Palladium Catalysed Allene Carbocyclisation

A thesis submitted in partial fulfilment of the requirement for the degree of

Doctor of Philosophy (D. Phil.)

Meiling Li

Supervisor: Professor Darren J. Dixon

Contents

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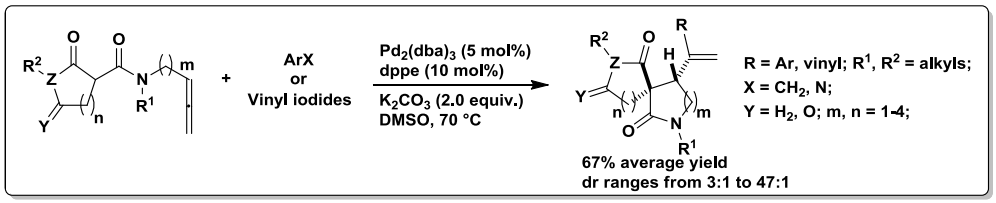
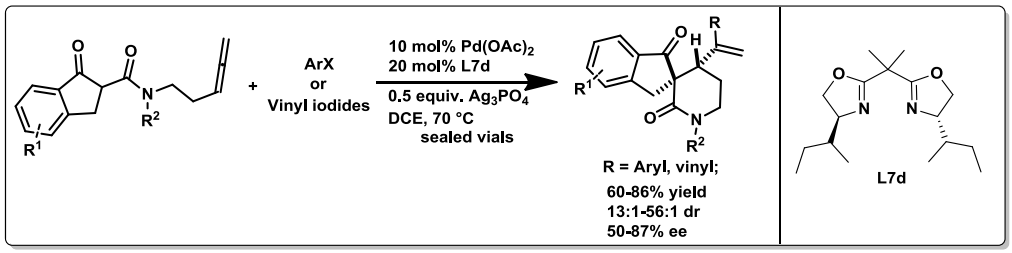
Abstract

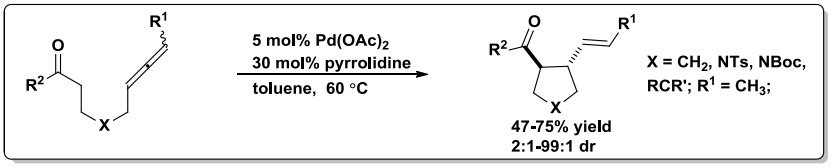
In this thesis, firstly, a Pd-catalysed diastereoselective carbocyclisation of allenes with aryl halides or vinyl iodides was designed and developed to form arylative or vinylative spirolactam compounds. High yields and diastereoselectivities were obtained in the presence of $Pd_2(dba)_3$/dppe and K_2CO_3 in DMSO at 70 °C, particularly when spiropiperidin-2-ones were formed. The method is simple to perform and broad in scope.



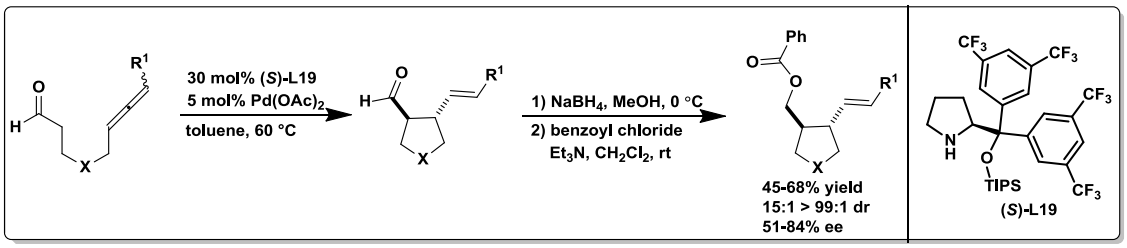
Having established the diastereoselective methodology for the arylative or vinylative allene carbocyclisation, a Pd-catalysed enantioselective version was developed by using bisoxazolines as chiral ligands. Aryl halides and vinyl iodides were investigated in this carbocyclisation. High yields and enantioselectivities were obtained in the presence of $Pd(OAc)_2$, a bisoxazoline ligand **L7d** derived from *L*-isoleucine and Ag_3PO_4 in 1,2-dichloroethane at 70 °C. No olefin isomerisation was observed when *cis*-vinyl iodides were used. The method is mild, efficient and broad in scope.



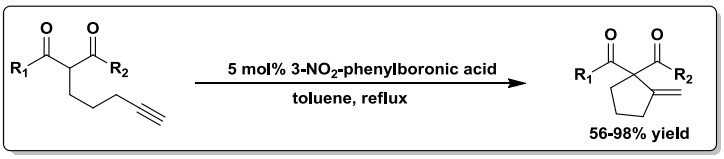
A palladium catalysed diastereoselective allene carbocyclisation reaction was developed via enamine catalysis and palladium catalysis, which allows for the efficient carbocyclisation of formyl or ketone allenes. Good yields and high diastereoselectivities were obtained in the presence of $Pd(OAc)_2$ and pyrrolidine in toluene at 60 °C when formyl allenes were investigated.



The cyclisation is diastereoselective and can also performed as a catalytic asymmetric reaction by using prolinol derivatives as chiral catalysts. Good yields and high diastereo- and enantioselectivities were obtained in the presence of catalyst **(*S*)-L19**.



Additionally, a boronic acid catalysed ene carbocyclisation of acetylenic dicarbonyl compounds was developed. An attempted transesterification of a β-ketoester substrate bearing a pendent terminal alkyne substituent at the β-position led to the discovery of an efficient 3-nitrobenzeneboronic acid catalysed ene carbocyclisation of acetylenic dicarbonyl compounds. The reaction is easy to perform, efficient, broad in scope and provides a convenient transition metal-free alternative to existing catalytic protocols.



Declaration

I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning. The work described in this thesis is entirely my own, except where I have either given a reference to a published source or a thesis. All the compounds in this thesis are racemic unless otherwise drawn. The relative stereochemistry of the compounds is not defined unless otherwise stated.

Meiling Li 05 April 2011

Abbreviations

^{o}C	degrees celcius
Ac	acetyl
Ar	aromatic group, including phenyl
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Bn	benzyl
br	broad
Boc_2O	di-*tert*-butyl dicarbonate
Bu	butyl
nBu_3P	tri-*n*-butylphosphine
c	concentration
cat.	catalyst or catalytic
COSY	correlation spectroscopy
Conv.	conversion
d	doublet
dd	doublet of doublets
DCM	dichloromethane
DCE	1,2-dichloroethane
DEPT	distortionless enhancement by polarization transfer
DHP	3,4-dihydro-2H-pyran
DIPA	diisopropylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide

dppb	1,2-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereoisomeric ratio
dt	doublet of triplets
EA	ethyl acetate
e.e.	enantiomeric excess
EI	electron impact
Equiv.	equivalent(s)
ES	electrospray
Et	ethyl
Et_2O	diethyl ether
EWG	electron withdrawing group
g	gram
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	High-Resolution Mass Spectrometry
HSQC	Heteronuclear Single-Quantum Coherence experiment
Hz	Hertz
i	iso
IPA	isopropyl alcohol or isopropanol (propan-2-ol)
IR	infra-red

KHMDS	potassium bis(trimethylsilyl)amide
L	ligand
LDA	lithium diisopropylamide
M	molar
m	multiplet
m	meta
max	maximum
m/z	mass to charge
Me	methyl
mg	milligram
MHz	MegaHertz
min	minute
mL	millilitre
μL	microlitre
mmol	millimole
MP	melting point
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
n	normal, linear chain
NMP	*N*-methylpyrrolidinone
NMR	Nuclear magnetic resonance
nOesy	Nulear Overhauser Effect Spectroscopy
N.R.	no reaction
Nu	nucleophile
o	*ortho*

p	*para*
p	pentet
PE	petrol ether
Ph	phenyl
ppm	parts per million
Pr	propyl
PS	polymer supported
PTSA	*p*-toluenesulphonic acid
q	quartet
R	any alkyl group
rac	racemic
RT	room temperature
s	singlet
t	tertiary/triplet
TBS	*tert*-butyldimethylsilyl
TCE	1,1,1-trichloroethane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TrCl	triphenylmethyl chloride or trityl chloride
p-TsCl	4-toluenesulfonyl chloride

Chapter One Introduction

1.1 Allenes

An allene is a hydrocarbon in which one atom of carbon is connected by double bonds with to other atoms of carbon (Figure 1.1). The central carbon of allene forms two sigma bonds and two pi bonds. The central carbon is *sp*-hybridized, and the two terminal carbon are sp^2-hybridized. The bond angles formed by the three carbons are 180 ° which indicates linear geometry for the carbon of allene. The two π-orbitals in allenes are perpendicular to each other, as are the two methylene groups.[1]

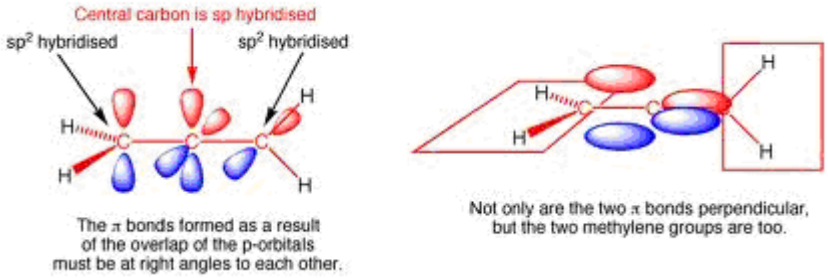


Figure 1.1 Bonding orbitals in allene

The unique structures of allenes result in good reaction activities spreading over three contiguous carbon atoms in many organic reactions, which have been successfully applied to the field of pharmaceuticals, dyes and polymers.[2]

The first synthesis of an allene can be traced back to 1887 by Burton and Pechmann,[3] however the structure was not confirmed until 1954.[4] As early as 1875, van't Hoff recognized and predicted that unsymmetrically substituted allenes should be chiral and exist in two enantiomeric forms.[5] In 1924, Staudinger and Ruzicka discovered that 1,2-diene moieties exist in naturally occurring molecules,[6] which triggered research activities aimed at developing synthetic routes to allenes. For a long period, allenes were considered highly unstable, and this fact hindered the development of the chemistry of allenes. However, during the last few decades, allenes have been shown to demonstrate a range of reactivities as well as

selectivities, which can usually be tuned by the electronic or steric effects and the nature of catalysts involved.

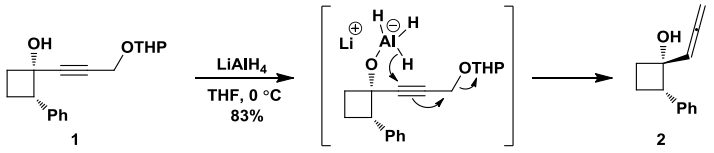
1.1.1 Synthesis of allenes

Allenes have allowed chemists to access a variety of structurally interesting and biologically active compounds. The emergence of allenes in organic synthesis is a direct result of the discovery and development of efficient protocols for their preparation. Allenes can be obtained through a variety of synthetic methods.

1.1.1.1 Synthesis of allenes with propargyl electrophiles

Aluminum hydride reagents, such as lithium aluminum hydride ($LiAlH_4$), and diisobutylaluminum hydride (DIBAL-H), are widely used to form allenes from propargyl moieties such as ethers, halides, alcohols and epoxides. This aluminium-mediated reduction involves a hydride delivery from the aluminium species to the electrophile via a S_N2' mechanism. This process results in the formation of a new carbon-hydrogen bond and a new carbon-carbon pi bond.[7]

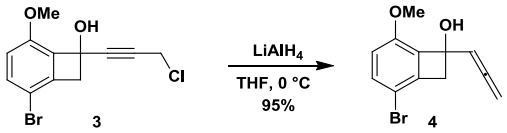
In 1973, Landor and co-workers developed the first hydroxyl-directed hydride delivery with $LiAlH_4$, which has proven to be a reliable method for the synthesis of allenes from propargyl mono-*O*-tetrahydropyranyl ethers of but-2-yn-1,4-diols.[8] This methodology is still widely used today to prepare α-hydroxyallenes.[7,9,10] Yashida and co-workers[11] used a $LiAlH_4$ reduction protocol to transform tetrahydropyranyl propargyl ether **1** into α-hydroxyallene **2** in 83% yield (Scheme 1.1).



Scheme 1.1 Synthesis of α-hydroxyallene **2** using $LiAlH_4$

The method is not limited to a tetrahydropyranyl ether serving as a leaving group; methyl ethers, [12] silyl ethers[13] or acetals[14] can be used. Like propargyl ethers, propargyl chlorides,

such as **3**, are excellent substrates for allene synthesis via alcohol-directed aluminium hydride reduction. Morris and co-workers[15] found that propargyl chloride **3** with $LiAlH_4$ in THF was converted to the mono-substituted hydroxyallene **4** in 95% yield (Scheme 1.2).

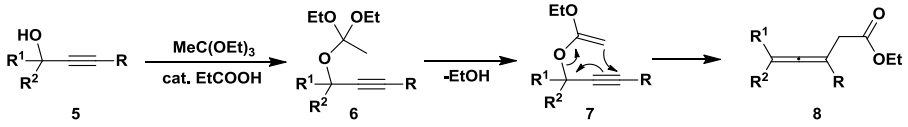


Scheme 1.2 Synthesis of allene **4** using $LiAlH_4$

1.1.1.2 Synthesis of allenes via skeletal rearrangement reactions

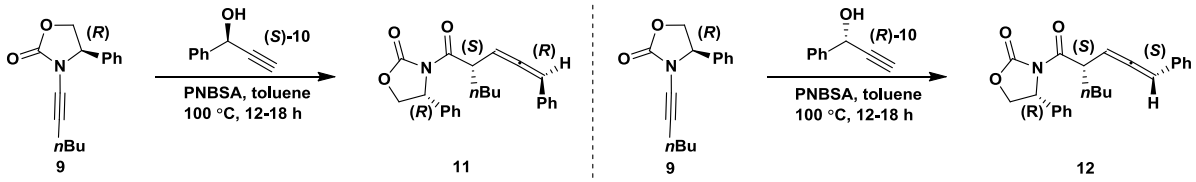
The Claisen rearrangement, a [3,3]-sigmatropic rearrangement used for carbon-carbon bond formation, has been used in allene synthesis.

The *ortho*-ester Claisen rearrangement has been a popular method for the construction of allenyl esters since Crandall and co-workers published their pioneering work in 1970.[16] Typically, the reaction conditions include heating propargyl alcohol **5** with triethyl orthoacetate in the presence of a catalytic amount of propionic acid (Scheme 1.3).



Scheme 1.3 Synthesis of allenes via Claisen rearrangement

In addition to the Claisen rearrangement, other [3,3]-sigmatropic rearrangements can be used for the construction of allenes from propargyl substrates.



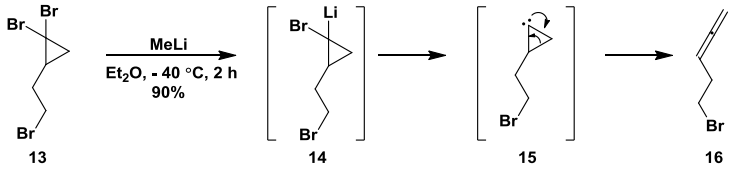
Scheme 1.4 Synthesis of allenes via [3,3]-sigmatropic rearrangements

For example, the stereoselective Saucy-Marbet rearrangement[17,18] has been used to access substituted allenes from chiral ynamides and propargyl alcohols. This rearrangement is catalysed by *p*-nitrobenzenesulphonic acid (PNSBA) and leads to homoallenyl amides in high

yields and diastereoselectivities (Scheme 1.4). Either **11** or **12** can be obtained depending on whether (*S*)- or (*R*)-propargyl alcohol **10** is used for the reaction.

1.1.1.3 Synthesis of allenes via Carbene rearrangement: The Doering-Moore-Skattebol Reaction (DMS reaction)

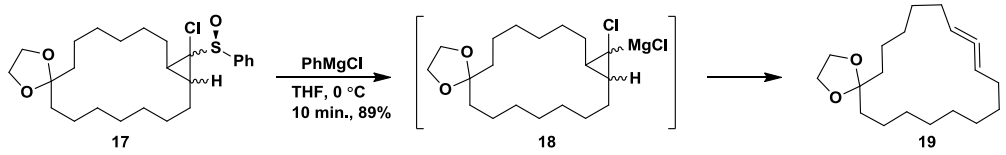
Pioneering work conducted by Doering and Laflamme[19] in 1958 showed that allenes can be obtained in moderate yields by reacting 1,1-dibromocyclopropanes with active metals such sodium or magnesium. Subsequently and independently, Moore[20] and Skattebol[21] in 1960 and 1961 respectively, demonstrated that reacting the same geminal dibromocyclopropanes with alkyllithium reagents such as methyl- and butyllithium produced the desired allenes in higher yields. Today this transformation is commonly referred to as the Doering-Moore-Skattebol (DMS) reaction, and is still used by chemists to construct allenes from *gem*-dihalocyclopropane precursors.[22] *gem*-Dibromocyclopropane derivatives are more commonly employed for this transformation (Scheme 1.5). For example, *gem*-dibromocyclopropane **13** is readily transformed into allene **16** in 90% yield when treated with methyllithium at a low temperature.[23] The first step in this reaction mechanism is a halogen-lithium exchange resulting in the formation of 1-lithio-1-bromo-cyclopropane **14**. This intermediate then undergoes α-elimination to give carbene **15**, which subsequently undergoes rearrangement to bromoallene **16**.



Scheme 1.5 Synthesis of allene **16** via a Doering-Moore-Skattebol reaction

Satoh and co-workers have demonstrated that 1-chloro-1-cyclopropyl phenyl sulfoxides are excellent substrates for a DMS-type reaction (Scheme 1.6).[24] Sulfoxide **17** is rapidly converted to magnesium cyclopropylidene **18** when treated with phenylmagnesium chloride in

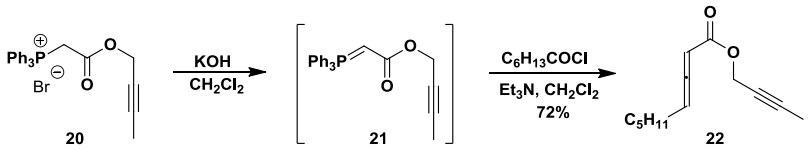
THF at 0 °C via a sulfoxide-magnesium exchange reaction. Magnesium cyclopropylidene **18** then rearranges to the cyclic allene **19** in 89% yield.



Scheme 1.6 Synthesis of allene **19** via a Doering-Moore-Skattebol reaction

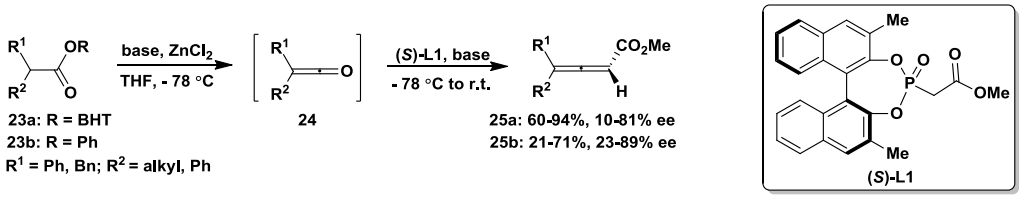
1.1.1.4 Synthesis of allenes via direct homologation reactions

Allenyl esters, ketones, lactones, lactams, and other functionalized allenes can be readily synthesised via a Wittig reaction between a phosphonium ylide and a ketene or an acid halide (ketene equivalent). For example, Brummond and Chen[25] have applied this methodology to the synthesis of allenyne **22** (Scheme 1.7). Phosphonium salt **20** is first transformed into ylide **21** with potassium hydroxide and treated with triethylamine and heptanonyl chloride to give allenyl ester **22**.



Scheme 1.7 Synthesis of allene **22** via direct homologation reactions

An asymmetric Horner-Wadsworth-Emmons (HWE) reaction can be used to access non-racemic chiral allenes using optically active phosphonate **(*S*)-L1** and various unsymmetric ketenes (Scheme 1.8). The transformation of BHT ester **23a** into ketene **24** could only be achieved with *n*-butyllithium, while KHMDS proved to be essential to the formation of allene **25a**.[26]

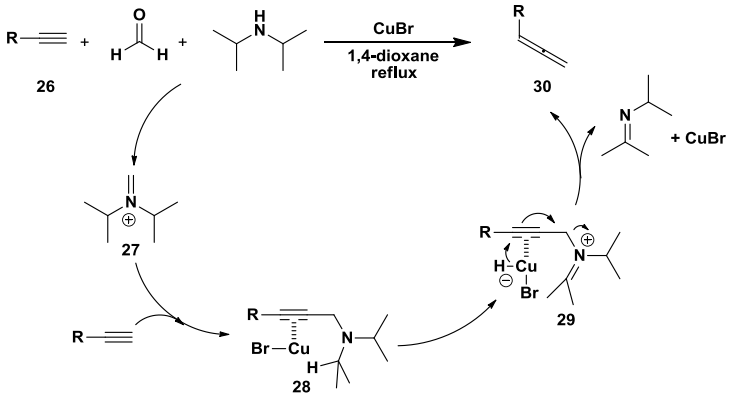


Scheme 1.8 Synthesis of allene **25** via direct homologation reactions

Alternatively, when phenyl ester **23b** was employed, lithium diisopropylamide could be used for both the generation of ketene **24** and subsequent HWE reaction.[27]

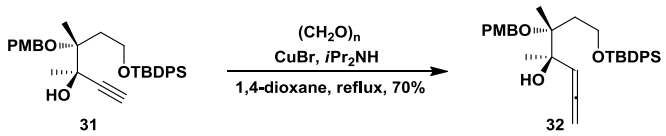
1.1.1.5 Synthesis of allenes via Crabbe homologation reaction

Since 1979, the Crabbe reaction has proven to be a useful method for the construction of monosubstituted allenes from terminal acetylenic precursors (Scheme 1.9).[28-31] The reaction mechanism consists of a copper-catalysed addition of alkyne **26** onto iminum ion **27**, which is formed from paraformaldehyde and diisopropylamine. Addition of cuprous bromide to the acetylenic triple bond results in intermediate complex **28**. Subsequent intramolecular hydride transfer from the amine moiety to the copper species occurs to afford copper(I) complex **29**. The hydride is then delivered to the carbon-carbon triple bond to yield allene **30**.[30]

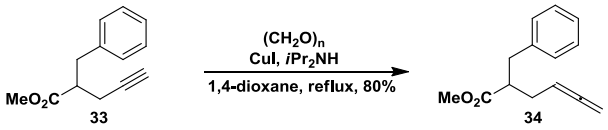


Scheme 1.9 Synthesis of allene **30** via Crabbe homologation reaction

The homologation reaction is commonly used to access a wide variety of functionalized monosubstituted allenes, such as allene-substituted alcohols, amides, carbamates and lactams. Crew and co-workers[32] applied this methodology to the synthesis of α-allenyl alcohol **32** (Scheme 1.10). Propargyl alcohol **31** was transformed into allene **32** when treated with paraformaldehyde, diisopropylamine and cuprous bromide in 1,4-dioxane at reflux. Similarly, Trost and co-workers employed cuprous iodide as a catalyst for the synthesis of allenyl ester **34** from terminal alkyne **33** (Scheme 1.11).[33]



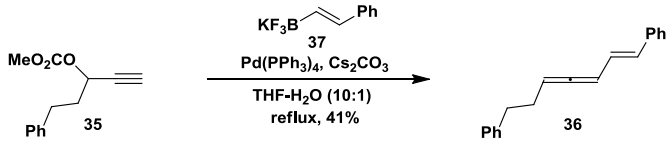
Scheme 1.10 Synthesis of allene **32** via Crabbe homologation reaction



Scheme 1.11 Synthesis of allene **34** via Crabbe homologation reaction

1.1.1.6 Transition-metal catalysed allene synthesis

The most common transition metal used for the synthesis of allenes is palladium which allows the formation of allenes under relatively mild conditions. Molander and co-workers[34] have shown that propargyl carbonate **35** can be coupled with alkenyl trifluoroborate **37** to afford the allene **36** in good yield (Scheme 1.12). The reaction conditions are tolerant of a wide range of functionalities such as nitriles, alcohols, silyl ethers, amines, thioethers and sulfones. Moreover, if the propargyl derivative is non-racemic, the corresponding enantioriched allenes can be obtained.



Scheme 1.12 Synthesis of allene **36** via palladium catalysis

In addition to palladium, other transition metals such as indium,[35-38] chromium,[39,40] ruthenium,[41] rhodium[41,43] and titanium[44,45] can also be employed in the preparation of allenes.

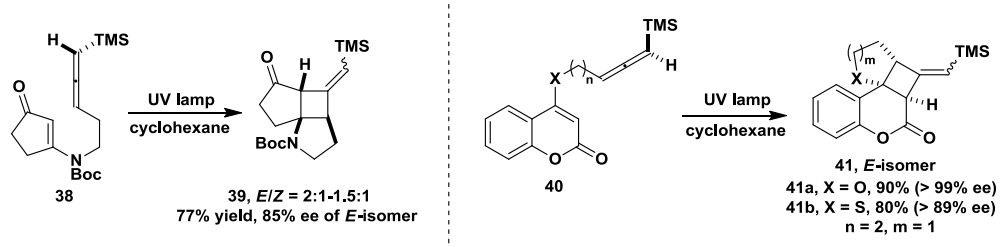
1.1.2 Reactivity of allenes

In recent years, the reactions of allenes have been widely investigated and have proven extremely useful and advantageous in organic synthesis. These transformations include: [2+2]-cycloaddition reactions, Myers-Saito cyclisations, cycloaddition reactions of metallocarbenes

with allenes, [4+2]-cycloadditions, [3+2]-cycloadditions, radical reactions, *N*-acyliminium cyclisations, nucleophilic additions, cyclometalations and carbometalation reactions.

1.1.2.1 [2+2]-Cycloaddition reactions

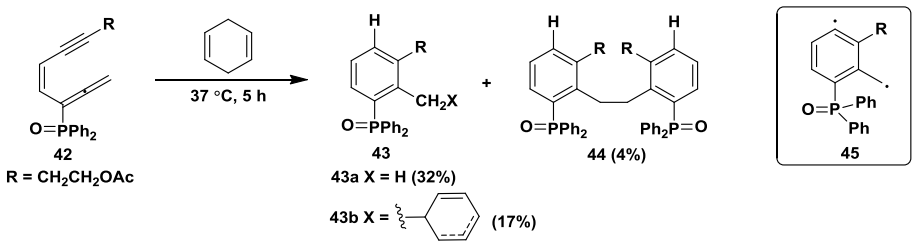
Carreira and co-workers reported that an enantioselective photoinduced intramolecular [2+2]-cycloaddition of optically active allenyl silanes with the C=C bond of α,β-unsaturated enones. The non silyl-substituted C=C bond in **38** or **40** in the allene moiety participated in the [2+2]-cycloaddition with high regioselectivity (Scheme 1.13).[46]



Scheme 1.13 [2+2]-Cycloaddition of allenyl silanes **38** and **40**

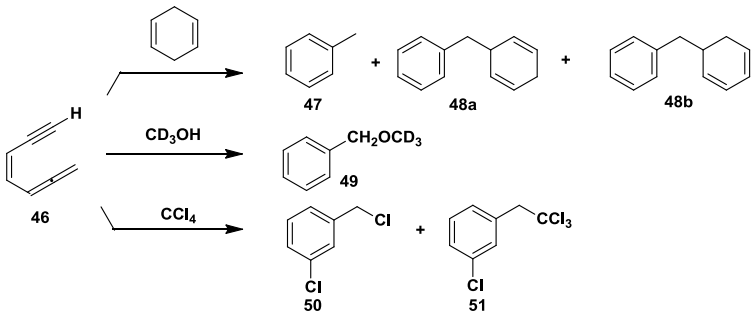
1.1.2.2 Myers-Saito cyclisations

In 1989, Saito and co-workers reported that the cyclisation of enyne-allenyl phosphine oxide **42** in the presence of 1,4-cyclohexadiene leads to the formation of aryl phosphine oxide **43** together with the homocoupling product **44** from the possible diradical intermediate **45** (Scheme 1.14).[47]



Scheme 1.14 Saito cyclisations

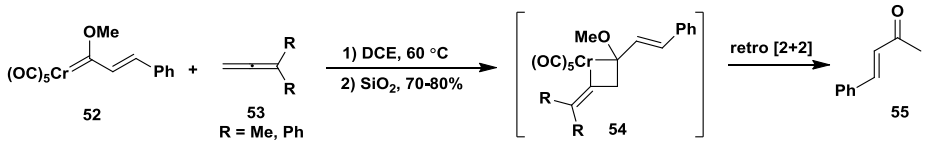
Almost at the same time, Myers and co-workers reported a similar reaction of 6-alkyn-1,2,4-triene **46** to access benzene derivatives under different conditions (Scheme 1.15).[48]



Scheme 1.15 Myers cyclisations

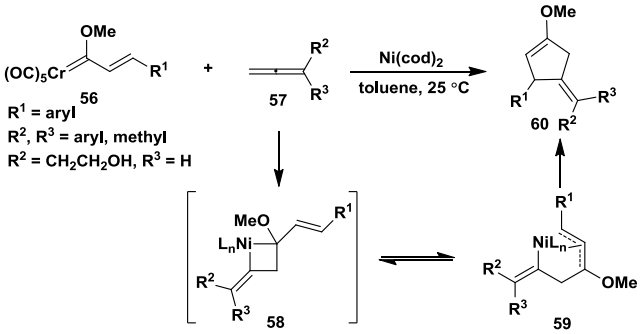
1.1.2.3 Cycloaddition reactions of metallocarbenes with allenes

Barluenga and co-workers reported that the [2+2]-cycloaddition of the C-Cr double bond in alkenyl chromium carbene complex **52** with 1,1-disubstituted allenes **53** leads to the formation of α,β-unsaturated enones **55** via the retro [2+2]-cycloaddition of intermediate **54** (Scheme 1.16).[49]



Scheme 1.16 Cycloaddition reaction of alkenyl chromium carbene complex **52** with 1,1-disubstituted allenes **53**

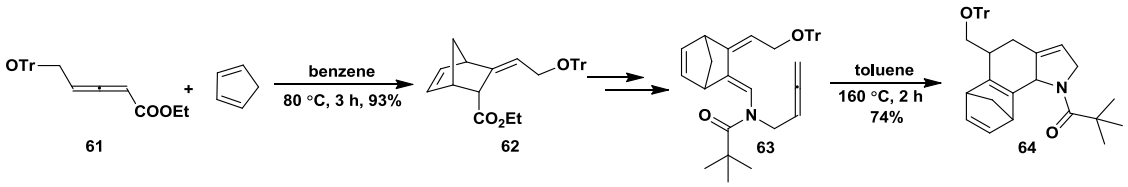
However, in the presence of one equivalent of $Ni(cod)_2$, four-membered intermediate **54** can undergo Cr-Ni exchange to afford **58**, which could be followed by an allylic rearrangement and reductive elimination to afford 4-alkylidenecyclopentenyl methyl ethers **60** (Scheme 1.17).[50]



Scheme 1.17 Cycloaddition reaction of alkenyl chromium carbene complex **56** with 1,1-disubstituted allenes **57** in the presence of $Ni(cod)_2$

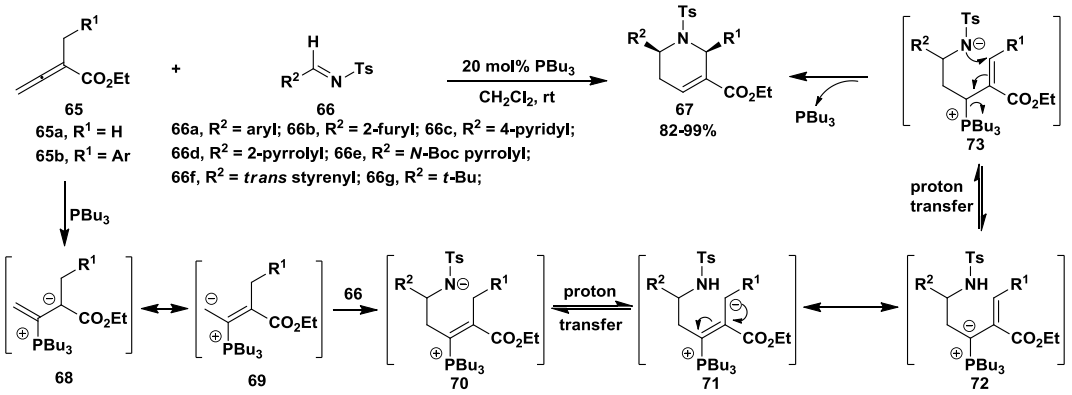
1.1.2.4 [4+2]-Cycloadditions

Kanematsu and co-workers reported that the intermolecular [4+2]-cyclisation of 2,3-allenoate **61** with cyclopentadiene leads to the formation of **62**,[51] which was converted to 1,3-diene-allene **63**. Allene **63** underwent intramolecular [4+2]-cycloaddition to afford bridged tetracyclic product **64** in several steps (Scheme 1.18).[51,52]



Scheme 1.18 [4+2]-Cycloaddition reaction of 2,3-allenoate **61**

Kwon and co-workers observed that under PBu_3 catalysis, 2-substituted buta-2,3-dienoates **65a-65b** can undergo formal [4+2]-cycloaddition reactions with imines **66a-66g** to afford tetrahydropyridine products **67** (Scheme 1.19).[53] In this transformation, tri-*n*-butylphosphine acts as a nucleophilic trigger and forms intermediate **68**, which exists as resonance-stabilized zwitterionic intermediates **68** and **69**. Allylic carbanion **69** adds to imine **66** to produce intermediate **70**. Two consecutive proton-transfer steps yield intermediate **73** which undergoes 6-*endo* cyclisation followed by expulsion of PBu_3 to generate tetrahydropyridines **67**.

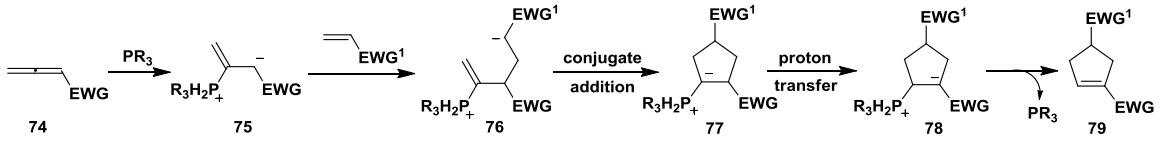


Scheme 1.19 Formal [4+2]-cycloaddition reaction of 2-substituted buta-2,3-dienoates **65**

1.1.2.5 [3+2]-Cycloadditions

Lu and co-workers established the PR_3-catalysed [3+2]-cycloaddition of electron-deficient allenes with alkenes bearing an electron-withdrawing group to afford cyclopentene

derivatives.[55] The reaction proceeded via the nucleophilic addition of PR_3 to **74** which led to the formation of intermediate **75**. Conjugate addition of **75** with an electron-deficient alkene afforded **76** intermediate. Intramolecular conjugate addition, proton transfer followed by PR_3-elimination afforded cyclopentenes **79** (Scheme 1.20).[54]



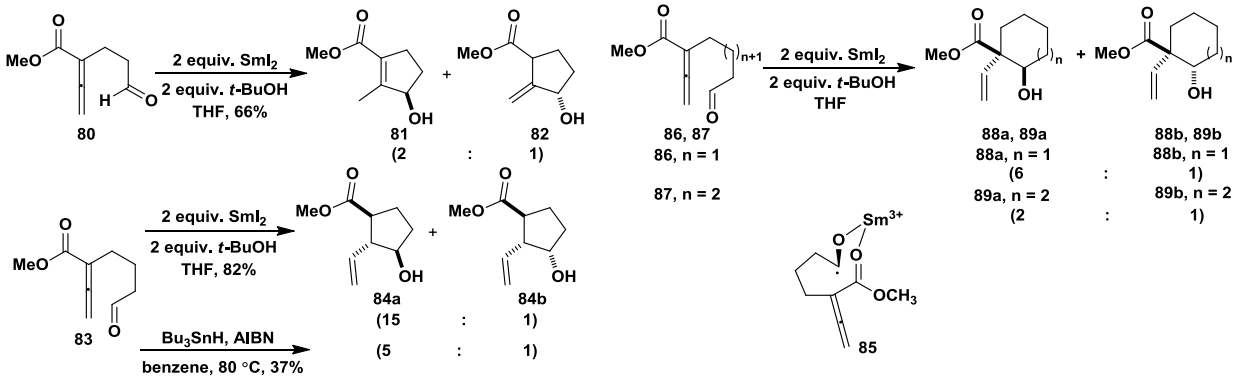
Scheme 1.20 [3+2]-Cycloadditions of allenes **74**

1.1.2.6 Radical reactions

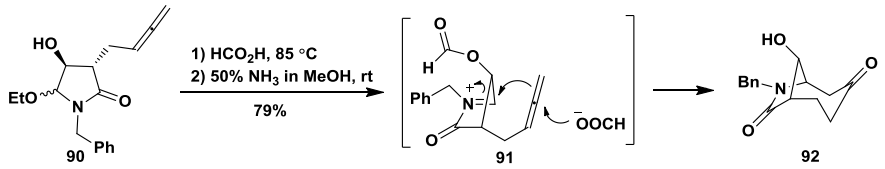
Gillman and co-workers studied a SmI_2-promoted intramolecular radical addition between aldehydes and the allenoate moiety in **80.** A mixture of C=C bond regioisomers **81** and **82** were formed. When the carbon chain between the allene moiety and the aldehyde functionality was extended by one carbon as in **83**, a highly selective reaction of the non-terminal C=C bond in the allene moiety with the aldehyde was observed to afford five-membered diastereoisomeric products **84a** and **84b**. The AIBN-initiated cyclisation in the presence of Bu_3SnH afforded the same products but with a much lower stereoselectivity 5:1 compared to 15:1 for SmI_2. The enhanced stereoselectivity can be explained by the observed formation of intermediate **85** which is formed by the coordination of samarium with oxygen on the aldehyde and ester. The formation of six-membered products **88a** and **88b** was achieved in 78% yield, while the formation of seven-membered products **89a** and **89b** was less successful with the conjugate reduction of the allenoate being the preferred pathway (Scheme 1.21).[55]

1.1.2.7 *N*-Acyliminium cyclisations

Hiemstra and co-workers developed a fairly direct synthesis of the enantiopure bicyclic ketone **87** via a novel and efficient *N*-acyliminium allene cyclisation. The cyclisation of allene **90** proceeded smoothly at 85 °C in formic acid to afford ketone **92** in 79% yield after subsequent deformylation via *N*-acyliminium allene intermediate **91** (Scheme 1.22).[56]



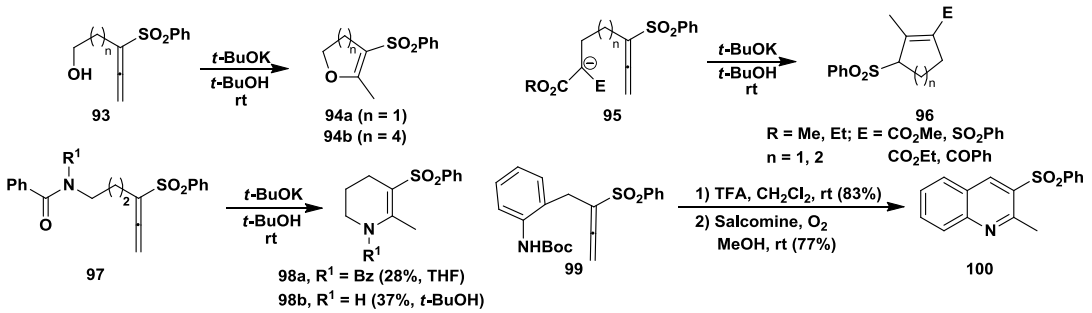
Scheme 1.21 Radical reactions of allene aldehydes



Scheme 1.22 *N*-Acyliminium cyclisations of allene **90**

1.1.2.8 Nucleophilic additions

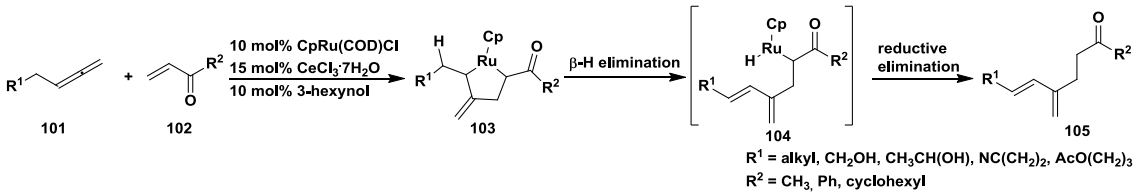
Recently, intramolecular additions of nucleophiles (alcohols, malonates and amines) to 1,2-allenyl sulfones have been established to prepare cyclic products including the eight-membered ring product **94b** (Scheme 1.23).[57]



Scheme 1.23 Intramolecular nucleophilic additions of 1,2-allenyl sulfones

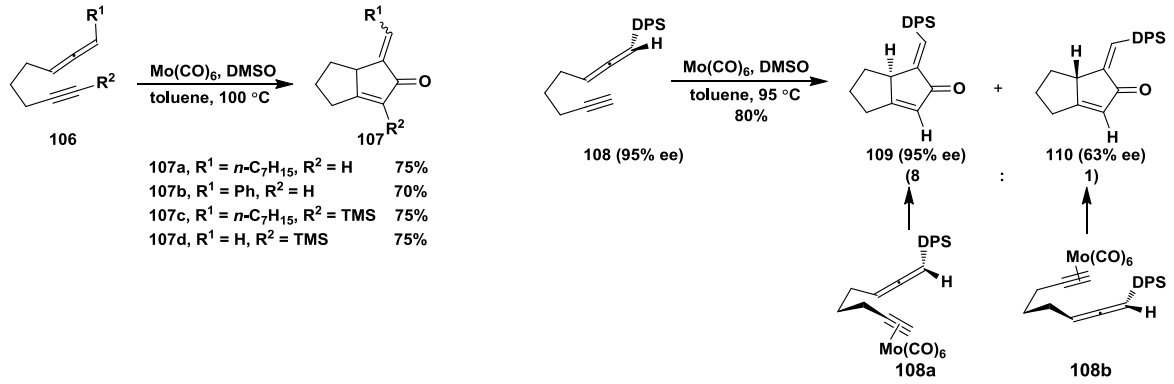
1.1.2.9 Cyclometalations

Trost and co-workers utilized a cyclometalation of terminal allenes **101** with α,β-unsaturated enones **102** and the subsequent β-H elimination and reductive elimination to prepare 3-methylene-4-(*E*)-alkenyl ketone **105** with high stereoselectivity (Scheme 1.24).[58]



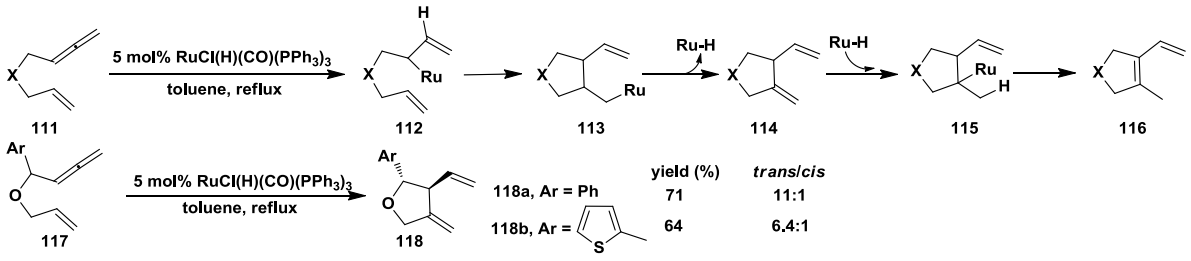
Scheme 1.24 Cyclometalations of terminal allenes **101** with α,β-unsaturated enones **102**

In 1995, Brummond reported the $Mo(CO)_6$-mediated Pauson-Khaud reaction of alkyne-1,3-disubstituted allene compounds.[59] When **106** was used, 5/5-fused bicyclic ketones **107a-107d** were obtained with the C=C bond in the allene moiety proximal to the alkyne moiety that was incorporated.[59, 60] When using $Mo(CO)_6$, the chirality in **108** could be transferred efficiently with a **109**:**110** ratio of 8:1 (Scheme 1.25).[59] In this case, the addition of the Mo-alkyne complex to the less hindered face of allene **108a** provided the (*E*)-α-silylidene cyclopentenone **109**. Alternatively, the addition of the Mo-alkyne complex to the more hindered face of allene **108b** afforded (*Z*)-α-silylidene cyclopentenone **110**. Therefore, the formation of (*E*)-α-alkylidene cyclopentenone **109** was preferred on the basis of steric control. (*E*)-α-Silylidene cyclopentenone **109** was obtained with a complete transfer of chirality from allene **108** to the product. However, for the (*Z*)-α-silylidene cyclopentenone **110,** the enantiomeric purity was only 63% ee. It was postulated that this loss in enantiomeric purity may be a result of an isomerisation of the (*E*)-isomer to the (*Z*)-isomer during the purification process since the crude *E*/*Z* ratios were higher than the chromatographically pure ratios.



Scheme 1.25 Cyclometalations of alkyne-1,3-disubstituted allenes

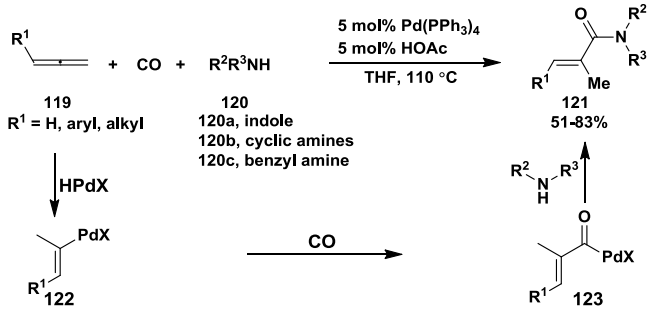
By using $RuCl(H)(CO)(PPh_3)_3$ as the catalyst, Kang and co-workers observed intramolecular hydrometalation-insertion-β-H and elimination-hydrometalation-β-H elimination reaction of 1,2,7-trienes **111** forming vinyl cyclopentene derivatived **116**. In most cases, the conjugated 1,3-dienes were obtained. However, for related ethers, 1,4-diene **118a** was formed as the only product as a *trans*/*cis* mixture (11:1), which indicated that the reaction stopped at the stage of **114** (Scheme 1.26).[61]



Scheme 1.26 Cyclometalations of 1,2,7-trienes

1.1.2.10 Carbometalation reactions

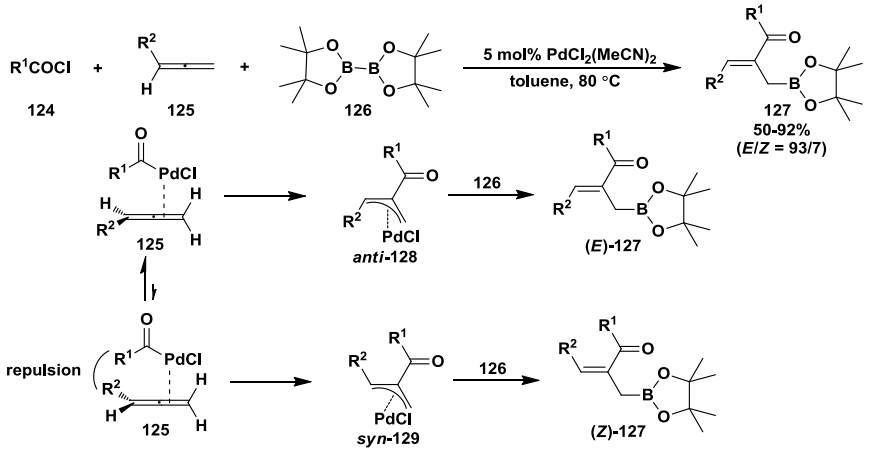
The palladium-catalysed reaction of aryl halides with allenes usually yields a π-allyl palladium intermediate, which may also undergo Tsuji-Trost type chemistry with nucleophiles.[62] For example, Grigg and co-workers reported an efficient synthesis of α,β-unsaturated amides **121** from the acylpalladation of allenes **119** in the presence of amines **120** (Scheme 1.27).[63]



Scheme 1.27 Carbometalation reactions of allenes **119**

The $PdCl_2(MeCN)_2$-catalysed three-component reaction of acyl chlorides, allenes and diboronate **126** in toluene at 80 °C yields 2-acylallylic boronate ***E*-127** efficiently and stereoselectivity (Scheme 1.28).[64] A mechanism based on face-selective coordination of allenes to the palladium centre was proposed. The terminal double bond of allene **125** was

bonded to the palladium moiety on the face opposite to substituent R^2 favorably to avoid steric congestion. The face-selective coordination resulted in a π-allylpalladium species with the R^2 group *anti* to the acyl moiety. Further reaction with **126** afforded allylboronate with *E* stereochemistry. Clearly, the latter step was faster than the *syn-anti* rearrangement of the π-allylpalladium species to obtain high *E* selectivity.



Scheme 1.28 Carbometalation reactions of allenes **125**

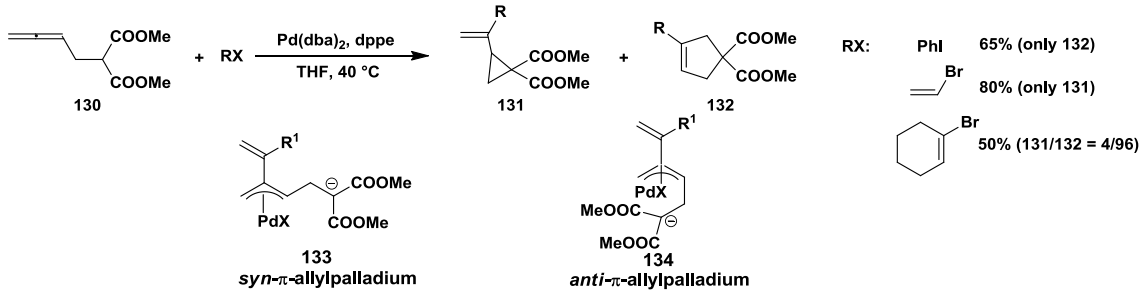
1.2 Palladium catalysed cyclisation of allenes

Palladium-catalysed reactions of allenes with carbon or heteroatom nucleophiles leading to the formation of carbon-carbon and carbon-heteroatom bonds generally proceed with the involvement of a π-allylpalladium intermediate. The mode of reactivity plays an ever increasing role in organic synthesis.[65]

1.2.1 Cyclisation of allenes with carbon nucleophiles

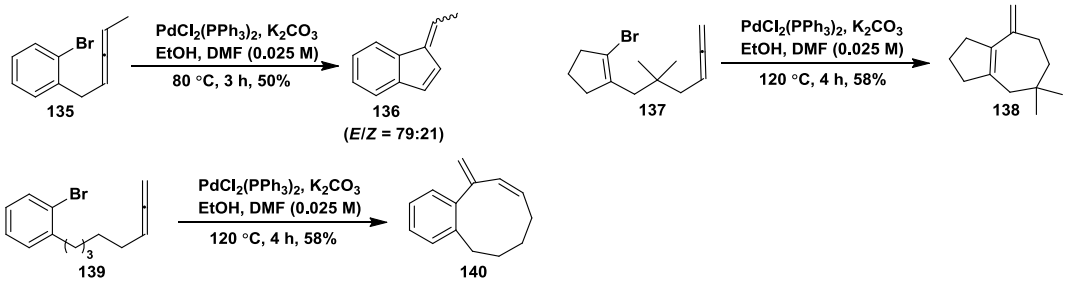
The carbopalladation reactions of allenes bearing a nucleophilic side chain, e.g. β-allenylmalonate **130**, leads to the formation of either cyclopropyl **131** or cyclopentene derivatives **132** (Scheme 1.29).[66] The regioselectivity for the formation of these rings is predominantly dependent on the bulkiness of the vinyl or aryl halides used, which allows one to assume that both *syn*-π-allylpalladium intermediate and the *anti*-π-allylpalladium intermediate are involved in the reaction. The most reasonable hypothesis is that the regioselectivity comes from a dissimilarity of configuration of the π-allylpalladium

intermediate; the *syn* configuration **133** would be favored when R^1 is an hydrogen and would lead exclusively to the formation of a cyclopropane ring **131** while in other cases the *anti* configuration **134** would only be present and cyclise to the cyclopentenyl product **132**.



Scheme 1.29 Pd-catalysed cyclisation of allenes with carbon nucleophiles

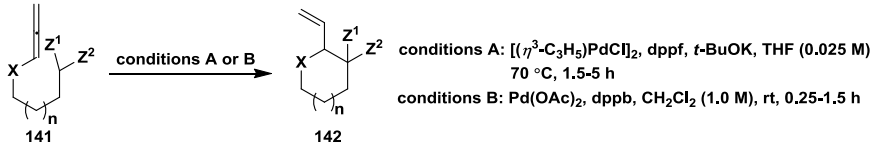
Negishi and co-workers utilized similar kinds of aryl and alkenyl halides for cyclic carbopalladation reactions in the presence of catalytic amount of $PdCl_2(PPh_3)_2$ involving a carbon-carbon bond formation at the central carbon of the allenes.[67,68] Five- to twelve-membered and even twenty-membered rings were formed in moderate to good yields. They used dilute conditions to encourage intramolecular nucleophilic attack and the addition of 1 equivalent of *n*-Bu_4NCl for an efficient reaction to occur (Scheme 1.30). It was observed that the allene moiety reacts much faster than alkenes or alkynes to yield the cyclised products.[68]



Scheme 1.30 Carbopalladation reactions of allenes

Allene compounds bearing a nucleophilic centre separated by three-five atoms from **X** afford generally five- to seven-membered rings. Yamamoto and co-workers used allenes of the type **141** for the synthesis of five- to seven-membered rings **142** (Scheme 1.31).[69] It was observed that a neutral Pd catalyst system (conditions B) is far superior to the basic one (conditions A)

for this reaction. When conditions B were employed, catalyst loadings as low as 0.1 mol% $Pd(OAc)_2$ and 0.2 mol% dppb were sufficient for good to excellent yields.



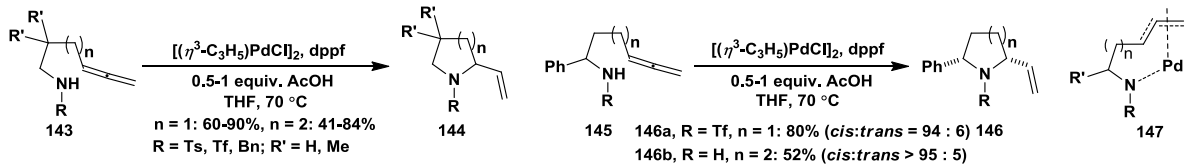
141 142

n	Z^1	Z^2	X	conditions	products (dr)
0	CN	CN	CH_2	A	88%
0	CN	CN	O	B	79%
0	CN	SO_2Ph	CH_2	A	82% (70:30)
1	CN	CN	CH_2	A	62%
1	CN	CN	O	B	86%
1	SO_2Ph	SO_2Ph	O	B	92%
2	CN	CN	O	B	88%

Scheme 1.31 Palladium-catalysed carbon nucleophilic addition onto allenes

1.2.2 Cyclisation of allenes with nitrogen nucleophiles

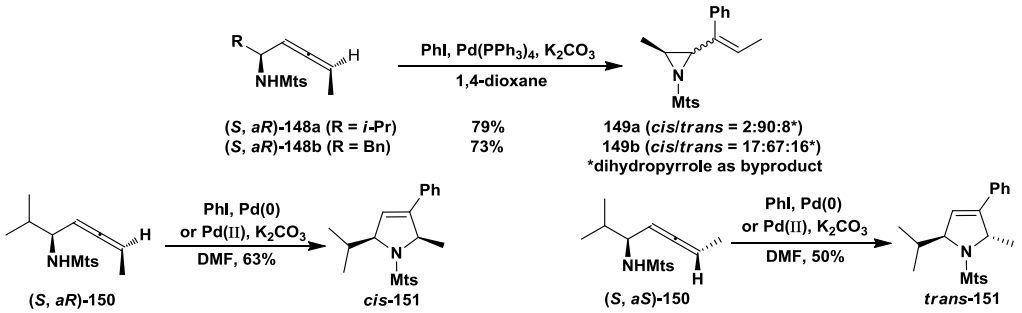
Allenes bearing a nucleophilic nitrogen functionality are extremely useful precursors for intramolecular palladium-catalysed cyclisation reactions. The development of these cyclisations by several research groups led to a variety of syntheses of, highly substituted 3- to 10-membered nitrogen heterocycles. Yamamoto and co-workers have recently developed a new type of intramolecular hydroamination (Scheme 1.32).[70] Aminoallenes **143** and **145** react smoothly in a 5-*exo*-trig or 6-*exo*-trig cyclisation to afford the corresponding vinyl-substituted heterocycles **144** and **146**, respectively. The nitrogen protecting group in the aminoallenes plays an important role. The use of *N*-triflyl, *N*-tosyl, or *N*-benzyl-substituted allenylallenes appears to be required for this type of hydroamination. When using other nitrogen-protecting groups the cyclisation of the aminoallenes failed. It is presumed that the hydroamination proceeds through the insertion of a Pd-H bond into the allenic double bond, resulting in the formation of intermediate **147**.



143 144 145 146a, R = Tf, n = 1: 80% (*cis*:*trans* = 94 : 6) 146
146b, R = H, n = 2: 52% (*cis*:*trans* > 95 : 5) 147

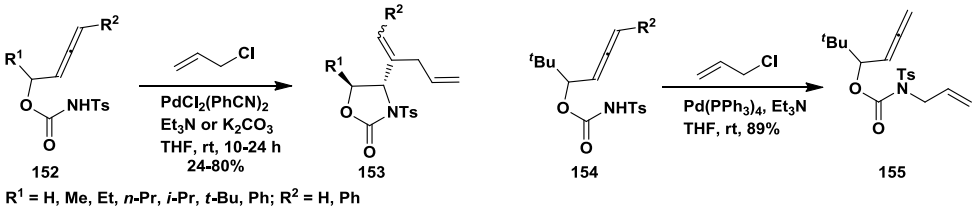
Scheme 1.32 Pd-catalysed cyclisation of allenes with nitrogen nucleophiles

Ibuka and co-workers described the palladium-catalysed aziridination reaction of aminoallenes,[71] where aziridine derivatives **149a** and **149b** were formed in good yields in the presence of $Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$ and 1,4-dioxane as a solvent (Scheme 1.33). On the other hand, when the same palladium-catalysed cyclisation was carried out in DMF, the corresponding dihydropyrrole derivative **151** was obtained as the sole product. This investigation demonstrates that the subtle choice of the solvent for palladium-catalysed reactions may be crucial.



Scheme 1.33 Arylative carbopalladation reactions with nitrogen nucleophiles

A few examples of palladium-catalysed allylative cyclisation reactions were reported by Tamaru and co-workers (Scheme 1.34).[72] The 4,5-disubstituted oxazolidines **153** were obtained in excellent stereoselectivities and in generally good yields by using $PdCl_2(PhCN)_2$, Et_3N or K_2CO_3 and a large excess of allyl chloride (up to 20 equiv.). However, the efficiency of palladium-catalysed allyl aminocyclisation depends markedly on Pd species used. $PdCl_2(PhCN)_2$ is the most effective catalyst in these cyclisations. $Pd_2(dba)_3{\cdot}CHCl_3$ and $PdCl_2$ may be used with similar efficiency. Interestingly, the most common Pd catalyst, $Pd(PPh_3)_4$ only gave the *N*-allylation product **155**. In spite of good stereoselectivity and good yields achieved under the optimal conditions, the reactions are restricted to the application of tosyl carbamates. So far no other *N*-substituted carbamate derivatives have been used in such a cyclisation.

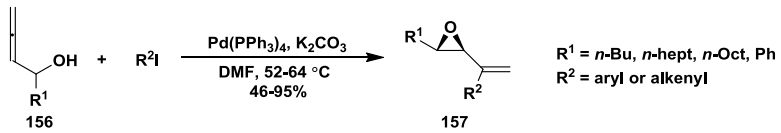


Scheme 1.34 Pd-catalysed allylative cyclisation of *N*-protected allene carbamates

1.2.3 Cyclisation of allenes with oxygen nucleophiles

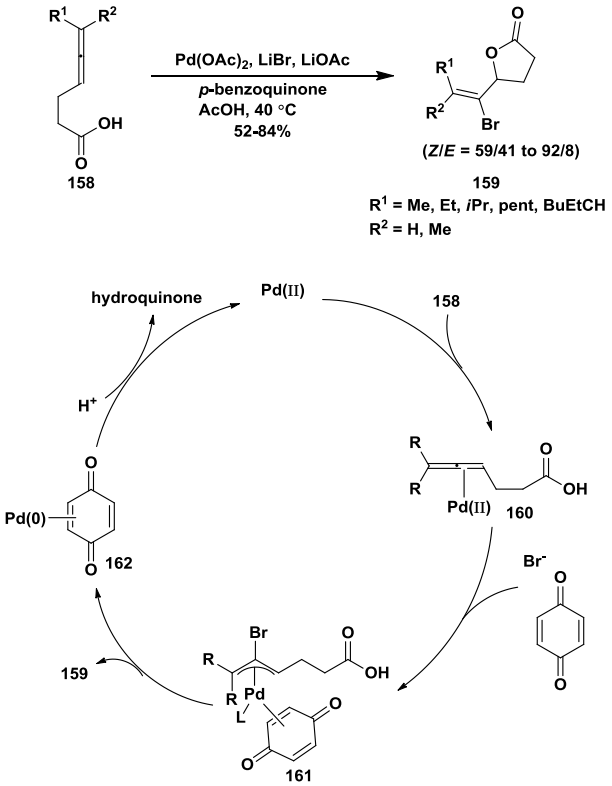
Contrary to the broad application of nitrogen nucleophiles in palladium-catalysed reactions of allenes, the use of oxygen nucleophiles has been less explored[73]

In 1999, Ma and co-workers developed an efficient synthesis of *trans*-2,3-disubstituted vinylic oxiranes **157**.[74] This palladium-catalysed cyclisation of α-allenic alcohols **156** with aryl or alkenyl iodides gave the corresponding epoxides **157** with high diastereoselectivities (dr = 92/8 to 99/1) (Scheme 1.35). Notably, the same cyclisation reaction using optically enriched α-allenic alcohols (95-98% ee) has also opened a new way to optically active oxiranes (96-98% ee).



Scheme 1.35 Carbopalladation reactions with alcohols as nucleophiles

Backvall and co-workers reported an efficient palladium-catalysed intramolecular 1,2-oxidation of allenic acids **158** in the presence of $Pd(OAc)_2$, LiBr and *p*-benzoquinone.[75] The bromovinyl-substituted lactones **159** were obtained with moderate to good (*Z*/*E*)-selectivity in up to 84% yield (Scheme 1.36). The intramolecular oxidation can be rationalized by assuming the following mechanism. Nucleophilic attack of the bromide ion onto the coordinated allene **160** gives π-allylpalladium species **161**. Subsequent intramolecular attack of the oxygen nucleophile provides **159** and a Pd(0)-quinone complex **162**. The complex then undergoes an internal redox reaction to give Pd(II) and hydroquinone.



Scheme 1.36 Carbopalladation reactions with carboxylic acids as nucleophiles

Chapter Two Palladium Catalysed Diastereoselective Arylative and Vinylative Allene Carbocyclisation Reactions

2.1 Concept and Aims

The aza-spirocyclic motif is found in many biologically active natural compounds ranging from the structurally simple to the architecturally complex, including Manzamine A[76] and the family members[77] which exhibit a broad range of interesting biological properties (Figure 2.1). Highly innovative and increasingly efficient ways of accessing these structures have been developed over the past decade.[76] We wished to extend our research in the field of transition metal catalysed carbocyclisations of alkynes[78] to appropriately substituted allenes to provide direct access to arylated spirolactam products of high synthetic value. As introduced in previous section (chapter one), allenes are a reactive class of compound able to undergo a diverse range of chemical transformations (most notably under palladium catalysis) making them useful starting materials and intermediates for organic synthesis.[79]

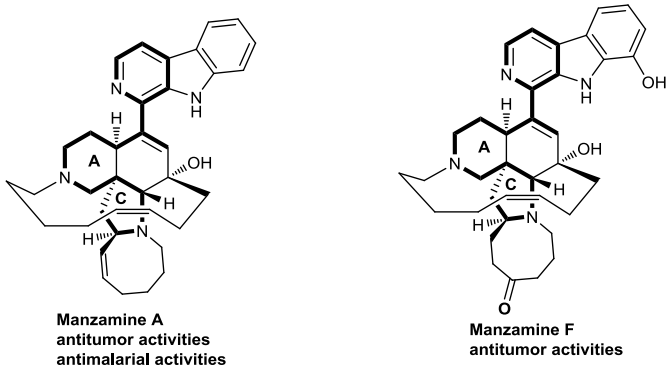
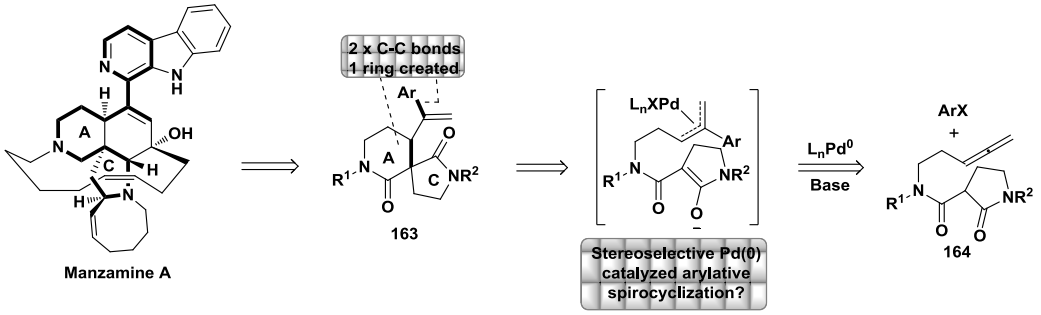


Figure 2.1 Structures of Manzamines A and F

Some palladium-catalysed arylated cyclisations of allenes with organic halides have been reported.[80-84] As part of an ongoing program of research targeting polycyclic alkaloid natural products,[76] we were interested in the possibility of developing an efficient and diastereoselective palladium-catalysed arylative and vinylative carbocyclisation of allene-tethered pro-nucleophiles (Scheme 2.1). Allene-linked pro-nucleophile **164** reacts with organic

halides to afford the arylative spirolactam **163** which makes up the core backbone of Manzamine A, which could be further developed to give the interesting natural product.

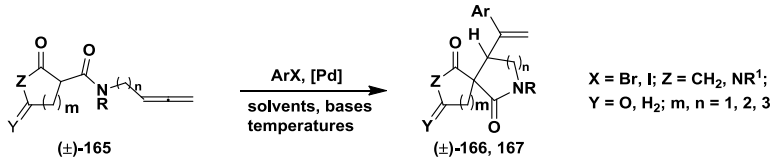


Scheme 2.1 Retrosynthetic route of Manzamine A

Specifically, the aims of this study were:

1) To synthesise a range of allene-linked ketoamides and test their reactivity in the palladium catalysed allene carbocyclisation with aromatic halides and vinyl iodides;

2) To find the optimal conditions for the palladium catalysed diastereoselective allene carbocyclisation with aryl halides by screening palladium catalysts, ligands, solvents, bases and temperatures (Scheme 2.2);



Scheme 2.2 General methodology for palladium catalysed diastereoselective arylative allene carbocyclisation

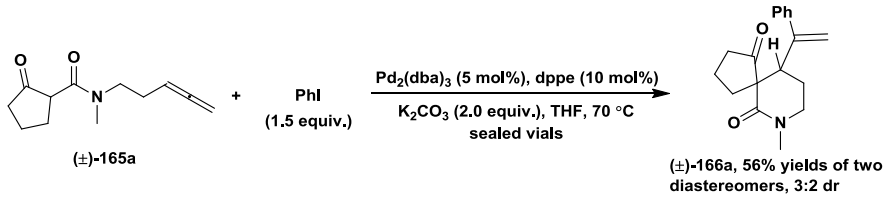
3) With a method established, demonstrate the scope of palladium catalysed diastereoselective allene carbocyclisation with aromatic halides and vinyl iodides.

2.2 Results and Discussion

2.2.1 Palladium catalysed diastereoselective arylative allene carbocyclisations

2.2.1.1 Proof of principle

In order to assess the reactivity of allene-linked ketoamides in our key palladium catalysed carbocyclisation reactions with aromatic halides, proof of reactivity studies were undertaken. Initially, allene-linked ketoamide **(±)-165a** was selected for the preliminary cyclisation studies. A screen of Pd(0) catalysts, ligands, bases and solvents in the presence of 1.5 equiv. of iodobenzene was rapidly met with some success. Spirolactam **(±)-166a** was isolated in 31% yield from a 3:2 mixture of diastereoisomers (56% combined yield) when 5 mol% $Pd_2(dba)_3$, 10 mol% dppe and 2.0 equiv. K_2CO_3 in THF at 70 °C (sealed vial) were employed (Scheme 2.3). With proof of principle established, we wished to improve the diastereoselectivity and develop a general methodology for the synthesis of the arylative spirocyclic motif.



Scheme 2.3 Proof of principle

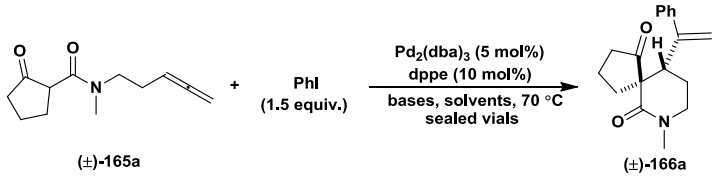
2.2.1.2 Optimisation of Pd-catalysed arylative allene carbocyclisations[94]

With allene-linked ketoamide **(±)-165a**, various palladium catalysts, ligands, temperature, bases and solvents were screened to assess their performance in the carbocyclisation of allenes with aromatic halides. Further studies showed that 5 mol% $Pd_2(dba)_3$ and 10 mol% dppe at 70 °C were the most efficient reaction conditions. Different bases and solvents were screened for the cyclisation in the presence of 5 mol% $Pd_2(dba)_3$ and 10 mol% dppe at 70 °C (Table 2.1). The results showed that the reaction diastereoselectivity was dependent on the solvent polarity. Almost no diastereoselectivity was observed in less polar solvents such as THF, 1,2-dichloroethane, DME and TBME (entries 1-3, 5). Polar aprotic solvents such as DMSO and

DMF tended to give higher yields and diastereoselectivities, 17:1 and 14:1 respectively (entries 7-11). When methanol was employed as a solvent only substrate decomposition was witnessed (entry 4).

A screen of typical inorganic bases showed that K_2CO_3, Cs_2CO_3 and K_3PO_4 were all effective, affording product **(±)-166a** with high diastereoselectivities and in moderate to good yields (entries 8-10). However, use of NaO^tBu resulted in the decomposition of **(±)-165a** (entry 11). Thus it was established that $Pd_2(dba)_3$ (5 mol%), dppe (10 mol%), iodobenzene (1.5 equiv.) and K_2CO_3 (2.0 equiv.) in DMSO at 70 °C were the optimal reaction conditions (entry 9).[95]

Table 2.1 Optimisation studies on test substrate **(±)-165a**



entry	solvents	bases	time/h	conv/%[b]	yield/%[c]	dr[d]
1	THF	K_2CO_3	24	100	31	3:2
2	DCE	K_2CO_3	48	100	33	3:2
3	DME	K_2CO_3	20	100	33	6:5
4	CH_3OH	K_2CO_3	16	-[a]	-	-
5	TBME	K_2CO_3	50	100	32	3:2
6	CH_3CN	K_2CO_3	20	100	60	10:1
7	DMF	K_2CO_3	19	100	58	14:1
8	DMF	Cs_2CO_3	16	100	32	9:1
9	**DMSO**	**K_2CO_3**	**16**	**100**	**58**	**17:1**
10	DMSO	K_3PO_4	17	100	50	15:1
11	DMSO	NaO^tBu	17	-[a]	-	-

[a]decomposed; [b]from crude ^{1}H NMR; [c]isolated yields of the major diastereoisomer; [d]determined from crude ^{1}H NMR before separation.

2.2.1.3 Synthesis of allene-linked ketoamides **(±)-165**

With the feasibility of the palladium catalysed diastereoselective carbocyclisation of allene **(±)-165a** with iodobenzene, we wished to synthesise a range of allene-linked ketoamides **(±)-165** for the scope of the reaction (Figure 2.2).

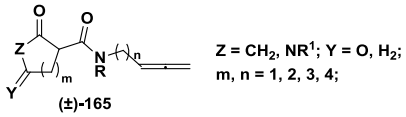
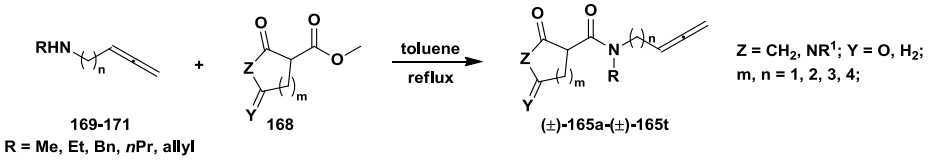


Figure 2.2 Substrates for the carbocyclisation of allenes

These substrates are prepared by direct amidation of the corresponding esters **168** with aminoallenes **169**-**171** in toluene at reflux (Scheme 2.4).[85] The aminoallenes can be *N*-methyl-buta-2,3-dien-1-amine **169**, *N*-alkyl-penta-3,4-dien-1-amines **170** and *N*-benzyl-hexa-4,5-dien-1-amine **171**. Compound **168** can bear five- to eight-membered rings. The racemic substrates **(±)-165** were obtained in moderate to good yields which ranged from 30% to 84%.

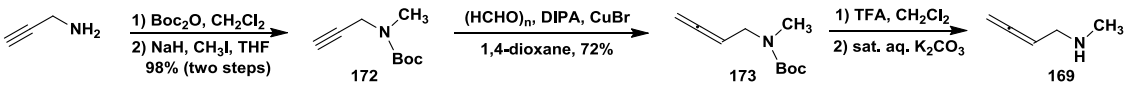


Scheme 2.4 Synthesis of allene-linked ketoamides **(±)-165**

2.2.1.3.1 Synthesis of aminoallenes **169**-**171**

2.2.1.3.1.1 Synthesis of *N*-methyl-buta-2,3-dien-1-amine **169**

Tert-Butyl methyl(prop-2-yn-1-yl)carbamate **172** was prepared from propargyl amine via Boc protection and methylation in 98% yield over two steps.[186] Treatment of **172** with paraformaldehyde, diisopropylamine and cuprous bromide in 1,4-dioxane at reflux afforded *tert*-butyl buta-2,3-dien-1-yl(methyl)carbamate **173** in 72% yield.[28,29] Deprotection with TFA in CH_2Cl_2 (v/v 1:1) followed by basification provided *N*-methyl-buta-2,3-dien-1-amine **169**, which was used directly in the next step (Scheme 2.5).

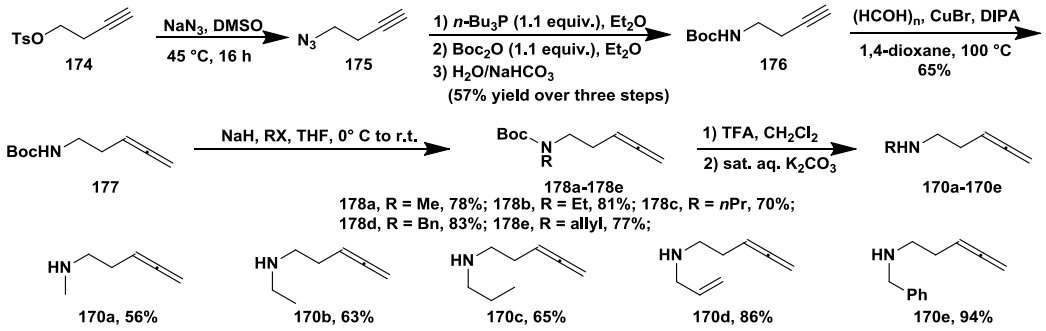


Scheme 2.5 Synthesis of *N*-methyl-buta-2,3-dien-1-amine **169**

2.2.1.3.1.2 Synthesis of *N*-alkyl-penta-3,4-dien-1-amines **170a-170e**

N-Alkyl-penta-3,4-dien-1-amines **170** were prepared from tosylated 3-butyn-1-ol **174**.[86] Treatment of **170** with sodium azide at 45 °C in DMSO gave the crude ethereal solution of azide **175**. *N*-Boc-butyl-1-yne-3-amine **176** was synthesised in 67% yield (over three steps) via

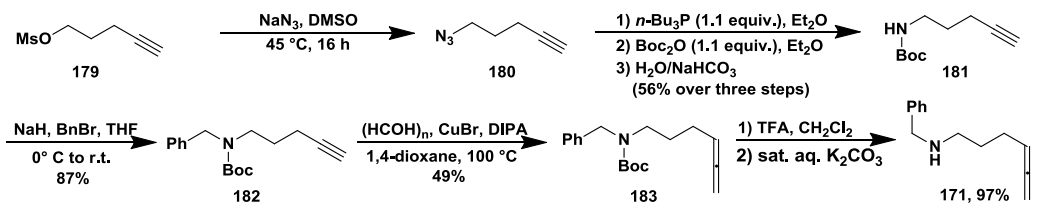
Staudinger reaction and subsequent Boc protection. *N*-Boc aminoallene **177** was obtained in 63% yield by treatment with paraformaldehyde, diisopropylamine and cuprous bromide in 1,4-dioxane at reflux.[30] Various *N*-Boc-*N*-alkyl aminoallenes **178** were obtained by alkylation with alkyl halides and sodium hydride in THF. Deprotection using TFA followed by basification provided *N*-alkyl-aminoallenes **170a-170e**, which were used directly in the next step (Scheme 2.6).



Scheme 2.6 Synthesis of *N*-alkyl-penta-3,4-dien-1-amines **170a-170e**

2.2.1.3.1.3 Synthesis of *N*-benzyl-hexa-4,5-dien-1-amine **171**

N-Benzyl-hexa-4,5-dien-1-amine **171** was synthesised from pent-4-yn-1-ol (Scheme 2.7). Mesylated pent-4-yn-1-ol **179**, derived from pent-4-yn-1-ol,[87] was treated with sodium azide at 45 °C in DMSO to give the crude ethereal solution of azide **180**. *N*-Boc-pent-4-yne-1-amine **181** was synthesised in 56% yield (over three steps) via Staudinger reaction and Boc protection. Treatment of **181** with benzyl bromide and sodium hydride in THF afforded *N*-Boc-*N*-benzyl-pent-4-yne-1-amine **182** in 87% yield. *N*-Boc-aminoallene **183** was obtained in 58% yield using paraformaldehyde, diisopropylamine and cuprous bromide in 1,4-dioxane at reflux.[30] Deprotection using TFA followed by basification provided *N*-benzyl-hexa-4,5-dien-1-amine **171**, which was used directly in the next step.



Scheme 2.7 Synthesis of *N*-benzyl-hexa-4,5-dien-1-amine **171**

2.2.1.3.2 Synthesis of allene-linked ketoamide **(±)-165a-(±)-165t**

With the corresponding esters **168** and aminoallenes **169-171** in hand, a wide variety of allene-linked ketoamides **(±)-165a-(±)-165t** were prepared in toluene at reflux (Scheme 2.4).[85] The yields ranged from moderate to good (Figure 2.3).

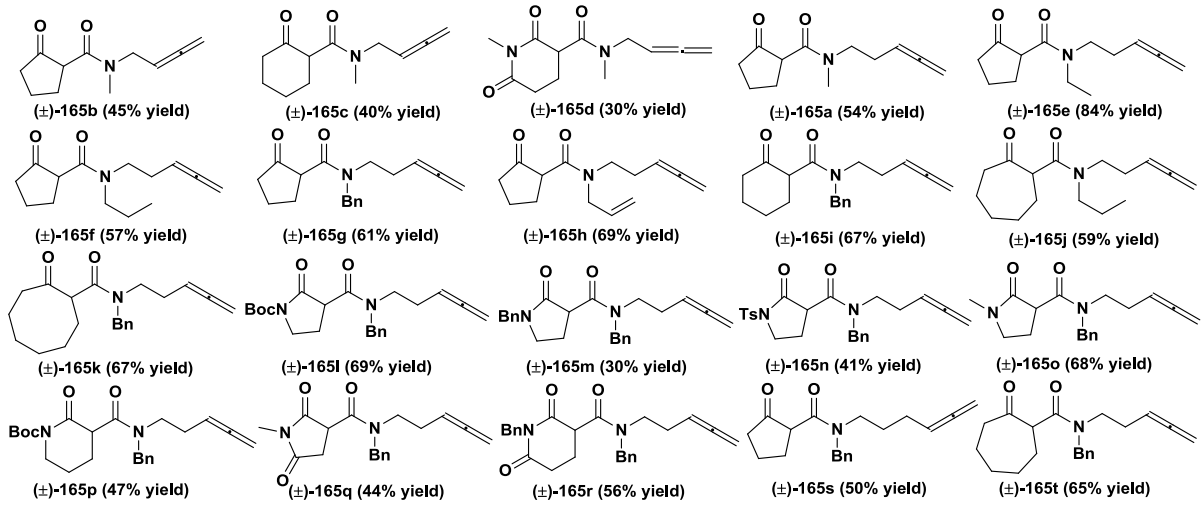
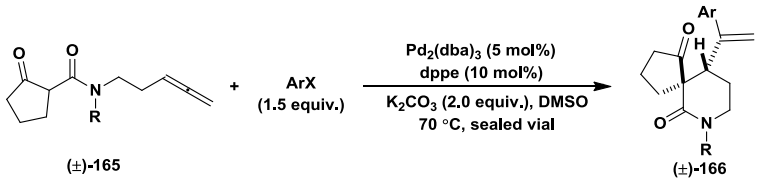


Figure 2.3 Synthesised allene-linked ketoamides **(±)-165a-(±)-165t**

2.2.1.4 Reaction scope

With optimal conditions established for **(±)-165a**, the scope of the diastereoselective arylative allene carbocyclisation cascade with respect to the (hetero)aromatic halide and the *N*-substituent of **(±)-165** was investigated. Electron-rich and electron-deficient (hetero)aromatic iodides were investigated, as were 1-bromonaphthalene, 2-bromonaphthalene and 2-bromopyridine (Table 2.2). The reactions with aryl bromides are slightly slower than those with aryl iodides. With **(±)-165a**, reaction yields were good to excellent and selectivities ranged from 13:1 to 22:1 (entries 1-6). Variation on the spectator nitrogen substituent was not only tolerated but in general led to notable improvements in the reaction diastereoselectivity; when *N*-benzyl substrate **(±)-165g** was reacted with various aryl and heteroaryl halides, the observed diastereoselectivities ranged from 25:1 to 47:1 (entries 7-10). Altogether 5 different *N*-substituents and 12 different (hetero)aryl halides (iodides and bromides) were successfully employed in the reaction.

Table 2.2 Scope of Pd(0)-catalysed arylative allene carbocyclisation cascades



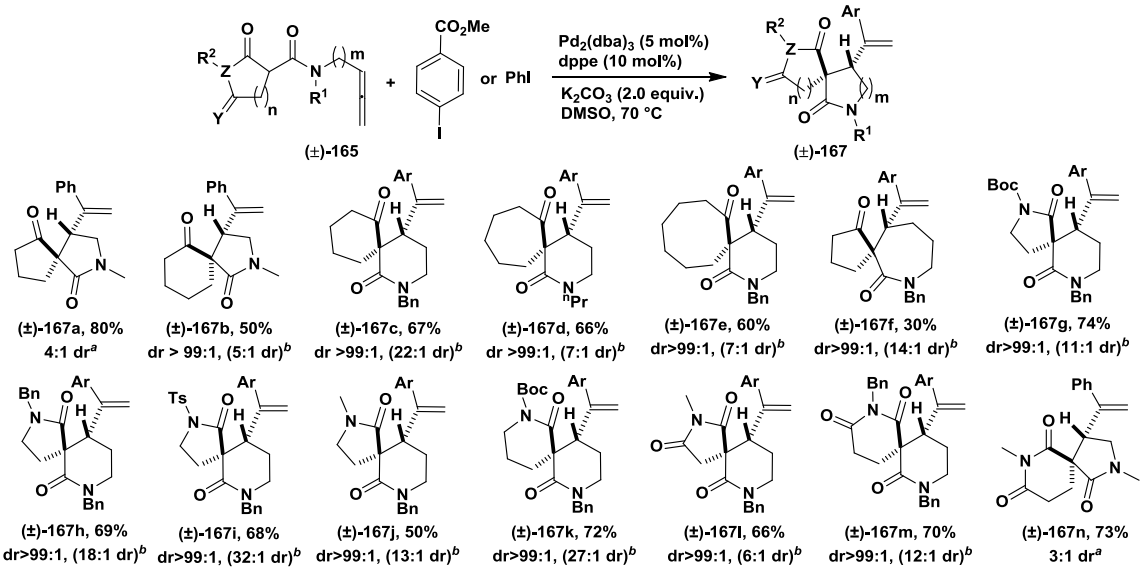
(±)-165 (±)-166

entry	R	165	ArX	time/h	166	yield/%[a]	dr[b]
1	Me	**(±)-165a**	*p*-MeOC$_6$H$_4$I	12	**(±)-166b**	79	18:1
2	Me	**(±)-165a**	3,5-Me$_2$C$_6$H$_3$I	12	**(±)-166c**	66	15:1
3	Me	**(±)-165a**	*p*-MeOC(O)C$_6$H$_4$I	10	**(±)-166d**	83	22:1
4	Me	**(±)-165a**	*m*-MeOC(O)C$_6$H$_4$I	10	**(±)-166e**	86	13:1
5	Me	**(±)-165a**	2-bromonaphthalene	16	**(±)-166f**	61	15:1
6	Me	**(±)-165a**	*p*-BrC$_6$H$_4$I	45	**(±)-166g**	61	15:1
7	Bn	**(±)-165g**	*p*-N(CH$_3$)$_2$C$_6$H$_4$I	20	**(±)-166h**	50	33:1
8	Bn	**(±)-165g**	2-iodothiophene	16	**(±)-166i**	77	25:1
9	Bn	**(±)-165g**	*m*-NO$_2$C$_6$H$_4$I	12	**(±)-166j**	74	30:1
10	Bn	**(±)-165g**	*p*-MeOC(O)C$_6$H$_4$I	16	**(±)-166k**	67	47:1
11	Pr	**(±)-165f**	1-bromonaphthalene	24	**(±)-166l**	65	16:1
12	Pr	**(±)-165f**	*p*-MeOC(O)C$_6$H$_4$I	10	**(±)-166m**	70	19:1
13	ally	**(±)-165h**	*p*-MeOC(O)C$_6$H$_4$I	14	**(±)-166n**	66	30:1
14	Et	**(±)-165e**	*p*-MeOC(O)C$_6$H$_4$I	12	**(±)-166o**	75	36:1
15	Et	**(±)-165e**	2-bromopyridine	20	**(±)-166p**	53	12:1

[a]isolated yield of single major diastereoisomer; [b]dr from ^{1}H NMR spectroscopic analysis of the crude products.

Additionally, extension of this cyclisation methodology to homologous and structurally modified allene-linked pro-nucleophilic substrates was also achieved and provided access to a range of spirocyclic scaffolds. Following the optimised procedure, either iodobenzene or methyl 4-iodobenzoate was employed as the haloarene (Scheme 2.8). In the formation of spiropiperidin-2-ones, good reactivity was observed with substrates possessing six-, seven- and eight-membered ring cyclic ketones (for 5-membered rings see Table 2.2) and diastereoselectivities ranged from 6:1 to 22:1 (**(±)-167c-(±)-167e, (±)-167g-(±)-167m)**. Spiropyrrolidin-2-ones **(±)-167a**, **(±)-167b** and **(±)-167n** were also accessible in good to excellent yield albeit with moderate diastereoselectivity. A single attempt of synthesizing spiroazapan-2-one **(±)-167f** was met with partial success; **(±)-167f** was isolated in 30% yield and 14:1 dr. A range of differentially *N*-substituted γ- and δ-lactam derived allene-linked pro-nucleophilic substrates underwent cyclisation with methyl 4-iodobenzoate to give spiropiperidin-2-ones **(±)-167g-(±)-167k** in moderate to good yields and good to excellent

diastereoselectivities. Similarly *N*-protected succinimide or glutarimide substrates had good reactivity and afforded spiropyrrolidin-2-ones **(±)-167n** and spiropiperidin-2-ones **(±)-167l**-**(±)-167m** in good yields and with moderate to good diastereoselectivities.

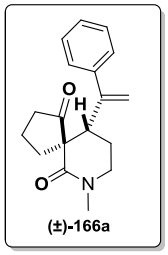


[a]inseparable; [b]dr in crude product.

Scheme 2.8 Scope of the arylative allene carbocyclisation cascade

2.2.1.5 Relative configuration of spirolactams **(±)-166** and **(±)-167**

No nOe responses between H5, H3 and H3' was observed in the nOe analysis of **(±)-166a** (Figure 2.4), therefore the relative stereochemistry could not be confirmed by the nOe analysis.



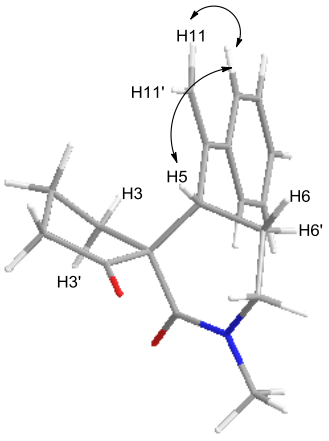


Figure 2.4 nOe responses of relevant protons of **(±)-166a**

The relative stereochemistries of all the major diastereoisomeric products of **(±)-166** and **(±)-167** were assigned by analogy to that of **(±)-167i** which was determined by single crystal X-ray diffraction (Figure 2.5).

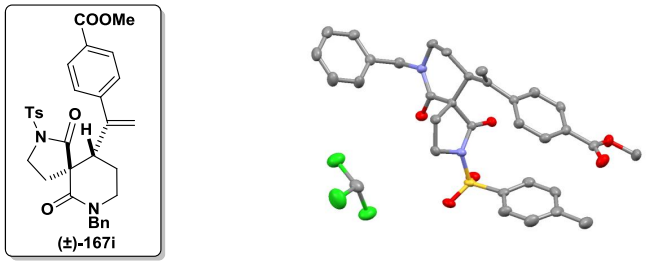
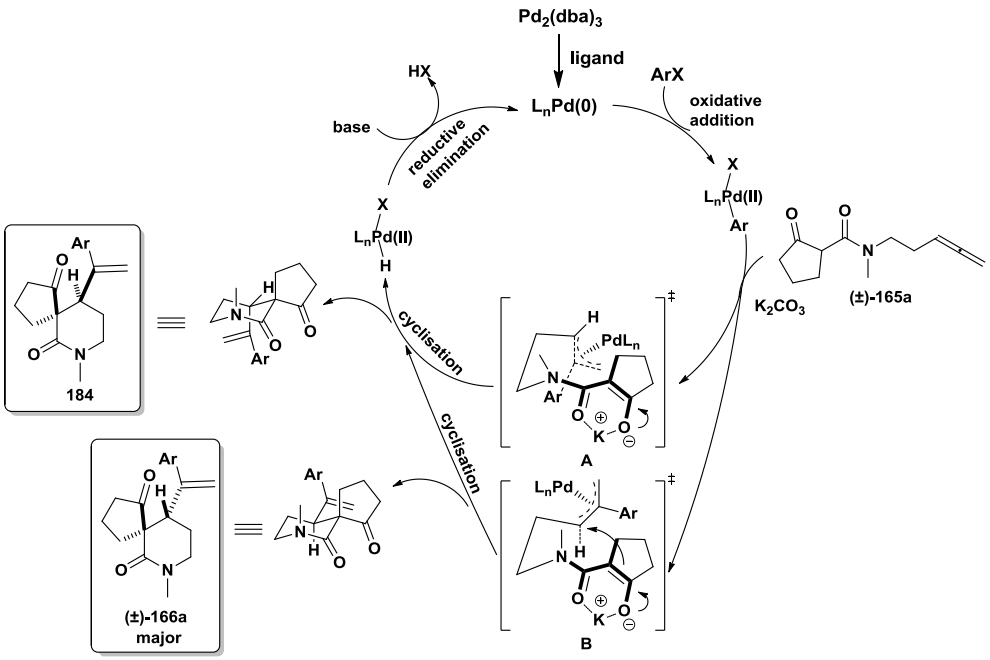


Figure 2.5 X-Ray of spirolactam **(±)-167i** with $CDCl_3$

2.2.1.6 Proposed mechanism

Our research showed that the reaction diastereoselectivity was dependent on the solvent polarity. Several reports[95] have performed extensive theoretical studies on the mechanism of general carbopalladation reactions of allenes with aryl iodides. By applying these studies to our system, a mechanism was proposed (Scheme 2.9). The first step is oxidative addition of palladium(0) to the organic halide to generate an organopalladium(II) species, which then generates π-allylpalladium complexes **A** and **B** by reaction with **(±)-165a** in the presence of K_2CO_3. The π-allylpalladium moiety in **A** and **B** would be sufficiently electrophilic to undergo intramolecular nucleophilic attack by the α-carbon of the enolate, affording two diastereomers **(±)-184** and **(±)-166a**, respectively. Transition state **B** is favoured probably because the π-allylpalladium moiety is equatorial, which leads to the major diastereomer **(±)-166a**.



Scheme 2.9 Proposed mechanism of palladium catalysed arylative allene carbocyclisation

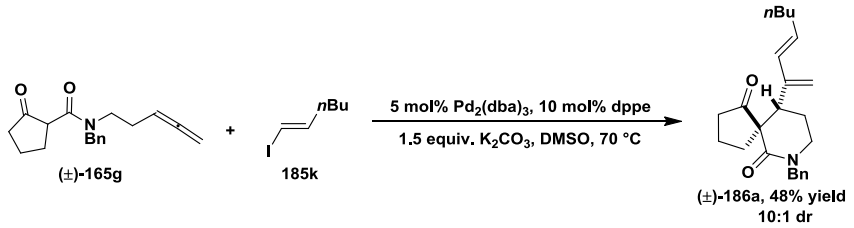
2.2.1.7 Summary

In summary, we have developed a mild, efficient and diastereoselective cyclisation methodology for the synthesis of a range of stereodefined arylative spirolactam compounds. Altogether 15 different spirocyclic structures have been accessed using this new methodology. Being operationally simple and tolerating multiple points of diversity this reaction should be of use in complex natural product synthesis as well as compound library synthesis.

2.2.2 Palladium catalysed diastereoselective vinylative allene carbocyclisation reactions

2.2.2.1 Proof of reactivity

Vinyl halides are very useful organic intermediates in organic synthesis. They have been widely used as extremely useful building blocks in transition-metal-catalysed organic transformations and natural product synthesis.[96] In particular, vinyl halides have been employed in the palladium-catalysed reaction of allenes instead of aromatic halides.[97] Therefore, it is possible to replace aryl halides with vinyl halides in our Pd-catalysed diastereoselective allene carbocyclisations. Initially, **(±)-165g** underwent smooth cyclisation with (*E*)-1-iodohex-1-ene **185k** under the optimal reaction condition for arylative allene carbocyclisation. Pleasingly, the spirocyclic conjugated diene **(±)-186a** was isolated in 48% yield and with 14:1 dr (Scheme 2.10). The vinylative carbocyclisation was shown to be a feasible arylative reaction partner, and so the methodology was expanded to a range of substrates.



Scheme 2.10 Proof of principle of vinylative allene carbocyclisation

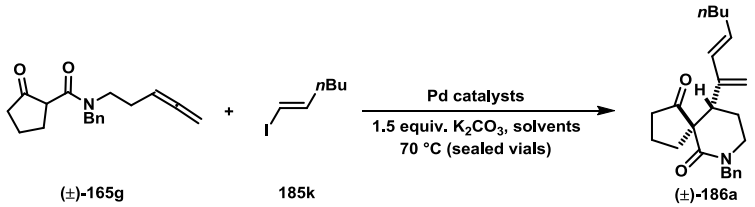
2.2.2.2 Optimisation studies

Based on the developed reaction conditions for arylative carbocyclisation, the cyclisation with vinyl halides were optimised in terms of palladium catalysts and solvents in the presence of K_2CO_3 at 70 °C (Table 2.3).

The results showed that $PdCl_2$(dppf) is more active for the reaction than $Pd_2(dba)_3$/dppe in terms of yield although the diastereoselectivity is slightly lower (entries 1 and 2). The loading of $PdCl_2$(dppf) only affects the speed of the reaction but the diastereoselectivity is mostly dependent on the solvent polarity (entries 2-4). Lower conversion was observed in less polar

solvents such as THF, 1,4-dioxane, toluene and 1,2-dichloroethane after 24 h (entries 6, 8-10). The reaction was completed in CH_3CN after 24 h albeit with a very low diastereoselectivity (entry 7). Polar aprotic solvents such as DMSO and DMF tended to give higher yields and diastereoselectivities, 13:1 and 15:1 respectively (entries 7-11). DMF was chosen as the reaction solvent because it gave high diastereoselectivity. Thus it was established that $PdCl_2$(dppf) (5 mol%), vinyl iodides (1.5 equiv.) and K_2CO_3 (1.5 equiv.) in DMF at 70 °C were the optimal reaction conditions (entry 5).

Table 2.3 Optimisation studies on test substrate **(±)-165g**



entry	Pd catalysts	solvents	time/h	conv./%[a]	yield/%[b]	dr[c]
1	5 mol% $Pd_2(dba)_3$/10 mol% dppe	DMSO	< 10	100	48	14:1
2	10 mol% $PdCl_2$(dppf)	DMSO	< 10	100	65	13:1
3	2.5 mol% $PdCl_2$(dppf)	DMSO	48	100	65	14:1
4	5 mol% $PdCl_2$(dppf)	DMSO	11	100	68	13:1
5	5 mol% $PdCl_2$(dppf)	DMF	11	100	65	15:1
6	5 mol% $PdCl_2$(dppf)	THF	24	60	-	3:1
7	5 mol% $PdCl_2$(dppf)	CH_3CN	24	100	55	6:1
8	5 mol% $PdCl_2$(dppf)	1,4-dioxane	24	40	-	2:1
9	5 mol% $PdCl_2$(dppf)	toluene	24	20	-	-
10	5 mol% $PdCl_2$(dppf)	DCE	24	23	-	-

[a]conversion was determined from crude ^{1}H NMR spectroscopic analysis; [b]isolated yield; [c]dr was determined from crude ^{1}H NMR spectroscopic analysis.

2.2.2.3 Synthesis of vinyl iodides

With proof of reactivity and optimal conditions established, a series of vinyl iodides were synthesised, including (*E*)-(2-iodovinyl)benzene **185m**,[88] (*E*)-ethyl 3-iodoacrylate **185o**,[89] (*Z*)-ethyl 3-iodoacrylate **185n**,[89] (*Z*)-(2-iodovinyl)benzene **185a**,[90,91] (*E*)-2-(2-iodovinyl)thiophene **185s**,[90] (*E*)-1-iodohex-1-ene **185k**,[90] (*Z*)-1-iodohex-1-ene **185l**,[91] (*E*)-

1-(2-iodovinyl)-4-methoxybenzene **185p**,[92] (*E*)-1-chloro-4-(2-iodovinyl)benzene **185q**,[93] (*E*)-methyl 4-(2-iodovinyl)benzoate **185r** [93] (Figure 2.6).

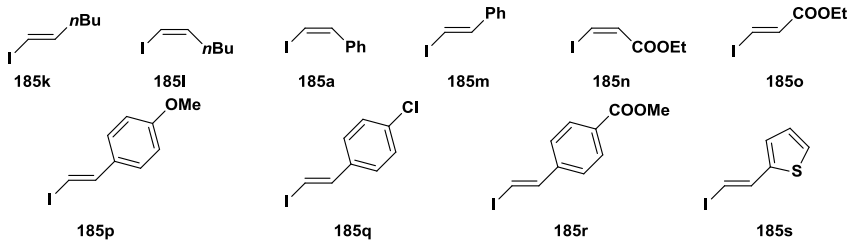
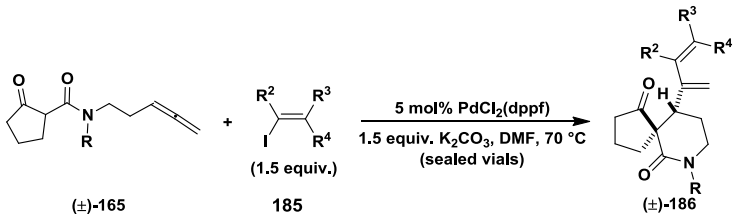


Figure 2.6 Synthesised vinyl iodides

2.2.2.4 Reaction scope

With optimal conditions established for **(±)-165g**, the scope of the diastereoselective vinylative allene carbocyclisation cascade with respect to vinyl iodides and *N*-substituent of **(±)-165** was investigated.

Table 2.4 Scope of Pd(0)-catalysed vinylative allene carbocyclisation cascades



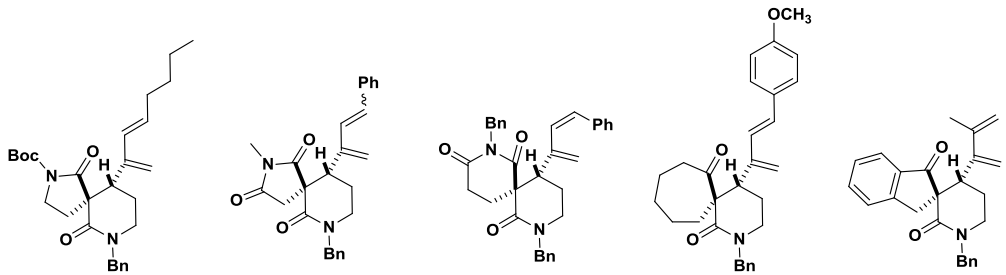
entry	R	**165**	vinyl iodides	time/h	**186**	yield/%	dr[b]
1	Bn	**(±)-165g**	(*Z*)-*n*BuCH=CHI	8	**(±)-186b**	66	11:1
2	Bn	**(±)-165g**	(*Z*)-PhCH=CHI	8	**(±)-186c**	72	15:1
3	Bn	**(±)-165g**	(*E*)-PhCH=CHI	10	**(±)-186d**	63	16:1
4	Bn	**(±)-165g**	(*E*)-4-MeOC$_6$H$_4$CH=CHI	10	**(±)-186e**	75	13:1
5	Bn	**(±)-165g**	(*E*)-MeOC(O)CH=CHI	16	**(±)-186f**	68	12:1
6	allyl	**(±)-165h**	(*E*)-4-MeOC$_6$H$_4$CH=CHI	10	**(±)-186g**	67	16:1
7	Et	**(±)-165e**	(*E*)-4-MeOC$_6$H$_4$CH=CHI	10	**(±)-186h**	76	15:1
8	Et	**(±)-165e**	(*E*)-2-thiophene-CH=CHI	16	**(±)-186i**	65	15:1
9	Et	**(±)-165e**	(*E*)-PhCH=CHI	12	**(±)-186j**	77	17:1
10	*n*Pr	**(±)-165f**	(*E*)-4-ClC$_6$H$_4$CH=CHI	12	**(±)-186k**	69	13:1
11	*n*Pr	**(±)-165f**	(*E*)-4-MeOC(O)C$_6$H$_4$CH=CHI	16	**(±)-186l**	66	14:1

[a]isolated yield; [b]dr was determined from ^{1}H NMR spectroscopic analysis of the crude products.

Aliphatic vinyl iodides, electron-rich and electron-deficient β-aryl vinyl iodides were tolerated in this carbocyclisation (Table 2.4). Reaction yields were good to excellent and selectivities ranged from 11:1 to 17:1 (entries 1-10). However, olefin isomerisation was observed when

cis-β-aryl vinyl iodides variation was employed in the cyclisation. Variation on the spectator nitrogen substituent was not only tolerated but as observed before in general led to slight improvements in the reaction diastereoselectivity (entries 5-11). Altogether 4 different *N*-substituents and 8 different (hetero)aryl halides (iodides and bromides) were successfully employed in the reaction.

Additionally, extension of this cyclisation methodology to homologous and structurally modified allene-linked pro-nucleophilic substrates was also achieved and provided access to a range of spirocyclic scaffolds. Following the optimised procedure, either *cis*-β-aryl vinyl iodides or *trans*-β-aryl vinyl iodides was employed as the haloarene (Figure 2.7). In the formation of spiropiperidin-2-ones, good reactivities were observed with substrates **(±)-165l**, **(±)-165q**, **(±)-165t** and **(±)-215a**. *N*-Boc-*γ*-lactam derived allene-linked pro-nucleophile **(±)-165l** underwent cyclisation with (*E*)-1-iodohex-1-ene **185k** to give spiropiperidin-2-one product **(±)-186m** in 64% yield with 15:1 dr. The spiropiperidin-2-one product **(±)-186p** was obtained in 48% yield with 10:1 dr from substrate **(±)-165t** and (*E*)-1-(2-iodovinyl)-4-methoxybenzene **185p**. However, olefin isomerisation was observed when using *cis*-β-aryl vinyl iodide. The mixture of *trans*-**(±)-186n** and *cis*-**(±)-186n** were obtained when (*Z*)-(2-iodovinyl)benzene **185a** was used in the cyclisation with *N*-protected succinimide **(±)-165q**. Only the *cis*-product **(±)-186o** was obtained using pro-nucleophile **(±)-165r** if the reaction was stopped as soon as completed. 2-Bromoprop-1-ene was successfully employed in the cyclisation with pro-nucleophile allene **(±)-215a** (see chapter three) to afford the cyclic diene product **(±)-186q** in 70% yield and 19:1 dr.

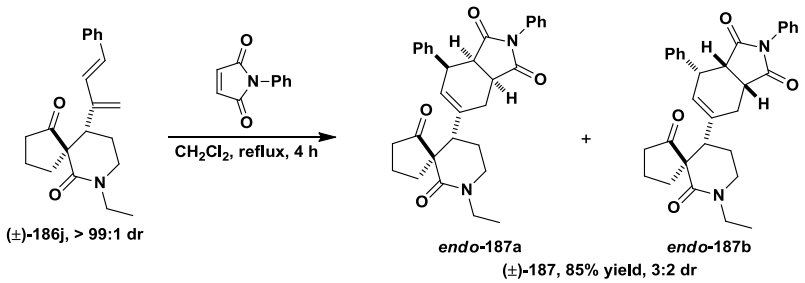


[a]dr from ^{1}H NMR spectroscopic analysis of the crude product; [b]the isolated yields of two isomers.

Figure 2.7 Scope of Pd(0)-catalysed vinylative allene carbocyclisation cascades

2.2.2.5 Application

Various stereodefined cyclic products possessing conjugated dienes were accessed using this methodology. It is known that conjugated dienes are functional groups which occur in nature and are also widely used in the polymer industry. The conjugated dienes show good reactivities in organic reactions, such as, polymerization and cycloadditions. In particular, an important reaction for conjugated dienes is the Diels-Alder reaction which is the most powerful synthetic method for accessing unsaturated six-membered rings. Accordingly, conjugated diene **(±)-186j,** which was obtained from allene **165e** and iodobenzene as a single diastereoisomer, was tested in the Diels-Alder reaction with *N*-phenylmaleimide in anhydrous dichloromethane at reflux for 4 h. The product **(±)-187** obtained in 85% overall yield (Scheme 2.11). Only two diastereomers **187a** and **187b** with a ratio of 3:2 were observed. Based one the previous reports and Alder-Stein rules, it was presumed that the two diastereomers were achieved via an *endo* approach.



Scheme 2.11 A Diels-Alder reaction of conjugated diene **186j** with *N*-phenylmaleimide

2.2.2.6 Summary

In summary, we have developed a mild, efficient and diastereoselective cyclisation methodology for the synthesis of a range of stereodefined vinylative spirolactam compounds. The various spirocyclic structures which have been accessed using this new methodology can be of use in complex natural product synthesis as well as compound library synthesis by exploiting the reactivity of conjugated dienes.

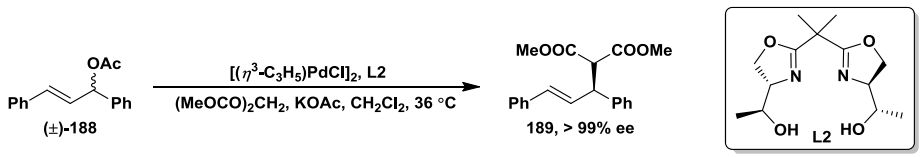
Chapter Three Palladium Catalysed Enantioselective Allene Arylative or Vinylative Carbocyclisation Reaction Cascades

3.1 Introduction

3.1.1 Palladium catalysed asymmetric alkylation

Metal-catalysed asymmetric allylic substitution, which involves the attack of diverse nucleophiles at an allylic metal intermediate, has been investigated with great intensity.[98-100] Besides a high level of asymmetric induction, the enantioselective palladium catalysed allylic substitution reaction has been shown to be a useful means of forming new chiral carbon-carbon,[101] carbon-nitrogen,[102] carbon-oxygen[103] and carbon-sulfur[104] bonds.

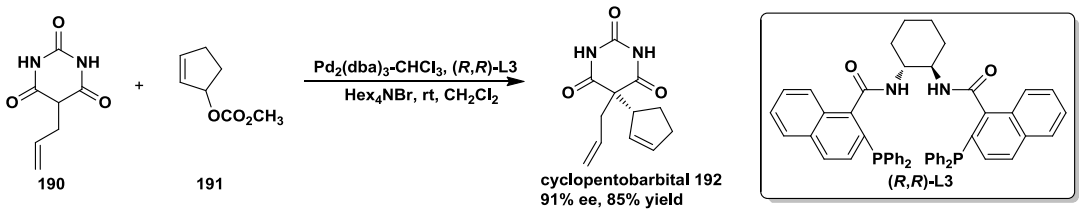
Among these metal catalysed asymmetric allylations, palladium is the most efficient metal for this reaction. Optically active C_2-symmetric bisoxazoline ligands have been used extensively for the highly enantioselective allylic alkylation. In 2004, Ait-Haddou and co-workers[105] reported palladium-catalysed asymmetric allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate **(±)-188** with dimethyl malonate using chiral hydroxyl bisoxazoline "BO" ligand which is derived from (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (Scheme 3.1). The enantioenriched product **189** was obtained with 99% ee from *rac*-1,3-diphenyl-2-propenyl acetate **(±)-188** with dimethyl malonate in the presence of the chiral bisoxazoline **L2**.



Scheme 3.1 Pd-catalysed enantioselective allylic alkylation of *rac*-**188** using ligand **L2**

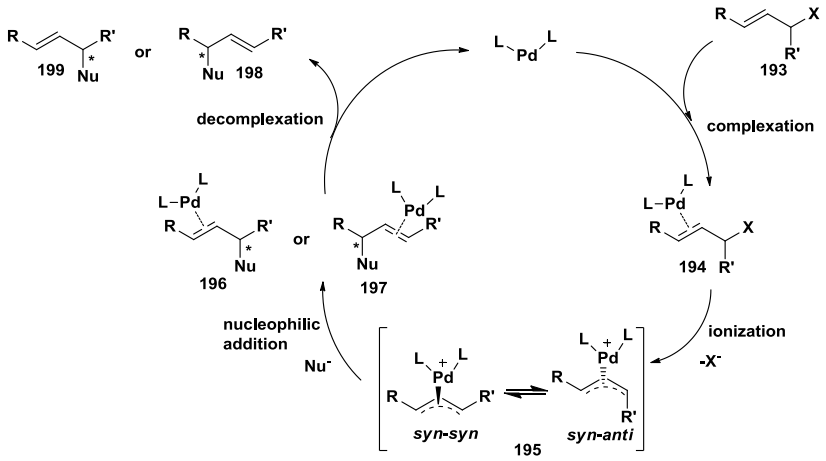
The asymmetric allylic alkylation reaction has been widely applied in organic synthesis. The majority of applications in total synthesis are with cyclic electrophiles, particularly those involving five- or six-membered rings. Trost and co-workers demonstrated the asymmetric allylic alkylation reaction with cyclic allylic electrophiles and applied it to the synthesis of

barbituric acid derivatives. Asymmetric allylic alkylation utilizing barbiturate derivative **190** as a nucleophile with simple allylic carboxylate **191** as an electrophile afforded cyclopentobarbital **192** in 85% yield and with 91% ee (Scheme 3.2).[106] This transformation used bisphosphine ligand **(*R*,*R*)-L3** and palladium dibenzylidene acetone chloroform complex as the palladium source was necessary in order to completely suppress the typical *N*-alkylation reaction.



