>$_2$C(OCH$_3$)$_2$), 1.73 (bs, 3H, C=CC<u>H</u>$_3$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}NaO_3^+$) requires *m/z* 285.1461, found *m/z* 285.1461.

5.7.2.18 Synthesis and characterisation of 242

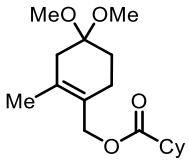
3-methyl-4-(phenoxymethyl)cyclohex-3-en-1-one (242)



The title compound was prepared according to general procedure **V** from ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methoxy)benzene (**241**) (142 mg, 0.541 mmol). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to afford the title compound (**242**) in 79% yield (92.1 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.25 – 7.14 (m, 2H, ArH), 6.94 – 6.84 (m, 3H, Ar<u>H</u>), 4.16 (s, 2H, C<u>H_2</u>OPh), 2.58 – 2.38 (bs, 2H, CC<u>H_2</u>C(=O)), 2.25 – 2.18 (m, 2H, C<u>H_2</u>CH_2C(=O)), 2.18 – 2.11 (m, 2H, CH_2C<u>H_2</u>C(=O)), 1.28 (bs, 3H, C<u>H_3</u>).

5.7.2.19 Synthesis and characterisation of E26

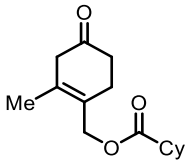
(4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl cyclohexanecarboxylate (E26)



Cyclohexane carbonyl chloride (108 µl, 0.806 mmol, 1.50 eq) was added to a stirred solution of **223** (100 mg, 0.537 mmol, 1.00 eq) in pyridine (1.75 ml). The reaction was stirred overnight at which point sat. aq. $NaHCO_3$ (10 ml) was added. The aqueous layer was extracted with Et_2O (3 x 20 ml). The combined organic layers were washed with $CuSO_4$ solution (2 x 20 ml), brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 95/5 to 9/1) to provide the title compound (**E26**) as a colourless oil in 83% yield (159 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 4.50 (s, 2H, C$\underline{H_2}$O), 2.42 (d, *J* = 2.0 Hz, 2H, CC$\underline{H_2}$C(=O)), 2.24 (tt, *J* = 11.0, 3.5 Hz, 1H, C$\underline{H}$C(=O)), 2.18 – 2.09 (m, 4H, C$\underline{H_2}$C$\underline{H_2}$C(=O)), 1.94 – 1.85 (m, 2H, CyC$\underline{H}$), 1.64 – 1.38 (m, 5H, CyC$\underline{H}$), 1.34 (d, *J* = 2.0 Hz, 3H, C$\underline{H_3}$), 1.17 – 1.02 (m, 3H, CyC$\underline{H}$); **IR** (film) ν_{max}/cm^{-1}: 2931, 2855 (C-H), 1721 (C=O), 1310, 1164 (C-O).

5.7.2.20 Synthesis and characterisation of 246

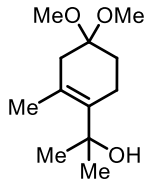
(2-methyl-4-oxocyclohex-1-en-1-yl)methyl cyclohexanecarboxylate (246)



The title compound was prepared according to general procedure **V** from (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl cyclohexanecarboxylate (**E26**) (60 mg, 0.20 mmol). The reaction mixture was diluted with Et_2O (10 ml) and H_2O (10 ml). The phases were partitioned and the aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product (**246**) was obtained in 91% yield (45.6 mg) and taken on without further purification. **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 4.50 (s, 2H, C$\underline{H_2}$OC(=O)), 2.42 (t, *J* = 1.5 Hz, 2H, C=CC$\underline{H_2}$C(=O)), 2.24 (tt, *J* = 11.0, 3.5 Hz, 1H, C$\underline{H}$C(=O)O), 2.18 – 2.09 (m, 4H), 1.94 – 1.81 (m, 2H), 1.66 – 1.36 (m, 5H), 1.34 (d, *J* = 1.9 Hz, 3H, C$\underline{H_3}$), 1.18 – 0.98 (m, 4H); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}O_3^+$) requires *m/z* 273.1461, found *m/z* 273.1462.

5.7.2.21 Synthesis and characterisation of 248

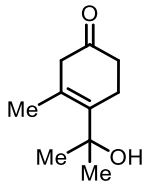
2-(4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)propan-2-ol (248)



MeLi (1.65 ml, 2.63 mmol, 2.40 eq) was added dropwise to a stirred solution of **219** (250 mg, 1.95 mmol, 1.00 eq) in THF (6.4 ml) at 0 °C. The reaction was monitored by TLC (pentane/EtOAc = 8/2) until completion was observed at which point sat. aq. NH_4Cl (20 ml) was added. The aqueous phase was extracted with Et_2O (3 x 30 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 8/2 to 4/6) to provide the title compound (**248**) as a colourless oil in 58% yield (137 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 3.10 (s, 6H, C(OC$\underline{H}_3)_2$), 2.20 (dt, *J* = 2.0, 1.0 Hz, 2H, C$\underline{H}_2$CCH$_3$), 1.96 (tq, *J* = 6.0, 2.0 Hz, 2H, C$\underline{H}_2$CH$_2$C(OMe)$_2$), 1.91 (tt, *J* = 2.0, 1.0 Hz, 3H, C$\underline{H}_3$CCH$_2$), 1.78 – 1.72 (m, 2H, C$\underline{H}_2$CH$_2$C(OMe)$_2$), 1.35 (s, 1H, O$\underline{H}$), 1.25 (s, 6H, C(C$\underline{H}_3)_2$); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 135.9 (one of $\underline{C}$=C), 125.3 (one of C=$\underline{C}$), 99.6 ($\underline{C}$(OMe)$_3$), 73.6 ($\underline{C}$(OH)), 47.6 (C(O$\underline{C}$H$_3)_2$), 42.8 ($\underline{C}$H$_2$CCH$_3$), 29.8 (C($\underline{C}$H$_3)_2$), 29.6 ($\underline{C}$H$_2$CH$_2$C(OMe)$_3$), 26.1 (CH$_2\underline{C}$H$_2$C(OMe)$_3$), 21.5 (C=C$\underline{C}$H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3460 (O-H), 2941, 2829 (C-H), 1117 (C-O).

5.7.2.22 Synthesis and characterisation of 249

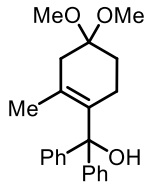
4-(2-hydroxypropan-2-yl)-3-methylcyclohex-3-en-1-one (249)



The title compound was prepared according to general procedure **V** from 2-(4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)propan-2-ol (**248**) (200 mg, 0.933 mmol). The crude product was purified by silica gel column chromatography (pentane/EtOAc = 2/3) to afford the title compound (**249**) as a colourless oil in 83% yield (131 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 2.83 – 2.78 (m, 2H, $CC\underline{H_2}C(=O)$), 2.46 (ddq, *J* = 8.5, 4.5, 1.5 Hz, 2H, $CH_2\underline{CH_2}C(=O)$), 2.37 (ddd, *J* = 7.5, 6.5, 1.5 Hz, 2H, $CH_2CH_2C(=O)$), 1.94 (tt, *J* = 1.5, 1.0 Hz, 3H, $C=CC\underline{H_3}$), 1.79 – 1.67 (m, 1H, $O\underline{H}$), 1.41 (s, 6H, $C(C\underline{H_3})_2$); **IR** (film) ν_{max}/cm^{-1}: 3435 (O-H), 2972, 2928 (C-H), 1708 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{16}NaO_2^+$) requires *m/z* 191.1043, found *m/z* 191.1044.

5.7.2.23 Synthesis and characterisation of E27

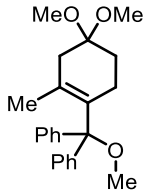
(4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)diphenylmethanol (E27)



Phenyl lithium (3.15 ml, 5.26 mmol, 2.40 eq) was added dropwise to a stirred solution of **219** (500 mg, 2.19 mmol, 1.00 eq) in THF (12.9 ml) at −78 °C. The reaction was allowed to warm to 0 °C. The reaction was monitored by TLC (pentane/EtOAc = 8/2) until completion was observed at which point sat. aq. NH_4Cl (20 ml) was added. The aqueous phase was extracted with Et_2O (3 x 30 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 7/3 to 2/3) to provide the title compound (**E27**) as an off-white solid in 73% yield (545 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.46 – 7.39 (m, 4H, Ar<u>H</u>), 7.15 – 7.10 (m, 3H, Ar<u>H</u> (other Ar<u>H</u> proton is below solvent residue peak)), 7.10 – 7.02 (m, 2H, Ar<u>H</u>), 3.05 (s, 6H, C(OC<u>H</u>$_3$)$_2$), 2.38 (s, 1H, O<u>H</u>), 2.21 (td, *J* = 2.0, 1.0 Hz, 2H, C<u>H</u>$_2$C(OCH$_3$)$_2$), 1.97 (tq, *J* = 6.0, 2.0 Hz, 2H, C<u>H</u>$_2$CH$_2$C(OCH$_3$)$_2$), 1.76 – 1.65 (m, 2H, CH$_2$C<u>H</u>$_2$C(OCH$_3$)$_2$), 1.37 (tt, *J* = 2.0, 1.0 Hz, 3H, C=CC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 148.1, 136.1, 129.8, 128.11, 127.1, 99.5, 82.4, 47.6, 42.7, 29.7, 29.2, 22.5; **IR** (powder) ν_{max}/cm^{-1}: 3373 (O-H), 2991, 2888, 2830 (C-H); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}NaO_3^+$) requires *m/z* 361.1774, found *m/z* 361.1774; **MP**: 126 – 128 °C.

5.7.2.24 Synthesis and characterisation of 251

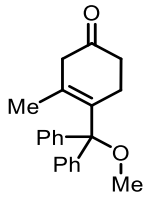
((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)(methoxy)methylene)dibenzene (251)



n-BuLi (2.5 M in hexanes) (0.310 ml, 0.780 mmol, 1.05 eq) was added dropwise to a stirred solution of (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)diphenylmethanol (**E27**) (250 mg, 0.739 mmol, 1.00 eq) in THF (9.2 ml) at −78 °C. The reaction was stirred for 30 min at which point iodomethane (0.46 ml, 7.4 mmol, 10 eq) was added. The reaction was allowed to warm to room temperature overnight at which point an additional 10.0 eq of iodomethane was added. The reaction was monitored by TLC (pentane/EtOAc = 3/3) until completion was observed at which point sat. aq. NH_4Cl (20 ml) was added. The aqueous phase was extracted with Et_2O (3 x 30 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**251**) as a white solid in 62% yield (161 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.66 – 7.60 (m, 4H, Ar<u>H</u>), 7.18 – 7.14 (m, 3H, Ar<u>H</u> other Ar<u>H</u> proton is below solvent residue peak), 7.05 (ddt, *J* = 8.0, 6.5, 1.5 Hz, 2H, Ar<u>H</u>), 3.13 (s, 3H, $Ph_2COC\underline{H}_3$), 3.12 (s, 6H, $C(OC\underline{H}_3)_2$), 2.26 (dt, *J* = 2.0, 1.0 Hz, 2H, $C\underline{H}_2C(OCH_3)_2$), 2.22 (tq, *J* = 6.0, 2.0 Hz, 2H, $C\underline{H}_2CH_2C(OCH_3)_2$), 1.73 (tt, *J* = 6.0, 1.0 Hz, 2H, $C\underline{H}_2CH_2C(OCH_3)_2$), 1.46 (td, *J* = 2.0, 1.0 Hz, 3H, $C{=}CC\underline{H}_3$).

5.7.2.25 Synthesis and characterisation of 252

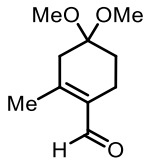
4-(methoxydiphenylmethyl)-3-methylcyclohex-3-en-1-one (252)



The title compound was prepared according to general procedure **VI** from ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)(methoxy)methylene)dibenzene (**251**) (130 mg, 0.369 mmol). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to afford the title compound (**252**) in 72% yield (80.9 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.42 – 7.33 (m, 4H, Ar<u>H</u>), 7.19 – 7.08 (m, 4H, Ar<u>H</u>), 7.08 – 6.99 (m, 2H, Ar<u>H</u>), 2.84 (s, 3H, OC<u>H</u>$_3$), 2.54 (q, *J* = 1.0 Hz, 2H, CC<u>H</u>$_2$C(=O)), 2.12 (dtd, *J* = 6.5, 3.5, 3.0, 1.5 Hz, 2H, CH_2CH_2C(=O)), 1.99 – 1.92 (m, 2H, CH_2CH_2C(=O)), 1.42 – 1.35 (m, 3H, CC<u>H</u>$_3$).

5.7.2.26 Synthesis and characterisation of 255

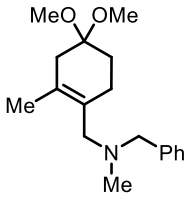
4,4-dimethoxy-2-methylcyclohex-1-ene-1-carbaldehyde (255)



This Swern oxidation was carried out according to a literature procedure.[233] For the following procedure the temperature should be rigorously maintained below -70 °C. DMSO (0.84 ml, 11.8 mmol, 2.2 eq) was added dropwise to oxalyl chloride (0.51 ml, 5.91 mmol, 1.1 eq) in CH_2Cl_2 (29.6 ml) at −78 °C. The reaction was stirred for 20 min. At this point **223** (1.0 g, 5.37 mmol, 1.0 eq) in CH_2Cl_2 (53.7 ml) was added dropwise. Upon completion of the addition the reaction was stirred for a further 15 min at which point NEt_3 (3.7 ml, 26.9 mmol, 5.0 eq) was added dropwise. The temperature was raised to −20 °C and completion was deemed by TLC (Et_2O). H_2O (50 ml) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 ml). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product (**255**) was taken on without further purification (976 mg, 99%). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 10.01 (s, 1H, C<u>H</u>O), 2.99 (s, 6H, C(OC<u>H</u>$_3$)$_2$), 2.40 (tp, *J* = 7.5, 2.0 Hz, 2H, $CH_2C\underline{H_2}C(OCH_3)_2$), 2.08 (bs, 2H, $CC\underline{H_2}C(OCH_3)_2$), 1.70 – 1.61 (m, 2H, $C\underline{H_2}CH_2C(OMe)_3$), 1.48 (dp, *J* = 2.0, 1.0 Hz, 3H, C=CC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 189.3 (<u>C</u>=O), 150.1 (<u>C</u>=CC(=O)), 133.3 (C=<u>C</u>C(=O)), 99.0 (<u>C</u>(OCH$_3$)$_2$), 47.6 (C(O<u>C</u>H$_3$)$_2$), 42.6 (C<u>C</u>H$_2$C(OCH$_3$)$_2$), 28.2 (<u>C</u>H$_2$CH$_2$C(OMe)$_3$), 21.3 (CH$_2$<u>C</u>H$_2$C(OMe)$_3$), 17.4 (C=C<u>C</u>H$_3$).

5.7.2.27 Synthesis and characterisation of 257

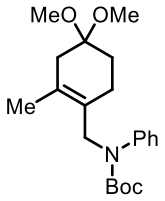
N-benzyl-1-(4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)-N-methylmethanamine (257)



According to a literature procedure,[234] $NaBH(OAc)_3$ (80.5 mg, 0.38 mmol, 1.4 eq) was added to a stirred solution of **255** (50 mg, 0.27 mmol, 1.0 eq) and N-benzylmethylamine (35 µl, 0.27 mmol, 1.0 eq) in DCE (0.94 ml). The reaction was monitored by TLC (pentane/Et_2O = 6/4) until complete consumption of starting material was observed. Upon completion sat. aq. $NaHCO_3$ was added, and the aqueous layer was extracted with EtOAc (3 x 10 ml). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The compound was purified by silica gel column chromatography (pentane/EtOAc/NEt_3 = 5:95:2) and the title compound (**257**) was obtained as a yellow oil in 72% yield (56 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.38 (ddt, *J* = 7.5, 1.3, 0.7 Hz, 2H, ArH), 7.27 – 7.19 (m, 2H, ArH), 7.14 – 7.07 (m, 1H, ArH), 3.35 (s, 2H, one of CH_2N), 3.10 (s, 6H, $C(OCH_3)_2$), 2.87 (s, 2H, one of CH_2N), 2.32 (ddt, *J* = 6.5, 4.0, 2.0 Hz, 2H, $CH_2CH_2C(OCH_3)_2$), 2.22 (s, 2H, CH_2CCH_3), 2.07 (s, 3H, CH_3N), 1.90 – 1.82 (m, 2H, $CH_2CH_2C(OCH_3)_2$), 1.64 – 1.56 (m, 3H, CH_3C=C). **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{28}NO_2^+$) requires *m/z* 290.2115, found *m/z* 290.2113.

5.7.2.28 Synthesis and characterisation of E28

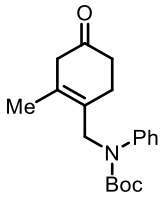
tert-butyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(phenyl)carbamate (E28)



The title compound was prepared according to general procedure **IV** from (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (400 mg, 2.15 mmol) with *tert*-butyl phenylcarbamate as a nucleophile and *n*-BuLi (2.5 M in hexanes) as the base. The compound was purified by silica gel column chromatography (pentane/Et_2O = 85/15) and the title compound (**E28**) was obtained as a colourless oil in 50% yield (386 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.18 – 7.04 (m, 4H, Ar$\underline{H}$), 6.99 – 6.91 (m, 1H, Ar$\underline{H}$), 4.35 (s, 2H, C$\underline{H_2}$N), 3.02 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.26 (m, 2H, $CH_2C\underline{H_2}C(OCH_3)_2$), 2.03 (s, 2H, C$\underline{H_2}CCH_3$), 1.76 (t, J = 6.5 Hz, 2H, C$\underline{H_2}CH_2C(OCH_3)_2$), 1.40 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.20 (s, 3H, $CH_2CC\underline{H_3}$); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 155.0 ($\underline{C}$=O), 143.0 (Ar$\underline{C}$), 128.6 (Ar$\underline{C}$H), 127.4 (one of $\underline{C}$=C), 126.9 (one of C=$\underline{C}$), 126.1 (Ar$\underline{C}$H), 99.7 ($\underline{C}(OCH_3)_2$), 79.5 ($\underline{C}(CH_3)_3$), 50.4 ($\underline{C}H_2N$), 47.5 (C(O$\underline{C}$H$_3$)$_2$), 40.7 ($\underline{C}H_2CCH_3$), 29.3 ($\underline{C}H_2CH_2C(OCH_3)_2$), 28.4 (C($\underline{C}H_3$)$_3$), 26.5 ($CH_2\underline{C}H_2C(OCH_3)_2$), 18.6 ($CH_2C\underline{C}H_3$) (one Ar$\underline{C}$H is hidden beneath the solvent peak); **IR** (film) ν_{max}/cm^{-1}: 2936, 2828 (C-H), 1694 (C=O), 1597, 1496 (C=C), 1127 (C-O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{31}NNaO_4^+$) requires *m/z* 384.2145, found *m/z* 384.2146.

5.7.2.29 Synthesis and characterisation of 259

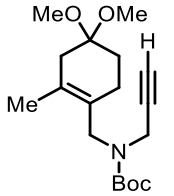
tert-butyl ((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)(phenyl)carbamate (259)



The title compound was prepared according to general procedure **VI** from *tert*-butyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(phenyl)carbamate (**E28**) (330 mg, 0.913 mmol). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 7/3) to afford the title compound (**259**) as a white solid in 89% yield (256 mg). **^{1}H NMR** (600 MHz, Acetone-d_6) δ(ppm): 7.37 – 7.28 (m, 2H, Ar<u>H</u>), 7.28 – 7.22 (m, 2H, Ar<u>H</u>), 7.22 – 7.10 (m, 1H, Ar<u>H</u>), 4.45 (s, 2H, C<u>H_2</u>N), 2.65 (s, 2H, CC<u>H_2</u>C(=O)), 2.46 – 2.39 (m, 2H, C<u>H_2</u>CH_2C(=O)), 2.29 (t, *J* = 7.0 Hz, 2H, CH_2C<u>H_2</u>C(=O)), 1.48 (s, 3H, C=CC<u>H_3</u>), 1.40 (s, 9H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** (151 MHz, Acetone-d_6) δ(ppm): 209.1 (CH_2<u>C</u>(=O)), 155.4 (N<u>C</u>(=O)), 143.2 (Ar<u>C</u>), 129.6 (C=<u>C</u>CH_3), 129.3 (Ar<u>C</u>H), 128.5 (<u>C</u>=CCH_3), 128.3 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 80.2 (O<u>C</u>(CH$_3$)$_3$), 50.3 (<u>C</u>H_2N), 46.0 (C<u>C</u>H_2C(=O)), 39.1 (CH_2<u>C</u>H_2C(=O)), 28.5 (C(<u>C</u>H$_3$)$_3$), 28.0 (<u>C</u>H_2CH_2C(=O)), 18.4 (C=C<u>C</u>H$_3$); **IR** (powder) ν_{max}/cm^{-1}: 2979, 3048 (C-H), 1717 (ketone C=O), 1687 (boc C=O), 754, 702 (C-H); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{26}NO_3^+$) requires *m/z* 316.1907, found *m/z* 316.1908; **MP**: 52-54 °C.

5.7.2.30 Synthesis and characterisation of E29

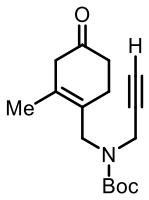
tert-butyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(prop-2-yn-1-yl)carbamate (E29)



The title compound was prepared according to general procedure **IV** from (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (400 mg, 2.15 mmol) with *tert*-butyl prop-2-yn-1-ylcarbamate as a nucleophile and KHMDS (0.5 M in toluene) as the preferred base. The compound was purified by silica gel column chromatography (pentane/Et_2O = 90/10 to 80/20) and the title compound (**E29**) was obtained as a colourless oil in 44% yield (304 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 4.02 (s, 2H, C$\underline{H_2}$NCH_2C≡CH), 3.90 (bs, 2H, CH_2NC$\underline{H_2}$C≡CH), 3.15 (s, 6H, C(OC$\underline{H_3}$)$_2$), 2.69 (t, J = 2.5 Hz, 1H, C≡C$\underline{H}$), 2.21 (bs, 2H, CH_3CC$\underline{H_2}$C(OCH_3)$_2$), 1.99 – 1.92 (m, 2H, C$\underline{H_2}$CH_2C(OCH_3)$_2$), 1.78 – 1.70 (m, 5H, CH_2C$\underline{H_2}$C(OCH_3)$_2$ and C$\underline{H_3}$C=C), 1.46 (s, 9H, C(C$\underline{H_3}$)$_3$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 155.6 (C=O), 128.9 (C=$\underline{C}$CH$_3$) 126.1 ($\underline{C}$=CCH$_3$), 100.1 ($\underline{C}$(OCH$_3$)$_2$), 80.9 ($\underline{C}$≡CH), 80.2 ($\underline{C}$(CH$_3$)$_3$), 72.5 (C≡$\underline{C}$H), 47.8 (C(O$\underline{C}$H$_3$)$_2$), 46.6 ($\underline{C}$H$_2$NCH$_2$C≡CH), 41.3 ($\underline{C}$H$_2$CCH$_3$), 34.7 ($\underline{C}$H$_2$C≡CH), 29.4 (CH$_2\underline{C}$H$_2$C(OCH$_3$)$_2$), 28.5 (C($\underline{C}$H$_3$)$_3$), 26.1 ($\underline{C}$H$_2$CH$_2$C(OCH$_3$)$_2$), 18.9 (C=C$\underline{C}$H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3251 (C≡C-H), 2975 (C-H), 1694 (C=O), 1126 (C-O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{29}NNaO_4^+$) requires m/z 346.1989, found m/z 346.1987.

5.7.2.31 Synthesis and characterisation of 260

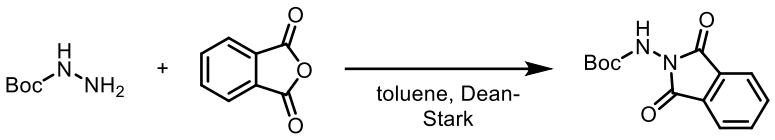
tert-butyl ((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)(prop-2-yn-1-yl)carbamate (260)



The title compound was prepared according to general procedure **VI** from *tert*-butyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(prop-2-yn-1-yl)carbamate (**E29**) (255 mg, 0.788 mmol). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 8/2) to afford the title compound (**260**) as a white solid in 85% yield (185 mg). **^{1}H NMR** (600 MHz, Acetone-d_6) δ(ppm): 4.12 (s, 2H, C=CC$\underline{H_2}$N), 3.97 (bs, 2H, C$\underline{H_2}$C≡CH), 2.81 (s, 2H, CC$\underline{H_2}$C(=O) (beneath H_2O peak)), 2.71 (t, J = 2.5 Hz, 1H, C≡C$\underline{H}$), 2.42 – 2.35 (m, 4H, C$\underline{H_2}$$CH_2$C(=O) and CH_2C$\underline{H_2}$C(=O)), 1.81 (m, 3H, C=CC$\underline{H_3}$), 1.47 (s, 9H, C(C$\underline{H_3}$)$_3$); **^{13}C NMR** (151 MHz, Acetone-d_6) δ(ppm): 209.1 ($CH_2$$\underline{C}$(=O)), 155.7 (N$\underline{C}$(=O)), 130.4 (C=$\underline{C}$$CH_3$), 127.7 ($\underline{C}$=$CCH_3$), 80.9 (O$\underline{C}$(CH$_3$)$_3$), 80.4 ($\underline{C}$≡CH), 72.6 (C≡$\underline{C}$H), 46.5 (C=C$\underline{C}$$H_2$N), 46.1 (C$\underline{C}$$H_2$C(=O)), 39.1 ($CH_2$$\underline{C}$$H_2$C(=O)), 35.3 ($\underline{C}$$H_2$C≡CH), 28.5 (C($\underline{C}H_3$)$_3$), 27.6 ($\underline{C}$$H_2$$CH_2$C(=O)), 18.6 (C=C$\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3235 (C≡C-H), 2929, 2855 (C-H), 2362 (C≡C), 1689 (C=O); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{16}H_{23}NNaO_3^+$) requires *m/z* 300.1570, found *m/z* 300.1571; **MP**: 46-48 °C.

5.7.2.32 Synthesis and characterisation of E30

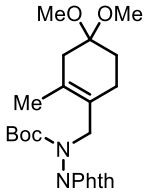
tert-butyl (1,3-dioxoisoindolin-2-yl)carbamate (E30)



According to a modified literature procedure,[235] phthalic anhydride (5.60 g, 37.8 mmol, 1.00 eq) was added to a stirred solution of *tert*-butyl carbazate (5.00 g, 37.8 g, 1.00 eq) in toluene (76 ml). The solution was refluxed under Dean-Stark conditions until no more H_2O was liberated at which point the solution was cooled and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 85/15 to 80/20 to 70/30 to 40/60 to MeOH). The product crashed out on the column after 3.31 g was isolated as a white solid (33%). The remaining product was removed from the column by with MeOH and left to slowly crystalise. The crystals were filtered and washed with MeOH to provide the remainder of the product as colourless crystals in 35% yield (3.49 g) (total yield = 69%, 6.80 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.89 (dt, *J* = 7.5, 3.5 Hz, 2H, Ar<u>H</u>), 7.77 (dd, *J* = 5.5, 3.0 Hz, 2H, Ar<u>H</u>), 6.72 (s, 1H, N<u>H</u>), 1.49 (s, 9H, C($C\underline{H}_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 165.6 (N(<u>C</u>(=O)$_2$), 153.6 (O<u>C</u>(=O)), 134.8 (Ar<u>C</u>H), 130.1 (Ar<u>C</u>), 124.1 (Ar<u>C</u>H), 83.2 (O<u>C</u>(CH_3)$_3$), 28.2 (OC(<u>C</u>H_3)$_3$). Data are consistent with that published in the literature.[235]

5.7.2.33 Synthesis and characterisation of E31

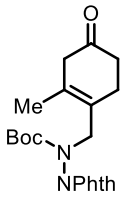
tert-butyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(1,3-dioxoisoindolin-2-yl)carbamate (E31)



The title compound was prepared according to general procedure **IV** from (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (400 mg, 2.15 mmol) with *tert*-butyl (1,3-dioxoisoindolin-2-yl)carbamate as a nucleophile and KHMDS (0.5 M in toluene) as the base. The compound was purified by silica gel column chromatography (pentane/EtOAc = 70/30) and the title compound (**E31**) was obtained as an unstable white solid (foam) in 61% yield (565 mg) which was quickly taken on to the next step.

5.7.2.34 Synthesis and characterisation of 261

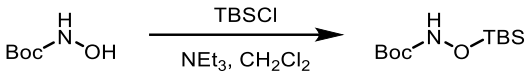
tert-butyl (1,3-dioxoisoindolin-2-yl)((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)carbamate (261)



The title compound was prepared according to general procedure **IV** from *tert*-butyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(1,3-dioxoisoindolin-2-yl)carbamate (**223**) (255 mg, 0.788 mmol). The crude product was purified by silica gel column chromatography (pentane/EtOAc = 6/4) to afford the title compound (**261**) as a white solid (foam) in 44% yield over two steps (363 mg). **^{1}H NMR** (400 MHz, Methanol-d_4) δ(ppm): 8.06 – 7.84 (m, 4H, ArH), 4.40 (s, 2H, CH_2N), 2.71 (s, 2H, $CCH_2C(=O)$), 2.68 – 2.58 (m, 2H, $CH_2CH_2C(=O)$), 2.52 – 2.43 (m, 2H, $CH_2CH_2C(=O)$), 1.55 (s, 3H, $C=CCH_3$), 1.53 (s, 3H, $C(CH_3)_3$ (minor rotamer)), 1.33 (s, 6H, $C(CH_3)_3$ (major rotamer)); **^{13}C NMR** (101 MHz, Methanol-d_4) δ(ppm): 212.8 ($CH_2C(=O)$), 166.7 (ArC(=O)), 155.3 ($OC(=O)$), 136.5 (ArCH, major rotamer), 136.4 (ArCH, minor rotamer), 132.7 (ArC), 130.9 ($C=CCH_3$), 126.9 ($C=CCH_3$), 124.9 (ArCH), 84.6 ($OC(CH_3)_3$, minor rotamer), 83.6 ($OC(CH_3)_3$, major rotamer), 51.0 (CH_2N, minor rotamer), 49.1 (CH_2N, major rotamer), 46.1 ($CCH_2C(=O)$), 39.5 ($CH_2CH_2C(=O)$), 28.7 ($CH_2CH_2C(=O)$), 28.4 ($C(CH_3)_3$ minor rotamer), 28.1 ($C(CH_3)_3$ major rotamer), 18.3 ($C=CCH_3$); **IR** (powder) ν_{max}/cm^{-1}: 2981, 2889 (C-H), 1732, 1704 (C=O), 1425 (C-O), 1149 (C-N); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}N_2NaO_5$) requires *m/z* 407.1577, found *m/z* 407.1573; **MP**: 106-109 °C.

5.7.2.35 Synthesis and characterisation of E32

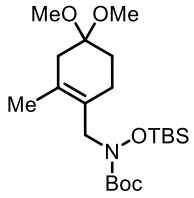
tert-butyl ((tert-butyldimethylsilyl)oxy)carbamate (E32)



According to a literature procedure,[236] TBSCl (3.40 g, 22.5 mmol, 1.00 eq) was added to a stirred solution of *tert*-butyl hydroxycarbamate (3.00 g, 22.5 mmol, 1.00 eq) and NEt_3 (3.45 ml, 24.8 mmol, 1.10 eq) in CH_2Cl_2 (30 ml) at 0 °C. The reaction was stirred overnight and allowed to warm to room temperature. H_2O (30 ml) was added and the phases were partitioned. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide *tert*-butyl ((*tert*-butyldimethylsilyl)oxy)carbamate (**E32**) as a white solid in 83% yield (4.65 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 6.75 (s, 1H, N<u>H</u>), 1.47 (s, 9H, OC(C<u>H</u>$_3$)$_3$), 0.94 (s, 9H, SiC(C<u>H</u>$_3$)$_3$), 0.15 (s, 6H, Si(CH$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 157.9 (<u>C</u>=O), 81.5 (O<u>C</u>(CH$_3$)$_3$), 28.2 (one of C(C<u>H</u>$_3$)$_3$), 25.9 (one of C(C<u>H</u>$_3$)$_3$), 18.0 (Si<u>C</u>(CH$_3$)$_3$), -5.8 (Si(<u>C</u>H$_3$)$_2$); **IR** (powder) ν_{max}/cm^{-1}: 3279 (N-H), 2931, 2896, 2859 (C-H), 1692 (C=O), 1098 (C-O). Data are consistent with that published in the literature.[236]

5.7.2.36 Synthesis and characterisation of E33

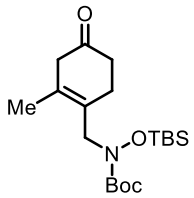
tert-butyl ((tert-butyldimethylsilyl)oxy)((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)carbamate (E33)



The title compound was prepared according to general procedure **IV** from (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (400 mg, 2.15 mmol) with *tert*-butyl ((*tert*-butyldimethylsilyl)oxy)carbamate (**E32**) as a nucleophile and KHMDS (0.5 M in toluene) as the preferred base. The compound was purified by silica gel column chromatography (pentane/Et_2O = 90/10) and the title compound (**E33**) was obtained as a colourless oil in 41% yield (365 mg). **^{1}H NMR** (400 MHz, Acetone-d_6) δ(ppm): 4.11 (s, 2H, C$\underline{H}_2$N), 3.14 (s, 6H, C(OC$\underline{H}_3$)$_2$), 2.17 (s, 2H, C$\underline{H}_2$CCH$_3$), 2.11 – 2.06 (m, 2H, C$\underline{H}_2$CH$_2$C(OCH$_3$)$_3$), 1.74 (t, J = 6.5 Hz, 2H, CH$_2$C$\underline{H}_2$C(OCH$_3$)$_3$), 1.66 (s, 3H, C=CC$\underline{H}_3$), 1.47 (s, 9H, OC(C$\underline{H}_3$)$_3$), 0.94 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.15 (s, 6H, Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 158.9 (C=O), 127.7 (C=$\underline{C}$CH$_3$), 126.7 (C=$\underline{C}$CH$_3$), 100.0 ($\underline{C}$(OCH$_3$)$_2$), 81.2 (O$\underline{C}$(CH$_3$)$_3$), 54.1 ($\underline{C}$H$_2$N), 47.7 (C(O$\underline{C}$H$_3$)$_2$), 41.2 (C$\underline{C}$H$_2$C(OCH$_3$)$_2$), 29.5 (CH$_2$$\underline{C}H_2$C(OCH$_3$)$_3$), 28.41 (OC($\underline{C}H_3$)$_3$), 26.3 ($\underline{C}H_2CH_2$C(OCH$_3$)$_3$ or SiC($\underline{C}$H$_3$)$_3$), 26.3 ($\underline{C}$H$_2$CH$_2$C(OCH$_3$)$_3$ or SiC($\underline{C}$H$_3$)$_3$), 19.1 (C=C$\underline{C}$H$_3$), 18.3 (Si$\underline{C}$(CH$_3$)$_3$), -4.7 (Si($\underline{C}$H$_3$)$_2$); **IR** (film) ν_{max}/cm^{-1}: 2953, 2931, 2896, 2858, 2828 (C-H), 1702 (C=O), 1391 (N-O), 1056 (C-O); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{21}H_{41}NNaO_5Si^+$) requires *m/z* 438.2646, found *m/z* 438.2643.

5.7.2.37 Synthesis and characterisation of 262

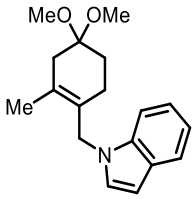
tert-butyl ((tert-butyldimethylsilyl)oxy)((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)carbamate (262)



The title compound was prepared according to general procedure **V** from *tert*-butyl ((*tert*-butyldimethylsilyl)oxy)((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)carbamate (**E33**) (331 mg, 0.796 mmol). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to afford the title compound (**262**) as a colourless oil in 60% yield (176 mg). **^{1}H NMR** (400 MHz, Acetone-d_6) δ(ppm): 4.23 (s, 2H, C$\underline{H}_2$N), 2.79 (s, 2H, CC$\underline{H}_2$C(=O)), 2.49 – 2.43 (m, 2H, C$\underline{H}_2$CH$_2$C(=O)), 2.43 – 2.35 (m, 2H, CH$_2$C$\underline{H}_2$C(=O)), 1.76 (s, 3H, C=CC$\underline{H}_3$), 1.48 (s, 9H, OC(C$\underline{H}_3$)$_3$), 0.93 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.17 (s, 6H, Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 209.1 (CH$_2$$\underline{C}$(=O)), 158.9 (N$\underline{C}$(=O)), 129.6 (C=$\underline{C}CH_3$), 128.1 ($\underline{C}$=CCH$_3$), 81.5 (O$\underline{C}$(CH$_3$)$_3$, 53.8 ($\underline{C}H_2$N), 46.1 (C$\underline{C}H_2$C(=O)), 39.0 (CH$_2$$\underline{C}H_2$C(=O)), 28.4 (OC($\underline{C}H_3$)$_3$), 28.3 ($\underline{C}H_2CH_2$C(=O)), 26.2 (SiC($\underline{C}H_3$)$_3$), 18.9 (C=C$\underline{C}H_3$), 18.3 (Si$\underline{C}$(CH$_3$)$_3$), -4.7 (Si($\underline{C}H_3$)$_2$); **IR** (film) ν_{max}/cm^{-1}: 2957. 2931, 2852 (C-H), 1721 (ketone C=O), 1700 (boc C=O); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{19}H_{35}NNaO_4Si^+$) requires *m/z* 392.2228, found *m/z* 392.2226.

5.7.2.38 Synthesis and characterisation of E34

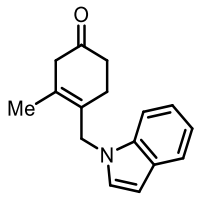
1-((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)-1H-indole (E34)



The title compound was prepared according to general procedure **IV** from (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (400 mg, 2.15 mmol) with indole as a nucleophile and KHMDS (0.5 M in toluene) as the preferred base. The compound was purified by silica gel column chromatography (pentane/Et_2O = 95/5 to 90/10 to 80/20) and the title compound (**E34**) was obtained as a colourless oil in 21% yield (130 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 7.55 (dt, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.39 (dq, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.17 (d, *J* = 3.0 Hz, 1H, ArH), 7.13 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H, ArH), 7.02 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, ArH), 6.43 (dd, *J* = 3.0, 1.0 Hz, 1H, ArH), 4.80 (s, 2H, CH_2N), 3.12 (s, 6H, $C(OCH_3)_2$), 2.28 (s, 2H, CH_2CCH_3), 1.88 (s, 3H, CCH_3), 1.83 – 1.77 (m, 2H, $CH_2CH_2C(OCH_3)_2$), 1.68 – 1.63 (m, 2H, $CH_2CH_2C(OCH_3)_2$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 137.5 (ArC), 129.8 (ArC), 128.7 (CCH_3), 128.6 (ArCH), 126.6 ($C{=}CCH_3$), 121.9 (ArCH), 121.3 (ArCH), 119.8 (ArCH), 110.5 (ArCH), 101.5 (ArCH), 100.0 ($C(OCH_3)_3$), 47.8 ($C(OCH_3)_3$), 47.7 (CH_2N), 41.2 (CH_2CCH_3), 29.4 ($CH_2CH_2C(OCH_3)_3$), 26.2 ($CH_2CH_2C(OCH_3)_3$), 19.1 (CCH_3); **IR** (film) ν_{max}/cm^{-1}: 2938, 2828 (C-H), 1612, 1511, 1461 (C=C), 1127 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{24}NO_2^+$) requires m/z 286.1802, found m/z 286.1804.

5.7.2.39 Synthesis and characterisation of 263

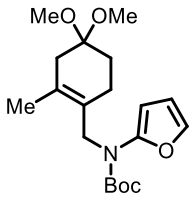
4-((1H-indol-1-yl)methyl)-3-methylcyclohex-3-en-1-one (263)



The title compound was prepared according to general procedure **VI** from 1-((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)-1H-indole (**E34**) (113 mg, 0.397 mmol). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 8/2) to afford the title compound (**263**) as a white solid in 95% yield (85.0 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 7.56 (dt, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.40 (dq, *J* = 8.5, 1.0 Hz, 1H, ArH), 7.26 (d, *J* = 3.0 Hz, 1H, ArH), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, ArH), 7.02 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, ArH), 6.46 (dd, *J* = 3.0, 1.0 Hz, 1H, ArH), 4.94 (s, 2H, CH_2N), 2.89 (s, 2H, $CCH_2C(=O)$), 2.27 (t, *J* = 7.0 Hz, 2H, $CH_2CH_2C(=O)$), 2.19 – 2.11 (m, 2H, $CH_2CH_2C(=O)$), 2.01 – 1.97 (m, 3H, CH_3); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 208.8 (C=O), 137.5 (ArC), 129.9 (ArC), 129.8 (CH_3C=C), 129.0 (ArCH), 128.0 (CH_3C=C), 122.1 (ArCH), 121.5 (ArCH), 120.0 (ArCH), 110.4 (ArCH), 101.8 (ArCH), 47.6 (CH_2N), 46.0 ($CCH_2C(=O)$), 38.9 ($CH_2CH_2C(=O)$), 27.5 ($CH_2CH_2C(=O)$), 18.8 (CH_3); **IR** (powder) ν_{max}/cm^{-1}: 2980, 2913 (C-H), 1715 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{18}NO^+$) requires *m/z* 240.1383, found *m/z* 240.1384; **MP**: 72-74 °C.

5.7.2.40 Synthesis and characterisation of E35

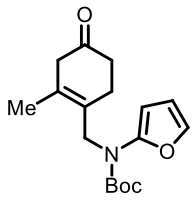
tert-butyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(furan-2-yl)carbamate (E35)



The title compound was prepared according to general procedure **IV** from (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (300 mg, 1.61 mmol) with *tert*-butyl furan-2-ylcarbamate as a nucleophile and KHMDS (0.5 M in toluene) as the preferred base. The compound was purified by silica gel column chromatography (pentane/Et_2O = 90/10 to 80/20) and the title compound (**E35**) was obtained as a colourless oil in 62% yield (348 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 6.90 (dd, J = 2.0, 1.0 Hz, 1H, NCCHCHC<u>H</u>O), 6.06 (dd, J = 3.0, 2.0 Hz, 1H, NCCHC<u>H</u>CHO), 5.96 (s, 1H, NCC<u>H</u>CHCHO), 4.30 (s, 2H, C<u>H_2</u>N), 3.03 (s, 6H, C(OC<u>H_3</u>)$_2$), 2.26 – 2.14 (m, 2H, C<u>H_2</u>$CH_2C(OCH_3)_3$), 2.08 (s, 2H, CC<u>H_2</u>$C(OCH_3)_2$), 1.77 (t, J = 6.5, 2H, CH_2C<u>H_2</u>$C(OCH_3)_3$), 1.39 (s, 9H, C(C<u>H_3</u>)$_3$), 1.35 (s, 3H, C<u>H_3</u>C=C); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 154.5 (N<u>C</u>(=O)), 148.9 (N<u>C</u>CHCHCHO), 138.5 (NCCHCH<u>C</u>HO), 126.2 (CH_3C=<u>C</u> (the other is beneath the solvent peak)), 111.1 (NCCH<u>C</u>HCHO), 102.5 (NC<u>C</u>HCHCHO), 100.0 (<u>C</u>$(OCH_3)_2$), 80.4 (O<u>C</u>$(CH_3)_3$), 49.3 (<u>C</u>H_2N), 47.5 (OC(<u>C</u>H_3)$_3$), 40.9 (C<u>C</u>$H_2C(OCH_3)_2$), 29.3 (CH_2<u>C</u>$H_2C(OCH_3)_2$), 28.2 (C(<u>C</u>H_3)$_3$), 26.2 (<u>C</u>$H_2CH_2C(OCH_3)_2$), 18.6 (<u>C</u>H_3C=C); **IR** (film) ν_{max}/cm^{-1} 2980 (C-H), 1711 (C=O), 1366, 1150 (C-O ester), 1055 (C-O acetal); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{29}NNaO_5^+$) requires m/z 374.1938, found m/z 374.1934.

5.7.2.41 Synthesis and characterisation of 264

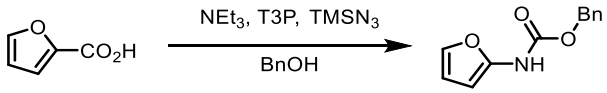
tert-butyl furan-2-yl((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)carbamate (264)



The title compound was prepared according to general procedure **VI** from *tert*-butyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(furan-2-yl)carbamate (**E35**) (307 mg, 0.870 mmol). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 8/2 to 7/3) to afford the title compound (**264**) as a colourless oil in 86% yield (229 mg). **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 6.83 (dd, *J* = 2.0, 1.0 Hz, 1H, NCCHCHC<u>H</u>O), 6.00 (dd, *J* = 3.0, 2.0 Hz, 1H, NCCHC<u>H</u>CHO), 5.76 (bs, 1H, NCC<u>H</u>CHCHO), 4.20 (s, 2H, C<u>H$_2$</u>N), 2.36 (s, 2H, CC<u>H$_2$</u>C(=O)), 2.25 – 2.18 (m, 2H, C<u>H$_2$</u>CH$_2$C(=O)), 2.12 (t, *J* = 7.0 Hz, 2H, CH$_2$C<u>H$_2$</u>C(=O)), 1.36 (s, 9H, C(C<u>H</u>$_3$)$_3$), 1.19 (s, 3H, C=CC<u>H</u>$_3$); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 207.5 (CH$_2$<u>C</u>(=O)), 154.4 (N<u>C</u>(=O)), 148.8 (N<u>C</u>CHCHCHO), 138.6 (NCCHCH<u>C</u>HO), 129.5 (CH$_3$<u>C</u>=C), 127.2 (CH$_3$C=<u>C</u>), 111.1 (NCCH<u>C</u>HCHO), 102.4 (NC<u>C</u>HCHCHO), 80.8 (<u>C</u>(CH$_3$)$_3$), 49.1 (<u>C</u>H$_2$N), 45.5 (C<u>C</u>H$_2$C(=O)), 38.7 (CH$_2$<u>C</u>H$_2$C(=O)), 28.2 (C(<u>C</u>H$_3$)$_3$), 27.4 (<u>C</u>H$_2$CH$_2$C(=O)), 18.1 (<u>C</u>H$_3$C=C); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}NO_4^+$) requires *m/z* 306.1700, found *m/z* 306.1701.

5.7.2.42 Synthesis and characterisation of E36

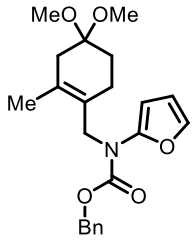
benzyl furan-2-ylcarbamate (E36)



To a solution of furan-2-carboxylic acid (2.00 g, 17.8 mmol, 1.00 eq) in toluene (45 mL) was added NEt_3 (3.73 mL, 26.8 mmol, 1.50 eq) followed by T3P (50% in EtOAc, 12.8 mL, 21.4 mmol, 1.20 eq), azidotrimethylsilane (2.84 mL, 21.4 mmol, 1.20 eq) and benzyl alcohol (3.69 mL, 35.7 mmol, 2.00 eq) sequentially. The reaction was refluxed at 120 ˚C for 16 h at which point it was quenched with dilute aq. K_2CO_3 (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 19/1) to provide benzyl furan-2-ylcarbamate (**E36**) in 64% yield (2.48 g) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.33-7.44 (m, 5H, PhC<u>H</u>), 7.09 (s, 1H, OC<u>H</u>CHCHCN), 6.92 (s, 1H, N<u>H</u>), 6.37 (dd, J = 3.0, 2.0 Hz, 1H, OCHC<u>H</u>CHCN), 6.11 (d, J = 15.0 Hz, 1H, OCHCHC<u>H</u>CN), 5.22 (s, 2H, C<u>H</u>$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 144.9 (<u>C</u>=O), 136.7 (O<u>C</u>HCHCHCN), 135.9 (OCHCHCH<u>C</u>N), 128.7 (Ph<u>C</u>), 111.6 (OCH<u>C</u>HCHCN), 108.1 (OCHCH<u>C</u>HCN), 67.80 (<u>C</u>H$_2$); **LRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{11}NNaO_3^+$) requires *m/z* 240, found *m/z* 240; **MP**: 42-45 ˚C. Data are consistent with that published in the literature.[237]

5.7.2.43 Synthesis and characterisation of E37

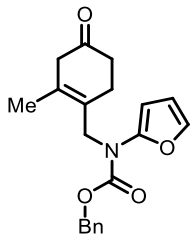
benzyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(furan-2-yl)carbamate (E37)



The title compound was prepared according to general procedure **IV** from (4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methanol (**223**) (219 mg, 1.18 mmol) with benzyl furan-2-ylcarbamate (**E36**) as a nucleophile and KHMDS (0.5 M in toluene) as the base. The compound was purified by silica gel column chromatography (pentane/Et_2O = 90/10) and the title compound (**E37**) was obtained as a colourless oil in 37% yield (170 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 7.39 – 7.26 (m, 6H, ArC<u>H</u> and NCCHCHC<u>H</u>O), 6.38 (dd, *J* = 3.5, 2.0 Hz, 1H, NCCHC<u>H</u>CHO), 6.08 (dd, *J* = 3.5, 1.0 Hz, 1H, NCC<u>H</u>CHCHO), 5.16 (s, 2H, OC<u>H</u>$_2$), 4.25 (s, 2H, C<u>H</u>$_2$N), 3.12 (s, 6H, C(OC<u>H</u>$_3$)$_2$), 2.09 (s, 2H, CC<u>H</u>$_2$C(OCH$_3$)$_2$), 2.04 – 1.98 (m, 2H, C<u>H</u>$_2$CH$_2$C(OCH$_3$)$_2$), 1.72 – 1.66 (m, 2H (CH$_2$C<u>H</u>$_2$C(OCH$_3$)$_2$)), 1.43 (s, 3H, C<u>H</u>$_3$C=C; **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 155.9 (N<u>C</u>(=O)), 148.1 (N<u>C</u>CHCHCHO), 140.2 (NCCHCHC<u>H</u>O), 137.8 (Ar<u>C</u>), 129.6 (CH$_3$<u>C</u>=C), 129.2 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 125.8 (CH$_3$C=<u>C</u>), 111.8 (NCCH<u>C</u>HCHO), 104.3 (NC<u>C</u>HCHCHO), 100.0 (<u>C</u>(OCH$_3$)$_2$), 67.9 (O<u>C</u>H$_2$), 50.2 (<u>C</u>H$_2$N), 47.7 (C(O<u>C</u>H$_3$)$_2$), 41.2 (C<u>C</u>H$_2$C(OCH$_3$)$_2$), 29.5 (CH$_2$<u>C</u>H$_2$C(OCH$_3$)$_2$), 26.5 (<u>C</u>H$_2$CH$_2$C(OCH$_3$)$_2$), 18.7 (C<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1} 2981 (C-H), 1718 (C=O), 1151 (C-O ester), 1054 (C-O acetal); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{27}NNaO_5^+$) requires 408.1781, found 408.1777.

5.7.2.44 Synthesis and characterisation of 265

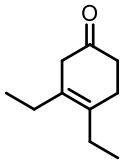
benzyl furan-2-yl((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)carbamate (265)



The title compound was prepared according to general procedure **VI** from *tert*-butyl benzyl ((4,4-dimethoxy-2-methylcyclohex-1-en-1-yl)methyl)(furan-2-yl)carbamate (**E37**) (157 mg, 0.408 mmol). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 8/2 to 7/3) to afford the title compound (**265**) as a colourless oil in 82% yield (114 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 7.42 – 7.24 (m, 6H, ArC<u>H</u> and NCCHCHC<u>H</u>O), 6.40 (dd, *J* = 3.5, 2.0 Hz, 1H, NCCHC<u>H</u>CHO), 6.17 (dd, *J* = 3.5, 1.0 Hz, 1H, NCC<u>H</u>CHCHO), 5.17 (s, 2H, C<u>H$_2$</u>O), 4.38 (s, 2H, C<u>H$_2$</u>N), 2.70 (s, 2H, CC<u>H$_2$</u>C(=O)), 2.45 – 2.36 (m, 2H, C<u>H$_2$</u>CH$_2$C(=O)), 2.32 (m, 2H, CH$_2$C<u>H$_2$</u>C(=O)), 1.55 (s, 3H, C<u>H$_3$</u>); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 209.0 (CH$_2$<u>C</u>(=O)), 155.9 (NC(=O)), 148.3 (N<u>C</u>CHCHCHO), 140.3 (NCCHCH<u>C</u>HO), 137.7 (Ar<u>C</u>), 131.0 (CH$_3$<u>C</u>), 129.3 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 127.3 (CH$_3$C=<u>C</u>), 111.9 (NCCH<u>C</u>HCHO), 104.2 (NC<u>C</u>HCHCHO), 68.1 (<u>C</u>H$_2$O), 50.2 (<u>C</u>H$_2$N), 46.0 (C<u>C</u>H$_2$C(=O)), 39.1 (CH$_2$<u>C</u>H$_2$C(=O)), 28.0 (<u>C</u>H$_2$CH$_2$C(=O)), 18.4 (<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 2981 (C-H), 1717 (C=O ester), 1612 (C=O ketone), 1395, 1277, 1154 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{22}NO_4^+$) requires *m/z* 340.1543, found *m/z* 340.1544.

