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Photochemical approaches to the synthesis of highly functionalised cyclobutanes

Photochemical Approaches to the Synthesis of Highly Functionalised Cyclobutanes

Mark Deeprose

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Abstract

A new method has been developed to obtain densely functionalised cyclobutanes, wherein *α*-halo maleimides undergo sensitised [2+2] photocycloaddition under UV (366 nm) conditions to give *α*-halocyclobutanes and cyclobutenes in a highly regioselective manner in up to **78%** yields over multiple steps. The dehalogenation of the *α*-chloride, by visible-light photocatalysis, gives a tertiary cyclobutyl radical, leading to radical addition to a range of suitable substrates to form a quaternary carbon-carbon bond in a diastereoselective manner in up to **94%** yields of the desired highly functionalised cyclobutane. The protocol shows broad functional group tolerance and the succinimide ring can be further functionalised regioselectively in a variety of ways. These results are discussed in **Chapter 1**.

A novel approach towards cyclobutyl spirocycles was developed. An alkyne tethered redox active ester was found to undergo a visible-light [2+2] photocycloaddition with a maleimide to give a cyclobutene containing a redox active tether using a novel thioxanthone sensitiser. Introducing a diboron source such as B_2cat_2, acts as a reductant and produces alkyl radical. The pertinent radical undergoes 5-*exo*-trig cyclisation forming a cyclobutyl spirocycle which can trap out boron to give the desired functionalised cyclobutane. The development of this methodology is discussed in **Chapter 2**.

A total synthesis of albiflorin has been undertaken. The current proposed route was based on the protocol developed described in **Chapter 1**, and therefore has scalability and is transition-metal free. The synthetic route and methodology developed is discussed in **Chapter 3**.

The results in this thesis have been communicated:

M. J. Deeprose, M. Lowe, A. Noble, K. I. Booker-Milburn, and V. K. Aggarwal, *Org. Lett.* **2022** 24, 137-141.

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To the KBM group of past and present; the friendships and memories I have made while being part of this group have truly defined my experience in Bristol. From boardgame and movie nights in to canoeing or bouldering days out, I've been extremely lucky to have had such a great group of people to go through it all with. In order of appearance, I'd like to thank Dan for the many laughs, Thursday Yak's and burritos, and "KBM" pub trips. Hannah thank you for being an excellent office and lab neighbour and for being good craic in day-to-day life. Thank you to Beth D for being the fellow boardgame enthusiast and (short-lived) flatmate, and thank you to Beth G for all the chats and being there to help with any question I had. To Dawn, Kate and Maria, labs in lockdown wouldn't have been nearly as bearable if you weren't there for random conversations, lunchtime crosswords or any of the weird shenanigans that happened in the KBM orphanage over the last year and a half. I would also like to thank Jon for helping me troubleshoot my problems in my first year in the lab, and Luke for a phrase that I've taken to life in general "just do stuff that works".

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A special thank you to Laura, my family and parents for their unwavering and continued support, encouragement and interest throughout my life and PhD.

Authors Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

Mark Deeprose

6th March 2022

Abbreviations

2,2'-diBrTX	2,7-Dibromo-9H-thioxanthen-9-one
3DPAFIPN	2,4,6-Tris(diphenylamino)-5-fluoroisophthalonitrile
4CzIPN	1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
AHCA	Alpha-hydroxy carboxylic acid
BCB	Bicyclobutane
BDE	Bond dissociation energy
Bpy	Bipyridiyl
Bz	Benzoyl
CFL	Compact fluorescent lamp
d.r.	Diastereomeric ratio
DCM	Dichloromethane
DDC	*N,N*'-Dicyclohexylcarbodiimide
DIPEA	*N,N*-Diisopropylethylamine
DMSO	Dimethyl sulfoxide
EDA	Electron donor-acceptor
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
Eq.	Equivalent
ESI	Electrospray ionisation
E_T	Triplet energy
FDA	U.S. Food and Drug Administration
g	Gram
h	Hour
HAT	Hydrogen atom transfer

HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared
ISC	Intersystem crossing
LA	Lewis-acid
LUMO	Lowest unoccupied molecular orbital
NMR	Nuclear magnetic resonance
NOE	Nuclear Oppenhauser effect
Pyr*N*O	Pyridine *N*-oxide
r.r.	Regioisomeric ratio
SCE	Saturated calomel electrode
SCS	Sin-centre shift
SER	Single electron reduction
SET	Single electron transfer
TBAC	*Tetra*-butyl ammonium chloride
TLC	Thin layer chromatography
UV	Ultraviolet
wt	Weight
XAT	Halogen atom transfer
τ	Half-life

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Introduction

1.1. Cyclobutane-containing natural products

Cyclobutanes are important structures found in the core of a range of natural products (Figure **1**).[1–4] The structure of cyclobutanes lends itself to adopting a 3-dimensional puckered, or *"butterfly"* conformation to relieve strain on the bond angles (Figure **2**). The bond angles are 88° compared with a tetrahedral geometry of 109.5°, giving the ring system a high strain energy (110 kJ/mol). This puts cyclobutanes in a state of relative conformational stability but with high ring strain. The availability of chemical space through functionalisation of cyclobutanes, due to their unique 3-dimensional shape, enables access to diverse chemical libraries for targeted drug discovery.

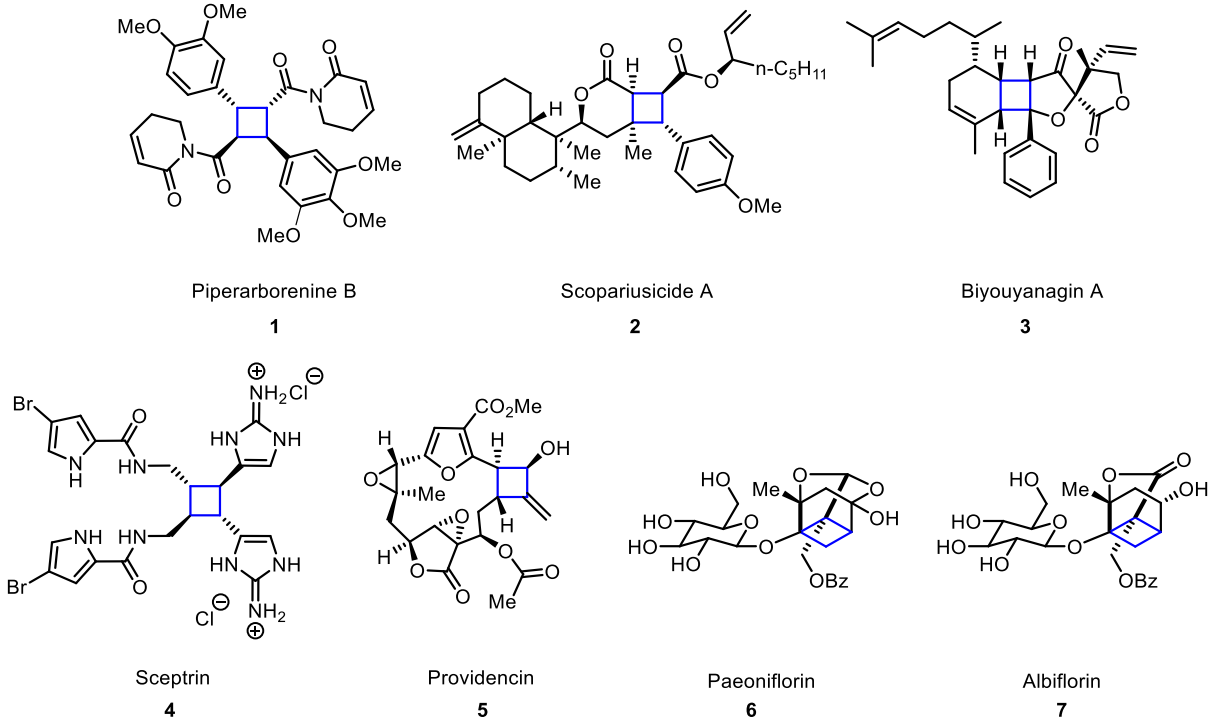


Figure 1 *- Cyclobutane-containing natural products.*

Functionalisation of these highly strained ring systems remains a challenge in chemistry and has therefore been a topic of interest, especially the regio-, stereo- and enantio-specific control over their synthesis.[5–7] The structural novelty, complexity and potential for bioactivity, based around a simple building block, makes cyclobutanes an attractive target for medicinally relevant compounds.

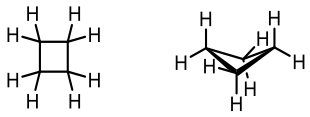
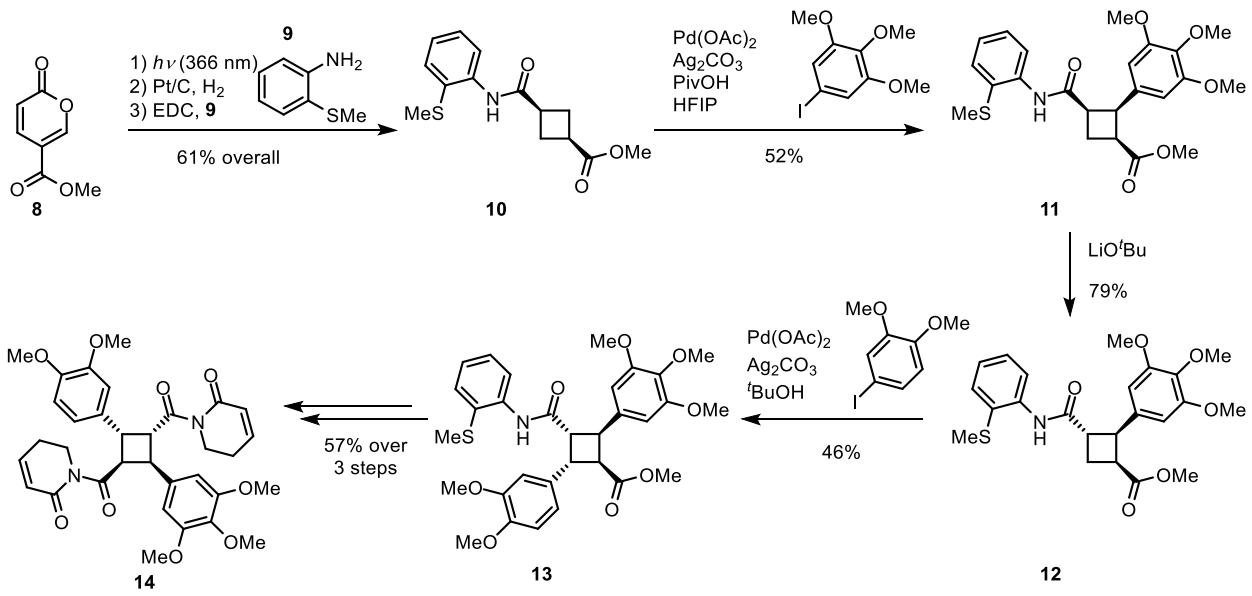


Figure 2 *– 2-Dimensional and 3-dimensional representations of cyclobutanes.*

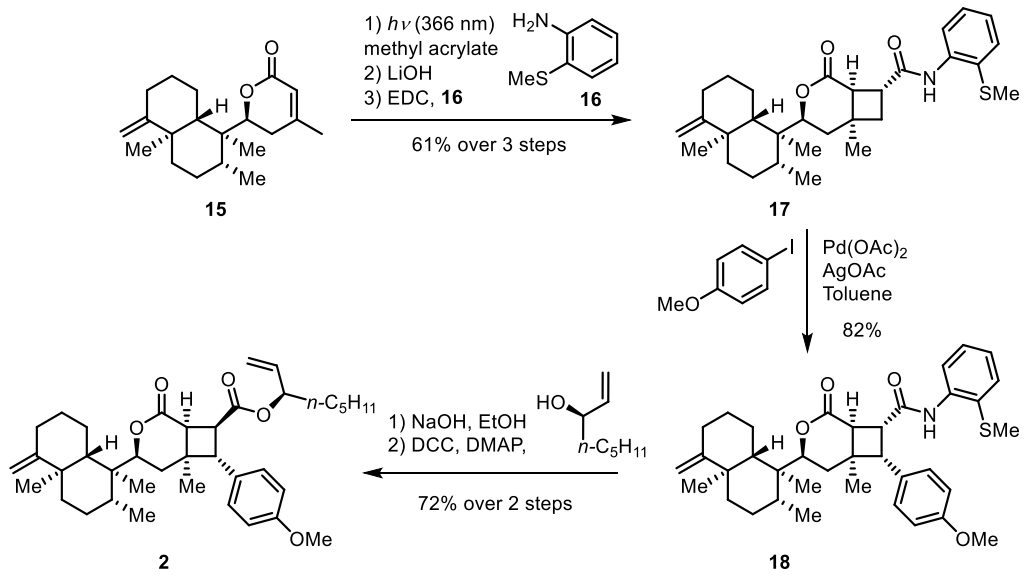
Many natural product syntheses of cyclobutane-containing compounds have been achieved over the past few decades. The most popular approach in recent times has been transition-metal catalysed C–H functionalisation.[8] This modular approach commonly exploits palladium catalysts to achieve the activation of typically inert C–H bonds for further functionalisation. For example, Baran *et al.* utilised this approach in the total synthesis of piperarborenine B (Scheme **1**).[9] The diastereoselective synthesis was achieved by the initial electrocyclisation of lactone **8**, reduction and coupling with 2-aminothioanisole **9** to give the *cis*-cyclobutane **10**. The amide directing group allowed for C–H functionalisation of the cyclobutane to give the *cis*-arylated cyclobutane **11**. Epimerisation of **11** and subsequent C–H functionalisation gave the *cis*-arylated product **13**. Further steps lead to the synthesis of piperarborenine B **14** on a 100 mg scale.



Scheme 1 *- Selected key steps in the total synthesis of piperarborenine B by* Baran *et al.* [9]

Pu *et al.* utilised a similar methodology in the total synthesis of scopariusicide A **2** (Scheme **2**).[1] Initial [2+2] cycloaddition lactone with **15** and subsequent amide coupling gave cyclobutane **17**. Palladium

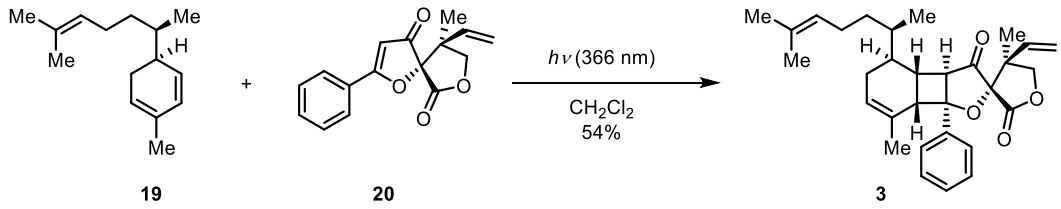
C–H activation gave the *cis*-arylated product **18** which underwent further steps to the synthesis of scopariusicide A **2**.



Scheme 2 *- Selected key steps in the total synthesis of scopariusicide A by* Pu *et al.*[1]

This modular approach using palladium functionalisations of cyclobutanes is limited to arylations. An increasing demand exists for sp^3 rich carbon centres in drug scaffolds and the movement away from "flatland" calls for alternative approaches to functionalise cyclobutanes.[10]

The majority of cyclobutane functionalisation in natural product synthesis relies upon C–H activation and carbonyl chemistry. Other utilised methods use [2+2] photocycloaddition in the final steps of a synthesis, for example, in the total synthesis of biyouyanagin A by Burton *et al.* (Scheme **3**).[11] The methodology required the synthesis of a highly functionalised alkene **19** and Michael acceptor **20** with a UV active chromophore, followed by photocycloaddition to give the natural product **3**.



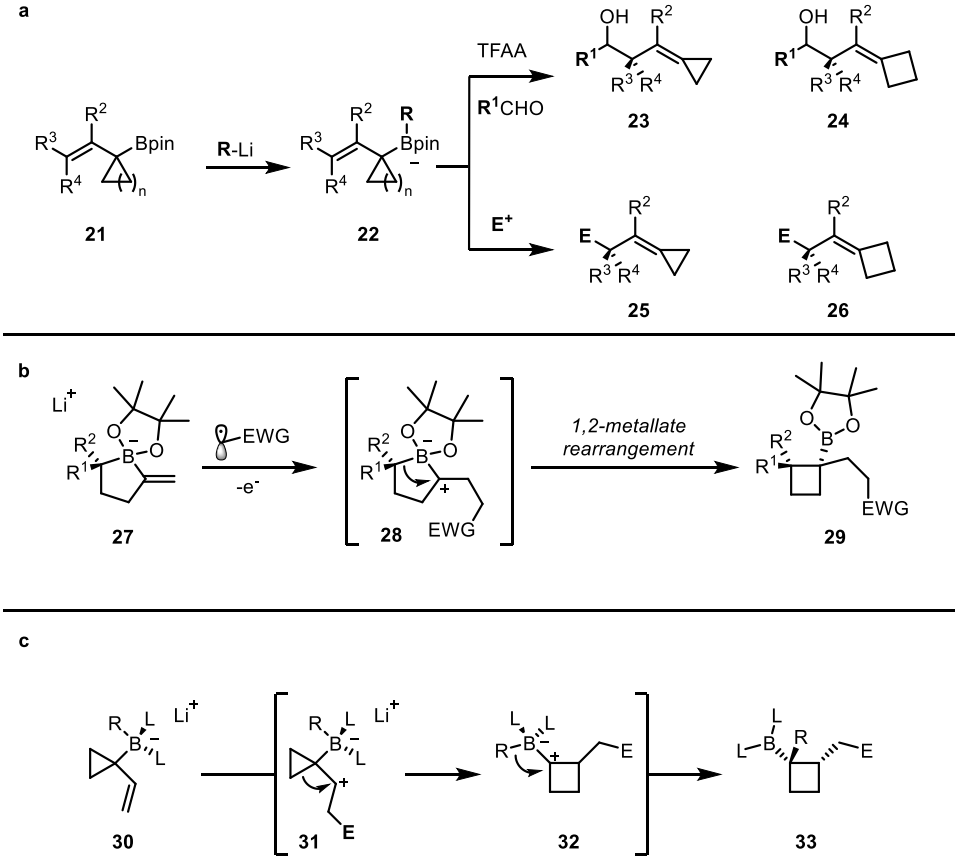
Scheme 3 *- Selected step in the total synthesis of biyoutanagin A by* Burton *et al.*[11]

Currently, only four FDA approved drugs contain a cyclobutane ring.[12] Only one of these has been brought to market in the past 20 years. The scarcity of cyclobutane-containing drugs reveals an area of medicinal chemistry that has yet to be exploited. To achieve a development in this area, a large, diverse library of highly functionalised cyclobutanes is required. The methodology to achieve this has been relatively underexplored, with recent advances in boron chemistry and [2+2]

photocycloadditions showing new general methodologies towards functionalised cyclobutanes.[13,14] Alternatively, modern photoredox catalysis may provide an alternative route for the scalable, modular access of highly functionalised cyclobutanes.[15,16]

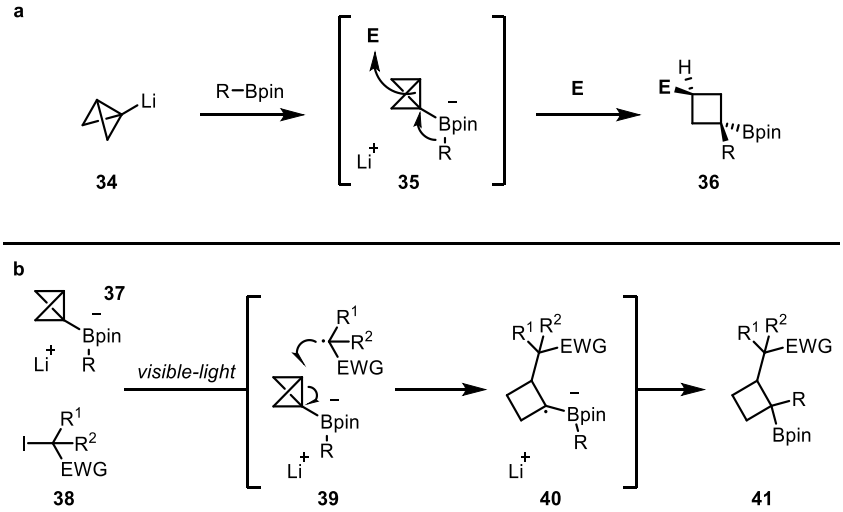
1.2. Recent advances towards the synthesis of cyclobutanes

Several strategies towards functionalised cyclobutanes have been developed. The Aggarwal group have produced several examples of synthesising highly functionalised cyclobutanes *via* boronic esters. For example, a protocol was developed where lithiation of allyl cyclopropyl boronic ester **21** lead to a 1,2-metallate shift of metallate **22** forming cyclobutyl ring **24** (Scheme **4a**).[17] The anion formed is then trapped by a suitable electrophile. Cyclobutanes can also be accessed by a ring contraction protocol, whereby lithiation of a boronic ester with an alkenyliodide quantitively forms compound **27** (Scheme **4b**).[18] Radical addition from a suitable alkyl iodide gives complex **28**, followed by 1,2-metallate shift/ring contraction to give cyclobutyl boronic ester **29** in good to excellent yields. Conversely, a ring expansion protocol was developed, whereby an intermolecular lithiation to give metallate **30** and subsequent radical addition/ring expansion gives cyclobutane **33** in excellent yields and diastereoselectivity (Scheme **4c**).[19]



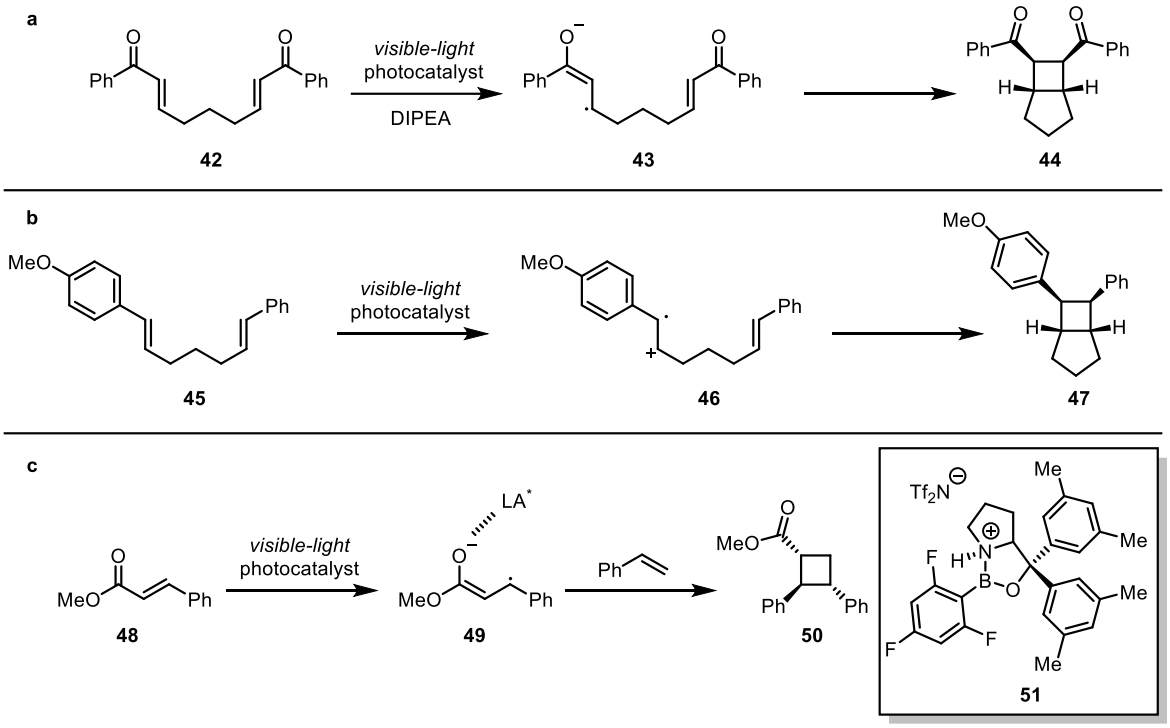
Scheme 4 *– **a)** Strain-increase allylboration [17], **b)** Visible-light driven ring contraction [18], **c)** Ring expansion induced 1,2-metallate rearrangement.*[19]

Another strategy towards functionalised cyclobutyl boronic esters is through the addition of alkyl synthons to bicyclobutanes (BCBs). In one example, BCB lithium **34** undergoes borylation followed by a 1,2-metallate shift and ring opening to give the 1,3-disubstituted cyclobutane **36** after trapping with a suitable electrophile (Scheme **5a**).[20] The cyclobutane ring still contains a functional boronic ester handle for further derivatisation, making this approach highly versatile for functionalising cyclobutanes.



Scheme 5 *– **a)** Electrophilic addition to BCB boronate complexes[20], **b)** Visible-light initiated radical addition to BCB boronate complexes.[13]*

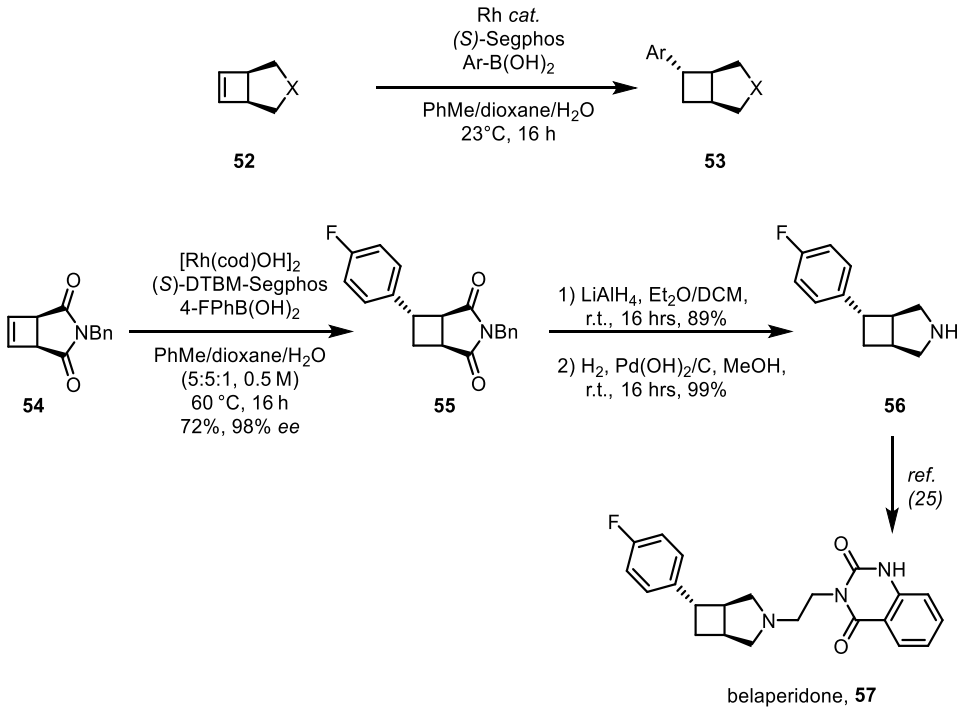
BCB boronic esters can also be activated by radical addition from suitable radicals (Scheme **5b**).[13] BCB **37** undergoes radical addition/ring opening to form the cyclobutyl radical *alpha* to the boronic ester. 1,2-Metallation gives the 1,2-disubstituted cyclobutane **41**, leaving the boronic ester as a handle for further functionalisation. These complementary protocols form a diverse and orthogonal strategies using borylation techniques to give access to a vast library of cyclobutyl motifs.



Scheme 6 *– **a)** Reductive SET and subsequent cyclisation to give diastereoselective fused cyclobutanes*[21]*, **b)** Oxidative SET and subsequent cyclisation to give diastereoselective fused cyclobutanes*[22]*, **c)** Lewis-acid mediated visible-light intermolecular [2+2] cycloaddition.*[23]

In 2008, Yoon *et al.* published a visible-light approach to forming diastereoselective cyclobutanes using ruthenium photocatalysis (Scheme **6a**).[21] Bis(enone) **42** undergoes single electron transfer (SET) to form a radical anion **43** which then cyclises intramolecularly to form cyclobutane **44** in high diastereoselectivity. Other examples followed, where SET to form a radical cation on styrene derivatives **45**, lead to cyclisation in a similar fashion as above to give cyclobutane **47** in high diastereoselectivity (Scheme **6b**).[22] The work was improved upon to include intermolecular examples. This was achieved by involving Lewis-acid catalyst **51** to decrease the triplet energy barrier for sensitisation of methyl cinnamate **48** and 5 equivalents of styrene to achieve sensitised intermolecular [2+2] cycloaddition (Scheme **6c**).[23] Inclusion of a chiral Lewis-acid catalyst oxazaborolidine **51** gave high enantioselectivity to the products with up to 99% *ee* and 9:1 diastereomeric ratio (*d.r.*) The methodology produced from this collective work demonstrates facile access to a broad scope of enantio- and diastereoselective cyclobutanes through [2+2] photocycloadditions.

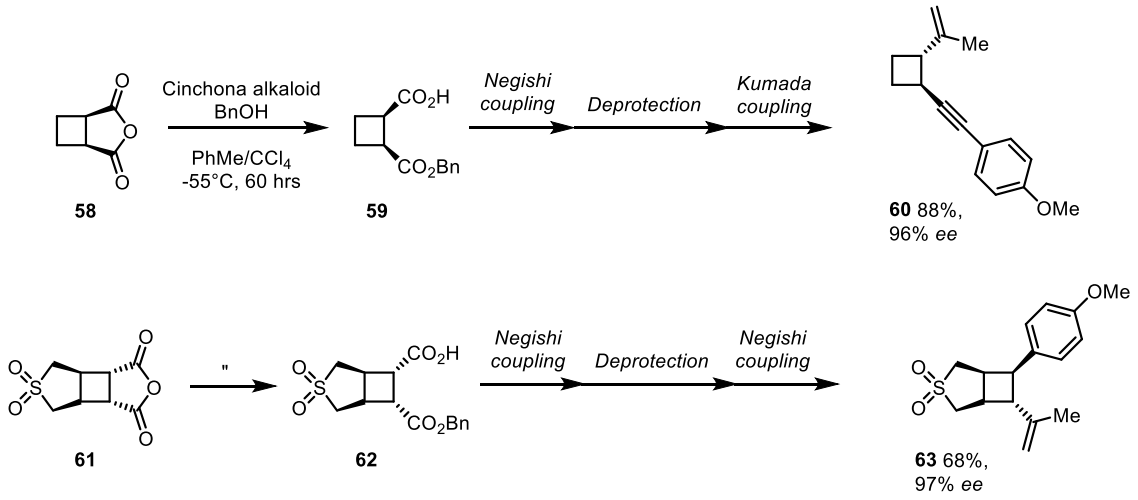
Post-cycloaddition functionalisation also plays an important role in generating highly functionalised cyclobutanes. Previously C–H activation of cyclobutanes has been the most common transition metal approach to cyclobutane functionalisation. However, in recent times, more versatile strategies which do not require a directing group have been established.[24–26] For example, Fletcher *et al.* developed a rhodium catalysed hydroarylation of substituted cyclobutenes (Scheme **7**).[26]



Scheme 7 *– Transition metal catalysed functionalisation of cyclobutene derivatives.*[26,27]

The work takes symmetrically substituted cyclobutene **52** and a chiral ligand and produces functionalised cyclobutane **53** with up to 99% *ee* at room temperature. The conditions can also be applied to cyclobutyl succinimide fused rings with excellent yields and high enantioselectivities. The scope is limited to arylboronic acids, however, a broad range of cyclobutenes can be used with good to excellent results in yields and enantioselectivity. This was demonstrated by the application of the protocol in the total synthesis of belaperidone **57**.[26]

Work by Baran *et al.* unlocks sp^3-rich complex molecular scaffolds by combining a cycloaddition step by asymmetrical ring opening of a succinic anhydride **58** to give a benzyl ester and free carboxylic acid **59** (Scheme **8**).[28] Through transition metal catalysis, arylations, and other C–C bond formations can be done in an enantioselective manner giving excellent *ee*. The methodology can be applied to [4+2], [3+2] and [2+2] cycloadditions and generate a large library of complex cyclobutanes through modular additions. To demonstrate its versatility, the protocol was applied to the synthesis of various natural products and other bioactive compounds giving good overall yields and enantioselectivity, in some cases reducing the number of steps previously required.



Scheme 8 *– Transition metal catalysed modular functionalisation of cyclobutyl carboxylic acids.*[28]

The recent surge in the development of functionalised cyclobutanes demonstrates the high value of the cyclobutyl motif in application to drug discovery.

1.3. Ultra-violet photochemistry

Photochemistry has been exploited for the past century due to its ability to access high energy states that are unavailable through thermal processes.[29] The Jablonski-Perrin diagram (Figure **3**) illustrates the fundamental mechanism by which photoexcitation occurs. Upon absorption of a photon, an electron is excited into the singlet state. In this state, the excited electron can either lose energy through vibrational processes (non-radiative) undergo internal conversion followed by dropping back to the ground state by fluorescence (radiative process) or by intersystem crossing (ISC; non-radiative process) to the triplet state. ISC gives a lower energy electronic state due to repulsion of the unpaired electrons. The electron in this state can either go back to the ground state configuration by phosphorescence (spin-forbidden radiative process) or by chemical reaction. Since the return to the ground state by phosphorescence is spin-forbidden by Laporte's rule, the lifetime of triplet states is a lot longer than singlet states (milliseconds *vs* nanoseconds). It is this property that is exploited in photochemistry.

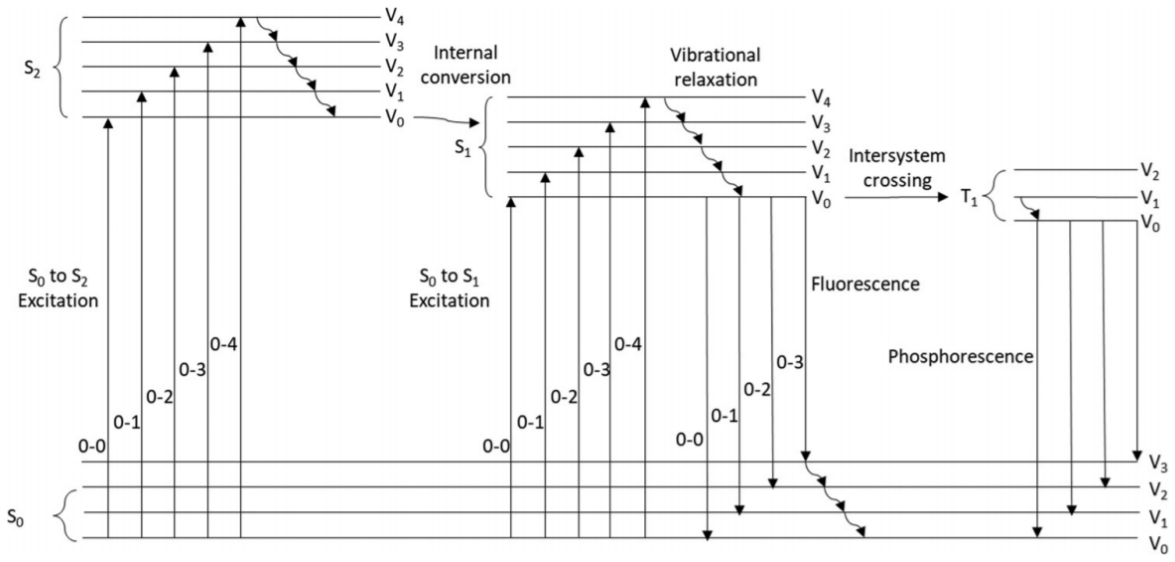
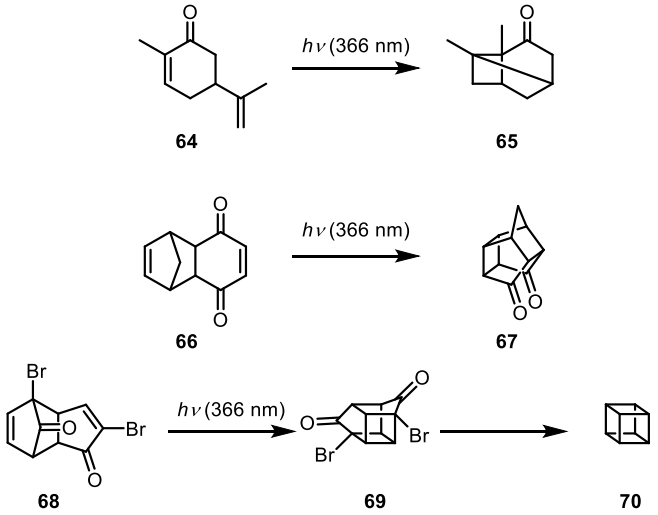


Figure 3 *– Jablonski-Perrin diagram. Energy is depicted in the vertical axis, straight arrows represent radiative processes, curved arrows depict non-radiative processes.*[30]

In the late 19th century, Giacomo Ciamician observed the photochemical conversion of quinone to quinol.[31] This discovery led to a lifelong fascination with photochemistry and its ability to transform simple molecules to highly complex molecular scaffolds. As Ciamician was an early pioneer of photochemistry, his dream was to harness the ability of plants to take simple molecules, such as carbonic acid from CO_2 and water, and convert them into complex molecules using solar radiation. To this day, organic synthesis often requires harsh acids or bases, transition metals, high heat, or

anhydrous solvents under inert atmospheres to replicate what plants can synthesise at room temperature, in aqueous conditions using sunlight.

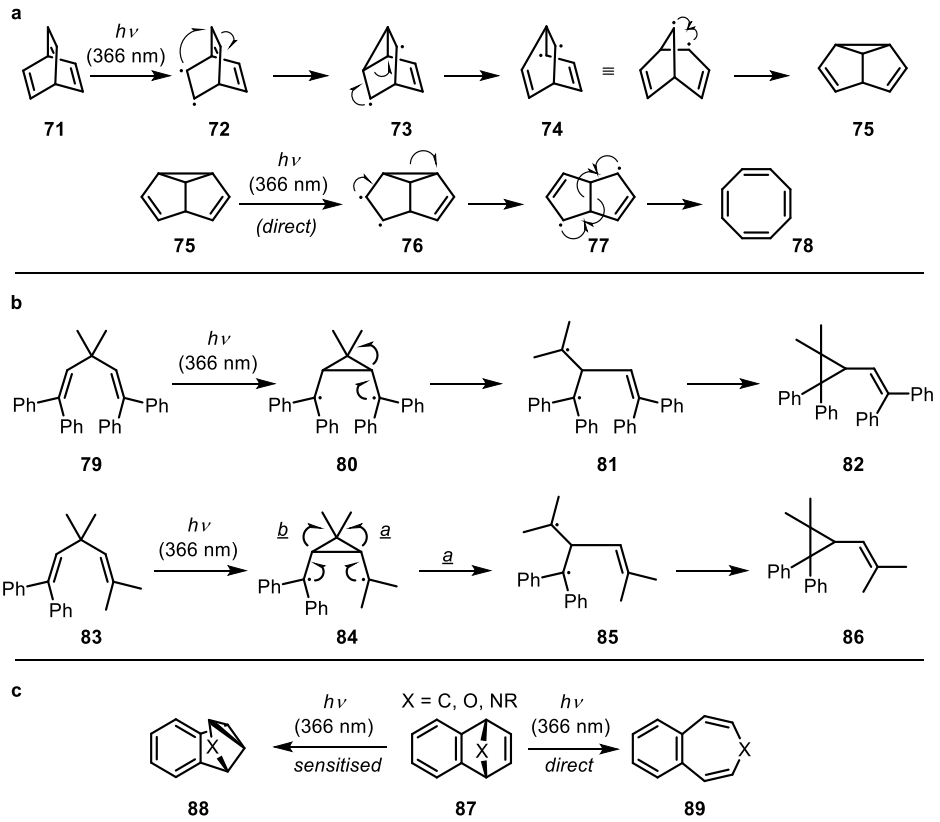
Work by Ciamician uncovered a range of photochemical reactions and transformations that could be achieved by irradiation with sunlight (Scheme **9**). For example, in 1908 the conversion of carvone **64** to camphor **65** was observed as the first [2+2] photocycloaddition reaction.[32] The findings were later confirmed by Buchi *et al*. and the process was expanded upon to give other [2+2] adducts, such as Cookson's diketone **67** formed by the irradiation of Diels–Alder adduct **66** of cyclopentadiene and benzoquinone and the synthesis of cubane **70**.[33–35]



Scheme 9 - Lead discoveries in organic photochemical reactions.[32–35]

Since the discovery of photochemical reactions, the subject of photochemistry in chemical synthesis has exploded to give a wide variety of general synthetic methodologies and application in the total synthesis of many natural products. More recently still, the emergence of visible-light photochemistry lowers the cost and equipment barriers for synthetic chemists. Now more than ever, photochemistry is accessible to all chemical synthesis laboratories.

Ultra-violet photochemistry for organic synthesis has been accepted as an extremely valuable tool as it offers a route into complex molecular scaffolds from simple building blocks. The di-π-methane rearrangement is an excellent example of this and produces a vinylic cyclopropane from an alkyl diene in one photochemical step. Work by Zimmerman *et al.* elucidated the mechanism behind the transformation observed when barrelene **71** is irradiated with UV light.[36,37] The product produced was semi-bullvalene **75** (Scheme **10a**).



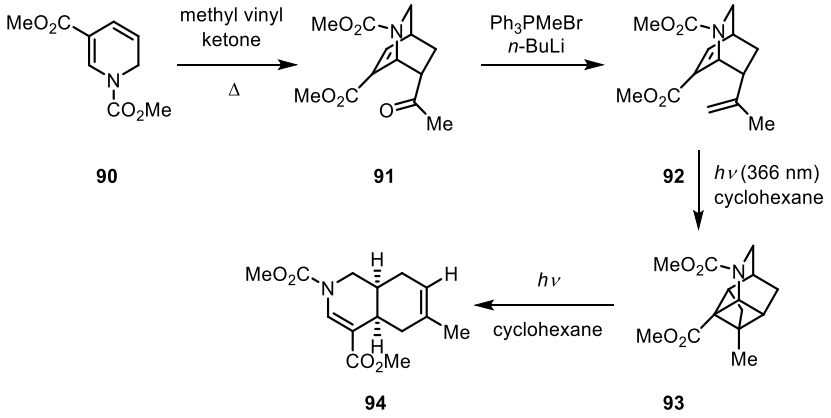
Scheme 10 *– Initial discovery and development of the di-π-methane rearrangement.* ***a)*** *Photochemical rearrangement of barrelene.* ***b)*** *Mechanistic study for the regioselectivity of the rearrangement.* ***c)*** *Example of sensitised vs direct irradiation for the di-π-methane rearrangement.*

Further work by Zimmerman showed that the mechanism was general and other substrates could undergo the rearrangement. It was found that when the reaction was performed in the presence of a sensitiser such as acetone, then the expected product would be observed. However, when performed in the absence of a sensitiser, cyclooctatetraene **78** was observed. This was through the direct excitation of the semi-bullvalene product **75**, to then undergo ring opening to compound **77** and finally ring expansion to cyclooctatetraene **78**.

The protocol was found to have a general mechanism starting from a di-*π*-methane structure (Scheme **10b**). Starting from the Mariano diene **79** the same type of rearrangement was observed giving vinyl cyclopropane **82**. The mechanism was probed further, and it was found from the Pratt diene **83** that the most stable radical pathway is preferred, with the rearrangement preserving benzylic radical **85** giving pathway *a* as the major pathway giving vinyl cyclopropane **86** (Scheme **10b**).[38]

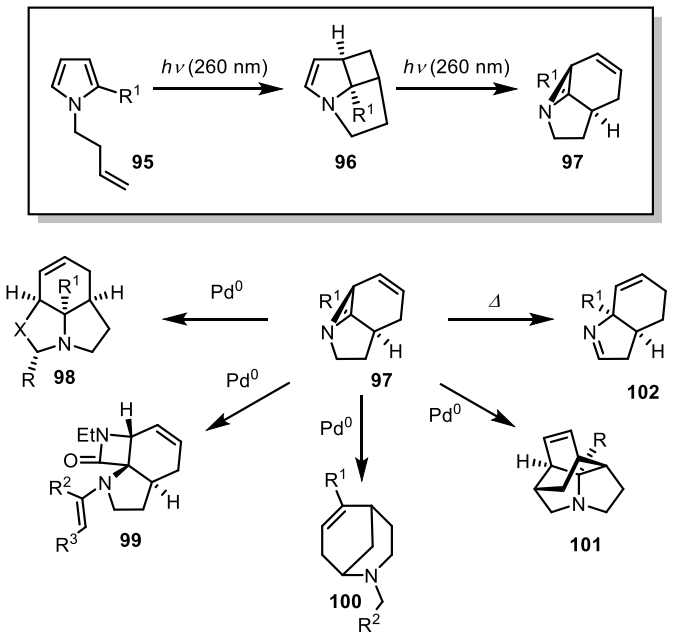
Furthermore, other fused ring systems such as benzonorbornadiene **87** were found to undergo the same process giving highly strained fused cyclopropyl rings **88** (Scheme **10c**).[39] This work was expanded upon by Swenton *et al.* to employ amines and ethers into the strained system.[40]

More recently, UV photochemistry is utilised to give ring expansion products. For example, White *et al.* synthesised functionalised isoquinolines *via* photoadduct **93** (Scheme **11**).[41] The azatetracyclodecane could be synthesised from two simple steps starting from the parent 1,2-dihydropyridine derivative. A Diels–Alder reaction to give the tricyclic product **92** followed by a [2+2] photocycloaddition produces fused cyclobutane **93.** Ring expansion of the cyclobutane gave the desired isoqunioline **94**.



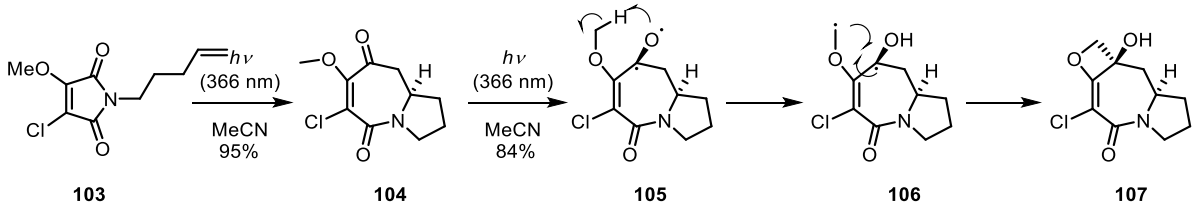
Scheme 11 *- Use of intramolecular photocycloadditions in the synthesis of functionalised isoquinolines by White et al.*[41]

Work by the Booker-Milburn group has demonstrated a useful photochemical rearrangement to give a tricyclic aziridine **97**.[42] The aziridine formed can undergo many useful synthetic transformations, all starting from simple pyrrole building blocks (Scheme **12**).[43–47] From the diversity of molecular scaffolds (**98** – **102**) that can be achieved by sequential photocyclisation/palladation to achieve polycyclic nitrogen containing heterocycles, the power of photochemistry to create complex molecular scaffolds from simple building blocks is displayed.



Scheme 12 *– Photochemical synthesis of fused aziridines and their subsequent transformations.*[42–47]

Another example of sequential photochemistry involved an intramolecular [5+2] cycloaddition of a maleimide derived chromophore **103** to give azepine-fused oxetanol **107** (Scheme **13**).[48] This was achieved by an initial [5+2] photocycloaddition of **103** followed by irradiation of the produced ketone **104** to give the hydroxyl radical **105**. 1,5-Hydrogen atom transfer and radical recombination gives the oxetanol product **107**. The scope produced from this reaction shows the reliability of this chromophore and the range of radical chemistry that can be utilised.



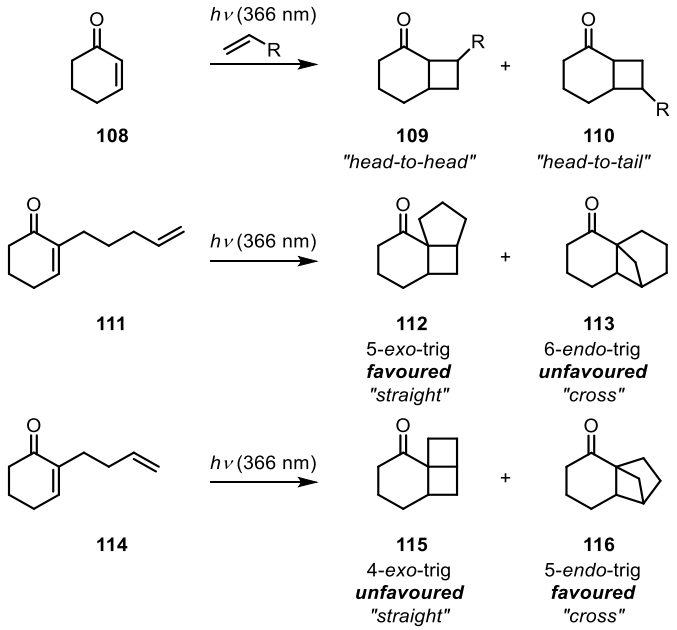
Scheme 13 *- Synthesis of azepine-fused oxetanols by Booker-Milburn et al.*[48]

1.3.1. General [2+2] photocycloaddition chemistry

[2+2] Photocycloadditions are a well-known, scalable approach to form cyclobutanes. It is the most popular method to synthesise cyclobutanes due to the formation of two carbon–carbon bonds and four stereogenic centres in a single step with high atom economy.[29] The process has been well explored with a large variety of substrates, forming complex molecules from simple starting materials.

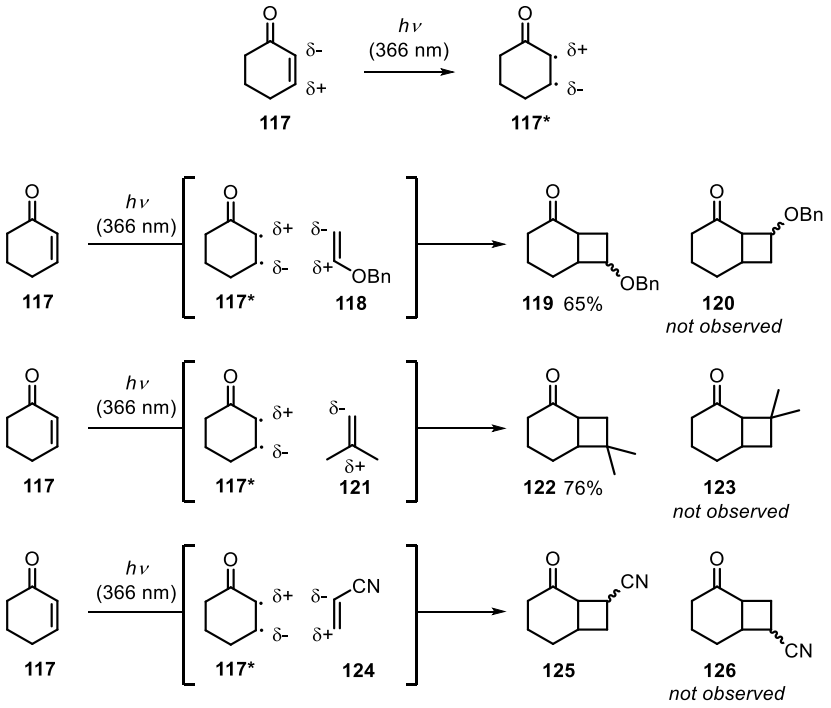
It is difficult to control the regio- and enantioselectivity of [2+2] photocycloadditions. Similar to ground state cycloadditions, such as a Diels–Alder reaction, photocycloadditions can give a large range of isomers from a bimolecular reaction. Intermolecular photocycloadditions can lead to head-to-tail or head-to-head cycloadducts such as **109** and **110** (Scheme **14**). The arrangement of these cycloadducts

can be dependent on either electronic or steric effects of the alkene substituent. Part of this problem can be controlled by intramolecular photocycloadditions. The alkene tether encourages regioselectivity and generally gives one diastereomer. But regioselectivity can also occur from "straight" and "crossed" cycloadducts such as from enones **111** and **114**, being favoured by Baldwin's rules of cyclisation.[49–51]



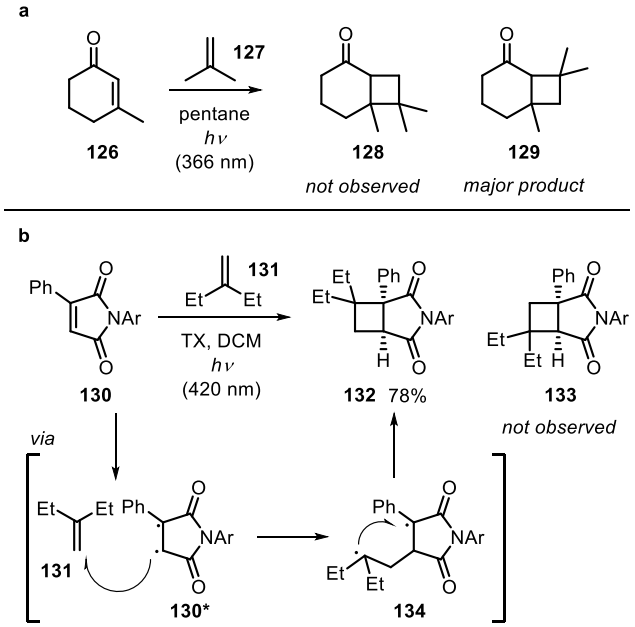
Scheme 14 *- Depiction of the regioisomeric products formed from photocycloadditions.*[49–51]

Electronic factors arise from the reverse partial charge incurred on an enone when it becomes a diradical (Scheme **15**).[52–54] This reverse in polarity is used to explain the regioselectivity observed when different olefins react with 2-cyclohexenone **117**. Electron rich olefins (**118** and **121**) give "head-to-tail" cyclobutanes (**119** and **122**) as the major product and electron poor olefins (**124**) give "head-to-head" cyclobutanes (**125**) as the major product. In the case of Scheme **15** the electron-match is the key driving force in the regioselectivity.



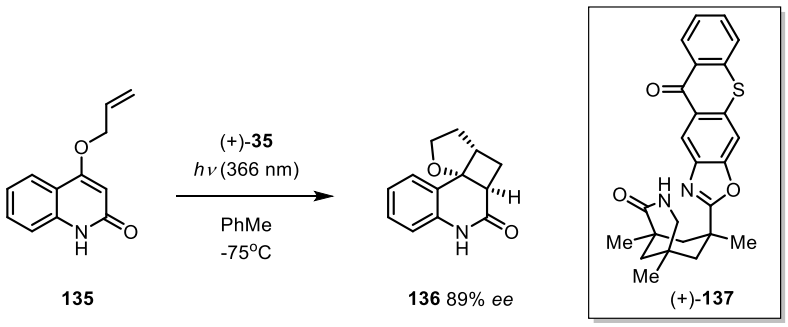
Scheme 15 *– Electronic parameters controlling the regioselectivity of cyclobutane formation using different electron rich and electron poor olefins.*[52–54]

Alternatively, regioselectivity can be achieved through steric interactions. Substitution of the 3-position on enone **126** gives the opposite regioselectivity observed in cyclobutane **129** (Scheme **16a**).[52] From this result, the steric hinderance from the methyl group overcomes any electronic stability towards the "head-to-tail" regioselectivity and the opposite stereoisomer is observed. An interesting result, countering the previous observation, is in the [2+2] photocycloaddition of maleimide **130** with 3-methylenepentane **131** to give exclusively "head-to-head" regioselectivity (Scheme **16b**).[55] The authors rationalise this by the formation of 1,4-diradical **134** containing two stabilised tertiary radicals, forming the cyclobutane product **132**. Another rationale behind this can be due to the stepwise process leading to the least hindered sites reacting first, leading to diradical **134**, and then forming cyclobutane **132**.



Scheme 16 *– **a)** Change in regioselectivity when 3-methyl substituent is employed onto enone **126**.*[52] ***b)*** *Exclusive "head-to-head" regioisomer observed when employing 1,1-disubstitued alkenes into photocycloadditions with substituted maleimides.*[55]

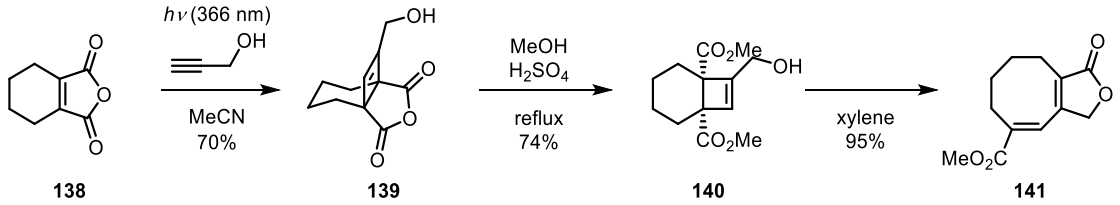
Enantioselectivity cannot be achieved through this method. Advances in enantioselective photochemistry is limited, but a few examples of enantioenriched photocycloadditions have come about, particularly in recent years.[56–59] Bach *et al.* approached the problem with a template "host-guest" solution (Scheme **17**).[57] This method gave enantioenriched [2+2] cycloadducts with up to 99% *ee*. While specific to quinolines and hydropyridones, this demonstrates that a template design for the control of enantiomers is feasible.



Scheme 17 *-Template design for the enantioenriched photocycloaddition of quinolines by Bach et al.*[57]

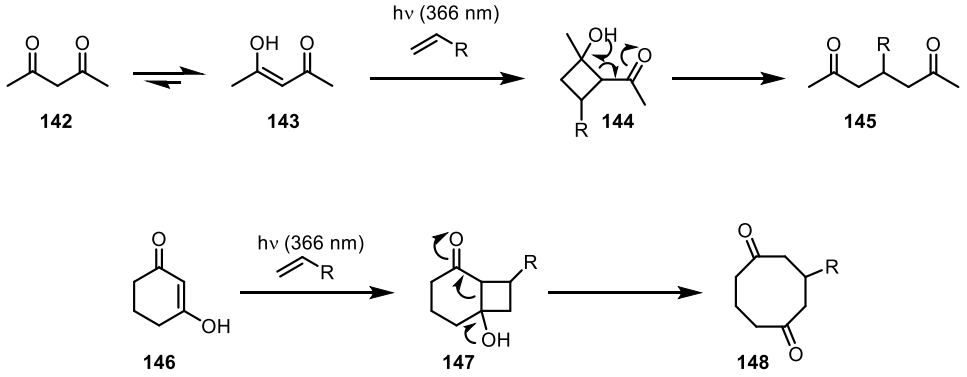
Previous work in the Booker-Milburn group has focused on the chromophores of maleic anhydride and maleimide derivatives.[60–62] These compounds are cheap and easy to diversify before photocycloadditions. For example, a maleic anhydride derivative **138** was used as the chromophore in the photocycloaddition of propargyl alcohol to give cyclobutene **139** (Scheme **18**).[61] Subsequent hydrolysis gave the fused 6-4 membered ring system **140** which could undergo electrocyclic ring

expansion into cyclooctadiene lactone **141**. The photochemistry involved allowed for the synthesis of multigram quantities of compound **139** with a productivity of 1.3 gh^{-1}.



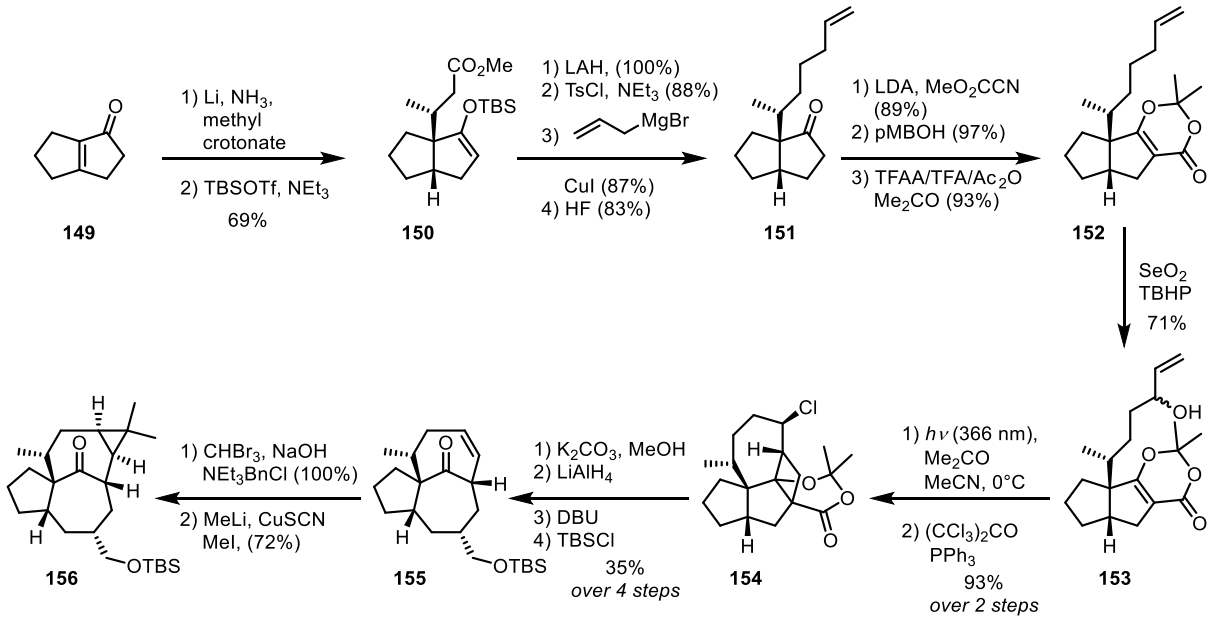
Scheme 18 *- Photochemical methods towards the electrocyclic ring opening of cyclobutenes by Booker-Milburn et al.*[61]

However, this is not the first example of where the synthesis of strained cyclobutanes is used to induce ring expansion. The de Mayo reaction can also lead to ring expansion protocols to give functionalised medium rings. A common use of the de Mayo reaction is in the extension of an enol-containing alkyl chain **142** by two carbon units (Scheme **19**). However, when applied to a cyclic ketone/enol **146**, the fused bicyclic system can open to give the ring expanded product **148**.



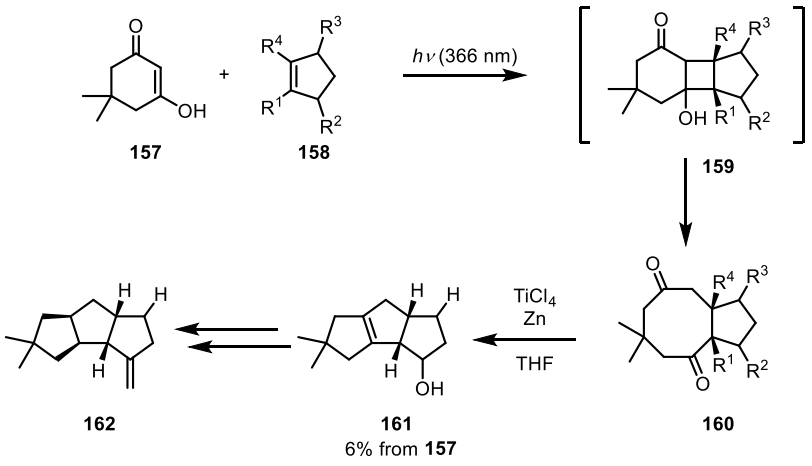
Scheme 19 *– The de Mayo rearrangement and ring expansion reactions.*[63,64]

The de Mayo ring expansion of fused cyclobutanes has been used in the total synthesis of numerous natural products.[65,66] This is due to ring expansion protocols being a popular approach for generating 7-8 membered rings, as cyclisation of linear substrates to form medium sized rings is highly disfavoured due to transannular interactions. For example, work by Winkler *et al.* produced the total synthesis of ingenol **156** in 43 steps with the key formation of the bridged 10 membered ring by a de Mayo ring expansion (Scheme **20**).[65] A decade later, the total synthesis was completed in 14 steps by Baran *et al.* through a Pauson-Khand cyclisation.[67]



Scheme 20 *– Total synthesis of ingenol utilising the de Mayo ring expansion as a key step.*[65]

Another example in the application of the de Mayo ring expansion is the total synthesis of hirsutene **156** by Weedon *et al.* (Scheme **21**).[66] This early application of the de Mayo reaction demonstrates its longstanding utility in the formation of medium rings. In this example, the ring expansion protocol is subsequently followed by a ring contraction by a McMurry coupling, overall transforming the tricyclic 6-4-5 ring system to the 5-5-5 system observed in the natural product.

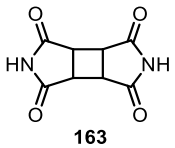


Scheme 21 *- Total synthesis of hirsutene utilising the de Mayo ring expansion as a key step.*[66]

1.3.2. Photochemistry in the synthesis of azabicyclo[3.2.0]heptanes

The use of maleimides in photochemistry was first observed in 1961 with the dimerisation of *N*-H maleimide to give the fused cyclobutane **163** (Figure **4**).[68] Later on, the use of maleimide cycloadducts with benzene was investigated in the use as a prodrug.[69] Since then, the use of maleimides in

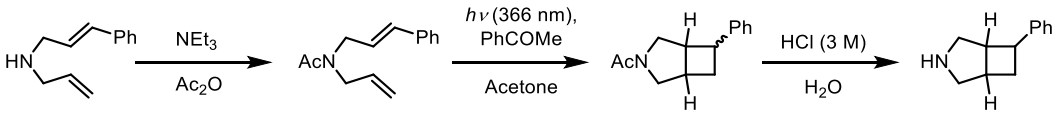
photochemistry to produce medicinally useful azabicyclo[3.2.0]heptanes has been widely developed and continues to produce complex molecular scaffolds from simple starting materials.



163

Figure 4 *– Dimer of maleimide from a [2+2] photocycloaddition.*

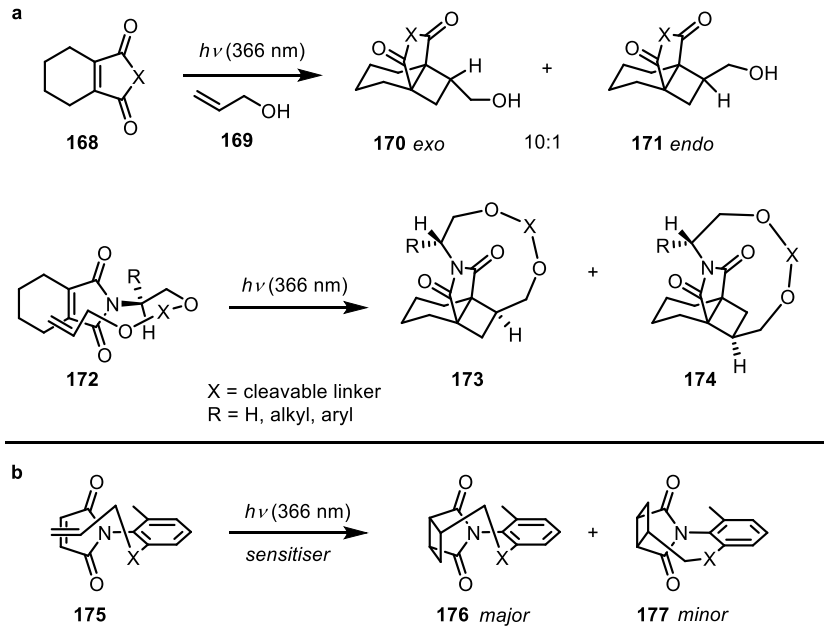
For example, the intramolecular [2+2] photocycloaddition of linear chain dienes (**164**) has been found to furnish azabicycles with good enantio- and high diastereoselectivity (Scheme **22**).[70] The desired transformation was achieved by photoexcitation of the styrene π-bond to give the high energy diradical, which then undergoes radical cyclisation in a 5-*exo*-trig manner, giving the azabicycle **167** as the product. These types of motifs have been sought after by other cyclisation methods for their uses in medicinal chemistry.[71] This [2+2] methodology was further developed to achieve the cyclobutane in a 2-step process, increasing the ease with which these azabicyclic molecules can be synthesised and therefore increasing the accessibility towards medicinally relevant cyclobutanes.[72]



164 **165** **166** **167**

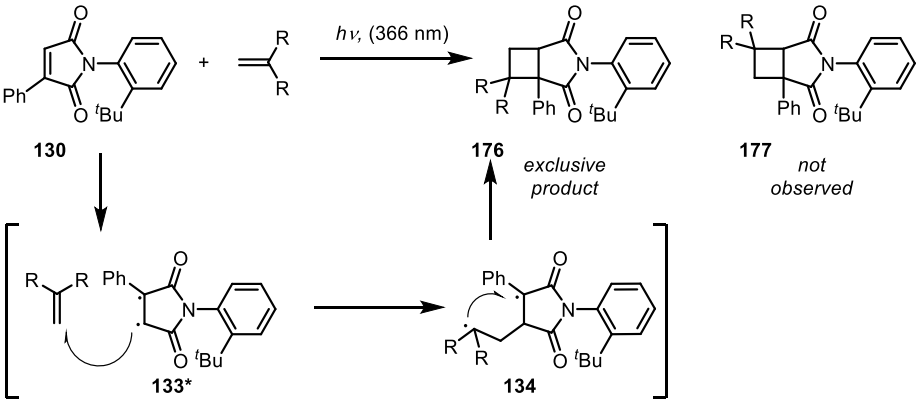
Scheme 22 *– Photochemical synthesis of 3-azabicyclo[3.2.0]heptanes.*[72]

The use of tethered maleimides was another approach to forming diastereoselective cyclobutanes through [2+2] photocycloadditions. Work by Booker-Milburn *et al.* identified the key regioselectivity issue in photocycloadditions and sought to solve this by utilising a cleavable tether from the *N*-terminus of maleimide **172**. This would successfully undergo [2+2] cycloaddition to form medium ring tricyclic cyclobutanes with low diastereoselectivity (Scheme **23a**).[73] This was developed further by Sivaguru where enantioselectivity could also be observed with high selectivity and high diastereoselectivity (Scheme **23b**).[74] This was achieved by using atropisomeric maleimides **175** with tethered alkenes, where axial chirality in the starting material was transferred to the enantioselectivity of the product. Regioselectivity driven by substitution of the maleimide double bond was found to have the most dominant effect, although an effect was also observed because of the substitution on the alkene tether.



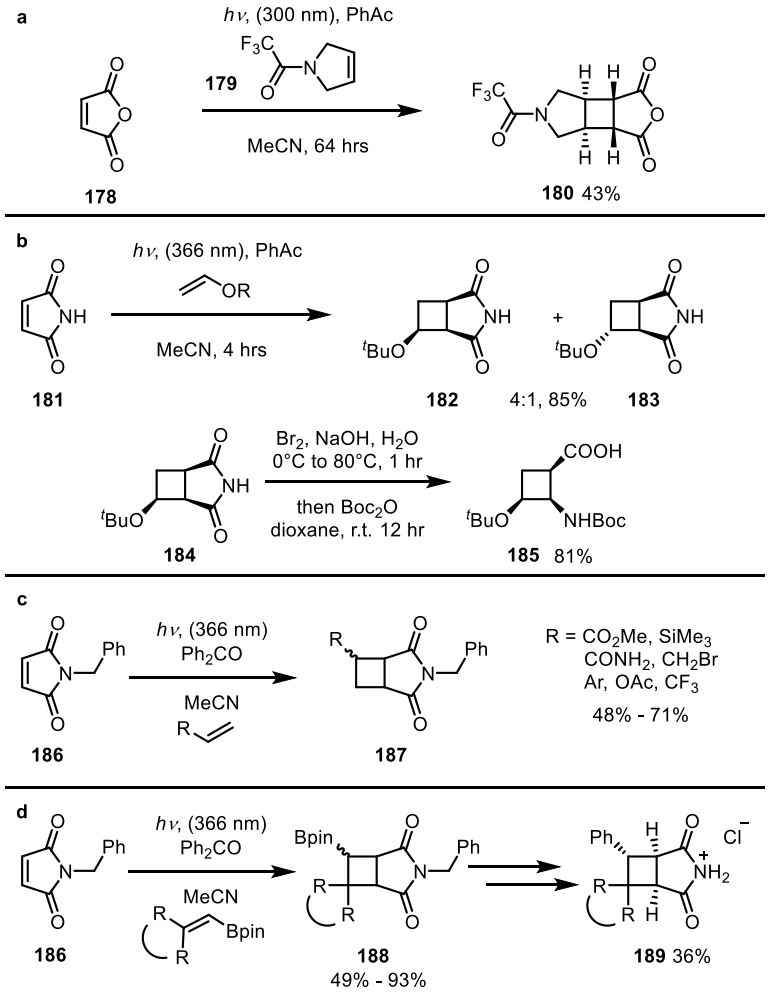
Scheme 23 *– Tethered maleimide [2+2] photocycloadditions.*[73,74]

Work by Sivaguru went on to further the development of enantio- and regioselectivity to intermolecular reactions.[55] Axial chirality was achieved through HPLC purification of the maleimide starting material, to give optically pure phenyl maleimide. Again, the driving force for regioselectivity was the substitution on the maleimide double bond, and the axial chirality of the maleimide was transferred through to the cycloadduct. The regioselectivity could be explained by the stepwise cyclisation of the formed diradical **134** (Scheme **24**). The least hindered ends of the maleimide and alkene undergo C–C bond formation first, leading to the head-to-head arrangement of the cyclobutane **176**. In the case where the alkene adduct is asymmetrical, lower diastereoselectivity is observed, however, the *ee* in the products isolated still remains high (99%) due to the initial axial chirality.



Scheme 24 *– Regioselective intermolecular [2+2] photocycloadditions.*

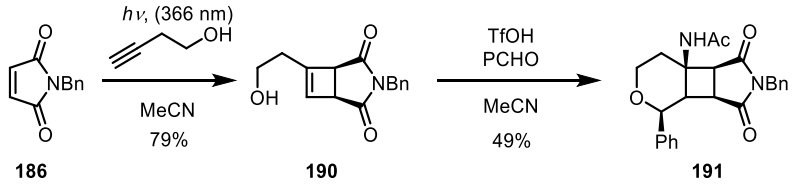
In the past decade, several procedures to access 3-azabicyclo[3.2.0]heptanes have been developed, utilising different alkene substrates with a maleimide or anhydride as the photoexcited alkene (Scheme **25a**).[75–78] Diastereoselectivity was observed in all cases with favouring of the *endo* product of the cycloaddition for vinyl ethers, *α,β*-unsaturated esters/amides, vinyl silanes, allyl halides, vinyl sulfonates and vinyl pyridines (Scheme **25b** and **25c**). Methyl vinyl ketone gave a low yield (5%), due to the electron mismatch with maleimide, favouring dimerisation of the maleimide. The opposite diastereoselectivity was observed with vinyl boronic esters, favouring the *exo* product, albeit in low selectivity (Scheme **25d**). The boronic substituent can be further functionalised by a range of protocols, highlighting the diversity that can be achieved from simple building blocks.



Scheme 25 *– Examples of triplet sensitised [2+2] photocycloadditions towards 3-azabicyclo[3.2.0]heptanes.*[75–78]

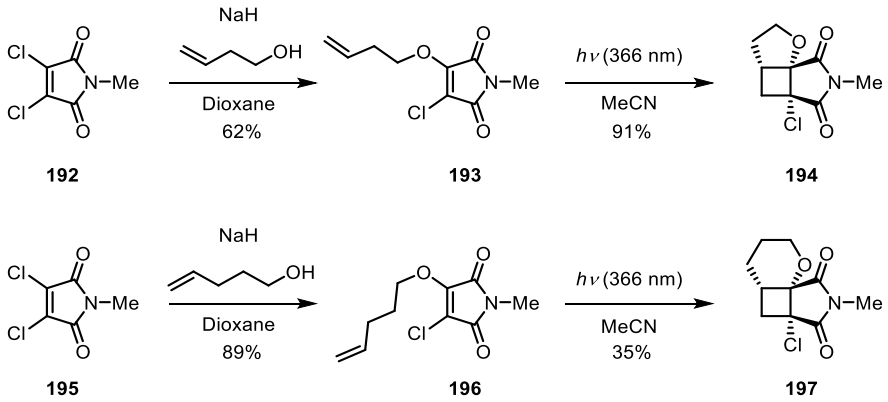
Work in the Booker-Milburn group has established a sequential photocycloaddition-Prins cyclisation approach to tricyclic cyclobutane derivatives (Scheme **26**).[25] This approach negates the selectivity issues faced when using alkenes in [2+2] photocycloadditions, by using alkyne derivatives such as propargyl alcohol. The cyclobutene formed is an ideal *π*-bond for the Prins cyclisation, generating 5

contiguous stereocentres with complete diastereoselectivity. The procedure can be applied to a range of aldehydes with a variety of nucleophiles, including fluoride.



Scheme 26 *– Sequential [2+2] and Prins cyclisation reaction.*[25]

Previous work also showed that heterocyclic fused cyclobutane-containing ring systems can be obtained by an intramolecular photocycloaddition (Scheme **27**).[79] This was achieved by initial Michael addition of an alkenyl alcohol to the parent maleimide **192** followed by irradiation of substituted maleimide **193** to give the [2+2] cycloadduct **194**. The product formed is left with an *α*-chloro handle for future functionalisation. A similar reaction was performed with the longer alkene tethered maleimide **196**. Interestingly, potentially due to slower 6-*endo*-trig cyclisation, a lower yield was observed.



Scheme 27 *- Photocycloadditions of tethered maleimides.*[79]

From the range of polycyclic heterocycles that can be generated from a [2+2] photocycloaddition with maleimide starting materials, it's evident that further development of this procedure has a lot to offer and gives access to rapid formation of complex structures.

1.4. Visible-light photochemistry

Visible-light photoredox catalysis has fast emerged as an alternative method to generate radical intermediates.[80] Visible-light photocatalysts are able to undergo excitation under mild conditions and then perform SET processes (Figure **5**). Depending on the oxidation state, the catalyst will either undergo oxidative quenching from an electron acceptor (path **A**, red), or reductive quenching from an electron donor (path **B**, blue). The radical ion produced can revert to the ground state photocatalyst to complete the redox cycle. This method allows for generation of radicals in organic chemistry, without the need for stoichiometric amounts of radical initiator. The mild conditions required for SET makes photocatalysts a powerful tool in the formation of complex molecules.[81]

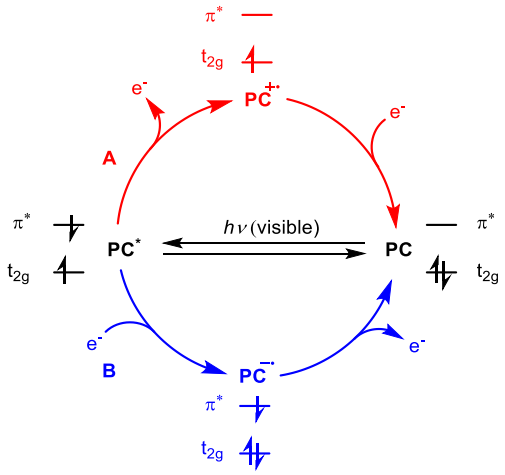
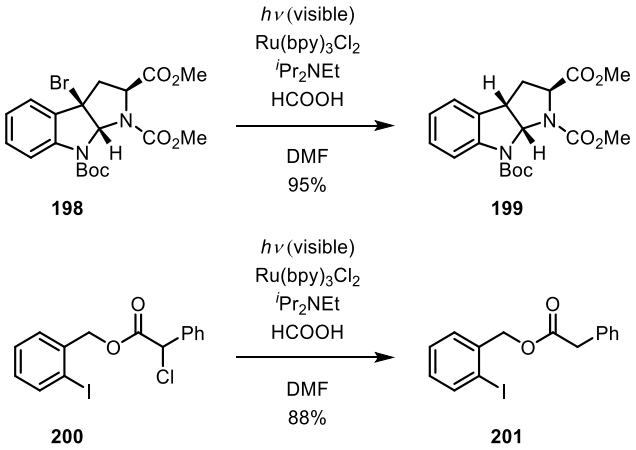


Figure 5 *- Oxidative and reductive quenching cycles of photoredox catalysts.*

Due to the prevalence of starting materials and the diverse functionality that can be achieved through activation, the two most common protocols from photoredox functionalisation falls on dehalogenation of alkyl and aryl halides and decarboxylation of aryl and alkyl carboxylic acids.

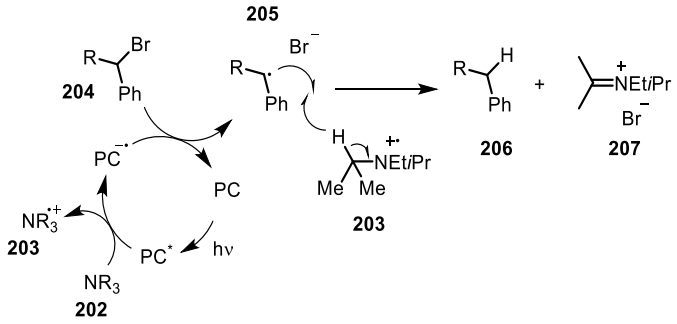
1.4.1. Photocatalysed dehalogenation

Visible-light photocatalysed reductive dehalogenation was first reported by Stephenson *et al.* with the dehalogenation of *α*-acyl and benzylic halides **198** and **200** (Scheme **28**).[82] This work was based on the previous success of MacMillan and Yoon's work with the photocatalyst, $Ru(bpy)_3Cl_2$.[22,83]



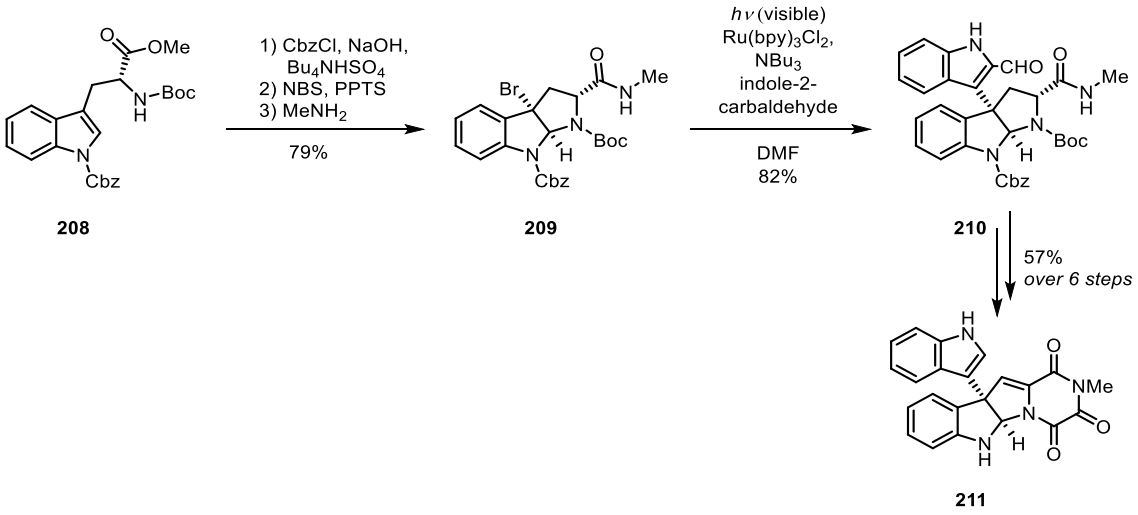
Scheme 28 *- Reductive dehalogenation of benzylic and acylic positions by Stephenson et al.*[82]

The catalyst was found to successfully reduce C–Cl and C–Br bonds in benzylic and α-acyl positions. The radical formed **205** was quenched by the amine radical cation **203** *via* H-atom transfer (HAT) to give the iminium ion **207** (Scheme **29**). The conditions were tolerant of silyl ethers and carbamates as well as free hydroxyl groups, and the reduction was selective over vinyl iodides and haloalkanes. This chemistry was developed further to employ radical addition to the radical formed, achieving radical additions to form tertiary and quaternary carbon–carbon bonds.



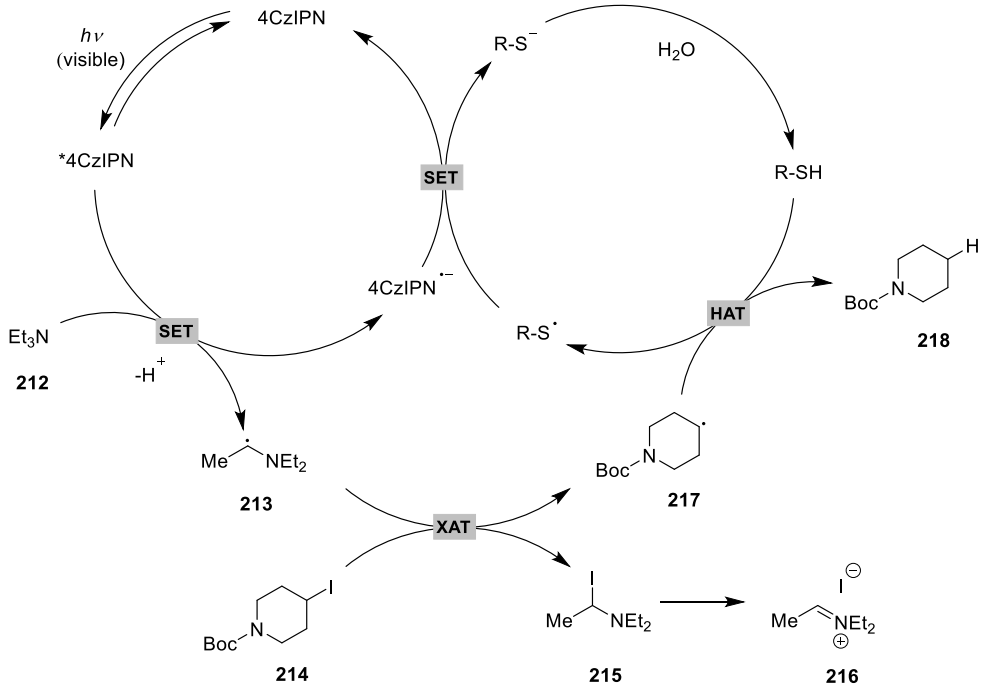
Scheme 29 *- Proposed general reaction mechanism for the hydrodehalogenation of alkanes.*[82]

The chemistry developed was utilised in the key step of a total synthesis of (+)-gliocladin C, **66** (Scheme **30**), with the radical addition of a tertiary radical to a functionalised indole as the key step.[84]



Scheme 30 *- Selected key steps in the total synthesis of gliocladin C by Stephenson et al.*[84]

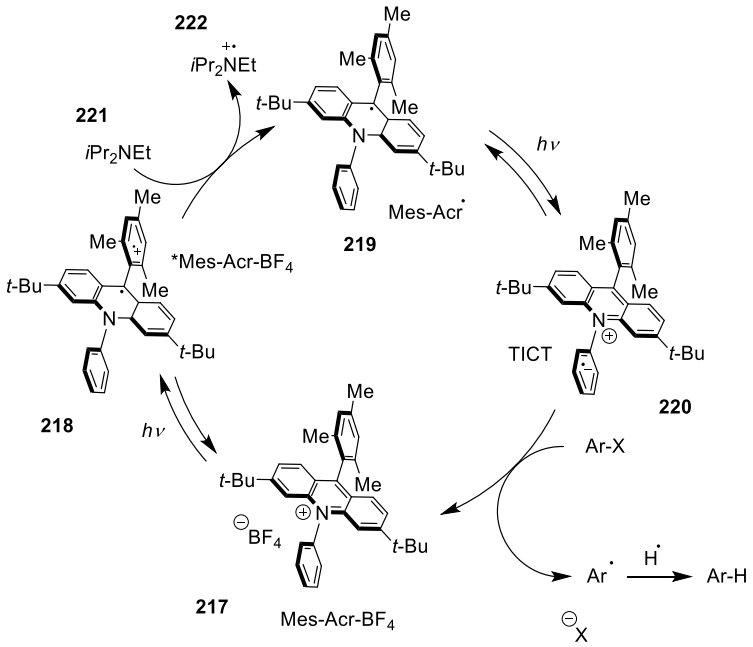
Leonori *et al.* published work studying the hypothesis of tertiary amines being used as halogen atom transfer (XAT) agents.[85] This hypothesis suggests that rather than the catalyst proceeding *via* a SET mechanism to reductively dehalogenate alkyl-halide bonds, instead, an amine base **212** is oxidised and forms an *α*-amino radical **213** (Scheme **31**). This radical is then able to undergo XAT to provide the desired alkyl radical **217** and iminium halide complex **215**. This mechanism negates the requirement for photocatalysts with low reduction potentials as the energy barrier comes from the cleavage of C–X bonds, which have relatively weak bond dissociation energies (BDE).



Scheme 31 *- Tertiary amines as XAT agents in photoredox chemistry.*[85]

Evidence for this was given by providing a range of amino-radical initiators that did not have the capability of reductive dehalogenation in the presence of triethylamine. In each case, reductive dehalogenation was observed. This hypothesis was used to explain why 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN), with a reduction potential of -1.21 V, is able to dehalogenate C–I and C–Br bonds which have a much lower reductive potential (<-1.50 V).

Conversely, Nicewicz *et al.* published findings of an excited state acridine reductant **220**, with the reducing power of -3.36 V (Scheme **32**).[86] This catalyst was able to reductively cleave arylchloride and *N*-tosyl bonds, which have a very large BDE, and therefore must go *via* a SET reductive dehalogenation pathway. Previously, the catalyst **217** was only reported to have a reductive potential of -0.59 V by cyclic voltammetry (*vs* SCE). This highly reductive state was achieved by initial SER of the excited catalyst by a tertiary amine **221**, followed by further irradiation to give a high energy twisted intramolecular charge-transfer state.

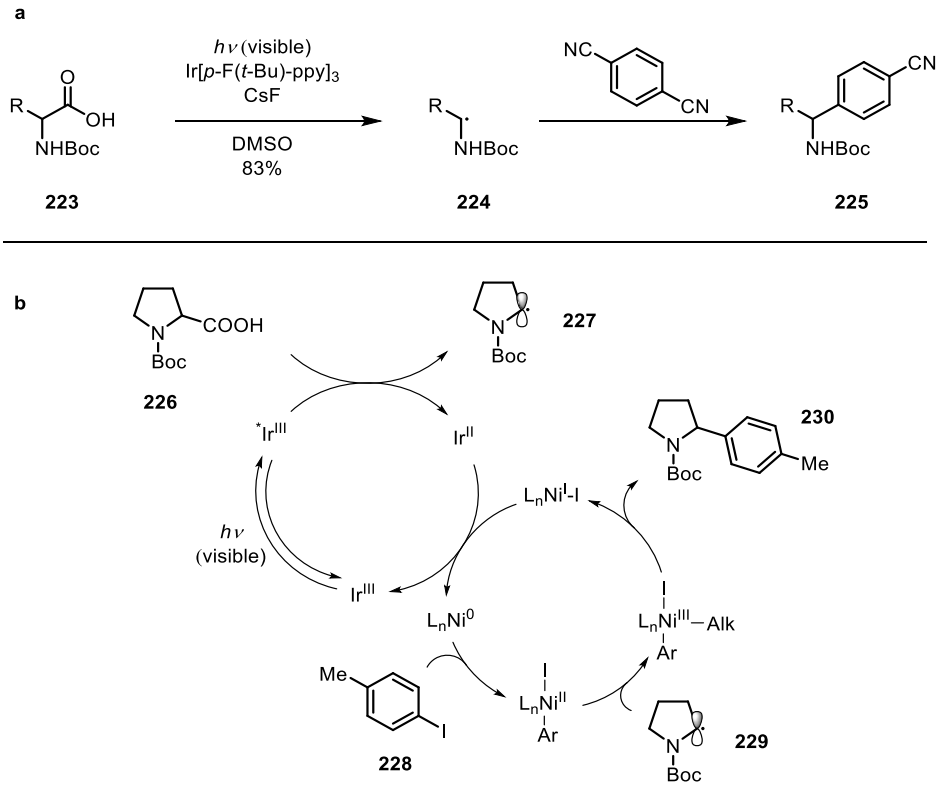


Scheme 32 *- Mes-Acr-BF$_4$ as a highly reducing photocatalyst.*[86]

1.4.2. Photocatalysed decarboxylation

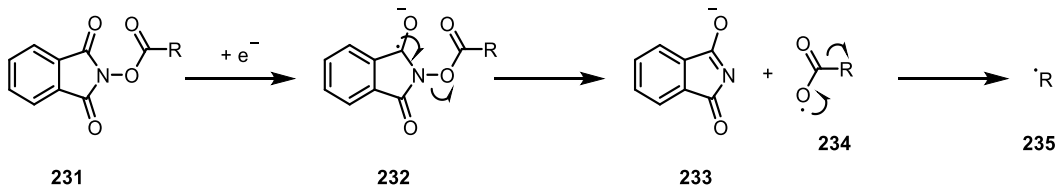
Oxidative decarboxylation *via* iridium photocatalysts has become a very popular approach to radical functionalisation.[80,87,88] The use of a carboxylate salt as a traceless activating group to generate a radical enables a broad range of radical chemistry to be achieved from simple building blocks. Work by MacMillan *et al.* have pioneered the use of iridium photocatalysts in decarboxylation-radical addition chemistry.[89,90] For example, in the use of the carboxyl functional group in amino acids as a

point of diversification to produce drug pharmacophores (Scheme **33a**).[91] Benzonitrile is used as the coupling reagent to produce a sp^3-sp^2 carbon–carbon bond. This strategy has been used in conjunction with nickel chemistry to couple carboxylic containing compounds to a vast array of aryl halides (Scheme **33b**).[92]



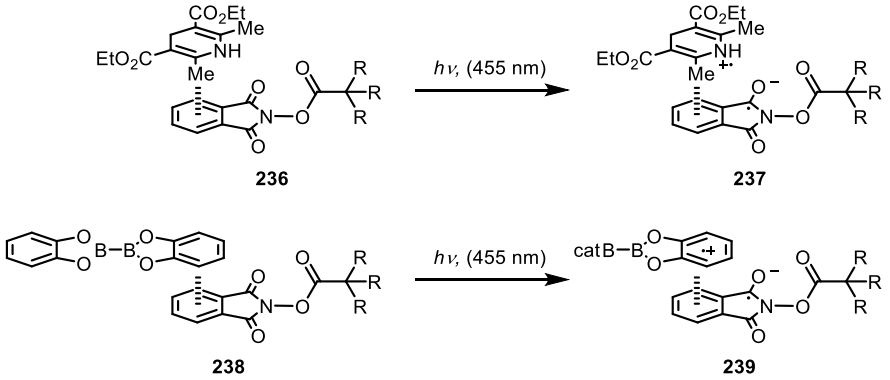
Scheme 33 *- **a)** Synthesis of benzylic amines via photocatalysis.*[91] ***b)** Dual catalysis for the functionalisation of amino acid derivatives.*[92]

Other decarboxylation strategies have taken advantage of activated carboxylic acids. *N*-Acyloxy phthalimide esters have been previously used in transition metal chemistry for arylations and alkylations.[93] However, their use as alkyl and aryl radical precursors has been taken up by photoredox chemistry. In much the same way that a carboxylate anion can undergo single electron oxidation, redox active esters **231** can undergo single electron reduction (SER) to give a radical anion on the imide ring **232** (Scheme **34**). Decarboxylation gives one molecule of CO_2 and a phthalimide anion **233**, leaving the aryl or alkyl radical **235** to proceed in the next step of the cycle.



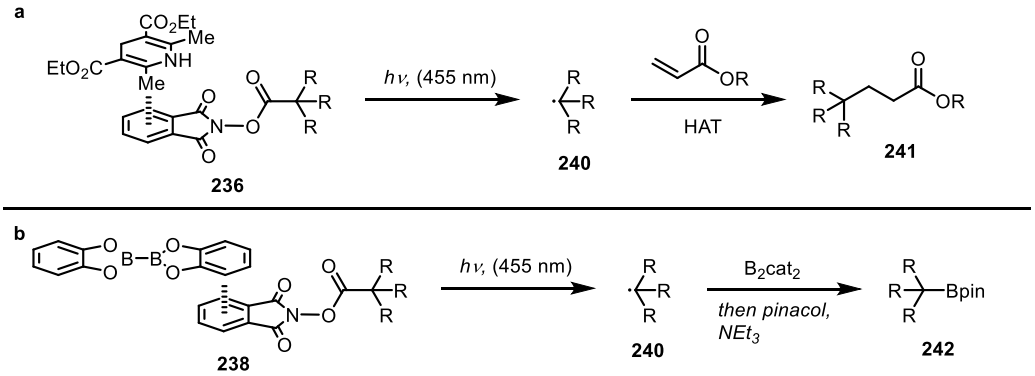
Scheme 34 *– Reductive decarboxylation of acyloxy-phthalimides.*[94]

In visible-light photochemistry, *N*-acyloxy phthalimide esters are most commonly reduced by a photocatalyst to generate the pertinent radical. A wide range of photocatalysts have been found to be successful in their application into redox active ester radical coupling. However, photocatalyst-free systems have been developed by forming an electron donor-acceptor (EDA) complex (Scheme **35**).[95,96] This complex arises from an electron rich aromatic ring and the electron poor phthalimide ring system. Upon excitation with the suitable wavelength of light, the SET can take place and the decarboxylation process is initiated. This mechanism has been proven by the bathochromic shift observed when a UV/vis absorption is measured of a solution of phthalimide and reductant. While in their independent state, absorption is in the UV range, however when combined, the absorption shifts into the visible range, demonstrating the EDA complex formed.



Scheme 35 *– Electron donor-acceptor (EDA) complexes formed onto N-acyloxy-phthalimides.*[95,96]

When a Hantschz ester is used in stoichiometric amounts, the redox active ester can be reduced, and a H-atom can be abstracted as the radical termination step (Scheme **36a**). However, work by Aggarwal *et al.* has shown that biscatechol diboron (B_2cat_2) has the same reductive effect in the absence of a photocatalyst and will also provide the boronic ester as the radical termination step (Scheme **36b**).[95] This work allows for borylation of activated carboxylic acids using only B_2cat_2, negating the need for transition metal catalysis.



