Visible Light-Mediated Cyclizations of Cyclic Enones

Nicholas Alexander Parker

A dissertation presented in partial fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

of the

University of Oxford





Chemistry Research Laboratory
12 Mansfield Road
Oxford, OX1 3TA

Keble College
Parks Road
Oxford, OX1 3PG

Dedication

This thesis is dedicated to my family, who have always provided guidance and unconditional support throughout my life.

Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford and in Medicinal Chemistry at Vertex Pharmaceuticals, Boston, MA, USA between June 2016 and December 2019. The dissertation is a product of my own work and includes no results obtained through collaboration except where specifically indicated in the text.

Nicholas Alexander Parker

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List of Abbreviations

Δ	error
µ	micro-
Å	ångström
Ac	acetyl
aq	aqueous
Ar	generic aryl substituent
Boc	*tert*-butoxycarbonyl
Bn	benzyl
b.p.	boiling point
bpy	2,2'-bipyridine
Bt	benzotriazole
Bu	butyl
°C	degrees Celsius
CFL	compact fluorescent light
CH_2Cl_2	dichloromethane
CI	chemical ionization
conc.	concentration (table)/concentrated (text or figures)
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
dtbbpy	4,4'-di-*tert*-butyl-2,2'-dipyridyl
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt
e.e.	enantiomeric excess
equiv.	equivalents

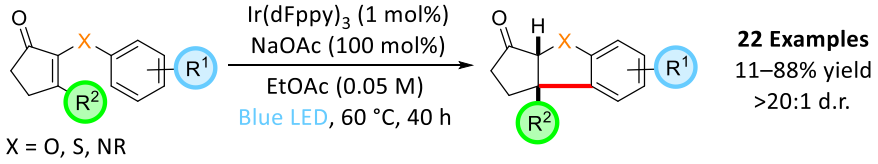
e.r.	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Formalin	37 wt% aqueous solution of formaldehyde
FWHM	full width at half maximum
g	gram(s)
HPLC	high performance liquid chromatography
h	hour(s)
hv	light
HAT	hydrogen atom transfer
HetAr	generic heteroaromatic substituent
HFIP	hexafluoroisopropanol
HFX	1,3-bis(trifluoromethyl)benzene
HRMS	high resolution mass spectrometry
Hz	hertz
i	*iso*-
IC	internal conversion
IUPAC	International Union of Pure and Applied Chemistry
i-$PrNEt_2$	*N*,*N*-diisopropylethylamine (Hünig's base)
IR	infrared
ISC	intersystem crossing
J	coupling constant
k	rate constant
L	litre(s)
LA	Lewis acid
LDA	lithium diisopropylamide
LED	light emitting diode
m	multiplet (NMR)

M	moles per litre
m	milli-
m-	*meta*-
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min	minute(s)
mol	moles
mol%	mole percentage
m.p.	melting point
nm	nanometre(s)
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
o-	*ortho*-
p-	*para*-
Ph	phenyl
$PhCF_3$	trifluorotoluene
PhOH	phenol
ppm	parts per million
ppy	2-phenylpyridine
Pr	propyl
quant.	quantitative
R	generic substituent
r.t.	ambient temperature (typically 21–23 °C)
t	*tert*-
T	temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TET	triplet energy transfer
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography

Ts	*para*-toluenesulfonyl
v/v	volume ratio
W	watt(s)
wt%	weight per weight loading
X	generic heteroatom

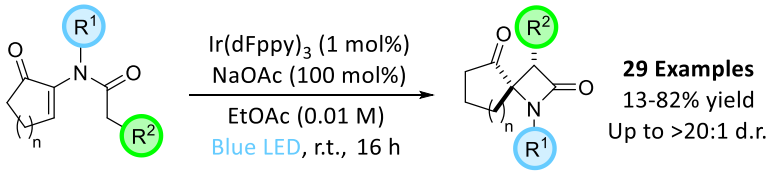
Abstract

The work outlined in this thesis covers the development of visible light-mediated cyclizations of cyclic enones. Chapter one provides an overview of photochemical cyclizations, focusing on visible light-mediated cyclizations using triplet energy transfer from a suitable sensitizer, as well as an overview of the photochemical cyclizations of cyclic enones. Chapter two discusses the development of a visible light-mediated intramolecular arylation of cyclic 2-arylheteroenones to generate a wide range of *cis*-fused heterocycles (**Scheme I**).



Scheme I. Visible light-mediated cyclization of cyclic 2-arylheteroenones

Chapter three details efforts into the photochemical synthesis of spirocyclic compounds *via* intramolecular hydrogen atom abstraction using a cyclic enone chromophore. Chapter four discusses the development of a visible light-mediated spirocyclization of cyclic 2-amidoenones (**Scheme II**). After initial optimization, the scope and scalability of the reaction was explored, and derivatization of the products investigated. Subsequent mechanistic experiments provided insight into the high diastereoselectivity of the reaction.



Scheme II. Visible light-mediated cyclization of cyclic 2-*N*-amidoenones

Chapter five looks at applications of the previously developed reactions to acyclic chromophore systems, and the challenges present in this modification.

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1 Introduction

1.1 Photochemistry

The use of light instead of heat to provide energy to chemical reactions has a long history, with the first recorded example dating back to 1834.[1,2] The direct transfer of energy to the substrate enables access to excited electronic states and their associated unusual reactivity.[3] Traditionally photochemistry has used short wavelength, high energy ultraviolet light to excite molecules to an excited singlet state S_n via absorption of a photon.[4,5] Typically, the molecule rapidly relaxes to the lowest energy singlet excited state S_1 from any higher singlet excited state S_n by a process known as internal conversion (IC).[6] The molecule can then react directly or undergo intersystem crossing (ISC) to the lowest energy triplet excited state T_1 before performing the desired reaction.[7] Alternatively the molecule can return to ground state S_0 from excited singlet state S_1 either non-radiatively by IC, or radiatively by fluorescence. Relaxation to the ground state from T_1 can also occur non-radiatively by ISC, or radiatively by phosphorescence. These transitions can be illustrated using Jablonski diagrams (**Figure 1**).

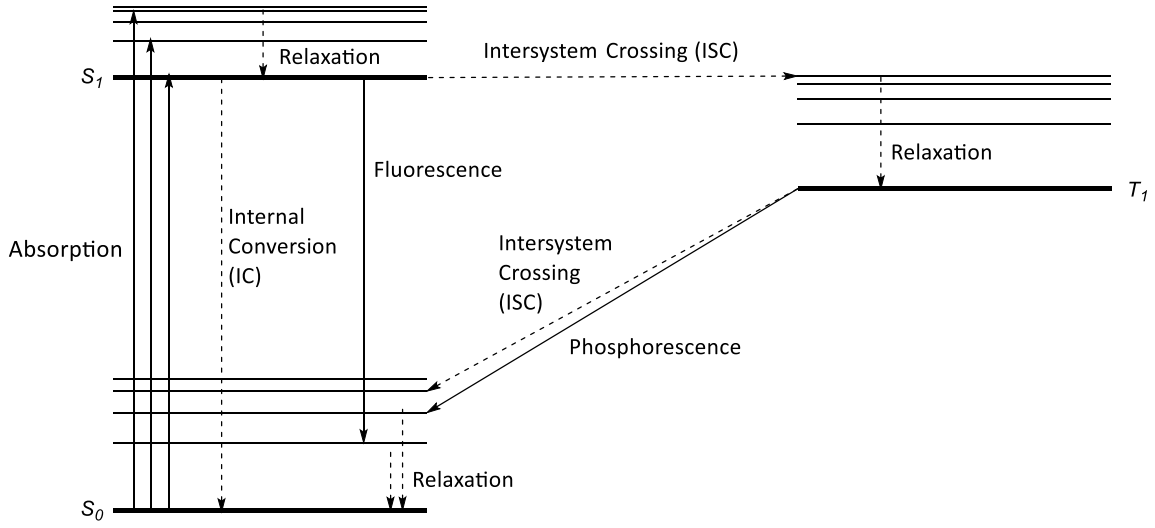


Figure 1. Jablonski diagram illustrating typical photochemical processes. Radiative processes are indicated with full arrows, whilst non-radiative processes are indicated with dashed arrows

If the singlet state reactivity is desired, direct irradiation works well, but if triplet state reactivity is desired unwanted photochemical process or side reactions can occur before ISC. This happens less frequently if ISC is efficient, such as when the singlet excited state S_1 and triplet excited state T_1 are close in energy or if the molecule contains a heavy atom.[8,9]

1.1.1 Triplet energy transfer

An alternative approach to directly access a molecule's triplet excited state is to use a sensitizer to excite the reacting molecule in a process known as triplet energy transfer (TET). This typically occurs *via* a Dexter-type mechanism as outlined in **Figure 2**.[10] Here, the ground state sensitizer $^1D_0$ is promoted to its excited singlet state $^1D_1$, before undergoing rapid ISC to its excited triplet state $^3D_1$. Once in close proximity (typically less than 1 nm), the sensitizer and the reacting molecule in its ground state $^1A_0$ exchange an electron *via* a Dexter mechanism, leading to the sensitizer returning to its ground state $^1D_0$ and the reacting molecule being excited directly to its triplet excited state $^3A_1$.

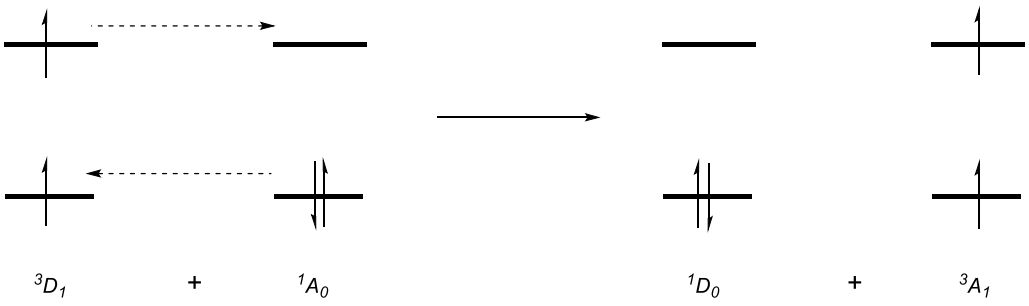
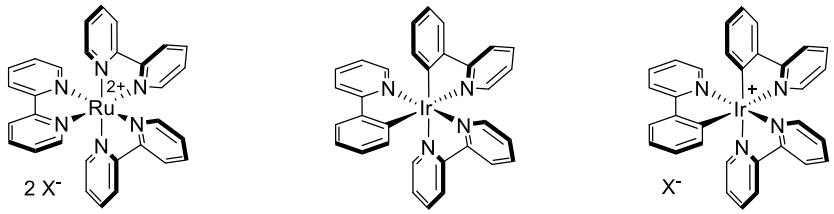


Figure 2. Illustration of Dexter triplet energy transfer

In addition to an overlap with the wavefunction of the quenching molecule, an efficient sensitizer requires a much higher absorption coefficient of the incident light than the reacting molecule, as well as a singlet excited state and triplet excited state which are close in energy to promote effective ISC.[11] Historically, ketones such as acetone or benzophenone have been the sensitizers of choice when used in combination with ultraviolet light, largely due to their low cost.[5] More recently, work on phosphorescent

dyes for light emitting diodes (LEDs) has led to the development of a variety of phosphors that are not only efficient triplet sensitizers but which also absorb strongly in the visible range.[12] In particular, ruthenium and iridium based bipyridyl or phenylpyridyl compounds have received significant attention from the synthetic organic community, mainly in the field of photoredox catalysis (**Figure 3**).[10,13–17] The heavy metal atom at the centre of these complexes enables efficient ISC, and metal-ligand charge transfer gives their excited triplet states long lifetimes.[18] The modular nature of the bipyridyl or phenylpyridyl ligands also allows for fine-tuning of various catalyst properties, including triplet state energy, which enables effective sensitization of the desired molecule.[19]



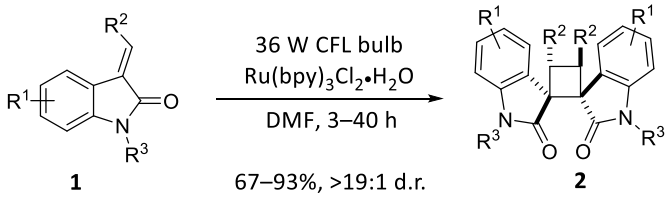
Ruthenium Homoleptic Iridium Heteroleptic Iridium

Figure 3. Core structures of common ruthenium or iridium based photocatalysts

1.2 Visible light-mediated energy transfer cyclizations

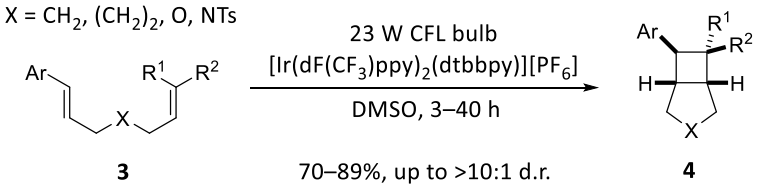
1.2.1 Racemic methods

The development of these new, efficient triplet state sensitizers has led to their extensive application in the field of synthetic organic chemistry.[10,17] Xiao and co-workers reported the visible light-mediated intermolecular homodimerization of 3-ylideneoxindoles **1** in the presence of a ruthenium photosensitizer (**Scheme 1**).[20]



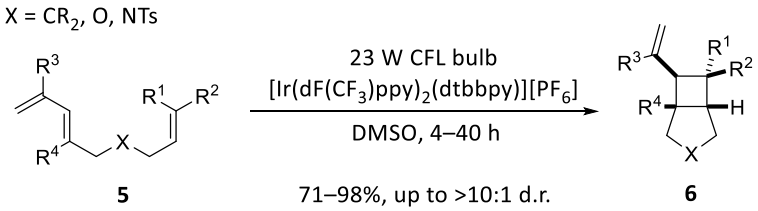
Scheme 1. Intermolecular [2+2] dimerization of 3-ylideneoxindoles

Concurrently, Yoon and co-workers reported an intramolecular visible light-mediated [2+2] cycloaddition of styrenes and pendant alkenes in the presence of an iridium photosensitizer, allowing for functionalised *cis*-fused cyclobutanes **4** to be synthesised under mild conditions (**Scheme 2**).[21]



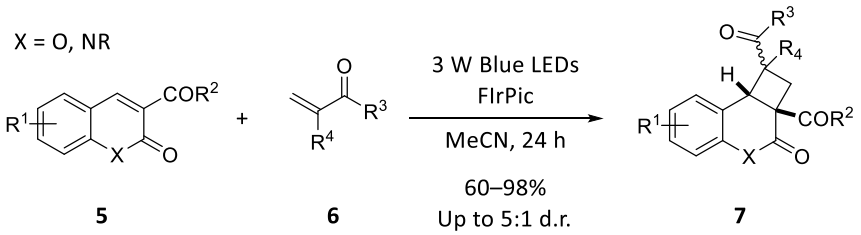
Scheme 2. Intramolecular [2+2] cycloaddition of styrenes

Yoon and co-workers subsequently expanded their intramolecular [2+2] cyclization to sensitize 1,3-dienes **5**, broadening the scope of the chemistry (**Scheme 3**).[22]



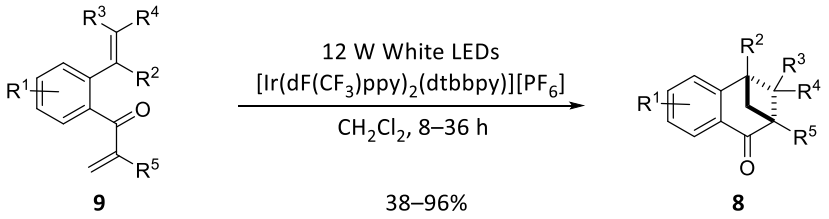
Scheme 3. Intramolecular [2+2] cycloaddition of 1,3-dienes

The first visible light-mediated intermolecular [2+2] heterodimeric cyclization was reported by Liu and co-workers in 2015 (**Scheme 4**).[23] By using FIrPic, an iridium photosensitizer, in combination with blue LED lights they were able to effect the intramolecular cycloaddition between coumarin-3-carboxylates **5** and acrylamides **6**.



Scheme 4. Intermolecular [2+2] cycloaddition coumarin-3-carboxylates and acrylamides

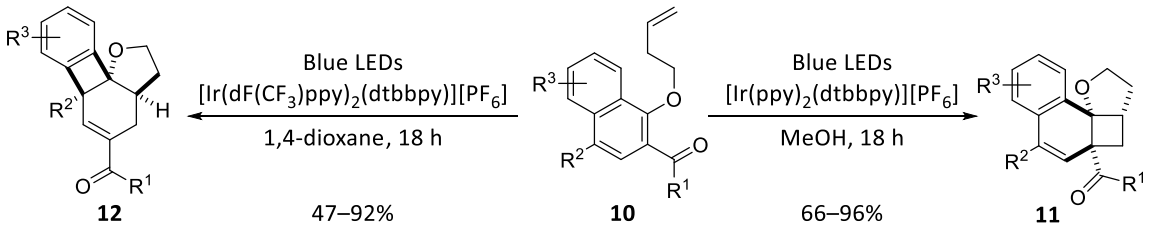
More recently, the Kwon group reported an intramolecular crossed [2+2] cycloaddition to synthesise bridged bicycloheptanones **8** from styrenic vinyl ketones **9** using an iridium photocatalyst in combination with white light (**Scheme 5**).[24]



Scheme 5. Intramolecular [2+2] cycloaddition to synthesise bridged bicycloheptanones

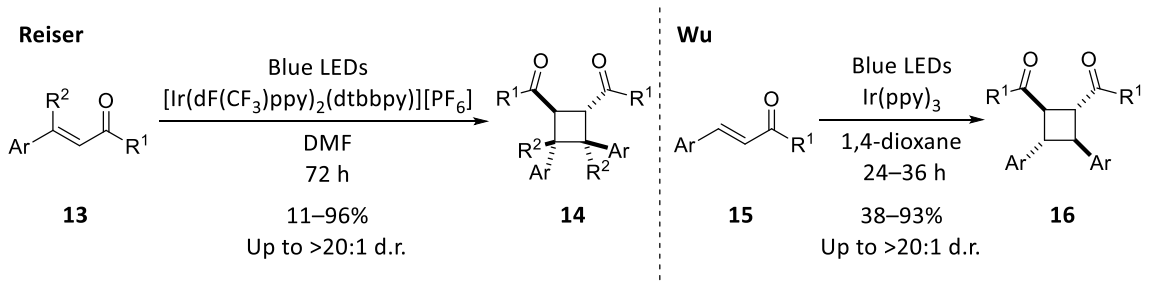
Photochemical [2+2] cycloadditions can also be incorporated into more complex photochemical cascades, such as that reported by Glorius and co-workers in 2018 (**Scheme 6**).[25] Electron deficient napthalenes with a pendant alkene such as **10** undergo efficient visible light-mediated intramolecular [2+2] cycloaddition to form tetracyclic cyclobutanes **11** in the presence of $[Ir(ppy)_2(dtbbpy)][PF_6]$ as the photocatalyst. However when $[Ir(dF(CF_3)ppy)_2(dtbbpy)][PF_6]$ was used as the photocatalyst, benzocyclobutanes **12** were formed as the product instead. The authors proposed the formation of cyclobutane **11** in both cases; however the higher triplet energy of the $[Ir(dF(CF_3)ppy)_2(dtbbpy)][PF_6]$ photocatalyst allows it to excite the styrene moiety in cyclobutane **11** *via* triplet energy transfer. Subsequent cyclobutane ring fragmentation in the triplet state, followed by

intersystem crossing and radical recombination, leads to the alternative benzocyclobutane products **12**.



Scheme 6. Catalyst-dependent intramolecular [2+2] cycloaddition cascade to form benzocyclobutanes

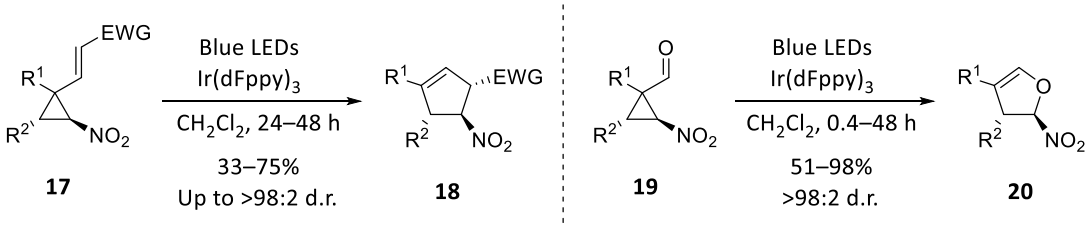
Concurrent work by Reiser and co-workers and Wu and co-workers led to the development of an intermolecular head-to-head homodimerization of chalcones and cinnamic acid derivatives (**Scheme 7**).[26,27] Reiser and co-workers extended their conditions to heterodimerization of cinnamic acid derivatives, whilst Wu and co-workers extended their conditions to the cross [2+2] reaction of stilbenes with electron deficient alkenes.



Scheme 7. Intermolecular [2+2] cycloaddition of chalcones and cinnamic acid derivatives

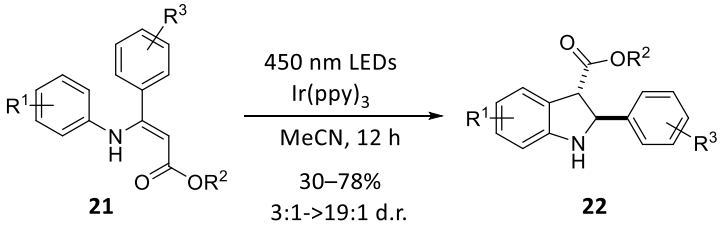
Outside of [2+2] cycloadditions, there have been significantly fewer reports of visible light-mediated energy transfer ring-forming reactions. These have mainly focussed on azide sensitization and cyclization of the resultant nitrene generated by extrusion of nitrogen gas to form pyrroles and indoles.[28–30] Alemán and co-workers reported a visible light-mediated intramolecular cyclopropane ring expansion, enabling the synthesis of

substituted cyclopentenes **18** and dihydrofurans **20** with good retention of starting material e.e. (**Scheme 8**).



Scheme 8. Intramolecular cyclopropane ring expansion

Wu and co-workers reported a visible light-mediated intramolecular cyclization of 3-aryl-3-anilino acrylates **21** to 2-aryl indolines **22** in the presence of an iridium photocatalyst (Scheme **9**).[31] The products were obtained in moderate yield and diastereoselectivity, and mechanistic investigations suggested that the reaction proceeds *via* triplet energy transfer.

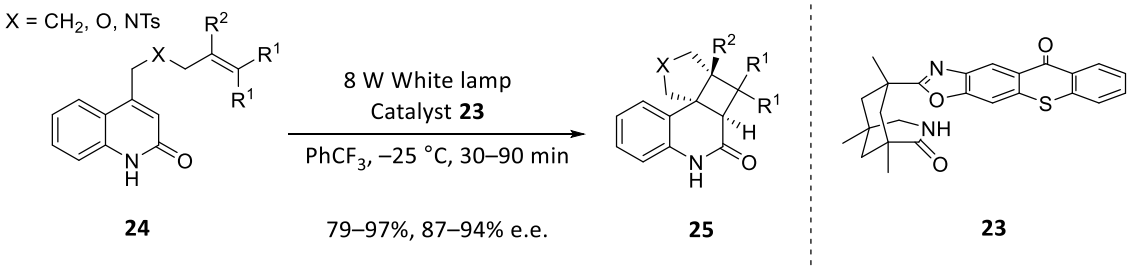


Scheme 9. Intramolecular arylation of 3-aryl-3-anilino acrylates

1.2.2 Catalytic enantioselective methods

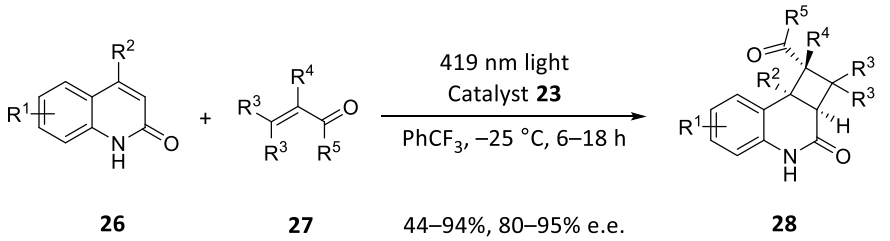
Pioneering work by Bach and co-workers allowed for the development of the first catalytic enantioselective intramolecular [2+2] cycloaddition by using a catalyst **23** with a thioxanthone sensitizer linked to a hydrogen bonding motif (**Scheme 10**).[32,33] By choosing a sensitizer with a short triplet lifetime, and having a complementary hydrogen bonding motif on the substrate **24**, only substrates bound in the correct orientation to the

photocatalyst would be excited and undergo the desired [2+2] cycloaddition enantioselectively.



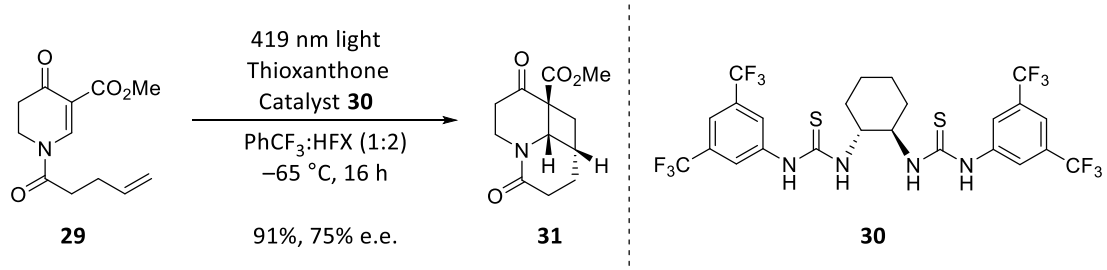
Scheme 10. Catalytic enantioselective intramolecular [2+2] cycloaddition of quinolones with pendant alkenes

Subsequently, the same group applied the same strategy to intermolecular [2+2] cycloaddition reactions of quinolones **26** with α,β-unsaturated carbonyl compounds **27** using the same catalyst (**Scheme 11**).[34]



Scheme 11. Catalytic enantioselective intermolecular [2+2] cycloaddition of quinolones with alkenes

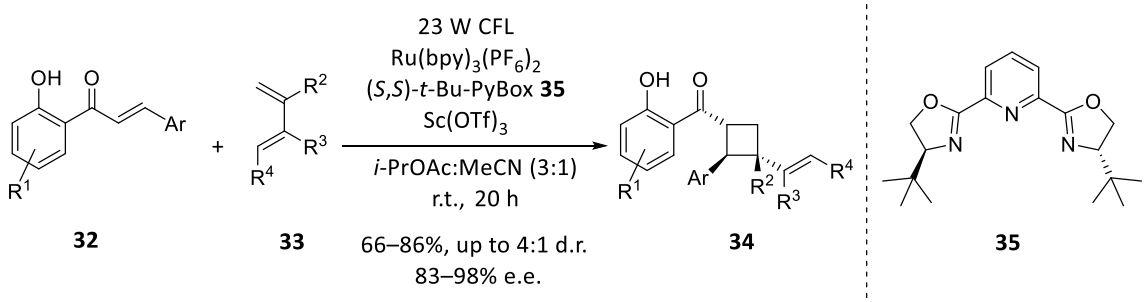
More recent work from Bach and co-workers demonstrated that the chiral hydrogen bonding recognition and the sensitizer could be separated whilst still allowing for the product to be obtained enantioselectively (**Scheme 12**).[35] By irradiating enone substrate **29** with visible light in the presence of chiral bisthiourea **30** and thioxanthone, the enantioenriched [2+2] intramolecular cycloaddition product **31** could be obtained in good yields and good e.e.. Preferential addition of the pendant alkene to the *si* face of the dihydropyridone was achieved by selective binding of the substrate **29** to one thiourea moiety in a single orientation, leading to the other thiourea moiety blocking the *re* face.



Scheme 12. Catalytic enantioselective intramolecular [2+2] cycloaddition using a chiral bisthiourea

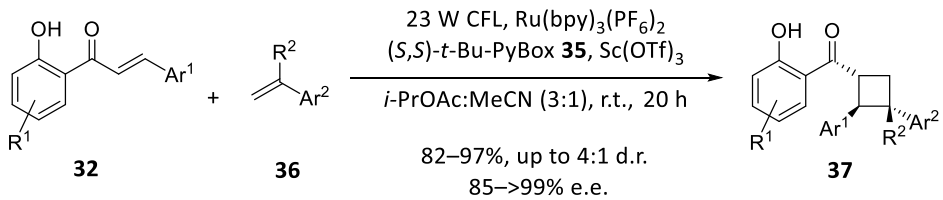
HFX = 1,3-bis(trifluoromethyl)benzene (Hexafluoro-*m*-xylene)

Yoon and co-workers used an alternative strategy to develop a catalytic enantioselective intermolecular [2+2] cycloaddition of 2'-hydroxychalcones **32** with 1,3-dienes **33** (**Scheme 13**).[36] Coordination of a chiral Lewis acid to substrate **32** leads to the formation of a complex with a lower triplet energy than the original molecule. When used in combination with a suitable triplet sensitizer and visible light irradiation, the products could be obtained in good yield and with high enantioselectivity.



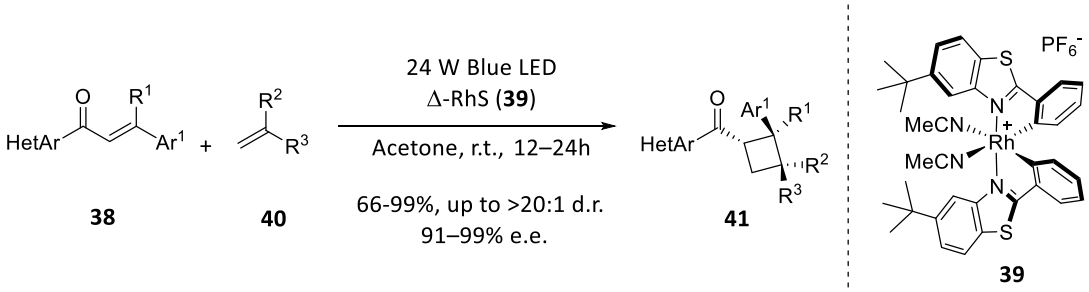
Scheme 13. Intermolecular cycloaddition of 1,3-dienes and 2'-hydroxychalcones using a chiral Lewis acid

Subsequent work in the group also allowed the same strategy to be applied to the [2+2] cycloaddition of 2'-hydroxychalcones **32** with styrenes **36** (**Scheme 14**).[37]



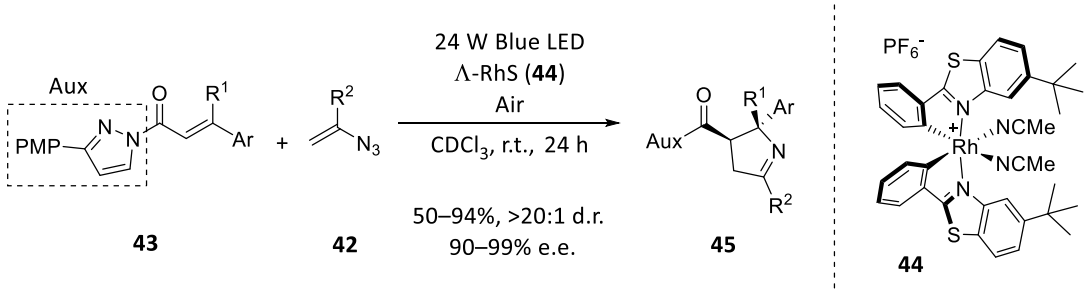
Scheme 14. Intermolecular [2+2] cycloaddition of styrenes and 2'-hydroxychalcones using a chiral Lewis acid

Octahedrally chiral-at-metal photocatalysts were first used in the context of asymmetric catalysis by Meggers and co-workers for the photoredox α-alkylation of 2-acyl imidazoles.[38] Subsequently, the group developed a rhodium based chiral-at-metal photocatalyst which enabled the enantioselective [2+2] cycloaddition of α,β-unsaturated 2-acyl imidazoles with a variety of alkenes (**Scheme 15**).[39] The substrate **38** binds to catalyst **39** at the labile acetonitrile ligand sites in a two point fashion *via* the heteroaromatic nitrogen and pendant carbonyl oxygen. This leads to sensitization of the substrate only when the *re* face of the catalyst is blocked by the benzothiazole ligand, leading to selective addition of the alkene **40** to the *si* face of substrate **38**.



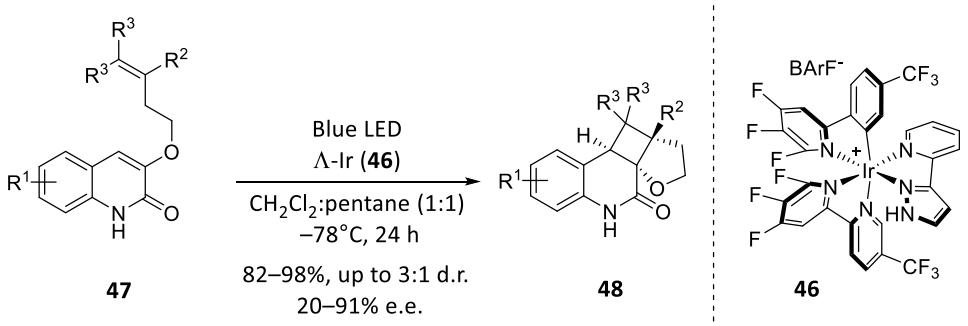
Scheme 15. [2+2] cycloaddition of α,β-unsaturated 2-acyl imidazoles using a chiral-at-metal photocatalyst

Further reaction development allowed for the synthesis of nitrogen heterocycles from vinyl azides **42** and α,β-unsaturated 2-acyl pyrazoles **43** in the presence of the enantiomeric chiral-at-metal photocatalyst **44** (**Scheme 16**).[40]



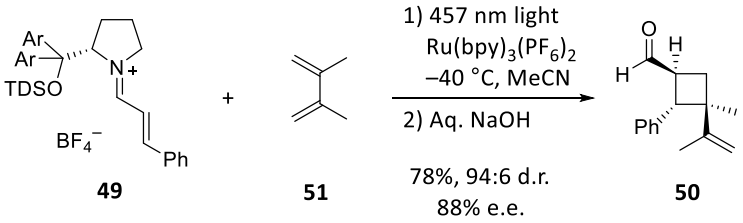
Scheme 16. [2+2] cycloaddition of α,β-unsaturated 2-acyl imidazoles using a chiral-at-metal photocatalyst

A combination of these strategies can also be used to generate products in high enantioselectivity. Yoon and co-workers synthesised a chiral-at-metal iridium complex **46** which contained a hydrogen bonding motif, allowing them to cyclize 3-alkyoxy-2-quinolones such as **47** with good enantioselectivity (**Scheme 17**).[41]



Scheme 17. [2+2] cycloaddition of quinolones and a pendant alkene using a chiral-at-metal photocatalyst

More recently, Bach and co-workers demonstrated that eiminium cations **49** are suitable substrates for visible light-mediated energy transfer cyclizations and can undergo intra or intermolecular [2+2] cycloadditions in the presence of a suitable sensitizer (**Scheme 18**).[42] Notably, the use of a chiral eiminium ion leads to enantioenriched products **50** after hydrolysis of the chiral amine auxiliary.



Scheme 18. [2+2] cycloadditions of eiminium ions

1.3 Photochemical cyclizations of cyclic enones

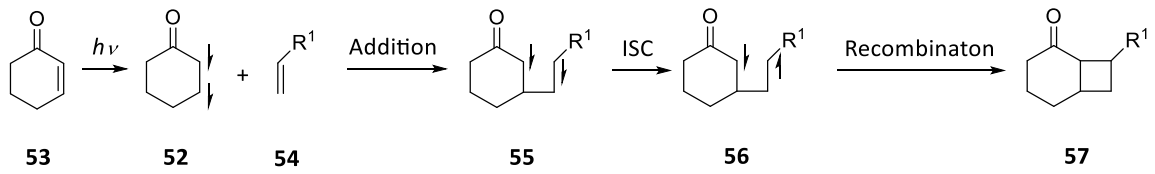
The photochemistry of cyclic enones has been extensively studied in the chemical literature.[43,44] In contrast to acyclic enones, which can rotate around their carbon–carbon double bond in their triplet excited state leading to easier non-radiative decay, the

geometrical constraint imposed by their cyclic nature restricts rotation about the carbon−carbon double bond, resulting in a longer triplet excited state lifetime.[45,46]

1.3.1 [2+2] cycloaddition

The most widely studied and arguably most important cyclization reaction of cyclic enones is their [2+2] cycloaddition with alkenes.[47,48] This has been achieved by both direct irradiation with ultraviolet light[49,50] and sensitization in combination with ultraviolet light.[51]

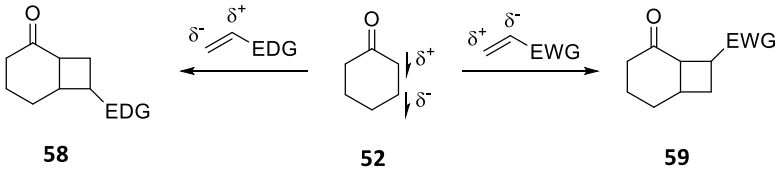
The mechanism of the reaction has been extensively investigated, and is thought to proceed *via* the excited triplet state of the enone **52** (**Scheme 19**).[47,51–53] This triplet intermediate can be generated either through direct irradiation of **53** followed by intersystem crossing, or by energy transfer from a suitable triplet sensitizer. Subsequent addition of one of the radicals to an alkene **54** leads to the formation of triplet diradical **55**, which upon intersystem crossing to the ground state **56** can undergo recombination to form cyclobutane **57**.



Scheme 19. Proposed mechanism of the [2+2] photocycloaddition between cyclic enones and alkenes

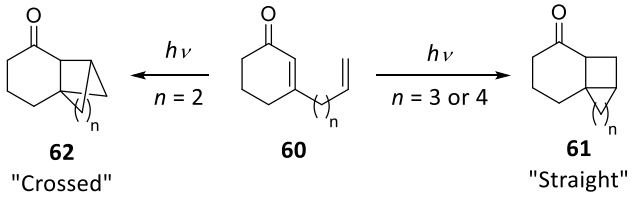
For intermolecular cycloadditions, the regioselectivity of the cycloaddition can be rationalised by the relative polarity of the alkene and triplet excited enone (**Scheme 20**).[49,54] The triplet excited state of cyclic enone **52** is nucleophilic at the β-position and electrophilic at the α-position due to occupation of the π* orbital by one electron. Thus, alkenes react to form 1,4-biradical intermediates (and subsequently the corresponding cyclobutanes) where opposite polarity atoms combine preferentially. This means that

alkenes with electron donating groups (EDG) form head-to-tail adducts such as **58**, whilst alkenes with electron withdrawing groups (EWG) form head-to-head adducts such as **59**.



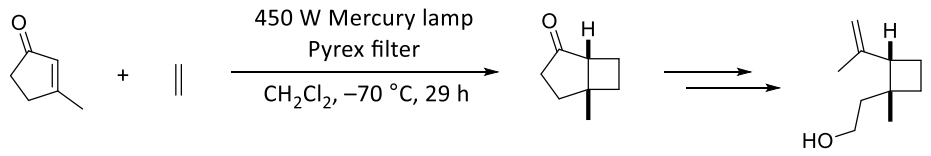
Scheme 20. Regioselectivity of the intermolecular [2+2] cycloaddition

The regioselectivity of the intramolecular [2+2] cycloaddition is less dependent on electronics, and instead is governed by the length of the linker between the cyclic enone and the pendant alkene (**Scheme 21**).[48,55] For three and four atom long linkers, a "straight" dimerization occurs (**61**), whilst for two atom linkers a "crossed" product is formed (**62**). The selectivity of these products is determined by the speed of formation of different 1,4-biradical intermediates, and those biradical intermediates containing a five membered ring form fastest and are thus favoured along with their corresponding final cyclobutene products.[56]



Scheme 21. Regioselectivity of the intramolecular [2+2] cycloaddition and its dependence on linker length

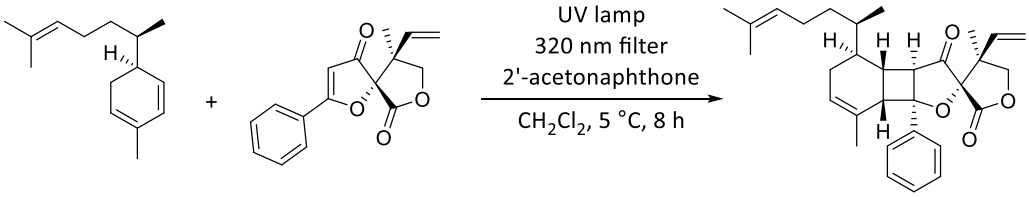
The [2+2] cycloaddition of cyclic enones and alkenes has found widespread synthetic application to make cyclobutane rings.[47] A simple example is highlighted in the [2+2] cycloaddition of 3-methyl-2-cyclopenten-1-one **63** and ethylene **64** (**Scheme 22**). This was used by Cargill and Wright to form cyclobutane **65** as part of their synthetic studies towards the total synthesis of (±)-grandisol **66**.[57]



63 **64** 85% **65** **66**

Scheme 22. Intramolecular [2+2] cycloaddition of 3-methyl-2-cyclopenten-1-one and ethylene as part of a total synthesis of (±)-grandisol

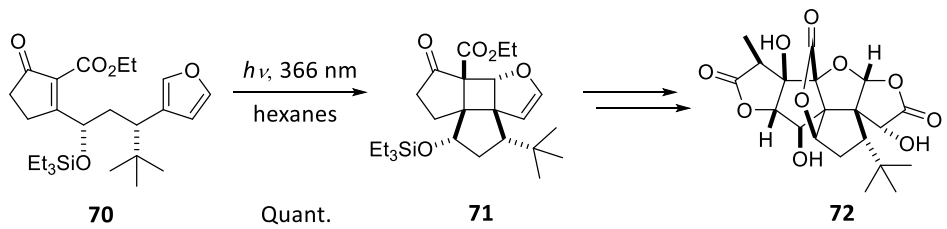
More complex substrates are also amenable to intermolecular [2+2] photocycloaddition. Nicolaou and co-workers used a [2+2] cycloaddition as the final step in their total synthesis of biyouyanagin A **67** between terpene **68** and cyclic enone **69** (**Scheme 23**).[58,59]



68 **69** 54% **67**

Scheme 23. Intramolecular [2+2] cycloaddition to form biyouyanagin A.

The intramolecular [2+2] photocycloaddition of cyclic enones has also been widely used in a variety of synthetic applications.[60] Crimmins and co-workers used an intramolecular dearomative [2+2] cycloaddition between a tethered cylopentenone and furan to generate tetracyclic core **71** in quantitative yield as part of their synthesis of (±)-ginkgolide B **72** (**Scheme 24**).[61]

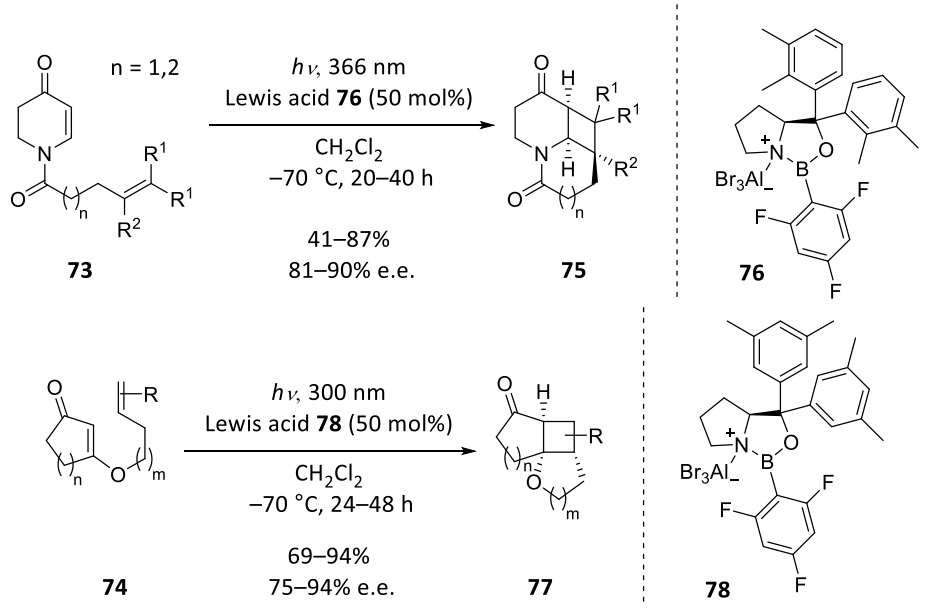


70 Quant. **71** **72**

Scheme 24. Intramolecular [2+2] cycloaddition as a key step in the total synthesis of (±)-ginkgolide B

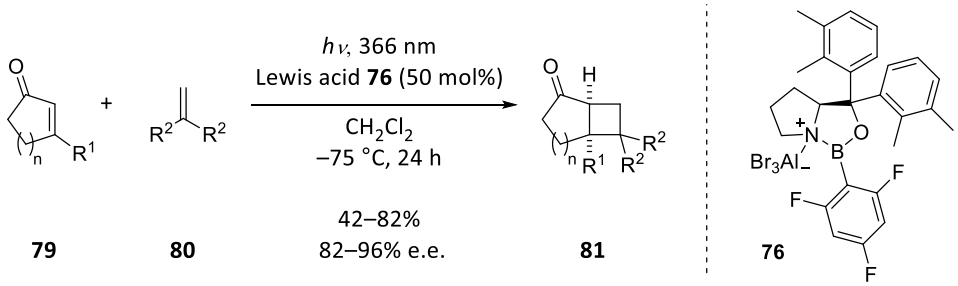
Catalytic asymmetric variants of the cyclic enone [2+2] cycloaddition have been developed more recently by Bach and co-workers by employing a chiral Lewis acid.[62–64] Upon

coordination to the enone carbonyl, a significant bathochromic shift occurs and intersystem crossing is enhanced due to the presence of heavy atoms (bromine) in the Lewis acid. By the correct choice of irradiation wavelength, only the chiral complex is excited and undergoes the desired photochemical reaction, allowing for the [2+2] product to be obtained with excellent enantioselectivity. Initial efforts focussed on intramolecular examples, such as 4-amidoenone **73** or 3-alkoxyenone **74** (**Scheme 25**).[62,63]



Scheme 25. Catalytic enantioselective intramolecular [2+2] cycloaddition *via* Lewis acid coordination

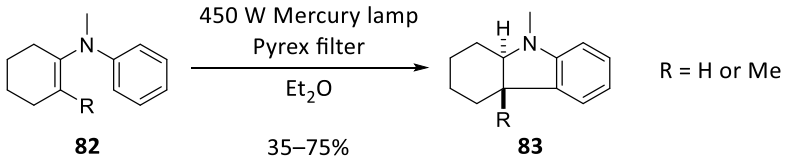
Subsequent work allowed the same strategy to be applied to intermolecular reactions, including the [2+2] cycloaddition of cyclohexenones **79** and simple alkenes **80** (**Scheme 26**).[64] This strategy was ultimately applied to an enantioselective six-step synthesis of (–)-grandisol.



Scheme 26. Catalytic enantioselective intermolecular [2+2] cycloaddition *via* Lewis acid coordination

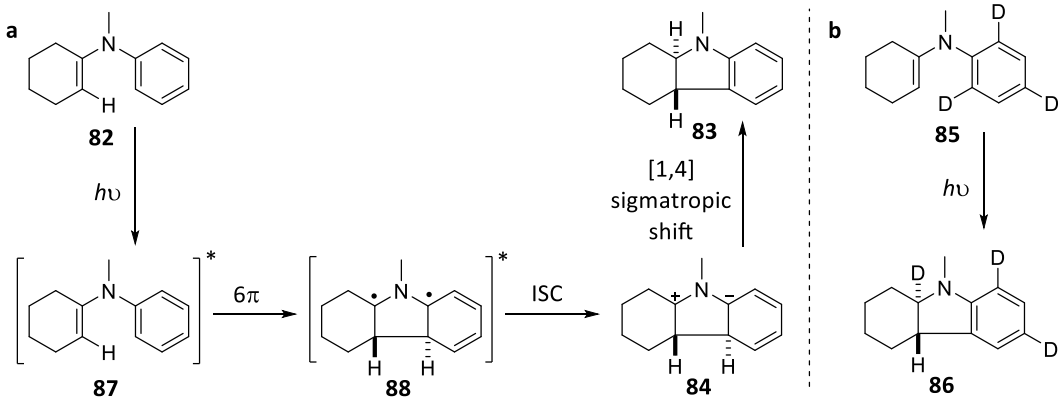
1.3.2 6π heterocyclization

Initial work by Chapman showed that *N*-aryl enamines **82** cyclize under irradiation with Pyrex-filtered ultraviolet light in ether solution to form the corresponding *trans*-fused indolines **83** (**Scheme 27**).[65,66]



Scheme 27. Photocyclization of *N*-aryl enamines *via* direct irradiation

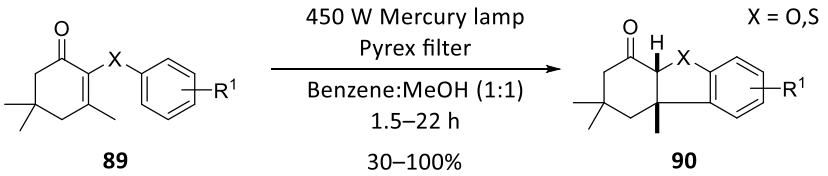
The mechanism of the cyclization was suggested to proceed *via* conrotatory 6π photochemical electrocyclization of **82**, followed by relaxation to zwitterionic ground state **84** and subsequent suprafacial [1,4] sigmatropic shift of a hydrogen atom to give *trans* fused indoline **83** (**Scheme 28a**). This subsequent [1,4] sigmatropic shift was consistent with deuterium labelling experiments with substrate **85**, which showed complete migration of the deuterium label to give deuterated indoline **86** (**Scheme 28b**).



Scheme 28a. Proposed mechanism of the 6π photocyclization **b.** Deuterium labelling experiment

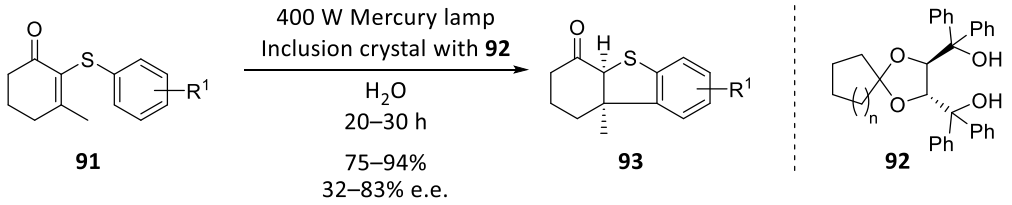
Subsequent work by Schultz and co-workers expanded on the scope of the reaction to demonstrate that 2-aryloxycyclohexenones and 2-arylthiocyclohexenones **89** cyclize under irradiation with Pyrex-filtered ultraviolet light to selectively form *cis*-fused dihydrobenzofurans and dihydrobenzothiophenes **90** respectively in protic solvent

mixtures (**Scheme 29**).[67–72] This difference in diastereoselectivity in protic solvents was postulated to arise from either protonation of the carbonyl ylide or solvent-mediated epimerization of the *trans*-fused product to the thermodynamically more stable *cis*-fused product **90**. When the reaction was performed in benzene only the *trans*-fused diastereomer was obtained, confirming the dependence of diastereoselectivity on solvent choice.



Scheme 29. Photocyclization of 2-aryloxycyclohexenones and 2-arylthiocyclohexenones *via* direct irradiation

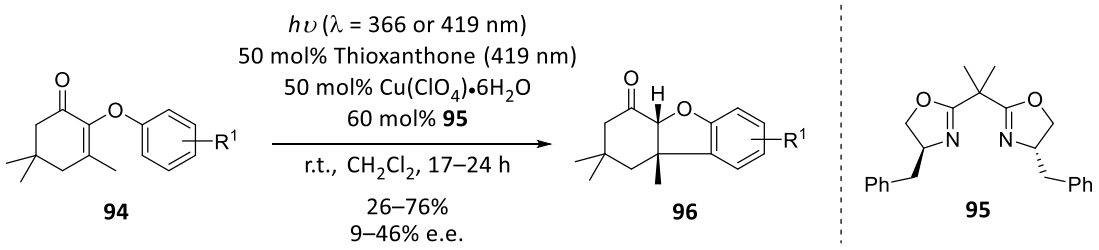
More recent work has enabled the development of enantioselective variants of the reaction. Toda and co-workers demonstrated that photocyclization of 2-arylthiocyclohexenones **91** inside an inclusion crystal with chiral host molecule **92** proceeded smoothly to give *cis*-fused dihydrobenzothiophenes **93** in good yields (75–94%) and with moderate to good enantioselectivity (32–83% e.e.) (**Scheme 30**).[73]



Scheme 30. Enantioselective photocyclization of inclusion crystals of 2-arylthiocyclohexenones **91** and **92**

Work by Bach and co-workers led to the development of an enantioselective photocyclization of 2-aryloxycyclohexenone **94** in combination with copper (II) perchlorate and a chiral bisoxazoline ligand **95** acting as a chiral Lewis acid (**Scheme 31**).[74] When the reaction was performed under direct irradiation with ultraviolet light, modest levels of enantioselectivity were observed (29–46% e.e.). The reaction could also be performed

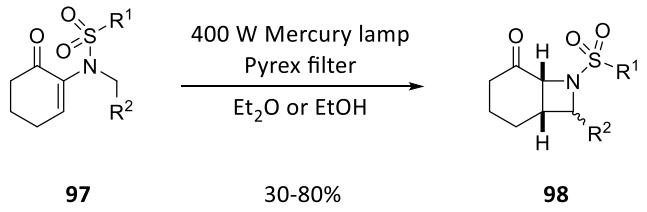
using sub-stoichiometric quantities of thioxanthone sensitizer and visible light to achieve similar levels of enantioselectivity.



Scheme 31. Enantioselective photocyclization of 2-aryloxycyclohexenones **94** in combination with a chiral Lewis acid under direct irradiation and sensitization

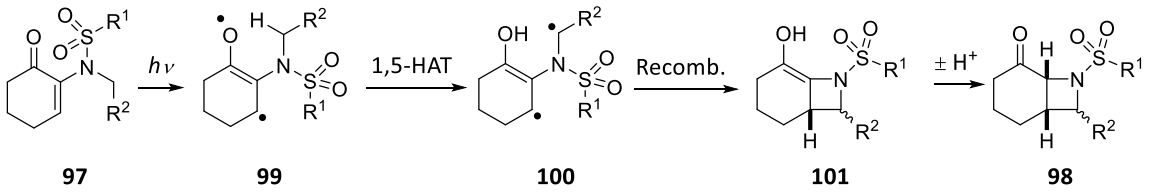
1.3.3 Other Reactions

Work by Pete and co-workers showed that upon Pyrex-filtered irradiation in ethanolic or ethereal solvents, *N*-sulfonamido-2-cyclohexen-1-ones **97** underwent a photochemical cyclization reaction to form *cis*-fused azetidines **98** (**Scheme 32**).[75]



Scheme 32. Photocyclization of *N*-sulfonamido-2-cyclohexen-1-ones

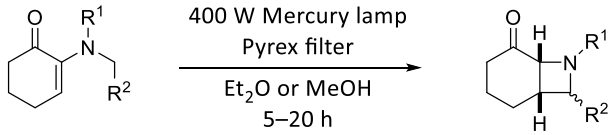
The reaction is thought to proceed *via* the excited singlet state **99**, where the radical located on the enone oxygen abstracts a hydrogen in a 1,5-hydrogen atom transfer (HAT) to give 1,4-biradical **100** (**Scheme 33**). The subsequent biradical **100** then undergoes recombination to give enol **101**, which is then protonated to give *cis*-fused azetidine **98**.



97 **99** **100** **101** **98**

Scheme 33. Proposed mechanism of the formation of *cis*-fused azetidine **98**

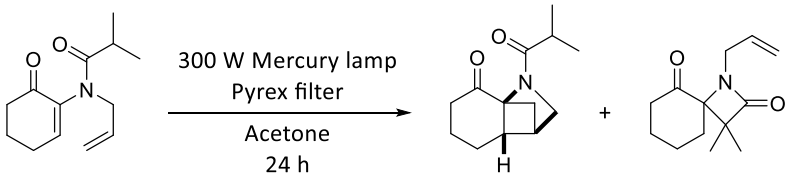
Subsequently, the same research group extended this reactivity to *N*,*N*-dialkylamino-2-cyclohexen-1-ones **102**, enabling the synthesis of *N*-alkyl *cis*-fused azetidines **103** (**Scheme 34**).[76]



102 30–65% **103**

Scheme 34. Photocyclization of *N*,*N*-dialkylamino-2-cyclohexen-1-ones

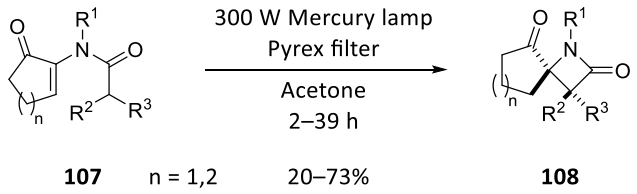
During their studies on the [2+2] photocycloaddition of 2-(*N*-acyl-*N*-allylamino)cyclohex-2-enone **104**, Ikeda and co-workers noted the formation of side product **105** in addition to the expected cyclobutane **106** (**Scheme 35**).[77]



104 **106** **105**

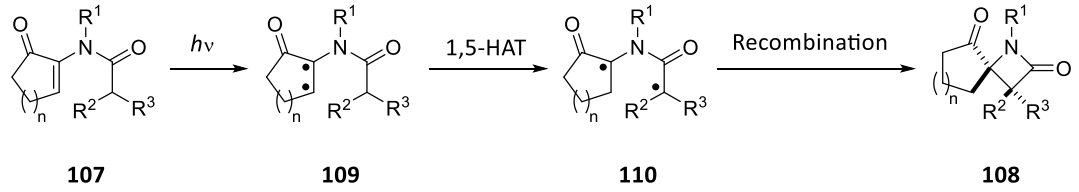
Scheme 35. Unexpected product in the [2+2] photocyclization of 2-(*N*-acyl-*N*-allylamino)cyclohex-2-enone

Subsequently, they investigated the photochemical reactivity of other 2-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones **107** to form spirocyclic β-lactams **108** under ultraviolet irradiation (**Scheme 36**).[78,79] These products were obtained in moderate to good yields (28–73%) and with excellent diastereoselectivity (>20:1 d.r.).



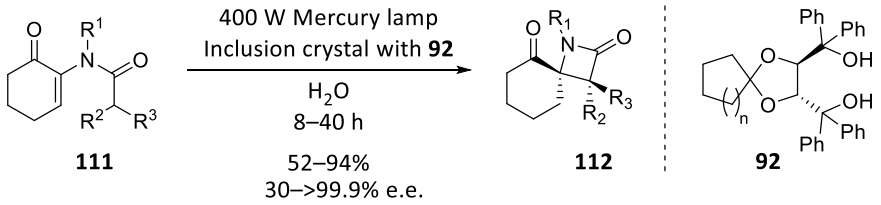
Scheme 36. Photocyclization of 2-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones

The proposed mechanism for the reaction is outlined below (**Scheme 37**). After excitation of the enone **107** to its singlet excited state **109**, 1,5-hydrogen atom abstraction can occur to give 1,4-diradical intermediate **110**, which can then recombine to form the desired spirocyclic β-lactam product **108**. The origin of the stereoselectivity of the reaction is uncertain but could be attributed to steric factors in the diradical recombination transition state.



Scheme 37. Proposed mechanism of the photocyclization of 2-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones

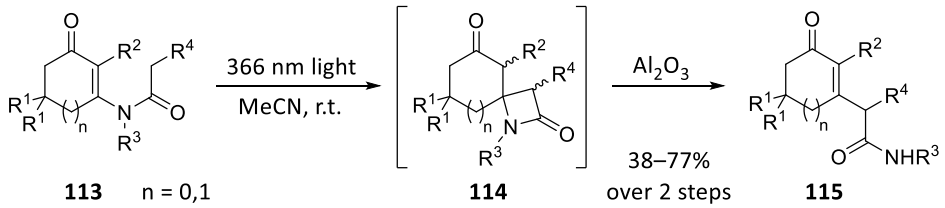
More recent work from Toda and co-workers demonstrated that the reaction could be made enantioselective by forming an inclusion crystal of **111** with **92** (**Scheme 38**), allowing the products **112** to be made in good yield (52–94%) and moderate to excellent enantioselectivity (30 –>99.9% e.e.).[80–83]



Scheme 38. Enantioselective photocyclization of inclusion crystals of enaminone **111** and **92**

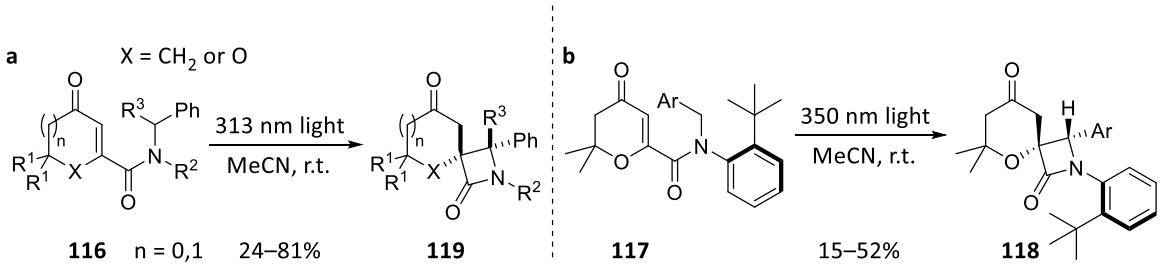
Pete and co-workers demonstrated that 3-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones **113** exhibit a similar reactivity (**Scheme 39**).[84,85] Under direct irradiation at 366 nm in

acetonitrile solution, enaminone **113** cyclized to form spirocyclic β-lactams **114**. Treatment of the product with alumina led to C–N bond fragmentation, giving β-substituted enones **115**.



Scheme 39. Photocyclization of 3-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones

Compounds with a reversed amide linker (**116**) also underwent the same photochemical cyclization (**Scheme 40a**).[86] Subsequent work by Sivaguru and co-workers demonstrated that substrates containing a nearby stable atropisomeric axis, such as *ortho*-*tert*-butyl anilide **117**, cyclize diastereoselectively to generate the spirocyclic β-lactam products **118** in >95% e.e. (**Scheme 40b**).[87] The large *tert*-butyl group on the anilide moiety blocks the recombination of the singlet 1,4-diradical from one face leading to a single point chiral enantiomer.

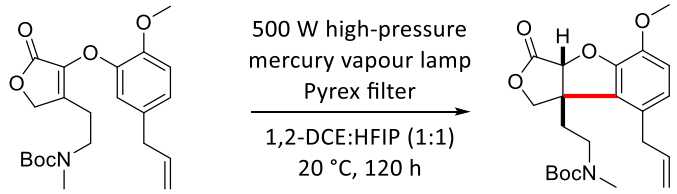


Scheme 40a. Photocyclization of *N*-benzyl-α,β-unsaturated-oxoamides **b.** Axial to point chirality transfer

2 6π heterocyclization

2.1 Previous group work

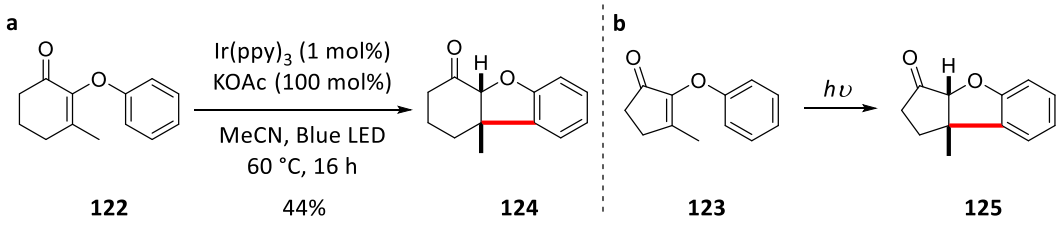
The Smith group's interest in photochemical cyclizations was sparked by a key step total synthesis of morphine by Shuyu Chu (**Scheme 41**).[88] The photochemical cyclization of 3-aryloxybutenolide **120** gave the desired *cis*-fused dihydrobenzofuran **121** with excellent diastereoselectivity, but required extended irradiation times of 120 hours in order to achieve a modest yield of 37%.



120 **121**

Scheme 41. A stereodetermining photochemical cyclization in the total synthesis of (±)-morphine

Prior investigation by Schultz suggested that the cyclization likely proceeded *via* the triplet state,[69] and so we considered the possibility of exciting **120** to the triplet state by sensitization. To reduce the synthetic complexity of the substrates, we initially focussed on the sensitized cyclization of 2-aryloxycyclohexenones. Initial work on this project by Dr. Niels Münster led to the development of a visible light-mediated cyclization of 2-aryloxycyclohexenones **122** using $Ir(ppy)_3$ as a photocatalyst (**Scheme 42a**). In order to improve the synthetic utility of this method, we wanted to expand the scope to other ring sizes and heteroatom linkers. As such, 2-aryloxycyclopentenone **123** was chosen as a model substrate for further investigation (**Scheme 42b**).



Scheme 42a. Initial optimization by Dr. Niels Münster **b.** Proposed new optimization substrate **123**

2.2 Substrate synthesis

2.2.1 Strategy

Our strategy to synthesise the desired aryloxy substrates **126** followed a similar disconnection to that previously employed by Schultz and co-workers (**Figure 4**).[69] This involved a base-mediated opening of epoxide **127** with phenol or thiophenols **128**, followed by an *in-situ* E1cB to form the desired enone motif. The modular nature of this approach enabled a diverse range of phenols and thiophenols to be coupled to a variety of epoxide **127**, allowing for a broad substrate scope to be rapidly assembled.

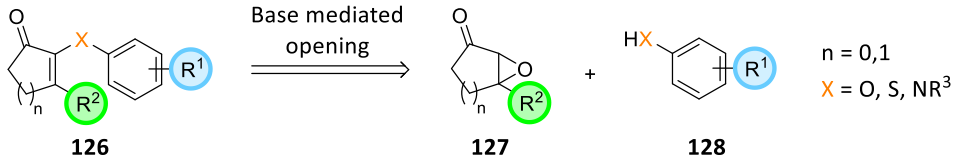
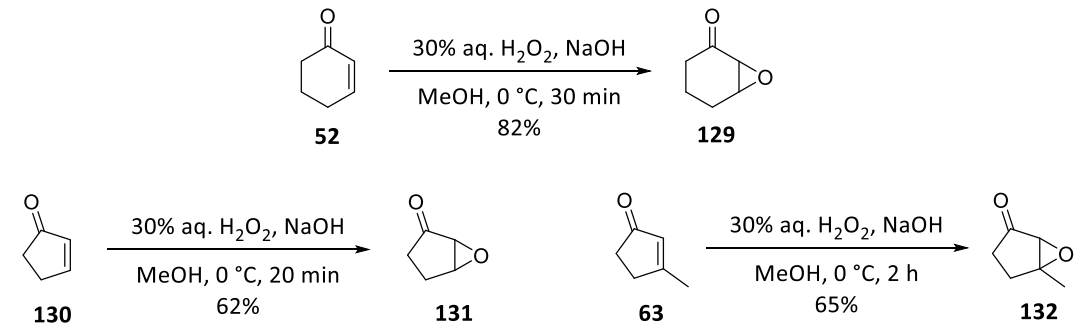


Figure 4. Alternative epoxide opening strategy

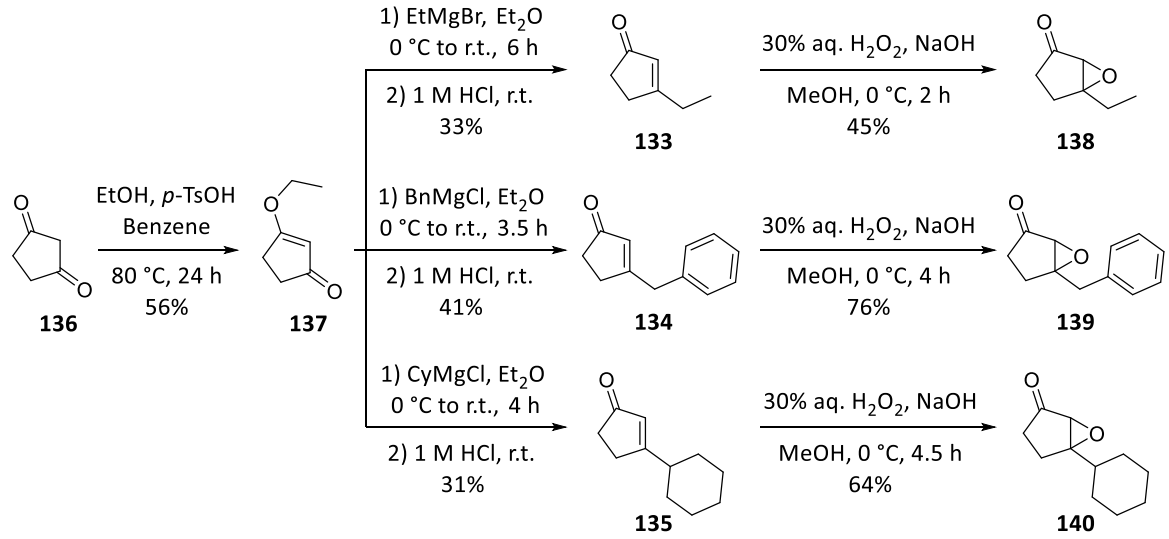
2.2.2 Epoxide synthesis

Nucleophilic epoxidation of 2-cyclohexen-1-one **52** with basic hydrogen peroxide gave epoxide **129** in good yield and high purity after work-up, even on a multi-gram scale (**Scheme 43**).[89] The same procedure was then applied to other commercially available enones **63** and **130**, with similarly good results.



Scheme 43. Nucleophilic epoxidation of cyclic enones

Cyclopentenones **133**–**135** bearing a substituent at the β position were prepared from 1,3-cyclopentanedione **136** in two steps (**Scheme 44**). Following etherification with ethanol and *para*-toluenesulfonic acid, 3-ethoxy-2-cyclopenten-1-one **137** was reacted with a variety of Grignard reagents followed by acidic work up to give enones **133**–**135** in moderate yield.[90,91] Subsequent epoxidation with basic hydrogen peroxide, as described previously, gave the corresponding epoxides **138**–**140** in good yield.

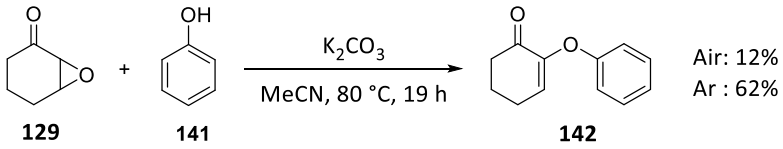


Scheme 44. Synthesis of β susbstituted cyclohexenones and their epoxidation.

2.2.3 Epoxide opening

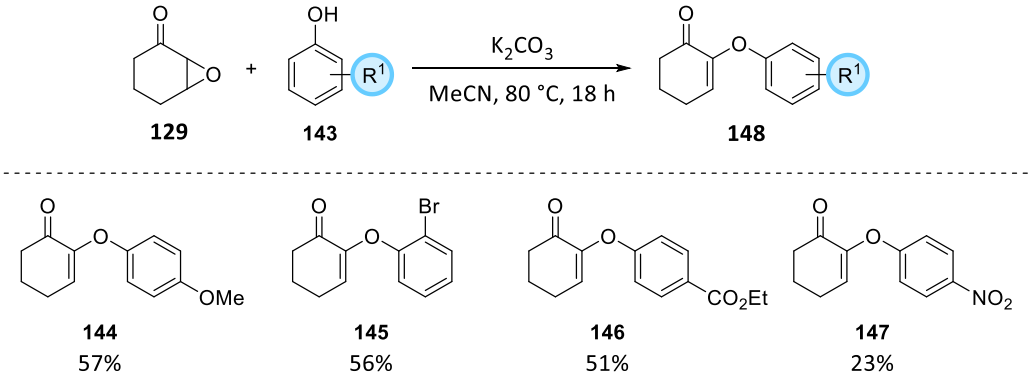
Initial attempts at opening epoxide **129** with phenol **141** and potassium carbonate in acetonitrile, using modified literature conditions, gave the desired product **142** in low yield

(**Scheme 45**).[92] Pleasingly, performing the reaction under an inert argon atmosphere gave an improved yield of the product, likely due to preventing oxidation of phenol **141**.



Scheme 45. Initial attempts at epoxide opening

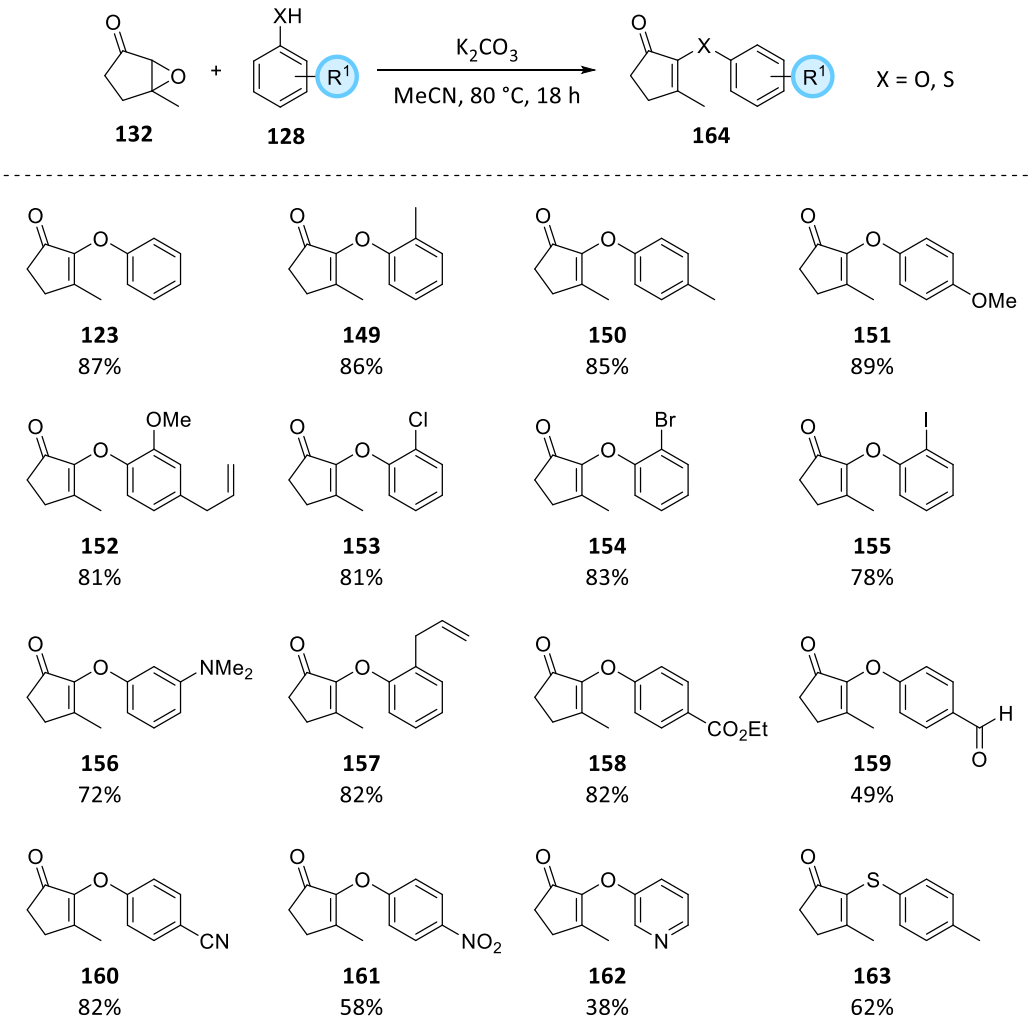
With a robust epoxide opening procedure in hand, a variety of phenols **143** were reacted with epoxide **129** (**Scheme 46**). The procedure worked moderately well to synthesise electron rich 4-OMe substrate **144** in 57% yield, electron neutral 2-Br substrate **145** in 56% yield and electron poor 4-CO_2Et substrate **146** in 51% yield. However, 4-NO_2 substrate **147** was only obtained in 23% yield, possibly due to the lower nucleophilicity of the corresponding phenolate anion.



Scheme 46. Synthesis of cyclohexenone derived substrates

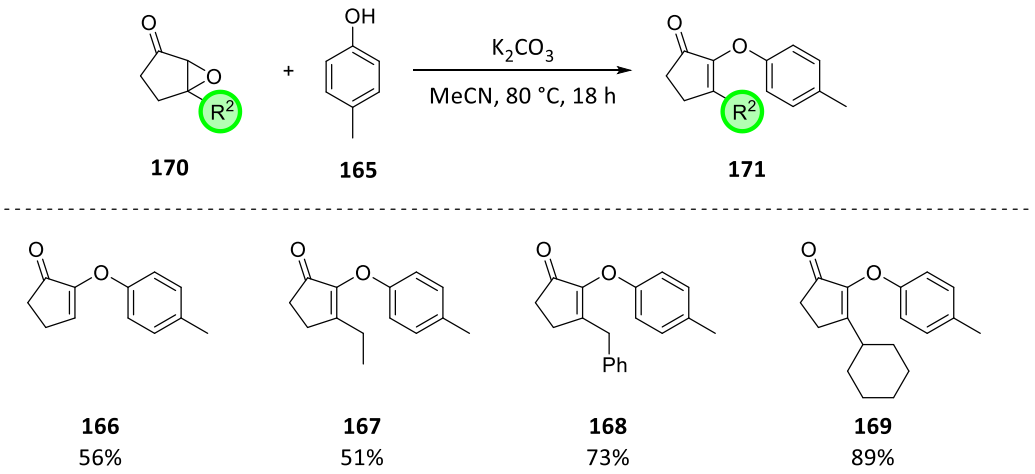
Additional substrates containing a 3-methyl cyclopentenone ring were synthesised following the same procedure using phenols and thiophenols **128** in combination with epoxide **132** (**Scheme 47**). In contrast to epoxide **129**, the products derived from epoxide **132** were obtained in good to excellent isolated yields of 38–89%. Phenol derived substrate **123** was obtained in 87% yield, and *ortho*- and *para*-cresol derived substrates **149** and **150** were obtained in similarly good yields of 85% and 86% respectively. *Para*- and

ortho-methoxy substituents were also well tolerated, as shown by hydroquinone derived substrate **151** and eugenol derived substrate **152**, which were obtained in 89% and 81% yield respectively. Halogen atoms could be incorporated in good yield, including chlorine (**153**, 81%), bromine (**154**, 83%) and iodine (**155**, 78%). *Meta*-substitution was well tolerated, as shown by dimethylamino substituted substrate **156** which was obtained in 72% yield. Alkenes were possible to incorporate as evidenced by 2-allylphenol derived substrate **157**, which was obtained in 82% yield. Electron deficient substrates could also be synthesised in good yield by this method, including ethyl ester **158** (82%), aldehyde **159** (49%), nitrile **160** (82%) and nitrobenzene **161** (58%). The incorporation of heterocyclic rings occurred in lower yield, as shown by pyridine **162** which was obtained in 38% yield. Thiophenols were amenable to this epoxide opening procedure, allowing sulfide **163** to be obtained in 62% yield.



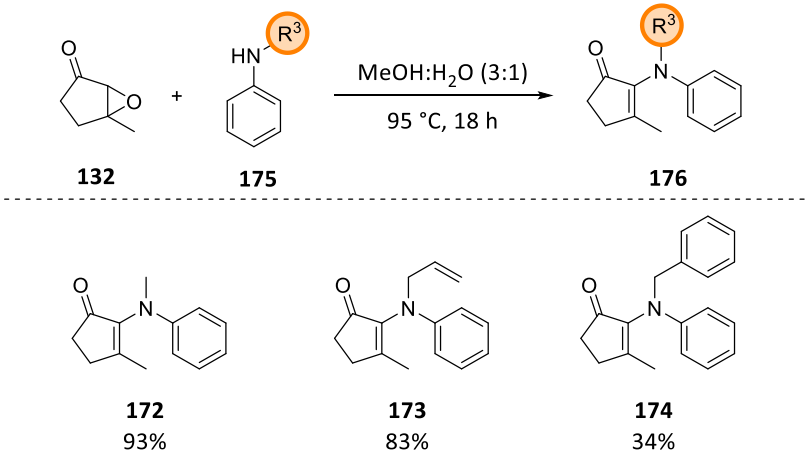
Scheme 47. Synthesis of 3-methyl cyclopentenone derived substrates

Additional substrates with varying substitution at the β position of the enone were synthesised following the same procedure using *para*-cresol **165** in combination with epoxides **131** and **138–140** (**Scheme 48**). Unsubstituted and ethyl substituted cyclopentenones **166** and **167** were obtained in moderate yields of 56% and 51% respectively. Benzyl substituted cyclopentenone **168** was obtained in a higher yield of 73%, whilst cyclohexyl substituted cyclopentenone **169** was obtained in an excellent 89% yield.



Scheme 48. Synthesis of additional cyclopentenone derived substrates

Aniline derived substrates **172–174** were synthesised by heating the desired aniline **175** with epoxide **132** in a 3:1 solution of methanol:water (**Scheme 49**).[75] Condensation of epoxide **132** with *N*-methyl aniline and *N*-allyl aniline proceeded smoothly, giving the desired enaminones **172** and **173** in 93% and 83% yield respectively. In contrast, *N*-benzyl substrate **174** was obtained in a lower yield of 34%.



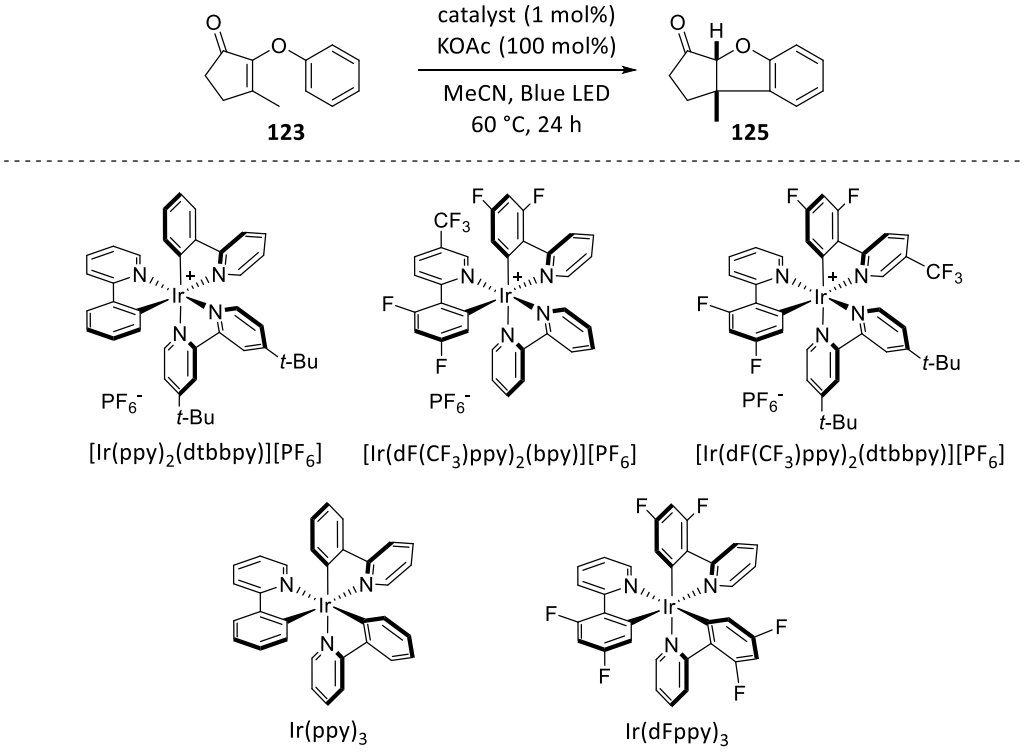
Scheme 49. Synthesis of additional cyclopentenone derived substrates

The modular nature of the epoxide opening reaction thus allowed for the construction of a variety of different cyclization precursors, in generally good to excellent yields (23–93%).

2.3 Photochemical cyclization

2.3.1 Optimization

Model substrate **123** was subjected to the cyclization conditions developed previously in the group by Dr. Niels Münster for the visible light-mediated cyclization of 2-aryloxycyclohexenones (**Table 1**, **Entry 1**). Unfortunately, only unreacted starting material was returned. We therefore decided to screen a variety of other photocatalysts with different triplet state energies, E_T (**Entries 2**–**5**). Disappointingly, most catalysts returned only unreacted starting material (**Entries 2**–**4**). Pleasingly, $Ir(dFppy)_3$ successfully catalysed the reaction, giving the desired product **125** as a single diastereomer in 66% yield at 66% conversion after 24 h (**Entry 5**).

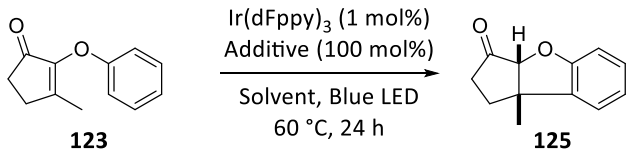


Entry	Catalyst	E_T[i]	Conversion[ii]	NMR Yield[ii]
1	$[Ir(ppy)_3]$	55.2	0%	0%
2	$[Ir(ppy)_2(dtbbpy)][PF_6]$	49.2	0%	0%
3	$[Ir(dF(CF_3)ppy)_2(dtbbpy)][PF_6]$	60.1	0%	0%
4	$[Ir(dF(CF_3)ppy)_2(bpy)][PF_6]$	60.4	0%	0%
5	**$[Ir(dFppy)_3]$**	**63.5**	**66%**	**66%**

Reaction conditions: **123** (0.05 mmol), catalyst (1 mol%), KOAc (100 mol%), MeCN ([**123**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. [i] E_T = Triplet state energy measured in kcal/mol.[10,15] [ii] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard.

Table 1. Evaluation of commercial photocatalysts[10,15]

Having found a competent catalyst, we then performed further optimisation on the reaction (**Table 2**; for additional data see **Appendix 8.2**). Removal of the potassium acetate from the reaction resulted in slightly increased conversion, but decreased yield (**Entry 2**). Changing the additive to sodium acetate gave a similar result (**Entry 3**); however, changing the additive to sodium bicarbonate gave a small increase in both yield and conversion (**Entry 4**). The use of stronger bases as additives inhibited the reaction (**Entries 5**–**7**). Changing the solvent to acetone (**Entry 8**) or ethyl acetate (**Entry 9**), whilst using sodium bicarbonate as the additive, increased conversion but decreased yield. A similar effect was observed for potassium acetate in acetone (**Entry 10**), but using potassium acetate in ethyl acetate improved both yield and conversion (**Entry 11**). Sodium acetate gave similarly good results in combination with ethyl acetate as the solvent (**Entry 12**). As potassium acetate always led to the formation of an inseparable by-product which was visible by NMR, sodium acetate was chosen as the optimal additive in spite of its slightly lower conversion and yield.



Entry	Additive	Solvent	Conversion[i]	NMR Yield[i]
1	KOAc	MeCN	66%	66%[ii]
2	None	MeCN	82%	60%
3	NaOAc	MeCN	70%	58%
4	$NaHCO_3$	MeCN	78%	76%
5	K_2CO_3	MeCN	0%	0%
6	K_3PO_4	MeCN	0%	0%
7	NaOH	MeCN	0%	0%
8	$NaHCO_3$	Acetone	91%	62%
9	$NaHCO_3$	EtOAc	76%	63%
10	KOAc	Acetone	87%	66%[ii]
11	KOAc	EtOAc	97%	89%[ii]
12	**NaOAc**	**EtOAc**	**95%**	**87%**

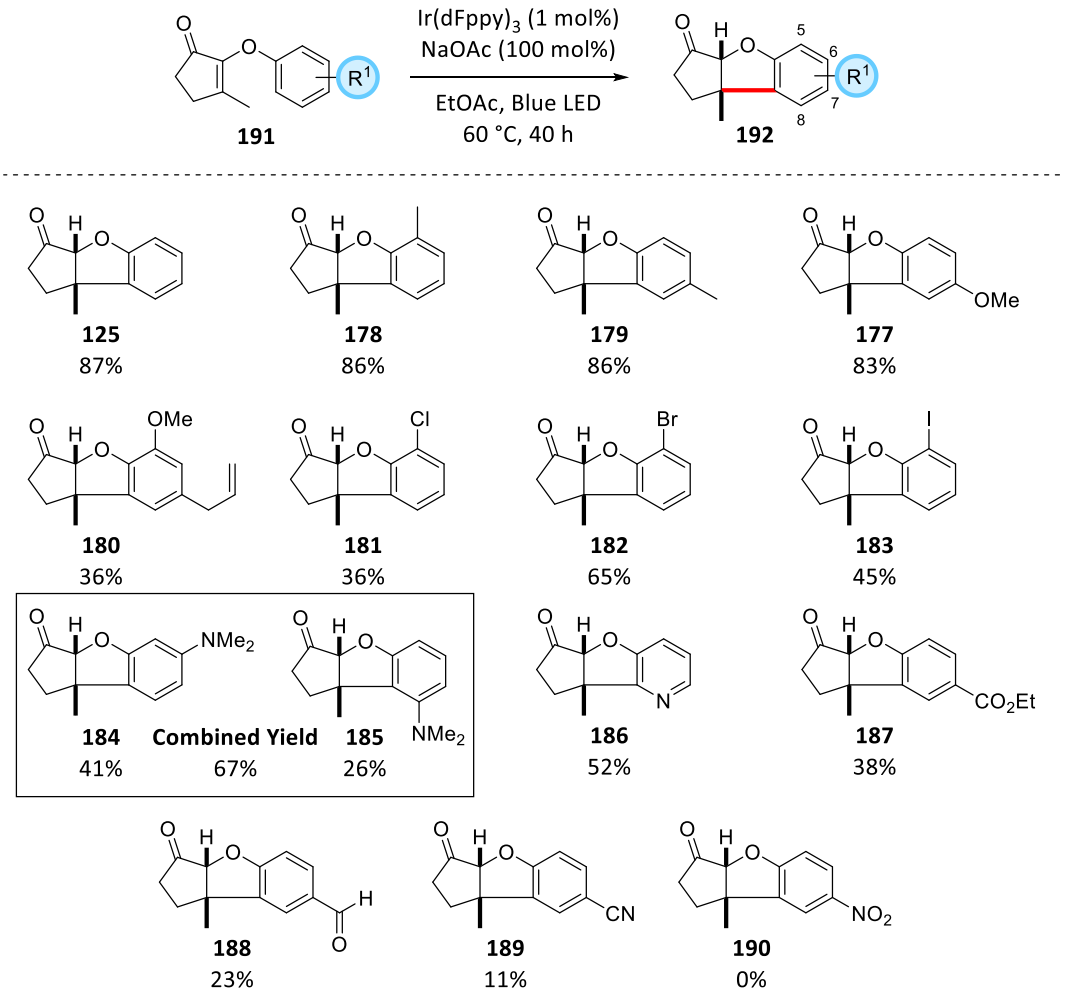
Reaction conditions: **123** (0.05 mmol), $Ir(dFppy)_3$ (1 mol%), additive (100 mol%), solvent ([**123**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard. [ii] Additional side product visible by ^1H NMR.

Table 2. Selected optimization

2.3.2 Substrate Scope

With optimized reaction conditions in hand, we explored the substrate scope of the reaction, starting with varying substitution patterns on the aromatic ring (**Scheme 50**). The relative stereochemical configuration was assigned as *cis* by nOe correlation (see **Experimental** for full details) and subsequently confirmed by an x-ray crystal structure of dihydrobenzofuran **177** (see **Appendix 8.8.1**). Unsubstituted optimization substrate **123** cyclized cleanly to afford the desired dihydrobenzofuran **125** in 87% yield. Alkyl

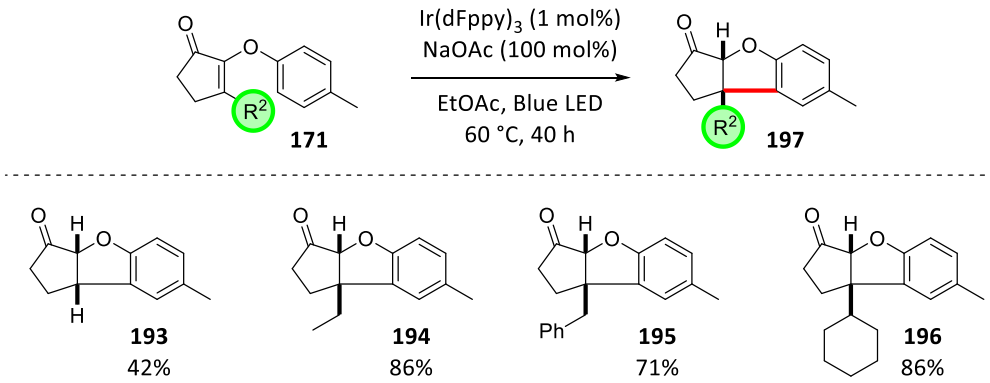
substitution on the aromatic ring was well tolerated in both *ortho* and *para* positions, giving both 5-methyl dihydrobenzofuran **178** and 7-methyl dihydrobenzofuran **179** in 86% yield. More electron rich oxygen-containing substituents were also amenable to cyclization, forming 7-methoxy dihydrobenzofuran **177** in 83% yield and 5-methoxy-7-allyl dihydrobenzofuran **180** in 36% yield. *Ortho* halogens were tolerated, forming 5-chloro, 5-bromo and 5-iodo dihydrobenzofurans **181**, **182** and **183** in 36%, 65% and 45% yield respectively. *Meta* substitution led to the formation of a mixture of regioisomeric products. For *meta* dimethylamino substituted substrate **156**, the two regioisomers were separable by flash column chromatography, allowing for 6-dimethylamino dihydrobenzofuran **184** to be isolated in 41% yield and 8-dimethylamino dihydrobenzofuran **185** to be isolated in 26% yield leading to a 67% combined yield of both regioisomers in a 1.6:1 ratio. Interestingly, for pyridine containing substrate **162** only one regioisomer **186** was formed in the reaction in 52% yield. This selectivitiy can be rationalised by the relative ease of Minisci-type addition *ortho* to the pyridine nitrogen compared with *meta* addition. Electron withdrawing substituents in the *para* position gave diminished yields, with ethyl ester **187**, aldehyde **188** and nitrile **189** being formed in 38%, 23% and 11% yield respectively. Nitro substituted substrate **190** was unreactive under the reaction conditions, returning only starting material.



Reaction conditions: **191** (0.30 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), EtOAc ([**191**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. All yields are isolated yields after purification. Compounds **184** and **185** were formed as a separable 1.6:1 mixture of regioisomers in a 67% combined yield from compound **156**.

Scheme 50. Aryl ring substitution scope

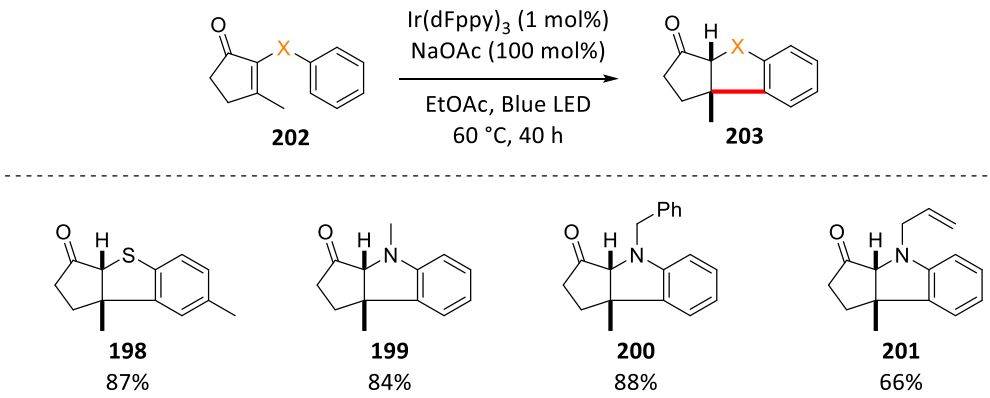
Further exploration of the substrate scope focussed on variation at the β-position of the enone (**Scheme 51**). Unsubstituted enone **166** cyclized to give dihydrobenzofuran **193** in 42% yield; this lower yield was likely due to undesired oxidation to the corresponding benzofuran, which was formed as a by-product in the reaction in 21% yield. Ethyl and benzyl substituted enones **167** and **168** cyclized cleanly to give the corresponding dihydrobenzofurans **194** and **195** in 86% and 71% yield respectively. Even larger substitutents such as a cyclohexyl group were well tolerated, allowing for dihydrobenzofuran **196** to be isolated in 86% yield.



Reaction conditions: **171** (0.30 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), EtOAc ([**171**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. All yields are isolated yields after purification.

Scheme 51. Enone substitution scope

Additional scope of the reaction looked at variation of the heteroatom linker (**Scheme 52**). Sulfur was as suitable a linker as oxygen, as evidenced by *para*-thiocresol derived substrate **163** which cyclized cleanly to form dihydrobenzothiophene **198** in 87% yield. Nitrogen was also tolerated as a linker atom, allowing for the formation of *N*-methyl and *N*-benzyl indolines **199** and **200** in 84% and 88% yield respectively. Interestingly *N*-allyl substituted enone **173** cyclized to form the desired indoline **201** in 66% yield, with no evidence of competitive intramolecular [2+2] cycloaddition between the enone and the allyl alkene.

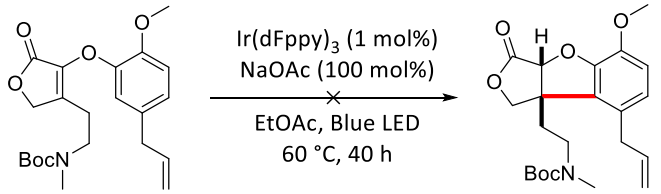


Reaction conditions: **202** (0.30 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), EtOAc ([**202**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. All yields are isolated yields after purification.

Scheme 52. Heteroatom linker scope

2.3.3 More complex substrates

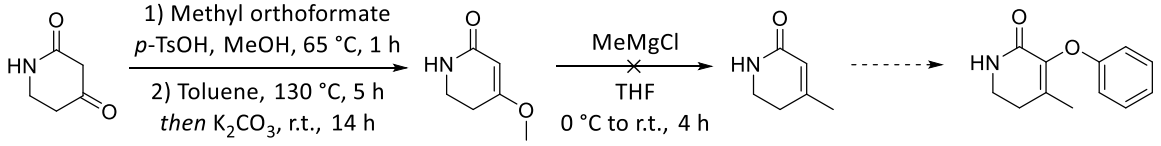
Returning to the original inspiration for the project, we hoped to perform the photocyclization from the morphine total synthesis under our new conditions (**Scheme 53**).[88] Unfortunately, when butenolide **120** was subjected to the cyclization conditions only starting material was returned. This is likely due to the higher triplet energy (≈75 kcal/mol)[93] of the butenolide chromophore compared with the cyclopentenone chromophore (≈62.5 kcal/mol),[94] meaning efficient sensitization with $Ir(dFppy)_3$ (E_T = 63.5 kcal/mol)[10] is not achievable. Instead, a photocatalyst with a higher triplet energy would need to be used to achieve the desired sensitized photocylization.



120 **121**

Scheme 53. Unsuccessful visible light-mediated cyclization of butenolide **120**

Synthesis of an α,β-unsaturated lactam containing substrate **204** was also attempted from 2,4-piperidinedione **205** (**Scheme 54**). Initial ketone *O*-alkylation was achieved in 45% yield using methyl orthoformate and *para*-toluenesulfonic acid.[95] However, subsequent Grignard addition returned only starting material **206**.