5.7.2.45 Synthesis and characterisation of 279

3,4-diethylcyclohex-3-en-1-one (279)

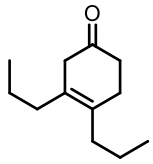


According to a literature procedure,[139] hex-3-yne(500 mg, 6.09 mmol, 1.00 eq) and (buta-1,3-dien-2-yloxy)trimethylsilane (**278**) (1.61 ml, 9.13 mmol, 1.50 eq) were added sequentially to a solution of $CoBr_2$(py-imine) (**277**) (270 mg, 0.609 mmol, 0.100 eq), ZnI_2 (389 mg, 1.22 mmol, 0.200 eq) and Zn (79.6 mg, 1.22 mmol, 0.200 eq) in CH_2Cl_2 (6 ml). The reaction was stirred vigorously under Ar overnight. The reaction mixture was taken up in THF/H_2O = 5/1 (60 ml) and added to a freshly prepared solution of TBAF (1 g of TBAB in sat. aq. KF solution (12 ml) brought to pH 7 by the addition of 1.0 M AcOH). The mixture was stirred vigorously for 1 h at which point Et_2O (30 ml) was added and the phases were separated. The aqueous layer was extracted with Et_2O (2 x 30 ml) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to afford the title compound (**279**) as a colourless oil in 66% yield (616 mg). **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 2.59 (s, 2H, CC$\underline{H_2}$C(=O)), 2.12 (t, *J* = 7.0 Hz, 2H, $CH_2C\underline{H_2}$C(=O)), 1.92 (t, *J* = 7.0 Hz, 2H, $C\underline{H_2}CH_2$C(=O)), 1.81 (q, *J* = 7.5 Hz, 2H, $CH_3C\underline{H_2}$C=CCH_2C(=O)), 1.73 (q, *J* = 7.5 Hz, 2H, $CH_3C\underline{H_2}CCH_2$C(=O)), 0.79 (t, *J* = 7.5 Hz, 3H, $C\underline{H_3}CH_2$C=CCH_2C(=O)), 0.74 (t, *J* = 7.5 Hz, 3H, $C\underline{H_3}CH_2CCH_2$C(=O)); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 208.6 (<u>C</u>=O), 132.2 (<u>C</u>=CCH_2C(=O)), 129.5 (C=<u>C</u>CH_2C(=O)), 43.1 (C<u>C</u>H_2C(=O)), 39.0 ($CH_2\underline{C}H_2$C(=O)), 29.1 (<u>C</u>H_2CH_2C(=O)), 25.7 (2 x <u>C</u>H_2CH_3), 13.1 (<u>C</u>H_3CH_2C=CCH_2C(=O)), 13.0 (<u>C</u>$H_3CH_2CCH_2$C(=O)); **HRMS** (ES+) exact mass

calculated for $[M+H]^+$ ($C_{10}H_{17}O^+$) requires *m/z* 153.1274, found *m/z* 153.1275. Data are consistent with that published in the literature.[139]

5.7.2.46 Synthesis and characterisation of 280

3,4-dipropylcyclohex-3-en-1-one (280)

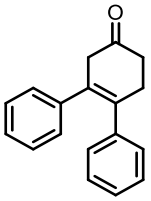


According to a literature procedure,[139] oct-4-yne (671 mg, 6.09 mmol, 1.00 eq) and (buta-1,3-dien-2-yloxy)trimethylsilane (**278**) (1.61 ml, 9.13 mmol, 1.50 eq) were added sequentially to a solution of $CoBr_2$(py-imine) (**277**) (270 mg, 0.609 mmol, 0.100 eq), ZnI_2 (389 mg, 1.22 mmol, 0.200 eq) and Zn (79.6 mg, 1.22 mmol, 0.200 eq) in CH_2Cl_2 (6 ml). The reaction was stirred vigorously under Ar overnight. The reaction mixture was taken up in THF/H_2O = 5/1 (60 ml) and added to a freshly prepared solution of (1 g of TBAB in sat. aq. KF solution (12 ml) brought to pH 7 by the addition of 1.0 M AcOH). The mixture was stirred vigorously for 1 h at which point Et_2O (30 ml) was added and the phases were separated. The aqueous layer was extracted with Et_2O (2 x 30 ml) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by silica gel column chromatography (pentane/Et_2O = 95/5 followed by pentane/CH_2Cl_2 = 7/3 to 6/4 to remove an impurity) to afford the title compound (**280**) as a colourless oil in 21% yield (233 mg). **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 2.61 (s, 2H, CC$\underline{H_2}$C(=O)), 2.13 (t, J = 7.0 Hz, 2H, $CH_2C\underline{H_2}C(=O)$), 1.98 – 1.91 (m, 2H, $C\underline{H_2}CH_2C(=O)$), 1.90 – 1.83 (m, 2H, $CH_3CH_2C\underline{H_2}C{=}CCH_2C(=O)$), 1.82 – 1.76 (m, 2H, $CH_3CH_2C\underline{H_2}CCH_2C(=O)$), 1.27 – 1.14 (m, 4H, $CH_3C\underline{H_2}CH_2C{=}CCH_2C(=O)$ and $CH_3C\underline{H_2}CH_2CCH_2C(=O)$), 0.80 (t, J = 7.5 Hz, 3H, $C\underline{H_3}CH_2CH_2C{=}CCH_2C(=O)$), 0.76 (t, J = 7.5 Hz, 3H, $C\underline{H_3}CH_2CH_2CCH_2C(=O)$); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 208.6 ($\underline{C}$=O), 131.6 ($\underline{C}{=}CCH_2C(=O)$), 128.7 (C=$\underline{C}CH_2C(=O)$), 43.7 (C$\underline{C}H_2C(=O)$), 38.8 ($CH_2\underline{C}H_2C(=O)$), 34.9

($CH_3CH_2\underline{C}H_2C{=}CCH_2C(=O)$), 34.7 ($CH_3CH_2\underline{C}H_2CCH_2C(=O)$), 29.4 ($\underline{C}H_2CH_2C(=O)$), 21.7 ($CH_3\underline{C}H_2CH_2C{=}CCH_2C(=O)$), 21.5 ($CH_3\underline{C}H_2CH_2CCH_2C(=O)$), 14.2 ($\underline{C}H_3CH_2CH_2C{=}CCH_2C(=O)$), 14.1 ($\underline{C}H_3CH_2CH_2CCH_2C(=O)$); **IR** (film) ν_{max}/cm^{-1}: 2959, 2871 (C-H), 1717 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{21}O^+$) requires *m/z* 181.1587, found *m/z* 181.1589.

5.7.2.47 Synthesis and characterisation of 281

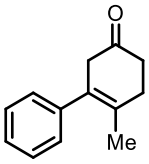
5',6'-dihydro-[1,1':2',1''-terphenyl]-4'(3'H)-one (281)



According to a literature procedure,[139] 1,2-diphenylethyne (96.2 mg, 0.54 mmol, 1.00 eq) and (buta-1,3-dien-2-yloxy)trimethylsilane (**278**) (119 mg, 0.810 mmol, 1.50 eq) were added sequentially to a solution of $CoBr_2$(DPPE) (**276**) (33.3 mg, 0.0540 mmol, 0.100 eq), ZnI_2 (32.5 mg, 0.108 mmol, 0.200 eq) and Zn (7.06 mg, 0.108 mmol, 0.200 eq) in CH_2Cl_2 (0.54 ml). The reaction was stirred vigorously under Ar overnight. The reaction mixture was taken up in THF/H_2O = 5/1 (5.4 ml) and added to a freshly prepared solution of TBAF (ca. 100 mg TBAB in sat. aq. KF solution (1.08 ml) brought to pH 7 by the addition of 1.0 M AcOH). The mixture was stirred vigorously for 1 h at which point the phases were separated. The organic layer was taken up in Et_2O (10 ml), washed with H_2O (3 x 20 ml), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by trituration with Et_2O to afford the title compound (**281**) as a white solid in 26% yield (35.3 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.18 – 7.08 (m, 6H, Ar<u>H</u>), 7.00 (m, 4H, Ar<u>H</u>), 3.35 (t, *J* = 1.5 Hz, 2H, CC<u>H$_2$</u>C(=O)), 2.94 (tt, *J* = 7.0, 1.5 Hz, 2H, C<u>H$_2$</u>CH$_2$C(=O)), 2.72 (t, *J* = 7.0 Hz, 2H, CH$_2$C<u>H$_2$</u>C(=O)); **^{13}C NMR (**126 MHz, $CDCl_3$) δ(ppm): 210.2 (<u>C</u>=O), 141.8 (Ar<u>C</u>), 141.1 (Ar<u>C</u>), 135.6 (<u>C</u>=CCH$_2$C(=O)), 132.0 (C=<u>C</u>CH$_2$C(=O)), 129.0 (Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 45.9 (C<u>C</u>H$_2$C(=O)), 38.8 (CH$_2$<u>C</u>H$_2$C(=O)), 32.0 (<u>C</u>H$_2$CH$_2$C(=O)); **IR** (powder) ν_{max}/cm^{-1}: 1714 (C=O), 1666 (C=C), 754, 698 (C-H). Data are consistent with that published in the literature.[238]

5.7.2.48 Synthesis and characterisation of 282

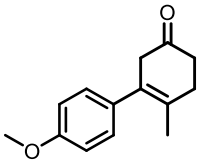
6-methyl-4,5-dihydro-[1,1'-biphenyl]-3(2H)-one (282)



According to a literature procedure,[139] prop-1-yn-1-ylbenzene (0.348 mg, 3.00 mmol, 1.00 eq) and (buta-1,3-dien-2-yloxy)trimethylsilane (**278**) (0.780 ml, 4.50 mmol, 1.50 eq) were added sequentially to a solution of $CoBr_2$(py-imine) (**277**) (132 mg, 0.300 mmol, 0.100 eq), ZnI_2 (192 mg, 0.600 mmol, 0.200 eq) and Zn (39.3 mg, 0.600 mmol, 0.200 eq) in CH_2Cl_2 (3 ml). The reaction was stirred vigorously under Ar overnight. The reaction mixture was taken up in THF/H_2O = 5/1 (30 ml) and added to a freshly prepared solution of TBAF (600 mg of TBAB in sat. aq. KF solution (6 ml) brought to pH 7 by the addition of 1.0 M AcOH). The mixture was stirred vigorously for 1 h at which point Et_2O (20 ml) was added and the phases were separated. The aqueous layer was extracted with Et_2O (2 x 20 ml) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by silica gel column chromatography (pentane/Et_2O = 95/5 to 9/1) to afford the title compound (**282**) as a colourless oil in 40% yield (223 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 7.41 – 7.31 (m, 2H, Ar<u>H</u>), 7.30 – 7.17 (m, 3H, Ar<u>H</u>), 3.09 – 3.04 (m, 2H, CC<u>H$_2$</u>C(=O)), 2.59 – 2.48 (m, 4H, C<u>H$_2$</u>C<u>H$_2$</u>C(=O)), 1.72 – 1.69 (m, 3H, C<u>H$_3$</u>); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 209.1 (<u>C</u>=O), 142.8 (Ar<u>C</u>), 130.8 (CH$_3$<u>C</u>=C or CH$_3$C=<u>C</u>), 130.8 (CH$_3$<u>C</u>=C or CH$_3$C=<u>C</u>), 129.1 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 45.8 (C<u>C</u>H$_2$C(=O)), 38.9 (CH$_2$<u>C</u>H$_2$C(=O)), 32.1 (<u>C</u>H$_2$CH$_2$C(=O)), 20.3 (<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 2980, 2908, 2889 (C-H), 1713 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O^+$) requires *m/z* 187.1117, found *m/z* 187.1120.

5.7.2.49 Synthesis and characterisation of 283

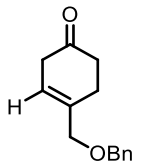
4'-methoxy-6-methyl-4,5-dihydro-[1,1'-biphenyl]-3(2H)-one (283)



According to a literature procedure,[139] 1-methoxy-4-(prop-1-yn-1-yl)benzene (439 mg, 3.00 mmol, 1.00 eq) and (buta-1,3-dien-2-yloxy)trimethylsilane (**278**) (0.780 ml, 4.50 mmol, 1.50 eq) were added sequentially to a solution of $CoBr_2$(py-imine) (**277**) (132 mg, 0.300 mmol, 0.100 eq), ZnI_2 (192 mg, 0.600 mmol, 0.200 eq) and Zn (39.3 mg, 0.600 mmol, 0.200 eq) in CH_2Cl_2 (3 ml). The reaction was stirred vigorously under Ar overnight. The reaction mixture was taken up in THF/H_2O = 5/1 (30 ml) and added to a freshly prepared solution of TBAF (ca. 600 mg TBAB in sat. aq. KF solution (6 ml) brought to pH 7 by the addition of AcOH). The mixture was stirred vigorously for 1 h at which point the phases were separated. The organic layer was taken up in Et_2O (20 ml), washed with H_2O (3 x 30 ml), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by silica gel column chromatography (pentane/Et_2O = 95/5 to 9/1) to afford the title compound (**283**) as a yellow oil in 36% yield (234 mg). **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 7.16 – 7.10 (m, 2H, ArH), 6.94 – 6.89 (m, 2H, ArH), 3.80 (s, 3H, OCH_3), 3.06 – 3.01 (m, 2H, $CCH_2C(=O)$), 2.56 – 2.46 (m, 4H, $CH_2CH_2C(=O)$), 1.72 – 1.69 (m, 3H, CCH_3); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 209.2 (C=O), 159.4 (ArC), 135.0 (ArC), 130.3 (CH_3C=C or CH_3C=C), 130.3 (CH_3C=C or CH_3C=C), 130.2 (ArCH), 114.4 (ArCH), 55.5 (OCH_3), 45.9 ($CCH_2C(=O)$), 38.9 ($CH_2CH_2C(=O)$), 32.1 ($CH_2CH_2C(=O)$), 20.4 (CH_3C); **IR** (film) ν_{max}/cm^{-1}: 2910, 2838 (C-H), 1715 (C=O), 1510 (C=C), 1244 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}O_2^+$) requires *m/z* 217.1223, found *m/z* 217.1226.

5.7.2.50 Synthesis and characterisation of 289

4-((benzyloxy)methyl)cyclohex-3-en-1-one (289)



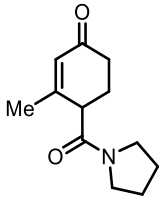
ii. According to a literature procedure,[139] ((prop-2-yn-1-yloxy)methyl)benzene (100 mg, 0.684 mmol, 1.00 eq) and (buta-1,3-dien-2-yloxy)trimethylsilane (**278**) (181 µl, 1.03 mmol, 1.50 eq) were added sequentially to a solution of $CoBr_2$(DPPE) (**276**) (42.0 mg, 0.0680 mmol, 0.100 eq), ZnI (44.0 mg, 0.137 mmol, 0.200 eq) and Zn (8.70 mg, 0.137 mmol, 0.200 eq) in CH_2Cl_2 (0.68 ml) in a schlenk tube under an atmosphere of Ar. The reaction was stirred vigorously overnight. The reaction mixture was taken up in THF/H_2O = 5/1 (6.8 ml) and added to a freshly prepared solution of TBAF (ca. 100 mg TBAB in sat. aq. KF solution (1.4 ml) brought to pH 7 by the addition of 1.0 M AcOH). The mixture was stirred vigorously for 1 h at which point the phases were separated. The reaction was diluted with H_2O (20 ml) and the aqueous phase was extracted with EtOAc (3 x 20 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was taken up in Et_2O (10 ml), filtered through a plug of celite, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1 to 8/2) to provide the title compound (**289**) as a colourless oil in 64% yield (94 mg). **^{1}H NMR** (400 MHz, Acetone-d_6) δ(ppm): 7.40 – 7.31 (m, 4H, ArC<u>H</u>), 7.28 (m, 1H, ArC<u>H</u>), 5.79 (tt, *J* = 3.5, 1.5 Hz, 1H, C=C<u>H</u>), 4.50 (s, 2H, C<u>H$_2$</u>Ph), 4.03 – 3.99 (m, 2H, C<u>H$_2$</u>OCH$_2$Ph), 2.87 – 2.82 (m, 2H, CHC<u>H$_2$</u>C(=O)), 2.53 – 2.41 (m, 4H, C<u>H$_2$</u>CH$_2$C(=O) and CH$_2$C<u>H$_2$</u>C(=O)); **^{13}C NMR** (151 MHz, Acetone-d_6) δ(ppm): 209.0 (<u>C</u>=O), 139.8 (Ar<u>C</u>), 136.8 (<u>C</u>=CH), 129.1 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 122.0 (C=<u>C</u>H), 73.9 (<u>C</u>H$_2$OCH$_2$Ph), 72.4

($CH_2O\underline{C}H_2Ph$), 39.8 ($CH\underline{C}H_2C(=O)$), 38.7 ($CH_2\underline{C}H_2C(=O)$), 26.7 ($\underline{C}H_2CH_2C(=O)$); **IR** (film) ν_{max}/cm^{-1}: 2980, 2889, 2852 (C-H), 1714 (C=O), 1073 (C-O), 737, 697 (C-H); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}NaO_2^+$) requires *m/z* 239.1043, found *m/z* 239.1045.

5.7.3 Synthesis and characterisation of products obtained in the enantioselective prototropic shift of β,γ-unsaturated cyclohexenones

5.7.3.1 Synthesis and characterisation of 222

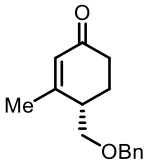
3-methyl-4-(pyrrolidine-1-carbonyl)cyclohex-2-en-1-one (222)



3-methyl-4-(pyrrolidine-1-carbonyl)cyclohex-3-en-1-one (**221**) (5.00 mg, 0.0240 mmol, 1.00 eq) was reacted according to general procedure **VII** with preformed BIMP catalyst **119a**. The reaction mixture was purified by silica gel column chromatography (CH_2Cl_2/Acetone = 7/3) to yield 1-tosyloctahydro-6H-indol-6-one (**222**) as a colourless oil in 63% yield (4.4 mg) and 5% ee [determined by HPLC chiralpak AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 220 nm, t (minor) = 32.5 min, t (major) =37.4 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 6.01 (p, *J* = 1.5 Hz, 1H, $CH_3CC\underline{H}C(=O)$), 3.65 – 3.45 (m, 4H, 2 x $C\underline{H_2}N$), 3.42 (t, *J* = 6.0 Hz, 1H, $C\underline{H}C(=O)N$), 2.65 (ddd, *J* = 16.5, 8.0, 5.5 Hz, 1H, one of $C\underline{H_A}H_BC(=O)$), 2.36 – 2.26 (m, 1H, one of $CH_A\underline{H_B}C(=O)$), 2.24 – 2.17 (m, 2H, $C\underline{H_2}CH_2C(=O)$), 2.09 – 1.98 (m, 2H, one of $(C\underline{H_2})_A(CH_2)_BCH_2N$), 1.96 – 1.88 (m, 5H, $C\underline{H_3}$ and one of $(CH_2)_A(C\underline{H_2})_BCH_2N$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 198.8 ($CH_2\underline{C}(=O)$), 169.9 ($\underline{C}(=O)N$), 158.4 ($\underline{C}=CH$), 129.2 ($C=\underline{C}H$), 47.4 (one of $\underline{C}H_2N$), 46.3 (one of $\underline{C}H_2N$), 45.4 ($\underline{C}HC(=O)N$), 34.8 ($\underline{C}H_2C(=O)$), 26.4 (one of $(\underline{C}H_2)_A(CH_2)_BCH_2N$), 26.1 ($\underline{C}H_2CH_2C(=O)$), 24.5 (one of $(CH_2)_A(\underline{C}H_2)_BCH_2N$), 23.1 ($\underline{C}H_3$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{17}NNaO_2^+$) requires *m/z* 230.1152, found *m/z* 230.1151.

5.7.3.2 Synthesis and characterisation of 227

(S)-4-((benzyloxy)methyl)-3-methylcyclohex-2-en-1-one (227)

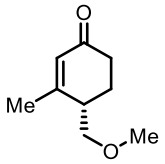


The title compound was prepared according to general procedure **VII** from 4-((benzyloxy)methyl)-3-methylcyclohex-3-en-1-one (**225**) (59.9 mg, 0.260 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/EtOAc = 9/1 to 8/2) to provide the title compound (**227**) as a colourless oil in 90% yield (54.2 mg) and 99% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 220 nm, t(major) = 15.19 min, t(minor) = 22.07 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.41 – 7.26 (m, 5H, ArH), 5.92 – 5.88 (m, 1H, CHC(=O)), 4.57 (d, *J* =12.0 Hz, 1H, CH_AH_BPh), 4.51 (d, *J* =12.0 Hz, 1H, CH_AH_BPh), 3.60 (d, *J* = 6.0 Hz, 2H, $CHCH_2O$), 2.57 (p, *J* = 5.5 Hz, 1H, $CHCH_2$), 2.45 (ddd, *J* = 17.5, 10.0, 5.5 Hz, 1H, one of $CH_AH_BC(=O)$), 2.35 – 2.26 (m, 1H, one of $CH_AH_BC(=O)$), 2.11 (m, 2H, $CH_2CH_2C(=O)$), 1.98 (m, 3H, CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 199.4 (C=O), 162.4 (CCH_3), 138.0 (ArC), 128.6 (ArCH), 128.3 ($C=CCH_3$), 127.9 (ArCH), 127.7 (ArCH), 73.4 (CH_2Ph), 70.5 ($CHCH_2O$), 40.4 ($CHCH_2O$), 34.6 ($CH_2C(=O)$), 25.8 ($CH_2CH_2C(=O)$), 23.1 (CH_3); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –91.22 (*c* 2.01, $CHCl_3$) (99% ee); lit: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +65.8 (*c* 1.98, $CHCl_3$) 81% ee, (*R*)-4-((benzyloxy)methyl)-3-methylcyclohex-2-en-1-one).[144] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +62.6 (*c* 1.05, $CHCl_3$), (*R*)-4-((benzyloxy)methyl)-3-methylcyclohex-2-en-1-one).[239]

Data are consistent with that published in the literature. [144,239]

5.7.3.3 Synthesis and characterisation of 235

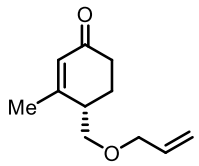
(S)-4-(methoxymethyl)-3-methylcyclohex-2-en-1-one (235)



The title compound was prepared according to general procedure **VII** from 4-(methoxymethyl)-3-methylcyclohex-3-en-1-one (**230**) (20.0 mg, 0.130 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 7/3) to provide the title compound (**235**) as a colourless oil in 58% yield (11.6 mg) and 96% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 95/5, 1 ml/min, λ = 230 nm, t(major) = 8.24 min, t(minor) = 8.90 min]. **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 5.92 – 5.90 (m, 1H, C$\underline{H}$C(=O)), 2.97 – 2.90 (m, 5H, OC$\underline{H_3}$ and OC$\underline{H_2}$), 2.30 (ddd, *J* = 17.0, 10.0, 5.0 Hz, 1H, one of C$\underline{H_A}$H$_B$C(=O)), 2.10 (ddd, *J* = 17.0, 7.5, 5.0 Hz, 1H, one of CH$_A$$\underline{H_B}$C(=O)), 1.96 (p, *J* = 5.5 Hz, 1H, C$\underline{H}$CH$_2$O), 1.79 – 1.71 (m, 1H, one of C$\underline{H_A}$H$_B$CH$_2$C(=O)), 1.59 (ddt, *J* = 13.5, 10.0, 5.0 Hz, 1H, one of CH$_A$$\underline{H_B}CH_2$C(=O)), 1.47 (s, 3H, C$\underline{H_3}$C); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 197.1 ($\underline{C}$=O), 160.4 ($\underline{C}$CH$_3$), 128.6 (C=$\underline{C}$H), 73.2 ($\underline{C}$H$_2$O), 58.6 ($\underline{C}$H$_3$O), 40.3 ($\underline{C}$HCH$_2$O), 34.9 ($\underline{C}$H$_2$C(=O)), 25.9 ($\underline{C}$H$_2$CH$_2$C(=O)), 22.6 (C$\underline{C}$H$_3$); **IR** (film) ν_{max}/cm^{-1}: 2926, 2873 (C-H), 1667 (C=O), 1625 (C=C), 1207 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{15}O_2^+$) requires *m/z* 155.1067, found *m/z* 155.1066; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –84 (*c* 0.265, $CHCl_3$).

5.7.3.4 Synthesis and characterisation of 236

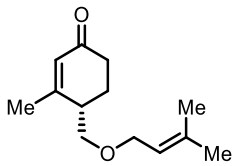
(S)-4-((allyloxy)methyl)-3-methylcyclohex-2-en-1-one (236)



The title compound was prepared according to general procedure **VII** from 4-((allyloxy)methyl)-3-methylcyclohex-3-en-1-one (**231**) (23.4 mg, 0.130 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**236**) as a colourless oil in 78% yield (18.3 mg) and 98% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 240 nm, t(major) = 12.70 min, t(minor) = 17.07 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 5.94 – 5.83 (m, 2H, C$\underline{H}$=CH_2 and C$\underline{H}$C(=O)), 5.26 (dq, *J* = 17.0, 1.5 Hz, 1H, one of CH=C$\underline{H_A}H_B$), 5.18 (dq, *J* = 10.5, 1.5 Hz, 1H, one of CH=C$H_A\underline{H_B}$), 4.04 – 3.92 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.57 – 3.54 (m, 2H, C$\underline{H_2}$COCH_2CH=CH_2), 2.54 (p, *J* = 5.5 Hz, 1H, $CH_2CH_2C\underline{H}CH_2O$), 2.51 – 2.41 (m, 1H, one of C$\underline{H_A}H_B$C(=O)), 2.35 – 2.25 (m, 1H, C$H_A\underline{H_B}$C(=O)), 2.13 – 2.03 (m, 2H, C$\underline{H_2}$CHCH_2O), 1.99 (dd, *J* = 1.5, 1.0 Hz, 3H, C$\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 199.5 (C=O), 162.5 (CCH_3), 134.5 (CH=CH_2), 128.3 (C=CCH_3), 117.4 (CH=CH_2), 72.3 (CH_2CH=CH_2), 70.5 (CH_2OCH_2CH=CH_2), 40.4 (CHCH_2OCH_2CH=CH_2), 34.6 (CH_2C(=O)), 25.8 (CH_2CH_2C(=O)), 23.2 (CH_3); **IR** (film) ν_{max}/cm^{-1}: 2980, 2867 (C-H), 1667 (C=O), 1625 (C=C), 1135 (C-O), 925 (C=C-H); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{17}O_2^+$) requires *m/z* 181.1223, found *m/z* 181.1223; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –116.7 (*c* 0.185, $CHCl_3$).

5.7.3.5 Synthesis and characterisation of 237

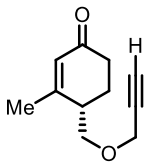
(S)-3-methyl-4-(((3-methylbut-2-en-1-yl)oxy)methyl)cyclohex-2-en-1-one (237)



The title compound was prepared according to general procedure **VII** from 3-methyl-4-(((3-methylbut-2-en-1-yl)oxy)methyl)cyclohex-3-en-1-one (**232**) (27.1 mg, 0.130 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 75/25) to provide the title compound (**237**) as a yellow oil in 85% yield (23.0 mg) and 99% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 95/5, 1 ml/min, λ = 240 nm, t(major) = 39.05 min, t(minor) = 56.23 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 5.89 (t, *J* = 1.5 Hz, 1H, C$\underline{H}$C(=O)), 5.36 – 5.29 (m, 1H, C$\underline{H}$C$(CH_3)_2$), 4.04 – 3.92 (m, 2H, OC$\underline{H_2}$CH=C), 3.54 (d, *J* = 6.0 Hz, 2H, C$\underline{H_2}$OCH_2CH=C), 2.53 (p, J = 5.5, 1H, C$\underline{H}$CH_2CH_2), 2.47 (ddd, *J* = 17.0, 9.5, 5.5 Hz, 1H, one of C$\underline{H_A}$$H_B$C(=O)), 2.30 (ddd, *J* = 17.0, 6.5, 5.5 Hz, 1H, one of C$H_A$$\underline{H_B}$C(=O)), 2.14 – 2.02 (m, 2H, C$\underline{H_2}$CH_2C(=O)), 2.01 – 1.97 (m, 3H, C$\underline{H_3}$C=CHC(=O)), 1.75 (s, 3H, one of C(C$\underline{H_3}$)$_A$$(CH_3)_B$), 1.67 (s, 3H, one of C$(CH_3)_A$(C$\underline{H_3}$)$_B$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 199.6 (C=O), 162.7 (C=CHC(=O)), 137.5 (C$(CH_3)_2$), 128.3 (C=CHC(=O)), 120.9 (CH=C$(CH_3)_2$), 70.2 (CH_2OCH_2CH=C), 67.8 (CH_2OCH_2CH=C), 40.5 (CH_2CHCCH_3), 34.6 (CH_2CH_2C(=O)), 25.9 (one of C(CH_3)$_A$$(CH_3)_B$), 25.7 (C$H_2CH_2$C(=O)), 23.2 (C$H_3$C=CHC(=O)), 18.2 (one of C$(CH_3)_A$(CH_3)$_B$); **IR** (film) ν_{max}/cm^{-1}: 2970, 2914, 2865, (C-H), 1667 (C=O), 1625 (C=C), 1089 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{21}O_2^+$) requires *m/z* 209.1536, found *m/z* 209.1538; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –74.0 (*c* 0.115, $CHCl_3$).

5.7.3.6 Synthesis and characterisation of 238

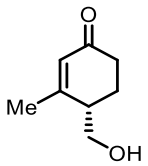
(S)-3-methyl-4-((prop-2-yn-1-yloxy)methyl)cyclohex-2-en-1-one (238)



The title compound was prepared according to general procedure **VII** from 3-methyl-4-((prop-2-yn-1-yloxy)methyl)cyclohex-3-en-1-one (**233**) (23.2 mg, 0.130 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**238**) as a colourless oil in 96% yield (22.2 mg) and 99% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 230 nm, t(minor) = 25.83 min, t(major) = 27.16 min]. **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 5.91 – 5.86 (m, 1H, C$\underline{H}$C(=O)), 3.72 (dd, *J* = 16.0, 2.5 Hz, 1H, C$\underline{H}_A$H$_B$C≡CH), 3.67 (dd, *J* = 16.0, 2.5 Hz, 1H, CH$_A\underline{H}_B$C≡CH), 3.16 (dd, *J* = 9.0, 7.0 Hz, 1H, one of COC$\underline{H}_A$H$_B$CHCH$_2$CH$_2$), 3.09 (dd, *J* = 9.0, 4.5 Hz, 1H, one of COCH$_A\underline{H}_B$CHCH$_2$CH$_2$), 2.30 (ddd, *J* = 17.0, 10.0, 5.0 Hz, 1H, one of C$\underline{H}_A$H$_B$C(=O)), 2.08 (ddd, *J* = 17.0, 7.5, 5.0 Hz, 1H, one of CH$_A\underline{H}_B$C(=O)), 2.03 (t, *J* = 2.5 Hz, 1H, C≡C$\underline{H}$), 1.96 (p, *J* = 6.0 Hz, 1H, C$\underline{H}$CH$_2$CH$_2$), 1.81 – 1.70 (m, 1H, one of C$\underline{H}_A$H$_B$CH$_2$C(=O)), 1.62 – 1.52 (m, 1H, one of CH$_A\underline{H}_B$CH$_2$C(=O)), 1.47 (dd, *J* = 1.5, 1.0 Hz, 3H, C$\underline{H}_3$); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 197.0 (C=O), 160.0 (C$\underline{C}$H$_3$), 128.7 (C$\underline{C}$HC(=O)), 79.9 (C$\underline{C}$≡CH), 74.8 (C≡C$\underline{H}$), 70.1 (O$\underline{C}$H$_2$CHCH$_2$), 58.2 (C$\underline{H}_2$C≡CH), 40.1 (C$\underline{H}$CH$_2$CO), 34.9 (C$\underline{H}_2$C(=O)), 25.8 (C$\underline{H}_2$CH$_2$C(=O)), 22.5 (C$\underline{H}_3$); **IR** (film) ν_{max}/cm^{-1}: 3248 (C≡C-H), 2916, 2869 (C-H), 2113 (C≡C), 1664 (C=O), 1625 (C=C), 1204 (C-O); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{11}H_{15}O_2^+$) requires *m/z* 179.1067, found *m/z* 179.1067; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –121.9 (*c* 0.130, $CHCl_3$).

5.7.3.7 Synthesis and characterisation of 239

(S)-4-(hydroxymethyl)-3-methylcyclohex-2-en-1-one (239)

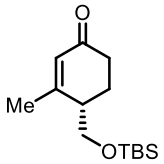


The title compound was prepared according to general procedure **VII** from 4-(hydroxymethyl)-3-methylcyclohex-3-en-1-one (**E20**) (9.00 mg, 0.065 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (Et_2O) to provide the title compound (**239**) as a yellow oil in 67% yield (6.0 mg) and 85% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 230 nm, t(minor) = 12.56 min, t(major) = 15.93 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 5.93 – 5.90 (m, 1H, C<u>H</u>C(=O)), 3.87 – 3.75 (m, 2H, C<u>H$_2$</u>OH), 2.57 – 2.42 (m, 2H, one of C<u>H$_A$</u>H$_B$C(=O) and C<u>H</u>CH$_2$OH), 2.37 – 2.27 (m, 1H, one of CH$_A$<u>H$_B$</u>C(=O)), 2.17 – 2.04 (m, 3H, C<u>H$_2$</u>CH$_2$C(=O) and O<u>H</u>), 2.01 (s, 3H, C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 199.5 (<u>C</u>=O), 162.2 (<u>C</u>CH$_3$), 128.7 (<u>C</u>=CCH$_3$), 63.3 (<u>C</u>H$_2$OH), 42.4 (C<u>H</u>CH$_2$OH), 34.5 (CH$_2$<u>C</u>H$_2$C(=O)), 25.2 (<u>C</u>H$_2$CH$_2$C(=O)), 23.2 (<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3406 (O-H), 2980, 2885 (C-H), 1649 (C=O), 1074 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_8H_{13}O_2^+$) requires *m/z* 141.0910, found *m/z* 141.0910. Data are consistent with that published in the literature.[240]

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –37.6 (c 1.005, CHCl3). (96% ee)

5.7.3.8 Synthesis and characterisation of 240

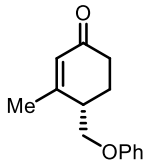
(S)-4-(((tert-butyldimethylsilyl)oxy)methyl)-3-methylcyclohex-2-en-1-one (240)



The title compound was prepared according to general procedure **VII** from 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylcyclohex-3-en-1-one (**234**) (1.50 g, 5.90 mmol). The crude reaction mixture was flushed through a silica plug (Et_2O), concentrated *in vacuo* and then purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**240**) as a colourless oil in 90% yield (1.35 g) and 99% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 230 nm, t(major) = 8.39 min, t(minor) = 11.86 min]. **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 5.80 – 5.79 (m, 1H, C=C<u>H</u>), 3.89 (dd, *J* = 10.0, 6.0 Hz, 1H, C<u>H$_A$</u>H$_B$O), 3.85 (dd, *J* = 10.0, 4.0 Hz, 1H, CH$_A$<u>H$_B$</u>O), 2.49 (p, *J* = 5.5 Hz, 1H, C<u>H</u>CH$_2$O), 2.43 (ddd, *J* = 17.0, 9.5, 5.5 Hz, 1H, one of C<u>H$_A$</u>H$_B$C(=O)), 2.20 (ddd, *J* = 17.0, 7.0, 5.5 Hz, 1H, one of CH$_A$<u>H$_B$</u>C(=O)), 2.13 – 2.02 (m, 2H, C<u>H$_2$</u>CH$_2$C(=O)), 2.02 – 1.99 (m, 3H, C=CC<u>H$_3$</u>), 0.90 (s, 9H, C(C<u>H$_3$</u>)$_3$), 0.09 (2 x s, 6H, Si(C<u>H$_3$</u>)$_A$(C<u>H$_3$</u>)$_B$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 198.3 (<u>C</u>=O), 162.7 (C=<u>C</u>CH$_3$), 128.6 (<u>C</u>=CCH$_3$), 64.4 (<u>C</u>H$_2$O), 43.0 (<u>C</u>HCH$_2$O), 35.3 (<u>C</u>H$_2$C(=O)), 26.4 (<u>C</u>H$_2$CH$_2$C(=O)), 26.2 (C(<u>C</u>H$_3$)$_3$), 22.9 (C=C<u>C</u>H$_3$), 18.8 (<u>C</u>(CH$_3$)$_3$), -5.4 (one of Si(<u>C</u>H$_3$)$_A$(CH$_3$)$_B$), -5.4 (one of Si(CH$_3$)$_A$(<u>C</u>H$_3$)$_B$); **IR** (film) ν_{max}/cm^{-1}: 2953, 2929, 2857 (C-H), 1670 (C=O), 1626 (C=C), 1102 (C-O); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{14}H_{27}O_2Si^+$) requires *m/z* 255.1775, found *m/z* 255.1775; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –94.0 (*c* 0.205, $CHCl_3$).

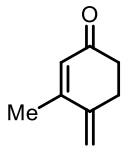
5.7.3.9 Synthesis and characterisation of 243

(S)-3-methyl-4-(phenoxymethyl)cyclohex-2-en-1-one (243)



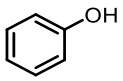
The title compound was prepared according to general procedure **VII** from 3-methyl-4-(phenoxymethyl)cyclohex-3-en-1-one (**242**) (28.1 mg, 0.130 mmol). The crude reaction mixture was purified by silica gel column chromatography to provide the title compound (**243**) as a colourless oil in 15% yield (4.3 mg) and 48% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 230 nm, t(major) = 28.75 min, t(minor) = 32.64 min].**^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.17 – 7.10 (m, 2H, ArH), 6.93 – 6.85 (m, 1H, ArH), 6.79 – 6.71 (m, 2H, ArH), 5.95 (p, *J* = 1.5 Hz, 1H, CHC(=O)), 3.49 (qd, *J* = 9.5, 5.5 Hz, 2H, CH$_2$OPh), 2.37 – 2.23 (m, 1H, one of CH$_A$H$_B$C(=O)), 2.11 (ddt, *J* = 14.0, 5.0, 4.0 Hz, 2H, one of CH$_A$H$_B$C(=O) and CHCH$_2$OPh), 1.80 (dddd, *J* = 13.5, 7.5, 6.0, 5.0 Hz, 1H, one of CH$_A$H$_B$CH$_2$C(=O)), 1.62 (ddt, *J* = 13.5, 10.0, 5.0 Hz, 1H, one of CH$_A$H$_B$CH$_2$C(=O)), 1.45 (t, *J* = 1.0 Hz, 3H, CH$_3$).

3-methyl-4-methylenecyclohex-2-en-1-one (244)



244 was isolated as a side product in the prototropic shift of compound **243**. **244** was isolated in 40% yield (6.3 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 5.65 (t, J = 1.5 Hz, 1H, C<u>H</u>(=O)), 4.66 (t, J = 1.0 Hz, 1H, one of C=C<u>H$_A$</u>H$_B$), 4.61 (t, J = 1.5 Hz, 1H, one of C=CH$_A$<u>H$_B$</u>), 2.05 – 1.94 (m, 4H, C<u>H$_2$</u>C<u>H$_2$</u>C(=O)), 1.31 (d, J = 1.5 Hz, 3H, CH$_3$). Data are consistent with that published in the literature.[132]

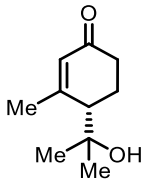
phenol (245)



Phenol (**245**) was isolated as a side product in the prototropic shift of compound **243**. **245** was isolated in 35% yield (4.3 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 6.90 – 6.77 (m, 2H, Ar<u>H</u>), 6.61 – 6.49 (m, 1H, Ar<u>H</u>), 6.39 – 6.27 (m, 2H, Ar<u>H</u>), 3.74 (s, 1H, O<u>H</u>).

5.7.3.10 Synthesis and characterisation of 250

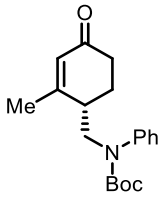
(S)-4-(2-hydroxypropan-2-yl)-3-methylcyclohex-2-en-1-one (250)



The title compound was prepared according to general procedure **VII** from 4-(2-hydroxypropan-2-yl)-3-methylcyclohex-3-en-1-one (**249**) (21.9 mg, 0.130 mmol). The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 2/3) to provide the title compound (**250**) as a colourless oil in 42% yield (9.1 mg) and 23% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 29.97 nm, t(minor) = 54.20 min, t(major) = 54.20 min]. **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 6.04 (t, *J* = 1.5 Hz, 1H, C=C$\underline{H}$), 2.51 (ddq, *J* = 19.5, 11.5, 5.0, 4.5 Hz, 1H, one of C$\underline{H}_A$H$_B$C(=O)), 2.11 (ddd, *J* = 17.5, 6.0, 4.0 Hz, 1H, one of CH$_A\underline{H}_B$C(=O)), 1.74 (bm, 4H, C$\underline{H}$C(CH$_3$)$_2$ and C=CC$\underline{H}_3$), 1.56 (dtdd, *J* = 24.0, 12.0, 9.0, 6.0 Hz, 2H, C$\underline{H}_2$CH$_2$C(=O)), 0.98 – 0.90 (m, 3H, one of C(C$\underline{H}_3$)$_A$(CH$_3$)$_B$), 0.87 (bm, 3H, one of C(CH$_3$)$_A$(C$\underline{H}_3$)$_B$).

5.7.3.11 Synthesis and characterisation of 266

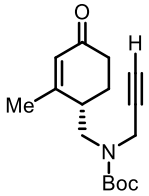
tert-butyl (S)-((2-methyl-4-oxocyclohex-2-en-1-yl)methyl)(phenyl)carbamate (266)



The title compound was prepared according to general procedure **VII** from *tert*-butyl ((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)(phenyl)carbamate (**259**) (41 mg, 0.13 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 6/4) to provide the title compound (**266**) as a colourless oil in 83% yield (34 mg) and 98% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 230 nm, t(major) = 6.16 min, t(minor) = 7.32 min]. **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 7.43 – 7.37 (m, 2H, ArH), 7.37 – 7.33 (m, 2H, ArH), 7.24 (tt, *J* = 7.0, 1.5 Hz, 1H, ArH), 5.77 (s, 1H, CHC(=O)), 4.03 (dd, *J* = 14.5, 10.5 Hz, 1H, one of CH_AH_BN), 3.83 (dd, *J* = 14.5, 4.0 Hz, 1H, one of CH_AH_BN), 2.54 – 2.40 (m, 2H, $CHCH_2N$ and one of $CH_AH_BC(=O)$), 2.11 (dt, *J* = 17.5, 4.5 Hz, 1H, one of $CH_AH_BC(=O)$), 2.02 – 1.96 (m, 2H, $CH_2CH_2C(=O)$), 1.90 (d, *J* = 1.5 Hz, 3H, $C=CCCH_3$), 1.43 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 198.0 (C=O), 162.6 (C=CH), 155.3 (NC(=O)), 143.1 (ArC), 129.6 (ArCH), 128.3 (C=CH), 128.0 (ArCH), 126.9 (ArCH), 80.7 ($C(CH_3)_3$), 50.0 (CH_2N), 39.8 ($CHCH_2N$), 33.7 ($CH_2C(=O)$), 28.4 ($C(CH_3)_3$), 25.3 ($CH_2CH_2C(=O)$), 22.9 ($C=CCH_3$); **IR** (film) ν_{max}/cm^{-1}: 2977 (C-H), 1692, 1667 (C=O), 1153 (C-N); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{25}NNaO_3^+$) requires *m/z* 338.1727, found *m/z* 338.1726; $[\alpha]_D^{25}$ = –1.72 (*c* 0.145, $CHCl_3$).

5.7.3.12 Synthesis and characterisation of 267

tert-butyl (S)-((2-methyl-4-oxocyclohex-2-en-1-yl)methyl)(prop-2-yn-1-yl)carbamate (267)

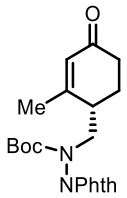


The title compound was prepared according to general procedure **VII** from *tert*-butyl ((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)(prop-2-yn-1-yl)carbamate (**260**) (36.0 mg, 0.130 mmol) and left for 48 h. The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 6/4) to provide the title compound (**267**) as an off-white solid in 75% yield (27.1 mg) and 96% ee. [determined by HPLC chiralpak AD, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 240 nm, t(major) = 7.50 min, t(minor) = 8.62 min]. **^{1}H NMR** (500 MHz, Toluene-d_8, 363 K) δ(ppm): 5.78 (s, 1H, C<u>H</u>C(=O)), 3.94 – 3.73 (m, 2H, C<u>H_2</u>C≡CH), 3.38 – 3.28 (m, 1H, one of CHC<u>H_A</u>H_BN), 3.23 (dd, *J* = 14.5, 4.5 Hz, 1H, one of CHCH_A<u>H_B</u>N), 2.51 – 2.37 (m, 1H, one of C<u>H_A</u>H_BC(=O)), 2.37 – 2.28 (m, 1H, C<u>H</u>CH_2N), 2.17 – 2.12 (m, 1H, one of CH_A<u>H_B</u>C(=O)), 1.88 – 1.81 (m, 1H, C≡C<u>H</u>), 1.78 – 1.67 (m, 2H, C<u>H_2</u>CH_2C(=O)), 1.60 (s, 3H, C<u>H_3</u>C=C), 1.38 (s, 9H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** (126 MHz, Toluene-d_8, 363 K) δ(ppm): 195.8 (CH<u>C</u>(=O)), 159.3 (C=<u>C</u>CH_3), 155.0 (N<u>C</u>(=O)), 128.8 (<u>C</u>HC(=O)), 80.5 (O<u>C</u>$(CH_3)_3$), 79.9 (<u>C</u>≡CH), 72.0 (C≡<u>C</u>H), 47.6 (CH<u>C</u>H_2N), 39.2 (<u>C</u>HCH_2N), 37.1 (C<u>H_2</u>C≡CH), 33.7 (CH_2<u>C</u>H_2C(=O)), 28.4 (C(<u>C</u>H_3)$_3$), 25.5 (<u>C</u>H_2CH_2C(=O)), 22.3 (C=C<u>C</u>H_3); **IR** (powder) ν_{max}/cm^{-1}: 3235 (C≡C-H), 2981, 2934, 2892, 2872 (C-H), 2110 (C≡C), 1667 (C=O), 1632 (C=C); **HRMS** (ES+) exact mass calculated for [M+H]$^+$

($C_{16}H_{24}NO_3^+$) requires *m/z* 278.1751, found *m/z* 278.1752; **MP**: 74-76 ˚C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = – 103.9 (*c* 0.095, $CHCl_3$).

5.7.3.13 Synthesis and characterisation of 268

tert-butyl (S)-(1,3-dioxoisoindolin-2-yl)((2-methyl-4-oxocyclohex-2-en-1-yl)methyl)carbamate (268)

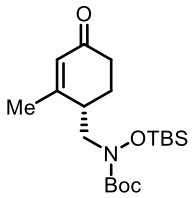


The title compound was prepared according to general procedure **VII** from *tert*-butyl (1,3-dioxoisoindolin-2-yl)((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)carbamate (**261**) (50 mg, 0.13 mmol) and left for 48 h. The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/EtOAc = 4/6) to provide the title compound (**268**) as a white solid (foam) in 62% yield (31.1 mg) and 93% ee. [determined by HPLC chiralpak AD, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 230 nm, t(minor) = 11.10 min, t(major) = 12.97 min]. **^{1}H NMR** (400 MHz, Methanol-d_4) δ(ppm): 8.00 – 7.88 (m, 4H, ArH), 5.88 (s, 1H, CHC(=O)), 3.97 (m, 1H, one of CH_AH_BN, minor and major rotamer), 3.79 – 3.61 (m, 1H, one of CH_AH_BN, minor and major rotamer), 2.72 – 2.52 (m, 2H, $CHCH_2N$ and one of $CH_AH_BC(=O)$), 2.40 – 2.09 (m, 3H, one of $CH_AH_BC(=O)$ and $CH_2CH_2C(=O)$), 1.99 (d, *J* = 1.5 Hz, 3H, $C=CCH_3$), 1.54 (s, 3.46:5.45, $C(CH_3)_3$ minor rotamer), 1.30 (s, 3.46:5.47, $C(CH_3)_3$ major rotamer); **^{13}C NMR** (101 MHz, Methanol-d_4) δ(ppm): 202.0 (CHC(=O) major rotamer), 201.6 (CHC(=O) minor rotamer), 167.2 (ArC(=O) minor rotamer), 166.8 (ArC(=O) major rotamer), 165.6 ($C=CCH_3$ major rotamer), 165.3 ($C=CCH_3$ major rotamer), 155.0 ($CH_2NC(=O)$), 136.4 (ArCH major rotamer), 136.3 (ArCH minor rotamer), 131.2 (ArC major rotamer), 131.2 (ArC minor rotamer), 128.7 (CHC(=O) minor rotamer), 128.6 (CHC(=O) major rotamer), 124.9 (ArCH), 85.1 ($C(CH_3)_3$ minor rotamer), 83.8 ($C(CH_3)_3$

major rotamer), 51.9 (CH_2N minor rotamer), 50.5 (CH_2N major rotamer), 40.4 (CHCH_2N minor rotamer), 40.2 (CHCH_2N major rotamer), 34.2 (CH_2C(=O)), 28.4 (C(CH_3)$_3$ minor rotamer), 28.1 (C(CH_3)$_3$ major rotamer), 25.9 (CH_2CH_2C(=O) major rotamer), 25.8 (CH_2CH_2C(=O) minor rotamer), 23.1 (C=CCH_3 minor rotamer), 23.0 (C=CCH_3 minor rotamer); **IR** (powder) ν_{max}/cm^{-1}: 2933, 2871 (C-H), 1733, 1665 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}N_2NaO_5^+$) requires *m/z* 407.1577, found *m/z* 407.1577; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +29.5 (*c* 0.06, $CHCl_3$).

5.7.3.14 Synthesis and characterisation of 269

tert-butyl (S)-((tert-butyldimethylsilyl)oxy)((2-methyl-4-oxocyclohex-2-en-1-yl)methyl)carbamate (269)

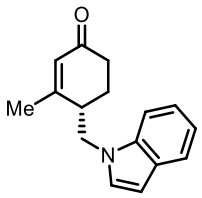


The title compound was prepared according to general procedure **VII** from *tert*-butyl ((*tert*-butyldimethylsilyl)oxy)((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)carbamate (**262**) (48 mg, 0.13 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 9/1 to 8/2) to provide the title compound (**269**) as a colourless oil in 53% yield (25.6 mg) and 94% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 240 nm, t(major) = 6.82 min, t(minor) = 8.09 min]. **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 5.80 (s, 1H, C$\underline{H}$C(=O)), 3.81 (dd, *J* = 14.5, 10.0 Hz, 1H, one of C$\underline{H}_A$H$_B$N), 3.56 (dd, *J* = 14.5, 4.0 Hz, 1H, one of CH$_A\underline{H}_B$N), 2.94 – 2.87 (m, 1H, C$\underline{H}$CH$_2$N), 2.49 (ddd, *J* = 17.5, 12.5, 5.5 Hz, 1H, one of C$\underline{H}_A$H$_B$C(=O)), 2.23 – 2.13 (m, 1H, one of CH$_A\underline{H}_B$C(=O)), 2.02 (m, 1H, one of C$\underline{H}_A$H$_B$CH$_2$C(=O)), 2.00 (d, *J* = 1.5 Hz, 3H, C$\underline{H}_3$C=C), 1.99 – 1.93 (m, 1H, one of CH$_A\underline{H}_B$CH$_2$C(=O)), 1.49 (s, 9H, OC(C$\underline{H}_3$)$_3$), 0.98 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.22 (2x s, 3H, Si(C$\underline{H}_3$)$_A$(CH$_3$)$_B$), 0.22 (2x s, 3H, Si(CH$_3$)$_A$(C$\underline{H}_3$)$_B$); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 198.0 (CH$\underline{C}$=O), 162.7 (C=$\underline{C}$CH$_3$), 157.9 (N$\underline{C}$=O), 128.4 (C=$\underline{C}$H), 81.8 (O$\underline{C}$(CH$_3$)$_3$), 52.2 ($\underline{C}$H$_2$N), 38.2 ($\underline{C}$HCH$_2$N), 33.7 ($\underline{C}$H$_2$C(=O)), 28.4 (OC($\underline{C}$H$_3$)$_3$), 26.2 (SiC($\underline{C}$H$_3$)$_3$), 25.5 ($\underline{C}$H$_2$CHCH$_2$N), 23.1 (C=C$\underline{C}$H$_3$), 18.4 (Si$\underline{C}$(CH$_3$)$_3$), -4.8 (one of Si($\underline{C}$H$_3$)$_A$(CH$_3$)$_B$), -4.8 (one of Si(CH$_3$)$_A$($\underline{C}$H$_3$)$_B$); **IR** (film) ν_{max}/cm^{-1}: 2955, 2931, 2859 (C-H), 1696 (ketone C=O), 1673 (boc C=O), 1630 (C=C),

1156 (C-N); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{35}NNaO_4Si^+$) requires *m/z* 392.2228, found *m/z* 392.2227; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –42.6 (*c* 0.08, $CHCl_3$).

5.7.3.15 Synthesis and characterisation of 270

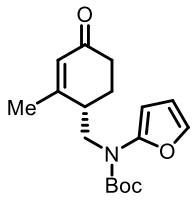
(S)-4-((1H-indol-1-yl)methyl)-3-methylcyclohex-2-en-1-one (270)



The title compound was prepared according to general procedure **VII** from 4-((1H-indol-1-yl)methyl)-3-methylcyclohex-3-en-1-one (**263**) (31.4 mg, 0.130 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 7/3) to provide the title compound (**270**) as a yellow amorphous solid in 81% yield (25.3 mg) and 90% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 95/5, 1 ml/min, λ = 230 nm, t(major) = 8.92 min, t(minor) = 10.08 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.69 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.37 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.27 (m, 1H, Ar<u>H</u>), 7.19 – 7.14 (m, 1H, Ar<u>H</u>), 7.10 (d, *J* = 3.0 Hz, 1H, Ar<u>H</u>), 6.57 (d, *J* = 3.0 Hz, 1H, Ar<u>H</u>), 6.00 (s, 1H, C<u>H</u>(C=O)), 4.49 (dd, *J* = 14.5, 5.5 Hz, 1H, one of C<u>H$_A$</u>H$_B$N), 4.15 (dd, *J* = 14.5, 10.0 Hz, 1H, one of CH$_A$<u>H$_B$</u>N), 2.96 – 2.89 (m, 1H, C<u>H</u>CH$_2$N), 2.50 (ddd, *J* = 17.5, 12.0, 5.0 Hz, 1H, one of C<u>H$_A$</u>H$_B$C(=O)), 2.33 (dt, *J* = 17.0, 5.0 Hz, 1H, one of CH$_A$<u>H$_B$</u>C(=O)), 2.01 (s, 3H, C<u>H$_3$</u>), 1.99 – 1.89 (m, 1H, one of C<u>H$_A$</u>H$_B$CH$_2$C(=O)), 1.81 – 1.72 (m, 1H, one of CH$_A$<u>H$_B$</u>CH$_2$C(=O)); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 198.4 (<u>C</u>=O), 161.5 (<u>C</u>CH$_3$), 135.9 (Ar<u>C</u>), 128.8 (Ar<u>C</u>), 128.5 (<u>C</u>HC(=O)), 127.9 (Ar<u>C</u>H), 122.0 (Ar<u>C</u>H), 121.4 (Ar<u>C</u>H), 119.8 (Ar<u>C</u>H), 109.1 (Ar<u>C</u>H), 102.1 (Ar<u>C</u>H), 47.3 (<u>C</u>H$_2$N), 40.3 (<u>C</u>HCH$_2$N), 33.1 (<u>C</u>H$_2$C(=O)), 25.3 (<u>C</u>H$_2$CH$_2$C(=O)), 23.2 (<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3051, 2944 (C-H), 1664 (C=O), 1626 (C=C); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{18}NO^+$) requires *m/z* 240.1383, found *m/z* 240.1386; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –34.9 (*c* 0.16, $CHCl_3$).