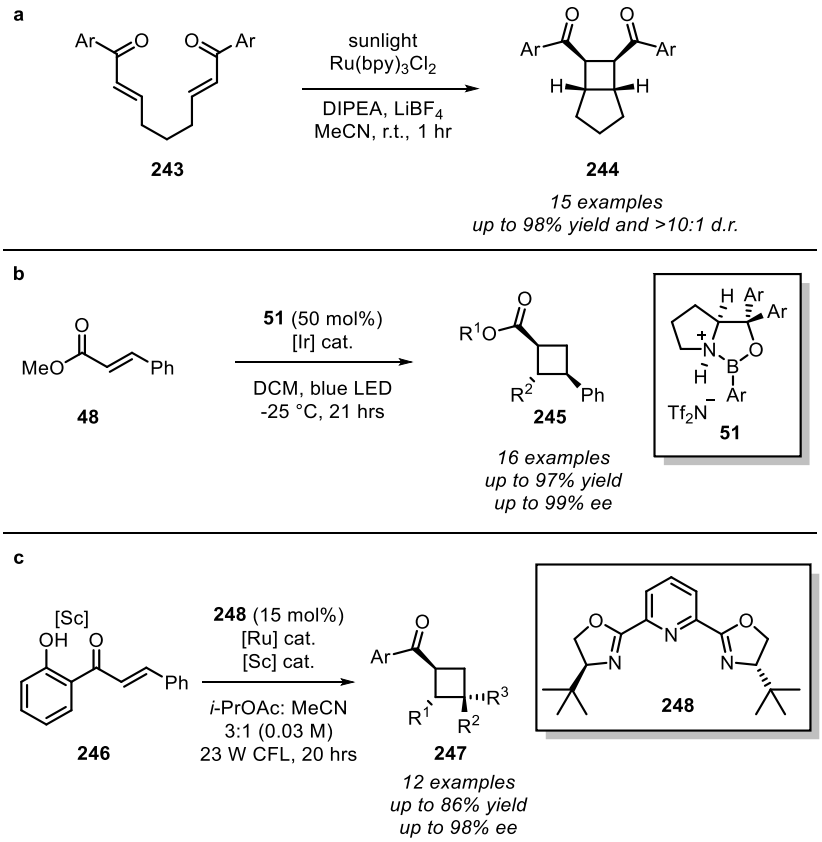
Scheme 36 *– Alkylations and borylations of N-acyloxy-phthalimides.*[95,96]

More recently, organic dyes have been used instead of rare transition metals as photocatalysts. These catalysts can be readily synthesised and give a large range of oxidation and reduction potentials beyond more traditional iridium and ruthenium photocatalysts. They can be altered electronically to give differing oxidation and reduction potentials and are far cheaper than their transition metal counterparts.[15,97]

1.4.3. Visible-light triplet sensitisers

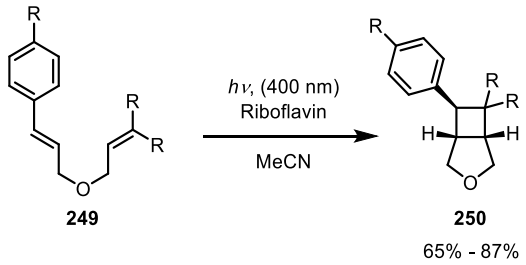
A recent surge in visible-light photochemistry is in the use of well-established photocatalysts as triplet sensitisers. Previously, UV photochemistry has benefitted from using photosensitisers in a wide array of photochemical reactions as they either boost the rate of reaction and/or have a positive impact on product yield. Sensitisers can also have an impact on the photochemistry occurring, for example in the di-π-methane rearrangement, if the reaction is sensitised, then the reaction stops at semi-bullvalene. However, under direct irradiation, a further photochemical transformation occurs to give the cyclooctatetraene product. Photosensitisers are well-established in photochemistry, with triplet energies (E_T) and half-lives (τ) either calculated or measured. However, visible-light triplet sensitisation still remains an underdeveloped area. This is due to the physical constraints of achieving high energy triplet sensitisation with a low energy wavelength of light. If a photosensitiser can be found that is able to absorb a longer wavelength of light, but achieves a high energy triplet state needed for photochemical reactions, then the non-visible world of ultra-violet photochemistry can be brought into the visible-light of modern day.

Several approaches to obtaining [2+2] cycloadducts through visible-light photochemistry have been developed over the past decade. Initial approaches by Yoon *et al.* led to diastereoselective cyclobutanes through intramolecular cyclisations (Scheme **37a**).[21] His work was further developed to include enantio- and diastereoselective synthesis of cyclobutanes through Lewis-acid assisted intermolecular [2+2] photocycloadditions (Scheme **37b**).[23,98] Since the first report in 2008, the protocol has been developed through visible-light triplet sensitisation, rather than the SET process in previous work. The first example in this system was demonstrated by Yoon *et al.* where the drawback of SET cycloaddition was recognised as being limited to the electronic properties of the substrate. An iridium catalyst was employed that was not able to undergo SET with the substrate, but that a triplet energy could be transferred from the excited state catalyst to the substrate (Scheme **37c**).[99]



Scheme 37 *– Visible-light mediated [2+2] photocycloadditions.* ***a)*** *SET using a ruthenium catalyst to initiate intramolecular cycloaddition.*[21] ***b)*** *SET using an iridium catalyst, gives enantioselective cycloaddition giving cyclobutanes with up to 99% ee.*[21] ***c)*** *Triplet sensitised cycloaddition using ruthenium and scandium co-catalysts generating cyclobutanes with high ee.*[99]

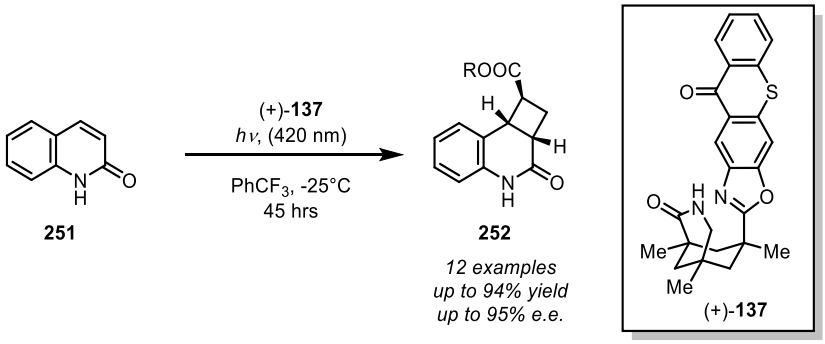
The reaction was a success under visible-light conditions (compact fluorescent light bulbs, CFL) and validated the wider application of visible-light triplet sensitisers. The work was expanded upon by Cibulka *et al.* in the use of flavins as sensitisers for synthesis of diastereoselective azabicycles and other fused polycyclic cyclobutanes.[100,101] The work employed the use of violet light (400 nm) to achieve sensitisation, but proved the wider scope available to triplet-sensitised [2+2] photocycloadditions not possible by SET of photoredox catalysis (Scheme **38**).



Scheme 38 *– Visible-light mediated intramolecular [2+2] cycloaddition.*[100,101]

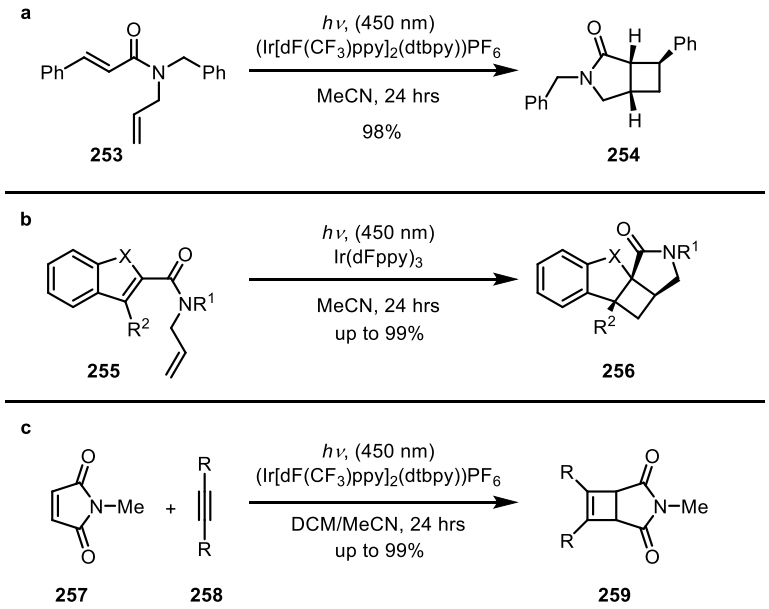
Other examples followed, with Bach *et al.* focussing on thioxanthone derived template **137** (Scheme **39**) for intramolecular enantioselective [2+2] photocycloadditions of quinolines using violet light (420 nm). [55,58,74,102–104] Unfortunately, all these examples required a higher energy wavelength of light (420

nm), making the application of the more widely used wavelengths of light (>450 nm) impossible, and requiring specialised equipment.



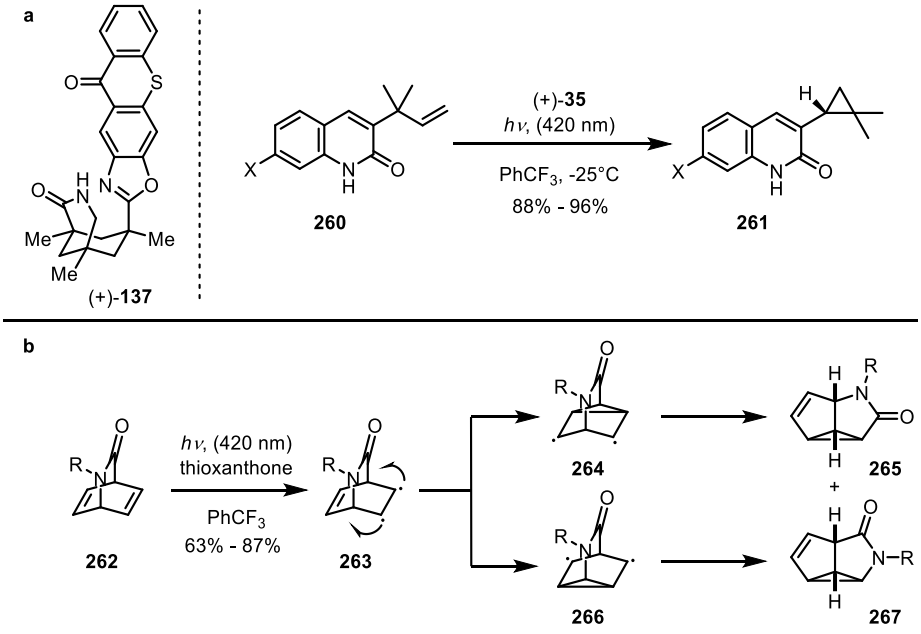
Scheme 39 *– Enantioselective intermolecular [2+2] photocycloadditions mediated by a thioxanthone template.*

However, the application of iridium pyridyl complexes as triplet sensitisers has enabled the triplet sensitised photochemical reactions to be utilised in the visible-light range. Several examples were developed including expansion on Yoon's work by intramolecular [2+2] photocycloaddition of *N*-allylcinnamamide and cinnamamines to form azabicyclo[3.2.0]heptanes (Scheme **40a**).[105] Further inter- and intramolecular cycloadditions were explored by cyclising onto aromatic molecules using 450 nm visible-light and iridium photosensitisers (Scheme **40b**).[106–108] Finally, an iridium photosensitised protocol for the excitation of maleimides and maleic anhydrides in the [2+2] photocycloaddition of alkynes was established (Scheme **40c**). The range of alkynes used was broad and the electronic effect of substituents was explored on the maleimide substrate. It was found that the reaction conditions favoured most substitutions on the maleimide, however, the *N*-phenyl substrate gave low yields, which was rationalised by spin density calculations on the maleimide double bond. The protocol established shows that visible-light (>420 nm) triplet sensitisation of maleimide is possible and can be utilised in intermolecular [2+2] photocycloadditions.[109]



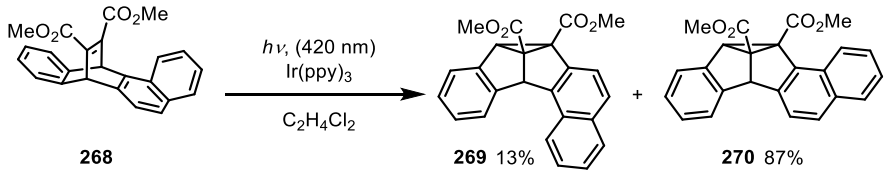
Scheme 40 *– Examples of visible-light mediated [2+2] photocycloadditions.*[105–109]

Further photochemical reactions have been unlocked in the visible-light range by photosensitisation. For example, the di-π-rearrangement was found to be accessible under high energy visible-light (400-420 nm) by Bach *et al.* (Scheme **41a**).[110,111] One example showed that the well-established enantioselective thioxanthone **137** could sensitise the di-π-methane rearrangement to give enantioselective cyclopropylquinolones. In another finding, azabarrellenones were able to undergo the di-π-methane rearrangement to give the tricyclic heterocycle, albeit with low regioselectivity (Scheme **41b**).



Scheme 41 *– Enantioselective photochemical reactions through the use of a chiral template.* [110,111]

Work by Ihmels *et al.* has shown that the di-π-rearrangement is possible using visible-light (>450 nm) and iridium as a photosensitiser, a range of substituted semi-bullvalene products in excellent selectivity and yields (Scheme **42**).[112]



Scheme 42 *– Visible-light mediated di-π-methane rearrangements.*[112]

Recently, there has been work into the functionalisation of thioxanthone sensitisers to induce a bathochromic shift. This would allow for the sensitisers to absorb lower wavelengths of light and therefore undergo excitation to the triplet state under visible-light conditions. Work by Sivaguru *et al.* demonstrated that induction of a bathochromic shift by changing of the electronics of the thioxanthone, through substitution with bromine, leads to a drop-off in the triplet state energy.[113] Work by Booker-Milburn *et al.* has shown that changing the electronics of the thioxanthone with other electron donating and withdrawing substituents will incur a bathochromic shift while maintaining a triplet energy that can be used in visible-light transformations (Figure **6**).[114]

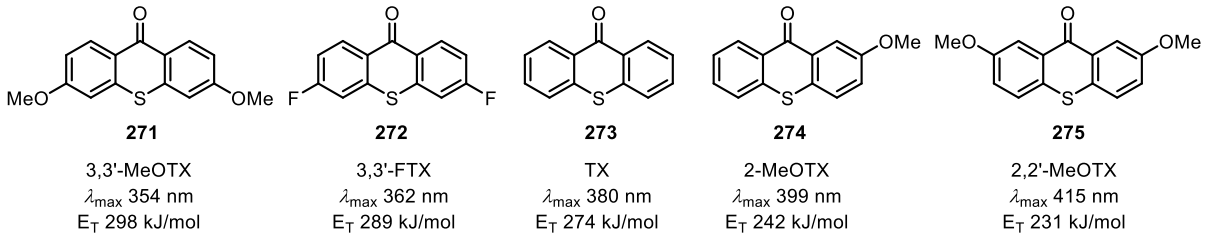


Figure 6 *– Examples of functionalised thioxanthone triplet sensitisers and their electronic properties.*[114]

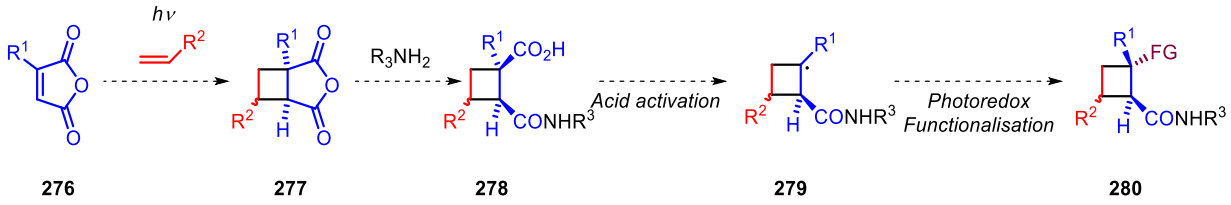
From these numerous examples it can be seen that visible-light triplet energy sensitisers are incredibly useful in the application to photochemical reactions and rearrangements. The sensitisers used have predominantly been transition metal catalysts taken from visible-light photocatalysis, which means their use is restricted to compounds that are not able to undergo SET reactions. However, other sensitisers that do not have SET properties have been developed and successfully utilised in photochemical reactions.

Chapter 1

2.1. Sequential photocatalysis towards the synthesis of diastereoselective cyclobutanes

2.1.1. Aims

The initial aim of the work described herein involves taking advantage of cheap anhydride derivatives **276**, and scalable [2+2] photochemistry to generate a library of anhydride containing functionalised cyclobutanes (Scheme **43**). Hydrolysis of these anhydrides can give the carboxylic acid required for further photoredox functionalisation through decarboxylative radical generation.

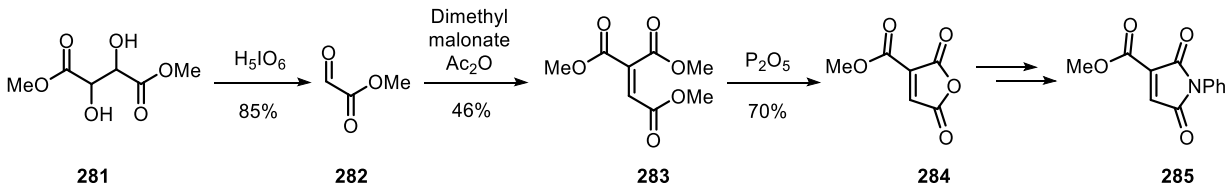


Scheme 43 *- Outline of synthetic route to highly functionalised cyclobutanes.*

This project aims to take advantage of the novel photocatalysed radical addition reactions, palladium chemistry and previous knowledge in the group of [2+2] photocycloadditions to create a diverse library of highly functionalised, rigid cyclobutanes for biological assay.

2.1.2. Anhydride ester synthesis and [2+2] photochemistry

The project began with the synthesis of anhydride derivatives. Anhydrides contain a relatively poor chromophore and so an electron withdrawing group at the 3-position improves its photochemical properties through increasing the energy level of the HOMO (highest occupied molecular orbital). The synthetic route to this anhydride derivative was previously utilised for the synthesis of *N*-phenylmaleimide **285** (Scheme **44**).[115] This was accomplished by initial oxidative cleavage of dimethyl tartrate **281** to give two equivalents of methyl glyoxalate **282**. Condensation of methyl glyoxylate **282** and dimethyl malonate gave **283**, which ring-closed upon heating with phosphorous pentoxide. The resulting mixture was distilled under reduced pressure to give anhydride ester **284** in an overall yield of 27% from dimethyl tartrate **281**.

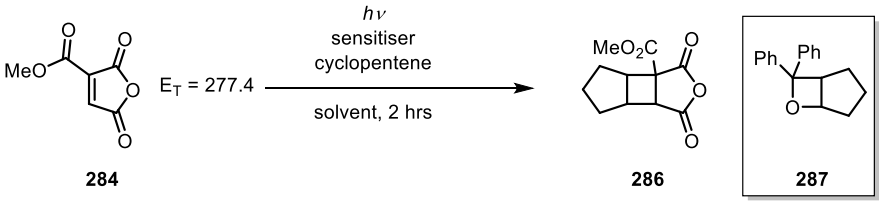


Scheme 44 *- Synthetic route to anhydride ester **284**.*

A UV/vis measurement showed that the resulting anhydride **284**, absorbed in the UV range (191 - 350 nm) (Figure **S3**). Photoexcitation of this chromophore was therefore possible at this wavelength, allowing for potential photoexcitation on this substrate. However, it was found that under a range of

conditions and solvents, the substrate did not produce the desired cycloadduct **286** (Table **1**). Instead, photocycloaddition of benzophenone and cyclopentene gave undesired Paterno–Buchi product **287** (Entries 3 + 4). The reaction may have been successful with the use of acetone as solvent and sensitiser (Entry 8) however, the products were too unstable to be purified or taken any further synthetically.

Table 1 *- [2+2] reactions with anhydride ester* ***284****.*



Entry	Sensitiser	Triplet state energy (E_T) /kJmol^{-1}	Solvent	Products
1	-	-	MeCN	None
2	*I*TX	181	MeCN	None
3	Benzophenone	287	MeCN	**287**
4	Benzophenone	287	EtOAc	**287**
5	DFBPN	294	MeCN	None
6	DFBPN	294	EtOAc	None
7	Xanthone	310	EtOAc	None
8	-	332	Acetone	**286** (*trace*)

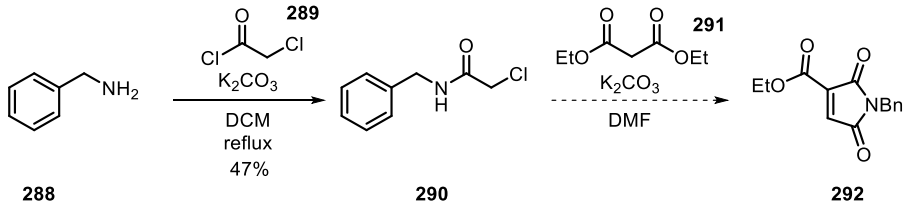
In all cases the starting material was observed to not undergo complete degradation. It was decided that the chromophore of the anhydride was too weak, and the anhydride itself was too unstable to hydrolysis, to reliably produce the range of cyclobutanes desired.

2.1.3. Maleimide ester synthesis

Figure 7 *- Maleic anhydride* ***178*** *and maleimide* ***181****.*

Maleimides are a class of compounds similar to maleic anhydrides (Figure **7**). Maleimides have a stronger chromophore and are more resilient to hydrolysis than their anhydride counterparts. A similar derivative of the ester anhydride was chosen as our target compound. However, no synthetic route to this compound existed, so a methodology was adapted from work by Ahmed *et al.* (Scheme

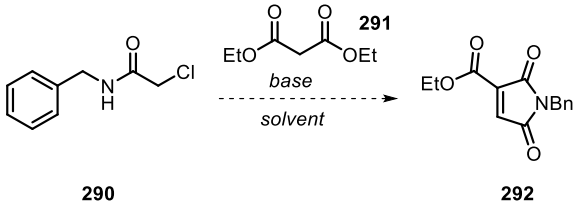
45).[116] This methodology provided a route to a range of maleimide derivatives, from a chloroacetamide precursor **290** and a selection of 1,3-dicarbonyls (**291**).



Scheme 45 *- Synthetic route to maleimide ester **292**.*

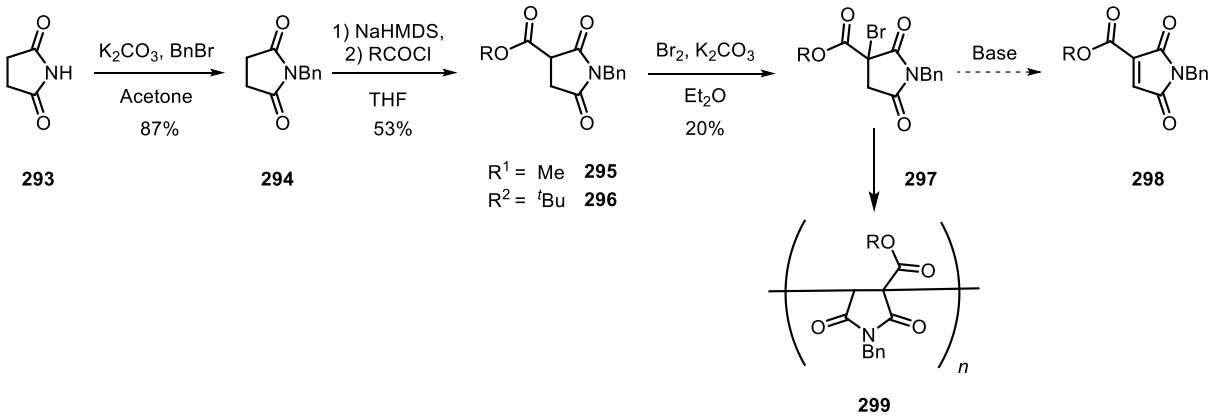
However, this methodology was not successful and did not produce any of the desired maleimides in any of the trialled conditions (Table **2**). Nucleophilic attack of the malonate to chloroacetamide **290** was successful under different basic conditions, however, ring closure to form the succinimide was not achieved.

Table 2 *- Conditions run for the cyclisation of **290** to form maleimide **292**.*



Entry	Solvent	Base	**292** (% Yield)
1	PhCN	K_2CO_3	0%
2	Xylene	K_2CO_3	0%
3	DMF	K_2CO_3	0%
4	DMA	K_2CO_3	0%
5	DMF (wet)	K_2CO_3	0%
6	DMSO	K_2CO_3	0%
7	DMF	$CsCO_3$	0%

A different approach was taken to synthesise succinimide **293** (Scheme **46**).[117] This approach was successful in producing the succinimide derivatives **295** and **296**. From this compound, deprotonation of the 1,3-carbonyl followed by subsequent bromination would give intermediate **297** which if subsequently eliminated, would give the desired maleimide **298**.



Scheme 46 *- Synthetic route to maleimide ester **298**.*

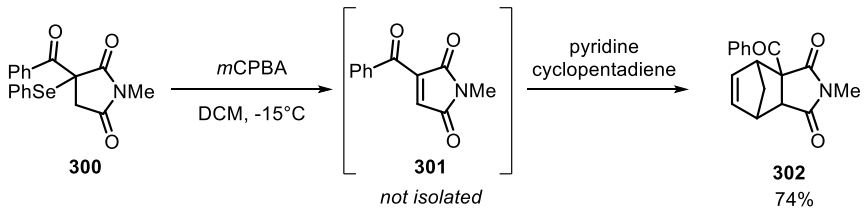
The synthesis of the bromo-succinimide **297** was accomplished, however, the elimination step only degraded the starting material, or formed oligomer **299** despite a range of bases being investigated (Table **3**). The *tert*-butyl ester **296** was synthesised to counteract the formation of oligomer **299**, however, the steric bulk did not have the desired preventative effect (Table **3** Entry **8** – **10**).

Table 3 *- Base condition screening for the elimination of **297** to form maleimide ester **298**.*

Entry	Ester	Bases	Product
1	R^1	NEt_3	**299**
2	R^1	DBU	**299**
3	R^1	K_2CO_3	None **(297)**
4	R^1	$N(iPr)_2Et$	**299**
5	R^1	NaH	*Degradation*
6	R^1	NaHMDS	*Degradation*
7	R^1	Proton Sponge	**299**
8	R^2	NEt_3	**299**
9	R^2	DBU	**299**
10	R^2	$N(iPr)_2Et$	**299**

Previous work has shown that *in-situ* elimination of succinimides under reaction conditions can give cycloadducts (Scheme **47**).[118] However this was not achieved in the case of succinimide **297** under UV conditions and only degradation of the starting material was observed. From these results, and results

of previous work, it can be deduced that the desired maleimide ester cannot be used as a viable method to synthesis cyclobutanes.[115,119]

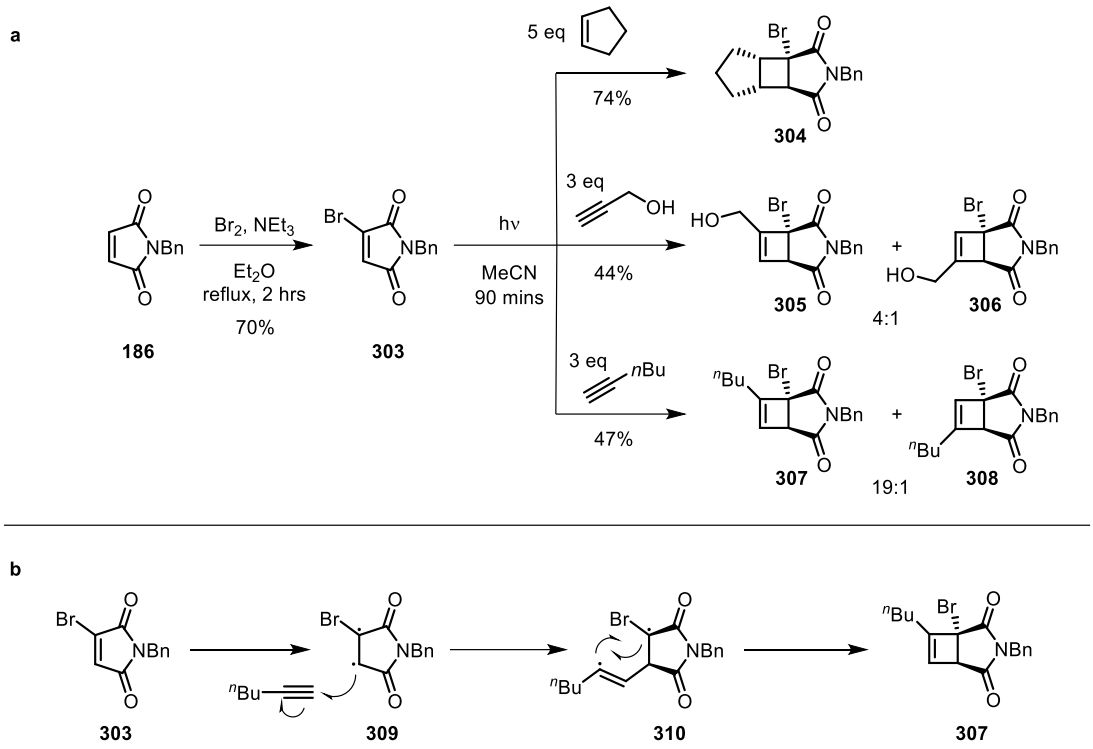


***Scheme 47** – In-situ elimination and trapping of the dieneophile with cyclopentadiene.*[118]

2.2. Halo-maleimide and succinimide derivatives

2.2.1. Synthesis and [2+2] photochemistry

Previous work in the group has featured halo-substituted maleimides (Scheme **48**). It was found that maleimide **186** gave a good absorption in the UV spectrum (Figure **S4**) and was able to undergo [2+2] photochemistry in good yield with cyclopentene (Scheme **48a**). The α-bromo-succinimides (**304** – **308**) produced were good candidates for photoredox catalysed reductive dehalogenation. The *N*-benzyl bromo maleimide precursor **303** was synthesised in very good yield to test out the scope of the [2+2] chemistry. The photocycloadduct compounds obtained show that the preferred orientation of the [2+2] cyclisation is head-to-head (Scheme **48b**). This suggests that the photocycloaddition happens in a stepwise process, favouring the least hindered radical addition first **309**, followed by the second radical-radical coupling to close the ring **310**.

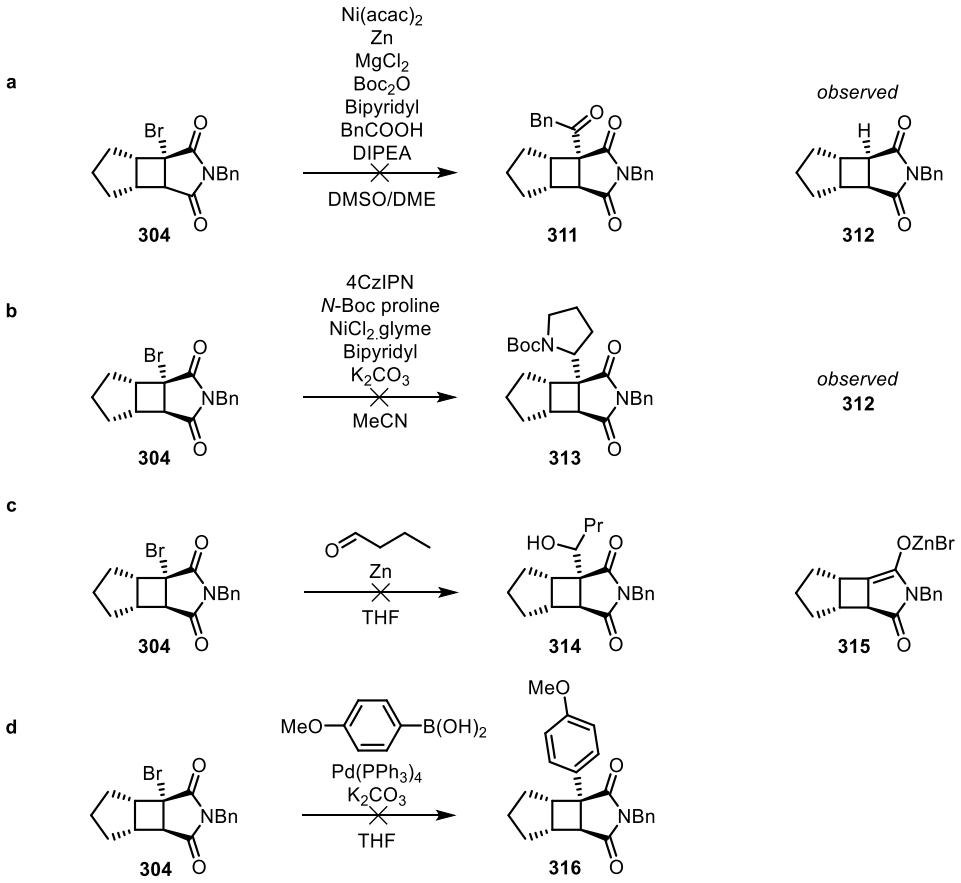


***Scheme 48** - **a)** Synthetic route to the synthesis of functionalised cyclobutanes. **b)** Proposed mechanism by which [2+2] photocycloaddition takes place to give the head-to-tail ratio observed.*

2.2.2. Functionalisation of α-halo cyclobutanes

Initial studies into these cycloadducts involved metal insertion to the C–Br bond. The first attempt employed nickel chemistry to insert into the C–Br bond of **304** (Scheme **49a**).[120] The nickel (II) complex formed would be able to undergo reductive elimination with the benzoic ketone to give **311**. However, only dehalogenated product **312** was recovered. Another attempt was made with nickel-photoredox dual catalysis, taken from previous success of work by MacMillan *et al.* (Scheme **49b**).[92] However, only dehalogenated product **312** was formed. The α-bromosuccinimide **304** was also a good target for Reformatsky-style chemistry (Scheme **49c**).[121] The zinc enolate **315** formed would act as a high energy nucleophile due to the ring strain from the internal alkene formed. However, no reaction was observed possibly due to the high steric strain of forming the zinc enolate. Palladium insertion into the C–Br bond of **304** would allow access to a range of palladium reactions (Scheme **49d**). To test this, a Suzuki cross-coupling of phenyl boronic acid with cyclobutane **304** was trialled, however no reaction was observed with only starting materials recovered.

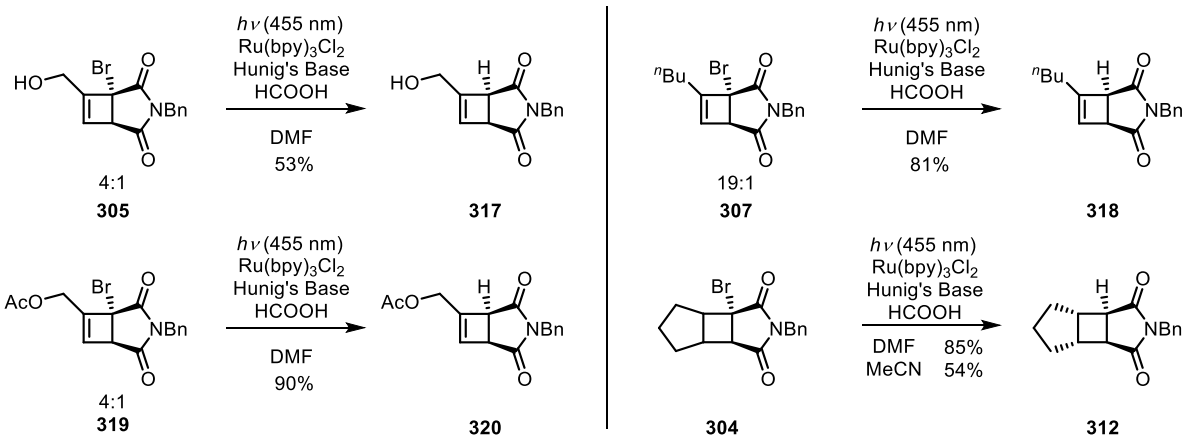
Experimental evidence so far suggests that transition metal chemistry is not a viable pathway into implementing functionality into this position. The tertiary carbon centre may be too difficult to access using transition metals and therefore an alternative method is needed.



Scheme 49 *- Metal insertion reactions.* ***a)*** *Nickel carboxylic acid coupling.* ***b)*** *Nickel-photoredox dual catalysis alkyl radical coupling.* ***c)*** *Zinc mediated Reformatsky functionalisation.* ***d)*** *Palladium catalysed Suzuki coupling.*

2.2.3. Photocatalysed dehalogenation chemistry

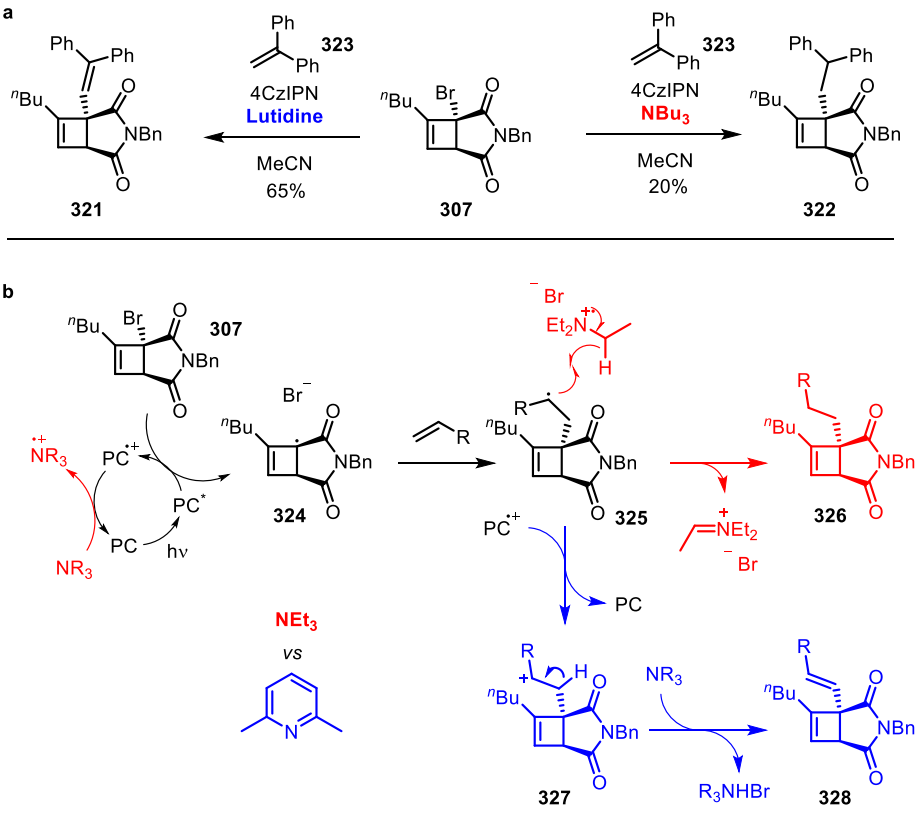
The α-bromo cyclobutanes **304** – **308** were taken forward and subject to Stephenson's conditions for reductive dehalogenation.[82] Each compound successfully underwent photoredox catalysed dehalogenation reactions (Scheme **50**). It was observed that the free alcohol **305** did not tolerate the reaction conditions as well as the protected alcohol **319**. The next step from this position is the trapping of the radical formed with an alkene. Stephenson *et al.* have shown promising work with coupling bromomalonate esters to indoles and other electron rich alkenes.[122,123] It was envisaged that this process would fit well with the compounds synthesised. However, it became apparent that electron rich aromatic compounds and other non-aromatic electron rich alkenes were not suitable radical acceptors for the radical generated, leaving only the protodehalogenated compounds.



Scheme 50 *- Substrates were subject to Stephenson's hydrodehalogenative conditions.*

2.2.4. Radical coupling

The use of lutidine instead of tributylamine gave the unsaturated adduct **321** with an improved yield and no dehalogenation by-products (Scheme **51a**). This is due to the lack of an *α*-hydrogen to the nitrogen in lutidine, forcing the reaction to proceed *via* a secondary mechanism (Scheme **51b**).



Scheme 51 *- **a)** Different saturation of products observed when different bases were used. **b)** Proposed mechanism for the synthesis of the observed products.*

Interestingly, the reaction does not proceed when styrene was used as the radical acceptor. This may be due to the stability of the radical formed after radical coupling, or due to polymerisation under

reaction conditions. The applicability of activated alkenes was investigated by a range of α-phenyl alkenes and other activated alkenes (Figure **8**). The more electron poor alkenes had success with radical couplings (Figure **9**). The conditions with lutidine showed higher yielding results, however it could not be employed to non-redox neutral reaction conditions, such as with ethyl acrylate to give **344**. Interestingly, silyl enol ether gave ketone **342** in good yield, applying the same conditions with an endocyclic alkene **336** did not give any product, possibly due to steric strain. Generally, conditions with an α-amino hydrogen atom source gave the lowest yields.

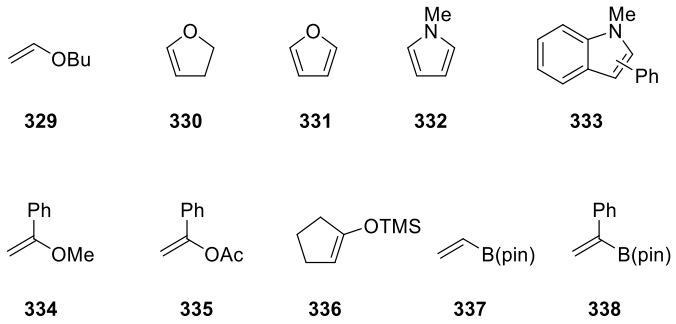


Figure 8 *- α-Phenyl- and other stabilised alkenes screened for trapping the formed alkyl radical.*

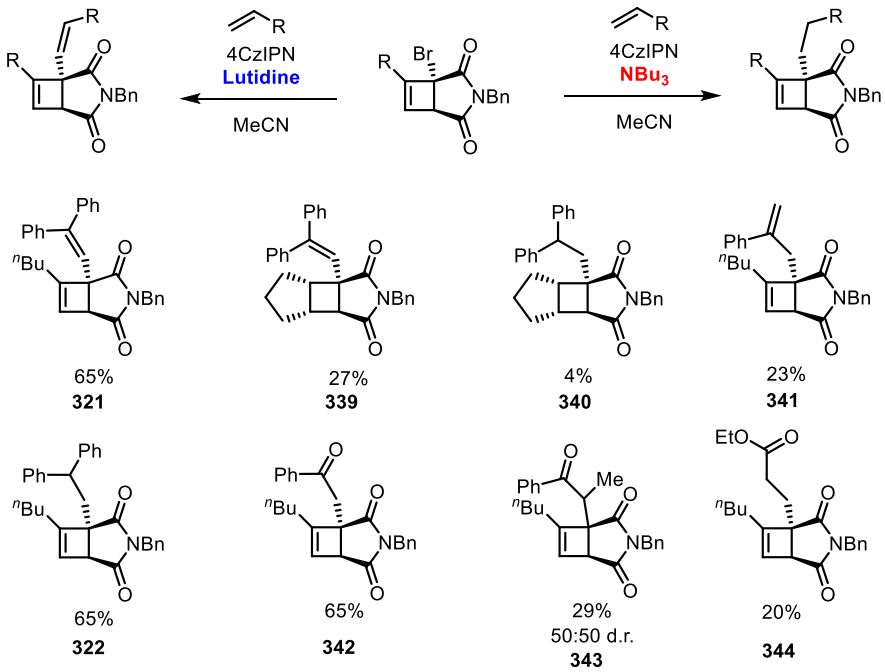


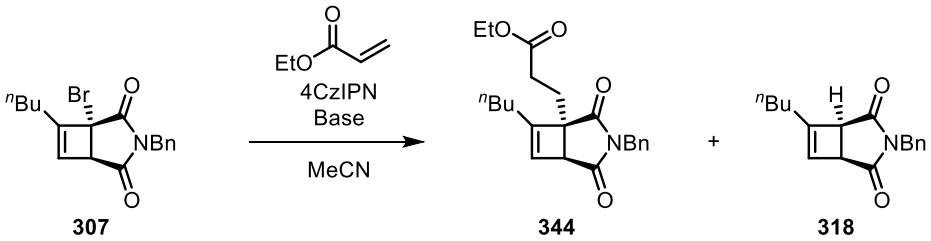
Figure 9 *- Scope of dehalogenation and radical coupling.*

Focus was placed on electron neutral and electron poor alkenes as a target for radical coupling. Electron poor alkenes have reacted previously with **307** to give **344** (Figure **9**). The electron poor radical acceptor chosen was ethyl acrylate. Ethyl acrylate gave some promising early results, however, for this reaction to proceed a HAT agent is required, and so a competing side product of this reaction

was the hydrodehalogenation product **318**. A series of optimisations were carried out to achieve the best conditions for radical addition to electron poor alkenes.

Initial studies focussed on the best equivalents to use to lower protodehalogenation products, but in all cases, undesired dehalogenation product **318** was observed (Table **4**). Furthermore, a range of amine bases were tested, and it was found that DBU gave a significant increase in yield with low protodehalogenation products (Entry 8).

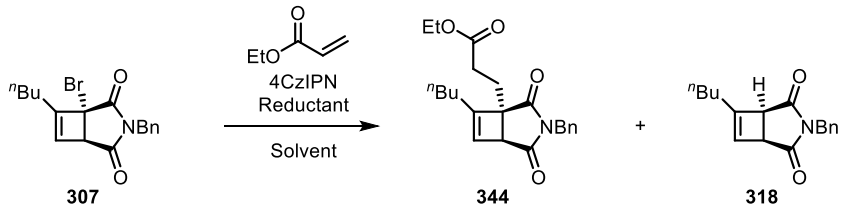
Table 4 *- Screening amine sources for the optimisation of radical coupling to electron poor alkenes.*



Entry	Base	(eq)	Time (h)	344 (% Yield)	318 (% Yield)	307 (% Yield)
1	Tributylamine	1.2	3	20 (isolated)	2	0
2	Tributylamine	1	6	4	1	5
3	Tributylamine	0	6	0	0	-
4	Triethylamine	1.2	6	8	0	5
5	DIPEA	1.2	4	23	4	0
6	NEt_2Ph	1.2	6	0	0	65
7	DABCO	1.2	6	0	0	8
8	**DBU**	**1.2**	**6**	**42**	**5**	**0**

Taking DBU forward as the amine, other conditions such as concentration, solvent composition and equivalents of radical acceptor gave lower yields (Table **5**, Entries 1 – 5).

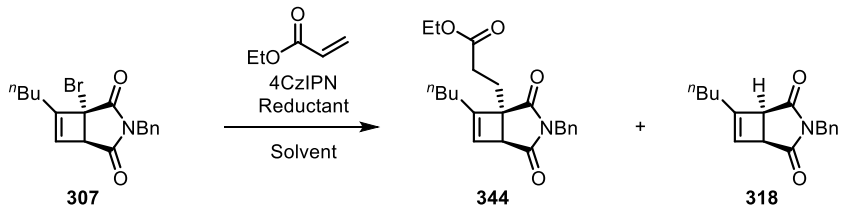
Table 5 *- Screening conditions for the optimisation of radical coupling to electron poor alkenes.*



Entry	Reductant	(eq)	Conc. (M)	Solvent	344 (% Yield)	318 (% Yield)	307 (% Yield)	Time (h)
1	DBU	1.1	0.1	MeCN	24	5	0	6
2	DBU	1.2	0.2	MeCN	40	5	0	4
3	DBU	1.2	0.05	MeCN	25	5	0	6
4	DBU	1.2	0.1	CH_2Cl_2	25	6	5	6
5	DBU	1.2	0.1	MeCN/MeOH 4/3	6	0	0	2

α-Hydroxy carboxylic acids (AHCA) such as ascorbic acid have been reported to undergo two electron oxidation processes.[122] This process can be exploited in SET dehalogenation chemistry, as one electron reduces the catalyst and the second can reduce the radical formed on the product. This process eliminates the need for a HAT, nullifying the need of an amine base and therefore, preventing hydrodehalogenation products. However, only mandelic acid and ascorbic acid gave products and the yield was low in both cases (Table **6**). Due to low recovery of mass and low productivity of the reaction conditions, the use of AHCA were not further investigated.

Table 6 *- AHCA screening for the radical coupling to electron poor alkenes.*

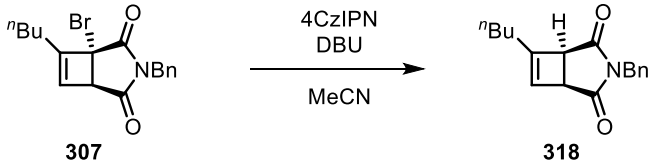


Entry	Reductant	(eq)	Base	344 (% Yield)	318 (% Yield)	307 (% Yield)	Time (h)
1	Ascorbic Acid	2	K_2HPO_4	0	0	49	5
2	Tartaric Acid	2	K_2HPO_4	0	0	8	5
3	Lactic Acid	2	K_2HPO_4	0	0	35	5
4	Mandelic Acid	2	K_2HPO_4	29	0	0	5

2.2.5. Degradation studies

Studies into the low mass balance due to possible degradation of the starting material **307** were performed to elucidate the conditions responsible (Table **7**). The results show that the main factor in the degradation of the starting material **307** was the effect of the base (Entries 1 – 3). This may be possibly due to hydrolysis of the succinimide ring in the presence of trace amounts of water. Other factors effecting the rate of degradation is the presence of the catalyst in exposure to light, enabling SET processes (Entries 4 – 7). The consequence of these conditions was the further degradation of the starting material with a small amount of the protodehalogenated product **318** being formed. A higher recovery of starting material **307** and a lower overall degradation was found in the "wet" solvent conditions (Entries 5 and 7), suggesting that water negatively effects the rate of reductive dehalogenation, but impedes degradation from the activated photocatalyst.

Table 7 *- Studies into the effect of conditions on the degradation of substrate.*



307 **318**

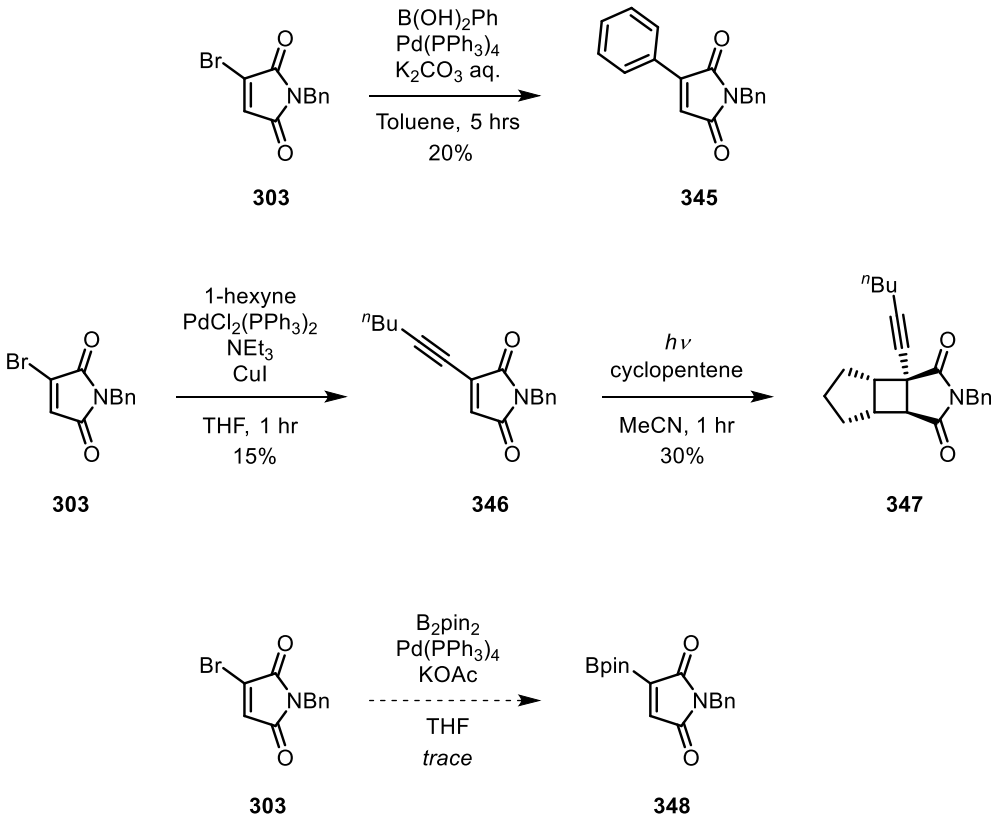
Entry	Solvent	Catalyst	Conditions	Time (h)	N_2 /Flame dried glassware	307 (% Yield)	318 (% Yield)
1	Dry	No	Dark	14	No	42	0
2	Wet	No	Dark	14	No	42	0
3	Dry	Yes	Dark	14	No	43	0
4	Dry	Yes	Light	14	No	11	7
5	Wet	Yes	Light	14	No	26	1
6	Dry	Yes	Light	14	Yes	0	15
7	Wet	Yes	Light	14	Yes	30	0

2.2.6. Palladium catalysed Miyaura coupling

In the pursuit of an alternative way to produce modular functionalisation to cyclobutane scaffolds, the functionalisation of the bromo-maleimide **303** directly was undertaken. By using Miyaura conditions a range of palladium cross-coupling reactions may be available. Previous work has shown that Miyaura–Suzuki and Sonogashira couplings are accessible.[124,125] These maleimide derivatives may then be utilised in [2+2] photocycloadditions to access functionalised cyclobutanes.

Initial work into Sonogashria and Suzuki cross-coupling of the bromo maleimide **303** gave products **345** and **346** in low yield (Scheme **52**). This may be due to the presence of base and trace amounts of

water in the reaction causing ring opening of the maleimide, or by the quality of the palladium source used. The Sonogashira product was taken forward for photocycloaddition with cyclopentene and gave the cycloadduct **347** in low yields. These steps require optimisation to be used as a viable method of synthesising maleimide derivatives.

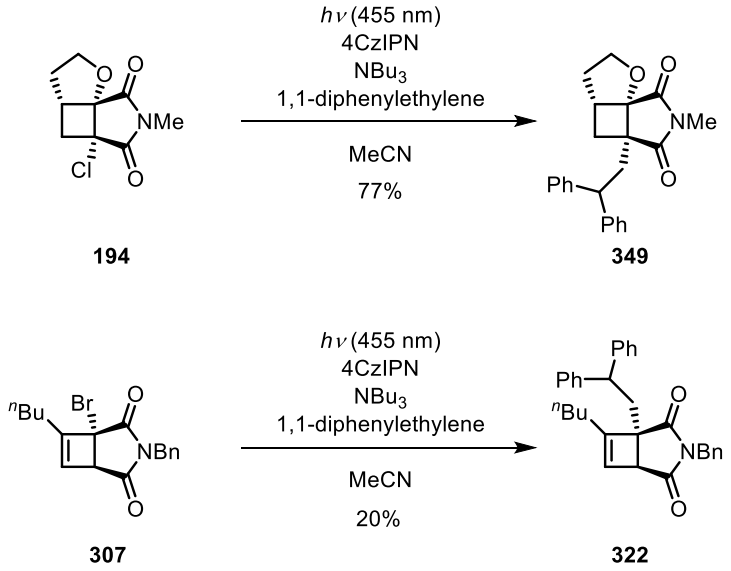


Scheme 52 *- Palladium catalysed Miyaura coupling and photocycloadditions.*

A Miyaura–borylation of bromo-maleimide **303** was attempted to produce the boronated maleimide derivative **348**. However, due to protodeboronation, the compound could not be purified.[126] Trace signals were observed in the ^{1}H NMR spectrum of the crude product. Finding an alternative method to achieve borylation would provide an excellent handle for further functionalisation of the cyclobutane ring.

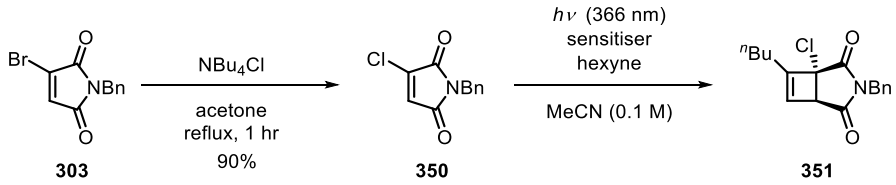
2.3. Synthesis of *α*-chloro analogue and functionalisation

Another approach was taken into the functionalisation *via* reductive dehalogenation by using the *α*-chlorosuccinimide derivative **194**. The *α*-chloro analogue showed some promise in the addition to 1,1-diphenylethylene, giving a higher yield with no dehalogenation products than its *α*-bromo counterpart (Scheme **53**).



Scheme 53 *- Modular functionalisation of α-halosuccinimides.*

Initial steps were taken to synthesise a direct analogue of the *α*-bromo succinimide **307**. This was accomplished by treating the synthesised bromo maleimide **303** with ammonium tetra-*n*-butyl chloride. This gave the chloro-maleimide **350** in 90% yield, however, upon concentration *in-vacuo* after column chromatography, the chloro-maleimide polymerised. This suggests that the more electronegative substituent on the maleimide ring made it more susceptible to Michael addition and subsequent polymerisation in the presence of a nucleophile such as water. A solution to this was taking the crude chloro-maleimide through the [2+2] photocycloaddition step without any further purification (Scheme **54**).

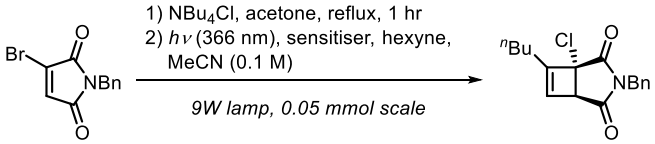


Scheme 54 *– Synthesis of chloromaleimide **350**.*

2.3.1. Optimisation of [2+2] photocycloaddition

Initial studies into the synthesis of chloro-cyclobutenes gave good yields of the [2+2] cycloadduct, but low productivity (Table **8**, Entry 1).

Table 8 *- [2+2] Photocycloaddition optimisations.*

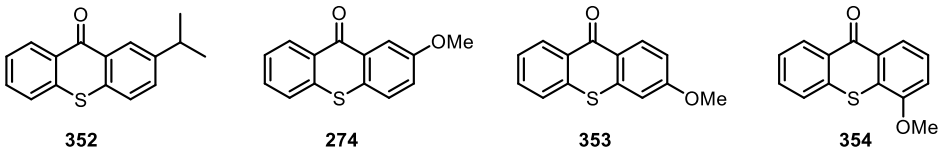


303 **351**

Entry	Sensitiser (mol %)	E_T (J/mol)	**Time** (hr)	**Conversion** (%)	**351** (% Yield)
1*	-	-	20	100	75
2	-	-	2.5	8	-
3	ITX (5)	266	2.5	100	-
4	2-OMe ITX (5)	242	2.5	0	-
5	3-OMe ITX (5)	284	2.5	100	-
6	4-OMe ITX (5)	267	2.5	100	-
7	3-OMe ITX (5)	284	1	100	-
8	3-OMe ITX (3)	284	1	100	-
9	3-OMe ITX (1)	284	1	100	-
10*	3-OMe ITX (1)	284	1.5	100	74

Yields calculated by NMR using trimethoxybenzene as an internal standard
**Conditions performed with a 125W lamp at 15 mmol scale.*

Photosensitisers have strong chromaphores and therefore are very efficient at absorbing light. This property is used in efficiently accessing the triplet energy in a photosensitiser, so that an energy transfer can take place and excite the desired substrate to a triplet state. Conditions of several different photosensitisers were screened (Entry 2 – 9) to determine the best triplet energy required and the best loading of the sensitiser (Figure **10**).

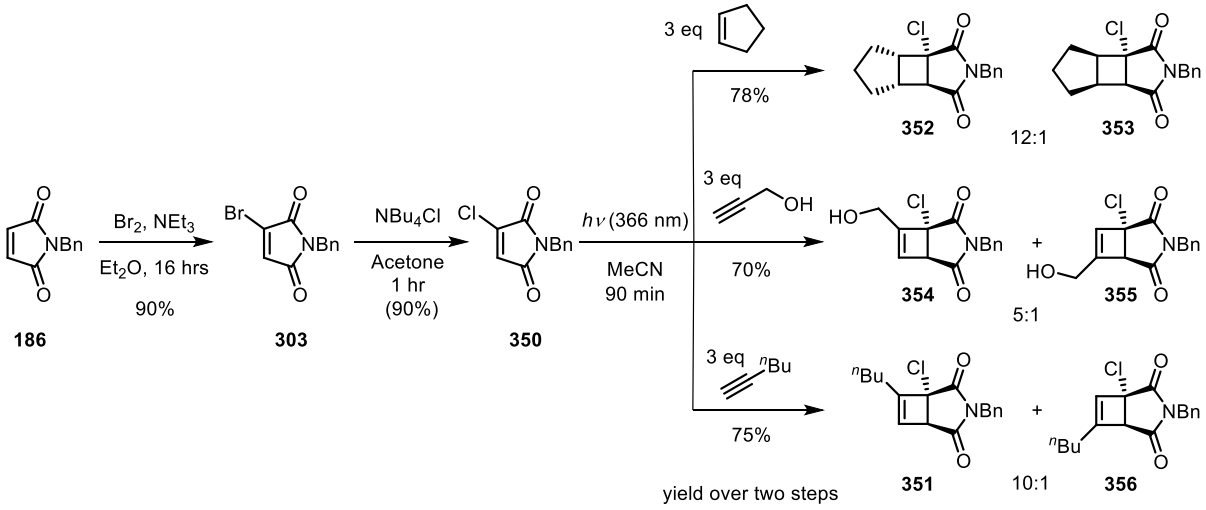


352 *iTX* | **274** *2-OMe TX* | **353** *3-OMe TX* | **354** *4-OMe TX*

Figure 10 *– Thioxanthones tested for triplet energy transfer.*

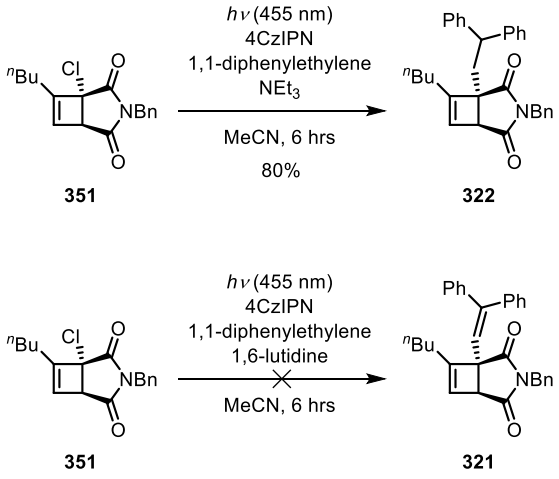
It was found that both 3-OMe TX **353** and *i*TX **352** were good candidates for energy transfer to maleimide **350** low sensitiser loading, giving full conversion in just 90 mins compared to 20 hrs of direct irradiation. Using these conditions, large scale production (23 mmol/hr) of **351** can be achieved.

The [2+2] photocycloaddition was a success and gave higher overall yields than the bromo-maleimide counterparts (Scheme **55**). This may be due to the higher bond dissociation energy (BDE) of the C–Cl bond over the C–Br bond.



Scheme 55 *- Synthetic route to α-chloro succinimide cycloadducts.*

The *α*-chloro succinimide cycloadduct was then subject to photoredox conditions to find that a significant improvement to the yield of **322** was achieved compared to its *α*-bromo succinimide analogue (Scheme **56**). These results suggest that due to a higher energy required to break the C–Cl bond, a lower amount of degradation is observed along with a lower production of the hydrodehalogenation product. Another point of interest is the reaction when lutidine is used as a non-H-atom abstracting amine base no longer gave any radical addition product.



Scheme 56 *- α-Chloro succinimide subject to photoredox conditions.*

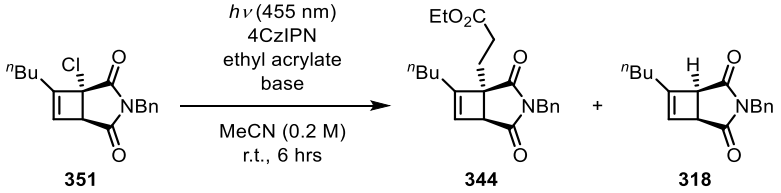
This may be due to the higher energy required to dehalogenate the C–Cl bond, meaning the photocatalyst would have to provide SET through a different mechanism, no longer allowing direct reduction of **351** with the neutral excited state photocatalyst. If SER of the photocatalyst is required

first, then lutidine cannot be applied to this mechanism. Further mechanistic studies will be required to fully understand the underlying reason for the lower rate of dehalogenation.

2.3.2. 3-Chloro-succinimide subjected to photoredox conditions

Initial screening of visible-light photocatalysed dehalogenation of the chloro-cyclobutene analogue **351** with ethyl acrylate as the radical acceptor was performed (Table **9**). A range of sacrificial reductants were tested using optimised conditions from the bromo-cyclobutene analogue **307** (Table **9**, Entries 1 – 6). Triethylamine as the amine base was shown to give the highest mass balance with the lowest dehalogenation side products (Entry 4). Triethylamine was then trialled with a range of different equivalents of ethyl acrylate and starting material to determine which would be the best limiting reagent (Entries 7 – 9). It was found that the original conditions of high equivalents of radical acceptor and using cyclobutene **351** as the limiting reagent gave the best yields.

Table 9 *- Reductant screen for photoredox conditions.*

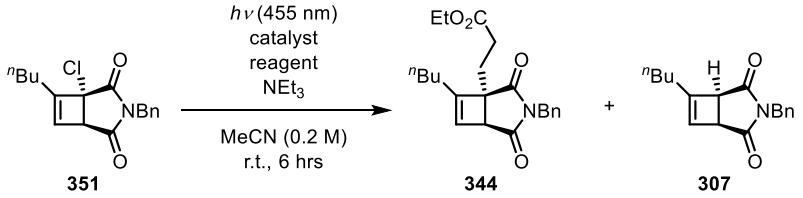


Entry	Reductant (eq)	Ethyl **acrylate** (eq)	351 (eq)	351 (% Yield)	344 (% Yield)	318 (% Yield)
1	DBU (1.2)	3	1	0	0	15
2	NBu_3 (1.5)	3	1	0	24	12
3	DIPEA (2.0)	3	1	48	19	2
4	NEt_3 (2.0)	3	1	34	29	4
5	NaAsc (2.0)	3	1	64	0	0
6	mandelic acid (2.0) K_2HPO_4 (2.0)	3	1	58	0	0
7	NEt_3 (2.0)	1	3	40	20	0
8	NEt_3 (2.0)	1	1.2	0	20	20
9	NEt_3 (2.0)	1.2	1	0	19	16

Yields calculated by NMR using trimethoxybenzene as an internal standard.

A range of photocatalysts with varying reduction and oxidation potentials were screened using the optimised conditions (Table **10**, Entries 1 – 3). Unfortunately, no improvements in yield were observed. Interestingly, although more reducing than its counterpart, the dicyanobenzene derivative 3DPAFIPN gave much lower yields than 4CzIPN (Entry 2 + 5).

Table 10 *- Catalyst screen for the dehalogenation of cyclobutene* ***351****.*



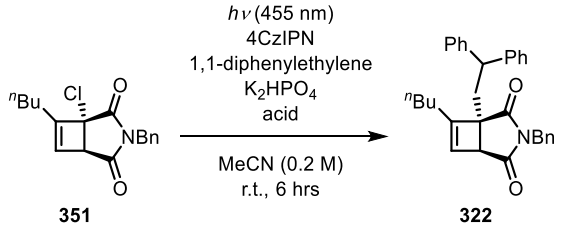
Entry	Catalyst	Reagent	**351** (% Yield)	**344** (% Yield)	**307** (% Yield)
1	Catalyst †	ethyl acrylate	40	0	0
2	3DPAFIPN	ethyl acrylate	2	1	8
3	$Ru(bpz)PF_6$	ethyl acrylate	64	0	0
4	4CzIPN	1,1-diphenylethylene	0	80	0
5	3DPAFIPN	1,1-diphenylethylene	0	54	0

Yields calculated by NMR using trimethoxybenzene as an internal standard
† 5,10-Di(4-methoxyphenyl)-5,10-dihydrophenazine

The optimised conditions for 1,1-diphenylethylene were also tested with a more reducing analogue of 4CzIPN, 3DPAFIPN, to determine if a stronger reduction potential would enhance the reaction (Table **9**, Entries 4 – 5).[127] It was observed that the more strongly reducing catalyst gave only good yields of the 1,1-diphenylethylene adduct **322**.

A range of AHCAs as sacrificial reductants capable of performing two reductive SET were screened to determine if milder acid/base reductant conditions could be utilised to prevent loss of product mass (Table **11**). Although the total mass of the reaction improved, the yields were not nearly high enough to take the reaction conditions forward for consideration.

Table 11 *– Trialling 2-electron reductants.*



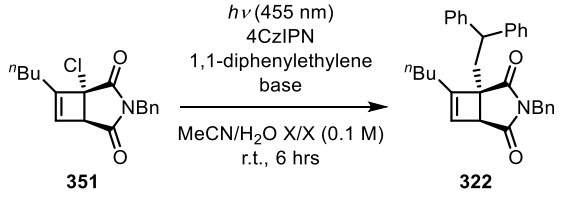
Entry	**Reductant** (2 eq)	**351** (% Yield)	**322** (% Yield)
1	Ascorbic acid	69	4
2	Tartaric acid	69	-
3	Lactic acid	63	2
4	Mandelic acid	59	6
5	NaAsc	85	2
6*	NaAsc	58	10

Yields calculated by NMR using trimethoxybenzene as an internal standard
**methanol as solvent*

2.3.3. Utilising water as solvent

From degradation studies summarised previously in Table **7,** it was hypothesised that the addition of water could potentially suppress hydrodehalogenation by-product **318** while maintaining the yield of the desired radical adduct.[128,129] Initial studies were performed using 1,1-diphenyl ethylene to determine how much the presence of water would affect the yield of the reaction (Table **12**).

Table 12 *- The effect of water in visible-light photoredox conditions.*



Entry	**Solvent** (X/X)	**Base** (2 eq)	**351** (% Yield)	**322** (% Yield)
1	MeCN	NEt_3	0	80
2	MeCN/H_2O (9/1)	NEt_3	14	47
3	MeCN/H_2O (1/1)	NEt_3	0	61
4	H_2O	NEt_3	8	34
5	MeCN/H_2O (1/1)	DIPEA	0	55
6	MeCN/H_2O (1/1)	NBu_3	0	72
7	MeOH/H_2O (1/1)	NEt_3	0	56

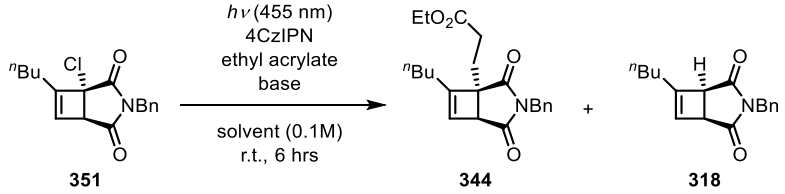
Yields calculated by NMR using trimethoxybenzene as an internal standard.

It was observed that a 1/1 ratio of acetonitrile to water gave the best conversion to **322** (Entry 3). It was also observed that the reaction could be performed in water as the exclusive solvent (Entry 4),

despite most reagents being insoluble in water. A screen of amines was run to determine if changing the tertiary amine would improve product yields (Entries 5 – 7), in which tributylamine gave the highest yields (72%, Entry 6).

The optimised conditions were taken forward and utilised in the addition of the slower radical accepter, ethyl acrylate (Table **13**). A comparison between tributylamine and triethylamine as bases in both aqueous and dry conditions showed that triethylamine was the best reductant of choice (Entry 1 – 4). The effect of "hydrophilicity" of the aqueous phase was determined by addition of TBAC into the reaction to act as a phase transfer catalyst (Entry 5). The converse of this was also test by the addition of brine instead of water to reduce the "lipophilicity" of the aqueous phase (Entry 6). Both these conditions showed that deionised water gave the best yields. The equivalents of base were also trialled to determine if lowering the loading of base would lower the competitive rate of formation of **318** (Entries 7 – 8). It was found that 1.2 equivalents of base gave the lowest yields of **318** (Entry 8). Further study showed that the effect of water was not due to the increase in concentration of the organic solvent (Entries 9 – 10). Scale up of entry 8 gave the highest yield of **344** with a low production of **318**.

Table 13 *- Effect of water on hydrodehalogenation and base optimisation.*

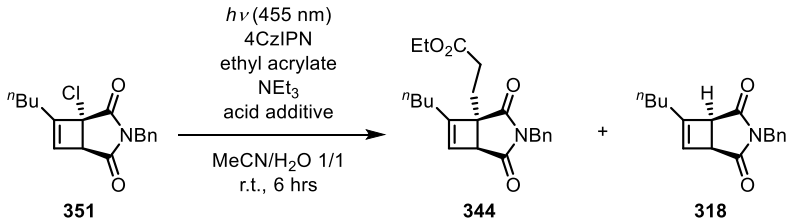


Entry	**Solvent** (X/X)	**Base** (eq)	**351** (% Yield)	**344** (% Yield)	**318** (% Yield)	**Ratio: 344/318**
1	MeCN	NEt_3 (2.0 eq)	34	29	7	4.1
2	MeCN	NBu_3 (2.0 eq)	0	24	12	2.0
3	MeCN/H_2O (1/1)	NEt_3 (2.0 eq)	0	40	6	6.7
4	MeCN/H_2O (1/1)	NBu_3 (2.0 eq)	0	2	1	2.0
5[a]	MeCN/H_2O (1/1)	NEt_3 (2.0 eq)	0	31	6	5.2
6[b]	MeCN/H_2O (1/1)	NEt_3 (2.0 eq)	0	36	9	4.0
7	MeCN/H_2O (1/1)	NEt_3 (1.5 eq)	4	35	4	8.8
8	MeCN/H_2O (1/1)	NEt_3 (1.2 eq)	16	33	3	11.0
9[c]	MeCN	NEt_3 (2.0 eq)	22	25	5	5.0
10[d]	MeCN	NEt_3 (2.0 eq)	17	5	6	0.8
11[e]	MeCN/H_2O (1/1)	NEt_3 (1.2 eq)	11	51	4	12.8

Yields calculated by NMR using trimethoxybenzene as an internal standard
[a] 1 eq TBAC added as additive
[b] Brine used as aqueous solvent in place of water
[c] 0.2 M concentration
[d] 0.3 M concentration
[e] 10 x scale up (1.6 mmol)

Further optimisations were tested involving concentration variation and inclusion of an acid additive (Table **14**). It was found that 0.3 M concentration gave a slight improvement on the yield of ester **344** (Entry 1 – 5). A range of acids were screened as additives to determine if the addition of an acid as a buffer may prevent starting material/product degradation under basic conditions. The best yield was found to be with 1.2 equivalents of formic acid to give 51% of the desired product **344**. Increasing the amount of acid equivalents seemed to stop the reaction, which may be due to high coordination to the amine lone pair and preventing initial reduction of the photocatalyst in the excited state. However, this reaction was not reproducible after several repeats and so was not taken forward.

Table 14 *- Trialling concentration and additives for dehalogenative radical addition.*



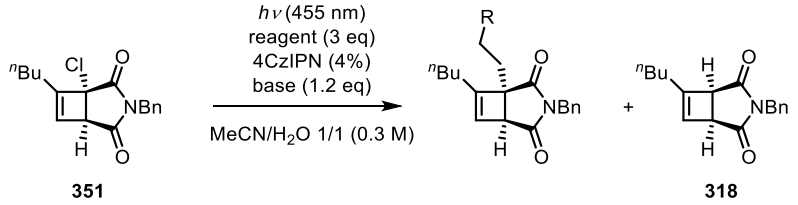
Entry	**Concentration** (M)	**Acid** (eq)	**351** (% Yield)	**344** (% Yield)	**318** (% Yield)
1	0.10	-	16	33	3
2	0.15	-	23	31	2
3	0.25	-	26	29	2
4	0.30	-	7	43	3
5	0.50	-	25	25	3
6	0.30	HCOOH (0.5)	21	23	0
7	0.30	HCOOH (1.0)	28	23	0
8	0.30	HCOOH (1.2)	0	51	4
9	0.30	HCOOH (2.0)	51	0	0
10	0.30	HCOOH (3.0)	50	0	0
11	0.30	Ascorbic (1.2)	28	15	0
12	0.30	Ascorbic (1.0)	43	13	0
13	0.30	Ascorbic (0.5)	23	27	0
14	0.30	Ascorbic (0.1)	17	36	4

Yields calculated by NMR using trimethoxybenzene as an internal standard.

2.3.4. Exploring scope

The optimised conditions identified in Table **14** were taken forward and tested against methyl vinyl ketone (MVK) and *α*-methyl styrene (Table **15**). Unfortunately, the product yields were very low despite altering the conditions with different bases.

Table 15 *- Trialling different alkenes and amines.*



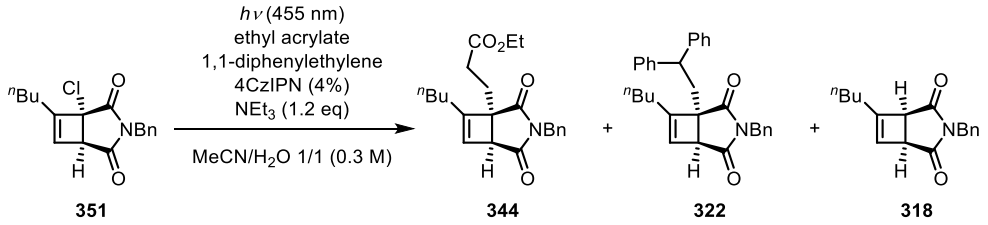
Entry	Reagent	Base	**351** (% Yield)	**Product** (% Yield)	**318** (% Yield)
1	ethyl acrylate	NEt_3	0	40	6
2	ethyl acrylate	NBu_3	0	30	14
3	MVK	NEt_3	4	13	4
4	MVK	NBu_3	0	18	17
5	α-Me styrene	NEt_3	0	7	2
6	α-Me styrene	NBu_3	0	5	2

Yields calculated by NMR using trimethoxybenzene as an internal standard.

2.3.5. Studying the reaction rate on effect of yield

A competitive study was undertaken to determine if faster kinetics correlated with yield (Table **16**). Different equivalent ratios of ethyl acrylate *vs* 1,1-diphenylethylene were used in the dehalogenation reaction conditions. It was found that 1,1-diphenylethylene gave a higher yielding adduct in all cases, demonstrating the relationship of higher rate of reaction correlating to the product yield. This hypothesis explains why sterically hindered or electronically mismatched alkenes may give poor yields, due to unwanted radical processes becoming competitive factors at slower reaction rates.

Table 16 *- Competition study between 1,1-diphenylethylene and ethyl acrylate.*

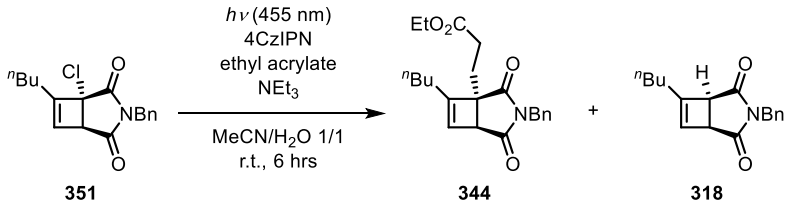


Entry	**Acrylate** (eq)	**Diphenyl** (eq)	**351** (% Yield)	**344** (% Yield)	**322** (% Yield)	**318** (% Yield)
1	3	3	0	0	45	0
2	3	2	19	6	33	0
3	3	1	9	17	26	7

Yields calculated by NMR using trimethoxybenzene as an internal standard.

It was hypothesised that the acrylate used may be polymerising under the reaction conditions and lowering the rate of reaction through that pathway. Ethyl acrylate was therefore added portion-wise to the reaction (Table **17**). Unfortunately, the yields of **344** did not improve despite the increased equivalents and portion-wise addition. This suggests that the acrylate does not, in fact, polymerise over the course of the reaction.

Table 17 *- Portion-wise addition of reagent to reduce the amount of protodehalogenated product* ***318****.*



Entry	Addition eq 0hrs	2 hrs	4hrs	**351** (% Yield)	**344** (% Yield)	**318** (% Yield)
1	3	1	1	31	28	1
2	2	1	1	12	37	3
3	1	1	1	14	21	5
4	0.5	0.5	0.5	9	12	4

Yields calculated by NMR using trimethoxybenzene as an internal standard

To gain further insight into the reaction, the reaction was run at 6 different time intervals to determine at what point starting material **351** was degrading (Figure **11**). It was observed that within the first hour 75% of cyclobutene **351** was converted but only 28% of ester **344** was formed, indicating that nearly 50% of starting material **351** undergoes degradation in the first hour of the reaction. For the remaining 5 hours, the reaction appeared to undergo low conversion to the product. This suggests that cyclobutene **351** was degrading in the first hour of the reaction but appears to convert in high efficiency to ester **344** in the remaining 5 hours.

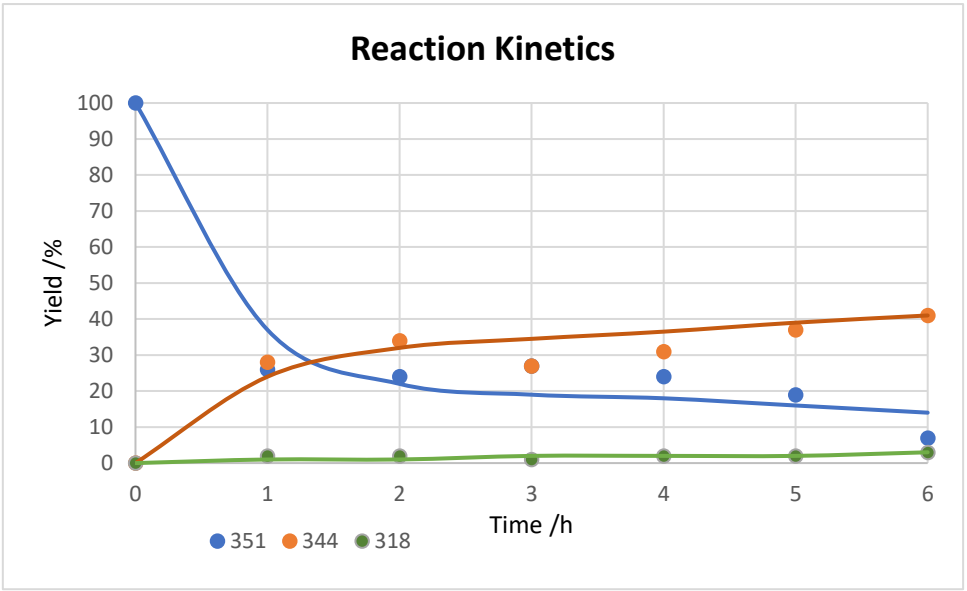
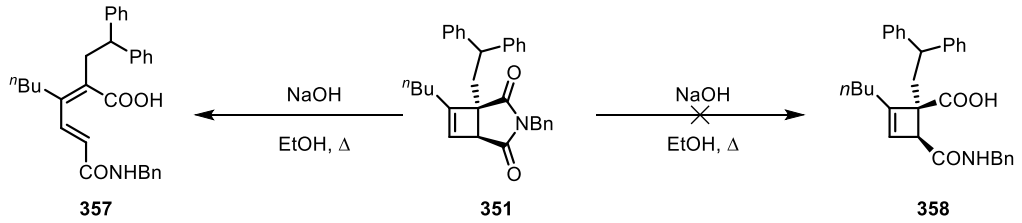


Figure 11 *- Graph representing the yield of starting material, product and dehalogenated product over time. Yields calculated by NMR using trimethoxybenzene as an internal standard.*

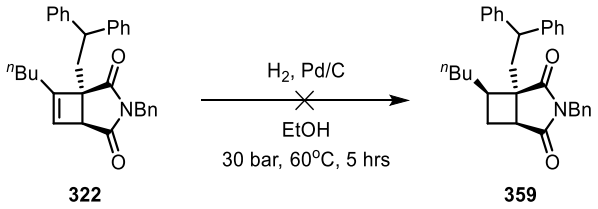
2.3.6. Ring opening of functionalised succinimide and hydrogenation

To further functionalise the cyclobutene ring, **322** was subjected to hydrolytic conditions. Hydrolysis of the functionalised cyclobutene gave an undesired product **357** (Scheme **57**). This is due to the high strain imposed upon the cyclobutene ring. Under thermal conditions, ring opening of the succinimide can lead to a fragmentation of the 4-membered ring to form a diene. This feature of the cyclobutene ring suggests that hydrolysis of succinimide **322** to cyclobutene **358** may not be possible. Therefore, the saturated cyclobutane ring will need to be obtained.



Scheme 57 *- Hydrolysis of functionalised cyclobutene.*

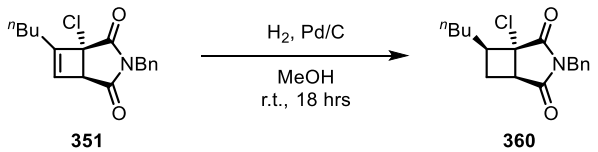
Several conditions were run to hydrogenate the cyclobutene ring of **322**. However, even at 30 bar pressure and 60°C, no reaction occurred (Scheme **58**). This may be due to the large steric bulk of the diphenyl group and the succinimide ring on both sides of the cyclobutene ring, blocking coordination to the palladium surface.



Scheme 58 *- Attempted hydrogenation of functionalised cyclobutene product.*

Hydrogenation would, therefore, need to occur on the chloro-cyclobutene analogue **351**. A range of catalyst loadings showed that at room temperature, the Pd/C w/w loading could be as low as 5% and still achieve near quantitative yields of **360** and absolute diastereoselectivity (Table **18**).

Table 18 *- Hydrogenation of chloro-cyclobutene.*

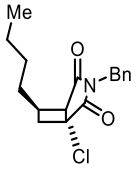


Entry	**Pd** %w/w	**Conversion** (%)	**360** (% yield)
1	20	100	-
2	10	100	-

3	5	100	97

Yields calculated by NMR using trimethoxybenzene as an internal standard.

This is due to the succinimide ring blocking the front face of the cyclobutene. *Syn*-addition hydrogenation, therefore, pushes the *n*-butyl chain forward, giving a cup-like shape with the chlorine atom facing backwards (Figure **12**).



360

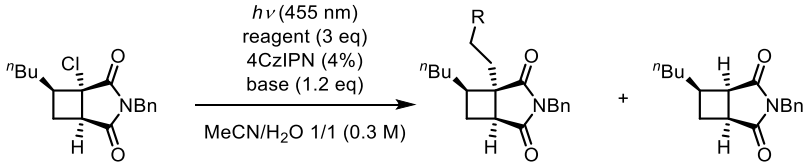
Figure 12 *– Cup-like arrangement of* ***360****.*

This new conformation of cyclobutane **360** removes the steric hindrance from the *n*-butyl chain for radical acceptors to undergo radical addition. The saturated cyclobutane system also provides a higher energy radical due to the lack of a π-allyl system for the radical to be conjugated into, as well as the inability to conjugate into the imide carbonyl as the intermediate formed is highly strained. This highly activated radical, combined with a larger space for radical addition, should in turn, provide a much more ideal reaction centre for photoredox catalysed reactions.

2.4. Chloro-cyclobutane subjected to photoredox conditions

Reactions of **360** with 1,1-diphenylethylene produced excellent yields of the desired styrene adduct **361**. Reactions with ethyl acrylate, however, gave a lower yield of ester **362** with a large amount of hydrodehalogenation product **363** (Table **19**).

Table 19 *- Amine base screen for optimising product yield.*



360 **363**

Entry	Reagent (eq)	Base	**360** (% Yield)	**Product** (% Yield)	**363** (% Yield)
1	1,1-diphenylethylene (2.0)	NEt_3	0	**361** (75)	0
2	ethyl acrylate (2.0)	NEt_3	0	**362** (29)	14
3	ethyl acrylate (3.0)	NEt_3	28	**362** (51)	3
4	ethyl acrylate (2.0)	NBu_3	0	**362** (52)	18
5	ethyl acrylate (3.0)	NBu_3	0	**362** (36)	30
6	ethyl acrylate (3.0)	DIPEA	0	**362** (64)	0
7*	ethyl acrylate (3.0)	DIPEA	0	**362** (72)	0

Yields calculated by NMR using trimethoxybenzene as an internal standard.
**Reaction performed on a 0.65 mmol scale, isolated yield shown.*

After increasing the equivalents of acrylate and screening conditions with tributylamine and diisopropylethyl amine, the desired product **362** was obtained in 72% yield and with no hydrodehalogenation products.

2.4.1. Substrate scope

After extensive screening, the optimised conditions were used successfully against a variety of acrylate and styrene derivatives (Figure **13**). Interestingly, pyrrole was successfully used as a radical acceptor (**368**) despite having the opposite alkene electronics of the acrylates. Both electron rich alkene examples (**368** and **369**) gave lower yields than the electron neutral or electron poor examples. The alkyl acrylates gave good yields, with the exception of methyl, benzyl and *t*-butyl acrylate, which gave lower yields, possibly due to steric bulk for the latter two. The low yields observed may also be due to

the presence of radical stabilisers such as hydroquinone which are present in commercially available acrylates.

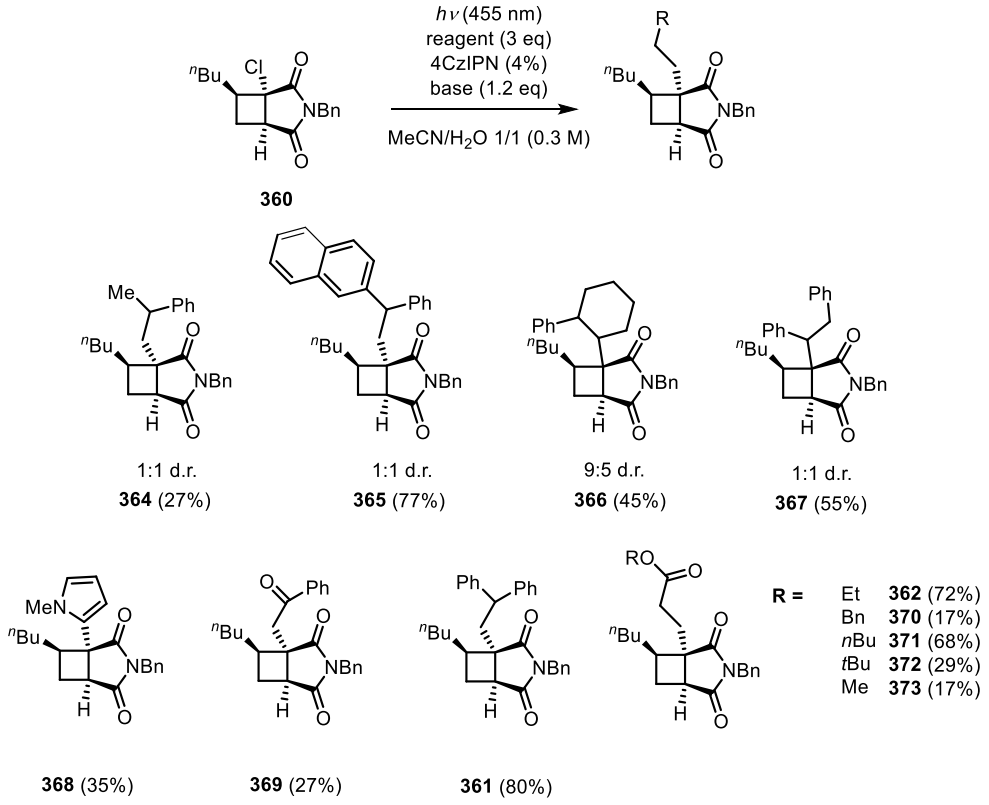


Figure 13 *- Scope of photoredox reaction with chloro-cyclobutane.*

To further broaden the scope of this radical addition, a range of silyl enol ethers were trialled. Silyl groups are able to be hydrolysed in either acid or basic conditions. The effect of silyl group was trialled to determine if a more robust silane would improve the yields of the ketone product **369** (Figure **14**). However, it was found that the reactions either gave very low conversions or low yields of adduct **369**. The possibility of adding a range of silyl enol ethers as activated alkenes was not feasible.

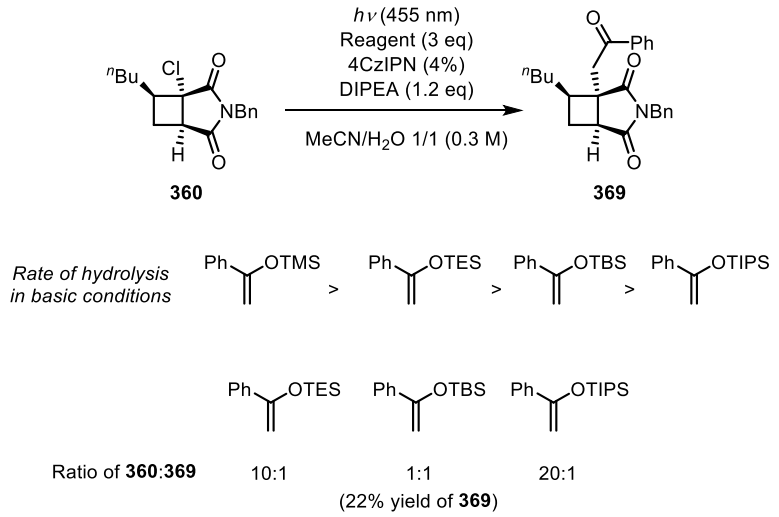
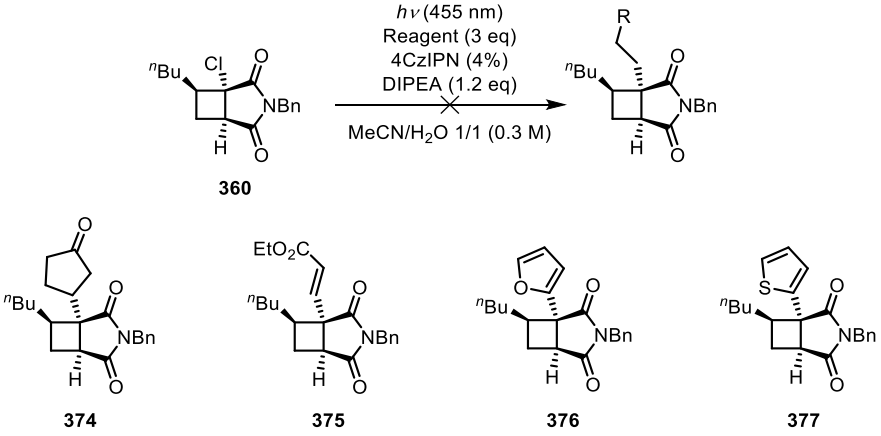


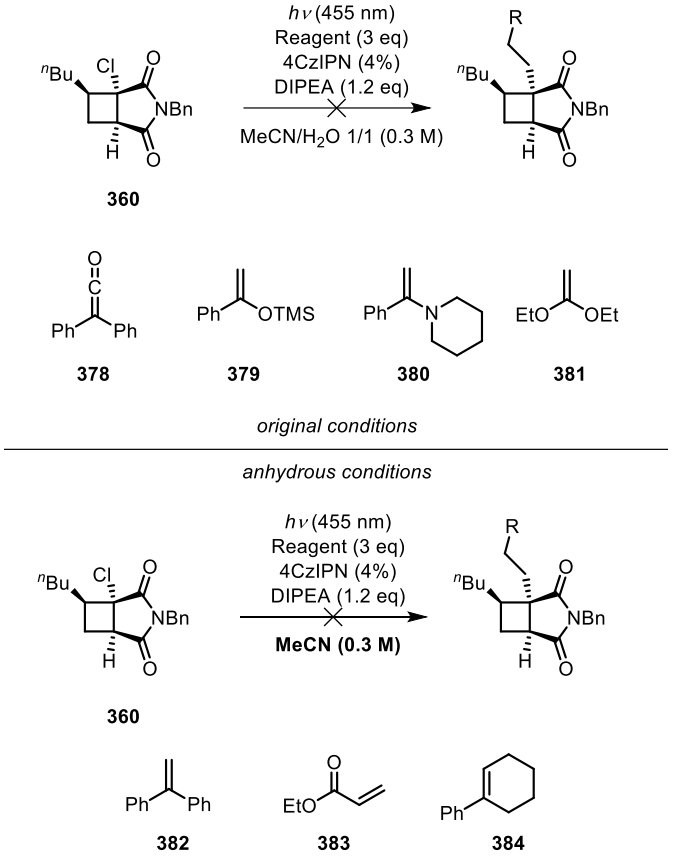
Figure 14 *- Silyl enol ether optimisation. Yields calculated by NMR using trimethoxybenzene as an internal standard.*

Other reagents were found to not proceed in the conditions given (Scheme **59**). This may be due to a range of reasons such as volatility, due to the reaction being run under a positive pressure of nitrogen, or due to the alkene not having the desired electronics to accept a radical.



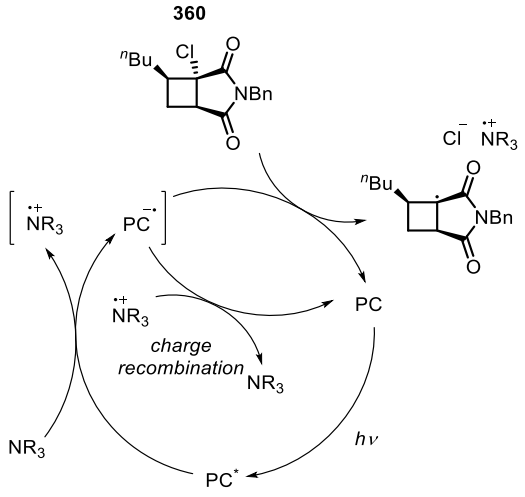
Scheme 59 *- Unsuccessful radical acceptors.*

It is evident that some alkenes do not participate due to their intolerance to water as the solvent, and ability to be readily hydrolysed, such as enamines and ketenes (Scheme **60**). It was hypothesised that running these reactions under dry conditions in acetonitrile only would give the desired products. However, after testing reagents that have worked in the previous aqueous conditions under dry conditions, it was found that none of the reactions proceeded. Only starting material **360** was observed.