Scheme 3.2 Asymmetric alkylation in the synthesis of cyclopentobarbital **192**

The general catalytic cycle of the asymmetric allylic alkylation offers at least five opportunities for enantiodiscrimination.[89] In some instances, more than one mechanism is operative when chiral elements at the electrophile and nucleophile are set in the same reaction. The general cycle involves olefin complexation, subsequent ionization of a leaving group, and then nucleophilic addition and decomplexation (Scheme 3.3).[100] Except for decomplexation of olefin from the palladium-ligand system, where the chirality has already been set, each of these steps provides an opportunity for enantioselection. In the π-allyl intermediate, the complex may be *syn-syn*, *syn-anti*, or *anti-anti*. As shown in the catalytic cycle, the complexes **195** that result from *E* olefins prefer the *syn-syn* configuration, while cyclic substrates are necessarily locked into the *anti-anti* geometry.[100]

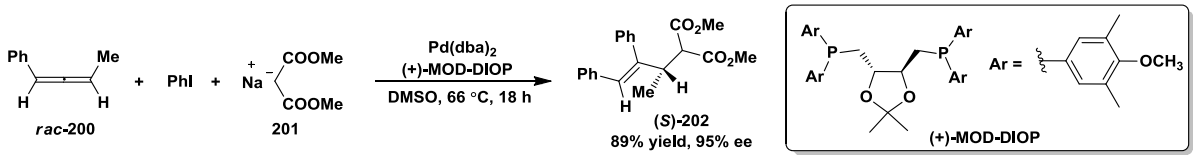


Scheme 3.3 Catalytic cycle in Pd-catalysed asymmetric allylic alkylations

3.1.2 Asymmetric arylative carbopalladation reactions of allenes

The previous chapter described the palladium catalysed diastereoselective arylative allene carbocyclisation as a method for the direct construction of arylative aza-spirocyclic motifs. However, there is no report on catalytic enantioselective coupling reactions of allenes with organic halides to afford optically active aza-spirocyclic compounds.

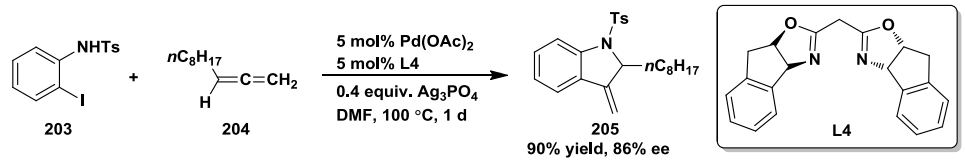
In 1998, Hiroi and co-workers reported the intermolecular asymmetric direct α,β-functionalization of allenes via asymmetric carbopalladation reactions with good enantioselectivities by using phosphine ligands.[107,108] The palladium-catalysed asymmetric reactions of a racemic allene **200**, with iodobenzene and sodium malonate **201** in DMSO at 66 °C in the presence of $Pd(dba)_2$ and (4*R*,5*R*)-(1)-4,5-bis[bis(4′-methoxy-3′,5′-dimethylphenyl)phosphinomethyl]-2,2-dimethyl-1,3-dioxolane [(+)-MOD-DIOP], afforded **(*S*)-202** in 89% yield and with up to 95% ee (Scheme 3.4).



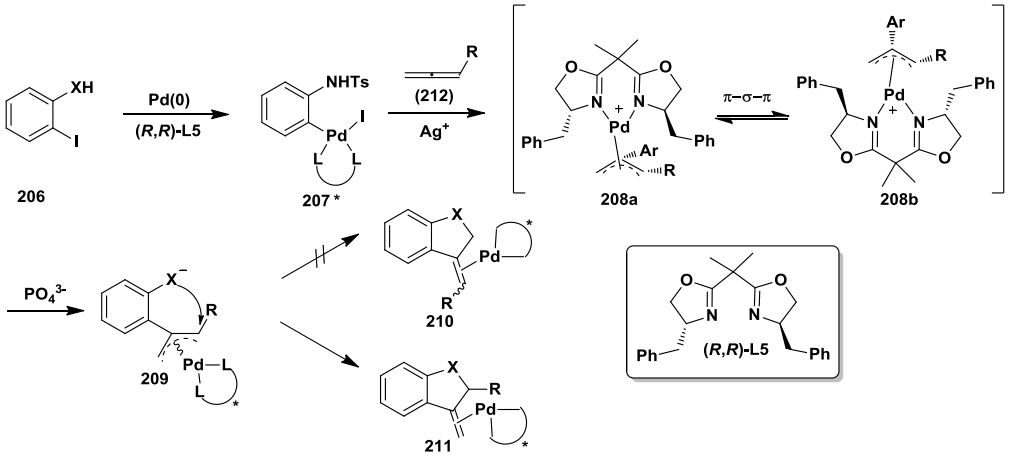
Scheme 3.4 Asymmetric intermolecular carbopalladation reaction of allene **200**

Asymmetric induction in intramolecular π-allylpalladium displacements has received far less attention than the intermolecular reactions. In 1995, Larock and co-workers reported

asymmetric palladium-catalysed hetero- and carboannulation of allenes using functionalized aryl and vinyl iodides with ees of up to 86% by using bisoxazolines as chiral ligands.[109,110] The asymmetric reaction of *N*-tosyl-2-iodoaniline **203** and 1,2-undecadiene **204** occurred in DMF at 100 °C in the presence of 5 mol% $Pd(OAc)_2$, 5 mol% **L4** and 1.2 ion equiv. of Ag_3PO_4 to give the product **205** in 90% yield with up to 86% ee (Scheme 3.5). It should be noted that silver salts significantly enhanced levels of asymmetric induction in this reaction. It is thought that in the presence of Ag^+, I^- was precipitated as AgI, allowing stronger coordination of the chiral ligand to palladium.[111]



Scheme 3.5 Asymmetric Pd-catalysed hetero- and carboannulation of allenes

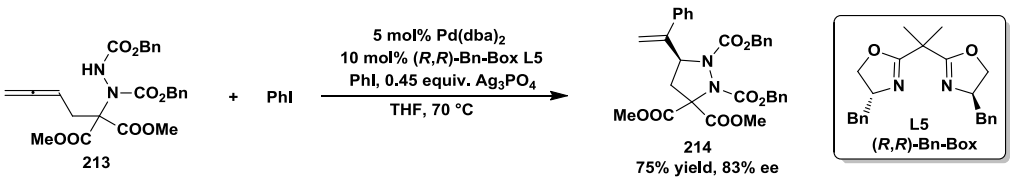


Scheme 3.6 Mechanism of asymmetric Pd-catalysed hetero- and carboannulation of allenes

The mechanism of this reaction is outlined in Scheme 3.6. The first step is reduction of Pd(II) to Pd(0), followed by oxidative addition of the organic halides. The π-allylpalladium compound **208** was formed via the addition of aryl or vinyl palladium compound **207** to allene **212**.[110] In the presence of Ag^+, I^- is removed as AgI to allow the formation of a 16 electron, positively charged Pd intermediate which can coordinate with the bidentate chiral ligand. The interconversion between two diastereoisomers **208a** and **208b** is accomplished via a π-σ-π

process.[112] This interconversion occurs rapidly in terminal π-allylpalladium species, a process which is important to eventual enantiodiscrimination. The steric interactions between the benzyl group of **(*R*,*R*)-L5** and the terminal alkyl substituent of the π-allylpalladium intermediate leads to a preference for one diastereoisomer **208a** over the other one **208b**, which goes on to form the major enantiomer **211**. Therefore the enantioselectivity is achieved due to minimization of steric interactions.

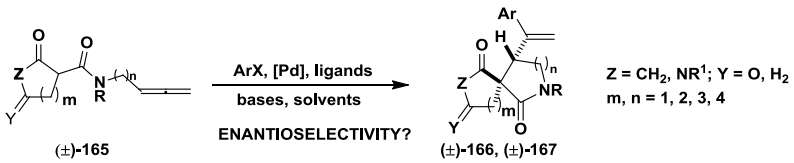
Ma and co-workers reported a convenient route to optically active pyrazolidine derivatives from Pd(0)/(*R*,*R*)-Bn-Box-catalysed enantioselective cyclisation of 3,4-allenylic hydrazines in the presence of organic halides (Scheme 3.7).[113] The palladium catalysed asymmetric cyclisation of 3,4-allenylic hydrazine **213** with iodobenzene occurred in the presence of 5 mol% $Pd(dba)_2$, 10 mol% (*R*,*R*)-Bn-Box **L5** and 0.45 equiv. Ag_3PO_4 in THF at 70 °C to give the cyclised product **214** in 75% yield with 83% ee. It should be noted again that silver salts significantly improved the levels of asymmetric induction.



Scheme 3.7 Synthesis of pyrazolidine derivative **214** through asymmetric cyclisation

3.2 Concept and Aims

As demonstrated in the introduction (**3.1**, chapter **3**) the palladium-catalysed asymmetric allylic alkylation is an important method to form new chiral centres. In the previous chapter we have reported the palladium catalysed diastereoselective allene carbocyclisation with aryl halides as a method for the direct construction of the arylative aza-spirocyclic motif. The chiral nature of the π-allylpalladium intermediates involved encouraged us to examine asymmetric versions of this carbocyclisation of allenes. Our concept was to develop an asymmetric variant of this process through employing chiral ligands, chiral bases or phase transfer catalysts (Scheme 3.8).



Scheme 3.8 The concept to develop asymmetric variants

Specific aims of this investigation:

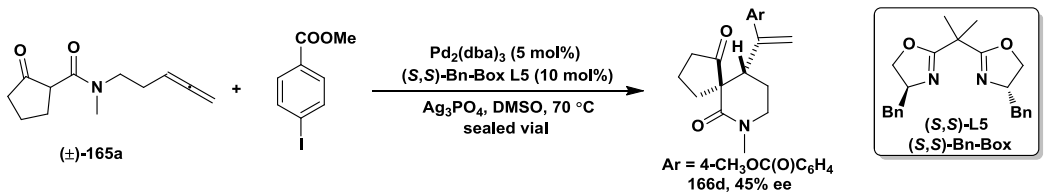
1) To find a catalyst which could perform a highly enantioselective arylative and vinylative allene carbocyclisation reaction;

2) To establish the scope of the reaction with respect to both pro-nucleophiles and electrophiles.

3.3 Results and Discussion

3.3.1 Proof of principle

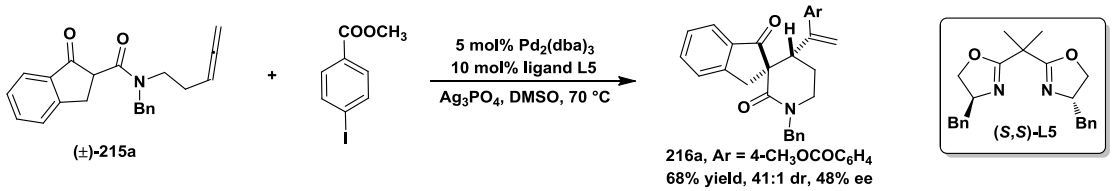
As described in previous chapter (chapter two), the reaction of pro-nucleophile **(±)-165a** and 4-iodobenzoate was carried out in the presence of 5 mol% $Pd_2(dba)_3$, 10 mol% dppe and 2.0 molar equivalents of K_2CO_3 in DMSO at 70 °C. Initial attempts to induce asymmetry used these same conditions, but dppe was replaced with chiral ligands. However, no enantioselectivity was observed. Previous reports have shown that silver salts can significantly enhance the asymmetric induction in related processes. For this reason, reaction conditions were altered to replace K_2CO_3 with a silver base. Pleasingly, with pro-nucleophile **(±)-165a**, the cyclised product **166d** was obtained with 45% ee albeit with a low conversion in the presence of Ag_3PO_4 and bisoxazoline (*S*,*S*)-Bn-Box **L5** (Scheme 3.9).



Scheme 3.9 Proof of principle

Accordingly, a more reactive pro-nucleophile allene-linked ketoamide **(±)-215a** derived from indanone was selected as an alternative representative pro-nucleophile in this cyclisation.

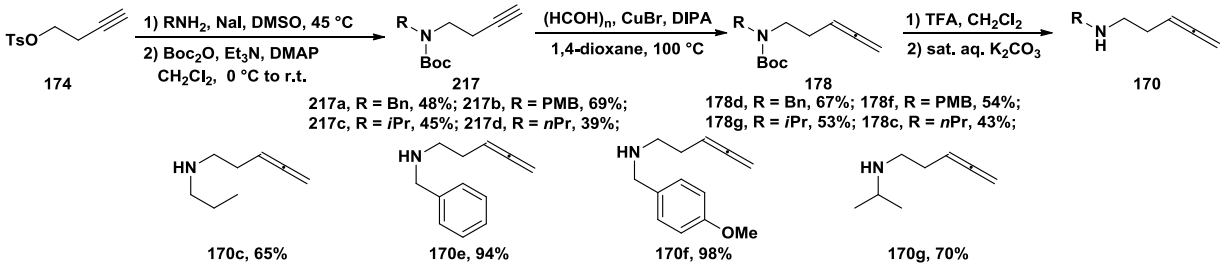
Since only one equiv. of Ag^+ is theoretically needed, the amount of Ag_3PO_4 was reduced to 0.5 molar equiv. (1.5 ion equiv.), and under these conditions product **216a** was obtained in 68% yield with 41:1 dr and 48% ee (Scheme 3.10).



Scheme 3.10 Further optimisation of the asymmetric carbocyclisation

3.3.2 Synthesis of allene-linked ketoamides **(±)-215a-(±)-215k**

3.3.2.1 Synthesis of *N*-alkyl-penta-3,4-dien-1-amines **170**



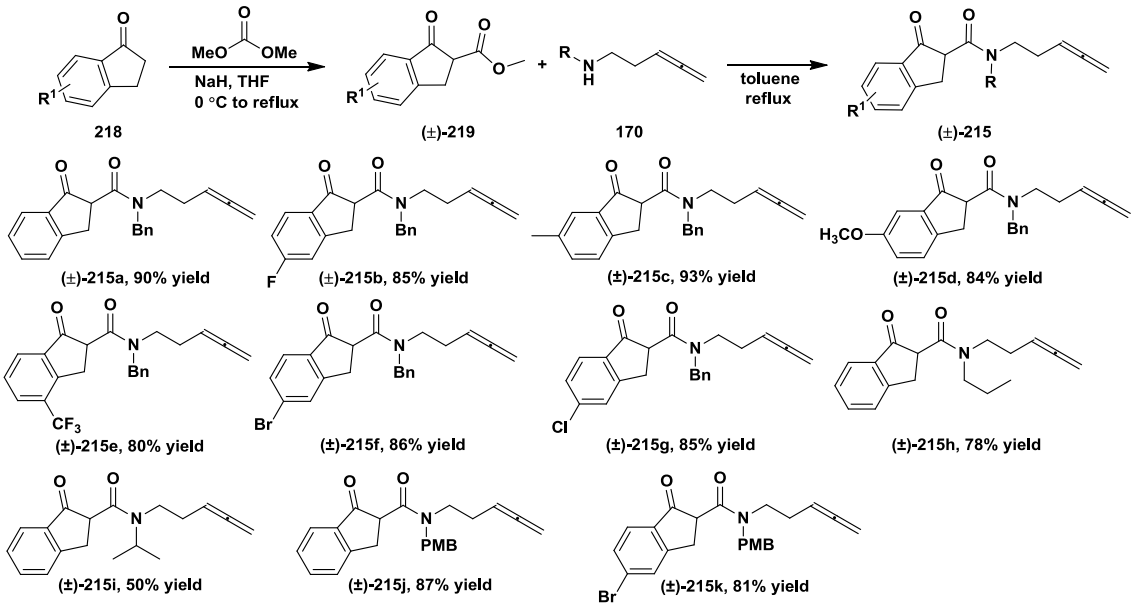
Scheme 3.11 Synthesis of aminoallenes **170c**, **170e-170g**

Tosylated 3-butyn-1-ol **174** derived from 3-butyn-1-ol[86] was treated with primary amines (2 equiv.) and sodium iodide (2.5 mol%) at 45 °C in DMSO to give secondary amines in good yields.[114] Treatment of secondary amines with di-*tert*-butyl dicarbonate afforded *N*-Boc protected amines **217**. *N*-Boc-*N*-alkyl-aminoallenes **178** were obtained by treatment with paraformaldehyde, diisopropylamine and cuprous bromide in 1,4-dioxane at reflux.[30] Deprotection with TFA followed by basification provided aminoallenes **170c** and **170e-170g**, which were used directly in the next step (Scheme 3.11).

3.3.2.2 Synthesis of allene-linked ketoamides **(±)-215a-(±)-215k**

A wide variety of substrates were prepared from the reactions between the corresponding esters **219** and aminoallenes **170** in toluene at reflux.[85] The yields were good to excellent. Methyl esters **(±)-219** were prepared from the corresponding indanones **218** and dimethyl

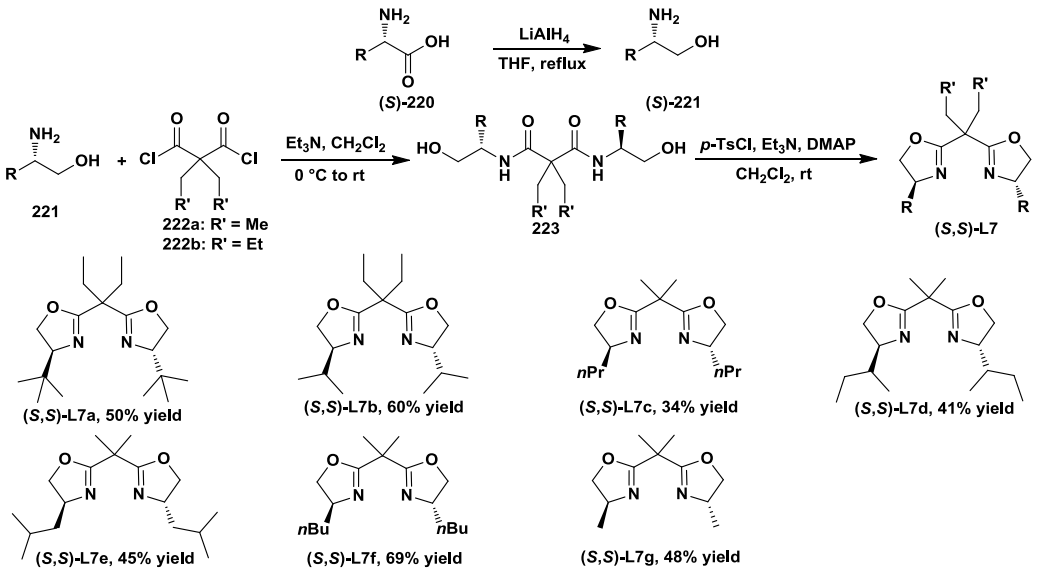
carbonate using NaH in THF (Scheme 3.12). Allene-linked ketoamides **(±)-215a-(±)-215k** were prepared following this general method.



Scheme 3.12 Synthesis of allene-linked ketoamides **(±)-215a-(±)-215k**

3.3.3 Synthesis of bisoxazolines **L7**[115,116]

According to preliminary studies, we reasoned that bisoxazoline ligands (Box ligands) were required for the asymmetric induction in this cyclisation. Therefore, a range of bioxazolines were prepared in order to achieve high enantioselectivities.

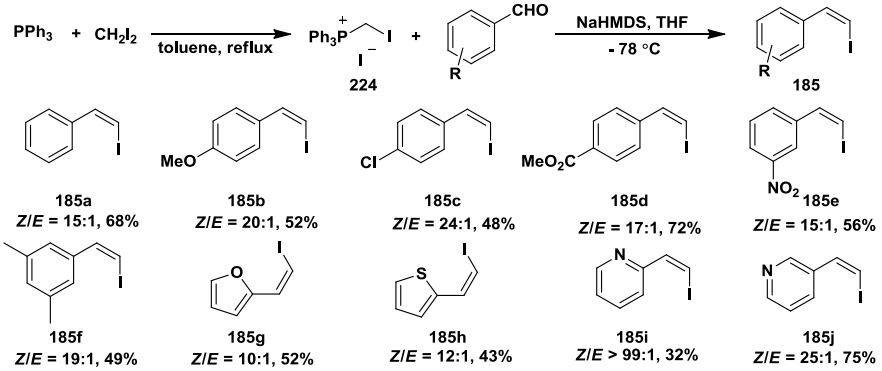


Scheme 3.13 Synthesis of bisoxazolines **(*S*,*S*)-L7a-(*S*,*S*)-L7g**

Aminols **(*S*)-221**, which were prepared from the corresponding amino acids **(*S*)-220** by using $LiAlH_4$ in THF at reflux, were used directly in the next step. Treatment of aminols **(*S*)-221** with malonyl dichloride **222** and triethylamine at 0 °C afforded (*S*,*S*)-bisamides **223**. Bisoxazolines **(*S*,*S*)-L7** were obtained via activation with *p*-toluenesulphonyl chloride and substitution under basic conditions. Bisoxazolines **(*S*,*S*)-L7a-(*S*,*S*)-L7g** were prepared by following this general method (Scheme 3.13).

3.3.4 Synthesis of vinyl iodides

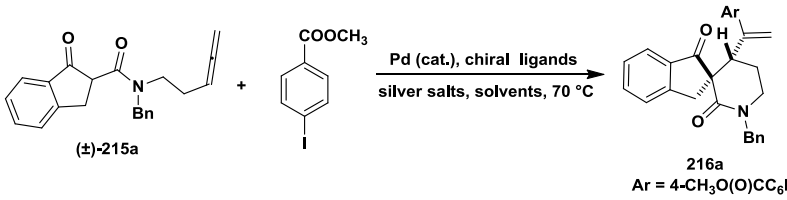
Both aryl halides and vinyl iodides were employed in the diastereoselective carbocyclisation of allenes (see chapter two). A series of vinyl iodides were synthesised according to reported procedures, including (*E*)-ethyl 3-iodoacrylate **185o**,[89] (*Z*)-ethyl 3-iodoacrylate **185n**,[89] (*E*)-(2-iodovinyl)benzene **185m**,[88] (*E*)-1-iodohex-1-ene **185k**,[91] particularly a range of (*Z*)-β-arylvinyl iodides **185a-185j** which were synthesised from the corresponding aldehydes (Scheme 3.14).[91] Iodomethylenetriphenylphosphonium iodide **224** was prepared from triphenylphosphine and diiodomethane in toluene at reflux for 40 h.[117] Treatment of aldehydes with compound **224** and NaHMDS in THF at - 78 °C afforded a range of (*Z*)-β-arylvinyl iodides **185a-185j**.

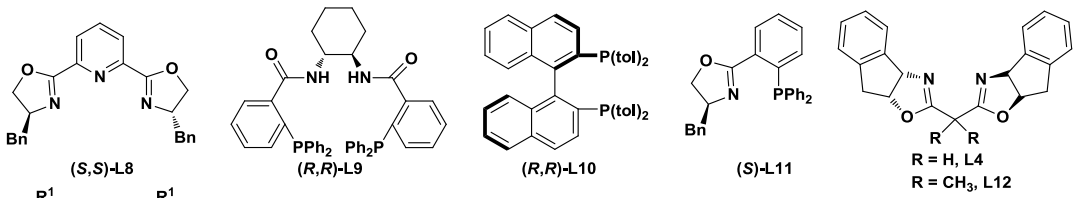


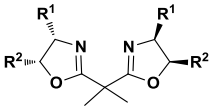
Scheme 3.14 Synthesis of vinyl iodides **185a-185j**

3.3.5 Optimisation studies of asymmetric allene carbocyclisation

Table 3.1 Optimisation studies for asymmetric carbocyclisation







R^1 = Ph, R^2 = H, (*S*,*S*)-L6; R^1 = Bn, R^2 = H, (*S*,*S*)-L5; R^1 = *i*Pr, R^2 = H (*S*,*S*)-L13
R^1 = *n*Pr, R^2 = H, (*S*,*S*)-L7c; R^1 = *n*Bu, R^2 = H, (*S*,*S*)-L7f; R^1 = *i*Bu, R^2 = H, (*S*,*S*)-L7d
R^1 = *t*Bu, R^2 = H, (*S*,*S*)-L14; R^1 = CH_3, R^2 = H, (*S*,*S*)-L7g; R^1 = CH_3, R^2 = Ph, L15
R^1 = $CH_2CH(CH_3)_2$, R^2 = H, (*S*,*S*)-L7e

entry	Pd (cat.)	solvents	chiral ligands	Ag salts	time/h	yield/%[a]	dr[b]	ee/%[c]
1	$Pd_2(dba)_3$	DMSO	**(*S*,*S*)-L5**	Ag_3PO_4	12	68	41:1	48
2	$Pd(OAc)_2$	DMSO	**(*S*,*S*)-L5**	Ag_3PO_4	10	77	27:1	59
3	$Pd(OAc)_2$	DMSO	**(*S*,*S*)-L5**	Ag_2O	12	-*	-	-
4	$Pd(OAc)_2$	DMSO	**(*S*,*S*)-L5**	Ag_2CO_3	12	-*	-	-
5	$Pd(OAc)_2$	DMSO	**(*S*,*S*)-L5**	AgOAc	24	no reaction	-	-
6	$Pd(OAc)_2$	DMSO	**(*S*,*S*)-L8**	Ag_3PO_4	20	80	16:1	11
7	$Pd(OAc)_2$	DMSO	**(*R*,*R*)-L9**	Ag_3PO_4	36	60	22:1	7
8	$Pd(OAc)_2$	DMSO	**(*R*,*R*)-L10**	Ag_3PO_4	12	82	18:1	21
9	$Pd(OAc)_2$	DMSO	**(*S*)-L11**	Ag_3PO_4	16	83	33:1	3
10	$Pd(OAc)_2$	DMSO	**L4**	Ag_3PO_4	24	50	18:1	39
11	$Pd(OAc)_2$	DMSO	**L12**	Ag_3PO_4	12	58	20:1	59
12	$Pd(OAc)_2$	DMSO	**(*S*,*S*)-L6**	Ag_3PO_4	12	40	8:1	25
13	$Pd(OAc)_2$	DMSO	**(*S*,*S*)-L5**	Ag_3PO_4	16	77	27:1	59
14	$Pd(OAc)_2$	DMSO	**(*S*,*S*)-L13**	Ag_3PO_4	12	45	33:1	67
15	$Pd(OAc)_2$	DMSO	**(*S*,*S*)-L14**	Ag_3PO_4	16	57	16:1	0
16	$Pd(OAc)_2$	DMF	**(*S*,*S*)-L13**	Ag_3PO_4	64	76	37:1	71
17	$Pd(OAc)_2$	NMP	**(*S*,*S*)-L13**	Ag_3PO_4	24	77	17:1	66
18	$Pd(OAc)_2$	1,4-dioxane	**(*S*,*S*)-L13**	Ag_3PO_4	24	70	5:1	80
19	$Pd(OAc)_2$	THF	**(*S*,*S*)-L13**	Ag_3PO_4	36	75	6:1	81
20	$Pd(OAc)_2$	CH_3CN	**(*S*,*S*)-L13**	Ag_3PO_4	48	78	27:1	80
21	$Pd(OAc)_2$	DCE	**(*S*,*S*)-L13**	Ag_3PO_4	16	70	> 99:1	80
22	$Pd(OAc)_2$	toluene	**(*S*,*S*)-L13**	Ag_3PO_4	24	82	4:1	80
23	$Pd(OAc)_2$	DME	**(*S*,*S*)-L13**	Ag_3PO_4	48	78	12:1	79
24	$Pd(OAc)_2$	DCE	**(*S*,*S*)-L7c**	Ag_3PO_4	34	70	50:1	82
25	$Pd(OAc)_2$	DCE	**(*S*,*S*)-L7f**	Ag_3PO_4	38	82	47:1	77
26	**$Pd(OAc)_2$**	**DCE**	**(*S*,*S*)-L7d**	**Ag_3PO_4**	**36**	**84**	**> 99:1**	**85**
27	$Pd(OAc)_2$	DCE	**(*S*,*S*)-L7g**	Ag_3PO_4	35	85	49:1	65
28	$Pd(OAc)_2$	DCE	**L15**	Ag_3PO_4	48	72	23:1	64
29	$Pd(OAc)_2$	DCE	**(*S*,*S*)-L7e**	Ag_3PO_4	36	81	60:1	79

All the reactions were carried out using 10 mol% Pd catalysts, 20 mol% chiral ligands in sealed vials at 70 °C. *decomposed; [a]the overall yield of two diastereoisomers; [b]dr was determined by ^{1}H NMR spectroscopic analysis of the crude product; [c]enantiomeric excess was determined by HPLC analysis.

With allene-linked ketoamide **(±)-215a**, various palladium catalysts, chiral ligands, bases and solvents were screened to assess their performance in the asymmetric carbocyclisation of allenes with 4-iodobenzoate (Table 3.1).

3.3.5.1 Palladium catalyst and base screen

As described in **3.3.1**, preliminary studies revealed that the reaction using $Pd_2(dba)_3$, **(*S*,*S*)-L5** and Ag_3PO_4 gave the product **216a** in 68% yield with 41:1 dr and 48% ee (Table 3.1, entry 1). Pleasingly, replacement of $Pd_2(dba)_3$ with $Pd(OAc)_2$ led to an improved enantioselectivity 59% ee (entry 2). With the optimal palladium catalyst $Pd(OAc)_2$ in hand, a screen of silver salts was carried out in this reaction (entries 2-5). However, decomposition was observed when Ag_2O and Ag_2CO_3 were used instead of Ag_3PO_4 (entries 3 and 4). No reaction was observed using AgOAc presumably because it is less basic than Ag_3PO_4 (entry 5). Results described in Table 3.1 indicated that significantly enhanced levels of asymmetric induction can be achieved by using silver salts. It is thought that in the presence of Ag^+, I^- is precipitated as AgI, allowing stronger coordination of the chiral ligand to palladium.[118]

3.3.5.2 Solvent screen

Variation of solvents had a pronounced effect on the diastereoselectivity and enantioselectivity (Table 3.1). With **(*S*,*S*)-L13**, the reactions in polar solvents such as DMSO, DMF and NMP gave excellent diastereoselectivities and moderate enantiomeric excess (entries 14, 16 and 17). Less polar solvent systems were optimal for high levels of enantiocontrol. However, toluene, THF and 1,4-dioxane afforded lower diastereoselectivities (entries 18, 19 and 22). 1,2-Dichloroethane furnished product **216a** with an 80% ee as a single diastereoisomer (entry 21).

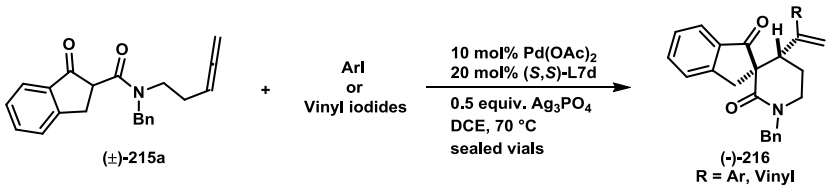
3.3.5.3 Chiral ligand screen

The final variable examined was the chiral ligand itself. A variety of chiral ligands were purchased or home-made[119] and used in the reaction of allene-linked indanone ketoamide **(±)-215a** and methyl 4-iodobenzoate (Table 3.1). Best results were obtained using the

bisoxazoline ligands, particularly **(*S*,*S*)-L7d** with 85% ee and > 99:1 dr (entry 26). Bisoxazoline ligands with geminal methyl groups gave higher enantiocontrol than those without any substitution (entries 10 and 11). However, no enantioselectivity was observed by using **(*S*,S)-L14** probably because of steric hindrance from *tert*-butyl group (entry 15).

3.3.6 Reaction scope

Table 3.2 Carbocyclisation of allene-linked ketoamide **(±)-215a** with aryl and vinyl iodides



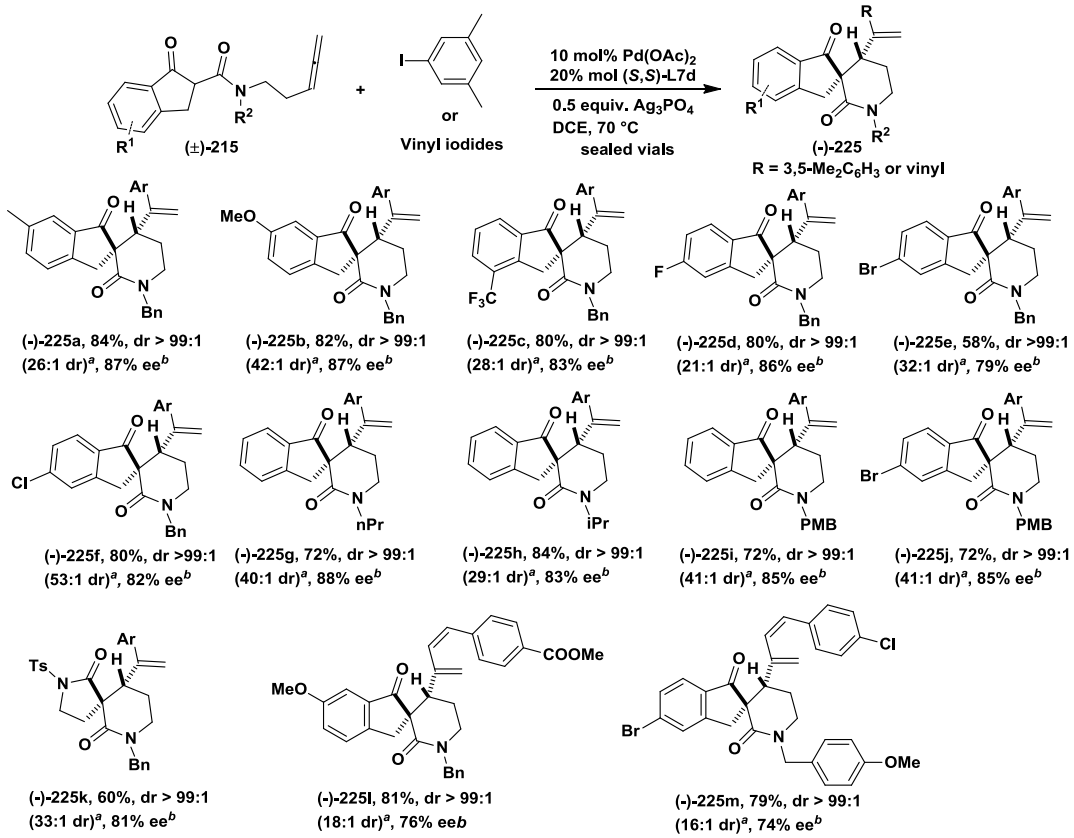
entry	ArI or vinyl iodides	time/h	**216**	yield (%)[a]	d.r.[b]	ee (%)[c]
1	PhI	96	**(-)-216b**	82	45:1	87
2	*p*-$MeOC_6H_4I$	48	**(-)-216c**	85	56:1	86
3	3,5-$Me_2C_6H_3I$	60	**(-)-216d**	76	39:1	88
4	*m*-$MeOC(O)C_6H_4I$	48	**(-)-216e**	86	41:1	85
5	*p*-BrC_6H_4I	84	**(-)-216f**	79	25:1	86
6	*p*-ClC_6H_4I	72	**(-)-216g**	84	33:1	86
7	*m*-$NO_2C_6H_4I$	40	**(-)-216h**	77	35:1	85
8	2-iodothiophene	72	**(-)-216i**	70	40:1	75
9	(*E*)-EtOC(O)CH=CHI	10	**(-)-216j**	76	13:1	0
10	(*Z*)-EtOC(O)CH=CHI	20	**(-)-216k**	78	15:1	50
11	(*E*)-PhCH=CHI	36	**(-)-216l**	61	21:1	54
12	(*Z*)-PhCH=CHI	72	**(-)-216m**	72	23:1	79
13	(*Z*)-3,5-$Me_2C_6H_3$CH=CHI	96	**(-)-216n**	60	18:1	83
14	(*Z*)-4-$MeOC_6H_4$CH=CHI	72	**(-)-216o**	67	20:1	65
15	(*Z*)-4-ClC_6H_4CH=CHI	96	**(-)-216p**	78	18:1	78
16	(*Z*)-3-$NO_2C_6H_4$CH=CHI	36	**(-)-216q**	77	16:1	80
17	(*Z*)-4-$MeOC(O)C_6H_4$CH=CHI	36	**(-)-216r**	68	17:1	82
18	(*Z*)-2-furan-CH=CHI	96	**(-)-216s**	70	19:1	71
19	(*Z*)-2-thiophene-CH=CHI	64	**(-)-216t**	65	18:1	75

[a]isolated yield of the single major diastereoisomer; [b]dr from ^{1}H NMR spectroscopic analysis of the crude products; [c]enantiomeric excess of single major diastereoisomer.

With optimal conditions established for **(±)-215a**, the scope of the enantio- and diastereoselective arylative or vinylative allene carbocyclisation cascade was investigated with respect to aryl or vinyl iodides and *N*-substituent of **(±)-215** (Table 3.2). In all cases, the highest enantiomeric excesses have been obtained by using 1.5 equivalent of aryl or vinyl iodides, 1 equivalent of pronucleophile **(±)-215**, and 0.5 equivalent of Ag_3PO_4 in DCE in the presence of 10 mol% $Pd(OAc)_2$/20 mol% **(*S*,*S*)-L7d** at 70 °C. Pleasingly, no olefin isomerisation was observed in the carbocyclisation using vinylic iodides. In general, the

reactions using aryl iodides afforded higher diastereo- and enantioselectivity than those using vinyl iodides.

With **(±)-215a** and aryl iodides, reaction yields were good to excellent and diastereoselectivities were up to 45:1 and enantioselectivities were generally around 80% (entries 1-8). For vinyl iodides, *cis*-isomers provided much higher enantiomeric excesses than *trans*-isomers (entries 9-19). Therefore, *cis*-vinyl iodides were used for this transformation. With *cis*-vinyl iodides, diastereoselectivities ranged from 13:1 to 23:1 (entries 10, 12-19) and enantioselectivity was up to 83% (entry 13). The electron-deficient aryl or vinyl iodides proceeded faster than the electron-rich ones.



[a]dr in crude product; [b]enantiomeric excess of single major diastereoisomer.

Scheme 3.15 Carbocyclisation of (±)-**215** with 3,5-dimethyl iodobenzene and vinyl iodides

Additionally, extension of this cyclisation methodology to structurally modified allene-linked pro-nucleophiles has been achieved. Following the optimised reaction conditions, 3,5-dimethyl iodobenzene and other vinyl iodides were employed (Scheme 3.15). With 3,5-

dimethyl iodobenzene, a range of pro-nucleophiles showed good reactivities. Reaction yields were good to excellent. Diastereoselectivities ranged from 21:1 to 42:1 and enantioselectivities were up to 88% ee (**(-)-225a**-**(-)-225i**). Reactivity and selectivity were not affected by the substituents on nitrogen or on the indanone rings (**(-)-225a**-**(-)-225l**). Electron-rich and electron-deficient substituents were well tolerated. *N*-tosyl γ-lactam derived pro-nucleophilic **(±)-165n** underwent cyclisation with 3,5-dimethyl iodobenzene to give spiropiperidin-2-one product **(-)-225k** in good yield with 33:1 dr and 81% ee although pro-nucleophile **(±)-165n** is less reactive than the substrates **215** derived from indanone. The cyclisation with vinyl iodides gave lower diastereo- and enantioselectivities than the one with aryl iodides (**(-)-225l** and **(-)-225m**).

3.3.7 Assignment of relative stereochemistry

The nOe analysis of **225h** revealed that very weak nOe responses were observed between H1 and H4, H4' (Figure 3.1). It means that the relative stereochemistry could not be confirmed by the nOe analysis. However, the major diastereoisomeric products **216** and **225** are in consistent with the racemic diastereoisomeric products **166** and **167** by ^{1}H NMR analysis. Therefore the relative stereochemistries of all the major diastereoisomeric products of **216** and **225** were assigned by analogy to that of **(±)-167i** which was determined by single crystal X-ray diffraction (Figure 2.5).

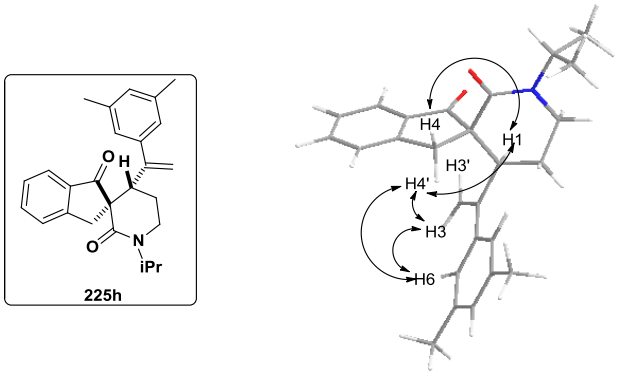


Figure 3.1 nOe responses of relevant protons of **225h**

3.3.8 Summary

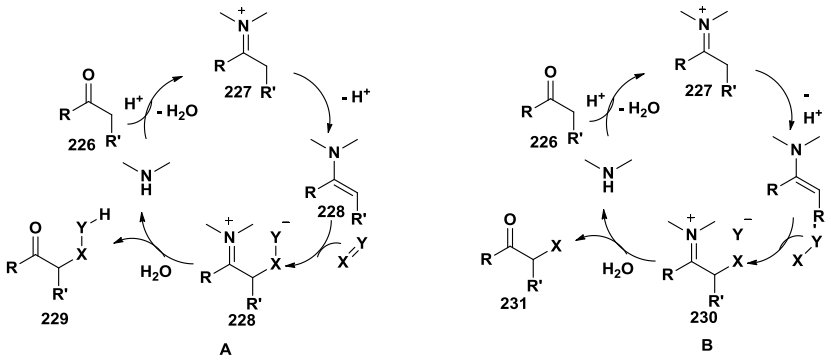
In conclusion, we have developed a mild, efficient diastereo- and enantioselective carbocyclisation methodology for the synthesis of a range of arylative and vinylative spirolactam compounds. Being operationally simple and tolerating multiple points of diversity, this reaction should be of use in complex natural product synthesis as well as compound library synthesis.

Chapter Four Carbocyclisation of Allenes via Enamine Catalysis

4.1 Introduction

4.1.1 Enamine catalysis[120-122]

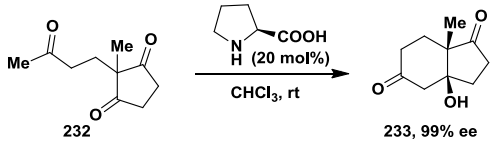
Catalysis by primary and secondary amines of electrophilic substitution reactions in the α-position of carbonyl compounds and related reactions via enamine intermediates is called enamine catalysis.[123,124] The enamine is generated by reacting a carbonyl compound with an amine under dehydrating conditions. Reaction of the enamine can proceed via an addition or substitution route depending on the nature of the electrophile used. On one hand, double bond containing electrophiles such as aldehydes, imines, Michael acceptors, etc. are inserted into the α-C-H bond of the carbonyl compound via a nucleophilic addition reaction of the enamine intermediate. On the other hand, single bond containing electrophiles such as alkyl halides react in a nucleophilic substitution reaction and lead to a stoichiometric byproduct. In both cases, iminium ions which are usually formed are then hydrolyzed to afford the product (Scheme 4.1). A wide range of transformations have been achieved via enamine chemistry.[125]



Scheme 4.1 Chemistry of preformed enamine

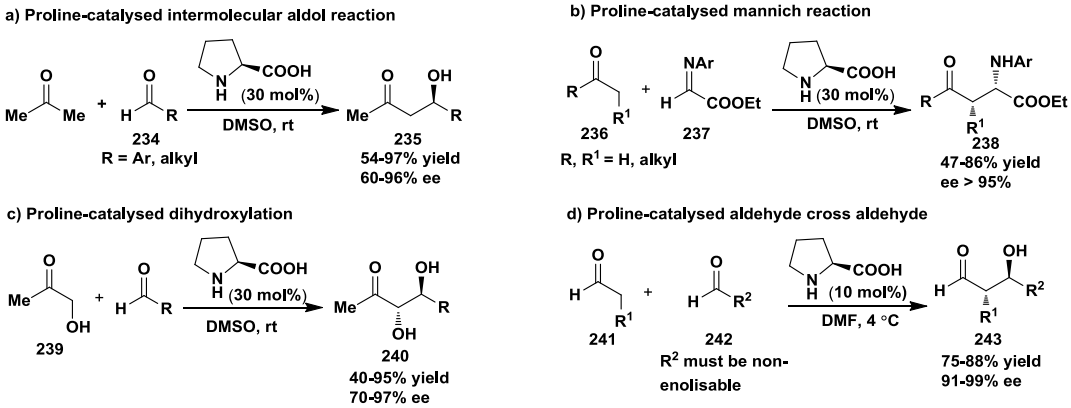
Recently, enamine catalysis has developed into a powerful strategy for asymmetric synthesis. The first organocatalytic reaction involving an enamine intermediate in the aldol process was reported simultaneously by Hajos, Parrish, Wiechert, Eder and Sauer during the early 1970's

(Scheme 4.2).[126,127] This transformation provided a simple method of forming highly advanced, enantioenriched intermediates that are useful in synthesis.



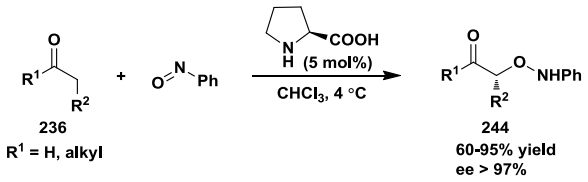
Scheme 4.2 Proline-catalysed intramolecular aldol reactions

In 2000, List and co-workers reported an intermolecular aldol reaction via enamine catalysis (a, Scheme 4.3). Since this publication, there have been many subsequent publications on catalytic reaction via enamine catalysis. The closely related Mannich reaction can also be catalysed by proline to form *syn* β-amino aldehydes and ketones that can be converted into a range of amino acids and alcohol products (b, Scheme 4.3).[128,129] A one-pot imine formation-Mannich reaction is also possible, although the enantiomeric excess is moderate in some cases.[130] A powerful application of this aldol reaction was the use of hydroxyl ketones as enamine precursors in a reaction with aldehydes that affords anti-diols and offers a complementary approach to the Sharpless dihydroxylation products (c, Scheme 4.3).[131] MacMillan and co-workers described a cross aldehyde aldol coupling (d, Scheme 4.3).[132,133] In this reaction the aldehyde can be defined as donor and acceptor. Hence only one aldehyde should be able to form an enamine (donor) and the other one can act as the acceptor. The chemoselective coupling reaction leads to excellent yields, diastereo- and enantioselective *anti*-aldol product.



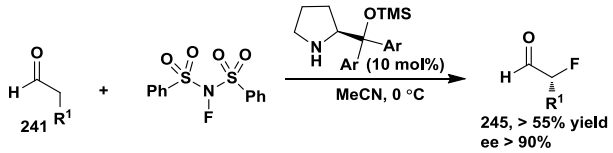
Scheme 4.3 Proline-catalysed aldol and mannich reactions

In addition to reactions that involve carbon-carbon bond formation via enamine catalysis, several carbon-heteroatom bond-forming processes have been developed. Particularly, the α-functionalisation of aldehydes is a versatile process. The reactions that have received the most attention include the α-aminoxylation of aldehydes with nitrosobenzene (Scheme 4.4). A broad range of carbonyls work well and the aminoxylation of aldehyde and ketone provides a convenient method for the rapid synthesis of useful chiral building blocks for natural product synthesis.[134]



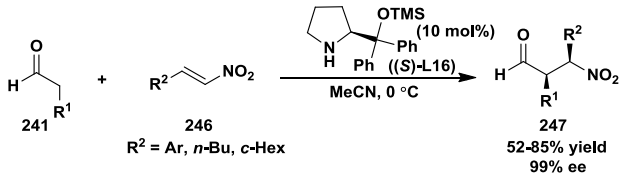
Scheme 4.4 Proline-catalysed aminoxylation of aldehydes

Also important is the asymmetric formation of C-halogen bonds and catalytically generated enamine can be used to form α-F carbonyls.[135] Jørgensen's and MacMillan's systems afford the most general procedure for the synthesis of these important compounds with excellent enantiomeric excess, and represent one of the most simple and general methods for the asymmetric introduction of C-F bonds (Scheme 4.5).[136,137]



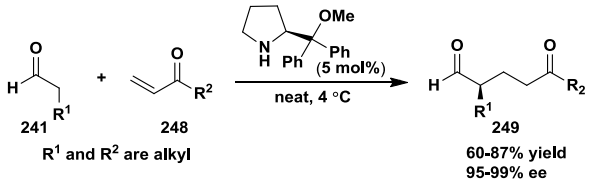
Scheme 4.5 Secondary amine-catalysed fluorination of aldehydes

Other reactions that have received attention in the area of asymmetric catalysis are conjugate addition-type reaction, for example, addition of ketones and aldehydes to nitro olefins via an enamine. The best example of this reaction is the use of a prolinol-derived catalyst **(*S*)-L16** which provides excellent yields and enantiomeric excess (Scheme 4.6).[138]



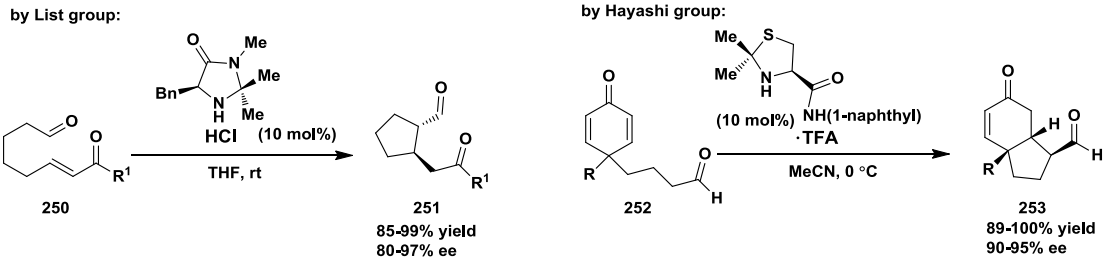
Scheme 4.6 Secondary amine-catalysed nitroalkene conjugate additions

Although the addition of enamines to enones has been a troublesome reaction, Gellman and co-workers recently showed that a similar pyrrolidine catalyst affected the addition of aldehydes **241** to simple enones **248** in excellent enantiomeric excess (Scheme 4.7).[139, 140]



Scheme 4.7 Secondary amine-catalysed conjugate additions

Intramolecular conjugate additions have also been reported by the groups of List[141] and Hayashi[142] to efficiently form five-membered ring systems, in the latter case with the control of three stereocentres (Scheme 4.8).



Scheme 4.8 Secondary amine-catalysed intramolecular conjugate additions

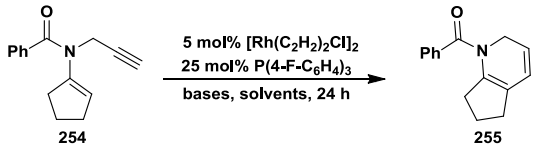
Many reactions can be catalysed via enamine catalysis. However, it is likely that many processes remain to be exploited. A better understanding of this reaction is essential. Especially, the kinetic parameters of the process will help in the design of better catalysts for new and existing processes.

4.1.2 Combination of enamine catalysis and transition-metal catalysis

The chemistry of preformed enamines, especially their utility as enolate equivalents, has been a well-investigated area in chemical research since the 1950's.[124] Enamine catalysis has

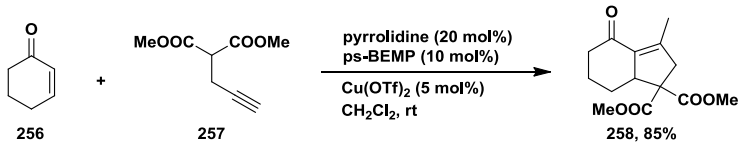
become one of the key catalytic concepts in organocatalysis, especially in asymmetric catalysis. Recently, the combination of organocatalysis with transition-metal catalysis has received increasing attention and has proven to be an important strategy for the development of many unprecedented transformations.

It was in 2006 that Lee and co-workers described a new mode of reactivity arising from the union of enamines and a non-classical rhodium vinylidene electrophile (Scheme 4.9).[143] The method allows a broad range of *N*-propargylic enamines to undergo a novel cycloisomerisation to produce six-membered aza-cyclic products under simple and mild reaction conditions.



Scheme 4.9 Rh-catalysed cyclisations of *N*-propargylic enamine

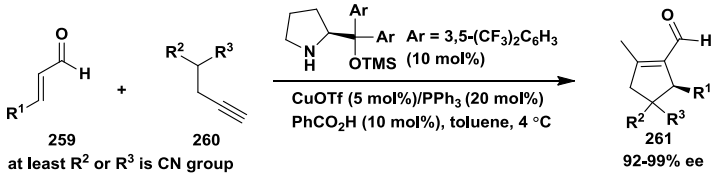
Dixon and co-workers developed a one pot, multistep reaction cascade which combined amino- and copper-catalysis in a one pot cascade reaction of α,β-unsaturated ketones and propargylated malonates forming racemic cyclopentene products (Scheme 4.10).[144] Initiated through a Michael addition to the iminium ion activated enone, the enamine intermediate undergoes carbon-carbon bond formation with the copper(I) activated alkyne. Subsequent protonolysis, hydrolysis and isomerisation provide the cyclopentenes products **258** in 85% yield.



Scheme 4.10 A combination catalysis cascade to cyclopentenes

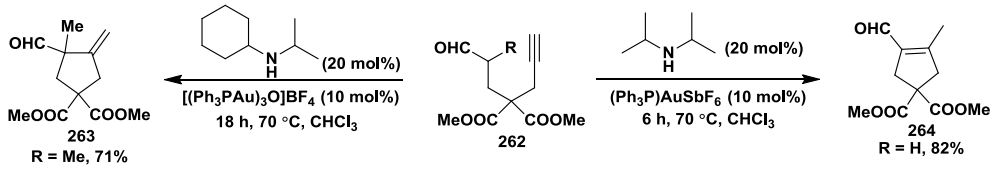
Similarly, Jørgensen and co-workers reported an enantioselective Michael addition and nucleophilic addition tandem cascade via a combination of copper and organocatalysis to synthesise cyclopentene carbaldehydes (Scheme 4.11).[145a] The products were obtained in

good yields and excellent enantio- and diastereoselectivities, however, substrates **260** are restricted to cyanoacetates rather than 1,3-dicarbonyl compounds because cyanoacetates are more reactive nucleophiles in the Michael addition step. Another similar reaction using enones as the starting material instead of aldehydes has been reported by the Jørgensen group.[145b]



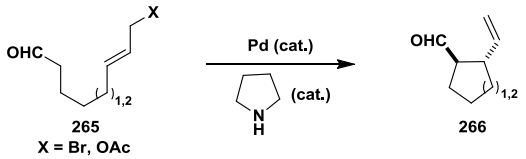
Scheme 4.11 A combination of enamine catalysis and copper(I) catalysis

Kirsch and workers were able to combine gold- and amino-catalysis in a carbocyclisation of aldehydes with alkynes (Scheme 4.12).[146] A wide range of substrates were investigated and the cyclopentene carbaldehydes were obtained in good to excellent yields.



Scheme 4.12 A combination of enamine catalysis and gold catalysis

Saicic and co-workers developed a new reaction based on double catalysis - a combination of organocatalysis and transition-metal activated allyl complex catalysis. The reaction allows for the efficient synthesis of five- and six-membered rings (Scheme 4.13).[147] The cyclisation is stereoselective and can be a catalytic asymmetric reaction by using chiral catalysts.

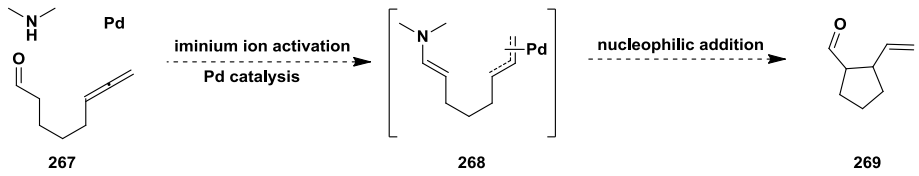


Scheme 4.13 A combination of organocatalysis and transition metal catalysis

4.2 Concept and Aims

Carbanions and their equivalents are important intermediates in organic synthesis, and many exceptionally useful reactions rely on their utilization.[124] Examples include classic C-C bond-forming reactions, such as the Grignard, aldol and Wittig reactions. Among the many various

C-C bond formations that proceed through a palladium-catalysed activation of allenes toward nucleophilic attack, the addition of activated methylene compounds such as malonates[148] and bis(phenylsulfonyl)methanes[149], β-ketoamides[94] to an allene has been well-studied. As an alternative strategy, the catalysis of carbonyl transformations by primary and second amines via enamine intermediates is a powerful strategy for the catalytic generation and use of carbanion equivalents. Therefore, our idea was to investigate the catalytic cyclisation of allene-linked aldehyde **267** via enamine catalysis and palladium catalysis (Scheme 4.14). In this transformation, allene linked aldehyde could be activated by an amine catalyst and palladium catalysis to form the π-allylpalladium enamine intermediate. The carbocyclic product **269** could be obtained via intramolecular nucleophilic addition and subsequent protonolysis and hydrolysis steps. With the development of asymmetric enamine catalysis, an asymmetric variant could be developed by using chiral amines. With many points of diversity present in the reaction products, this reaction would be a useful method for both vinylative cyclopentene library generation and target synthesis.



Scheme 4.14 Concept for palladium-secondary amine catalysis

Specific aims for this investigation:

1) To synthesise a range of allene-linked aldehydes and ketones and test reactivity for the palladium catalysed allene carbocyclisation via enamine catalysis;

2) To find the optimal conditions for the palladium catalysed stereoselective allene carbocyclisation via enamine catalysis;

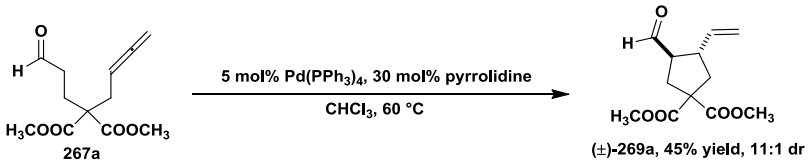
3) With a method established, demonstrate the scope of palladium catalysed stereoselective allene carbocyclisation via enamine catalysis.

4.3 Results and Discussion

4.3.1 Palladium catalysed diastereoselective allene carbocyclisations via enamine catalysis

4.3.1.1 Proof of principle

Based on earlier results from our group[144], pyrrolidine was used as the amine catalyst in our initial screen. To test the activation concept, the catalysed cyclisation was first evaluated with the use of formyl allene **267a**. Pleasingly, treatment of **267a** with 5 mol% $Pd(PPh_3)_4$ and 30 mol% pyrrolidine in $CHCl_3$ at 60 °C resulted in the formation of the *trans*-cyclic product **269a** in 45% yield and with 11:1 dr (Scheme 4.15). Thus it appeared feasible to optimise the reaction to achieve high selectivity.



Scheme 4.15 Proof of principle

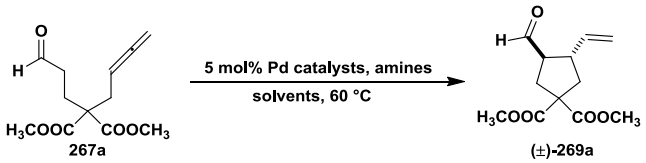
4.3.1.2 Optimisation studies

With formyl allene **267a** as the starting material, various palladium catalysts, amine catalysts and solvents were screened to assess their performance in the carbocyclisation reaction (Table 4.1).

No reaction took place in the absence of either amines or palladium catalysts, thus comfirming the proposed mechanism which probably involves the double activation via enamine catalysis and palladium catalysis (entries 2 and 3). Various amines were investigated. Changing pyrrolidine to piperidine led to a dramatically diminished reaction conversion and diastereoselectivity (entries 1 and 4). Only traces of product were observed when 30 mol% morpholine was used (entry 5), presumably because morpholine is less nucleophilic. Good diastereoselectivity was obtained using diisopropylamine albeit in a very low conversion (entry 8). No reaction was observed using *L*-proline or *R*-α-methyl benzylamine even if the polar solvent such as DMSO was used to improve the solubility of *L*-proline for this reaction

(entries 6, 7 and 9). Changing $Pd(PPh_3)_4$ to $Pd(OAc)_2$ led to increased reaction yields and diastereoselectivities (entries 1 and 10). Screening the typical reaction solvents in the presence of 5 mol% $Pd(OAc)_2$ and 30 mol% pyrrolidine showed that toluene provided the best results, both in terms of yield (68%) and diastereoselectivity (13:1 dr). Lowering the pyrrolidine loading led to a significant loss in reaction efficiency and only 20% conversion was observed (entry 18). Furthermore, base or acid additives led to slightly decreased reaction yields and diastereoselectivities (entries 16 and 17).

Table 4.1 Optimisation studies



entry	Pd	solvents	amines	time/h	conv./%	yield/%[c]	dr[d]
1	$Pd(PPh_3)_4$	$CHCl_3$	30 mol% pyrrolidine	16	73	45	11:1
2	$Pd(PPh_3)_4$	$CHCl_3$	-	16	no reaction	-	-
3	-	$CHCl_3$	30 mol% pyrrolidine	16	no reaction	-	-
4	$Pd(PPh_3)_4$	$CHCl_3$	30 mol% piperidine	24	60	-	5:1
5	$Pd(PPh_3)_4$	$CHCl_3$	30 mol% morpholine	24	trace	-	-
6	$Pd(PPh_3)_4$	$CHCl_3$	30 mol% *L*-proline	24	no reaction	-	-
7	$Pd(PPh_3)_4$	DMSO	30 mol% *L*-proline	24	no reaction	-	-
8	$Pd(PPh_3)_4$	$CHCl_3$	30 mol% diisopropylamine	24	22		10:1
9	$Pd(PPh_3)_4$	$CHCl_3$	30 mol% *R*-α-methyl benzylamine	24	no reaction	-	-
10	$Pd(OAc)_2$	$CHCl_3$	30 mol% pyrrolidine	14	100	58	13:1
11	$Pd(OAc)_2$	THF	30 mol% pyrrolidine	14	100	51	13:1
12	$Pd(OAc)_2$	1,4-dioxane	30 mol% pyrrolidine	14	100	46	13:1
13	$Pd(OAc)_2$	CH_3CN	30 mol% pyrrolidine	14	100	32	12:1
14	**$Pd(OAc)_2$**	**toluene**	**30 mol% pyrrolidine**	**14**	**100**	**68**	**13:1**
15	$Pd(OAc)_2$	DMF	30 mol% pyrrolidine	14	100	42	12:1
16[a]	$Pd(OAc)_2$	toluene	30 mol% pyrrolidine	20	100	39	10:1
17[b]	$Pd(OAc)_2$	toluene	30 mol% pyrrolidine	13	100	46	10:1
18	$Pd(OAc)_2$	toluene	20 mol% pyrrolidine	16	20	-	-

[a]with 50 mol% Et_3N; [b]with 50 mol% benzoic acid; [c]isolated yields of two diastereoisomers; [d]dr from ^1H NMR spectroscopic analysis of the crude products.

4.3.1.3 Synthesis of allene-linked aldehydes and ketones **267**

With the feasibility of the palladium catalysed allene carbocyclisation via enamine catalysis, we wished to synthesise a range of allene-linked aldehydes and ketones **267** for the scope of this reaction (Figure 4.1).

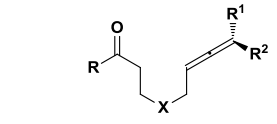
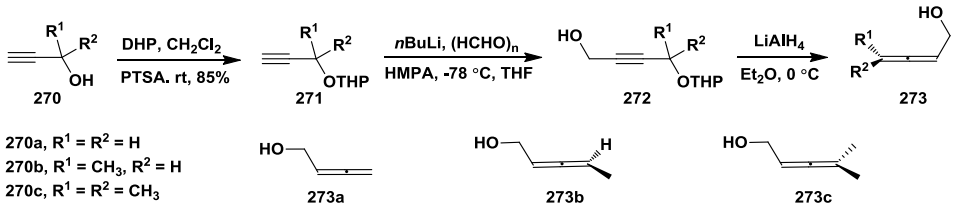


Figure 4.1 Structures of allene-linked aldehydes and ketones **267**

4.3.1.3.1 Synthesis of substituted buta-2,3-dien-1-ols **273a-273c**

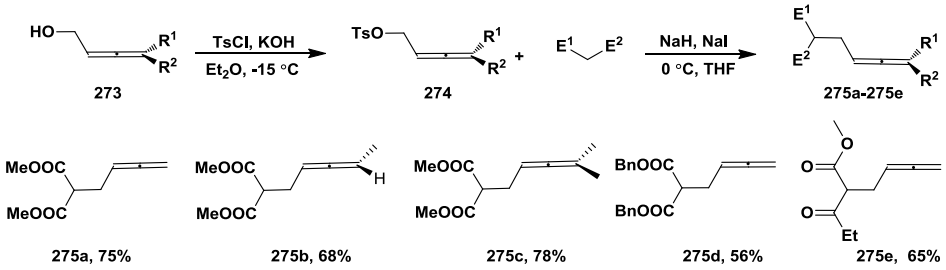


Scheme 4.16 Synthesis of buta-2,3-dien-1-ols **273a-273c**

Buta-2,3-dien-1-ols **273a-273c** were obtained from propargyl alcohols **270** (Scheme 4.16).[150] Treatment of THP-protected propargyl alcohols **271** with *n*BuLi, HMPA and paraformaldehyde in THF afforded the monoprotected diols **272** in good yields. Reduction of **272** using $LiAlH_4$ provided buta-2,3-dien-1-ols **273a-273c** which were purified by distillation.

4.3.1.3.2 Synthesis of pro-nucleophiles **275a-275e**[151,152]

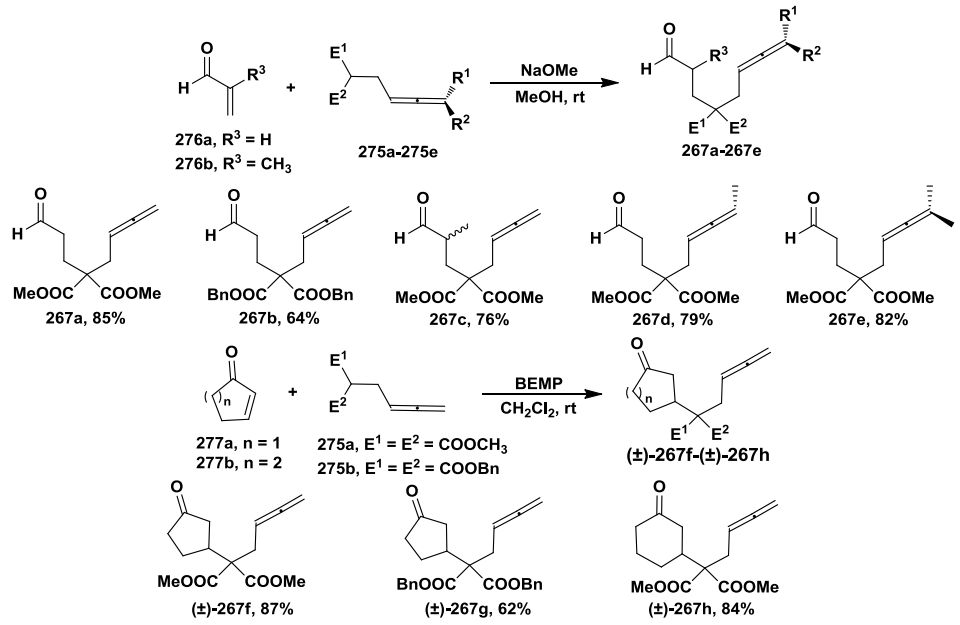
Pro-nucleophiles **275a-275e** required for the preparation of allene-linked aldehydes **267** were synthesised by using S_N2 reactions of doubly activated methylene pro-nucleophiles with tosylated buta-2,3-dien-1-ols **274**. Compounds **274** were prepared from allene alcohols **273** by treatment with 4-methylbenzenesulphonyl chloride in the presence of KOH at -15 ° C in diethyl ether (Scheme 4.17).



Scheme 4.17 Synthesis of pro-nucleophiles **275a-275e**

4.3.1.3.3 Synthesis of allene-linked aldehydes and ketones **267a-267h**

A range of Michael adducts were synthesised by base catalysed Michael addition to provide allene-linked aldehydes **267** required to test the carbocyclisation reaction (Scheme 4.18). Allene-linked aldehydes **267a-267e** were prepared via Michael addition using NaOMe in MeOH in good to excellent yields,[153] while allene-linked ketones **267f-267h** were obtained via a Michael addition using BEMP in dichloromethane in good to excellent yields.[144]

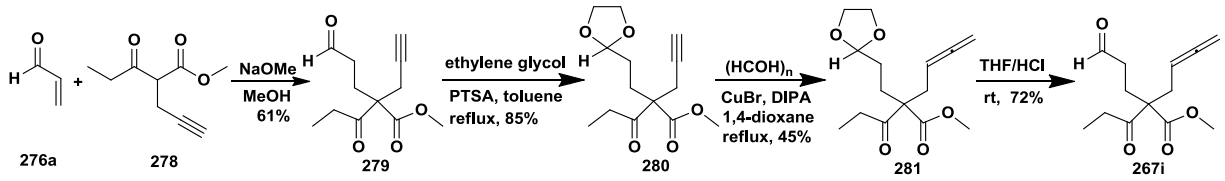


Scheme 4.18 Synthesis of allene-linked aldehydes and ketones **267**

4.3.1.3.4 Synthesis of allene-linked aldehydes **267i-267m**

4.3.1.3.4.1 Synthesis of allene-linked aldehyde **267i**

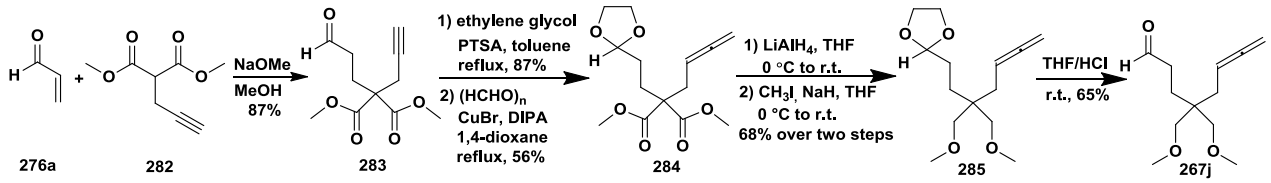
Michael adduct **279** was obtained from acrolein and pro-nucleophile **278**. Protection of aldehyde by using ethylene glycol provided compound **280**. Treatment of terminal alkyne **280** with paraformaldehyde, CuBr and diisopropylamine afforded allene **281**.[28,29] Deprotection of compound **281** using THF/1.0 M aq. HCl (v/v 1:3) afforded allene-linked aldehyde **267i** in 72% yield (Scheme 4.19).



Scheme 4.19 Synthesis of allene-linked aldehyde **267i**

4.3.1.3.4.2 Synthesis of allene-linked aldehyde **267j**

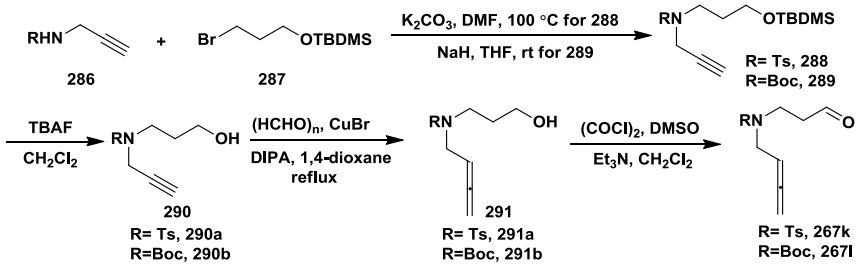
Compound **284** was obtained via Michael addition,[153] protection and methylation in good yield. Reduction of compound **284** with $LiAlH_4$ afforded the crude diol. Treatment of the crude diol with NaH and CH_3I gave methyl ether **285**. The allene-linked aldehyde **267j** was obtained via deprotection using THF/1.0 M aq. HCl (v/v 1:3) (Scheme 4.20).



Scheme 4.20 Synthesis of allene-linked aldehyde **267j**

4.3.1.3.4.3 Synthesis of allene-linked aldehydes **267k** and **267l**

Compounds **267k**[153] and **267l**[154] were synthesised according to reported procedures to test the carbocyclisation (Scheme 4.21). Compound **288** was prepared by using K_2CO_3 in DMF at 100 °C, while compound **289** was obtained by using NaH in THF at room temperature.

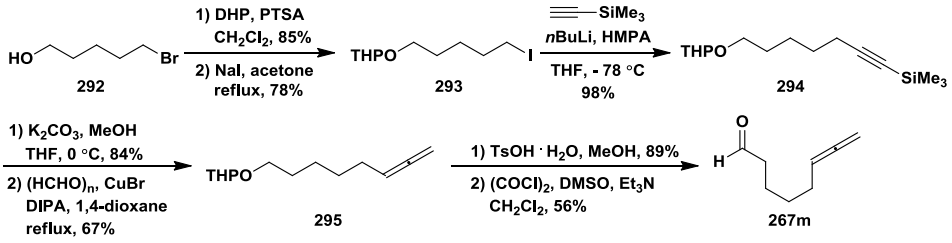


Scheme 4.21 Synthesis of allene-linked aldehydes **267k** and **267l**

4.3.1.3.4.4 Synthesis of allene-linked aldehyde **267m**

Compound **267m** was synthesised from 5-bromopentan-1-ol **292** (Scheme 4.22). Compound **293** was obtained from 5-bromopentan-1-ol via protection[155] and a Finkelstein reaction with NaI.[159] Treatment of **293** with ethynyltrimethylsilane and *n*BuLi afforded product **294** in

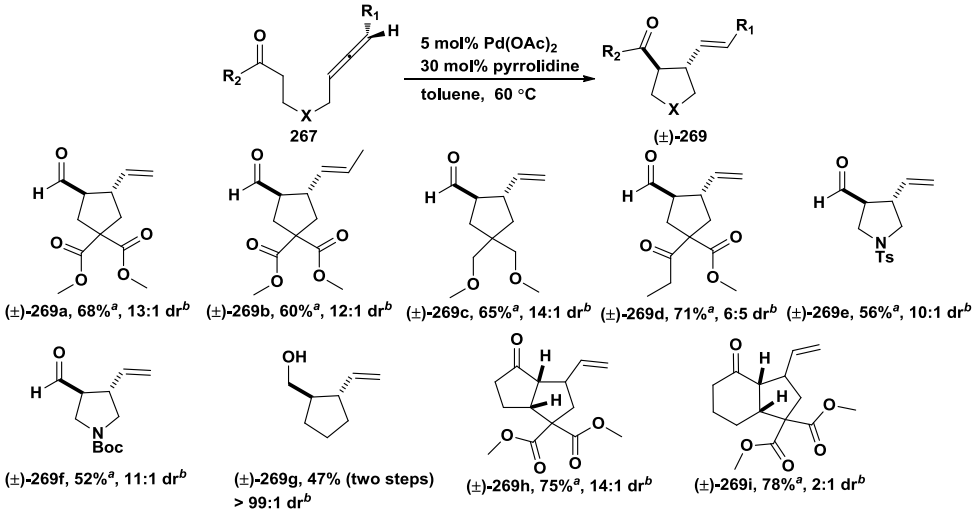
good yield. Deprotection and methylation[28,29] gave allene **295**. The allene-linked aldehyde **267m** was obtained through deprotection and Swern oxidation.



Scheme 4.22 Synthesis of allene-linked aldehyde **267m**

4.3.1.4 Reaction scope

With proof of principle established and the optimal reaction condition identified, a range of formyl allenes and ketone allenes cyclised smoothly in the presence of 5 mol% $Pd(OAc)_2$ and 30 mol% pyrrolidine at 60 °C (Scheme 4.23). Substrates having a carbon chain led to the desired products with good reaction yields and diastereoselectivities (**(±)-269a**-**(±)-269d**, **(±)-269g**). The substrates bearing substituents on the chain, for example, malonates, ethers and ketoesters, reacted faster than those without any substituent (**(±)-269a**-**(±)-269d**). The alcohol **(±)-269g** was obtained from the corresponding aldehyde **267m** as a single diastereoisomer after $NaBH_4$ reduction. Formyl allene **267d** bearing an internal allene, also afforded product **(±)-269b** with good selectivity, but with prolonged reaction time. The substrates **267k** and **267l** bearing nitrogen included in the chain gave products **(±)-269e** and **(±)-269f** with good diastereoselectivities although with lower yields. Treatment of cyclic ketones such as **(±)-267f** and **(±)-267h** with 5 mol% $Pd(OAc)_2$ and 30 mol% pyrrolidine in toluene at 60 °C in a sealed vial gave the products, but the reactions were slightly slower. In the case of five-membered cyclic ketone **(±)-267f**, cyclisation gave the product **(±)-269h** in 75% yield with 14:1 dr. However, six-membered cyclic ketone **(±)-267h** afforded the cyclic product **(±)-269i** in 78% yield but with only 2:1 dr.

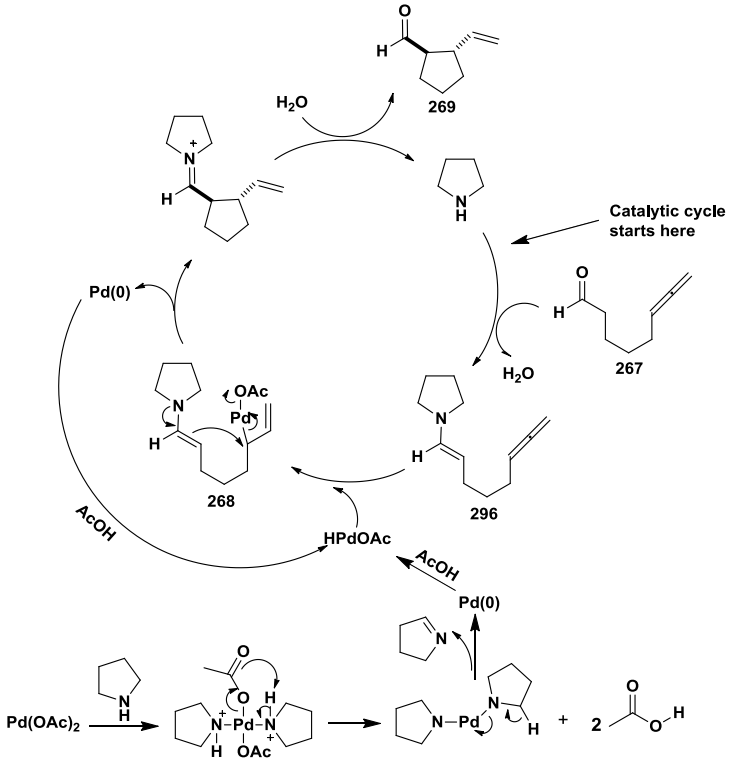


[a]yield of two diastereoisomers; [b]dr was determined from ^{1}H NMR after flash column chromatography.

Scheme 4.23 Carbocyclisation of formyl and ketone allenes **267**

4.3.1.5 Proposed mechanism

Since the presence of a secondary amine was required for cyclisation in all cases, this outcome is in accord with the hypothesis that a combination of a Lewis acidic palladium(II) complex and appropriate amine can act as a cooperative catalytic system for the dual activation of formyl or ketone allenes (Scheme 4.24).



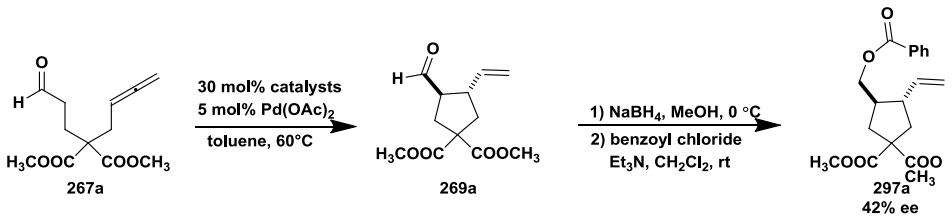
Scheme 4.24 Proposed mechanism

The active palladium species is hydridopalladium acetate which is generated *in situ* from palladium(II) acetate and pyrrolidine. An enamine intermediate **296** is formed via organocatalytic activation of the aldehyde **267** and an allylpalladium complex **268** is formed via the activation of the allene moiety by hydridopalladium complex. Subsequently, nucleophilic attack of the enamine onto the allylpalladium complex occurs and palladium(0) is released back to the catalytic cycle. Hydrolysis of iminium ion leads to the *trans*-product **269**.

4.3.2 Palladium catalysed enantioselective allene carbocyclisation via enamine catalysis

4.3.2.1 Proof of principle

Having established the diastereoselective allene carbocyclisation, the next logical step was to examine whether the carbocyclisation could be performed as a catalytic asymmetric reaction. Initial attempts with (*R*)-BINAP were not successful, as the Pd[(*R*)-BINAP] complex did not catalyse the reaction. Replacement of pyrrolidine with chiral secondary amine **L16** led to the formation of cyclic product **269a** with 42% ee, which was determined by the analysis of the derivative **297a** on HPLC (Scheme 4.25). The result encouraged us to find out the optimal conditions for high enantioselectivities.



Scheme 4.25 Proof of principle

4.3.2.2 Design and synthesis of chiral secondary amines **L16-L26**

A range of chiral secondary amines were synthesised to test the asymmetric reaction (Figure 4.2). Catalysts **(*S*)-L16-(*S*)-L25**[157], **(*S*)-L23**,[158] **(*S*)-L24** and **(*S*)-L25**,[159] were prepared from *L*-proline by following reported procedures and **L26** was commercial available. Catalyst **(*S*)-L22** was obtained from (*S*)-methyl 1-benzylpyrrolidine-2-carboxylate **(*S*)-298** via Grignard reagent addition, methylation and reduction (Scheme 4.26).[160-162]

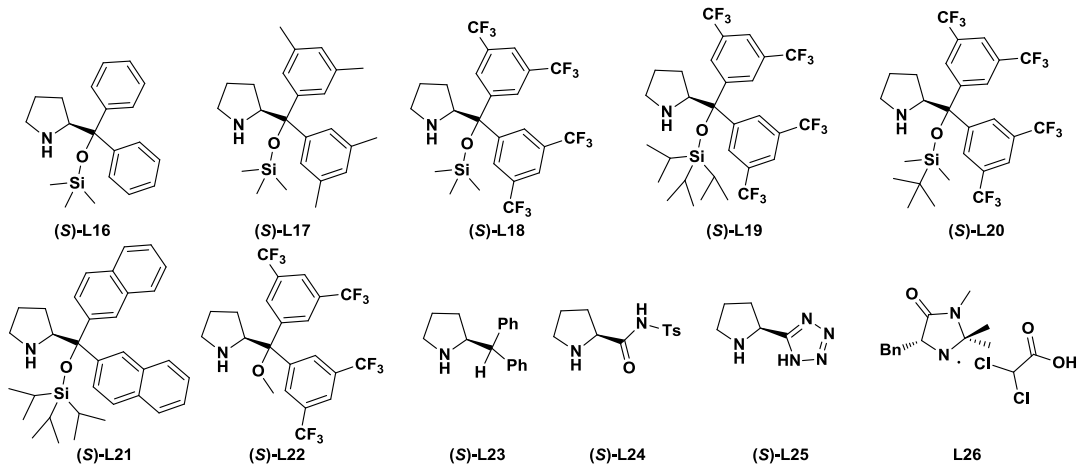
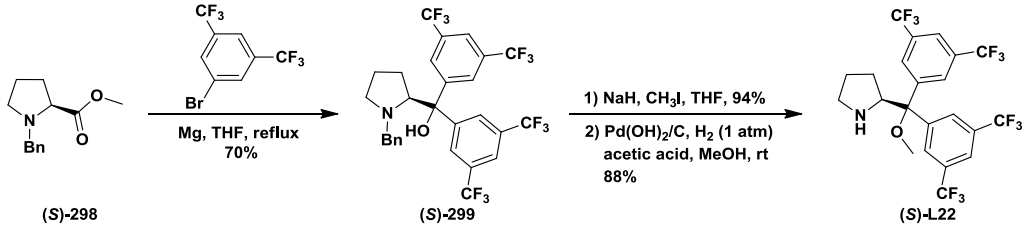


Figure 4.2 Synthesised secondary amines **L16-L26**



Scheme 4.26 Synthesis of secondary amine **(*S*)-L22**

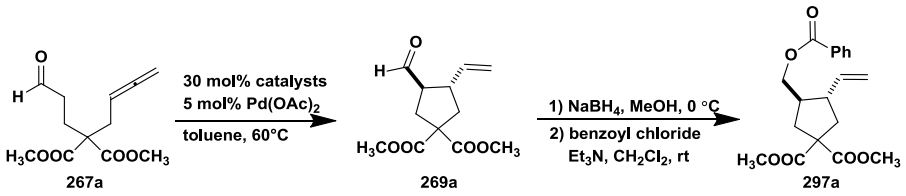
4.3.2.3 Optimisation studies

Various types of organocatalysts (chiral amines **(*S*)-L23-(*S*)-L25**, MacMillan's catalyst **L26**[163] and Jørgensen's catalysts **(*S*)-L16-(*S*)-L22**[164]) were investigated (Table 4.2). No reaction was observed when catalysts **(*S*)-L24** and **(*S*)-L25** were used in this reaction (Table 4.2, entries 2 and 3). The product was obtained using MacMillan's catalyst **L26** with 13:1 dr and 46% ee (entry 4), while using chiral amine **(*S*)-L23** afforded the product with 10:1 dr and 39% ee (entry 1). Higher level of asymmetric induction was achieved by using Jørgensen's catalyst **(*S*)-L17** derived from *L*-proline (entry 5).

A range of Jørgensen's catalysts was investigated. Changing aromatic ring from electron-deficient 3,5-bis(trifluoromethyl)phenyl to electron-rich 3,5-dimethylphenyl or 2-naphthalene decreased the enantioselectivity from 67% to 55% (entries 5-7, 10). With 3,5-bis(trifluoromethyl)phenyl as the aromatic ring, the enantioselectivity improved when R was a bulky silyl group. Catalyst **(*S*)-L19** bearing triisopropylsilyl group afforded the product with

13:1 dr and 84% ee (entry 7) and catalyst **(*S*)-L20** possessing di-*tert*-butylmethylsilyl gave the product with 12:1 and 79% ee (entry 8), however, catalyst **(*S*)-L18** bearing trimethylsilyl provided the product only with 11:1 dr and 67% ee (entry 6). Catalyst **(*S*)-L22** still efficiently catalysed the reaction to provide the desired product with 79% ee and 13:1 dr when R is methyl group (entry 9). Screening of a range of Jørgensen's catalysts identified **(*S*)-L19** as the lead chiral catalyst for the carbocyclisation.

Table 4.2 Screen of chiral secondary amines



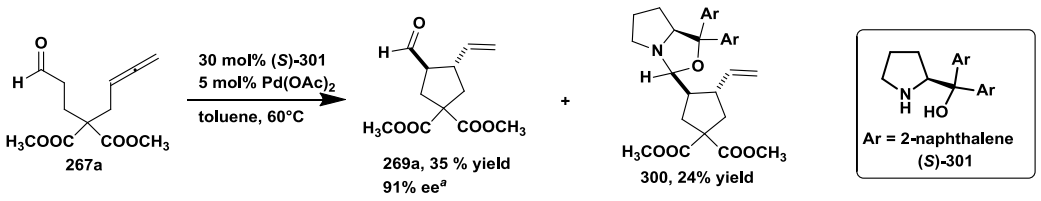
entry	catalysts	time/h	yield /%[a] of **269a**	dr[b] of **269a**	yield/%[a] of **297a**	dr[b] of **297a**	ee/%[c] of **297a**
1	**(*S*)-L23**	36	24	10:1	85	10:1	39
2	**(*S*)-L24**	36	no reaction	-	-	-	-
3	**(*S*)-L25**	36	no reaction	-	-	-	-
4	**L26**	48	36	13:1	87	13:1	46
5	**(*S*)-L17**	20	59	14:1	80	14:1	60
6	**(*S*)-L18**	12	65	11:1	88	11:1	67
7	**(*S*)-L19**	20	72	13:1	89	13:1	84
8	**(*S*)-L20**	12	70	12:1	79	12:1	79
9	**(*S*)-L22**	12	62	13:1	75	13:1	79
10	**(*S*)-L21**	20	58	12:1	82	12:1	55

[a]isolated yield of two diastereoisomers; [b]dr was determined from ^{1}H NMR spectroscopic analysis after flash column chromatography; [c]ee of **269a** was determined by measuring ee of derivative **297a** on HPLC.

4.3.2.4 Allene carbocyclisation by using aminols as a catalyst

Additionally, aminols were investigated as chiral catalysts. However, product **269a** was obtained together with a significant amount of the side product **300** (Scheme 4.27). Surprisingly, when aminol **(*S*)-301** was used as catalyst instead of **(*S*)-L19**, the opposite enantiomer of product **269a** was obtained with 91% ee.

A possible explanation for this result could be that aminol **(*S*)-301** selectively reacts with one enantiomer of the cyclised species **269a**, forming side product **300**, thereby giving rise to a resolution process. The hydrolysis of the side product **300** under strongly acidic conditions was unsuccessful, even after prolonged heating.

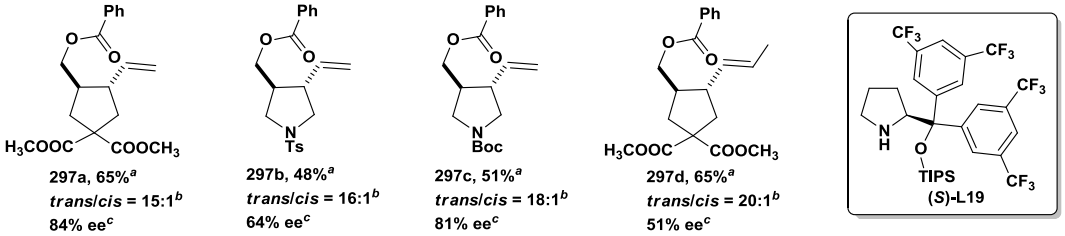


[a]enantiomeric excess was determined by analysing the derivative on HPLC, and it showed product **269a** is the other enantiomer compared to the one catalysed by catalyst **(*S*)-L19**.

Scheme 4.27 The formation of side product **300** by using aminol **(*S*)-301**

4.3.2.5 Reaction scope

We investigated the scope of asymmetric cyclisation catalysed by Jørgensen's catalyst **(*S*)-L19** under the reaction conditions established for **297a** (Figure 4.3). However, the scope was restricted under these reaction conditions. All the reactions are slower than those catalysed by pyrrolidine because of the steric hindrance. Substrate **267k** was cyclised smoothly to product **269b** with 64% ee and 16:1 dr. The cyclised product **297c** was obtained with 81% ee and 18:1 dr. Pleasingly, substrate **267d** bearing an internal allene, also proceeded efficiently to afford the cyclised product **297d** with 51% ee and 20:1 dr. No reaction was observed for other substrates using catalyst **(*S*)-L19**.



[a]yield of cyclised aldehydes; [b]dr is determined after flash column chromatography of the corresponding esters **297**; [c]ee is determined by measuring the corresponding esters **297** on HPLC.

Figure 4.3 Scope of catalytic asymmetric allene carbocyclisation

4.3.3 Assignment of relative stereochemistry

The nOesy analysis of **279a** revealed that the aldehyde group and the vinyl group were *anti* (Figure 4.4).

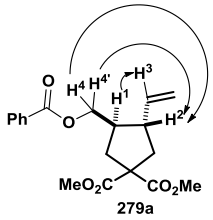


Figure 4.4 nOesy responses of relevant protons on **279a**

The relative stereochemistries of all the major diastereoisomeric products of **269** were assigned by analogy to that of **279a** which was determined by nOesy analysis. Since H^1 has a through-space interaction with H^3 and H^4, $H^{4'}$ has a through-space interaction with H^2, the most plausible explanation is that H^1 and H^2 are *anti* and therefore the *anti*-cyclic products are obtained in the allene carbocyclisation.

4.3.4 Summary

A palladium-catalysed carbocyclisation of formyl or ketone allenes has been developed using a synergic combination of organocatalysis and transition-metal catalysis. The cyclisation is stereoselective and an enantioselective variant has been developed. Research directed towards establishing the scope and limitation of the reaction, and the search for the optimal organocatalyst **(*S*)-L19**, is underway.

Chapter Five Boronic Acid Catalysed Ene Carbocyclisation of Acetylenic Dicarbonyl Compounds

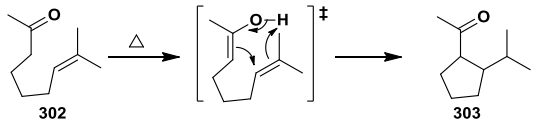
5.1 Introduction

Ene reactions represent an atom efficient and powerful reaction for the formation of carbon-carbon bonds. The carbocyclisation of 1,3-dicarbonyl compounds to pendent alkyne functionality, first discovered by Eglinton and Whiting[165] and then developed by Conia and Perchec,[166] has received much attention in recent years. This reaction is a popular alternative to enolate alkylations. Traditionally, it is thought of as an intramolecular ene reaction of unsaturated ketones and aldehydes, in which the carbonyl serves as the ene component via its enol tautomer.[170] The reaction is generally conducted at very high temperatures to overcome the large activation energy barrier of the reaction.

5.1.1 The thermal cyclisation of unsaturated carbonyl compounds[166]

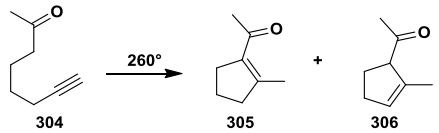
The reactivity of the carbonyl group in intra- and intermolecular reactions can be regarded in various different ways depending on the nature of the reactive centre and the energy sources. One class of intramolecular reactions of the carbonyl group is the thermal reaction of unsaturated carbonyl compounds. Such compounds are able to undergo considerable changes in structure, under relatively mild conditions, by intramolecular hydrogen displacement leading to ring closure. In fact, this type of process is an intramolecular variant of the general intermolecular "ene" reaction. As is usually the case, this class of six electron process, which involves an enol hydrogen shift, follows a concerted route and is therefore stereospecific.

The most significant example of the thermal behaviour of unsaturated carbonyl compounds is represented by the thermal cyclisation of the oct-7-en-2-one system in which four carbon atoms separate the two unsaturated termini. Oct-7-en-2-one **286**,[167] heated in a sealed tube or in the vapour phase at around 350 °C, is converted smoothly and quantitatively into 2-methylacetylcyclo pentanes **287** (Scheme 5.1).[167]



Scheme 5.1 Thermal cyclisation of compound **302**

Carbonyl compounds containing an alkynic bond seem to be less favourable precursors for cyclisation; Strain increase is expected by the participation of a triple bond in the transition state and by the presence of a double bond in the final cyclic product. However, this is largely compensated for by the difference in dissociation energy between alkynic and alkenic bonds. Several examples of thermal cyclisation of octynones have been reported. Oct-7-yn-2-one **304** under thermal conditions (3 h, 260°) reacts quantitatively to give a mixture of conjugated and *endo*-unconjugated 1-acetyl-2-methylcyclopentenes **305** and **306** (Scheme 5.2). [168]



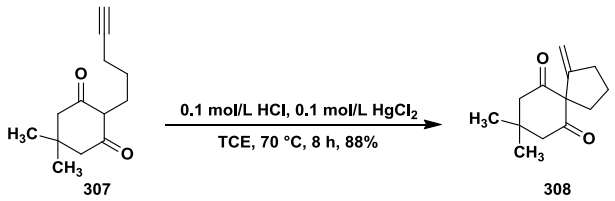
Scheme 5.2 Thermal cyclisation of compound **304**

5.1.2 Strong acid catalysed Conia-ene reactions

The thermal cyclisation of unsaturated carbonyl compounds has been extensively studied. However it requires rather high temperatures (210-370 °C for enones, 180-320 °C for ynones) which limits the application in organic synthesis; Moreover, the olefinic products obtained from acetylenic starting materials in this manner frequently undergo isomerisation.[169]

In a few cases, catalysts have been used, more or less successfully, e.g., water to accelerate the enolization of the unsaturated carbonyl compounds at high temperature, zinc iodide, zinc stearate, and tin(IV) chloride.[173] The Conia group investigated the reaction at lower temperature with the system H^+/Hg^{2+} to to accelerate enolization and to activate the triple bond toward nuclephilic addition of the enol respectively.[169] The reactions were performed either in 1,1,2,2-tetrachloroetnane (for reactions above 40 °C) or in dichloromethane (for reactions

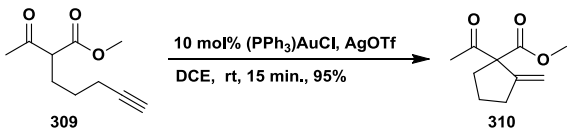
below 40 °C). For example, 2-(4'-alkynyl)-1,3-diketone **307** was converted to product **308** at 70 ºC with double catalysis by H^+/ Hg^{2+} in 88% yield (Scheme 5.3).[169]



Scheme 5.3 Conia-ene reaction catalysed by strong acid

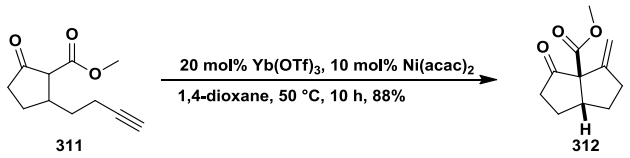
5.1.3 Metals-catalysed Conia-ene reactions

The high temperature of the thermal cyclisation of unsaturated carbonyl compounds limited its synthetic utility. The use of transition-metal catalysts allows the reaction to proceed at lower temperatures, but strong base,[171] strong acid,[169] or UV irradiation is still required.[172] Balme and co-workers, for example, have reported that the Conia-ene reactions α-alkynic β-ketoesters could be conducted smoothly in moderate to excellent yields using CuI as the catalyst. However, a strong base, *tert*-BuOK, was necessary to improve the reaction. Consequently, much recent attention has focused on the development of mild and neutral conditions for the ene reaction.[173] Recently Toste reported a mild and efficient $(PPh)_3AuCl/AgOTf$-catalysed Conia-ene intramolecular reaction of α-alkynic β-ketoesters **309** to give **310** in good yields (Scheme 5.4).[174]



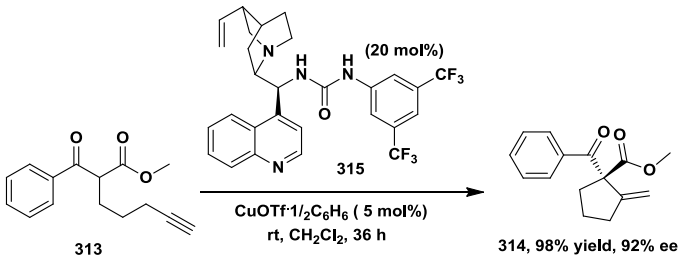
Scheme 5.4 Conia-ene raction catalysed by Au(I)

Yang and co-workers developed a mild and effective protocol for the Conia-ene reactions of α-alkynic β-ketoesters using the $Ni(acac)_2/Yb(OTf)_3$ catalytic system. Ene reaction of cyclopentanone **311** afforded *cis*-fused 5,5-heterocyclic compound **312** in 88% yield by using both catalysts (Scheme 5.5).[175]



Scheme 5.5 Conia-ene raction catalysed by Yb(III) and Ni(II)

Dixon and co-workers reported a mutually compatible and cooperative combination of copper(I) triflate and bifunctional 9-amino-9-deoxyepicinchona-derived urea **315** for the enantioselective Conia-ene cyclisation of alkyne-tethered *β*-ketoester substrate **313** (Scheme 5.6).[78]



Scheme 5.6 Conia-ene raction catalysed by Copper(I) salts

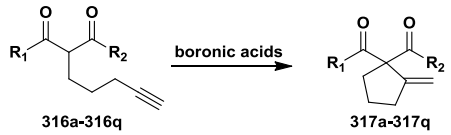
5.1.4 Summary

Conia-ene type reactions, which are an important method of the formation of carbon-carbon bonds, have been extensively explored in recent years. The reaction can proceed smoothly with high temperature, strong acids or transition metals at lower temperature.

5.2 Concept and Aims

The Conia-ene reaction is an effective methodology for the formation of carbon-carbon bonds, but the high temperature requried for this reaction limits its application in organic synthesis. Although the use of transition-metal catalysts allows the reaction to proceed at lower temperatures, strong base, strong acid, or UV irradiation is still required. Other than the use of strong mineral acids or alkoxide bases, to the best of our knowledge, no other transition-metal free method has been reported to efficiently catalyse the ene carbocyclisation of acetylenic dicarbonyl compounds. Herein, we wish to describe the discovery and development of the ene

carbocyclisation of acetylenic dicarbonyl compounds catalysed by aryl boronic acids (Scheme 5.7).



Scheme 5.7 Concept of Conia-ene reaction catalysed by boronic acids

Specific aims of this investigation:

1) To synthesise a range of β-pentynyl-β-ketoesters and test reactivity for the boronic acid catalysed ene carbocyclisation of acetylenic dicarbonyl compounds;

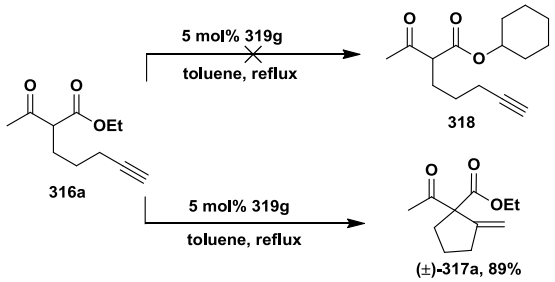
2) To find the optimal conditions for the boronic acid catalysed ene carbocyclisation of acetylenic dicarbonyl compounds;

3) With a method established, demonstrate the scope of boronic acid catalysed ene carbocyclisation of acetylenic dicarbonyl compounds.

5.3 Results and Discussion

5.3.1 Proof of reactivity[187]

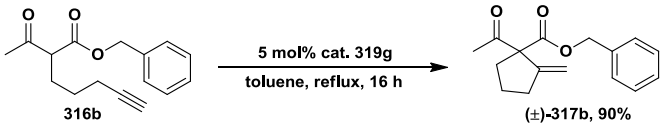
During some recent investigations in our laboratories,[78] we required β-pentynyl-β-ketoesters **318** and, to us, a direct route from **316a** was attractive.



Scheme 5.8 Discovery of boronic acid catalysed ene carbocyclisation

Following the report of Tale and co-workers, we attempted the transesterification of **316a** with cyclohexanol in the presence of 5 mol% 3-nitrobenzeneboronic acid **319g**.[176] To our surprise, the cyclised product1 **317a** was formed in 89% yield, and no evidence of the expected ester **318** was detected in the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 5.8).

In order to further assess whether boronic acids were sufficient for the direct cyclisation of unsaturated carbonyl compounds with alkyne groups, β-ketoester **316b** was boiled in toluene in the presence of 3-NO_2-phenylboronic acid **319g**. Compound **317b** was obtained in 90% yield (Scheme 5.9).



Scheme 5.9 The cyclisation of β-ketoester **316b**

This result showed that the boronic acid was able to mediate the intramolecular cyclisation of 1,3-dicarbonyl compounds with alkyne groups. Furthermore, the reaction proceeded smoothly, in excellent yield, and under mild conditions. Having uncovered a new catalytic process, we decided to explore the scope and mechanism of this reaction.

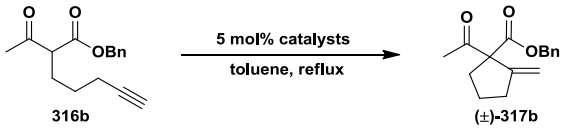
5.3.2 Optimisation studies[187]

With a good reactivity profile with β-ketoester **316b** established, a selection of catalysts **319a-319g** were screened for the performance in the cyclisation of **316b** to **317b** (Table 5.1).

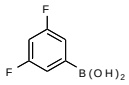
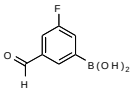
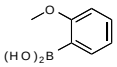
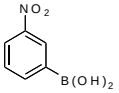
Initially a range of catalysts related to 3-nitrobenzeneboronic acid were screened for catalytic activity in the ene carbocyclisation of **316b**. Indeed many benzeneboronic acids were catalytically active, as was the Lewis acid tris(pentafluorophenyl)borane **319f** which gave good conversion (95%) after 16 hours in boiling toluene (entry 6). However, boric acid **319a** only gave 8% conversion under the same conditions (entry 1). Of the benzeneboronic acids those bearing electron withdrawing groups afforded better reactivity than those with electron donating groups, presumably due to their increased acidity.[177] The most efficient was found to be 3-nitrobenzeneboronic acid **319g** (entry 7). In order to identify the optimal conditions, a further screen of catalyst loading using 3-nitrobenzeneboronic acid **319g** was also performed. Complete conversion was achieved with 5 and 10 mol% boronic acid **319g** in 30 h and 20 h

respectively (entry 7). When 2 mol% of boronic acid **319g** was used, a slower reaction rate was observed (45% conversion after 48 h in boiling toluene).

Table 5.1 Identification of optimal catalysts **319** and loading



316b (±)-317b

entry	catalysts	loading/mol %	time/h	conv./%[a]
1	$B(OH)_3$ **319a**	5	16	8
2	 **319b**	5	16	67
3	 **319c**	5	16	82
4	 **319d**	5	16	78
5	 **319e**	5	16	47
6	$B(C_6F_5)_3$ **319f**	5	16	95
7	 **319g**	5 2 10	16 48 20	100 45 100

[a]Conversion by ^{1}H NMR spectroscopic analysis of crude products.

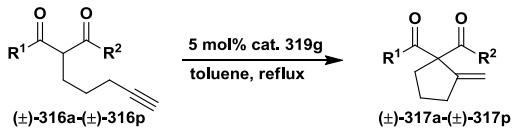
5.3.3 Reaction scope[190]

With optimal conditions established, a range of β-pentynyl-β-ketoesters was readily prepared[181] and treated with 5 mol% of 3-nitrobenzeneboronic acid **319g** in boiling toluene (Table 5.2).

As expected from our initial discovery presented in Scheme 5.1 and the subsequent optimisation study in Table 5.1, linear and β-branched aliphatic keto-esters were good substrates and were efficiently transformed to the corresponding carbocyclic products (entries 1-4). Both electron-rich and electron-deficient aryl ketone substrates reacted smoothly and efficiently. However, prolonged reaction times were required for aryl ketones substituted with *para*-electron donating groups (entry 11) while *ortho*- and *meta*- substituted aromatic

substrates gave comparable reaction rates. The ester moiety had minimal influence on the reaction rate and methyl, ethyl, benzyl and *tert*-butyl esters were all well-tolerated. Also a keto-amide substrate **316o** proved to be an excellent substrate, affording the carbocyclic product **317o** in 75% isolated yield (entry 15). The 3-nitrobenzeneboronic acid catalysis was also effective in the case of 1,3-ketones; diketone **316p** was converted to methylene cyclopentane **317p** in an excellent 95% yield after 30 h (entry 16).

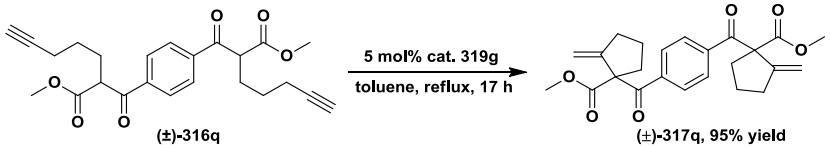
Table 5.2 The scope of the ene carbocyclisation catalysed by **319g**



entry	products	R^1	R^2	time/h	yield[a] / %
1	**(±)-317b**	Me	OBn	16	90
2	**(±)-317a**	Me	OEt	22	92
3	**(±)-317c**	Et	OMe	54	56
4	**(±)-317d**	*i*-Pr	OMe	23	88
5	**(±)-317e**	Ph	OEt	18	97
6	**(±)-317f**	Ph	O^{t}Bu	16	93
7	**(±)-317g**	Ph	OBn	16	98
8	**(±)-317h**	*o*-Me-C_6H_4	OMe	30	76
9	**(±)-317i**	*m*-Me-C_6H_4	OMe	36	96
10	**(±)-317j**	*m*-OMe-C_6H_4	OMe	24	98
11	**(±)-317k**	*p*-OMe-C_6H_4	OMe	190	91
12	**(±)-317l**	3,4-di-Cl-C_6H_3	OMe	16	95
13	**(±)-317m**	*p*-Br-C_6H_4	OMe	70	90
14	**(±)-317n**	*p*-Ph-C_6H_4	OMe	30	96
15	**(±)-317o**	Ph	NHPh	40	75
16	**(±)-317p**	Ph	Me	30	95

[a] isolated yield ; [b] the reaction was treated with 10 mol% catalyst **319g**.

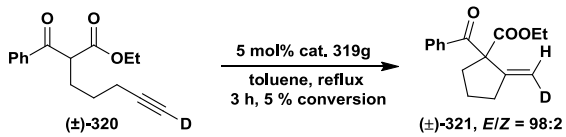
To further extend the scope of the reaction, bis ketoester **316q** was subjected to the optimal conditions and afforded **(±)-317q**, the product of two sequential carbocyclic reactions, in an excellent 95% yield after 17 h (Scheme 5.10).



Scheme 5.10 Extension to a doubly substituted substrate

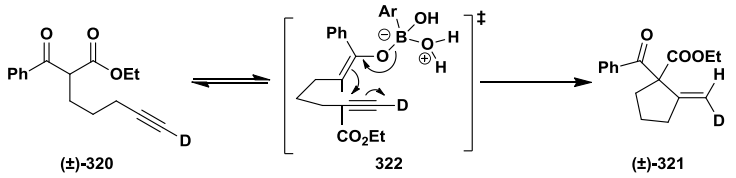
5.3.4 Proposed mechanism[187]

As well as synthetically useful, 3-nitrobenzeneboronic acid **319g** catalysed ene carbocyclisation of acetylenic dicarbonyl compounds was also interesting from a mechanistic point of view. Carbocyclisation using deuterium labeled ketoester **320** with catalyst **319g** resulted in the stereospecific production of **(*E*)-321** consistent with a concerted *syn*-addition step to the alkyne (Scheme 5.11).



Scheme 5.11 Deuterium labelling study

Although a number of mechanistic pathways consistent with this data can be envisaged, the most likely role of the 3-nitrobenzeneboronic acid **319g** is to catalyse the enolization of the 1,3-dicarbonyl starting material. A subsequent concerted ene reaction of the enol form of the starting material would then afford product **321** with observed stereochemistry (Scheme 5.12). This pathway is consistent with the obtained data and is aligned to previous mechanistic proposals.[166,175]



Scheme 5.12 Postulated mechanistic pathway

5.4 Summary

In summary, an attempted trans esterification of a β-ketoester substrate bearing a pendent terminal alkyne substituent at the β-position lead to the discovery of an efficient 3-nitrobenzeneboronic acid catalysed ene carbocyclisation of acetylenic dicarbonyl compounds. The reaction is easy to perform, efficient, broad in scope and provides a convenient transition metal-free alternative to existing catalytic protocols.

Chapter Six Experimental Session

6.1 General Experimental

All reactions were performed without special precautions to avoid the presence of moisture unless otherwise stated. For reactions conducted under anhydrous conditions glassware was dried in an oven at 100 °C and carried out under a nitrogen atmosphere.

Solvents and Reagents

Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Petroleum ether refers to distilled light petroleum of fraction (30-60°C). Solvents used are dry solvents. Dichloromethane was distilled over CaH_2; tetrahedrofuran, diethyl ether and toluene were distilled over sodium chips and benzophenone ketyl radical; dimethyl sulfoxide and dimethyl formamide were dried over molecular sieves. All other solvents were used as purchased. Commerial reagents were used as purchased without any further purification unless otherwise stated.

Chromatography

Column chromatography was carried out using Merck Kieselgel 60 silica gel (230-400 mesh). Thin-layer chromatography (TLC) was carried out using Merck Kieselgel 60 F_{254} (230-400 mesh) fluorescent treated silica which were visualised under UV light (250 nm) or by staining with aqueous basic potassium permanganate solutions or a *para*-anisaldehyde alcoholic solution. In all cases of chromatography, HPLC grade solvents or distilled solvents used as eluents.

Enantiometric excesses were determined using high performance liquid chromatography (HPLC) performed on a Agilent 1200 Series system or a Hewlett-Packard 1050 Series system (column and solvents conditions are given with the compound).

Melting Points

Melting points were recorded on a Leica Galen III apparatus where the sample was placed between two cover glass windows, at ambient pressure and are uncorrected.

Infra-Red Spectroscopy

IR spectra were recorded on an ATI Mattson: Genesis Series FT-IR spectrometer or a Bruker Tensor 27 FT-IR spectrometer, from a thin film deposited on a sodium chloride plate. Only selected maximum absorbances are reported.