5.7.3.16 Synthesis and characterisation of 271

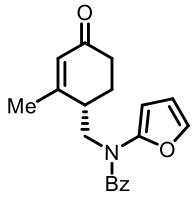
tert-butyl (S)-furan-2-yl((2-methyl-4-oxocyclohex-2-en-1-yl)methyl)carbamate (271)



The title compound was prepared according to general procedure **VII** from *tert*-butyl furan-2-yl((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)carbamate (**264**) (39.7 mg, 0.130 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**271**) as an off-white solid in quantitative yield (39.7 mg) and 99% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 230 nm, t (major) = 5.62 min, t (minor) = 6.33 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.18 (dd, *J* = 2.0, 1.0 Hz, 1H, NCCHCHC<u>H</u>O), 6.35 (dd, *J* = 3.5, 2.0 Hz, 1H, NCCHC<u>H</u>CHO), 6.03 (bs, 1H, NCC<u>H</u>CHCHO), 5.86 (s, 1H, C=C<u>H</u>C(=O)), 3.81 – 3.69 (m, 2H, C<u>H_2</u>N), 2.61 – 2.54 (m, 1H, C<u>H</u>CH_2N), 2.48 (ddd, *J* = 17.5, 11.5, 6.0 Hz, 1H, one of C<u>H_A</u>H_BC(=O)), 2.54 – 2.42 (m, 1H, one of CH_A<u>H_B</u>C(=O)), 2.08 – 1.96 (m, 2H, C<u>H_2</u>CH_2C(=O)), 1.94 (d, *J* = 1.5 Hz, 3H, C<u>H_3</u>C=C), 1.45 (s, 9H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 199.1 (CH_2<u>C</u>(=O)), 162.1 (CH_3<u>C</u>=C), 153.9 (N<u>C</u>(=O)), 148.3 (N<u>C</u>CHCHCHO), 138.3 (NCCHCH<u>C</u>HO), 128.2 (CH_3C=<u>C</u>H), 111.2 (NCCH<u>C</u>HCHO), 101.3 (N<u>C</u>CHCHCHO), 81.9 (O<u>C</u>(CH_3)$_3$), 48.6 (<u>C</u>H_2N), 39.4 (<u>C</u>HCH_2N), 33.3 (<u>C</u>H_2C(=O)), 28.3 (OC(<u>C</u>H_3)$_3$), 24.7 (<u>C</u>H_2CH_2C(=O)), 23.0 (<u>C</u>H_3C=C); **IR** (film) ν_{max}/cm^{-1}: 2921 (C-H), 1712 (C=O ester), 1670 (C=O ketone), 1157 (C-O); **HRMS** (ESI+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{23}NNaO_4^+$) requires *m/z* 328.1519, found *m/z* 328.1519; **MP**: 42-45 ˚C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –39.2 (*c* 0.50, $CHCl_3$).

5.7.3.17 Synthesis and characterisation of 272

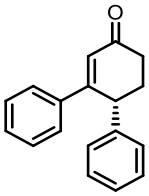
benzyl (S)-furan-2-yl((2-methyl-4-oxocyclohex-2-en-1-yl)methyl)carbamate (272)



The title compound was prepared according to general procedure **VII** from benzyl furan-2-yl((2-methyl-4-oxocyclohex-1-en-1-yl)methyl)carbamate (**265**) (44.1 mg, 0.130 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 7/3) to provide the title compound (**272**) as colourless oil in 80% yield (35.3 mg) and 97% ee. [determined by HPLC chiralpak IA, hexane/isopropanol = 90/10, 1 ml/min, λ = 230 nm, t (major) = 16.47 min, t (minor) = 20.68 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.46 – 7.15 (m, 6H, ArC<u>H</u> and NCCHCHC<u>H</u>O), 6.39 (dd, *J* = 3.5, 2.0 Hz, 1H, NCCHC<u>H</u>CHO), 6.09 (bs, 1H, NCC<u>H</u>CHCHO), 5.86 (s, 1H, CH_3C=C<u>H</u>), 5.19 (s, 2H, C<u>H</u>$_2$O), 3.93 – 3.64 (m, 2H, C<u>H</u>$_2$O), 2.64 – 2.53 (m, 1H, C<u>H</u>CH_2N), 2.46 (bs, 1H, one of C<u>H</u>$_A$H$_B$C(=O)), 2.32 – 2.14 (bm, 1H, one of CH_A<u>H</u>$_B$C(=O)), 2.13 – 1.95 (bm, 2H, C<u>H</u>$_2$CH$_2$C(=O)), 1.91 (bs, 3H, C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 199.0 (CH_2<u>C</u>=O), 161.7 (CH_3<u>C</u>=C), 155.1 (N<u>C</u>(=O)), 147.5 (N<u>C</u>CHCHCHO), 139.1 (NCCHCH<u>C</u>HO), 135.9 (Ar<u>C</u>), 128.6 (CH_3C=<u>C</u>H), 128.4 (Ar<u>C</u>H (may be two under this peak)), 127.6 (Ar<u>C</u>H), 111.4 (NCCH<u>C</u>HCHO), 102.7 (NC<u>C</u>HCHCHO), 68.1 (O<u>C</u>H$_2$), 49.4 (<u>C</u>H$_2$N), 39.2 (<u>C</u>HCH$_2$N), 33.2 (<u>C</u>H$_2$C(=O)), 24.6 (<u>C</u>H$_2$CH$_2$C(=O)), 22.9 (<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 2922 (C-H), 1718 (C=O ester/amide), 1669 (C=O ketone), 1281, 1167 (C-O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{21}NNaO_4^+$) requires *m/z* 362.1363, found *m/z* 362.1363; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –20.8 (*c* 0.49, $CHCl_3$).

5.7.3.18 Synthesis and characterisation of 284

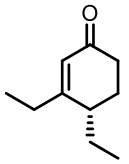
(R)-5',6'-dihydro-[1,1':2',1''-terphenyl]-4'(1'H)-one (284)



The title compound was prepared according to general procedure **VII** from 5',6'-dihydro-[1,1':2',1''-terphenyl]-4'(3'H)-one (**281**) (16.1 mg, 0.0650 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**284**) as a yellow solid in 76% yield (12.3 mg) and 94% ee. [determined by HPLC chiralpak OD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 230 nm, t(minor) = 9.40 min, t(major) = 13.19 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.48 – 7.43 (m, 2H, ArH), 7.35 – 7.21 (m, 8H, ArH), 6.70 (s, 1H, CHC(=O)), 4.31 (dd, *J* = 5.0, 3.0 Hz, 1H, CHPh), 2.57 (dddd, *J* = 13.0, 12.0, 6.0, 5.0 Hz, 1H, one of $CH_AH_BCH_2C(=O)$), 2.44 – 2.31 (m, 2H, $CH_2CH_2C(=O)$), 2.24 – 2.18 (m, 1H, one of $CH_AH_BCH_2C(=O)$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 200.1 (C=O), 159.6 (ArC), 140.3 (ArC), 138.0 (C=CH), 130.0 (ArCH), 129.0 (ArCH), 128.9 (ArCH), 128.2 (ArCH), 127.2 (ArCH), 127.1 (ArCH), 127.0 (C=CH), 43.3 (CHPh), 32.9 ($CH_2C(=O)$), 32.1 ($CH_2CH_2C(=O)$); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –237.9 (*c* 0.55, $CHCl_3$). Data are consistent with that published in the literature.[238]

5.7.3.19 Synthesis and characterisation of 285

(S)-3,4-diethylcyclohex-2-en-1-one (285)

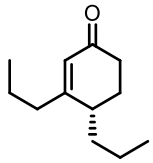


The title compound was prepared according to general procedure **VIII** from 3,4-diethylcyclohex-3-en-1-one (**279**) (9.9 mg, 0.0650 mmol) using Et_2O (0.43 ml). The crude reaction mixture was concentrated under a stream of nitrogen and transferred directly onto silica then purified by silica gel column chromatography (pentane/Et_2O = 85/15) to provide the title compound (**285**) as a yellow oil in 63% yield (6.2 mg) and 97% ee.* [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 240 nm, t(minor) = 19.23 min, t(major) = 28.23 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 5.83 (s, 1H, C=C$\underline{H}$), 2.45 (ddd, *J* = 17.0, 11.5, 5.5 Hz, 1H, one of C$\underline{H_A}H_BC$(=O)), 2.38 – 2.14 (m, 4H, one of $CH_A\underline{H_B}C$(=O), C$\underline{H}CH_2$ and C$\underline{H_2}$C=C), 2.09 – 1.90 (m, 2H, C$\underline{H_2}CH_2C$(=O)), 1.67 (dddd, *J* = 14.0, 11.5, 7.5, 3.5 Hz, 1H, one of CHC$\underline{H_A}CH_BCH_3$), 1.54 – 1.39 (m, 1H, one of $CHCH_AC\underline{H_B}CH_3$), 1.10 (t, *J* = 7.5 Hz, 3H, C$\underline{H_3}CH_2$C=C), 1.01 (t, *J* = 7.5 Hz, 3H, C$\underline{H_3}CH_2$CH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 200.0 (C=O), 171.7 (C=CH), 124.3 (C=CH), 40.1 (CHC=C), 33.8 (CH_2C(=O)), 28.8 (CH_2C=C), 25.7 (CH_2CH_2C(=O)), 24.1 (CH_3CH_2CH), 12.7 (CH_3CH_2CH), 11.7 (CH_3CH_2C=C); **IR** (film) ν_{max}/cm^{-1}: 2965, 2931, 2876 (C-H), 1671 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{17}O^+$) requires *m/z* 153.1274, found *m/z* 153.1273; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –78.4 (*c* 0.54, $CHCl_3$).

*Care should be taken when removing solvent from this compound as it appears to be volatile.

5.7.3.20 Synthesis and characterisation of 286

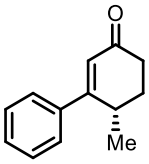
(S)-3,4-dipropylcyclohex-2-en-1-one (286)



The title compound was prepared according to general procedure **VIII** from 3,4-dipropylcyclohex-3-en-1-one (**280**) (11.7 mg, 0.0650 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 95/5) to provide the title compound (**286**) as a yellow oil in 50% yield (5.8 mg) and 97% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 240 nm, t(minor) = 20.13 min, t(major) = 31.25 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 5.81 (s, 1H, C=C$\underline{H}$), 2.45 (ddd, *J* = 17.5, 12.0, 5.0 Hz, 1H, one of C$\underline{H_A}H_B$C(=O)), 2.32 – 2.12 (m, 4H, one of C$H_A\underline{H_B}$C(=O), C$\underline{H}CH_2$ and C$\underline{H_2}$C=C), 2.06 – 1.97 (m, 1H, one of C$\underline{H_A}H_BCH_2$C(=O)), 1.96 – 1.89 (m, 1H, one of C$H_A\underline{H_B}CH_2$C(=O)), 1.65 – 1.21 (m, 8H, 2 x C$\underline{H_2}CH_3$ and 2 x $CH_3CH_2C\underline{H_2}$CH), 0.98 – 0.91 (m, 6H, 2 x C$\underline{H_3}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 200.0 (C=O), 170.5 ($\underline{C}$=CH), 125.3 (C=$\underline{C}$H), 38.0 ($\underline{C}HCH_2$ and $\underline{C}H_2$C=C), 33.6 ($\underline{C}H_2$C(=O)), 33.1 ($CH_3CH_2\underline{C}H_2CH$), 26.1 ($\underline{C}H_2CH_2$C(=O)), 21.3 ($CH_3\underline{C}H_2CH_2CH$), 20.6 ($CH_3\underline{C}H_2CH_2$C=C), 14.2 (one of $\underline{C}H_3$), 14.0 (one of $\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2957, 2930, 2872 (C-H), 1673 (C=O), 1622 (C=C); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{21}O^+$) requires *m/z* 181.1587, found *m/z* 181.1587; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –81.9 (*c* 0.47, $CHCl_3$).

5.7.3.21 Synthesis and characterisation of 287

(S)-6-methyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (287)

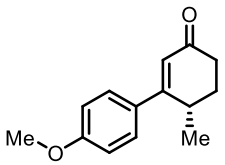


The title compound was prepared according to general procedure **VIII** from 6-methyl-4,5-dihydro-[1,1'-biphenyl]-3(2H)-one (**282**) (24.2 mg, 0.130 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**287**) as an amorphous yellow solid in 63% yield (15.2 mg) and 95% ee. [determined by HPLC chiralpak OD-H, hexane/isopropanol = 85/15, 1 ml/min, λ = 280 nm, t(minor) = 8.50 min, t(major) = 9.71 min]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.53 – 7.46 (m, 2H, Ar<u>H</u>), 7.41 (m, 3H, Ar<u>H</u>), 6.25 (s, 1H, C<u>H</u>C(=O)), 3.16 (ddq, J = 11.0, 7.5, 4.0, 3.5 Hz, 1H, C<u>H</u>CH_3), 2.60 (ddd, *J* = 17.5, 13.0, 5.0 Hz, 1H, one of C<u>H_A</u>H_BC(=O)), 2.44 (dt, *J* = 17.0, 4.5 Hz, 1H, one of CH_A<u>H_B</u>C(=O)), 2.37 – 2.24 (m, 1H, one of C<u>H_A</u>$H_B$$CH_2$C(=O)), 1.98 (dtd, *J* = 13.5, 5.0, 3.5 Hz, 1H, one of CH_A<u>H_B</u>CH_2C(=O)), 1.18 (d, *J* = 7.0 Hz, 3H, C<u>H_3</u>); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 199.9 (<u>C</u>=O), 165.4 (<u>C</u>=CC(=O)), 138.4 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 125.2 (C=<u>C</u>C(=O)), 33.3 (<u>C</u>H_2C(=O)), 31.3 (<u>C</u>HCH_3), 29.7 (<u>C</u>$H_2$$CH_2$C(=O)), 18.5 (<u>C</u>$H_3$); **IR** (film) ν_{max}/cm^{-1}: 2963, 2929, 2869 (C-H), 1665 (C=O), 1601 (C=C); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O^+$) requires *m/z* 187.1117, found *m/z* 187.1118. Data are consistent with that published in the literature.[241]

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –287.4 (*c* 0.85, $CHCl_3$).

5.7.3.22 Synthesis and characterisation of 288

(S)-4'-methoxy-6-methyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (288)

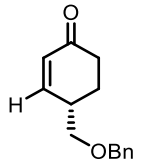


The title compound was prepared according to general procedure **VIII** from 4'-methoxy-6-methyl-4,5-dihydro-[1,1'-biphenyl]-3(2H)-one (**283**) (28.1 mg, 0.130 mmol). The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 7/3) to provide the title compound (**288**) as an amorphous yellow solid in 52% yield (14.6 mg) and 93% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 220 nm, t(major) = 10.00 min, t(minor) = 11.67 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.56 – 7.41 (m, 2H, ArC<u>H</u>), 6.99 – 6.88 (m, 2H, ArC<u>H</u>), 6.25 (s, 1H, C<u>H</u>C(=O)), 3.84 (s, 3H, OC<u>H</u>$_3$), 3.19 – 3.10 (m, 1H, C<u>H</u>CH_3), 2.58 (ddd, *J* = 17.5, 13.5, 5.0 Hz, 1H, one of C<u>H</u>$_A$$H_B$C(=O)), 2.46 – 2.38 (m, 1H, one of CH_A<u>H</u>$_B$C(=O)), 2.34 – 2.22 (m, 1H, one of C<u>H</u>$_A$$CH_B$$CH_2$C(=O)), 2.01 – 1.93 (m, 1H, one of CH_AC<u>H</u>$_B$$CH_2$C(=O)), 1.20 (d, *J* = 7.0 Hz, 3H, CHC<u>H</u>$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 199.8 (<u>C</u>=O), 164.6 (Ar<u>C</u>), 161.3 (Ar<u>C</u>), 130.2 (<u>C</u>=CC(=O)), 128.3 (Ar<u>C</u>H), 123.4 (<u>C</u>HC(=O)), 114.3 (Ar<u>C</u>H), 55.5 (O<u>C</u>H_3), 32.9 (<u>C</u>H_2C(=O)), 30.8 (<u>C</u>HCH_3), 29.5 (<u>C</u>$H_2$$CH_2$C(=O)), 18.4 (CH<u>C</u>$H_3$); **IR** (film) ν_{max}/cm^{-1}: 2932, 2839 (C-H), 1659 (C=O), 1593 (C=C), 1251 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}O_2^+$) requires *m/z* 217.1223, found *m/z* 217.1223. Data are consistent with that published in the literature.[242]

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –66.0 (*c* 0.69, $CHCl_3$).

5.7.3.23 Synthesis and characterisation of 297

(S)-4-((benzyloxy)methyl)cyclohex-2-en-1-one (297)

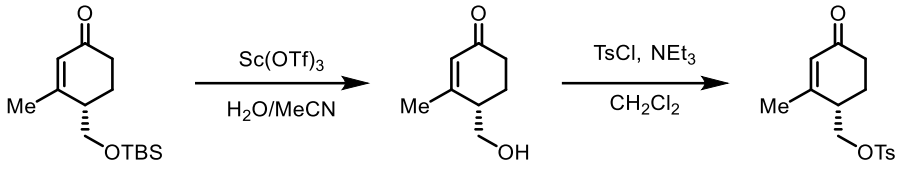


The title compound was prepared according to general procedure **VII** from 4-((benzyloxy)methyl)cyclohex-3-en-1-one (**289**) (28.1 mg, 0.130 mmol) at 30 °C. The crude reaction mixture was transferred directly onto silica and purified by silica gel column chromatography (pentane/Et_2O = 8/2). Mixed fractions were re-purified by silica gel column chromatography (pentane/Et_2O = 9/1) three times to provide the title compound (**297**) as a colourless oil in 62% yield (17.5 mg) and 94% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 230 nm, t(minor) = 16.47 min, t(major) = 47.98 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.41 – 7.28 (m, 5H, Ar<u>H</u>), 6.95 (ddd, *J* = 10.0, 2.5, 1.5 Hz, 1H, C<u>H</u>CHC(=O)), 6.04 (ddd, *J* = 10.0, 2.5, 1.0 Hz, 1H, CHC<u>H</u>C(=O)), 4.55 (s, 2H, C<u>H</u>$_2$Ph), 3.51 (dd, *J* = 9.0, 6.5 Hz, 1H, C<u>H</u>$_A$H$_B$OCH$_2$Ph), 3.47 (dd, *J* = 9.0, 7.0 Hz, 1H, CH$_A$<u>H</u>$_B$OCH$_2$Ph), 2.80 – 2.68 (m, 1H, C<u>H</u>CH$_2$O), 2.57 – 2.47 (m, 1H, one of C<u>H</u>$_A$H$_B$C(=O)), 2.44 – 2.33 (m, 1H, one of CH$_A$<u>H</u>$_B$C(=O)), 2.18 – 2.06 (m, 1.5 Hz, 1H, one of C<u>H</u>$_A$H$_B$CH$_2$C(=O)), 1.89 – 1.74 (m, 1H one of C<u>H</u>$_A$H$_B$CH$_2$C(=O)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 199.7 (<u>C</u>=O), 151.7 (<u>C</u>HCHC(=O)), 138.1 (Ar<u>C</u>), 130.2 (CH<u>C</u>HC(=O)), 128.6 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 73.5 (<u>C</u>H$_2$Ph), 72.6 (<u>C</u>H$_2$OCH$_2$Ph), 37.1 (<u>C</u>HCH$_2$O), 36.9 (<u>C</u>H$_2$C(=O)), 26.0 (<u>C</u>H$_2$CH$_2$C(=O)); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= –86.5 (*c* 1.75, MeOH); lit: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$= –109.4 (*c* 3.58, MeOH) (S)-4-((benzyloxy)methyl)cyclohex-2-en-1-one.[99] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= –124.4 (*c* 1.72, MeOH) (*R*)-4-((benzyloxy)methyl)cyclohex-2-en-1-one.[243] Data are consistent with that published in the literature.[99,243,244]

5.7.4 Synthesis and characterisation of products obtained through derivatisation of enantioenriched α,β-unsaturated cyclohexenones

5.7.4.1 Synthesis and characterisation of 290

(S)-(2-methyl-4-oxocyclohex-2-en-1-yl)methyl 4-methylbenzenesulfonate (290)



a) According to a literature procedure,[142] to a stirred solution of (*S*)-4-(hydroxymethyl)-3-methylcyclohex-2-en-1-one (**240**) (99% ee) (479 mg, 1.88 mmol, 1.00 eq) in MeCN (9.5 ml) was added H_2O (170 µl, 5.00 eq, 9.4 mmol) followed by $Sc(OTf)_3$ (4.60 mg, 0.009 mmol, 0.005 eq). The reaction was stirred overnight at which point pH 7 phosphate buffer was added (15 ml). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc) to afford **239** as a yellow oil in 58% yield (154 mg) and 99% ee.

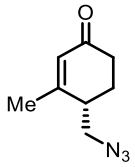
b) To a stirred solution of **239** (99% ee) (98.0 mg, 0.700 mmol, 1.00 eq) in CH_2Cl_2 (2.3 ml) at 0 °C was added NEt_3 (117 µl, 0.840 mmol, 1.20 eq) followed by tosyl chloride (147 mg, 0.770 mmol, 1.10 eq). The reaction was stirred overnight at which point sat. aq. NH_4Cl (10 ml) was added. The aqueous layer was extracted with EtOAc (3 x 20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 50/50 to 0/100) to afford the title compound (**290**) as a colourless oil in 76% yield (157 mg) and 99% ee. [determined by HPLC chiralpak AD-

H, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 240 nm, t(major) = 18.90 min, t(minor) = 19.89 min].* **^{1}H NMR** (500 MHz, Acetone-d_6) δ(ppm): 7.89 – 7.80 (m, 2H, ArH), 7.55 – 7.45 (m, 2H, ArH), 5.81 – 5.78 (m, 1H, CHC(=O)), 4.31 (dd, *J* = 10.0, 6.5 Hz, 1H, one of CH_AH_BO), 4.23 (dd, *J* = 10.0, 4.0 Hz, 1H, one of CH_AH_BO), 2.78 – 2.71 (m, 1H, $CHCH_2O$), 2.45 (s, 3H, $ArCH_3$), 2.29 (ddd, *J* = 17.0, 9.0, 5.0 Hz, 1H, one of $CH_2CH_AH_BC(=O)$), 2.20 (ddd, *J* = 17.0, 8.0, 5.0 Hz, 1H, one of $CH_2CH_AH_BC(=O)$), 2.00 – 1.93 (m, 2H, $CH_2CH_2C(=O)$ and solvent peak), 1.91 (dd, *J* = 1.5, 1.0 Hz, 3H, CCH_3); **^{13}C NMR** (126 MHz, Acetone-d_6) δ(ppm): 197.8 (C=O), 159.8 (CH_3C=CHC(=O)), 146.2 (ArC), 133.9 (ArC), 131.0 (ArCH), 129.5 (CH_3C=CHC(=O)), 128.8 (ArCH), 70.9 (CH_2O), 39.9 ($CHCH_2O$), 34.9 ($CH_2CH_2C(=O)$), 25.8 ($CH_2CH_2C(=O)$), 22.4 (CH_3C=CHC(=O)), 21.5 ($ArCH_3$); **IR** (film) ν_{max}/cm^{-1}: 2955 (C-H), 1667 (C=O), 1121 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}O_4S^+$) requires *m/z* 295.0999, found *m/z* 295.1000; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –91.4 (*c* 0.05, $CHCl_3$).

*The title compound should be stored in a freezer to avoid decomposition which occurs over a period of hours at ambient temperature.

5.7.4.2 Synthesis and characterisation of 291

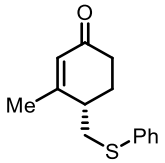
(S)-4-(azidomethyl)-3-methylcyclohex-2-en-1-one (291)



According to a literature procedure,[78] behind a blast shield, sodium azide (43.5 mg, 0.680 mmol, 5.00 eq) was added to a stirred solution of (*S*)-(2-methyl-4-oxocyclohex-2-en-1-yl)methyl 4-methylbenzenesulfonate (**290**) (99% ee) (40.0 mg, 0.136 mmol, 1.00 eq) in DMF (0.68 ml). The reaction was warmed to 45 °C and stirred for 1 hour at which point the reaction was deemed complete by TLC analysis (pentane/Et_2O = 1/1). H_2O (10 ml) was added, and the aqueous layer extracted with EtOAc (3 x 10 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 1/1) to afford the title compound (**291**) as a colourless oil in 51% yield (11.4 mg) and 99% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 230 nm, t(minor) = 19.37 min, t(major) = 25.50 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 5.94 (s, 1H, C$\underline{H}$C(=O)), 3.57 (dd, *J* = 12.5, 4.5 Hz, 1H, one of C$\underline{H_A}H_BN_3$), 3.49 (dd, *J* = 12.5, 8.0 Hz, 1H, one of $CH_A\underline{H_B}N_3$), 2.55 – 2.43 (m, 2H, C$\underline{H}CH_2N_3$ and one of C$\underline{H_A}H_BC$(=O)), 2.35 (ddd, *J* = 17.5, 7.5, 5.0 Hz, 1H, one of $CH_A\underline{H_B}C$(=O)), 2.17 – 2.02 (m, 2H, C$\underline{H_2}CH_2C$(=O)), 2.00 (s, 3H, C$\underline{H_3}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 198.6 (C$\underline{=O}$), 160.6 ($CH_3\underline{C}$=C), 129.1 (CH_3C=$\underline{C}$), 52.7 ($\underline{C}H_2N_3$), 39.8 ($\underline{C}HCH_2N_3$), 34.2 ($\underline{C}H_2C$(=O)), 25.9 ($\underline{C}H_2CH_2C$(=O)), 22.9 ($\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2980, 2884 (C-H), 2095 (N=N=N), 1665 (C=O), 1626 (C=C); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_8H_{11}N_3NaO^+$) requires *m/z* 188.0794, found *m/z* 188.0796; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –88.5 (*c* 0.225, $CHCl_3$).

5.7.4.3 Synthesis and characterisation of 292

(S)-3-methyl-4-((phenylthio)methyl)cyclohex-2-en-1-one (292)

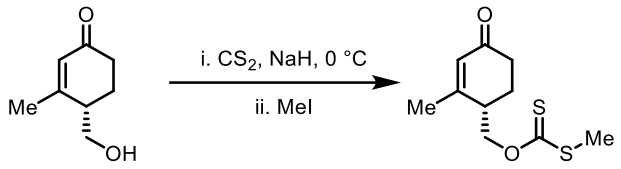


To a solution of 60% NaH (6.00 mg, 0.150 mmol, 1.10 eq) in DMF (0.7 ml) at 0 °C was added thiophenol (16.4 µl, 0.16 mmol, 1.20 eq). The suspension was stirred for 30 min at which point (*S*)-(2-methyl-4-oxocyclohex-2-en-1-yl)methyl 4-methylbenzenesulfonate (**290**) (99% ee) (40.0 mg, 0.140 mmol, 1.00 eq) in DMF (0.7 ml) was added at 0 °C. The reaction was deemed complete by TLC analysis at 1 h (pentane/Et_2O = 1/1) at which point sat. aq. NH_4Cl (10 ml) was added. The aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 8/2 to 7/3) to afford the title compound (**292**) as a yellow oil in 75% yield (24.4 mg) and 97% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 230 nm, t(minor) = 28.27 min, t(major) = 38.01 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.41 – 7.34 (m, 2H, Ar$\underline{H}$), 7.34 – 7.27 (m, 2H, Ar$\underline{H}$), 7.25 – 7.18 (m, 1H, Ar$\underline{H}$), 5.87 (t, *J* = 1.5 Hz, 1H, C=C$\underline{H}$), 3.24 (dd, *J* = 13.0, 3.5 Hz, 1H, one of C$\underline{H_A}H_BS$), 2.94 (dd, *J* = 13.0, 10.0 Hz, 1H, one of $CH_A\underline{H_B}S$), 2.53 – 2.45 (m, 1H, C$\underline{H}CH_2S$), 2.45 – 2.37 (m, 1H, one of C$\underline{H_A}H_BC(=O)$), 2.35 – 2.17 (m, 2H, one of $CH_A\underline{H_B}C(=O)$ and one of C$\underline{H_A}H_BCH_2C(=O)$), 2.17 – 2.05 (m, 1H, one of $CH_A\underline{H_B}CH_2C(=O)$), 1.96 (dd, *J* = 1.5, 0.5 Hz, 3H, C$\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 198.8 ($\underline{C}$=O), 162.7 ($CH_3\underline{C}$), 135.9 (Ar$\underline{C}$), 130.1 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 127.9 ($\underline{C}$HC(=O)), 126.8 (Ar$\underline{C}$H), 39.3 ($\underline{C}HCH_2S$), 35.8 ($\underline{C}H_2S$), 33.6 ($\underline{C}H_2C(=O)$), 26.1 ($\underline{C}H_2CH_2C(=O)$), 22.9 ($\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2980, 2930, 2890 (C-H), 1665 (C=O),

1626 (C=C); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}OS^+$) requires *m/z* 233.0995, found *m/z* 233.0996; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –8.76 (*c* 0.25, $CHCl_3$).

5.7.4.4 Synthesis and characterisation of 293

(S)-S-methyl O-((2-methyl-4-oxocyclohex-2-en-1-yl)methyl) carbonodithioate (293)

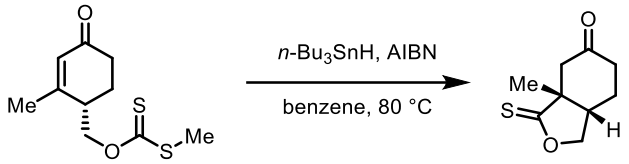


According to a modified literature procedure,[143] to a stirred solution of **239** (99% ee) (50.0 mg, 0.357 mmol, 1.00 eq) in THF (0.7 ml) at 0 °C was added CS_2 (43.0 µl, 0.714 mmol, 2.00 eq). The solution was stirred for 30 min at which point 60% NaH (14.3 mg, 1.43 mmol, 4.00 eq) was added. The reaction was stirred for a further hour at which point methyl iodide (88.9 µl, 1.43 mmol, 4.00 eq) was added. The reaction was stirred until completion was observed by TLC analysis (Et_2O) at which point H_2O (10 ml) was added. The aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 7/3 to 6/4) to provide the title compound (**293**) as a yellow oil in 71% (58.4 mg) and 99% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 280 nm, t(major) = 25.27 min, t(minor) = 27.73 min]. **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 5.86 – 5.71 (m, 1H, C=C<u>H</u>), 4.31 (dd, *J* =11.0, 4.5 Hz, 1H C<u>H$_A$</u>H$_B$O), 4.27 (dd, *J* =11.0, 7.0 Hz, 1H CH$_A$<u>H$_B$</u>O), 2.16 (ddd, *J* = 17.0, 9.5, 5.0 Hz, 1H, one of C<u>H$_A$</u>H$_B$-C(=O)), 2.09 (s, 3H, SC<u>H$_3$</u>), 1.97 – 1.94 (m, 2H, one of CH$_A$H$_B$C(=O) and C<u>H</u>CH$_2$O), 1.53 – 1.40 (m, 2H, C<u>H$_2$</u>CH$_2$C(=O)), 1.32 (t, *J* = 1.0 Hz, 3H, CC<u>H$_3$</u>); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 216.2 (<u>C</u>=S), 196.3 (<u>C</u>=O), 157.7 (C=<u>C</u>CH$_3$), 129.5 (<u>C</u>=CCH$_3$), 73.3 (<u>C</u>H$_2$O), 38.9 (<u>C</u>HCH$_2$O), 34.6 (<u>C</u>H$_2$C(=O)), 25.6 (<u>C</u>H$_2$CH$_2$C(=O)), 22.1 (C<u>C</u>H$_3$), 18.9 (S<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 2950 (C-H), 1670 (C=O) 1627 (C=C); **HRMS**

(ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{14}NaO_2S_2^+$) requires *m/z* 253.0327, found *m/z* 253.0328; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –119.1 (*c* 0.23, $CHCl_3$).

5.7.4.5 Synthesis and characterisation of 294

(3aR,7aS)-3a-methyl-3-thioxohexahydroisobenzofuran-5(3H)-one (294)

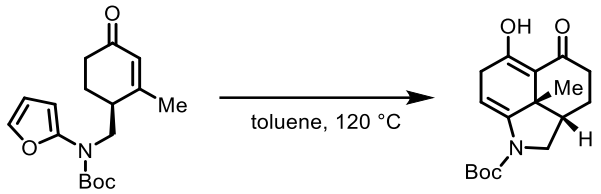


According to a modified literature procedure,[143] a solution of (*S*)-S-methyl O-((2-methyl-4-oxocyclohex-2-en-1-yl)methyl) carbonodithioate (**293**) (99% ee) (20.0 mg, 87.0 µmol, 1.00 eq), *n*-Bu_3SnH (35.0 µl, 0.13 mmol, 1.15 eq) and AIBN (1.40 mg, 8.70 µmol, 0.100 eq) were heated to 80 °C in degassed benzene (2.9 ml) under an atmosphere of argon in a schlenk tube. The reaction mixture was stirred overnight and then allowed to cool to room temperature at which point the reaction mixture was transferred directly onto a column of silica. The compound was purified by silica gel column chromatography (pentane/EtOAc = 9/1 to 8/2 to 4/6) and the title compound (**294**) was obtained as a white solid in 39% yield (6.2 mg) and 97% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 254 nm, t(minor) = 18.18 min, t(major) = 22.75 min].* The resulting solid could be crystallised by slow evaporation of Et_2O. The crystal obtained was >99% ee. **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 3.71 (dd, *J* = 9.5, 7.0 Hz, 1H, one of $C\underline{H_A}H_BO$), 3.40 (dd, *J* = 9.5, 4.5 Hz, 1H, one of $CH_A\underline{H_B}O$), 2.58 (d, *J* = 15.5 Hz, 1H, one of $C\underline{H_A}H_BCCH_3$), 2.05 (dd, *J* = 15.5, 1.0 Hz, 1H, one of $CH_A\underline{H_B}CCH_3$), 1.75 – 1.53 (m, 2H, $CH_2C\underline{H_2}C(=O)$), 1.30 – 1.21 (m, 1H, $C\underline{H}CH_2CO$), 1.01 – 0.93 (m, 1H, one of $C\underline{H_A}H_BCH_2C(=O)$), 0.90 – 0.86 (m, 1H, one of $CH_A\underline{H_B}CH_2C(=O)$), 0.84 (s, 3H, $C\underline{H_3}$); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 227.4 ($\underline{C}$=S), 205.4 ($\underline{C}$=O), 76.8 ($\underline{C}$-O), 56.4 ($\underline{C}CH_3$), 48.4 ($\underline{C}H_2CCH_3$), 41.2 ($\underline{C}HCH_2CO$), 36.6 ($CH_2\underline{C}H_2C(=O)$), 26.9 ($\underline{C}H_3$), 24.7 ($\underline{C}H_2CH_2C(=O)$); **IR** (film) ν_{max}/cm^{-1}: 2948, 2911, 2857 (C-H), 1714 (C=O) 1228 (C=S); **MP**: 92-94 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –51.3 (*c* 0.065, $CHCl_3$).

*The presence of oxygen in this reaction will result in the formation of the lactone which is inseparable from the thionolactone by silica gel column chromatography.

5.7.4.6 Synthesis and characterisation of 295

tert-Butyl (2aS,2a1S)-6-hydroxy-2a1-methyl-5-oxo-2a,2a1,3,4,5,7-hexahydrobenzo[cd]indole-1(2H)-carboxylate (295)



A solution of *tert*-butyl (*S*)-furan-2-yl((2-methyl-4-oxocyclohex-2-en-1-yl)methyl)carbamate (**271**) (7.2 mg, 0.024 mmol) in distilled and degassed toluene (0.72 mL) was heated to 120 °C for 72 h. The reaction was allowed to cool to room temperature at which point the crude mixture was flushed through a plug of silica (pentane/Et_2O = 1/1) to provide the product (**295**) as a red-orange oil in 96% yield (6.9 mg) and 98% ee. [determined by HPLC chiralpak AS, hexane/isopropanol = 99/1, 1 ml/min, λ = 240 nm, t(major) = 15.64 t(minor) = 22.00].* **^{1}H NMR** (500 MHz, Methanol-d_4) δ(ppm): 5.76 (bs, 1H, C=C$\underline{H}$), 4.07 (dd, *J* = 11.5, 8.0 Hz, 1H, one of C$\underline{H_A}H_BN$), 3.55 – 3.45 (dd, *J* = 11.0 Hz, 1H, one of $CH_A\underline{H_B}N$ (minor tautomer peak underneath)), 3.24 (dd, *J* = 21.0, 2.0 Hz, 1H, one of C$\underline{H_A}H_BC$=CN), 2.90 (dd, *J* = 21.0, 6.5 Hz, 1H, one of $CH_A\underline{H_B}C$=CN), 2.38 (ddd, *J* = 17.0, 13.0, 4.0 Hz, 1H, one of $CH_2C\underline{H_A}H_BC$(=O)), 2.32 – 2.22 (m, 1H, one of $CH_2CH_A\underline{H_B}C$(=O)), 2.15 (dddd, *J* = 13.0, 8.0, 4.5, 2.0 Hz, 1H, C$\underline{H}CH_2N$), 1.90 – 1.82 (m, 1H, one of C$\underline{H_A}H_BCH_2C$(=O)), 1.51 (d, *J* = 3.5 Hz, 9H, C(C$\underline{H_3}$)$_3$), 1.41 – 1.29 (m, 1H, one of $CH_A\underline{H_B}CH_2C$(=O) (minor tautomer peak underneath)), 1.25 (s, 3H, CHCC$\underline{H_3}$); **^{13}C NMR** (126 MHz, Methanol-d_4) δ(ppm): 196.4 ($CH_2\underline{C}$(=O)), 184.5 ($\underline{C}$OH), 153.8 (N$\underline{C}$(=O)), 148.4 (N$\underline{C}$=CH), 113.1 ($\underline{C}$C(=O)), 96.6 (NC=$\underline{C}$H), 82.0 ($\underline{C}(CH_3)_3$), 54.7 ($\underline{C}H_2N$), 46.0 (CH$\underline{C}CH_3$), 43.0 ($CH_3C\underline{C}H$), 36.0 (C=C$\underline{C}H_2$), 32.8 (C($\underline{C}H_3$)$_3$), 28.6 ($\underline{C}H_2CH_2C$(=O)), 28.5 ($\underline{C}H_2CH_2C$(=O)), 27.8 (CHC$\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2974 (C-

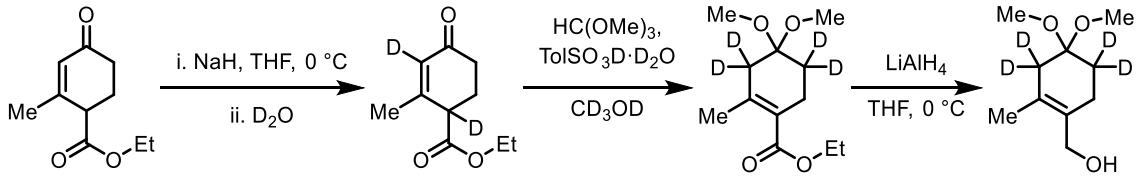
H), 1709 (C=O), 1392, 1370, 1146 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}NO_4^+$) requires *m/z* 306.1700, found *m/z* 306.1700; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +84.8 (*c* 0.55, $CHCl_3$).

*Trace impurities from the prototropic shift visible by staining with ninhydrin appear to inhibit this reaction.

5.8 Deuterium labelling experiments

5.8.1 Synthesis and characterisation of deuterium labelled compounds

5.8.1.2 Synthesis and characterisation of 223-D

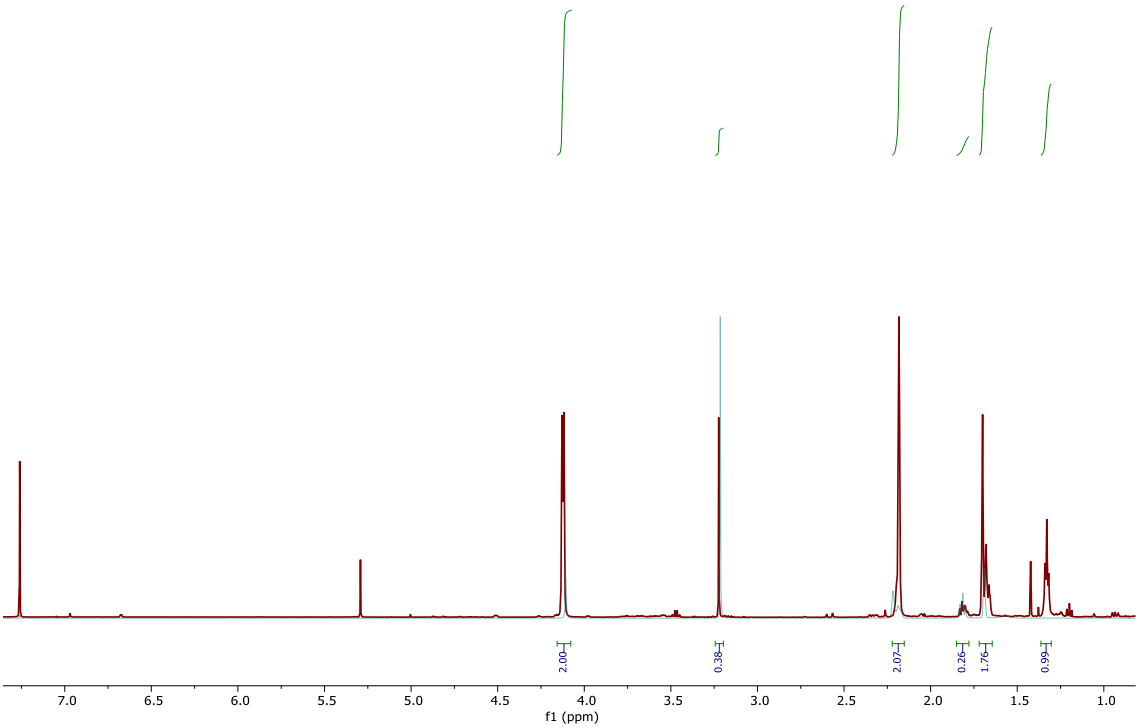


a) To a stirred solution of 60% NaH (242 mg, 6.04 mmol, 1.10 eq) in THF (27.5 ml) was added Hagemann's ester (**218**) (1.00 g, 5.49 mmol, 1.00 eq). The reaction was stirred at 0 °C for 10 min at which point D_2O (10 ml) was added. The aqueous phase was extracted with EtOAc (3 x 20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The entire process was repeated a second time to afford **218-D** in 72% yield (728 mg) which was taken on without further purification.

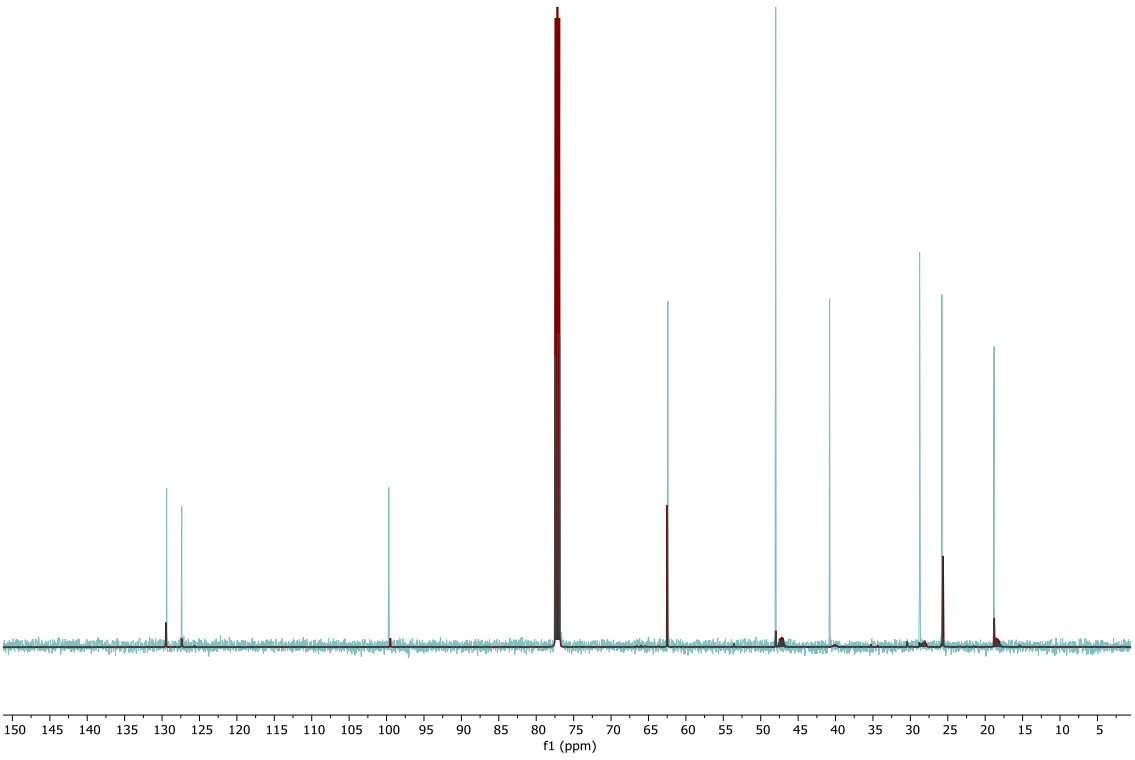
b) *p*TsOH·H_2O (150 mg, 0.790 mmol, 0.200 eq) was dissolved in D_2O (5 ml) and concentrated *in vacuo.* This process was repeated twice to provide *p*TsOD·D_2O. *p*TsOD·D_2O was placed under an atmosphere of Ar and CD_3OD (22 ml) was added. To this solution was added deuterated **218-D** (728 mg, 3.95 ml, 1.00 eq) followed by trimethyl orthoformate (1.30 ml, 11.9 mmol, 3.00 eq). The reaction was stirred for 3 hours at which point a saturated solution of K_2CO_3 in D_2O was added (20 ml). The aqueous layer was extracted with EtOAc (3 x 20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product (**219-D**) as a yellow oil in 65% yield (614 mg) which was taken on without further purification.

c) To a solution of **219-D** (614 mg, 2.67 mmol, 1.00 eq) in THF (4.5 ml) at 0° C was added $LiAlH_4$ (506 mg, 13.3 mmol, 5.00 eq). The reaction was stirred for 2 h at which point the reaction was diluted with Et_2O (20 ml) and cooled to 0 °C. H_2O (0.5 ml) was added, followed by 15% aqueous NaOH solution (0.5 ml), followed by H_2O (1.5 ml). The biphasic mixture was stirred for 15 min at rt at which point $MgSO_4$ was added and stirring was maintained for a further 15 min. The mixture was filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Et_2O) to provide **223-D** in 46% yield (243 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 4.12 (d, *J* = 5.0 Hz, 2H, $C\underline{H_2}OH$), 3.22 (s, $C(OCH_3)_2$ (partial deuterium incorporation)), 2.18 (s, 2H, $CC\underline{H_2}C(OCH_3)_2$ (deuterated) and $C\underline{H_2}CH_2C(OCH_3)_2$), 1.81 (m, $CH_2C\underline{H_2}C(OCH_3)_2$ (deuterated)), 1.73 – 1.63 (m, 2H, $CC\underline{H_3}$ (partial deuterium incorporation)), 1.33 (t, *J* = 5.5 Hz, 1H, OH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 129.5 ($\underline{C}CH_2OH$), 127.4 ($\underline{C}CH_3$), 99.5 ($\underline{C}(OCH_3)_2$), 62.5($\underline{C}H_2OH$), 48.0 ($C(O\underline{C}H_3)_2$), 47.8 – 46.6 (m, $C(O\underline{C}D_3)_2$), 40.0 (m, $C\underline{C}D_2C(OCH_3)_2$), 28.9 – 27.7 (m, $\underline{C}H_2CD_2C(OCH_3)_2$), 25.9 – 25.4 (m, $CH_2\underline{C}D_2C(OCH_3)_2$), 19.1 – 17.7 (m, $C\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3401 (O-H), 2215, 2129, 2070 (C-H), 1118, 1052 (C-O).

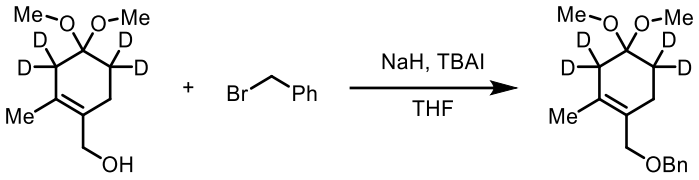
^{1}H NMR (500 MHz, $CDCl_3$) of **223-D** overlaid with **223**



^{1}H NMR (500 MHz, $CDCl_3$) of **223-D** overlaid with **223**

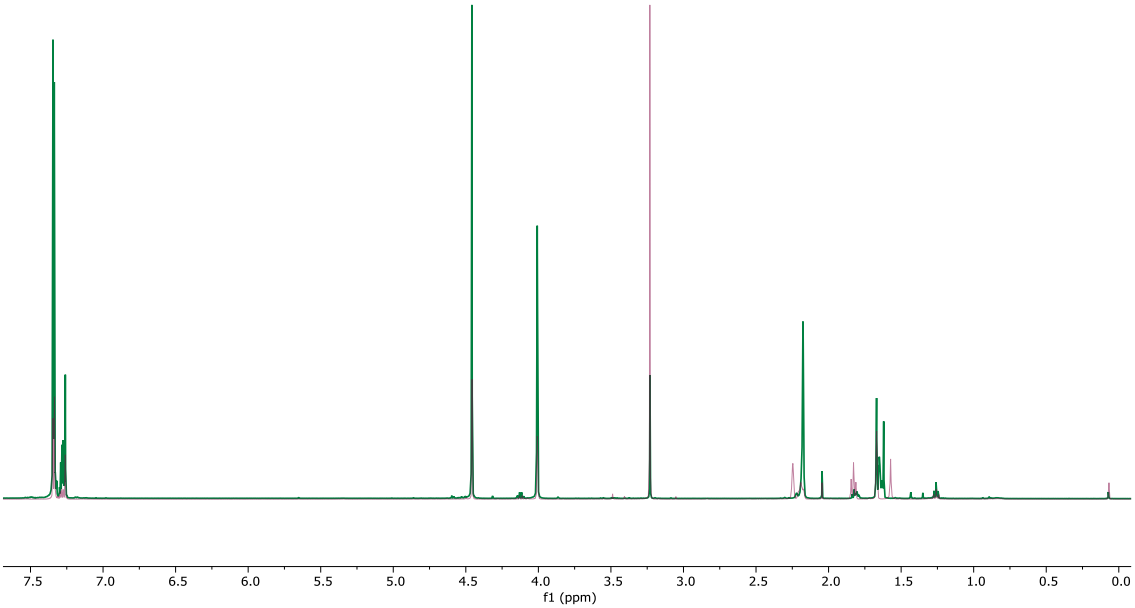


5.8.1.3 Synthesis and characterisation of 224-D

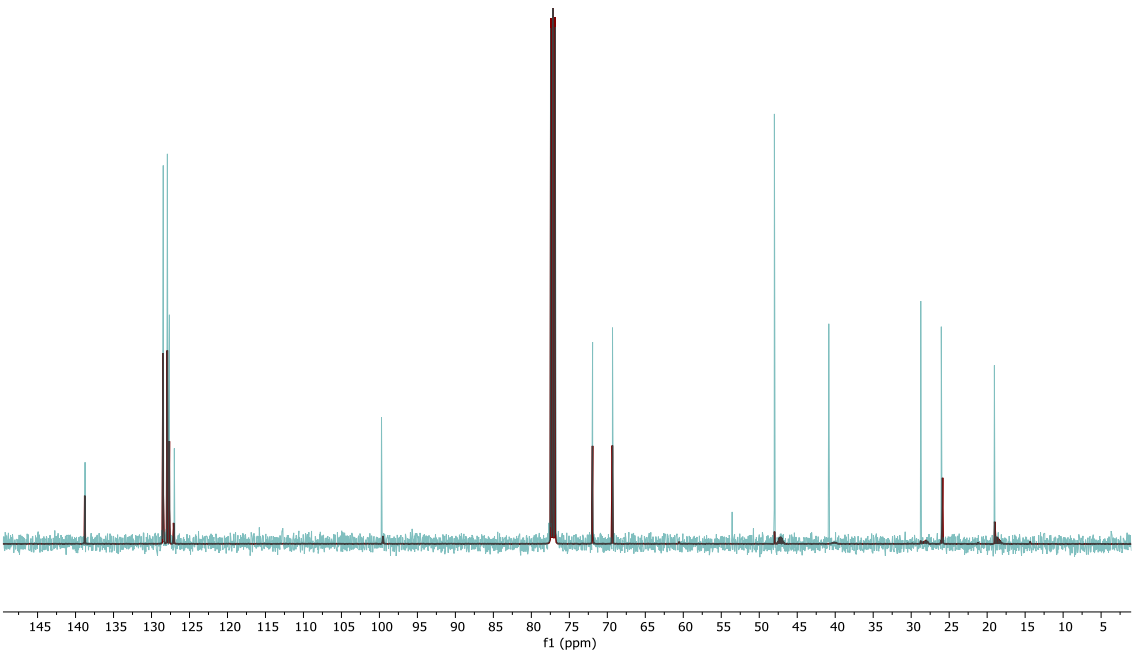


To a solution of **223-D** (282 mg, 1.22 mmol, 1.00 eq) in THF (3.1 ml) at 0 °C was added 60% NaH (98 mg, 2.45 mmol, 2.00 eq). The suspension was stirred for 30 min at which point BnBr (315 mg, 1.84 mmol, 1.50 eq) and TBAI (44.0 mg, 0.12 mmol, 0.100 eq) were added. The reaction was stirred overnight at which point sat. aq NH_4Cl (20 ml) was added. The aqueous layer was extracted with EtOAc (3 x 20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O 9/1 to 8/2) to afford the title compound (**224-D**) as a yellow oil in 68% yield (238 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.34 (d, *J* = 4.5 Hz, 4H, Ar$\underline{H}$), 7.30 – 7.26 (m, 1H, Ar$\underline{H}$), 4.46 (s, 2H, C$\underline{H_2}$Ph), 4.01 (s, 2H, C$\underline{H_2}$OCH$_2$Ph), 3.23 (s, C(OC$\underline{H_3}$)$_2$ (partial deuterium incorporation)), 2.22 (s, CC$\underline{H_2}$C(OCH$_3$), (deuterated)), 2.18 (s, 2H, C$\underline{H_2}$CH$_2$C(OCH$_3$)), 1.81 (dt, *J* = 9.5, 6.5 Hz, CH$_2$C$\underline{H_2}$C(OCH$_3$), (deuterated)), 1.70 – 1.60 (m, CC$\underline{H_3}$ (partial deuterium incorporation)); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 138.8 (Ar$\underline{C}$), 128.5 ($\underline{C}$CH$_2$OBn), 127.9 (Ar$\underline{C}$H), 127.7 (Ar$\underline{C}$H), 127.1 ($\underline{C}$CH$_3$), 99.5 ($\underline{C}$(OCH$_3$)$_2$), 72.0 ($\underline{C}$H$_2$Ph), 69.3 ($\underline{C}$H$_2$O), 48.0 (O$\underline{C}$H$_3$), 47.2 (m, O$\underline{C}$D$_3$), 41.5 – 39.3 (m, $\underline{C}$D$_2$CCH$_3$), 28.9 – 27.6 (m, CH$_2$$\underline{C}D_2$C(OCH$_3$)$_2$), 25.9 (m, $\underline{C}$H$_2$CH$_2$C(OCH$_3$)$_2$), 19.2 – 18.0 (m, C$\underline{C}$H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3030, 2981, 2916, 2851 (C-H), 1715 (C=O), 1066 (C-O).