Scheme 60 *– Results showing water is essential for the photoredox reaction.*

This observation suggests that water is completely necessary for the reductive dehalogenation step. This could be rationalised by "charge recombination" of the reduced photocatalyst and the oxidised amine (Scheme **61**).[130] If the reductive dehalogenation step is slow due to formation of an activated radical by cleavage on a strong C–Cl bond, then the photocatalyst will undergo charge recombination and go back to the ground state.



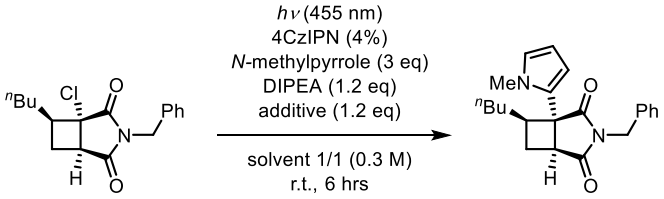
Scheme 61 *- Charge recombination of amine and photocatalyst preventing dehalogenation.*

However, if in the presence of a polar protic solvent, the charge recombination can be inhibited due to the solvation of the two ions. This allows for the slower dehalogenation step to take place and gives a potential reason to the results observed.

2.4.2. Optimisation of sp^3-sp^2 C–H activation and DoE study

The pyrrole product **368** obtained introduces the possibility to access a range of heteroaromatic ring sp^2-sp^3 functionalisations. Direct addition of these sp^2 aromatic species is highly desirable in medicinal chemistry and can lead to a diverse range of sp^2 and sp^3 rich cyclobutane centres. However, the yield obtained under the original conditions were low, so further optimisations were necessary. Initial changes to the solvent to trial more polar protic and aprotic solvents (Table **20**, Entry 2 – 10) gave no improvement on the overall yield.

Table 20 *- Screening of solvent and acid additives.*



Entry	Solvent	Additive	**360** (% Yield)	**368** (% Yield)
1	MeCN/H_2O	-	22	27
2	MeCN/MeOH	-	60	12
3	MeCN/EtOH	-	58	8
4	MeCN/iPrOH	-	54	5
5	DMF/H_2O	-	34	4
6	MeOH/H_2O	-	17	2
7	DCM	-	59	5
8	DMF	-	65	4
9	Acetone	-	53	7
10	MeOH	-	66	3
11	MeCN/H_2O	HCOOH	70	6
12	MeCN/H_2O	MeCOOH	41	30
13	MeCN/H_2O	$NaHCO_3$	0	24
14	MeCN/H_2O	Ascorbic Acid	80	7
15	MeCN/H_2O	$AlCl_3$	80	0
16	MeCN/H_2O	$FeCl_3$	0	0

Yields calculated by NMR using trimethoxybenzene as an internal standard

The addition of an acid additive was shown to be potentially beneficial in previous work earlier in this chapter. A range of Brønsted and Lewis-acids were screened, and acetic acid was found to give a slightly higher yield of the desired product and a significant increase to the mass balance of the

reaction (Entry 11 – 16). Unlike previous work with formic acid, the acetic acid additive was found to give reproducible yields, and so was taken forward for further optimisations. Interestingly, all other acid additives gave no improvement to the compound yield. However, formic and ascorbic acid, along with aluminium- and iron trichloride returned a high yield of the starting material **360**, suggesting that the reaction was hindered by strong coordination to the amine lone pair.

All previous attempts at optimisation of the redox neutral radical addition to pyrrole have been performed by changing one variable at a time (OVAT). This is where variables are individually altered while keeping all others constant. The downside to using this process is that a "true optimum" can be missed as only one variable is being tested at a time, whereas a combination of effects may be incurred by two separate variables, which is not observed by testing one variable at a time. Optimisation is also inefficient as several conditions are required down each "line" of optimisation. Design of Experiment (DoE) is a systematic approach to gathering data about reaction parameters (Figure **15**).

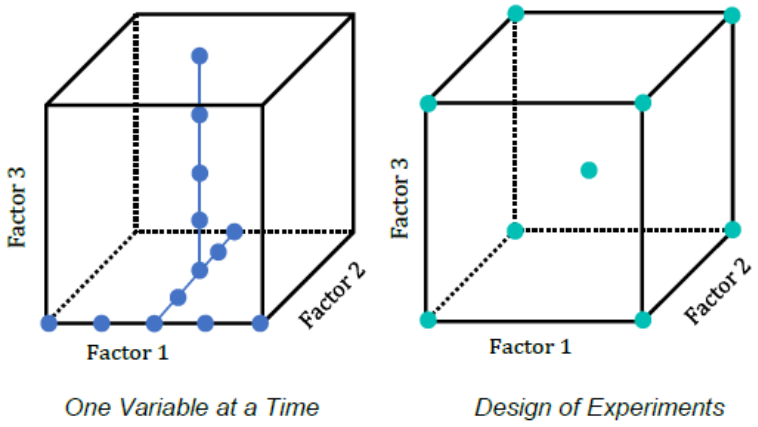


Figure 15 *– "Chemical space" representation of different approaches to optimisation.*

A DoE is performed by taking pre-existing known high and low extremes of experimental parameters of each of the conditions (given as an integer value) as well as a centre point of all conditions being tested as a control. The values chosen for these conditions are based on previous knowledge of the reaction to give the most representative results. The output can then be chosen, such as the % yield of various products or conversion, so that the effect of each of the variables on a certain aspect of the reaction can be tested. The advantages of this method are that it requires a small number of experiments to achieve a significant model of the data. It also allows the elucidation of variables that are influenced by each other as well as the variables with the most impact on the selected outcomes. This is represented as a bar graph (Figure **16**), where each variable is plotted against the selected outcome (*e.g.* % yield of product). The bar graphs where the error bars cross zero are considered not significant.

A Design of Experiment was performed on the existing conditions for the generation of the pyrrole product (Table **21**).

Table 21 *– Factors and parameters chosen for DoE (fractional-factorial design with 3 replicates at centre point).*

Factor	Units	High	Low
Catalyst loading	mol%	10	1
Concentration	[M]	0.5	0.1
Reagent	equiv.	5	1
Amine/acid ratio	-	75	33
Organic/aqueous solvent ratio	-	75	25

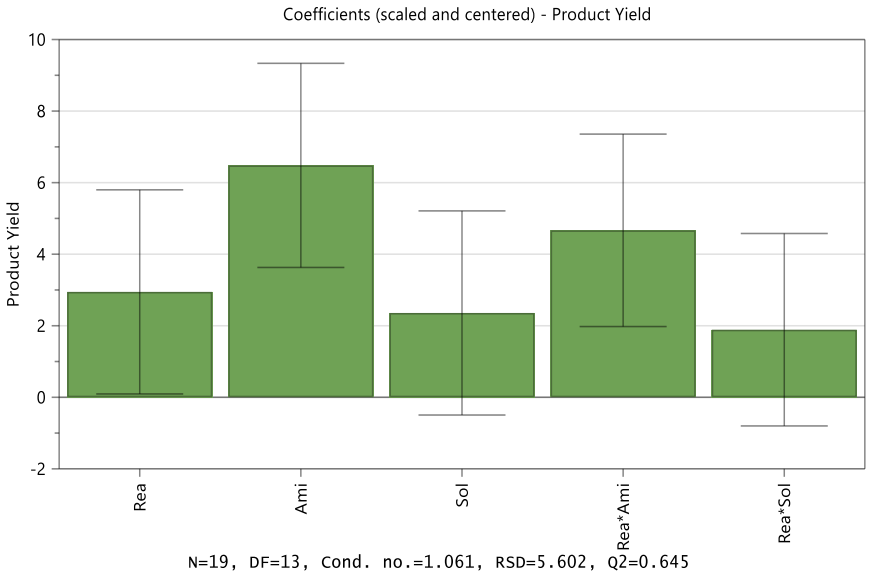
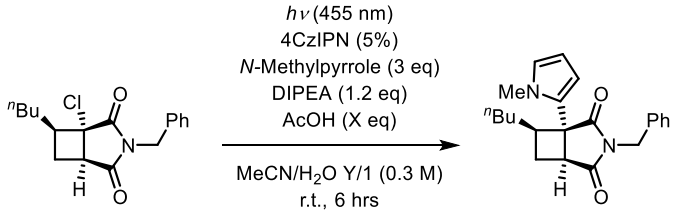


Figure 16 *– Graphic representation of DoE output. Reagent eq. (Rea), amine/acid ratio (Ami), organic/aqueous solvent ratio (Sol), combination effects of Rea/Ami (Rea*Ami), combination effects of Rea/Sol (Rea*Sol).*

The results obtained showed that the only significant result to be taken from the conditions screened was that the higher the equivalents of the alkene (in this case pyrrole), the higher the yield should be. However, the increase was not very significant. Other factors that were important were the ratio of amine base to acid additive and the ratio of the aqueous *vs* organic solvent.

These results were then applied to a screening of the solvent ratio (Table **22**, Entry 1 – 4) and of the amine to acid ratio (Entry 5 – 9). The most optimised conditions (Entry 7) were scaled up to 0.65 mmol to give the desired product in a 41% yield. This is still a moderate yield and requires further optimisation or understanding of the reaction mechanism to improve the yield further.

***Table 22** - Altering solvent ratio and additive equivalents.*



360 **368**

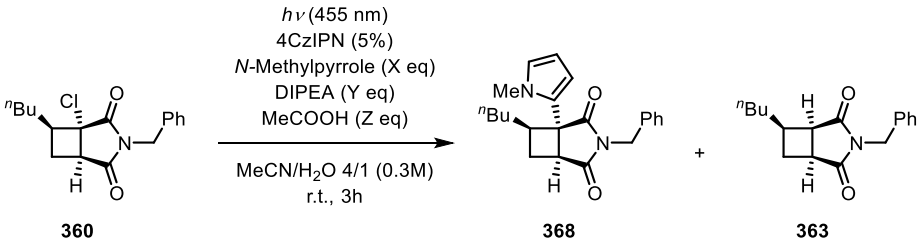
Entry	Solvent	Ratio (Y/1)	**AcOH** (eq)	**360** (% yield)	**368** (% yield)	**Total Mass Recovered** (%)
1	MeCN/H_2O	1.5/1	1.2	83	12	95
2	MeCN/H_2O	2.0/1	1.2	61	18	79
3	MeCN/H_2O	3.0/1	1.2	38	22	60
4	MeCN/H_2O	4.0/1	1.2	60	18	78
5	MeCN/H_2O	4.0/1	1.1	57	17	74
6	MeCN/H_2O	4.0/1	1.0	28	26	54
7	MeCN/H_2O	4.0/1	0.8	12	37	49
8	MeCN/H_2O	4.0/1	0.6	21	25	46
9*	MeCN/H_2O	4.0/1	0.8	0	41	41

Yields calculated by NMR using trimethoxybenzene as an internal standard
**Reaction performed on a 0.65 mmol scale*

Further optimisations were trialled to determine if changing the amine equivalents would improve the yields of **368** (Table **23**). As the reaction proceeds, HCl is produced as a by-product, making the reaction more acidic over time. It was hypothesised that the increase in acidity was inhibiting the lone pair on the amine base and thus slowing the reaction.

It was found that increasing the equivalents of the amine base gave higher yields of the hydrodehalogenation by-product **363** (Entry 1 – 5). Another way around this is to add an amine base such as lutidine, that does not interfere in the reaction process (Entry 6). However, although the recovered mass was higher, the yield of **368** was significantly lower. Portion-wise addition of DIPEA also gave high amounts of the hydrodehalogenation product **363**, and so was not taken forward for further optimisations.

Table 23 *- Altering base/acid/reagent equivalents.*

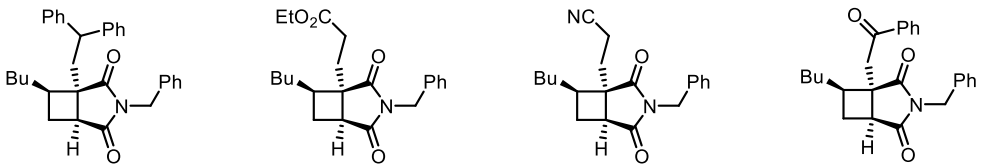


Entry	DIPEA (eq)	Acid (eq)	Reagent (eq)	360 (% Yield)	368 (% Yield)	363 (% Yield)	Total mass (% Yield)
1	1.8	0.8	3.00	0	31	31	62
2	1.8	1.2	3.00	0	35	17	52
3	2.5	1.7	3.00	0	35	30	65
4	3.0	2.0	3.00	0	22	30	52
5	2.5	1.7	6.25	0	34	23	57
6*	1.2	0.8	3.00	48	24	0	72
7**	2.4	0.8	3.00	0	38	23	61

Yields calculated by NMR using trimethoxybenzene as an internal standard.
** 2 equivalents of lutidine added.*
*** DIPEA added in two portions, 1.2 eq @ 0 hr, 1.2 eq @ 3 hr, 6 hr reaction time.*

2.4.3. Improvement on yields in previous scope and proposed mechanism

The most optimised conditions were taken forward and applied to the already existing scope of reactions (Figure **17**). It was found that the optimised conditions from the pyrrole DoE increased the product yield of the previously best yielding reactions.

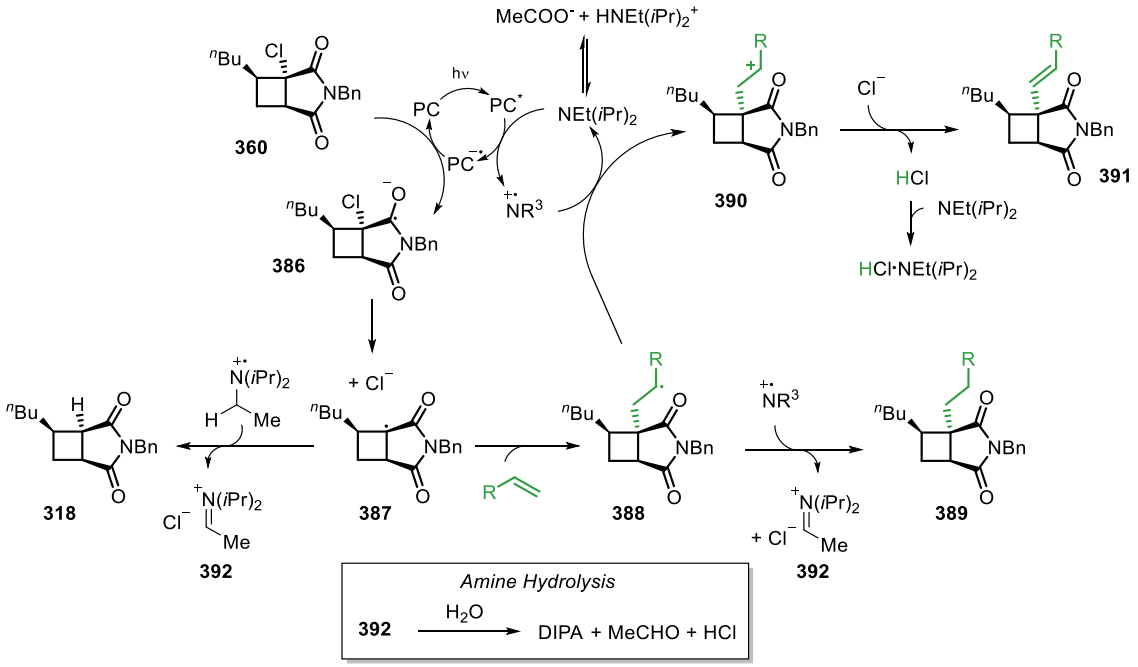


361 (80%) (86%) **362** (72%) (75%) **385** (70%) **369** (0%) (12%)

Figure 17 *- Effect of new conditions on the yield of photoredox reactions.*

From the findings observed in the conditions screened, along with previous research into the area, the proposed mechanism for the radical addition to aromatic and non-aromatic alkenes is as follows (Scheme **62**).[130–132] Initial photoexcitation of the photocatalyst allows for oxidation of the sacrificial amine. The reduced catalyst is then able to reductively dehalogenate the water-coordinated carbonyl-chloride on **360** to give a radical and chloride anion **386** through a spin-centre shift process described in Scheme **65**, recycling the photocatalyst. The formed radical **387** is then able to undergo two different steps; hydrogen abstraction with the oxidised amine to give the undesired hydrodehalogenated product **318** or insertion of a radical acceptor to give the radical adduct **388**. The

radical adduct can then undergo one of two options: for aromatic radical acceptors, charge transfer with the amine radical cation to recycle the amine base and give the cationic adduct **390**. This species can then rearomatize by loss of H^+. The proton forms HCl which complexes irreversibly with the amine base. Meaning a stoichiometric amount of amine is required despite regenerating it in the cycle. For non-aromatic compounds, radical HAT with the amino radical cation gives the fully saturated compound **389** and an equivalent of the iminium chloride salt **392**.

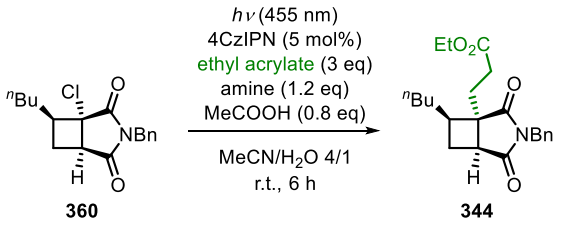


Scheme 62 *- Proposed mechanism for the redox neutral sp^3-sp^2 radical addition.*

The effect of using acetic acid as an additive seems to reversibly complex to the amine base. This prevents a large concentration of the amino radical cation from forming, as these highly active intermediates can go on to oxidise to imines and hydrolyse irreversibly to form aldehydes and secondary amines. Loss of the amine reductant this way leads to low conversion of the starting material to the desired radical adduct. However, using higher equivalents of the amine leads to undesired hydrodehalogenation product **318**, and higher equivalents of the acid additive hinders the reaction completely. Finding the correct balance of these three conditions will give the most general conditions for this methodology.

Control studies were taken of the reaction conditions. We decided using ethyl acrylate as a radical acceptor would demonstrate all the effects observed from changing each of the reaction conditions (Table **24**).

***Table 24** – Control reactions for the dehalogenation/functionalisation of cyclobutane **360**.*



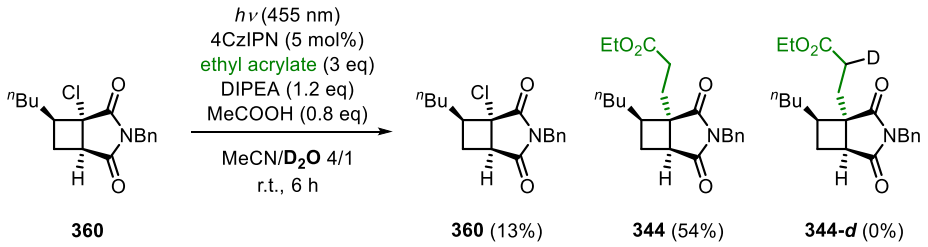
Entry	4CzIPN	DIPEA	Water	AcOH	Light	N_2 Sparge	Product (%)
1	N	Y	Y	Y	Y	Y	-
2	Y	N	Y	Y	Y	Y	-
3	Y	Y	N	Y	Y	Y	52
4	Y	Y	Y	N	Y	Y	63
5	Y	Y	Y	Y	N	Y	-
6	Y	Y	Y	Y	Y	N	16
7	Y	Y	N	N	Y	Y	-
8[a]	Y	XS	Y	Y	Y	Y	67 (14)
9[b]	Y	Y	Y	XS	Y	Y	47

a) XS (3 eq.) DIPEA used. **b)** XS (3 eq.) acid used. Protodehalogenation product yield shown in parenthesise.

From the reaction conditions we can observe that the necessary parameters are the photocatalyst, tertiary amine, Brønsted acid and light source (Entries 1, 2, 5 and 7). The low yield from lack of nitrogen sparging confirms that the reaction is sensitive to the formation of hyperoxide radicals (Entry 6). The HAT side product is promoted by the excess of DIPEA in the reaction (Entry 8) and the addition of excess acetic acid quenches the lone pair on the tertiary amine, reducing the efficacy of the reaction (Entry 9).

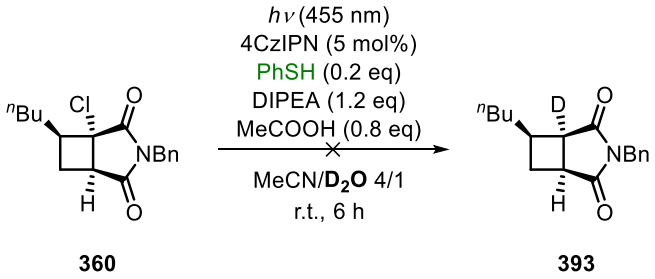
2.4.4. Deuteration studies

When the reaction of **360** with ethyl acrylate was performed with D_2O in place of water, no deuterium incorporation α to the ester group in adduct **344** was observed (Scheme **63**). This implies that the intermediate α-carbonyl radical does not undergo SER to an anion followed by protonation. Therefore, we propose that the α-carbonyl radical undergoes a hydrogen atom transfer (HAT) with DIPEA (or the radical cation of DIPEA) to generate the adduct **344**.



Scheme 63 *- No deuteration α to the ester group signifies that the radical formed is not reduced to the anion, but instead undergoes HAT with DIPEA or DIPEA•+.*

Work by Leonori *et al.* showed that halogen atom transfer (XAT) is possible when using a suitable amine base in the presence of a catalyst or radical initiator.[85] To demonstrate that this process was not taking place in our reaction, the conditions of the XAT followed by deuterium atom transfer using thiophenol was repeated (Scheme **64**). Again, no deuteration was observed under the reaction conditions, suggesting that a deuterium atom transfer *via* thiophenol is not possible, and hence not supporting the mechanism of XAT.



Scheme 64 *– No deuteration observed when using conditions developed by Leonori et al. for XAT.*

2.4.5. Cyclic voltammetry and mechanism determination

Due to the increase in productivity from the presence of water on the reaction, the effect of water on the reduction potential of α-cyclobutane **360** was investigated. If the addition of water shifted the reduction potential higher, then this would explain the ability of the catalyst to reduce substrate **360**. First, background voltammograms of MeCN and MeCN doped with water were recorded (Figure **18**), which showed that no reduction peaks occur in the region between 0 V and –2.5 V.

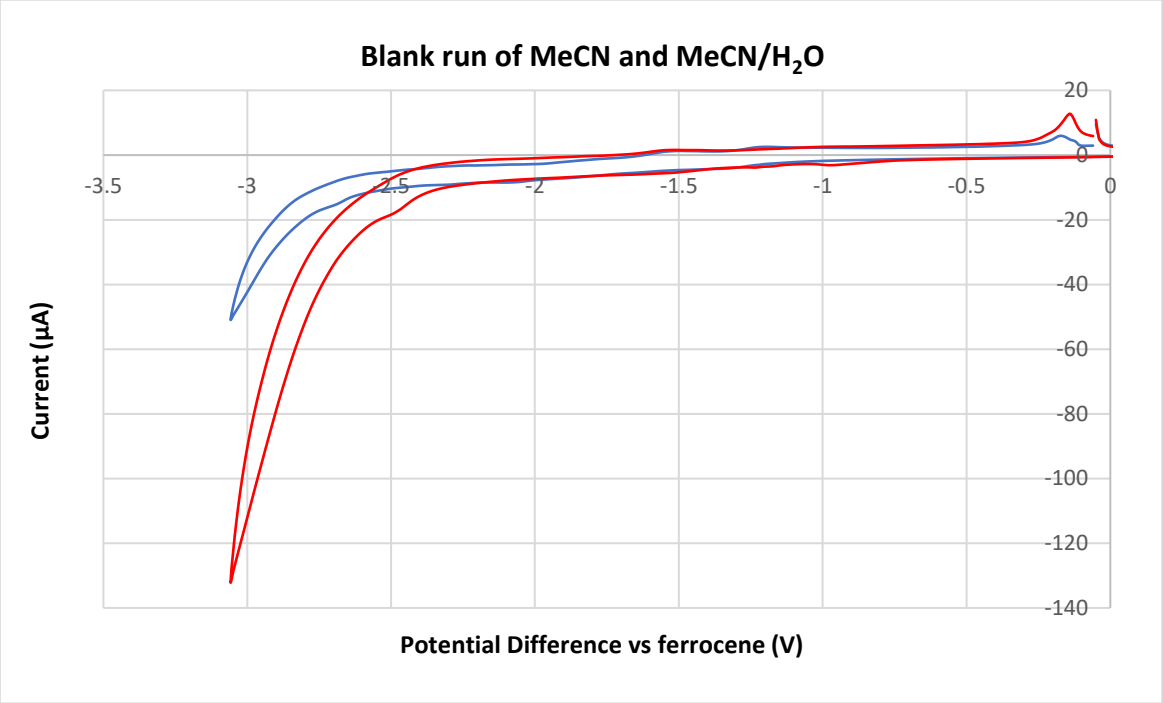


Figure 18 *- Blank run of dry MeCN (blue) and MeCN doped with 2 drops of water (red) with tetra-butylammonium hexafluorophosphate as the electrolyte (0.1 M) at a scan rate of 0.1 V s^{-1}, referenced to ferrocene using a glassy carbon electrode.*

Next, the reduction potential of 4CzIPN was recorded so that a direct comparison of reduction potentials could be made (Figure **19**).

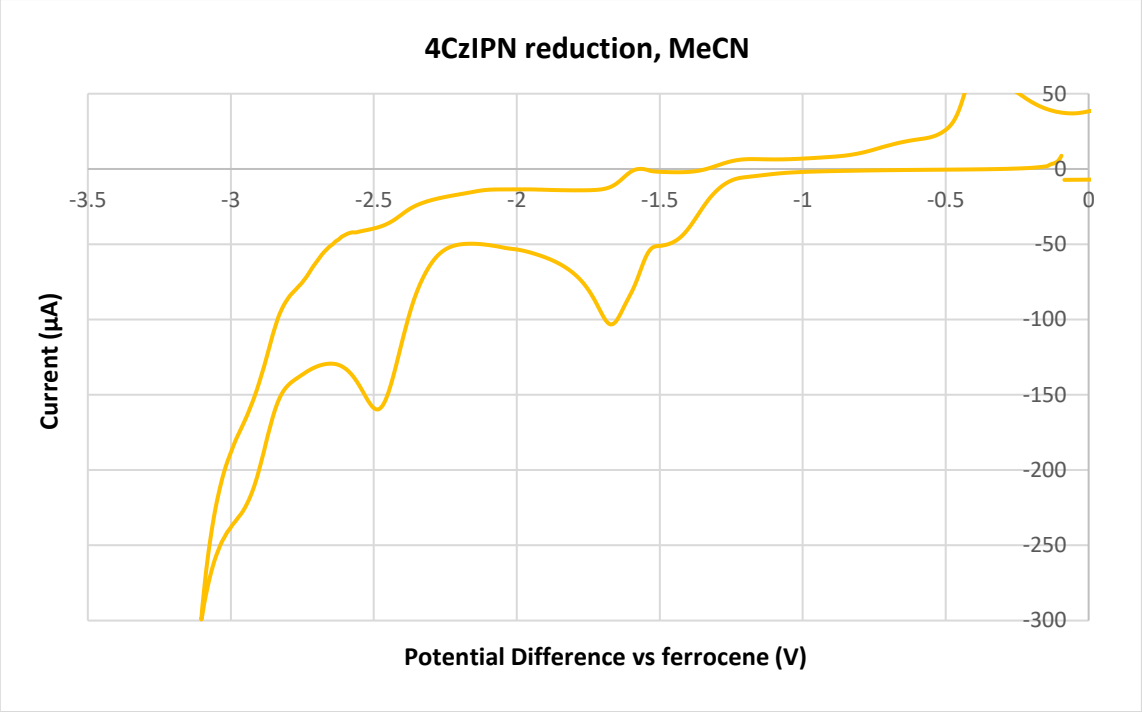


Figure 19 *- 4CzIPN (3 mM) run in dry MeCN (yellow) with tetra-butylammonium hexafluorophosphate as the electrolyte (0.1 M) at a scan rate of 0.1 V s^{-1}, referenced to ferrocene using a glassy carbon electrode. Reductive maxima = −2.45 V.*

When the voltammograms of chloro-cyclobutane **360** (Figure **20**) and cyclobutane **363** (Figure **21**) were compared in dry MeCN and MeCN doped with water, a significant difference was observed in their reduction potentials. It was found that the presence of water resulted in a substantial shift in the reduction peaks to more positive potentials for both chloro-cyclobutane **360** and cyclobutane **363**, therefore enabling the catalyst to facilitate SER.

The similar reduction potentials of chloro-cyclobutane **360** and cyclobutane **363** suggest that the reductive dehalogenation proceeds *via* a two-step process involving initial reduction of the imide carbonyl followed by chloride elimination, rather than direct reduction of the C–Cl bond (Figure **22**).

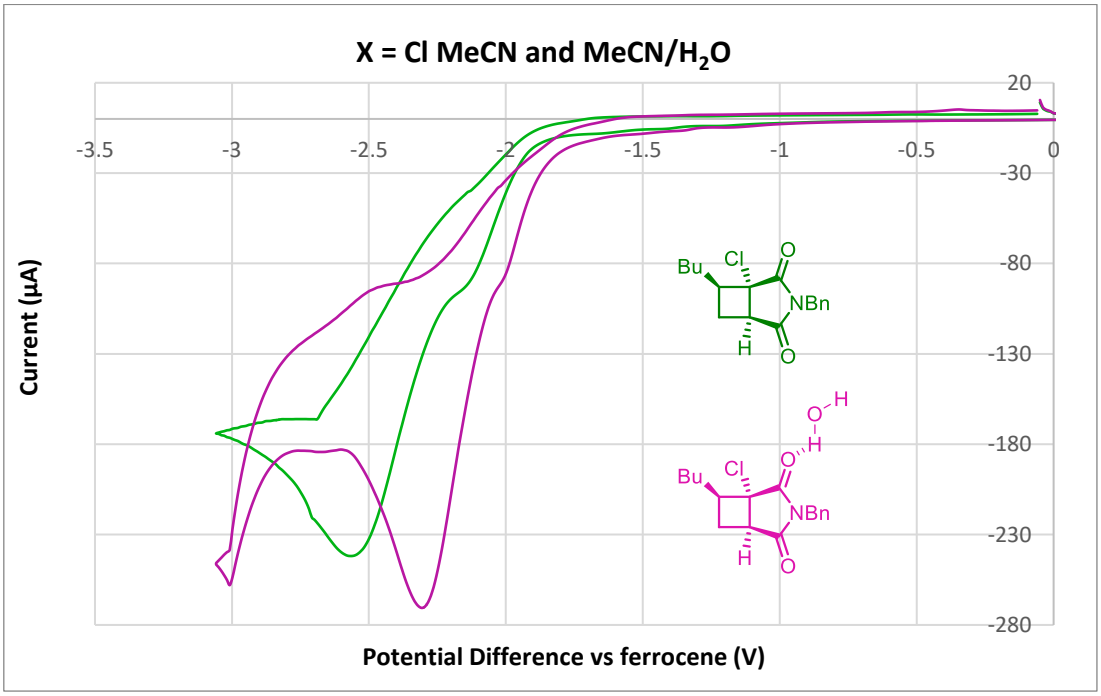


Figure 20 *- Compound 4 run in dry MeCN (green) and in MeCN doped with 2 drops of water (pink) (5 mM) with tetra-butylammonium hexafluorophosphate as the electrolyte (0.1 M) at a scan rate of 0.1 V s^{-1}, referenced to ferrocene using a glassy carbon electrode. Respective reductive maxima taken as −2.53 V (green) and −2.29 V (pink).*

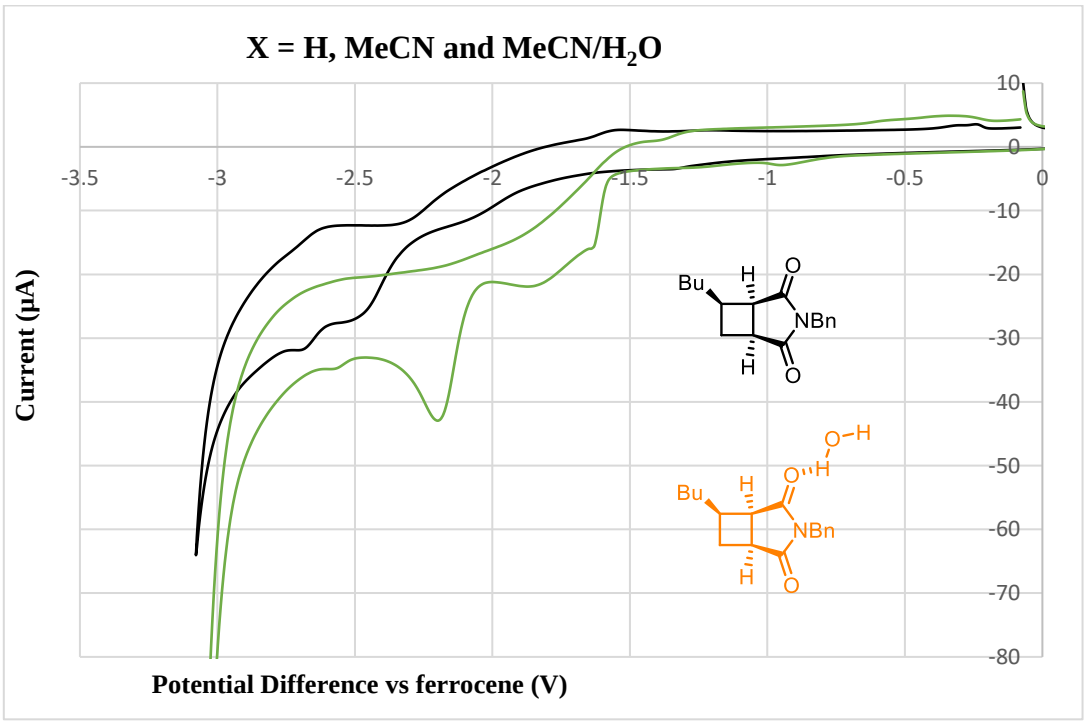


Figure 21 *- Hydrodechlorinated-4 run in dry MeCN (black) and in MeCN doped with 2 drops of water (orange) (5 mM) with tetra-butylammonium hexafluorophosphate as the electrolyte (0.1 M) at a scan rate of 0.1 V s^{-1}, referenced to ferrocene using a glassy carbon electrode. Respective reductive maxima taken as −2.52 V (black) and −2.20 V (orange).*

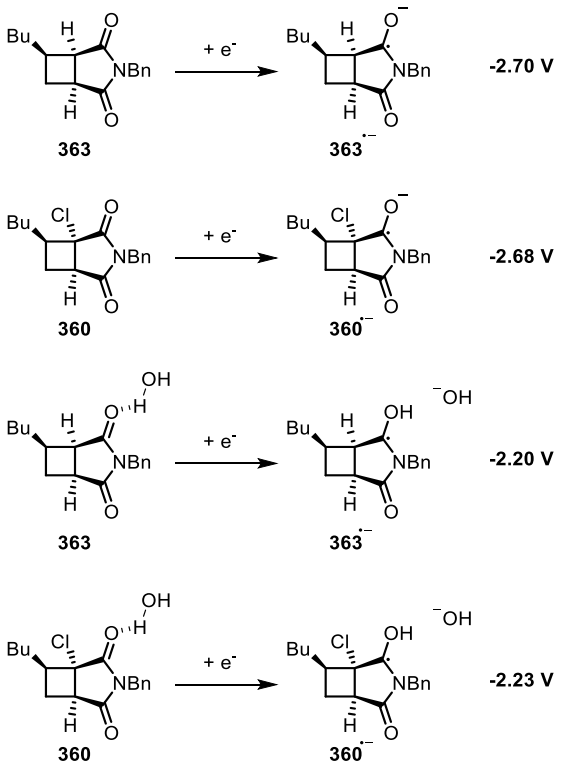
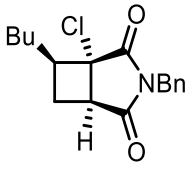


Figure 22 *– Summary and comparison of reduction potential between different derivatives of cyclobutane* ***360****.*

Further evidence towards the reduction of the imide carbonyl over the direct C–Cl bond can be found through DFT studies of **360**. Orbital energies of **360** calculated for the LUMO (lowest unoccupied molecular orbital) shows that the electron density sits on the imide carbonyl adjacent to the C–Cl bond (Figure **23**). The same DFT calculation was performed on compound **363** and showed that the electron density also sits on the imide carbonyls in the LUMO. These findings suggest that the attacking electron will come into the carbonyl over the C–Cl bond, hence why water has such an effect on the productivity of the reaction in aqueous conditions.



HOMO LUMO

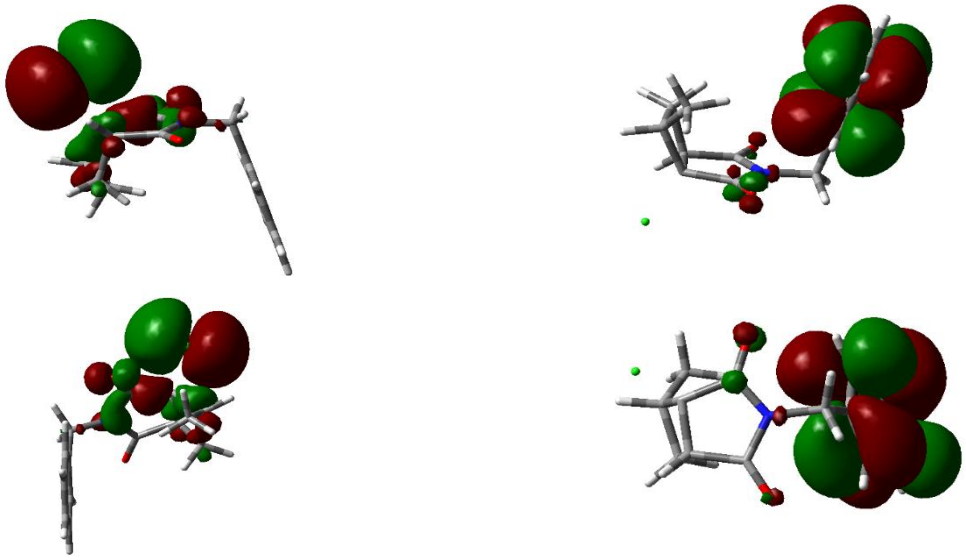
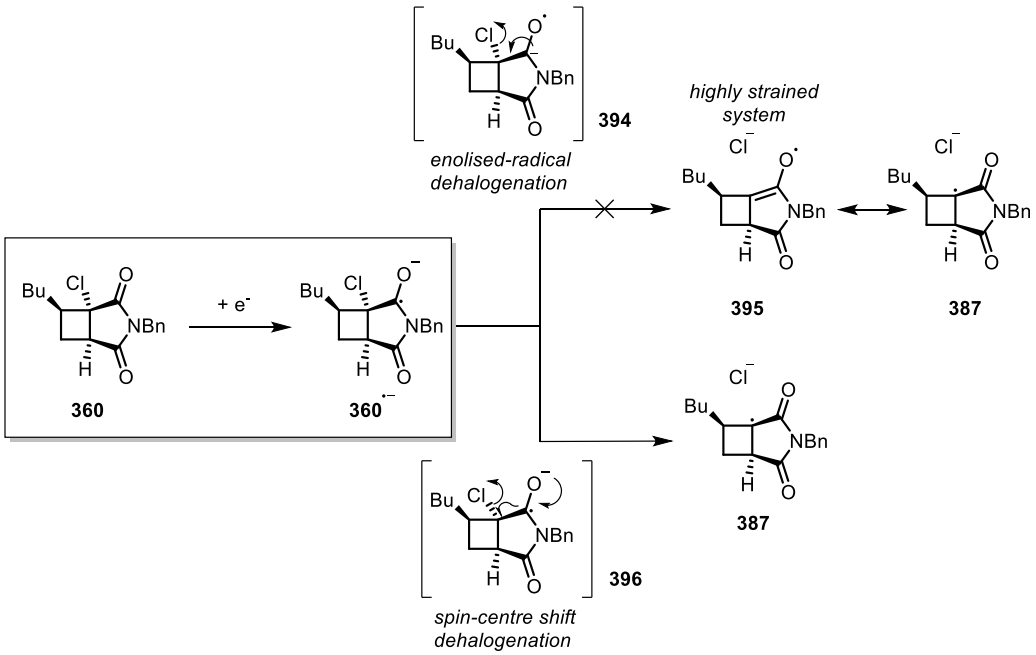


Figure 23 *– HOMOs and LUMOs calculated for compound* ***360****. LUMOs demonstrate that the reduction will happen on the carbonyl α to the C–Cl bond.*

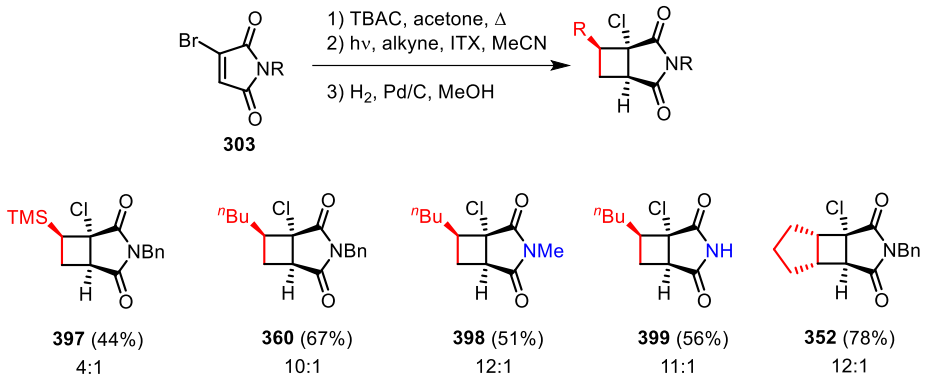
From this observation, it is clear that the carbonyl LUMO undergo SER followed by dehalogenation to give the carbon centred radical and chloride anion. However, the mechanism of this is not possible by resonance to the enolate form, due to the high strain encountered with the cyclobutane ring and exocyclic sp^2 double bond in compound **395** (Scheme **65**). Instead, the carbon radical is formed through a process commonly encountered in biological mechanisms, a spin-centre shift dehalogenation *via* compound **396**. This mechanism mitigates the formal double-bond and therefore the strained system encountered *via* the enolate complex, hence leading to radical **387**.



Scheme 65 *– Mechanistic pathways for enolised-radical dehalogenation (dis-favoured), or spin-centre shift (favoured).*

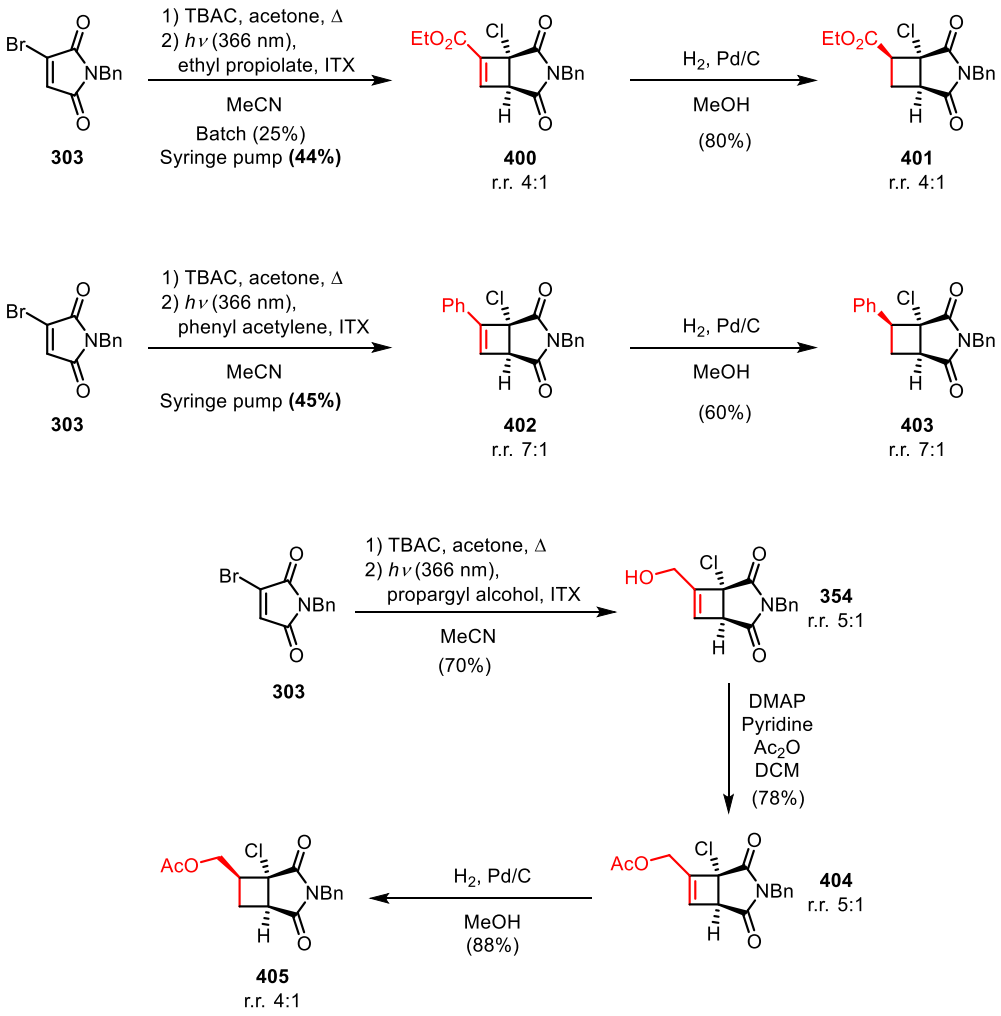
2.5. [2+2] Photocycloaddition scope

The scope of the [2+2] photocycloaddition was analysed, and it was considered appealing to explore various alkynes for the [2+2], to demonstrate the tolerance of broad functionality. Initial studies looked at ethynltrimethylsilane, cyclopentene, propargyl alcohol and ethyl propiolate (Scheme **66**). It was found that TMS acetylene was able to give moderate yields over three steps without need for purification until the end step. Due to the stepwise cyclisation of the [2+2] step, good regioselectivity is observed in the cycloadduct. Then, different *N*-substituents on the maleimide were trialled. The bromination of each *N*-substituted maleimide was previously known in literature, and synthesis of each was trivial. Pleasingly, each went through the chlorination step to give moderate to good yields of the desired chloro-maleimide compounds. Once obtained, the new chloro-maleimides were subjected to [2+2] reaction conditions with 1-hexyne to give the desired cycloadduct, followed by hydrogenation with Pd/C to give compounds **398** and **399** in moderate overall yields. Cyclopentene also gave excellent diastereoselectivity due to the preferred *exo*-conformation during the [2+2] cycloaddition. These scaffolds, once subjected to the optimised conditions, would give rise to a wider library of multi-substituted cyclobutanes.



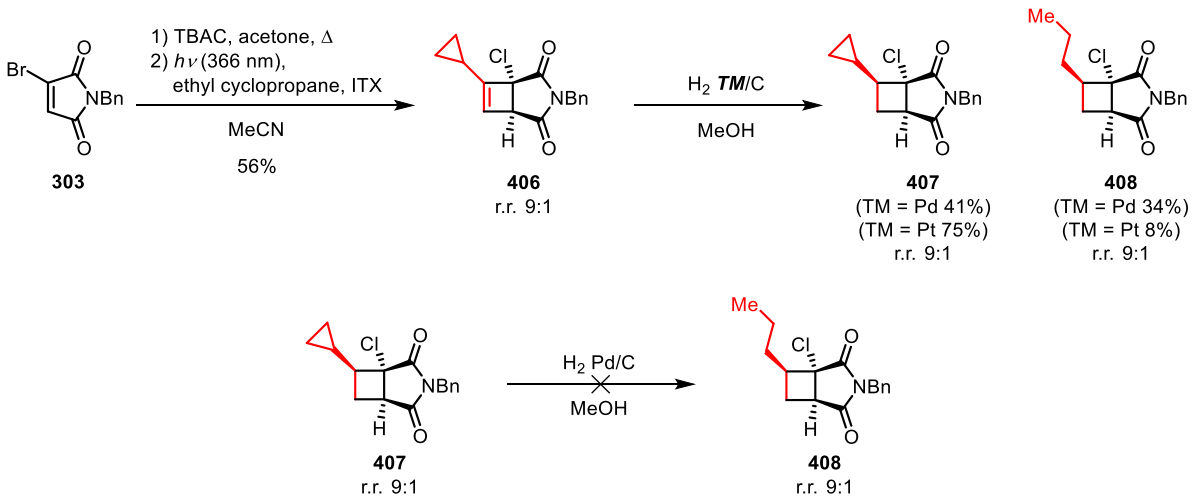
Scheme 66 *- [2+2] Photocycloaddition scope.*

Ethyl propiolate required syringe pump addition of maleimide **350** due to dimerisation outcompeting the slower hetero-cycloaddition (Scheme **67**). This is due to the electronic mismatch of the maleimide and propiolate. However, after obtaining the cyclobutene **400**, the saturated cyclobutane **401** could be obtained in very good yield. Phenyl acetylene then gave the cyclobutene product **402**, albeit in a low yield. Employing syringe pump conditions boosted the yield slightly and hydrogenation gave the cyclobutane product **403** with very good regioselectivity. The propargyl alcohol adduct **354** also required protection of the alcohol group before hydrogenation, due to the low yields obtained if the hydroxyl group is left exposed. Once protected to give the acetate **404**, the reaction went in good yield to give the saturated cyclobutane **405** as a diasterioisomeric ratio of 4:1.



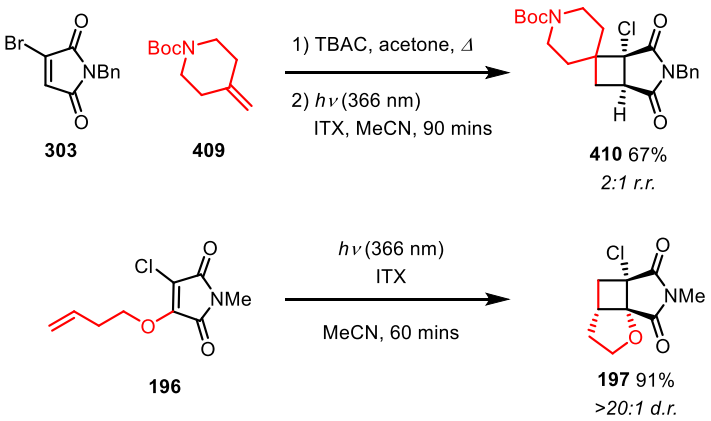
Scheme 67 *- Stepwise [2+2] and hydrogenation required for some cyclobutane products.*

Then, focus was turned to the photocycloaddition of ethynyl cyclopropane (Scheme **68**) and exocyclic alkene **409** (Scheme **69**). Pleasingly, ethynyl cyclopropane gave excellent regioselectivity and good yield, without ring fragmentation of the cyclopropyl group. Next, the hydrogenation of formed cyclobutene **406** was performed under standard conditions of Pd/C lead to form the ring opened *n*-propyl chain **408** in a 1:1 ratio with the desired cyclopropane product **407**. To investigate at what stage the ring was opening, the separated saturated cyclopropyl cyclobutane **407** was resubjected into the hydrogenation conditions and found that only starting material was observed, with no C–C bond cleavage with the saturated cyclobutane. This suggests that the coordination to the vinyl cyclopropane motif of **406** was key to C–C bond cleavage and hence formation of product **408**. To mitigate the ring cleavage, Pt/C was used in the hydrogenation step, giving only 90:10 ratio of the *n*-propyl product.



Scheme 68 *– [2+2] Photocycloaddition followed by Pt/C to give desired cyclopropylcyclobutane product* ***407****. No hydrogenation of cyclopropane ring observed when Pd/C was used in cyclobutane substrate* ***407****.*

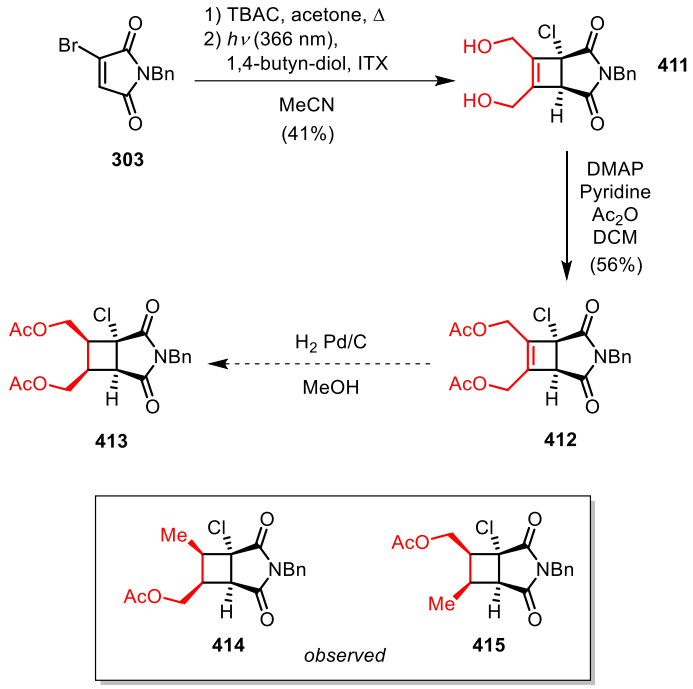
While investigating alkenes as cycloadducts, *N*-Boc methylenepiperidine **409** was employed into the reaction conditions and gave a mix of regioisomers (67%), although in low regioselectivity (2:1). The regioisomers could be separated by column chromatography, giving 45% yield of the desired regioisomer **410**. The intramolecular [2+2] photocycloaddition from compound **196** was included as part of the scope of alkenes. The tolerance of the [2+2] photocycloaddition consolidates the applicability of a variety of different functional motifs on the cyclobutanes.



Scheme 69 *– Alkene [2+2] scope.*

2.5.1. Unsuccessful [2+2] alkyne cycloadducts

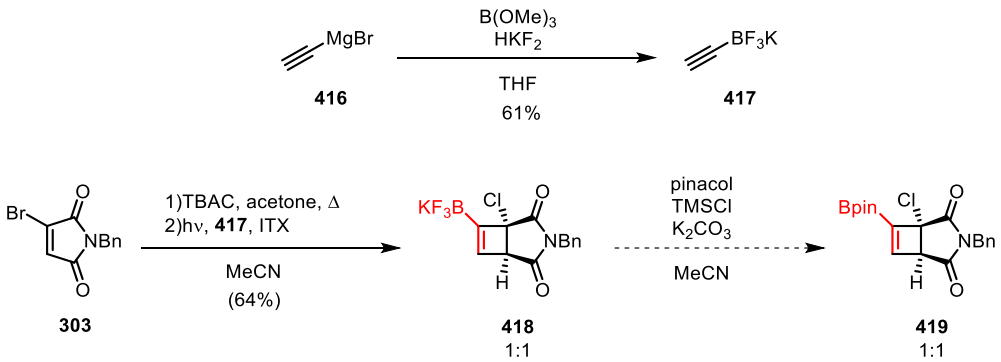
Other alkynes were subjected to the reaction conditions to achieve saturated cyclobutanes but were found to be unsuccessful. For example, the photocycloaddition with 1,4-butyn-diol, a symmetrical derivative of propargyl alcohol successfully gave desired cyclobutene **411** and was further protected to give diacetate **412** (Scheme **70**).



Scheme 70 *– Symmetric [2+2] with 1,4-butynediol and acetate protection. Deacetylated products observed upon hydrogenation with Pd/C.*

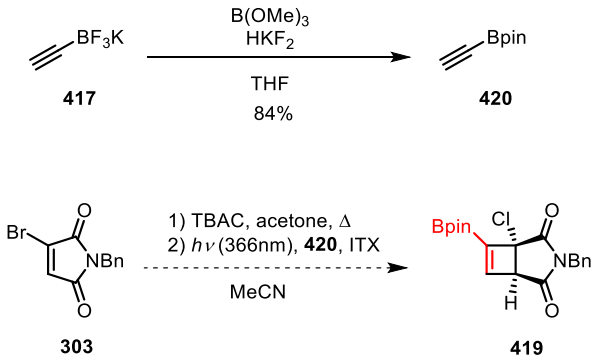
However, upon hydrogenation with Pd/C, none of the desired product **413** was observed and complete consumption of the cyclobutene had occurred. Instead, by ^{1}H NMR of the crude material, methyl peaks were observed, suggesting that the allyl acetate group would undergo palladation and reductive cleavage of the acetate group. Further work towards this product was therefore not pursued.

Boronic esters are an incredibly useful organic derivative with a wide range of organic transformations available. To incorporate this motif into the cyclobutane would be a highly valuable scaffold to demonstrate. To investigate this, acetylene trifluoroboronic potassium salt **417** was synthesised (Scheme **71**).



Scheme 71 *– Synthesis and [2+2] photocycloaddition of cyclobutyl trifluoroboronic potassium salt.*

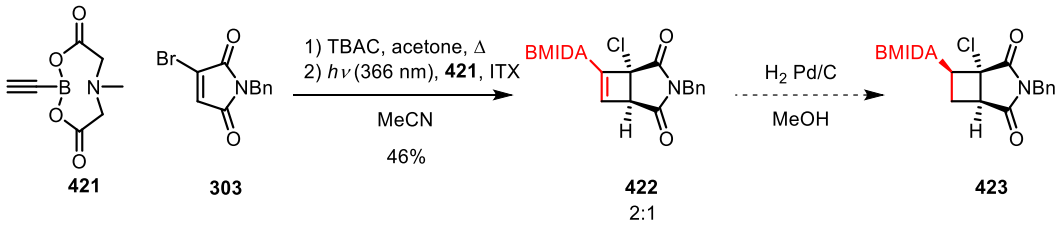
Upon irradiation of **417** in the presence of maleimide **350**, cycloadduct **418** was observed in a 1:1 ratio by ^{1}H NMR. However, upon conversion of the product to the desired boronic pinacol ester **419**, no reaction was observed and any boronic ester containing compounds formed decomposed upon purification.



Scheme 72 *- Synthesis and [2+2] photocycloaddition of cyclobutyl boronic esters.*

Acetylene boronic ester **420** was synthesised from alkyne **417**, and the product was employed into the [2+2] photocycloaddition. However, upon irradiation under the reaction conditions in the presence of maleimide **350**, none of the cyclobutene boronic ester product **419** was observed (Scheme **72**). This may be due to the instability of the synthesised boronic ester **420** under UV conditions, coupled with the electron deficient nature of the alkyne, causing a slow reaction due to the electron mis-match with chloro-maleimide **350**, this effect was observed in other successful alkynes in the substrate scope. The combination of slow reaction kinetics and low stability of the boronic ester, would have led to no product being observed.

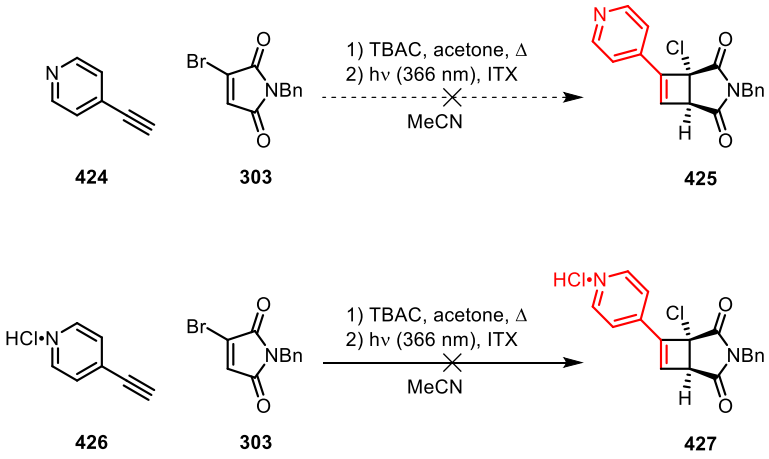
To mitigate the instability of boronic ester **420**, a MIDA ester **421** was used in the reaction conditions (Scheme **73**). Initially, the low solubility of **421** in acetonitrile led to low yields of the desired boronic ester **422**. To mitigate this, compound **421** was initially dissolved in a minimal amount of DMSO and injected into the reaction. Pleasingly, the cyclobutene was observed, however, the regioselectivity and yield were low and further hydrogenation was not achieved.



Scheme 73 *- [2+2] Photocycloaddition of cyclobutyl boronic MIDA ester.*

Finally, pyridyl acetylene **424** was employed into the reaction conditions (Scheme **74**). However, the reaction immediately turned black upon irradiation, and no product was observed. This may be due

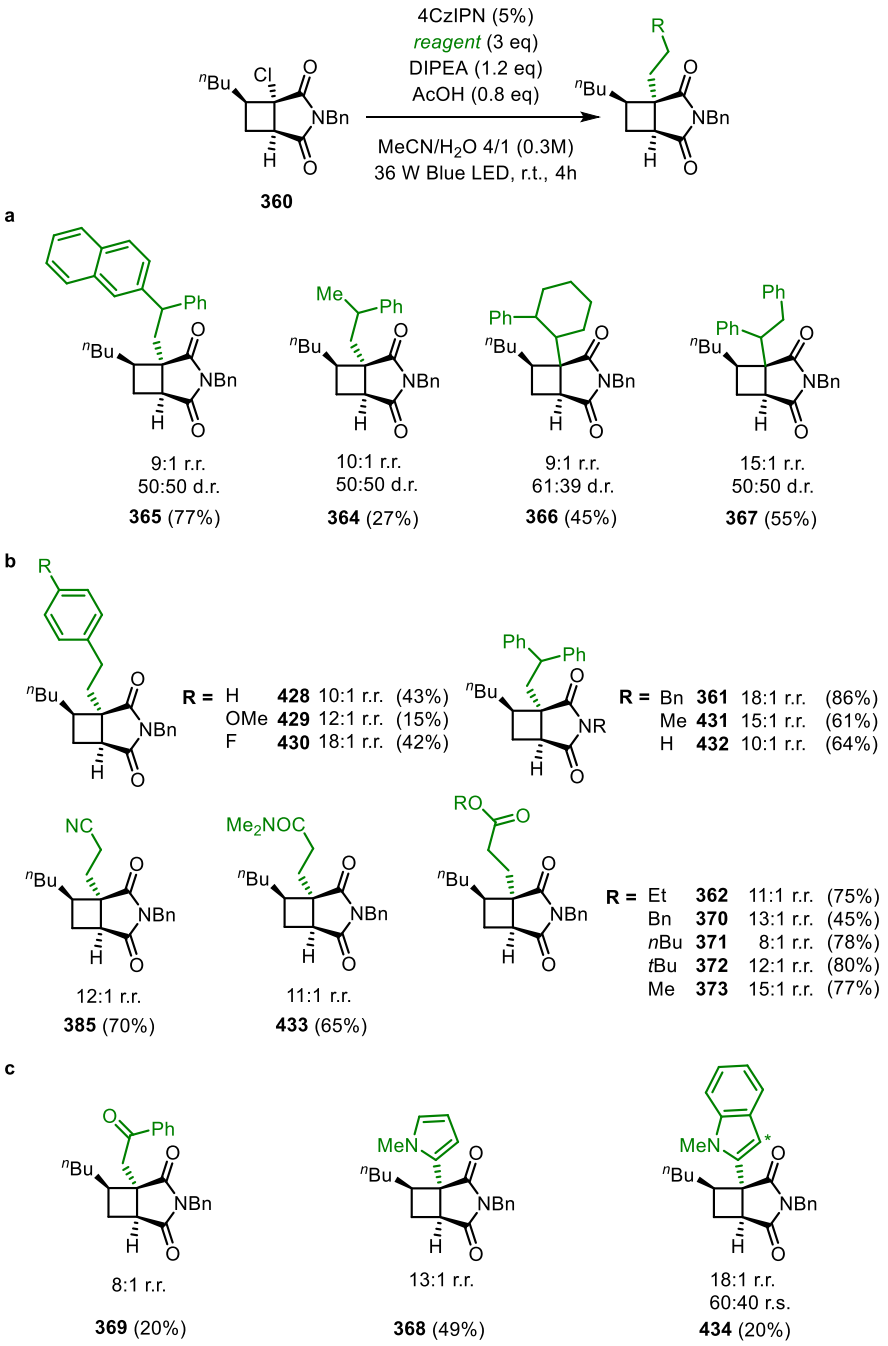
to the instability of pyridine under UV conditions. To mitigate this, the pyridyl hydrochloride salt **427** was formed to avoid any undesired interaction from the pyridine lone pair. Unfortunately, upon subjecting this to UV reaction conditions, the same problem was encountered, and no product was observed.



Scheme 74 *– [2+2] Photocycloaddition of 4-acetylpyridine.*

2.6. Photocatalysed dehalogenation scope

Upon optimisation to give general conditions for the photoredox step, we set about applying the optimised conditions across a range of electron rich and electron poor radical acceptors (Scheme **75**).



Scheme 75 *– Photoredox scope against a range of styrenes (**a**), electron poor (**b**) and electron rich radical acceptors including aromatics (**c**).*

Compound **360** was taken forward as the main substrate as synthesis from maleimide **303** required no chromatography, giving good yields, regioselectivity and diastereoselectivity and could be prepared on a 10-gram scale. On reaction with a range of styrenes, the substrate gave moderate to good yields where α and β substituents were involved on the sp^2 carbon (Scheme **75a**). Variation of the *N*-

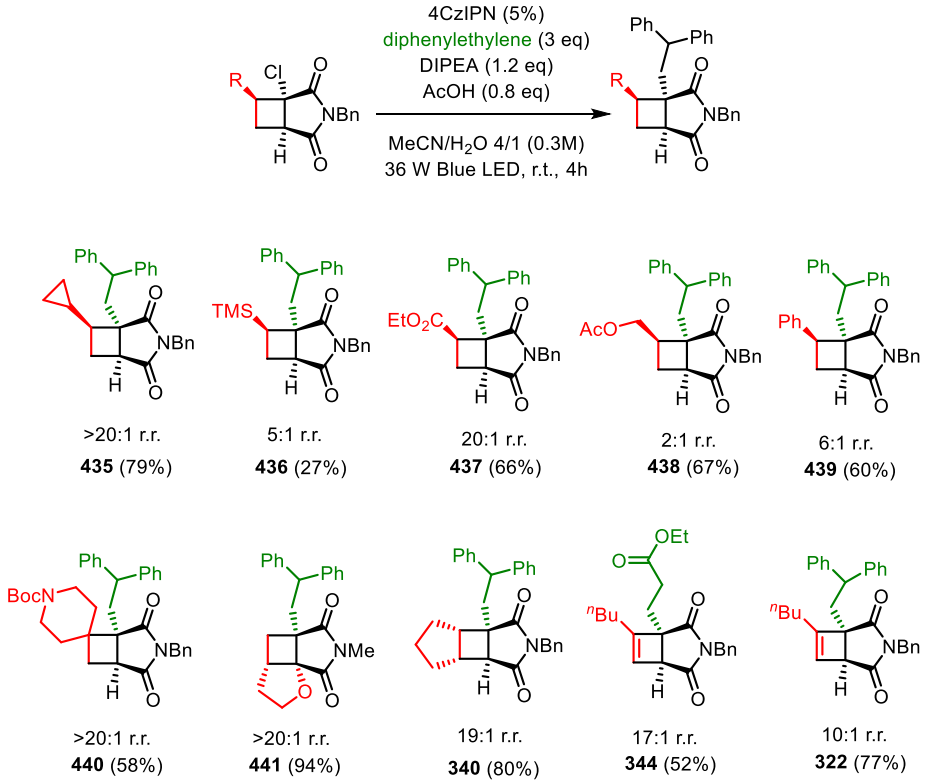
substituent on the succinimide ring showed good tolerance to the reaction conditions. Where the reaction gave complete diastereoselective control to the newly formed cyclobutyl quaternary centre, no stereoselectivity was observed for the HAT to the radical adduct. Furthermore, electron rich aromatic styrenes such as 4-vinylanisole (**429**) gave the lowest yields, suggesting that an electron deficient radical is preferred.

Next, a range of electron deficient radical acceptors were investigated, and pleasingly gave high yields of the desired radical adduct in all cases but benzyl acrylate **370** (Scheme **75b**). In addition to acrylates, acrylonitrile and dimethylacrylamide demonstrated similar results to give compounds **385** and **433**. The observed results from the radical reaction between the electron deficient radical acceptors and the electron deficient cyclobutyl radical was unexpected, as the electron mismatch would lead to a slow reaction between the pair. However, this may be explained by the type of radical formed in compound **360**, as no conjugation into the α-carbonyl can occur, thus increasing its reactivity.

The reaction scope was then turned to more challenging coupling partners (Scheme **75c**). Compound **368** from the radical addition with pyrrole was improved by the addition of excess pyrrole (10 equivalents) to reduce the side reactions that can happen through SET of the pyrrole lone pair. *N*-methyl indole was also successfully used in the reaction conditions with the same equivalents, however giving low yields and regioselectivity of compound **434**. In addition, silyl enol ether of acetophenone was used in the new conditions and radical adduct **369** was obtained in low yield.

2.6.1. Functional group tolerance

Subsequently, the functional group tolerance of the remaining cycloadducts was investigated by coupling with 1,1-diphenylethylene under the optimized reaction conditions (Scheme **76**).



Scheme 76 *– Functional group tolerance of photoredox reaction conditions.*

Pleasingly, good yields and complete diastereoselectivities were obtained with each novel cyclobutane motif as observed with compound **361**. Derivatisations on the cyclobutane ring, including silyl (**435**), cyclopropyl (**435**), ester (**437**, **438**) and aryl groups demonstrated good tolerance. Compound **440**, **441** and **340**, despite the steric clash from the cyclobutane substituents, also gave good yields of the radical adducts. As observed before, complete regioselectivity was observed with the allylic radical cyclobutene adducts **344** and **322**, with a lower yield from their saturated counterparts.

2.6.2. Unsuccessful radical acceptors

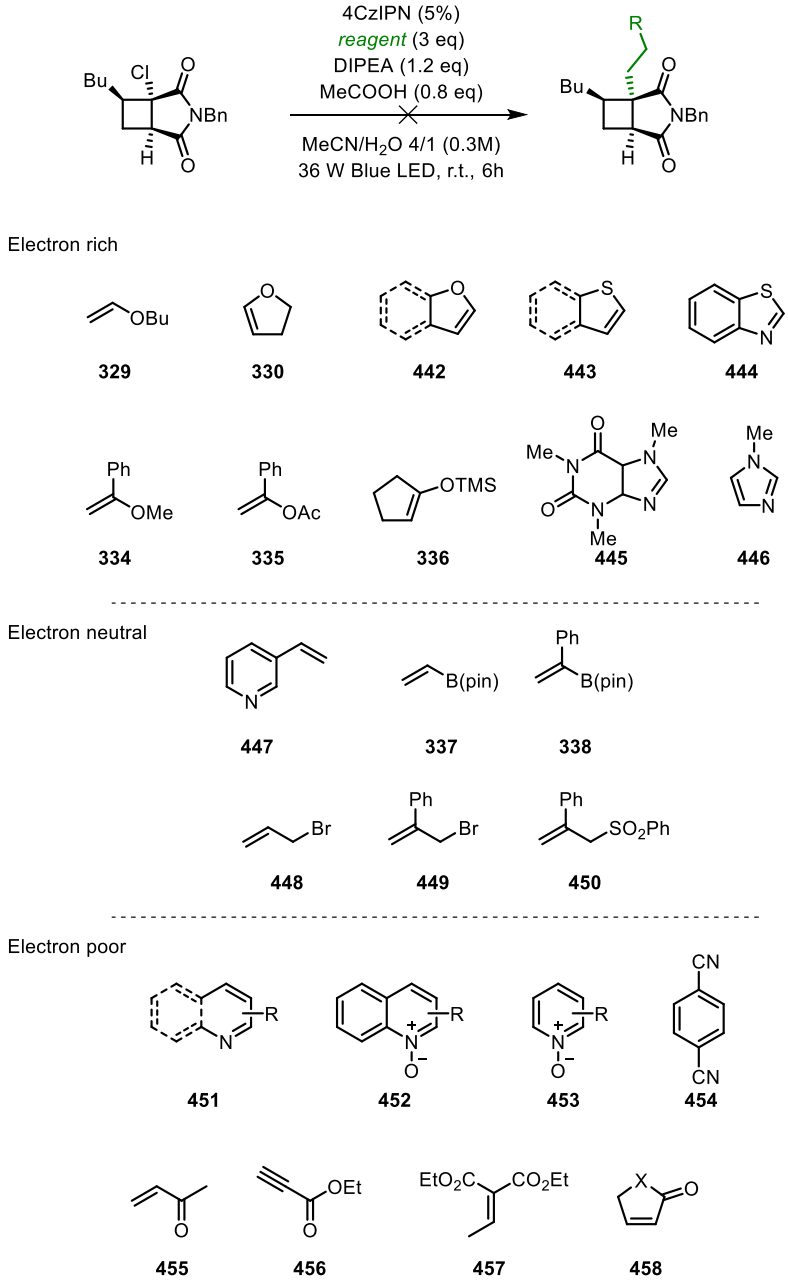


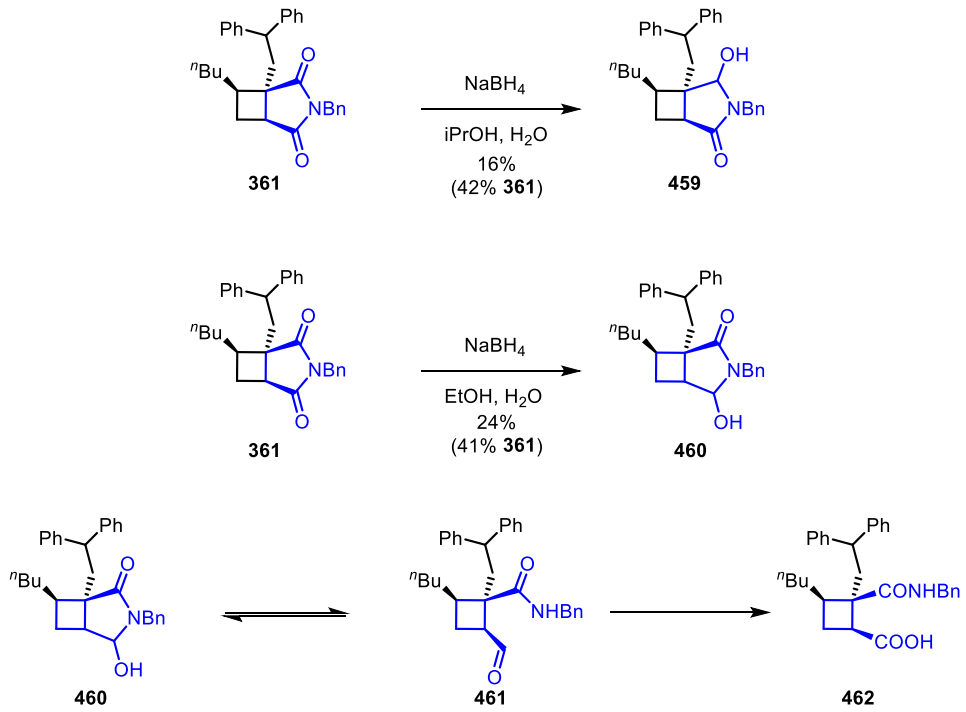
Figure 24 *– Unsuccessful radical acceptors.*

The unsuccessful radical acceptors found from the scope of the reactions show that endocyclic and internal sp^2 bonds were difficult coupling agents due to steric hinderance when forming quaternary-tertiary bonds (Figure **24**). Furthermore, allylic bromide **448** and **449** did not give the desired allylation reaction, however, the allylic sulphone **450** did give the desired allylic adduct, albeit in low yields under the reaction conditions. For this reason, allylation of the cyclobutane was not included in the reaction scope. Minisci reactions also did not show any of the desired heteroaromatic products under the reaction conditions, with either *N*-heteroaromatic or *N*-oxide heteroaromatics. This may also be due to the steric hinderance faced with forming sp^3-sp^2 bonds on a crowded centre.

2.7. Regioselective ring opening of succinimide

2.7.1. Selective carbonyl reduction

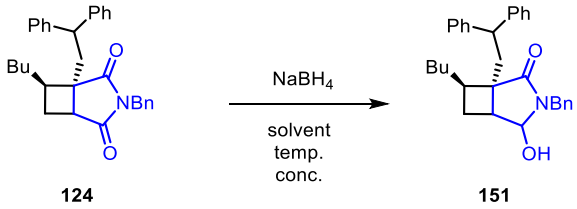
Upon successful functionalisation of the cyclobutene ring, focus was then applied to the ring opening of the succinimide. It was previously reported in the group that the use of $NaBH_4$ could be used to selectively reduce one side of the succinimide ring to give the hemiaminal. This was performed upon the succinimde **361** and found that the reduction was completely regioselective (Scheme **77**). Switching solvents to a less sterically bulky alcohol also gave rise to the opposite regioselectivity. Direct oxidation of the hemiaminal did not give the desired carboxylic acid **462**, suggesting that there is no equilibrium towards formation of the aldehyde and amide **461**.



Scheme 77 *- Regioselective reduction of imide carbonyls.*

The yields obtained for the reduction of the imide carbonyls were found to be poor. An initial screen of changing solvent, concentration and temperature conditions gave no improvement to the original yields (Table **25**). Fortunately, further increasing the temperature to 70°C using ethanol as solvent, gave full conversion to the desired hemiaminal **151**.

Table 25 *- Screening conditions for selective reduction of succinimide.*



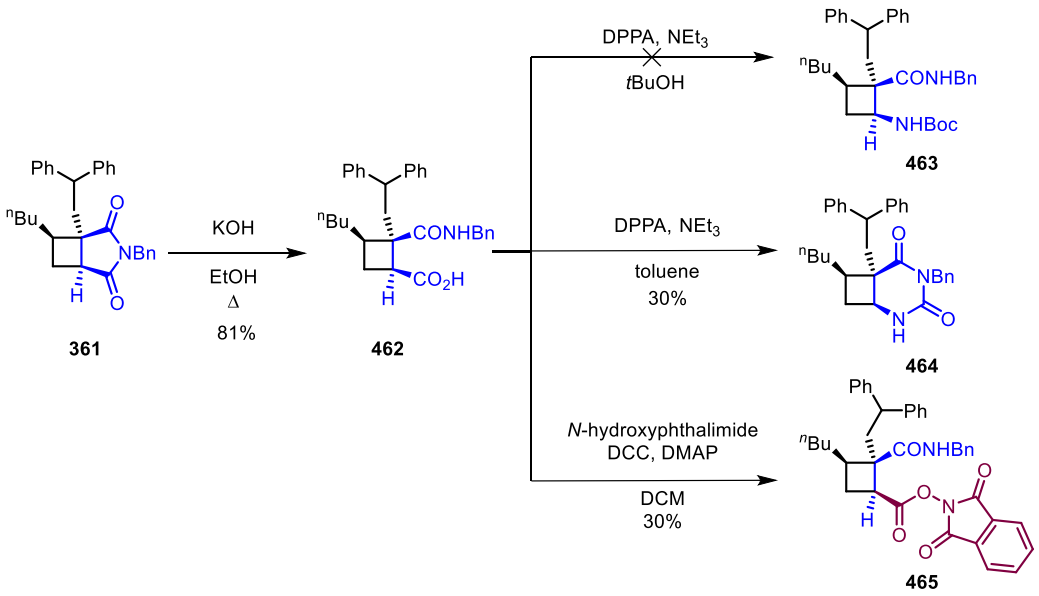
124 **151**

Entry	**Solvent**	**Temp** (°C)	**Conc** (M)	**151** (% Yield)	**124** (% Yield)
1	DCM	r.t.	0.12	0	-
2	DCM/H_2O	r.t.	0.12	0	-
3	THF/MeOH	r.t.	0.12	0	-
4	MeOH	r.t.	0.12	0	-
5	EtOH/H_2O	r.t.	0.06	14	46
6	EtOH/H_2O	r.t.	0.24	7	44
7	EtOH/H_2O	0	0.12	9	62
8	EtOH/H_2O	50	0.12	17	33
9	EtOH	70	0.10	72	0

Yields calculated by NMR using trimethoxybenzene as an internal standard.

2.7.2. Hydrolysis and subsequent functionalisation

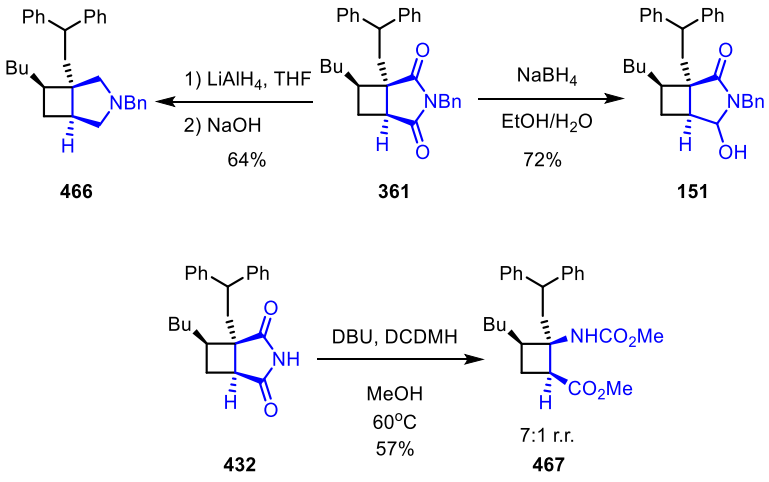
Pleasingly, hydrolysis of compound **361** gave the desired ring-opened product **462** with excellent regioselectivity and yield. Further functionalisation of the free carboxylic acid was undertaken (Scheme **78**). A Curtius rearrangement in the presence of *tert*-butyl alcohol as solvent and nucleophile, did not give any of the desired cyclobutylamine product **463**. This transformation would have been highly valuable due to obtaining the opposite regioisomer to cyclobutylamine **467** of the Hofmann rearrangement (Scheme **79**). However, under conditions where no nucleophile was present, the Curtius rearrangement was observed, however, in moderate yields, but gave the ring expanded uracil product **464**. Furthermore, carboxylic acid activation was undertaken using *N*-hydroxyphthalimide to give the redox active ester **465**. These esters are highly valuable motifs for radical functionalisation and so are an important structure to achieve. The compound was obtained, although in low yields, and demonstrates that further radical functionalisation to the cyclobutane can be reasonably obtained through this ester. All yields through carboxylic acid chemistry were low due to ring closure to go back to succinimide **361**. This is due to the active intermediates formed when functionalising the carboxylic acid providing an ideal electrophilic carbonyl for the amide to cyclise onto.



Scheme 78 *– Hydrolysis of the succinimide ring and subsequent carboxylic acid functionalisation.*

2.7.3. Carbonyl reduction

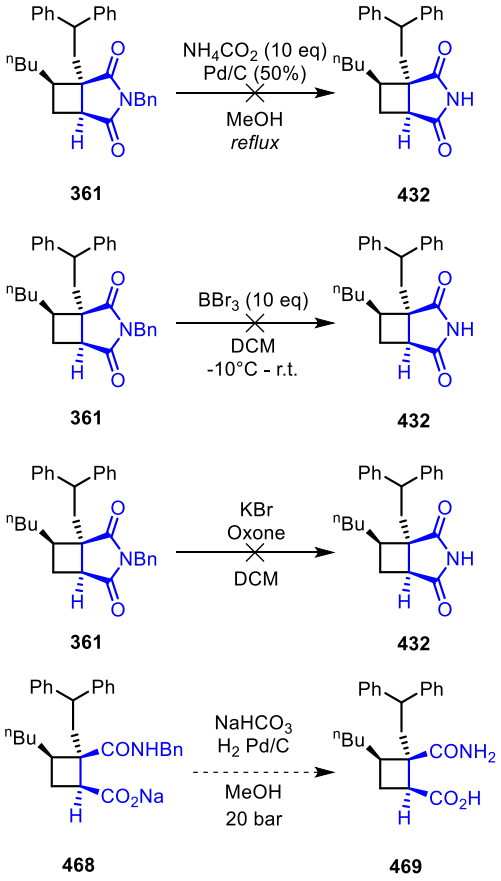
Further functionalisations of the succinimide ring were investigated. Pleasingly each transformation took place under previous literature conditions without need for optimisation (Scheme **79**). Under basic hydrolysis, the free carboxylic acid **462** was obtained with high regioselectivity and excellent yield. Furthermore, the complete reduction of the succinimide carbonyls was completed in moderate yields to give azabicyclo[3.2.0]alkane **466**. Finally, **432** was employed into conditions for a Hofmann rearrangement, giving cyclobutylamine **467** with excellent regioselectivity but moderate yield. These functionalisations further demonstrate the scale of diversity available to this structural motif.



Scheme 79 *– Scope of succinimide functionalisation.*

2.7.4. Debenzylation reactions

We sought a method for the debenzylation of compound **361** (Scheme **80**). However, upon employment of numerous literature conditions for debenzylation of amides and imides, no debenzylation products were observed by ^{1}H NMR. One promising reaction with the carboxylate **468**, using hydrogen with palladium on carbon under high pressure conditions, the debenzylated product **469** was observed by ^{1}H NMR but low productivity (9:1 **468**:**469** after 18 hours). After leaving for 48 hours, decomposition of the starting material was observed and no signs of product **469** remained. It was decided that no further investigations would be undertaken.



Scheme 80 *- Attempted debenzylation of compound* ***361****.*

Chapter 2

3.1. Previous synthesis of spirocycles

Cyclobutane-containing spirocycles have a complex 3-dimensional structure that is highly valued in medicinal chemistry. Since the landmark paper "Escape from Flatland", which outlines the success of potential drug compounds correlating with the presence of sp^3 rich carbon centres, spirocyclic compounds have become a key target in medicinal chemistry.[133,134] Several examples of spirocycles exist in current drugs (Figure **25**).

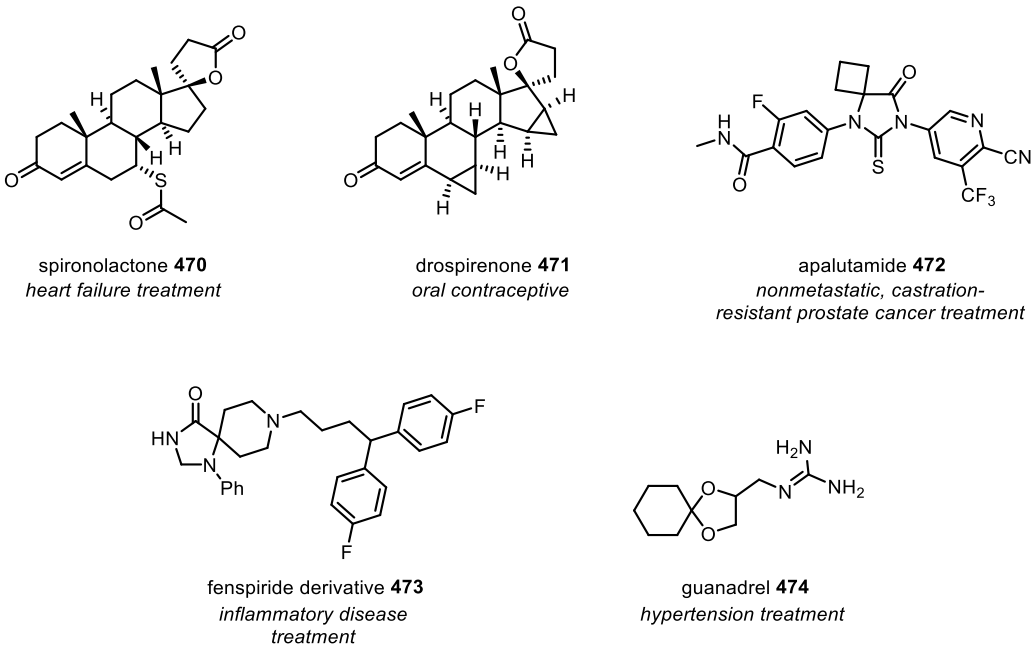
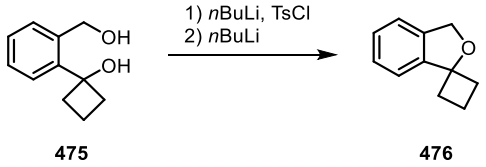


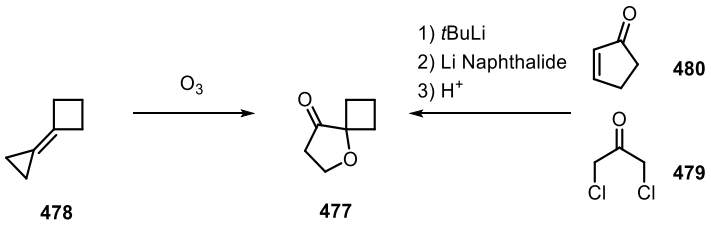
Figure 25 *– Examples of spirocycles in drug molecules.*

Access to these structures can be achieved in a variety of ways. The majority of spirocyclisations in previous literature require an sp^3 carbon quaternary centre to previously exist in the molecule, and cyclisation to occur at a less hindered centre (Scheme **81**).[135]



Scheme 81 *- Spirocyclisation to form a 1-oxaspiro[3.4]octane.*

Other examples involve various forms of cyclisation onto a preformed or formed *in situ* carbocycle, in most cases, utilising enolate or transition metal chemistry.[136] For example, work by de Boer *et al.* furnished oxaspiropentanes through oxidation of a exocyclic double bond followed by a pinacol-like rearrangement to give the spirocycle (Scheme **82**). Access to this structure has also been achieved through a multistep process from cyclopentanone and 1,3-dichloroacetone.[137]



Scheme 82 *– Two methods towards the synthesis of spirocycle* ***477.***

An advantage of spirocycles is the 3-dimensional rich chemical space that can be accessed. Spirocycles can be employed as a useful analogue of other heterocycles such as morpholine, piperazine and tetrahydropyrans and further develop the building blocks available for drug development. The use of these analogues can greatly enhance the exit vectors – positions on a molecule where additional modifications can be made – available for further functionalisation of a drug scaffold (Figure **26**).

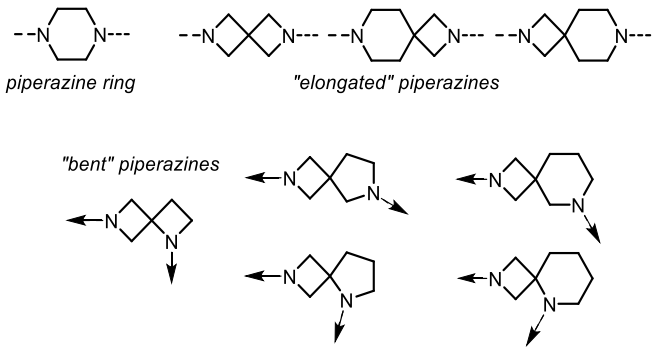
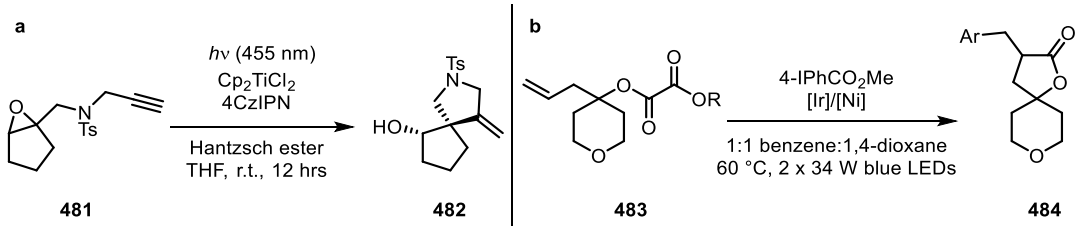


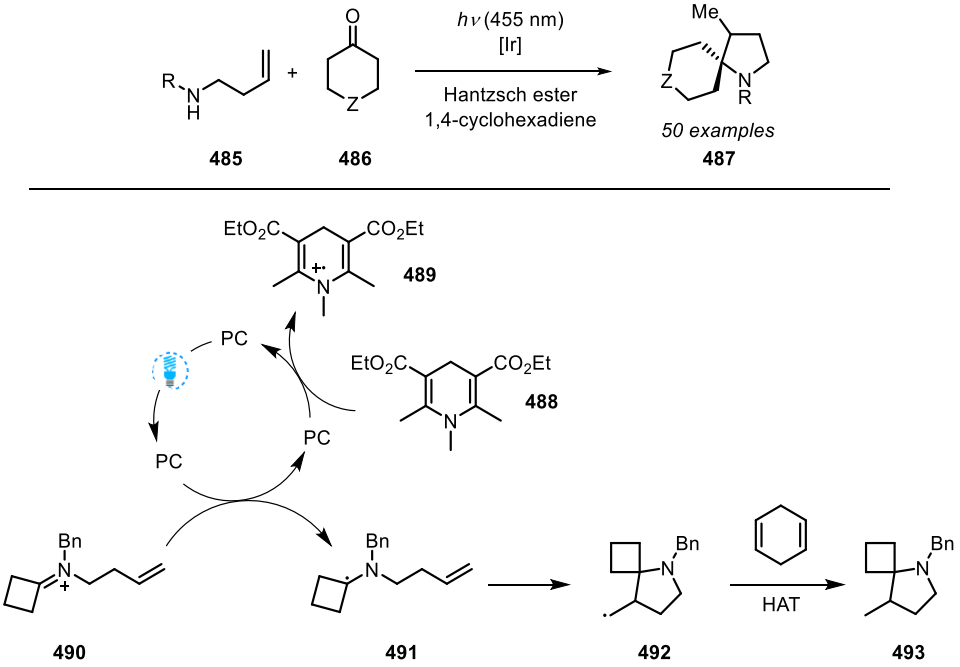
Figure 26 *– Demonstration of "exit vectors" made possible from aza-spiro-alkanes*

Photoredox catalysis has become an extremely useful tool in the past decade for the formation of radicals under mild conditions.[15,138] The use of radicals in cyclisation reactions has been used extensively, however, previous literature into the use of photoredox catalysis into the formation of spirocycles has been very limited. However in the past few years there has been a rapid development in this area.[139–141] These examples include the use of transition metals in tandem with photoredox to achieve spirocyclisation of propargyl amine **481** (Scheme **83a**).[140] Other methods require oxidative decarboxylation or sacrificial Hantzsch ester to achieve the desired radical and spirocyclisation of **483** (Scheme **83b**).[142,143]



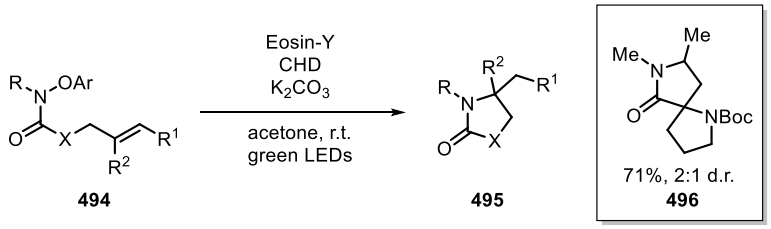
Scheme 83 *- Previous photoredox approaches to form* ***a)*** *2-azaspiro[4.4]nonanes and* ***b)*** *1,8-dioxaspiro[4.5]decanes.*

More recently work by Gaunt *et al.* developed a protocol for the synthesis of *N*-heterocyclic spirocycles from alkenyl amines **485** and aliphatic aldehydes and ketones **486** (Scheme **84**).[144] The protocol makes use of an iridium photocatalyst to reduce the preformed iminium cation **490** to an *α*-amino radical that is able to cyclise in a 5-*exo*-trig manner to give the desired spirocycle **493** in excellent yields but low diastereoselectivity.



Scheme 84 *– Mechanism towards the synthesis of spirocycles from ketones and secondary amines.*

Another example by Leonori *et al.* focussed on forming an *N*-centred radical that undergoes subsequent hydroamination across a tethered double bond of compound **491** (Scheme **85**).[145] The protocol did not focus on the synthesis of spirocycles, however, several examples were synthesised in the substrate scope in good to excellent yield but with low diastereoselectivity.

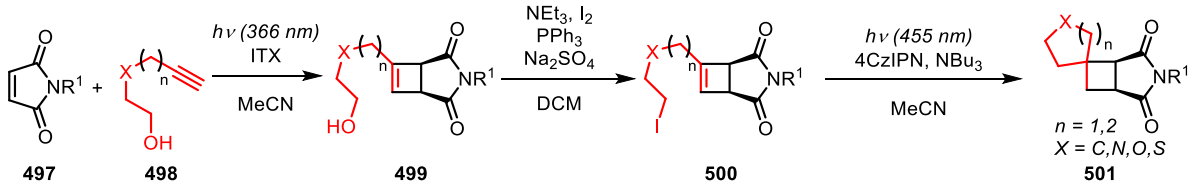


Scheme 85 *– General conditions towards cyclised amines.*

3.2. Initial project proposal

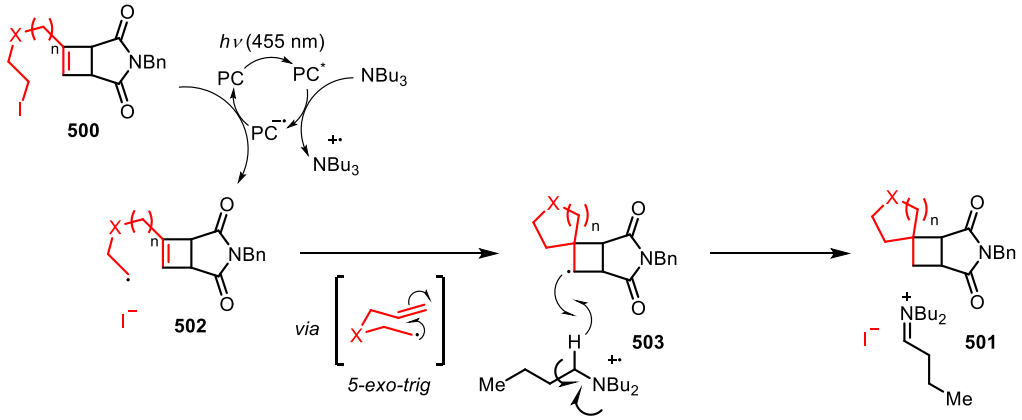
The initial proposal for the synthesis of cyclobutene spirocycles began with the [2+2] photocycloaddition of maleimide **497** and alkynol **498** to give a cyclobutene alcohol **499** (Scheme **86**).

An Appel reaction of the alcohol gives an alkyl iodine **500**, which under visible-light photoredox conditions produces spirocycle **501**.