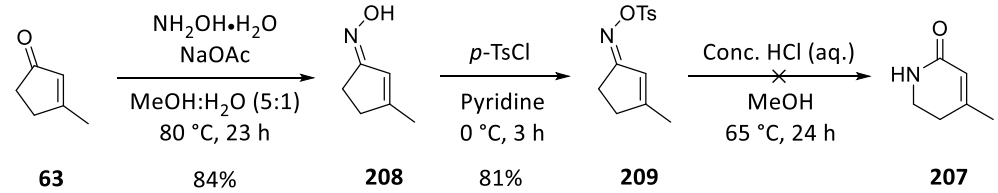


205 45% **206** **207** **204**

Scheme 54. Initial attempts at synthesising α,β-unsaturated lactam **204**

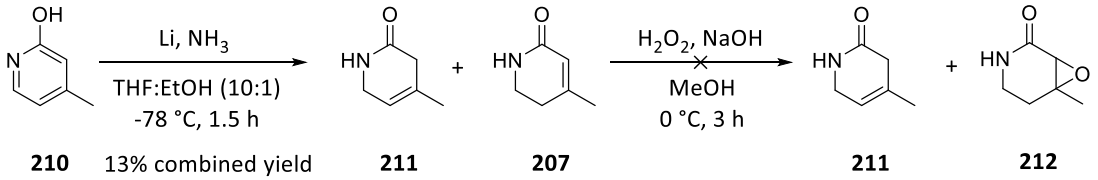
An alternative strategy using a ring-expansion Beckmann rearrangement following literature precedent was then investigated to synthesise unsaturated lactam **207** (**Scheme 55**).[96] Condensation of 3-methyl-2-cyclopenten-1-one **63** with hydroxylamine proceeded

smoothly to give oxime **208** in 84% yield as a 4:1 mixture of *E*:*Z* diastereomers. Subsequent tosylation of **208** with *para*-toluenesulfonyl chloride in pyridine gave tosylated oxime **209** in 81% yield, which was then treated with methanolic concentrated hydrochloric acid in order to effect the desired Beckmann rearrangement. Although formation of α,β-unsaturated lactam **207** was detected by ^{1}H NMR in the crude reaction mixture, purification was challenging and prevented clean isolation of the desired product.



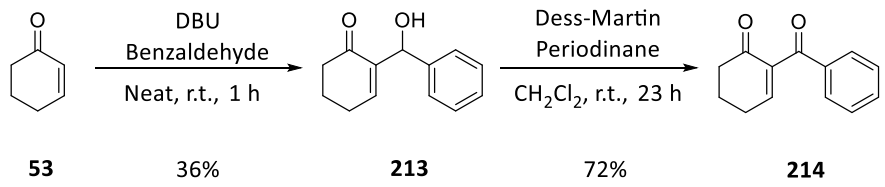
Scheme 55. Alternative strategy to synthesise α,β-unsaturated lactam **207**

A third approach used a Birch reduction of 2-hydroxy-4-methylpyridine **210** to generate the desired α,β-unsaturated lactam **207** (**Scheme 56**).[97] Pleasingly, the desired product was formed, albeit in only 13% yield and as a mixture of alkene isomers **211** and **207**. Disappointingly, treatment of this mixture with basic hydrogen peroxide returned only starting material instead of epoxide **212**.



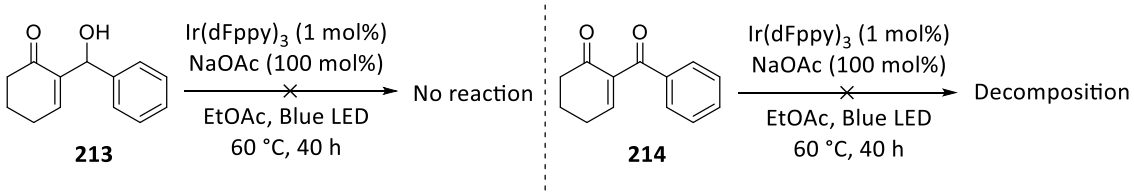
Scheme 56. Birch reduction approach to synthesise α,β-unsaturated lactam **207**

Carbon linked substrates **213** and **214** were synthesised *via* a Baylis-Hillman reaction with 2-cyclohexen-1-one **53** and benzaldehyde (**Scheme 57**).[98] For substrate **214**, this was followed by subsequent oxidation with Dess-Martin periodinane.[99]



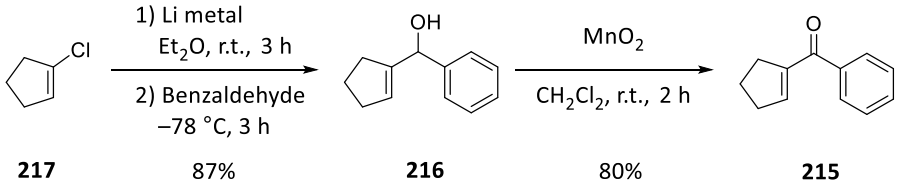
Scheme 57. Synthesis of carbon linked substrates **213** and **214**

Unfortunately, when substrate **213** was subjected to the optimized reaction conditions, only starting material was returned (**Scheme 58**). In contrast, substrate **214** decomposed under the reaction conditions, resulting in a complex mixture of products.



Scheme 58. Unsuccessful visible light-mediated cyclizations of substrates **213** and **214**

A related substrate **215** was synthesised in two steps *by* organometallic addition to benzaldehyde followed by oxidation of alcohol **216** with MnO_2 (**Scheme 59**).[100,101] Whilst this substrate (**215**) was fully consumed under the previously optimized reaction conditions, none of the desired cyclization product was observed by ^1H NMR. Instead, a series of broad peaks were observed, possibly indicating polymerization of the substrate.



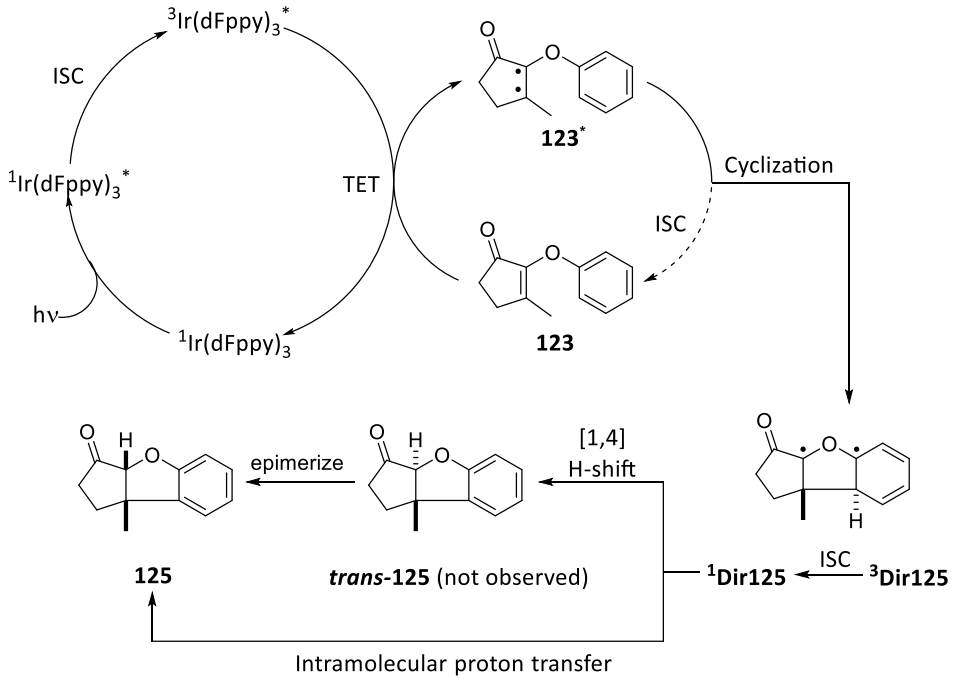
Scheme 59. Synthesis of carbon linked substrate **215**

2.3.4 Mechanistic investigations

In an attempt to trap any potential radical intermediates, TEMPO and 1,1-diphenylethylene were added to the reaction. However, in each case only unreacted

starting material was recovered. This is likely because both compounds are also triplet state quenchers and could inhibit the reaction by quenching of the photocatalyst or substrate.[5]

A proposed mechanism is outlined below (**Scheme 60**). Excitation of ground state $Ir(dFppy)_3$ by blue light followed by fast ISC leads to the generation of $Ir(dFppy)_3$ in its triplet excited state. The photocatalyst can then undergo Dexter energy transfer with substrate **123**, which leads to excitation of **123** to its triplet excited state whilst returning the photocatalyst to its ground state. The substrate can then undergo a conrotatory cyclization to form triplet diradical **^{3}Dir125**, which after ISC leads to open-shell singlet diradical **^{1}Dir125**. Subsequent intermolecular proton transfer or intramolecular proton transfer followed by epimerization leads to the observed *cis* diastereomer **125**.

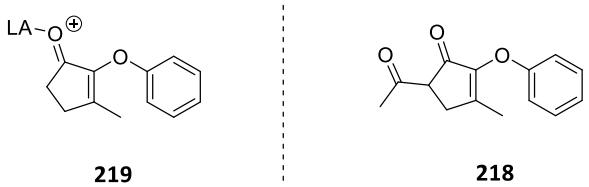


Scheme 60. Proposed mechanism of the photochemical cyclization of **123** to **125**

In order to assess the efficiency of the energy transfer process, the quantum yield of the reaction was measured. This was achieved using ferrioxalate actinometry to calculate the photon flux of the apparatus, before irradiating a sample of reaction mixture for a known period of time (2 h) and measuring the yield of product (see **Experimental** section for full details).[102,103] The quantum yield for the reaction was determined to be 7.7%.

2.3.5 Attempts at enantioselectivity

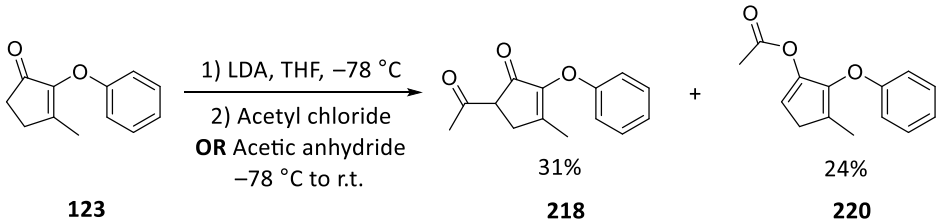
Concurrent work by Bach and co-workers demonstrated the feasibility of using a pre-coordinated chiral Lewis acid to induce modest enantioselectivity (<60% e.e.) in the photocyclization under direct irradiation or sensitization.[74] We proposed that modification of the substrate to include a 1,3-dicarbonyl motif should enable bidentate binding to a chiral Lewis acid. As such, we reasoned that 5-acyl cyclopentenone **218** would be a suitable model substrate to test this hypothesis (**Figure 5**).



219 **218**

Figure 5. Improved Lewis acid binding of **218** over **219** *via* bidentate binding.

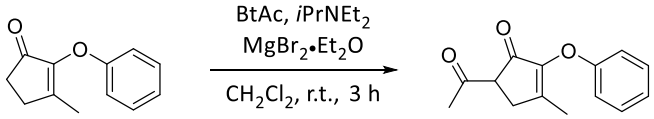
The synthetic strategy focused on selective *C*-acylation of previously synthesised photocyclization precursor **123** (**Scheme 61**). Initial attempts using lithium diisopropylamide in conjunction with acetyl chloride or acetic anhydride resulted in a mixture of *O*- and *C*-acylated products **220** and **218** respectively.[104]



123 31% **218** 24% **220**

Scheme 61. Initial attempts at synthesis of 5-acylcyclopentenone **218**

To improve the yield of the desired product, *N*-acylbenzotriazole (BtAc) was synthesised and employed as a selective *C*-acylation reagent.[105] Early attempts at acylation with this reagent in combination with the lithium enolate of cyclopentenone **123** (generated using lithium diisopropylamide) proved unsuccessful. However, alternative "soft" enolization conditions using Hünig's base in combination with magnesium bromide etherate allowed for selective *C*-acylation, giving the desired 5-acylcyclopentenone **218** in 69% yield (**Scheme 62**).[106]



Scheme 62. Improved synthesis of 5-acylcyclopentenone **218**

Disappointingly, subjecting 5-acylcyclopentenone **218** to the previously optimized reaction conditions returned only starting material. Reactions in the presence of scandium triflate (as a Lewis acid) with a variety of other photocatalysts gave a similar negative result.

Bach and co-workers had also demonstrated that eniminium ions such as **221** were also amenable to triplet energy transfer in combination with a suitable photocatalyst (**Figure 6**).[42] Unfortunately, attempts at forming the corresponding eniminium cation **222** from cyclization precursor **154** under Bach's conditions resulted in the formation of a red polymeric product that was not amenable to further purification or characterization.

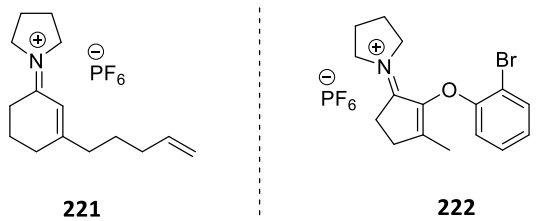
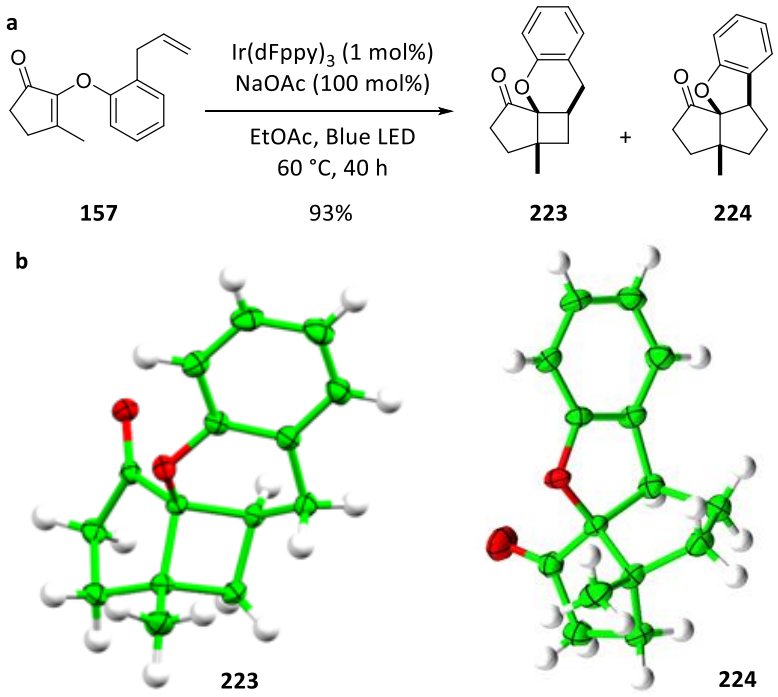


Figure 6. Photosensitizable eniminium ion reported by Bach **221** and eniminium cyclization precursor **222**

2.4 Alternative reactivity

2.4.1 [2+2] cycloaddition

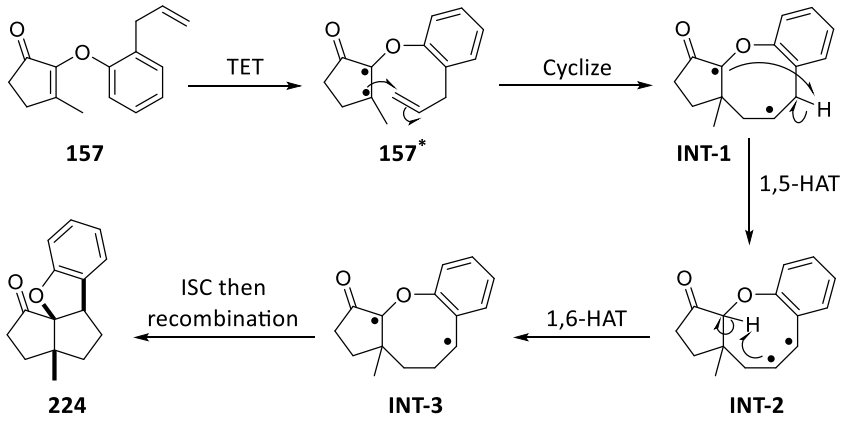
When subjected to the optimized reaction conditions, *ortho*-allyl substituted substrate **157** cyclized to form an inseparable 2:1 mixture of cyclobutane **223** and cyclopentane **224** respectively (**Scheme 63a**). The structures of the two products were elucidated by John Joliffe who manually separated two different crystals from a solid mixture of the two compounds and acquired X-ray crystal structures of both (**Scheme 63b;** see **Appendices 8.8.2** and **8.8.3** for full details).



Scheme 63a Alternative reactivity of substrate **157 b** X-ray crystal structures of products **223** and **224**.

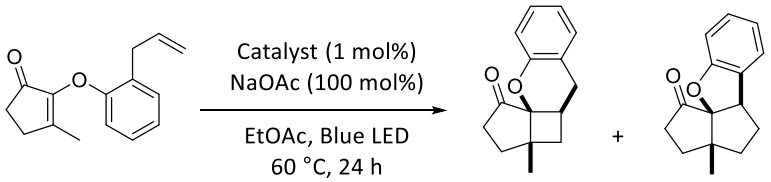
Whilst product **223** appears to have been formed by an intramolecular [2+2] cycloaddition between the cyclopentenone carbon-carbon double bond and the pendant allylic alkene, the formation of **224** was more puzzling. A potential mechanism of formation is outlined in **Scheme 64**. After excitation to the triplet state, **157** could undergo intramolecular radical cyclization to diradical **INT-1**. Subsequent 1,5-hydrogen atom abstraction would result in

diradical **INT-2**. 1,6-hydrogen atom abstraction to form **INT-3**, followed by ISC and recombination would then lead to the observed product **224**.



Scheme 64 Possible mechanism of formation of **224** from **157**

Attempts at separating the two products by flash column chromatography or semi-preparative HPLC were unsuccessful, so further modification of the reaction conditions was investigated in the hope that one product could be biased over the other. Initially, the effect that different photocatalysts had on the product ratio was investigated (**Table 3**). The optimal catalyst for the 6π heterocyclization, $Ir(dFppy)_3$, once again gave the highest conversion and combined yield of products (**Entry 1**). When $Ir(ppy)_3$ was used as a photocatalyst it returned only unreacted starting material, possibly due to its lower triplet state energy (**Entry 2**). Other catalysts with suitable triplet energies ($E_T \approx 60$ kcal/mol) showed a similar product distribution to $Ir(dFppy)_3$, but at lower conversions (**Entries 3**–**6**).[10,15]



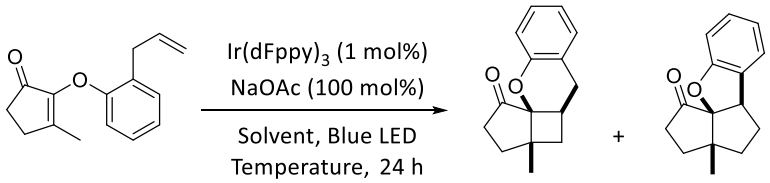
157 **223** **224**

Entry	Catalyst	Conversion[i]	Yield **223**[i]	Yield **224**[i]
1	$Ir(dFppy)_3$	65%	40%	20%
2	$Ir(ppy)_3$	0%	0%	0%
3	FIrPic	35%	26%	10%
4	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$	40%	26%	9%
5	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	35%	24%	10%
6	$[Ir(dF(CF_3)ppy)_2(phen)]PF_6$	25%	15%	5%

Reaction conditions: **157** (0.05 mmol), Catalyst (1 mol%), NaOAc (100 mol%), EtOAc ([**157**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard.

Table 3. Effect of catalyst on product distribution between **223** and **224**.

Variation of the additive had little to no effect on the reaction, with a similar conversion and product distribution observed across all additives (see **Appendix 8.3**). The effect of solvent on product distribution was also investigated (**Table 4**). Acetone and THF showed a slightly higher conversion, but a similar ratio of products to ethyl acetate (**Entries 1–2**). Using toluene as a solvent resulted in a lower conversion, but a slightly improved bias towards cyclobutane **223** (**Entry 4**). Dichloromethane gave an improved conversion and combined yield of products, and an improved bias towards cyclopentane **224** (**Entry 5**). Isopropanol proved to be an unsuitable solvent for the reaction, resulting in complete recovery of starting material **157** (**Entry 6**). In spite of some improvements in yield and conversion, the product ratio did not significantly change upon variation of the reaction solvent.



157 **223** **224**

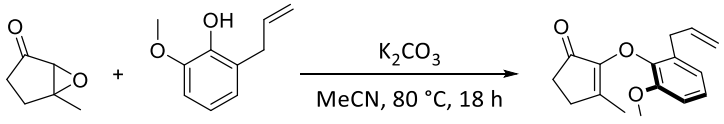
Entry	Solvent	Conversion[i]	Yield **223**[i]	Yield **224**[i]
1	EtOAc	65%	40%	20%
2	Acetone	80%	45%	25%
3	THF	75%	41%	27%
4	Toluene	50%	28%	8%
5	CH_2Cl_2	90%	51%	34%
6	Isopropanol	0%	0%	0%

Reaction conditions: **157** (0.05 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), solvent ([**157**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard.

Table 4. Effect of solvent on product distribution between **223** and **224**.

In order to attempt to trap any potential radical intermediates, TEMPO or 1,1-diphenylethylene were added to the reaction. However, only unreacted starting material was recovered in both cases. This is likely because both compounds are also triplet state quenchers, and so the photocatalyst is preferentially quenched by these compounds instead of undergoing energy transfer with substrate **157**.

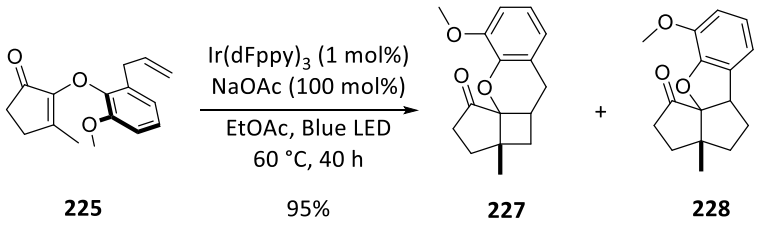
To investigate the effect of aryl ring substitution on product distribution, 6-methoxy-2-allylphenol derived substrate **225** was synthesised *via* a similar synthetic sequence (**Scheme 65**).



132 **226** **225**

Scheme 65. Synthesis of substrate **225**.

Upon subjection of substrate **225** to the reaction conditions, an inseparable 2:1 mixture of cyclobutane **227** and cyclopentane **228** was obtained in a similar result to the previous substrate (**Scheme 66**).

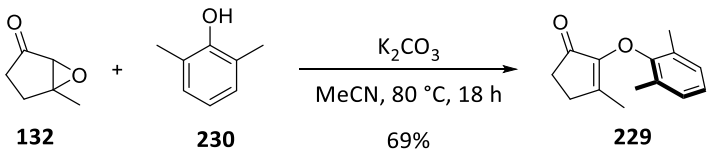


Scheme 66. Photocyclization of **225**.

Having explored a variety of changes to alter the product distribution with minimal success, the project was discontinued.

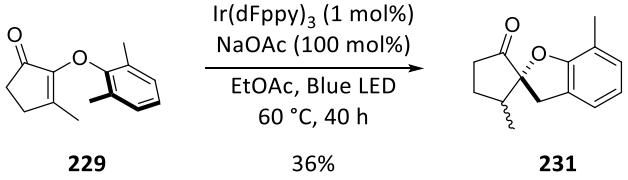
2.4.2 Blocked *ortho* position

To investigate the effect of blocking both *ortho* positions of the aromatic ring, substrate **229** was prepared from 2,6-dimethylphenol using the same conditions discussed previously (**Scheme 67**).



Scheme 67. Synthesis of substrate **229**.

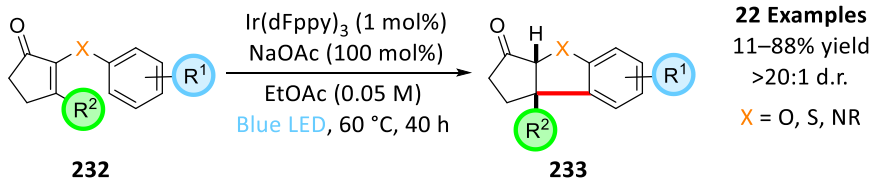
When this substrate was subjected to the optimized reaction conditions, spirocyclic dihydrobenzofuran **231** was obtained as the major isolable product (**Scheme 68**). In order to identify its mechanism of formation and develop the reactivity further, additional investigation was carried out as detailed in **Chapter 3**.



Scheme 68. Unexpected photocyclization of **229**.

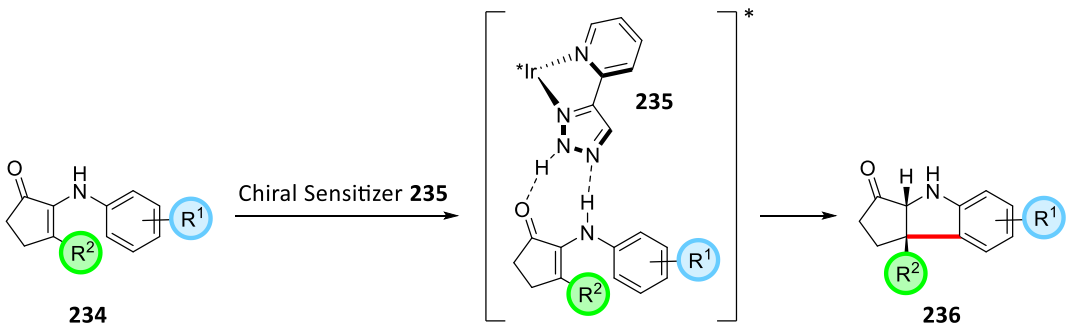
2.5 Conclusions and Further Work

We have developed a highly diastereoselective visible light-mediated cyclization of cyclic 2-arylheteroenones using an iridium photocatalyst as a suitable sensitizer (**Scheme 69**). The substrates could be rapidly constructed using a modular synthetic sequence, allowing for a wide variety of molecular scaffolds to be generated. The scope of the reaction was broad, although particularly electron poor substrates suffered from reduced yields, and invariably gave the desired product with excellent diastereoselectivity.



Scheme 69. Visible light-mediated cyclization of cyclic 2-arylheteroenones

Attempts at making the reaction enantioselective proved challenging and met with little success. This is unsurprising given the challenges faced when Bach and co-workers developed an enantioselective variant of the reaction under direct irradiation.[74] One possible direction for future work would be to use a similar strategy to Bach[32,34], Meggers[39,40] and Yoon[41] by using aniline-derived substrate **234** in combination with an octahedrally chiral triplet sensitizer such as **235** (**Scheme 70**). By only sensitizing the substrate in a chiral environment, one product enantiomer **236** could be favoured over the other.



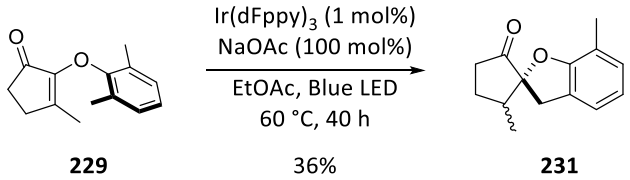
Scheme 70. A potential strategy for enantioselective 6π heterocyclization

3 Hydrogen atom abstraction

3.1 Dihydrobenzofuran

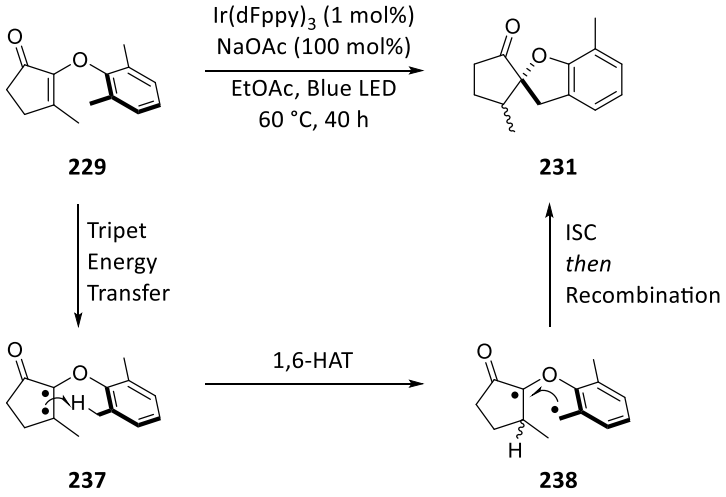
3.1.1 Precedent and previous work

As described in **Chapter 2**, blocking both *ortho* positions of 6π heterocyclization substrate **229** with methyl groups and subjecting it to the reaction conditions led to the formation of a spirocyclic dihydrobenzofuran **231** (**Scheme 71**).



Scheme 71. Unexpected photocyclization of **229**.

A working hypothesis on the mechanism of the reaction is outlined below (**Scheme 72**). Triplet energy transfer from the $Ir(dFppy)_3$ photocatalyst to the substrate leads to the generation of triplet diradical **237**. A 1,6-hydrogen atom transfer from a benzylic methyl group to the β-position of enone diradical **237** led to the formation of 1,5 triplet diradical **238**. Intersystem crossing followed by radical recombination led to the formation of spirocyclic dihydrobenzofuran **231**.

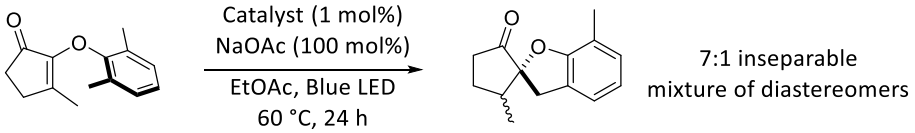


Scheme 72. Proposed mechanism for the photochemical spirocyclization of **229** to form **231**.

Extension of this strategy to the formation of other small ring spirocyclic systems would provide a valuable new synthetic method for the expedient generation of such structures.

3.1.2 Reaction Optimization

In order to improve the selectivity and the yield of the initial hit reaction, optimization was performed. Initial efforts focussed on screening a variety of photocatalysts (**Table 5**). The optimal catalyst for the previous reaction, $Ir(dFppy)_3$, gave the highest yield and conversion of all the catalysts tested (**Entry 1**). Using $Ir(ppy)_3$ as the photocatalyst resulted only in recovery of starting material, possibly due to its lower triplet state energy (**Entry 2**). Other photocatalysts with suitable triplet state energies for sensitization showed clean reactivity, but lower yields than $Ir(dFppy)_3$ (**Entries 3**–**6**).



229 **231**

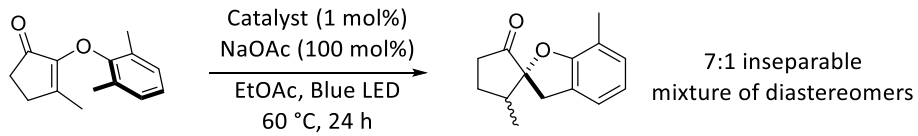
Entry	Catalyst	Conversion[i]	Yield[i]
1	$Ir(dFppy)_3$	38%	38%
2	$Ir(ppy)_3$	0%	0%
3	FIrPic	16%	16%
4	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$	<5%	<5%
5	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	8%	7%
6	$[Ir(dF(CF_3)ppy)_2(phen)]PF_6$	<5%	<5%

Reaction conditions: **229** (0.05 mmol), Catalyst (1 mol%), NaOAc (100 mol%), EtOAc ([**229**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard. Yield represents combined yield of both diastereomers.

Table 5. Catalyst screen for the photospirocyclization of **229**.

Variation of the additive in the reaction resulted in little change to the conversion of starting material or yield of product (**See Appendix 8.4**). In contrast, varying the reaction

solvent had a more pronounced effect (**Table 6**). Ethyl acetate gave the desired product in 50% yield at 54% starting material consumption (**Entry 1**). Dichloromethane, acetone and THF gave similar or greater conversions, but lower yields of the product (**Entries 2**–**4**). Acetonitrile gave lower conversion and yield, but a better ratio of yield to conversion (**Entry 5**). Ethyl acetate was selected as the optimal reaction solvent as a compromise between reaction time and yield to conversion ratio.



229 **231**

Entry	Solvent	Conversion[i]	Yield[i]
1	EtOAc	54%	50%
2	CH_2Cl_2	66%	27%
3	Acetone	50%	28%
4	THF	100%	20%
5	MeCN	20%	20%

Reaction conditions: **229** (0.05 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), solvent ([**229**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard. Yield represents combined yield of both diastereomers.

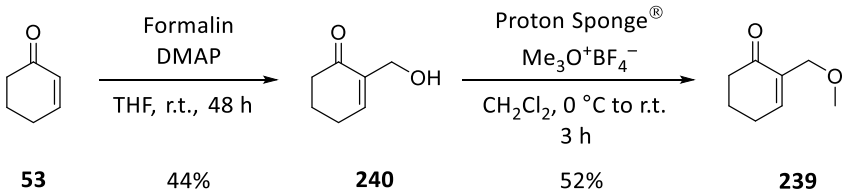
Table 6. Effect of solvent on product distribution between **229** and **231**.

The reaction was then further optimized and scoped by Terence Wu, a Part II student under my supervision, and details can be found in his thesis.[107]

3.2 Other substrates

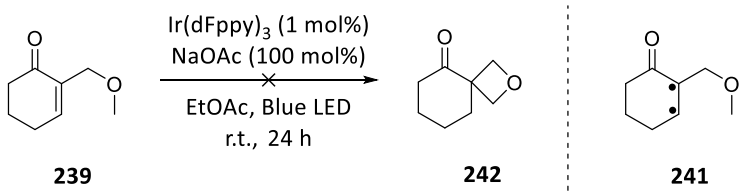
In order to broaden the applicability of this spirocyclization, methoxymethyl substrate **239** was synthesised in two steps from cyclohexenone (**Scheme 73**).[108] Following a Morita-Baylis-Hillman reaction between cyclohexenone **53** and formaldehyde,

intermediate alcohol **240** was selectively *O*-alkylated with trimethyloxonium tetrafluoroborate in the presence of Proton sponge® to give methoxymethyl enone **239**.



Scheme 73. Synthesis of methoxymethyl substrate **239**

Disappointingly, when substrate **239** was subjected to the optimized reaction conditions only starting material was recovered (**Scheme 74**). Given the significant structural differences between substrate **229** and substrate **239**, this is in hindsight not unsurprising. In contrast to spirocyclization substrate **229**, methoxymethyl ether **239** lacks the electron-donating heteroatom at the 2- position of the enone, resulting in reduced captodative stabilization at the α- position of triplet diradical **241**. This in turn may reduce its triplet lifetime, leading to relaxation to the ground state being faster than hydrogen atom abstraction, and thus the observed lack of reactivity.



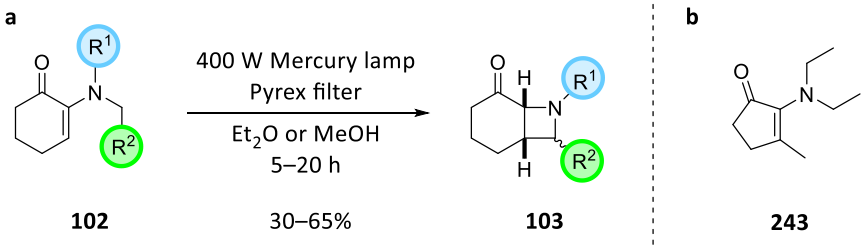
Scheme 74. Attempted photocyclization of **239**.

3.3 Ring fused Azetidine

3.3.1 Previous work and precedent

Due to the lack of success in improving the yield of the spirocyclic dihydrobenzofuran **229** by reaction optimization, the literature was examined for other suitable systems. A paper by Arnould and co-workers had shown that *N*,*N*-dialkylamino-2-cyclohexen-1-ones **102**

underwent photochemical cyclization to give *cis*-fused azetidines **103** (**Scheme 75a**).[76] The authors proposed a mechanism similar to that for *N*-tosylamino-2-cyclohexen-1-ones as discussed in **Chapter 1**.[75]



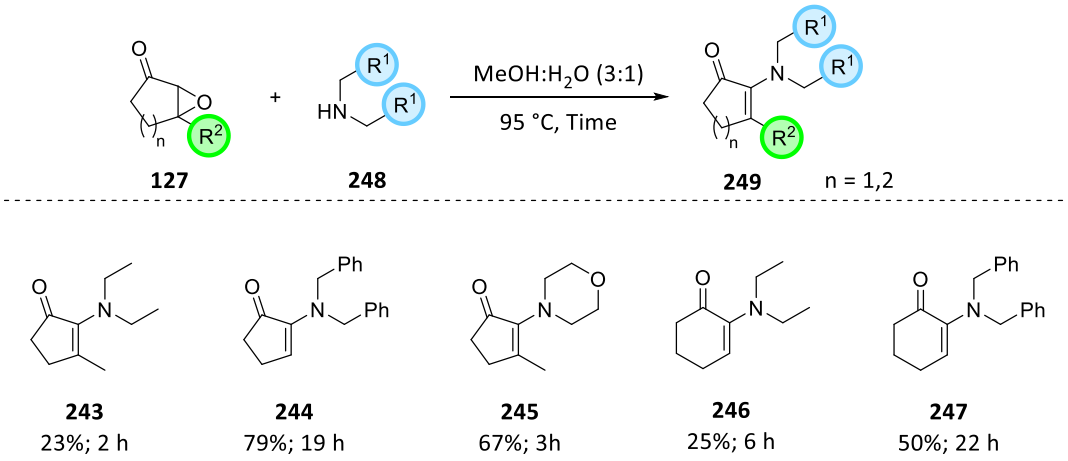
Scheme 75. **a** Photocyclization of *N*,*N*-dialkylamino-2-cyclohexen-1-ones. **b** Model substrate **243**

Given the structural similarity of the 2-aminocyclohexen-1-one chromophore to other 2-heterocyclohexen-1-one substrates that had been amenable to triplet energy transfer, it was conjectured that this substrate would also be excitable using a similar strategy. Although the original paper proposed that the desired reactivity occurred in the singlet excited state, the previously described photochemical spirocyclization of 2-(2,6-dimethyl)phenoxycyclohexene-1-ones had demonstrated that similar hydrogen atom abstraction could occur in the triplet excited state. In order to test this hypothesis, substrate **243** was proposed as a suitable model and efforts towards its synthesis commenced (**Scheme 75b**).

3.3.2 Substrate Synthesis

A variety of enaminones were synthesised by heating the requisite epoxide and secondary amine in a 3:1 mixture of methanol and water at reflux (**Scheme 76**).[109] Initial condensation of epoxide **132** and diethylamine gave enaminone **243** in 23% yield. The low yield of the product may be due to the volatility of the diethylamine under the reaction conditions. Less volatile amines, such as dibenzylamine and morpholine, condensed to

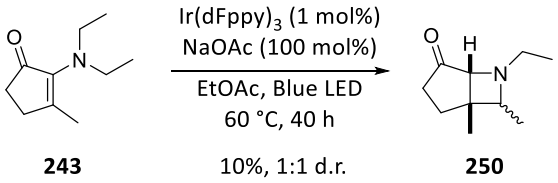
form the desired enaminones **244** and **245** in higher yields (79% and 67% yield respectively). Cyclohexenone-derived epoxide **129** could also be opened by a suitable secondary amine, allowing the formation of diethylamine derived enaminone **246** in 25% yield and dibenzylamine derived enaminone **247** in 50% yield.



Scheme 76. Synthesis of enaminone substrates

3.3.3 Cyclization

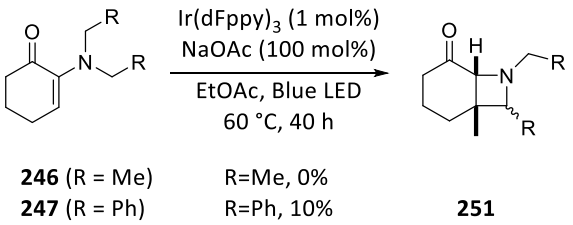
Test substrate **243** was subjected to the previously optimized reaction conditions to identify any possible photochemical reactivity (**Scheme 77**). Although the mass balance of the reaction was poor, *cis*-fused azetidine **250** was obtained from the reaction in 10% yield as a 1:1 mixture of diastereomers at the indicated stereocentre.



Scheme 77. Photochemical formation of azetidine **250**.

Six membered enaminone test substrates were also investigated (**Scheme 78**). Disappointingly, cyclization of diethylenaminone **246** (R = Me) resulted in only recovered starting material. In contrast, dibenzylenaminone **247** (R = Ph) cyclized to form the

corresponding *cis*-fused azetidine **251** in 10% yield as a mixture of diastereomers. The difference in reactivity between the two substrates can be attributed to the relative strength of the C-H bonds to be broken during any potential hydrogen atom abstraction, with the benzylic C-H bond being significantly weaker (89.7 kcal/mol) than the aliphatic C-H bond (101.1 kcal/mol) due to the stabilization of the benzylic radical by the aryl π system.[110]



Scheme 78. Difference in photochemical reactivity of substrates **246** and **247**.

Due to the low yields of the desired *cis*-fused azetidine products in the reactions and complex mixture of products formed in the reaction, the project was curtailed at this early stage in favour of a more promising concurrent project (see **Chapter 4** for further details).

3.4 Conclusions and Further Work

The results of the work described in this chapter highlight that the triplet excited state of cyclic 2-aryloxyenones is sufficiently reactive to undergo intramolecular hydrogen atom transfer to afford a 1,6-diradical, which can then recombine upon intersystem crossing to the ground state. Disappointingly, attempts at optimizing this reactivity met with little success.[107] Attempts at generalizing the reaction to other systems also proved challenging, though some moderate success was observed for *N*,*N*-dialkylamino-2-cyclic enones.

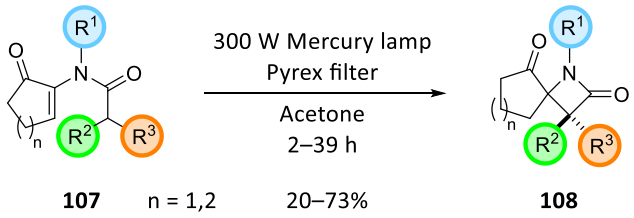
One potential reason for the poor reactivity of these substrates is perhaps due to the hydrogen atom abstraction being slow relative to relaxation back to the ground state. This in turn may be due to the length and limited flexibility of the linker between the enone chromophore and the site of hydrogen atom abstraction. A more flexible shorter linker would allow for a 1,5-hydrogen atom transfer, which should be kinetically favoured and could potentially provide a system with improved reactivity.[111]

4 β lactam spirocyclization

4.1 Precedent and previous work

Following on from the work described in **Chapter 3**, we sought to develop a system with a more flexible linker between the enone chromophore and the site of hydrogen atom abstraction. Such a system would ideally have a weak carbon-hydrogen bond five atoms away from the β position of the enone to allow for a 1,5-hydrogen atom transfer.

A review of the literature highlighted the work of Ikeda and co-workers, who reported the photocyclization of 2-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones **107** under Pyrex-filtered irradiation in acetone to give spirocyclic β lactam products **108** (**Scheme 79**).[78,79] Although the authors propose that the reaction proceeds *via* 1,5-hydrogen atom abstraction in the singlet excited state, previous results with other *N*,*N*-dialkyl-2-cyclic enones had demonstrated that similar 1,5-hydrogen atom abstractions could occur in the triplet excited state (see **Chapter 3** for further details). We therefore embarked on the synthesis of these substrates in order to test our hypothesis.

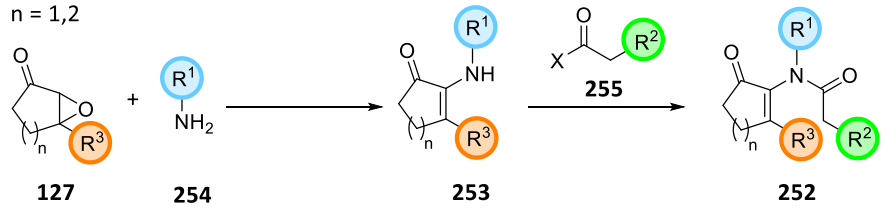


107 n = 1,2 20–73% **108**

Scheme 79 Photocyclization of 2-(*N*-acyl-*N*-alkylamino)cyclohex-2-enones

4.2 Substrate synthesis

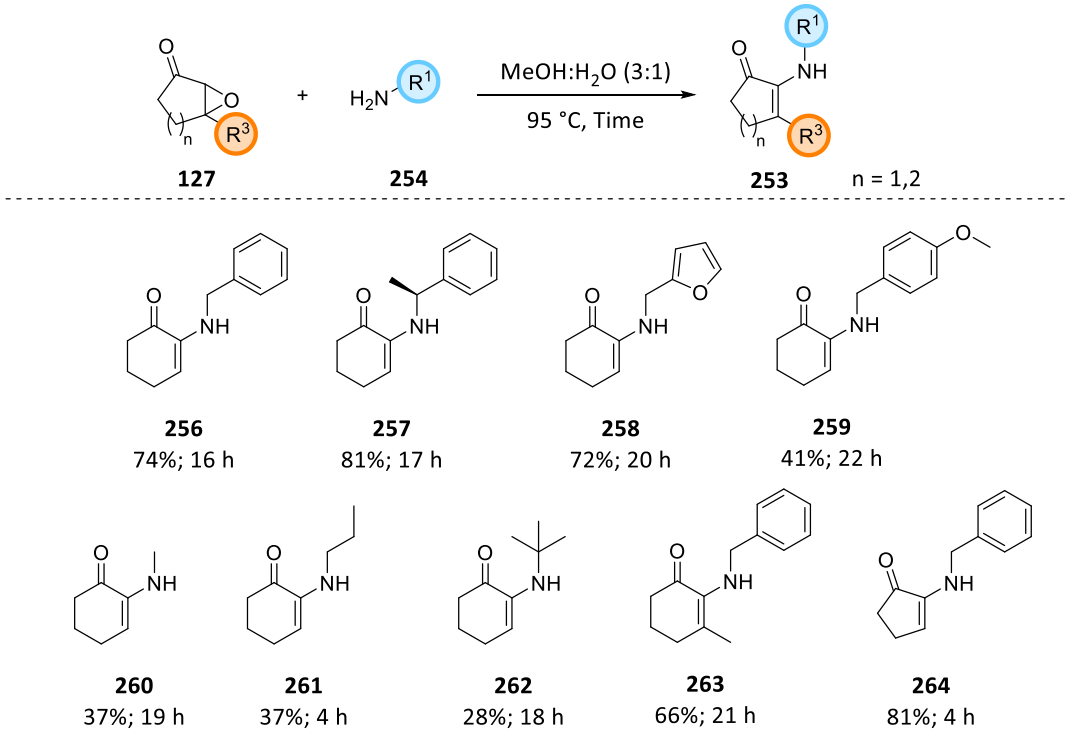
N-acyl enaminones **252** were synthesised by acylation of intermediate enaminone **253**, which in turn was synthesised from condensation of a primary amine **254** and an epoxide **127** (**Scheme 80**).



Scheme 80. Strategy to synthesise *N*-acyl enaminones **252**

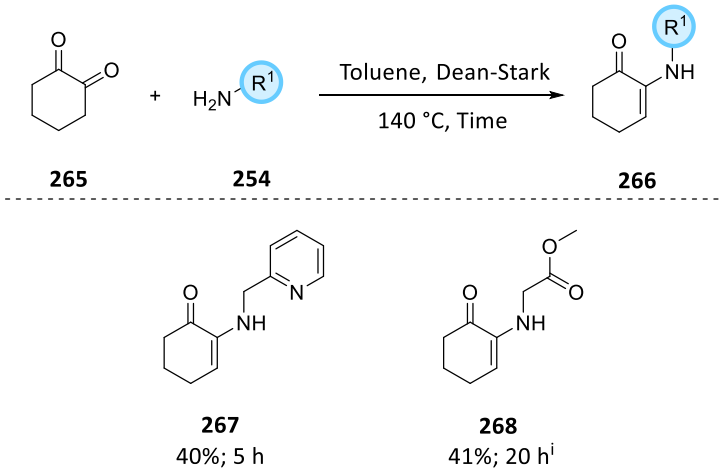
4.2.1 Amine condensation

Several intermediate enaminones were prepared following an epoxide opening procedure similar to that in previous projects (**Scheme 81**).[75,112] Benzylic amines typically gave the desired enaminone in good yield, as shown by benzylamine-derived enaminone **256** (74% yield), 1-phenylethylamine-derived enaminone **257** (81% yield) and furfurylamine-derived enaminone **258** (72% yield). One exception was *para*-methoxybenzylamine derived enaminone **259**, which was obtained in a lower 41% yield. Aliphatic primary amines generally gave lower yields of the corresponding enaminone, as demonstrated by methylamine-derived enaminone **260** (37% yield), *n*-propylamine-derived enaminone **261** (37% yield) and *tert*-butylamine-derived enaminone **262** (28% yield). The epoxide coupling partner could also be varied, allowing for β-methyl enaminone **263** to be synthesised in 66% yield, and cyclopentenone-derived enaminone **264** to be made in 81% yield.



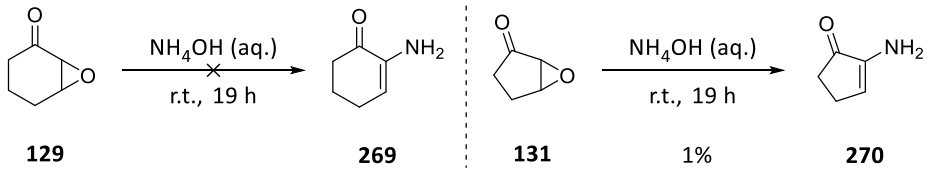
Scheme 81. Scope of the amine epoxide opening

A couple of amines did not form intermediate enaminone **253** under the epoxide opening procedure and therefore required an alternative method to synthesise. Pleasingly, condensation of the desired primary amine **254** with 1,2-cyclohexanedione **265** in toluene at 140 °C under Dean-Stark conditions led to the formation of the desired enaminone **266** (**Scheme 82**).[112] This allowed for 2-picolyl amine-derived enaminone **267** to be synthesised in 40% yield, and glycine-derived enaminone **268** to be synthesised in 41% yield.



Scheme 82. Intermediate enaminones synthesised by dione condensation. [i] With 1.1 equivalents of $NaHCO_3$.

Attempts were made to synthesise primary enaminones **269** and **270** by condensation of ammonia with epoxides **129** and **131** respectively following literature procedure (**Scheme 83**).[113] Disappointingly enaminone **269** was not obtained and instead starting material **129** recovered, whilst enaminone **270** was only obtained in a 1% yield.



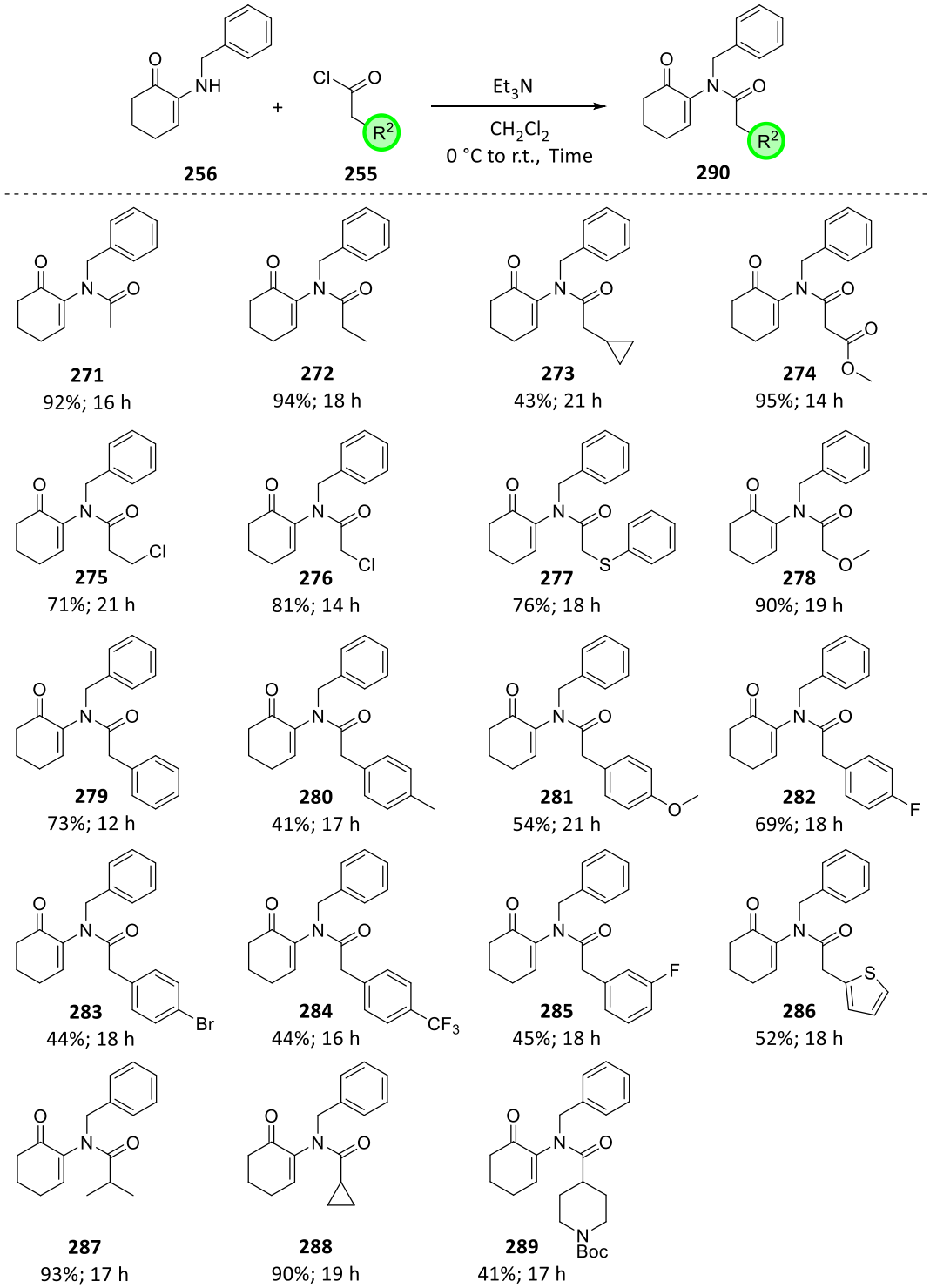
129 **269** **131** 1% **270**

Scheme 83. Attempted synthesis of primary enaminones **269** and **270**

4.2.2 Acylation

Initial amide coupling conditions used the desired acid chloride in combination with triethylamine to generate a variety of substrates (**Scheme 84**).[114] Acylation with acetyl or propionyl chloride gave the desired *N*-acyl enaminones in excellent yield (92% for *N*-acetyl enaminone **271** and 95% yield for *N*-propionyl enaminone **272**). In contrast, acylation with cyclopropylacetyl chloride gave the desired enaminone **273** in much lower yield (43%). Methyl malonyl chloride acylated intermediate enaminone **256** to give the desired enaminone **274** in 95% yield. Chloroacyl chlorides also proved effective acylating agents, with 3-chloropropionyl chloride giving enaminone **275** in 71% yield and chloroacetyl chloride giving enaminone **276** in 86% yield. In addition, heteroatom-containing acyl chlorides could be used, allowing for (phenylthiol)acetyl chloride-derived enaminone **277** to be synthesied in 76% yield and methoxyacetyl chloride-derived enaminone **278** to be synthesised in 90% yield. A range of phenylacetyl chlorides also proved effective coupling partners, allowing for the incorporation of unsubstituted phenyl rings (**279**, 73%), electron rich phenyl rings (4-methyl **280**, 41%; 4-methoxy **281**, 54%) and electron poor phenyl rings (4-fluoro **282**, 69%; 4-bromo, **283**, 44%; 4-trifluoromethyl **284**, 44%; 3-fluoro **285**, 45%).

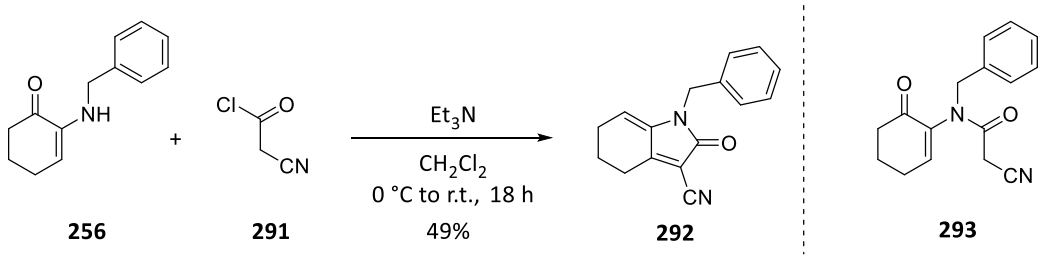
Heteroaromatic rings could also be incorporated, such as 2-thiophenylacetyl chloride-derived enaminone **286**, which was formed in 52% yield.



Scheme 84. Variation of the acylating agent

Di-substituted acyl chlorides also showed the desired reactivity, allowing for isobutyryl enaminone **287** to be synthesised in 93% yield and cyclopropylamide-containing enaminone **288** to be synthesised in 90% yield. More functionalised acyl chlorides could be coupled to enaminone **256**, allowing for *N*-Boc-piperidine containing enaminone **289** to be synthesised in 41% yield.

One limitation of these conditions was highlighted when enaminone **256** was subjected to the coupling conditions in combination with cyanoacetyl chloride **291** (**Scheme 85**). The major product of the reaction was **292** instead of the desired *N*-acyl enaminone **293**, likely to be due to the intramolecular addition of the amidonitrile anion to the enone carbonyl followed by E1cb to eliminate water.[115]

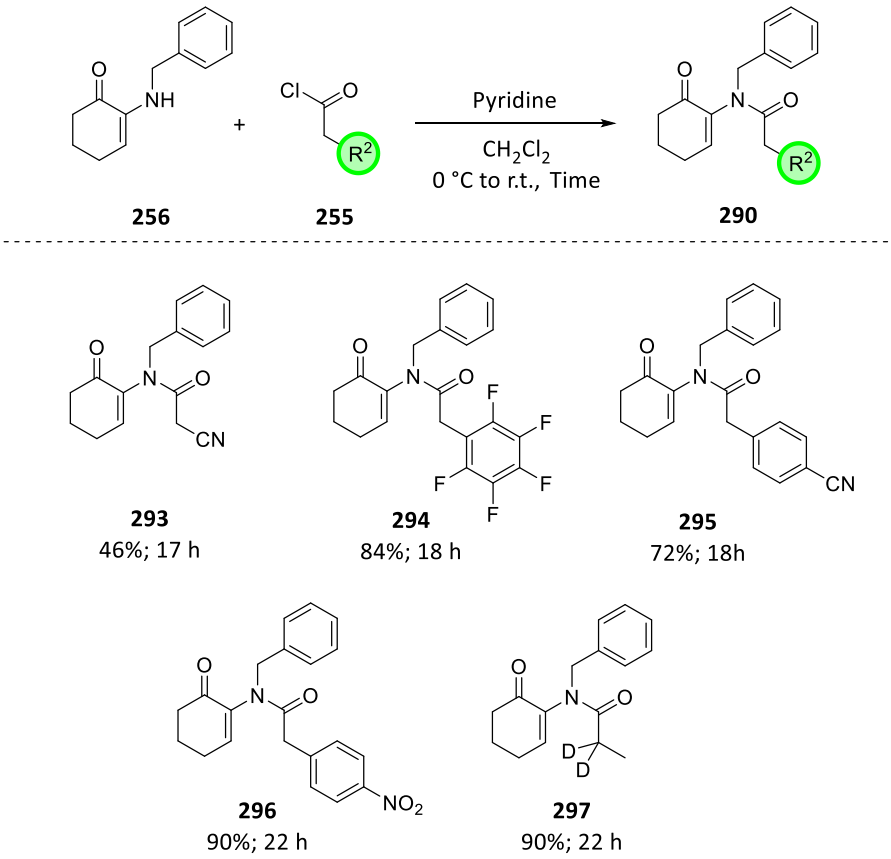


256 **291** **292** **293**

Scheme 85. Overreaction in the presence of triethylamine

To resolve this issue, pyridine was used in place of triethylamine to couple acyl chlorides with particularly acidic α protons (**Scheme 86**). Pleasingly, cyanoacetyl enaminone **293** was synthesised in 46% yield without any condensation by-product. The new conditions also permitted a range of strongly electron poor phenylacetyl chlorides to be used as coupling partners, allowing the synthesis of pentafluorophenyl-containing enaminone **294** in 84% yield, 4-cyanophenylacetyl-derived enaminone **295** in 72% yield and 4-nitrophenylacetyl-derived enaminone **296** in 90% yield. In addition, these conditions

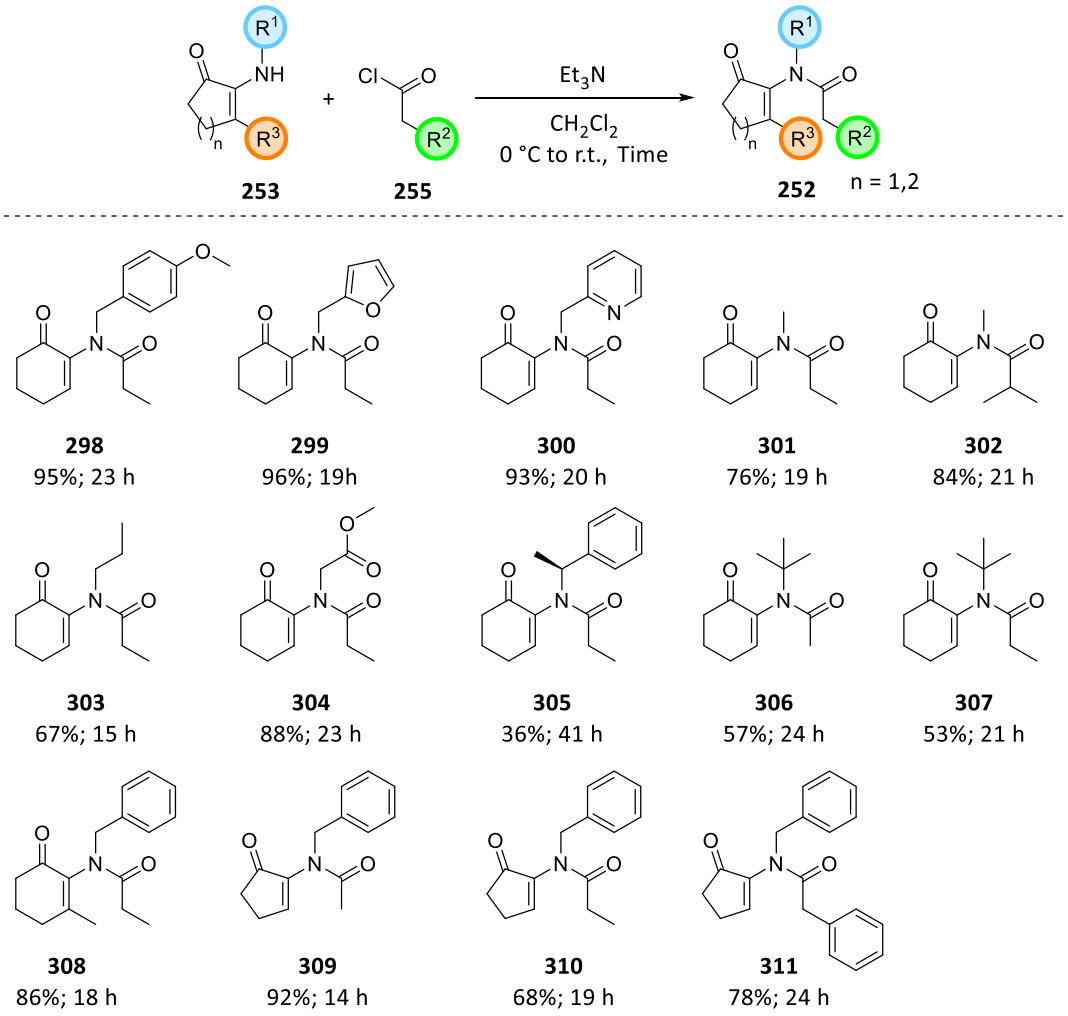
were used to synthesise d_2-propionyl enaminone **297** in 90% yield to prevent solvent exchange mediated loss of the deuterium label.



Scheme 86. Acylation using pyridine as the base

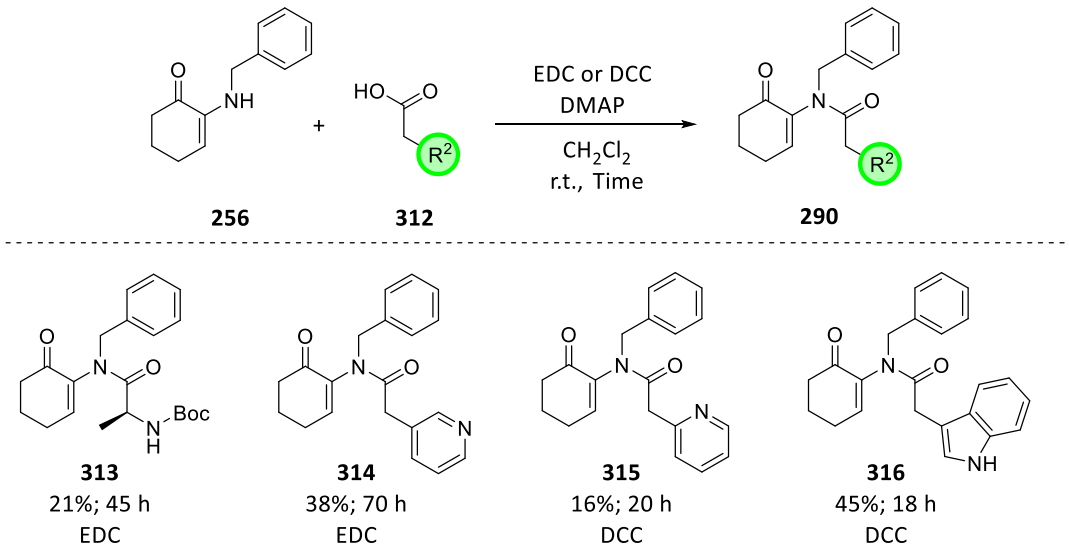
A variety of intermediate enaminones **253** were also subjected to the coupling conditions in combination with selected acyl chlorides (**Scheme 87**). Acylation of other benzylic enaminones with propionyl chloride proceeded smoothly allowing *para*-methoxybenzyl enaminone **298** to be synthesised in 95% yield. Pendant heteroaromatic groups on the enaminone nitrogen could be incorporated, allowing furfuryl enaminone **299** to be made in 96% yield and picolyl enaminone **300** to be formed in 93% yield. Smaller *N*-alkyl substituents were also competent coupling partners, allowing *N*-methyl enaminones **301** and **302** to be synthesised in 76% yield and 84% yield respectively, and *N*-*n*-propyl enaminone **303** to be synthesised in 67% yield. Acylation of glycine derived enaminone **268**

with propionyl chloride gave the corresponding acylated enaminone **304** in 88% yield. Increased steric bulk around the enaminone nitrogen led to reduced yields of the *N*-acyl enaminone. This was demonstrated by 1-phenethylamine derived enaminone **305**, which was obtained in 36% yield, and by *N*-*tert*-butyl enaminones **306** and **307** which were obtained in 57% and 53% yield respectively. Enaminones with substitution at the β-position of the enone were also competent coupling partners, allowing *N*-propionyl enaminone **308** to be synthesised in 86% yield. In addition, smaller ring size enaminones were able to be synthesised, such as cyclopentenone-derived enaminones **309**, **310** and **311**, which were synthesied in 92%, 68% and 78% yield respectively.



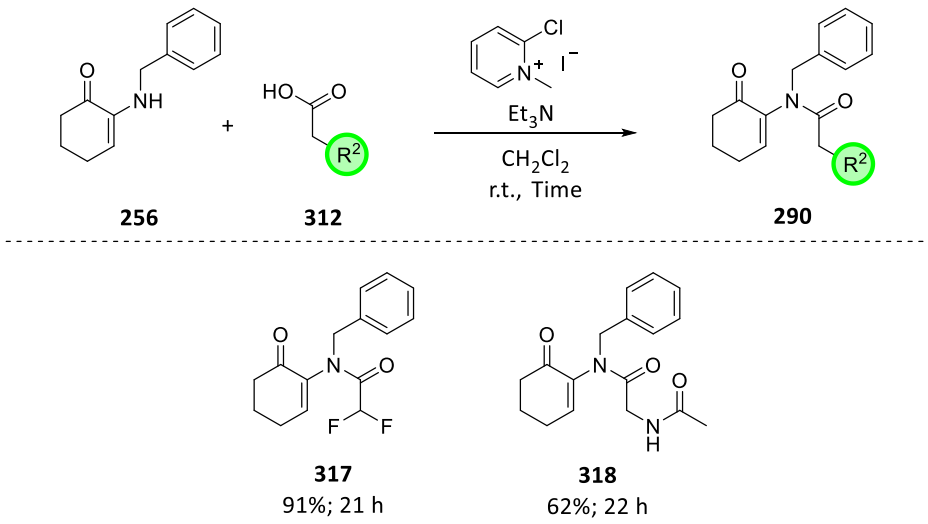
Scheme 87. Variation of the amine linker substituent

For some substrates, the corresponding carboxylic acid **312** was used in combination with a suitable coupling reagent to synthesise the amide **290** (**Schemes 84** and **85**). This was particularly important for substrates with a stereogenic centre adjacent to the coupling carbonyl, such as **313**, where formation of the acyl chloride in combination with basic conditions could lead to racemization. Carbodiimide coupling reagents, such as EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) or DCC (*N*,*N*'-dicyclohexylcarbodiimide) performed the desired coupling reaction, although longer reaction times were required in comparison to using the acyl chloride (**Scheme 88**). *N*-Boc-alanine containing enaminone **313** was synthesised in 21% yield using EDC as the coupling reagent, and pleasingly showed little evidence of racemization. 2- and 3-pyridyl acetic acids were also suitable coupling partners in combination with either EDC or DCC, allowing 3-pyridyl containing enaminone **314** to be synthesised in 38% yield and 2-pyridyl containing enaminone **315** to be synthesised in 16% yield. DCC also allowed for indole-3-acetic acid to be coupled to enaminone **256**, giving enaminone **316** in 45% yield.



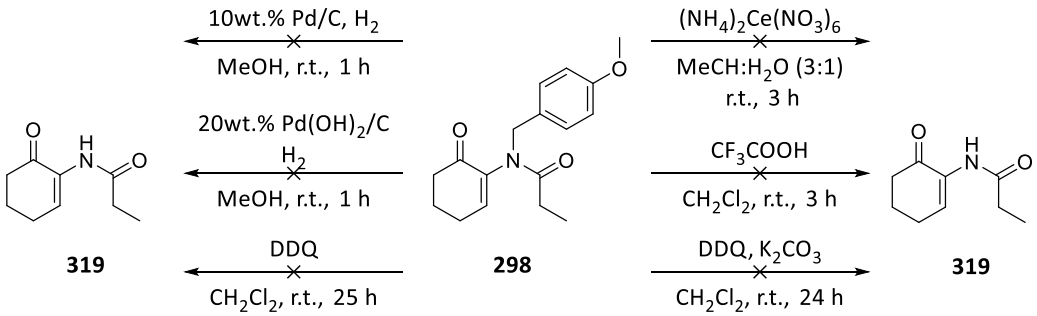
Scheme 88. Acylation using carboxylic acids and carbodiimide reagents. DMAP = 4-(Dimethylamino)pyridine; EDC = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; DCC = *N*,*N*'-Dicyclohexylcarbodiimide

Mukaiyama's reagent, *N*-methyl-2-chloropyridinium iodide, also proved a competent coupling reagent (**Scheme 89**). Difluoroacetyl enaminone **317** was prepared in 91% yield, whilst amide-containing enaminone **318** was prepared in 62% yield from *N*-acetyl glycine.



Scheme 89. Acylation using carboxylic acids and Mukaiyama's reagent

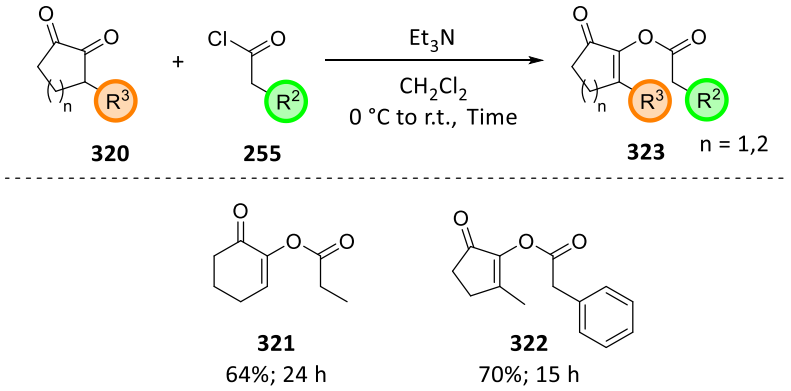
Several attempts were made to try to synthesise a secondary enaminone **319** by removal of the *para*-methoxybenzyl (PMB) group from substrate **298** (**Scheme 90**). Disappointingly, all attempts resulted in either decomposition or recovery of starting material.



Scheme 90. Unsuccessful attempts to remove the PMB group from substrate **298**

Other heteroatom linkers, such as oxygen, were also synthesised as potential substrates (**Scheme 91**). These enol ethers were prepared by *O*-acylation of the corresponding diketone **320** with a suitable acyl chloride in the presence of triethylamine.

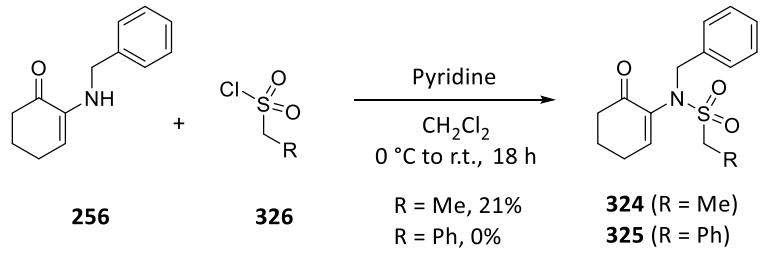
Cyclohexane-1,2-dione-derived substrate **321** was synthesised in 64% yield, whilst 3-methyl-cyclopentane-1,2-dione-derived substrate **322** was formed in 70% yield.



Scheme 91. Variation of the heteroatom linker

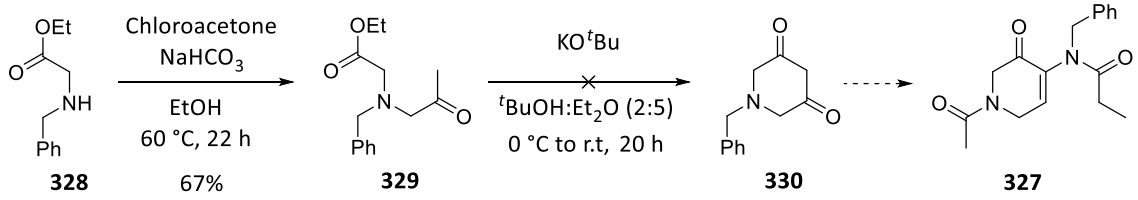
4.2.3 Additional Substrates

Other substrates were considered for the reaction, including *N*-sulfonyl enaminones such as **324** or **325** (**Scheme 92**). The synthesis of these compounds by *N*-sulfonylation with the appropriate sulfonyl chloride **326** proved challenging, and initial attempts using triethylamine as the base in the reaction led to decomposition of the starting material and sulfonyl chloride. Switching to pyridine enabled ethyl sulfonamide enaminone **324** to be synthesised in 21% yield; however, benzyl sulfonamide enaminone **325** was not formed under these conditions and instead only starting material was recovered.[75] Further attempts at synthesising benzyl sulfonamide **325** using an elevated temperature (80 °C) in a higher boiling point solvent (1,2-dichloroethane) led to decomposition of starting material **256**.



Scheme 92. Synthesis of *N*-sulfonyl enaminones

Synthesis of a 5-amino substituted substrate **327** was also attempted (**Scheme 93**). *N*-alkylation of commercially available *N*-benzylglycine ethyl ester **328** with chloroacetone following literature procedure gave tertiary amine **329** in 67% yield.[116,117] A subsequent Dieckmann condensation in the presence of potassium *tert*-butoxide was attempted. However, only a sticky yellow polymeric product which was insoluble in most solvents was obtained, rather than diketone **330**. This product could be formed by hydrolysis of the ethyl ester with potassium hydroxide, which could be generated *in situ* from water present in the *tert*-butanol in combination with potassium *tert*-butoxide.

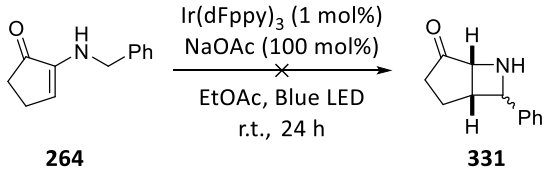


Scheme 93. Attempts towards the synthesis of 5-amino substituted enaminone **327**

4.3 Photocyclization

4.3.1 Optimization

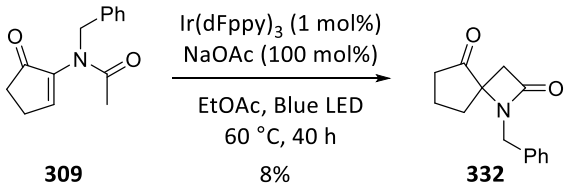
Initial attempts at photocyclization of secondary enaminones such as **264** under similar conditions to those described in **Chapter 3** were unsuccessful, resulting only in recovery of starting material (**Scheme 94**).



264 **331**

Scheme 94. Unsuccessful photocyclization of secondary enaminone **263**

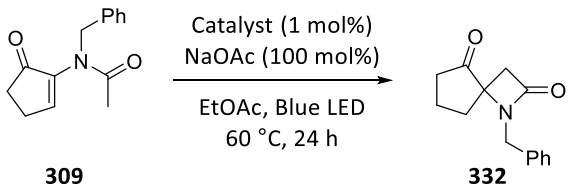
Pleasingly when *N*-acyl substrate **309** was subjected to the previously optimized reaction conditions, the desired β-lactam product **332** was formed in 8% yield (**Scheme 95**).



309 8% **332**

Scheme 95. Photocyclization of *N*-acyl enaminone **308**

To improve the yield of the desired β-lactam product, optimization was performed on the reaction using substrate **309**, with the initial focus being on a catalyst screen (**Table 7**). Disappointingly, $Ir(ppy)_3$ showed no reactivity at all (**Entry 1**), and all other catalysts tested gave very sluggish conversion and yield (**Entries 2**–**5**). Performing the reaction at ambient temperature instead of 60 °C showed no change in reactivity (**Entry 6**). Similarly changing the light source from a 12 W blue LED strip to a 40 W Kessil blue LED lamp also showed no significant change in reactivity (**Entry 7**).



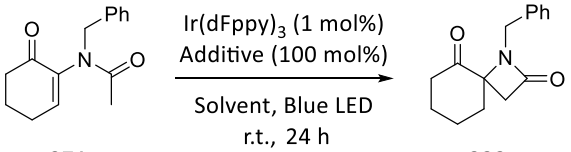
309 **332**

Entry	Catalyst	Conversion[i]	Yield[i]
1	$Ir(ppy)_3$	0%	0%
2	$Ir(dFppy)_3$	<5%	<5%
3	FIrPic	<5%	<5%
4	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$	<5%	<5%
5	$[Ir(dF(CF_3)ppy)_2(phen)]PF_6$	<5%	<5%
6	$Ir(dFppy)_3$[ii]	<5%	<5%
7	$Ir(dFppy)_3$[iii]	<5%	<5%

Reaction conditions: **309** (0.05 mmol), Catalyst (1 mol%), NaOAc (100 mol%), EtOAc ([**309**] = 0.05 M), 12 W blue LED, 60 °C, 24 h. [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard.[ii] Reaction performed at ambient temperature (r.t.) . [iii] Using a 40 W Kessil Blue LED lamp in place of 12 W blue LED strips at ambient temperature.

Table 7. Catalyst screen for the photocyclization of **309**.

As substrate **309** showed poor reactivity, substrate **271** was chosen instead for further optimization (**Table 8**). Initial experiments comparing different blue light sources using the previously optimized conditions indicated that the 40 W Kessil blue LED lamp gave a better yield (10%) and conversion (40%) of the desired β-lactam **333** compared with the 12 W blue LED strip used in previous reactions (20% conversion and <5% yield; **Entries 1 & 2**). Varying the additive in the reaction generally gave higher conversion of starting material, but a lower yield of the desired product (**Entries 3–5**). Pleasingly, lowering the concentration of the reaction to 0.01 M improved the yield of the desired product (**Entry 6**). However, further optimization yielded no better results, even after screening several more catalysts, additives and additional parameters (see **Appendix 8.5** for full details).



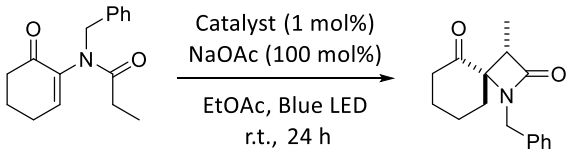
271 **333**

Entry	Solvent	Additive	Conversion[i]	Yield[i]
1	EtOAc[ii]	NaOAc	20%	<5%
2	EtOAc	NaOAc	40%	10%
3	EtOAc	None	90%	15%
4	MeCN	KOAc	63%	7%
5	MeCN	NaOAc	47%	4%
6	EtOAc[iii]	NaOAc	60%	27%

Reaction conditions: **271** (0.05 mmol), $Ir(dFppy)_3$ (1 mol%), Additive (100 mol%), Solvent ([**271**] = 0.05 M), 40 W Kessil blue LED, r.t., 24 h. [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard.[ii] Using 12 W blue LED strips at 60 °C.[iii] Reaction run at 0.01 M [**271**].

Table 8. Selected optimization for the photocyclization of **271**. See **Appendix 8.5** for full optimization table.

Further optimization was performed using substrate **272**, as it was hoped that changing the acetyl group to a propionyl group would help to stabilise any reactive intermediates (**Table 9**). Pleasingly the new substrate showed quantitative conversion and 86% yield under the previously optimized conditions (**Entry 1**). Although a mixture of diastereomers was expected, only a single diastereomer was observed by ^1H NMR in the crude reaction mixture. Subsequently, the relative stereochemistry was assigned as the (3*S**,4*S**) structure shown in **Table 9** based on nOe analysis (see **Experimental** for full details). A small screen of other photocatalysts with suitable triplet state energies showed that $Ir(dFppy)_3$ was still the optimal catalyst for the reaction (**Entries 2–4**). Lowering the concentration of the reaction to 0.01 M also had a positive impact on the reaction, allowing the desired product **334** to be obtained in 98% yield at full conversion after 24 h (**Entry 5**).



272 **334**

Entry	Catalyst	Conversion[i]	Yield[i]
1	$Ir(dFppy)_3$	100%	86%
2	FIrPic	100%	83%
3	$[Ir(dF(CF_3)ppy_2)(bpy)][PF_6]$	70%	60%
4	4CzIPN	100%	18%
5	$Ir(dFppy)_3$[ii]	100%	98%

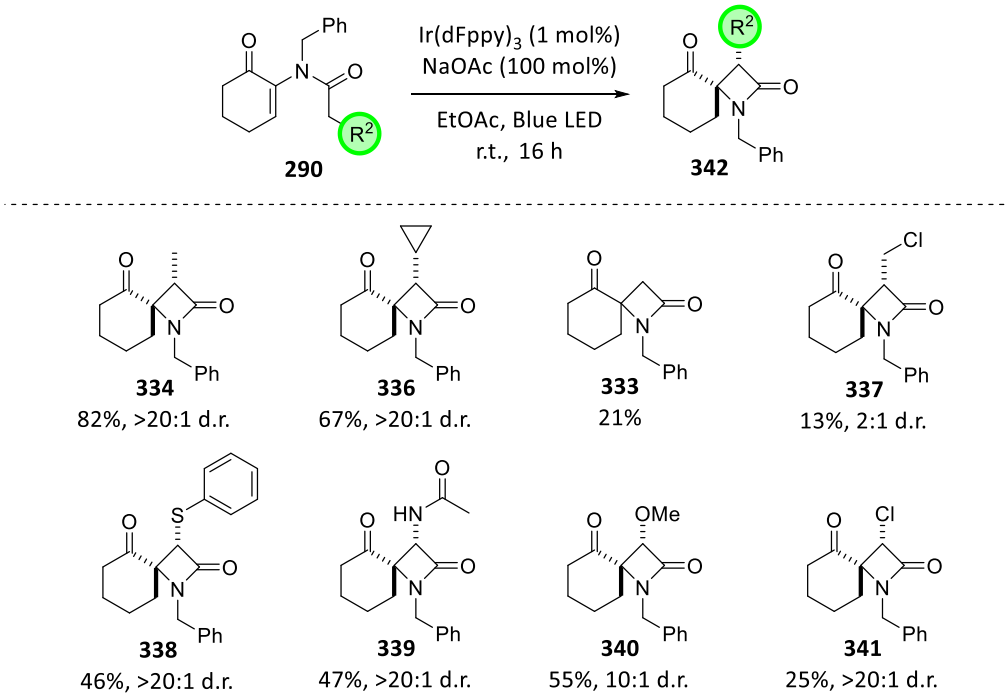
Reaction conditions: **272** (0.05 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), EtOAc ([**272**] = 0.05 M), 40 W Kessil blue LED, r.t., 24 h. [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard.[ii] Reaction run at 0.01 M [**272**].

Table 9. Selected optimization for the photocyclization of **272**. See **Appendix 8.6** for full optimization table.

4.3.2 Substrate Scope

With optimized reaction conditions in hand, the substrate scope of the reaction was investigated (**Schemes 96–99**). Initially, variation of the group attached to the amide carbonyl was investigated, with particular focus on non-aryl substituents (**Scheme 96**). In nearly all cases the reaction was highly diastereoselective, producing the desired β-lactam in >20:1 d.r.. The assignment of the relative stereochemistry was based on nOe analysis for each compound (see **Experimental** for full details), which in turn was corroborated by an X-ray crystal structure of compound **335** (see **Appendix 8.8.4** for full details). Optimization substrate **272** gave the desired reactivity cleanly, with β-lactam **334** obtained in 82% yield. Other alkyl substituents could also be used, including a cyclopropyl ring which allowed β-lactam **336** to be synthesised in 67% yield. Surprisingly, no products corresponding to the ring-opening of an α-methyl cyclopropyl radical were observed. A simple acetyl substituent on the enaminone nitrogen was tolerated under the reaction conditions, with previous

optimization substrate **271** giving unsubstituted β-lactam **333** in 21% yield. Although chloromethyl β-lactam **337** was formed under the reaction conditions, it occurred in low yield (13%) and with poor diastereoselectivity (2:1 d.r.). This could be due to competitive β-elimination of a chloride radical from the 1,4-diradical intermediate after hydrogen atom abstraction. Heteroatomic substituents could also be incorporated, allowing thioether β-lactam **338** to be obtained in 46% yield, and *N*-acyl β-lactam **339** to be obtained in 47% yield. Methyl ether β-lactam **340** was also obtained in good yield (55%) but showed lower diastereoselectivity of product formation (10:1 d.r.), possibly due to its smaller steric size. α-Chloro β-lactam **341** was synthesised in 25% yield under the reaction conditions, highlighting the functional group tolerance of the cyclization conditions.

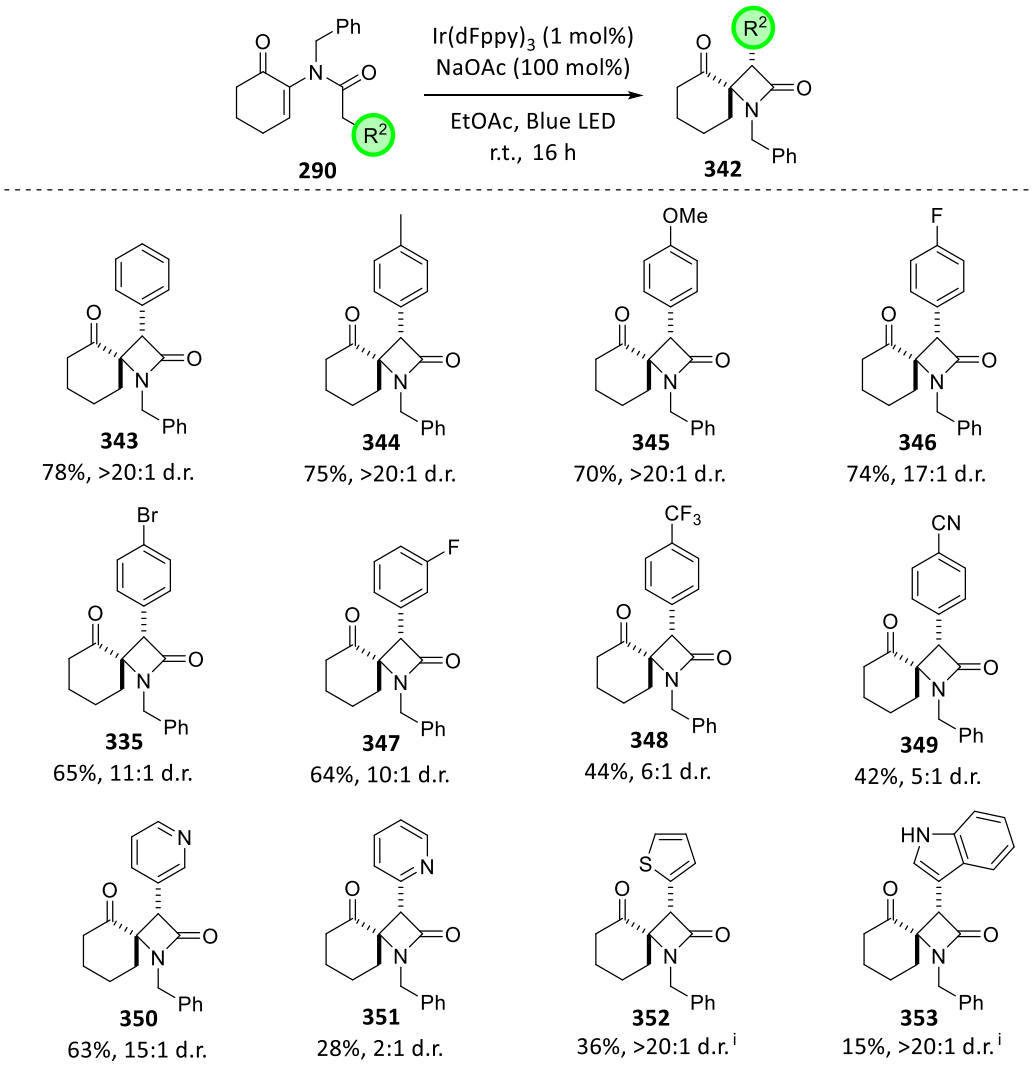


Reaction conditions: **290** (0.30 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), EtOAc ([**290**] = 0.01 M), 40 W Kessil blue LED lamp, r.t., 16 h. All yields are isolated yields after purification.

Scheme 96. Variation of the amide α-carbon substituent (non-aryl)

Aryl substituents attached to the amide carbonyl were then investigated and generally showed good functional group tolerance (**Scheme 97**). Unsubstituted phenyl ring substrate

279 cyclized diastereoselectively in 78% yield and >20:1 d.r. to obtain β-lactam **343** as essentially a single diastereomer. Electron-rich aryl substituents led to diastereoselective cyclization, with 4-methylphenyl β-lactam **344** formed in 75% yield and >20:1 d.r., and 4-methoxyphenyl β-lactam **345** obtained in 70% yield and >20:1 d.r.. Halogen substituents were well tolerated in the cyclization, allowing for the synthesis of 4-fluorophenyl β-lactam **346** (74% yield and 17:1 d.r.), 4-bromophenyl β-lactam **335** (65% yield and 11:1 d.r.) and 3-fluorophenyl β-lactam **347** (64% yield and 10:1 d.r.). Electron poor arenes showed reduced diastereoselectivity in the photocyclization, as evidenced by 4-(trifluoromethyl)phenyl β-lactam **348** formed in 44% yield and 6:1 d.r., and 4-cyanophenyl β-lactam **349** obtained in 42% yield and 5:1 d.r.. Heteroaromatic substituents were also tolerated in the cyclization, allowing for the synthesis of 3-pyridyl β-lactam **350** (63% yield, 15:1 d.r.), 2-pyridyl β-lactam **351** (28% yield, 2:1 d.r.), 2-thiophenyl β-lactam **352** (36% yield, >20:1 d.r.) and 3-indole β-lactam **353** (15% yield, >20:1 d.r.). In the case of 2-thiophenyl β-lactam **352** and 3-indole β-lactam **353**, an additional product was formed, which is discussed further under section **4.3.6** (Alternative Reactivity).

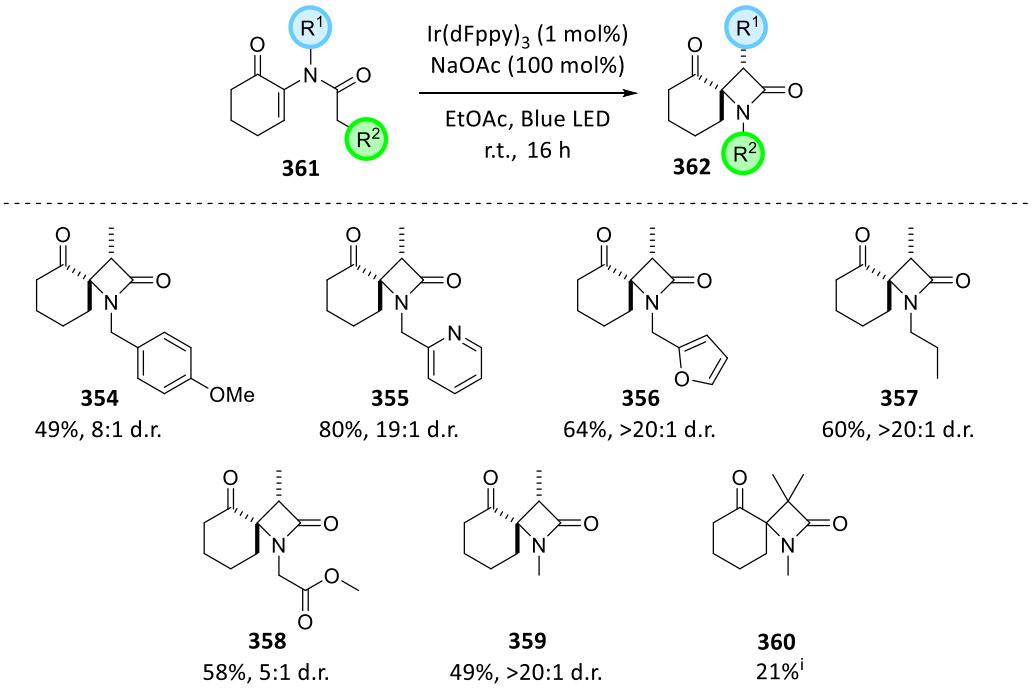


Reaction conditions: **290** (0.30 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), EtOAc ([**290**] = 0.01 M), 40 W Kessil blue LED lamp, r.t., 16 h. All yields are isolated yields after purification.
[i]Additional product formed.

Scheme 97. Variation of the amide α-carbon substituent (aryl)

Variation of the group attached to the nitrogen linker was also investigated (**Scheme 98**). Changing the *N*-benzyl group to a *para*-methoxybenzyl (PMB) group led to a reduction in yield and diastereoselectivity, with PMB β-lactam **354** formed in 49% yield and 8:1 d.r.. Heterobenzylic nitrogen substituted compounds were also competent substrates for the reaction, with 2-picolyl β-lactam **355** obtained in 80% yield and 19:1 d.r., and 2-furfuryl β-lactam **356** synthesised in 64% yield and >20:1 d.r.. Simple alkyl substituents were also well tolerated, allowing *N*-propyl β-lactam **357** to be made in 60% yield and >20:1 d.r..

Glycine-derived β-lactam **358** was formed in good yield (58%) under the reaction conditions, but showed reduced diastereoselectivity of 5:1 d.r.. *N*-methyl substrates gave lower yields of the desired product than other substituents but excellent diastereoselectivity as evidenced by β-lactam **359**, which was formed in 49% yield and >20:1 d.r.. Notably the use of an *N*-methyl group instead of an *N*-benzyl group allowed for substrates with multiple substitution α- to the amide carbonyl to be cyclized, such as dimethyl β-lactam **360**, which was formed in 21% yield. For this substrate, an additional side product was formed which is further discussed under section **4.3.6.** (Alternative Reactivity).

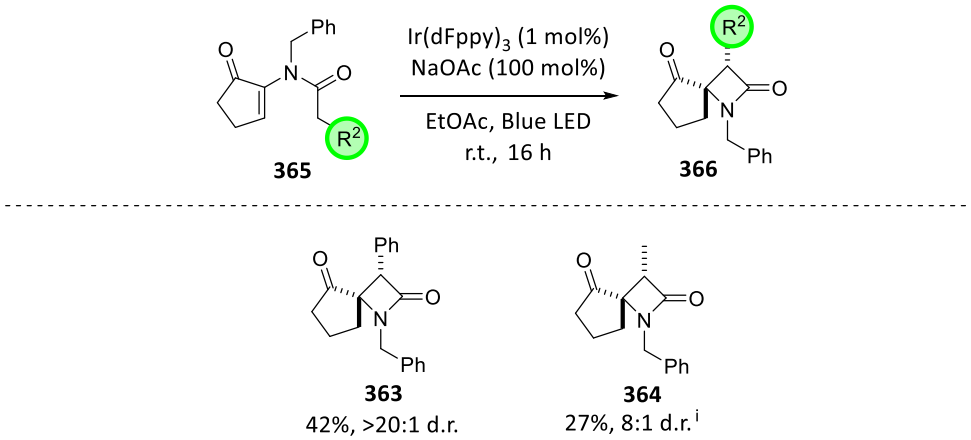


Reaction conditions: **361** (0.30 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), EtOAc ([**361**] = 0.01 M), 40 W Kessil blue LED lamp, r.t., 16 h. All yields are isolated yields after purification.
[i]Additional product formed

Scheme 98. Variation of the group attached to nitrogen

Different enaminone ring sizes were also investigated (**Scheme 99**). The cyclopentenone derived enaminones gave the desired β-lactam products in lower yields, but maintained an excellent level of diastereoselectivity in the cyclization as evidenced by phenyl β-lactam

363, which was obtained in 42% yield and >20:1 d.r.. However, smaller substituents showed a reduced diastereoselectivity in comparison to their cyclohexanone derived counterparts, as shown by methyl β-lactam **364**, which was obtained in 27% yield and 8:1 d.r.. This substrate also formed an additional product and is discussed in greater detail in section **4.3.6.** (Alternative Reactivity).