NMR Spectroscopy

^{1}H NMR spectra were recorded in deuterated solvents on a Bruker 500 MHz and Bruker 400 MHz spectrometers at 500 MHz and 400 MHz respectively, with residual protic solvents as the internal standard. ^{13}C NMR spectra were recorded in deuterated solvents on a Bruker 500 MHz and Bruker 400 MHz spectrometers at 125 MHz and 100 MHz respectively, with the central peak of the deuterated solvent as the internal standard. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as δ/ppm downfield from tetramethylsilane (multiplicity, number of protons, coupling constants J/Hz, assignment). The ^{13}C NMR spectra are reported as δ/ppm downfield from tetramethylsilane (multiplicity where needed, number of signals where needed, coupling constants J/Hz, assignment). Assignments were aided by the use of DEPT 135, COSY, HMQC, HMBC and HSQC spectra where necessary.

Mass Spectrometry

Low resolution mass spectrometry (EI) was recorded on a Fissions VG Trio 2000 quadrupole mass spectrometer or a Waters LCT premier XE mass spectrometer. High resolution mass spectra (accurate mass) were recorded on a Thermo Finnigan Mat 95XP mass spectrometer or a Bruker MicroTof mass spectrometer (electrospray technique).

Polarimetry (optical rotation)

Optical rotations were recorded using a Perkin-Elmer 241 polarimeter; Specific rotation (SR) ($[\alpha]_D$) are reported in 10^{-1} deg.cm^2.g^{-1}; concentrations (*c*) are quoted in g/100 mL; *D* refers to the D-line of sodium (589 nm); Temperatures (*T*) are given in degrees Celsius (°C).

X-Ray Crystallographic Data

X-ray crystallographic analyse were performed on a Bruker Smart Apex CCD diffractometer (crystals were mounted on top of fomblin (perfluoromethyl isopropyl ether) oil in a Hamilton Cryoloop) or an Enraf-Nonius KCCD diffractometer.

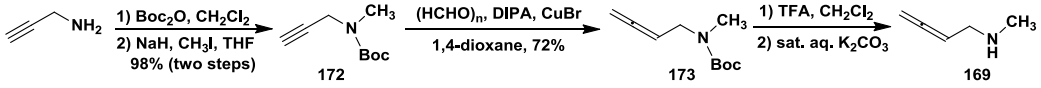
Literature References

Known compounds are indicated by a reference to a previous literature report in their title line. Any data that is referred to from a different source is noted separately in the characterisation text and the corresponding reference is given. If a literature procedure was followed, this is indicated explicitly in the method text.

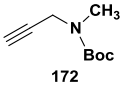
6.2 Practical Experimental

6.2.1 Experimental for Chapter Two

6.2.1.1 Synthesis of *N*-methyl-buta-2,3-dien-1-amine **169**



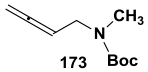
Synthesis and characterisation of *tert*-butyl methyl(prop-2-yn-1-yl)carbamate 172 [189]



Into a solution of propargylamine (810 mg, 14.6 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added Boc_2O (3.50 g, 15.4 mmol) in CH_2Cl_2 (10 mL). After completion, the reaction mixture was washed with brine. The organic layer was dried (Na_2SO_4) and concentrated. The crude *N*-Boc-propargylamine was added to a solution of sodium hydride (1.25 g, 30.7 mmol, 60% dispersion in mineral oil) in anhydrous THF (30 mL) at 0 °C. Iodomethane (4.70 mL, 76.0 mmol) was added to the resultant solution over 15 min. The ice bath was removed, and the solution was stirred at ambient temperature for 20 h. The reaction was stopped by the addition of water (30 mL). The aqueous fraction was extracted with diethyl ether (3 × 50 mL), washed with brine, dried (Na_2SO_4) and the solvent was removed at reduced pressure. The crude product was purified by flash column chromatography on silica gel (PE/Et_2O = 20/1) to give compound **172** (1.85 g, 75%) as a light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.05 (brs, 2H, NC***H*****$_2$**), 2.93 (s, 3H, NC***H*****$_3$**), 2.23 (t, *J* = 2.5 Hz, 1H, C≡C***H***), 1.48 (s, 9H, OC(C***H*****$_3$**)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C 155.3 (***C***=O), 85.2 (HC≡***C***), 80.1 (O***C***$(CH_3)_3$), 71.2 (H***C***≡C), 35.2 (***C***H_3N), 30.4 (N***C***H_2), 27.4 (3C, OC(***C***$H_3)_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3348 (C≡C-H), 2976 (C-H), 2130 (C≡C), 1692 (C=O); **MS** (ES+) m/z (rel. intensity %) 192.14 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_9H_{15}NNaO_2$ $[M+Na]^+$ 192.1053, found 192.1052.

Synthesis and characterisation of *tert*-butyl buta-2,3-dien-1-yl(methyl)carbamate 173[30]

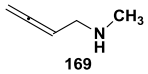


173

A solution of compound **172** (507 mg, 3.00 mmol)**,** cuprous bromide (214 mg, 1.50 mmol), paraformaldehyde (225 mg, 7.50 mmol) and diisopropylamine (0.84 mL, 6.00 mmol) in 1,4-dioxane (21 mL) was heated at reflux and stirred for 16 hours and cooled to room temperature. The reaction was diluted with water (20 mL) followed by the addition of 30 mL of diethyl ether and acidified with 1.0 M aq. HCl until the reaction mixture became a clear solution. The aqueous solution was extracted with diethyl ether (2 × 30 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (PE/Et_2O = 8:1) to afford allene **173** (0.40 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.08-5.11 (m, 1H, C***H***=C=CH_2), 4.69-4.72 (m, 2H, CH=C=C***H₂***), 3.64 (brs, 2H, NC***H₂***), 2.77 (s, 3H, NC***H₃***), 1.39 (s, 9H, OC(C***H₃***)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.5 (CH=***C***=CH_2), 156.0 (***C***=O), 89.6 (***C***H=C=CH_2), 81.7 (O***C***$(CH_3)_3$), 76.2 (CH=C=***C***H_2), 48.4 (N***C***H_2), 38.5 (N***C***H_3), 28.4 (3C, O*C*(***C***$H_3)_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2956 (C-H), 2928 (C-H), 1955 (CH=C=CH_2), 1698 (C=O); **MS** (ES+) m/z (rel. intensity %) 206.15 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{10}H_{17}NNaO_2$ $[M+Na]^+$ 206.1089, found 206.1086.

Synthesis and characterisation of *N*-methyl-buta-2,3-dien-1-amine 169



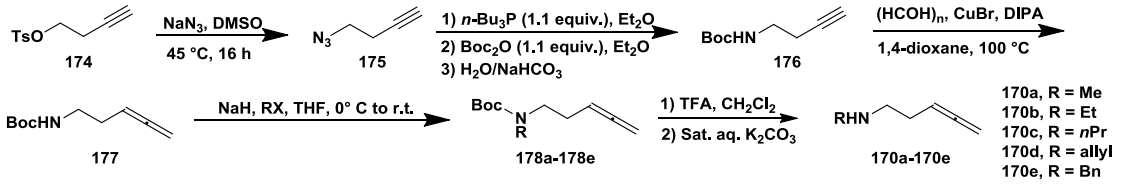
169

Compound **173** was stirred with TFA in dichloromethane (1:1, v/v) and the reaction was monitored by TLC. On completion, the reaction mixture was basified by saturated aqueous potassium carbonate to pH 8. The mixture was extracted three times with dichloromethane. The extracts were combined and washed with brine, dried (Na_2SO_4) and concentrated.

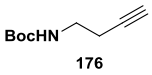
Crude compound **169**: **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 5.06-5.10 (m, 1H, C***H***=C=CH_2), 4.69-4.72 (m, 2H, CH=C=C***H₂***), 2.92-2.95 (m, 2H, NC***H₂***), 2.67 (s, 3H, NC***H₃***); **^{13}C NMR** (100

MHz, $CDCl_3$) δ_C 208.7 (CH=***C***=CH_2), 89.3 (***C***H=C=CH_2), 76.8 (CH=C=***C***H_2), 48.3 (N***C***H_2), 36.3 (N***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} ν_{max} (film)/cm^{-1} 1955 (C=C=C).

6.2.1.2 Synthesis and characterisation of aminoallenes 170



Preparation and characterisation of *tert*-butyl but-3-yn-1-ylcarbamate 176[179, 94]

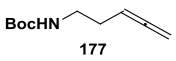


Sodium azide (1.43 g, 22.0 mmol) was added to a solution of tosylated product **174** (1.97 g, 8.8 mmol) in anhydrous DMSO (15 mL). The mixture was stirred overnight at 45 °C. The reaction mixture was poured into water (20 mL) and extracted with diethyl ether (30 mL × 3). The organic phase was then dried (Na_2SO_4), and filtered without further purification. To the crude azide **175** in diethyl ether was added dropwise tri-*n*-butylphosphine (1.95 g, 9.68 mmol) at room temperature under nitrogen. After 2 hours (effervescence had ceased) the reaction mixture was cooled to -50 °C and a solution of di-*tert*-butyldicarbonate (2.11 g, 9.68 mmol) in anhydrous diethyl ether was added dropwise via cannula, and the reaction mixture stirred for a further hour at -50 °C. Saturated aqueous $NaHCO_3$ (26 mL) was added. The cooling bath was removed to allow the reaction to warm to room temperature. The reaction mixture was extracted three times with diethyl ether. The combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 10:1) to give the product **176** (845 mg, 57% over three steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.84 (brs, 1H, N***H***), 3.20-3.24 (m, 2H, NC***H***$_2$), 2.30-2.33 (m, 2H, C***H***$_2$C≡CH), 1.94 (t, *J* = 2.6 Hz, 1H, C≡C***H***), 1.38 (s, 9H, OC(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 155.7 (***C***=O), 81.7 (***C***≡CH), 79.5 (C≡***C***H), 69.8 (O***C***$(CH_3)_3$), 39.2 (N***C***H_2), 28.4 (3C, OC(***C***$H_3)_3$), 19.9 (***C***H_2C≡CH); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3348 (N-H), 3305 (C≡C-H), 2798 (C-H),

2133 (C≡CH), 1695 (C=O); **MS** (ES+) m/z (rel. intensity %) 192.15 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_9H_{15}NNaO_2$ $[M+Na]^+$ 192.1104, found 192.1106.

Preparation and characterisation of *tert*-butyl penta-3,4-dien-1-ylcarbamate 177[30]

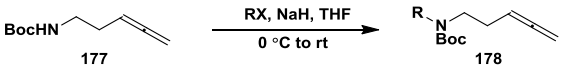


177

A solution of compound **176** (500 mg, 2.95 mmol)**,** cuprous bromide (211 mg, 1.45 mmol), paraformaldehyde (221 mg, 7.40 mmol) and diisopropylamine (0.83 mL, 5.9 mmol) in 1,4-dioxane (20 mL) was gently heated at reflux and stirred for 12 hours, and cooled to room temperature. The reaction was diluted with water (20 mL) followed by the addition of 30 mL of diethyl ether and acidified with 1.0 M aq. HCl until the reaction mixture became a clear solution. The aqueous solution was extracted with diethyl ether (2 × 30 mL). The organic extracts were combined and washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 10:1) to give product **177** (350 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.05-5.11 (m, 1H, C***H***=C=CH_2), 4.70-4.74 (m, 2H, CH=C=C***H₂***), 4.64-4.69 (brs, 1H, N***H***), 3.21-3.24 (m, 2H, NC***H₂***), 2.15-2.22 (m, 2H, NCH_2C***H₂***), 1.44 (s, 9H, $OC(CH_3)_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 208.9 (CH=***C***=CH_2), 155.8 (***C***=O), 87.1 (***C***H=C=CH_2), 79.2 (O***C***$(CH_3)_3$), 75.3 (CH=C=***C***H_2), 39.8 (N***C***H_2), 28.8 (NCH_2***C***H_2), 28.4 (3C, $OC(CH_3)_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3345 (N-H), 2850 (C-H), 1955 (CH=C=CH_2), 1676 (C=O); **MS** (ES+) m/z (rel. intensity %) 206.16 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{10}H_{17}NNaO_2$ $[M+Na]^+$ 206.1257, found 206.1255.

General procedure A for the synthesis of *N*-alkyl-(*tert*-butoxycarbonyl) penta-3,4-dienylamines 178 [94]

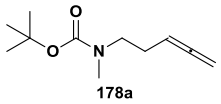


177 178

To a solution of sodium hydride (1.5 equiv., 60% dispersion in mineral oil) in anhydrous THF at 0 °C was added dropwise a solution of *tert*-butyl penta-3,4-dien-1-ylcarbamate **177** (1

equiv.) in anhydrous THF. The reaction mixture was stirred for 30 min at 0 °C and then alkylhalide **RX** (2.0 equiv.) was added to the resultant solution. The ice bath was removed, and the solution was stirred at ambient temperature for 20 hours. The reaction was quenched by the addition of water (10 mL). The aqueous fraction was extracted with diethyl ether (3 × 20 mL), washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel to give *N*-alkyl-(*tert*-butoxycarbonyl) penta-3,4-dienylamines **178**.

Preparation and characterisation of *tert*-butyl methyl(penta-3,4-dien-1-yl)carbamate 178a

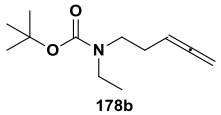


178a

Synthesised from *tert*-butyl penta-3,4-dien-1-ylcarbamate **177** (5.40 g, 31.9 mmol) according to general procedure A. Compound **178a** (4.80, 78%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 20:1) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.04-5.11 (m, 1H, C***H***=C=CH_2), 4.65-4.73 (m, 2H, CH=C=C***H₂***), 3.23-3.41 (m, 2H, NC***H₂***), 3.85 (s, 3H, NC***H₃***), 2.17-2.25 (m, 2H, NCH_2C***H₂***), 1.45 (s, 9H, $C(C$***H₃***$)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.5 (CH=***C***=CH_2), 155.6 (***C***=O), 87.3 (***C***H=C=CH_2), 79.5 (O***C***$(CH_3)_3$), 75.2 (CH=C=***C***H_2), 39.5 (N***C***H_2), 37.8 (N***C***H_3), 28.8 (NCH_2***C***H_2), 28.4 (3C, C(***C***$H_3)_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1955 (C=C=C), 1626 (C=O); **MS** (ES+) m/z (rel. intensity %) 220.16 (M + Na^+, 80); **HRMS** (ESI+) calcd. for $C_{11}H_{19}NNaO_2$ $[M+Na]^+$ 220.1313, found 220.1315.

Preparation and characterisation of *tert*-butyl ethyl(penta-3,4-dien-1-yl)carbamate 178b

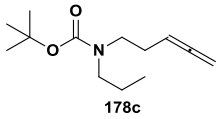


178b

Synthesised from *tert*-butyl penta-3,4-dien-1-ylcarbamate **177** (1.83 g, 10.0 mmol) according to general procedure A. Compound **178b** (1.70 g, 81%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 20:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 5.03-5.09 (m, 1H, C***H***=C=CH_2), 4.65-4.68 (m, 2H, CH=C=C***H₂***), 3.24 (s, 4H, CH_3C***H₂*** and NC***H₂***CH_2), 2.17-2.23 (m, 2H, NCH_2C***H₂***), 1.45 (s, 9H, C(C***H₃***)$_3$), 1.10 (t, 3H, *J* = 7.1 Hz, C***H₃***CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (CH=***C***=CH_2), 155.8 (***C***=O), 87.0 (***C***H=C=CH_2), 79.1 (***C***$(CH_3)_3$), 74.8 (CH=C=***C***H_2), 46.3 (CH_3***C***H_2), 42.0 (N***C***H_2CH_2), 28.4 (3C, C(***C***$H_3)_3$), 27.5 (NCH_2***C***H_2), 17.2 (NCH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1956 (C=C=C), 1627 (C=O); **MS** (ES+) m/z (rel. intensity %) 234.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{21}NNaO_2$ $[M+Na]^+$ 234.1470, found 234.1473.

Preparation and characterisation of *tert*-butyl penta-3,4-dien-1-yl(propyl)carbamate 178c



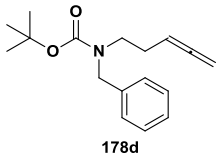
178c

Synthesised from *tert*-butyl penta-3,4-dien-1-ylcarbamate **177** (1.3 g, 7.1 mmol) according to general procedure A. Compound **178c** (1.1 g, 70%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 20:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 5.04-5.07 (m, 1H, C***H***=C=CH_2), 4.65-4.67 (m, 2H, CH=C=C***H₂***), 3.23 (brs, 2H, C***H₂***CH_2CH=C=CH_2), 3.13 (NC***H₂***CH_2CH_3), 2.19-2.21 (m, C***H₂***CH=C=CH_2), 1.50-1.55 (m, 2H, C***H₂***CH_3), 1.45 (s, 9H, C(C***H₃***)$_3$), 0.87 (t, 3H, *J* = 7.6 Hz, CH_2C***H₃***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (CH=***C***=CH_2), 155.6 (***C***=O), 87.0 (***C***H=C=CH_2), 79.0 (***C***$(CH_3)_3$), 74.8 (CH=C=***C***H_2), 49.0 (N***C***$H_2CH_2CH_3$), 46.7 (***C***H_2CH_2CH=C=CH_2), 28.4 (3C, C(***C***$H_3)_3$), 27.5 (***C***H_2CH=C=CH_2), 22.5 (***C***H_2CH_3), 11.2 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1956 (C=C=C), 1628 (C=O); **MS** (ES+) m/z (rel. intensity

%) 248.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{23}NNaO_2$ $[M+Na]^+$ 248.1672, found 248.1675.

Preparation and characterisation of *tert*-butyl benzyl(penta-3,4-dien-1-yl)carbamate 178d

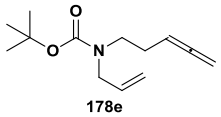


178d

Synthesised from *tert*-butyl penta-3,4-dien-1-ylcarbamate **177** (1.83 g, 10.0 mmol) according to general procedure A. Compound **178d** (2.40 g, 83%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.24-7.35 (m, 5H, 5 × ArH), 5.04-5.06 (m, 1H, C***H***=C=CH_2), 4.65-4.68 (m, 2H, PhC***H₂***), 4.46-4.49 (m, 2H, CH=C=C***H₂***), 3.22-3.32 (m, 2H, NC***H₂***CH_2), 2.18-2.21 (m, 2H, NCH_2C***H₂***), 1.45 (s, 9H, C(C***H₃***)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (CH=***C***=CH_2), 155.6 (***C***=O), 137.8 (***C***, Ar), 128.4 (2***C***H, Ar), 127.6 (2***C***H, Ar), 127.0 (***C***, Ar), 86.9 (***C***H=C=CH_2), 79.7 (***C***$(CH_3)_3$), 74.9 (CH=C=***C***H_2), 50.7 (Ph***C***H_2), 46.2 (N***C***H_2CH_2), 28.4 (3C, C(***C***$H_3)_3$), 27.3 (NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1955 (C=C=C), 1624 (C=O); **MS** (ES+) m/z (rel. intensity %) 296.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{17}H_{23}NNaO_2$ $[M+Na]^+$ 296.1757, found 296.1759.

Preparation and characterisation of *tert*-butyl allyl(penta-3,4-dien-1-yl)carbamate 178e



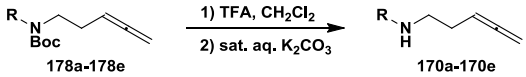
178e

Synthesised from *tert*-butyl penta-3,4-dien-1-ylcarbamate **177** (0.89 g, 4.86 mmol) according to general procedure A. Compound **178e** (0.82 g, 77%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 5.73-5.83 (m, 1H, C***H***=CH_2), 5.06-5.13 (m, 3H, CH=C***H₂*** and C***H***=C=CH_2), 4.66-4.69 (m, 2H, CH=C=C***H₂***), 3.81-3.85 (m, 2H, C***H₂***CH=CH_2), 3.22-3.25 (m,

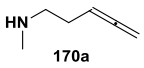
2H, NC***H₂***CH_2), 2.20-2.22 (m, 2H, NCH_2C***H₂***), 1.45 (s, 9H, C(C***H₃***)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (CH=***C***=CH_2), 155.6 (***C***=O), 134.3 (***C***H=CH_2), 117.2 (CH=***C***H_2), 86.9 (***C***H=C=CH_2), 79.5 (***C***$(CH_3)_3$), 74.9 (CH=C=***C***H_2), 50.7 (***C***H_2CH=CH_2), 46.2 (N***C***H_2CH_2), 28.4 (3C, C(***C***$H_3)_3$), 27.8 (NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3030 (C=CH_2), 1956 (C=C=C), 1920 (C=C), 1624 (C=O); **MS** (ES+) m/z (rel. intensity %) 246.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{21}NNaO_2$ $[M+Na]^+$ 246.1505, found 246.1503.

General procedure B for the synthesis of aminoallenes 170a-170e



Compounds **178a-178e** were stirred with TFA in dichloromethane (1:1, v/v) and the reactions were monitored by TLC. On completion, the reaction mixtures were basified by saturated aqueous potassium carbonate to pH 8. The reaction mixtures were extracted three times with dichloromethane. The organic extracts were combined and washed with brine, dried (Na_2SO_4) and concentrated. The crude products **170a-170e** were used directly in the next step.

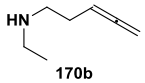
Synthesis and characterisation of *N*-methylpenta-3,4-dien-1-amine 170a



Compound **170a** was synthesised according to general procedure B from *tert*-butyl methyl(penta-3,4-dien-1-yl)carbamate **178a** (4.80 g, 24.4 mmol) as a yellow oil in 56% yield of crude product **170a**.

Crude compound **170a**: **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 5.05-5.12 (m, 1H, C***H***=C=CH_2), 4.69-4.72 (m, 2H, CH=C=C***H₂***), 2.65-2.68 (m, 2H, NC***H₂***), 2.43 (s, 3H, NC***H₃***), 2.17-2.23 (m, 2H, NCH_2C***H₂***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.7 (CH=***C***=CH_2), 87.5 (***C***H=C=CH_2), 75.3 (CH=C=***C***H_2), 48.3 (N***C***H_2), 36.3 (N***C***H_3), 28.4 (NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1956 (C=C=C).

Synthesis and characterisation of *N*-ethylpenta-3,4-dien-1-amine 170b

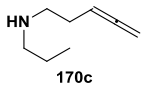


170b

Compound **170b** was synthesised according to general procedure B from *tert*-butyl ethyl(penta-3,4-dien-1-yl)carbamate **178b** (1.7 g, 8.1 mmol) as a yellow oil in 63% yield of crude product **170b**.

Crude compound **170b**: **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 5.05-5.12 (m, 1H, C***H***=C=CH_2), 4.67-4.70 (m, 2H, CH=C=C***H$_2$***), 3.18 (brs, 1H, N***H***), 2.67-2.76 (m, 4H, NC***H$_2$***CH_3 and NC***H$_2$***CH_2), 2.19-2.24 (m, 2H, NCH_2C***H$_2$***), 1.13 (t, 3H, *J* = 7.2 Hz, C***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.7 (CH=***C***=CH_2), 87.4 (***C***H=C=CH_2), 75.2 (CH=C=***C***H_2), 48.4 (N***C***H_2CH_2), 43.6 (N***C***H_2CH_3), 28.0 (NCH_2***C***H_2), 14.6 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1955 (C=C=C); **MS** (ES+) m/z (rel. intensity %) 112.20 (M + H$^+$, 100); **HRMS** (ESI+) calcd. for $C_7H_{14}N$ $[M+H]^+$ 112.1569, found 112.1572.

Synthesis and characterisation of *N*-propylpenta-3,4-dien-1-amine 170c

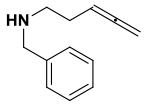


170c

Compound **170c** was synthesised according to general procedure B from *tert*-butyl penta-3,4-dien-1-yl(propyl)carbamate **178c** (1.1 g, 4.9 mmol) as a yellow oil in 65% yield of crude product **170c**.

Crude compound **170c**: **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 5.05-5.12 (m, 1H, C***H***=C=CH_2), 4.66-4.69 (m, 2H, CH=C=C***H$_2$***), 2.72 (t, 2H, *J* = 6.9 Hz, C***H$_2$***CH_2CH=C=CH_2), 2.59 (t, 2H, *J* = 7.6 Hz, NC***H$_2$***CH_2CH_3), 2.45 (brs, 1H, N***H***), 2.17-2.24 (m, 2H, C***H$_2$***CH=C=CH_2), 1.47-1.56 (m, 2H, C***H$_2$***CH_3), 0.91 (t, 3H, *J* = 7.4 Hz, CH_2C***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.7 (CH=***C***=CH_2), 87.6 (***C***H=C=CH_2), 75.1 (CH=C=***C***H_2), 51.4 (NC***H$_2$***CH_2CH_3), 48.7 (***C***H_2CH_2CH=C=CH_2), 28.3 (***C***H_2CH=C=CH_2), 22.8 (***C***H_2CH_3), 14.7 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1955 (C=C=C); **MS** (ES+) m/z (rel. intensity %) 126.17 (M + H$^+$, 100); **HRMS** (ESI+) calcd. for $C_8H_{16}N$ $[M+H]^+$ 126.1320, found 126.1321.

Synthesis and characterisation of *N*-benzylpenta-3,4-dien-1-amine 170e

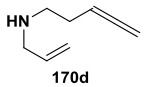


170e

Compound **170e** was synthesised according to general procedure B from *tert*-butyl benzyl(penta-3,4-dien-1-yl)carbamate **178d** (2.4 g, 8.8 mmol) as a yellow oil in 94% yield of crude product **170e**.

Crude compound **170e**: **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 7.30-7.36 (m, 5H, 5 × Ar***H***), 5.06-5.12 (m, 1H, C***H***=C=CH_2), 4.66-4.69 (m, 2H, CH=C=C***H₂***), 3.82 (s, 2H, PhC***H₂***), 2.72-2.76 (m, 2H, NC***H₂***CH_2), 2.20-2.26 (m, 2H, NCH_2C***H₂***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.7 (CH=***C***=CH_2), 134.0 (***C***, Ar), 128.9 (2***C***H, Ar), 128.3 (2***C***H, Ar), 127.6 (***C***, Ar), 87.6 (***C***H=C=CH_2), 75.1 (CH=C=***C***H_2), 53.5 (Ph***C***H_2), 48.2 (N***C***H_2CH_2), 28.5 (NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1956 (C=C=C); **MS** (ES+) m/z (rel. intensity %) 174.17 ($M + H^+$, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{16}N$ $[M+H]^+$ 174.1311, found 174.1311.

Synthesis and characterisation of *N*-allylpenta-3,4-dien-1-amine 170d



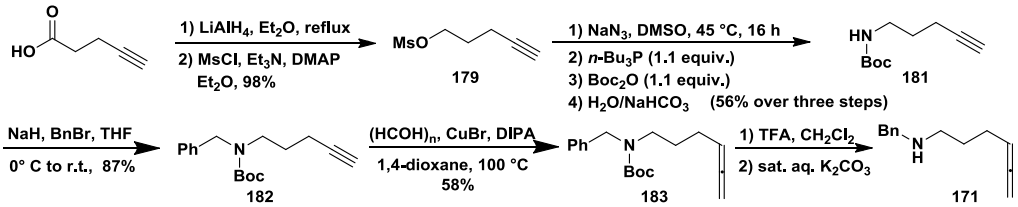
170d

Compound **170d** was synthesised according to general procedure B from *tert*-butyl allyl(penta-3,4-dien-1-yl)carbamate **178e** (0.82 g, 3.67 mmol) as a yellow oil in 86% yield of crude product **170d**.

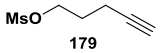
Crude compound **170d**: **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 5.78-5.85 (m, 1H, C***H***=CH_2), 5.33-5.38 (m, 1H, C***H***=C=CH_2), 5.19-5.22 (m, 2H, CH=C***H₂***), 4.67-4.71 (m, 2H, CH=C=C***H₂***), 3.22-3.25 (m, 2H, C***H₂***CH=CH_2), 2.71-2.75 (m, 2H, NC***H₂***CH_2), 2.18-2.22 (m, 2H, NCH_2C***H₂***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.8 (CH=***C***=CH_2), 135.4 (***C***H=CH_2), 117.5 (CH=***C***H_2), 87.5 (***C***H=C=CH_2), 75.0 (CH=C=***C***H_2), 52.0 (***C***H_2CH=CH_2), 48.6 (N***C***H_2CH_2), 28.5 (NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3030 (C=CH_2), 1956 (C=C=C), 1920 (C=C); **MS** (ES+) m/z (rel.

intensity %) 124.18 (M + H^+, 100); **HRMS** (ESI+) calcd. for $C_8H_{14}N$ $[M+H]^+$ 124.1426, found 124.1425.

6.2.1.3 Synthesis and characterisation of *N*-benzyl-hexa-4,5-dien-1-amine 171



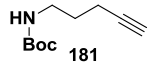
Synthesis and characterisation of pent-4-yn-1-yl methanesulfonate 179[90]



To a suspension of $LiAlH_4$ (1.30 g, 35.0 mmol) in anhydrous diethyl ether (20 mL) was added dropwise a solution of pent-4-ynoic acid (1.38 g, 14.0 mmol) in anhydrous diethyl ether (10 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was heated to reflux and stirred for 2 h. On completion, the reaction mixture was cooled to 0 °C and then an excess of $Na_2SO_4{\cdot}10H_2O$ was added. The resulting mixture was stirred for 1 h, and filtered through a pad of Celite. Diethyl ether was removed by flushing with nitrogen. The crude alcohol (0.91 g, 10.8 mmol) was dissolved in anhydrous diethyl ether (15 mL). Methanesulfonyl chloride (1.0 mL, 12.9 mmol), triethylamine (1.8 mL, 12.9 mmol) and DMAP (4.0 mg, 0.03 mmol) were added subsequently at 0 °C under nitrogen atmosphere. After 4 h, water was added to the reaction mixture. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 4:1) to afford product **179** (1.7 g, 98%).

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 4.38 (t, 2H, J = 6.2 Hz, C***H*****$_2$**O), 3.03 (s, 3H, SO_2C***H*****$_3$**), 2.35-2.40 (m, 2H, C***H*****$_2$**C≡CH), 1.93-2.05 (m, 3H, C***H*****$_2$**$CH_2C{\equiv}C$***H***); **^{13}C NMR** (100 MHz, $CHCl_3$) δ_C 83.5 (***C***≡CH), 71.0 (*C*≡***C***H), 70.2 (***C***H_2O), 37.2 (SO_2***C***H_3), 29.0 (***C***$H_2CH_2C{\equiv}CH$), 15.2 (***C***$H_2C{\equiv}CH$). Analytical data in agreement with the previous report.[90]

Synthesis and characterisation of *tert*-butyl pent-4-yn-1-ylcarbamate 181[182]

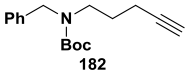


181

Sodium azide (1.6 g, 25.0 mmol) was added to a solution of the mesylated product **179** (1.6 g, 10.0 mmol) in anhydrous DMSO (15 mL). The mixture was stirred overnight at 45 °C and then was poured into water (20 mL). The resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and filtered without further purification. To the crude azide in diethyl ether was added dropwise tri-*n*-butylphosphine (3.1 mL, 11.0 mmol) at room temperature under nitrogen. After 2 hours (effervescence had ceased) the reaction mixture was cooled to -50 °C and a solution of di-*tert*-butyldicarbonate (2.5 g, 11.0 mmol) in anhydrous diethyl ether was added dropwise via cannula. The reaction mixture was stirred for a further hour at -50 °C. Saturated aqueous $NaHCO_3$ (29 mL) was added. The cooling bath was removed to allow the reaction to warm to room temperature. The reaction mixture was extracted three times with diethyl ether. The combined organic phase was dried (Na_2SO_4), concentrated and chromatographed on silica gel (petrol/diethyl ether) to give product **181** (1.0 g, 56%).

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 4.66 (brs, 1H, N***H***), 3.22-3.28 (m, 2H, NC***H*****$_2$**), 2.21-2.25 (m, 2H, C***H*****$_2$**C≡CH), 1.97 (t, 1H, *J* = 2.7 Hz, C≡C***H***), 1.68-1.75 (m, 2H, NCH_2C***H*****$_2$**), 1.44 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CHCl_3$) δ_C 155.9 (***C***=O), 83.4 (***C***≡CH), 79.0 (***C***$(CH_3)_3$), 68.9 (*C*≡***C***H), 39.5 (N***C***H_2), 28.6 (NCH_2***C***H_2), 28.4 (3C, C(***C***$H_3)_3$), 15.9 (***C***H_2C≡CH); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3310 (C≡C-H), 2136 (C≡CH), 1690 (C=O); **MS** (ES+) m/z (rel. intensity %) 206.16 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{10}H_{17}NNaO_2$ $[M+Na]^+$ 206.1178, found 206.1180.

Synthesis and characterisation of *tert*-butyl benzyl(pent-4-yn-1-yl)carbamate 182[97]

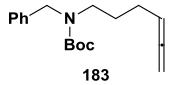


182

To a suspension of sodium hydride (0.42 g, 10.3 mmol, 60% dispersion in mineral oil) in anhydrous THF (30 mL) at 0 °C was added dropwise a solution of compound **181** (1.26 g, 6.9 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred for 30 min at 0 °C and benzyl bromide (1.65 mL, 13.8 mmol) was added. The ice bath was removed, and the solution was stirred at ambient temperature for 20 hours. The reaction was quenched by the addition of water (10 mL). The aqueous fraction was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (PE/Et_2O = 6:1) on silica gel to give product **182** (1.65 g, 87%).

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.24-7.34 (m, 5H, 5 × Ar***H***), 4.44-4.46 (m, 2H, PhC***H*****$_2$**), 3.24-3.31 (m, 2H, NC***H*****$_2$**CH_2), 2.16-2.19 (m, 2H, C***H*****$_2$**C≡CH), 1.95 (t, 1H, *J* = 2.7 Hz, C≡C***H***), 1.70-1.74 (m, 2H, NCH_2C***H*****$_2$**), 1.45 (s, 9H, C(C***H*****$_3$**$)_3$); **^{13}C NMR** (100 MHz, $CHCl_3$) δ_C 155.9 (***C***=O), 138.3 (***C***, Ar), 128.5 (4***C***H, Ar), 127.1 (***C***, Ar), 83.2 (***C***≡CH), 79.8 (***C***$(CH_3)_3$), 68.7 (*C*≡***C***H), 51.3 (Ph***C***H_2), 46.8 (N***C***H_2CH_2), 28.4 (3C, C(***C***$H_3)_3$), 27.0 (NCH_2***C***H_2), 15.9 (***C***H_2C≡CH); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3310 (C≡C-H), 2154 (C≡C), 1637 (C=O); **MS** (ES+) m/z (rel. intensity %) 296.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{17}H_{23}NNaO_2$ $[M+Na]^+$ 296.1757, found 296.1759.

Synthesis and characterisation of *tert*-butyl benzyl(hexa-4,5-dien-1-yl)carbamate 183[29]



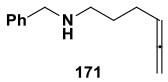
183

A suspension of compound **182** (1.65 g, 6.04 mmol)**,** cuprous bromide (429 mg, 3.0 mmol), paraformaldehyde (453 mg, 15.1 mmol) and diisopropylamine (1.87 mL, 12.1 mmol) in 1,4-dioxane (37 mL) was gently heated at reflux and stirred for 12 hours, cooled to room temperature. The reaction was diluted with water (30 mL) followed by the addition of 30 mL of diethyl ether and acidified with 1.0 M aq. HCl until the reaction mixture became a clear solution. The aqueous solution was extracted with diethyl ether (2 × 50 mL). The organic

extracts were combined and washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (PE/Et_2O = 8:1) on silica gel to give product **183** (850 mg, 49%).

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.24-7.34 (m, 5H, 5 × Ar***H***), 5.07-5.10 (m, 1H, C***H***=C=CH_2), 4.64-4.67 (m, 2H, CH=C=C***H₂***), 4.44 (d, *J* = 10.8 Hz, 2H, PhC***H₂***), 3.16-3.25 (m, 2H, NC***H₂***CH_2), 1.95-1.98 (m, 2H, C***H₂***CH=C=CH_2), 1.62-1.65 (m, 2H, NCH_2C***H₂***), 1.46 (s, 9H, C(C***H₃***)$_3$); **^{13}C NMR** (100 MHz, $CHCl_3$) δ_C 208.4 (CH=***C***=CH_2), 155.7 (***C***=O), 138.8 (***C***, Ar), 128.4 (2***C***H, Ar), 127.7 (***C***, Ar), 127.0 (2***C***H, Ar), 89.4 (***C***H=C=CH_2), 79.6 (***C***$(CH_3)_3$), 75.1 (CH=C=***C***H_2), 51.8 (Ph***C***H_2), 47.5 (N***C***H_2CH_2), 28.4 (3C, C(***C***$H_3)_3$), 27.6 (***C***H_2CH=C=CH_2), 25.4 (NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1954 (C=C=C), 1628 (C=O); **MS** (ES+) m/z (rel. intensity %) 310.22 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{25}NNaO_2$ $[M+Na]^+$ 310.1983, found 310.1986.

Synthesis and characterisation of *N*-benzylhexa-4,5-dien-1-amine 171



171

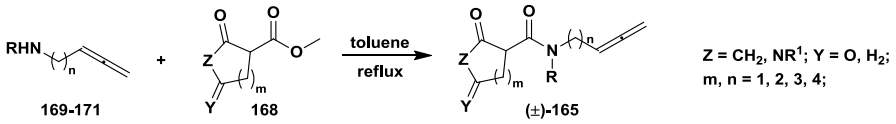
Compound **183** (0.85 g, 2.96 mmol) was stirred with TFA (2.0 mL) in dichloromethane (2 mL) and the reaction was monitored by TLC. On completion, the reaction mixture was basified by saturated aqueous potassium carbonate to pH 8. The mixture was extracted three times with dichloromethane. The organic extracts were combined and washed with brine, dried (Na_2SO_4) and concentrated. The crude amine **171** was used directly in the next step.

Crude compound **171**: **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 7.30-7.36 (m, 5H, 5 × Ar***H***), 5.10-5.15 (m, 1H, C***H***=C=CH_2), 4.66-4.69 (m, 2H, CH=C=C***H₂***), 3.82 (s, 2H, PhC***H₂***), 2.65-2.70 (m, 2H, NC***H₂***CH_2), 2.02-2.10 (m, 2H, C***H₂***CH=C=CH_2), 1.65-1.69 (m, 2H, NCH_2C***H₂***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.4 (CH=***C***=CH_2), 134.8 (***C***, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.6 (***C***, Ar), 87.5 (***C***H=C=CH_2), 75.3 (CH=C=***C***H_2), 52.9 (Ph***C***H_2), 48.8 (N***C***H_2CH_2), 28.3 (***C***H_2CH=C=CH_2), 26.4 (NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1955 (C=C=C); **MS** (ES+) m/z

(rel. intensity %) 188.18 (M + H^+, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{18}N$ $[M+H]^+$ 188.1439, found 188.1440.

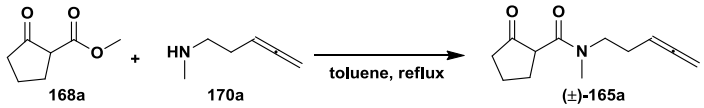
6.2.1.4 Synthesis of substrates for optimisation studies and diastereoselective allene carbocyclisation cascade

General procedure C for the synthesis of starting materials (±)-165[85, 94]



The solution of the rotameric starting materials **168** and amino allenes **169-171** in anhydrous toluene (0.14 mmol per mL of **168**) were heated at reflux. The reaction was monitored by TLC. On completion, the reaction was washed with 1.0 M aq. HCl, brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the substrates **(±)-165a-(±)-165s**. Compound **(±)-165k** was proved to exist as rotamers at ambient temperature by measuring NMR at 100 ºC. All the compounds are racemic.

Preparation and characterisation of *rac*-*N*-methyl-2-oxo-*N*-(penta-3,4-dien-1-yl)cyclopentanecarboxamide (±)-165a

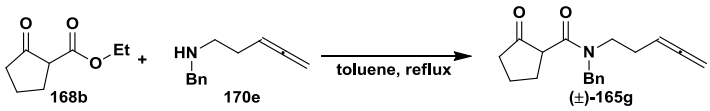


Synthesised from methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **168a** (950 mg, 5.0 mmol) and amine **170a** (1.36 g, 14.0 mmol) according to general procedure C. Compound **165a** was isolated after flash column chromatography (PE/EA = 1:2) on silica gel as a yellow oil (782 mg, 54% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.02-5.031 (m, both, 2H, C***H***=C=CH_2), 4.61-4.66 (m, both, 4H, CH=C=C***H₂***), 3.56-3.66 (m, one rotamer, 1H, C***H***), 3.35-3.43 (m, both, 4H, NC***H₂***), 3.25-3.31 (m, one rotamer, 1H, C***H***), 3.06 (s, one rotamer, 3H, NC***H₃***), 2.89 (s, one rotamer, 3H, NC***H₃***), 2.35-2.44 (m, one rotamer, 2H, C***H₂***), 2.09-2.24 (m,

both, 12H, C***H₂***), 1.74-1.84 (m, one rotamer, 2H, C***H₂***); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 214.6 (one rotamer, ***C***=O), 214.5 (one rotamer, ***C***=O), 209.0 (one rotamer, CH=***C***=CH_2), 208.9 (one rotamer, CH=***C***=CH_2), 168.6 (2C, both, N***C***=O), 86.8 (one rotamer, ***C***H=C=CH_2), 86.1 (one rotamer, ***C***H=C=CH_2), 75.6 (one rotamer, CH=C=***C***H_2), 75.1 (one rotamer, CH=C=***C***H_2), 52.1 (one rotamer, ***C***H), 51.7 (one rotamer, ***C***H), 49.6 (one rotamer, N***C***H_2), 47.8 (one rotamer, N***C***H_2), 38.6 (one rotamer, C(O)***C***H_2), 38.5 (one rotamer, C(O)***C***H_2), 36.0 (one rotamer, N***C***H_3), 33.8 (one rotamer, N***C***H_3), 27.7 (one rotamer, NCH_2***C***H_2), 27.2 (one rotamer, NCH_2***C***H_2), 26.2 (2***C***, both, CH***C***H_2), 21.1 (one rotamer, $CHCH_2$***C***H_2), 21.0 (one rotamer, $CHCH_2$***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2970 (C-H), 1956 (C=C=C), 1745 (C=O), 1641 (NC=O); **MS** (ES+) m/z (rel. intensity %) 230.13 (M + Na^+, 90); **HRMS** (ESI+) calcd. for $C_{12}H_{17}NNaO_2$ $[M+Na]^+$ 230.1157, found 230.1160.

Preparation and characterisation of *rac*-*N*-benzyl-2-oxo-*N*-(penta-3,4-dien-1-yl)cyclopentanecarboxamide (±)-165g



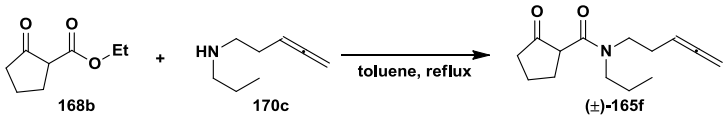
168b 170e (±)-165g

Synthesised from ethyl 2-oxocyclopentanecarboxylate **165a** (329 mg, 2.0 mmol) and amine **170e** (693 mg, 4.0 mmol) according to general procedure C. Compound **165g** was isolated after flash column chromatography (PE/EA = 2:1) on silica gel as a yellow oil (345 mg, 61% yield).

Two rotamers in a 1.4:1 ratio. **^{1}H NMR** (400 MHz, *d*$_6$-DMSO) δ_H 7.23-7.37 (m, both, 10H, 10 × Ar***H***), 5.14-5.21 (m, major, 1H, C***H***=C=CH_2), 5.07-5.14 (m, minor, 1H, C***H***=C=CH_2), 4.72-4.80 (m, both, 6H, C***H$_A$***$H_B$$C_6H_5$ and CH=C=C***H₂***), 4.58 (d, minor, 1H, *J* = 17.2 Hz, CH_A***H$_B$***C_6H_5), 4.32 (d, major, 1H, *J* = 15.5 Hz, CH_A***H$_B$***C_6H_5), 3.78 (t, major, 1H, *J* = 9.1 Hz, C***H***CH_2), 3.65 (t, minor, 1H, *J* = 9.1 Hz, C***H***CH_2), 3.56 (td, major, 1H, *J* = 15.3 Hz, *J* = 7.8 Hz, NC***H$_A$***H_B), 3.32-3.44 (m, minor, 1H, NC***H$_A$***H_B), 3.08-3.25 (m, both, 2H, NCH_A***H$_B$***), 1.74-2.32 (m, both, 16H, 4 × C***H₂***); **^{13}C NMR** (100 MHz, *d*$_6$-DMSO) δ_C 215.9 (one rotamer, ***C***=O),

215.6 (one rotamer, ***C***=O), 209.0 (2C, both, CH=***C***=CH_2), 170.4 (one rotamer, N***C***=O), 170.1 (one rotamer, N***C***=O), 138.7 (***C***, one rotamer, Ar), 138.4 (***C***, one rotamer, Ar), 129.5 (2***C***H, both, Ar), 129.2 (2***C***H, both, Ar), 128.1 (2***C***H, both, Ar), 127.9 (2***C***H, both, Ar), 127.9 (***C***H, one rotamer, Ar), 127.7 (***C***H, one rotamer, Ar), 87.7 (one rotamer, ***C***H=C=CH_2), 87.3 (one rotamer, ***C***H=C=CH_2), 76.4 (2***C***, both, CH=C=***C***H_2), 52.4 (2C, both, ***C***HCH_2), 51.4 (one rotamer, ***C***$H_2C_6H_5$), 48.4 (one rotamer, ***C***$H_2C_6H_5$), 47.2 (one rotamer, N***C***H_2CH_2), 45.8 (one rotamer, N***C***H_2CH_2), 39.0 (one rotamer, C(O)***C***H_2), 38.9 (one rotamer, C(O)***C***H_2), 28.5 (one rotamer, NCH_2***C***H_2), 28.4 (one rotamer, NCH_2***C***H_2), 27.9 (one rotamer, CH***C***H_2), 26.6 (one rotamer, CH***C***H_2), 21.4 (one rotamer, CHCH_2***C***H_2), 21.3 (one rotamer, CHCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2966 (C-H), 1955 (C=C=C), 1740 (C=O), 1639 (NC=O); **MS** (ES+) m/z (rel. intensity %) 260.16 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{21}NNaO_2$ $[M+Na]^+$ 306.1465, found 306.1469.

Preparation and characterisation of *rac*-2-oxo-*N*-(penta-3,4-dien-1-yl)-*N*-propylcyclopentanecarboxamide (±)-165f



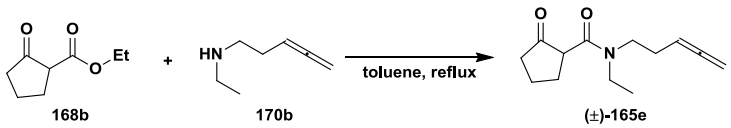
168b 170c (±)-165f

Synthesised from ethyl 2-oxocyclopentanecarboxylate **168b** (239 mg, 1.5 mmol) and amine **170c** (287 mg, 2.3 mmol) according to general procedure C. Compound **165f** was isolated after flash column chromatography (PE/EA = 2:1) on silica gel as a yellow oil (200 mg, 57% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.03-5.07 (m, both, 2H, C***H***=C=CH_2), 4.64-4.70 (m, both, 4H, CH=C=C***H$_2$***), 3.05-3.66 (m, both, 10H, C***H***CH_2 and NC***H$_2$*** and NC***H$_2$***CH_2CH_3), 2.38-2.49 (m, both, 4H, C***H$_2$***), 2.12-2.29 (m, both, 10H, C***H$_2$***), 1.77-1.90 (m, both, 2H, C***H$_2$***), 1.48-1.68 (m, both, 4H, C***H$_2$***), 0.84-0.91 (m, both, 6H, C***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 214.8 (one rotamer, ***C***=O), 214.7 (one rotamer, ***C***=O), 208.9

(one rotamer, CH=***C***=CH_2), 208.8 (one rotamer, CH=***C***=CH_2), 168.8 (one rotamer, N***C***=O), 168.7 (one rotamer, N***C***=O), 86.9 (one rotamer, ***C***H=C=CH_2), 86.2 (one rotamer, ***C***H=C=CH_2), 75.7 (one rotamer, CH=C=***C***H_2), 75.1 (one rotamer, CH=C=***C***H_2), 51.8 (one rotamer, ***C***HCH_2), 51.6 (one rotamer, ***C***HCH_2), 50.1 (one rotamer, N***C***H_2), 47.8 (one rotamer, N***C***H_2), 47.3 (one rotamer, N***C***H_2), 45.9 (one rotamer, N***C***H_2), 38.5 (2C, both, C(O)***C***H_2), 27.7 (one rotamer, ***C***H_2CH=C=CH_2), 27.6 (one rotamer, ***C***H_2CH=C=CH_2), 26.5 (one rotamer, CH***C***H_2), 22.5 (one rotamer, CH***C***H_2), 21.1 (2C, both, CHCH_2***C***H_2), 21.0 (one rotamer, ***C***H_2CH_3), 20.9 (one rotamer, ***C***H_2CH_3), 11.2 (one rotamer, ***C***H_3), 11.1 (one rotamer, ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2965 (C-H), 1955 (C=C=C), 1741 (C=O), 1636 (NC=O); **MS** (ES+) m/z (rel. intensity %) 258.17 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{14}H_{21}NNaO_2$ $[M+Na]^+$ 258.1465, found 258.1468.

Preparation and characterisation of *rac*-*N*-ethyl-2-oxo-*N*-(penta-3,4-dien-1-yl)cyclopentanecarboxamide (±)-165e



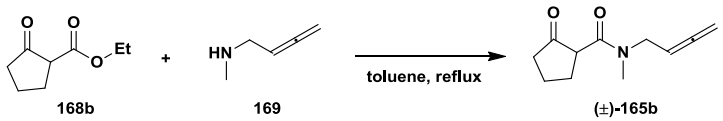
168b 170b (±)-165e

Synthesised from ethyl 2-oxocyclopentanecarboxylate **168b** (358 mg, 2.3 mmol) and amine **170b** (111 mg, 4.6 mmol) according to general procedure C. Compound **165e** was isolated after flash column chromatography (PE/EA = 1:1) on silica gel as a yellow oil (454 mg, 84% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.04-5.06 (m, both, 2H, C***H***=C=CH_2), 4.67-4.71 (m, one rotamer, 2H, CH=C=C***H$_2$***), 4.63-4.66 (m, one rotamer, 2H, CH=C=C***H$_2$***), 3.56-3.64 (m, both, 2H, C***H$_A$***$H_B$$CH_3$ and NC***H$_A$***$H_B$$CH_2$), 3.46-3.53 (m, both, 2H, CH_A***H$_B$***CH_3 and NCH_A***H$_B$***CH_2), 3.20-3.39 (m, both, 6H, C***H$_A$***$H_B$$CH_3$ and NC***H$_A$***$H_B$$CH_2$ and C***H***CH_2), 2.40-2.46 (m, both, 2H, C***H$_2$***), 2.12-2.31 (m, both, 10H, C***H$_2$***), 1.78-1.88 (m, both, 2H, C***H$_2$***), 1.16 (t, one rotamer, 3H, *J* = 7.2 Hz, C***H$_3$***), 1.10 (t, one rotamer, 3H, *J* = 7.1 Hz,

C***H₃***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 214.8 (one rotamer, ***C***=O), 214.7 (one rotamer, ***C***=O), 208.9 (one rotamer, CH=***C***=CH_2), 208.8 (one rotamer, CH=***C***=CH_2), 168.7 (one rotamer, N***C***=O), 168.6 (one rotamer, N***C***=O), 86.9 (one rotamer, ***C***H=C=CH_2), 86.2 (one rotamer, ***C***H=C=CH_2), 75.7 (one rotamer, CH=C=***C***H_2), 75.1 (one rotamer, CH=C=***C***H_2), 51.8 (one rotamer, ***C***HCH_2), 51.7 (one rotamer, ***C***HCH_2), 47.1 (one rotamer, N***C***H_2CH_2), 45.4 (one rotamer, N***C***H_2CH_2), 42.9 (one rotamer, N***C***H_2CH_3), 41.2 (one rotamer, N***C***H_2CH_3), 38.6 (one rotamer, C(O)***C***H_2), 38.5 (one rotamer, C(O)***C***H_2), 27.8 (one rotamer, NCH_2***C***H_2), 27.7(one rotamer, NCH_2***C***H_2), 27.6 (one rotamer, CH***C***H_2), 26.6 (one rotamer, CH***C***H_2), 21.1 (2C, both, $CHCH_2$***C***H_2), 14.5 (one rotamer, ***C***H_3), 12.9 (one rotamer, ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2971 (C-H), 1956 (C=C=C), 1741 (C=O), 1635 (NC=O); **MS** (ES+) m/z (rel. intensity %) 244.15 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{19}NNaO_2$ $[M+Na]^+$ 244.1308, found 244.1312.

Preparation and characterisation of *rac*-*N*-(buta-2,3-dien-1-yl)-*N*-methyl-2-oxocyclopentanecarboxamide (±)-165b



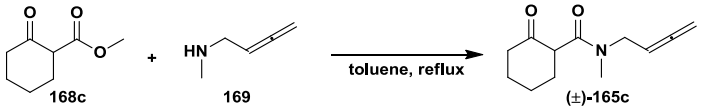
168b 169 (±)-165b

Synthesised from ethyl 2-oxocyclopentanecarboxylate **168b** (115 mg, 0.7 mmol) and *N*-methylbuta-2,3-dien-1-amine **169** (102 mg, 1.2 mmol) according to general procedure C. Compound **165b** was isolated after flash column chromatography (PE/EA = 1:1) on silica gel as a yellow oil (60.7 mg, 45% yield).

Two rotamers in a ratio of 1:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.06-5.12 (m, both, C***H***=C=CH_2), 4.77-4.86 (m, both, 4H, CH=C=C***H₂***), 4.26-4.32 (m, one rotamer, 1H, NC***H$_A$***H_B), 4.04-4.11 (m, one rotamer, 1H, NCH_A***H$_B$***), 3.75-3.94 (m, both, 2H, NC***H₂***), 3.41-3.47 (m, both, 2H, C***H***CH_2), 3.10 (s, one rotamer, 3H, NC***H₃***), 2.95 (s, one rotamer, 3H, NC***H₃***), 2.40-2.50 (m, one rotamer, 2H, C***H₂***), 2.27-2.30 (m, both, 4H, C***H₂***), 2.13-2.18 (m, both, 4H, C***H₂***), 1.80-1.90 (m, one rotamer, 2H, C***H₂***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 214.8 (one rotamer, ***C***=O), 214.5 (one rotamer, ***C***=O), 209.2 (one rotamer, CH=***C***=CH_2), 208.3 (one

rotamer, CH=***C***=CH_2), 168.8 (one rotamer, N***C***=O), 168.7 (one rotamer, N***C***=O), 86.9 (one rotamer, ***C***H=C=CH_2), 86.1 (one rotamer, ***C***H=C=CH_2), 77.8 (one rotamer, CH=C=***C***H_2), 76.4 (one rotamer, CH=C=***C***H_2), 52.0 (one rotamer, ***C***HCH_2), 51.9 (one rotamer, ***C***HCH_2), 48.4 (one rotamer, N***C***H_2), 46.7 (one rotamer, N***C***H_2), 38.6 (one rotamer, ***C***$H_2C(O)$), 38.5 (one rotamer, ***C***$H_2C(O)$), 35.3 (one rotamer, N***C***H_3), 34.1 (one rotamer, N***C***H_3), 27.6 (one rotamer, CH***C***H_2), 27.3 (one rotamer, CH***C***H_2), 21.1 (one rotamer, $CHCH_2$***C***H_2), 21.0 (one rotamer, $CHCH_2$***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2923 (C-H), 1956 (C=C=C), 1735 (C=O), 1617 (NC=O); **MS** (ES+) m/z (rel. intensity %) 216.11 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{11}H_{15}NNaO_2$ $[M+Na]^+$ 216.0995, found 216.0999.

Preparation and characterisation of *rac*-*N*-(buta-2,3-dien-1-yl)-*N*-methyl-2-oxocyclohexanecarboxamide (±)-165c

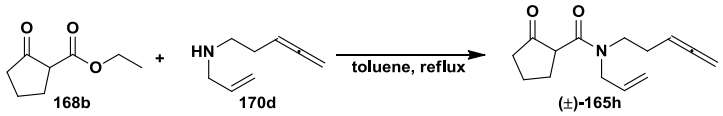


Synthesised from methyl 2-oxocyclohexanecarboxylate **168c** (173 mg, 1.0 mmol) and *N*-methylbuta-2,3-dien-1-amine **169** (149 mg, 1.8 mmol) according to general procedure C. Compound **165c** was obtained after flash column chromatography (PE/EA = 1:1) on silica gel as a yellow oil (83 mg, 40% yield).

Two rotamers in a ratio of 1:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.08-5.14 (m, both, 2H, C***H***=C=CH_2), 4.75-4.85 (m, both, 4H, CH=C=C***H$_2$***), 4.00-4.10 (m, one rotamer, 1H, NC***H$_A$***H_B), 3.83-3.96 (m, both, 2H, NC***H$_2$***), 3.64-3.72 (m, both, 1H, NCH_A***H$_B$***), 3.53-3.57 (m, both, 2H, C***H***CH_2), 2.94 (s, one rotamer, 3H, NC***H$_3$***), 2.88 (s, one rotamer, 3H, NC***H$_3$***), 1.60-2.58 (m, both, 16H, 4 × C***H$_2$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 209.2 (one rotamer, ***C***=O), 208.3 (one rotamer, ***C***=O), 207.7 (one rotamer, CH=***C***=CH_2), 207.4 (one rotamer, CH=***C***=CH_2), 169.6 (one rotamer, N***C***=O), 169.4 (one rotamer, N***C***=O), 86.9 (one rotamer, ***C***H=C=CH_2), 86.3 (one rotamer, ***C***H=C=CH_2), 77.7 (one rotamer, CH=C=***C***H_2), 76.3 (one rotamer, CH=C=***C***H_2), 54.5 (one rotamer, ***C***HCH_2), 54.3 (one rotamer, ***C***HCH_2), 48.3 (one

rotamer, N***C***H_2), 46.5 (one rotamer, N***C***H_2), 41.9 (one rotamer, ***C***H_2C(O)), 41.8 (one rotamer, ***C***H_2C(O)), 34.9 (one rotamer, N***C***H_3), 33.8 (one rotamer, N***C***H_3), 30.5 (one rotamer, CH***C***H_2), 30.0 (one rotamer, CH***C***H_2), 27.1 (one rotamer, ***C***H_2CH_2C(O)), 27.0 (one rotamer, ***C***H_2CH_2C(O)), 23.5 (one rotamer, $CHCH_2$***C***H_2), 23.4 (one rotamer, $CHCH_2$***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2925 (C-H), 1956 (C=C=C), 1740 (C=O), 1619 (NC=O); **MS** (ES+) m/z (rel. intensity %) 230.14 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{17}NNaO_2$ $[M+Na]^+$ 230.1156, found 230.1160.

Preparation and characterisation of *rac*-2-oxo-*N*-(penta-3,4-dien-1-yl)-*N*-(prop-2-en-1-yl) cyclopentane carboxamide (±)-165h

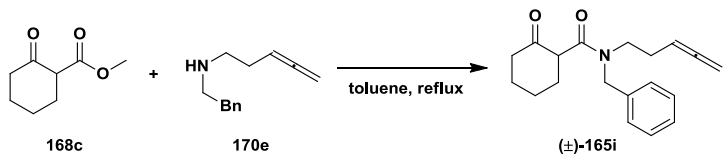


Synthesised from ethyl 2-oxocyclopentanecarboxylate **168b** (260 mg, 1.6 mmol) and amine **170d** (317 mg, 2.5 mmol) according to general procedure C. Compound **165h** was isolated after flash column chromatography (PE/EA = 3:1) on silica gel as a yellow oil (257 mg, 69% yield).

Two rotamers in a ratio of 1:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.71-5.87 (m, both, 2H, C***H***=CH_2), 5.12-5.22 (m, both, 4H, CH=C***H$_2$***), 5.03-5.12 (m, both, 2H, C***H***=C=CH_2), 4.66-4.73 (m, both, 4H, CH=C=C***H$_2$***), 4.31-4.37 (m, one rotamer, 1H, C***H$_A$***H_BCH=CH_2), 4.19-4.24 (m, one rotamer, 1H, CH_A***H$_B$***CH=CH_2), 3.77-3.88 (m, both, 2H, C***H$_2$***CH=CH_2), 3.61-3.72 (m, both, 2H, NC***H$_2$***CH_2), 3.46 (t, one rotamer, 1H, *J* = 8.6 Hz, C***H***CH_2), 3.26-3.36 (m, both, 2H, C***H***CH_2 and NC***H$_A$***$H_B$$CH_2$), 3.19 (td, one rotamer, 1H, *J* = 13.4 Hz, *J* = 7.5 Hz, NCH_A***H$_B$***CH_2), 2.40-2.53 (m, both, 2H, C***H$_2$***), 2.12-2.33 (m, both, 12H, C***H$_2$***), 1.78-1.90 (m, both, 2H, C***H$_2$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 214.7 (one rotamer, ***C***=O), 214.6 (one rotamer, ***C***=O), 208.9 (one rotamer, CH=***C***=CH_2), 208.8 (one rotamer, CH=***C***=CH_2), 169.0 (one rotamer, CH***C***(O)N), 168.7 (one rotamer, CH***C***(O)N), 133.4 (one rotamer, ***C***H=CH_2), 132.9 (one rotamer, ***C***H=CH_2), 116.7 (one rotamer, CH=***C***H_2), 116.4 (one rotamer, CH=***C***H_2), 86.9 (one

rotamer, ***C***H=C=CH_2), 86.2 (one rotamer, ***C***H=C=CH_2), 75.7 (one rotamer, CH=C=***C***H_2), 75.1 (one rotamer, CH=C=***C***H_2), 52.0 (one rotamer, ***C***HCH_2), 51.8 (one rotamer, ***C***HCH_2), 50.4 (one rotamer, ***C***H_2CH=CH_2), 48.3 (one rotamer, ***C***H_2CH=CH_2), 46.9 (one rotamer, N***C***H_2CH_2), 46.2 (one rotamer, N***C***H_2CH_2), 38.6 (2C, both, C(O)***C***H_2), 27.7 (one rotamer, NCH_2***C***H_2), 27.6 (one rotamer, NCH_2***C***H_2), 27.5 (one rotamer, CH***C***H_2), 26.6 (one rotamer, CH***C***H_2), 21.1 (one rotamer, CHCH_2***C***H_2), 21.0 (one rotamer, CHCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2969 (C-H), 1955 (C=C=C), 1740 (C=O), 1637 (NC=O); **MS** (ES+) m/z (rel. intensity %) 256.15 (M + Na^+, 60); **HRMS** (ESI+) calcd. for $C_{14}H_{19}NNaO_2$ $[M+Na]^+$ 256.1308, found 256.1313.

Preparation and characterisation of *rac*-*N*-benzyl-2-oxo-*N*-(penta-3,4-dien-1-yl)cyclohexanecarboxamide (±)-165i

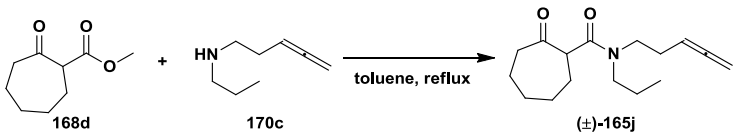


168c 170e (±)-165i

Synthesised from methyl 2-oxocyclohexanecarboxylate **168c** (160 mg, 1.0 mmol) and amine **170e** (346 mg, 2.0 mmol) according to general procedure C. Compound **165i** was isolated after flash column chromatography (PE/EA = 2:1) on silica gel as a yellow oil (199 mg, 67% yield). Two rotamers in a ratio of 1:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.14-7.36 (m, both, 10H, 10 × Ar***H***), 5.08-5.12 (m, one rotamer, 1H, C***H***=C=CH_2), 4.98-5.04 (m, both, 2H, C***H***=C=CH_2 and C***H***$_A$H$_B$C$_6$H$_5$), 4.63-4.70 (m, both, 4H, CH=C=C***H$_2$***), 4.53 (d, one rotamer, 1H, *J* = 17.3 Hz, C***H***$_A$H$_B$C$_6$H$_5$), 4.29-4.39 (m, both, 2H, CH$_A$***H***$_B$C$_6$H$_5$ and CH$_A$***H***$_B$C$_6$H$_5$), 3.69-3.77 (m, one rotamer, 1H, NC***H***$_A$H$_B$CH$_2$), 3.63-3.68 (m, one rotamer, 1H, C***H***), 3.46-3.51 (m, one rotamer, 1H, C***H***), 3.21-3.29 (m, one rotamer, 1H, NC***H***$_A$H$_B$CH$_2$), 3.09-3.17 (m, both, 2H, NC***H$_2$***CH$_2$), 2.52-2.60 (m, both, 2H, C***H$_2$***),1.52-2.60 (m, both, 18H, C***H$_2$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (one rotamer, ***C***=O), 208.8 (one rotamer, ***C***=O), 207.5 (2C, both, CH=***C***=CH_2), 170.1 (one rotamer, N***C***=O), 169.9 (one rotamer, N***C***=O), 137.3 (***C***, one rotamer, Ar), 136.8 (***C***, one

rotamer, Ar), 128.9 (2***C***H, both, Ar), 128.5 (2***C***H, both, Ar), 127.6 (2***C***H, both, Ar), 127.1 (2***C***H, both, Ar), 126.2 (2***C***H, both, Ar), 87.0 (one rotamer, ***C***H=C=CH_2), 86.1 (one rotamer, ***C***H=C=CH_2), 75.8 (one rotamer, CH=C=***C***H_2), 75.1 (one rotamer, CH=C=***C***H_2), 54.5 (one rotamer, ***C***HCH_2), 54.4 (one rotamer, ***C***HCH_2), 51.3 (one rotamer, ***C***$H_2C_6H_5$), 48.2 (one rotamer, ***C***$H_2C_6H_5$), 46.3 (one rotamer, N***C***H_2CH_2), 46.1 (one rotamer, N***C***H_2CH_2), 41.9 (one rotamer, C(O)***C***H_2), 41.8 (one rotamer, C(O)***C***H_2), 30.5 (one rotamer, CH***C***H_2), 30.3 (one rotamer, CH***C***H_2), 27.1 (one rotamer, NCH_2***C***H_2), 27.0 (one rotamer, NCH_2***C***H_2), 26.9 (one rotamer, ***C***H_2CH_2C(O)), 26.3 (one rotamer, ***C***H_2CH_2C(O)), 23.7 (one rotamer, $CHCH_2$***C***H_2), 23.4 (one rotamer, $CHCH_2$***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2938 (C-H), 1955 (C=C=C), 1709 (C=O), 1642 (NC=O); **MS** (ES+) m/z (rel. intensity %) 320.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{19}H_{23}NNaO_2$ $[M+Na]^+$ 320.1621, found 320.1626.

Preparation and characterisation of *rac*-2-oxo-*N*-(penta-3,4-dien-1-yl)-*N*-propylcycloheptanecarboxamide (±)-165j

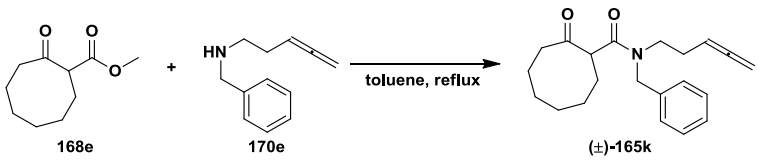


Synthesised from methyl 2-oxocycloheptanecarboxylate **168d** (272 mg, 1.6 mmol) and amine **170c** (325 mg, 2.6 mmol) according to general procedure C. Compound **165j** was isolated after flash column chromatography (PE/EA = 2:1) on silica gel as a yellow oil (248 mg, 59% yield).

Two rotamers in a 1.3:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 5.19-5.21 (m, minor, 1H, C***H***=C=CH_2), 5.10-5.12 (m, major, 1H, C***H***=C=CH_2), 4.73-4.79 (m, both, 4H, CH=C=C***H$_2$***), 3.69-3.75 (m, both, 2H, C***H***CH_2), 3.08-3.32 (m, both, 8H, NC***H$_2$*** and C***H$_2$***CH_2CH_3), 1.31-2.66 (m, both, 28H, 7 × C***H$_2$***), 0.84 (t, major, 3H, J = 7.3 Hz, C***H$_3$***), 0.79 (t, minor, 3H, J = 7.4Hz, C***H$_3$***); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 211.4 (2C, both, ***C***=O), 209.1 (one rotamer, CH=***C***=CH_2), 209.0 (one rotamer, CH=***C***=CH_2), 170.8 (one rotamer, N***C***=O), 170.6 (one

rotamer, N***C***=O), 87.8 (one rotamer, ***C***H=C=CH_2), 87.4 (one rotamer, ***C***H=C=CH_2), 76.4 (one rotamer, CH=C=***C***H_2), 76.2 (one rotamer, CH=C=***C***H_2), 56.3 (one rotamer, ***C***HCH_2), 56.2 (one rotamer, ***C***HCH_2), 49.8 (one rotamer, N***C***H_2CH_2), 47.4 (one rotamer, N***C***H_2CH_2), 45.5 (one rotamer, N***C***$H_2CH_2CH_3$), 43.7 (one rotamer, N***C***$H_2CH_2CH_3$), 30.6 (one rotamer, C(O)***C***H_2), 30.5 (one rotamer, C(O)***C***H_2), 28.9 (2C, both, CH***C***H_2), 28.5 (one rotamer, ***C***H_2CH=C=CH_2), 28.4 (one rotamer, ***C***H_2CH=C=CH_2), 26.9 (2C, both, ***C***H_2), 25.4 (one rotamer, ***C***H_2), 25.3 (one rotamer, ***C***H_2), 22.9 (2C, both, ***C***H_2), 21.2 (2C, both, ***C***H_2), 11.9 (one rotamer, ***C***H_3), 11.7 (one rotamer, ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2931 (C-H), 1955 (C=C=C), 1703 (C=O), 1637 (NC=O); **MS** (ES+) m/z (rel. intensity %) 286.20 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{16}H_{25}NNaO_2$ $[M+Na]^+$ 286.1778, found 286.1783.

Preparation and characterisation of *rac*-*N*-benzyl-2-oxo-*N*-(penta-3,4-dien-1-yl)cyclooctanecarboxamide (±)-165k



168e 170e (±)-165k

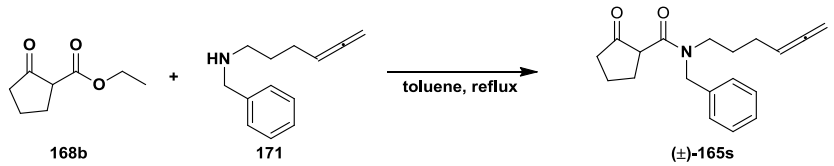
Synthesised from methyl 2-oxocyclooctanecarboxylate **168e** (184 mg, 1.0 mmol) and amine **170e** (259 mg, 1.5 mmol) according to general procedure C. Compound **165k** was isolated after flash column chromatography (PE/EA = 4:1) as a yellow oil (218 mg, 67% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO, measured at ambient temperature) δ_H 7.14-7.39 (m, both, 10H, 10 × Ar***H***), 5.17-5.23 (m, one rotamer, 1H, ***C***H=C=CH_2), 5.05-5.12 (m, one rotamer, 1H, ***C***H=C=CH_2), 4.70-4.79 (m, both, 4H, CH=C=C***H$_2$***), 4.57-4.64 (m, both, 3H, C***H$_2$***C_6H_5), 4.41 (d, one rotamer, 1H, *J* = 16.0 Hz, C***H$_A$***$H_BC_6H_5$), 3.80 (dd, one rotamer, 1H, *J* = 12.0 Hz, *J* = 4.0 Hz, C***H***), 3.64 (dd, one rotamer, 1H, *J* = 12.0 Hz, *J* = 4.0 Hz, C***H***), 3.31-3.43 (m, both, 3H, NC***H$_2$***CH_2), 3.17-3.29 (m, both, 2H, C***H$_2$***), 2.06-2.33 (m, both, 9H, C***H$_2$***), 1.30-1.87 (m, both, 18H, C***H$_2$***); **^{13}C NMR** (100 MHz**,** d_6-DMSO, measured at ambient temperature) δ_C 214.4 (one rotamer, ***C***=O), 214.1 (one rotamer, ***C***=O), 209.1 (2***C***,

both, CH=***C***=CH_2), 170.4 (one rotamer, N***C***=O), 170.2 (one rotamer, N***C***=O), 138.7 (***C***, one rotamer, Ar), 138.2 (***C***, one rotamer, Ar), 129.5 (2***C***H, both, Ar), 129.3 (2***C***H, both, Ar), 128.2 (***C***H, one rotamer, Ar), 128.0 (2***C***H, both, Ar), 127.8 (***C***H, one rotamer, Ar), 127.4 (2***C***H, both, Ar), 87.7 (one rotamer, ***C***H=C=CH_2), 87.2 (one rotamer, ***C***H=C=CH_2), 76.5 (one rotamer, CH=C=***C***H_2), 76.2 (one rotamer, CH=C=***C***H_2), 56.4 (one rotamer, ***C***$H_2C_6H_5$), 56.1 (one rotamer, ***C***$H_2C_6H_5$), 51.3 (one rotamer, ***C***HCH_2), 48.2 (one rotamer, ***C***HCH_2), 47.0 (one rotamer, N***C***H_2CH_2), 46.0 (one rotamer, N***C***H_2CH_2), 29.0 (one rotamer, ***C***H_2), 28.7 (one rotamer, ***C***H_2), 28.4 (one rotamer, NCH_2***C***H_2), 28.2 (one rotamer, NCH_2***C***H_2), 27.7 (one rotamer, ***C***H_2), 27.0 (one rotamer, ***C***H_2), 26.9 (2C, both, ***C***H_2), 26.8 (one rotamer, ***C***H_2), 26.6 (one rotamer, ***C***H_2), 26.5 (one rotamer, ***C***H_2), 26.0 (one rotamer, ***C***H_2), 25.3 (one rotamer, ***C***H_2), 25.1 (one rotamer, ***C***H_2).

^{1}H NMR (500 MHz, d_6-DMSO, measured at 100° C) δ_H 7.34 (t, 2H, *J* = 7.4 Hz, 2 × Ar***H***), 7.27 (t, 1H, *J* = 7.2 Hz, Ar***H***), 7.22 (d, 2H, *J* = 7.3 Hz, 2 × Ar***H***), 5.09-5.15 (m, 1H, C***H***=C=CH_2), 4.71-4.73 (m, 2H, CH=C=C***H$_2$***), 4.65 (d, 1H, *J* = 16.0 Hz, C***H$_A$***$H_B C_6H_5$), 4.51 (d, 1H, *J* = 16.0 Hz, CH_A***H$_B$***C_6H_5), 3.75 (dd, 1H, *J* = 11.0 Hz, *J* = 3.1 Hz, C***H***CH_2), 3.43 (td, 1H, *J* = 14.6 Hz, *J* = 7.4 Hz, NC***H$_A$***$H_B CH_2$), 3.29 (td, 1H, *J* = 14.3 Hz, *J* = 7.3 Hz, NCH_A***H$_B$***CH_2), 2.78-2.81 (m, 1H, C***H$_2$***), 2.27-2.34 (m, 2H, C***H$_2$***), 2.16-2.21 (m, 2H, C***H$_2$***), 1.82-1.89 (m, 2H, C***H$_2$***), 1.60-1.72 (m, 3H, C***H$_2$***), 1.42-1.58 (m, 3H, C***H$_2$***), 1.21-1.27 (m, 1H, C***H$_2$***); **^{13}C NMR** (125 MHz**,** d_6-DMSO, measured at 100° C) δ_C 213.2 (***C***=O), 209.4 (CH=***C***=CH_2), 170.4 (N***C***=O), 138.6 (***C***, Ar), 129.3 (2***C***H, Ar), 127.9 (3***C***H, Ar), 87.5 (***C***H=C=CH_2), 75.9 (CH=C=***C***H_2), 56.8 (***C***HCH_2), 46.9 (N***C***H_2), 29.2 (***C***H_2), 28.0 (2C, NCH_2***C***H_2), 26.9 (3C, ***C***H_2), 25.6 (2C, ***C***H_2)**;** **FT-IR** ν_{max}(NaCl)/cm^{-1} 2928 (C-H), 1955 (C=C=C), 1699 (C=O), 1641 (NC=O); **MS** (ES+) m/z (rel. intensity %) 348.22 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{21}H_{27}NNaO_2$ $[M+Na]^+$ 348.1934, found 348.1936.

Preparation and characterisation of *rac*-*N*-benzyl-*N*-(hexa-4,5-dien-1-yl)-2-oxocyclopentanecarboxamide (±)-165s



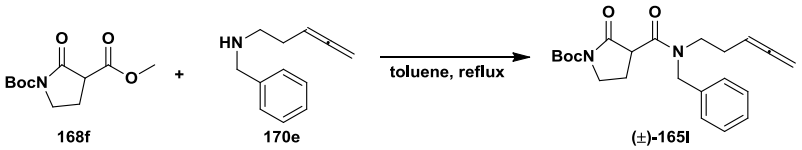
168b 171 (±)-165s

Synthesised from ethyl 2-oxocyclopentanecarboxylate **168b** (300 mg, 1.9 mmol) and *N*-benzylhexa-4,5-dien-1-amine **171** (542 mg, 2.9 mmol) according to general procedure C. Compound **165s** was isolated after flash column chromatography (PE/EA = 4:1) as a yellow oil (282 mg, 50% yield).

Two rotamers in a 1.4:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.37 (t, both, 2H, J = 7.6 Hz, 2 × Ar***H***), 7.28-7.33 (m, both, 4H, 4 × Ar***H***), 7.23 (t, both, 4H, J = 7.2 Hz, 4 × Ar***H***), 5.12-5.20 (m, both, 2H, C***H***=C=CH_2), 4.71-4.81 (m, both, 6H, C***H$_A$***H$_B$$C_6H_5$ and CH=C=C***H$_2$***), 4.52 (d, minor, 1H, J = 17.2 Hz, CH_A***H$_B$***C_6H_5), 4.33 (d, major, 1H, J = 15.4 Hz, CH_A***H$_B$***C_6H_5), 3.75 (t, major, 1H, J = 9.1 Hz, C***H***CH_2), 3.64 (t, minor, 1H, J = 9.1 Hz, C***H***CH_2), 3.42-3.52 (m, both, 2H, NC***H$_A$***H$_B$$CH_2$), 3.11-3.18 (m, major, 1H, NCH_A***H$_B$***CH_2), 2.99-3.06 (m, minor, 1H, NCH_A***H$_B$***CH_2), 1.49-2.32 (m, both, 20H, 5 × C***H$_2$***); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 215.8 (one rotamer, ***C***=O), 215.6 (one rotamer, ***C***=O), 208.6 (2C, both, CH=***C***=CH_2), 170.3 (one rotamer, N***C***=O), 170.1 (one rotamer, N***C***=O), 138.7 (***C***, one rotamer, Ar), 138.5 (***C***, one rotamer, Ar), 129.5 (2***C***H, both, Ar), 129.2 (2***C***H, both, Ar), 128.1 (***C***H, one rotamer, Ar), 127.9 (2***C***H, both, Ar), 127.7 (2***C***H, both, Ar), 127.5 (***C***H, one rotamer, Ar), 90.2 (one rotamer, ***C***H=C=CH_2), 90.0 (one rotamer, ***C***H=C=CH_2), 76.6 (one rotamer, CH=C=***C***H_2), 76.4 (one rotamer, CH=C=***C***H_2), 52.5 (one rotamer, ***C***HCH_2), 52.3 (one rotamer, ***C***HCH_2), 51.3 (one rotamer, ***C***$H_2C_6H_5$), 48.5 (one rotamer, ***C***$H_2C_6H_5$), 47.3 (one rotamer, N***C***H_2CH_2), 45.7 (one rotamer, N***C***H_2CH_2), 39.0 (one rotamer, C(O)***C***H_2), 38.9 (one rotamer, C(O)***C***H_2), 31.5 (one rotamer, CH***C***H_2), 28.5 (2C, both, ***C***H_2CH=C=CH_2), 27.3 (one rotamer, CH***C***H_2), 25.7 (one rotamer, NCH_2***C***H_2), 25.3 (one rotamer, NCH_2***C***H_2), 21.4 (one rotamer, C(O)CH_2***C***H_2), 21.3

(one rotamer, C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2941 (C-H), 1955 (C=C=C), 1740 (C=O), 1639 (NC=O); **MS** (ES+) m/z (rel. intensity %) 320.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{19}H_{23}NNaO_2$ $[M+Na]^+$ 320.1621, found 320.1626.

Preparation and characterisation of *rac*-*tert*-butyl 3-[benzyl(penta-3,4-dien-1-yl)carbamoyl]-2-oxopyrrolidine-1-carboxylate (±)-165l



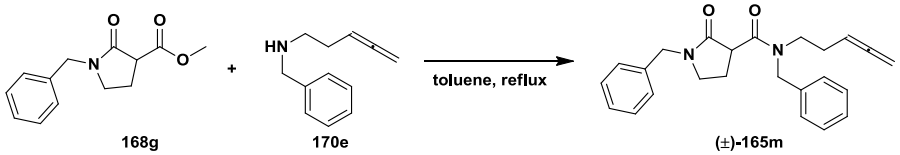
168f 170e (±)-165l

Synthesised from methyl 1-*tert*-butyl 3-methyl 2-oxopyrrolidine-1,3-dicarboxylate **168f** (365 mg, 1.5 mmol) and amine **170e** (442 mg, 2.55 mmol) according to general procedure C. Compound **165l** was isolated after flash column chromatography (PE/EA = 2:1) on silica gel as a yellow oil (397 mg, 69% yield).

Two rotamers in a 1.5:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.38 (t, both, 2H, *J* = 7.6 Hz, 2 × Ar***H***), 7.32 (dd, both, 4H, *J* = 12.9 Hz, *J* = 6.0 Hz, 4 × Ar***H***), 7.25 (t, both, 4H, *J* = 7.4 Hz, 4 × Ar***H***), 5.16-5.23 (m, major, 1H, C***H***=C=CH_2), 5.09-5.15 (m, minor, 1H, C***H***=C=CH_2), 4.85 (d, minor, 1H, *J* = 17.2 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.74-4.81 (m, 6H, CH=C=C$\boldsymbol{H_2}$ for both and C$\boldsymbol{H_A}H_BC_6H_5$ for major), 4.61 (d, minor, 1H, *J* = 17.2 Hz, $CH_A\boldsymbol{H_B}C_6H_5$), 4.37 (d, major, 1H, *J* = 15.4 Hz, $CH_A\boldsymbol{H_B}C_6H_5$), 4.20 (t, major, 1H, *J* = 8.9 Hz, C***H***CH_2), 4.07 (t, minor, 1H, *J* = 8.6 Hz, C***H***CH_2), 3.69-3.79 (m, both, 2H, C$\boldsymbol{H_A}H_B$N(Boc)), 3.52-3.65 (m, major, 2H, $CH_A\boldsymbol{H_B}$N(Boc) and N(Bn)C$\boldsymbol{H_A}H_B$), 3.39-3.47 (m, minor, 1H, N(Bn)C$\boldsymbol{H_A}H_B$), 3.13-3.27 (m, both, 2H, N(Bn)$CH_A\boldsymbol{H_B}$), 2.19-2.34 (m, both, 6H, C$\boldsymbol{H_2}$CH=C=CH_2 and CHC$\boldsymbol{H_A}H_B$), 2.00-2.15 (m, both, 2H, $CHCH_A\boldsymbol{H_B}$), 1.46 (s, minor, 9H, C(C$\boldsymbol{H_3}$)$_3$), 1.45 (s, major, 9H, C(C$\boldsymbol{H_3}$)$_3$); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 209.0 (2C, both, CH=***C***=CH_2), 171.5 (one rotamer, BocN***C***(O)), 171.3 (one rotamer, BocN***C***(O)), 169.6 (one rotamer, N***C***=O), 169.5 (one rotamer, N***C***=O), 150.4 (2C, both, $C(CH_3)_3$O***C***(O)), 138.5 (***C***, one rotamer, Ar), 138.2 (***C***, one rotamer, Ar), 129.5 (2***C***H, both, Ar), 129.2 (2***C***H, both, Ar), 128.2 (2***C***H, both, Ar), 128.0 (2***C***H, both,

Ar), 127.8 (***C***H, one rotamer, Ar), 127.6 (***C***H, one rotamer, Ar), 87.7 (one rotamer, ***C***H=C=CH_2), 87.3 (one rotamer, ***C***H=C=CH_2), 82.8 (2C, both, ***C***$(CH_3)_3$), 76.5 (one rotamer, CH=C=***C***H_2), 76.3 (one rotamer, CH=C=***C***H_2), 51.5 (one rotamer, ***C***$H_2C_6H_5$), 48.8 (one rotamer, ***C***$H_2C_6H_5$), 47.6 (one rotamer, ***C***HCH_2), 47.4 (one rotamer, ***C***HCH_2), 47.3 (one rotamer, ***C***H_2N(Boc)), 46.1 (one rotamer, ***C***H_2N(Boc)), 45.6 (one rotamer, N(Bn)***C***H_2), 45.5 (one rotamer, N(Bn)***C***H_2), 28.5 (6C, both, C(***C***$H_3)_3$), 28.0 (one rotamer, NCH_2***C***H_2), 26.6 (one rotamer, NCH_2***C***H_2), 22.6 (2C, both, CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2980 (C-H), 1955 (C=C=C), 1785 (C=O), 1735 (C=O), 1647 (NC=O); MS (ES+) m/z (rel. intensity %) 407.21 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{28}N_2NaO_4$ $[M+Na]^+$ 407.1941, found 407.1937.

Preparation and characterisation of *rac*-*N*,*N*-dibenzyl-2-oxo-*N*-(penta-3,4-dien-1-yl)pyrrolidine-3-carboxamide (±)-165m



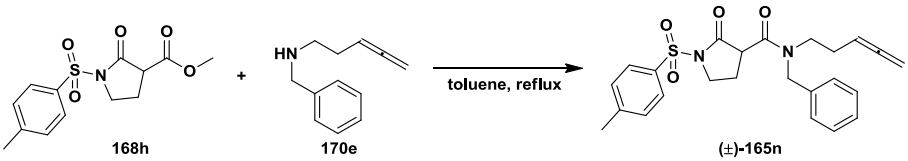
168g 170e (±)-165m

Synthesised from methyl 1-benzyl-2-oxopyrrolidine-3-carboxylate **168g** (466 mg, 2.0 mmol) and amine **170e** (520 mg, 3.0 mmol) according to general procedure C. Compound **165m** was isolated after flash column chromatography (PE/EA = 1:2) on silica gel as a yellow oil (224 mg, 30% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.21-7.39 (m, both, 20H, 20 × Ar***H***), 5.43 (d, one rotamer, 1H, *J* = 17.8 Hz, C***H***$_A$$H_BC_6H_5$), 5.04-5.14 (m, both, 2H, C***H***=C=CH_2), 4.98 (d, one rotamer, 1H, *J* = 15.3 Hz, C***H***$_A$$H_BC_6H_5$), 4.66-4.73 (m, both, 4H, CH=C=C***H*****$_2$**), 4.38-4.56 (m, both, 6H, C***H*****$_2$**C_6H_5), 3.99-4.07 (m, one rotamer, 1H, N(Bn)C***H***$_A$$H_B$), 3.82-3.93 (m, both, 2H, C***H*** and N(Bn)C***H***$_A$$H_B$), 3.70 (dd, one rotamer, 1H, *J* = 9.2 Hz, *J* = 5.7 Hz, C***H***), 3.42-3.55 (m, one rotamer, 2H, NC***H*****$_2$**CH_2), 3.23-3.37 (m, both, 2H, N(Bn)CH_A***H*****$_B$**), 3.13-3.25 (m, both, 2H, NC***H*****$_2$**CH_2), 2.57-2.66 (m, both, 2H, C***H***$_A$$H_B$CH=C=$CH_2$), 2.26-2.35 (m, both, 4H, CH_A***H***$_B$CH=C=CH_2 and CHC***H***$_A$$H_B$), 2.11-2.21

(m, one rotamer, 1H, $CHCH_A\boldsymbol{H_B}$), 1.96-2.06 (m, one rotamer, 1H, $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (2C, both, CH=***C***=CH_2), 171.0 (one rotamer, N***C***=O), 170.9 (one rotamer, N***C***=O), 169.9 (one rotamer, N***C***=O), 169.8 (one rotamer, N***C***=O), 137.2 (***C***, one rotamer, Ar), 137.1 (***C***, one rotamer, Ar), 136.1 (***C***, one rotamer, Ar), 136.0 (***C***, one rotamer, Ar), 128.9 (2***C***H, both, Ar), 128.7 (4***C***H, both, Ar), 128.6 (2***C***H, both, Ar), 128.0 (***C***H, one rotamer, Ar), 127.9 (***C***H, one rotamer, Ar), 127.6 (2***C***H, both, Ar), 127.5 (2***C***H, both, Ar), 127.4 (2***C***H, both, Ar), 127.1 (2***C***H, both, Ar), 126.1 (2***C***H, both, Ar), 86.8 (one rotamer, ***C***H=C=CH_2), 86.2 (one rotamer, ***C***H=C=CH_2), 75.7 (one rotamer, CH=C=***C***H_2), 75.3 (one rotamer, CH=C=***C***H_2), 51.3 (one rotamer, ***C***$H_2C_6H_5$), 48.9 (one rotamer, ***C***$H_2C_6H_5$), 47.0 (one rotamer, ***C***$H_2C_6H_5$), 46.9 (one rotamer, ***C***$H_2C_6H_5$), 46.8 (one rotamer, N(Bn)***C***H_2), 46.7 (one rotamer, N(Bn)***C***H_2), 45.9 (one rotamer, N***C***H_2CH_2), 45.6 (one rotamer, N***C***H_2CH_2), 45.5 (one rotamer, ***C***HCH_2), 45.3 (one rotamer, ***C***HCH_2), 27.5 (one rotamer, $NCH_2\boldsymbol{C}H_2$), 26.4 (one rotamer, $NCH_2\boldsymbol{C}H_2$), 22.5 (one rotamer, CH***C***H_2), 22.2 (one rotamer, CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2925 (C-H), 1955 (C=C=C), 1686 (C=O), 1644 (C=O); **MS** (ES+) m/z (rel. intensity %) 397.20 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{26}N_2NaO_2$ $[M+Na]^+$ 397.1886, found 397.1886.

Preparation and characterisation of *rac*-*N*-benzyl-1-[(4-methylphenyl)sulfonyl]-2-oxo-*N*-(penta-3,4-dien-1-yl)pyrrolidine-3-carboxamide (±)-165n

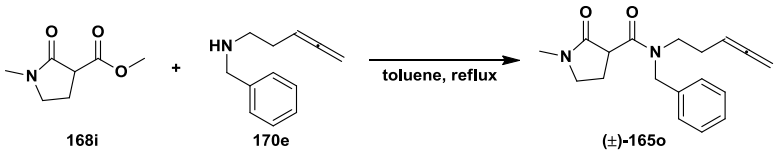


168h 170e (±)-165n

Synthesised from methyl 1-[(4-methylphenyl)sulfonyl]-2-oxopyrrolidine-3-carboxylate **168h** (445 mg, 1.5 mmol) and amine **170e** (415 mg, 2.4 mmol) according to general procedure C. Compound **165n** was isolated after flash column chromatography (PE/EA = 2:1) on silica gel as a yellow oil (269 mg, 41% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.90 (t, both, 4H, *J* = 8.4 Hz, 4 × Ar***H***), 7.24-7.36 (m, both, 10H, 10 × Ar***H***), 7.07-7.12 (m, both, 4H, 4 × Ar***H***), 5.09 (d, one rotamer, 1H, *J* = 17.7 Hz, C***H***$_A$H$_B$C$_6$H$_5$), 4.93-5.04 (m, both, 2H, C***H***=C=CH$_2$), 4.88 (d, one rotamer, 1H, *J* = 15.3 Hz, C***H***$_A$H$_B$C$_6$H$_5$), 4.63-4.69 (m, both, 4H, CH=C=C***H***$_2$), 4.40 (d, one rotamer, 1H, *J* = 17.8 Hz, CH$_A$***H***$_B$C$_6$H$_5$), 4.26 (d, one rotamer, 1H, *J* = 15.3 Hz, CH$_A$***H***$_B$C$_6$H$_5$), 3.64-4.13 (m, both, 8H, N(Bn)C***H***$_2$ and TsNC***H***$_2$), 3.21 (m, one rotamer, 1H, C***H***), 2.94-3.08 (m, one rotamer, 1H, C***H***), 2.62 (m, both, 2H, CHC***H***$_A$H$_B$), 2.43 (s, both, 6H, C***H***$_3$), 2.04-2.26 (m, both, 6H, CHCH$_A$***H***$_B$ and C***H***$_2$CH=C=CH$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (2C, both, CH=***C***=CH$_2$), 169.9 (one rotamer, TsN***C***=O), 169.8 (one rotamer, TsN***C***=O), 167.5 (one rotamer, N***C***=O), 167.4 (one rotamer, N***C***=O), 145.3 (***C***, one rotamer, Ar), 145.2 (***C***, one rotamer, Ar), 136.7 (***C***, one rotamer, Ar), 136.4 (***C***, one rotamer, Ar), 134.8 (***C***, one rotamer, Ar), 134.7 (***C***, one rotamer, Ar), 129.7 (2***C***H, both, Ar), 129.0 (2***C***H, both, Ar), 128.6 (2***C***H, both, Ar), 128.0 (4***C***H, both, Ar), 127.7 (2***C***H, both, Ar), 127.3 (2***C***H, both, Ar), 127.2 (2***C***H, both, Ar), 126.0 (2***C***H, both, Ar), 86.6 (one rotamer, ***C***H=C=CH$_2$), 85.9 (one rotamer, ***C***H=C=CH$_2$), 75.9 (one rotamer, CH=C=***C***H$_2$), 75.3 (one rotamer, CH=C=***C***H$_2$), 51.2 (one rotamer, ***C***H$_2$C$_6$H$_5$), 48.7 (one rotamer, ***C***H$_2$C$_6$H$_5$), 46.7 (one rotamer, ***C***H), 46.6 (one rotamer, ***C***H), 46.5 (one rotamer, N(Bn)***C***H$_2$), 46.4 (one rotamer, N(Bn)***C***H$_2$), 46.3 (2C, both, N(Ts)***C***H$_2$), 27.2 (one rotamer, ***C***H$_2$CH=C=CH$_2$), 26.2 (one rotamer, ***C***H$_2$CH=C=CH$_2$), 22.6 (one rotamer, CH***C***H$_2$), 22.3 (one rotamer, CH***C***H$_2$), 21.7 (2C, both, ***C***H$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2923 (C-H), 1955 (C=C=C), 1732 (C=O), 1645 (NC=O); **MS** (ES+) m/z (rel. intensity %) 461.17 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{26}N_2NaO_4S$ [M+Na]$^+$ 461.1505, found 461.1498.

Preparation and characterisation of *rac*-*N*-benzyl-1-methyl-2-oxo-*N*-(penta-3,4-dien-1-yl)pyrrolidine-3-carboxamide (±)-165o



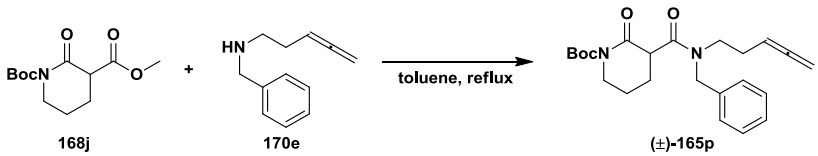
168i 170e (±)-165o

Synthesised from methyl 1-methyl-2-oxopyrrolidine-3-carboxylate **168i** (188 mg, 1.20 mmol) and amine **170e** (364 mg, 2.10 mmol) according to general procedure C. Compound **165o** was isolated after flash column chromatography (PE/EA = 1:3) on silica gel as a yellow oil (240 mg, 68% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.20-7.38 (m, both, 10H, 10 × Ar***H***), 5.39 (d, one rotamer, 1H, *J* = 17.8 Hz, C***H*****$_A$**$H_BC_6H_5$), 5.02-5.12 (m, both, 2H, C***H***=C=CH_2), 4.94 (d, 1H, one rotamer, *J* = 15.3 Hz, C***H*****$_A$**$H_BC_6H_5$), 4.65-4.71 (m, both, 4H, CH=C=C***H*****$_2$**), 4.50 (d, one rotamer, 1H, *J* = 17.8 Hz, CH_A***H*****$_B$**C_6H_5), 4.40 (d, one rotamer, 1H, *J* = 15.3 Hz, CH_A***H*****$_B$**C_6H_5), 3.94-4.02 (m, one rotamer, 1H, NC***H*****$_A$**H_B), 3.78-3.87 (m, both, 2H, NC***H*****$_A$**H_B and C***H***CH_2), 3.52-3.64 (m, both, 3H, NC***H*****$_2$** and C***H***CH_2), 3.25-3.40 (m, both, 3H, NC***H*****$_2$**), 3.14 (td, one rotamer, 1H, *J* = 13.4 Hz, *J* = 7.6 Hz, NCH_A***H*****$_B$**), 2.89 (s, one rotamer, 3H, NC***H*****$_3$**), 2.85 (s, one rotamer, 3H, NC***H*****$_3$**), 2.59-2.69 (m, both, 2H, CHC***H*****$_2$**), 2.15-2.34 (m, both, 4H, C***H*****$_2$**CH=C=CH_2), 1.98-2.07 (m, both, 2H, CHC***H*****$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (2C, both, CH=***C***=CH_2), 170.9 (one rotamer, N***C***=O), 170.8 (one rotamer, N***C***=O), 170.0 (one rotamer, N***C***=O), 169.9 (one rotamer, N***C***=O), 137.2 (2***C***, both, Ar), 128.9 (2***C***H, both, Ar), 128.6 (2***C***H, both, Ar), 128.4 (2***C***H, both, Ar), 127.1 (2***C***H, both, Ar), 126.1 (2***C***H, both, Ar), 86.8 (one rotamer, ***C***H=C=CH_2), 86.2 (one rotamer, ***C***H=C=CH_2), 75.7 (one rotamer, CH=C=***C***H_2), 75.2 (one rotamer, CH=C=***C***H_2), 51.3 (one rotamer, ***C***$H_2C_6H_5$), 48.9 (one rotamer, ***C***$H_2C_6H_5$), 48.2 (one rotamer, N(CH_3)***C***H_2), 48.1 (one rotamer, N(CH_3)***C***H_2), 46.9 (one rotamer, N***C***H_2CH_2), 46.8 (one rotamer, N***C***H_2CH_2), 45.3 (one rotamer, ***C***HCH_2), 45.0 (one rotamer, ***C***HCH_2), 30.0 (one rotamer, N***C***H_3), 29.9 (one rotamer, N***C***H_3), 27.4 (one

rotamer, ***C***H_2CH=C=CH_2), 26.3 (one rotamer, ***C***H_2CH=C=CH_2), 22.4 (one rotamer, CH***C***H_2), 22.1 (one rotamer, CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2926 (C-H), 1955 (C=C=C), 1686 (C=O), 1643 (NC=O); **MS** (ES+) m/z (rel. intensity %) 321.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{22}N_2NaO_2$ $[M+Na]^+$ 321.1573, found 321.1582.

Preparation and characterisation of *rac*-*tert*-3-[benzyl(penta-3,4-dien-1-yl)carbamoyl]-2-oxopiperidine-1-carboxylate (±)-165p



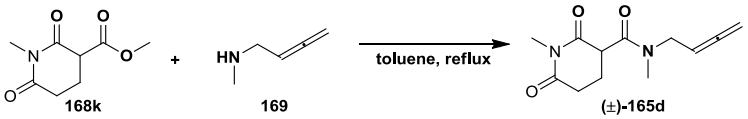
168j 170e (±)-165p

Synthesised from methyl 1-*tert*-butyl 3-methyl 2-oxopiperidine-1,3-dicarboxylate **168j** (314 mg, 1.2 mmol) and amine **170e** (381 mg, 2.2 mmol) according to general procedure C. Compound **165p** was isolated after flash column chromatography (PE/EA = 1:1) on silica gel as a yellow oil (224 mg, 47% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.19-7.38 (m, both, 10H, 10 × Ar***H***), 5.06-5.16 (m, one rotamer, 1H, C***H***=C=CH_2), 5.02-5.05 (m, one rotamer, 1H, C***H***=C=CH_2), 4.97 (d, one rotamer, 1H, *J* = 17.7 Hz, C***H*****$_A$**$H_B$$C_6H_5$), 4.91 (d, one rotamer, 1H, *J* = 15.3 Hz, C***H*****$_A$**$H_B$$C_6H_5$), 4.64-4.72 (m, both, 4H, CH=C=C***H*****$_2$**), 4.49 (d, one rotamer, 1H, *J* = 17.7 Hz, CH_A***H*****$_B$**C_6H_5), 4.42 (d, one rotamer, 1H, *J* = 15.3 Hz, CH_A***H*****$_B$**C_6H_5), 3.84 (dd, one rotamer, 1H, *J* = 9.4 Hz, *J* = 6.9 Hz, C***H***), 3.60-3.78 (m, both, 8H, C***H*** and NC***H*****$_2$**), 3.19-3.30 (m, one rotamer, 1H, NC***H*****$_A$**H_B), 2.20-2.34 (m, both, 6H, C***H*****$_A$**H_BCH=C=CH_2 and CHC***H*****$_2$**), 2.08-2.18 (m, one rotamer, 1H, CH_A***H*****$_B$**CH=C=CH_2), 1.98-2.06 (m, both, 2H, CH_A***H*****$_B$**CH=C=CH_2 and $CHCH_2C$***H*****$_A$**H_B), 1.78-1.88 (m, both, 2H, $CHCH_2C$***H*****$_A$**H_B and $CHCH_2CH_A$***H*****$_B$**), 1.61-1.71 (m, one rotamer, 1H, $CHCH_2CH_A$***H*****$_B$**), 1.53 (s, one rotamer, 9H, C(C***H*****$_3$**$)_3$), 1.51 (s, one rotamer, 9H, C(C***H*****$_3$**$)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (one rotamer, CH=***C***=CH_2), 208.8 (one rotamer, CH=***C***=CH_2), 170.5 (one rotamer, CH***C***(O)N), 170.3 (one rotamer, CH***C***(O)N), 168.2 (2C, both, BocN***C***(O)), 152.3 (one rotamer,

N***C***(O)C(CH_3)$_3$), 152.2 (one rotamer, N***C***(O)C(CH_3)$_3$), 137.1 (***C***, one rotamer, Ar), 137.0 (***C***, one rotamer, Ar), 128.9 (2***C***H, both, Ar), 128.6 (2***C***H, both, Ar), 127.5 (2***C***H, both, Ar), 127.1 (2***C***H, both, Ar), 126.1 (2***C***H, both, Ar), 86.9 (one rotamer, ***C***H=C=CH_2), 86.2 (one rotamer, ***C***H=C=CH_2), 83.2 (2C, both, NC(O)***C***(CH_3)$_3$), 75.8 (one rotamer, CH=C=***C***H_2), 75.2 (one rotamer, CH=C=***C***H_2), 51.9 (one rotamer, ***C***$H_2C_6H_5$), 48.8 (one rotamer, ***C***$H_2C_6H_5$), 48.1 (one rotamer, ***C***HCH_2), 47.9 (one rotamer, ***C***HCH_2), 47.1 (one rotamer, N***C***H_2), 46.7 (one rotamer, N***C***H_2), 46.6 (one rotamer, N***C***H_2), 46.5 (one rotamer, N***C***H_2), 27.9 (6C, both, NC(O)C(***C***H_3)$_3$), 26.5 (one rotamer, ***C***H_2CH=C=CH_2), 26.2 (one rotamer, ***C***H_2CH=C=CH_2), 25.3 (one rotamer, CH***C***H_2), 24.9 (one rotamer, CH***C***H_2), 21.7 (one rotamer, $CHCH_2$***C***H_2), 21.5 (one rotamer, $CHCH_2$***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2979 (C-H), 1955 (C=C=C), 1767 (C=O), 1716 (C=O), 1644 (NC=O); **MS** (ES+) m/z (rel. intensity %) 421.23 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{23}H_{30}N_2NaO_4$ $[M+Na]^+$ 421.2098, found 421.2096.

Preparation and characterisation of *rac*-*N*-(buta-2,3-dien-1-yl)-*N*,1-dimethyl-2,6-dioxopiperidine-3-carboxamide (±)-165d

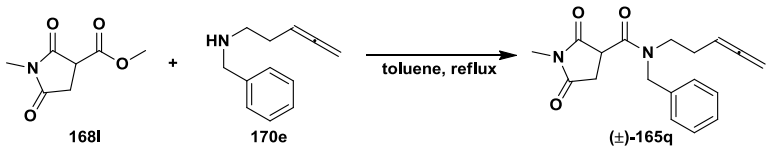


Synthesised from methyl 1-methyl-2,6-dioxopiperidine-3-carboxylate **168k** (185 mg, 1.0 mmol) and *N*-methylbuta-2,3-dien-1-amine **169** (149 mg, 1.8 mmol) according to general procedure C. Compound **165d** was obtained after flash column chromatography (PE/EA = 2:1) on silica gel as a yellow oil (71 mg, 30% yield).

Mp 43-45 °C; two rotamers in a 1.2:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.12-5.18 (m, minor, 1H, C***H***=C=CH_2), 5.03-5.10 (m, major, 1H, C***H***=C=CH_2), 4.78-4.91 (m, minor, 2H, CH=C=C***H$_2$***), 4.71-4.78 (m, major, 2H, CH=C=C***H$_2$***), 4.10-4.18 (m, minor, 1H, N(CH_3)C***H$_A$***H_B), 4.06 (tdd, major, 1H, *J* = 14.6 Hz, *J* = 6.1 Hz, *J* = 2.9 Hz, N(CH_3)C***H$_A$***H_B), 3.78-3.90 (m, both, 4H, N(CH_3)CH_A***H$_B$*** and C***H***), 3.09 (s, both, 6H, CON(C***H$_3$***)C(O)), 2.93 (s, both, 6H, C(O)N(C***H$_3$***)CH_2), 2.85-2.97 (m, both, 2H, C***H$_A$***H_BC(O)), 2.50-2.60 (m, both, 2H,

$CH_A\boldsymbol{H_B}C(O)$), 2.17-2.29 (m, both, 2H, $C\boldsymbol{H_A}H_BCH_2C(O)$), 1.94-2.06 (m, both, 2H, $CH_A\boldsymbol{H_B}CH_2C(O)$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 209.1 (major, CH=$\boldsymbol{C}$=CH_2), 208.2 (minor, CH=$\boldsymbol{C}$=CH_2), 172.1 (major, $CH_2C(O)N(CH_3)\boldsymbol{C}(O)$), 172.0 (minor, $CH_2C(O)N(CH_3)\boldsymbol{C}(O)$), 170.1 (major, $CH_2\boldsymbol{C}(O)N(CH_3)C(O)$), 169.9 (minor, $CH_2\boldsymbol{C}(O)N(CH_3)C(O)$), 168.5 (major, $CH\boldsymbol{C}(O)N(CH_3)$), 168.3 (minor, $CH\boldsymbol{C}(O)N(CH_3)$), 86.9 (minor, $\boldsymbol{C}H=C=CH_2$), 85.9 (major, $\boldsymbol{C}H=C=CH_2$), 78.3 (minor, CH=C=$\boldsymbol{C}H_2$), 76.7 (major, CH=C=$\boldsymbol{C}H_2$), 48.6 (minor, $\boldsymbol{C}$H), 46.6 (major, $\boldsymbol{C}$H), 45.7 (major, $C(O)N(CH_3)\boldsymbol{C}H_2$), 45.4 (minor, $C(O)N(CH_3)\boldsymbol{C}H_2$), 35.6 (2C, both, $C(O)N(\boldsymbol{C}H_3)C(O)$), 34.3 (major, $C(O)N(\boldsymbol{C}H_3)CH_2$), 30.3 (minor, $C(O)N(\boldsymbol{C}H_3)CH_2$), 27.5 (2C, both, $\boldsymbol{C}H_2C(O)$), 20.6 (2C, both, $\boldsymbol{C}H_2CH_2C(O)$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2921 (C-H), 1955 (C=C=C), 1671 (C=O), 1638 (NC=O); **MS** (ES+) m/z (rel. intensity %) 237.15 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{17}O_3N_2$ $[M+H]^+$ 237.1234, found 237.1239.

Preparation and characterisation of *rac*-*N*-benzyl-1-methyl-2,5-dioxo-*N*-(penta-3,4-dien-1-yl)pyrrolidine-3-carboxamide (±)-165q

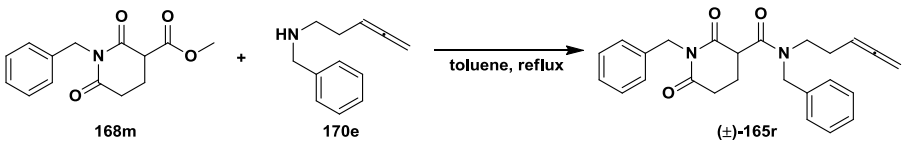


Synthesised from methyl 1-methyl-2,5-dioxopyrrolidine-3-carboxylate **168l** (274 mg, 1.6 mmol) and amine **170e** (415 mg, 2.4 mmol) according to general procedure C. Compound **165q** was isolated after flash column chromatography (PE/EA = 3:1) on silica gel as a yellow oil (219 mg, 44% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 (m, both, 10H, 10 × Ar$\boldsymbol{H}$), 5.28 (d, one rotamer, 1H, *J* = 17.7 Hz, $C\boldsymbol{H_A}H_BC_6H_5$), 5.05-5.10 (m, both, 2H, $C\boldsymbol{H}$=C=CH_2), 4.97 (d, one rotamer, 1H, *J* = 15.2 Hz, $C\boldsymbol{H_A}H_BC_6H_5$), 4.68-4.75 (m, both, 4H, CH=C=C$\boldsymbol{H_2}$), 4.59 (d, one rotamer, 1H, *J* = 17.8 Hz, $CH_A\boldsymbol{H_B}C_6H_5$), 4.39 (d, one rotamer, 1H, *J* = 15.2 Hz, $CH_A\boldsymbol{H_B}C_6H_5$), 4.19 (dd, one rotamer, 1H, *J* = 8.9 Hz, *J* = 4.4 Hz, C$\boldsymbol{H}$), 3.96 (dd, one rotamer, 1H, *J* = 8.8 Hz, *J* = 4.2 Hz, C$\boldsymbol{H}$), 3.85-3.93 (m, both, 2H, $NC\boldsymbol{H_A}H_BCH_2$), 3.38-3.42 (m, one

rotamer, 1H, CHC$\boldsymbol{H_A}$H$_B$), 3.35-3.37 (m, one rotamr, 1H, CHC$\boldsymbol{H_A}$H$_B$), 3.17-3.24 (m, both, NCH$_A$$\boldsymbol{H_B}CH_2$), 3.03 (s, one rotamer, 3H, NC$\boldsymbol{H_3}$), 2.99 (s, one rotamer, 3H, NC$\boldsymbol{H_3}$), 2.82 (dd, one rotamer, 1H, *J* = 17.9 Hz, *J* = 8.9 Hz, CHCH$_A$$\boldsymbol{H_B}$), 2.63 (dd, one rotamer, 1H, *J* = 18.0 Hz, *J* = 8.9 Hz, CHCH$_A$$\boldsymbol{H_B}$), 2.27-2.34 (m, both, 4H, C$\boldsymbol{H_2}$CH=C=CH$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (2C, both, CH=$\boldsymbol{C}$=CH$_2$), 176.1 (one rotamer, N(CH$_3$)$\boldsymbol{C}$(O)CH$_2$), 176.0 (one rotamer, N(CH$_3$)$\boldsymbol{C}$(O)CH$_2$), 173.9 (2C, both, N(CH$_3$)$\boldsymbol{C}$(O)CH), 167.1 (one rotamer, N$\boldsymbol{C}$=O), 167.0 (one rotamer, N$\boldsymbol{C}$=O), 136.6 ($\boldsymbol{C}$, one rotamer, Ar), 136.3 ($\boldsymbol{C}$, one rotamer, Ar), 129.1 (2$\boldsymbol{C}$H, both, Ar), 128.7 (2$\boldsymbol{C}$H, both, Ar), 127.9 (2$\boldsymbol{C}$H, both, Ar), 127.5 (2$\boldsymbol{C}$H, both, Ar), 126.0 (2$\boldsymbol{C}$H, both, Ar), 86.5 (one rotamer, $\boldsymbol{C}$H=C=CH$_2$), 85.9 (one rotamer, $\boldsymbol{C}$H=C=CH$_2$), 76.0 (one rotamer, CH=C=$\boldsymbol{C}$H$_2$), 75.4 (one rotamer, CH=C=$\boldsymbol{C}$H$_2$), 51.7 (one rotamer, $\boldsymbol{C}$H$_2$C$_6$H$_5$), 49.3 (one rotamer, $\boldsymbol{C}$H$_2$C$_6$H$_5$), 47.3 (one rotamer, N$\boldsymbol{C}$H$_2$CH$_2$), 47.0 (one rotamer, N$\boldsymbol{C}$H$_2$CH$_2$), 43.9 (one rotamer, $\boldsymbol{C}$H), 43.5 (one rotamer, $\boldsymbol{C}$H), 32.8 (one rotamer, CH$\boldsymbol{C}$H$_2$), 32.5 (one rotamer, CH$\boldsymbol{C}$H$_2$), 27.3 (one rotamer, $\boldsymbol{C}$H$_2$CH=C=CH$_2$), 26.4 (one rotamer, $\boldsymbol{C}$H$_2$CH=C=CH$_2$), 25.4 (one rotamer, N$\boldsymbol{C}$H$_3$), 25.3 (one rotamer, N$\boldsymbol{C}$H$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2945 (C-H), 1955 (C=C=C), 1779 (C=O), 1703 (C=O), 1646 (C=O); **MS** (ES+) m/z (rel. intensity %) 335.16 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{20}N_2NaO_3$ [M+Na]$^+$ 335.1366, found 335.1355.