Scheme 86 *– Proposed synthetic methodology to fused spirocycles.*

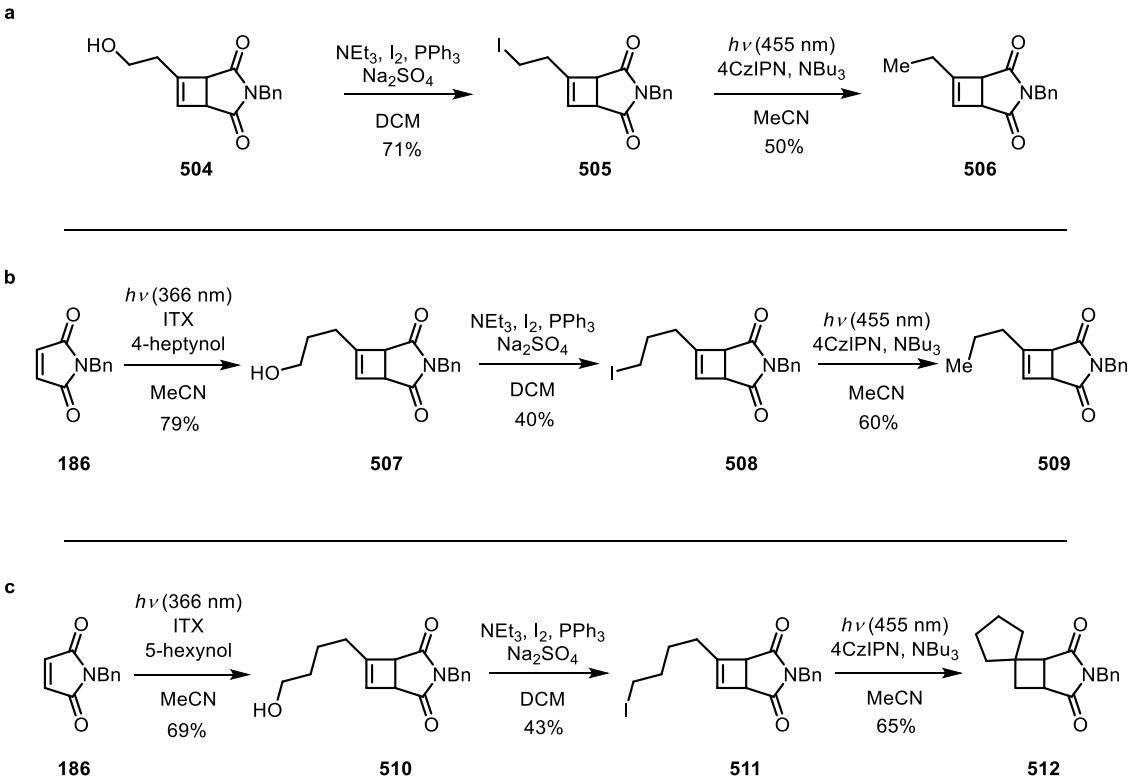
The proposed mechanism would use previously developed conditions for the dehalogenation of iodoalkanes (Scheme **87**).[85,130] First the photocatalyst is excited by a photon of light, the excited photocatalyst undergoes reduction by tributylamine, the reduced catalyst can then donate an electron to the alkyl iodide, giving the ground state catalyst, alkyl radical **502** and iodide anion as a by-product. The radical **502** can undergo cyclisation in a 5-*exo*-manner to give the spirocycle and a cyclobutyl radical **503**. The cyclobutyl radical **503** can then under HAT from the earlier oxidised tertiary amine to give the iminium iodide complex and the reduced spirocycle **501**.



Scheme 87 *– Proposed mechanism for the radical mediated cyclisation.*

Initial studies into the formation of alcohol cyclobutenes have been completed by previous work in the group. Alkynyl alcohols undergo facile [2+2] photocycloadditions in good yield (Scheme **88**).[25]

Converting cyclobutene alcohols **504**, **507**, **510** to iodoalkanes **505**, **508**, and **511** respectively was successful. Compounds **505** and **508** were unable to cyclise under these conditions, potentially due to the high energy conformation required for formation of a [2.3] or a [3.3] spirocycle (Scheme **88a**, **b**). Compound **511**, however, was able to give the spiro[3.4]octane in 65% yield (Scheme **88c**).

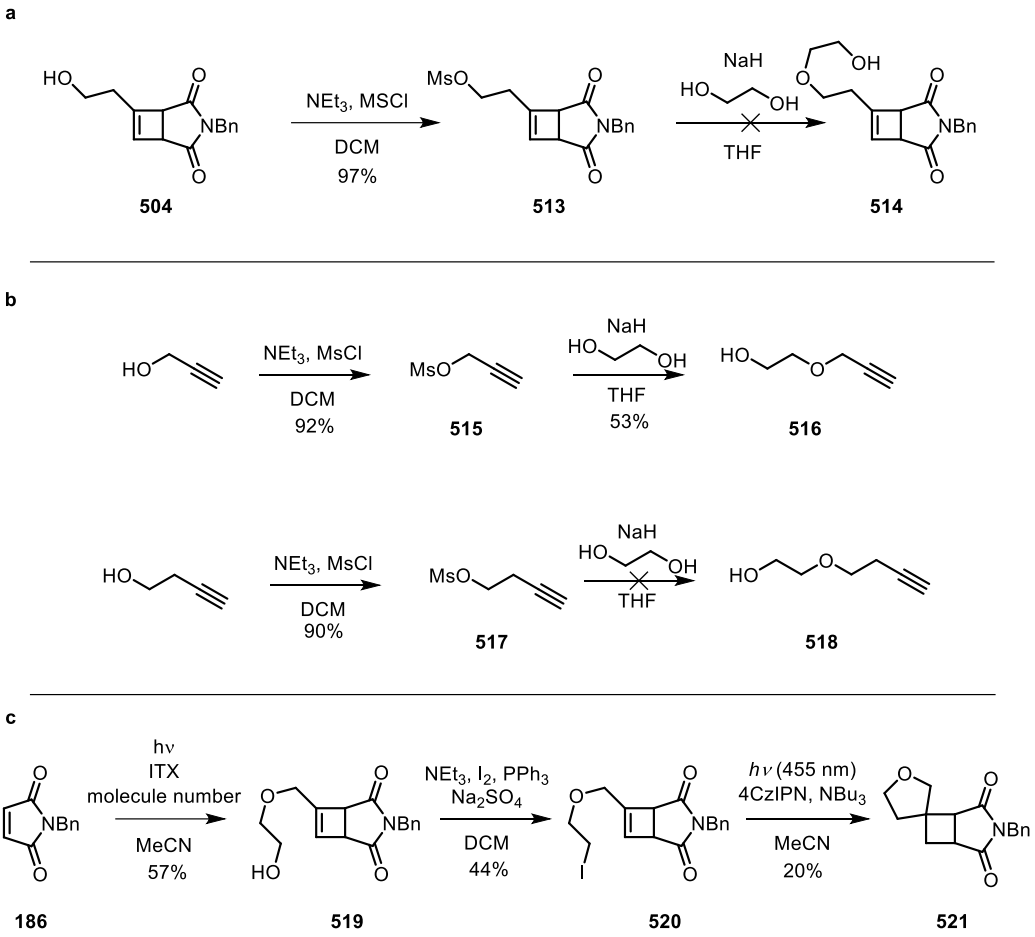


Scheme 88 *- Synthesis of spiro[n.3]alkane* ***512****.*

3.2.1. Synthesis of ether chain

In an effort to introduce functionality on the spirocycle, initial studies were focussed on tetrahydrofuran or pyrrolidine-based heterocycles (Scheme **89**). Since the [2+2]-photocycloaddition worked well with alkynyl alcohols, it was considered that conversion of the alcohol to a leaving group and displacement with a nucleophile would give access to the photoredox precursor **520** with the appropriate tether for heteroatomic spirocycle formation (Scheme **89a**). However, after mesylation of **504** in excellent yield, further functionalisation proved to be difficult due to the harsh conditions required in the presence of the succinimide ring.

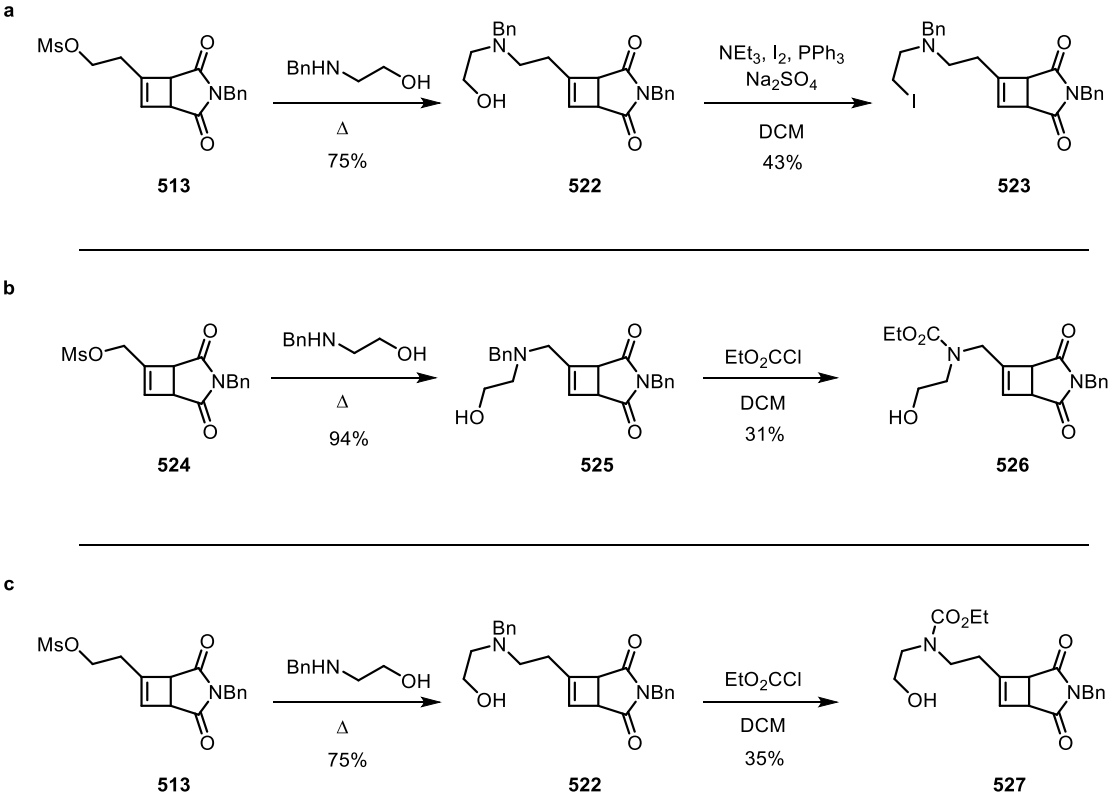
Instead, focus was redirected to mesylation and functionalisation of the alkynyl alcohols prior to the [2+2] photocycloaddition step. This was successful in the case of **515**, however, **517** did not give any alkylated products and only returned unreacted starting material (Scheme **89b**).



Scheme 89 *- Synthesis of functionalised oxaspiro[n.3]alkanes.*

Photocycloaddition of **186** and **516** gave good yields of cyclobutene alcohol **519** (Scheme **89c**). Subjecting the alcohol to Appel reaction conditions gave only fair yields of **520**, possibly due to the presence of water in the starting material. Cyclisation of **520**, gave a single diastereomer of the desired product but in 20% yields. NOE NMR studies were performed to try to elucidate the stereochemistry of spirocycle **521**, however, no conclusive results could be obtained. Future work into determination of which diasterioisomer has been isolated will be necessary.

3.2.2. Synthesis of amino alkyl chain



Scheme 90 *– Procedure towards the synthesis of azaspiro[n.3]alkanes.*

Direct alkylation of benzylaminoethanol with **513** was successful in excellent yield of **522** (Scheme **90a**). Appel functionalisation of **522** gave the desired iodo product **523**. Upon exposure to photoredox conditions, the benzyl amine was oxidised by SET and Shono-oxidation/hydrolysis products were observed. None of the desired spirocycle product was observed. This is due to the reactivity of the amine lone pair in the starting material existing at a sufficiently low oxidation potential to compete with the oxidation of tributylamine.[146] Deactivating the basicity of the amine, and increasing the oxidation potential, would prevent undesirable oxidation, and this was initially attempted by directly exchanging the benzyl substituent for a carbamate (**526** and **527**) (Scheme **90b**, **c**). However, this reaction proceeded in low yields and so the pursuit of this methodology was stopped.

3.3. One-pot cycloaddition/cyclisation/borylation

A new protocol towards the synthesis of cyclobutane spirocycles was proposed (Figure **27**). If the initial [2+2] photocycloaddition of **497** and **528** could be performed under visible-light irradiation then the subsequent cyclisation of cyclobutene **529** could be achieved under previously developed conditions by Aggarwal *et al*.. This protocol undergoes a photocatalyst-free decarboxylative borylation through SER from B_2cat_2, which then can undergo a radical borylation forming the desired C–B bond. This

proposed method could be performed as a potential one-pot procedure by the addition of B_2cat_2 dissolved in DMAc to the reaction solution on completion of the photocycloaddition step.

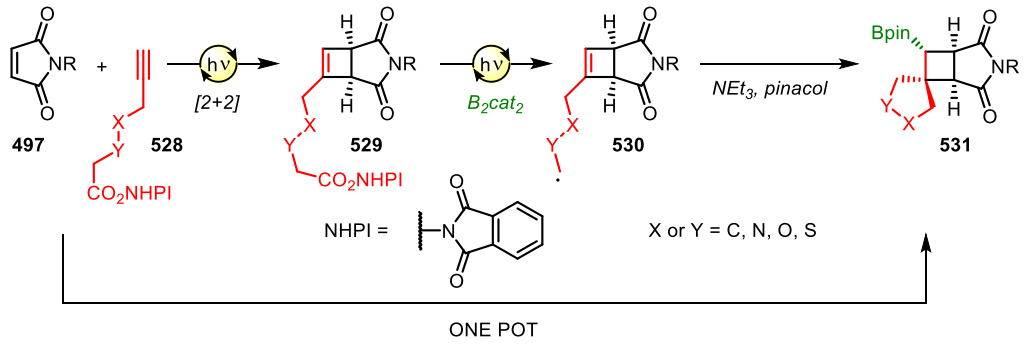
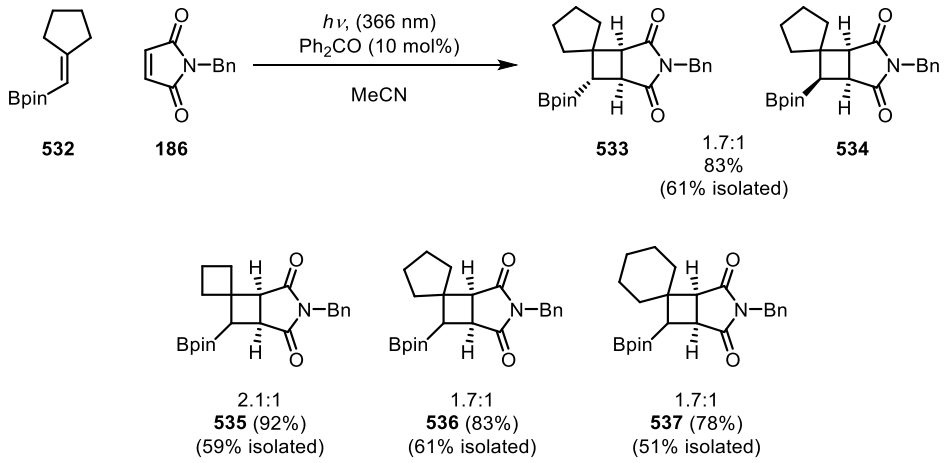


***Figure 27** – Proposed "one-pot" access to fused spiro[3.4]cyclobutylboronic esters.*

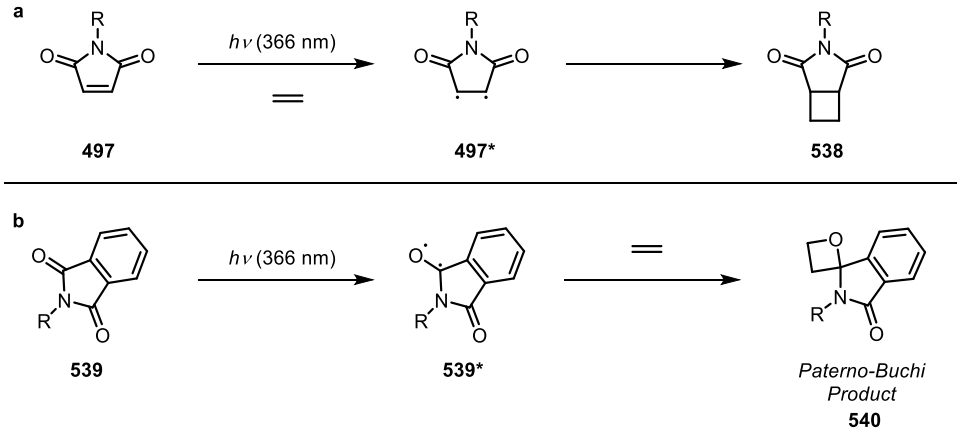
Previous work into the synthesis of boron containing cyclobutane spirocycles has been developed by Grygorenko *et al*.[78] The spirocycles were formed in a one-step photocycloaddition of maleimides and exocyclic alkenes under UV conditions. The formed boronic spirocycles gave excellent yields with low diastereoselectivity (Scheme **91**).



***Scheme 91** – UVA mediated [2+2] photocycloaddition with vinylic boronic esters.*

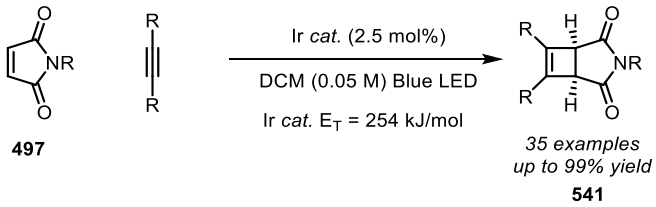
3.3.1. Visible-light triplet sensitised [2+2] photocycloaddition

The initial challenged faced with this new proposal, was the competing reactions of maleimides and phthalimides under UV conditions. For maleimides to undergo [2+2] photocycloadditions, the maleimide is required to enter its triplet state before cyclising to give **538** (Scheme **92a**). However, under these same conditions, phthalimides are also able to undergo excitation to their triplet state and undergo Paterno-Buchi cyclisations to give compound **540** (Scheme **92b**).



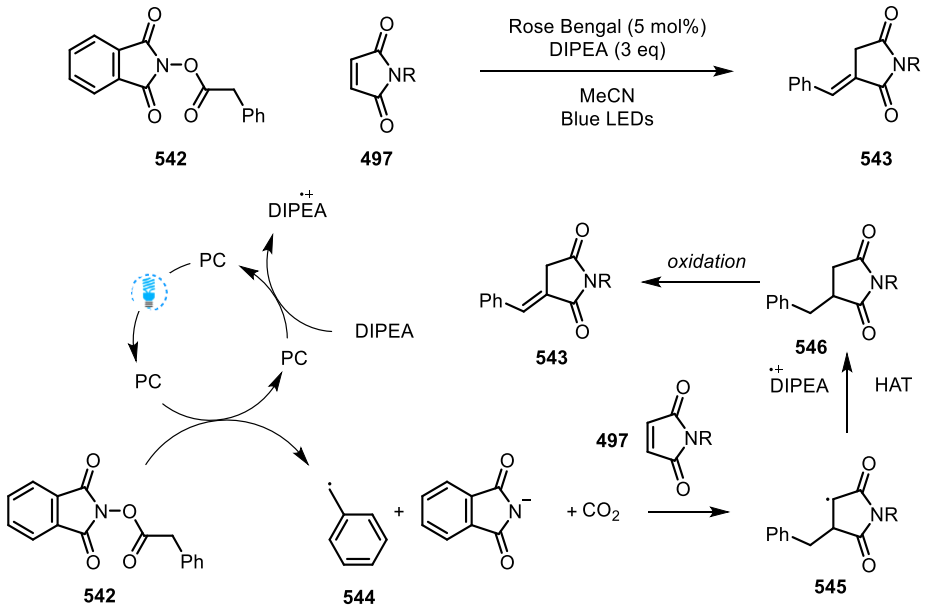
Scheme 92 *– Paterno-Buchi side reaction of phthalimides.*

To get around this, visible-light can be used in place of high energy UV light to avoid excitation of the phthalimide. However, to catalyse the photocycloaddition reaction, a triplet energy sensitiser is required that can perform efficient energy transfer selectively to the maleimide. A recent paper by Park *et al.* demonstrated that such an energy transfer was possible using an iridium photocatalyst (Scheme **93**).[109] A range of photocatalysts were trialled and found that the energy transfer from $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ was the most efficient triplet energy sensitiser. The protocol was able to produce a large scope of photocycloadditions to give cyclobutene **541** with good functional group tolerance.



Scheme 93 *– Ir catalysed visible-light [2+2] photocycloadditions, non-maleimide adducts not included.*

However, applying this protocol with a tethered redox active ester would undergo a reduction *via* SET triggering decarboxylation and therefore unwanted radical reactions. An example of this was found by Muraka *et al.* when a redox active ester underwent SER from a photoexcited Rose Bengal catalyst followed by formation of a carbon centred radical **544** after decarboxylation (Scheme **94**). Radical addition to the maleimide double bond and subsequent HAT from DIPEA gave the radical adduct **545**. Under the reaction conditions, the formed σ-bond undergoes oxidation to form an exocyclic alkene **543**.

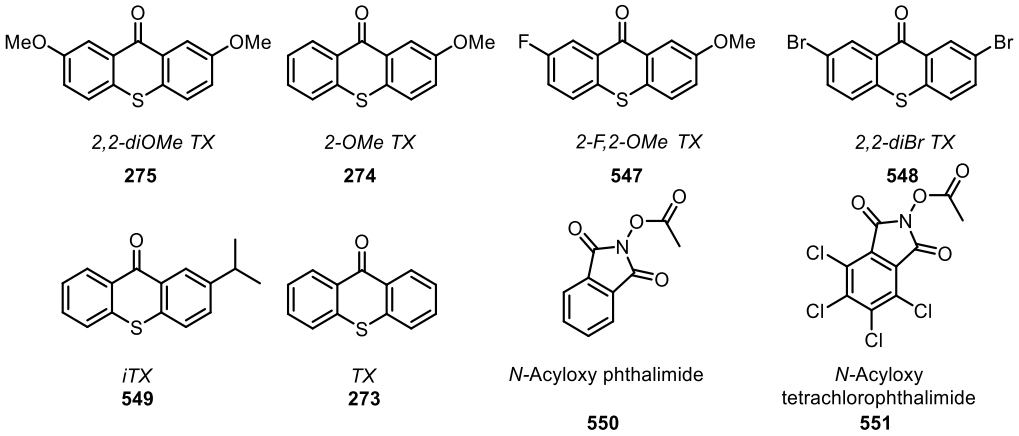


Scheme 94 *– Radical addition to maleimides from redox active esters.*

To mitigate this issue, an appropriate sensitiser is required that will not undergo SET processes. Sensitisers such as this have been widely used in UV photochemical reactions and have been found to improve the efficiency of photochemical reactions drastically. In recent work by the Booker-Milburn group, DFT led design of a variety of substituted thioxanthone sensitisers using a range of electron donating and withdrawing groups on the aryl rings was reported.[114] Through substitution in the 2-position of the thioxanthone the absorption underwent a bathochromic shift and absorption in the visible range was possible. The designed triplet energy sensitisers were utilised in a variety of photochemical reactions and, under visible-light (455 nm) conditions, were able to outperform the efficiency of the same reactions under UV conditions.

A range of thioxanthone derivatives were chosen based on their triplet energies compared with the triplet energy calculated for phthalimide derivatives (Table **26**).

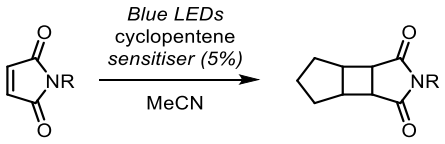
Table 26 *– Triplet energies (DFT and measured) for a range of thioxanthones and N-acyloxy phthalimides.*



Molecule	E_T kJ/mol
Phthalimide **550**	323 (DFT)
Tetrachlorophthalimide **551**	256 (DFT)
2,2-diOMe TX **275**	231
2-F, 2-OMe TX **547**	235
2-OMe TX **274**	242
$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	254
2,2-diBr TX **548**	264
*i*TX **549**	266
TX **273**	274
N-Benzyl maleimide **186**	296 (DFT)
Blue light (λ_{max} 455 nm)	263

While the *N*-(acyloxy)phthalimide **550** is of higher triplet energy by DFT when compared to the maleimide **186**, this shows that the possibility of energy transfer between the sensitiser and maleimide without excitation of the redox active ester is possible. The sensitisers with triplet energy above that of $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (254 kJ/mol) were considered to give the best results. With this in mind, initial study of the triplet sensitised [2+2] photocycloaddition was performed (Table **27**).

Table 27 *– Trialling a range of thioxanthones for successful energy transfer.*



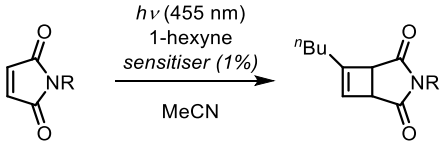
497

Entry	R	Sensitiser (5%)	Time (hrs)	SM	Prod
1	Bn	2,2-diMeO TX **275**	2	100	0
2	Bn	2-F, 2-OMe TX **547**	2	99	0
3	Bn	2-OMe TX **274**	2	98	0
4*	Bn	2,2-diBr TX **548**	2	98	2
5	Bn	*i*TX **549**	2	96	3
6	Bn	TX **273**	2	98	1
7*	Me	2,2-diBr TX **548**	2	88	5
8	Me	*i*TX **549**	2	89	-
9	Me	TX **273**	2	100	-
10*†	Me	2,2-diBr TX **548**	6	-	*trace*

**solvent is toluene, † 1 g scale*

The lower energy triplet sensitisers (Entries 1 – 3) showed no evidence of triplet sensitisation. However, the sensitisers of triplet energies above 254 kJ/mol (Entries 4 – 6) showed that sensitisation at this wavelength was possible, albeit at low conversion, and that from the initial reactions, 2,2'diBr TX **548** (Entry 4 + 7) gave the desired cycloadduct with both derivatives of maleimide. Toluene was used as the solvent of choice for sensitiser **548** due to solubility issues in acetonitrile. On scale up to 1 gram, the reaction did not give any sign of the desired cycloadduct (Entry 10). The potential reasoning behind this was due to the reaction conditions being under a positive pressure of nitrogen and cyclopentene having a lower boiling point (*b.p.* 44°C) than the solvent (*b.p.* 110°C). The slow reaction conditions and heat from the light source would have led to evaporation of the cyclopentene substrate. For this reason, a new substrate, 1-hexyne (*b.p.* 71°C), was chosen due to its higher boiling point and previous success in [2+2] photocycloadditions (Table **28**).

Table 28 *– Comparison of N-benzyl and N-methyl maleimides with high energy sensitisers.*

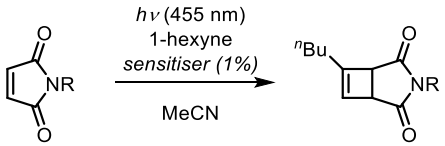


497

Entry	R	Sensitiser (1 mol%)	Time (hrs)	SM	Prod
1*	Me	2,2-diBr TX **548**	4h	18	16
2	Me	*i*TX **549**	4h	-	trace
3	Me	TX **273**	4h	-	0
4*	Bn	2,2-diBr TX **548**	4h	45	9
5	Bn	*i*TX **549**	4h	-	trace
6	Bn	TX **273**	4h	-	0

Results from using 1-hexyne as the cycloadduct confirmed that 2,2-diBrTX (Entries 1 + 4) gave the best results for photocycloaddition. The overall mass balance for the reactions were still low however, and so further changes to the reaction conditions were required. As **548** was the only sensitiser to give the desired cycloadduct, it was used as the sensitiser for all subsequent optimisations (Table **29**).

Table 29 *– Optimisation of [2+2] photocycloaddition.*



497

Entry	R	Sens. loading	Solvent	Time (mins)	SM	Prod
1	Me	2%	Toluene	2h	62	3
2	Me	5%	Toluene	2h	56	6
3	Me	10%	Toluene	2h	36	11
4	Me	15%	Toluene	2h	45	7
5	**Me**	**10%**	**DCM**	**2h**	**0**	**81**
6	Me	10%	DMF	2h	0	20
7	Me	10%	DMA	2h	0	31

Sensitiser loadings were trialled (Entries 1 – 4) and found that the addition of 10 mol% gave the best yields when using toluene as a solvent. Solubility issues were found when using 15 mol% loading which may have led to scattering of light in the reaction vessel, reducing the reaction performance. The reaction was then screened under different solvent conditions, with solubility issues being found with DMF and DMA (Entries 6 + 7). However, when DCM was used as the solvent the sensitiser could be dissolved completely and gave an excellent yield of 81% of the desired cycloadduct. While DCM is a non-polar aprotic solvent, similar to toluene, it can be rationalised that the large increase in yield was due to the solubility of the reagents in DCM being far greater than that of toluene.

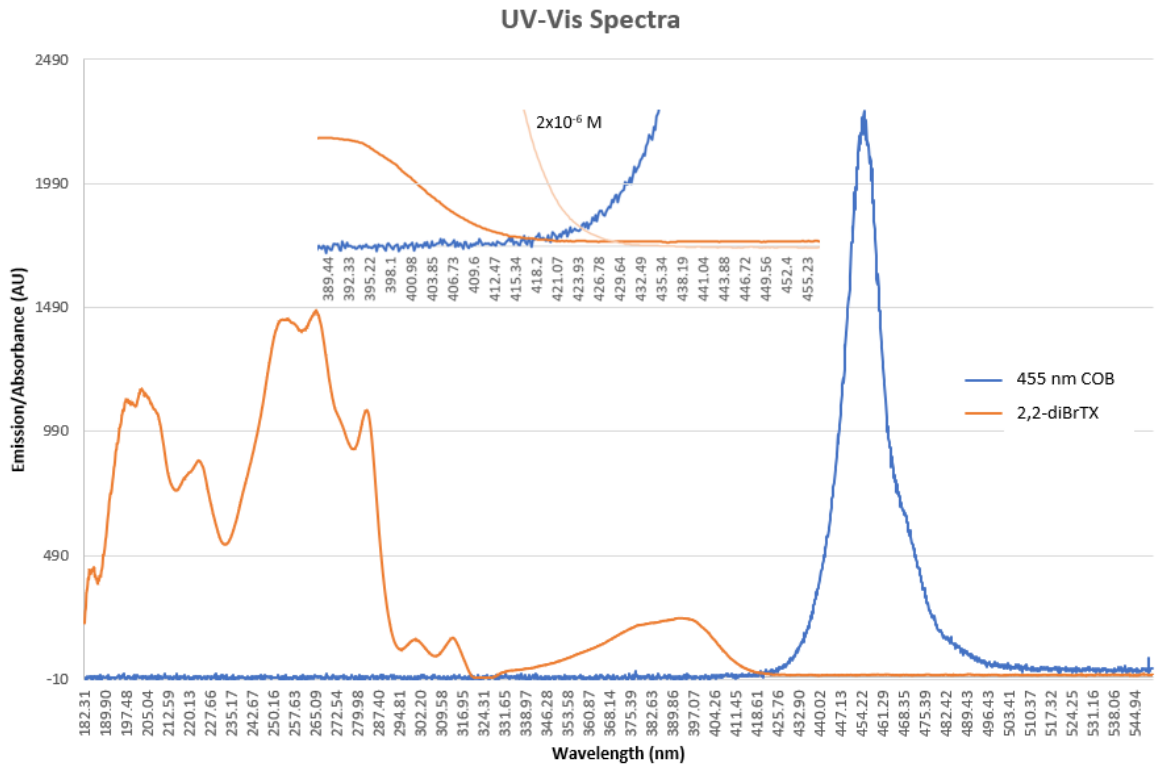


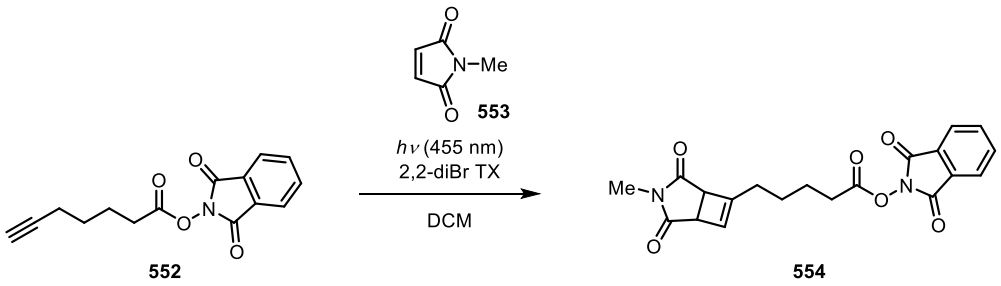
Figure 28 *– UV/Vis spectra of 455nm COB and 2,2'-diBrTX.*

Interestingly, the UV/Vis absorption spectra of sensitiser **548** and the emission spectra of the 455 nm COB LED shows that there is a very small overlap between the two to enable adequate sensitisation (Figure **28**). The overlap occurs at approximately 423 nm which gives an excitation energy of 282 kJ/mol *vs* the triplet energy of **548** which is 264 kJ/mol. This shows that an adequate amount of excitation energy from the LED is being provided, although the majority of the photons emitted will not be high enough energy.

As the UV/Vis spectra demonstrates the difficulty of pairing high excitation energy with low wavelength adsorption, the sensitiser was taken forward without considering any further synthetic

alterations and apply the optimum conditions to the desired photocycloaddition of the redox active ester and maleimide (Table **30**).

Table 30 *– Optimisation of [2+2] photocycloaddition of redox active ester and N-methyl maleimide.*



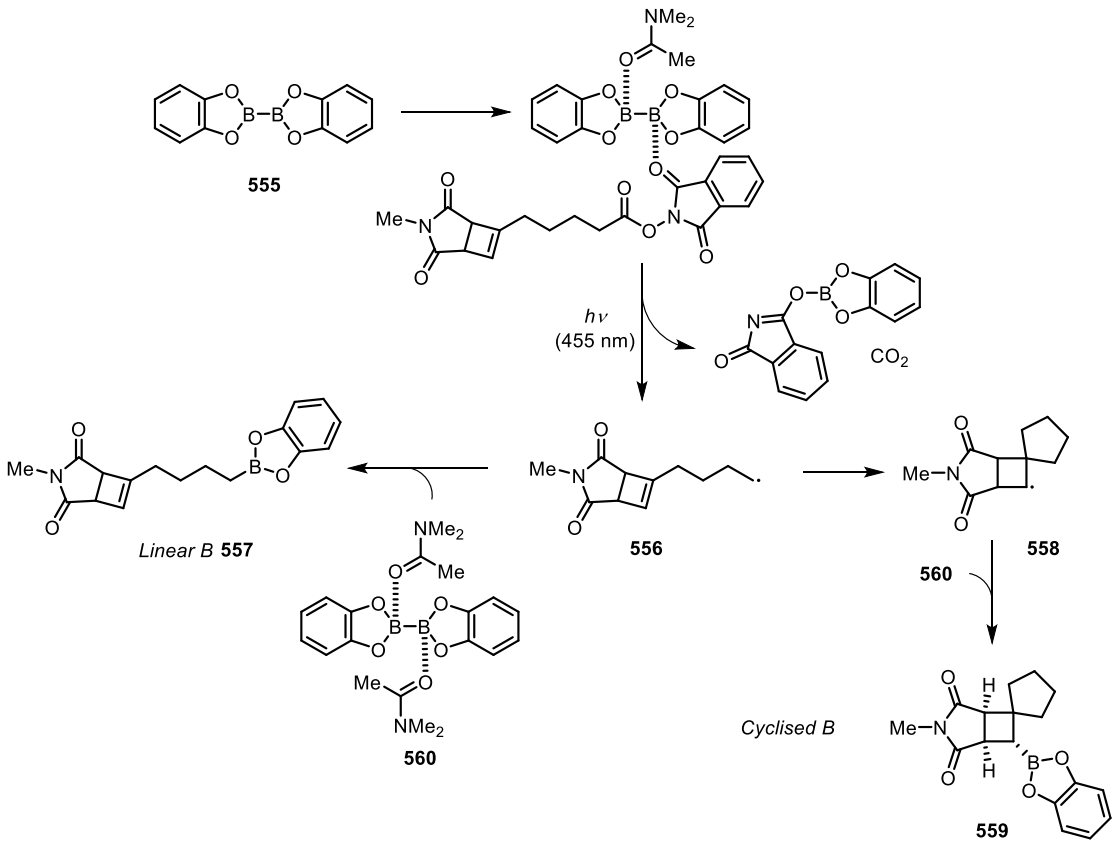
Entry	Sensitiser (%)	Conc. [M]	552 (eq)	553 (eq)	Time (h)	553 (%)	Product (% Yield)
1	10	0.10	1.5	1.0	2	0	67
2	5	0.10	1.5	1.0	2	4	69
3	2	0.10	1.5	1.0	2	15	60
4	1	0.10	1.5	1.0	2	41	34
5	5	0.30	1.5	1.0	2	28	31
6	5	0.15	1.5	1.0	2	13	53
7	5	0.05	1.5	1.0	2	12	56
8	5	0.10	1.0	1.5	2	36 (**552**)	48
9*	5	0.10	1.0	1.5	3	0 (**552**)	68
10*	5	0.10	1.5	1.0	3	0	58

*anhydrous conditions

Applying the optimum conditions from the previous trials gave good yields of 67% (Entry 1), and 5% loading of the sensitiser was found to give the best yields (Entries 2 – 4). Changing the concentration of the reaction (Entries 5 – 7) gave no improvement to the yield and reversing the limiting reagent to **552** demonstrated that the yield of **554** could be maintained.

3.3.2. Tandem cyclisation/1,2-carboboration

With success in achieving a good yield of the cycloadduct without reducing the redox active ester, focus was applied to the cyclisation and borylation stage of the reaction. From previous work undertaken on this protocol, a mechanism for the tandem cyclisation/borylation is proposed as such (Scheme **95**).



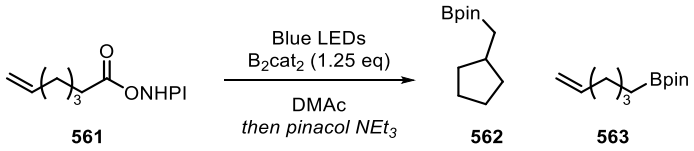
Scheme 95 *– Proposed mechanism for cyclisation/borylation.*

The diboron species **555** undergoes coordination to the solvent and the amide carbonyl of the redox active ester. The aryl rings form an EDA complex where an electron can be donated between the electron rich catechol to the electron poor phthalimide ester. The SET triggers decarboxylation and the amide oxygen forms an irreversible bond with boron. The generated alkyl radical then undergoes one of two processes depending on reaction conditions.

The radical acceptor **560** can undergo radical addition to the alkyl radical (*fast process due to electron match*) to give the linear borylated product **557**. Alternatively, the alkyl radical can undergo 5-*exo*-trig cyclisation (which is a slow process due to electron mismatch) to give the cyclobutyl radical, which can then undergo borylation to give the desired spirocycle **559**.

Previous work using this protocol has found that the 5-*exo*-trig cyclisation did not favour cyclisation before borylation (Table **31**), even when the reaction was diluted to 0.01 M concentrations, the ratio of cyclised **562** to linear **563** products was still close to 1:1.[114] It was thought that with applying **554** to these conditions, that the strain release from forming a cyclobutane from a cyclobutene would enhance the yield of cyclisation observed.

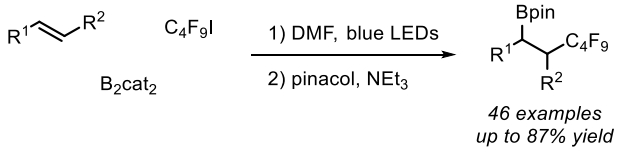
Table 31 *– Table of results for 5-exo-trig cyclisation/borylation.*



561 **562** **563**

Entry	**Conc.** (M)	**563** (Lin.) %	**562** (Cyc.) %	**Total Yield** %	**563:562**
1	1.00	36.5	6.3	42.8	5.8:1
2	0.50	41.1	9.1	50.2	4.5:1
3	0.20	48.6	20.3	68.9	2.4:1
4	0.10	46.0	31.0	77.0	1.5:1
5	0.01	34.3	48.8	83.1	0.7:1

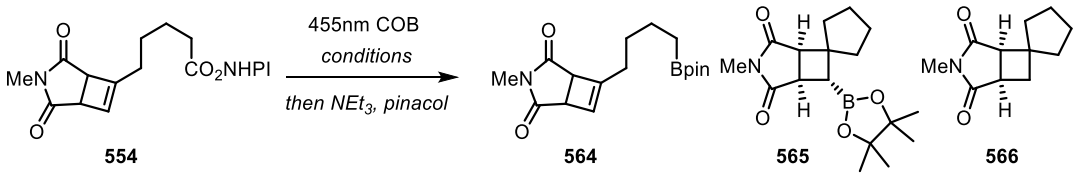
Work by Studer *et al.* on radical mediated borylation has shown that electron poor alkyl radicals such as perfluoroalkanes have enough of an electron mismatch to diboron **555** that they will undergo radical addition to an alkene, followed by addition to boron. This protocol allows for 1,2-carboboration across unactivated alkenes (Scheme **96**).[147]



Scheme 96 *– Conditions for the 1,2-carboboration of unactivated alkenes.*[147]

An initial scope of the cyclisation/borylation conditions was taken to determine if the protocol developed by Aggarwal *et al.* would suit the desired system (Table **32**).

Table 32 *– Optimisation of the tandem cyclisation/1,2-carboboration.*



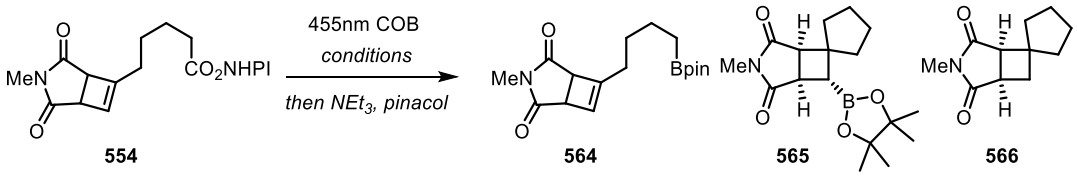
Entry	B_2cat_2 (eq)	**Solvent** (M)	**Additive** (eq)	**Sensitiser** (%)	**564** (% Yield)	**565** (% Yield)	**566** (% Yield)
1	1.25	DCM (0.10)	DMF (10)	-	70	0	0
2*	1.25	DCM (0.10)	DMF (10)	-	66	0	0
3	1.25	DCM (0.10)	DMF (10)	**548** (5)	73	0	0
4	1.25	DCM (0.01)	DMF (10)	**548** (5)	36	8	0
5	1.25	DMAc (0.10)	-	-	76	8	0
6	1.25	DMAc (0.01)	-	-	0	0	47
7†	2.00	DMAc (0.05)	-	-	60	10	0
8	3.00	DMAc (0.05)	-	-	72	8	0
9	3.00	DMAc (0.025)	-	-	77	15	0
10	3.00	DMAc (0.01)	-	-	48	26	0

*dry glassware and solvents, †Studer conditions.[147]

Initially the reaction was run in DCM as the solvent as this would allow for compatibility with the one-pot procedure in future reactions. However, on addition of DMF as a boron coordinating additive, only the linear product **564** was observed although in very good yields and that the presence of the sensitiser **548** (Entries 3 + 4) did not hinder the yields of linear product **564**. When lowering the concentration of the reaction to 0.01 M (Entry 4) a large drop-off in mass balance and a small amount of desired cyclised product **565** was observed due to favouring the intramolecular reaction. When swapping to using DMAc as both the solvent and coordinating agent, a similar result was observed and at high concentration a small amount of cyclised product **565** was observed (Entry 5). When the concentration was reduced to 0.01 M, a drop in mass balance was again observed with no borylation products and only the fully reduced cyclised product **566** remaining. The lack of borylated products was due to the low concentration of diboron **555** in the reaction conditions. On increasing the equivalents of the diboron **555** to increase the rate of borylation at these low concentrations, the mass balance was restored and a trend towards the cyclised product was observed, albeit with low yields of the desired compound **565** (Entries 8 – 10). A reaction was included to demonstrate the conditions used in the protocol developed by Studer *et al.* (Entry 7). The conditions fit in with the trend we observed for formation compound **565** and therefore concluded that the electronics of this reaction were pivotal for the 1,2-carboboration process.

Another mechanism was proposed whereby an amine additive could take the place of the solvent as a coordination source. A strong σ-donation into the empty *p*-orbital of the boron atom could increase the electron density of the diboron **555** as a radical acceptor, hence slowing the rate of radical addition to diboron **555** over cyclisation onto cyclobutene **556**. A range of tertiary amine substrates were trialled (Table **33**).

Table 33 *– Optimisation of the tandem cyclisation/1,2-carboboration.*

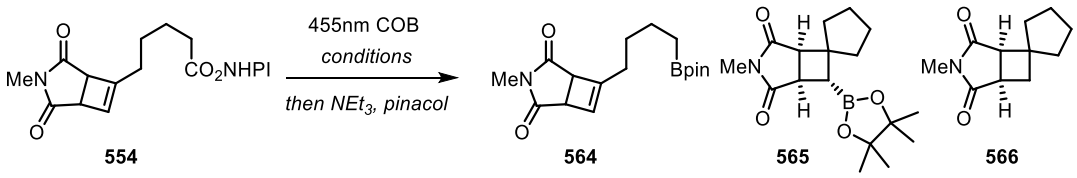


Entry	B_2cat_2 (eq)	Amine (eq)	Solvent (M)	Additive (eq)	564 (% Yield)	565 (% Yield)	566 (% Yield)
1	1.25	DABCO (3)	DCM (0.100)	-	8	11	26
2	1.25	Pyridine (3)	DCM (0.100)	-	35	9	9
3	1.25	Lutidine (3)	DCM (0.100)	-	58	8	0
4	1.25	NBu_3 (3)	DCM (0.100)	-	40	19	9
5	1.25	NEt_3 (3)	DCM (0.100)	-	35	17	9
6	3.00	NBu_3 (2)	DCM (0.025)	-	30	27	0
7	3.00	NBu_3 (2)	DCM (0.025)	AcOH (2)	38	22	0
8	3.00	NBu_3 (2)	DCM (0.010)	AcOH (2)	16	18	0
9	3.00	DIPEA (2)	DCM (0.025)	AcOH (2)	34	37	0
10	3.00	DIPEA (2)	DCM (0.010)	AcOH (2)	15	47	0
11	3.00	DIPEA (2)	DCM (0.010)	-	21	49	0

The results from using tertiary amines as the coordination species demonstrated that similar to using DMAc in solvent quantities, cyclisation could be observed at higher concentrations (Entries 1 – 5) only using stoichiometric quantities with triethylamine and tributylamine giving the best results for cyclisation (Entries 4 + 5). Tributylamine was taken forward for further investigations and another more sterically hindered tertiary amine diisopropylethylamine was included (Entries 6 – 11). Acetic acid was added as an additive to assist in maintaining the *p*H of the reaction to reduce the amount of product loss to basic hydrolysis of the succinimide ring (Entries 7 – 10). Diisopropylethylamine was found to give the highest yield of cyclised product (Entries 10 + 11) albeit in less than 50% yield.

Other diboron sources were considered to reduce the efficacy towards forming C–B bonds. This was proposed as a way to reduce the amount of linear product observed and increase the probability of cyclisation before borylation (Table **34**).

Table 34 *– Optimisation of the tandem cyclisation/1,2-carboboration.*



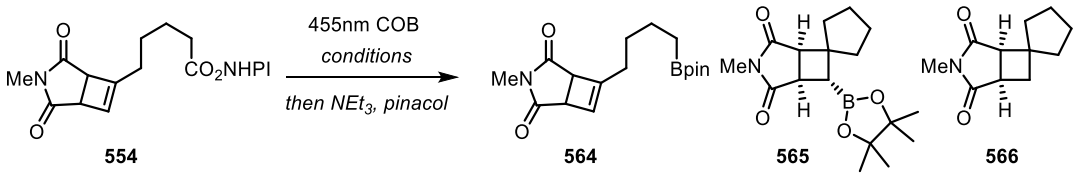
Entry	$B_2(OH)_4$ (eq)	B_2pin_2 (eq)	**Amine** (eq)	**Solvent** (M)	**554** (%)	**564** (% Yield)	**565** (% Yield)	**566** (% Yield)
1	3	-	DIPEA (2)	DCM (0.01)	0	0	0	68
2†	3	-	DIPEA (2)	DCM (0.01)	31	0	0	37
3*	3	-	DIPEA (2)	DCM (0.05)	15	0	0	41
4*	3	-	DIPEA (2)	DCM (0.10)	0	0	0	48
5*	3	-	DIPEA (2)	DCM (0.20)	17	0	0	31
6*	3	-	DIPEA (2)	DCM (0.30)	28	0	0	19
7**	-	3	DIPEA (2)	DCM (0.05)	10	0	0	57
8**	3	-	Pyridine (2)	DCM (0.10)	0	60	0	0
9**	3	-	Lutidine (2)	DCM (0.10)	0	54	0	0

*† 3 eq catechol, * 0.5 hr reaction, ** 1 hr reaction*

When employing tetrahydroxy diboron ($B_2(OH)_4$) or bis(pinacolato)diboron (B_2pin_2) there was no observed borylation of the substrate in either the liner or cyclised products (Entries 1 – 7). In the case of $B_2(OH)_4$ this is potentially due to the acidic protons interacting with the amine lone pair and preventing coordination. At higher concentrations, the reaction time was found to be significantly shorter (Entries 3 – 9) where in the cases where the amine could act as an HAT agent, the cyclised product was observed (Entries 3 – 7) and where it was absent, linear borylated product was observed (Entries 8 – 9). It was therefore concluded that diboron **555** would be the borylation agent of choice.

Further optimisation of **565** in the reaction conditions lead to 2 equivalents of DIPEA and 1.5 equivalents of **555** gave the highest ratio of cyclised product **565** to the undesired side products **564** and **566** (Table **35**, Entry 2).

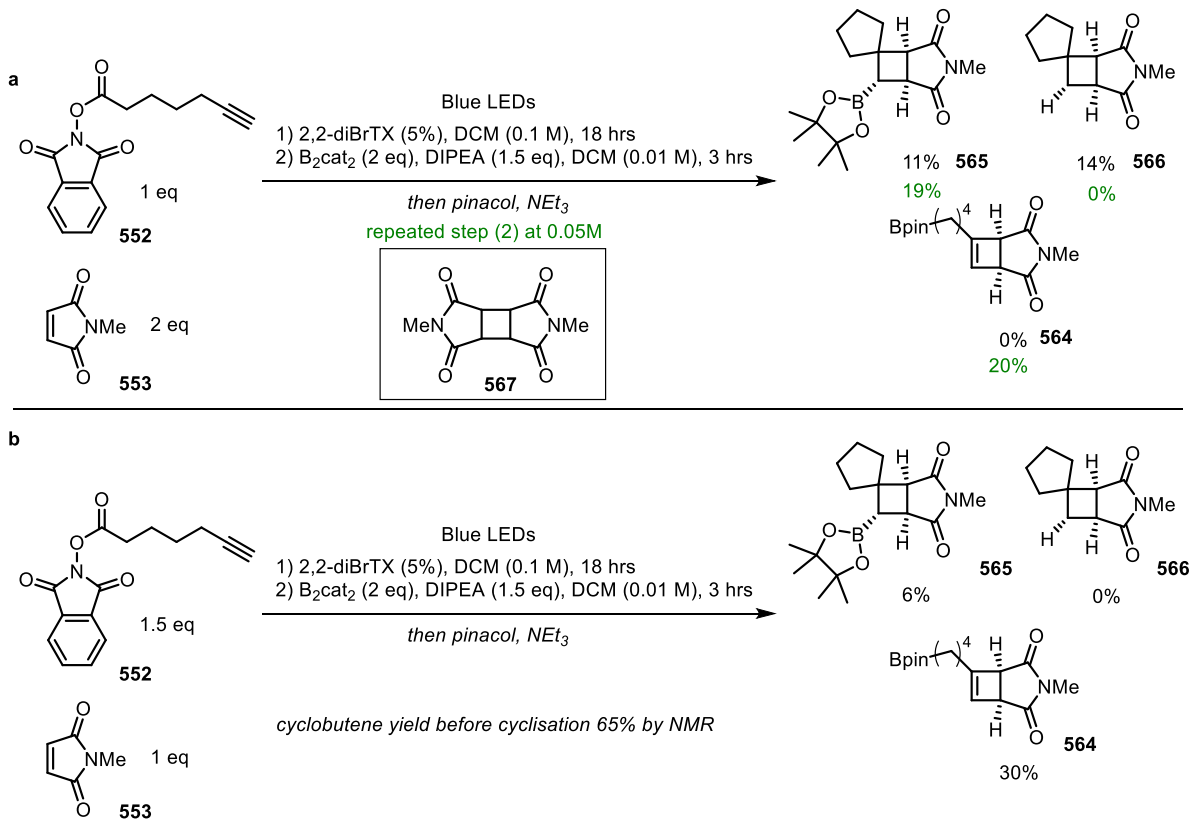
Table 35 *– Optimisation of the tandem cyclisation/1,2-carboboration.*



Entry	B_2cat_2 (eq)	DIPEA (eq)	Solvent (M)	554 (%)	564 (% Yield)	565 (% Yield)	566 (% Yield)
1	2	1.1	DCM (0.01)	9	25	31	2
2	2	1.5	DCM (0.01)	3	10	42	9
3	1.5	1.1	DCM (0.01)	14	20	30	29
4	1.5	0.5	DCM (0.01)	20	22	30	2

3.3.3. Application to a "one-pot" procedure

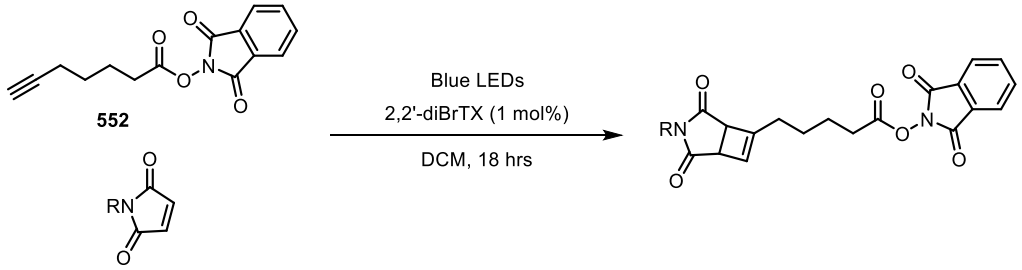
The conditions were taken forward and applied in a one-pot procedure from **553** and **552** as the starting materials (Scheme **97**). While the one-pot procedure demonstrated its feasibility in acquiring the desired product, the overall yields were low and the results had low reproducibility (Scheme **97a**). The low yields were potentially due to the formation of dimer **567** in the first step, which is insoluble in DCM. The precipitate would cause scattering of light in the second step hindering the photon induced SET. To combat this, the excess reagent was changed to the redox active ester to prevent excess dimer formation. However, a low yield was observed of the desired compound **565** (Scheme **97b**).



Scheme 97 *– Application of reaction conditions into a "one-pot" procedure.*

Due to difficulties in separating the products through column chromatography, the substrate could be purified through HPLC. Other *N*-substituted maleimides were trialled to incorporate a UV active chromophore to enable detection in the HPLC (Table **36**).

Table 36 *– Investigation into the effect of N-substituted maleimides.*



Entry	R (eq)	Alkyne (eq)	Conc. (M)	SM	Product	Side Product	Maleimide
1	Me (1.5)	1	0.05	10	53	18	0
2	H (1.5)	1	0.05	36	43	0	36
3	Bn (1.5)	1	0.05	12	67	9	4
4	Ph (1.5)	1	0.05	89	2	-	125

To investigate the *N*-terminus of the maleimide, conditions were applied from previous work by Park *et al.* to compare different substituted maleimides.[109] It was found that *N*-benzyl maleimide gave the best yields, whereas *N*-phenyl gave very low yield products. The same result was found by Park *et al.* and rationalised by the low spin density of the maleimide double bond, reducing the reactivity (Figure **29**). From this study, a side product was observed by ^{1}H NMR and accounted for 18% yield by integration for the *N*-methyl maleimide and 9% for the *N*-benzyl maleimide.

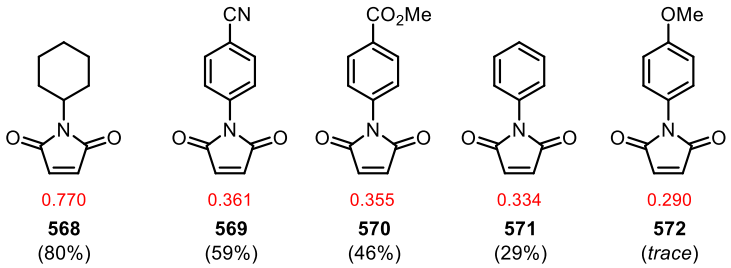
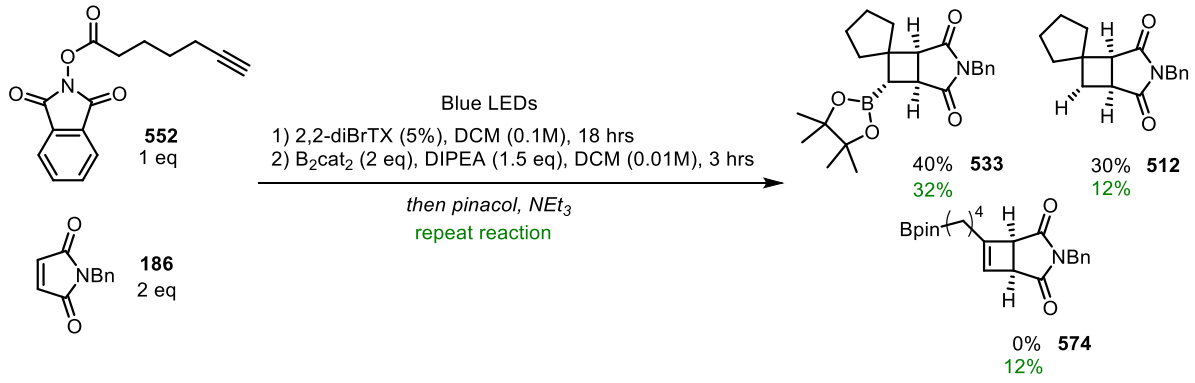


Figure 29 *– Spin densities labelled in red of N-substituted maleimides.*

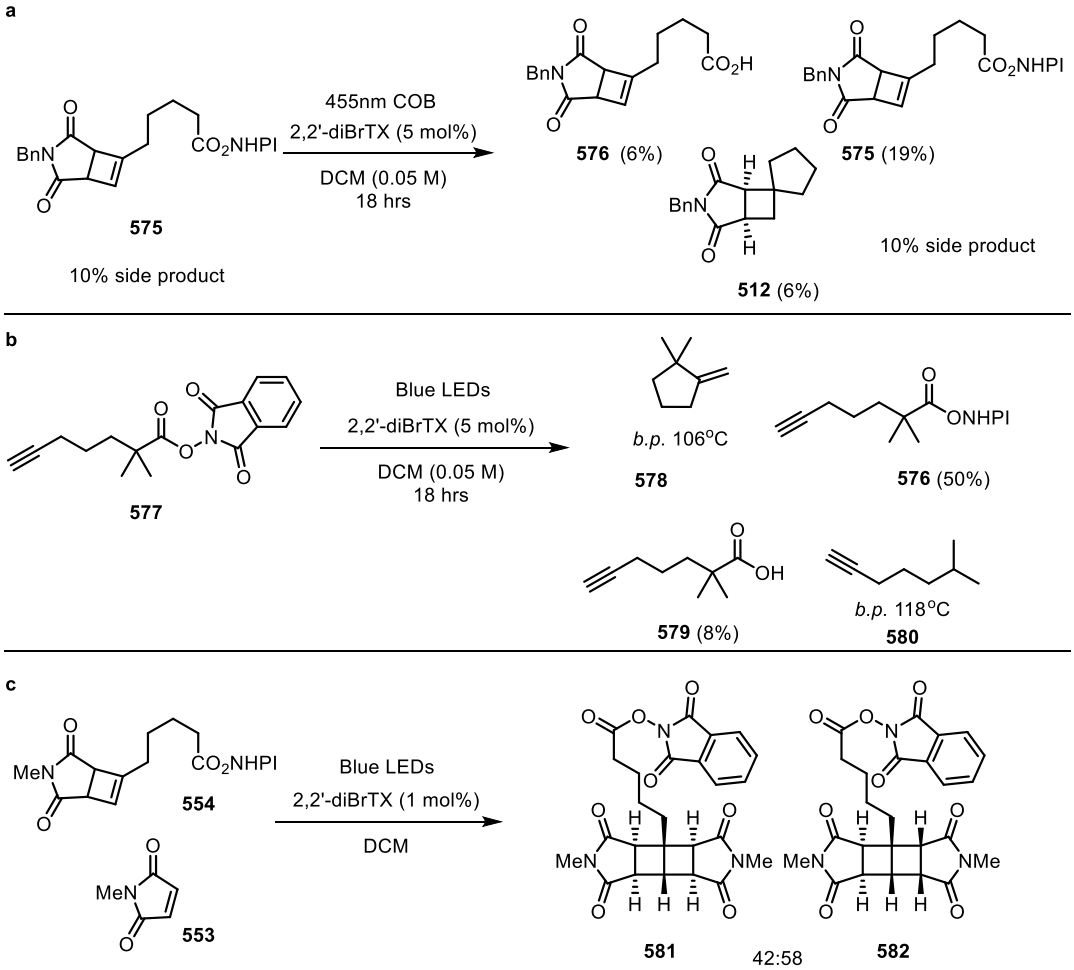
The *N*-benzyl maleimide **186** was employed into the one-pot procedure and it was found that the linear borylated product **574** was not observed (Scheme **98**).



Scheme 98 *– Application of N-benzyl maleimide into the "one-pot" procedure.*

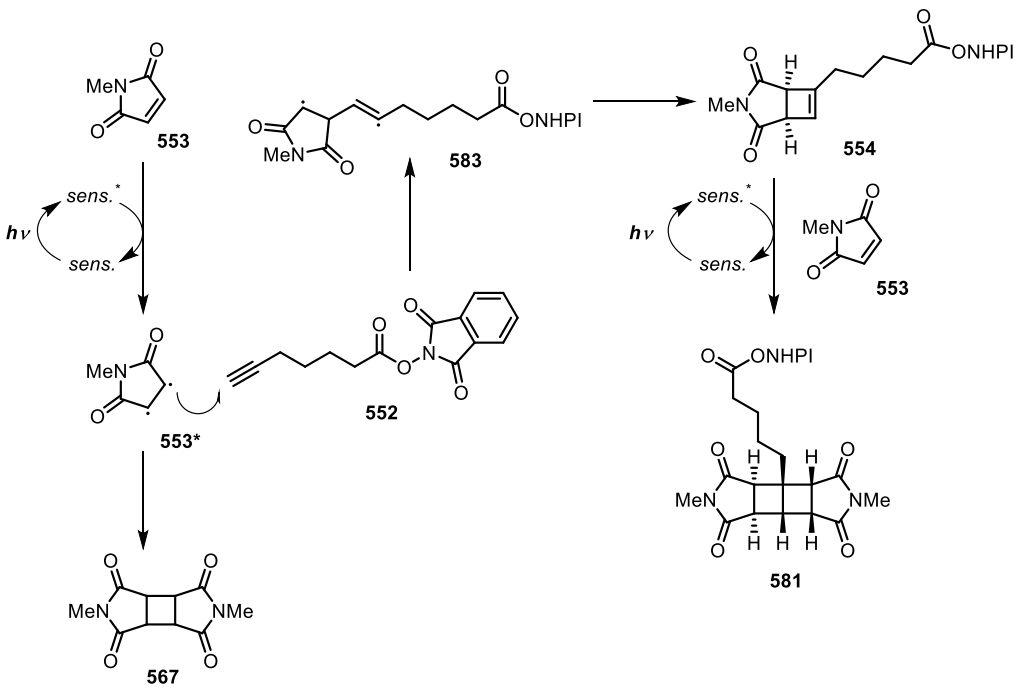
Further optimisation of the reaction conditions gave no improvement to the yield of the cycloadduct, and upon repetition of the initial reaction, a lower yield was observed of **533** and the linear product **574** was observed. To tackle the difficulty in reproducibility, a series of degradation studies were undertaken to identify the side product and its effect on the reaction (Scheme **99**).

3.3.4. Investigation into degradation



Scheme 99 *– Investigations into the degradation pathways for the "one-pot" procedure.*

The cyclobutene adduct **575** was subjected to the reaction conditions without diboron **555** to elucidate its stability under the reaction conditions. It was found that although the side product was maintained, only 19% of the redox active ester **575** was recovered with only 12% of mass going to observable products **576** and **512**. Next, the redox active alkyne **577** was observed under the same conditions and although it was found to be more robust (50% drop in yield), several side products were observed under the reaction conditions (**578** – **580**). Furthermore, it was proposed that the side product was a further photocycloaddition of remaining maleimide **553** and the cyclobutene **552** based on the mass spectroscopy and ^{1}H NMR. Employing these compounds under the reaction conditions gave the observed side product, elucidating the loss in yield to this side reaction. To combat this, the alkyne could be used as the excess reagent used in this photocycloaddition step to prevent a high ratio of maleimide in the presence of the product (Scheme **100**).

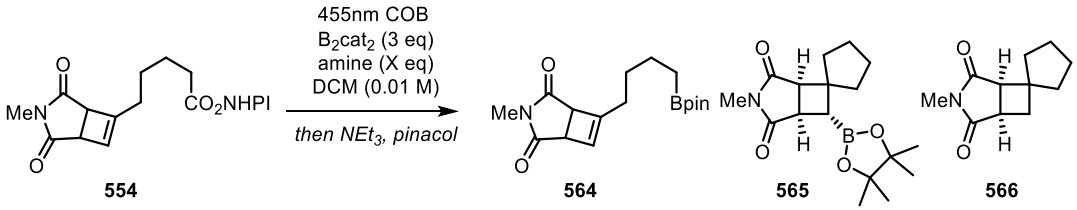


Scheme 100 *– Proposed mechanism for the formation of cycloadduct* ***581****.*

3.3.5. Investigation towards effect of amine ligands on B_2cat_2

To further investigate the effect of a coordinating species on the kinetics of radical addition to diboron species **555**, a range of sterically hindered and basic amines were examined (Table **37**).

Table 37 *– Optimisation of the tandem cyclisation/1,2-carboboration.*

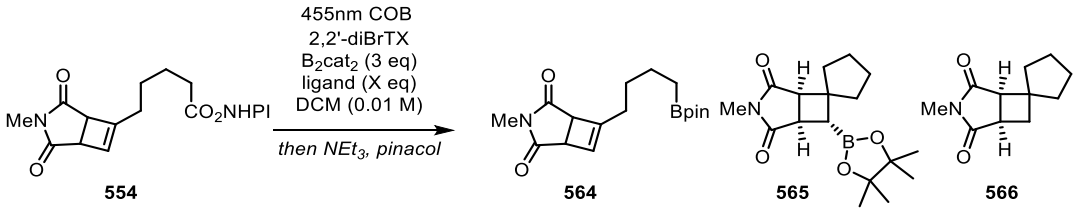


Entry	**Amine** (eq)	**554** (%)	**564** (% Yield)	**565** (% Yield)	**566** (% Yield)
1	Bpy (2)	59	18	0	0
2	Pyridine dimethanol (2)	17	13	19	0
3	DABCO (2)	9	7	10	0
4	DIPA (2)	0	19	39	0
5	Tetramethyl piperidine (2)	0	9	23	0
6	Pentamethyl piperidine (2)	0	30	36	0
7	DBU (2)	17	11	36	0

The trend observed supported the σ-donating properties of the tertiary amine enhancing the electron density on the diboron **555**.

To further explore this, a range of phosphine ligands and other ligands were employed into the reaction conditions (Table **38**).

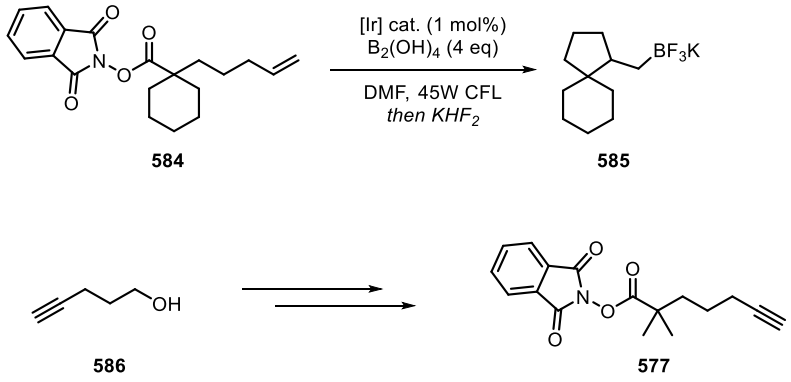
Table 38 *– Optimisation of the tandem cyclisation/1,2-carboboration.*



Entry	Ligand (eq)	**554** (%)	**564** (% Yield)	**565** (% Yield)	**566** (% Yield)
1	PPh_3 (2)	0	58	8	0
2	XPhos (2)	0	33	24	0
3	PCy_3(2)	0	26	29	0
4	DMSO (2)	0	19	0	5
5	PyrNO (2)	0	-	-	-

Again, the effect of sigma donation on the ratio of linear to cyclised product is observed in more classical examples of σ-donating ligands. However, in the more strongly donating ligands, such as DMSO and pyridine *N*-oxide (Entries 4 + 5) none of the desired product **565** was observed.

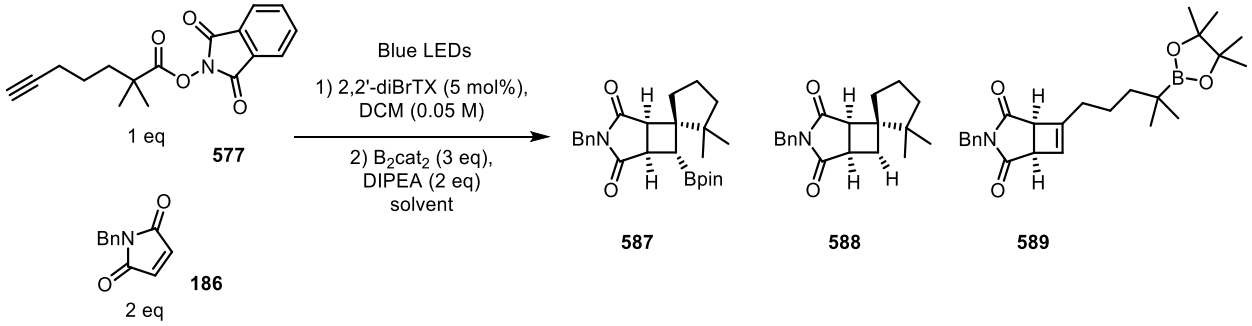
We turned our attention to taking advantage of steric bulk within the reaction. From previous work, it has been observed that borylation of tertiary alkanes is relatively slow compared to secondary and primary alkyl radicals (Scheme **101**). A secondary interaction of the dimethyl group is the Thorpe-Ingold effect, encouraging cyclisation through steric repulsion. To utilise this in the formation of the spirocycle, a tertiary carboxylic acid was synthesised to replicate compound **552** but will form a tertiary alkyl radical after decarboxylation.



Scheme 101 *– Synthesis of tertiary alkyl N-acyloxy phthalimide.*

Initial results from the [2+2] photocycloaddition gave a lower yield than previously achieved with **554**, however, enough material was obtained to continue to the cyclisation step (Table **39**).

Table 39 *– Optimisation of the tandem cyclisation/1,2-carboboration.*



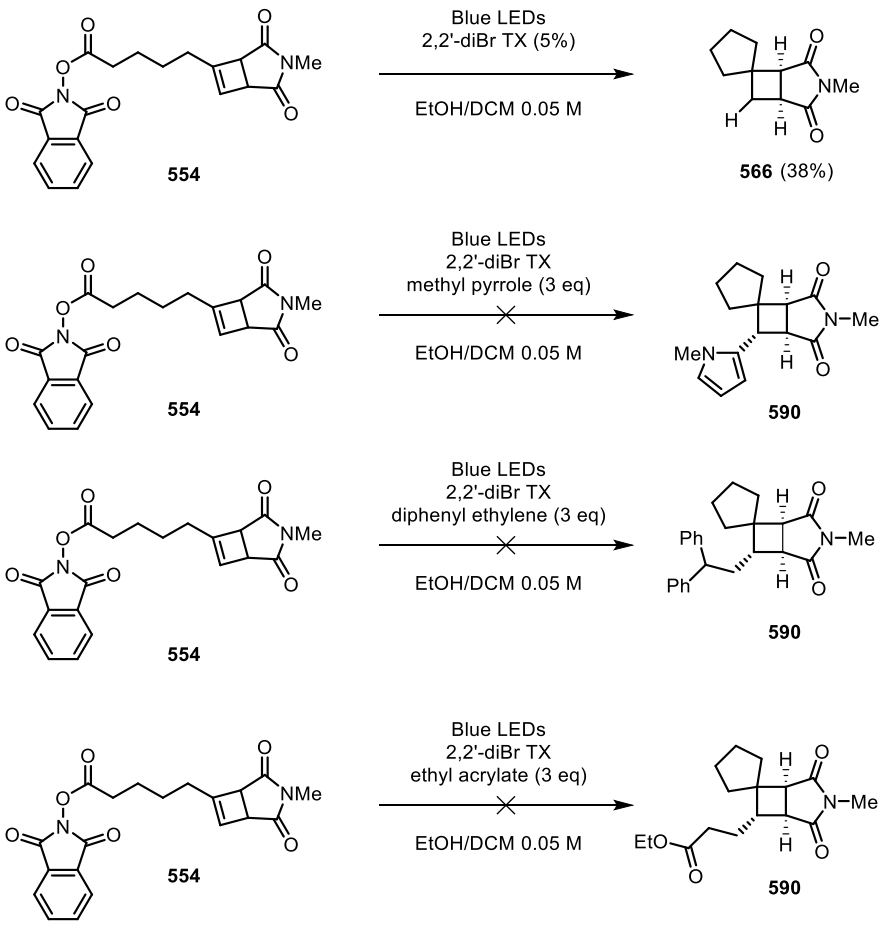
Entry	**DIPEA** (eq)	**B_2cat_2** (eq)	**Conc.** (M)	**577** (%)	**587** (% Yield)	**588** (% Yield)	**589** (% Yield)
1	2	3	0.010	0	40	10	0
2	2	3	0.010	0	34	25	0
3*	-	3	0.025	0	35	36	0

*DMF as solvent in second step

Pleasingly, none of the linear product was observed and both cyclised borylated and reduced cyclised products **587** and **588** were observed, albeit in low yield. To combat this and increase the amount of borylated product obtained, an increased amount of **555** was employed. Unfortunately, no improvement to the yield of **565** was observed.

3.3.6. Alternative radical acceptors

To explore alternatives to 1,2-carboboration, a range of sp^2 carbon radical traps were examined (Scheme **102**).



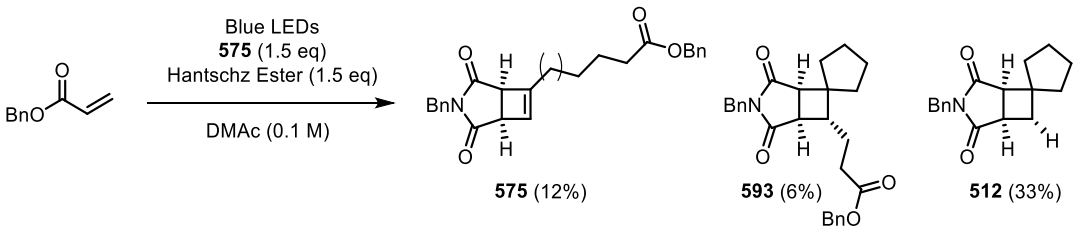
Scheme 102 *– Investigating effect of electronic properties for the best radical trap.*

Reaction conditions involving ethanol as a reduction source were found to give good yield of **566** without need of a diboron source **555**. These conditions were taken forward with the desired radical traps of differing electron densities. However, none of the desired radical acceptors gave the desired compounds, and even shut down the decarboxylative pathway observed in the initial reaction. From these results, it was decided to explore other radical acceptors that have previous literature behind 1,2-dicarbonation from redox active esters (Scheme **103**).

Scheme 103 *- Example of tandem 5-exotrig cyclisation/1,2-dicarbonation.*

Work by Shang *et al.* has developed a protocol for Giese type additions to alkyl redox active esters (Scheme **104**).[96] This is performed by employing a Hantzsch ester for the SER of the redox active ester. 30 examples were achieved in good to excellent yield and protodecarboxylation can be achieved using the Hantzsch ester. One of the control studies used employs a 5-*exo*-trig cyclisation before undergoing radical addition to the generated methyl radical. The work presented a 75% yield of the cyclised

product exclusively, however when the same conditions were applied to our substrate, all products were observed by ^{1}H NMR in low yield.



Scheme 104 *– Application of Shang's conditions for the synthesis of functionalised spirocycles.*

3.3.7. DoE studies

Due to lack of results from 1,2-dicarbonation, we turned our attention back to 1,2-carboboration and improving the yield of the desired spirocycle **533**. To further optimise the yield from the studies already undertaken, we decided to employ the reaction conditions in a Design of Experiment. This method has previously been discussed in Chapter 1 for the optimisation of the dehalogenation/functionalisation of cyclobutanes. In this case we aimed to look at 4 different parameters of the reaction conditions; concentration, equivalents of DIPEA, equivalents of diboron **555** and the polarity of the solvent by employing a non-polar solvent into the reaction as a co-solvent (Table **40**). The parameters of each factor were set to 4 – 2 equivalents of diboron **555**, 1 – 3 equivalents of DIPEA, a concentration range of 5 – 20 mM and the addition of a non-polar solvent with a ratio of 1:0 – 1:1, DCM:toluene. The responses followed were the yield of compounds **533**, **573** and **574** in the reaction. The design of experiment was run at full factorial, resolution (V) with 4 replicate points.

Table 40 *- Factors and parameters chosen for DoE (full factorial design with 4 replicates at centre point).*

Factor	Units	High	Low
B_2cat_2	equiv.	4	2
DIPEA	equiv.	3	1
Concentration	mM	20	5
Solvent Ratio DCM:PhMe	-	50:50	100:0

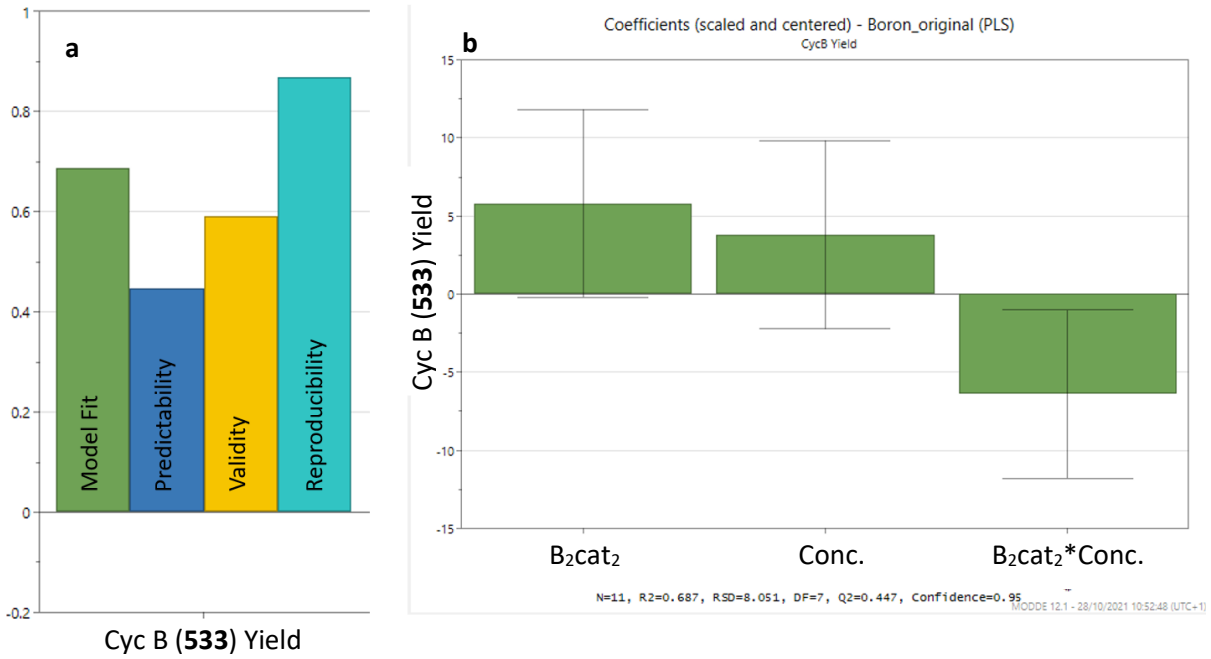


Figure 30 *– **a)** Graph representing the model fit, predictability, validity and reproducibility on a scale of 0-1.* ***b)*** *Bar graph representing the effects of various factors. N = 11, R2 = 0.687, R SD = 8.051, DF = 7, Q2 = 0.447, Confidence = 0.95.*

Pleasingly the results obtained showed good outcomes in all these areas, giving confidence to using the model as a means of designing the best reaction conditions (Figure **30a**, see experimental section for DoE data). From here we could eliminate the factors that are statistically insignificant to leave factors that have an effect on the reaction outcome (Figure **30b**). From the initial screen of conditions, the solvent polarity and equivalents of DIPEA did not have an effect on the reaction conditions. However, increasing the equivalents of **555** (B_2cat_2) and concentration (Conc.) independently both had a positive impact on the yield of spirocycle **533**. The combination of increasing both equivalents of diboron **555** and concentration in the same reaction gives a negative effect on the reaction yield (Figure **31**).

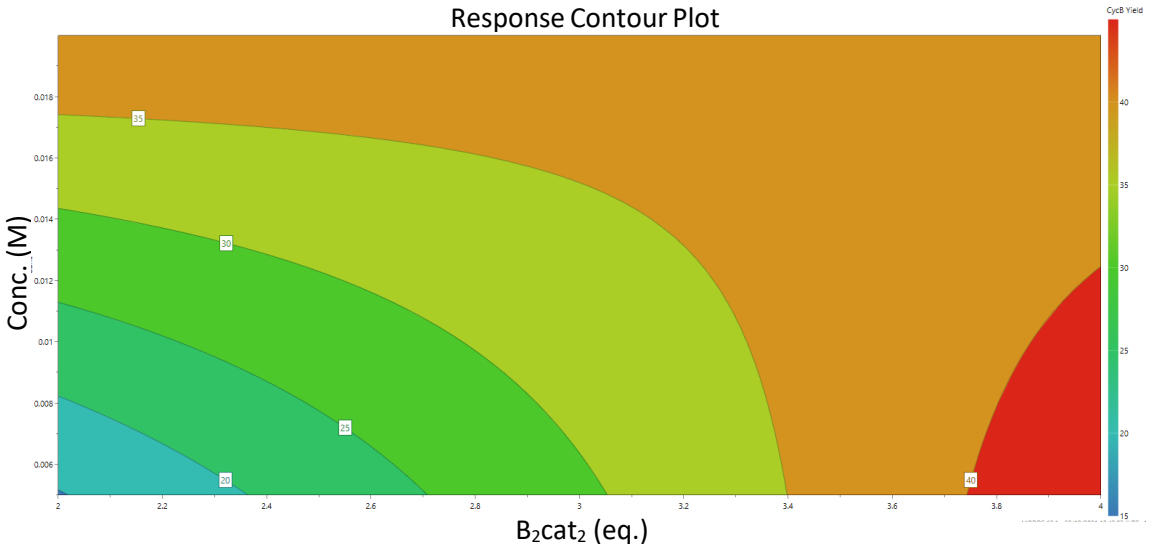


Figure 31 *– Contour plot of the yield of spirocycle* ***533*** *vs equivalents of diboron* ***555*** *and concentration.*

From the contour plot it's evident that increasing equivalents of diboron **555** and decreasing concentration gives the highest yields (Figure **32**). These predictions match those found by initial optimisations of the reaction conditions.

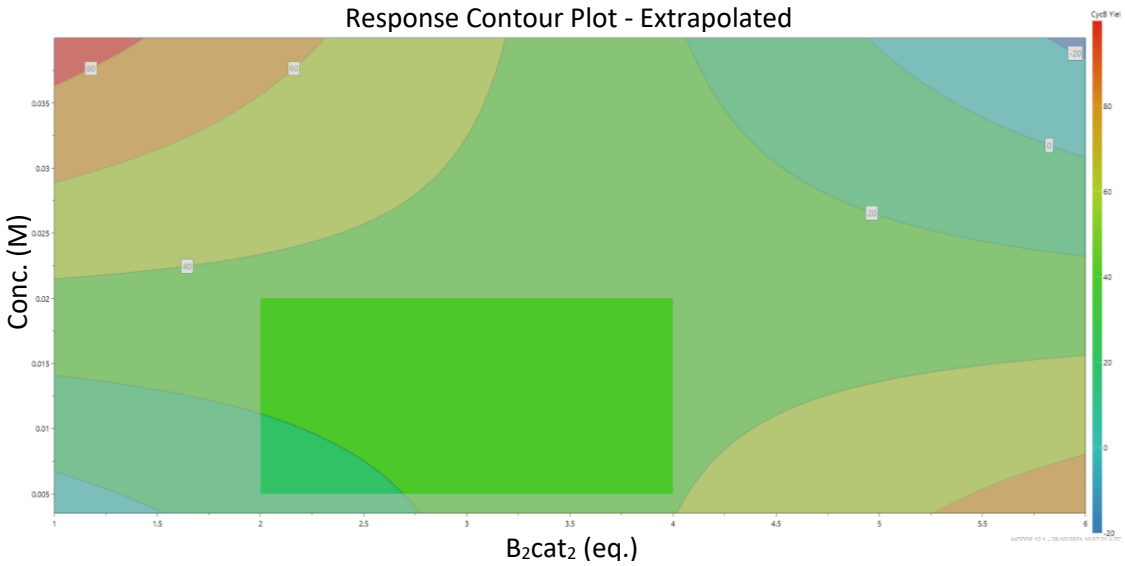


Figure 32 *– Extrapolation of Figure* ***31****.*

Upon extrapolation of Figure **31**, it can be observed that as well as an increase in the yield of **533** from increasing equivalents of diboron **555** and decreasing concentration, an increase in yield of **533** can be obtained from a higher concentration and lower equivalents of diboron **555**.

From these results we decided to focus on two regions of the extrapolated contour graph. The area with high concentration and low diboron loading, and the area with low concentration and high diboron loading. The limits we took the factors were; low concentration conditions: 2.5 – 4.5 mM, and 4 – 6 equivalents of diboron **555**; high concentration conditions: 40 – 22 mM, and 1 – 2 equivalents of diboron **555**. The experiments were run at full factorial and resolution V with 3 replicates each (Table **41** and **42**).

Table 41 *- Factors and parameters chosen for DoE (full factorial design with 3 replicates at centre point).*

Factor	Units	High	Low
B_2cat_2	equiv.	2	1
Concentration	mM	40	22

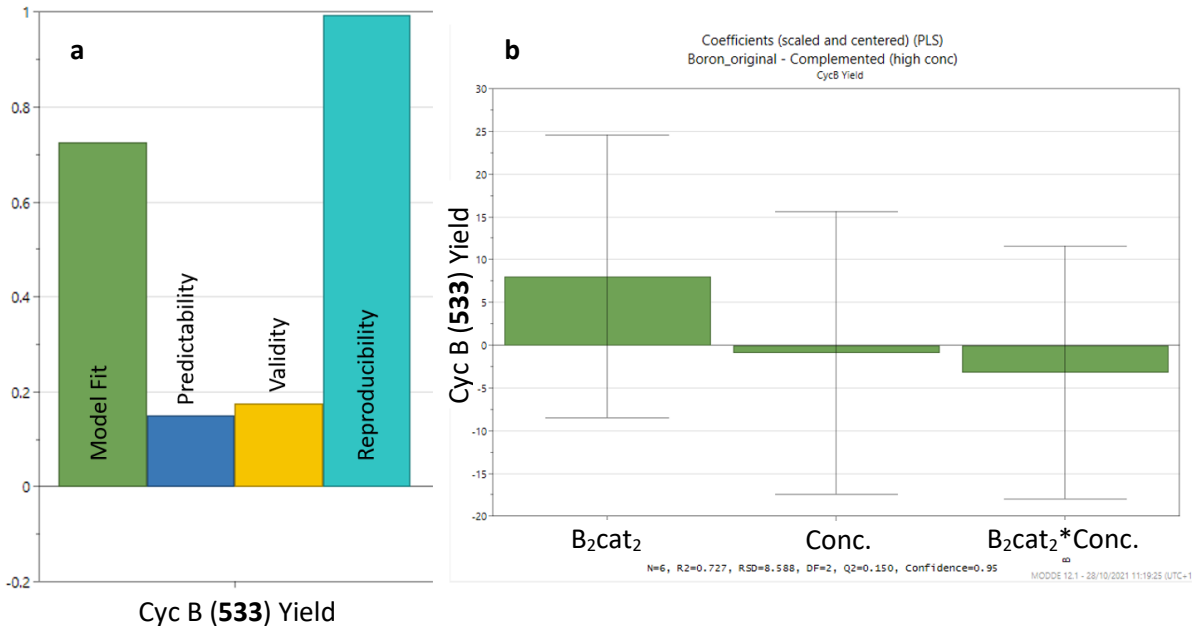


Figure 33 *- **a)** Graph representing the model fit, predictability, validity and reproducibility on a scale of 0-1. **b)** Bar graph representing the effects of various factors. N = 6, R2 = 0.727, R SD = 8.588, DF = 2, Q2 = 0.150, Confidence = 0.95.*

The model for high concentration conditions showed good fit and excellent reproducibility, however, the model did not have good predictability and never gave any improvement of the yield of **533** (Figure **33**, see experimental for DoE data). The trend that can be seen from the contour graph demonstrates that the yield increase of **533** would be achieved by decreasing concentration and increasing equivalents of diboron **555** (Figure **34**). For these reasons, the reaction conditions were not followed up at these concentrations.

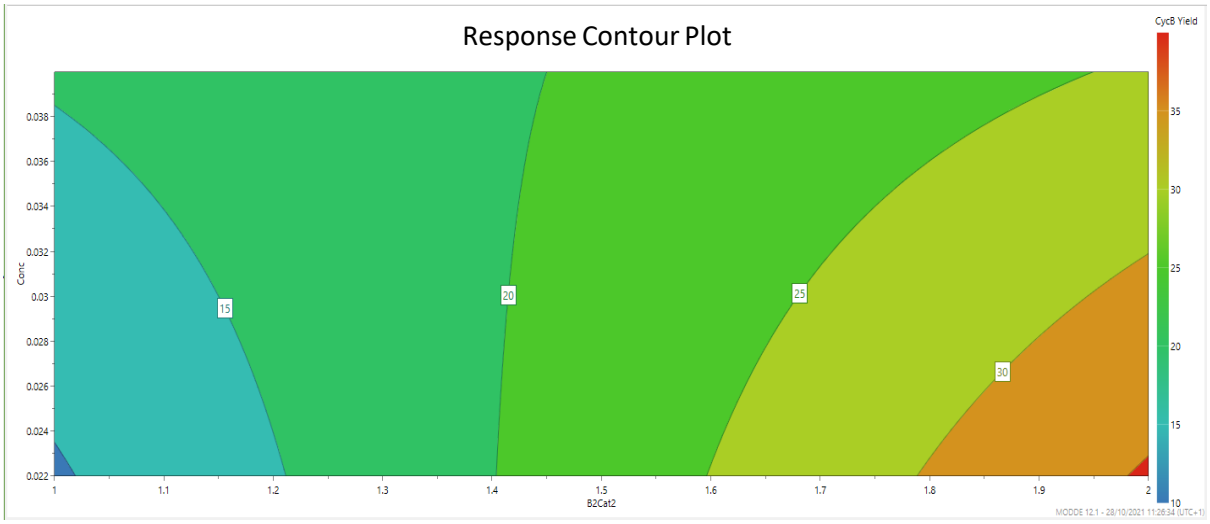


Figure 34 *- Contour plot of the yield of **533**, (B_2cat_2) vs equivalents of DIPEA and concentration (Conc.).*

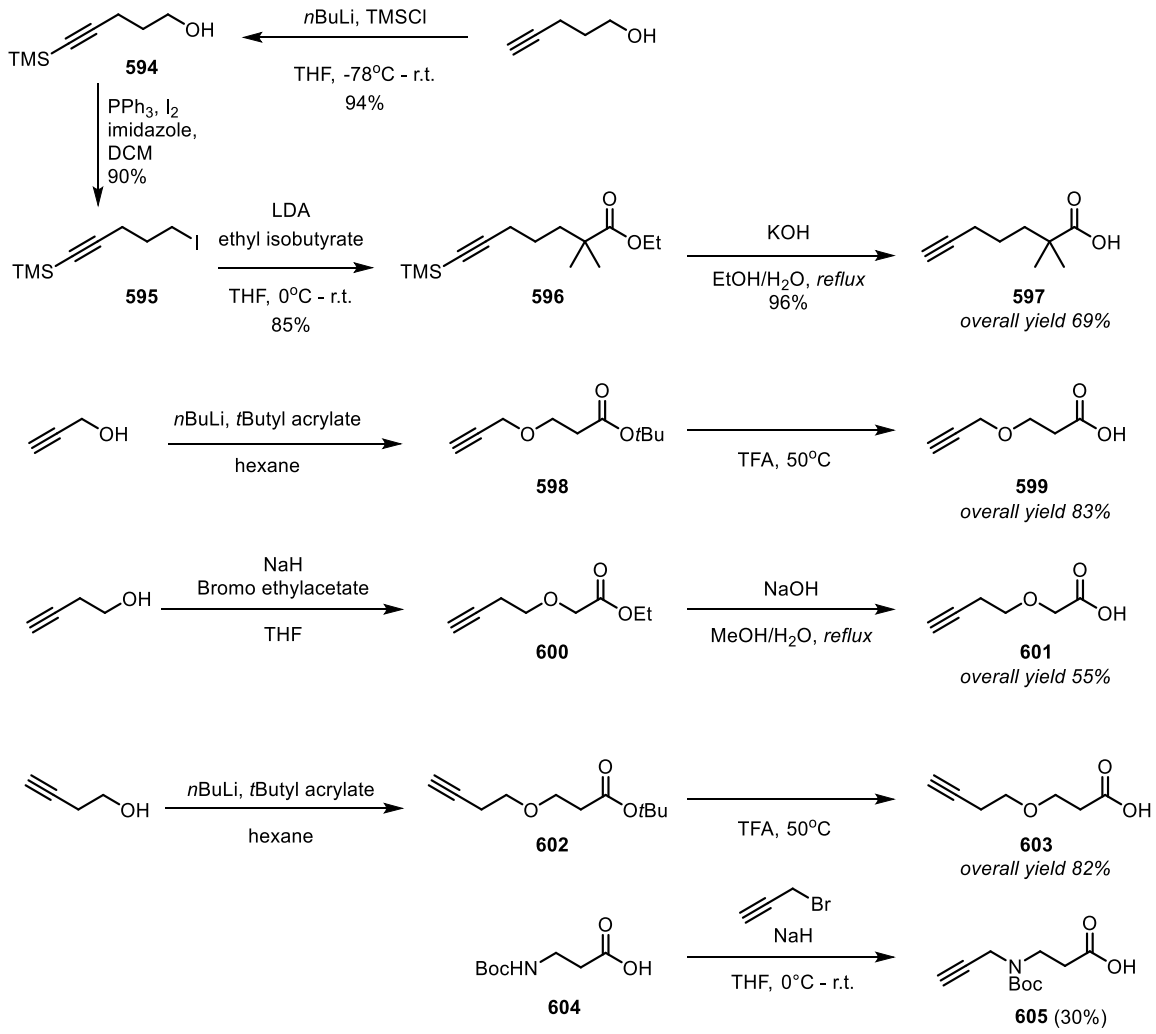
Table 42 *- Factors and parameters chosen for DoE (full factorial design with 3 replicates at centre point).*

Factor	Units	High	Low
B_2cat_2	equiv.	6	4
Concentration	mM	4.5	2.5

The second study of lower concentration conditions gave irreproducible results for the yield of **533** (see experimental section for DoE data). The study was run once more but again gave no reproducible results. To keep the volume constant across the whole study, low amounts of starting material **575** (6 – 8 mg) being added causing large differences in the reaction yield. For this reason, the results from this study were not continued upon.

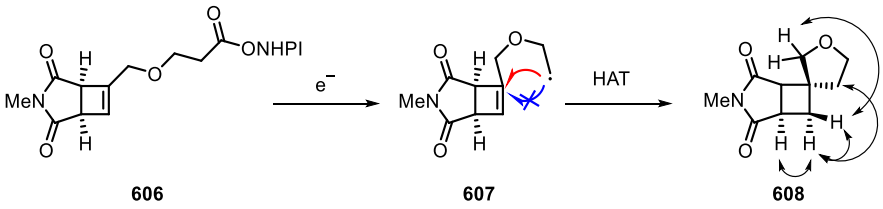
3.4. Alkyne acid scope

To analyse the applicability of the most optimised conditions (Table **S2**), a series of functionalised alkyne-carboxylic acids were synthesised (Scheme **105**). The acids can be synthesised from readily available starting materials in very good yield over multiple steps on a multigram scale.