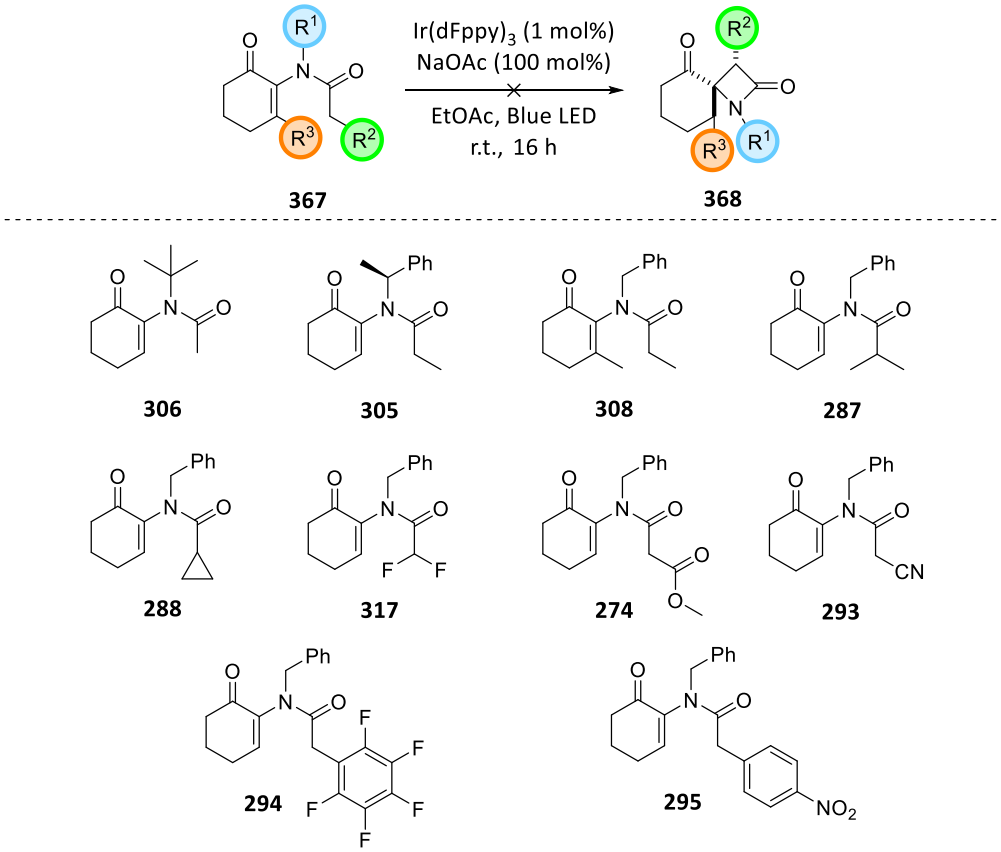


Reaction conditions: **365** (0.30 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), EtOAc ([**365**] = 0.01 M), 40 W Kessil blue LED lamp, r.t., 16 h. All yields are isolated yields after purification.
[i]Additional product formed

Scheme 99. Substrate scope varying enone ring size

Several substrates demonstrated no reactivity under the optimized reaction conditions (**Scheme 100**). Substrates with large substituents attached to the enaminone nitrogen atom showed no reactivity, as evidenced by *tert*-butyl substrate **306** and (*S*)-1-phenylethyl substrate **305**. Similarly, substitution at the β-position of the enone, such as in β-methyl enaminone **308**, inhibited the reaction entirely. Substituents with significant steric bulk at these positions of the molecule likely prevent the substrate from adopting the required conformation to undergo hydrogen atom abstraction in the triplet excited state, resulting in apparently unreactive substrates. Although tolerated with a small nitrogen substituent such as a methyl group, multiple substitution α- to the amide carbonyl was generally not tolerated even for small groups like isobutyryl enaminone **287**, cyclopropyl enaminone **288**

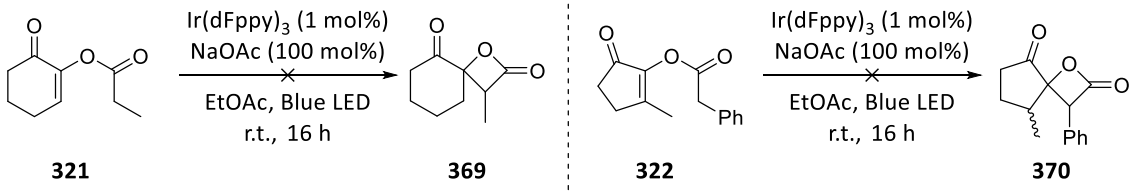
or difluoro enaminone **317**. Strongly electron withdrawing substituents also had a negative effect on the reaction, with malonate derivative **274** and nitrile **293** not showing the desired reactivity. In a similar manner, very strong electron withdrawing aryl groups were also not tolerated, such as pentafluorophenyl substrate **294** or nitrobenzene **296**.



Reaction conditions: **367** (0.30 mmol), Ir(dFppy)$_3$ (1 mol%), NaOAc (100 mol%), EtOAc ([**367**] = 0.01 M), 40 W Kessil blue LED lamp, r.t., 16 h. All yields are isolated yields after purification.

Scheme 100. Unreactive photocyclization substrates

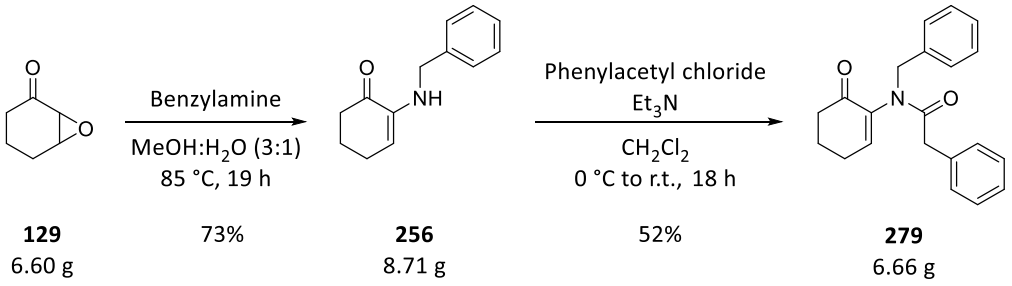
Disappointingly, attempts at cyclization of oxygen linked substrates were also unsuccessful, leading to complete recovery of starting material (**Scheme 101**).



Scheme 101. Unsuccessful photocyclization of *O*-acyl enol ethers **321** and **322**

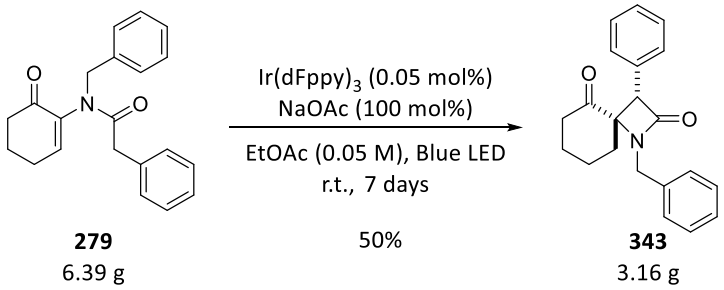
4.3.3 Large Scale Reaction

Having explored the scope of the reaction, the scalability of the reaction was then tested. Pleasingly, the substrate synthesis was amenable to scale-up, and only required one silica filtration and a final recrystallization to obtain over 6 g of enaminone **279** from epoxide **129** in two steps (**Scheme 102**).



Scheme 102. Larger scale synthesis of substrate **279**

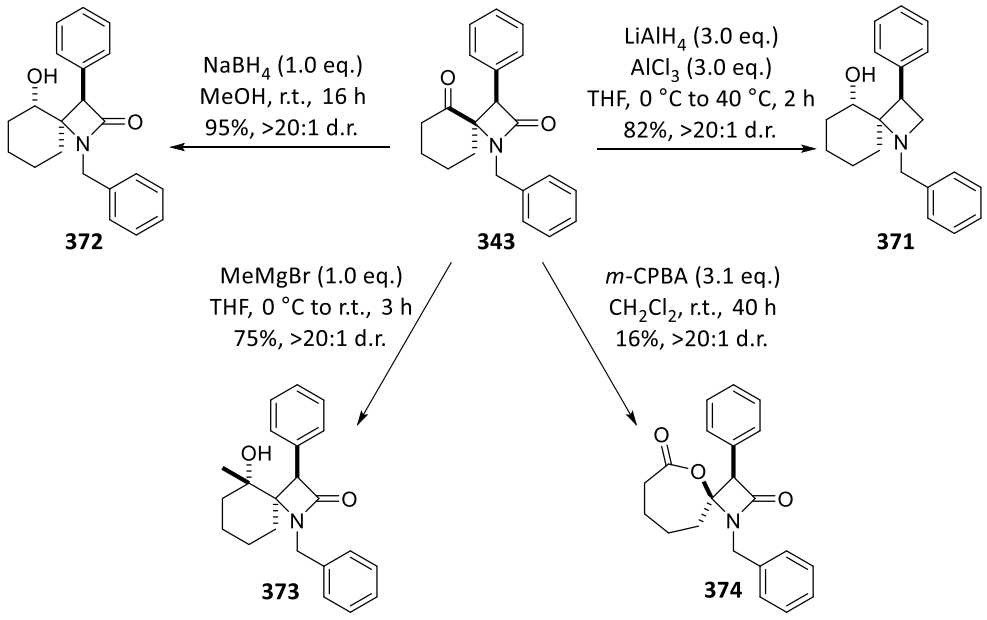
Subsequently, the photochemical cyclization was performed on a 20 mmol scale (6.39 g of enaminone **279**) at a higher concentration of 0.05 M and using a lowered catalyst loading of 0.05 mol% (**Scheme 103**). Unfortunately, the reaction required an extended irradiation time of 7 days, likely due to the lowered catalyst loading, and did not achieve full conversion of starting material. Nevertheless, the desired β-lactam **343** was obtained in multi-gram quantities (3.2 g, 50% yield) after purification by recrystallization. This material was subsequently used to explore derivatization of the products.



Scheme 103. Larger scale photocyclization of substrate **279**

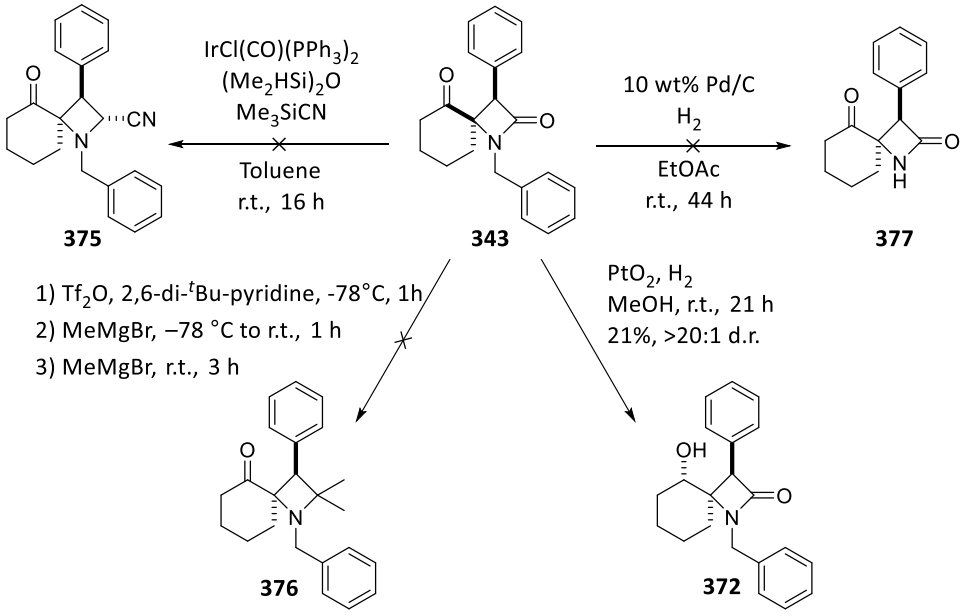
4.3.4 Derivatization

β-lactam **343** was subjected to a variety of different reactions in order to investigate its amenability to derivatization (**Scheme 104**). Pleasingly, a variety of methods allowed selective functionalization of the core in generally good yields and excellent diastereoselectivity. Reduction of the β-lactam moiety using *in-situ* generated $AlClH_2$ allowed access to the corresponding azetidine **371** without ring opening, and led to simultaneous diastereoselective reduction of the ketone.[118] Regioselective reduction of the ketone with sodium borohydride gave the corresponding secondary alcohol **372** cleanly and with excellent diastereoselectivity. Addition of organometallic reagents to the ketone carbonyl also proceeded regioselectively and diastereoselectively, allowing tertiary alcohol **373** to be synthesised in 75% yield and >20:1 d.r.. Oxidative Baeyer-Villiger rearrangements could also be performed diastereoselectively, allowing lactone **374** to be synthesised in 16% yield.



Scheme 104. Diastereoselective derivatization of β-lactam **343**

Unfortunately, there were some limitations with respect to derivatization, particularly when attempting to regioselectively derivatize the β-lactam moiety of the molecule (**Scheme 105**). Attempts to utilise Dixon's reductive lactam cyanation conditions resulted in decomposition rather than formation of nitrile **375**, likely due to the instability of the putative azetidinium intermediate that would be formed in the reaction.[119] Similarly, attempts to carry out *in-situ* triflation followed by organometallic addition to form azetidine **376** resulted in decomposition of the starting material.[120] Removal of the *N*-benzyl group *via* metal catalysed hydrogenation to form β-lactam **377** also proved challenging. No reaction was observed when palladium-on-carbon was used as the hydrogenation catalyst, whilst with platinum (IV) oxide reduction of the ketone occurred preferentially to form alcohol **372**, and the benzyl group remained intact.

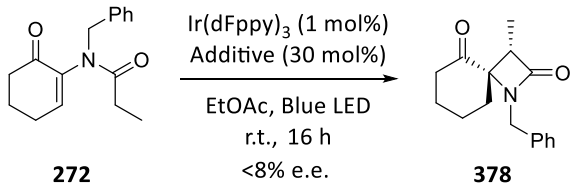


Scheme 105. Unsuccessful derivatization of β-lactam **343**

4.3.5 Attempts at enantioselectivity

A couple of strategies to develop an enantioselective variant of the reaction were tried; however, in both cases the results demonstrated low enantioselectivity. Initially, a chiral

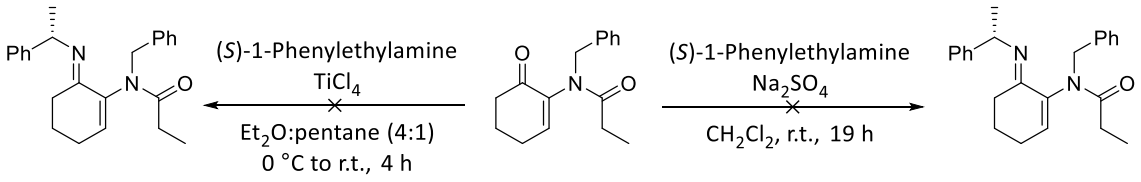
Lewis Acid strategy similar to those of Bach[35,62] and Yoon[36] was attempted with substrate **272** (**Scheme 106**). Disappointingly, cyclization in the presence of $Ir(dFppy)_3$, $Cu(OTf)_2$ and chiral ligands gave the desired product as a racemate or with slight enantioenrichment (<8% e.e.; see **Appendix 8.7** for full details). The low enantioenrichment of product **378** is perhaps unsurprising given the presence of a fast background reaction from the $Ir(dFppy)_3$ catalyst in the absence of any Lewis acid additives.



272 **378**

Scheme 106. Initial attempts at enantioselectivity using a chiral Lewis Acid or chiral hydrogen bond donor

Chiral auxiliary approaches were also employed in an attempt to generate a single enantiomer of the product. Attempts were made to condense cyclization substrate **272** with (*S*)-1-phenylethylamine as a model primary amine under a couple of conditions (**Scheme 107**). Unfortunately, compound **379** was not obtained in either case, and instead either decomposition or recovery of starting material **272** was observed (**Scheme 102**).



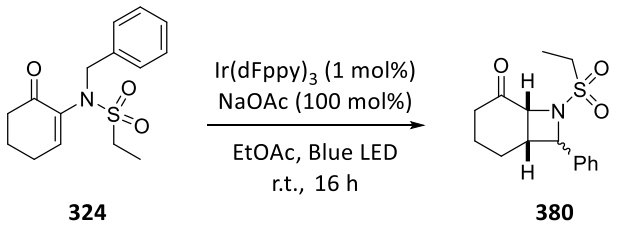
379 **272** **379**

Scheme 107. Attempts at synthesising an enantiopure iminone.

4.3.6 Alternate reactivity

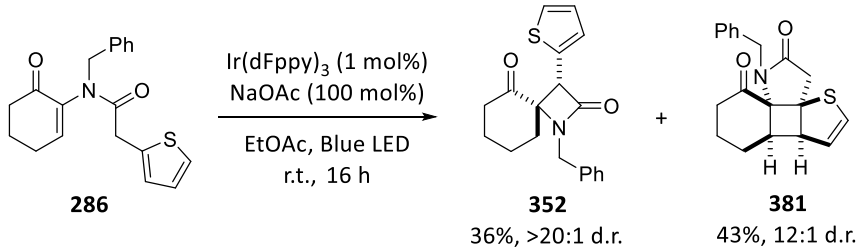
Some substrates demonstrated alternate reactivity or additional side products under the reaction conditions. Cyclization of *N*-sulfonyl enamine **324** led to the formation of *cis*-fused

azetidine **380**, consistent with previous reports in the literature for *para*-tosyl sulphonamide enaminones (**Scheme 108**).[75]



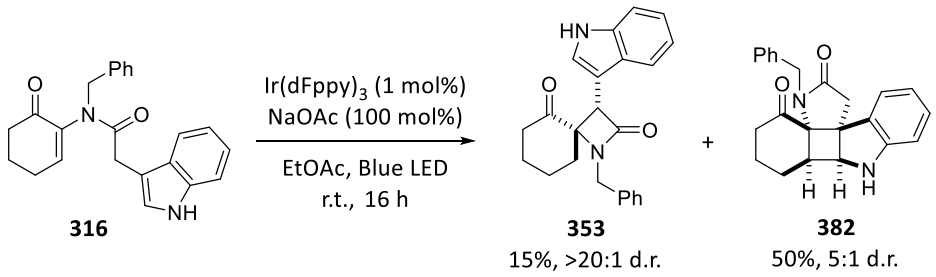
Scheme 108. Photocyclization of *N*-sulfonyl enamine **324**

Photocyclization of thiophene substituted enaminone **286** led to the formation of an additional tetracyclic product **381**, which was isolated in 43% yield and 12:1 d.r. (**Scheme 109**). This product likely arose from competitive intramolecular [2+2] cycloaddition between the enone triplet diradical and one of the carbon-carbon double bonds in the thiophene ring.



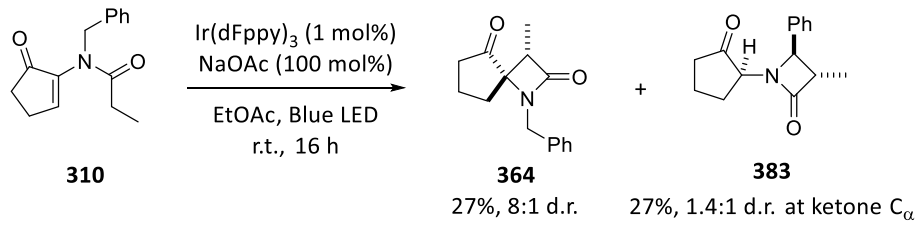
Scheme 109. Intramolecular dearomative [2+2] cycloaddition as a side reaction for thiophene substrate **286**

The same reactivity was also observed for indole substituted enaminone **316**, leading to the formation of pentacyclic product **382** in 50% yield and 5:1 d.r. (**Scheme 110**).



Scheme 110. Intramolecular dearomative [2+2] cycloaddition as a side reaction for indole substrate **316**

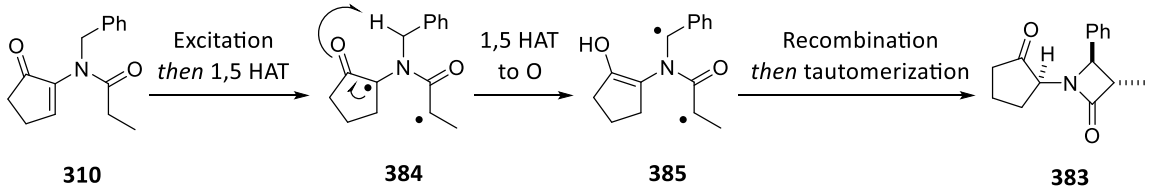
Photocyclization of cyclopentenone-derived enaminone **310** led to the formation of the desired spirocyclic β-lactam **364** in 27% yield and 8:1 d.r., but also generated β-lactam **383** in 27% yield and 1.4:1 d.r. (**Scheme 111**).



310 **364** 27%, 8:1 d.r. **383** 27%, 1.4:1 d.r. at ketone C_α

Scheme 111. Side product formation during the photocyclization of cyclopentenone-derived enaminone **310**. The major diastereomer formed in the reaction is the structure drawn above.

This 2-cyclopentanone substituted β-lactam **383** could potentially be formed from the same postulated diradical intermediate that forms spirocyclic β-lactam **364** (**Scheme 112**). After hydrogen atom abstraction from the β position of enone **310**, a second hydrogen atom abstraction could occur from the oxygen of enone **384** to give diradical enol ether **385**, which upon radical recombination and tautomerization would form to β-lactam **383**.

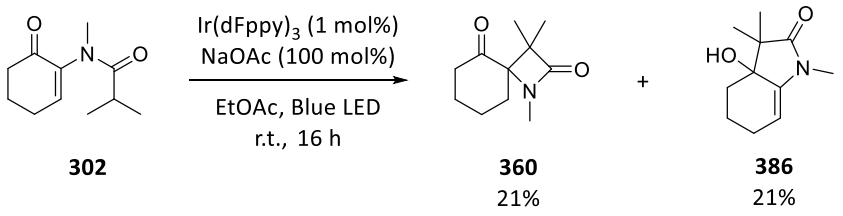


310 **384** **385** **383**

Scheme 112. Possible mechanism of formation of β-lactam **383**

After the photocyclization of *N*-isobutyryl enaminone **302**, alcohol **386** was isolated as a side product in 21% yield along with the desired β-lactam **360** in 21% yield (**Scheme 113**). When the reaction was repeated in the absence of light only starting material was returned, indicating that the formation of **386** must involve a photochemical step. In an

attempt to elucidate the nature of its formation, and to better understand the mechanism of the reaction, further experiments were performed and are detailed in the next section.



Scheme 113. Unexpected side product formed during the photocyclization of *N*-isobutyryl enaminone **302**

4.4 Mechanistic Investigations

4.4.1 Hammett Plot

In addition to generally high diastereoselectivity for what should nominally be a radical-radical recombination, one noticeable trend in the aryl substituted substrates **387** was a decrease in diastereoselectivity with decreasing electron density in the aryl substituent. To probe this further, a Hammett relationship was constructed plotting literature tabulated σ values for different substituents against the logarithm of the *cis*-to-*trans* ratio of diastereomers (**Figure 7**).[121,122] Pleasingly, a linear regression fitted the data exceptionally well (R^2 = 0.9955). Interestingly, the value for the reaction constant, ρ, was negative and close to unity (–0.8994), suggesting that either positive charge is built up on the benzylic carbon, or negative charge is lost on the benzylic carbon in the diastereoselective step. This would not be consistent with radical recombination, where no significant change in charge would be expected, but it would be consistent with an anion at the benzylic position losing negative charge as it is forming a bond. Indeed, comparison with Hammett plots constructed for the thermal Staudinger ketene-imine [2+2] cycloaddition shows a similar trend and comparable values for ρ, suggesting a similar mechanism of ring closure

from a common zwitterionic intermediate.[123] With this insight, a modified mechanism can be proposed.

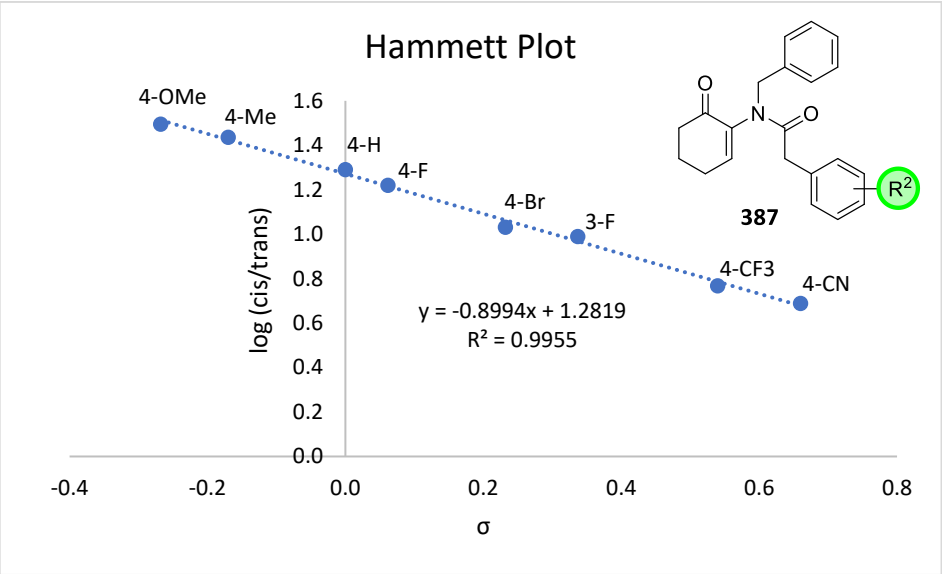
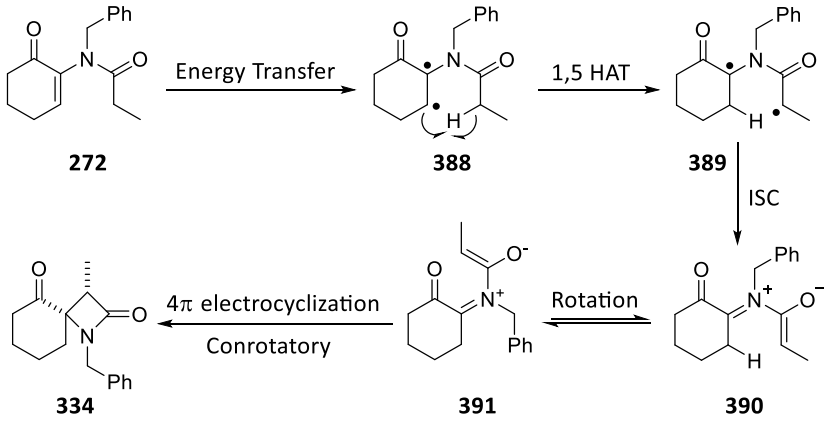


Figure 7. Hammett plot comparing the *cis*-to-*trans* ratio of diastereomers to σ values

4.4.2 Revised Mechanism

With insight from the experimental Hammett plot, a modified mechanism for the reaction was proposed which helped to rationalise the high diastereoselectivity and its dependence on the electronic nature of the amide substituent (**Scheme 114**). Triplet energy transfer from the excited state photocatalyst, $Ir(dFppy)_3$, to the ground state substrate **272** provides access to triplet diradical **388**, which then undergoes a 1,5-hydrogen atom transfer (HAT) to give 1,4-triplet diradical **389**. Relaxation to the ground state *via* intersystem crossing (ISC) leads to zwitterion **390**, with a single fixed enolate geometry set by the corresponding α-amido radical formed in the hydrogen atom abstraction step. Subsequent rotation around the C-N bond can occur readily due to a low energy open-shell singlet state, leading to the formation of geometrical isomer **391** which has a lower barrier to electrocyclic ring closure compared with isomer **390**. Thermal 4π conrotatory electrocyclization therefore

predominantly occurs from isomer **391**, leading to the observed *cis*-diastereomer of β-lactam product **334**.



Scheme 114. Revised mechanism for the photocyclization

4.4.3 ReactIR

Due to the significant infrared shift between the carbonyl peaks of the starting material and product, an initial attempt was made to monitor the reaction using ReactIR (see **Experimental** for full details). Optimization substrate **272** was used to benchmark the reaction, and the infrared spectra for both the parent enaminone and the product β-lactam **334** were recorded in advance from analytically pure samples of both. To reduce background signal from other carbonyl peaks, the sodium acetate was removed from the reaction and the solvent switched to acetonitrile. Previous screening during optimization had shown the product **334** to be formed under these conditions (see **Appendix 8.5**), and the modification of the reaction would allow for easier detection of changes in the carbonyl region. Although at the limit of the sensitivity of the apparatus, the disappearance of the enone carbonyl stretch (1683 cm^{-1}) and the appearance of the product ketone carbonyl stretch (1747 cm^{-1}) can be clearly seen in **Figure 8**.

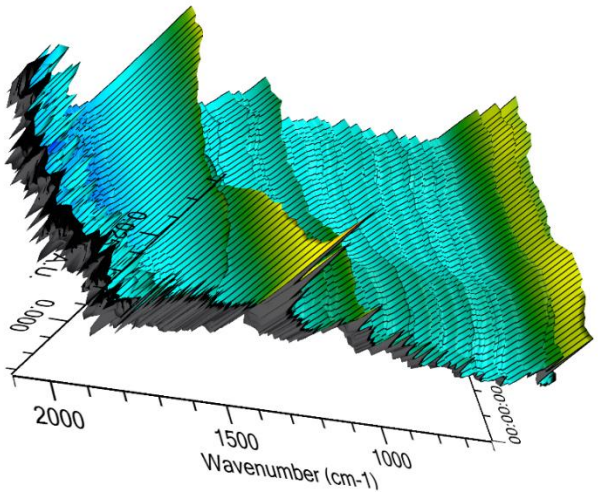


Figure 8. Initial ReactIR surface plot of wavenumber against absorbance against time.

As the method appeared to be a suitable way to monitor the reaction and the concentration of starting material and product over time, it was envisaged that it could be used to investigate reaction kinetics for different substrates. Disappointingly, when aryl substituted substrate **279** was used in place of optimization substrate **272**, no significant change in the infrared spectrum during the reaction could be observed. Further investigations using ReactIR were not carried out due to the limited sensitivity of the instrument and the resulting lack of reproducibility of the data.

4.4.4 Stern-Volmer Quenching

In order to confirm energy transfer between the photocatalyst and the substrate, Stern-Volmer quenching studies were performed (see **Experimental** for further details). Qualitatively, the stacked averaged emission spectra shown in Figure **9** of the $Ir(dFppy)_3$ photocatalyst with increasing concentration of substrate **272** show a decrease in intensity, suggesting quenching of the photocatalyst by the substrate.

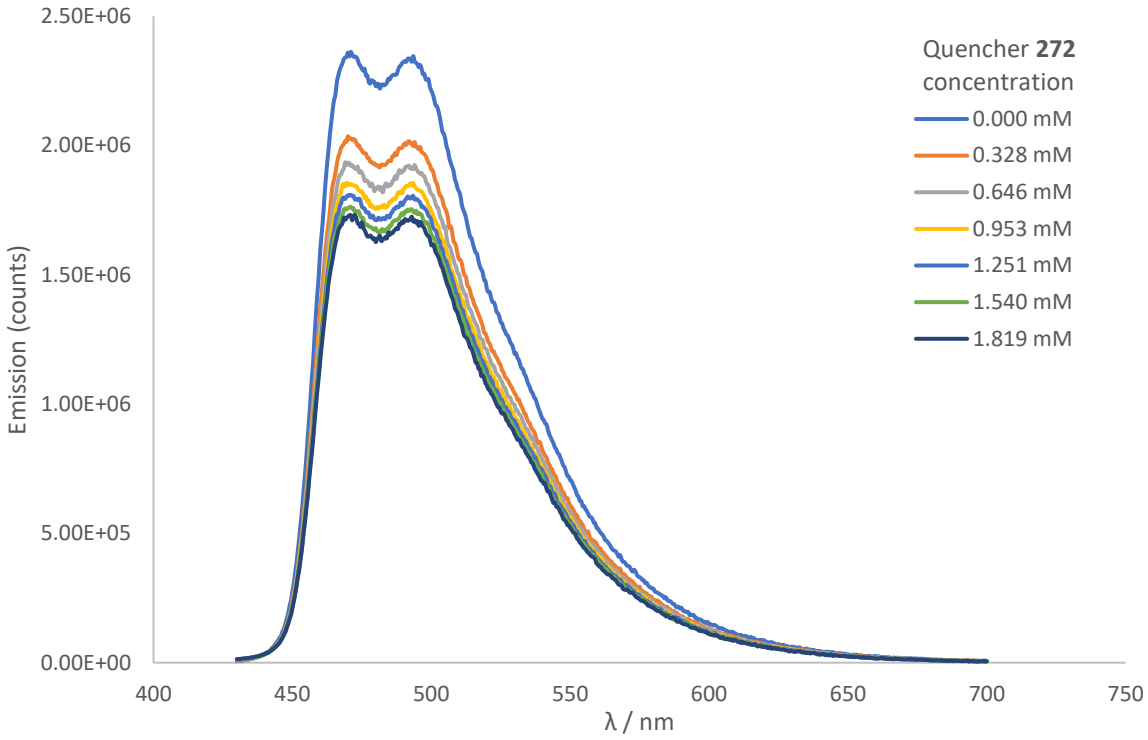


Figure 9. Stacked emission spectra of $Ir(dFppy)_3$ on addition of increasing amounts of substrate **272**

To analyse this more rigorously, the Stern-Volmer relationship was used to relate emission intensity and quencher concentration:

$$\frac{I_0}{I} = k_q[Q] + 1$$

Where I_0 is the emission of the photocatalyst in the absence of a quencher, I is the emission of the photocatalyst at a known quencher concentration, [Q], and k_q is the rate of quenching. A graph of (I_0/I) against substrate **272** concentration ([Q]) was plotted and is shown in **Figure 10**. The plot is a good straight line fit (R^2 = 0.9195) and indicates quenching of the catalyst by substrate **272** with a quenching rate constant k_q of $3.02 \times 10^2\ M^{-1}$.

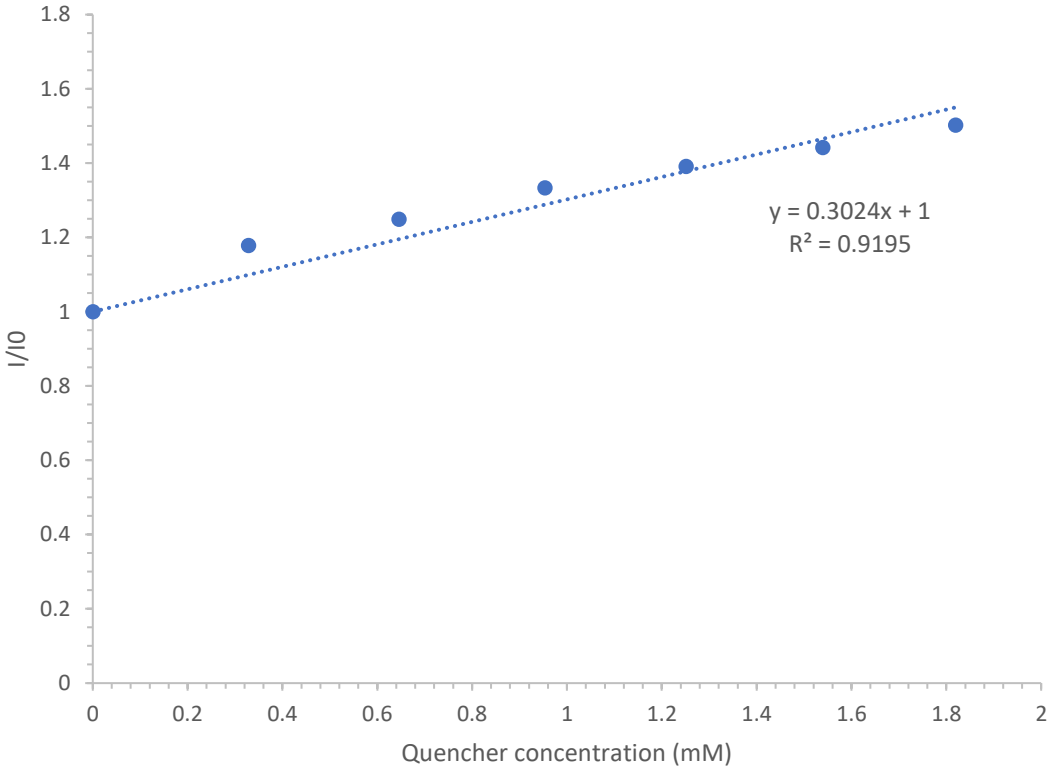
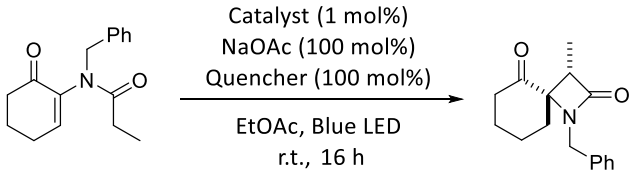


Figure 10. Stern-Volmer plot of I_0/I against quencher concentration

4.4.5 Addition of Triplet state quenchers

A variety of known triplet state quenchers were added to the reaction to determine their effect on reactivity (**Table 10**). Interestingly, reaction was slower when the triplet state quenchers were present, but was not completely inhibited when compared to the control (**Entry 1**). 1,1-diphenylethylene and TEMPO both slowed the reaction down by a similar amount (**Entries 2 & 3**), although addition of TEMPO led to raised conversion without an increase in yield (**Entry 3**). Addition of 2,5-dimethyl-2,4-hexadiene had a more pronounced effect on slowing down the reaction, resulting in only 13% yield at 13% starting material conversion after 16 h (**Entry 4**). The relative ability of the different quenchers to slow the reaction can be rationalised based on their triplet state energies. 1,1-Diphenylethylene has a triplet state energy of 60.8 kcal/mol,[124] which is slightly higher than that of the catalyst or

substrate, whilst TEMPO has a triplet state energy of 52 kcal/mol,[125] which is slightly lower than that of the catalyst or substrate. In contrast, 2,5-dimethyl-2,4-hexadiene has a triplet state energy of 57–58 kcal/mol,[5,124] which is approximately equal to that of the substrate, and so is likely to be a more efficient triplet state quencher of $Ir(dFppy)_3$ due to better Franck-Condon overlap.[5]



272 **334**

Entry	Quencher	E_T (kcal/mol)	Conversion[i]	Yield[i]
1	None	-	100%	80%
2	1,1-Diphenylethylene	60.8	53%	53%
3	TEMPO	52	72%	53%
4	2,5-Dimethyl-2,4-hexadiene	58	13%	13%

Reaction conditions: **272** (0.05 mmol), $Ir(dFppy)_3$ (1 mol%), NaOAc (100 mol%), Quencher (100 mol%), EtOAc ([**272**] = 0.01 M), 40 W Kessil blue LED, r.t., 16 h. E^T = triplet state energy.[5,121,122] [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard.

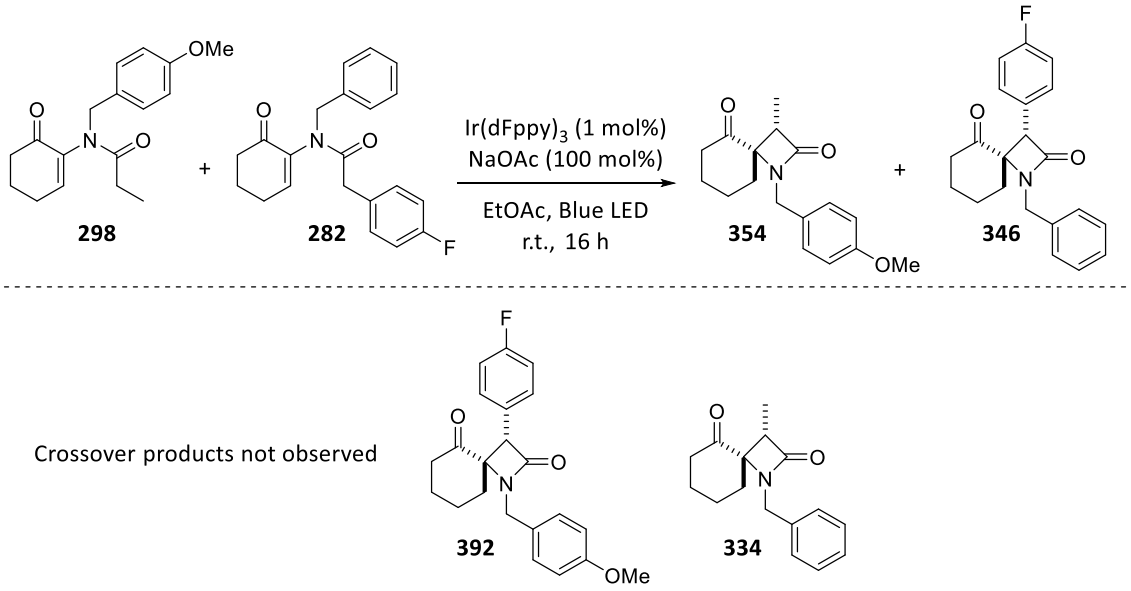
Table 10. Effect of adding triplet state quenchers to the reaction[5,124,125]

4.4.6 Quantum Yield

In order to further probe the efficiency of $Ir(dFppy)_3$ as a triplet sensitizer, the quantum yield of the reaction was measured for substrate **272**. Ferrioxalate actinometry was used as discussed previously in **Chapter 2** to determine the photon flux of the apparatus (see **Experimental** for full details).[102,103] The yield of product **334** after 1 hour of irradiation was then measured, and the quantum yield for the reaction was calculated to be 14.6%, which is consistent with a triplet energy transfer mechanism.

4.4.7 Crossover Experiment

To evaluate whether any dissociation to ketene or imine intermediates was occurring in the reaction, a crossover experiment was performed using a 1:1 mixture of substrates **282** and **298** under the standard reaction conditions (**Scheme 115**, see **Experimental** for full details). Analysis of both the ^{1}H NMR spectrum and LC-MS of the crude reaction mixture showed only the formation of intramolecular reaction products **354** and **346**, and no evidence of any intermolecular combination products **392** and **334**. This suggests that the reaction does not proceed *via* any dissociation event to putative ketene and imine intermediates, and instead occurs in an intramolecular manner after the triplet energy transfer step.

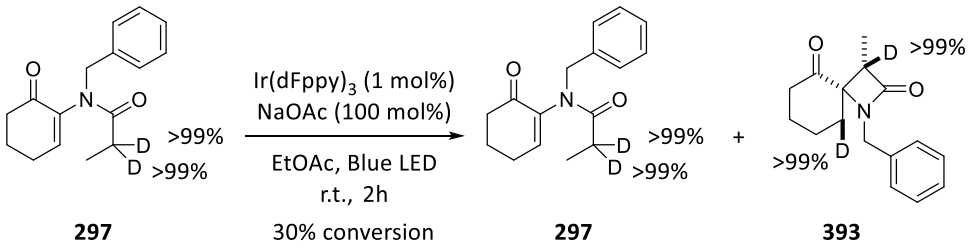


Scheme 115. Crossover experiment using substrates **282** and **298**

4.4.8 Deuterium Labelling

In order to probe the nature of the proposed hydrogen atom transfer, deuterated substrate **297** was synthesised and subjected to the reaction conditions (**Scheme 116**, see **Experimental** for full details). Running the reaction to 30% conversion and isolating the

recovered starting material showed no loss in deuterium label and no change in the location of the deuterium atoms in the molecule. Additionally, the product β-lactam **393** was isolated as the single diastereomer shown with retention of both deuterium atoms. The level of deuterium of incorporation was shown to be >99% at both sites indicated in all molecules *via* a combination of mass spectrometry, ^{1}H NMR and ^{2}H NMR. The lack of change in the labelling of the recovered starting material precludes the hydrogen atom transfer step from being reversible unless it is exceptionally stereospecific, and also indicates that deprotonation α to the amide by the acetate base in the reaction does not occur. The complete retention of the label in the product is consistent with intramolecular hydrogen atom transfer followed by recombination, whilst the diastereoselectivity of the deuterium incorporation suggests that the new stereocentre formed in the hydrogen atom transfer step influences the other two stereocentres formed later in the reaction.

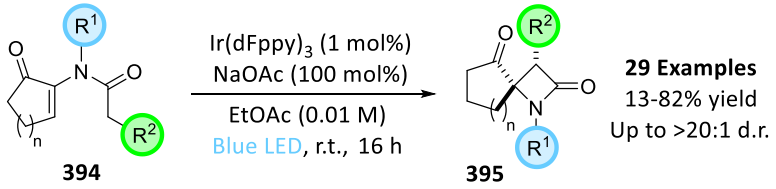


Scheme 116. Photocyclization of deuterated substrate **297**

4.5 Conclusions and Further Work

This chapter describes the development of a diastereoselective photocyclization of cyclic 2-*N*-amidoenones **394** to form spirocyclic β lactams **395** (**Scheme 117**). The substrates for the reaction can be assembled in a rapid and modular fashion using robust and scalable chemistry. This allowed for a diverse scope to test the reaction, which demonstrated excellent functional group tolerance allowing a large number of functionalized spirocyclic

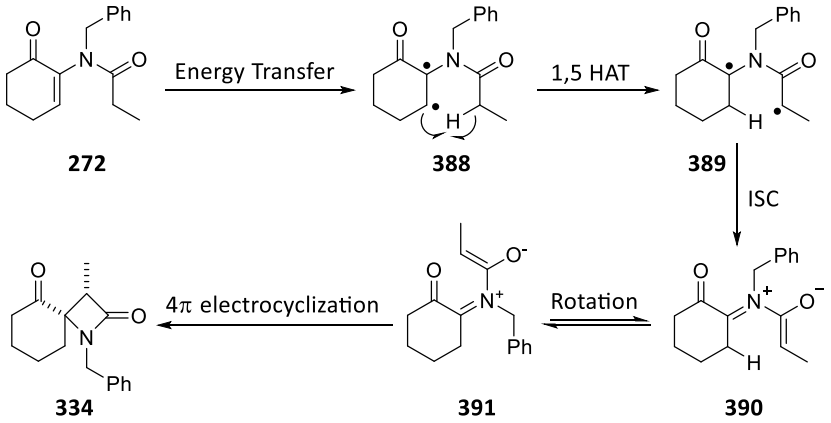
β-lactam products to be synthesised in good yield (up to 82%) and excellent diastereoselectivity (up to >20:1 d.r.).



Scheme 117. Visible light-mediated cyclization of cyclic 2-*N*-amidoenones

Pleasingly, the reaction could also be performed on a multi-gram scale with no loss in diastereoselectivity, and only a slight loss in yield. Derivatization of the product β-lactams was also explored and proved exceptionally diastereoselective in all cases.

Mechanistic investigations also provided insight into the surprisingly high diastereoselectivity of the reaction and provided a revised mechanistic proposal for the reaction (**Scheme 118**). After triplet energy transfer from the photocatalyst and subsequent 1,5-hydrogen atom transfer in the triplet excited state, intersystem crossing to the ground state leads to zwitterionic intermediate **390** rather than the corresponding singlet diradical. After rotation around the C-N bond *via* the open-shell singlet state, zwitterion **391** then undergoes 4π electrocyclization to form the observed β lactam product **334**.



Scheme 118. Revised mechanism for the photocyclization

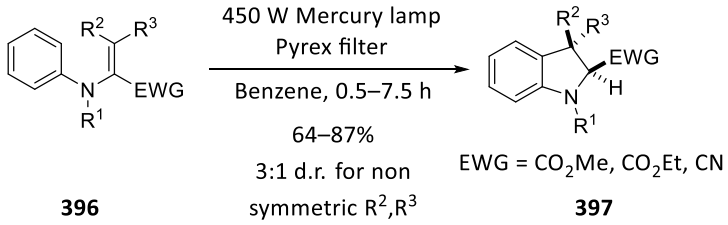
Although attempts at developing an enantioselective variant of the reaction were made, further work remains to be done in this area. In a similar fashion to the 6π heterocyclization, a chiral triplet sensitizer with a suitable hydrogen bonding or Lewis acidic motif could be used to induce enantioselectivity in the reaction *via* pre-coordination.[39,41] Work on this topic is an area of ongoing investigation within the Smith group.

5 Acyclic systems[1]

5.1 Precedent and previous work

Having explored the visible light-mediated cyclizations of cyclic enones in **Chapters 2**,**3** and **4**, we sought to generalize the reactivity to acyclic systems. In contrast to cyclic systems, acyclic α,β-unsaturated carbonyl systems undergo rapid relaxation to the ground state by *cis-trans* isomerization, resulting in significantly shorter triplet state lifetimes.[45,46]

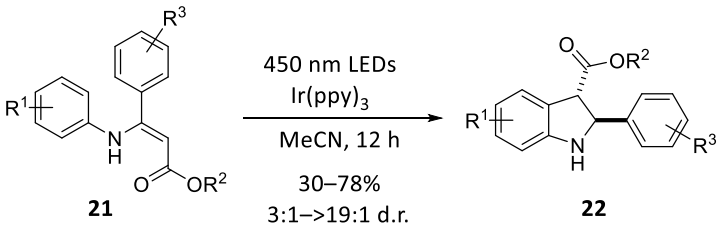
Nevertheless, there is significant precedent in the literature for acyclic α,β-unsaturated carbonyl compounds to undergo photochemical cyclizations, particularly [2+2] cycloadditions.[48,126] Work by Schultz and co-workers in the early 1980s demonstrated that 2-anilino acrylates and acrylonitriles **396** undergo photochemical cyclization under Pyrex-filtered irradiation to form indolines **397** (**Scheme 119**).[71]



Scheme 119. Synthesis of indolines *via* photochemical cyclization of 2-anilino acrylates or acrylonitriles

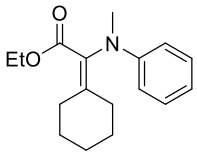
More recently, Wu and co-workers demonstrated that 3-aryl-3-anilino acrylates **21** cyclize under visible light irradiation in the presence of $Ir(ppy)_3$ as a photocatalyst to form indolines **22** *via* a proposed triplet energy transfer mechanism (**Scheme 120**).

[1] The work in this chapter was carried out in part at Vertex Pharmaceuticals, Boston, MA, USA under the supervision of Michael Boyd and Sarathy Kesavan.



Scheme 120. Visible light-mediated cyclization of 3-aryl-3-anilino acrylates to form 2-aryl-3-carboxy indolines

Given the precedent in the literature, we sought to further expand the scope of the 6π visible-light mediated heterocyclization discussed in **Chapter 2** to acyclic substrates. As such, ethyl 3-cyclohexylidine-2-*N*-methylanilino acrylate **398** was chosen as a suitable model substrate to perform further optimization (**Figure 11**).



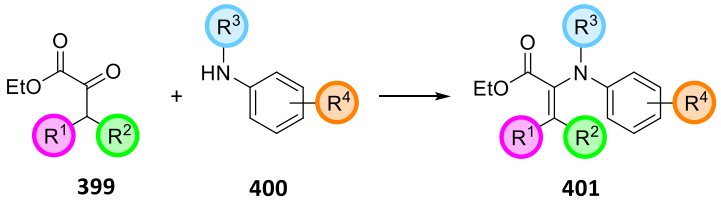
398

Figure 11. Ethyl 3-cyclohexylidine-2-*N*-methylanilino acrylate **398** as a model substrate

5.2 Substrate synthesis

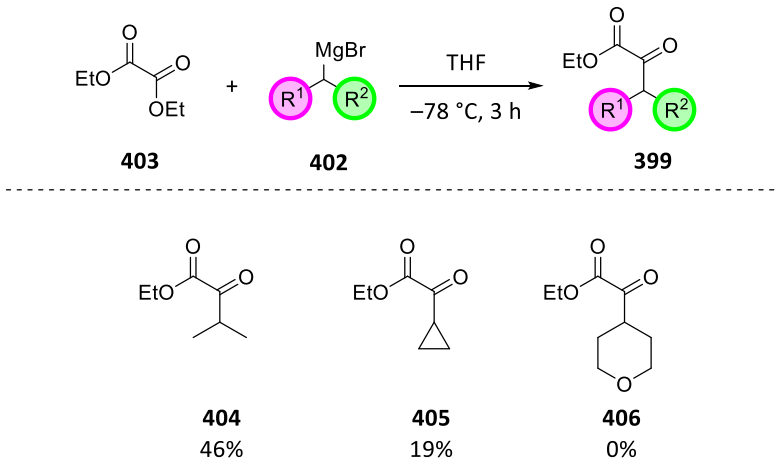
5.2.1 α-Ketoester strategy

The initial strategy to assemble the photocyclization substrates relied on condensation of an aniline **399** with an α-ketoester **400** and subsequent tautomerization to give the desired 2-anilino acrylate **401** (**Scheme 121**).[71]



Scheme 121. α-Ketoester strategy to synthesise 2-anilino acrylates **401**

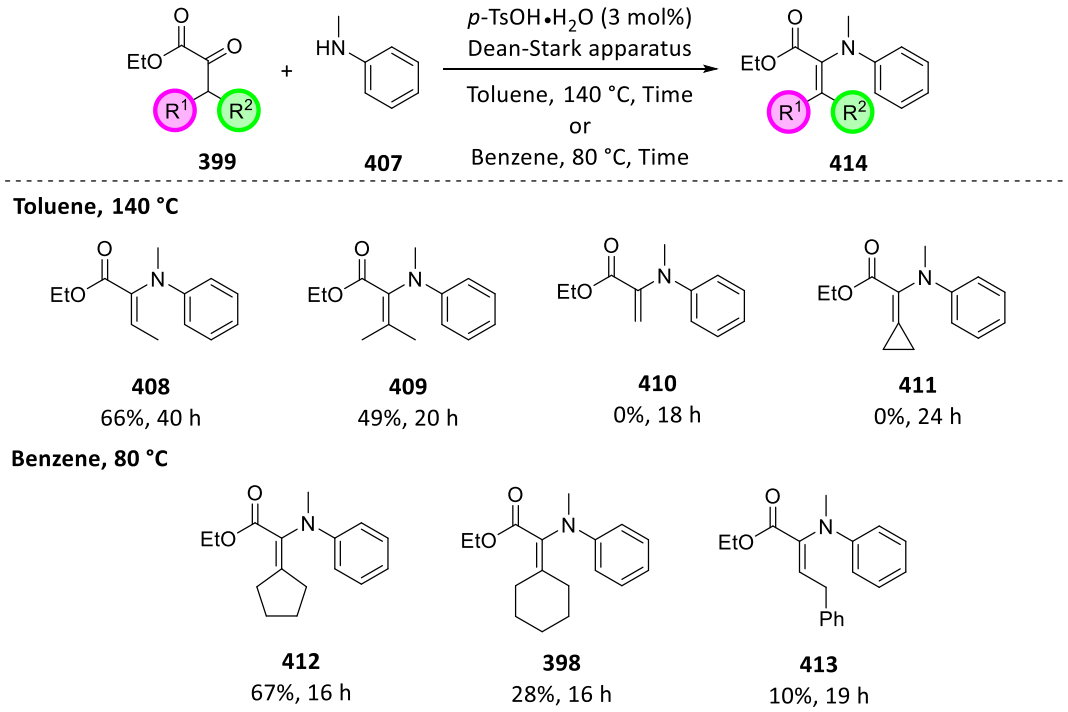
Due to limited commercial availability, additional α-ketoesters were prepared *via* addition of Grignard reagent **402** to diethyl oxalate **403** at –78 °C following literature procedure (**Scheme 122**).[127] Addition of isopropylmagnesium bromide gave oxobutanoate **404** in 46% yield, whilst addition of freshly prepared cyclopropylmagnesium bromide gave volatile cyclopropyl α-ketoester **405** in 19% yield. Attempts at synthesising tetrahydropyran-containing α-ketoester **406** proved unsuccessful, returning only 4-bromotetrahydropyran starting material.



Scheme 122. α-Ketoesters prepared by Grignard addition to diethyl oxalate

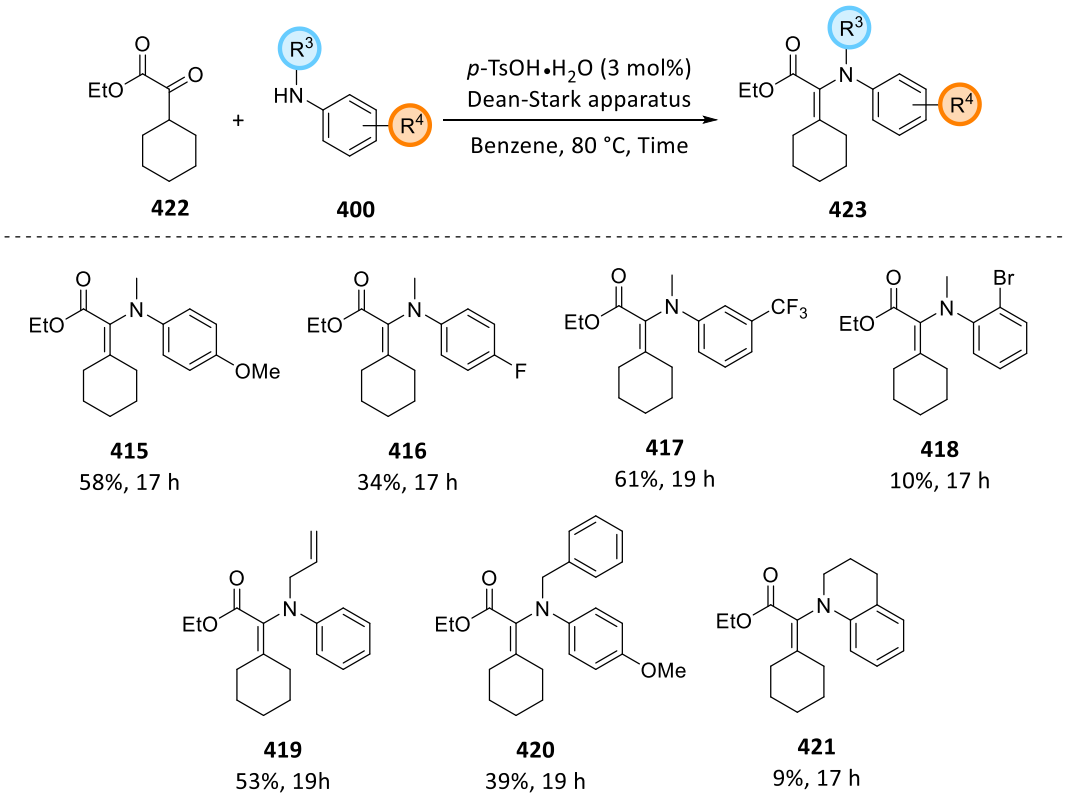
Condensation of *N*-methyl aniline **407** with a variety of α-ketoesters in a Dean-Stark apparatus enabled the synthesis of several substrates (**Scheme 123**). Methyl substrate **408** was obtained in 66% yield as a single *Z* diastereomer, and dimethyl substrate **409** was obtained in 56% yield using toluene as the reaction solvent. Using ethyl pyruvate as the α-ketoester led to decomposition rather than the desired unsubstituted product **410**. A similar result was obtained when cyclopropyl α-ketoester **405** was used as the coupling partner, with no cyclopropyl substrate **411** detected in the crude reaction mixture. α-Ketoesters containing larger rings were more amenable to coupling, allowing cyclopentyl-containing substrate **412** to be obtained in 67% yield, and cyclohexyl-

containing substrate **398** to be obtained in 28% yield. Aryl substituents on the α-ketoester partner led to a reduced yield of the desired product, such as in the case for benzyl substrate **413**.



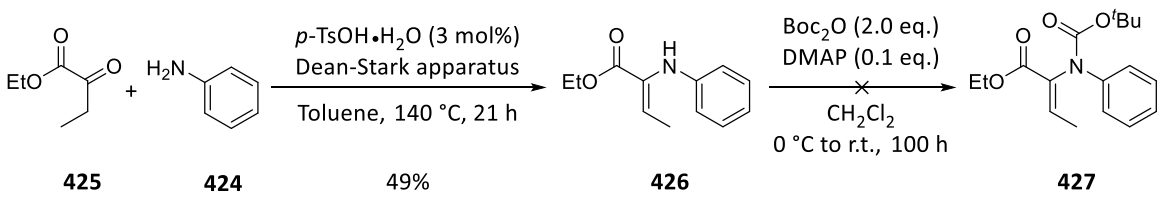
Scheme 123. Variation of the α-ketoester component

Variation of the aniline coupling partner was also explored (**Scheme 124**). Electron rich anilines could be successfully incorporated, allowing 4-methoxy substituted substrate **415** and 4-fluoro substituted substrate **416** to be synthesised in 58% yield and 34% yield respectively. Electron poor anilines were also amenable to coupling, with 3-trifluoromethyl substituted substrate **417** obtained in 61% yield. *Ortho*-substituted anilines showed reduced reactivity, with 2-bromo substituted substrate **418** obtained in only 10% yield. Pleasingly, variation of the *N*-alkyl substituent was well tolerated, allowing *N*-allyl substrate **419** and *N*-benzyl substrate **420** to be synthesised in 53% yield and 39% yield respectively. Bulkier substituents such as tetrahydroquinoline showed reduced reactivity, leading to the corresponding substrate **421** being formed in 9% yield.



Scheme 124. Variation of the aniline component

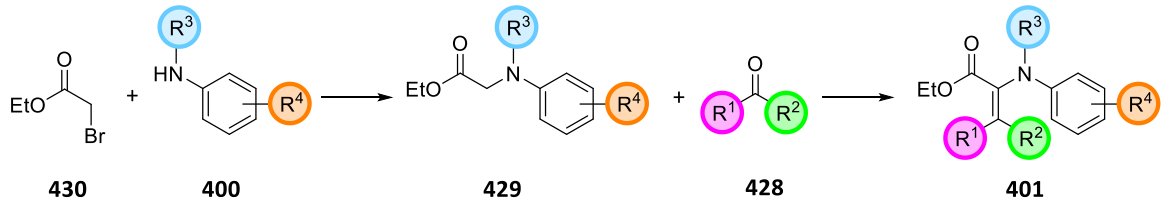
Attempts at making an *N*-Boc protected substrate proved challenging (**Scheme 125**). Condensation of aniline **424** under Dean-Stark conditions with 2-oxobutyric acid **425** gave unsubstituted substrate **426** in 49% yield as a single *Z* diastereomer. Unfortunately, treatment of enamine **426** with Boc anhydride and catalytic DMAP returned only unreacted starting material rather than *N*-Boc protected substrate **427**.



Scheme 125. Attempts at synthesising *N*-Boc protected substrate **427**

5.2.2 Additional strategies

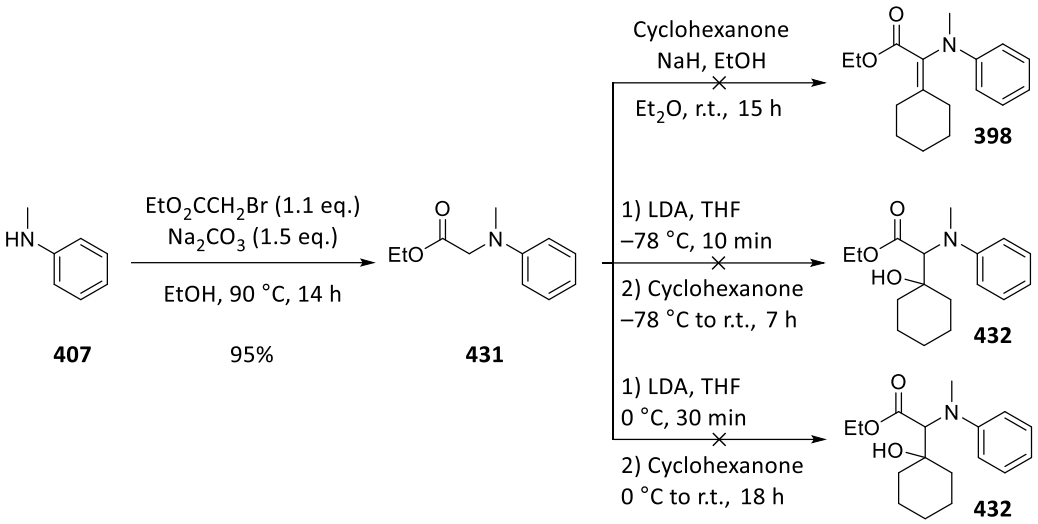
In order to broaden the substrate scope of the reaction, a variety of other strategies to assemble 2-anilino acrylate **401** were investigated. One potential strategy using an aldol condensation to combine ketone or aldehyde **428** with *N*-phenyl glycine ethyl ester **429** was particularly appealing due to the abundance of ketone and aldehyde precursors that could potentially be used to increase variation at the R^1 and R^2 positions of the substrate (**Scheme 126**). The *N*-phenyl glycine ethyl ester **429** could itself be made *via* S_N2 alkylation of ethyl bromoacetate **430** with aniline **400.**



430 **400** **429** **428** **401**

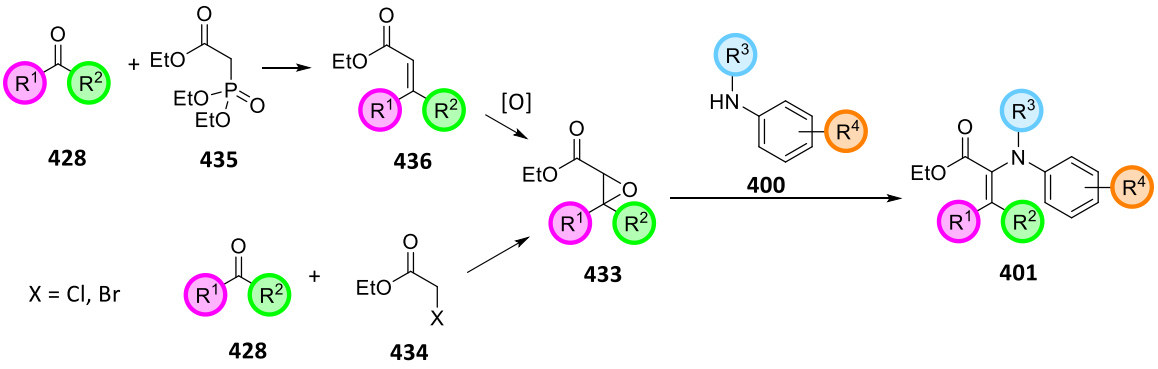
Scheme 126. Aldol strategy to synthesise 2-anilino acrylate **401**

Initial alkylation of *N*-methyl aniline **407** with ethyl bromoacetate **430** following literature procedure proceeded smoothly in 95% yield to give *N*-methyl-*N*-phenyl glycine ethyl ester **431** (**Scheme 127**).[128] Subsequent attempts at a one-pot aldol condensation with cyclohexanone following a similar literature procedure led to complete consumption of the starting material **431** without any formation of desired acrylate product **398**.[129] Attempts at an aldol addition between starting material **431** and cyclohexanone under basic conditions to form intermediate tertiary alcohol **432** following an alternative literature procedure led to complete recovery of the starting material.[130,131]



Scheme 127. Attempts to synthesise **398** *via* aldol condensation

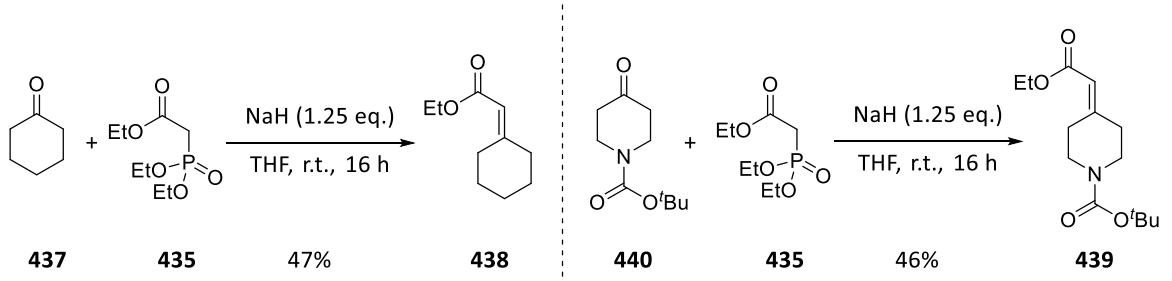
Due to the apparent difficulty in condensing *N*-methyl-*N*-phenyl glycine ethyl ester **421** with cyclohexanone as a model ketone, another alternative strategy was investigated (**Scheme 128**). Substrate **401** could potentially be synthesised by a similar amine epoxide opening reaction between aniline **400** and epoxide **433**. This epoxide could in turn be synthesised either *via* a Darzens condensation of aldehyde or ketone **428** and ethyl haloacetate **434**, or via a Horner-Wadsworth-Emmons (HWE) reaction of aldehyde or ketone **428** with triethyl phosphonoacetate **435** followed by epoxidation.



Scheme 128. Epoxide opening strategy to synthesise 2-anilino acrylate **401**

The HWE reaction of triethyl phosphonoacetate **435** with cyclohexanone **437** in the presence of sodium hydride proceeded smoothly to give acrylate **438** in 47% yield

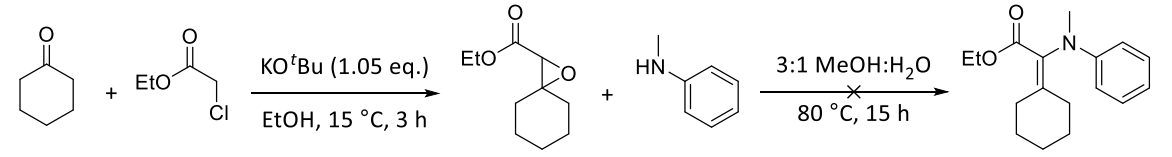
following a literature procedure (**Scheme 129**).[132] The same procedure could be applied to synthesise *N*-Boc-piperidine acrylate **439** in 46% yield from *N*-Boc piperidone **440**.



437 **435** **438** **440** **435** **439**

Scheme 129. Horner-Wadsworth-Emmons synthesis of acrylates **438** and **439**

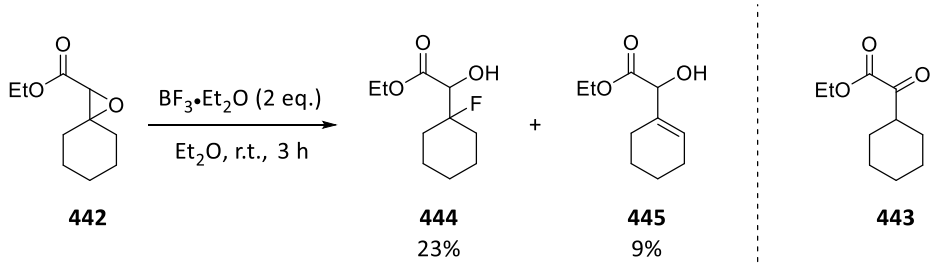
The Darzens condensation between cyclohexanone **437** and ethyl chloroacetate **441** in the presence of potassium *tert*-butoxide following literature procedure gave the desired epoxide **442** in 23% yield after distillation (**Scheme 130**).[133] Disappointingly, subjecting this epoxide **442** and *N*-methyl aniline **407** to the previously developed conditions returned only unreacted starting materials.



437 **441** **442** **407** **398**

Scheme 130. Darzens condensation to form epoxide **442** and subsequent attempt at coupling

Attempts at isomerizing epoxide **442** to the corresponding α-ketoester also proved unsuccessful (**Scheme 131**). Treatment with boron trifluoride diethyl etherate in ether did not result in the desired α-ketoester **443** but instead formed fluorinated alcohol **444** in 23% yield and 1:1 d.r. and allylic alcohol **445** in 9% yield.



442 **444** 23% **445** 9% **443**

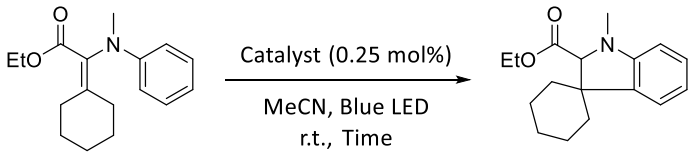
Scheme 131. Attempts at isomerizing epoxide **442** to α-ketoester **443**

Due to the lack of success of these alternative strategies to synthesise the desired substrates, the α-ketoester strategy was prioritized for any further substrate synthesis.

5.3 Photocyclization

5.3.1 Optimization

In order to investigate the photochemical reactivity of acyclic systems 2-anilino acrylate **398** was chosen as a model substrate and a variety of photocatalysts were screened (**Table 11**). Irradiating an acetonitrile solution of substrate **398** in the absence of any catalyst with a 420 nm LED lamp for 2 hours gave the desired product in 18% yield (**Entry 1**). Pleasingly, addition of the photocatalyst $Ir(ppy)_3$ to the reaction led to a significant enhancement in product formation, with indoline **446** formed in 34% yield after only 1 hour (**Entry 2**). Several other commercial photocatalysts were then screened to attempt to improve the yield of the desired product **446** (**Entries 3**–**6**). $Ir(dFppy)_3$ proved to be the optimal catalyst, giving indoline **446** in 64% yield after 1 hour (**Entry 6**), and running the reaction for a longer time of 2 hours led to full conversion and quantitative yield of the desired product (**Entry 7**). Performing the reaction in the absence of light returned only unreacted starting material, indicating that irradiation is required for the reaction to occur (**Entry 8**). Alternative sources of blue light illumination, such as two 420 nm, 40 W Kessil LED lamps, gave similar results to the photoreactor with the optimized conditions (**Entry 9**).



398 **446**

Entry	Catalyst	Time (h)	Conversion[i]	Yield[i]
1	None	2	20%	18%
2	$Ir(ppy)_3$	1	38%	34%
3	$[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$	1	18%	7%
4	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	1	23%	18%
5	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$	1	41%	40%
6	$Ir(dFppy)_3$	1	66%	64%
7	$Ir(dFppy)_3$	2	100%	Quant.
8	$Ir(dFppy)_3$[ii]	2	0%	0%
9	$Ir(dFppy)_3$[iii]	2	100%	Quant.

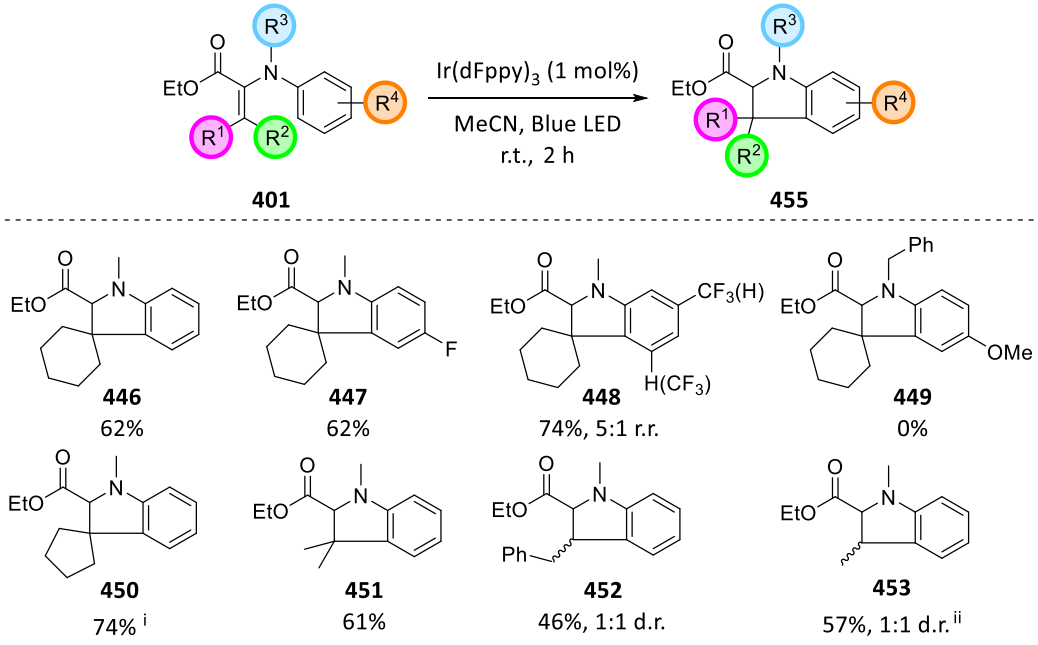
Reaction conditions: **398** (0.05 mmol), Catalyst (0.25 mol%), MeCN ([**398**] = 0.05 M), 420 nm Penn photoreactor, r.t.. [i] Determined by ^1H NMR spectroscopy against 1,4-dinitrobenzene as an internal standard.[ii] No light. [iii] Reaction performed using two 40 W Kessil blue LED lamps as an alternative light source

Table 11. Catalyst screen for the photocyclization of **398**.

5.3.2 Initial Scope

With optimized reaction conditions in hand, the scope of the reaction was investigated (**Scheme 132**). Although the reaction showed quantitative conversion by ^1H NMR of the crude reaction mixture, the products underwent decomposition when exposed to air. Nevertheless, optimization substrate **398** cyclized smoothly on a larger scale (0.15 mmol) to give indoline **446** in 62% yield. Substitution of fluorine at the *para*- position of the aniline moiety had no effect on the reaction, allowing fluoro indoline **447** to be synthesised in 62% yield. A *meta*-substituent on the aniline moiety gave a mixture of regioisomers; in the case of *meta*-trifluoromethyl indoline **448** the products were obtained in 74% yield and

a 5:1 mixture of 6-CF_3:4-CF_3 regioisomers. An electron rich substituent such as a methoxy group was not tolerated, and instead led to decomposition rather than formation of indoline **449**. The R^1 and R^2 substituents could also be varied with little effect in yield; spiro-cyclopenyl indoline **450** was obtained in 74% yield (on a larger 1.50 mmol scale) and 3,3-dimethyl indoline **451** was obtained in 61% yield. Asymmetrically substituted substrates gave little to no diastereoselectivity under the optimized conditions, with 3-benzyl indoline **452** obtained in 46% yield as a 1:1 mixture of diastereomers. In one case, the corresponding indole was formed under the reaction conditions. Cyclization of substrate **408** gave 3-methyl indoline **453** in 57% yield as a 1:1 mixture of diastereomers, as well as indole **454** in 20% yield.



Reaction conditions: **401** (0.15 mmol), $Ir(dFppy)_3$ (1 mol%) MeCN ([**401**] = 0.05 M), 420 nm Penn photoreactor **OR** 40 W Kessil blue LED lamp, r.t., 2 h. All yields are isolated yields after purification. r.r. = regioisomeric ratio; minor regioisomer shown in parentheses. [i] Reaction performed on a 1.50 mmol scale [ii] Additional indole product formed.

Scheme 132. Scope of the acyclic photochemical cyclization

5.3.3 Further Optimization

In order to find conditions to supress the formation of this indole side product and to try to improve the diastereoselectivity of the cyclization, further optimization was performed on asymmetrical substrate **408**. Initial focus looked at varying the photocatalyst used in the reaction (**Table 12**). Changing the photocatalyst to $Ir(ppy)_3$ led to an increase in the formation of indole side product **454** at the expense of indoline **453**, and a reduction in the diastereoselectivity of the cyclization from 1.3:1 to 1.2:1 (**Entries 1 & 2**). The relative stereochemical configuration of the diastereomers was subsequently assigned as *cis*:*trans* based on nOe correlations (see **Experimental** for full details). $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ showed lower conversion of starting material, but increased formation of indole **454** (27% yield) and lower diastereoselectivity in the cyclization to form indoline **453** in a 1.1:1 mixture of *cis*:*trans* diastereomers (**Entry 3**). Interestingly, $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ showed a similar conversion but a lower yield of indole **454** (19%) and reversed diastereoselectivity of 1:1.3 ratio of *cis*:*trans* diastereomers (**Entry 4**). Disappointingly, both ruthenium and organic triplet sensitizers gave no conversion and returned only unreacted starting materials (**Entries 5 & 6**).



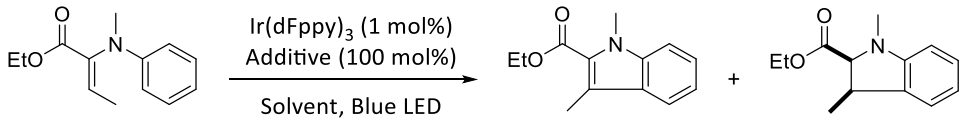
408 **454** **453**

Entry	Catalyst	Conversion[i]	Yield **454**[i]	Yield **453**[i]	d.r.[i]
1	$Ir(dFppy)_3$	100%	8%	91%	1.3:1
2	$Ir(ppy)_3$	100%	13%	78%	1.2:1
3	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$	89%	27%	62%	1.1:1
4	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	86%	19%	67%	1:1.3
5	$[Ru(bpy)_3][PF_6]_2$	0%	0%	0%	-
6	4CzIPN	0%	0%	0%	-

Reaction conditions: **408** (0.05 mmol), Catalyst (1 mol%), MeCN ([**408**] = 0.05 M), 40 W Kessil blue LED lamp, r.t.. [i] Determined by ^{1}H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard.

Table 12. Catalyst screen for the photocyclization of **408**

With no improvement in the yield or diastereoselectivity by changing the catalyst, the solvent and additives used in the reaction were screened (**Table 13**). Changing the solvent from acetonitrile to ethyl acetate supressed formation of indole **454** and led to quantitative formation of indoline **453** (**Entry 2**). Pleasingly, the cyclization was also more diastereoselective giving the indoline **453** in a 1.6:1 ratio of *cis*:*trans* diastereomers. Addition of sodium acetate to the reaction also supressed indole formation in acetonitrile and led to an increase in diastereoselectivity (**Entry 3**). Performing the reaction under an atmosphere of air instead of argon in either acetonitrile or ethyl acetate led to increased formation of indole **454** (**Entries 5 & 6**). This suggests that indole **454** may form *via* an oxidative process using atmospheric oxygen as a terminal oxidant. Addition of 10 mol% of benzoquinone (BQ) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) further increased the amount of indole formed (**Entries 7 & 8**). Using stoichiometric DDQ in the reaction further increased the amount of indole product formed to 42% (**Entry 9**).



408 **454** **453**

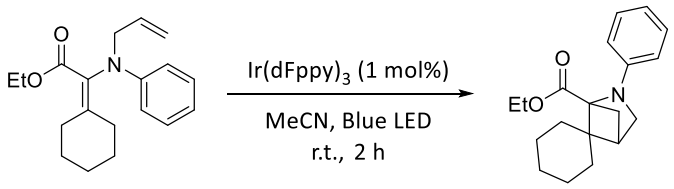
Entry	Additive	Solvent	Conversion[i]	Yield **454**[i]	Yield **453**[i]	d.r.[i]
1	None	MeCN	100%	9%	90%	1.3:1
2	None	EtOAc	100%	0%	Quant.	1.6:1
3	NaOAc	MeCN	100%	2%	98%	1.5:1
4	NaOAc	EtOAc	100%	0%	Quant.	1.6:1
5	NaOAc[ii]	MeCN	100%	10%	90%	1.5:1
6	NaOAc[ii]	EtOAc	100%	6%	93%	1.4:1
7	NaOAc + BQ (10 mol%)[ii]	EtOAc	100%	27%	30%	1.5:1
8	NaOAc + DDQ (10 mol%)[ii]	EtOAc	100%	12%	30%	1.3:1
9	DDQ[ii]	EtOAc	100%	42%	6%	1:1

Reaction conditions: **408** (0.05 mmol), $Ir(dFppy)_3$ (1 mol%), Additive (100 mol%), Solvent ([**408**] = 0.05 M), 40 W Kessil blue LED lamp, r.t., Argon atmosphere. [i] Determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard. [ii] Reaction performed under an atmosphere of air

Table 13. Further optimization for the photocyclization of **408**

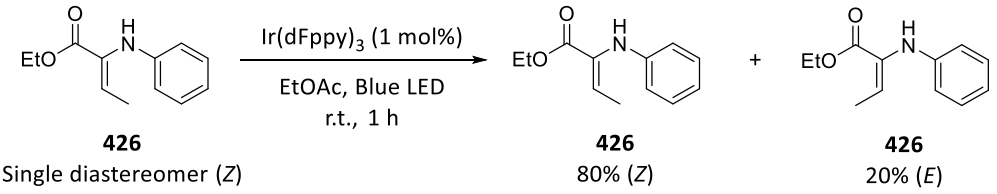
5.3.4 Alternative reactivity

A couple of substrates exhibited alternative reactivity under the reaction conditions. Under the optimized reaction conditions *N*-allyl substrate **419** underwent intramolecular [2+2] cycloaddition between the *N*-allyl group and the acrylate moiety to form azaspiro compound **456** in 30% yield instead of the desired cyclization (**Scheme 133**). This reactivity contrasts with that of the cyclic 2-*N*-allyl-anilino enone **173**, which underwent the desired cyclization rather than [2+2] cycloaddition (see **Chapter 2**). This may be due to greater conformational flexibility in the triplet excited state of the acyclic substrate when compared to the cyclic substrate.



Scheme 133. Intramolecular [2+2] cycloaddition of substrate **419**

Aniline derived substrate **426** did not perform the desired cyclization reaction but did undergo *E*/*Z* isomerization under the optimized asymmetrical substrate reaction conditions (**Scheme 134**). A >20:1 d.r. sample of *Z* substrate **426** was subjected to the reaction conditions, and after 1 hour a 4:1 *Z*:*E* mixture of diastereomers of **426** was recovered. This *E*/*Z* isomerization is likely to be photochemical in nature, suggesting that the substrate is able to be excited by the photocatalyst. However, the triplet state may not be long enough lived to undergo the desired reactivity, and so the substrate relaxes back to the ground state *via* unproductive *E*/*Z* isomerization rather than cyclizing.

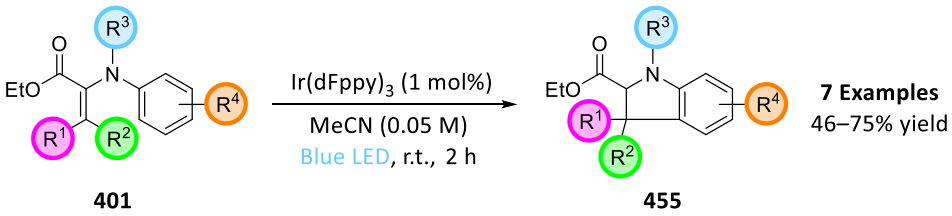


Scheme 134. *E*/*Z* isomerization of substrate **426**

5.4 Conclusions and Further work

This chapter described the development of a visible light-mediated intramolecular arylation of 2-anilino acrylates **401** to form indolines **455** (**Scheme 135**). The substrates can be rapidly assembled by condensation between suitable anilines and α-ketoesters, which in turn can be synthesised *via* organometallic addition to diethyl oxalate. The cyclization

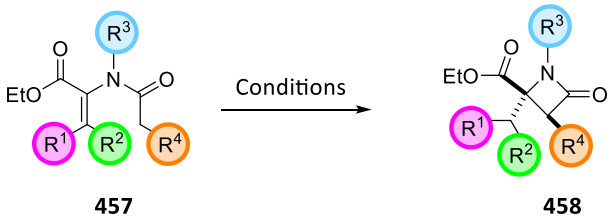
proceeds cleanly and shows good functional group tolerance, although only low levels of diastereoselectivity were observed for substrates with asymmetrical substitution at the β- position of the acrylate moiety.



Scheme 135. Visible light-mediated cyclization of 2-anilino acrylates

Disappointingly, the indoline products of the reaction were prone to decomposition, even when stored in the absence of light, moisture and oxygen. One possible way to circumvent this may be to perform *in situ* derivatization on the products, allowing further complexity to be incorporated into the products.

Another area of possible exploration would be the application of the hydrogen atom spirocyclization reaction discussed in **Chapter 4** to this acyclic acrylate chromophore (**Scheme 136**). Ultimately, this work could potentially allow for the modification of dehydroalanine residues in a peptide oligomer or protein to generate a β-lactam moiety.

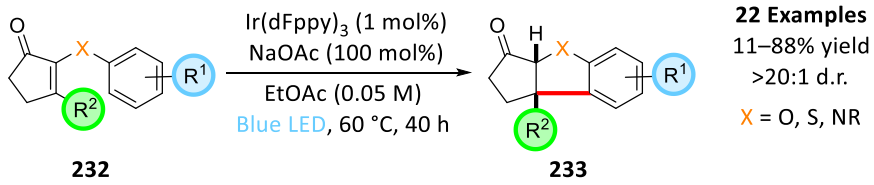


Scheme 136. Potential visible light-mediated spirocyclization of 2-*N*-amido acrylates

6 Summary

The main focus of this thesis has been on the development of visible light-mediated cyclizations of cyclic enones.

Chapter two details the development of a diastereoselective photochemical cyclization of cyclic 2-arylheteroenones **232** to the corresponding dihydroheterocycles **233**. Photocatalyst optimization proved critical in order to achieve the desired reactivity, and minor improvements in yield were achieved by modification of the solvent and additive. The optimized conditions enabled the synthesis of a variety of *cis*-fused heterocycles in a highly diastereoselective manner (**Scheme 137**).

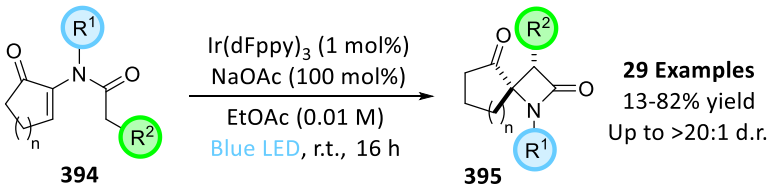


Scheme 137. Visible light-mediated cyclization of cyclic 2-arylheteroenones

Attempts at developing an enantioselective variant of the reaction were met with little success, although the subject has by no means been extensively explored.

In chapter three the alternative hydrogen atom abstraction reactivity of one of the 2-arylheteroenone substrates was further investigated and attempts at optimization and generalization of the reaction were performed. Disappointingly, this proved unsuccessful in most cases, though more work remains to be carried out in this area.

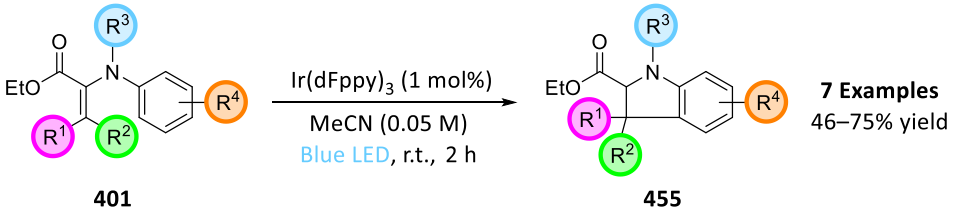
Chapter four documents the development of a photochemical spirocyclization of cyclic 2-*N*-amidoenones **394** to form spirocyclic β lactams **395** in a diastereoselective manner (**Scheme 138**).



Scheme 138. Visible light-mediated cyclization of cyclic 2-*N*-amidoenones

The reaction could be performed on a multi-gram scale, and the product β-lactam scaffolds elaborated in a highly diastereoselective fashion. Mechanistic investigations into the reaction suggested the reaction proceeds *via* 1,5-hydrogen atom transfer in the triplet excited state, followed by intersystem crossing and interception of the zwitterionic intermediate of the Staudinger [2+2] cyclization. Subsequent 4π electrocyclization leads to the observed β-lactam products.

Chapter five covers the application of the photochemical arylation reaction disclosed in chapter two to acyclic chromophores (**Scheme 139**). Although the desired reactivity proceeded cleanly and showed a good substrate scope, the products formed in the reaction were unstable under ambient conditions. Further work on *in situ* derivatization of these products is ongoing in the Smith group.



Scheme 139. Visible light-mediated cyclization of 2-anilino acrylates

7 Experimental

7.1 General Information

All reagents and solvents were used as supplied commercially without further purification unless stated otherwise. Dry acetonitrile, CH_2Cl_2, Et_2O, THF and toluene were purified by filtration through activated alumina columns employing the method of Grubbs *et al.*[134] Dry methanol and ethanol were dried by addition of activated 3 Å molecular sieves and stored under an argon atmosphere. Water was purified using an Elix® UV-10 system. Brine refers to a saturated aqueous solution of sodium chloride. Petrol ether 40–60 refers to the fraction of petroleum ether which boils in the range 40–60 °C.

Thin Layer Chromatography (TLC) was performed using pre-coated aluminium-backed Merck TLC Silica Gel 60 F_{254} plates and visualised using UV irradiation (λ = 254 nm) or staining with potassium permanganate solution. Flash column chromatography was performed with Merck Geduran® Si 60 Silicagel (40–63 μm particle size) according to the method by W. C. Still *et al*.[135] All solvents used for chromatographic purification were HPLC grade or equivalent and supplied by Sigma-Aldrich.

Fourier-transform infrared (FT-IR) spectra were recorded from evaporated films on a Bruker Tensor 27 spectrometer equipped with a Pike Miracle Attenuated Total Reflectance (ATR) sampling accessory. Absorption maxima are quoted in wavenumbers, ν_{max}/cm^{-1}, for the range 3500–600 cm^{-1}.

Ultraviolet-visible (UV-vis) absorption spectra were recorded at 25 °C with a Perkin-Elmer Lambda 20 or Lambda 25 photospectrometer using Starna quartz cuvettes (10 mm path

length). Emission spectra were recorded at 25 °C on a FS5 fluorescence spectrophotometer (Edinburgh Instruments). All spectra were recorded for each compound at the stated concentration dissolved in HPLC grade solvent.

All Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker AVIIIHD 400 nanobay spectrometers at ambient temperature in solutions of deuterated solvent. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra at 101 MHz with broadband proton decoupling and ^{19}F NMR spectra at 377 MHz. The deuterated solvent acted as the internal deuterium lock. Residual protic solvent signal acted as an internal reference for ^{1}H NMR and the deuterated solvent carbon signal acted as an internal reference for ^{13}C NMR ($CDCl_3$: ^{1}H NMR = 7.26 ppm, ^{13}C NMR = 77.16 ppm). ^{19}F NMR spectra were referenced externally to $CFCl_3$ and are reported proton decoupled. Chemical shifts, δ, are given in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and ^{19}F and 0.1 ppm for ^{13}C NMR. The multiplicity of a signal is reported as such: s–singlet, d–doublet, t–triplet, q–quartet, quint–quintet, m–multiplet, br–broad, or combinations thereof. Coupling constants, *J*, are reported as observed in Hz. Diastereotopic protons are denoted by letters; for example H_AH_B etc. Structural assignments were made with the aid of DEPT135, COSY, HSQC, HMBC and NOESY experiments. Observed nOe correlations used to assign the relative stereochemistry of diastereomers are indicated by double headed arrows.

Low resolution mass spectra were obtained using a Micro Mass LCT Premier spectrometer using electrospray ionization (ESI). High resolution mass spectra (HRMS) using electrospray ionisation (ESI) were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using an eluent system of

H_2O:MeOH:HCOOH (10:89.9:0.1). The system uses a heated electrospray ionisation (HESI-II) probe for ESI^+, and has a resolution of 50,000 FWHM under conditions for maximum sensitivity, with an accuracy exceeding 5 ppm for 24 h following external calibration on the day of analysis. HRMS using ammonia chemical ionisation (CI) were recorded on a Waters GCT system equipped with a Time of Flight (TOF) spectrometer. The mass reported is that containing the most abundant isotopes, with each value given to 4 decimal places, and within 5 ppm of the calculated mass.

Melting points (m.p.) were measured using a Reichert melting point apparatus or a Leica VMTG heated-stage microscope equipped with a Testo 720 thermometer and are reported uncorrected. All compounds were crystallised from chloroform ($CHCl_3$) unless stated otherwise.

Optical rotations were measured using a Schmidt-Haensch Unipol L2000 polarimeter, and values are given in units of $°dm^2g^{-1}$. Concentrations are quoted in g/100 mL (c = 1.0)

Analytical chiral HPLC was performed using a Dionex UltiMate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler and TCC-3000SD column compartment together with a Daicel Chiralpak IC column (0.46 cm × 25 cm) equipped with an appropriate guard column (0.4 cm × 1 cm). A solvent system of 10% isopropanol and 90% hexane with a flow rate of 1.0 mL/min was used.

Systematic names in accordance with the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC) were generated using the computer program

ChemDraw. However, the numbering on the structures shown does not necessarily correspond to the systematic name. The numbering system shown on the structures is used for NMR assignment for easier comparison of data.

7.2 General Procedures

7.2.1 General Procedure A: Enone Epoxidation

Modified literature procedure.[89] To a 3-necked round-bottom flask equipped with a magnetic stirring bar was added enone (1.00 equiv.) and methanol (1 mL per mmol substrate). The solution was cooled to 0 °C before addition of 30% aqueous hydrogen peroxide (3.00 equiv.), followed by 3 M aqueous sodium hydroxide solution (0.200 equiv.). The reaction mixture was stirred at 0 °C until complete consumption of the enone was observed as monitored by TLC. The reaction mixture was then poured into a separating funnel containing ice (15 mL) and brine (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then used directly in **General Procedure C** if volatile or purified by flash column chromatography.

7.2.2 General Procedure B: Grignard addition

Modified literature procedure.[91] A flame dried round-bottom flask was charged with a solution of the selected Grignard reagent and cooled to 0 °C under an argon atmosphere. 3-ethoxycyclopentenone (1.00 g, 7.90 mmol, 1.00 equiv.) dissolved in Et_2O (6 mL) was added to the flask dropwise. Once addition was complete, the reaction mixture was left to warm to ambient temperature until complete disappearance of the starting material (4–6h). The reaction was then quenched at 0 °C by dropwise addition of 1 M aqueous hydrochloric acid solution (50 mL). The aqueous phase was separated and extracted further with Et_2O (3 × 15 mL). The combined organic extracts were washed successively with saturated sodium bicarbonate solution (50 mL), water (50 mL) and brine (50 mL)

before being dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography.

7.2.3 General Procedure C: Phenol and Thiophenol Epoxide Opening

Modified literature procedure.[92] The appropriate phenol (1.50 equiv.), epoxide (1.00 equiv.) and potassium carbonate (1.20 equiv.) were added to a 100 mL round-bottom flask fitted with a condenser. The system was evacuated and backfilled with argon three times. Dry, degassed acetonitrile (5 mL per mmol epoxide) was then added and the mixture heated at 80 °C for 18 h under an atmosphere of argon before being cooled to ambient temperature. The resulting mixture was poured into 1 M aqueous sodium hydroxide solution (12.5 mL per mmol epoxide) and the aqueous layer was then extracted with Et_2O (2 × 7.5 mL per mmol epoxide). The combined organic extracts were washed with brine (7.5 mL per mmol epoxide), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography.

7.2.4 General Procedure D: Amine Epoxide opening

Modified literature procedure.[75,136] The appropriate nucleophile (1.20 equiv.) and epoxide (1.00 equiv.) were added to a 25 mL round-bottom flask fitted with a condenser. Methanol (1.8 mL per mmol epoxide) and water (0.6 mL per mmol epoxide) were added and the resulting solution was degassed by sparging with argon for 30 min. The mixture was heated to reflux (95 °C) for 18–20 h under an atmosphere of argon before being cooled to ambient temperature. The reaction mixture was poured into water (10 mL per mmol epoxide) and extracted with Et_2O (3 × 10 mL per mmol epoxide). The combined organic extracts were

washed with brine (5 mL per mmol epoxide), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography.

7.2.5 General Procedure E: Photochemical Cyclization

EtOAc was sparged with argon for at least 30 minutes. The desired substrate (1.00 equiv.), sodium acetate (1.00 equiv.) and $Ir(dFppy)_3$ (0.01 equiv.) were dissolved in this degassed solution (0.05 M substrate concentration) in a screw top vial and sealed whilst under an argon atmosphere. The sample was then irradiated using a 12 W blue LED strip. After 40 h, the solvent was removed *in vacuo* and the product purified by flash column chromatography.

7.2.6 General Procedure F: Acylation of Enaminones (Acid chloride)

Modified literature procedure.[112] The appropriate enaminone (1.00 equiv.) was dissolved in CH_2Cl_2 (5 mL per mmol enaminone; 0.2 M substrate concentration) and cooled to 0 °C. The desired acid chloride (1.1 equiv.) was then added dropwise, followed by Et_3N (1.1 equiv.). The mixture was then allowed to warm to ambient temperature and stirred at ambient temperature for 14–24 h until complete consumption of enaminone by TLC. The reaction mixture was then diluted with CH_2Cl_2 (5 mL per mmol enaminone) and then washed with water (12.5 mL per mmol enaminone) and brine (12.5 mL per mmol enaminone). The organic phase was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography.

7.2.7 General Procedure G: Acylation of Enaminones (Carboxylic acid)

To a solution of the specified carboxylic acid (1.10 equiv.) in CH_2Cl_2 (5 mL per mmol carboxylic acid) was added oxalyl chloride (2.20 equiv.) and DMF (10 µL) and the reaction stirred at ambient temperature for 1 h until effervescence stopped. The resulting solution was concentrated *in vacuo* and the crude residue dissolved in CH_2Cl_2 (2.5 mL per mmol carboxylic acid). This solution was added dropwise at 0 °C to a solution of the specified enaminone (1.00 equiv.) in CH_2Cl_2 (2.5 mL per mmol enaminone). Et_3N (1.10 equiv.) was then added dropwise and the reaction mixture warmed to ambient temperature and stirred for 16–22 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL per mmol enaminone) and washed with water (25 mL per mmol enaminone) and brine (25 mL per mmol enaminone). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography.

7.2.8 General Procedure H: *N*-Acylation of Enaminones (EDC coupling)

The specified enaminone (1.00 equiv.), the specified carboxylic acid (1.10 equiv.), EDC (1.50 equiv.), and DMAP (0.100 equiv.) were dissolved in CH_2Cl_2 (10 mL per mmol enaminone) and the reaction mixture stirred at ambient temperature for 45–70 h. The reaction mixture was then diluted with water (20 mL per mmol enaminone), the organic phase separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL per mmol enaminone). The combined organic extracts were then washed with brine (20 mL per mmol enaminone), dried (Na_2SO_4), filtered and concentrated *in vacuo* before being purified by flash column chromatography.