Preparation and characterisation of *rac*-*N*,1-dibenzyl-2,6-dioxo-*N*-(penta-3,4-dien-1-yl)piperidine-3-carboxamide (±)-165r



168m 170e (±)-165r

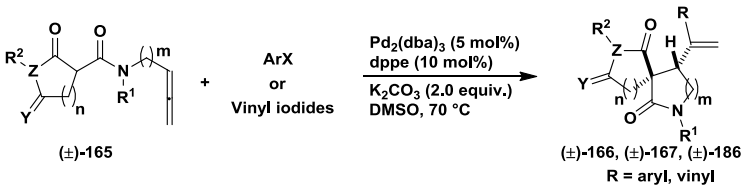
Synthesised from methyl 1-benzyl-2,6-dioxopiperidine-3-carboxylate **168m** (392 mg, 1.5 mmol) and amine **170e** (418 mg, 2.4 mmol) according to general procedure C. Compound **165r** was isolated after flash column chromatography (PE/EA = 3:1) as a yellow oil (337 mg, 56% yield).

Two rotamers in a 1:1 ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.20-7.41 (m, both, 20H, 20 × Ar***H***), 4.91-5.14 (m, both, 6H, C***H***=C=CH_2 and C(O)N(C***H*****$_2$**C_6H_5)C(O)), 4.79-4.84 (m, both, 2H, C***H*****$_A$**$H_B C_6H_5$), 4.68-4.74 (m, both, 4H, CH=C=C***H*****$_2$**), 4.57 (d, one rotamer, 1H, *J* = 9.7 Hz, CH_A***H*****$_B$**C_6H_5), 4.53 (d, one rotamer, 1H, *J* = 7.3 Hz, CH_A***H*****$_B$**C_6H_5), 3.97 (dd, one rotamer, 1H, *J* = 7.7 Hz, *J* = 5.6 Hz, C***H***), 3.79 (dd, one rotamer, 1H, *J* = 7.6 Hz, *J* = 5.6 Hz, C***H***), 3.64-3.71 (m, one rotamer, 1H, NC***H*****$_A$**$H_B CH_2$), 3.48-3.59 (m, one rotamer, 1H, NCH_A***H*****$_B$**CH_2), 3.27-3.41 (m, both, 2H, NC***H*****$_2$**CH_2), 2.97-3.11 (m, both, 2H, C(O)C***H*****$_A$**H_B), 2.66 (ddd, one rotamer, 1H, *J* = 17.4 Hz, *J* = 9.0 Hz, *J* = 5.2 Hz, C(O)CH_A***H*****$_B$**), 2.53 (ddd, one rotamer, 1H, *J* = 17.4 Hz, *J* = 8.9 Hz, *J* = 5.2 Hz, C(O)CH_A***H*****$_B$**), 2.23-2.41 (m, both, 6H, CHC***H*****$_A$**H_B and C***H*****$_2$**CH=C=CH_2), 2.12 (tdd, one rotamer, 1H, *J* = 10.9 Hz, *J* = 7.3 Hz, *J* = 5.4 Hz, $CHCH_A$***H*****$_B$**), 1.97 (tdd, one rotamer, 1H, *J* = 10.8 Hz, *J* = 7.4 Hz, *J* = 5.3 Hz, $CHCH_A$***H*****$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (one rotamer, CH=***C***=CH_2), 208.8 (one rotamer, CH=***C***=CH_2), 171.8 (one rotamer, N***C***(O)CH_2), 171.7 (one rotamer, N***C***(O)CH_2), 169.9 (2C, both, CH***C***(O)N), 169.1 (one rotamer, CON***C***(O)CH), 168.8 (one rotame, CON***C***(O)CH), 136.9 (***C***, one rotamer, Ar), 136.9 (***C***, one rotamer, Ar), 136.8 (***C***, one rotamer, Ar), 136.4 (***C***, one rotamer, Ar), 129.1 (2***C***H, both, Ar), 128.7 (2***C***H, both, Ar), 128.5 (4***C***H, both, Ar), 128.4 (2***C***H, both, Ar), 127.9 (2***C***H, both, Ar), 127.6 (2***C***H, both, Ar), 127.5 (2***C***H, both, Ar), 127.4 (2***C***H, both, Ar), 126.1 (2***C***H, both, Ar), 86.8 (one rotamer, ***C***H=C=CH_2), 85.9 (one rotamer, ***C***H=C=CH_2), 76.1 (one rotamer, CH=C=***C***H_2), 75.4 (one rotamer, CH=C=***C***H_2), 51.8 (one rotamer, ***C***$H_2C_6H_5$), 48.7 (one rotamer, ***C***$H_2C_6H_5$), 46.9 (one rotamer, N***C***H_2CH_2), 46.5 (one rotamer, N***C***H_2CH_2), 45.9 (one rotamer, ***C***HCH_2), 45.6 (one rotamer, ***C***HCH_2), 43.2 (one rotamer, CON(***C***$H_2C_6H_5$)C(O)), 43.0 (one rotamer, CON(***C***$H_2C_6H_5$)C(O)), 30.7 (one rotamer, C(O)***C***H_2), 30.5 (one rotamer, C(O)***C***H_2), 27.3 (one rotamer, NCH_2***C***H_2), 26.4 (one rotamer, NCH_2***C***H_2), 20.9 (one rotamer, CH***C***H_2), 20.7 (one rotamer, CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2946 (C-H), 1955 (C=C=C),

1726 (C=O), 1677 (C=O), 1641 (NC=O); **MS** (ES+) m/z (rel. intensity %) 425.21 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{25}H_{26}N_2NaO_3$ $[M+Na]^+$ 425.1836, found 425.1831.

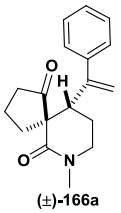
6.2.1.5 Synthesis of arylative and vinylative spiro-lactams 166, 167 and 186

General procedure D for the synthesis of arylative and vinylative spiro-lactams 166, 167 and 186 [94]



$Pd_2(dba)_3$ (5 mol%) and dppe (10 mol%) were stirred for 30 mins in DMSO at room temperature. Substrates **165a-165s** (1 equiv.), aromatic halides (1.5 equiv.) or vinyl iodides and K_2CO_3 (2 equiv.) were added subsequently. The reaction mixtures were stirred at 70 ºC in sealed vials and monitored by TLC. On completion, water was added, and the resultant mixtures were extracted with diethyl ether, dried (Na_2SO_4) and concentrated. The residues were purified by flash column chromatography on silica gel (petrol/ethyl acetate) to give products **166**, **167** and **186**. All the compounds are racemates.

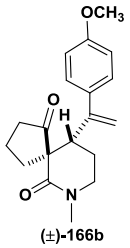
Preparation and characterisation of (±)-(5*R*,10*S*)-7-methyl-10-(1-phenylethenyl)-7-azaspiro[4.5]decane-1,6-dione (±)-166a



Synthesised from substrate **165a** (42.0 mg, 0.2 mmol) and iodobenzene (61.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166a** was obtained (single diastereoisomer, 33.0 mg, 58% yield) as a colourless oil after flash column chromatography on silica gel (PE/EA = 2:1). Analysis of the ^1H NMR spectrum of the crude reaction mixture showed a 17:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.19-7.21 (m, 5H, 5 × Ar***H***), 5.32 (s, 1H, C=C***H***$_A$H$_B$), 4.98 (s, 1H, C=CH$_A$***H***$_B$), 3.38-3.46 (m, 2H, C***H*** and NC***H***$_A$H$_B$), 3.30 (td, 1H, *J* = 12.2 Hz, *J* = 5.1 Hz, NCH$_A$***H***$_B$), 2.87 (s, 3H, NC***H***$_3$), 2.32 (ddd, *J* = 13.8 Hz, *J* = 8.0 Hz, *J* = 6.2 Hz, 1H, CC***H***$_A$H$_B$), 2.23-2.12 (m, 3H, CCH$_A$***H***$_B$ and C(O)C***H***$_A$H$_B$ and CHC***H***$_A$H$_B$), 1.97-2.03 (m, 1H, C(O)CH$_2$C***H***$_A$H$_B$), 1.75-1.83 (m, 1H, CHCH$_A$***H***$_B$), 1.63-1.72 (m, 1H, C(O)CH$_2$CH$_A$***H***$_B$), 1.49-1.58 (m, 1H, C(O)CH$_A$***H***$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.0 (***C***=O), 171.0 (N***C***=O), 148.7 (***C***=CH$_2$), 141.0 (***C***, Ar), 128.2 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.5 (***C***H, Ar), 115.9 (C=***C***H$_2$), 59.3 (C(O)***C***C(O)N), 48.0 (N***C***H$_2$), 42.5 (***C***H), 38.5 (***C***H$_2$C(O)), 35.0 (N***C***H$_3$), 31.4 (C***C***H$_2$), 24.5 (CH***C***H$_2$), 20.0 (C(O)CH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2951 (C-H), 1742 (C=O), 1630 (NC=O); **MS** (ES+) m/z (rel. intensity %) 306.17 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{21}NNaO_2$ $[M+Na]^+$ 306.1465, found 306.1470.

Preparation and characterisation of (±)-(5*R*,10*S*)-10-[1-(4-methoxyphenyl)ethenyl]-7-methyl-7-azaspiro[4.5]decane-1,6-dione (±)-166b



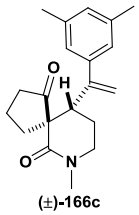
(±)-166b

Synthesised from substrate **165a** (42.0 mg, 0.2 mmol) and 1-iodo-4-methoxybenzene (72.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166b** was obtained (single diastereoisomer, 47.0 mg, 79% yield) as a colourless oil after flash column chromatography (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 18:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18-7.22 (m, 2H, 2 × Ar***H***), 6.78-6.82 (m, 2H, 2 × Ar***H***), 5.31 (s, 1H, C=C***H***$_A$H$_B$), 4.98 (s, 1H, C=CH$_A$***H***$_B$), 3.79 (s, 3H, OC***H***$_3$), 3.46-3.50 (m, 2H, C***H***CH$_2$ and NC***H***$_A$H$_B$), 3.35 (ddd, 1H, *J* = 12.2 Hz, *J* = 5.3 Hz, *J* = 4.3 Hz, NCH$_A$***H***$_B$), 2.93 (s, 3H, NC***H***$_3$), 2.33 (ddd, 1H, *J* = 13.5 Hz, *J* = 8.1 Hz, *J* = 6.2 Hz, CC***H***$_A$H$_B$), 2.16-2.27 (m, 3H,

CCH_AH_B and $C(O)CH_AH_B$ and $CHCH_AH_B$), 2.05-2.12 (m, 1H, $C(O)CH_2CH_AH_B$), 1.82-1.91 (m, 1H, $CHCH_AH_B$), 1.67-1.78 (m, 1H, $C(O)CH_2CH_AH_B$), 1.56 (ddd, 1H, *J* = 18.1 Hz, *J* = 9.0 Hz, *J* = 6.8 Hz, $C(O)CH_AH_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.4 (***C***=O), 171.2 (N***C***=O), 159.4 (***C***, Ar), 148.1 (***C***=CH_2), 133.1 (***C***, Ar), 128.7 (2***C***H, Ar), 114.7 (C=***C***H_2), 113.4 (2***C***H, Ar), 59.4 (C(O)***C***C(O)N), 55.2 (O***C***H_3), 48.2 (N***C***H_2), 42.5 (***C***HCH_2), 38.6 (***C***$H_2C(O)$), 34.9 (N***C***H_3), 31.4 (C***C***H_2), 24.7 (CH***C***H_2), 20.0 ($C(O)CH_2$***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2953 (C-H), 1741(C=O), 1628 (NC=O), 1511 (C=C); **MS** (ES+) m/z (rel. intensity %) 336.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{19}H_{23}NNaO_3$ $[M+Na]^+$ 336.1570, found 336.1572.

Preparation and characterisation of (±)-(5*R*,10*S*)-10-[1-(3,5-dimethylphenyl)ethenyl]-7-methyl-7-azaspiro[4.5]decane-1,6-dione (±)-166c



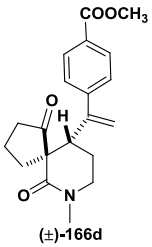
(±)-166c

Synthesised from substrate **165a** (42.0 mg, 0.2 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166c** was obtained (single diastereoisomer, 41.0 mg, 66% yield) as a colourless oil after flash column chromatography (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 15:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.92 (m, 1H, Ar***H***), 6.88 (d, 2H, *J* = 0.6 Hz, 2 × Ar***H***), 5.37 (s, 1H, C=C***H***$_A$$H_B$), 4.98 (s, 1H, C=$CH_A$***H***$_B$), 3.42-3.50 (m, 2H, C***H*** and NC***H***$_A$$H_B$), 3.37 (td, 1H, *J* = 12.2 Hz, *J* = 5.3 Hz, NCH_A***H***$_B$), 2.94 (s, 3H, NC***H***$_3$), 2.39-2.45 (m, 1H, CC***H***$_A$$H_B$), 2.30 (s, 6H, 2 × C***H***$_3$), 2.08-2.28 (m, 4H, CCH_A***H***$_B$ and COC***H***$_A$$H_B$ and CHC***H***$_A$$H_B$ and $C(O)CH_2$C***H***$_A$$H_B$), 1.70-1.84 (m, 3H, $C(O)CH_2CH_A$***H***$_B$ and $C(O)CH_A$***H***$_B$ and $CHCH_A$***H***$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.9 (***C***=O), 170.9 (N***C***=O), 148.6 (***C***=CH_2), 141.2 (***C***, Ar), 137.6 (***C***, Ar), 129.6 (***C***, Ar), 125.2 (3***C***H, Ar), 115.3 (C=***C***H_2), 59.9 (C(O)***C***C(O)N), 47.9

(N***C***H_2), 42.5 (***C***H), 38.5 (***C***H_2C(O)), 35.0 (N***C***H_3), 31.6 (C***C***H_2), 24.2 (CH***C***H_2), 21.3 (2C, 2 × ***C***H_3), 19.0 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2948 (C-H), 1742 (C=O), 1632 (NC=O), 1599 (C=C); **MS** (ES+) m/z (rel. intensity %) 334.20 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{20}H_{25}NNaO_2$ $[M+Na]^+$ 334.1778, found 334.1776.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(7-methyl-1,6-dioxo-7-azaspiro[4.5]dec-10-yl) ethenyl]benzoate (±)-166d



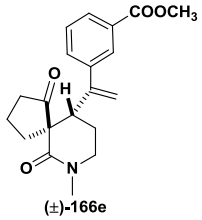
(±)-166d

Synthesised from substrate **165a** (42.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166d** was obtained (single diastereoisomer, 57.0 mg, 83% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 22:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.94-4.97 (m, 2H, 2 × Ar***H***), 7.33-7.36 (m, 2H, 2 × Ar***H***), 5.46 (s, 1H, C=C***H***$_A$H$_B$), 5.15 (s, 1H, C=CH$_A$***H***$_B$), 3.90 (s, 3H, OC***H***$_3$), 3.46-3.55 (m, 2H, C***H*** and NC***H***$_A$H$_B$), 3.37 (td, 1H, *J* = 12.2 Hz, *J* = 4.9 Hz, NCH$_A$***H***$_B$), 2.93 (s, 3H, NC***H***$_3$), 2.37 (ddd, 1H, *J* = 13.5 Hz, *J* = 7.6 Hz, *J* = 6.1 Hz, CC***H***$_A$H$_B$), 2.15-2.30 (m, 3H, CCH$_A$***H***$_B$ and C(O)C***H***$_A$H$_B$ and CHC***H***$_A$H$_B$), 2.05-2.14 (m, 1H, C(O)CH_2C***H***$_A$H$_B$), 1.83-1.93 (m, 1H, CHCH$_A$***H***$_B$), 1.69-1.79 (m, 1H, C(O)CH_2CH$_A$***H***$_B$), 1.61 (ddd, 1H, *J* = 17.9 Hz, *J* = 8.7 Hz, *J* = 6.9 Hz, C(O)CH$_A$***H***$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.8 (***C***=O), 170.8 (N***C***=O), 166.7 (***C***(O)OCH_3), 148.0 (***C***=CH_2), 145.6 (***C***, Ar), 129.6 (2***C***H, Ar), 129.5 (***C***, Ar), 127.4 (2***C***H, Ar), 117.6 (C=***C***H_2), 59.2 (C(O)***C***C(O)N), 52.1 (O***C***H_3), 48.0 (N***C***H_2), 42.2 (***C***H), 38.7 (***C***H_2C(O)), 34.9 (N***C***H_3), 31.4 (C***C***H_2), 24.6 (CH***C***H_2), 19.9 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2951

(C-H), 1740 (C=O), 1719 (C=O), 1629 (NC=O); **MS** (ES+) m/z (rel. intensity %) 364.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{20}H_{23}NNaO_4$ $[M+Na]^+$ 364.1519, found 364.1517.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 3-[1-(7-methyl-1,6-dioxo-7-azaspiro[4.5]dec-10-yl)ethenyl]benzoate (±)-166e

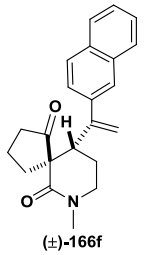


(±)-166e

Synthesised from substrate **165a** (42.0 mg, 0.2 mmol) and methyl 3-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166e** was obtained (single diastereoisomer, 59.0 mg, 86% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 13:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93-7.96 (m, 2H, 2 × Ar***H***), 7.45-7.49 (m, 1H, Ar***H***), 7.35-7.39 (m, 1H, Ar***H***), 5.44 (s, 1H, C=C***H***$_A$H$_B$), 5.11 (s, 1H, C=CH$_A$***H***$_B$), 3.92 (s, 3H, OC***H***$_3$), 3.46-3.54 (m, 2H, C***H*** and NC***H***$_A$H$_B$), 3.38 (td, 1H, *J* = 12.2 Hz, *J* = 5.0 Hz, NCH$_A$***H***$_B$), 2.93 (s, 3H, NC***H***$_3$), 2.39 (ddd, 1H, *J* = 13.7 Hz, *J* = 7.7 Hz, *J* = 6.2 Hz, CC***H***$_A$H$_B$), 2.18-2.24 (m, 3H, CCH$_A$***H***$_B$ and C(O)C***H***$_A$H$_B$ and CHC***H***$_A$H$_B$), 2.08-2.09 (m, 1H, C(O)CH$_2$C***H***$_A$H$_B$), 1.87 (ddd, 1H, *J* = 14.0 Hz, *J* = 9.8 Hz, *J* = 5.0 Hz, CHCH$_A$***H***$_B$), 1.71-1.79 (m, 1H, C(O)CH$_2$CH$_A$***H***$_B$), 1.59-1.67 (m, 1H, C(O)CH$_A$***H***$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) 217.8 (***C***=O), 170.8 (N***C***=O), 166.8 (***C***(O)OCH$_3$), 147.8 (***C***=CH$_2$), 141.5 (***C***, Ar), 131.8 (***C***, Ar), 130.1 (***C***H, Ar), 129.1 (***C***H, Ar), 128.4 (***C***H, Ar), 128.3 (***C***H, Ar), 117.1 (C=***C***H$_2$), 59.1 (C(O)***C***C(O)N), 52.2 (O***C***H$_3$), 48.0 (N***C***H$_2$), 42.3 (***C***H), 38.7 (***C***H$_2$C(O)), 34.9 (N***C***H$_3$), 31.4 (C***C***H$_2$), 24.4 (CH***C***H$_2$), 19.9 (C(O)CH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2951 (C-H), 1741 (C=O), 1722 (C=O), 1630 (NC=O); **MS** (ES+) m/z (rel. intensity %) 364.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{20}H_{23}NNaO_4$ $[M+Na]^+$ 364.1519, found 364.1520.

Preparation and characterisation of (±)-(5*R*,10*S*)-7-methyl-10-[1-(2-naphthyl)vinyl]-7-azaspiro[4.5]decane-1,6-dione (±)-166f

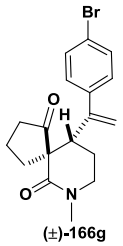


(±)-166f

Synthesised from substrate **165a** (42.0 mg, 0.2 mmol) and 2-bromonaphthalene (62.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166f** was obtained (single diastereoisomer, 41.0 mg, 61% yield) as a colourless oil after flash column chromatography (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 15:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76-7.82 (m, 3H, 3 × Ar***H***), 7.72 (s, 1H, Ar***H***), 7.42-7.48 (m, 3H, 3 × Ar***H***), 5.53 (s, 1H, C=C***H*****$_A$**H_B), 5.15 (s, 1H, C=CH_A***H*****$_B$**), 3.65 (dd, 1H, *J* = 9.9 Hz, *J* = 2.9 Hz, C***H***), 3.54 (ddd, 1H, *J* = 12.4 Hz, *J* = 9.3 Hz, *J* = 4.9 Hz, NC***H*****$_A$**H_B), 3.41 (td, 1H, *J* = 12.1 Hz, *J* = 5.1 Hz, NCH_A***H*****$_B$**), 2.96 (s, 3H, NC***H*****$_3$**), 2.44 (ddd, 1H, *J* = 13.8 Hz, *J* = 7.4 Hz, *J* = 6.6 Hz, CC***H*****$_A$**H_B), 2.27-2.36 (m, 2H, C(O)C***H*****$_A$**H_B and CHC***H*****$_A$**H_B), 2.17-2.26 (m, 1H), 2.05-2.15 (m, 1H, CCH_A***H*****$_B$**), 1.86-1.96 (m, 1H, CHCH_A***H*****$_B$**), 1.74-1.84 (m, 1H, C(O)CH_2C***H*****$_A$**H_B), 1.58 (ddd, 1H, *J* = 17.5 Hz, *J* = 8.6 Hz, *J* = 6.7 Hz, C(O)CH_A***H*****$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.9 (***C***=O), 171.0 (N***C***=O), 148.5 (***C***=CH_2), 138.3 (***C***, Ar), 133.0 (***C***, Ar), 132.9 (***C***, Ar), 128.1 (***C***H, Ar), 127.8 (***C***H, Ar), 127.6 (***C***H, Ar), 126.4 (***C***H, Ar), 126.3 (***C***H, Ar), 126.2 (***C***H, Ar), 125.4 (***C***H, Ar), 116.4 (C=***C***H_2), 59.3 (C(O)***C***C(O)N), 48.1 (N***C***H_2), 42.4 (***C***H), 38.5 (***C***H_2C(O)), 35.0 (N***C***H_3), 31.5 (C***C***H_2), 24.5 (CH***C***H_2), 20.0 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2927 (C-H), 1741 (C=O), 1627 (NC=O), 1510 (C=C); **MS** (ES+) m/z (rel. intensity %) 356.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{23}NNaO_2$ $[M+Na]^+$ 356.1621, found 356.1611.

Preparation and characterisation of (±)-(5*R*,10*S*)-10-[1-(4-bromophenyl)vinyl]-7-methyl-7-azaspiro[4.5]decane-1,6-dione (±)-166g

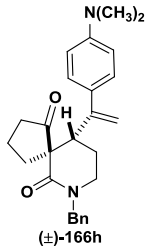


(±)-166g

Synthesised from substrate **165a** (42.0 mg, 0.2 mmol) and 1-bromo-4-iodobenzene (85.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166g** was obtained (single diastereoisomer, 44.0 mg, 61% yield) as a colourless oil after flash column chromatography (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 15:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32-7.36 (m, 2H, 2 × Ar***H***), 7.06-7.10 (m, 2H, 2 × Ar***H***), 5.31 (s, 1H, C=C***H*****$_A$**H_B), 5.01 (s, 1H, C=CH_A***H*****$_B$**), 3.38-3.46 (m, 2H, C***H*** and NC***H*****$_A$**H_B), 3.29 (ddd, 1H, *J* = 12.3 Hz, *J* = 5.4 Hz, *J* = 4.4 Hz, NCH_A***H*****$_B$**), 2.87 (s, 3H, NC***H*****$_3$**), 1.97-2.32 (m, 5H, CC***H*****$_2$** and C(O)C***H*****$_A$**H_B and CHC***H*****$_A$**H_B and C(O)CH_2C***H*****$_A$**H_B), 1.77-1.83 (m, 1H, CHCH_A***H*****$_B$**), 1.52-1.69 (m, 2H, C(O)CH_2CH_A***H*****$_B$** and C(O)CH_A***H*****$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.3 (***C***=O), 170.9 (N***C***=O), 147.7 (***C***=CH_2), 139.8 (***C***, Ar), 131.3 (2***C***H, Ar), 129.0 (2***C***H, Ar), 122.2 (***C***, Ar), 116.6 (C=***C***H_2), 59.3 (C(O)***C***C(O)N), 48.1 (N***C***H_2), 42.2 (***C***H), 38.7 (***C***H_2C(O)), 34.9 (N***C***H_3), 31.4 (C***C***H_2), 24.6 (CH***C***H_2), 20.0 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2922 (C-H), 1741 (C=O), 1629 (NC=O); **MS** (ES+) m/z (rel. intensity %) 384.09 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{20}BrNNaO_2$ $[M+Na]^+$ 384.0570, 386.0550, found 384.0583, 386.0565.

Preparation and characterisation of (±)-(5*R*,10*S*)-7-benzyl-10-{1-[4-(dimethylamino)phenyl]vinyl}-7-azaspiro[4.5]decane-1,6-dione (±)-166h

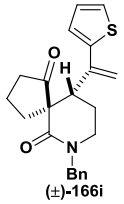


(±)-166h

Synthesised from substrate **165g** (57.0 mg, 0.2 mmol) and 4-bromo-*N*,*N*-dimethylaniline (60.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166h** was obtained (single diastereoisomer, 40.0 mg, 50% yield) as a colourless oil after flash column chromatography (PE:EA 4:1). Analysis of the ^{1}H NMR spectram of the crude reaction mixture showed a 33:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.26-7.37 (m, 5H, 5 × Ar***H***), 7.14-7.18 (m, 2H, 2 × Ar***H***), 6.61-6.64 (m, 2H, 2 × Ar***H***), 5.28 (s, 1H, C=C***H$_A$***H$_B$), 4.89 (s, 1H, C=CH$_A$***H$_B$***), 4.60 (s, 2H, C***H$_2$***C$_6$H$_5$), 3.51 (dd, 1H, *J* = 10.1 Hz, *J* = 2.6 Hz, C***H***), 3.30-3.41 (m, 2H, NC***H$_2$***CH$_2$), 2.97 (s, 6H, N(C***H$_3$***)$_2$), 2.43 (ddd, 1H, *J* = 14.1 Hz, *J* = 7.9 Hz, *J* = 6.5 Hz, CC***H$_A$***H$_B$), 2.08-2.39 (m, 4H, C(O)C***H$_A$***H$_B$ and CHC***H$_A$***H$_B$ and C(O)CH$_2$C***H$_A$***H$_B$ and CCH$_A$***H$_B$***), 1.71-1.84 (m, 2H, CHCH$_A$***H$_B$*** and C(O)CH$_2$CH$_A$***H$_B$***), 1.62 (ddd, 1H, *J* = 17.9 Hz, *J* = 8.9 Hz, *J* = 6.6 Hz, C(O)CH$_A$***H$_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.4 (***C***=O), 171.6 (N***C***=O), 150.2 (***C***, Ar), 148.2 (***C***=CH$_2$), 136.8 (***C***, Ar), 128.7 (2***C***H, Ar), 128.3 (2***C***H, Ar), 128.2 (***C***, Ar), 127.9 (2***C***H, Ar), 127.4 (***C***H, Ar), 112.9 (C=***C***H$_2$), 111.7 (2***C***H, Ar), 59.6 (C(O)***C***C(O)N), 50.3 (***C***H$_2$C$_6$H$_5$), 45.6 (N***C***H$_2$CH$_2$), 42.5 (***C***H), 40.3 (2C, N(***C***H$_3$)$_2$), 38.4 (***C***H$_2$C(O)), 31.7 (C***C***H$_2$), 24.7 (CH***C***H$_2$), 20.1 (C(O)CH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2949 (C-H), 1738 (C=O), 1673 (NC=O), 1626 (C=C); **MS** (ES+) m/z (rel. intensity %) 425.24 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{26}H_{30}N_2NaO_2$ [M+Na]$^+$ 425.2199, found 425.2197.

Preparation and characterisation of (±)-(5*R*,10*S*)-7-benzyl-10-[1-(thiophen-2-yl)ethenyl]-7-azaspiro[4.5]decane-1,6-dione (±)-166i

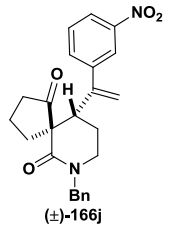


(±)-166i

Synthesised from substrate **165b** (57.0 mg, 0.2 mmol) and 2-iodothiophene (63.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166i** was obtained (single diastereoisomer, 56.0 mg, 77% yield) as a colourless oil after flash column chromatography (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 25:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.26-7.37 (m, 5H, 5 × Ar***H***), 7.17 (d, 1H, *J* = 4.9 Hz, thiophene-***H***), 6.94-6.98 (m, 2H, 2 × thiophene-***H***), 5.57 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 4.93 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.56-4.65 (m, 2H, C$\boldsymbol{H_2}C_6H_5$), 3.27-3.42 (m, 3H, NC$\boldsymbol{H_2}CH_2$ and C$\boldsymbol{H}CH_2$), 2.58 (td, 1H, *J* = 13.7 Hz, *J* = 7.6 Hz, CC$\boldsymbol{H_A}H_B$), 2.22-2.44 (m, 3H, C(O)C$\boldsymbol{H_A}H_B$ and CHC$\boldsymbol{H_A}H_B$ $CCH_A\boldsymbol{H_B}$), 2.08-2.17 (m, 1H, C(O)CH_2C$\boldsymbol{H_A}H_B$), 1.91-2.00 (m, 1H, C(O)$CH_A\boldsymbol{H_B}$), 1.74-1.86 (m, 2H, C(O)$CH_2CH_A\boldsymbol{H_B}$ and $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.0 (***C***=O), 170.8 (N***C***=O), 143.9 (***C***=CH_2), 140.9 (***C***, thiophene), 136.7 (***C***, Ar), 128.7 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.5 (***C***H, Ar), 127.4 (***C***H, thiophene), 125.2 (***C***H, thiophene), 124.9 (***C***H, thiophene), 114.3 (C=***C***H_2), 59.6 (C(O)***C***C(O)N), 50.5 (***C***$H_2C_6H_5$), 45.1 (N***C***H_2CH_2), 42.9 (***C***H), 38.6 (***C***H_2C(O)), 32.3 (C***C***H_2), 24.4 (CH***C***H_2), 20.3 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2955 (C-H), 1738 (C=O), 1628 (NC=O); **MS** (ES+) m/z (rel. intensity %) 388.16 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{23}NNaO_2S$ $[M+Na]^+$ 388.1342, found 388.1343.

Preparation and characterisation of (±)-(5*R*,10*S*)-7-benzyl-10-[1-(3-nitrophenyl)ethenyl]-7-azaspiro[4.5]decane-1,6-dione (±)-166j

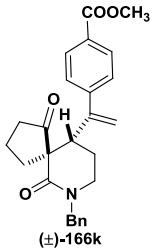


(±)-166j

Synthesised from substrate **165g** (57.0 mg, 0.2 mmol) and 1-iodo-3-nitrobenzene (75.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166j** was obtained (single diastereoisomer, 60.0 mg, 74% yield) as a yellow oil after flash column chromatography (PE/EA = 4:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 30:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.11-8.16 (m, 2H, 2 × Ar***H***), 7.61 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.46-7.51 (m, 1H, Ar***H***), 7.25-7.38 (m, 5H, 5 × Ar***H***), 5.49 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.20 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.67 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.49 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.55 (dd, 1H, *J* = 10.3 Hz, *J* = 2.5 Hz, C***H***), 3.42 (ddd, 1H, *J* = 12.6 Hz, *J* = 9.6 Hz, *J* = 4.8 Hz, NC$\boldsymbol{H_A}H_BCH_2$), 3.30-3.36 (m, 1H, NC$H_A\boldsymbol{H_B}CH_2$), 2.32-2.50 (m, 2H, CC$\boldsymbol{H_A}H_B$ and C(O)C$\boldsymbol{H_A}H_B$), 2.15-2.29 (m, 3H, CHC$\boldsymbol{H_A}H_B$ and CC$H_A\boldsymbol{H_B}$ and C(O)CH_2C$\boldsymbol{H_A}H_B$) 1.65-1.90 (m, 3H, C(O)C$H_A\boldsymbol{H_B}$ and C(O)CH_2C$H_A\boldsymbol{H_B}$ and CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.4 (***C***=O), 170.7 (N***C***=O), 148.1 (***C***=CH_2), 146.7 (***C***, Ar), 142.9 (***C***, Ar), 136.6 (***C***, Ar), 134.9 (***C***H, Ar), 133.3 (***C***H, Ar), 129.2 (***C***H, Ar), 128.7 (***C***H, Ar), 127.9 (***C***H, Ar), 127.5 (***C***H, Ar), 123.6 (***C***H, Ar), 122.8 (***C***H, Ar), 122.1 (***C***H, Ar), 118.6 (C=***C***H_2), 59.2 (C(O)***C***C(O)N), 50.3 (***C***$H_2C_6H_5$), 45.3 (N***C***H_2CH_2), 42.2 (***C***H), 38.9 (***C***H_2C(O)), 31.7 (C***C***H_2), 24.5 (CH***C***H_2), 19.9 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2925 (C-H), 1741 (C=O), 1628 (NC=O), 1528 (NO_2), 1349 (NO_2); **MS** (ES+) m/z (rel. intensity %) 427.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{24}N_2NaO_4$ $[M+Na]^+$ 427.1628, found 427.1628.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(7-benzyl-1,6-dioxo-7-azaspiro[4.5]dec-10-yl)vinyl]benzoate (±)-166k

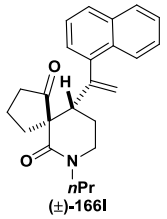


(±)-166k

Synthesised from substrate **165g** (45.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166k** was obtained (single diastereoisomer, 56.0 mg, 67% yield) as a white solid after flash column chromatography (PE/EA = 4:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 47:1 dr.

Mp 144.6-146.5 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.95-7.97 (m, 2H, 2 × Ar***H***), 7.35-7.39 (m, 4H, 4 × Ar***H***), 7.22-7.30 (m, 3H, 3 × Ar***H***), 5.45 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.13 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.63 (d, 1H, *J* = 14.7 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.54 (d, 1H, *J* = 14.7 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.91 (s, 3H, COOC$\boldsymbol{H_3}$), 3.54 (dd, 1H, *J* = 10.1 Hz, *J* = 2.5 Hz, C***H***), 3.40 (ddd, 1H, *J* = 12.4 Hz, *J* = 9.3 Hz, *J* = 4.8 Hz, NC$\boldsymbol{H_A}H_BCH_2$), 3.31 (td, 1H, *J* = 12.2 Hz, *J* = 5.1 Hz, NC$H_A\boldsymbol{H_B}CH_2$), 2.46 (ddd, 1H, *J* = 13.5 Hz, *J* = 7.7 Hz, *J* = 6.0 Hz, CC$\boldsymbol{H_A}H_B$), 2.12-2.32 (m, 4H, CC$H_A\boldsymbol{H_B}$ and CHC$\boldsymbol{H_A}H_B$ and C(O)C$\boldsymbol{H_A}H_B$ and C(O)CH_2C$\boldsymbol{H_A}H_B$), 1.63-1.82 (m, 3H, CHC$H_A\boldsymbol{H_B}$ and C(O)C$H_A\boldsymbol{H_B}$ and C(O)CH_2C$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.7 (***C***=O), 170.9 (N***C***=O), 166.7 (***C***(O)OCH_3), 147.9 (***C***=CH_2), 145.6 (***C***, Ar), 136.7 (***C***, Ar), 129.6 (***C***, Ar), 129.5 (2***C***H, Ar), 128.7 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.5 (***C***H, Ar), 127.4 (2***C***H, Ar), 117.6 (C=***C***H_2), 59.3 (C(O)***C***C(O)N), 52.1 (O***C***H_3), 50.3 (***C***$H_2C_6H_5$), 45.3 (N***C***H_2CH_2), 42.2 (***C***H), 38.6 (C(O)***C***H_2CH_2), 31.7 (CC$\boldsymbol{H_2}$), 24.5 (CH***C***H_2), 20.0 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2951 (C-H), 1741 (C=O), 1720 (C=O), 1628 (C=O); **MS** (ES+) m/z (rel. intensity %) 440.22 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{26}H_{27}NNaO_4$ $[M+Na]^+$ 440.1832, found 440.1826.

Preparation and characterisation of (±)-(5*R*,10*S*)-10-[1-(1-naphthyl)vinyl]-7-propyl-7-azaspiro[4.5]decane-1,6-dione (±)-166l

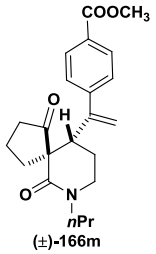


(±)-166l

Synthesised from substrate **165f** (45.0 mg, 0.2 mmol) and methyl 1-bromonaphthalene (62.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166l** was obtained (single diastereoisomer, 47.0 mg, 65% yield) as a colourless oil after flash column chromatography (PE/EA = 1:2). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 16:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95-7.99 (m, 1H, Ar***H***), 7.84-7.87 (m, 1H, Ar***H***), 7.79 (d, 1H, *J* = 8.3 Hz, Ar***H***), 7.47-7.52 (m, 2H, 2 × Ar***H***), 7.38-7.42 (m, 1H, Ar***H***), 7.22 (d, 1H, *J* = 7.0 Hz, Ar***H***), 5.43 (s, 1H, C=C***H$_A$***H$_B$), 5.38 (s, 1H, C=CH$_A$***H$_B$***), 3.39-3.51 (m, 3H, C***H*** and CHCH$_2$C***H$_2$***N), 3.24-3.35 (m, 2H, NC***H$_2$***CH$_2$CH$_3$), 2.49-2.63 (m, 2H, CC***H$_A$***H$_B$ and COC***H$_A$***H$_B$), 2.36-2.44 (m, 1H, CHC***H$_A$***H$_B$), 2.20-2.34 (m, 2H, CCH$_A$***H$_B$*** and C(O)CH$_2$C***H$_A$***H$_B$), 1.80-1.95 (m, 3H, C(O)CH$_A$***H$_B$*** and C(O)CH$_2$CH$_A$***H$_B$*** and CHCH$_A$***H$_B$***), 1.53-1.62 (m, 2H, C***H$_2$***CH$_3$), 0.91 (t, 3H, *J* = 7.4 Hz, C***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.1 (***C***=O), 170.0 (N***C***=O), 133.7 (***C***=CH$_2$), 131.3 (***C***, Ar), 128.7 (***C***, Ar), 128.5 (***C***, Ar), 128.2 (***C***H, Ar), 126.1 (***C***H, Ar), 125.9 (***C***H, Ar), 125.8 (***C***H, Ar), 125.5 (***C***H, Ar), 125.0 (***C***H, Ar), 124.9 (***C***H, Ar), 118.6 (C=***C***H$_2$), 59.2 (C(O)***C***C(O)N), 49.2 (N***C***H$_2$CH$_2$CH$_3$), 45.6 (N***C***H$_2$CH$_2$CH), 44.4 (***C***H), 38.1 (***C***H$_2$C(O)), 31.4 (***C***H$_2$CH), 23.4 (CH***C***H$_2$), 20.1 (***C***H$_2$CH$_3$), 19.6 (C(O)CH$_2$***C***H$_2$), 11.3 (CH$_2$***C***H$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2961 (C-H), 1741 (C=O), 1627 (C=C); **MS** (ES+) m/z (rel. intensity %) 384.22 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{27}NNaO_2$ [M+Na]$^+$ 384.1934, found 384.1937.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(1,6-dioxo-7-propyl-7-azaspiro[4.5]dec-10-yl)vinyl]benzoate (±)-166m

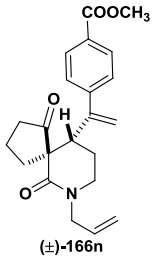


(±)-166m

Synthesised from substrate **165f** (47.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166m** was obtained (single diastereoisomer, 52.0 mg, 70% yield) as a colourless oil after flash column chromatography (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 19:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.94-7.96 (m, 2H, 2 × Ar***H***), 7.27-7.36 (m, 2H, 2 × Ar***H***), 5.46 (s, 1H, C=C***H***$_A$H$_B$), 5.15 (s, 1H, C=CH$_A$***H***$_B$), 3.90 (s, 3H, OC***H***$_3$), 3.44-3.52 (m, 2H, C***H*** and CHCH$_2$C***H***$_A$H$_B$), 3.38 (td, 1H, *J* = 12.3 Hz, *J* = 5.0 Hz, CHCH$_2$CH$_A$***H***$_B$), 3.29 (ddd, 2H, *J* = 8.2 Hz, *J* = 6.3 Hz, *J* = 1.9 Hz, NC***H***$_2$CH$_2$CH$_3$), 2.37 (ddd, 1H, *J* = 13.3 Hz, *J* = 7.7 Hz, *J* = 6.0 Hz, CC***H***$_A$H$_B$), 2.04-2.30 (m, 4H, C(O)C***H***$_A$H$_B$ and CHC***H***$_A$H$_B$ and CCH$_A$***H***$_B$ and C(O)CH$_2$C***H***$_A$H$_B$), 1.80-1.88 (ddd, 1H, *J* = 14.1 Hz, *J* = 9.9 Hz, *J* = 4.9 Hz, CHCH$_A$***H***$_B$), 1.66-1.77 (m, 1H, COCH$_2$CH$_A$***H***$_B$), 1.56-1.64 (m, 3H, NCH$_2$C***H***$_2$CH$_3$ and COCH$_A$***H***$_B$), 0.89 (t, 3H, *J* = 7.4 Hz, CH$_2$C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.9 (***C***=O), 170.5 (N***C***=O), 166.6 (***C***(O)OCH$_3$), 148.0 (***C***=CH$_2$), 145.6 (***C***, Ar), 129.6 (***C***, Ar), 129.5 (***C***H, Ar), 128.9 (***C***H, Ar), 127.4 (***C***H, Ar), 126.7 (***C***H, Ar), 117.5 (C=***C***H$_2$), 59.2 (C(O)***C***C(O)N), 52.1 (O***C***H$_3$), 49.1 (N***C***H$_2$CH$_2$CH$_3$), 45.9 (N***C***H$_2$CH$_2$CH), 42.2 (***C***H), 38.6 (***C***H$_2$C(O)), 31.6 (C***C***H$_2$), 24.7 (CH***C***H$_2$), 20.1 (C(O)CH$_2$***C***H$_2$), 19.9 (***C***H$_2$CH$_3$), 11.2 (***C***H$_2$CH$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2959 (C-H), 1740 (C=O), 1721 (C=O), 1627 (C=O); **MS** (ES+) m/z (rel. intensity %) 392.21 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{27}NNaO_4$ [M+Na]$^+$ 392.1832, found 392.1839.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(7-allyl-1,6-dioxo-7-azaspiro[4.5]dec-10-yl)vinyl]benzoate (±)-166n

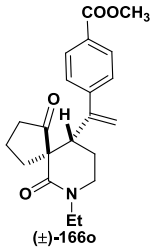


(±)-166n

Synthesised from substrate **165h** (47.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166n** was obtained (single diastereoisomer, 48.0 mg, 66% yield) as a colourless oil after flash column chromatography (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 30:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.35 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 5.75 (tdd, 1H, *J* = 17.2 Hz, *J* = 9.9 Hz, *J* = 5.8 Hz, C***H***=CH_2), 5.47 (s, 1 H, C=C***H***$_A$H$_B$), 5.20-5.24 (m, 1H, CH=C***H***$_A$H$_B$), 5.18 (d, 1H, *J* = 1.1 Hz, CH=CH$_A$***H***$_B$), 5.16 (s, 1H, C=CH$_A$***H***$_B$), 4.03 (dd, 1H, *J* = 15.1 Hz, *J* = 5.6 Hz, C***H***$_A$H$_B$CH=CH_2), 3.87-3.94 (m, 4H, CH$_A$***H***$_B$CH=CH_2 and OC***H***$_3$), 3.52 (dd, 1H, *J* = 10.0 Hz, *J* = 2.7 Hz, C***H***), 3.34-3.48 (m, 2H, NC***H***$_2$$CH_2$), 2.40 (ddd, 1H, *J* = 13.5 Hz, *J* = 7.5 Hz, *J* = 6.2 Hz, CC***H***$_A$H$_B$), 2.20-2.31 (m, 3H, CHC***H***$_A$H$_B$ and C(O)C***H***$_A$H$_B$ and CCH$_A$***H***$_B$), 2.05-2.16 (m, 1H, C(O)CH_2C***H***$_A$H$_B$), 1.60-1.90 (m, 3H, C(O)CH_2CH$_A$***H***$_B$ and CHCH$_A$***H***$_B$ and C(O)CH$_A$***H***$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.7 (***C***=O), 170.5 (N***C***=O), 166.7 (***C***(O)OCH_3), 147.9 (***C***=CH_2), 145.6 (***C***, Ar), 132.1 (***C***H=CH_2), 129.6 (***C***, Ar), 129.5 (2***C***H, Ar), 127.4 (2***C***H, Ar), 117.6 (C=***C***H_2 or CH=***C***H_2), 117.5 (C=***C***H_2 or CH=***C***H_2), 59.3 (C(O)***C***C(O)N), 52.1 (O***C***H_3), 49.7 (***C***H_2CH=CH_2), 45.4 (N***C***$H_2$$CH_2$), 42.3 (***C***H), 38.6 (***C***H_2C(O)), 31.6 (C***C***H_2), 24.5 (CH***C***H_2), 19.9 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2952 (C-H), 1740 (C=O), 1720 (C=O), 1627 (C=O); **MS** (ES+) m/z (rel. intensity %) 390.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{25}NNaO_4$ $[M+Na]^+$ 390.1676, found 390.1674.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(7-ethyl-1,6-dioxo-7-azaspiro[4.5]dec-10-yl)vinyl]benzoate (±)-166o

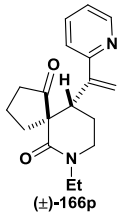


(±)-166o

Synthesised from substrate **165e** (45.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166o** was obtained (single diastereoisomer, 53.0 mg, 75% yield) as a colourless oil after flash column chromatography (PE/EA = 1:2). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 36:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.35 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 5.46 (s, 1H, C=C***H*****$_A$**H_B), 5.14 (s, 1H, C=CH_A***H*****$_B$**), 3.90 (s, 3H, OC***H*****$_3$**), 3.32-3.51 (m, 5H, C***H*** and NC***H*****$_2$**CH_2 and NC***H*****$_2$**CH_3), 2.38 (ddd, 1H, *J* = 13.4 Hz, *J* = 7.6 Hz, *J* = 6.1 Hz, CC***H*****$_A$**H_B), 2.05-2.35 (m, 4H, CHC***H*****$_A$**H_B and C(O)C***H*****$_A$**H_B and CCH_A***H*****$_B$** and C(O)CH_2C***H*****$_A$**H_B), 1.80-1.86 (m, 1H, CHCH_A***H*****$_B$**), 1.69-1.77 (m, 1H, C(O)CH_2CH_A***H*****$_B$**), 1.57-1.66 (m, 1H, C(O)CH_A***H*****$_B$**), 1.12 (t, 3H, *J* = 7.2 Hz, CH_2C***H*****$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.9 (***C***=O), 170.2 (N***C***=O), 166.7 (***C***(O)OCH_3), 148.0 (***C***=CH_2), 145.6 (***C***, Ar), 129.5 (2***C***H, Ar), 127.4 (2***C***H and ***C***, Ar), 117.5 (C=***C***H_2), 59.1 (C(O)***C***C(O)N), 52.1 (O***C***H_3), 45.3 (N***C***H_2CH_3), 42.3 (N***C***H_2CH_2), 42.2 (***C***H), 38.6 (C(O)***C***H_2CH_2), 31.5 (C***C***H_2), 24.6 (CH***C***H_2), 19.9 (C(O)CH_2***C***H_2),11.9 (NCH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2952 (C-H), 1721 1740 (C=O), (C=O), 1627 (C=O); **MS** (ES+) m/z (rel. intensity %) 378.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{21}H_{25}NNaO_4$ $[M+Na]^+$ 378.1676, found 378.1670.

Preparation and characterisation of (±)-(5*R*,10*S*)-7-ethyl-10-[1-(pyridin-2-yl)vinyl]-7-azaspiro[4.5]decane-1,6-dione (±)-166p

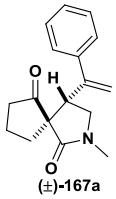


(±)-166p

Synthesised from substrate **165e** (45.0 mg, 0.2 mmol) and 2-bromopyridine (47.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-166p** was obtained (single diastereoisomer, 31.0 mg, 53% yield) as a colourless oil after flash column chromatography (PE/EA = 1:2). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 12:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.54-8.57 (m, 1H, Ar***H***), 7.63 (dt, 1H, *J* = 7.8 Hz, *J* = 1.8 Hz, Ar***H***), 7.42 (dd, 1H, *J* = 7.9 Hz, *J* = 0.8 Hz, Ar***H***), 7.17 (ddd, 1H, *J* = 7.3 Hz, *J* = 4.8 Hz, *J* = 1.0 Hz, Ar***H***), 5.78 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.20 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 3.88 (dd, 1H, *J* = 8.3 Hz, *J* = 3.5 Hz, C***H***), 3.30-3.51 (m, 4H, $CH_2C\boldsymbol{H_2}N$ and $NC\boldsymbol{H_2}CH_3$), 2.49-2.56 (m, 1H, C$\boldsymbol{H_A}H_B$), 2.27-2.41 (m, 2H, CHC$\boldsymbol{H_A}H_B$ and C(O)C$\boldsymbol{H_A}H_B$), 2.17-2.23 (m, 1H, C$CH_A\boldsymbol{H_B}$), 1.91-2.10 (m, 2H, C(O)$CH_2C\boldsymbol{H_A}H_B$ and C(O)$CH_A\boldsymbol{H_B}$), 1.72-1.84 (m, 2H, CHC$H_A\boldsymbol{H_B}$ and C(O)$CH_2CH_A\boldsymbol{H_B}$), 1.13 (t, 3H, *J* = 7.2 Hz, C$\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.2 (***C***=O), 169.9 (N***C***=O), 158.4 (***C***, Ar), 148.8 (***C***=CH_2), 147.6 (***C***H, Ar), 136.4 (***C***H, Ar), 122.6 (***C***H, Ar), 121.2 (***C***H, Ar), 117.6 (C=***C***H_2), 59.1 (C(O)***C***C(O)N), 44.8 (N***C***H_2CH_2), 42.5 (N***C***H_2CH_3), 40.0 (***C***H), 38.5 (***C***H_2C(O)), 32.0 (C***C***H_2), 23.7 (CH***C***H_2), 19.9 (C(O)CH_2***C***H_2), 11.9 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2970 (C-H), 1738 (C=O), 1626 (C=O), 1584 (C=C); **MS** (ES+) m/z (rel. intensity %) 299.20 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{23}N_2O_2$ $[M+H]^+$ 299.1754, found 299.1752.

Preparation and characterisation of (±)-(5*R*,10*S*)-2-methyl-4-(1-phenylethenyl)-2-azaspiro[4.4]nonane-1,6-dione (±)-167a



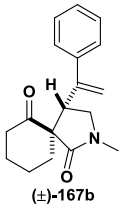
(±)-167a

Synthesised from substrate **165b** (43.0 mg, 0.22 mmol) and iodobenzene (67.0 mg, 0.33 mmol) according to general procedure D. Compound **(±)-167a** was obtained as a mixture of inseparable diastereoisomers with a 4:1 dr after flash column chromatography (PE/EA = 1:2, 47.0 mg, 80% yield).

Two diastereoisomers: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29-7.36 (m, both, 10H, 5 × Ar***H***), 5.43 (s, minor, 1H, C=C***H*****$_A$**H_B), 5.39 (s, major, 1H, C=C***H*****$_A$**H_B), 5.22 (s, major, 1H, C=CH_A***H*****$_B$**), 5.11 (s, minor, 1H, C=CH_A***H*****$_B$**), 3.89-3.94 (m, both, 2H, C***H*****$_A$**H_BN), 3.69-3.76 (m, minor, 1H, CH_A***H*****$_B$**N), 3.55-3.60 (m, major, 1H, CH_A***H*****$_B$**N), 3.47 (dd, minor, 1H, *J* = 9.1 Hz, *J* = 7.8 Hz, C***H***CH_2), 3.41 (dd, major, 1H, *J* = 9.1 Hz, *J* = 7.8 Hz, C***H***CH_2), 2.98 (s, major, 3H, NC***H*****$_3$**), 2.89 (s, minor, 3H, NC***H*****$_3$**), 2.47 (td, major, 1H, *J* = 13.5 Hz, *J* = 7.8 Hz, CC***H*****$_A$**H_B), 2.24-2.32 (m, minor, 1H, CC***H*****$_A$**H_B), 2.14-2.23 (m, major, 1H, C(O)C***H*****$_A$**H_B), 2.05-2.12 (m, minor, 1H, C(O)C***H*****$_A$**H_B), 1.95-2.03 (m, both, 2H, C***H*****$_2$**), 1.81-1.92 (m, both, 2H, C***H*****$_2$**), 1.58-1.67 (m, both, 2H, C***H*****$_2$**), 1.18-1.26 (m, both, 2H, C***H*****$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.7 (minor, ***C***=O), 216.3 (major, ***C***=O), 173.3 (minor, N***C***=O), 172.7 (major, N***C***=O), 147.2 (minor, ***C***=CH_2), 144.2 (major, ***C***=CH_2), 142.2 (***C***, major, Ar), 140.6 (***C***, minor, Ar), 128.6 (2***C***H, major, Ar), 128.4 (2***C***H, minor, Ar), 128.1 (***C***H, minor, Ar), 128.0 (***C***H, major, Ar), 127.0 (2***C***H, minor, Ar), 126.9 (2***C***H, major, Ar), 117.1 (major, C=***C***H_2), 115.3 (minor, C=***C***H_2), 62.5 (major, C(O)***C***C(O)N), 61.8 (minor, C(O)***C***C(O)N), 51.7 (minor, N***C***H_2), 51.4 (minor, N***C***H_2), 47.3 (major, ***C***HCH_2), 43.1 (minor, ***C***HCH_2), 39.3 (major, ***C***H_2C(O)), 37.9 (minor, ***C***H_2C(O)), 32.3 (major, N***C***H_3), 30.1 (major, C***C***H_2), 29.8 (minor, N***C***H_3). 28.9

(minor, C***C***H_2), 19.4 (2C, both, ***C***H_2CH_2C(O)); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2924 (C-H), 1734 (C=O), 1688 (C=O); **MS** (ES+) m/z (rel. intensity %) 292.16 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{17}H_{19}NNaO_2$ $[M+Na]^+$ 292.1308, found 292.1312.

Preparation and characterisation of (±)-(5*R*,10*S*)-2-methyl-4-(1-phenylethenyl)-2-azaspiro[4.5]decane-1,6-dione (±)-167b

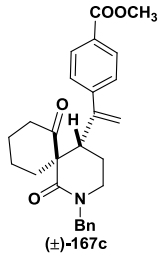


(±)-167b

Synthesised from substrate **165c** (42.0 mg, 0.2 mmol) and iodobenzene (61.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167b** was obtained (single diastereoisomer, 28.0 mg, 50% yield) as a yellow oil after flash column chromatography (PE/EA = 1:2). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 5:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28-7.41 (m, 5H, 5 × Ar***H***), 5.38 (s, 1H, C=C***H***$_A$$H_B$), 5.13 (s, 1H, C=C$H_A$***H***$_B$), 3.66 (t, 1H, *J* = 8.3 Hz, C***H***$_A$$H_B$N), 3.37-3.45 (m, 2H, C***H***CH_2 and NCH_A***H***$_B$), 2.94 (s, 3H, NC***H***$_3$), 2.42 (ddd, 1H, *J* = 16.2 Hz, *J* = 7.0 Hz, *J* = 5.4 Hz, C***H***$_A$$H_B$C(O)), 2.13-2.25 (m, 2H, CH_A***H***$_B$C(O) and CC***H***$_A$$H_B$), 1.80-1.89 (m, 1H, CC$H_A$***H***$_B$), 1.67-1.76 (m, 1H, C$CH_2$C***H***$_A$$H_B$), 1.56-1.62 (m, 1H, C***H***$_A$$H_B$$CH_2$C(O)), 1.48-1.54 (m, 1H, CCH_2CH_A***H***$_B$), 1.10-1.19 (m, 1H, CH_A***H***$_B$$CH_2$C(O)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.7 (***C***=O), 173.5 (N***C***=O), 145.2 (***C***=CH_2), 142.3 (***C***, Ar), 128.8 (***C***H, Ar), 128.6 (***C***H, Ar), 127.9 (***C***H, Ar), 127.5 (***C***H, Ar), 127.0 (***C***H, Ar), 116.5 (C=***C***H_2), 62.7 (C(O)***C***C(O)N), 52.3 (N***C***H_2), 48.9 (***C***H), 41.6 (***C***H_2C(O)), 34.8 (***C***H_2C), 30.0 (N***C***H_3), 24.1 (***C***H_2CH_2C(O)), 20.9 (CCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2927 (C-H), 1680 (C=O), 1634 (C=O); **MS** (ES+) m/z (rel. intensity %) 306.17 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{21}NNaO_2$ $[M+Na]^+$ 306.1465, found 306.1474.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(2-benzyl-1,7-dioxo-2-azaspiro[5.5]undec-5-yl)vinyl]benzoate (±)-167c

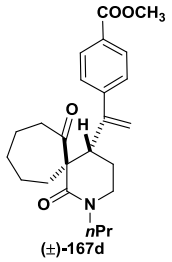


(±)-167c

Synthesised from substrate **165i** (59.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167c** was obtained (single diastereoisomer, 58.0 mg, 67% yield) as a yellow oil after flash column chromatography (PE/EA = 4:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 22:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.01 (d, 2H, *J* = 5.9 Hz, 2 × Ar***H***), 7.23-7.39 (m, 7H, 7 × Ar***H***), 5.46 (s, 1H, C=C***H*****$_A$**H$_B$), 5.04 (s, 1H, C=CH$_A$***H*****$_B$**), 4.80 (d, 1H, *J* = 14.6 Hz, C***H*****$_A$**H$_B$C$_6$H$_5$), 4.44 (d, 1H, *J* = 14.6 Hz, CH$_A$***H*****$_B$**C$_6$H$_5$), 3.92 (s, 3H, OC***H*****$_3$**), 3.81 (dd, 1H, *J* = 7.0 Hz, *J* = 4.0 Hz, C***H***), 3.22-3.33 (m, 2H, NC***H*****$_2$**CH$_2$), 2.36-2.51 (m, 2H, C***H*****$_A$**H$_B$C(O) and CC***H*****$_A$**H$_B$), 2.13-2.21 (m, 2H, CH$_A$***H*****$_B$**C(O) and CCH$_A$***H*****$_B$**), 1.91-2.01 (m, 2H, CHC***H*****$_A$**H$_B$ and CCH$_2$C***H*****$_A$**H$_B$), 1.73-1.87 (m, 3H, C***H*****$_2$**CH$_2$C(O) and CHCH$_A$***H*****$_B$**), 1.49-1.63 (m, 1H, CCH$_2$C***H*****$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 210.5 (***C***=O), 170.2 (N***C***=O), 166.7 (***C***(O)OCH$_3$), 146.7 (***C***=CH$_2$), 146.2 (***C***, Ar), 136.8 (***C***, Ar), 129.8 (***C***H, Ar), 129.6 (***C***, Ar), 129.4 (***C***H, Ar), 128.6 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.4 (***C***H, Ar), 127.1 (2***C***H, Ar), 117.8 (C=***C***H$_2$), 59.9 (C(O)***C***C(O)N), 52.1 (O***C***H$_3$), 50.5 (***C***H$_2$C$_6$H$_5$), 44.1 (N***C***H$_2$CH$_2$), 41.9 (***C***H), 39.1 (***C***H$_2$C(O)), 31.0 (C***C***H$_2$), 25.6 (***C***H$_2$CH$_2$C(O)), 23.5 (CH***C***H$_2$), 20.8 (CCH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2947 (C-H), 1719 (C=O), 1630 (C=O), 1607 (C=O); **MS** (ES+) m/z (rel. intensity %) 454.23 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{27}H_{29}NNaO_4$ [M+Na]$^+$ 454.1989, found 454.1979.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(7-oxo-1-propyl-1-azaspiro[5.6]dodec-4-yl)vinyl]benzoate (±)-167d

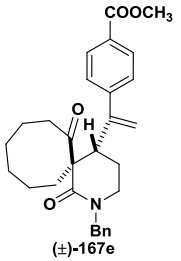


(±)-167d

Synthesised from substrate **165j** (53.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167d** was obtained (single diastereoisomer, 52.0 mg, 66% yield) as a colourless oil after flash column chromatography (PE/EA = 4:1, ^{1}H NMR of the crude reaction mixture showed a 7:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.98 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.38 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 5.50 (s, 1H, C=C***H$_A$***H$_B$), 5.10 (s, 1H, C=CH$_A$***H$_B$***), 3.91 (s, 3H, OC***H$_3$***), 3.61 (dd, 1H, *J* = 6.6 Hz, *J* = 4.3 Hz, C***H***), 3.30-3.38 (m, 4H, CHCH$_2$C***H$_2$*** and NC***H$_2$***CH$_2$CH$_3$), 2.33-2.41 (m, 2H, C***H$_2$***), 2.03-2.23 (m, 2H, C***H$_2$***),1.79-1.86 (m, 3H, C***H$_2$***),1.57-1.73 (m, 7H, C***H$_2$***), 0.92 (t, 3H, *J* = 7.4 Hz, CH$_2$C***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 212.3 (***C***=O), 169.8 (N***C***=O), 166.7 (***C***(O)OCH$_3$), 146.9 (***C***, Ar), 146.5 (***C***=CH$_2$), 129.7 (2***C***H, Ar), 128.9 (***C***, Ar), 127.0 (2***C***H, Ar), 117.5 (C=***C***H$_2$), 62.4 (C(O)***C***C(O)N), 52.1 (O***C***H$_3$), 49.5 (N***C***H$_2$CH$_2$CH), 44.9 (N***C***H$_2$CH$_2$CH$_3$), 44.2 (C***H***), 41.7 (***C***H$_2$C(O)), 31.3 (***C***H$_2$), 30.8 (***C***H$_2$), 25.7 (***C***H$_2$), 25.4 (***C***H$_2$), 24.1 (***C***H$_2$), 20.0 (***C***H$_2$), 11.4 (CH$_2$C***H$_3$***); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2932 (C-H), 1721 (C=O), 1633 (C=O), 1607 (C=O); **MS** (ES+) m/z (rel. intensity %) 420.24 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{31}NNaO_4$ [M+Na]$^+$ 420.2145, found 420.2138.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(2-benzyl-1,7-dioxo-2-azaspiro[5.7]tridec-5-yl)vinyl]benzoate (±)-167e



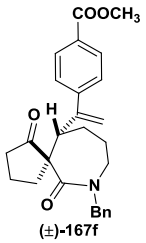
(±)-167e

Synthesised from substrate **165k** (65.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167e** was obtained (single diastereoisomer, 55.0 mg, 60% yield) as a colourless oil after flash column chromatography (PE/EA = 5:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 7:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.97-7.99 (m, 2H, 2 × Ar***H***), 7.42-7.44 (m, 2H, 2 × Ar***H***), 7.24-7.35 (m, 5H, 5 × Ar***H***), 5.52 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 4.86 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.80 (d, 1H, *J* = 14.3 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.43 (d, 1H, *J* = 14.4 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.91 (s, 3H, OC$\boldsymbol{H_3}$), 3.68 (dd, 1H, *J* = 5.4 Hz, *J* = 3.1 Hz, C***H***), 3.28-3.45 (m, 2H, C$\boldsymbol{H_A}H_B$C(O) and NC$\boldsymbol{H_A}H_BCH_2$), 3.10-3.16 (ddd, 1H, *J* = 12.6 Hz, *J* = 6.1 Hz, *J* = 3.0 Hz, NC$H_A\boldsymbol{H_B}CH_2$), 2.98 (ddd, 1H, *J* = 15.4 Hz, *J* = 12.2 Hz, *J* = 3.2 Hz, CC$\boldsymbol{H_A}H_B$), 2.58-2.65 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 2.08-2.22 (m, 2H, C$H_A\boldsymbol{H_B}$C(O) and CC$H_A\boldsymbol{H_B}$), 1.88-1.96 (m, 1H, C$\boldsymbol{H_A}H_BCH_2$C(O)), 1.69-1.82 (m, 2H, C$H_A\boldsymbol{H_B}CH_2$C(O) and C$\boldsymbol{H_A}H_B$), 1.39-1.65 (m, 3H, CHC$H_A\boldsymbol{H_B}$ and C$\boldsymbol{H_2}$), 0.98-1.33 (m, 3H, C$\boldsymbol{H_2}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 213.4 (***C***=O), 168.5 (N***C***=O), 166.7 (***C***(O)OCH_3), 147.2 (***C***=CH_2), 146.4 (***C***, Ar), 136.8 (***C***, Ar), 130.2 (***C***, Ar), 129.8 (2***C***H, Ar), 129.3 (***C***H, Ar), 128.6 (***C***H, Ar), 128.2 (***C***H, Ar), 127.5 (***C***H, Ar), 127.2 (***C***H, Ar), 126.2 (2***C***H, Ar), 116. 7 (C=***C***H_2) , 62.3 (C(O)***C***C(O)N), 52.1 (O***C***H_3), 51.3 (***C***$H_2C_6H_5$), 43.5 (N***C***H_2CH_2), 39.7 (***C***H), 37.1 (***C***H_2C(O)), 29.3 (***C***H_2CH_2C(O)), 28.6 (C***C***H_2), 25.9 (***C***H_2), 24.4 (***C***H_2), 23.5 (***C***H_2), 22.6 (***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2929 (C-H), 1721 (C=O), 1702 (C=O),1634 (C=O), 1607

(C=C); **MS** (ES+) m/z (rel. intensity %) 482.25 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{29}H_{33}NNaO_4$ $[M+Na]^+$ 482.2302, found 482.2298.

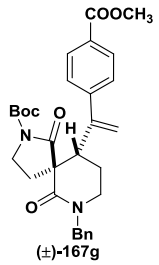
Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(7-benzyl-1,6-dioxo-7-azaspiro[4.6]undec-11-yl)vinyl]benzoate (±)-167f



(±)-167f

Synthesised from substrate **165s** (59.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167f** was obtained (single diastereoisomer, 26.0 mg, 30% yield) as a colourless oil after flash column chromatography (PE/EA = 4:1). Analysis of ^{1}H NMR spectrum of the crude reaction mixture showed a 14:1 dr. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.99 (d, 2H, *J* = 8.3 Hz, 2 × Ar***H***), 7.42 (d, 2H, *J* = 8.3 Hz, 2 × Ar***H***), 7.21-7.32 (m, 5H, 5 × Ar***H***), 5.27 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.18 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.73 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.50 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.91 (s, 3H, OC$\boldsymbol{H_3}$), 3.63-3.72 (m, 1H, NC$\boldsymbol{H_A}H_BCH_2$), 3.30-3.36 (m, 2H, NC$H_A\boldsymbol{H_B}CH_2$ and C***H***), 2.67-2.70 (m, 1H, CC$\boldsymbol{H_A}H_B$), 2.50 (ddd, 1H, *J* = 17.8 Hz, *J* = 8.2 Hz, *J* = 4.4 Hz, C$\boldsymbol{H_A}H_BC(O)$), 2.32-2.39 (m, 1H, C$CH_A\boldsymbol{H_B}$), 1.96-2.15 (m, 4H, C$\boldsymbol{H_A}H_BC(O)$ and CHC$\boldsymbol{H_A}H_B$ and C$\boldsymbol{H_2}CH_2C(O)$), 1.72-1.80 (m, 2H, $NCH_2C\boldsymbol{H_2}$), 1.45-1.55 (m, 1H, $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.9 (***C***=O), 172.8 (N***C***=O), 166.9 (***C***(O)OCH_3), 148.4 (***C***=CH_2), 137.5 (***C***, Ar), 129.6 (2***C***H, Ar), 129.0 (***C***, Ar), 128.6 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.4 (***C***, Ar), 127.2 (***C***H, Ar), 126.8 (2***C***H, Ar), 115.7 (C=***C***H_2), 64.8 (C(O)***C***C(O)N), 53.3 (***C***$H_2C_6H_5$), 52.1 (O***C***H_3), 47.9 (N***C***H_2CH_2), 42.9 (***C***H), 38.2 (***C***$H_2C(O)$), 32.2 (C***C***H_2), 31.5 ($NCH_2\boldsymbol{C}H_2$), 26.9 (CH***C***H_2), 19.2 (C(O)$CH_2\boldsymbol{C}H_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2949 (C-H), 1750 (C=O), 1719 (C=O), 1609 (C=O); **MS** (ES+) m/z (rel. intensity %) 454.23 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{27}H_{29}NNaO_4$ $[M+Na]^+$ 454.1989, found 454.1989.

Preparation and characterisation of (±)-(5*R*,10*S*)-*tert*-butyl 7-benzyl-10-{1-[4-(methoxycarbonyl)phenyl]vinyl}-1,6-dioxo-2,7-diazaspiro[4.5]decane-2-carboxylate (±)-167g



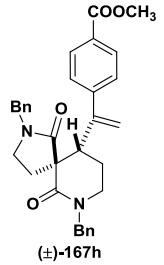
(±)-167g

Synthesised from substrate **165l** (79.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167g** was obtained (single diastereoisomer, 77.0 mg, 74% yield) as a colourless oil after flash column chromatography (PE/EA = 1:3). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 11:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.26-7.40 (m, 7H, 7 × Ar***H***), 5.45 (s, 1H, C=C***H***$_A$H$_B$), 5.11 (s, 1H, C=CH$_A$***H***$_B$), 4.63 (d, 1H, *J* = 14.5 Hz, C***H***$_A$H$_B$C$_6$H$_5$), 4.59 (d, 1H, *J* = 14.6 Hz, CH$_A$***H***$_B$C$_6$H$_5$), 3.87 (s, 3H, OC***H***$_3$), 3.80 (dt, 1H, *J* = 9.6 Hz, *J* = 6.2 Hz, N(Boc)C***H***$_A$H$_B$), 3.68 (dd, 1H, *J* = 10.0 Hz, *J* = 2.5 Hz, C***H***), 3.38-3.49 (m, 2H, N(Boc)C***H***$_A$H$_B$ and C***H***$_A$H$_B$N(Bn)), 3.31 (td, 1H, *J* = 12.3 Hz, *J* = 4.9 Hz, CH$_A$***H***$_B$N(Bn)), 2.35-2.39 (m, 2H, CC***H***$_A$H$_B$ and CHC***H***$_A$H$_B$), 2.14 (ddd, 1H, *J* = 13.3 Hz, *J* = 9.4 Hz, *J* = 6.2 Hz, CCH$_A$***H***$_B$), 1.71-1.80 (m, 1H, CHCH$_A$***H***$_B$), 1.35 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.5 (N(Boc)***C***(O)), 169.9 (***C***(O)NBn), 166.6 (***C***(O)OCH$_3$), 149.5 (C(CH$_3$)$_3$O***C***(O)), 147.9 (***C***=CH$_2$), 144.9 (***C***, Ar), 136.4 (***C***, Ar), 129.7 (***C***, Ar), 129.6 (***C***H, Ar), 129.5 (***C***H, Ar), 128.7 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.5 (***C***H, Ar), 127.0 (***C***H, Ar), 117.3 (C=***C***H$_2$), 82.6 (***C***(CH$_3$)$_3$O), 57.6 (C(O)***C***C(O)N), 52.0 (O***C***H$_3$), 50.7 (***C***H$_2$C$_6$H$_5$), 45.3 (N(Bn)***C***H$_2$), 44.4 (N(Boc)***C***H$_2$), 43.2 (***C***H), 27.7 (3C, OC(***C***H$_3$)$_3$), 25.5 (N(Boc)CH$_2$***C***H$_2$), 24.2 (CH***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2981 (C-H), 1782 (C=O), 1719 (C=O), 1637 (C=O),

1608 (C=O); **MS** (ES+) m/z (rel. intensity %) 541.26 (M + Na^+, 80); **HRMS** (ESI+) calcd. for $C_{30}H_{34}N_2NaO_6$ $[M+Na]^+$ 541.2309, found 541.2324.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(2,7-dibenzyl-1,6-dioxo-2,7-diazaspiro[4.5]dec-10-yl)vinyl]benzoate (±)-167h



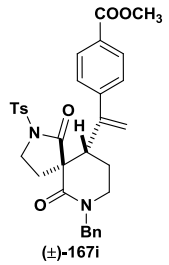
(±)-167h

Synthesised from substrate **165m** (75.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167h** was obtained (single diastereoisomer, 70.0 mg, 69% yield) as a colourless oil after flash column chromatography on silica gel (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 18:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.01 (d, 2H, *J* = 8.2 Hz, 2 × Ar***H***), 7.44 (d, 2H, *J* = 8.2 Hz, 2 × Ar***H***), 7.25-7.39 (m, 8H, 8 × Ar***H***), 7.07 (d, 2H, *J* = 7.6 Hz, 2 × Ar***H***), 5.46 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.13 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.81 (d, 1H, *J* = 14.7 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.51 (d, 1H, *J* = 14.8 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 4.23 (d, 1H, *J* = 15.0 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 3.93 (s, 3H, OC$\boldsymbol{H_3}$), 3.76 (dd, 1H, *J* = 10.3 Hz, *J* = 2.4 Hz, C***H***), 3.60 (d, 1H, *J* = 15.0 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.44-3.51 (m, 1H, $CHCH_2C\boldsymbol{H_A}H_B$), 3.31-3.41 (m, 2H, $CHCH_2CH_A\boldsymbol{H_B}$ and C$\boldsymbol{H_A}H_BCH_2C$), 2.94 (dt, 1H, *J* = 9.2 Hz, *J* = 4.4 Hz, C$H_A\boldsymbol{H_B}CH_2C$), 2.35-2.43 (m, 2H, CHC$\boldsymbol{H_A}H_B$ and C$\boldsymbol{H_A}H_BC$), 2.13-2.19 (m, 1H, C$H_A\boldsymbol{H_B}C$), 1.80-1.84 (m, 1H, $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 173.0 (N(Bn)***C***=O), 170.9 (N(Bn)***C***=O), 166.8 (***C***(O)OCH_3), 148.2 (***C***=CH_2), 145.2 (***C***, Ar), 138.8 (***C***, Ar), 136.7 (***C***, Ar), 135.8 (***C***, Ar), 129.7 (***C***H, Ar), 129.4 (***C***H, Ar), 128.7 (***C***H, Ar), 128.6 (***C***H, Ar), 128.5 (***C***H, Ar), 128.0 (***C***H, Ar), 127.9 (***C***H, Ar), 127.8 (***C***H, Ar), 127.6 (***C***H, Ar), 127.5 (***C***H, Ar), 127.3 (***C***H, Ar), 126.9 (***C***H, Ar), 125.7 (***C***H, Ar), 125.3 (***C***H, Ar), 117.4 (C=***C***H_2), 56.2 (C(O)***C***C(O)N), 52.1 (O***C***H_3), 50.7 (***C***$H_2C_6H_5$), 46.6 (***C***$H_2C_6H_5$), 45.5 (N***C***H_2CH_2CH),

44.8 (N***C***H_2CH_2C), 42.6 (***C***H), 26.8 (NCH_2***C***H_2C), 24.7 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2950 (C-H), 1719 (C=O), 1687 (C=O), 1636 (C=O), 1607 (C=C); **MS** (ES+) m/z (rel. intensity %) 531.25 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{32}H_{32}N_2NaO_4$ $[M+Na]^+$ 531.2254, found 531.2241.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-(1-{7-benzyl-2-[(4-methylphenyl)sulfonyl]-1,6-dioxo-2,7-diazaspiro[4.5]dec-10-yl}vinyl)benzoate (±)-167i



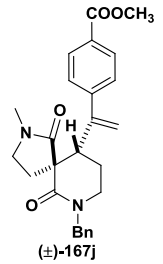
(±)-167i

Synthesised from substrate **165n** (88.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167i** was obtained (single diastereoisomer, 70.0 mg, 68% yield) as a white solid after flash column chromatography (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 32:1 dr.

Mp 140.0-143.8 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.98 (d, 2H, *J* = 8.3 Hz, 2 × Ar***H***), 7.84 (d, 2H, *J* = 8.3 Hz, 2 × Ar***H***), 7.31-7.33 (m, 2H, 2 × Ar***H***), 7.26-7.28 (m, 5H, 5 × Ar***H***), 7.08 (dd, 2H, *J* = 6.5 Hz, *J* = 2.9 Hz, 2 × Ar***H***), 5.45 (s, 1H, C=C***H*****$_A$**H_B), 4.98 (s, 1H, C=CH_A***H*****$_B$**), 4.59 (d, 1H, *J* = 14.7 Hz, C***H*****$_A$**$H_BC_6H_5$), 4.38 (d, 1H, *J* = 14.7 Hz, CH_A***H*****$_B$**C_6H_5), 4.03 (q, 1H, *J* = 8.3 Hz, TsNC***H*****$_A$**H_B), 3.88-3.92 (m, 4H, OC***H*****$_3$** and TsNCH_A***H*****$_B$**), 3.49 (dd, 1H, *J* = 7.1 Hz, *J* = 3.6 Hz, C***H***), 3.20-3.31 (m, 2H, N(Bn)C***H*****$_2$**), 2.55-2.63 (m, 2H, CHC***H*****$_A$**H_B and $TsNCH_2C$***H*****$_A$**H_B), 2.38 (s, 3H, C***H*****$_3$**C_6H_4), 2.20 (td, 1H, *J* = 13.2 Hz, *J* = 8.8 Hz, $TsNCH_2CH_A$***H*****$_B$**), 1.57 (dt, 1H, *J* = 12.9 Hz, *J* = 5.8 Hz, $CHCH_A$***H*****$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.5 (TsN***C***(O)), 168.4 (N***C***=O), 166.6 (***C***(O)OCH_3), 146.7 (***C***=CH_2), 145.4 (***C***, Ar), 144.9 (***C***, Ar), 136.3 (***C***, Ar), 134.5 (***C***, Ar), 129.8 (***C***, Ar), 129.7 (***C***H, Ar), 129.5 (***C***H, Ar), 128.6 (***C***H, Ar), 128.2 (***C***H, Ar), 128.1 (***C***H, Ar), 127.7 (***C***H, Ar), 127.5 (***C***H, Ar), 126.7

(***C***H, Ar), 126.1 (***C***H, Ar), 117.1 (C=***C***H_2), 56.1 (C(O)***C***C(O)), 52.1 (O***C***H_3), 50.4 (***C***$H_2C_6H_5$), 45.7 (TsN***C***H_2CH_2), 44.4 (N(Bn)***C***H_2), 43.5 (***C***H), 27.9 (TsNCH$_2$***C***H_2), 23.1 (CH***C***H_2), 21.7 (***C***$H_3C_6H_4$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2950 (C-H), 1720 (C=O), 1638 (C=O), 1607 (C=O), 1359 (SO_2), 1112 (SO_2); **MS** (ES+) m/z (rel. intensity %) 595.21 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{32}H_{32}N_2NaO_6S$ $[M+Na]^+$ 595.1873, found 595.1880.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(7-benzyl-2-methyl-1,6-dioxo-2,7-diazaspiro[4.5]dec-10-yl)vinyl]benzoate (±)-167j



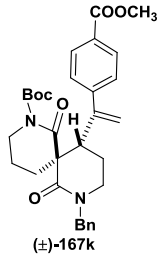
(±)-167j

Synthesised from substrate **165o** (60.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167j** was obtained (single diastereoisomer, 43.0 mg, 50% yield) as a colourless oil after flash column chromatography (PE/EA = 1:3). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 13:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.98 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.40 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.27-7.35 (m, 5H, 5 × Ar***H***), 5.45 (s, 1H, C=C***H$_A$***H$_B$), 5.13 (s, 1H, C=CH$_A$***H$_B$***), 4.73 (d, 1H, *J* = 14.6 Hz, C***H$_A$***H$_B$C$_6$H$_5$), 4.52 (d, 1H, *J* = 14.7 Hz, CH$_A$***H$_B$***C$_6$H$_5$), 3.91 (s, 3H, OC***H$_3$***), 3.69 (dd, 1H, *J* = 10.5 Hz, *J* = 1.7 Hz, C***H***), 3.38-3.48 (m, 2H, N(Bn)C***H$_A$***H$_B$ and N(CH$_3$)C***H$_A$***H$_B$), 3.27-3.34 (m, 1H, CH$_A$***H$_B$***N(Bn)), 3.02 (dt, 1H, *J* = 9.2 Hz, *J* = 5.1 Hz, N(CH$_3$)CH$_A$***H$_B$***), 2.42 (ddd, 1H, *J* = 14.3 Hz, *J* = 9.4 Hz, *J* = 5.1 Hz, CC***H$_A$***H$_B$), 2.28-2.35 (m, 4H, NC***H$_3$*** and CHC***H$_A$***H$_B$), 2.17 (ddd, 1H, *J* = 13.9 Hz, *J* = 9.2 Hz, *J* = 5.0 Hz, CCH$_A$***H$_B$***), 1.74-1.83 (m, 1H, CHCH$_A$***H$_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.6 (N(CH$_3$)***C***=O), 171.0 (N(Bn)***C***=O) 166.7 (***C***(O)OCH$_3$), 148.4 (***C***=CH$_2$), 145.0 (***C***, Ar), 136.7 (***C***, Ar), 129.5 (***C***, Ar), 129.3 (2***C***H, Ar), 128.7 (2***C***H, Ar), 128.0 (2***C***H, Ar), 127.4 (***C***H, Ar), 126.8 (2***C***H, Ar), 117.1

(C=***C***H_2), 56.0 (C(O)***C***C(O)N), 52.1 (O***C***H_3), 50.7 (***C***$H_2C_6H_5$), 47.4 (N(Bn)***C***H_2), 45.5 (N(CH_3)***C***H_2), 42.6 (***C***H), 29.4 (N***C***H_3), 26.7 ($N(CH_3)CH_2$***C***H_2), 24.6 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2924 (C-H), 1719 (C=O), 1691 (C=O), 1635 (C=O), 1607 (C=C); **MS** (ES+) m/z (rel. intensity %) 455.22 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{26}H_{28}N_2NaO_4$ $[M+Na]^+$ 455.1941, found 454.1945.

Preparation and characterisation of (±)-(5*R*,10*S*)-*tert*-butyl 8-benzyl-11-{1-[4-(methoxycarbonyl)phenyl]vinyl}-1,7-dioxo-2,8-diazaspiro[5.5]undecane-2-carboxylate (±)-167k



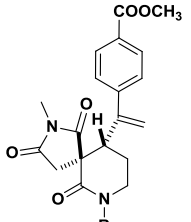
(±)-167k

Synthesised from substrate **165p** (60.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167k** was obtained (single diastereoisomer, 77.0 mg, 72% yield) as a colourless oil after flash column chromatography (PE/EA = 4:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 27:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93-7.99 (m, 2H, 2 × Ar***H***), 7.38-7.40 (m, 2H, 2 × Ar***H***), 7.34 (dd, 2H, *J* = 5.9 Hz, *J* = 2.3 Hz, 2 × Ar***H***), 7.25-7.29 (m, 3H, 3 × Ar***H***), 5.41 (s, 1H, C=C***H*****$_A$**H_B), 5.16 (s, 1H, C=CH_A***H*****$_B$**), 4.67 (d, 1H, *J* = 14.7 Hz, C***H*****$_A$**$H_BC_6H_5$), 4.51 (d, 1H, *J* = 14.7 Hz, CH_A***H*****$_B$**C_6H_5), 4.09-4.14 (m, 1H, C***H***), 3.87 (s, 3H, OC***H*****$_3$**), 3.68-3.73 (m, 1H, N(Boc)C***H*****$_A$**H_B), 3.45-3.53 (m, 1H, N(Bn)C***H*****$_A$**H_B), 3.26-3.31 (m, 1H, N(Bn)CH_A***H*****$_B$**), 3.02 (ddd, 1H, *J* = 12.6 Hz, *J* = 10.9 Hz, *J* = 3.4 Hz, N(Boc)CH_A***H*****$_B$**), 2.22-2.33 (m, 1H, N(Boc)CH_2C***H*****$_A$**H_B), 2.09 (ddd, 1H, *J* = 17.7 Hz, *J* = 10.7 Hz, *J* = 6.6 Hz, CHC***H*****$_A$**H_B), 1.95-2.01 (m, 3H, $CHCH_A$***H*****$_B$** and CC***H*****$_2$**), 1.71 (dq, 1H, *J* = 8.8 Hz, *J* = 4.8 Hz, N(Boc)CH_2CH_A***H*****$_B$**), 1.31 (s, 9H, C(C***H*****$_3$**)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 171.5

(N(Boc)***C***=O), 170.4 (N***C***=O), 166.6 (***C***(O)OCH_3), 151.5 (C$(CH_3)_3$***C***(O)N), 148.7 (***C***=CH_2), 145.1 (***C***, Ar), 136.7 (***C***, Ar), 129.6 (***C***, Ar), 129.5 (3***C***H, Ar), 128.7 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.4 (2***C***H, Ar), 118.5 (C=***C***H_2), 82.5 (***C***$(CH_3)_3$), 56.0 (C(O)***C***C(O)N), 51.9 (O***C***H_3), 50.4 (***C***$H_2C_6H_5$), 46.1 (N***C***H_2CH_2CH or N(Boc)***C***H_2), 46.0 (N***C***H_2CH_2CH or N(Boc)***C***H_2), 44.7 (***C***H), 28.1 (C***C***H_2), 27.7 (3C, C(***C***$H_3)_3$), 24.1 (CH***C***H_2), 20.4 (CCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2979 (C-H), 1768 (C=O), 1718 (C=O), 1634 (C=O); **MS** (ES+) m/z (rel. intensity %) 555.27 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{31}H_{36}N_2NaO_6$ $[M+Na]^+$ 555.2466, found 555.2460.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(7-benzyl-2-methyl-1,3,6-trioxo-2,7-diazaspiro[4.5]dec-10-yl)vinyl]benzoate (±)-167l



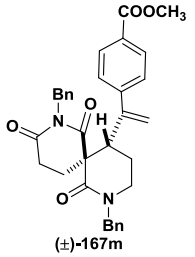
(±)-167l

Synthesised from substrate **165q** (64.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167l** was obtained (single diastereoisomer, 77.0 mg, 66% yield) as a colourless oil after flash column chromatography (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 6:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.97 (d, 2H, *J* = 8.2 Hz, 2 × Ar***H***), 7.26-7.42 (m, 7H, 7 × Ar***H***), 5.44 (s, 1H, C=C***H***$_A$$H_B$), 5.19 (s, 1H, C=C$H_A$***H*****$_B$**), 4.68 (d, 1H, *J* = 14.5 Hz, C***H***$_A$$H_B$$C_6H_5$), 4.57 (d, 1H, *J* = 14.6 Hz, CH_A***H***$_B$$C_6H_5$), 3.91 (s, 3H, OC***H*****$_3$**), 3.81 (d, 1H, *J* = 11.7 Hz, C***H***), 3.53 (dt, 1H, *J* = 12.0 Hz, *J* = 4.0 Hz, NC***H***$_A$$H_B$$CH_2$), 3.38 (ddd, 1H, *J* = 12.3 Hz, *J* = 4.8 Hz, *J* = 2.5 Hz, NCH_A***H***$_B$$CH_2$), 2.90 (d, 1H, *J* = 17.6 Hz, C(O)C***H***$_A$$H_B$) 2.82 (d, 1H, *J* = 17.7 Hz, C(O)CH_A***H***$_B$), 2.30 (s, 3H, NC***H*****$_3$**), 2.20 (dd, 1H, *J* = 13.1 Hz, *J* = 2.0 Hz, CHC***H***$_A$$H_B$), 1.80-1.92 (m, 1H, $CHCH_A$***H***$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 176.9

(N(CH_3)***C***(O)C), 175.4 (CH_2***C***(O)), 168.5 (N(Bn)***C***=O), 166.5 (***C***(O)OCH_3), 147.3 (***C***=CH_2), 144.5 (***C***, Ar), 136.0 (***C***, Ar), 129.9 (***C***, Ar), 129.5 (2***C***H, Ar), 128.9 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.8 (***C***H, Ar), 127.0 (2***C***H, Ar), 118.8 (C=***C***H_2), 55.3 (NC(O)***C***C(O)N), 52.2 (O***C***H_3), 50.9 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 42.34 (***C***H), 37.2 (***C***H_2C(O)), 25.0 (CH***C***H_2), 24.7 (N***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2950 (C-H), 1780 (C=O), 1707 (C=O), 1640 (C=O), 1607 (C=O); **MS** (ES+) m/z (rel. intensity %) 469.20 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{26}H_{26}N_2NaO_5$ $[M+Na]^+$ 469.1734, found 469.1741.

Preparation and characterisation of (±)-(5*R*,10*S*)-methyl 4-[1-(2,8-dibenzyl-1,7,9-trioxo-2,8-diazaspiro[5.5]undec-5-yl)vinyl]benzoate (±)-167m



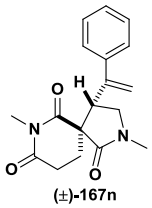
(±)-167m

Synthesised from substrate **165r** (80.0 mg, 0.2 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167m** was obtained (single diastereoisomer, 75.0 mg, 70% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 12:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95-7.97 (m, 2H, 2 × Ar***H***), 7.09-7.38 (m, 12H, 12 × Ar***H***), 5.37 (s, 1H, C=C***H*****$_A$**H_B), 5.15 (s, 1H, C=CH_A***H*****$_B$**), 4.78 (d, 1H, *J* = 14.7 Hz, C***H*****$_A$**$H_B$$C_6H_5$), 4.44 (d, 1H, *J* = 14.7 Hz, CH_A***H*****$_B$**C_6H_5), 4.39 (d, 1H, *J* = 14.5 Hz, C***H*****$_A$**$H_B$$C_6H_5$), 4.11 (dd, 1H, *J* = 9.8 Hz, *J* = 5.2 Hz, C***H***), 4.05 (d, 1H, *J* = 14.5 Hz, CH_A***H*****$_B$**C_6H_5), 3.93 (s, 3H, OC***H*****$_3$**), 3.46-3.53 (m, 1H, CH_2C***H*****$_A$**H_BN), 3.35 (td, 1H, *J* = 8.1 Hz, *J* = 4.4 Hz, CH_2CH_A***H*****$_B$**N), 3.12 (ddd, 1H, *J* = 16.9 Hz, *J* = 12.6 Hz, *J* = 6.0 Hz, C(O)C***H*****$_A$**H_B), 2.64 (td, 1H, *J* = 16.7 Hz, *J* = 4.5 Hz, C(O)CH_A***H*****$_B$**), 2.30 (ddd, 1H, *J* = 13.8 Hz, *J* = 12.8 Hz, *J* = 5.0 Hz, CC***H*****$_A$**H_B), 2.02-2.15 (m, 3H, CCH_A***H*****$_B$** and CHC***H*****$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.3

(CH_2(O)C(Bn)N***C***(O)), 171.6 ((Bn)N***C***(O)CH_2), 168.9 (***C***(O)NBn), 166.6 (***C***(O)OCH_3), 147.8 (***C***=CH_2), 145.6 (***C***, Ar), 136.5 (***C,*** Ar), 136.3 (***C***, Ar), 129.6 (***C***, Ar), 129.4 (2***C***H, Ar), 128.8 (2***C***H, Ar), 128.2 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.7 (2***C***H, Ar), 127.5 (2***C***H, Ar), 126.9 (2***C***H, Ar), 118.9 (C=***C***H_2), 53.6 (C(O)***C***C(O)), 52.2 (O***C***H_3), 50.4 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 43.5 (***C***H), 43.4 (***C***$H_2C_6H_5$), 29.5 (C(O)***C***H_2CH_2), 23.6 (CH***C***H_2), 22.2 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2950 (C-H), 1721 (C=O), 1678 (C=O), 1632 (C=O), 1607 (C=O); **MS** (ES+) m/z (rel. intensity %) 559.25 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{33}H_{32}N_2NaO_5$ $[M+Na]^+$ 559.2203, found 559.2200.

Preparation and characterisation of (±)-(5*R*,10*S*)-2, 7-dimethyl-4-(1-phenylvinyl)-2,7-diazaspiro[4.5]decane-1,6,8-trione (±)-167n



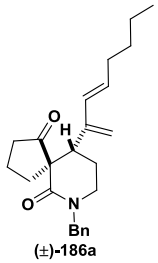
(±)-167n

Synthesised from substrate **165d** (50.0 mg. 0.2 mmol) and iodobenzene (61.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-167n** was obtained as a mixture of inseparable diastereoisomers with a 3:1 dr after flash column chromatography (PE/EA = 2:1) on silica gel (45.0 mg, 73% yield).

Two diastereoisomers: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28-7.13 (m, both, 10H, 10 × Ar***H***), 5.34 (d, major, 1H, *J* = 0.6 Hz, C=C***H$_A$***H_B), 5.31 (s, minor, 1H, C=C***H$_A$***H_B), 5.19 (s, minor, 1H, C=CH_A***H$_B$***), 5.07 (d, major, 1H, *J* = 1.5 Hz, C=CH_A***H$_B$***), 4.53 (t, major, 1H, *J* = 8.4 Hz, C***H***), 3.77 (t, minor, 1H, *J* = 9.2 Hz, CHC***H$_A$***H_BN), 3.55-3.65 (m, major, 2H, CHC***H$_2$***N), 3.42-3.50 (td, minor, 2H, $CHCH_A$***H$_B$***N and C***H***), 2.86-3.03 (m, major, 1H, C***H$_A$***H_BCO), 3.00 (s, minor, 3H, C(O)N(C***H$_3$***)C(O)), 2.95 (s, minor, 3H, C(O)N(C***H$_3$***)CH_2), 2.89 (s, major, 3H, C(O)N(C***H$_3$***)C(O)), 2.76 (s, major, 3H, C(O)N(C***H$_3$***)CH_2), 2.68-2.74 (m, minor, 1H, C***H$_A$***H_BC(O)), 2.41 (td, major, 1H, *J* = 17.0 Hz, *J* = 4.3 Hz, CH_A***H$_B$***C(O)), 2.31-2.36 (m, minor,

1H, $CH_AH_BC(O)$), 1.81-1.91 (m, minor, 2H, CCH_2), 1.79-1.69 (m, major, 2H, CCH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.2 (2C, both, $C(O)NCH_3$), 171.7 (2C, both, $C(O)N(CH_3)C(O)CH_2$), 171.0 (2C, both, $C(O)N(CH_3)C(O)CH_2$), 145.8 (major, $C=CH_2$), 144.3 (minor, $C=CH_2$), 139.8 (major, Ar), 135.8 (minor, Ar), 125.5-128.9 (10C, both, Ar), 117.5 (minor, $C=CH_2$), 116.0 (major, $C=CH_2$), 56.7 (minor, $C(O)CC(O)$), 54.7 (major, $C(O)CC(O)$), 52.8 (minor, $CH_2N(CH_3)$), 50.1 (major, $CH_2N(CH_3)$), 49.1 (minor, CH), 44.0 (major, CH), 30.3 (2C, both, $C(O)N(CH_3)CH_2$), 28.6 (2C, both, $CH_2CH_2C(O)$), 27.1 (major, $C(O)N(CH_3)CH_2$), 26.5 (minor, $C(O)N(CH_3)C(O)$), 26.1 (minor, $CH_2CH_2C(O)$), 21.1 (major, $CH_2CH_2C(O)$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2950 (C-H), 1726 (C=O), 1697 (C=O), 1693 (C=O), 1609 (C=C); **MS** (ES+) m/z (rel. intensity %) 335.15 (M + Na^+, 100); **HRMS** (ESI+) calcd. $C_{18}H_{20}O_3N_2Na$ $[M+Na]^+$ 335.1369, found 335.1366.

Preparation and characterisation of (±)-(5*R*,10*S*)-7-benzyl-10-((*E*)-octa-1,3-dien-2-yl)-7-azaspiro[4.5]decane-1,6-dione (±)-186a



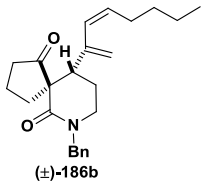
(±)-186a

Synthesised from substrate **165g** (57.0 mg, 0.2 mmol) and (*E*)-1-iodohex-1-ene (63.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186a** was obtained (single diastereoisomer, 47.0 mg, 65% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 4:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 15:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.25-7.35 (m, 5H, 5 × Ar*H*), 5.72-5.85 (m, 2H, *n*BuC*H*=C*H*), 5.17 (s, 1H, $C=CH_AH_B$), 4.74 (s, 1H, $C=CH_AH_B$), 4.60 (d, 1H, *J* = 14.7 Hz, $CH_AH_BC_6H_5$), 4.56 (d, 1H, *J* = 14.7 Hz, $CH_AH_BC_6H_5$), 3.20-3.32 (m, 2H, NCH_2CH_2), 3.08 (dd, 1H, *J* = 9.6 Hz, *J* = 2.9 Hz, CH), 2.44-2.54 (m, 2H, $C(O)CH_AH_B$ and $C(O)CCH_AH_B$), 2.01-2.26 (m, 6H,

CH=CHC$\boldsymbol{H_2}$ and CHC$\boldsymbol{H_A}$H$_B$ and C(O)CH$_A$$\boldsymbol{H_B}$ and C(O)CCH$_A$$\boldsymbol{H_B}$ and C(O)CH$_2$C$\boldsymbol{H_A}$H$_B$), 1.69-1.78 (m, 2H, CHCH$_A$$\boldsymbol{H_B}$ and C(O)CH$_2$CH$_A$$\boldsymbol{H_B}$), 1.26-1.39 (m, 4H, CH$_3C\boldsymbol{H_2}$ and CH$_3$CH$_2$C$\boldsymbol{H_2}$), 0.89 (t, 3H, J = 7.0 Hz, C$\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.4 (***C***=O), 171.1 (N***C***=O), 145.2 (***C***=CH$_2$), 136.8 (***C***, Ar), 132.1 (*n*BuCH=***C***H), 131.0 (*n*Bu***C***H=CH), 128.6 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.4 (***C***H, Ar), 113.9 (C=***C***H$_2$), 59.5 (C(O)***C***C(O)N), 50.4 (***C***H$_2$C$_6$H$_5$), 45.4 (N***C***H$_2$CH$_2$), 40.8 (***C***H), 39.2 (C(O)***C***H$_2$), 32.5 (CH=CH***C***H$_2$), 32.1 (C(O)C***C***H$_2$), 31.3 (CH$_3$CH$_2$***C***H$_2$), 24.3 (CH***C***H$_2$), 22.3 (CH$_3$***C***H$_2$), 20.2 (C(O)CH$_2$***C***H$_2$), 13.9 (***C***H$_3$CH$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2956 (C-H), 2930 (C-H), 1739 (C=O), 1628 (C=O), 1494 (C=C), 1453 (C=C); **MS** (ES+) m/z (rel. intensity %) 388.25 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{31}NNaO_2$ $[M+Na]^+$ 388.2247, found 388.2247.

Preparation and characterisation of (5*R*,10*S*)-7-benzyl-10-[(3*Z*)-octa-1,3-dien-2-yl]-7 azaspiro[4.5]decane-1,6-dione (±)-186b



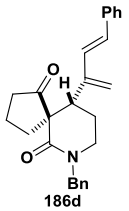
(±)-186b

Synthesised from substrate **165g** (57.0 mg, 0.2 mmol) and (*E*)-1-iodohex-1-ene (63.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186b** was obtained (single diastereoisomer, 48.0 mg, 66% yield) as a colourless oil after flash column chromatography (PE/Et$_2$O = 4:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 11:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.23-7.35 (m, 5H, 5 × Ar***H***), 5.59 (d, 1H, J = 11.7 Hz, *n*BuCH=C***H***), 5.47 (td, 1H, J = 11.7 Hz, J = 7.1 Hz, *n*BuC***H***=CH), 5.04 (s, 1H, C=C$\boldsymbol{H_A}$H$_B$), 5.00 (s, 1H, C=CH$_A$$\boldsymbol{H_B}$), 4.66 (d, 1H, J = 14.7 Hz, C$\boldsymbol{H_A}$H$_B$C$_6$H$_5$), 4.44 (d, 1H, J = 14.7 Hz, CH$_A$$\boldsymbol{H_B}C_6H_5$), 3.21-3.33 (m, 2H, NC$\boldsymbol{H_2}CH_2$), 2.97 (dd, 1H, J = 11.2 Hz, J = 2.5 Hz, C***H***), 2.55 (m, 1H, C(O)CC$\boldsymbol{H_A}$H$_B$), 2.31-2.35 (m, 1H, C(O)C$\boldsymbol{H_A}$H$_B$), 2.12-2.26 (m, 5H, C(O)CH$_A$$\boldsymbol{H_B}$ and C(O)CCH$_A$$\boldsymbol{H_B}$ and C(O)CH$_2$C$\boldsymbol{H_A}$H$_B$ and C$\boldsymbol{H_2}$CH=CH), 1.98-2.04 (m, 1H, CHC$\boldsymbol{H_A}$H$_B$), 1.73-

1.83 (m, 2H, $CHCH_A\boldsymbol{H_B}$ and $C(O)CH_2CH_A\boldsymbol{H_B}$), 1.28-1.36 (m, 4H, $C\boldsymbol{H_2}C\boldsymbol{H_2}CH_3$), 0.90 (t, 3H, *J* = 7.0 Hz, $C\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.8 (***C***=O), 171.3 (N***C***=O), 143.7 (***C***=CH_2), 136.7 (***C***, Ar), 134.2 (*n*BuCH=***C***H), 129.3 (*n*Bu***C***H=CH), 128.6 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.4 (***C***H, Ar), 116.1 (C=***C***H_2), 59.7 (CO***C***CON), 50.1 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 44.2 (***C***H), 39.4 (C(O)***C***H_2), 32.1 (C(O)C***C***H_2), 31.4 (CH_3CH_2***C***H_2), 28.8 (***C***H_2CH=CH_2), 24.4 (CH***C***H_2), 22.5 (***C***H_2CH_3), 19.8 ($C(O)CH_2$***C***H_2), 14.0 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2957 (C-H), 2871 (C-H), 1740 (C=O), 1628 (NC=O), 1494 (C=C), 1453 (C=C); **MS** (ES+) m/z (rel. intensity %) 388.26 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{31}NNaO_2$ $[M+Na]^+$ 388.2242, found 388.2247.

Preparation and characterisation of (±)-(5*R*,10*S*)-7-benzyl-10-((*E*)-4-phenylbuta-1,3-dien-2-yl)-7-azaspiro[4.5]decane-1,6-dione (±)-186d



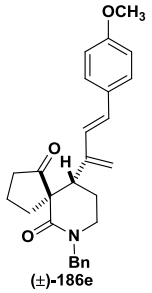
186d

Synthesised from substrate **165g** (57.0 mg, 0.2 mmol) and (*E*)-(2-iodovinyl)benzene (69.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186d** was obtained (single diastereoisomer, 49.0 mg, 63% yield) as a colourless oil after flash column chromatography (PE/ Et_2O = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 16:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.25-7.40 (m, 10H, 10 × Ar***H***), 6.65 (d, 1H, *J* = 16.3 Hz, PhC***H***=CH), 6.56 (d, 1H, *J* = 16.3 Hz, PhCH=C***H***), 5.43 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 4.94 (s, 1H, C=$CH_A\boldsymbol{H_B}$), 4.61 (d, 1H, *J* = 14.7 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.58 (d, 1H, *J* = 14.7 Hz, $CH_A\boldsymbol{H_B}C_6H_5$), 3.24-3.39 (m, 3H, NC$\boldsymbol{H_2}CH_2$ and C***H***), 2.46-2.55 (m, 2H, C(O)C$\boldsymbol{H_A}H_B$ and C(O)CC$\boldsymbol{H_A}H_B$), 2.11-2.26 (m, 4H, CHC$\boldsymbol{H_A}H_B$ and $C(O)CH_A\boldsymbol{H_B}$ and $C(O)CCH_A\boldsymbol{H_B}$ and $C(O)CH_2C\boldsymbol{H_A}H_B$), 1.74-1.87 (m, 2H, $CHCH_A\boldsymbol{H_B}$ and $C(O)CH_2CH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.5

(***C***=O), 171.0 (N***C***=O), 145.0 (***C***=CH_2), 136.8 (2***C***, Ar), 129.8 (PhCH=***C***H), 129.6 (Ph***C***H=CH), 128.7 (3***C***H, Ar), 127.9 (3***C***H, Ar), 127.4 (***C***H, Ar), 126.5 (3***C***H, Ar), 115.9 (C=***C***H_2), 59.5 (C(O)***C***C(O)N), 50.4 (***C***$H_2C_6H_5$), 45.4 (N***C***H_2CH_2), 40.9 (***C***H), 39.1 (C(O)***C***H_2), 32.2 (C(O)C***C***H_2), 24.3 (CH***C***H_2), 20.1 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2956 (C-H), 1737 (C=O), 1626 (NC=O), 1494 (C=C), 1452 (C=C); **MS** (ES+) m/z (rel. intensity %) 408.23 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{26}H_{27}NNaO_2$ $[M+Na]^+$ 408.1928, found 408.1934.

Preparation and characterisation of (5*R*,10*S*)-7-benzyl-10-[(3*E*)-4-(4-methoxyphenyl)buta-1,3-dien-2-yl]-7-azaspiro[4.5]decane-1,6-dione (±)-186e



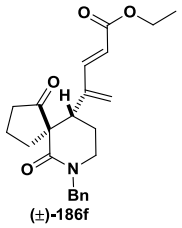
(±)-186e

Synthesised from substrate **165g** (57.0 mg, 0.2 mmol) and (*E*)-1-(2-iodovinyl)-4-methoxybenzene (78.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186e** was obtained (single diastereoisomer, 62.0 mg, 75% yield) as a colourless oil after flash column chromatography on silica gel (PE/Et_2O = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 13:1 dr.

^{1}HNMR (400 MHz, $CDCl_3$) δ_H 7.26-7.36 (m, 7H, 7 × Ar***H***), 6.86 (d, 2H, *J* = 8.7 Hz, 2 × Ar***H***), 6.60 (d, 1H, *J* = 16.2 Hz, ArCH=C***H***), 6.42 (d, 1H, *J* = 16.2 Hz, ArCH=C***H***), 5.38 (s, 1H, C=C***H*****$_A$**H_B), 4.89 (s, 1H, C=CH_A***H*****$_B$**), 4.60 (d, 1H, *J* = 14.7 Hz, C***H*****$_A$**$H_B$$C_6H_5$), 4.56 (d, 1H, *J* = 14.7 Hz, CH_A***H*****$_B$**C_6H_5), 3.81 (s, 3H, OC***H*****$_3$**), 3.22-3.34 (m, 3H, NC***H*****$_2$**CH_2 and C***H***), 2.47-2.54 (m, 2H, C(O)C***H*****$_A$**H_B and C(O)CC***H*****$_A$**H_B), 2.09-2.25 (m, 4H, CHC***H*****$_A$**H_B and C(O)CH_A***H*****$_B$** and C(O)CCH_A***H*****$_B$** and C(O)CH_2C***H*****$_A$**H_B), 1.74-1.86 (m, 2H, CHCH_A***H*****$_B$** and C(O)CH_2CH_A***H*****$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.6 (***C***=O), 171.0 (N***C***=O), 159.5 (***C***, Ar), 145.2 (***C***=CH_2),

136.8 (***C***, Ar), 129.5 (***C***, Ar), 129.1 (ArCH=***C***H), 128.6 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.8 (2***C***H, Ar), 127.4 (Ar***C***H=CH), 114.9 (C=***C***H_2), 114.1 (2***C***H, Ar), 59.5 (C(O)***C***C(O)N), 55.3 (O***C***H_3), 50.4 (***C***$H_2C_6H_5$), 45.5 (N***C***H_2CH_2), 40.9 (***C***H), 39.1 (C(O)***C***H_2), 32.1 (C(O)C***C***H_2), 24.3 (CH***C***H_2), 20.1 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2958 (C-H), 1742 (C=O), 1627 (NC=O), 1494 (C=C), 1452 (C=C); **MS** (ES+) m/z (rel. intensity %) 438.24 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{27}H_{29}NNaO_3$ $[M+Na]^+$ 438.1988, found 438.1986.

Preparation and characterisation of ethyl (2*E*)-4-[(5*R*,10*S*)-7-benzyl-1,6-dioxo-7 azaspiro[4.5]dec-10-yl]penta-2,4-dienoate (±)-186f



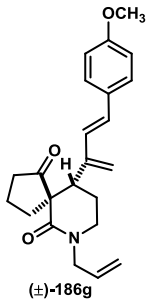
(±)-186f

Synthesised from substrate **165g** (57.0 mg, 0.2 mmol) and (*E*)-ethyl 3-iodoacrylate (67.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186f** was obtained (single diastereoisomer, 52.0 mg, 68% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 12:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18-7.37 (m, 6H, 5 × Ar***H*** and (O)CCH=C***H***), 5.97 (d, 1H, *J* = 16.0 Hz, (O)CC***H***=CH), 5.61 (s, 1H, C=C***H_A***H_B), 5.19 (s, 1H, C=CH_A***H_B***), 4.59 (d, 1H, *J* = 14.7 Hz, C***H_A***$H_B$$C_6H_5$), 4.56 (d, 1H, *J* = 14.7 Hz, CH_A***H_B***C_6H_5), 4.21 (dq, 2H, *J* = 7.1 Hz, *J* = 1.5 Hz, CH_3C***H_2***O), 3.19-3.33 (m, 2H, NC***H_2***CH_2), 3.11 (dd, 1H, *J* = 8.1 Hz, *J* = 3.4 Hz, C***H***), 2.48-2.63 (m, 2H, C(O)CC***H_A***H_B and C(O)C***H_A***H_B), 2.03-2.32 (m, 4H, CHC***H_A***H_B and C(O)CH_A***H_B*** and C(O)CCH_A***H_B*** and C(O)CH_2C***H_A***H_B),1.67-1.78 (m, 2H, C(O)CH_2CH_A***H_B*** and CHCH_A***H_B***), 1.30 (t, 3H, *J* = 7.1 Hz, C***H_3***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.2 (***C***=O), 170.1 (N***C***=O), 166.7 (O***C***=O), 145.4 ((O)CCH=***C***H), 143.0 (***C***=CH_2), 136.6 (***C***, Ar), 128.7 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.5 (***C***H, Ar), 123.7 ((O)C***C***H=CH), 119.4 (C=***C***H_2), 60.6

(***C***H_2O), 59.0 (C(O)***C***C(O)N), 50.5 (***C***$H_2C_6H_5$), 44.8 (N***C***H_2CH_2), 39.5 (***C***H), 38.8 (C(O)***C***H_2), 32.3 (C(O)C***C***H_2), 23.6 (CH***C***H_2), 20.0 (C(O)CH_2***C***H_2), 14.2 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2927 (C-H), 1713 (C=O), 1629 (NC=O), 1493 (C=C), 1452 (C=C); **MS** (ES+) m/z (rel. intensity %) 404.21 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{23}H_{27}NNaO_4$ $[M+Na]^+$ 404.1833, found 404.1832.