Scheme 105 *– Synthesis of alkyne acids.*

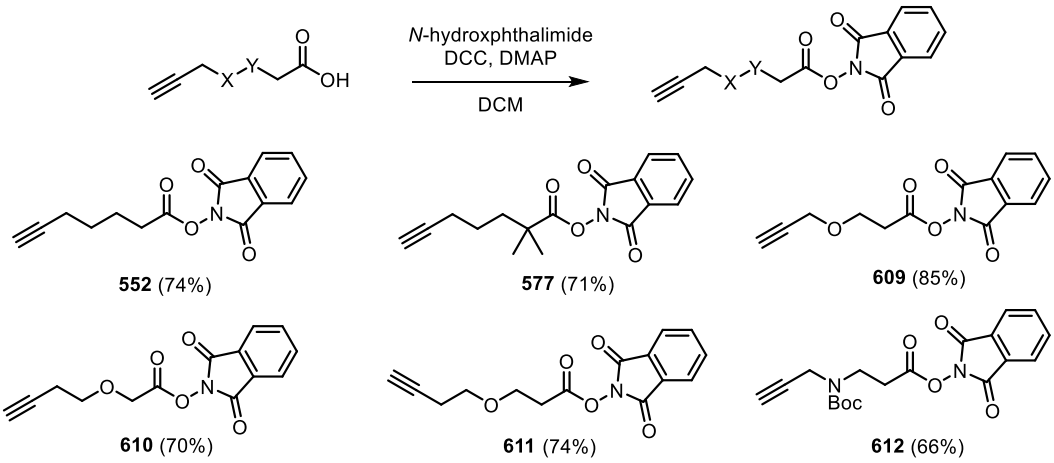
One of the objectives to explore with changing the position of the heteroatom in the alkyl chain, is the control of diastereoselectivity in the product (Scheme **106**). If the alkyl chain cyclises onto the back face of the cyclobutene, to avoid the succinimide ring, then the compound should show high stereoselectivity. This has been observed in previous reactions where reduced spirocycle **512** is formed (Scheme **88**). Using NOE NMR studies, the exact stereoselectivity of compound **608** was identified to show that the alkyl chain does undergo radical addition from the opposite face of the cyclobutene from the succinimide.



Scheme 106 *– Mechanism depicting diastereoselectivity from radical cyclisation. Red arrow represents attack from opposite face of succinimide. Blue arrow represents attack from the same face of succinimide (blocked due to steric hindrance of succinimide).*

3.5. Activation scope

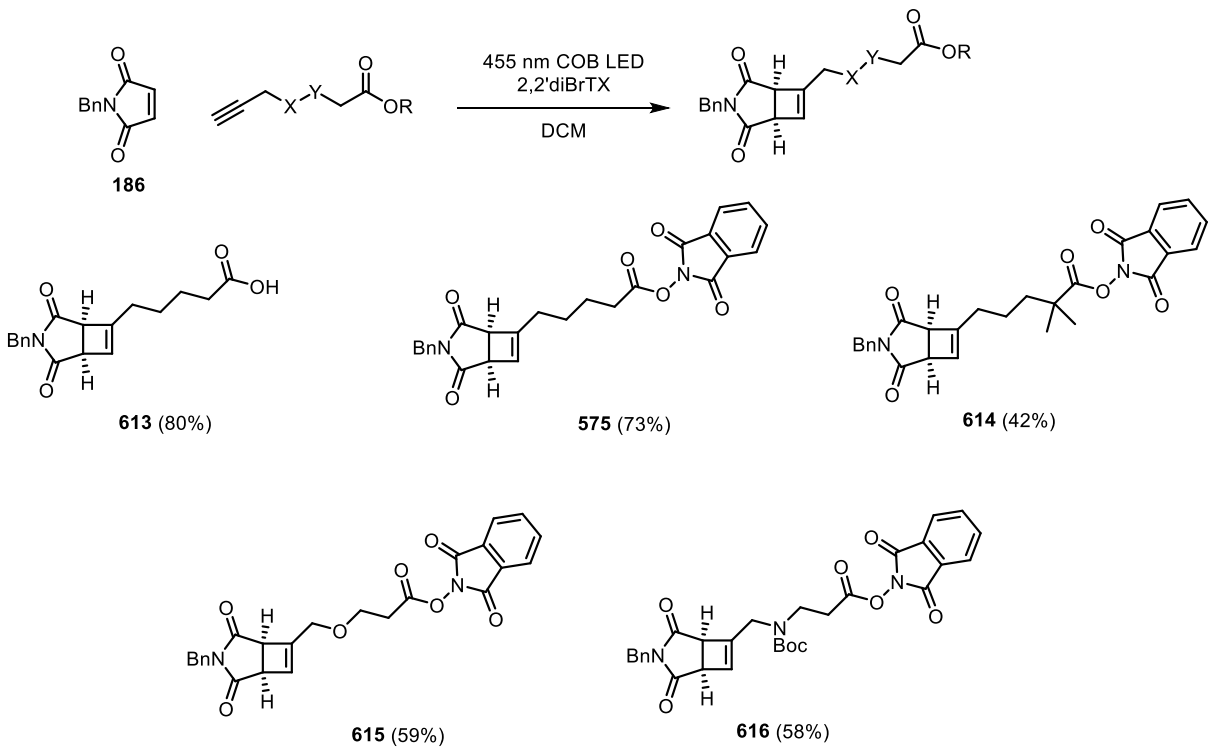
Activation of the carboxylic acid through esterification with *N*-acyloxy phthalimide gave very good yields of the activated alkyne acids across a broad range of functional groups (Scheme **107**).



Scheme 107 *– Alkyne acid activation scope*

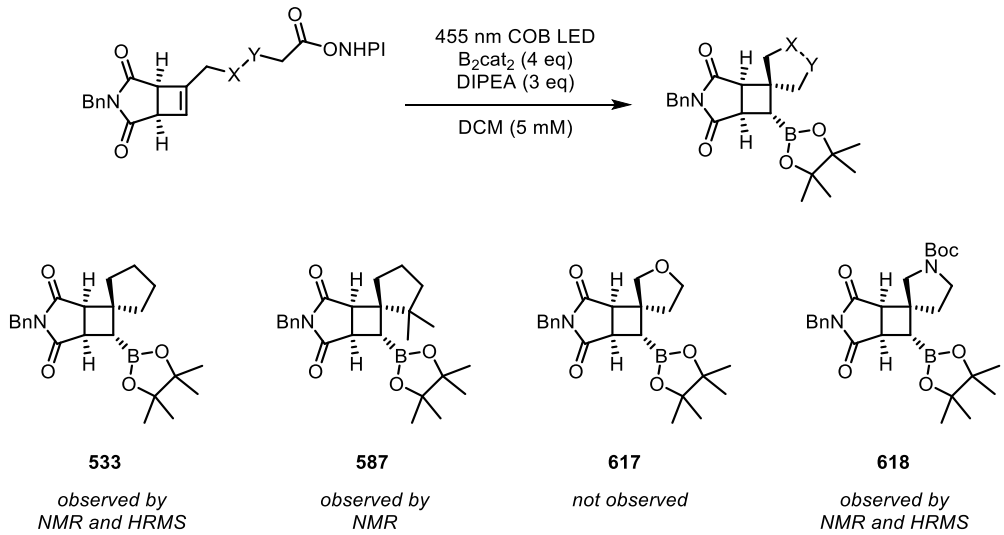
3.6. Triplet sensitised [2+2] photocycloaddition and subsequent cyclisation

With these results in mind, the [2+2] photocycloaddition was performed on each of the activated acids (Scheme **108**). Pleasingly the reaction gave the desired products **552** – **612** in moderate to good yields while maintaining the redox active ester. It was found that for the best yields the redox active ester had to be freshly purified and stored in a freezer away from light. The active ester could be used in 0.5 equivalents excess to give the highest yield of cycloadduct and avoid unwanted side product **581**. On purification, excess of the ester could be recovered from the reaction.



Scheme 108 *– Scope of visible-light [2+2] photocycloaddition of redox active esters.*

From here the cyclobutene adducts can undergo cyclisation using the most optimised conditions from the DOE study (Scheme **109**, see experimental section for data).



Scheme 109 *– Scope of tandem cyclisation/1,2-carboboration reactions.*

Difficulties were found in the purification of the boronic esters. Compound **533** was inseparable from the fully reduced spirocycle **512**. However, the presence of compound **533** was confirmed by high resolution mass spectrometry (HRMS). Unfortunately, only the fully reduced spirocycle was observed for compound **587**, demonstrating that a high concentration and high equivalents of diboron **555** is required for the borylation of compound **577**. While compound **617** was observed by ^{1}H NMR,

purification did not lead to isolation of the product, possibly due to the low yields observed by NMR yield with an internal standard. Pleasingly the *N*-heterocyclic spirocycle was observed by ^{1}H NMR and HRMS, however, purification did not give clean product **618** by ^{1}H NMR with flash column chromatography or HPLC.

Chapter 3

4.1. Total synthesis of albiflorin

Albiflorin **7**, a monoterpene glycoside, a with a similar structure to that of pinane **6**, is the main component of Shaoyao-Gancao, along with paeoniflorin.[148,149] Shaoyao-Gancao is a Chinese herbal medicine commonly used in pain relief and muscle spasms.[149] It was first recorded nearly 1800 years ago in the *"Treatise on Cold Damage",* a compilation of therapeutic texts by Zhongjing Zhang (150-219 AD). To this day albiflorin and paeoniflorin have been identified in the roots of *paeonia lactiflora*, more commonly known as the Chinese Peony (Figure **35**).[150]

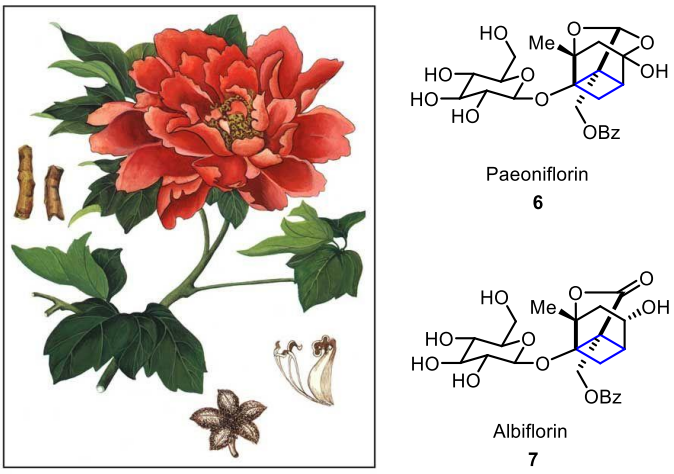
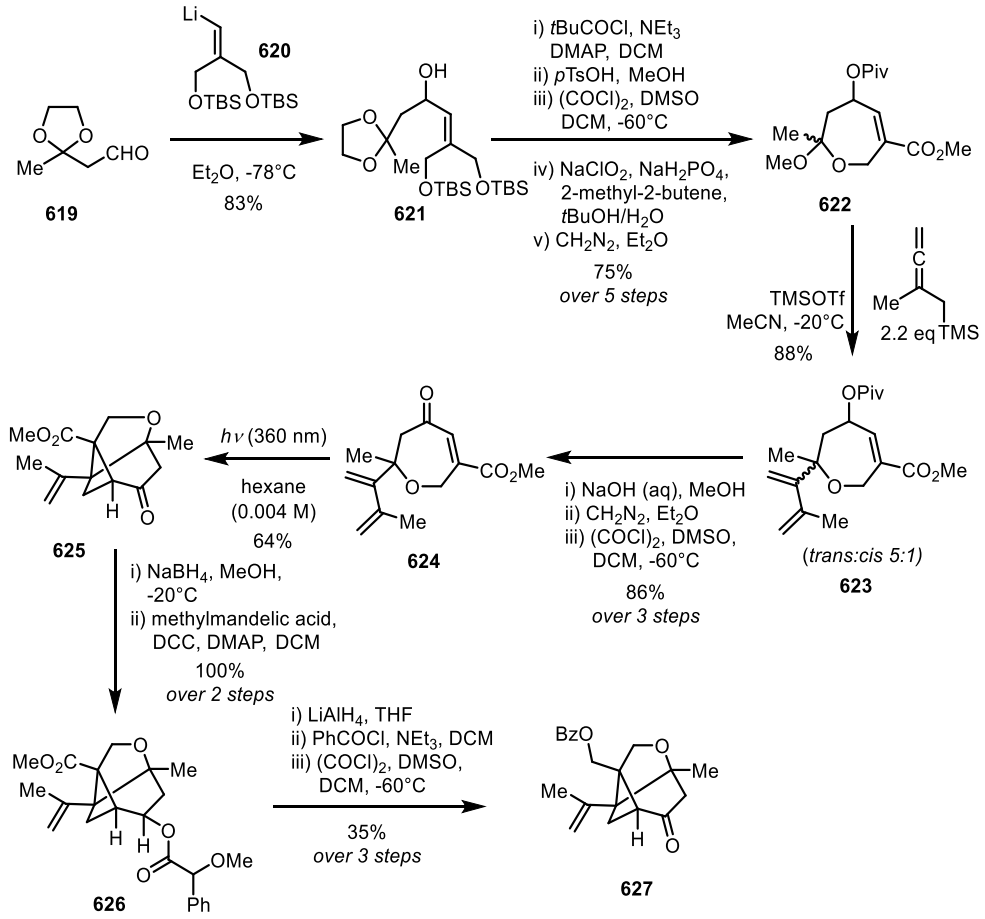


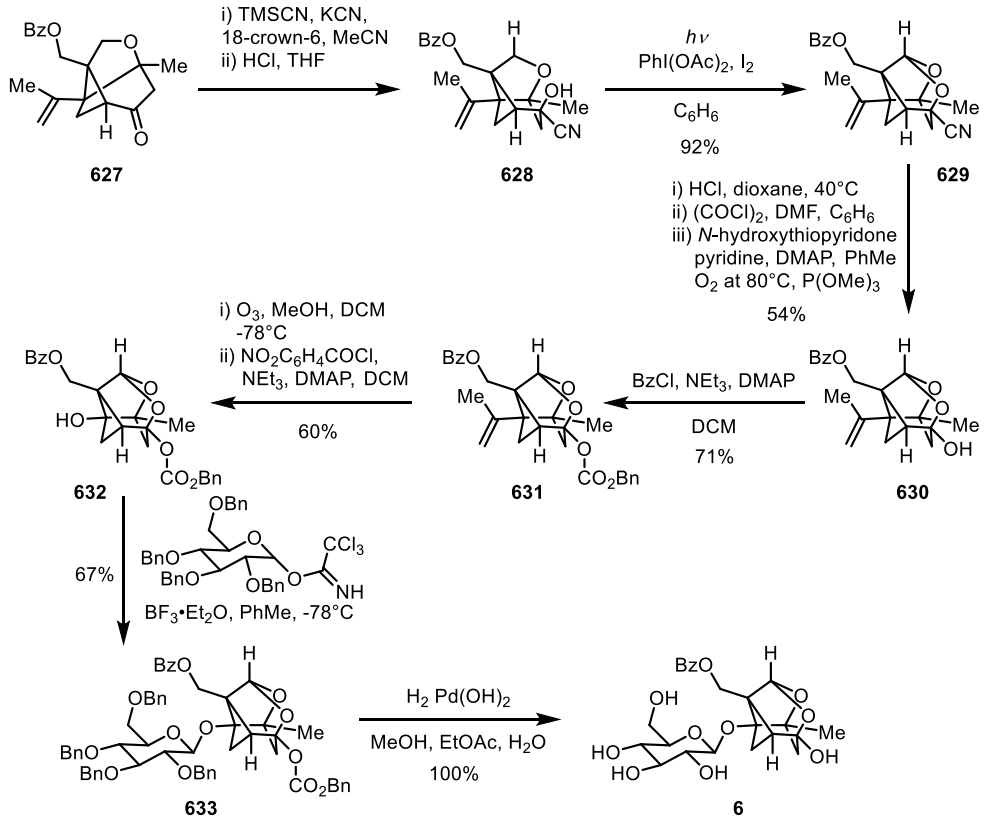
Figure 35 *– Pictorial diagram of Paeonia Lactiflora.*

Of the two, only paeoniflorin has a synthetic route with a total yield of 1.5% in 27 steps published in 1994.[151] Albiflorin has yet to be synthesised. The synthesis of paeoniflorin was performed by Takano *et al.,* approached by starting with an acetal protected *β*-ketoaldehyde **619** (Scheme **110**). Addition to the aldehyde using organolithium **620** gave alcohol **621**. Protection with pivalic acid chloride followed by acetal deprotection sets up a reaction to form the 7-membered ring product. Oxidation of the alcohol to a carboxylic acid and subsequent methylation with diazomethane gives enone **622**. Treatment of enone **622** with TMSOTf in the presence of an allene derivative gives the alkylated product **623**. Deprotection of the alcohol and subsequent oxidation gives the desired ketone product **624**. Exposing low concentrations of ketone **624** to UV conditions gives the desired intramolecular cyclised product **625**. Reduction of ketone **625** and subsequent protection with methylmandelic acid gives methyl ester **626**. Reduction of the methyl ester to give the methylene alcohol unit and subsequent benzylation, followed by oxidation of the deprotected secondary alcohol to the ketone gives product **627**.



Scheme 110 *– Part 1 of the total synthesis of paeoniflorin.*

Reaction of **627** with potassium cyanide followed by acidic work up gives tertiary alcohol **628** (Scheme **111**). Irradiation of intermediate **628** in the presence of hyper-valent iodine and iodine gives the cyclised product **629** in 92% yield. The cyano group was then hydrolysed to a carboxylic acid, and subsequent decarboxylative radical oxidation from an activated amide gave hemiacetal **630**. Protection of the hemiacetal alcohol gives product **631** and ozonolysis gives tertiary alcohol **632**. Glycosylation of alcohol **632** gives ester **633** that undergoes palladium catalysed debenzylation and subsequent spontaneous decarboxylation to afford paeoniflorin **6**.



Scheme 111 *- Part 2 of the total synthesis of paeoniflorin.*

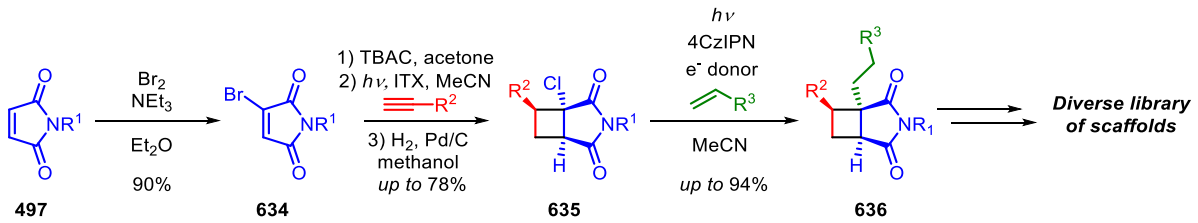
Interest into the total synthesis of albiflorin **6** was expressed by the Takano group, however no successful publication of a synthetic route has been achieved.[151]

Currently, there are 1023 references for albiflorin on Scifinder™ (*Nov 2021*), 53 of which were in 2021, demonstrating its relevance in biological studies. Albiflorin has a wide array of bioactive properties, including, but not limited to, anti-organ damage, cardiovascular protection, nervous system protection, anti-inflammatory, analgesic and antioxidant properties.[152]

Most recently, work by Wang *et al.* has shown the anti-depressant effects exhibited by albiflorin in mice and rats.[153] The studies made use of several animal models of depression including forced swim and tail suspension tests. When compared to fluoxetine, a serotonin reuptake inhibitor under the commercial name Prozac, albiflorin showed similar levels of anti-depressant effects. When the mechanism was probed, it was found that albiflorin went partially by a pathway that involves the expression of brain-derived neurotrophic factors (BDNF), which is again similar to fluoxetine. Other work has found similar effects.[154] Albiflorin was also found to exhibit anti-PTSD-like effects in rats, when compared to sertraline, a commercially available anti-depressant used in the treatment of PTSD. Probing the mechanism also showed links to BDNF expression.[155]

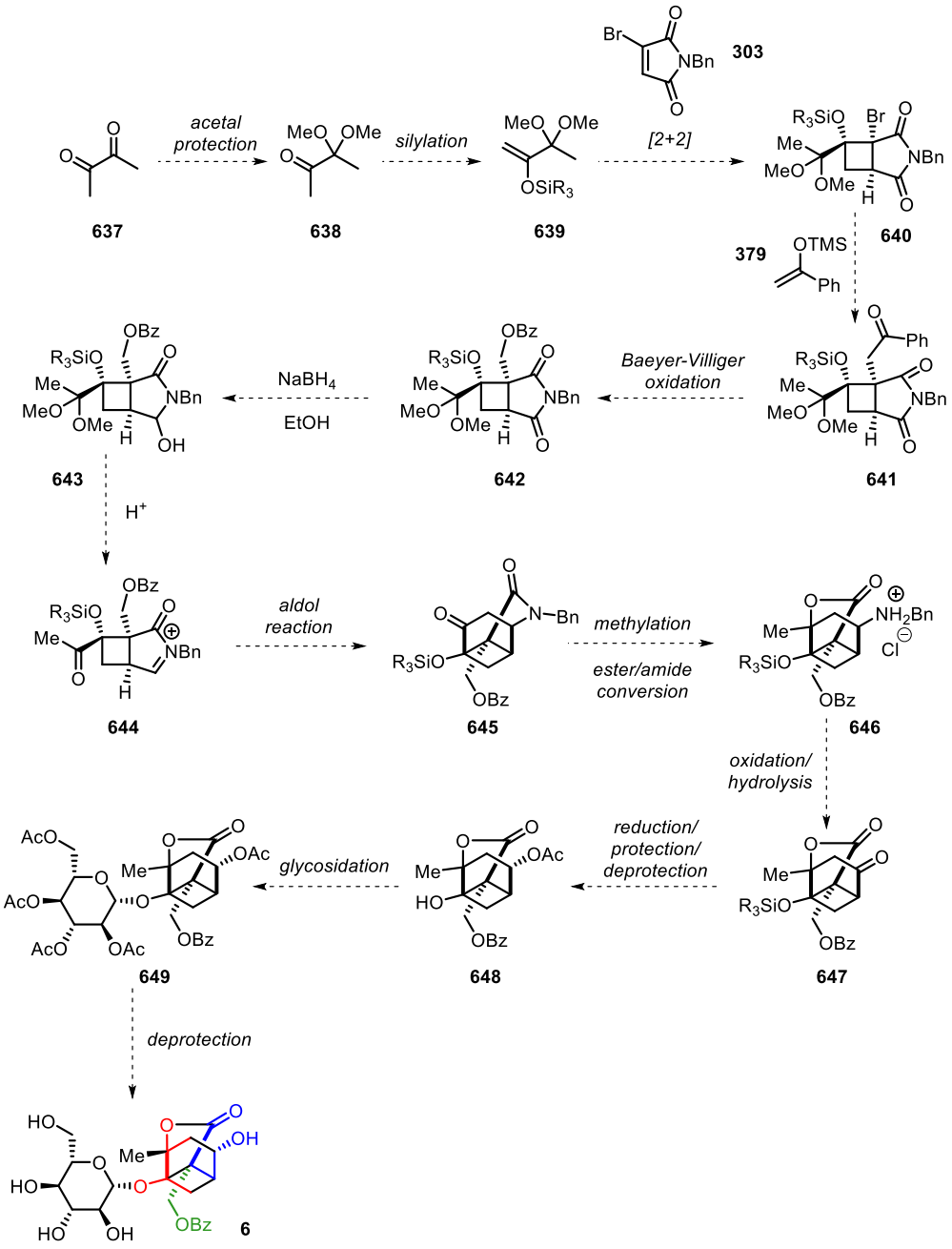
Most studies focus on the anti-depressant properties exhibited by albiflorin, where **6** is isolated from the roots of Chinese Peonies or is commercially available at £215/mg (*Merck, Nov 2021*). Since the dosage is administered at ~10 mg/kg, *in vivo* studies require a costly amount of highly pure **6**. Therefore, a primary aim for the total synthesis would be to have a low material cost and scalable approach to ensure that the synthesis of albiflorin can be utilised as a source in its biological application. The approach would also have to involve steps where derivatives can be included to expand the efficacy or selectivity of the derived natural product. We initially proposed a synthetic route to albiflorin from a modified methodology developed in Chapter 1 (Scheme **112**).

4.2. Initial proposal for the total synthesis of albiflorin



Scheme 112 *– Methodology towards the synthesis of highly functionalised cyclobutanes.*

The bromo-cyclobutane **635** can undergo radical addition to a silyl enol ether to give compound **636**. Previous work has shown that carbonyl reduction can be performed regioselectively to give the hemi-aminal, which can then undergo cyclisation through an intramolecular aldol reaction from a pertinent ketyl group (R^2 = Ac). A total synthetic procedure was initially proposed (Scheme **113**).



Scheme 113 *-Proposed retro-synthetic route towards the total synthesis of albiflorin.*

By linear synthesis; a silyl enol ether **639** could be synthesised from a dimethyl acetal protected butan-2-one **637**. Bromo-maleimide **303** and alkene **639** can undergo a [2+2] photocycloaddition to give the cyclised product **640** in a regio-and diastereoselective manner, as previously developed in this thesis (Chapter 1, Scheme **48**). Stereoselectivity of the [2+2] requires the silane group to possess large steric bulk, and so TIPS or TBDMS as a silylation agent was proposed to be employed into the reaction conditions. Bromo cyclobutane **640** can then undergo dehalogenation/radical addition with silyl enol ether of acetophenone **379**, to give adduct **641**. Baeyer-Villiger oxidation of **641** gives ester **642** before regioselective hydride reduction and subsequent acid deprotection/elimination of acetal **643** to give

644. The formed ketone **644** can undergo an intramolecular aldol reaction with the iminium intermediate to form the desired tricyclic structure **645**. Successive oxidation of the benzylic amine **646** to an amide and then further oxidation to an alkyl-ylidene amide followed by hydrolysis of the imine gives ketone **647**. Ketone **647** can be reduced diastereoselectively from the least hindered face to give compound **648** after protection of the alcohol and deprotection of the silane. Tertiary alcohol **649** can undergo glycosylation to give the acetyl protected natural product **649** and subsequent deprotection gives albiflorin **6**. This route offers several points of derivation, which would allow the generation of a library of compounds whose biological activity can be tested (Figure **36**).

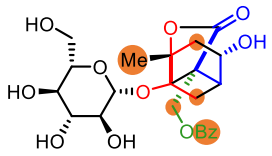
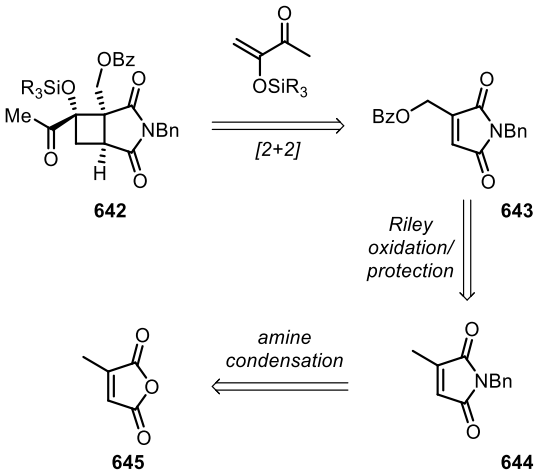


Figure 36 *–Points of derivatisation in albiflorin.*

4.3. New proposed route and intermolecular [2+2] photocycloadditions

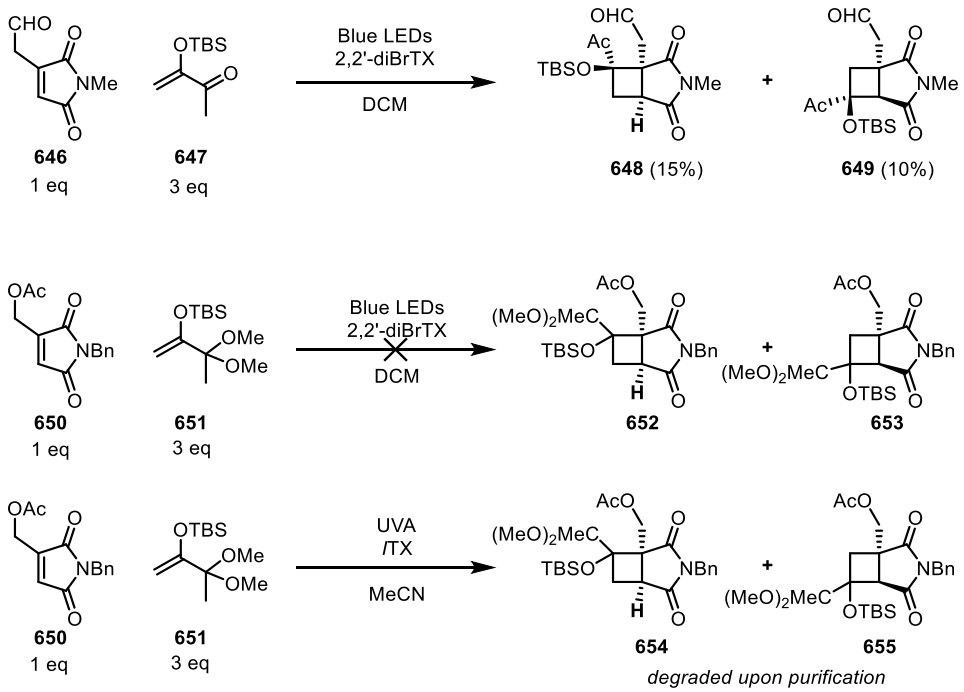
To decrease the number of steps, a new proposed route to compound **642** was examined. Synthesis of maleimide **643** would remove the need of photoredox dehalogenation and regioselective Bayer-Villiger oxidation between compounds **640** and **641**, giving access to compound **642** in 3 steps (Scheme **114**).



Scheme 114 *–Alternative approach to compound* ***642.***

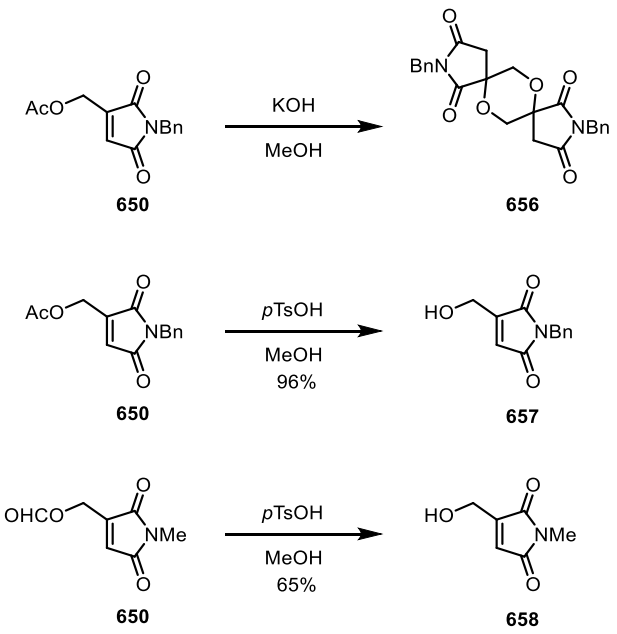
Maleimide **644** was synthesised through a condensation reaction with benzylamine in 86% yield. This *α*-methylene can be oxidised with SeO_2 to give **643**. However, under the reaction conditions an acetate protected allylic alcohol **650** was observed, potentially due to condensation with acetic acid which was used as a solvent. To confirm this finding, and to investigate the possibility of direct addition of the benzoic ester to the alcohol, formic acid was used instead of acetic acid as the solvent. The formic

ester **646** was observed in similar yields. The yields of the reaction were low (27%), with 41% of starting material remaining, due to the electron deficient maleimide bond leading to unfavourable attack to SeO_2. From here, formate **646** could undergo a [2+2] photocycloaddition to give **648** and **649**. The yield of the desired regioisomer were low and unfortunately, only the undesired diasterioisomer was observed in NOE studies (see Experimental). To apply this substrate into the total synthesis, ketone **647** would have to be protected. Several methods to achieve the product in the correct regio- and diastereoselectivity were trialled, all of which proved to be unsuccessful in giving the desired cycloadduct in the correct regio- or diastereoselectivity (Scheme **115**).



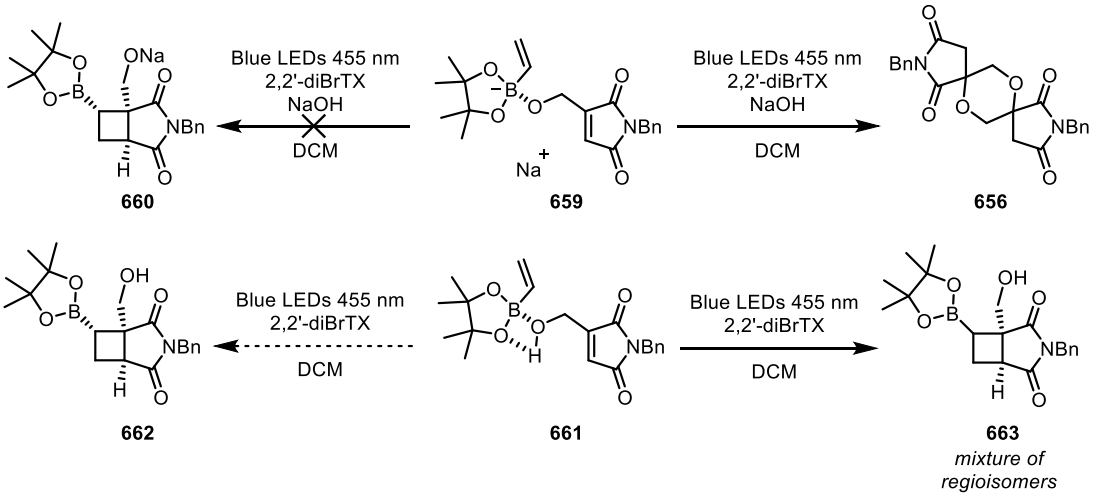
Scheme 115 *- Intermolecular [2+2] photocycloadditions of protected ketones.*

To access the desired maleimide alcohol **657**, the hydrolysis of the acetate group was necessary. Upon basic hydrolysis conditions, a side product **656** was observed as the exclusive product (Scheme **116**). This was identified to be the result of deprotection of acetate **650**, followed by a Michael addition to the electron deficient maleimide ring to form a dimer **656** (confirmed by mass spectrometry, found [M+Na^+]: 457.3). Acid hydrolysis pleasingly gave the desired alcohol **657** in 96% yield. The hydrolysis of the formic ester was investigated but a lower yield of alcohol **658** was observed.



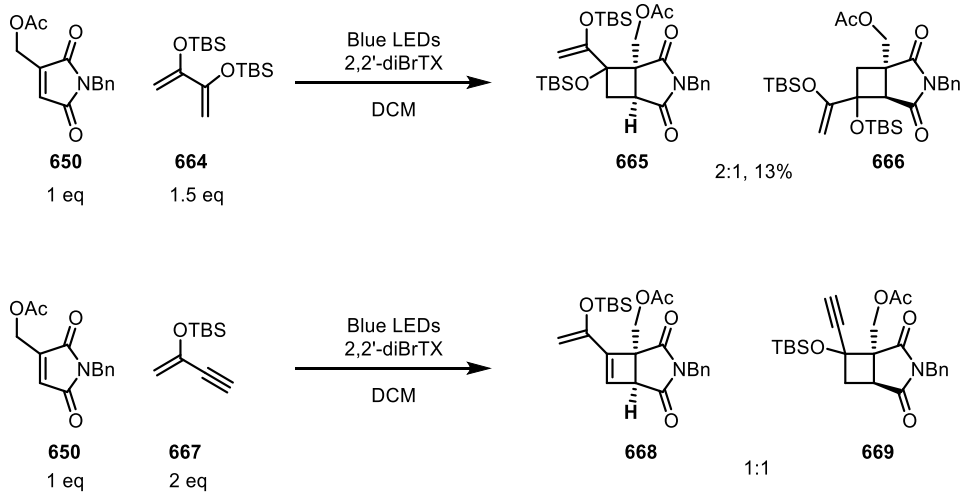
Scheme 116 *– Hydrolysis of acetate* ***650****.*

Further investigations lead to the application of vinyl boronic ester **659** as a [2+2] substrate (Scheme **117**). The boronic ester could act as both a tether to the maleimide hydroxyl group, and as a functional group with the ability to be converted diastereoselectively to an alcohol. Initially, alcohol **657** was deprotonated in the presence of a base to give the anionic hydroxide to better coordinate to the boronic ester, however, the exclusive product observed upon photocycloaddition conditions was the dimer **656**. To prevent dimerisation through basic conditions, the maleimide alcohol **657** was not treated with a base in the hope that the H–bond coordination would have enough of an influence. Unfortunately, only a mixture of regio- and diastereoisomers were observed by ^{1}H NMR.



Scheme 117 *– Vinyl boronic esters in the diastereoselective synthesis of cyclobutane* ***663****.*

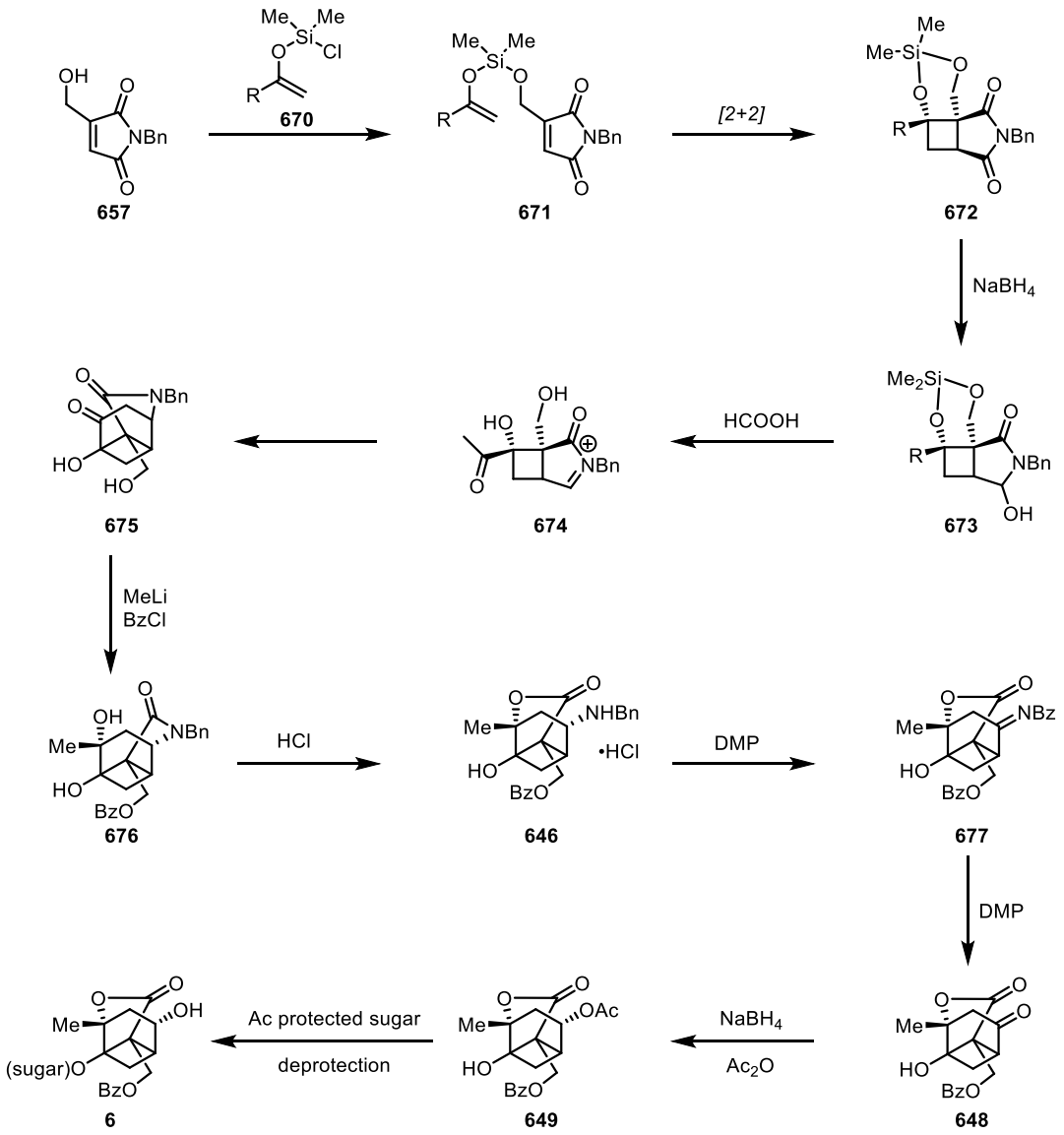
Finally, a silyl enol ether with an alkyne tether was trialled as a cycloadduct in the [2+2] synthesis (Scheme **118**). Since alkynyl esters and ketones were slow in the photocycloaddition with maleimides due to their electron mismatch, it was thought that the [2+2] would favour the alkene exclusively over the alkyne. However, upon treatment with these conditions it was found that both alkene and alkyne were equally favoured in the [2+2] photocycloaddition.



***Scheme 118** – Intermolecular [2+2] photocycloadditions of dienes. Compounds **668, 669** observed by ^{1}H NMR.*

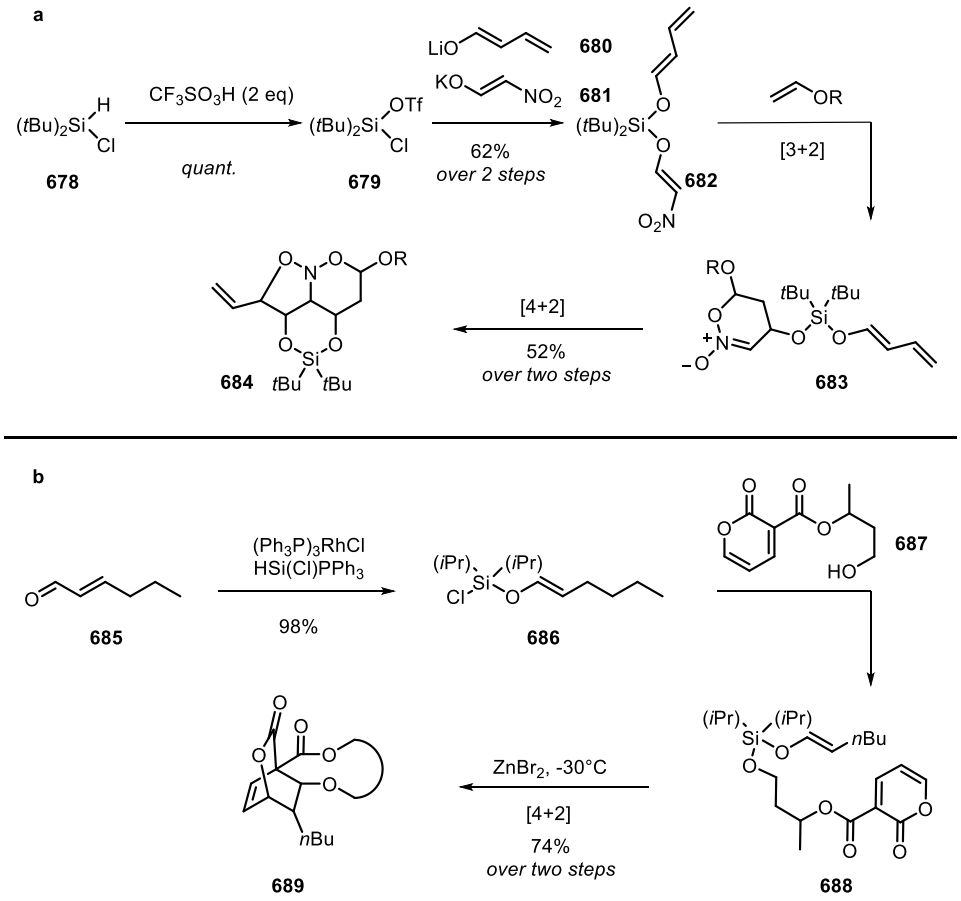
4.4. Intramolecular [2+2] photocycloadditions

An explanation for the lack of the desired diasterioisomer being observed, even where steric hindrance would favour the desired orientation, may be due to a favourable *endo*-interaction between the silane ether and maleimide (Scheme **119**). This interaction has been observed in previous [2+2] photocycloadditions between maleimides and silyl enol ethers, where the exclusive product observed is the *cis* orientation of the silane with respect to the maleimide.[156–159] Due to a lack of desired diasterioisomer being formed through an intermolecular [2+2] photocycloaddition, the intramolecular photocycloaddition then was explored. Connection of a cleavable tether to alcohol **657**, synthesised from the deprotection of **650** under acidic conditions, gives diene **671** that under [2+2] photocycloaddition would give desired product **672** in a high regio- and diastereoselectivity (Scheme **119**). Product **672** would also have two protected alcohols, negating the need for further protection steps.



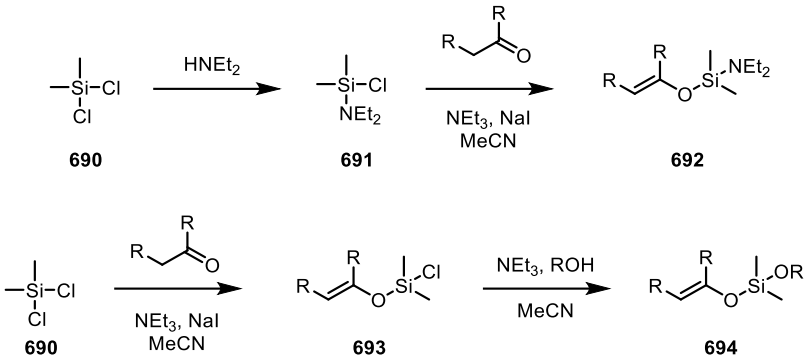
Scheme 119 *– Intramolecular approach to the total synthesis of albiflorin.*

Previous literature into the cycloaddition of tethered alkenes and silyl enol ethers has been completed in the key step in other synthesis work. For example, work by Martinborough *et al.* utilised heterofunctionalisation of silanes starting from di-*tert*-butylchlorosilane in the synthesis of polyhydroxylated alkaloids.[160] Treatment with triflic acid gives two pathways of nucleophilic substitution, giving difunctionalised silane **682**. Sequential [3+2] and [4+2] cycloadditions gives the desired molecular scaffold **684** (Scheme **120a**). Another example by Tsugawa *et al.* in the total synthesis of vitamin D analogues (Scheme **120b**).[161] Transition metal silylation of unsaturated aldehyde **685** gives chlorosilylenol ether **686**. From **686** nucleophilic substitution with alcohol **687** gives heterofunctionalised silane **688**. A [4+2] cycloaddition gives desired scaffold **689**.



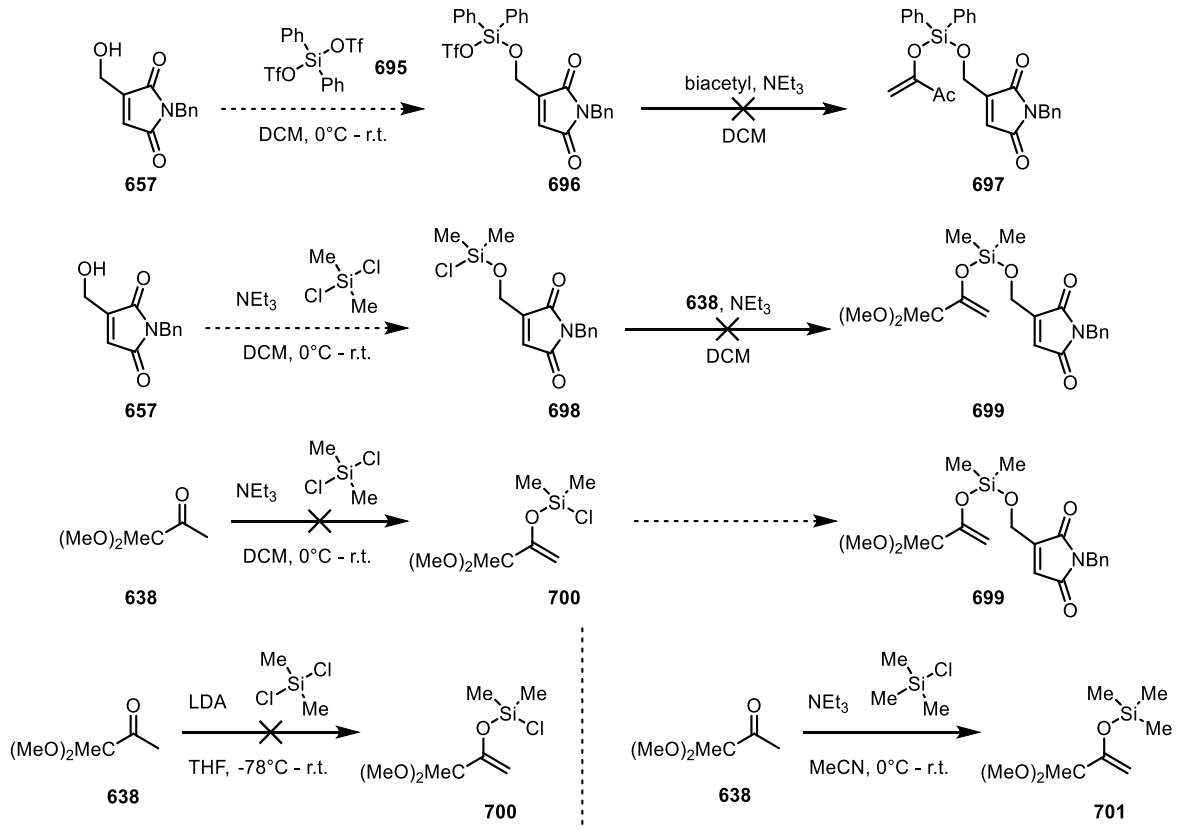
Scheme 120 *– Difunctionalisation of silanes.*

Previous work into the heterofunctionalisation of silanes has been completed under several conditions (Scheme **121**).[162,163] A general methodology towards difunctionalised silanes was developed by initial formation of a silyl enol ether from a desired ketone and dimethyldichlorosilane **690**, followed by nucleophilic substitution with a desired alcohol to give silane **692**. Azasilanes were also synthesised whereby nucleophilic substitution was performed first followed by formation of difunctionalised enol ether **694**. Due to the general reaction conditions and broad functional group tolerance, it was thought that the reaction protocol would be ideally suited for forming substrates for the total synthesis.



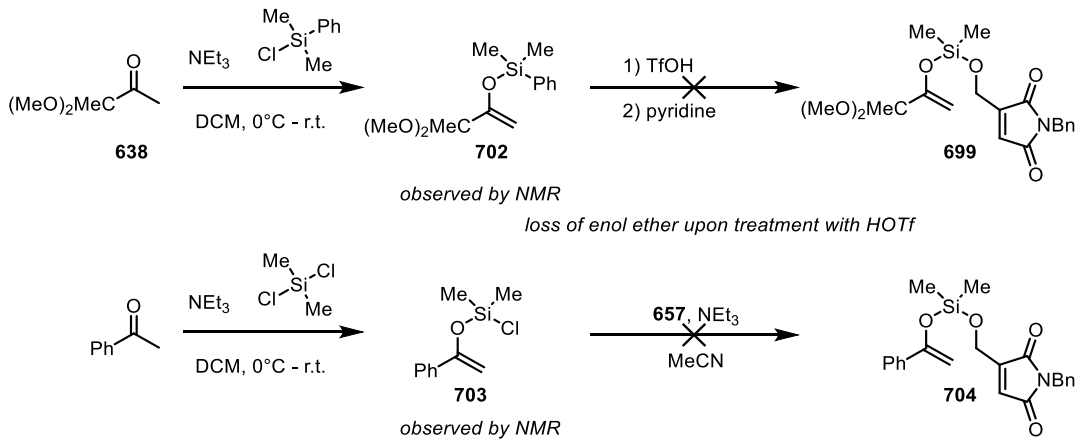
Scheme 121 *– General protocol towards the difunctionalisation of silanes.*

Alcohol **657** was subjected to the reaction conditions described above (Scheme **121**) to furnish desired compound **697** (Scheme **122**). Initial investigations were focussed on forming the silane ether bond with alcohol **657**, as it was a concern that **657** was not stable in the presence of base while a free alcohol was present due to the formation of dimer **656**. Reacting **657** with silane **695** showed full consumption by TLC (thin-layer chromatography), however no further reaction was observed upon treatment with biacetyl. This may be due to an aldol addition of the free ketone formed in the addition reaction, reacting with the maleimide double bond. In addition to this, it wasn't clear if the key intermediate **697** was being formed as no change was observed by ^{1}H NMR and isolation was not achieved. For this reason, the reaction conditions were changed to better suit previous literature conditions. Alcohol **657** was treated with triethylamine and dimethyldichlorosilane. From this point, with no purification, dimethyl acetal protected ketone **638** was used in the reaction conditions with an extra equivalent of triethylamine. However, no product was observed. It was proposed that this may be due to the addition of the enolized ketone acting as a nucleophile to the intermediate **698** which has two electrophilic positions. For this reason, the order of addition was reversed so that the silyl enol ether was formed first, followed by addition of the deprotonated alcohol. However, formation of the silyl enol ether with dimethyldichlorosilane was not observed by NMR under standard reaction conditions, or even harsher conditions using LDA as the base. To determine whether a silyl enol ether could be formed, ketone **638** was treated with TMSCl, upon which the desired enol ether **701** was observed and could be isolated.



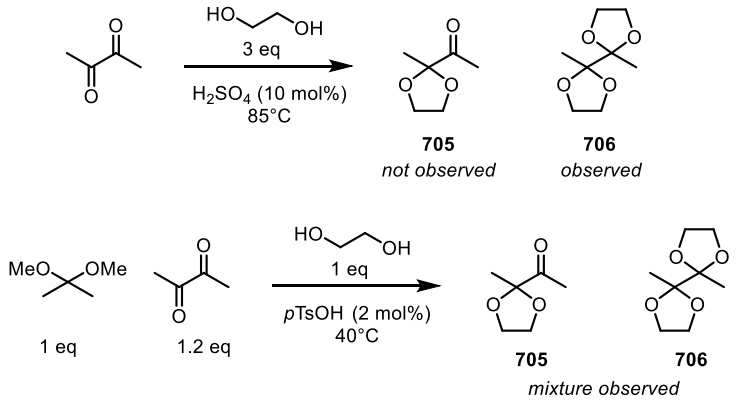
Scheme 122 *– Investigations towards the difunctionalisation of silanes.*

To circumnavigate the issue of dichlorodimethylsilane addition, chlorodimethylphenylsilane was used (Scheme **123**). For heterofunctionalisation of silane **702**, the application of triflic acid cleaves the Si-Ph bond to give the silyltriflate, opening the option for further functionalisation with alcohol **657**. Pleasingly, treatment of ketone **638** in the presence of dimethylchlorophenyl silane gave the silyl enol ether **702**, however in low yield. Further activation of the silane using triflic acid, however, saw loss of the enol ether protons by ^{1}H NMR analysis and, as such, this methodology was not pursued further. To determine if ketone **638** was not compatible with the reaction conditions involving dichlorodimethylsilane, acetophenone was subjected to the reaction conditions instead. Pleasingly, enol ether **703** was observed by ^{1}H NMR, however, upon further functionalisation using alcohol **657**, no product was observed.



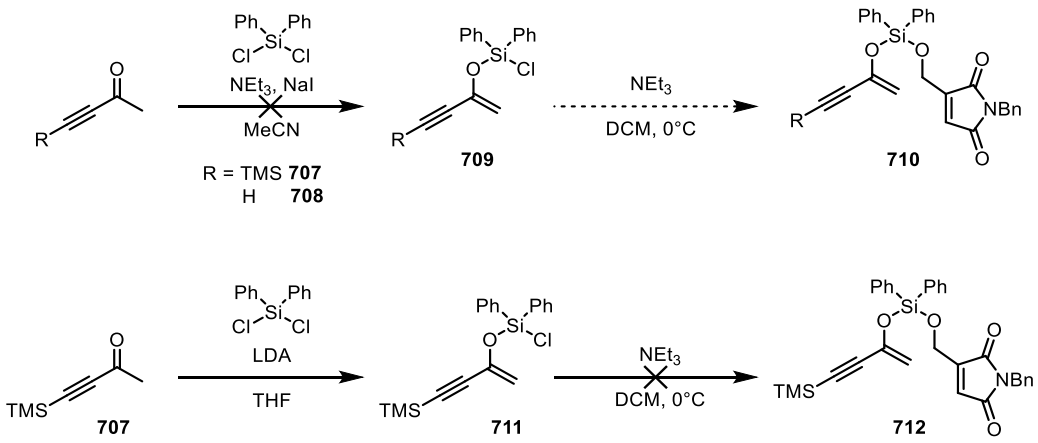
Scheme 123 *– Investigations towards the difunctionalisation of silanes.*

Further investigations into the use of a different protected diketone **705** were undertaken, with focus on acetal protection using ethylene glycol. Unfortunately, in both conditions the di-acetal protected ketone **706** was observed and could not be separated through chromatography or distillation (Scheme **124**).



Scheme 124 *– Monoprotection of biacetyl..*

An alternative ketones **707** and **708** were investigated (Scheme **125**). The alkyne substituent could be converted into a ketone by alkyne hydration, after reduction of the imide carbonyl in compound **642**. Due to the low boiling point of the alkynyl ketone, diphenyldichlorosilane was used. Using literature conditions for the formation of the silyl enol ether, no product was observed by ^{1}H NMR. Upon treatment with LDA, however, the enol ether was observed by ^{1}H NMR (δ_H = 4.90 (1 H, d, *J* = 1.2 Hz), 4.76 (1 H, d, *J* = 1.2 Hz)) and was not lost to vacuum upon concentration. Unfortunately, upon treatment with alcohol **657** and triethylamine for the second functionalisation step, no product was observed by ^{1}H NMR.



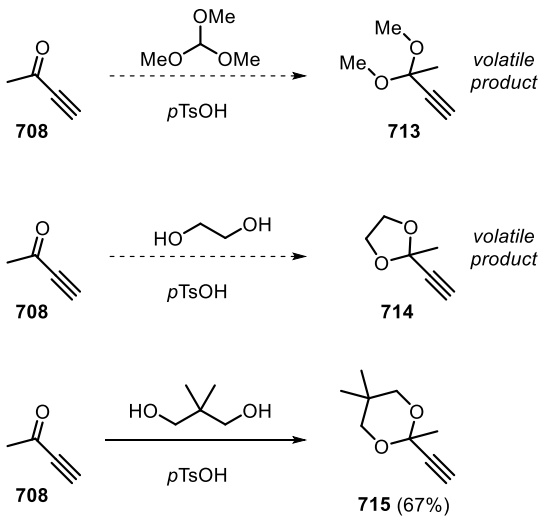
Scheme 125 *- Investigations towards the difunctionalisation of silanes.*

Although the intramolecular [2+2] photocycloaddition would give the desired diasterioisomer in a single step the synthesis of the precursor was not investigated any further due to the lack of initial results from the incompatibility of the substrate in the reaction conditions.

4.5. Alkyne-alkene [2+2] photocycloaddition

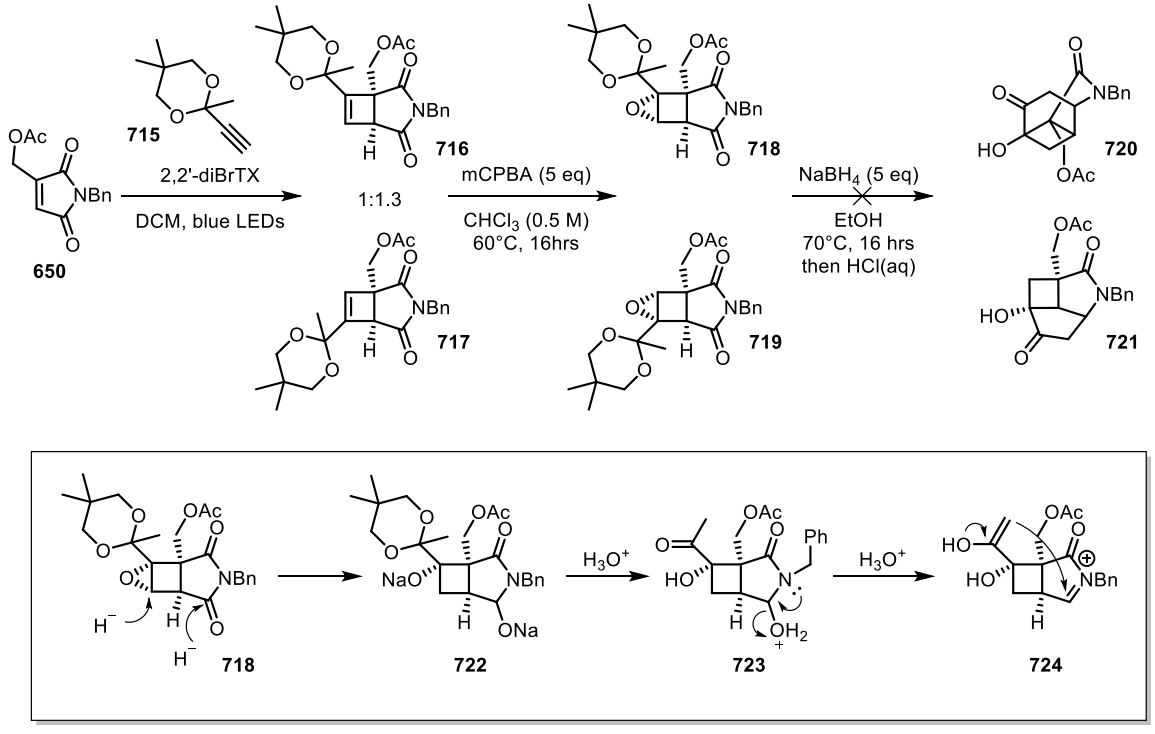
Attention was turned towards an intermolecular [2+2] photocycloaddition that would give only regioselectivity issues. By using an acetal protected 4-butyn-2-one **715** to the [2+2] step, a mixture of only regioisomers would be observed, allowing for the diastereoselective functionalisation of the cyclobutene as a potential pathway to **720** (Scheme **127**).

3-Butyn-2-one **708** was protected with neopentyl glycol as other protecting groups gave a product that were too volatile and susceptible to loss on exposure to low pressure/high heat (Scheme **126**). Acetal **715** gave a crystalline solid in a 67% yield, which could be synthesised on a gram scale. [2+2] Photocycloaddition with alkyne **715** gave cyclobutenes **716** and **717** in a 1:1.3 regioselectivity (Scheme **127**). This lack of selectivity poses a problem with the overall yield of the reaction, as immediately 50% of the product is an undesired regioisomer. However, this could potentially be overcome by the addition of a Lewis-acid coordinator to encourage the head-to-head arrangement.



Scheme 126 *– Approaches to the protection of ketone* ***708****.*

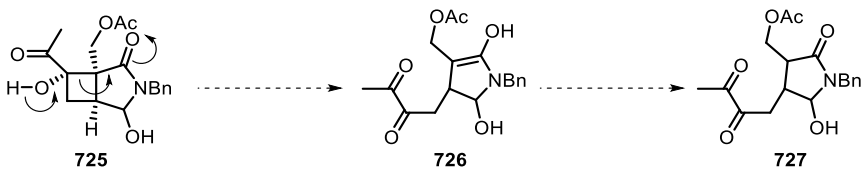
Regioisomers **716** and **717** could not be separated though column chromatography, and so were taken through as a mixture of compounds in the next step. Oxidation with *m*-CPBA gave cyclobutyl epoxides **718** and **719** in a combined 30% yield (Scheme **127**). However, on treatment of epoxide **718** with $NaBH_4$, the starting material was consumed by TLC, however, on aqueous work-up with HCl as the acid, only degradation of the starting material was observed by ^1H NMR of the crude material.



Scheme 127 *– Approach to structure* ***720*** *through cyclobutene* ***716****.*

The lack of cyclised product **720** may be due to an unwanted side reaction posed by forming the free tertiary cyclobutyl alcohol. Due to the *β*-position of the alcohol to the imide carbonyl across the

cyclobutane ring, a De Mayo rearrangement could take place cleaving the cyclobutane ring to give compound **727** (Scheme **128**).



Scheme 128 *– De Mayo ring cleavage of cyclobutyl alcohol* ***725****.*

Due to time constraints, no further progress was made with this total synthesis. However, the synthesis of epoxide **718** gives a promising active intermediate that under the right conditions should give a route into the key structural core of albiflorin. Furthermore, alternative approaches towards the synthesis of alkenyl silyl ether **671** would give a very encouraging result towards the synthesis of the desired diasterioisomer of the cyclobutane precursor **672**.

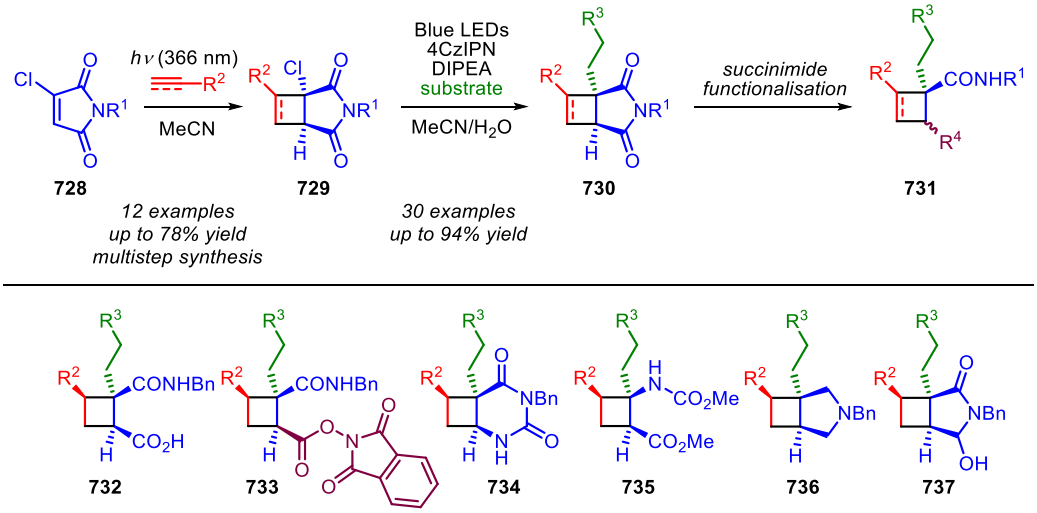
Conclusions and Future Work

5.1. Chapter 1

In summary, a new method has been developed for the modular functionalisation of cyclobutanes. A scalable approach to forming halo-cyclobutanes has been achieved and is capable of producing up to 6.3 gh^{-1} on a 400W UV (366 nm) lamp. The halo-cyclobutanes produced are able to undergo photoredox conditions to form alkyl radicals that can be trapped with a range of alkene substituents with yields of up to 94%.

Mechanistic studies into the photoredox catalysed dehalogenation elucidated competing rates of HAT of the starting material *vs* the alkene adduct. Furthermore, the necessity of water in the reaction was determined to be due to the coordinating effect to the imide carbonyl. Coordination lowers the reduction potential allowing for the catalyst to reduce the imide carbonyl, followed by *SCS* dehalogenation to give the desired α-carbonyl radical. Further investigation into the HOMO-LUMOs of the α-carbonyl chloride demonstrated that the LUMO sits across the imide carbonyl and not across the C–Cl bond.

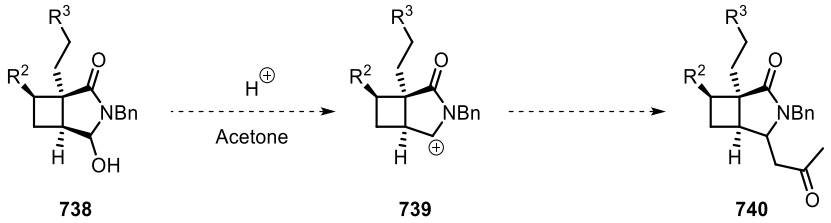
Further work can be done into the sequential [2+2] photocycloaddition and photocatalysed dehalogenation reactions such as scaling up synthesis and employing flow conditions to achieve rapid access to large scale production of complex cyclobutanes from simple starting materials (Scheme **129**).



Scheme 129 *- Outline of methodology from Chapter 1.*

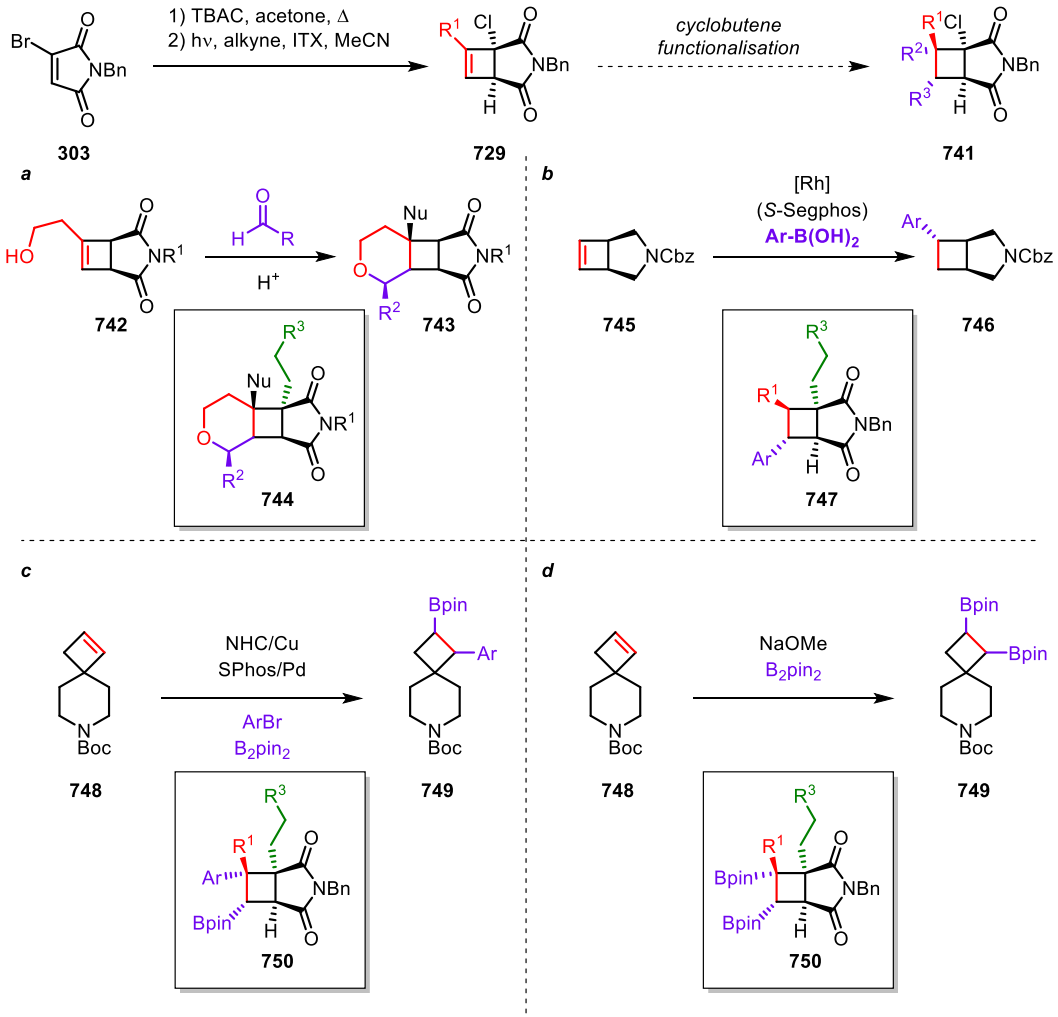
Additionally, succinimide functionalisation was successfully achieved through hydrolysis under basic conditions. Pleasingly, the reaction was highly regioselective and gave an excellent yield, so further functionalisation of the carboxylic acid **732** could be performed. However, upon activation of the

carboxylic acid, spontaneous ring closure to form the succinimide ring occurred giving **730** as the major product. Carbonyl reduction and imide functionalisation gave desired compounds in good yield.



Scheme 130 *– Alkylation of hemiaminal* ***728****.*

Further nucleophilic functionalisation of the hemiaminal of compound **738** to give alkylated products would give additional functionality to the succinimide ring (Scheme **130**). These types of functionalisations have been common in electrochemical oxidation of cyclic amines.[164–167]



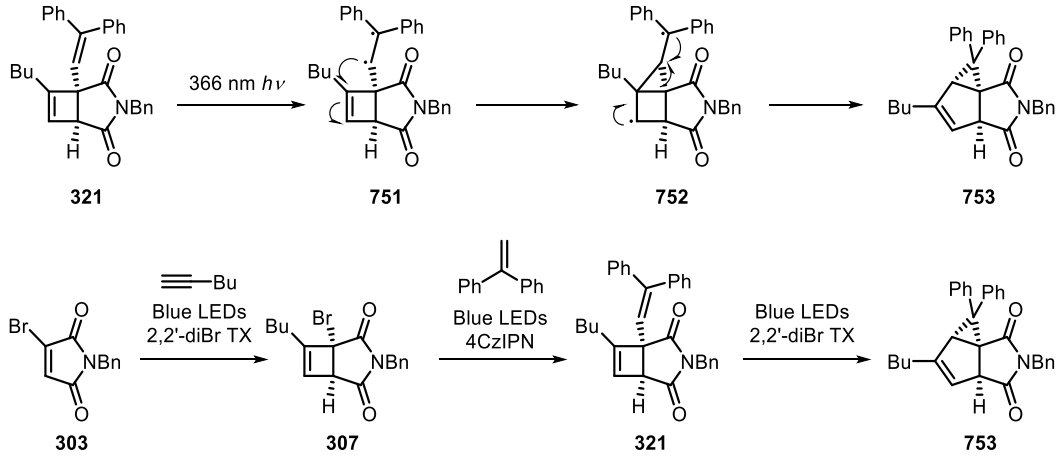
Scheme 131 *– Cyclobutene functionalisations.*[24–26,144]

In past decade, functionalisations of cyclobutenes have become popular due to the rapid access to functionalised cyclobutanes through strain release reactions of the internal alkene (Scheme **131**). To

incorporate this step into the developed methodology, the hydrogenation step can be replaced with a variety of cyclobutene functionalisations.

For example, work in the Booker-Milburn group took advantage of the nucleophilic nature of cyclobutene in an acid promoted Prins-type cyclisation to give compound **743** (Scheme **131a**).[25] An analogue of this was synthesised in Chapter 1 to give regioselective cyclobutene **354** (Scheme **55**). Application of the Prins cyclisation would substitute well into the current methodology to replace the alcohol protection and cyclobutene saturation steps. Subsequent photocatalysed dehalogenation would give a highly functionalised regio- and diastereospecific compound **744**.

Further functionalisations of cyclobutenes have been developed to include rhodium catalysed arylations,[26] metal catalysed 1,2-carboborations,[144] and transition metal free 1,2-diborylations.[24] All of which can substitute the hydrogenation of the cyclobutene step (Scheme **131b**, **c**, **d**).

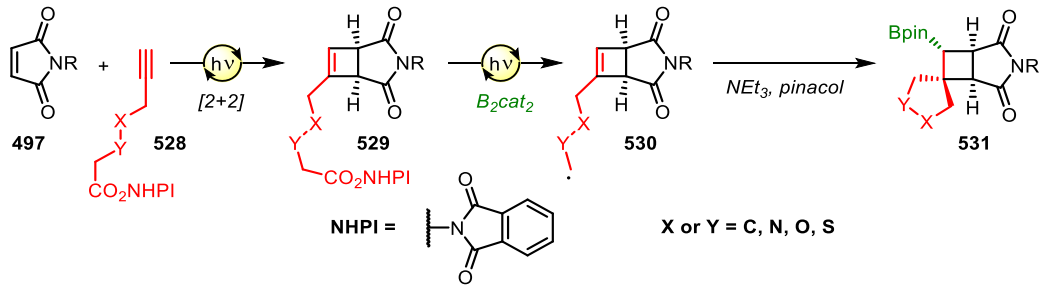


Scheme 132 *– Di-π-methane rearrangement of* ***321****.*

Compound **321** was synthesised through the redox-neutral reaction with bromo cyclobutene **307** and 1,1-diphenylethylene. The diene formed is set up for a di-*π*-methane rearrangement under UV irradiation (Scheme **132**). Access to these novel scaffolds would be achieved through three consecutive light-promoted reactions and enables a diverse range of fused polyheterocycles to be synthesised in this fashion. Furthermore, if visible-light mediated [2+2] conditions were employed, a potential one-pot procedure to compound **753** may be possible when combined with visible-light mediated di-*π*-methane rearrangement.

5.2. Chapter 2

A method towards the synthesis of cyclobutane-containing spirocycles was developed (Scheme **133**). The methodology involves the activation of alkyne-carboxylic acids followed by a visible-light mediated [2+2] photocycloaddition.



Scheme 133 *– Developed cycloaddition/1,2-carboboration protocol.*

The cyclobutene formed **529** is then able to undergo cyclisation/borylation to give highly functionalised cyclobutyl spirocycle **531**. Unfortunately, a robust set of conditions for the cyclisation/borylation step was not developed and so a scope of the cyclobutane spirocycles was not possible.

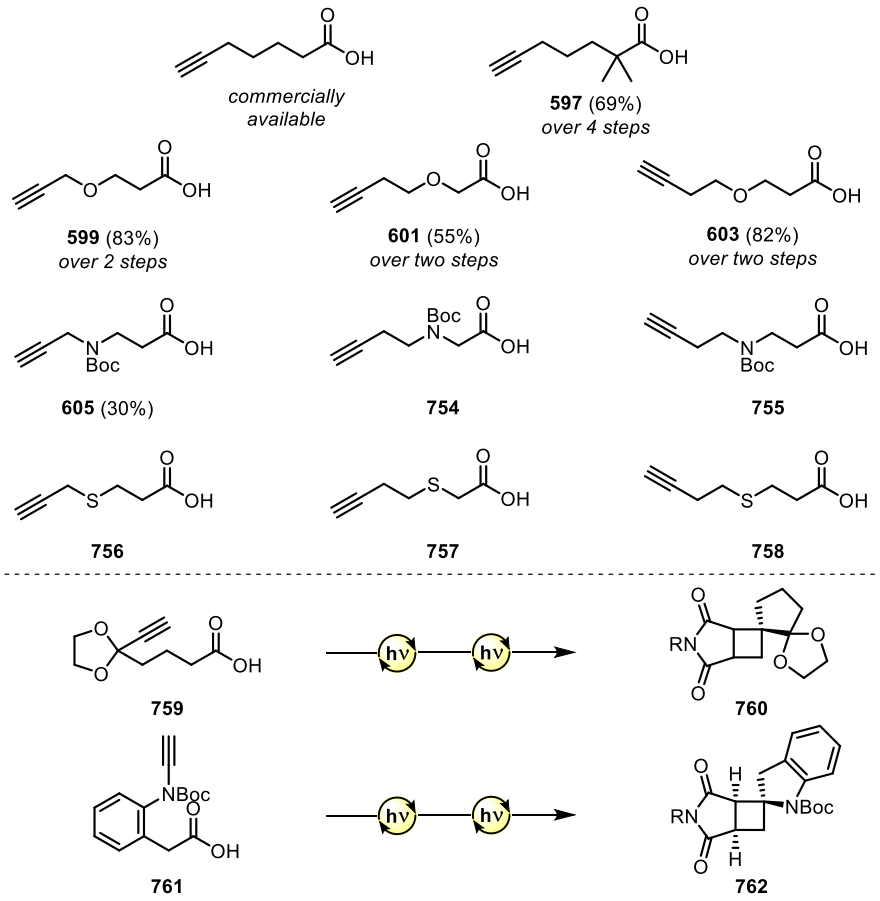
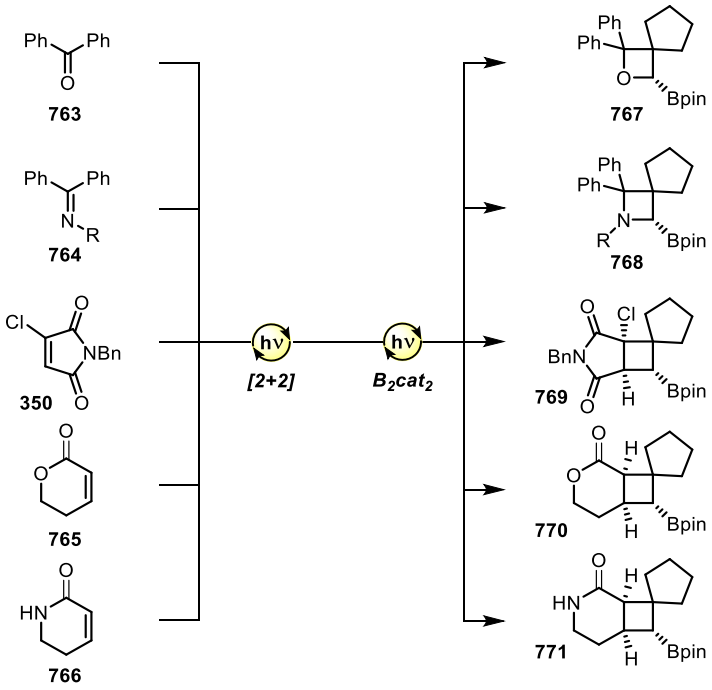


Figure 37 *– Scope of alkyne carboxylic acids and future synthetic opportunities.*

A range of alkyne carboxylic acids were successfully synthesised. Further derivatives may be synthesised, including thioalkanes, which would generate highly functionalised spirocyclic compounds, including a polyspirocyclic acetal **760** and isoindoline structures **762** (Figure **37**).

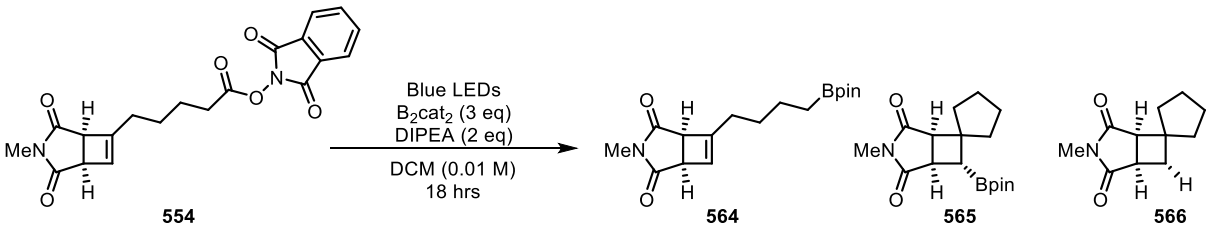
Furthermore, the scope of alkenes for visible-light mediated [2+2] photocycloaddition can be predicted by DFT before employment into the reaction conditions. Previous success has been achieved with Paterno-Buchi and aza-Paterno-Buchi visible-light [2+2] photocycloadditions.[168–170] Using these alkenes would lead to highly valuable azetidines and oxetanes which could then undergo cyclisation to give spirocyclic structures **767** – **768** (Scheme **134**).



Scheme 134 *– Future scope of alkenes.*

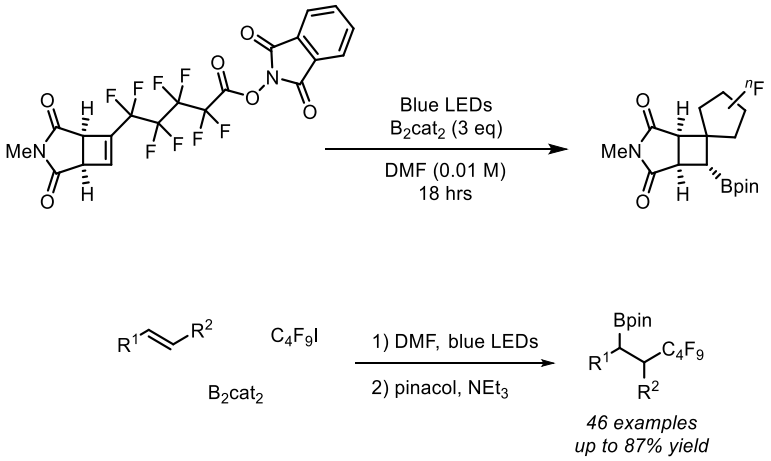
Halo-maleimide **350** can also be employed to the reaction protocol, furthering the work developed in Chapter 1, enabling photoredox functionalisation of the final product **769**. Other alkenes such as **765** and **766** is also possible, further expanding the scope of spirocycles that can be synthesised from easily accessible starting materials.

A robust visible-light mediated [2+2] photocycloaddition involving a redox active ester has been developed to give gram scale production of activated cyclobutenes. The protocol enables the cycloaddition onto the alkyne under radical mediated process while maintaining the redox active *N*-acyloxy phthalimide. However, in the second step, the cyclisation issues stemmed from an electronic mis-match between cyclisation between an electron rich alkene and alkyl radical, which therefore favoured the linear borylated product **564** (Scheme **135**)**.**



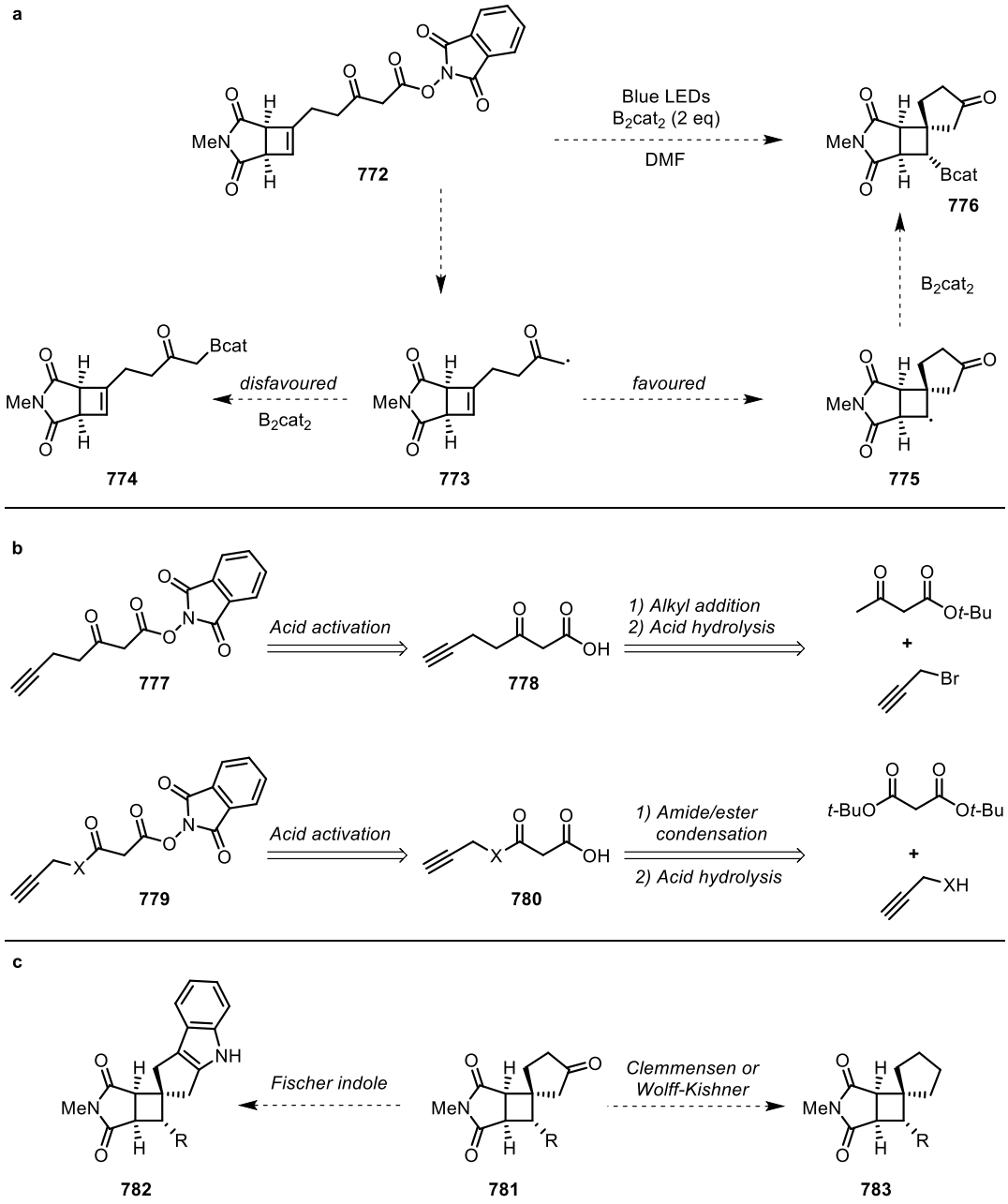
Scheme 135 *– Cyclisation/1,2-carboboration.*

Several ways to circumnavigate this issue is possible. For example, using perfluoroalkanes would favour the cyclisation step over the radical addition to the diboronic ester, as reflected in 1,2-carboboration work by Studer *et al.* (Scheme **136**).[147]



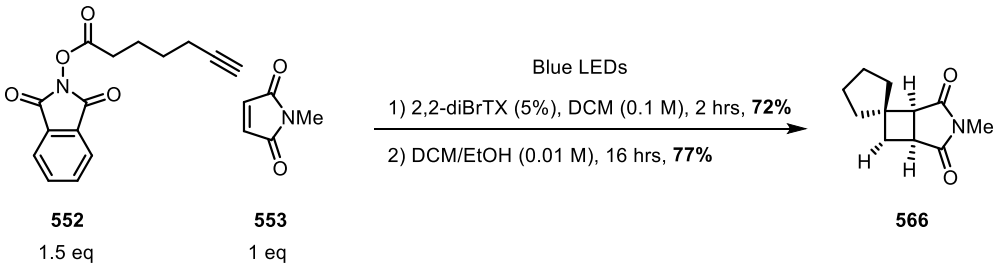
Scheme 136 *– Perfluoroalkanes employed into the 1,2-carboboration conditions.*[147]

The most applicable way to generate an electron deficient radical in the reaction conditions while maintaining a broad scope, would be to generate an *α*-carbonyl radical **773** (Scheme **137a**). The radical **773** would be stable enough to undergo cyclisation and electrophilic to avoid C–B bond formation. The generated nucleophilic cyclobutyl radical **775** would then undergo radical addition to the B_2cat_2 source, similar to previous work by Studer *et al*. (Scheme **136**). The carbonyl functionality would also lead to a modular approach in the synthesis of alkyne substrates (Scheme **137b**). The carbonyl functionality in the spirocycle would act as a further point of derivatisation for example a Fischer indole synthesis, or can be reduced to give the all-carbon/ether/amine containing spirocycle (Scheme **137c**).



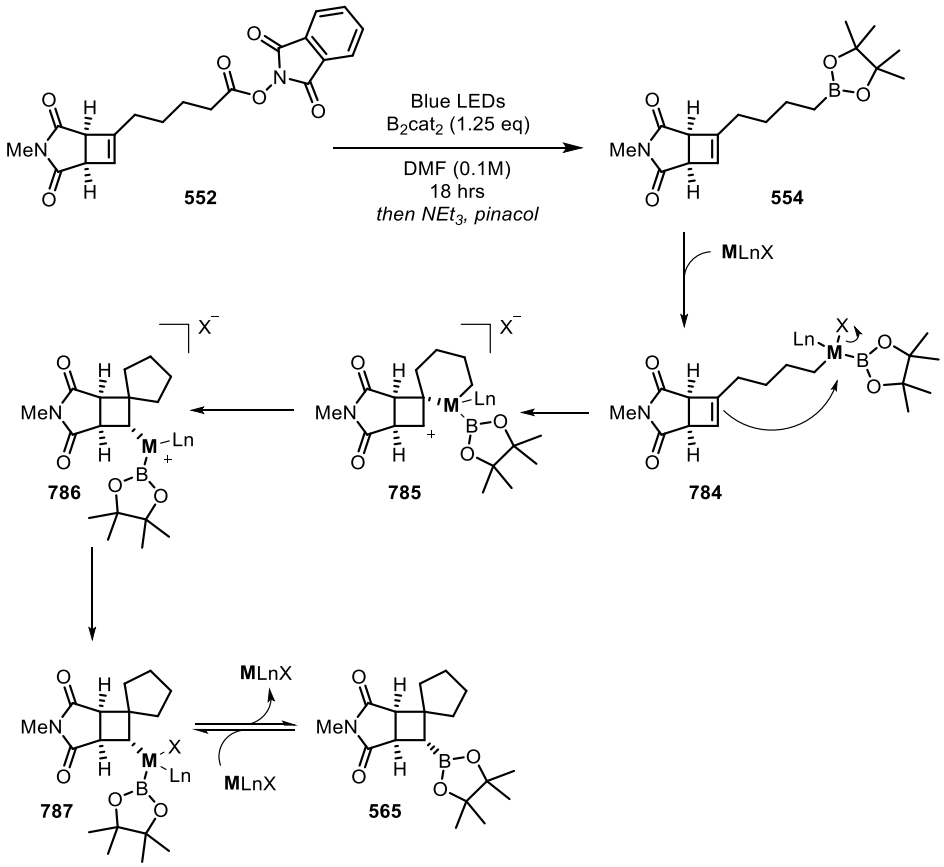
Scheme 137 *– **a)** Decarboxylation/1,2-carboboration of ketone **772**. **b)** Modular synthesis of alkyne acid derivatives. **c)** Functionalisation of ketone group after functionalisation of boronic ester.*

Another option is to focus on cyclisation and HAT rather than 1,2-carboboration. Previous success into the synthesis of spiro[3.4]octanes and oxaspiro[3.4]octanes was possible from application of reductive SET of both iodoalkanes and redox active esters. Conditions encountered during optimisation of the 1,2-carboboration gave high yield of the fully reduced spirocycle (Scheme **102**). Using these conditions in a one-pot synthesis would give rapid access to the desired spirocycle (Scheme **138**).



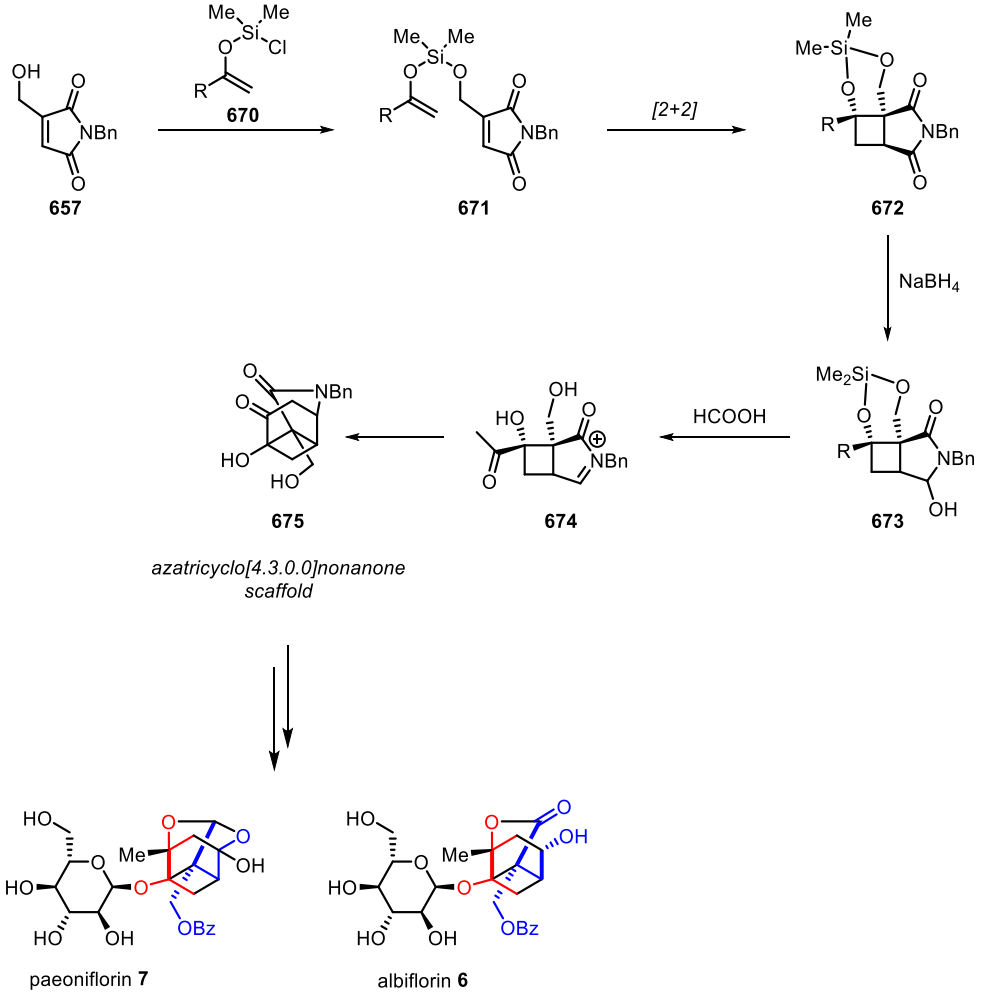
Scheme 138 *– Synthesis of diastereoselective spirocycles.*

Due to the high yielding and facile access to linear borylated compound **554**, transition-metal mediated cyclisation of boronic ester **554** may give the desired spirocycle **565** (Scheme **139**).[171,172] Oxidative addition into the alkylboronic ester gives compound **554**, which can undergo a Heck-type reaction to give the desired spirocycle and cyclobutyl-metal complex **787**. The reductive elimination step to give the boronic ester **565** will be reversible and may allow for functionalisation of aryl and alkyl halides. This protocol would take advantage of easily accessible compound **554** while also enabling further alkylation or arylation at the cyclobutyl position, giving functionalised cyclobutanes from readily available starting materials.