7.2.9 General Procedure J: *N*-Acylation of Enaminones (DCC coupling)

To a solution of the specified enaminone (1.00 equiv.) and the specified carboxylic acid (1.00 equiv.) in CH_2Cl_2 (10 mL per mmol enaminone) was added DCC (1.00 equiv.) and the reaction stirred at ambient temperature for 18–20 h. The reaction mixture was then filtered and concentrated *in vacuo*. The crude residue was suspended in EtOAc (1 mL per mmol enaminone), the solids filtered off and the filtrate concentrated *in vacuo*. The crude product was then purified by flash column chromatography.

7.2.10 General Procedure K: *N*-Acylation of Enaminones (Mukaiyama reagent coupling)

To a solution of the specified carboxylic acid (1.10 equiv.) in dry CH_2Cl_2 (2.5 mL per mmol carboxylic acid) under an argon atmosphere was added 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent; 2.20 equiv.). A solution of the specified enaminone (1.00 equiv.) in CH_2Cl_2 (2.5 mL per mmol enaminone) was then added to the reaction mixture, followed by the specified base (3.30 equiv.). The reaction mixture was then stirred in the dark for 19–22 h before being diluted with CH_2Cl_2 (10 mL per mmol enaminone) and washed with water (20 mL per mmol enaminone) and brine (20 mL per mmol enaminone). The organic phase was then dried (Na_2SO_4), filtered and concentrated *in vacuo* and the crude product purified by flash column chromatography.

7.2.11 General Procedure L: Photochemical Spirocyclization

EtOAc was sparged with argon for at least 30 minutes. The desired substrate (1.00 equiv.), sodium acetate (1.00 equiv.) and $Ir(dFppy)_3$ (0.01 equiv.) were dissolved in this degassed solution (0.01 M substrate concentration) in a Schlenk tube and sealed whilst under an argon atmosphere. The sample was then irradiated using a 40 W Kessil Blue LED lamp.

After 40 h, the solvent was removed *in vacuo* and the product purified by flash column chromatography.

7.2.12 General Procedure M: Grignard addition to diethyl oxalate

Modified literature procedure.[127] Magnesium turnings (1.05 equiv.) were heated at 150 °C under vacuum (0.5 mbar) in a flame-dried round bottom flask for 1 h. After cooling to ambient temperature, the magnesium was placed under an argon atmosphere, and a solution of the specified alkyl bromide (0.350 equiv.) in THF (1 mL per mmol alkyl bromide) was added. If necessary, the reaction was heated gently until Grignard formation initiated, at which point the external heating was removed. After initiation, additional alkyl bromide (0.700 equiv.) in THF (1 mL per mmol alkyl bromide) was added to the reaction mixture before it was heated to reflux (60 °C) for 2 h, followed by cooling to ambient temperature. In a different round bottomed flask, a solution of diethyl oxalate (1.00 equiv.) in THF (2 mL per mmol diethyl oxalate) was cooled to -78 °C under an argon atmosphere. The specified Grignard reagent solution (1.05 equiv.) was then added dropwise over 30 minutes. The reaction was stirred at -78 °C for a further 3 h before being warmed to 0 °C and quenched by addition of saturated aqueous ammonium chloride solution (2 mL per mmol diethyl oxalate). The mixture was then extracted with Et_2O (3 × 20 mL), and the combined organic extracts dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography.

7.2.13 General Procedure N: Enamine formation with anilines and α-ketoesters

The specified α-ketoester (1.00 equiv.), the specified aniline (1.40 equiv.) and *para*-toluenesulfonic acid monohydrate (0.0300 equiv.) were dissolved in toluene or

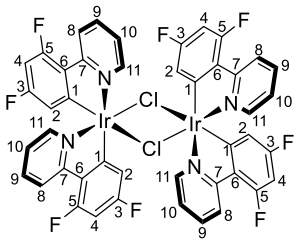
benzene (10 mL per mmol α-ketoester) and heated to reflux (140 °C or 80 °C respectively) in a Dean-Stark water separator for 21–40 h. After cooling to ambient temperature, the reaction mixture was washed with saturated aqueous sodium bicarbonate solution (10 mL per mmol α-ketoester), 1 M aqueous hydrochloric acid (10 mL per mmol α-ketoester), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography.

7.2.14 General Procedure P: Photochemical cyclization of *N*-aryl-2-amino acrylates

To a 7 mL screw-top vial was added the desired substrate (0.15 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (1.2 mg, 1.57 µmol, 0.0100 equiv.) and acetonitrile (3.0 mL; 0.05 M substrate concentration). The vial was sealed with a septum and sparged with nitrogen for at least 15 minutes, before being sealed with a screw top cap. The reaction was then stirred for 2 h whilst being irradiated in a 420 nm Penn OC M1 photoreactor or by a 40 W Kessil blue LED lamp. The solvent was then removed *in vacuo* and the product purified by flash column chromatography.

7.3 Data for Individual Compounds

Dichlorotetrakis[3,5-difluoro-2-(2-pyridinyl)phenyl]diiridium(III), S1



Prepared according to literature procedure.[137] To a 250 ml round-bottom flask fitted with a condenser was added iridium chloride hydrate (600 mg, 2.01 mmol, 1.00 equiv.), 2-(2,4-difluorophenyl)-pyridine (0.78 ml, 961 mg, 5.03 mmol, 2.50 equiv.), 2-ethoxyethanol (46 mL) and water (15 mL). The system was evacuated and backfilled with argon three times, before being heated to reflux (125 °C) in a pre-heated oil bath for 17 h. After cooling to ambient temperature, water (90 mL) was added and the mixture filtered under reduced pressure. The residue was then washed with ethanol:water (1:1 v/v, 50 mL) to afford dichlorotetrakis[3,5-diluoro-2-(2-pyridinyl)phenyl]diiridium(III) (**S1**) as a yellow solid (800 mg, 0.66 mmol, 66%).

m.p. = >300 °C

IR (film) ν_{max}/cm^{-1} = 1601, 1573, 1557, 1478, 1429, 1404, 1295, 1270, 1250, 1162, 1114, 1104, 1070, 990, 848, 831, 784, 756, 737, 718, 710, 612.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.14 (4H, dd, *J* = 6.0, 1.5 Hz, C11H), 8.37–8.29 (4H, m, C8H), 7.86 (4H, ddt, *J* = 8.5, 7.0, 1.5 Hz, C9H), 6.85 (4H, ddd, *J* = 7.5, 6.0, 1.5 Hz, C10H), 6.36 (4H, ddd, *J* = 12.5, 9.0, 2.5 Hz, C4H), 5.31 (4H, dd, *J* = 9.0, 2.5 Hz, C2H).

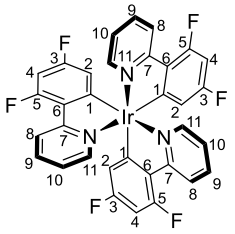
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 165.3 (C7), 151.3 (C11H), 147.6 (C1), 137.5 (C9H), 122.8 (C8H), 122.6 (C10H), 112.8 (C6), 112.6 (C2H), 100.0 (C3F), 98.1 (C4H), 97.9 (C5F).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -107.71 (ddd, *J* = 9.5 Hz, C3F), -110.29 (ddd, *J* = 12.5, 10.0, 2.5 Hz, C5F).

LRMS (ESI^+) Found $[Ir(C_{11}H_6F_2N)_2]^+$ = 573.0.

The data matched that reported in the literature.[137]

***fac*-Tris[2-(4,6-difluorophenyl)pyridinato-C^2,*N*]iridium(III), S2**



Modified literature procedure.[94] To a 50 ml round-bottom flask fitted with a condenser was added $[Ir(dFppy)_2Cl]_2$ (**S1**) (608 mg, 0.50 mmol, 1.00 equiv.) and 2-ethoxyethanol (17 mL). The system was evacuated and backfilled with argon three times, followed by addition of silver trifluoromethanesulfonate (385 mg, 1.50 mmol, 3.0 equiv.) and 2-(2,4-difluorophenyl)pyridine (0.46 ml, 574 mg, 3.00 mmol, equiv.). The mixture was heated to reflux (125 °C) for 4 hours, before being cooled to ambient temperature. The solvent was removed *in vacuo* by azeotropic distillation with toluene. Purification by flash column chromatography (3:1 v/v CH_2Cl_2:Petrol ether 40–60) gave *fac*-tris[2-(4,6-difluorophenyl)pyridinato-C^2,*N*]iridium (III) (**S2**) as a yellow solid (440 mg, 0.58 mmol, 58%).

m.p. = >300 °C.

IR (film) ν_{max}/cm^{-1} = 1595, 1567, 1554, 1472, 1423, 1397, 1286, 1266, 1235, 1160, 1114, 1100, 1067, 1040, 983, 856, 841, 821, 804, 786, 750, 734, 717.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.30 (3H, d, *J* = 8.7 Hz, C11H), 7.69 (3H, t, *J* = 7.8 Hz, C9H), 7.45 (3H, d, *J* = 5.7 Hz, C8H), 6.93 (3H, t, *J* = 6.7 Hz, C10H), 6.45–6.34 (3H, m, C4H), 6.25 (3H, dd, *J* = 8.7, 2.2 Hz, C2H).

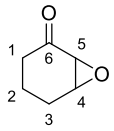
^{13}C NMR ($CDCl_3$, 101 MHz): Signal too weak to observe peaks.

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -108.64 (q, *J* = 9.3 Hz, C3F), -110.53 (m, C5F).

LRMS (ESI^+) Found $[Ir(C_{11}H_6F_2N)_2]^+$ = 573.0, $[Ir(C_{11}H_6F_2N)_3]^+$ = 763.1.

The data matched that reported in the literature and that of a commercial sample.[94,137,138]

7-Oxabicyclo[4.1.0]heptan-2-one, 129



Prepared according to **General Procedure A** with 2-cyclohexen-1-one (9.68 mL, 9.61 g, 100 mmol, 1.00 eq.) for 30 minutes to afford 7-oxabicyclo[4.1.0]heptan-2-one (**129**) as a colourless oil (9.18 g, 81.9 mmol, 82 % yield).

IR (neat) ν_{max}/cm^{-1} 2949, 1708, 1406, 1341, 1250, 970, 881, 817, 749.

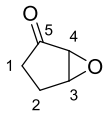
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.61–3.55 (1H, m, C4H), 3.21 (1H, d, *J* = 3.9 Hz, C5H), 2.61–2.46 (1H, m, C1$\underline{H_A}H_B$), 2.29–2.23 (1H, m, C3$\underline{H_A}H_B$), 2.16–2.00 (1H, m, C1$H_A\underline{H_B}$), 2.00–1.84 (2H, m, C2$\underline{H_A}H_B$ & C3$H_A\underline{H_B}$), 1.73–1.62 (1H, m, C3$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 206.0 (C6), 55.9 (C4H), 55.1 (C5H), 36.4 ($C1H_2$), 22.9 ($C3H_2$), 17.0 ($C2H_2$).

HRMS (CI) Found $[M+H]^+$ = 113.0600; $[C_6H_9O_2]^+$ requires 113.0603, Δ -2.91 ppm.

The data matched that reported in the literature.[89]

6-Oxabicyclo[3.1.0]hexan-2-one, 131



Prepared according to **General Procedure A** with 2-cyclopenten-1-one (2.00 g, 24.4 mmol) to afford 6-oxabicyclo[3.1.0]hexan-2-one (**131**) as a colourless oil (1.48 g, 15.0 mmol, 62%).

IR (film) ν_{max}/cm^{-1} 2942, 1743, 1448, 1410, 1371, 1176, 967, 840, 802.

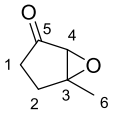
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.92 (1H, m, C3H), 3.32 (1H, d, J = 2.1 Hz, C4H), 2.45–2.23 (2H, m, C1$\underline{H_A}H_B$ & C2$\underline{H_A}H_B$), 2.14–2.01 (2H, m, C1$H_A\underline{H_B}$ & C2$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 210.1 (C5), 57.9 (C3H), 54.8 (C4H), 30.5 ($C1H_2$), 23.2 ($C2H_2$).

HRMS (CI) Found $[M+NH_4]^+$ = 116.0705; $[C_5H_{10}NO_2]^+$ requires 116.0706, Δ 0.05 ppm.

The data matched that reported in the literature.[139]

5-Methyl-6-oxabicyclo[3.1.0]hexan-2-one, 132



Prepared according to **General Procedure A** with 3-methyl-2-cyclopenten-1-one (9.613 g, 100 mmol) to afford 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) as a colourless oil (7.339 g, 65.4 mmol, 65%).

IR (film) ν_{max}/cm^{-1} = 2936, 1744, 1448, 1404, 1256, 1223, 1170, 1062, 975, 898, 836, 794, 693.

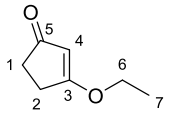
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.15 (1H, s, C4H), 2.44–2.34 (1H, m, C1$\underline{H_A}H_B$), 2.34–2.23 (1H, m, C2$\underline{H_A}H_B$), 2.14–2.03 (1H, m, C1$H_A\underline{H_B}$), 2.01–1.88 (1H, m, C2$H_A\underline{H_B}$), 1.58 (3H, s, C6H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.0 (C5), 66.0 (C3), 61.3 (C4H), 33.0 (C1H_2), 27.9 (C2H_2), 18.1 (C6H_3).

HRMS (Methane CI) Found $[M+H]^+$ = 113.0593; $[C_6H_9O_2]^+$ requires 113.0597, Δ 1.71 ppm.

The data matched that reported in the literature.[140]

3-Ethoxycyclopent-2-en-1-one, 137



Modified literature procedure.[90] 1,3-cyclopentanedione (4.90 g, 50.0 mmol, 1.00 equiv.), anhydrous ethanol (7.50 ml, 128 mmol, 2.56 equiv.) and toluene-4-sulfonic acid (1 mg) were dissolved in benzene. The solution was stirred and refluxed (80 °C) for 24 h, before the solvents were removed under reduced pressure. Purification by flash column chromatography (2:3 v/v Petrol ether 40–60:EtOAc) gave 3-ethoxycyclopent-2-en-1-one (**137**) as a pale yellow oil (3.52 g, 27.9 mmol, 56%).

IR (film) ν_{max}/cm^{-1} = 2955, 2923, 1745, 1585, 1482, 1459, 1237, 1169, 1105, 1049, 1029, 999, 751, 616.

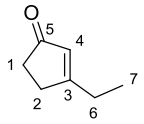
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.23 (1H, s, C4H), 3.99 (2H, q, J = 7.1 Hz, C6H_2), 2.59–2.51 (2H, m, C2H_2), 2.41–2.33 (2H, m, C1H_2), 1.35 (3H, t, J = 7.1 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 206.1 (C5), 190.2 (C3), 104.7 (C4H), 67.7 (C6H_2), 34.0 (C1H_2), 28.6 (C2H_2), 14.12 (C7H_3).

LRMS (ESI^+) Found $[C_7H_{11}O_2]^+$ = 127.0.

The data matched that reported in the literature.[90,141]

3-Ethylcyclopent-2-en-1-one, 133



Prepared according to **General Procedure B** with 1 M ethylmagnesium bromide solution in THF (12.0 ml, 12.0 mmol, 1.50 equiv.) for 6 h. Purification by flash column chromatography (1:1 v/v pentane:Et_2O) gave 3-ethylcyclopent-2-en-1-one (**133**) as a pale yellow oil (291 mg, 2.64 mmol, 33%).

IR (film) ν_{max}/cm^{-1} = 2971, 1712, 1672, 1614, 1461, 1408, 1261, 1235, 1179, 980, 857, 839, 631.

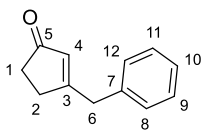
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.86 (p, J = 1.6 Hz, C4H), 2.52 (2H, m, $C2H_2$), 2.43–2.29 (4H, m, $C1H_2$ & $C7H_2$), 1.11 (3H, t, J = 7.2 Hz, $C7H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 210.1 (C5), 184.6 (C3), 128.5 (C4H), 35.30 ($C1H_2$), 31.4 ($C2H_2$), 26.7 ($C6H_2$), 11.4 ($C7H_3$).

LRMS (ESI^+) Found $[C_7H_{11}O]^+$ = 111.2

The data matched that reported in the literature.[142]

3-Benzylcyclopent-2-en-1-one, 134



Prepared according to **General Procedure B** with 1.4 M benzylmagnesium chloride solution in THF (11.3 ml, 15.8 mmol, 2.00 equiv.) for 3.5 h. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave 3-benzylcyclopent-2-en-1-one (**134**) as an orange oil (506 mg, 3.25 mmol, 41%).

IR (film) ν_{max}/cm^{-1} = 3062, 3028, 2920, 1703, 1673, 1616, 1495, 1454, 1437, 1235, 1183, 759, 702.

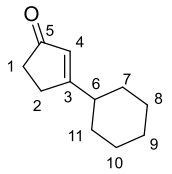
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.30 (2H, m, C9H & C11H), 7.30–7.22 (1H, m, C10H), 7.22–7.14 (2H, m, C8H & C12H), 5.90 (1H, p, J = 1.6 Hz, C4H), 3.72 (2H, s, $C6H_2$), 2.61–2.52 (2H, m, $C2H_2$), 2.44–2.37 (2H, m, $C1H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 209.9 (C5), 181.1 (C3), 137.0 (C7), 130.8 (C4H), 129.1 (C8H & C12H), 128.9 (C9H & C11H), 127.1 (C10H), 40.2 ($C6H_2$), 35.7 ($C1H_2$), 31.2 ($C2H_2$).

LRMS (ESI^+) Found $[C_{12}H_{13}O]^+$ = 173.2; $[C_{12}H_{12}ONa]^+$ = 195.0

The data matched that reported in the literature.[143,144]

3-Cyclohexylcyclopent-2-en-1-one, 135



Prepared according to **General Procedure B** with 1.0 M cyclohexylmagnesium chloride solution in 2-methyl THF (15.8 ml, 15.8 mmol, 2.00 equiv.) for 4 h. Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) gave 3-cyclohexylcyclopent-2-en-1-one (**135**) as a pale yellow oil (400 mg, 2.44 mmol, 31%).

IR (film) ν_{max}/cm^{-1} = 2924, 2852, 1708, 1676, 1607, 1448, 1408, 1335, 1270, 1228, 1185, 984, 846, 626.

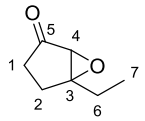
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.91 (1H, q, J = 1.6 Hz, C4H), 2.63–2.55 (2H, m, $C2H_2$), 2.41–2.35 (2H, m, $C1H_2$), 2.35–2.23 (1H, m, C6H), 1.93–1.85 (2H, m, $C7\underline{H_A}H_B$ & $C11\underline{H_A}H_B$), 1.85–1.72 (2H, m, $C8\underline{H_A}H_B$ & $C10\underline{H_A}H_B$), 1.72–1.63 (1H, m, $C9\underline{H_A}H_B$), 1.44–1.11 (5H, m, $C7H_A\underline{H_B}$, $C8H_A\underline{H_B}$, $C9H_A\underline{H_B}$, $C10H_A\underline{H_B}$ & $C11H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 210.6 (C5), 187.8 (C3), 128.0 (C4H), 42.0 (C6H), 35.2 ($C1H_2$), 31.4 ($C7H_2$ & $C11H_2$), 29.7 ($C2H_2$), 26.1 ($C8H_2$ & $C10H_2$), 26.1 ($C9H_2$).

HRMS (Methane CI) Found $[M+H]^+$ = 165.1279; $[C_{11}H_{17}O]^+$ requires 165.1274, Δ -3.10 ppm.

The data matched that reported in the literature.[144]

5-Ethyl-6-oxabicyclo[3.1.0]hexan-2-one, 138



Prepared according to **General Procedure A** with 3-ethyl-2-cyclopenten-1-one (**133**) (275 mg, 2.50 mmol) for 2 h to afford 5-ethyl-6-oxabicyclo[3.1.0]hexan-2-one (**138**) as colourless oil (141 mg, 1.18 mmol, 45%).

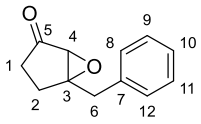
IR (film) ν_{max}/cm^{-1} = 2973, 2938, 1749, 1464, 1402, 1195, 1170, 918, 853, 805, 691.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.17 (1H, s, C4H), 2.51–2.21 (2H, m, $C1\underline{H_A}H_B$ & $C2\underline{H_A}H_B$), 2.18–2.04 (1H, m, $C1H_A\underline{H_B}$), 2.01–1.78 (3H, m, $C2H_A\underline{H_B}$ & $C6\underline{H_A}H_B$), 1.01 (3H, t, J = 7.5 Hz, $C7H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.2 (C5), 69.9 (C3), 60.2 (C4H), 32.7 ($C1H_2$), 25.7 ($C2H_2$), 24.9 ($C6H_2$), 9.2 ($C7H_3$).

HRMS (Methane CI) Found $[M+H]^+$ = 127.0758; $[C_7H_{11}O_2]^+$ requires 127.0754, Δ -3.52 ppm.

5-Benzyl-6-oxabicyclo[3.1.0]hexan-2-one, 139



Prepared according to **General Procedure A** with 3-benzyl-2-cyclopenten-1-one (**134**) (517 mg, 3.00 mmol) for 4 h. Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) gave 5-benzyl-6-oxabicyclo[3.1.0]hexan-2-one (**139**) as a yellow oil (430 mg, 2.28 mmol, 76%).

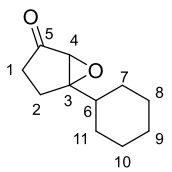
IR (film) ν_{max}/cm^{-1} = 3030, 2934, 1746, 1496, 1455, 1398, 1257, 1181, 1076, 937, 799, 762, 704, 644.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.27 (2H, m, C9H & C11H), 7.27–7.23 (1H, m, C10H), 7.23–7.16 (2H, m, C8H & C12H), 3.16 (1H, s, C4H), 3.15 (1H, d, *J* = 14.6 Hz, C6$\underline{H_A}H_B$), 3.10 (1H, d, *J* = 14.6 Hz, C6$H_A\underline{H_B}$), 2.33 (1H, ddd, *J* = 17.5, 9.2, 8.1 Hz, C1$\underline{H_A}H_B$), 2.18 (1H, dd, *J* = 13.7, 9.3 Hz, C2$\underline{H_A}H_B$), 2.05 (1H, dd, *J* = 17.8, 9.2 Hz, C1$H_A\underline{H_B}$), 1.92 (1H ddd, *J* = 13.8, 9.2, 8.1 Hz, C2$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 210.5 (C5), 135.6 (C7), 129.5 (C9H & C11H), 128.74 (C8H & C12H, 127.2 (C10H), 69.1 (C3), 60.2 (C4H), 38.5 ($C6H_2$), 32.8 ($C1H_2$), 25.6 ($C2H_2$).

HRMS (Methane CI) Found $[M+H]^+$ = 189.0912; $[C_{12}H_{13}O_2]^+$ requires 189.0910, Δ -1.03 ppm.

5-Cyclohexyl-6-oxabicyclo[3.1.0]hexan-2-one, 140



Prepared according to **General Procedure A** with 3-cyclohexyl-2-cyclopenten-1-one (**135**) (361 mg, 2.20 mmol) for 4.5 h. Purification by flash column chromatography (5:1 v/v Petrol ether 40–60:Et_2O) gave 5-cyclohexyl-6-oxabicyclo[3.1.0]hexan-2-one (**140**) as a colourless oil (254 mg, 1.41 mmol, 64%).

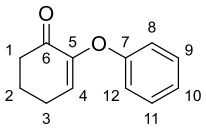
IR (film) ν_{max}/cm^{-1} = 2928, 2854, 1747, 1450, 1402, 1262, 1183, 930, 851, 809, 727.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.18 (1H, s, C4H), 2.42–2.29 (1H, m, C1$\underline{H_A}H_B$), 2.29–2.21 (1H, m, C2$\underline{H_A}H_B$), 2.14–2.02 (1H, m, C1$H_A\underline{H_B}$), 2.02–1.89 (1H, m, C2$H_A\underline{H_B}$), 1.85–1.77 (2H, m, C7$\underline{H_A}H_B$ & C11$\underline{H_A}H_B$), 1.77–1.59 (4H, m, C6H, C8$\underline{H_A}H_B$, C9$\underline{H_A}H_B$ & C10$\underline{H_A}H_B$), 1.34–1.04 (5H, m, C7$H_A\underline{H_B}$, C8$H_A\underline{H_B}$, C9$H_A\underline{H_B}$, C10$H_A\underline{H_B}$ & C11$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.37 (C5), 72.3 (C3), 59.8 (C4H), 39.7 (C6H), 32.5 (C1H_2), 29.0 (C7H_2), 28.6 (C11H_2), 26.2 (C9H_2), 26.1 (C8H_2), 25.9 (C10H_2), 23.7 (C2H_2).

HRMS (Methane CI) Found $[M+H]^+$ = 181.1228; $[C_{11}H_{17}O_2]^+$ requires 181.1223, Δ -2.74 ppm.

2-Phenoxycyclohex-2-en-1-one, 142



Prepared according to **General Procedure C** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (896 mg, 8.00 mmol, 1.00 equiv.) and phenol (1.13 g, 12.0 mmol, 1.50 equiv.). Purification by flash column chromatography (5:2 v/v Petrol ether 40–60:Et_2O) afforded 2-phenoxycyclohex-2-en-1-one (**142**) as a white solid (931 mg, 4.95 mmol, 62%).

m.p. = 39–41 °C.

IR (film) ν_{max}/cm^{-1} 2955, 1685, 1589, 1488, 1249, 1219, 1107, 904, 753, 685.

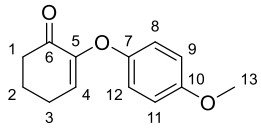
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.19 (2H, m, C9H & C11H), 7.00 (1H, tt, *J* = 7.4, 1.2 Hz, C10H), 6.92–6.84 (2H, m, C8H & C12H), 6.20 (1H, t, *J* = 4.5 Hz, C4H), 2.53 (2H, dd, *J* = 7.5 Hz, 6.0 Hz, $C1H_2$), 2.39 (2H, td, *J* = 6.0, 4.5 Hz, $C3H_2$), 2.00 (2H, dq, *J* = 8.1, 6.1 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 193.8 (C6), 156.3 (C7), 150.0 (C5), 129.7 (C9H & C11H), 129.6 (C4H) 123.4 (C10H), 118.2 (C8H & C12H), 38.8 ($C1H_2$), 24.7 ($C3H_2$), 22.9 ($C2H_2$).

HRMS (CI) Found $[M+H]^+$ = 189.0914; $[C_{12}H_{13}O_2]^+$ requires 189.0916, Δ -1.18 ppm.

The data matched that reported in the literature.[145]

2-(4-Methoxyphenoxy)cyclohex-2-en-1-one, 144



Prepared according to **General Procedure C** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (448 mg, 4.00 mmol, 1.00 equiv.) and 4-methoxyphenol (496.6 mg, 4.00 mmol, 1.00 equiv.). Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) afforded 2-(4-methoxyphenoxy)cyclohex-2-en-1-one (**144**) as a clear, colourless oil (502 mg, 2.29 mmol, 57%).

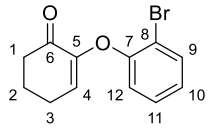
IR (film) ν_{max}/cm^{-1} 2930, 2834, 1681, 1623, 1504, 1460, 1245, 1210, 1175, 1105, 1037, 910, 881, 844, 741.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.98–6.91 (2H, m, C8H & C12H), 6.89–6.82 (2H, m, C9H & C11H), 6.05 (1H, t, *J* = 4.6 Hz, C4H), 3.80 (3H, s, $C13H_3$), 2.60 (2H, dd, *J* = 6.4, 5.6 Hz, $C1H_2$), 2.42 (2H, td, *J* = 6.0, 4.6 Hz, $C3H_2$), 2.11–2.00 (2H, m, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 193.9 (C6), 156.0 (C5), 151.2 (C7), 149.1 (C10), 126.0 (C4H), 120.5 (C10H & C11H), 114.7 (C8H & C12H), 55.6 ($C13H_3$), 38.8 ($C1H_2$), 24.6 ($C3H_2$), 22.9 ($C2H_2$).

HRMS (CI) Found $[M+H]^+$ = 219.1020; $[C_{13}H_{14}O_3]^+$ requires 219.1016 , Δ -1.94 ppm.

2-(2-Bromophenoxy)cyclohex-2-en-1-one, 145



Prepared according to **General Procedure C** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (448 mg, 4.00 mmol, 1.00 equiv.) and 2-bromophenol (1.04 g, 6.00 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) gave 2-(2-bromophenoxy)cyclohex-2-en-1-one (**145**) as a white solid (601 mg, 2.25 mmol, 56%).

m.p. = 55–57 °C.

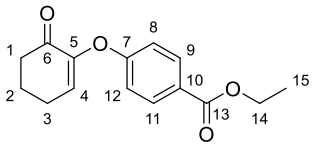
IR (film) ν_{max}/cm^{-1} 3016, 2951, 1687, 1632, 1583, 1472, 1443, 1352, 1250, 1228, 1141, 1105, 1029, 912, 746, 665.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.51 (1H, dd, *J* = 8.0, 1.6 Hz, C9H), 7.19–7.14 (1H, m, C11H), 6.91 (1H, ddd, *J* = 7.9, 7.4, 1.5 Hz, C10H), 6.84 (1H, dd, *J* = 8.1, 1.5 Hz, C12H), 6.06 (1H, t, *J* = 4.5 Hz, C4H), 2.56–2.51 (2H, m, $C1H_2$), 2.39 (2H, td, *J* = 6.0, 4.5 Hz, $C3H_2$), 2.06–1.96 (2H, m, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 193.0 (C6), 152.8 (C7), 149.3 (C5), 133.8 (C9H), 128.5 (C4H & C11H), 125.1 (C10H), 119.7 (C12H), 114.3 (C8), 38.8 ($C1H_2$), 24.7 ($C3H_2$), 22.8 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ 267.0014; $[C_{12}H_{12}O_2Br]^+$ requires 267.0015 , Δ -0.43 ppm.

Ethyl 4-((6-oxocyclohex-1-en-1-yl)oxy)benzoate, 146



Prepared according to **General Procedure C** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (448 mg, 4.00 mmol, 1.00 equiv.) and ethyl 4-hydroxybenzoate (997 mg, 6.00 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) gave ethyl 4-((6-oxocyclohex-1-en-1-yl)oxy)benzoate (**146**) as a white solid (540 mg, 2.06 mmol, 51%).

m.p. = 58–60 °C.

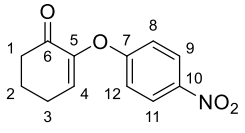
IR (film) ν_{max}/cm^{-1} 2939, 1688, 1600, 1504, 1274, 1249, 1226, 1161, 1098, 1015, 909, 851, 769, 752, 694.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.06–7.96 (2H, m, C9H & C11H), 6.99–6.90 (2H, m, C8H & C12H), 6.57 (1H, t, *J* = 4.5 Hz, C4H), 4.36 (2H, q, *J* = 7.1 Hz, $C14H_2$), 2.66–2.59 (2H, m, $C1H_2$), 2.56 (2H, td, *J* = 6.0, 4.5 Hz, $C3H_2$), 2.19–2.08 (2H, m, $C2H_2$), 1.39 (3H, t, *J* = 7.1 Hz, $C15H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 193.2 (C6), 166.1 (C13), 160.8 (C7), 148.5 (C5), 133.7 (C4H), 131.6 (C9H & C11H), 124.9 (C10), 116.3 (C8H & C12H), 60.8 ($C14H_2$), 38.8 ($C1H_2$), 24.9 ($C3H_2$), 22.8 ($C2H_2$), 14.4 ($C15H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ 283.0938; $[C_{15}H_{16}O_4Na]^+$ requires 283.0941, Δ -0.95 ppm.

2-(4-Nitrophenoxy)cyclohex-2-en-1-one, 147



Prepared according to **General Procedure C** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (448 mg, 4.00 mmol, 1.00 equiv.) and 4-nitrophenol (835 mg, 6.00 mmol, 1.50 equiv.). Purification by flash column chromatography (3:1→1:1 v/v Petrol ether 40–60:Et_2O) afforded 2-(4-nitrophenoxy)cyclohex-2-en-1-one (**147**) as an off-white solid (218 mg, 0.935 mmol, 23%).

m.p. = 119–121 °C.

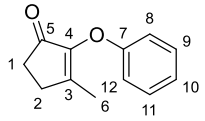
IR (film) ν_{max}/cm^{-1} 2969, 1684, 1608, 1587, 1514, 1503, 1486, 1335, 1250, 1229, 1164, 1140, 1106, 908, 848, 750, 689.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.16–8.07 (2H, m, C9H & C11H), 6.91–6.85 (2H, m, C8H & C12H), 6.66 (1H, t, J = 4.4 Hz, C4H), 2.59–2.48 (4H, m, $C1H_2$ & $C3H_2$), 2.14–2.02 (2H, m, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 192.7 (C6), 162.4 (C7), 147.7 (C5), 144.4 (C10), 136.0 (C4H), 125.9 (C9H & C11H), 116.0 (C8H & C12H), 38.7 ($C1H_2$), 25.0 ($C3H_2$), 22.7 ($C2H_2$).

HRMS (CI) Found $[M+NH_4]^+$ 251.1033; $[C_{12}H_{15}N_2O_4]^+$ requires 251.1026, Δ -2.51 ppm.

3-Methyl-2-phenoxycyclopent-2-en-1-one, 123



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (561 mg, 5.00 mmol, 1.00 equiv.) and phenol (706 mg, 7.50 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→3:2 v/v Petrol ether 40–60:Et_2O) gave 3-methyl-2-phenoxycyclopent-2-en-1-one (**123**) as a white solid (815 mg, 4.33 mmol, 87%).

m.p. = 64–66 °C.

IR (film) ν_{max}/cm^{-1} = 2912, 1707, 1654, 1590, 1490, 1379, 1330, 1220, 1167, 1088, 894, 831, 816, 757, 721, 688, 638.

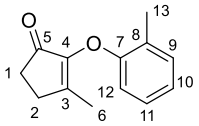
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.21 (2H, m, C9H & C11H), 7.05–6.96 (1H, m, C10H), 6.92–6.84 (2H, m, C8H & C12H), 2.65–2.56 (2H, m, $C2H_2$), 2.55–2.46 (2H, m, $C1H_2$), 2.01 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.7 (C5), 160.2 (C4), 156.7 (C7), 149.3 (C3), 129.6 (C9H & C11H), 122.5 (C10H), 115.6 (C8H & C12H), 32.9 ($C1H_2$), 27.8 ($C2H_2$), 15.4 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 189.0911 ; $[C_{12}H_{13}O_2]^+$ requires 189.0910, Δ 0.31 ppm.

The data matched that reported in the literature.[146]

3-Methyl-2-(*o*-tolyloxy)cyclopent-2-en-1-one, 149



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 4-methylphenol (406 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) gave 3-methyl-2-(*o*-tolyloxy)cyclopent-2-en-1-one (**149**) as a white solid (431 mg, 2.13 mmol, 85%).

m.p. = 78–80 °C.

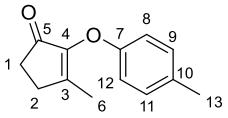
IR (film) ν_{max}/cm^{-1} = 2975, 1707, 1652, 1588, 1488, 1461, 1438, 1383, 1332, 1232, 1200, 1180, 1118, 1087, 1044, 987, 953, 841, 813, 770, 751, 672, 634.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.17 (1H, d, *J* = 7.4 Hz, C9H), 7.04 (1H, t, *J* = 7.7 Hz, C11H), 6.92 (1H, t, *J* = 7.3 Hz, C10H), 6.56 (1H, d, *J* = 8.1 Hz, C12H), 2.63–2.55 (2H, m, $C2H_2$), 2.52–2.45 (2H, m, $C1H_2$), 2.35 (3H, s, $C13H_3$), 1.99 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.8 (C5), 159.2 (C4), 154.9 (C7), 149.7 (C3), 131.2 (C9H), 127.0 (C8), 126.6 (C11H), 122.4 (C10H), 113.6 (C12H), 32.8 ($C1H_2$), 27.7 ($C2H_2$), 16.3 ($C13H_3$), 15.3 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 203.1068; $[C_{13}H_{15}O_2]^+$ requires 203.1067, Δ 0.76 ppm.

3-Methyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one, 150



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 4-methylphenol (406 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→3:2 v/v Petrol ether 40–60:Et_2O) gave 3-methyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one (**150**) as a white solid (436 mg, 2.15 mmol, 86%).

m.p. = 65–67 °C.

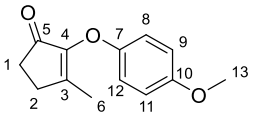
IR (film) ν_{max}/cm^{-1} = 3031, 2924, 1699, 1656, 1607, 1504, 1435, 1385, 1333, 1219, 1167, 1091, 845, 820, 624.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.05 (2H, d, *J* = 8.2 Hz, C9H & C11H), 6.79 (2H, d, *J* = 8.8 Hz, C8H & C12H), 2.64–2.55 (2H, m, $C2H_2$), 2.53–2.45 (2H, m, $C1H_2$), 2.28 (3H, s, $C13H_3$), 2.01 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.9 (C5), 159.7 (C4), 154.6 (C7), 149.5 (C3), 131.9 (C10), 130.0 (C9H & C11H), 115.5 (C8H & C12H), 32.9 ($C1H_2$), 27.8 ($C2H_2$), 20.7 ($C13H_3$), 15.4 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 203.1066; $[C_{13}H_{15}O_2]^+$ requires 203.1067, Δ -0.21 ppm.

2-(4-Methoxyphenoxy)-3-methylcyclopent-2-en-1-one, 151



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 4-methoxyphenol (466 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) gave 2-(4-methoxyphenoxy)-3-methylcyclopent-2-en-1-one (**151**) as a white solid (488 mg, 2.24 mmol, 89%).

m.p. = 49–51 °C.

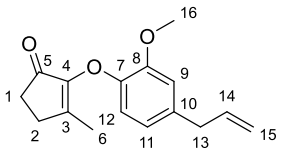
IR (film) ν_{max}/cm^{-1} = 1703, 1651, 1503, 1458, 1444, 1382, 1333, 1247, 1207, 1183, 1089, 1030, 826, 807, 758, 732, 667.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.88–6.81 (2H, m, C8H & C12H), 6.81–6.74 (2H, m, C9H & C11H), 3.75 (3H, s, $C13H_3$), 2.62–2.53 (2H, m, $C2H_2$), 2.52–2.43 (2H, m, $C1H_2$), 2.00 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 202.0 (C5), 159.3 (C4), 155.1 (C10), 150.7 (C7), 149.9 (C3), 116.8 (C8H & C12H), 114.7 (C9H & C11H), 55.8 ($C13H_3$), 32.9 ($C1H_2$), 27.7 ($C2H_2$), 15.4 ($C6H_3$).

HRMS (Methane CI) Found $[M+H]^+$ = 219.1012; $[C_{13}H_{15}O_3]^+$ requires 219.1016, Δ 1.81 ppm.

2-(4-Allyl-2-methoxyphenoxy)-3-methylcyclopent-2-en-1-one, 152



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 4-allyl-2-methoxyphenol (eugenol; 616 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave 2-(4-allyl-2-methoxyphenoxy)-3-methylcyclopent-2-en-1-one (**152**) as a yellow oil that solidified on standing (522 mg, 2.02 mmol, 81%).

m.p. = 38–40 °C.

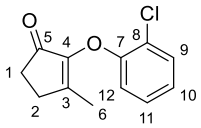
IR (film) ν_{max}/cm^{-1} = 2913, 1710, 1655, 1596, 1506, 1419, 1384, 1334, 1264, 1218, 1153, 1130, 1084, 1034, 993, 913, 851, 804, 752, 653, 622.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.72 (1H, s, C12H), 6.59 (2H, d, J = 1.1 Hz, C9H & C11H), 5.91 (1H, ddt, J = 16.8, 10.0, 6.7 Hz, C14H), 5.09–4.97 (2H, m, $C15H_2$), 3.84 (3H, s, $C16H_3$), 3.29 (2H, dt, J = 6.6, 1.5 Hz, $C13H_2$), 2.58–2.48 (2H, m, $C2H_2$), 2.47–2.36 (2H, m, $C1H_2$), 1.98 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.1 (C5), 158.6 (C4), 149.4 (C3), 149.0 (C8), 143.9 (C7), 137.4 (C14H), 134.9 (C10), 120.2 (C11H), 115.7 ($C15H_2$), 115.2 (C9H), 112.8 (C12H), 56.0 ($C16H_3$), 39.8 ($C13H_2$), 32.7 ($C1H_2$), 27.5 ($C2H_2$), 15.1 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 259.1326; $[C_{16}H_{19}O_3]^+$ requires 259.1329, Δ -1.17 ppm.

2-(2-Chlorophenoxy)-3-methylcyclopent-2-en-1-one, 153



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 2-chlorophenol (482 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave 2-(2-chlorophenoxy)-3-methylcyclopent-2-en-1-one (**153**) as a white solid (453 mg, 2.03 mmol, 81%).

m.p. = 98–100 °C.

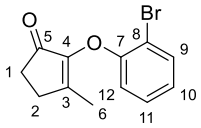
IR (film) ν_{max}/cm^{-1} = 2928, 1699, 1651, 1583, 1476, 1444, 1381, 1334, 1270, 1236, 1191, 1089, 1058, 1036, 835, 758, 697, 668, 626.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37 (1H, dd, *J* = 7.9, 1.7 Hz, C9H), 7.11 (1H, td, *J* = 7.9, 1.6 Hz, C11H), 6.96 (1H, td, *J* = 7.7, 1.5 Hz, C10H), 6.72 (1H, dd, *J* = 8.2, 1.5 Hz, C12H), 2.65–2.55 (2H, m, $C2H_2$), 2.55–2.45 (2H, m, $C1H_2$), 2.04 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.9 (C5), 160.0 (C4), 152.2 (C7), 149.1 (C3), 130.7 (C9H), 127.6 (C11H), 123.4 (C10H), 123.0 (C8), 115.9 (C12H), 32.8 ($C1H_2$), 27.7 ($C2H_2$), 15.3 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 223.0522; $[C_{12}H_{12}O_2Cl]^+$ requires 223.0520, Δ 0.63 ppm.

2-(2-Bromophenoxy)-3-methylcyclopent-2-en-1-one, 154



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (561 mg, 5.00 mmol, 1.00 equiv.) and 2-bromophenol (1.298 g, 7.50 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave 2-(2-bromophenoxy)-3-methylcyclopent-2-en-1-one (**154**) as a white solid (1.11 g, 4.17 mmol, 83%).

m.p. = 105–107 °C.

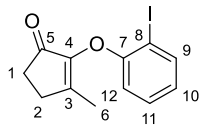
IR (film) ν_{max}/cm^{-1} = 2913, 1706, 1653, 1577, 1471, 1331, 1268, 1237, 1084, 1029, 747.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.55 (1H, dd, *J* = 7.9, 1.6 Hz, C9H), 7.16 (1H, ddd, *J* = 8.2, 7.4, 1.6 Hz, C11H), 6.90 (1H, ddd, *J* = 8.0, 7.8, 1.3 Hz, C10H), 6.69 (1H, dd, *J* = 8.2, 1.5 Hz, C12H), 2.66–2.56 (2H, m, $C2H_2$), 2.55–2.46 (2H, m, $C1H_2$), 2.04 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.8 (C5), 160.1 (C4), 153.2 (C7), 149.3 (C3), 133.7 (C9H), 128.3 (C11H), 123.9 (C10H), 115.7 (C12H), 112.0 (C8), 32.9 ($C1H_2$), 27.8 ($C2H_2$), 15.4 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 267.0017; $[C_{12}H_{12}O_2Br]^+$ requires 267.0015, Δ 0.83 ppm.

2-(2-Iodophenoxy)-3-methylcyclopent-2-en-1-one, 155



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 2-iodophenol (825 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave 2-(2-iodophenoxy)-3-methylcyclopent-2-en-1-one (**155**) as a white solid (611 mg, 1.95 mmol, 78%).

m.p. = 96–98 °C.

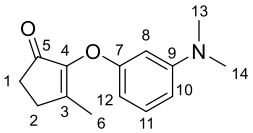
IR (film) ν_{max}/cm^{-1} = 3057, 2921, 1704, 1653, 1578, 1467, 1437, 1381, 1331, 1268, 1230, 1192, 1120, 1088, 1019, 830, 756, 655, 627.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.78 (1H, dd, *J* = 7.8, 1.6 Hz, C9H), 7.20 (1H, td, *J* = 7.5, 1.6 Hz, C11H), 6.77 (1H, td, *J* = 7.6, 1.4 Hz, C10H), 6.61 (1H, dd, *J* = 8.2, 1.4 Hz, C12H), 2.66–2.57 (2H, m, $C2H_2$), 2.55–2.46 (2H, m, $C1H_2$), 2.04 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.9 (C5), 160.4 (C4), 155.6 (C7), 149.5 (C3), 139.8 (C9H), 129.4 (C11H), 124.3 (C10H), 114.5 (C12H), 85.8 (C8), 32.9 ($C1H_2$), 27.8 ($C2H_2$), 15.5 ($C6H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 336.9695; $[C_{12}H_{11}O_2INa]^+$ requires 336.9696, Δ -0.15 ppm.

2-(3-(Dimethylamino)phenoxy)-3-methylcyclopent-2-en-1-one, 156



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 3-(dimethylamino)phenol (514 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (1:1 v/v Petrol ether 40–60:Et_2O) gave 2-(3-(dimethylamino)phenoxy)-3-methylcyclopent-2-en-1-one (**156**) as a red-brown solid (417 mg, 1.80 mmol, 72%).

m.p. = 57–59 °C.

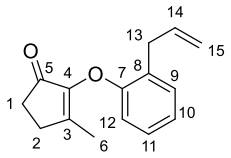
IR (film) ν_{max}/cm^{-1} = 2914, 2805, 1710, 1653, 1607, 1572, 1500, 1438, 1383, 1333, 1219, 1142, 1088, 997, 880, 823, 752, 684.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.07 (1H, t, *J* = 8.2 Hz, C11H), 6.39 (1H, ddd, *J* = 8.3, 2.5, 0.8 Hz, C12H), 6.36 (1H, t, *J* = 2.4 Hz, C8H), 6.12 (1H, ddd, *J* = 8.1, 2.3, 0.8 Hz, C10H), 2.92 (6H, s, $C13H_3$ & $C14H_3$), 2.64–2.55 (2H, m, $C2H_2$), 2.52–2.45 (2H, m, $C1H_2$), 2.01 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.9 (C5), 159.8 (C4), 157.8 (C7), 152.1 (C9), 149.4 (C3), 129.7 (C11H), 107.2 (C12H), 102.8 (C10H), 100.6 (C8H), 40.6 ($C13H_3$ & $C14H_3$), 32.9 ($C1H_2$), 27.8 ($C2H_2$), 15.4 ($C6H_3$).

HRMS (EI) Found $[M]^+$ = 231.1257; $[C_{14}H_{17}NO_2]^+$ requires 231.1254, Δ -1.24 ppm.

2-(2-Allylphenoxy)-3-methylcyclopent-2-en-1-one, 157



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 2-allylphenol (503 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) gave 2-(2-allylphenoxy)-3-methylcyclopent-2-en-1-one (**157**) as a white solid (478 mg, 2.06 mmol, 82%).

m.p. = 57–59 °C.

IR (film) ν_{max}/cm^{-1} = 2913, 1715, 1656, 1585, 1488, 1454, 1405, 1383, 1332, 1219, 1174, 1117, 1091, 996, 915, 837, 759, 657.

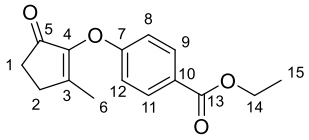
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.18 (1H, dd, *J* = 7.5, 1.7 Hz, C9H), 7.08 (1H, td, *J* = 7.8, 1.8 Hz, C11H), 6.96 (1H, td, *J* = 7.4, 1.2 Hz, C10H), 6.57 (1H, dd, *J* = 8.1, 1.2 Hz, C12H), 6.05 (1H, ddt,

J = 16.8, 10.1, 6.6 Hz, C14H), 5.15–5.03 (2H, m, $C15H_2$), 3.51 (2H, dt, *J* = 6.6, 1.5 Hz, $C13H_2$), 2.65–2.57 (2H, m, $C2H_2$), 2.57–2.46 (2H, m, $C1H_2$), 1.99 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.6 (C5), 159.5 (C4), 154.4 (C7), 149.6 (C3), 136.7 (C14H), 130.4 (C9H), 128.8 (C8), 127.2 (C11H), 122.6 (C10H), 115.8 ($C15H_2$), 113.6 (C12H), 34.4 ($C13H_2$), 32.9 ($C1H_2$), 27.8 ($C2H_2$), 15.4 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 229.1224; $[C_{15}H_{17}O_2]^+$ requires 229.1223, Δ 0.30 ppm.

Ethyl 4-((2-methyl-5-oxocyclopent-1-en-1-yl)oxy)benzoate, 158



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (561 mg, 5.00 mmol, 1.00 equiv.) and ethyl 4-hydroxybenzoate (997 mg, 7.50 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave ethyl 4-((2-methyl-5-oxocyclopent-1-en-1-yl)oxy)benzoate (**158**) as a white solid (1.11 g, 4.11 mmol, 82%).

m.p. = 71–73 °C.

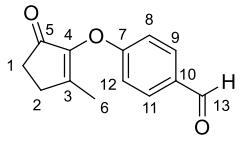
IR (film) ν_{max}/cm^{-1} = 1703, 1657, 1600, 1505, 1332, 1275, 1230, 1165, 1101, 1086, 1019, 860, 772, 685.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.01–7.93 (2H, m, C9H & C11H), 6.92–6.85 (2H, m, C8H & C12H), 4.34 (2H, q, *J* = 7.1 Hz, $C14H_2$), 2.68–2.61 (2H, m, $C2H_2$), 2.55–2.48 (2H, m, $C1H_2$), 2.03 (3H, s, $C6H_3$), 1.36 (3H, t, *J* = 7.1 Hz, $C15H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.1 (C5), 166.2 (C13), 160.9 (C4), 160.2 (C7), 148.8 (C3), 131.7 (C9H & C11H), 124.8 (C10), 115.2 (C8H & C12H), 60.9 ($C14H_2$), 32.9 ($C1H_2$), 27.8 ($C2H_2$), 15.4 ($C6H_3$), 14.5 ($C15H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 283.0942; $[C_{15}H_{16}O_4Na]^+$ requires 283.0941, Δ 0.45 ppm.

4-((2-Methyl-5-oxocyclopent-1-en-1-yl)oxy)benzaldehyde, 159



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 4-hydroxybenzaldehyde (438 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (1:1→0:1 v/v Petrol ether 40–60:Et_2O) gave 4-((2-methyl-5-oxocyclopent-1-en-1-yl)oxy)benzaldehyde (**159**) as a white solid (264 mg, 1.21 mmol, 49%).

m.p. = 62–64 °C.

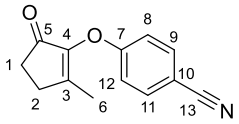
IR (film) ν_{max}/cm^{-1} = 2909, 2848, 2757, 1711, 1684, 1656, 1595, 1579, 1504, 1431, 1406, 1378, 1329, 1300, 1235, 1164, 1082, 860, 834, 813, 678, 648.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.89 (1H, s, C13H), 7.82 (2H, d, J = 8.9 Hz, C9H & C11H), 6.98 (2H, d, J = 8.5 Hz, C8H & C12H), 2.70–2.62 (2H, m, $C2H_2$), 2.56–2.49 (2H, m, $C1H_2$), 2.05 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.8 (C5), 190.8 (C13H), 161.4 (C7), 161.3 (C4), 148.5 (C3), 132.0 (C9H & C11H), 131.4 (C10), 116.0 (C8H & C12H), 32.9 ($C1H_2$), 27.9 ($C2H_2$), 15.4 ($C6H_3$).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 239.0679; $[C_{13}H_{12}O_3Na]^+$ requires 239.0679, Δ 0.02 ppm.

4-((2-Methyl-5-oxocyclopent-1-en-1-yl)oxy)benzonitrile, 160



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 4-hydroxybenzonitrile (447 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (1:1→0:1 v/v Petrol ether 40–60:Et_2O) gave 4-((2-methyl-5-oxocyclopent-1-en-1-yl)oxy)benzonitrile (**160**) as a white solid (435 mg, 2.04 mmol, 82%).

m.p. = 126–128 °C.

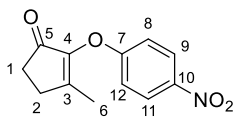
IR (film) ν_{max}/cm^{-1} = 2220, 1710, 1661, 1597, 1497, 1382, 1331, 1242, 1169, 1087, 843, 667.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.56 (2H, d, J = 8.8 Hz, C9H & C11H), 6.93 (d, J = 8.9 Hz, C8H & C12H), 2.70–2.62 (2H, m, $C2H_2$), 2.56–2.48 (2H, m, $C1H_2$), 2.05 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.7 (C5), 161.6 (C4), 159.8 (C7), 148.3 (C3), 134.1 (C9H & C11H), 118.9 (C13), 116.4 (C8H & C12H), 106.0 (C10), 32.9 ($C1H_2$), 27.9 ($C2H_2$), 15.3 ($C6H_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 214.0865; $[C_{13}H_{12}O_2N]^+$ requires 214.0863, Δ 1.01 ppm.

3-Methyl-2-(4-nitrophenoxy)cyclopent-2-en-1-one, 161



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 4-nitrophenol (522 mg, 3.75 mmol,

1.50 equiv.). Purification by flash column chromatography (1:1→1:2 v/v Petrol ether 40–60:Et_2O) gave 3-methyl-2-(4-nitrophenoxy)cyclopent-2-en-1-one (**161**) as an off-white solid (339 mg, 1.45 mmol, 58%).

m.p. = 120–122 °C.

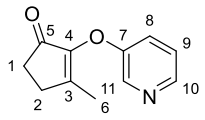
IR (film) ν_{max}/cm^{-1} = 1712, 1661, 1587, 1504, 1488, 1384, 1329, 1237, 1167, 1107, 1087, 855, 755, 690.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.22–8.13 (2H, m, C9H & C11H), 6.99–6.90 (2H, m, C8H & C12H), 2.72–2.64 (2H, m, $C2H_2$), 2.58–2.53 (2H, m, $C1H_2$), 2.07 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.5 (C5), 161.7 (C4), 161.4 (C7), 148.4 (C3), 142.9 (C10), 126.0 (C9H & C11H), 115.8 (C8H & C12H), 32.9 ($C1H_2$), 27.9 ($C2H_2$), 15.4 ($C6H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 256.0581; $[C_{12}H_{11}O_4NNa]^+$ requires 256.0580, Δ 0.30 ppm.

3-Methyl-2-(pyridin-3-yloxy)cyclopent-2-en-1-one, 162



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (561 mg, 5.00 mmol, 1.00 equiv.) and 3-hydroxypyridine (713 mg, 7.50 mmol, 1.50 equiv.). Purification by flash column chromatography (EtOAc) gave 3-methyl-2-(pyridine-3-yloxy)cyclopent-2-en-1-one (**162**) as a brown solid (357 mg, 1.89 mmol, 38%).

m.p. = 56–58 °C.

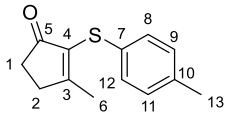
IR (film) ν_{max}/cm^{-1} = 1698, 1654, 1572, 1478, 1425, 1335, 1252, 1228, 1187, 1021, 807, 707, 613.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.32–8.26 (2H, m, C10H & C11H), 7.25–7.13 (2H, m, C8H & C9H), 2.68–2.61 (2H, m, $C2H_2$), 2.55–2.48 (2H, m, $C1H_2$), 2.06 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.0 (C5), 160.7 (C4), 153.1 (C7), 148.8 (C3), 144.0 (C10H), 138.7 (C11H), 124.0 (C9H), 122.8 (C8H), 32.9 ($C1H_2$), 27.8 ($C2H_2$), 15.4 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 190.0863; $[C_{11}H_{12}O_2N]^+$ requires 190.0863, Δ 0.34 ppm.

3-Methyl-2-(*p*-tolylthio)cyclopent-2-en-1-one, 163



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 4-methylbenzenethiol (466 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) gave 3-methyl-2-(*p*-tolylthio)cyclopent-2-en-1-one (**163**) as a brown solid (340 mg, 1.56 mmol, 62%).

m.p. = 53–55 °C.

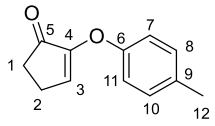
IR (film) ν_{max}/cm^{-1} = 1695, 1601, 1490, 1424, 1397, 1374, 1266, 1156, 1116, 1087, 1038, 1015, 960, 941, 803, 666.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.13 (2H, d, *J* = 8.2 Hz, C8H & C12H), 7.03 (2H, d, *J* = 8.0 Hz, C9H & C11H), 2.75–2.67 (2H, m, $C2H_2$), 2.55–2.48 (2H, m, $C1H_2$), 2.28 (3H, s, $C13H_3$), 2.25 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 205.3 (C5), 181.1 (C3), 136.4 (C10), 133.8 (C4), 130.9 (C7), 129.8 (C9H & C11H), 129.3 (C8H & C12H), 34.3 ($C1H_2$), 32.5 ($C2H_2$), 21.1 ($C13H_3$), 19.1 ($C6H_3$).

HRMS (EI) Found $[M]^+$ = 218.0754; $[C_{13}H_{14}OS]^+$ requires 218.0765, Δ 2.17 ppm.

2-(*p*-Tolyloxy*)*cyclopent-2-en-1-one, 166



Prepared according to **General Procedure C** with 6-oxabicyclo[3.1.0]hexan-2-one (**131**) (491 mg, 5.00 mmol, 1.00 equiv.) and 4-methylphenol (811 mg, 7.5 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave 2-(*p*-tolyloxy)cyclopent-2-en-1-one (**166**) as a white solid (524 mg, 2.78 mmol, 56%).

m.p. = 67–69 °C.

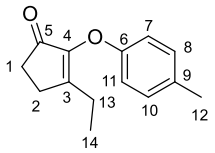
IR (film) ν_{max}/cm^{-1} = 2924, 1712, 1625, 1607, 1505, 1447, 1404, 1339, 1300, 1263, 1219, 1166, 1080, 1018, 929, 843, 785.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.13 (2H, d, *J* = 8.3 Hz, C8H & C10H), 6.98 (2H, d, *J* = 8.4 Hz, C7H & C11H), 6.41 (1H, t, *J* = 1.9 Hz, C3H), 2.53–2.45 (4H, m, $C1H_2$ & $C2H_2$), 2.30 (3H, s, $C12H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 202.0 (C5), 156.7 (C4), 153.4 (C6), 134.4 (C9), 133.6 (C3H), 130.3 (C8H & C10H), 119.6 (C7H & C11H), 33.3 ($C1H_2$), 21.9 ($C2H_2$), 20.8 ($C12H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 189.0911; $[C_{12}H_{13}O_2]^+$ requires 189.0910, Δ 0.63 ppm.

3-Ethyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one, 167



Prepared according to **General Procedure C** with 5-ethyl-6-oxabicyclo[3.1.0]hexan-2-one (**138**) (126 mg, 1.0 mmol, 1.00 equiv.) and 4-methylphenol (162 mg, 1.5 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave 3-ethyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one (**167**) as a yellow oil (110 mg, 0.509 mmol, 51%).

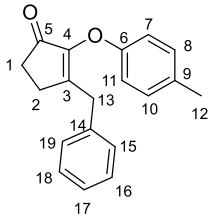
IR (neat) ν_{max}/cm^{-1} = 2972, 2924, 1710, 1648, 1609, 1505, 1461, 1351, 1298, 1219, 1167, 1090, 1063, 816, 762, 619.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.05 (2H, d, *J* = 8.3 Hz, C8H & C10H), 6.77 (2H, d, *J* = 8.4 Hz, C7H & C11H), 2.65–2.58 (2H, m, $C2H_2$), 2.52–2.47 (m, $C1H_2$), 2.43 (2H, q, *J* = 7.7 Hz, $C13H_2$), 2.28 (3H, s, $C12H_3$), 1.12 (3H, t, *J* = 7.6 Hz, $C14H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 202.2 (C5), 165.0 (C4), 154.7 (C6), 148.6 (C3), 131.8 (C9), 130.1 (C8H & C10H), 115.3 (C7H & C11H), 32.9 ($C1H_2$), 25.1 ($C2H_2$), 22.5 ($C13H_2$), 20.7 ($C12H_3$), 11.5 ($C14H_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 217.1224; $[C_{14}H_{17}O_2]^+$ requires 217.1223, Δ 0.25 ppm.

3-Benzyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one, 168



Prepared according to **General Procedure C** with 5-benzyl-6-oxabicyclo[3.1.0]hexan-2-one (**139**) (369 mg, 1.96 mmol, 1.00 equiv.) and 4-methylphenol (324 mg, 3.00 mmol, 1.50 equiv.). Purification by flash column chromatography (3:1 v/v Petrol ether 40–60:Et_2O) gave 3-benzyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one (**168**) as a yellow oil (398 mg, 1.43 mmol, 73%).

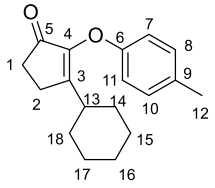
IR (film) ν_{max}/cm^{-1} = 3028, 2922, 1710, 1650, 1608, 1504, 1454, 1406, 1343, 1228, 1208, 1168, 1079, 817, 756, 701.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.17 (3H, m, C16H, C17H & C18H), 7.16–7.10 (2H, m, C15H & C19H), 7.04 (2H, d, *J* = 8.6 Hz, C8H & C10H), 6.79 (2H, d, *J* = 8.6 Hz, C7H & C11H), 3.68 (2H, s, $C13H_2$), 2.48–2.41 (2H, m, $C2H_2$), 2.41–2.35 (2H, m, $C1H_2$), 2.26 (3H s, $C12H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.9 (C5), 161.2 (C4), 154.6 (C6), 148.8 (C3), 136.8 (C14), 132.0 (C9), 130.1 (C8H & C10H), 129.1 (C15H & C19H), 128.9 (C16H & C18H), 127.0 (C17H), 115.5 (C7H & C11H), 35.5 ($C13H_2$), 32.9 ($C1H_2$), 25.1 ($C2H_2$), 20.7 ($C12H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 279.1380; $[C_{19}H_{19}O_2]^+$ requires 279.1380, Δ 0.05 ppm.

3-Cyclohexyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one, 169



Prepared according to **General Procedure C** with 5-cyclohexyl-6-oxabicyclo[3.1.0]hexan-2-one (**140**) (196 mg, 1.09 mmol, 1.00 equiv.) and 4-methylphenol (176 mg, 1.63 mmol, 1.50 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether

40–60:Et_2O) gave 3-cyclohexyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one (**169**) as a yellow solid (262 mg, 0.970 mmol, 89%).

m.p. = 42–44 °C.

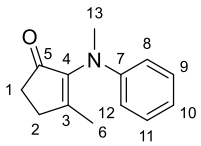
IR (film) ν_{max}/cm^{-1} = 2925, 2853, 1711, 1643, 1609, 1505, 1448, 1337, 1167, 1105, 1072, 846, 816.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.05 (2H, d, *J* = 8.5 Hz, C8H & C10H), 6.78 (2H, d, *J* = 8.5 Hz, C7H & C11H), 2.71 (1H, tt, *J* = 11.9, 3.4 Hz, C13H), 2.63–2.55 (2H, m, $C2H_2$), 2.51–2.42 (2H, m, $C1H_2$), 2.28 (3H, s, $C12H_3$), 1.82–1.65 (5H, m, $C14\underline{H_A}H_B$, $C15\underline{H_A}H_B$, $C16\underline{H_A}H_B$, $C17\underline{H_A}H_B$ & $C18\underline{H_A}H_B$), 1.46–1.11 (5H, m, $C14H_A\underline{H_B}$, $C15H_A\underline{H_B}$, $C16H_A\underline{H_B}$, $C17H_A\underline{H_B}$ & $C18H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 202.3 (C5), 168.2 (C4), 154.7 (C6), 147.8 (C3), 131.7 (C9), 130.1 (C8H & C10H), 115.3 (C7H & C11H), 38.2 (C13H), 32.9 ($C1H_2$), 30.3 ($C14H_2$ & $C18H_2$), 26.0 ($C15H_2$ & $C17H_2$), 25.9 ($C16H_2$), 23.0 ($C2H_2$), 20.7 ($C12H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 271.1692; $[C_{18}H_{23}O_2]^+$ requires 271.1693, Δ -0.36 ppm.

3-Methyl-2-(methyl(phenyl)amino)cyclopent-2-en-1-one, 172



Prepared according to **General Procedure D** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and *N*-methylaniline (0.325 ml, 321 mg, 3.00 mmol, 1.20 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave 3-methyl-2-(methyl(phenyl)amino)cyclopent-2-en-1-one (**172**) as a yellow oil (470 mg, 2.34 mmol, 93%).

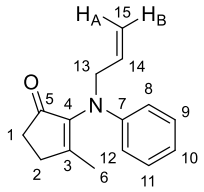
IR (neat) ν_{max}/cm^{-1} = 2909, 1703, 1639, 1597, 1498, 1387, 1357, 1286, 1221, 1186, 1156, 1110, 1033, 949, 811, 747, 692.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.14 (2H, m, C9H & C11H), 6.78–6.69 (1H, m, C10H), 6.63–6.55 (2H, m, C8H & C12H), 3.13 (3H, s, $C13H_3$), 2.67–2.59 (2H, m, $C2H_2$), 2.53–2.46 (2H, m, $C1H_2$), 1.92 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 206.3 (C5), 168.2 (C3), 147.4 (C7), 144.2 (C4), 129.1 (C9H & C11H), 117.8 (C10H), 113.1 (C8H & C12H), 37.4 ($C13H_3$), 33.8 ($C1H_2$), 29.5 ($C2H_2$), 17.6 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 202.1227; $[C_{13}H_{16}ON]^+$ requires 202.1226, Δ 0.20 ppm.

2-(Allyl(phenyl)amino)-3-methylcyclopent-2-en-1-one, 173



Prepared according to **General Procedure D** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and *N*-allylaniline (0.407 ml, 400 mg, 3.00 mmol, 1.20 equiv.). Purification by flash column chromatography (3:1→5:2 v/v Petrol ether 40–60:Et_2O) gave 2-(allyl(phenyl)amino)-3-methylcyclopent-2-en-1-one (**173**) as a yellow oil (472 mg, 2.08 mmol, 83%).

IR (neat) ν_{max}/cm^{-1} = 2914, 1701, 1638, 1596, 1497, 1438, 1392, 1367, 1284, 1236, 1205, 1141, 1047, 991, 917, 810, 747, 692.

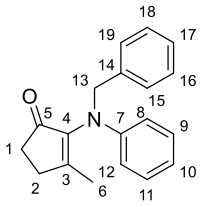
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.17 (2H, t, *J* = 7.5 Hz, C9H & C11H), 6.73 (1H, t, *J* = 7.3 Hz, C10H), 6.61 (2H, d, *J* = 8.1 Hz, C8H & C12H), 5.96–5.81 (1H, m, C14H), 5.26 (1H, dt, *J* = 17.3,

1.7 Hz, C15H$_A$), 5.13 (1H, dt, *J* = 10.4, 1.6 Hz, C15H$_B$), 4.17 (2H, dd, *J* = 5.4, 1.7 Hz, C13H$_2$), 2.67–2.56 (2H, m, C2H$_2$), 2.53–2.45 (2H, m, C1H$_2$), 1.92 (3H, s, C6H$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 206.3 (C5), 169.0 (C3), 146.9 (C7), 142.7 (C4), 134.9 (C14H), 129.1 (C9H & C11H), 118.0 (C10H), 116.3 (C15H$_A$H$_B$), 113.8 (C8H & C12H), 52.3 (C13H$_2$), 33.8 (C1H$_2$), 29.5 (C2H$_2$), 17.8 (C6H$_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 228.1381 ; $[C_{15}H_{18}ON]^+$ requires 228.1383, Δ -0.81 ppm.

2-(Benzyl(phenyl)amino)-3-methylcyclopent-2-en-1-one, 174



Prepared according to **General Procedure D** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and *N*-benzylaniline (550 mg, 3.00 mmol, 1.20 equiv.). Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:Et_2O) gave 2-(benzyl(phenyl)amino)-3-methylcyclopent-2-en-1-one (**174**) as a yellow solid (239 mg, 0.860 mmol, 34%).

m.p. = 99–101 °C

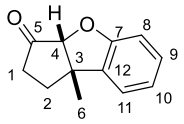
IR (neat) ν_{max}/cm^{-1} = 3028, 2893, 2856, 1694, 1646, 1597, 1497, 1450, 1441, 1388, 1270, 1208, 1132, 1056, 990, 975, 810, 748, 739, 715, 691, 668.

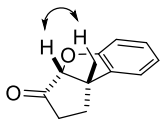
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.39–7.27 (4H, m, C15H, C16H, C18H & C19H), 7.27–7.19 (1H, m, C17H), 7.19–7.11 (2H, m, C9H & C11H), 6.79–6.68 (1H, m, C10H), 6.65–6.58 (2H, m, C8H & C12H), 4.82 (2H, s, C13H$_2$), 2.64–2.56 (2H, m, C2H$_2$), 2.53–2.38 (2H, m, C1H$_2$), 1.94 (3H, s, C6H$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 206.3 (C5), 169.0 (C3), 147.2 (C7), 142.8 (C4), 139.3 (C14), 129.2 (C9H & C11H), 128.6 (C15H & C19H), 127.0 (C17H), 126.9 (C16H & C18H), 118.4 (C10H), 113.9 (C8H & C12H), 53.8 ($C13H_2$), 33.8 ($C1H_2$), 29.5 ($C2H_2$), 18.0 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 278.1538; $[C_{19}H_{20}ON]^+$ requires 278.1539, Δ -0.37 ppm.

(3a*R,8b*S**)-8b-Methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 125**





Prepared according to **General Procedure E** with 3-methyl-2-phenoxycyclopent-2-en-1-one (**123**) (56.5 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-8b-methyl-1,2,3a,8b,tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**125**) as a clear oil (49.0 mg, 0.260 mmol, 87%).

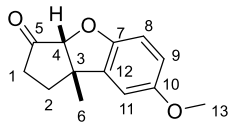
IR (film) ν_{max}/cm^{-1} = 2959, 2869, 1750, 1595, 1475, 1460, 1243, 1182, 1016, 982, 827,750, 642.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.23–7.10 (2H, m, C9H & C11H), 6.96 (1H, td, *J* = 7.4, 1.0 Hz, C10H), 6.84 (1H, dt, *J* = 7.9, 0.8 Hz, C8H), 4.35 (1H, s, C5H), 2.52–2.30 (2H, m, $C1H_{\underline{A}}H_B$ & $C2H_{\underline{A}}H_B$), 2.19–2.02 (2H, m, $C1H_AH_{\underline{B}}$ & $C2H_AH_{\underline{B}}$), 1.53 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.8 (C5), 158.7 (C7), 132.9 (C12), 129.0 (C11H), 123.0 (C9H), 122.0 (C10H), 110.3 (C8H), 90.1 (C4H), 49.9 (C3), 37.1 ($C1H_2$), 33.0 ($C2H_2$), 26.8 ($C6H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 211.0731; $[C_{12}H_{12}O_2Na]^+$ requires 211.0730, Δ 0.80 ppm.

(3a*R,8b*S**)-7-Methoxy-8b-methyl-1,2,3a,8b-tetrahydro-3H-cyclopenta[b]benzofuran-3-one, 177**



Prepared according to **General Procedure E** with 2-(4-methoxyphenoxy)-3-methylcyclopent-2-en-1-one (**151**) (65.5 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-7-methoxy-8b-methyl-1,2,3a,8b-tetrahydro-3H-cyclopenta[b]benzofuran-3-one (**177**) as a white solid (54.4 mg, 0.249 mmol, 83%).

m.p. = 85–87 °C.

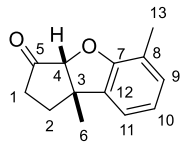
IR (film) ν_{max}/cm^{-1} = 2962, 1753, 1477, 1426, 1292, 1214, 1181, 1152, 1124, 1030, 987, 862, 816, 790, 731, 659, 638.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.78–6.66 (3H, m, C8H, C9H & C11H), 4.32 (1H, s, C4H), 3.77 (3H, s, C13H_3), 2.51–2.33 (2H, m, C1$H_A$$H_B$ & C2$H_A$$H_B$), 2.22–2.02 (2H, m, C1$H_A$$H_B$ & C2$H_A$$H_B$), 1.52 (3H, s, C6$H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.3 (C5), 155.3 (C10), 152.8 (C7), 133.8 (C12), 113.9 (C8H), 110.4 (C11H), 108.9 (C9H), 90.4 (C4H), 56.1 (C13H_3), 50.4 (C3), 37.0 (C1$H_A$$H_B$), 32.8 (C2$H_A$$H_B$), 26.7 (C6$H_3$).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 241.0837; $[C_{13}H_{14}O_3Na]^+$ requires 241.0835, Δ 0.62 ppm.

(3a*R,8b*S**)-5,8b-Dimethyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 178**



Prepared according to **General Procedure E** with 3-methyl-2-(*o*-tolyloxy)cyclopent-2-en-1-one (**149**) (60.7 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-5,8b-dimethyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**178**) as a clear oil (52.2 mg, 0.258 mmol, 86%).

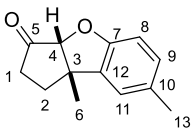
IR (film) ν_{max}/cm^{-1} = 2958, 2869, 1751, 1595, 1460, 1322, 1262, 1179, 1019, 986, 826, 777, 747.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.00 (2H, m, C9H & C11H), 6.86 (1H, t, *J* = 7.5 Hz, C10H), 4.34 (1H, s, C4H), 2.50–2.33 (2H, m, C1$\underline{H_A}H_B$ & C2$\underline{H_A}H_B$), 2.22 (3H, s, C13H_3), 2.17–2.01 (2H, m, C1$H_A\underline{H_B}$ & C2$H_A\underline{H_B}$), 1.52 (3H, s, C6H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.1 (C5), 157.2 (C7), 132.2 (C12), 130.2 (C9H), 121.9 (C10H), 120.5 (C8), 120.2 (C11H), 89.8 (C4H), 50.2 (C3), 37.1 (C1H_2), 33.1 (C2H_2), 26.8 (C6H_3), 15.3 (C13H_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 225.0887; $[C_{13}H_{14}O_2Na]^+$ requires 225.0886, Δ 0.44 ppm.

(3a*R,8b*S**)-7,8b-Dimethyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 179**



Prepared according to **General Procedure E** with 3-methyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one (**150**) (60.7 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-7,8b-dimethyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**179**) as a clear oil (51.9 mg, 0.257 mmol, 86%).

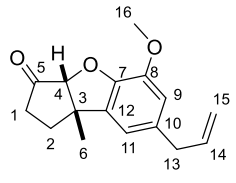
IR (film) ν_{max}/cm^{-1} = 2959, 2865, 1752, 1609, 1483, 1451, 1402, 1253, 1186, 1014, 985, 886, 809, 785, 737, 636.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.97 (1H, s, C11H), 6.96 (1H, d, *J* = 8.0 Hz, C9H), 6.73 (1H, d, *J* = 7.9 Hz, C8H), 4.32 (1H, s, C4H), 2.50–2.33 (2H, m, $C1H_{\underline{A}}H_B$ & $C2H_{\underline{A}}H_B$), 2.30 (3H, s, $C13H_3$), 2.19–2.01 (2H, m, $C1H_AH_{\underline{B}}$ & $C2H_AH_{\underline{B}}$), 1.52 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.2 (C5), 156.7 (C7), 132.8 (C12), 131.4 (C10), 129.5 (C9H), 123.4 (C11H), 109.9 (C8H), 90.2 (C4H), 50.0 (C3), 37.1 ($C1H_AH_B$), 32.0 ($C2H_AH_B$), 26.9 ($C6H_3$), 21.0 ($C13H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 225.0888; $[C_{13}H_{14}O_2Na]^+$ requires 225.0886, Δ 0.91 ppm.

(3a*R,8b*S**)-7-Allyl-5-methoxy-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 180**



Prepared according to **General Procedure E** with 2-(4-allyl-2-methoxyphenoxy)-3-methylcyclopent-2-en-1-one (**152**) (77.4 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether

40–60:Et_2O) gave (3a*R**,8b*S**)-7-allyl-5-methoxy-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**180**) as a colourless oil (28.0 mg, 0.108 mmol, 36%).

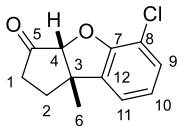
IR (film) ν_{max}/cm^{-1} = 2958, 1753, 1604, 1492, 1451, 1336, 1315, 1202, 1139, 1050, 987, 914, 843, 800, 749.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.60 (1H, d, *J* = 1.6 Hz, C11H), 6.58 (1H, d, *J* = 1.6 Hz, C9H), 5.94 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, C14H), 5.13–5.00 (2H, m, $C15H_2$), 4.37 (1H, s, C4H), 3.84 (3H, s, $C16H_3$), 3.33 (2H, d, *J* = 6.8 Hz, $C13H_2$), 2.48–2.32 (2H, m, $C1\underline{H_A}H_B$ & $C2\underline{H_A}H_B$), 2.21–1.98 (2H, m, $C1H_A\underline{H_B}$ & $C2H_A\underline{H_B}$), 1.51 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.3 (C5), 145.5 (C7), 144.3 (C8), 137.7 (C14H), 135.0 (C10), 134.1 (C12), 115.9 ($C15H_2$), 114.5 (C11H), 112.6 (C9H), 90.7 (C4H), 56.1 ($C16H_3$), 50.7 (C3), 40.2 ($C13H_2$), 37.1 ($C1H_2$), 32.9 ($C2H_2$), 26.7 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 259.1328; $[C_{16}H_{19}O_3]^+$ requires 259.1329, Δ -0.11 ppm.

(3a*R,8b*S**)-5-Chloro-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 181**



Prepared according to **General Procedure E** with 2-(2-chlorophenoxy)-3-methylcyclopent-2-en-1-one (**153**) (66.8 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-5-chloro-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**181**) as a white solid (24.3 mg, 0.109 mmol, 36%).

m.p. = 99–101 °C.

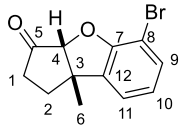
IR (film) ν_{max}/cm^{-1} = 2961, 1753, 1605, 1586, 1446, 1403, 1326, 1211, 1117, 1052, 1014, 979, 829, 779, 736, 646.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.18 (1H, dd, *J* = 7.9, 1.2 Hz, C9H), 7.08 (1H, dd, *J* = 7.5, 1.2 Hz, C11H), 6.91 (1H, t, *J* = 7.7 Hz, C10H), 4.45 (1H, s, C4H), 2.56–2.28 (2H, m, C1$\underline{H_A}H_B$ & C2$\underline{H_A}H_B$), 2.28–2.02 (2H, m, C1H_AH_B & C2H_AH_B), 1.54 (3H, s, C6H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.0 (C5), 154.7 (C7), 134.8 (C12), 129.5 (C9H), 123.1 (C10H), 121.3 (C11H), 115.7 (C8), 90.4 (C4H), 50.9 (C3), 37.1 (C1H_2), 33.2 (C2H_2), 26.7 (C6H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 223.0524; $[C_{12}H_{12}O_2Cl]^+$ requires 223.0520, Δ 1.57 ppm.

(3a*R,8b*S**)-5-Bromo-8b-methyl-1,2,3a,8b-tetrahydro-3H-cyclopenta[b]benzofuran-3-one, 182**



Prepared according to **General Procedure E** with 2-(2-bromophenoxy)-3-methylcyclopent-2-en-1-one (**154**) (80.1 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-5-bromo-8b-methyl-1,2,3a,8b-tetrahydro-3H-cyclopenta[b]benzofuran-3-one (**182**) as a white solid (52.0 mg, 0.195 mmol, 65%).

m.p. = 88–90 °C.

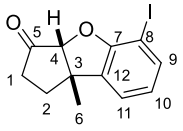
IR (film) ν_{max}/cm^{-1} = 2948, 1750, 1443, 1406, 1324, 1263, 1236, 1211, 1175, 1093, 1051, 1014, 986, 971, 828, 804, 778, 736, 642.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33 (1H, dd, *J* = 7.9, 1.2 Hz, C9H), 7.12 (1H, dd, *J* = 7.5, 1.2 Hz, C11H), 6.84 (1H, t, *J* = 7.7 Hz, C10H), 4.47–4.41 (1H, m, C4H), 2.53–2.32 (2H, m, $C1H_{\underline{A}}H_B$ & $C2H_{\underline{A}}H_B$), 2.23–2.03 (2H, m, $C1H_AH_{\underline{B}}$ & $C2H_AH_{\underline{B}}$), 1.54 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.0 (C5), 156.1 (C7), 134.5 (C12), 132.3 (C9H), 123.5 (C10H), 122.0 (C11H), 103.2 (C8), 90.1 (C4H), 51.1 (C3), 37.1 ($C1H_AH_B$), 33.3 ($C2H_AH_B$), 26.8 ($C6H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 288.9835; $[C_{12}H_{11}O_2BrNa]^+$ requires 288.9835, Δ 0.27 ppm.

(3a*R,8b*S**)-5-Iodo-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 183**



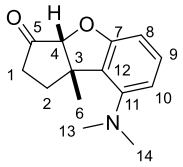
Prepared according to **General Procedure E** with 2-(2-iodophenoxy)-3-methylcyclopent-2-en-1-one (**155**) (94.2 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-5-iodo-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**183**) as a colourless oil (42.2 mg, 0.134 mmol, 45%)

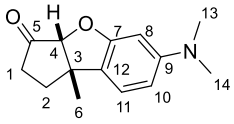
IR (film) ν_{max}/cm^{-1} = 2959, 1751, 1596, 1433, 1324, 1209, 1175, 1091, 1050, 1014, 980, 828, 775, 738, 642.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.55 (1H, dd, *J* = 7.8, 1.2 Hz, C9H), 7.17 (1H, dd, *J* = 7.4, 1.2 Hz, C11H), 6.75 (1H, t, *J* = 7.6 Hz, C10H), 4.45 (1H, s, C4H), 2.56–2.33 (2H, m, $C1H_{\underline{A}}H_B$ & $C2H_{\underline{A}}H_B$), 2.24–2.05 (2H, m, $C1H_AH_{\underline{B}}$ & $C2H_AH_{\underline{B}}$), 1.56 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.1 (C5), 159.2 (C7), 137.9 (C9H), 133.2 (C12), 123.9 (C10H), 122.9 (C11H), 89.5 (C4H), 74.2 (C8), 51.4 (C3), 37.1 ($C1H_2$), 33.4 ($C2H_2$), 26.8 ($C6H_3$). **HRMS** (ESI^+) Found $[M+Na]^+$ = 336.9695; $[C_{12}H_{11}O_2INa]^+$ requires 336.9696, Δ -0.15 ppm.

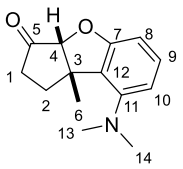
(3a*R,8b*S**)-8-(Dimethylamino)-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one**, **184** and **(3a*R**,8b*S**)-6-(dimethylamino)-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 185**





Prepared according to **General Procedure E** with 2-(3-(dimethylamino)phenoxy)-3-methylcyclopent-2-en-1-one (**156**) (69.4 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (4:1→1:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-8-(dimethylamino)-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**184**) as a clear oil (17.9 mg, 0.0774 mmol, 26%) along with (3a*R**,8b*S**)-6-(dimethylamino)-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**185**) as a light pink solid (28.5 mg, 0.123 mmol, 41%).

Data for **(3a*R**,8b*S**)-8-(dimethylamino)-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 184**



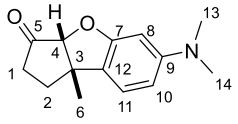
IR (film) ν_{max}/cm^{-1} = 2975, 2937, 2861, 2824, 2783, 1753, 1589, 1484, 1438, 1329, 1257, 1178, 1045, 1012, 987, 800, 744, 636.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.14 (1H, t, *J* = 8.0 Hz, C9H), 6.84 (1H, dd, *J* = 8.0, 0.9 Hz, C10H), 6.64 (1H, dd, *J* = 8.0, 0.9 Hz, C8H), 4.27 (1H, s, C4H), 2.93–2.78 (1H, m, $C2H_{\underline{A}}H_B$), 2.67 (6H, s, $C13H_3$ and $C14H_3$), 2.53–2.38 (1H, m, $C1H_{\underline{A}}H_B$), 2.27–1.88 (2H, m, $C\text{-}1H_AH_{\underline{B}}$ & $C2H_{\underline{A}}H_{\underline{B}}$), 1.62 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.8 (C5), 159.9 (C7), 153.4 (C11), 129.9 (C9H), 127.3 (C12), 115.7 (C10H), 107.2 (C8H), 90.8 (C4H), 50.6 (C3), 46.6 ($C13H_3$ & $C14H_3$), 37.3 ($C1H_2$), 31.7 ($C2H_2$), 25.7 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 232.1334; $[C_{14}H_{18}O_2N]^+$ requires 232.1332, Δ 0.81 ppm.

Data for **(3a*R**,8b*S**)-6-(dimethylamino)-8b-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 185**



m.p. = 108–110 °C.

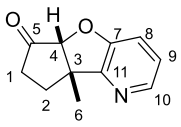
IR (film) ν_{max}/cm^{-1} = 2955, 2918, 2869, 2803, 1751, 1624, 1579, 1510, 1445, 1357, 1241, 1138, 1076, 987, 880, 816, 790, 729, 642.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.01 (1H, d, *J* = 8.3 Hz, C11H), 6.33 (1H, dd, *J* = 8.3, 2.3 Hz, C10H), 6.23 (1H, d, *J* = 2.3 Hz, C8H), 4.31 (1H, s, C4H), 2.91 (6H, s, $C13H_3$ & $C14H_3$), 2.46–2.32 (2H, m, $C1H_{\underline{A}}H_B$ & $C2H_{\underline{A}}H_B$), 2.22– 1.98 (2H, m, $C1H_AH_{\underline{B}}$ & $C2H_AH_{\underline{B}}$), 1.49 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.8 (C5), 160.3 (C7), 152.1 (C9), 122.9 (C11H), 120.2 (C12), 106.5 (C10H), 94.6 (C8H), 90.7 (C4H), 49.5 (C3), 40.9 ($C13H_3$ & $C14H_3$), 37.0 ($C1H_2$), 32.7 ($C2H_2$), 27.0 ($C6H_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 232.1334; $[C_{14}H_{18}O_2N]^+$ requires 232.1332, Δ 0.74 ppm.

(5a*R,8a*S**)-8a-Methyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-6-one, 186**



Prepared according to **General Procedure E** with 3-methyl-2-(pyridine-3-yloxy)cyclopent-2-en-1-one (**162**) (56.8 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (2:1→0:1 v/v Petrol ether 40–60:Et_2O) gave (5a*R**,8a*S**)-8a-methyl-5a,7,8,8a-tetrahydro-6*H*-cyclopenta[4,5]furo[3,2-*b*]pyridine-6-one (**186**) as a yellow oil (29.8 mg, 0.158 mmol, 52%).

m.p. = 67–69 °C.

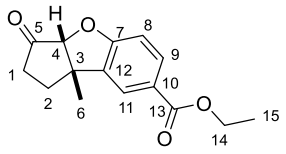
IR (film) ν_{max}/cm^{-1} = 2963, 1752, 1602, 1575, 1425, 1266, 1169, 1098, 964, 835, 796, 734, 647.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.17 (1H, dd, *J* = 4.5, 1.7 Hz, C10H), 7.15–7.03 (2H, m, C8H & C9H), 4.47 (1H, s, C4H), 2.68–2.56 (1H, m, $C2H_{\underline{A}}H_B$), 2.56–2.40 (1H, m, $C1H_{\underline{A}}H_B$), 2.18–2.01 (2H, m, $C1H_AH_{\underline{B}}$ & $C2H_AH_{\underline{B}}$), 1.58 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.7 (C5), 153.8 (C11), 152.3 (C7), 143.6 (C10H), 123.2 (C9H), 117.0 (C8H), 89.8 (C4H), 49.4 (C3), 37.1 ($C1H_2$), 31.7 ($C2H_2$), 25.1 ($C6H_3$).

HRMS (ESI$^-$) Found $[M-H]^-$ = 188.0714; $[C_{11}H_{10}O_2N]^-$ requires 188.0717, Δ -1.38 ppm.

Ethyl (3a*R,8b*S**)-8b-Methyl-3-oxo-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-7-carboxylate, 187**



Prepared according to **General Procedure E** with ethyl 4-((2-methyl-5-oxocyclopent-1-en-1-yl)oxy)benzoate (**158**) (78.0 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave ethyl (3a*R**,8b*S**)-8b-methyl-3-oxo-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-7-carboxylate (**187**) as a clear oil (30.0 mg, 0.115 mmol, 38%).

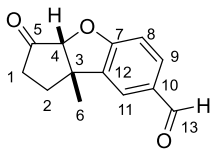
IR (film) ν_{max}/cm^{-1} = 2961, 1755, 1705, 1610, 1481, 1452, 1366, 1287, 1261,1240, 1174, 1100, 1014, 980, 835, 772, 744, 662.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.98–7.87 (2H, m, C9H & C11H), 6.86 (1H, d, *J* = 8.4 Hz, C8H), 4.45 (1H, s, C4H), 4.35 (2H, q, *J* = 7.1 Hz, $C14H_2$), 2.55–2.34 (2H, m, $C1H_AH_B$ & $C2H_AH_B$), 2.22–2.04 (2H, m, $C1H_AH_B$ & $C2H_AH_B$), 1.56 (3H, s, $C6H_3$), 1.38 (3H, t, *J* = 7.1 Hz, $C15H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.5 (C5), 166.3 (C13), 162.6 (C7), 133.6 (C12), 131.8 (C11H), 125.1 (C9H), 124.8 (C10), 110.1 (C8H), 91.0 (C4H), 61.0 ($C14H_2$), 49.6 (C3), 37.1 ($C1H_2$), 33.1 ($C2H_2$), 26.8 ($C6H_3$), 14.5 ($C15H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 261.1123; $[C_{15}H_{17}O_4]^+$ requires 261.1121, Δ 0.47 ppm.

(3a*R,8b*S**)-8b-Methyl-3-oxo-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-7-carbaldehyde, 188**



Prepared according to **General Procedure E** with 4-((2-methyl-5-oxocyclopent-1-en-1-yl)oxy)benzaldehyde (**159**) (64.8 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (1:1→0:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-8b-methyl-3-oxo-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-7-carbaldehyde (**188**) as a yellow oil (15.0 mg, 0.0694 mmol, 23%).

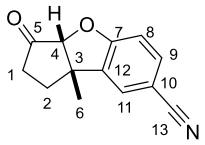
IR (film) ν_{max}/cm^{-1} = 2961, 1754, 1686, 1605, 1588, 1480, 1454, 1437, 1329, 1254, 1191, 1078, 977, 936, 894, 822, 729, 644.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.87 (1H, s, C13H), 7.81 (1H, d, *J* = 1.4 Hz, C11H), 7.72 (1H, dd, *J* = 8.3, 1.7 Hz, C9H), 6.96 (1H, d, *J* = 8.3 Hz, C8H), 4.50 (1H, s, C4H), 2.58–2.29 (2H, m, $C1H_{\underline{A}}H_B$ & $C2H_{\underline{A}}H_B$), 2.23–2.06 (2H, m, $C1H_AH_{\underline{B}}$ & $C2H_AH_{\underline{B}}$), 1.58 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 212.9 (C5), 190.6 (C13H), 164.0 (C7), 135.0 (C12), 134.1 (C9H), 131.9 (C10), 124.0 (C11H), 110.7 (C8H), 91.3 (C4H), 49.4 (C3), 37.0 ($C1H_2$), 33.2 ($C2H_2$), 26.8 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 217.0862; $[C_{13}H_{13}O_3]^+$ requires 217.0859, Δ 1.13 ppm.

(3a*R,8b*S**)-8b-Methyl-3-oxo-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-7-carbonitrile, 189**



Prepared according to **General Procedure E** with 4-((2-methyl-5-oxocyclopent-1-en-1-yl)oxy)benzonitrile (**160**) (64.0 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (1:1→0:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-8b-methyl-3-oxo-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-7-carbonitrile (**189**) as a white solid (6.9 mg, 0.0324 mmol, 11%).

m.p. = 124–126 °C.

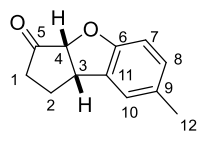
IR (film) ν_{max}/cm^{-1} = 2963, 2224, 1755, 1609, 1479, 1316, 1257, 1190, 1172, 1014, 977, 782.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.56–7.46 (2H, m, C9H & C11H), 6.92 (1H, d, *J* = 8.4 Hz, C8H), 4.48 (1H, s, C4H), 2.60–2.30 (2H, m, $C1H_{\underline{A}}H_B$ & $C2H_{\underline{A}}H_B$), 2.23–2.07 (2H, m, $C1H_AH_{\underline{B}}$ & $C2H_AH_{\underline{B}}$), 1.57 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 212.4 (C5), 162.1 (C7), 135.0 (C12), 134.4 (911), 127.6 (911), 119.2 (C10), 111.5 (C8H), 105.6 (C13), 90.9 (C4H), 49.7 (C3), 37.0 ($C1H_2$), 33.3 ($C2H_2$), 26.8 ($C6H_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 214.0867; $[C_{13}H_{12}O_2N]^+$ requires 214.0863, Δ 1.96 ppm.

(3a*R,8b*S**)-7-Methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 193**



Prepared according to **General Procedure E** with 2-(*p*-tolyloxy)cyclopent-2-en-1-one (**166**) (56.5 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-7-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**193**) as a colourless, viscous oil (23.8 mg, 0.126 mmol, 42%).

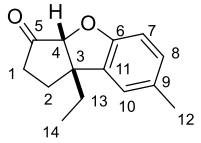
IR (film) ν_{max}/cm^{-1} = 2922, 1750, 1612, 1485, 1459, 1402, 1282, 1246, 1196, 1048, 985, 810.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.03 (1H, d, *J* = 1.7 Hz, C10H), 6.96 (1H, dd, *J* = 8.2, 1.8 Hz, C8H), 6.72 (1H, d, *J* = 8.1 Hz, C7H), 4.75 (1H, d, *J* = 8.8, 1.4 Hz, C4H), 4.24–4.14 (1H, m, C3H), 2.46–2.32 (2H, m, C1$\underline{H_A}H_B$ & C2$\underline{H_A}H_B$), 2.30 (3H, s, C12H_3), 2.27–2.21 (1H, m, C2$H_A\underline{H_B}$), 2.19–2.05 (1H, m, C1$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.1 (C5), 157.3 (C6), 131.3 (C9), 129.5 (C8H), 128.4 (C11), 124.9 (C10H), 109.7 (C7H), 84.1 (C4H), 43.0 (C3H), 35.1 (C1H_2), 25.7 (C2H_2), 21.0 (C12H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 189.0912; $[C_{12}H_{13}O_2]^+$ requires 189.0910, Δ 0.79 ppm.

(3a*R,8b*S**)-8b-Ethyl-7-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 194**



Prepared according to **General Procedure E** with 3-ethyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one (**167**) (64.9 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1 v/v Petrol ether 40–60:Et_2O) gave 8b-ethyl-7-methyl-1,2,3a,8b-tetrahydro-3*H*-

cyclopenta[*b*]benzofuran-3-one (**194**) as a colourless, viscous oil. (55.5 mg, 0.257 mmol, 86%).

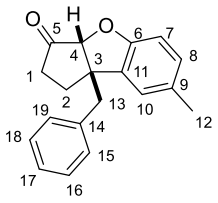
IR (film) ν_{max}/cm^{-1} = 2963, 1753, 1610, 1483, 1460, 1241, 1184, 991, 889, 810, 785.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.00–6.92 (2H, m, C8H & C10H), 6.72 (1H, d, *J* = 8.0 Hz, C7H), 4.38 (1H, s, C4H), 2.49–2.32 (2H, m, C1$\underline{H_A}H_B$ & C2$\underline{H_A}H_B$), 2.31 (3H, s, C12H_3), 2.19–2.02 (2H, m, C1$H_A\underline{H_B}$ & C2$H_A\underline{H_B}$), 1.92–1.74 (2H, m, C13H_2), 0.85 (3H, t, *J* = 7.4 Hz, C14H_3).

^{13}C NMR ($CDCl_3$, 101 MHZ) δ = 215.5 (C5), 157.5 (C6), 131.2 (C9), 130.9 (C11), 129.6 (C8H), 123.9 (C10H), 109.7 (C7H), 88.5 (C4), 54.4 (C3), 36.8 (C1H_2), 32.9 (C13H_2), 31.3 (C2H_2), 21.1 (C12H_3), 9.2 (C14H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 217.1225; $[C_{14}H_{17}O_2]^+$ requires 217.1223, Δ 0.67 ppm.

(3a*R,8b*R**)-8b-Benzyl-7-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 195**



Prepared according to **General Procedure E** with 3-benzyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one (**168**) (83.5 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (3:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*R**)-8b-benzyl-7-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**195**) as a colourless, viscous oil. (59.1 mg, 0.212 mmol, 71%).

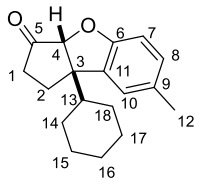
IR (film) ν_{max}/cm^{-1} = 2920, 1751, 1604, 1484, 1454, 1402, 1235, 1191, 996, 969, 910, 811, 784, 767, 730, 702.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.38–7.14 (3H, m, C16H, C17H & C18H), 7.10–7.01 (2H, m, C15H & C19H), 6.97 (1H, dd, *J* = 8.1, 1.8 Hz, C8H), 6.81 (1H, d, *J* = 1.8 Hz, C10H), 6.69 (1H, d, *J* = 8.3 Hz, C7H), 4.52 (1H, s, C4H), 3.10 (1H, d, *J* = 13.4 Hz, C13$\underline{H_A}H_B$), 3.01 (1H, d, *J* = 13.4 Hz, C13$H_A\underline{H_B}$), 2.46–2.21 (3H, m, C1$\underline{H_A}\underline{H_B}$ & C2$\underline{H_A}H_B$), 2.30 (3H, s, C12H_3) 2.11–1.94 (1H, m, C2$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.5 (C5), 157.2 (C6), 136.7 (C14), 131.1 (C9), 130.8 (C11), 130.3 (C15H & C19H), 129.8 (C8H), 128.3 (C16H & C18H), 127.0 (C17H), 124.3 (C10H), 109.9 (C7H), 87.5 (C4H), 54.6 (C3), 45.4 (C13H_2), 36.7 (C1H_2), 29.7 (C2H_2), 21.0 (C12H_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 301.1200; $[C_{19}H_{18}O_2Na]^+$ requires 301.1199, Δ 0.31 ppm.

(3a*R,8b*R**)-8b-Cyclohexyl-7-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one, 196**



Prepared according to **General Procedure E** with 3-cyclohexyl-2-(*p*-tolyloxy)cyclopent-2-en-1-one (**169**) (81.1 mg, 0.300 mmol, 1.00 equiv). Purification by flash column chromatography (5:1→4:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*R**)-8b-cyclohexyl-7-methyl-1,2,3a,8b-tetrahydro-3*H*-cyclopenta[*b*]benzofuran-3-one (**196**) as a white solid (69.5 mg, 0.257 mmol, 86%).

m.p. = 116–118 °C.