Preparation and characterisation of (5*R*,10*S*)-7-allyl-10-[(3*E*)-4-(4-methoxyphenyl)buta-1,3-dien-2-yl]-7-azaspiro[4.5]decane-1,6-dione (±)-186g



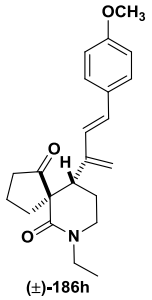
(±)-186g

Synthesised from substrate **165h** (47.0 mg, 0.2 mmol) and (*E*)-1-(2-iodovinyl)-4-methoxybenzene (78.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186g** was obtained (single diastereoisomer, 51.0 mg, 67% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 16:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 (d, 2H, *J* = 8.7 Hz, 2 × Ar***H***), 6.86 (d, 2H, *J* = 8.7 Hz, 2 × Ar***H***), 6.60 (d, 1H, *J* = 16.2 Hz, ArCH=C***H***), 6.42 (d, 1H, *J* = 16.2 Hz, ArC***H***=CH), 5.71-5.81 (m, 1H, C***H***=CH_2), 5.40 (s, 1H, C=C***H_A***H_B), 5.18-5.23 (m, 2H, CH=C***H_2***), 4.91 (s, 1H, C=CH_A***H_B***), 4.05 (dd, 1H, *J* = 15.1 Hz, *J* = 5.6 Hz, C***H_A***H_BCH=CH_2), 3.91 (dd, 1H, *J* = 15.1 Hz, *J* = 5.6 Hz, CH_A***H_B***CH=CH_2), 3.81 (s, 3H, OC***H_3***), 3.29-3.38 (m, 2H, NC***H_2***CH_2), 3.22 (dd, 1H, *J* = 9.5 Hz, *J* = 3.0 Hz, C***H***), 2.40-2.48 (m, 2H, C(O)C***H_A***H_B and C(O)CC***H_A***H_B), 2.09-2.26 (m, 4H, CHC***H_A***H_B and C(O)CH_A***H_B*** and C(O)CCH_A***H_B*** and C(O)CH_2C***H_A***H_B), 1.71-1.89 (m, 2H, CHCH_A***H_B*** and C(O)$CH_2$$CH_A$***$H_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.5 (***C***=O), 170.7 (N***C***=O), 159.5 (***C***, Ar), 145.2 (***C***=CH_2), 132.2 (ArCH=***C***H), 129.9 (***C***, Ar), 129.5

(***C***H=CH_2), 129.1 (Ar***C***H=CH), 127.8 (2***C***H, Ar), 117.4 (CH=***C***H_2), 114.9 (C=***C***H_2), 114.1 (2***C***H, Ar), 59.4 (C(O)***C***C(O)N), 55.3 (O***C***H_3), 49.7 (***C***H_2CH=CH_2), 45.5 (N***C***H_2CH_2), 40.9 (***C***H), 39.1 (C(O)***C***H_2), 32.1 (C(O)C***C***H_2), 24.3 (CH***C***H_2), 20.0 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2955 (C-H), 1736 (C=O), 1625 (NC=O), 1510 (C=C), 1492 (C=C); **MS** (ES+) m/z (rel. intensity %) 388.23 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{23}H_{27}NNaO_3$ $[M+Na]^+$ 388.1886, found 388.1883.

Preparation and characterisation of (5*R*,10*S*)-7-ethyl-10-[(3*E*)-4-(4-methoxyphenyl)buta-1,3-dien-2-yl]-7-azaspiro[4.5]decane-1,6-dione (±)-186h



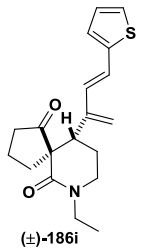
(±)-186h

Synthesised from substrate **165e** (45.0 mg, 0.2 mmol) and (*E*)-1-(2-iodovinyl)-4-methoxybenzene (78.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186h** was obtained (single diastereoisomer, 54.0 mg, 76% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 15:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30-7.34 (m, 2H, 2 × Ar***H***), 6.84-6.86 (m, 2H, 2 × Ar***H***), 6.59 (d, 1H, *J* = 16.2 Hz, ArCH=C***H***), 6.42 (d, 1H, *J* = 16.2 Hz, ArC***H***=CH), 5.39 (s, 1H, C=C***H***$_A$$H_B$), 4.90 (s, 1H, C=$CH_A$***H***$_B$), 3.80 (s, 3H, O***C***$H_3$), 3.28-3.43 (m, 4H, C***H***$_2$$CH_3$ and NC***H***$_2$$CH_2$), 3.19 (dd, 1H, *J* = 9.6 Hz, *J* = 3.0 Hz, C***H***), 2.39-2.48 (m, 2H, C(O)C***H***$_A$$H_B$ and C(O)CC***H***$_A$$H_B$), 2.04-2.26 (m, 4H, CHC***H***$_A$$H_B$ and C(O)CH_A***H***$_B$ and C(O)CCH_A***H***$_B$ and C(O)CH_2C***H***$_A$$H_B$), 1.69-1.88 (m, 2H, CH$CH_A$***H***$_B$ and C(O)$CH_2$$CH_A$***H***$_B$), 1.13 (t, 3H, *J* = 7.2 Hz, CH_2C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.7 (***C***=O), 170.3 (N***C***=O), 159.5 (***C***, Ar), 145.3 (***C***=CH_2), 129.5 (***C***, Ar), 129.1 (ArCH=***C***H), 127.8 (Ar***C***H=CH), 127.7 (2***C***H, Ar), 114.9

(C=***C***H_2), 114.1 (2***C***H, Ar), 59.3 (C(O)***C***C(O)N), 55.3 (O***C***H_3), 45.5 (N***C***H_2CH_2), 42.4 (***C***H_2CH_3), 40.9 (***C***H), 39.1 (C(O)***C***H_2), 32.1 (C(O)C***C***H_2), 24.4 (CH***C***H_2), 20.0 (C(O)CH_2***C***H_2), 11.9 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2962 (C-H), 2937 (C-H), 1736 (C=O), 1625 (NC=O), 1515 (C=C), 1493 (C=C); **MS** (ES+) m/z (rel. intensity %) 376.22 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{27}NNaO_3$ $[M+Na]^+$ 376.1878, found 376.1883.

Preparation and characterisation of (5*R*,10*S*)-7-ethyl-10-[(3*E*)-4-(2-thienyl)buta-1,3-dien-2-yl]-7-azaspiro[4.5]decane-1,6-dione (±)-186i



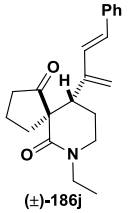
(±)-186i

Synthesised from substrate **165e** (45.0 mg, 0.2 mmol) and (*E*)-2-(2-iodovinyl)thiophene (70.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186i** was obtained (single diastereoisomer, 43.0 mg, 65% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 4:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 15:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.17 (d, 1H, *J* = 5.0 Hz, thiophene-***H***), 6.95-7.00 (m, 2H, 2 × thiophene-***H***), 6.77 (d, 1H, *J* = 16.1 Hz, thiophene-CH=C***H***), 6.41 (d, 1H, *J* = 16.1 Hz, thiophene-C***H***=CH), 5.40 (s, 1H, C=C***H***$_A$H$_B$), 4.94 (s, 1H, C=CH$_A$***H***$_B$), 3.31-3.39 (m, 4H, NC***H***$_2$$CH_3$ and NC***H***$_2$$CH_2$), 3.16 (dd, 1H, *J* = 9.3 Hz, *J* = 3.1 Hz, C***H***), 2.45 (m, 2H, C(O)C***H***$_A$H$_B$ and C(O)CC***H***$_A$H$_B$), 2.06-2.27 (m, 4H, CHC***H***$_A$H$_B$ and C(O)CH$_A$***H***$_B$ and C(O)CCH$_A$***H***$_B$ and C(O)CH_2C***H***$_A$H$_B$), 1.69-1.87 (m, 2H, CHCH$_A$***H***$_B$ and C(O)CH_2CH$_A$***H***$_B$), 1.13 (t, 3H, *J* = 7.2 Hz, C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.5 (***C***=O), 170.1 (N***C***=O), 144.6 (***C***=CH_2), 142.2 (thiophene-***C***), 129.4 (thiophene-CH=***C***H), 127.6 (thiophene-***C***H), 126.5 (thiophene-***C***H), 124.7 (thiophene-***C***H), 122.7 (thiophene-***C***H=CH), 116.2 (C=***C***H_2), 59.3 (C(O)***C***C(O)N), 45.2 (N***C***H_2CH_2), 42.5 (***C***H_2CH_3), 40.4 (***C***H), 39.1 (C(O)***C***H_2), 32.1

(C(O)C***C***H_2), 24.3 (CH***C***H_2), 20.0 (C(O)CH_2***C***H_2), 11.9 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2966 (C-H), 2875 (C-H), 1737 (C=O), 1624 (NC=O), 1491 (C=C), 1456 (C=C); **MS** (ES+) m/z (rel. intensity %) 352.15 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{19}H_{23}NNaO_2S$ $[M+Na]^+$ 352.1342, found 352.1350.

Preparation and characterisation of (5*R*,10*S*)-7-ethyl-10-[(3*E*)-4-phenylbuta-1,3-dien-2-yl]-7-azaspiro[4.5]decane-1,6-dione (±)-186j



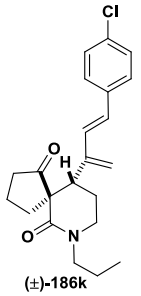
(±)-186j

Synthesised from substrate **165e** (45.0 mg, 0.2 mmol) and (*E*)-(2-iodovinyl)benzene (68.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186j** was obtained (single diastereoisomer, 50.0 mg, 77% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 4:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 17:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.21-7.39 (m, 5H, 5 × Ar***H***), 6.64 (d, 1H, *J* = 16.3 Hz, PhCH=C***H***), 6.56 (d, 1H, *J* = 16.3 Hz, PhC***H***=CH), 5.44 (s, 1H, C=C***H_A***H_B), 4.95 (s, 1H, C=CH_A***H_B***), 3.29-3.51 (m, 4H, NC***H_2***CH_3 and NC***H_2***CH_2), 3.21 (dd, 1H, *J* = 9.5 Hz, *J* = 3.0 Hz, C***H***), 2.40-2.49 (m, 2H, C(O)C***H_A***H_B and C(O)CC***H_A***H_B), 2.05-2.27 (m, 4H, CHC***H_A***H_B and C(O)CH_A***H_B*** and C(O)CCH_A***H_B*** and C(O)CH_2C***H_A***H_B), 1.80-1.89 (m, 1H, CHCH_A***H_B***), 1.69-1.76 (m, 1H, C(O)CH_2CH_A***H_B***), 1.13 (t, 3H, *J* = 7.2 Hz, C***H_3***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.7 (***C***=O), 170.3 (N***C***=O), 145.2 (***C***=CH_2), 136.8 (***C***, Ar), 129.9 (PhCH=***C***H), 129.6 (Ph***C***H=CH), 128.7 (2***C***H, Ar), 127.8 (***C***, Ar), 126.5 (2***C***H, Ar), 115.9 (C=***C***H_2), 59.3 (C(O)***C***C(O)N), 45.3 (N***C***H_2CH_2), 42.4 (N***C***H_2CH_3), 40.8 (***C***H), 39.1 (C(O)***C***H_2), 32.1 (C(O)C***C***H_2), 24.4 (CH***C***H_2), 20.0 (C(O)CH_2***C***H_2), 11.9 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2969 (C-H), 2875 (C-H), 1737 (C=O), 1626 (NC=O), 1492 (C=C), 1451 (C=C); **MS** (ES+) m/z (rel.

intensity %) 346.20 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{21}H_{25}NNaO_2$ $[M+Na]^+$ 346.1778, found 346.1788.

Preparation and characterisation of (5*R*,10*S*)-10-[(3*E*)-4-(4-chlorophenyl)buta-1,3-dien-2-yl]-7-propyl-7-azaspiro[4.5]decane-1,6-dione (±)-186k



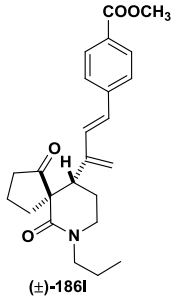
(±)-186k

Synthesised from substrate **165f** (47.0 mg, 0.2 mmol) and (*E*)-1-chloro-4-(2-iodovinyl)benzene (79.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186k** was obtained (single diastereoisomer, 52.0 mg, 69% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 13:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.26-7.32 (m, 4H, 4 × Ar***H***), 6.59 (d, 1H, *J* = 16.3 Hz, ArCH=C***H***), 6.51 (d, 1H, *J* = 16.3 Hz, ArC***H***=CH), 5.45 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 4.99 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 3.29-3.45 (m, 4H, NC$\boldsymbol{H_2}CH_2CH_3$ and NC$\boldsymbol{H_2}CH_2CH$), 3.21 (dd, 1H, *J* = 9.9 Hz, *J* = 2.9 Hz, C***H***), 2.35-2.49 (m, 2H, C(O)C$\boldsymbol{H_A}H_B$ and C(O)CC$\boldsymbol{H_A}H_B$), 2.06-2.24 (m, 4H, CHC$\boldsymbol{H_A}H_B$ and C(O)C$H_A\boldsymbol{H_B}$ and C(O)CC$H_A\boldsymbol{H_B}$ and C(O)CH_2C$\boldsymbol{H_A}H_B$), 1.80-1.90 (m, 1H, CHC$H_A\boldsymbol{H_B}$), 1.68-1.77 (m, 1H, C(O)CH_2C$H_A\boldsymbol{H_B}$), 1.55-1.61 (m, 2H, CH_3C$\boldsymbol{H_2}$), 0.91 (t, 3H, *J* = 7.4 Hz, C$\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.7 (***C***=O), 170.8 (N***C***=O), 145.1 (***C***=CH_2), 135.3 (***C***, Ar), 133.5 (***C***, Ar), 130.5 (ArCH=***C***H), 128.8 (2***C***H, Ar), 128.3 (Ar***C***H=CH), 127.7 (2***C***H, Ar), 116.4 (C=***C***H_2), 59.3 (C(O)***C***C(O)N), 49.2 (N***C***H_2CH_2CH), 46.0 (N***C***$H_2CH_2CH_3$), 40.8 (***C***H), 39.1 (C(O)***C***H_2), 32.1 (C(O)C***C***H_2), 24.4 (CH***C***H_2), 20.2 (***C***H_2CH_3), 20.0 (C(O)CH_2***C***H_2), 11.2 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2963 (C-H), 2874 (C-H), 1738 (C=O), 1626 (NC=O), 1491 (C=C), 1457 (C=C); **MS** (ES+) m/z (rel. intensity %) 394.18

(M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{26}ClNNaO_2$ $[M+Na]^+$ 394.1544, found 394.1550.

Preparation and characterisation of methyl 4-{(1*E*)-3-[(5*R*,10*S*)-1,6-dioxo-7-propyl-7-azaspiro[4.5]dec-10-yl]buta-1,3-dien-1-yl}benzoate (±)-186l



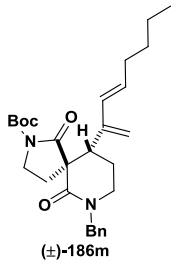
(±)-186l

Synthesised from substrate **165f** (47.0 mg, 0.2 mmol) and (*E*)-methyl 4-(2-iodovinyl)benzoate (86.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186l** was obtained (single diastereoisomer, 52.0 mg, 69% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 13:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.98 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.44 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 6.64-6.68 (m, 2H, ArC***H***=C***H***), 5.50 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.04 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 3.91 (s, 3H, C$\boldsymbol{H_3}$O), 3.29-3.45 (m, 4H, NC$\boldsymbol{H_2}CH_2CH_3$ and NC$\boldsymbol{H_2}CH_2$CH), 3.23 (dd, 1H, *J* = 9.6 Hz, *J* = 3.0 Hz, C***H***), 2.41-2.50 (m, 2H, C(O)C$\boldsymbol{H_A}H_B$ and C(O)CC$\boldsymbol{H_A}H_B$), 2.06-2.26 (m, 4H, CHC$\boldsymbol{H_A}H_B$ and C(O)C$H_A\boldsymbol{H_B}$ and C(O)CC$H_A\boldsymbol{H_B}$ and C(O)CH_2C$\boldsymbol{H_A}H_B$), 1.81-1.90 (m, 1H, CHC$H_A\boldsymbol{H_B}$), 1.68-1.75 (m, 1H, C(O)$CH_2CH_A\boldsymbol{H_B}$), 1.48-1.62 (m, 2H, $CH_3C\boldsymbol{H_2}$), 0.91 (t, 3H, *J* = 7.4 Hz, C$\boldsymbol{H_3}CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 218.6 (***C***=O), 170.5 (N***C***=O), 166.8 ($CH_3O\boldsymbol{C}$(O)), 145.0 (***C***=CH_2), 141.3 (***C***, Ar), 132.3 (Ar***C***H=CH), 129.9 (2***C***H, Ar), 129.3 (***C***, Ar), 128.5 (ArCH=***C***H), 126.4 (2***C***H, Ar), 117.5 (C=***C***H_2), 59.3 (C(O)***C***C(O)N), 52.1 (***C***H_3O), 49.2 (N***C***H_2CH_2CH), 46.0 (N***C***$H_2CH_2CH_3$), 40.6 (***C***H), 39.2 (C(O)***C***H_2), 32.1 (C(O)C***C***H_2), 24.5 (CH***C***H_2), 20.2 (***C***H_2CH_3), 20.0 (C(O)$CH_2\boldsymbol{C}H_2$), 11.2 ($CH_2\boldsymbol{C}H_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2963 (C-H), 2875 (C-H), 1720 (C=O), 1626 (NC=O), 1492 (C=C), 1456 (C=C); **MS** (ES+)

m/z (rel. intensity %) 396.25 ($M + H^+$, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{30}NO_4$ $[M+H]^+$ 396.2169, found 396.2172.

Preparation and characterisation of *tert*-butyl (5*S*,10*S*)-7-benzyl-10-[(3*E*)-octa-1,3-dien-2-yl]-1,6-dioxo-2,7-diazaspiro[4.5]decane-2-carboxylate (±)-186m



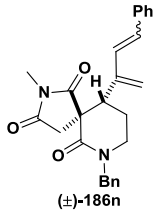
(±)-186m

Synthesised from substrate **165l** (77.0 mg, 0.2 mmol) and (*E*)-1-iodohex-1-ene (63.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186m** was obtained (single diastereoisomer, 60 mg, 64% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 1:1). Analysis of the ^1H NMR spectrum of the crude reaction mixture showed a 15:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.26-7.35 (m, 5H, 5 × Ar***H***), 5.78-5.92 (m, 2H, *n*BuC***H***=C***H***), 5.16 (s, 1H, C=C***H$_A$***H$_B$), 4.69 (s, 1H, C=CH$_A$***H$_B$***), 4.56-4.65 (m, 2H, C***H$_2$***C$_6$H$_5$), 3.89 (dt, 1H, *J* = 9.4 Hz, *J* = 6.3 Hz, BocNC***H$_A$***H$_B$), 3.55 (dt, 1H, *J* = 9.5 Hz, *J* = 6.3 Hz, BocNCH$_A$***H$_B$***), 3.22-3.34 (m, 3H, NC***H$_2$***CH$_2$C***H***), 2.40-2.51 (m, 2H, BocNCH$_2$C***H$_A$***H$_B$ and CHC***H$_A$***H$_B$CH$_2$), 1.97-2.07 (m, 3H, BocNCH$_2$CH$_A$***H$_B$*** and CH=CHC***H$_2$***), 1.63-1.73 (m, 1H, CHCH$_A$***H$_B$***). 1.52 (s, 9H, C(C***H$_3$***)$_3$), 1.23-1.40 (m, 4H, CH$_3$C***H$_2$***C***H$_2$***), 0.89 (t, 3H, *J* = 7.0 Hz, CH$_2$C***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 173.7 (BocN***C***(O)), 169.8 (N***C***(O)), 150.0 (N***C***(O)), 145.0 (***C***=CH$_2$), 136.5 (***C***, Ar), 132.1 (*n*BuCH=***C***H), 130.6 (*n*Bu***C***H=CH), 128.7 (2***C***H, Ar), 128.0 (2***C***H, Ar), 127.4 (***C***H, Ar), 113.8 (C=***C***H$_2$), 82.8 (O***C***(CH$_3$)$_3$), 57.3 (C(O)***C***C(O)N), 50.8 (***C***H$_2$C$_6$H$_5$), 45.2 (N***C***H$_2$CH$_2$), 44.7 (BocN***C***H$_2$), 41.5 (***C***H), 32.4 (***C***H$_2$CH=CH), 31.2 (BocNCH$_2$***C***H$_2$), 28.0 (3C, C(***C***H$_3$)$_3$), 26.5 (CH$_3$CH$_2$***C***H$_2$), 23.8 (CH***C***H$_2$), 22.3 (CH$_3$***C***H$_2$), 13.9 (***C***H$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2958 (C-H), 2931 (C-H), 2872 (C-H), 1781 (C=O), 1719 (C=O), 1638

(NC=O), 1494 (C=C), 1454 (C=C); **MS** (ES+) m/z (rel. intensity %) 489.29 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{28}H_{38}N_2NaO_4$ $[M+Na]^+$: 489.2726, found: 489.2724.

Preparation and characterisation of (5*S*,10*S*)-7-benzyl-2-methyl-10-[(3*E*)-4-phenylbuta-1,3-dien-2-yl]-2,7-diazaspiro[4.5]decane-1,3,6-trione (±)-186n



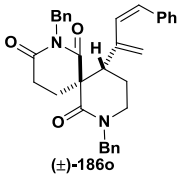
(±)-186n

Synthesised from substrate **165q** (62.0 mg, 0.2 mmol) and (*Z*)-(2-iodovinyl)benzene (69.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186n** was obtained (two diastereoisomers, 66.0 mg, 80% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a ratio of *cis*/*trans* 5:4.

The ratio of *cis*/*trans* is 5:4. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.21-7.37 (m, 20H, 20 × Ar***H***, both), 6.66 (d, 1H, *J* = 16.2 Hz, *trans*-PhCH=C***H***), 6.52 (d, 1H, *J* = 16.2 Hz, *trans*-PhC***H***=CH), 6.41 (d, 1H, *J* = 12.4 Hz, *cis*-PhCH=C***H***), 5.81 (d, 1H, *J* = 12.4 Hz, *cis*-PhC***H***=CH), 5.44 (s, 1H, C=C$\boldsymbol{H_A}H_B$, *trans*), 5.37 (s, 1H, C=C$\boldsymbol{H_A}H_B$, *cis*), 5.03 (s, 1H, C=C$H_A\boldsymbol{H_B}$, *cis*) 4.92 (s, 1H, C=C$H_A\boldsymbol{H_B}$, *trans*), 4.70 (d, 2H, *J* = 14.9 Hz, C$\boldsymbol{H_A}H_BC_6H_5$, both), 4.59 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$, *trans*), 4.46 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$, *cis*), 3.42-3.52 (m, 2H, NC$\boldsymbol{H_A}H_BCH_2$, both), 3.20-3.36 (m, 4H, NC$\boldsymbol{H_A}H_BCH_2C\boldsymbol{H}$, both), 2.76-3.00 (m, 10H, C$\boldsymbol{H_3}$ and COC$\boldsymbol{H_2}$, both), 2.23 (ddd, 1H, *J* = 13.2 Hz, *J* = 6.7 Hz, *J* = 3.6 Hz, $NCH_2C\boldsymbol{H_A}H_B$, *trans*), 2.06 (ddd, 1H, *J* = 13.4 Hz, *J* = 6.6 Hz, *J* = 3.5 Hz, $NCH_2C\boldsymbol{H_A}H_B$, *cis*), 1.71-1.88 (m, 2H, $NCH_2CH_A\boldsymbol{H_B}$, both); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 178.0 ($CH_2C(O)N(CH_3)\boldsymbol{C}(O)$, *trans*), 177.3 ($CH_2C(O)N(CH_3)\boldsymbol{C}(O)$, *cis*), 175.8 ($CH_2\boldsymbol{C}(O)N(CH_3)C(O)$, *trans*), 175.7 ($CH_2\boldsymbol{C}(O)N(CH_3)C(O)$, *cis*), 168.5 (2C, N***C***=O, both), 144.5 (***C***=CH_2, *trans*), 142.8 (***C***=CH_2, *cis*), 136.5 (***C***, Ar, *trans*), 136.3 (***C***, Ar, *cis*), 136.2 (***C***, Ar, *trans*), 136.1 (***C***, Ar, *cis*), 131.9

(PhCH=***C***H, *cis*), 130.3 (PhCH=***C***H, *trans*), 129.0 (2C, Ph***C***H=CH, both), 128.8 (3***C***H, Ar), 128.7 (2***C***H, Ar), 128.6 (2***C***H, Ar), 128.4 (3***C***H, Ar), 128.1 (***C***H, Ar), 128.0 (2***C***H, Ar), 127.9 (2***C***H, Ar), 127.8 (***C***H, Ar), 127.7 (***C***H, Ar), 127.6 (***C***H, Ar), 126.6 (2***C***H, Ar), 118.3 (C=***C***H_2, *cis*), 116.1 (C=***C***H_2, *trans*), 55.6 (C(O)***C***C(O)N, *cis*), 55.5 (C(O)***C***C(O)N, *trans*), 50.9 (***C***$H_2C_6H_5$, *trans*), 50.7 (***C***$H_2C_6H_5$, *cis*), 45.8 (N***C***H_2CH_2, *trans*), 45.7 (N***C***H_2CH_2, *cis*), 43.4 (***C***H, *cis*), 41.3 (***C***H, *trans*), 37.5 (***C***H_2C(O), *trans*), 37.4 (***C***H_2C(O), *cis*), 25.3 (2C, ***C***H_3, both), 24.7 (CH***C***H_2, *trans*), 24.3 (CH***C***H_2, *cis*); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2925 (C-H), 2855 (C-H), 1779 (C=O), 1706 (C=O), 1640 (C=O), 1493 (C=C), 1434 (C=C); **MS** (ES+) m/z (rel. intensity %) 437.21 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{26}H_{26}N_2NaO_3$ $[M+Na]^+$ 437.1832, found 437.1836.

Preparation and characterisation of (6*S*,11*S*)-2,8-dibenzyl-11-[(3*Z*)-4-phenylbuta-1,3-dien-2-yl]-2,8-diazaspiro[5.5]undecane-1,3,7-trione (±)-186o



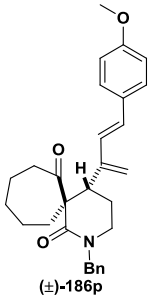
(±)-186o

Synthesised from substrate **165r** (81.0 mg, 0.2 mmol) and (*Z*)-(2-iodovinyl)benzene (69.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186o** was obtained (single diastereoisomer, 55.0 mg, 55% yield) as a colourless oil after flash column chromatography (PE/EA = 1:2). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 14:1 dr.

^{1}HNMR (400 MHz, $CDCl_3$) δ_H 7.20-7.40 (m, 15H, 15 × Ar***H***), 6.04 (d, 1H, *J* = 12.4 Hz, PhCH=C***H***), 5.67 (d, 1H, *J* = 12.4 Hz, PhC***H***=CH), 5.20 (s, 1H, C=C***H_A***H_B), 5.07 (d, 1H, *J* = 14.1 Hz, C***H_A***$H_B$$C_6H_5$), 4.92-4.96 (m, 2H, C=$CH_A$***$H_B$*** and CH_A***H_B***C_6H_5), 4.76 (d, 1H, *J* = 14.7 Hz, C***H_A***$H_B$$C_6H_5$), 4.37 (d, 1H, *J* = 14.7 Hz, CH_A***H_B***C_6H_5), 3.62 (dd, 1H, *J* = 10.9 Hz, *J* = 4.4 Hz, C***H***), 3.26-3.31 (m, 2H, CH_2C***H_2***N), 3.15 (ddd, 1H, *J* = 17.1 Hz, *J* = 12.6 Hz, *J* = 6.1 Hz, C***H_A***H_BC(O)), 2.65 (td, 1H, *J* = 17.1 Hz, *J* = 4.6 Hz, CH_A***H_B***C(O)), 2.21 (ddd, 1H, *J* = 14.0 Hz,

J = 12.7 Hz, *J* = 5.1 Hz, C***H*****$_A$**H$_B$CH$_2$C(O)), 2.05-2.11 (m, 1H, CH$_A$***H*****$_B$**CH$_2$C(O)), 1.90-1.99 (m, 2H, C***H*****$_2$**CH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.7 (CH$_2$C(O)N(Bn)***C***(O)), 172.0 (CH$_2$***C***(O)N(Bn)**C**(O)), 168.8 (N***C***=O), 143.1 (***C***=CH$_2$), 136.9 (***C***, Ar), 136.7 (***C***, Ar), 136.4 (***C***, Ar), 131.1 (PhCH=***C***H), 130.1 (Ph***C***H=CH), 128.8 (2***C***H, Ar), 128.5 (2***C***H, Ar), 128.4 (2***C***H, Ar), 128.3 (2***C***H, Ar), 128.2 (2***C***H, Ar), 127.8 (2***C***H, Ar), 127.6 (***C***H, Ar), 127.3 (***C***H, Ar), 127.1 (***C***H, Ar), 118.6 (C=***C***H$_2$), 54.2 (C(O)***C***C(O)N), 50.4 (C(O)N(***C***H$_2$C$_6$H$_5$)C(O)), 45.9 (C(O)N***C***H$_2$C$_6$H$_5$), 44.3 (N***C***H$_2$CH$_2$), 43.9 (***C***H), 29.4 (***C***H$_2$C(O)), 22.9 (CH***C***H$_2$), 22.2 (***C***H$_2$CH$_2$C(O)); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2954 (C-H), 2854 (C-H), 1725 (C=O), 1677 (C=O), 1633 (NC=O), 1493 (C=C), 1453 (C=C); **MS** (ES+) m/z (rel. intensity %) 527.27 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{33}H_{32}N_2NaO_3$ $[M+Na]^+$ 527.2287, found 527.2305.

Preparation and characterisation of (5*S*,6*R*)-2-benzyl-5-[(3*E*)-4-(4-methoxyphenyl)buta-1,3-dien-2-yl]-2-azaspiro[5.6]dodecane-1,7-dione (±)-186p



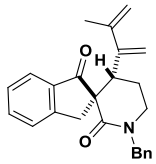
(±)-186p

Synthesised from substrate **165t** (63.0 mg, 0.2 mmol) and (*E*)-1-(2-iodovinyl)-4-methoxybenzene (78.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186p** was obtained (single diastereoisomer, 43.0 mg, 48% yield) as a colourless oil after flash column chromatography (PE/Et$_2$O = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 10:1 dr.

^{1}HNMR (400 MHz, $CDCl_3$) δ_H 7.32-7.37 (m, 7H, 7 × Ar***H***), 6.84-6.89 (m, 2H, ArC***H***=C***H***), 6.55 (d, 2H, *J* = 8.0 Hz, 2 × Ar***H***), 5.36 (s, 1H, C=C***H*****$_A$**H$_B$), 4.87 (s, 1H, C=CH$_A$***H*****$_B$**), 4.82 (d, 1H, *J* = 14.6 Hz, C***H*****$_A$**H$_B$C$_6$H$_5$), 4.48 (d, 1H, *J* = 14.6 Hz, CH$_A$***H*****$_B$**C$_6$H$_5$), 3.83 (s, 3H, OC***H*****$_3$**), 3.44-3.46 (m, 1H, C***H***), 3.21 (m, 2H, CH$_2$C***H*****$_2$**N), 2.61-2.64 (m, 1H, C***H*****$_A$**H$_B$C(O)), 2.44-2.50

(m, 1H, C(O)CC***H*****$_A$**H$_B$), 1.69-2.11 (m, 10H, CH$_A$***H*****$_B$**C(O), C(O)CCH$_A$***H*****$_B$** and 4 × C***H*****$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 212.0 (***C***=O), 170.4 (N***C***=O), 158.8 (***C***, Ar), 143.1 (***C***=CH_2), 136.9 (***C***, Ar), 130.3 (ArCH=***C***H), 129.9 (2***C***H, Ar), 129.4 (***C***, Ar), 129.2 (***C***H, Ar), 128.5 (2***C***H, Ar), 128.2 (2***C***H, Ar), 127.2 (Ar***C***H=CH), 118.7 (C=***C***H_2), 113.6 (2***C***H, Ar), 62.5 (C(O)***C***C(O)N), 55.2 (O***C***H_3), 50.4 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 44.5 (***C***H), 41.6 (C(O)***C***H_2), 31.1 (***C***H_2), 30.9 (***C***H_2), 26.2 (***C***H_2), 25.5 (CH***C***H_2), 24.1 (***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2955 (C-H), 1739 (C=O), 1623 (NC=O), 1495 (C=C), 1453 (C=C); **MS** (ES+) m/z (rel. intensity %) 466.27 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{29}H_{33}NNaO_3$ $[M+Na]^+$ 466.2335, found 466.2353.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-(3-methylbuta-1,3-dien-2-yl)-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (±)-186q



(±)-186q

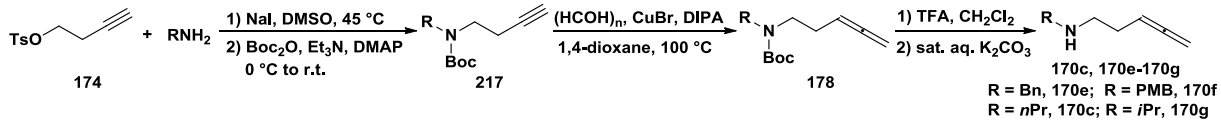
Synthesised from substrate **215a** (66.0 mg, 0.2 mmol) and 2-bromoprop-1-ene (36.0 mg, 0.3 mmol) according to general procedure D. Compound **(±)-186q** was obtained (single diastereoisomer, 60.0 mg, 70% yield) as a colourless oil after flash column chromatography (PE/Et_2O = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 19:1 dr.

^{1}HNMR (400 MHz, $CDCl_3$) δ_H 7.71 (d, 1H, *J* = 7.6 Hz, Ar***H***), 7.56 (dt, 1H, *J* = 7.6 Hz, *J* = 1.2 Hz, Ar***H***), 7.29-7.42 (m, 7H, 7 × Ar***H***), 5.22 (s, 1H, C***H*****$_A$**H$_B$=C(CH_3)), 4.86 (s, 1H, CH$_A$***H*****$_B$**=C(CH_3)), 4.74 (s, 2H, CH_2=C(CH_3)-C=C***H*****$_2$**), 4.60-4.68 (m, 2H, C***H*****$_2$**C_6H_5), 3.68 (d, 1H, *J* = 17.1 Hz, C(O)CC***H*****$_A$**H$_B$), 3.31-3.45 (m, 3H, NC***H*****$_2$**CH_2C***H***), 3.21 (d, 1H, *J* = 17.1 Hz, C(O)CCH$_A$***H*****$_B$**), 2.45-2.53 (m, 1H, C***H*****$_A$**H$_B$CH), 1.73-1.82 (m, 1H, CH$_A$***H*****$_B$**CH), 1.62 (s, 3H, C***H*****$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.0 (***C***=O), 170.1 (N***C***=O), 154.3 (***C***, Ar), 148.2 (CH_2=C(CH_3)-***C***=CH_2), 142.9 (CH_2=***C***(CH_3)), 136.9 (***C***, Ar), 135.9 (***C***, Ar), 134.8 (***C***H, Ar),

128.6 (2***C***H, Ar), 128.0 (2***C***H, Ar), 127.4 (***C***H, Ar), 127.3 (***C***H, Ar), 126.0 (***C***H, Ar), 124.7 (***C***H, Ar), 113.9 (***C***H_2=C(CH_3)), 113.4 (CH_2=C(CH_3)-C=***C***H_2), 60.0 (C(O)***C***C(O)N), 50.7 (***C***$H_2C_6H_5$), 45.3 (N***C***H_2CH_2), 40.9 (***C***H), 37.1 (C(O)C***C***H_2), 24.1 (CH***C***H_2), 21.4 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2924 (C-H), 2855 (C-H), 1715 (C=O), 1632 (NC=O), 1491 (C=C), 1453 (C=C); **MS** (ES+) m/z (rel. intensity %) 394.20 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{25}H_{25}N_2NaO_2$ $[M+Na]^+$ 394.1772, found 394.1778.

6.2.2 Experimental for Chapter Three

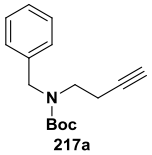
6.2.2.1 Synthesis of aminoallenes 170c, 170e-170g



General procedure E for the synthesis of aminoalkynes 217

Amines (2.0 equiv.) and sodium iodide (2.5 mol%) were added to a solution of but-3-ynyl toluene-*p*-sulphonate **174** (1.0 equiv.)[86] in anhydrous DMSO. After being stirred for 40 h at 45 ºC, the reaction mixture was poured onto 2 % aq. NaOH and extracted three times with diethyl ether. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure.[117] The resulting residue was dissolved in dichloromethane. Di-*tert*-butyl dicarbonate (2.0 equiv.), triethylamine (2.0 equiv.) and 4-(dimethylamino)pyridine (3 mol%) were added at 0 ºC. The reaction mixture was stirred at ambient temperature for 16 h and was poured onto water. The reaction mixture was seperated. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The resulting residue was subjected to column chromatography (petrol/diethyl ether) to give *N*-Boc-protected amines **217a-217d**.

Preparation and characterisation of *tert*-butyl benzyl(but-3-yn-1-yl)carbamate 217a

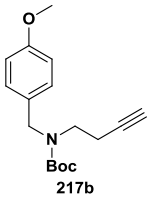


217a

Synthesised from but-3-ynyl toluene-*p*-sulphonate **174** (15.0 g, 66.8 mmol) according to general procedure E. Compound **217a** (8.1 g, 48%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.25-7.35 (m, 2H, 2 × Ar***H***), 4.52 (s, 2H, PhC***H*****$_2$**), 3.31-3.40 (m, 2H, NC***H*****$_2$**CH_2), 2.36-2.42 (m, 2H, C***H*****$_2$**C≡CH), 1.96 (t, 1H, *J* = 2.6 Hz, C≡C***H***), 1.48 (s, 9H, C(C***H*****$_3$**$)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 155.6 (***C***=O), 138.4 (***C***, Ar), 128.5 (2***C***H, Ar), 127.7 (***C***H, Ar), 127.0 (2 ***C***H, Ar), 84.5 (***C***≡CH), 79.8 (***C***$(CH_3)_3$), 69.5 (*C*≡***C***H), 51.4 (Ph***C***H_2), 45.4 (N***C***H_2CH_2), 28.4 (3C, C(***C***$H_3)_3$), 18.3 (***C***H_2C≡CH); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3305 (C≡C-H), 2150 (C≡C), 1630 (C=O); **MS** (ES+) m/z (rel. intensity %) 282.18 (M + Na^+, 80); **HRMS** (ESI+) calcd. for $C_{16}H_{21}NNaO_2$ $[M+Na]^+$ 282.1470, found 282.1474.

Preparation and characterisation of *tert*-butyl but-3-yn-1-yl(4-methoxybenzyl)carbamate 217b



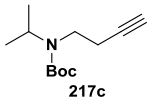
217b

Synthesised from but-3-ynyl toluene-*p*-sulphonate **174** (4.49 g, 20.0 mmol) according to general procedure E. Compound **217b** (4.00 g, 69%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.15-7.21 (m, 2H, 2 × Ar***H***), 6.86-6.91 (m, 2H, 2 × Ar***H***), 4.45 (s, 2H, PhC***H*****$_2$**), 3.82 (s, 3H, OC***H*****$_3$**), 3.25-3.36 (m, 2H, NC***H*****$_2$**CH_2), 2.30-2.41 (m, 2H, C***H*****$_2$**C≡CH), 1.98 (t, 1H, *J* = 2.7 Hz, C≡C***H***), 1.46 (s, 9H, C(C***H*****$_3$**$)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.9 (***C***, Ar), 155.5 (***C***=O), 131.5 (2***C***H, Ar), 128.5 (***C***, Ar), 115.1 (2***C***H, Ar), 84.6 (***C***≡CH), 79.6 (***C***$(CH_3)_3$), 69.7 (*C*≡***C***H), 51.2 (Ph***C***H_2), 45.8 (N***C***H_2CH_2), 28.4 (3C, C(***C***$H_3)_3$), 18.5 (***C***H_2C≡CH); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3303 (C≡C-H), 2154 (C≡C), 1637 (C=O); **MS** (ES+) m/z (rel. intensity %) 312.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{17}H_{23}NNaO_3$

$[M+Na]^+$ 312.1576, found 312.1575.

Preparation and characterisation of *tert*-butyl but-3-yn-1-yl(isopropyl)carbamate 217c

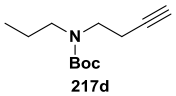


217c

Synthesised from but-3-ynyl toluene-*p*-sulphonate **174** (6.70 g, 30.0 mmol) according to general procedure E. Compound **217c** (2.82 g, 45%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 4.28-4.35 (m, 1H, C***H***$(CH_3)_2$), 3.20-3.25 (m, 2H, NC***H₂***CH_2), 2.39-2.42 (m, 2H, C***H₂***C≡CH), 1.98 (t, 1H, *J* = 2.6 Hz, C≡C***H***), 1.46 (s, 9H, C(C***H₃***)$_3$), 1.13 (d, 6H, *J* = 6.8 Hz, CH(C***H₃***)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.3 (***C***=O), 84.4 (***C***≡CH), 79.8 (***C***$(CH_3)_3$), 69.9 (*C*≡***C***H), 51.0 (***C***H$(CH_3)_2$), 45.9 (N***C***H_2CH_2), 28.5 (3C, C(***C***$H_3)_3$), 20.7 (2C, CH(***C***$H_3)_2$), 18.6 (***C***H_2C≡CH); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3300 (C≡C-H), 2153 (C≡C), 1628 (C=O); **MS** (ES+) m/z (rel. intensity %) 234.17 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{21}NNaO_2$ $[M+Na]^+$ 234.1470, found 234.1473.

Preparation and characterisation of *tert*-butyl but-3-yn-1-yl(propyl)carbamate 217d



217d

Synthesised from but-3-ynyl toluene-*p*-sulphonate **174** (6.70 g, 30.0 mmol) according to general procedure E. Compound **217d** (2.60 g, 39%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

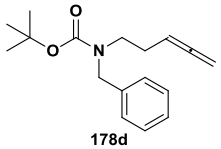
^{1}H NMR (400 MHz, $CHCl_3$) δ_H 3.31-3.35 (m, 2H, NC***H₂***CH_2), 3.15-3.20 (m, 2H, NC***H₂***CH_2CH_3), 2.30-2.44 (m, 2H, C***H₂***C≡CH), 1.98 (t, 1H, *J* = 2.6 Hz, C≡C***H***), 1.42-1.50 (m, 11H, C***H₂***CH_3 and C(C***H₃***$)_3$), 0.89 (t, 3H, *J* = 7.6 Hz, CH_2C***H₃***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.7 (***C***=O), 84.5 (***C***≡CH), 79.6 (***C***$(CH_3)_3$), 69.7 (*C*≡***C***H), 47.8 (N***C***H_2CH_2), 46.7 (N***C***$H_2CH_2CH_3$), 28.4 (3C, C(***C***$H_3)_3$), 21.8 (***C***H_2CH_3), 19.0 (***C***H_2C≡CH), 11.2 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3310 (C≡C-H), 2155 (C≡C), 1629 (C=O); **MS** (ES+) m/z (rel. intensity %)

234.17 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{21}NNaO_2$ $[M+Na]^+$ 234.1470, found 234.1472.

General procedure F for the synthesis of aminoallenes 178[30,94]

A solution of compound **217** (1.0 equiv.)**,** cuprous bromide (0.5 equiv.), paraformaldehyde (2.5 equiv.) and diisopropylamine (2.0 equiv.) in 1,4-dioxane (0.67 mmol per mL of compound **217**) was gently heated at reflux and stirred for 12 hours, cooled to room temperature. The reaction was diluted with water followed by an addition of diethyl ether and acidified with 1.0 M aq. HCl until the mixture became clear. The ether layer was separated. The aqueous solution was extracted twice with diethyl ether. The ether extracts were combined and washed with brine, dried ($MgSO_4$) and concentrated. The crude products were purified by silica gel column chromatography (petrol/diethyl ether) on silica gel to give products **178**.[30]

Preparation and characterisation of *tert*-butyl benzyl(penta-3,4-dien-1-yl)carbamate 178d



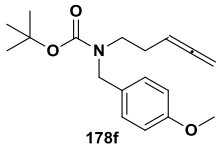
178d

Synthesised from *tert*-butyl benzyl(but-3-yn-1-yl)carbamate **217a** (13.2 g, 50.9 mmol) according to general procedure F. Compound **178d** (9.3 g, 67%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.24-7.35 (m, 5H, 5 × Ar***H***), 5.04-5.06 (m, 1H, C***H***=C=CH_2), 4.65-4.68 (m, 2H, PhC***H₂***), 4.46-4.49 (m, 2H, CH=C=C***H₂***), 3.22-3.32 (m, 2H, C***H₂***CH_2CH=C=CH_2), 2.18-2.21 (m, C***H₂***CH=C=CH_2), 1.45 (s, 9H, C(C***H₃***)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (CH=***C***=CH_2), 155.6 (***C***=O), 137.8 (***C***, Ar), 128.4 (2***C***H, Ar), 127.6 (2***C***H, Ar), 127.0 (***C***H, Ar), 86.9 (***C***H=C=CH_2), 79.7 (***C***$(CH_3)_3$), 74.9 (CH=C=***C***H_2), 50.7 (Ph***C***H_2), 46.2 (N***C***H_2CH_2), 28.4 (3C, C(***C***$H_3)_3$), 27.3 (***C***H_2CH=C=CH_2); **FT-IR** $\nu_{max}(NaCl)/cm^{-1}$

1955 (C=C=C), 1624 (C=O); **MS** (ES+) m/z (rel. intensity %) 296.19 (M + Na^+, 70); **HRMS** (ESI+) calcd. for $C_{17}H_{23}NNaO_2$ $[M+Na]^+$ 296.1626, found 296.1628.

Preparation and characterisation of *tert*-butyl (4-methoxybenzyl)penta-3,4-dien-1-ylcarbamate 178f

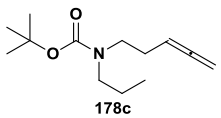


178f

Synthesised from *tert*-butyl but-3-yn-1-yl(4-methoxybenzyl)carbamate **217b** (4.00 g, 13.8 mmol) according to general procedure F. Compound **178f** (2.17 g, 54%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 7.15-7.17 (m, 2H, 2 × Ar***H***), 6.85-6.87 (m, 2H, 2 × Ar***H***), 5.01-5.04 (m, 1H, C***H***=C=CH_2), 4.64-4.67 (m, 2H, C***H₂***$C_6H_4OCH_3$), 4.37-4.40 (m, 2H, CH=C=C***H₂***), 3.80 (s, 3H, OC***H₃***), 3.19-3.27 (m, 2H, NC***H₂***CH_2), 2.15-2.17 (m, 2H, C***H₂***CH=C=CH_2), 1.48 (s, 9H, C(C***H₃***)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (CH=***C***=CH_2), 158.8 (***C***, Ar), 155.6 (***C***=O), 131.8 (2***C***H, Ar), 128.5 (***C***, Ar), 113.8 (2***C***H, Ar), 87.0 (***C***H=C=CH_2), 79.6 (***C***$(CH_3)_3$), 74.9 (CH=C=***C***H_2), 55.2 (O***C***H_3), 52.7 (***C***$H_2C_6H_4OCH_3$), 45.9 (N***C***H_2CH_2), 28.5 (3C, C(***C***$H_3)_3$), 27.3 (***C***H_2CH=C=CH_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1956 (C=C=C), 1625 (C=O); **MS** (ES+) m/z (rel. intensity %) 326.20 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{25}NNaO_3$ $[M+Na]^+$ 326.1732, found 326.1734.

Preparation and characterisation of *tert*-butyl penta-3,4-dien-1-yl(propyl)carbamate 178c

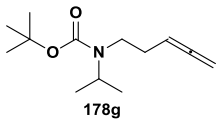


178c

Synthesised from *tert*-butyl but-3-yn-1-yl(propyl)carbamate **217d** (4.45 g, 20.0 mmol) according to general procedure F. Compound **178c** (2.0 g, 43%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 5.04-5.07 (m, 1H, C***H***=C=CH_2), 4.65-4.67 (m, 2H, CH=C=C***H₂***), 3.23 (br s, 2H, C***H₂***CH_2CH=C=CH_2), 3.11-3.15 (m, 2H, NC***H₂***CH_2CH_3), 2.19-2.21 (m, 2H, C***H₂***CH=C=CH_2), 1.50-1.55 (m, 2H, C***H₂***CH_3), 1.45 (s, 9H, C(C***H₃***)$_3$), 0.87 (t, 3H, *J* = 7.6 Hz, CH_2C***H₃***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.9 (CH=***C***=CH_2), 155.6 (***C***=O), 87.0 (***C***H=C=CH_2), 79.0 (***C***$(CH_3)_3$), 74.8 (CH=C=***C***H_2), 49.0 (N***C***$H_2CH_2CH_3$), 46.7 (***C***H_2CH_2CH=C=CH_2), 28.4 (3C, C(***C***$H_3)_3$), 27.5 (***C***H_2CH=C=CH_2), 22.5 (***C***H_2CH_3), 11.2 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1956 (C=C=C), 1628 (C=O); **MS** (ES+) m/z (rel. intensity %) 248.19 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{23}NNaO_2$ $[M+Na]^+$ 248.1626, found 248.1627.

Preparation and characterisation of *tert*-butyl isopropyl(penta-3,4-dien-1-yl)carbamate 178g



178g

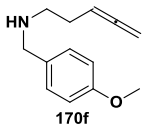
Synthesised from *tert*-butyl but-3-yn-1-yl(isopropyl)carbamate **217c** (2.28 g, 10.8 mmol) according to general procedure F. Compound **178g** (1.2 g, 53%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$) δ_H 5.03-5.10 (m, 1H, C***H***=C=CH_2), 4.65-4.68 (m, 2H, CH=C=C***H₂***), 4.26-4.32 (m, 1H, C***H***$(CH_3)_2$), 3.09-3.12 (m, 2H, NC***H₂***CH_2), 2.19-2.21 (m, 2H, C***H₂***CH=C=CH_2), 1.45 (s, 9H, C(C***H₃***)$_3$), 1.12 (d, 6H, *J* = 6.8 Hz, CH(C***H₃***)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.8 (CH=***C***=CH_2), 155.3 (***C***=O), 87.2 (***C***H=C=CH_2), 79.1 (***C***$(CH_3)_3$), 74.9 (CH=C=***C***H_2), 51.0 (N***C***H), 46.0 (N***C***H_2), 28.5 (3C, C(***C***$H_3)_3$), 27.6 (***C***H_2CH=C=CH_2), 20.8 (2C, CH(***C***$H_3)_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1956 (C=C=C), 1628 (C=O); **MS** (ES+) m/z (rel. intensity %) 248.20 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{23}NNaO_2$ $[M+Na]^+$ 248.1621, found 248.1622.

General procedure G for the synthesis of secondary amines 170f-170g

Compounds **178** were stirred with TFA in dichloromethane (1:1, v/v) and monitored by TLC. On completion, the reaction mixture was basified with saturated aqueous potassium carbonate to pH 8. The mixture was extracted three times with dichloromethane. The organic extracts were combined and washed with brine, dried (Na_2SO_4) and concentrated.[95] The crude products **170f-170g** were used directly in the next step.

Preparation and characterisation of *N*-(4-methoxybenzyl)penta-3,4-dien-1-amine 170f

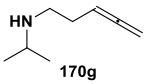


170f

Compound **170f** was synthesised according to general procedure G from *tert*-butyl (4-methoxybenzyl)penta-3,4-dien-1-ylcarbamate **178f** (2.17 g, 7.16 mmol) as a yellow oil in 98% yield of crude product **170f**.

Crude compound **170f**: **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 7.25-7.29 (m, 2H, 2 × Ar***H***), 6.86-6.89 (m, 2H, 2 × Ar***H***), 5.08-5.13 (m, 1H, C***H***=C=CH_2), 4.68-4.70 (m, 2H, CH=C=C***H$_2$***), 3.81 (s, 3H, OC***H$_3$***), 3.73 (s, 2H, C***H$_2$***C_6H_4), 2.71-2.75 (m, 2H, NC***H$_2$***CH_2), 2.21-2.25 (m, 2H, C***H$_2$***CH=C=CH_2), 1.70 (brs, 1H, N***H***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.7 (CH=***C***=CH_2), 158.7 (***C***, Ar), 131.8 (2***C***H, Ar), 128.5 (***C***, Ar), 113.5 (2***C***H, Ar), 87.5 (***C***H=C=CH_2), 75.0 (CH=C=***C***H_2), 55.3 (O***C***H_3), 52.7 (***C***$H_2C_6H_4$), 47.8 (N***C***H_2CH_2), 28.4 (***C***H_2CH=C=CH_2); **FT-IR** $\nu_{max}(NaCl)/cm^{-1}$ 1955 (C=C=C); **MS** (ES+) m/z (rel. intensity %) 204.17 ($M + H^+$, 50); **HRMS** (ESI+) calcd. for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1388, found 204.1385.

Preparation and characterisation of *N*-isopropylpenta-3,4-dien-1-amine 170g



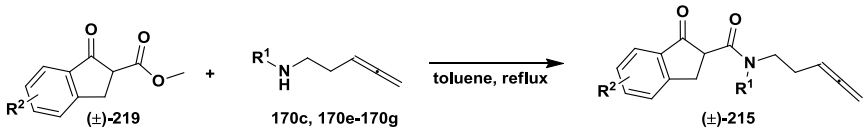
170g

Compound **170g** was synthesised according to general procedure G from *tert*-butyl isopropyl(penta-3,4-dien-1-yl)carbamate **178g** (1.20 g, 5.33 mmol) as a yellow oil in 70% yield of crude product **170g**.

Crude compound **170g**: **^{1}H NMR** (400 MHz, $CHCl_3$) δ_H 5.11-5.16 (m, 1H, C***H***=C=CH_2), 4.68-4.72 (m, 2H, CH=C=C***H$_2$***), 3.79-3.83 (m, 1H, C***H***$(CH_3)_2$), 2.67-2.72 (m, 2H, NC***H$_2$***CH_2), 2.17-2.21 (m, 2H, NCH_2C***H$_2$***), 1.50 (brs, 1H, NH), 1.07 (d, 6H, *J* = 6.8 Hz, CH(C***H$_3$***$)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.6 (CH=***C***=CH_2), 87.7 (***C***H=C=CH_2), 75.1 (CH=C=***C***H_2), 51.8 (N***C***H), 46.9 (N***C***H_2), 28.0 (NCH_2***C***H_2), 20.9 (2C, CH(C***H$_3$***$)_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 1955 (C=C=C); **MS** (ES+) m/z (rel. intensity %) 126.17 (M + H^+, 100); **HRMS** (ESI+): calcd. for $C_8H_{16}N$ $[M+H]^+$ 126.1283, found 126.1285.

6.2.2.2 Synthesis and characterisation of substrates for optimisation and enantioselective allene carbocyclisation cascade[85, 94]

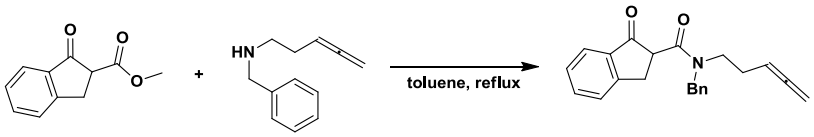
General procedure I for the synthesis of allene-linked ketoamides (±)-215



(±)-219 170c, 170e-170g (±)-215

The rotameric allene-linked ketoamides **215a-215l** were prepared from the corresponding esters **219** (1.0 equiv.) and secondary amines **170c, 170e-170g** (1.5 equiv.) in toluene at reflux until the reaction was complete by TLC. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (petrol/ethyl acetate) on silica gel to give products **(±)-215**.

Preparation and characterisation of *N*-benzyl-1-oxo-*N*-(penta-3,4-dien-1-yl)indane-2-carboxamide (±)-215a

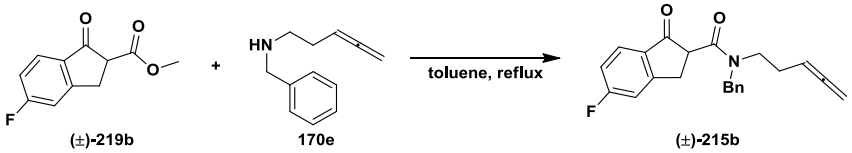


(±)-219a 170e (±)-215a

Synthesised from methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **219a** (950 mg, 5.00 mmol) and amine **170e** (1.30 g, 7.50 mmol) according to general procedure I. Compound (±)-**215a** (1.49 g, 90% yield) was isolated after flash column chromatography (PE/EA = 1:2) as a yellow oil.

Two rotamers in a 1.6:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.59-7.73 (m, both, 6H, 6 × Ar***H***), 7.39-7.47 (m, both, 4H, 4 × Ar***H***), 7.32-7.36 (m, both, 4H, 4 × Ar***H***), 7.23-7.27 (m, both, 4H, 4 × Ar***H***), 5.24 (p, major, 1H, *J* = 6.9 Hz, C***H***=C=CH_2), 5.12 (p, minor, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.03 (d, minor, 1H, *J* = 17.0 Hz, C***H*****$_A$**$H_B$$C_6H_5$), 4.85 (d, major, 1H, *J* = 15.4 Hz, C***H*****$_A$**$H_B$$C_6H_5$), 4.73-4.77 (m, 5H, CH_A***H*****$_B$**C_6H_5 for minor and CH=C=C***H*****$_2$** for both), 4.41 (dd, major, 1H, *J* = 7.6 Hz, *J* = 3.9 Hz, C***H***), 4.37 (d, major, 1H, *J* = 15.5Hz, CH_A***H*****$_B$**C_6H_5), 4.30 (dd, minor, 1H, *J* = 7.8 Hz, *J* = 3.6 Hz, C***H***), 3.83 (td, major, 1H, *J* = 15.3 Hz, *J* = 7.7 Hz, NC***H*****$_A$**H_B), 3.43-3.47 (m, minor, 1H, NC***H*****$_A$**H_B), 3.37-3.40 (m, major, 3H, NCH_A***H*****$_B$** and CHC***H*****$_2$**), 3.28-3.37 (m, minor, 2H, CHC***H*****$_2$**), 3.15-3.24 (m, minor, 1H, NCH_A***H*****$_B$**), 2.28-2.34 (m, major, 2H, NCH_2C***H*****$_2$**), 2.07-2.21 (m, minor, 2H, NCH_2C***H*****$_2$**); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 209.1 (major, CH=***C***=CH_2), 209.0 (minor, CH=***C***=CH_2), 203.0 (2***C***, both, 2 × ***C***=O), 170.2 (minor, N***C***=O), 169.9 (major, N***C***=O), 155.8 (***C***, major, Ar), 155.5 (***C***, minor, Ar), 138.6 (***C***, major, Ar), 138.4 (***C***, minor, Ar), 136.2 (***C***, major, Ar), 136.1 (***C***, minor, Ar), 129.5 (2***C***H, both, Ar), 129.3 (2***C***H, both, Ar), 128.5 (2***C***H, both, Ar), 128.2 (2***C***H, both, Ar), 127.9 (2***C***H, both, Ar), 127.8 (2***C***H, both, Ar), 127.7 (2***C***H, both, Ar), 127.6 (2***C***H, both, Ar), 124.4 (2***C***H, both, Ar), 87.7 (minor, ***C***H=C=CH_2), 87.4 (major, ***C***H=C=CH_2), 76.4 (major, CH=C=***C***H_2), 76.3 (minor, CH=C=***C***H_2), 51.8 (minor, ***C***$H_2C_6H_5$), 50.9 (2C, both, 2 × ***C***H), 48.7 (major, ***C***$H_2C_6H_5$), 46.0 (minor, N***C***H_2), 47.6 (major, N***C***H_2), 31.9 (2C, both, 2 × CH***C***H_2), 28.1 (major, NCH_2***C***H_2), 26.6 (minor, NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2927 (C-H), 1955 (C=C=C), 1710 (C=O), 1641 (NC=O); **MS** (ES+) m/z (rel. intensity %) 354.17 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{21}NNaO_2$ $[M+Na]^+$ 354.1465, found 354.1462.

Preparation and characterisation of *N*-benzyl-5-fluoro-1-oxo-*N*-(penta-3,4-dien-1-yl)indane-2-carboxamide (±)-215b

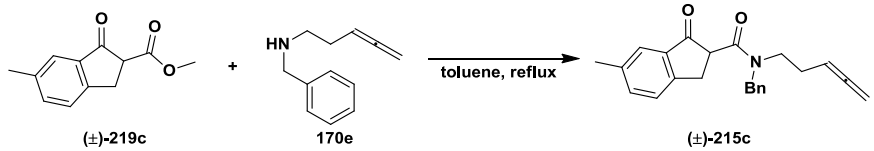


Synthesised from compound **219b** (1.04 g, 5.00 mmol) and amine **170e** (1.30 g, 7.50 mmol) according to general procedure I. Compound (±)-**215b** was isolated after flash column chromatography (PE/EA = 1:2) as a yellow oil (1.48 g, 85% yield).

Two rotamers in a 1.6:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.70-7.76 (m, both, 2H, 2 × Ar***H***), 7.45-7.51 (m, both, 2H, 2 × Ar***H***), 7.40-7.42 (m, both, 2H, 2 × Ar***H***), 7.25-7.35 (m, both, 10H, 10 × Ar***H***), 5.24 (p, major, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.11 (p, minor, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.02 (d, minor, 1H, *J* = 17.0 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.85 (d, major, 1H, *J* = 15.4 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.72-4.77 (m, 5H, $CH_A\boldsymbol{H_B}C_6H_5$ for minor and CH=C=C$\boldsymbol{H_2}$ for both), 4.45 (dd, major, 1H, *J* = 7.6 Hz, *J* = 3.8 Hz, C***H***CH_2), 4.36 (d, major, 1H, *J* = 15.5 Hz, $CH_A\boldsymbol{H_B}C_6H_5$), 4.32-4.34 (m, minor, 1H, C***H***CH_2), 3.82 (td, major, 1H, *J* = 15.3 Hz, *J* = 7.8 Hz, NC$\boldsymbol{H_A}H_B$), 3.26-3.47 (m, 6H, CHC$\boldsymbol{H_2}$ and NC$\boldsymbol{H_A}H_B$ for minor and $NCH_A\boldsymbol{H_B}$ for major), 3.14-3.21 (m, minor, 1H, $NCH_A\boldsymbol{H_B}$), 2.30-2.32 (m, major, 2H, $NCH_2C\boldsymbol{H_2}$), 2.09-2.18 (m, 2H, minor, $NCH_2C\boldsymbol{H_2}$); **^{13}C NMR** (100 MHz, d_6-DMSO) (the spectrum could not be fully assigned due to the the presence of rotamers and splitting due to the C-F coupling) δ_C 209.1 (major, CH=***C***=CH_2), 209.0 (minor, CH=***C***=CH_2), 201.5 (major**,** ***C***=O), 201.2 (minor, ***C***=O), 169.9 (minor, N***C***=O), 169.7 (major**,** N***C***=O), 167.2 (2***C***, both, Ar), 159.0 (***C***, major, Ar), 158.8 (***C***, minor, Ar), 138.6 (2***C***, both, Ar), 132.8 (2***C***, both, Ar), 129.3 (2***C***H, both, Ar), 128.3 (2***C***H, both, Ar), 127.9 (2***C***H, both, Ar), 127.8 (2***C***H, both, Ar), 127.2 (***C***H, major, Ar), 127.1 (2***C***H, both, Ar), 127.0 (***C***H, minor, Ar), 116.8 (***C***H, major, Ar), 116.6 (***C***H, minor, Ar), 114.4 (***C***H, major, Ar), 114.2 (***C***H, minor, Ar), 87.7 (minor, ***C***H=C=CH_2), 87.4 (major**,** ***C***H=C=CH_2), 76.4 (major, CH=C=***C***H_2), 76.3 (minor, CH=C=***C***H_2), 51.8 (minor, ***C***$H_2C_6H_5$), 51.2 (2***C***, both**,** 2 ×

CHCH$_2$), 48.7 (major**,** ***C***H$_2$C$_6$H$_5$), 47.6 (major**,** **N*C***H$_2$CH$_2$), 46.0 (minor, N***C***H$_2$CH$_2$), 31.9 (2***C***, both, 2 × CH***C***H$_2$), 28.0 (major**,** NCH$_2$***C***H$_2$), 26.6 (minor, NCH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2929 (C-H), 1955 (C=C=C), 1714 (C=O), 1642 (NC=O); **MS** (ES+) m/z (rel. intensity %) 372.16 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{20}FNNaO_2$ $[M+Na]^+$ 372.1370, found 372.1357.

Preparation and characterisation of *N*-benzyl-6-methyl-1-oxo-*N*-(penta-3,4-dien-1-yl)indane-2-carboxamide (±)-215c



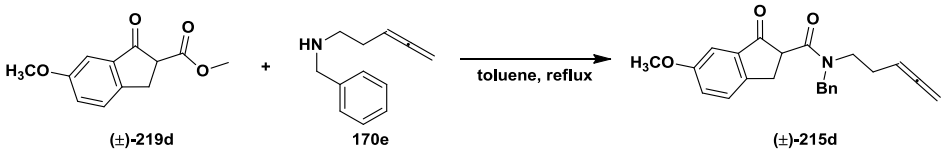
(±)-219c 170e (±)-215c

Synthesised from compound **219c** (1.02 g, 5.00 mmol) and amine **170e** (1.30 g, 7.50 mmol) according to general procedure I. Compound (±)-**215c** was isolated after flash column chromatography (PE/EA = 1:2) as a yellow oil (1.60 g, 93% yield).

Two rotamers in a 1.5:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.25-7.52 (m, both, 16H, 16 × Ar***H***), 5.24 (p, major, 1H, *J* = 6.8 Hz, C***H***=C=CH$_2$), 5.12 (p, minor, 1H, *J* = 6.8 Hz, C***H***=C=CH$_2$), 5.02 (d, minor, 1H, *J* = 17.0 Hz, C***H$_A$***H$_B$C$_6$H$_5$), 4.84 (d, major, 1H, *J* = 15.4 Hz, C***H$_A$***H$_B$C$_6$H$_5$), 4.71-4.77 (m, 5H, CH$_A$***H$_B$***C$_6$H$_5$ for minor and CH=C=C***H$_2$*** for both), 4.34-4.40 (m, major, 2H, CH$_A$***H$_B$***C$_6$H$_5$ and C***H***CH$_2$), 4.27 (dd, minor, 1H, *J* = 7.8 Hz, *J* = 3.6 Hz, C***H***CH$_2$), 3.83 (td, major, 1H, *J* = 15.3 Hz, *J* = 7.7 Hz, NC***H$_A$***H$_B$), 3.41-3.49 (m, minor, 1H, NC***H$_A$***H$_B$), 3.27-3.40 (m, 4H, NCH$_A$***H$_B$*** for major and CHC***H$_2$*** for major and CHC***H$_A$***H$_B$ for minor), 3.14-3.25 (m, minor, 2H, NCH$_A$***H$_B$*** and CHCH$_A$***H$_B$***), 2.37 (s, major, 3H, C***H$_3$***), 2.36 (s, minor, 3H, C***H$_3$***), 2.28-2.32 (m, major, 2H, NCH$_2$C***H$_2$***), 2.11-2.18 (m, minor, 2H, NCH$_2$C***H$_2$***); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 209.1 (major, CH=***C***=CH$_2$), 209.0 (minor, CH=***C***=CH$_2$), 203.2 (major, ***C***=O), 203.0 (minor, ***C***=O), 170.2 (minor, N***C***=O), 170.0 (major, N***C***=O), 153.2 (***C***, major, Ar), 152.9 (***C***, minor, Ar), 138.7 (2***C***, both, Ar), 138.0 (2***C***, both, Ar), 137.3 (***C***, major, Ar), 137.2 (***C***, minor, Ar), 136.4 (***C***H, minor, Ar), 136.3 (***C***H, major, Ar), 129.5 (2***C***H,

both, Ar), 129.2 (2***C***H, both, Ar), 128.2 (2***C***H, both, Ar), 127.9 (2***C***H, both, Ar), 127.8 (2***C***H, both, Ar), 127.3 (2***C***H, both, Ar), 124.2 (2***C***H, both, Ar), 87.7 (minor, ***C***H=C=CH_2), 87.4 (major, ***C***H=C=CH_2), 76.4 (major, CH=C=***C***H_2), 76.3 (minor, CH=C=***C***H_2), 51.8 (minor, ***C***$H_2C_6H_5$), 51.2 (2C, both, 2 × ***C***HCH_2), 48.7 (major, ***C***$H_2C_6H_5$), 47.6 (major, N***C***H_2), 46.0 (minor, N***C***H_2), 31.5 (2C, both, 2 × CH***C***H_2), 28.1 (major, ***C***$H_2CH=C=CH_2$), 26.6 (minor, ***C***$H_2CH=C=CH_2$), 21.4 (2C, both, 2 × ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2924 (C-H), 1955 (C=C=C), 1708 (C=O), 1642 (NC=O); **MS** (ES+) m/z (rel. intensity %) 368.18 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{23}H_{23}NNaO_2$ $[M+Na]^+$ 368.1621, found 368.1614.

Preparation and characterisation of *N*-benzyl-6-methoxy-1-oxo-*N*-(penta-3,4-dien-1-yl)indane-2-carboxamide (±)-215d



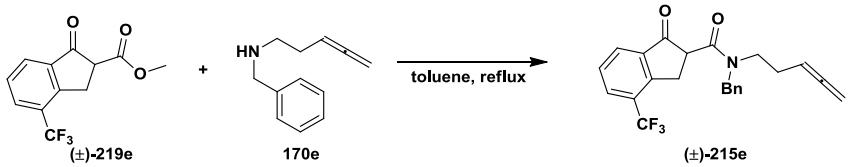
(±)-219d 170e (±)-215d

Synthesised from compound **219d** (1.02 g, 5.00 mmol) and amine **170e** (1.30 g, 7.50 mmol) according to general procedure I. Compound (±)-**215d** (1.51 g, 84% yield) was isolated after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow oil.

Two rotamers in a 1.6:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.50-7.52 (m, both, 2H, 2 × Ar***H***), 7.40-7.42 (m, both, 2H, 2 × Ar***H***), 7.25-7.35 (m, both, 10H, 10 × Ar***H***), 7.10-7.13 (m, both, 2H, 2 × Ar***H***), 5.24 (p, major, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.12 (p, minor, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.01 (d, minor, 1H, *J* = 17.0 Hz, C***H$_A$***$H_B$$C_6H_5$), 4.85 (d, major, 1H, *J* = 15.4 Hz, C***H$_A$***$H_B$$C_6H_5$), 4.73-4.77 (m, 5H, CH=C=C***H$_2$*** for both and CH_A***H$_B$***C_6H_5 for minor), 4.42 (dd, major, 1H, *J* = 7.4 Hz, *J* = 3.7 Hz, C***H***CH_2), 4.37 (d, major, 1H, *J* = 15.4 Hz, CH_A***H$_B$***C_6H_5), 4.30 (dd, minor, 1H, *J* = 7.6 Hz, *J* = 3.4 Hz, C***H***CH_2), 3.84-3.86 (m, major, 1H, NC***H$_A$***H_B), 3.81 (s, major, 3H, OC***H$_3$***), 3.80 (s, minor, 3H, OC***H$_3$***), 3.41-3.48 (m, minor, 1H, NC***H$_A$***H_B), 3.25-3.37 (m, both, 4H, NCH_A***H$_B$*** and CHC***H$_2$*** for major, CHC***H$_A$***H_B for minor), 3.15-3.23 (m, minor, 2H, $CHCH_A$***H$_B$*** and NCH_A***H$_B$***), 2.30-2.32 (m, major, 2H, NCH_2C***H$_2$***),

2.11-2.18 (m, minor, 2H, $NCH_2C\boldsymbol{H_2}$); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 209.1 (major, CH=***C***=CH_2), 209.0 (minor, CH=***C***=CH_2), 203.0 (major, ***C***=O), 202.8 (minor, ***C***=O), 170.2 (minor, N***C***=O), 170.0 (major, N***C***=O), 160.0 (2***C***, both, Ar), 148.4 (***C***, major, Ar), 148.1 (***C***, minor, Ar), 138.7 (***C***, major, Ar), 138.4 (***C***, minor, Ar), 137.4 (***C***, minor, Ar), 137.3 (***C***, major, Ar), 129.5 (2***C***H, both, Ar), 129.2 (2***C***H, both, Ar), 128.4 (***C***H, major, Ar), 128.3 (***C***H, minor, Ar), 128.2 (2***C***H, both, 2C, Ar), 128.0 (***C***H, major, Ar), 127.9 (***C***H, minor, Ar), 127.8 (***C***H, minor, Ar), 127.7 (***C***H, major, Ar), 124.9 (***C***H, major, Ar), 124.7 (***C***H, minor, Ar), 106.1 (2***C***H, both, Ar), 87.7 (minor, ***C***H=C=CH_2), 87.4 (major, ***C***H=C=CH_2), 76.4 (major, CH=C=***C***H_2), 76.3 (minor, CH=C=***C***H_2), 56.4 (2C, both, 2 × O***C***H_3), 51.8 (minor, ***C***$H_2C_6H_5$), 51.6 (2C, both, 2 × ***C***HCH_2), 48.7 (major, ***C***$H_2C_6H_5$), 47.6 (major, N***C***H_2), 46.0 (minor, N***C***H_2), 31.2 (2C, both, 2 × CH***C***H_2), 28.1 (major, $NCH_2\boldsymbol{C}H_2$), 26.6 (minor, $NCH_2\boldsymbol{C}H_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2930 (C-H), 1955 (C=C=C), 1708 (C=O), 1641 (NC=O); **MS** (ES+) m/z (rel. intensity %) 384.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{23}H_{23}NNaO_3$ $[M+Na]^+$ 384.1570, found 384.1566.

Preparation and characterisation of *N*-benzyl-1-oxo-*N*-(penta-3,4-dien-1-yl)-4-(trifluoromethyl)indane-2-carboxamide (±)-215e

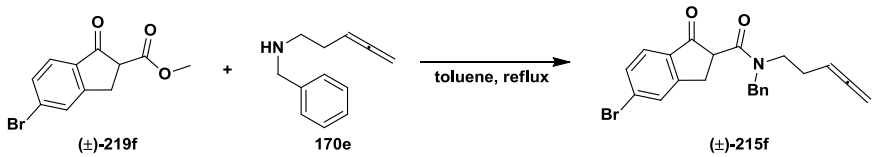


Synthesised from compound **219e** (1.29 g, 5.00 mmol) and amine **170e** (1.30 g, 7.50 mmol) according to general procedure I. Compound (±)-**215e** (1.59 g, 80% yield) was isolated after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow oil.

Two rotamers in a 1.6:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 8.08 (t, both, 2H, *J* = 7.9 Hz, 2 × Ar***H***), 7.94-7.99 (m, both, 2H, 2 × Ar***H***), 7.69 (dd, both, 2H, *J* = 14.4 Hz, *J* = 7.3 Hz, 2 × Ar***H***), 7.41 (d, both, 2H, *J* = 7.5 Hz, 2 × Ar***H***), 7.34 (dd, both, 4H, *J* = 13.2 Hz, *J* = 5.1 Hz, 4 × Ar***H***), 7.26 (d, both, 4H, *J* = 6.9 Hz, 4 × Ar***H***), 5.24 (p, major, 1H, *J* = 6.9 Hz, C***H***=C=CH_2), 5.11 (p, minor, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.03 (d, minor, 1H, *J* = 17.0 Hz, C$\boldsymbol{H_A}H_BC_6H_5$),

4.85 (d, major, 1H, *J* = 15.4 Hz, C***H*****$_A$**H$_B$C$_6$H$_5$), 4.72-4.78 (m, 5H, CH=C=C***H*****$_2$** for both and CH$_A$***H*****$_B$**C$_6$H$_5$ for minor), 4.54-4.56 (m, major, 1H, C***H***CH$_2$), 4.43 (dd, minor, 1H, *J* = 7.6 Hz, *J* = 3.6 Hz, C***H***CH$_2$), 4.38 (d, major, 1H, *J* = 15.4 Hz, CH$_A$***H*****$_B$**C$_6$H$_5$), 3.83 (td, major, 1H, *J* = 15.3 Hz, *J* = 7.7 Hz, NC***H*****$_A$**H$_B$CH$_2$), 3.36-3.51 (m, 6H, CHC***H*****$_2$** for both and NC***H*****$_A$**H$_B$CH$_2$ for minor and NCH$_A$***H*****$_B$**CH$_2$ for major), 3.16-3.23 (m, minor, 1H, NCH$_A$***H*****$_B$**CH$_2$), 2.32-2.36 (m, major, 2H, NCH$_2$C***H*****$_2$**), 2.13-2.16 (m, minor, 2H, NCH$_2$C***H*****$_2$**); **^{13}C NMR** (100 MHz, *d*$_6$-DMSO) (the spectrum could not be fully assigned due to the the presence of rotamers and splitting due to the C-F coupling) δ_C 209.1 (major, CH=***C***=CH$_2$), 209.0 (minor, CH=***C***=CH$_2$), 201.9 (major, ***C***=O), 201.7 (minor, ***C***=O), 169.5 (minor, N***C***=O), 169.2 (major, N***C***=O), 152.4 (***C***, major, Ar), 152.2 (***C*****,** minor, Ar), 138.5 (***C*****,** major, Ar), 138.2 (***C*****,** minor, Ar), 137.8 (***C*****,** minor, Ar), 137.7 (***C*****,** major, Ar), 132.9 (***C***H**,** major, Ar), 132.8 (***C***H**,** minor, Ar), 129.7 (2***C***H, both, Ar), 129.5 (2***C***H, both, Ar), 129.3 (2***C***H, both, Ar), 128.8 (2***C***H, both, Ar), 128.3 (2***C***H, both, Ar), 127.9 (2***C***H, both, Ar), 127.8 (2***C***H, both, Ar), 127.5 (2***C***, both, Ar), 123.4 (2C, both, ***C***F$_3$), 87.7 (minor, ***C***H=C=CH$_2$), 87.3 (major, ***C***H=C=CH$_2$), 76.4 (major, CH=C=***C***H$_2$), 76.3 (minor, CH=C=***C***H$_2$), 51.8 (minor, ***C***H$_2$C$_6$H$_5$), 50.7 (2C, both, 2 × ***C***HCH$_2$), 48.8 (major, ***C***H$_2$C$_6$H$_5$), 47.7 (major, N***C***H$_2$), 46.1 (minor, N***C***H$_2$), 30.9 (2C, both, 2 × CH***C***H$_2$), 28.0 (major, NCH$_2$***C***H$_2$), 26.6 (minor, NCH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2935 (C-H), 1956 (C=C=C), 1722 (C=O), 1644 (C=O); **MS** (ES+) m/z (rel. intensity %) 422.15 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for C$_{23}$H$_{20}$F$_3$NNaO$_2$ [M+Na]$^+$ 422.1338, found 422.1335.

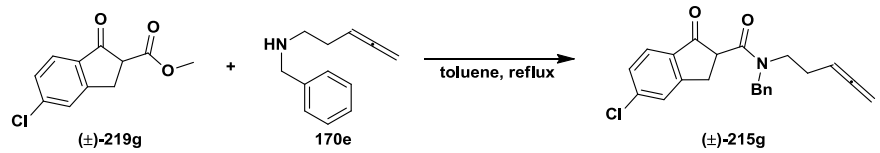
Preparation and characterisation of *N*-benzyl-5-bromo-1-oxo-*N*-(penta-3,4-dien-1-yl)indane-2-carboxamide (±)-215f



Synthesised from compound **219f** (1.33 g, 5.00 mmol) and amine **170e** (1.30 g, 7.50 mmol) according to general procedure I. Compound (±)-**215f** (1.75 g, 86% yield) was isolated after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow oil.

Two rotamers in a 1.6:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.91 (d, both, 2H, J = 13.5 Hz, 2 × Ar***H***), 7.61 (td, both, 4H, J = 18.1 Hz, J = 8.3 Hz, 4 × Ar***H***), 7.41 (t, both, 2H, J = 7.7 Hz, 2 × Ar***H***), 7.31-7.34 (m, both, 4H, 4 × Ar***H***), 7.25 (dd, both, 4H, J = 4.9 Hz, J = 2.9 Hz, 4 × Ar***H***), 5.23 (p, major, 1H, J = 6.8 Hz, C***H***=C=CH_2), 5.11 (p, minor, 1H, J = 6.8 Hz, C***H***=C=CH_2), 5.01 (d, minor, 1H, J = 17.0 Hz, C***H$_A$***$H_B$$C_6H_5$), 4.83 (d, major, 1H, J = 15.5 Hz, C***H$_A$***$H_B$$C_6H_5$), 4.72-4.77 (m, 5H, CH=C=C***H$_2$*** for both and CH_A***H$_B$***C_6H_5 for minor), 4.43 (dd, major, 1H, J = 7.6 Hz, J = 3.9 Hz, C***H***), 4.37 (d, major, 1H, J = 15.4 Hz, CH_A***H$_B$***C_6H_5), 4.31 (dd, minor, 1H, J = 7.8 Hz, J = 3.6 Hz, C***H***), 3.80 (td, major, 1H, J = 15.2 Hz, J = 7.7 Hz, NC***H$_A$***H_B), 3.25-3.49 (m, 6H, CHC***H$_2$*** for both and NC***H$_A$***H_B for minor and NCH_A***H$_B$*** for major), 3.14-3.21 (m, minor, 1H, NCH_A***H$_B$***), 2.29-2.32 (m, major, 2H, NCH_2C***H$_2$***), 2.09-2.17 (m, minor, 2H, NCH_2C***H$_2$***); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 209.1 (major, CH=***C***=CH_2), 209.0 (minor, CH=***C***=CH_2), 202.2 (major, ***C***=O), 202.0 (minor, ***C***=O), 169.8 (minor, N***C***=O), 169.6 (major, N***C***=O), 157.8 (***C***, major, Ar), 157.5 (***C***, minor, Ar), 138.6 (***C***, major, Ar), 138.3 (***C***, minor, Ar), 135.3 (***C***, minor, Ar), 135.2 (***C***, major, Ar), 131.8 (2***C***, both, 2 × Ar), 130.8 (***C***H, major, Ar), 130.7 (***C***H, minor, Ar), 130.5 (2***C***H, both, Ar), 130.4 (2***C***H, both, Ar), 129.5 (2***C***H, both, Ar), 129.3 (2***C***H, both, Ar), 127.9 (2***C***H, both, Ar), 127.8 (2***C***H, both, Ar), 126.1 (2***C***H, both, Ar), 87.7 (minor, ***C***H=C=CH_2), 87.3 (major, ***C***H=C=CH_2), 76.4 (2C, both, CH=C=***C***H_2), 51.8 (minor, ***C***$H_2C_6H_5$), 51.0 (2C, both, ***C***HCH_2), 48.7 (major, ***C***$H_2C_6H_5$), 47.6 (major, N***C***H_2), 46.0 (minor, N***C***H_2), 31.7 (2C, both, CH***C***H_2), 28.0 (major, NCH_2***C***H_2), 26.6 (minor, NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2926 (C-H), 1955 (C=C=C), 1714 (C=O), 1641 (C=O); **MS** (ES+) m/z (rel. intensity %) 432.08, 434.07 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{20}BrNNaO_2$ $[M+Na]^+$ 432.0570, 434.0550, found 432.0570, 434.0556;

Preparation and characterisation of *N*-benzyl-5-chloro-1-oxo-*N*-(penta-3,4-dien-1-yl)indane-2-carboxamide (±)-215g

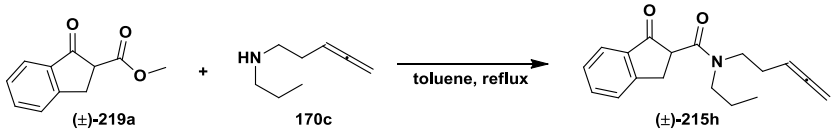


Synthesised from compound **219g** (1.12 g, 5.00 mmol) and amine **170e** (1.30 g, 7.50 mmol) according to general procedure I. Compound (±)-**215g** (1.55 g, 85% yield) was isolated after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow oil.

Two rotamers in a 1.6:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.75 (d, both, 2H, *J* = 13.5 Hz, 2 × Ar***H***), 7.67 (t, both, 2H, *J* = 9.2 Hz, 2 × Ar***H***), 7.50 (t, both, 2H, *J* = 7.4 Hz, 2 × Ar***H***), 7.41 (t, both, 2H, *J* = 7.6 Hz, 2 × Ar***H***), 7.31-7.35 (m, both, 4H, 4 × Ar***H***), 7.25 (d, both, 4H, *J* = 6.5 Hz, 4 × Ar***H***), 5.23 (p, major, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.11 (p, minor, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.01 (d, minor, 1H, *J* = 17.0 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.84 (d, major, 1H, *J* = 15.4 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.72-4.77 (m, 5H, CH=C=C$\boldsymbol{H_2}$ for both and $CH_A\boldsymbol{H_B}C_6H_5$ for minor), 4.45 (dd, major, 1H, *J* = 7.5 Hz, *J* = 3.9 Hz, C***H***), 4.37 (d, major, 1H, *J* = 15.5 Hz, $CH_A\boldsymbol{H_B}C_6H_5$), 4.32-4.34 (m, minor, 1H, C***H***), 3.81 (td, major, 1H, *J* = 15.2 Hz, *J* = 7.7 Hz, NC$\boldsymbol{H_A}H_B$), 3.25-3.49 (m, 6H, NC$\boldsymbol{H_A}H_B$ for minor and $NCH_A\boldsymbol{H_B}$ for major and CHC$\boldsymbol{H_2}$ for both), 3.14-3.21 (m, minor, 1H, $NCH_A\boldsymbol{H_B}$), 2.30-2.32 (m, major, 2H, $NCH_2C\boldsymbol{H_2}$), 2.07-2.17 (m, minor, 2H, $NCH_2C\boldsymbol{H_2}$); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 209.1 (major, CH=***C***=CH_2), 209.0 (minor, CH=***C***=CH_2), 202.0 (major, ***C***=O), 201.8 (minor, ***C***=O), 169.9 (minor, N***C***=O), 169.6 (major, N***C***=O), 157.6 (***C***, major, Ar), 157.4 (***C***, minor, Ar), 141.1 (***C***, major, Ar), 141.0 (***C***, minor, Ar), 138.6 (***C***, major, Ar), 138.3 (***C***, minor, Ar), 135.0 (***C***, minor, Ar), 134.9 (***C***, major, Ar), 129.5 (2***C***H, both, Ar), 129.3 (2***C***H, both, Ar), 129.0 (2***C***H, both, Ar), 128.3 (2***C***H, both, Ar), 127.9 (2***C***H, both, Ar), 127.7 (2***C***H, both, Ar), 126.1 (2***C***H, both, Ar), 126.0 (2***C***H, both, Ar), 87.7 (minor, ***C***H=C=CH_2), 87.3 (major, ***C***H=C=CH_2), 76.4 (major, CH=C=***C***H_2), 76.3 (minor, CH=C=***C***H_2), 51.8 (minor, ***C***$H_2C_6H_5$), 51.1 (2C, both, ***C***HCH_2), 48.7 (major, ***C***$H_2C_6H_5$), 47.6

(major, N***C***H_2), 46.0 (minor, N***C***H_2), 31.7 (2C, both, CH***C***H_2), 28.0 (major, NCH_2***C***H_2), 26.6 (minor, NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2928 (C-H), 1955 (C=C=C), 1714 (C=O), 1643 (NC=O); **MS** (ES+) m/z (rel. intensity %) 388.13 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{20}NNaO_2$ $[M+Na]^+$ 388.1075, found 388.1075.

Preparation and characterisation of 1-oxo-*N*-(penta-3,4-dien-1-yl)-*N*-propylindane-2-carboxamide (±)-215h



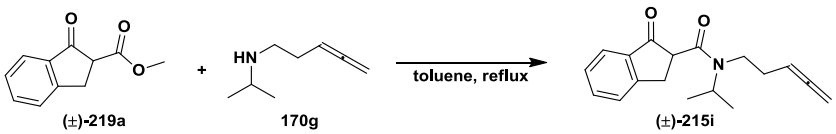
(±)-219a 170c (±)-215h

Synthesised from compound **219a** (950 mg, 5.00 mmol) and amine **170c** (937 mg, 7.50 mmol) according to general procedure I. Compound (±)-**215h** (1.10 g, 78% yield) was isolated after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow oil.

Two rotamers in a 1.2:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.70 (t, both, 2H, *J* = 7.4 Hz, 2 × Ar***H***), 7.63 (t, both, 4H, *J* = 7.9 Hz, 4 × Ar***H***), 7.44 (t, both, 2H, *J* = 7.4 Hz, 2 × Ar***H***), 5.25 (p, minor, 1H, *J* = 6.9 Hz, C***H***=C=CH_2), 5.15 (p, major, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 4.75-4.79 (m, both, 4H, CH=C=C***H_2***), 4.24-4.28 (m, both, 2H, C***H***), 3.79 (td, minor, 1H, *J* = 15.1 Hz, *J* = 7.6 Hz, NC***H_A***$H_B$$CH_2$), 3.58-3.68 (m, major, 1H, NC***H_A***$H_B$$CH_2$), 3.06-3.67 (m, both, 10H, NC***H_2***CH_2CH_3 and NCH_A***H_B***CH_2 and CHC***H_2***), 2.26-2.37 (m, minor, 2H, C***H_2***CH=CCH_2), 2.10-2.19 (m, major, 2H, C***H_2***CH=C=CH_2), 1.56-1.72 (m, major, 2H, C***H_2***CH_3), 1.41-1.54 (m, minor, 2H, C***H_2***CH_3), 0.89 (t, major, 3H, *J* = 7.3 Hz, C***H_3***), 0.81 (t, minor, 3H, *J* = 7.4 Hz, C***H_3***); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 209.2 (major, CH=***C***=CH_2), 209.1 (minor, CH=***C***=CH_2), 203.2 (2C, both, 2 × ***C***=O), 169.6 (major, N***C***=O), 169.3 (minor, N***C***=O), 155.7 (***C***, minor, Ar), 155.6 (***C***, major, Ar), 136.3 (***C***, minor, Ar), 136.1 (***C***, major, Ar), 128.4 (2***C***H, both, Ar), 127.6 (2***C***H, both, Ar), 124.4 (2***C***H, both, Ar), 124.3 (2***C***H, both, Ar), 87.8 (major, ***C***H=C=CH_2), 87.5 (minor, ***C***H=C=CH_2), 76.3 (minor, CH=C=***C***H_2), 76.2 (major, CH=C=***C***H_2), 50.9 (major, ***C***H), 50.7 (minor, ***C***HCH_2), 50.3 (major, N***C***H_2), 47.9 (minor,

N***C***$H_2CH_2CH_3$), 47.8 (minor, N***C***H_2), 46.1 (major, N***C***$H_2CH_2CH_3$), 31.9 (2C, both, CH***C***H_2), 28.5 (major, ***C***$H_2CH{=}C{=}CH_2$), 27.0 (minor, ***C***$H_2CH{=}C{=}CH_2$), 23.0 (major, ***C***H_2CH_3), 21.4 (minor, ***C***H_2CH_3), 11.9 (minor, ***C***H_3), 11.8 (major, ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2932 (C-H), 1955 (C=C=C), 1711 (C=O), 1637 (NC=O); **MS** (ES+) m/z (rel. intensity %) 306.18 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{21}NNaO_2$ $[M+Na]^+$ 306.1465, found 306.1474.

Preparation and characterisation of *N*-isopropyl-1-oxo-*N*-(penta-3,4-dien-1-yl)indane-2-carboxamide (±)-215i



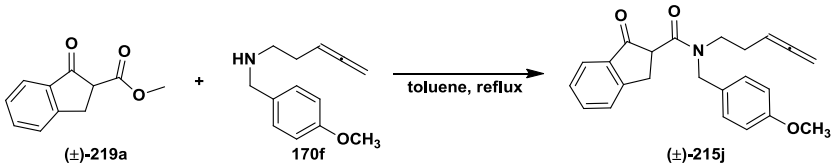
(±)-219a 170g (±)-215i

Synthesised from compound **219a** (950 mg, 5.00 mmol) and amine **170g** (937 mg, 7.50 mmol) according to general procedure I. Compound (±)-**215i** (707 mg, 50% yield) was isolated after flash column chromatography (PE/EA = 1:1) as a yellow solid.

Two rotamers in a 1.5:1 ratio. **Mp** 43.5-46.0 °C; **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.70 (t, both, 2H, *J* = 7.4 Hz, 2 × Ar***H***), 7.62 (t, both, 4H, *J* = 7.7 Hz, 4 × Ar***H***), 7.44 (t, both, 2H, *J* = 7.4 Hz, 2 × Ar***H***), 5.27 (p, minor, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.17 (p, major, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 4.75-4.81 (m, both, 4H, CH=C=C***H₂***), 4.39-4.51 (m, both, 2H, NC***H***), 4.36 (dd, major, 1H, *J* = 7.9 Hz, *J* = 3.6 Hz, C***H***CH_2), 4.15 (t, minor, 1H, *J* = 5.7 Hz, C***H***CH_2), 3.62-3.70 (m, major, 1H, NC***H$_A$***H_B), 3.11-3.48 (m, 7H, NCH_A***H$_B$*** and CHC***H₂*** for both, NC***H₂*** for minor), 2.30-2.32 (m, minor, 2H, NCH_2C***H₂***), 2.07-2.16 (m, major, 2H, NCH_2C***H₂***), 1.30 (d, major, 3H, *J* = 6.5 Hz, CH(C***H₃***)$_A$(CH_3)$_B$), 1.18 (d, major, 3H, *J* = 6.6 Hz, CH(CH_3)$_A$(C***H₃***)$_B$), 1.11-1.14 (m, minor, 6H, CH(C***H₃***)$_2$); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 209.0 (minor, CH=***C***=CH_2), 208.9 (major, CH=***C***=CH_2), 203.4 (minor, ***C***=O), 203.0 (major, ***C***(O)), 168.7 (2C, two rotamers, ***C***(O)N), 155.8 (***C***, minor, Ar), 155.5 (***C***, major, Ar), 136.2 (***C***, major, Ar), 136.1 (***C***, minor, Ar), 136.0 (2***C***H, both, Ar), 128.4 (2***C***H, both, Ar), 127.6 (2***C***H, both, Ar), 124.4 (2***C***H, both, Ar), 88.1 (major, ***C***H=C=CH_2), 87.5 (minor, ***C***H=C=CH_2), 76.5 (minor,

CH=C=***C***H_2), 76.3 (major, CH=C=***C***H_2), 51.5 (minor, ***C***HCH_2), 51.1 (major, ***C***HCH_2), 49.2 (major, N***C***H), 46.8 (minor, N***C***H), 43.6 (major, N***C***H_2), 41.1 (minor, N***C***H_2), 32.1 (minor, CH***C***H_2), 31.7 (major, CH***C***H_2), 30.4 (minor, NCH_2***C***H_2), 28.2 (major, NCH_2***C***H_2), 22.1 (major, CH(***C***$H_3)_A(CH_3)_B$), 22.0 (major, $CH(CH_3)_A$(***C***$H_3)_B$), 21.0 (minor, CH(***C***$H_3)_A(CH_3)_B$), 20.9 (minor, $CH(CH_3)_A$(***C***$H_3)_B$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2974 (C-H), 1955 (C=C=C), 1713 (C=O), 1637 (NC=O); MS (ES+) m/z (rel. intensity %) 306.18 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{18}H_{21}NNaO_2$ $[M+Na]^+$ 306.1465, found 306.1471.

Preparation and characterisation of *N*-(4-methoxybenzyl)-1-oxo-*N*-(penta-3,4-dien-1-yl)indane-2-carboxamide (±)-215j



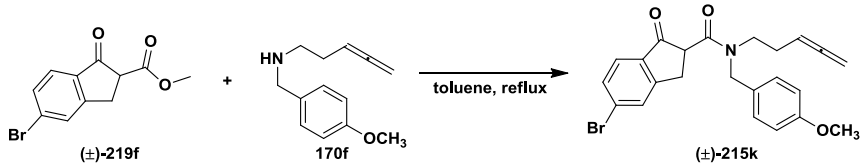
(±)-219a 170f (±)-215j

Synthesised from compound **219a** (950 mg, 5.00 mmol) and amine **170f** (1.52 g, 7.50 mmol) according to general procedure I. Compound (±)-**215j** (1.57 g, 87% yield) was isolated after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow oil.

Two rotamers in a 1.5:1 ratio. **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.60-7.73 (m, both, 6H, 6 × Ar***H***), 7.45 (dd, both, 2H, *J* = 12.6 Hz, *J* = 7.1 Hz, 2 × Ar***H***), 7.29 (d, minor, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.19 (d, major, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 6.96 (d, minor, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 6.89 (d, major, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 5.23 (p, major, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.11 (p, minor, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 4.92 (d, minor, 1H, *J* = 16.6 Hz, C***H$_A$***$H_BC_6H_4$), 4.74-4.79 (m, 5H, C***H$_A$***$H_BC_6H_4$ and CH=C=C***H$_2$*** for both), 4.67 (d, minor, 1H, *J* = 16.6 Hz, CH_A***H$_B$***C_6H_4), 4.37 (dd, major, 1H, *J* = 7.7 Hz, *J* = 3.9 Hz, C***H***), 4.33-4.35 (m, minor, 1H, C***H***), 4.30 (d, major, 1H, *J* = 15.0 Hz, CH_A***H$_B$***C_6H_4), 3.70-3.82 (m, major, 1H, NC***H$_A$***H_BCH_2), 3.75 (s, minor, 3H, OC***H$_3$***), 3.73 (s, major, 3H, OC***H$_3$***), 3.26-3.43 (m, both, 6H, NC***H$_A$***H_BCH_2 for minor and NCH_A***H$_B$***CH_2 for major and CHC***H$_2$*** for both), 3.14-3.21 (m, minor, 1H, NCH_A***H$_B$***CH_2), 2.26-2.31 (m, major, 2H, NCH_2C***H$_2$***), 2.06-2.18 (m, minor, 2H, NCH_2C***H$_2$***);

^{13}C NMR (100 MHz, d_6-DMSO) δ_C 209.1 (major, CH=***C***=CH_2), 209.0 (minor, CH=***C***=CH_2), 203.3 (major, ***C***=O), 203.1 (minor, ***C***=O), 170.0 (minor, N***C***=O), 169.9 (major, N***C***=O), 159.5 (***C***, minor, Ar), 159.2 (***C***, major, Ar), 155.8 (***C***, major, Ar), 155.5 (***C***, minor, Ar), 136.2 (2***C***, both, Ar), 136.1 (2***C***, both, Ar), 130.5 (2***C***H, both, Ar), 130.0 (2***C***H, both, Ar), 129.5 (2***C***H, both, Ar), 129.2 (2***C***H, both, Ar), 128.5 (2***C***H, both, Ar), 127.7 (***C***H, major, Ar), 127.6 (***C***H, minor, Ar), 124.5 (***C***H, major, Ar), 124.4 (***C***H, minor, Ar), 114.9 (***C***H, minor, Ar), 114.7 (***C***H, major, Ar), 87.7 (minor, ***C***H=C=CH_2), 87.4 (major, ***C***H=C=CH_2), 76.4 (major, CH=C=***C***H_2), 76.3 (minor, CH=C=***C***H_2), 55.9 (minor, O***C***H_3), 55.8 (major, O***C***H_3), 51.3 (minor, ***C***$H_2C_6H_4$), 50.9 (2C, both, ***C***HCH_2), 48.0 (major, ***C***$H_2C_6H_4$), 45.7 (minor, N***C***H_2), 47.3 (major, N***C***H_2), 31.9 (2C, both, CH***C***H_2), 28.0 (major, NCH_2***C***H_2), 26.6 (minor, NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2930 (C-H), 1955 (C=C=C), 1709 (C=O), 1639 (NC=O); **MS** (ES+) m/z (rel. intensity %) 384.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{23}H_{23}NNaO_3$ $[M+Na]^+$ 384.1570, found 384.1563.

Preparation and characterisation of 5-bromo-*N*-(4-methoxybenzyl)-1-oxo-*N*-(penta-3,4-dien-1-yl)indane-2-carboxamide (±)-215k



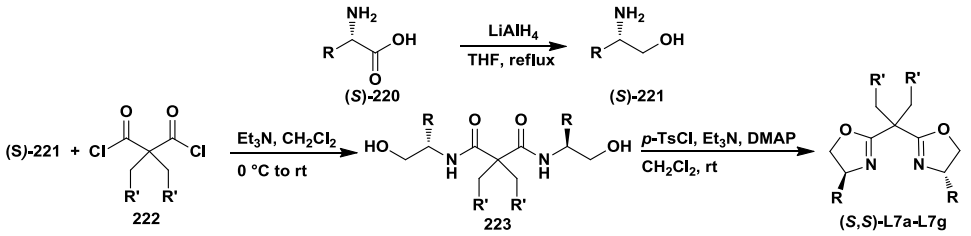
Synthesised from compound **219f** (1.33 g, 5.00 mmol) and amine **170f** (1.52 g, 7.50 mmol) according to general procedure I. Compound (±)-**215k** (1.76 g, 81% yield) was isolated after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow solid.

Two rotamers in a 1.5:1 ratio. **Mp** 70.0-72.9 °C; **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 7.90 (d, both, 2H, *J* = 10.3 Hz, 2 × Ar***H***), 7.64 (t, both, 2H, *J* = 6.4 Hz, 2 × Ar***H***), 7.58 (dd, both, 2H, *J* = 8.1 Hz, *J* = 5.2 Hz, 2 × Ar***H***), 7.27 (d, both, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.17 (d, both, 2H, *J* = 8.3 Hz, 2 × Ar***H***), 6.95 (d, both, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 6.88 (d, both, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 5.22 (p, major, 1H, *J* = 6.8 Hz, C***H***=C=CH_2), 5.10 (p, minor, 1H, *J* = 6.8 Hz,

C***H***=C=CH_2), 4.89 (d, minor, 1H, *J* = 16.6 Hz, C***H***$_A$$H_B$$C_6H_4$), 4.72-4.77 (m, 5H, C***H***$_A$$H_B$$C_6H_4$ for major and CH=C=C***H*****$_2$** for both), 4.65 (d, minor, 1H, *J* = 16.6 Hz, CH_A***H***$_B$$C_6H_4$), 4.33-4.39 (m, both, 2H, C***H***CH_2), 4.29 (d, major, 1H, *J* = 15.0 Hz, CH_A***H***$_B$$C_6H_4$), 3.75 (s, minor, 3H, OC***H*****$_3$**), 3.73 (s, major, 3H, OC***H*****$_3$**), 3.67-3.77 (m, both, 2H, NC***H***$_A$$H_B$), 3.28-3.37 (m, 5H, NCH_A***H***$_B$ for major and CHC***H*****$_2$** for both), 3.13-3.20 (m, minor, 1H, NCH_A***H***$_B$), 2.27-2.29 (m, major, 2H, NCH_2C***H*****$_2$**), 2.10-2.12 (m, minor, 2H, NCH_2C***H*****$_2$**); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 209.1 (major, CH=***C***=CH_2), 209.0 (minor, CH=***C***=CH_2), 202.3 (major, ***C***=O), 202.1 (minor, ***C***=O), 169.7 (minor, N***C***=O), 169.6 (major, N***C***=O), 159.5 (***C***, minor, Ar), 159.2 (***C***, major, Ar), 157.8 (***C***, major, Ar), 157.5 (***C***, minor, Ar), 135.3 (***C***, minor, Ar), 135.2 (***C***, major, Ar), 131.8 (2***C***, both, Ar), 130.8 (2***C***, both, Ar), 130.5 (2***C***H, both, Ar), 130.4 (2***C***H, both, Ar), 129.9 (2***C***H, both, Ar), 129.5 (2***C***H, both, Ar), 129.2 (2***C***H, both, Ar), 126.1 (2***C***H, both, Ar), 114.9 (***C***H, minor, Ar), 114.7 (***C***H, major, Ar), 87.7 (minor, ***C***H=C=CH_2), 87.4 (major, ***C***H=C=CH_2), 76.4 (major, CH=C=***C***H_2), 76.3 (minor, CH=C=***C***H_2), 55.9 (2C, both, O***C***H_3), 51.2 (minor, ***C***$H_2C_6H_4$), 51.0 (2C, both, ***C***HCH_2), 48.1 (major, ***C***$H_2C_6H_4$), 47.3 (major, N***C***H_2CH_2), 45.7 (minor, N***C***H_2CH_2), 31.7 (2C, both, CH***C***H_2), 28.0 (major, NCH_2***C***H_2), 26.5 (minor, NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2928 (C-H), 1955 (C=C=C), 1714 (C=O), 1639 (NC=O); **MS** (ES+) m/z (rel. intensity %) 462.09, 464.08 (M + Na^+, 80); **HRMS** (ESI+) calcd. for $C_{23}H_{22}BrNNaO_3$ $[M+Na]^+$ 462.0675, 464.0656, found 462.0670, 464.0651.

6.2.2.3 Synthesis and characterisation of bisoxazolines (*S*,*S*)-L7[115,116]

General procedure H for the synthesis of bisoxazolines (*S*,*S*)-L7



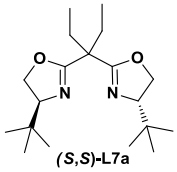
Into a dry flask under nitrogen, lithium aluminium hydride was weighed out (5.44 equiv.), and suspended in tetrahydrofuran (1.7 mL per mmol of **(*S*)-220**). The suspension was cooled to

0 °C and **(*S*)-220** (1 equiv.) was added in small portions. The reaction mixture was stirred at 0 °C for 15 min and stirred at room temperature for 1 h. The flask was mounted with a condenser and the reaction mixture was heated at reflux for 16 hours. The suspension was cooled to room temperature. It was diluted with diethyl ether and the excess hydride was quenched by slow addition of sodium sulfate decahydrate (100 milligram per mmol of **(*S*)-220**) and stirred for 1 hour at room temperature. The suspension was filtered through a pad of silica gel, washing thoroughly with ethyl acetate. The filtrate was concentrated *in vacuo* to afford crude aminol **(*S*)-221** that was used in the next step without further purification.

To an ice-cooled solution of aminol **(*S*)-221** (2.25 equiv.) in CH_2Cl_2 (1.0 mL/mmol of **(*S*)-221**) was added Et_3N (5.0 equiv.) and a solution of malonyl dichloride **222** (1.0 equiv.) in CH_2Cl_2 (1.0 mL/mmol of **(*S*)-221**) dropwise. The reaction mixture was warmed to room temperature, stirred for 2 hours and diluted with CH_2Cl_2 (8 mL/mmol of **(*S*)-221**). The layers were separated and the organic layer was washed with aqueous 1.0 M HCl, sat. aq. $NaHCO_3$ solution and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude products **(*S,S*)-223** were used directly in the next step.

To an ice-cooled solution of (*S,S*)-bisamides **223** (1.0 equiv.) and DMAP (0.1 equiv.) in CH_2Cl_2 (3.8 mL/mmol of **(*S,S*)-223**) was added Et_3N (6.0 equiv.) and a solution of *para*-toluene sulphonyl chloride (*p*-TsCl, 2.0 equiv.) in CH_2Cl_2 (2.0 mL/mmol of **(*S,S*)-223**). The cooling bath was then removed and the reaction was monitored by TLC. On completion, the reaction was quenched by the addition of sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (PE/EA) on silica gel provided bis(oxazolines) **(*S,S*)-L7a-(*S,S*)-L7f**.

Preparation and characterisation of (4*S*,4'*S*)-2,2'-pentane-3,3-diylbis(4-*tert*-butyl-4,5-dihydro-1,3-oxazole) (*S*,*S*)-L7a

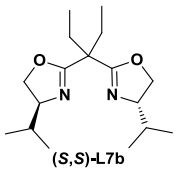


(*S*,*S*)-L7a

Synthesised on 0.8 mmol scale of diethylmalonyl dichloride (157 mg) according to general procedure H. Compound **(*S*,*S*)-L7a** (122 mg, 50% over two steps) was obtained after flash column chromatography on silica gel (PE/EA = 20:1 to 10:1) as a white solid.

$[\alpha]_D^{25}$ = - 128.0 (*c* 1.75, $CHCl_3$); **Mp** 36-37 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.13 (dd, 2H, *J* = 10.1 Hz, *J* = 8.7 Hz, C***H*****$_A$**H_BO), 4.03 (t, 2H, *J* = 8.4 Hz, CH_A***H*****$_B$**O), 3.87 (dd, 2H, *J* = 10.1 Hz, *J* = 7.4 Hz, C***H***^{t}Bu), 2.02-2.11 (m, 2H, C***H*****$_2$**CH_3), 1.88-1.97 (m, 2H, C***H*****$_2$**CH_3), 0.83-0.88 (m, 24H, 2 × CH_2C***H*****$_3$** and 2 × C(C***H*****$_3$**$)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 167.2 (2C, ***C***=N), 75.5 (2C, 2 × ***C***HN=C), 68.4 (2C, 2 × ***C***H_2O), 47.5 (***C***$(CH_2CH_3)_2$), 33.8 (2C, 2 × ***C***$(CH_3)_3$), 30.9 (2C, 2 × ***C***H_2CH_3), 25.8 (6C, 2 × C(***C***$H_3)_3$), 8.4 (2C, 2 × CH_2***C***H_3). Analytical data in agreement with the previous report.[115]

Preparation and characterisation of (4*S*,4'*S*)-2,2'-pentane-3,3-diylbis(4-isopropyl-4,5-dihydro-1,3-oxazole) (*S*,*S*)-L7b



(*S*,*S*)-L7b

Synthesised on 1.6 mmol scale of diethylmalonyl dichloride (314 mg) according to general procedure H. Compound **(*S*,*S*)-L7b** (282 mg, 60% yield over two steps) was obtained after flash column chromatography on silica gel (PE/EA = 20:1 to 10:1) as a colourless oil.

$[\alpha]_D^{25}$ = - 108.0 (*c* 1.75, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.11-4.19 (m, 2H, 2 × C***H***N=C), 3.89-3.98 (m, 4H, 2 × C***H*****$_2$**O), 1.89-2.08 (m, 4H, 2 × C***H*****$_2$**CH_3), 1.76-1.87 (m, 2H, 2 × C***H***$(CH_3)_2$), 0.91 (d, 6H, *J* = 6.8 Hz, CH(C***H*****$_3$**$)_A(CH_3)_B$), 0.80-0.88 (m, 12H,

$CH(CH_3)_A(C\boldsymbol{H_3})_B$ and 2 × $CH_2C\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 167.7 (2C, 2 × ***C***=N), 71.9 (2C, 2 × ***C***HN=C), 69.5 (2C, 2 × ***C***H_2O), 46.6 (***C***$(CH_2CH_3)_2$), 32.3 (2C, 2 × ***C***$(CH_3)_2$), 25.2 (2C, 2 × ***C***H_2CH_3), 18.7 ($CH(\boldsymbol{C}H_3)_A(CH_3)_B$), 17.6 ($CH(CH_3)_A(\boldsymbol{C}H_3)_B$), 8.3 (2C, 2 × $CH_2\boldsymbol{C}H_3$). Analytical data in agreement with the previous report.[115]

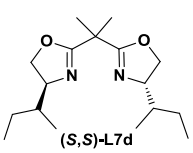
Preparation and characterisation of (4*S*,4'*S*)-2,2'-propane-2,2-diylbis(4-propyl-4,5-dihydro-1,3-oxazole) (*S*,*S*)-L7c

(*S*,*S*)-L7c

Synthesised on 2.0 mmol scale of dimethylmalonyl dichloride (338 mg) according to general procedure H. Compound **(*S*,*S*)-L7c** (282 mg, 34% yield over two steps) was synthesised after flash column chromatography on silica gel (PE/EA = 20:1 to 10:1) as a colourless oil.