Scheme 139 *– Potential mechanism for transition-metal mediated spirocyclisation of* ***565****.*

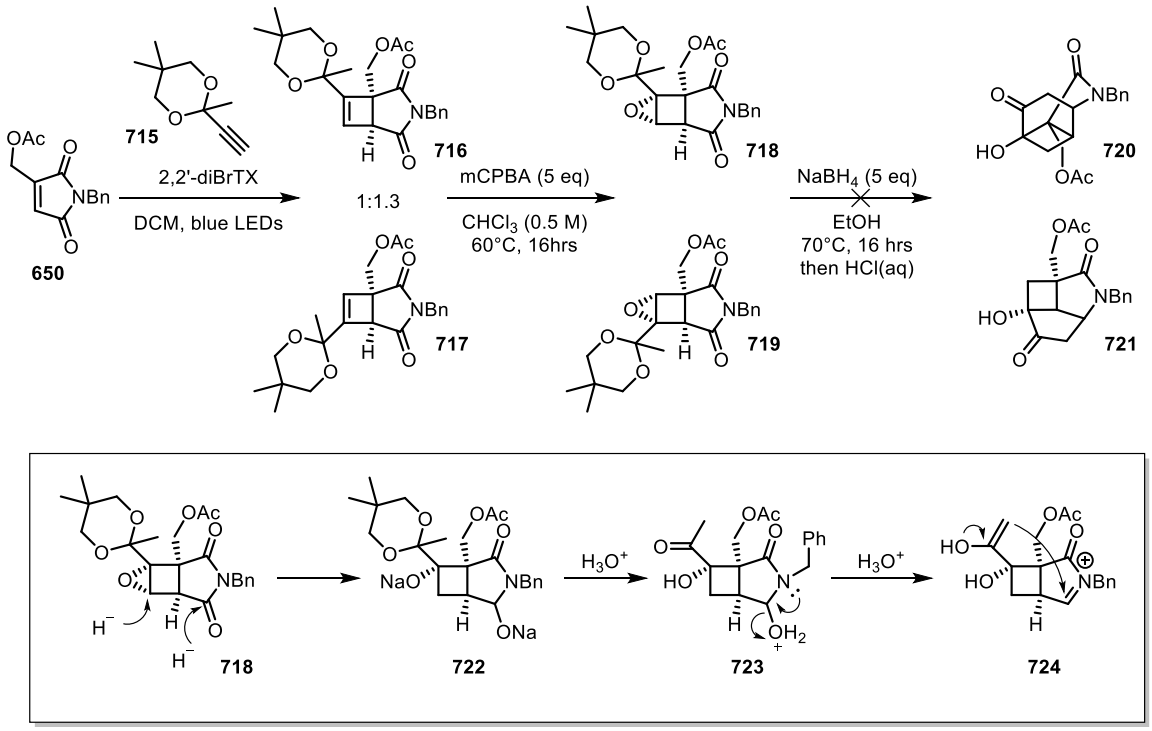
5.3. Chapter 3



Scheme 140 *– Proposed total synthesis towards albiflorin and paeoniflorin, with compound* ***675*** *as key intermediate.*

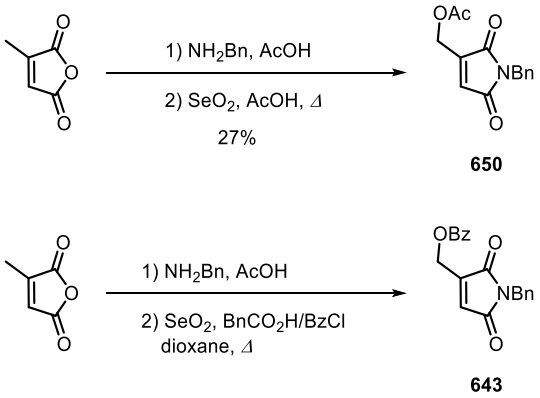
A potential synthetic route to the total synthesis of albiflorin has been established, utilising chemistry developed from Chapter 1 (Scheme **140**). For a highly stereoselective approach to the synthesis of intermediate **675**, an intramolecular [2+2] step was investigated, however, no product was observed of the difunctionalised silane **671**. Further work into the synthesis of compound **672** would be highly valuable as it would give the desired cyclobutane in extremely high diastereoselectivity.

However, due to the lack of success of an intramolecular compound being synthesised, an intermolecular reaction was established using alkyne **715** (Scheme **141**). Maleimide **650** is synthesised from readily available citraconic anhydride, however, the methodology to form the methyl hydroxy substituent **657** is low yielding and gives the acetate protected alcohol, which would need further deprotection/benzoylation.



Scheme 141 *– Synthetic route to compound* ***720*** *using alkyne-alkene [2+2] photocycloaddition.*

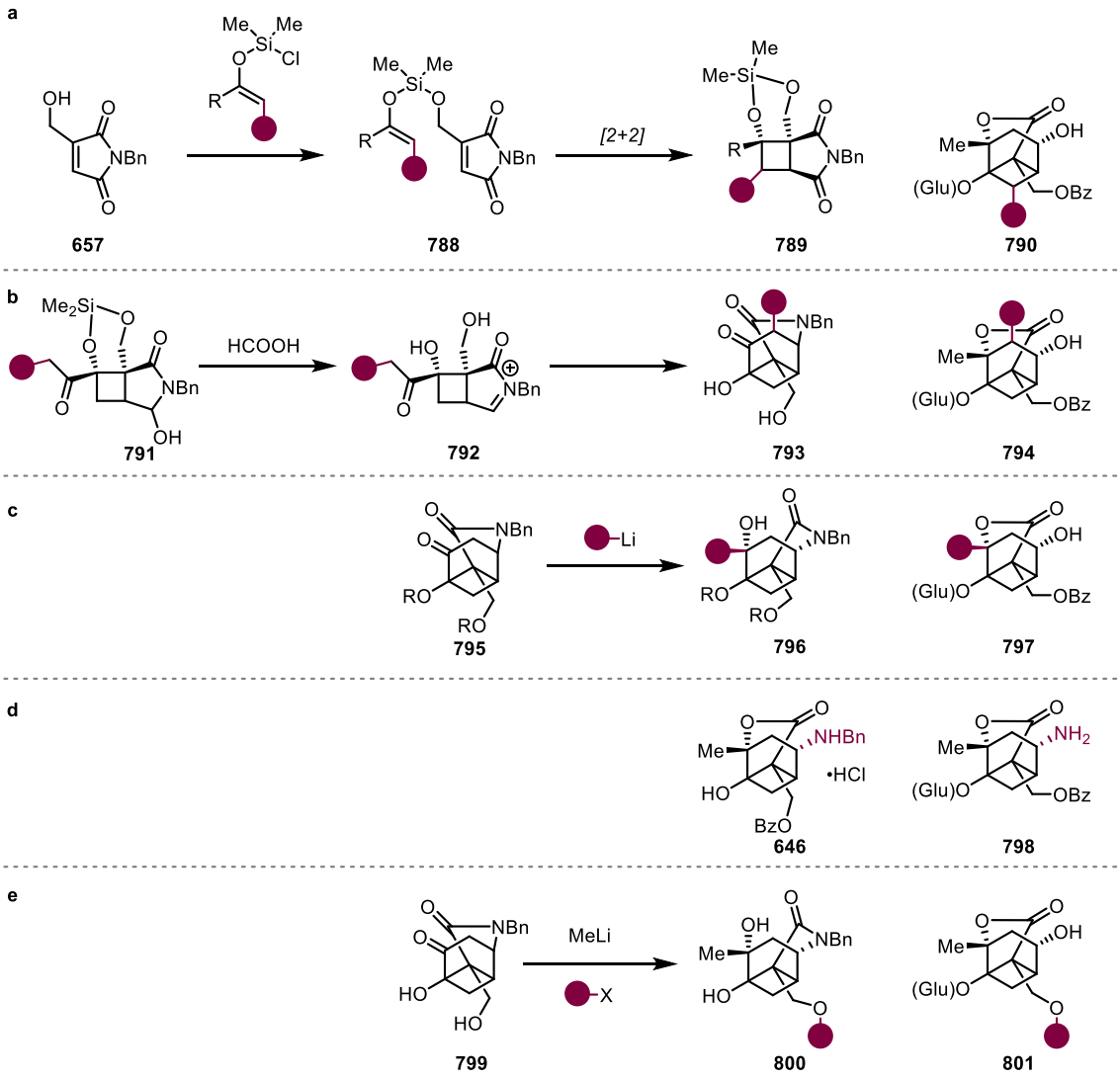
An alternative synthesis of maleimide **643** may utilize either phenylacetic acid, or benzoyl chloroformate as the electrophile under the oxidation conditions. This would lead directly to the desired Bz protected alcohol on the maleimide, reducing the number of steps required in the total synthesis (Scheme **142**).



Scheme 142 *– Alternative synthesis of maleimide* ***643****.*

Upon completion of the total synthesis, to establish the versatility and scalability of the synthetic route, a series of derivatisations could be installed. This would demonstrate its applicability into medicinal chemistry studies and offer a route towards designing more potent bioactive compounds for further investigations.

For example, substitution at α-keto position in compound **788** would give a tertiary centre at the cyclobutane, giving a tertiary/quaternary centre on all four carbons of the cyclobutane (Scheme **143a**). Additionally, it would be interesting to investigate the diastereoselectivity of the [2+2] photocycloaddition with a substitution at this centre.



Scheme 143 *– **a)** Starting with an α-functionalised ketone would give a substitution at the shown position in compound **790**. **b)** Substitution of the protected/hidden ketone in the α-position would give a substitution at the shown position in compound **794**. **c)** Introducing a variety of organolithium species would give a substitution at the shown position in compound **797**. **d)** Glycosylation with compound **646** would give amino-albiflorin **798**. **e)** Introducing an electrophile for substitution with alcohol **799** would give compound **801**.*

Another substitution in the α-position of ketone formed in compound **791**, would give access to derivatisation in the opposite side of the cyclohexyl ring, forming another tertiary carbon centre (Scheme **143b**). A range of organolithium compounds can be substituted into the ketone in compound **795** (Scheme **143c**). This would allow for insertion of CF_3, cyclopropyl, isopropene, or long chain alkyl groups to increase lipophilicity of the compound. Isolation of amine **646** and glycosylation of the tertiary alcohol would give amino-albiflorin **798** (Scheme **143d**). This would reduce the number of

steps required to convert amine **646** to alcohol **649** in a stereoselective manner, and change the bioactive properties of the final product, as the number of H-bond donor/acceptors will have changed. Introducing a different electrophile in compound **799** could generate a large change in bioactive properties (Scheme **143e**). The ester could be changed to give a less lipophilic substituent, or an ether could be formed instead of an ester, changing the metabolism of the whole compound, and again changing the number of H-bond donors/acceptors.

Experimental

6.1. General methods

6.2. Solvents, reagents, glassware and reaction setup

All reactions, unless otherwise specified, were conducted under normal atmospheric conditions with no need for drying glassware or alterations to commercially sourced chemicals. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe into the reaction vessels through rubber septa. Heating of reactions, where required, was achieved by placing the reaction vessel in an oil bath at the specified temperature. Unless otherwise specified, all reagents were purchased at highest commercial quality and used as received. Non-anhydrous solvents were purchased (unless specified) at the highest commercial quality and used as received. Acetone and diethyl ether were purchased from Sigma. Acetonitrile (MeCN), dichloromethane (DCM) and tetrahydrofuran (THF) were dried on an Anhydrous Engineering alumina column drying system.

6.3. Analytical methods

Chromatography: Flash column chromatography was carried out using Sigma-Aldrich silica gel (60 Å, 230-400 mesh, 40-63 μm) flash purification system. Reactions were followed by TLC, where practical, using aluminium-backed Merck Kieselgel 60 F254 fluorescent treated silica gel plates, which were visualised under UV light or by staining with aqueous basic $KMnO_4$, acidic *p*-anisaldehyde solution in ethanol, or phosphomolybdic acid solution in ethanol.

IR: IR spectra were recorded on neat compounds using a Perkin Elmer (Spectrum One) FT-IR spectrometer (ATR sampling accessory). Selected absorbances (*vmax*, expressed in cm^{-1}) are reported.

^{1}H NMR: Spectra were recorded on Jeol ECS (400 MHz), Jeol ECZ (400 MHz or Bruker Avance (400 MHz or 500 MHz) instruments. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s). Coupling constants (*J*) are given in Hertz (Hz) and refer to apparent multiplicities (s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, etc.). The ^{1}H NMR spectra are reported as follows: chemical shift (proton count, multiplicity, coupling constants,assignments).

^{13}C NMR: Spectra were recorded on a Jeol ECS (100 MHz), Jeol ECZ (100 MHz or Bruker Avance (100 MHz or 125 MHz) instruments. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s).

HRMS: High resolution mass spectrometry was performed on a Bruker Daltronics MicroTOF II (ESI), Thermo Scientific Orbitrap (ESI, APCI) or Thermo Scientific QExactive (EI). Only molecular ion peaks ($[M+H]^+$ or $[M+Na]^+$ for ESI and APCI; M^+ for EI) are reported.

LRMS: Low resolution mass spectrometry was performed using an Agilent Technologies 7890B GC system using electron ionisation (EI). Only major peaks are reported.

Mp: Melting points were recorded in degrees Celsius (°C), using a Stuart SMP30 melting point apparatus and are reported uncorrected.

6.4. Photochemical equipment and setup

The UV lamps used were 125 W medium pressure Hg lamp (λ_{max} = 366 nm). The UV lamp with Pyrex® cooling jacket was immersed in the reaction solution and with a positive pressure of nitrogen sparging through the solution and out through a paraffin oil bubbler (Figure S1).

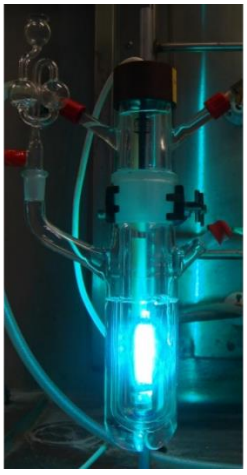


Figure S1 - [2+2] Photocycloaddition immersion well setup.

The blue LEDs used were 36 W blue chip-on-board (COB) LEDs manufactured by Citizen Electronics (CLU048-1212-B455, λ_{max} = 455 nm). All photocatalysed dehalogenation reactions were carried out at room temperature (r.t.) with fan-assisted cooling to maintain a temperature of 30–40 °C. The reactions were run in 50 mL round bottomed flasks positioned 3 cm above a single 36 W COB LED with a fan positioned next to the reaction (Figure S2).

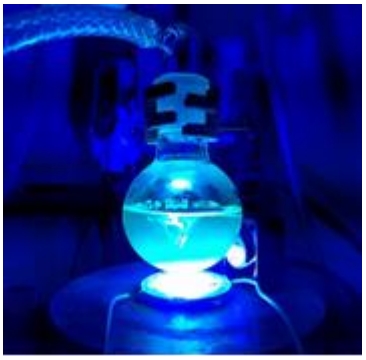


Figure S2 - Visible-light photocatalysed dehalogenation reaction setup

General Procedures

7.1. General Procedure 1: Bromination of Maleimides

To a round bottomed flask equipped with a stirrer bar, a solution of specified maleimide (100 mol%) and diethyl ether (0.7 M) was made. To this, bromine (110 mol%) was added over 5 minutes at r.t. and left to stir at reflux for 2 hours. On completion of bromination, the solution should turn lighter in colour. To this, triethylamine (110 mol%) was added over 5 minutes at 0 °C. The solution was left to stir for 18 hours. The solids were removed by filtration through celite, and the filtrate was concentrated *in vacuo* to give the crude product as an orange oil. The crude product was diluted with EtOAc (1.5 mL/mmol), washed with water (1 mL/mmol) and brine (0.5 mL/mmol) and dried over $MgSO_4$. The solvent was concentrated *in vacuo* and the resulting oil was triturated in petroleum ether (40/60), and the supernatant carefully decanted off. This step was repeated twice more. The solids obtained were collected by filtration through a glass frit and washed with ice cold methanol to give the bromomaleimide product.

7.2. General Procedure 2: Chlorination of Bromomaleimides

To a round bottomed flask equipped with stirrer bar, a solution of bromomaleimide (100 mol%) and tetrabutylammonium chloride (TBAC, 110–300 mol%) was made in acetone (0.3 M) and heated to reflux for 1–4 hours. The solvent was concentrated *in vacuo* and the crude material was diluted in EtOAc (1 mL/mmol) and washed with water (1 mL/mmol) and saturated aqueous NH_4Cl (1 mL/mmol). The organic layer was dried over $MgSO_4$, and the solvent removed to give the crude product, which was used without further purification. The chloromaleimides were found to be unstable to flash column chromatography on silica gel, however, upon concentration under vacuum they were found to be unstable to polymerisation.

7.3. General Procedure 3: [2+2] Photocycloadditions

Batch - In a UV reaction vessel, a solution of the specified maleimide or anhydride (100 mol%) and specified degassed solvent (150 mL) was made. To this solution the specified substrate (300-500 mol%) and specified sensitiser (1-10 mol%) was added. This was exposed to UV light while being agitated by bubbling nitrogen at r.t. for the specified amount of time. The solution was concentrated *in vacuo* and purified *via* flash column chromatography with the specified eluent system.

Syringe Pump Addition - In a UV reaction vessel, a solution of the specified degassed solvent (150 mL), the specified substrate (300-500 mol%) and specified sensitiser (5-10 mol%) was made. This was

exposed to UVA irradiation while being agitated by bubbling nitrogen at r.t. for the specified amount of time. A solution of the specified maleimide or anhydride (100 mol%) in the selected degassed solvent was added dropwise over the specified time to the substrate solution. On completion, the solution was concentrated *in vacuo* and purified *via* flash column chromatography with the specified eluent system.

Visible-Light – In a 7 mL *via*l, a solution of the specified substrate (100 mol%), 2,7-dibromo-4a,9a-dihydro-9H-thioxanthen-9-one (5 mol%), the specified alkyne (100 – 300 mol%) and DCM (0.1 – 0.05 M) was added. The solution was sparged for 5 minutes with nitrogen and sealed. The solution was then exposed to 36 W, 455 nm LEDs for the specified amount of time until completion by TLC. The solvent was concentrated *in vacuo* and the crude product was purified *via* flash column chromatography with the specified eluent system.

7.4. General Procedure 4: Hydrogenation of Cyclobutenes

In a 250 mL round bottomed flask, a mixture of cyclobutene (100 mol%), 5% Pd/C (5% w/w) and methanol (0.1 M) was made. This was sparged for 15 minutes with H_2 and left under a H_2 atmosphere (balloon) at r.t. for 16 hours. The Pd/C was removed by vacuum filtration over celite, and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography gave the chlorocyclobutane product.

7.5. General Procedure 5: Visible-Light Photoredox Reactions

Hydrodehalogenation - In a 7 mL *via*l, a solution of the specified substrate (100 mol%), $Ru(bpy)_3Cl_2.6H_2O$ (1 mol%), diisopropylethylamine (1000 mol%), formic acid (1000 mol%) and anhydrous DMF (1 mL) was made and sparged for 20 mins. The *via*l was sealed and exposed to 36 W, 455 nm LEDs for 20 minutes. The reaction completion was observed by TLC. The solution was washed with water, extracted with Et_2O (2 x 10 mL) and dried over anhydrous $MgSO_4$. No further purification was taken unless otherwise stated.

Atom Transfer Radical Addition - In a 7 mL *via*l, a solution of the specified substrate (100 mol%), the specified base (200 mol%), 4CzIPN (2 mol%) and the specified solvent (1 mL) were sparged for 15 mins. The solution was exposed to visible-light for 5 hours. On completion the solution was washed with water (10 mL) and extracted with Et_2O (2 x 10 mL) and dried over $MgSO_4$. The solvent was then concentrated *in vacuo* and the crude product was purified *via* flash column chromatography with the specified eluent system.

Dechlorinative Functionalisations of Cyclobutanes - In a 50 mL round bottomed flask, a solution of chlorocyclobutane (0.65 mmol, 100 mol%), diisopropylethylamine (DIPEA, 120 mol%), 4CzIPN (5 mol%), acetic acid (80 mol%), and the specified reagent (300 mol%) in MeCN/water (4/1, 2.0 mL) was sparged with nitrogen for 10 minutes. The solution was exposed to a 36 W Blue LED (455 nm) for the specified time. On completion, water (20 mL) was added, and the mixture extracted with ethyl acetate (2 × 30 mL). The combined extracts were dried over $MgSO_4$, and the solvent was concentrated *in vacuo*. Purification *via* flash column chromatography gave the functionalised cyclobutane product.

Deiodinative Spirocyclisation - In a 50 mL round bottomed flask, a solution of the specified iodoalkane (100 mol%), tri-*n*-butyl amine (300 mol%), 4CzIPN (2.5 mol%) and dry acetonitrile (0.025 M) was sparged with N_2 for 10 mins. The solution was exposed to 24 W Blue LED (455 nm) for 16 hours. On completion the solution was washed with water (20 mL) and extracted with ethyl acetate (2 x 30 mL) and dried over $MgSO_4$. The solvent was then concentrated *in vacuo* and the crude product was purified *via* flash column chromatography with the specified eluent system.

Decarboxylation of *N*-Acyloxy Phthalimides - In a 7 mL *via*l, a solution of the specified substrate (100 mol%), the bis(catecholato)diboron (300 mol%), diisopropylethylamine (200 mol%) and specified solvent (100 mL/mmol) were sparged with nitrogen for 15 mins. The reaction vessel was sealed and exposed to 36 W, 455 nm LEDs for the specified time. The solution was then treated with 12 equivalents of pinacol and stirred for 1.5 hours. The solvent was concentrated *in vacuo* to give the crude mixture, which was then purified *via* flash column chromatography with the specified eluent system.

7.6. General Procedure 6: Appel Reaction of Alcohols

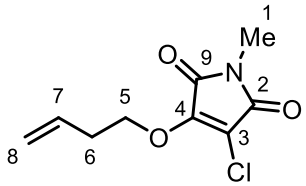
To a round bottomed flask, the specified alcohol (100 mol%), triethylamine (130 mol%), triphenyl phosphine (143 mol%), sodium sulphate (200 mol%) and dry DCM (1.28 M) were added to a flame dried flask under a N_2 atmosphere. The solution was cooled to 0°C and I_2 (134 mol%) was added portion-wise. The solution was stirred at r.t. for 1 hour. The solution was diluted in ethyl acetate (20 mL) and washed with water (10 mL). The organic layer was separated, and the aqueous layer was extracted twice more with ethyl acetate (2 x 10 mL). The combined organic layers were dried over $MgSO_4$. The solvent was then concentrated *in vacuo* and the crude product was purified *via* flash column chromatography with the specified eluent system.

7.7. General Procedure 7: Acid Activation

To a round-bottomed flask, the specified acid (120 mol%), *N*-Hydroxy phthalimide (100 mol%), DMAP (10 mol%) and DCM (0.25 M) was added and stirred at r.t. for 5 min. DCC (120 mol%) was then added portion-wise to the solution and left to stir at r.t. for 16 hours. The solids were filtered off over celite and the solvent was concentrated *in vacuo* to give the crude product. The product was purified *via* flash column chromatography using the specified solvent system.

Experimental Data

3-(But-3-en-1-yloxy)-4-chloro-1-methyl-1*H*-pyrrole-2,5-dione **196**



To a flame dried two-necked round bottomed flask, 2,3-dichloro-*N*-methylmaleimide (150 mg, 0.833 mmol) and dry dioxane (8.4 mL) were added and stirred under a nitrogen atmosphere. In a separate flask, 3-buten-1-ol (145 µL, 1.68 mmol) was added dropwise over 5 minutes to a suspension of sodium hydride (60% suspension in mineral oil, 50.4 mg, 1.26 mmol) in dry dioxane (13 mL) and r.t., and the mixture was stirred at r.t. for a further 15 minutes. The resulting alkoxide solution was added dropwise over 5 minutes to the solution of maleimide and the reaction stirred at r.t. for 18 hours. Saturated aqueous ammonium chloride (40 mL) was added, and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined extracts were washed with water (40 mL), then brine (40 mL), and the solvent was concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 95/5 to 90/10) to give the title compound (112 mg, 62%) as a pale-yellow oil.

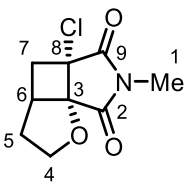
^{1}H NMR (400 MHz, CDCl3) δ 5.76 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz, C**7**-H), 5.17 – 5.04 (2H, m, C**8**-H_2), 4.60 (2H, t, *J* = 7.0 Hz, C**5**-H_2), 2.96 (3H, s, C**1**-H_3), 2.49 (2H, *apparent* q, *J* = 7.0 Hz, C**6**-H_2).

^{13}C NMR (100 MHz, CDCl3) δ 165.7 (C**2**), 164.2 (C**9**), 150.1 (C**4**), 132.4 (C**7**), 118.4 (C**8**), 103.8 (C**3**), 71.6 (C**5**), 34.0 (C**6**), 24.2 (C**1**).

IR *vmax*/cm-1: 2953 (w), 1713 (s), 1650 (s), 1440 (m), 1285 (m), 1048 (m), 739 (m).

HRMS (ESI) m/z calcd for $C_9H_{10}ClNNaO_3$ [$(M+Na)^+$] 582.1847, found 582.1840.

(4a*S**,7a*S**)-4a-Chloro-6-methyltetrahydrofuro[2',3':1,4]cyclobuta[1,2-c]pyrrole-5,7(2*H*,6*H*)-dione **197**



General Procedure 3 – Batch. Using **196** (990 mg, 4.59 mmol). The reaction was exposed to UVA irradiation for 60 minutes. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 75/25 to 60/40) gave the title compound (897 mg, 91%) as a colourless crystalline solid.

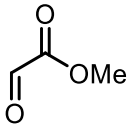
^{1}H NMR (400 MHz, CDCl3) δ 4.55 (1H, ddt, *J* = 10.5, 8.0, 2.0 Hz, C**4**-HH), 4.37 – 4.25 (1H, m, C**4**-HH), 3.21 – 3.03 (1H, m, C**6**-H), 3.11 (3H, s, C**1**-H_3) 2.88 (1H, ddd, *J* = 14.0, 8.0, 3.0 Hz, C**7**-HH), 2.25 – 2.07 (2H, m, C**7**-HH, C**5**-HH), 2.05 – 1.91 (1H, m, C**5**-HH).

^{13}C NMR (100 MHz, CDCl3) δ 173.1 (C**9**), 172.6 (C**2**), 86.0 (C**3**), 72.0 (C**4**), 59.6 (C**8**), 41.7 (C**6**), 35.7 (C**7**), 31.4 (C**5**), 25.6 (C**1**).

IR *vmax*/cm-1: 2994 (w), 1712 (s), 1428 (w), 1375 (m), 1258 (w), 1026 (s), 944 (m), 696 (s).

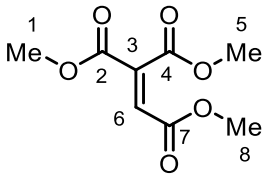
HRMS (ESI) m/z calcd for $C_9H_{10}ClNNaO_3$ [$(M+Na)^+$] 238.0214, found 238.0245.

Methyl 2-oxoacetate **282**



Periodic acid (6.77 g, 28.0 mmol) was added to a solution of dimethyl tartrate (4.45 g, 25.0 mmol) and diethyl ether (50 mL) and stirred at r.t. for 2 hours. On completion, the solid was filtered off and washed with ethyl acetate (3 x 50 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$ for 30 minutes. After flitration the solvent was concentrated *in vacuo* to give the title compound (3.96 g, 90%) as a colourless oil, which was used in the next step without any further purification.

Trimethyl ethene-1,1,2-tricarboxylate **283**



trimethyl ethene-1,1,2-tricarboxylate

Crude methyl glyoxylate **282** (4.0 g, 45 mmol), dimethyl malonate (5.1 mL, 45 mmol) and acetic anhydride (4.3 mL, 45 mmol) were added to a round bottomed flask with a condenser and stirred at 130 °C for 31 hours. The resulting solution was cooled to r.t. and distilled using a Kugelrhor distillation apparatus. Reactants and by products were collected at 100 °C. The product was collected at 120 °C at 1 mBar to isolate the title compound (4.3 g, 46%) as a colourless crystalline solid.

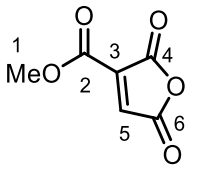
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, s, C**6**-H), 3.90 (3H, s, C**1**/**5**/**8**-H_3), 3.85 (3H, s, C**1**/**5**/**8**-H_3), 3.80 (3H, s, C**1**/**5**/**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7 (C**2**/**4**), 163.9 (C**2**/**4**), 162.6 (C**7**), 138.6 (C**3**), 130.2 (C**6**), 53.3 (C**1**/**5**), 53.0 (C**1**/**5**), 52.7 (C**8**).

IR *vmax*/cm^{-1}: 2957 (w), 1727 (s), 1436 (m), 1259 (s), 1070 (m).

All recorded data match literature values.[115]

Methyl 2,5-dioxo-2,5-dihydrofuran-3-carboxylate **284**



Crystalline trimethyl ethene-1,1,2-tricarboxylate **283** (5.00 g, 25 mmol) and P_2O_5 (3.5 g, 50 mmol) were mixed in a flame-dried round bottomed flask with a fitted condenser and heated to 160 °C for 5 hours. The solids formed a melt and turned black on completion of reaction. The black mass was cooled to r.t. and distilled using a Kugelrhor distillation apparatus at 160 °C at 1 mBar pressure. Crystals collected were washed with petroleum ether to give the title compound (1.50 g, 40%) as colourless crystalline solid.

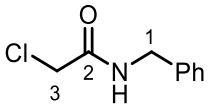
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, s, C**5**-H), 3.97 (3H, s, C**1**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7 (C**2**), 159.6 (C**4**), 158.3 (C**6**), 138.7 (C**5**), 138.2 (C**3**), 53.7 (C**1**).

IR *vmax*/cm^{-1}: 2960 (br), 1735 (s), 1438 (m), 1263 (m).

All recorded data match literature values.[115]

N-Benzyl-2-chloroacetamide **290**



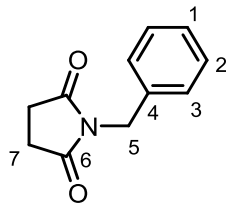
Benzylamine (5.1 mL, 46.7 mmol) was added to a solution of anhydrous potassium carbonate (7.74 g, 56 mmol) and DCM (93 mL, 0.5 M). The solution was stirred at r.t. at which point acetyl chloride was added dropwise over 5 mins. The reaction was stirred for 30 mins at r.t. followed by stirring at reflux for 4 hours. The solution was cooled to r.t. and stirred for 30 mins before being quenched with water. The solution was extracted with DCM (3 x 30 mL) and the organic extracts were combined and washed with water (10 mL) and brine (10 mL). The organic extracts were dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (petrol/ethylacetate: 1/1) to give the title compound (4.0 g, 47%) as a colourlesscrystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (5H, m, 5 x **Ar**-H), 4.49 (2H, d, *J* = 6.0 Hz, C**3**-H_2), 4.10 (2H, s, C**1**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (C**2**), 137.2 (**Ar**), 128.8 (**Ar**), 127.8 (**Ar**), 43.8 (C**3**), 42.6 (C**1**).

All recorded data match literature values.[173]

1-Benzylpyrrolidine-2,5-dione **294**



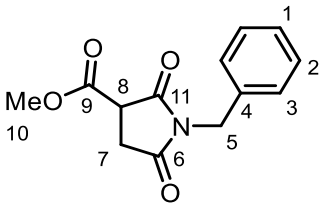
A solution of succinimide (2.0 g, 20.2 mmol), benzyl bromide (2.64 mL, 22.2 mmol), anhydrous potassium carbonate (3.35 g, 24.2 mmol) and acetone (30 mL) was stirred at reflux for 18 hours. After cooling to r.t., the solution was filtered to remove KBr and the solvent was concentrated *in vacuo* to give the title compound (3.3 g, 87%) as a colourless crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (5H, m, 5 x **Ar**-H), 4.65 (2H, s, C**5**-H_2), 2.70 (4H, s, 2 x C**7**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (C**6**), 135.7 (C**4**), 128.9 (C**3**), 128.6 (C**2**), 128.0 (C**1**), 42.4 (C**5**), 28.2 (C**7**).

All recorded data match literature values.[174]

Methyl 1-benzyl-2,5-dioxopyrrolidine-3-carboxylate **295**



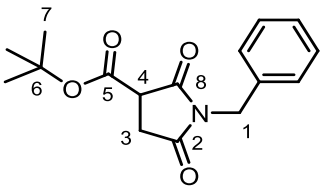
To a flame dried, dual necked round bottomed flask, a solution of compound **294** (0.95 g, 5.0 mmol) and anhydrous THF (17 mL) was cooled to -78 °C under a nitrogen atmosphere. To this, NaHMDS (2 M THF, 5 mL, 10 mmol) was added dropwise over 5 mins. The solution was stirred at -78 °C for 60 mins. On completion, methyl chloroformate (0.39 mL, 5.0 mmol) was added and left to stir for 18 hours and allowed to warm to r.t. over this time. The solution was washed with *sat.* NH_4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with water (10 mL) and brine (10 mL). The organic extracts were dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 9/1 to 1/1) to give the title compound (650 mg, 53%) as a clear colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (5H, m, 5 x **Ar**-H), 4.71 – 4.56 (2H, m, C**5**-H_2), 3.77 (3H, s, C**10**-H_3), 3.74 (1H, ddd, *J* = 10.0, 5.0, 1.0 Hz, C**7**-H), 3.08 (1H, ddd, *J* = 18.5, 5.0, 1.0 Hz, 1 x C**8**-H_2), 2.87 (1H, ddd, *J* = 18.5, 10.0, 1.0 Hz, 1 x C**8**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 (C**6**), 171.9 (C**9**), 167.8 (C**11**), 135.1 (C**4**), 128.7 (C**2** + C**3**), 128.1 (C**1**), 49.6 (C**10**), 46.3 (C**5**), 43.0 (C**8**), 32.2(C**7**).

All recorded data match literature values.[117]

tert-Butyl 1-benzyl-2,5-dioxopyrrolidine-3-carboxylate **296**



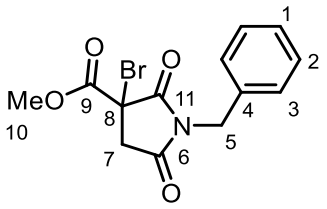
To a flame-dried, dual necked round bottomed flask, a solution of compound **294** (1.9 g, 10 mmol) and anhydrous THF (40 mL) was cooled to -78 °C under a nitrogen atmosphere. To this, NaHMDS (2 M THF, 10 mL, 20 mmol) was added dropwise over 5 mins. The solution as stirred at -78 °C for 60 mins. On completion, was added and left to stir for 18 hours and allowed to warm to r.t. over this time. The solution was washed with saturated NH_4Cl and extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with water (10 mL) and brine (10 mL). The organic extracts were dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 4/1) to give the title compound (760 mg, 26%) as beige crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (5H, m, 5 x **Ar**-H), 4.67 – 4.54 (2H, m, C**5**-H_2), 3.58 (1H, dd, *J* = 9.0, 4.5 Hz, C**8**-H), 2.96 (1H, dd, *J* = 18.0, 4.5 Hz, 1 x C**7**-H_2), 2.79 (1H, dd, *J* = 18.0, 9.0 Hz, 1 x C**7**-H_2), 1.38 (9H, s, 3 x C**11**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C**2**), 171.6 (C**5**), 162.8 (C**8**), 147.4 (**Ar**), 128.6 (**Ar**), 128.6 (**Ar**), 128.0 (**Ar**), 47.7 (C**4**), 42.7 (C**1**), 37.1 (C**6**), 32.3 (C**3**), 27.8 (C**7**).

All recorded data match literature values.[117]

Methyl 1-benzyl-3-bromo-2,5-dioxopyrrolidine-3-carboxylate **297**-Me



A solution of compound **295** (100 mg, 0.4 mmol), anhydrous potassium carbonate (110.6 mg, 0.8 mmol) and diethyl ether (1.0 mL) was stirred under reflux for 1 hour. The solution was cooled and bromine was added at r.t.. The solution was stirred at reflux for 1 hour before being quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL) and washed with water (10 mL) and brine (10 mL). The organic extracts were dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. The crude product was distilled using a Kugel Rohr distillation set up (0.1 mBar, 150 °C) to give the title compound (26 mg, 20%) as a yellow oil.

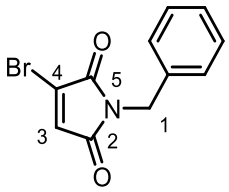
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.15 (5H, m, 5 x **Ar**-H), 4.66 (2H, s, C**5**-H_2), 3.78 (3H, s, C**10**-H_3), 3.67 (1H, d, *J* = 19.0 Hz, 1 x C**7**-H_2), 3.18 (1H, d, *J* = 19.0 Hz, 1 x C**7**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (C**6**), 171.6 (C**9**), 165.6 (C**11**), 134.4 (C**4**), 128.9 (C**2**), 128.8 (C**3**), 128.4 (C**1**), 54.9 (C**10**), 51.0 (C**8**), 44.9 (C**7**), 43.5 (C**5**).

IR *vmax*/cm^{-1}: 2956 (w), 1704 (s), 1395 (m), 1170 (m), 700 (w).

HRMS (ESI) m/z calcd for $C_{13}H_{12}BrNNaO_4$ [$(M+Na)^+$] 347.9847, found 347.9850.

1-Benzyl-3-bromo-1H-pyrrole-2,5-dione **303**



General Procedure 1. *N*-Benzyl maleimide (107 mmol) and diethyl ether (156 mL) were used. Purification by washing with cold methanol gave the title compound (25.8 g, 90%) as a beige solid.

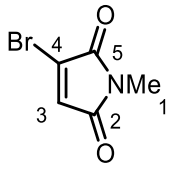
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (5H, m, 5 x **Ar**-H), 6.87 (1H, s, C**3**-H), 4.71 (2H, s, C**1**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C**2**), 165.0 (C**5**), 135.6 (C**3**), 131.9 (**Ar**), 131.5 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 128.1 (C**4**), 42.4 (C**1**).

Mp (petroleum ether): 47–50 °C.

All recorded data match literature values.[175]

3-Bromo-1-methyl-1*H*-pyrrole-2,5-dione **303**-Me



General Procedure 1. *N*-methylmaleimide (2.00 g, 18.0 mmol) and diethyl ether (25 mL) were used. The brown crystals were washed with pentane to give the title compound (2.77 g, 82%) as pale brown platelets.

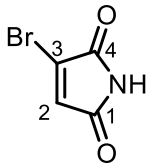
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.90 (1H, s, C**3**-H), 3.10 (3H, s, C**1**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.6 (C**2**), 165.4 (C**5**), 131.9 (**3**), 131.4 (C**4**), 24.6 (C**1**).

Mp (petroleum ether): 102–105 °C.

All recorded data match literature values.[176]

3-Bromo-1*H*-pyrrole-2,5-dione **303**-H



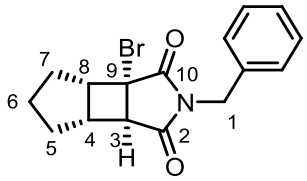
A solution of 1*H*-maleimide (3.9 g, 40 mmol), Br_2 (2.5 mL, 50 mmol) and DCM (60 mL) was stirred at reflux. On completion of bromination, the solvent and excess bromine were concentrated *in vacuo* and the crude material was dissolved in THF (80 mL). Triethylamine (6 mL, 40 mmol) was added slowly over 5 mins at 0 °C. The solution was allowed to warm to r.t. and stirred for 3 hours. Subsequent work up, following the procedure described in general procedure 1, gave the title compound (5.60 g, 80%) as a colourless solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (1H, s, N-H), 6.91 (1H, d, *J* = 1.5 Hz, C**2**-H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7 (C**4**), 164.7 (C**1**), 132.9 (C**2**), 132.2 (C**3**).

All recorded data match literature values.[177]

(3a*S**,3b*S**,6a*R**,6b*R**)-2-Benzyl-3a-bromohexahydrocyclopenta[3,4]cyclobuta[1,2-c]pyrrole-1,3(2*H*,3a*H*)-dione **304**



>20:1 d.r.

General Procedure 3 – Batch. Compound **303** (285 mg, 1.07 mmol) and propargyl alcohol (0.47 mL, 5.35 mmol) were used. The crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 9/1) to give the title compound (175 mg, 74%) as pale-yellow crystals.

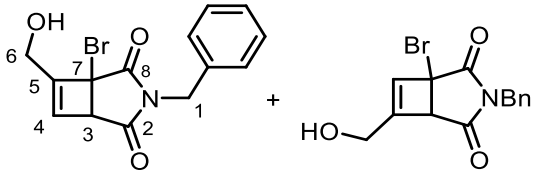
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.21 (5H, m, **Ar**-H), 4.74 – 4.60 (2H, m, C**1**-H_2), 2.90 (1H, t, *J* = 6.5 Hz, C**4**-H), 2.77 (1H, d, *J* = 3.5 Hz, C**3**-H), 2.72 (1H, td, *J* = 6.5, 3.5 Hz, C**8**-H), 2.14 – 2.03 (1H, m, 1 x C**6**-H), 1.90 – 1.79 (2H, m, 1 x C**7**-H, 1 x C**5**-H), 1.78 – 1.63 (2H, m, 1 x C**6**-H, 1 x C**5**-H), 1.57 – 1.46 (1H, m, C**7**-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.1 (C**2**), 175.6 (C**10**), 135.3 (**Ar**), 128.8 (**Ar**), 128.4 (**Ar**), 128.1 (**Ar**), 53.3 (C**9**), 52.9 (C**3**), 45.7 (C**4**), 43.0 (C**1**), 42.9 (C**8**), 33.0 (C**7**), 31.3 (C**6**), 24.8 (C**5**).

IR *vmax*/cm^{-1}: 2953 (w), 1710 (s), 1387 (m), 1340 (w), 1181 (w), 699 (w).

HRMS (ESI) m/z calcd for $C_{16}H_{16}BrNNaO_2$ $[(M+Na)^+]$ 356.0262, found 356.0252.

3-Benzyl-1-bromo-7-(hydroxymethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **305**



4 : 1

General Procedure 3 - Batch. Compound **303** (300 mg, 1.13 mmol) and propargyl alcohol (0.2 mL, 3.38 mmol) were used. The crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 3/2 to 2/3) to give the title compound (160 mg, 44%) as a colourless crystalline solid.

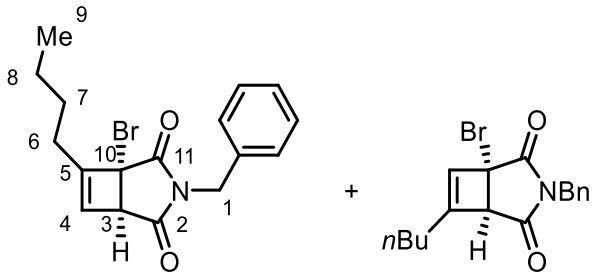
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.35 – 7.25 (5H, m, 5 x **Ar**-H), 6.43 – 6.46 (1H, m, C**4**-H), 4.75 – 4.58 (2H, m, C**1**-H_2), 4.29 (2H, t, *J* = 1.5 Hz, C**6**-H_2), 3.80 (1H, td, *J* = 2.0, 1.5 Hz, C**3**-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 171.9 (C**2**), 170.9 (C**8**), 152.1 (C**5**), 134.9 (**Ar**), 130.4 (C**4**), 128.8 (**Ar**), 128.5 (**Ar**), 128.1 (**Ar**), 57.7 (C**6**), 54.1 (C**3**), 54.0 (C**7**), 42.9 (C**1**).

IR *vmax*/cm^{-1}: 3471 (br), 2927 (w), 1709 (s), 1432 (w), 1385 (m), 1169 (w), 700 (w).

HRMS (ESI) m/z calcd for $C_{14}H_{12}BrNNaO_3$ [$(M+Na)^+$] 343.9898, found 343.9932.

(1*R**,5*R**)-3-Benzyl-1-bromo-7-butyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **307**



19 : 1

General Procedure 3 – Batch. Compound **303** (300 mg, 1.13 mmol) and propargyl alcohol (0.38 mL, 3.39 mmol) were used. The crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 98/2) to give the title compound (183 mg, 46%) as pale-yellow crystals.

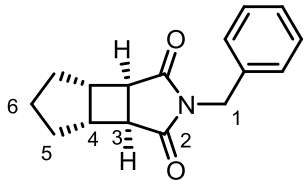
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.40 – 7.20 (5H, m, 5 x **Ar**-H), 6.18 – 6.22 (1H, m, C**4**-H), 4.74 – 4.57 (2H, m, C**1**-H_2), 3.73 (1H, td, *J* = 2.0, 1.0 Hz, C**3**-H), 2.18 (2H, dt, *J* = 10.5, 4.0, Hz, C**6**-H_2), 1.55 – 1.32 (2H, m, C**7**-H_2), 1.32 – 1.17 (2H, m, C**8**-H_2), 0.85 (3H, t, *J* = 7.5 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 172.7 (C**2**), 171.0 (C**11**), 155.1 (C**5**), 135.2 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.0 (**Ar**), 53.9 (C**3**), 53.4 (C**10**), 42.7 (C**1**), 27.3 (C**7**), 27.2 (C**6**), 22.1 (C**8**), 13.7 (C**9**).

IR *vmax*/cm^{-1}: 2927 (w), 1713 (s), 1384 (w).

HRMS (ESI) m/z calcd for $C_{17}H_{18}BrNNaO_2$ [$(M+Na)^+$] 370.0419, found 370.0422.

(3a*R**,3b*S**,6a*R**,6b*S**)-2-Benzylhexahydrocyclopenta[3,4]cyclobuta[1,2-c]pyrrole-1,3(2*H*,3a*H*)-dione **312**



>20:1 d.r.

General Procedure 5 - Photoredox-Catalysed Hydrodehalogenation. Compound **304** (25 mg, 0.076 mmol) was used. Extraction gave the title compound (16.6 mg, 85%) as a pale-yellow oil, with no further purification.

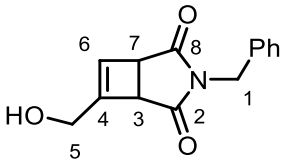
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (5H, m, 5 x **Ar**-H), 4.67 (2H, s, C**1**-H_2), 2.76 – 2.80 (2H, m, *J* = 5.0 Hz, 2 x C**4**-H), 2.62 (2H, m, 2 x C**3**-H), 1.93 (1H, dt, *J* = 12.5, 6.0 Hz, C**6**-HH), 1.83 (2H, dd, *J* = 12.5, 5.5 Hz, 2 x C**5**-HH), 1.64 – 1.56 (3H, m, C**6**-HH, 2 x C**5**-HH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3 (C**2**), 136.0 (**Ar**), 128.6 (**Ar**), 128.4 (**Ar**), 127.8 (**Ar**), 42.5 (C**4**), 42.3 (C**1**), 42.0 (C**3**), 32.7 (C**5**), 24.1 (C**6**).

IR *vmax*/cm^{-1}: 2950 (w), 1702 (s), 1602 (s), 1457 (w), 1392 (w), 1205 (m), 1151 (s), 1067 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{17}NNaO_2$ [$(M+Na)^+$] 278.1157, found 278.1147.

3-Benzyl-6-(hydroxymethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **317**



General Procedure 5 – Photoredox-Catalysed Hydrodehalogenation. Bromosuccinimide **305** (25 mg, 0.078 mmol) was used. Extraction gave the title compound (10 mg, 53%) as a pale-yellow oil, with no further purification.

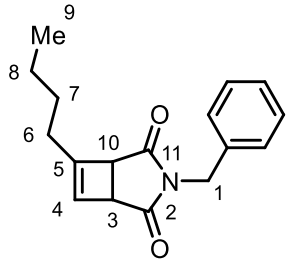
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.28 – 7.20 (5H, m, 5 x **Ar**-H), 6.21 – 6.24 (1H, m, C**6**-H), 4.54 (2H, s, C**1**-H_2), 4.22 – 4.09 (2H, m, C**5**-H_2), 3.75 (1H, dd, *J* = 3.0, 1.0 Hz, C**7**-H), 3.63 (1H, dtd, *J* = 3.0, 2.0, 1.0, C**3**-H), 1.78 (1H, t, *J* = 6.0 Hz, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.5 (C**2**), 174.2 (C**8**), 151.5 (C**4**), 135.7 (C**6**), 130.5 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 59.6 (C**5**), 47.3 (C**7**), 44.2 (C**3**), 42.3 (C**1**).

IR *vmax*/cm^{-1}): 3445 (m), 1565 (s), 1694 (s).

HRMS (ESI) m/z calcd for $C_{14}H_{13}NNaO_3$ [(M+Na)$^+$] 266.0793, found 266.0791.

3-Benzyl-6-butyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **318**



General Procedure 5 – Photoredox-Catalysed Hydrodehalogenation. Compound **307** (20 mg, 0.6 mmol) used. Extraction gave the title compound (13 mg, 81%) as a pale yellow oil, with no further purification.

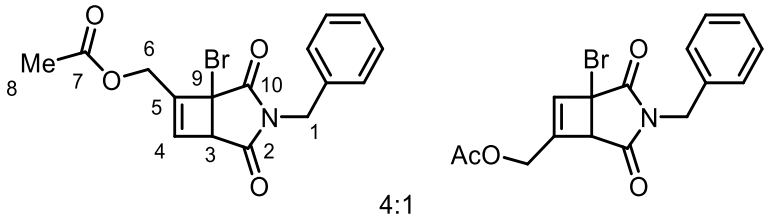
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.14 (5H, m, **Ar**-H), 5.97 – 6.01 (1H, m, C**4**-H), 4.54 (2H, s, C**1**-H_2), 3.61 (1H, d, *J* = 3.0 Hz, C**3**-H), 3.51 – 3.56 (1H, m, C**10**-H), 2.07 (2H, t, *J* = 7.5 Hz, C**6**-H_2), 1.37-1.33 (2H, m, C**7**-H_2), 1.28 – 1.11 (2H, m, C**8**-H_2), 0.79 (3H, t, *J* = 7.5 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.4 (C**2**), 174.5 (C**11**), 154.3 (C**5**), 135.9 (**Ar**), 129.3 (C**4**), 128.6 (**Ar**), 128.5 (**Ar**), 127.8 (**Ar**), 48.7 (C**3**), 43.9 (C**10**), 42.0 (C**1**), 29.6 (C**6**), 28.1 (C**7**), 22.2 (C**8**), 13.7 (C**9**).

IR *vmax*/cm^{-1}: 2924 (m), 1701 (s), 1388 (m), 1066 (m).

HRMS (ESI) m/z calcd for $C_{17}H_{20}NO_2$ [(M+H)$^+$] 270.1494, found 270.1482.

(3-Benzyl-5-bromo-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)methyl acetate **319**



A solution of compound **305** (273 mg, 0.85 mmol), DMAP (11 mg, 0.09 mmol), pyridine (0.7 mL, 0.85 mmol) and DCM (3.5 mL) was stirred at r.t. for 5 mins. To this solution, Ac_2O (1.6 mL, 1.7 mmol)was added and the solution was stirred at r.t. for 16 hours. The reaction was quenched with 1 M HCl (6 mL) and extracted with DCM (3 x 10 mL), the organic extracts were washed with water (20 mL), brine

(20 mL) and dried over $MgSO_4$. The solvent was concentrated *in vacuo* and the crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 1/1) to give the title compound (140 mg, 45%) as a yellow oil.

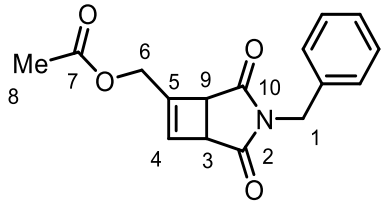
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.32 – 7.26 (5H, m, 5 x **Ar**-H), 6.45 – 6.49 (1H, m, C**4**-H), 4.70 – 4.59 (4H, m, C**1**-H_2 and C**6**-H_2), 3.80 (1H, td, *J* = 2.0, 1.0 Hz, C**3**-H), 2.02 (3H, s, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 171.5 (C**10**), 170.2 (C**7**), 170.0 (C**2**), 148.1 (C**5**), 135.0 (**Ar**), 132.8 (C**4**), 128.8 (**Ar**), 128.4 (**Ar**) 128.1 (**Ar**), 57.8 (C**6**), 54.4 (C**3**), 51.4 (C**9**), 42.9 (C**1**), 20.5 (C**8**).

IR *vmax*/cm^{-1}: 2923 (m), 2883 (w), 1777 (w), 1745 (m), 1708 (s), 1380 (m), 1221 (s), 1029 (m), 698 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{15}BrNO_4$ [$(M+H)^+$] 364.0184, found 364.0172.

(3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)methyl acetate **320**



General Procedure 5 – Photoredox-Catalysed Hydrodehalogenation. Compound **319** (20 mg, 0.6 mmol) used. Extraction gave the title compound (15.4 mg, 90%) as a pale yellow oil , with no further purification.

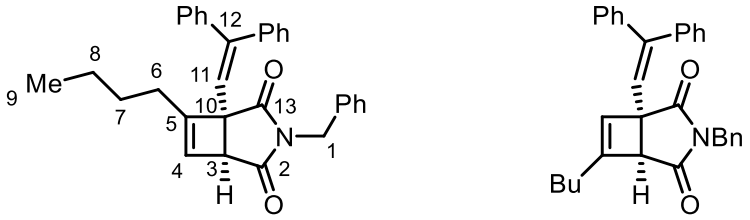
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.29 – 7.13 (5H, m, 5 x **Ar**-H), 6.25 (1H, d, *J* = 1.5 Hz, C**4**-H), 4.70 – 4.46 (4H, m, C**6**-H_2, and C**1**-H_2), 3.73 (1H, d, *J* = 3.0 Hz, C**3**-H), 3.60 – 3.65 (1H, m, C**9**-H), 1.99 (3H, s, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.1 (C**2**), 173.3 (C**10**), 170.4 (C**7**), 147.0 (C**5**), 135.7 (**Ar**), 133.1 (C**4**), 128.6 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 59.8 (C**6**), 47.6 (C**9**), 44.6 (C**3**), 42.2 (C**1**), 20.6 (C**8**).

IR *vmax*/cm^{-1}: 2969 (m), 1702 (s), 1388 (m), 1230 (w), 1070 (w), 753 (w).

HRMS (ESI) m/z calcd for $C_{16}H_{16}NO_4$ [$(M+H)^+$] 286.1079, found 286.1074.

(1*S**,5*S**)-3-Benzyl-7-butyl-1-(2,2-diphenylvinyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **321**



17:1 r.r.

General Procedure 5 – Atom Transfer Radical Addition. Compound **307** (20 mg, 0.06 mmol), 1,1-diphenylethylene (32 µL, 0.18 mmol) and 2,6-lutidine (14 µL, 0.12 mmol) were used. Purification *via* flash column chromatography (petrol/ethyl acetate: 19/1) gavethe title compound (17 mg, 65%) as a pale yellow oil.

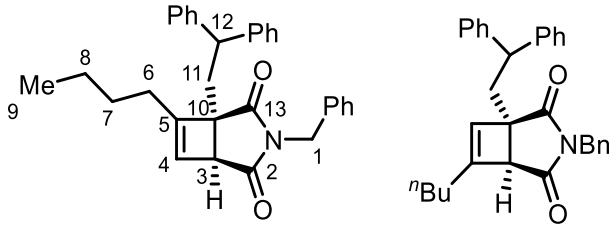
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.24 – 7.13 (12H, m, 12 x **Ar**-H), 7.04 (2H, m, 2 x **Ar**-H), 6.88 – 6.92 (2H, m, **Ar**-H), 6.28 (1H, d, *J* = 2.0 Hz, C**4**-H), 5.84 (1H, s, C**11**-H), 4.37 – 4.23 (2H, m, C**1**-H_2), 2.93 – 2.96 (1H, m, C**3**-H), 2.14 (2H, td, *J* = 8.0, 2.0 Hz, C**6**-H_2), 1.35 (2H, tt, *J* = 13.0 Hz, 6.5, C**7**-H_2), 1.26 – 1.15 (2H, m, C**8**-H_2), 0.79 (3H, t, *J* = 7.5 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 176.0 (C**13**), 174.7 (C**2**), 157.2 (C**5**), 147.0 (**Ar**), 141.1 (**Ar**), 138.9 (C**12**), 135.8 (**Ar**), 129.2 (**Ar**), 128.7 (**Ar**), 128.6 (C**11**), 128.5 (**Ar**), 128.4 (**Ar**), 128.2 (**Ar**), 128.1 (**Ar**), 128.0 (**Ar**), 127.7 (**Ar**), 127.3 (**Ar**), 120.0 (C**4**), 59.0 (C**10**), 50.7 (C**3**), 41.9 (C**1**), 27.8 (C**7**), 27.4 (C**6**), 22.3 (C**8**), 13.8 (C**9**).

IR *vmax*/cm^{-1}: 2960 (m), 1700 (s), 1385 (m), 1065 (m).

HRMS (ESI) m/z calcd for $C_{31}H_{30}NO_2$ $[(M+H)^+]$ 448.2277, found 448.2263.

(1*S**,5*S**)-3-Benzyl-7-butyl-1-(2,2-diphenylethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **322**



>20:1 r.r.

General Procedure 5 – Dechlorinative Functionalisations of Cyclobutanes. General procedure 5. Using chlorocyclobutene **351** (197 mg, 0.65 mmol, 10:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water

(4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petrol/ethyl acetate: 98/2) gave the title compound (224 mg, 77%) as a clear colourless oil.

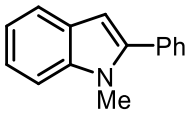
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.01 (15H, m, 13 x **Ar**-H), 6.92 – 6.82 (2H, m, 2 x **Ar**-H), 5.82 (1H, s, C**4**-H), 4.44 (2H, m, C**1**-H_2), 3.81 (1H, dd, *J* = 10.0, 5.5 Hz, C**12**-H), 2.81 (1H, dd, *J* = 14.0, 5.5 Hz, C**11**-HH), 2.42 (1H, s, C**3**-H), 2.37 (1H, dd, *J* = 14.0, 10.0 Hz, C**11**-HH), 2.00 – 1.86 (2H, m, C**6**-H_2), 1.37 – 1.08 (4H, m, C**7**-H_2, C**8**-H_2), 0.82 – 0.71 (3H, m, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.6 (C**13**), 175.1 (C**2**), 157.4 (C**5**), 143.9 (**Ar**), 143.6 (**Ar**), 136.0 (**Ar**), 128.9 (**Ar**), 128.9 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 127.9 (C**4**), 127.8 (**Ar**), 127.5 (**Ar**), 126.9 (**Ar**), 126.6 (**Ar**), 58.2 (C**10**), 48.1 (C**3**), 47.9 (C**11**), 42.0 (C**1**), 34.8 (C**12**), 27.8 (C**7**), 27.2 (C**6**), 22.3 (C**8**), 13.8 (C**9**).

IR *vmax*/cm^{-1}: 2928 (w), 1699 (s), 1388 (m), 1166 (w), 701 (m).

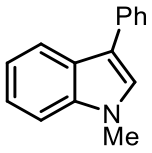
HRMS (ESI) m/z calcd for $C_{31}H_{32}NO_2$ $[(M+H)^+]$ 450.2433, found 450.2418.

1-Methyl-2-phenyl-1H-indole **333**-2-Ph



To a flame-dried round bottomed flask, sodium hydride (60% in mineral oil, 383 mg, 9.6 mmol), was added portion wise over 5 mins, to a solution of 2-phenyl indole (1.1 g, 5.7 mmol) in THF (17 mL) at 0°C. The solution was stirred at 0°C for 1 hr, followed by the addition of iodomethane (0.37 mL, 6 mmo) dropwise over 2 mins. The solution was allowed to warm to r.t. before the addition of water (5 mL) to quench the reaction. The phases were separated and the organic phase was washed with water (2 x 10 mL) and dried over $MgSO_4$. The solvent was removed to give the title compound (1.03 g, 86%) as an orange oil. The crude product was used in the next step without further purification.[178]

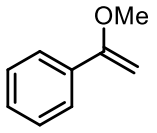
1-Methyl-3-phenyl-1H-indole **333**-3-Ph



To a flamed dried round bottomed flask, sodium hydride(60% in mineral oil, 383 mg, 9.6 mmol), was added portion wise over 5 mins, to a solution of 3-phenyl indole (1.1 g, 5.7 mmol) in THF (17 mL) at 0

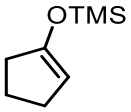
°C. The solution was stirred at 0 °C for 1 hr, followed by the addition of iodomethane (0.37 mL, 6 mmo) dropwise over 2 mins. The solution was allowed to warm to r.t. before the addition of water (5 mL) to quench the reaction. The solution was diluted in EtOAc (20 mL) phases were separated and the organic phase was washed with water (2 x 10 mL) and dried over $MgSO_4$. The solvent was removed to give the title compound (992 mg, 83%) as an orange oil. The crude product was used in the next step without further purification.[178]

(1-Methoxyvinyl)benzene **334**



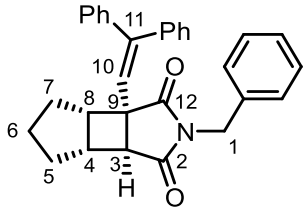
To a round bottomed flask, acetophenone (1.0 mL, 8.57 mmol), trimethyl orthoformate (1 mL, 9.42 mmol), and *p*-toluene sulfonic acid (8.2 mg, 0.043 mmol) was added. The solution was stirred at r.t. for 24 hours. The crude product was distilled at 70°C for 4 hours. The crude product was used in the next step without further purification.[179]

(Cyclopent-1-en-1-yloxy)trimethylsilane **336**



To a flame-dried dual necked round bottomed flask, cyclopentanone (0.86 mL, 9.86 mmol) NaI (169 mg, 12.22 mmol), triethylamine (1.69 mL, 12.22 mmol) and acetonitrile (9.7 mL) were added under a nitrogen atmosphere at r.t.. To this TMSCl (1.53 mL, 12.22 mmol) was added dropwise over 5 mins. A white precipitate was formed on addition. The mixture was left to stir for 1 hour. At 0 °C, cold pentane (20 mL) and cold water (20 mL) was added. The aqueous layer was extracted with pentane (2 x 20 mL) and the organic layers were washed with NH_4Cl (*sat.* aqueous, 2 x 10 mL). The organic layers were dried over $MgSO_4$ and the solvent was concentrated *in vacuo* to afford the crude compound (384 mg, 25%) as a colourless oil. The crude product was used in the next step without further purification.[180]

(3a*S**,3b*S**,6a*R**,6b*S**)-2-Benzyl-3a-(2,2-diphenylvinyl)hexahydrocyclopenta[3,4]cyclobuta[1,2-c]pyrrole-1,3(2H,3aH)-dione **339**



>20:1 d.r.

General Procedure 5 – Atom Transfer Radical Addition. Compound **304** (20 mg, 0.06 mmol), 1,1-diphenylethylene (32 µL, 0.18 mmol) and 2,6-lutidine (14 µL, 0.12 mmol) were used. Purification *via* flash column chromatography (petrol/ethyl acetate: 19/1) gave the title compound (7.0 mg, 27%) as a pale yellow oil.

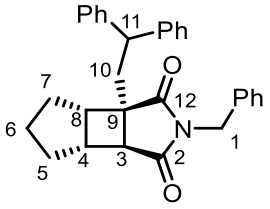
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.51 – 7.46 (2H, m, 2 x **Ar**-H), 7.41 – 7.37 (2H, m, 2 x **Ar**-H), 7.37 – 7.32 (1H, m, **Ar**-H), 7.28 – 7.24 (3H, m, 3 x **Ar**-H), 7.21 – 7.16 (2H, m, 2 x **Ar**-H), 7.03 – 7.07 (2H, m, 2 x **Ar**-H), 6.76 – 6.71 (2H, m, 2 x **Ar**-H), 6.24 (1H, s, C**10**-H), 4.68 – 4.56 (2H, m, C**1**-H_2), 3.00 (1H, t, *J* = 6.5 Hz, C**8**-H), 2.55 (1H, td, *J* = 6.5, 3.5 Hz, C**4**-H), 2.28 – 2.23 (1H, m, C**7**-HH), 1.84 (1H, q, *J* = 5.0 Hz, C**6**-H), 1.76 (1H, d, *J* = 3.5 Hz, C**3**-H), 1.62 – 1.52 (3H, m, C**5**-HH, C**6**-HH, C**7**-HH), 1.51 – 1.43 (1H, m, C**5**-HH).

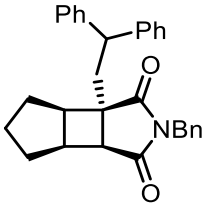
^{13}C NMR (125 MHz, $CDCl_3$) δ_C 181.0 (C**12**), 178.2 (C**2**), 145.1 (C**11**), 141.6 (**Ar**), 138.6 (**Ar**), 135.9 (**Ar**), 129.2 (**Ar**), 129.0 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.2 (**Ar**), 128.1 (**Ar**), 128.0 (**Ar**), 127.9 (**Ar**), 127.2 (**Ar**), 121.5 (C**10**), 49.0 (C**9**), 47.8 (C**3**), 42.5 (C**8**), 45.88 (C**1**) 40.8 (C**4**), 32.4 (C**5**), 27.8 (C**7**), 24.3 (C**6**).

IR *vmax*/cm^{-1}: 2919 (w), 1766 (w), 1697 (s), 1389 (m), 1179 (w).

HRMS (ESI) m/z calcd for $C_{30}H_{28}NO_2$ $[(M+H)^+]$ 434.2120, found 434.2109.

(3a*R**,3b*S**,6a*R**,6b*S**)-2-Benzyl-3a-(2,2-diphenylethyl)hexahydrocyclopenta[3,4]cyclobuta[1,2-c]pyrrole-1,3(2*H*,3a*H*)-dione **340**





General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **352** (188 mg, 0.65 mmol, 12:1 d.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water

(4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2) gave the title compound (224 mg, 79%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.63 – 7.02 (13H, m, 13 x **Ar**-H), 6.83 – 6.68 (2H, m, 2 x **Ar**-H), 4.68 – 4.46 (2H, m, C**1**-H_2), 3.56 (1H, dd, *J* = 10.5, 5.0 Hz, C**11**-H), 2.76 (1H, d, *J* = 7.0 Hz, C**8**-H), 2.54 (1H, ddd, *J* = 11.5, 7.5, 4.5 Hz, C**3**-H), 2.50 – 2.38 (3H, m, C**5**-HH, C**10**-H_2), 2.02 (1H, dd, *J* = 13.0, 5.0 Hz, C**7**-HH), 1.93 (1 H, dd, *J* = 11.5, 6.0 Hz, C**5**-HH), 1.67 (2H, m, C**4**-H, C**6**-HH), 1.64 – 1.40 (3H, m, C**5**-HH, C**6**-HH, C**7**-HH).

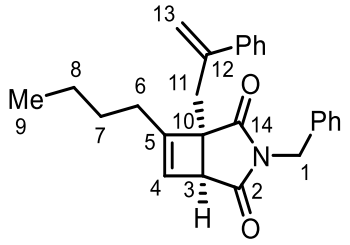
^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 182.5 (C**12**), 178.6 (C**2**), 144.1 (**Ar**), 142.8 (**Ar**), 136.3 (**Ar**), 129.2 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.4 (**Ar**), 128.1 (**Ar**), 127.6 (**Ar**), 127.3 (**Ar**), 127.0 (**Ar**), 126.4 (**Ar**), 47.9 (C**9**), 47.4 (C**11**), 46.8 (C**4**), 44.4 (C**3**), 42.4 (C**1**), 41.5 (C**8**), 33.0 (C**10**), 32.3 (C**6**), 27.4 (C**7**), 25.4 (C**5**).

IR *vmax*/cm^{-1}: 2942 (w), 2862 (w), 1688 (s), 1392 (m), 700 (s).

HRMS (ESI) m/z calcd for $C_{30}H_{29}NNaO_2$ [$(M+Na)^+$] 458.2090, found 458.2108.

Mp ($CHCl_3$): 137–140 °C.

(1*S**,5*S**)-3-Benzyl-7-butyl-1-(2-phenylallyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **341**



General Procedure 5 – Atom Transfer Radical Addition. Compound **307** (20 mg, 0.06 mmol), α-methylstyrene (23.4 µL, 0.18 mmol) and 2,6-lutidine (14 µL, 0.12 mmol) were used. Purification *via* flash column chromatography (petrol/ethyl acetate: 19/1) to give the title compound (27 mg, 23%) as a pale yellow oil.

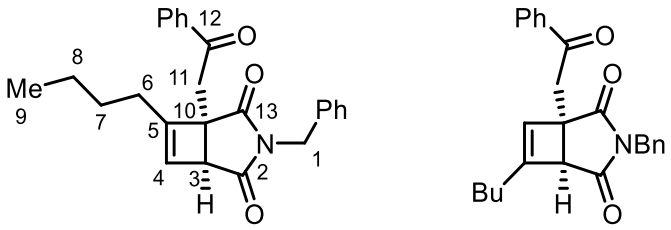
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.35 – 7.04 (10H, m, **Ar**-H), 5.83 (1H, d, *J* = 1.5 Hz, C**4**-H), 5.07 (1 H, d, *J* = 1.3 Hz, C**13**-HH), 5.01 (1 H, d, *J* = 1.2 Hz, C**13**-HH), 4.48 – 4.31 (2H, m, C**1**-H_2), 3.17 (1H, d, *J* = 14.5 Hz, C**11**-HH), 2.98 (1H, d, *J* = 1.5 Hz, C**3**-H), 2.84 (1H, d, *J* = 14.5 Hz, C**11**-HH), 1.97 – 1.83 (2H, m, C**6**-H_2), 1.35 – 1.19 (2H, m, C**7**-H_2), 1.18 – 1.07 (2H, m, C**8**-H_2), 0.75 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 176.3 (C**14**), 175.2 (C**2**), 157.1 (C**5**), 144.6 (**Ar**), 141.3 (C**12**), 136.0 (**Ar**), 129.5 (**Ar**) 128.4 (**Ar**), 128.1 (C**4**) 127.9 (**Ar**), 127.8 (**Ar**), 127.7 (**Ar**), 126.5 (**Ar**), 116.6 (C**13**), 58.4 (C**10**), 47.7 (C**3**), 41.9 (C**1**), 34.8 (C**11**), 27.7 (C**7**), 27.6 (C**6**), 22.3 (C**8**), 13.8 (C**9**).

IR *vmax*/cm^{-1}: 2958 (w), 1713 (s), 1324 (m), 1071 (w).

HRMS (ESI) m/z calcd for $C_{26}H_{28}NO_2$ [$(M+H)^+$] 386.2120, found 386.2110.

(1*S**,5*S**)-3-Benzyl-7-butyl-1-(2-oxo-2-phenylethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **342**



13:1 r.r.

General Procedure 5 – Atom Transfer Radical Addition. Compound **307** (20 mg, 0.06 mmol), trimethyl((1-phenylvinyl)oxy)silane (34.6 mg, 0.18 mmol) and 2,6-lutidine (14 µL, 0.12 mmol) were used. Purification *via* flash column chromatography (petrol/ethyl acetate: 19/1) gave the title compound (15 mg, 65%) as a pale yellow oil.

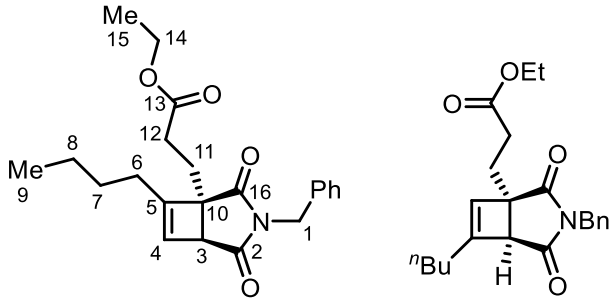
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.88 – 7.81 (2H, m, 2 x **Ar**-H), 7.57 – 7.11 (8H, m, 8 x **Ar**-H), 6.01 (1H, s, C**4**-H), 4.73 – 4.54 (2H, m, C**1**-H_2), 3.92 (1H, d, *J* = 18.5 Hz, C**11**-HH), 3.37 (1H, s, C**3**-H), 3.24 (1H, d, *J* = 18.5 Hz, C**11**-HH), 2.05 (2H, t, *J* = 7.5 Hz, C**6**-H_2), 1.39 – 1.27 (2H, m, C**7**-H_2), 1.24 – 1.11 (2H, m, C**8**-H_2), 0.78 (3H, t, *J* = 7.5 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 196.6 (C**13**), 176.8 (C**12**), 175.5 (C**2**), 156.3 (C**5**), 136.1 (**Ar**), 135.8 (**Ar**), 133.7 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**)128.5 (C**4**), 128.1 (**Ar**), 128.0 (**Ar**) 127.4 (**Ar**), 55.0 (C**10**), 49.3 (C**3**), 42.0 (C**1**), 38.5 (C**11**), 28.0 (C**7**), 27.8 (C**6**), 22.3 (C**8**), 13.8 (C**9**).

IR *vmax*/cm^{-1}: 2917 (s), 1699 (s), 1383 (m), 1072 (m).

HRMS (ESI) m/z calcd for $C_{25}H_{25}NNaO_3$ [$(M+Na)^+$] 410.1732, found 410.1723.

Ethyl 3-((1*S**,5*S**)-3-benzyl-7-butyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-1-yl)propanoate **344**



19:1 r.r.

General Procedure 5 – Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutene **307** (197 mg, 0.65 mmol, 10:1 r.r.), ethyl acrylate (212 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petrol: 90/10 to remove the catalyst, followed by petrol/ethyl acetate: 95:5) gave the title compound (124 mg, 52%) as a clear colourless oil.

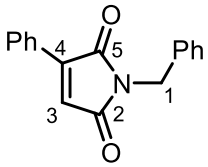
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.35 – 7.15 (5H, m, 5 x **Ar**-H), 5.98 (1H, d, *J* = 1.5 Hz, C**4**-H), 4.59 – 4.48 (2H, m, C**1**-H_2), 4.03 (2H, q, *J* = 7.0 Hz, C**14**-H_2), 3.26 (1H, d, *J* = 2.0 Hz, C**3**-H), 2.27 – 2.20 (3H, m, C**12**-H_2, C**11**-H), 2.12 - 2.04 (1H, m, C**11**-H), 1.98 (2H, dt, *J* = 7.5, 2.0 Hz, C**6**-H_2), 1.34 – 1.24 (2H, m, C**7**-H_2), 1.22 – 1.10 (5H, m, C**8**-H_2, C**15**-H_3), 0.77 (3H, t, *J* = 7.5 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 176.4 (C**16**), 174.6 (C**2**), 173.1 (C**13**), 157.0 (C**5**), 135.8 (**Ar**), 128.6 (C**4**), 128.2 (**Ar**), 127.7 (**Ar**), 60.8 (C**14**), 57.4 (C**10**), 47.8 (C**3**), 42.0 (C**1**), 29.9 (C**12**), 29.7 (C**7**), 27.8 (C**6**), 23.9 (C**11**), 22.2 (C**8**), 14.1 (C**15**), 13.7 (C**9**).

IR *vmax*/cm^{-1}: 2960 (m), 1732 (s), 1703 (s), 1387 (w), 1169 (m).

HRMS (ESI) m/z calcd for $C_{22}H_{27}NNaO_4$ [$(M+Na)^+$] 392.1838, found 392.1827.

1-Benzyl-3-phenyl-1*H*-pyrrole-2,5-dione **345**



To a dual-necked round bottomed flask, toluene (2.0 mL), ethanol (1.0 mL) and *sat.* aqueous sodium hydrogen carbonate (6.5 mL) was added. To this solution, 1-benzyl-3-bromo-1H-pyrrole-2,5-dione **303** (100 mg, 0.38 mmol), benzene-1,4-diboronic acid (56.1 mg, 0.46 mmol) and palladium tetrakis (23.1

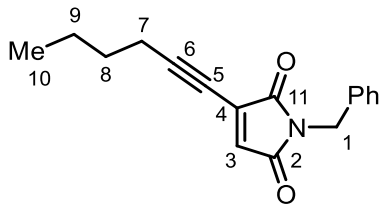
mg, 0.02 mmol). The reaction mixture was stirred at 90 °C for 5 hours under a nitrogen atmosphere. After cooling to r.t., the mixture was quenched with distilled water (3 mL) followed by extraction with ethyl acetate (2 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL) and dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 19/1) to give the title compound (20 mg, 20%) as a colourlesssolid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.90 – 7.76 (2H, m, **Ar**), 7.42 – 7.14 (8H, m, **Ar**-H), 6.66 (1H, s, C**3**-H), 4.67 (2H, s, C**1**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.4 (C**5**), 170.0 (C**2**), 143.9 (C**4**), 136.4 (**Ar**), 131.2 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.5 (C**3**), 127.8 (**Ar**), 123.9 (**Ar**), 41.6 (C**1**).

All recorded data match literature values.[181]

1-Benzyl-3-(hex-1-yn-1-yl)-1*H*-pyrrole-2,5-dione **346**

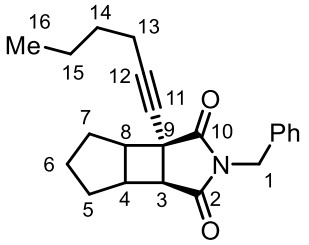


To a flame-dried dual-necked round bottomed flask, 1-benzyl-3-bromo-1H-pyrrole-2,5-dione **303** (1 g, 3.80 mmol), 1-hexyne (0.65 mL, 5.70 mmol), triethylamine (0.79 mL, 5.70 mmol), copper iodide (72 mg, 0.38 mmol), Bis(triphenylphosphine)palladium (II) dichloride (130 mg, 0.19 mmol) and THF (70 mL) were added at 0°C under a nitrogen atmosphere. The solution was left to stir at 0 °C for 1 hour. Ethyl acetate (50 mL) and water (10 mL) were added to the solution. The organic later was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 9/1) to give the title compound (147 mg, 15%) as an orange solid.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.29 – 7.13 (5H, m, **Ar**), 6.45 (1H, s, C**3**-H), 4.59 (2H, s, C**1**-H_2), 2.42 (2H, t, *J* = 7.0 Hz, C**7**-H_2), 1.58 – 1.46 (2H, m, C**8**-H_2), 1.44 – 1.30 (2H, m, C**9**-H_2), 0.85 (3H, t, *J* = 7.5 Hz, C**10**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C**11**), 167.4 (C**2**), 136.1 (C**3**), 131.6 (C**4**), 130.7 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 109.9 (C**6**), 70.9 (C**5**), 41.9 (C**1**), 30.0 (C**8**), 22.0 (C**9**), 19.9 (C**7**), 13.5 (C**10**).

(3a*R**,6b*S**)-2-Benzyl-3a-(hex-1-yn-1-yl)hexahydrocyclopenta[3,4]cyclobuta[1,2-c]pyrrole-1,3(2*H*,3a*H*)-dione **347**



General Procedure 3 – Batch. 1-Benzyl-3-(hex-1-yn-1-yl)-1H-pyrrole-2,5-dione **346** (100 mg, 0.37 mmol), cyclopentene (0.17 mL, 5.0 mmol) and degassed acetonitrile (150 mL) were used. The solvent was removed and the crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 19/1) to give the title compound (33 mg, 26%) as a clear colourless oil.

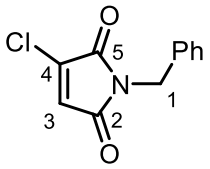
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.20 (5H, m, 5 x **Ar**-H), 4.70 – 4.57 (2H, m, C**1**-H_2), 2.77 (1H, t, *J* = 7.0 Hz, C**8**-H), 2.61 (1H, td, *J* = 7.0, 3.5 Hz, C**4**-H), 2.55 (1H, d, *J* = 3.5 Hz, C**3**-H), 2.16 (2H, t, *J* = 7.0 Hz, C**13**-H_2), 2.13 – 2.04 (1H, m, 1 x C**5**-H), 1.86 – 1.69 (3H, m, C**7**-H_2, C**6**-HH), 1.54 – 1.38 (4H, m, 1 x C**6**-H, 1 x C**5**-H, C**14**-H_2), 1.37 – 1.28 (2H, m, C**15**-H_2), 0.83 (3H, t, *J* = 7.0 Hz, C**16**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.7 (C**10**), 177.6 (C**2**), 135.8 (**Ar**), 128.7 (**Ar**), 128.4 (**Ar**), 127.9 (**Ar**), 88.7 (C**11**), 72.6 (C**12**), 49.9 (C**3**), 45.2 (C**8**), 42.8 (C**9**) 42.8 (C**1**), 41.4 (C**4**), 32.6 (C**6**), 30.7 (C**14**), 29.7 (C**5**), 24.7 (C**7**), 21.9 (C**15**), 18.6 (C**13**), 13.6 (C**16**).

IR *vmax*/cm^{-1}: 2953 (m), 1775 (w), 1703 (s), 1388 (m), 1175 (m), 699 (m).

HRMS (ESI) m/z calcd for $C_{22}H_{25}NO_2$ [$(M+H)^+$] 336.1964, found 336.1953.

1-Benzyl-3-chloro-1*H*-pyrrole-2,5-dione **350**



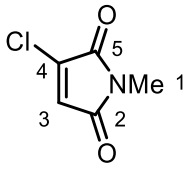
Prepared according to general procedure 2, using 1-benzyl-3-bromomaleimide **303** (5.00 g, 18.8 mmol), tetrabutylammonium chloride (5.75 g, 20.7 mmol) and acetone (56 mL), and stirred at reflux for 1 hour.

The yield was determined to be 90% by ^{1}H NMR using 1,3,5-trimethoxy benzene as an internal standard. The crude material was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.20 – 7.05 (5H, m, 5 x **Ar**-H), 6.50 (1H, s, C**3**-H), 4.51 (2H, s, C**1**-H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 167.3 (C**2**), 164.5 (C**5**), 140.8 (C**4**), 135.5 (**Ar**), 128.6 (C**3**), 128.3 (**Ar**), 128.0 (**Ar**), 126.8 (**Ar**), 42.1 (C**1**).

1-Benzyl-3-chloro-1*H*-pyrrole-2,5-dione (**350**-Me)



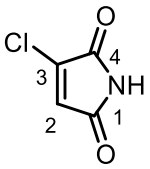
Prepared according to general procedure 2, using 1-methyl-3-bromomaleimide **303**-Me (1.30 g, 6.80 mmol), tetrabutylammonium chloride (2.78 g, 10.0 mmol) and acetone (20 mL), and stirred at reflux for 2 hours. The yield was determined to be 70% by ^{1}H NMR using 1,3,5-trimethoxy benzene as an internal standard. The crude material was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.39 (1H, s, C**3**-H), 2.72 (3H, s, C**1**)).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 167.5 (C**2**), 164.8 (C**5**), 140.6 (C**4**), 126.8 (C**3**), 24.2 (C**1**).

GC-MS m/z: [M] calcd for $C_5H_4ClNO_2$ 221.0, found 221.0.

1-Benzyl-3-chloro-1*H*-pyrrole-2,5-dione (**350**-H)



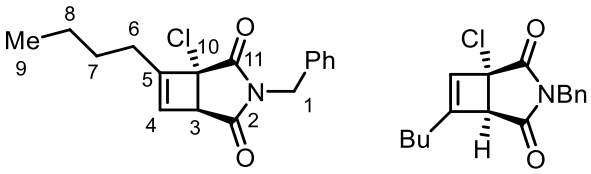
Prepared according to general procedure 2, using 1*H*-3-bromomaleimide **303**-H (1.32 g, 7.50 mmol), tetrabutylammonium chloride (6.25 g, 22.5 mmol) and acetone (22 mL), and stirred at reflux for 4 hours.

The yield was determined to be 81% by ^{1}H NMR using 1,3,5-trimethoxy benzene as an internal standard. The crude material was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 11.86 (1H, s, *N*-H), 6.18 (1H, s, C**2**-H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.7 (C**1**), 165.7 (C**4**), 140.5 (C**3**), 127.1 (C**2**).

(1*R**,5*R**)-3-Benzyl-7-butyl-1-chloro-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **351**



15:1 r.r.

General Procedure 3 – Batch. Compound **350** was taken forward assuming quantitative yield (15 mmol), 1-hexyne (5.15 mL, 45 mmol), 2-methoxy-9H-thioxanthen-9-one (36.3 mg, 0.75 mmol) and degassed acetonitrile (150 mL) were used. The reaction was exposed to UVA irradiation for 2 hours. The solvent was removed and the crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 99/1) to give the title compound (3.39 g, 74%) as a pale yellow oil.

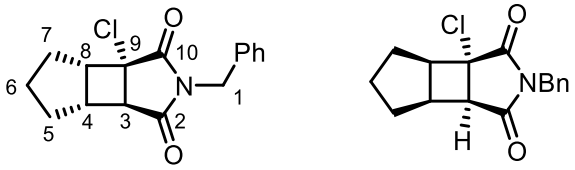
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.39 – 7.28 (5H, m, 5 x **Ar**-H), 6.20 (1H, d, *J* = 1.5 Hz, C**4**-H_2), 4.75 – 4.59 (2H, m, C**1**-H_2), 3.69 (1H, dd, *J* = 2.0, 1.0 Hz, C**3**-H), 2.20 (2H, td, *J* = 8.5, 2.0 Hz, C**6**-H_2), 1.54 – 1.34 (2H, m, C**7**-H_2), 1.32 – 1.21 (2H, m, C**8**-H_2), 0.88 (3H, t, *J* = 7.5 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 172.6 (C**11**), 171.0 (C**2**), 154.7 (C**5**), 135.2 (**Ar**), 129.9 (C**4**), 128.7 (**Ar**), 128.5 (**Ar**), 128.1 (**Ar**), 64.0 (C**5**), 53.4 (C**3**), 42.6 (C**1**), 27.4 (C**7**), 26.8 (C**6**), 22.2 (C**8**), 13.7 (C**9**).

IR *vmax*/cm^{-1}: 2957 (w), 2931 (w), 1778 (w), 1711 (s), 1382 (m), 1340 (m), 699 (m).

HRMS (ESI) m/z calcd for $C_{17}H_{18}ClNNaO_2$ $[(M+Na)^+]$ 326.0924, found 326.0909.

(3a*S**,3b*S**,6a*R**,6b*R**)-2-Benzyl-3a-chlorohexahydrocyclopenta[3,4]cyclobuta[1,2-c]pyrrole-1,3(2H,3aH)-dione **352**



12:1 r.r.

General Procedure 3 – Batch. **350** was taken forward assuming quantitative yield (7.5 mmol), cyclopentene (1.0 mL, 11.25), 2-isopropyl-9H-thioxanthen-9-one (20 mg, 0.08 mmol) and degassed

acetonitrile (150 mL) were used. The reaction was exposed to UVA irradiation for 2 hours. The solvent was removed and the crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 19/1) to give the title compound (1.29 g, 62%) as a coloulress solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.43 – 7.29 (5H, m, 5 x **Ar**-H), 4.82 – 4.69 (2H, m, C**1**-H_2), 3.07 – 3.00 (1H, m, C**4**-H), 2.79 (1H, dd, *J* = 3.5, 1.0 Hz, C**3**-H), 2.70 (1H, td, *J* = 6.0, 3.5 Hz, C**8**-H), 2.27 – 2.18 (1H, m, C**6**-HH), 2.04 – 1.95 (1H, m, C**7**-HH), 1.90 – 1.93 (1H, m, C**5**-HH), 1.88 – 1.76 (1H, m, C**7**-HH), 1.68 – 1.70 (1H, m, C**6**-HH), 1.62 – 1.65 (1H, m, C**5**-HH).

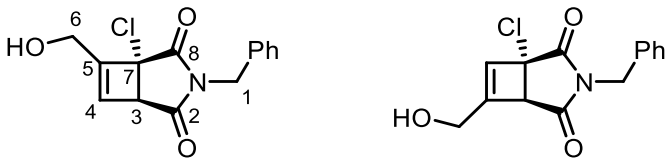
^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 175.7 (C**2** or C**10**), 175.6 (C**2** or C**10**), 135.3 (**Ar**), 128.8 (**Ar**), 128.4 (**Ar**), 128.1 (**Ar**), 60.9 (C**9**), 52.2 (C**3**), 45.5 (C**4**), 43.0 (C**1**), 41.5 (C**8**), 32.9 (C**5**), 29.0 (C**6**), 24.8 (C**7**).

IR *vmax*/cm^{-1}: 2957 (w), 2931 (w), 1779 (s), 1712 (s), 1383 (m), 700 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{16}ClNNaO_2$ [$(M+Na)^+$] 312.0767, found 312.0763.

Mp ($CDCl_3$): 77–80 °C.

(1*R**,5*R**)-3-Benzyl-1-chloro-7-(hydroxymethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **354**



major 5:1 r.r.

General Procedure 3 - Batch. Chloromaleimide **350** (1.0 g, 3.8 mmol), propargyl alcohol (0.66 mL, 11.3 mmol) and ITX (10 mg, 0.04 mmol) were used. The crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 3/2 to 2/3) to give the title compound (766 mg, 70%) as a thick orange oil.

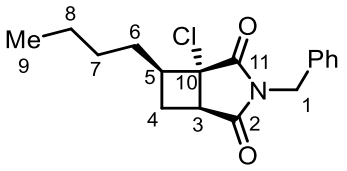
^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.37 – 7.29 (5H, m, **Ar**), 6.45 (1H, q, *J* = 1.5 Hz, C**4**-H), 4.73 – 4.63 (2H, m, C**1**-H_2), 4.31 (2H, s, C**6**-H_2), 3.77 (1H, dd, *J* = 2.0, 1.0 Hz, C**3**-H), 1.79 (1H, s, OH).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 171.8 (C**2**), 170.8 (C**8**), 151.8 (C**5**), 135.0 (**Ar**), 131.1 (C**4**), 128.9 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 128.2 (**Ar**), 62.6 (C**7**), 57.4 (C**6**), 53.6 (C**3**), 42.9 (C**1**).

IR *vmax*/cm^{-1}: 3474 (br), 2952 (w), 1778 (w), 1710 (s), 1386 (m), 1340 (m), 700 (w).

HRMS (ESI) m/z calcd for $C_{14}H_{13}ClNO_3$ [(M+H)$^+$] 278.0584, found 278.0573.

(1*S**,5*R**,7*R**)-3-Benzyl-7-butyl-1-chloro-3-azabicyclo[3.2.0]heptane-2,4-dione **360**



General procedure 3 – Batch. Using crude **350** (16.9 mmol), ITX (46 mg, 0.19 mmol), and 1-hexyne (6.43 mL, 56.4 mmol). The reaction was exposed to UVA irradiation for 90 minutes.

General procedure 4. Using the crude material from the previous step (14.1 mmol), 5% Pd/C (1.00 g, 20% w/w) and methanol (150 mL). Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 99/1) gave the title compound (3.83 g, 67%) as a colourless oil.

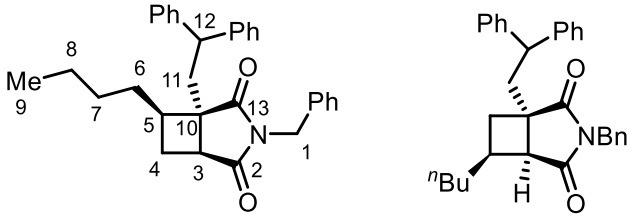
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.20 (5H, m, 5 x **Ar**-H), 4.63 – 4.69 (2H, m, C**1**-H_2), 3.23 (1H, dd, *J* = 10.5, 5.5 Hz, C**3**-H), 2.85 (1H, dt, *J* = 16.0, 8.0 Hz, C**5**-H), 2.75 (1H, dd *J* = 12.5, 10.5 Hz, C**4**-HH), 1.56 – 1.48 (1H, m, C**6**-HH), 1.39 (1H, ddd, *J* = 12.5, 8.0, 6.0 Hz, C**4**-HH), 1.27 – 1.06 (4H, m, C**7**-H_2, C**8**-H_2), 1.05 – 0.93 (1H, m, C**6**-HH), 0.76 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.8 (C**2**), 172.8 (C**11**), 135.4 (**Ar**), 128.8 (**Ar**), 128.7 (**Ar**), 128.2 (**Ar**), 62.7 (C**10**), 46.3 (C**5**), 44.9 (C**3**), 42.9 (C**1**), 31.6 (C**6**), 28.5 (C**7**), 26.9 (C**4**), 22.3 (C**8**), 13.8 (C**9**).

IR *vmax*/cm^{-1}: 2932 (w), 1714 (s), 1385 (w), 1341 (w), 699 (w).

HRMS (ESI) m/z calcd for $C_{17}H_{21}ClNO_2$ [(M+H)$^+$] 306.1261, found 306.1270.

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(2,2-diphenylethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **361**



18:1 r.r.

General procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5.0 mol%) and MeCN/water

(4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 99/1) gave the title compound (251 mg, 86%) as a colourless oil.

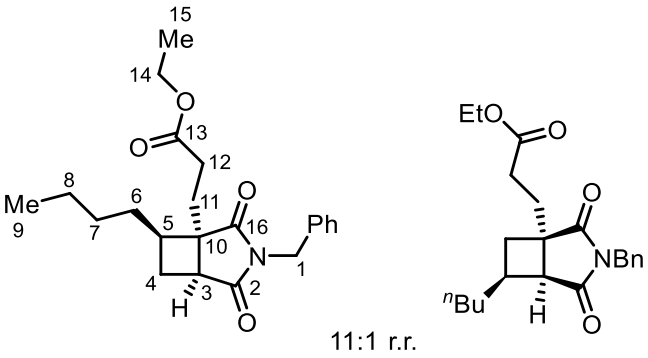
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.46 – 6.70 (15H, m, 15 x **Ar**-H), 4.57 – 4.44 (2H, m, C**1**-H_2), 3.71 (1H, dd, *J* = 10.5, 5.0 Hz, C**12**-H_2), 2.71 (1H, dd, *J* = 14.0, 5.0 Hz, C**11**-HH), 2.45 – 2.34 (2H, m, C**11**-HH, C**4**-HH), 2.22 (1H, dd, *J* = 9.5, 7.0 Hz, C**5**-H), 2.05 (1 H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 1.42 – 1.32 (1 H, m, C**6**-HH), 1.27 (2 H, ddd, *J* = 12.5, 7.5, 5.5 Hz, C**4**-HH), 1.11 – 0.91 (5H, m, C**7**-H_2, C**8**-H_2), 0.83 (3 H, td, *J* 11.5, 5.5, C**6**-HH), 0.72 (3 H, t, *J* 7.0, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1 (C**2**), 179.0 (C**13**), 144.1 (**Ar**), 143.3 (**Ar**), 136.2 (**Ar**), 129.4 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 128.4 (**Ar**), 128.1 (**Ar**), 127.7 (**Ar**), 127.4 (**Ar**), 126.9 (**Ar**), 126.4 (**Ar**), 52.1 (C**10**), 47.8 (C**12**), 42.4 (C**5**), 42.3 (C**1**), 40.3 (C**11**), 38.8 (C**3**), 32.2 (C**6**), 29.0 (C**7**), 27.2 (C**4**), 22.4 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 2929 (m), 2855 (m), 1697 (s), 1389 (m), 699 (m).

HRMS (ESI) m/z calcd for $C_{31}H_{34}NO_2$ [(M+H)$^+$] 452.2584, found 452.2587.

Ethyl 3-((1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-1-yl)propanoate **362**



11:1 r.r.

General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), ethyl acrylate (212 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5.0 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (90/10 toluene/petroleum ether to remove the catalyst, followed by 95/5 petroleum ether/ethyl acetate) gave the title compound (181 mg, 75%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.44 – 7.18 (5H, m, 5 x **Ar**-H), 4.74 – 4.58 (2H, m, C**1**-H_2), 4.08 (2H, qq, *J* = 7.0, 3.5 Hz, C**14**-H_2), 2.87 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 2.70 – 2.56 (1H, m, C**4**-HH), 2.37 – 2.27 (1H, m, C**5**-H), 2.27 – 2.15 (3H, m, C**11**-H_2, C**12**-HH), 2.08 – 1.96 (1H, m,

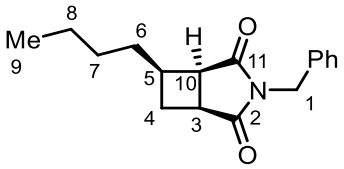
C**12**-H<u>H</u>), 1.50 (1H, ddd, *J* = 12.5, 7.5, 5.0 Hz, C**4**-H<u>H</u>), 1.46 – 1.37 (1H, m, C**6**-H<u>H</u>), 1.18 – 1.03 (4H, m, C**7**-H<u>$_2$</u>, C**8**-H<u>$_2$</u>), 0.97 – 0.84 (1H, m, C**6**-H<u>H</u>), 0.79 (3H, t, *J* = 7.0 Hz, C**9**-H<u>$_3$</u>).

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1 (C**2**), 178.8 (C**16**), 172.7 (C**13**), 136.1 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 60.7 (C**15**) ,51.2 (C**10**), 42.4 (C**1**), 40.9 (C**5**), 39.1 (C**3**), 32.4 (C**6**), 29.5 (C**11**), 29.4 (C**12**), 29.0 (C**7**), 26.7 (C**4**), 22.4 (C**8**), 14.1 (C**15**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 2930 (w), 1732 (m), 1698 (s), 1389 (m), 1166 (m), 700 (w).

HRMS (ESI) m/z calcd for $C_{22}H_{30}NO_4$ [(M+H)$^+$] 372.2169, found 372.2173.

(1*S**,5*R**,6*R**)-3-Benzyl-6-butyl-3-azabicyclo[3.2.0]heptane-2,4-dione **363**



General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), DIPEA (350 µL, 1.95 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2 to 95/5) gave the title compound (118 mg, 67%) as a colourless oil.

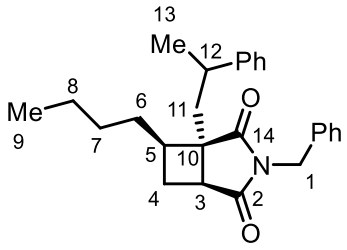
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.51 – 7.22 (5H, m, 5 x **Ar**-H<u></u>), 4.70 (2H, s, C**1**-H<u>$_2$</u>), 3.38 – 3.30 (1H, m, C**10**-H<u></u>), 3.19 (1H, dd, *J* = 10.5, 6.0 Hz, C**3**-H<u></u>), 2.84 – 2.66 (2H, m, C**5**-H<u></u>, C**4**-H<u></u>H), 2.34 – 2.15 (1H, m, C**4**-H<u></u>H), 1.61 – 1.43 (1H, m, C**6**-H<u></u>H), 1.30 – 1.07 (4H, m, C**7**-H<u>$_2$</u>, C**8**-H<u>$_2$</u>), 1.01 (1H, td, *J* = 9.5, 5.0 Hz, C**6**-H<u></u>), 0.83 (3H, t, *J* = 7.0 Hz, C**9**-H<u>$_3$</u>).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 180.0 (C**2**), 177.5 (C**11**), 136.1 (**Ar**), 128.9 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 42.4 (C**1**), 42.2 (C**10**), 40.9 (C**3**), 35.4 (C**5**), 34.5 (C**6**), 29.7 (C**4**), 28.7 (C**7**), 22.4 (C**8**), 13.9 (C**9**).