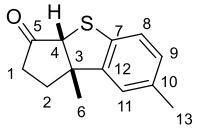
IR (film) ν_{max}/cm^{-1} = 2926, 2853, 1752, 1610, 1484, 1450, 1196, 1115, 997, 884, 810, 784.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.00–6.92 (2H, m, C8H & C10H), 6.70 (1H, d, J = 8.2 Hz, C7H), 4.41 (1H, s, C4H), 2.50–2.33 (2H, m, C1$\underline{H_A}H_B$ & C2$\underline{H_A}H_B$), 2.31 (3H, s, C12H_3), 2.20–1.97 (2H, m, C1$H_A\underline{H_B}$ & C2$H_A\underline{H_B}$), 1.84–1.74 (3H, m, C14$\underline{H_A}H_A$, C17$\underline{H_A}H_B$ & C18$\underline{H_A}H_B$), 1.74–1.64 (1H, m, C15$\underline{H_A}H_B$), 1.64–1.52 (1H, m, C16$\underline{H_A}H_B$), 1.58 (1H, s, C13H), 1.30–1.18 (3H, m, C14$H_A\underline{H_B}$, C15$H_A\underline{H_B}$ & C17$H_A\underline{H_B}$), 1.18–0.97 (1H, m, C16$H_A\underline{H_B}$), 0.73–0.58 (1H, m, C18$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 216.1 (C5), 157.9 (C6), 130.8 (C9), 129.6 (C8H), 129.4 (C11), 125.0 (C10H), 109.6 (C7H), 88.4 (C4H), 57.4 (C3), 47.3 (C13H), 36.9 (C1H_2), 29.6 (C2H_2), 28.2 (C18H_2), 27.4 (C14H_2), 26.6 (C17H_2), 26.4 (C15H_2), 26.3 (C16H_2), 21.2 (C12H_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 293.1503; $[C_{18}H_{22}O_2Na]^+$ requires 293.1512, Δ -2.95 ppm.

(3a*R,8b*S**)-7,8b-Dimethyl-1,2,3a,8b-tetrahydro-3*H*-benzo[*b*]cyclopenta[*d*]thiophen-3-one, 198**



Prepared according to **General Procedure E** with 3-methyl-2-(*p*-tolylthio)cyclopent-2-en-1-one (**163**) (65.5 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-7,8b-dimethyl-1,2,3a,8b-tetrahydro-3*H*-benzo[*b*]cyclopenta[*d*]thiophen-3-one (**198**) as a pale yellow solid. (57.0 mg, 0.261 mmol, 87%).

m.p. = 83–85 °C.

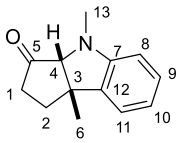
IR (film) ν_{max}/cm^{-1} = 2970, 2956, 2913, 2866, 1739, 1466, 1403, 1372, 1323, 1253, 1173, 1148, 1121, 1052, 1039, 986, 883, 816, 708, 629.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.05–6.93 (3H, m, C8H, C9H & C11H), 3.60 (1H, s, C4H), 2.57–2.36 (2H, m, C1$\underline{H_A}H_B$ & C2$\underline{H_A}H_B$), 2.31 (3H, s, C13H), 2.25–2.04 (2H, m, C1$H_A\underline{H_B}$ & C2$H_A\underline{H_B}$), 1.49 (3H, s, C6H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 216.8 (C5), 144.9 (C7), 136.2 (C12), 135.1 (C10), 129.3 (C11H), 124.1 (C9H), 121.8 (C8H), 62.8 (C4H), 56.5 (C3), 37.7 (C1H_2), 35.1 (C2H_2), 26.4 (C6H_3), 21.2 (C13H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 219.0840; $[C_{13}H_{15}OS]^+$ requires 219.0838, Δ 0.92 ppm.

(3a*R,8b*S**)-4,8b-Dimethyl-1,3a,4,8b-tetrahydrocyclopenta[*b*]indol-3(2*H*)-one, 199**



Prepared according to **General Procedure E** with 3-methyl-2-(methyl(phenyl)amino)cyclopent-2-en-1-one (**172**) (72.3 mg, 0.30 mmol, 1.00 equiv.). Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-4,8b-dimethyl-1,3a,4,8b-tetrahydrocyclopenta[*b*]indol-3(2*H*)-one (**199**) as a colourless oil. (50.9 mg, 0.25 mmol, 84%).

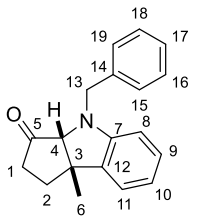
IR (film) ν_{max}/cm^{-1} = 3050, 2956, 2868, 1740, 1605, 1484, 1451, 1372, 1303, 1219, 1157, 1120, 1093, 1020, 985, 784, 744.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.13 (1H, t, *J* = 7.9 Hz, C9H), 7.08 (1H, d, *J* = 7.0 Hz, C11H), 6.74 (1H, t, *J* = 7.4 Hz, C10H), 6.45 (1H, d, *J* = 7.8 Hz, C8H), 3.23 (1H, s, C4H), 2.91 (3H, s, C13H_3), 2.48–2.33 (1H, m, C1$\underline{H_A}H_B$), 2.33–2.22 (1H, m, C1$H_A\underline{H_B}$), 2.22–2.11 (1H, m, C2$\underline{H_A}H_B$), 2.05–1.93 (1H, m, C2$H_A\underline{H_B}$), 1.48 (3H, s, C6H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 216.0 (C5), 150.6 (C7), 135.8 (C12), 128.4 (C9H), 122.0 (C11H), 118.2 (C10H), 107.0 (C8H), 78.8 (C4H), 49.7 (C3), 38.3 ($C1H_2$), 35.2 ($C2H_2$), 33.5 ($C13H_3$), 24.9 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 202.1227; $[C_{13}H_{16}ON]^+$ requires 202.1226, Δ 0.05 ppm.

(3a*R,8b*S**)-4-Benzyl-8b-methyl-1,3a,4,8b-tetrahydrocyclopenta[*b*]indol-3(2*H*)-one, 200**



Prepared according to **General Procedure E** with 2-(benzyl(phenyl)amino)-3-methylcyclopent-2-en-1-one (**174**) (83.2 mg, 0.30 mmol, 1.00 equiv.). Purification by flash column chromatography (7:1→6:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-4-benzyl-8b-methyl-1,3a,4,8b-tetrahydrocyclopenta[*b*]indol-3(2*H*)-one (**200**) as a yellow oil. (73.6 mg, 0.27 mmol, 88%).

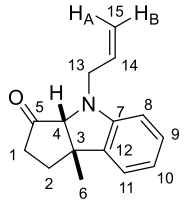
IR (film) ν_{max}/cm^{-1} = 3028, 2955, 1738, 1603, 1481, 1452, 1351, 1310, 1178, 1158, 1077, 1026, 913, 743, 698.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.14 (5H, m, C15H, C16H, C17H, C18H & C19H), 7.07–6.96 (2H, m, C9H & C11H), 6.66 (1H, td, *J* = 7.4, 0.9 Hz, C10H), 6.33 (1H, d, *J* = 7.8 Hz, C8H), 4.52 (1H, d, *J* = 15.9 Hz, $C13\underline{H_A}H_B$), 4.44 (1H, d, *J* = 15.8 Hz, $C13H_A\underline{H_B}$), 3.32 (1H, s, C4H), 2.41–2.26 (1H, m, 1H), 2.26–2.11 (2H, m, 2H), 2.00–1.86 (1H, m, 1H), 1.39 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 216.6 (C5), 149.7 (C7), 138.0 (C14), 135.3 (C12), 128.6 (C15H & C19H), 128.4 (C9H), 127.7 (C16H & C18H), 127.2 (C17H), 122.3 (C11H), 118.1 (C10H), 106.9 (C8H), 75.3 (C4), 49.6 (C3), 49.5 ($C13H_2$), 38.3 ($C1H_2$), 34.8 ($C2H_2$), 25.9 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 278.1539; $[C_{19}H_{20}ON]^+$ requires 278.1539, Δ -0.26 ppm.

(3a*R,8b*S**)-4-Allyl-8b-methyl-1,3a,4,8b-tetrahydrocyclopenta[*b*]indol-3(2*H*)-one, 201**



Prepared according to **General Procedure E** with 2-(allyl(phenyl)amino)-3-methylcyclopent-2-en-1-one (**173**) (68.1 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (20:1→10:1 v/v Petrol ether 40–60:Et_2O) gave (3a*R**,8b*S**)-4-allyl-8b-methyl-1,3a,4,8b-tetrahydrocyclopenta[*b*]indol-3(2*H*)-one (**201**) as a yellow oil (45.2 mg, 0.199 mmol, 66%).

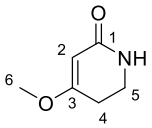
IR (film) ν_{max}/cm^{-1} = 2956, 2922, 2867, 1740, 1604, 1482, 1462, 1255, 1159, 1133, 1024, 991, 921, 744.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.15–7.05 (2H, m, C9H & C11H), 6.72 (1H, t, *J* = 7.4 Hz, C10H), 6.46 (1H, d, *J* = 7.8 Hz, C8H), 5.89–5.74 (m, C14H), 5.26 (1H, dt, *J* = 17.2, 1.6 Hz, $C15H_A$), 5.19 (1H, dt, *J* = 10.1, 1.5 Hz, $C15H_B$), 4.03–3.86 (2H, m, $C13H_2$), 3.42 (1H, s, C4H), 2.46–2.32 (1H, m, $C1\underline{H_A}H_B$), 2.32–2.14 (2H, m, $C1H_A\underline{H_B}$ & $C2\underline{H_A}H_B$), 2.08–1.93 (1H, m, $C2H_A\underline{H_B}$), 1.47 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 216.3 (C5), 149.4 (C7), 135.8 (C12), 133.1 (C14H), 128.3 (C9H), 122.2 (C11H), 118.1 (C10H), 117.5 ($C15H_2$), 107.3 (C8H), 75.7 (C4H), 49.6 (C3), 48.6 ($C13H_2$), 38.1 ($C1H_2$), 35.3 ($C2H_2$), 25.6 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 228.1384; $[C_{15}H_{18}ON]^+$ requires 228.1383, Δ 0.47 ppm.

4-Methoxy-5,6-dihydropyridin-2(1*H*)-one, 206



Modified literature procedure.[95] To a solution of 2,4-piperidinedione (56.6 mg, 0.50 mmol, 1.00 equiv.) in methanol (1.0 mL) was added methyl orthoformate (0.11 ml, 1.00 mmol, 2.00 equiv.) and *p*-toluenesulfonic acid (10 mg, 0.05 mmol, 0.100 equiv.) and the mixture heated under reflux (70 °C) for 1 h. The solvent was then removed *in vacuo* and the residue dissolved in toluene before being heated to reflux (140 °C) for 5 h. The mixture was cooled to ambient temperature and potassium carbonate (30 mg, 0.22 mmol, 0.500 equiv.) was added. The mixture was then stirred overnight at ambient temperature before the solvent was removed *in vacuo*. The residue was then dissolved in EtOAc (5 mL) and washed with water (5 mL) and brine (2 × 5 mL). The organic layer was then dried (Na_2SO_4), filtered and the solvents removed *in vacuo* to afford crude 4-methoxy-5,6-dihydropyridin-2(1*H*)-one (**206**) as an off-white solid (28.9 mg, 0.225 mmol, 45% yield). The product was then used without further purification.

m.p. = 105–107 °C (lit. 115-117 °C).

IR (film) ν_{max}/cm^{-1} = 3273, 2917, 2850, 1651, 1610, 1454, 1382, 1336, 1227, 1197, 1171, 1120, 1008, 825.

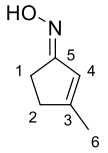
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.90 (1H, br s, NH), 5.05 (1H, s, C2H), 3.68 (3H, s, $C6H_3$), 3.41 (2H, td, J = 7.1, 2.6 Hz, $C5H_2$), 2.44 (2H, t, J = 7.0 Hz, $C4H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 170.5 (C1), 169.9 (C3), 93.8 (C2H), 55.7 ($C6H_3$), 38.8 ($C5H_2$), 27.8 ($C4H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 128.0707; $[C_6H_{10}O_2N]^+$ requires 128.0706, Δ 0.45 ppm.

The data matched that reported in the literature.[95]

3-Methylcyclopent-2-en-1-one oxime, 208



Modified literature procedure.[96] To a solution of 3-methyl-2-cyclopenten-1-one (10.3 g, 107 mmol, 1.00 equiv.) in methanol (200 mL) was added sodium acetate (21.2 g, 258 mmol, 1.20 equiv.), hydroxylamine hydrochloride (8.70 g, 125 mmol, 2.40 equiv.) and water (40 mL). The mixture was refluxed (70 °C) for 23 h before being cooled to ambient temperature and the solvents removed *in vacuo*. Water (50 mL) was added and the product extracted with chloroform (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (40 mL), brine (40 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Crude 3-methylcyclopent-2-en-1-one oxime (**208**) was obtained as a white solid (9.96 g, 89.6 mmol, 84% yield, 4:1 d.r. *E*:*Z*) and was used without further purification.

Only NMR peaks corresponding to the major diastereomer are reported.

m.p. = 118–120 °C

IR (film) ν_{max}/cm^{-1} = 3175, 3093, 2868, 1657, 1621, 1486, 1437, 1378, 1330, 1308, 1251, 1221, 1156, 984, 959, 949, 908, 842, 811, 717.

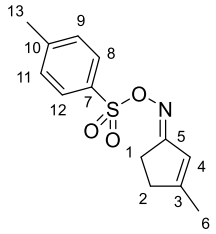
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.06 (1H, s, O<u>H</u>), 5.92 (1H, h, *J* = 1.6 Hz, C4H), 2.76–2.68 (2H, m, $C1H_2$), 2.50–2.40 (2H, m, $C2H_2$), 1.93 (3H, q, *J* = 1.3 Hz, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 169.3 (C3), 158.8 (C5), 123.9 (C4H), 34.9 ($C2H_2$), 25.8 ($C1H_2$), 18.0 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 112.0758; $[C_6H_{10}ON]^+$ requires 112.0757, Δ 1.29 ppm.

The data matched that reported in the literature.[147]

3-Methylcyclopent-2-en-1-one *O*-tosyl oxime, 209



Modified literature procedure.[96] To a solution of 3-methylcyclopent-2-en-1-one oxime (**208**) (8.43 g, 75.9 mmol, 1.00 equiv.) in pyridine (57 mL) at 0 °C under argon was added *p*-toluenesulfonyl chloride (17.3 g, 90.7 mmol, 1.20 equiv.) and the mixture stirred for 3 h. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution (100 mL) and the solvents removed *in vacuo*. Water (50 mL) was added and the product extracted with EtOAc (3 × 30 mL). The combined organic layers were successively washed with 3 M aqueous hydrochloric acid (50 mL), water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Crude 3-methylcyclopent-2-en-1-one *O*-tosyl oxime (**209**) obtained from this procedure (16.4 g, 61.7 mmol, 81% yield, 5:1 d.r. *E*:*Z*) was used without further purification.

Only NMR peaks corresponding to the major diastereomer are reported.

m.p. = 82–84 °C

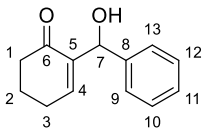
IR (film) ν_{max}/cm^{-1} = 3074, 2914, 1620, 1597, 1439, 1365, 1340, 1296, 1189, 1177, 1091, 972, 853, 806, 705, 683, 659.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.87–7.81 (2H, m, C9H & C11H), 7.33–7.28 (2H, m, C8H & C12H), 5.86 (1H, h, J = 1.6 Hz, C4H), 2.80–2.72 (2H, m, $C1H_2$), 2.50–2.43 (2H, m, $C2H_2$), 2.41 (3H, s, $C13H_3$), 1.94 (3H, q, J = 1.2 Hz, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 176.9 (C3), 165.7 (C5), 144.8 (C7), 133.0 (C10), 129.6 (C8H & C12H), 128.7 (C9H & C11H), 122.2 (C4H), 35.0 ($C2H_2$), 27.7 ($C1H_2$), 21.7 ($C13H_3$), 18.3 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 266.0846; $[C_{13}H_{16}O_3NS]^+$ requires 266.0845, Δ 0.09 ppm.

2-(Hydroxy(phenyl)methyl)cyclohex-2-en-1-one, 213



Modified literature procedure.[98] To a mixture of 2-cyclohexen-1-one (0.774 mL, 769 mg, 8.00 mmol, 1.00 equiv.) and benzaldehyde (0.813 mL, 849 mg, 8.00 mmol, 1.00 equiv.) under an atmosphere of nitrogen was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.20 mL, 1.22 g, 8.00 mmol, 1.00 equiv.) and the resulting mixture stirred for 1 h. The reaction was then diluted with Et_2O (30 mL), and washed with 1 M aqueous hydrochloric acid (30 mL) and water (20 mL). The organic phase was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:EtOAc) gave 2-(hydroxy(phenyl)methyl)cyclohex-2-en-1-one (**213**) as a yellow oil (584 mg, 2.89 mmol, 36%).

IR (neat) ν_{max}/cm^{-1} = 3409, 3060, 3030, 2926, 2869, 2826, 1659, 1602, 1585, 1492, 1453, 1427, 1374, 1322, 1247, 1193, 1170, 1134, 1103, 1079, 1033, 1020, 976, 916, 892, 871, 845, 800, 731, 699, 666, 629, 606.

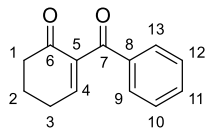
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.20 (4H, m, C9H, C10H, C12H & C13H), 7.20–7.10 (1H, m, C11H), 6.67 (1H, t, *J* = 4.2 Hz, C4H), 5.46 (1H, s, C7H), 3.49 (1H, br s, O<u>H</u>), 2.39–2.32 (2H, m, $C1H_2$), 2.32–2.24 (2H, m, $C3H_2$), 1.97–1.82 (2H, m, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.4 (C6), 147.4 (C4H), 141.8 (C5), 141.1 (C8), 128.3 (C10H & C12H), 127.5 (C11H), 126.5 (C9H & C13H), 72.3 (C7H), 38.6 ($C1H_2$), 25.8 ($C3H_2$), 22.6 ($C2H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 225.0887; $[C_{13}H_{14}O_2Na]^+$ requires 225.0886, Δ 0.57 ppm.

The data matched that reported in the literature.[148]

2-Benzoylcyclohex-2-en-1-one, 214



Modified literature procedure.[99] To a solution of 2-(hydroxy(phenyl)methyl)cyclohex-2-en-1-one (**213**) (202 mg, 1.00 mmol, 1.00 equiv.) in CH_2Cl_2 (4 mL) under an argon atmosphere was added Dess-Martin Periodinane (509 mg, 1.20 mmol, 1.20 equiv.) and the reaction stirred at ambient temperature for 23 h. The crude reaction mixture was concentrated *in vacuo*, before purification by flash column chromatography (3:1→2:2 v/v Petrol ether 40–60:EtOAc) gave 2-benzoylcyclohex-2-en-1-one (**214**) as a yellow oil (144 mg, 0.719 mmol, 72%).

IR (neat) ν_{max}/cm^{-1} = 3059, 2950, 2886, 1680, 1665, 1635, 1596, 1562, 1489, 1448, 1422, 1358, 1316, 1271, 1230, 1176, 1163, 1122, 1092, 1074, 1048, 1026, 1001, 979, 940, 914, 835, 814, 781, 725, 694.

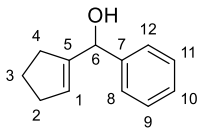
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.85–7.69 (2H, m, C9H & C13H), 7.61–7.50 (1H, m, C11H), 7.46–7.37 (2H, m, C10H & C12H), 7.24 (1H, t, J = 4.1 Hz, C4H), 2.64–2.51 (4H, m, $C1H_2$ & $C3H_2$), 2.21–2.10 (2H, m, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.5 (C6), 195.0 (C7), 152.1 (C4), 141.2 (C5), 136.8 (C8), 133.5 (C11H), 129.5 (C9H & C13H), 128.5 (C10H & C12H), 38.5 ($C1H_2$), 26.0 ($C3H_2$), 22.6 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 201.0911; $[C_{13}H_{13}O_2]^+$ requires 201.0910, Δ 0.19 ppm.

The data matched that reported in the literature.[99]

Cyclopent-1-en-1-yl(phenyl)methanol, 216



Modified literature procedure.[100] Lithium metal wire (463 mg, 66.7 mmol, 6.70 equiv.) was cut into small pieces (1 mm × 0.2 mm) and added to a dry flask under argon containing Et_2O (15 mL) and broken glass. 1-chlorocyclopent-1-ene (2.37 g, 23.1 mmol, 2.30 equiv.) was added in one portion and the mixture stirred for 3 h at ambient temperature, taking care to monitor the temperature in case of large rises. The mixture was then heated under reflux in a pre-heated oil bath (50 °C) for 1 h. The reaction was then cooled to ambient temperature and the supernatant transferred to another dry flask under argon by syringe. The grey slurry was diluted with further dry Et_2O (65 mL) before being cooled to -78 °C. A solution of benzaldehyde (1.06 g, 10.0 mmol. 1.00 equiv.) in dry Et_2O (40 mL) was added to

this slurry dropwise and the mixture stirred for 3 h at -78 °C before being quenched with isopropanol (15 mL) and allowed to warm to ambient temperature overnight. Saturated aqueous sodium bicarbonate solution (40 mL) was added and the mixture stirred vigorously for 10 minutes, before being extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (9:1→7:3 v/v Petrol ether 40–60:Et_2O) gave cyclopent-1-en-1-yl(phenyl)methanol (**216**) as a yellow oil (1.51 g, 8.67 mmol, 87%).

IR (film) ν_{max}/cm^{-1} = 3348, 2950, 2847, 1493, 1452, 1190, 1142, 1077, 1039, 1010, 951, 918, 798, 764, 699, 621.

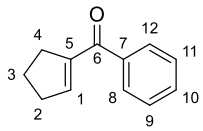
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.28 (4H, m, C8H, C9H, C11H & C12H), 7.28–7.18 (1H, m, C10H), 5.71–5.63 (1H, m, C1H), 5.29 (1H, s, C6H), 2.39–2.27 (2H, m, $C2H_2$), 2.22–2.12 (2H, m, $C4H_2$), 1.97–1.91 (1H, m, O<u>H</u>), 1.91–1.75 (2H, m, $C3H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 146.5 (C5), 142.6 (C7), 128.5 (C8H & C12H), 127.7 (C10H), 126.5 (C9H & C11H), 126.3 (C1H), 74.1 (C6H), 32.4 ($C2H_2$), 31.7 ($C4H_2$), 23.5 ($C3H_2$).

HRMS (EI) Found $[M]^+$ = 174.1034; $[C_{12}H_{14}O]^+$ requires 174.1039, Δ 2.97 ppm.

The data matched that reported in the literature.[149,150]

Cyclopent-1-en-1-yl(phenyl)methanone, 215



Modified literature procedure.[101] To a solution of cyclopent-1-en-1-yl(phenyl)methanol (**216**) (1.31 g, 7.50 mmol, 1.00 equiv.) in CH_2Cl_2 (130 mL) was added activated manganese dioxide (13.0 g, 150 mmol, 20.0 equiv.) and the reaction stirred for 1 h. An additional

portion of manganese dioxide (13.0 g, 150 mmol, 20.0 equiv.) was added and the reaction stirred for a further 1 h until disappearance of the starting material by thin layer chromatography. The crude mixture was filtered through Celite® and the filter cake washed with CH_2Cl_2 (2 × 20 mL). The combined filtrate was then concentrated *in vacuo*. Purification by flash column chromatography (19:1→9:1 v/v Petrol ether 40–60:Et_2O) gave cyclopent-1-en-1-yl(phenyl)methanone (**215**) as a yellow oil (1.04 g, 6.01 mmol, 80%).

IR (film) ν_{max}/cm^{-1} = 3060, 2965, 2854, 1638, 1609, 1576, 1446, 1353, 1296, 1272, 1126, 957, 899, 754, 706, 697, 667.

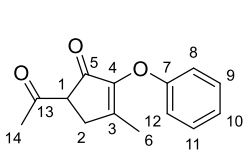
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.77–7.69 (2H, m, C8H & C12H), 7.57–7.47 (1H, m, C10H), 7.47–7.37 (2H, m, C9H & C11H), 6.57–6.50 (1H, m, C1H), 2.80–2.69 (2H, m, $C4H_2$), 2.67–2.56 (2H, m, $C2H_2$), 2.01 (2H, p, J = 7.5 Hz, $C3H_2$).

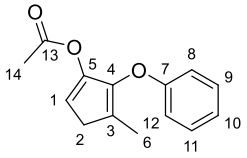
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.3 (C6), 147.1 (C1H), 144.6 (C5), 139.1 (C7), 131.9 (C10H), 128.9 (C8H & C12H), 128.3 (C9H & C11H), 34.5 ($C2H_2$), 32.0 ($C4H_2$), 22.9 ($C3H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 173.0961; $[C_{12}H_{13}O]^+$ requires 173.0961, Δ 0.23 ppm.

The data matched that reported in the literature.[151]

5-Acetyl-3-methyl-2-phenoxycyclopent-2-en-1-one, 218 and **4-methyl-5-phenoxycyclopenta-1,4-dien-1-yl acetate, 220**

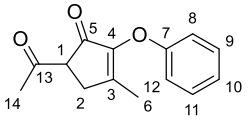


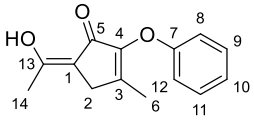


Modified literature procedure.[104] To a solution of diisopropylamine (392 µL, 283 mg, 2.80 mmol, 1.40 equiv.) in THF (10 mL) at -78 °C was added *n*-BuLi (2.5 M solution in

hexanes; 1.04 ml, 2.60 mmol, 1.30 equiv.) and the resulting solution stirred for 1 h at -78 °C. A solution of 3-methyl-2-phenoxycyclopent-2-en-1-one (**123**) (376 mg, 2.00 mmol, 1.00 equiv.) in THF (10 mL) was then added dropwise and the resulting mixture stirred for a further 30 mins at -78 °C. Acetic anhydride (284 µl, 306 mg, 3.00 mmol, 1.50 equiv.) was then added to the mixture slowly, and the resulting mixture stirred for an additional 2 h at -78 °C. After warming to ambient temperature, the mixture was quenched with saturated ammonium chloride solution (40 mL) and the organic layer separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic extracts washed with brine (40 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave 5-acetyl-3-methyl-2-phenoxycyclopent-2-en-1-one (**218**) as a viscous pale yellow oil (113 mg, 0.489 mmol, 24%) and 4-methyl-5-phenoxycyclopenta-1,4-dien-1-yl acetate (**220**) as a pale yellow oil (145 mg, 0.628 mmol, 31%).

Data for **5-acetyl-3-methyl-2-phenoxycyclopent-2-en-1-one, 218**





Compound exists as a 1:1 mixture of diketone:enol in $CDCl_3$.

IR (film) ν_{max}/cm^{-1} = 2917, 2849, 1759, 1704, 1688, 1616, 1591, 1490, 1421, 1381, 1336, 1258, 1220, 1207, 1178, 1079, 1023, 934, 857, 755, 690.

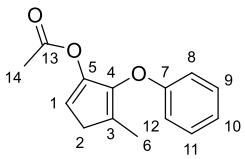
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.21 (4H, m, C9H & C11H diketone & enol), 7.08–6.98 (2H, m, C8H & C12H diketone or enol), 6.97–6.88 (2H, m, C8H & C12H diketone or enol), 6.86–6.79 (2H, m, C10H diketone & enol), 3.76 (1H, dd, *J* = 6.3, 2.3 Hz, C1H diketone), 3.15 (1H, ddq, *J* = 18.2, 2.3, 1.2 Hz, C2$\underline{H_A}H_B$ diketone), 3.11–3.08 (2H, m, $C2H_2$ enol), 2.56 (1H,

ddq, *J* = 18.2, 6.3, 1.2 Hz, $C2H_AH_B$ diketone), 2.41 (3H, s, $C14H_3$ diketone), 2.23 (1H, s, OH enol), 2.06 (3H, dd, *J* = 1.0 Hz, $C6H_3$ diketone), 2.05 (3H, t, *J* = 1.0 Hz, $C6H_3$ enol), 2.03 (3H, s, $C14H_3$ enol).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.2 (C13 diketone), 194.7 (C5 diketone), 191.9 (C5 enol), 168.3 (C13 enol), 161.2 (C3 diketone), 156.8 (C7 diketone or enol), 156.4 (C7 diketone or enol), 149.2 (C3 enol), 148.9 (C4 enol), 146.6 (C4 diketone), 129.7 (C9H & C11H diketone or enol), 129.6 (C9H & C11H diketone or enol), 122.8 (C10H diketone or enol), 122.6 (C10H diketone or enol), 115.8 (C8H & C12H diketone or enol), 115.5 (C8H & C12 diketone or enol), 107.0 (C1 enol), 58.2 (C1H diketone), 31.8 ($C2H_2$ enol), 30.4 ($C14H_3$ diketone), 29.5 ($C2H_2$ diketone), 18.8 ($C14H_3$ enol), 15.4 ($C6H_3$ diketone), 14.3 ($C6H_3$ enol).

HRMS (ESI^+) Found $[M+H]^+$ = 231.1015; $[C_{14}H_{15}O_3]^+$ requires 231.1016, Δ -0.30 ppm.

Data for **4-methyl-5-phenoxycyclopenta-1,4-dien-1-yl acetate, 220**



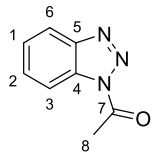
IR (film) ν_{max}/cm^{-1} = 2915, 1771, 1661, 1592, 1490, 1390, 1364, 1236, 1199, 1164, 1136, 1038, 973, 891, 838, 754, 690.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.18 (2H, m, C9H & C11H), 7.05–6.97 (1H, m, C10H), 6.97–6.88 (2H, m, C8H & C12H), 5.91 (1H, t, *J* = 2.0 Hz, $C1H_2$), 2.92 (2H, d, *J* = 2.0 Hz, $C2H_2$), 1.89 (3H, s, $C14H_3$), 1.84 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 168.3 (C13), 157.5 (C7), 146.5 (C5), 143.8 (C4), 129.5 (C9H & C11H), 124.6 (C3), 122.2 (C10H), 115.8 (C8H & C12H), 111.6 (C1H), 36.9 ($C2H_2$), 20.7 ($C14H_3$), 12.3 ($C6H_3$).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 253.0838; $[C_{14}H_{14}O_3Na]^+$ requires 253.0841, Δ -1.20 ppm.

1-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)ethan-1-one, S3



Modified literature procedure.[105] A solution of benzotriazole (11.9 g, 100 mmol, 1.00 equiv.) in CH_2Cl_2 (200 mL) under an argon atmosphere was cooled to 0 °C and Et_3N (17.0 ml, 120 mmol, 1.20 equiv.) was added dropwise. Acetyl chloride (7.82 ml, 8.64 g, 110 mmol, 1.10 equiv.) was then added and the mixture stirred at ambient temperature for 30 mins. The reaction was quenched by addition of 1M aqueous hydrochloric acid (150 mL) and the organic layer separated. The organic layer was then washed with further 1M aqueous hydrochloric acid (2 × 50 mL), water (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was then recrystalised from *n*-hexane to afford 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)ethan-1-one (**S3**) as off white needle-like crystals (11.0 g, 68.0 mmol, 68%).

m.p. = 46–48 °C (*n*-hexane) [lit. 51–52 °C]

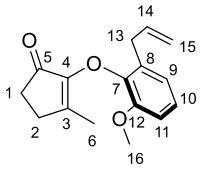
IR (film) ν_{max}/cm^{-1} = 3019, 1731, 1607, 1595, 1481, 1448, 1424, 1389, 1372, 1352, 1327, 1309, 1286, 1211, 1125, 1081, 1043, 954, 783, 772, 754, 687, 621.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.29 (1H, dt, *J* = 8.3, 1.0 Hz, C3H), 8.12 (1H, dt, *J* = 8.3, 1.0 Hz, C6H), 7.66 (1H, ddd, *J* = 8.2, 7.1, 1.0 Hz, C2H), 7.51 (1H, ddd, *J* = 8.2, 7.1, 1.1 Hz, C1H), 3.00 (3H, s, $C8H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 169.7 (C7), 146.4 (C5), 131.2 (C4), 130.6 (C2H), 126.3 (C1H), 120.3 (C6H), 114.6 (C3H), 23.4 ($C8H_3$).

The data matched that reported in the literature.[105]

2-(2-Allyl-6-methoxyphenoxy)-3-methylcyclopent-2-en-1-one, 225



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (224 mg, 2.00 mmol, 1.00 equiv.) and 2-allyl-6-methoxyphenol (493 mg, 3.00 mmol, 1.50 equiv.). Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave 2-(2-allyl-6-methoxyphenoxy)-3-methylcyclopent-2-en-1-one (**225**) as a colourless oil (282 mg, 1.09 mmol, 54%).

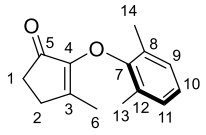
IR (neat) ν_{max}/cm^{-1} = 2913, 2839, 1709, 1652, 1583, 1476, 1439, 1385, 1334, 1272, 1211, 1175, 1079, 913, 754.

$^{-1}$H NMR ($CDCl_3$, 400 MHz) δ = 7.02 (1H, t, *J* = 7.9 Hz, C10H), 6.85–6.72 (2H, m, C9H & C11H), 5.94 (ddt, *J* = 16.8, 10.0, 6.7 Hz, C14H), 5.12–4.98 (2H, m, $C15H_2$), 3.74 (3H, s, $C16H_3$), 3.42 (2H, dt, *J* = 6.6, 1.5 Hz, $C13H_2$), 2.48–2.39 (2H, m, $C2H_2$), 2.39–2.32 (2H, m, $C1H_2$), 1.84 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.9 (C5), 151.7 (C12), 150.6 (C4), 149.6 (C3), 143.0 (C7), 136.6 (C14H), 133.0 (C8), 124.5 (C10H), 122.0 (C9H), 115.9 ($C15H_2$), 110.6 (C11H), 56.3 ($C16H_3$), 34.4 ($C13H_2$), 32.6 ($C1H_2$), 27.7 ($C2H_2$), 15.0 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 259.1339; $[C_{16}H_{19}O_3]^+$ requires 259.1334, Δ 1.9 ppm.

2-(2,6-Dimethylphenoxy)-3-methylcyclopent-2-en-1-one, 229



Prepared according to **General Procedure C** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and 2,6-dimethylphenol (458 mg, 3.75 mmol, 1.50 equiv.). Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:Et_2O) gave 2-(2,6-dimethylphenoxy)-3-methylcyclopent-2-en-1-one (**229**) as a white solid (373 mg, 1.73 mmol, 69%).

m.p. = 92–94 °C.

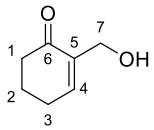
IR (film) ν_{max}/cm^{-1} = 2957, 2918, 1696, 1650, 1475, 1438, 1384, 1334, 1309, 1264, 1213, 1178, 1095, 1077, 991, 839, 767.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.03–6.91 (3H, m, C9H, C10H & C11H), 2.49–2.43 (2H, m, $C2H_2$), 2.43–2.37 (2H, m, $C1H_2$), 2.18 (6H, s, $C13H_3$ & $C14H_3$), 1.62 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.5 (C5), 152.6 (C7), 149.5 (C4), 147.7 (C3), 130.1 (C8 & C12), 128.6 (C9H & C11H), 124.7 (C10H), 32.4 ($C1H_2$), 28.2 ($C2H_2$), 16.6 ($C13H_3$ & $C14H_3$), 14.8 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 217.1224; $[C_{14}H_{17}O_2]^+$ requires 217.1223, Δ 0.39 ppm.

2-(Hydroxymethyl)cyclohex-2-en-1-one, 240



Modified literature procedure.[108] To a solution of 2-cyclohexen-1-one (0.968 mL, 961 mg, 10.0 mmol, 1.00 equiv.) in THF (5 mL) under an argon atmosphere was added 37% w/v formaldehyde aqueous solution (1.50 mL, 20.0 mmol, 2.00 equiv.) followed by DMAP (122 mg, 1.00 mmol, 0.10 equiv.), and the resulting solution was stirred at ambient temperature for 48 h. The reaction was quenched by addition of 1 M aqueous hydrochloric acid (≈ 1 mL) at 0 °C until the solution turned red in colour at pH 3. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave 2-(hydroxymethyl)cyclohex-2-en-1-one (**240**) as a colourless oil (554 mg, 4.39 mmol, 44%).

IR (neat) ν_{max}/cm^{-1} = 3418, 2929, 2870, 1661, 1455, 1393, 1249, 1173, 1136, 1110, 1077, 1037, 976, 909, 884, 860.

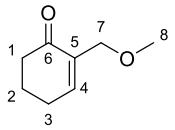
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.93 (1H, t, *J* = 4.2 Hz, C4H), 4.23 (2H, s, $C7H_2$), 2.55 (1H, br s, O<u>H</u>), 2.44 (2H, t, *J* = 6.6 Hz, $C1H_2$), 2.39 (2H, q, *J* = 5.3 Hz, $C3H_2$), 2.00 (2H, quint, *J* = 6.3 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.8 (C6), 147.1 (C4H), 138.3 (C5), 62.2 ($C7H_2$), 38.3 ($C1H_2$), 25.7 ($C3H_2$), 22.8 ($C2H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 149.0573; $[C_7H_{10}O_2Na]^+$ requires 149.0573, Δ 0.06 ppm.

The data matched that reported in the literature.[152]

2-(Methoxymethyl)cyclohex-2-en-1-one, 239



Modified literature procedure.[153] To a solution of 2-(hydroxymethyl)cyclohex-2-en-1-one (**240**) (252 mg, 2.00 mmol, 1.00 equiv.) in dry CH_2Cl_2 (10 mL) under an argon atmosphere was added Proton sponge® (N^1, N^1, N^8, N^8-tetramethylnaphthalene-1,8-diamine; 2.57 g, 12.0 mmol, 6.00 equiv.) in one portion. After cooling to 0 °C, trimethyloxonium tetrafluoroborate (887 mg, 6.00 mmol, 3.00 equiv.) was added in one portion. The reaction mixture was then warmed to ambient temperature and stirred for 3 h, before the reaction was quenched by addition of 1 M aqueous hydrochloric acid (20 mL). The crude mixture was then filtered and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:1 v/v pentane:Et_2O) gave 2-(methoxymethyl)cyclohex-2-en-1-one (**239**) as a colourless oil (147 mg, 1.04 mmol, 52%).

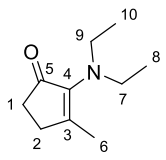
IR (neat) ν_{max}/cm^{-1} = 2920, 1669, 1455, 1430, 1402, 1336, 1251, 1198, 1174, 1138, 1086, 1050, 960, 908, 885, 861, 806, 702.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.96 (1H, t, *J* = 4.0 Hz, C4H), 4.03 (2H, s, $C7H_2$), 3.34 (3H, s, $C8H_3$), 2.45–2.33 (4H, m, $C1H_2$ & $C3H_2$), 1.97 (2H, quint, *J* = 6.3 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 198.7 (C6), 146.7 (C4H), 136.2 (C5), 69.2 ($C7H_2$), 58.8 ($C8H_3$), 38.3 ($C1H_2$), 25.8 ($C3H_2$), 22.8 ($C2H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 163.0729; $[C_8H_{12}O_2Na]^+$ requires 163.0730, Δ -0.55 ppm.

2-(Diethylamino)-3-methylcyclopent-2-en-1-one, 243



Prepared according to **General Procedure D** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and diethylamine (0.320 ml, 226 mg, 3.00 mmol, 1.20 equiv.). Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:Et_2O) gave 2-(diethylamino)-3-methylcyclopent-2-en-1-one (**243**) as a yellow oil (97.9 mg, 0.585 mmol, 23%).

IR (neat) ν_{max}/cm^{-1} = 2968, 2918, 2849, 1695, 1640, 1445, 1401, 1376, 1333, 1216, 1162, 1085, 1013, 953, 814, 636.

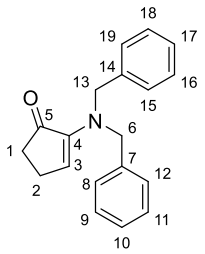
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.02 (4H, q, J = 7.2 Hz, C7H_2 & C9H_2), 2.51–2.43 (2H, m, C2H_2), 2.34–2.27 (2H, m, C1H_2), 2.01 (3H, s, C6H_3), 0.91 (6H, t, J = 7.2 Hz, C8H_3 & C10H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.4 (C5), 166.5 (C3), 145.6 (C4), 46.4 (C7H_2 & C9H_2), 33.8 (C1H_2), 29.6 (C2H_2), 17.2 (C6H_3), 13.9 (C8H_3 & C10H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 168.1383; $[C_{10}H_{18}ON]^+$ requires 168.1383, Δ 0.09 ppm.

The data matched that reported in the literature.[154]

2-(Dibenzylamino)cyclopent-2-en-1-one, 244



Prepared according to **General Procedure D** with 6-oxabicyclo[3.1.0]hexan-2-one (**131**) (245 mg, 2.50 mmol, 1.00 equiv.) and dibenzylamine (0.576 ml, 593 mg, 3.00 mmol, 1.20 equiv.). Purification by flash column chromatography (19:1 v/v Petrol ether

40–60:Et_2O) gave 2-(dibenzylamino)cyclopent-2-en-1-one (**244**) as a yellow oil (548 mg, 1.98 mmol, 79%).

IR (neat) ν_{max}/cm^{-1} = 3028, 2922, 1694, 1603, 1494, 1453, 1408, 1298, 1250, 1214, 1126, 1076, 1028, 993, 736, 699.

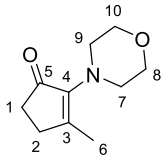
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.35–7.27 (4H, m, C8H, C12H, C15H & C19H), 7.27–7.20 (6H, m, C9H, C10H, C11H, C16H, C17H & C18H), 6.08 (1H, t, *J* = 3.2 Hz, C3H), 4.41 (4H, s, $C6H_2$ & $C13H_2$), 2.51–2.45 (2H, m, $C1H_2$), 2.44–2.38 (2H, m, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 205.5 (C5), 148.1 (C4), 138.4 (C7 & C14), 132.1 (C3H), 128.5 (C8H, C12H, C15H & C19H), 128.0 (C9H, C11H, C16H & C18H), 127.1 (C10H & C17H), 53.4 ($C6H_2$ & $C13H_2$), 35.7 ($C1H_2$), 23.2 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 278.1539; $[C_{19}H_{20}ON]^+$ requires 278.1539, Δ -0.04 ppm.

The data matched that reported in the literature.[155]

3-Methyl-2-morpholinocyclopent-2-en-1-one, 245



Prepared according to **General Procedure D** with 5-methyl-6-oxabicyclo[3.1.0]hexan-2-one (**132**) (280 mg, 2.50 mmol, 1.00 equiv.) and morpholine (0.262 ml, 261 mg, 3.00 mmol, 1.20 equiv.). Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:Et_2O) gave 3-methyl-2-morpholinocyclopent-2-en-1-one (**245**) as a yellow oil (304 mg, 1.68 mmol, 67%).

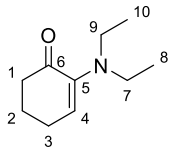
IR (neat) ν_{max}/cm^{-1} = 2955, 2913, 2850, 1691, 1624, 1451, 1387, 1263, 1195, 1112, 1068, 1015, 906, 881, 837, 699, 676.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.72 (4H, t, *J* = 4.6 Hz, C8H_2 & C10H_2), 3.11 (4H, t, *J* = 4.6 Hz, C7H_2 & C9H_2), 2.46–2.39 (2H, m, C2H_2), 2.35–2.28 (2H, m, C1H_2), 2.07 (3H, s, C6H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 206.9 (C5), 158.4 (C3), 146.3 (C4), 67.7 (C8H_2 & C10H_2), 50.1 (C7H_2 & C9H_2), 33.9 (C1H_2), 29.8 (C2H_2), 17.4 (C6H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 182.1176; $[C_{10}H_{16}O_2N]^+$ requires 182.1176, Δ 0.22 ppm.

2-(Diethylamino)cyclohex-2-en-1-one, 246



Prepared according to **General Procedure D** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (280 mg, 2.50 mmol, 1.00 equiv.) and diethylamine (0.320 ml, 226 mg, 3.00 mmol, 1.20 equiv.). Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:Et_2O) gave 2-(diethylamino)cyclohex-2-en-1-one (**246**) as a yellow oil (105 mg, 0.625 mmol, 25%).

IR (neat) ν_{max}/cm^{-1} = 2932, 1678, 1603, 1454, 1377, 1322, 1260, 1213, 1189, 1130, 1097, 1008, 880, 820, 785, 749.

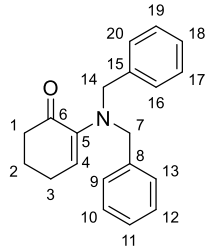
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.94 (1H, t, *J* = 4.5 Hz, C4H), 2.95 (4H, q, *J* = 7.0 Hz, C7H_2 & C9H_2), 2.49–2.35 (4H, m, C1H_2 & C3H_2), 1.98–1.87 (2H, m, C2H_2), 0.97 (6H, t, *J* = 7.1 Hz, C8H_3 & C10H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 197.7 (C6), 144.7 (C5), 129.2 (C4H), 44.3 ($C7H_2$ & $C9H_2$), 40.0 ($C1H_2$), 25.8 ($C3H_2$), 23.3 ($C2H_2$), 11.5 ($C8H_3$ & $C10H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 168.1382; $[C_{10}H_{18}ON]^+$ requires 168.1383, Δ -0.72 ppm.

The data matched that reported in the literature.[109]

2-(Dibenzylamino)cyclohex-2-en-1-one, 247



Prepared according to **General Procedure D** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (280 mg, 2.50 mmol, 1.00 equiv.) and dibenzylamine (0.576 ml, 593 mg, 3.00 mmol, 1.20 equiv.). Purification by flash column chromatography (9:1→17:3 v/v Petrol ether 40–60:Et_2O) gave 2-(dibenzylamino)cyclohex-2-en-1-one (**247**) as a white solid (362 mg, 1.24 mmol, 50%).

m.p. = 71–73 °C.

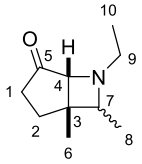
IR (neat) ν_{max}/cm^{-1} = 3027, 2936, 1676, 1604, 1494, 1453, 1366, 1249, 1181, 1115, 1076, 1028, 950, 909, 860, 826, 740, 698.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.25 (8H, m, C9H, C10H, C12H, C13H, C16H, C17H, C19H & C20H), 7.25–7.18 (2H, m, C11H & C18H), 5.79 (1H, t, J = 4.6 Hz, C4H), 4.06 (4H, s, $C7H_2$ & $C14H_2$), 2.50 (t, J = 6.5 Hz, $C1H_2$), 2.27 (q, J = 5.6 Hz, $C3H_2$), 1.89 (2H, quint, J = 6.4 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 197.4 (C6), 144.2 (C5), 138.4 (C8 & C15), 130.4 (C4H), 128.5 (C9H, C13H, C16H & C20H), 128.2 (C10H, C12H, C17H & C19H), 127.0 (C11H & C18H), 54.7 ($C7H_2$ & $C14H_2$), 40.1 ($C1H_2$), 25.7 ($C3H_2$), 23.1 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 292.1696; $[C_{20}H_{22}ON]^+$ requires 292.1696, Δ -0.12 ppm.

(1*S,5*R**)-6-Ethyl-1,7-dimethyl-6-azabicyclo[3.2.0]heptan-4-one, 250**



Prepared according to **General Procedure E** with 2-(diethylamino)-3-methylcyclopent-2-en-1-one (**243**) (50.2 mg, 0.300 mmol, 1.00 equiv.). Purification by flash column chromatography (10:1→1:1 v/v Petrol ether 40–60:Et_2O) gave (6-ethyl-1,7-dimethyl-6-azabicyclo[3.2.0]heptan-4-one (**250**) as a yellow oil (5.0 mg, 0.0299 mmol, 10%, 1:1 d.r.).

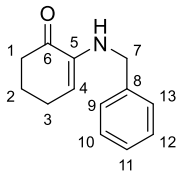
IR (neat) ν_{max}/cm^{-1} = 2967, 2917, 2849, 1731, 1566, 1462, 1376, 1344, 1297, 1214, 1171, 1111, 1065, 1032, 789.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.00–2.80 (m, 1H), 2.78–2.73 (m, 1H), 2.64–2.54 (m, 1H), 2.45–2.34 (m, 1H), 2.32–1.79 (m, 4H), 1.26–1.15 (m, 3H), 1.05–1.00 (m, 3H), 1.00–0.94 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.3, 74.8, 46.3, 45.6, 44.8, 37.3, 34.8, 34.2, 30.2, 27.4, 19.6, 19.2, 14.7, 14.3, 14.0, 13.9.

HRMS (ESI^+) Found $[M+H]^+$ = 168.1384; $[C_{10}H_{18}ON]^+$ requires 168.1383, Δ 0.84 ppm.

2-(Benzylamino)cyclohex-2-en-1-one, 256



Prepared according to **General Procedure D** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (561 mg, 5.00 mmol, 1.00 equiv.) and benzylamine (0.655 ml, 643 mg, 6.00 mmol, 1.20 equiv.). Purification by flash column chromatography (9:1→4:1 v/v Petrol ether 40–60:Et_2O) gave 2-(benzylamino)cyclohex-2-en-1-one (**256**) as a yellow-green solid (700 mg, 3.48 mmol, 70%).

m.p. = 56–58 °C.

IR (neat) ν_{max}/cm^{-1} = 3399, 3030, 2924, 2864, 2829, 1669, 1628, 1486, 1453, 1343, 1277, 1210, 1160, 1129, 1059, 1028, 970, 902, 868, 797, 740, 698.

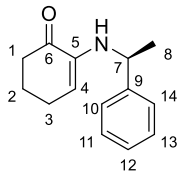
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.38–7.22 (5H, m, C9H, C10H, C11H, C12H & C13H), 5.43 (1H, t, *J* = 4.7 Hz, C4H), 4.61 (1H, br s, N<u>H</u>), 4.09 (2H, s, $C7H_2$), 2.49 (2H, t, *J* = 6.6 Hz, C1H), 2.34 (2H, q, *J* = 5.6 Hz, $C3H_2$), 1.96 (2H, quint, *J* = 6.3 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.0 (C6), 140.5 (C5), 139.1 (C8), 128.6 (C9H & C13H), 127.5 (C10H & C12H), 127.2 (C11H), 111.9 (C4H), 47.7 ($C7H_2$), 38.0 ($C1H_2$), 24.6 ($C3H_2$), 23.6 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 202.1226; $[C_{13}H_{16}ON]^+$ requires 202.1226, Δ -0.26 ppm.

The data matched that reported in the literature.[136]

(*S*)-2-((1-Phenylethyl)amino)cyclohex-2-en-1-one, 257



Prepared according to **General Procedure D** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (480 mg, 4.28 mmol, 1.00 equiv.) and (*S*)-1-phenylethan-1-amine (0.662 mL, 622 mg, 5.14 mmol, 1.20 equiv.) for 17 h. Purification by flash column chromatography (19:1→9:1 v/v Petrol ether 40–60:Et_2O) gave (*S*)-2-((1-phenylethyl)amino)cyclohex-2-en-1-one (**257**) as a yellow oil (749 mg, 3.48 mmol, 81%).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25.0}}$ = +10 °dm^2g^{-1} (*c* = 1.0, $CHCl_3$).

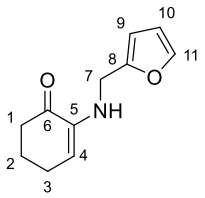
IR (neat) ν_{max}/cm^{-1} = 3402, 3029, 2926, 2866, 2830, 1669, 1627, 1486, 1450, 1415, 1372, 1355, 1342, 1276, 1218, 1195, 1161, 1136, 1123, 1077, 1015, 984, 946, 909, 867, 799, 762, 730, 700, 647.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.12 (5H, m, C10H, C11H, C12H, C13H & C14H), 5.12 (1H, t, *J* = 4.7 Hz, C4H), 4.58 (1H, s, N<u>H</u>), 4.09 (1H, q, *J* = 6.7 Hz, C7H), 2.41 (2H, td, *J* = 6.3, 2.2 Hz, $C1H_2$), 2.15 (2H, quint, *J* = 5.4 Hz, $C3H_2$), 1.82 (2H, quint, *J* = 6.1 Hz $C2H_2$), 1.39 (3H, d, *J* = 6.8 Hz, $C8H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.1 (C6), 145.1 (C5), 139.4 (C9), 128.6 (C11H & C13H), 126.8 (C12H), 125.8 (C10H & C14H), 113.0 (C4H), 53.1 (C7H), 37.9 ($C1H_2$), 25.1 ($C3H_2$), 24.5 ($C8H_3$), 23.5 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 216.1384; $[C_{14}H_{18}ON]^+$ requires 216.1383, Δ 0.35 ppm.

2-((Furan-2-ylmethyl)amino)cyclohex-2-en-1-one, 258



Prepared according to **General Procedure D** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (336 mg, 3.00 mmol, 1.00 equiv.) and 2-(aminomethyl)furan (0.318 mL, 350 mg, 3.60 mmol, 1.20 equiv.) for 20 h. Purification by flash column chromatography (9:1→4:1 v/v Petrol ether 40–60:Et_2O) gave 2-((furan-2-ylmethyl)amino)cyclohex-2-en-1-one (**258**) as a yellow oil (414 mg, 2.17 mmol, 72%).

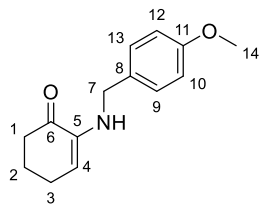
IR (neat) ν_{max}/cm^{-1} = 3398, 2927, 1669, 1630, 1485, 1455, 1340, 1277, 1196, 1161, 1129, 1074, 1012, 919, 884, 869, 801, 736.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.32 (1H, m, C11H), 6.34–6.28 (1H, m, C10H), 6.21–6.15 (1H, m, C9H), 5.54 (1H, t, J = 4.7 Hz, C4H), 4.54 (1H, br s, NH), 4.06 (2H, s, $C7H_2$), 2.48 (2H, t, J = 6.5 Hz, $C1H_2$), 2.36 (2H, q, J = 5.6 Hz, $C3H_2$), 1.95 (2H, quint, J = 6.1 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.8 (C6), 152.5 (C8), 142.0 (C11H), 140.3 (C5), 112.3 (C4H), 110.4 (C10H), 107.0 (C11H), 40.8 ($C7H_2$), 38.0 ($C1H_2$), 24.6 ($C3H_2$), 23.5 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 192.1019; $[C_{11}H_{14}O_2N]^+$ requires 192.1019, Δ -0.12 ppm.

2-((4-Methoxybenzyl)amino)cyclohex-2-en-1-one, 259



Prepared according to **General Procedure D** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (673 mg, 6.00 mmol, 1.00 equiv.) and 4-methoxybenzylamine (0.941 mL, 988 mg, 7.20 mmol, 1.20 equiv.) for 22 h. Purification by flash column chromatography (9:1→4:1 v/v Petrol ether 40–60:Et_2O) gave 2-((4-methoxybenzyl)amino)cyclohex-2-en-1-one (**259**) as an off-white solid (568 mg, 2.45 mmol, 41%).

m.p. = 56–58°C (*n*-hexane).

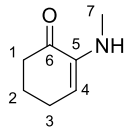
IR (neat) ν_{max}/cm^{-1} = 3403, 2917, 2832, 1662, 1623, 1612, 1585, 1509, 1495, 1467, 1453, 1433, 1416, 1356, 1341, 1283, 1246, 1213, 1179, 1168, 1159, 1126, 1108, 1087, 1068, 1032, 1011, 976, 928, 887, 869, 810, 797, 743, 721, 711, 698, 624.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.25–7.18 (2H, m, C9H & C13H), 6.90–6.82 (2H, m, C10H & C12H), 5.44 (1H, t, *J* = 4.7 Hz, C4H), 4.51 (1H, br s, NH), 4.00 (2H, d, *J* = 4.7 Hz, $C7H_2$), 3.80 (3H, s, $C14H_3$), 2.52–2.44 (2H, m, $C1H_2$), 2.39–2.30 (2H, m, $C3H_2$), 2.00–1.89 (2H, m, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.0 (C6), 158.9 (C11), 140.6 (C5), 131.2 (C8), 128.8 (C9H & C13H), 114.1 (C10H & C12H), 111.8 (C4H), 55.4 ($C14H_3$), 47.2 ($C7H_2$), 38.1 ($C1H_2$), 24.7 ($C3H_2$), 23.6 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 232.1334; $[C_{14}H_{18}O_2N]^+$ requires 232.1332, Δ 0.74 ppm.

2-(Methylamino)cyclohex-2-en-1-one, 260



Prepared according to **General Procedure D** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (1.12 g, 10.0 mmol, 1.00 equiv.) and 40 wt% methylamine aqueous solution (1.73 mL, 1.55 g, 20.0 mmol, 1.20 equiv.) for 19 h. Purification by flash column chromatography

(19:1→4:1 v/v Petrol ether 40–60:Et_2O) gave 2-(methylamino)cyclohex-2-en-1-one (**260**) as an orange liquid (457 mg, 3.65 mmol, 37%).

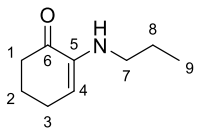
IR (neat) ν_{max}/cm^{-1} = 3406, 2922, 2827, 1668, 1627, 1489, 1441, 1425, 1339, 1280, 1203, 1176, 1151, 1128, 1074, 1039, 982, 886, 867, 795, 708.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.38 (1H, t, *J* = 4.7 Hz, C4H), 4.14 (1H, br s, NH), 2.60 (3H, s, $C7H_3$), 2.45 (2H, t, *J* = 6.1 Hz, $C1H_2$), 2.37 (2H, q, *J* = 5.6 Hz, $C3H_2$), 1.94 (2H, quint, *J* = 6.2 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.1 (C6), 141.8 (C5), 110.9 (C4H), 38.1 ($C1H_2$), 29.9 ($C7H_3$), 24.6 ($C3H_2$), 23.7 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 126.0913; $[C_7H_{12}ON]^+$ requires 126.0913, Δ -0.71 ppm.

2-(Propylamino)cyclohex-2-en-1-one, 261



Prepared according to **General Procedure D** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (561 mg, 5.00 mmol, 1.00 equiv.) and *n*-propylamine (0.617 mL, 443 mg, 7.50 mmol, 1.20 equiv.) for 4 h. Purification by flash column chromatography (19:1 v/v Petrol ether 40–60:EtOAc) gave 2-(propylamino)cyclohex-2-en-1-one (**261**) as a yellow oil (285 mg, 1.86 mmol, 37%).

IR (neat) ν_{max}/cm^{-1} = 3399, 2931, 2871, 2829, 1672, 1627, 1489, 1456, 1416, 1383, 1340, 1275, 1245, 1201, 1167, 1127, 1078, 1046, 999, 984, 897, 867, 793, 757, 709.

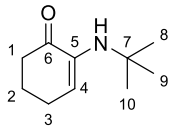
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.41 (1H, t, *J* = 4.7 Hz, C4H), 4.10 (1H, s, N<u>H</u>), 2.78 (2H, t, *J* = 7.1 Hz, $C7H_2$), 2.46 (2H, t, *J* = 6.7 Hz, $C1H_2$), 2.36 (2H, q, *J* = 5.6 Hz, $C3H_2$), 1.93 (2H, quint, *J* = 6.3 Hz, $C2H_2$), 1.56 (2H, quint, *J* = 7.3 Hz, $C8H_2$), 0.94 (3H, t, *J* = 7.3 Hz, $C9H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.1 (C6), 140.8 (C5), 111.0 (C4), 45.2 ($C7H_2$), 38.1 ($C1H_2$), 24.7 ($C3H_2$), 23.7 ($C2H_2$), 22.3 ($C8H_2$), 11.9 ($C9H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 154.1226; $[C_9H_{16}ON]^+$ requires 154.1226, Δ -0.24 ppm.

The data matched that reported in the literature.[136]

2-(*tert*-Butylamino)cyclohex-2-en-1-one, 262



Prepared according to **General Procedure D** with 7-oxabicyclo[4.1.0]heptan-2-one (**129**) (1.12 g, 10.0 mmol, 1.00 equiv.) and *tert*-butyl amine (1.26 ml, 878 mg, 12.0 mmol, 1.20 equiv.). Purification by flash column chromatography (7:1→5:1 v/v Petrol ether 40–60:Et_2O) gave 2-(*tert*-butylamino)cyclohex-2-en-1-one (**262**) as a yellow oil (465 mg, 2.78 mmol, 28%).

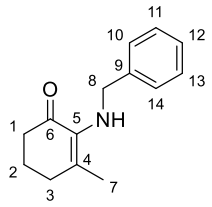
IR (neat) ν_{max}/cm^{-1} = 3387, 2968, 1672, 1625, 1502, 1456, 1390, 1364, 1334, 1278, 1234, 1195, 1153, 1125, 987, 967, 866, 798, 708.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.75 (1H, t, *J* = 4.8 Hz, C4H), 4.10 (1H, br s, N<u>H</u>), 2.45 (2H, t, *J* = 6.6 Hz, $C1H_2$), 2.37 (2H, q, *J* = 5.6 Hz, $C3H_2$), 1.91 (2H, quint, *J* = 6.2 Hz, $C2H_2$), 1.22 (9H, s, $C8H_3$, $C9H_3$ & $C10H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.9 (C6), 138.8 (C5), 115.0 (C4H), 50.2 (C7), 38.1 ($C1H_2$), 29.2 ($C8H_3$, $C9H_3$ & $C10H_3$), 25.1 ($C3H_2$), 23.4 ($C2H_2$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 168.1383; $[C_{10}H_{18}ON]^+$ requires 168.1383, Δ 0.27 ppm.

2-(Benzylamino)-3-methylcyclohex-2-en-1-one, 263



Prepared according to **General Procedure D** with 6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (379 mg, 3.00 mmol, 1.00 equiv.) and benzylamine (0.393 mL, 386 mg, 3.60 mmol, 1.20 equiv.) for 21 h. Purification by flash column chromatography (9:1→2:1 v/v Petrol ether 40–60:Et_2O) gave 2-(benzylamino)-3-methylcyclohex-2-en-1-one (**263**) as a yellow oil (426 mg, 1.98 mmol, 66%).

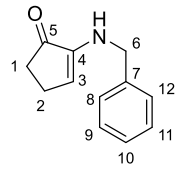
IR (neat) ν_{max}/cm^{-1} = 3323, 3062, 3028, 2937, 2865, 1661, 1633, 1482, 1453, 1374, 1346, 1326, 1292, 1249, 1191, 1169, 1134, 1091, 1058, 1029, 993, 922, 864, 823, 738, 699, 648.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.17 (5H, m, C10H, C11H, C12H, C13H & C14H), 4.21 (1H, br s, N<u>H</u>), 3.98 (2H, s, $C8H_2$), 2.43–2.37 (2H, m, $C1H_2$), 2.37–2.30 (2H, m, $C3H_2$), 1.97 (3H, t, J = 1.2 Hz, $C7H_3$), 1.90–1.78 (2H, m, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.2 (C6), 140.3 (C5), 140.0 (C4), 139.0 (C9), 128.5 (C10H & C14H), 127.8 (C11H & C13H), 127.1 (C12H), 52.5 ($C8H_2$), 37.1 ($C1H_2$), 32.4 ($C3H_2$), 22.1 ($C2H_2$), 20.4 ($C7H_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 216.1380; $[C_{14}H_{18}ON]^+$ requires 216.1383, Δ -1.55 ppm.

2-(Benzylamino)cyclopent-2-en-1-one, 264



Prepared according to **General Procedure D** with 6-oxabicyclo[3.1.0]hexan-2-one (**131**) (245 mg, 2.50 mmol, 1.00 equiv.) and benzylamine (0.328 ml, 322 mg, 3.00 mmol, 1.20 equiv.). Purification by flash column chromatography (9:1 v/v Petrol ether 40–60:Et_2O) gave 2-(benzylamino)cyclopent-2-en-1-one (**264**) as a yellow solid (381 mg, 2.03 mmol, 81%).

m.p. = 85–87 °C.

IR (neat) ν_{max}/cm^{-1} = 3377, 3062, 2920, 1693, 1635, 1493, 1453, 1405, 1361, 1326, 1288, 1213, 1141, 1028, 992, 772, 735, 698.

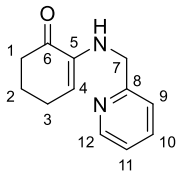
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.15 (5H, m, C8H, C9H, C10H, C11H & C12H), 5.83 (1H, t, J = 3.1 Hz, C3H), 4.20 (1H, br s, N<u>H</u>), 4.13 (2H, s, $C6H_2$), 2.43–2.38 (2H, m, $C2H_2$), 2.36–2.30 (2H, m, $C1H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 204.8 (C5), 146.2 (C4), 138.7 (C7), 128.7 (C8H & C12H), 127.4 (C9H & C11H), 127.4 (C10H), 122.3 (C3H), 48.7 ($C6H_2$), 33.7 ($C1H_2$), 23.7 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 188.1071; $[C_{12}H_{14}ON]^+$ requires 188.1070, Δ 0.77 ppm.

The data matched that reported in the literature.[156]

2-((Pyridin-2-ylmethyl)amino)cyclohex-2-en-1-one, 267



Modified literature procedure.[112] To a solution of 1,2-cyclohexanedione (561 mg, 5.00 mmol, 1.00 equiv.) in toluene (50 mL) was added 2-picolylamine (0.567 mL, 595 mg, 5.50 mmol, 1.10 equiv.), and the resulting solution was heated to reflux (140 °C) in a Dean-Stark water separator for 5 h. After cooling to ambient temperature, the reaction mixture was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated i*n vacuo*. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave 2-((pyridin-2-ylmethyl)amino)cyclohex-2-en-1-one (**267**) as an orange oil (406 mg, 2.01 mmol, 40%).

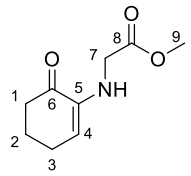
IR (neat) ν_{max}/cm^{-1} = 3051, 2938, 2865, 1669, 1627, 1591, 1571, 1474, 1456, 1435, 1398, 1341, 1277, 1197, 1162, 1130, 1099, 1048, 995, 914, 869, 755, 727, 642, 621.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.59–8.51 (1H, m, C12H), 7.63 (1H, td, *J* = 7.7, 1.8 Hz, C10H), 7.31–7.23 (1H, m, C9H), 7.19–7.11 (1H, m, C11H), 5.39 (1H, t, *J* = 4.7 Hz, C4H), 5.01 (1H, br s, NH), 4.23 (2H, s, $C7H_2$), 2.49 (2H, t, *J* = 6.8 Hz, $C1H_2$), 2.31 (2H, q, *J* = 5.5 Hz, $C3H_2$), 1.93 (2H, quint, *J* = 6.3 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.9 (C6), 158.9 (C8), 149.4 (C12H), 140.4 (C5), 136.7 (C10H), 122.1 (C11H), 121.3 (C9H), 112.2 (C4H), 49.2 ($C7H_2$), 38.1 ($C1H_2$), 24.6 ($C3H_2$), 23.6 ($C2H_2$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 203.1180; $[C_{12}H_{15}ON_2]^+$ requires 201.1179, Δ 0.6 ppm.

Methyl (6-oxocyclohex-1-en-1-yl)glycinate, 268



To a solution of 1,2-cyclohexanedione (561 mg, 5.00 mmol, 1.00 equiv.) in toluene (50 mL) was added sodium bicarbonate (462 mg, 5.50 mmol, 1.10 equiv.) and then glycine methyl ester hydrochloride salt (691 mg, 5.50 mmol, 1.10 equiv.). After effervescence had stopped, the mixture was then heated to reflux (140 °C) in a Dean-Stark water separator for 19.5 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (25 mL), washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:EtOAc) gave methyl (6-oxocyclohex-1-en-1-yl)glycinate (**268**) as a yellow oil (378 mg, 2.06 mmol, 41%).

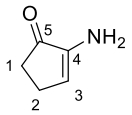
IR (neat) ν_{max}/cm^{-1} = 2400, 2021, 2951, 2867, 2832, 1745, 1671, 1631, 1487, 1438, 1322, 1276, 1201, 1167, 1133, 1098, 1077, 1046, 1014, 984, 921, 888, 870, 800, 709.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.33 (1H, t, *J* = 4.7 Hz, C4H), 4.72 (1H, t, *J* = 6.0 Hz, NH), 3.72 (3H, s, $C9H_3$), 3.66 (2H, d, *J* = 5.8 Hz, $C7H_2$), 2.47 (2H, t, *J* = 6.6 Hz, $C1H_2$), 2.32 (2H, q, *J* = 5.6 Hz, $C3H_2$), 1.92 (2H, quint, *J* = 6.3 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.2 (C6), 171.2 (C8), 139.9 (C5), 112.0 (C4H), 52.2 ($C9H_3$), 45.1 ($C7H_2$), 37.8 ($C1H_2$), 24.4 ($C3H_2$), 23.4 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 184.0970; $[C_9H_{14}O_3N]^+$ requires 184.0968, Δ 0.90 ppm.

2-Aminocyclopent-2-en-1-one, 270



Modified literature procedure.[113] 6-Oxabicyclo[3.1.0]hexan-2-one (**131**) (245 mg, 2.50 mmol, 1.00 equiv.) was dissolved in 35% w/v aqueous ammonia solution (10 mL) and the solution stirred vigorously at ambient temperature for 2 h. The solution was then neutralised to pH 7 by dropwise addition of concentrated hydrochloric acid, and then saturated by addition of solid sodium chloride. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1→1:2 v/v Petrol ether 40–60:Et_2O) gave 2-aminocyclopent-2-en-1-one (**270**) (3.0 mg, 0.031 mmol, 1.00 equiv.) as a yellow solid.

m.p. = 134–136 °C.

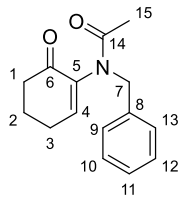
IR (neat) ν_{max}/cm^{-1} = 3364, 3104, 2916, 1699, 1635, 1523, 1441, 1410, 1351, 1304, 1257, 1131, 1055, 991, 948, 852, 778, 732.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.48 (1H, t, J = 3.2 Hz, C3H), 2.62–2.54 (2H, m, $C2H_2$), 2.42–2.35 (2H, m, $C1H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 203.6 (C5), 139.6 (C4), 127.1 (C3H), 32.5 ($C1H_2$), 24.0 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 98.0600; $[C_5H_8ON]^+$ requires 98.0600, Δ -0.17 ppm.

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)acetamide, 271**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (403 mg, 2.00 mmol, 1.00 equiv.), acetyl chloride (0.160 mL, 173 mg, 2.20 mmol, 1.10 equiv.), Et_3N (0.310 mL, 223 mg, 2.20 mmol, 1.10 equiv.) and CH_2Cl_2 (10 mL) for 16 h. Purification by flash column chromatography (1:1→1:2 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**271**) as an off white solid (447 mg, 1.84 mmol, 92%).

m.p. = 64–66 °C.

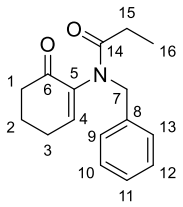
IR (neat) ν_{max}/cm^{-1} = 2945, 1673, 1646, 1621, 1497, 1428, 1393, 1359, 1295, 1259, 1208, 1162, 1135, 1030, 1010, 982, 930, 892, 825, 793, 727, 699, 641, 611.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–7.12 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.48 (1H, t, *J* = 4.3 Hz, C4H), 5.30 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.90 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 2.50–2.41 (2H, m, C1H_2), 2.38–2.26 (2H, m, C3H_2), 2.02–1.91 (2H, m, C2H_2), 1.87 (3H, s, C15H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 170.5 (C14), 149.5 (C4H), 139.5 (C5), 137.6 (C8), 129.1 (C9H & C13H), 128.5 (C10H & C12H), 127.5 (C11H), 50.6 (C7H_2), 38.5 (C1H_2), 26.0 (C3H_2), 22.5 (C2H_2), 22.0 (C15H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 244.1332; $[C_{15}H_{18}O_2N]^+$ requires 244.1332, Δ -0.17 ppm.

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)propionamide, 272**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (805 mg, 4.00 mmol, 1.00 equiv.), propionyl chloride (0.384 mL, 407 mg, 1.10 mmol, 1.10 equiv.), Et_3N (0.613 mL, 445 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (20 mL) for 18 h. Purification by flash column chromatography (3:2→1:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)propionamide (**272**) as an off-white solid (964 mg, 3.74 mmol, 94%).

m.p. = 55–57 °C.

IR (neat) ν_{max}/cm^{-1} = 3030, 2976, 2938, 2875, 1683, 1658, 1630, 1585, 1495, 1455, 1397, 1362, 1345, 1263, 1227, 1205, 1189, 1153, 1124, 1076, 1029, 1006, 976, 915, 888, 812, 756, 722, 702, 662, 618.

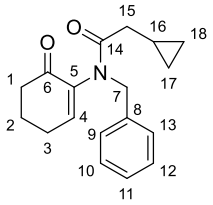
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.20 (3H, m, C10H, C11H & C12H), 7.20–7.14 (2H, m, C9H & C13H), 6.48 (1H, t, *J* = 4.3 Hz, C4H), 5.34 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.88 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 2.57–2.43 (2H, m, C1H_2), 2.41–2.26 (2H, m, C3H_2), 2.23–2.09 (1H, m, C15$\underline{H_A}H_B$), 2.06–1.89 (3H, m, C2H_2 & C15$H_A\underline{H_B}$), 1.08 (3H, t, *J* = 7.4 Hz, C16H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.2 (C6), 173.8 (C14), 149.6 (C4H), 139.0 (C5), 137.8 (C8), 129.1 (C9H & C13H), 128.4 (C10H & C12H), 127.4 (C11H), 50.7 (C7H_2), 38.6 (C1H_2), 27.2 (C15H_2), 26.0 (C3H_2), 22.5 (C2H_2), 9.7 (C16H_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 280.1307; $[C_{16}H_{19}O_2NNa]^+$ requires 280.1308, Δ -0.22 ppm.

The data matched that reported in the literature.[79]

***N*-Benzyl-2-cyclopropyl-*N*-(6-oxocyclohex-1-en-1-yl)acetamide, 273**



Prepared according to **General Procedure G** with cyclopropylacetic acid (110 mg, 1.10 mmol, 1.10 equiv.), oxalyl chloride (0.189 mL, 280 mg, 2.20 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (10 mL) for 21 h. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-2-cyclopropyl-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**273**) as a yellow oil (121 mg, 0.425 mmol, 43%).

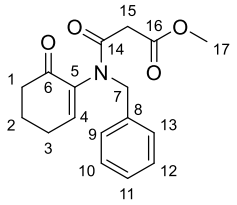
IR (neat) ν_{max}/cm^{-1} = 2930, 1685, 1659, 1630, 1495, 1400, 1342, 1260, 1224, 1189, 1154, 1122, 1079, 1018, 977, 840, 721, 702.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.16 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.48 (1H, t, *J* = 4.4 Hz, C4H), 5.37 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.90 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 2.55–2.30 (4H, m, C1H_2 & C3H_2), 2.11–1.87 (4H, m, C2H_2 & C15H_2), 1.10–0.97 (1H, m, C16H), 0.52 (2H, d, *J* = 8.3 Hz, C17$\underline{H_A}H_B$ & C18$\underline{H_A}H_B$), 0.17–0.00 (2H, m, C17$H_A\underline{H_B}$ & C18$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.2 (C6), 172.7 (C14), 149.6 (C4H), 139.0 (C5), 137.8 (C8), 129.2 (C9H & C13H), 128.5 (C10H & C12H), 127.5 (C11H), 50.7 (C7H_2), 39.1 (C15H_2), 38.6 (C1H_2), 26.0 (C3H_2), 22.5 (C2H_2), 7.6 (C16H), 4.7 (C17H_2), 4.5 (C18H_2).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 306.1464; $[C_{18}H_{21}O_2NNa]^+$ requires 306.1465, Δ -0.09 ppm.

Methyl 3-(benzyl(6-oxocyclohex-1-en-1-yl)amino)-3-oxopropanoate, 274



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), methyl malonyl chloride (0.118 mL, 150 mg, 1.10 mmol, 1.10 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (5 mL). Purification by flash column chromatography (1:1 v/v Petrol ether 40–60:EtOAc) gave methyl 3-(benzyl(6-oxocyclohex-1-en-1-yl)amino)-3-oxopropanoate (**274**) as a yellow oil (287 mg, 0.954 mmol, 95%).

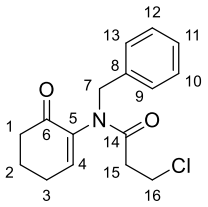
IR (neat) ν_{max}/cm^{-1} = 2952, 1739, 1684, 1660, 1631, 1496, 1399, 1326, 1252, 1205, 1153, 1125, 1080, 1006, 997, 913, 847, 721, 705, 665, 631.

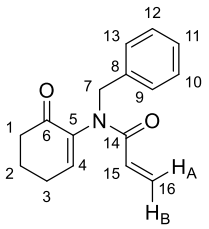
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.15 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.57 (1H, t, J = 4.3 Hz, C4H), 5.32 (1H, d, J = 14.5 Hz, C7$\underline{H_A}H_B$), 3.93 (1H, d, J = 14.6 Hz, C7$H_A\underline{H_B}$), 3.67 (3H, s, C17H_3), 3.22 (2H, s, C15H_2), 2.55–2.38 (2H, m, C1H_2), 2.38–2.20 (2H, m, C3H_2), 2.01–1.84 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.8 (C6), 168.2 (C16), 165.8 (C14), 150.9 (C4H), 138.2 (C5), 136.9 (C8), 129.0 (C9H & C13H), 128.5 (C10H & C12H), 127.6 (C11H), 52.4 (C17H_3), 50.9 (C7H_2), 41.7 (C15H_2), 38.3 (C1H_2), 26.0 (C3H_2), 22.2 (C2H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 302.1384; $[C_{17}H_{20}O_4N]^+$ requires 302.1387, Δ -0.85 ppm.

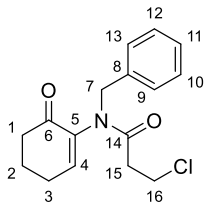
***N*-Benzyl-3-chloro-*N*-(6-oxocyclohex-1-en-1-yl)propanamide, 275** and ***N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)acrylamide, S4**





Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), 3-chloropropionyl chloride (0.166 mL, 283 mg, 1.65 mmol, 1.10 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 21 h. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-3-chloro-*N*-(6-oxocyclohex-1-en-1-yl)propanamide (**275**) as an off-white solid (321 mg, 1.10 mmol, 73%) and *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)acrylamide (**S4**) as a yellow oil (74.0 mg, 0.290 mmol, 19%).

Data for ***N*-benzyl-3-chloro-*N*-(6-oxocyclohex-1-en-1-yl)propanamide, 275**



m.p. = 53–55 °C.

IR (neat) ν_{max}/cm^{-1} = 3030, 2933, 1683, 1657, 1631, 1496, 1404, 1362, 1267, 1222, 1190, 1153, 1123, 1081, 1029, 1006, 977, 924, 885, 845, 805, 758, 722, 702, 660, 619.

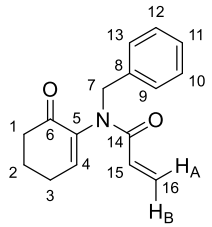
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.22 (3H, m, C10H, C11H & C12H), 7.21–7.14 (2H, m, C9H & C13H), 6.56 (1H, t, *J* = 4.3 Hz, C4H), 5.31 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.96 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.91–3.83 (1H, m, C16$\underline{H_A}H_B$), 3.75–3.65 (1H, m, C16$H_A\underline{H_B}$), 2.72–2.59

(1H, m, C15$\underline{H_A}H_B$), 2.55–2.44 (3H, m, C1H_2& C14$H_A\underline{H_B}$), 2.42–2.26 (2H, m, C3H_2), 2.03–1.90 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.0 (C6), 169.8 (C14), 150.2 (C4H), 138.5 (C5), 137.2 (C8), 129.0 (C9H & C13H), 128.5 (C10H & C12H), 127.6 (C11H), 51.0 (C7H_2), 40.3 (C16H_2), 38.4 (C1H_2), 36.7 (C15H_2), 26.0 (C3H_2), 22.4 (C2H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 292.1100; $[C_{16}H_{19}O_2NCl]^+$ requires 292.1099, Δ 0.45 ppm.

Data for ***N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)acrylamide, S4**



IR (neat) ν_{max}/cm^{-1} = 3030, 2931, 1684, 1655, 1616, 1496, 1454, 1410, 1339, 1261, 1229, 1188, 1153, 1123, 1080, 1059, 1030, 976, 919, 817, 791, 757, 722, 702, 662, 618.

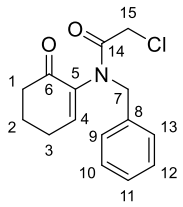
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.18 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.48 (1H, t, *J* = 4.4 Hz, C4H), 6.36 (1H, dd, *J* = 16.8, 1.9 Hz, C16H_A), 6.13 (1H, dd, *J* = 16.8, 10.2 Hz, C15H), 5.58 (1H, dd, *J* = 10.2, 1.8 Hz, C16H_B), 5.37 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 4.02 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 2.49–2.43 (2H, m, C1H_2), 2.40–2.30 (2H, m, C3H_2), 2.00–1.93 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.8 (C6), 165.8 (C14), 149.8 (C4H), 138.3 (C5), 137.3 (C8), 129.1 (C9H & C13H), 128.4 (C10H & C12H), 128.1 (C15H), 128.1 (C16H_2), 127.5 (C11H), 50.7 (C7H_2), 38.4 (C1H_2), 26.0 (C3H_2), 22.4 (C2H_2).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 278.1151; $[C_{16}H_{17}O_2NNa]^+$ requires 278.1152, Δ -0.03 ppm.

The data matched that reported in the literature.[157]

***N*-Benzyl-2-chloro-*N*-(6-oxocyclohex-1-en-1-yl)acetamide, 276**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (403 mg, 2.00 mmol, 1.00 equiv.), 2-chlorocaetyl chloride (0.175 mL, 248 mg, 2.20 mmol, 1.10 equiv.), Et_3N (0.307 mL, 223 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (10 mL) for 14 h. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-2-chloro-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**276**) as a yellow oil (450 mg, 1.62 mmol, 81%).

IR (neat) ν_{max}/cm^{-1} = 3031, 2950, 2870, 1682, 1632, 1585, 1496, 1454, 1396, 1360, 1343, 1255, 1227, 1205, 1189, 1152, 1124, 1080, 1050, 1028, 1006, 977, 915, 876, 834, 791, 754, 701, 665, 620.

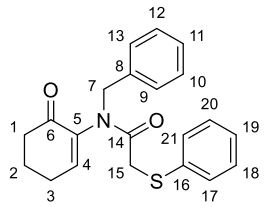
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.23 (3H, m, C10H, C11H & C12H), 7.22–7.13 (2H, m, C9H & C13H), 6.63 (1H, t, *J* = 4.3 Hz, C4H), 5.26 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 4.00 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.87 (2H, s, C15H_2), 2.57–2.42 (2H, m, C1H_2), 2.42–2.25 (2H, m, C3H_2), 2.06–1.87 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.9 (C6), 166.5 (C14), 150.8 (C4H), 137.7 (C5), 136.6 (C8), 129.1 (C9H & C13H), 128.6 (C10H & C12H), 127.8 (C11H), 51.4 (C7H_2), 41.7 (C15H_2), 38.3 (C1H_2), 26.0 (C3H_2), 22.3 (C2H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 278.0944; $[C_{15}H_{17}O_2NCl]^+$ requires 278.0942, Δ 0.57 ppm.

The data matched that reported in the literature.[112]

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(phenylthiol)acetamide, 277**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), (phenylthiol)acetyl chloride (0.163 mL, 205 mg, 1.10 mmol, 1.10 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (10 mL) for 18 h. Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(phenylthiol)acetamide (**277**) as an orange oil (269 mg, 0.764 mmol, 76%).

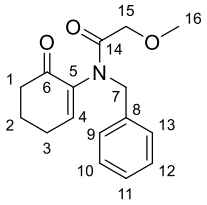
IR (neat) ν_{max}/cm^{-1} = 3030, 2926, 1682, 1656, 1629, 1583, 1495, 1481, 1454, 1438, 1391, 1360, 1342, 1292, 1217, 1188, 1152, 1123, 1079, 1026, 1004, 976, 907, 835, 740, 721, 692, 665, 616.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41–7.34 (2H, m, C17H & C21H), 7.28–7.11 (8H, m, C9H, C10H, C11H, C12H, C13H, C18H, C19H & C20H), 6.34 (1H, t, *J* = 4.3 Hz, C4H), 5.31 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.90 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.53 (1H, d, *J* = 14.1 Hz, C15$\underline{H_A}H_B$), 3.47 (1H, d, *J* = 14.2 Hz, C15$H_A\underline{H_B}$), 2.52–2.37 (2H, m, C1H_2), 2.30–2.18 (2H, m, C3H_2), 1.94–1.86 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.0 (C6), 168.7 (C14), 150.4 (C4H), 138.1 (C5), 137.0 (C8), 135.3 (C16), 130.4 (C17H & C21H), 129.0 (C9H, C13H, C18H & C20H), 128.4 (C10H & C12H), 127.5 (C11H), 127.0 (C19H), 51.1 (C7H_2), 38.4 (C1H_2), 37.3 (C15H_2), 25.9 (C3H_2), 22.2 (C2H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 352.1366; $[C_{21}H_{22}O_2NS]^+$ requires 352.1366, Δ 0.01 ppm.

***N*-Benzyl-2-methoxy-*N*-(6-oxocyclohex-1-en-1-yl)acetamide, 278**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), methoxyacetyl chloride (0.101 mL, 119 mg, 1.10 mmol, 1.10 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (5 mL) for 19 h. Purification by flash column chromatography (1:3 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-2-methoxy-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**278**) as a yellow oil (245 mg, 0.896 mmol, 90%).

IR (neat) ν_{max}/cm^{-1} = 2929, 1683, 1631, 1496, 1453, 1404, 1340, 1269, 1195, 1154, 1124, 1080, 1005, 976, 933, 839, 722, 702.

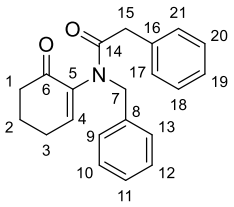
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–7.16 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.46 (1H, t, *J* = 4.3 Hz, C4H), 5.36 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.95 (2H, d, *J* = 13.9 Hz, C7$H_A\underline{H_B}$ & C15$\underline{H_A}H_B$), 3.80 (1H, d, *J* = 14.6 Hz, C15$H_A\underline{H_B}$), 3.34 (3H, s, C16H_3), 2.58–2.41 (2H, m, C1H_2), 2.41–2.22 (2H, m, C3H_2), 2.06–1.90 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.9 (C6), 169.3 (C14), 148.5 (C4H), 137.7 (C5) 137.1 (C8), 129.1 (C9H & C13H), 128.5 (C10H & C12H), 127.6 (C11H), 71.1 (C15H_2), 59.1 (C16H_3), 50.9 (C7H_2), 38.4 (C1H_2), 26.0 (C3H_2), 22.4 (C2H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 274.1435; $[C_{16}H_{20}O_3N]^+$ requires 274.1438, Δ -0.94 ppm.

The data matched that reported in the literature.[79]

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-phenylacetamide, 279**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (403 mg, 2.00 mmol, 1.00 equiv.), phenylacetyl chloride (0.290 mL, 340 mg, 2.20 mmol, 1.10 equiv.), Et_3N (0.310 mL, 223 mg, 2.20 mmol, 1.10 equiv.) and CH_2Cl_2 (10 mL) for 12 h. Purification by flash column chromatography (1:1→1:2 v/v Petrol ether 40–60:Et_2O) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-phenylacetamide (**279**) as an off–white solid (469 mg, 1.47 mmol, 73%).

m.p. = 109–111 °C from $CHCl_3$ (lit. 111–112 °C from EtOAc:Et_2O).

IR (neat) ν_{max}/cm^{-1} = 3029, 2931, 1684, 1656, 1632, 1603, 1584, 1495, 1454, 1396, 1361, 1344, 1263, 1233, 1191, 1152, 1123, 1080, 1005, 977, 912, 846, 721, 701.

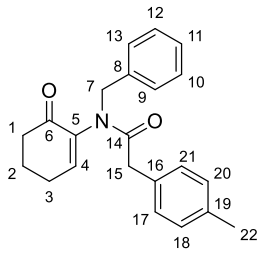
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.06 (10H, m, C9H, C10H, C11H, C12H, C13H, C17H, C18H, C19H, C20H & C21H), 6.15 (1H, t, *J* = 4.3 Hz, C4H), 5.32 (1H, d, *J* = 14.4 Hz, C7$\underline{H_A}H_B$), 3.83 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.50 (1H, d, *J* = 15.0 Hz, C15$\underline{H_A}H_B$), 3.36 (1H, d, *J* = 15.0 Hz, C15$H_A\underline{H_B}$), 2.36 (2H, t, *J* = 6.8 Hz, C1H_2), 2.23–2.12 (2H, m, C3H_2), 1.97–1.78 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.0 (C6), 170.8 (C14), 150.5 (C4H), 138.4 (C5), 137.4 (C16), 135.6 (C8), 129.0 (C17H & C21H), 128.9 (C9H & C13H), 128.5 (C18H & C20H), 128.4 (C10H & C12H), 127.4 (C19H), 126.7 (C11H), 50.7 (C7H_2), 41.6 (C15H_2), 38.4 (C1H_2), 25.9 (C3H_2), 22.3 (C2H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 320.1644; $[C_{21}H_{22}O_2N]^+$ requires 320.1645, Δ -0.43 ppm.

The data matched that reported in the literature.[79]

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(p-tolyl)acetamide, 280**



Prepared according to **General Procedure G** with *p*-tolylacetic acid (248 mg, 1.65 mmol, 1.10 equiv.), oxalyl chloride (0.283 mL, 419 mg, 3.30 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.70 equiv.) and CH_2Cl_2 (7.5 mL) for 17 h. Purification by flash column chromatography (4:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(p-tolyl)acetamide (**280**) as an off-white solid (203 mg, 0.610 mmol, 41%).

m.p. = 68–70 °C.

IR (neat) ν_{max}/cm^{-1} = 3029, 2924, 1685, 1656, 1631, 1515, 1496, 1454, 1416, 1394, 1361, 1343, 1263, 1234, 1191, 1152, 1123, 1080, 1028, 1006, 977, 919, 803, 778, 757, 722, 702.

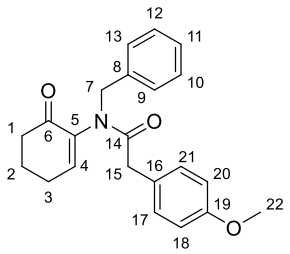
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.21 (3H, m, C10H, C11H & C12H), 7.19–7.15 (2H, m, C9H & C13H), 7.12–7.03 (4H, m, C17H, C18H, C20H & C21H), 6.23 (1H, t, *J* = 4.2 Hz, C4H), 5.39 (1H, d, *J* = 14.4 Hz, C7$\underline{H_A}H_B$), 3.90 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.52 (1H, d, *J* = 14.9 Hz, C15$\underline{H_A}H_B$), 3.38 (1H, d, *J* = 15.0 Hz, C15$H_A\underline{H_B}$), 2.47–2.41 (2H, m, C1H_2), 2.30 (3H, s, C22H_3), 2.27–2.20 (2H, m, C3H_2), 2.01–1.90 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 171.1 (C14), 150.5 (C4H), 138.5 (C5), 137.6 (C8), 136.3 (C19), 132.6 (C16), 129.3 (C17H & C21H), 129.1 (C9H & C13H), 128.8 (C18H & C20H),

128.4 (C10H & C12H), 127.4 (C11H), 50.7 ($C7H_2$), 41.3 ($C15H_2$), 38.5 ($C1H_2$), 26.0 ($C3H_2$), 22.4 ($C2H_2$), 21.2 ($C22H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 334.1805; $[C_{22}H_{24}O_2N]^+$ requires 334.18026, Δ 0.97 ppm.

_N_-Benzyl-2-(4-methoxyphenyl)-_N_-(6-oxocyclohex-1-en-1-yl)acetamide, 281



Prepared according to **General Procedure G** with 4-methoxyphenylacetic acid (274 mg, 1.65 mmol, 1.10 equiv.), oxalyl chloride (0.283 mL, 419 mg, 3.30 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 21 h. Purification by flash column chromatography (4:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-2-(4-methoxyphenyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**281**) as an off-white solid (283 mg, 0.810 mmol, 54%).

m.p. = 55–57 °C.

IR (neat) ν_{max}/cm^{-1} = 2934, 1684, 1656, 1631, 1612, 1584, 1511, 1454, 1425, 1395, 1343, 1301, 1246, 1177, 1152, 1123, 1080, 1032, 1006, 977, 918, 814, 783, 758, 723, 702.

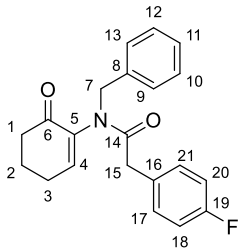
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.20 (3H, m, C10H, C11H & C12H), 7.20–7.13 (2H, m, C9H & C13H), 7.10 (2H, d, *J* = 8.1 Hz, C17H & C21H), 6.82 (2H, d, *J* = 8.5 Hz, C18H & C20H), 6.25 (1H, t, *J* = 4.3 Hz, C4H), 5.38 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.89 (1H, d, *J* = 14.5 Hz,

C7$H_A$$\underline{H_B}$), 3.77 (3H, s, C22$H_3$), 3.49 (1H, d, *J* = 14.9 Hz, C15$\underline{H_A}H_B$), 3.36 (1H, d, *J* = 15.0 Hz, C15$H_A$$\underline{H_B}$), 2.53–2.40 (2H, m, C1$H_2$), 2.33–2.18 (2H, m, C3$H_2$), 2.05–1.88 (2H, m, C2$H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 171.2 (C14), 158.5 (C19), 150.4 (C4H), 138.5 (C5), 137.6 (C8), 130.0 (C17H & C21H), 129.1 (C9H & C13H), 128.5 (C10H & C12H), 127.7 (C16), 127.5 (C11H), 114.0 (C18H & C20H), 55.4 (C22H_3), 50.8 (C7H_2), 40.7 (C15H_2), 38.5 (C1H_2), 26.0 (C3H_2), 22.5 (C2H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 350.1751; $[C_{22}H_{24}O_3N]^+$ requires 350.1751, Δ 0.20 ppm.

_N_-Benzyl-2-(4-fluorophenyl)-_N_-(6-oxocyclohex-1-en-1-yl)acetamide, 282



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), 4-fluorophenylacetyl chloride (0.226 mL, 285 mg, 1.65 mmol, 1.10 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 18 h. Purification by flash column chromatography (5:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-2-(4-fluorophenyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**282**) as an off-white solid (348 mg, 1.03 mmol, 69%).

m.p. = 96–98 °C.

IR (neat) ν_{max}/cm^{-1} = 2932, 1685, 1658, 1631, 1605, 1509, 1396, 1344, 1263, 1222, 1157, 1123, 1080, 1006, 817, 723, 702.

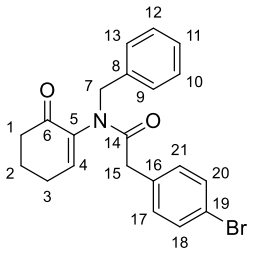
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28–7.23 (3H, m, C10H, C11H & C12H), 7.19–7.12 (4H, m, C9H, C13H, C17H & C21H), 6.97 (2H, t, *J* = 8.6 Hz, C18H & C20H), 6.31 (1H, t, *J* = 4.3 Hz, C4H), 5.36 (1H, d, *J* = 14.4 Hz, C7$\underline{H_A}H_B$), 3.92 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.49 (1H, d, *J* = 15.1 Hz, C15$\underline{H_A}H_B$), 3.40 (1H, d, *J* = 15.2 Hz, C15$H_A\underline{H_B}$), 2.51–2.42 (2H, m, C1H_2), 2.33–2.24 (2H, m, C3H_2), 2.01–1.92 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 170.8 (C14), 161.9 (d, *J* = 245.0 Hz, C19F), 150.3 (C4H), 138.7 (C5), 137.5 (C8), 131.3 (d, *J* = 3.1 Hz, C16), 130.7 (d, *J* = 7.9 Hz, C17H & C21H) 129.2 (C9H & C13H), 128.5 (C10H & C12H), 127.6 (C11H), 115.4 (d, *J* = 21.5 Hz, C18H & C20H), 51.0 (C7H_2), 40.6 (C15H_2), 38.5 (C1H_2), 26.1 (C3H_2), 22.5 (C2H_2).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -116.20 (tt, *J* = 8.9, 5.3 Hz, C19F).

HRMS (ESI^+) Found $[M+H]^+$ = 338.1551; $[C_{21}H_{21}O_2NF]^+$ requires 338.1551, Δ 0.11 ppm.

_N_-Benzyl-2-(4-bromophenyl)-_N_-(6-oxocyclohex-1-en-1-yl)acetamide, 283



Prepared according to **General Procedure G** with 4-bromophenylacetic acid (237 mg, 1.10 mmol, 1.10 equiv.), oxalyl chloride (0.189 mL, 280 mg, 2.20 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 18 h. Purification by flash column chromatography (4:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-2-(4-bromophenyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**283**) as an off-white solid (177 mg, 0.444 mmol, 44%).

m.p. = 94–96 °C.

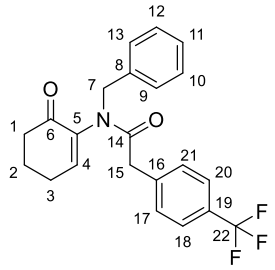
IR (neat) ν_{max}/cm^{-1} = 3030, 2929, 1684, 1658, 1632, 1488, 1454, 1394, 1344, 1262, 1232, 1198, 1152, 1123, 1071, 1012, 977, 919, 801, 722, 702, 613.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.38 (2H, d, *J* = 8.0 Hz, C18H & C20H), 7.26–7.21 (3H, m, C10H, C11H & C12H), 7.16–7.12 (2H, m, C9H & C13H), 7.04 (2H, d, *J* = 8.0 Hz, C17H & C21H), 6.29 (1H, t, *J* = 4.2 Hz, C4H), 5.32 (1H, d, *J* = 14.4 Hz, C7$\underline{H_A}H_B$), 3.90 (1H, d, *J* = 14.4 Hz, C7$H_A\underline{H_B}$), 3.44 (1H, d, *J* = 15.2 Hz, C15$\underline{H_A}H_B$), 3.35 (1H, d, *J* = 15.2 Hz, C15$H_A\underline{H_B}$), 2.47–2.41 (2H, m, C1H_2), 2.30–2.23 (2H, m, C3H_2), 1.98–1.89 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 170.4 (C14), 150.4 (C4H), 138.6 (C5), 137.4 (C16), 134.6 (C8), 131.7 (C18H & C20H), 130.9 (C17H & C21H), 129.2 (C9H & C13H), 128.5 (C10H & C12H), 127.6 (C11H), 120.8 (C19), 51.0 (C7H_2), 40.8 (C15H_2), 38.5 (C1H_2), 26.0 (C3H_2), 22.5 (C2H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 398.0751; $[C_{21}H_{21}O_2NBr]^+$ requires 398.0750, Δ 0.29 ppm.

_N_-Benzyl-_N_-(6-oxocyclohex-1-en-1-yl)-2-(4-(trifluoromethyl)phenyl)acetamide, 284



Prepared according to **General Procedure G** with 4-(trifluoromethyl)phenylacetic acid (337 mg, 1.65 mmol, 1.70 equiv.), oxalyl chloride (0.283 mL, 419 mg, 3.30 mmol, 3.40 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (192 mg, 0.950 mmol, 1.00 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.70 equiv.) and CH_2Cl_2 (7.5 mL) for 16 h. Purification by

flash column chromatography (4:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*--(6-oxocyclohex-1-en-1-yl)-2-(4-(trifluoromethyl)phenyl)acetamide (**284**) as an off-white solid (196 mg, 0.507 mmol, 53%).

m.p. = 89–91 °C.