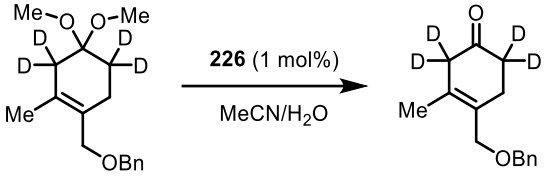
^{1}H NMR (500 MHz, $CDCl_3$) of **224-D** overlaid with **224**



^{13}C NMR (126 MHz, $CDCl_3$) of **224-D** overlaid with **224**

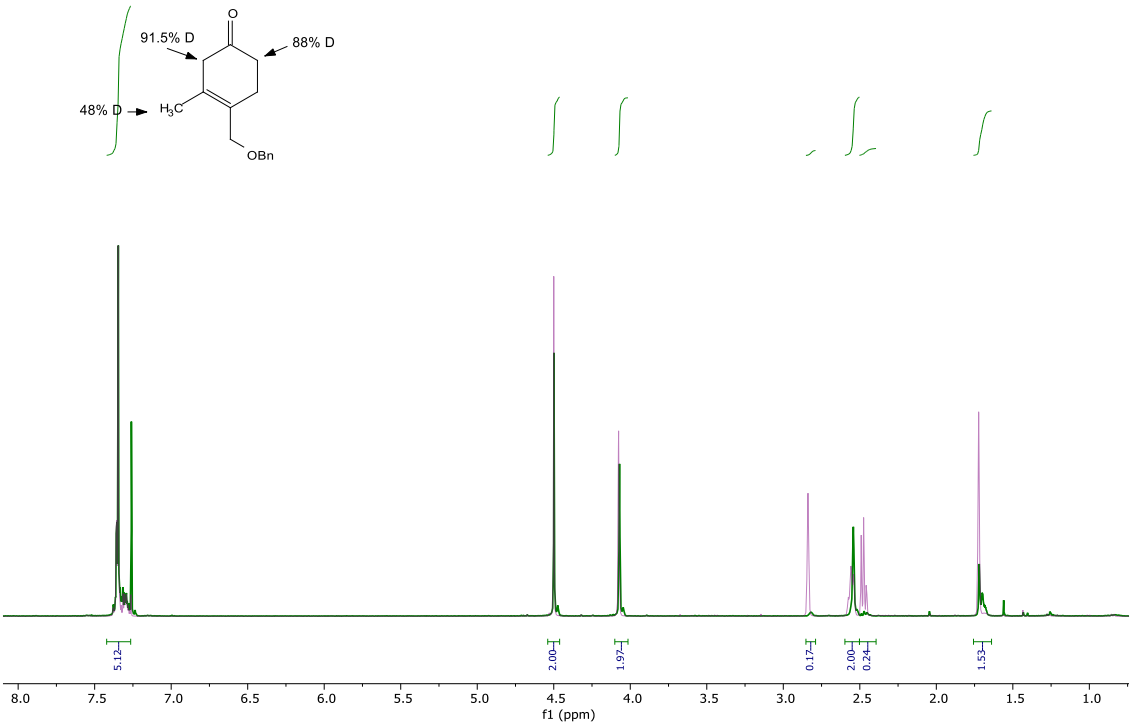


5.8.1.4 Synthesis and characterisation of 225-D

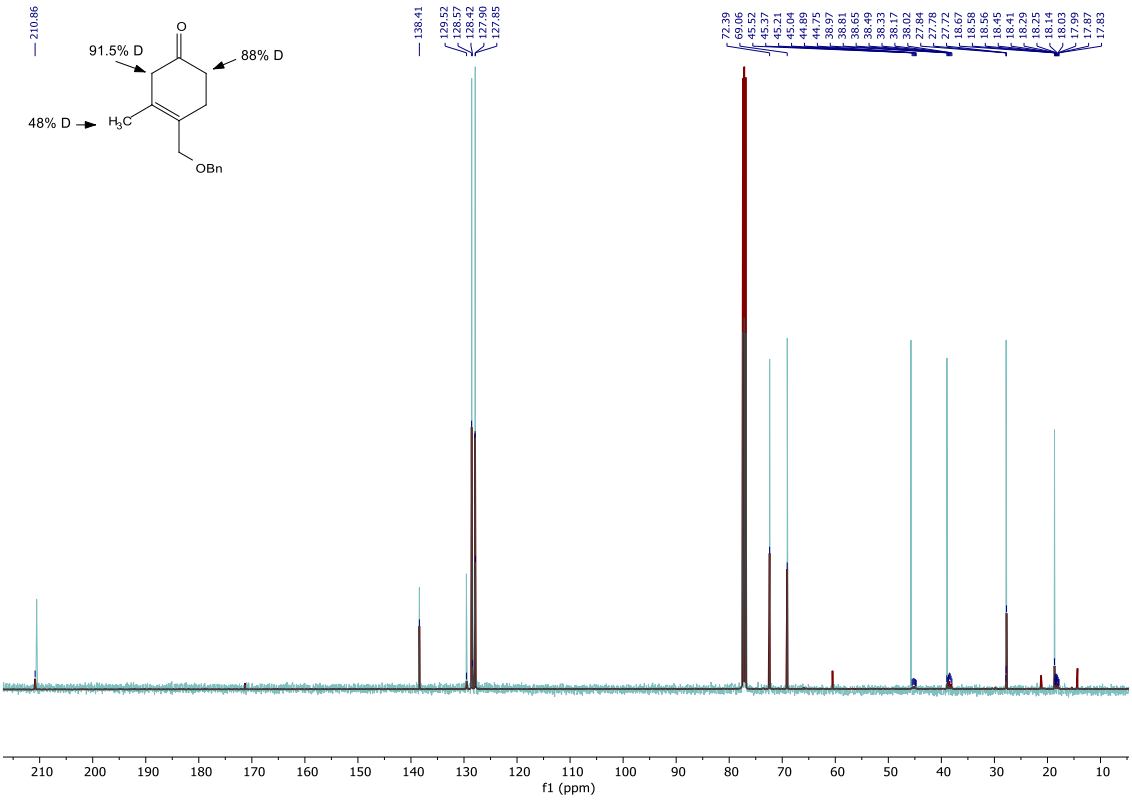


Compound **225-D** was prepared according to general procedure **V** from **224-D** (218 mg, 0.78 mmol, 1.00 eq). Upon completion of the reaction as judged by TLC analysis (pentane/Et_2O = 9/1) the reaction mixture was transferred directly to silica gel and purified by silica gel column chromatography (pentane/Et_2O = 95/5) to afford the title compound (**225-D**) as a yellow oil. Yield assumed quantitative. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.42 – 7.26 (m, 5H, Ar<u>H</u>), 4.50 (s, 2H, C<u>H_2</u>Ph), 4.06 (s, 2H, C<u>H_2</u>OCH_2Ph), 2.82 (s, 91.5 % D, CC<u>H_2</u>C(=O)), 2.54 (s, 2H, C<u>H_2</u>CH_2C(=O)), 2.47 (m, 88% D, CH_2C<u>H_2</u>C(=O)), 1.76 – 1.66 (m, 48% D, C<u>H_3</u>); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 210.9 (<u>C</u>=O), 138.4 (Ar<u>C</u>), 129.5 (CH_3<u>C</u>), 128.6 (Ar<u>C</u>H), 128.4 (CH_3C=<u>C</u>), 127.9 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 72.4 (<u>C</u>H_2Ph), 69.1 (<u>C</u>H_2OCH_2Ph), 45.13 (m, C<u>C</u>H_2C(=O)), 39.05 – 37.84 (m, <u>C</u>$H_2$$CH_2$C(=O)), 27.88 – 27.59 (m, CH_2<u>C</u>H_2C(=O)), 18.84 – 17.64 (m, <u>C</u>H_3); **IR** (film) ν_{max}/cm^{-1}: 2030, 2905, 2845 (C-H), 1674 (C=C), 1069 (C-O).

^{1}H NMR (400 MHz, $CDCl_3$) of **225-D** overlaid with **225**.



^{13}C NMR (126 MHz, $CDCl_3$) of **225-D** overlaid with **225**.



5.8.2 Labelling experiments for the BIMP catalysed prototropic shift

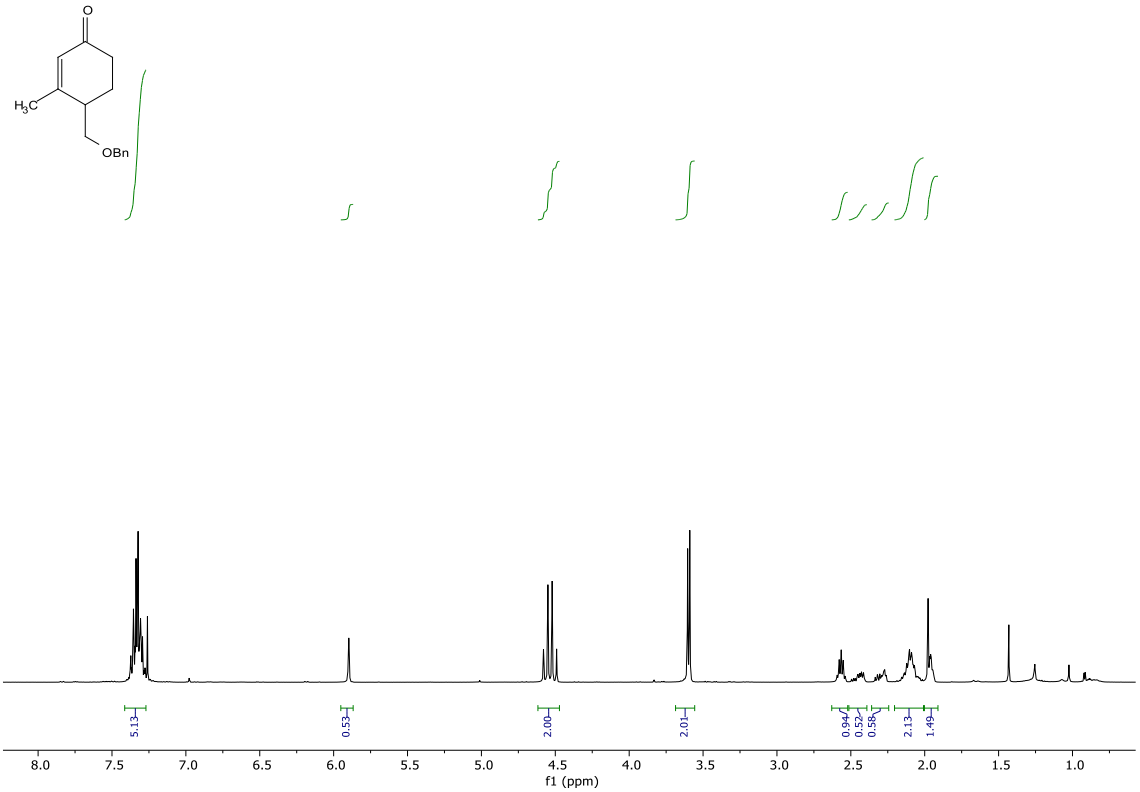
5.8.2.1 Crossover experiment with substrates 225-D and 234



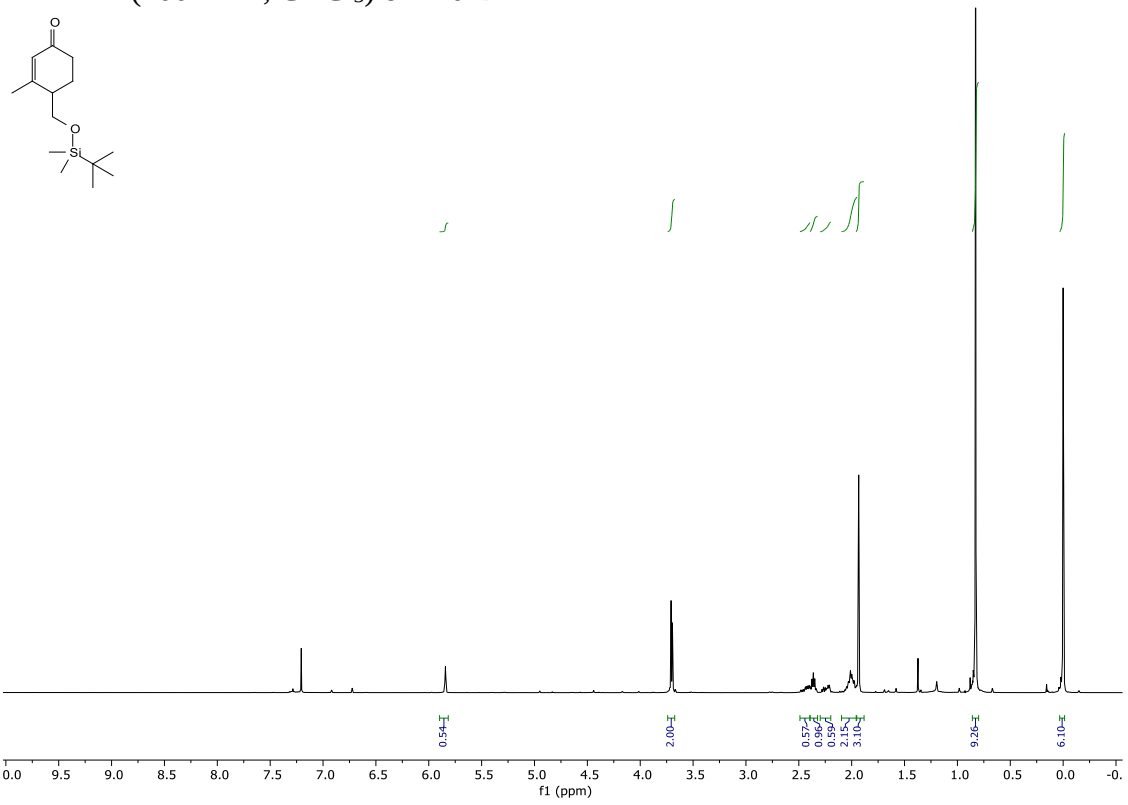
Labelled substrate **225-D** (15.4 mg, 0.065 mmol, 0.50 eq) and unlabelled substrate **234** (16.5 mg, 0.065 mmol, 0.50 eq) were subjected to the prototropic shift reaction conditions (general procedure **VII**) with catalyst **229a** (10 mol% wrt total mmol). Product **240-D** was obtained in 86% yield and 98% ee. Product **240-D** was obtained in 82% yield and 97% ee. Exchange of the α-protons was observed, resulting in approximately 50% deuterium incorporation in both α-positions of the final products. This is consistent with the pre-equilibrium described in the literature as well as computational studies.[124] Only low levels of deuterium incorporation were observed at the γ-position consistent with reprotonation being the turnover limiting step.

Quantitative NMR spectra obtained after crossover experiment between **225-D** and **234**:

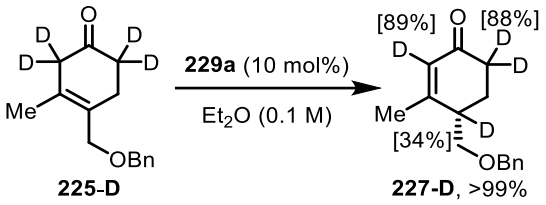
^{1}H NMR (400 MHz, $CDCl_3$) of **227-D**



^{1}H NMR (400 MHz, $CDCl_3$) of **240-D**



5.8.2.2 Labelling experiment with substrate 225-D and catalyst 229a



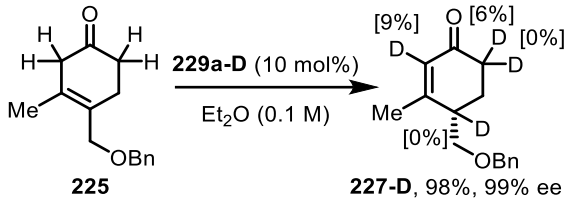
Substrate **225-D** (15.4 mg, 0.065 mmol, 1.00 eq) was subjected to the prototropic shift reaction conditions (general procedure **VII**) with catalyst **229a** (10 mol%). The isolated product (**227-D**) was obtained in >99% yield and with high levels of deuterium incorporation at both α-positions (88% and 89%) however lower levels of deuterium were incorporated at the γ-position (34%).

5.8.2.3 Labelling experiment with substrate 225-D and catalyst 229a-D



Catalyst azide precursor **229** (3.7 mg, 0.0065 mmol, 0.10 eq) was dissolved in methanol-d^4 and concentrated *in vacuo*. This process was repeated three times. The deuterated azide precursor was transformed into the active BIMP catalyst **229a-D** according to general procedure **I**. Substrate **225-D** (15.4 mg, 0.065 mmol, 1.00 eq) was subjected to the prototropic shift reaction conditions (general procedure **VII**) with catalyst **229a-D** (10 mol%). The isolated product (**227-D**) was obtained in 82% yield and with high levels of deuterium incorporation at both α-positions (93% and 92.5%) however lower levels of deuterium were incorporated at the γ-position (50%).

5.8.2.4 Labelling experiment with substrate 225 and catalyst 229a-D



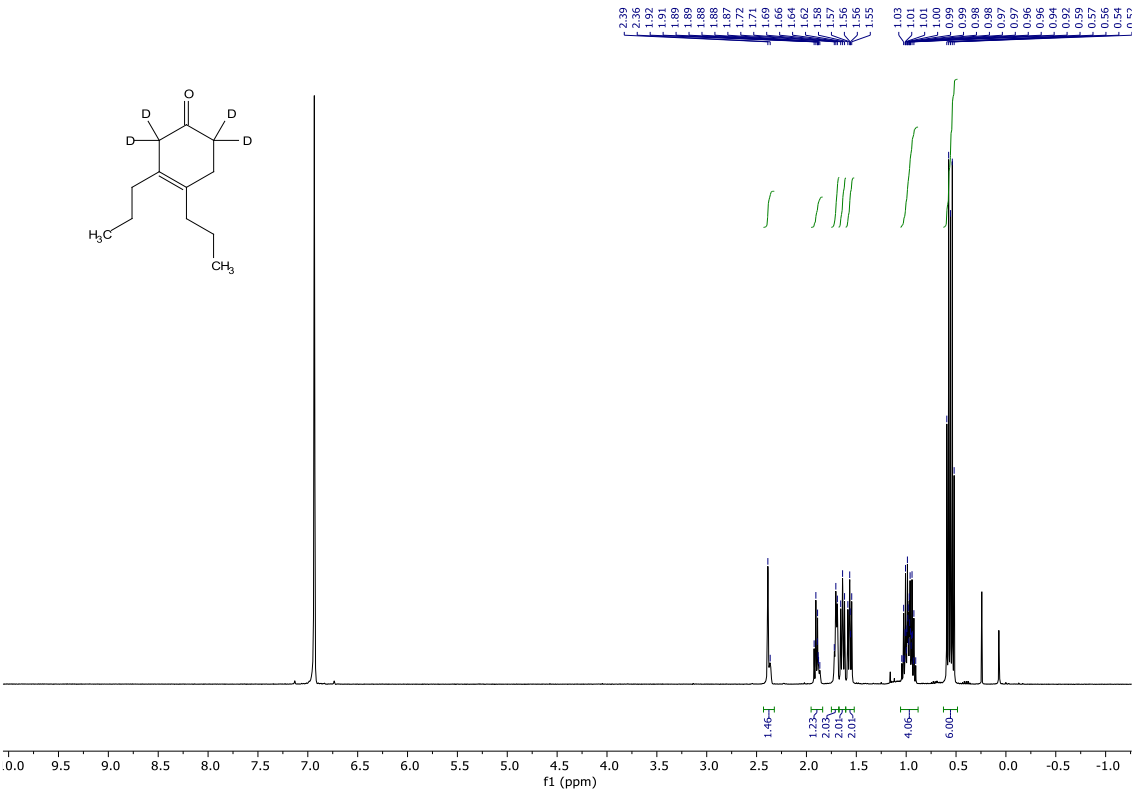
Catalyst azide precursor **229** (3.7 mg, 0.0065 mmol, 0.10 eq) was dissolved in methanol-d^4 and concentrated *in vacuo*. This process was repeated three times. The deuterated azide precursor was transformed into the active BIMP catalyst **229a-D** according to general procedure **I**. Unlabelled substrate **225** (15.0 mg, 0.065 mmol, 1.0 eq) was subjected to the prototropic shift reaction conditions (general procedure **VII**) with catalyst **229a-D**. The isolated product (**227-D**) was obtained in 98% yield and 99% ee low levels of deuterium incorporation were observed at both α-positions (9% and 6%) however no deuterium was incorporated at the γ-position.

5.8.2.5 Crossover experiment with substrates 225-D and 280



Labelled substrate **225-D** (7.70 mg, 0.0325 mmol, 0.500 eq) and unlabelled substrate **280** (5.90 mg, 0.0325 mmol, 0.5 eq) were subjected to the prototropic shift reaction conditions (general procedure **VII**) with catalyst **229a** (10 mol% wrt total mmol). Exchange of the α-protons was observed on product **227-D** (43% and 40% deuterium incorporation) which was isolated in 92% yield and 99% ee. Only low levels of deuterium incorporation were observed at the γ-position (5%). Substrate **280-D** was re-isolated (63%), only low levels of deuterium incorporation were observed at the α-positions (28% and 38.5%) suggesting a lower acidity in comparison with substrate **225**.

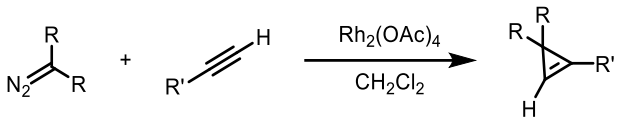
^{1}H NMR (400 MHz, $CDCl_3$) of **280-D**



5.9 The enantioselective deconjugation of cyclopropenes

5.9.1 General procedures

General procedure IX for the $Rh_2(OAc)_4$ addition of diazonium compounds to terminal alkynes



According to a literature procedure,[245] the desired diazonium compound (1.0 eq) in CH_2Cl_2 (0.5 M) was added dropwise overnight using a syringe pump to a solution of $Rh_2(OAc)_4$ (1.0 mol%) in the desired terminal alkyne (3.0 eq). Following the addition, the reaction was monitored by TLC and further equivalents of alkene and $Rh_2(OAc)_4$ were added until complete disappearance of the diazonium compound was observed. The crude product was flushed through a plug of celite with CH_2Cl_2 and purified by silica gel column chromatography to provide the desired terminal cyclopropene.

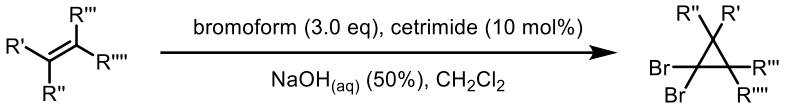
General procedure X for the addition of terminal cyclopropenes to electrophiles



LHMDS (1.0 M in THF, 1.0 eq) was added dropwise to a stirred solution of the desired terminal cyclopropene (1.0 eq) and electrophile (1.5 eq) at −78 °C in THF (0.3 M). The solution was stirred at −78 °C until completion was observed by TLC. The reaction was quenched with sat. aq. NH_4Cl and the aqueous phase was extracted with Et_2O (3 x 20 ml) (if an isocyante was used the reaction was quenched with 1.0 M $HCl_{(aq)}$). The combined organic extracts were washed with brine then dried over Na_2SO_4, filtered and

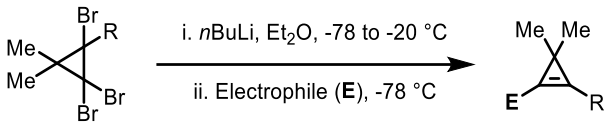
concentrated *in vacuo*. The crude material was purified by silica gel column chromatography to provide the desired cyclopropene.

General procedure XII for the addition of dibromocarbenes to alkenes



According to a literature procedure,[246] 50% NaOH (2.5 x CH_2Cl_2) was added dropwise via a syringe pump (10 ml/h) to a stirred solution of the desired alkene (1.0 eq), cetrimide (10 mol%) and bromoform (3.0 eq) in CH_2Cl_2 (10 M) at ambient temperature. The reaction was stirred and monitored by TLC until complete disappearance of the alkene was observed (1-5 days). To aid reaction progression extra equivalents of bromoform and NaOH solution were added and in some cases the reaction was warmed to 50 °C. Upon completion of the reaction H_2O was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x), the combined organic layers were dried over Na_2SO_4 (addition of brine is not recommended as it results in precipitation of the phase transfer catalyst) and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography to provide the desired tribromocyclopropane. Excess bromoform may be removed under a stream of nitrogen.

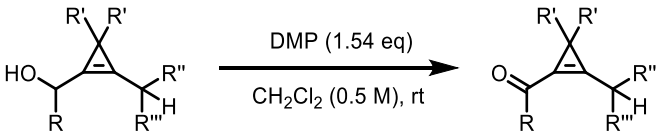
General procedure XI for the addition of tribromocyclopropanes to electrophiles



According to a modified literature procedure,[193] *n*-BuLi (2.5 M in hexanes, 2.0 eq) was added dropwise to a stirred solution of the desired tribromocyclopropane (1.0 eq) in Et_2O (0.1 M) at −78 °C. The reaction was stirred at −78 °C for 1 h at which point the

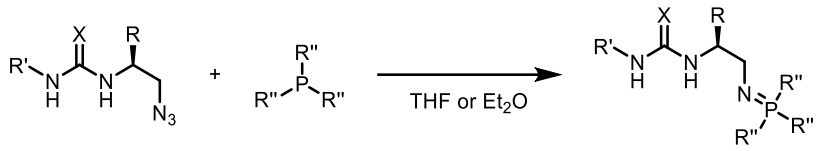
temperature was raised to −20 °C and stirred for a further 2 h. The reaction mixture was then cooled to −78 °C and decanted via cannula at that temperature into a −78 °C solution of the desired electrophile (1.5 eq) (in cases where 1.2 eq of chloroformate is used, the chloroformate was added directly to the lithiated cyclopropene solution) in Et_2O (1.0 M). The reaction mixture was stirred until completion was observed by TLC at which point the reaction was quenched with sat. aq. NH_4Cl and the aqueous phase was extracted with Et_2O (3 x 20 ml) (if an isocyante was used the reaction was quenched with 1.0 M $HCl_{(aq)}$). The combined organic extracts were washed with brine then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography to provide the desired cyclopropene. Compounds synthesised by this method often contain an inseparable impurity (generally 5-10%). See section **5.9.2.21** for further information.

General procedure XIII for the oxidation of alcohols



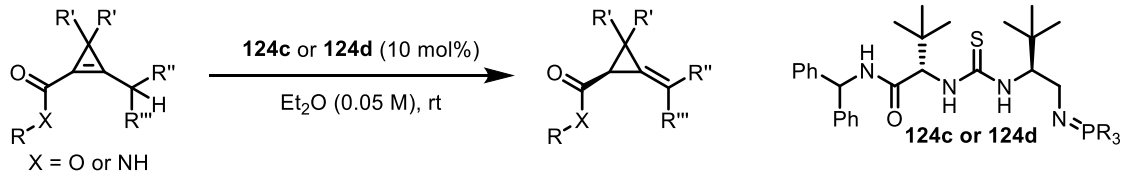
According to a literature procedure,[233] DMP (1.54 eq) was added portion wise to a solution of the desired alcohol (1.0 eq) in CH_2Cl_2 (0.5 M). The reaction was monitored by TLC until complete disappearance of the alcohol was observed (ca. 5 min). Upon completion sat. aq. $NaHCO_3$ was added. The aqueous layer was extracted with Et_2O (3 x) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography to provide the desired ketone.

General procedure II for *in situ* generation of active BIMP catalysts



To a mass spectrometry vial was weighed the desired azide (1.00 eq) and the desired phosphine (1.00 eq) (in the case of electron poor phosphines 1.50 eq of the phosphine was used and the reaction was heated to 40 °C, this alternate procedure was also followed when reactions were carried out on small scale ≤0.025 mmol). The vial was placed under an atmosphere of Ar and THF (0.2 M) was added. The cap was replaced and sealed with parafilm® and the mixture was stirred for 18 – 24 h. The volatiles were removed under reduced pressure or under a constant stream of Ar an the crude iminophosphorane was used without further purification.

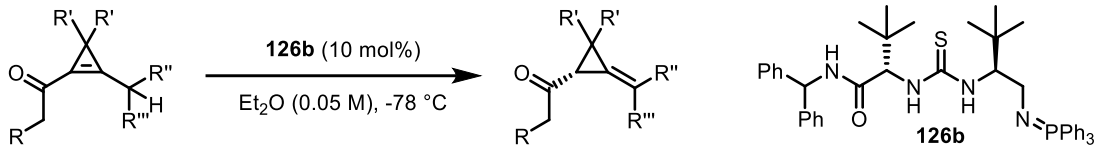
General procedure XIV for the enantioselective deconjugation of cyclopropenes (esters and amides)



The desired cyclopropene (1.0 eq) was transferred in a solution of Et_2O (0.05 M) to preformed BIMP catalyst **124c** or **124d** (10 mol%) (see general procedure **II**) or vice versa depending on the reaction scale. The reaction was monitored by TLC and quenched with AcOH (20 mol%, stock solution in Et_2O) upon completion (care must be taken to avoid racemisation of the ACP if the reaction is left for extended time periods. Formation of tertiary ACPs appeared to form more rapidly than quaternary ACPs which in turn formed quicker than secondary ACPs). The crude reaction mixture was concentrated

under a stream of N_2 and purified by silica gel column chromatography to afford the desired enantioenriched ACP. Racemic versions of the compounds could be synthesised by addition of DBU (3.0 eq) to a stirred solution of the cyclopropene in THF (0.1 M). Racemic compounds were also synthesised using ***rac*-124c** or ***rac*-124d** (formed using an equimolar amount of the two catalyst enantiomers). AS-H and AD-H columns appear best for separating all diastereomers and starting material.

General procedure XV for the enantioselective deconjugation of cyclopropenes (ketones)

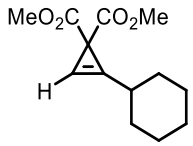


A solution of preformed BIMP catalyst **126b** (10 mol%) in Et_2O (0.1 M wrt cyclopropene) was added dropwise to a stirred solution of the desired cyclopropene (1.0 eq) in Et_2O (0.1 M) at −78 °C The reaction was monitored by TLC and quenched with AcOH (20 mol%, stock solution in Et_2O) upon completion. The crude reaction mixture was concentrated under a stream of N_2 and purified by silica gel column chromatography to afford the desired enantioenriched ACP. Racemic versions of the compounds could be synthesised by addition of DBU (3.0 eq) to a stirred solution of the cyclopropene in THF (0.1 M). AS-H and AD-H columns appear best for separating all diastereomers and starting material.

5.9.2 Synthesis and characterisation of substrates used in the enantioselective deconjugation of cyclopropenes

5.9.2.1 Synthesis and characterisation of 376

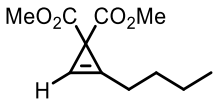
dimethyl 2-cyclohexylcycloprop-2-ene-1,1-dicarboxylate (376)



Compound **376** was synthesised according to general procedure **IX** by the addition of dimethyl diazomalonate (605 mg, 3.83 mmol, 1.00 eq) to cyclohexyne (1.50 ml, 11.48 mmol, 3.00 eq). The crude product was purified by silica gel column chromatography (pentane/EtOAc = 9/1) to provide the title compound (**376**) as a yellow oil in 46% yield (418 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 6.31 (d, *J* = 1.5 Hz, 1H, C=C$\underline{H}$), 3.70 (s, 6H, C($CO_2C\underline{H}_3)_2$), 2.69 – 2.58 (m, 1H, C$\underline{H}$C=CH), 1.98 – 1.84 (m, 2H, C$\underline{H}_A$$H_BCHC\underline{H}_C$$H_D$), 1.79 – 1.52 (m, 3H, C$\underline{H}_A\underline{H}_B$$CH_2CHCH_2C\underline{H}_C$$H_D$), 1.52 – 1.15 (m, 5H, C$\underline{H}_A$$H_BCHC\underline{H}_C$$H_D$, $CH_AH_BCH_2CHCH_2CH_C\underline{H}_D$ and $CHCH_2CH_2C\underline{H}_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 172.1 (C=O), 117.9 (C=CH), 92.5 (C=CH), 52.3 ($C(CO_2\underline{C}H_3)_2$), 34.0 (CHC=CH), 32.4 ($C(CO_2CH_3)_2$), 30.2 ($CH\underline{C}H_2$), 25.9 ($CHCH_2CH_2\underline{C}H_2$), 25.3 ($CHCH_2\underline{C}H_2CH_2$); **IR** (film) ν_{max}/cm^{-1}: 3137, 2930, 2855 (C-H), 1723 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{18}NaO_4^+$) requires *m/z* 261.1097, found *m/z* 261.1096.

5.9.2.2 Synthesis and characterisation of 433

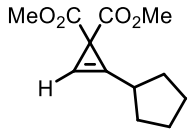
dimethyl 2-butylcycloprop-2-ene-1,1-dicarboxylate (433)



Compound **433** was synthesised according to general procedure **IX** by the addition of dimethyl diazomalonate (1.21 g, 7.66 mmol, 1.00 eq) to 1-hexyne (2.64 ml, 23.0 mmol, 3.00 eq). After the addition extra 1-hexyne (1.30 ml, 11.5 mmol, 1.50 eq) and $Rh_2(OAc)_4$ (34.0 mg, 0.0770 mmol, 0.0100 eq). The crude product was purified by silica gel column chromatography (pentane/EtOAc = 95/5 to 9/1) to provide the title compound (**433**) as a yellow oil in 67% yield (1.07 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.34 (t, *J* = 1.5 Hz, 1H, C=C<u>H</u>), 3.69 (s, 6H, $C(CO_2C\underline{H}_3)_2$), 2.53 (td, *J* = 7.5, 1.5 Hz, 2H, $C\underline{H}_2C$=CH), 1.62 – 1.51 (m, 2H, $CH_3CH_2C\underline{H}_2$), 1.43 – 1.31 (m, 2H, $CH_3C\underline{H}_2CH_2$), 0.90 (t, *J* = 7.5 Hz, 3H, $C\underline{H}_3CH_2CH_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.0 ($C(\underline{C}O_2Me)_2$), 114.7 (<u>C</u>=CH), 93.6 (C=<u>C</u>H), 52.3 ($C(CO_2\underline{C}H_3)_2$), 32.5 ($\underline{C}(CO_2Me)_2$), 28.5 ($CH_2C\underline{H}_2CH_2CH_3$), 23.8 ($C\underline{H}_2CH_2CH_2CH_3$), 22.3 ($CH_2CH_2C\underline{H}_2CH_3$), 13.7 ($CH_2CH_2CH_2C\underline{H}_3$); **IR** (film) ν_{max}/cm^{-1}: 3137, 2956, 2874 (C-H), 1724 (C=O). Data are consistent with that published in the literature.[247]

5.9.2.3 Synthesis and characterisation of E38

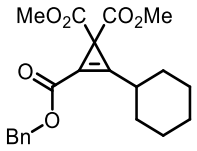
dimethyl 2-cyclopentylcycloprop-2-ene-1,1-dicarboxylate (E38)



Compound **E38** was synthesised according to general procedure **IX** by the addition of dimethyl diazomalonate (1.21 g, 7.66 mmol, 1.00 eq) to cyclopentylacetylene (2.67 ml, 23.0 mmol, 3.00 eq). The crude product was purified by silica gel column chromatography (pentane/EtOAc = 95/5) to provide the title compound (**E38**) as a yellow oil in 53% yield (907 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 6.29 (d, *J* = 1.5 Hz, 1H, C=C$\underline{H}$), 3.69 (s, 6H, C(COC$\underline{H}_3$)$_2$), 3.10 – 2.96 (m, 1H, C$\underline{H}$C=CH), 1.98 – 1.81 (m, 2H, 2 of CHC$\underline{H}_A$H$_B$CH$_2$CH$_2$C$\underline{H}_B$H$_C$), 1.77 – 1.51 (m, 6H, 2 of CHCH$_A$$\underline{H}_BCH_2CH_2CH_B$$\underline{H}_C$ and CHCH$_A$H$_B$C$\underline{H}_2$C$\underline{H}_2$CH$_B$H$_C$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 172.1 (C($\underline{C}$O$_2$Me)$_2$), 118.0 ($\underline{C}$=CH), 92.4 (C=$\underline{C}$H), 52.2 (C(CO$_2$$\underline{C}H_3$)$_2$), 35.1 ($\underline{C}$HC=CH), 33.1 ($\underline{C}$(CO$_2CH_3$)$_2$), 31.0 (CH$\underline{C}H_2CH_2CH_2$$\underline{C}H_2$), 25.2 (CHCH$_2$$\underline{C}H_2$$\underline{C}H_2CH_2$); **IR** (film) ν_{max}/cm^{-1}: 3137, 2954, 2872 (C-H), 1722 (C=O). Data are consistent with that published in the literature.[248]

5.9.2.4 Synthesis and characterisation of 378

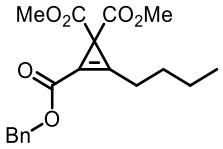
2-benzyl 1,1-dimethyl 3-cyclohexylcycloprop-2-ene-1,1,2-tricarboxylate (378)



Compound **378** was synthesised according to general procedure **X** by the addition of **376** (400 mg, 1.68 mmol, 1.00 eq) to benzyl chloroformate (**377**) (0.35 ml, 2.52 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (1st column: CH_2Cl_2, 2nd column: pentane/CH_2Cl_2 = 1/1, 3rd column: pentane/Et_2O = 95:5) to provide the title compound (**378**) as a white solid in 44% yield (277 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm):7.40 – 7.28 (m, 5H, Ar$\underline{H}$), 5.28 (s, 2H, C$\underline{H_2}$Ph), 3.72 (s, 6H, C($CO_2C\underline{H_3}$)), 2.80 (tt, *J* = 10.0, 4.0 Hz, 1H, C$\underline{H}$C=CC(=O)), 1.97 – 1.89 (m, 2H, C$\underline{H_A}H_BCHC\underline{H_C}H_D$), 1.71 (m, 2H, C$\underline{H_A}H_BCH_2CHCH_2C\underline{H_C}H_D$), 1.65 – 1.56 (m, 2H, cyclohexyl ring), 1.50 (m, 2H, $CH_A\underline{H_B}CHCH_C\underline{H_D}$), 1.42 – 1.24 (m, 2H cyclohexyl ring); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 169.7 (C($\underline{C}O_2CH_3$)), 157.3 (CHC=C$\underline{C}$(=O)), 135.3 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$H), 128.5 (Ar$\underline{C}$H), 128.2 ($\underline{C}$=CC(=O)), 128.1 (Ar$\underline{C}$H), 97.7 (C=$\underline{C}$C(=O)), 67.5 ($\underline{C}H_2$Ph), 52.6 (C($CO_2\underline{C}H_3$)), 36.2 ($\underline{C}$(CO_2CH_3)), 35.1 ($\underline{C}$HC=CC(=O)), 29.8 (CH$\underline{C}H_2CH_2CH_2$), 25.7 ($CHCH_2CH_2\underline{C}H_2$), 25.1 ($CHCH_2\underline{C}H_2CH_2$); **IR** (powder) ν_{max}/cm^{-1}: 2933, 2856 (C-H), 1720 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{25}O_6^+$) requires *m/z* 373.1646, found *m/z* 373.1646; **MP**: 34 – 36 °C.

5.9.2.5 Synthesis and characterisation of 386

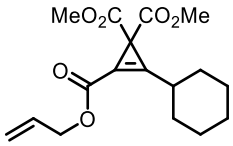
2-benzyl 1,1-dimethyl 3-butylcycloprop-2-ene-1,1,2-tricarboxylate (386)



Compound **386** was synthesised according to general procedure **X** by the addition of **433** (250 mg, 1.18 mmol, 1.00 eq) to benzyl chloroformate (**377**) (0.250 ml, 1.77 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (1st column: pentane/Et_2O = 8/2, 2nd column: pentane/Et_2O = 85/15 to 8/2) to provide the title compound (**386**) as a yellow oil in 46% yield (187 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.40 – 7.30 (m, 5H, Ar<u>H</u>), 5.28 (s, 2H, C<u>H</u>$_2$Ph), 3.72 (s, 6H, C(CO_2C<u>H</u>$_3$)$_2$), 2.69 (t, *J* = 7.5 Hz, 2H, C<u>H</u>$_2$$CH_2CH_2CH_3$), 1.67 (app-p, *J* = 7.5 Hz, 2H, CH_2C<u>H</u>$_2$$CH_2CH_3$), 1.41 (app-dq, *J* = 14.5, 7.5 Hz, 2H, CH_2CH_2C<u>H</u>$_2$$CH_3$), 0.90 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_2$C<u>H</u>$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 169.6 (C(<u>C</u>O_2CH_3)$_2$), 157.3 (<u>C</u>O_2Bn), 135.2 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 125.4 (<u>C</u>=CC(=O)), 98.6 (C=<u>C</u>C(=O)), 67.7 (<u>C</u>H_2Ph), 52.7 (C(CO_2<u>C</u>H_3)$_2$), 36.4 (<u>C</u>(CO_2CH_3)$_2$), 28.4 (CH_2<u>C</u>$H_2CH_2CH_3$), 25.0 (<u>C</u>$H_2CH_2CH_2CH_3$), 22.3 (CH_2CH_2<u>C</u>H_2CH_3), 13.7 ($CH_2CH_2CH_2$<u>C</u>H_3); **IR** (film) ν_{max}/cm^{-1}: 2956, 2874 (C-H), 1879, 1720 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}O_6^+$) requires *m/z* 347.1489, found *m/z* 347.1495.

5.9.2.6 Synthesis and characterisation of E39

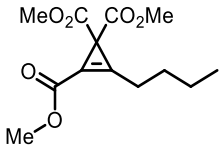
2-allyl 1,1-dimethyl 3-cyclohexylcycloprop-2-ene-1,1,2-tricarboxylate (E39)



Compound **E39** was synthesised according to general procedure **X** by the addition of **376** (200 mg, 0.84 mmol, 1.00 eq) to allyl chloroformate (0.130 ml, 1.26 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/acetone = 97/3 to 95/5) to provide the title compound (**E39**) as a colourless oil in 62% yield (168 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 5.93 (ddt, *J* = 17.0, 10.5, 5.5 Hz, 1H, C$\underline{H}$=CH_2), 5.35 (app-dq, *J* = 17.0, 1.5 Hz, 1H, one of C=C$\underline{H_A}H_B$), 5.27 (app-dq, *J* = 10.5, 1.5 Hz, 1H, one of C=C$\underline{H_A}H_B$), 4.74 (dt, *J* = 5.5, 1.5 Hz, 2H, C$\underline{H_2}$CH=CH_2), 3.73 (s, 6, C($CO_2C\underline{H_3}$)$_2$), 2.81 (tt, *J* = 10.0, 2.0 Hz, 1H, C$\underline{H}$C=CC(=O)), 1.99 – 1.90 (m, 2H, cyclohexyl ring), 1.73 (dq, *J* = 13.5, 4.5 Hz, 2H, cyclohexyl ring), 1.65 – 1.45 (m, 3H, cyclohexyl ring), 1.41 – 1.22 (m, 3H, cyclohexyl ring); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.7 (C($\underline{C}O_2CH_3$)$_2$), 157.1 ($\underline{C}$(=O)OCH_2CH), 131.4 ($\underline{C}$H=CH_2), 128.0 ($\underline{C}$=CC(=O)), 118.7 (CH=$\underline{C}H_2$), 97.6 (C=$\underline{C}$C(=O)), 66.4 ($\underline{C}H_2$CH=CH_2), 52.6 (C($CO_2\underline{C}H_3$)$_2$), 36.2 ($\underline{C}$(CO_2CH_3)$_2$), 35.1 ($\underline{C}$HC=CC(=O)), 29.8 (CH$\underline{C}H_2CH_2CH_2$), 25.7 ($CHCH_2CH_2\underline{C}H_2$), 25.1 ($CHCH_2\underline{C}H_2CH_2$); **IR** (film) ν_{max}/cm^{-1}: 2933, 2856 (C-H), 1721 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{22}NaO_6^+$) requires *m/z* 345.1309, found *m/z* 345.1305.

5.9.2.7 Synthesis and characterisation of E40

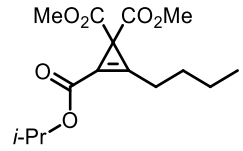
trimethyl 3-butylcycloprop-2-ene-1,1,2-tricarboxylate (E40)



Compound **E40** was synthesised according to general procedure **X** by the addition of **433** (250 mg, 1.18 mmol, 1.00 eq) to methyl chloroformate (0.140 ml, 1.77 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1 to 85/15) to provide the title compound (**E40**) as a colourless oil in 46% yield (146 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 3.84 (s, 3H, C=CC(=O)OC$\underline{H_3}$), 3.73 (s, 6H, C($CO_2C\underline{H_3}$)$_2$), 2.69 (t, *J* = 7.5 Hz, 2H, C$\underline{H_2}CH_2CH_2CH_3$), 1.73 – 1.63 (m, 1H, $CH_2C\underline{H_2}CH_2CH_3$), 1.48 – 1.37 (m, 2H, $CH_2CH_2C\underline{H_2}CH_3$), 0.93 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_2C\underline{H_3}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 169.6 (C($CO_2C\underline{H_3}$)$_2$), 157.9 (C=C$\underline{C}$(=O)), 125.3 ($\underline{C}$=CC(=O)), 98.5 (C=$\underline{C}$C(=O)), 52.9 (C=CC(=O)O$\underline{C}H_3$), 52.7 (C($CO_2\underline{C}H_3$)$_2$), 36.4 ($\underline{C}$(CO_2CH_3)$_2$), 28.4 ($CH_2\underline{C}H_2CH_2CH_3$), 24.9 ($\underline{C}H_2CH_2CH_2CH_3$), 22.3 ($CH_2CH_2\underline{C}H_2CH_3$), 13.7 ($CH_2CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2958, 2875 (C-H), 1721 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{19}O_6^+$) requires *m/z* 271.1176, found *m/z* 271.1175.

5.9.2.8 Synthesis and characterisation of E41

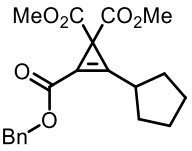
2-isobutyl 1,1-dimethyl 3-butylcycloprop-2-ene-1,1,2-tricarboxylate (E41)



Compound **E41** was synthesised according to general procedure **X** by the addition of **433** (250 mg, 1.18 mmol, 1.00 eq) to isobutyl chloroformate (0.230 ml, 1.77 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1 to 85/15) to provide the title compound (**E41**) as a colourless oil in 43% yield (159 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 4.02 (d, *J* = 6.5 Hz, 2H, $OC\underline{H}_2$), 3.73 (s, 6H, $C(CO_2C\underline{H}_3)_2$), 2.69 (t, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH_2CH_2CH_3$), 2.00 (hep, *J* = 13.5, 6.5 Hz, 1H, $C\underline{H}(CH_3)_2$), 1.74 – 1.65 (m, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 1.49 – 1.39 (m, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 0.96 – 0.90 (m, 9H, $CH_2CH_2CH_2C\underline{H}_3$ and $CH(C\underline{H}_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 169.5 ($C(\underline{C}O_2Me)_2$), 157.4 (C=C$\underline{C}$(=O)), 124.5 ($\underline{C}$=CC(=O)), 98.6 (C=$\underline{C}$C(=O)), 71.8 ($O\underline{C}H_2$), 52.5 ($C(CO_2\underline{C}H_3)_2$), 36.3 ($\underline{C}(CO_2CH_3)_2$), 28.3 ($CH_2\underline{C}H_2CH_2CH_3$), 27.7 ($\underline{C}H(CH_3)_2$), 24.8 ($\underline{C}H_2CH_2CH_2CH_3$), 22.1 ($CH_2CH_2\underline{C}H_2CH_3$), 18.9 ($CH(\underline{C}H_3)_2$), 13.6 ($CH_2CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2959, 2876 (C-H), 1719 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{24}NaO_6^+$) requires *m/z* 335.1465, found *m/z* 335.1461.

5.9.2.9 Synthesis and characterisation of E42

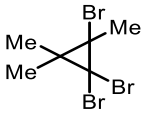
2-benzyl 1,1-dimethyl 3-cyclopentylcycloprop-2-ene-1,1,2-tricarboxylate (E42)



Compound **E42** was synthesised according to general procedure **X** by the addition of **E38** (250 mg, 1.11 mmol, 1.00 eq) to benzyl chloroformate (**377**) (285 mg, 1.67 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1 (use CH_2Cl_2 TLC to check the fractions)) to provide the title compound (**E42**) as a colourless oil in 22% yield (87 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.41 – 7.28 (m, 5H, Ar$\underline{H}$), 5.28 (s, 2H, C$\underline{H_2}$Ph), 3.72 (s, 6H, C($CO_2C\underline{H_3}$)$_2$), 3.19 (tt, *J* = 8.0, 6.5 Hz, 1H, C$\underline{H}$C=C), 2.01 – 1.91 (m, 2H, C$\underline{H_A}H_BCHC\underline{H_C}H_D$), 1.82 – 1.74 (m, 2H, $CH_A\underline{H_B}CHCH_C\underline{H_D}$), 1.74 – 1.66 (m, 2H, C$\underline{H_A}H_BCH_2CHCH_2C\underline{H_C}H_D$), 1.66 – 1.59 (m, 2H, $CH_A\underline{H_B}CH_2CHCH_2CH_C\underline{H_D}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 169.6 (C($\underline{C}O_2CH_3$)$_2$), 157.3 ($\underline{C}O_2$Bn), 135.3 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$H), 128.7 ($\underline{C}$=CC(=O)Bn), 128.5 (Ar$\underline{C}$H), 128.1 (Ar$\underline{C}$H), 97.3 (C=$\underline{C}$C(=O)Bn), 67.5 ($\underline{C}H_2$Ph), 52.6 (C($CO_2\underline{C}H_3$)$_2$), 36.7 ($\underline{C}$(CO_2Me)), 36.1 ($\underline{C}$HC=C), 31.1 ($\underline{C}H_2CH\underline{C}H_2$), 25.3 ($\underline{C}H_2CH_2CHCH_2\underline{C}H_2$); **IR** (film) ν_{max}/cm^{-1}:2954 (C-H), 1739, 1732 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{23}O_6^+$) requires *m/z* 359.1489, found *m/z* 359.1494.

5.9.2.10 Synthesis and characterisation of 361

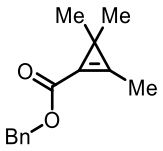
1,1,2-tribromo-2,3,3-trimethylcyclopropane (361)



Compound **361** was synthesised according to general procedure **XII** by addition of bromoform (11.3 ml, 129 mmol, 3.00 eq) to 2-bromo-3-methylbut-2-ene (5.00 ml, 43.1 mmol, 1.00 eq). The reaction was stirred at room temperature overnight. H_2O (50 ml) was added, the layers were separated, and the aqueous phase extracted with CH_2Cl_2 (2 x 50 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane) to provide the title compound (**361**) as a white solid in 19% yield (2.64 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 2.00 (s, 3H, C(Br)(C$\underline{H}_3$)), 1.51 (s, 3H, one of C(C$\underline{H}_3$)$_A$(CH$_3$)$_B$), 1.37 (s, 3H, one of C(CH$_3$)$_A$(C$\underline{H}_3$)$_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 51.8 ($\underline{C}Br_2$ or $\underline{C}$(Br)(CH$_3$)), 51.2 ($\underline{C}Br_2$ or $\underline{C}$(Br)(CH$_3$)), 33.4 ($\underline{C}(CH_3)_2$), 27.2 (one of C($\underline{C}$H$_3$)$_A$(CH$_3$)$_B$), 26.8 (C(Br)($\underline{C}$H$_3$)), 21.0 (one of C(CH$_3$)$_A$($\underline{C}$H$_3$)$_B$); **IR** (powder) ν_{max}/cm^{-1}: 2991, 2971, 2930, 2889 (C-H), 2161, 2016. Data are consistent with that published in the literature.[249]

5.9.2.11 Synthesis and characterisation of 399

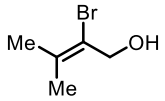
benzyl 2,3,3-trimethylcycloprop-1-ene-1-carboxylate (399)



Compound **399** was synthesised according to general procedure **XI** by the addition of tribromocyclopropane **361** (300 mg, 0.940 mmol, 1.00 eq) to benzyl chloroformate (**377**) (0.200 ml, 1.40 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 99/1) to provide the title compound (**399**) as a colourless oil in 51% yield (104 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.41 – 7.30 (m, 5H, Ar<u>H</u>), 5.23 (s, 2H, C<u>H</u>$_2$Ph), 2.24 (s, 3H, C<u>H</u>$_3$C=C), 1.22 (s, 6H, C(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.3 (<u>C</u>=O), 145.7 (CH_3<u>C</u>=C), 136.3 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 117.6 (CH_3C=<u>C</u>), 66.3 (<u>C</u>H$_2$Ph), 25.3 (C(<u>C</u>H$_3$)$_2$), 24.8 (<u>C</u>(CH$_3$)$_2$), 11.1 (<u>C</u>H$_3$C=C); **IR** (film) ν_{max}/cm^{-1}: 3382, 3324 (C-H), 1753 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}O_2^+$) requires *m/z* 217.1223, found *m/z* 217.1223.