$[\alpha]_D^{25}$ = - 120.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.30 (t, 2H, *J* = 8.1 Hz, 2 × $C\boldsymbol{H_A}H_BO$), 4.08-4.15 (m, 2H, 2 × C***H***N=C), 3.90 (t, 2H, *J* = 8.1 Hz, 2 × $CH_A\boldsymbol{H_B}O$), 1.59-1.68 (m, 4H, 2 × $C\boldsymbol{H_2}CH_2CH_3$), 1.51 (s, 6H, $C(C\boldsymbol{H_3})_2$), 1.32-1.48 (m, 4H, 2 × $CH_2C\boldsymbol{H_2}CH_3$), 0.94 (t, 6H, *J* = 7.2 Hz, 2 × $CH_2CH_2C\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 171.1 (2C, ***C***=N), 71.7 (2C, ***C***HN=C), 66.1 (2C, ***C***H_2O), 35.4 (***C***$(CH_3)_2$), 34.8 (2C, ***C***$H_2CH_2CH_3$), 25.1 (2C, $C(\boldsymbol{C}H_3)_2$), 19.5 (2C, $CH_2\boldsymbol{C}H_2CH_3$), 13.4 (2C, $CH_2CH_2\boldsymbol{C}H_3$). Analytical data in agreement with the previous report.[115]

Preparation and characterisation of (R,4S,4'S)-2,2'-(Propane-2,2-diyl)bis(4-sec-butyl-4,5-dihydrooxazole) (*S*,*S*)-L7d



(*S*,*S*)-L7d

Synthesised on 2.0 mmol scale of dimethylmalonyl dichloride (338 mg) according to general procedure H. Compound **(*S*,*S*)-L7d** (282 mg, 41% yield over two steps) was synthesised after flash column chromatography on silica gel (PE/EA = 20:1 to 10:1) as a colourless oil.

$[\alpha]_D^{25}$ = - 120.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.17 (t, 2H, *J* = 7.6 Hz, 2 × C***H***$_A$H$_B$O), 4.06-4.11 (m, 2H, 2 × C***H***N=C), 3.98 (t, 2H, *J* = 7.2 Hz, 2 × CH$_A$***H***$_B$O), 1.63-1.69 (m, 2H, 2 × CH$_3$C***H***CH$_2$CH$_3$), 1.50 (s, 6H, 2 × C(C***H***$_3$)$_2$), 1.36-1.47 (m, 2H, 2 × C***H***$_A$H$_B$CH$_3$), 1.09-1.20 (m, 2H, 2 × CH$_A$***H***$_B$CH$_3$), 0.90 (t, 6H, *J* = 7.2 Hz, 2 × C***H***$_3$CH), 0.78 (d, 6H, *J* = 6.8 Hz, 2 × CH$_2$C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 168.7 (2C, 2 × ***C***=N), 70.0 (2C, 2 × C=N***C***H), 69.3 (2C, 2 × ***C***H$_2$O), 38.5 (2C, 2 × CH$_3$***C***HCH$_2$CH$_3$), 26.0 (2C, 2 × ***C***H$_2$CH$_3$), 24.4 (2C, C(***C***H$_3$)$_2$), 13.6 (2C, 2 × ***C***H$_3$CH), 11.7 (2C, 2 × CH$_2$***C***H$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2950 (C-H), 1660 (C=N); **MS** (ES+) m/z (rel. intensity %) 317.24 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{17}H_{30}N_2NaO_2$ $[M+Na]^+$ 317.2205, found 317.2206.

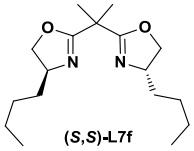
Preparation and characterisation of (4*S*,4'*S*)-2,2'-propane-2,2-diylbis(4-isobutyl-4,5-dihydro-1,3-oxazole) (*S*,*S*)-L7e

(*S*,*S*)-L7e

Synthesised on 2.0 mmol scale of dimethylmalonyl dichloride (338 mg) according to general procedure H. Compound **(*S*,*S*)-L7e** (282 mg, 45% yield over two steps) was obtained after flash column chromatography silica gel (PE/EA = 20:1 to 10:1) as a colourless oil.

$[\alpha]_D^{25}$ = - 115.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.33 (dd, 2H, *J* = 9.2 Hz, *J* = 8.1 Hz, 2 × C***H***$_A$H$_B$O), 4.11-4.18 (m, 2H, 2 × C***H***N=C), 3.86 (t, 2H, *J* = 7.8 Hz, 2 × CH$_A$***H***$_B$O), 1.59-1.73 (m, 10H, 2 × C***H***$_2$CH(CH$_3$)$_2$ and C(C***H***$_3$)$_2$), 1.29 (ddd, 2H, *J* = 13.2 Hz, *J* = 8.5 Hz, *J* = 5.8 Hz, 2 × C***H***(CH$_3$)$_2$), 0.93 ("t", 12H, *J* = 6.7 Hz, 2 × CH(C***H***$_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.7 (2C, 2 × ***C***=N), 71.4 (2C, 2 × ***C***HN=C), 65.2 (2C, 2 × ***C***H$_2$O), 41.6 (2C, 2 × ***C***H$_2$CH(CH$_3$)$_2$), 35.7 (***C***(CH$_3$)$_2$), 25.1 (2C, 2 × C(***C***H$_3$)$_2$), 24.7 (2C, 2 × ***C***H(CH$_3$)$_2$), 21.9 (4C, 2 × CH(***C***H$_3$)$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2980 (C-H), 1665 (C=N); **MS** (ES+) m/z (rel. intensity %) 317.24 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{17}H_{30}N_2NaO_2$ $[M+Na]^+$: 317.2205, found 317.2206.

Preparation and characterisation of (4*S*,4'*S*)-2,2'-propane-2,2-diylbis(4-butyl-4,5-dihydro-1,3-oxazole) (*S*,*S*)-L7f

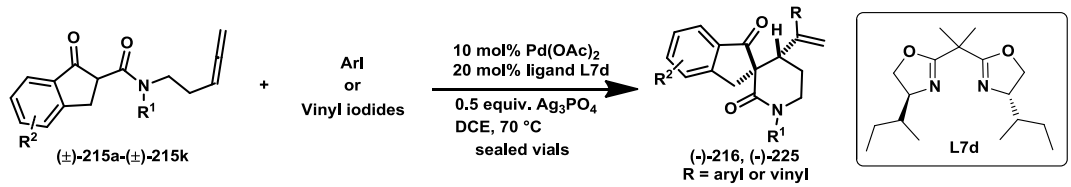


Synthesised on 2.0 mmol scale of dimethylmalonyl dichloride (338 mg) according to general procedure H. Compound **(*S*,*S*)-L7f** (403 mg, 69% yield over two steps) was obtained after flash column chromatography on silica gel (PE/EA = 20:1 to 10:1) as a colourless oil (69% yield over two steps).

$[\alpha]_D^{25}$ = - 90.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.30 (dd, 2H, *J* = 9.2 Hz, *J* = 8.2 Hz, 2 × C***H*****$_A$**H_BO), 4.06-4.14 (m, 2H, 2 × C***H***N=C), 3.91 (t, 2H, *J* = 7.7 Hz, 2 × CH_A**H_B**O), 1.61-1.71 (m, 4H, 2 × CHC***H*****$_2$**), 1.44-1.51 (m, 10H, 2 × C***H*****$_2$**CH_2CH_3 and C(C***H*****$_3$**$)_2$), 1.26-1.39 (m, 4H, 2 × C***H*****$_2$**CH_3), 0.91 (t, 6H, *J* = 6.9 Hz, 2 × CH_2C***H*****$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.5 (2C, 2 × ***C***=N), 71.6 (2C, 2 × ***C***HN=C), 65.7 (2C, 2 × ***C***H_2O), 35.5 (***C***$(CH_3)_2$), 33.8 (2C, 2 × CH***C***H_2), 27.9 (2C, 2 × ***C***$H_2CH_2CH_3$), 25.1 (2C, 2 × C(***C***$H_3)_2$), 22.6 (2C, 2 × ***C***H_2CH_3), 13.8 (2C, 2 × CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2984 (C-H), 1662 (C=N); **MS** (ES+) m/z (rel. intensity %) 317.25 (M + Na^+, 75); **HRMS** (ESI+) calcd. for $C_{17}H_{30}N_2NaO_2$ $[M+Na]^+$ 317.2205, found 317.2206.

6.2.2.4 Synthesis and characterisation of arylative and vinylative spirolactams 216, 225

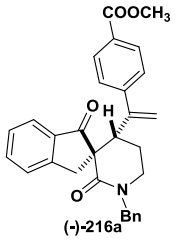
General procedure J for the synthesis of arylative and vinylative spirolactams 216, **225**



$Pd(OAc)_2$ (10 mol%) and bisoxazoline **(*S*,*S*)-L7d** (20 mol%) were stirred for 1 h in 1,2-dichloroethane (4 mL) at room temperature. Substrates (±)-**215a**-(±)-**215k** (0.2 mmol), aryl or vinyl iodides (0.3 mmol) and Ag_3PO_4 (0.1 mmol) were added. The reaction mixture was

stirred in a sealed tube at 70 ºC and monitored by TLC. On completion, the mixture was filtered through a short pad of silica gel and washed three times with diethyl ether. The combined organic phases were dired (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (petrol/ethyl acetate) to give the products **(-)-216** and **(-)-225.**

Preparation and characterisation of methyl 4-{1-[(2*R*,4'*S*)-1'-benzyl-1,2'-dioxo-1,3-dihydrospiro[indene-2,3'-piperidin]-4-yl]vinyl}benzoate (-)-216a



(-)-216a

Synthesised from substrate **(±)-215a** (66.2 mg, 0.20 mmol) and methyl 4-iodobenzoate (79.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216a** (single diastereoisomer, 78.0 mg, 84% yield) was obtained as a colourless oil after flash column chromatography on silica gel (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a > 99:1 dr.

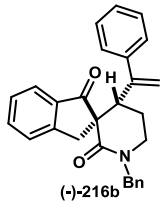
Ee = 85% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 8.2 min, minor t_R = 11.1 min); $[\alpha]_D^{25}$ = - 4.8 (*c* 1.3, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.49-7.53 (m, 1H, Ar***H***), 7.30-7.39 (m, 6H, 6 × Ar***H***), 7.14-7.22 (m, 2H, 2 × Ar***H***), 6.89 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 5.28 (s, 1H, C=C$\boldsymbol{H_A}$H$_B$), 5.14 (s, 1H, C=CH$_A$$\boldsymbol{H_B}$), 4.70 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}$H$_B$C$_6$H$_5$), 4.59 (d, 1H, *J* = 14.6 Hz, CH$_A$$\boldsymbol{H_B}C_6H_5$), 3.89 (s, 3H, OC$\boldsymbol{H_3}$), 3.71 (dd, 1H, *J* = 10.5 Hz, *J* = 2.0 Hz, C***H***), 3.49-3.58 (m, 2H, C(O)CC$\boldsymbol{H_A}$H$_B$ and CHCH$_2$C$\boldsymbol{H_A}$H$_B$), 3.38-3.43 (m, 1H, CHCH$_2$CH$_A$$\boldsymbol{H_B}$), 3.33 (d, 1H, *J* = 17.0 Hz, C(O)CCH$_A$$\boldsymbol{H_B}$), 2.35 (ddd, 1H, *J* = 13.1 Hz, *J* = 6.9 Hz, *J* = 4.0 Hz, CHC$\boldsymbol{H_A}$H$_B$), 1.91 (dtd, 1H, *J* = 13.7 Hz, *J* = 10.4 Hz, *J* = 5.2 Hz, CHCH$_A$$\boldsymbol{H_B}$);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 204.8 (***C***=O), 170.4 (N***C***=O), 166.7 (***C***OOCH$_3$), 153.9

(***C***=CH_2), 148.3 (***C***, Ar), 145.4 (***C***, Ar), 136.7 (***C***, Ar), 136.4 (***C***, Ar), 134.9 (2***C***H, Ar), 129.0 (2***C***H, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.5 (***C***, Ar), 127.3 (***C***H, Ar), 126.9 (2***C***H, Ar), 125.8 (***C***H, Ar), 124.2 (***C***H, Ar), 117.2 (C=***C***H_2), 60.0 (CO***C***CH_2), 52.1 (COO***C***H_3), 50.6 (***C***$H_2C_6H_5$), 45.7 (N***C***H_2CH_2), 43.9 (***C***H), 36.5 (COC***C***H_2), 24.9 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2928 (C-H), 1718 (C=O), 1632 (NC=O), 1595 (C=C); **MS** (ES+) m/z (rel. intensity %) 488.21 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{30}H_{27}NNaO_4$ $[M+Na]^+$ 488.1832, found 488.1833.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-(1-phenylvinyl)-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216b



(-)-216b

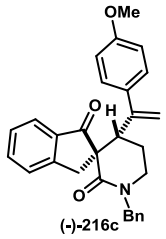
Synthesised from compound **(±)-215a** (66.2 mg, 0.20 mmol) and iodobenzene (61.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216b** (single diastereoisomer, 67.0 mg, 82% yield) was obtained as a colourless oil after flash column chromatography on silica gel (PE/EA = 3:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 45:1 dr.

Ee = 87% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 5.5 min, minor t_R = 14.4 min); $[\alpha]_D^{25}$ = - 16.6 (*c* 1.34, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49-7.53 (m, 1H, Ar***H***), 7.27-7.39 (m, 7H, 7 × Ar***H***), 7.18 (t, 1H, *J* = 7.4 Hz, Ar***H***), 7.08-7.11 (m, 1H, Ar***H***), 7.00-7.04 (m, 2H, 2 × Ar***H***), 6.86-6.88 (m, 2H, 2 × Ar***H***), 5.24 (s, 1H, C=C***H$_A$***H$_B$), 5.05 (s, 1H, C=CH$_A$***H$_B$***), 4.65 (s, 2H, C***H$_2$***C_6H_5), 3.68 (dd, 1H, *J* = 10.1 Hz, *J* = 2.1 Hz, C***H***), 3.58 (d, 1H, *J* = 16.9 Hz, C(O)CC***H$_A$***H$_B$), 3.49-3.54 (m, 1H, CH_2C***H$_A$***H$_B$N), 3.39-3.44 (m, 1H, CH_2CH$_A$***H$_B$***N), 3.36 (d, 1H, *J* = 17.0 Hz, C(O)CCH$_A$***H$_B$***), 2.39-2.45 (m, 1H, CHC***H$_A$***H$_B$), 1.83-1.92 (m, 1H, CHCH$_A$***H$_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$)

δ_C 204.9 (***C***=O), 170.5 (N***C***=O), 154.1 (***C***=CH_2), 149.0 (***C***, Ar), 140.8 (***C***, Ar), 136.8 (***C***, Ar), 136.3 (***C***, Ar), 134.7 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.7 (2***C***H, Ar), 127.5 (***C***H, Ar), 127.4 (***C***H, Ar), 127.1 (***C***H, Ar), 126.9 (2***C***H, Ar), 125.8 (***C***H, Ar), 124.3 (***C***H, Ar), 115.6 (C=***C***H_2), 60.0 (C(O)***C***CH_2), 50.7 (***C***$H_2C_6H_5$), 45.7 (N***C***H_2CH_2), 44.1 (***C***H), 36.7 (C(O)C***C***H_2), 24.6 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2926 (C-H), 1717 (C=O), 1631 (NC=O), 1590 (C=C); **MS** (ES+) m/z (rel. intensity %) 430.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{28}H_{25}NNaO_2$ $[M+Na]^+$ 430.1778, found 430.1777.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[1-(4-methoxyphenyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216c



(-)-216c

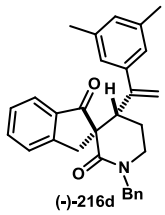
Synthesised from substrate **(±)-215a** (66.2 mg, 0.20 mmol) and 1-iodo-4-methoxybenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216c** (single diastereoisomer, 74.0 mg, 85% yield) was obtained as a colourless oil after flash column chromatography on silica gel (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 56:1 dr.

Ee = 86% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 6.3 min, minor t_R = 8.7 min); $[\alpha]_D^{25}$ = - 1.4 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48-7.52 (m, 1H, Ar***H***), 7.30-7.37 (m, 7H, 7 × Ar***H***), 7.17 (t, 1H, *J* = 7.4 Hz, Ar***H***), 6.78 (dd, 2H, *J* = 9.2 Hz, *J* = 2.5 Hz, 2 × Ar***H***), 6.53-6.55 (m, 2H, 2 × Ar***H***), 5.18 (s, 1H, C=C***H$_A$***H_B), 4.99 (s, 1H, C=CH_A***H$_B$***), 4.63 (s, 2H, C***H$_2$***C_6H_5), 3.73 (s, 3H, OC***H$_3$***), 3.65 (dd, 1H, *J* = 10.2 Hz, *J* = 1.4 Hz, C***H***), 3.49-3.56 (m, 2H, C(O)CC***H$_A$***H_B and CH_2C***H$_A$***H_BN), 3.39-3.43 (m, 1H, CH_2CH_A***H$_B$***N), 3.35 (d, 1H, *J* = 16.9 Hz, C(O)CCH_A***H$_B$***), 2.38 (ddd, 1H, *J* = 12.9 Hz, *J* = 7.4 Hz, *J* = 4.3 Hz, CHC***H$_A$***H_B), 1.87 (dtd, 1H, *J* = 15.1 Hz, *J*

= 10.1 Hz, *J* = 5.2 Hz, $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.1 (***C***=O), 170.7 (N***C***=O), 159.0 (***C***, Ar), 154.2 (***C***=CH_2), 148.5 (***C***, Ar), 136.8 (***C***, Ar), 136.4 (***C***, Ar), 134.6 (***C***, Ar), 133.1 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.2 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.4 (***C***H, Ar), 126.9 (***C***H, Ar), 125.7 (***C***H, Ar), 124.2 (***C***H, Ar), 114.4 (C=***C***H_2), 113.1 (2C, Ar), 60.1 (C(O)***C***CH_2), 55.2 (O***C***H_3), 50.7 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 44.3 (***C***H), 36.6 (C(O)C***C***H_2), 24.7 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2928 (C-H), 1716 (C=O), 1631 (NC=O), 1607 (C=C); **MS** (ES+) m/z (rel. intensity %) 460.21 (M + Na^+, 70); **HRMS** (ESI+) calcd. for $C_{29}H_{27}NNaO_3$ $[M+Na]^+$ 460.1883, found 460.1881.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[1-(3,5-dimethylphenyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216d



(-)-216d

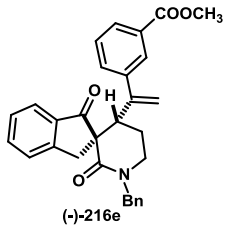
Synthesised from substrate **(±)-215a** (66.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216d** (single diastereoisomer, 66.0 mg, 76% yield) was obtained as a white solid after flash column chromatography on silica gel (PE/EA = 2:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 39:1 dr.

Ee = 88% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 4.3 min, minor t_R = 14.9 min); $[\alpha]_D^{25}$ = - 9.8 (*c* 1.84, CH_2Cl_2).

Mp 106.0-109.4 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.50-7.54 (m, 1H, Ar***H***), 7.23-7.39 (m, 7H, 7 × Ar***H***), 7.20 (t, 1H, *J* = 7.4 Hz, Ar***H***), 6.73 (s, 1H, Ar***H***), 6.45 (s, 2H, 2 × Ar***H***), 5.20 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.00 (s, 1H, C=$CH_A\boldsymbol{H_B}$), 4.71 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.58 (d, 1H, *J* = 14.6 Hz, $CH_A\boldsymbol{H_B}C_6H_5$), 3.63 (dd, 1H, *J* = 9.9 Hz, *J* = 2.5 Hz, C***H***), 3.57 (d, 1H, *J* = 17.0 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 3.49-3.53 (m, 1H, $CH_2C\boldsymbol{H_A}H_BN$), 3.38-3.41 (m, 1H, $CH_2CH_A\boldsymbol{H_B}N$), 3.34

(d, 1H, *J* = 17.0 Hz, C(O)CCH$_A$***H$_B$***), 2.38-2.45 (m, 1H, CHC***H$_A$***H$_B$), 2.11 (s, 6H, 2 × C***H$_3$***), 1.85 (m, 1H, CHCH$_A$***H$_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.0 (***C***=O), 170.6 (N***C***=O), 154.2 (***C***=CH_2), 149.3 (***C***, Ar), 140.8 (***C***, Ar), 137.1 (2***C***, Ar), 136.9 (***C***, Ar), 136.3 (***C***, Ar), 134.4 (***C***H, Ar), 129.1 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.4 (***C***H, Ar), 127.0 (***C***H, Ar), 125.8 (***C***H, Ar), 125.1 (2***C***H, Ar), 124.2 (***C***H, Ar), 114.9 (C=***C***H_2), 60.0 (C(O)***C***CH_2), 50.7 (***C***$H_2C_6H_5$), 45.6 (N***C***H_2CH_2), 44.5 (***C***H), 36.8 (C(O)C***C***H_2), 24.5 (CH***C***H_2), 21.1 (2C, 2 × ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2920 (C-H), 1718 (C=O), 1631 (NC=O), 1590 (C=C); **MS** (ES+) m/z (rel. intensity %) 458.23 (M + Na^+, 80); **HRMS** (ESI+) calcd. for $C_{30}H_{29}NNaO_2$ $[M+Na]^+$ 458.2091, found 458.2087.

Preparation and characterisation of methyl 3-{1-[(2*R*,4'*S*)-1'-benzyl-1,2'-dioxo-1,3-dihydrospiro[indene-2,3'-piperidin]-4'-yl]vinyl}benzoate (-)-216e



(-)-216e

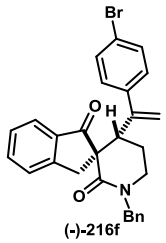
Synthesised from substrate **(±)-215a** (66.0 mg, 0.20 mmol) and methyl 3-iodobenzoate (79.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216e** (single diastereoisomer, 80.0 mg, 86% yield) was obtained as a colourless oil after flash column chromatography on silica gel (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 41:1 dr.

Ee = 85% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 6.3 min, minor t_R = 17.2 min); $[\alpha]_D^{25}$ = - 0.32 (*c* 2.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (d, 1H, *J* = 7.5 Hz, Ar***H***), 7.49 (t, 1H, *J* = 7.3 Hz, Ar***H***), 7.30-7.40 (m, 7H, 7 × Ar***H***), 7.20 (d, 1H, *J* = 7.6 Hz, Ar***H***), 7.06-7.15 (m, 3H, 3 × Ar***H***), 5.26 (s, 1H, C=C***H$_A$***H$_B$), 5.12 (s, 1H, C=CH$_A$***H$_B$***), 4.70 (d, 1H, *J* = 14.6 Hz, C***H$_A$***H$_B$$C_6H_5$), 4.59 (d, 1H, *J* = 14.6 Hz, CH$_A$***H$_B$***C_6H_5), 3.85 (s, 3H, OC***H$_3$***), 3.69-3.72 (m, 1H, C***H***), 3.50-3.59 (m, 2H,

$CH_2C\boldsymbol{H_A}H_BN$ and $C(O)CC\boldsymbol{H_A}H_B$), 3.39-3.44 (m, 1H, $CH_2CH_A\boldsymbol{H_B}N$), 3.35 (d, 1H, *J* = 17.0 Hz, $C(O)CCH_A\boldsymbol{H_B}$), 2.36 (ddd, 1H, *J* = 13.0 Hz, *J* = 6.9 Hz, *J* = 3.9 Hz, $CHC\boldsymbol{H_A}H_B$), 1.91 (ddt, 1H, *J* = 15.6 Hz, *J* = 10.5 Hz, *J* = 5.2 Hz, $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 204.9 (***C***=O), 170.5 (N***C***=O), 166.6 (***C***(O)OCH_3), 153.9 (***C***=CH_2), 148.3 (***C***, Ar), 141.1 (***C***, Ar), 136.8 (***C***, Ar), 136.4 (***C***, Ar), 134.7 (***C***, Ar), 131.4 (***C***H, Ar), 129.5 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.6 (***C***H, Ar), 128.5 (***C***H, Ar), 128.1 (2***C***H, Ar), 127.7 (***C***H, Ar), 127.5 (***C***H, Ar), 127.1 (***C***H, Ar), 125.9 (***C***H, Ar), 124.1 (***C***H, Ar), 116.7 (C=***C***H_2), 59.9 (C(O)***C***CH_2), 52.0 (O***C***H_3), 50.6 (***C***$H_2C_6H_5$), 45.7 (N***C***H_2CH_2), 44.2 (***C***H), 36.5 (C(O)C***C***H_2), 24.8 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2918 (C-H), 1719 (C=O), 1631 (NC=O), 1589 (C=C); **MS** (ES+) m/z (rel. intensity %) 488.21 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{30}H_{27}NNaO_4$ $[M+Na]^+$ 488.1832, found 488.1826.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[1-(4-bromophenyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216f



(-)-216f

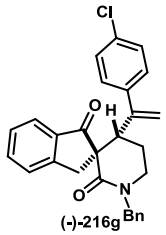
Synthesised from substrate **(±)-215a** (66.0 mg, 0.20 mmol) and 1-bromo-4-iodobenzene (85.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216f** (single diastereoisomer, 76.0 mg, 79% yield) was obtained after flash column chromatography on silica gel (PE/EA = :1) as a white solid. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 25:1 dr.

Ee = 86% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 5.9 min, minor t_R = 8.6 min); $[\alpha]_D^{25}$ = - 24.8 (*c* 2.68, CH_2Cl_2).

Mp 58.0-61.7 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.49-7.53 (m, 1H, Ar***H***), 7.27-7.39 (m, 7H, 7 × Ar***H***), 7.21 (t, 1H, *J* = 7.4 Hz, Ar***H***). 7.10 (dd, 2H, *J* = 8.8 Hz, *J* = 2.1 Hz, 2 × Ar***H***), 6.68

(dd, 2H, *J* = 8.8 Hz, *J* = 2.1 Hz, 2 × Ar***H***), 5.21 (s, 1H, C=C***H*****$_A$**H$_B$), 5.08 (s, 1H, C=CH$_A$***H*****$_B$**), 4.68 (d, 1H, *J* = 14.6 Hz, C***H*****$_A$**H$_B$C$_6$H$_5$), 4.61 (d, 1H, *J* = 14.6 Hz, CH$_A$***H*****$_B$**C$_6$H$_5$), 3.65 (dd, 1H, *J* = 10.8 Hz, *J* = 1.5 Hz, C***H***), 3.48-3.57 (m, 2H, CH$_2$C***H*****$_A$**H$_B$N and C(O)CC***H*****$_A$**H$_B$), 3.39 (td, 1H, *J* = 12.3 Hz, *J* = 4.5 Hz, CH$_2$CH$_A$***H*****$_B$**N), 3.31 (d, 1H, *J* = 17.0 Hz, C(O)CCH$_A$***H*****$_B$**), 2.32 (ddd, 1H, *J* = 13.2 Hz, *J* = 6.9 Hz, *J* = 4.0 Hz, CHC***H*****$_A$**H$_B$), 1.90 (dtd, 1H, *J* = 13.5 Hz, *J* = 10.6 Hz, *J* = 5.2 Hz, CHCH$_A$***H*****$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.1 (***C***=O), 170.6 (N***C***=O), 154.0 (***C***=CH$_2$), 148.1 (***C***, Ar), 139.5 (***C***, Ar), 136.7 (***C***, Ar), 136.5 (***C***, Ar), 134.8 (***C***H, Ar), 130.7 (2***C***H, Ar), 128.7 (2***C***H, Ar), 128.6 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.5 (***C***H, Ar), 127.1 (***C***H, Ar), 125.8 (***C***H, Ar), 124.3 (***C***H, Ar), 121.6 (***C***, Ar), 116.3 (C=***C***H$_2$), 60.0 (C(O)***C***CH$_2$), 50.6 (***C***H$_2$C$_6$H$_5$), 45.8 (N***C***H$_2$CH$_2$), 44.1 (***C***H), 36.5 (C(O)C***C***H$_2$), 24.9 (CH***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2924 (C-H), 1716 (C=O), 1631 (NC=O), 1588 (C=C); **MS** (ES+) m/z (rel. intensity %) 508.10, 510.11 (M + Na$^+$, 80); **HRMS** (ESI+) calcd. for $C_{28}H_{24}BrNNaO_2$ $[M+Na]^+$ 508.0883, 510.0864, found 508.0877, 510.0863.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[1-(4-chlorophenyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216g



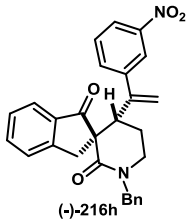
(-)-216g

Synthesised from substrate **(±)-215a** (66.0 mg, 0.20 mmol) and 1-chloro-4-iodobenzene (71.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216g** (single diastereoisomer, 74.0 mg, 84% yield) was obtained after flash column chromatography on silica gel (PE/EA = 2:1) as a white solid. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 33:1 dr.

Ee = 86% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 5.7 min, minor t_R = 8.5 min); $[\alpha]_D^{25}$ = - 14.8 (*c* 3.1, CH_2Cl_2).

Mp 57.6-59.5 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52 (dd, 1H, *J* = 10.8 Hz, *J* = 3.9 Hz, Ar***H***), 7.27-7.39 (m, 7H, 7 × Ar***H***), 7.20 (t, 1H, *J* = 7.4 Hz, Ar***H***), 6.95 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 6.74 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 5.20 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.08 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.68 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.61 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.66 (dd, 1H, *J* = 10.6 Hz, *J* = 1.5 Hz, C***H***), 3.49-3.57 (m, 2H, $CH_2C\boldsymbol{H_A}H_BN$ and C(O)CC$\boldsymbol{H_A}H_B$), 3.39 (td, 1H, *J* = 12.3 Hz, *J* = 4.6 Hz, $CH_2CH_A\boldsymbol{H_B}N$), 3.32 (d, 1H, *J* = 17.0 Hz, C(O)C$CH_A\boldsymbol{H_B}$), 2.32 (ddd, 1H, *J* = 13.1 Hz, *J* = 6.8 Hz, *J* = 3.8 Hz, CHC$\boldsymbol{H_A}H_B$), 1.85-1.95 (m, 1H, CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.0 (***C***=O), 170.6 (N***C***=O), 154.0 (***C***=CH_2), 148.1 (***C***, Ar), 139.1 (***C***, Ar), 136.5 (***C***, Ar), 134.8 (2***C***, Ar), 133.4 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.3 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.7 (2***C***H, Ar), 127.5 (***C***H, Ar), 127.1 (***C***H, Ar), 125.8 (***C***H, Ar), 124.3 (***C***H, Ar), 116.2 (C=***C***H_2), 60.0 (C(O)***C***CH_2), 50.6 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 44.1 (***C***H), 36.5 (C(O)C***C***H_2), 24.9 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2925 (C-H), 1716 (C=O), 1631 (NC=O), 1589 (C=C); **MS** (ES+) m/z (rel. intensity %) 464.15 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{28}H_{24}ClNNaO_2$ $[M+Na]^+$ 464.1388, found 464.1384.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[1-(3-nitrophenyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine] 1,2'(3*H*)-dione (-)-216h



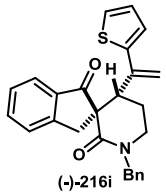
(-)-216h

Synthesised from substrate **(±)-215a** (66.0 mg, 0.20 mmol) and 1-iodo-3-nitrobenzene (75.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216h** (single diastereoisomer, 69.0 mg, 77% yield) was obtained after flash column chromatography on silica gel (PE/EA = 1:2) as a colourless oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 35:1 dr.

Ee = 85% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 7.3 min, minor t_R = 20.0 min); $[\alpha]_D^{25}$ = - 8.2 (*c* 1.34, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.89-7.94 (m, 1H, Ar***H***), 7.50 (ddd, 1H, *J* = 8.2 Hz, *J* = 5.8 Hz, *J* = 2.6 Hz, Ar***H***), 7.24-7.42 (m, 9H, 9 × Ar***H***), 7.08-7.12 (m, 2H, 2 × Ar***H***), 5.30 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.23 (d, 1H, *J* = 0.7 Hz, C=C$H_A\boldsymbol{H_B}$), 4.73 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.57 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.73-3.75 (m, 1H, C***H***), 3.59 (dt, 1H, *J* = 11.8 Hz, *J* = 4.3 Hz, $CH_2C\boldsymbol{H_A}H_BN$), 3.48 (d, 1H, *J* = 17.0 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 3.42 (ddd, 1H, *J* = 12.3 Hz, *J* = 5.1 Hz, *J* = 3.1 Hz, $CH_2CH_A\boldsymbol{H_B}N$), 3.33 (d, 1H, *J* = 17.0 Hz, C(O)CC$H_A\boldsymbol{H_B}$), 2.26-2.31 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.94-2.04 (m, 1H, CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.0 (***C***=O), 170.4 (N***C***=O), 153.8 (***C***=CH_2), 147.4 (***C***, Ar), 147.3 (***C***, Ar), 142.3 (***C***, Ar), 136.6 (***C***, Ar), 136.5 (***C***, Ar), 135.2 (***C***H, Ar), 132.9 (***C***H, Ar), 129.0 (***C***H, Ar), 128.7 (***C***H, Ar), 128.4 (***C***H, Ar), 128.1 (***C***H, Ar), 127.6 (***C***H, Ar), 127.2 (***C***H, Ar), 126.0 (***C***H, Ar), 123.9 (***C***H, Ar), 122.5 (2***C***H, Ar), 122.3 (***C***H, Ar), 118.2 (C=***C***H_2), 59.9 (C(O)***C***CH_2), 50.6 (***C***$H_2C_6H_5$), 45.9 (N***C***H_2CH_2), 44.2 (***C***H), 36.3 (C(O)C***C***H_2), 25.2 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2927 (C-H), 1716 (C=O), 1630 (NC=O), 1592 (C=C); **MS** (ES+) m/z (rel. intensity %) 475.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{28}H_{24}N_2NaO_4$ $[M+Na]^+$ 475.1628, found 475.1630.

Preparation and characterisation of (2*R*,4'*R*)-1'-benzyl-4'-[1-(2-thienyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216i



(-)-216i

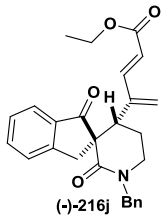
Synthesised from substrate **(±)-215a** (66.0 mg, 0.20 mmol) and 2-iodothiophene (63.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216i** (single diastereoisomer, 58.0 mg, 70% yield) was obtained after flash column chromatography on silica gel (PE/EA =

2:1) as a colourless oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 40:1 dr.

Ee = 75% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 6.5 min, minor t_R = 16.8 min); $[\alpha]_D^{25}$ = - 42.8 (*c* 1.96, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.53 (ddd, 2H, *J* = 10.5 Hz, *J* = 5.9 Hz, *J* = 2.0 Hz, Ar***H***), 7.23-7.40 (m, 7H, 7 × Ar***H***), 7.01 (dd, 1H, *J* = 4.5 Hz, *J* = 1.6 Hz, Ar***H***), 6.82-6.84 (m, 2H, 2 × Ar***H***), 5.49 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 4.94 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.73 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.61 (d, 1H, *J* = 14.7Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.73 (d, 1H, *J* = 17.0 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 3.56 (dd, 1H, *J* = 8.2 Hz, *J* = 3.3 Hz, C***H***), 3.38-3.51 (m, 2H, $CH_2C\boldsymbol{H_2}N$), 3.32 (d, 1H, *J* = 17.1 Hz, C(O)CC$H_A\boldsymbol{H_B}$), 2.59-2.66 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.84-1.92 (m, 1H, CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 204.9 (***C***=O), 169.9 (N***C***=O), 154.3 (***C***=CH_2), 143.8 (***C***, Ar), 141.3 (***C***, Ar), 136.8 (***C***, Ar), 135.6 (***C***, thiophene), 134.9 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.5 (***C***H, thiophene), 127.3 (***C***H, Ar), 127.1 (***C***H, thiophene), 125.9 (***C***H, thiophene), 124.9 (***C***H, Ar), 124.6 (***C***H, Ar), 124.5 (***C***H, Ar), 114.0 (C=***C***H_2), 60.1 (C(O)***C***CH_2), 50.8 (***C***$H_2C_6H_5$), 45.2 (N***C***H_2CH_2), 44.4 (***C***H), 37.2 (C(O)C***C***H_2), 24.1 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2926 (C-H), 1714 (C=O), 1632 (NC=O), 1590 (C=C); **MS** (ES+) m/z (rel. intensity %) 436.15 (M + Na^+, 75); **HRMS** (ESI+) calcd. for $C_{26}H_{23}NNaO_2S$ $[M+Na]^+$ 436.1342, found 436.1345.

Preparation and characterisation of ethyl (2*E*)-4-[(2*R*,4'*S*)-1'-benzyl-1,2'-dioxo-1,3-dihydrospiro[indene-2,3'-piperidin]-4'-yl]penta-2,4-dienoate (-)-216j



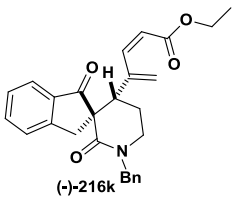
(-)-216j

Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*E*)-ethyl 3-iodoacrylate (67.5 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216j** (single diastereoisomer,

65.0 mg, 76% yield) was obtained after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 13:1 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.57 (t, 1H, *J* = 7.4 Hz, Ar***H***), 7.27-7.41 (m, 7H, 7 × Ar***H***), 7.09 (d, 1H, *J* = 16.0 Hz, OC-CH=C***H***), 5.80 (d, 1H, *J* = 16.0 Hz, (O)CC***H***=CH), 5.52 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.20 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.71 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.57 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 4.16 (q, 2H, *J* = 7.1 Hz, C$\boldsymbol{H_2}CH_3$), 3.79 (d, 1H, *J* = 17.2 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 3.37-3.44 (m, 1H, CHCH_2C$\boldsymbol{H_A}H_B$), 3.28-3.34 (m, 1H, CHCH_2C$H_A\boldsymbol{H_B}$), 3.24 (dd, 1H, *J* = 6.9 Hz, *J* = 3.6 Hz, C***H***), 3.11 (d, 1H, *J* = 17.1 Hz, C(O)CC$H_A\boldsymbol{H_B}$), 2.63-2.71 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.71-1.79 (m, 1H, CHC$H_A\boldsymbol{H_B}$), 1.26 (t, 3H, *J* = 7.1 Hz, C$\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 204.5 (***C***=O), 169.3 (***C***(O)OCH_2), 166.5 (N***C***=O), 154.0 (***C***, Ar), 145.2 ((O)CCH=***C***H), 143.5 (***C***=CH_2), 136.7 (***C***, Ar), 135.3 (***C***, Ar), 135.2 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.0 (2***C***H, Ar), 127.6 (***C***H, Ar), 127.5 (***C***H, Ar), 126.0 (***C***H, Ar), 124.8 (***C***H, Ar), 123.1 (C=***C***H_2), 119.1 ((O)C***C***H=CH), 60.5 (O***C***H_2), 59.5 (C(O)***C***CH_2), 50.8 (***C***$H_2C_6H_5$), 44.9 (N***C***H_2CH_2), 40.8 (***C***H), 37.2 (C(O)C***C***H_2), 23.2 (CH***C***H_2), 14.2 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2979 (C-H), 1715 (C=O), 1631 (C=O), 1590 (C=C); **MS** (ES+) m/z (rel. intensity %) 452.22 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{27}H_{27}NNaO_4$ $[M+Na]^+$ 452.1832, found 452.1830.

Preparation and characterisation of ethyl (2*Z*)-4-[(2*R*,4'*S*)-1'-benzyl-1,2'-dioxo-1,3-dihydrospiro[indene-2,3'-piperidin]-4'-yl]penta-2,4-dienoate (-)-216k



(-)-216k

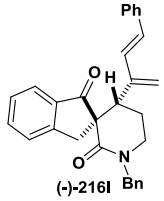
Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*Z*)-ethyl 3-iodoacrylate (67.5 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216k** (single diastereoisomer,

67.0 mg, 78% yield) was obtained after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 15:1 dr.

Ee = 50% (Chiralcel AD, 80:20 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 9.7 min, minor t_R = 13.8 min); $[\alpha]_D^{25}$ = - 11.3 (*c* 0.47, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.54 (t, 1H, *J* = 7.4 Hz, Ar***H***), 7.42 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.27-7.36 (m, 6H, 6 × Ar***H***), 6.10 (d, 1H, *J* = 12.2 Hz, OC-CH=C***H***), 5.43 (d, 1H, *J* = 12.2 Hz, (O)CC***H***=CH), 5.29 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.14 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.72 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.48 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.83-3.94 (m, 2H, C$\boldsymbol{H_2}CH_3$), 3.32-3.50 (m, 5H, C***H*** and $CHCH_2C\boldsymbol{H_2}$ and C(O)CC$\boldsymbol{H_2}$), 2.22-2.28 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.87-1.97 (m, 1H, CHC$H_A\boldsymbol{H_B}$), 1.14 (t, 3H, *J* = 7.1 Hz, C$\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.7 (***C***=O), 170.5 (***C***(O)OCH_2), 165.1 (N***C***=O), 154.5 (***C***, Ar), 144.2 ((O)CCH=***C***H), 142.4 (***C***=CH_2), 136.8 (***C***, Ar), 134.8 (***C***, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.9 (***C***H, Ar), 127.5 (***C***H, Ar), 127.3 (***C***H, Ar), 126.4 (***C***H, Ar), 124.3 (***C***H, Ar), 121.1 ((O)C***C***H=CH), 118.1 (C=***C***H_2), 60.0 (C(O)***C***CH_2), 59.9 (O***C***H_2), 50.5 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 44.2 (***C***H), 36.4 (C(O)C***C***H_2), 24.3 (CH***C***H_2), 13.9 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2980 (C-H), 1716 (C=O), 1632 (NC=O), 1590 (C=C); **MS** (ES+) m/z (rel. intensity %) 452.22 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{27}H_{27}NNaO_4$ $[M+Na]^+$ 452.1832, found 452.1822.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[(3*E*)-4-phenylbuta-1,3-dien-2-yl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216l



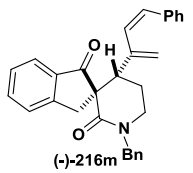
(-)-216l

Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*E*)-(2-iodovinyl)benzene (69.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216l** (single diastereoisomer, 53.0 mg, 61% yield) was obtained after flash column chromatography on silica gel (PE/EA = 1:1) as a yellow oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 21:1 dr.

Ee = 54% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 6.1 min, minor t_R = 8.7 min); $[\alpha]_D^{25}$ = - 10.1 (*c* 0.68, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.53 (t, 1H, *J* = 7.4 Hz, Ar***H***), 7.21-7.42 (m, 12H, 12 × Ar***H***), 6.36-6.49 (m, 2H, PhC***H***=C***H***), 5.32 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 4.94 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.64-4.67 (m, 2H, C$\boldsymbol{H_2}C_6H_5$), 3.72 (d, 1H, *J* = 17.1 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 3.35-3.50 (m, 3H, $CH_2C\boldsymbol{H_2}$N and C***H***), 3.26 (d, 1H, *J* = 17.1 Hz, C(O)C$CH_A\boldsymbol{H_B}$), 2.56-2.63 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.82-1.90 (m, 1H, C$HCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.3 (***C***=O), 170.0 (N***C***=O), 154.3 (***C***, Ar), 145.3 (***C***=CH_2), 136.9 (***C***, Ar), 136.7 (***C***, Ar), 135.9 (***C***, Ar), 135.0 (***C***H, Ar), 129.7 (Ph***C***H=CH), 129.3 (PhCH=***C***H), 128.7 (2***C***H, Ar), 128.5 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.7 (***C***H, Ar), 127.4 (***C***H, Ar), 127.3 (***C***H, Ar), 126.5 (2***C***H, Ar), 126.1 (***C***H, Ar), 124.6 (***C***H, Ar), 115.9 (C=***C***H_2), 59.9 (C(O)***C***CH_2), 50.7 (***C***$H_2C_6H_5$), 45.3 (N***C***H_2CH_2), 41.7 (***C***H), 37.1 (C(O)C***C***H_2), 23.8 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2926 (C-H), 1712 (C=O), 1631 (C=O), 1589 (C=C); **MS** (ES+) m/z (rel. intensity %) 456.23 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{30}H_{27}NNaO_2$ $[M+Na]^+$ 456.1934, found 456.1925.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[(3*Z*)-4-phenylbuta-1,3-dien-2-yl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216m



(-)-216m

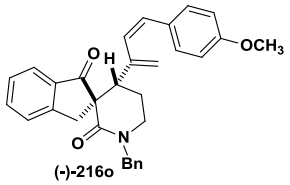
Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*Z*)-(2-iodovinyl)benzene (69.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216m** (single

diastereoisomer, 63.0 mg, 72% yield) was obtained after flash column chromatography on silica gel (PE/EA = 1:1) as a colourless oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 23:1 dr.

Ee = 77% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 6.1 min, minor t_R = 10.2 min); $[\alpha]_D^{25}$ = - 8.0 (*c* 0.2, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.77 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.51-7.54 (m, 1H, Ar***H***), 7.20-7.42 (m, 12H, 12 × Ar***H***), 6.18 (d, 1H, *J* = 12.5 Hz, PhC***H***=CH), 5.69 (d, 1H, *J* = 12.5 Hz, PhCH=C***H***), 5.15 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 4.97 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.73 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.46 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.52 (d, 1H, *J* = 17.0 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 3.34-3.42 (m, 2H, CHCH_2C$\boldsymbol{H_2}$), 3.22-3.27 (m, 2H, C***H*** and C(O)CC$H_A\boldsymbol{H_B}$), 2.15-2.19 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.83-1.95 (m, 1H, CHC$H_A\boldsymbol{H_B}$). **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 205.2 (***C***=O), 170.6 (N***C***=O), 154.1 (***C***, Ar), 143.6 (***C***=CH_2), 136.8 (***C***, Ar), 136.7 (***C***, Ar), 134.9 (***C***, Ar), 131.0 (***C***H, Ar), 130.2 (PhCH=***C***H), 128.7 (Ph***C***H=CH), 128.6 (2***C***H, Ar), 128.3 (2***C***H, Ar), 128.0 (***C***H, Ar), 127.9 (2***C***H, Ar), 127.5 (***C***H, Ar), 127.4 (***C***H, Ar), 126.9 (***C***H, Ar), 126.5 (***C***H, Ar), 126.3 (***C***H, Ar), 124.5 (***C***H, Ar), 117.4 (C=***C***H_2), 60.1 (CO***C***CH_2), 50.4 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 44.8 (***C***H), 36.5 (C(O)C***C***H_2), 24.6 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2925 (C-H), 1714 (C=O), 1632 (NC=O), 1590 (C=C); **MS** (ES+) m/z (rel. intensity %) 456.23 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{30}H_{27}NNaO_2$ $[M+Na]^+$ 456.1934, found 456.1927.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[(3*Z*)-4-(4-methoxyphenyl)buta-1,3-dien-2-yl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216o



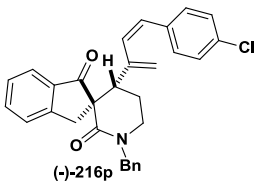
(-)-216o

Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*Z*)-1-(2-iodovinyl)-4-methoxybenzene (78.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216o** was obtained (single diastereoisomer, 62.0 mg, 67% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 20:1 dr.

Ee = 63% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 7.6 min, minor t_R = 14.1 min); $[\alpha]_D^{25}$ = - 10.7 (*c* 1.23, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.64 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.51-7.54 (m, 1H, Ar***H***), 7.24-7.41 (m, 7H, 7 × Ar***H***), 7.17 (dd, 2H, *J* = 9.3 Hz, *J* = 2.3 Hz, 2 × Ar***H***), 6.79-6.81 (m, 2H, 2 × Ar***H***), 6.32 (brs, 2H, ArC***H***=C***H***), 5.27 (s, 1H, C=C***H$_A$***H$_B$), 4.88 (s, 1H, C=CH$_A$***H$_B$***), 4.69 (d, 1H, *J* = 14.6 Hz, C***H$_A$***H$_B$C$_6$H$_5$), 4.61 (d, 1H, *J* = 14.6 Hz, CH$_A$***H$_B$***C$_6$H$_5$), 3.80 (s, 3H, OC***H$_3$***), 3.71 (d, 1H, *J* = 17.1 Hz, C(O)CC***H$_A$***H$_B$), 3.36-3.44 (m, 3H, CHCH$_2$C***H$_2$*** and C***H***), 3.26 (d, 1H, *J* = 17.1 Hz, C(O)CCH$_A$***H$_B$***), 2.56-2.62 (m, 1H, CHC***H$_A$***H$_B$), 1.81-1.87 (m, 1H, CHCH$_A$***H$_B$***); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 205.4 (***C***=O), 170.2 (N***C***=O), 159.3 (***C***, Ar), 154.3 (***C***, Ar), 145.4 (***C***=CH$_2$), 136.9 (***C***, Ar), 135.9 (***C***, Ar), 134.9 (ArCH=***C***H), 129.5 (Ar***C***H=CH), 128.8 (***C***, Ar), 128.6 (2***C***H, Ar), 128.0 (2***C***H, Ar), 127.7 (2***C***H, Ar), 127.6 (***C***H, Ar), 127.4 (***C***H, Ar), 127.2 (***C***H, Ar), 126.0 (***C***H, Ar), 124.6 (***C***H, Ar), 114.9 (C=***C***H$_2$), 113.9 (2***C***H, Ar), 59.9 (C(O)***C***CH$_2$), 55.2 (O***C***H$_3$), 50.7 (***C***H$_2$C$_6$H$_5$), 45.3 (N***C***H$_2$CH$_2$), 41.7 (***C***H), 37.1 (C(O)C***C***H$_2$), 23.8 (CH***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2923 (C-H), 1718 (C=O), 1633 (NC=O), 1589 (C=C); **MS** (ES+) m/z (rel. intensity %) 486.23 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{31}H_{29}NNaO_3$ [M+Na]$^+$ 486.2040, found 486.2030.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[(3*Z*)-4-(4-chlorophenyl)buta-1,3-dien-2-yl]-2'*H*-spiro[indene-2,3'-piperidine]1,2'(3*H*)-dione (-)-216p



(-)-216p

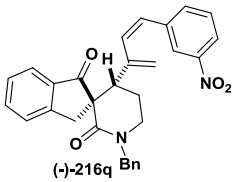
Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*Z*)-1-chloro-4-(2-iodovinyl)benzene (79.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216p** was obtained (single diastereoisomer, 73.0 mg, 78% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 18:1 dr.

Ee = 77% (Chiralcel AD, 70:30 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 8.3 min, minor t_R = 20.4 min); $[\alpha]_D^{25}$ = - 13.4 (*c* 0.53, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.54 (dt, 1H, *J* = 7.5 Hz, *J* = 1.2 Hz, Ar***H***), 7.27-7.41 (m, 7H, 7 × Ar***H***), 6.99-7.02 (m, 2H, 2 × Ar***H***), 6.81-6.84 (m, 2H, 2 × Ar***H***), 6.09 (d, 1H, *J* = 12.5 Hz, ArC***H***=CH), 5.70 (dd, 1H, *J* = 12.5 Hz, *J* = 0.8 Hz, ArCH=C***H***), 5.14 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.00 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.77 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.42 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.49 (d, 1H, *J* = 17.1 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 3.33-3.43 (m, 3H, C(O)CC$H_A\boldsymbol{H_B}$ and CHCH_2C$\boldsymbol{H_2}$), 3.24 (dd, 1H, *J* = 11.6 Hz, *J* = 2.4 Hz, C***H***), 2.09-2.15 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.87-1.97 (m, 1H, CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.2 (***C***=O), 170.6 (N***C***=O), 153.9 (***C***, Ar), 143.2 (***C***=CH_2), 136.8 (***C***, Ar), 136.7 (***C***, Ar), 135.2 (***C***, Ar), 134.9 (***C***, Ar), 132.5 (ArCH=***C***H), 130.9 (***C***H, Ar), 129.6 (Ar***C***H=CH), 129.5 (2***C***H, Ar), 128.7 (***C***H, Ar), 128.6 (***C***H, Ar), 128.1 (2***C***H, Ar), 128.0 (2***C***H, Ar), 127.6 (***C***H, Ar), 127.5 (***C***H, Ar), 126.3 (***C***H, Ar), 124.5 (***C***H, Ar), 117.7 (C=***C***H_2), 60.1 (C(O)***C***CH_2), 50.4 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 44.8 (***C***H), 36.4 (C(O)C***C***H_2), 24.7 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2931 (C-H), 1713 (C=O), 1631 (NC=O), 1596 (C=C); **MS** (ES+) m/z

(rel. intensity %) 490.15 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{30}H_{26}ClNNaO_2$ $[M+Na]^+$ 490.1544, found 490.1540.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[(3*Z*)-4-(3-nitrophenyl)buta-1,3-dien-2-yl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216q



(-)-216q

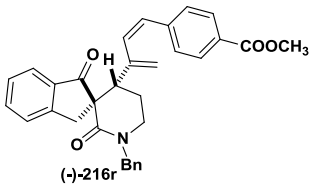
Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*Z*)-1-(2-iodovinyl)-3-nitrobenzene (82.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216q** was obtained (single diastereoisomer, 74.0 mg, 77% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 16:1 dr.

Ee = 77% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 9.8 min, minor t_R = 19.5 min); $[\alpha]_D^{25}$ = - 11.9 (*c* 0.87, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.02 (d, 1H, *J* = 1.7 Hz, Ar***H***), 7.92-7.95 (m, 1H, Ar***H***), 7.72 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.19-7.46 (m, 10H, 10 × Ar***H***), 6.12 (d, 1H, *J* = 12.5 Hz, 3-ArC***H***=CH), 5.82 (d, 1H, *J* = 12.5 Hz, ArCH=C***H***), 5.21 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.11 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.79 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.40 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.37-3.51 (m, 4H, C(O)CC$\boldsymbol{H_2}$ and $CHCH_2C\boldsymbol{H_2}$), 3.30 (dd, 1H, *J* = 11.7 Hz, *J* = 1.9 Hz, C***H***), 2.14-2.19 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.93-2.05 (m, 1H, C$HCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.3 (***C***=O), 170.5 (N***C***=O), 153.7 (***C***, Ar), 147.8 (***C***, Ar), 143.2 (***C***=CH_2), 138.0 (***C***, Ar), 136.8 (***C***, Ar), 136.6 (***C***, Ar), 134.8 (***C***H, Ar), 134.7 (***C***H, Ar), 133.5 (ArCH=***C***H), 128.9 (Ar***C***H=CH), 128.7 (2***C***H, Ar), 128.1 (3***C***H, Ar), 127.6 (***C***H, Ar), 127.5 (***C***H, Ar), 126.4 (***C***H, Ar), 124.4 (***C***H, Ar), 122.7 (***C***H, Ar), 121.7 (***C***H, Ar), 118.0 (C=***C***H_2), 60.0 (C(O)***C***CH_2), 50.4 (***C***$H_2C_6H_5$), 45.9 (N***C***H_2CH_2), 44.8 (***C***H), 36.4 (C(O)C***C***H_2), 24.7 (CH***C***H_2); **FT-IR**

ν_{max}(NaCl)/cm^{-1} 2919 (C-H), 1716 (C=O), 1631 (NC=O), 1589 (C=C); **MS** (ES+) m/z (rel. intensity %) 501.20 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{30}H_{26}N_2NaO_4$ $[M+Na]^+$ 501.1785, found 501.1787.

Preparation and characterisation of methyl 4-{(1*Z*)-3-[(2*R*,4'*S*)-1'-benzyl-1,2'-dioxo-1,3-dihydrospiro[indene-2,3'-piperidin]-4'-yl]buta-1,3-dien-1-yl}benzoate (-)-216r



(-)-216r

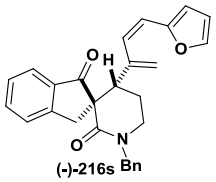
Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*Z*)-methyl 4-(2-iodovinyl)benzoate (86.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216r** was obtained (single diastereoisomer, 67.0 mg, 68% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 17:1 dr.

Ee = 82% (Chiralcel AD, 70:30 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 15.2 min, minor t_R = 25.4 min); $[\alpha]_D^{25}$ = - 7.9 (*c* 2.36, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.71-7.77 (m, 3H, 3 × Ar***H***), 7.52-7.55 (m, 1H, Ar***H***), 7.42 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.26-7.34 (m, 6H, 6 × Ar***H***), 6.95 (d, 2H, *J* = 8.2 Hz, 2 × Ar***H***), 6.17 (d, 1H, *J* = 12.5 Hz, ArC***H***=CH), 5.78 (d, 1H, *J* = 12.4 Hz, ArCH=C***H***), 5.11 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 4.99 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.75 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.43 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.89 (s, 3H, OC$\boldsymbol{H_3}$), 3.49 (d, 1H, *J* = 17.0 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 3.33-3.39 (m, 3H, CHCH_2C$\boldsymbol{H_2}$ and C(O)CC$H_A\boldsymbol{H_B}$), 3.24 (dd, 1H, *J* = 11.6 Hz, *J* = 2.1 Hz, C***H***), 2.09-2.14 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.89-1.97 (m, 1H, CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 205.2 (***C***=O), 170.6 (N***C***=O), 166.8 (***C***(O)OCH_3), 153.9 (***C***, Ar), 143.1 (***C***=CH_2), 141.6 (***C***, Ar), 136.8 (***C***, Ar), 136.7 (***C***, Ar), 135.0 (ArCH=***C***H), 132.2 (***C***, Ar), 129.9 (Ar***C***H=CH), 129.3 (2***C***H, Ar), 128.7 (2***C***H, Ar), 128.3 (***C***H, Ar), 128.2 (2***C***H, Ar), 128.0 (2***C***H, Ar), 127.7 (***C***H, Ar), 127.5

(***C***H, Ar), 126.3 (***C***H, Ar), 124.5 (***C***H, Ar), 118.0 (C=***C***H_2), 60.1 (C(O)***C***CH_2), 52.0 (O***C***H_3), 50.4 (***C***$H_2C_6H_5$), 45.9 (N***C***H_2CH_2), 44.8 (***C***H), 36.3 (C(O)C***C***H_2), 24.7 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2950 (C-H), 1717 (C=O), 1632 (NC=O), 1608 (C=C); **MS (ES)** m/z (rel. intensity %) 492.24 (M + H^+, 100); **ESI HRMS** calcd. for $C_{32}H_{30}NO_4$ $[M+H]^+$ 492.2169, found 492.2168.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[(3*Z*)-4-(2-furyl)buta-1,3-dien-2-yl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216s



(-)-216s

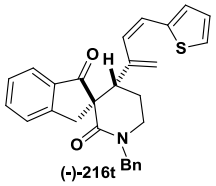
Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*Z*)-2-(2-iodovinyl)furan (66.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216s** was obtained (single diastereoisomer, 59.0 mg, 70% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 19:1 dr.

Ee = 71% (Chiralcel AD, 70:30 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 6.5 min, minor t_R = 9.4 min); $[\alpha]_D^{25}$ = - 8.2 (*c* 0.60, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (d, 1H, *J* = 7.6 Hz, Ar***H***), 7.29-7.38 (m, 6H, 6 × Ar***H***), 7.20 (dd, 2H, *J* = 15.3 Hz, *J* = 7.6 Hz, 2 × Ar***H***), 7.04 (d, 1H, *J* = 1.8 Hz, furan-***H***), 6.14 (dd, 1H, *J* = 3.3 Hz, *J* = 1.8 Hz, furan-***H***), 6.08 (d, 1H, *J* = 3.3 Hz, furan-***H***), 5.78 (d, 1H, *J* = 12.6 Hz, furan-C***H***=CH), 5.51 (d, 1H, *J* = 12.6 Hz, furan-CH=C***H***), 5.34 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.16 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.77 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.45 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.35-3.50 (m, 4H, C(O)CC***H$_2$*** and CHCH_2C***H$_2$***), 3.31 (dd, 1H, *J* = 11.2 Hz, *J* = 2.3 Hz, C***H***), 2.21-2.27 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.88-1.95 (m, 1H, CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.9 (***C***=O), 170.8 (N***C***=O), 154.1 (***C***, Ar), 151.4 (furan-***C***), 143.8 (***C***=CH_2),

141.2 (furan-***C***H), 136.8 (furan-CH=***C***H), 136.7 (***C***, Ar), 134.3 (***C***, Ar), 128.6 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.7 (***C***H, Ar), 127.4 (***C***H, Ar), 127.1 (***C***H, Ar), 126.1 (***C***H, Ar), 124.1 (***C***H, Ar), 118.4 (furan-***C***H=CH), 116.6 (furan-***C***H), 110.9 (furan-***C***H), 110.5 (C=***C***H_2), 60.1 (C(O)***C***CH_2), 50.5 (***C***$H_2C_6H_5$), 45.9 (N***C***H_2CH_2), 45.1 (***C***H), 36.5 (C(O)C***C***H_2), 24.4 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2925 (C-H), 1713 (C=O), 1629 (NC=O), 1593 (C=C); **MS** (ES+) m/z (rel. intensity %) 446.20 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{28}H_{25}NNaO_3$ $[M+Na]^+$ 446.1727, found 446.1730.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[(3*Z*)-4-(2-thienyl)buta-1,3-dien-2-yl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-216t



(-)-216t

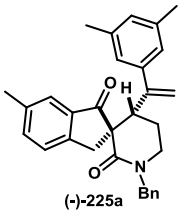
Synthesised from substrate **(±)-215a** (67.0 mg, 0.20 mmol) and (*Z*)-2-(2-iodovinyl)thiophene (71.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-216t** was obtained (single diastereoisomer, 57.0 mg, 65% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 18:1 dr.

Ee = 75% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 8.2 min, minor t_R = 11.3 min); $[\alpha]_D^{25}$ = - 14.3 (*c* 0.50, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.69 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.28-7.36 (m, 6H, 6 × Ar***H***), 7.22 (dd, 1H, *J* = 11.0 Hz, *J* = 3.8 Hz, Ar***H***), 7.16 (d, 1H, *J* = 7.6 Hz, Ar***H***), 7.01 (d, 1H, *J* = 5.1 Hz, thiophene-***H***), 6.77 (dd, 1H, *J* = 5.1 Hz, *J* = 3.6 Hz, thiophene-***H***), 6.67 (d, 1H, *J* = 3.6 Hz, thiophene-***H***), 6.15 (d, 1H, *J* = 12.2 Hz, thiophene-C***H***=CH), 5.51 (d, 1H, *J* = 12.3 Hz, thiophene-CH=C***H***), 5.48 (s, 1H, C=C***H***$_A$H$_B$), 5.23 (s, 1H, C=CH_A***H$_B$***), 4.76 (d, 1H, *J* = 14.6 Hz, C***H***$_A$H$_B$$C_6H_5$), 4.45 (d, 1H, *J* = 14.6 Hz, CH_A***H$_B$***C_6H_5), 3.37-3.48 (m, 4H, C(O)CC***H$_2$*** and CHCH_2C***H$_2$***), 3.30 (dd, 1H, *J* = 10.9 Hz, *J* = 2.3 Hz, C***H***), 2.27-2.32 (m, 1H, CHC***H***$_A$H$_B$),

1.92-2.00 (m, 1H, $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.8 (***C***=O), 170.6 (N***C***=O), 153.9 (***C***, Ar), 144.1 (***C***=CH_2), 138.6 (thiophene-***C***), 136.8 (thiophene-CH=***C*****H)**, 134.4 (***C***, Ar), 129.9 (thiophene-***C***H), 128.6 (***C***, Ar), 128.2 (2***C***H, Ar), 128.1 (2***C***H, Ar), 128.0 (thiophene-***C***H), 127.4 (thiophene-***C***H), 127.1 (***C***H, Ar), 126.3 (***C***H, Ar), 126.0 (***C***H, Ar), 125.1 (***C***H, Ar), 124.1 (***C***H, Ar), 123.9 (thiophene-***C***H=CH), 117.8 (C=***C***H_2), 60.1 (C(O)***C***CH_2), 50.5 (***C***$H_2C_6H_5$), 45.9 (N***C***H_2CH_2), 45.1 (***C***H), 36.7 (C(O)C***C***H_2), 24.5 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2924 (C-H), 1714 (C=O), 1630 (NC=O), 1590 (C=C); **MS** (ES+) m/z (rel. intensity %) 440.20 (M + H$^+$, 100); **HRMS** (ESI+) calcd. for $C_{28}H_{26}NO_2S$ $[M+H]^+$ 440.1679, found 440.1674.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[1-(3,5-dimethylphenyl)vinyl]-6-methyl-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225a



(-)-225a

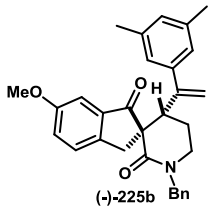
Synthesised from substrate **(±)-215c** (69.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225a** (single diastereoisomer, 75.0 mg, 84% yield) was obtained after flash column chromatography on silica gel (PE/EA = 2:1) as a colourless oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 26:1 dr.

Ee = 87% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 4.2 min, minor t_R = 6.5 min); $[\alpha]_D^{25}$ = - 23.4 (*c* 2.1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.26-7.39 (m, 7H, 7 × Ar***H***), 7.11 (s, 1H, Ar***H***), 6.75 (s, 1H, Ar***H***), 6.44 (s, 2H, 2 × Ar***H***), 5.19 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 4.99 (s, 1H, C=$CH_A\boldsymbol{H_B}$), 4.73 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.56 (d, 1H, *J* = 14.6 Hz, $CH_A\boldsymbol{H_B}C_6H_5$), 3.62 (dd, 1H, *J* = 9.9 Hz, *J* = 2.4 Hz, C***H***), 3.48-3.54 (m, 2H, C(O)CC$\boldsymbol{H_A}H_B$ and $CHCH_2C\boldsymbol{H_A}H_B$), 3.40 (td, 1H, *J* = 12.2

Hz, *J* = 5.0 Hz, $CHCH_2CH_A\boldsymbol{H_B}$), 3.29 (d, 1H, *J* = 16.8 Hz, $C(O)CCH_A\boldsymbol{H_B}$), 2.40 (ddd, 1H, *J* = 12.8 Hz, *J* = 7.7 Hz, *J* = 4.5 Hz, $CHC\boldsymbol{H_A}H_B$), 2.32 (s, 3H, $C\boldsymbol{H_3}$), 2.12 (s, 6H, 2 × $C\boldsymbol{H_3}$), 1.79-1.89 (m, 1H, $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.0 (***C***=O), 170.6 (N***C***=O), 151.5 (***C***=CH_2), 149.3 (***C***, Ar), 141.0 (***C***, Ar), 137.1 (2***C***, Ar), 136.9 (***C***, Ar), 136.7 (***C***, Ar), 136.6 (***C***, Ar), 135.8 (***C***H, Ar), 128.9 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.4 (***C***H, Ar), 125.5 (***C***H, Ar), 125.1 (2***C***H, Ar), 124.1 (***C***H, Ar), 114.9 (C=***C***H_2), 60.4 (C(O)***C***CH_2), 50.6 (***C***$H_2C_6H_5$), 45.6 (N***C***H_2CH_2), 44.5 (***C***H), 36.4 (C(O)C***C***H_2), 24.6 (CH***C***H_2), 21.1 (2C, 2 × ***C***H_3), 20.9 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2920 (C-H), 1716 (C=O), 1632 (NC=O), 1600 (C=C); **MS** (ES+) m/z (rel. intensity %) 472.24 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{31}H_{31}NNaO_2$ $[M+Na]^+$ 472.2247, found 472.2244.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[1-(3,5-dimethylphenyl)vinyl]-6-methoxy-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225b



(-)-225b

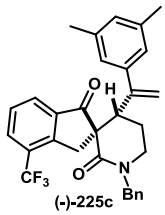
Synthesised from substrate **(±)-215d** (72.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225b** (single diastereoisomer, 76.0 mg, 82% yield) was obtained after flash column chromatography on silica gel (PE/EA = 2:1) as a white solid. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 42:1 dr.

Ee = 87% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 4.5 min, minor t_R = 6.4 min); $[\alpha]_D^{25}$ = - 31.0 (*c* 2.8, CH_2Cl_2).

Mp 54.7-57.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30-7.39 (m, 5H, 5 × Ar***H***), 7.26 (d, 1H, *J* = 8.0 Hz, Ar***H***), 7.13 (dd, 1H, *J* = 8.3 Hz, *J* = 2.5 Hz, Ar***H***), 6.73 (s, 1H, Ar***H***), 6.69 (d, 1H, *J* = 2.3 Hz, Ar***H***), 6.42 (s, 2H, 2 × Ar***H***), 5.18 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.00 (s, 1H, C=$CH_A\boldsymbol{H_B}$), 4.76

(d, 1H, *J* = 14.6 Hz, C***H*****$_A$**H$_B$C$_6$H$_5$), 4.54 (d, 1H, *J* = 14.6 Hz, CH$_A$***H*****$_B$**C$_6$H$_5$), 3.74 (s, 3H, OC***H*****$_3$**), 3.63-3.65 (m, 1H, C***H***), 3.52-3.58 (m, 1H, CH$_2$C***H*****$_A$**H$_B$N, 3.44 (d, 1H, *J* = 16.8 Hz, C(O)CC***H*****$_A$**H$_B$), 3.37-3.41 (m, 1H, CH$_2$CH$_A$***H*****$_B$**N, 3.25 (d, 1H, *J* = 16.6 Hz, C(O)CCH$_A$***H*****$_B$**), 2.32-2.36 (m, 1H, CHC***H*****$_A$**H$_B$), 2.13 (s, 6H, 2 × C***H*****$_3$**), 1.87-1.90 (m, 1H, CHCH$_A$***H*****$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 204.9 (***C***=O), 170.7 (N***C***=O), 159.0 (***C***=CH$_2$), 149.3 (***C***, Ar), 147.1 (***C***, Ar), 140.9 (***C***, Ar), 137.8 (***C***, Ar), 137.1 (2***C***, Ar), 136.9 (***C***, Ar), 129.0 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.4 (***C***H, Ar), 126.5 (***C***H, Ar), 125.1 (2***C***H, Ar), 124.1 (***C***H, Ar), 115.1 (C=***C***H$_2$), 105.2 (***C***H, Ar), 60.9 (C(O)***C***CH$_2$), 55.4 (O***C***H$_3$), 50.6 (***C***H$_2$C$_6$H$_5$), 45.8 (N***C***H$_2$CH$_2$), 44.5 (***C***H), 36.0 (C(O)C***C***H$_2$), 24.9 (CH***C***H$_2$), 21.1 (2C, 2 × ***C***H$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2929 (C-H), 1715 (C=O), 1632 (NC=O), 1600 (C=C); **MS** (ES+) m/z (rel. intensity %) 488.24 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{31}H_{31}NNaO_3$ $[M+Na]^+$ 488.2196, found 488.2198.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[1-(3,5-dimethylphenyl)vinyl]-4-(trifluoromethyl)-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225c



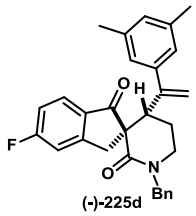
(-)-225c

Synthesised from substrate **(±)-215e** (79.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225c** (single diastereoisomer, 80.0 mg, 80% yield) was obtained after flash column chromatography on silica gel (PE/EA = 1:2) as a colourless oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 28:1 dr.

Ee = 83% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 4.1 min, minor t_R = 10.7 min); $[\alpha]_D^{25}$ = - 2.7 (*c* 2.88, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (d, 1H, *J* = 7.5 Hz, Ar***H***), 7.30-7.40 (m, 6H, 6 × Ar***H***), 7.23-7.27 (m, 1H, Ar***H***), 6.64 (s, 1H, Ar***H***), 6.37 (s, 2H, 2 × Ar***H***), 5.21 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.07 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.70 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.60 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.75 (d, 1H, *J* = 11.1 Hz, C***H***), 3.58-3.62 (m, 1H, CHCH_2C$\boldsymbol{H_A}H_B$), 3.55 (d, 2H, *J* = 4.0 Hz, C(O)CC$\boldsymbol{H_2}$), 3.39-3.44 (m, 1H, CHCH_2C$H_A\boldsymbol{H_B}$), 2.29 (dd, 1H, *J* = 13.4 Hz, *J* = 2.9 Hz, CHC$\boldsymbol{H_A}H_B$), 2.06 (s, 6H, 2 × C$\boldsymbol{H_3}$), 1.89-2.01 (m, 1H, CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 204.4 (***C***=O), 170.4 (N***C***=O), 151.7 (q, $^3J_{C,F}$ = 4.6 Hz, ***C***, Ar), 149.1 (***C***=CH_2), 140.2 (***C***, Ar), 137.9 (***C***, Ar), 137.0 (2***C***, Ar), 136.6 (***C***, Ar), 130.6 (q, $^3J_{C,F}$ = 4.8 Hz, ***C***H, Ar), 129.2 (***C***H, Ar), 128.8 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.6 (***C***H, Ar), 127.3 (***C***H, Ar), 127.2 (***C***, Ar), 125.4 (2***C***H, Ar), 123.8 (q, $^1J_{C,F}$ = 271.8 Hz, ***C***F_3), 115.5 (C=***C***H_2), 59.9 (C(O)***C***CH_2), 50.7 (***C***$H_2C_6H_5$), 46.0 (N***C***H_2CH_2), 44.6 (***C***H), 35.4 (C(O)C***C***H_2), 25.2 (CH***C***H_2), 21.0 (2C, 2 × ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2920 (C-H), 1726 (C=O), 1633 (NC=O), 1596 (C=C); **MS** (ES+) m/z (rel. intensity %) 526.21 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{31}H_{28}F_3NNaO_2$ $[M+Na]^+$ 526.1964, found 526.1968.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-4'-[1-(3,5-dimethylphenyl)vinyl]-5-fluoro-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225d



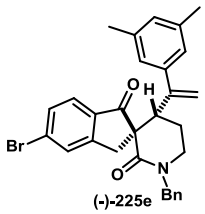
(-)-225d

Synthesised from substrate **(±)-215b** (70.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225d** (single diastereoisomer, 72.0 mg, 81% yield) was obtained after flash column chromatography (PE/EA = 2:1) on silica gel as an off-white solid. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 21:1 dr.

Ee = 86% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 4.7 min, minor t_R = 12.9 min); $[\alpha]_D^{25}$ = - 15.3 (*c* 2.8, CH_2Cl_2).

Mp 122.1-125.6 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.33 (m, 6H, 6 × Ar***H***), 7.04 (dd, 1H, *J* = 8.4 Hz, *J* = 0.9 Hz, Ar***H***), 6.88 (dt, 1H, *J* = 8.7 Hz, *J* = 2.0 Hz, Ar***H***), 6.73 (s, 1H, Ar***H***), 6.47 (s, 2H, 2 × Ar***H***), 5.22 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.01 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.70 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.58 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.66 (dd, 1H, *J* = 10.1 Hz, *J* = 2.0 Hz, C***H***), 3.49-3.56 (m, 2H, C(O)CC$\boldsymbol{H_A}H_B$ and $CH_2C\boldsymbol{H_A}H_BN$), 3.38-3.43 (m, 1H, $CH_2CH_A\boldsymbol{H_B}N$), 3.31 (d, 1H, *J* = 17.2 Hz, C(O)CC$H_A\boldsymbol{H_B}$), 2.35-2.41 (ddd, 1H, *J* = 12.8 Hz, *J* = 7.2 Hz, *J* = 4.2 Hz, CHC$\boldsymbol{H_A}H_B$), 2.13 (s, 6H, 2 × C$\boldsymbol{H_3}$), 1.85 (dtd, 1H, *J* = 15.1 Hz, *J* = 10.1 Hz, *J* = 5.1 Hz, CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 203.1 (***C***=O), 170.4 (N***C***=O), 167.1 (***C***, $^1J_{C,F}$ = 255.0 Hz, Ar***C***-F), 157.1 (d, $^3J_{C,F}$ = 10.0 Hz, ***C***, Ar), 149.2 (***C***=CH_2), 140.6 (2***C***, Ar***C***-CH_3), 137.2 (2***C***, Ar), 136.8 (***C***, Ar), 132.9 (***C***, Ar), 129.2 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.5 (***C***H, Ar), 126.4 (d, ***C***H, $^3J_{C,F}$ = 10.5 Hz, Ar), 125.1 (2***C***H, Ar), 115.2 (d, $^2J_{C,F}$ = 23.6 Hz, ***C***H, Ar), 115.1 (C=***C***H_2), 112.4 (d, $^2J_{C,F}$ = 22.3 Hz, ***C***H, Ar), 60.4 (C(O)***C***CH_2), 50.7 (***C***$H_2C_6H_5$), 45.7 (N***C***H_2CH_2), 44.4 (***C***H), 36.5 (C(O)C***C***H_2), 24.7 (CH***C***H_2), 19.4 (2C, 2 × ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2921 (C-H), 1719 (C=O), 1632 (NC=O), 1594 (C=C); **MS** (ES+) m/z (rel. intensity %) 476.21 (M + Na^+, 85); **HRMS** (ESI+) calcd. for $C_{30}H_{28}FNNaO_2$ $[M+Na]^+$ 476.1996, found 476.2000.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-5-bromo-4'-[1-(3,5-dimethylphenyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225e



(-)-225e

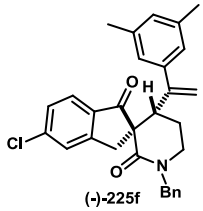
Synthesised from substrate **(±)-215f** (81.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225e** (single

diastereoisomer, 60.0 mg, 58% yield) was obtained after flash column chromatography on silica gel (PE/EA = 2:1) as a white solid. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 32:1 dr.

Ee = 79% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 5.2 min, minor t_R = 14.0 min); $[\alpha]_D^{25}$ = - 37.7 (*c* 0.98, CH_2Cl_2).

Mp 131.2-135.0 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.55 (s, 1H, Ar***H***), 7.35-7.39 (m, 2H, 2 × Ar***H***), 7.27-7.32 (m, 4H, 4 × Ar***H***), 7.10 (d, 1H, *J* = 8.1 Hz, Ar***H***), 6.71 (s, 1H, Ar***H***), 6.43 (s, 2H, 2 × Ar***H***), 5.21 (s, 1H, C=C***H$_A$***H$_B$), 5.01 (s, 1H, C=CH$_A$***H$_B$***), 4.70 (d, 1H, *J* = 14.6 Hz, C***H$_A$***H$_B$C$_6$H$_5$), 4.57 (d, 1H, *J* = 14.6 Hz, CH$_A$***H$_B$***C$_6$H$_5$), 3.66 (dd, 1H, *J* = 10.5 Hz, *J* = 1.5 Hz, C***H***), 3.52-3.57 (m, 1H, CH$_2$C***H$_A$***H$_B$N, 3.48 (d, 1H, *J* = 17.3 Hz, C(O)CC***H$_A$***H$_B$), 3.40 (td, 1H, *J* = 12.2 Hz, *J* = 4.6 Hz, CH$_2$CH$_A$***H$_B$***N), 3.30 (d, 1H, *J* = 17.2 Hz, C(O)CCH$_A$***H$_B$***), 2.31-2.37 (m, 1H, CHC***H$_A$***H$_B$) 2.12 (s, 6H, 2 × C***H$_3$***), 1.86 (ddt, 1H, *J* = 15.6 Hz, *J* = 10.5 Hz, *J* = 5.1 Hz, CHCH$_A$***H$_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 204.0 (***C***=O), 170.4 (N***C***=O), 155.8 (***C***=CH$_2$), 149.2 (***C***, Ar), 140.4 (***C***, Ar), 137.2 (2***C***, Ar), 136.7 (***C***, Ar), 135.4 (***C***, Ar), 130.5 (***C***H, Ar), 129.7 (***C***H, Ar), 129.1 (***C***H, Ar), 128.9 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.5 (***C***, Ar), 125.3 (2***C***H, Ar), 125.1 (***C***H, Ar), 115.2 (C=***C***H$_2$), 60.2 (C(O)***C***CH$_2$), 50.7 (***C***H$_2$C$_6$H$_5$), 45.8 (N***C***H$_2$CH$_2$), 44.5 (***C***H), 36.3 (C(O)C***C***H$_2$), 24.9 (CH***C***H$_2$), 21.1 (2C, 2 × ***C***H$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2921 (C-H), 1720 (C=O), 1633 (NC=O), 1597 (C=C); **MS** (ES+) m/z (rel. intensity %) 536.14, 538.13 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{30}H_{28}BrNNaO_2$ [M+Na]$^+$ 536.1196, 538.1177, found 536.1201, 538.1175.

Preparation and characterisation of (2*R*,4'*S*)-1'-benzyl-5-chloro-4'-[1-(3,5-dimethylphenyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225f



(-)-225f

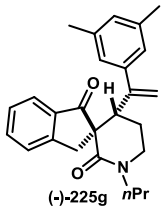
Synthesised from substrate **(±)-215g** (73.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225f** (single diastereoisomer, 75.0 mg, 80% yield) was obtained after flash column chromatography on silica gel (PE/EA = 2:1) as a white solid. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 53:1 dr.

Ee = 82% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 5.0 min, minor t_R = 13.5 min); $[\alpha]_D^{25}$ = - 32.0 (*c* 3.35, CH_2Cl_2).

Mp 170.4-173.9 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36-7.39 (m, 3H, 3 × Ar***H***), 7.29-7.33 (m, 3H, 3 × Ar***H***), 7.13-7.19 (m, 2H, 2 × Ar***H***), 6.72 (s, 1H, Ar***H***), 6.44 (s, 2H, 2 × Ar***H***), 5.22 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.02 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.70 (d, 1H, *J* = 14.6 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.58 (d, 1H, *J* = 14.6 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.67 (dd, 1H, *J* = 10.6 Hz, *J* = 1.8 Hz, C***H***), 3.52-3.57 (m, 1H, CHCH_2C$\boldsymbol{H_A}H_B$), 3.48 (d, 1H, *J* = 17.2 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 3.36-3.43 (m, 1H, CHCH_2C$H_A\boldsymbol{H_B}$), 3.31 (d, 1H, *J* = 17.2 Hz, C(O)CC$H_A\boldsymbol{H_B}$), 2.32-2.38 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 2.13 (s, 6H, 2 × C$\boldsymbol{H_3}$), 1.82-1.91 (m, 1H, CHC$H_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 203.7 (***C***=O), 170.4 (N***C***=O), 155.7 (***C***=CH_2), 149.2 (***C***, Ar), 140.9 (***C***, Ar), 140.5 (***C***, Ar), 137.2 (2***C***,, Ar), 136.7 (***C***, Ar), 135.0 (***C***, Ar), 129.2 (***C***H, Ar), 128.7 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.7 (***C***H, Ar), 127.5 (***C***H, Ar), 125.9 (***C***H, Ar), 125.3 (2***C***H,, Ar), 125.1 (***C***H, Ar), 115.2 (C=***C***H_2), 60.3 (C(O)***C***CH_2), 50.7 (***C***$H_2C_6H_5$), 45.8 (N***C***H_2CH_2), 44.5 (***C***H), 36.4 (C(O)C***C***H_2), 24.8 (CH***C***H_2), 21.1 (2C, 2 × ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2920 (C-H), 1719 (C=O), 1632 (NC=O), 1600

(C=C); **MS** (ES+) m/z (rel. intensity %) 492.19 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{30}H_{28}ClNNaO_2$ $[M+Na]^+$ 492.1701, found 492.1700.

Preparation and characterisation of (2*R*,4'*S*)-4'-[1-(3,5-dimethylphenyl)vinyl]-1'-propyl-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225g



(-)-225g

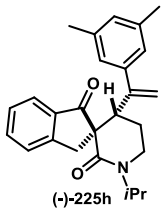
Synthesised from substrate **(±)-215h** (57.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225g** (single diastereoisomer, 56.0 mg, 72% yield) was obtained after flash column chromatography (PE/EA = 2:1) on silica gel as a white solid. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 40:1 dr.

Ee = 89% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 3.8 min, minor t_R = 11.8 min); $[\alpha]_D^{25}$ = - 3.2 (*c* 2.4, CH_2Cl_2).

Mp 105.6-108.7 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.47-7.51 (m, 1H, Ar***H***), 7.36 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.29 (t, 1H, *J* = 8.3 Hz, Ar***H***), 7.17 (t, 1H, *J* = 7.4 Hz, Ar***H***), 6.72 (s, 1H, Ar***H***), 6.46 (s, 2H, 2 × Ar***H***), 5.22 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.02 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 3.57-3.63 (m, 2H, C***H*** and $CHCH_2C\boldsymbol{H_A}H_B$), 3.43-3.52 (m, 2H, C(O)C$\boldsymbol{H_A}H_B$ and $CHCH_2CH_A\boldsymbol{H_B}$), 3.33-3.39 (m, 2H, N$\boldsymbol{H_2}$), 3.29 (d, 1H, *J* = 17.0 Hz, C(O)C$H_A\boldsymbol{H_B}$), 2.43-2.49 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 2.11 (s, 6H, 2 × ArC$\boldsymbol{H_3}$), 1.83-1.93 (m, 1H, C$HCH_A\boldsymbol{H_B}$), 1.63 (qt, 2H, *J* = 14.2 Hz, *J* = 7.0 Hz, C$\boldsymbol{H_2}CH_3$), 0.93 (t, 3H, *J* = 7.4 Hz, $CH_2C\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.1 (***C***=O), 170.0 (N***C***=O), 154.3 (***C***=CH_2), 149.4 (***C***, Ar), 140.9 (***C***, Ar), 137.1 (2***C***, Ar), 136.3 (***C***, Ar), 134.3 (***C***H, Ar), 129.1 (***C***H, Ar), 126.8 (***C***H, Ar), 125.7 (***C***H, Ar), 125.1 (2***C***H, Ar), 124.1 (***C***H, Ar), 114.8 (C=***C***H_2), 59.9 (C(O)***C***CH_2), 49.4 (N***C***$H_2CH_2CH_3$), 46.3 ($CHCH_2$***C***H_2), 44.5 (***C***H), 36.7 (C(O)C***C***H_2), 24.6 (CH***C***H_2), 21.1(2C, Ar(***C***$H_3)_2$), 20.2 (***C***H_2CH_3), 11.3 (CH_2***C***H_3); **FT-**

IR ν_{max}(NaCl)/cm^{-1} 2929 (C-H), 1718 (C=O), 1632 (NC=O), 1588 (C=C); **MS** (ES+) m/z (rel. intensity %) 410.23 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{26}H_{29}NNaO_2$ [M+Na]$^+$ 410.2091, found 410.2088.

Preparation and characterisation of (2*R*,4'*S*)-4'-[1-(3,5-dimethylphenyl)vinyl]-1'-isopropyl-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225h



(-)-225h

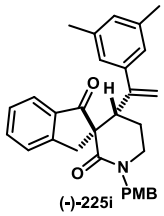
Synthesised from substrate **(±)-215i** (57.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225h** (single diastereoisomer, 65.0 mg, 84% yield) was obtained after flash column chromatography on silica gel (PE/EA = 2:1) as a colourless oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 29:1 dr.

Ee = 86% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 3.7 min, minor t_R = 5.5 min); $[\alpha]_D^{25}$ = - 0.4 (*c* 3.9, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46-7.50 (m, 1H, Ar***H***), 7.35 (d, 1H, *J* = 7.7 Hz, Ar***H***), 7.28 (d, 1H, *J* = 7.8 Hz, Ar***H***), 7.15 (t, 1H, *J* = 7.4 Hz, Ar***H***), 6.71 (s, 1H, Ar***H***), 6.45 (s, 2H, 2 × Ar***H***), 5.21 (s, 1H, C=C***H$_A$***H$_B$), 5.02 (s, 1H, C=CH$_A$***H$_B$***), 4.83 (sept., 1H, *J* = 6.8 Hz, C***H***(CH$_3$)$_2$), 3.58 (dd, 1H, *J* = 10.1 Hz, *J* = 2.0 Hz, C***H***), 3.41-3.49 (m, 3H, CHCH$_2$C***H$_2$*** and C(O)CC***H$_A$***H$_B$), 3.28 (d, 1H, *J* = 17.0 Hz, C(O)CCH$_A$***H$_B$***), 2.42-2.49 (m, 1H, CHC***H$_A$***H$_B$), 2.10 (s, 6H, 2 × C***H$_3$***), 1.78-1.88 (m, 1H, CHCH$_A$***H$_B$***) 1.21 (d, 3H, *J* = 6.9 Hz, CH(C***H$_3$***)$_A$(CH$_3$)$_B$), 1.14 (d, 3H, *J* = 6.8 Hz, CH(CH$_3$)$_A$(C***H$_3$***)$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.2 (***C***=O), 169.7 (N***C***=O), 154.3 (***C***=CH$_2$), 149.6 (***C***, Ar), 140.9 (***C***, Ar), 137.1 (2***C***, Ar), 136.4 (***C***, Ar), 134.3 (***C***H, Ar), 129.1 (***C***H, Ar), 126.8 (***C***H, Ar), 125.7 (***C***H, Ar), 125.1 (2***C***H, Ar), 124.1 (***C***H, Ar), 114.7 (C=***C***H$_2$), 60.2 (C(O)***C***CH$_2$), 44.8 (***C***HCH$_2$), 44.2 (***C***H(CH$_3$)$_2$), 39.3 (N***C***H$_2$), 36.9

(C(O)C***C***H_2), 24.8 (CH***C***H_2), 21.1 (2C, 2 × ***C***H_3), 19.3 (CH(***C***$H_3)_A(CH_3)_B$), 19.0 ($CH(CH_3)_A$(***C***$H_3)_B$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2923 (C-H), 1718 (C=O), 1624 (NC=O), 1586 (C=C); **MS** (ES+) m/z (rel. intensity %) 410.24 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{26}H_{29}NNaO_2$ $[M+Na]^+$ 410.2091, found 410.2097.

Preparation and characterisation of (2*R*,4'*S*)-1'-(4-methoxybenzyl)-4'-[1-(3,5-dimethylphenyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225i



(-)-225i

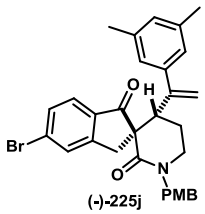
Synthesised from substrate **(±)-215j** (72.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225i** (single diastereoisomer, 69.0 mg, 75% yield) was obtained after flash column chromatography on silica gel (PE/EA = 1:1) as a white solid. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 41:1 dr.

Ee = 88% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 5.0 min, minor t_R = 16.6 min); $[\alpha]_D^{25}$ = - 13.2 (*c* 2.26, CH_2Cl_2).

Mp 135.3-138.9 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52 (t, 1H, *J* = 7.4 Hz, Ar***H***), 7.38 (d, 1H, *J* = 7.6 Hz, Ar***H***), 7.33 (d, 1H, *J* = 7.6 Hz, Ar***H***), 7.25-7.27 (m, 2H, 2 × Ar***H***), 7.19 (t, 1H, *J* = 7.4 Hz, Ar***H***), 6.90 (d, 2H, *J* = 8.5 Hz, 2 × Ar***H***), 6.73 (s, 1H, Ar***H***), 6.44 (s, 2H, 2 × Ar***H***), 5.19 (s, 1H, C=C***H$_A$***H_B), 4.99 (s, 1H, C=CH_A***H$_B$***), 4.64 (d, 1H, *J* = 14.4 Hz, C***H$_A$***$H_BC_6H_4$), 4.51 (d, 1H, *J* = 14.4 Hz, CH_A***H$_B$***C_6H_4), 3.82 (s, 3H, OC***H$_3$***), 3.62 (dd, 1H, *J* = 10.0 Hz, *J* = 2.5 Hz, C***H***), 3.55 (d, 1H, *J* = 17.0 Hz, C(O)CC***H$_A$***H_B), 3.46-3.52 (m, 1H, $CHCH_2$C***H$_A$***H_B), 3.37-3.42 (m, 1H, $CHCH_2CH_A$***H$_B$***), 3.32 (d, 1H, *J* = 17.0 Hz, C(O)CCH_A***H$_B$***), 2.37-2.43 (m, 1H, CHC***H$_A$***H_B), 2.11 (s, 6H, 2 × C***H$_3$***), 1.78-1.88 (m, 1H, $CHCH_A$***H$_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.0 (***C***=O), 170.4 (N***C***=O), 159.0 (***C***, Ar), 154.2 (***C***=CH_2), 149.3 (***C***, Ar), 140.8

(***C***, Ar), 137.1 (2***C***, Ar), 136.3 (***C***, Ar), 134.4 (***C***H, Ar), 129.5 (2***C***H, Ar), 129.1 (***C***, Ar), 129.0 (***C***H, Ar), 126.9 (***C***H, Ar), 125.8 (***C***H, Ar), 125.1 (2***C***H, Ar), 124.2 (***C***H, Ar), 114.9 (C=***C***H_2), 114.0 (2***C***H, Ar), 60.0 (C(O)***C***CH_2), 55.3 (O***C***H_3), 50.1 (***C***$H_2C_6H_4$), 45.4 (N***C***H_2CH_2), 44.4 (***C***H), 36.8 (C(O)C***C***H_2), 24.6 (CH***C***H_2), 21.1 (2C, 2 × ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2930 (C-H), 1955 (C=C=C), 1717 (C=O), 1630 (C=O); **MS** (ES+) m/z (rel. intensity %) 488.24 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{31}H_{31}NNaO_3$ $[M+Na]^+$ 488.2196, found 488.2191.

Preparation and characterisation of (2*R*,4'*S*)-1'-(4-methoxybenzyl)-5-bromo-4'-[1-(3,5-dimethylphenyl)vinyl]-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225j



(-)-225j

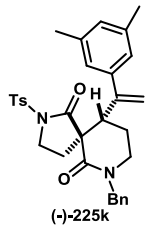
Synthesised from substrate **(±)-215k** (88.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225j** (single diastereoisomer, 78.0 mg, 72% yield) was obtained after flash column chromatography (PE/EA = 1:1) as a white solid. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 41:1 dr.

Ee = 82% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 7.1 min, minor t_R = 15.3 min); $[\alpha]_D^{25}$ = - 33.5 (*c* 1.68, CH_2Cl_2).

Mp 123.8-126.5 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.54 (s, 1H, Ar***H***), 7.24-7.31 (m, 3H, 3 × Ar***H***), 7.10 (d, 1H, *J* = 8.1 Hz, Ar***H***), 6.90 (d, 2H, *J* = 8.6 Hz, 2 × Ar***H***), 6.71 (s, 1H, Ar***H***), 6.43 (s, 2H, 2 × Ar***H***), 5.20 (s, 1H, C=C***H$_A$***H_B), 5.00 (s, 1H, C=CH_A***H$_B$***), 4.63 (d, 1H, *J* = 14.4 Hz, C***H$_A$***$H_BC_6H_4$), 4.49 (d, 1H, *J* = 14.4 Hz, CH_A***H$_B$***C_6H_4), 3.82 (s, 3H, OC***H$_3$***), 3.63-3.65 (m, 1H, C***H***), 3.50-3.55 (m, 1H, $CHCH_2$C***H$_A$***H_B), 3.46 (d, 1H, *J* = 16.4 Hz, C(O)CC***H$_A$***H_B), 3.36-3.45 (m, 1H, $CHCH_2CH_A$***H$_B$***), 3.28 (d, 1H, *J* = 17.2 Hz, C(O)CCH_A***H$_B$***), 2.30-2.35 (m, 1H, CHC***H$_A$***H_B), 2.12 (s, 6H, 2 × C***H$_3$***), 1.79-1.89 (m, 1H, $CHCH_A$***H$_B$***); **^{13}C NMR** (100 MHz,

$CDCl_3$) δ_C 204.0 (***C***=O), 170.2 (***C***=ON), 159.1 (***C***, Ar), 155.9 (***C***=CH_2), 149.3 (***C***, Ar), 144.4 (***C***, Ar), 137.2 (2***C***, Ar), 135.4 (***C***, Ar), 130.5 (2***C***H, Ar), 129.7 (***C***, Ar), 129.5 (***C***H, Ar), 129.1 (***C***, Ar), 128.9 (***C***H, Ar), 128.8 (***C***H, Ar), 125.3 (2***C***H, Ar), 125.1 (***C***H, Ar), 115.1 (C=***C***H_2), 114.1 (2***C***H, Ar), 60.2 (C(O)***C***CH_2), 55.3 (O***C***H_3), 50.1 (***C***$H_2C_6H_4$), 45.6 (N***C***H_2CH_2), 44.5 (***C***H), 36.3 (C(O)C***C***H_2), 24.9 (CH***C***H_2), 21.1 (2C, 2 × ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2920 (C-H), 1719 (C=O), 1631 (NC=O), 1597 (C=C); **MS** (ES+) m/z (rel. intensity %) 566.15, 568.15 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{31}H_{30}BrNNaO_3$ $[M+Na]^+$ 566.1301, 568.1283, found 566.1297, 568.1284.

Preparation and characterisation of (5*S*,10*S*)-7-benzyl-10-[1-(3,5-dimethylphenyl)vinyl]-2-[(4-methylphenyl)sulfonyl]-2,7-diazaspiro[4.5]decane-1,6-dione (-)-225k



(-)-225k

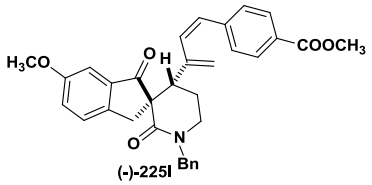
Synthesised from substrate **(±)-165n** (88.0 mg, 0.20 mmol) and 1-iodo-3,5-dimethylbenzene (70.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225k** (single diastereoisomer, 65.0 mg, 60% yield) was obtained after flash column chromatography (PE/EA = 1:2) as a colourless oil. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 33:1 dr.

Ee = 81% (Chiralcel AD, 60:40 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 5.7 min, minor t_R = 8.1 min); $[\alpha]_D^{25}$ = - 23.4 (*c* 1.80, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.89 (d, 2H, *J* = 8.3 Hz, 2 × Ar***H***), 7.26-7.31 (m, 5H, 5 × Ar***H***), 7.07-7.09 (m, 2H, 2 × Ar***H***), 6.94 (s, 1H, Ar***H***), 6.87 (s, 2H, 2 × Ar***H***), 5.36 (s, 1H, C=C***H*****$_A$**H_B), 4.80 (s, 1H, C=CH_A***H*****$_B$**), 4.68 (d, 1H, *J* = 14.7 Hz, C***H*****$_A$**$H_BC_6H_5$), 4.31 (d, 1H, *J* = 14.8 Hz, CH_A***H*****$_B$**C_6H_5), 4.05 (q, 1H, *J* = 8.3 Hz, TsNC***H*****$_A$**H_B), 3.91 (dt, 1H, *J* = 8.9 Hz, *J* = 2.6 Hz, TsNCH_A***H*****$_B$**), 3.43 (t, 1H, *J* = 4.8 Hz, C***H***), 3.27-3.34 (m, 1H, CHCH_2C***H*****$_A$**H_B), 3.17-3.23

(m, 1H, $CHCH_2CH_A\boldsymbol{H_B}$), 2.64-2.72 (m, 2H, $CHC\boldsymbol{H_A}H_B$ and $TsNCH_2C\boldsymbol{H_A}H_B$), 2.40 (s, 3H, $C\boldsymbol{H_3}$ of Ts), 2.32 (s, 6H, 2 × $ArC\boldsymbol{H_3}$), 2.18 (td, 1H, *J* = 13.3 Hz, *J* = 8.6 Hz, $TsNCH_2CH_A\boldsymbol{H_B}$), 1.48-1.56 (m, 1H, $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.9 (TsN***C***=O), 168.5 (N***C***=O), 147.3 (***C***=CH_2), 144.9 (***C***, Ar), 141.0 (***C***, Ar), 138.1 (2***C***, Ar), 136.4 (***C***, Ar), 134.6 (***C***, Ar), 129.8 (***C***H, Ar), 129.5 (2***C***H, Ar), 128.6 (2***C***H, Ar), 128.1 (2***C***H, Ar), 127.7 (2***C***H, Ar), 127.4 (***C***H, Ar), 124.5 (2***C***H, Ar), 114.6 (C=***C***H_2), 55.8 (C(O)***C***C(O)), 50.5 (***C***$H_2C_6H_5$), 45.8 (TsN***C***H_2), 44.2 ($CHCH_2\boldsymbol{C}H_2$), 44.1 (***C***H), 28.5 (N(Ts)$CH_2\boldsymbol{C}H_2$), 22.6 (CH***C***H_2), 21.7 (***C***H_3 of Ts), 21.3 (2C, 2 × ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2950 (C-H), 1720 (NC=O), 1638 (NC=O), 1359 (SO_2), 1112 (SO_2); **MS** (ES+) m/z (rel. intensity %) 565.24 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{32}H_{34}N_2NaO_4S$ $[M+Na]^+$ 565.2137, found 565.2138.

Preparation and characterisation of methyl 4-{(1*Z*)-3-[(2*R*,4'*S*)-1'-benzyl-6-methoxy-1,2'-dioxo-1,3-dihydrospiro[indene-2,3'-piperidin]-4'-yl]buta-1,3-dien-1-yl}benzoate (-)-225l



(-)-225l

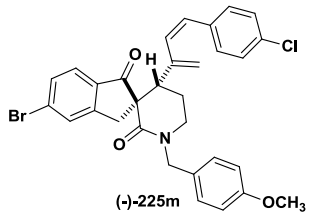
Synthesised from substrate **(±)-215d** (73.0 mg, 0.20 mmol) and (*Z*)-methyl 4-(2-iodovinyl)benzoate (86.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225l** was obtained (single diastereoisomer, 59.0 mg, 81% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 18:1 dr.

Ee = 76% (Chiralcel AD, 70:30 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 11.8 min, minor t_R = 20.8 min); $[\alpha]_D^{25}$ = - 13.9 (*c* 0.54, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.72-7.74 (m, 2H, 2 × Ar***H***), 7.25-7.36 (m, 6H, 6 × Ar***H***), 7.18 (d, 1H, *J* = 2.5 Hz, Ar***H***), 7.10-7.13 (m, 1H, Ar***H***), 6.99-7.01 (m, 2H, 2 × Ar***H***), 6.19 (d, 1H, *J* = 12.5 Hz, ArC***H***=CH), 5.79 (d, 1H, *J* = 12.5 Hz, ArCH=C***H***), 5.12 (s, 1H, C=C$\boldsymbol{H_A}H_B$),

5.00 (s, 1H, C=CH_A***H_B***), 4.77 (d, 1H, *J* = 14.6 Hz, C***H_A***$H_B$$C_6H_5$), 4.40 (d, 1H, *J* = 14.6 Hz, CH_A***H_B***C_6H_5), 3.90 (s, 3H, OC***H_3***), 3.80 (s, 3H, C***H_3***O), 3.28-3.39 (m, 4H, C(O)CC***H_2*** and $CHCH_2C$***H_2***), 3.25 (dd, 1H, *J* = 11.6 Hz, *J* = 2.1 Hz, C***H***), 2.06-2.11 (m, 1H, CHC***H_A***H_B), 1.88-1.96 (m, 1H, $CHCH_A$***H_B***); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 205.1 (***C***=O), 170.6 (N***C***=O), 166.7 (***C***$OOCH_3$), 159.6 (***C***, Ar), 146.8 (***C***, Ar), 143.2 (***C***=CH_2), 141.6 (***C***, Ar), 138.0 (***C***, Ar), 136.7 (***C***, Ar), 132.3 (ArCH=***C***H), 129.8 (Ar***C***H=CH), 129.7 (***C***, Ar), 129.3 (2***C***H, Ar), 128.7 (2***C***H, Ar), 128.4 (***C***H, Ar), 128.2 (***C***H, Ar), 128.1 (2***C***H, Ar), 127.4 (***C***H, Ar), 127.0 (***C***H, Ar), 124.5 (***C***H, Ar), 117.9 (C=***C***H_2), 105.5 (***C***H, Ar), 60.8 (C(O)***C***CH_2), 55.6 (***C***H_3O), 52.0 (***C***$H_3OC(O)$), 50.4 (***C***$H_2C_6H_5$), 45.9 (N***C***H_2CH_2), 44.7 (***C***H), 35.7 (C(O)C***C***H_2), 29.7 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2924 (C-H), 1715 (C=O), 1632 (NC=O), 1590 (C=C); **MS** (ES+) m/z (rel. intensity %) 544.23 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{33}H_{31}NNaO_5$ $[M+Na]^+$ 544.2094, found 544.2094.

Preparation and characterisation of (2*R*,4'*S*)-5-bromo-4'-[(3*Z*)-4-(4-chlorophenyl)buta-1,3-dien-2-yl]-1'-(4-methoxybenzyl)-2'*H*-spiro[indene-2,3'-piperidine]-1,2'(3*H*)-dione (-)-225m



(-)-225m

Synthesised from substrate **(±)-215k** (88.0 mg, 0.20 mmol) and (*Z*)-1-chloro-4-(2-iodovinyl)benzene (79.0 mg, 0.30 mmol) according to general procedure J. Compound **(-)-225m** was obtained (single diastereoisomer, 91.0 mg, 79% yield) as a colourless oil after flash column chromatography (PE/EA = 1:1). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 16:1 dr.

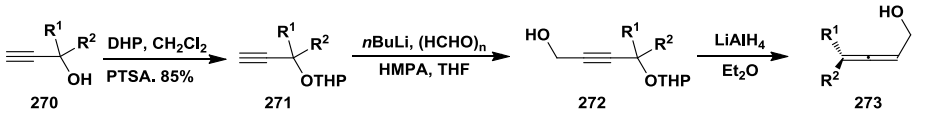
Ee = 71% (Chiralcel AD, 70:30 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 11.4 min, minor t_R = 16.7 min); $[\alpha]_D^{25}$ = - 18.8 (*c* 0.90, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.58 (d, 1H, *J* = 8.2 Hz, Ar***H***), 7.50 (d, 1H, *J* = 0.8 Hz, Ar***H***), 7.43-7.45 (m, 1H, Ar***H***), 7.20 (d, 2H, *J* = 8.6 Hz, 2 × Ar***H***), 7.05-7.08 (m, 2H, 2 × Ar***H***), 6.86-6.92 (m, 4H, 4 × Ar***H***), 6.06 (d, 1H, *J* = 12.5 Hz, ArC***H***=CH), 5.67 (d, 1H, *J* = 12.5 Hz, ArCH=C***H***), 5.19 (s, 1H, C=C$\boldsymbol{H_A}H_B$), 5.03 (s, 1H, C=C$H_A\boldsymbol{H_B}$), 4.67 (d, 1H, *J* = 14.4 Hz, C$\boldsymbol{H_A}H_BC_6H_5$), 4.33 (d, 1H, *J* = 14.4 Hz, C$H_A\boldsymbol{H_B}C_6H_5$), 3.81 (s, 3H, OC$\boldsymbol{H_3}$), 3.20-3.42 (m, 5H, C(O)CC$\boldsymbol{H_2}$ and $CHCH_2C\boldsymbol{H_2}$ and C***H***), 2.08-2.13 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.83-1.92 (m, 1H, $CHCH_A\boldsymbol{H_B}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 204.1 (***C***=O), 170.1 (N***C***=O), 159.1 (***C***, Ar), 155.4 (***C***, Ar), 143.4 (***C***=CH_2), 135.7 (***C***, Ar), 134.9 (***C***, Ar), 132.9 (***C***, Ar), 131.2 (ArCH=***C***H), 130.9 (***C***, Ar), 130.4 (***C***, Ar), 129.8 (Ar***C***H=CH), 129.6 (3***C***H, Ar), 129.5 (2***C***H, Ar), 128.7 (***C***H, Ar), 128.2 (2***C***H, Ar), 125.5 (***C***H, Ar), 117.7 (C=***C***H_2), 114.0 (2***C***H, Ar), 60.2 (C(O)***C***CH_2), 55.3 (***C***H_3O), 49.8 (***C***$H_2C_6H_5$), 45.6 (N***C***H_2CH_2), 44.7 (***C***H), 36.0 (C(O)C***C***H_2), 24.6 (CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2931 (C-H), 1717 (C=O), 1631 (C=O), 1596 (C=C); **MS** (ES+) m/z (rel. intensity %) 598.10, 600.11 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{31}H_{27}BrClNNaO_3$ $[M+Na]^+$ 598.0755, 600.0735 found 598.0745, 600.0718.

6.2.3 Experimental for Chapter Four

6.2.3.1 Synthesis and characterisation of allene alcohols 273a-273c

General procedure K for the synthesis of allenealcohols 273a-273c[150]



273a, $R^1 = R^2 = H$; 273b, $R^1 = CH_3$, $R^2 = H$; 273c, $R^1 = R^2 = CH_3$

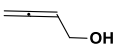
Into a mixture of propargyl alcohol **270** (1.0 equiv.) and a catalytic amount of *p*-toluenesulphonic acid (5 mol%) in anhydrous dichloromethane (2.0 mmol per mL of **270**) was added 3,4-dihydro-2H-pyran (1.0 equiv.) in one portion at 0 °C. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 12 h. After neutralization with sat. aq. $NaHCO_3$, the mixture was extracted three times with diethyl ether. The combined organic

extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 10:1) to afford product **271**.

Into a solution of **271** (1.0 equiv.) in anhydrous THF (1.0 mmol per mL of of **271**) was added dropwise *n*BuLi (2.5 M in hexane, 1.1 equiv.) at - 78 °C under nitrogen atmosphere. The reaction mixture was stirred for 3 h at the same temperature. Paraformaldehyde (1.2 equiv.) was added in small portions at - 78 °C, and the mixture was stirred for 2 h. After allowing to warm up to room temperature, sat. aq. NH_4Cl was added. The resulting mixture was extracted three times with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 4:1) to provide product **272**.

Into a suspension of $LiAlH_4$ (2 equiv.) in anhydrous diethyl ether was added dropwise compounds **272** (1 equiv.) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 4 h at 0 °C. On completion, the reaction mixture was quenched with water (1.0 equiv. of weight of $LiAlH_4$), 15% NaOH (1.0 equiv. of weight of $LiAlH_4$) and then water (3.0 equiv. of weight of $LiAlH_4$) at 0 °C. Anhydrous Na_2SO_4 was added to remove excess water. The resulting mixture was filtered and concentrated. The residue was purified by flash column chromatography on silica gel to give product **273**.

Synthesis and characterisation of buta-2,3-dien-1-ol 273a

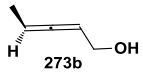


273a

Synthesised from propargyl alcohol **270a** (5.6 g, 0.1 mol) according to general procedure K. Compound **273a** was obtained after flash column chromatography on silica gel (PE/Et_2O = 6:1) as a colourless oil (4.2 g, 60 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.33-5.39 (m, 1H, C***H***=C=CH_2), 4.86-4.89 (m, 2H, CH=C=C***H$_2$***), 4.14-4.18 (m, 2H, C***H$_2$***OH). Analytical data in agreement with the previous report.[150]

Synthesis and characterisation of penta-2,3-dien-1-ol 273b

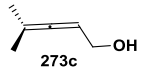


273b

Synthesised from but-3-yn-2-ol **270b** (5.60 g, 0.08 mol) according to general procedure K. Compound **273b** was obtained after flash column chromatography on silica gel (PE/Et_2O = 6:1) as a colourless oil (3.00 g, 45 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.25-5.32 (m, 2H, C***H***=C=C***H***CH_3), 4.12 (dd, 2H, *J* = 8.5 Hz, *J* = 5.3 Hz, C***H*****$_2$**OH), 1.70 (dd, 3H, *J* = 6.7 Hz, *J* = 3.5 Hz, C***H*****$_3$**). Analytical data in agreement with the previous report.[150]

Synthesis and characterisation of 4-methylpenta-2,3-dien-1-ol 273c



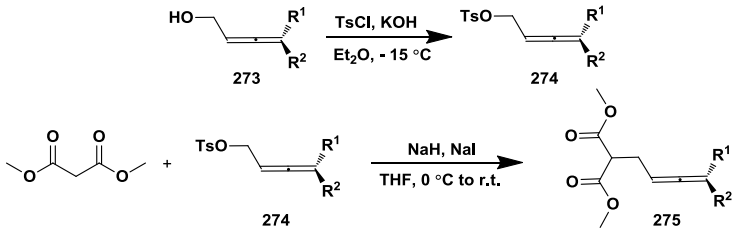
273c

Synthesised from 2-methylbut-3-yn-2-ol **270c** (4.20 g, 0.05 mol) according to general procedure K. Compound **273c** was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:1) as a colourless oil (2.80 g, 57 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.17-5.23 (m, 1H, C***H***=C=C$(CH_3)_2$), 4.08 (t, 2H, *J* = 5.2 Hz, C***H*****$_2$**OH), 3.67 (t, 1H, *J* = 6.3 Hz, CH_2O***H***), 1.73 (s, 3H, C***H*****$_3$**), 1.72 (s, 3H, C***H*****$_3$**). Analytical data in agreement with the previous report.[150]

6.2.3.2 Synthesis and characterisation of pro-nucleophiles 275

General procedure L for synthesis of pro-nucleophiles 275 [151,152]

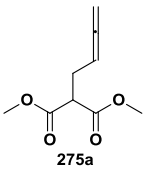


A solution of alcohol **273**a-**273c** (1.0 equiv.) and 4-methylbenzenesulphonyl chloride (1.05 equiv.) in anhydrous diethyl ether was cooled to - 15 °C. Crushed KOH powder (5.0 equiv.) was added in a small portion. The resulting mixture was stirred for 3 hours and monitored by TLC. Anhydrous Na_2SO_4 was added to remove water which was produced during the reaction.