IR (neat) ν_{max}/cm^{-1} = 2934, 1656, 1660, 1632, 1496, 1421, 1396, 1324, 1263, 1161, 1120, 1067, 1020, 977, 921, 818, 758, 702.

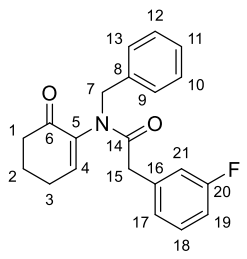
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.48 (2H, d, *J* = 7.9 Hz, C18H & C20H), 7.25 (2H, d, *J* = 7.9 Hz, C17H & C21H), 7.22–7.15 (3H, m, C10H, C11H & C12H), 7.11 (2H, d, *J* = 7.0 Hz, C9H & C13H), 6.30 (1H, t, *J* = 4.4 Hz, C4H), 5.27 (1H, d, *J* = 14.4 Hz, C7$\underline{H_A}H_B$), 3.89 (1H, d, *J* = 14.4 Hz, C7$H_A\underline{H_B}$), 3.49 (1H, d, *J* = 15.3 Hz, C15$\underline{H_A}H_B$), 3.42 (1H, d, *J* = 15.4 Hz, C15$H_A\underline{H_B}$), 2.48–2.37 (2H, m, C1H_2), 2.32–2.21 (2H, m, C3H_2), 1.98–1.86 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 170.2 (C14), 150.4 (C4H), 139.7 (C16), 138.6 (C5), 137.3 (C8), 129.6 (C17H & C21H), 129.2 (C9H, C13H & C19), 128.6 (C10H & C12H), 127.7 (C11H), 125.5 (q, *J* = 3.7 Hz, C18H & C20H), 123.0 (C22F_3), 51.1 (C7H_2), 41.0 (C15H_2), 38.5 (C1H_2), 26.0 (C3H_2), 22.5 (C2H_2).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -62.44 (s, C22F_3)

HRMS (ESI^+) Found $[M+H]^+$ = 388.1519; $[C_{22}H_{21}O_2NF_3]^+$ requires 388.1519, Δ -0.01 ppm.

_N_-Benzyl-2-(3-fluorophenyl)-_N_-(6-oxocyclohex-1-en-1-yl)acetamide, 285



Prepared according to **General Procedure G** with 3-fluorophenylacetic acid (170 mg, 1.10 mmol, 1.10 equiv.), oxalyl chloride (0.189 mL, 280 mg, 2.20 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (10 mL) for 18 h. Purification by flash column chromatography (4:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-2-(3-fluorophenyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**285**) as an off-white solid (153 mg, 0.455 mmol, 45%).

m.p. = 86–88 °C.

IR (neat) ν_{max}/cm^{-1} = 3031, 2930, 1685, 1657, 1632, 1616, 1589, 1488, 1449, 1428, 1396, 1361, 1344, 1265, 1190, 1152, 1124, 1080, 1029, 1004, 977, 955, 912, 875, 838, 757, 722, 702, 685.

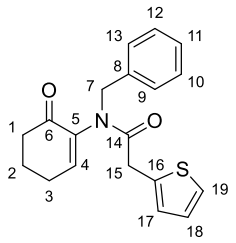
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.29 (4H, m, C9H, C11H, C13H & C18H), 7.28–7.22 (2H, m, C10H & C12H), 7.09–6.94 (3H, m, C17H, C19H & C21H), 6.38 (1H, t, *J* = 4.3 Hz, C4H), 5.43 (1H, d, *J* = 14.4 Hz, C7$H_A$$H_B$), 4.02 (1H, d, *J* = 14.4 Hz, C7$H_A$$H_B$), 3.61 (1H, d, *J* = 15.1 Hz, C15$H_A$$H_B$), 3.50 (1H, d, *J* = 15.2 Hz, C15$H_A$$H_B$), 2.58–2.51 (2H, m, C1$H_2$), 2.40–2.32 (2H, m, C3$H_2$), 2.09–2.00 (2H, m, C2$H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.0 (C6), 170.3 (C14), 162.9 (d, *J* = 245.6 Hz, C20F), 150.4 (C4H), 138.6 (C5), 138.1 (d, *J* = 7.8 Hz, C16), 137.4 (C8), 130.0 (d, *J* = 8.6 Hz, C18H), 129.2 (C10H & C12H), 128.5 (C9H & C13H), 127.6 (C11H), 124.8 (d, *J* = 3.0 Hz, C17H), 116.2 (d, *J* = 21.6 Hz, C21H), 113.8 (d, *J* = 21.2 Hz, C19H), 51.0 (C7H_2), 41.2 (C15H_2), 38.5 (C1H_2), 26.0 (C3H_2), 22.5 (C2H_2).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -113.22 (td, *J* = 9.4, 6.0 Hz, C20F).

HRMS (ESI^+) Found $[M+Na]^+$ = 360.1371; $[C_{21}H_{20}O_2NFNa]^+$ requires 360.1370, Δ 0.16 ppm.

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(thiophen-2-yl)acetamide, 286**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), 2-thiopheneacetyl chloride (0.136 mL, 177 mg, 1.10 mmol, 1.10 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (10 mL) for 18 h. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(thiophen-2-yl)acetamide (**286**) as an off-white solid (170 mg, 0.520 mmol, 52%).

m.p. = 107–109 °C.

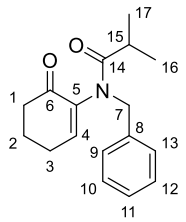
IR (neat) ν_{max}/cm^{-1} = 3030, 2926, 1684, 1659, 1631, 1495, 1454, 1399, 1344, 1262, 1233, 1186, 1154, 1123, 1079, 1029, 1006, 977, 919, 849, 821, 755, 703.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–7.23 (3H, m, C10H, C11H & C12H), 7.23–7.14 (3H, m, C9H, C13H & C19H), 6.93 (1H, dd, *J* = 5.2, 3.4 Hz, C18H), 6.85 (1H, d, *J* = 3.5 Hz, C17H), 6.37 (1H, t, *J* = 4.3 Hz, C4H), 5.38 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.95 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.70 (1H, d, *J* = 15.6 Hz, C15$\underline{H_A}H_B$), 3.66 (1H, d, *J* = 15.6 Hz, C15$H_A\underline{H_B}$), 2.58–2.40 (2H, m, C1H_2), 2.40–2.20 (2H, m, C3H_2), 2.06–1.89 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.0 (C6), 169.9 (C14), 150.6 (C4H), 138.4 (C5), 137.3 (C16), 137.0 (C8), 129.2 (C9H & C13H), 128.5 (C10H & C12H), 127.6 (C11H), 126.9 (C18H), 126.3 (C17H), 124.7 (C19H), 51.0 (C7H_2), 38.5 (C1H_2), 35.7 (C15H_2), 26.1 (C3H_2), 22.5 (C2H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 326.1211; $[C_{19}H_{20}NS]^+$ requires 326.1209, Δ 0.61 ppm.

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)isobutyramide, 287**



Prepared according to **General Procedure F** with 2-(benzylamino)cyclohex-2-en-1-one (**256**) (127 mg, 0.63 mmol, 1.00 equiv.), isobutyryl chloride (72.6 µL, 73.8 mg, 0.693 mmol, 1.10 equiv.), Et_3N (96.6 µL, 70.1 mg, 0.693 mmol, 1.10 equiv.) and CH_2Cl_2 (4 mL) for 22 h. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)isobutyramide (**287**) as a yellow oil (96.5 mg, 0.356 mmol, 56%).

IR (neat) ν_{max}/cm^{-1} = 3062, 3030, 2970, 2933, 2872, 1686, 1656, 1629, 1496, 1470, 1455, 1400, 1360, 1258, 1226, 1205, 1190, 1172, 1153, 1123, 1091, 1079, 1049, 1030, 1003, 977, 921, 873, 823, 801, 750, 722, 701, 658, 614.

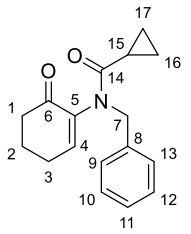
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.21 (3H, m, C10H, C11H & C12H), 7.21–7.14 (2H, m, C9H & C13H), 6.47 (1H, t, *J* = 4.3 Hz, C4H), 5.34 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.85 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 2.60–2.44 (2H, m, C1H_2), 2.43–2.24 (3H, m, C3H_2 & C15H), 2.08–1.86 (2H, m, C2H_2), 1.07 (6H, d, *J* = 6.7 Hz, C16H_3 & C17H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.3 (C6), 177.5 (C14), 148.7 (C4H), 139.1 (C5), 137.9 (C8), 129.0 (C9H & C13H), 128.5 (C10H & C12H), 127.4 (C11H), 50.7 (C7H_2), 38.6 (C1H_2), 32.1 (C15H), 26.0 (C3H_2), 22.5 (C2H_2), 20.5 (C16H_3), 19.3 (C17H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 272.1646; $[C_{17}H_{22}O_2N]^+$ requires 272.1645, Δ 0.50 ppm.

The data matched that reported in the literature.[79]

***N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)cyclopropanecarboxamide, 288**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), cyclopropanecarbonyl chloride (0.100 mL, 115 mg, 1.10 mmol, 1.10 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (5 mL). Purification by flash column chromatography (3:1→1:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)cyclopropanecarboxamide (**288**) as a yellow oil (243 mg, 0.902 mmol, 90%).

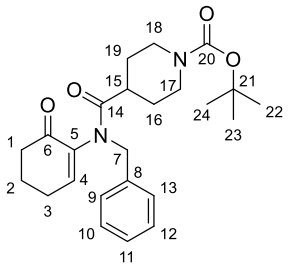
IR (neat) ν_{max}/cm^{-1} = 2931, 1685, 1651, 1628, 1496, 1311, 1364, 1261, 1229, 1201, 1153, 1123, 1080, 1031, 1002, 976, 911, 873, 825, 735, 702, 613.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.15 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.59 (1H, s, C4H), 5.36 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.95 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 2.60–2.45 (2H, m, C1H_2), 2.45–2.26 (2H, m, C3H_2), 2.09–1.90 (2H, m, C2H_2), 1.46–1.35 (1H, m, C15H), 1.12–0.95 (2H, m, C16$\underline{H_A}H_B$ & C17$\underline{H_A}H_B$), 0.74–0.61 (2H, m, C16$H_A\underline{H_B}$ & C16$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 173.7 (C14), 149.6 (C4H), 139.0 (C5), 137.9 (C8), 129.1 (C9H & C13H), 128.4 (C10H & C12H), 127.4 (C11H), 50.8 (C7H_2), 38.6 (C1H_2), 26.1 (C3H_2), 22.6 (C2H_2), 12.5 (C15H), 8.6 (C16H_2 & C17H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 270.1487; $[C_{17}H_{20}O_2N]^+$ requires 270.1489, Δ -0.42 ppm.

***tert*-Butyl 4-(benzyl(6-oxocyclohex-1-en-1-yl)carbamoyl)piperidine-1-carboxylate, 289**



Prepared according to **General Procedure G** with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (378 mg, 1.65 mmol, 1.10 equiv.), oxalyl chloride (0.283 mL, 419 mg, 3.30 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 18 h. Purification by flash column chromatography (1:1→1:3 v/v Petrol ether 40–60:EtOAc) gave *tert*-butyl 4-(benzyl(6-oxocyclohex-1-en-1-yl)carbamoyl)piperidine-1-carboxylate (**289**) as a white solid (242 mg, 0.586 mmol, 39%).

m.p. = 122–124 °C.

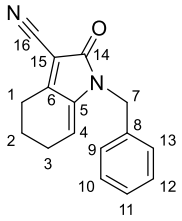
IR (neat) ν_{max}/cm^{-1} = 2928, 1685, 1655, 1631, 1452, 1404, 1365, 1343, 1276, 1221, 1167, 1123, 1077, 980, 919, 871, 816, 728, 701, 646.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–7.20 (3H, m, C10H, C11H & C12H), 7.17–7.13 (2H, m, C9H & C13H), 6.48 (1H, t, *J* = 4.2 Hz, C4H), 5.29 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 4.15–4.03 (2H, m, C17$\underline{H_A}H_B$ & C18$\underline{H_A}H_B$), 3.88 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 2.66–2.53 (2H, m, C17$H_A\underline{H_B}$ & C18$H_A\underline{H_B}$), 2.53–2.45 (2H, m, C1H_2), 2.40–2.29 (2H, m, C3H_2), 2.19–2.10 (1H, m, C15H), 2.00–1.92 (2H, m, C2H_2), 1.81–1.67 (2H, m, C16$\underline{H_A}H_B$ & C19$\underline{H_A}H_B$), 1.66–1.50 (2H, m, C16$H_A\underline{H_B}$ & C19$H_A\underline{H_B}$), 1.43 (9H, s, C22H_3, C23H_3 & C24H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.3 (C6), 174.9 (C14), 154.8 (C20), 148.9 (C4H), 138.9 (C5), 137.6 (C8), 129.0 (C9H & C13H), 128.5 (C10H & C12H), 127.5 (C11H), 79.6 (C21), 50.9 ($C7H_2$), 43.2 ($C17H_2$ & $C18H_2$), 40.5 (C15H), 38.5 ($C1H_2$), 29.3 ($C16H_2$), 28.5 ($C22H_3$, $C23H_3$ & $C24H_3$), 28.0 ($C19H_2$), 26.0 ($C3H_2$), 22.5 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 413.2424; $[C_{24}H_{32}O_4N_2]^+$ requires 413.2435, Δ -2.69 ppm.

1-Benzyl-2-oxo-2,4,5,6-tetrahydro-1*H*-indole-3-carbonitrile, 292



Prepared according to **General Procedure G** with cyanoacetic acid (140 mg, 1.65 mmol, 1.10 equiv.), oxalyl chloride (0.283 mL, 419 mg, 3.30 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 18 h. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave 1-benzyl-2-oxo-2,4,5,6-tetrahydro-1*H*-indole-3-carbonitrile (**292**) as a yellow oil (217 mg, 0.810 mmol, 49%).

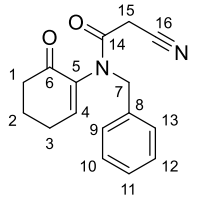
IR (neat) ν_{max}/cm^{-1} = 2935, 2228, 1695, 1649, 1607, 1496, 1435, 1377, 1340, 1318, 1264, 1214, 1167, 1144, 1077, 992, 966, 914, 877, 809, 764, 740, 700, 647.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.16 (3H, m, C10H, C11H & C12H), 7.16–7.09 (2H, m, C9H & C13H), 5.81 (1H, t, *J* = 4.8 Hz, C4H), 4.71 (2H, s, $C7H_2$), 2.76 (2H, t, *J* = 6.6 Hz, $C1H_2$), 2.31 (2H, td, *J* = 5.9, 4.7 Hz, $C3H_2$), 1.82 (2H, q, *J* = 6.2 Hz, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 164.6 (C14), 157.8 (C5), 137.8 (C6), 136.3 (C8), 128.9 (C10H & C12H), 127.8 (C11H), 127.3 (C9H & C13H), 118.5 (C4H), 112.3 (C16), 101.9 (C15), 43.5 ($C7H_2$), 24.6 ($C3H_2$), 24.3 ($C1H_2$), 22.6 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 251.1179; $[C_{16}H_{15}ON_2]^+$ requires 251.1179, Δ 0.00 ppm.

***N*-Benzyl-2-cyano-*N*-(6-oxocyclohex-1-en-1-yl)acetamide, 293**



Prepared according to **General Procedure G** with cyanoacetic acid (140 mg, 1.65 mmol, 2.20 equiv.), oxalyl chloride (0.283 mL, 419 mg, 3.30 mmol, 4.40 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (151 mg, 0.750 mmol, 1.00 equiv.), pyridine (0.133 mL, 131 mg, 1.65 mmol, 2.20 equiv.) and CH_2Cl_2 (7.5 mL) for 17 h. Purification by flash column chromatography (3:2→1:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-2-cyano-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**293**) as a yellow oil (184 mg, 0.683 mmol, 46%).

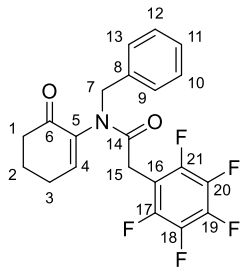
IR (neat) ν_{max}/cm^{-1} = 2927, 2259, 1668, 1632, 1496, 1409, 1347, 1259, 1229, 1189, 1154, 1125, 1081, 1005, 977, 949, 916, 841, 757, 721, 702, 671, 619.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.20 (3H, m, C10H, C11H & C12H), 7.20–7.13 (2H, m, C9H & C13H), 6.69 (1H, t, *J* = 4.3 Hz, C4H), 5.17 (1H, d, *J* = 14.4 Hz, $C7\underline{H_A}H_B$), 4.09 (1H, d, *J* = 14.4 Hz, $C7H_A\underline{H_B}$), 3.32 (1H, d, *J* = 18.0 Hz, $C15\underline{H_A}H_B$), 3.25 (1H, d, *J* = 18.0 Hz, $C15H_A\underline{H_B}$), 2.59–2.44 (2H, m, $C1H_2$), 2.44–2.27 (2H, m, $C3H_2$), 2.07–1.90 (2H, m, $C2H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.8 (C6), 162.0 (C14), 151.9 (C4H), 137.6 (C5), 136.1 (C8), 129.2 (C9H & C13H), 128.7 (C10H & C12H), 128.0 (C11H), 114.4 (C16), 51.9 ($C7H_2$), 38.2 ($C1H_2$), 26.1 ($C3H_2$), 25.3 ($C15H_2$), 22.2 ($C2H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 291.1106; $[C_{16}H_{16}O_2N_2Na]^+$ requires 291.1104, Δ 0.65 ppm.

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(perfluorophenyl)acetamide, 294**



Prepared according to **General Procedure G** with 2-(perfluorophenyl)acetic acid (373 mg, 1.65 mmol, 1.10 equiv.), oxalyl chloride (0.283 mL, 419 mg, 3.30 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), pyridine (0.133 mL, 131 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 18 h. Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(perfluorophenyl)acetamide (**294**) as a pale pink solid (516 mg, 1.26 mmol, 84%).

m.p. = 112–114 °C.

IR (neat) ν_{max}/cm^{-1} = 3032, 2936, 1685, 1668, 1633, 1522, 1505, 1455, 1397, 1360, 1346, 1306, 1259, 1229, 1188, 1154, 1125, 1080, 1001, 967, 912, 846, 759, 721, 702, 664, 639, 617.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.25 (3H, m, C10H, C11H & C12H), 7.24–7.14 (2H, m, C9H & C13H), 6.65 (1H, t, *J* = 4.3 Hz, C4H), 5.30 (1H, d, *J* = 14.4 Hz, $C7\underline{H_A}H_B$), 4.00 (1H, d,

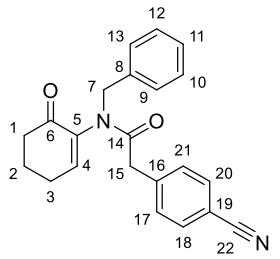
J = 14.4 Hz, C7H$_A$H$_B$), 3.59 (1H, d, *J* = 16.2 Hz, C16H$_A$H$_B$), 3.47 (1H, d, *J* = 16.2 Hz, C16H$_A$H$_B$), 2.56–2.49 (2H, m, C1H$_2$), 2.46–2.32 (2H, m, C3H$_2$), 2.06–1.97 (2H, m, C2H$_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.7 (C6), 167.5 (C14), 150.5 (C4H), 146.8 (C18F & C20F), 144.3 (C19F), 138.7 (C5), 137.0 (C8), 136.2 (C17F & C21F), 129.2 (C9H & C13H), 128.6 (C10H & C12H), 127.8 (C11H), 109.6 (C16), 51.6 (C7H$_2$), 38.5 (C1H$_2$), 27.7 (C15H$_2$), 26.1 (C3H$_2$), 22.5 (C2H$_2$).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -142.18 (2F, dd, *J* = 22.3, 8.2 Hz, C17F & C21F), -156.13 (1F, t, *J* = 20.9 Hz, C19F), -162.80 (2F, td, *J* = 22.0, 8.2 Hz, C18F & C20F).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 432.0992; $[C_{21}H_{16}O_2NF_5Na]^+$ requires 432.0993, Δ -0.37 ppm.

_N_-Benzyl-2-(4-cyanophenyl)-_N_-(6-oxocyclohex-1-en-1-yl)acetamide, 295



Prepared according to **General Procedure G** with (4-cyanophenyl)acetic acid (266 mg, 1.65 mmol, 1.10 equiv.), oxalyl chloride (0.283 mL, 419 mg, 3.30 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256R**) (302 mg, 1.50 mmol, 1.00 equiv.), pyridine (0.133 mL, 131 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 18 h. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-2-(4-cyanophenyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**295**) as an off-white solid (370 mg, 1.07 mmol, 72%).

m.p. = 111–113 °C (EtOAc).

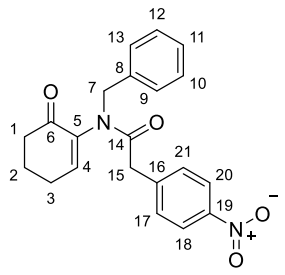
IR (neat) ν_{max}/cm^{-1} = 3032, 2946, 2227, 1683, 1656, 1631, 1607, 1496, 1454, 1417, 1395, 1361, 1344, 1263, 1232, 1197, 1153, 1123, 1080, 1023, 1005, 977, 919, 871, 815, 758, 722, 703, 666, 618.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.53 (2H, d, *J* = 8.1 Hz, C18H & C20H), 7.28 (2H, d, *J* = 8.1 Hz, C17H & C21H), 7.24–7.17 (3H, m, C10H, C11H & C12H), 7.15–7.09 (2H, m, C9H & C13H), 6.37 (1H, t, *J* = 4.4 Hz, C4H), 5.25 (1H, d, *J* = 14.4 Hz, C7$\underline{H_A}H_B$), 3.92 (1H, d, *J* = 14.4 Hz, C7$H_A\underline{H_B}$), 3.49 (1H, d, *J* = 15.3 Hz, C15$\underline{H_A}H_B$), 3.41 (1H, d, *J* = 15.3 Hz, C15$H_A\underline{H_B}$), 2.46–2.40 (2H m, C1H_2), 2.32–2.25 (2H, m, C3H_2), 1.96–1.88 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.9 (C6), 169.7 (C14), 150.3 (C4H), 141.1 (C16), 138.7 (C5), 137.1 (C8), 132.3 (C18H & C20H), 130.2 (C17H & C21H), 129.2 (C9H & C13H), 128.6 (C10H & C12H), 127.7 (C11H), 118.9 (C22), 110.8 (C19), 51.2 (C7H_2), 41.0 (C15H_2), 38.4 (C1H_2), 26.0 (C3H_2), 22.4 (C2H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 345.1599; $[C_{22}H_{21}O_2N_2]^+$ requires 345.1598, Δ 0.28 ppm.

_N_-Benzyl-2-(4-nitrophenyl)-_N_-(6-oxocyclohex-1-en-1-yl)acetamide, 296



Prepared according to **General Procedure G** with 2-(4-nitrophenyl)acetic acid (299 mg, 1.65 mmol, 1.10 equiv.), oxalyl chloride (0.283 mL, 419 mg, 3.30 mmol, 2.20 equiv.), DMF (100 µL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), pyridine (0.133 mL, 131 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 21 h. Purification by flash column chromatography (4:1→2:1 v/v Petrol

ether 40–60:EtOAc) gave *N*-benzyl-2-(4-nitrophenyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**296**) as an orange solid (492 mg, 1.35 mmol, 90%).

m.p. = 103–105 °C.

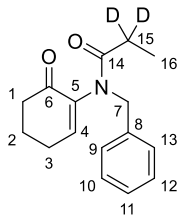
IR (neat) ν_{max}/cm^{-1} = 2945, 1683, 1657, 1631, 1604, 1516, 1495, 1395, 1343, 1262, 1233, 1200, 1153, 1110, 1080, 1005, 977, 912, 858, 823, 723, 701, 647, 614.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.12 (2H, d, *J* = 8.7 Hz, C18H & C20H), 7.36 (2H, d, *J* = 8.7 Hz, C17H & C21H), 7.29–7.22 (3H, m, C10H, C11H & C12H), 7.19–7.13 (2H, m, C9H & C13H), 6.46 (1H, t, *J* = 4.2 Hz, C4H), 5.27 (1H, d, *J* = 14.4 Hz, C7$\underline{H_A}H_B$), 3.97 (1H, d, *J* = 14.4 Hz, C7$H_A\underline{H_B}$), 3.55 (2H, s, C15H_2), 2.51–2.45 (2H, m, C1H_2), 2.38–2.30 (2H, m, C3H_2), 2.02–1.94 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.0 (C6), 169.6 (C14), 150.4 (C4H), 146.9 (C19), 143.2 (C16), 138.6 (C5), 137.0 (C8), 130.3 (C17H & C21H), 129.1 (C9H & C13H), 128.5 (C10H & C12H), 127.7 (C11H), 123.6 (C18H & C20H), 51.2 (C7H_2), 40.6 (C15H_2), 38.4 (C1H_2), 26.0 (C3H_2), 22.4 (C2H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 365.1497; $[C_{21}H_{21}O_4N_2]^+$ requires 365.1496, Δ 0.20 ppm.

_N_-Benzyl-_N_-(6-oxocyclohex-1-en-1-yl)propionamide-2,2-d_2, 297



Prepared according to **General Procedure G** with propionic acid-d_2 (0.075 mL, 77.1 mg, 1.10 mmol, 1.10 equiv.), oxalyl chloride (0.102 mL, 153 mg, 1.20 mmol, 1.20 equiv.), DMF

(100 μL) and CH_2Cl_2 (5 mL) followed by 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), pyridine (0.089 mL, 87.0 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (5 mL) for 22 h. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)propionamide-2,2-d_2 (**297**) as a white solid (235 mg, 0.904 mmol, 90%).

m.p. = 47–49 °C.

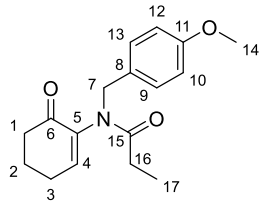
IR (neat) ν_{max}/cm^{-1} = 2937, 1684, 1654, 1496, 1454, 1389, 1154, 1124, 1079, 1029, 977, 918, 854, 701.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.20 (3H, m, C10H, C11H & C12H), 7.20–7.13 (2H, m, C9H & C13H), 6.48 (1H, t, *J* = 4.3 Hz, C4H), 5.33 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.88 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 2.56–2.40 (2H, m, C1H_2), 2.40–2.22 (2H, m, C3H_2), 2.06–1.87 (2H, m, C2H_2), 1.06 (3H, s, C16H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.2 (C6), 173.8 (C14), 149.6 (C4H), 139.0 (C5), 137.7 (C8), 129.0 (C9H & C13H), 128.4 (C10H & C12H), 127.4 (C11H), 50.6 (C7H_2), 38.6 (C1H_2), 26.6 (C15D_2) 26.0 (C3H_2), 22.5 (C2H_2), 9.5 (C16H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 260.1616; $[C_{16}H_{18}{}^2H_2O_2N]^+$ requires 260.1614, Δ 0.58 ppm.

_N_-(4-Methoxybenzyl)-_N_-(6-oxocyclohex-1-en-1-yl)propionamide, 298



Prepared according to **General Procedure F** with 2-((4-methoxybenzyl)amino)cyclohex-2-en-1-one (**259**) (463 mg, 2.00 mmol, 1.00 equiv.),

propionyl chloride (0.192 mL, 204 mg, 2.20 mmol, 1.10 equiv.), Et_3N (0.307 mL, 223 mg, 2.20 mmol, 1.10 equiv.) and CH_2Cl_2 (10 mL) for 23 h. Purification by flash column chromatography (4:1→1:1 v/v Petrol ether 40–60:EtOAc) gave *N*-(4-methoxybenzyl)-*N*-(6-oxocyclohex-1-en-1-yl)propionamide (**298**) as a yellow oil (546 mg, 1.90 mmol, 95%).

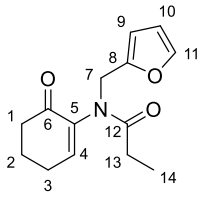
IR (neat) ν_{max}/cm^{-1} = 2937, 2836, 1683, 1656, 1629, 1612, 1585, 1511, 1461, 1399, 1363, 1343, 1301, 1246, 1176, 1153, 1123, 1111, 1088, 1031, 977, 911, 895, 849, 817, 758, 726, 661.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.13–7.04 (2H, m, C9H & C13H), 6.81–6.73 (2H m, C10H & C12H), 6.44 (1H, t, *J* = 4.2 Hz, C4H), 5.24 (1H, d, *J* = 14.3 Hz, C7H_AH_B), 3.82 (1H, d, *J* = 14.3 Hz, C7H_AH_B), 3.75 (3H, s, C14H_3), 2.54–2.41 (2H, m, C1H_2), 2.38–2.26 (2H, m, C3H_2), 2.20–2.06 (1H, m, C16H_AH_B), 2.03–1.91 (3H, m, C3H_2 & C16H_AH_B), 1.05 (3H, t, *J* = 7.4 Hz, C17H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.2 (C6), 173.6 (C15), 158.9 (C11), 149.6 (C4H), 138.9 (C5), 130.4 (C9H & C13H), 129.8 (C8), 113.7 (C10H & C12H), 55.3 (C14H_3), 50.0 (C7H_2), 38.5 (C1H_2), 27.1 (C16H_2), 26.0 (C3H_2), 22.5 (C2H_2), 9.6 (C17H_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 310.1415; $[C_{17}H_{21}O_3NNa]^+$ requires 310.1414, Δ 0.37 ppm.

_N_-(Furan-2-ylmethyl)-_N_-(6-oxocyclohex-1-en-1-yl)propionamide, 299



Prepared according to **General Procedure F** with 2-((furan-2-ylmethyl)amino)cyclohex-2-en-1-one (**258**) (287 mg, 1.50 mmol, 1.00 equiv.),

propionyl chloride (0.144 mL, 153 mg, 1.65 mmol, 1.10 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 19 h. Purification by flash column chromatography (3:2→1:1 v/v Petrol ether 40–60:EtOAc) gave *N*-(furan-2-ylmethyl)-*N*-(6-oxocyclohex-1-en-1-yl)propionamide (**299**) as a yellow oil (357 mg, 1.45 mmol, 96%).

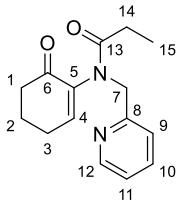
IR (neat) ν_{max}/cm^{-1} = 2939, 1683, 1661, 1633, 1504, 1399, 1257, 1214, 1178, 1150, 1124, 1074, 1013, 976, 923, 885, 811, 751.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28 (1H, d, *J* = 1.8 Hz, C11H), 6.63 (1H, t, *J* = 4.3 Hz, C4H), 6.24 (1H, dd, *J* = 3.2, 1.9 Hz, C10H), 6.14 (1H, d, *J* = 3.2 Hz, C9H), 5.19 (1H, d, *J* = 15.2 Hz, C7$\underline{H_A}H_B$), 4.02 (1H, d, *J* = 15.2 Hz, C7$H_A\underline{H_B}$), 2.50–2.44 (2H, m, C1H_2), 2.43–2.29 (2H, m, C3H_2), 2.13 (1H, dq, *J* = 15.0, 7.4 Hz, C13$\underline{H_A}H_B$), 2.03–1.89 (3H, m, C2H_2 & C13$H_A\underline{H_B}$), 1.03 (3H, t, *J* = 7.4 Hz, C14H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 173.6 (C12), 151.1 (C8), 149.7 (C4H), 142.2 (C11H), 138.8 (C5), 110.4 (C10H), 109.3 (C9H), 43.3 (C7H_2), 38.4 (C1H_2), 27.1 (C13H_2), 26.1 (C3H_2), 22.4 (C2H_2), 9.5 (C14H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 248.1280; $[C_{14}H_{18}O_3N]^+$ requires 248.1281, Δ -0.64 ppm.

_N_-(6-Oxocyclohex-1-en-1-yl)-_N_-(pyridin-2-ylmethyl)propionamide, 300



Prepared according to **General Procedure F** with 2-((pyridine-2-ylmethyl)amino)cyclohex-2-en-1-one (**259**) (303 mg, 1.50 mmol,

1.00 equiv.), propionyl chloride (0.144 mL, 153 mg, 1.65 mmol, 1.10 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 20 h. Purification by flash column chromatography (97:3→94:6 v/v CH_2Cl_2:MeOH) gave *N*-(6-oxocyclohex-1-en-1-yl)-*N*-(pyridin-2-ylmethyl)propionamide (**300**) as an orange oil (361 mg, 1.40 mmol, 93%).

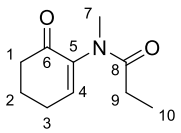
IR (neat) ν_{max}/cm^{-1} = 2938, 2876, 1685, 1663, 1633, 1591, 1571, 1474, 1461, 1435, 1395, 1346, 1273, 1236, 1221, 1193, 1155, 1125, 1087, 1037, 1007, 995, 978, 906, 812, 757, 723, 667, 636, 615.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.46 (1H, d, *J* = 4.8 Hz, C12H), 7.62 (1H, td, *J* = 7.7, 1.8 Hz, C10H), 7.41 (1H, d, *J* = 7.8 Hz, C9H), 7.14 (1H, t, *J* = 7.8, 4.6 Hz, C11H), 6.84 (1H, t, *J* = 4.3 Hz, C4H), 5.14 (1H, d, *J* = 15.0 Hz, C7$\underline{H_A}H_B$), 4.34 (1H, d, *J* = 15.0 Hz, C7$H_A\underline{H_B}$), 2.56–2.47 (2H, m, C1H_2), 2.47–2.39 (2H, m, C3H_2), 2.23–2.04 (2H, m, C14H_2), 2.04–1.96 (2H, m, C2H_2), 1.08 (3H, t, *J* = 7.4 Hz, C15H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 174.1 (C13), 157.8 (C8), 149.1 (C4H), 148.9 (C12H), 140.1 (C5), 136.8 (C10H), 123.5 (C9H), 122.3 (C11H), 53.6 (C7H_2), 38.5 (C1H_2), 27.0 (C2H_2), 26.1 (C3H_2), 22.5 (C14H_2), 9.6 (C15H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 259.1446; $[C_{15}H_{19}N_2O_2]^+$ requires 259.1447, Δ -0.40 ppm.

_N_-Methyl-_N_-(6-oxocyclohex-1-en-1-yl)propionamide, 301



Prepared according to **General Procedure F** with 2-(methylamino)cyclohex-2-en-1-one (**260**) (188 mg, 1.50 mmol, 1.00 equiv.), propionyl chloride (0.144 mL, 153 mg, 1.65 mmol,

1.10 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 19 h. Purification by flash column chromatography (1:1→0:1 v/v Petrol ether 40–60:EtOAc) gave *N*-methyl-*N*-(6-oxocyclohex-1-en-1-yl)propionamide (**301**) as a yellow oil (207 mg, 1.14 mmol, 76%).

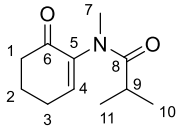
IR (neat) ν_{max}/cm^{-1} = 2922, 1682, 1656, 1631, 1462, 1422, 1383, 1353, 1311, 1277, 1224, 1162, 1130, 1112, 1072, 976, 914, 875, 814, 722.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.91 (1H, t, *J* = 4.2 Hz, C4H), 2.96 (3H, s, $C7H_3$), 2.53–2.48 (4H, m, $C1H_2$ & $C3H_2$), 2.10–2.01 (3H, m, $C2H_2$ & $C9\underline{H_A}H_B$), 2.00–1.88 (1H, m, $C9H_A\underline{H_B}$), 1.02 (3H, t, *J* = 7.5 Hz, $C10H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 173.0 (C8), 147.7 (C4H), 141.6 (C5), 38.5 ($C1H_2$), 35.9 ($C7H_3$), 26.8 ($C9H_2$), 26.0 ($C3H_2$), 22.6 ($C2H_2$), 9.7 ($C10H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 204.0996; $[C_{10}H_{15}O_2NNa]^+$ requires 204.0995, Δ 0.54 ppm.

_N_-Methyl-_N_-(6-oxocyclohex-1-en-1-yl)isobutyramide, 302



Prepared according to **General Procedure F** with 2-(methylamino)cyclohex-2-en-1-one (**260**) (188 mg, 1.50 mmol, 1.00 equiv.), isobutyryl chloride (0.173 mL, 176 mg, 1.65 mmol, 1.10 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 21 h. Purification by flash column chromatography (1:1→0:1 v/v Petrol ether 40–60:EtOAc) gave *N*-methyl-*N*-(6-oxocyclohex-1-en-1-yl)isobutyramide (**302**) as a yellow oil (247 mg, 1.27 mmol, 84%).

IR (neat) ν_{max}/cm^{-1} = 2969, 2872, 1685, 1655, 1630, 1471, 1457, 1422, 1387, 1356, 1312, 1268, 1223, 1161, 1130, 1089, 978, 928, 874, 806, 752, 722, 686, 657.

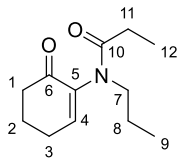
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.94–6.87 (1H, m, C4H), 2.93 (3H, s, $C7H_3$), 2.53–2.48 (4H, m, $C1H_2$ & $C3H_2$), 2.33 (1H, quint, *J* = 6.5 Hz, C9H), 2.04 (2H, quint, *J* = 6.3 Hz, $C2H_2$), 1.01–0.94 (6H, m, $C10H_3$ & $C11H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 177.6 (C8), 147.2 (C4H), 141.6 (C5), 38.5 ($C1H_2$), 36.0 ($C7H_3$), 31.6 (C9H), 25.9 ($C3H_2$), 22.6 ($C2H_2$), 20.2 ($C10H_3$), 19.3 ($C11H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 218.1152; $[C_{11}H_{17}O_2NNa]^+$ requires 218.1152, Δ 0.32 ppm.

The data matches that reported in the literature.[79]

***N*-(6-Oxocyclohex-1-en-1-yl)-*N*-propylpropionamide, 303**



Prepared according to **General Procedure F** with 2-(propylamino)cyclohex-2-en-1-one (**261**) (153 mg, 1.00 mmol, 1.00 equiv.), propionyl chloride (0.096 mL, 102 mg, 1.10 mmol, 1.10 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (5 mL) for 15 h. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave *N*-(6-oxocyclohex-1-en-1-yl)-*N*-propylpropionamide (**303**) as a yellow oil (140 mg, 0.667 mmol, 67%).

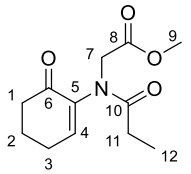
IR (neat) ν_{max}/cm^{-1} = 2962, 2936, 2874, 1684, 1657, 1629, 1461, 1402, 1375, 1345, 1264, 1237, 1210, 1134, 1120, 1081, 1020, 976, 942, 912, 889, 874, 813, 778, 723, 665.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.85 (1H, t, J = 4.3 Hz, C4H), 3.63 (1H, dt, J = 14.1, 7.4 Hz, C7$\underline{H_A}H_B$), 3.02 (1H, dt, J = 14.3, 7.4 Hz, C7$H_A\underline{H_B}$), 2.54–2.49 (4H, m, C1H_2 & C3H_2), 2.09–2.01 (3H, m, C2H_2 & C11$\underline{H_A}H_B$), 1.90 (1H, dq, J = 15.0, 7.3 Hz, C11$H_A\underline{H_B}$), 1.39 (2H, q, J = 7.5 Hz, C8H_2), 1.00 (3H, t, J = 7.4 Hz, C12H_3), 0.81 (3H, t, J = 7.4 Hz, C9H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.4 (C6), 173.6 (C10), 148.3 (C4H), 140.1 (C5), 49.3 (C7H_2), 38.6 (C1H_2), 27.1 (C11H_2), 26.1 (C3H_2), 22.6 (C2H_2), 21.3 (C8H_2), 11.3 (C9H_3), 9.6 (C12H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 210.1486; $[C_{12}H_{20}O_2N]^+$ requires 210.1489, Δ -1.12 ppm.

Methyl *N*-(6-oxocyclohex-1-en-1-yl)-*N*-propionylglycinate, 304



Prepared according to **General Procedure F** with methyl (6-oxocyclohex-1-en-1-yl)glycinate (**268**) (275 mg, 1.50 mmol, 1.00 equiv.), propionyl chloride (0.144 mL, 153 mg, 1.65 mmol, 1.10 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.5 mL) for 23 h. Purification by flash column chromatography (1:1→1:2 v/v Petrol ether 40–60:EtOAc) gave methyl *N*-(6-oxocyclohex-1-en-1-yl)-*N*-propionylglycinate (**304**) as a yellow oil (315 mg, 1.32 mmol, 88%).

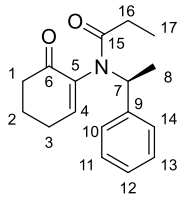
IR (neat) ν_{max}/cm^{-1} = 2942, 1749, 1683, 1664, 1418, 1390, 1362, 1282, 1199, 1157, 1127, 1051, 1016, 979, 906, 813, 728, 661.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.23 (1H, t, J = 4.3 Hz, C4H), 4.74 (1H, br s, C7$\underline{H_A}H_B$), 3.64 (3H, s, C9H_3), 3.35 (1H, br s, C7$H_A\underline{H_B}$), 2.53–2.44 (4H, m, C1H_2 & C3H_2), 2.15 (1H, s, C11$\underline{H_A}H_B$), 2.05–1.94 (3H, m, C2H_2 & C11$H_A\underline{H_B}$), 0.99 (3H, t, J = 7.4 Hz, C12H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.0 (C6), 173.9 (C10), 170.2 (C8), 150.3 (C4H), 139.5 (C5), 52.0 ($C9H_3$), 48.8 ($C7H_2$), 38.4 ($C1H_2$), 26.5 ($C11H_2$), 26.0 ($C3H_2$), 22.3 ($C2H_2$), 9.2 ($C12H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 240.1231; $[C_{12}H_{18}O_4N]^+$ requires 240.1230, Δ 0.18 ppm.

(*S*)-*N*-(6-Oxocyclohex-1-en-1-yl)-*N*-(1-phenylethyl)propionamide, 305



Prepared according to **General Procedure F** with (*S*)-2-((1-phenylethyl)amino)cyclohex-2-en-1-one (**257**) (431 mg, 2.00 mmol, 1.00 equiv.), propionyl chloride (0.192 mL, 204 mg, 2.20 mmol, 1.10 equiv.), Et_3N (0.307 mL, 223 mg, 2.20mmol, 2.20 equiv.) and CH_2Cl_2 (10 mL) for 41 h. Purification by flash column chromatography (3:1→1:1 v/v Petrol ether 40–60:EtOAc) gave (*S*)-*N*-(6-oxocyclohex-1-en-1-yl)-*N*-(1-phenylethyl)propionamide (**305**) as an off-white solid (196 mg, 0.722 mmol, 36%).

Compound exists as 2:1 mixture of rotamers in $CDCl_3$ at 298K. Only NMR peaks corresponding to the major rotamer are reported.

$[\alpha]_D^{25.0}$ = -97 °dm^2g^{-1} (*c* = 1.0, $CHCl_3$).

m.p. = 127–129 °C.

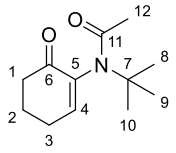
IR (neat) ν_{max}/cm^{-1} = 3031, 2975, 2937, 2875, 1686, 1653, 1625, 1495, 1453, 1389, 1266, 1252, 1208, 1156, 1124, 1075, 1033, 1014, 989, 947, 902, 876, 818, 782, 760, 723, 700, 672, 616.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.12 (5H, m, C10H, C11H, C12H, C13H & C14H), 6.11 (1H, q, J = 7.2 Hz, C7H), 5.96 (1H, t, J = 4.3 Hz, C4H), 2.61–2.37 (2H, m, $C1H_2$), 2.35–2.10 (2H, m, $C3H_2$), 2.08–1.85 (4H, m, $C2H_2$ & $C16H_2$), 1.29 (3H, d, J = 7.2 Hz, $C8H_3$), 1.03 (3H, t, J = 7.4 Hz, $C17H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.3 (C6), 173.6 (C15), 150.6 (C4H), 142.0 (C5), 136.4 (C9), 128.3 (C10H & C14H), 128.0 (C11H & C13H), 127.5 (C12H), 52.2 (C7H), 38.6 ($C1H_2$), 27.6 ($C2H_2$), 26.2 ($C3H_2$), 22.5 ($C16H_2$), 15.9 ($C8H_3$), 9.7 ($C17H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 294.1462; $[C_{17}H_{21}O_2NNa]^+$ requires 294.1465, Δ -0.71 ppm.

***N*-(*tert*-Butyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide, 306**



Prepared according to **General Procedure F** with 2-(*tert*-butylamino)cyclohex-2-en-1-one (**262**) (167 mg, 1.00 mmol, 1.00 equiv.), acetyl chloride (78.2 µL, 86.4 mg, 1.10 mmol, 1.10 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (5 mL) for 24 h. Purification by flash column chromatography (2:1→1:2 v/v Petrol ether 40–60:EtOAc) gave *N*-(*tert*-butyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**306**) as a yellow oil (119 mg, 0.569 mmol, 57%).

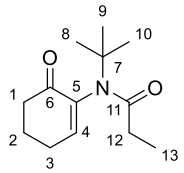
IR (neat) ν_{max}/cm^{-1} = 2959, 1685, 1656, 1627, 1428, 1363, 1332, 1275, 1201, 1154, 1122, 1031, 980, 956, 825, 779, 722, 618.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.80 (1H, t, J = 4.3 Hz, C4H), 2.63–2.44 (4H, m, $C1H_2$ & $C3H_2$), 2.06 (2H, quint, J = 6.4 Hz, $C2H_2$), 1.77 (3H, s, $C12H_3$), 1.34 (9H, s, $C8H_3$, $C9H_3$ & $C10H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.5 (C6), 170.4 (C11), 148.7 (C4H), 141.1 (C5), 58.0 (C7), 38.6 ($C12H_3$), 28.7 ($C8H_3$, $C9H_3$ & $C10H_3$), 26.2 ($C3H_2$), 25.2 ($C12H_3$), 22.6 ($C2H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 232.1309; $[C_{12}H_{19}O_2NNa]^+$ requires 232.1308, Δ 0.52 ppm.

***N*-(*tert*-Butyl)-*N*-(6-oxocyclohex-1-en-1-yl)propionamide, 307**



Prepared according to **General Procedure F** with 2-(*tert*-butylamino)cyclohex-2-en-1-one (**262**) (83.6 mg, 0.500 mmol, 1.00 equiv.), propionyl chloride (48.1 µL, 50.9 mg, 0.550 mmol, 1.10 equiv.), Et_3N (76.7 µL, 55.7 mg, 0.550 mmol, 1.10 equiv.) and CH_2Cl_2 (5 mL) for 21 h. Purification by flash column chromatography (2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-(*tert*-butyl)-*N*-(6-oxocyclohex-1-en-1-yl)propionamide (**307**) as a yellow oil (59.4 mg, 0.266 mmol, 53%).

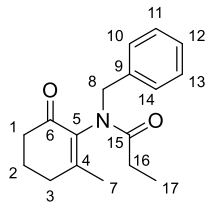
IR (neat) ν_{max}/cm^{-1} = 2975, 2927, 1685, 1656, 1627, 1484, 1459, 1419, 1373, 1361, 1297, 1255, 1231, 1202, 1154, 1121, 1078, 1037, 1008, 980, 957, 927, 896, 876, 817, 775, 723, 658.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.77 (1H, t, *J* = 4.3 Hz, C4H), 2.61–2.42 (4H, m, $C1H_2$ & $C3H_2$), 2.14–1.97 (3H, m, $C2H_2$ & $C12\underline{H_A}H_B$), 1.80 (1H, dq, *J* = 16.2, 7.3 Hz, $C12H_A\underline{H_B}$), 1.32 (9H, s, $C8H_3$, $C9H_3$ & $C10H_3$), 0.95 (3H, t, *J* = 7.3 Hz, $C13H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.7 (C6), 173.4 (C11), 148.8 (C4H), 140.3 (C5), 57.9 (C7), 38.6 ($C1H_2$), 29.5 ($C12H_2$), 28.8 ($C8H_3$, $C9H_3$ & $C10H_3$), 26.2 ($C3H_2$), 22.5 ($C2H_2$), 9.6 ($C13H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 224.1647; $[C_{13}H_{22}O_2N]^+$ requires 224.1645, Δ 0.88 ppm.

***N*-Benzyl-*N*-(2-methyl-6-oxocyclohex-1-en-1-yl)propionamide, 308**



Prepared according to **General Procedure F** with 2-(benzylamino)-3-methylcyclohex-2-en-1-one (**263**) (215 mg, 1.00 mmol, 1.00 equiv.), propionyl chloride (96.2 µL, 102 mg, 1.10 mmol, 1.10 equiv.), Et_3N (0.153 mL, 111 mg, 1.10 mmol, 1.10 equiv.) and CH_2Cl_2 (5 mL) for 18 h. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(2-methyl-6-oxocyclohex-1-en-1-yl)propionamide (**308**) as a white solid (232 mg, 0.856 mmol, 86%).

m.p. = 108–110°C.

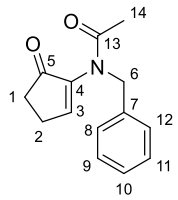
IR (neat) ν_{max}/cm^{-1} = 3029, 2937, 2874, 1673, 1656, 1628, 1495, 1455, 1398, 1379, 1325, 1291, 1233, 1190, 1171, 1136, 1078, 1031, 973, 925, 895, 844, 804, 760, 723, 702, 630.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28–7.15 (5H, m, C10H, C11H, C12H, C13H & C14H), 5.21 (1H, d, J = 13.9 Hz, C8$\underline{H_A}H_B$), 3.96 (1H, d, J = 13.9 Hz, C8$H_A\underline{H_B}$), 2.42 (2H, t, J = 6.7 Hz, C1H_2), 2.39–2.22 (2H, m, C3H_2), 2.01–1.93 (2H, m, C16H_2), 1.92–1.78 (2H, m, C2H_2), 1.40 (3H, s, C7H_3), 1.05 (3H, t, J = 7.4 Hz, C17H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.6 (C6), 173.9 (C15), 160.3 (C5), 137.1 (C4), 135.1 (C9), 130.1 (C10H & C14H), 128.2 (C11H & C13H), 127.5 (C12H), 50.5 (C8H_2), 38.2 (C1H_2), 32.2 (C3H_2), 26.7 (C16H_2), 21.8 (C2H_2), 20.4 (C7H_3), 9.4 (C17H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 272.1644; $[C_{17}H_{22}O_2N]^+$ requires 272.1645, Δ -0.39 ppm.

***N*-Benzyl-*N*-(5-oxocyclopent-1-en-1-yl)acetamide, 309**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclopent-2-en-1-one (**264**) (281 mg, 1.50 mmol, 1.00 equiv.), acetyl chloride (0.120 mL, 138 mg, 1.65 mmol, 1.10 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.50 mL). Purification by flash column chromatography (1:1 v/v Petrol ether 40–60:Et_2O) gave *N*-benzyl-*N*-(5-oxocyclopent-1-en-1-yl)acetamide (**309**) as a yellow oil which solidified on standing (317 mg, 1.38 mmol, 92%).

m.p. = 38–40 °C.

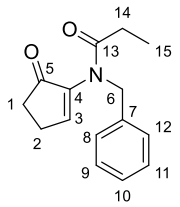
IR (neat) ν_{max}/cm^{-1} = 2927, 1710, 1661, 1625, 1496, 1436, 1388, 1361, 1277, 1237, 1136, 1062, 987, 927, 788, 737, 703, 612.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–7.15 (6H, m, C3H, C8H, C9H, C10H, C11H & C12H), 4.77 (2H, s, $C6H_2$), 2.61–2.56 (2H, m, $C2H_2$), 2.46–2.41 (2H, m, $C1H_2$), 2.02 (3H, s, $C14H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 204.1 (C5 & C13), 157.9 (C3H), 137.4 (C4), 128.6 (C8H & C12H), 128.1 (C7), 127.5 (C9H, C10H & C11H), 50.4 ($C6H_2$), 33.6 ($C1H_2$), 24.7 ($C2H_2$), 22.2 ($C14H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 230.1177; $[C_{14}H_{16}O_2N]^+$ requires 230.1176, Δ 0.59 ppm.

***N*-Benzyl-*N*-(5-oxocyclopent-1-en-1-yl)propionamide, 310**



Prepared according to **General Procedure F** with 2-(benzylamino)cyclopent-2-en-1-one (**264**) (375 mg, 2.00 mmol, 1.00 equiv.), propionyl chloride (0.192 mL, 204 mg, 2.20 mmol, 1.10 equiv.), Et_3N (0.307 mL, 223 mg, 2.20 mmol, 1.10 equiv.) and CH_2Cl_2 (10 mL) for 19 h. Purification by flash column chromatography (1:1→1:2 v/v Petrol ether 40–60:EtOAc) gave *N*-benzyl-*N*-(5-oxocyclopent-1-en-1-yl)propionamide (**310**) as a yellow oil (332 mg, 1.36 mmol, 68%).

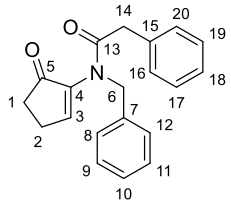
IR (neat) ν_{max}/cm^{-1} = 3063, 3031, 2978, 2878, 1712, 1662, 1625, 1496, 1455, 1435, 1394, 1359, 1301, 1268, 1224, 1135, 1075, 1030, 1015, 1001, 973, 926, 882, 850, 811, 788, 736, 702, 669.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.13 (6H, m, C3H, C8H, C9H, C10H, C11H & C12H), 4.74 (2H, s, $C6H_2$), 2.60–2.52 (2H, m, $C1H_2$), 2.45–2.38 (2H, m, $C2H_2$), 2.21 (2H, q, J = 7.3 Hz, $C14H_2$), 1.10 (3H, t, J = 7.4 Hz, $C15H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 204.3 (C5), 173.5 (C13), 158.2 (C3H), 144.8 (C4), 137.5 (C7), 128.5 (C8H & C12H), 128.0 (C9H & C11H), 127.4 (C10H), 50.4 ($C6H_2$), 33.5 ($C1H_2$), 27.2 ($C14H_2$), 24.6 ($C2H_2$), 9.5 ($C15H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 244.1332; $[C_{15}H_{18}O_2N]^+$ requires 244.1332, Δ 0.14 ppm.

***N*-benzyl-*N*-(5-oxocyclopent-1-en-1-yl)-2-phenylacetamide, 311**



Prepared according to **General Procedure F** with 2-(benzylammino)cyclopent-2-en-1-one (**264**) (281 mg, 1.50 mmol, 1.00 equiv.), phenylacetyl chloride (0.220 mL, 255 mg, 1.65 mmol, 1.10 equiv.), Et_3N (0.230 mL, 167 mg, 1.65 mmol, 1.10 equiv.) and CH_2Cl_2 (7.50 mL). Purification by flash column chromatography (1:1→1:2 v/v Petrol ether 40–60:Et_2O) gave *N*-benzyl-*N*-(5-oxocyclopent-1-en-1-yl)-2-phenylacetamide (**311**) as a yellow oil (356 mg, 1.16 mmol, 78%).

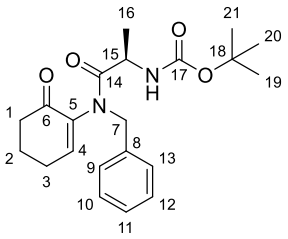
IR (neat) ν_{max}/cm^{-1} = 3029, 1711, 1660, 1627, 1495, 1454, 1434, 1389, 1359, 1301, 1267, 1232, 1197, 1128, 1079, 1030, 1014, 1001, 972, 926, 786, 749, 720, 698.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.17 (10H, m, C8H, C9H, C10H, C11H, C12H, C16H, C17H, C18H, C19H & C20H), 7.07 (1H, br s, C3H), 4.81 (2H, s, $C6H_2$), 3.65 (2H, s, $C14H_2$), 2.56–2.48 (2H, m, $C2H_2$), 2.46–2.38 (2H, m, $C1H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 204.1 (C5), 170.8 (C13), 159.2 (C3H), 144.5 (C4), 137.3 (C7), 135.3 (C15), 129.0 (C8H & C12H), 128.7 (C16H & C20H), 128.6 (C9H & C11H), 128.2 (C17H & C19H), 127.6 (C10H), 126.9 (C18H), 50.6 ($C6H_2$), 41.7 ($C14H_2$), 33.5 ($C1H_2$), 24.7 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 306.1489; $[C_{20}H_{20}O_2N]^+$ requires 306.1489, Δ 0.23 ppm.

***tert*-Butyl (*R*)-(1-(benzyl(6-oxocyclohex-1-en-1-yl)amino)-1-oxopropan-2-yl)carbamate, 313**



Prepared according to **General Procedure H** with 2-(benzylamino)cyclohex-2-en-1-one (**256**) (91.4 mg, 0.450 mmol, 1.00 equiv.), *N*-(*tert*-butoxycarbonyl)-*L*-alanine (95.0 mg, 0.500 mmol, 1.10 equiv.), EDC (130 mg, 0.680 mmol, 1.50 equiv.), DMAP (6.1 mg, 0.050 mmol, 0.050 equiv.) and CH_2Cl_2 (5 mL) for 45 h. Purification by flash column chromatography (7:1→5:1 v/v Petrol ether 40–60:Et_2O) gave *tert*-butyl (*R*)-(1-(benzyl(6-oxocyclohex-1-en-1-yl)amino)-1-oxopropan-2-yl)carbamate (**313**) as a yellow oil (34.5 mg, 0.0927 mmol, 21%).

Compound exists as 2:1 mixture of rotamers in $CDCl_3$ at 298K. Only NMR peaks corresponding to the major rotamer are reported.

$[\alpha]_D^{25.0}$ = +17 °dm^{2}g^{-1} (*c* = 1.0, $CHCl_3$).

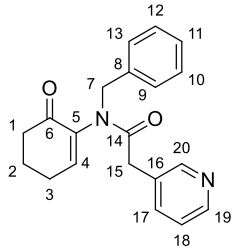
IR (neat) ν_{max}/cm^{-1} = 3323, 2977, 1687, 1656, 1496, 1453, 1408, 1365, 1246, 1163, 1122, 1064, 1028, 915, 864, 731, 701.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–7.20 (3H, m, C10H, C11H & C12H), 7.20–7.11 (2H, m, C9H & C13H), 6.67 (1H, t, *J* = 4.3 Hz, C4H), 5.43 (1H, d, *J* = 15.3 Hz C7$\underline{H_A}H_B$), 5.31–5.21 (1H, m, N$\underline{H}$), 4.44–4.32 (1H, m, C15H), 3.83 (d, *J* = 15.4 Hz, C7$H_A\underline{H_B}$), 2.61–2.35 (3H, m, C1H_2 & C2$\underline{H_A}H_B$), 2.35–2.21 (1H, m, C2$H_A\underline{H_B}$), 2.10–1.86 (2H, m, C3H_2), 1.40 (9H, s, C19H_3, C20H_3 & C21H_3), 1.16 (3H, d, *J* = 6.9 Hz, C16H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.4 (C6), 173.3 (C14), 155.2 (C17), 151.9 (C4H), 137.3 (C5), 137.0 (C8), 129.0 (C9H & C13H), 128.5 (C10H & C12H), 127.5 (C11H), 79.6 (C18), 50.6 ($C7H_2$), 46.6 (C15H), 38.6 ($C1H_2$), 28.4 ($C19H_3$, $C20H_3$ & $C21H_3$), 26.2 ($C3H_2$), 22.4 ($C2H_2$), 18.7 ($C16H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 395.1941; $[C_{21}H_{28}O_4N_2Na]^+$ requires 395.1941, Δ -0.14 ppm.

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2(pyridin-3-yl)acetamide, 314**



Prepared according to **General Procedure H** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), 3-pyridylacetic acid hydrochloride salt (191 mg, 1.10 mmol, 1.10 equiv.), EDC (288 mg, 1.50 mmol, 1.50 equiv.), DMAP (12.2 mg, 0.100 mmol, 0.100 equiv.), Et_3N (0.220 mL, 158 mg, 1.10 mmol, 1.10 equiv.), and CH_2Cl_2 (10 mL) for 70 h. Purification by flash column chromatography (100:0→95:5 v/v EtOAc:MeOH) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2(pyridin-3-yl)acetamide (**314**) as an off-white solid (121 mg, 0.378 mmol, 38%).

m.p. = 66–68 °C.

IR (neat) ν_{max}/cm^{-1} = 3030, 29833, 1684, 1658, 1632, 1577, 1495, 1480, 1454, 1426, 1397, 1361, 1345, 1266, 1218, 1190, 1153, 1124, 1080, 1029, 1006, 977, 916, 854, 795, 711, 627.

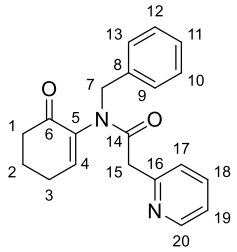
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.51–8.44 (1H, m, C19H), 8.34 (1H, s, C20H), 7.70–7.62 (1H, m, C17H), 7.29–7.23 (4H, m, C10H, C11H, C12H & C18H), 7.19–7.13 (2H, m, C9H & C13H),

6.39 (1H, t, *J* = 4.3 Hz, C4H), 5.33 (1H, d, *J* = 14.4 Hz, C7$\underline{H_A}H_B$), 3.95 (1H, d, *J* = 14.4 Hz, C7$H_A\underline{H_B}$), 3.49 (1H, d, *J* = 15.3 Hz, C15$\underline{H_A}H_B$), 3.44 (1H, d, *J* = 15.3 Hz, C15$H_A\underline{H_B}$), 2.51–2.43 (2H, m, C1H_2), 2.40–2.27 (2H, m, C3H_2), 2.03–1.93 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.0 (C6), 170.1 (C14), 150.5 (C4H), 150.3 (C20H), 148.4 (C19H), 138.6 (C5), 137.2 (C8), 136.9 (C17H), 131.3 (C16), 129.2 (C9H & C13H), 128.6 (C10H & C12H), 127.7 (C18H), 123.6 (C11H), 51.1 (C7H_2), 38.5 (C1H_2), 38.4 (C15H_2), 26.0 (C3H_2), 22.5 (C2H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 321.1597; $[C_{20}H_{21}O_2N_2]^+$ requires 321.1598, Δ -0.08 ppm.

_N_-Benzyl-_N_-(6-oxocyclohex-1-en-1-yl)-2-(pyridine-2-yl)acetamide, 315



Prepared according to **General Procedure J** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), 2-pyridylacetic acid hydrochloride salt (260 mg, 1.50 mmol, 1.00 equiv.), DCC (310 mg, 1.50 mmol, 1.00 equiv.) and CH_2Cl_2 (10 mL) for 20 h. Purification by flash column chromatography (100:0→90:10 v/v EtOAc:MeOH) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2(pyridin-2-yl)acetamide (**315**) as a yellow solid (79.2 mg, 0.247 mmol, 16%).

m.p. = 104–106 °C.

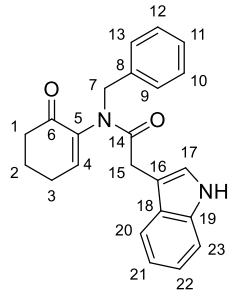
IR (neat) ν_{max}/cm^{-1} = 3062, 2933, 1721, 1681, 1595, 1571, 1496, 1474, 1454, 1433, 1402, 1344, 1303, 1216, 1175, 1098, 1081, 1049, 1030, 989, 911, 839, 803, 732, 699, 669, 643, 620.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.41 (1H, dd, *J* = 4.9, 1.8 Hz, C20H), 7.57 (1H, td, *J* = 7.7, 1.9 Hz, C18H), 7.30 (1H, d, *J* = 7.8 Hz, C17H), 7.22–7.11 (5H, m, C9H, C10H, C11H, C12H & C13H), 7.07 (1H, dd, *J* = 7.6, 4.9 Hz, C19H), 6.36 (1H, t, *J* = 4.3 Hz, C4H), 5.33 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.88 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.69 (1H, d, *J* = 15.2 Hz, C15$\underline{H_A}H_B$), 3.64 (1H, d, *J* = 15.2 Hz, C15$H_A\underline{H_B}$), 2.45–2.33 (2H, m, C1H_2), 2.30–2.15 (2H, m, C3H_2), 1.97–1.82 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.1 (C6), 170.1 (C14), 156.0 (C16), 150.8 (C4H), 149.2 (C20H), 138.5 (C5), 137.5 (C8), 136.6 (C18H), 129.2 (C9H & C13H), 128.5 (C10H & C12H), 127.5 (C11H), 124.1 (C17H), 122.0 (C19H), 50.9 (C7H_2), 44.1 (C15H_2), 38.5 (C1H_2), 26.1 (C3H_2), 22.4 (C2H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 321.1597; $[C_{20}H_{21}O_2N_N]^+$ requires 321.1598, Δ -0.08 ppm.

_N_-Benzyl-2-(1_H_-indol-3-yl)-_N_-(6-oxocyclohex-1-en-1-yl)acetamide, 316



Prepared according to **General Procedure J** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), 3-indoleacetic acid (175 mg, 1.00 mmol, 1.10 equiv.), DCC (206 mg, 1.00 mmol, 1.00 equiv.) and CH_2Cl_2 (10 mL) for 18 h. Purification by flash column chromatography (3:1→1:1 v/v Petrol ether 40–60:EtOAc) gave

N-benzyl-2-(1*H*-indol-3-yl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**316**) as an off-white solid (163 mg, 0.455 mmol, 45%).

m.p. = 52–54 °C.

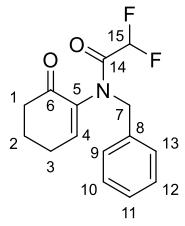
IR (neat) ν_{max}/cm^{-1} = 3308, 3058, 2929, 1682, 1651, 1627, 1554, 1495, 1456, 1408, 1341, 1264, 1225, 1153, 1124, 1099, 1081, 1028, 1008, 977, 911, 848, 817, 743, 725, 701, 672, 647.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.20 (1H, s, N$\underline{H}$), 7.47 (1H, d, *J* = 7.8 Hz, C20H), 7.33 (1H, d, *J* = 8.1 Hz, C23H), 7.27–7.18 (5H, m, C9H, C10H, C11H, C12H & C13H), 7.18–7.14 (1H, m, C22H), 7.12–7.04 (2H, m, C17H & C21H), 6.27 (1H, t, *J* = 4.2 Hz, C4H), 5.46 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 3.91 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.67 (1H, d, *J* = 15.6 Hz, C15$\underline{H_A}H_B$), 3.62 (1H, d, *J* = 15.6 Hz, C15$H_A\underline{H_B}$), 2.40–2.21 (2H, m, C1H_2), 2.16–2.00 (2H, m, C3H_2), 1.86–1.75 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 195.2 (C6), 171.6 (C14), 150.0 (C4H), 138.6 (C5), 137.7 (C8), 136.0 (C19), 129.1 (C10H & C12H), 128.5 (C9H & C13H), 127.5 (C11H), 127.2 (C18), 123.3 (C17H), 122.2 (C22H), 119.6 (C21H), 118.5 (C20H), 111.4 (C23H), 109.7 (C16), 50.8 (C7H_2), 38.4 (C1H_2), 31.4 (C15H_2), 26.0 (C3H_2), 22.3 (C2H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 359.1755; $[C_{28}H_{23}O_2N_2]^+$ requires 359.1754, Δ 0.11 ppm.

_N_-Benzyl-2,2-difluoro-_N_-(6-oxocyclohex-1-en-1-yl)acetamide, 317



Prepared according to **General Procedure K** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.), 2,2-diflouroacetic acid (0.104 mL, 158 mg, 1.65 mmol, 1.10 equiv.), 2-chloro-1-methylpyridinium iodide (843 mg, 3.30 mmol, 2.20 equiv.), Et_3N (0.690 mL, 501 mg, 3.30 mmol, 3.30 equiv.) and CH_2Cl_2 (7.5 mL) for 21 h. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave 2 *N*-benzyl-2,2-difluoro-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**317**) as a yellow oil (381 mg, 1.36 mmol, 91%).

IR (neat) ν_{max}/cm^{-1} = 2952, 1688, 1633, 1497, 1451, 1343, 1269, 1189, 1138, 1062, 977, 910, 864, 722, 701.

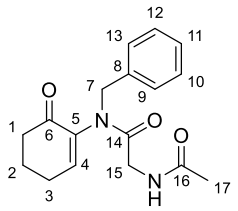
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.23 (3H, m, C10H, C11H & C12H), 7.23–7.13 (2H, m, C9H & C13H), 6.57 (1H, t, *J* = 4.3 Hz, C4H), 5.93 (1H, t, *J* = 53.4 Hz, C15H), 5.29 (1H, d, *J* = 14.5 Hz, C7$\underline{H_A}H_B$), 4.03 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 2.56–2.42 (2H, m, C1H_2), 2.42–2.25 (2H, m, C3H_2), 2.05–1.88 (2H, m, C2H_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.7 (C6), 162.1 (t, *J* = 25 Hz, C14), 151.0 (C4H), 135.8 (C5), 135.7 (C8), 129.2 (C9H & C13H), 128.7 (C10H & C12H), 128.0 (C11H), 108.6 (t, *J* = 253 Hz, C15H) , 51.5 (C7H_2), 38.1 (C1H_2), 25.9 (C3H_2), 22.2 (C2H_2).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -120.91 (dd, *J* = 309.5, 53.6 Hz C15$\underline{F_A}F_B$), -122.31 (d, *J* = 309.6, 53.4 Hz, C15$F_A\underline{F_B}$).

HRMS (ESI^+) Found $[M+H]^+$ = 280.1143; $[C_{15}H_{16}O_2NF_2]^+$ requires 280.1144, Δ -0.26 ppm.

2-Acetamido-N-benzyl-N-(6-oxocyclohex-1-en-1-yl)acetamide, 318



Prepared according to **General Procedure K** with 2-(benzylammino)cyclohex-2-en-1-one (**256**) (201 mg, 1.00 mmol, 1.00 equiv.), *N*-acetylglycine (129 mg, 1.10 mmol, 1.10 equiv.), 2-chloro-1-methylpyridinium iodide (562 mg, 2.20 mmol, 2.20 equiv.), Et_3N (0.360 mL, 261 mg, 3.30 mmol, 3.30 equiv.) and CH_2Cl_2 (10 mL) for 22 h. Purification by flash column chromatography (100:0→85:15 v/v EtOAc:MeOH) gave 2-acetamido-*N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**318**) as a yellow oil (187 mg, 0.621 mmol, 62%).

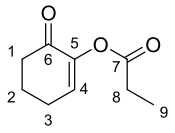
IR (neat) ν_{max}/cm^{-1} = 3460, 2935, 2456, 1652, 1580, 1542, 1412, 1363, 1268, 1233, 1190, 1155, 1125, 1006, 977, 877, 840, 762, 721, 703.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.25 (3H, m, C10H, C11H & C12H), 7.19–7.14 (2H, m, C9H & C13H), 6.57 (1H, t, *J* = 4.3 Hz, C4H), 6.51 (1H, s, N$\underline{H}$), 5.36 (1H, d, *J* = 14.4 Hz, C7$\underline{H_A}H_B$), 4.07 (1H, dd, *J* = 17.6, 5.1 Hz, C15$\underline{H_A}H_B$), 3.91 (1H, d, *J* = 14.5 Hz, C7$H_A\underline{H_B}$), 3.50 (1H, dd, *J* = 17.6, 3.3 Hz, C15$H_A\underline{H_B}$), 2.59–2.41 (3H, m, C1$\underline{H_A}H_B$, C1$H_A\underline{H_B}$ & C3$\underline{H_A}H_B$), 2.36–2.24 (1H, m, C3$H_A\underline{H_B}$), 2.12–2.03 (1H, m, C2$\underline{H_A}H_B$), 2.02 (3H, s, C17H_3), 1.99–1.88 (1H, m, C2$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.9 (C6), 170.1 (C16), 168.5 (C14), 151.5 (C4H), 137.0 (C5), 136.6 (C8), 129.1 (C9H & C13H), 128.7 (C10H & C12H), 127.9 (C11H), 51.2 (C7H_2), 41.6 (C15H_2), 38.4 (C1H_2), 26.1 (C3H_2), 23.2 (C17H_3), 22.3 (C2H_2).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 323.1367; $[C_{17}H_{20}O_3N_2Na]^+$ requires 323.1366, Δ 0.22 ppm.

6-Oxocyclohex-1-en-1-yl propionate, 321



To a stirred solution of 1,2-cyclohexanedione (449 g, 4.00 mmol, 1.00 equiv.) in CH_2Cl_2 (20 mL) at 0 °C was added propionyl chloride (0.392 mL, 407 mg, 4.40 mmol, 1.10 equiv.) dropwise, followed by Et_3N (0.613 mL, 445 mg, 4.40 mmol, 1.10 equiv.). The solution was warmed to ambient temperature and stirred for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL), and the combined organic solution washed sequentially with water (30 mL) and brine (30 mL) before being dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (19:1→4:1 v/v Petrol ether 40–60:EtOAc) gave 6-oxocyclohex-1-en-1-yl propionate (**321**) as a colourless oil (428 mg, 2.54 mmol, 64% yield).

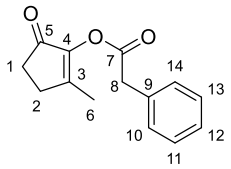
IR (neat) ν_{max}/cm^{-1} = 2944, 2360, 1759, 1689, 1650, 1461, 1419, 1353, 1268, 1244, 1173, 1139, 1106, 1074, 977, 914, 896, 805, 729, 711.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.53 (1H, t, *J* = 4.4 Hz, C4H), 2.54–2.39 (6H, m, $C1H_2$, $C3H_2$ & $C8H_2$), 2.02 (2H, quint, *J* = 6.1 Hz, $C2H_2$), 1.16 (3H, t, *J* = 7.6 Hz, $C9H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 191.8 (C6), 172.4 (C7), 145.4 (C5), 136.0 (C4H), 38.0 ($C1H_2$), 27.0 ($C8H_2$), 24.8 ($C3H_2$), 22.6 ($C2H_2$), 9.0 ($C9H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 191.0679; $[C_9H_{12}O_3Na]^+$ requires 191.0679, Δ 0.31 ppm.

2-Methyl-5-oxocyclopent-1-en-1-yl-2-phenylacetate, 322



To a stirred solution of 3-methylcyclopentane-1,2-dione (1.12 g, 10.0 mmol, 1.00 equiv.) in CH_2Cl_2 (50 mL) at 0 °C was added 2-phenylacetyl chloride (1.46 mL, 1.70 g, 11.0 mmol, 1.10 equiv.) dropwise, followed by Et_3N (1.54 mL, 1.11 g, 11.0 mmol, 1.10 equiv.). The solution was warmed to ambient temperature and stirred for 14 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL), and the combined organic solution washed sequentially with water (100 mL) and brine (100 mL) before being dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 v/v Petrol ether 40–60:Et_2O) gave 2-methyl-5-oxocyclopent-1-en-1-yl-2-phenylacetate (**322**) as a white solid (1.61 g, 6.97 mmol, 70% yield).

m.p. = 61–62 °C.

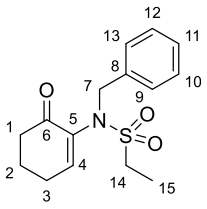
IR (neat) ν_{max}/cm^{-1} = 3030, 2916, 1753, 1712, 1664, 1498, 1438, 1410, 1386, 1349, 1325, 1215, 1195, 1129, 1086, 1030, 932, 842, 813, 780, 733, 702, 665.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.43–7.18 (5H, m, C10H, C11H, C12H, C13H & C14H), 3.86 (2H, s, $C8H_2$), 2.58–2.51 (2H, m, $C2H_2$), 2.49–2.41 (2H, m, $C1H_2$), 1.87 (3H, s, $C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 200.0 (C5), 168.5 (C7), 161.0 (C4), 146.3 (C3), 133.4 (C9), 129.4 (C10H & C14H), 128.8 (C11H & C13H), 127.5 (C12H), 40.8 ($C8H_2$), 32.6 ($C1H_2$), 28.1 ($C2H_2$), 15.3 ($C6H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 231.1017; $[C_{14}H_{15}O_3]^+$ requires 231.1016, Δ 0.49 ppm.

***N*-Benzyl-*N*-(6-oxocyclohex-1-en-1-yl)ethanesulfonamide, 324**



To a solution of 2-(benzylammino)cyclohex-2-en-1-one (**256**) (302 mg, 1.50 mmol, 1.00 equiv.) in CH_2Cl_2 (7.5 mL) at 0 °C was added ethanesulfonyl chloride (0.156 mL, 213 mg, 1.65 mmol, 1.10 equiv.) dropwise followed by pyridine (0.133 mL, 131 mg, 1.65 mmol, 1.10 equiv.) dropwise. The mixture was warmed to ambient temperature and allowed to stir for 96 h, before being diluted with CH_2Cl_2 (10 mL). The crude reaction mixture was washed with water (20 mL), brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (9:1→1:1 v/v Petrol ether 40–60:Et_2O) gave *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)ethanesulfonamide (**324**) as a yellow oil (93.9 mg, 0.320 mmol, 21%).

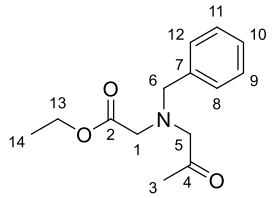
IR (neat) ν_{max}/cm^{-1} = 2941, 1682, 1592, 1496, 1455, 1331, 1288, 1239, 1207, 1186, 1144, 1120, 1092, 1064, 1046, 1029, 976, 917, 891, 799, 722, 701, 613.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.18 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.80 (1H, t, *J* = 4.3 Hz, C4H), 4.62 (2H, s, $C7H_2$), 3.14 (2H, q, *J* = 7.4 Hz, $C14H_2$), 2.41 (2H, t, *J* = 6.6 Hz, $C1H_2$), 2.31 (2H, q, *J* = 5.3 Hz, $C3H_2$), 1.88 (2H, quint, *J* = 6.1 Hz, $C2H_2$), 1.44 (3H, t, *J* = 7.4 Hz, $C15H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 196.2 (C6), 155.6 (C4H), 136.6 (C5), 134.7 (C8), 128.9 (C9H & C13H), 128.6 (C10H & C12H), 127.9 (C11H), 52.7 ($C7H_2$), 47.5 ($C14H_2$), 38.7 ($C1H_2$), 26.4 ($C3H_2$), 22.2 ($C2H_2$), 8.3 ($C15H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 294.1160; $[C_{15}H_{20}O_3NS]^+$ requires 294.1158, Δ 0.64 ppm.

Ethyl *N*-benzyl-*N*-(2-oxopropyl)glycinate, 329



Modified literature procedure.[116] To a solution of ethyl benzylglycinate (*N*-benzylglycine ethyl ester; 5.25 g, 27.2 mmol, 1.00 equiv.) in ethanol (15 mL) under an atmosphere of argon was added sodium bicarbonate (2.78 g, 32.6 mmol, 1.20 equiv.) and the resulting mixture heated to 55 °C. A solution of chloroacetone (2.16 mL, 2.52 g, 27.2 mmol, 1.00 equiv.) in ethanol (5 mL) was then added dropwise over the course of 5 minutes, before the reaction was heated at 60 °C for a further 22 h. After cooling to ambient temperature, the crude reaction mixture was filtered and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (9:1→2:1 v/v pentane:EtOAc) gave ethyl *N*-benzyl-*N*-(2-oxopropyl)glycinate (**329**) as a yellow oil (4.55 g, 18.3 mmol, 67%).

IR (neat) ν_{max}/cm^{-1} = 2982, 2905, 1728, 1495, 1454, 1415, 1354, 1189, 1149, 1077, 1028, 964, 918, 852, 808, 742, 700, 626.

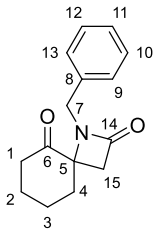
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.39–7.24 (5H, m, C8H, C9H, C10H, C11H & C12H), 4.16 (2H, q, J = 7.2 Hz, $C13H_2$), 3.84 (2H, s, $C7H_2$), 3.53 (2H, s, $C5H_2$), 3.46 (2H, s, $C1H_2$), 2.12 (3H, s, $C3H_3$), 1.26 (3H, t, J = 7.1 Hz, ($C14H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.1 (C4), 171.3 (C2), 138.3 (C7), 129.2 (C9H & C11H), 128.6 (C8H & C12H), 127.6 (C10H), 63.3 ($C5H_2$), 60.6 ($C13H_2$), 58.6 ($C7H_2$), 54.5 ($C1H_2$), 27.7 ($C3H_3$), 14.4 ($C14H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 250.1438; $[C_{14}H_{20}O_3N]^+$ requires 250.1438, Δ -0.07 ppm.

The data matched that reported in the literature.[116,117]

1-Benzyl-1-azaspiro[3.5]nonane-2,5-dione, 333



Prepared according to **General Procedure L** with *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**271**) (73.0 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (2:1→1:2 v/v Petrol ether 40–60:EtOAc) gave 1-benzyl-1-azaspiro[3.5]nonane-2,5-dione (**333**) as a yellow oil (15.3 mg, 0.0629 mmol, 21%).

IR (neat) ν_{max}/cm^{-1} = 2940, 2864, 1753, 1715, 1650, 1496, 1389, 1197, 1127, 1076, 1060, 966, 926, 861, 724, 699.

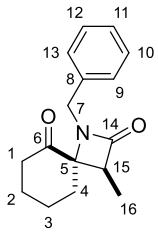
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.24 (5H, m, C9H, C10H, C11H, C12H & C13H), 4.91 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.21 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 2.90 (2H, s, C15H_2), 2.54–2.44 (1H, m, C1$\underline{H_A}H_B$), 2.43–2.30 (1H, m, C1$H_A\underline{H_B}$), 2.05–1.97 (1H, m, C2$\underline{H_A}H_B$), 1.83–1.76 (1H, m, C3$\underline{H_A}H_B$), 1.75–1.69 (1H, m, C4$\underline{H_A}H_B$), 1.61–1.51 (3H, m, C2$H_A\underline{H_B}$, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$).

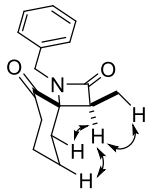
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.5 (C6), 164.8 (C14), 137.2 (C8), 128.7 (C9H & C13H), 128.6 (C10H & C12H), 127.7 (C11H), 65.9 (C5), 48.3 (C15H_2), 45.2 (C7H_2), 40.4 (C1H_2), 37.2 (C4H_2), 26.2 (C2H_2), 23.4 (C3H_2).

HRMS (ESI^+) Found $[M+Na]^+$ = 266.1154; $[C_{15}H_{17}O_2NNa]^+$ requires 266.1152, Δ 0.89 ppm.

The data matched that reported in the literature.[79]

(3*S,4*S**)-1-Benzyl-3-methyl-1-azaspiro[3.5]nonane-2,5-dione, 334**





Prepared according to **General Procedure L** with *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)propionamide (**272**) (77.2 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-methyl-1-azaspiro[3.5]nonane-2,5-dione (**334**) as a yellow oil (63.5 mg, 0.248 mmol, 82%, >20:1 d.r.).

IR (neat) ν_{max}/cm^{-1} = 3030, 2935, 2862, 1747, 1710, 1602, 1496, 1454, 1398, 1350, 1156, 1107, 1077, 1029, 1013, 970, 913, 875, 856, 822, 782, 731.

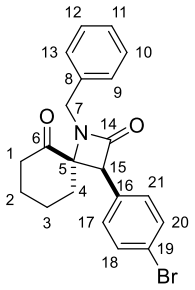
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.19 (5H, m, C9H, C10H, C11H, C12H & C13H), 4.88 (1H, d, *J* = 15.4 Hz, C7H_AH_B), 4.10 (1H, d, *J* = 15.4 Hz, C7H_AH_B), 3.08 (1H, q, *J* = 7.5 Hz, C15H), 2.64–2.53 (1H, m, C1H_AH_B), 2.22–2.11 (1H, m, C1H_AH_B), 2.04–1.95 (1H, m, C2H_AH_B), 1.80–1.70 (2H, m, C3H_AH_B & C4H_AH_B), 1.60–1.47 (3H, m, C2H_AH_B, C3H_AH_B & C4H_AH_B), 1.20 (3H, d, *J* = 7.5 Hz, C16H_3).

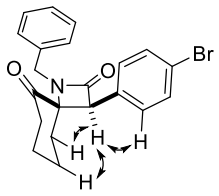
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.2 (C6), 168.4 (C14), 137.3 (C8), 128.7 (C9H & C13H), 128.5 (C10H & C12H), 127.6 (C11H), 71.1 (C5), 55.7 (C15H), 44.8 (C7H_2), 42.5 (C1H_2), 37.8 (C4H_2), 26.0 (C2H_2), 23.4 (C3H_2), 11.0 (C16H_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 280.1307; $[C_{16}H_{19}O_2Na]^+$ requires 280.1308, Δ -0.44 ppm.

The data matched that reported in the literature.[79]

(3*S,4*S**)-1-Benzyl-3-(4-bromophenyl)-1-azaspiro[3.5]nonane-2,5-dione, 335**





Prepared according to **General Procedure L** with 2-*N*-benzyl-2-(4-bromophenyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**283**) (119.5 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-(4-bromophenyl)-1-azaspiro[3.5]nonane-2,5dione (**335**) as an off-white solid (77.7 mg, 0.195 mmol, 65%, 11:1 d.r.).

m.p. = 201–203 °C.

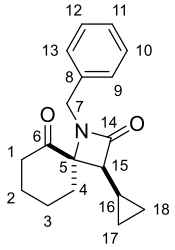
IR (neat) ν_{max}/cm^{-1} = 2935, 2861, 1752, 1710, 1592, 1489, 1454, 1397, 1350, 1234, 1172, 1133, 1106, 1074, 1055, 1012, 908, 866, 834, 791, 730, 702, 645.

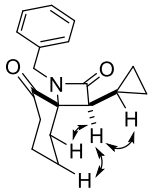
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41 (2H, d, *J* = 8.1 Hz, C18H & C20H), 7.31–7.21 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.99 (2H, d, *J* = 8.0 Hz, C17H & C21H), 5.01 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.23 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 4.19 (1H, s, C15H), 2.15–2.08 (1H, m, C1$\underline{H_A}H_B$), 1.87–1.74 (3H, m, C2$\underline{H_A}H_B$, C3$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.62–1.54 (2H, m, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.45–1.34 (1H, m, C2$H_A\underline{H_B}$), 1.26–1.17 (1H, m, C1$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.4 (C6), 165.7 (C14), 137.0 (C16), 132.3 (C18H & C20H), 131.5 (C8), 130.8 (C17H & C21H), 128.8 (C9H & C13H), 128.6 (C10H & C12H), 127.9 (C11H), 122.7 (C19), 73.8 (C5), 66.8 (C15H), 45.1 ($C7H_2$), 42.0 ($C1H_2$), 38.5 ($C4H_2$), 26.1 ($C2H_2$), 23.4 ($C3H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 398.0751; $[C_{21}H_{21}O_2NBr]^+$ requires 398.0750, Δ 0.29 ppm.

(3*S,4*S**)-1-Benzyl-3-cyclopropyl-1-azaspiro[3.5]nonane-2,5-dione, 336**





Prepared according to **General Procedure L** with *N*-benzyl-2-cyclopropyl-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**273**) (85.0 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-cyclopropyl-1-azaspiro[3.5]nonane-2,5-dione (**336**) as a yellow oil (55.7 mg, 0.197 mmol, 66%, >20:1 d.r.).

IR (neat) ν_{max}/cm^{-1} = 3006, 2935, 2862, 1746, 1709, 1604, 1496, 1453, 1430, 1402, 1384, 1350, 1313, 1163, 1101, 1078, 1063, 1026, 967, 915, 851, 830, 733, 700.

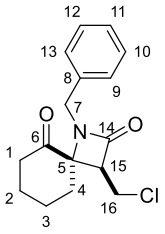
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.10 (5H, m, C9H, C10H, C11H, C12H & C13H), 4.85 (1H, d, *J* = 15.4 Hz, $C7\underline{H_A}H_B$), 4.07 (1H, d, *J* = 15.4 Hz, $C7H_A\underline{H_B}$), 2.58–2.42 (3H, m, $C1H_2$ & C15H), 2.04–1.91 (1H, m, $C2\underline{H_A}H_B$), 1.82–1.65 (1H, m, $C3\underline{H_A}H_B$), 1.65–1.54 (1H, m, $C4\underline{H_A}H_B$), 1.54–1.37 (3H, m, $C2H_A\underline{H_B}$, $C3H_A\underline{H_B}$ & $C4H_A\underline{H_B}$), 0.78–0.65 (1H, m, C16H), 0.65–0.56 (1H, m,

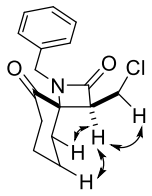
C18$\underline{H_A}H_B$), 0.56–0.46 (1H, m, C17$\underline{H_A}H_B$), 0.46–0.35 (1H, m, C18$H_A\underline{H_B}$), 0.35–0.22 (1H, m, C17$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.7 (C6), 166.9 (C14), 137.4 (C8), 128.6 (C9H & C13H), 128.5 (C10H & C12H), 127.6 (C11H), 71.4 (C5), 65.8 (C15H), 44.7 ($C7H_2$), 42.0 ($C1H_2$), 37.7 ($C4H_2$), 26.1 ($C2H_2$), 23.5 ($C3H_2$), 7.5 (C16H), 4.4 ($C17H_2$), 3.9 ($C18H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 284.1643; $[C_{18}H_{22}O_2N]^+$ requires 284.1645, Δ -0.81 ppm.

(3*S,4*S**)-1-Benzyl-3-(chloromethyl)-1-azaspiro[3.5]nonane-2,5-dione, 337**





Prepared according to **General Procedure L** with for *N*-benzyl-3-chloro-*N*-(6-oxocyclohex-1-en-1-yl)propanamide (**275**) (87.5 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (4:1→2:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-(chloromethyl)-1-azaspiro[3.5]nonane-2,5-dione (**337**) as a yellow solid (11.4 mg, 0.0391 mmol, 13%, 2:1 d.r.) and recovered *N*-benzyl-3-chloro-*N*-(6-oxocyclohex-1-en-1-yl)propanamide (**275**) (13.7 mg, 0.0470 mmol, 15% BRSM).

Only NMR peaks corresponding to the major diastereomer are reported.

m.p. = 86–88 °C.

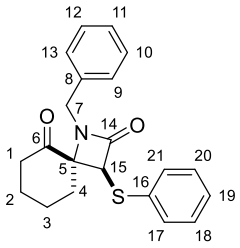
IR (neat) ν_{max}/cm^{-1} = 3031, 2939, 2864, 1755, 1710, 1496, 1452, 1399, 1316, 1285, 1179, 1131, 1106, 1077, 1029, 1001, 970, 919, 855, 750, 698.

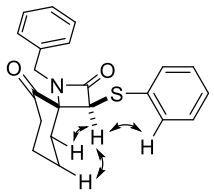
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–7.25 (5H, m, C9H, C10H, C11H, C12H & C13H), 4.87 (1H, d, J = 15.4 Hz, C7$\underline{H_A}H_B$), 4.05 (1H, d, J = 15.4 Hz, C7$H_A\underline{H_B}$), 3.93–3.84 (1H, m, C16$\underline{H_A}H_B$), 3.48–3.36 (2H, m, C15H & C16$H_A\underline{H_B}$), 2.81–2.72 (1H, m, C1$\underline{H_A}H_B$), 2.64–2.57 (1H, m, C1$H_A\underline{H_B}$), 2.09–2.01 (1H, m, C2$\underline{H_A}H_B$), 1.81–1.70 (3H, m, C3H_2 & C4$\underline{H_A}H_B$), 1.60–1.57 (1H, m, C4$H_A\underline{H_B}$), 1.55–1.46 (1H, m, C2$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.1 (C6), 164.2 (C14), 136.6 (C8), 128.8 (C9H & C13H), 128.6 (C10H & C12H), 127.9 (C11H), 71.2 (C5), 64.8 (C15), 45.1 (C7H_2), 41.8 (C1H_2), 39.1 (C16H_2), 37.3 (C4H_2), 25.7 (C2H_2), 22.7 (C3H_2).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 314.0920; $[C_{16}H_{18}O_2NClNa]^+$ requires 314.0918, Δ 0.39 ppm.

(3*S,4*R**)-1-Benzyl-3-(phenylthiol)-1-azaspiro[3.5]nonane-2,5-dione, 338**





Prepared according to **General Procedure L** with *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(phenylthiol)acetamide (**277**) (105.4 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*R**)-1-benzyl-3-(phenylthiol)-1-azaspiro[3.5]nonane-2,5-dione (**338**) as a yellow oil (48.5 mg, 0.138 mmol, 46%, >20:1 d.r.).

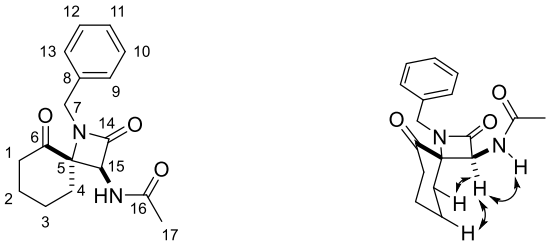
IR (neat) ν_{max}/cm^{-1} = 3060, 2936, 2861, 1756, 1712, 1583, 1496, 1481, 1439, 1391, 1351, 1311, 1164, 1130, 1106, 1077, 1026, 1002, 956, 916, 860, 735, 698.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.55–7.42 (2H, m, C17H & C21H), 7.31–7.17 (8H, m, C9H, C10H, C11H, C12H, C13H, C18H, C19H & C20H), 4.85 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.24 (1H, s, C15H), 4.09 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 2.64–2.48 (2H, m, C1H_2), 1.92–1.84 (1H, m, C2$\underline{H_A}H_B$), 1.70–1.61 (2H, m, C3$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.55–1.47 (1H, m, C4$H_A\underline{H_B}$), 1.46–1.27 (2H, m, C2$H_A\underline{H_B}$ & C3$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 206.6 (C6), 164.3 (C14), 136.8 (C8), 133.2 (C16), 131.7 (C17H & C21H), 129.4 (C18H & C20H), 128.8 (C9H & C13H), 128.6 (C10H & C12H), 128.1 (C19H), 127.8 (C11H), 73.2 (C5), 63.1 (C15H), 45.3 (C7H_2), 42.6 (C1H_2), 37.9 (C4H_2), 26.2 (C2H_2), 23.3 (C3H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 352.1367; $[C_{21}H_{22}O_2NS]^+$ requires 352.1366, Δ 0.23 ppm.

_N_-((3_S_*,4_S_*)-1-Benzyl-2,5-dioxo-1-azaspiro[3.5]nonan-3-yl)acetamide, 339



Prepared according to **General Procedure L** with 2-acetamido-*N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**318**) (90.1 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (1:2→1:5 v/v Petrol ether 40–60:EtOAc) gave *N*-((3*S**,4*S**)-1-benzyl-2,5-dioxo-1-azaspiro[3.5]nonan-3-yl)acetamide (**339**) as an off-white solid (42.3 mg, 0.140 mmol, 47%, >20:1 d.r.).

m.p. = 147–149 °C.

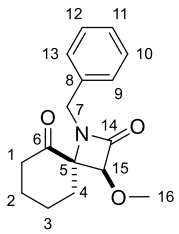
IR (neat) ν_{max}/cm^{-1} = 3275, 3033, 2942, 2865, 1753, 1711, 1667, 1540, 1497, 1453, 1401, 1372, 1286, 1176, 1136, 1102, 1079, 1050, 1005, 918, 804, 731, 701, 646.

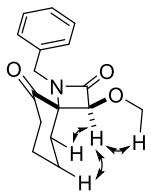
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.23 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.79 (1H, d, J = 8.4 Hz, N$\underline{H}$), 5.06 (1H, d, J = 8.4 Hz, C15H), 4.96 (1H, d, J = 15.4 Hz, C7$\underline{H_A}H_B$), 4.11 (1H, d, J = 15.4 Hz, C7$H_A\underline{H_B}$), 2.55–2.43 (1H, m, C1$\underline{H_A}H_B$), 2.10–1.91 (3H, m, C1$H_A\underline{H_B}$, C2$\underline{H_A}H_B$ & C3$\underline{H_A}H_B$), 2.02 (3H, s, C17H_3), 1.88–1.78 (1H, m, C4$\underline{H_A}H_B$), 1.78–1.68 (1H, m, C3$H_A\underline{H_B}$), 1.60–1.37 (2H, m, C2$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.2 (C6), 170.8 (C16), 165.1 (C14), 136.4 (C8), 128.8 (C9H & C13H), 128.5 (C10H & C12H), 128.0 (C11H), 74.5 (C5), 66.0 (C15H), 45.1 (C7H_2), 41.9 (C1H_2), 35.9 (C4H_2), 25.7 (C2H_2), 23.1 (C17H_3), 22.3 (C3H_2).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 323.1368; $[C_{17}H_{20}O_3N_2Na]^+$ requires 323.1366, Δ 0.51 ppm.

(3*S,4*S**)-1-Benzyl-3-methoxy-1-azaspiro[3.5]nonane-2,5-dione, 340**





Prepared according to **General Procedure L** with *N*-benzyl-2-methoxy-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**278**) (82.0 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography

(3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-methoxy-1-azaspiro[3.5]nonane-2,5-dione (**340**) as a yellow oil (44.9 mg, 0.164 mmol, 55%, 10:1 d.r.).

Only NMR peaks corresponding to the major diastereomer are reported.

IR (neat) ν_{max}/cm^{-1} = 2937, 1753, 1716, 1496, 1452, 1394, 1350, 1215, 1167, 1145, 1108, 1077, 1050, 1004, 818, 700.

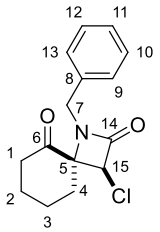
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.20 (5H, m, C9H, C10H, C11H, C12H & C13H), 4.93 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.30 (1H, s, C15H), 4.16 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 3.57 (3H, s, C16H_3), 2.57–2.47 (1H, m, C1$\underline{H_A}H_B$), 2.47–2.34 (1H, m, C1$H_A\underline{H_B}$), 2.07–1.94 (1H, m, C2$\underline{H_A}H_B$), 1.84–1.73 (1H, m, C3$\underline{H_A}H_B$), 1.72–1.57 (2H, m, C3$H_A\underline{H_B}$ & C4$\underline{H_A}H_B$), 1.57–1.40 (2H, m, C2$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$).

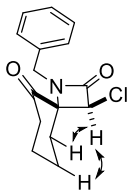
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 206.8 (C6), 165.4 (C14), 137.0 (C8), 128.7 (C9H & C13H), 128.5 (C10H & C12H), 127.8 (C11H), 90.5 (C15H), 72.8 (C5), 58.9 (C16H_3), 44.6 (C7H_2), 42.0 (C1H_2), 36.2 (C4H_2), 26.2 (C2H_2), 23.4 (C3H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 274.1439; $[C_{16}H_{20}O_3N]^+$ requires 274.1438, Δ 0.33 ppm.

The data matched that reported in the literature.[79]

(3*S,4*R**)-1-Benzyl-3-chloro-1-azaspiro[3.5]nonane-2,5-dione, 341**





Prepared according to **General Procedure L** with *N*-benzyl-2-chloro-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**276**) (83.3 mg, 0.300 mmol,

1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (4:1→2:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*R**)-1-benzyl-3-chloro-1-azaspiro[3.5]nonane-2,5-dione (**341**) as an off-white solid (20.7 mg, 0.0745 mmol, 25%, >20:1 d.r.) and recovered *N*-benzyl-2-chloro-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**276**) as a yellow oil (24.9 mg, 0.0896 mmol).

m.p. = 103–105°C.