5.9.2.12 Synthesis and characterisation of 402

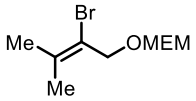
2-bromo-3-methylbut-2-en-1-ol (402)



According to a literature procedure,[250] bromine (15.4 ml, 305 mmol, 1.05 eq) was added dropwise to a stirred solution of 3-methyl-but-2-en-1-ol (**401**) (25.0 ml, 290 mmol, 1.00 eq) in CH_2Cl_2 (484 ml) at 0 °C over 2 h using a syringe pump. The solution was allowed to warm to room temperature overnight at which point DBU (68.6 ml, 459 mmol, 1.58 eq) was added. The solution was heated to reflux for 4 h. The reaction mixture was allowed too cool to room temperature and sat. aq. Sodium thiosulfate was added (200 ml). The phases were separated, and the aqueous layer was extracted with Et_2O (3 x 300 ml). The combined organic layers were washed with 1.0 M $HCl_{(aq)}$ (3 x 200 ml), sat. aq. $NaHCO_3$ (200 ml) and brine then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product (**402**) was taken on without further purification (31.5 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 4.36 (s, 2H, C$\underline{H_2}$OH), 1.97 (d, *J* = 3.5 Hz, 1H, O$\underline{H}$), 1.90 (s, 3H, C$\underline{H_3}$), 1.86 (s, 3H, C$\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 134.8 (one of $\underline{C}$=C), 121.2 (one of C=$\underline{C}$), 64.8 ($\underline{C}H_2OH$), 25.5 ($\underline{C}H_3$), 20.6 ($\underline{C}H_3$). Data are consistent with that published in the literature.[250]

5.9.2.13 Synthesis and characterisation of 403

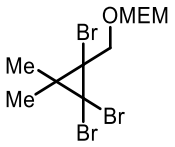
2-bromo-1-((2-methoxyethoxy)methoxy)-3-methylbut-2-ene (403)



DIPEA (41.5 ml, 238 mmol, 1.25 eq) was added to a stirred solution of 2-bromo-3-methylbut-2-en-1-ol (**402**) (31.5 g, 191 mmol, 1.00 eq) and MEMCl (32.7 ml, 286 mmol, 1.50 eq) in CH_2Cl_2 (636 ml) at 0 °C. The reaction was allowed to warm to room temperature overnight at which point H_2O was added (200 ml) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 300 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 8/2) to provide the title compound (**403**) as a yellow oil in 88% yield (42.9 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 4.74 (s, 2H, OC$\underline{H_2}$O), 4.41 – 4.35 (m, 2H, C=CC$\underline{H_2}$O), 3.79 – 3.68 (m, 2H, $CH_2OCH_2OC\underline{H_2}CH_2$), 3.59 – 3.54 (m, 2H, $CH_2OCH_2OCH_2C\underline{H_2}$), 3.39 (s, 3H, OC$\underline{H_3}$), 1.91 (s, 3H, one of C=C(C$\underline{H_3}$)$_A$(CH_3)$_B$), 1.87 (s, 3H, one of C=C(CH_3)$_A$(C$\underline{H_3}$)$_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 137.4 ($\underline{C}$=CBr), 116.8 (C=$\underline{C}$Br), 94.2 (O$\underline{C}H_2$O), 71.9 ($CH_2OCH_2OCH_2\underline{C}H_2$), 68.7 (C=C$\underline{C}H_2$O), 67.1 ($CH_2OCH_2O\underline{C}H_2CH_2$), 59.1 (O$\underline{C}H_3$), 25.6 (one of C=C($\underline{C}H_3$)$_A$($CH_3$)$_B$), 20.8 (one of C=C($CH_3$)$_A$($\underline{C}H_3$)$_B$); **IR** (film) ν_{max}/cm^{-1}: 1998, 2981 (C-H), 1655 (C=C); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($BrC_9H_{18}O_3^+$) requires *m/z* 253.0434, found *m/z* 253.0435.

5.9.2.14 Synthesis and characterisation of 404

1,1,2-tribromo-2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcyclopropane (404)

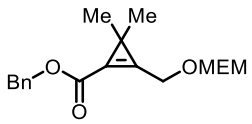


Compound **404** was synthesised according to general procedure **XII** by addition of bromoform (45.5 ml, 510 mmol, 3.00 eq) to **403** (42.9 g, 170 mmol, 1.00 eq). The reaction mixture was warmed to 50 °C and after 5 days more bromoform (45.5 ml, 510 mmol, 3.00 eq) and 50% aq. NaOH (42.5 ml) was added. The reaction was stirred for a further 5 days at which point H_2O (300 ml) was added, the layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 300 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (1st column: pentane/EtOAc = 8/2, 2nd column: pentane/EtOAc = 1/0 to 95/5 to 9/1 to 1/1) to provide the title compound (**404**) as a yellow oil in 84% yield (60.6 g). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 4.84 (d, *J* = 7.0 Hz, 1H, one of $OC\underline{H_A}H_BO$), 4.82 (d, *J* = 7.0 Hz, 1H, one of $OCH_A\underline{H_B}O$), 4.06 (d, *J* = 11.5 Hz, 1H, one of $C\underline{H_A}H_BCBr$), 4.02 (d, *J* = 11.5 Hz, 1H, one of $CH_A\underline{H_B}CBr$), 3.86 – 3.71 (m, 2H, $C\underline{H_2}CH_2OCH_3$), 3.58 – 3.55 (m, 2H, $CH_2C\underline{H_2}OCH_3$), 3.40 (s, 3H, $CH_2CH_2OC\underline{H_3}$), 1.52 (s, 3H, one of $C(C\underline{H_3})_A(CH_3)_B$), 1.45 (s, 3H, one of $C(CH_3)_A(C\underline{H_3})_B$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 95.8 ($O\underline{C}H_2O$), 73.2 ($O\underline{C}H_2CBr$), 71.8 ($\underline{C}H_2OCH_3$), 67.4 ($\underline{C}H_2CH_2OCH_3$), 59.2 ($O\underline{C}H_3$), 53.5 ($CH_2\underline{C}Br$ or $\underline{C}Br_2$), 48.12 ($CH_2\underline{C}Br$ or $\underline{C}Br_2$), 33.9 ($\underline{C}(CH_3)_3$), 27.0 (one of $C(\underline{C}H_3)_A(CH_3)_B$), 21.1 ($C(CH_3)_A(\underline{C}H_3)_B$); **IR** (film) ν_{max}/cm^{-1}: 2990, 2930, 2884 (C-H), 1456, 1370, 1043;

HRMS (MSS+) exact mass calculated for $[M+Na]^+$ ($C_{10}Br_3H_{17}Na^+$) requires *m/z* 444.8620, found *m/z* 444.8620.

5.9.2.15 Synthesis and characterisation of 405

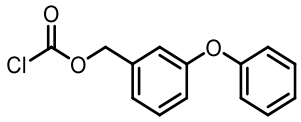
benzyl 2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcycloprop-1-ene-1-carboxylate (405)



Compound **405** was synthesised according to general procedure **XI** by the addition of tribromocyclopropane **404** (3.00 g, 7.11 mmol, 1.00 eq) to benzyl chloroformate (**377**) (1.53 ml, 10.7 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (1st column: pentane/EtOAc = 9/1, 2nd column: pentane/Et_2O = 9/1) to provide the title compound (**405**) as a colourless oil in 32% yield (739 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.44 – 7.29 (m, 5H, Ar<u>H</u>), 5.23 (s, 2H, C<u>H_2</u>Ph), 4.79 (s, 2H, OC<u>H_2</u>OCH_2C=C), 4.72 (s, 2H, OCH_2OC<u>H_2</u>C=C), 3.73 – 3.67 (m, 2H, C<u>H_2</u>OCH_2OCH_2C=C), 3.58 – 3.51 (m, 2H, C<u>H_2</u>$CH_2OCH_2OCH_2$C=C), 3.38 (s, 3H, OC<u>H_3</u>), 1.29 (s, 6H, C(C<u>H_3</u>)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 161.6 (<u>C</u>=O), 144.2 (<u>C</u>=CC(=O)), 136.0 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 119.2 (C=<u>C</u>C(=O)), 94.6 (<u>C</u>H_2C=C), 71.9 (<u>C</u>H_2OCH_3), 67.3 (<u>C</u>$H_2CH_2OCH_3$), 66.6 (<u>C</u>H_2Ph), 61.9 (O<u>C</u>H_2O), 59.2 (O<u>C</u>H_3), 26.7 (<u>C</u>(CH_3)$_2$), 25.7 (C(<u>C</u>H_3)$_2$); **IR** (film) ν_{max}/cm^{-1}: 3035, 2941, 2887 (C-H), 1703 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{25}O_5^+$) requires *m/z* 321.1697, found *m/z* 321.1697.

5.9.2.16 Synthesis and characterisation of 408

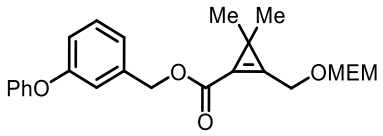
3-phenoxybenzyl carbonochloridate (408)



According to a literature procedure,[251] (3-phenoxyphenyl)methanol (**407**) (1.74 ml, 10.0 mmol, 1.00 eq) in toluene (20 ml) was added dropwise over 30 min to a stirred mixture of triphosgene (1.54 g, 5.20 mmol, 0.52 eq), Na_2CO_3 (1.06 g, 10.0 mmol, 1.00 eq) and DMF (0.210 ml) in toluene (20 ml) at 0 °C. The reaction was stirred overnight and allowed to reach room temperature at which point completion was observed by TLC (pentane/EtOAc = 7/3). The reaction mixture was filtered through a pad of celite and concentrated *in vacuo*. The crude reaction mixture was flushed through a pad of silica (pentane/Et_2O = 95/5) to provide the title compound (**408**) as a colourless oil in 85% yield (2.24 g) which was taken on without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.41 – 7.32 (m, 3H, Ar<u>H</u>), 7.18 – 7.09 (m, 2H, Ar<u>H</u>), 7.06 – 6.97 (m, 4H, Ar<u>H</u>), 5.26 (s, 2H).

5.9.2.17 Synthesis and characterisation of 410

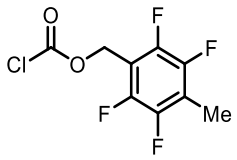
3-phenoxybenzyl 2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcycloprop-1-ene-1-carboxylate (410)



Compound **410** was synthesised according to general procedure **XI** by the addition of tribromocyclopropane **404** (3.00 g, 7.11 mmol, 1.00 eq) to **408** (2.24 g, 8.53 mmol, 1.20 eq). The crude product was purified by silica gel column chromatography (1st column: pentane/Et_2O = 8/2 to 6/4, 2nd column: pentane/Et_2O = 9/1 to 8/2, 3rd column: CH_2Cl_2/Et_2O = 1/0 to 95/5) to provide the title compound (**410**) as a colourless oil in 30% yield (879 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.39 – 7.28 (m, 3H, Ar<u>H</u>), 7.15 – 7.05 (m, 2H, Ar<u>H</u>), 7.05 – 6.98 (m, 3H, Ar<u>H</u>), 6.95 (m, 1H, Ar<u>H</u>), 5.20 (s, 2H, C<u>H_2</u>Ph), 4.79 (s, 2H, OC<u>H_2</u>OCH_2C=C), 4.71 (s, 2H, OCH_2OC<u>H_2</u>C=C), 3.75 – 3.67 (m, 2H, C<u>H_2</u>OCH_2OCH_2C=C), 3.58 – 3.49 (m, 2H, C<u>H_2</u>CH_2OCH_2OCH_2C=C), 3.38 (s, 3H, OC<u>H_3</u>), 1.27 (s, 6H, C(<u>C</u>H_3)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 161.4 (<u>C</u>=O), 157.7 (Ar<u>C</u>), 157.0 (Ar<u>C</u>), 144.5 (<u>C</u>=CC(=O)), 138.0 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 130.0 (Ar<u>C</u>H), 123.7 (Ar<u>C</u>H), 122.6 (Ar<u>C</u>H), 119.3 (C=<u>C</u>C(=O)), 119.1 (Ar<u>C</u>H), 118.4 (Ar<u>C</u>H), 118.1 (Ar<u>C</u>H), 94.6 (<u>C</u>H_2C=C), 71.9 (<u>C</u>H_2OCH_3), 67.3 (<u>C</u>H_2CH_2OCH_3), 66.1 (<u>C</u>H_2Ar), 61.9 (O<u>C</u>H_2O), 59.2 (O<u>C</u>H_3), 26.8 (<u>C</u>(CH_3)$_2$), 25.6 (C(<u>C</u>H_3)$_2$); **IR** (film) ν_{max}/cm^{-1}: 2942, 2887 (C-H), 1750 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{28}NaO_6^+$) requires *m/z* 435.1778, found *m/z* 435.1774.

5.9.2.18 Synthesis and characterisation of E43

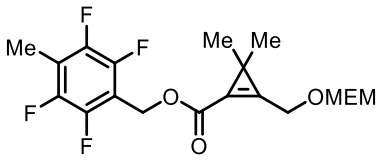
2,3,5,6-tetrafluoro-4-methylbenzyl carbonochloridate (E43)



According to a literature procedure,[251] (2,3,5,6-tetrafluoro-4-methylphenyl)methanol (1.94 ml, 10.0 mmol, 1.00 eq) in toluene (20 ml) was added dropwise over 30 min to a stirred mixture of triphosgene (1.54 g, 5.20 mmol, 0.52 eq), Na_2CO_3 (1.06 g, 10.0 mmol, 1.00 eq) and DMF (0.21 ml) in toluene (20 ml) at 0 °C. The reaction was stirred overnight and allowed to reach room temperature at which point completion was observed by TLC (pentane/EtOAc = 7/3). The reaction mixture was filtered through a pad of celite and concentrated *in vacuo*. The crude reaction mixture was flushed through a pad of silica (pentane/Et_2O = 95/5) to provide the title compound (**E43**) as a colourless oil in >99% yield (2.61 g) which was taken on without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 5.41 (t, J_{HF} = 1.5 Hz, 2H, C$\underline{H_2}$OC(=O)), 2.31 (t, J_{HF} = 2.0 Hz, 3H, C$\underline{H_3}$).

5.9.2.19 Synthesis and characterisation of E44

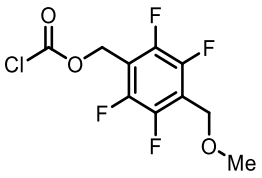
2,3,5,6-tetrafluoro-4-methylbenzyl 2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcycloprop-1-ene-1-carboxylate (E44)



Compound **E44** was synthesised according to general procedure **XI** by the addition of tribromocyclopropane **404** (1.00 g, 2.37 mmol, 1.00 eq) to **E43** (0.727 g, 2.84 mmol, 1.20 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1 to 8/2) to provide the title compound (**E44**) as a colourless oil in 41% yield (399 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.31 (t, J_{HF} = 1.5 Hz, 2H, CH_2Ar), 4.79 (s, 2H, CH_2C=CCO_2), 4.70 (s, 2H, OCH_2O), 3.74 – 3.69 (m, 2H, CH_2CH_2OCH_2O), 3.58 – 3.52 (m, 2H, C$H_2$$CH_2OCH_2$O), 3.38 (s, 3H, OC$H_3$), 2.29 (t, *J* = 2.0 Hz, 3H, CH_3Ar), 1.27 (s, 6H, C(CH_3)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.1 (C$O_2$$CH_2$), 146.5 – 145.8 (m, ArC), 145.3 (ArC), 144.1 (C=CCO_2), 118.7 (C=CCO_2), 117.5 (t, J_{CF} = 19.0 Hz, ArC), 111.46 (t, J_{CF} = 17.0 Hz, ArC), 94.5 (OCH_2O), 71.9 (C$H_2$$OCH_3$), 67.3 (C$H_2$$CH_2$$OCH_3$), 61.8 (C$H_2$C=C$CO_2$), 59.2 (OC$H_3$), 54.2 (d, J_{CF} = 3.5 Hz, CH_2Ph), 26.9 (CMe_2), 25.6 (C(CH_3)$_2$), 7.9 (CH_3Me); **^{19}F NMR** (471 MHz, $CDCl_3$) δ(ppm): -143.5 – -143.6 (m, 2 x ArCF), -144.18 – -144.30 (m, 2 x ArCF);); **IR** (film) ν_{max}/cm^{-1}: 2981, 2888 (C-H), 1832, 1712 (C=O), 1490; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}F_4H_{22}NaO_5^+$) requires *m/z* 429.1296, found *m/z* 429.1295.

5.9.2.20 Synthesis and characterisation of E45

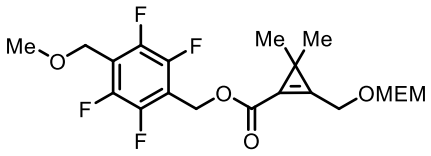
2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl carbonochloridate (E45)



According to a literature procedure,[251] (2,3,5,6-tetrafluoro-4-(methoxymethyl)phenyl)methanol (2.24 ml, 10.0 mmol, 1.00 eq) in toluene (20 ml) was added dropwise over 30 min to a stirred mixture of triphosgene (1.54 g, 5.20 mmol, 0.52 eq), Na_2CO_3 (1.06 g, 10.0 mmol, 1.00 eq) and DMF (0.21 ml) in toluene (20 ml) at 0 °C. The reaction was stirred overnight and allowed to reach room temperature at which point completion was observed by TLC (pentane/EtOAc = 7/3). The reaction mixture was filtered through a pad of celite and concentrated *in vacuo*. The crude reaction mixture was flushed through a pad of silica (pentane/Et_2O = 95/5) to provide the title compound (**E45**) as a colourless oil in >97% yield (2.78 g) which was taken on without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 5.43 (t, J_{HF} = 1.5 Hz, 3H, one of OC$\underline{H}_3$), 4.60 (t, J_{HF} = 2.0 Hz, 3H, one of OC$\underline{H}_3$), 3.41 (s, 4H, C$\underline{H}_2$OC(=O) and C$\underline{H}_2$OCH$_3$).

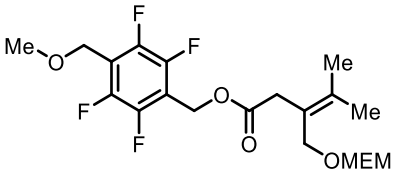
5.9.2.21 Synthesis and characterisation of E46

2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl 2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcycloprop-1-ene-1-carboxylate (E46)



Compound **E46** was synthesised according to general procedure **XI** by the addition of tribromocyclopropane **404** (1.00 g, 2.37 mmol, 1.00 eq) to **E45** (0.814 g, 2.84 mmol, 1.20 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 8/2 to 7/3) to provide the title compound (**E46**) as a colourless oil in 44% yield (451 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 5.33 (t, J_{HF} = 1.5 Hz, 2H, C$\underline{H_2}$Ar), 4.79 (s, 2H, OC$\underline{H_2}$O), 4.70 (s, 2H, $OCH_2O\underline{C}H_2$), 4.58 (t, J_{HF} = 2.0 Hz, 2H, ArC$\underline{H_2}OCH_3$), 3.74 – 3.68 (m, 2H, $CH_3OCH_2C\underline{H_2}O$), 3.57 – 3.52 (m, 2H, $CH_3OC\underline{H_2}CH_2O$), 3.41 (s, 3H, C$\underline{H_3}OCH_2$Ar), 3.38 (s, 3H, C$\underline{H_3}OCH_2CH_2O$), 1.27 (s, 6H, C(C$\underline{H_3}$)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 161.0 ($\underline{C}O_2CH_2$), 146.4 – 146.0 (m, Ar$\underline{C}$), 145.7 ($\underline{C}$=CCO_2), 144.5 – 144.1 (m, Ar$\underline{C}$), 118.6 (C=$\underline{C}CO_2$), 117.8 (t, J_{CF} = 18.0 Hz, Ar$\underline{C}$), 114.6 (t, J_{CF} = 17.0 Hz, Ar$\underline{C}$), 94.5 (O$\underline{C}H_2O$), 71.9 ($CH_3O\underline{C}H_2CH_2O$), 67.3 ($CH_3OCH_2\underline{C}H_2O$), 61.8 (C=C$\underline{C}H_2OCH_2O$), 61.6 (t, J_{CF} = 2.5 Hz, Ar$\underline{C}H_2OCH_3$), 59.1 ($\underline{C}H_3OCH_2CH_2O$), 58.7 ($ArCH_2O\underline{C}H_3$), 54.2 – 54.0 (m, $\underline{C}H_2$Ar), 26.9 ($\underline{C}$(CH_3)$_2$), 25.5 (C($\underline{C}H_3$)$_2$); **^{19}F NMR** (471 MHz, $CDCl_3$) δ(ppm): -142.6 – -142.7 (m, 2 x Ar$\underline{C}$F), -143.36 – -143.51 (m, 2 x Ar$\underline{C}$F); **IR** (film) ν_{max}/cm^{-1}: 2928, 2888 (C-H), 1832, 1712 (C=O), 1489; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}F_4H_{24}NaO_6^+$) requires *m/z* 459.1401, found *m/z* 459.1400.

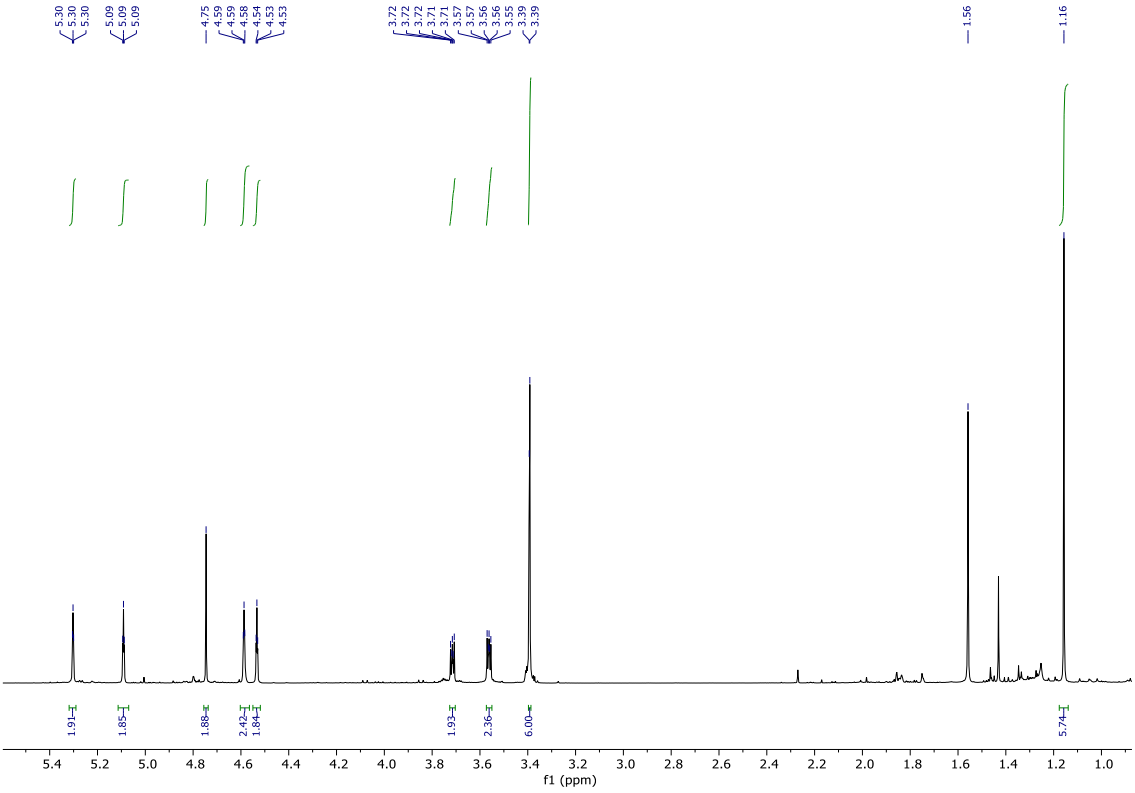
2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl 3-(((2-methoxyethoxy)methoxy)methyl)-4-methylpent-3-enoate (E47)



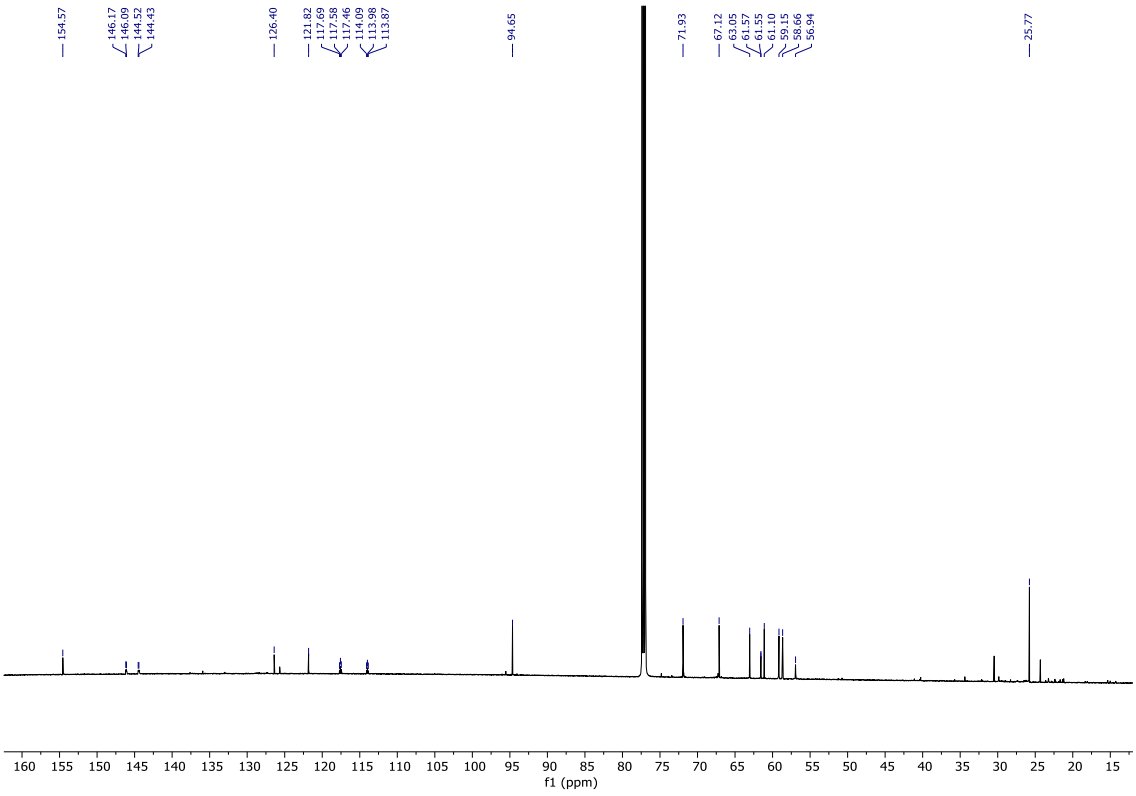
Compound **E47** is a side product in the synthesis of compound **E46** and is inseparable from **E46**. Compounds of a similar structure are found in many compounds synthesised according to general procedure **XI** and are generally inseparable from the desired product however only low levels are produced (generally 5-10% by NMR). The impurity appears to have little effect on the BIMP catalysed deconjugation and can be removed after conversion of the ACP to the cyclopropylaldehyde for example compound **413**. The NMR sprectra for compound **E47** has been included for future reference. **^{1}H NMR** (600 MHz, $CDCl_3$) δ(ppm): 5.30 (d, *J* = 1.5 Hz, 2H, $CO_2C\underline{H}_2Ar$), 5.09 (t, *J* = 2.0 Hz, 2H, $C\underline{H}_2CO_2CH_2Ar$), 4.75 (s, 2H, $OC\underline{H}_2O$), 4.59 (s, 2H, $ArC\underline{H}_2OCH_3$), 4.53 (t, *J* = 2.0 Hz, 2H, $C\underline{H}_2OMEM$), 3.74 – 3.66 (m, 2H, $C\underline{H}_2CH_2OCH_3$), 3.58 – 3.53 (m, 2H, $CH_2C\underline{H}_2OCH_3$), 3.39 (d, *J* = 2.0 Hz, 6H, $CH_2CH_2OC\underline{H}_3$ and $ArCH_2OC\underline{H}_3$), 1.16 (s, 6H, $C=C(C\underline{H}_3)_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 154.6 ($\underline{C}$=O), 146.1 (d, *J* = 13.5 Hz, Ar$\underline{C}$F), 144.5 (d, *J* = 13.5 Hz, Ar$\underline{C}$F), 126.4 ($\underline{C}$=C$(CH_3)_2$ or C=$\underline{C}(CH_3)_2$), 121.8 ($\underline{C}$=C$(CH_3)_2$ or C=$\underline{C}(CH_3)_2$), 117.6 (t, *J* = 18.0 Hz, Ar$\underline{C}$C), 114.0 (t, *J* = 17.0 Hz, Ar$\underline{C}$C), 94.7 ($O\underline{C}H_2O$), 71.9 ($CH_2\underline{C}H_2OCH_3$), 67.1 ($\underline{C}H_2CH_2OCH_3$), 63.1 ($\underline{C}H_2C$(=O)), 61.6 ($Ar\underline{C}H_2OCH_3$), 61.1 ($\underline{C}H_2OMEM$), 59.2 ($CH_2CH_2O\underline{C}H_3$), 58.7 ($ArCH_2O\underline{C}H_3$), 56.9 ($CO_2\underline{C}H_2$), 25.8 (C=$\underline{C}(CH_3)_2$).

*Full data has not yet been obtained for compound **E47**, this is a proposed structure.

^{1}H NMR (600 MHz, $CDCl_3$) of compound **E47**

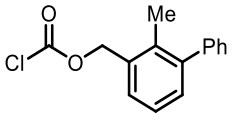


^{13}C NMR (151 MHz, $CDCl_3$) of compound **E47**



5.9.2.22 Synthesis and characterisation of E48

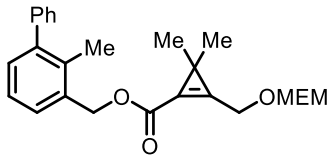
(2-methyl-[1,1'-biphenyl]-3-yl)methyl carbonochloridate (E48)



According to a literature procedure,[251] (2-methyl-[1,1'-biphenyl]-3-yl)methanol (1.98 ml, 10.0 mmol, 1.00 eq) in toluene (20 ml) was added dropwise over 30 min to a stirred mixture of triphosgene (1.54 g, 5.20 mmol, 0.52 eq), Na_2CO_3 (1.06 g, 10.0 mmol, 1.00 eq) and DMF (0.21 ml) in toluene (20 ml) at 0 °C. The reaction was stirred overnight and allowed to reach room temperature at which point completion was observed by TLC (pentane/EtOAc = 7/3). The reaction mixture was filtered through a pad of celite and concentrated *in vacuo*. The crude reaction mixture was flushed through a pad of silica (pentane/Et_2O = 95/5) to provide the title compound (**E48**) as a colourless oil in >98% yield (2.56 g) which was taken on without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.46 – 7.40 (m, 2H, Ar<u>H</u>), 7.40 – 7.33 (m, 2H, Ar<u>H</u>), 7.33 – 7.22 (m, 4H, Ar<u>H</u>), 5.42 (s, 2H, C<u>H</u>$_2$), 2.26 (s, 3H, C<u>H</u>$_3$).

5.9.2.23 Synthesis and characterisation of E49

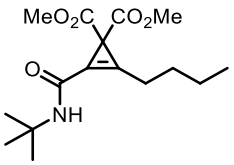
(2-methyl-[1,1'-biphenyl]-3-yl)methyl 2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcycloprop-1-ene-1-carboxylate (E49)



Compound **E49** was synthesised according to general procedure **XI** by the addition of tribromocyclopropane **404** (1.00 g, 2.37 mmol, 1.00 eq) to **E48** (0.740 g, 2.84 mmol, 1.20 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**E49**) as a colourless oil in 35% yield (343 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.44 – 7.33 (m, 4H, ArC<u>H</u>), 7.32 – 7.27 (m, 2H, ArC<u>H</u>), 7.26 – 7.18 (m, 2H, ArC<u>H</u>), 5.31 (s, 2H, C<u>H$_2$</u>Ar), 4.80 (s, 2H, OC<u>H$_2$</u>O), 4.72 (s, 2H, $OCH_2O\underline{C}H_2C{=}C$), 3.73 – 3.68 (m, 2H, $CH_3OCH_2C\underline{H_2}O$), 3.56 – 3.51 (m, 2H, $CH_3O\underline{CH_2}CH_2O$), 3.38 (s, 3H, $\underline{CH_3}OCH_2CH_2O$), 2.23 (s, 3H, ArC<u>H$_3$</u>), 1.30 (s, 6H, $C(\underline{CH_3})_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 161.6 ($\underline{C}O_2CH_2$), 144.2 ($\underline{C}{=}CCO_2$), 143.0 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 134.6 (Ar<u>C</u>), 134.5 (Ar<u>C</u>), 130.4 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 119.2 ($C{=}\underline{C}CO_2$), 94.6 ($O\underline{C}H_2O$), 71.9 ($CH_3O\underline{C}H_2CH_2O$), 67.3 ($CH_3OCH_2\underline{C}H_2O$), 65.6 (Ar<u>C</u>H$_2$), 61.9 ($C{=}C\underline{C}H_2OCH_2O$), 59.2 ($\underline{C}H_3OCH_2CH_2O$), 26.7 ($\underline{C}(CH_3)_2$), 25.7 ($C(\underline{C}H_3)_2$), 16.3 (Ar<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 2970, 2887 (C-H), 1832, 1703 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{25}H_{30}NaO_5^+$) requires *m/z* 433.1985, found *m/z* 433.1985.

5.9.2.24 Synthesis and characterisation of 420

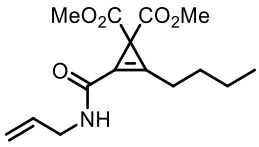
dimethyl 2-butyl-3-(tert-butylcarbamoyl)cycloprop-2-ene-1,1-dicarboxylate (420)



Compound **420** was synthesised according to general procedure **X** by the addition of **433** (500 mg, 2.40 mmol, 1.00 eq) to *tert*-butyl isocyanate (0.410 ml, 3.60 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (1st column: pentane/EtOAc = 8/2, 2nd column: pentane/EtOAc = 85/15) to provide the title compound (**420**) as an amorphous yellow solid in 50% yield (377 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 6.28 (s, 1H, N<u>H</u>), 3.72 (s, 6H, $C(CO_2C\underline{H}_3)_2$), 2.60 (t, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH_2CH_2CH_3$), 1.68 – 1.56 (m, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 1.44 – 1.37 (m, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 1.36 (s, 9H, $C(C\underline{H}_3)_3$), 0.89 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_2C\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 170.6 ($C(\underline{C}O_2CH_3)_2$), 155.9 (<u>C</u>(=O)NH), 119.2 (<u>C</u>=CC(=O)N), 101.6 (C=<u>C</u>C(=O)N), 52.6 ($C(CO_2\underline{C}H_3)_2$), 52.1 ($N\underline{C}(CH_3)_3$), 37.3 ($\underline{C}(CO_2CH_3)_2$), 28.7 ($NC(\underline{C}H_3)_3$), 28.5 ($CH_2\underline{C}H_2CH_2CH_3$), 24.5 ($\underline{C}H_2CH_2CH_2CH_3$), 22.2 ($CH_2CH_2\underline{C}H_2CH_3$), 13.7 ($CH_2CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3237 (N-H), 2962, 2875 (C-H), 2210, 1732 (C=O ester), 1651 (C=O amide); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{25}NaO_5^+$) requires *m/z* 334.1625, found *m/z* 334.1624.

5.9.2.25 Synthesis and characterisation of 421

dimethyl 2-(allylcarbamoyl)-3-butylcycloprop-2-ene-1,1-dicarboxylate (421)

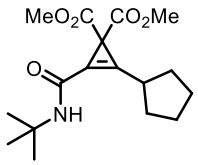


Compound **421** was synthesised according to general procedure **X** by the addition of **433** (250 mg, 1.18 mmol, 1.00 eq) to allyl isocyanate (0.156 ml, 1.77 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 1/1) to provide the title compound (**421**) as a yellow oil in 10% yield (37.2 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 6.50 (bs, 1H, N<u>H</u>), 5.85 (ddt, *J* = 17.0, 10.5, 5.5 Hz, 1H, C<u>H</u>=CH_2), 5.24 – 5.19 (m, one of C=C<u>H_A</u>H_B), 5.17 (app-dq, *J* = 10.5, 1.5 Hz, 1H, one of C=CH_A<u>H_B</u>), 3.97 (tt, *J* = 5.5, 1.5 Hz, 2H, NHC<u>H_2</u>), 3.75 (s, 6H, C(CO_2C<u>H_3</u>)$_2$), 2.67 (t, *J* = 7.5 Hz, 2H, C<u>H_2</u>$CH_2CH_2CH_3$), 1.67 (tt, *J* = 7.5, 6.5 Hz, 2H, CH_2C<u>H_2</u>CH_2CH_3), 1.47 – 1.36 (m, 2H, CH_2CH_2C<u>H_2</u>CH_3), 0.93 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_2C$<u>H_3</u>); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.5 (C(<u>C</u>O_2Me)$_2$), 156.5 (<u>C</u>(=O)NH), 133.3 (<u>C</u>H=CH_2), 120.6 (<u>C</u>=CC(=O)), 117.0 (CH=<u>C</u>H_2), 100.6 (C=<u>C</u>C(=O)), 52.8 (C(CO_2<u>C</u>H_3)$_2$), 42.0 (<u>C</u>H_2NH), 37.0 (<u>C</u>(CO_2CH_3)$_2$), 28.5 (CH_2<u>C</u>$H_2CH_2CH_3$), 24.7 (<u>C</u>$H_2CH_2CH_2CH_3$), 22.3 (CH_2CH_2<u>C</u>H_2CH_3), 13.7 ($CH_2CH_2CH_2$<u>C</u>H_3); **IR** (film) ν_{max}/cm^{-1}: 3342 (N-H), 2957, 2874 (C-H), 1729, 1657 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}NO_5^+$) requires *m/z* 296.1492, found *m/z* 296.1494.

5.9.2.26 Synthesis and characterisation of 422

dimethyl 2-(tert-butylcarbamoyl)-3-cyclopentylcycloprop-2-ene-1,1-dicarboxylate

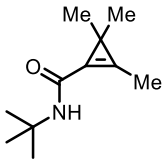
(422)



Compound **422** was synthesised according to general procedure **X** by the addition of **E38** (250 mg, 1.11 mmol, 1.00 eq) to *tert*-butyl isocyanate (0.190 ml, 1.67 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 8/2 to 7/3) to provide the title compound (**422**) as a yellow solid in 74% yield (266 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 6.26 (s, 1H, N$\underline{H}$), 3.74 (s, 6H, C($CO_2C\underline{H_3}$)$_2$), 3.13 (tt, *J* = 8.0, 6.5 Hz, 1H, C$\underline{H}$C=C), 2.01 – 1.89 (m, 2H, C$\underline{H_A}H_BCHC\underline{H_C}H_D$), 1.82 – 1.67 (m, 3H, C$\underline{H_A}H_BCH_2CHCH_2C\underline{H_C}H_D$ and $CH_A\underline{H_B}CHCH_CH_D$), 1.67 – 1.54 (m, 3H, $CH_A\underline{H_B}CH_2CHCH_2CH_C\underline{H_D}$ and $CH_AH_BCHC\underline{H_C}H_D$), 1.39 (s, 9H, C($C\underline{H_3}$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 170.7 ($\underline{C}O_2Me$), 156.0 ($\underline{C}ONH$), 122.9 ($CH\underline{C}$=C), 100.5 (CHC=$\underline{C}$), 52.7 (C($CO_2\underline{C}H_3$)$_2$), 52.2 (N$\underline{C}$(CH_3)$_3$), 37.7 ($\underline{C}$(CO_2CH_3)$_2$), 35.8 ($\underline{C}$HC=C), 31.2 ($CH_2\underline{C}H_2CH\underline{C}H_2CH_2$), 28.8 (NC($\underline{C}H_3$)$_3$), 25.4 ($\underline{C}H_2CH_2CHCH_2\underline{C}H_2$); **IR** (film) ν_{max}/cm^{-1}: 1736 (C=O ester), 1667 (C=O amide); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{25}NNaO_5^+$) requires *m/z* 346.1625, found *m/z* 346.1624.

5.9.2.27 Synthesis and characterisation of 423

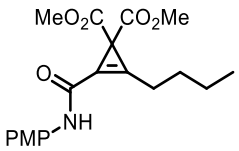
N-(tert-butyl)-2,3,3-trimethylcycloprop-1-ene-1-carboxamide (423)



Compound **423** was synthesised according to general procedure **XI** by the addition of tribromocyclopropane **361** (300 mg, 0.940 mmol, 1.00 eq) to *tert*-butyl isocyanate (0.160 ml, 1.41 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/EtOAc = 7/3) to provide the title compound (**423**) as a white solid in 34% yield (57.5 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 5.34 (bs, 1H, N<u>H</u>), 2.18 (s, 3H, C<u>H</u>$_3$C=C), 1.40 (s, 9H, C(C<u>H</u>$_3$)$_3$), 1.20 (s, 6H, C(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 161.0 (<u>C</u>=O), 137.8 (<u>C</u>=CC(=O)), 120.2 (C=<u>C</u>C(=O)), 51.6 (<u>C</u>(CH$_3$)$_3$), 29.1 (C(<u>C</u>H$_3$)), 25.1 (C(<u>C</u>H$_3$)$_2$), 23.7 (<u>C</u>(CH$_3$)$_2$), 10.4 (<u>C</u>H$_3$C=C); **IR** (film) ν_{max}/cm^{-1}: 3222, 3046 (C-H), 1624 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{20}NO^+$) requires *m/z* 182.1539, found *m/z* 182.1541; **MP**: 92 °C (sublimation).

5.9.2.28 Synthesis and characterisation of 424

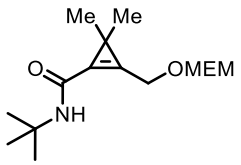
dimethyl 2-butyl-3-((4-methoxyphenyl)carbamoyl)cycloprop-2-ene-1,1-dicarboxylate (424)



Compound **424** was synthesised according to general procedure **X** by the addition of **433** (250 mg, 1.18 mmol, 1.00 eq) to 4-Methoxyphenyl isocyanate (0.230 ml, 1.77 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/EtOAc = 7/3) and the isolated product was washed with Et_2O to provide the title compound (**424**) as a white solid in 48% yield (206 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 8.31 (s, 1H, N<u>H</u>), 7.55 – 7.46 (m, 2H, Ar<u>H</u>), 6.92 – 6.84 (m, 2H, Ar<u>H</u>), 3.80 (s, 3H, ArOC<u>H</u>$_3$), 3.78 (s, 6H, C(CO_2C<u>H</u>$_3$)$_2$), 2.70 (t, *J* = 7.5 Hz, 2H, C<u>H</u>$_2$$CH_2CH_2CH_3$), 1.70 (tt, *J* = 7.5, 6.5 Hz, 2H, CH_2C<u>H</u>$_2$$CH_2CH_3$), 1.51 – 1.38 (m, 2H, CH_2CH_2C<u>H</u>$_2$$CH_3$), 0.94 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_2C$<u>H</u>$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 170.7 (C(<u>C</u>O_2Me)$_2$), 157.0 (Ar<u>C</u>), 154.4 (<u>C</u>(=O)NH), 130.4 (Ar<u>C</u>), 121.5 (Ar<u>C</u>H), 121.1 (<u>C</u>=CC(=O)NH), 114.4 (Ar<u>C</u>H), 101.4 (C=<u>C</u>C(=O)NH), 55.6 (ArO<u>C</u>H$_3$), 52.9 (C(CO_2<u>C</u>H$_3$)$_2$), 37.5 (<u>C</u>(CO_2CH_3)$_2$), 28.5 (CH_2<u>C</u>$H_2CH_2CH_3$), 24.8 (<u>C</u>$H_2CH_2CH_2CH_3$), 22.3 (CH_2CH_2<u>C</u>H_2CH_3), 13.7 ($CH_2CH_2CH_2$<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3314 (N-H), 2981, 2886 (C-H), 1745 (C=O ester), 1653 (C=O amide); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{23}NNaO_6^+$) requires *m/z* 384.1418, found *m/z* 384.1416; **MP**: 116 – 118 °C.

5.9.2.29 Synthesis and characterisation of 425

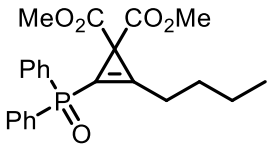
N-(tert-butyl)-2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcycloprop-1-ene-1-carboxamide (425)



Compound **425** was synthesised according to general procedure **XI** by the addition of tribromocyclopropane **404** (300 mg, 0.710 mmol, 1.00 eq) to *tert*-butyl isocyanate (0.122 ml, 1.07 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/EtOAC = 7/3) to provide the title compound (**425**) as a colourless oil in 33% yield (67.0 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 6.25 (bs, 1H, N<u>H</u>), 4.82 (s, 2H, C<u>H$_2$</u>C=C), 4.65 (s, 2H, C<u>H$_2$</u>OCH$_2$C=C), 3.81 – 3.71 (m, 2H, CH$_3$OCH$_2$C<u>H$_2$</u>OCH$_2$O), 3.62 – 3.53 (m, 2H, CH$_3$OC<u>H$_2$</u>CH$_2$OCH$_2$O), 3.39 (s, 3H, C<u>H$_3$</u>OCH$_2$CH$_2$OCH$_2$O), 1.38 (s, 9H, C(C<u>H$_3$</u>)$_3$), 1.29 (s, 6H, C(C<u>H$_3$</u>)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 159.6 (<u>C</u>=O), 135.8 (<u>C</u>=CC(=O)), 124.3 (C=<u>C</u>C(=O)), 95.3 (<u>C</u>H$_2$OCH$_2$OCH$_2$CH$_2$OCH$_3$), 71.86 (CH$_2$O<u>C</u>H$_2$OCH$_2$CH$_2$OCH$_3$), 67.51 (CH$_2$OCH$_2$OCH$_2$<u>C</u>H$_2$OCH$_3$), 63.7 (CH$_2$OCH$_2$O<u>C</u>H$_2$CH$_2$OCH$_3$), 59.2 (CH$_2$OCH$_2$OCH$_2$CH$_2$O<u>C</u>H$_3$), 51.5 (<u>C</u>(CH$_3$)$_3$), 29.0 C(<u>C</u>H$_3$)$_3$, 27.2 (<u>C</u>(CH$_3$)$_3$), 25.9 (C(<u>C</u>H$_3$)$_3$); **IR** (film) ν_{max}/cm^{-1}: 3364 (N-H), 2970, 2887 (C-H), 1830, 1650 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{28}O_4N^+$) requires *m/z* 286.2013, found *m/z* 286.2010.

5.9.2.30 Synthesis and characterisation of 435

dimethyl 2-butyl-3-(diphenylphosphoryl)cycloprop-2-ene-1,1-dicarboxylate (435)

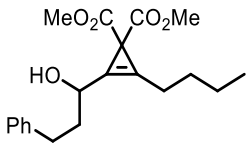


Compound **435** was synthesised according to general procedure **X** by the addition of **433** (250 mg, 1.18 mmol, 1.00 eq) to chlorodiphenylphosphine (**437**) (196 µl, 1.06 mmol, 0.900 eq). The crude product was purified by silica gel column chromatography (pentane/EtOAc = 6/4) to provide the title compound (**435**) as a yellow solid in 33% yield (161 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 4H, Ar<u>H</u>), 7.59 – 7.54 (m, 2H, Ar<u>H</u>), 7.52 – 7.45 (m, 4H, Ar<u>H</u>), 3.52 (s, 6H, $C(CO_2C\underline{H}_3)_2$), 2.70 (td, *J* = 7.5, 1.0 Hz, 2H, $C\underline{H}_2CH_2CH_2CH_3$), 1.56 (p, *J* = 7.5 Hz, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 1.38 – 1.29 (m, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 0.85 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_2C\underline{H}_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 169.7 (d, J_{CP} = 2.5 Hz, $C(\underline{C}O_2Me)_2$), 132.6 (d, J_{CP} = 3.0 Hz, Ar<u>C</u>H), 132.0 (d, J_{CP} = 10.0 Hz, Ar<u>C</u>), 131.5 (d, J_{CP} = 11.0 Hz, Ar<u>C</u>H), 130.59 (d, J_{CP} = 60.0 Hz, $CH_2\underline{C}$=CP(=O)), 128.7 (d, *J* = 13.0 Hz, Ar<u>C</u>H), 100.3 (d, J_{CP} = 119.5 Hz, $CH_2C=\underline{C}P(=O)$), 52.4 ($C(CO_2\underline{C}H_3)_2$), 37.2 ($\underline{C}(CO_2CH_3)_2$), 28.5 ($CH_2\underline{C}H_2CH_2CH_3$), 25.1 ($\underline{C}H_2CH_2CH_2CH_3$), 22.4 ($CH_2CH_2\underline{C}H_2CH_3$), 13.7 ($CH_2CH_2CH_2\underline{C}H_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ(ppm): 15.6 (<u>P</u>=O); **IR** (film) ν_{max}/cm^{-1}: 2967, 2953, 2932, 2871 (C-H), 1840, 1742, 1711; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{26}O_5P^+$) requires *m/z* 413.1512, found *m/z* 413.1516; **MP**: 49-50 °C.

5.9.2.31 Synthesis and characterisation of 438

dimethyl 2-butyl-3-(1-hydroxy-3-phenylpropyl)cycloprop-2-ene-1,1-dicarboxylate

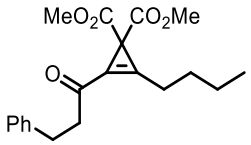
(438)



Compound **438** was synthesised according to general procedure **X** by the addition of **433** (408 mg, 1.92 mmol, 1.00 eq) to 3-phenylpropanal (**437**) (0.760 ml, 5.76 mmol, 3.00 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 6/4) to provide the title compound (**438**) as a colourless oil in 86% yield (570 mg). **^{1}H NMR** (600 MHz, $CDCl_3$) δ(ppm): 7.32 – 7.27 (m, 2H, Ar<u>H</u>), 7.24 – 7.17 (m, 3H, Ar<u>H</u>), 4.67 (t, *J* = 6.5 Hz, 1H, C<u>H</u>OH), 3.73 (s, 3H, one of $C(CO_2C\underline{H}_3)_A(CO_2CH_3)_B$), 3.73 (s, 3H, one of $C(CO_2CH_3)_A(CO_2C\underline{H}_3)_B$), 2.87 (s, 1H, O<u>H</u>), 2.75 (bt, *J* = 7.5 Hz, 2H, C<u>H</u>$_2$Ph), 2.52 (ddt, *J* = 9.5, 7.5, 1.0 Hz, 2H, C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 2.10 – 1.95 (m, 2H, C<u>H</u>$_2$CH$_2$Ph), 1.62 – 1.53 (m, 2H, CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 1.41 – 1.32 (m, 2H, CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 0.91 (t, *J* = 7.5 Hz, 3H, CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 172.4 (one of $C(\underline{C}O_2CH_3)_A(CO_2CH_3)_B$), 172.3 (one of $C(CO_2CH_3)_A(\underline{C}O_2CH_3)_B$), 141.4 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 108.7 (<u>C</u>=CCOH), 106.5 (C=<u>C</u>COH), 65.1 (<u>C</u>OH), 52.67 – 52.38 (m, $C(CO_2\underline{C}H_3)_2$), 37.3 (<u>C</u>H$_2$CHOH), 35.6 ($\underline{C}(CO_2CH_3)_2$), 31.4 (<u>C</u>H$_2$Ph), 28.8 (CH$_2$<u>C</u>H$_2CH_2CH_3$), 23.6 (<u>C</u>H$_2CH_2CH_2CH_3$), 22.4 (CH$_2CH_2$<u>C</u>H$_2CH_3$), 13.8 (CH$_2CH_2CH_2$<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 3468 (O-H), 2954, 2872 (C-H), 1726 (C=O), 1278, 1242, 1063; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{26}NaO_5^+$) requires *m/z* 369.1672, found *m/z* 369.1669.

5.9.2.32 Synthesis and characterisation of 439

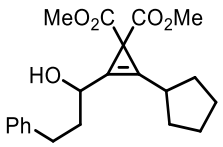
dimethyl 2-butyl-3-(3-phenylpropanoyl)cycloprop-2-ene-1,1-dicarboxylate (439)



Compound **439** was synthesised according to general procedure **XIII** by oxidation of compound **438** (535 mg, 1.54 mmol, 1.00 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**439**) as a colourless oil in 89% yield (472 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.27 – 7.18 (m, 2H, Ar<u>H</u>), 7.18 – 7.07 (m, 3H, Ar<u>H</u>), 3.65 (s, 6H, C($CO_2C\underline{H}_3$)$_2$), 3.04 – 2.95 (m, 2H, C<u>H</u>$_2$CH$_2$Ph), 2.95 – 2.86 (m, 2H, CH$_2$C<u>H</u>$_2$Ph), 2.61 (t, *J* = 7.5 Hz, 2H, C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 1.67 – 1.53 (m, 2H, CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 1.40 – 1.26 (m, 3H, CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 0.85 (t, *J* = 7.5 Hz, 3H, CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 188.8 (C=C<u>C</u>(=O)), 169.8 (C(<u>C</u>O_2CH_3)$_2$), 140.5 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 126.5 (Ar<u>C</u>H), 123.2 (<u>C</u>=CC(=O)), 103.6 (C=<u>C</u>C(=O)), 52.8 (C($CO_2\underline{C}H_3$)$_2$), 45.3 (<u>C</u>H$_2$CH$_2$Ph), 36.6 (<u>C</u>(CO_2CH_3)$_2$), 29.7 (CH$_2$<u>C</u>H$_2$Ph), 28.6 (CH$_2$<u>C</u>H$_2$CH$_2$CH$_3$), 25.2 (<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 22.5 (CH$_2$CH$_2$<u>C</u>H$_2$CH$_3$), 13.8 (CH$_2$CH$_2$CH$_2$<u>C</u>H$_3$); **IR** (film) ν_{max}/cm^{-1}: 2956, 2873 (C-H), 1857, 1727, 1686 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{25}O_5^+$) requires *m/z* 345.1697, found *m/z* 345.1695.