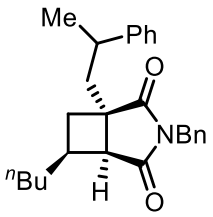
IR *vmax*/cm^{-1}: 2928 (w), 1695 (s), 1387 (m), 1160 (m), 700 (m).

HRMS (ESI) m/z calcd for $C_{17}H_{21}NNaO_2$ [(M+Na)$^+$] 294.1464, found 294.1470.

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(2-phenylpropyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **364**



52:48 d.r.



10:1 r.r.

General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), α-methyl styrene (253 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5.0 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2) gave the title compound (69 mg, 27%) as a colourless oil.

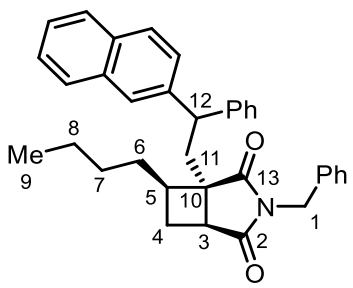
^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*mixture of diastereomers, A+B, of major regioisomer reported*) 8.16 – 8.07 (1H, m, Ar-H), 7.59 – 7.30 (4H, m, Ar-H), 7.26 – 6.63 (5H, m, Ar-H), 4.75 – 4.63 (2H, m, C**1**-H_2), 2.52 (1H, dqd, *J* = 11.0, 7.0, 4.0 Hz, C**12**-H), 2.42 (1H, dt, *J* = 13.0, 10.0 Hz, C**4**-HH), 2.35 (1H, dd, *J* = 14.0, 4.0 Hz, C**11**-HH), 2.23 – 2.14 (1H, m, C**5**-H), 1.97 – 1.89 (1H, m, C**4**-HH), 1.83 (1H, dd, *J* = 10.5, 5.0, C**3**-H), 1.47 (2H, ddd, *J* = 14.0, 6.5, 3.5 Hz, C**6**-HH), 1.39 – 1.00 (8H, m, C**7**-H_2, C**4**-HH, C**13**-H_3, C**8**-H_2), 0.97 – 0.79 (4H, m, C**6**-HH, C**9**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*mixture of diastereomers of major regioisomer reported*) 179.5 (C**2**), 179.3 (C**2**), 179.3 (C**14**), 179.0 (C**14**), 145.5 (**Ar**), 145.4 (**Ar**), 136.2 (**Ar**), 136.1 (**Ar**), 129.6 (**Ar**), 128.8 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.1 (**Ar**), 127.8 (**Ar**), 127.2 (**Ar**), 126.7 (**Ar**), 126.6 (**Ar**), 52.3 (C**10**), 51.7 (C**10**), 43.2 (C**11**), 42.7 (C**11**), 42.5 (C**5**), 42.4 (C**5**), 42.1 (C**1**), 42.1 (C**1**), 39.0 (C**3**), 38.8 (C**3**), 37.3 (C**12**), 37.1 (C**12**), 32.2 (C**6**), 32.1 (C**6**), 29.0 (C**7**), 29.0 (C**7**), 27.1 (C**4**), 27.0 (C**4**), 23.7 (C**13**), 23.4 (C**13**), 22.4 (C**8**), 22.4 (C**8**), 13.9 (C**9**), 13.8 (C**9**).

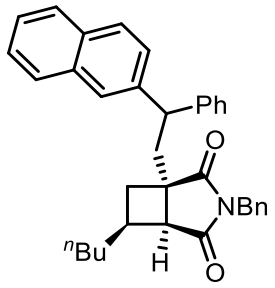
IR *vmax*/cm^{-1}: 2966 (m), 1700 (s), 1391 (m), 1055 (m), 700 (w).

HRMS (ESI) m/z calcd for $C_{26}H_{31}NNaO_2$ [$(M+Na)^+$] 412.2247, found 412.2235.

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(2-(naphthalen-2-yl)-2-phenylethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **365**



56:44 d.r.



9:1 r.r.

General procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (177 mg, 0.58 mmol, 10:1 r.r.), 2-(1-phenylvinyl)naphthalene (452 mg, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5.0 mol%), and MeCN/water (4/1, 2.0 mL) and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petrol/ethyl acetate: 98/2) gave the title compound (222 mg, 77%) as a colourless oil.

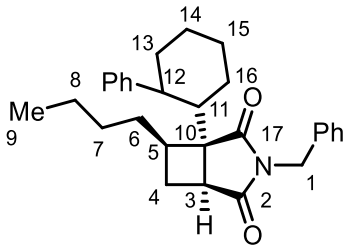
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*mixture of diastereomers, A+B (56:44), of major regioisomer reported*) 7.83 – 7.64 (3H, m, A+B, 3 x **Ar**-H), 7.62 – 7.27 (9H, m, A+B, 10 x **Ar**-H), 7.22 – 7.11 (3H, m, A+B, 3 x **Ar**-H), 7.00 – 6.89 (1H, m, A+B, 1 x **Ar**-H), 4.70 – 4.42 (2H, m, A+B, C**1**-H_2), 4.01 (1H, ddd, *J* = 10.0, 5.5, 2.0 Hz, A/B, C**12**-H), 2.95 (1H, ddd, *J* = 14.0, 5.5, 3.5 Hz, A/B, C**11**-HH), 2.64 – 2.52 (1H, m, A+B, C**11**-HH), 2.52 – 2.41 (1H, m, A+B, C**4**-HH), 2.35 (0.44H, tdd, *J* = 9.5, 7.5, 6.0 Hz, B, C**3**-H), 2.21 (0.56H, td, *J* = 10.0, 5.0 Hz, A, C**3**-H), 1.53 – 1.43 (1H, m, A+B, C**6**-HH), 1.42 – 1.29 (2H, m, A+B, C**4**-HH), 1.18 – 1.03 (4H, m, A+B, C**7**-H_2, C**8**-H_2), 1.01 – 0.87 (1H, m, A+B, C**6**-HH), 0.82 (3H, t, *J* = 7.0 Hz, A+B, C**9**-H_3).

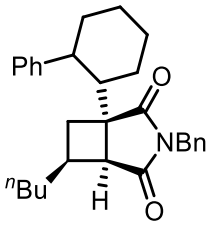
δ_C (*mixture of diastereomers of major regioisomer reported*) 179.2 (C**2**), 179.1 (C**2**), 179.0 (C**13**), 178.9 (C**13**), 143.9 (**Ar**), 143.2 (**Ar**), 141.5 (**Ar**), 140.9 (**Ar**), 136.4 (**Ar**), 136.2 (**Ar**), 133.5 (**Ar**), 133.4 (**Ar**), 132.3 (**Ar**), 132.2 (**Ar**), 129.4 (**Ar**), 129.4 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.2 (**Ar**), 128.1 (**Ar**), 128.1 (**Ar**), 127.9 (**Ar**), 127.8 (**Ar**), 127.7 (**Ar**), 127.6 (**Ar**), 127.6 (**Ar**), 127.6 (**Ar**), 127.0 (**Ar**), 126.6 (**Ar**), 126.6 (**Ar**), 126.3 (**Ar**), 126.1 (**Ar**), 126.1 (**Ar**), 125.9 (**Ar**), 125.8 (**Ar**), 125.7 (**Ar**), 125.2 (**Ar**), 52.2 (C**10**), 52.1 (C**10**), 47.9 (C**12**), 47.8 (C**12**), 42.5 (C**5**), 42.5 (C**5**), 42.4 (C**1**), 42.3 (C**1**), 40.0 (C**11**), 39.9 (C**11**), 38.9 (C**3**), 38.8 (C**3**), 32.2 (C**6**), 32.2 (C**6**), 29.1 (C**7**), 29.0 (C**7**), 27.3 (C**4**), 27.2 (C**4**), 22.5 (C**8**), 22.5 (C**8**), 13.9 (C**9**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 2929 (w), 2858 (w), 1697 (s), 1389 (m), 1167 (w), 700 (m).

HRMS (ESI) m/z calcd for $C_{35}H_{35}NNaO_2$ [$(M+Na)^+$] 524.2560, found 524.2543.

(1*S**,5*S**,7*R**)-3-Benzyl-7-butyl-1-((1*R*)-2-phenylcyclohexyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **366**





61:39 d.r.

9:1 r.r.

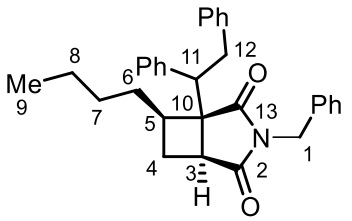
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*mixture of diastereomers, A+B, of major regioisomer reported*) 7.44 – 6.93 (10H, m, **Ar**-H x10), 4.46 – 4.26 (0.8H, m, B, C**1**-H_2), 4.18 – 3.92 (1.2H, m, A, C**1**-H_2), 3.09 (0.6H, s, A, C**3**-H), 2.69 (0.4H, dd, *J* = 10.5, 5.0 Hz, B, C**3**-H), 2.44 – 0.50 (22H, m, A+B, C**4**-H_2, C**5**-H, C**6**-H_2, C**7**-H_2, C**8**-H_2, C**9**-H_3, C**11**-H, C**12**-H, C**13**-H_2, C**14**-H_2, C**15**-H_2, C**16**-H_2).

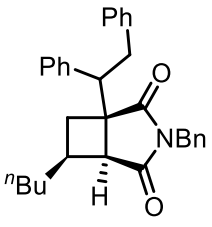
^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*mixture of diastereomers of major regioisomer reported*) 179.6 (C**2**), 179.1 (C**2**), 178.7 (C**17**), 143.4 (**Ar**), 143.2 (**Ar**), 136.2 (**Ar**), 135.9 (**Ar**), 130.2 (**Ar**), 129.8 (**Ar**), 129.7 (**Ar**), 129.4 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.23 (**Ar**), 128.20 (**Ar**), 128.0 (**Ar**), 127.9 (**Ar**), 127.6 (**Ar**), 126.7 (**Ar**), 55.7 (C**10**), 55.1 (C**10**), 46.1 (C**12**), 42.2 (C**1**), 42.2 (C**3**), 41.8 (C**1**), 41.7 (C**5**), 41.1 (C**12**), 39.7 (C**11**), 38.0 (C**3**), 37.7 (C**5**), 36.9 (C**11**), 33.1 (C**6**), 32.8 (C**6**), 31.9 (C**13**), 29.0 (C**13**), 27.0 (C**14**), 26.6 (C**7**), 26.5 (C**14**), 26.1 (C**15**), 23.9 (C**14**), 23.0 (C**15**), 22.9 (C**16**), 22.42 (C**16**), 22.39 (C**7**), 20.9 (C**4**), 20.8 (C**4**), 17.5 (C**8**), 14.7 (C**8**), 13.9 (C**9**), 13.8 (C**9**).

IR *vmax*/cm^{-1}: 2925 (m), 1694 (s), 1391 (m), 1055 (m), 701 (m).

HRMS (ESI) m/z calcd for $C_{29}H_{36}NO_2$ $[(M+H)^+]$ 430.2741, found 430.2736.

(1*S**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(1,2-diphenylethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **367**





54:46 d.r.

15:1 r.r.

General procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (177 mg, 0.58 mmol, 10:1 r.r.), *trans*-stilbene (348 mg, 1.95 mmol), DIPEA (140

µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5.0 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petrol/ethyl acetate: 98/2) gave the title compound (143 mg, 55%) as a colourless oil.

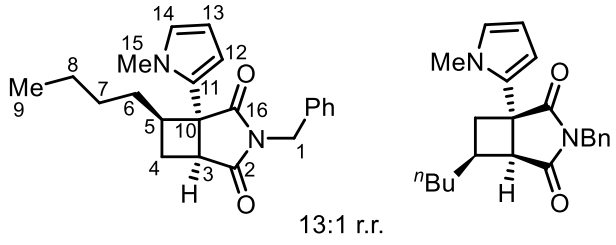
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*mixture of diastereomers, A+B (1.5:1), of major regioisomer reported*) 7.28 – 6.77 (15H, m, A+B, **Ar**-H x15), 4.57 – 4.40 (2H, m, A+B, C**1**-H_2 x2), 3.27 – 3.18 (1.5H, m, A+B, 2 x C**11**-H C**12**-HH), 3.12 (0.5H, dd, *J* = 13.5, 5.0 Hz, A/B, C**12**-HH), 2.98 (0.5H, dd, *J* = 12.0, 1.5 Hz, A/B, C**12**-HH), 2.94 – 2.82 (1.5H, m, A+B, C**12**-HH, C**3**-H x2), 2.61 – 2.41 (1.5H, m, A+B, C**5**-H, C**4**-HH x2), 2.29 (0.5H, tdd, *J* = 10.0, 7.0, 5.0 Hz, A/B, C**5**-H), 1.58 – 1.44 (1H, m, A+B, C**6**-HH, C**7**-HH), 1.44 – 1.34 (1H, m, A+B, C**4**-HH, C**4**-HH), 1.31 – 0.62 (8H, m, A+B, C**6**-HH x3, C**7**-HH x3, C**8**-H_2 x2, C**9**-H_3 x2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*mixture of diastereomers of major regioisomer reported*) 179.2 (C**2**), 179.1 (C**2**), 178.2 (C**13**), 178.2 (C**13**), 139.9 (**Ar**), 139.4 (**Ar**), 139.2 (**Ar**), 138.6 (**Ar**), 135.9 (**Ar**), 135.8 (**Ar**), 129.0 (**Ar**), 129.0 (**Ar**), 128.9 (**Ar**), 128.8 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 128.1 (**Ar**), 127.8 (**Ar**), 127.7 (**Ar**), 127.2 (**Ar**), 127.1 (**Ar**), 126.2 (**Ar**), 125.9 (**Ar**), 56.0 (C**10**), 55.9 (C**10**), 53.3 (C**11**), 50.8 (C**11**), 42.4 (C**1**), 42.3 (C**1**), 40.5 (C**5**), 39.5 (C**3**), 38.5 (C**3**), 38.1 (C**5**), 37.3 (C**12**), 36.1 (C**12**), 33.1 (C**6**), 32.4 (C**6**), 29.1 (C**7**), 28.7 (C**7**), 27.0 (C**4**), 26.2 (C**4**), 22.4 (C**8**), 22.2 (C**8**), 13.9 (C**9**), 13.8 (C**9**).

IR *vmax*/cm^{-1}: 2932 (m), 2855 (w), 1698 (s), 1389 (m), 699 (m).

HRMS (ESI) m/z calcd for $C_{31}H_{33}NNaO_2$ [$(M+Na)^+$] 474.2404, found 474.2412.

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(1-methyl-1H-pyrrol-2-yl)-3-azabicyclo[3.2.0]heptane-2,4-dione **368**



General procedure 5 – Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), *N*-methylpyrrole (580 µL, 6.50 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2 to 95/5) gave the title compound (112 mg, 49%) as a yellow oil.

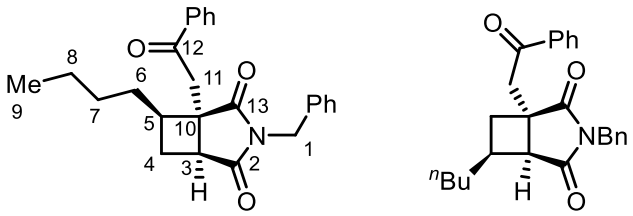
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.38 – 7.33 (2H, m, 2 x **Ar**-H), 7.26 – 7.19 (3H, m, 3 x **Ar**-H), 6.49 (1H, dd, *J* = 2.5, 2.0 Hz, C**14**-H), 6.00 – 5.94 (2H, m, C**12**-H, C**13**-H), 4.69 – 4.60 (2H, m, C**1**-H_2), 3.34 (3H, s, C**15**-H_3), 3.26 (1H, ddd, *J* = 10.5, 4.5, 0.5 Hz, C**3**-H), 2.88 – 2.78 (1H, m, C**5**-H), 2.69 (1H, dd, *J* = 13.0, 10.0 Hz, C**4**-HH), 1.66 (1H, ddd, *J* = 9.5, 7.5, 4.0 Hz, C**6**-HH), 1.60 (1H, ddd, *J* = 13.0, 6.5, 4.5 Hz, C**4**-HH), 1.18 – 1.02 (4H, m, C**7**-H_2, C**8**-H_2), 1.02 – 0.91 (1H, m, C**6**-HH), 0.77 – 0.71 (3H, m, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 178.8 (C**2**), 176.7 (C**16**), 135.8 (**Ar**), 129.1 (**Ar**), 129.0 (C**11**), 128.6 (**Ar**), 128.1 (**Ar**), 124.7 (C**14**), 108.1 (C**13**), 106.9 (C**12**), 50.4 (C**10**), 42.7 (C**1**), 41.0 (C**3**), 40.8 (C**5**), 35.0 (C**15**), 32.6 (C**6**), 28.7 (C**7**), 26.7 (C**4**), 22.3 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 2961 (m), 2919 (s), 2855 (m), 1702 (m), 1392 (m), 1055 (m).

HRMS (ESI) m/z calcd for $C_{22}H_{27}N_2O_2$ [$(M+H)^+$] 351.2067, found 351.2064.

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(2-oxo-2-phenylethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **369**



8:1 r.r.

General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), trimethyl((1-phenylvinyl)oxy)silane (**379**, 375 mg, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petrol: 90/10 to remove the catalyst, thenpetrol/ethyl acetate: 95/5) gave the title compound (51 mg, 20%) as a colourless oil.

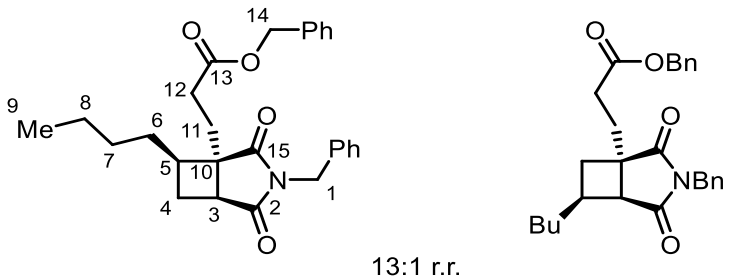
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.96 – 7.03 (10H, m, 10 x **Ar**-H), 4.83 – 4.57 (2H, m, C**1**-H_2), 3.78 (1H, d, *J* = 18.5 Hz, C**11**-HH), 3.34 (1H, d, *J* = 18.5 Hz, C**11**-HH), 2.98 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 2.65 (1H, dd *J* = 13.0, 10.0 Hz, C**4**-HH), 2.34 (1H, tt, *J* = 10.0, 6.5 Hz, C**5**-H), 1.58 – 1.52 (1H, m, C**4**-HH), 1.37 (1H, ddd, *J* = 13.5, 10.0, 6.0 Hz, C**6**-HH), 1.10 – 0.99 (4H, m, C**7**-H_2, C**8**-H_2), 0.92 – 0.85 (1H, m, C**6**-HH), 0.72 (3H, t, *J* = 6.9 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 196.9 (C**12**), 179.6 (C**2**), 179.3 (C**13**), 136.3 (**Ar**), 136.0 (**Ar**), 133.6 (**Ar**), 128.7 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.0 (**Ar**), 127.7 (**Ar**), 48.7 (C**10**), 43.3 (C**11**), 42.5 (C**1**), 40.9 (C**5**), 39.9 (C**3**), 31.9 (C**6**), 29.0 (C**7**), 27.2 (C**4**), 22.4 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 3678 (w), 2971 (s), 2902 (s), 1701 (s), 1393 (m), 1055 (s).

HRMS (ESI) m/z calcd for $C_{25}H_{27}NNaO_3$ [$(M+Na)^+$] 412.1883, found 412.1890.

Benzyl 3-((1*R**,5*S**,7*R**)-3-benzyl-7-butyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-1-yl)propanoate **370**



13:1 r.r.

General procedure 5. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), benzyl acrylate (296 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10, to remove the catalyst, followed by petroleum ether/ethyl acetate: 95/5) gave the title compound (127 mg, 45%) as a yellow oil.

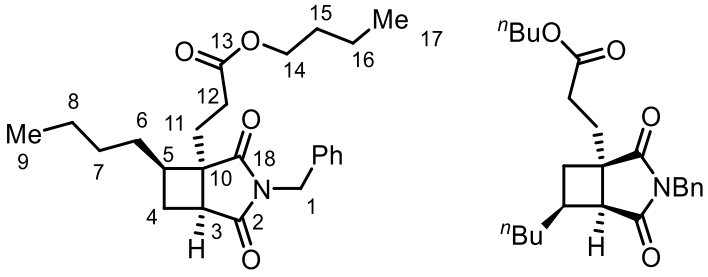
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.40 – 7.26 (10H, m, 10 x **Ar**-H), 5.11 – 5.02 (2H, m, C**14**-H_2), 4.69 – 4.61 (2H, m, C**1**-H_2), 2.86 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 2.77 (1H, t, *J* = 6.5, C**12**-HH), 2.67 – 2.59 (1H, m, C**12**-HH), 2.39 – 2.20 (3H, m, C**5**-H, C**4**-HH, C**11**-HH), 2.07 – 2.00 (1H, m, C**11**-HH), 1.50 (1H, ddd, *J* = 12.5, 7.5, 5.0 Hz, C**4**-HH), 1.47 – 1.37 (1H, m, C**6**-HH), 1.19 – 1.01 (4H, m, C**8**-H_2, C**7**-H_2), 0.92 – 0.85 (1H, m, C**6**-HH), 0.78 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.0 (C**2**), 178.8 (C**15**), 172.4 (C**13**), 136.1 (**Ar**), 135.7 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.6 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 127.9 (**Ar**), 66.5 (C**14**), 51.1 (C**10**), 42.4 (C**1**), 40.8 (C**5**), 39.1 (C**3**), 29.4 (C**6**), 29.3 (C**11**), 29.0 (C**12**), 28.0 (C**7**), 26.7 (C**4**), 22.4 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 2929 (w), 1736 (s), 1697 (s), 1366 (m), 1156 (m), 697 (m).

HRMS (ESI) m/z calcd for $C_{27}H_{31}NNaO_4$ [$(M+Na)^+$] 456.2145, found 456.2157.

Butyl 3-((1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-1-yl)propanoate **371**



8:1 r.r.

General procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), *n*-butyl acrylate (282 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10 to remove the catalyst, followed by petroleum ether/ethyl acetate: 95/5) gave the title compound (203 mg, 78%) as a colourless oil.

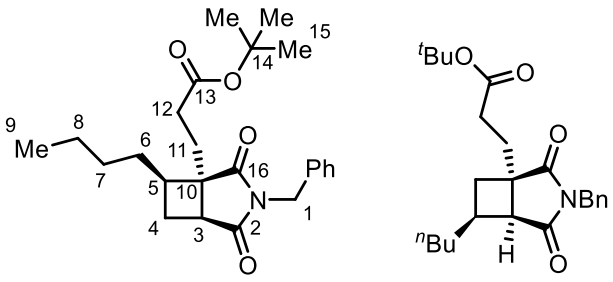
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.43 – 7.26 (5H, m, 5 x **Ar**), 4.73 – 4.61 (2H, m, C**1**-$\underline{H_2}$), 4.12 – 3.97 (2H, m, C**14**-$\underline{H_2}$), 2.87 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-$\underline{H}$), 2.69 – 2.54 (1H, m, C**4**-$\underline{H}$H), 2.38 – 2.27 (2H, m, C**5**-$\underline{H}$), 2.27 – 2.15 (3H, m, C**11**-$\underline{H_2}$, C**12**-$\underline{H}$H), 2.08 – 1.97 (1H, m, C**12**-$\underline{H}$H), 1.64 – 1.45 (4H, m, C**6**-$\underline{H}$H, C**15**-$\underline{H_2}$, C**4**-$\underline{H}$H), 1.45 – 1.24 (2H, m, C**16**-$\underline{H_2}$), 1.20 – 1.01 (4H, m, C**7**-$\underline{H_2}$, C**8**-$\underline{H_2}$), 0.96 – 0.89 (4H, m, C**6**-$\underline{H}$H, C**17**-$\underline{H_3}$), 0.81 – 0.75 (3H, m, C**9**-$\underline{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.1 (C**2**), 178.9 (C**18**), 172.7 (C**13**), 136.1 (**Ar**), 128.8 (**Ar**), 128.6 **Ar**), 127.9 (**Ar**), 64.6 (C**14**), 51.2 (C**10**), 42.4 (C**1**), 40.9 (C**5**), 39.1 (C**3**), 32.4 (C**6**), 30.6 (C**15**), 29.5 (C**11**), 29.3 (C**12**), 29.0 (C**7**), 26.7 (C**4**), 22.4 (C**8**), 19.1 (C**16**), 13.9 (C**9**), 13.7 (C**17**).

IR *vmax*/cm^{-1}: 2958 (m), 2931 (m), 2877 (w), 1732 (m), 1699 (s), 1389 (m), 1166 (m), 700 (w).

HRMS (ESI) m/z calcd for $C_{24}H_{34}NO_4$ $[(M+H)^+]$ 400.2482, found 400.2471.

tert-Butyl 3-((1*R**,5*S**,7*R**)-3-benzyl-7-butyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-1-yl)propanoate **372**



12:1 r.r.

General procedure 5. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), *t*-butyl acrylate (284 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10, to remove the catalyst, followed by petroleum ether/ethyl acetate: 95/5) gave the title compound (207 mg, 80%) as a yellow oil.

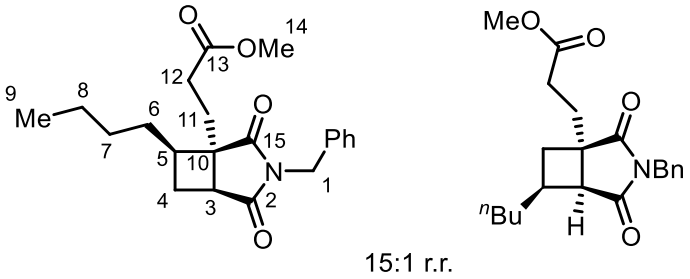
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.36 – 7.20 (5H, m, 5 x **Ar**-H), 4.55 – 4.65 (2H, m, C**1**-H_2), 2.82 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 2.63 – 2.52 (1H, m, C**4**-HH), 2.32 – 2.24 (1H, m, C**5**-H), 2.15 – 2.01 (3H, m, C**12**-H_2, C**11**-HH), 1.99 – 1.87 (1H, m, C**11**-HH), 1.51 – 1.38 (2H, m, C**4**-HH), 1.34 (10H, s, 3 x C**15**-H_3, C**6**-HH), 1.13 – 0.97 (4H, m, C**7**-H_2, C**8**-H_2), 0.90 – 0.77 (1H, m, C**6**-HH), 0.77 – 0.70 (3H, m, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.2 (C**2**), 179.0 (C**16**), 172.0 (C**13**), 136.1 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 80.8 (C**14**), 51.3 (C**10**), 42.4 (C**1**), 40.9 (C**5**), 39.1 (C**3**), 32.4 (C**6**), 30.5 (C**11**), 29.5 (C**12**), 29.0 (C**7**), 28.0 (C**15**), 26.8 (C**4**), 22.4 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 2970 (w), 2930 (w), 1726 (s), 1698 (s), 1366 (m), 1149 (s), 689 (m).

HRMS (ESI) m/z calcd for $C_{24}H_{33}NNaO_4$ [$(M+Na)^+$] 422.2295, found 422.2302.

Methyl 3-((1*R**,5*S**,7*R**)-3-benzyl-7-butyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-1-yl)propanoate **373**



15:1 r.r.

General procedure 5. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), methyl acrylate (175 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10, to remove the catalyst, followed by petroleum ether/ethyl acetate: 95/5) gave the title compound (179 mg, 77%) as a yellow oil.

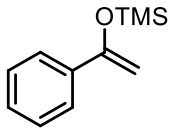
^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.46 – 7.14 (5H, m, 5 x **Ar**-H), 4.78 – 4.62 (2H, m, C**1**-H_2), 3.64 (3H, s, C**14**-H_3), 2.88 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 2.71 – 2.58 (1H, m, C**4**-HH), 2.40 – 2.29 (1H, m, C**5**-H, C**12**-H_2), 2.25 (2H, ddd, *J* = 18.0, 10.5, 5.0 Hz, C**11**-HH, C**12**-HH), 2.09 – 1.99 (1H, m, C**11**-HH), 1.53 (1H, ddd, *J* = 12.5, 7.5, 5.0 Hz, C**4**-HH), 1.48 – 1.40 (1H, m, C**6**-H), 1.22 – 1.07 (4H, m, C**7**-H_2, C**8**-H_2), 0.98 – 0.87 (1H, m, C**6**H-H), 0.82 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.1 (C**2**), 178.8 (C**13**), 173.1 (C**12**), 136.1 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 125.3 (**Ar**), 51.8 (C**14**), 51.2 (C**10**), 42.4 (C**1**), 40.9 (C**5**), 39.1 (C**3**), 32.4 (C**6**), 29.5 (C**11**), 29.2 (C**10**), 29.0 (C**7**), 26.7 (C**4**), 22.4 (C**8**), 13.9 (C**9**)

IR *vmax*/cm^{-1}: 2929 (w), 1737 (s), 1696 (s), 1388 (m), 1166 (m), 699 (m).

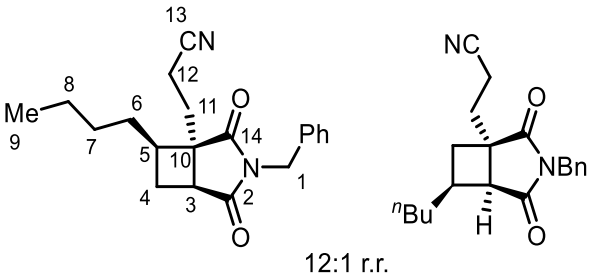
HRMS (ESI) m/z calcd for $C_{21}H_{27}NNaO_4$ [$(M+Na)^+$] 380.1832, found 380.1836.

Trimethyl((1-phenylvinyl)oxy)silane **379**



To a flame-dried dual-necked round bottomed flask, acetophenone (1.0 mL, 8.57 mmol), NaI (147 mg, 10.62 mmol), triethylamine (1.47 mL, 10.62 mmol) and acetonitrile (8.6 mL) were added under a nitrogen atmosphere at r.t.. To this, TMSCl (1.32 mL, 10.62 mmol) was added dropwise over 5 mins. A white precipitate was formed on addition. The mixture was left to stir for 1 hour. At 0 °C, cold pentane (20 mL) and cold water (20 mL) was added. The aqueous layer was extracted with pentane (2 x 20 mL) and the organic layers were washed with NH_4Cl (*sat.* aqueous, 2 x 10 mL). The organic layers were dried over $MgSO_4$ and the solvent was concentrated *in vacuo* to afford the title compound (1.00 g, 61%). The crude product was used in the next step without further purification.[180]

3-((1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-1-yl)propanenitrile **385**



12:1 r.r.

General Procedure 5 – Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), acrylonitrile (128 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10, to remove the catalyst, followed by petroleum ether/ethyl acetate: 80/20) gave the title compound (148 mg, 70%) as a colourless oil.

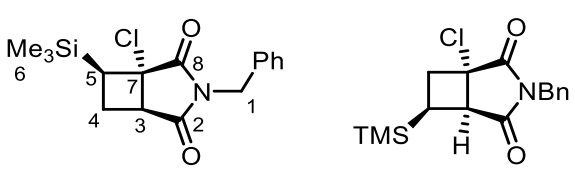
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.46 – 7.21 (5H, m, **Ar**-H x5), 4.68 (2H, s, C**1**-H_2), 3.01 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 2.70 (1H, dd, *J* = 13.0, 10.0, C**4**-HH), 2.45 – 2.33 (3H, m, C**12**-H_2, C**5**-H), 2.29 – 2.20 (1H, m, C**11**-HH), 2.04 (1H, ddd, *J* = 14.0, 9.0, 7.0 Hz, C**11**-HH), 1.60 – 1.52 (1 H, m, C**4**-HH), 1.47 – 1.38 (1H, m, C**6**-HH), 1.20 – 1.02 (4H, m, C**7**-H_2, C**8**-H_2), 0.96 – 0.86 (1 H, m, C**6**-HH), 0.79 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 178.3 (C**2**), 178.2 (C**14**), 135.8 (**Ar**), 128.8 (**Ar**), 128.7 (**Ar**), 128.1 (**Ar**), 118.7 (C**13**), 50.5 (C**10**), 42.6 (C**1**), 40.7 (C**5**), 39.1 (C**3**), 32.4 (C**6**), 30.0 (C**11**), 28.8 (C**7**), 26.7 (C**4**), 22.4 (C**8**), 13.8 (C**9**), 12.7 (C**12**).

IR *vmax*/cm^{-1}: 2934 (w), 2956 (w), 2239 (w), 1693 (s), 1390 (s), 937 (m), 698 (m).

HRMS (ESI) m/z calcd for $C_{20}H_{24}N_2NaO_2$ [$(M+Na)^+$] 347.1730, found 347.1735.

(1*S**,5*R**,7*R**)-3-Benzyl-1-chloro-7-(trimethylsilyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **397**



4:1 r.r.

General procedure 3 – Batch. Using crude **350** (16.9 mmol), ITX (48 mg, 0.19 mmol), and ethynyltrimethylsilane (7.80 mL, 56.4 mmol). The reaction was exposed to UVA irradiation for 2.5 hours.

General procedure 4. Using the crude material from the previous step (16.9 mmol), 5% Pd/C (1.00 g, 20% w/w) and methanol (150 mL), and stirred at r.t. for 18 hours. Purification *via* flash column chromatography (petrol/ethyl acetate: 99/1) gave the title compound (2.77 g, 44%) as a colourless oil.

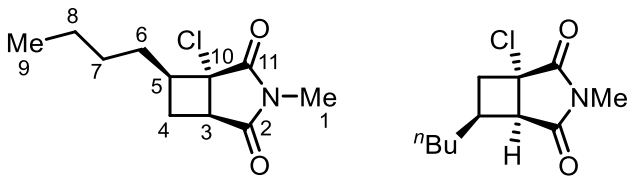
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.43 – 7.27 (5H, m, 5 x **Ar**-H), 4.81 – 4.59 (2H, m, C**1**-H_2), 3.57 (1H, dd, *J* =11.0, 6.0 Hz, C**3**-H), 2.81 – 2.68 (1H, m, C**4**-H), 2.60 – 2.51 (1H, m, C**5**-H), 1.73 (1H, ddd, *J* = 12.0, 9.5, 6.0 Hz, C**4**-H), -0.07 (9H, s, 3 x C**6**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 175.5 (C**2**), 174.3 (C**8**), 135.1 (**Ar**), 129.1 (**Ar**), 128.8 (**Ar**), 128.2 (**Ar**), 62.0 (C**7**), 48.4 (C**3**), 43.1 (C**1**), 36.3 (C**5**), 21.4 (C**4**), -3.4 (C**6**).

IR *vmax*/cm^{-1}: 2954 (w), 1711 (s), 1384 (m), 1249 (m), 837 (m), 697 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{24}ClN_2O_2Si$ [$(M+NH_4)^+$] 339.1290, found 339.1273.

(1*S**,5*R**,7*R**)-7-Butyl-1-chloro-3-methyl-3-azabicyclo[3.2.0]heptane-2,4-dione **398**



12:1 r.r.

General Procedure 3 – Batch. Using crude **303**-Me (6.8 mmol), ITX (18 mg, 0.070 mmol), and 1-hexyne (2.30 mL, 20.0 mmol). The reaction was exposed to UVA irradiation for 4.5 hours.

General procedure 4. Using the crude material from the previous step (5.0 mmol), 5% Pd/C (260 mg, 20% w/w) and methanol (70 mL), and stirred at r.t. for 18 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 95/5) gave the title compound (800 mg, 51%) as a colourless oil.

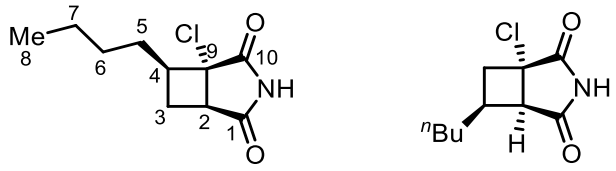
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 3.21 (1H, dd, *J* 10.5, 5.5, C**3**-H), 2.98 (3H, s, C**1**-H_3), 2.92 – 2.82 (1H, m, C**5**-H), 2.82 – 2.70 (1H, m, C**4**-HH), 1.67 – 1.53 (1H, m, C**6**-HH), 1.48 (1H, ddd, *J* = 12.5, 8.0, 6.0 Hz, C**4**-HH), 1.27 – 1.08 (5H, m, C**6**-HH), 0.78 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 175.5 (C**2**), 172.4 (C**11**), 62.2 (C**10**), 45.3 (C**5**), 44.2 (C**3**), 31.0 (C**6**), 27.9 (C**7**), 26.1 (C**4**), 24.7 (C**1**), 21.6 (C**8**), 13.2 (C**9**).

IR *vmax*/cm^{-1}: 2955 (m), 2858 (w), 1783 (w), 1706 (s), 1426 (s), 1374 (m), 1284 (m), 1164 (w), 1002 (s).

HRMS (ESI) m/z calcd for $C_{11}H_{16}ClNNaO_2$ [$(M+Na)^+$] 252.0762, found 252.0760.

(1*S**,5*R**,7*R**)-7-Butyl-1-chloro-3-azabicyclo[3.2.0]heptane-2,4-dione **399**



11:1 r.r.

General Procedure 3 – Batch. Using crude **303**-H (7.5 mmol), ITX (19 mg, 0.075 mmol), and 1-hexyne (2.48 mL, 22.0 mmol). The reaction was exposed to UVA irradiation conditions for 4.5 hours.

General procedure 4. Using the crude material from the previous step (5.19 mmol), 5% Pd/C (260 mg, 20% w/w) and methanol (75 mL), and stirred at r.t. for 24 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10) gave the title compound (906 mg, 56%) as a colourless oil.

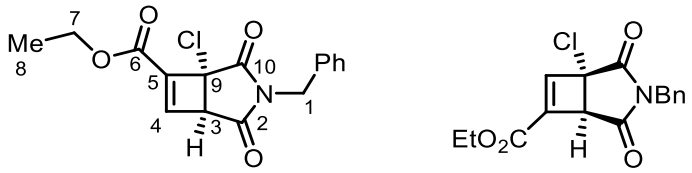
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 9.19 (1H, s, N-H), 3.35 – 3.28 (1H, *J* = 10.5, 5.5 Hz, C**2**-H), 2.97 (1H, dtd, *J* = 14.0, 7.5, 7.0, 4.0 Hz, C**4**-H), 2.93 – 2.83 (1H, m, C**3**-HH), 1.74 (2H, m, C**4**-HH, C**5**-HH), 1.39 – 1.17 (5H, m, C**5**-HH, C**6**-H_2, C**7**-H_2), 0.94 – 0.83 (3H, m, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 175.7 (C**1**), 172.6 (C**10**), 63.1 (C**9**), 45.4 (C**4**), 45.3 (C**2**), 31.0 (C**5**), 27.9 (C**6**), 26.3 (C**3**), 21.7 (C**7**), 13.2 (C**8**).

IR *vmax*/cm^{-1}: 3220 (br), 2957 (m), 2930 (m), 2858 (m), 1783 (m), 1713 (s), 1456 (w), 1333 (m), 1182 (s), 1032 (m).

HRMS (ESI) m/z calcd for $C_{10}H_{14}ClNNaO_2$ [$(M+Na)^+$] 238.0605, found 238.0613.

Ethyl (1*R**,5*R**)-3-Benzyl-5-chloro-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-ene-6-carboxylate **400**



4:1 r.r.

General procedure 3 – Syringe pump. Using crude **350** (16.9 mmol), ITX (46 mg, 0.19 mmol), and ethyl propiolate (5.70 mL, 56.4 mmol). Ethyl propiolate was added over 2 hours under UVA irradiation, and irradiation was continued for a further 2 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 95/5 to 90/10) gave the cyclobutene product (2.64 g, 44%) as a yellow solid.

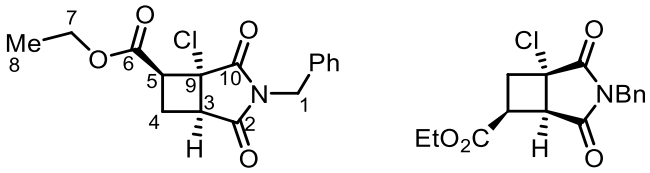
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.39 – 7.29 (5H, m, 5 x **Ar**-H), 7.17 (1H, d, *J* = 1.5 Hz, C**4**-H), 4.74 – 4.63 (2H, m, C**1**-H_2), 4.33 (2H, q, *J* = 7.0 Hz, C**7**-H_2), 3.85 (1 H, d, *J* = 1.5 Hz, C**3**-H), 1.36 (3 H, t, *J* = 7.0 Hz, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 169.8 (C**2**), 168.8 (C**10**), 158.6 (C**6**), 145.2 (C**4**), 141.8 (C**5**), 134.8 (**Ar**), 128.8 (**Ar**), 128.8 (**Ar**), 128.3 (**Ar**), 61.9 (C**9**) 61.8 (C**7**), 54.0 (C**3**), 43.2 (C**1**), 14.1 (C**8**).

IR *vmax*/cm^{-1}: 2991 (w), 1721 (s), 1384 (m), 1184 (m), 699 (s).

HRMS (ESI) m/z calcd for $C_{16}H_{15}ClNO_4$ $[(M+H)^+]$ 320.0684, found 320.0687.

Ethyl (1*R**,5*R**,6*S**)-3-Benzyl-5-chloro-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxylate **401**



4:1 r.r.

General procedure 4. Using the material **400** from the previous step (2.64 g, 8.26 mmol), 5% Pd/C (500 mg, 20% w/w) and methanol (83 mL). Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 95/5 to 90/10) gave the title compound (2.11 g, 79%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.44 – 7.29 (5H, m, 5 x **Ar**-H), 4.73 – 4.76 (2H, m, C**1**-H_2), 4.22 – 4.09 (2H, m, C**7**-H_2), 3.81 – 3.73 (1H, m, C**5**-H), 3.42 (1H, ddd, *J* = 10.5, 6.0, 3.5

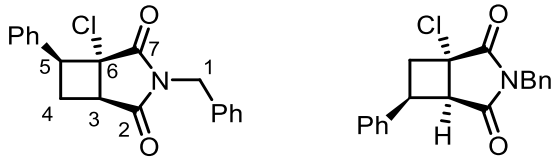
Hz, C**3**-H), 2.87 (1H, ddd, *J* = 13.0, 10.5, 2.5 Hz, C**4**-HH), 2.35 (1H, ddd, *J* = 13.0, 8.0, 6.0 Hz, C**4**-HH), 1.27 (3 H, t, *J* 7.0, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 174.3 (C**2**), 171.8 (C**10**), 169.0 (C**6**), 134.9 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.1 (**Ar**), 62.0 (C**7**), 60.9 (C**9**), 48.2 (C**5**), 45.0 (C**3**), 43.3 (C**1**), 22.5 (C**4**), 14.0 (C**8**).

IR *vmax*/cm^{-1}: 2987 (w), 1715 (s), 1385 (m), 1342 (m), 1202 (m), 699 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{17}ClNO_4$ [(M+H)$^+$] 322.0841, found 322.0832.

(1*S**,5*R**,7*S**)-3-Benzyl-1-chloro-7-phenyl-3-azabicyclo[3.2.0]heptane-2,4-dione **403**



7:1 r.r.

General Procedure 3 – Syringe pump. Using crude **350** (16.9 mmol), ITX (48 mg, 0.19 mmol), and phenylacetylene (6.2 mL, 56 mmol). Phenylacetylene was added over 2 hours under UVA irradiation, and irradiation was continued for a further 3 hours. Purification *via* flash column chromatography (100% petroleum ether, to remove excess phenylacetylene, followed by 90/10 petroleum ether/ethyl acetate) gave a mixture of cyclobutene and the [2+2]-dimer of *N*-benzyl maleimide, which was used in the following step without further purification.

General Procedure 4. Using the material from the previous step (16.9 mmol), 5% Pd/C (1.00 g, 20% w/w) and methanol (150 mL). Purification *via* flash column chromatography (98/2 petroleum ether/ethyl acetate) gave the title compound (1.20 g, 27%) as a colourless oil.

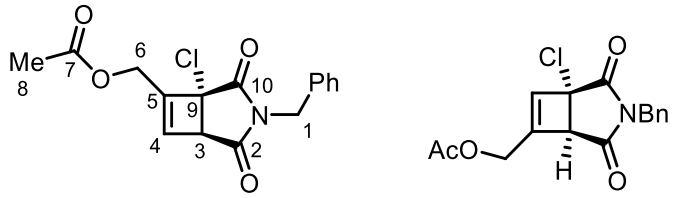
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.38 – 7.14 (8H, m, 8 x **Ar**-H), 7.05 – 6.92 (2H, m, 2 x **Ar**-H), 4.72 – 4.56 (2H, m, C**1**-H_2), 4.28 (1H, dd, *J* = 11.0, 8.5 Hz, C**5**-H), 3.49 (1H, dd, *J* = 10.5, 6.0 Hz, C**3**-H), 3.15 – 3.01 (1H, m, C**4**-HH), 2.27 (1H, ddd, *J* = 13.0, 8.5, 5.5 Hz, C**4**-HH).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 175.3 (C**2**), 171.7 (C**7**), 135.2 (**Ar**), 129.1 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.6 (**Ar**), 128.2 (**Ar**), 128.1 (**Ar**), 127.0 (**Ar**), 64.1 (C**6**), 50.7 (C**5**) 44.6 (C**3**), 42.9 (C**1**), 24.9 (C**4**).

IR *vmax*/cm^{-1}: 3031 (w), 1708 (s), 1384 (m), 1339 (m), 1163 (m), 694 (s).

HRMS (ESI) m/z calcd for $C_{19}H_{16}ClNNaO_2$ [(M+Na)$^+$] 348.0762, found 348.0774.

((1*R**,5*R**)-3-Benzyl-5-chloro-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)methyl acetate **404**



4:1 r.r.

General procedure 3 – Batch. Using crude **354** (16.9 mmol), ITX (48 mg, 0.19 mmol), and propargyl alcohol (3.28 mL, 56.4 mmol). The reaction was exposed to UVA irradiation for 90 minutes. Purification *via* flash column chromatography (petrol/ethyl acetate:60/40) gave the cyclobutene (3.65 g, 70%) as a colourless oil.

To a solution of the cyclobutene alcohol (2.87 g, 10.3 mmol) in DCM (41 mL) at r.t. was added 4-(dimethylamino)pyridine (126 mg, 1.03 mmol) and pyridine (0.81 mL, 10 mmol). The solution was stirred for 5 minutes before adding acetic anhydride (1.97 mL, 20.3 mmol) and stirring at r.t. for a further 16 hours. The solution was quenched with 1 M aqueous HCl (10 mL) and extracted with DCM (3 × 10 mL). The organic layers were combined and dried over $MgSO_4$, and the solvent was concentrated *in vacuo*. Purification *via* flash column chromatography (70/30 petroleum ether/ethyl acetate) gave the cyclobutene acetate (2.48 g, 78%) as an orange oil.

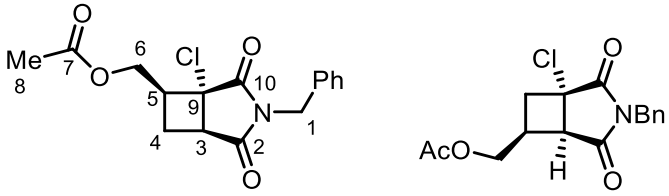
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.35 – 7.27 (7 H, m, 5 x Ar-H), 6.45 (1 H, q, *J* = 1.5, C**4**-H), 4.72 – 4.60 (4 H, m, C**1**-H_2, C**6**-H_2), 3.76 (1 H, td, *J* = 2.0, 1.0, C**3**-H), 2.03 (3 H, s, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 171.4 (C**2**), 170.2 (C**10**), 170.0 (C**7**) 147.7 (C**5**), 134.9 (**Ar**), 133.6 (C**4**), 128.8 (**Ar**), 128.4 (**Ar**), 128.1 (**Ar**), 62.8 (C**9**), 57.5 (C**6**), 53.9 (C**3**), 42.8 (C**1**), 20.5 (C**8**).

IR *vmax*/cm^{-1}: 1746 (m), 1713 (s), 1384 (m), 1224 (m), 700 (w).

HRMS (ESI) m/z calcd for $C_{16}H_{15}ClNO_4$ [$(M+H)^+$] 320.0684, found 320.0676.

((1*R**,5*S**,6*S**)-3-Benzyl-5-chloro-2,4-dioxo-3-azabicyclo[3.2.0]heptan-6-yl)methyl acetate **405**



4:1 r.r.

General procedure 4. Using compound **404** (200 mg, 0.624 mmol), 5% Pd/C (40 mg, 20% w/w) and methanol (6.3 mL). Purification *via* flash column chromatography (petrolether/ethyl acetate: 60:40) gave the title compound (177 mg, 88%) as a colourless oil.

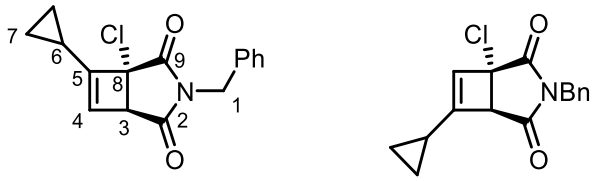
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*diastereomers of major regioisomer reported*) 7.38 – 7.19 (5H, m, 5 x **Ar**-H), 4.77 – 4.59 (2H, m, C**1**-H_2), 4.11 – 4.00 (2H, m, C**6**-H_2), 3.38 – 3.30 (1H, m, C**3**-H), 3.25 (1H, ddt, *J* = 10.5, 8.5, 5.0 Hz, C**5**-H), 2.83 – 2.69 (1H, m, C**4**-HH), 1.85 – 1.76 (4H, m, C**4**-HH, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*diastereomers of major regioisomer reported*) 175.0 (C**2**), 172.4 (C**10**), 170.3 (C**7**), 135.2 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.2 (**Ar**), 61.5 (C**6**), 60.8 (C**9**), 44.9 (C**3**), 44.6 (C**5**), 43.1 (C**1**), 22.9 (C**4**), 20.3 (C**8**).

IR *vmax*/cm^{-1}: 2947 (w), 1742 (m), 1711 (s), 1386 (m), 1232 (m), 1042 (w), 699 (w).

HRMS (ESI) m/z calcd for $C_{16}H_{17}ClNO_4$ [$(M+H)^+$] 322.0846, found 322.0828.

(1*R**,5*R**)-3-Benzyl-1-chloro-7-cyclopropyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **406**



9:1

General Procedure 3 – Batch. Using crude **350** (13.5 mmol), ITX (37 mg, 0.15 mmol), and cyclopropyl acetylene (3.81 mL, 45.0 mmol). The reaction was exposed to UVA irradiation for 90 minutes. The product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2) to give the cyclobutene (3.00 g, 56%) as a colourless oil in a 9:1 regioisomeric ratio.

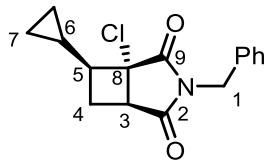
^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.38 – 7.26 (5H, m, 5 x **Ar**-H), 6.11 (1H, d, *J* = 1.0, C**4**-H), 4.76 – 4.57 (2H, m, C**1**-H_2), 3.64 (1H, d, *J* = 1.0 Hz, C**3**-H), 1.55 – 1.46 (1H, m, C**6**-H), 0.93 – 0.78 (4H, m, 2 x C**7**-H_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 172.5 (C**2**), 171.0 (C**9**), 155.0 (C**5**), 135.2 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.1 (**Ar**), 127.4 (C**4**), 63.5 (C**8**), 53.1 (C**3**), 42.6 (C**1**), 9.4 (C**6**), 6.6 (C**7**).

IR *vmax*/cm^{-1}: 3008 (w), 1702 (s), 1380 (m), 1183 (m), 853 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{14}ClNNaO_2$ [$(M+Na)^+$] 310.0605, found 310.0595.

(1*S**,5*R**,7*S**)-3-Benzyl-1-chloro-7-cyclopropyl-3-azabicyclo[3.2.0]heptane-2,4-dione **407**



>20:1 r.r.

Modified General Procedure 4. Using compound **406** (2.50 g, 8.69 mmol), 5% Pt/C (500 mg, 20% w/w) and methanol (87 mL), and stirred at r.t. for 18 hours. A small amount of the *n*-propyl product of cyclopropane cleavage was observed (8%) but this could be separated *via* flash column chromatography [*Note: when using Pd/C in place of Pt/C, the ratio of cyclopropyl:n-propyl products was 1:1*]. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2) gave the title compound (1.88 g, 75%) as a colourless oil (*the minor regioisomer was removed during purification*). 42% overall yield.

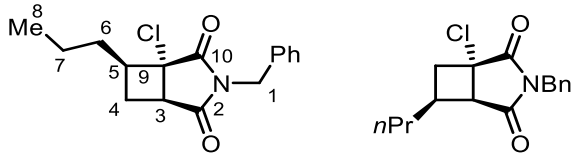
^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.48 – 7.29 (5H, m, 5 x **Ar**-H), 4.85 – 4.68 (2H, m, C**1**-H_2), 3.36 – 3.23 (1 H, m, C**3**-H), 2.82 – 2.59 (2H, m, C**5**-H, C**4**-HH), 1.51 (1H, ddd, *J* = 12.5, 7.5, 5.5 Hz, C**4**-HH), 0.69 (1H, dddd, *J* = 8.0, 5.0 Hz, C**6**-H), 0.57 – 0.47 (1H, m, C**7**-HH), 0.29 (1H, dddd, *J* = 9.0, 8.0, 6.0, 5.0 Hz, C**7**-HH), 0.19 (1H, ddt, *J* = 9.5, 6.0, 5.0 Hz, C**7**-HH), -0.13 (1H, ddd, *J* = 10.5, 9.5, 5.0 Hz, C**7**-HH).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 175.7 (C**2**), 172.8 (C**9**), 135.2 (**Ar**), 129.0 (**Ar**), 128.8 (**Ar**), 128.2 (**Ar**), 62.7 (C**8**), 50.0 (C**5**), 44.5 (C**3**), 43.0 (C**1**), 24.1 (C**4**), 10.8 (C**6**), 2.3 (C**7**).

IR *vmax*/cm^{-1}: 3004 (w), 1708 (s), 1383 (m), 1339 (m), 1177 (m), 696 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{16}ClNNaO_2$ [$(M+Na)^+$] 312.0762, found 312.0760.

(1*S**,5*R**,7*R**)-3-Benzyl-1-chloro-7-propyl-3-azabicyclo[3.2.0]heptane-2,4-dione **408**



13:1

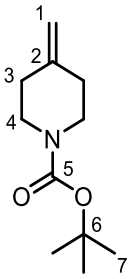
^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.48 – 7.28 (5H, m, 5 x **Ar**-H), 4.84 – 4.68 (2H, m, C**1**-H_2), 3.32 (1H, dd, *J* = 10.5, 6.0 Hz, C**3**-H), 2.97 (1H, dtd, *J* = 10.5, 8.5, 7.0 Hz, C**5**-H), 2.84 (1H, dt, *J* = 12.5, 10.5 Hz, C**4**-HH), 1.63 – 1.54 (2H, m, C**6**-HH), 1.49 (1H, ddd, *J* = 12.5, 8.0, 6.0 Hz, C**4**-HH), 1.35 (1H, dddd, *J* = 15.5, 14.0, 8.0, 3.5 Hz, C**7**-HH), 1.30 – 1.21 (1H, m, C**7**-HH), 1.13 – 1.04 (1H, m, C**6**-HH), 0.85 (3H, t, *J* = 7.5 Hz, C**8**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 175.8 (C**2**), 172.9 (C**10**), 135.4 (**Ar**), 128.8 (**Ar**), 128.7 (**Ar**), 128.2 (**Ar**), 62.7 (C**9**), 46.0 (C**5**), 44.9 (C**3**), 42.9 (C**1**), 34.0 (C**6**), 26.9 (C**4**), 19.7 (C**7**), 13.8 (C**8**).

IR *vmax*/cm^{-1}: 2958 (w), 1709 (s), 1383 (m), 1340 (m), 1175 (m), 698 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{18}ClNNaO_2$ $[(M+Na)^+]$ 314.0918, found 314.0914.

tert-Butyl 4-methylenepiperidine-1-carboxylate **409**



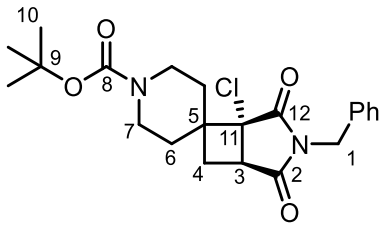
In a flame dried two-neck round bottomed flask, a solution of dry THF (100 mL) and methyltriphenylphosphonium bromide (10.80 g, 30.00 mmol) was made under a nitrogen atmosphere. To this, *n*-butyllithium (2.5 M in hexanes, 12 mL, 30 mmol) was added dropwise at –78 °C over 5 minutes and left to stir for 1 hour. To this solution, *N*-boc-piperidone was added before being allowed to warm to r.t. and subsequently stirred for 16 hours. The solvent was concentrated *in vacuo* and the residue was purified by column chromatography (petroleum ether/ethyl acetate: 70/30) to give the title compound (1.86 g, 31%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.76 (2 H, q, *J* = 1.0, C**1**-H_2), 3.48 – 3.40 (4 H, m, C**4**-H_2 x2), 2.20 (4 H, ddt, *J* = 6.5, 4.5, 1.0, C**3**-H_2 x2), 1.49 (9 H, s, C**7**-H_3 x3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 154.8 (C**5**), 145.5 (C**2**), 109.0 (C**1**), 79.5 (C**6**), 45.4 (C**4**), 34.5 (C**3**), 28.5 (C**7**).

All recorded data match literature values.[182]

tert-Butyl (1*R**,5*R**)-3-benzyl-5-chloro-2,4-dioxo-3-azaspiro[bicyclo[3.2.0]heptane-6,4'-piperidine]-1'-carboxylate **410**



General procedure 3 – Syringe Pump. Using crude **350** (5.6 mmol), ITX (16 mg, 0.06 mmol), and 1-boc-4-methylenepiperidine (1.86 g, 9.42 mmol). 1-Boc-4-methylenepiperidine was added over 90 minutes under UVA irradiation, and irradiation was continued for a further 90 minutes. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 95/5 to 90/10) gave the title compound (1.17 g, 45%) as a yellow oil, and the regioisomeric product (581 mg, 22%).

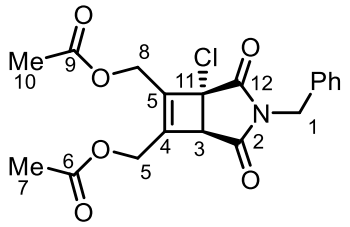
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 – 7.16 (5H, m, 5 x **Ar**-H), 4.74 – 4.54 (2H, m, C**1**-H_2), 3.94 – 3.69 (1H, m, C**7**-HH), 3.71 – 3.57 (1H, m, C**7**-HH), 3.29 – 3.18 (1H, m, C**3**-H), 3.12 – 2.85 (1H, m, C**7**-HH), 2.63 (1H, ddd, *J* = 14.0, 10.5, 3.0 Hz, C**7**-HH), 2.47 – 2.37 (1H, m, C**4**-HH), 1.88 – 1.78 (1H, m, C**6**-HH), 1.71 – 1.51 (3H, m, C**4**-HH, C**6**-H_2), 1.37 (9H, s, C**10**-H_3), 1.04 (1H, dddd, C**6**-HH).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.6 (C**2**), 173.0 (C**12**), 154.5 (C**8**), 135.2 (**Ar**), 128.8 (**Ar**), 128.8 (**Ar**), 128.3 (**Ar**), 79.9 (C**9**), 67.0 (C**11**) and (C**5**), 43.5 (C**3**), 43.0 (C**1**), 39.7 (C**7**), 34.0 (C**6**), 32.5 (C**4**), 28.4 (C**10**).

IR *vmax*/cm^{-1}: 2974 (w), 2938 (w), 1712 (s), 1687 (s), 1171 (m), 732 (s), 698 (s).

HRMS (ESI) m/z calcd for $C_{22}H_{27}ClN_2NaO_4$ [$(M+Na)^+$] 441.1552, found 441.1563.

((1*R**,5*R**)-3-Benzyl-1-chloro-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-ene-6,7-diyl)bis(methylene) diacetate **412**



General Procedure 3 – Batch. Using crude **350** (16.9 mmol), ITX (48 mg, 0.19 mmol), and 1,4-butynediol (4.86 g, 56.4 mmol). The reaction was exposed to UVA irradiation for 90 minutes. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 50/50) gave the cyclobutene alcohol **411** (2.38 g, 41%) as an orange oil.

To a solution of the cyclobutene alcohol **411** (2.38 g, 7.73 mmol) in DCM (31 mL) at r.t. was added 4-(dimethylamino)pyridine (94 mg, 0.77 mmol) and pyridine (0.62 mL, 7.73 mmol). The solution was stirred for 5 minutes before adding acetic anhydride (1.47 mL, 15.46 mmol) and stirring at r.t. for a further 16 hours. The solution was quenched with 1 M HCl (10 mL) and extracted with DCM (3 × 10 mL). The organic layers were combined and dried over $MgSO_4$, and the solvent was concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) gave the title compound (1.71 g, 56%) as an orange oil.

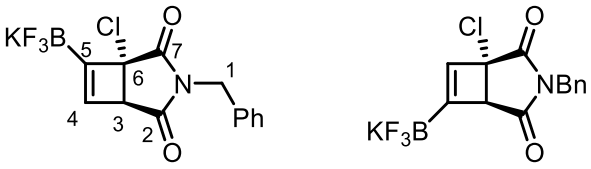
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.29 (5H, m, **Ar**-H x 5), 4.87 – 4.61 (6H, m, C**1**-H_2, C**5**-H_2, C**8**-H_2), 2.08 (3H, s, C**7**-H_3), 2.02 (3H, s, C**10**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.5 (C**2**), 170.3 (C**12**), 170.2 (C**6**), 169.9 (C**9**), 142.5 (C**4**), 141.4 (C**5**), 134.9 (**Ar**), 128.8 (**Ar**), 128.3 (**Ar**), 128.1 (**Ar**), 61.0 (C**11**), 58.2 (C**5**), 56.2 (C**8**), 54.8 (C**3**), 42.8 (C**1**), 20.5 (C**7**), 20.4 (C**10**).

IR *vmax*/cm^{-1}: 2977 (w), 1743 (m), 1711 (s), 1213 (s), 1027 (m), 699 (m).

HRMS (ESI) m/z calcd for $C_{19}H_{18}ClNNaO_6$ [$(M+Na)^+$] 414.0715, found 414.0730.

(1*R**,5*R**)-3-Benzyl-1-chloro-7-(trifluoro-l4-boraneyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione, potassium salt **418**



1:1 r.r.

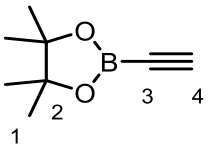
General Procedure 3 – Batch. Using crude **350** (6.90 mmol), ITX (20 mg, 0.08 mmol), and alkyne **417** (1.50 g, 11.5 mmol). The reaction was exposed to UVA irradiation for 90 minutes. Purification by trituration in MeCN/petrol, filtration and solvent removed from the solute gave the title compound (1.74 g, 64%) as a beige solid.

^{1}H NMR (400 MHz, DMSO) δ_{H} (*mixture of regioisomers reported*) 7.37 – 7.13 (5H, m, 5 x **Ar**-H), 6.33 (1H, m, C**4**-H), 4.65 – 4.47 (2H, m, C**1**-H_2), 3.79 (1H, s, C**3**-H).

^{13}C NMR (125 MHz, DMSO) δ_{C} (*mixture of regioisomers reported*) 174.1 (C**2**), 172.9 (C**2**), 172.3 (C**7**), 136.9 (C**5**), 136.5 (C**5**), 136.4 (**Ar**), 136.3 (**Ar**), 129.0 (**Ar**), 127.9 (C**4**), 127.5 (C**4**), 127.5 (**Ar**), 64.9 (C**6**), 62.8 (C**6**), 57.1 (C**3**), 55.7 (C**3**), 41.6 (C**1**), 31.2 (C**1**).

IR *vmax*/cm^{-1}: 3280 (w), 1701 (m), 1388 (m), 1027 (m), 971 (s).

2-Ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **420**



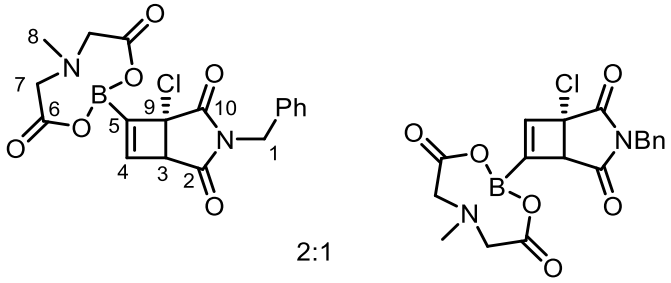
In a dual necked, flame dried round bottomed flask, a suspension of compound **417** (1.00 g, 7.56 mmol), 2,2,4,4,5,5,7,7-octamethyl-3,6-dioxa-2,7-disilaoctane (1.99 g, 7.56 mmol), and dry acetone (7.6 mL) was made under a nitrogen atmosphere. Trimethylsilyl chloride (1.91 mL, 15.15 mmol) was added and the solution was left to stir at r.t. over 16 hours. *While maintaining a nitrogen atmosphere,* the solids formed were filtered through a frit and the filtrate was concentrated *in vacuo*. The crude product was distilled by Kugelrhor distillation at 50°C, 5 mBar using a dry ice/acetone trap to give the title compound (965 mg, 84%) as a clear oil. The compound was stored in a freezer after being flushed with nitrogen.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.51 (1 H, s C**4**-H), 1.31 (12 H, s, 4 x C**1**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 90.1 (C**3**), 84.6 (C**2**), 57.3 (C**4**), 24.6 (C**1**).

All recorded data match literature values.[183]

2-((5*R**)-3-Benzyl-5-chloro-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione **422**



General procedure 3 – Batch. Using crude **350** (1.69 mmol), ITX (4.6 mg, 0.02 mmol), and a solution of 2-ethynyl-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (1.00 g, 5.64 mmol) in DMSO (2 mL). The reaction was exposed to UVA irradiation for 90 minutes. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (350 mg, 46%) as a beige solid.

1H NMR (500 MHz, $CDCl_3$) δ_H (*mixture of regioisomers reported*) 7.45 – 7.31 (5H, m, 5 x **Ar**-H), 7.11 – 6.85 (1H, m, C**4**-H), 4.90 – 4.53 (2H, m, C**1**-H_2), 3.96 – 3.64 (7H, m, 2 x C**7**-H_2, C**8**-H_3), 3.35 – 3.11 (1H, m, C**3**-H).

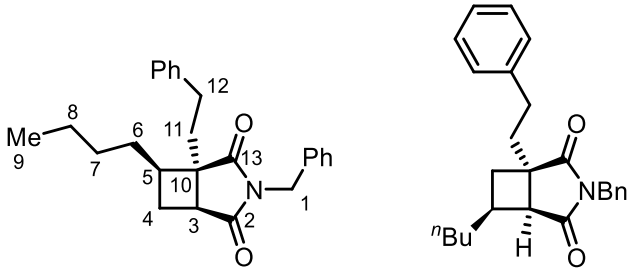
13C NMR (125 MHz, $CDCl_3$) δ_C (*mixture of regioisomers reported*) 173.5 (C**2**), 172.1 (C**2**), 171.2 (C**10**), 170.2 (C**10**), 166.4 (C**6**), 166.2 (C**6**), 166.1 (C**6**), 165.8 (C**6**), 161.5 (C**5**), 148.7 (C**4**), 135.1 (**Ar**), 134.1 (**Ar**), 129.4 (**Ar**), 128.9 (**Ar**), 128.9 (**Ar**), 128.8 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 62.0 (C**7**), 61.5 (C**7**), 61.4 (C**7**), 60.4 (C**7**), 56.5 (C**9**), 55.3 (C**9**), 47.6 (C**3**), 47.5 (C**3**), 45.6 (C**8**), 45.5 (C**8**), 42.9 (C**1**), 42.8 (C**1**).

IR *vmax*/cm^{-1}: 3270 (br), 3011 (w), 2077 (w), 1765 (s), 1706 (s), 1277 (s), 1277 (s), 1152 (m), 1023 (s), 1007 (s), 701 (m).

HRMS (ESI) m/z calcd for $C_{18}H_{16}BClN_2NaO_6$ [$(M+Na)^+$] 425.0685, found 425.0671.

Mp ($CHCl_3$): *decomposed.*

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-phenethyl-3-azabicyclo[3.2.0]heptane-2,4-dione **428**



10:1 r.r.

General procedure 5. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), styrene (223 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2) gave the title compound (105 mg, 43%) as a colourless oil.

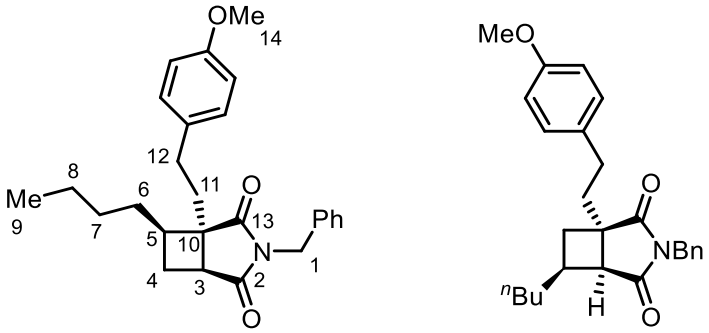
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.42 – 6.89 (10H, m, 5 x **Ar**-H), 4.71 – 4.48 (2H, m, C**1**-H_2), 2.65 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 2.61 – 2.49 (1H, m, C**4**-HH), 2.45 – 2.35 (2H, m, C**12**-H_2), 2.23 (2H, m, C**5**-H, C**11**-HH), 1.94 – 1.81 (1H, m, C**11**-HH), 1.54 – 1.33 (2H, m, C**6**-HH, C**4**-HH), 1.22 – 0.94 (4H, m, C**7**-H_2, C**8**-H_2), 0.91 – 0.80 (1H, m, C**6**-HH), 0.78 – 0.69 (3H, m, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.4 (C**2**), 179.2 (C**13**), 140.8 (**Ar**), 136.2 (**Ar**), 128.9 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.2 (**Ar**), 128.0 (**Ar**), 126.2 (**Ar**), 52.2 (C**10**), 42.4 (C**1**), 41.3 (C**5**), 39.1 (C**3**), 36.3 (C**11**), 32.4 (C**6**), 30.8 (C**12**), 29.1 (C**7**), 26.9 (C**4**), 22.4 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 2927 (w), 2857 (w), 1697 (s), 1388 (m), 1165 (m), 698 (s).

HRMS (ESI) m/z calcd for $C_{25}H_{29}NNaO_2$ [$(M+Na)^+$] 398.2090, found 398.2103.

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(4-methoxyphenethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **429**



12:1 r.r.

General Procedure 5 – Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), 4-vinylanisole (262 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2 to 95/5) gave the title compound (30 mg, 15%) as a colourless oil.

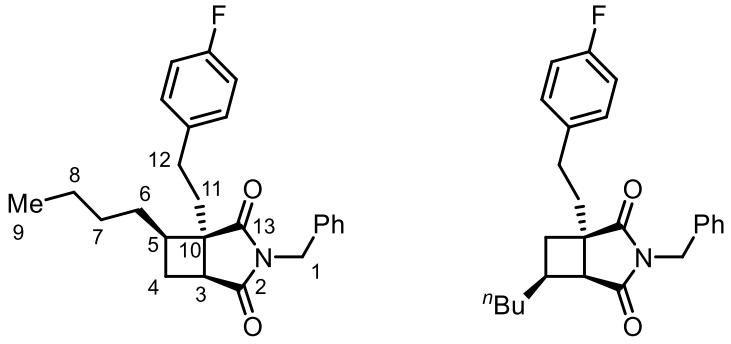
^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.44 – 7.47 (2H, m, 2 x **Ar**-H), 7.37 – 7.32 (2H, m, 2 x **Ar**-H), 7.32 – 7.27 (1H, m, **Ar**-H), 6.98 – 6.93 (2H, m, 2 x (MeO)-**Ar**-H), 6.81 – 6.75 (2H, m, 2 x (MeO)-**Ar**-H), 4.69 – 4.73 (2H, m, C**1**-H_2), 3.79 (3H, s, C**14**-H_3), 2.75 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 2.63 (1H, dd, *J* = 13.0, 10.0 Hz, C**4**-HH), 2.43 (2 H, dd, *J* 10.0, 7.5, C**12**-HH), 2.39 – 2.25 (2H, m, C**5**-H, C**11**-HH), 1.92 (1 H, ddd, *J* = 14.0, 9.0, 7.0 Hz, C**11**-HH), 1.50 (2H, m, C**4**-HH, C**6**-HH), 1.31 – 1.04 (5H, m, C**12**-HH, C**7**-H_2, C**8**-H_2), 1.01 – 0.85 (1H, m, C**6**-H), 0.82 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.4 (C**2**), 179.2 (C**13**), 158.0 (**Ar**), 136.2 (**Ar**), 132.8 (**Ar**), 129.1 (**Ar**), 129.0 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.0 (**Ar**), 113.9 (**Ar**), 113.7 (**Ar**), 55.3 (C**14**), 52.2 (C**10**), 42.4 (C**1**), 41.3 (C**5**), 39.0 (C**3**), 36.6 (C**11**), 32.4 (C**6**), 29.9 (C**12**), 29.1 (C**7**), 26.9 (C**4**), 22.4 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 2929 (w), 1696 (s), 1511 (m), 1387 (m), 1245 (m), 699 (s).

HRMS (ESI) m/z calcd for $C_{26}H_{32}NO_3$ $[(M+H)^+]$ 406.2377, found 406.2373.

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(4-fluorophenethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **430**



18:1 r.r.

General Procedure 5 – Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), 4-fluorostyrene (233 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (98/2 petroleum ether/ethyl acetate) gave the title compound (107 mg, 42%) as a colourless oil.

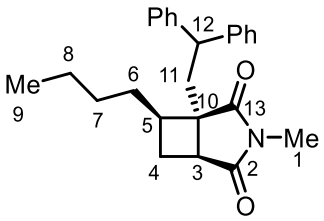
^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.49 – 7.29 (5H, m, 5 x **Ar**-H), 7.01 – 6.90 (4H, m, 4 x **Ar**-H), 4.68 – 4.72 (2H, m, C**1**-H_2), 2.76 (1H, dd, *J* = 10.5, 5.0 Hz, C**3**-H), 2.65 (1H, dd, *J* = 13.0, 10.0 Hz, C**4**-HH), 2.51 – 2.39 (2H, m, C**12**-H_2), 2.38 – 2.24 (2H, m, C**5**-H, C**11**-HH), 1.93 (1H, ddd, *J* = 14.0, 10.0, 6.5 Hz, C**11**-HH), 1.53 (1H, ddd, *J* = 12.5, 7.5, 5.0 Hz, C**4**-HH), 1.49 – 1.42 (1H, m, C**6**-HH), 1.23 – 1.06 (4H, m, C**7**-H_2, C**8**-H_2), 0.99 – 0.93 (1H, m, C**6**-HH), 0.82 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.3 (C**2**), 179.1 (C**13**), 162.4 (**Ar**), 160.4 (**Ar**), 136.1 (**Ar**), 129.6 (**Ar**), 129.5 (**Ar**), 128.9 (**Ar**), 128.6 (**Ar**), 128.0 (**Ar**), 115.4 (**Ar**), 115.2 (**Ar**), 52.1 (C**10**), 42.4 (C**1**), 41.3 (C**5**), 39.0 (C**3**), 36.5 (C**11**), 32.4 (C**6**), 30.0 (C**12**), 29.0 (C**7**), 26.9 (C**4**), 22.4 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 2928 (w), 1696 (s), 1508 (m), 1387 (m), 1218 (m), 680 (m).

HRMS (ESI) m/z calcd for $C_{25}H_{28}FNNaO_2$ [$(M+Na)^+$] 416.1996, found 416.2003.

(1*R**,5*S**,7*R**)-7-Butyl-1-(2,2-diphenylethyl)-3-methyl-3-azabicyclo[3.2.0]heptane-2,4-dione **431**



>20:1 r.r.

General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **398** (150 mg, 0.65 mmol, 12:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2) gave the title compound (149 mg, 61%) as a colourless solid.

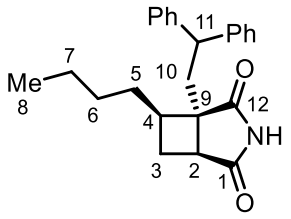
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.33 – 7.12 (10H, m, **Ar**-H x10), 3.98 (1H, dd, *J* = 9.0, 6.5, C**12**-H), 2.94 – 2.82 (4H, m, C**11**-HH, C**1**-H_3), 2.62 – 2.45 (2H, m, C**11**-HH, C**4**-HH), 2.45 – 2.31 (2H, m, C**3**-H, C**5**-H), 1.60 – 1.50 (1H, m, C**6**-HH), 1.46 (1H, ddd, *J* = 12.5, 7.5, 5.0 Hz, C**4**-HH), 1.30 – 1.11 (4H, m, C**7**-H_2, C**8**-H_2), 1.05 (1H, m, C**6**-HH), 0.87 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.7 (C**2**), 179.3 (C**13**), 143.6 (**Ar**), 143.6 (**Ar**), 128.8 (**Ar**), 128.5 (**Ar**), 127.6 (**Ar**), 127.6 (**Ar**), 127.0 (**Ar**), 126.6 (**Ar**), 52.2 (C**10**), 47.9 (C**12**), 42.3 (C**5**), 40.1 (C**11**), 39.0 (C**3**), 32.4 (C**6**), 29.1 (C**7**), 27.2 (C**4**), 24.6 (C**1**), 22.5 (C**8**), 14.0 (C**9**).

IR *vmax*/cm^{-1}: 3060 (w), 2956 (w), 2928 (w), 2871 (w), 1769 (w), 1699 (s), 1450 (w), 1428 (w), 1378 (w), 1272 (w), 1148 (w), 1056 (w).

HRMS (ESI) m/z calcd for $C_{25}H_{29}NNaO_2$ [(M+Na)$^+$] 398.2091, found 398.2097.

(1*R**,5*S**,7*R**)-7-Butyl-1-(2,2-diphenylethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **432**



>20:1 r.r.

General procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **399** (140 mg, 0.65 mmol, 11:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (90/10 toluene/petroleum ether to remove the catalyst, followed by 90/10 petroleum ether/ethyl acetate) gave the title compound (131 mg, 56%) as a clear colourless oil.

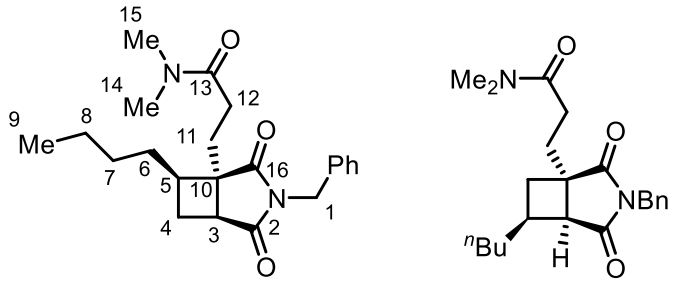
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.34 (1H, s, N-H), 7.24 – 7.03 (10H, m, 10 x **Ar**-H), 3.95 (1H, dd, *J* = 10.0, 5.5 Hz, C**11**-H), 2.72 (1H, dd, *J* = 14.0, 5.5 Hz, C**10**-HH), 2.51 – 2.35 (2H, m, C**10**-HH, C**3**-HH), 2.27 (1H, tdd, *J* = 13.0, 7.0, 3.5 Hz, C**4**-H), 2.15 (1H, dd, *J* = 10.5, 5.5 Hz, C**2**-H), 1.51 (2H, m, C**5**-HH, C**3**-HH), 1.21 – 1.02 (5H, m, C**5**-HH, C**6**-H_2, C**7**-H_2), 0.77 (3H, t, *J* = 7.0 Hz, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 179.9 (C**1**), 179.9 (C**12**), 143.9 (**Ar**), 143.5 (**Ar**), 129.0 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 127.6 (**Ar**), 127.1 (**Ar**), 126.6 (**Ar**), 53.8 (C**9**), 47.9 (C**11**), 42.2 (C**3**), 40.2 (C**2**), 40.2 (C**10**), 32.4 (C**5**), 29.1 (C**6**), 27.4 (C**4**), 22.5 (C**7**), 14.0 (C**8**).

IR *vmax*/cm^{-1}: 3214 (br), 3061 (w), 2955 (w), 2928 (m), 1772 (m), 1708 (s), 1493 (w), 1451 (w), 1341 (w), 1171 (w),1082 (w).

HRMS (ESI) m/z calcd for $C_{24}H_{27}NNaO_2$ [(M+Na)$^+$] 384.1934, found 384.1930.

3-((1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-2,4-dioxo-3-azabicyclo[3.2.0]heptan-1-yl)-*N*,*N*-dimethylpropanamide **433**



11:1 r.r.

General procedure 5. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), *N,N*-dimethyl acrylamide (201 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10, to remove the catalyst, followed by petroleum ether/ethyl acetate: 90/10 to 50/50) gave the title compound (156 mg, 65%) as a colourless oil.

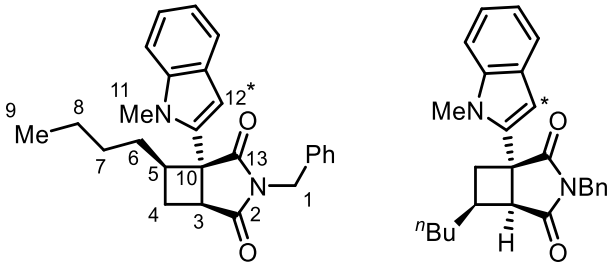
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.44 – 7.23 (5H, m, 5 x **Ar**-H), 4.63 – 4.72 (2H, m, C**1**-H_2), 2.94 – 2.85 (4H, m, C**3**-H, C**14**-H_3), 2.78 (3H, s, C**15**-H_3), 2.66 (1H, dd, *J* = 13.0, 10.0 Hz, C**4**-HH), 2.36 (1H, dd, *J* = 9.5, 7.5 Hz, C**5**-H), 2.28 – 2.16 (1H, m, C**11**-HH), 2.16 – 2.00 (3H, m, C**12**-H_2, C**11**-HH), 1.52 (1 H, ddd, *J* = 12.5, 7.5, 5.0 Hz, C**4**-HH), 1.47 – 1.39 (1H, m, C**6**-HH), 1.20 – 1.06 (4H, m, C**7**-H_2, C**8**-H_2), 1.00 – 0.86 (1H, m, C**6**-HH), 0.83 – 0.77 (3H, m, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.4 (C**2**), 179.3 (C**16**), 171.5 (C**13**), 136.3 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 51.5 (C**10**), 42.4 (C**5**), 41.0 (C**3**), 39.2 (C**15**), 37.0 (C**14**), 35.5 (C**6**), 32.5 (C**11**), 29.9 (C**7**), 29.0 (C**12**), 27.9 (C**1**), 26.8 (C**4**), 22.4 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 3454 (w), 2928 (m), 1738 (m), 1694 (s), 1643 (s), 1387 (m), 1166 (w), 699 (m).

HRMS (ESI) m/z calcd for $C_{22}H_{30}N_2NaO_3$ [$(M+Na)^+$] 393.2149, found 393.2156.

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(1-methyl-1*H*-indol-2-yl)-3-azabicyclo[3.2.0]heptane-2,4-dione **434**



60:40 C2:C3

20:1 r.r.

General procedure 5. Using chlorocyclobutane **360** (200 mg, 0.65 mmol, 10:1 r.r.), *N*-methylindole (812 µL, 6.50 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%), and MeCN/water (4:1, 2.0 mL), with a reaction time of 6 hours. Purification by column chromatography (95/5 to 90/10 petroleum ether/ethyl acetate) gave the title compound (52 mg, 20%) as an orange oil.

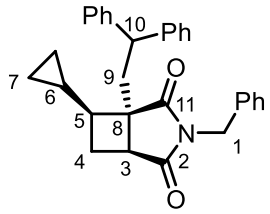
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.50 – 6.80 (9H, m, 9 x **Ar**-H), 5.90 – 5.85 (1H, m, C**12**-H), 4.82 – 4.57 (2H, m, C**1**-H_2), 3.65 (3H, s, C**11**-H_3), 3.61 – 3.52 (1H, s, C**3**-H), 3.27 – 3.11 (1H, m, C**5**-H), 2.75 – 2.62 (1H, m, C**4**-HH), 1.89 – 1.79 (1H, m, C**6**-HH), 1.71 – 1.56 (1H, m, C**4**-HH), 1.29 – 0.97 (5H, m, C**6**-HH, C**7**-H_2, C**8**-H_2), 0.88 – 0.70 (3H, m, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 179.8 (C**2**), 177.7 (C**13**), 137.1 (**Ar**), 136.0 (**Ar**), 130.6 (**Ar**), 129.0 (**Ar**), 129.0 (**Ar**), 127.9 (**Ar**), 126.6 (**Ar**), 122.1 (**Ar**), 121.5 (**Ar**), 119.5 (**Ar**), 117.5 (**Ar**), 112.3 (**Ar**), 109.8 (**Ar**), 109.2 (**Ar**), 99.1 (C**12**), 55.8 (C**10**), 42.8 (C**1**), 41.8 (C**3**), 40.7 (C**5**), 33.2 (C**11**), 33.0 (C**6**), 29.0 (C**7**), 27.5 (C**4**), 22.5 (C**8**), 14.0 (C**9**).

IR *vmax*/cm^{-1}: 2930 (w), 1738 (m), 1698 (s), 1348 (m), 1261 (m), 745 (m), 699 (m).

HRMS (ESI) m/z calcd for $C_{26}H_{28}N_2NaO_2$ [$(M+Na)^+$] 423.2043, found 423.2051.

(1*R**,5*S**,7*S**)-3-Benzyl-7-cyclopropyl-1-(2,2-diphenylethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **435**



>20:1 r.r.

General procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **407** (188 mg, 0.65 mmol, >20:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (98/2 petroleum ether/ethyl acetate) gave the title compound (223 mg, 79%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 – 7.67 (2H, m, 2 x **Ar**-H), 7.62 – 7.26 (11H, m, 11 x **Ar**-H), 7.10 – 6.97 (2H, m, 2 x **Ar**-H), 4.88 – 4.68 (2H, m, C**1**-H_2), 3.98 (1H, dd, *J* = 10.5, 5.0 Hz, C**10**-H), 3.02 (1H, dd, *J* = 14.0, 5.0 Hz, C**9**-HH), 2.70 – 2.49 (2H, m, C**9**-HH, C**4**-HH), 2.33 – 2.15 (2H, m, C**3**-H, C**5**-H), 1.58 (1H, ddd, *J* = 12.5, 7.5, 5.0 Hz, C**4**-HH), 0.80 – 0.69 (1H, m, C**6**-H), 0.61 (1H, dddd, *J* 9.0, 8.0, 5.5, 4.5, C**7**-HH), 0.39 (1H, dddd, *J* = 9.0, 8.0, 6.0, 4.5, C**7**-HH), 0.24 – 0.13 (1H, m, C**7**-HH), -0.01 (1H, dd, *J* = 10.0, 5.0, C**7**-HH).

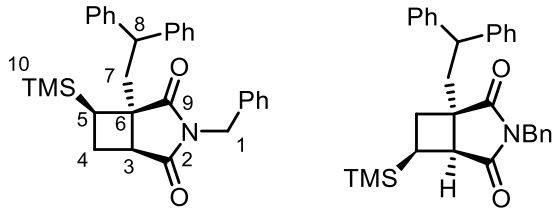
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 178.9 (C**11**, C**2**), 144.1 (**Ar**), 143.2 (**Ar**), 136.1 (**Ar**), 129.6 (**Ar**), 128.9 (**Ar**), 128.6 (**Ar**), 128.4 (**Ar**), 128.1 (**Ar**), 127.7 (**Ar**), 127.4 (**Ar**), 126.9 (**Ar**), 126.4 (**Ar**), 52.7 (C**8**), 47.8 (C**10**), 46.5 (C**5**), 42.4 (C**1**), 40.1 (C**9**), 38.7 (C**3**), 24.5 (C**4**), 11.5 (C**6**), 2.6 (C**7**), 2.1 (C**7**).

IR *vmax*/cm^{-1}: 3023 (w), 2931 (m), 1738 (s), 1690 (m), 1350 (m), 695 (m).

HRMS (ESI) m/z calcd for $C_{30}H_{29}NNaO_2$ [$(M+Na)^+$] 458.2090, found 458.2112.

Mp ($CHCl_3$): 122–125 °C.

(1*R**,5*S**,7*R**)-3-Benzyl-1-(2,2-diphenylethyl)-7-(trimethylsilyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **435**



4:1 r.r.

General Procedure 5 – Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **397** (209 mg, 0.65 mmol, 4:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 99.5/0.5) gave the title compound (83 mg, 27%) as a colourless oil.

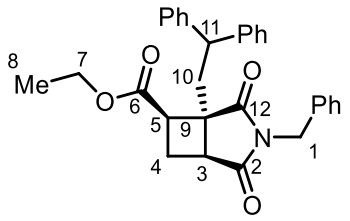
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.70 – 7.08 (13H, m, 13 x **Ar**-H), 6.85 – 6.69 (2H, m, 2 x **Ar**-H), 4.83 – 4.58 (2H, m, C**1**-H_2), 3.70 (1H, dd, *J* = 11.0, 4.0 Hz, C**8**-H), 2.74 (1H, dd, *J* = 14.0, 4.0 Hz, C**7**-HH), 2.61 (1H, dd, *J* = 14.0, 11.5, C**7**-HH), 2.49 (1H, dd, *J* = 12.5, 11.0, C**4**-HH), 2.33 – 2.25 (1H, m, C**3**-H), 2.00 (1H, dd, *J* = 11.0, 9.5 Hz, C**5**-H), 1.74 (1H, ddd, *J* = 12.5, 9.0, 5.0 Hz, C**4**-HH), 0.00 (9H, m, 3 x C**10**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 180.6 (C**2**), 178.8 (C**9**), 144.3 (**Ar**), 143.0 (**Ar**), 136.0 (**Ar**), 130.0 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 127.7 (**Ar**), 127.2 (**Ar**), 126.9 (**Ar**), 126.4 (**Ar**), 50.2 (C**6**), 47.7 (C**8**), 42.6 (C**1**), 42.0 (C**7**), 41.7 (C**3**), 32.0 (C**5**), 21.8 (C**4**), -3.2 (C**10**).

IR *vmax*/cm^{-1}: 2969 (w), 2950 (m), 1710 (s), 1384 (m), 1341 (m), 836 (m), 697 (s).

HRMS (ESI) m/z calcd for $C_{30}H_{33}NNaO_2Si$ [$(M+Na)^+$] 490.2173, found 490.2190.

Ethyl (1*S**,5*S**,6*R**)-3-benzyl-5-(2,2-diphenylethyl)-2,4-dioxo-3-azabicyclo[3.2.0]heptane-6-carboxylate **436**



>20:1 r.r.

General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **401** (209 mg, 0.65 mmol, 4:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10, to remove the catalyst, followed by petroleum ether/ethyl acetate: 90/10 to 80/20) gave the title compound (200 mg, 66%) as a clear colourless oil.

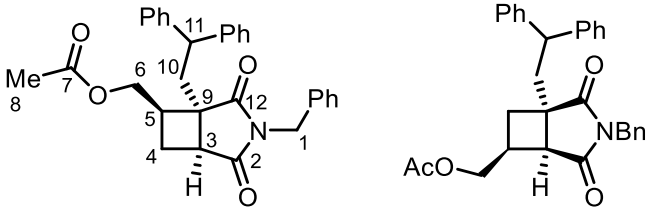
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49 – 6.96 (13H, m, 13 x **Ar**-H), 6.71 – 6.56 (2H, m, 2 x **Ar**-H), 4.66 – 4.42 (2H, m, C**1**-H_2), 4.08 – 3.92 (2H, m, C**7**-H_2), 3.62 – 3.53 (1H, m, C**11**-H), 3.19 – 3.06 (1H, m, C**3**-H), 2.83 (1H, ddd, *J* = 14.0, 4.5, 3.0 Hz, C**10**-HH), 2.60 – 2.45 (1H, m, C**10**-HH), 2.36 – 2.27 (1H, m, C**4**-HH), 2.21 – 2.08 (1H, m, C**4**-HH), 2.04 (1H, dd, *J* = 10.0, 5.5 Hz, C**5**-H), 1.15 (3H, t, *J* = 7.0 Hz, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.7 (C**2**), 177.4 (C**12**), 170.8 (C**6**), 143.8 (**Ar**), 142.7 (**Ar**), 135.9 (**Ar**), 129.5 (**Ar**), 129.0 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.2 (**Ar**), 127.6 (**Ar**), 127.2 (**Ar**), 127.1 (**Ar**), 126.6 (**Ar**), 61.3 (C**7**), 52.1 (C**9**), 47.6 (C**11**), 44.8 (C**3**), 42.8 (C**1**), 40.2 (C**10**), 39.1 (C**5**), 23.0 (C**4**), 14.2 (C**8**).

IR *vmax*/cm^{-1}: 3028 (w), 2931 (w), 1698 (s), 1390 (m), 1199 (m), 697 (s).

HRMS (ESI) m/z calcd for $C_{30}H_{29}NNaO_4$ [(M+Na)$^+$] 490.1989, found 490.2002.

((1*S**,5*R**,6*R**)-3-Benzyl-5-(2,2-diphenylethyl)-2,4-dioxo-3-azabicyclo[3.2.0]heptan-6-yl)methyl acetate **437**



3:1 r.r.

General procedure 5 – Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **405** (209 mg, 0.65 mmol, 4:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (90/10 toluene/petroleum ether to remove the catalyst, followed by petroleum ether/ethyl acetate: 90/10 to 70/30) gave the title compound (200 mg, 67%) as a colourless solid.

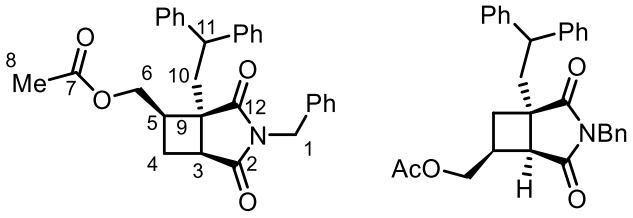
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.42 – 7.46 (2H, m, *J* 7.0, 1.5, 2 x **Ar**-H), 7.34 – 6.97 (12H, m, 12 x **Ar**-H), 6.74 – 6.60 (2H, m, 2 x **Ar**-H), 4.63 – 4.45 (3H, m, C**1**-H$_2$), 3.94 (1H, dd, *J* = 12.0, 6.5 Hz, C**6**-H), 3.80 (1H, dd, *J* = 12.0, 5.5 Hz, C**6**-H), 3.62 (1H, dd, *J* = 10.5, 4.5 Hz, C**11**-H), 2.76 – 2.69 (1H, m, C**10**-HH), 2.68 – 2.56 (1H, m, C**5**-H), 2.46 – 2.31 (2H, m, C**10**-HH, C**4**-HH), 2.04 (1H, dd, *J* = 10.0, 5.5 Hz, C**3**-H), 1.86 (3H, s, C**8**-H$_3$), 1.57 (1H, ddd, *J* = 13.0, 8.0, 5.5 Hz, C**4**-HH).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 178.3 (C**2**), 178.2 (C**12**), 170.5 (C**7**), 143.9 (**Ar**), 142.9 (**Ar**), 136.0 (**Ar**), 129.6 (**Ar**), 129.5 (**Ar**), 129.1 (**Ar**), 128.9 (**Ar**), 128.9 (**Ar**), 128.8 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 127.7 (**Ar**), 127.4 (**Ar**), 127.3 (**Ar**), 127.0 (**Ar**), 126.5 (**Ar**), 63.4 (C**6**), 50.9 (C**9**), 47.5 (C**1**), 42.6 (C**11**), 40.4 (C**10**), 40.4 (C**5**), 39.0 (C**3**), 23.7 (C**4**), 20.7 (C**8**).

IR *vmax*/cm^{-1}: 2934 (br), 1741 (m), 1698 (s), 1391 (m), 1235 (m), 702 (m).

HRMS (ESI) m/z calcd for $C_{30}H_{30}NO_4$ [(M+H)$^+$] 468.2169, found 468.2169.

((1*S**,5*R**,6*R**)-3-Benzyl-5-(2,2-diphenylethyl)-2,4-dioxo-3-azabicyclo[3.2.0]heptan-6-yl)methyl acetate **437**



3:1 r.r.

General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **405** (209 mg, 0.65 mmol, 4:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10, to remove the catalyst, followed by petroleum ether/ethyl acetate: 90/10 to 70/30) gave the title compound (200 mg, 67%) as a colourless solid.

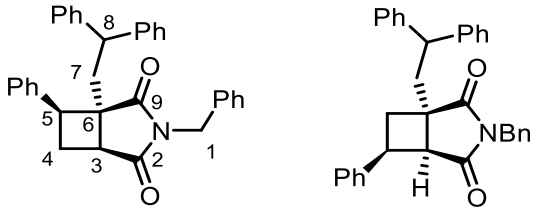
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.50 – 6.95 (13H, m, 13 x **Ar**-H), 6.71 – 6.61 (2H, m, 2 x **Ar**-H), 4.62 – 4.44 (2H, m, C**1**-H_2), 3.99 – 3.77 (2H, m, C**6**-H_2), 3.61 (1H, dd, *J* = 10.5, 4.5 Hz, C**11**-H), 2.79 – 2.68 (1H, m, C**10**-HH), 2.65 – 2.55 (1H, m, C**3**-H), 2.48 – 2.31 (2H, m, C**10**-HH, C**4**-HH), 2.03 (1H, dd, *J* = 10.0, 5.5 Hz, C**5**-H), 1.87 (3H, s, C**8**-H_3), 1.57 (1H, ddd, *J* = 13.0, 8.0, 5.5 Hz, C**4**-HH).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 178.3 (C**2**), 178.2 (C**12**), 170.6 (C**7**), 143.9 (**Ar**), 142.9 (**Ar**), 136.0 (**Ar**), 129.6 (**Ar**), 128.9 (**Ar**), 128.8 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 127.7 (**Ar**), 127.1 (**Ar**), 126.5 (**Ar**), 63.4 (C**6**), 50.9 (C**9**), 47.5 (C**11**), 42.6 (C**1**), 40.4 (C**3**), 40.3 (C**10**), 39.0 (C**5**), 23.7 (C**4**), 20.7 (C**8**).