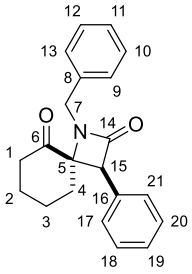
IR (neat) ν_{max}/cm^{-1} = 2942, 2864, 1770, 1717, 1497, 1453, 1394, 1351, 1312, 1180, 1136, 1108, 1078, 1054, 1029, 1005, 945, 906, 861, 822, 797, 735, 699, 638.

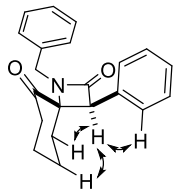
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.38–7.20 (5H, m, C9H, C10H, C11H, C12H & C13H), 4.96 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.57 (1H, s, C15H), 4.19 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 2.71–2.48 (2H, m, C1H_2), 2.11–2.01 (1H, m, C2$\underline{H_A}H_B$), 1.88–1.79 (1H, m, C3$\underline{H_A}H_B$), 1.76–1.70 (1H, m, C4$\underline{H_A}H_B$), 1.64–1.50 (3H, m, C2$H_A\underline{H_B}$, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 205.1 (C6), 161.7 (C14), 136.3 (C8), 128.9 (C9H & C13H), 128.7 (C10H & C12H), 128.1 (C11H), 72.9 (C5), 62.7 (C15H), 45.7 (C7H_2), 42.4 (C1H_2), 37.2 (C4H_2), 26.1 (C2H_2), 23.2 (C3H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 278.0943; $[C_{15}H_{17}O_2NCl]^+$ requires 278.0942, Δ 0.35 ppm.

(3*S,4*S**)-1-Benzyl-3-phenyl-1-azaspiro[3.5]nonane-2,5-dione, 343**





Prepared according to **General Procedure L** with *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-phenylacetamide (**279**) (95.8 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-phenyl-1-azaspiro[3.5]nonane-2,5-dione (**343**) as an off-white solid (74.9 mg, 0.238 mmol, 78%, >20:1 d.r.).

m.p. = 133–135 °C from $CHCl_3$ (lit. 152–153 °C from EtOAc).

IR (neat) ν_{max}/cm^{-1} = 2935, 1749, 1710, 1497, 1454, 1395, 1349, 1159, 1133, 1108, 1077, 1056, 1029, 1001, 956, 914, 843, 807, 758, 731, 699, 646, 621.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.23 (8H, m, C10H, C11H, C12H, C17H, C18H, C19H, C20H & C21H), 7.19–7.12 (2H, m, C9H & C13H), 5.07 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.29 (1H, d, *J* = 15.1 Hz, C7$H_A\underline{H_B}$), 4.28 (1H, s, C15H) 2.14–2.04 (1H, m, C1$\underline{H_A}H_B$), 1.94–1.73 (3H, m, C2$\underline{H_A}H_B$, C3$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.71–1.56 (2H, m, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.50–1.35 (1H, m, C2$H_A\underline{H_B}$), 1.32–1.18 (1H, m, C1$H_A\underline{H_B}$).

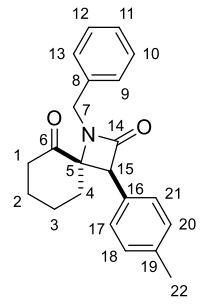
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.7 (C6), 166.3 (C14), 137.3 (C8), 132.4 (C16), 129.1 (C9H, C13H, C17H & C21H), 128.8 (C18H & C20H), 128.6 (C10H & C12H), 128.5 (C19H), 127.8

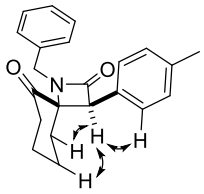
(C11H), 74.0 (C5), 67.6 (C15H), 45.0 ($C7H_2$), 41.8 ($C1H_2$), 38.7 ($C4H_2$), 26.2 ($C2H_2$), 23.4 ($C3H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 320.1645; $[C_{21}H_{22}O_2N]^+$ requires 320.1645, Δ -0.05 ppm.

The data matched that reported in the literature.[78,79]

(3*S,4*S**)-1-Benzyl-3-(*p*-tolyl)-1-azaspiro[3.5]nonane-2,5-dione, 344**





Prepared according to **General Procedure L** with *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(p-tolyl)acetamide (**280**) (100.0 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (5:1→4:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-(*p*-tolyl)-1-azaspiro[3.5]nonane-2,5-dione (**344**) as an off-white solid (75.0 mg, 0.225 mmol, 75%, >20:1 d.r.).

m.p. = 164–166 °C.

IR (neat) ν_{max}/cm^{-1} = 2931, 2861, 1750, 1710, 1517, 1496, 1453, 1395, 1350, 1160, 1133, 1109, 1078, 1056, 1003, 917, 829, 791, 730, 699, 646.

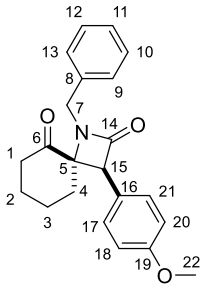
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.25 (5H, m, C9H, C10H, C11H, C12H & C13H), 7.12 (2H, d, *J* = 7.7 Hz, C18H & C20H), 7.04 (2H, d, *J* = 7.8 Hz, C17H & C21H), 5.07 (1H, d, *J* = 15.3 Hz, $C7\underline{H_A}H_B$), 4.29 (1H, d, *J* = 15.3 Hz, $C7H_A\underline{H_B}$), 4.25 (1H, s, C15H), 2.30 (3H, s, $C22H_3$), 2.14–

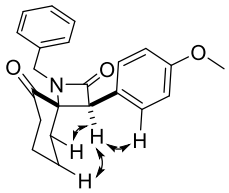
2.06 (1H, m, C1$\underline{H_A}H_B$), 1.90–1.76 (3H, m, C2$\underline{H_A}H_B$, C3$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.70–1.56 (2H, m, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.48–1.36 (1H, m, C2$H_A\underline{H_B}$), 1.33–1.23 (1H, m, C1$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.9 (C6), 166.6 (C15), 138.3 (C19), 137.3 (C8), 129.8 (C18H & C20H), 129.3 (C16), 129.0 (C17H & C21H), 128.7 (C9H & C13H), 128.6 (C10H & C12H), 127.7 (C11H), 74.0 (C5), 67.3 (C15H), 45.0 ($C7H_2$), 41.9 ($C1H_2$), 38.6 ($C4H_2$), 26.2 ($C2H_2$), 23.4 ($C3H_2$), 21.3 ($C22H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 334.1803; $[C_{22}H_{24}O_2N]^+$ requires 334.1802, Δ 0.33 ppm.

(3*S,4*S**)-1-Benzyl-3-(4-methoxyphenyl)-1-azaspiro[3.5]nonane-2,5-dione, 345**





Prepared according to **General Procedure L** with *N*-benzyl-2-(4-methoxyphenyl)-*N*--(6-oxocyclohex-1-en-1-yl)acetamide (**281**) (104.8 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (4:1→2:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-(4-methoxyphenyl)-1-azaspiro[3.5]nonane-2,5-dione (**345**) as a white solid (73.8 mg, 0.211 mmol, 70%, >20:1 d.r.).

m.p. = 163–165 °C.

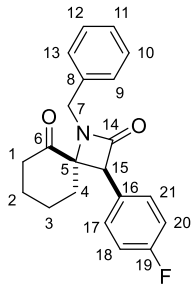
IR (neat) ν_{max}/cm^{-1} = 2935, 1751, 1710, 1612, 1515, 1454, 1396, 1297, 1251, 1181, 1134, 1111, 1056, 1030, 917, 837, 798, 728, 700.

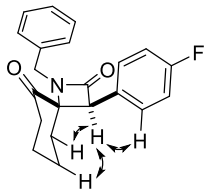
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28–7.18 (5H, m, C9H, C10H, C11H, C12H & C13H), 7.00 (2H, d, *J* = 8.5 Hz, C17H & C21H), 6.77 (2H, d, *J* = 8.5 Hz, C18H & C20H), 4.98 (1H, d, *J* = 15.2 Hz, C7$\underline{H_A}H_B$), 4.18 (1H, d, *J* = 15.2 Hz, C7$H_A\underline{H_B}$), 4.17 (1H, s, C15H), 3.69 (3H, s, C22H_3), 2.08–2.00 (1H, m, C1$\underline{H_A}H_B$), 1.82–1.75 (2H, m, C2$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.74–1.67 (1H, m, C3$\underline{H_A}H_B$), 1.61–1.52 (2H, m, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.40–1.30 (1H, m, C2$H_A\underline{H_B}$), 1.26–1.17 (1H, m, C1$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.0 (C6), 166.8 (C14), 159.6 (C19), 137.3 (C8), 130.3 (C17H & C21H), 128.8 (C9H & C13H), 128.6 (C10H & C12H), 127.8 (C11H), 124.3 (C16), 114.5 (C18H & C20H), 74.0 (C5), 67.0 (C15H), 55.4 (C22H_3), 45.0 (C7H_2), 42.0 (C1H_2), 38.5 (C4H_2), 26.2 (C2H_2), 23.4 (C3H_2).

HRMS (ESI^+) Found $[M+H]^+$ = 350.1752; $[C_{22}H_{24}O_3N]^+$ requires 350.1751, Δ 0.37 ppm.

(3*S,4*S**)-1-Benzyl-3-(4-fluorophenyl)-1-azaspiro[3.5]nonane-2,5-dione, 346**





Prepared according to **General Procedure L** with *N*-benzyl-2-(4-fluorophenyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**282**) (101.2 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (4:1→2:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-(4-fluorophenyl)-1-azaspiro[3.5]nonane-2,5-dione (**346**) as a white solid (75.2 mg, 0.223 mmol, 74%, 17:1 d.r.).

m.p. = 140–142 °C.

IR (neat) ν_{max}/cm^{-1} = 2935, 1750, 1711, 1606, 1511, 1453, 1397, 1350, 1226, 1161, 1134, 1101, 1056, 1004, 917, 841, 802, 731, 699, 648.

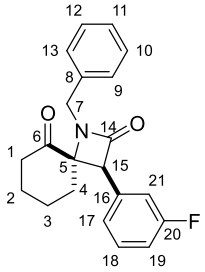
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.16 (5H, m, C9H, C10H, C11H, C12H & C13H), 7.10–7.00 (2H, m, C17H & C21H), 6.99–6.86 (2H, m, C18H & C20H), 4.98 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.30–4.08 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 4.19 (1H, s, C15H) 2.11–1.98 (1H, m, C1$\underline{H_A}H_B$), 1.88–1.70 (3H, m, C2$\underline{H_A}H_B$, C3$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.63–1.51 (2H, m, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.43–1.32 (1H, m, C2$H_A\underline{H_B}$), 1.22–1.11 (1H, m, C1$H_A\underline{H_B}$).

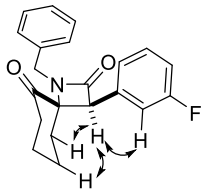
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.6 (C6), 166.1 (C14), 162.7 (d, *J* = 248.0 Hz, C19F), 137.1 (C8), 130.93 (d, *J* = 8.5 Hz, C17H & C21H), 128.8 (C9H & C13H), 128.6 (C10H & C12H), 128.3 (d, *J* = 3.7 Hz, C16), 127.8 (C11H), 116.2 (d, *J* = 21.8 Hz, C18H & C20H), 73.9 (C5), 66.7 (C15H), 45.1 ($C7H_2$), 42.0 ($C1H_2$), 38.5 ($C4H_2$), 26.2 ($C2H_2$), 23.4 ($C3H_2$).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -112.92 (tt, *J* = 8.9, 5.3 Hz, C19F).

HRMS (ESI^+) Found $[M+H]^+$ = 338.1552; $[C_{21}H_{21}O_2NF]^+$ requires 338.1551, Δ 0.47 ppm.

(3*S,4*S**)-1-Benzyl-3-(3-fluorophenyl)-1-azaspiro[3.5]nonane-2,5-dione, 347**





Prepared according to **General Procedure L** with *N*-benzyl-2-(3-fluorophenyl)-*N*-(6 -oxocyclohex-1-en-1-yl)acetamide (**285**) (101.2 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg,

0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-(3-fluorophenyl)-1-azaspiro[3.5]nonane-2,5-dione (**347**) as an off-white solid (65.2 mg, 0.193 mmol, 64%, 10:1 d.r.).

m.p. = 105–107 °C.

IR (neat) ν_{max}/cm^{-1} = 3031, 2938, 2862, 1751, 1711, 1615, 1589, 1489, 1451, 1397, 1351, 1310, 1271, 1241, 1224, 1182, 1150, 1133, 1107, 1077, 1055, 1029, 1003, 964, 914, 858, 782, 731, 699, 683, 647, 608.

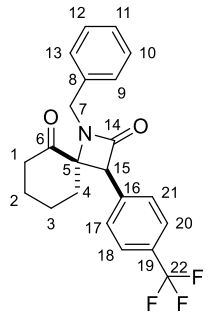
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–7.23 (6H, m, C9H, C10H, C11H, C12H, C13H & C18H), 7.00–6.90 (2H, m, C17H & C19H), 6.89–6.82 (1H, m, C21H), 5.03 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.25 (1H, d, *J* = 15.2 Hz, C7$H_A\underline{H_B}$), 4.23 (1H, s, C15H), 2.16–2.09 (1H, m, C1$\underline{H_A}H_B$), 1.88–1.76 (3H, m, C2$\underline{H_A}H_B$, C3$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.66–1.57 (2H, m, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.47–1.36 (1H, m, C2$H_A\underline{H_B}$), 1.30–1.22 (1H, m, C1$H_A\underline{H_B}$).

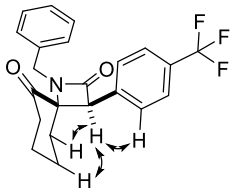
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.3 (C6), 165.6 (C14), 162.91 (d, *J* = 247.9 Hz, C20F), 137.1 (C8), 134.8 (d, *J* = 7.5 Hz, C16), 130.8 (d, *J* = 8.6 Hz, C18H), 128.8 (C10H & C12H), 128.6 (C9H & C13H), 127.9 (C11H), 124.9 (d, *J* = 2.9 Hz, C17H), 116.3 (d, *J* = 22.1 Hz, C21H), 115.6 (d, *J* = 20.8 Hz, C19H), 73.9 (C5), 66.9 (d, *J* = 1.9 Hz, C15H), 45.1 ($C7H_2$), 41.9 ($C1H_2$), 38.6 ($C4H_2$), 26.2 ($C2H_2$), 23.4 ($C3H_2$).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -111.52 (td, *J* = 9.0, 5.9 Hz, C20F).

HRMS (ESI^+) Found $[M+Na]^+$ = 360.1372; $[C_{21}H_{20}O_2NFNa]^+$ requires 360.1370, Δ 0.41 ppm.

(3*S,4*S**)-1-Benzyl-3-(4-trifluoromethyl)phenyl)-1-azaspiro[3.5]nonane-2,5-dione, 348**





Prepared according to **General Procedure L** with *N*-benzyl-*N*-(6-oxocyclohex-1-en1-yl)-2-(4-(trifluoromethyl)phenyl)acetamide (**284**) (116.2 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (4:1→3:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-benzyl-3-(4-trifluoromethyl)phenyl)-1-azaspiro[3.5]nonane-2,5-dione (**348**) as an off-white solid (50.8 mg, 0.134 mmol, 44%, 6:1 d.r.).

m.p. = 141–143 °C.

IR (neat) ν_{max}/cm^{-1} = 2939, 1755, 1713, 1620, 1496, 1453, 1421, 1398, 1324, 1260, 1166, 1124, 1113, 1070, 1019, 955, 918, 845, 798, 734, 701, 646.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.51 (2H, d, *J* = 8.1 Hz, C18H & C20H), 7.28–7.17 (7H, m, C9H, C10H, C11H, C12H, C13H, C17H & C21H), 4.99 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.24 (1H, s, C15H), 4.19 (1H, d, *J* = 15.2 Hz, C7$H_A\underline{H_B}$), 2.11–2.04 (1H, m, C1$\underline{H_A}H_B$), 1.86–1.73 (3H, m, C2$\underline{H_A}H_B$, C3$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.59–1.52 (2H, m, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.42–1.31 (1H, m, C2$H_A\underline{H_B}$), 1.17–1.07 (1H, m, C1$H_A\underline{H_B}$).

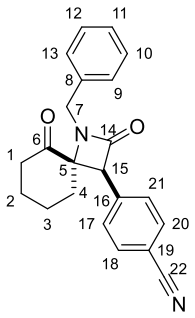
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.2 (C6), 165.4 (C14), 137.0 (C16), 136.6 (C8), 130.7 (d, *J* = 32.8 Hz, C19), 129.6 (C17H & C21H), 128.9 (C9H & C13H), 128.7 (C10H & C12H), 128.0

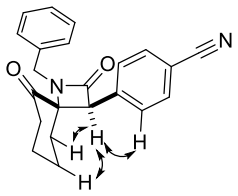
(C11H), 126.2 (q, *J* = 4.0 Hz, C18H & C20H), 125.3 ($C22F_3$), 73.9 (C5), 66.9 (C15H), 45.2 ($C7H_2$), 42.0 ($C1H_2$), 38.6 ($C4H_2$), 26.1 ($C2H_2$), 23.5 ($C3H_2$).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -62.76 (s, $C22F_3$)

HRMS (ESI^+) Found $[M+H]^+$ = 388.1521; $[C_{22}H_{21}O_2NF_3]^+$ requires 388.1519, Δ 0.46 ppm.

4-((3*S,4*S**)-1-Benzyl-2,5-dioxo-1-azaspiro[3.5]nonan-3-yl)benzonitrile, 349**





Prepared according to **General Procedure L** with *N*-benzyl-2-(4-cyanophenyl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**295**) (103.3 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave 4-((3*S**,4*S**)-1-benzyl-2,5-dioxo-1-azaspiro[3.5]nonan-3-yl)benzonitrile (**349**) as an off-white solid (43.1 mg, 0.125 mmol, 42%, 5:1 d.r.).

m.p. = 179–181 °C.

IR (neat) ν_{max}/cm^{-1} = 2940, 2229, 1752, 1711, 1608, 1496, 1452, 1398, 1351, 1134, 1110, 1055, 1004, 916, 844, 796, 729, 699, 648.

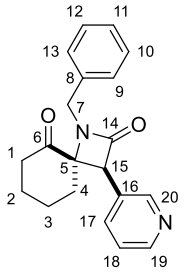
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.58–7.52 (2H, m, C18H & C20H), 7.27–7.19 (7H, m, C9H, C10H, C11H, C12H, C13H, C17H & C21H), 4.97 (1H, d, *J* = 15.2 Hz, $C7\underline{H_A}H_B$), 4.24 (1H, s,

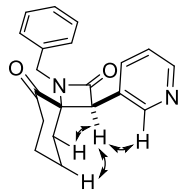
C15H), 4.19 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 2.13–2.06 (1H, m, C1$\underline{H_A}H_B$), 1.88–1.75 (3H, m, C2$\underline{H_A}H_B$, C3$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.61–1.48 (2H, m, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.44–1.33 (1H, m, C2$H_A\underline{H_B}$), 1.15–1.04 (1H, m, C1$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 206.8 (C6), 164.9 (C14), 137.9 (C16), 136.8 (C7), 132.8 (C18H & C20H), 130.0 (C17H & C21H), 128.9 (C9H & C13H), 128.6 (C10H & C12H), 128.0 (C11H), 118.3 (C22), 112.5 (C19), 73.9 (C5), 66.9 (C15H), 45.2 ($C7H_2$), 42.0 ($C1H_2$), 38.5 ($C4H_2$), 26.0 ($C2H_2$), 23.5 ($C3H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 345.1599; $[C_{22}H_{21}O_2N_2]^+$ requires 345.1598, Δ 0.46 ppm.

(3*S,4*S**)-1-Benzyl-3-(pyridin-3-yl)-1-azaspiro[3.5]nonane-2,5-dione, 350**





Prepared according to **General Procedure L** with *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2(pyridin-3-yl)acetamide (**314**) (96.1 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (0%→4% v/v MeOH in EtOAc) gave (3*S**,4*S**)-1-benzyl-3-(pyridin-3-yl)-1-azaspiro[3.5]nonane-2,5-dione (**350**) as an off-white solid (60.3 mg, 0.188 mmol, 63%, 15:1 d.r.).

m.p. = 161–163 °C.

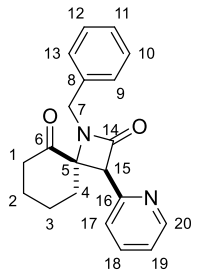
IR (neat) ν_{max}/cm^{-1} = 3031, 2936, 2861, 1751, 1710, 1574, 1496, 1481, 1453, 1426, 1397, 1350, 1310, 1267, 1170, 1133, 1106, 1078, 1064, 1028, 1003, 955, 917, 865, 785, 731, 714, 646, 623.

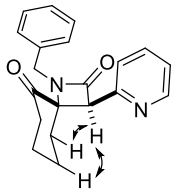
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.52 (1H, dd, *J* = 4.9, 1.7 Hz, C19H), 8.47 (1H, d, *J* = 2.2 Hz, C20H), 7.44 (1H, dt, *J* = 8.0, 2.0 Hz, C17H), 7.36–7.31 (4H, m, C9H, C10H, C12H, C13H), 7.29 (1H, dd, *J* = 5.5, 3.0 Hz, C18H), 7.26–7.22 (1H, m, C11H), 5.04 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.30 (1H, s, C15H), 4.23 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 2.20–2.12 (1H, m, C1$\underline{H_A}H_B$), 1.95–1.90 (1H, m, C4$\underline{H_A}H_B$), 1.89–1.80 (2H, m, C2$\underline{H_A}H_B$ & C3$\underline{H_A}H_B$), 1.68–1.59 (2H, m, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.50–1.36 (1H, m, C2$H_A\underline{H_B}$), 1.24–1.15 (1H, m, C1$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.0 (C6), 165.1 (C14), 150.7 (C20H), 149.8 (C19H), 136.7 (C8), 135.8 (C17H), 128.8 (C9H & C13H), 128.5 (C10H & C12H), 128.4 (C16), 127.9 (C18H), 123.8 (C11H), 73.5 (C5), 64.3 (C15H), 45.1 ($C7H_2$), 42.0 ($C1H_2$), 38.2 ($C4H_2$), 25.8 ($C3H_2$), 23.3 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 321.1599; $[C_{20}H_{21}O_2N]^+$ requires 321.1598, Δ 0.30 ppm.

(3*R,4*S**)-1-Benzyl-3-(pyridine-2-yl)-1-azaspiro[3.5]nonane-2,5-dione, 351**





Prepared according to **General Procedure L** with *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(pyridine-2-yl)acetamide (**315**) (64.0 mg, 0.200 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (1.5 mg, 0.002 mmol, 0.01 equiv.), NaOAc (16.4 mg, 0.200 mmol, 1.00 equiv.) and EtOAc (20 mL) for 16 h. Purification by flash column chromatography (2%→4% v/v MeOH in EtOAc) gave

(3*R**,4*S**)-1-benzyl-3-(pyridine-2-yl)-1-azaspiro[3.5]nonane-2,5-dione (**351**) as a viscous yellow gum (17.9 mg, 0.559 mmol, 28%, 2:1 d.r.).

Only NMR peaks corresponding to the major diastereomer are reported.

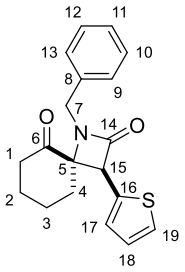
IR (neat) ν_{max}/cm^{-1} = 3062, 2939, 2864, 1744, 1714, 1684, 1589, 1571, 1496, 1473, 1435, 1398, 1350, 1122, 1062, 995, 919, 739, 703.

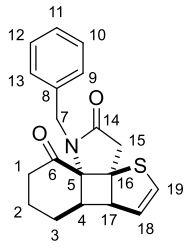
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.57 (1H, ddd, *J* = 4.8, 1.9, 1.0 Hz, C20H), 7.65 (1H, td, *J* = 7.7, 1.8 Hz, C18H), 7.36–7.31 (5H, m, C9H, C10H, C11H, C12H & C13H), 7.23–7.17 (2H, m, C17H & C19H), 5.07 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.51 (1H, s, C15H), 4.30 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 2.14–2.08 (1H, m, C1$\underline{H_A}H_B$), 1.96–1.92 (1H, m, C4$\underline{H_A}H_B$), 1.91–1.87 (2H, m, C2$\underline{H_A}H_B$ & C3$\underline{H_A}H_B$), 1.82–1.78 (1H, m, C3$H_A\underline{H_B}$), 1.65–1.61 (1H, m, C4$H_A\underline{H_B}$), 1.44–1.37 (2H, m, C1$H_A\underline{H_B}$ & C2$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.8 (C6), 165.3 (C14), 153.1 (C16), 150.1 (C20H), 137.3 (C18H), 137.2 (C8), 128.8 (C9H & C13H), 128.7 (C10H & C12H), 127.8 (C11H), 123.7 (C17H), 123.1 (C19H), 73.2 (C5), 69.1 (C15H), 45.2 ($C7H_2$), 41.8 ($C1H_2$), 38.8 ($C4H_2$), 26.4 ($C2H_2$), 23.2 ($C3H_2$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 321.1599; $[C_{20}H_{21}O_2N_2]^+$ requires 321.1598, Δ 0.3 ppm.

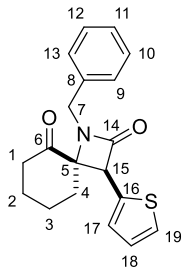
(3*S,4*S**)-1-Benzyl-3-(thiophen-2-yl)-1-azaspiro[3.5]nonane-2,5-dione, 352** and **(3a*S**,6a*R**,6b*R**,10a*R**)-1-benzyl-6b,7,8,9-tetrahydro-1*H*-benzo[1,4]thieno[2',3':2,3]cyclobuta[1,2-*b*]pyrrole-2,10(3*H*,6a*H*)-dione, 381**

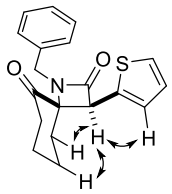




Prepared according to **General Procedure L** with *N*-benzyl-*N*-(6-oxocyclohex-1-en-1-yl)-2-(thiophen-2-yl)acetamide (**286**) (97.6 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (9:1→2:1 v/v Petrol ether 40–60:EtOAc) gave ((3*S**,4*S**)-1-benzyl-3-(thiophen-2-yl)-1-azaspiro[3.5]nonane-2,5-dione (**352**) as a viscous pale yellow oil (35.4 mg, 0.109 mmol, 36%, >20:1 d.r.) and (3a*S**,6a*R**,6b*R**,10a*R**)-1-benzyl-6b,7,8,9-tetrahydro-1*H*-benzo[1,4]thieno[2',3':2,3]cyclobuta[1,2-*b*]pyrrole-2,10(3*H*,6a*H*)-dione (**381**) as an off-white solid (41.9 mg, 0.129 mmol, 43%, 12:1 d.r.).

Data for **(3*S**,4*S**)-1-benzyl-3-(thiophen-2-yl)-1-azaspiro[3.5]nonane-2,5-dione, 352**





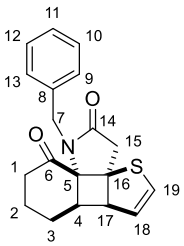
IR (neat) ν_{max}/cm^{-1} = 2932, 2859, 1753, 1710, 1496, 1452, 1394, 1351, 1311, 1269, 1160, 1133, 1105, 1077, 1052, 1002, 955, 916, 852, 800, 727, 699.

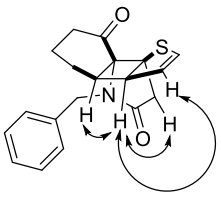
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.20 (5H, m, C9H, C10H, C11H, C12H & C13H), 7.17 (1H, dd, *J* = 5.2, 1.2 Hz, C19H), 6.90 (1H, dd, *J* = 5.2, 3.5 Hz, C18H), 6.81 (1H, dd, *J* = 3.6, 1.1 Hz, C17H), 4.99 (1H, d, *J* = 15.3 Hz, C7$\underline{H_A}H_B$), 4.44 (1H, s, C15H), 4.19 (1H, d, *J* = 15.3 Hz, C7$H_A\underline{H_B}$), 2.23–2.09 (1H, m, C1$\underline{H_A}H_B$), 1.87–1.78 (2H, m, C2$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.76–1.69 (1H, m, C3$\underline{H_A}H_B$), 1.67–1.60 (1H, m, C3$H_A\underline{H_B}$), 1.60–1.52 (1H, m, C4$H_A\underline{H_B}$), 1.47–1.34 (2H, m, C1$H_A\underline{H_B}$ & C2$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.6 (C6), 165.5 (C14), 137.0 (C8), 133.4 (C16), 128.8 (C9H & C13H), 128.6 (C10H & C12H), 128.1 (C11H), 128.0 (C17H), 127.9 (C18H), 126.1 (C19H), 74.2 (C5), 61.5 (C15H), 45.1 ($C7H_2$), 41.7 ($C1H_2$), 38.2 ($C4H_2$), 26.1 ($C2H_2$), 23.2 ($C3H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 326.1210; $[C_{19}H_{20}O_2S]^+$ requires 326.1209, Δ 0.14 ppm.

Data for **(3a*S**,6a*R**,6b*R**,10a*R**)-1-benzyl-6b,7,8,9-tetrahydro-1*H*-benzo[1,4]thieno[2',3':2,3]cyclobuta[1,2-*b*]pyrrole-2,10(3*H*,6a*H*)-dione, 381**





m.p. = 124–126 °C.

IR (neat) ν_{max}/cm^{-1} = 3063, 2937, 1687, 1584, 1496, 1455, 1388, 1357, 1326, 1276, 1209, 1162, 1130, 1801, 1029, 1004, 972, 904, 800, 779, 754, 731, 703, 650, 614.

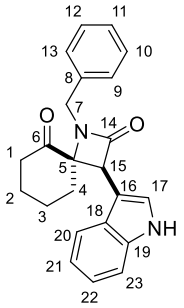
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28–7.05 (5H, m, C9H, C10H, C11H, C12H & C13H), 6.17 (1H, dd, *J* = 6.0, 1.0 Hz, C19H), 5.34 (1H, dd, *J* = 6.1, 3.5 Hz, C18H), 4.83 (1H, d, *J* = 14.9 Hz, C7$\underline{H_A}H_B$), 3.86 (1H, d, *J* = 15.0 Hz, C7$H_A\underline{H_B}$), 3.69–3.62 (1H, m, C17H), 2.85 (1H, d, *J* = 17.8 Hz, C15$\underline{H_A}H_B$), 2.62 (1H, d, *J* = 17.9 Hz, C15$H_A\underline{H_B}$), 2.46 (1H, q, *J* = 8.8 Hz, C4H), 2.40–2.30

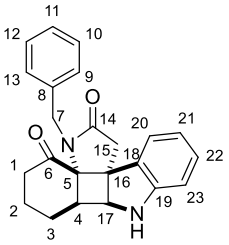
(1H, m, C1$\underline{H_A}H_B$), 2.28–2.20 (1H, m, C1$H_A\underline{H_B}$), 1.91–1.81 (1H, m, C2$\underline{H_A}H_B$), 1.63–1.50 (1H, m, C3$\underline{H_A}H_B$), 1.44–1.25 (2H, m, C2$H_A\underline{H_B}$ & C3$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.3 (C6), 173.3 (C14), 136.4 (C8), 130.9 (C19H), 129.3 (C10H & C12H), 128.8 (C9H & C13H), 128.1 (C11H), 120.9 (C18H), 74.1 (C5), 60.7 (C16), 55.9 (C17H), 45.4 ($C7H_2$), 44.1 (C4H), 43.6 ($C15H_2$), 41.8 ($C1H_2$), 23.2 ($C3H_2$), 20.1 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 326.1210; $[C_{19}H_{20}O_2S]^+$ requires 326.1209, Δ 0.33 ppm.

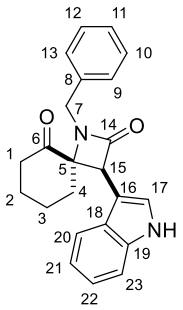
(3*S,4*S**)-1-Benzyl-3-(1*H*-indol-3-yl)-1-azaspiro[3.5]nonane-2,5-dione, 353** and **(3a*S**,7a*R**,7b*S**,12a*S**)-3-benzyl-5,6,7,7a,7b,8-hexahydro-1*H*,4*H*-benzo[3,4]pyrrolo[3',2':2,3]cyclobuta[1,2-*b*]indole-2,4(3*H*)-dione, 382**

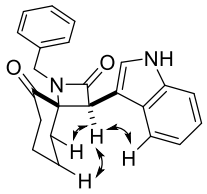




Prepared according to **General Procedure L** with *N*-benzyl-2-(1*H*-indol-3-yl)-*N*-(6-oxocyclohex-1-en-1-yl)acetamide (**316**) (97.6 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (9:1→2:1 v/v Petrol ether 40–60:EtOAc) (3*S**,4*S**)-1-benzyl-3-(1*H*-indol-3-yl)-1-azaspiro[3.5]nonane-2,5-dione (**353**) as a viscous pale yellow gum (16.6 mg, 0.0.0463 mmol, 15%, >20:1 d.r.) and (3a*S**,7a*R**,7b*S**,12a*S**)-3-benzyl-5,6,7,7a,7b,8-hexahydro-1*H*,4*H*-benzo[3,4]pyrrolo[3',2':2,3]cyclobuta[1,2-*b*]indole-2,4(3*H*)-dione (**382**) as an off-white gum (54.1 mg, 0.151 mmol, 50%, 5:1 d.r.).

Data for **(3*S**,4*S**)-1-benzyl-3-(1*H*-indol-3-yl)-1-azaspiro[3.5]nonane-2,5-dione, 353**





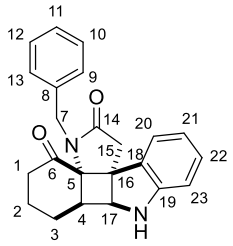
IR (neat) ν_{max}/cm^{-1} = 3653, 3299, 2979, 2887, 1742, 1712, 1545, 1458, 1393, 1252, 1155, 1074, 955, 814, 735, 700.

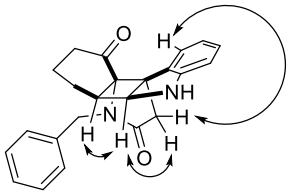
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.42 (1H, s, NH), 7.60–7.56 (1H, m, C20H), 7.40–7.28 (6H, m, C9H, C10H, C11H, C12H, C13H & C23H), 7.20 (1H, ddd, *J* = 8.2, 7.0, 1.3 Hz, C22H), 7.15 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz, C21H), 7.01 (1H, d, *J* = 2.6 Hz, C17H), 5.12 (1H, d, *J* = 15.3 Hz, C7H_AH_B), 4.61 (1H, s, C15H), 4.27 (1H, d, *J* = 15.3 Hz, C7H_AH_B), 2.04–1.95 (2H, m, C1H_AH_B & C4H_AH_B), 1.88–1.80 (2H, m, C3H_AH_B & C3H_AH_B), 1.79–1.75 (1H, m, C2H_AH_B), 1.68–1.63 (1H, m, C4H_AH_B), 1.45–1.35 (1H, m, C2H_AH_B), 1.32–1.27 (1H, m, C1H_AH_B).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.8 (C6), 167.7 (C14), 137.4 (C8), 136.1 (C19), 128.8 (C9H & C13H), 128.7 (C10H & C12H), 127.8 (C11H), 126.9 (C18), 124.3 (C17H), 122.6 (C22H), 120.3 (C21H), 118.1 (C20H), 111.8 (C23H), 106.3 (C16), 74.4 (C5), 58.5 (C15H), 45.1 ($C7H_2$), 41.7 ($C1H_2$), 37.7 ($C4H_2$), 26.0 ($C2H_2$), 23.5 ($C3H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 359.1754; $[C_{23}H_{23}O_2N_2]^+$ requires 359.1754, Δ -0.17 ppm.

Data for **(3a*S***,7a*R***,7b*S***,12a*S***)-3-benzyl-5,6,7,7a,7b,8-hexahydro-1*H*,4*H*-benzo[3,4]pyrrolo[3',2':2,3]cyclobuta[1,2-*b*]indole-2,4(3*H*)-dione, 382**





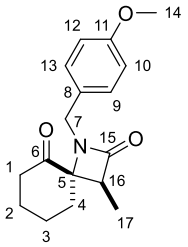
IR (neat) ν_{max}/cm^{-1} = 3342, 2944, 1675, 1606, 1481, 1466, 1395, 1328, 1248, 1153, 1122, 1082, 1054, 1028, 908, 728, 703, 646, 615.

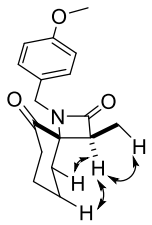
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.26 (5H, m, C9H, C10H, C11H, C12H & C13H), 7.10–7.05 (1H, m, C22H), 6.85 (1H, dd, *J* = 7.4, 1.2 Hz, C20H), 6.70 (1H, td, *J* = 7.4, 1.0 Hz, C21H), 6.64 (1H, dt, *J* = 7.9, 0.8 Hz, C23H), 4.98 (1H, d, *J* = 14.9 Hz, C7$\underline{H_A}H_B$), 4.28 (1H, d, *J* = 7.6 Hz, C17H), 3.93 (1H, d, *J* = 14.9 Hz, C7$H_A\underline{H_B}$), 2.88 (1H, d, *J* = 17.7 Hz, C15$\underline{H_A}H_B$), 2.74 (1H, d, *J* = 17.7 Hz, C15$H_A\underline{H_B}$), 2.52–2.46 (1H, m, C4H), 2.14–2.07 (1H, m, C1$\underline{H_A}H_B$), 1.64–1.51 (3H, m, C1$H_A\underline{H_B}$, C2$\underline{H_A}H_B$ & C3$\underline{H_A}H_B$), 1.45–1.38 (1H, m, C2$H_A\underline{H_B}$), 1.35–1.27 (1H, m, C3$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.2 (C6), 174.4 (C14), 153.1 (C19), 136.6 (C8), 129.9 (C22H), 129.4 (C9H & C13H), 128.7 (C10H & C12H), 128.0 (C11H), 127.6 (C18), 125.0 (C20H), 120.0 (C21H), 110.5 (C23H), 74.3 (C5), 61.6 (C17H), 58.6 (C16), 45.5 ($C7H_2$), 45.1 (C4H), 41.8 ($C15H_2$), 41.2 ($C1H_2$), 21.6 ($C2H_2$), 20.1 ($C3H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 359.1754; $[C_{23}H_{23}O_2N_2]^+$ requires 359.1754, Δ 0.03 ppm

(3*S,4*S**)-1-(4-Methoxybenzyl)-3-methyl-1-azaspiro[3.5]nonane-2,5-dione, 354**





Prepared according to **General Procedure L** with *N*-(4-methoxybenzyl)-*N*-(6-oxocyclohex-1-en-1-yl)propionamide (**258**) (86.2 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (2:1→1:2 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-(4-methoxybenzyl)-3-methyl-1-azaspiro[3.5]nonane-2,5-dione (**354**) as a yellow oil (42.6 mg, 0.148 mmol, 49%, 8:1 d.r.).

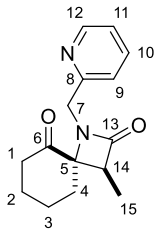
IR (neat) ν_{max}/cm^{-1} = 2935, 2862, 1745, 1709, 1613, 1586, 1513, 1453, 1421, 1398, 1348, 1304, 1245, 1177, 1102, 1080, 1064, 1032, 970, 914, 879, 847, 822, 766, 682.

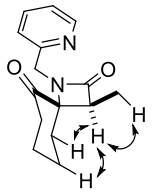
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.19 (2H, d, *J* = 8.5 Hz, C9H & C13H), 6.82 (2H, d, *J* = 8.5 Hz, C10H & C12H), 4.83 (1H, d, *J* = 15.2 Hz, C7$\underline{H_A}H_B$), 4.06 (1H, d, *J* = 15.2 Hz, C7$H_A\underline{H_B}$), 3.78 (3H, s, C14H_3), 3.06 (1H, q, *J* = 7.5 Hz, C16H), 2.64–2.54 (1H, m, C1$\underline{H_A}H_B$), 2.21–2.11 (1H, m, C1$H_A\underline{H_B}$), 2.03–1.95 (1H, m, C2$\underline{H_A}H_B$), 1.80–1.68 (2H, m, C3$\underline{H_A}H_B$ & C4$\underline{H_A}H_B$), 1.56–1.44 (3H, m, C2$H_A\underline{H_B}$, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.20 (3H, d, *J* = 7.5 Hz, C17H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.3 (C6), 168.4 (C15), 159.1 (C11), 129.9 (C9H & C13H), 129.3 (C8), 114.0 (C10H & C12H), 71.0 (C5), 55.6 (C16H), 55.4 (C14H_3), 44.2 (C7H_2), 42.6 (C1H_2), 37.9 (C4H_2), 26.0 (C2H_2), 23.4 (C3H_2), 11.1 (C17H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 288.1594; $[C_{17}H_{22}O_3N]^+$ requires 288.1594, Δ 0.01 ppm.

(3*S,4*S**)-3-Methyl-1-(pyridine-2-ylmethyl)-1-azaspiro[3.5]nonane-2,5-dione, 355**





Prepared according to **General Procedure L** with *N*-(6-oxocyclohex-1-en-1-yl)-*N*-(pyridine-2-ylmethyl)propionamide (**300**) (77.5 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (98:2→95:5 v/v CH_2Cl_2:MeOH) gave (3*S**,4*S**)-3-methyl-1-(pyridine-2-ylmethyl)-1-azaspiro[3.5]nonane-2,5-dione (**355**) as a yellow oil (61.8 mg, 0.239 mmol, 80%, 19:1 d.r.).

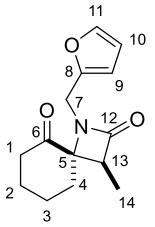
IR (neat) ν_{max}/cm^{-1} = 2937, 2863, 1749, 1711, 1592, 1571, 1475, 1436, 1397, 1375, 1339, 1312, 1270, 1154, 1132, 1110, 1092, 1080, 1064, 1049, 1013, 995, 953, 912, 878, 856, 825, 753, 729, 683, 646, 632.

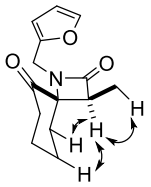
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.52–8.40 (1H, m, C12H), 7.64 (1H, td, *J* = 7.7, 1.8 Hz, C10H), 7.40 (1H, dd, *J* = 7.9, 1.2 Hz, C9H), 7.21–7.11 (1H, m, C11H), 4.81 (1H, d, *J* = 15.8 Hz, C7$\underline{H_A}H_B$), 4.30 (1H, d, *J* = 15.9 Hz, C7$H_A\underline{H_B}$), 3.10 (1H, q, *J* = 7.5 Hz, C14H), 2.62–2.49 (1H, m, C1$\underline{H_A}H_B$), 2.23–2.08 (1H, m, C1$H_A\underline{H_B}$), 2.08–1.94 (1H, m, C2$\underline{H_A}H_B$), 1.91–1.77 (3H, m, C3$\underline{H_A}H_B$, $C4H_2$), 1.66–1.46 (2H, m, C2$H_A\underline{H_B}$ & C3$H_A\underline{H_B}$), 1.19 (3H, d, *J* = 7.6 Hz, $C15H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.5 (C6), 168.6 (C13), 157.1 (C8), 149.2 (C12H), 136.9 (C10H), 123.1 (C9H), 122.5 (C11H), 71.1 (C5), 55.6 (C14H), 46.8 ($C7H_2$), 42.4 ($C1H_2$), 37.2 ($C4H_2$), 25.9 ($C2H_2$), 23.4 ($C3H_2$), 11.0 ($C15H_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 259.1441; $[C_{15}H_{19}O_2N_2]^+$ requires 259.1441, Δ 0.12 ppm.

(3*S,4*S**)-1-(Furan-2-ylmethyl)-3-methyl-1-azaspiro[3.5]nonane-2,5-dione, 356**





Prepared according to **General Procedure L** with *N*-(furan-2-ylmethyl)-*N*-(6-oxocyclohex-1-en-1-yl)propionamide (**299**) (74.2 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (2:1→1:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-(furan-2-ylmethyl)-3-methyl-1-azaspiro[3.5]nonane-2,5-dione (**356**) as a yellow oil (47.4 mg, 0.192 mmol, 64%, 19:1 d.r.).

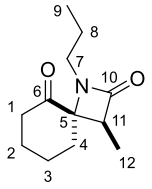
IR (neat) ν_{max}/cm^{-1} = 2938, 2865, 1748, 1709, 1600, 1504, 1453, 1424, 1397, 1350, 1309, 1275, 1234, 1148, 1106, 1075, 1014, 972, 954, 922, 884, 856, 818, 749, 683.

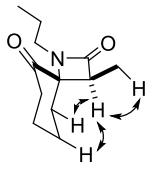
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34 (1H, dd, *J* = 1.9, 0.9 Hz, C11H), 6.30 (1H, dd, *J* = 3.2, 1.9 Hz, C10H), 6.24–6.19 (1H, m, C9H), 4.77 (1H, d, *J* = 15.8 Hz, C7$\underline{H_A}H_B$), 4.25 (1H, d, *J* = 15.8 Hz, C7$H_A\underline{H_B}$), 3.07 (1H, q, *J* = 7.5 Hz, C13H), 2.64–2.56 (1H, m, C1$\underline{H_A}H_B$), 2.23–2.12 (1H, m, C1$H_A\underline{H_B}$), 2.10–1.95 (1H, m, C2$\underline{H_A}H_B$), 1.91–1.80 (2H, m, C3$H_A\underline{H_B}$ & C4$\underline{H_A}H_B$), 1.72–1.51 (3H, m, C2$H_A\underline{H_B}$, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.20 (3H, d, *J* = 7.5 Hz, C14H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.0 (C6), 168.1 (C12), 149.6 (C8), 142.3 (C11H), 110.7 (C10H), 108.8 (C9H), 70.6 (C5), 55.7 (C13H), 42.5 (C1H_2), 37.1 (C7H_2), 36.7 (C4H_2), 26.0 (C2H_2), 23.4 (C3H_2), 11.0 (C14H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 248.1283; $[C_{14}H_{18}O_3N]^+$ requires 248.1281, Δ 0.52 ppm.

(3*S,4*S**)-3-Methyl-1-propyl-1-azaspiro[3.5]nonane-2,5-dione, 357**





Prepared according to **General Procedure L** with *N*-(6-oxocyclohex-1-en-1-yl)-*N*-propylpropionamide (**303**) (62.8 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (2:1→1:2 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-3-methyl-1-propyl-1-azaspiro[3.5]nonane-2,5-dione (**357**) as a yellow oil (37.8 mg, 0.181 mmol, 60%, >20:1 d.r.).

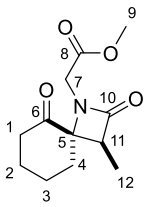
IR (neat) ν_{max}/cm^{-1} = 2935, 2874, 1744, 1712, 1454, 1401, 1339, 1236, 1210, 1183, 1156, 1114, 1078, 1059, 956, 916, 854, 779, 680.

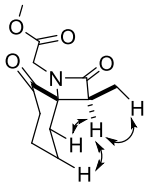
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.34–3.20 (1H, m, C7H_AH_B), 3.06–2.92 (2H, m, C7$H_A\underline{H_B}$ & C11H), 2.64–2.51 (1H, m, C1$\underline{H_A}H_B$), 2.26–1.91 (5H, m, C1$H_A\underline{H_B}$, C2$\underline{H_A}H_B$, C3$\underline{H_A}H_B$, C4H_2), 1.72–1.54 (4H, m, C2$H_A\underline{H_B}$, C3$H_A\underline{H_B}$ & C8H_2), 1.15 (3H, d, *J* = 7.5 Hz, C12H_3), 0.89 (3H, t, *J* = 7.4 Hz, C9H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.9 (C6), 168.7 (C10), 70.7 (C5), 55.1 (C11H), 43.0 (C7H_2), 42.5 (C1H_2), 37.2 (C4H_2), 26.1 (C2H_2), 23.5 (C3H_2), 22.5 (C8H_2), 11.8 (C12H_3), 11.0 (C9H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 210.1489; $[C_{12}H_{20}O_2N]^+$ requires 210.1489, Δ 0.19 ppm.

Methyl 2-((3*S,4*S**)-3-methyl-2,5-dioxo-1-azaspiro[3.5]nonan-1-yl)acetate, 358**





Prepared according to **General Procedure L** with methyl *N*-(6-oxocyclohex-1-en-1-yl)-*N*-propionylglycinate (**304**) (71.8 mg, 0.300 mmol, 1.00 equiv.), Ir(dFppy)$_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (1:1→1:4 v/v Petrol ether 40–60:EtOAc) gave methyl 2-((3*S**,4*S**)-3-methyl-2,5-dioxo-1-azaspiro[3.5]nonan-1-yl)acetate (**358**) as a yellow oil (41.4 mg, 0.173 mmol, 58%, 5:1 d.r.).

Only NMR peaks corresponding to the major diastereomer are reported.

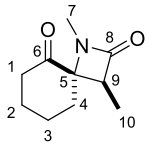
IR (neat) ν_{max}/cm^{-1} = 2942, 2867, 1745, 1712, 1420, 1402, 1361, 1310, 1278, 1259, 1209, 1110, 1082, 1021, 1004, 971, 883, 857, 824, 784, 670.

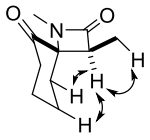
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.34 (1H, d, *J* = 18.1 Hz, C7$\underline{H_A}H_B$), 3.77 (1H, d, *J* = 18.1 Hz, C7$H_A\underline{H_B}$), 3.70 (3H, s, C9H_3), 3.17 (1H, q, *J* = 7.5 Hz, C11H), 2.64–2.47 (1H, m, C1$\underline{H_A}H_B$), 2.30–2.10 (2H, m, C1$H_A\underline{H_B}$ & C4$\underline{H_A}H_B$), 2.10–1.89 (3H, m, C2$\underline{H_A}H_B$, C3$\underline{H_A}H_B$ & C4$H_A\underline{H_B}$), 1.73–1.53 (2H, m, C2$H_A\underline{H_B}$ & C3$H_A\underline{H_B}$), 1.20 (3H, d, *J* = 7.6 Hz, C12H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.0 (C6), 169.2 (C8), 168.6 (C10), 71.2 (C5), 55.6 (C11H), 52.4 (C9H_3), 42.5 (C1H_2), 41.9 (C7H_2), 37.3 (C4H_2), 26.3 (C2H_2), 23.5 (C3H_2), 11.1 (C12H_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 262.1052; $[C_{12}H_{17}O_4NNa]^+$ requires 262.1050, Δ 0.82 ppm.

(3*S,4*S**)-1,3-Dimethyl-1-azaspiro[3.5]nonane-2,5-dione, 359**





Prepared according to **General Procedure L** with *N*-methyl-*N*-(6-oxocyclohex-1-en-1-yl)propionamide (**301**) (54.3 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (2:1→0:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1,3-dimethyl-1-azaspiro[3.5]nonane-2,5-dione (**359**) as a yellow oil (26.6 mg, 0.147 mmol, 49%, >20:1 d.r.).

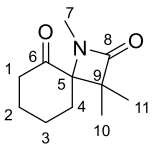
IR (neat) ν_{max}/cm^{-1} = 2936, 2864, 1744, 1709, 1451, 1424, 1392, 1319, 1260, 1113, 1071, 1048, 991, 955, 894, 857, 780, 740.

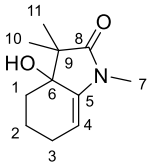
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.03 (1H, qd, *J* = 7.6, 0.8 Hz, C9H), 2.79 (3H, d, *J* = 0.7 Hz, $C7H_3$), 2.63–2.55 (1H, m, $C1\underline{H_A}H_B$), 2.25–2.12 (1H, m, $C1H_A\underline{H_B}$), 2.12–2.03 (2H, m, $C2\underline{H_A}H_B$ & $C4\underline{H_A}H_B$), 2.03–1.93 (2H, m, $C3\underline{H_A}H_B$ & $C4H_A\underline{H_B}$), 1.70–1.60 (2H, m, $C2H_A\underline{H_B}$ & $C3H_A\underline{H_B}$), 1.17 (3H, d, *J* = 7.5 Hz, $C10H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.0 (C6), 168.4 (C8), 69.9 (C5), 55.4 (C9H), 42.5 ($C1H_2$), 35.6 ($C4H_2$), 26.2 ($C2H_2$), 25.4 ($C7H_3$), 23.3 ($C3H_2$), 10.9 ($C10H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 204.0997; $[C_{10}H_{15}O_2NNa]^+$ requires 204.0995, Δ 0.91 ppm.

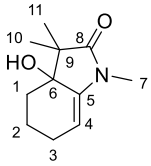
1,3,3-Trimethyl-1-azaspiro[3.5]nonane-2,5-dione, 360 and **3a-hydroxy-1,3,3-trimethyl-1,3,3a,4,5,6-hexahydro-2*H*-indol-2-one, 386**





Prepared according to **General Procedure L** with *N*-methyl-*N*-(6-oxocyclohex-1-en-1-yl)isobutyramide (**302**) (58.5 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (2:1→0:1 v/v Petrol ether 40–60:EtOAc) gave 3a-hydroxy-1,3,3-trimethyl-1,3,3a,4,5,6-hexahydro-2*H*-indol-2-one (**386**) as a yellow oil (12.5 mg, 0.0641 mmol, 21%) and 1,3,3-trimethyl-1-azaspiro[3.5]nonane-2,5-dione (**360**) as a yellow oil (12.6 mg, 0.0646 mmol, 21%).

Data for **3a-Hydroxy-1,3,3-trimethyl-1,3,3a,4,5,6-hexahydro-2*H*-indol-2-one, 386**



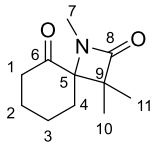
IR (neat) ν_{max}/cm^{-1} = 3413, 2936, 1718, 1672, 1434, 1396, 1312, 1086, 972.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.99 (1H, dd, J = 4.6, 2.8 Hz, C4H), 2.93 (3H, s, $C7H_3$), 2.34–2.22 (1H, m, $C3\underline{H_A}H_B$), 2.19–2.07 (1H, m, $C3H_A\underline{H_B}$), 1.89–1.82 (2H, m, $C2H_2$), 1.81 (1H, s, O$\underline{H}$), 1.78–1.71 (1H, m, $C1\underline{H_A}H_B$), 1.68–1.63 (1H, m, $C1H_A\underline{H_B}$), 1.21 (3H, s, $C10H_3$), 0.97 (3H, s, $C11H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 179.4 (C8), 142.9 (C5), 100.6 (C4H), 74.3 (C6), 48.4 (C9), 27.6 ($C1H_2$), 26.5 ($C7H_3$), 23.4 ($C3H_2$), 23.2 ($C11H_3$), 17.7 ($C2H_2$), 15.7 ($C10H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 196.1335; $[C_{11}H_{18}O_2N]^+$ requires 196.1332, Δ 1.42 ppm.

Data for **1,3,3-Trimethyl-1-azaspiro[3.5]nonane-2,5-dione, 360**



IR (neat) ν_{max}/cm^{-1} = 2940, 2870, 1746, 1709, 1426, 1396, 1132, 1052.

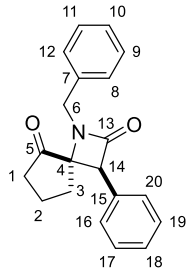
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.77 (3H, s, $C7H_3$), 2.65–2.55 (1H, m, $C1\underline{H_A}H_B$), 2.27–2.13 (2H, m, $C1H_A\underline{H_B}$ & $C4\underline{H_A}H_B$), 2.12–2.03 (1H, m, $C2\underline{H_A}H_B$), 1.99–1.85 (2H, m, $C3\underline{H_A}H_B$ & $C4H_A\underline{H_B}$), 1.72–1.59 (2H, m, $C2H_A\underline{H_B}$ & $C3H_A\underline{H_B}$), 1.38 (3H, s, $C10H_3$), 1.16 (3H s, $C11H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 209.1 (C6), 171.7 (C8), 73.0 (C5), 57.1 (C9), 43.1 ($C1H_2$), 32.0 ($C4H_2$), 26.4 ($C2H_2$), 25.2 ($C7H_3$), 23.3 ($C3H_2$), 19.5 ($C11H_3$), 17.4 ($C10H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 218.1153; $[C_{11}H_{17}O_2NNa]^+$ requires 218.1152, Δ 0.74 ppm.

The data matched that reported in the literature.[79]

(3*S,4*S**)-1-Benzyl-3-phenyl-1-azaspiro[3.4]octane-2,5-dione, 363**



Prepared according to **General Procedure L** with *N*-benzyl-*N*-(5-oxocyclopent-1-en-1-yl)-2-phenylacetamide (**311**) (91.6 mg, 0.300 mmol,

1.00 equiv.), Ir(dFppy)$_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 40 h. Purification by flash column chromatography (2:1→3:1 v/v Petrol ether 40–60:Et$_2$O) gave (3*S**,4*S**)-1-benzyl-3-phenyl-1-azaspiro[3.4]octane-2,5-dione (**363**) as a yellow oil (38.3 mg, 0.125 mmol, 42%, >20:1 d.r.).

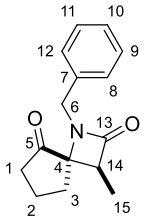
IR (neat) ν_{max}/cm^{-1} = 2961, 1753, 1603, 1497, 1454, 1392, 1355, 1173, 1077, 1037, 1001, 962, 741, 699, 635.

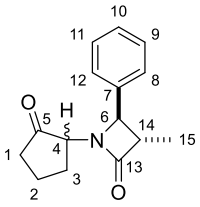
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42–7.17 (10H, m, C8H, C9H, C10H, C11H, C12H, C16H, C17H, C18H, C19H & C20H), 4.95 (1H, d, *J* = 15.3 Hz, C6$\underline{H_A}H_B$), 4.43 (1H, s, C14H), 4.06 (1H, d, *J* = 15.3 Hz, C6$H_A\underline{H_B}$), 2.12–2.04 (1H, m, C3$\underline{H_A}H_B$), 1.97–1.81 (3H, m, C2H$_2$ & C1$\underline{H_A}H_B$), 1.79–1.65 (2H, m, C1$H_A\underline{H_B}$ & C3$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.4 (C5), 166.5 (C13), 136.1 (C15), 131.8 (C7), 129.0 (C16H & C20H), 128.9 (C8H, C12H, C17H & C19H), 128.5 (C9H & C11H), 128.4 (C18H), 128.0 (C10H), 72.8 (C4), 68.4 (C14H), 44.6 (C6H$_2$), 35.4 (C1H$_2$), 32.5 (C3H$_2$), 17.2 (C2H$_2$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 306.1488; $[C_{20}H_{20}O_2N]^+$ requires 306.1489, Δ -0.27 ppm.

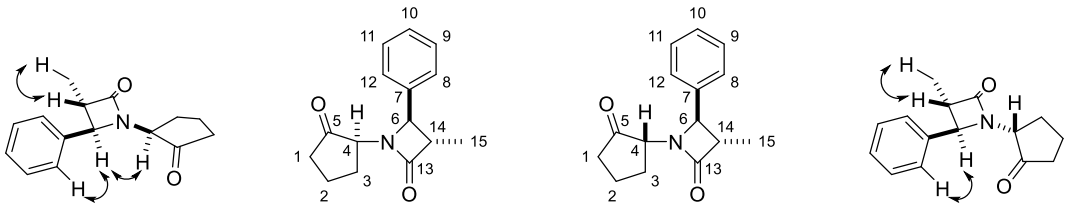
(3*S,4*S**)-1-Beznyl-3-methyl-1-azaspiro[3.4]octane-2,5-dione, 364** and **(3S*,4*R**)-3-methyl-1-(2-oxocyclopentyl)-4-phenylazetidin-2-one, 383**





Prepared according to **General Procedure L** with *N*-benzyl-*N*-(5-oxocyclopent1-en-1-yl)propionamide (**310**) (73.0 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h. Purification by flash column chromatography (3:1→2:1 v/v Petrol ether 40–60:EtOAc) gave (3*S**,4*S**)-1-beznyl-3-methyl-1-azaspiro[3.4]octane-2,5-dione (**364**) as a yellow oil (19.4 mg, 0.0797 mmol, 27%, 8:1 d.r.) and (3S*,4*R**)-3-methyl-1-(2-oxocyclopentyl)-4-phenylazetidin-2-one (**383**) as a yellow oil (19.4 mg, 0.0797 mmol, 27%, 1.4:1 d.r.).

Data for **(3S*,4*R**)-3-methyl-1-((*S**)-2-oxocyclopentyl)-4-phenylazetidin-2-one, 383** and **(3*S**,4*R**)-3-methyl-1-((*R**)-2-oxocyclopentyl)-4-phenylazetidin-2-one, 383**



IR (neat) ν_{max}/cm^{-1} = 2967, 1758, 1738, 1456, 1399, 1153, 746, 701.

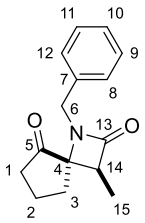
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.29 (10H, m, C8H, C9H, C10H, C11H & C12H *R** and *S**), 4.39 (1H, d, *J* = 2.2 Hz, C6H *S**), 4.28 (1H, d, *J* = 2.3 Hz, C6H *R**), 4.16–4.10 (1H, m, C4H *R**), 3.50–3.40 (1H, m, C4H *S**), 3.13–2.97 (2H, m, C14H *R** and *S**), 2.46–2.36(1H, m, C3H_AH_B *S**), 2.34–2.25 (3H, m, C1H_AH_B *R** and *S** & C3H_AH_B *S**), 2.17–2.01 (5H, m, C1H_AH_B *R** and *S**, C2H_AH_B *S** and *R** & C3H_AH_B *R**), 1.92–1.85 (1H, m, C2H_AH_B *R**), 1.76–1.67 (2H, m, C2H_AH_B *R** and *S**), 1.54–1.45 (1H, m, C3H_AH_B *R**), 1.42 (3H, d, *J* = 7.3 Hz, C15H_3 *R**), 1.40 (3H, d, *J* = 7.4 Hz, C15H_3 *S**).

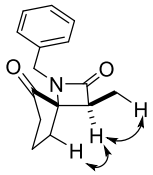
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.9 (C5 *S**), 212.6 (C5 *R**), 172.3 (C13 *R**), 171.3 (C13 *S**), 138.9 (C7 *R**), 138.2 (C7 *S**), 129.1 (C9H & C11H *S**), 129.0 (C9H & C11H *R**), 128.7 (C10H

*R** and *S**), 126.7 (C8H & C12H *R** and *S**), 64.2 (C6H *S**), 62.4 (C6H *R**), 59.4 (C4H *S**), 58.6 (C4H *R**), 55.8 (C14H *R**), 55.1 (C14H *S**), 36.1 ($C1H_2$ *S**), 35.8 ($C1H_2$ *R**), 27.9 ($C3H_2$ *R**), 27.5 ($C3H_2$ *S**), 19.1 ($C2H_2$ *S**), 18.6 ($C2H_2$ *R**), 13.2 ($C15H_3$ *R**), 13.0 ($C15H_3$ *S**).

HRMS (ESI^+) Found $[M+Na]^+$ = 266.1153; $[C_{15}H_{17}O_2NNa]^+$ requires 266.1152, Δ 0.43 ppm.

Data for **(3*S**,4*S**)-1-beznyl-3-methyl-1-azaspiro[3.4]octane-2,5-dione, 364**





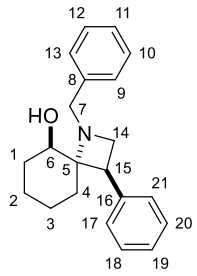
IR (neat) ν_{max}/cm^{-1} = 2966, 1738, 1455, 1394, 1158, 1094, 951, 731, 701.

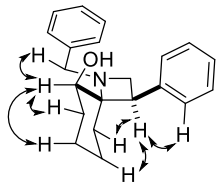
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.21 (5H, m, C8H, C9H, C10H, C11H & C12H), 4.75 (1H, d, *J* = 15.3 Hz, $C6\underline{H_A}H_B$), 3.96 (1H, d, *J* = 15.3 Hz, $C6H_A\underline{H_B}$), 3.18 (1H, q, *J* = 7.4 Hz, C14H), 2.29–2.21 (1H, m, $C1\underline{H_A}H_B$), 2.12–2.02 (1H, m, $C1H_A\underline{H_B}$), 1.94–1.86 (2H, m, $C2\underline{H_A}H_B$ & $C3\underline{H_A}H_B$), 1.71–1.65 (2H, m, $C2H_A\underline{H_B}$ & $C3H_A\underline{H_B}$), 1.14 (3H, d, *J* = 7.4 Hz, $C15H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.1 (C5), 169.0 (C13), 136.1 (C7), 128.8 (C8H & C12H), 128.5 (C9H & C11H), 127.9 (C10H), 70.1 (C4), 57.1 (C14H), 44.5 ($C6H_2$), 36.5 ($C1H_2$), 32.6 ($C3H_2$), 17.9 ($C2H_2$), 10.7 ($C15H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 244.1335; $[C_{15}H_{18}O_2N]^+$ requires 244.1332, Δ 1.02 ppm.

(3*R,4*S**,5*R**)-1-Benzyl-3-phenyl-1-azaspiro[3.5]nonan-5-ol, 371**





To a solution of $AlCl_3$ (120 mg, 0.900 mmol, 3.00 equiv.) in dry THF (4.0 mL) under at atmosphere of argon at 0 °C was added $LiAlH_4$ (34.2 mg, 0.900 mmol, 3.00 equiv.) in one portion. The reaction was stirred for 10 minutes at 0 °C and then for a further 30 minutes at reflux (40 °C). The reaction mixture was then cooled to 0 °C and a solution of (3*S**,4*S**)-1-benzyl-3-phenyl-1-azaspiro[3.5]nonane-2,5-dione (**343**) (95.8 mg, 0.300 mmol, 1.00 equiv.) in THF (2.0 mL) was added dropwise. The reaction mixture was then heated to reflux (40 °C) for 1 h before being cooled to 0 °C where it was quenched by sequential addition of water (0.300 mL), 3 M aqueous sodium hydroxide solution (0.300 mL) and water (0.900 mL) (Fieser method). The resulting suspension was stirred for 15 minutes at ambient temperature before being diluted with EtOAc (20 mL) and water (10 mL). The organic layer was separated, and the aqueous layer extracted with further EtOAc (2 ×20 mL). The combined organic extracts were then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (90:10:1→80:20:1 Petrol ether 40–60:EtOAc:Et_3N) gave (3*R**,4*S**,5*R**)-1-benzyl-3-phenyl-1-azaspiro[3.5]nonan-5-ol (**371**) as a yellow oil (75.8 mg, 0.247 mmol, 82%, >20:1 d.r.).

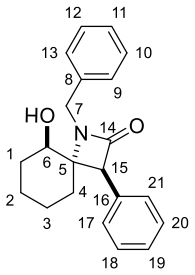
IR (neat) ν_{max}/cm^{-1} = 3580, 3472, 3027, 2922, 2855, 1603, 1495, 1453, 1359, 1324, 1180, 1082, 1029, 1011, 986, 927, 851, 749, 724, 699.

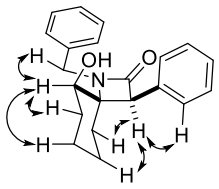
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.46–7.39 (2H, m, C17H & C21H), 7.39–7.20 (7H, m, C9H, C10H, C11H, C12H, C13H, C17H, C18H & C20H), 7.20–7.13 (1H, m, C19H), 3.85 (1H, d, *J* = 12.9 Hz, C7$\underline{H_A}H_B$), 3.58–3.51 (2H, m, C7$H_A\underline{H_B}$ & C14$\underline{H_A}H_B$), 3.41 (1H, dd, *J* = 8.6, 7.4 Hz, C14$H_A\underline{H_B}$), 3.37–3.29 (2H, m, C6H & C15H), 3.01 (1H, s, O$\underline{H}$), 2.24–2.12 (1H, m, C4$\underline{H_A}H_B$), 1.83–1.73 (1H, m, C3$\underline{H_A}H_B$), 1.69–1.59 (3H, m, C2$\underline{H_A}H_B$, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.58–1.51 (1H, m, C1$\underline{H_A}H_B$), 1.27–1.20 (2H, m, C1$H_A\underline{H_B}$ & C2$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 139.6 (C16), 138.8 (C8), 129.5 (C17H & C21H), 128.6 (C18H & C20H), 128.5 (C9H & C13H), 128.1 (C10H & C12H), 127.1 (C11H), 126.7 (C19H), 73.5 (C6H), 72.6 (C5), 54.3 ($C14H_2$), 53.9 ($C7H_2$), 46.4 (C15H), 30.9 ($C4H_2$), 29.0 ($C1H_2$), 23.6 ($C2H_2$), 22.8 ($C3H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 308.2008; $[C_{21}H_{26}ON]^+$ requires 308.2009, Δ -0.38 ppm.

(3S*,4*S,5*R**)-1-Benzyl-5-hydroxy-3-phenyl-1-azaspiro[3.5]nonan-2-one, 372**





To a solution of (3*S**,4*S**)-1-benzyl-3-phenyl-1-azaspiro[3.5]nonane-2,5-dione (**343**) (95.8 mg, 0.300 mmol, 1.00 equiv.) in MeOH (3.0 mL) was added $NaBH_4$ (11.3 mg, 0.300 mmol, 1.00 equiv.) in one portion. The reaction was stirred at ambient temperature until completion as monitored by thin layer chromatography (16 h), before being quenched with water (10 mL). The reaction mixture was then extracted with EtOAc (3 × 10 mL), and the combined organic extracts dried (Na_2SO_4), filtered and concentrated *in*

vacuo to afford an analytically pure sample of (3S*,4S*,5R*)-1-benzyl-5-hydroxy-3-phenyl-1-azaspiro[3.5]nonan-2-one (**372**) (91.8 mg, 0.285 mmol, 95%, >20:1 d.r.).

m.p. = 163–165 °C.

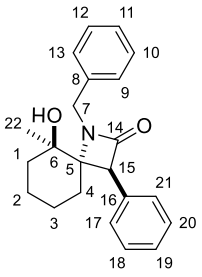
IR (neat) ν_{max}/cm^{-1} = 3414, 3029, 2935, 2859, 1730, 1603, 1497, 1453, 1409, 1353, 1207, 1177, 1089, 1029, 997, 911, 880, 845, 762, 731, 702, 646, 610.

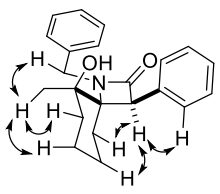
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.17 (10H, m, C9H, C10H, C11H, C12H, C13H, C17H, C18H, C19H, C20H & C21H), 4.47 (1H, d, *J* = 15.4 Hz, C7$\underline{H_A}H_B$), 4.40 (1H, d, *J* = 15.5 Hz, C7$H_A\underline{H_B}$), 4.11 (1H, s, C15H), 3.46 (1H, dt, *J* = 9.5, 4.6 Hz, C6H), 1.78–1.71 (1H, m, C4$\underline{H_A}H_B$), 1.65–1.56 (2H, m, C2$\underline{H_A}H_B$ & C3$\underline{H_A}H_B$), 1.51–1.40 (3H, m, C1$\underline{H_A}H_B$, C3$H_A\underline{H_B}$ & C4$H_A\underline{H_B}$), 1.12–1.06 (1H, m, C2$H_A\underline{H_B}$), 1.04–0.98 (1H, m, C1$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 168.1 (C14), 137.5 (C16), 133.2 (C8), 130.5 (C18H & C20H), 129.0 (C10H & C12H), 128.8 (C17H & C21H), 128.3 (C9H & C13H), 127.9 (C11H), 127.9 (C19H), 71.7 (C6H), 69.2 (C5), 64.7 (C15H), 43.4 ($C7H_2$), 36.3 ($C4H_2$), 31.5 ($C1H_2$), 23.9 ($C2H_2$ & $C3H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 344.1622; $[C_{21}H_{23}O_2NNa]^+$ requires 344.1621, Δ 0.29 ppm.

(3S*,4S*,5R*)-1-Benzyl-5-hydroxy-5-methyl-3-phenyl-1-azaspiro[3.5]nonan-2-one, 373





To a solution of (3*S**,4*S**)-1-benzyl-3-phenyl-1-azaspiro[3.5]nonane-2,5-dione (**343**) (95.8 mg, 0.300 mmol, 1.00 equiv.) in dry THF (1.5 mL) under an atmosphere of argon at

0 °C was added a solution of methyl magnesium bromide in Et_2O (3 M, 0.1 mL, 0.300 mmol, 1.00 equiv.) dropwise. The reaction was then warmed to ambient temperature and stirred for 2.5 h, before being quenched by addition of saturated aqueous ammonium chloride solution (10 mL). The reaction mixture was then extracted with EtOAc (3 × 10 mL), and the combined organic extracts washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1→1:1 Petrol ether 40–60:EtOAc) gave (3S*,4S*,5R*)-1-benzyl-5-hydroxy-5-methyl-3-phenyl-1-azaspiro[3.5]nonan-2-one (**373**) as a pale yellow oil (75.5 mg, 0.225 mmol, 75%, >20:1 d.r.).

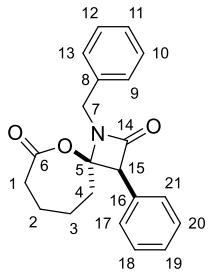
IR (neat) ν_{max}/cm^{-1} = 3438, 2935, 2865, 1735, 1497, 1453, 1396, 1352, 1177, 1158, 1127, 1016, 912, 865, 759, 730, 700, 647.

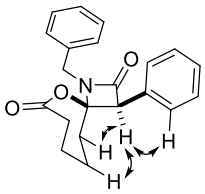
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34–7.29 (2H, m, C17H & C21H), 7.29–7.24 (2H, m, C9H & C13H), 7.23–7.17 (4H, m, C10H, C12H, C18H & C20H), 7.14–7.10 (2H, m, C11H & C19H), 4.47 (1H, d, *J* = 15.8 Hz, C7$\underline{H_A}H_B$), 4.37 (1H, d, *J* = 15.8 Hz, C7$H_A\underline{H_B}$), 4.07 (1H, s, C15H), 1.76–1.66 (1H, m, C4$\underline{H_A}H_B$), 1.63–1.54 (2H, m, C3$\underline{H_A}H_B$ & C4$H_A\underline{H_B}$), 1.53–1.45 (2H, m, C2$\underline{H_A}H_B$ & C3$H_A\underline{H_B}$), 1.24–1.14 (3H, m, C1H_2 & C2$H_A\underline{H_B}$), 0.96 (3H, s, C22H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 169.3 (C14), 137.7 (C8), 134.1 (C16), 130.9 (C17H & C21H), 129.0 (C18H & C20H), 128.8 (C10H & C12H), 128.0 (C9H & C13H), 128.0 (C19H), 127.6 (C11H), 74.3 (C6), 73.9 (C5), 66.0 (C15H), 45.0 (C7H_2), 39.3 (C1H_2), 35.8 (C4H_2), 25.0 (C22H_3), 24.3 (C3H_2), 23.0 (C2H_2).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 358.1778; $[C_{22}H_{25}O_2NNa]^+$ requires 358.1778, Δ 0.13 ppm.

(3*S,4*R**)-1-Benzyl-3-phenyl-5-oxa-1-azaspiro[3.6]decane-2,6-dione, 374**





To a solution of (3*S**,4*S**)-1-benzyl-3-phenyl-1-azaspiro[3.5]nonane-2,5-dione (**343**) (95.8 mg, 0.300 mmol, 1.00 equiv.) in dry THF (1.5 mL) under an atmosphere of argon at 0 °C was added a solution of methyl magnesium bromide in Et_2O (3 M, 0.1 mL, 0.300 mmol, 1.00 equiv.) dropwise. The reaction was then warmed to ambient temperature and stirred for 2.5 h, before being quenched by addition of saturated aqueous ammonium chloride solution (10 mL). The reaction mixture was then extracted with EtOAc (3 × 10 mL), and the combined organic extracts washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1→1:1 Petrol ether 40–60:EtOAc) gave (3S**,4S**,5R**)-1-benzyl-5-hydroxy-5-methyl-3-phenyl-1-azaspiro[3.5]nonan-2-one (**374**) as a pale yellow oil (75.5 mg, 0.225 mmol, 75%, >20:1 d.r.).

m.p. = 126–128 °C

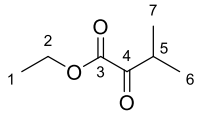
IR (neat) ν_{max}/cm^{-1} = 3657, 2980, 1765, 1737, 1604, 1497, 1455, 1397, 1350, 1331, 1281, 1237, 1217, 1179, 1152, 1125, 1095, 1081, 1070, 1026, 990, 941, 917, 862, 829, 730, 701, 619.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.45–7.27 (10H, m, 10H), 4.84 (1H, d, *J* = 15.5 Hz, C7$\underline{H_A}H_B$), 4.49 (1H, s, C15H), 4.31 (1H, d, *J* = 15.5 Hz, C7$H_A\underline{H_B}$), 2.28–2.19 (1H, m, C1$\underline{H_A}H_B$), 2.01–1.95 (2H, m, C4H_2), 1.95–1.87 (1H, m, C3$\underline{H_A}H_B$), 1.75–1.63 (2H, m, C2$H_A\underline{H_B}$ & C3$\underline{H_A}H_B$), 1.59–1.52 (1H, m, C1$H_A\underline{H_B}$), 1.42–1.32 (1H, m, C2$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.8 (C6), 166.1 (C14), 136.6 (C8), 130.8 (C16), 130.5 (C17H & C21H), 129.2 (C18H & C20H), 129.1 (C19H), 129.0 (C10H & C12H), 128.6 (C9H & C13H), 128.0 (C11H), 94.7 (C5), 64.8 (C15H), 43.1 ($C7H_2$), 37.5 ($C4H_2$), 36.8 ($C1H_2$), 26.2 ($C3H_2$), 22.2 ($C2H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 336.1595; $[C_{21}H_{22}O_3N]^+$ requires 336.1594, Δ 0.10 ppm.

Ethyl 3-methyl-2-oxobutanoate, 404



Prepared according to **General Procedure M** with diethyl oxalate (1.36 mL, 1.46 g, 10.0 mmol, 1.00 equiv.), isopropylmagnesium bromide solution (1.00 M in THF; 5.00 mL, 5.00 mmol, 1.00 equiv.) and THF (10 mL) for 3 h. Purification by flash column chromatography (49:1→24:1 v/v Petrol ether 40–60:EtOAc) gave ethyl 3-methyl-2-oxobutanoate (**404**) as a colourless oil (330 mg, 2.29 mmol, 46%).

IR (neat) ν_{max}/cm^{-1} = 2924, 2852, 1737, 1242, 1191, 1041, 914, 747.

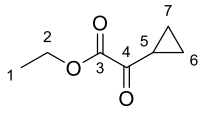
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.33 (2H, q, J = 7.2 Hz, $C2H_2$), 3.34–3.18 (1H, m, C5H), 1.37 (3H, t, J = 7.1 Hz, $C1H_3$), 1.16 (6H, d, J = 6.9 Hz, $C6H_3$ & $C7H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 198.4 (C4), 162.0 (C3), 62.4 ($C2H_2$), 37.2 (C5H), 17.3 ($C6H_3$ & $C7H_3$), 14.2 ($C1H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 145.0862; $[C_7H_{13}O_3]^+$ requires 145.0859, Δ 1.75 ppm.

The data matched that reported in the literature.[158]

Ethyl 2-cyclopropyl-2-oxoacetate, 405



Prepared according to **General Procedure M** with magnesium turnings (128 mg, 5.25 mmol, 1.05 equiv.), cyclopropyl bromide (0.421 mL, 635 mg, 5.25 mmol, 1.05 equiv.), diethyl oxalate (679 mL, 731 mg, 5.00 mmol, 1.00 equiv.) and THF (10 mL) for 5.5 h. Purification by flash column chromatography (49:1→24:1 v/v Petrol ether 40–60:EtOAc) gave ethyl 3-methyl-2-oxobutanoate (**405**) as a colourless oil (330 mg, 2.29 mmol, 46%).

IR (neat) ν_{max}/cm^{-1} = 2920, 1712, 1448, 1366, 1270, 1188, 1099, 1060, 1026, 888, 703.

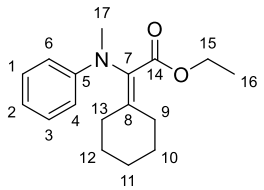
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.35 (2H, q, J = 7.1 Hz, C2H_2), 2.79–2.70 (1H, m, C5H), 1.38 (3H, t, J = 7.1 Hz, C1H_3), 1.27–1.22 (2H, m, C6$\underline{H_A}H_B$ & C7$\underline{H_A}H_B$), 1.18–1.13 (2H, m, C6$H_A\underline{H_B}$ & C7$H_A\underline{H_B}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 194.5 (C4), 161.3 (C3), 62.6 (C2H_2), 18.2 (C5H_3), 14.2 (C6H_2 & C7H_2), 14.2 (C1H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 143.0703; $[C_7H_{11}O_3]^+$ requires 143.0703, Δ 0.11 ppm.

The data matched that reported in the literature.[159,160]

Ethyl 2-cyclohexylidene-2-(methyl(phenyl)amino)acetate, 398



Prepared according to **General Procedure N** with ethyl 2-cyclohexyl-2-oxo-acetate (1.00 g, 5.43 mmol, 1.00 equiv.), *N*-methylaniline (0.700 mL, 708 mg, 6.46 mmol, 1.20 equiv.),

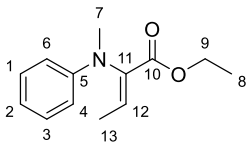
p-toluenesulfonic acid monohydrate (50.0 mg, 0.263 mmol, 0.0500 equiv.) and benzene (8.0 mL) for 16 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 2-cyclohexylidene-2-(*N*-methylanilino)acetate (**398**) as a brown oil (423 mg, 1.55 mmol, 28%).

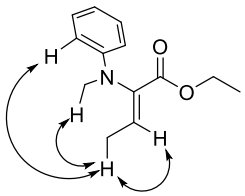
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.10–7.02 (2H, m, C1H & C3H), 6.61–6.56 (1H, m, C2H), 6.55–6.47 (2H, m, C4H & C6H), 3.90 (2H, q, J = 7.1 Hz, C15H_2), 2.92 (3H, s, C17H_3), 2.65–2.57 (2H, m, C9$H_A$$H_B$ & C13$H_A$$H_B$), 2.19–2.11 (2H, m, C9$H_A$$H_B$ & C13$H_A$$H_B$), 1.64–1.44 (6H, m, C10$H_2$, C11$H_2$ & C12H_2), 0.90 (3H, t, J = 7.1 Hz, C16H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.9 (C14), 153.9 (C8), 148.9 (C5), 129.6 (C7), 129.1 (C1H & C3H), 117.1 (C2H), 112.5 (C4H & C6H), 60.3 (C15H_2), 39.4 (C17H_3), 31.3 (C9H_2), 30.6 (C13H_2), 28.2 (C10H_2), 28.1 (C12H_2), 26.6 (C11H_2), 14.2 (C16H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 274.1802; $[C_{17}H_{24}O_2N]^+$ requires 274.1802, Δ 0.15 ppm.

Ethyl (Z)-2-(methyl(phenyl)amino)but-2-enoate, 408





Prepared according to **General Procedure N** with ethyl 2-oxobutanoate (465 mg, 4.00 mmol, 1.00 equiv.), *N*-methylaniline (0.607 mL, 600 mg, 5.60 mmol, 1.40 equiv.), *p*-toluenesulfonic acid monohydrate (22.8 mg, 0.120 mmol, 0.0300 equiv.) and toluene (40 mL) for 40 h. Purification by flash column chromatography (49:1→19:1 v/v pentane:Et_2O) gave ethyl (Z)-2-(methyl(phenyl)amino)but-2-enoate (**408**) as a yellow oil (577 mg, 2.63 mmol, 66%).

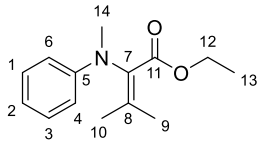
IR (neat) ν_{max}/cm^{-1} = 2937, 1717, 1650, 1599, 1500, 1382, 1357, 1308, 1249, 1202, 1123, 1044, 994, 868, 748, 693.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.25–7.18 (2H, m, C1H & C3H), 6.96 (1H, q, *J* = 7.0 Hz, C12H), 6.76 (1H, tt, *J* = 7.2, 1.0 Hz, C2H), 6.69–6.61 (2H, m, C4H & C6H), 4.14 (2H, q, *J* = 7.1 Hz, $C9H_2$), 3.08 (3H, s, $C7H_3$), 1.79 (3H, d, *J* = 7.0 Hz, $C13H_3$), 1.17 (3H, t, *J* = 7.1 Hz, $C8H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 165.7 (C10), 148.2 (C5), 137.7 (C11), 137.2 (C12H), 129.1 (C1H & C3H), 117.5 (C2H), 112.5 (C4H & C6H), 60.8 ($C9H_2$), 38.1 ($C7H_3$), 14.3 ($C8H_3$), 13.6 ($C13H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 220.1333; $[C_{13}H_{18}O_2N]^+$ requires 220.1332, Δ 0.50 ppm.

Ethyl 3-methyl-2-(methyl(phenyl)amino)but-2-enoate, 409



Prepared according to **General Procedure N** with ethyl 2-oxoisovalerate (**404**) (512 mg, 4.45 mmol, 1.00 equiv.), *N*-methylaniline (0.500 mL, 495 mg, 4.62 mmol, 1.05 equiv.), *p*-toluenesulfonic acid monohydrate (20 mg, 0.105 mmol, 0.0250 equiv.) and toluene (8.0 mL) for 20 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 3-methyl-2-(*N*-methylanilino)but-2-enoate (**409**) as a yellow oil (507 mg, 2.17 mmol, 49%).

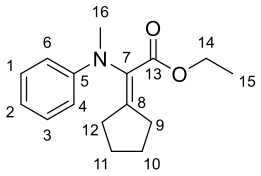
IR (neat) ν_{max}/cm^{-1} = 2981, 2935, 1710, 1635, 1598, 1577, 1498, 1474, 1446, 1369, 1342, 1270, 1215, 1121, 1096, 1078, 1045, 990, 867, 781, 747, 692, 645.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.25–7.15 (2H, m, C1H & C3H), 6.72 (1H, tt, *J* = 7.3, 1.1 Hz, C2H), 6.65–6.57 (2H, m, C4H & C6H), 4.05 (2H, q, *J* = 7.1 Hz, $C12H_2$), 3.04 (3H, s, $C14H_3$), 2.22 (3H, s, $C9H_3$), 1.86 (3H, s, $C10H_3$), 1.05 (3H, t, *J* = 7.1 Hz, $C13H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.6 (C11), 148.6 (C5), 148.4 (C8), 132.0 (C7), 129.1 (C1H & C3H), 117.1 (C4H & C6H), 112.3 (C2H), 60.2 ($C12H_2$), 38.5 ($C14H_3$), 22.1 ($C9H_3$), 20.9 ($C10H_3$), 14.2 ($C13H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 234.1488; $[C_{14}H_{20}NO_2]^+$ requires 234.1494, Δ -2.56 ppm.

Ethyl 2-cyclopentylidene-2-(methyl(phenyl)amino)acetate, 412



Prepared according to **General Procedure N** with ethyl 2-cyclopentyl-2-oxo-acetate (867 mg, 5.09 mmol, 1.00 equiv.), *N*-methylaniline (0.700 mL, 708 mg, 6.46 mmol, 1.27 equiv.), *p*-toluenesulfonic acid monohydrate (20.0 mg, 0.105 mmol, 0.0200 equiv.) and benzene (8.0 mL) for 16 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 2-cyclopentylidene-2-(*N*-methylanilino)acetate (**412**) as a brown oil (890 mg, 3.43 mmol, 67%).

IR (neat) ν_{max}/cm^{-1} = 2956, 1707, 1642, 1596, 1576, 1499, 1474, 1366, 1347, 1298, 1263, 1187, 1154, 1113, 1095, 1048, 1034, 989, 952, 866, 794, 746, 691.

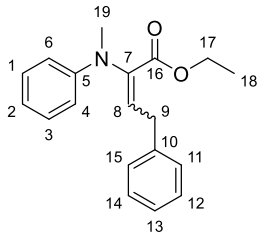
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.24–7.14 (2H, m, C1H & C3H), 6.70 (1H, tt, *J* = 7.2, 1.0 Hz, C2H), 6.63–6.55 (2H, m, C4H & C6H), 4.09 (2H, q, *J* = 7.1 Hz, $C14H_2$), 3.03 (3H, s, $C16H_3$),

2.92–2.82 (2H, m, $C9H_2$), 2.43–2.35 (2H, m, C12H), 1.85–1.74 (2H, m, $C10H_2$), 1.70–1.58 (2H, m, $C11H_2$), 1.11 (3H, t, J = 7.1 Hz, $C15H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.3 (C13), 164.0 (C8), 148.3 (C5), 129.2 (C1H &C3H), 128.1 (C2H), 116.8 (C4H & C6H), 111.9 (C7), 60.1 ($C14H_2$), 37.6 ($C16H_3$), 33.5 ($C9H_2$), 32.9 ($C12H_2$), 27.3 ($C10H_2$), 25.4 ($C11H_2$), 14.4 ($C15H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 260.1646; $[C_{16}H_{22}NO_2]^+$ requires 260.1645, Δ 0.38 ppm.

Ethyl 2-(methyl(phenyl)amino)-4-phenylbut-2-enoate, 413



Prepared according to **General Procedure N** with ethyl 2-oxo-4-phenyl-butyrate (700 mg, 3.39 mmol, 1.00 equiv.), *N*-methylaniline (0.500 mL, 495 mg, 4.62 mmol, 1.40 equiv.), *p*-toluenesulfonic acid monohydrate (35 mg, 0.184 mmol, 0.0250 equiv.) and benzene (8.0 mL) for 19 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 2-(N-methylanilino)-4-phenyl-but-2-enoate (**413**) as a yellow oil (96.3 mg, 0.326 mmol, 10%, 1:1 d.r.).

IR (neat) ν_{max}/cm^{-1} = 2980, 1716, 1646, 1597, 1578, 1498, 1475, 1453, 1371, 1279, 1243, 1199, 1110, 1093, 1040, 990, 948, 903, 868, 746, 692.

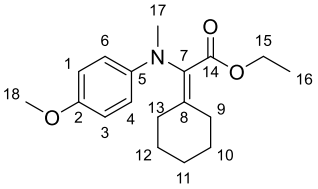
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.30 (5H, m, C11H, C12H, C13H, C14H & C15H), 7.27–7.23 (2H, m, C1H & C3H), 7.13–7.08 (1H, m, C2H), 6.89–6.85 (1H, m, C8H), 6.81–6.75

(2H, m, C4H & C6H), 4.20 (2H, q, *J* = 7.1 Hz, $C17H_2$), 3.61 (2H, d, *J* = 7.5 Hz, $C9H_2$), 3.21 (3H, s, $C19H_3$), 1.22 (t, *J* = 7.1 Hz, $C18H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 165.5 (C16), 148.2 (C5), 140.3 (C10), 138.4 (C7), 136.8 (C8H), 129.2 (C11H & C15H), 128.7 (C1H & C3H), 128.7 (C12H & C14H), 126.6 (C13H), 117.8 (C4H & C6H), 112.7 (C2H), 60.9 ($C17H_2$), 38.7 ($C19H_3$), 34.1 ($C9H_2$), 14.2 ($C18H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 234.1646; $[C_{19}H_{22}NO_2]^+$ requires 234.1651, Δ -2.14 ppm.

Ethyl 2-cyclohexylidene-2-((4-methoxyphenyl)(methyl)amino)acetate, 415



Prepared according to **General Procedure N** with ethyl 2-cyclohexyl-2-oxo-acetate (520 mg, 2.82 mmol, 1.00 equiv.), 4-methoxy-*N*-methyl-aniline (600 mg, 4.37 mmol, 1.55 equiv.), *p*-toluenesulfonic acid monohydrate (14.5 mg, 0.0762 mmol, 0.0300 equiv.) and benzene (8.0 mL) for 17 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 2-cyclohexylidene-2-(4-methoxy-*N*-methyl-anilino)acetate (**415**) as a yellow oil (488 mg, 1.61 mmol, 58%).

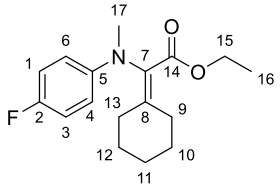
IR (neat) ν_{max}/cm^{-1} = 2928, 1709, 1508, 1464, 1444, 1337, 1260, 1239, 1224, 1189, 1104, 1037, 817, 796, 745.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.82–6.76 (2H, m, C4H & C6H), 6.61–6.55 (2H, m, C1H & C3H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.74 (3H, s, $C18H_3$), 3.02 (3H, s, $C17H_3$), 2.73–2.65 (2H, m, $C9H_2$), 2.34–2.26 (2H, m, $C13H_2$), 1.76–1.58 (6H, m, $C10H_2$, $C11H_2$ & $C12H_2$), 1.02 (3H, t, *J* = 7.1 Hz, $C16H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 167.1 (C14), 152.8 (C2), 151.9 (C8), 143.4 (C5), 130.2 (C7), 114.8 (C1H & C3H), 113.6 (C4H & C6H), 60.2 ($C15H_2$), 55.9 ($C18H_3$), 39.8 ($C17H_3$), 31.1 ($C9H_2$), 30.6 ($C13H_2$), 28.2 ($C10H_2$), 28.1 ($C12H_2$), 26.6 ($C11H_2$), 14.2 ($C16H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 304.1896; $[C_{18}H_{26}NO_3]^+$ requires 304.1907, Δ -3.62 ppm.

Ethyl 2-cyclohexylidene-2-((4-fluorophenyl)(methyl)amino)acetate, 416



Prepared according to **General Procedure N** with ethyl 2-cyclohexyl-2-oxo-acetate (500 mg, 2.71 mmol, 1.00 equiv.), 4-fluoro-*N*-methylaniline (0.450 mL, 468 mg, 3.74 mmol, 1.40 equiv.), *p*-toluenesulfonic acid monohydrate (30.0 mg, 0.158 mmol, 0.0600 equiv.) and benzene (8.0 mL) for 17 h. Purification by flash column chromatography (1:0→9:1 v/v heptane:EtOAc) gave ethyl 2-cyclohexylidene-2-(4-fluoro-*N*-methyl-anilino)acetate (**416**) as a yellow oil (268 mg, 0.921 mmol, 34%).

IR (neat) ν_{max}/cm^{-1} = 2929, 2855, 1709, 1506, 1471, 1448, 1331, 1260, 1223, 1189, 1159, 1101, 1072, 1041, 1021, 818, 750.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.95–6.84 (2H, m, C1H & C3H), 6.60–6.50 (2H, m, C4H & C6H), 4.02 (2H, q, *J* = 7.1 Hz, $C15H_3$), 3.02 (3H, s, $C17H_3$), 2.75–2.68 (2H, m, $C9H_2$), 2.33–2.24 (2H, m, $C13H_2$), 1.76–1.59 (6H, m, $C10H_2$,$C1H_2$ & $C12H_2$), 1.02 (3H, t, *J* = 7.1 Hz, $C16H_3$).

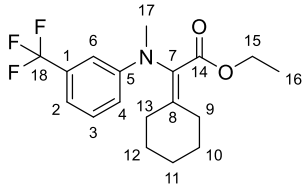
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.8 (C14), 157.1 (C8), 154.3 (d, *J* = 93.9 Hz, C2F), 145.5 (d, *J* = 1.0 Hz, C5), 129.8 (C7), 115.5 (d, *J* = 22.2 Hz, C1H & C3H), 113.3 (d, *J* = 8.1 Hz, C4H &

C6H), 60.3 ($C15H_2$), 39.8 ($C17H_3$), 31.2 ($C9H_2$), 30.6 ($C13H_2$), 28.2 ($C10H_2$), 28.1 ($C12H_2$), 26.6 ($C11H_2$), 14.2 ($C16H_3$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ = -129.17 (tt, J = 8.3, 4.2 Hz, C2F).

HRMS (ESI^+) Found $[M+H]^+$ = 292.1709; $[C_{17}H_{23}FNO_2]^+$ requires 292.1707, Δ 0.68 ppm.

Ethyl 2-cyclohexylidene-2-(methyl(3-(trifluoromethyl)phenyl)amino)acetate, 417



Prepared according to **General Procedure N** with ethyl 2-cyclohexyl-2-oxo-acetate (520 mg, 2.82 mmol, 1.00 equiv.), *N*-methyl-3-(trifluoromethyl)aniline (0.500 mL, 601 mg, 3.43 mmol, 1.30 equiv.), *p*-toluenesulfonic acid monohydrate (14.5 mg, 0.0762 mmol, 0.0300 equiv.) and benzene (8.0 mL) for 18.5 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 2-cyclohexylidene-2-[*N*-methyl-3-(trifluoromethyl)aniline]acetate (**417**) as a yellow oil (585 mg, 1.71 mmol, 61%).

IR (neat) ν_{max}/cm^{-1} = 2931, 2857, 1712, 1609, 1588, 1497, 1477, 1452, 1359, 1247, 1321, 1258, 1227, 1192, 1161, 1118, 1096, 1071, 1042, 1023, 991, 930, 899, 877, 854, 781, 748, 697, 657.

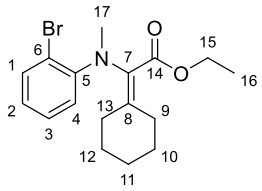
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.23 (1H, m, C3H), 6.98–6.91 (1H, m, C6H), 6.86–6.80 (1H, m, C2H), 6.79–6.72 (1H, m, C4H), 4.05 (2H, q, J = 7.1 Hz, $C15H_2$), 3.07 (3H, s, $C17H_3$), 2.29–2.21 (2H, m, $C9H_2$), 1.79–1.67 (2H, m, $C13H_2$), 1.65–1.53 (6H, m, $C10H_2$, $C11H_2$ & $C12H_2$), 1.04 (3H, t, J = 7.1 Hz, $C16H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.3 (C14), 155.4 (C8), 149.1 (C5), 131.6 (C1), 129.5 (C3H), 128.8 (C7), 126.0 ($C18F_3$), 115.6 (C4H), 113.6 (d, *J* = 4.0 Hz, C2H), 108.6 (C6H), 60.4 ($C15H_2$), 39.4 ($C17H_3$), 31.4 ($C9H_2$), 30.7 ($C13H_2$), 28.2 ($C10H_2$), 28.0 ($C12H_2$), 26.5 ($C11H_2$), 14.2 ($C16H_3$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ = -62.69 (s, $C18F_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 342.1678; $[C_{19}H_{23}F_3NO_2]^+$ requires 342.1681, Δ -0.88 ppm.

Ethyl 2-((2-bromophenyl)(methyl)amino)-2-cyclohexylideneacetate, 418



Prepared according to **General Procedure N** with ethyl 2-cyclohexyl-2-oxo-acetate (511 mg, 2.77 mmol, 1.00 equiv.), 2-broro-*N*-methylaniline (0.450 mL, 715 mg, 3.84 mmol, 1.40 equiv.), *p*-toluenesulfonic acid monohydrate (30.0 mg, 0.158 mmol, 0.0600 equiv.) and benzene (8.0 mL) for 17 h. Purification by flash column chromatography (1:0→3:2 v/v heptane:CH_2Cl_2) gave ethyl 2-(2-bromo-*N*-methyl-anilino)-2-cyclohexylidene-acetate (**418**) as a yellow oil (97.3 mg, 0.276 mmol, 10%).

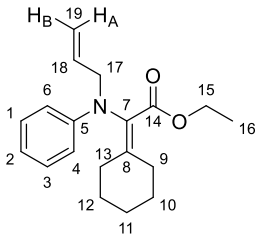
IR (neat) ν_{max}/cm^{-1} = 2927, 2854, 1709, 1585, 1475, 1446, 1314, 1285, 1253, 1236, 1158, 1116, 1102, 1072, 1051, 1036, 1025, 802, 749, 717, 651.