5.9.2.33 Synthesis and characterisation of E50

dimethyl 2-cyclopentyl-3-(1-hydroxy-3-phenylpropyl)cycloprop-2-ene-1,1-dicarboxylate (E50)

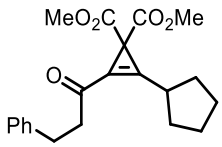


Compound **E50** was synthesised according to general procedure **X** by the addition of **E38** (250 mg, 1.11 mmol, 1.00 eq) to 3-phenylpropanal (**437**) (0.220 ml, 1.67 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 1:1) to provide the title compound (**E50**) as a colourless oil in 64% yield (254 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.33 – 7.26 (m, 2H, Ar<u>H</u>), 7.22 – 7.15 (m, 3H, Ar<u>H</u>), 4.67 (t, *J* = 6.5 Hz, 1H, C<u>H</u>OH), 3.73 (s, 3H, one of $C(CO_2C\underline{H}_3)_A(CO_2CH_3)_B$), 3.73 (s, 3H, one of $C(CO_2CH_3)_A(CO_2C\underline{H}_3)_B$), 3.08 – 2.97 (m, 1H, C<u>H</u>C=CCHOH), 2.91 (bs, 1H, O<u>H</u>), 2.75 (t, *J* = 8.0 Hz, 2H, $CH_2C\underline{H}_2Ph$), 2.11 – 1.96 (m, 2H, $C\underline{H}_2CH_2Ph$), 1.96 – 1.86 (m, 2H, $C\underline{H}_2$ - cyclopentane ring), 1.74 – 1.66 (m, 2H, $C\underline{H}_2$ - cyclopentane ring), 1.62 (m, 4H, 2 x $C\underline{H}_2$ - cyclopentane ring); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 172.5 (one of $C(\underline{C}O_2CH_3)_A(CO_2CH_3)_B$), 172.4 (one of $C(CO_2CH_3)_A(\underline{C}O_2CH_3)_B$), 141.5 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 112.1 (CH<u>C</u>=CCHOH), 105.3 (CHC=<u>C</u>CHOH), 65.0 (<u>C</u>HOH), 52.6 (one of $C(CO_2\underline{C}H_3)_A(CO_2CH_3)_B$), 52.5 (one of $C(CO_2CH_3)_A(CO_2\underline{C}H_3)_B$), 37.4 ($\underline{C}H_2CH_2Ph$), 35.9 ($\underline{C}(CO_2Me)_2$), 35.0 (<u>C</u>HC=CCHOH), 31.4 ($CH_2\underline{C}H_2Ph$), 31.2 ($\underline{C}H_2$ – cyclopentane ring), 25.2 (CH_2 - cyclopentane ring); **IR** (film) ν_{max}/cm^{-1}: Unlabelled broad peak around 3400 (O-H), 1731 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{26}NaO_5^+$) requires *m/z* 381.1672, found *m/z* 381.1671.

5.9.2.34 Synthesis and characterisation of E51

dimethyl 2-cyclopentyl-3-(3-phenylpropanoyl)cycloprop-2-ene-1,1-dicarboxylate

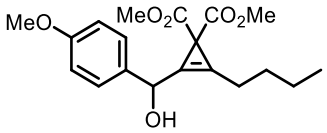
(E51)



Compound **E51** was synthesised according to general procedure **XIII** by oxidation of compound **E50** (239 mg, 0.670 mmol, 1.00 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 7/3) to provide the title compound (**E51**) as a colourless oil in 75% yield (178 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.33 – 7.27 (m, 2H, Ar<u>H</u>), 7.20 (tt, *J* = 8.0, 1.5 Hz, 3H, Ar<u>H</u>), 3.72 (s, 6H, C($CO_2C\underline{H_3}$)$_2$), 3.23 – 3.13 (m, 1H, C<u>H</u>C=CC(=O)), 3.05 (ddd, *J* = 8.5, 6.5, 1.5 Hz, 2H, C<u>H_2</u>CH_2Ph), 2.98 (ddd, *J* = 8.5, 6.5, 1.5 Hz, 2H, $CH_2C\underline{H_2}$Ph), 2.03 – 1.93 (m, 2H two of C<u>H_A</u>$H_B$$CH_2CH_2C$<u>$H_C$</u>$H_D$), 1.78 – 1.60 (m, 6H, two of $CH_A\underline{H_B}CH_2CH_2CH_C\underline{H_D}$ and $CH_2C\underline{H_2}C\underline{H_2}CH_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 188.7 (C=C<u>C</u>(=O)), 169.8 (C(<u>C</u>O_2Me)$_2$), 140.5 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 126.4 (<u>C</u>=CC(=O)), 126.3 (Ar<u>C</u>H), 102.2 (C=<u>C</u>C(=O)), 52.7 (C($CO_2\underline{C}H_3$)$_2$), 45.2 (<u>C</u>H_2CH_2Ph), 36.7 (<u>C</u>(CO_2CH_3)$_2$), 36.3 (<u>C</u>HC=CC(=O)), 31.3 (C=CCH<u>C</u>H_2CH_2), 29.6 ($CH_2\underline{C}H_2$Ph), 25.4 (C=CCH$CH_2\underline{C}H_2$); **IR** (film) ν_{max}/cm^{-1}: 3028, 2953, 2872 (C-H), 1726 (C=O ester), 1685 (C=O ketone); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}NaO_5^+$) requires *m/z* 379.1516, found *m/z* 379.1511.

5.9.2.35 Synthesis and characterisation of E52

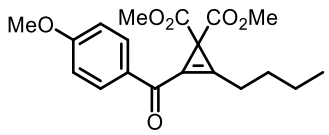
dimethyl 2-butyl-3-(hydroxy(4-methoxyphenyl)methyl)cycloprop-2-ene-1,1-dicarboxylate (E52)



Compound **E52** was synthesised according to general procedure **X** by the addition of **433** (250 mg, 1.18 mmol, 1.00 eq) to 4-anisaldehyde (0.220 ml, 1.77 mmol, 1.50 eq). The crude product was purified by silica gel column chromatography (pentane/Et_2O = 6/4) to provide the title compound (**E52**) as a colourless oil in 80% yield (329 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.36 – 7.29 (m, 2H, Ar<u>H</u>), 6.93 – 6.85 (m, 2H, Ar<u>H</u>), 5.65 (d, *J* = 4.5 Hz, 1H, C<u>H</u>OH), 3.80 (s, 3H, ArOC<u>H</u>$_3$), 3.70 (s, 3H, one of C($CO_2C\underline{H}_3$)$_A$(CO_2CH_3)$_B$), 3.62 (s, 3H, one of C(CO_2CH_3)$_A$($CO_2C\underline{H}_3$)$_B$), 3.43 (d, *J* = 5.0 Hz, 1H, O<u>H</u>), 2.44 (app-tt, *J* = 7.0, 1.0 Hz, 2H, C<u>H</u>$_2$C=C), 1.44 (tt, *J* = 7.5, 6.5 Hz, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 1.32 – 1.22 (m, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 0.84 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_2C\underline{H}_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 172.2 (one of C($\underline{C}O_2Me$)$_A$(CO_2Me)$_B$), 172.2 (one of C(CO_2Me)$_A$($\underline{C}O_2Me$)$_B$), 159.7 (Ar<u>C</u>), 132.2 (Ar<u>C</u>), 127.8 (Ar<u>C</u>H), 114.0 (Ar<u>C</u>H), 108.7 ($CH_2\underline{C}$=C), 106.7 (CH_2C=<u>C</u>), 67.4 (<u>C</u>HOH), 55.5 (ArO<u>C</u>H$_3$), 52.6 (one of C($CO_2\underline{C}H_3$)$_A$(CO_2CH_3)$_B$), 52.4 (one of C(CO_2CH_3)$_A$($CO_2\underline{C}H_3$)$_B$), 36.2 (<u>C</u>(CO_2Me)$_2$), 28.6 ($CH_2\underline{C}H_2CH_2CH_3$), 23.5 (<u>C</u>$H_2CH_2CH_2CH_3$), 22.3 ($CH_2CH_2\underline{C}H_2CH_3$), 13.7 ($CH_2CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: Unlabelled broad peak around 3500 (O-H), 1731 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{24}NaO_6^+$) requires *m/z* 371.1465, found *m/z* 371.1466.

5.9.2.36 Synthesis and characterisation of E53

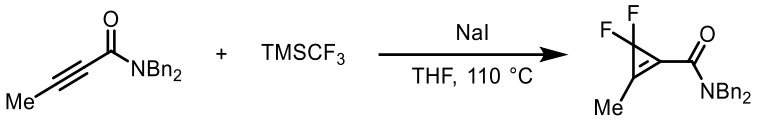
dimethyl 2-butyl-3-(4-methoxybenzoyl)cycloprop-2-ene-1,1-dicarboxylate (E53)



Compound **E53** was synthesised according to general procedure **XIII** by oxidation of compound **E52** (314 mg, 0.9 mmol, 1.00 eq). The crude product was purified by silica gel column chromatography (1st column: pentane/Et_2O = 7/3 to 6/4, 2nd column: pentane/EtOAc = 9/1 to 8/2, 3rd column: toluene/EtOAc = 95/5) to provide the title compound (**E53**) as a colourless oil in 52% yield (162 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 8.08 – 8.01 (m, 2H, Ar<u>H</u>), 7.02 – 6.95 (m, 2H, Ar<u>H</u>), 3.90 (s, 3H, ArO<u>C</u>H_3), 3.74 (s, 6H, C($CO_2C\underline{H}_3$)$_2$), 2.83 (t, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH_2CH_2CH_3$), 1.69 (tt, *J* = 7.5, 6.5 Hz, 2H, $CH_2C\underline{H}_2CH_2CH_3$), 1.48 – 1.37 (m, 2H, $CH_2CH_2C\underline{H}_2CH_3$), 0.93 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_2C\underline{H}_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 178.7 (Ar<u>C</u>=O), 170.0 (C(<u>C</u>O_2Me)$_2$), 164.6 (Ar<u>C</u>), 131.7 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>), 121.6 (<u>C</u>=CC(=O)), 114.32(Ar<u>C</u>H), 102.9 (C=<u>C</u>C(=O)), 55.8 (PhO<u>C</u>H_3), 52.7 (C($CO_2\underline{C}H_3$)$_2$), 36.3 (<u>C</u>(CO_2CH_3)$_2$), 28.4 ($CH_2\underline{C}H_2CH_2CH_3$), 25.2 (<u>C</u>$H_2CH_2CH_2CH_3$), 22.5 ($CH_2CH_2CH_2CH_3$), 13.8 ($CH_2CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2956, 2873 (C-H), 1725 (C=O ester), 1644 (C=O ketone); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}O_6^+$) requires *m/z* 347.1493, found *m/z* 347.1489.

5.9.2.37 Synthesis and characterisation of 448

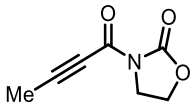
N,N-dibenzyl-3,3-difluoro-2-methylcycloprop-1-ene-1-carboxamide (448)



According to a literature procedure,[189] N,N-dibenzylbut-2-ynamide (**447**) (263 mg, 1.00 mmol, 1.00 eq), $TMSCF_3$ (296 µl, 2.00 mmol, 2.00 eq) and sodium iodide (330 mg, 2.20 mmol, 2.20 eq) were heated to 110 °C in THF (0.3 M) in a microwave vial behind a blast shield. The reaction was stirred overnight at which point water (10 ml) was added. The aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/EtOAc = 95/5) to provide the title compound (**448**) as a colourless oil in 16% yield (51.2 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.41 – 7.27 (m, 6H, Ar<u>H</u>), 7.27 – 7.22 (m, 2H, Ar<u>H</u>), 7.22 – 7.15 (m, 2H, Ar<u>H</u>), 4.56 (s, 2H, C<u>H</u>$_2$), 4.49 (s, 2H, C<u>H</u>$_2$), 2.30 (t, J_{HF} = 2.0 Hz, 3H, C<u>H</u>$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 157.6 (<u>C</u>=O), 137.1 (t, *J* = 10.0 Hz, <u>C</u>=CC(=O)), 135.9 (Ar<u>C</u>), 135.3 (Ar<u>C</u>), 129.0 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 122.70 (t, *J* = 12.0 Hz, C=<u>C</u>C(=O)), 100.3 (t, *J* = 276.2 Hz, <u>C</u>F$_2$), 50.4 (<u>C</u>H$_2$), 47.0 (<u>C</u>H$_2$), 8.9 (<u>C</u>H$_3$); **^{19}F NMR** (565 MHz, $CDCl_3$) δ(ppm): -102.6 (C<u>F</u>$_2$); **IR** (film) ν_{max}/cm^{-1}: 3032, 2927 (C-H), 1791, 1644 (C=O); **HRMS** (MSS+) exact mass calculated for $[M+H]^+$ ($C_{19}F_2H_{18}^+$) requires *m/z* 314.1351, found *m/z* 314.1352.

5.9.2.38 Synthesis and characterisation of E54

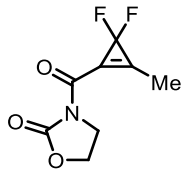
3-(3,3-difluoro-2-methylcycloprop-1-ene-1-carbonyl)oxazolidin-2-one (E54)



According to a literature procedure,[252] pivaloyl chloride (1.52 g, 12.3 mmol, 1.03 eq) and NEt_3 (1.73 ml, 12.4 mmol, 1.04 eq) were added to a stirred solution of butynoic acid (1.00 g, 11.9 mmol, 1.00 eq) in THF (80 ml) at −78 °C. The reaction was stirred at −78 °C for 15 min at which point it was warmed to 0 °C and stirred for a further 45 min. The reaction mixture was then cooled to −78 °C. In a separate flask *n*-BuLi (2.5 M in hexanes) (4.90 ml, 12.3 mmol, 1.03 eq) was added to a solution of 2-oxazolidinone (1.04 g, 11.9 mmol, 1.00 eq) in THF (34 ml) at −78 °C. The reaction was stirred for 15 min at which point it was transferred to the butynoic acid reaction mixture by cannular. The reaction was warmed to room temperature and stirred for a further 16 h. The reaction was quenched with sat. aq. NH_4Cl (50 ml) and the aqueous phase was extracted with EtOAc (3 x 50 ml). The combined organic extracts were washed with brine then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (pentane/EtOAc = 8/2) to provide the title compound (**E54**) as an off-white solid in 40% yield (0.722 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 4.41 (dd, *J* = 8.5, 7.5 Hz, 2H, C$\underline{H_2}$N), 4.04 (dd, *J* = 8.5, 7.5 Hz, 2H, C$\underline{H_2}$O), 2.11 (s, 3H, C$\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 152.2 (<u>C</u>=O), 150.9 (<u>C</u>=O), 95.1 ($CH_3\underline{C}$≡C), 72.6 (CH_3C≡<u>C</u>), 62.0 (<u>C</u>H_2N), 42.4 (<u>C</u>H_2O), 4.6 (CH_3); **IR** (powder) ν_{max}/cm^{-1}: 2991, 2888 (C-H), 1783, 1657 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_7H_8NO_3^+$) requires *m/z* 154.0499, found *m/z* 154.0498; **MP**: 80 – 82 °C.

5.9.2.39 Synthesis and characterisation of 449

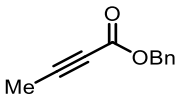
3-(3,3-difluoro-2-methylcycloprop-1-ene-1-carbonyl)oxazolidin-2-one (449)



According to a literature procedure,[189] TFDA (**357**) (970 µl, 4.90 mmol, 3.00 eq) was added dropwise over 3 h to a solution of 3-(but-2-ynoyl)oxazolidin-2-one (250 mg, 1.63 mmol, 1.00 eq) and NaF (6.80 mg, 0.163 mmol, 0.100 eq) in diglyme (0.33 ml) at 120 °C. After the addition the reaction was stirred for 1 h at which point the crude reaction mixture was cooled and purified by silica gel column chromatography (1st column: pentane/EtOAc = 8/2 to 7/3, 2nd column: CH_2Cl_2) to provide the title compound (**449**) as a yellow solid in 37% yield (124 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 4.51 (dd, *J* = 8.5, 7.5 Hz, 2H, C$\underline{H_2}$N), 4.12 (dd, *J* = 8.5, 7.5 Hz, 2H, C$\underline{H_2}$O), 2.36 (t, J_{HF} = 2.0 Hz, 3H, C$\underline{H_3}$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 154.6 (C=C$\underline{C}$(=O)), 152.0 (O$\underline{C}$(=O)N), 140.35 (t, J_{CF} = 10.0 Hz, $\underline{C}$=CC(=O)), 120.5 (t, J_{CF} = 13.0 Hz, C=$\underline{C}$C(=O)), 100.1 (t, J_{CF} = 275.5 Hz, $\underline{C}F_2$), 62.7 ($\underline{C}H_2$N), 42.3 ($\underline{C}H_2$O), 10.0 (CH_3); **^{19}F NMR** (377 MHz, $CDCl_3$) δ(ppm): -105.8 ($C\underline{F_2}$); **IR** (powder) ν_{max}/cm^{-1}: 2991 (C-H), 1799, 1669 (C=O); **HRMS** (MSS+) exact mass calculated for $[M+Na]^+$ ($C_8F_2H_7NNaO_3^+$) requires *m/z* 226.0286, found *m/z* 226.0288; **MP**: 84 – 85 °C.

5.9.2.40 Synthesis and characterisation of 356

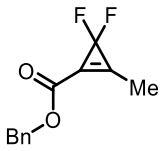
benzyl but-2-ynoate (356)



To a stirred solution of butynoic acid (2.00 g, 23.8 mmol, 1.00 eq) and benzyl alcohol (2.47 ml, 23.8 mmol, 1.00 eq) in CH_2Cl_2 (231 ml) at 0 °C was added DMAP (896 mg, 7.30 mmol, 0.0600 eq) followed by DCC (4.91 g, 23.8 mmol, 1.00 eq). The reaction was stirred overnight and allowed to reach room temperature. The mixture was filtered through a plug of celite and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the crude product (**356**) as a colourless oil in 67% yield (2.76 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 5H, Ar<u>H</u>), 5.18 (s, 2H, C<u>H</u>$_2$Ph), 1.98 (s, 3H, C<u>H</u>$_3$). Data are consistent with that published in the literature.[189]

5.9.2.41 Synthesis and characterisation of 358

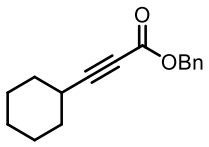
benzyl 3,3-difluoro-2-methylcycloprop-1-ene-1-carboxylate (358)



According to a literature procedure,[189] TFDA (**357**) (3.40 ml, 17.2 mmol, 6.00 eq) was added dropwise over 3 h to a solution of benzyl but-2-ynoate (**356**) (500 mg, 2.87 mmol, 1.00 eq) and NaF (12.2 mg, 0.290 mmol, 0.100 eq) in diglyme (0.57 ml) at 120 °C. After the addition the reaction was stirred for 1 h at which point the crude reaction mixture was cooled and purified by silica gel column chromatography (pentane/Et_2O = 95/5) to provide the title compound (**358**) as a colourless oil in 66% yield (426 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.45 – 7.32 (m, 5H, Ar<u>H</u>), 5.30 (s, 2H, C<u>H_2</u>Ph), 2.30 (t, J_{HF} = 2.0 Hz, 3H, C<u>H_3</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 156.5 (<u>C</u>=O), 140.1 (<u>C</u>=CC(=O)), 134.7 (Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 121.3 (C=<u>C</u>C(=O)), 99.9 (t, *J* = 275.5 Hz, <u>C</u>F_2), 67.9 (<u>C</u>H_2), 9.5 (<u>C</u>H_3); **^{19}F NMR** (377 MHz, $CDCl_3$) δ(ppm): -106.3 (m, C<u>F_2</u>). Data are consistent with that published in the literature.[189]

5.9.2.42 Synthesis and characterisation of E55

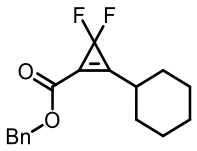
benzyl 3-cyclohexylpropiolate (E55)



According to a literature procedure,[253] *n*-BuLi (2.5 M in hexanes) (7.35 ml, 18.4 mmol 1.20 eq) was added dropwise to a solution of cyclohexyl acetylene (2.00 ml, 15.3 mmol, 1.00 eq) in THF (40 ml) at −78 °C over 30 min. The reaction was stirred for a further 30 min at which point benzyl chloroformate (**377**) (2.62 ml, 18.4 mmol, 1.20 eq) was added dropwise over 45 min at which point the temperature was raised to 0 °C for 15 min. The reaction was quenched with sat. aq. NH_4Cl (50 ml) and the aqueous phase was extracted with Et_2O (3 x 50 ml). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 98/2 to 95/5) to provide the title compound (**E55**) as a colourless oil in 93% yield (3.45 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.52 – 7.32 (m, 5H, Ar<u>H</u>), 5.21 (s, 2H, C<u>H</u>$_2$Ph), 2.53 (tt, *J* = 9.0, 2.0 Hz, 1H, C<u>H</u>C≡C), 1.91 – 1.80 (m, 2H, cyclohexane ring), 1.73 (m, 2H, cyclohexane ring), 1.53 (m, 3H, cyclohexane ring), 1.42 – 1.28 (m, 3H, cyclohexane ring). Data are consistent with that published in the literature.[254]

5.9.2.43 Synthesis and characterisation of 350

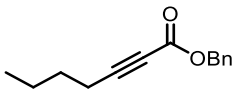
benzyl 2-cyclohexyl-3,3-difluorocycloprop-1-ene-1-carboxylate (350)



According to a literature procedure,[189] TFDA (**357**) (1.70 ml, 8.64 mmol, 6.00 eq) was added dropwise over 1 h to a solution of benzyl 3-cyclohexylpropiolate (**E55**) (350 mg, 1.44 mmol, 1.00 eq) and NaF (6.00 mg, 0.140 mmol, 0.100 eq) in diglyme (0.30 ml) at 120 °C. After the addition the reaction was stirred for 1 h at which point the crude reaction mixture was cooled and purified by silica gel column chromatography (pentane/Et_2O = 97/3) to provide the title compound (**350**) as a colourless oil in 74% yield (312 mg).**^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.13 – 7.07 (m, 2H, Ar$\underline{H}$), 7.07 – 6.97 (m, 3H, Ar$\underline{H}$), 4.90 (s, 2H, C$\underline{H_2}$Ph), 2.24 – 2.11 (m, 1H, C$\underline{H}$C=C), 1.60 – 1.49 (m, 2H, C$\underline{H_A}H_B$CHC$\underline{H_C}H_D$), 1.44 – 1.15 (m, 6H, $CH_A\underline{H_B}$CHC$H_C\underline{H_D}$, C$\underline{H_A}H_B$CH$_2$CHCH$_2$C$\underline{H_C}H_D$ and CHCH$_2$CH$_2$C$\underline{H_2}$), 1.05 – 0.87 (m, 2H, $CH_A\underline{H_B}$CH$_2$CHCH$_2$C$H_C\underline{H_D}$); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 156.4 (C$\underline{}$=O), 147.6 (C$\underline{}$=CC(=O)), 135.3 (ArC$\underline{}$), 128.8 (ArC$\underline{}$H), 128.7 (ArC$\underline{}$H), 128.7 (ArC$\underline{}$H), 119.9 (C=C$\underline{}$C(=O)), 103.78 – 97.90 (t, J_{CF} = 275.5 Hz, C$\underline{}F_2$), 67.6 (C$\underline{}$H$_2$Ph), 34.8 (C$\underline{}$HC=C), 29.9 (C$\underline{}$H$_2$CH), 25.6 (CHCH$_2$CH$_2$C$\underline{}$H$_2$), 24.9 (CHCH$_2$C$\underline{}$H$_2$CH$_2$); **^{19}F NMR** (377 MHz, Benzene-d_6) δ(ppm): -104.70 (d, J = 2.0 Hz, C$\underline{F_2}$); **IR** (film) ν_{max}/cm^{-1}: 3036, 2933, 2857 (C-H), 1789, 1723 (C=O).

5.9.2.44 Synthesis and characterisation of E56

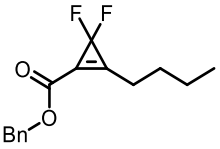
benzyl hept-2-ynoate (E56)



According to a literature procedure,[253] *n*-BuLi (2.5 M in hexanes) (7.35 ml, 18.4 mmol 1.20 eq) was added dropwise to a solution of hex-1-yne (1.76 ml, 15.3 mmol, 1.00 eq) in THF (40 ml) at −78 °C over 30 min. The reaction was stirred for a further 30 min at which point benzyl chloroformate (**377**) (2.62 ml, 18.4 mmol, 1.20 eq) was added dropwise over 45 min. The reaction was quenched with sat. aq. NH_4Cl (50 ml) and the aqueous phase was extracted with Et_2O (3 x 50 ml). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 98/2 to 95/5) to provide the title compound (**E56**) as a colourless oil in 95% yield (3.14 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.43 – 7.30 (m, 5H, Ar<u>H</u>), 5.19 (s, 2H, C<u>H$_2$</u>Ph), 2.33 (t, *J* = 7.0 Hz, 2H, C<u>H$_2$</u>C≡C), 1.62 – 1.49 (m, 2H, $CH_2C\underline{H_2}CH_2CH_3$), 1.49 – 1.35 (m, 2H, $CH_2CH_2C\underline{H_2}CH_3$), 0.91 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_2C\underline{H_3}$). Data are consistent with that published in the literature.[253]

5.9.2.45 Synthesis and characterisation of 451

benzyl 2-butyl-3,3-difluorocycloprop-1-ene-1-carboxylate (451)

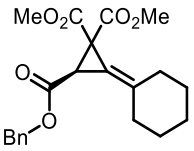


According to a literature procedure,[189] TFDA (**357**) (3.40 ml, 17.2 mmol, 6.00 eq) was added dropwise over 1 h to a solution of benzyl hept-2-ynoate (**E56**) (621 mg, 2.87 mmol, 1.00 eq) and NaF (12.0 mg, 0.290 mmol, 0.100 eq) in diglyme (0.57 ml) at 120 °C. After the addition the reaction was stirred for 1 h at which point the crude reaction mixture was cooled and purified by silica gel column chromatography (pentane/Et_2O = 99/1) to provide the title compound (**451**) as a colourless oil in 55% yield (416 mg). **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.13 – 6.98 (m, 4H, Ar<u>H</u>), 4.89 (s, 2H, C<u>H_2</u>Ph), 1.92 (tt, J = 7.5, 2.0 Hz, 2H, C<u>H_2</u>$CH_2CH_2CH_3$), 1.27 – 1.16 (m, 2H, CH_2C<u>H_2</u>CH_2CH_3), 1.06 – 0.95 (m, 2H, CH_2CH_2C<u>H_2</u>CH_3), 0.64 (t, J = 7.5 Hz, 3H, C<u>H_3</u>); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 156.4 (<u>C</u>=O), 144.5 (t, J_{CF} = 10.0 Hz, <u>C</u>=CC(=O)), 135.2 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 120.9 (t, J_{CF} = 12.5 Hz, C=<u>C</u>C(=O)), 102.13 (t, J_{CF} = 275.5 Hz, <u>C</u>F_2), 67.7 (<u>C</u>H_2Ph), 28.3 (CH_2<u>C</u>$H_2CH_2CH_3$), 24.1 (<u>C</u>$H_2CH_2CH_2CH_3$), 22.2 (CH_2CH_2<u>C</u>H_2CH_3), 13.48 (s, $CH_2CH_2CH_2$<u>C</u>H_3). Missing Ar<u>C</u>H is beneath the solvent peak; **^{19}F NMR** (377 MHz, Benzene-d_6) δ(ppm): -105.3 (C<u>F_2</u>); **IR** (film) ν_{max}/cm^{-1}: 3038, 2961, 2935, 2875 (C-H), 1794, 1724 (C=O).

5.9.3 Synthesis and characterisation of products obtained in the enantioselective deconjugation of cyclopropenes

5.9.3.1 Synthesis and characterisation of 379

2-benzyl 1,1-dimethyl (R)-3-cyclohexylidenecyclopropane-1,1,2-tricarboxylate (379)

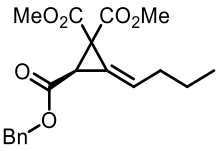


The title compound was prepared according to general procedure **XIV** from 2-benzyl 1,1-dimethyl 3-cyclohexylcycloprop-2-ene-1,1,2-tricarboxylate (**378**) (18.6 mg, 0.0500 mmol, 1.00 eq) with catalyst **124c**. After 4 h the crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**379**) as a colourless oil in 99% yield (18.4 mg) and 97% ee. [determined by HPLC chiralpak OG, hexane/isopropanol = 98/2, 1 ml/min, λ = 220 nm, t(minor) = 14.04 min, t(major) = 17.93 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.41 – 7.28 (m, 5H, Ar$\underline{H}$), 5.14 (d, *J* = 12.5 Hz, 1H, one of C$\underline{H}_A$$H_B$Ph), 5.10 (d, *J* = 12.5 Hz, 1H, one of C$H_A$$\underline{H}_B$Ph), 3.74 (s, 3H, one of C($CO_2C\underline{H}_3$)$_A$(CO_2CH_3)$_B$), 3.60 (s, 3H, one of C(CO_2CH_3)$_A$($CO_2C\underline{H}_3$)$_B$), 3.32 – 3.26 (bm, 1H, C$\underline{H}$C(=O)), 2.49 (dt, *J* = 12.0, 5.5 Hz, 1H, one of C=CC$\underline{H}_A$$H_B$$CH_2CH_2CH_2CH_C$$H_D$), 2.25 (qdd, *J* = 19.5, 17.5, 10.0, 4.5 Hz, 3H, C=CC$H_A$$\underline{H}_B$$CH_2CH_2CH_2C\underline{H}_C\underline{H}_D$), 1.71 – 1.46 (m, 6H, C=C$CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 168.1 ($\underline{C}O_2$Bn), 167.9 (one of C($\underline{C}O_2CH_3$)$_A$(CO_2CH_3)$_B$), 165.8 (one of C(CO_2CH_3)$_A$($\underline{C}O_2CH_3$)$_B$), 136.6 ($\underline{C}$=CCHCO$_2$Bn), 135.6 (Ar$\underline{C}$), 128.67 (Ar$\underline{C}$H) 128.5 (Ar$\underline{C}$H), 128.4 (Ar$\underline{C}$H), 111.6 (C=$\underline{C}$CHCO$_2$Bn), 67.2 ($\underline{C}H_2$Ph), 53.3 (one of C($CO_2C\underline{H}_3$)$_A$(CO_2CH_3)$_B$), 52.9 (one of C(CO_2CH_3)$_A$($CO_2C\underline{H}_3$)$_B$), 38.9 ($\underline{C}$(CO_2Me)$_2$), 33.4 (C=C$\underline{C}H_2CH_2CH_2CH_2CH_2$), 33.4

(C=C$CH_2CH_2CH_2CH_2\underline{C}H_2$), 30.5 ($\underline{C}HCO_2Bn$), 27.5 (C=C$CH_2\underline{C}H_2CH_2\underline{C}H_2CH_2$), 26.2 (C=C$CH_2CH_2\underline{C}H_2CH_2CH_2$); **IR** (film) ν_{max}/cm^{-1}: 3033, 2934, 2854 (C-H), 1734 (C=O), 1435, 1250; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{25}O_6^+$) requires *m/z* 373.1646, found *m/z* 373.1644; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –59.63 (*c* 0.35, $CHCl_3$).

5.9.3.2 Synthesis and characterisation of 387

2-benzyl 1,1-dimethyl (R,Z)-3-butylidenecyclopropane-1,1,2-tricarboxylate (387)

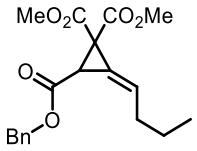


The title compound was prepared according to general procedure **XIV** from 2-benzyl 1,1-dimethyl 3-butylcycloprop-2-ene-1,1,2-tricarboxylate (**386**) (34.6 mg, 0.100 mmol, 1.00 eq) with catalyst **124c**. After 30 min the reaction was quenched with sat. aq. NH_4Cl (5 ml) and extracted with Et_2O (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* providing the crude compound in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**387**) as a colourless solid in 97% yield (32.5 mg), 95% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 210 nm, t(minor) = 7.31 min, t(major) = 10.12 min]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H, Ar<u>H</u>), 6.10 (td, *J* = 7.5, 2.0 Hz, 1H, $CH_2C\underline{H}$=C), 5.14 (d, *J* = 12.5 Hz, 1H, one of $C\underline{H}_AH_BPh$), 5.10 (d, *J* = 12.5 Hz, 1H, one of $CH_A\underline{H}_BPh$), 3.75 (s, 3H, one of $(CO_2C\underline{H}_3)_A(CO_2CH_3)_B$), 3.61 (s, 3H, one of $(CO_2CH_3)_A(CO_2C\underline{H}_3)_B$), 3.30 (app-q, *J* = 2.0 Hz, 1H, C<u>H</u>CO_2Bn), 2.41 – 2.24 (m, 2H, CHC<u>H</u>$_2$), 1.50 (h, *J* = 7.5 Hz, 2H, $CHCH_2C\underline{H}_2$), 0.90 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.8 (<u>C</u>O_2Bn), 167.4 (one of $(\underline{C}O_2CH_3)_A(CO_2CH_3)_B$), 165.3 (one of $(CO_2CH_3)_A(\underline{C}O_2CH_3)_B$), 135.4 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H) (one Ar<u>C</u>H is hidden), 124.8 ($CH_2\underline{C}H$=C), 119.8 (CH_2CH=<u>C</u>), 67.4 (<u>C</u>H_2Ph), 53.4 (one of $(CO_2\underline{C}H_3)_A(CO_2CH_3)_B$), 52.9 (one of $(CO_2CH_3)_A(CO_2\underline{C}H_3)_B$), 38.5 (<u>C</u>$(CO_2Me)_2$), 33.4 (<u>C</u>$H_2$CH=C), 30.5 (<u>C</u>H$CO_2$Bn), 21.9 ($CH_2\underline{C}H_2CH_3$), 13.7 ($CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3027, 2956, 2873 (C-H), 1733 (C=O), 1713 (C=O), 1604 (C=C); **HRMS** (ES+)

exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}O_6^+$) requires *m/z* 347.1489, found *m/z* 347.1494; **MP**: 32 – 34 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –109.06 (*c* 3.25, $CHCl_3$).

5.9.3.3 Synthesis and characterisation of *E*-387

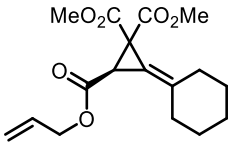
2-benzyl 1,1-dimethyl (Z)-3-butylidenecyclopropane-1,1,2-tricarboxylate (E-387)



To a stirred solution of BEMP (2.00 mg, 0.007 mmol, 0.100 eq) in THF (0.3 ml) was added 2-benzyl 1,1-dimethyl 3-butylcycloprop-2-ene-1,1,2-tricarboxylate (**386**) (10.0 mg, 0.0290 mmol, 1.00 eq). The reaction was stirred overnight then concentrated under a stream of N_2. The crude reaction mixture was putrified by silica gel column chromatography (pentane/Et_2O = 95/5 to 9/1) to provide the title compound (***E*-387**) as a colourless oil in 42% yield (4.20 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.44 – 7.29 (m, 5H, Ar<u>H</u>), 6.25 (td, *J* = 7.0, 2.5 Hz, 1H, $CH_3CH_2CH_2C$<u>H</u>), 5.13 (s, 2H, C<u>H_2</u>Ph), 3.74 (s, 3H, one of $(CO_2C$<u>H_3</u>$)_A(CO_2CH_3)_B$), 3.60 (s, 3H, one of $(CO_2CH_3)_A(CO_2C$<u>H_3</u>$)_B$), 3.30 (q, *J* = 2.0 Hz, 1H, C<u>H</u>CO_2Bn), 2.19 (qd, *J* = 7.5, 1.5 Hz, 2H, CH_3CH_2C<u>H_2</u>CH), 1.53 – 1.39 (m, 2H, CH_3C<u>H_2</u>CH_2CH), 0.87 (t, *J* = 7.5 Hz, 3H, C<u>H_3</u>CH_2CH_2CH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 167.6 (one of $(\underline{C}O_2CH_3)_A(CO_2CH_3)_B$), 167.5 ($\underline{C}O_2$Bn), 165.3 (one of $(CO_2CH_3)_A(\underline{C}O_2CH_3)_B$), 135.5 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.6 (2 x Ar<u>C</u>H), 124.3 (CH_2<u>C</u>H=C), 119. ($CH_2CH=$<u>C</u>), 67.4 (<u>C</u>H_2Ph), 53.4 (one of $(CO_2\underline{C}H_3)_A(CO_2CH_3)_B$), 53.0 (one of $(CO_2CH_3)_A(CO_2\underline{C}H_3)_B$), 38.4 (<u>C</u>$(CO_2Me)_2$), 33.4 (<u>C</u>$H_2$CH=C), 30.34 (<u>C</u>H$CO_2$Bn), 21.6 ($CH_2\underline{C}H_2CH_3$), 13.8 ($CH_2CH_2\underline{C}H_3$).

5.9.3.4 Synthesis and characterisation of 388

2-allyl 1,1-dimethyl (R)-3-cyclohexylidenecyclopropane-1,1,2-tricarboxylate (388)

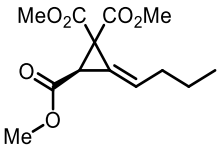


The title compound was prepared according to general procedure **XIV** from 2-allyl 1,1-dimethyl 3-cyclohexylcycloprop-2-ene-1,1,2-tricarboxylate (**E39**) (16.1 mg, 0.0500 mmol, 1.00 eq) with catalyst **124c**. After 9 h the reaction was quenched and the crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 8/2 then toluene/Et_2O = 97.5:2.5) to provide the title compound (**388**) as a colourless oil in 75% yield (12.1 mg) and 97% ee. [determined by HPLC chiralpak OG, hexane/isopropanol = 98/2, 1 ml/min, λ = 220 nm, t(minor) = 9.66 min, t(major) = 11.97 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 5.87 (ddt, *J* = 17.0, 10.5, 5.5 Hz, 1H, C$\underline{H}$=CH_2), 5.30 (app-dq, *J* = 17.0, 1.5 Hz, 1H, one of CH=C$\underline{H_A}H_B$), 5.22 (app-dq, *J* = 10.5, 1.5 Hz, 1H, one of CH=$CH_A\underline{H_B}$), 4.66 – 4.49 (m, 2H, OC$\underline{H_2}$), 3.74 (s, 3H, one of OC$\underline{H_3}$), 3.72 (s, 3H, one of OC$\underline{H_3}$), 3.26 – 3.23 (m, 1H, C$\underline{H}$C(=O)), 2.53 – 2.43 (m, 1H, one of C=C(C$\underline{H_A}H_B$)($CH_C\underline{H_D}$)), 2.37 – 2.13 (m, 3H, three of C=C($CH_A\underline{H_B}$)(C$\underline{H_C}H_D$)), 1.71 – 1.49 (m, 6H, $CH_2C\underline{H_2}C\underline{H_2}C\underline{H_2}CH_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 167.9 (one of $\underline{C}O_2$Me), 167.8 (one of $\underline{C}O_2$Me), 165.8 ($\underline{C}O_2CH_2$), 136.6 ($\underline{C}$=C$(CH_2)_2$ or C=$\underline{C}(CH_2)_2$), 131.8 ($\underline{C}$H=CH_2), 118.5 (CH=$\underline{C}H_2$), 111.6 ($\underline{C}$=C$(CH_2)_2$ or C=$\underline{C}(CH_2)_2$), 66.0 (O$\underline{C}H_2$), 53.2 (one of O$\underline{C}H_3$), 52.9 (one of O$\underline{C}H_3$), 38.9 ($\underline{C}(CO_2Me)$), 33.4 ($\underline{C}H_2CH_2CH_2CH_2CH_2$ or $CH_2CH_2CH_2CH_2\underline{C}H_2$), 33.3 ($\underline{C}H_2CH_2CH_2CH_2CH_2$ or $CH_2CH_2CH_2CH_2\underline{C}H_2$), 30.4 ($\underline{C}$HC(=O)), 27.5 ($CH_2\underline{C}H_2CH_2CH_2CH_2$ or $CH_2CH_2CH_2\underline{C}H_2CH_2$), 27.5 ($CH_2\underline{C}H_2CH_2CH_2CH_2$ or $CH_2CH_2CH_2\underline{C}H_2CH_2$), 26.2 ($CH_2CH_2\underline{C}H_2CH_2CH_2$); **IR** (film) ν_{max}/cm^{-1}: 2933, 2856 (C-H), 1731 (C=O); **HRMS**

(ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}O_6^+$) requires *m/z* 323.1489, found *m/z* 323.1489; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –73.00 (*c* 0.34, $CHCl_3$).

5.9.3.5 Synthesis and characterisation of 389

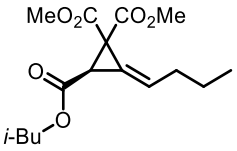
trimethyl (R,Z)-3-butylidenecyclopropane-1,1,2-tricarboxylate (389)



The title compound was prepared according to general procedure **XIV** from trimethyl 3-butylcycloprop-2-ene-1,1,2-tricarboxylate (**E40**) (27.0 mg, 0.100 mmol, 1.00 eq) with catalyst **124c**. After 2 h the crude mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude product was purified by silica gel column chromatography (pentane/Et_2O = 7/3) to provide the title compound (**389**) as a colourless oil in quantitative yield (27.2 mg) and 92% ee. [determined by HPLC chiralpak OD, hexane/isopropanol = 98/2, 1 ml/min, λ = 220 nm, t(minor) = 14.21 min, t(minor) = 23.87 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 6.10 (td, *J* = 7.5, 2.0 Hz, 1H, C=C<u>H</u>), 3.77 (s, 3H, one of $CO_2C\underline{H}_3$), 3.76 (s, 3H, one of $CO_2C\underline{H}_3$), 3.70 (s, 3H, one of $CO_2C\underline{H}_3$), 3.25 (q, *J* = 2.0 Hz, 1H, C<u>H</u>CO_2Me), 2.41 – 2.24 (m, 2H, C<u>H</u>$_2CH_2CH_3$), 1.50 (h, *J* = 7.5 Hz, 2H, $CH_2C\underline{H}_2CH_3$), 0.90 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2C\underline{H}_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 168.3 (one of <u>C</u>=O), 167.5 (one of <u>C</u>=O), 165.4 (one of <u>C</u>=O), 124.8 (C=<u>C</u>H), 119.8 (<u>C</u>=CH), 53.4 (one of $CO_2\underline{C}H_3$), 53.1 (one of $CO_2\underline{C}H_3$), 52.7 (one of $CO_2\underline{C}H_3$), 38.4 (<u>C</u>(CO_2Me)), 33.4 (<u>C</u>$H_2CH_2CH_3$), 30.4 (C<u>H</u>CO_2Me), 21.9 ($CH_2\underline{C}H_2CH_3$), 13.8 ($CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2957 (C-H), 1736 (C=O), 1436, 1283, 1250; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{19}O_6^+$) requires *m/z* 271.1176, found *m/z* 271.1177; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –129.1 (*c* 0.54, $CHCl_3$).

5.9.3.6 Synthesis and characterisation of 390

2-isobutyl 1,1-dimethyl (R,Z)-3-butylidenecyclopropane-1,1,2-tricarboxylate (390)

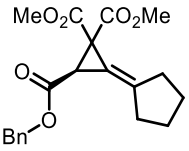


The title compound was prepared according to general procedure **XIV** from 2-isobutyl 1,1-dimethyl 3-butylcycloprop-2-ene-1,1,2-tricarboxylate (**E41**) (31.2 mg, 0.100 mmol, 1.00 eq) with catalyst **124c**. After 3 h the reaction mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**390**) as a colourless oil in 96% yield (29.8 mg) and 94% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 99/1, 1 ml/min, λ = 220 nm, t(minor) = 15.56 min, t(major) = 23.75 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 6.09 (td, *J* = 7.5, 2.0 Hz, 1H, C=C$\underline{H}$), 3.92 (dd, *J* = 10.5, 7.0 Hz, 1H, one of OC$\underline{H_A}H_B$), 3.81 (dd, *J* = 10.5, 6.5 Hz, 1H, one of O$CH_A\underline{H_B}$), 3.76 (s, 3H, one of $C(CO_2C\underline{H_3})_A(CO_2CH_3)_B$), 3.75 (s, 3H, one of $C(CO_2CH_3)_A(CO_2C\underline{H_3})_B$), 3.26 (q, *J* = 2.0 Hz, 1H, C$\underline{H}$C(=O)), 2.40 – 2.25 (m, 2H, $C\underline{H_2}CH_2CH_3$), 1.91 (dp, *J* = 13.5, 6.5 Hz, 1H, C$\underline{H}(CH_3)_2$), 1.50 (h, *J* = 7.5 Hz, 2H, $CH_2C\underline{H_2}CH_3$), 0.94 – 0.87 (m, 9H, $CH_2CH_2C\underline{H_3}$ and $CH(C\underline{H_3})_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 167.9 ($\underline{C}O_2$*i*-Bu), 167.6 (one of $C(\underline{C}O_2CH_3)_A(CO_2CH_3)_B$), 165.4 (one of $C(CO_2CH_3)_A(\underline{C}O_2CH_3)_B$), 124.5 (C=$\underline{C}$H), 120.0 ($\underline{C}$=CH), 71.7 ($CO_2\underline{C}H_2$), 53.4 (one of $C(CO_2\underline{C}H_3)_A(CO_2CH_3)_B$), 53.0 (one of $C(CO_2CH_3)_A(CO_2\underline{C}H_3)_B$), 38.3 ($\underline{C}(CO_2Me)$), 33.4 ($\underline{C}H_2CH_2CH_3$), 30.6 ($C\underline{H}CO_2$*i*-Bu), 27.8 ($\underline{C}H(CH_3)_2$), 22.0 ($CH_2\underline{C}H_2CH_3$), 19.1 ($CH(\underline{C}H_3)_2$), 13.8 ($CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 2960, 2875 (C-H), 1735 (C=O),

1435, 1281, 1248; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{25}O_6^+$) requires *m/z* 313.1646, found *m/z* 313.1645; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –121.7 (*c* 0.53, $CHCl_3$).

5.9.3.7 Synthesis and characterisation of 391

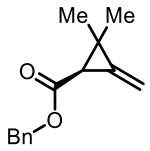
2-benzyl 1,1-dimethyl (R)-3-cyclopentylidenecyclopropane-1,1,2-tricarboxylate (391)



The title compound was prepared according to general procedure **XIV** from **E42** (17.9 mg, 0.0500 mmol, 1.00 eq) with catalyst **124c**. After 5 h the reaction was quenched and the crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**391**) as a colourless oil in 96% yield (17.2 mg) and 94% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 98/2, 1 ml/min, λ = 220 nm, t(major) = 18.85 min, t(minor) = 20.59 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.40 – 7.28 (m, 5H, Ar$\underline{H}$), 5.15 (d, *J* = 12.5 Hz, 1H, one of C$\underline{H_A}H_BPh$), 5.10 (d, *J* = 12.5 Hz, 1H, , one of $CH_A\underline{H_B}Ph$), 3.75 (s, 3H, one of $C(CO_2C\underline{H_3})_A(CO_2CH_3)_B$), 3.62 (s, 3H, one of $C(CO_2CH_3)_A(CO_2C\underline{H_3})_B$), 3.25 (p, *J* = 2.5 Hz, 1H, C$\underline{H}$C(=O)), 2.80 – 2.62 (m, 1H, one of C$\underline{H_A}H_BCCH_CH_D$), 2.49 – 2.30 (m, 3H, three of $CH_A\underline{H_B}CC\underline{H_C}\underline{H_D}$), 1.75 (m, 4H, C$\underline{H_2}CH_2CCH_2C\underline{H_2}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 167.9 ($\underline{C}O_2Bn$), 167.8 (one of $C(\underline{C}O_2CH_3)_A(CO_2CH_3)_B$), 165.9 (one of $C(CO_2CH_3)_A(\underline{C}O_2CH_3)_B$), 140.4 ($CH_2\underline{C}$=C), 135.7 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$H), 128.5 (Ar$\underline{C}$H), 128.4 (Ar$\underline{C}$H), 109.7 ($CH_2C$=$\underline{C}$), 67.2 ($\underline{C}H_2Ph$), 53.3 (one of $C(CO_2\underline{C}H_3)_A(CO_2CH_3)_B$), 52.8 (one of $C(CO_2CH_3)_A(CO_2\underline{C}H_3)_B$), 39.0 ($\underline{C}(CO_2Me)_2$), 32.5 (one of $(\underline{C}H_2)_AC(CH_2)_B$), 32.3 (one of $(CH_2)_AC(\underline{C}H_2)_B$), 30.8 ($\underline{C}$HC(=O)), 26.6 (one of $(\underline{C}H_2)_ACH_2CCH_2(CH_2)_B$), 26.6 (one of $(CH_2)_ACH_2CCH_2(\underline{C}H_2)_B$); **IR** (film) ν_{max}/cm^{-1}: 2952 (C-H), 1732 (C=O), 1249; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{23}O_6^+$) requires *m/z* 359.1489, found *m/z* 359.1493; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –56.4 (*c* 0.17, $CHCl_3$).

5.9.3.8 Synthesis and characterisation of 400

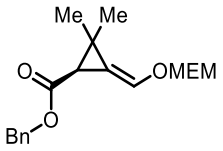
benzyl (S)-2,2-dimethyl-3-methylenecyclopropane-1-carboxylate (400)



The title compound was prepared according to general procedure **XIV** from benzyl 2,3,3-trimethylcycloprop-1-ene-1-carboxylate (**399**) (21.6 mg, 0.100 mmol, 1.00 eq) with catalyst **124c**. After 24 h the reaction was quenched, and the crude reaction mixture was purified by silica gel column chromatography (pntane/Et_2O = 99/1) to provide the title compound (**400**) as a colourless oil in 97% yield (20.9 mg) and 90% ee. [determined by HPLC chiralpak IA, hexane, 1 ml/min, λ = 220 nm, t(minor) = 19.08 min, t(major) = 20.18 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.43 – 7.29 (m, 5H, Ar$\underline{H}$), 5.45 (d, *J* = 2.5 Hz, 1H, one of C=C$\underline{H_A}H_B$), 5.41 (d, *J* = 1.5 Hz, 1H, one of C=C$H_A\underline{H_B}$), 5.18 – 5.14 (m, 1H, one of C$\underline{H_A}H_B$Ph), 5.11 (d, *J* = 12.5 Hz, 1H, one of C$H_A\underline{H_B}$Ph), 2.13 (dd, *J* = 2.5, 1.5 Hz, 1H, C$\underline{H}$(C=O)), 1.32 (s, 3H, one of C(C$\underline{H_3}$)$_A$(CH_3)$_B$), 1.30 (s, 3H, one of C(CH_3)$_A$(C$\underline{H_3}$)$_B$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ(ppm): 170.8 ($\underline{C}$=O), 141.5 ($\underline{C}$=CH_2), 136.4 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$H), 128.4 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 103.3 (C=$\underline{C}H_2$), 66.4 ($\underline{C}H_2$O), 30.1 ($\underline{C}$HC(=O)), 26.9 ($\underline{C}Me_2$), 26.1 (one of C($\underline{C}H_3$)$_A$(CH_3)$_B$), 18.4 (one of C(CH_3)$_A$($\underline{C}H_3$)$_B$); **IR** (film) ν_{max}/cm^{-1}: 2955, 2927 (C-H), 1729 (C=O), 1331, 1150, 900 (C=C); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}O_2^+$) requires *m/z* 217.1223, found *m/z* 217.1223; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –62.0 (*c* 0.25, $CHCl_3$).

5.9.3.9 Synthesis and characterisation of 406

benzyl (Z)-3-(((2-methoxyethoxy)methoxy)methylene)-2,2-dimethylcyclopropane-1-carboxylate (406)

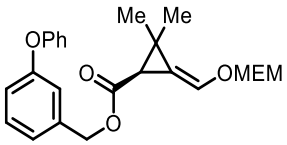


The title compound was prepared according to general procedure **XIV** from benzyl 2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcycloprop-1-ene-1-carboxylate (**405**) (32.0 mg, 0.100 mmol) with catalyst **124d**. After 1 h the reaction mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (pentane/EtOAc = 9/1) to provide the title compound (**406**) as a colourless oil in 90% yield (28.9 mg) and 98% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 98/2, 1 ml/min, λ = 220 nm, t(major) = 14.80 min, t(minor) = 22.53 min]. **^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.28 – 7.18 (m, 2H, ArH), 7.14 – 6.99 (m, 3H, ArH), 6.58 (d, *J* = 1.5 Hz, 1H, C=CH(OMEM)), 5.07 (d, *J* = 1.5 Hz, 2H, CH_AH_BPh), 4.78 (d, *J* = 6.0 Hz, 1H, OCH_AH_BO), 4.72 (d, *J* = 6.0 Hz, 1H, OCH_AH_BO), 3.57 – 3.53 (m, 2H, $OCH_2CH_2OCH_3$), 3.28 – 3.24 (m, 2H, $OCH_2CH_2OCH_3$), 3.07 (s, 3H, OCH_3), 2.20 (d, *J* = 1.5 Hz, 1H, $CHCO_2Bn$), 1.45 (s, 3H, one of $C(CH_3)_A(CH_3)_B$), 1.15 (s, 3H, one of $C(CH_3)_A(CH_3)_B$); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 170.5 (C=O), 137.0 (ArC), 136.0 (C=CH(OMEM)), 128.7 (ArCH), 128.6 (ArCH), 128.2 (ArCH), 109.9 (C=CH(OMEM)), 94.7 (OCH_2O), 72.0 (CH_2OCH_3), 68.1 ($CH_2CH_2OCH_3$), 66.3 (CH_2Ph), 58.6 (OCH_3), 29.6 ($CHCO_2Bn$), 28.3 ($C(CH_3)_2$), 26.2 (one of $C(CH_3)_A(CH_3)_B$), 19.2 (one of $C(CH_3)_A(CH_3)_B$); **IR** (film) ν_{max}/cm^{-1}: 2953, 2928, 2890 (C-H), 1727 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$

($C_{18}H_{24}NaO_5^+$) requires *m/z* 343.1516, found *m/z* 343.1517; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –51.1 (*c* 0.31, $CHCl_3$).