The reaction mixture was filtered through celite. The ethereal solution was concentrated and the residue **274** was used directly in the next step.[151]

To a suspension of NaH (2.0 equiv., 60% dispersion in mineral oil) in THF at 0 °C under N_2 was added dimethyl malonate (2.0 equiv.) dropwise. The reaction mixture was warmed up to room temperature and stirred for 1 h. A solution of allene **274** (1 equiv.) was added dropwise at 0 °C and the resultant mixture was stirred at room temperature. The reaction was monitored by TLC. On completion, sat. aq. NH_4Cl was added slowly and the resulting mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (petrol/diethyl ether) to afford the following products **275a-275c**.

Synthesis and characterisation of dimethyl buta-2,3-dien-1-ylmalonate 275a

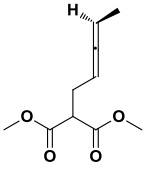


275a

Synthesised from compound **274a** (3.58 g, 16.0 mmol) according to general procedure L. Compound **275a** was obtained after flash column chromatography on silica gel (PE/Et_2O = 20:1) as a colourless oil (2.2 g, 75 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.07-5.14 (m, 1H, C***H***=C=CH_2), 4.68-4.71 (m, 2H, CH=C=C***H$_2$***), 3.72 (s, 6H, 2 × OC***H$_3$***), 3.49 (t, 1H, *J* = 7.5 Hz, C***H***), 2.54-2.59 (m, 2H, C***H$_2$***CH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.6 (CH=***C***=CH_2), 169.2 (2C, 2 × ***C***O), 86.5 (***C***H=C=CH_2), 76.2 (CH=C=***C***H_2), 52.5 (2C, 2 × O***C***H_3), 51.1 (***C***H), 27.3 (***C***H_2CH). Analytical data in agreement with the previous report.[152]

Synthesis and characterisation of dimethyl penta-2,3-dien-1-ylmalonate 275b

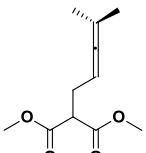


275b

Synthesised from compound **274b** (4.52 g, 19.0 mmol) according to general procedure L. Compound **275b** was obtained after flash column chromatography on silica gel (PE/Et_2O = 20:1) as a colourless oil (2.44 g, 65 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.04-5.12 (m, 2H, C***H***=C=C***H***CH_3), 3.71 (s, 6H, 2 × OC***H*****$_3$**), 3.49 (t, 1H, *J* = 7.5 Hz, C***H***), 2.52-2.57 (m, 2H, CH_2), 1.59 (q, 3H, *J* = 3.4 Hz, CH=C=CHC***H*****$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 204.8 (CH=***C***=$CHCH_3$), 169.3 (2C, 2 × ***C***O), 87.6 (***C***H=C=$CHCH_3$), 86.8 (CH=C=***C***HCH_3), 52.4 (2C, 2 × O***C***H_3), 51.1 (***C***H), 27.8 (***C***H_2CH), 14.3 (CH=C=CH***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2980 (C-H), 2850 (C-H), 1955 (C=C=C), 1738 (C=O), 1225 (C-O); **MS** (ES+) m/z (rel. intensity %) 221.10 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{10}H_{14}NaO_4$ $[M+Na]^+$ 221.0790, found 221.0792.

Synthesis and characterisation of dimethyl (4-methylpenta-2,3-dien-1-yl)malonate 275c



275c

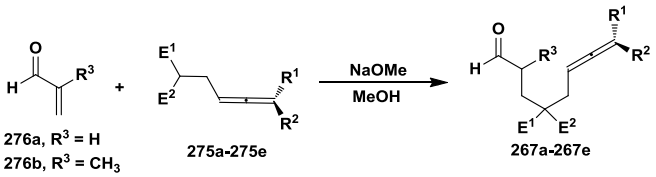
Synthesised from compound **274c** (10.5 g, 42.0 mmol) according to general procedure L. Compound **275c** was obtained after flash column chromatography on silica gel (PE/Et_2O = 20:1) as a colourless oil (2.20 g, 68 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.75 (s, 6H, 2 × OC***H*****$_3$**), 3.49 (t, 1H, *J* = 7.5 Hz, C***H***), 2.52-2.58 (m, 2H, C***H*****$_2$**), 2.13 (6H, 2 × C***H*****$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.6 (CH=***C***=CH_2), 169.5 (2C, 2 × ***C***O), 92.3 (***C***$(CH_3)_2$), 86.5 (***C***H=C=$CH(CH_3)_2$), 52.5 (2C, 2 × O***C***H_3), 51.1 (***C***H), 28.2 (***C***H_2CH), 20.5 (2C, $CH(CH_3)_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2978 (C-H), 2845 (C-H), 1956 (C=C=C), 1740 (C=O), 1226 (C-O); **MS** (ES+) m/z (rel. intensity %) 235.12 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{11}H_{16}NaO_4$ $[M+Na]^+$ 235.0946, found 235.0948.

6.2.3.3 Synthesis of Michael adducts

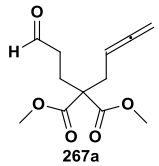
6.2.3.3.1 Synthesis of Michael adducts from α,β-unsaturated aldehydes

General procedure M for the synthesis of Michael adducts 267a-267e, 279 and 283[153]



Into a round-bottomed flask equipped with a stirring bar and containing a solution of α,β-unsaturated aldehydes **276** (1 equiv.) and Michael acceptors **275** (1.5 equiv.) in MeOH (0.33 mmol per mL of **275**) at room temperature, was added NaOMe (20 mol%) slowly. The resultant mixture was stirred for 2-4 hours. After completion of the reaction, methanol was evaporated under reduced pressure. The residue was dissolved in diethyl ether and washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (petrol/diethyl ether) to give the products **267a-267e, 279** and **283**.

Preparation and characterisation of dimethyl buta-2,3-dien-1-yl(3-oxopropyl)malonate 267a

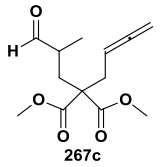


Synthesised from dimethyl buta-2,3-dien-1-ylmalonate **275a** (368 mg, 2.0 mmol) according to general procedure M. Compound **267a** (374 mg, 78%) was obtained as a colourless oil after flash column chromatography on silica gel (PE/Et_2O = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.73 (s, 1H, ***H***C=O), 4.90-4.97 (m, 1H, C***H***=C=CH_2), 4.66-4.68 (m, 2H, CH=C=C***H$_2$***), 3.72 (s, 6H, 2 × OC***H$_3$***), 2.60 (d, 2H, *J* = 8.0 Hz, C***H$_2$***CH=C=CH_2), 2.46-2.49 (m, 2H, HC(O)C***H$_2$***), 2.23 (t, 2H, *J* = 7.8 Hz, HC(O)CH_2C***H$_2$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 210.0 (CH=***C***=CH_2), 200.6 (H***C***=O), 171.0 (2C, ***C***(O)OCH_3), 83.9 (***C***H=C=CH_2), 74.9 (CH=C=***C***H_2), 56.8 (C(O)***C***C(O)), 52.6 (2C, 2 × O***C***H_3), 39.1 (HC(O)***C***H_2), 32.9 (***C***H_2CH=*C*=CH_2), 24.8 (HC(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2955 (C-H), 2842 (C-H),

1956 (C=C=C), 1732 (C=O); **MS** (ES+) m/z (rel. intensity %) 263.11 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{16}NaO_5$ $[M+Na]^+$ 263.0895, found 263.0893.

Preparation and characterisation of dimethyl buta-2,3-dien-1-yl(2-methyl-3-oxopropyl)malonate 267c

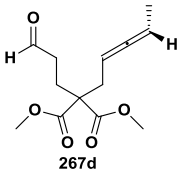


267c

Synthesised from dimethyl buta-2,3-dien-1-ylmalonate **275a** (368 mg, 2.0 mmol) according to general procedure M. Compound **267c** (304 mg, 60%) was obtained as a colourless oil after flash column chromatography on silica gel (PE/Et_2O = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.53 (d, 1H, *J* = 1.8 Hz, ***H***C=O), 4.87-5.01 (m, 1H, C***H***=C=CH_2), 4.66-4.72 (m, 2H, CH=C=C***H$_2$***), 3.72 (s, 6H, 2 × OC***H$_3$***), 2.61-2.67 (m, 2H, C***H$_2$***CH=C=CH_2), 2.47-2.59 (m, 2H, HC(O)CHC***H$_2$***), 1.80-1.92 (m, 1H, C***H***CH_3), 1.11 (d, 3H, *J* = 7.0 Hz, CHC***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 210.0 (CH=***C***=CH_2), 203.2 (H***C***=O), 171.2 (2C, ***C***(O)OCH_3), 84.0 (***C***H=C=CH_2), 74.8 (CH=C=***C***H_2), 56.9 ((O)C***C***C(O)), 52.5 (2C, O***C***H_3), 42.3 (HC(O)***C***HCH_3), 35.7 (***C***H_2CH=*C*=CH_2), 33.1 (HC(O)CH***C***H_2), 15.4 (CH***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2956 (C-H), 2844 (C-H), 1955 (C=C=C), 1735 (C=O), 1227 (C-O); **MS** (ES+) m/z (rel. intensity %) 277.12 (M + Na^+, 90); **HRMS** (ESI+) calcd. for $C_{13}H_{18}NaO_5$ $[M+Na]^+$ 277.1052, found 277.1050.

Preparation and characterisation of dimethyl (3-oxopropyl)(penta-2,3-dien-1-yl)malonate 267d

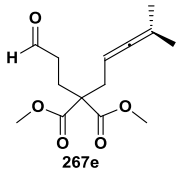


267d

Synthesised from dimethyl penta-2,3-dien-1-ylmalonate **275b** (396 mg, 2.0 mmol) according to general procedure M. Compound **267d** (381 mg, 75%) was obtained as a colourless oil after flash column chromatography on silica gel (PE/Et_2O = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.73 (t, 1H, *J* = 1.1 Hz, ***H***C=O), 5.02-5.10 (m, 1H, C***H***=C=CH), 4.82-4.90 (m, 1H, CH=C=C***H***CH_3), 3.72 (s, 6H, 2 × OC***H₃***), 2.56-2.59 (m, 2H, C***H₂***CH=C=CH), 2.45-2.49 (m, 2H, HC(O)C***H₂***), 2.23-2.27 (m, 2H, HC(O)CH_2C***H₂***), 1.61 (dd, 3H, *J* = 7.0 Hz, *J* = 3.1 Hz, CHC***H₃***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 206.6 (CH=***C***=$CHCH_3$), 200.7 (H***C***=O), 171.1 (2C, 2 × ***C***(O)OCH_3), 85.9 (***C***H=C=$CHCH_3$), 83.9 (CH=C=***C***HCH_3), 56.8 ((O)C***C***C(O)), 52.5 (2C, 2 × O***C***H_3), 39.1 (HC(O)***C***H_2), 33.4 (***C***H_2CH=*C*=CH), 24.7 (HC(O)CH_2***C***H_2), 14.2 (CH***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2958 (C-H), 2840 (C-H), 1955 (C=C=C), 1735 (C=O), 1226 (C-O); **MS** (ES+) m/z (rel. intensity %) 277.12 (M + Na^+, 70); **HRMS** (ESI+) calcd. for $C_{13}H_{18}NaO_5$ $[M+Na]^+$ 277.1052, found 277.1050.

Preparation and characterisation of dimethyl (4-methylpenta-2,3-dien-1-yl)(3-oxopropyl)malonate 267e

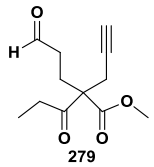


267e

Synthesised from dimethyl (4-methylpenta-2,3-dien-1-yl)malonate **275c** (424 mg, 2.0 mmol) according to general procedure M. Compound **267e** (348 mg, 65%) was obtained as a colourless oil after flash column chromatography on silica gel (PE/Et_2O = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.75 (s, 1H, ***H***C=O), 4.73-4.80 (m, 1H, C***H***=C=C$(CH_3)_2$), 3.73 (s, 6H, 2 × OC***H₃***), 2.57 (d, 2H, *J* = 7.6 Hz, C***H₂***CH=C=C), 2.45-2.49 (m, 2H, HC(O)C***H₂***), 2.27 (m, 2H, HC(O)CH_2C***H₂***), 1.65 (s, 6H, C(***C***$H_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 203.7 (CH=***C***=CH_2), 200.8 (H***C***=O), 171.2 (2C, 2 × ***C***(O)OCH_3), 95.5 (CH=C=***C***$(CH_3)_2$), 82.3 (***C***H=C=C$(CH_3)_2$), 56.7 ((O)C***C***C(O)), 52.5 (2C, 2 × O***C***H_3), 39.1 (HC(O)***C***H_2), 33.4 (***C***H_2CH=*C*=C), 24.6 (HC(O)CH_2***C***H_2), 20.4 (2C, CH=C=C(***C***$H_3)_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2959 (C-H), 2846 (C-H), 1956 (C=C=C), 1736 (C=O), 1226 (C-O); **MS** (ES+) m/z (rel. intensity %) 291.15 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{14}H_{20}NaO_5$ $[M+Na]^+$ 291.1208, found 291.1209.

Preparation and characterisation of methyl 2-(3-oxopropyl)-2-propionylpent-4-ynoate 279

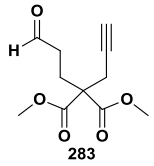


279

Synthesised from methyl 2-propionylpent-4-ynoate **278** (1.4 g, 8.3 mmol) according to general procedure M. Compound **279** (1.1 g, 61%) was obtained as a colourless oil after flash column chromatography (PE/Et_2O = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.73 (s, 1H, ***H***C=O), 3.74 (s, 3H, OC***H$_3$***), 2.76-2.82 (m, 2H, C***H$_2$***C≡CH), 2.27-2.51 (m, 6H, HC(O)C***H$_2$***C***H$_2$*** and C***H$_2$***CH_3), 2.02 (t, 1H, *J* = 2.6 Hz, C≡C***H***), 1.05 (t, 3H, *J* = 7.2 Hz, CH_2C***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.6 (***C***(O)CH_2CH_3), 200.4 (H***C***=O), 171.2 (***C***(O)OCH_3), 78.5 (***C***≡CH), 72.0 (C≡***C***H), 61.3 (C(O)***C***C(O)), 52.9 (O***C***H_3), 38.7 (HC(O)***C***H_2), 32.1 (C(O)***C***H_2CH_3), 23.9 (HC(O)CH_2***C***H_2), 22.3 (***C***H_2C≡CH), 7.9 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3308 (C≡C-H), 2970 (C-H), 2846 (C-H), 1743 (C=O), 1715 (C=O); **MS** (ES+) m/z (rel. intensity %) 247.09 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{16}NaO_4$ $[M+Na]^+$ 247.0946, found 249.0944.

Preparation and characterisation of dimethyl (3-oxopropyl)(prop-2-yn-1-yl)malonate 283



283

Synthesised from dimethyl 2-(prop-2-yn-1-yl)malonate **282** (5.1 g, 30 mmol) according to the general procedure M. Compound **283** (5.9 g, 87%) was obtained as a colourless oil after flash column chromatography (PE/Et_2O = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.76 (d, 1H, *J* = 1.1 Hz, ***H***C=O), 3.76 (s, 6H, 2 × OC***H$_3$***), 2.84 (d, 2H, *J* = 2.7 Hz, C***H$_2$***C≡CH), 2.51-2.55 (m, 2H, HC(O)C***H$_2$***), 2.39 (m, 2H, HC(O)CH_2C***H$_2$***), 2.05 (t, 1H, *J* = 2.7 Hz, C≡C***H***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.2 (H***C***=O), 171.1 (2C, 2 × ***C***$OOCH_3$), 79.2 (***C***≡CH), 71.0 (C≡***C***H), 58.3 (C(O)***C***C(O)), 52.5 (2C, 2 × O***C***H_3), 38.3

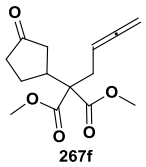
(HC(O)***C***H_2), 24.9 (HC(O)CH_2***C***H_2), 22.9 (***C***H_2C≡CH); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3309 (C≡C-H), 2967 (C-H), 1745 (C=O), 1713 (C=O); **MS** (ES+) m/z (rel. intensity %) 249.10 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{11}H_{14}NaO_5$ $[M+Na]^+$ 249.0740, found 249.0742.

6.2.3.3.2 Synthesis of Michael adducts from α,β-enones

General procedure N for the synthesis of Michael adducts 267f and **267h**[144]

To a round-bottomed flask was equipped with a stirring bar was added a solution of nucleophiles **275a** (1.2 equiv.) and α,β-enones **277a-277b** (1.0 equiv.) in CH_2Cl_2 (1.6 mL per mmol of **275a**) at room temperature. BEMP (0.1 equiv.) was added and the resulting suspension was stirred for 48 h. After completion of the reaction, concentration, the residue was purified by flash column chromatography on silica gel to afford products **267f** and **267h**.

Preparation and characterisation of dimethyl buta-2,3-dien-1-yl(3-oxocyclopentyl)malonate (±)-267f



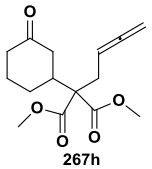
267f

Synthesised from dimethyl buta-2,3-dien-1-ylmalonate **275a** (220 mg, 1.2 mmol) and cyclopent-2-enone **277a** (84.0 µL, 1.0 mmol) according to general procedure N. Compound **(±)-267f** (246 mg, 92%) was obtained as a colourless oil after flash column chromatography on silica gel (PE/Et_2O = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.94-5.02 (m, 1H, C***H***=C=CH_2), 4.68-4.70 (m, 2H, CH=C=C***H_2***), 3.74 (s, 6H, 2 × OC***H_3***), 2.82-2.91 (m, 1H, C***H***CH_2C(O)), 2.66-2.69 (m, 2H, C***H_2***CH=C=CH_2), 2.50 (dd, 1H, *J* = 18.6 Hz, *J* = 8.0 Hz, C(O)C***H_A***H_BCH), 2.13-2.34 (m, 4H, C(O)CH_A***H_B***CH and C***H_A***H_BC***H_2***C(O)), 1.63-1.73 (m, 1H, CH_A***H_B***CH_2C(O)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.4 (***C***=O), 208.9 (CH=***C***=CH_2), 170.5 (2C, 2 × ***C***(O)OCH_3), 84.2 (***C***H=C=CH_2), 75.0 (CH=C=***C***H_2), 60.0 ((O)C***C***C(O)), 52.4 (2C, 2 × O***C***H_3), 41.1 (C(O)***C***H_2CH), 39.7 (C(O)CH_2***C***H), 38.5 (CH_2***C***H_2C(O)), 33.3 (***C***H_2CH=*C*=CH_2), 25.0

(***C***H_2CH_2C(O)); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2955 (C-H), 2845 (C-H), 1955 (C=C=C), 1741 (C=O), 1729 (C=O); **MS** (ES+) m/z (rel. intensity %) 289.14 (M + Na^+, 80); **HRMS** (ESI+) calcd. for $C_{14}H_{18}NaO_5$ $[M+Na]^+$ 289.1052, found 289.1050.

Preparation and characterisation of dimethyl buta-2,3-dien-1-yl(3-oxocyclohexyl)malonate (±)-267h

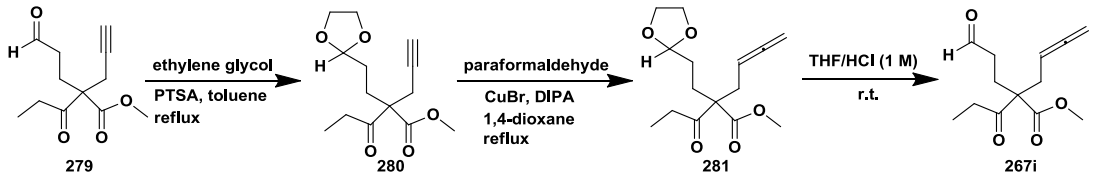


267h

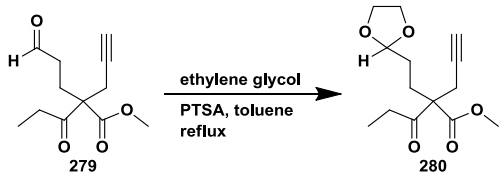
Synthesised from dimethyl buta-2,3-dien-1-ylmalonate **275a** (220 mg, 1.2 mmol) and cyclopent-2-enone **277b** (96.0 µL, 1.0 mmol) according to general procedure N. Compound **(±)-267h** (270 mg, 96%) was obtained as a colourless oil after flash column chromatography on silica gel (PE/Et_2O = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.95-5.03 (m, 1H, C***H***=C=CH_2), 4.66-4.68 (m, 2H, CH=C=C***H_2***), 3.74 (s, 6H, 2 × OC***H_3***), 2.63-2.65 (m, 2H, C***H_2***CH=C=CH_2), 2.37-2.62 (m, 3H, C***H***CH_2C(O) and C(O)C***H_A***H_BCH and C(O)C***H_A***$H_B$$CH_2$), 2.17-2.29 (m, 2H, C(O)CH_A***H_B***CH and C(O)CH_A***H_B***CH_2), 2.02-2.09 (m, 2H, C***H_A***H_BC***H_A***H_BCH), 1.55-1.67 (m, 1H, CH_A***H_B***CH_2CH), 1.33-1.43 (m, 1H, CH_2CH_A***H_B***CH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 210.0 (***C***=O), 209.8 (CH=***C***=CH_2), 170.4 (***C***(O)OCH_3), 170.2 (***C***(O)OCH_3), 84.4 (***C***H=C=CH_2), 74.9 (CH=C=***C***H_2), 61.1 ((O)C***C***C(O)), 52.3 (2C, 2 × O***C***H_3), 43.6 (CH_2***C***H_2C(O)), 41.4 (C(O)***C***H_2CH), 41.1 (CH***C***H_2C(O)), 32.8 (***C***H_2CH=*C*=CH_2), 27.1 (CH_2***C***H_2CH), 24.7 (***C***H_2CH_2CH); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2954 (C-H), 2868 (C-H), 1955 (C=C=C), 1727 (C=O); **MS** (ES+) m/z (rel. intensity %) 303.13 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{15}H_{20}NaO_5$ $[M+Na]^+$ 303.1208, found 303.1205.

6.2.3.4 Synthesis of methyl 2-(3-oxopropyl)-2-propionylhexa-4,5-dienoate 267i



6.2.3.4.1 Synthesis and characterisation of methyl 2-[2-(1,3-dioxolan-2-yl)ethyl]-2-propionylpent-4-ynoate 280

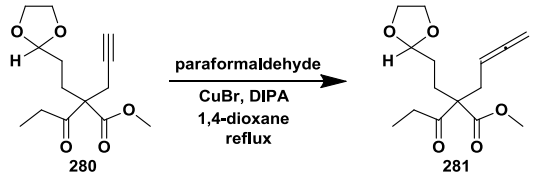


Into a 250 mL round-bottomed flask equipped with a condenser and a Dean-Stark apparatus was added a solution of compound **279** (1.1 g, 4.9 mmol), ethylene glycol (914 mg, 14.7 mmol) in toluene (80 mL), and *p*-toluenesulphonic acid (42.0 mg, 0.24 mmol) was added. The resulting mixture was refluxed for 16 h and monitored by TLC. After completion of this reaction, toluene was removed under vacuum. The residue was dissolved in ethyl acetate, and then washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 2:1) to afford product **280** (1.16 g, 85%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.87 (t, 1H, *J* = 4.4 Hz, OC***H***O), 3.83-3.98 (m, 4H, OC$\boldsymbol{H_2}$C$\boldsymbol{H_2}$O), 3.74 (s, 3H, OC$\boldsymbol{H_3}$), 2.76 (d, 2H, *J* = 2.6 Hz, C$\boldsymbol{H_2}$C≡CH), 2.48 (dq, 2H, *J* = 7.2 Hz, *J* = 2.4 Hz, C$\boldsymbol{H_2}$$CH_3$), 2.09-2.28 (m, 2H, $CHCH_2C\boldsymbol{H_2}$), 2.00 (t, 1H, *J* = 2.6 Hz, C≡C***H***), 1.49-1.60 (m, 1H, CHC$\boldsymbol{H_A}H_B$), 1.37-1.45 (m, 1H, $CHCH_A\boldsymbol{H_B}$),1.05 (t, 3H, *J* = 7.2 Hz, $CH_2C\boldsymbol{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.9 (***C***(O)CH_2), 171.4 (***C***(O)OCH_3), 103.7 (O***C***HO), 78.9 (***C***≡CH), 71.5 (C≡***C***H), 64.9 (2C, O***C***H_2***C***H_2O), 62.0 (C(O)***C***C(O)), 52.7 (O***C***H_3), 32.0 (C(O)***C***H_2), 28.3 (CH***C***H_2), 25.5 ($CHCH_2$***C***H_2), 21.7 (***C***H_2C≡CH), 7.9 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3295 (C≡C-H), 2976 (C-H), 2945 (C-H), 2890 (C-H), 1740 (C=O),

1715 (C=O); **MS** (ES+) m/z (rel. intensity %) 291.11 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{14}H_{20}NaO_5$ $[M+Na]^+$ 291.1207, found 291.1205.

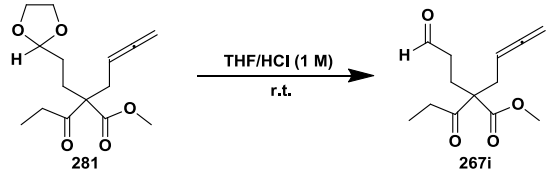
6.2.3.4.2 Synthesis and characterisation of methyl 2-[2-(1,3-dioxolan-2-yl)ethyl]-2-propionylhexa-4,5-dienoate 281[28,29]



A solution of compound **280** (676 mg, 2.52 mmol)**,** cuprous bromide (179 mg, 1.25 mmol), paraformaldehyde (190 mg, 6.3 mmol) and diisopropylamine (0.71 mL, 5.04 mmol) in 1,4-dioxane (20 mL) was heated at reflux and stirred for 12 hours, cooled to room temperature. The reaction was diluted with water followed by an addition of diethyl ether and acidified with 1.0 M aq. HCl until the resulting mixture became a clear solution. The ether layer was separated. The aqueous solution was extracted twice with diethyl ether. The ether extracts were combined and washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (PE/Et_2O = 3:1) on silica gel to give product **281** (320 mg, 45%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.84-4.92 (m, 2H, OC***H***O and C***H***=C=CH_2), 4.64-4.66 (m, 2H, CH=C=C***H₂***), 3.82-3.92 (m, 4H, OC***H₂***C***H₂***O), 3.72 (s, 3H, OC***H₃***), 2.56-2.58 (m, 2H, C***H₂***CH=C=CH_2), 2.44 (q, 2H, *J* = 7.2 Hz, C***H₂***CH_3), 1.94-2.11 (m, 2H, $CHCH_2$C***H₂***), 1.38-1.57 (m, 2H, CHC***H₂***), 1.04 (t, 3H, *J* = 7.2 Hz, CH_2C***H₃***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 209.7 (***C***(O)CH_2), 207.1 (CH=***C***=CH_2), 172.3 (***C***(O)OCH_3), 103.8 (O***C***HO), 84.1 (***C***H=C=CH_2), 74.7 (CH=C=***C***H_2), 64.9 (2C, O***C***H_2***C***H_2O), 62.8 (C(O)***C***C(O)), 52.3 (O***C***H_3), 32.2 (C(O)***C***H_2), 31.0 (***C***H_2CH=*C*=CH_2), 28.3 (CH***C***H_2), 25.4 ($CHCH_2$***C***H_2), 8.0 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2976 (C-H), 2953 (C-H), 2884 (C-H), 1956 (C=C=C), 1742 (C=O), 1713 (C=O); **MS** (ES+) m/z (rel. intensity %) 305.12 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{15}H_{22}NaO_5$ $[M+Na]^+$ 305.1365, found 305.1368.

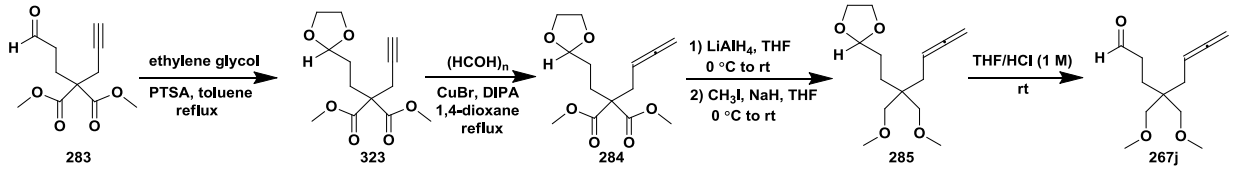
6.2.3.4.3 Synthesis and characterisation of methyl 2-(3-oxopropyl)-2-propionylhexa-4,5-dienoate 267i[180]



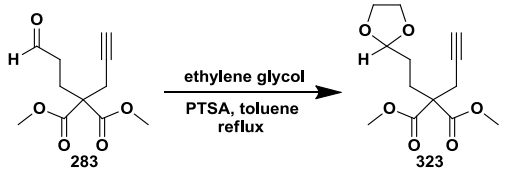
A solution of allene **281** (320 mg, 1.13 mmol) in 1.0 M aq. HCl (17 mL) and THF (6 mL) was stirred for 20 h at room temperature. The reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was extracted three times with diethyl ether. The ether extracts were combined, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 2:1) to afford the product **267i** (191 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.73 (s, 1H, ***H***C=O), 4.84-4.92 (m, 1H, C***H***=C=CH_2), 4.66-4.68 (m, 2H, CH=C=C***H$_2$***), 3.73 (s, 3H, OC***H$_3$***), 2.58 (d, 2H, *J* = 7.9 Hz, C***H$_2$***CH=C=CH_2), 2.36-2.48 (m, 4H, C***H$_2$***CH_3 and HC(O)C***H$_2$***), 2.14-2.31 (m, 2H, HC(O)CH_2C***H$_2$***), 1.05 (t, 3H, *J* = 7.2 Hz, CH_2C***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 209.8 (***C***OCH_2), 206.9 (CH=***C***=CH_2), 200.6 (H***C***(O)), 172.1 (***C***(O)OCH_3), 83.9 (***C***H=C=CH_2), 75.0 (CH=C=***C***H_2), 62.2 (C(O)***C***C(O)), 52.5 (O***C***H_3), 38.8 (HC(O)***C***H_2), 32.3 (C(O)***C***H_2CH_3), 31.7 (***C***H_2CH=*C*=CH_2), 23.8 (HC(O)CH_2***C***H_2), 7.9 (CH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2953 (C-H), 1955 (C=C=C), 1713 (C=O); **MS** (ES+) m/z (rel. intensity %) 261.12 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{18}NaO_4$ $[M+Na]^+$ 261.1103, found 261.1105.

6.2.3.5 Synthesis of 4,4-bis(methoxymethyl)octa-6,7-dienal 267j



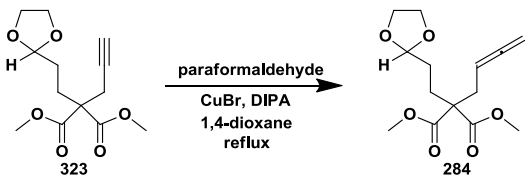
6.2.3.5.1 Synthesis and characterisation of dimethyl [2-(1,3-dioxolan-2-yl)ethyl](prop-2-yn-1-yl)malonate 323



Into a 500 mL round-bottomed flask equipped with a condenser and a Dean-Stark apparatus was added a solution of aldehyde **283** (5.9 g, 26.0 mmol), ethylene glycol (4.9 g, 78.2 mmol) in toluene (350 mL), and then *p*-toluenesulphonic acid (224 mg, 1.3 mmol) was added. The resulting mixture was refluxed for 16 h and monitored by TLC. After completion of this reaction, toluene was removed under vacuum. The residue was dissolved in ethyl acetate, and then washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 2:1) to afford the product **323** (6.1 g, 87%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.87 (t, 1H, *J* = 4.5 Hz, OC***H***O), 3.82-3.97 (m, 4H, OC***H*****$_2$**C***H*****$_2$**O), 3.73 (s, 6H, 2 × OC***H*****$_3$**), 2.80-2.81 (m, 2H, C***H*****$_2$**C≡CH), 2.15-2.19 (m, 2H, $CHCH_2C$***H*****$_2$**), 2.01 (t, 1H, *J* = 2.7 Hz, C≡C***H***), 1.55-1.60 (m, 2H, CHC***H*****$_2$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.4 (2C, 2 × ***C***(O)), 103.8 (O***C***HO), 78.5 (***C***≡CH), 71.5 (C≡***C***H), 64.9 (2C, O***C***H_2***C***H_2O), 56.5 ((O)C***C***C(O)), 52.8 (2C, 2 × O***C***H_3), 28.6 (CH***C***H_2), 26.4 ($CHCH_2$***C***H_2), 23.1 (***C***H_2C≡CH); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3289 (C≡C-H), 2953 (C-H), 2886 (C-H), 2122 (C≡C), 1735 (C=O); **MS** (ES+) m/z (rel. intensity %) 293.13 (M + Na$^+$, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{18}NaO_6$ $[M+Na]^+$ 293.1002, found 293.1004.

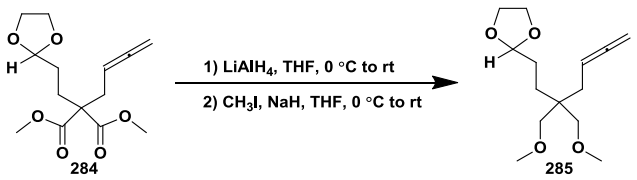
6.2.3.5.2 Synthesis and characterisation of dimethyl buta-2,3-dien-1-yl[2-(1,3-dioxolan-2-yl)ethyl]malonate 284[28,29]



A solution of compound **323** (5.8 g, 21.5 mmol)**,** cuprous bromide (1.38 g, 9.67 mmol), paraformaldehyde (1.62 g, 54.0 mmol) and diisopropylamine (6.0 mL, 43.0 mmol) in 1,4-dioxane (180 mL) was heated at reflux and stirred for 12 hours, cooled to room temperature. The reaction was diluted with water followed by an addition of diethyl ether and acidified with 1.0 M aq. HCl until the resulting mixture became a clear solution. The aqueous solution was extracted twice with diethyl ether. The ether extracts were combined and washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (PE/Et_2O = 3:1) on silica gel to give the product **284** (3.4 g, 56%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.90-4.97 (m, 1H, C***H***=C=CH_2), 4.85 (t, 1H, *J* = 4.5 Hz, OC***H***O), 4.64-4.66 (d, 2H, CH=C=C***H$_2$***), 3.82-3.97 (m, 4H, OC***H$_2$***C***H$_2$***O), 3.71 (s, 6H, 2 × OC***H$_3$***), 2.60 (d, 2H, *J* = 8.0 Hz, C***H$_2$***CH=C=CH_2), 2.02-2.06 (m, 2H, $CHCH_2$C***H$_2$***), 1.57 (td, 2H, *J* = 12.8 Hz, *J* = 4.5 Hz, CHC***H$_2$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 210.0 (CH=***C***=CH_2), 171.3 (2C, 2 × ***C***(O)), 103.9 (O***C***HO), 84.0 (***C***H=C=CH_2), 74.6 (CH=C=***C***H_2), 64.9 (2C, O***C***H_2***C***H_2O), 57.3 ((O)C***C***C(O)), 52.4 (2C, 2 × O***C***H_3), 32.2 (***C***H_2CH=*C*=CH_2), 28.6 (CH***C***H_2), 26.5 ($CHCH_2$***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2954 (C-H), 2885 (C-H), 1956 (C=C=C), 1734 (C=O); **MS** (ES+) m/z (rel. intensity %) 307.10 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{14}H_{20}NaO_6$ $[M+Na]^+$ 307.1158, found 307.1155.

6.2.3.5.3 Synthesis and characterisation of 2-[3,3-bis(methoxymethyl)hepta-5,6-dien-1-yl]-1,3-dioxolane 285



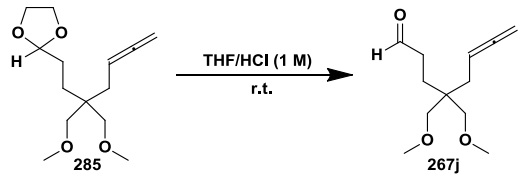
To a suspension of $LiAlH_4$ (519 mg, 13.6 mmol) in anhydrous THF (16 mL) was added dropwise compound **284** (777 mg, 2.73 mmol) in THF (6 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 0 °C. After completion of the reaction, water (0.51 mL) was added dropwise at 0 °C. 15% NaOH (0.51 mL) was added slowly and

another 1.5 mL water was added slowly. Anhydrous Na_2SO_4 was added to remove excess water. The resulting mixture was concentrated to afford the crude diol (594 mg).

To a suspension of NaH (156 mg, 3.9 mmol, 60% dispersion in mineral oil) in anhydrous THF (15 mL) was added the crude diol (300 mg, 1.3 mmol) in THF (5 mL) dropwise at 0 °C under nitrogen atmosphere. After 0.5 h, CH_3I (0.41 mL, 6.5 mmol) was added slowly at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 16 h. After completion of the reaction, water was added dropwise at 0 °C. The resulting mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 6:1) to provide the product **285** (220 mg, 68%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.98-5.06 (m, 1H, C***H***=C=CH_2), 4.80 (t, 1H, *J* = 4.8 Hz, OC***H***O), 4.60-4.62 (m, 2H, CH=C=C***H₂***), 3.79-3.99 (m, 4H, OC***H₂***C***H₂***O), 3.29 (s, 6H, 2 × OC***H₃***), 3.18 ("t", 4H, *J* = 9.6 Hz, 2 × OC***H₂***), 2.00 (td, 2H, *J* = 8.1 Hz, *J* = 2.2 Hz, C***H₂***CH=C=CH_2), 1.60-1.65 (m, 2H, CHC***H₂***), 1.38-1.42 (m, 2H, $CHCH_2C$***H₂***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 209.9 (CH=***C***=CH_2), 105.1 (O***C***HO), 85.1 (***C***H=C=CH_2), 75.1 (2C, 2 × CH_3O***C***H_2), 73.5 (CH=C=***C***H_2), 64.8 (2C, O***C***H_2***C***H_2O), 59.2 (2C, 2 × O***C***H_3), 41.4 (CH_2***C***CH_2), 31.5 (***C***H_2CH=*C*=CH_2), 27.7 (CH***C***H_2), 26.2 ($CHCH_2$***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2955 (C-H), 2878 (C-H), 1954 (C=C=C); **MS** (ES+) m/z (rel. intensity %) 279.16 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{14}H_{24}NaO_4$ $[M+Na]^+$ 279.1572, found 279.1571.

6.2.3.5.4 Synthesis and characterisation of 4,4-bis(methoxymethyl)octa-6,7-dienal 267j[180]

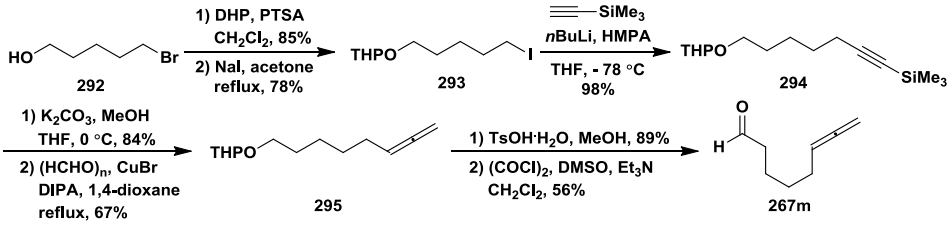


A solution of allene **285** (220 mg, 0.86 mmol) in 1.0 M aq. HCl (13 mL) and THF (4 mL) was stirred for 20 h at room temperature. The reaction mixture was monitored by TLC. After

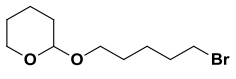
completion of the reaction, the reaction mixture was extracted three times with diethyl ether. The ether extracts were combined, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 2:1) to afford the product **267j** (110 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.71 (s, 1H, ***H***C(O)), 4.98-5.05 (m, 1H, C***H***=C=CH_2), 4.62-4.64 (m, 2H, CH=C=C***H₂***), 3.29 (s, 6H, 2 × OC***H₃***), 3.18 ("q", 4H, *J* = 9.2 Hz, 2 × CH_3OC***H₂***), 2.42-2.46 (m, 2H, HC(O)C***H₂***), 2.02 (dd, 2H, *J* = 8.1 Hz, *J* = 2.1 Hz, C***H₂***CH=C=CH_2), 1.67 (t, 2H, *J* = 8.1 Hz, HC(O)CH_2C***H₂***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 210.0 (CH=***C***=CH_2), 202.7 (H***C***(O)), 84.9 (***C***H=C=CH_2), 75.0 (2C, 2 × O***C***H_2), 73.7 (CH=C=***C***H_2), 59.1 (2C, 2 × O***C***H_3), 41.4 (CH_2***C***CH_2), 38.4 (HC(O)***C***H_2), 31.7 (***C***H_2CH=*C*=CH_2), 24.7 (HC(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2982 (C-H), 2925 (C-H), 2878 (C-H), 1954 (C=C=C), 1725 (C=O); **MS** (ES+) m/z (rel. intensity %) 235.14 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{20}NaO_3$ $[M+Na]^+$ 235.1310, found 235.1311.

6.2.3.6 Synthesis of octa-6,7-dienal 267m



6.2.3.6.1 Synthesis and characterisation of 2-(5-bromopentyloxy)-tetrahydro-2H-pyran **324**[155]



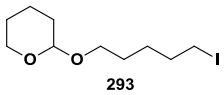
324

To a solution of 5-bromo-1-pentanol **292** (6.5 g, 40.0 mmol) and 4-methylbenzenesulfonic acid (344 mg, 2.0 mmol) in anhydrous dichloromethane (130 mL) at 0 °C under nitrogen atmosphere was added dropwise 3,4-dihydro-2H-pyran (5.1 mL, 60 mmol) and the solution was stirred at the same temperature for 12 h. To the solution were added successively sat. aq. $NaHCO_3$ and water. The organic layer was separated. The aqueous layer was extracted with

dichloromethane. The combined organic extracts were dried (Na_2SO_4) and evaporated. Purification by flash column chromatography on silica gel (PE/Et_2O = 30:1) provided 2-(5-bromopentyloxy)-tetrahydro-2H-pyran **324** (6.7 g, 67%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.55-4.60 (m, 1H), 3.86-3.89 (m, 1H), 3.72-3.76 (m, 1H), 3.47-3.51 (m, 1H), 3.36-3.40 (m, 3H), 1.80-1.95 (m, 3H), 1.45-1.70 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 98.9, 67.4, 62.4, 33.7, 32.6, 30.8, 28.9, 25.5, 25.0, 19.7. Analytical data in agreement with the previous report.[158]

6.2.3.6.2 Synthesis and characterisation of 2-(5-iodopentyloxy)-tetrahydro-2H-pyran[156] **293**

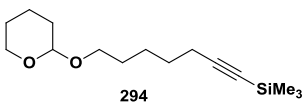


293

The mixture of 2-(5-bromopentyloxy)-tetrahydro-2H-pyran **324** (6.7 g, 27 mmol) and NaI (9.0 g, 60 mmol) in acetone (54 mL) was refluxed for 16 h. Acetone was removed under reduced pressure, and the residue was dissolved in water. The resulting mixture was extracted three times with diethyl ether. The combined organic extracts was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 20:1) to afford 2-(5-iodopentyloxy)-tetrahydro-2H-pyran **293** (3.30 g, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.55-4.59 (m, 1H), 3.85-3.90 (m, 1H), 3.73-3.78 (m, 1H), 3.50-3.54 (m, 1H), 3.36-3.40 (m, 1H), 3.18-3.21 (m, 2H), 1.80-1.88 (m, 3H), 1.45-1.72 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 98.9, 67.4, 62.4, 33.4, 30.9, 28.8, 27.4, 25.6, 25.0, 19.7, 6.8. Analytical data in agreement with the previous report.[156]

6.2.3.6.3 Synthesis and characterisation of trimethyl[7-(tetrahydro-2*H*-pyran-2-yloxy)hept-1-yn-1-yl]silane 294[181]



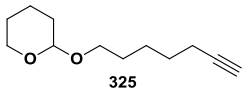
294

*n*BuLi (1.6 M in hexane, 13.0 mL, 20.8 mmol) was added to a stirred and cooled solution of trimethylsilylacetylene (2.9 mL, 20.8 mmol) in THF (50 mL) at -78 °C. Stirring at -78 °C was

continued for 2 h, and then 2-(5-iodopentyloxy)-tetrahydro-2H-pyran **293** (2.7 g, 9.06 mmol) in THF (10 mL) and HMPA (3.80 mL, 21.7 mmol) were added rapidly, each in one portion. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and water (10 mL), and then extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 20:1) to afford the product **294** (2.4 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.57-4.58 (m, 1H), 3.84-3.89 (m, 1H), 3.72-3.77 (m, 1H), 3.48-3.52 (m, 1H), 3.37-3.42 (m, 1H), 2.24 (t, 2H, *J* = 7.0 Hz), 1.79-1.86 (m, 1H), 1.69-1.75 (m, 1H), 1.46-1.61 (m, 10H), 0.15 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 107.5, 98.8, 84.4, 67.4, 62.3, 30.7, 29.2, 28.4, 25.5 (2C), 19.8, 19.6, 0.15 (3C); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2941 (C-H), 2866 (C-H), 2174 (C≡C), 1249 (C-O); **MS** (ES+) m/z (rel. intensity %) 291.18 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{15}H_{28}NaO_2Si$ $[M+Na]^+$ 291.1756, found 291.1756.

6.2.3.6.4 Synthesis and characterisation of 2-(hept-6-yn-1-yloxy)tetrahydro-2*H*-pyran **325**[181]



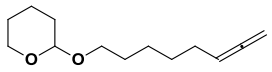
325

K_2CO_3 (1.18 g, 8.58 mmol) was added in one portion to a stirred and cooled solution of **294** at 0 °C in MeOH (77 mL) and THF (38 mL). The resulting mixture was stirred at 0 °C for 6 h, and allowed to stir for 12 h at room temperature. The reaction mixture was filtered through a pad of Celite using diethyl ether as a rinse. Product **325** (1.4 g, 84%) was obtained after flash column chromatography on silica gel (PE/Et_2O = 8:1) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.56-4.57 (m, 1H), 3.84-3.89 (m, 1H), 3.72-3.77 (m, 1H), 3.47-3.51 (m, 1H), 3.36-3.42 (m, 1H), 2.18-2.22 (m, 2H), 1.94 (t, 1H, *J* = 2.5 Hz), 1.78-1.86 (m, 1H), 1.46-1.74 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 98.8, 84.5, 68.2, 67.4, 62.3, 30.7, 29.2, 28.3, 25.5, 25.4, 19.7, 18.3; **FT-IR** ν_{max}(NaCl)/cm^{-1} 3296 (C≡C-H), 2940 (C-H),

2866 (C-H), 2117 (C≡C), 1137 (C-O); **MS** (ES+) m/z (rel. intensity %) 219.15 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{20}NaO_2$ $[M+Na]^+$ 219.1361, found 219.1359.

6.2.3.6.5 Synthesis and characterisation of 2-(octa-6,7-dien-1-yloxy)tetrahydro-2*H*-pyran 295[28,29]

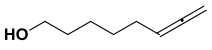


295

A solution of compound **325** (1.3 g, 6.78 mmol)**,** cuprous bromide (436 mg, 3.05 mmol), paraformaldehyde (509 mg, 16.9 mmol) and diisopropylamine (1.9 mL, 13.5 mmol) in 1,4-dioxane (44 mL) was heated at reflux and stirred for 12 hours, cooled to room temperature. The reaction was diluted with water followed by the addition of diethyl ether and acidified with 1.0 M aq. HCl until the resulting mixture became a clear solution. The ether layer was separated. The aqueous solution was extracted twice with diethyl ether. The organic extracts were combined and washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/Et_2O = 20:1) on silica gel to give the product **295** (876 mg, 67%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.05-5.12 (m, 1H), 4.62-4.65 (m, 2H), 4.56-4.57 (m, 1H), 3.84-3.89 (m, 1H), 3.70-3.76 (m, 1H), 3.47-3.52 (m, 1H), 3.35-3.41 (m, 1H), 1.97-2.04 (m, 2H), 1.78-1.86 (m, 1H), 1.68-1.74 (m, 1H), 1.37-1.62 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.5, 98.8, 89.9, 74.6, 67.5, 62.3, 30.8, 29.5, 28.9, 28.2, 25.7, 25.5, 19.7; **FT-IR** ν_{max}(NaCl)/cm^{-1} 2938 (C-H), 2859 (C-H), 1956 (CH=C=CH_2), 1156 (C-O); **MS** (ES+) m/z (rel. intensity %) 233.18 ($M + Na^+$, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{22}NaO_2$ $[M+Na]^+$ 233.1628, found 233.1626.

6.2.3.6.6 Synthesis and characterisation of octa-6,7-dien-1-ol 326[181]



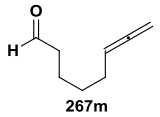
326

A solution of compound **295** (762 mg, 3.63 mmol) and TsOH (62 mg, 0.36 mmol) in methanol (18 mL) was stirred at room temperature for 16 h. The solvent was removed under reduced

pressure and the residue was dissolved in diethyl ether. The resulting mixture was washed with sat. aq. $NaHCO_3$, brine and dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 1:1) to afford the alcohol **326** (406 mg, 89%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.05-5.12 (m, 1H), 4.65-4.68 (m, 2H), 3.61-3.65 (m, 2H), 2.00-2.07 (m, 2H), 1.55-1.61 (m, 3H), 1.35-1.46 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.4, 89.9, 74.6, 62.8, 32.3, 30.8, 25.8, 25.1; **FT-IR** ν_{max}(NaCl)/cm^{-1} 3318 (O-H), 2933 (C-H), 2858 (C-H), 1956 (CH=C=CH_2), 1072 (C-O); **MS** (ES+) m/z (rel. intensity %) 149.10 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_8H_{14}NaO$ $[M+Na]^+$ 149.0942, found 149.0942.

6.2.3.6.7 Synthesis and characterisation of octa-6,7-dienal 267m[181]



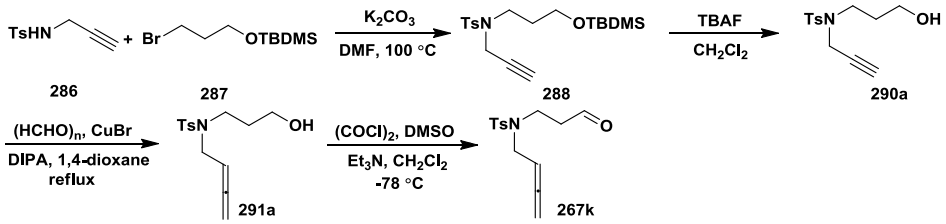
267m

To a solution of oxalyl chloride (0.58 mL, 6.76 mmol) in anhydrous dichloromethane (10 mL) was added dropwise DMSO (0.96 mL, 13.5 mmol) over 10 min at - 78 °C. The reaction mixture was stirred for 10 min and then a solution of compound **326** (787 mg, 6.15 mmol) in dichloromethane (10 mL) was added dropwise for 10 min at - 78 °C. The reaction was allowed to stir for 20 min, and then Et_3N (4.3 mL, 30.7 mmol) was added dropwise. The reaction mixture was stirred for 15 min and then warmed to room temperature over 2 h. Water (14 mL) was added. The resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash column chromatography on silica gel (PE/Et_2O = 3:1) afforded the aldehyde **267m** (479 mg, 62%).

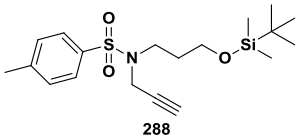
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.77 (t, 1H, *J* = 1.8 Hz, ***H***C=O), 5.07-5.11 (m, 1H, C***H***=C=CH_2), 4.65-4.68 (m, 2H, CH=C=C***H$_2$***), 2.44 (td, 2H, *J* = 7.3 Hz, *J* = 1.8 Hz, HC(O)C***H$_2$***), 2.00-2.06 (m, 2H, C***H$_2$***CH=C=CH_2), 1.65-1.71 (m, 2H, HC(O)CH_2C***H$_2$***), 1.45-1.50 (m, 2H, C***H$_2$***CH_2CH=C=CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.6 (CH=***C***=CH_2),

202.5 (***C***=O), 89.4 (***C***H=C=CH_2), 74.5 (CH=C=***C***H_2), 43.6 (HCO***C***H_2), 28.4 (***C***H_2CH=C=CH_2), 27.8 (***C***H_2CH_2CH=C=CH_2), 21.5 (HC(O)CH_2***C***H_2). Analytical data in agreement with previous report.[154]

6.2.3.7 Synthesis of *N*-(buta-2,3-dien-1-yl)-4-methyl-*N*-(3-oxopropyl)benzenesulfonamide 267k[153]



6.2.3.7.1 Synthesis and characterisation of *N*-(3-{[*tert*-butyl(dimethyl)silyl]oxy}propyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 288[153]

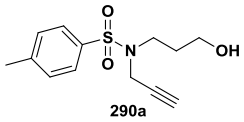


To a solution of compound **286** (3.1 g, 15 mmol) and compound **287** (4.6 g, 18 mmol) in anhydrous DMF (80 mL) was added K_2CO_3 (6.26 g, 45 mmol) at room temperature. The reaction mixture was heated at 100 °C for 12 h, and cooled to room temperature. The reaction mixture was quenched with water, and extracted with diethyl ether (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 20:1) to give compound **288** (5.4 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (d, 2H, *J* = 8.2 Hz, 2 × Ar***H***), 7.29 (d, 2H, *J* = 8.1 Hz, 2 × Ar***H***), 4.15 (d, 2H, *J* = 2.3 Hz, C***H$_2$***C≡CH), 3.66 (t, 2H, *J* = 6.0 Hz, OC***H$_2$***), 3.27-3.30 (m, 2H, NC***H$_2$***CH_2), 2.42 (s, 3H, C***H$_3$***), 2.02 (t, 1H, *J* = 2.3 Hz, C≡C***H***), 1.77-1.80 (m, 2H, OCH_2C***H$_2$***), 0.89 (s, 9H, SiC(C***H$_3$***)$_3$), 0.05 (s, 6H, Si(C***H$_3$***)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.4 (***C***, Ar), 136.5 (***C***, Ar), 129.4 (2***C***H, Ar), 127.7 (2***C***H, Ar), 76.8 (***C***≡CH), 73.5 (C≡***C***H), 60.2 (O***C***H_2), 43.7 (N***C***H_2CH_2), 36.7 (***C***H_2C≡CH), 31.0 (OCH_2***C***H_2), 25.8 (3C, SiC(***C***H_3)$_3$),

18.2 (Si***C***$(CH_3)_3$), 21.5 (***C***H_3 of Ar), - 5.4 (2C, Si(***C***$H_3)_2$). Analytical data in agreement with previous report.[153]

6.2.3.7.2 Synthesis and characterisation of *N*-(3-hydroxypropyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide 290a[153]

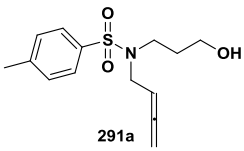


290a

To a solution of compound **288** (5.2 g, 13.7 mmol) in dichloromethane (50 mL) was added TBAF (1.0 M in THF, 16.4 mL, 16.4 mmol) at room temperature. The reaction mixture was stirred for 36 h and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 1:2) to afford product **290a** (2.6 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (d, 2H, *J* = 8.2 Hz, 2 × Ar***H***), 7.30 (d, 2H, *J* = 8.1 Hz, 2 × Ar***H***), 4.15 (d, 2H, *J* = 2.3 Hz, C***H$_2$***C≡CH), 3.74 (t, 2H, *J* = 6.0 Hz, OC***H$_2$***), 3.31-3.35 (m, 2H, NC***H$_2$***CH_2), 2.42 (s, 3H, C***H$_3$***), 2.02 (t, 1H, *J* = 2.3 Hz, C≡C***H***), 1.77-1.80 (m, 2H, OCH_2C***H$_2$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.6 (***C***, Ar), 135.6 (***C***, Ar), 129.2 (2***C***H, Ar), 127.5 (2***C***H, Ar), 76.8 (***C***≡CH), 73.4 (C≡***C***H), 60.5 (O***C***H_2), 43.4 (N***C***H_2CH_2), 36.5 (***C***H_2C≡CH), 31.3 (OCH_2***C***H_2), 21.5 (***C***H_3). Analytical data in agreement with previous report.[153]

6.2.3.7.3 Synthesis and characterisation of *N*-(buta-2,3-dien-1-yl)-*N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide 291a[28,29]



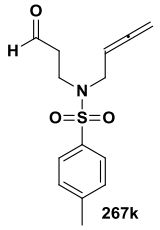
291a

A solution of compound **290a** (3.0 g, 11.2 mmol)**,** cuprous bromide (795 mg, 5.5 mmol), paraformaldehyde (842 mg, 28 mmol) and diisopropylamine (3.1 mL, 22.4 mmol) in 1,4-dioxane (50 mL) was heated at reflux and stirred for 10 hours and then cooled to room temperature. The reaction was diluted with water followed by an addition of diethyl ether and

acidified with 1.0 M aq. HCl until the resulting mixture became a clear solution. The aqueous solution was extracted twice with diethyl ether. The ether extracts were combined and washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/Et_2O = 1:2) on silica gel to give product **291**a (1.97 g, 77%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (d, 2H, *J* = 8.3 Hz, 2 × Ar***H***), 7.30 (d, 1H, *J* = 8.1 Hz, 2 × Ar***H***), 4.86-4.92 (m, 1H, C***H***=C=CH_2), 4.68-4.71 (m, 2H, CH=C=C***H₂***), 3.86 (td, 2H, *J* = 7.2 Hz, *J* = 2.4 Hz, C***H₂***CH=C=CH_2), 3.74 (t, 2H, *J* = 5.7 Hz, OC***H₂***), 3.31 (t, 2H, *J* = 6.5 Hz, N***C***H_2CH_2), 2.42 (s, 3H, C***H₃***), 1.73-1.79 (m, 2H, OCH_2C***H₂***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 209.4 (CH=***C***=CH_2), 143.5 (***C***, Ar), 136.8 (***C***, Ar), 129.8 (2***C***H, Ar), 127.1 (2***C***H, Ar), 85.7 (***C***H=C=CH_2), 76.3 (CH=C=***C***H_2), 58.7 (O***C***H_2), 46.9 (N***C***H_2CH_2), 43.5 (***C***H_2CH=C=CH_2), 31.3 (OCH_2***C***H_2), 21.5 (***C***H_3). Analytical data in agreement with previous report.[153]

6.2.3.7.4 Synthesis and characterisation of *N*-(buta-2,3-dien-1-yl)-4-methyl-*N*-(3-oxopropyl)benzenesulfonamide 267k[153]



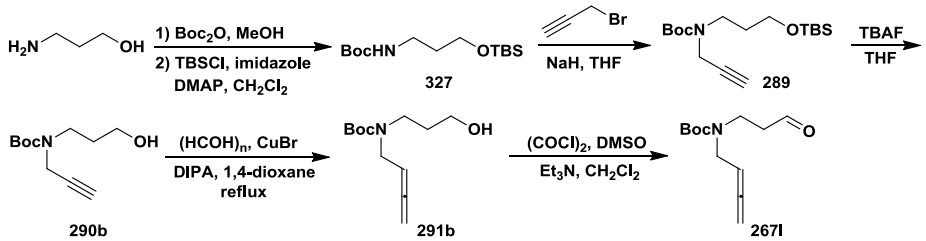
267k

To a solution of oxalyl chloride (0.76 mL, 9.02 mmol) in anhydrous dichloromethane (13 mL) was added dropwise DMSO (1.3 mL, 18.0 mmol) over 10 min at - 78 °C. The reaction mixture was stirred for 10 min and then a solution of compound **291a** (2.3 g, 8.2 mmol) in dichloromethane (13 mL) was added dropwise for 10 min at - 78 °C. The reaction was allowed to stir for 20 min, and Et_3N (5.7 mL, 41.0 mmol) was added dropwise. The reaction mixture was stirred for 15 min and then warmed to room temperature over 2 h. Water (20 mL) was added. The resulting mixture was extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification by

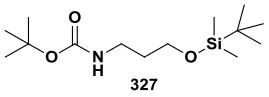
flash column chromatography on silica gel (PE/Et_2O = 1:1) afforded the aldehyde **267k** (2.0 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.76 (d, 1H, *J* = 3.3 Hz, ***H***C=O), 7.69 (dd, 2H, *J* = 4.6 Hz, *J* = 3.5 Hz, 2 × Ar***H***), 7.29-7.31 (m, 2H, 2 × Ar***H***), 4.87-4.94 (m, 1H, C***H***=C=CH_2), 4.70-4.72 (m, 2H, CH=C=C***H*****$_2$**), 3.82-3.84 (m, 2H, C***H*****$_2$**CH=C=CH_2), 3.45-3.49 (m, 2H, HC(O)CH_2C***H*****$_2$**), 2.81-2.84 (m, 2H, HC(O)C***H*****$_2$**CH_2), 2.42 (s, 3H, C***H*****$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 209.8 (CH=***C***=CH_2), 200.3 (H***C***=O), 143.6 (***C***, Ar), 136.4 (***C***, Ar), 129.8 (2***C***H, Ar), 127.2 (2***C***H, Ar), 85.8 (***C***H=C=CH_2), 76.5 (CH=C=***C***H_2), 47.6 (***C***H_2CH=*C*=CH_2), 43.5 (HC(O)***C***H_2), 40.8 (HC(O)CH_2***C***H_2), 21.5 (***C***H_3). Analytical data in agreement with the previous report.[153]

6.2.3.8 Synthesis of *tert*-butyl buta-2,3-dien-1-yl(3-oxopropyl)carbamate 267l[154]



6.2.3.8.1 Synthesis and characterisation of *tert*-butyl (3-((*tert*-butyldimethylsilyl)oxy)propyl)carbamate 327[154]

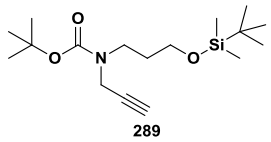


327

A solution of 3-aminopropan-1-ol (1.90 g, 25 mmol) in methanol (50 mL) was added di-*t*-butyldicarbonate (5.6 g, 25 mmol) at room temperature and the reaction mixture was stirred for 4 h. Methanol was removed under reduced pressure. The residue was dissolved in dichloromethane (60 mL) and TBSCl (4.14 g, 27.5 mmol), imidazole (2.55 g, 37.5 mmol) and DMAP (458 mg, 3.75 mmol) were successively added. The reaction mixture was stirred for 16 h and quenched with sat. aq. NH_4Cl. The resulting mixture was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 10:1) to afford the product **327** (7.5 g, 97%) as a clear colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.11 (brs, 1H, N***H***), 3.71 (t, 2H, *J* = 5.7 Hz, OC***H₂***), 3.21-3.24 (m, 2H, NC***H₂***), 1.67-1.69 (m, 2H, OCH_2C***H₂***), 1.40 (s, 9H, OC(C***H₃***)$_3$), 0.88 (s, 9H, SiC(C***H₃***)$_3$), 0.03 (s, 6H, Si(C***H₃***)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 155.8 (***C***=O), 78.6 (O***C***$(CH_3)_3$), 62.0 (O***C***H_2), 39.0 (N***C***H_2), 32.0 (OCH_2***C***H_2), 28.3 (3C, OC(***C***$H_3)_3$), 25.8 (3C, SiC(***C***$H_3)_3$), 18.1 (Si***C***$(CH_3)_3$), -5.6 (2C, Si(***C***$H_3)_2$). Analytical data in agreement with the previous report.[154]

6.2.3.8.2 Synthesis and characterisation of *tert*-butyl (3-((*tert*-butyldimethylsilyl)oxy)propyl)(prop-2-yn-1-yl)carbamate 289[154]

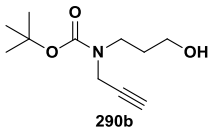


289

To a suspension of NaH (1.50 g, 30.0 mmol, 60% dispersion in mineral oil) in anhydrous THF (38 mL) was added dropwise compound **327** (7.2 g, 25 mmol) in THF (5 mL) at 0 °C under nitrogen atmosphere and stirred for 2 h. To the reaction mixture was added propargyl bromide (80 wt% in toluene, 5.6 mL, 38 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 20 h and quenched with sat. aq. NH_4Cl. Water was added to the dark brown reaction mixture and extracted with diethyl ether (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 15:1) to afford the product **289** (4.4 g, 54%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.04 (brs, 2H, OC***H₂***), 3.63-3.65 (m, 2H, C***H₂***C≡CH), 3.37-3.40 (m, 2H, NC***H₂***CH_2), 2.10 (t, 1H, *J* = 2.4 Hz, C≡C***H***), 1.75-1.80 (m, 2H, OC***H₂***CH_2), 1.46 (s, 9H, OC(C***H₃***)$_3$), 0.90 (s, 9H, SiC(C***H₃***)$_3$), 0.05 (s, 6H, Si(C***H₃***)$_2$). Analytical data in agreement with the previous report.[154]

6.2.3.8.3 Synthesis and characterisation of *tert*-butyl (3-hydroxypropyl)prop-2-yn-1-ylcarbamate 290b[154]

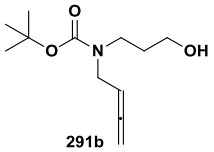


290b

To a solution of compound **289** (4.1 g, 12.5 mmol) in THF (10 mL) was added TBAF (75 wt% aq. Solution, 8.7 g, 25 mmol) at room temperature. The reaction mixture was stirred for 14 h and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 1:1) to afford the product **290b** (2.6 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.96 (brs, 2H, C***H*****$_2$**C≡CH), 3.57 (brs, 2H, OC***H*****$_2$**), 3.46-3.50 (m, 2H, NC***H*****$_2$**CH_2), 2.15 (t, 1H, *J* = 2.5 Hz, C≡C***H***), 1.75-1.80 (m, 2H, OC***H*****$_2$**CH_2), 1.49 (s, 9H, OC(C***H*****$_3$**$)_3$). Analytical data in agreement with the previous report.[154]

6.2.3.8.4 Synthesis and characterisation of *tert*-butyl buta-2,3-dien-1-yl(3 hydroxypropyl)carbamate 291b[28,29]

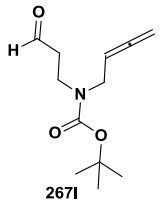


291b

A solution of compound **290b** (2.40 g, 11.2 mmol)**,** cuprous bromide (786 mg, 5.5 mmol), paraformaldehyde (845 mg, 28.0 mmol) and diisopropylamine (3.1 mL, 22.5 mmol) in 1,4-dioxane (50 mL) was heated at reflux and stirred for 10 hours, cooled to room temperature. The reaction was diluted with water followed by an addition of diethyl ether and acidified with 1.0 M aq. HCl until the mixture became a clear solution. The ether layer was separated. The aqueous solution was extracted twice with diethyl ether. The ether extracts were combined and washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (PE/Et_2O = 1:2) on silica gel to give the product **291b** (1.97 g, 77%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.09-5.13 (m, 1H, C***H***=C=CH_2), 4.75-4.79 (m, 2H, CH=C=C***H₂***), 3.75-3.80 (m, 2H, C***H₂***CH=C=CH_2), 3.52-3.58 (m, 2H, OC***H₂***), 3.35-3.39 (m, 2H, NC***H₂***), 1.63-1.66 (m, 2H, OCH_2C***H₂***), 1.43 (s, 9H, OC(C***H₃***)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.8 (CH=***C***=CH_2), 156.8 (***C***=O), 87.1 (***C***H=C=CH_2), 80.3 (O***C***$(CH_3)_3$), 76.3 (CH=C=***C***H_2), 58.3 (O***C***H_2), 46.2 (C***H₂***CH=C=CH_2), 42.6 (NC***H₂***), 30.4 (OCH_2***C***H_2), 28.3 (OC(C***H₃***)$_3$). Analytical data in agreement with the previous report.[154]

6.2.3.8.5 Synthesis and characterisation of *tert*-butyl buta-2,3-dien-1-yl(3-oxopropyl)carbamate 267l[154]



267l

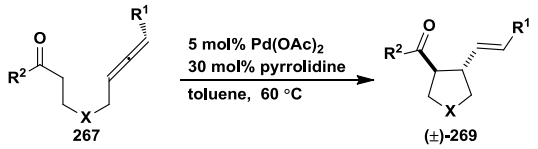
To a solution of oxalyl chloride (0.76 mL, 9.02 mmol) in anhydrous dichloromethane (13 mL) was added dropwise DMSO (1.3 mL, 18.0 mmol) over 10 min at - 78 °C. The reaction mixture was stirred for 10 min and then a solution of compound **291b** (1.86 g, 8.2 mmol) in dichloromethane (13 mL) was added dropwise for 10 min at - 78 °C. The reaction was allowed to stir for 20 min at - 78 °C, and then Et_3N (5.7 mL, 41.0 mmol) was added dropwise. The reaction mixture was stirred for 15 min at - 78 °C and then warmed to room temperature over 2 h. Water (20 mL) was added. The resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash column chromatography on silica gel (PE/Et_2O = 1:1) afforded aldehyde **267l** (1.65 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.74 (s, 1H, ***H***C=O), 5.04-5.06 (m, 1H, C***H***=C=CH_2), 4.73-4.75 (m, 2H, CH=C=C***H₂***), 3.79 (s, 2H, C***H₂***CH=C=CH_2), 3.49 (t, 2H, *J* = 5.8 Hz, HC(O)CH_2C***H₂***), 2.67 (t, 2H, *J* = 5.8 Hz, HC(O)C***H₂***), 1.40 (s, 9H, 3 × C***H₃***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 208.6 (CH=***C***=CH_2), 201.0 (H***C***=O), 155.0 (N***C***OO), 87.2 (***C***H=C=CH_2),

80.0 (O***C***$(CH_3)_3$), 76.5 (CH=C=***C***H_2), 46.7 (***C***H_2CH=*C*=CH_2), 43.3 (HC(O)***C***H_2), 40.9 (HC(O)CH_2***C***H_2), 28.3 (OC(***C***$H_3)_3$). Analytical data in agreement with previous report.[154]

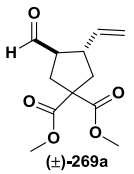
6.2.3.9 Diastereoselective carbocyclisation of allenes 267 via enamine catalysis

General procedure O for the carbocyclisation of allenes 267



To a solution of $Pd(OAc)_2$ (10 mol%) in toluene (0.1 mmol per mL of **267**) were added substrate **267** (1.0 equiv.) and pyrrolidine (30 mol%) in sealed vials. The reaction was stirred at 60 °C and monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and purified by flash column chromatography on silica gel to afford the product **(±)-269**.

Preparation and characterisation of *rac*-dimethyl (3*R*,4*S*)-3-formyl-4-vinylcyclopentane-1,1-dicarboxylate 269a

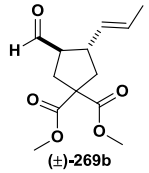


Synthesised from compound **267a** (49.0 mg, 0.2 mmol) according to general procedure O. Compound **(±)-269a** (two diastereoisomers, 33.0 mg, 68%) was obtained as a colourless oil after flash column chromatography (PE/Et_2O = 6:1). Product **(±)-269a** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 13:1, as determined by ^{1}H NMR.

Major diastereoisomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.62 (d, 1H, *J* = 2.3 Hz, ***H***C(O)), 5.77 (ddd, 1H, *J* = 17.5 Hz, *J* = 10.3 Hz, *J* = 7.6 Hz, C***H***=CH_2), 5.07-5.15 (m, 2H, CH=C***H$_2$***), 3.75 (s, 6H, 2 × OC***H$_3$***), 2.85-2.92 (m, 1H, C***H***CH=CH_2), 2.67-2.73 (m, 1H, HC(O)C***H***), 2.59-2.63 (m, 1H, C***H$_A$***H_BCHCH=CH_2), 2.53-2.55 (m, 2H, HC(O)CHC***H$_2$***), 2.09 (dd, 1H, *J* = 13.5 Hz, *J* = 10.8 Hz, CH_A***H$_B$***CHCH=CH_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 201.4 (H***C***(O)), 172.0 (***C***(O)OCH_3), 171.9 (***C***$OOCH_3$), 138.1 (***C***H=CH_2), 116.4 (CH=***C***H_2), 58.9 ((O)C***C***C(O)), 56.2

(HC(O)***C***H), 52.9 (2C, 2 × O***C***H_3), 44.7 (***C***HCH=CH_2), 40.3 (***C***H_2CHCH=CH_2), 33.8 (HC(O)CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2955 (C-H), 1732 (C=O), 1642 (C=C); **MS** (ES+) m/z (rel. intensity %) 263.12 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{16}NaO_5$ $[M+Na]^+$ 263.0895, found 263.0893.

Preparation and characterisation of *rac*-dimethyl (3*R*,4*S*)-3-formyl-4-[(1*E*)-prop-1-en-1-yl]cyclopentane-1,1-dicarboxylate (±)-269b

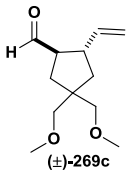


(±)-269b

Synthesised from compound **267d** (52.0 mg, 0.2 mmol) according to general procedure O. Compound **(±)-269b** (two diastereoisomers, 31.0 mg, 60%) was obtained as a colourless oil after flash column chromatography (PE/Et_2O = 2:1). Product **(±)-269b** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 12:1, as determined by ^{1}H NMR.

Major diastereoisomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.59 (d, 1H, *J* = 2.4 Hz, ***H***C(O)), 5.51-5.58 (m, 1H, CH=C***H***CH_3), 5.34-5.39 (m, 1H, C***H***=$CHCH_3$), 3.74 (s, 6H, 2 × OC***H$_3$***), 2.78-2.85 (m, 1H, C***H***CH=CH), 2.55-2.66 (m, 2H, HC(O)C***H*** and C***H$_A$***H_BCHCH=CH), 2.49-2.52 (m, 2H, HC(O)CHC***H$_2$***), 2.03 (dd, 1H, *J* = 13.5 Hz, *J* = 10.9 Hz, CH_A***H$_B$***CHCH=CH), 1.66 (dd, 3H, *J* = 6.4 Hz, *J* = 1.3 Hz, CH=CHC***H$_3$***); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 201.8 (H***C***(O)), 172.1 (***C***(O)OCH_3), 172.0 (***C***(O)OCH_3), 130.8 (***C***H=$CHCH_3$), 127.3 (CH=***C***HCH_3), 58.9 ((O)C***C***C(O)), 56.6 (HC(O)***C***H), 52.9 (2 × O***C***H_3), 44.2 (***C***HCH=CH), 40.8 (***C***H_2CHCH=CH), 33.8 (HC(O)CH***C***H_2), 17.8 (CH=CH***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2955 (C-H), 1733 (C=O), 1638 (C=C); **MS** (ES+) m/z (rel. intensity %) 277.13 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{18}NaO_5$ $[M+Na]^+$ 277.1052, found 277.1050.

Preparation and characterisation of *rac*-(1*R*,2*S*)-4,4-bis(methoxymethyl)-2-vinylcyclopentanecarbaldehyde (±)-269c

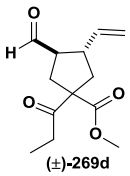


(±)-269c

Synthesised from compound **267j** (43.0 mg, 0.2 mmol) according to general procedure O. Compound **(±)-269c** (two diastereoisomers, 28.0 mg, 65%) was obtained as a colourless oil after flash column chromatography (PE/Et_2O = 6:1). Product **(±)-269c** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 14:1, as determined by ^{1}H NMR.

Major diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.57 (d, 1H, *J* = 3.2 Hz, ***H***C(O)), 5.75 (ddd, 1H, *J* = 17.5 Hz, *J* = 10.2 Hz, *J* = 7.5 Hz, C***H***=CH_2), 4.99-5.09 (m, 2H, CH=C***H₂***), 3.35 (s, 6H, 2 × C***H₃***), 3.24 (s, 4H, 2 × C***H₂***), 2.77-2.86 (m, 1H, C***H***CH=CH_2), 2.56-2.64 (m, 1HC(O)C***H***), 1.90 (dd, 1H, *J* = 13.2 Hz, *J* = 7.6 Hz, HC(O)CHC***H$_A$***H_B), 1.72-1.85 (m, 2H, HC(O)CHCH_A***H$_B$*** and C***H$_A$***H_BCHCH=CH_2), 1.44 (dd, 1H, *J* = 13.2 Hz, *J* = 11.1 Hz, CH_A***H$_B$***CHCH=CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 203.4 (H***C***(O)), 139.5 (***C***H=CH_2), 115.2 (CH=***C***H_2), 59.2 (2C, 2 × O***C***H_3), 57.1 (2C, 2 × O***C***H_2), 46.9 (HC(O)***C***H), 45.3 (***C***HCH=CH_2), 39.1 (CH_2***C***CH_2), 32.8 (***C***H_2CHCH=CH_2), 22.3 (HC(O)CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2960 (C-H), 1733 (C=O), 1648 (C=C); **MS** (ES+) m/z (rel. intensity %) 235.16 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{20}NaO_3$ $[M+Na]^+$ 235.1310, found 235.1312.

Preparation and characterisation of *rac*-methyl (3*R*,4*S*)-3-formyl-1-propionyl-4-vinylcyclopentanecarboxylate (±)-269d

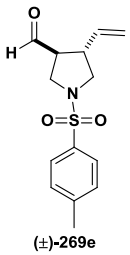


(±)-269d

Synthesised from compound **267i** (48.0 mg, 0.2 mmol) according to general procedure O. Compound **(±)-269d** (two diastereoisomers, 34.0 mg, 71%) was obtained as a colorless oil after flash column chromatography (PE/Et_2O = 2:1). Product **(±)-269d** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 6:5, as determined by ^{1}H NMR.

Two diastereoisomers: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.60 (d, 2H, *J* = 2.2 Hz, ***H***C(O), both), 5.70-5.80 (m, 2H, C***H***=CH_2, both), 5.05-5.14 (m, 4H, CH=C***H$_2$***, both), 3.75 (s, 6H, OC***H$_3$***, both), 2.40-2.75 (m, 14H, C***H***CH=CH_2 and HC(O)C***H*** and HC(O)CHC**H$_2$** and C***H$_A$***H_BCHCH=CH_2 and C***H$_2$***CH_3, both), 1.90-2.05 (m, 2H, CH_A***H$_B$***CHCH=CH_2, both), 1.08 (dt, 6H, *J* = 7.2 Hz, *J* = 2.2 Hz, CH_2C***H$_3$***, both); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 205.5 (CH_2***C***(O), one isomer), 205.3 (CH_2***C***(O), one isomer), 201.5 (2C, H***C***(O), both), 173.1 (***C***(O)OCH_3, one isomer), 173.0 (***C***(O)OCH_3, one isomer), 138.1 (2C, ***C***H=CH_2, both), 116.4 (2C, CH=***C***H_2, both), 65.1 ((O)C***C***C(O), one isomer), 64.9 ((O)C***C***C(O), one isomer), 56.2 (HC(O)***C***H, one isomer), 56.1 (HC(O)***C***H, one isomer), 52.9 (O***C***H_3, one isomer), 52.8 (O***C***H_3, one isomer), 45.0 (***C***HCH=CH_2, one isomer), 44.7 (***C***HCH=CH_2, one isomer), 39.3 (***C***H_2CHCH=CH_2, one isomer), 38.7 (***C***H_2CHCH=CH_2, one isomer), 32.4 (CH_3***C***H_2, one isomer), 32.2 (CH_3***C***H_2, one isomer), 31.8 (HC(O)CH***C***H_2, one isomer), 31.5 (HC(O)CH***C***H_2, one isomer), 8.3 (2C, CH_2***C***H_3, both); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2954 (C-H), 1715 (C=O), 1642 (C=C); **MS** (ES+) m/z (rel. intensity %) 261.14 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{13}H_{18}NaO_4$ $[M+Na]^+$ 261.1103, found 261.1103.

Preparation and characterisation of *rac*-(3*S*,4*S*)-1-[(4-methylphenyl)sulfonyl]-4-vinylpyrrolidine-3-carbaldehyde (±)-269e

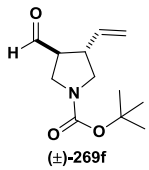


(±)-269e

Synthesised from compound **267k** (56.0 mg, 0.2 mmol) according to general procedure O. Compound **(±)-269e** (two diastereoisomers, 31 mg, 56%) was obtained as a colorless oil after flash column chromatography (PE/Et_2O = 1:1). Product **(±)-269e** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 10:1, as determined by ^{1}H NMR.

Major diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.53 (d, 1H, *J* = 1.8 Hz, ***H***C(O)), 7.73 (d, 2H, *J* = 8.3 Hz, 2 × Ar***H***), 7.36 (d, 2H, *J* = 8.0 Hz, 2 × Ar***H***), 5.61-5.70 (m, 1H, C***H***=CH_2), 5.10-5.15 (m, 2H, CH=C***H$_2$***), 3.45-3.60 (m, 3H, HC(O)CHC***H$_2$*** and C***H$_A$***H_BCHCH=CH_2), 3.05 (dd, 1H, *J* = 9.8 Hz, *J* = 7.9 Hz, CH_A***H$_B$***CHCH=CH_2), 2.91-2.99 (m, 1H, C***H***CH=CH_2), 2.73-2.79 (m, 1H, HC(O)C***H***), 2.46 (s, 3H, C***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 198.7 (H***C***(O)), 144.0 (***C***, Ar), 135.4 (***C***H=CH_2), 133.5 (***C***, Ar), 129.8 (2***C***H, Ar), 127.6 (2***C***H, Ar), 118.0 (CH=***C***H_2), 55.2 (HC(O)***C***HCH_2), 52.3 (***C***H_2CHCH=CH_2), 46.7 (HC(O)CH***C***H_2), 43.6 (***C***HCH=CH_2), 21.5 (***C***H_3). The ^{1}H NMR and ^{13}C NMR are identical with the previous report and show that the major isomer has *trans*-configuration.[147]

Preparation and characterisation of *rac*-*tert*-butyl (3*S*,4*S*)-3-formyl-4-vinylpyrrolidine-1-carboxylate (±)-269f



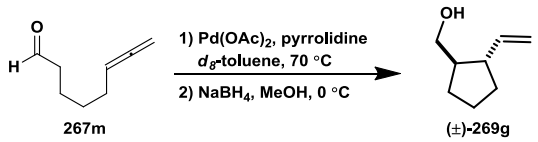
(±)-269f

Synthesised from compound **267l** (45.0 mg, 0.2 mmol) according to general procedure O. Compound **(±)-269f** (two diastereoisomers, 24 mg, 52%) was obtained as a colorless oil after flash column chromatography (PE/Et_2O = 1:1). Product **(±)-269f** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 11:1, as determined by ^{1}H NMR.

Major diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.66 (d, 1H, *J* = 2.0 Hz, ***H***C(O)), 5.76-5.83 (m, 1H, C***H***=CH_2), 5.16-5.22 (m, 2H, CH=C***H$_2$***), 3.60-3.66 (m, 1H, HC(O)CHC***H$_A$***H_B), 3.47-3.51 (m, 1H, C***H$_A$***H_BCHCH=CH_2), 3.19-3.24 (m, 1H, HC(O)CHCH_A***H$_B$***), 3.07 (m, 1H, CH_A***H$_B$***CHCH=CH_2), 2.32-2.34 (m, 1H, HC(O)C***H***), 2.21 (s,

1H, C***H***CH=CH_2), 1.46 (s, 9H, C(C***H*****3**)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.6 (H***C***(O)), 155.0 (N***C***(O)), 137.3 (***C***H=CH_2), 115.0 (CH=***C***H_2), 80.2 (***C***$(CH_3)_3$), 54.0 (N***C***H_2CHCH=CH_2), 48.0 (HC(O)***C***H_2), 44.9 (HC(O)CH***C***H_2), 40.2 (***C***HCH=CH_2), 28.6 (3C, ***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2976 (C-H), 2928 (C-H), 1726 (C=O), 1697 (C=O), 1646 (C=C); **MS** (ES+) m/z (rel. intensity %) 248.15 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{12}H_{19}NNaO_3$ $[M+Na]^+$ 248.1263, found 248.1265.

Preparation and characterisation of *rac*-[(1*R*,2*S*)-2-vinylcyclopentyl]methanol 269g

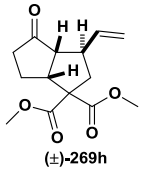


267m (±)-269g

To a solution of $Pd(OAc)_2$ (8.9 mg, 0.4 mmol) in d_8-toluene (0.4 mL) were added substrate **267m** (50.0 mg, 0.4 mmol) and pyrrolidine (10.0 µL, 0.12 mmol) and the reaction vial was sealed. The reaction mixture was stirred at 70 °C and monitored by TLC. After completion of the reaction, methanol was added. The reaction mixture was cooled to 0 °C. $NaBH_4$ (46 mg, 1.2 mmol) was added in several portions. After 5 min., the reaction mixture was diluted with diethyl ether, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (PE/Et_2O = 2:1) afforded compound **(±)-269g** (24.0 mg, 47% over two steps). Product **(±)-269g** was obtained as a single diastereoisomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.85-5.89 (m, 1H, C***H***=CH_2), 4.94-5.07 (m, 2H, CH=C***H*****$_2$**), 3.66 (dd, 1H, *J* = 11.1 Hz, *J* = 7.6 Hz, HOC***H*****$_A$**H_B), 3.55 (dd, 1H, *J* = 11.1 Hz, *J* = 6.5 Hz, $HOCH_A$***H*****$_B$**), 2.70 (“q”, 1H, *J* = 7.4 Hz, O***H***), 2.12-2.18 (m, 1H, $HOCH_2$C***H***), 1.31-1.88 (m, 7H, C***H***CH=CH_2 and 3 × C***H*****$_2$**). The ^{1}H NMR is identical with the previous report and show that the major isomer has *trans*-configuration.[184]

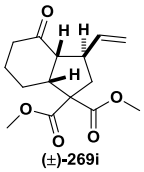
Preparation and characterisation of *rac*-dimethyl (3*R*,3a*R*,6a*R*)-4-oxo-3-vinylhexahydropentalene-1,1(2*H*)-dicarboxylate (±)-269h


(±)-269h

Synthesised from compound **267f** (54.0 mg, 0.2 mmol) according to general procedure O. Compound **(±)-269h** (two diastereoisomers, 40 mg, 75%) was obtained as a colorless oil after flash column chromatography (PE/Et_2O = 4:1). Product **(±)-269h** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 14:1, as determined by ^{1}H NMR.

Major diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.75 (ddd, 1H, *J* = 17.1 Hz, *J* = 10.2 Hz, *J* = 6.9 Hz, C***H***=CH_2), 5.01-5.10 (m, 2H, CH=C***H$_2$***), 3.76 (s, 6H, 2 × OC***H$_3$***), 3.50-3.59 (m, 1H, C(O)CHC***H***), 2.76-2.89 (m, 2H, C***H***CH=CH_2 and C***H$_A$***H_BCHCH=CH_2), 2.66 (t, 1H, *J* = 8.1 Hz, C***H***C(O)), 2.25-2.42 (m, 2H, CH_A***H$_B$***CHCH=CH_2 and C***H$_A$***H_BC(O)), 1.99-2.12 (m, 2H, C***H$_A$***$H_B$$CH_2$C(O) and CH_A***H$_B$***C(O)), 1.59-1.65 (m, 1H, CH_A***H$_B$***CH_2C(O)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 217.8 (C=O), 172.2 (***C***(O)OCH_3), 170.5 (***C***(O)OCH_3), 139.3 (***C***H=CH_2), 115.2 (CH=***C***H_2), 63.4 ((O)C***C***C(O)), 57.6 (C(O)***C***HCH), 52.9 (O***C***H_3), 52.5 (O***C***H_3), 47.4 (***C***HCH=CH_2), 44.7 (C(O)CH***C***H), 40.1 (***C***H_2C(O)), 38.4 (***C***H_2CHCH=CH_2), 23.5 (***C***$H_2$$CH_2$C(O)); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2956 (C-H), 1732 (C=O), 1640 (C=C); **MS** (ES+) m/z (rel. intensity %) 289.14 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{19}H_{22}NaO_6$ $[M+Na]^+$ 289.10452, found 289.1050.

Preparation and characterisation of *rac*-dimethyl (3*R*,3a*R*,7a*R*)-4-oxo-3-vinyloctahydro-1*H*-indene-1,1-dicarboxylate (±)-269i

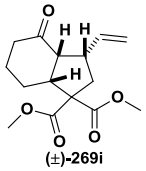

(±)-269i

Synthesised from compound **267h** (56.0 mg, 0.2 mmol) according to general procedure O. Compound **(±)-269i** (two diastereoisomers, 40.0 mg, 75%) was obtained as a colourless oil

after flash column chromatography (PE/Et_2O = 4:1). Product **(±)-269i** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 2:1, as determined by ^{1}H NMR.

Major diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.80-5.89 (m, 1H, C***H***=CH_2), 5.14 (td, 1H, *J* = 17.2 Hz, *J* = 1.3 Hz, CH=C***H***$_A$H$_B$), 5.00-5.02 (m, 1H, CH=CH$_A$***H***$_B$), 3.77 (s, 3H, OC***H***$_3$), 3.74 (s, 3H, OC***H***$_3$), 2.87-2.92 (m, 1H, C(O)CHC***H***), 2.52 (ddd, 1H, *J* = 13.6 Hz, *J* = 10.1 Hz, *J* = 0.9 Hz, C***H***CH=CH_2), 2.34-2.43 (m, 3H, C(O)C***H*** and C***H***$_A$H$_B$CHCH=CH_2 and C(O)C***H***$_A$H$_B$), 2.11-2.29 (m, 4H, CH$_A$***H***$_B$CHCH=CH_2 and C(O)CH$_A$***H***$_B$ and CHC***H***$_2$), 1.63-1.75 (m, 1H, C(O)CH_2C***H***$_A$H$_B$), 1.29-1.39 (m, 1H, C(O)CH_2CH$_A$***H***$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 209.1 (***C***=O), 171.9 (***C***(O)OCH_3), 171.6 (***C***(O)OCH_3), 139.6 (***C***H=CH_2), 115.0 (CH=***C***H_2), 61.2 ((O)C***C***C(O)), 59.4 (C(O)***C***HCH), 52.9 (O***C***H_3), 52.6 (O***C***H_3), 52.4 (***C***HCH=CH_2), 41.5 (C(O)CH***C***H), 39.8 (C(O)***C***H_2), 38.1 (***C***H_2CHCH=CH_2), 27.7 (CH***C***H_2), 26.9 (C(O)CH_2***C***H_2);

Minor diastereoisomer: ***rac*-dimethyl (3*S*,3a*R*,7a*R*)-4-oxo-3-vinyloctahydro-1*H*-indene-1,1-dicarboxylate (±)-269i**

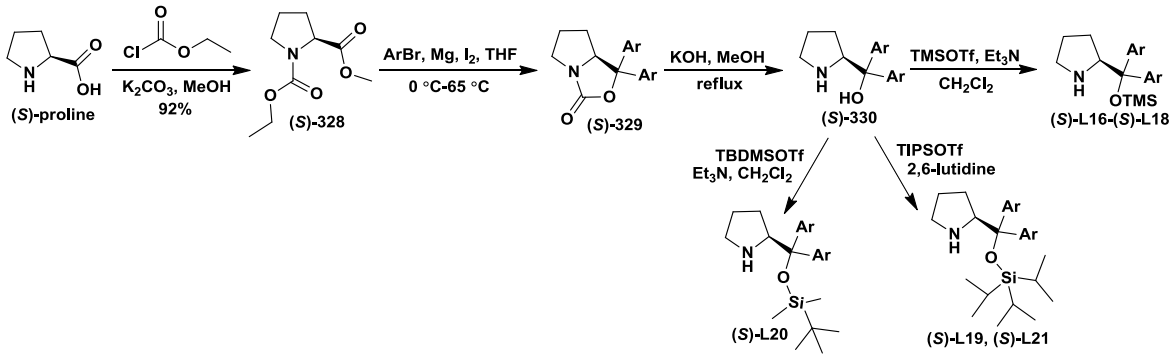


(±)-269i

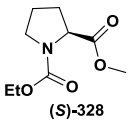
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.50-5.74 (m, 1H, C***H***=CH_2), 4.98-5.08 (m, 2H, CH=C***H***$_2$), 3.74 (s, 6H, 2 × OC***H***$_3$), 3.16-3.26 (m, 1H, C(O)CHC***H***), 2.93-3.06 (m, 2H, C(O)C***H*** and C***H***CH=CH_2), 2.61-2.67 (m, 1H, C***H***$_A$H$_B$CHCH=CH_2), 2.43-2.49 (m, 1H, C***H***$_A$H$_B$C(O)), 2.32-2.35 (m, 2H, CH$_A$***H***$_B$CHCH=CH_2 and CH$_A$***H***$_B$C(O)), 1.97-2.06 (m, 1H, C(O)CH_2C***H***$_A$H$_B$), 1.89-1.94 (m, 1H, C(O)CH_2CH$_A$***H***$_B$), 1.64-1.75 (m, 1H, CHC***H***$_A$H$_B$), 1.37-1.48 (m. 1H, CHCH$_A$***H***$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 210.4 (***C***=O), 172.1 (***C***(O)OCH_3), 170.2 (***C***(O)OCH_3), 138.8 (***C***H=CH_2), 115.6 (CH=***C***H_2), 63.5 ((O)C***C***C(O)), 58.7 (C(O)***C***HCH), 52.9 (O***C***H_3), 52.5 (O***C***H_3), 47.6 (***C***HCH=CH_2), 45.0 (C(O)CH***C***H), 38.1 (C(O)***C***H_2), 36.1 (***C***H_2CHCH=CH_2), 24.1 (CH***C***H_2), 23.6 (C(O)CH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2953 (C-H),

1732 (C=O), 1707 (C=O), 1641 (C=C); **MS** (ES+) m/z (rel. intensity %) 303.13 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{15}H_{20}NaO_5$ $[M+Na]^+$ 303.1208, found 303.1205.

6.2.3.10 Synthesis of chiral secondary amines



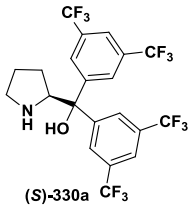
6.2.3.10.1 Preparation and characterisation of (2*S*)-1-ethyl-2-methyl pyrrolidine-1,2-dicarboxylate (*S*)-328[183]



To a stirred suspension of (*S*)-proline (5.75 g, 0.05 mol) and potassium carbonate (6.9 g, 0.05 mol) in anhydrous methanol (50 mL) at 0 °C was added ethyl chloroformate (11 mL, 0.115 mol). The resulting reaction mixture was then stirred at room temperature for 12 h. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was filtered and the filtrate was concentrated, diluted with diethyl ether, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (PE/Et_2O = 3:1) on silica gel to afford the product **(*S*)-328** (9.3 g, 92%).

Two rotamers: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.35 (dd, one rotamer, 1H, J = 8.7 Hz, J = 3.5 Hz), 4.28 (dd, one rotamer, 1H, J = 8.7 Hz, J = 3.7 Hz), 4.05-4.20 (m, both, 4H), 3.72 (s, one rotamer, 3H), 3.70 (s, one rotamer, 3H), 3.41-3.59 (m, both, 4H), 2.15-2.25 (m, both, 2H), 1.86-2.01 (m, both, 6H), 1.25 (t, one rotamer, 3H, J = 7.1 Hz), 1.18 (t, one rotamer, 3H, J = 7.1 Hz). Analytical data in agreement with the previous report.[183]

6.2.3.10.2 Preparation and characterisation of bis[3,5-bis(trifluoromethyl)phenyl][(2*S*)-pyrrolidin-2-yl]methanol (*S*)-330a[157,184]



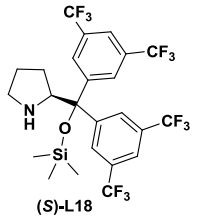
(*S*)-330a

Magnesium turnings (1.15 g, 48 mmol) were added into a 250 mL three-necked flsak fitted with a dropping funnel and stirred for 10 min. 1-Bromo-3,5-bis(trifluoromethyl)benzene (11.7 g, 40 mmol) in THF (100 mL) were introduced into the dropping funnel and added dropwise over 30 min. The resulting mixture was heated at reflux for 2 h. The Grignard reagent in THF (100 mL) was transferred dropwise at 0 °C via cunnula to a solution of **(*S*)-328** (2.75 g, 13.6 mmol) in THF (50 mL). The resulting reaction mixture was warmed up to room temperature and gradually heated to 65 °C. After keeping stirring for 16 h, the reaction was quenched with sat. aq. NH_4Cl and extracted with diethyl ether. The extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in MeOH (60 mL) and DMSO (20 mL) and then freshly crushed potassium hydroxide (3.05 g, 54 mmol) was added at room temperature. The reaction mixture was heated at reflux for 24 h. On completion, the reaction mixture was concentrated and dissolved in water. The aqueous solution was extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was then purified by flash column chromatography on silica gel (PE/EA = 5:1) to afford (2*S*)-bis(3,5-trifluoromethyl)phenyl(pyrrolidi-2-yl)methanol **(*S*)-330a** (2.5 g, 31% over two steps) as an off-white solid.[184]

$[\alpha]_D^{25}$ = - 55.0 (*c* 1.0, $CHCl_3$); **Mp** 119-123 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.05 (s, 2H, 2 × Ar***H***), 7.96 (s, 2H, 2 × Ar***H***), 7.77 (s, 2H, 2 × Ar***H***), 5.10 (br s, 1H, N***H***), 4.37 (t, 1H, *J* = 7.7 Hz, C***H***), 3.02-3.10 (m, 2H, NC***H₂***), 1.74-1.83 (m, 2H, NCH_2C***H₂***), 1.50-1.61 (m, 2H, NCHC***H₂***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 149.4 (***C***, Ar), 146.4 (***C***, Ar), 132.1 (q, $^2J_{C,F}$ =

33.1 Hz, 2***C***, Ar), 131.8 (q, $^{2}J_{C,F}$ = 33.1 Hz, 2***C***, Ar), 126.2 (q, $^{3}J_{C,F}$ = 2.4 Hz, 2***C***H, Ar), 125.6 (q, $^{3}J_{C,F}$ = 2.5 Hz, 2***C***H, Ar), 123.4 (q, $^{1}J_{C,F}$ = 271.4 Hz, 4***C***, ***C***F_3), 121.8 (hept., $^{3}J_{C,F}$ = 3.5 Hz, ***C***H, Ar), 121.5 (hept., $^{2}J_{C,F}$ = 3.7 Hz, ***C***H, Ar), 119.1 (***C***-O), 64.2 (N***C***H), 46.9 (N***C***H_2), 26.7 (NCH***C***H_2), 25.5 (NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3384 (O-H), 2979 (C-H), 2980 (C-H), 1684 (C=C), 1569 (C=C), 1371 (C-N), 1279 (C-O); **MS** (ES+) m/z (rel. intensity %) 526.12 ($M + H^+$, 100); **HRMS** (ESI+) calcd. for $C_{21}H_{16}F_{12}NO$ $[M+H]^+$ 526.1040, found 526.1043.

6.2.3.10.3 Preparation and characterisation of (2*S*)-2-{bis[3,5 bis(trifluoromethyl)phenyl][(trimethylsilyl)oxy]methyl}pyrrolidine (*S*)-L18 [157]



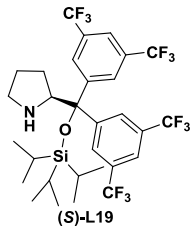
(*S*)-L18

To a stirred solution of **(*S*)-330a** (1.05 g, 2.0 mmol) and triethylamine (0.85 mL, 6.0 mmol) in anhydrous dichloromethane (8 mL) at 0 °C was added trimethylsilyl trifuloromethanesulfonate (0.55 mL, 3.0 mmol). The resulting reaction mixture was warmed up to room temperature and stirred for 12 h. The reaction was concentrated, diluted with water and then extracted three times with diethyl ether. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 15:1) to afford product **(*S*)-L18** (966 mg, 84%).

$[\alpha]_D^{25}$ = - 7.5 (*c* 1.1, CH_2Cl_2); **Mp** 50-56 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.02 (s, 2H, 2 × Ar***H***), 7.84 (s, 2H, 2 × Ar***H***), 7.77 (s, 2H, 2 × Ar***H***), 4.23 (t, 1H, *J* = 7.2 Hz, C***H***), 2.90-2.96 (m, 1H, NC***H***$_A$$H_B$), 2.54-2.60 (m, 1H, NCH_A***H***$_B$), 1.66-1.73 (m, 1H, NCHC***H***$_A$$H_B$), 1.43-1.56 (m, 2H, $NCHCH_A$***H***$_B$ and NCH_2C***H***$_A$$H_B$), 1.07-1.67 (m, 1H, NCH_2CH_A***H***$_B$), - 0.07 (s, 9H, Si(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 148.1 (***C***, Ar), 146.3 (***C***, Ar), 131.7 (q, $^{2}J_{C,F}$ = 33.4 Hz, 2***C***, Ar), 131.3 (q, $^{2}J_{C,F}$ = 33.4 Hz, 2***C***, Ar), 128.9 (q, $^{3}J_{C,F}$ = 3.1 Hz, 2***C***H, Ar), 128.3 (q, $^{2}J_{C,F}$ = 3.1 Hz, 2***C***H, Ar), 123.7 (q, $^{1}J_{C,F}$ = 271 Hz, 2***C***, ***C***F_3), 123.1 (q, $^{1}J_{C,F}$ = 271 Hz, 2***C***,

CF_3), 121.9 (hept., $^3J_{C,F}$ = 3.8 Hz, ***C***H, Ar), 121.7 (hept., $^3J_{C,F}$ = 3.8 Hz, ***C***H, Ar), 82.3 (***C***-O), 64.2 (N***C***H), 47.2 (N***C***H_2), 27.5 (NCH***C***H_2), 25.2 (NCH_2***C***H_2), 1.84 (3C, Si(***C***H_3)$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2962 (C-H), 2880 (C-H), 1624 (C=C of aromatic ring), 1508 (C=C of aromatic ring), 1257 (C-N); **MS** (ES+) m/z (rel. intensity %) 598.13 (M + H^+, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{24}F_{12}NOSi$ $[M+H]^+$ 598.1430, found 598.1437.

6.2.3.10.4 Preparation and characterisation of (2*S*)-2-{bis[3,5-bis(trifluoromethyl)phenyl][(triisopropylsilyl)oxy]methyl}pyrrolidine (*S*)-L19[157]



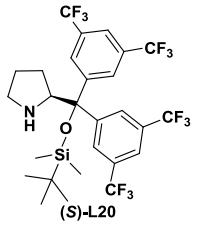
(*S*)-L19

To a stirred solution of **(*S*)-330a** (0.53 g, 1.0 mmol) and 2,6-lutidine (0.58 mL, 5.0 mmol) in anhydrous dichloromethane (2 mL) at 0 °C was added triisopropylsilyl trifuloromethanesulfonate (0.81 mL, 3.0 mmol). The resulting reaction mixture was heated at reflux for 24 h. The reaction was concentrated, diluted with water and then extracted three times with diethyl ether. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 20:1) to afford product **(*S*)-L19** (550 mg, 81%).

$[\alpha]_D^{25}$ = - 28.5 (*c* 1.5, CH_2Cl_2); **Mp** 89-95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.13 (s, 2H, 2 × Ar***H***), 7.86 (s, 2H, 2 × Ar***H***), 7.79 (s, 2H, 2 × Ar***H***), 4.37 (dd, 1H, *J* = 8.2 Hz, *J* = 5.6 Hz, C***H***), 2.85-2.90 (m, 1H, NC***H***$_A$$H_B$), 2.42-2.48 (m, 1H, NC$H_A$***H***$_B$), 1.87-1.94 (m, 1H, NCHC***H***$_A$$H_B$), 1.77 (s, 1H, N***H***), 1.40-1.51 (m, 2H, NCHCH_A***H***$_B$ and NCH_2C***H***$_A$$H_B$), 0.94 (dd, 18H, *J* = 11.1 Hz, *J* = 7.4 Hz, Si(CH(C***H***$_3$)$_2$)$_3$), 0.72-0.82 (m, 4H, Si(C***H***$(CH_3)_2)_3$ and NCH_2CH_A***H***$_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.5 (***C***, Ar), 145.7 (***C***, Ar), 131.5 (q, $^2J_{C,F}$ = 33.4 Hz, 2***C***, Ar), 131.2 (q, $^2J_{C,F}$ = 33.4 Hz, 2***C***, Ar), 129.8 (q, $^3J_{C,F}$ = 3.1 Hz, 2***C***H, Ar), 129.3 (q, $^2J_{C,F}$ = 3.1 Hz, 2***C***H, Ar), 124.8 (q, $^1J_{C,F}$ = 271.4 Hz, 2***C***, ***C***F_3), 124.4 (q, $^1J_{C,F}$ = 271.4 Hz, 2***C***, ***C***F_3), 122.1

(hept., $^{3}J_{C,F}$ = 3.8 Hz, ***C***H, Ar), 121.9 (hept., $^{3}J_{C,F}$ = 3.8 Hz, ***C***H, Ar), 82.7 (***C***-O), 64.4 (N***C***H), 47.2 (N***C***H_2), 28.0 (NCH***C***H_2), 25.5 (NCH_2***C***H_2), 18.1 (3C, Si(***C***H(CH_3)$_2$)$_3$), 13.4 (6C, Si(CH(***C***H_3)$_2$)$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2951 (C-H), 2872 (C-H), 1622 (C=C of aromatic ring), 1465 (C=C of aromatic ring), 1278 (C-N); **MS** (ES+) m/z (rel. intensity %) 682.22 (M + H^+, 100); **HRMS** (ESI+) calcd. for $C_{30}H_{36}F_{12}NOSi$ $[M+H]^+$ 682.2369, found 682.2376.

6.2.3.10.5 Preparation and characterisation of (2*S*)-2(bis[3,5bis(trifluoromethyl)phenyl]{[*tert*butyl(dimethyl)silyl]oxy}methyl)pyrrolidine (*S*)-L20 [157]



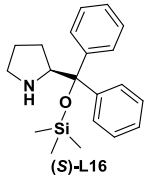
(*S*)-L20

To a stirred solution of **(*S*)-330a** (0.57 g, 1.09 mmol) and triethylamine (0.91 mL, 6.5 mmol) in anhydrous dichloromethane (3 mL) at 0 °C was added *tert*-butyldimethylsilyl trifuloromethanesulfonate (0.75 mL, 3.27 mmol). The resulting reaction mixture was heated at reflux for 20 h. The reaction was concentrated, diluted with water and then extracted three times with diethyl ether. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 50:1) to afford product **(*S*)-L20** (180 mg, 28%).

$[\alpha]_D^{25}$ = - 19.6 (*c* 1.5, CH_2Cl_2); **Mp** 105-109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.11 (s, 2H, 2 × Ar***H***), 7.86 (s, 2H, 2 × Ar***H***), 7.75 (s, 2H, 2 × Ar***H***), 4.25 (dd, 1H, *J* = 8.0 Hz, *J* = 6.0 Hz, NC***H***), 2.88-2.94 (m, 1H, NC***H$_A$***H$_B$), 2.52-2.57 (m, 1H, NCH$_A$***H$_B$***), 1.75-1.81 (m, 2H, N***H*** and NCHC***H$_A$***H$_B$), 1.45-1.52 (m, 2H, NCHCH$_A$***H$_B$*** and NCH$_2$C***H$_A$***H$_B$), 0.96 (brs, 10H, NCH$_2$CH$_A$***H$_B$*** and SiC(C***H$_3$***)$_3$)), - 0.19 (s, 3H, SiC***H$_3$***), - 0.46 (s, 3H, SiC***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.0 (***C***, Ar), 145.9 (***C***, Ar), 131.8 (q, $^{2}J_{C,F}$ = 33.0 Hz, 2***C***, Ar), 131.4 (q, $^{2}J_{C,F}$ = 33.0 Hz, 2***C***, Ar), 129.0 (q, $^{3}J_{C,F}$ = 3.4 Hz, 2***C***H, Ar), 128.5 (q, $^{2}J_{C,F}$ = 3.4 Hz, 2***C***H, Ar),

124.3 (q, $^{1}J_{C,F}$ = 270.0 Hz, 2***C***, ***C***F_3), 124.0 (q, $^{1}J_{C,F}$ = 270.0 Hz, 2***C***, ***C***F_3), 122.2 (hept., $^{3}J_{C,F}$ = 3.2 Hz, ***C***H, Ar), 121.6 (hept., $^{3}J_{C,F}$ = 3.2 Hz, ***C***H, Ar), 82.5 (***C***-O), 64.3 (N***C***H), 47.0 (N***C***H_2), 28.2 (NCH***C***H_2), 25.6 (NCH_2***C***H_2), 24.8 (3C, SiC(***C***$H_3)_3$), 18.2 (Si***C***$(CH_3)_3$), -2.0 (2C, Si(***C***$H_3)_2$); **FT-IR** ν_{max}(NaCl)/cm^{-11} 2958 (C-H), 2887 (C-H), 1623 (C=C of aromatic ring), 1472 (C=C of aromatic ring), 1278 (C-N); **MS** (ES+) m/z (rel. intensity %) 640.18 (M + H^+, 100); **HRMS** (ESI+) calcd. for $C_{27}H_{30}F_{12}NOSi$ $[M+H]^+$ 640.1900, found 640.1907.

6.2.3.10.6 Preparation and characterisation of (2*S*)-2 {diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine (*S*)-L16 [185]

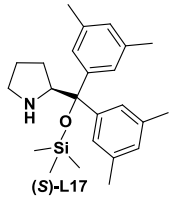


(*S*)-L16

Synthesised from **(*S*)-328** (2.01 g, 10 mmol) and phenyl magnesiumbromide (14 mL, 40 mmol) according to the procedure for synthesis of compound **L18**. Compound **(*S*)-L16** (1.6 g, 51% over three steps) was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow oil.

$[\alpha]_D^{25}$ = - 32.8 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.46-7.48 (m, 2H, 2 × Ar***H***), 7.36-7.38 (m, 2H, 2 × Ar***H***), 7.21-7.31 (m, 6H, 6 × Ar***H***), 4.05 (t, 1H, *J* = 7.4 Hz, C***H***), 2.77-2.89 (m, 2H, NC***H₂***), 1.72 (s, 1H, N***H***), 1.53-1.63 (m, 3H, NCHC***H₂*** and $NCH_2C\boldsymbol{H_A}H_B$), 1.35-1.42 (m, 1H, $NCH_2CH_A\boldsymbol{H_B}$), - 0.08 (s, 9H, Si(C***H₃***)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 146.8 (***C***, Ar), 145.8 (***C***, Ar), 128.4 (2***C***H, Ar), 127.6 (2***C***H, Ar), 127.5 (2***C***H, Ar), 126.8 (2***C***H, Ar), 126.7 (2***C***H, Ar), 83.1 (***C***-O), 65.4 (N***C***H), 47.1 (N***C***H_2), 27.5 (NCH***C***H_2), 25.0 (NCH_2***C***H_2), 2.10 (3C, Si(***C***$H_3)_3$). Analytical data in agreement with the previous report.[186]

6.2.3.10.7 Preparation and characterisation of (2*S*)-2-{bis(3,5-dimethylphenyl)[(trimethylsilyl)oxy]methyl}pyrrolidine (*S*)-L17 [185]

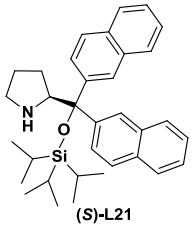


(*S*)-L17

Synthesised from **(*S*)-328** (1.84 g, 9.2 mmol) and 1-bromo-3,5-dimethylbenzene (5.55 g, 30 mmol) magnesium (0.86 g, 36.0 mmol) according to the procedure for synthesis of compound **(*S*)-L18**. Compound **(*S*)-L17** (1.5 g, 45% over three steps) was obtained after flash column chromatography on silica gel (PE/EA = 5:1) as a yellow oil.