^{1}H NMR (CD_3CN, 400 MHz) δ = 7.44 (1H, dd, *J* = 8.0, 1.5 Hz, C1H), 7.26 (1H, ddd, *J* = 8.4, 7.0, 1.5 Hz, C3H), 7.21 (1H, dd, *J* = 8.2, 1.8 Hz, C4H), 6.82 (1H, ddd, *J* = 7.9, 7.0, 1.8 Hz, C2H), 3.94 (2H, q, *J* = 7.1 Hz, $C15H_2$), 3.02 (3H, s, $C17H_3$), 2.51–2.44 (2H, m, $C9H_2$), 2.37–2.30 (2H, m, $C13H_2$), 1.64–1.53 (6H, m, $C10H_2$, $C11H_2$ & $C12H_2$), 1.01 (3H, t, *J* = 7.1 Hz, $C16H_3$).

^{13}C NMR (CD_3CN, 101 MHz) δ = 166.8 (C14), 149.5 (C8), 147.2 (C5), 134.9 (C1H), 132.5 (C3H), 128.9 (C7), 123.9 (C2H), 123.3 (C4H), 116.3 (C6), 60.8 ($C15H_2$), 42.6 ($C17H_3$), 31.5 ($C9H_2$), 31.4 ($C13H_2$), 28.3 ($C10H_2$ & $C12H_2$), 27.1 ($C11H_2$), 14.4 ($C16H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 352.0907; $[C_{17}H_{23}BrNO_2]^+$ requires 352.0907, Δ 0.09 ppm.

Ethyl 2-(allyl(phenyl)amino)-2-cyclohexylideneacetate, 419



Prepared according to **General Procedure N** with ethyl 2-cyclohexyl-2-oxo-acetate (460 mg, 2.50 mmol, 1.00 equiv.), *N*-allylaniline (0.450 mL, 442 mg, 3.32 mmol, 1.30 equiv.), *p*-toluenesulfonic acid monohydrate (14.5 mg, 0.0762 mmol, 0.0300 equiv.) and benzene (8.0 mL) for 18.5 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 2-(*N*-allylanilino)-2-cyclohexylidene-acetate (**419**) as a yellow oil (395 mg, 1.32 mmol, 53%).

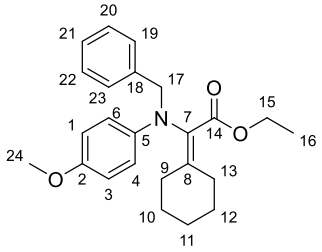
IR (neat) ν_{max}/cm^{-1} = 2928, 2854, 1709, 1596, 1498, 1447, 1367, 1316, 1258, 1215, 1175, 1134, 1106, 1082, 1050, 1034, 991, 919, 800, 746, 691.

^{1}H NMR (CD_3CN, 400 MHz) δ = 7.20–7.09 (2H, m, C1H & C3H), 6.72–6.63 (3H, m, C2H, C4H & C6H), 5.97 (1H, ddt, *J* = 17.2, 10.2, 5.9 Hz, C18H), 5.25 (1H, dq, *J* = 17.2, 1.7 Hz, C19$\underline{H_A}H_B$), 5.14 (1H, dq, *J* = 10.3, 1.6 Hz, C19$H_A\underline{H_B}$), 4.03 (2H, q, *J* = 7.1 Hz, $C15H_2$), 3.98 (2H, dt, *J* = 6.1, 1.6 Hz, $C17H_2$), 2.74–2.67 (2H, m, $C9H_2$), 2.27–2.20 (2H, m, $C13H_2$), 1.73–1.50 (6H, m, $C10H_2$, $C11H_2$ & $C12H_2$), 1.07 (3H, t, *J* = 7.1 Hz, $C16H_3$).

^{13}C NMR (CD_3CN, 101 MHz) δ = 167.4 (C14), 154.8 (C8), 149.2 (C5), 136.2 (C18H), 129.8 (C1H & C3H), 129.2 (C7), 117.2 (C2H, C4H & C6H), 114.1 ($C19H_2$), 61.0 ($C15H_2$), 55.6 ($C17H_2$), 32.1 ($C9H_2$), 31.3 ($C13H_2$), 28.8 ($C10H_2$), 28.4 ($C12H_2$), 27.0 ($C11H_2$), 14.5 ($C16H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 300.1961; $[C_{19}H_{26}NO_2]^+$ requires 300.1964, Δ -1.00 ppm.

Ethyl 2-(benzyl(4-methoxyphenyl)amino)-2-cyclohexylideneacetate, 420



Prepared according to **General Procedure N** with ethyl 2-cyclohexyl-2-oxo-acetate (500 mg, 2.71 mmol, 1.00 equiv.), *N*-benzyl-4-methoxyaniline (700 mg, 3.28 mmol, 1.20 equiv.), *p*-toluenesulfonic acid monohydrate (16.0 mg, 0.0841 mmol, 0.0300 equiv.) and benzene (8.0 mL) for 18.5 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 2-(*N*-benzyl-4-methoxy-anilino)-2-cyclohexylidene-acetate (**420**) as a yellow oil (406 mg, 1.07 mmol, 39%).

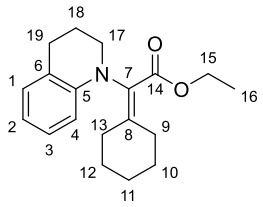
IR (neat) ν_{max}/cm^{-1} = 2930, 1706, 1508, 1451, 1240, 1215, 1163, 1104, 1035, 907, 819, 697, 648.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.26 (4H, m, C19H, C20H, C22H & C23H), 7.24–7.17 (1H, m, C21H), 6.79–6.70 (2H, m, C4H & C6H), 6.67–6.61 (2H, m, C1H & C3H), 4.54 (2H, s, $C17H_2$), 4.08 (2H, q, J = 7.1 Hz, $C15H_2$), 3.72 (3H, s, $C24H_3$), 2.66–2.58 (2H, m, $C9\underline{H_A}H_B$ & $C13\underline{H_A}H_B$), 2.28–2.20 (2H, m, $C9H_A\underline{H_B}$ & $C13H_A\underline{H_B}$), 1.67–1.39 (6H, m, $C10H_2$, $C11H_2$ & $C12H_2$), 1.10 (3H, t, J = 7.1 Hz, $C16H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 167.2 (C14), 152.8 (C2), 152.3 (C8), 143.0 (C18), 139.1 (C5), 129.9 (C20H & C22H), 128.4 (C21H), 127.7 (C19H & C23H), 126.8 (C7), 115.4 (C1H & C3H), 114.5 (C4H & C6H), 60.4 ($C15H_2$), 56.9 ($C17H_2$), 55.8 ($C24H_3$), 31.4 ($C9H_2$), 30.9 ($C13H_2$), 28.1 ($C10H_2$), 27.6 ($C12H_2$), 26.5 ($C11H_2$), 14.3 ($C16H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 380.2207; $[C_{24}H_{30}NO_3]^+$ requires 380.2220, Δ -3.41 ppm.

Ethyl 2-cyclohexylidene-2-(3,4-dihydroquinolin-1(2H)-yl)acetate, 421



Prepared according to **General Procedure N** with ethyl 2-cyclohexyl-2-oxo-acetate (520 mg, 2.82 mmol, 1.00 equiv.), 1,2,3,4-tetrahydroquinoline (0.500 mL, 531 mg, 3.98 mmol, 1.41 equiv.), *p*-toluenesulfonic acid monohydrate (28 mg, 0.147 mmol, 0.0500 equiv.) and benzene (8.0 mL) for 17 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 2-cyclohexylidene-2-(3,4-dihydro-2H-quinolin-1-yl)acetate (**421**) as a yellow oil (73.1 mg, 0.244 mmol, 9%).

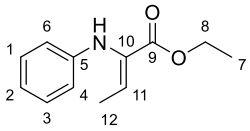
IR (neat) ν_{max}/cm^{-1} = 2926, 2853, 1709, 1601, 1577, 1494, 1447, 1304, 1263, 1222, 1202, 1183, 1164, 1107, 1090, 1077, 1031, 743, 718.

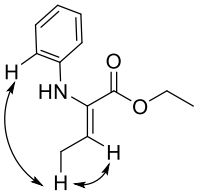
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.01–6.93 (2H, m, C1H & C3H), 6.65–6.57 (1H, m, C4H), 6.45–6.38 (1H, m, C2H), 4.09 (2H, q, *J* = 7.1 Hz, $C15H_2$), 3.58–3.47 (1H m, $C17\underline{H_A}H_B$), 3.36–3.26 (1H, m, $C17H_A\underline{H_B}$), 2.94–2.58 (4H, m, $C9\underline{H_A}H_B$, $C13\underline{H_A}H_B$ & $C19H_2$), 2.42–2.21 (2H, m, $C9H_A\underline{H_B}$ & $C13H_A\underline{H_B}$), 2.11–1.95 (2H, m, $C18H_2$), 1.82–1.59 (6H, m, $C10H_2$, $C11H_2$ & $C12H_2$), 1.09 (3H, t, *J* = 7.1 Hz, $C16H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.9 (C14), 154.0 (C8), 144.8 (C5), 129.1 (C1H), 128.6 (C7), 126.9 (C3H), 122.0 (C6), 116.6 (C2H), 112.4 (C4H), 60.1 ($C15H_2$), 50.7 ($C17H_2$), 31.2 ($C9H_2$), 30.6 ($C13H_2$), 28.2 ($C10H_2$), 28.1 ($C12H_2$), 28.0 ($C19H_2$), 26.6 ($C11H_2$), 22.0 ($C18H_2$), 14.1 ($C16H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 300.1955; $[C_{19}H_{26}NO_2]^+$ requires 300.1964, Δ -3.00 ppm.

Ethyl (Z)-2-(phenylamino)but-2-enoate, 426





Prepared according to **General Procedure N** with ethyl 2-oxobutanoate (581 mg, 5.00 mmol, 1.00 equiv.), aniline (0.456 mL, 466 mg, 5.00 mmol, 1.00 equiv.), *p*-toluenesulfonic acid monohydrate (47.6 mg, 0.250 mmol, 0.0500 equiv.) and toluene (50 mL) for 21 h. Purification by flash column chromatography (24:1→47:3 v/v pentane:Et_2O) gave ethyl (Z)-2-(phenylamino)but-2-enoate (**426**) as a yellow oil (506 mg, 2.47 mmol, 49%).

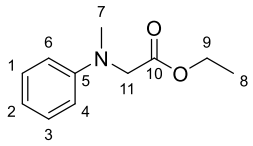
IR (neat) ν_{max}/cm^{-1} = 3378, 2981, 1705, 1648, 1600, 1498, 1440, 1382, 1368, 1345, 1262, 1174, 1136, 1084, 1064, 1035, 850, 747, 694.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.25 (2H, m, C1H & C3H), 6.90 (1H, tt, *J* = 7.4, 1.1 Hz, C2H), 6.76–6.73 (2H, m, C4H & C6H), 6.66 (1H, q, *J* = 7.3 Hz, C11H), 5.64 (1H, s, NH), 4.31 (2H, q, *J* = 7.1 Hz, $C8H_2$), 1.78 (3H, d, *J* = 7.3 Hz, $C12H_3$), 1.37 (3H, t, *J* = 7.1 Hz, $C7H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 165.9 (C9), 144.3 (C5), 130.6 (C10), 129.0 (C1H & C3H), 126.3 (C11H), 119.5 (C2H), 115.6 (C4H & C6H), 61.3 ($C8H_2$), 14.6 ($C12H_3$), 14.3 ($C7H_3$).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 228.0996; $[C_{12}H_{15}O_2NNa]^+$ requires 228.0995, Δ 0.48 ppm.

Ethyl *N*-methyl-*N*-phenylglycinate, 431



Modified literature procedure.[128] To a solution of *N*-methylaniline (1.08 mL, 1.07 g, 10.0 mmol, 1.00 equiv.) in ethanol (20 mL) was added sodium carbonate (1.59 g, 15.0 mmol, 1.50 equiv.) and ethyl 2-bromoacetate (1.22 mL, 1.84 g, 11.0 mmol, 1.10 equiv.), and the resulting suspension stirred at reflux (80 °C) for 14 h. After cooling to ambient temperature, the reaction was quenched with water (50 mL) and extracted with EtOAc (4 × 20 mL). The combined organic extracts were washes with water (4 × 25 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (19:1 v/v Petrol ether 40–60:EtOAc) gave ethyl *N*-methyl-*N*-phenylglycinate (**431**) as a yellow oil (1.84 g, 9.53 mmol, 95%).

IR (neat) ν_{max}/cm^{-1} = 2981, 1745, 1600, 1506, 1419, 1367, 1253, 1186, 1118, 1028, 989, 946, 863, 748, 690.

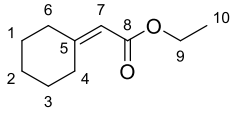
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.21 (2H, m, C1H & C3H), 6.78 (1H, tt, *J* = 7.3, 1.0 Hz, C2H), 6.74–6.68 (2H, m, C4H & C6H), 4.20 (2H, q, *J* = 7.1 Hz, $C9H_2$), 4.08 (2H, s, $C11H_2$), 3.09 (3H, s, $C7H_3$), 1.27 (3H, t, *J* = 7.1 Hz, $C8H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.1 (C10), 149.0 (C5), 129.2 (C1H & C3H), 117.4 (C2H), 112.4 (C4H & C6H), 60.9 ($C9H_2$), 54.6 ($C11H_2$), 39.6 ($C7H_3$), 14.3 ($C8H_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 194.1177; $[C_{11}H_{16}O_2N]^+$ requires 194.1176, Δ 0.80 ppm.

The data matched that reported in the literature.[128]

Ethyl 2-cyclohexylideneacetate, 438



Modified literature procedure.[132] To a suspension of 60% w/w sodium hydride in mineral oil (400 mg, 10.0 mmol, 1.25 equiv.) in THF (50 mL) under an atmosphere of argon was added triethyl phosphonoacetate (1.98 mL, 2.24 g, 10.0 mmol, 1.25 equiv.), and the mixture stirred for 45 minutes. Cyclohexanone (0.830 mL, 785 mg, 8.00 mmol, 1.00 equiv.) was then added and the mixture stirred for a further 22 h before being quenched with water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (49:1→24:1 v/v Petrol ether 40–60:EtOAc) gave ethyl 2-cyclohexylideneacetate (**438**) as a colourless oil (783 mg, 4.66 mmol, 47%).

IR (neat) ν_{max}/cm^{-1} = 2931, 1713, 1648, 1447, 1379, 1271, 1238, 1205, 1153, 1128, 1105, 1039, 852.

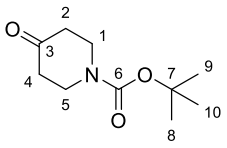
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.57 (1H, p, *J* = 1.2 Hz, C7H), 4.11 (2H, q, *J* = 7.1 Hz, $C9H_2$), 2.84–2.76 (2H, m, $C4H_2$), 2.21–2.12 (2H, m, $C6H_2$), 1.65–1.53 (6H, m, $C1H_2$, $C2H_2$ & $C3H_2$), 1.25 (3H, t, *J* = 7.1 Hz, $C10H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.9 (C8), 163.6 (C5), 113.1 (C7H), 59.5 ($C9H_2$), 38.1 ($C6H_2$), 29.9 ($C4H_2$), 28.7 ($C1H_2$), 27.9 ($C3H_2$), 26.4 ($C2H_2$), 14.4 ($C10H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 169.1225; $[C_{10}H_{17}O_2]^+$ requires 169.1223, Δ 0.99 ppm.

The data matched that reported in the literature.[132]

***tert*-Butyl 4-oxopiperidine-1-carboxylate, 440**



Modified literature procedure.[161] To a solution of piperidone hydrochloride monohydrate (4.61 g, 30.0 mmol, 1.00 equiv.) in 10:1 CH_2Cl_2 (50 mL): MeOH (5 mL) at 0 °C was added Et_3N (7.59 g, 10.5 mL, 75.0 mmol, 2.50 equiv.) dropwise, followed by di-*tert*-butyl dicarbonate (8.27 mL, 7.86 g, 36.0 mmol, 1.20 equiv.) dropwise. The mixture was then warmed to ambient temperature and stirred at this temperature for 4 h before being diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was washed with *n*-hexane (3 × 25 mL) to give sufficiently pure *tert*-butyl 4-oxopiperidine-1-carboxylate (**440**) as a white solid (2.98 g, 15.0 mmol, 50%) which was used without further purification.

m.p. = 67–69 °C.

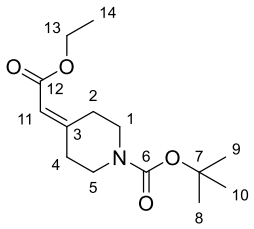
IR (neat) ν_{max}/cm^{-1} = 2977, 1714, 1685, 1427, 1365, 1316, 1275, 1242, 1167, 1120, 990, 861, 769.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.71 (4H, t, *J* = 6.2 Hz, C1H_2 & C5H_2), 2.43 (4H, t, *J* = 6.2 Hz, C2H_2 & C4H_2), 1.48 (9H, s, C8H_3, C9H_3 & C10H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.9 (C3), 154.6 (C6), 80.6 (C7), 43.2 (C1H_2 & C5H_2), 41.3 (C2H_2 & C4H_2), 28.5 (C8H_3, C9H_3 & C10H_3).

The data matched that reported in the literature.[162]

***tert*-Butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate, 439**



Modified literature procedure.[132] To a suspension of 60% w/w sodium hydride in mineral oil (400 mg, 10.0 mmol, 1.25 equiv.) in THF (40 mL) under an atmosphere of argon was added triethyl phosphonoacetate (1.98 mL, 2.24 g, 10.0 mmol, 1.25 equiv.), and the mixture stirred for 45 minutes. A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (**440**) (1.59 mg, 8.00 mmol, 1.00 equiv.) in THF (10 mL) was then added, and the mixture stirred for a further 22 h before being quenched with water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were then washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (9:1→4:1 v/v Petrol ether 40–60:Et_2O) gave *tert*-butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (**439**) as a white solid (997 mg, 3.70 mmol, 46%).

m.p. = 74–76 °C.

IR (neat) ν_{max}/cm^{-1} = 2978, 1696, 1652, 1420, 1366, 1308, 1253, 1205, 1164, 1140, 1115, 1038, 997, 865.

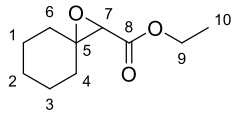
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.70 (1H, s, C11H), 4.15 (2H, q, J = 7.1 Hz, C13H_2), 3.53–3.42 (4H, m, C1H_2 & C5H_2), 2.92 (2H, t, J = 5.9 Hz, C2H_2), 2.27 (2H, t, J = 5.9 Hz, C4H_2), 1.46 (9H, s, C8H_3, C9H_3 & C10H_3), 1.27 (3H, t, J = 7.1 Hz, C14H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.5 (C12), 158.0 (C3), 154.7 (C6), 115.4 (C11H), 80.0 (C7), 59.9 ($C13H_2$), 44.5 ($C1H_2$ & $C5H_2$), 36.6 ($C4H_2$), 29.7 ($C2H_2$), 28.6 ($C8H_3$, $C9H_3$ & $C10H_3$), 14.4 ($C14H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 292.1522; $[C_{14}H_{23}O_4NNa]^+$ requires 292.1519, Δ 0.79 ppm.

The data matched that reported in the literature.[132]

Ethyl 1-oxaspiro[2.5]octane-2-carboxylate, 442



Modified literature procedure.[133] To a flame dried 3-neck 500 mL round bottom flask equipped with a thermometer, magnetic stirrer and pressure equalizing dropping funnel under an atmosphere of nitrogen was added cyclohexanone (15.3 mL, 14.5 g, 148 mmol, 1.00 equiv.) and ethyl chloroacetate (15.9 mL, 18.2 g, 148 mmol, 1.00 equiv.) as 0 °C. Potassium *tert*-butoxide (17.4 g, 155 mmol, 1.05 equiv.) was dissolved in ethanol (125 mL) and added to the reaction mixture dropwise over 1.5 h via the dropping funnel. The resulting solution was stirred at ≈10 °C for a further 1.5 h, before being concentrate *in vacuo*. This residue was then diluted with Et_2O (100 mL) before being washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by distillation under reduced pressure (134−137 °C at 27 mbar) to give ethyl 1-oxaspiro[2.5]octane-2-carboxylate (**442**) as a clear oil (6.29 g, 33.4 mmol, 23%).

IR (neat) ν_{max}/cm^{-1} = 2934, 2858, 1750, 1727, 1447, 1370, 1303, 1191, 1125, 1033, 939, 837.

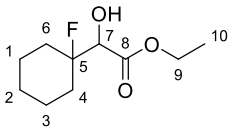
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.25 (2H, q, *J* = 7.1 Hz, C9H_2), 3.32 (1H, s, C7H), 1.78–1.50 (10H, m, C1H_2, C2H_2, C3H_2, C4H_2 & C6H_2), 1.30 (3H, t, *J* = 7.1 Hz, C10H_3).

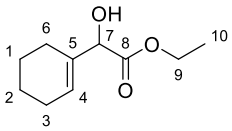
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 168.5 (C8), 65.0 (C5), 61.4 (C9H_2), 59.6 (C7H), 35.1 (C4H_2), 28.9 (C6H_2), 25.4 (C3H_2), 25.2 (C1H_2), 24.9 (C2H_2), 14.4 (C10H_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 207.0995; $[C_{10}H_{16}O_3Na]^+$ requires 207.0992, Δ 1.49 ppm.

The data matched that reported in the literature.[163]

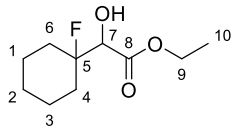
Ethyl 2-(1-fluorocyclohexyl)-2-hydroxyacetate, 444 and **ethyl 2-(cyclohex-1-en-1-yl)-2-hydroxyacetate, 445**





To a solution of ethyl 1-oxaspiro[2.5]octane-2-carboxylate (**442**) (92.1 mg, 0.500 mmol, 1.00 equiv.) in Et_2O (5 mL) was added boron trifluoride diethyl etherate (0.123 mL, 142 mg, 1.00 mmol, 2.00 equiv.), and the mixture was then stirred at ambient temperature for 3 h. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 mL), transferred to a separating funnel and extracted with Et_2O (10 mL). The separated organic extracts were then washed with saturated aqueous sodium bicarbonate (20 mL), water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (19:1→17:3 v/v pentane:Et_2O) gave ethyl 2-(1-fluorocyclohexyl)-2-hydroxyacetate (**444**) as a white solid (23.7 mg, 0.116 mmol, 23%) and ethyl 2-(cyclohex-1-en-1-yl)-2-hydroxyacetate (**445**) as a colourless oil (8.1 mg, 0.0440 mmol, 9%).

Data for **ethyl 2-(1-fluorocyclohexyl)-2-hydroxyacetate, 444**



m.p. = 36–38 °C.

IR (neat) ν_{max}/cm^{-1} = 3496, 2937, 2866, 1733, 1449, 1370, 1270, 1223, 1199, 1153, 1098, 1062, 1023, 956, 852, 818, 734, 628.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.35–4.23 (2H, m, C9H_2), 4.04 (1H, dd, *J* = 17.5, 8.3 Hz, C7H), 2.98 (1H, dd, *J* = 8.4, 0.6 Hz, O$\underline{H}$), 1.95–1.83 (2H, m, C4$\underline{H_A}H_B$ & C6$\underline{H_A}H_B$), 1.65–1.50 (7H, m, C1H_2, C2$\underline{H_A}H_B$, C3H_2, C4$H_A\underline{H_B}$ & C6$H_A\underline{H_B}$), 1.32 (3H, t, *J* = 7.1 Hz, C10H_3), 1.28–1.22 (1H, m, C2$H_A\underline{H_B}$).

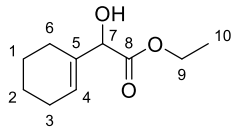
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.0 (d, *J* = 2.3 Hz, C8), 96.2 (d, *J* = 178.8 Hz, C5F), 75.5 (d, *J* = 24.8 Hz, C7H), 62.1 (C9H_2), 32.0 (d, *J* = 22.1 Hz, C4H_2), 31.1 (d, *J* = 22.3 Hz, C6H_2), 25.2 (C2H_2), 21.66 (d, *J* = 2.9 Hz, C3H_2), 21.6 (d, *J* = 2.9 Hz, C1H_2), 14.3 (C10H_3).

^{19}F NMR ($CDCl_3$, 377 MHz) δ = -168.09 (s, C5F)

HRMS (ESI^+) Found $[M+Na]^+$ = 227.1056 $[C_{10}H_{17}O_3FNa]^+$ requires 227.1054, Δ 1.00 ppm.

The data matched that reported in the literature.[159]

Data for **ethyl 2-(cyclohex-1-en-1-yl)-2-hydroxyacetate, 445**



IR (neat) ν_{max}/cm^{-1} = 3500, 2931, 2859, 1731, 1448, 1368, 1253, 1202, 1154, 1091, 1067, 1022, 920, 861, 801.

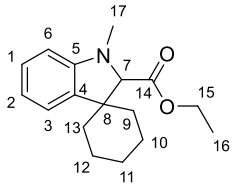
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.87–5.79 (1H, m, C4H), 4.46 (1H, d, J = 5.4 Hz, C7H), 4.30–4.22 (2H, m, $C9H_2$), 3.02 (1H, d, J = 5.7 Hz, O$\underline{H}$), 2.17–2.10 (1H, m, $C6\underline{H_A}H_B$), 2.09–2.04 (2H, m, $C3H_2$), 1.82–1.74 (1H, m, $C6H_A\underline{H_B}$), 1.67–1.59 (4H, m, $C1H_2$ & $C2H_2$), 1.29 (3H, t, J = 7.1 Hz, $C10H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 174.0 (C8), 135.0 (C5), 127.4 (C4H), 75.4 (C7H), 61.8 ($C9H_2$), 25.1 ($C3H_2$), 23.7 ($C6H_2$), 22.4 ($C1H_2$), 22.1 ($C2H_2$), 14.2 ($C10H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 207.0994; $[C_{10}H_{16}O_3Na]^+$ requires 207.0992, Δ 0.89 ppm.

The data matched that reported in the literature.[164]

Ethyl 1'-methylspiro[cyclohexane-1,3'-indoline]-2'-carboxylate, 446



Prepared according to **General Procedure P** with ethyl 2-cyclohexylidene-2-(*N*-methylanilino)acetate (**398**) (41.0 mg, 0.150 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (1.2 mg, 0.0015 mmol, 0.01 equiv.) and MeCN (3 mL) for 2 h. Purification by reverse phase chromatography (100:0→0:100 v/v H_2O:MeCN) gave ethyl 1'-methylspiro[cyclohexane-1,3'-indoline]-2'-carboxylate (**446**) as a yellow oil (25.4 mg, 0.0930 mmol, 62%).

IR (neat) ν_{max}/cm^{-1} = 2923, 2853, 1742, 1728, 1605, 1487, 1454, 1262, 1179, 1041, 736.

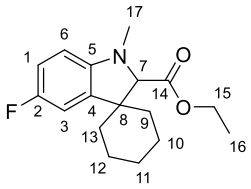
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.16 (1H, dd, J = 7.4, 1.3 Hz, C3H), 7.11 (1H, td, J = 7.7, 1.3 Hz, C1H), 6.69 (1H, td, J = 7.4, 1.0 Hz, C2H), 6.47 (1H, dd, J = 7.8, 1.0 Hz, C6H), 4.33–4.12 (2H, m, $C15H_2$), 3.90 (1H, s, C7H), 2.75 (3H, s, $C17H_3$), 2.02–1.89 (1H, m, $C9\underline{H_A}H_B$), 1.86–1.73 (2H,

m, C9$H_A\underline{H_B}$ & C13$\underline{H_A}H_B$), 1.71–1.61 (3H, m, C10$\underline{H_A}H_B$, C12$\underline{H_A}H_B$ & C13$H_A\underline{H_B}$), 1.58–1.50 (4H, m, C10$H_A\underline{H_B}$, C11H_2 & C12$H_A\underline{H_B}$), 1.28 (3H, t, *J* = 7.1 Hz, C16H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.1 (C14), 151.0 (C5), 136.8 (C4), 127.9 (C1H), 123.0 (C3H), 117.7 (C2H), 106.8 (C6H), 77.9 (C7H), 60.6 (C15H_2), 48.5 (C8), 37.1 (C17H_3), 34.0 (C9H_2), 32.2 (C13H_2), 25.8 (C11H_2), 22.9 (C10H_2), 22.3 (C12H_2), 14.4 (C16H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 273.1725; $[C_{17}H_{24}NO_2]^+$ requires 273.1729, Δ -1.46 ppm.

Ethyl 5'-fluoro-1'-methylspiro[cyclohexane-1,3'-indoline]-2'-carboxylate, 447



Prepared according to **General Procedure P** with ethyl 2-cyclohexylidene-2-(4-fluoro-*N*-methyl-anilino)acetate (**416**) (44.0 mg, 0.150 mmol, 1.00 equiv.), Ir(dFppy)$_3$ (1.2 mg, 0.0015 mmol, 0.01 equiv.) and MeCN (3 mL) for 2 h. Purification by flash column chromatography (1:0→9:1 v/v heptane:EtOAc) gave ethyl 5'-fluoro-1'-methylspiro[cyclohexane-1,3'-indoline]-2'-carboxylate (**447**) as a yellow oil (27.1 mg, 0.0930 mmol, 62%).

IR (neat) ν_{max}/cm^{-1} = 2925, 2854, 1736, 1489, 1454, 1371, 1300, 1262, 1182, 1115, 1097, 1039, 868, 804.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.87 (1H, dd, *J* = 8.9, 2.6 Hz, C3H), 6.78 (1H, ddd, *J* = 9.3, 8.5, 2.6 Hz, C1H), 6.32 (1H, dd, *J* = 8.5, 4.2 Hz, C6H), 4.32–4.11 (2H, m, C15H_2), 3.89 (1H, s, C7H), 2.71 (3H, s, C17H_3), 2.00–1.89 (1H, m, C9$\underline{H_A}H_B$), 1.82–1.70 (2H, m, C9$H_A\underline{H_B}$ & C13$\underline{H_A}H_B$),

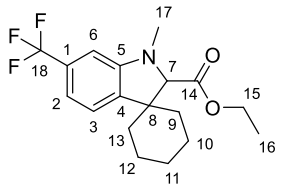
1.69–1.60 (2H, m, C10$\underline{H_A}H_B$ & C13$H_A\underline{H_B}$), 1.59–1.49 (5H, m, C10$H_A\underline{H_B}$, C11H_2 & C12$\underline{H_A}H_B$), 1.27 (3H, t, *J* = 7.1 Hz, C16H_3).

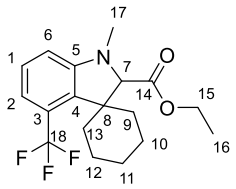
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.0 (C14), 156.6 (d, *J* = 235.3 Hz, C2F), 147.3 (C5), 138.5 (d, *J* = 8.1 Hz, C4), 113.5 (d, *J* = 23.2 Hz, C3H), 111.1 (d, *J* = 24.2 Hz, C1H), 106.7 (d, *J* = 8.1 Hz, C6H), 78.3 (C7H), 60.7 (C15H_2), 48.5 (d, *J* = 2.0 Hz, C8), 36.9 (C17H_3), 34.5 (C9H_2), 32.1 (C13H_2), 25.8 (C11H_2), 22.9 (C10H_2), 22.4 (C12H_2), 14.5 (C16H_3).

^{19}F NMR ($CDCl_3$, 376 MHz) δ = -127.38 (s, C2F).

HRMS (ESI$^+$) Found $[M+H]^+$ = 292.1708; $[C_{17}H_{23}FNO_2]^+$ requires 292.1707, Δ 0.34 ppm.

Ethyl 1'-methyl-6'-(trifluoromethyl)spiro[cyclohexane-1,3'-indoline]-2'-carboxylate), 448a and **ethyl 1'-methyl-4'-(trifluoromethyl)spiro[cyclohexane-1,3'-indoline]-2'-carboxylate), 448b**





Prepared according to **General Procedure P** with ethyl 2-cyclohexylidene-2-[*N*-methyl-3-(trifluoromethyl)aniline]acetate (**417**) (51.2 mg, 0.150 mmol, 1.00 equiv.), Ir(dFppy)$_3$ (1.2 mg, 0.0015 mmol, 0.01 equiv.) and MeCN (3 mL) for 2 h. Purification by flash column chromatography (1:0→9:1 v/v heptane:EtOAc) gave ethyl 1'-methyl-6'-(trifluoromethyl)spiro[cyclohexane-1,3'-indoline]-2'-carboxylate (**448a**) and ethyl 1'-methyl-4'-(trifluoromethyl)spiro[cyclohexane-1,3'-indoline]-2'-carboxylate (**448b**) as a yellow oil (37.8 mg, 0.111 mmol, 74%, 5:1 inseparable mixture of regioisomers 6':4').

Only NMR peaks corresponding to the major regioisomer (6'; 448a) are reported.

IR (neat) ν_{max}/cm^{-1} = 2933, 2857, 1732, 1615, 1498, 1475, 1451, 1418, 1375, 1312, 1264, 1228, 1160, 1114, 1059, 1040, 999, 967, 918, 846, 813, 793, 733, 667, 647.

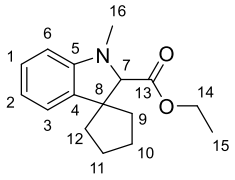
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.14–7.09 (1H, m, C3H), 6.94–6.90 (1H, m, C6H), 6.60–6.56 (1H, m, C2H), 4.27–4.13 (2H, m, C15H_2), 4.04 (1H, s, C7H), 2.78 (3H, s, C17H_3), 1.97–1.88 (1H, m, C9$\underline{H_A}H_B$), 1.81–1.72 (2H, m, C9$H_A\underline{H_B}$ & C13$\underline{H_A}H_B$), 1.71–1.58 (5H, m, C10$\underline{H_A}H_B$, C11$\underline{H_A}\underline{H_B}$, C12$\underline{H_A}H_B$ & C13$H_A\underline{H_B}$), 1.54–1.44 (2H, m, C10$H_A\underline{H_B}$ & C12$H_A\underline{H_B}$), 1.26 (3H, t, J = 7.1 Hz, C16H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 170.7 (C14), 151.5 (C5), 140.9 (C4), 130.4 (q, J = 23.7 Hz, C1), 126.11 (C3H), 122.52 (C18), 114.8 (q, J = 4.0 Hz, C2H), 102.4 (q, J = 4.0 Hz, C6H), 74.6 (C7H), 60.8 (C15H_2), 48.9 (C8), 37.4 (C17H_3), 33.2 (C9H_2), 31.8 (C13H_2), 25.7 (C11H_2), 22.8 (C10H_2), 22.6 (C12H_2), 14.4 (C16H_3).

^{19}F NMR ($CDCl_3$, 376 MHz) δ = -62.24 (s, C18F_3).

HRMS (ESI^+) Found $[M+H]^+$ = 342.1679; $[C_{18}H_{23}F_3NO_2]^+$ requires 342.1681, Δ -0.58 ppm.

Ethyl 1'-methylspiro[cyclopentane-1,3'-indoline]-2'-carboxylate, 450



Prepared according to **General Procedure P** with ethyl 2-cyclohexylidene-2-(*N*-methylanilino)acetate (**412**) (390 mg, 1.50 mmol, 1.00 equiv.), Ir(dFppy)$_3$ (5.0 mg, 0.00656 mmol, 0.005 equiv.) and MeCN (30 mL) for 6 h. Purification by flash column chromatography (1:0→9:1 v/v heptane:EtOAc) gave ethyl

1'-methylspiro[cyclopentane-1,3'-indoline]-2'-carboxylate (**450**) as a yellow oil (287 mg, 1.11 mmol, 74%).

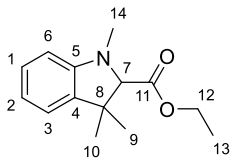
IR (neat) ν_{max}/cm^{-1} = 2955, 2870, 1710, 1678, 1612, 1490, 1470, 1374, 1299, 1191, 1124, 1093, 1022, 752.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.11 (1H, td, *J* = 7.6, 1.3 Hz, C3H), 7.03–6.97 (1H, m, C1H), 6.73 (1H, td, *J* = 7.4, 1.0 Hz, C2H), 6.52 (1H, dt, *J* = 7.9, 0.7 Hz, C6H), 4.35–4.19 (2H, m, $C14H_2$), 3.86 (1H, s, C7H), 2.77 (3H, s, $C16H_3$), 2.19–2.00 (2H, m, $C9\underline{H_A}H_B$ & $C12\underline{H_A}H_B$), 1.89–1.76 (4H, m, $C9H_A\underline{H_B}$, $C10\underline{H_A}H_B$, $C11\underline{H_A}H_B$ & $C12H_A\underline{H_B}$), 1.70–1.61 (2H, m, $C10H_A\underline{H_B}$ & $C11H_A\underline{H_B}$), 1.31 (3H, t, *J* = 7.1 Hz, $C15H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.2 (C13), 150.7 (C5), 138.0 (C4), 127.7 (C1H), 121.7 (C3H), 118.8 (C2H), 107.5 (C6H), 78.9 (C7H), 60.8 ($C14H_2$), 55.1 (C8), 39.4 ($C16H_3$), 36.2 ($C9H_2$), 35.1 ($C12H_2$), 25.5 ($C10H_2$), 25.1 ($C11H_2$), 14.4 ($C15H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 260.1645; $[C_{16}H_{22}NO_2]^+$ requires 260.1645, Δ -0.04 ppm.

Ethyl 1,3,3-trimethylindoline-2-carboxylate, 451



Prepared according to **General Procedure P** with ethyl 3-methyl-2-(methyl(phenyl)amino)but-2-enoate (**409**) (35.0 mg, 0.150 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (1.2 mg, 0.0015 mmol, 0.01 equiv.) and MeCN (3 mL) for 2 h. Purification by flash column chromatography (1:0→7:3 v/v heptane:EtOAc) gave ethyl 1,3,3-trimethylindoline-2-carboxylate (**451**) as a yellow oil (21.3 mg, 0.0913 mmol, 61%).

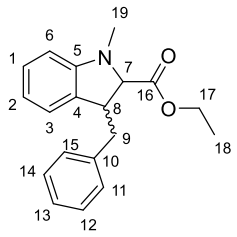
IR (neat) ν_{max}/cm^{-1} = 2965, 1723, 1606, 1488, 1461, 1363, 1301, 1186, 1122, 1095, 1041, 1023, 983, 860, 811, 742.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.12 (1H, td, *J* = 7.7, 1.3 Hz, C3H), 7.00 (1H, ddd, *J* = 7.3, 1.3, 0.5 Hz, C1H), 6.76 (1H td, *J* = 7.4, 1.0 Hz, C2H), 6.56 (1H, dt, *J* = 7.9, 0.7 Hz, C6H), 4.41–4.19 (2H, m, $C12H_2$), 3.71 (1H, s, C7H), 2.79 (3H, s, $C14H_3$), 1.53 (3H, s, $C9H_3$), 1.35 (3H, t, *J* = 7.1 Hz, $C13H_3$), 1.13 (3H, s, $C10H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.0 (C11), 150.6 (C5), 137.2 (C4), 128.0 (C1H), 121.6 (C3H), 119.0 (C2H), 108.1 (C6H), 79.7 (C7H), 60.9 ($C12H_2$), 44.4 (C8), 35.4 ($C14H_3$), 27.2 ($C9H_3$), 24.8 ($C10H_3$), 14.6 ($C13H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 234.1489; $[C_{14}H_{20}NO_2]^+$ requires 234.1494, Δ -2.14 ppm.

Ethyl 3-benzyl-1-methylindoline-2-carboxylate, 452



Prepared according to **General Procedure P** with ethyl 2-(*N*-methylanilino)-4-phenyl-but-2-enoate (**413**) (44.3 mg, 0.150 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (1.2 mg, 0.0015 mmol, 0.01 equiv.) and MeCN (3 mL) for 2 h. Purification by flash column chromatography (1:0→9:1 v/v heptane:EtOAc) gave ethyl 3-benzyl-1-methylindoline-2-carboxylate (**452**) as a yellow oil (20.6 mg, 0.0697 mmol, 46%).

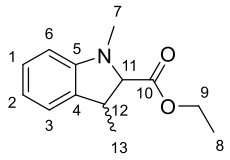
IR (neat) ν_{max}/cm^{-1} = 3028, 2929, 2859, 1744, 1606, 1485, 1466, 1454, 1376, 1345, 1260, 1235, 1193, 1179, 1124, 1085, 1040, 1023, 742, 699.

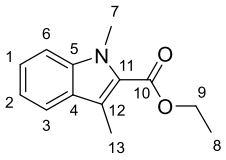
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.21 (4H, m, C11H, C12H, C14H & C15H), 7.10–7.05 (2H, m, C1H & C13H), 6.59 (1H, d, *J* = 7.8 Hz, C3H), 6.53 (1H, td, *J* = 7.4, 1.0 Hz, C2H), 6.24 (1H, ddt, *J* = 7.3, 1.4, 0.7 Hz, C6H), 4.29–4.15 (2H, m, $C17H_2$), 4.13 (1H, d, *J* = 8.5 Hz, C7H), 3.75–3.71 (1H, m, C8H), 2.91 (1H, dd, *J* = 13.2, 5.5 Hz, $C9\underline{H_A}H_B$), 2.81 (3H, s, $C19H_3$), 2.68 (dd, *J* = 13.3, 10.5 Hz, $C9H_A\underline{H_B}$), 1.31 (3H, t, *J* = 7.1 Hz, $C18H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.0 (C16), 151.9 (C5), 139.1 (C10), 130.5 (C4), 129.7 (C12H & C14H), 128.3 (C11H & C15H), 126.4 (C1H), 125.0 (C3H), 123.7 (C13H), 118.5 (C2H), 108.4 (C6H), 73.2 (C7H), 61.1 ($C17H_2$), 45.3 (C8H), 36.8 ($C9H_2$), 35.6 ($C19H_3$), 14.5 ($C18H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 296.1649; $[C_{19}H_{22}NO_2]^+$ requires 296.1651, Δ -0.68 ppm.

Ethyl 1,3-dimethylindoline-2-carboxylate, 453 and **ethyl 1,3-dimethyl-1*H*-indole-2-carboxylate, 454**

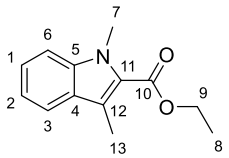




To a 7 mL screw-top vial was added ethyl (Z)-2-(methyl(phenyl)amino)but-2-enoate (**408**) (65.8 mg, 0.300 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (0.600 mg, 7.5 µmol, 0.00250 equiv.) and acetonitrile (6 mL). The vial was sealed with a septum and sparged with nitrogen for at least 15 minutes, before being sealed with a screw top cap. The reaction was then stirred for 2 h whilst being irradiated by a 40 W Kessil Blue LED 440 nm lamp. The solvent was then removed *in vacuo* and the product purified by flash column chromatography (49:1→19:1 v/v pentane:Et_2O) to give ethyl 1,3-dimethyl-1*H*-indole-2-carboxylate (**454**) as

a white solid (13.4 mg, 0.617 mmol, 20%) and ethyl 1,3-dimethylindoline-2-carboxylate (**453**) as a pale-yellow oil (37.6 mg, 0.171 mmol, 57%, 1:1 d.r.).

Data for **ethyl 1,3-dimethyl-1*H*-indole-2-carboxylate, 454**



m.p. = 61–63 °C.

IR (neat) ν_{max}/cm^{-1} = 2926, 1695, 1530, 1469, 1415, 1382, 1355, 1336, 1260, 1165, 1139, 1110, 1029, 774, 739.

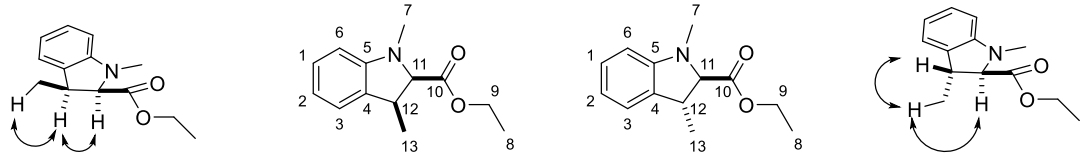
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.67 (1H, dt, *J* = 8.1, 1.0 Hz, C3H), 7.39–7.30 (2H, m, C1H & C6H), 7.17–7.10 (1H, m, C2H), 4.42 (2H, q, *J* = 7.1 Hz, $C9H_2$), 4.01 (3H, s, $C7H_3$), 2.60 (3H, s, $C13H_3$), 1.44 (3H, t, *J* = 7.1 Hz, $C8H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 163.3 (C10), 138.9 (C5), 129.3 (C11), 127.3 (C4), 125.3 (C1H), 120.9 (C3H), 120.7 (C12), 119.8 (C2H), 110.1 (C6H), 60.5 ($C9H_2$), 32.2 ($C7H_3$), 14.6 ($C8H_3$), 11.0 ($C13H_3$).

HRMS (APCI) Found $[M+H]^+$ = 218.1180; $[C_{13}H_{16}O_2N]^+$ requires 218.1176, Δ 2.16 ppm.

The data matched that reported in the literature.[165]

Data for **ethyl (2*R**,3*S**)-1,3-dimethylindoline-2-carboxylate, 453a** and **ethyl (2*R**,3R*)-1,3-dimethylindoline-2-carboxylate, 453b**



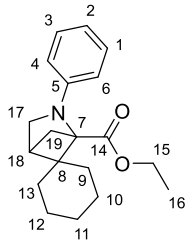
IR (neat) ν_{max}/cm^{-1} = 2967, 1745, 1608, 1486, 1455, 1375, 1179, 1124, 1092, 1036, 745.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.17–7.07 (2H, m, C1H [*R**,*S**] and [*R**,*R**]), 7.07–6.96 (2H, m, C3H [*R**,*S**] and [*R**,*R**]), 6.74 (2H, tdd, *J* = 7.3, 6.3, 1.0 Hz, C2H [*R**,*S**] and [*R**,*R**]), 6.53 (2H, dd, *J* = 7.8, 2.6 Hz, C6H [*R**,*S**] and [*R**,*R**]), 4.38–4.18 (4H, m, $C9H_2$ [*R**,*S**] and [*R**,*R**]), 4.10 (1H, d, *J* = 9.1 Hz, C11H [*R**,*S**]), 3.67–3.52 (2H, m, C11H [*R**,*R**] and C12H [*R**,*S**]), 3.46–3.32 (1H, m, C12H [*R**,*R**]), 2.82 (3H, s, $C7H_3$ [*R**,*R**]), 2.79 (3H, s, $C7H_3$ [*R**,*S**]), 1.47 (d, *J* = 6.8 Hz, $C13H_3$ [*R**,*R**]), 1.38–1.28 (m, $C8H_3$ [*R**,*S**] and [*R**,*R**]), 1.18 (d, *J* = 7.2 Hz, $C13H_3$ [*R**,*S**]).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.7 (C10 [*R**,*R**]), 170.9 (C10 [*R**,*S**]), 151.8 (C5 [*R**,*R**]), 151.6 (C5 [*R**,*S**]), 133.1 (C4 [*R**,*S**]), 132.4 (C4 [*R**,*R**]), 128.1 (C1H [*R**,*S**] and [*R**,*R**]), 123.3 (C3H [*R**,*S**]), 122.8 (C3H [*R**,*R**]), 118.7 (C2H [*R**,*S**] and [*R**,*R**], 107.7 (C6H [*R**,*S**] and [*R**,*R**]), 76.7 (C11H [*R**,*R**]), 72.9 (C11H [*R**,*S**]), 61.2 ($C9H_2$ [*R**,*S**] or [*R**,*R**]), 60.9 ($C9H_2$ [*R**,*S**] or [*R**,*R**]), 41.1 (C12H [*R**,*R**]), 38.8 (C12H [*R**,*S**]), 35.7 ($C7H_3$ [*R**,*R**]), 35.0 ($C7H_3$ [*R**,*S**]), 18.4 ($C13H_3$ [*R**,*R**]), 16.5 ($C13H_3$ [*R**,*S**]), 14.5 ($C8H_3$ [*R**,*S**] or [*R**,*R**]), 14.4 ($C8H_3$ [*R**,*S**] or [*R**,*R**]).

HRMS (ESI^+) Found $[M+H]^+$ = 220.1333; $[C_{13}H_{18}O_2N]^+$ requires 220.1332, Δ 0.36 ppm.

Ethyl 2-phenyl-2-azaspiro[bicyclo[2.1.1]hexane-5,1'-cyclohexane]-1-carboxylate, 456



Prepared according to **General Procedure P** with ethyl 2-(*N*-allylanilino)-2-cyclohexylidene-acetate (**419**) (44.9 mg, 0.150 mmol, 1.00 equiv.), $Ir(dFppy)_3$ (1.2 mg, 0.0015 mmol, 0.01 equiv.) and MeCN (3 mL) for 2 h. Purification by

flash column chromatography (1:0→0:1 v/v heptane:EtOAc) gave 2-phenyl-2-azaspiro[bicycle[2.1.1]hexane-5,1'-cyclohexane]-1-carboxylate (**456**) as a yellow oil (13.4 mg, 0.0448 mmol, 30%).

IR (neat) ν_{max}/cm^{-1} = 2924, 2852, 1724, 1599, 1492, 1370, 1306, 1212, 1181, 1143, 1124, 1090, 754, 694.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.21–7.14 (2H, m, C1H & C3H), 6.79 (1H, tt, *J* = 7.3, 1.0 Hz, C2H), 6.73–6.66 (2H, m, C4H & C6H), 4.31–4.20 (2H, m, $C15H_2$), 3.88–3.81 (1H, m, $C17\underline{H_A}H_B$), 3.08–3.01 (1H, m, $C17H_A\underline{H_B}$), 2.70–2.60 (2H, m, $C19H_2$), 2.16–2.05 (2H, m, $C9\underline{H_A}H_B$ & C18H), 1.70–1.60 (3H, m, $C9H_A\underline{H_B}$ & $C13\underline{H_A}\underline{H_B}$), 1.57–1.36 (3H, m, $C10\underline{H_A}H_B$, $C11\underline{H_A}H_B$ & $C12\underline{H_A}H_B$), 1.27–1.22 (6H, m, $C10H_A\underline{H_B}$, $C11H_A\underline{H_B}$, $C12H_A\underline{H_B}$ & $C16H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 169.5 (C14), 152.2 (C5), 129.0 (C1H & C3H), 119.5 (C2H), 116.6 (C4H & C6H), 73.7 (C7), 61.0 ($C15H_2$), 58.5 ($C17H_2$), 58.2 (C8), 40.4 (C18H), 34.6 ($C19H_2$), 29.3 ($C9H_2$), 28.0 ($C13H_2$), 26.7 ($C11H_2$), 24.2 ($C10H_2$), 23.3 ($C12H_2$), 14.6 ($C16H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 300.1960; $[C_{19}H_{26}NO_2]^+$ requires 300.1964, Δ -1.33 ppm.

7.4 Mechanistic Experiments

7.4.1 Quantum Yield

Actinometry

Ferrioxalate actinometry was used to determine the photon flux through the apparatus.[103] A 0.15 M ferrioxalate solution was prepared by dissolving potassium ferrioxalate hydrate (1.84 g) in 0.05 M aqueous sulfuric acid (25 mL) in a 25 mL volumetric flask in the dark. A buffered phenanthroline solution was prepared in a 50 mL volumetric flask by dissolving 1,10-phenanthroline (50 mg) and sodium acetate (11.25 g) in 0.05 M aqueous sulfuric acid (50 mL) in the dark. Both solutions were spared with argon for at least 30 minutes before use.

In the dark, 1 mL of the ferrioxalate solution was added to a septum-sealed cuvette and irradiated for 5 seconds at 440 nm (Kessil Blue LED lamp). Subsequently, 0.175 mL of the phenanthroline buffer solution was added to the cuvette, the solution mixed well and allowed to sit in the dark for at least 30 minutes to allow for the Fe^{2+} ions to coordinate to the phenanthroline. The absorbance of the solution at 510 nm was then measured using a UV-vis spectrophotometer. The procedure was then repeated without the 5 seconds of irradiation to act as a "dark" control.

The amount of Fe^{2+} ions in solution was then calculated using the following relationship:

$$mol\ Fe^{2+} = \frac{V \times \Delta A}{l \times \varepsilon}$$

Where V is the total volume in the cuvette (1.175 mL), ΔA is the difference in absorbance at 510 nm between the irradiated and non-irradiated solutions, l is the path length (1.00

cm) and ε is the molar absorptivity constant for the solution at 510 nm (1.11×10^7 mLmol^{-1}cm^{-1}).

The photon flux can then be calculated using the relationship:

$$Photon\ Flux = \frac{mol\ Fe^{2+}}{\varphi_{ferriox} \times t \times f}$$

Where $\phi_{ferriox}$ is the quantum yield for the ferrioxalate actinometer (1.01 for a 0.15 M solution at 436 nm), t is the irradiation time (5.0 s) and f is the fraction of light absorbed at 436 nm (0.99854). The fraction of light absorbed at 436 nm was calculated using the relationship:

$$f = 1 - 10^{-A}$$

Where A is the measured absorbance at 436 nm.

Using the average of four experiments, the photon flux was calculated to be 3.619×10^{-8} einsteins/s.

Quantum yield

The quantum yield for a reaction was then determined using the following relationship:

$$\varphi = \frac{mol\ Product}{photon\ flux \times t \times f}$$

Where "mol Product" is the moles of product formed in the reaction (determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard), "photon flux" is the photon flux as previously determined by actinometry, t is the reaction time and f is the fraction of light absorbed by the reaction mixture at 436 nm (can be approximated to 1 for most visible light photocatalysts).[103]

For the 6π heterocyclization detailed in **Chapter 2** optimization substrate **123** was used. After 2 hours of irradiation, the yield of the reaction performed on a 0.05 mmol scale was determined to be 40%. The quantum yield was then calculated to be 7.7%.

For the spircocyclization detailed in **Chapter 4** optimization substrate **272** was used. After 1 hour of irradiation, the yield of the reaction performed on a 0.05 mmol scale was determined to be 38%. The quantum yield was then calculated to be 14.6%.

7.4.2 ReactIR

The ReactIR data was collected with the following parameters:

Samples Acquired: 960

ReactIR 15 (SN:Unspecified) with MCT Detector using HappGenzel apodization; DiComp (Diamond) probe (SN:DSTFP-6-203-1.5-20563) connected via AgX 6mm × 1.5m Fiber (Silver Halide); Sampling 2000 to 650 at 4 wavenumber resolution; Scan option: AutoSelect; Gain: 1×.

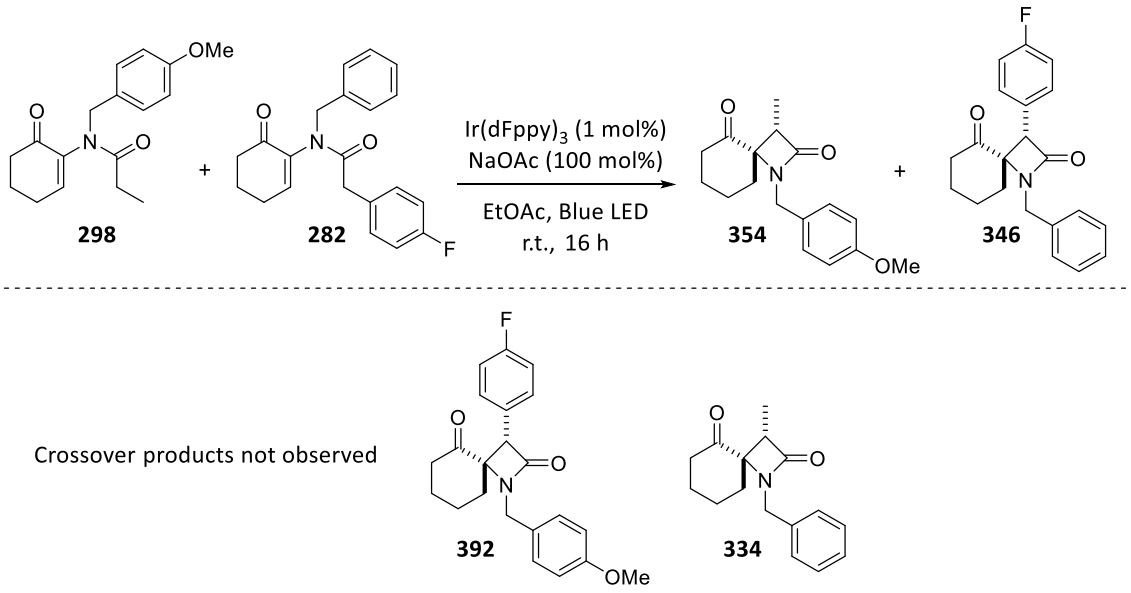
7.4.3 Stern-Volmer Quenching Experiment

A stock solution of $Ir(dFppy)_3$ (2.0 mg) in EtOAc (10.0 mL; 0.26 mM) was prepared by adding argon sparged EtOAc to a volumetric flask under argon containing the photocatalyst. A stock solution of substrate **272** (10.3 mg) in EtOAc (2.0 mL; 20 mM) was prepared in a similar manned by adding argon sparged EtOAc to a vial containing subsrate **272** sealed with a septum under an atmosphere of argon.

Samples were prepared in 4.0 mL quartz cuvettes equipped with a septum under an argon atmosphere by adding 2.0 mL of the photocatalyst stock solution which was diluted with a

further 1.0 mL of argon sparged EtOAc (final concentration of photocatalyst = 0.175 mM). The resulting solution was excited at 400 nm and three emission spectra recorded from 430 to 700 nm. To this solution was then added 50 µL of substrate **272** stock solution under argon, and three emission spectra recorded as before. This process was then repeated five further times.

7.4.4 Crossover Experiment



Scheme 140. Crossover experiment of **282** and **298**.

A 1:1 mixture of **298** (86.2 mg, 0.300 mmol, 1.00 equiv.) and **282** (101.2 mg, 0.300 mmol, 1.00 equiv.) were subjected to **General Procedure L** with $Ir(dFppy)_3$ (2.3 mg, 0.003 mmol, 0.01 equiv.), NaOAc (24.6 mg, 0.300 mmol, 1.00 equiv.) and EtOAc (30 mL) for 16 h (**Scheme 140**). Analysis of both the ^1H NMR spectrum and LC-MS of the crude reaction mixture showed only the formation of **346** and **354**, with no trace of any crossover byproducts **334** and **392**.

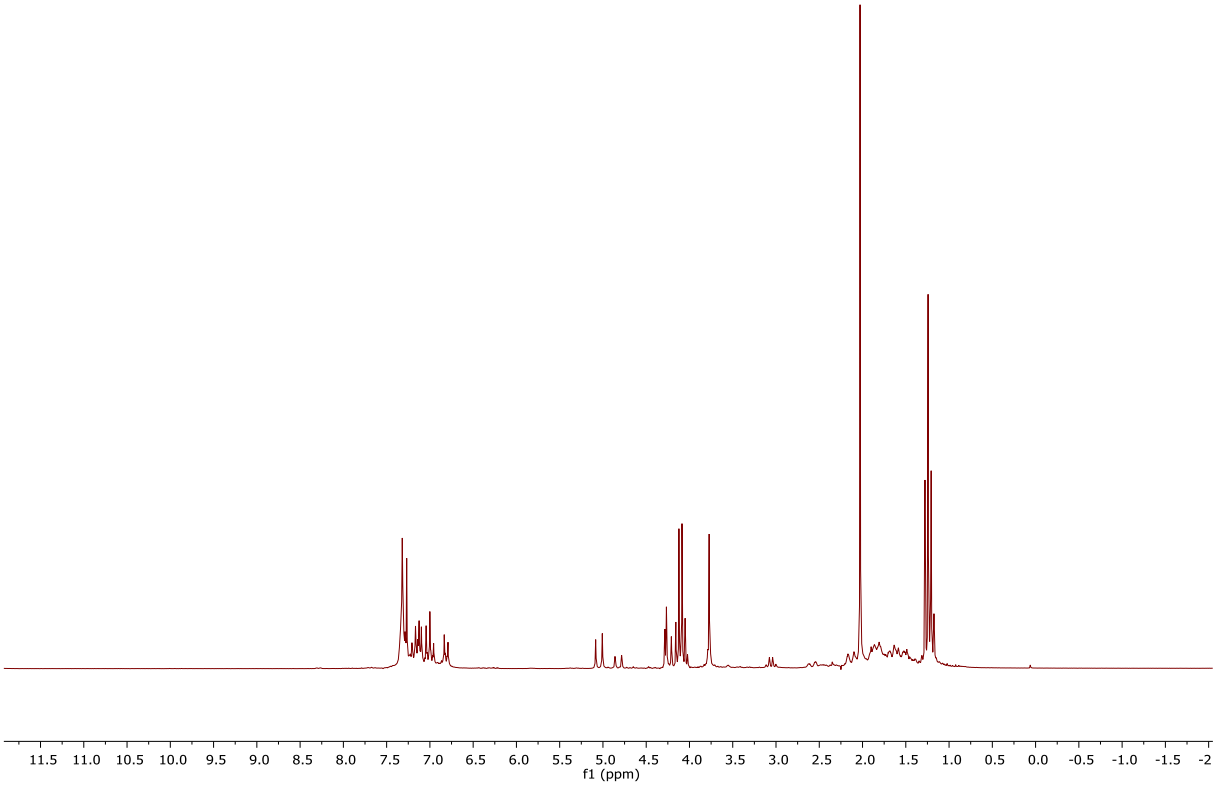
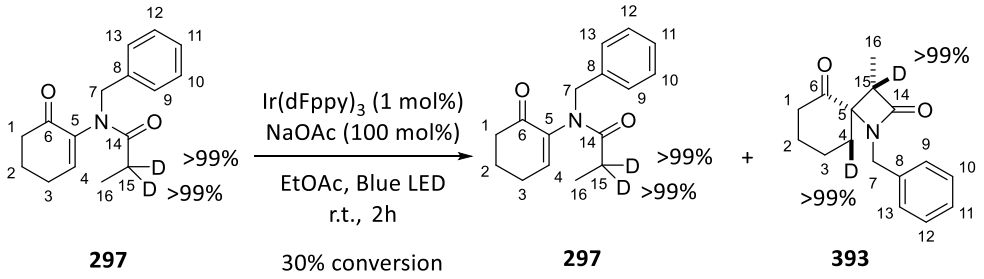


Figure 12. ^{1}H NMR spectrum of the crude reaction mixture from the crossover experiment.

7.4.5 Deuterium Labelling



Scheme 141. Photocyclization of deuterated substrate **297**.

Deuterated substrate **297** (6NAP025) was subjected to the photocyclization conditions as outlined in **Scheme 141**, and the NMR spectra compared with the corresponding non-deuterated compounds **272** and **334**. The starting material **297** recovered in the reaction was identical to the previous material, with no change in the level or location of

deuterium label. In the ^{1}H NMR of deuterated product **393**, the signals corresponding to H_{15} and one of H_4 were not present, and the doublet at 1.20 ppm in the protic compound was present as a broad singlet instead (**Figure 13**). The stereochemistry of the deuterated product **393** was assigned based on the assignment of the corresponding protons in the protic product **334**. In the ^{13}C NMR of deuterated compound **393**, the signals corresponding to C_4 and C_{15} were not present or significantly weakened in intensity, further supporting the incorporation of deuterium at those carbon atoms (**Figure 14**). The ^{2}H NMR of the deuterated starting material **297** showed only two diastereotopic ^{2}H signal corresponding to the deuterated methylene deuterium atoms (**Figure 15**). The ^{2}H NMR of the deuterated product **393** showed only two ^{2}H signals corresponding to $^{2}H_{15}$ and one environment at $^{2}H_4$ (**Figure 16**).

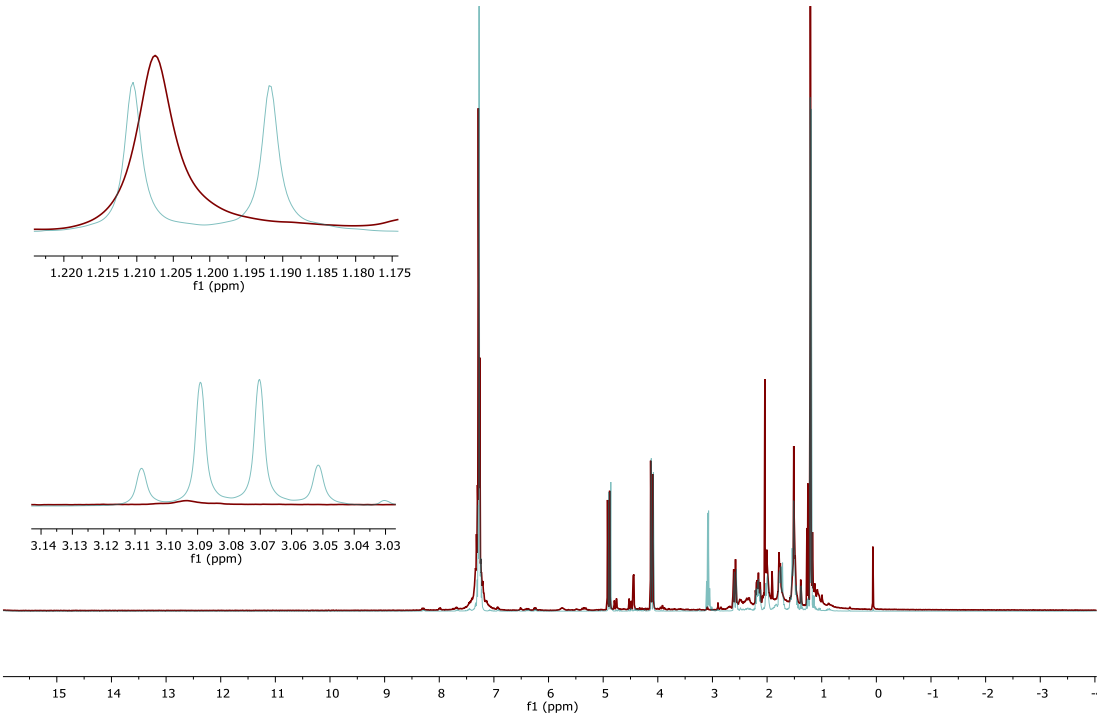


Figure 13. Superimposed ^{1}H NMR spectra of protic compound **334** (blue) and deuterated **393** (red).

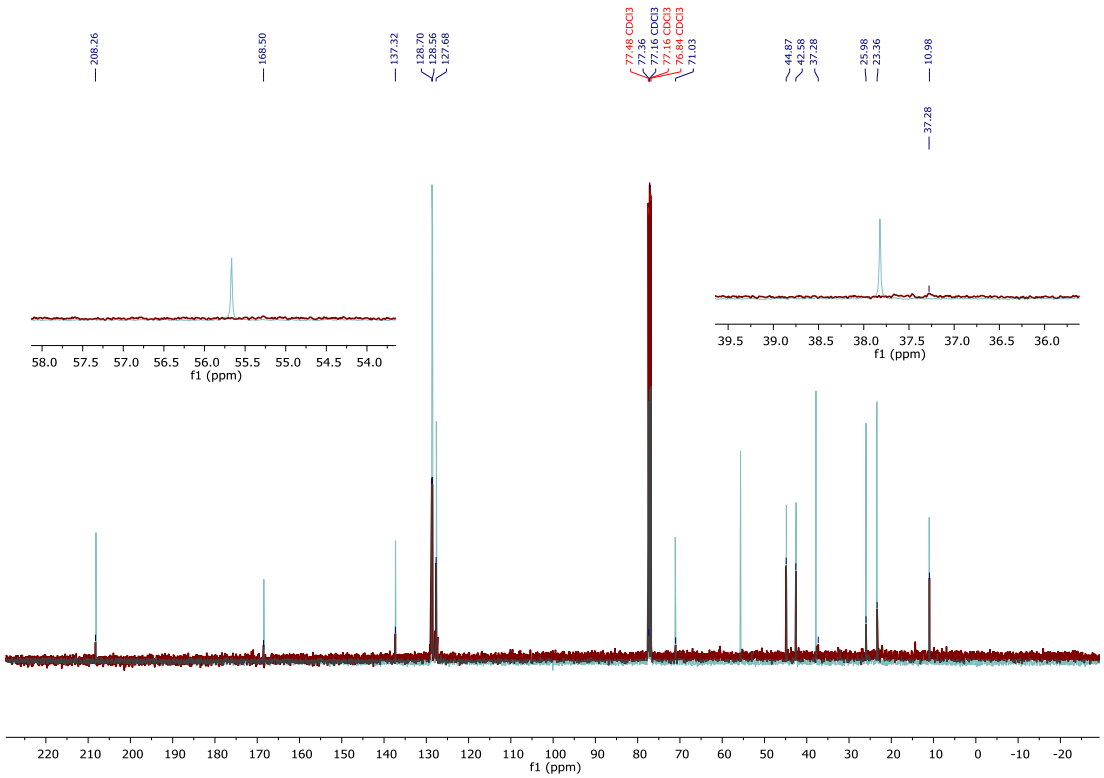


Figure 14. Superimposed ^{13}C NMR spectra of protic compound **334** (blue) and deuterated **393** (red).

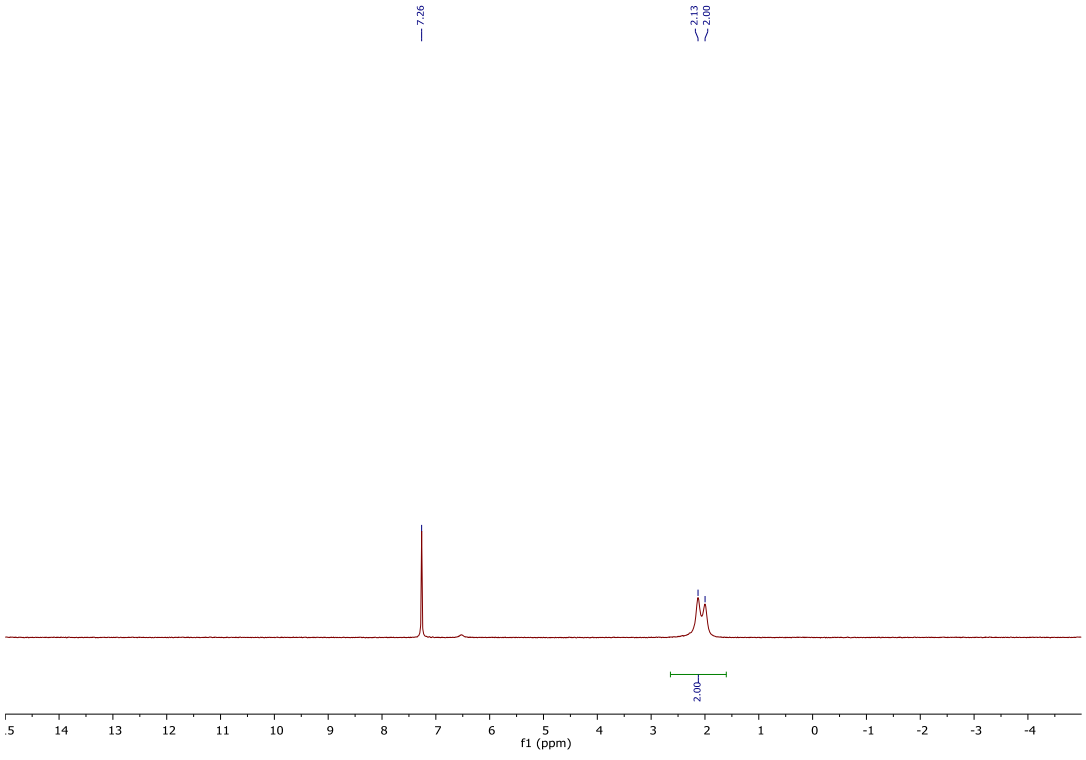


Figure 15. ^{2}H NMR spectra of deuterated starting material **297**.

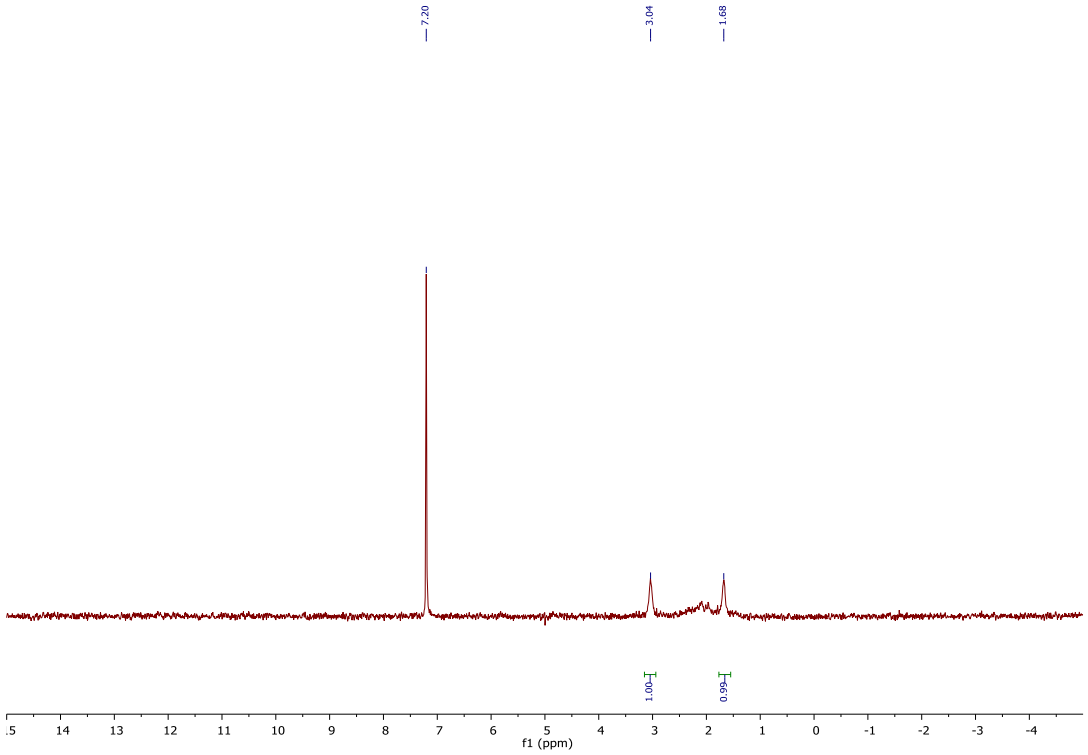
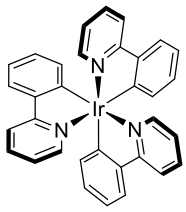


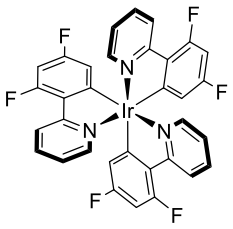
Figure 16. ^{2}H NMR spectra of deuterated product **393**.

8 Appendices

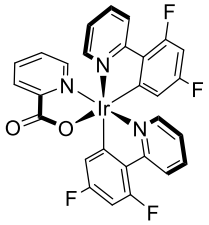
8.1 Appendix 1: Index of Photocatalysts used



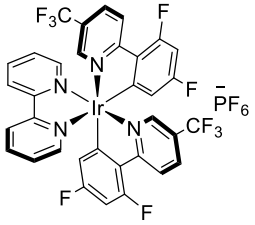
Ir(ppy)$_3$



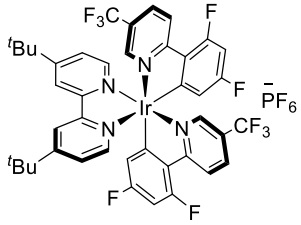
Ir(dFppy)$_3$



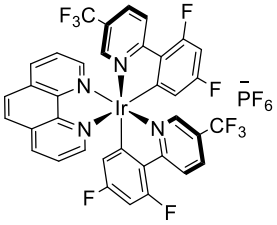
FIrPic



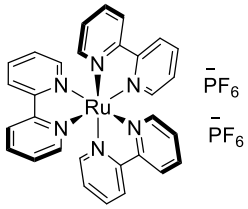
[Ir[*d*F(CF$_3$)ppy]$_2$(bpy)][PF$_6$]



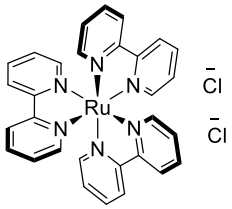
[Ir[*d*F(CF$_3$)ppy]$_2$(dtbbpy)][PF$_6$]



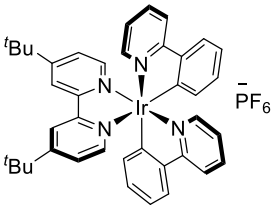
[Ir[*d*F(CF$_3$)ppy]$_2$(phen)][PF$_6$]



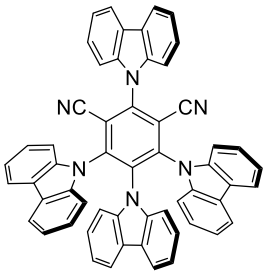
[Ru(bpy)$_3$][PF$_6$]$_2$



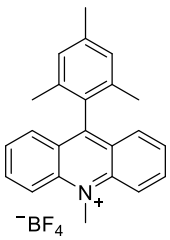
[Ru(bpy)$_3$][Cl]$_2$



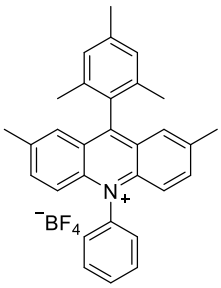
[Ir(ppy)$_2$(dtbbpy)][PF$_6$]



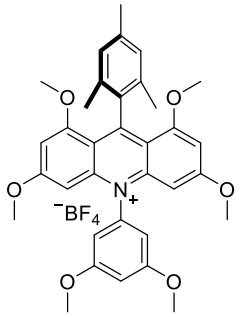
4CzIPN



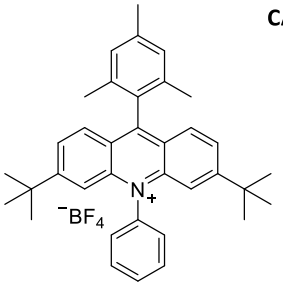
CAT-1



CAT-2

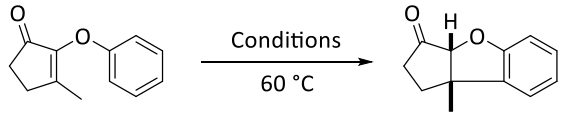


CAT-3



CAT-4

8.2 Appendix 2: Optimization of the photocyclization of 123

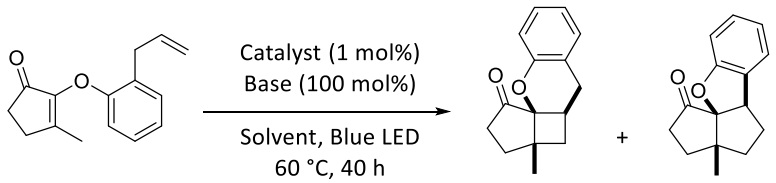


123 **125**

Entry	Catalyst	Cat. (mol%)	Base	Base (eq.)	Solvent	Time	Conv.[i]	Yield[i]
1	$[Ir(ppy)_3]$	1	KOAc	1	MeCN	66 h	0%	0%
2	$[Ir(ppy)_2(dtbbpy)][PF_6]$	1	KOAc	1	MeCN	24 h	0%	0%
3	$[Ir(dF(CF_3)ppy)_2(bpy)][PF_6]$	1	KOAc	1	MeCN	24 h	0%	0%
4	$[Ir(dF(CF_3)ppy)_2(dtbbpy)][PF_6]$	1	KOAc	1	MeCN	24 h	0%	0%
5	$[Ir(dFppy)_3]$	1	KOAc	1	MeCN	24 h	66%	66%[ii]
6	$[Ir(dFppy)_3]$	1	None	-	MeCN	24 h	82%	60%
7	$[Ir(dFppy)_3]$	1	NaOAc	1	MeCN	24 h	70%	58%
8	$[Ir(dFppy)_3]$	1	NH_4OAc	1	MeCN	24 h	25%	0%
9	$[Ir(dFppy)_3]$	1	Bu_4NOAc	1	MeCN	24 h	0%	0%
10	$[Ir(dFppy)_3]$	1	K_2CO_3	1	MeCN	24 h	0%	0%
11	$[Ir(dFppy)_3]$	1	$NaHCO_3$	1	MeCN	24 h	78%	76%
12	$[Ir(dFppy)_3]$	1	K_3PO_4	1	MeCN	24 h	0%	0%
13	$[Ir(dFppy)_3]$	1	NaOH	1	MeCN	24 h	0%	0%
14	$[Ir(dFppy)_3]$	1	Na_2CO_3	1	MeCN	24 h	74%	69%
15	$[Ir(dFppy)_3]$	1	$PhCO_2Na$	1	MeCN	24 h	72%	62%
16	$[Ir(dFppy)_3]$	1	Cl_3CO_2Na	1	MeCN	24 h	69%	66%
17	$[Ir(dFppy)_3]$	1	$PhSO_2Na$	1	MeCN	24 h	29%	29%
18	$[Ir(dFppy)_3]$	1	$NaHCO_3$	1	MeCN	72 h	68%	61%
19	$[Ir(dFppy)_3]$	1	$KHCO_3$	1	MeCN	72 h	45%	40%
20	$[Ir(dFppy)_3]$	1	Li_2CO_3	1	MeCN	72 h	23%	11%
21	$[Ir(dFppy)_3]$	1	Cs_2CO_3	1	MeCN	72 h	0%	0%
22	$[Ir(dFppy)_3]$	1	$NaHCO_3$	1	DMSO	24 h	25%	12%
23	$[Ir(dFppy)_3]$	1	$NaHCO_3$	1	NMP	24 h	55%	16%
24	$[Ir(dFppy)_3]$	1	$NaHCO_3$	1	EtOH	24 h	0%	0%
25	$[Ir(dFppy)_3]$	1	$NaHCO_3$	1	Acetone	24 h	91%	62%
27	$[Ir(dFppy)_3]$	1	KOAc	1	Acetone	24 h	87%	66%[ii]
28	$[Ir(dFppy)_3]$	1	$NaHCO_3$	1	EtOAc	24 h	76%	63%
29	$[Ir(dFppy)_3]$	1	NaOAc	1	EtOAc	24 h	95%	87%[ii]
30	$[Ir(dFppy)_3]$	1	KOAc	1	EtOAc	24 h	97%	89%
31	$[Ir(dFppy)_3]$	1	NaOAc	0.1	EtOAc	24 h	91%	70%
32	$[Ir(dFppy)_3]$	1	NaOAc	0.3	EtOAc	24 h	90%	71%
33	$[Ir(dFppy)_3]$	1	NaOAc	1	EtOAc	24 h	88%	74%
34	$[Ir(dFppy)_3]$	1	NaOAc	3	EtOAc	24 h	90%	75%
35	$[Ir(dFppy)_3]$	1	NaOAc	10	EtOAc	24 h	94%	84%
36	$[Ir(dFppy)_3]$	0.5	NaOAc	1	EtOAc	24 h	94%	79%
37	$[Ir(dFppy)_3]$	2	NaOAc	1	EtOAc	24 h	84%	75%
38	$[Ir(dFppy)_3]$[iii]	1	NaOAc	1	EtOAc	24 h	90%	90%
39	$[Ir(dFppy)_3]$[iv]	1	NaOAc	1	EtOAc	24 h	66%	57%
40	FIrPic	1	NaOAc	1	MeCN	24 h	30%	33%
41	FIrPic	1	NaOAc	1	EtOAc	24 h	40%	33%

Reaction conditions: **123** (0.05 mmol), [**123**] = 0.05 M, 12 W blue LED, 60 °C. [i]Determined by ^{1}H NMR spectroscopy against an internal standard of 1,3,5-trimethoxybenzene. [ii]Additional side product visible by ^{1}H NMR. [iii][**123**] = 0.01 M. [iv][**123**] = 0.25 M.

8.3 Appendix 3: Optimization of the photocyclization of 157

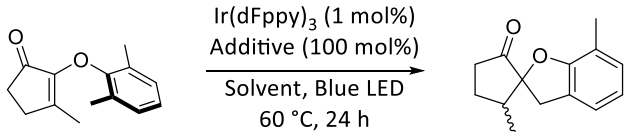


157 **223** **224**

Entry	Catalyst	Base	Solvent	Conv.[i]	Yield **223**[i]	Yield **224**[i]
1	$[Ir(dFppy)_3]$[iii]	NaOAc	EtOAc	0%	0%	0%
2	$[Ir(dFppy)_3]$[iv]	NaOAc	EtOAc	0%	0%	0%
3	$[Ir(dFppy)_3]$	NaOAc	EtOAc	65%	40%	20%
4	$Ir(ppy)_3$	NaOAc	EtOAc	0%	0%	0%
5	FIrPic	NaOAc	EtOAc	36%	26%	10%
6	$[Ir(dF(CF_3)ppy)_2(bpy)][PF_6]$	NaOAc	EtOAc	40%	26%	9%
7	$[Ir(dF(CF_3)ppy)_2(dtbbpy)][PF_6]$	NaOAc	EtOAc	35%	24%	10%
8	$[Ir(dF(CF_3)ppy)_2(phen)][PF_6]$	NaOAc	EtOAc	25%	15%	5%
9	$[Ir(dFppy)_3]$	KOAc	EtOAc	65%	52%	21%
10	$[Ir(dFppy)_3]$	$NaHCO_3$	EtOAc	65%	46%	17%
11	$[Ir(dFppy)_3]$	Na_2CO_3	EtOAc	75%	48%	19%
12	$[Ir(dFppy)_3]$	$PhCO_2Na$	EtOAc	0%	0%	0%
13	$[Ir(dFppy)_3]$	$^{i}Pr_2NEt$	EtOAc	75%	56%	22%
14	$[Ir(dFppy)_3]$	NaOAc	Acetone	80%	45%	25%
15	$[Ir(dFppy)_3]$	NaOAc	Toluene	50%	28%	8%
16	$[Ir(dFppy)_3]$	NaOAc	CH_2Cl_2	90%	51%	34%
17	$[Ir(dFppy)_3]$	NaOAc	THF	75%	41%	27%
18	$[Ir(dFppy)_3]$	NaOAc	IPA	0%	0%	0%

Reaction conditions: **157** (0.05 mmol), catalyst (1 mol%), base (100 mol%), [**157**] = 0.05 M, 12 W blue LED, 60 °C, 24 h. IPA = isopropanol. [i]Determined by ^1H NMR spectroscopy against an internal standard of 1,3,5-trimethoxybenzene. [ii]Reaction performed on 0.30 mmol scale. [iii]With 100 mol% TEMPO. [iv]With 100 mol% 1,1-diphenylethylene.

8.4 Appendix 4: Optimization of the photocyclization of 229

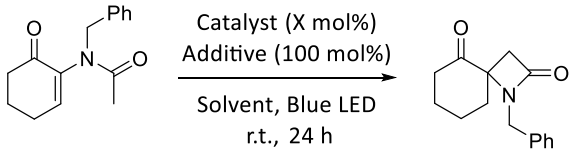


229 **231**

Entry	Additive	Solvent	Conv.[i]	Yield[i]
1	NaOAc	EtOAc	56%	30%
2	KOAc	EtOAc	51%	29%
3	$NaHCO_3$	EtOAc	46%	29%
4	Na_2CO_3	EtOAc	68%	30%
5	iPr_2NEt	EtOAc	100%	0%[ii]
6	2,6-lutidine	EtOAc	63%	29%
7	NaOAc	EtOAc	54%	50%
8	NaOAc	CH_2Cl_2	66%	27%
9	NaOAc	MeCN	20%	20%
10	NaOAc	THF	100%	20%
11	NaOAc	Acetone	50%	28%
12	None	EtOAc	57%	28%
13	NaOAc	EtOAc	53%	28%
14	Pyrrolidine	EtOAc	100%	0%[ii]
15	Morpholine	EtOAc	27%	26%
16	$tBuNH_2$	EtOAc	38%	27%
17	Piperidine	EtOAc	15%	15%

Reaction conditions: **229** (0.05 mmol), $Ir(dFppy)_3$ (1 mol%) [**229**] = 0.05 M, 60 °C, 24 h. [i]Determined by ^1H NMR spectroscopy against an internal standard of 1,3,5-trimethoxybenzene; combined yield of both diastereomers. [ii]Additional side product visible by ^1H NMR.

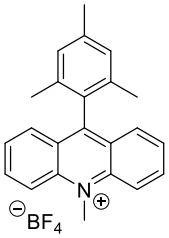
8.5 Appendix 5: Optimization of the photocyclization of 271



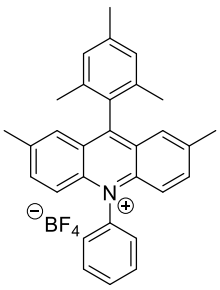
271 **333**

Entry	Catalyst	Cat. load (mol%)	Additive	Solvent	Conc. (M)	Conv.[i]	Yield[i]
1	$[Ir(dFppy)_3]$	1	NaOAc	EtOAc	0.05	40%	10%
2	$[Ir(dFppy)_3]$	1	None	EtOAc	0.05	90%	15%
3	$[Ir(dFppy)_3]$	1	KOAc	MeCN	0.05	63%	7%
4	$[Ir(dFppy)_3]$	1	NaOAc	MeCN	0.05	47%	4%
5	$[Ir(dFppy)_3]$	1	NaOAc	EtOAc	0.01	60%	27%
6	$[Ir(dFppy)_3]$	1	KOAc	EtOAc	0.01	70%	17%
7	$[Ir(dFppy)_3]$	1	NaOAc	EtOAc	0.01	70%	13%
8	$[Ir(dFppy)_3]$	1	None	EtOAc	0.01	83%	13%
9	$[Ir(dFppy)_3]$	1	$PhCO_2Na$	EtOAc	0.01	72%	12%
10	$[Ir(dFppy)_3]$	1	$NaHCO_3$	EtOAc	0.01	87%	20%
11	$[Ir(dFppy)_3]$	0.5	$PhCO_2Na$	EtOAc	0.01	77%	13%
12	$[Ir(dFppy)_3]$	1	$PhCO_2Na$	EtOAc	0.01	85%	15%
13	$[Ir(dFppy)_3]$	2	$PhCO_2Na$	EtOAc	0.01	69%	23%
14	$[Ir(dFppy)_3]$	5	$PhCO_2Na$	EtOAc	0.01	68%	18%
15	CAT-1	1	None	EtOAc	0.05	0%	0%
16	CAT-2	1	None	EtOAc	0.05	0%	0%
17	CAT-3	1	None	EtOAc	0.05	0%	0%
18	CAT-4	1	None	EtOAc	0.05	0%	0%

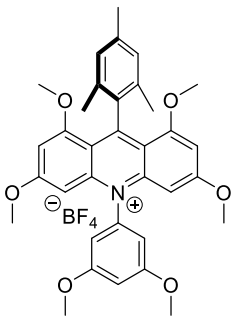
Reaction conditions: **271** (0.05 mmol), 40 W Kessil blue LED lamp, r.t., 24 h. [i]Determined by ^1H NMR spectroscopy against an internal standard of 1,3,5-trimethoxybenzene.



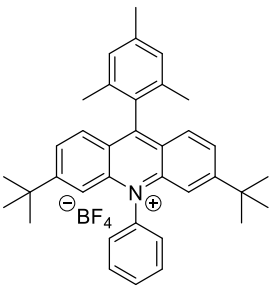
CAT-1



CAT-2

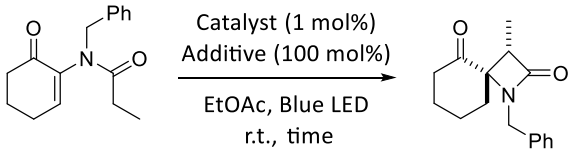


CAT-3



CAT-4

8.6 Appendix 6: Optimization of the photocyclization of 272



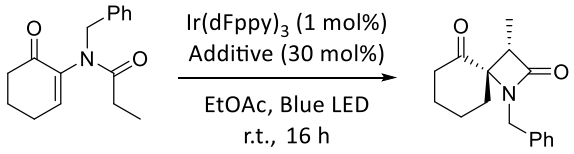
272 **334**

Entry	Catalyst	Base	Conc. (M)	Time	Conv.[i]	Yield[i]
1	$[Ir(dFppy)_3]$	NaOAc	0.05	24 h	100%	86%
2	$[Ir(dFppy)_3]$	None	0.05	24 h	100%	76%
3	$[Ir(dFppy)_3]$	NaOAc	0.01	24 h	100%	98%
4	$[Ir(dFppy)_3]$	None	0.01	24 h	100%	76%
5	FIrPic	NaOAc	0.05	24 h	100%	83%
6	$[Ir(dF(CF_3)ppy)_2(bpy)][PF_6]$	NaOAc	0.05	24 h	70%	60%
7	$[Ir(dFppy)_3]$	None	0.05	16 h	100%	76%
8	$[Ir(dFppy)_3]$	NaOAc	0.05	16 h	100%	76%
9	$[Ir(dFppy)_3]$	NaOAc	0.05	16 h	100%	84%
10	4CzIPN	None	0.05	16 h	100%	21%
11	4CzIPN	NaOAc	0.05	16 h	100%	18%

Reaction conditions: **272** (0.05 mmol), catalyst (1 mol%), EtOAc, 40 W Kessil blue LED lamp, r.t..

[i]Determined by ^{1}H NMR spectroscopy against an internal standard of 1,3,5-trimethoxybenzene.

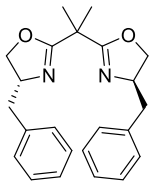
8.7 Appendix 7: Attempts towards enantioselective cyclization of 272



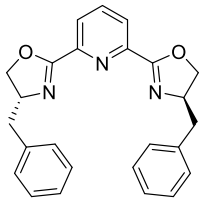
272 **378**

Entry	Additive	e.r.[i]
1	$Cu(OTf)_2$ & Benzyl BOX	51:49
2	$Cu(OTf)_2$ & Benzyl PYBOX	50:50
3	$Cu(OTf)_2$ & ^{t}Butyl PYBOX	46:54
4	Thiourea **A**	50.5:49.5
5	Urea **A**	50.5:49.5
6	Thiourea **B**	50.5:49.5

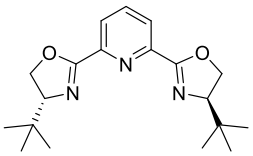
Reaction conditions: **272** (0.05 mmol), $Ir(dFppy)_3$ (1 mol%), Additive (30 mol%), EtOAc ([**272**] = 0.05 M), 40 W Kessil blue LED lamp, r.t., 16 h. [i]Determined by Chiral HPLC.



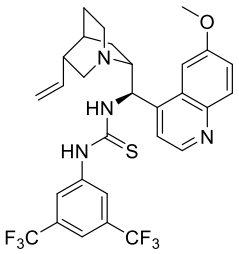
Benzyl BOX



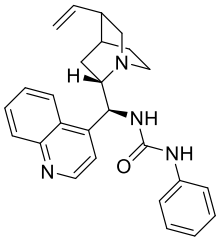
Benzyl PYBOX



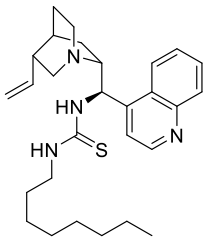
^{t}Butyl PYBOX



Thiourea A



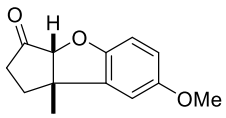
Urea A



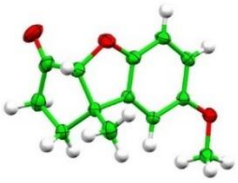
Thiourea B

8.8 Appendix 8: X-ray Crystallographic Data

8.8.1 X-ray crystallographic data and structure refinement for compound 177

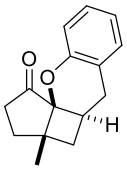


177



Identification code	046JDJ17	
Empirical formula	$C_{13}H_{14}O_3$	
Formula weight	218.25	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 9.9018 Å	α = 90°
	b = 8.2508 Å	β = 90°
	c = 26.5095 Å	γ = 90°
Volume	2165.77 $Å^3$	
Z,Z'	Z: 8 Z': 0	
Density (calculated)	1.339 Mg m^{-3}	
Absorption coefficient	0.772 mm^{-1}	
F(000)	928.0	
Crystal size	0.07 × 0.18 × 0.26 mm^3	
Theta range for data collection	5.577° to 76.220°	
Reflections collected	21711	
Independent reflections	2265	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.998	
Final R indices [I>2σ(I)]	R^1 = 0.0405, wR^2 = 0.1039	
R indices (all data)	R^1 = 0.0433, wR^2 = 0.1066	

8.8.2 X-ray crystallographic data and structure refinement for compound 223

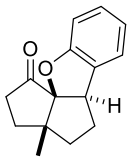


223

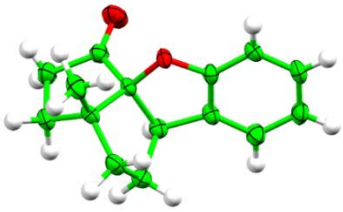


Identification code	051JDJ17	
Empirical formula	$C_{15}H_{16}O_2$	
Formula weight	228.29	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	P $2_1/c$	
Unit cell dimensions	a = 6.0453 Å	α = 90°
	b = 19.2327 Å	β = 104.108°
	c = 10.3762 Å	γ = 90°
Volume	1170.03 $Å^3$	
Z,Z'	Z: 4 Z': 0	
Density (calculated)	1.296 Mg m^{-3}	
Absorption coefficient	0.672 mm^{-1}	
F(000)	488.0	
Crystal size	0.28 × 0.34 × 0.52 mm ^{3}	
Theta range for data collection	8.100° to 76.159°	
Reflections collected	7732	
Independent reflections	2423	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	1.005	
Final R indices [I>2σ(I)]	R^1 = 0.0365, wR^2 = 0.0878	
R indices (all data)	R^1 = 0.0374, wR^2 = 0.0884	

8.8.3 X-ray crystallographic data and structure refinement for compound 224

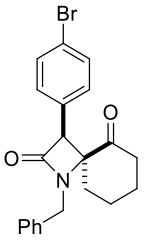


224

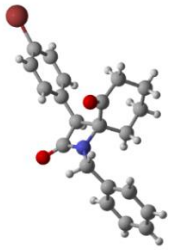


Identification code	054JDJ17	
Empirical formula	$C_{15}H_{16}O_2$	
Formula weight	228.29	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	P 2_1/n	
Unit cell dimensions	a = 6.8599 Å	α = 90°
	b = 18.9802 Å	β = 101.067°
	c = 9.2187 Å	γ = 90°
Volume	1177.97 $Å^3$	
Z,Z'	Z: 4 Z': 0	
Density (calculated)	1.287 Mg m^{-3}	
Absorption coefficient	0.668 mm^{-1}	
F(000)	488.0	
Crystal size	0.17 × 0.31 × 0.60 mm ^{3}	
Theta range for data collection	4.660° to 75.728°	
Reflections collected	6023	
Independent reflections	2423	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	1.001	
Final R indices [I>2σ(I)]	R^1 = 0.0549, wR^2 = 0.1438	
R indices (all data)	R^1 = 0.0584, wR^2 = 0.1469	

8.8.4 X-ray crystallographic data and structure refinement for compound 335



335



Identification code	7096	
Empirical formula	$C_{21}H_{20}BrNO_2$	
Formula weight	398.30	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 18.96700(10)Å	α = 90°
	b = 8.72610(10) Å	β = 90°
	c = 21.5097(2) Å	γ = 90°
Volume	3560.03(6) $Å^3$	
Z	8	
Density (calculated)	1.486 Mg m^{-3}	
Absorption coefficient	3.254 mm^{-1}	
F(000)	1632	
Crystal size	0.35 × 0.18 × 0.03 mm^3	
Theta range for data collection	4.111° to 76.198°	
Reflections collected	39793	
Independent reflections	3709	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	1.0091	
Final R indices [I>2σ(I)]	R^1 = 0.0252, wR^2 = 0.0674	
R indices (all data)	R^1 = 0.0273, wR^2 = 0.0698	

9 Bibliography

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