5.9.3.10 Synthesis and characterisation of 411

3-phenoxybenzyl (Z)-3-(((2-methoxyethoxy)methoxy)methylene)-2,2-dimethylcyclopropane-1-carboxylate (411)

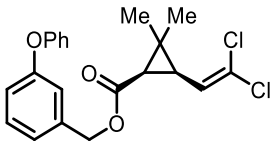


The title compound was prepared according to general procedure **XIV** from 3-phenoxybenzyl 2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcycloprop-1-ene-1-carboxylate (**410**) (41.2 mg, 0.100 mmol) with catalyst **124d**. After 1 h the reaction mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (pentane/EtOAc = 9/1) to provide the title compound (**411**) as a colourless oil in 88% yield (36.2 mg) and 98% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 95/5, 1 ml/min, λ = 220 nm, t(major) = 10.76 min, t(minor) = 21.54 min]. **^{1}H NMR** (400 MHz, Benzene-d_6) δ 7.10 – 6.90 (m, 7H, ArH), 6.89 – 6.81 (m, 2H, ArH), 6.56 (d, *J* = 1.5 Hz, 1H, C=CH(OMEM)), 4.98 (d, 13.0 Hz, 1H, one of CH_AH_BPh), 4.97 (d, 13.0 Hz, 1H, one of CH_AH_BPh), 4.77 (d, *J* = 6.0 Hz, 1H, one of OCH_AH_BO), 4.72 (d, *J* = 6.0 Hz, 1H, one of OCH_AH_BO), 3.57 – 3.53 (m, 2H, $CH_2CH_2OCH_3$), 3.28 – 3.24 (m, 2H, $CH_2CH_2OCH_3$), 3.07 (s, 3H, OCH_3), 2.17 (d, *J* = 1.5 Hz, 1H, $CHCO_2CH_2Ar$), 1.43 (s, 3H, one of $C(CH_3)_A(CH_3)_B$), 1.14 (s, 3H, one of $C(CH_3)_A(CH_3)_B$); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 170.4 (C=O), 158.1 (ArC), 157.6 (ArC), 139.2 (ArC), 136.0 (C=CH(OMEM)), 130.12(ArCH), 130.1 (ArCH), 123.6 (ArCH), 123.1 (ArCH), 119.4 (ArCH), 118.8 (ArCH), 109.9 (C=CH(OMEM)), 94.7 (OCH_2O), 72.0 (CH_2OCH_3), 68.1 ($CH_2CH_2OCH_3$), 65.7 (CH_2Ph), 58.6 (OCH_3), 29.6 ($CHCO_2CH_2Ar$), 28.4 ($C(CH_3)_2$), 26.2 (one of $C(CH_3)_A(CH_3)_B$), 19.3 (one of $C(CH_3)_A(CH_3)_B$); **IR** (film) ν_{max}/cm^{-1}: 2929,

1729 (C=O), 1584, 1487; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{28}NaO_6^+$) requires *m/z* 435.1778, found *m/z* 435.1777; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –50.6 (*c* 0.81, $CHCl_3$).

5.9.3.11 Synthesis and characterisation of 302

(1R, 3R)-cis-Permethrin (302)

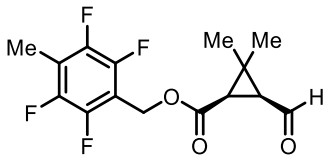


The title compound was prepared according to general procedure **XIV** from 3-phenoxybenzyl 2-(((2-methoxyethoxy)methoxy)methyl)-3,3-dimethylcycloprop-1-ene-1-carboxylate (**410**) (41.2 mg, 0.100 mmol, 1.00 eq) with catalyst **124d**. After 1 h $HCl_{(aq)}$ (1.0 M, 2.0 ml) was added, and the reaction was stirred vigorously overnight. The aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Triphenyl phosphine (105 mg, 0.400 mmol, 4.00 eq) was dissolved in CH_2Cl_2 (0.1 ml) and CCl_4 (0.2 ml) was added at 0 °C The crude product was dissolved in CH_2Cl_2 (0.24 ml) and added to the solution of triphenyl phosphine. The reaction was warmed to room temperature. H_2O (5 ml) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 99/1) to provide the title compound (**302**) as a white solid in 31% yield (12.2 mg) and 98% ee. [determined by HPLC chiralpak IB, hexane/isopropanol = 99/1, 1 ml/min, λ = 230 nm, t(major) = 7.51 min, t(minor) = 8.08 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.38 – 7.29 (m, 3H, Ar<u>H</u>), 7.14 – 7.06 (m, 2H, Ar<u>H</u>), 7.04 – 7.00 (m, 3H, Ar<u>H</u>), 6.98 – 6.91 (m, 1H, Ar<u>H</u>), 6.26 (d, *J* = 9.0 Hz, 1H, C<u>H</u>=CCl_2), 5.09 (d, *J* = 12.5 Hz, 1H, one of C<u>H</u>$_A$H$_B$Ar), 5.05 (d, *J* = 12.5 Hz, 1H, one of CH$_A$<u>H</u>$_B$Ar), 2.04 (app-t, *J* = 8.5 Hz, 1H, C<u>H</u>CH=CCl_2), 1.89 (d, *J* = 8.5 Hz, 1H, C<u>H</u>C(=O)OCH_2), 1.24 (s, 3H, one of C(C<u>H</u>$_3$)$_A$(CH$_3$)$_B$), 1.24 (s, 3H, one of

C(CH_3)$_A$(C$\underline{H}_3$)$_B$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 170.4 ($\underline{C}$=O), 157.7 (Ar$\underline{C}$), 157.1 (Ar$\underline{C}$), 138.1 (Ar$\underline{C}$), 130.1 (Ar$\underline{C}$H), 130.0 (Ar$\underline{C}$H), 124.9 ($\underline{C}$=CCl_2), 123.6 (Ar$\underline{C}$H), 122.8 (Ar$\underline{C}$H), 121.0 (C=$\underline{C}Cl_2$), 119.2 (Ar$\underline{C}$H), 118.6 (Ar$\underline{C}$H), 118.4 (Ar$\underline{C}$H), 65.9 (O$\underline{C}H_2$), 32.9 ($\underline{C}$HCH=CCl_2), 32.0 ($\underline{C}$HC(=O)CH_2), 28.5 (one of C($\underline{C}H_3$)$_A$(CH_3)$_B$), 27.8 ($\underline{C}$(CH_3)$_2$), 15.1 (one of C($\underline{C}H_3$)$_A$(CH_3)$_B$); **IR** (film) ν_{max}/cm^{-1}: 3067, 2957 (C-H), 1726 (C=O), 1585, 1488, 1258, 1215, 1180, 1135, 1084; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +1.81 (*c* 1.43, CH_2Cl_2). Lit: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +2.6 (*c* 1.5, CH_2Cl_2).[214] Data are consistent with that published in the literature.[214]

5.9.3.12 Synthesis and characterisation of 412

2,3,5,6-tetrafluoro-4-methylbenzyl (1R,3S)-3-formyl-2,2-dimethylcyclopropane-1-carboxylate (412)

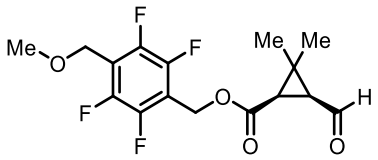


The title compound was prepared according to general procedure **XIV** from **E44** (40.6 mg, 0.100 mmol, 1.00 eq) with catalyst **124d**. After 60 min $HCl_{(aq)}$ (1.0 M, 2 ml) was added and the reaction was stirred vigorously overnight. The aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* which provided the crude product in >20:1 d.r.. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**412**) as a colourless oil in 75% yield (23.9 mg) and 98% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 98/2, 1 ml/min, λ = 210 nm, t(major) = 18.91 min, t(minor) = 25.58 min]. **^{1}H NMR** (600 MHz, $CDCl_3$) δ(ppm): 9.75 (d, *J* = 6.5 Hz, 1H, C<u>H</u>O), 5.27 – 5.21 (m, 2H, C<u>H$_A$H$_B$</u>Ar), 2.29 (t, J_{HF} = 2.0 Hz, 3H, C<u>H$_3$</u>Ar), 2.12 (d, *J* = 8.5 Hz, 1H, C<u>H</u>CHO), 1.87 (dd, *J* = 8.5, 6.5 Hz, 1H, C<u>H</u>CO$_2$CH$_2$), 1.56 (s, 3H, one of C(C<u>H$_3$</u>)$_A$(CH$_3$)$_B$), 1.27 (s, 3H, one of C(CH$_3$)$_A$(C<u>H$_3$</u>)$_B$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 200.1 (<u>C</u>HO), 169.4 (<u>C</u>O$_2$CH$_2$), 146.2 – 145.5 (m, Ar<u>C</u>), 144.7 – 143.9 (m, Ar<u>C</u>), 117.7 (t, J_{CF} = 19.0 Hz, Ar<u>C</u>), 111.3 (t, J_{CF} = 17.0 Hz, Ar<u>C</u>), 54.5 – 54.26 (m, <u>C</u>H$_2$Ar), 41.1 (<u>C</u>HCO$_2$CH$_2$), 35.8 (<u>C</u>HCHO), 30.3 (<u>C</u>Me$_2$), 28.3 (one of C(<u>C</u>H$_3$)$_A$(CH$_3$)$_B$), 15.0 (one of C(CH$_3$)$_A$(<u>C</u>H$_3$)$_B$), 8.1 – 7.7 (m, <u>C</u>H$_3$Ar); **^{19}F NMR** (565 MHz, $CDCl_3$) δ(ppm): -143.3 (dd, *J* = 21.5, 13.0 Hz, 2 x ArC<u>F</u>), -144.4 (dd, *J* = 21.5, 13.0 Hz, 2 x ArC<u>F</u>); **IR** (film) ν_{max}/cm^{-1}: 3056, 2960 (C-H) 1729

(C=O ester), 1693 (C=O aldehyde) 1660; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}F_4H_{14}NaO_3^+$) requires *m/z* 341.0771, found *m/z* 341.0772; **MP**: 72 – 73 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = −47.4 (*c* 0.56, $CHCl_3$).

5.9.3.13 Synthesis and characterisation of 413

2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl (1R,3S)-3-formyl-2,2-dimethylcyclopropane-1-carboxylate (413)

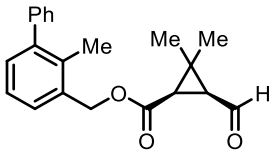


The title compound was prepared according to general procedure **XIV** from **E46** (43.6 mg, 0.100 mmol, 1.00 eq) with catalyst **124d**. After 60 min $HCl_{(aq)}$ (1.0 M, 2 ml) was added and the reaction was stirred vigorously overnight. The aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* which provided the crude product in >20:1 d.r.. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**413**) as a white solid in 76% yield (26.3 mg) and 97% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 97/3, 1 ml/min, λ = 210 nm, t(major) = 28.46 min, t(minor) = 36.97 min]. **^{1}H NMR** (600 MHz, $CDCl_3$) δ(ppm): 9.75 (d, *J* = 6.5 Hz, 1H, C<u>H</u>O), 5.29 (dt, *J* = 12.0, 1.5 Hz, 1H, one of C<u>H</u>$_A$H$_B$Ar), 5.25 (dt, *J* = 12.0, 1.5 Hz, 1H, one of CH$_A$<u>H</u>$_B$Ar), 4.59 (t, J_{HF} = 2.0 Hz, 2H, C<u>H$_2$</u>OCH$_3$), 3.41 (s, 3H, OC<u>H$_3$</u>), 2.12 (d, *J* = 8.5 Hz, 1H, C<u>H</u>CO$_2$CH$_2$), 1.88 (dd, *J* = 8.5, 6.5 Hz, 1H, C<u>H</u>CHCO$_2$), 1.56 (s, 3H, one of C(C<u>H$_3$</u>)$_A$(CH$_3$)$_B$), 1.27 (s, 3H, one of C(CH$_3$)$_A$(C<u>H$_3$</u>)$_B$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 201.9 – 198.1 (m, <u>C</u>HO), 169.4 (<u>C</u>O$_2$CH$_2$), 146.3 – 145.9 (m, Ar<u>C</u>), 144.7 – 144.2 (m, Ar<u>C</u>), 117.4 (t, J_{CF} = 18.0 Hz, Ar<u>C</u>), 114.4 (t, J_{CF} = 17.0 Hz, Ar<u>C</u>), 61.6 (t, J_{CF} = 36.0 Hz, <u>C</u>H$_2$OCH$_3$), 58.9 (t, J_{CF} = 37.5 Hz, CH$_2$O<u>C</u>H$_3$), 54.7 – 53.6 (m, CO$_2$<u>C</u>H$_2$), 41.6 – 40.7 (m, <u>C</u>HCHO), 35.7 (d, J_{CF} = 72.0 Hz, <u>C</u>HCO$_2$CH$_2$), 30.3 (<u>C</u>(CH$_3$)$_2$), 28.28 (q, J_{CF} = 16.5 Hz, one of C(<u>C</u>H$_3$)$_A$(CH$_3$)$_B$), 14.99

(t, J_{CF} = 38.0 Hz, one of $C(CH_3)_A(\underline{C}H_3)_B$); **^{19}F NMR** (565 MHz, $CDCl_3$) δ(ppm): -142.8 (dd, *J* = 22.0, 13.5 Hz, 2 x ArC<u>F</u>), -143.2 (dd, *J* = 22.0, 14.0 Hz, 2 x ArC<u>F</u>); **IR** (film) ν_{max}/cm^{-1}: 2970 (C-H), 1733 (C=O ester), 1700 (C=O aldehyde); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}F_4H_{16}NaO_4^+$) requires *m/z* 371.0877, found *m/z* 371.0877; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = −37.1 (*c* 0.67, $CHCl_3$).

5.9.3.14 Synthesis and characterisation of 414

(2-methyl-[1,1'-biphenyl]-3-yl)methyl (1R,3S)-3-formyl-2,2-dimethylcyclopropane-1-carboxylate (414)

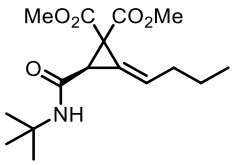


The title compound was prepared according to general procedure **XIV** from **E49** (41.5 mg, 0.100 mmol, 1.00 eq) with catalyst **124d**. After 60 min $HCl_{(aq)}$ (1.0 M, 2 ml) was added and the reaction was stirred vigorously overnight. The aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* which provided the crude product in >20:1 d.r.. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**414**) as a colourless oil in 74% yield (23.7 mg) and 98% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 95/5, 1 ml/min, λ = 210 nm, t(major) = 19.53 min, t(minor) = 24.47 min]. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.79 (d, *J* = 6.5 Hz, 1H, C<u>H</u>O), 7.44 – 7.40 (m, 2H, Ar<u>H</u>), 7.38 – 7.33 (m, 2H, Ar<u>H</u>), 7.32 – 7.27 (m, 2H, Ar<u>H</u>), 7.25 (d, *J* = 2.5 Hz, 2H, Ar<u>H</u>), 5.24 (s, 2H, C<u>H$_A$H$_B$</u>Ar), 2.23 (s, 3H, C<u>H$_3$</u>Ar), 2.20 (d, *J* = 8.5 Hz, 1H, C<u>H</u>CHO), 1.88 (dd, *J* = 8.5, 6.5 Hz, 1H, C<u>H</u>CO_2CH_2), 1.58 (s, 3H, one of C(C<u>H$_3$</u>)$_A$(CH_3)$_B$), 1.28 (s, 3H, one of C(CH_3)$_A$(C<u>H$_3$</u>)$_B$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 200.5 (C<u>H</u>O), 170.0 (<u>C</u>O_2CH_2), 143.2 (Ar<u>C</u>), 141.9 (Ar<u>C</u>), 134.7 (Ar<u>C</u>), 134.2 (Ar<u>C</u>), 130.7 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 66.1 (CO_2<u>C</u>H_2), 41.1 (<u>C</u>HCO_2CH_2), 36.4 (<u>C</u>HCHCO_2CH_2), 30.1 (<u>C</u>Me_2), 28.4 (one of C(<u>C</u>H_3)$_A$(CH_3)$_B$), 16.4 (<u>C</u>H_3Ar), 15.1 (one of C(CH_3)$_A$(<u>C</u>H_3)$_B$); **IR** (film) ν_{max}/cm^{-1}: 2980, 2888 (C-H) 1723 (C=O ester),

1698 (C=O aldehyde); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{22}NaO_3^+$) requires *m/z* 345.1461, found *m/z* 345.1462; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = −38.8 (*c* 0.67, $CHCl_3$).

5.9.3.15 Synthesis and characterisation of 426

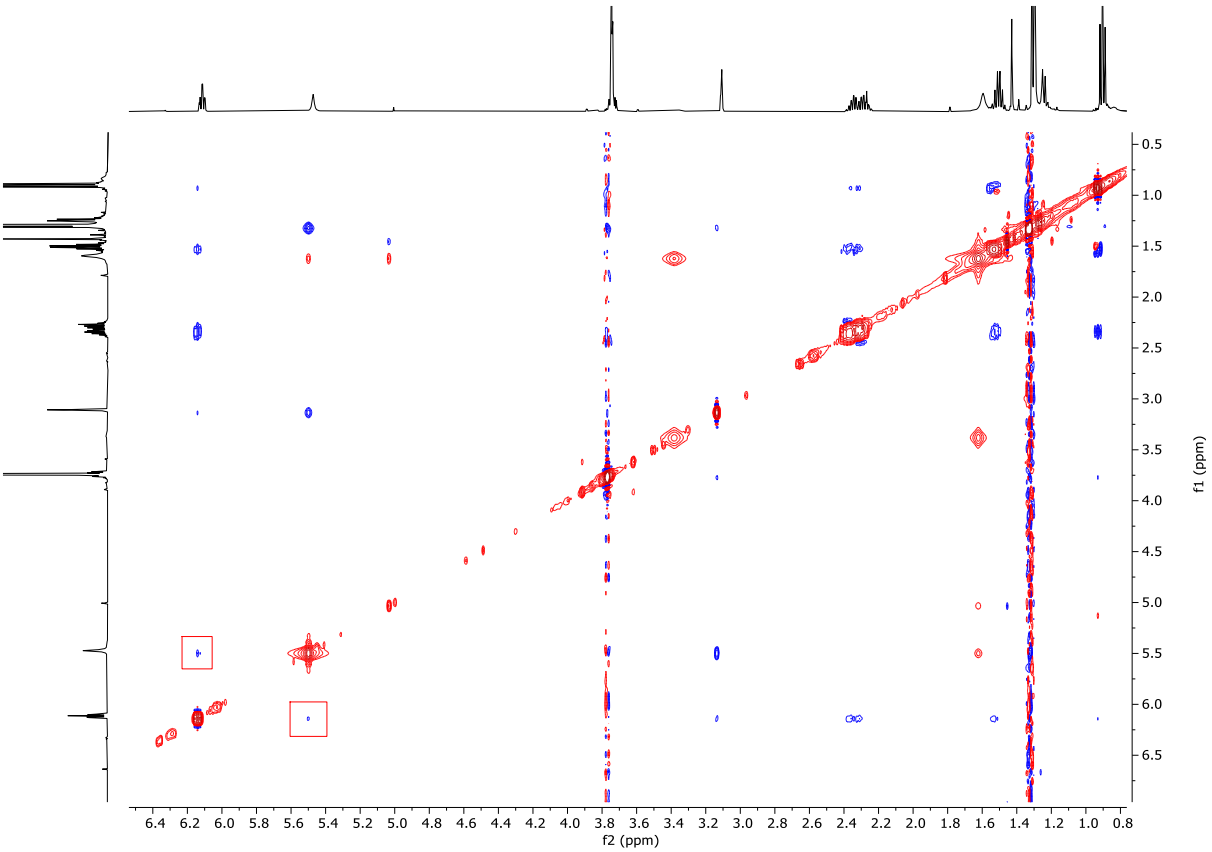
dimethyl (R,Z)-2-(tert-butylcarbamoyl)-3-butylidenecyclopropane-1,1-dicarboxylate (426)



The title compound was prepared according to general procedure **XIV** from dimethyl 2-butyl-3-(*tert*-butylcarbamoyl)cycloprop-2-ene-1,1-dicarboxylate (**420**) (31.1 mg, 1.00 mmol, 1.00 eq) with catalyst **124c**. After 45 min the reaction mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 7/3 to 6/4) to provide the title compound (**426**) as a yellow oil in >99% yield (31.0 mg) and 99% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 98/2, 1 ml/min, λ = 210 nm, t(major) = 21.94 min, t(minor) = 27.01 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 6.11 (td, *J* = 7.5, 2.0 Hz, 1H, C=C<u>H</u>), 5.47 (bs, 1H, N<u>H</u>), 3.75 (s, 3H, one of $C(CO_2C\underline{H}_3)_A(CO_2CH_3)_B$), 3.74 (s, 3H, one of $C(CO_2CH_3)_A(CO_2C\underline{H}_3)_B$), 3.11 (q, *J* = 2.0 Hz, 1H, C<u>H</u>CONH), 2.41 – 2.22 (m, 2H, $C\underline{H}_2CH_2CH_3$), 1.51 (hd, *J* = 7.5, 1.0 Hz, 2H, $CH_2C\underline{H}_2CH_3$), 1.30 (s, 9H, $C(C\underline{H}_3)_3$), 0.90 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2C\underline{H}_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 167.8 (one of <u>C</u>O_2Me), 165.9 (one of <u>C</u>O_2Me), 164.7 (<u>C</u>ONH), 124.9 (C=<u>C</u>H), 120.6 (<u>C</u>=CH), 53.2 (one of $C(CO_2\underline{C}H_3)_A(CO_2CH_3)_B$), 53.0 (one of $C(CO_2CH_3)_A(CO_2\underline{C}H_3)_B$), 51.7 ($N\underline{C}(CH_3)_3$), 37.9 (<u>C</u>($CO_2$Me)), 33.8 (<u>C</u>HCONH), 33.5 ($\underline{C}H_2CH_2CH_3$), 28.7 ($NC(\underline{C}H_3)_3$), 22.0 ($CH_2\underline{C}H_2CH_3$), 13.8 ($CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3314 (N-H), 2969 (C-H), 1734 (C=O ester), 1656 (C=O amide); **HRMS** (ES+) exact mass calculated

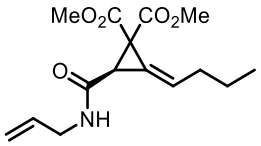
for $[M+H]^+$ ($C_{16}H_{26}NO_5^+$) requires *m/z* 312.1805, found *m/z* 312.1805; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –75.5 (*c* 0.48, $CHCl_3$).

NOESY of compound **426**: Cross-peaks are observed between N<u>H</u> and C=C<u>H</u>.



5.9.3.16 Synthesis and characterisation of 427

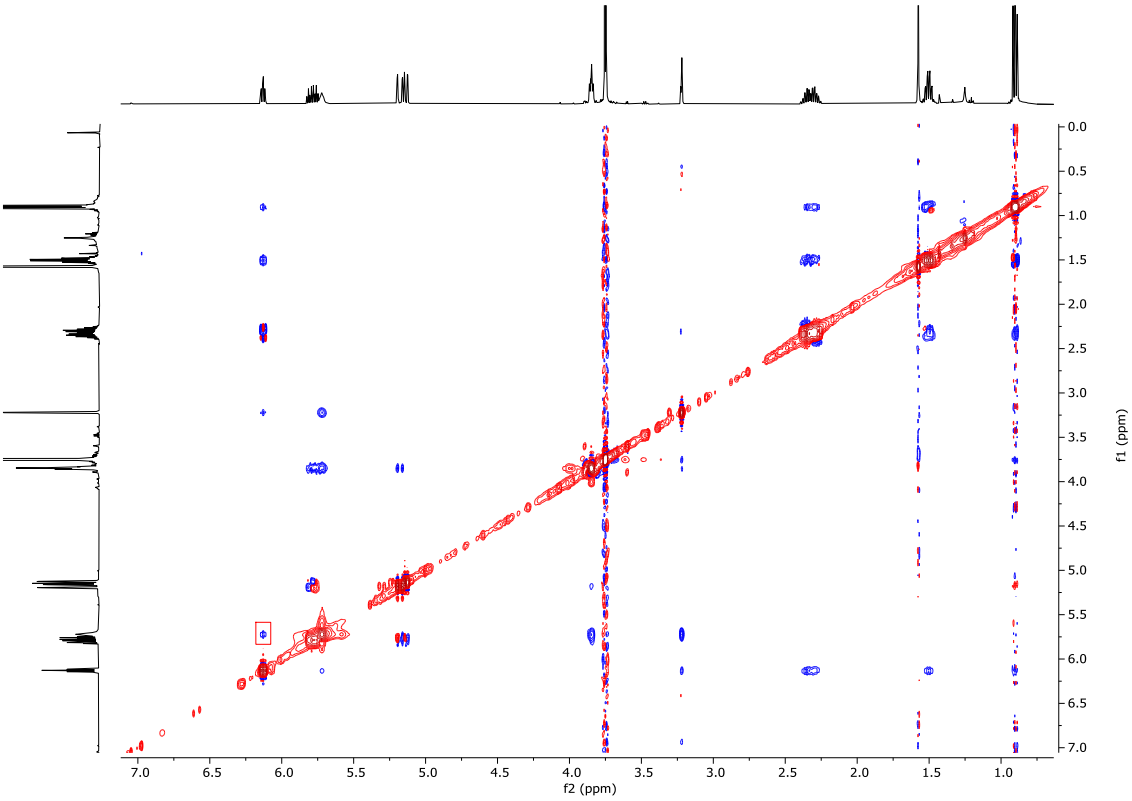
dimethyl (R,Z)-2-(allylcarbamoyl)-3-butylidenecyclopropane-1,1-dicarboxylate (427)



The title compound was prepared according to general procedure **XIV** from **421** (14.8 mg, 0.0500 mmol, 1.00 eq) with catalyst **124c**. After 2 h the reaction mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (pentane/EtOAc = 7/3) to provide the title compound (**427**) as a yellow oil in 73% yield (10.8 mg) and 97% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 220 nm, t(minor) = 11.67 min, t(major) = 27.68 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 6.13 (td, *J* = 7.0, 2.0 Hz, 1H, C=C<u>H</u>CH_2CH_2), 5.79 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 1H, C<u>H</u>=CH_2), 5.72 (bs, 1H, N<u>H</u>), 5.22 – 5.07 (m, 2H, CH=C<u>H</u>$_2$), 3.85 (tq, *J* = 5.5, 1.5 Hz, 2H, NHC<u>H</u>$_2$), 3.76 (s, 3H, one of C($CO_2C\underline{H}_3$)$_A$(CO_2CH_3)$_B$), 3.75 (s, 3H, one of C(CO_2CH_3)$_A$($CO_2C\underline{H}_3$)$_B$), 3.22 (q, *J* = 2.0 Hz, 1H, C<u>H</u>C(=O)), 2.41 – 2.21 (m, 2H, C<u>H</u>$_2CH_2CH_3$), 1.50 (hd, *J* = 7.5, 2.0 Hz, 2H, $CH_2C\underline{H}_2CH_3$), 0.90 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2C\underline{H}_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 167.7 (one of C($\underline{C}O_2CH_3$)$_A$(CO_2CH_3)$_B$), 166.0 (one of C(CO_2CH_3)$_A$($\underline{C}O_2CH_3$)$_B$), 165.6 (<u>C</u>(=O)NH), 133.8 (<u>C</u>H=CH_2), 125.1 (C=<u>C</u>HCH_2CH_2), 120.4 (<u>C</u>=CHCH_2CH_2), 117.0 (CH=<u>C</u>H_2), 53.3 (one of C($CO_2\underline{C}H_3$)$_A$(CO_2CH_3)$_B$), 53.2 (one of C(CO_2CH_3)$_A$($CO_2\underline{C}H_3$)$_B$), 42.3 (NH<u>C</u>H_2), 38.1 (<u>C</u>(CO_2Me)$_2$), 33.5 (<u>C</u>$H_2CH_2CH_3$), 32.8 (<u>C</u>HC(=O)NH), 22.0 ($CH_2\underline{C}H_2CH_3$), 13.8 ($CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3307 (N-H), 2957, 2932 (C-H), 1736 (C=O ester), 1655 (C=O amide), 1543, 1281, 1254; **HRMS** (ES+) exact mass

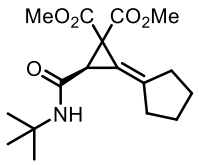
calculated for $[M+Na]^+$ ($C_{15}H_{21}NNaO_5^+$) requires *m/z* 318.1312, found *m/z* 318.1313; $[\alpha]_D^{25}$ = –92.1 (*c* 0.33, $CHCl_3$).

NOESY of compound **427**: Cross-peaks are observed between N<u>H</u> and C=C<u>H</u>$CH_2CH_2CH_3$.



5.9.3.17 Synthesis and characterisation of 428

dimethyl (R)-2-(tert-butylcarbamoyl)-3-cyclopentylidenecyclopropane-1,1-dicarboxylate (428)

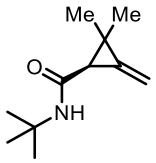


The title compound was prepared according to general procedure **XIV** from dimethyl 2-(*tert*-butylcarbamoyl)-3-cyclopentylcycloprop-2-ene-1,1-dicarboxylate (**422**) (32.3 mg, 0.100 mmol, 1.00 eq) with catalyst **124c**. After being deemed complete by TLC (pentane/EtOAC = 7/3) the reaction was quenched and the crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 8/2 then pentane/EtOAc = 9/1) to provide the title compound (**428**) as a white solid in 93% yield (30.1 mg) and 99% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 98/2, 1 ml/min, λ = 220 nm, t(major) = 31.20 min, t(minor) = 44.53 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 5.41 (s, 1H, N$\underline{H}$), 3.74 (s, 3H, one of $C(CO_2C\underline{H_3})_A(CO_2CH_3)_B$), 3.73 (s, 3H, one of $C(CO_2CH_3)_A(CO_2C\underline{H_3})_B$), 3.08 (p, *J* = 3.0 Hz, 1H, C$\underline{H}$C(=O)), 2.74 – 2.63 (m, 1H, one of $C\underline{H_A}H_BCCH_CH_D$), 2.44 (m, two of one of $CH_A\underline{H_B}CC\underline{H_C}H_D$ 2H), 2.42 – 2.30 (m, 1H, one of one of $CH_AH_BCCH_C\underline{H_D}$), 1.84 – 1.69 (m, 4H, $C\underline{H_2}CH_2CCH_2C\underline{H_2}$), 1.29 (s, 9H, $C(C\underline{H_3})_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 168.0 (one of $C(\underline{C}O_2CH_3)_A(CO_2CH_3)_B$), 166.5 (one of $C(CO_2CH_3)_A(\underline{C}O_2CH_3)_B$), 164.9 (C$\underline{O}$NH), 140.4 ($CH_2\underline{C}$=C), 110.5 ($CH_2C=\underline{C}$), 53.1 (one of $C(CO_2\underline{C}H_3)_A(CO_2CH_3)_B$), 52.9 (one of $C(CO_2CH_3)_A(CO_2\underline{C}H_3)_B$), 51.6 ($\underline{C}(CH_3)_3$), 38.5 ($\underline{C}(CO_2Me)_2$), 34.2 (C$\underline{H}$C(=O)), 32.4 (one of $(\underline{C}H_2)_AC(CH_2)_B$), 32.3 (one of $(CH_2)_AC(\underline{C}H_2)_B$), 28.7 ($C(\underline{C}H_3)_3$), 26.8 (one of $(\underline{C}H_2)_ACH_2CCH_2(CH_2)_B$), 26.5 (one of $(CH_2)_ACH_2CCH_2(\underline{C}H_2)_B$); **IR** (film) ν_{max}/cm^{-1}:

3325 (N-H), 2956 (C-H), 1734 (C=O ester), 1680 (C=C), 1660 (C=O amide); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{26}O_5N^+$) requires *m/z* 324.1805, found *m/z* 324.1807; **MP**: 122 – 124 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –42.4 (*c* 0.43, $CHCl_3$).

5.9.3.18 Synthesis and characterisation of 429

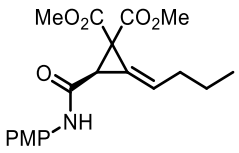
(S)-N-(tert-butyl)-2,2-dimethyl-3-methylenecyclopropane-1-carboxamide (429)



The title compound was prepared according to general procedure **XIV** from N-(*tert*-butyl)-2,3,3-trimethylcycloprop-1-ene-1-carboxamide (**423**) (9.1 mg, 0.050 mmol, 1.00 eq) with catalyst **124d**. After 24 h the reaction was quenched and the crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 7/3) to provide the title compound (**429**) as a white solid in 78% yield (7.1 mg) and 99% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 98/2, 1 ml/min, λ = 210 nm, t(minor) = 5.66 min, t(major) = 9.24 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 5.47 (d, *J* = 2.0 Hz, 1H, one of C=C$\underline{H_A}H_B$), 5.45 (d, *J* = 2.0 Hz, 1H, one of C=C$H_A\underline{H_B}$), 5.40 (bs, 1H, N$\underline{H}$), 1.95 (t, *J* = 2.0 Hz, 1H, C$\underline{H}$C(=O)), 1.32 (s, 9H, C($C\underline{H_3}$)$_3$), 1.26 (s, 3H, one of C($C\underline{H_3}$)$_A$(CH_3)$_B$), 1.22 (s, 3H, one of C(CH_3)$_A$($C\underline{H_3}$)$_B$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 168.2 ($\underline{C}$=O), 143.3 ($\underline{C}$=CH_2), 103.5 (C=$\underline{C}H_2$), 51.2 ($\underline{C}$(CH_3)$_3$), 33.5 ($\underline{C}$HC(=O)), 28.9 (C($\underline{C}H_3$)$_3$), 25.9 (one of C($\underline{C}H_3$)$_A$(CH_3)$_B$), 24.0 ($\underline{C}$(CH_3)$_2$), 18.7 (one of C(CH_3)$_A$($\underline{C}H_3$)$_B$); **IR** (film) ν_{max}/cm^{-1}: 3287 (N-H), 2966, 2923 (C-H), 1632 (C=O), 1555; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{20}NO^+$) requires *m/z* 182.1539, found *m/z* 182.1542; **MP**: 72 °C (sublimation); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +42.9 (*c* 0.12, $CHCl_3$).

5.9.3.19 Synthesis and characterisation of 430

dimethyl (R,Z)-2-butylidene-3-((4-methoxyphenyl)carbamoyl)cyclopropane-1,1-dicarboxylate (430)

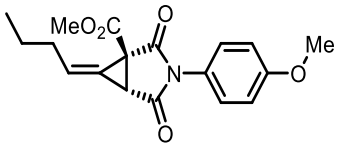


The title compound was prepared according to general procedure **XIV** from dimethyl 2-butyl-3-((4-methoxyphenyl)carbamoyl)cycloprop-2-ene-1,1-dicarboxylate (**424**) (18.1 mg, 0.0500 mmol, 1.00 eq) with catalyst **124c** in THF (1 ml). After 1.75 h the reaction mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (pentane/EtOAc = 8/2 to 7/3) to provide the title compound (**430**) as a colourless oil in >99% yield (18.1 mg) and 94% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 240 nm, t(minor) = 19.35 min, t(major) = 23.19 min]. **^{1}H NMR** (600 MHz, $CDCl_3$) δ(ppm): 7.38 – 7.33 (m, 2H, Ar<u>H</u>), 7.31 (s, 1H, N<u>H</u>), 6.87 – 6.81 (m, 2H, Ar<u>H</u>), 6.23 (td, *J* = 7.0, 2.0 Hz, 1H, C=C<u>H</u>CH_2), 3.78 (s, 3H, one of $C(CO_2C\underline{H}_3)_A(CO_2CH_3)_B$), 3.78 (s, 3H, $C\underline{H}_3OAr$), 3.72 (s, 3H, one of $C(CO_2CH_3)_A(CO_2C\underline{H}_3)_B$), 3.35 (q, *J* = 2.0 Hz, 1H, C<u>H</u>C(=O)), 2.45 – 2.29 (m, 2H, $CH_2CH_2CH_3$), 1.62 – 1.51 (m, 2H, $CH_2C\underline{H}_2CH_3$), 0.94 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2C\underline{H}_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ(ppm): 167.4 (one of $C(\underline{C}O_2CH_3)_A(CO_2CH_3)_B$), 166.0 (one of $C(CO_2CH_3)_A(\underline{C}O_2CH_3)_B$), 163.7 (<u>C</u>(=O)NH), 156.9 (Ar<u>C</u>), 130.5 (Ar<u>C</u>), 125.7 (C=<u>C</u>HCH_2), 121.9 (Ar<u>C</u>H), 120.4 (<u>C</u>=$CHCH_2$), 114.3 (Ar<u>C</u>H), 55.6 ($ArO\underline{C}H_3$), 53.4 (one of $C(CO_2\underline{C}H_3)_A(CO_2CH_3)_B$), 53.3 (one of $C(CO_2CH_3)_A(CO_2\underline{C}H_3)_B$), 38.4 (<u>C</u>$(CO_2Me)_2$), 33.7 (<u>C</u>$H_2CH_2CH_3$), 33.6 (<u>C</u>HC(=O)), 22.0 ($CH_2\underline{C}H_2CH_3$), 13.8 ($CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3299 (N-H), 2958, 2839

(C-H), 1733, 1686 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{24}O_6N^+$) requires *m/z* 362.1598, found *m/z* 362.1601; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –76.8 (*c* 0.38, $CHCl_3$).

5.9.3.20 Synthesis and characterisation of 431

dimethyl (R,Z)-2-butylidene-3-((4-hydroxyphenyl)carbamoyl)cyclopropane-1,1-dicarboxylate (431)

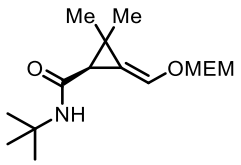


The title compound was prepared according to general procedure **XIV** from dimethyl 2-butyl-3-((4-methoxyphenyl)carbamoyl)cycloprop-2-ene-1,1-dicarboxylate (**424**) (36.1 mg, 0.100 mmol, 1.00 eq) with catalyst **124c** (the substrate is sparingly soluble however enters solution overnight). After 24 h the crude reaction mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (pentane/EtOAc = 8/2 to 7/3) to provide the title compound (**431**) as a colourless oil in 61% yield (20.0 mg) and 97% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 90/10 to 70/30, 1 ml/min, λ = 230 nm, t(major) = 23.73 min, t(minor) = 28.31 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.12 – 7.07 (m, 2H, Ar<u>H</u>), 6.98 – 6.92 (m, 2H, Ar<u>H</u>), 6.22 (td, *J* = 7.0, 2.0 Hz, 1H, C=C<u>H</u>CH_2), 3.85 (s, 3H, $CO_2C\underline{H_3}$), 3.81 (s, 3H, ArO$C\underline{H_3}$), 3.50 (q, *J* = 1.5 Hz, 1H, C<u>H</u>C(=O)), 2.29 (dddd, *J* = 17.0, 14.5, 7.5, 6.0 Hz, 2H, $C\underline{H_2}CH_2CH_3$), 1.53 – 1.44 (m, 2H, $CH_2C\underline{H_2}CH_3$), 0.90 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2C\underline{H_3}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 169.8 (one of <u>C</u>(=O)NC(=O)), 167.5 (one of C(=O)N<u>C</u>(=O)), 164.7 (<u>C</u>O_2Me), 159.8 (Ar<u>C</u>), 128.0 (Ar<u>C</u>H), 124.2 (Ar<u>C</u>), 123.0 (C=<u>C</u>HCH_2), 122.7 (<u>C</u>=CHCH_2), 114.7 (Ar<u>C</u>H), 55.7 (ArO$C\underline{H_3}$), 53.3 ($CO_2C\underline{H_3}$), 35.9 (<u>C</u>CO_2Me), 33.2 ($\underline{C}H_2CH_2CH_3$), 31.7 (C<u>H</u>C(=O)), 21.7 ($CH_2\underline{C}H_2CH_3$), 13.7 ($CH_2CH_2\underline{C}H_3$); **IR** (film) ν_{max}/cm^{-1}: 3052, 2959, 2934, 2873 (C-H), 1786, 1714 (has a shoulder) (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$

($C_{18}H_{20}O_5N$) requires *m/z* 330.1336, found *m/z* 330.1336; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –148.7 (*c* 0.32, $CHCl_3$).

5.9.3.21 Synthesis and characterisation of 432

(Z)-N-(tert-butyl)-3-(((2-methoxyethoxy)methoxy)methylene)-2,2-dimethylcyclopropane-1-carboxamide (432)

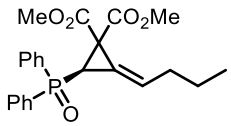


The title compound was prepared according to general procedure **XIV** from **425** (14.3 mg, 0.0500 mmol) with catalyst **124d**. The crude reaction mixture was purified by silica gel column chromatography (pentane/EtOAc = 7/3 to 6/4) to provide the title compound (**432**) as a colourless oil in 84% yield (12.0 mg) and >90% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 97/3, 1 ml/min, λ = 210 nm, t(minor) = 15.38 min, t(major) = 19.19 min].* **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 6.51 (d, J = 1.5 Hz, 1H, C=C<u>H</u>), 5.21 (bs, 1H, N<u>H</u>), 4.76 (s, 2H, OC<u>H</u>$_2$O), 3.55 (td, J = 4.5, 1.5 Hz, 2H, C<u>H</u>$_2$CH$_2$OCH$_3$), 3.26 (dd, J = 5.5, 4.5 Hz, 2H, CH$_2$C<u>H</u>$_2$OCH$_3$), 3.06 (s, 3H, OC<u>H</u>$_3$), 1.97 (d, J = 1.5 Hz, 1H, C<u>H</u>C(=O)), 1.38 (s, 3H, one of C(C<u>H</u>$_3$)$_A$(CH$_3$)$_B$), 1.27 (s, 9H, C(C<u>H</u>$_3$)$_3$), 1.19 (s, 3H, one of C(CH$_3$)$_A$(C<u>H</u>$_3$)$_B$); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 167.8 (<u>C</u>=O), 135.3 (C=<u>C</u>H(OMEM)), 110.3 (<u>C</u>=CH), 94.6 (O<u>C</u>H$_2$OCH$_2$CH$_2$OCH$_3$), 72.0 (OCH$_2$OCH$_2$<u>C</u>H$_2$OCH$_3$), 68.1 (OCH$_2$O<u>C</u>H$_2$CH$_2$OCH$_3$), 58.6 (OCH$_2$OCH$_2$CH$_2$O<u>C</u>H$_3$), 50.8 (<u>C</u>(CH$_3$)$_3$), 33.1 (<u>C</u>HC(=O)), 28.8 (C(<u>C</u>H$_3$)$_3$), 26.4 (one of C(<u>C</u>H$_3$)$_a$(CH$_3$)$_b$), 25.6 (<u>C</u>(CH$_3$)$_2$), 19.4 (one of C(CH$_3$)$_A$(<u>C</u>H$_3$)$_B$); **IR** (film) ν_{max}/cm^{-1}: 3318 (N-H), 2969, 2926, 2890 (C-H), 1647 (C=O); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{15}H_{27}NNaO_4^+$) requires m/z 308.1832, found m/z 308.1832; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –21.8 (c 0.17, $CHCl_3$).*Only an estimate for the ee is available due to the quality of the HPLC trace. The product appears to be unstable.

5.9.3.22 Synthesis and characterisation of 436

dimethyl (R,E)-2-butylidene-3-(diphenylphosphoryl)cyclopropane-1,1-dicarboxylate

(436)

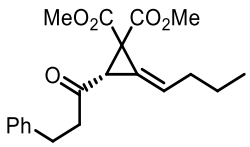


The title compound was prepared according to general procedure **XIV** from **436** (20.6 mg, 0.0500 mmol) with catalyst **124c**. The reaction was initiated at −78 °C and allowed to stir for 1 h at which point the temperature was raised to −20 °C. The reaction was stirred for a further 10 min at which point the temperature was raised to 0 °C. The reaction was allowed to progress at this temperature fo 1 h at which point the reaction was quenched with AcOH to give the crude product in 9:1 d.r.. The crude reaction mixture was purified by silica gel column chromatography (pentane/EtOAc = 1/1) to provide the title compound (**436**) as a colourless oil in 95% yield (18.9 mg) and 99% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, t(major) = 7.16 min, t(minor) = 15.06 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.81 – 7.70 (m, 4H, Ar<u>H</u>), 7.60 – 7.42 (m, 6H, Ar<u>H</u>), 6.24 (ddd, *J* = 10.5, 7.5, 3.1 Hz, C=C<u>H</u>CH_2 minor diastereomer), 5.91 – 5.76 (m, 1H, C=C<u>H</u>CH_2 major diastereomer), 3.79 (s, one of $C(CO_2C\underline{H}_3)_A(CO_2CH_3)_B$ minor diastereomer), 3.77 (s, 3H, one of $C(CO_2C\underline{H}_3)_A(CO_2CH_3)_B$ major diastereomer), 3.70 (s, 3H, one of $C(CO_2CH_3)_A(CO_2C\underline{H}_3)_B$ major diastereomer), 3.67 (s, one of $C(CO_2CH_3)_A(CO_2C\underline{H}_3)_B$ minor diastereomer), 3.28 (ddt, *J* = 9.5, 3.5, 2.0 Hz, C<u>H</u>P(=O) minor diastereomer), 3.20 (dq, *J* = 9.0, 2.0 Hz, 1H, C<u>H</u>P(=O) major diastereomer), 2.42 – 2.21 (m, 2H, $C\underline{H}_2CH_2CH_3$), 1.53 – 1.37 (m, 2H, $CH_2C\underline{H}_2CH_3$), 0.86 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2C\underline{H}_3$, major diastereomer), 0.67 (t, *J* = 7.5 Hz, $CH_2CH_2C\underline{H}_3$, minor diastereomer); **^{13}C NMR**

(101 MHz, $CDCl_3$) δ 168.2 (one of $C(\underline{C}O_2CH_3)_A(CO_2CH_3)_B$), 165.5 (one of $C(CO_2CH_3)_A(\underline{C}O_2CH_3)_B$), 133.4 (Ar<u>C</u>), 132.4 (Ar<u>C</u>), 132.2 (Ar<u>C</u>H), 132.2 (Ar<u>C</u>H), 131.5 (d, J_{CP} = 19.0, Ar<u>C</u>H) 131.36 (d, J_{CP} = 18.5 Hz, Ar<u>C</u>H), 128.8 (d, J = 6.5 Hz, Ar<u>C</u>H), 128.7 (d, J = 6.5 Hz, Ar<u>C</u>H), 123.8 (d, J_{CP} = 5.0 Hz, C=<u>C</u>HCH$_2$), 118.2 (d, J_{CP} = 8.0 Hz, <u>C</u>=CHCH$_2$), 53.5 (one of $C(CO_2\underline{C}H_3)_A(CO_2CH_3)_B$), 53.1 (one of $C(CO_2CH_3)_A(CO_2\underline{C}H_3)_B$), 33.55 (d, J_{CP} = 2.0 Hz, <u>C</u>H$_2$CH$_2$CH$_3$), 27.0 (<u>C</u>(CO$_2$Me)$_2$), 26.1 (<u>C</u>HP(=O)), 22.0 (d, J_{CP} = 2.0 Hz, CH$_2$<u>C</u>H$_2$CH$_3$), 13.8 (CH$_2$CH$_2$<u>C</u>H$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ(ppm): 24.8 (<u>P</u>=O, major diastereomer), 23.2 (<u>P</u>=O, minor diastereomer); **IR** (film) ν_{max}/cm^{-1}: 2958, 2924, 2852 (C-H), 1733 (C=O), 1458; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{26}O_5P^+$) requires *m/z* 413.1512, found *m/z* 413.1511; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = −33.5 (*c* 0.41, $CHCl_3$)

5.9.3.23 Synthesis and characterisation of 440

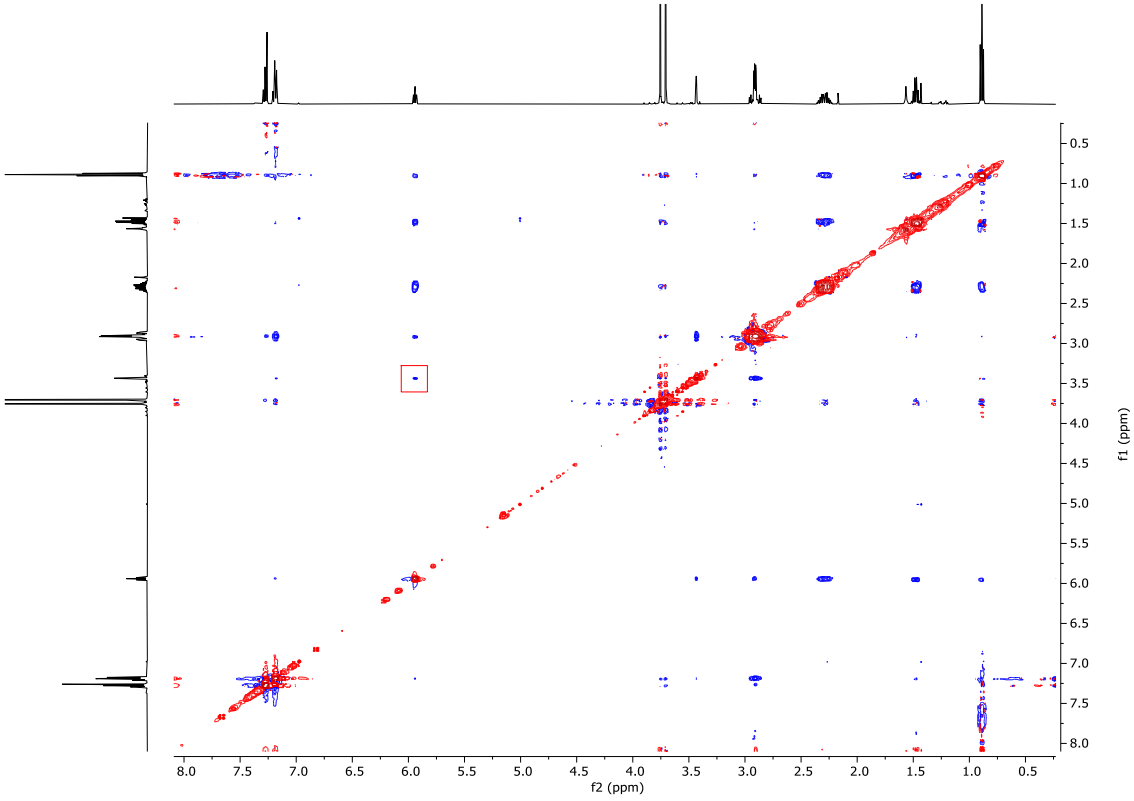
dimethyl (S,Z)-2-butylidene-3-(3-phenylpropanoyl)cyclopropane-1,1-dicarboxylate (440)



The title compound was prepared according to general procedure **XV** from dimethyl 2-butyl-3-(3-phenylpropanoyl)cycloprop-2-ene-1,1-dicarboxylate (**439**) (34.4 mg, 0.100 mmol, 1.00 eq) with catalyst **126b**. After 2 h the reaction mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 8/2) to provide the title compound (**440**) as a white solid in 99% yield (34.2 mg) and 93% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 220, 1 ml/min, λ = 20.74 nm, t(minor) = 20.74 min, t(major) = 24.47 min]. The sample was recrystallised by evaporation of pentane to provide a sample suitable for single crystal x-ray diffraction in 92% ee. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 7.33 – 7.24 (m, 2H, ArH), 7.23 – 7.16 (m, 3H, ArH), 5.94 (td, *J* = 7.5, 2.0 Hz, 1H, C=CH), 3.76 (s, 3H, one of $C(CO_2CH_3)_A(CO_2CH_3)_B$), 3.71 (s, 3H, one of $C(CO_2CH_3)_A(CO_2CH_3)_B$), 3.43 (q, *J* = 2.0 Hz, 1H, CHC(=O)), 2.98 – 2.83 (m, 4H, CH_2CH_2Ph), 2.29 (m, 2H, $CH_2CH_2CH_3$), 1.52 – 1.44 (m, 2H, $CH_2CH_2CH_3$), 0.89 (t, *J* = 7.5 Hz, 3H, $CH_2CH_2CH_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 202.8 ($CH_2C(=O)$), 167.7 (one of $C(CO_2CH_3)_A(CO_2CH_3)_B$), 165.7 (one of $C(CO_2CH_3)_A(CO_2CH_3)_B$), 140.8 (ArC), 128.7 (ArCH), 128.5 (ArCH), 126.3 (ArCH), 123.9 (CHC=CH), 121.2 (CHC=CH), 53.4 (one of $C(CO_2CH_3)_A(CO_2CH_3)_B$), 53.1 (one of $C(CO_2CH_3)_A(CO_2CH_3)_B$), 45.5 ($CH_2C(=O)$), 39.7 ($C(CO_2Me)$), 36.9 ($CH_2C(=O)CH$), 33.4 ($CH_2CH_2CH_3$), 29.7 ($CH_2Ph$), 22.0 ($CH_2CH_2CH_3$), 13.8 ($CH_2CH_2CH_3$); **IR** (film)

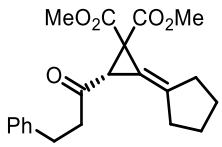
ν_{max}/cm^{-1}: 2957, 2873 (C-H), 1736 (C=O ester), 1714 (C=O ketone), 1497, 1454, 1435, 1277, 1247; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{25}O_5^+$) requires *m/z* 345.1697, found *m/z* 345.1694; **MP**: 58 – 60 °C; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +130.63 (*c* 0.65, $CHCl_3$).

NOESY of compound **440**: Cross-peaks are observed between C=C<u>H</u>CH$_2$ and CHC(=O).