$[\alpha]_D^{25}$ = - 75.2 (*c* 1.5, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.07 (s, 2H, 2 × Ar***H***), 6.99 (s, 2H, 2 × Ar***H***), 6.87 (d, *J* = 8.0 Hz, 2H, 2 × Ar***H***), 4.01 (t, *J* = 7.4 Hz, 1H, C***H***), 2.80-2.91 (m, 2H, NC**H$_2$**), 2.31 (s, 6H, 2 × C***H$_3$***), 2.98 (s, 6H, 2 × C***H$_3$***), 1.75 (s, 1H, N***H***), 1.55-1.66 (m, 3H, NCHC***H$_2$*** and $NCH_2C\boldsymbol{H_A}H_B$), 1.42-1.48 (m, 1H, $NCH_2CH_A\boldsymbol{H_B}$), - 0.05 (s, 9H, $Si(C\boldsymbol{H_3})_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 146.8 (***C***, Ar), 145.8 (***C***, Ar), 136.7 (4***C***, Ar), 128.4 (2***C***H, Ar), 126.0 (2***C***H, Ar), 125.3 (2***C***H, Ar), 83.3 (***C***-O), 65.4 (N***C***H), 47.1 (N***C***H_2), 27.5 (NCH***C***H_2), 25.1 ($NCH_2\boldsymbol{C}H_2$), 21.5 (4C, 4 × ***C***H_3), 2.27 (3C, $Si(\boldsymbol{C}H_3)_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2954 (C-H), 2868 (C-H), 1603 (C=C of aromatic ring), 1458 (C=C of aromatic ring), 1248 (C-N); **MS** (ES+) m/z (rel. intensity %) 382.27 (M + H$^+$, 100); **HRMS** (ESI+) calcd. for $C_{24}H_{36}NOSi$ $[M+H]^+$ 382.2561, found 382.2550.

6.2.3.10.8 Preparation and characterisation of (2*S*)-2-{di-2-naphthyl[(triisopropylsilyl)oxy]methyl}pyrrolidine (*S*)-L21[157]

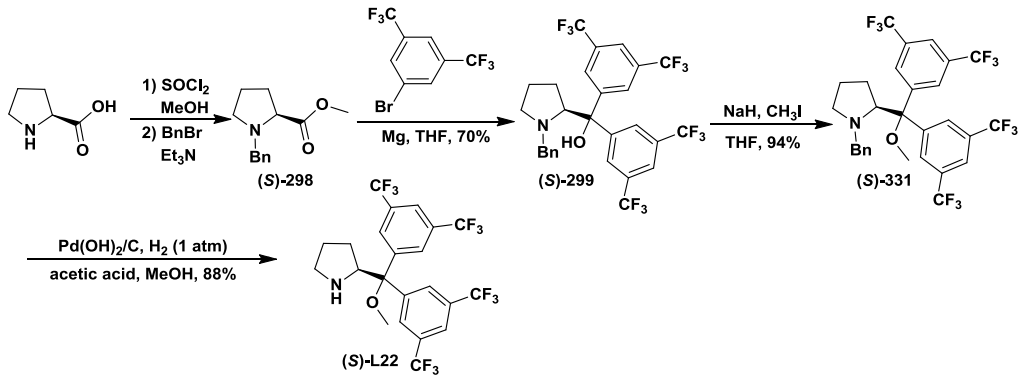


(*S*)-L21

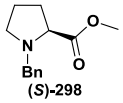
Synthesised from **(*S*)-328** (1.90 g, 9.5 mmol) and 2-bromo-naphthalene (6.2 g, 30 mmol) and magnesium (1.44 g, 60 mmol) according the procedure for synthesis of compound **(*S*)-L19**. Compound **(*S*)-L21** (1.7 g, 36% over three steps) was obtained after flash column chromatography on silica gel (PE/EA = 5:1).

$[\alpha]_D^{25}$ = - 65.9 (*c* 1.0, CH_2Cl_2); **Mp** 65-69 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.21 (s, 1H, Ar***H***), 8.12 (s, 1H, Ar***H***), 7.82-7.88 (m, 4H, 4 × Ar***H***), 7.74 (s, 1H, Ar***H***), 7.72 (s, 1H, Ar***H***), 7.49-7.55 (m, 5H, 5 × Ar***H***), 7.40 (dd, *J* = 8.7 Hz, *J* = 1.6 Hz, 1H, Ar***H***), 4.42 (t, *J* = 7.4 Hz, 1H, C***H***), 2.82-2.88 (m, 1H, NC$\boldsymbol{H_A}H_B$), 2.52-2.58 (m, 1H, $NCH_A\boldsymbol{H_B}$), 1.86-1.94 (m, 1H, NCHC$\boldsymbol{H_A}H_B$), 1.75-1.84 (m, 1H, $NCHCH_A\boldsymbol{H_B}$), 1.49-1.60 (m, 1H, $NCH_2C\boldsymbol{H_A}H_B$), 1.08-1.18 (m, 1H, $NCH_2CH_A\boldsymbol{H_B}$), 0.86-1.00 (m, 21H, Si(C***H***(C$\boldsymbol{H_3}$)$_2$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 143.2 (***C***, Ar), 142.3 (***C***, Ar), 132.6 (***C***, Ar), 132.5 (***C***, Ar), 128.5 (2***C***, Ar), 128.0 (2***C***H, Ar), 127.9 (***C***H, Ar), 127.7 (***C***H, Ar), 127.5 (***C***H, Ar), 127.4 (2***C***H, Ar), 127.1 (***C***H, Ar), 126.4 (***C***H, Ar), 126.1 (***C***H, Ar), 125.9 (2***C***H, Ar), 125.8 (2***C***H, Ar), 83.9 (***C***-O), 65.8 (N***C***H), 47.2 ($N\boldsymbol{C}H_2$), 28.1 (NCH$\boldsymbol{C}H_2$), 25.3 ($NCH_2\boldsymbol{C}H_2$), 18.5 (6C, 6 × $\boldsymbol{C}H_3$), 13.8 (3C, 3 × ***C***H$(CH_3)_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3020 (C=C-H), 2890 (C-H), 1245 (C-N); **MS** (ES+) m/z (rel. intensity %) 510.30 (M + H$^+$, 100); **HRMS** (ESI+) calcd. for $C_{34}H_{43}NOSi$ $[M+H]^+$ 510.3187, found 510.3175.

6.2.3.11 Synthesis of (2*S*)-2-{bis[3,5-bis(trifluoromethyl)phenyl](methoxy)methyl}pyrrolidine (*S*)-L22[157, 160-162]



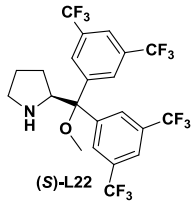
6.2.3.11.1 Preparation and characterisation of (*S*)-methyl 1-benzyl-*L*-prolinate (*S*)-298[160]



(*S*)-298

Thionyl chloride (5 mL, 60 mmol) was added dropwise into *L*-proline (5.8 g, 50 mmol) in MeOH (25 mL) at 0 °C. The reaction mixture was heated to reflux for 2 h. The solvent was removed at reduced pressure. The residue was dissolved in ethyl acetate (100 mL). Triethylamine (16 mL) was added at 0 °C and then benzylbromide (6 mL) was added. The reaction mixture was stirred for 16 h. on completion, water was added. The aqueous phase was extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/EA = 6:1) to afford product **(*S*)-298** (10.0 g, 45 mmol, 90%) as a colourless oil.

6.2.3.11.2 Preparation and characterisation of (2*S*)-2-{bis[3,5-bis(trifluoromethyl)phenyl](methoxy)methyl}pyrrolidine (*S*)-L22



(*S*)-L22

Magnesium turnings (0.45 g, 18.6 mmol) were added into a 100 mL three-necked flsak fitted with a dropping funnel and stirred for 10 min. 1-Bromo-3,5-bis(trifluoromethyl)benzene (4.2 g, 14.3 mmol) in THF (23 mL) were introduced into the dropping funnel and added dropwise over 30 min. The resulting mixture was heated to reflux and stirred for 1 h. The Grignard reagent in THF (23 mL) was transferred dropwise at 0 °C via cunnula to a solution of compound *N*-benzyl-(*S*)-proline methyl ester **(*S*)-298** (1.26 g, 5.78 mmol) in THF (5 mL). The reaction mixture was allowed to proceed for 12 h at room temperature. The mixture was diluted with diethyl ether, quenched with sat. aq. NH_4Cl and the organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 40:1) to provide product **(*S*)-299** (2.5 g, 70%).[157]

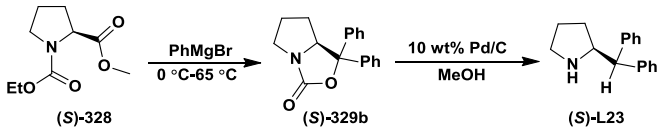
To a suspension of NaH (276 mg, 6.0 mmol, 60% dispersion in mineral oil) in THF (10 mL) was added **(*S*)-299** (2.49 g, 4.06 mmol) in THF (5 mL) at 0 °C. The resulting mixture was stirred for 30 min. Iodomethane (0.30 mL, 4.9 mmol) was added dropwise and the reaction was stirred for 16 h. When TLC indicated that the reaction was complete, the reaction was quenched with water, extracted three times with diethyl ether. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash column chromatography on silica gel (PE/Et_2O = 50:1) afforded product **(*S*)-331** (2.4 g, 94%).[161]

(*S*)-331 (2.4 g, 3.8 mmol) was dissolved in MeOH (118 mL) at room temperature. $Pd(OH)_2$/C (20 wt%, 0.48 g) and acetic acid (0.24 mL, 4.14 mmol) were added subsequently. The reaction mixture was stirred for 15 h under H_2 (1 atm). The reaction was monitored by TLC. On completion, the reaction mixture was filtered through Celite with sufficient rinsing (methanol). The filtrate was concentrated and dissolved in diethyl ether. The organic solution was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 9:1) to give product **(*S*)-L22** (1.8 g, 88%) as a yellow oil.[162]

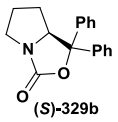
$[\alpha]_D^{25}$ = - 32.5 (*c* 1.5, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.99 (s, 2H, 2 × Ar***H***), 7.90 (s, 2H, 2 × Ar***H***), 7.86 (s, 2H, 2 × Ar***H***), 4.31 (dd, *J* = 8.3 Hz, *J* = 6.3 Hz, 1H, NC***H***), 3.12 (s, 3H, OC***H*****$_3$**), 2.82-2.88 (m, 1H, NC***H*****$_A$**H_B), 2.24-2.29 (m, 1H, NCH_A***H*****$_B$**), 1.90-1.97 (m, 1H, NCHC***H*****$_A$**H_B), 1.72 (s, 1H, N***H***), 1.45-1.53 (m, 2H, $NCHCH_A$***H*****$_B$** and NCH_2C***H*****$_A$**H_B), 1.03-1.12 (m, 1H, NCH_2CH_A***H*****$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 145.2 (***C***, Ar), 143.2 (***C***, Ar), 132.0 (q, $^2J_{C,F}$ = 33.1 Hz, 2***C***, Ar), 131.8 (q, $^2J_{C,F}$ = 33.0 Hz, 2***C***, Ar), 129.2 (q, $^3J_{C,F}$ = 3.4 Hz, 2***C***H, Ar), 128.9 (q, $^3J_{C,F}$ = 3.4 Hz, 2***C***H, Ar), 124.6 (q, $^1J_{C,F}$ = 150.0 Hz, 4C, ***C***F_3), 121.9 (hept., $^3J_{C,F}$ = 3.4 Hz, ***C***H, Ar), 121.4 (hept., $^3J_{C,F}$ = 3.7 Hz, ***C***H, Ar), 84.2 (***C***-O), 61.5 (N***C***H), 51.7 (O***C***H_3), 47.1 (N***C***H_2), 27.4 (NCH***C***H_2), 25.9 (NCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2970 (C-H), 1624 (C=C of Ph), 1466 (C=C of Ph), 1374 (C-O), 1279 (C-N); **MS** (ES+) m/z (rel.

intensity %) 540.09 (M + H^+, 100); **HRMS** (ESI+) calcd. for $C_{22}H_{18}F_{12}NO$ $[M+H]^+$ 540.1191, found 540.1189.

6.2.3.12 Synthesis of (2*S*)-2-(diphenylmethyl)pyrrolidine (*S*)-L23[158]



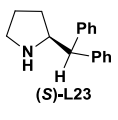
6.2.3.12.1 Preparation and characterisation of (7a*S*)-1,1-diphenyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (*S*)-329b[158]



Phenylmagnesium bromide (3.0 mol/L in Et_2O, 7.0 mL) was added dropwise at 0 °C to a solution of compound **(*S*)-328** (2.0 g, 10.0 mmol) in THF (50 mL). The resulting reaction mixture was warmed up to room temperature and gradually heated to 65 °C. After keeping stirring for 15 h, the reaction was quenched with sat. aq. NH_4Cl, extracted with diethyl ether. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purification by flash column chromatography on silica gel (PE/EA = 4:1) to afford product **(*S*)-329b** (2.1 g, 75%) as an off-white solide.

$[\alpha]_D^{25}$ = - 275 (*c* 0.1, CH_2Cl_2); **Mp** 148-151 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52-7.56 (m, 2H, 2 × Ar***H***), 7.23-7.38 (m, 8H, 8 × Ar***H***), 4.53-4.58 (m, 1H, NC***H***), 3.70-3.78 (m, 1H, NC$\boldsymbol{H_A}H_B$), 3.21-3.27 (m, 1H, $NCH_A\boldsymbol{H_B}$), 1.81-2.00 (m, 2H, NCHC$\boldsymbol{H_2}$), 1.67-1.75 (m, 1H, $NCH_2C\boldsymbol{H_A}H_B$), 1.05-1.15 (m, 1H, $NCH_2CH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 160.0 (C(O)), 139.9 (2***C***, Ar), 128.2 (4***C***H, Ar), 126.6 (4***C***H, Ar), 125.0 (2***C***H, Ar), 85.4 (***C***-O), 68.7 (N***C***H), 45.6 (N***C***H_2), 28.5 (NCH***C***H_2), 24.4 ($NCH_2\boldsymbol{C}H_2$).

6.2.3.12.2 Preparation and characterisation of (2*S*)-2-(diphenylmethyl)pyrrolidine (*S*)-L23[158]

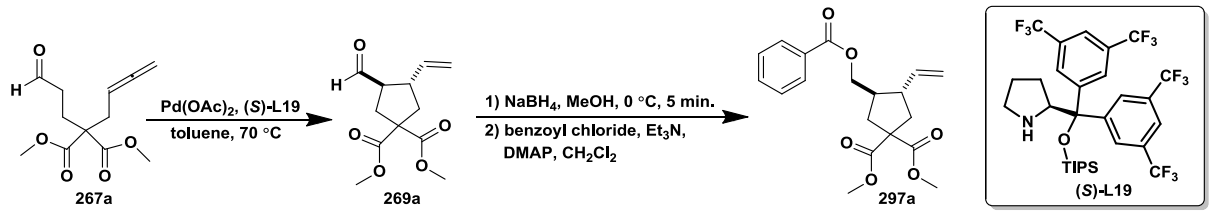


A mixture of **(*S*)-329b** (1.00 g, 3.58 mmol) and 10 wt % Pd/C (0.27 g) in methanol (30 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature for 40 h. The catalyst was filtered off and the methanol was removed under reduced pressure. Purification by flash column chromatography on silica gel (EA/MeOH = 1:1) afforded product **(*S*)-L23** (0.6 g, 71%) as a white solid.

$[\alpha]_D^{25}$ = - 7.5 (*c* 2.10, $CHCl_3$);[162] **Mp** 120.0-123.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.14-7.38 (m, 10H, 10 × Ar***H***), 3.78-3.90 (m, 2H, NC***H*** and C***H***Ph_2), 2.97-3.05 (m, 1H, NC$\boldsymbol{H_A}H_B$), 2.82-2.87 (m, 1H, $NCH_A\boldsymbol{H_B}$), 2.40 (brs, 1H, N***H***), 1.69-1.87 (m, 3H, NCHC$\boldsymbol{H_2}$ and $NCH_2C\boldsymbol{H_A}H_B$), 1.39-1.49 (m, 1H, $NCH_2CH_A\boldsymbol{H_B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 142.9 (2***C***, Ar), 128.6 (2***C***H, Ar), 128.4 (2***C***H, Ar), 127.9 (4***C***H, Ar), 126.4 (2***C***H, Ar), 62.1 (N***C***H), 57.2 (***C***HPh_2), 45.6 (N***C***H_2), 30.5 (NCH***C***H_2), 24.3 ($NCH_2\boldsymbol{C}H_2$); **FT-IR**ν_{max}(NaCl)/cm^{-1} 3300 (N-H), 1998 (C-H), 1550 (C=C of aromatic rings); **MS** (ES+) m/z (rel. intensity %) 238.18 (M + H^+, 100); **HRMS** (ESI+) calcd. for $C_{17}H_{20}N$ $[M+Na]^+$ 238.1596, found 238.1598.

6.2.3.13 Enantioselective carbocyclisation of allenes 297a-297d

6.2.3.13.1 Preparation and characterisation of dimethyl (3*R*,4*S*)-3-[(benzoyloxy)methyl]-4-vinylcyclopentane-1,1-dicarboxylate 297a



To a solution of $Pd(OAc)_2$ (4.48 mg, 0.2 mmol) in toluene (0.2 mL) were added substrate **267a** (48.0 mg, 0.2 mmol) and **(*S*)-L19** (41.0 mg, 0.06 mmol) in a sealed vial. The reaction mixture was stirred at 70 °C and monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel (PE/Et_2O = 2:1) to afford product **269a** (30.0 mg, 65%). Product **269a** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 15:1, as determined by ^{1}H NMR.

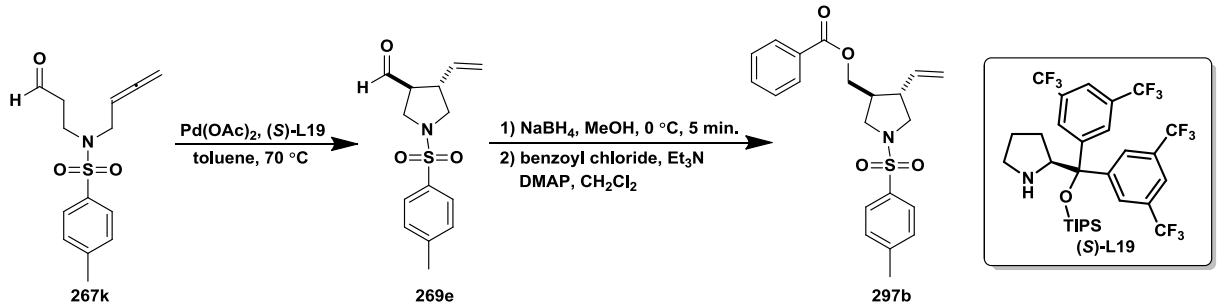
To a solution of compound **269a** (30.0 mg, 0.125 mmol) in MeOH (1.3 mL) at 0 °C was added $NaBH_4$ (24.0 mg, 0.62 mmol) in small portions. After 5 min., the reaction mixture was diluted with diethyl ether, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.3 mL), and then Et_3N (52 µL, 0.375 mmol), benzoyl chloride (29.0 µL, 0.25 mmol) and DMAP (1.5 mg, 0.0125 mmol) were added subsequently. The reaction mixture was warmed up to room temperature and stirred for 16 h. After the completion of the reaction, water was added and separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 4:1) to afford product **297a** (two diastereoisomers, 37.0 mg, 85% over two steps) as a colourless oil. The product was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 15:1, as determined by ^{1}H NMR.

Major diastereoisomer: **Ee** = 86% (Chiralcel OD, 98:2 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 8.3 min, minor t_R = 9.0 min); $[\alpha]_D^{25}$ = - 14.0 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.02-8.04 (m, 2H, 2 × Ar***H***), 7.54-7.58 (m, 1H, Ar***H***), 7.44 (t, 2H, *J* = 7.6 Hz, 2 × Ar***H***), 5.67-5.76 (m, 1H, C***H***=CH_2), 5.03-5.12 (m, 2H, CH=C***H$_2$***), 4.40 (dd, 1H, *J* = 11.1 Hz, *J* = 4.5 Hz, OC***H$_A$***H_B), 4.20 (dd, 1H, *J* = 11.1 Hz, *J* = 6.7 Hz, OCH_A***H$_B$***), 3.75 (s, 3H, OC***H$_3$***), 3.73 (s, 3H, OC***H$_3$***), 2.57-2.66 (m, 2H, OCH_2CHC***H$_A$***H_B and C***H$_A$***H_BCHCH=CH_2), 2.45-2.54 (m, 1H, C***H***CH=CH_2), 2.04-2.26 (m, 3H, OCH_2C***H*** and OCH_2CHCH_A***H$_B$*** and CH_A***H$_B$***CHCH=CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.7 (2C, 2 × ***C***(O)OCH_3), 166.5 (Ph***C***(O)), 139.1 (***C***H=CH_2), 132.9 (***C***, Ar), 130.1 (***C***H, Ar), 129.6 (2***C***H, Ar), 128.3 (2***C***H, Ar), 116.2 (CH=***C***H_2), 65.9 (O***C***H_2), 58.4 ((O)C***C***C(O)), 52.8 (2C, 2 × O***C***H_3), 46.7 (***C***HCH=CH_2), 44.1 (OCH_2***C***H), 40.6 (***C***H_2CHCH=CH_2), 37.4 (OCH_2CH***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2954 (C-H), 1734 (C=O), 1643 (C=C); **MS** (ES+) m/z (rel.

intensity %) 369.16 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{19}H_{22}NaO_6$ $[M+Na]^+$ 369.1309, found 369.1303.

6.2.3.13.3 Preparation and characterisation of {(3*S*,4*S*)-1-[(4-methylphenyl)sulfonyl]-4-vinylpyrrolidin-3-yl}methyl benzoate 297b



To a solution of $Pd(OAc)_2$ (4.48 mg, 0.2 mmol) in toluene (0.2 mL) were added substrate **267k** (56.0 mg, 0.2 mmol) and **(*S*)-L19** (41.0 mg, 0.06 mmol) in a sealed vial. The reaction mixture was stirred at 70 °C and monitored by TLC. After completion of the reaction, the reaction mixture was concentrated. The residue was purified by flash column chromatography on silica gel (PE/EA = 1:1) to afford product **269e** (30.0 mg, 55%). Product **269e** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 16:1, as determined by ^1H NMR.

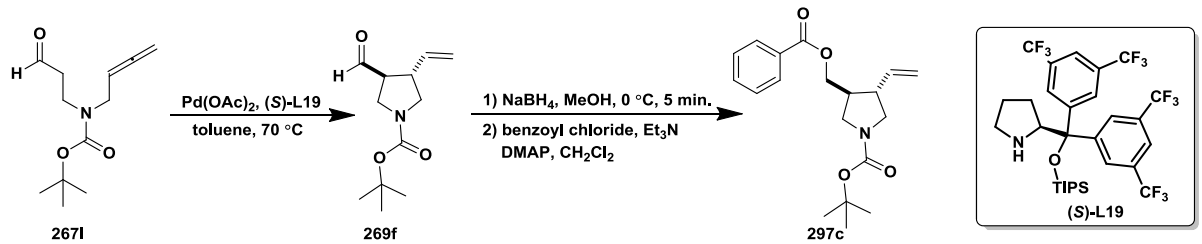
To a solution of compound **269e** (30.0 mg, 0.11 mmol) in MeOH (1.1 mL) at 0 °C was added $NaBH_4$ (21.0 mg, 0.55 mmol) in small portions. After 5 min., the reaction mixture was diluted with diethyl ether, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.1 mL) and then Et_3N (46.0 µL, 0.33 mmol), benzoyl chloride (26.0 µL, 0.22 mmol) and DMAP (1.4 mg, 0.011 mmol) were added subsequently. The reaction mixture was warmed up to room temperature and stirred for 16 h. After the completion of the reaction, water was added. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 2:1) to afford product **297b** (two diastereoisomers,

38.0 mg, 89% over two steps) as a colourless oil. Product **297b** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 16:1, as determined by ^{1}H NMR.

Major diastereoisomer: **Ee** = 64% (Chiralcel OD, 95:5 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 25.2 min, minor t_R = 28.2 min); $[\alpha]_D^{25}$ = - 10.5 (*c* 1.1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95-5.98 (m, 2H, 2 × Ar***H***), 7.72-7.74 (m, 2H, 2 × Ar***H***), 7.57-7.61 (m, 1H, Ar***H***), 7.43-7.47 (m, 2H, 2 × Ar***H***), 7.33 (d, 2H, *J* = 7.9 Hz, 2 × Ar***H***), 5.55-5.64 (m, 1H, C***H***=CH_2), 5.08-5.12 (m, 2H, CH=C***H$_2$***), 4.33 (dd, 1H, *J* = 11.3 Hz, *J* = 4.7 Hz, OC***H$_A$***H_B), 4.08 (dd, 1H, *J* = 11.3 Hz, *J* = 7.5 Hz, OCH_A***H$_B$***), 3.55-3.63 (m, 2H, OCH_2CHC***H$_A$***H_B and C***H$_A$***H_BCHCH=CH_2), 3.18 (dd, 1H, *J* = 10.0 Hz, *J* = 8.7 Hz, CH_A***H$_B$***CHCH=CH_2), 3.06 (dd, 1H, *J* = 10.0 Hz, *J* = 9.1 Hz, OCH_2CHCH_A***H$_B$***), 2.48-2.55 (m, 1H, C***H***CH=CH_2). 2.44 (s, 3H, C***H$_3$***), 2.28-2.36 (m, 1H, OCH_2C***H***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.2 (Ph***C***(O)), 143.6 (***C***, Ar), 135.9 (CHC***H***=CH_2), 133.5 (***C***, Ar), 133.4 (***C***, Ar), 133.2 (***C***H, Ar), 129.7 (2***C***H, Ar), 129.5 (2***C***H, Ar), 128.4 (2***C***H, Ar), 127.5 (2***C***H, Ar,), 117.9 (CH=***C***H_2), 64.1 (O***C***H_2), 52.6 (OCH_2CH***C***H_2), 50.6 (***C***$H_2CHCH=CH_2$), 45.4 (***C***HCH=CH_2), 43.4 (OCH_2***C***H), 21.5 (***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2954 (C-H), 1720 (C=O), 1599 (C=C), 1344 (SO_2), 1164 (SO_2); **MS** (ES+) m/z (rel. intensity %) 408.17 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{21}H_{23}NNaO_4S$ $[M+Na]^+$ 408.1240, found 408.1237.

6.2.3.13.4 Preparation and characterisation of *tert*-butyl (3*S*,4*S*)-3-[(benzoyloxy)methyl]-4-vinylpyrrolidine-1-carboxylate 297c



267l 269f 297c

To a solution of $Pd(OAc)_2$ (4.48 mg, 0.2 mmol) in toluene (0.2 mL) were added substrate **267l** (45.0 mg, 0.2 mmol) and **(*S*)-L19** (41.0 mg, 0.06 mmol) in a sealed vial. The reaction mixture was stirred at 70 °C and monitored by TLC. After completion of the reaction, the reaction

mixture was concentrated and the residue was purified by flash column chromatography on silica gel (PE/Et_2O = 1:1) to afford product **269f** (30.0 mg, 50%). The product was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 18:1, as determined by ^{1}H NMR.

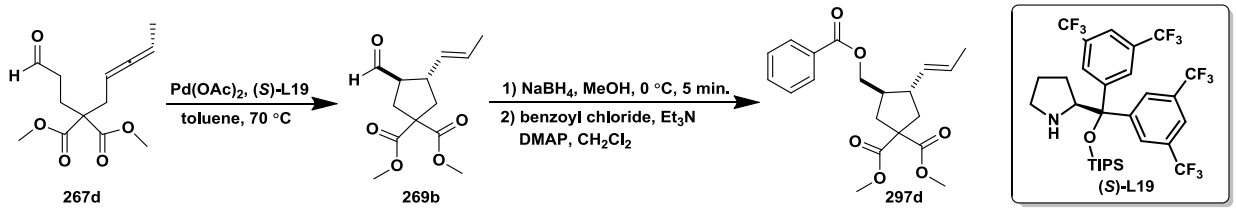
To a solution of compound **269f** (24.0 mg, 0.10 mmol) in MeOH (1.0 mL) at 0 °C was added $NaBH_4$ (19.0 mg, 0.50 mmol) in small portions. After 5 min., the reaction mixture was diluted with diethyl ether, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.0 mL) and Et_3N (42.0 µL, 0.30 mmol), benzoyl chloride (23.0 µL, 0.20 mmol) and DMAP (1.2 mg, 0.01 mmol) were added subsequently. The reaction mixture was warmed up to room temperature and stirred for 16 h. After the completion of the reaction, water was added and the resulting mixture was separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 3:1) to afford product **297c** (two diastereoisomers, 27 mg, 83% over two steps) as a colourless oil. The product was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 18:1, as determined by ^{1}H NMR.

Major diastereoisomer: **Ee** = 80% (Chiralcel AS-H, 98:2 hexane/isopropanol, 1.0 ml/min, 220 nm, major t_R = 6.9 min, minor t_R = 7.9 min); $[\alpha]_D^{25}$ = - 7.5 (*c* 0.8, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.03 (t, 2H, *J* = 7.1 Hz, 2 × Ar***H***), 7.56-7.61 (m, 1H, Ar***H***), 7.46 (dd, 2H, *J* = 16.2 Hz, *J* = 8.2 Hz, 2 × Ar***H***), 5.68-5.78 (m, 1H, C***H***=CH_2), 5.16 (t, 2H, *J* = 15.0 Hz, CH=C***H*****$_2$**), 4.46 (dt, 1H, *J* = 11.4 Hz, *J* = 4. 4 Hz, OC***H*****$_A$**H_B), 4.23 (td, 1H, *J* = 11.0 Hz, *J* = 7.8 Hz, OCH_A***H*****$_B$**), 3.63-3.83 (m, 2H, OCH_2CHC***H*****$_A$**H_B and C***H*****$_A$**H_BCHCH=CH_2), 3.13-3.29 (m, 2H, OCH_2CHCH_A***H*****$_B$** and CH_A***H*****$_B$**CHCH=CH_2), 2.63-2.72 (m, 1H, C***H***CH=CH_2), 2.43 (s, 1H, OCH_2C***H***), 1.47 (s, 9H, C(C***H*****$_3$**)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.3 (Ph***C***(O)), 154.3 (N***C***(O)), 136.8 (C***H***=CH_2), 133.1 (***C***, Ar), 130.1 (***C***H, Ar), 129.9 (***C***H,

Ar), 129.6 (2***C***H, Ar), 128.4 (***C***H, Ar), 117.5 (CH=***C***H_2), 79.4 (***C***$(CH_3)_3$), 64.5 (O***C***H_2), 51.1 (OCH_2CH***C***H_2), 49.0 (***C***$H_2CHCH=CH_2$), 45.7 (***C***$HCH=CH_2$), 43.6 (OCH_2***C***H), 28.5 (3C, C(***C***$H_3)_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2976 (C-H), 2938 (C-H), 2887 (C-H), 1721 (C=O), 1696 (C=O), 1645 (C=C); **MS** (ES+) m/z (rel. intensity %) 354.19 (M + Na^+, 90); **HRMS** (ESI+) calcd. for $C_{19}H_{25}NNaO_4$ $[M+Na]^+$ 354.1676, found 354.1677.

6.2.3.13.2 Preparation and characterisation of dimethyl (3*R*,4*S*)-3-[(benzoyloxy)methyl]-4-[(1*E*)-prop-1-en-1-yl]cyclopentane-1,1-dicarboxylate 297d



To a solution of $Pd(OAc)_2$ (4.48 mg, 0.2 mmol) in toluene (0.2 mL) were added substrate **267d** (52.0 mg, 0.2 mmol) and **(*S*)-L19** (41.0 mg, 0.06 mmol) in a sealed vial. The reaction mixture was stirred at 70 °C and monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel (PE/Et_2O = 2:1) to afford product **269b** (31.0 mg, 59%). Product **269b** was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 20:1, as determined by ^1H NMR.

To a solution of compound **269b** (31.0 mg, 0.122 mmol) in MeOH (1.2 mL) at 0 °C was added $NaBH_4$ (23.0 mg, 0.61 mmol) in small portions. After 5 min., the reaction mixture was diluted with diethyl ether, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.2 mL) and then Et_3N (51 µL, 0.366 mmol), benzoyl chloride (28.0 µL, 0.24 mmol) and DMAP (1.5 mg, 0.0122 mmol) were added subsequently. The reaction mixture was warmed up to room temperature and stirred for 16 h. After the completion of the reaction, water was added. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and

concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/Et_2O = 4:1) to afford product **297d** (two diastereoisomers, 39.0 mg, 88% over two steps) as a colourless oil. The product was obtained as a mixture of diastereoisomers in a ratio of *trans*/*cis* = 20:1, as determined by ^{1}H NMR.

Major diastereoisomer: **Ee** = 55% (Chiralcel AS-H, 98:2 hexane/isopropanol, 1.0 ml/min, 230 nm, major t_R = 8.8 min, minor t_R = 10.4 min); $[\alpha]_D^{25}$ = - 8.9 (*c* 1.1, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.02-8.04 (m, 2H, 2 × Ar***H***), 7.56 (m, 1H, Ar***H***), 7.44 (t, 2H, *J* = 7.8 Hz, 2 × Ar***H***), 5.48-5.54 (m, 1H, CH=C***H***CH_3), 5.29-5.34 (m, 1H, C***H***=$CHCH_3$), 4.39 (dd, 1H, *J* = 11.0 Hz, *J* = 4.5 Hz, OC***H$_A$***H_B), 4.18 (dd, 1H, *J* = 11.0 Hz, *J* = 6.7 Hz, OCH_A***H$_B$***), 3.75 (s, 3H, OC***H$_3$***), 3.73 (s, 3H, OC***H$_3$***), 2.54-2.65 (m, 2H, OCH_2CHC***H$_A$***H_B and C***H$_A$***$H_B$$CHCH=CH_2$), 2.43 (ddd, 1H, *J* = 18.3 Hz, *J* = 10.3 Hz, *J* = 8.1 Hz, C***H***$CH=CHCH_3$), 2.11-2.20 (m, 2H, OCH_2C***H*** and CH_A***H$_B$***$CHCH=CH_2$), 2.02 (dd, 1H, *J* = 13.4 Hz, *J* = 11.0 Hz, OCH_2CHCH_A***H$_B$***), 1.63 (dd, 3H, *J* = 6.4 Hz, *J* = 1.4 Hz, CH=CHC***H$_3$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.8 (2C, 2 × ***C***(O)OCH_3), 166.5 (Ph***C***(O)), 132.9 (***C***, Ar), 131.8 (***C***H=$CHCH_3$), 130.2 (***C***H, Ar), 129.6 (2***C***H, Ar), 128.3 (2***C***H, Ar), 126.9 (CH=***C***HCH_3), 66.2 (O***C***H_2), 58.4 ((O)C***C***C(O)), 52.8 (2C, 2 × O***C***H_3), 45.9 (***C***HCH=$CHCH_3$), 44.3 (OCH_2***C***H), 41.0 (***C***$H_2CHCH=CHCH_3$), 37.4 (OCH_2CH***C***H_2), 17.8 (CH=CH***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2954 (C-H), 1733 (C=O), 1635 (C=C); **MS** (ES+) m/z (rel. intensity %) 383.16 (M + Na^+, 100); **HRMS** (ESI+) calcd. for $C_{20}H_{24}NaO_6$ $[M+Na]^+$ 383.1471, found 383.1473.

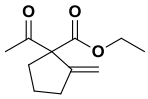
6.2.4 Experimental for Chapter Five

General procedure P for boronic acid catalysed Conia-ene reaction[187]

To a mixture of 1,3-dicarbonyl compounds **316a-316q** (0.2 mmol) and 3-NO_2-phenylboronic acid **319g** (1.7 mg, 0.01 mmol) was added toluene (5 mL). The resulting solutions were refluxed for 16 h to 170 h and monitored by TLC. Upon completion, the reaction mixtures

were evaporated. The residues were purified by flash chromatography column on silica gel to give the products **317a-317q**.

Preparation and characterisation of *rac*-1-acetyl-2-methylene-cyclopentanecarboxylic acid ethyl ester (±)-317a

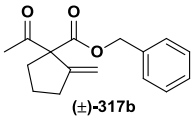


(±)-317a

Synthesised from compound **316a** (39.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317a** was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a colourless oil (36.0 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.22 (t, 1H, *J* = 2.0 Hz, C=C***H*****$_A$**H_B), 5.17 (t, 1H, *J* = 2.2 Hz, C=CH_A***H*****$_B$**), 4.10-4.19 (m, 2H, OC***H*****$_2$**), 2.28-2.43 (m, 3H, CH_2=CC***H*****$_2$** and C(O)CC***H*****$_A$**H_B), 2.15 (s, 3H, C(O)C***H*****$_3$**), 2.08-2.14 (m, 1H, C(O)CCH_A***H*****$_B$**), 1.58-1.73 (m, 2H, CH_2=CCH_2C***H*****$_2$**), 1.20 (t, 3H, *J* = 7.1 Hz, OCH_2C***H*****$_3$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 203.5 (CH_3***C***(O)), 171.1 (***C***(O)O), 148.7 (***C***=CH_2), 112.0 (C=***C***H_2), 70.4 (C(O)***C***), 61.5 (O***C***H_2), 35.0 (C(O)C***C***H_2), 34.0 (CH_2=C***C***H_2), 26.7 (***C***H_3C(O)), 24.0 (CH_2=CCH_2***C***H_2), 14.0 (OCH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2956 (C-H), 1734 (C=OO), 1721 (C=O), 1653 (C=C); **MS** (ES+) m/z (rel. intensity %) 219 ($M+Na^+$, 100); **HRMS** (ESI+) calcd. $C_{11}H_{16}O_3Na$ $[M+Na]^+$ 219.0992, found 219.0984.

Preparation and characterisation of *rac*-1-acetyl-2-methylene-cyclopentanecarboxylic acid benzyl ester (±)-317b

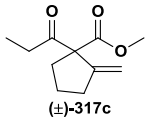


(±)-317b

Synthesised from compound **316b** (52.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317b** was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a colourless oil (46.0 mg, 88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.30-7.23 (m, 5H, 5 × Ar***H***), 5.21 (t, 1H, *J* = 1.8 Hz, C=C***H*$_A$**H$_B$), 5.14 (t, 1H, *J* = 2.2 Hz, C=CH$_A$***H*$_B$**), 5.11 (s, 2H, OC***H*$_2$**), 2.32-2.43 (m, 3H, CH_2=CC***H*$_2$** and C(O)CC***H*$_A$**H$_B$), 2.10-2.16 (m, 1H, C(O)CCH$_A$***H*$_B$**), 2.10 (s, 3H, C(O)C***H*$_3$**), 1.58-1.72 (m, 2H, CH_2=CCH$_2$C***H*$_2$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 203.3 (CH_3***C***(O)), 171.0 (***C***(O)O), 148.5 (***C***=CH_2), 135.4 (***C***, Ar), 128.6 (2***C***, Ar), 128.3 (***C***, Ar), 128.2 (2***C***, Ar), 112.3 (C=***C***H$_2$), 70.5 (C(O)***C***), 67.3 (O***C***H$_2$), 35.1 (C(O)C***C***H$_2$), 34.0 (CH_2=C***C***H$_2$), 26.6 (***C***H$_3$C(O)), 24.1 (CH_2=CCH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2958 (C-H), 2881 (C-H), 1711 (C=O), 1649 (C=C); **MS** (ES+) m/z (rel. intensity %) 281.14 (M+Na$^+$, 100); **HRMS** (ESI+) calcd. $C_{16}H_{18}O_3Na$ [M+Na]$^+$ 281.1148, found 281.1158.

Preparation and characterisation of *rac*-1-propionyl-2-methylene-cyclopentanecarboxylic acid methyl ester (±)-317c

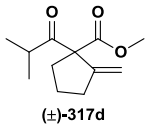


(±)-317c

Synthesised from compound **316c** (39.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317c** was obtained after flash column chromatography on silica gel (PE/Et_2O = 15:1) as a colourless oil (22.0 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.28 (t, 1H, *J* = 2.0 Hz, C=C***H*$_A$**H$_B$), 5.21 (t, 1H, *J* = 2.2 Hz, C=CH$_A$***H*$_B$**), 3.74 (s, 3H, OC***H*$_3$**), 2.58-2.61 (m, 1H, C(O)CC***H*$_A$**H$_B$), 2.37-2.57 (m, 4H, CH_2=CC***H*$_2$** and CH_3C***H*$_2$**C(O)), 2.18 (ddd, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, *J* = 6.9 Hz, C(O)CCH$_A$***H*$_B$**), 1.64-1.78 (m, 2H, CH_2=CCH$_2$C***H*$_2$**), 1.06 (t, 3H, *J* = 7.4 Hz, C***H*$_3$**CH$_2$C(O)); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 206.6 (CH_3CH_2***C***(O)), 171.8 (***C***(O)O), 148.7 (***C***=CH_2), 112.1 (C=***C***H$_2$), 70.2 (C(O)***C***), 52.6 (O***C***H$_2$CH$_3$), 35.1 (C(O)C***C***H$_2$), 33.9 (CH_3***C***H$_2$C(O)), 32.2 (CH_2=C***C***H$_2$), 24.1 (CH_2=CCH$_2$***C***H$_2$), 8.5 (***C***H$_3$CH$_2$C(O)); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2953 (C-H), 1739 (C=O), 1713 (C=O); **MS** (ES+**)** m/z (rel. intensity %) 219 (M+Na$^+$, 100); **HRMS** (ESI+) calcd. $C_{11}H_{16}O_3Na$ [M+Na]$^+$ 219.0992, found 219.0996.

Preparation and characterisation of *rac*-1-isobutyryl-2-methylenecyclopentanecarboxylic methyl ester (±)-317d

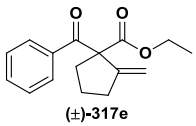


(±)-317d

Synthesised from compound **316d** (42.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317d** was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a colourless oil (37.0 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.23 (t, 1H, *J* = 2.0 Hz, C=C***H*****$_A$**H_B), 5.17 (t, 1H, *J* = 2.3 Hz, C=CH_A***H*****$_B$**), 3.67 (s, 3H, OC***H*****$_3$**), 2.89-2.92 (m, 1H, $(CH_3)_2$C***H***CO), 2.36-2.41 (m, 2H, CH_2=CC***H*****$_2$**), 2.29-2.35 (m, 1H, C(O)CC***H*****$_A$**H_B), 2.16-2.23 (m, 1H, C(O)CCH_A***H*****$_B$**), 1.57-1.69 (m, 2H, CH_2=CCH_2C***H*****$_2$**), 1.04 (d, 3H, *J* = 6.7 Hz, (C***H*****$_3$**)$_A$(CH_3)$_B$CH), 1.00 (d, 3H, *J* = 6.7 Hz, (CH_3)$_A$(C***H*****$_3$**)$_B$CH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 210.1 ((CH_3)$_2$CH***C***(O)), 171.7 (***C***(O)O), 148.3 (***C***=CH_2), 112.3 (C=***C***H_2), 70.8 (C(O)***C***), 52.5 (O***C***H_3), 37.3 ((CH_3)$_2$***C***HC(O)), 34.6 (C(O)C***C***H_2), 33.8 (CH_2=C***C***H_2), 24.0 (CH_2=CCH_2***C***H_2), 20.7 ((***C***H_3)$_A$(CH_3)$_B$CHC(O)), 20.6 ((***C***H_3)$_A$(***C***H_3)$_B$CHC(O)); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2971 (C-H), 2875 (C-H), 1744 (C=OO), 1714 (C=O), 1646 (C=C); **MS** (ES+) m/z (rel. intensity %) 233.2 (M+Na$^+$, 100); **HRMS** (ESI+) $[M+Na]^+$ 233.1157, found 233.1160.

Preparation and characterisation of *rac*-1-benzoyl-2-methylene-cyclopentanecarboxylic acid ethyl ester (±)-317e



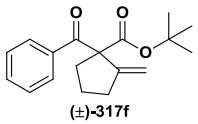
(±)-317e

Synthesised from compound **316e** (41.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317e** was obtained after flash column chromatography on silica gel (PE/Et_2O = 30:1) as a colourless oil (40.0 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77 (dd, 2H, *J* = 8.1 Hz, *J* = 0.8 Hz, 2 × Ar***H***), 7.45 (t, 1H, *J* = 7.4 Hz, Ar***H***), 7.34 (t, 2H, *J* = 7.7 Hz, 2 × Ar***H***), 5.29 (t, 1H, *J* = 1.8 Hz, C=C***H*****$_A$**H_B), 5.14 (t,

1H, *J* = 2.1 Hz, C=CH_A***H*****$_B$**), 3.99-4.12 (m, 2H, OC***H*****$_2$**), 2.78 (td, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, C(O)CC***H*****$_A$**H_B), 2.42-2.47 (m, 2H, CH_2=CC***H*****$_2$**), 2.08-2.15 (m, 1H, C(O)CCH_A***H*****$_B$**), 1.76-1.81 (m, 1H, CH_2=CCH_2C***H*****$_A$**H_B), 1.58-1.68 (m, 1H, CH_2=CCH_2CH_A***H*****$_B$**), 0.98 (t, 3H, *J* = 7.1 Hz, OCH_2C***H*****$_3$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 195.4 (Ph***C***(O)), 171.8 (***C***(O)O), 149.5 (***C***=CH_2), 135.4 (Ar), 132.7 (Ar), 128.8 (2C, Ar), 128.4 (2C, Ar), 111.8 (C=***C***H_2), 67.4 (C(O)***C***), 61.6 (O***C***H_2), 36.8 (C(O)C***C***H_2), 34.3 (CH_2=C***C***H_2), 24.4 (CH_2=CCH_2***C***H_2), 13.7 (OCH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2976 (C-H), 2957 (C-H), 1734 (C=OO), 1685 (C=O); **MS** (ES+) m/z (rel. intensity %) 281.1 (M+Na$^+$, 100); **HRMS** (ESI+) calcd. $C_{16}H_{18}O_3Na$ $[M+Na]^+$ 281.1148, found 281.1154.

Preparation and characterisation of *rac*-1-benzoyl-2-methylene-cyclopentanecarboxylic acid *tert*-butyl ester (±)-317f



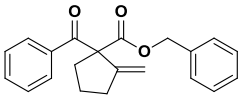
(±)-317f

Synthesised from compound **316f** (57.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317f** was obtained after flash column chromatography on silica gel (PE/Et_2O = 15:1) as a colourless oil (53.0 mg, 93%).

^{1}H NMR (400 MHz) δ_H 7.80 (td, 2H, *J* = 8.6 Hz, *J* = 1.7 Hz, 2 × Ar***H***), 7.43-7.47 (m, 1H, Ar***H***), 7.33-7.37 (m, 2H, 2 × Ar***H***), 5.29 (t, 1H, *J* = 2.0 Hz, C=C***H*****$_A$**H_B), 5.16 (t, 1H, *J* = 2.2 Hz, C=CH_A***H*****$_B$**), 2.72-2.80 (m, 1H, C(O)CC***H*****$_A$**H_B), 2.43 (tdd, 2H, *J* = 9.5 Hz, *J* = 7.4 Hz, *J* = 2.1 Hz, CH_2=CC***H*****$_2$**), 2.04-2.11 (m, 1H, C(O)CCH_A***H*****$_B$**), 1.77 (tdd, 1H, *J* = 14.6 Hz, *J* = 12.4 Hz, *J* = 7.2 Hz, CH_2=CCH_2C***H*****$_A$**H_B), 1.59-1.66 (m, 1H, CH_2=CCH_2CH_A***H*****$_B$**), 1.20 (s, 9H, C(C***H*****$_3$**)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 194.7 (Ph***C***(O)), 169.6 (***C***(O)O), 148.9 (***C***=CH_2), 134.7 (***C***, Ar), 131.5 (***C***, Ar), 127.8 (***C***, Ar), 127.5 (***C***, Ar), 127.3 (***C***, Ar), 127.0 (***C***, Ar), 110.2 (C=***C***H_2), 81.0 (C(O)***C***), 67.8 (O***C***$(CH_3)_3$), 35.7 (C(O)C***C***H_2), 33.5 (CH_2=C***C***H_2), 26.6 (OC(***C***H_3)$_3$), 21.2 (CH_2=CCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2976 (C-H), 2876 (C-H), 1728 (C=O), 1686 (C=O);

MS (ES+) m/z (rel. intensity %) 309.20 ($M+Na^+$, 100); **HRMS** (ESI+) calcd. $C_{18}H_{22}O_3Na$ $[M+Na]^+$ 301.1678, found 301.1680.

Preparation and characterisation of *rac*-1-benzoyl-2-methylene-cyclopentanecarboxylic acid benzyl ester (±)-317g

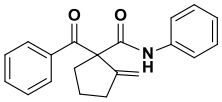


(±)-317g

Synthesised from compound **316g** (64.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317g** was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a colourless oil (63.0 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.77 (d, 2H, *J* = 7.3 Hz, 2 × Ar***H***), 7.48 (t, 1H, *J* = 7.7 Hz, Ar***H***), 7.33 (dd, 2H, *J* = 7.7 Hz, *J* = 7.3 Hz, 2 × Ar***H***), 7.20-7.27 (m, 3H, 3 × Ar***H***), 7.05 (d, 2H, *J* = 6.8 Hz, 2 × Ar***H***), 5.33 (t, 1H, *J* = 1.8 Hz, C=C***H*****$_A$**H_B), 5.17 (t, 1H, *J* = 2.1 Hz, C=CH_A***H*****$_B$**), 5.08 (s, 2H, OC***H*****$_2$**), 2.86 (ddd, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, *J* = 6.9 Hz, C(O)CC***H*****$_A$**H_B), 2.50-2.53 (m, 2H, CH_2=CC***H*****$_2$**), 2.20 (ddd, 1H, *J* = 13.7 Hz, *J* = 7.1 Hz, *J* = 7.1 Hz, C(O)CCH_A***H*****$_B$**), 1.82-1.93 (m, 1H, CH_2=CCH_2C***H*****$_A$**H_B), 1.68-1.75 (m, 1H, CH_2=CCH_2CH_A***H*****$_B$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 195.2 (Ph***C***(O)), 171.6 (***C***(O)O), 149.3 (***C***=CH_2), 135.2 (***C***, Ar), 134.9 (***C***, Ar), 132.6 (***C***, Ar), 128.8 (2***C***, Ar), 128.4 (2***C***, Ar), 128.4 (2***C***, Ar), 128.3 (2***C***, Ar), 128.2 (***C***, Ar), 112.0 (C=***C***H_2), 67.4 (2C, C(O)***C*** and O***C***H_2), 36.9 (C(O)C***C***H_2), 34.3 (CH_2=C***C***H_2), 24.3 (CH_2=CCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3065 (C-H of Ph), 2956 (C-H), 1734 (C=OO), 1682 (C=O), 1653 (C=C); **MS** (ES+) m/z (rel. intensity %) 321 ($M+H^+$, 81); **HRMS** (ESI+) calcd. $C_{21}H_{21}O_3$ $[M+H]^+$ 321.1485, found 321.1492.

Preparation and characterisation of *rac*-1-benzoyl-2-methylene-*N*-phenylcyclopentanecarboxamide (±)-317h

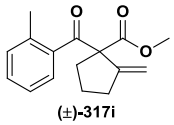


(±)-317h

Synthesised from compound **316h** (61.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317h** was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a yellow solid (46.0 mg, 75%).

Mp 90-91 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.95 (s, 1H, N***H***), 7.73-7.76 (m, 2H, 2 × Ar***H***), 7.41-7.45 (m, 3H, 3 × Ar***H***), 7.32 (t, 2H, *J* = 7.6 Hz, 2 × Ar***H***), 7.23-7.28 (m, 2H, 2 × Ar***H***), 7.06 (t, 1H, *J* = 7.4 Hz, Ar***H***), 5.40 (t, 1H, *J* = 2.0 Hz, C=C$\boldsymbol{H_A}H_B$), 5.27 (t, 1H, *J* = 2.3 Hz, C=$CH_A\boldsymbol{H_B}$), 2.72 (ddd, 1H, *J* = 12.6 Hz, *J* = 6.9 Hz, *J* = 5.4 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 2.54-2.60 (m, 2H, CH_2=CC$\boldsymbol{H_2}$), 2.43 (ddd, 1H, *J* = 13.2 Hz, *J* = 8.4 Hz, *J* = 7.4 Hz, C(O)C$CH_A\boldsymbol{H_B}$), 1.68-1.84 (m, 2H, CH_2=CCH_2C$\boldsymbol{H_2}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 199.3 (Ph***C***(O)), 168.4 (N***C***(O)), 152.2 (***C***=CH_2), 137.5 (***C***, Ar), 136.2 (***C***,Ar), 132.5 (***C***, Ar), 129.1 (2***C***, Ar), 129.0 (2***C***, Ar), 128.4 (2***C***, Ar), 124.8 (***C***, Ar), 120.0 (2***C***, Ar), 113.1 (C=***C***H_2), 71.6 (C(O)***C***), 37.2 (C(O)C***C***H_2), 34.1 (CH_2=C***C***H_2), 23.9 (CH_2=CCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 3346 (N-H), 2953 (C-H), 1662 (C=C), 1597 (NC=O); **MS** (ES+) m/z (rel. intensity %) 328.0 (M+Na$^+$, 100); **HRMS** (ESI+) calcd. $C_{20}H_{19}O_2NNa$ [M+Na]$^+$ 328.1309, found 328.1308.

Preparation and characterisation of *rac*-1-(2-methylbenzoyl)-2-methylene-cyclopentanecarboxylic acid methyl ester (±)-317i



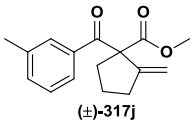
(±)-317i

Synthesised from compound **316i** (52.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317i** was obtained after flash column chromatography on silica gel (PE/Et_2O = 30:1) as a colourless oil (38.0 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.22-7.27 (m, 2H, 2 × Ar***H***), 7.17 (d, 1H, *J* = 7.5 Hz, Ar***H***), 7.09 (t, 1H, *J* = 7.5 Hz, Ar***H***), 5.28 (t, 1H, *J* = 1.9 Hz, C=C$\boldsymbol{H_A}H_B$), 5.17 (t, 1H, *J* = 2.1 Hz, C=$CH_A\boldsymbol{H_B}$), 3.59 (s, 3H, OC$\boldsymbol{H_3}$), 2.60 (td, 1H, *J* = 12.9 Hz, *J* = 6.4 Hz, C(O)CC$\boldsymbol{H_A}H_B$), 2.38-2.49 (m, 2H, CH_2=CC$\boldsymbol{H_2}$), 2.33 (s, 3H, PhC$\boldsymbol{H_3}$), 2.11 (td, 1H, *J* = 13.3 Hz, *J* = 7.5 Hz,

C(O)CCH$_A$***H$_B$***), 1.59-1.75 (m, 2H, CH$_2$=CCH$_2$C***H$_2$***); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 201.2 (Ph***C***(O)), 172.0 (***C***(O)O), 149.2 (***C***=CH$_2$), 137.9 (***C***, Ar), 137.5 (***C***, Ar), 131.7 (***C***, Ar), 130.4 (***C***, Ar), 126.4 (***C***, Ar), 125.1(***C***, Ar), 112.6 (C=***C***H$_2$), 69.8 (C(O)***C***), 52.7 (O***C***H$_3$), 36.9 (C(O)C***C***H$_2$), 34.3 (CH$_2$=C***C***H$_2$), 24.4 (CH$_2$=CCH$_2$***C***H$_2$), 20.8 (Ph-***C***H$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2953 (C-H), 1735 (C=O), 1688 (C=O); **MS** (ES+) m/z (rel. intensity %) 259.2 (M+H$^+$, 40), 281.2 (M+Na$^+$, 100); **HRMS** (ESI+) calcd. $C_{16}H_{19}O_3$ [M+H]$^+$ 259.1329, found 259.1339.

Preparation and characterisation of *rac*-1-(3-methylbenzoyl)-2-methylene-cyclopentanecarboxylic acid methyl ester (±)-317j

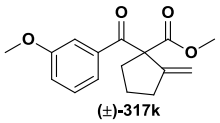


(±)-317j

Synthesised from compound **316j** (52.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317j** was obtained after flash column chromatography on silica gel (PE/Et$_2$O = 30:1) as a colourless oil (50.0 mg, 96%).

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.61 (s, 1H, Ar***H***), 7.51 (d, 1H, *J* = 7.5 Hz, Ar***H***), 7.19-7.28 (m, 2H, 2 × Ar***H***), 5.28 (t, 1H, *J* = 1.9 Hz, C=C***H$_A$***H$_B$), 5.11 (t, 1H, *J* = 2.1 Hz, C=CH$_A$***H$_B$***), 3.59 (s, 3H, OC***H$_3$***), 2.76 (td, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, C(O)CC***H$_A$***H$_B$), 2.42-2.46 (m, 2H, CH$_2$=CC***H$_2$***), 2.32 (s, 3H, PhC***H$_3$***), 2.08-2.15 (m, 1H, C(O)CCH$_A$***H$_B$***), 1.78 (qd, 1H, *J* = 12.7 Hz, *J* = 7.4 Hz, CH$_2$=CCH$_2$C***H$_A$***H$_B$), 1.58-1.68 (m, 1H, CH$_2$=CCH$_2$CH$_A$***H$_B$***); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 194.4 (Ph***C***(O)), 171.4 (***C***(O)O), 148.4 (***C***=CH$_2$), 137.4 (***C***, Ar), 134.2 (***C***, Ar), 132.5 (***C***, Ar), 128.4 (***C***, Ar), 127.2 (***C***, Ar), 124.9 (***C***, Ar), 110.9 (C=***C***H$_2$), 66.5 (C(O)***C***), 51.7 (O***C***H$_3$), 35.9 (C(O)C***C***H$_2$), 33.3 (CH$_2$=C***C***H$_2$), 23.3 (CH$_2$=CCH$_2$***C***H$_2$), 20.4 (Ph***C***H$_3$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2952 (C-H), 1734 (C=O), 1685 (C=O), 1600 (C=C); **MS** (ES+) m/z (rel. intensity %) 259.2 (M+H$^+$, 100); **HRMS** (ESI+) calcd. $C_{16}H_{19}O_3$ [M+H]$^+$ 259.1329, found 259.1335.

Preparation and characterisation of *rac*-1-(3-methoxybenzoyl)-2-methylene-cyclopentanecarboxylic acid methyl ester (±)-317k

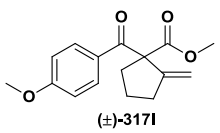


(±)-317k

Synthesised from compound **316k** (55.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317k** was obtained after flash column chromatography on silica gel (PE/Et_2O = 30:1) as a white solid (54.0 mg, 98%).

Mp 65-66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 (dd, 1H, *J* = 2.4 Hz, *J* = 1.7 Hz, Ar***H***), 7.29 (td, 1H, *J* = 7.7 Hz, *J* = 1.4 Hz, Ar***H***), 7.24 (t, 1H, *J* = 7.8 Hz, Ar***H***), 7.00 (ddd, 1H, *J* = 7.7 Hz, *J* = 2.6 Hz, *J* = 1.3 Hz, Ar***H***), 5.29 (t, 1H, *J* = 2.0 Hz, C=C***H$_A$***H$_B$), 5.12 (t, 1H, *J* = 2.2 Hz, C=CH$_A$***H$_B$***), 3.76 (s, 3H, PhOC***H$_3$***), 3.59 (s, 3H, C(O)OC***H$_3$***), 2.77 (td, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, C(O)CC***H$_A$***H$_B$), 2.44 (tt, 2H, *J* = 7.6 Hz, *J* = 1.9 Hz, CH_2=CC***H$_2$***), 2.09-2.16 (m, 1H, C(O)CCH$_A$***H$_B$***), 1.78 (pd, 1H, *J* = 12.6 Hz, *J* = 7.4 Hz, CH_2=CCH_2C***H$_A$***H$_B$), 1.64 (pd, 1H, *J* = 12.8 Hz, *J* = 6.9 Hz, CH_2=CCH_2CH$_A$***H$_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 195.0 (Ph***C***(O)), 172.3 (***C***(O)O), 159.7 (***C***, Ar), 149.3 (***C***=CH_2), 136.6 (***C***, Ar), 129.4 (***C***, Ar), 121.1 (***C***, Ar), 119.3 (***C***, Ar), 113.3 (***C***, Ar), 112.0 (C=***C***H_2), 67.6 (CO***C***), 55.4 (PhO***C***H_3), 52.7 (C(O)O***C***H_3), 36.9 (C(O)C***C***H_2), 34.3 (CH_2=C***C***H_2), 24.3 (CH_2=CCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2951 (C-H), 1737 (C=O), 1688 (C=O), 1596 (C=C); **MS (ES)**: 275.18 (M+H$^+$, 100); **HRMS (ES)** calcd. $C_{16}H_{19}O_4$ $[M+H]^+$ 275.1567, found 275.1569.

Preparation and characterisation of *rac*-1-(4-methoxybenzoyl)-2-methylene-cyclopentanecarboxylic acid methyl ester (±)-317l

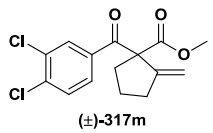


(±)-317l

Synthesised from compound **316l** (55.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317l** was obtained after flash column chromatography on silica gel (PE/Et_2O = 10:1) as a white solid (50.0 mg, 91%).

Mp 53-54 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.75 (d, 2H, *J* = 9.0 Hz, 2 × Ar***H***), 6.83 (d, 2H, *J* = 9.0 Hz, 2 × Ar***H***), 5.28 (t, 1H, *J* = 2.0 Hz, C=C***H$_A$***H$_B$), 5.11 (t, 1H, *J* = 2.2 Hz, C=CH$_A$***H$_B$***), 3.79 (s, 3H, PhOC***H$_3$***), 3.60 (s, 3H, C(O)OC***H$_3$***), 2.75 (td, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, C(O)CC***H$_A$***H$_B$), 2.41-2.46 (m, 2H, CH$_2$=CC***H$_2$***), 2.11 (td, 1H, *J* = 13.2 Hz, *J* = 7.1 Hz, C(O)CCH$_A$***H$_B$***), 1.77 (pd, 1H, *J* = 12.6 Hz, *J* = 7.4 Hz, CH$_2$=CCH$_2$C***H$_A$***H$_B$), 1.58-1.68 (m, 1H, CH$_2$=CCH$_2$CH$_A$***H$_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 193.1 (Ph***C***(O)), 172.6 (***C***(O)O), 163.1 (***C***, Ar), 149.5 (***C***=CH$_2$), 131.2 (2***C***, Ar), 127.9 (***C***, Ar), 113.7 (2***C***, Ar), 111.8 (C=***C***H$_2$), 67.3 (C(O)***C***), 55.5 (PhO***C***H$_3$), 52.7 (C(O)O***C***H$_3$), 37.0 (C(O)C***C***H$_2$), 34.3 (CH$_2$=C***C***H$_2$), 24.3 (CH$_2$=CCH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2952 (C-H), 1733 (C=O), 1679 (C=O), 1601 (C=C); **MS** (ES+) m/z (rel. intensity %) 297.0 (M+Na$^+$, 100); **HRMS** (ESI+) calcd. $C_{15}H_{16}O_3Na$ $[M+Na]^+$ 297.1097, found 297.1092.

Preparation and characterisation of *rac*-1-(3,4-dichlorobenzoyl)-2-methylene-cyclopentanecarboxylic acid methyl ester (±)-317m



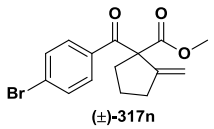
(±)-317m

Synthesised from compound **316m** (63.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317m** was obtained after flash column chromatography on silica gel (PE/Et_2O = 30:1) as a white solid (59.0 mg, 95%).

Mp 56-57 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 (d, 1H, *J* = 2.1 Hz, Ar***H***), 7.53 (dd, 1H, *J* = 8.4 Hz, *J* = 2.1 Hz, Ar***H***), 7.43 (d, 1H, *J* = 8.4 Hz, Ar***H***), 5.30 (t, 1H, *J* = 1.9 Hz, C=C***H$_A$***H$_B$), 5.10 (t, 1H, *J* = 2.1 Hz, C=CH$_A$***H$_B$***), 3.62 (s, 3H, OC***H$_3$***), 2.74 (td, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, C(O)CC***H$_A$***H$_B$), 2.44 (tt, 2H, *J* = 7.2 Hz, *J* = 2.0 Hz, CH$_2$=CC***H$_2$***), 2.03-2.10 (m, 1H, C(O)CCH$_A$***H$_B$***), 1.80 (pd, 1H, *J* = 12.7 Hz, *J* = 7.4 Hz, CH$_2$=CCH$_2$C***H$_A$***H$_B$), 1.59-1.69 (m, 1H, CH$_2$=CCH$_2$CH$_A$***H$_B$***); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 193.1 (Ph***C***(O)), 171.9 (***C***(O)O), 148.9 (***C***=CH$_2$), 137.4 (***C***, Ar), 134.9 (***C***, Ar), 133.3 (***C***,Ar), 130.9 (***C***H, Ar), 130.5 (***C***H, Ar), 127.6

(***C***H, Ar), 112.4 (C=***C***H_2), 67.4 (C(O)***C***), 53.0 (O***C***H_3), 36.7 (C(O)C***C***H_2), 34.2 (CH_2=C***C***H_2), 24.3 (CH_2=CCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2948 (C-H), 1740 (C=O), 1692 (C=O), 1581 (C=C); **MS** (ES+) m/z (rel. intensity %) 334.9 ($M+Na^+$, 100); **HRMS** (ESI+) calcd. $C_{15}H_{14}O_3Cl_2Na$ $[M+Na]^+$ 335.0212, found 335.0225.

Preparation and characterisation of *rac*-1-(4-bromobenzoyl)-2-methylene-cyclopentanecarboxylic acid methyl ester (±)-317n

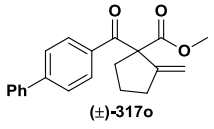


(±)-317n

Synthesised from compound **316n** (64.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317n** was obtained after flash column chromatography on silica gel (PE/Et_2O = 30:1) as a white solid (58.0 mg, 90%).

Mp 75-77 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.63 (d, 2H, *J* = 8.6 Hz, 2 × Ar***H***), 7.50 (d, 2H, *J* = 8.6 Hz, 2 × Ar***H***), 5.29 (t, 1H, *J* = 1.9 Hz, C=C***H*****$_A$**H_B), 5.10 (t, 1H, *J* = 2.1 Hz, C=CH_A***H*****$_B$**), 3.60 (s, 3H, OC***H*****$_3$**), 2.75 (td, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, C(O)CC***H*****$_A$**H_B), 2.44 (tt, 2H, *J* = 7.3 Hz, *J* = 2.0 Hz, CH_2=CC***H*****$_2$**), 2.04-2.11 (m, 1H, C(O)CCH_A***H*****$_B$**), 1.79 (pd, 1H, *J* = 12.7 Hz, *J* = 7.4 Hz, CH_2=CCH_2C***H*****$_A$**H_B), 1.58-1.68 (m, 1H, CH_2=C$CH_2$$CH_A$***H*****$_B$**); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 194.2 (Ph***C***(O)), 172.2 (***C***(O)O), 149.1 (***C***=CH_2), 134.0 (***C***, Ar), 131.8 (2***C***, Ar), 130.3 (2***C***, Ar), 127.9 (***C***, Ar), 112.2 (C=***C***H_2), 67.4 (C(O)***C***), 52.8 (O***C***H_3), 36.7 (C(O)C***C***H_2), 34.2 (CH_2=C***C***H_2), 24.3 (CH_2=CCH_2***C***H_2); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2948 (C-H), 1730 (C=O), 1685 (C=O); **MS** (ES+) m/z (rel. intensity %) 344.9, 346.7 ($M+Na^+$, 100); **HRMS** (ESI+) calcd. $C_{15}H_{15}O_3BrNa$ $[M+Na]^+$ 345.0097, found 345.0111.

Preparation and characterisation of *rac*-1-(biphenylcarbonyl)-2-methylene-cyclopentanecarboxylic acid methyl ester (±)**-317o**

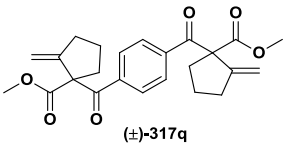


(±)-317o

Synthesised from compound **317o** (64.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-316o** was obtained after flash column chromatography on silica gel (PE/Et_2O = 30:1) as a white solid (62.0 mg, 96%).

Mp 163-165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.91 (d, 2H, *J* = 8.4 Hz, 2 × Ar***H***), 7.61-7.66 (m, 4H, 4 × Ar***H***), 7.47 (dd, 2H, *J* = 8.4 Hz, *J* = 7.2 Hz, 2 × Ar***H***), 7.40 (t, 1H, *J* = 7.2 Hz, Ar***H***), 5.38 (t, 1H, *J* = 1.9 Hz, C=C***H$_A$***H$_B$), 5.22 (t, 1H, *J* = 2.1 Hz, C=CH$_A$***H$_B$***), 3.69 (s, 3H, OC***H$_3$***), 2.87 (ddd, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, *J* = 6.9 Hz, C(O)CC***H$_A$***H$_B$), 2.52-2.55 (m, 2H, CH$_2$=CC***H$_2$***), 2.23 (ddd, 1H, *J* = 13.8 Hz, *J* = 7.1 Hz, *J* = 7.1 Hz, C(O)CCH$_A$***H$_B$***), 1.83-1.92 (m, 1H, CH$_2$=CCH$_2$C***H$_A$***H$_B$), 1.69-1.77 (m, 1H, CH$_2$=CCH$_2$CH$_A$***H$_B$***); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 194.7 (Ph***C***(O)), 172.5 (***C***(O)O), 149.3 (***C***=CH$_2$), 145.4 (***C***, Ar), 139.7 (***C***, Ar), 133.8 (***C***, Ar), 129.5 (2***C***, Ar), 129.0 (2***C***, Ar), 128.3 (***C***, Ar), 127.2 (2***C***, Ar), 127.1 (2***C***, Ar), 112.0 (C=***C***H$_2$), 67.5 (C(O)***C***), 52.8 (O***C***H$_3$), 36.9 (C(O)C***C***H$_2$), 34.3 (CH$_2$=C***C***H$_2$), 24.3 (CH$_2$=CCH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2952 (C-H), 1729 (C=O), 1680 (C=O), 1600 (C=C); **MS** (ES+) m/z (rel. intensity %) 321 (M+H$^+$, 100); **HRMS** (ESI+) calcd. $C_{21}H_{21}O_3$ [M+H]$^+$ 321.1485, found 321.1487.

Preparation and characterisation of *rac*-1,4-phenylene bis ((1-carboxyethyl-2-methylenecyclopentyl)methanone) (±)-317q



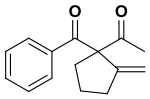
(±)-317q

Synthesised from compound **316q** (82.0 mg, 0.2 mmol) according to general procedure P. Compound **317q** was obtained after flash column chromatography (PE/Et_2O = 10:1) as a white solid (78.0 mg, 96%).

Mp 100-101 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.78 (s, 4H, 4 × Ar***H***), 5.30 (t, 2H, *J* = 1.8 Hz, 2 × C=C***H$_A$***H$_B$), 5.11 (t, 2H, *J* = 2.1 Hz, 2 × C=CH$_A$***H$_B$***), 3.61 (s, 6H, 2 × OC***H$_3$***), 2.75 (td, 2H, *J* = 13.5 Hz, *J* = 6.9 Hz, 2 × C(O)CC***H$_A$***H$_B$), 2.45 (tt, 4H, *J* = 7.6 Hz, *J* = 1.9 Hz, 2 ×

CH_2=CC***H*****$_2$**), 2.06-2.12 (m, 2H, 2 × C(O)CCH$_A$***H*****$_B$**), 1.80 (pd, 2H, *J* = 12.7 Hz, *J* = 7.4 Hz, 2 × CH_2=CCH$_2$C***H*****$_A$**H$_B$), 1.60-1.68 (m, 2H, 2 × CH_2=CCH$_2$CH$_A$***H*****$_B$**); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 194.7 (2***C***, Ph***C***(O)), 172.0 (2***C***, ***C***(O)O), 148.9 (2***C***, ***C***=CH_2), 138.3 (2***C***, Ar), 128.8 (4***C***, Ar), 112.3 (2***C***, C=***C***H$_2$), 67.6 (2***C***, C(O)***C***), 52.9 (2***C***, O***C***H$_3$), 36.6 (2***C***, C(O)C***C***H$_2$), 34.2 (2***C***, CH_2=C***C***H$_2$), 24.3 (2***C***, CH_2=CCH$_2$***C***H$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2953 (C-H), 1738 (C=O), 1688 (C=O); **MS** (ES+) m/z (rel. intensity %) 411.21 (M+H$^+$, 100); **HRMS** (ESI+) calcd. $C_{24}H_{27}O_6$ [M+H]$^+$ 411.1889, found 411.1891.

Preparation and characterisation of *rac*-1-acetyl-1-benzoyl-2-methylene-cyclopentane (±)-317p

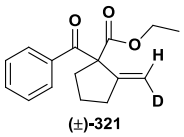


(±)-317p

Synthesised from compound **316p** (45.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-317p** was obtained after flash column chromatography on silica gel (PE/Et$_2$O = 15:1) as a colourless oil (42.0 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.77 (d, 2H, *J* = 7.4 Hz, 2 × ArH), 7.52 (t, 1H, *J* = 7.5 Hz, ArH), 7.41 (dd, 2H, *J* = 7.5 Hz, *J* = 7.4 Hz, 2 × ArH), 5.41 (t, 1H, *J* = 2.0 Hz, C=CH$_A$H$_B$), 5.12 (t, 1H, *J* = 2.2 Hz, C=CH$_A$H$_B$), 2.74 (ddd, 1H, *J* = 13.3 Hz, *J* = 6.5 Hz, *J* = 6.5 Hz, C(O)CCH$_A$H$_B$), 2.46-2.57 (m, 2H, CH_2=CCH$_2$), 2.19-2.25 (m, 1H, C(O)CCH$_A$H$_B$), 2.23 (s, 3H, C(O)CH$_3$), 1.73-1.85 (m, 2H, CH_2=CCH$_2$CH$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 204.5 (C(O)CH$_3$), 197.9 (PhC(O)), 148.9 (C=CH$_2$), 135.3 (C, Ar), 132.8 (C, Ar), 129.3 (2C, Ar), 128.4 (2C, Ar), 113.2 (C=CH$_2$), 75.4 (C(O)C), 35.8 (C(O)CH$_3$), 34.2 (C(O)CCH$_2$), 27.2 (CH_2=CCH$_2$), 24.2 (CH_2=CCH$_2$CH$_2$); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2957 (C-H), 1684 (C=O), 1596 (C=C); **MS** (ES+) m/z (rel. intensity %) 229.1 (M+H$^+$, 94); **HRMS** (ESI+) calcd. $C_{15}H_{17}O_2$ [M+H]$^+$ 229.1218, found 229.1223.

Preparation and characterisation of *rac*-(*E*)-1-benzoyl-2-deuteromethylene-cyclopentanecarboxylic acid ethyl ester (±)-321



(±)-321

Synthesised from compound **320** (52.0 mg, 0.2 mmol) according to general procedure P. Compound **(±)-321** was obtained after flash column chromatography on silica gel (PE/Et_2O = 15:1) as a colourless oil (33.0 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.76-7.78 (m, 2H, 2 × Ar***H***), 7.45 (t, 1H, *J* = 7.4 Hz, Ar***H***), 7.34 (t, 2H, *J* = 7.7 Hz, 2 × Ar***H***), 5.29 (t, 0.07H, *J* = 1.9 Hz, C=C***H$_A$***H_B), 5.13 (t, 0.9H, *J* = 2.2 Hz, C=CH_A***H$_B$***), 4.00-4.11 (m, 2H, OC***H$_2$***), 2.78 (td, 1H, *J* = 13.5 Hz, *J* = 6.9 Hz, C(O)CC***H$_A$***H_B), 2.43-2.46 (m, 2H, CH_2=CC***H$_2$***), 2.09-2.14 (m, 1H, C(O)CCH_A***H$_B$***), 1.74-1.83 (m, 1H, CH_2=CCH_2C***H$_A$***H_B), 1.59-1.64 (m, 1H, CH_2=CCH_2CH_A***H$_B$***), 0.99 (t, 3H, *J* = 7.1 Hz, OCH_2C***H$_3$***); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 195.4 (Ph***C***(O)), 171.8 (***C***(O)O), 149.4 (***C***=CH_2), 135.4 (***C***, Ar), 132.6 (***C***, Ar), 128.8 (2***C***, Ar), 128.4 (2***C***, Ar), 111.8 (C=***C***H_2), 67.4 (C(O)***C***), 61.6 (O***C***H_2), 36.8 (C(O)C***C***H_2), 34.3 (CH_2=C***C***H_2), 24.3 (CH_2=CCH_2***C***H_2), 13.7 (OCH_2***C***H_3); **FT-IR** ν_{max}(NaCl)/cm^{-1} 2979 (C-H), 1731 (C=O), 1677 (C=O), 1644 (C=C); **MS** (ES+) m/z (rel. intensity %) 282.18 (M+Na$^+$, 100); **HRMS** (ESI+) calcd. $C_{16}H_{17}DO_3$ [M+Na]$^+$ 282.1567, found 282.1568.

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Appendix One: List of Tables, Schemes and Figures

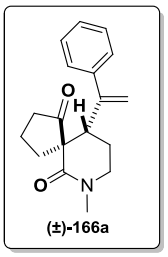
Chapter One Introduction

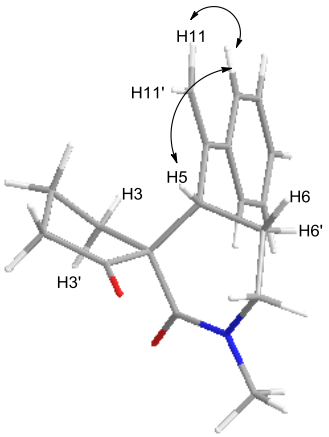
Chapter Two Palladium Catalysed Diastereoselective Arylative or Vinylative Allene Carbocyclisation Reactions

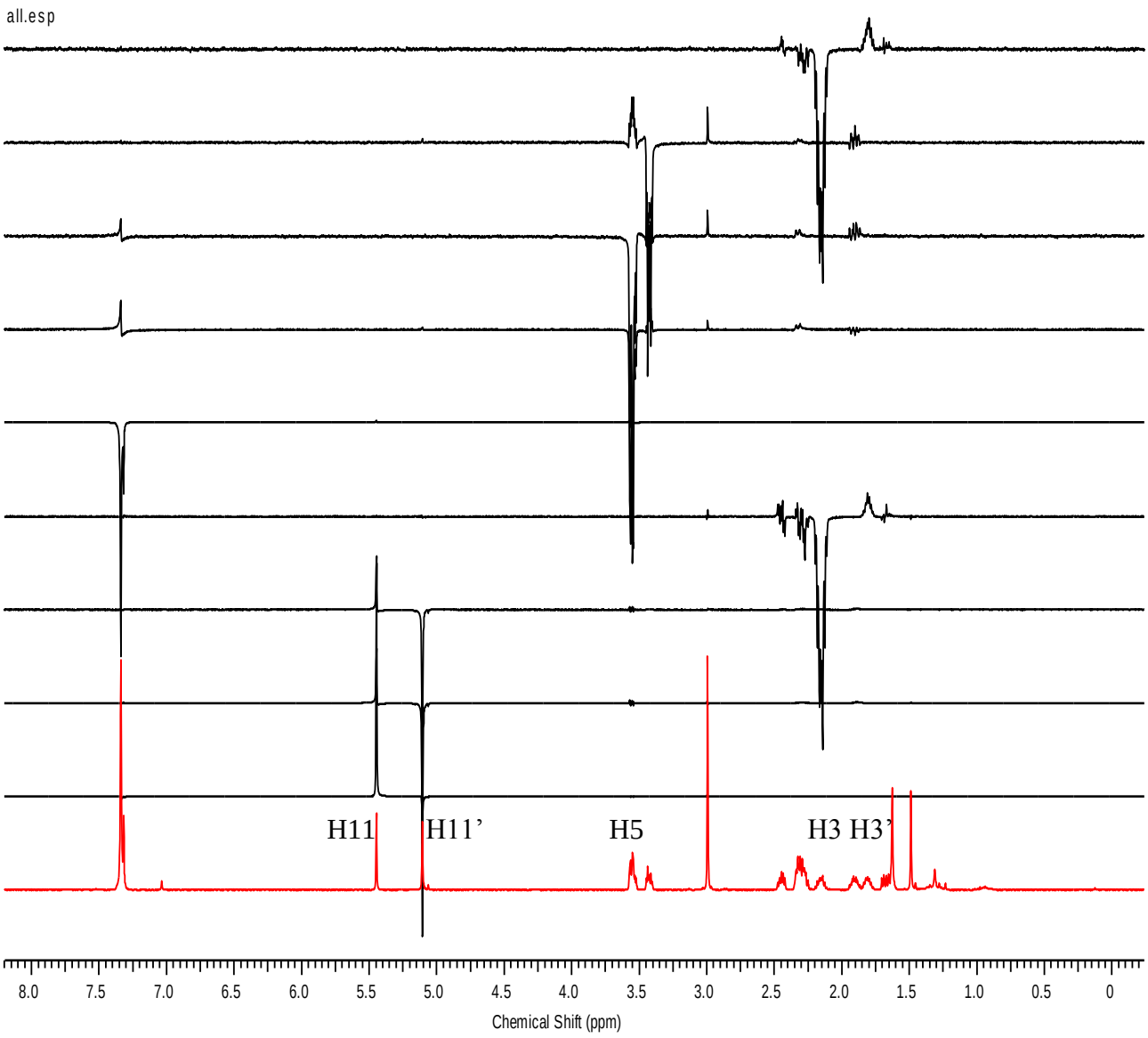
Chapter Four Carbocyclisation of Allenes via Enamine Catalysis

Chapter Five Boronic Acid Catalysed Ene Carbocyclization of Acetylenic Dicarbonyl Compounds

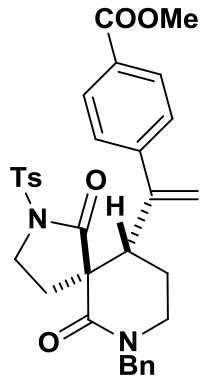
Appendix Two: nOe data for (±)-166a

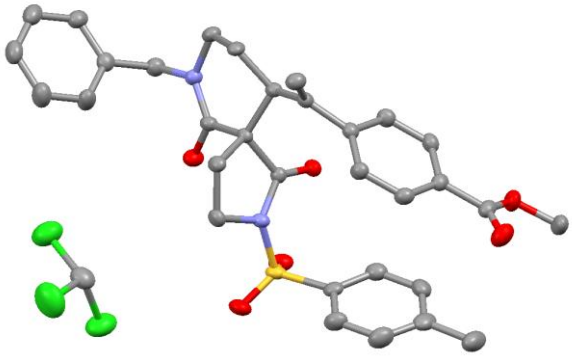


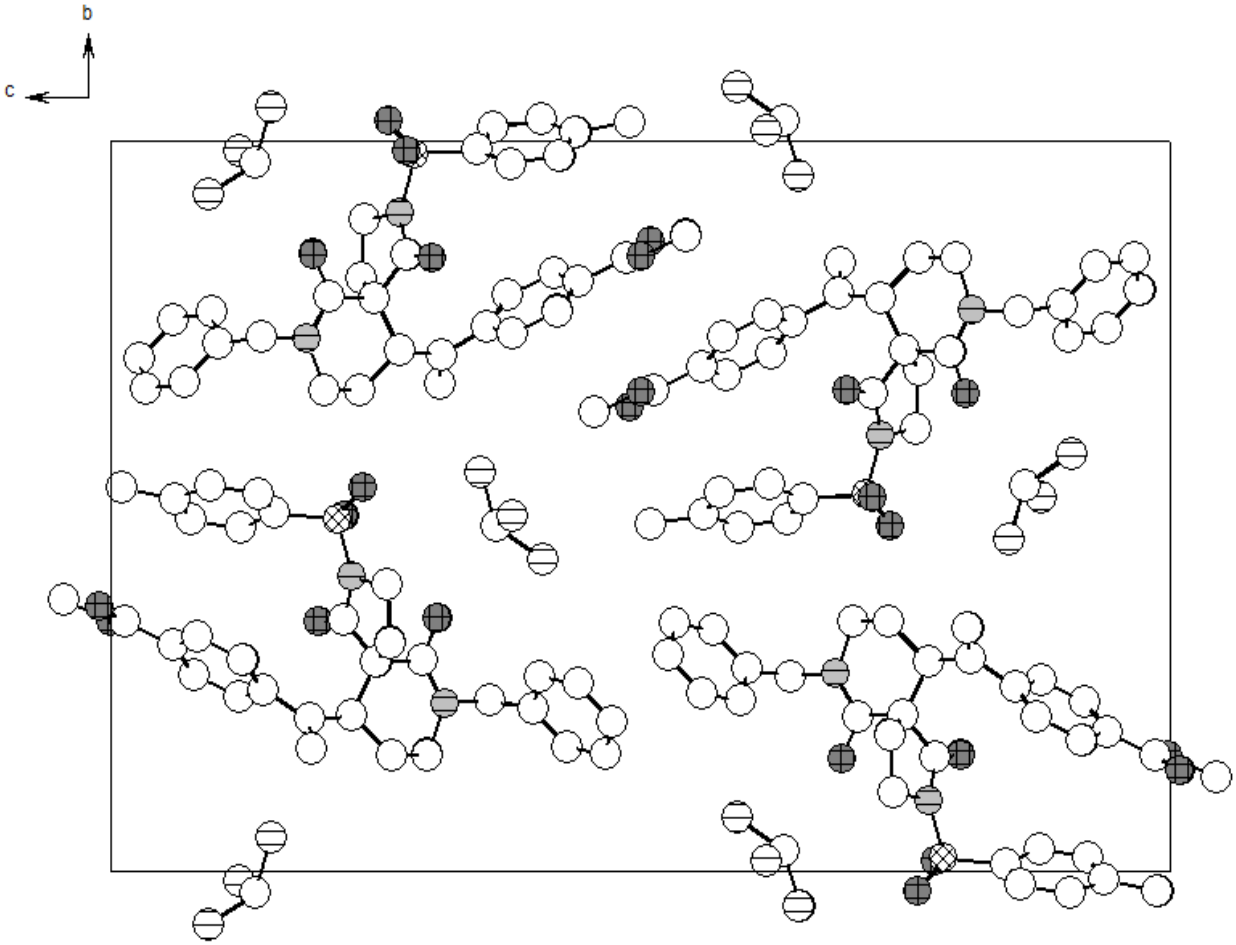




Appendix Three: Crystallographic data for (±)-167i (with $CDCl_3$)







Crystal data and structure refinement for (±)-167i

Crystal data

$C_{33}H_{33}C_{l3}N_2O_6S$	D_x = 1.418 Mg m^{-3}
Mr = 692.06	Melting point: not measured K
Orthorhombic, $P2_12_12_1$	Mo *K*α radiation, λ = 0.71073 Å
Hall symbol: P 2ac 2ab	Cell parameters from 4047 reflections
a = 5.7619 (1) Å	θ = 5–27°
b = 19.3032 (2) Å	μ = 0.40 mm−1
c = 29.1369 (5) Å	*T* = 150 K
V = 3240.70 (9) Å3	Block, colourless
Z = 4	0.26 × 0.10 × 0.10 mm
F(000) = 1440	

Data collection

Area diffractometer	5087 reflections with $I > 2.0\sigma(I)$
graphite	R_{int} = 0.067
ω scans	θ_{max} = 27.5°, θ_{min} = 5.2°
Absorption correction: multi-scan	
DENZO/SCALEPACK (Otwinowski & Minor, 1997)	*h* = −7→7
T_{min} = 0.87, T_{max} = 0.96	*k* = −24→24
27770 measured reflections	*l* = −37→37
7385 independent reflections	

Refinement

Refinement on F^2	0 restraints
Least-squares matrix: full	Primary atom site location: structure-invariant direct methods
$R[F^2 > 2\sigma(F^2)]$ = 0.052	Hydrogen site location: inferred from neighbouring sites

	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ··· + A_{n-1}]*T_{n-1}(x)]
$wR(F^2)$ = 0.133	where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2
	A_i are: 8.72 12.1 6.00 1.70
S = 0.95	$(\Delta/\sigma)_{max}$ = 0.0003
7359 reflections	$\Delta\rho_{max}$ = 0.88 e Å^{-3}
406 parameters	$\Delta\rho_{min}$ = - 0.60 e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
S1	0.82079 (17)	0.51830 (5)	0.28676 (3)	0.0254
O2	1.0649 (5)	0.51380 (14)	0.27959 (10)	0.0323
O3	0.6687 (5)	0.47272 (14)	0.26268 (10)	0.0347
N4	0.7312 (6)	0.59766 (15)	0.27260 (10)	0.0229
C5	0.8667 (6)	0.65587 (19)	0.27963 (12)	0.0198
O6	1.0361 (5)	0.65955 (13)	0.30385 (9)	0.0249
C7	0.7684 (6)	0.71438 (17)	0.24920 (12)	0.0198
C8	0.7685 (7)	0.78631 (17)	0.27302 (12)	0.0211
C9	0.5968 (7)	0.79219 (18)	0.31205 (13)	0.0222
C10	0.6441 (7)	0.75297 (19)	0.35538 (13)	0.0236
C11	0.8538 (7)	0.7621 (2)	0.37858 (14)	0.0276
C12	0.8941 (7)	0.7317 (2)	0.42078 (14)	0.0283

C13	0.7215 (7)	0.69092 (19)	0.44100 (13)	0.0255
C14	0.5140 (8)	0.6801 (2)	0.41791 (14)	0.0291
C15	0.4752 (7)	0.7105 (2)	0.37498 (13)	0.0266
C16	0.7538 (8)	0.6595 (2)	0.48680 (13)	0.0286
O17	0.6001 (6)	0.63701 (17)	0.51037 (11)	0.0426
O18	0.9790 (6)	0.65827 (17)	0.49959 (10)	0.0369
C19	1.0287 (10)	0.6288 (2)	0.54421 (15)	0.0434
C20	0.4094 (7)	0.8324 (2)	0.31022 (15)	0.0293
C21	0.7320 (8)	0.84103 (18)	0.23550 (13)	0.0250
C22	0.9326 (7)	0.84051 (19)	0.20158 (14)	0.0273
N23	0.9861 (6)	0.77038 (16)	0.18547 (11)	0.0241
C24	0.9236 (6)	0.71150 (18)	0.20650 (13)	0.0225
O25	0.9815 (5)	0.65390 (14)	0.19164 (9)	0.0320
C26	1.1155 (7)	0.7667 (2)	0.14207 (14)	0.0294
C27	0.9567 (7)	0.7766 (2)	0.10157 (13)	0.0267
C28	0.9938 (8)	0.8296 (2)	0.06985 (14)	0.0331
C29	0.8418 (9)	0.8392 (2)	0.03353 (15)	0.0391
C30	0.6540 (8)	0.7965 (2)	0.02763 (15)	0.0384
C31	0.6158 (9)	0.7434 (3)	0.05899 (16)	0.0428
C32	0.7638 (8)	0.7337 (2)	0.09544 (14)	0.0370
C33	0.5261 (7)	0.68709 (19)	0.23610 (14)	0.0261
C34	0.5409 (7)	0.60771 (19)	0.23944 (13)	0.0264
C35	0.7665 (7)	0.51042 (18)	0.34556 (13)	0.0266
C36	0.9332 (8)	0.5309 (2)	0.37746 (15)	0.0330
C37	0.8916 (8)	0.5195 (2)	0.42373 (15)	0.0365

C38	0.6864 (9)	0.4886 (2)	0.43884 (15)	0.0381
C39	0.5224 (9)	0.4700 (2)	0.40629 (17)	0.0428
C40	0.5587 (7)	0.4813 (2)	0.36017 (16)	0.0346
C41	0.6494 (11)	0.4734 (3)	0.48914 (16)	0.0522
C42	0.1004 (8)	0.5289 (2)	0.13659 (18)	0.0421
Cl43	0.2496 (3)	0.57361 (7)	0.09245 (5)	0.0636
Cl44	0.2486 (3)	0.45266 (7)	0.15098 (5)	0.0600
Cl45	-0.1849 (3)	0.51332 (10)	0.12058 (6)	0.0787
H81	0.9239	0.7930	0.2858	0.0255*
H111	0.9690	0.7899	0.3655	0.0342*
H121	1.0352	0.7389	0.4361	0.0348*
H141	0.3977	0.6535	0.4317	0.0351*
H151	0.3352	0.7027	0.3592	0.0343*
H193	0.9619	0.6570	0.5681	0.0678*
H192	1.1932	0.6265	0.5488	0.0683*
H191	0.9638	0.5831	0.5457	0.0681*
H201	0.3810	0.8587	0.2835	0.0362*
H202	0.3103	0.8346	0.3360	0.0359*
H261	1.1914	0.7216	0.1402	0.0373*
H262	1.2325	0.8032	0.1417	0.0370*
H281	1.1220	0.8585	0.0736	0.0410*
H291	0.8666	0.8751	0.0128	0.0490*
H301	0.5538	0.8032	0.0028	0.0480*
H311	0.4881	0.7142	0.0555	0.0529*
H321	0.7372	0.6983	0.1165	0.0454*

H331	0.4857	0.7013	0.2050	0.0316*
H332	0.4117	0.7041	0.2579	0.0316*
H341	0.3983	0.5878	0.2510	0.0331*
H342	0.5791	0.5871	0.2097	0.0329*
H361	1.0709	0.5512	0.3671	0.0400*
H371	1.0035	0.5323	0.4453	0.0448*
H391	0.3840	0.4494	0.4159	0.0521*
H401	0.4449	0.4697	0.3389	0.0431*
H413	0.7875	0.4852	0.5062	0.0781*
H412	0.5209	0.4999	0.5007	0.0781*
H411	0.6194	0.4252	0.4931	0.0783*
H421	0.0971	0.5588	0.1637	0.0520*
H212	0.7221	0.8863	0.2497	0.0319*
H211	0.5862	0.8312	0.2189	0.0322*
H222	1.0692	0.8593	0.2169	0.0341*
H221	0.8938	0.8694	0.1751	0.0343*

Atomic displacement parameters (Å2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0273 (5)	0.0148 (4)	0.0341 (5)	-0.0001 (4)	0.0025 (4)	0.0001 (4)
O2	0.0283 (14)	0.0236 (13)	0.0450 (17)	0.0051 (13)	0.0089 (13)	0.0021 (13)
O3	0.0411 (17)	0.0202 (14)	0.0428 (17)	-0.0042 (13)	-0.0006 (14)	-0.0043 (12)
N4	0.0245 (17)	0.0164 (13)	0.0278 (16)	-0.0014 (13)	-0.0010 (14)	-0.0004 (12)
C5	0.0167 (18)	0.0218 (17)	0.0209 (18)	0.0007 (14)	0.0008 (14)	0.0004 (14)
O6	0.0253 (14)	0.0233 (13)	0.0260 (14)	-0.0012 (11)	-0.0042 (12)	-0.0011 (11)
C7	0.0197 (18)	0.0171 (15)	0.0226 (17)	0.0001 (14)	-0.0010 (15)	-0.0021 (13)

C8	0.0217 (18)	0.0172 (15)	0.0245 (18)	0.0003 (15)	-0.0013 (15)	0.0010 (13)
C9	0.0235 (19)	0.0200 (17)	0.0231 (19)	-0.0016 (15)	0.0017 (15)	-0.0024 (14)
C10	0.025 (2)	0.0222 (17)	0.0237 (19)	0.0004 (15)	-0.0002 (16)	-0.0024 (15)
C11	0.024 (2)	0.029 (2)	0.030 (2)	-0.0028 (16)	0.0011 (17)	-0.0006 (16)
C12	0.029 (2)	0.030 (2)	0.026 (2)	-0.0006 (17)	-0.0045 (17)	-0.0043 (17)
C13	0.031 (2)	0.0228 (17)	0.0228 (18)	0.0029 (17)	0.0027 (17)	-0.0006 (15)
C14	0.030 (2)	0.0249 (19)	0.032 (2)	-0.0023 (17)	0.0031 (18)	0.0026 (16)
C15	0.024 (2)	0.027 (2)	0.028 (2)	-0.0028 (17)	-0.0010 (17)	0.0024 (16)
C16	0.039 (2)	0.0232 (18)	0.024 (2)	0.0047 (18)	0.0028 (19)	0.0024 (15)
O17	0.046 (2)	0.0451 (19)	0.0365 (19)	0.0056 (15)	0.0068 (15)	0.0119 (15)
O18	0.0442 (19)	0.0400 (17)	0.0265 (14)	-0.0046 (15)	-0.0094 (14)	0.0057 (13)
C19	0.060 (3)	0.040 (2)	0.030 (2)	-0.014 (2)	-0.015 (2)	0.0087 (19)
C20	0.030 (2)	0.025 (2)	0.033 (2)	0.0003 (17)	0.0043 (18)	0.0029 (17)
C21	0.035 (2)	0.0147 (15)	0.0251 (18)	0.0019 (16)	0.0016 (17)	0.0014 (14)
C22	0.033 (2)	0.0212 (17)	0.028 (2)	-0.0025 (17)	0.0008 (18)	0.0058 (16)
N23	0.0266 (17)	0.0218 (15)	0.0240 (16)	-0.0020 (13)	0.0026 (14)	0.0015 (13)
C24	0.0229 (18)	0.0176 (16)	0.0269 (19)	-0.0010 (14)	-0.0005 (16)	-0.0003 (15)
O25	0.0415 (17)	0.0230 (13)	0.0314 (15)	0.0016 (12)	0.0079 (13)	-0.0017 (12)
C26	0.030 (2)	0.030 (2)	0.029 (2)	-0.0023 (17)	0.0030 (17)	0.0011 (18)
C27	0.028 (2)	0.0277 (19)	0.0243 (19)	0.0041 (17)	0.0044 (17)	-0.0026 (15)
C28	0.042 (3)	0.026 (2)	0.031 (2)	0.0002 (19)	0.005 (2)	0.0015 (17)
C29	0.058 (3)	0.031 (2)	0.028 (2)	0.008 (2)	0.002 (2)	0.0015 (18)
C30	0.043 (3)	0.043 (3)	0.028 (2)	0.007 (2)	-0.007 (2)	-0.0015 (19)
C31	0.040 (3)	0.057 (3)	0.032 (2)	-0.010 (2)	-0.004 (2)	0.001 (2)
C32	0.040 (2)	0.045 (2)	0.026 (2)	-0.014 (2)	0.001 (2)	0.0061 (19)

C33	0.028 (2)	0.0211 (17)	0.030 (2)	0.0018 (16)	-0.0056 (18)	0.0025 (15)
C34	0.024 (2)	0.0265 (19)	0.028 (2)	-0.0037 (16)	-0.0046 (17)	-0.0024 (16)
C35	0.030 (2)	0.0172 (16)	0.0326 (19)	0.0027 (17)	0.0009 (17)	0.0052 (15)
C36	0.034 (2)	0.025 (2)	0.040 (2)	0.0013 (18)	0.001 (2)	0.0023 (17)
C37	0.050 (3)	0.025 (2)	0.035 (2)	0.000 (2)	-0.006 (2)	-0.0050 (19)
C38	0.056 (3)	0.0212 (19)	0.037 (2)	0.007 (2)	0.010 (2)	0.0002 (18)
C39	0.042 (3)	0.040 (3)	0.046 (3)	0.000 (2)	0.013 (2)	0.009 (2)
C40	0.028 (2)	0.032 (2)	0.044 (2)	-0.004 (2)	0.0009 (19)	0.008 (2)
C41	0.085 (4)	0.035 (3)	0.036 (3)	-0.001 (3)	0.015 (3)	0.003 (2)
C42	0.041 (3)	0.035 (2)	0.051 (3)	0.005 (2)	0.002 (2)	-0.010 (2)
Cl43	0.0665 (10)	0.0537 (8)	0.0705 (9)	0.0037 (7)	0.0094 (8)	0.0178 (7)
Cl44	0.0713 (9)	0.0407 (6)	0.0679 (9)	0.0153 (7)	0.0175 (8)	0.0092 (6)
Cl45	0.0482 (8)	0.1032 (13)	0.0848 (11)	-0.0090 (9)	-0.0107 (8)	-0.0161 (10)

Geometric parameters (Å, °)

S1—O2	1.425 (3)	N23—C24	1.341 (4)
S1—O3	1.426 (3)	N23—C26	1.470 (5)
S1—N4	1.668 (3)	C24—O25	1.239 (4)
S1—C35	1.748 (4)	C26—C27	1.505 (6)
N4—C5	1.384 (5)	C26—H261	0.976
N4—C34	1.474 (5)	C26—H262	0.975
C5—O6	1.207 (4)	C27—C28	1.395 (6)
C5—C7	1.544 (5)	C27—C32	1.397 (6)
C7—C8	1.552 (5)	C28—C29	1.387 (6)
C7—C24	1.533 (5)	C28—H281	0.933
C7—C33	1.540 (5)	C29—C30	1.371 (7)

C8—C9	1.512 (5)	C29—H291	0.930
C8—C21	1.535 (5)	C30—C31	1.391 (7)
C8—H81	0.979	C30—H301	0.934
C9—C10	1.497 (5)	C31—C32	1.375 (6)
C9—C20	1.330 (5)	C31—H311	0.933
C10—C11	1.396 (5)	C32—H321	0.932
C10—C15	1.394 (5)	C33—C34	1.538 (5)
C11—C12	1.381 (6)	C33—H331	0.974
C11—H111	0.935	C33—H332	0.972
C12—C13	1.399 (5)	C34—H341	0.967
C12—H121	0.938	C34—H342	0.979
C13—C14	1.388 (6)	C35—C36	1.394 (6)
C13—C16	1.478 (5)	C35—C40	1.390 (6)
C14—C15	1.400 (6)	C36—C37	1.387 (6)
C14—H141	0.935	C36—H361	0.935
C15—H151	0.940	C37—C38	1.396 (6)
C16—O17	1.201 (5)	C37—H371	0.933
C16—O18	1.350 (5)	C38—C39	1.386 (7)
O18—C19	1.448 (5)	C38—C41	1.510 (6)
C19—H193	0.964	C39—C40	1.377 (6)
C19—H192	0.959	C39—H391	0.934
C19—H191	0.958	C40—H401	0.930
C20—H201	0.946	C41—H413	0.965
C20—H202	0.944	C41—H412	0.961
C21—C22	1.521 (6)	C41—H411	0.954

C21—H212	0.968	C42—Cl43	1.771 (5)
C21—H211	0.988	C42—Cl44	1.752 (5)
C22—N23	1.466 (5)	C42—Cl45	1.735 (5)
C22—H222	0.975	C42—H421	0.979
C22—H221	0.977		
O2—S1—O3	119.79 (19)	C22—N23—C26	115.3 (3)
O2—S1—N4	108.99 (17)	C24—N23—C26	119.2 (3)
O3—S1—N4	104.76 (17)	C7—C24—N23	119.8 (3)
O2—S1—C35	108.36 (19)	C7—C24—O25	118.3 (3)
O3—S1—C35	108.56 (18)	N23—C24—O25	121.9 (3)
N4—S1—C35	105.48 (16)	N23—C26—C27	111.1 (3)
S1—N4—C5	122.3 (3)	N23—C26—H261	108.7
S1—N4—C34	120.9 (2)	C27—C26—H261	109.9
C5—N4—C34	114.2 (3)	N23—C26—H262	109.0
N4—C5—O6	126.2 (3)	C27—C26—H262	108.6
N4—C5—C7	107.6 (3)	H261—C26—H262	109.5
O6—C5—C7	126.1 (3)	C26—C27—C28	121.3 (4)
C5—C7—C8	113.4 (3)	C26—C27—C32	120.6 (4)
C5—C7—C24	103.0 (3)	C28—C27—C32	118.1 (4)
C8—C7—C24	113.3 (3)	C27—C28—C29	120.5 (4)
C5—C7—C33	103.0 (3)	C27—C28—H281	118.9
C8—C7—C33	114.7 (3)	C29—C28—H281	120.6
C24—C7—C33	108.4 (3)	C28—C29—C30	120.9 (4)
C7—C8—C9	113.8 (3)	C28—C29—H291	119.9
C7—C8—C21	107.3 (3)	C30—C29—H291	119.2

C9—C8—C21	113.2 (3)	C29—C30—C31	119.1 (4)
C7—C8—H81	106.9	C29—C30—H301	120.1
C9—C8—H81	107.5	C31—C30—H301	120.8
C21—C8—H81	107.8	C30—C31—C32	120.6 (5)
C8—C9—C10	118.5 (3)	C30—C31—H311	119.9
C8—C9—C20	123.0 (4)	C32—C31—H311	119.4
C10—C9—C20	118.5 (4)	C27—C32—C31	120.8 (4)
C9—C10—C11	120.2 (3)	C27—C32—H321	118.8
C9—C10—C15	121.0 (3)	C31—C32—H321	120.5
C11—C10—C15	118.7 (4)	C7—C33—C34	106.0 (3)
C10—C11—C12	121.6 (4)	C7—C33—H331	110.5
C10—C11—H111	119.3	C34—C33—H331	110.6
C12—C11—H111	119.1	C7—C33—H332	109.7
C11—C12—C13	119.6 (4)	C34—C33—H332	109.5
C11—C12—H121	120.5	H331—C33—H332	110.4
C13—C12—H121	119.9	C33—C34—N4	102.3 (3)
C12—C13—C14	119.6 (4)	C33—C34—H341	111.8
C12—C13—C16	121.5 (4)	N4—C34—H341	110.6
C14—C13—C16	119.0 (4)	C33—C34—H342	111.2
C13—C14—C15	120.5 (4)	N4—C34—H342	111.1
C13—C14—H141	119.5	H341—C34—H342	109.7
C15—C14—H141	120.0	S1—C35—C36	120.4 (3)
C14—C15—C10	120.1 (4)	S1—C35—C40	119.3 (3)
C14—C15—H151	120.4	C36—C35—C40	120.3 (4)
C10—C15—H151	119.6	C35—C36—C37	119.0 (4)

C13—C16—O17	124.9 (4)	C35—C36—H361	119.2
C13—C16—O18	112.2 (3)	C37—C36—H361	121.8
O17—C16—O18	123.0 (4)	C36—C37—C38	121.4 (4)
C16—O18—C19	116.4 (4)	C36—C37—H371	119.5
O18—C19—H193	110.4	C38—C37—H371	119.1
O18—C19—H192	109.8	C37—C38—C39	118.2 (4)
H193—C19—H192	108.7	C37—C38—C41	120.6 (5)
O18—C19—H191	108.9	C39—C38—C41	121.2 (5)
H193—C19—H191	109.4	C38—C39—C40	121.6 (4)
H192—C19—H191	109.7	C38—C39—H391	119.2
C9—C20—H201	119.2	C40—C39—H391	119.3
C9—C20—H202	119.0	C35—C40—C39	119.6 (4)
H201—C20—H202	121.8	C35—C40—H401	120.0
C8—C21—C22	110.7 (3)	C39—C40—H401	120.4
C8—C21—H212	109.0	C38—C41—H413	109.7
C22—C21—H212	109.2	C38—C41—H412	110.3
C8—C21—H211	109.5	H413—C41—H412	109.3
C22—C21—H211	109.0	C38—C41—H411	109.5
H212—C21—H211	109.4	H413—C41—H411	108.4
C21—C22—N23	112.0 (3)	H412—C41—H411	109.7
C21—C22—H222	108.3	Cl43—C42—Cl44	110.3 (3)
N23—C22—H222	108.7	Cl43—C42—Cl45	110.4 (3)
C21—C22—H221	109.6	Cl44—C42—Cl45	112.4 (3)
N23—C22—H221	108.8	Cl43—C42—H421	108.0
H222—C22—H221	109.4	Cl44—C42—H421	108.1

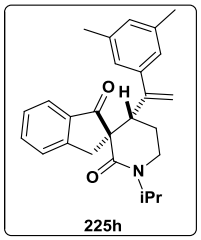
C22—N23—C24	125.5 (3)	Cl45—C42—H421	107.5

Hydrogen-bond geometry (Å, °)

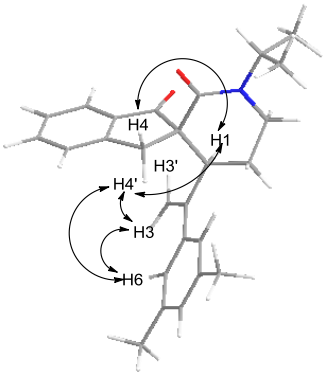
D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C15—H151···O6^{i}	0.94	2.50	3.415 (6)	163
C20—H201···O3^{ii}	0.95	2.59	3.472 (6)	155
C34—H341···O2^{i}	0.97	2.53	3.489 (6)	169
C42—H421···O25^{i}	0.98	2.12	2.977 (6)	146

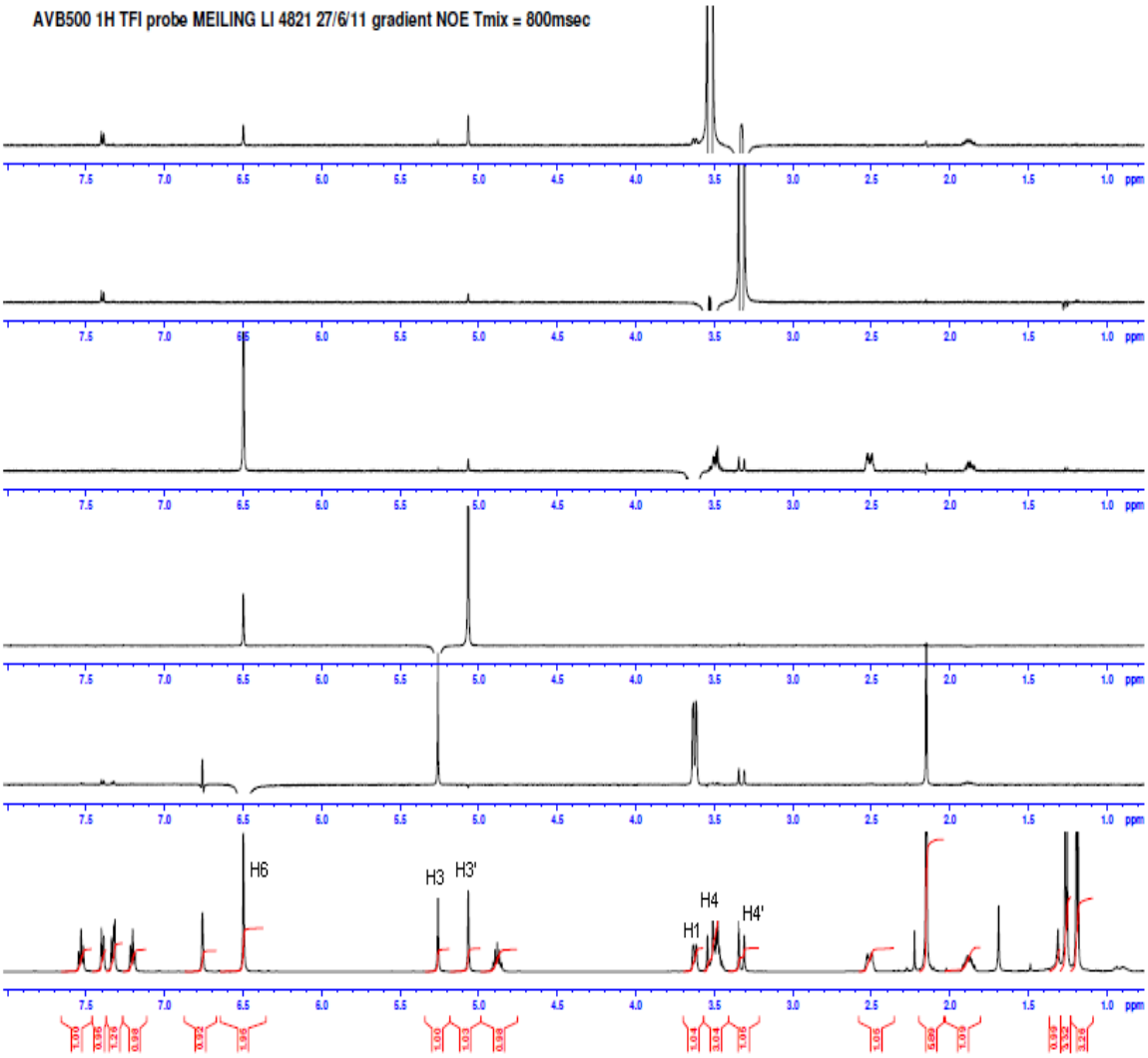
Symmetry codes: (i) *x*−1, *y*, *z*; (ii) −*x*+1, *y*+1/2, −*z*+1/2.

Appendix Four: nOe data for 225h

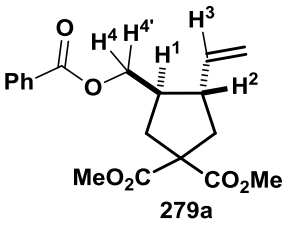


225h





Appendix Five: nOesy data for 279a



279a