5.9.3.24 Synthesis and characterisation of 445

dimethyl (S)-2-cyclopentylidene-3-(3-phenylpropanoyl)cyclopropane-1,1-dicarboxylate (445)

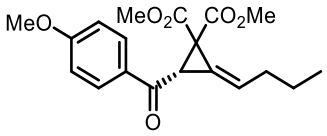


The title compound was prepared according to general procedure **XV** from dimethyl 2-cyclopentyl-3-(3-phenylpropanoyl)cycloprop-2-ene-1,1-dicarboxylate (**E51**) (35.6 mg, 0.100 mmol, 1.00 eq) with catalyst **126b**. After 4 h the reaction was quenched, and the crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 9/1) to provide the title compound (**445**) as a colourless oil in 90% yield (32.3 mg) and 99% ee. [determined by HPLC chiralpak AD-H, hexane/isopropanol = 98/2, 1 ml/min, λ = 220 nm, t(minor) = 20.74 min, t(major) = 24.47 min]. **^{1}H NMR** (500 MHz, Benzene-d_6) δ(ppm): 7.13 – 7.07 (m, 2H, Ar$\underline{H}$), 7.05 – 6.96 (m, 3H, Ar$\underline{H}$), 3.52 (p, J = 2.5 Hz, 1H, C$\underline{H}$C(=O)), 3.45 (s, 3H, one of C($CO_2C\underline{H}_3$)$_A$(CO_2CH_3)$_B$), 3.31 (s, 3H, one of C(CO_2CH_3)$_A$($CO_2C\underline{H}_3$)$_B$), 2.90 – 2.77 (m, 3H, C$\underline{H}_2$Ph and one of C$\underline{H}_A$H$_B$CH$_2$CH$_2$CHCH$_D$), 2.63 – 2.45 (m, 2H, C$\underline{H}_2$CH$_2$Ph), 2.46 – 2.33 (m, 1H, one of CH$_A\underline{H}_B$CH$_2$CH$_2$CHCH$_D$), 2.21 – 2.11 (m, 2H, two of CH$_A$H$_B$CH$_2$CH$_2$C$\underline{H}_C\underline{H}_D$), 1.54 – 1.33 (m, 4H, CH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$); **^{13}C NMR** (126 MHz, Benzene-d_6) δ(ppm): 201.4 ($\underline{C}$=OCH$_2$), 167.7 (one of C($\underline{C}O_2Me$)$_A$(CO_2Me)$_B$), 165.6 (one of C(CO_2Me)$_A$($\underline{C}O_2Me$)$_B$), 141.0 (Ar$\underline{C}$), 138.2 (CH$_2\underline{C}$=CCH), 128.4 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 125.9 (Ar$\underline{C}$H), 111.8 (CH$_2$C=$\underline{C}$CH), 52.2 (one of C($CO_2C\underline{H}_3$)$_A$(CO_2CH_3)$_B$), 52.1 (one of C(CO_2CH_3)$_A$($CO_2C\underline{H}_3$)$_B$), 45.1 ($\underline{C}$H$_2$CH$_2$Ph), 40.5 ($\underline{C}$(CO_2Me)$_2$), 37.1 ($\underline{C}$HC(=O)), 32.1 (one of CH$_2$($\underline{C}$H$_2$)$_A$(CH$_2$)$_B$CH$_2$), 32.0 (one of CH$_2$(CH$_2$)$_A$($\underline{C}$H$_2$)$_B$CH$_2$), 29.5 (CH$_2\underline{C}$H$_2$Ph),

26.3 (one of C=C($\underline{C}H_2$)$_A$(CH_2)$_B$), 26.3 (one of C=C(CH_2)$_A$($\underline{C}H_2$)$_B$); **IR** (film) ν_{max}/cm^{-1}: 2954 (C-H), 1732, 1711 (C=O); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{26}}$ = +87.5 (*c* 0.26, $CHCl_3$).

5.9.3.25 Synthesis and characterisation of 446

dimethyl (S,Z)-2-butylidene-3-(4-methoxybenzoyl)cyclopropane-1,1-dicarboxylate (446)

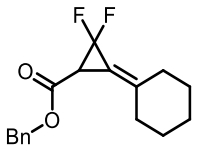


The title compound was prepared according to general procedure **XV** from dimethyl 2-butyl-3-(4-methoxybenzoyl)cycloprop-2-ene-1,1-dicarboxylate (**E53**) (34.6 mg, 0.100 mmol, 1.00 eq) with catalyst **126b**. After 2 h the reaction mixture was quenched with AcOH to give the crude product in >20:1 d.r. The crude reaction mixture was purified by silica gel column chromatography (toluene/EtOAc = 95/5 then pentane/Et_2O = 7/3) to provide the title compound (**446**) as a colourless oil in 97% yield (33.7 mg) and 84% ee. (If the reaction is left for 1 h the product is obtained in 91% yield and 88% ee) [determined by HPLC chiralpak AD-H, hexane/isopropanol = 95/5, 1 ml/min, λ = 220 nm, t(minor) = 36.13 min, t(major) = 35.01 min]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ(ppm): 8.05 – 7.97 (m, 2H, Ar<u>H</u>), 7.01 – 6.92 (m, 2H, Ar<u>H</u>), 6.07 (td, *J* = 7.5, 2.5 Hz, 1H, C=C<u>H</u>CH_2), 4.10 (q, *J* = 2.0 Hz, 1H, C<u>H</u>C=O), 3.88 (s, 3H, ArOC<u>H_3</u>), 3.82 (s, 3H, one of C(CO_2C<u>H_3</u>)$_A$(CO_2CH_3)$_B$), 3.68 (s, 3H, one of C(CO_2CH_3)$_A$(CO_2C<u>H_3</u>)$_B$), 2.41 – 2.23 (m, 2H, C<u>H_2</u>CH_2CH_3), 1.54 – 1.45 (m, 2H, CH_2C<u>H_2</u>CH_3), 0.91 (t, *J* = 7.5 Hz, 3H, CH_2CH_2C<u>H_3</u>); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(ppm): 190.7 (<u>C</u>=OAr), 167.9 (one of C(<u>C</u>O_2CH_3)$_A$(CO_2CH_3)$_B$), 166.2 (one of C(CO_2CH_3)$_A$(<u>C</u>O_2CH_3)$_B$), 164.1 (Ar<u>C</u>), 131.1 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>), 123.6 (C=<u>C</u>HCH_2), 121.5 (<u>C</u>=CHCH_2), 114.1 (Ar<u>C</u>H), 55.7 (ArO<u>C</u>H_3), 53.4 (one of C(CO_2<u>C</u>H_3)$_A$(CO_2CH_3)$_B$), 52.9 (one of C(CO_2CH_3)$_A$(CO_2<u>C</u>H_3)$_B$), 39.1 (<u>C</u>(CO_2CH_3)$_A$(CO_2CH_3)$_B$), 34.5 (C<u>H</u>C=O), 33.4 (<u>C</u>$H_2CH_2CH_3$), 22.1 (CH_2<u>C</u>H_2CH_3), 13.8 (CH_2CH_2<u>C</u>H_3); **IR** (film) ν_{max}/cm^{-1}: 2958, 2873,

2843 (C-H), 1732 (C=O ester), 1673 (C=O ketone), 1248 (C-O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}O_6^+$) requires *m/z* 347.1489, found *m/z* 347.1484; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26.1}}$ = –93.1 (*c* 0.45, $CHCl_3$).

5.9.3.26 Synthesis and characterisation of 455

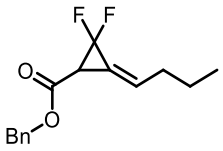
benzyl 3-cyclohexylidene-2,2-difluorocyclopropane-1-carboxylate (455)



The title compound was prepared according to general procedure **XIV** from benzyl 2-cyclohexyl-3,3-difluorocycloprop-1-ene-1-carboxylate (**450**) (29.2 mg, 0.100 mmol, 1.00 eq) with catalyst **124c**. After being deemed complete by TLC (pentane/Et_2O = 95/5) the reaction was quenched, and the crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 97/3 to 95/5) to provide the title compound (**455**) as a yellow oil in 86% yield (25.1 mg) and 0% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 220 nm, t = 4.34 min, t = 5.60 min]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm): 7.33 – 7.21 (m, 5H, Ar<u>H</u>), 5.11 (d, *J* = 12.5 Hz, 1H, one of C<u>H</u>$_A$H$_B$Ph), 5.07 (d, *J* = 12.5 Hz, 1H, one of CH$_A$<u>H</u>$_B$Ph), 2.92 (tp, J_{HH} and J_{HF} = 5.5, 2.0 Hz, 1H, C<u>H</u>C(=O)), 2.43 – 2.24 (m, 2H, 2 x C<u>H</u> cyclohexane ring), 2.24 – 2.09 (m, 2H, 2 x C<u>H</u> cyclohexane ring), 1.66 – 1.45 (m, 6H, 6 x C<u>H</u> cyclohexane ring); **^{13}C NMR** (101 MHz, Benzene-d_6) δ(ppm): 165.47 (d, *J* = 4.0 Hz, <u>C</u>=O), 147.0 (Ar<u>C</u>), 136.3 (<u>C</u>=CCHCO$_2$Bn), 128.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 109.90 – 103.85 (m, C=<u>C</u>CHCO$_2$Bn and <u>C</u>F$_2$), 67.0 (<u>C</u>H$_2$Ph), 34.3 (<u>C</u>HCO$_2$Ph), 32.8 (<u>C</u>H$_2$CH$_2$CH$_2$CH$_2$CH$_2$ or CH$_2$CH$_2$CH$_2$CH$_2$<u>C</u>H$_2$), 32.6 (<u>C</u>H$_2$CH$_2$CH$_2$CH$_2$CH$_2$ or CH$_2$CH$_2$CH$_2$CH$_2$<u>C</u>H$_2$)), 32.5 (t, J_{CF} = 13.5 Hz, <u>C</u>HCO$_2$Bn), 27.6 (CH$_2$<u>C</u>H$_2$CH$_2$CH$_2$CH$_2$ or CH$_2$CH$_2$CH$_2$<u>C</u>H$_2$CH$_2$), 27.3 (CH$_2$<u>C</u>H$_2$CH$_2$CH$_2$CH$_2$ or CH$_2$CH$_2$CH$_2$<u>C</u>H$_2$CH$_2$), 25.8 (CH$_2$CH$_2$<u>C</u>H$_2$CH$_2$CH$_2$); **^{19}F NMR** (377 MHz, $CDCl_3$) δ(ppm): -121.54 (d, *J* = 164.0 Hz), -133.83 (d, *J* = 164.0 Hz); **IR** (film) ν_{max}/cm^{-1}: 3035, 2938, 2859 (C-H), 1775, 1736 (C=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}F_2H_{18}NaO_2^+$) requires *m/z* 315.1167, found *m/z* 315.1167.

5.9.3.27 Synthesis and characterisation of 456

benzyl (Z)-3-butylidene-2,2-difluorocyclopropane-1-carboxylate (456)

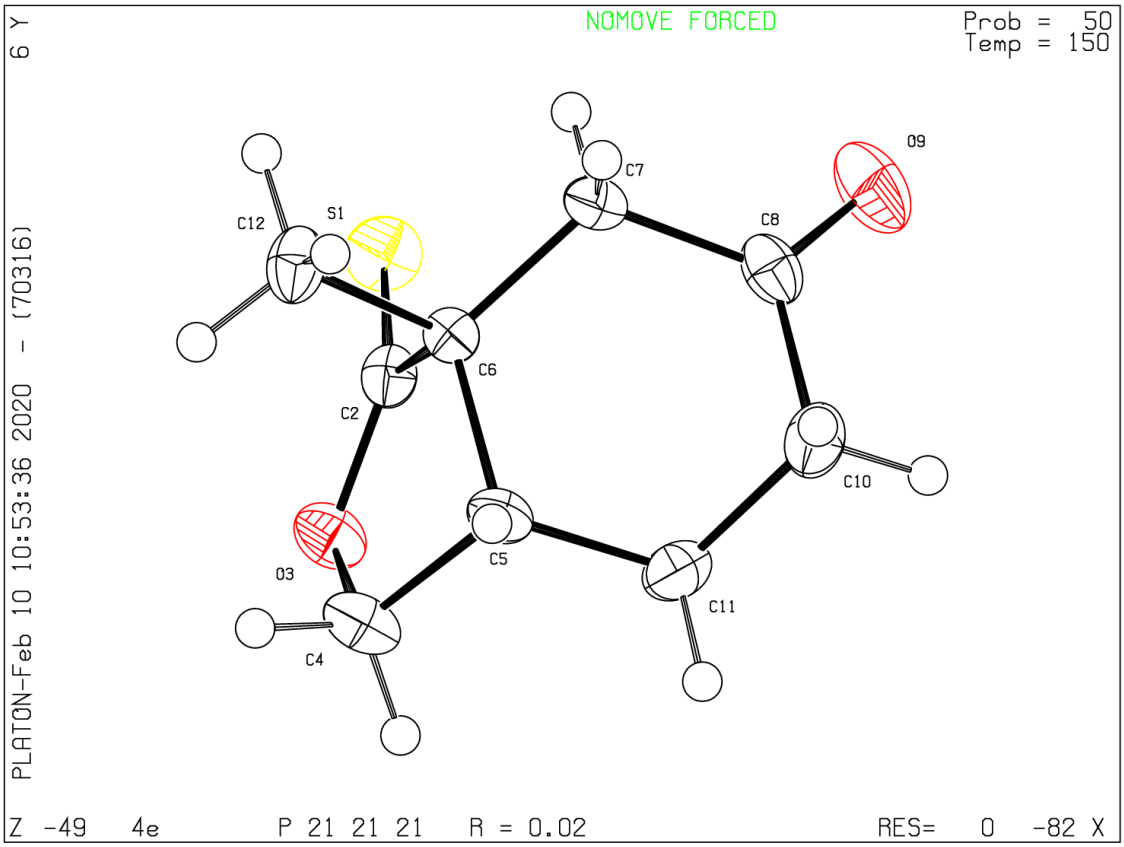


The title compound was prepared according to general procedure **XIV** from benzyl 2-butyl-3,3-difluorocycloprop-1-ene-1-carboxylate (**451**) (10 mg 0.038 mmol, 1.0 eq) with catalyst **124c**. After being deemed complete by TLC (pentane/Et_2O = 97/3) the reaction was quenched, and the crude reaction mixture was purified by silica gel column chromatography (pentane/Et_2O = 99/1) to provide the title compound (**456**) as a yellow oil in 43% yield (4.3 mg) and 2% ee. [determined by HPLC chiralpak AS-H, hexane/isopropanol = 98/2, 1 ml/min, λ = 210 nm, t(major) = 5.45 min, t(minor) = 6.04 min].**^{1}H NMR** (400 MHz, Benzene-d_6) δ(ppm): 7.13 (m, 1H, Ar<u>H</u>), 7.11 – 7.00 (m, 3H, Ar<u>H</u>), 5.78 (tq, J_{HH} and J_{HF} = 6.5, 2.0 Hz, 1H, C<u>H</u>CH_2), 4.99 (d, J = 12.5 Hz, 1H, C<u>H_A</u>H_BPh), 4.91 (d, J = 12.5 Hz, 1H, CH_A<u>H_B</u>Ph), 2.85 (ddd, J = 8.0, 5.5, 3.0 Hz, 1H, C<u>H</u>CO_2Bn), 1.82 (m, 2H, C<u>H_2</u>CH_2CH_3), 1.33 – 1.19 (m, 2H, CH_2C<u>H_2</u>CH_3), 0.68 (t, J = 7.5 Hz, 3H, CH_2CH_2C<u>H_3</u>); **^{13}C NMR** (151 MHz, Benzene-d_6) δ(ppm): 165.1 – 165.0 (m, <u>C</u>=O), 136.1 (Ar<u>C</u>), 134.3 (C=<u>C</u>HCH_2), 128.7 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 116.3 (t, J = 6.0 Hz, <u>C</u>=CHCH_2), 107.7 – 103.7 (m, <u>C</u>F_2), 67.2 (<u>C</u>H_2Ph), 34.4 (<u>C</u>$H_2CH_2CH_3$), 32.7 (t, J = 13.5 Hz, <u>C</u>HC(=O)), 20.8 (CH_2<u>C</u>H_2CH_3), 13.5 (CH_2CH_2<u>C</u>H_3); **^{19}F NMR** (565 MHz, C_6D_6) δ(ppm): -121.5 – -122.4 (m, one of C<u>F_A</u>F_B), -133.2 – -134.1 (m, one of CF_A<u>F_B</u>); **IR** (film) ν_{max}/cm^{-1}: 2961, 2933 (C-H), 1741 (C=O).

5.10 Single crystal X-ray diffraction data

5.10.1 Single crystal X-Ray diffraction data for compound 394

CCDC 1982997



Crystal data	
Chemical formula	$C_9H_{12}O_2S$
M_r	184.26
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	150
a, *b*, *c* (Å)	8.0589 (1), 9.1929 (1), 12.3333 (2)
V (Å^3)	913.71 (2)
Z	4
Radiation type	Cu *K*α
μ (mm^{-1})	2.80

Crystal size (mm)	0.20 × 0.10 × 0.10
Data collection	
Diffractometer	Oxford Diffraction SuperNova
Absorption correction	Multi-scan *CrysAlis PRO* (Rigaku Oxford Diffraction, 2017)
T_{min}, T_{max}	0.64, 0.76
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	14164, 1919, 1910
R_{int}	0.024
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.632
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.021, 0.058, 1.03
No. of reflections	1919
No. of parameters	110
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.20, −0.17
Absolute structure	Parsons, Flack & Wagner (2013), 785 Friedel Pairs
Absolute structure parameter	−0.009 (3)

Computer programs: SuperNova, (Oxford Diffraction, 2010), *CrysAlis PRO* (Rigaku Oxford Diffraction, 2017), *SUPERFLIP* (Palatinus & Chapuis, 2007), *CRYSTALS* (Betteridge *et al.*, 2003), *CAMERON* (Watkin *et al.*, 1996).

Table 2

Selected geometric parameters (Å, º)

S1—C2	1.6260 (11)	C6—C7	1.5333 (14)
C2—O3	1.3329 (14)	C6—C12	1.5426 (14)
C2—C6	1.5216 (14)	C7—C8	1.5042 (15)
O3—C4	1.4706 (14)	C8—O9	1.2122 (15)
C4—C5	1.5178 (15)	C8—C10	1.5028 (16)
C5—C6	1.5422 (14)	C10—C11	1.5249 (17)
C5—C11	1.5290 (16)		
S1—C2—O3	121.15 (9)	C2—C6—C7	114.24 (9)
S1—C2—C6	129.19 (8)	C5—C6—C12	111.30 (9)
O3—C2—C6	109.63 (9)	C2—C6—C12	106.86 (8)
C2—O3—C4	110.43 (8)	C7—C6—C12	108.60 (8)
O3—C4—C5	103.93 (9)	C6—C7—C8	115.71 (9)
C4—C5—C6	101.09 (9)	C7—C8—O9	121.70 (11)
C4—C5—C11	110.47 (10)	C7—C8—C10	115.44 (10)
C6—C5—C11	112.26 (9)	O9—C8—C10	122.83 (12)

C5—C6—C2	100.35 (8)	C8—C10—C11	110.18 (10)
C5—C6—C7	115.08 (9)	C5—C11—C10	112.23 (10)

Alert level C

PLAT230 ALERT 2 C Hirshfeld Test Diff for S1 --C2 . 6.4 s.u.

Alert level G

PLAT791 ALERT 4 G Model has Chirality at C5 (Chiral SPGR) S Verify

PLAT791 ALERT 4 G Model has Chirality at C6 (Chiral SPGR) R Verify

5.10.2 Single crystal X-Ray diffraction data for compound 440

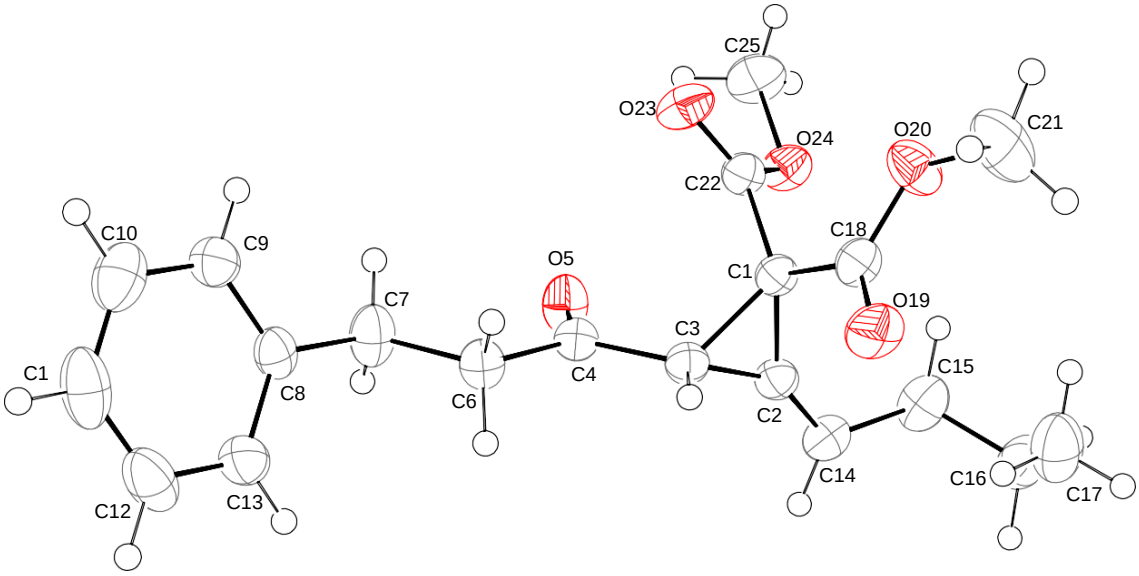


Table 1. Crystal data and structure refinement for **440**.

Identification code	7448	
Empirical formula	C20 H24 O5	
Formula weight	344.41	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.83500(10) Å	α= 90°.

	b = 8.68370(10) Å	β= 102.2435(17)°.
	c = 14.0099(2) Å	γ = 90°.
Volume	931.51(2) $Å^3$	
Z	2	
Density (calculated)	1.228 Mg/m^3	
Absorption coefficient	0.716 mm^{-1}	
F(000)	368	
Crystal size	0.19 x 0.11 x 0.06 mm^3	
Theta range for data collection	3.228 to 76.269°.	
Index ranges	-9<=h<=9, -10<=k<=10, -17<=l<=17	
Reflections collected	16967	
Independent reflections	3842 [R(int) = 0.034]	
Completeness to theta = 74.744°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.96 and 0.84	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3842 / 1 / 228	
Goodness-of-fit on F^2	0.9959	
Final R indices [I>2sigma(I)]	R1 = 0.0312, wR2 = 0.0800	
R indices (all data)	R1 = 0.0333, wR2 = 0.0823	
Absolute structure parameter	0.01(7)	
Extinction coefficient	19(3)	
Largest diff. peak and hole	0.04 and -0.05 $e.Å^{-3}$	

6. References

[1] S. W. Smith, *Toxicol. Sci.* **2009**, *110*, 4–30.

[2] N. Vargesson, *Birth Defects Res. Part C - Embryo Today Rev.* **2015**, *105*, 140–156.

[3] W. Lenz, *Teratology* **1988**, *38*, 203–215.

[4] C. Tian, P. Xiu, Y. Meng, W. Zhao, Z. Wang, R. Zhou, *Chem. - A Eur. J.* **2012**, *18*, 14305–14313.

[5] S.-Y. Kim, J.-Y. Kang, J. Hartman, S.-H. Park, D. Jones, C.-H. Yun, G. Boysen, G. Miller, *Drug Metab. Lett.* **2013**, *6*, 157–164.

[6] N. M. Maier, P. Franco, W. Lindner, *Separation of Enantiomers : Needs , Challenges , Perspectives*, **2001**.

[7] G. Subramanian, *Chiral Separation Techniques: A Practical Approach, 3rd, Completely Revised and Updated Edition*, Wiley, **2006**.

[8] D. A. Evans, L. R. McGee, *J. Am. Chem. Soc.* **1981**, *103*, 2876–2878.

[9] G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.

[10] C. Bolm, J. A. Gladysz, *Chem. Rev.* **2003**, *103*, 2761–2762.

[11] R. Noyori, *Asymmetric Catalysis In Organic Synthesis*, Wiley, **1994**.

[12] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

[13] W. Langebeck, *Die Organische Katalysatoren Und Ihre Beziehungen Zu Den Fermenten*, Springer-Verlag, Berlin, **1949**.

[14] W. Markwald, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349–354.

[15] S. Nakamura, *Org. Biomol. Chem.* **2014**, *12*, 394–405.

[16] R. Mahrwald, *Enantioselective Organocatalyzed Reactions 1: Enantioselective Oxidation, Reduction, Functionalization and Desymmetrization*, **2011**.

[17] G. Bredig, P. S. Fiske, *Biochem. Z.* **1913**, *46*, 7–23.

[18] H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22.

[19] Z. G. Hajos, D. R. Parrish, *J. Org. Chem* **1974**, *39*, 1615–1621.

[20] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496–497.

[21] H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417–430.

[22] J. I. Oku, S. Inoue, *J. Chem. Soc. Chem. Commun.* **1981**, 229–230.

[23] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[24] J. Hine, S. M. Linden, V. M. Kanagasabapathy, *J. Am. Chem. Soc.* **1985**, *107*, 1082–1083.

[25] T. R. Kelly, P. Meghani, V. S. Ekkundi, *Tetrahedron Lett.* **1990**, *31*, 3381–3384.

[26] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

[27] P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–870.

[28] G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103.

[29] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

[30] T. P. Yoon, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 466–468.

[31] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[32] A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

[33] T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki, Y. Takemoto, *Chem. Eur. J.* **2011**, *17*, 10470–10477.

[34] T. Inokuma, M. Furukawa, Y. Suzuki, T. Kimachi, Y. Kobayashi, Y. Takemoto, *ChemCatChem* **2012**, *4*, 983–985.

[35] Y. Kobayashi, R. Kuramoto, Y. Takemoto, *Beilstein J. Org. Chem.* **2015**, *11*, 2654–2660.

[36] Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma, Y. Takemoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 11114–11118.

[37] T. Nanjo, X. Zhang, Y. Tokuhiro, Y. Takemoto, *ACS Catal.* **2019**, *9*, 10087–10092.

[38] B. J. Li, L. Jiang, M. Liu, Y. C. Chen, L. S. Ding, Y. Wu, *Synlett* **2005**, 603–606.

[39] S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370.

[40] J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483.

[41] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.

[42] R. K. Jha, S. Rout, H. Joshi, A. Das, V. K. Singh, *Tetrahedron* **2020**, *76*, 130800.

[43] B. Y. Li, Y. Lin, D. M. Du, *J. Org. Chem.* **2019**, *84*, 11752–11762.

[44] C. J. Thomson, D. M. Barber, D. J. Dixon, *Angew. Chem. Int. Ed.* **2019**, *58*, 2469–2473.

[45] T. Ishikawa, *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*, Wiley, **2009**.

[46] K. Kaupmees, A. Trummal, I. Leito, *Croat. Chem. Acta* **2014**, *87*, 385–395.

[47] J. S. Bandar, T. H. Lambert, *J. Am. Chem. Soc.* **2012**, *134*, 5552–5555.

[48] P. B. Kisanga, J. G. Verkade, R. Schwesinger, *J. Org. Chem.* **2000**, *65*, 5431–5432.

[49] E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160.

[50] X. Fu, C. H. Tan, *Chem. Commun.* **2011**, *47*, 8210–8222.

[51] Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K. W. Huang, M. W. Wong, C. H. Tan, *Angew. Chem. Int. Ed.* **2009**, *48*, 3627–3631.

[52] T. Ishikawa, Y. Araki, T. Kumamoto, H. Seki, K. Fukuda, T. Isobe, *Chem. Commun.* **2001**, 245–246.

[53] S. Kobayashi, R. Yazaki, K. Seki, Y. Yamashita, *Angew. Chem. Int. Ed.* **2008**, *47*, 5613–5615.

[54] M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455.

[55] Y. Sohtome, S. Tanaka, K. Takada, T. Yamaguchi, K. Nagasawa, *Angew. Chem. Int. Ed.* **2010**, *49*, 9254–9257.

[56] Y. Yang, S. Dong, X. Liu, L. Lin, X. Feng, *Chem. Commun.* **2012**, *48*, 5040–5042.

[57] S. Dong, X. Liu, X. Chen, F. Mei, Y. Zhang, B. Gao, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 10650–10651.

[58] S. Dong, X. Liu, Y. Zhu, P. He, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2013**, *135*, 10026–10029.

[59] H. M. L. Davies, C. Venkataramani, T. Hansen, D. W. Hopper, *J. Am. Chem. Soc.* **2003**, *125*, 6462–6468.

[60] P. J. Walsh, M. C. Kozlowski, *Fundamentals of Asymmetric Catalysis*, University Science Books, **2009**.

[61] J. S. Bandar, A. Barthelme, A. Y. Mazori, T. H. Lambert, *Chem. Sci.* **2015**, *6*, 1537–1547.

[62] E. D. Nacsa, T. H. Lambert, *J. Am. Chem. Soc.* **2015**, *137*, 10246–10253.

[63] V. H. Lauridsen, L. Ibsen, J. Blom, K. A. Jørgensen, *Chem. Eur. J.* **2016**, *22*, 3259–3263.

[64] R. Schwesinger, *Chimia (Aarau).* **1985**, *39*, 269-272.

[65] R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. W. Rotter,

F. G. Bordwell, A. V. Satish, G. Z. Ji, E. M. Peters, K. Peters, H. G. Von Schnering, L. Walz, *Liebigs Ann.* **1996**, 1055–1081.

[66] S. Ullrich, B. Kovačević, X. Xie, J. Sundermeyer, *Angew. Chem. Int. Ed.* **2019**, *58*, 10335–10339.

[67] D. Uraguchi, S. Sakaki, T. Ooi, *J. Am. Chem. Soc.* **2007**, *129*, 12392–12393.

[68] R. Tsutsumi, S. Kim, D. Uraguchi, T. Ooi, *Synth.* **2014**, *46*, 871–878.

[69] D. Uraguchi, K. Yamada, T. Ooi, *Angew. Chem. Int. Ed.* **2015**, *54*, 9954–9957.

[70] D. Uraguchi, Y. Kawai, H. Sasaki, K. Yamada, T. Ooi, *Chem. Lett.* **2018**, *47*, 594–597.

[71] D. Uraguchi, K. Yamada, M. Sato, T. Ooi, *J. Am. Chem. Soc.* **2018**, *140*, 5110–5117.

[72] T. Takeda, M. Terada, *J. Am. Chem. Soc.* **2013**, *135*, 15306–15309.

[73] T. Takeda, M. Terada, *Aust. J. Chem.* **2014**, *67*, 1124–1128.

[74] A. Kondoh, M. Oishi, H. Tezuka, M. Terada, *Angew. Chem. Int. Ed.* **2020**, *59*, 7472–7477.

[75] A. Kondoh, S. Ishikawa, M. Terada, *J. Am. Chem. Soc.* **2020**, *142*, 3724–3728.

[76] M. Formica, D. Rozsar, G. Su, A. J. M. Farley, D. J. Dixon, *Acc. Chem. Res.* **2020**, *53*, 2235–2247.

[77] M. G. Núñez, A. J. M. Farley, D. J. Dixon, *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351.

[78] A. J. M. Farley, Development and Application of a New Class of Potent Bifunctional Organocatalysts, University of Oxford, **2015**.

[79] G. P. Robertson, A. J. M. Farley, D. J. Dixon, *Synlett* **2016**, *27*, 21–24.

[80] C. J. Thomson, D. M. Barber, D. J. Dixon, *Angew. Chem. Int. Ed.* **2020**, *59*, 5359–5364.

[81] A. J. M. Farley, C. Sandford, D. J. Dixon, *J. Am. Chem. Soc.* **2015**, *137*, 15992–15995.

[82] J. Yang, A. J. M. Farley, D. J. Dixon, *Chem. Sci.* **2016**, *8*, 606–610.

[83] M. Formica, G. Sorin, A. J. M. Farley, J. Díaz, R. S. Paton, D. J. Dixon, *Chem. Sci.* **2018**, *9*, 6969–6974.

[84] S. Oudeyer, J. F. Brière, V. Levacher, *Eur. J. Org. Chem. 2014*, **2014**, *2014*, 6103–6119.

[85] A. Frongia, F. Secci, N. Melis, *Comptes Rendus Chim.* **2015**, *18*, 456–467.

[86] J. Golec, Novel Bifunctional Superbase Organocatalysts And Their Reactions, University of Oxford, **2016**.

[87] J. L. Fulton, M. A. Horwitz, E. L. Bruske, J. S. Johnson, *J. Org. Chem.* **2018**, *83*, 3385–3391.

[88] M. A. Horwitz, J. L. Fulton, J. S. Johnson, *Org. Lett.* **2017**, *19*, 5783–5785.

[89] M. A. Horwitz, E. Massolo, J. S. Johnson, *Beilstein J. Org. Chem.* **2017**, *13*, 762–767.

[90] C. Sandford, Development and Application of Bifunctional Iminophosphorane Organocatalysts to Enantioselective Michael Additions of α,β-Unsaturated Esters, University of Oxford, **2013**.

[91] H. Shi, I. N. Michaelides, B. Darses, P. Jakubec, Q. N. N. Nguyen, R. S. Paton, D. J. Dixon, *J. Am. Chem. Soc.* **2017**, *139*, 17755–17758.

[92] X. Yang, J. Wang, P. Li, *Org. Biomol. Chem.* **2014**, *12*, 2499–2513.

[93] J. H. Lee, L. Deng, *J. Am. Chem. Soc.* **2012**, *134*, 18209–18212.

[94] S. Prado, Y. Li, B. Nay, *Diversity and Ecological Significance of Fungal Endophyte Natural Products*, Elsevier B.V., **2012**.

[95] L. I. Chia-Ying, W. U. Tian-Shung, *Chem. Pharm. Bull.* **2002**, *50*, 1305–1309.

[96] M. Tori, H. Furuta, Y. Asakawa, *J. Chem. Soc. Perkin Trans. 1*. **1991**, 1919–1922.

[97] J. K. Hexum, R. Tello-Aburto, N. B. Struntz, A. M. Harned, D. A. Harki, *ACS Med. Chem. Lett.* **2012**, *3*, 459–464.

[98] A. B. Smith, N. Kanoh, H. Ishiyama, N. Minakawa, J. D. Rainier, R. A. Hartz, Y. S. Cho, H. Cui, W. H. Moser, *J. Am. Chem. Soc.* **2003**, *125*, 8228–8237.

[99] G. Stork, P. C. Tang, M. Casey, B. Goodman, M. Toyota, *J. Am. Chem. Soc.* **2005**, *127*, 16255–16262.

[100] F. Fringuelli, L. Minuti, L. Radics, A. Taticchi, E. Wenkert, *J. Org. Chem.* **1988**, *53*, 4607–4610.

[101] F. Wang, H. Yang, S. Yu, Y. Xue, Z. Fan, G. Liang, M. Geng, A. Zhang, C. Ding, *Org. Biomol. Chem.* **2018**, *16*, 3376–3381.

[102] S. Poplata, T. Bach, *J. Am. Chem. Soc.* **2018**, *140*, 3228–3231.

[103] B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5839–5842.

[104] S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283.

[105] S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912.

[106] S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1976**, *98*, 4975–4983.

[107] S. G. Davies, R. L. Sheppard, A. D. Smith, J. E. Thomson, *Chem. Commun.* **2005**, 3802–3804.

[108] K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka, T. Akiyama, *Angew. Chem. Int. Ed.* **2009**, *48*, 9652–9654.

[109] J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2008**, *47*, 7656–7658.

[110] C. Agami, H. Sevestre, *J. Chem. Soc., Chem. Commun.* **1984**, 1385–1386.

[111] N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404–405.

[112] Q. Gu, Z. Q. Rong, C. Zheng, S. L. You, *J. Am. Chem. Soc.* **2010**, *132*, 4056–4057.

[113] H. H. Cheng, H. K. Wang, J. Ito, K. F. Bastow, Y. Tachibana, Y. Nakanishi, Z. Xu, T. Y. Luo, K. H. Lee, *J. Nat. Prod.* **2001**, *64*, 915–919.

[114] T. A. Wenderski, S. Huang, T. R. R. Pettus, *J. Org. Chem.* **2009**, *74*, 4104–4109.

[115] N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1272–1277.

[116] T. Akiyama, T. Katoh, K. Mori, *Angew. Chem. Int. Ed.* **2009**, *48*, 4226–4228.

[117] S. Maity, S. Sar, P. Ghorai, *Org. Lett.* **2018**, *20*, 1707–1711.

[118] C. Dehnhardt, M. McDonald, S. Lee, H. G. Ross, J. Mulzer, *J. Am. Chem. Soc.* **1999**, *121*, 10848–10849.

[119] C. D. Broaddus, *Acc. Chem. Res.* **1968**, *1*, 231–238.

[120] K. M. H. Lim, T. Hayashi, *J. Am. Chem. Soc.* **2015**, *137*, 3201–3204.

[121] D. M. H. Ascough, F. Duarte, R. S. Paton, *J. Am. Chem. Soc.* **2018**, *140*, 16740–16748.

[122] C. Hedberg, P. G. Andersson, *Adv. Synth. Catal.* **2005**, *347*, 662–666.

[123] W. M. Clark, A. M. Tickner-Eldridge, G. Kris Huang, L. N. Pridgen, M. A. Olsen, R. J. Mills, I. Lantos, N. H. Baine, *J. Am. Chem. Soc.* **1998**, *120*, 4550–4551.

[124] D. L. Whalen, J. F. Weimaster, A. M. Ross, R. Radhe, *J. Am. Chem. Soc.* **1976**, *98*, 7319–7324.

[125] Y. Saga, R. Motoki, S. Makino, Y. Shimizu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 7905–7907.

[126] Y. Wu, R. P. Singh, L. Deng, *J. Am. Chem. Soc.* **2011**, *133*, 12458–12461.

[127] S. Shirakawa, T. Tokuda, S. B. J. Kan, K. Maruoka, *Org. Chem. Front.* **2015**, *2*, 336–339.

[128] C. H. Lin, T. Z. Hoffman, P. Wirsching, C. F. Barbas, K. D. Janda, R. A. Lerner, *Proc. Natl. Acad. Sci.* **1997**, *94*, 11773–11776.

[129] Z. Huang, J. Huang, Y. Qu, W. Zhang, J. Gong, Z. Yang, *Angew. Chem. Int. Ed.* **2018**, *57*, 8744–8748.

[130] C. L. Hugelshofer, V. Palani, R. Sarpong, *J. Org. Chem.* **2019**, *84*, 14069–14091.

[131] G. P. Pollini, S. Benetti, C. De Risi, V. Zanirato, *Tetrahedron* **2010**, *66*, 2775–2802.

[132] J. W. Ward, Towards the Total Synthesis of Daphniyunnine B, The University of Manchester, **2010**.

[133] F. Juliá-Hernández, A. Arcas, J. Vicente, *Tetrahedron Lett.* **2014**, *55*, 1141–1144.

[134] J. Vicente, A. Arcas, F. Juliá Hernández, *Complejo Organometálico De Pd(II) Y Su Uso En La Hidrólisis De Cetales Y Acetales.*, **2012**, ES 2 372 457Al.

[135] A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407–414.

[136] R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 284–286.

[137] M. A. Schafroth, E. M. Carreira, *Synthesis of Phytocannabinoids*, Springer International Publishing Switzerland, **2017**.

[138] E. M. Carter, A Catalytic Enantioselective Intramolecular Diels-Alder Reaction, University of Oxford, **2018**.

[139] J. R. Kuttner, S. Warratz, G. Hilt, *Synthesis (Stuttg).* **2012**, *44*, 1293–1303.

[140] D. E. Gómez, L. Fabbrizzi, M. Licchelli, E. Monzani, *Org. Biomol. Chem.* **2005**, *3*, 1495–1500.

[141] J. C. Golec, E. M. Carter, J. W. Ward, W. G. Whittingham, L. Simón, R. S. Paton, D. J. Dixon, *Angew. Chem. Int. Ed.* **2020**, *59*, 17417–17422.

[142] T. Oriyama, Y. Kobayashi, K. Noda, *Synlett* **1998**, 1047–1048.

[143] S. Iwasa, M. Yamamoto, S. Kohmoto, K. Yamada, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1173–1176.

[144] A. B. Smith, E. G. Nolen, R. Shirai, F. R. Blase, M. Ohta, N. Chida, R. A. Hartz, D. M. Fitch, W. M. Clark, P. A. Sprengeler, *J. Org. Chem.* **1995**, *60*, 7837–7848.

[145] M. Toyota, T. Asoh, M. Matsuura, K. Fukumoto, *J. Org. Chem.* **1996**, *61*, 8687–8691.

[146] A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2014**, *114*, 7317–7420.

[147] G. P. Reynolds, P. Riederer, M. Sandler, *J. R. Soc. Med.* **1981**, *74*, 649–652.

[148] H. Weber-Grandke, G. Hahn, E. Mutschler, W. Möhrke, P. Langguth, H. Spahn-Langguth, *Br. J. Clin. Pharmacol.* **1993**, *36*, 363–365.

[149] T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712–8756.

[150] K. B. Wiberg, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312–322.

[151] S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, *36*, 255–263.

[152] D. Barnes-Seeman, M. Jain, L. Bell, S. Ferreira, S. Cohen, X. H. Chen, J. Amin, B. Snodgrass, P. Hatsis, *ACS Med. Chem. Lett.* **2013**, *4*, 514–516.

[153] A. de Meijere, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809–886.

[154] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.

[155] P. Eastwood, C. Esteve, J. González, S. Fonquerna, J. Aiguadé, I. Carranco, T. Doménech, M. Aparici, M. Miralpeix, J. Albertí, M. Córdoba, R. Fernández, M. Pont, N. Godessart, N. Prats, M. I. Loza, M. I. Cadavid, A. Nueda, B. Vidal, *ACS Med. Chem. Lett.* **2011**, *2*, 213–218.

[156] A. Chrustek, I. Hołyńska-Iwan, I. Dziembowska, J. Bogusiewicz, M. Wróblewski, A. Cwynar, D. Olszewska-Słonina, *Med.* **2018**, *54*, 1–15.

[157] L. E. Mokry, K. D. Hoagland, *Environ. Toxicol. Chem.* **1990**, *9*, 1045–1051.

[158] I. Werner, L. A. Deanovic, D. E. Hinton, J. D. Henderson, G. H. De Oliveira, B. W. Wilson, W. Krueger, W. W. Wallender, M. N. Oliver, F. G. Zalom, *Bull. Environ. Contam. Toxicol.* **2002**, *68*, 29–36.

[159] B. P. S. Khambay, *Pyrethroid Insecticides*, **2002**.

[160] W. Liu, J. Gan, D. Schlenk, W. A. Jury, *Proc. Natl. Acad. Sci.* **2005**, *102*, 701–706.

[161] H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894.

[162] H. Okamura, T. Fujioka, N. Mori, T. Taniguchi, K. Monde, H. Watanabe, H. Takikawa, *Tetrahedron Lett.* **2019**, *60*, 150917.

[163] M. Meazza, M. Ashe, H. Y. Shin, H. S. Yang, A. Mazzanti, J. W. Yang, R. Rios, *J. Org. Chem.* **2016**, *81*, 3488–3500.

[164] M. Sakai, Y. Ishikawa, S. Takamizawa, M. Oikawa, *Tetrahedron Lett.* **2013**, *54*, 5911–5912.

[165] L. S. Aitken, L. E. Hammond, R. Sundaram, K. Shankland, G. D. Brown, A. J. A. Cobb, *Chem. Commun.* **2015**, *51*, 13558–13561.

[166] S. Wang, Z. Guo, Y. Wu, W. Liu, X. Liu, S. Zhang, C. Sheng, *Org. Chem. Front.* **2019**, *6*, 1442–1447.

[167] F. Liu, X. Bugaut, M. Schedler, R. Fröhlich, F. Glorius, *Angew. Chem. Int. Ed* **2011**, *50*, 12626–12630.

[168] T. Dudding, K. N. Houk, *Proc. Natl. Acad.* **2004**, *101*, 5770–5775.

[169] K. J. Hawkes, B. F. Yates, *Eur. J. Org. Chem.* **2008**, 5563–5570.

[170] G. Ernouf, J. L. Brayer, B. Folléas, J. P. Demoute, C. Meyer, J. Cossy, *Org. Lett.* **2015**, *17*, 3786–3789.

[171] I. Marek, S. Simaan, A. Masarwa, *Angew. Chem. Int. Ed.* **2007**, *46*, 7364–7376.

[172] H. Pellissier, *Tetrahedron* **2014**, *70*, 4991–5031.

[173] G. Ernouf, J. L. Brayer, C. Meyer, J. Cossy, *Beilstein J. Org. Chem.* **2019**, *15*, 333–350.

[174] K. B. Wiberg, R. A. Fenoglio, *J. Am. Chem. Soc.* **1968**, *90*, 3395–3397.

[175] A. Masarwa, A. Stanger, I. Marek, *Angew. Chem. Int. Ed.* **2007**, *46*, 8039–8042.

[176] R. Sang, H. Bin Yang, M. Shi, *Tetrahedron Lett.* **2013**, *54*, 3591–3594.

[177] R. A. Weatherhead-Kloster, E. J. Corey, *Org. Lett.* **2006**, *8*, 171–174.

[178] V. P. Kolesov, M. P. Kozina, *Russ. Chem. Rev.* **1986**, *55*, 912–928.

[179] J. B. Pedley, R. D. Naylor, S. P. Kirby, *Thermochemical Data of Organic Compounds*, Chapman And Hall, **1986**.

[180] W. T. G. Johnson, W. T. Borden, *J. Am. Chem. Soc.* **1997**, *119*, 5930–5933.

[181] I. A. D'jakonov, M. I. Komendantov, *Vestn. Leningrad. Univ.* **1956**, *22*, 166–169.

[182] Z. Bin Zhu, Y. Wei, M. Shi, *Chem. Soc. Rev.* **2011**, *40*, 5534–5563.

[183] D. F. Taber, R. J. Herr, S. K. Pack, J. M. Geremia, *J. Org. Chem.* **1996**, *61*, 2908–2910.

[184] D. S. Müller, I. Marek, *Chem. Soc. Rev.* **2016**, *45*, 4552–4566.

[185] A. Padwa, J. M. Kassir, S. L. Xu, *J. Org. Chem.* **1997**, *62*, 1642–1652.

[186] P. Panne, J. M. Fox, *J. Am. Chem. Soc.* **2007**, *129*, 22–23.

[187] Y. Bessard, M. Schlosser, *Tetrahedron* **1991**, *47*, 7323–7328.

[188] W. Xu, Q. Y. Chen, *J. Org. Chem.* **2002**, *67*, 9421–9427.

[189] K. Yamani, H. Pierre, A. Archambeau, C. Meyer, J. Cossy, *Angew. Chem. Int. Ed.* **2020**, *59*, 18505–18509.

[190] K. Oshiro, Y. Morimoto, H. Amii, *Synthesis (Stuttg).* **2010**, *99*, 2080–2084.

[191] M. S. Baird, H. H. Hussain, W. Nethercott, *J. Chem. Soc. Perkin Trans. 1* **1986**, 1845–1853.

[192] P. J. Garratt, A. Tsotinis, *J. Org. Chem.* **1990**, *55*, 84–88.

[193] E. Zohar, I. Marek, *Org. Lett.* **2004**, *6*, 341–343.

[194] M. J. Schlatter, *J. Am. Chem. Soc.* **1941**, *63*, 1733–1737.

[195] K. B. Wiberg, W. J. Bartley, *J. Am. Chem. Soc.* **1960**, *82*, 6375–6380.

[196] P. Dowd, A. Gold, *Tetrahedron Lett.* **1969**, *10*, 85–86.

[197] M. S. Baird, H. H. Hussain, W. Clegg, *J. Chem. Res. Synopses* **1988**, 110–111.

[198] W. E. Billups, L. J. Lin, *Tetrahedron* **1986**, *42*, 1575–1579.

[199] Q. Deng, B. E. Thomas IV, K. N. Houk, P. Dowd, *J. Am. Chem. Soc.* **1997**, *119*, 6902–6908.

[200] R. Breslow, P. Dowd, *J. Am. Chem. Soc.* **1963**, *85*, 2729–2735.

[201] N. Yan, X. Liu, M. K. Pallerla, J. M. Fox, *J. Org. Chem.* **2008**, *73*, 4283–4286.

[202] A. Levin, I. Marek, *Chem. Commun.* **2008**, 4300–4302.

[203] N. Matsuo, *Proc. Jpn. Acad., Ser. B* **2019**, *95*, 378–400.

[204] M. Kawamoto, M. Moriyama, Y. Ashida, N. Matsuo, Y. Tanabe, *J. Org. Chem.* **2020**, *85*, 2984–2999.

[205] W. F. Barthel, F. B. LaForge, *J. Org. Chem.* **1944**, *9*, 242–249.

[206] H. Staudinger, L. Ruzicka, *Helv. Chim. Acta* **1924**, *7*, 177–201.

[207] Y. Inouye, Y. Takeshita, M. Ohno, *J. Agric. Chem. Soc. Japan* **1955**, *19*, 193–199.

[208] A. Krief, S. Jeanmart, A. Kremer, *Bioorganic Med. Chem.* **2009**, *17*, 4106–4126.

[209] I. G. M. Campbell, S. H. Harper, *J. Chem. Soc.* **1924**, 283–286.

[210] *Roussel-Uclaf Deltamethrine*, Roussel-Uclaf: Romainville, **1982**.

[211] J. Tessier, *Chem. Ind.* **1984**, *199*.

[212] J. Martel, *FR1580474A*, **1969**.

[213] J. Martel, *Chem. Abstr.* **1970**, *72*, 100136.

[214] W. Bicker, K. Kacprzak, M. Kwit, M. Lämmerhofer, J. Gawronski, W. Lindner, *Tetrahedron Asymmetry* **2009**, *20*, 1027–1035.

[215] L. Liu, W. Lee, M. Yuan, C. Acha, M. B. Geherty, B. Williams, O. Gutierrez, *Chem. Sci.* **2020**, *11*, 3146–3151.

[216] G. Nair, Anilkumar, S. Duca, Jose, B. DWYER, Michael, P. Kozlowski, Joseph, A. Rosenblum, Stuart, *Substituted 3-Azabicyclo[3.1.0]Hexane Derivatives Useful As CCR2 Antagonists*, **2012**, WO2012/125661 A1.

[217] G. Rulli, N. Duangdee, K. Baer, W. Hummel, A. Berkessel, H. Gröger, *Angew. Chem. Int. Ed.* **2011**, *50*, 7944–7947.

[218] K. B. Wiberg, M. Marquez, *J. Am. Chem. Soc.* **1998**, *120*, 2932–2938.

[219] A. Shibuya, M. Okada, Y. Nakamura, M. Kibashi, H. Horikawa, T. Taguchi, *Tetrahedron* **1999**, *55*, 10325–10340.

[220] H. S. Chong, H. A. Song, M. Dadwal, X. Sun, I. Sin, Y. Chen, *J. Org. Chem.* **2010**, *75*, 219–221.

[221] D. Rozsar, M. Formica, K. Yamazaki, T. Hamlin, D. J. Dixon, C. Rozsar, J. Darren, D. Rozsar, M. Formica, K. Yamazaki, T. A. Hamlin, D. J. Dixon, **2021**, DOI 10.26434/chemrxiv.14355422.v1.

[222] S. Duan, S. Li, X. Ye, N. N. Du, C. H. Tan, Z. Jiang, *J. Org. Chem.* **2015**, *80*, 7770–7778.

[223] J. Lu, *PhD Thesis, Tech. Univ. Dortmund, Dortmund.* **2009**.

[224] S. Zai, H. Gao, Z. Huang, H. Hu, H. Wu, Q. Wu, *ACS Catal.* **2012**, *2*, 433–440.

[225] D. J. Adams, J. A. Bennett, D. Duncan, E. G. Hope, J. Hopewell, A. M. Stuart, A. J. West, *Polyhedron* **2007**, *26*, 1505–1513.

[226] S. E. Tunney, J. K. Stille, *J. Org. Chem.* **1987**, *52*, 748–753.

[227] E. Le Gall, M. Troupel, J. Y. Nédélec, *Tetrahedron* **2003**, *59*, 7497–7500.

[228] J. Li, H. Fu, P. Hu, Z. Zhang, X. Li, Y. Cheng, *Chem. Eur. J.* **2012**, *18*, 13941–13944.

[229] F. Y. Kwong, C. W. Lai, M. Yu, K. S. Chan, *Tetrahedron* **2004**, *60*, 5635–5645.

[230] A. Reis, D. Dehe, S. Farsadpour, I. Munstein, Y. Sun, W. R. Thiel, *New J. Chem.* **2011**, *35*, 2488–2495.

[231] A. Matsuzawa, A. Kasamatsu, K. Sugita, *Tetrahedron Lett.* **2016**, *57*, 4585–4587.

[232] J. Bonjoch, A. J. Catena, N. Valls, *J. Org. Chem* **1996**, *61*, 7106–7115.

[233] G. Tojo, M. Fernández, *Oxidation of Alcoholsto Aldehydes and Ketones: A Guide to Current Common Practice*, Springer, **2006**.

[234] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849–3862.

[235] A. Iyer, S. Jockusch, J. Sivaguru, *Chem. Commun.* **2017**, *53*, 1692–1695.

[236] C. E. Murar, F. Thuaud, J. W. Bode, *J. Am. Chem. Soc.* **2014**, *136*, 18140–18148.

[237] H. Ishikawa, B. P. Bondzic, Y. Hayashi, *Eur. J. Org. Chem.* **2011**, 6020–6031.

[238] H. Zhang, C. Li, G. Xie, B. Wang, Y. Zhang, J. Wang, *J. Org. Chem.* **2014**, *79*, 6286–6293.

[239] A. Barco, S. Benetti, A. Bianchi, A. Casolari, G. P. Pollini, R. Romagnoli, G. Spalluto, V. Zanirato, *Tetrahedron* **1994**, *50*, 11743–11754.

[240] S. Yamaguchi, M. Ura, S. Izuta, A. Okamoto, *Bioconjug. Chem.* **2016**, *27*, 1976–1980.

[241] A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615.

[242] Y. Li, J. X. Li, X. H. Ouyang, Q. A. Wang, J. H. Li, *Org. Lett.* **2017**, *19*, 6172–6175.

[243] S. A. Kozmin, V. H. Rawal, *J. Am. Chem. Soc.* **1999**, *121*, 9562–9573.

[244] G. J. Jiang, X. F. Fu, Q. Li, Z. X. Yu, *Org. Lett.* **2012**, *14*, 692–695.

[245] F. Zhang, J. M. Fox, *Org. Lett.* **2006**, *8*, 2965–2968.

[246] A. Basheer, M. Mishima, I. Marek, *Org. Lett.* **2011**, *13*, 4076–4079.

[247] B. Muriel, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 4075–4079.

[248] Y. Yang, P. Antoni, M. Zimmer, K. Sekine, F. F. Mulks, L. Hu, L. Zhang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 5129–5133.

[249] A. N. Baumann, A. Music, K. Karaghiosoff, D. Didier, *Chem. Commun.* **2016**, *52*, 2529–2532.

[250] P. A. Jacobi, Y. Li, *Org. Lett.* **2003**, *5*, 701–704.

[251] A. R. A. S. Deshmukh, V. K. Gumaste, *PROCESS FOR PREPARING ALKYL/ARYLCHLOROFORMATES*, **2005**, US 2005/0065361 Al.

[252] S. Fonquerna, A. Moyano, M. A. Perichàs, A. Riera, *Tetrahedron Asymmetry* **1997**, *8*, 1685–1691.

[253] S. Ceylan, H. C. H. Law, A. Kirschning, P. H. Toy, *Synth.* **2017**, *49*, 145–150.

[254] C. K. W. Kwong, M. Y. Fu, H. C. H. Law, P. H. Toy, *Synlett* **2010**, 2617–2620.