IR *vmax*/cm^{-1}: 3028 (w), 2931 (w), 1698 (s), 1390 (m), 1199 (m), 697 (s).

HRMS (ESI) m/z calcd for $C_{30}H_{29}NNaO_4$ [$(M+Na)^+$] 490.1989, found 490.1994.

(1*R**,5*S**,7*S**)-3-Benzyl-1-(2,2-diphenylethyl)-7-phenyl-3-azabicyclo[3.2.0]heptane-2,4-dione **438**



6:1 r.r.

General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **403** (212 mg, 0.65 mmol, 7:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 98/2) gave the title compound (185 mg, 60%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.47 – 7.06 (15H, m, 15 x **Ar**-H), 6.90 (5H, dt, *J* = 7.5, 2.5, 5 x **Ar**-H), 4.47 (2H, d, *J* = 2.0, C**1**-H_2), 3.80 (1H, dd, *J* = 10.5, 5.0, C**8**-H), 3.71 (1H, dd, *J* = 10.0, 8.0 Hz, C**5**-H), 2.98 (1H, dd, *J* = 14.0, 5.0 Hz, C**7**-HH), 2.79 – 2.65 (2H, m, C**7**-HH, C**4**-HH), 2.30 (1H, dd, *J* = 10.0, 5.0 Hz, C**3**-H), 2.19 (1H, ddd, *J* = 13.0, 8.0, 5.0 Hz, C**4**-HH).

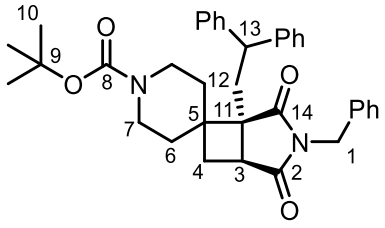
^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 178.5 (C**2**), 177.4 (C**9**), 143.9 (**Ar**), 143.1 (**Ar**), 137.6 (**Ar**), 136.0 (**Ar**), 129.7 (**Ar**), 129.0 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.1 (**Ar**), 127.8 (**Ar**), 127.4 (**Ar**), 127.3 (**Ar**), 127.2 (**Ar**), 127.1 (**Ar**), 126.5 (**Ar**), 54.9 (C**6**), 47.9 (C**8**), 47.6 (C**5**), 42.3 (C**1**), 40.7 (C**7**), 38.8 (C**3**), 25.4 (C**4**).

IR *vmax*/cm^{-1}: 3028 (w), 2931 (w), 1698 (s), 1390 (m), 1199 (m), 697 (s).

HRMS (ESI) m/z calcd for $C_{33}H_{29}NNaO_2$ [$(M+Na)^+$] 494.2090, found 494.2088.

Mp ($CHCl_3$): 107–110 °C.

tert-Butyl (1*S**,5*S**)-3-benzyl-5-(2,2-diphenylethyl)-2,4-dioxo-3-azaspiro[bicyclo[3.2.0]heptane-6,4'-piperidine]-1'-carboxylate **439**



General Procedure 5 - Photoredox-Catalysed Dechlorinative Functionalisations of Cyclobutanes. Using chlorocyclobutane **410** (272 mg, 0.65 mmol, >20:1 r.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10, to remove the catalyst, followed by petroleum ether/ethyl acetate: 90/10 to 80/20) gave the title compound (212 mg, 58%) as a yellow oil.

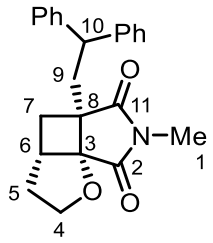
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62 – 7.10 (15H, m, 15 x **Ar**-H), 6.80 – 6.71 (1H, m, 1 x **Ar**-H), 4.70 – 4.53 (2H, m, C**1**-H_2), 4.00 (1H, d, *J* = 14.0 Hz, C**7**-HH), 3.80 (1H, d, *J* = 13.5, C**7**'-HH), 3.61 (1H, dd, *J* = 10.5, 4.5 Hz, C**13**-H), 2.74 (1H, t, *J* = 12.5 Hz, C**7**-HH), 2.69 – 2.59 (2H, m, C**12**-H_2), 2.59 – 2.46 (1H, m, C**7**-HH), 2.20 – 2.11 (2H, m, C**3**-H, C**4**-HH), 1.81 – 1.70 (1H, m, C**6**-HH), 1.70 – 1.58 (3H, m, C**6**-HH, C**4**-HH, C**6**'-HH), 1.45 (9H, s, C**10**-H_3 x3), 1.05 (1H, dd, *J* = 13.5, 2.5 Hz, C**6**'-HH).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 179.2 (C**2**), 178.8 (C**14**), 175.6 (C**8**), 154.5 (**Ar**), 144.2 (**Ar**), 142.9 (**Ar**), 136.0 (**Ar**), 129.7 (**Ar**), 129.0 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 127.7 (**Ar**), 127.2 (**Ar**), 127.1 (**Ar**), 126.4 (**Ar**), 79.7 (C**9**), 55.1 (C**11**), 47.5 (C**13**), 42.5 (C**1**), 41.2 (C**5**), 40.1 (C**7**), 39.4 (C**7**'), 37.7 (C**3**), 34.3 (C**6**), 33.8 (C**12**), 33.2 (C**6**'), 32.1 (C**4**), 28.4 (C**10**).

IR *vmax*/cm^{-1}: 3380 (Br), 2932 (w), 1696 (s), 1429 (m), 1264 (m), 1148 (m), 1072 (w), 961 (w), 702 (m).

HRMS (ESI) m/z calcd for $C_{36}H_{40}N_2NaO_4$ [$(M+Na)^+$] 587.2880, found 587.2855.

(3a*S**,4a*R**,7a*R**)-4a-(2,2-Diphenylethyl)-6-methyltetrahydrofuro[2',3':1,4]cyclobuta[1,2-c]pyrrole-5,7(2*H*,6*H*)-dione **440**



General Procedure 5 – Dechlorinative Functionalisation of Cyclobutanes. Using chlorocyclobutane **197** (140 mg, 0.65 mmol, >20:1 d.r.), 1,1-diphenylethylene (345 µL, 1.95 mmol), DIPEA (140 µL, 0.78 mmol), acetic acid (30 µL, 0.52 mmol), 4CzIPN (26 mg, 5 mol%) and MeCN/water (4:1, 2.0 mL), and stirred at r.t. for 6 hours. Purification *via* flash column chromatography (toluene/petroleum ether: 90/10, to remove the catalyst, followed by petroleum ether/ethyl acetate: 90/10 to 70/30) gave the title compound (221 mg, 94%) as a colourless powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28 – 7.19 (8H, m, 8 x **Ar**-H), 7.19 – 7.10 (2H, m, C**10**-H, 2 x **Ar**-H), 4.60 – 4.48 (1H, m, C**10**-H), 4.40 (1H, dd, *J* = 11.0, 4.5 HZ, C**4**-HH), 4.22 (1H, ddd, *J* = 10.5, 9.0, 6.0 Hz, C**4**-HH), 3.00 – 2.91 (1H, m, C**6**-H), 2.87 (1H, dd, *J* = 14.5, 11.0 Hz, C**9**-HH), 2.54 (3H, s, C**1**-H_3), 2.37 – 2.27 (2H, m, C**9**-HH, C**7**-HH), 2.08 (1H, ddt, *J* = 12.5, 10.5, 8.0 Hz, C**5**-HH), 1.81 (1H, ddt, *J* = 13.0, 6.0, 2.0 Hz, C**5**-HH), 1.65 (1H, dd, *J* = 13.5, 6.5 Hz, C**7**-HH).

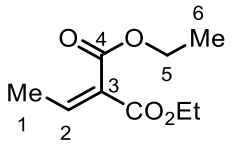
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 178.8 (C**2**), 175.6 (C**11**), 144.5 (**Ar**), 142.5 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 127.4 (**Ar**), 126.8 (**Ar**), 126.4 (**Ar**), 86.6 (C**3**), 72.2 (C**4**), 48.9 (C**8**), 46.9 (C**10**), 41.4 (C**6**), 37.5 (C**9**), 33.7 (C**7**), 31.3 (C**5**), 24.5 (C**1**).

IR *vmax*/cm-1: 3026 (w), 2941 (w), 1776 (w), 1705 (s), 1449 (m), 1377 (m), 1031(m), 702 (m).

HRMS (ESI) m/z calcd for $C_{23}H_{23}NNaO_3$ [$(M+Na)^+$] 384.1576, found 384.1563.

Mp ($CHCl_3$): 128-130 °C

Diethyl 2-ethylidenemalonate **457**



To a flame-dried dual-necked round bottomed flask, acetic anhydride (1.89 mL, 20 mmol), diethyl malonate (1.53 mL, 10 mmol) and lithium bromide (170 mg, 2.0 mmol) were stirred at 80 °C for 3 hours under a nitrogen atmosphere. The solution was allowed to cool to r.t. and acetaldehyde (1.68 mL, 30 mmol) was added. The solution was stirred at 80 °C for 4 hours under a nitrogen atmosphere. The solution was quenched with Na_2CO_3 *sat.* (25 mL), extracted with Et_2O (2 x 30 mL). The extracts were dried over anhydrous $MgSO_4$ and the solvent was concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (petrol/ethyl acetate: 9/1) to give the title compound (1.20 g, 67%) as a colourless oil.

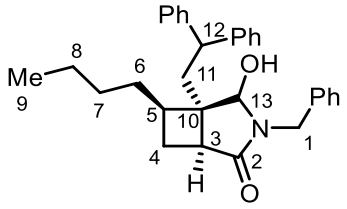
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, q, *J* = 7.3 Hz, C**2**-H), 4.30 (2H, q, *J* = 7.0 Hz, C**5**-H_2), 4.23 (2H, q, *J* = 7.0 Hz, C**5**-H_2), 1.95 (3H, d, *J* = 7.5 Hz, C**1**-H_3), 1.33 (3H, t, *J* = 7.0 Hz, C**6**-H_3), 1.28 (3H, t, *J* = 7.0 Hz, C**6**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C**4**), 163.9 (C**4**), 144.7 (C**1**), 129.7 (C**3**), 61.2 (C**5**), 15.5 (C**1**), 14.1 (C**6**).

IR *vmax*/cm^{-1}: 2964 (w), 1725 (s), 1370 (w), 1258 (s), 1221 (s), 1054 (m).

All recorded data match literature values.[184]

(1*S**,4*S**,5*R**,6*R**)-3-Benzyl-6-butyl-5-(2,2-diphenylethyl)-4-hydroxy-3-azabicyclo[3.2.0]heptan-2-one **459**

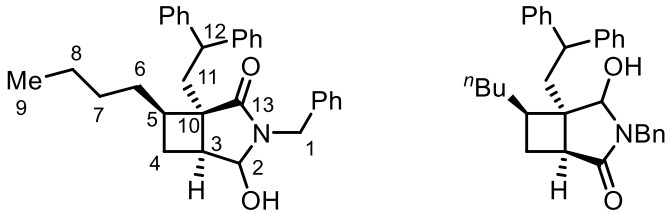


A solution of compound **361** (75 mg, 0.21 mmol) and $NaBH_4$ (12 mg, 0.32 mmol) in isopropyl alcohol (1.0 mL) and water (1.0 mL) was stirred at r.t. for 16 hours. The solution was diluted with ethyl acetate (20 mL) and washed with 1 M aqueous HCl (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10) gave the title compound (12 mg, 16%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.29 – 7.04 (15H, m, **Ar**-H x5), 4.83 (1H, d, *J* = 14.5 Hz, C**1**-HH), 4.17 (1H, d, *J* = 12.0 Hz, C**13**-H), 4.10 – 4.02 (1 H, m, C**12**-H), 3.96 (1 H, d, *J* = 14.5 Hz, C**1**-HH), 2.55 – 2.43 (2 H, m, C**11**-H_2), 2.20 (1 H, ddd, *J* = 11.5, 9.0, 9.0 Hz, C**4**-HH), 2.14 – 2.07 (1 H, m, C**5**-H), 2.00 (1 H, dd, *J* = 9.0, 6.5 Hz, C**3**-H), 1.57 – 1.50 (1 H, m, C**6**-HH), 1.16 – 0.90 (5H, m, C**8**-H_2, C**7**-H_2, C**6**-HH), 0.83 – 0.79 (1H, m, C**4**-HH), 0.77 (3H, t, *J* = 7.0, C**9**-H_3), 0.27 (1H, d, *J* = 12.0 Hz, C**13**-OH).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 174.6 (C**2**), 145.1 (**Ar**), 143.1 (**Ar**), 137.1 (**Ar**), 129.2 (**Ar**), 128.9 (**Ar**), 128.6 (**Ar**), 128.6 (**Ar**), 128.4 (**Ar**), 127.5 (**Ar**), 127.5 (**Ar**), 127.4 (**Ar**), 126.4 (**Ar**), 86.6 (C**13**), 52.8 (C**10**), 48.1 (C**12**), 43.7 (C**1**), 43.0 (C**11**), 40.7 (C**3**), 40.2 (C**5**), 32.0 (C**6**), 29.1 (C**7**), 28.1 (C**8**), 22.6 (C**4**), 14.0 (C**9**).

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(2,2-diphenylethyl)-4-hydroxy-3-azabicyclo[3.2.0]heptan-2-one **460**



10:1 r.r.

A solution of compound **361** (30 mg, 0.066 mmol) and $NaBH_4$ (13 mg, 0.33 mmol) in ethanol (0.6 mL) and water (0.4 mL) was stirred at 40 °C for 16 hours. The solution was diluted with ethyl acetate (20 mL) and washed with 1 M aqueous HCl (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the

solvent was concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 9/1) gave the title compound (22 mg, 72%) as a colourless solid.

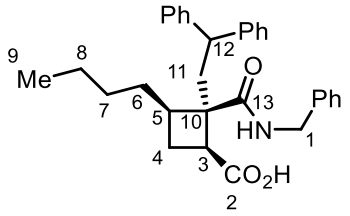
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.45 – 6.93 (13H, m, 13 x Ar-H), 6.73 – 6.67 (2H, m, 2 x Ar-H), 4.68 (1H, d, *J* = 14.0 Hz, C**1**-HH), 4.08 (1H, d, *J* = 14.0 Hz, C**1**-HH), 4.00 – 3.93 (1H, m, C**2**-H), 3.56 (1H, dd, *J* = 11.5, 4.0 Hz, C**12**-H), 2.53 (1H, dd, *J* = 14.0, 4.0, C**11**-HH), 2.38 (1H, dd, *J* = 14.0, 11.5 Hz, C**11**-HH), 2.11 – 1.97 (2H, m, C**3**-H, C**5**-H), 1.85 (1H, dt, *J* = 12.0, 9.0 Hz, C**4**-HH), 1.61 – 1.47 (1H, m, C**6**-HH), 1.38 (1H, ddd, *J* = 12.0, 9.0, 7.0 Hz, C**4**-HH), 1.24 – 1.04 (5H, m, C**6**-HH, C**7**-H_2, C**8**-H_2), 0.79 (3H, t, *J* = 7.0 Hz, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 174.4 (C**13**), 145.4 (**Ar**), 142.8 (**Ar**), 137.3 (**Ar**), 129.5 (**Ar**), 128.7 (**Ar**), 128.4 (**Ar**), 128.2 (**Ar**), 127.8 (**Ar**), 127.2 (**Ar**), 126.5 (**Ar**), 126.0 (**Ar**), 81.6 (C**2**), 53.9 (C**10**), 47.9 (C**12**), 43.5 (C**1**), 41.6 (C**11**), 40.9 (C**3**), 37.9 (C**5**), 31.9 (C**6**), 29.4 (C**7**), 22.7 (C**8**), 22.4 (C**4**), 14.1 (C**9**).

IR *vmax*/cm^{-1}: 3671 (br), 2921 (s), 1645 (w), 1451 (w), 1065 (m).

HRMS (ESI) m/z calcd for $C_{31}H_{35}NNaO_2$ [(M+Na)$^+$] 476.2560, found 476.2541.

(1*S**,2*R**,3*R**)-2-(Benzylcarbamoyl)-3-butyl-2-(2,2-diphenylethyl)cyclobutane-1-carboxylic acid **462**



>20:1 r.r.

A solution of compound **361** (50 mg, 0.11 mmol) and KOH (31 mg, 0.55 mmol) in ethanol (1.1 mL) was stirred at 60 °C for 4 hours. The solution was diluted with 1 M HCl until the solution reached pH 7. The solvent was concentrated *in vacuo* and the residue was diluted in ethyl acetate (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20 to 70/30) gave the title compound (42 mg, 81%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.02 (15 H, m, 5 x **Ar**-H), 5.42 (1H, dd, *J* = 7.0, 4.0 Hz, N-H), 4.47 – 4.33 (2H, m, C**1**-HH, C**12**-H), 3.54 (1H, dd, *J* = 14.5, 4.0 Hz, C**1**-HH), 2.94 (H, dd, *J* = 10.5, 9.0 Hz, C**3**-H), 2.70 (1H, dd, *J* = 15.0, 8.0 Hz, C**11**-HH), 2.56 (1H, dd, *J* = 15.0, 4.5 Hz, C**11**-HH), 2.33 – 2.02 (3H, m, C**4**-

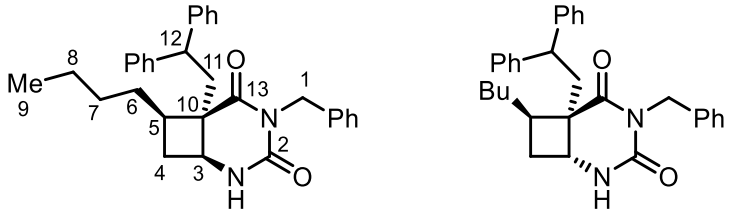
$\underline{H_2}$, C**5**-$\underline{H}$), 1.26 (1H, m, C**6**-$\underline{H}$H), 1.22 – 1.07 (4H, m, C**6**-$\underline{H}$H, C**7**-$\underline{H}$H, C**8**-$\underline{H_2}$), 1.04 – 0.94 (1H, m, C**7**-$\underline{H}$H), 0.80 (3H, t, *J* = 7.0 Hz, C**9**-$\underline{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 187.1 (C**2**) 172.2 (C**13**), 145.5 (**Ar**), 145.3 (**Ar**), 137.6 (**Ar**), 129.0 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 128.4 (**Ar**), 127.9 (**Ar**), 127.6 (**Ar**), 127.5 (**Ar**), 126.5 (**Ar**), 126.5 (**Ar**), 58.9 (C**10**), 47.3 (C**12**), 46.8 (C**11**), 44.8 (C**3**), 44.2 (C**5**), 43.9 (C**1**), 31.3 (C**6**), 29.1 (C**7**), 27.8 (C**4**), 22.6 (C**8**), 14.0 (C**9**).

IR *vmax*/cm^{-1}: 3375 (w), 2929 (m), 1717 (s), 1595 (m), 1544 (m), 1238 (m), 699 (s).

HRMS (ESI) m/z calcd for $C_{31}H_{35}NNaO_3$ [$(M+Na)^+$] 492.2509, found 492.2511.

(1*S**,6*R**,7*R**)-4-Benzyl-7-butyl-6-(2,2-diphenylethyl)-2,4-diazabicyclo[4.2.0]octane-3,5-dione **464**



7:1

To a solution of compound **462** (100 mg, 0.21 mmol) in dry toluene (2.1 mL) was added triethylamine (29 µL, 0.21 mmol), which upon addition the solution turned from to clear. The solution was heated to 70°C and diphenylphosphoryl azide (49 µL, 0.23 mmol) was added, and the solution was left to stir for 16 hours. The solution was quenched with NH_4Cl *sat.* (10 mL) and extracted with EtOAc (3 x 20 mL). The organic extracts were combined and dried over $MgSO_4$, filtered and the solvent was concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (29 mg, 30%) as a colourless oil.

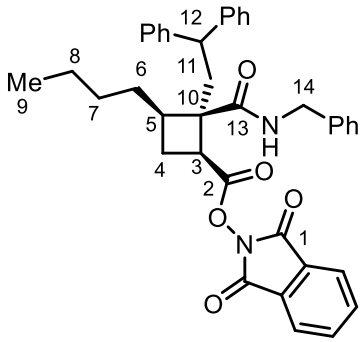
^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.54 – 7.01 (15H, m, 5 x **Ar**-$\underline{H}$), 4.96 – 4.73 (2H, m, C**1**-$\underline{H_2}$), 3.80 (1H, dd, *J* = 9.0, 6.0 Hz, C**12**-$\underline{H}$), 3.27 (1H, dd, *J* = 8.0, 5.0 Hz, C**3**-$\underline{H}$), 2.96 (1H, dd, *J* = 14.0, 6.0 Hz, C**11**-$\underline{H}$H), 2.42 – 2.27 (2H, m, C**11**-$\underline{H}$H, C**4**-$\underline{H}$H), 1.97 (1H, tdd, *J* = 10.0, 8.5, 5.5 Hz, C**5**-$\underline{H}$), 1.53 (1H, ddt, *J* 13.0, 10.0, 5.0 Hz, C**6**-$\underline{H}$H), 1.51 – 1.38 (1H, dd, *J* = 11.0, 8.5 Hz, C**4**-$\underline{H}$H), 1.27 – 1.04 (4H, m, C**7**-$\underline{H_2}$, C**8**-$\underline{H_2}$), 0.88 (1H, ddt, *J* = 13.0, 7.5, 4.0 Hz, C**6**-$\underline{H}$H), 0.83 (3H, t, *J* = 7.0 Hz, C**9**-$\underline{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 171.5 (C**13**), 152.9 (C**2**), 143.7 (**Ar**), 138.1 (**Ar**), 129.3 (**Ar**), 128.6 (**Ar**), 128.4 (**Ar**), 128.2 (**Ar**), 127.9 (**Ar**), 127.5 (**Ar**), 126.6 (**Ar**), 126.4 (**Ar**), 51.8 (C**10**), 48.0 (C**12**), 47.1 (C**3**), 45.4 (C**11**), 43.2 (C**1**), 42.3 (C**5**), 35.6 (C**4**), 31.9 (C**6**), 29.1 (C**7**), 22.6 (C**8**), 13.9 (C**9**).

IR *vmax*/cm^{-1}: 3385 (br), 3230 (br), 2923 (m), 2855 (w), 1717 (s), 1656 (s), 1493 (m), 1452 (m), 1435 (m), 1345 (m), 1220 (m), 1159 (m), 1078 (m).

HRMS (ESI) m/z calcd for $C_{31}H_{34}N_2NaO_2$ [(M+Na)$^+$] 489.2512, found 489.2491.

1,3-Dioxoisoindolin-2-yl (1*S**,2*R**,3*R**)-2-(benzylcarbamoyl)-3-butyl-2-(2,2-diphenylethyl)cyclobutane-1-carboxylate **465**



General Procedure 7. Compound **462** (100 mg, 0.21 mmol) was used. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) gave the title compound (37 mg, 33%) as a colourless cloudy oil.

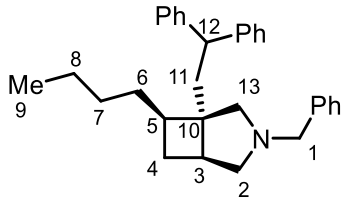
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.87 – 7.67 (4H, m, 4 x **Ar**-H), 7.33 – 6.99 (15H, m, 15 x **Ar**-H), 5.40 – 5.27 (1H, m, N-H), 4.53 – 4.43 (1H, m, C**14**-HH), 4.31 (1H, dd, *J* = 7.0, 4.5 Hz, C**12**-H), 3.67 (1H, dd, *J* = 14.0, 4.0 Hz, C**14**-HH), 3.12 (1H, dd, *J* = 10.0, 9.0 Hz, C**3**-H), 2.74 – 2.55 (2H, m, C**11**-H_2), 2.33 – 2.20 (2H, m, C**4**-H_2), 2.11 – 2.05 (1H, m, C**5**-H), 1.35 – 1.00 (5H, m, C**6**-H_2, C**7**-HH, C**8**-H_2), 0.93 – 0.87 (1H, m, C**7**-HH), 0.72 (3H, td, *J* = 7.0, 1.5 Hz, C**9**-H_3).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 170.0 (C**2**), 169.2 (C**13**), 161.9 (C**1**), 145.7 (**Ar**), 145.4 (**Ar**), 138.3 (**Ar**), 134.5 (**Ar**), 134.2 (**Ar**), 129.2 (**Ar**), 129.0 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 127.8 (**Ar**), 127.4 (**Ar**), 126.5 (**Ar**), 126.4 (**Ar**), 123.9 (**Ar**), 123.4 (**Ar**), 59.4 (C**10**), 47.5 (C**12**), 45.9 (C**11**), 43.9 (C**14**), 43.5 (C**5**), 41.1 (C**3**), 31.2 (C**6**), 29.2 (C**7**), 26.6 (C**4**), 22.6 (C**8**), 14.0 (C**9**).

IR *vmax*/cm^{-1}: 2927 (m), 2866 (w), 1697 (s), 1493 (m), 1452 (m), 1389 (m), 1341 (m), 1168 (m), 1032 (m).

HRMS (ESI) m/z calcd for $C_{39}H_{38}N_2NaO_5$ [(M+Na)$^+$] 637.2673, found 637.2658.

(1*R**,5*S**,7*R**)-3-Benzyl-7-butyl-1-(2,2-diphenylethyl)-3-azabicyclo[3.2.0]heptane **466**



Compound **361** (53 mg, 0.11 mmol) was dissolved in THF (0.5 mL) in a flame dried Schlenk tube and added to a suspension of lithium aluminium hydride (1 M THF, 0.27 mL) at 0 °C under a nitrogen atmosphere. The mixture was then stirred at reflux for 3 hours before being cooled to 0 °C and quenched with 30% aqueous NaOH (2 mL). The precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 95/5 to 90/10) gave the title compound (32 mg, 64%) as a colourless oil.

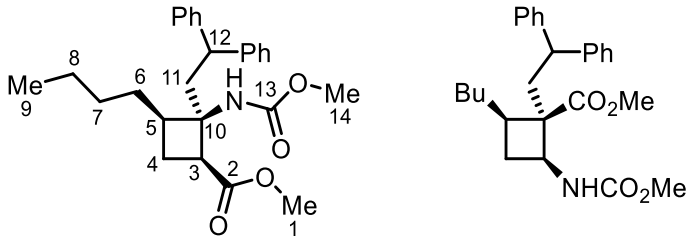
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 – 6.96 (15H, m, 15 x **Ar**-H), 3.78 (1H, t, *J* = 7.0 Hz, C**12**-H), 3.45 (2H, s, C**1**-H_2), 2.65 (1H, d, *J* = 10.0 Hz, C**13**-HH), 2.44 (2H, m, C**2**-HH, C**11**-HH), 2.20 (1H, dd, *J* = 14.0, 7.0 Hz, C**11**-HH), 2.00 (2H, m, C**5**-H, C**4**-HH), 1.83 – 1.81 (2H, m, C**2**-HH, C**3**-H), 1.58 (1 H, d, *J* = 10.0 Hz, C**13**-HH), 1.37 (1H, d, *J* = 8.5 Hz, C**6**-HH), 1.19 (2H, m, C**7**-HH, C**4**-HH), 1.08 – 1.11 (2H, m, *J* = 7.0 Hz, C**8**-H_2), 1.04 – 0.92 (1H, m, C**7**-HH), 0.77 (4H, m, C**6**-HH, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 140.1 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.0 (**Ar**), 127.9 (**Ar**), 127.8 (**Ar**), 126.5 (**Ar**), 126.1 (**Ar**), 60.3 (**10**), 60.2 (C**13**), 60.1 (C**1**), 59.4 (C**2**) 48.7 (C**12**), 46.7 (C**11**), 40.8 (C**5**), 39.8 (C**3**), 29.6 (C**6**), 29.4 (C**7**) 28.3 (C**4**) 22.8 (C**8**), 14.2 (C**9**).

IR *vmax*/cm^{-1}: 2953 (w), 2921 (m), 2783 (w), 1493 (m), 1216 (w), 751 (s), 696 (s).

HRMS (ESI) m/z calcd for $C_{31}H_{38}N$ [$(M+Na)^+$] 424.2999, found 424.3011.

Methyl (1*S**,2*R**,3*R**)-3-butyl-2-(2,2-diphenylethyl)-2-((methoxycarbonyl)amino)cyclobutane-1-carboxylate **467**



7:1 r.r.

Compound **432** (15 mg, 0.041 mmol, >20:1 r.r.) was added to a solution of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, 18 mg, 0.082 mmol) in dry methanol (0.2 mL) in a microwave *via*l. To the resulting solution was added DBU (19 µL, 0.12 mmol) the mixture was stirred at 100 °C for 2 hours under microwave irradiation. The solvent was concentrated *in vacuo* and the crude material was diluted with EtOAc (10 mL) and washed with water (2 × 10 mL) and brine (10 mL). The organic extracts were dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 19/1 to 9/1) gave the title compound (10 mg, 57%) as a colourless solid.

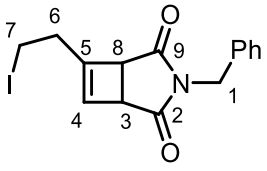
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.22 – 7.01 (10H, m, 5 x **Ar**-H), 6.00 (1H, s, N-H), 3.89 (1H, t, *J* = 7.0 Hz, C**12**-H), 3.46 (3H, s, C**1**-H_3), 3.44 (3H, s, C**14**-H_3), 3.09 – 2.97 (1H, m, C**11**-HH), 2.71 (1H, t, *J* = 9.0 Hz, C**3**-H), 2.64 (1H, dd, *J* = 14.5, 7.5 Hz, C**11**-HH), 2.04 (2H, m, C**4**-HH, C**5**-H), 1.75 – 1.66 (1H, m, C**4**-HH), 1.29 – 0.98 (5H, m, C**6**-HH, C**7**-H_2, C**8**-H_2), 0.92 (1H, s, C**6**-HH), 0.76 (3H, td, *J* = 7.0, 2.5 Hz, C**9**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 173.5 (C**2**), 155.9 (C**13**), 144.9 (**Ar**), 144.5 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.1 (**Ar**), 127.9 (**Ar**), 127.5 (**Ar**), 126. (**Ar**)1, 126.1 (**Ar**), 62.3 (C**10**), 51.7 (C**1**), 51.6 (C**14**), 47.4 (C**12**), 44.5 (C**11**), 44.4 (C**5**), 43.8 (C**3**), 29.1 (C**6**), 28.7 (C**7**), 27.1 (C**4**), 22.6 (C**8**), 14.1 (C**9**).

IR *vmax*/cm-1: 3670 (w), 3354 (br), 2953 (m), 2870 (w), 1728 (s), 1589 (m), 1504 (s), 1258 (m), 1128 (m), 1057 (m).

HRMS (ESI) m/z calcd for $C_{26}H_{33}NNaO_4$ [$(M+Na)^+$] 446.2302, found 446.2304.

3-Benzyl-6-(2-iodoethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **505**



General procedure 6. **504** (100 mg, 0.39 mmol) was used. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (102 mg, 71%) as a clear colourless oil.

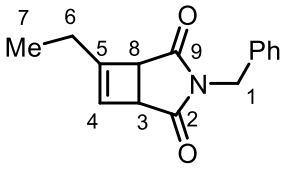
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.15 (5H, m, 5 x **Ar**-H), 6.17 (1H, d, *J* = 1.5 Hz, C**4**-H), 4.53 – 4.56 (2H, m, C**1**-H_2), 3.69 (1H, dd, *J* = 3.0, 1.0 Hz, C**8**-H), 3.58 (1 H, dd, *J* = 3.0, 1.5 Hz, C**3**-H), 3.21 – 3.05 (2 H, m, C**7**-H_2), 2.68 (2H, dt, *J* = 7.0, 1.0 Hz, C**6**-H_2).

^{1}H NMR (100 MHz, $CDCl_3$) δ_C 174.6 (C**2**), 174.1 (C**9**), 151.3 (C**5**), 135.8 (**Ar**), 132.0 (C**4**), 128.6 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 48.4 (C**8**), 44.2 (C**3**), 42.2 (C**1**), 33.9 (C**6**), -0.4 (C**7**).

IR *vmax*/cm^{-1}: 3033 (w), 1766 (w), 1694 (s), 1388 (m), 1164 (m).

HRMS (ESI) m/z calcd for $C_{15}H_{15}INO_2$ [$(M+H)^+$] 368.0147, found 368.0149.

3-Benzyl-6-ethyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **506**



General Procedure 5 – Deiodinative Spirocyclisation. **505** (36 mg, 0.1 mmol) was used. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 75/25) to give the title compound (12 mg, 50%) as a colourless oil.

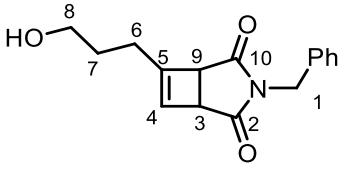
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 – 7.12 (5H, m, 5 x **Ar**-H), 6.00 (1H, td, *J* = 2.0, 1.0, C**4**-H), 4.54 (2H, s, C**1**-H_2), 3.62 (1H, dt, *J* = 3.0, 1.0, C**8**-H), 3.54 (1H, dtd, *J* = 3.0, 2.0, 1.0, C**3**-H), 2.18 – 1.99 (2H, m, C**6**-H_2), 0.96 (3H, t, *J* = 7.5, C**7**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.4 (C**2**), 174.6 (C**9**), 155.5 (C**5**), 136.0 (**Ar**), 128.6 (C**4**), 128.5 (**Ar**), 128.4 (**Ar**), 127.8 (**Ar**), 48.5 (C**8**), 43.8 (C**3**), 42.0 (C**1**), 23.2 (C**6**), 10.4 (C**7**).

IR *vmax*/cm^{-1}: 2960 (w), 1701 (s), 1332(w), 1167 (m).

HRMS (ESI) m/z calcd for $C_{15}H_{16}NO_2$ [$(M+H)^+$] 242.1181, found 242.1180.

3-Benzyl-6-(3-hydroxypropyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **507**



General Procedure 3 – Batch. Compound **186** (1 g, 5.34 mmol), 4-pentyn-1-ol (0.75 mL, 8 mmol), ITX (13 mg, 0.05 mmol) and acetonitrile (150 mL) were used. The reaction was exposed to UVA irradiation for 2 hours. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 60/40) to give the title compound (1.14 g, 79%) as a yellow oil.

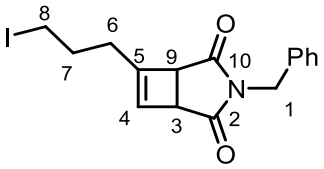
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.24 (5 H, m, 5 x **Ar**-H), 6.12 (1 H, q, *J* 1.5, C**4**-H), 4.71 – 4.56 (2 H, m, C**1**-H_2), 3.73 (1 H, dt, *J* 3.0, 1.0, C**8**-H), 3.65 (1 H, dtd, *J* 3.0, 2.0, 1.0, C**3**-H), 3.58 (2 H, t, *J* 6.5, C**8**-H_2), 2.28 (2 H, tq, *J* 7.5, 1.5, C**7**-H_2), 1.71 (2 H, tt, *J* 7.5, 6.5, C**6**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.2 (C**2**), 174.6 (C**10**), 153.5 (C**5**), 135.9 (**Ar**), 129.9 (C**4**), 128.6 (**Ar**), 128.5 (**Ar**), 127.8 (**Ar**), 61.8 (C**8**), 48.7 (C**9**), 43.9 (C**3**), 42.1 (C**1**), 29.0 (C**7**), 26.3 (C**6**).

IR *vmax*/cm^{-1}: 3493 (br), 2935 (w), 1766 (w), 1693 (s), 1389 (m), 1165 (m), 925 (w).

HRMS (ESI) m/z calcd for $C_{16}H_{18}NO_3$ [$(M+H)^+$] 272.1287, found 272.1280.

3-Benzyl-6-(3-iodopropyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **508**



General procedure 6. Compound **507** (100 mg, 0.37 mmol) was used. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (56 mg, 40%) as a clear colourless oil.

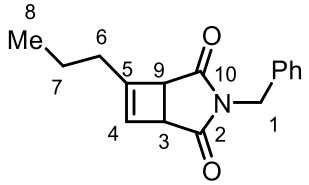
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.29 (5 H, m, 5 x **Ar**-H), 6.16 (1 H, td, *J* 1.5, 1.0, C**4**-H), 4.70 – 4.57 (2 H, m, C**1**-H_2), 3.71 (1 H, dt, *J* 3.0, 1.0, C**9**-H), 3.66 (1 H, dtd, *J* 3.0, 2.0, 1.0, C**3**-H), 3.07 (2 H, qt, *J* 10.0, 6.5, C**8**-H_2), 2.30 (2 H, ddt, *J* 8.0, 3.0, 1.5, C**6**-H_2), 1.96 (2 H, dt, *J* 7.5, 6.5, C**7**-H_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 175.0 (C**2**), 174.2 (C**10**), 151.9 (C**5**), 135.8 (**Ar**), 130.8 (C**4**), 128.7 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 48.6 (C**9**), 44.0 (C**3**), 42.1 (C**1**), 30.8 (C**6**), 29.5 (C**7**), 5.2 (C**8**).

IR *vmax*/cm^{-1}: 2978 (w), 1698 (s), 1388 (w), 1166 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{16}INNaO_2$ [$(M+Na)^+$] 404.0123, found 404.0112.

3-Benzyl-6-propyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **509**



General procedure 5 – Deiodinative Spirocyclisation. Compound **508** (50 mg, 0.13 mmol) was used. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (20 mg, 60%) as a clear colourless oil.

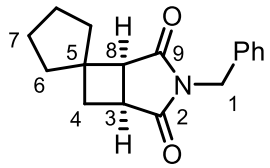
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28 – 7.14 (5H, m, 5 x **Ar**-H), 5.99 (1H, td, *J* = 1.5, 1.0 Hz, C**4**-H), 4.53 (2H, s, C**1**-H_2), 3.60 (1H, dt, *J* = 3.0, 1.0 Hz, C**9**-H), 3.54 (1H, dtd, *J* = 3.0, 2.0, 1.0 Hz, C**3**-H), 2.08 – 2.00 (2H, m, C**6**-H_2), 1.43 – 1.32 (2H, m, C**7**-H_2), 0.79 (3H, t, *J* = 7.5 Hz, C**8**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.4 (C**2**), 174.5 (C**10**), 154.1 (C**5**), 135.9 (**Ar**), 129.4 (C**4**), 128.5 (**Ar**), 127.7 (**Ar**), 48.6 (C**9**), 43.9 (C**3**), 42.0 (C**1**), 31.9 (C**6**), 19.4 (C**7**), 13.6 (C**8**).

IR *vmax*/cm^{-1}: 2923 (w), 1702 (s), 1336 (m), 1167 (w), 953 (w).

HRMS (ESI) m/z calcd for $C_{16}H_{17}NNaO_2$ [$(M+Na)^+$] 278.1157, found 278.1157.

(1*S**,5*S**)-3-Benzyl-3-azaspiro[bicyclo[3.2.0]heptane-6,1'-cyclopentane]-2,4-dione **512**



General procedure 5 – Deiodinative Spirocyclisation. Compound **511** (100 mg, 0.25 mmol) was used. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 75/25) to give the title compound (44 mg, 65%) as a colourless oil.

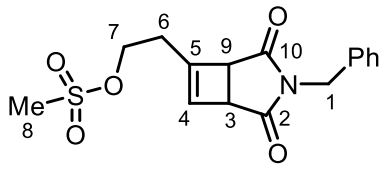
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.13 (5H, m, 5 x **Ar**-H), 4.60 (2H, s, C**1**-H_2), 3.09 (1H, ddd, *J* = 10.5, 6.5, 5.0 Hz, C**3**-H), 2.96 (1H, d, *J* = 6.5 Hz, C**8**-H), 2.34 (1H, ddd, *J* 12.8, 10.4, 1.0 Hz, C**4**-HH), 1.87 (1H, ddd, *J* = 13.0, 5.0, 1.0 Hz, C**4**-HH), 1.78 – 1.63 (2H, m, C**6**-H_2), 1.63 – 1.37 (5H, m, 2 x C**7**-H_2, C**6**-HH), 1.09 (1H, tdd, *J* = 7.5, 6.0, 4.5 Hz, C**6**-HH).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 179.9 (C**2**), 177.4 (C**9**), 136.1 (**Ar**), 128.9 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 47.8 (C**8**), 47.3 (C**5**), 42.3 (C**1**), 41.6 (C**6**), 35.7 (C**4**), 35.2 (C**6**), 33.7 (C**3**), 23.1 (C**7**), 22.7 (C**7**).

IR *vmax*/cm^{-1}: 2953 (m), 2931 (m), 1691 (s), 1393 (m), 1336 (m), 1171 (m), 689 (m).

HRMS (ESI) m/z calcd for $C_{17}H_{20}NO_2$ [$(M+Na)^+$] 270.1410, found 270.1410.

2-(3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)ethyl methanesulfonate **513**



In a round bottomed flask, a solution of the alcohol **504** (500 mg, 1.94 mmol), triethylamine (0.42 mL, 3.10 mmol) and DCM (2.32 mL, 0.8 M), was cooled to 0°C. Mesylchloride (0.17 mL, 2.17 mmol) was added at 0°C and stirred for 30 mins, followed by stirring at r.t. for 18 hours. The solution diluted with ethyl acetate (20 mL) was washed successively with 1 M HCl (10 mL), *sat.* $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was then concentrated *in vacuo* and the crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (632 mg, 97%) as a clear colourless oil.

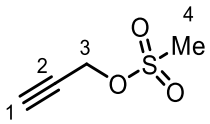
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.25 – 7.16 (5H, m, 5 x **Ar**-H), 6.20 (1H, d, *J* = 2.0 Hz, C**4**-H), 4.51 – 4.54 (2H, m, *J* = 1.5 Hz, C**1**-H_2), 4.32 – 4.18 (2H, m, C**7**-H_2), 3.70 (1H, dd, *J* = 3.0, 1.0 Hz, C**9**-H), 3.61 (1H, dd, *J* = 3.0, 2.0 Hz, C**3**-H), 2.87 (3H, s, C**8**-H_3), 2.55 (2H, td, *J* = 6.0, 1.0 Hz, C**6**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.5 (C**2**), 174.0 (C**10**), 148.2 (C**5**), 135.8 (**Ar**), 133.1 (C**4**), 128.7 (**Ar**), 128.4 (**Ar**), 127.9 (**Ar**), 65.9 (C**7**), 48.6 (C**9**), 44.4 (C**3**), 42.2 (C**1**), 37.5 (C**8**), 29.9 (C**6**).

IR *vmax*/cm^{-1}: 3023 (w), 1759 (w), 1686 (s), 1393 (m), 1339 (s), 1175 (s), 922 (s).

HRMS (ESI) m/z calcd for $C_{16}H_{17}NNaO_5S$ [$(M+Na)^+$] 358.0725, found 358.0718.

Prop-2-yn-1-yl methanesulfonate **515**



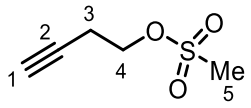
In a round bottomed flask, a solution of propargyl alcohol (4.12 mL, 71.3 mmol), triethylamine (15.0 mL, 107.0 mmol) and DCM (257 mL, 0.8 M), was cooled to 0°C. Mesylchloride (6.90 mL, 89.2 mmol) was added at 0°C and stirred for 30 mins, followed by stirring at r.t. for 18 hours. The solution was diluted with ethyl acetate (20 mL), washed successively with 1 M HCl (10 mL), *sat.* $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was then concentrated *in vacuo* and the crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 66/33) to give the title compound (8.76 g, 92%) as a clear colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.88 (2H, d, *J* = 2.5 Hz, C**3**-$\underline{H_2}$), 3.16 (3H, d, *J* = 2.5 Hz, C**4**-$\underline{H_3}$), 2.72 (1H, t, *J* = 2.5 Hz, C**1**-$\underline{H}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 77.9 (C**1**), 75.8 (C**2**), 57.2 (C**3**), 39.1 (C**4**).

All recorded data match literature values.[185]

But-3-yn-1-yl methanesulfonate **517**



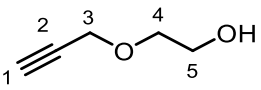
In a round bottomed flask, a solution of 3-butyn-1-ol (5.37 mL, 71.3 mmol), triethylamine (15.0 mL, 107.0 mmol) and DCM (257 mL, 0.8 M), was and cooled to 0°C. Mesylchloride (6.90 mL, 89.2 mmol) was added at 0°C and stirred for 30 mins, followed by stirring at r.t. for 18 hours. The solution was diluted with ethyl acetate (20 mL) washed successively with 1 M HCl (10 mL), *sat.* $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was then concentrated *in vacuo* and the crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 66/33to give the title compound (9.53 g, 90%) as a clear pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.35 – 4.24 (2H, m, C**4**-$\underline{H_2}$), 3.08 – 3.00 (3H, m, C**5**-$\underline{H_3}$), 2.71 – 2.57 (2H, m, C**3**-$\underline{H_2}$), 2.06 – 2.02 (1H, m, C**1**-$\underline{H}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 78.6 (C**2**), 71.0 (C**1**), 67.0 (C**4**), 37.7 (C**5**), 19.8 (C**3**).

All recorded data match literature values.[186]

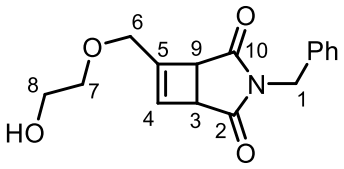
2-(Prop-2-yn-1-yloxy)ethan-1-ol **516**



In a flame dried round bottomed flask, sodium hydride (60% in mineral oil, 1.2 g, 30 mmol) was added slowly to ethylene glycol (2.52 mL, 45 mmol) in THF (15 mL, 1 mL/mmol) and stirred at r.t. for 30 mins. Compound **515** (2 g, 15 mmol) was added slowly to this solution and left to stir at r.t. for 18 hours. The solution was carefully quenched with water and extracted with ethyl acetate (3 x 20 mL). The solvent

was dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. The crude product was used in the next step without further purification

3-Benzyl-6-((2-hydroxyethoxy)methyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **519**



General Procedure 3 - Batch. Benzyl maleimide (874 mg, 4.67 mmol), compound **516** (700 mg, 7 mmol) and ITX (11.95 mg, 0.05 mmol) were used. The reaction was exposed to UVA irradiation for 2 hours. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 50/50) to give the title compound (764 mg, 57%) as a yellow oil.

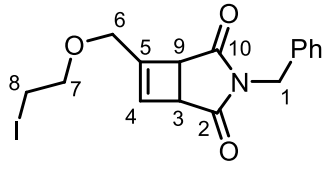
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.19 (5H, m, 5 x **Ar**-H), 6.23 (1H, dd, *J* = 2.5, 1.5 Hz, C**4**-H), 4.54 (2H, t, *J* = 4.0 Hz, C**1**-H_2), 4.09 – 3.94 (2H, m, C**6**-H_2), 3.74 (1H, dt, *J* = 3.0, 1.0 Hz, C**9**-H), 3.67 – 3.63 (1H, m, C**3**-H), 3.63 – 3.59 (2H, m, C**8**-H_2), 3.44 (2H, dd, *J* = 5.0, 4.0 Hz, C**7**-H_2), 2.47 (1H, s, O-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.4 (C**2**), 174.2 (C**10**), 149.2 (C**5**), 135.74 (**Ar**), 132.1 (C**4**), 128.6 (**Ar**), 127.88 (**Ar**), 72.40 (C**7**), 67.1 (C**6**), 61.7 (C**8**), 47.7 (C**9**), 44.50 (C**3**), 42.26 (C**1**).

IR *vmax*/cm^{-1}: 3449 (br), 2864 (w), 1693 (s), 1389 (m), 1167 (m), 889 (w).

HRMS (ESI) m/z calcd for $C_{16}H_{18}NO_4$ $[(M+H)^+]$ 288.1236, found 288.1232.

3-Benzyl-6-((2-iodoethoxy)methyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **520**



General procedure 6. Compound **519** (100 mg, 0.35 mmol) was used. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (61 mg, 44%) as a colourless oil.

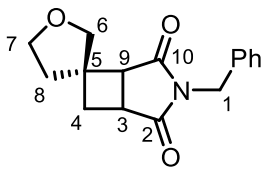
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 – 7.13 (5H, m, 5 x **Ar**-H), 6.28 (1H, dd, *J* = 2.5, 1.5 Hz, C**4**-H), 4.62 – 4.46 (2H, m, C**1**-H_2), 4.00 (2H, dd, *J* = 3.0, 2.0 Hz, C**6**-H_2), 3.73 (1H, dt, *J* = 3.0, 1.0 Hz, C**3**-H), 3.64 (1H, dtd, *J* = 3.0, 2.0, 1.0 Hz, C**11**-H), 3.57 (1d, *J* = 7.0 Hz, C**7**-H_2), 3.16 – 3.10 (2H, m, C**8**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.5 (C**10**), 173.6 (C**2**), 148.9 (C**5**), 135.8 (**Ar**), 132.5 (C**4**), 128.7 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 71.5 (C**7**), 66.6 (C**6**), 47.5 (C**3**), 44.6 (C**9**), 42.2 (C**1**), 2.3 (C**8**).

IR *vmax*/cm^{-1}: 2848 (w), 1685 (s), 1334 (m), 1167 (w), 1099 (m), 889 (w).

HRMS (ESI) m/z calcd for $C_{16}H_{17}INO_3$ [$(M+H)^+$] 398.0253, found 398.0256.

3-Benzyldihydro-2'*H*-3-azaspiro[bicyclo[3.2.0]heptane-6,3'-furan]-2,4-dione **521**



General procedure 5 – Deiodinative Spirocyclisation. Compound **520** (50 mg, 0.13 mmol) was used. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 70/30 to 50/50) to give the title compound (7 mg, 20%) as a colourless oil.

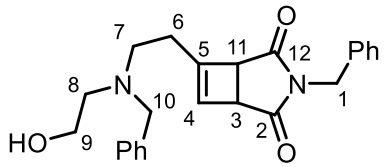
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43 – 7.27 (5H, m, 5 x **Ar**-H), 4.68 (2H, s, C**1**-H_2), 3.92 – 3.74 (2H, m, C**7**-H_2), 3.65 (1H, d, *J* = 9.0 Hz, C**6**-H), 3.30 – 3.15 (3H, m, C**9**-H C**6**-H, C**3**-H), 2.62 – 2.48 (1H, m, C**4**-H), 2.21 – 2.06 (3H, m, C**4**-H, C**8**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 178.9 (C**2**), 176.2 (C**10**), 135.8 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.1 (**Ar**), 74.2 (C**7**), 66.5 (C**6**), 46.6 (C**9**) 45.4 (C**5**), 42.5 (C**1**), 41.3 (C**8**), 35.0 (C**4**), 33.8 (C**3**).

IR *vmax*/cm^{-1}: 3020 (w), 1743 (s), 1368 (m), 1215 (m).

HRMS (ESI) m/z calcd for $C_{16}H_{18}NO_3$ [$(M+H)^+$] 272.1287, found 272.1285.

3-Benzyl-6-(2-(benzyl(2-hydroxyethyl)amino)ethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **522**



Benzyl aminoethanol (0.1 mL, 0.6 mmol) was added dropwise to compound **513** (91 mg, 0.3 mmol) and stirred at 80°C for 2 hours. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 50/50) to give the title compound (79.1 mg, 75%) as a yellow oil.

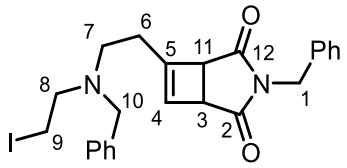
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 – 7.10 (10H, m, 10 x **Ar**-H), 5.95 (1H, dd, *J* = 2.5, 1.5 Hz, C**4**-H), 4.53 (2H, s, C**1**-H_2), 3.57 – 3.44 (5H, m, C**8**-H_2, C**10**-H_2, C**3**-H), 3.42 (1H, dd, *J* = 2.0, 1.0 Hz, C**11**-H), 2.66 – 2.48 (4H, m, C**7**-H_2, C**9**-H_2), 2.32 – 2.16 (2H, m, C**6**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.0 (C**12**), 174.4 (C**2**), 152.1 (C**5**), 138.5 (**Ar**), 135.9 (**Ar**), 130.8 (C**4**), 129.1 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 127.8 (**Ar**), 127.4 (**Ar**), 58.6 (C**8**), 58.3 (C**10**), 55.2 (C**9**), 50.3 (C**7**), 48.4 (C**11**), 44.2 (C**3**), 42.1 (C**1**), 27.7 (C**6**).

IR *vmax*/cm^{-1}: 3406 (br), 2886 (w), 1697 (s), 1332 (m), 1053 (m), 883 (w).

HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_3$ [$(M+H)^+$] 391.2022, found 391.2027.

3-Benzyl-6-(2-(benzyl(2-iodoethyl)amino)ethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **523**



General procedure 6. Compound **522** (50 mg, 0.13 mmol) was used. The crude product was purified *via* column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (28 mg, 43%) as a colourless oil.

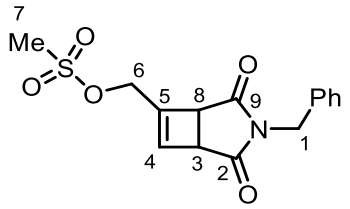
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.27 – 7.15 (10H, m, 10 x **Ar**-H), 6.01 – 5.96 (1H, m, C**4**-H), 4.55 – 4.47 (2H, m, C**1**-H_2), 3.58 – 3.46 (4H, m, C**10**-H_2, C**11**-H, C**3**-H), 3.04 (2H, t, *J* = 7.5 Hz, C**9**-H_2), 2.78 – 2.70 (2H, m, C**8**-H_2), 2.65 – 2.57 (1H, m, C**7**-H), 2.57 – 2.49 (1H, m, C**7**-H), 2.30 – 2.19 (2H, m, C**6**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.1 (C**2**), 174.4 (C**12**), 152.3 (C**5**) 135.9 (**Ar**), 130.8 (C**4**), 128.9 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 127.8 (**Ar**), 58.1 (C**10**), 56.4 (C**8**), 50.4 (C**7**), 48.7 (C**11**), 44.2 (C**3**), 42.1 (C**1**), 27.9 (C**6**), 3.8 (C**9**).

IR *vmax*/cm^{-1}: 3024 (w), 2970 (w), 1742 (s), 1368 (m), 1219 (m).

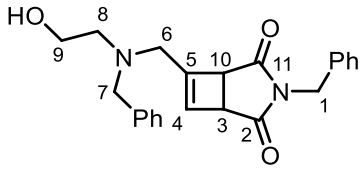
HRMS (ESI) m/z calcd for $C_{24}H_{26}IN_2O_2$ [$(M+H)^+$] 501.1039, found 501.1020.

(3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)methyl methanesulfonate **524**



In a round bottomed flask, a solution of alcohol **S8** (500 mg, 2.06 mmol), triethylamine (450 µL, 3.29 mmol) and DCM (2.47 mL, 0.8 M), was and cooled to 0°C. Mesylchloride (179 µL, 2.31 mmol) was added at 0°C and stirred for 30 mins, followed by stirring at r.t. for 18 hours. The solution diluted with ethyl acetate (20 mL) was washed successively with 1 M HCl (10 mL), *sat.* $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was then concentrated *in vacuo* and the crude product was taken to the next step without further purification.

3-Benzyl-6-((benzyl(2-hydroxyethyl)amino)methyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **525**



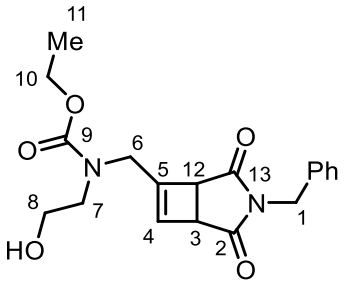
Benzyl aminoethanol (0.1 mL, 0.6 mmol) was added dropwise to compound **524** (125 mg, 0.33 mmol) and stirred at 80°C for 2 hours. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 50/50) to give the title compound (110 mg, 94%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.08 (10H, m, 10 x **Ar**-H), 6.17 (1H, m, C**4**-H), 4.67 – 4.45 (2H, m, C**1**-H_2), 3.69 (1H, dt, *J* = 3.0, 1.0 Hz, C**10**-H), 3.57 (1H, dq, *J* = 3.0, 1.5 Hz, C**3**-H), 3.49 (4H, m, C**7**-H_2, C**8**-H_2), 3.20 – 3.02 (2H, m, C**6**-H_2), 2.98 (1H, s, OH), 2.62 – 2.45 (2H, m, C**9**-H_2).

IR *vmax*/cm^{-1}: 3503 (br), 2877 (w), 1697 (s), 1429 (w), 1290 (m), 1167 (m), 1060 (m).

HRMS (ESI) m/z calcd for $C_{23}H_{25}N_2O_3$ [$(M+H)^+$] 377.1865, found 377.1854.

Ethyl ((3-benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)methyl)(2-hydroxyethyl)carbamate **526**



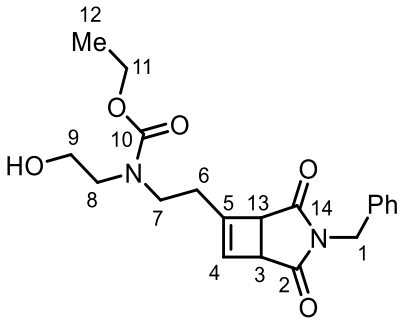
To a solution of compound **525** (100 mg, 0.27 mmol) and dry DCM (0.54 mL, 2 mL/mmol), ethyl chloroformate (51 µL, 0.54 mmol) was added and the solution was stirred at r.t. for 16 hours under an N_2 atmosphere. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 50/50) to give the title compound (30 mg, 31%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 – 7.15 (5H, m, 5 x **Ar**-H), 6.14 (1H, d, *J* = 8.0 Hz, C**4**-H), 4.61 – 4.47 (2H, m, C**1**-H_2), 4.19 – 3.94 (6H, m, C**10**-H_2, C**7**-H_2, C**6**-H_2), 3.82 (1H, m, OH), 3.67 (1H, d, *J* = 8.0 Hz, C**3**-H), 3.59 (1H, dtd, *J* = 3.0, 2.0, 1.0 Hz, C**12**-H), 3.31 (1H, s, C**8**-H), 3.18 (1H, d, *J* = 16.5 Hz, C**8**-H), 1.23 (3H, t, *J* = 7.0 Hz, C**11**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.5 (C**2**), 173.5 (C**12**), 154.9 (C**9**), 148.7 (C**5**), 135.9 (**Ar**), 131.9 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 65.8 (C**10**), 64.2 (C**7**), 61.9 (C**6**), 47.8 (C**3**), 46.9 (C**8**), 46.7 (C**8**), 44.2 (C**12**), 42.2 (C**1**), 14.6 (C**11**), 14.3 (C**11**).

IR *vmax*/cm^{-1}: 2980 (w), 1697 (s), 1388 (m), 1255 (s), 1010 (m), 845 (w).

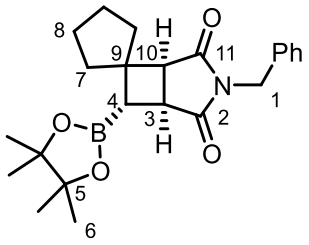
Ethyl (2-(3-benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)ethyl)(2-hydroxyethyl)carbamate **527**



A solution of compound **522** (50 mg, 0.13 mmol) and dry DCM (0.26 mL, 2 mL/mmol) was made in a round bottomed flask under an N_2 atmosphere. To this, ethyl chloroformate (25 µL, 0.26 mmol) was added and the solution was stirred at r.t. for 16 hours. The product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 50/50) to give the title compound (17 mg, 35%) as a yellow oil.

IR *vmax*/cm^{-1}: 3022 (w), 1742 (s), 1365 (m), 1218 (m).

(1*S**,5*S**,7*S**)-3-Benzyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azaspiro[bicyclo[3.2.0]heptane-6,1'-cyclopentane]-2,4-dione **533**



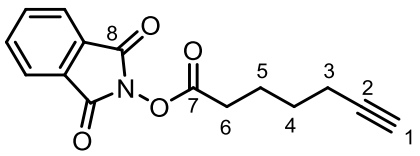
General Procedure 5 – Decarboxylation of *N*-Acyloxy phthalimides. Compound **575** (23 mg, 0.05 mmol), DIPEA (17 µL, 0.10 mmol), B_2cat_2 (36 mg, 0.15 mmol), 2,2'diBrTX (0.9 mg, 0.003 mmol) and DCM (5 mL) were used. Purification *via* flash column chromatography (acetone/hexane: 10/90) gave the title compound as a mixture of **533** and **512**.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*as a mixture of compounds*) 7.45 – 7.28 (5H, m, 5 x **Ar**-H), 4.71 – 4.69 (2H, m, C**1**-H_2), 3.25 (1H, dd, *J* = 6.5, 6.0 Hz, C**3**-H), 2.98 (1H, dd, *J* = 6.5, 1.0 Hz, C**10**-H), 1.81 (1H, dd, *J* = 6.0, 1.0 Hz, C**4**-H), 1.77 – 1.72 (2H, m, C**7**-H_2), 1.70 – 1.61 (2H, m, C**8**-H_2), 1.57 – 1.50 (3H, m, C**8**-H_2, C**7**-HH), 1.29 (12H, s, 4 x C**6**-H_3), 1.21 – 1.18 (1H, m, C**7**-HH).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*as a mixture of compounds*) 180.3 (C**2**), 177.6 (C**11**), 136.2 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 127.8 (**Ar**), 84.1 (C**9**), 48.4 (C**10**), 42.2 (C**1**), 39.0 (C**4**), 36.9 (C**7**), 34.6 (C**3**), 25.1 (C**6**), 22.7 (C**8'**), 22.4 (C**8**).

HRMS (ESI) m/z calcd for $C_{23}H_{31}BNO_4$ [$(M+H)^+$] 396.2341, found 396.2340.

1,3-Dioxoisoindolin-2-yl hept-6-ynoate **552**



General Procedure 7. Heptynoic acid (1.27 mL, 12 mmol) was used. The product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10) to give the title compound (2.02 g, 70%) as a colourless crystalline powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85 – 7.79 (2H, m, 2 x **Ar**-H), 7.75 – 7.70 (2H, m, 2 x **Ar**-H), 2.64 (2H, t, *J* = 7.5 Hz, C**6**-H_2), 2.21 (2H, td, *J* = 7.0, 2.5 Hz, C**3**-H_2), 1.91 (1H, t, *J* = 2.5 Hz, C**1**-H), 1.90 – 1.80 (2H, m, C**5**-H_2), 1.67 – 1.57 (2H, m, C**4**-H_2).

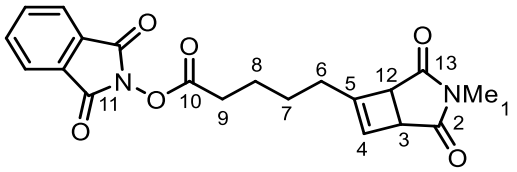
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.3 (C**7**), 162.0 (C**8**), 134.8 (**Ar**), 129.0 (**Ar**), 124.0 (**Ar**), 83.5 (C**2**), 69.0 (C**1**), 30.5 (C**6**), 27.4 (C**4**), 23.6 (C**5**), 18.0 (C**3**).

IR *vmax*/cm^{-1}: 3277 (m), 2925 (w), 1812 (m), 1737 (s), 1466 (m), 1372 (m), 1185 (m), 866 (s), 657 (s).

HRMS (ESI) m/z calcd for $C_{15}H_{13}NNaO_4$ [$(M+Na)^+$] 294.0737, found 294.07433.

Mp ($CHCl_3$): 68 – 71 °C

1,3-Dioxoisoindolin-2-yl 5-(3-methyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)pentanoate **554**



General Procedure 3 – Visible-Light. *N*-Methyl maleimide (33 mg, 0.30 mmol) and compound **552** (122 mg, 0.45 mmol) were stirred for 2 hours. The product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20 to 60/40) to give the title compound (79 mg, 69%) as a colourless crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.90 – 7.86 (2H, m, 2 x **Ar**-H), 7.80 – 7.75 (2H, m, 2 x **Ar**-H), 6.14 (1H, td, *J* = 1.5, 1.0 Hz, C**4**-H), 3.70 (1H, dt, *J* = 3.0, 1.0 Hz, C**12**-H), 3.62 (1H, dtd, *J* = 3.0, 2.0, 1.0 Hz, C**3**-H), 2.94 (3H, s, C**1**-H_3), 2.67 (2H, t, *J* = 7.0 Hz, C**9**-H_2), 2.27 – 2.18 (2H, m, C**6**-H_2), 1.84 – 1.73 (2H, m, C**8**-H_2), 1.73 – 1.59 (2H, m, C**7**-H_2).

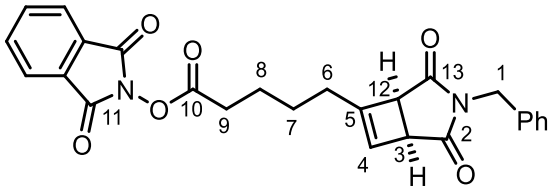
^{13}C NMR (125 MHz, $CDCl_3$) δ_C 175.7 (C**2**), 174.8 (C**13**), 169.3 (C**10**), 162.0 (C**11**), 153.1 (C**5**), 134.8 (**Ar**), 130.1 (C**4**), 128.9 (C**5**), 124.0 (**Ar**), 48.6 (C**12**), 44.0 (C**3**), 30.7 (C**9**), 29.4 (C**6**), 25.1 (C**8**), 24.8 (C**7**), 24.2 (C**1**).

IR *vmax*/cm^{-1}: 2936 (w), 1814 (m), 1785 (m), 1737 (s), 1695 (s), 1375 (m), 1279 (m), 1184 (m), 1123 (m), 1081 (m), 1051 (m).

HRMS (ESI) m/z calcd for $C_{20}H_{18}N_2NaO_6$ [$(M+Na)^+$] 405.1057, found 405.1074.

Mp ($CHCl_3$): 77 – 80 °C

1,3-Dioxoisoindolin-2-yl 5-((1*S**,5*S**)-3-benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)pentanoate **575**



General Procedure 3 – Visible-Light. Compound **552** (203 mg, 0.75 mmol), *N*-benzyl maleimide (94 mg, 0.5 mmol), 2,2'-diBrTX (9 mg, 0.025 mmol) and DCM (5.0 mL) were used and stirred at r.t. for 2 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20 to 60/40) to give the title compound (168 mg, 73%) as a colourless oil.

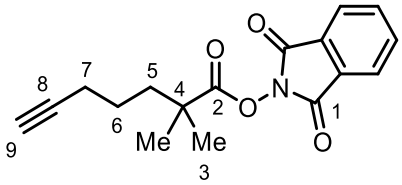
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.96 – 7.78 (4H, m, 4 x **Ar**-H), 7.38 – 7.29 (5H, m, 5 x **Ar**-H), 6.16 (1H, s, C**4**-H), 4.68 – 4.58 (2H, m, C**1**-H_2), 3.76 – 3.61 (2H, m C**12**-H + C**3**-H), 2.65 (2H, t, *J* = 7.0 Hz, C**9**-H_2), 2.24 (2H, t, *J* = 7.5 Hz, C**6**-H_2), 1.77 – 1.68 (2H, m, C**8**-H_2), 1.69 – 1.59 (2H, m, C**7**-H_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 175.3 (C**2**), 174.4 (C**13**), 169.3 (C**10**), 162.0 (C**11**), 153.1 (C**5**), 135.9 (**Ar**), 134.8 (**Ar**), 130.1 (**Ar**), 128.9 (**Ar**), 128.9 (**Ar**), 128.6 (C**4**), 128.5 (**Ar**), 127.8 (**Ar**), 124.0 (**Ar**), 48.6 (C**12**), 44.0 (C**3**), 42.1 (C**1**), 30.6 (C**9**), 29.4 (C**6**), 25.1 (C**8**), 24.1 (C**7**).

IR *vmax*/cm-1: 3702 (w), 3031 (w), 2844 (w), 1813 (w), 1786 (m), 1742 (s), 1700 (s), 1389 (m), 1349 (m), 1185 (m), 1033 (m), 878 (m), 697 (m).

HRMS (ESI) m/z calcd for $C_{26}H_{22}N_2NaO_6$ $[(M+Na)^+]$ 481.1370, found 481.1394.

1,3-Dioxoisoindolin-2-yl 2,2-dimethylhept-6-ynoate **577**



General Procedure 7. Compound **597** (200 mg, 1.30 mmol) was used and stirred at r.t. for 16 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) gave the title compound (230 mg, 71%) as a colourless oil.

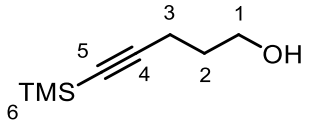
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.95 – 7.86 (2H, m, 2 x **Ar**-H), 7.86 – 7.75 (2H, m, 2 x **Ar**-H), 2.30 (2H, td, *J* = 7.0, 2.5 Hz, C**7**-H_2), 2.00 (1H, t, *J* = 2.5 Hz, C**9**-H), 1.93 – 1.82 (2H, m, C**5**-H_2), 1.77 – 1.66 (2H, m, C**6**-H_2), 1.44 (6H, s, 2 x C**3**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 173.7 (C**1**), 162.1 (C**2**), 134.7 (**Ar**), 129.1 (**Ar**), 123.9 (**Ar**), 83.9 (C**8**), 68.7 (C**9**), 41.9 (C**4**), 39.7 (C**5**), 25.1 (C**3**), 23.7 (C**6**), 18.8 (C**7**).

IR *vmax*/cm-1: 3291 (w), 2976 (w), 1781 (m), 1739 (s), 1468 (m), 1367 (m), 1186 (m), 1055 (s), 877 (s), 695 (s).

HRMS (ESI) m/z calcd for $C_{17}H_{17}NNaO_4$ [$(M+Na)^+$] 322.1050, found 322.1050

5-(Trimethylsilyl)pent-4-yn-1-ol **594**



A solution of 4-pentyn-1-ol (3.00 mL, 33 mmol) and THF (150 mL) was made and cooled to -78°C. To this, a solution of *n*BuLi in hexanes (42 mL, 1.6 M, 67 mmol) was added dropwise over 30 mins while maintaining -78°C. The solution was then stirred for 40 mins. On completion, trichloromethyl silane (10 mL, 81 mmol) was added dropwise over 10 mins. The solution was then allowed to warm to r.t. and stir for an addition 16 hours. On completion, an aqueous solution of 1 M HCl (50 mL) was added to the reaction mixture and stirred for 2 hours. The resulting solution was dilute with ethyl acetate (150 mL) washed with water (2 x 100 mL) and $NaHCO_3$ *sat.* (100 mL) and the aqueous layers were extracted with ethyl acetate (2 x 100 mL). The organic layers were then washed with brine (100 mL) and dried over $MgSO_4$, filtered and the solvent was concentrated *in vacuo* give the title compound (4.83 g, 95%) as a clear colourless oil.

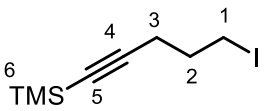
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.78 (2H, t, *J* = 6.0 Hz, C**3**-$\underline{H_2}$), 2.37 (2H, t, *J* = 7.0 Hz, C**1**-$\underline{H_2}$), 1.79 (2H, dt, *J* = 7.0, 6.0 Hz, C**2**-$\underline{H_2}$), 1.73 – 1.62 (1H, m, O-$\underline{H}$), 0.17 (9H, s, 3 x C**6**-$\underline{H_3}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 106.7 (C**5**), 85.3 (C**4**), 61.9 (C**1**), 31.2 (C**2**), 16.6 (C**3**), 0.1 (C**6**).

IR *vmax*/cm-1: 3341 (br), 2956 (w), 2899 (w), 2174 (m), 1248 (s), 1051 (m), 836 (s), 758 (m).

HRMS (ESI) m/z calcd for $C_8H_{16}NaOSi$ [$(M+Na)^+$] 179.0863, found 179.0854.

(5-Iodopent-1-yn-1-yl)trimethylsilane **595**



To a flame-dried round bottomed flask, a solution of compound **594** (1.00 mL, 5.50 mmol) in DCM (37 mL, 0.15 M) was made and cooled to 0°C. To this, triphenyl phosphine (2.16 g, 8.25 mmol) and imidazole (561 mg, 8.25 mmol) was added. Upon dissolution, iodine (2.09 g, 8.25 mmol) was added in two portions. The solution was allowed to warm to r.t. and stirred for 2 hours. The reaction mixture was diluted with a 10% aq. soln. of $Na_2S_2O_3$ (10 mL) and extracted with DCM (3 x 20 mL). The organic extracts were combined and dried over $MgSO_4$, the filtrate was concentrated *in vacuo*. The resulting oil was triturated in petroleum ether and the filtrate concentrated *in vacuo* to give the title compound (1.32 g, 90%) as a colourless oil.

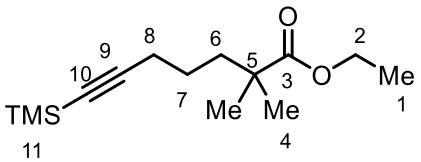
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.14 (2H, t, *J* = 7.0 Hz, C**3**-$\underline{H_2}$), 2.21 (2H, t, *J* = 7.0 Hz, C**1**-$\underline{H_2}$), 1.90 – 1.80 (2H, m, *J* = 7.0 Hz, C**2**-$\underline{H_2}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 104.9 (C**5**), 85.9 (C**4**), 32.1 (C**2**), 20.9 (C**3**), 5.1 (C**1**), 0.1 (C**6**).

IR *vmax*/cm-1: 2958 (w), 2899 (w), 2174 (w), 1426 (w), 1248 (s), 836 (s), 758 (w).

HRMS (ESI) m/z calcd for $C_7H_{12}ISi$ [$(M-CH_3)^+$] 250.9747, found 250.9747.

Ethyl 2,2-dimethyl-7-(trimethylsilyl)hept-6-ynoate **596**



In a flame-dried round bottomed flask, a solution of diisopropyl amine (0.53 mL, 3.76 mmol) in THF (4.0 mL) at 0°C, a solution of *n*BuLi in hexane (2.35 mL, 1.6 M) was added. After 15 mins, the solution was cooled to -78°C and methyl *iso*-butyrate (0.50 mL, 3.76 mmol) was added and the solution was stirred for 40 mins. While maintaining -78°C, compound **595** (1.00 g, 3.76 mmol) in THF (0.70 mL) was added and the solution was stirred for 30 mins at -78°C. The solution was diluted with NH_4Cl *sat.* (20 mL) and extracted with diethyl ether (3 x 25 mL). The organic extracts were combined and dried over $MgSO_4$, the filtrated was then concentrated *in vacuo* and purified *via* flash column chromatography (petroleum ether/ethyl acetate: 100/0 to 90/10) to give the title compound (808 mg, 85%) as a colourless oil.

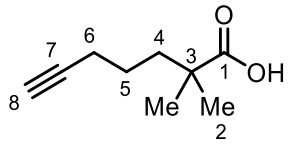
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.12 (2H, q, *J* = 7.0 Hz, C**2**-$\underline{H_2}$), 2.19 (2H, t, *J* = 7.0 Hz, C**8**-$\underline{H_2}$), 1.64 – 1.52 (2H, m, C**6**-$\underline{H_2}$), 1.52 – 1.41 (2H, m, C**7**-$\underline{H_2}$), 1.25 (3H, t, *J* = 7.0 Hz, C**1**-$\underline{H_3}$), 1.17 (6H, s, 2 x C**4**-$\underline{H_3}$), 0.14 (9H, s, 3 x C**11**-$\underline{H_3}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 177.8 (C**3**), 107.2 (C**10**), 84.6 (C**9**), 60.3 (C**2**), 42.0 (C**5**), 39.9 (C**6**), 25.1 (C**4**), 24.3 (C**7**), 20.3 (C**8**), 14.3 (C**1**), 0.2 (C**11**).

IR *vmax*/cm-1: 2959 (w), 2908 (w), 2174 (w), 1727 (s), 1474 (w), 1248 (s), 1176 (s), 1128 (s), 758 (w).

HRMS (ESI) m/z calcd for $C_{14}H_{26}NaO_2Si$ [$(M+Na)^+$] 277.1594, found 277.1589.

2,2-Dimethylhept-6-ynoic acid **597**



In a round-bottomed flask, compound **596** (500 mg, 1.97 mmol), potassium hydroxide (1.11 g, 19.7 mmol), ethanol (2.9 mL) and water (2.9 mL) were stirred at reflux for 24 hours. The solution was acidified to pH 3 using an aqueous solution of 6 M HCL and extracted with diethyl ether (3 x 20 mL). The organic extracts were washed with brine (20 mL) and dried over $MgSO_4$, filtered and the solvent was concentrated *in vacuo* to give the title compound (292 mg, 96%) as a colourless oil.

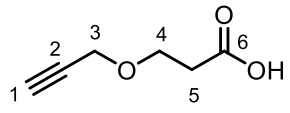
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.19 (2H, td, *J* = 7.0, 2.5 Hz, C**6**-$\underline{H_2}$), 1.96 (1H, t, *J* = 2.5 Hz, C**8**-$\underline{H}$), 1.73 – 1.59 (2H, m, C**4**-$\underline{H_2}$), 1.59 – 1.49 (2H, m, C**5**-$\underline{H_2}$), 1.21 (6H, s, 2 x C**2**-$\underline{H_3}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 184.0 (C**1**), 84.1 (C**7**), 68.5 (C**8**), 41.9 (C**3**), 39.5 (C**4**), 24.9 (C**2**), 24.0 (C**5**), 18.9 (C**6**).

IR *vmax*/cm-1: 3300 (w), 2973 (br), 2681 (w), 1695 (s), 1475 (m), 1279 (m), 1202 (m), 631 (s).

HRMS (ES-) m/z calcd for $C_9H_{13}O_2$ [$(M-H)^-$] 153.0916, found 153.0911.

3-(Prop-2-yn-1-yloxy)propanoic acid **599**



In a flame dried round-bottomed flask, a solution of *n*BuLi (4.4 mL, 2.5 M in hexane, 11 mmol) was added dropwise over 5 mins to neat propargyl alcohol (6.4 mL, 110 mmol) at 0°C. The solution was stirred for 5 minutes before adding *tert*-butyl acrylate (14.7 mL, 100 mmol) at 0°C. The solution was allowed to warm to r.t. and stirred for 18 hours. Trifluoroacetic acid (10 mL) was added dropwise until the solution was neutral before addition of the remaining volume. The solution was then left to stir at

50°C for 16 hours. The solvent was concentrated *in vacuo* to give the crude product. The product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10 to 50/50) to give the title compound (10.57 g, 83%) as a clear colourless oil.

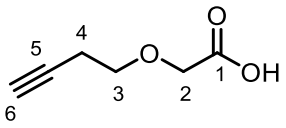
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.20 (2H, d, *J* = 2.4 Hz, C**3**-$\underline{H_2}$), 3.84 (2H, t, *J* = 6.5 Hz, C**4**-$\underline{H_2}$), 2.69 (2H, t, *J* = 6.5 Hz, C**5**-$\underline{H_2}$), 2.47 (1H, t, *J* = 2.5 Hz, C**1**-$\underline{H}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.8 (C**6**), 79.2 (C**2**), 74.8 (C**1**), 65.0 (C**4**), 58.3 (C**3**), 34.6 (C**5**).

IR *vmax*/cm^{-1}: 3287 (br), 2922 (w), 2118 (w), 1711 (s), 1404 (m), 1176 (s), 1099 (s), 1071 (s), 1032 (m).

HRMS (ES-) m/z calcd for $C_6H_7O_3$ [$(M-H)^-$] 127.0395, found 127.0399.

2-(But-3-yn-1-yloxy)acetic acid **601**



To a flame-dried round bottomed flask, a solution of 3-butynol (3.77 mL, 50 mmol) in THF (55 mL) was made. To this, NaH (60% in mineral oil, 2.20 g, 55 mmol) was added portion-wise at 0°C. After gas evolution had ended, ethyl 2-bromoacetate (6.08 mL, 55 mmol) was added over 5 mins. The solution was warmed to r.t. and stirred for 90 mins. The solution was diluted in water (20 mL), and diethyl ether (20 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the organic extracts were combined and dried over $MgSO_4$. The filtrate was concentrated *in vacuo* to give the crude product as an orange oil. The crude product was dissolved in methanol (100 mL) and a solution of NaOH aq. (100 mL, 2 M) was added and the solution stirred for 2 hours. The solution was acidified using 0.3 M HCl until pH 4. The methanol was concentrated *in vacuo* and the remaining aqueous solution was extracted with ethyl acetate (3 x 50 mL). The organic extracts were combined and dried over $MgSO_4$, the filtrate was concentrated *in vacuo* to give the crude product. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10 to 0/100) gave the title compound (3.50 g, 55%) as a colourless oil.

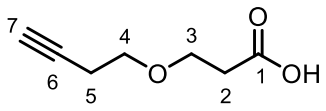
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.22 (2H, s, C**2**-$\underline{H_2}$), 3.74 (2H, t, *J* = 6.5 Hz, C**3**-$\underline{H_2}$), 2.56 (2H, td, *J* = 6.5, 2.5 Hz, C**4**-$\underline{H_2}$), 2.05 (1H, d, *J* = 5.5 Hz, C**6**-$\underline{H}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.1 (C**1**), 80.6 (C**5**), 69.8 (C**6**), 67.9 (C**2**), 59.5 (C**3**), 19.8 (C**4**).

IR *vmax*/cm-1: 3286 (m), 2922 (br), 2655 (w), 1726 (s), 1425 (m), 1197 (s), 980 (m), 653 (s).

HRMS (ES-) m/z calcd for $C_6H_7O_3$ [(M-H)$^-$] 127.0395, found 127.0397.

3-(But-3-yn-1-yloxy)propanoic acid **603**



In a flame dried round-bottomed flask, a solution of *n*BuLi (2.2 mL, 2.5 M in hexane, 5.5 mmol) was added dropwise over 5 mins to neat 3-butynol (3.77 mL, 55 mmol) at 0°C. The solution was stirred for 5 minutes before adding *tert*-butyl acrylate (7.30 mL, 50 mmol) at 0°C. The solution was allowed to warm to r.t. and stirred for 16 hours. Trifluoroacetic acid (10 mL) was added dropwise until the solution was neutral before addition of the remaining volume. The solution was then left to stir at 50°C for 16 hours. The solvent was concentrated *in vacuo* to give the crude product. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10 to 60/40) to give the title compound (5.85 g, 82%) as a clear colourless oil.

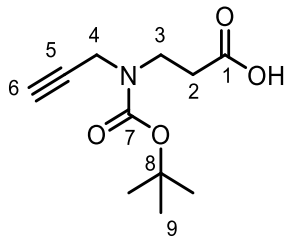
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.79 (2H, t, *J* = 6.0 Hz, C**3**-$\underline{H_2}$), 3.63 (2H, t, *J* = 7.0 Hz, C**4**-$\underline{H_2}$), 2.67 (2H, t, *J* = 6.0 Hz, C**2**-$\underline{H_2}$), 2.49 (2H, td, *J* = 7.0, 2.5 Hz, C**5**-$\underline{H_2}$), 2.01 (1H, t, *J* = 2.5 Hz, C**7**-$\underline{H}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 176.4 (C**1**), 81.0 (C**6**), 69.5 (C**7**), 69.2 (C**4**), 65.9 (C**3**), 34.7 (C**2**), 19.7 (C**5**).

IR *vmax*/cm-1: 3289 (w), 3044 (br), 2920 (w), 2878 (w), 1711 (s), 1422 (w), 1395 (w), 1184 (m), 1108 (s), 933 (w), 641 (s).

HRMS (ES-) m/z calcd for $C_7H_9O_3$ [(M-H)$^-$] 141.0552, found 141.0551.

3-(*N*-(Prop-2-yn-1-yl)pivalamido)propanoic acid **604**



To a flame-dried round bottomed flask, a solution of *N*-Boc-*β*-alanine (1.89 g, 10 mmol) and THF (40 mL) was made. The solution was cooled to 0°C and NaH (60% in mineral oil, 880 mg, 22 mmol) was added portion-wise over 10 mins. The solution was stirred at 0°C for 1 hour, and propargyl bromide

(80% in toluene, 1.22 mL, 11 mmol) was added and stirred for 16 hours at r.t. The reaction was acidified to pH 3 using 3 M HCl. The mixture was extracted with ethyl acetate (3 x 100 mL) and the organic extracts washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was concentrated *in vacuo*. The crude material was purified *via* flash column chromatography (10/189/1:ethyl acetate/petrol/acetic acid) to give the title compound (675 mg, 30%) as an orange oil.

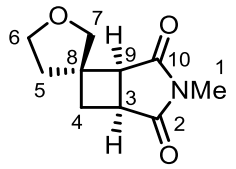
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.10 (2H, s, C**4**-$\underline{H_2}$), 3.63 (2H, t, *J* = 7.0 Hz, C**3**-$\underline{H_2}$), 2.76 – 2.67 (2H, m, C**2**-$\underline{H_2}$), 2.24 (1H, d, *J* = 5.0 Hz, C**6**-$\underline{H}$), 1.49 (9H, s, 3 x C**9**-$\underline{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.9 (C**1**), 154.8 (C**7**), 80.9 (C**4**), 79.5(C**5**), 71.9 (C**6**) 65.9 (**8**), 42.7 (C**3**), 33.2 (C**2**), 28.3 (C**9**).

IR *vmax*/cm-1: 3298 (w), 2977 (br), 2934 (w), 1693 (s), 1463 (m), 1409 (s), 1367 (m), 1249 (m), 1169 (s), 911 (m), 731 (s), 646 (m).

HRMS (ESI) m/z calcd for $C_{11}H_{16}NO_4$ $[(M-H)^-]$ 226.1079, found 226.1071.

(1*S**,5*S**,6*S**)-3-Methyldihydro-2'*H*-3-azaspiro[bicyclo[3.2.0]heptane-6,3'-furan]-2,4-dione **608**



General Procedure 3 – Visible-light. *N*-Methyl maleimide (1.64 g, 6 mmol), compound **609** (1.33 g, 12 mmol), 2,2'diBr TX (111 mg, 0.3 mmol) and DCM (60 mL, 0.1 M) was used. The reaction was stirred at r.t. for 12 hours. The solvent was removed and the crude product was taken forward with no further purification.

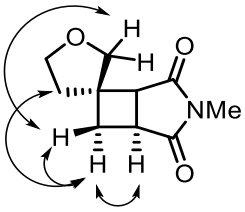
General Procedure 5 – Decarboxylation of *N*-Acyloxy Phthalimides. *A modified general procedure was used.* Using crude product from the previous step (6 mmol), DIPEA (2.10 mL, 12 mmol), 2,2'diBrTX (111 mg, 0.3 mmol), and DCM (120 mL, 0.05 M), was used. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20 to 60/40) gave the title compound (363 mg, 31%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.96 – 3.85 (2H, m, C**6**-$\underline{H_2}$), 3.83 (1H, d, *J* = 9.0 Hz, C**7**-$\underline{H}$), 3.48 (1H, d, *J* = 9.0 Hz, C**7**-$\underline{H}$), 3.30 (1H, ddd, *J* = 10.0, 6.5, 5.0 Hz, C**3**-$\underline{H}$), 3.26 (1H, d, *J* = 6.5 Hz, C**9**-$\underline{H}$), 3.06 (3H, s, C**1**-$\underline{H_3}$), 2.62 (1H, ddd, *J* = 13.0, 10.0, 1.5 Hz, C**4**-$\underline{H}$), 2.26 – 2.14 (3H, m, C**4**-$\underline{H}$, C**5**-$\underline{H_2}$).

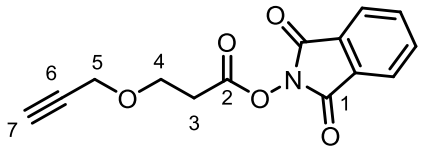
^{13}C NMR (125 MHz, $CDCl_3$) δ_C 179.4 (C**2**), 176.7 (C**10**), 74.4 (C**7**), 66.7 (C**6**), 47.0 (C**9**), 45.4 (C**8**), 41.3 (C**5**), 34.8 (C**4**), 33.9 (C**3**), 25.0 (C**1**).

IR *vmax*/cm-1: 2939 (w), 2864 (w), 1768 (w), 1693 (s), 1430 (m), 1379 (m), 1227 (m), 1134 (m), 1048 (m).

HRMS (ESI) m/z calcd for $C_{10}H_{13}NNaO_3$ [$(M+Na)^+$] 218.0788, found 218.0782.



1,3-Dioxoisoindolin-2-yl 3-(prop-2-yn-1-yloxy)propanoate **609**



General Procedure 7. Using compound **559** (8.00 g, 62 mmol) was used. The product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10) to give the title compound (12.11 g, 85%) as a colourless crystalline powder. The sample was stored in the dark at -18°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 – 7.88 (2H, m, 2 x **Ar**-H), 7.85 – 7.77 (2H, m, 2 x **Ar**-H), 4.26 (2H, d, *J* = 2.5 Hz, C**5**-H_2), 3.96 (2H, t, *J* = 6.5 Hz, C**4**-H_2), 3.01 (2H, t, *J* = 6.5 Hz, C**3**-H_2), 2.49 (1H, t, *J* = 2.5 Hz, C**7**-H).

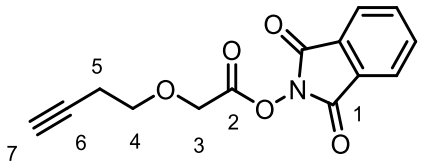
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.5 (C**1**), 161.8 (C**2**), 134.8 (**Ar**), 128.9 (**Ar**), 124.0 (**Ar**), 79.1 (C**6**), 75.0 (C**7**), 64.3 (C**4**), 58.5 (C**5**), 32.0 (C**3**).

IR *vmax*/cm-1: 3274 (m), 2889 (w), 2120 (w), 1813 (m), 1726 (s), 1359 (m), 1098 (s), 873 (s), 693 (s).

HRMS (ESI) m/z calcd for $C_{14}H_{11}NNaO_5$ [$(M+Na)^+$] 296.0529, found 296.0535.

Mp ($CHCl_3$): 62-63 °C

1,3-Dioxoisoindolin-2-yl 2-(but-3-yn-1-yloxy)acetate **610**



General Procedure 7. Compound **601** (2.00 g, 15.6 mmol) was used and stirred at r.t. for 16 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) gave the title compound (2.98 g, 70%) as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 – 7.91 (2H, m, 2 x **Ar**-H), 7.85 – 7.81 (2H, m, 2 x **Ar**-H), 4.21 (2H, s, C**3**-H_2), 3.74 (2H, t, *J* = 6.5 Hz, C**4**-H_2), 2.56 (2H, td, *J* = 6.5, 2.5 Hz, C**5**-H_2), 2.07 – 2.04 (1H, m, C**7**-H).

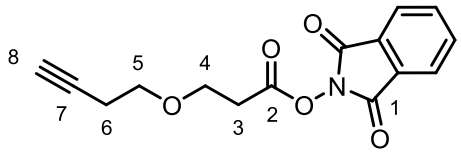
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.7 (C**2**), 161.6 (C**1**), 134.9 (**Ar**), 128.8 (**Ar**), 124.1 (**Ar**), 80.6 (C**6**), 70.2 (C**7**), 69.8 (C**4**), 67.9 (C**3**), 19.8 (C**5**).

IR *vmax*/cm-1: 3300 (w), 2973 (w), 1695 (s), 1475 (m), 1279 (m), 1202 (m), 1032 (w), 631 (s).

HRMS (ESI) m/z calcd for $C_{14}H_{11}NNaO_5$ [$(M+Na)^+$] 296.0529, found 296.0524.

Mp ($CHCl_3$): 111-114 °C

1,3-Dioxoisoindolin-2-yl 3-(but-3-yn-1-yloxy)propanoate **611**



General Procedure 7. Compound **603** (5.00 g, 35 mmol) was used and stirred at r.t. for 16 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) gave the title compound (6.19 g, 74%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 – 7.87 (2H, m, 2 x **Ar**-H), 7.86 – 7.77 (2H, m, 2 x **Ar**-H), 3.91 (2H, t, *J* = 6.5 Hz, C**4**-H_2), 3.67 (2H, t, *J* = 7.0 Hz, C**5**-H_2), 2.99 (2H, t, *J* = 6.5 Hz, C**3**-H_2), 2.54 (2H, td, *J* = 7.0, 2.5 Hz, C**6**-H_2), 2.02 (1H, t, *J* = 2.5 Hz, C**8**-H).

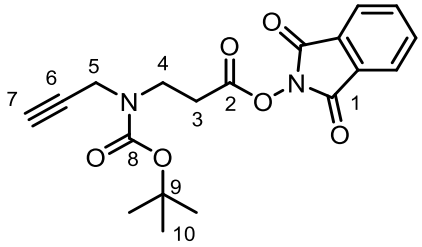
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 167.6 (C**2**), 161.8 (C**1**), 134.8 (**Ar**), 128.9 (**Ar**), 124.0 (**Ar**), 81.1 (C**7**), 69.4 (C**5**), 69.4 (C**8**), 65.5 (C**4**), 32.2 (C**3**), 19.7 (C**6**).

IR *vmax*/cm-1: 3133 (br), 2937 (w), 2923 (w), 1789 (m), 1736 (s), 1707 (s), 1463 (m), 1185 (m), 1130 (m), 1079 (m), 874 (s), 692 (s).

HRMS (ESI) m/z calcd for $C_{15}H_{13}NNaO_5$ [$(M+Na)^+$] 310.0686, found 310.0672.

Mp ($CHCl_3$): 63-64 °C

1,3-Dioxoisoindolin-2-yl 3-(N-(prop-2-yn-1-yl)pivalamido)propanoate **612**



General Procedure 7. Compound **605** (100 mg, 0.37 mmol) was used. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) gave the title compound (182 mg, 66%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.92 (2H, dd, *J* = 5.5, 3.0, 2 x **Ar**-H), 7.86 – 7.78 (2H, m, 2 x **Ar**-H), 4.23 – 4.08 (2H, m, C**4**-H_2), 3.76 (2H, t, *J* = 7.0 Hz, C**3**-H_2), 3.06 (2H, s, C**5**-H_2), 2.28 (1H, t, *J* = 2.5 Hz, C**7**-H), 1.52 (9H, s, 3 x C**10**-H_3).

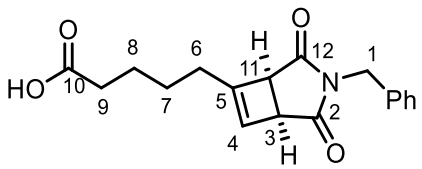
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 168.1 (C**8**), 161.8 (C**1**), 154.9 (C**2**), 134.8 (**Ar**), 128.9 (**Ar**), 124.0 (**Ar**), 77.2 (C**7**), 42.9 (C**3**), 37.8 (C**4**), 30.7 (C**5**), 28.3 (C**10**).

IR *vmax*/cm-1: 3235 (m), 2983 (w), 1820 (m), 1739 (s), 1664 (s), 1464 (m), 1363 (m), 1239 (s), 1074 (s), 980 (m), 878 (m), 692 (s).

HRMS (ESI) m/z calcd for $C_{19}H_{20}N_2NaO_6$ $[(M+Na)^+]$ 395.1214, found 395.1214.

Mp ($CHCl_3$): 78 – 81 °C

5-((1*S**,5*S**)-3-Benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)pentanoic acid **613**



General Procedure 3 – Visible-light. Heptynoic acid (249 mg, 1.00 mmol), *N*-benzyl maleimide (374 mg, 2.00 mmol), 2,2'-diBrTX (19 mg, 0.05 mmol) and DCM (20 mL) were used and stirred at r.t. for 2 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20 to 60/40) to give the title compound (249 mg, 80%) as a colourless oil.

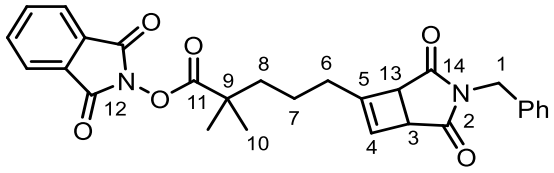
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43 – 7.19 (5H, m, 5 x **Ar**-H), 6.12 (1H, td, *J* = 1.5, 1.0 Hz, C**4**-H), 4.63 – 4.55 (2H, d, *J* = 2.0 Hz, C**1**-H_2), 3.71 (1H, dt, *J* = 3.0, 1.0 Hz, C**11**-H), 3.64 (1H, dtd, *J* = 3.0, 2.0, 1.0 Hz, C**3**-H), 2.35 (2H, t, *J* = 7.0 Hz, C**9**-H_2), 2.26 – 2.16 (2H, m, C**6**-H_2), 1.67 – 1.45 (4H, m, C**7**-H_2, C**8**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 178.0 (C**2**), 175.2 (C**13**), 174.4 (C**10**), 153.4 (C**5**), 135.9 (**Ar**), 129.9 (**Ar**), 128.6 (C**4**), 128.5 (**Ar**), 127.8 (**Ar**), 48.6 (C**11**), 43.9 (C**3**), 42.1 (C**1**), 33.3 (C**9**), 29.5 (C**6**), 25.4 (C**8**), 24.0 (C**7**).

IR *vmax*/cm-1: 2940 (br), 1764 (m), 1696 (s), 1429 (m), 1390 (m), 1167 (m), 1032 (m), 829 (m), 700 (m).

HRMS (ESI) m/z calcd for $C_{18}H_{19}NNaO_4$ [$(M+Na)^+$] 336.1206, found 336.1211.

1,3-Dioxoisoindolin-2-yl 5-(3-benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)-2,2-dimethylpentanoate **614**



General Procedure 3 – Visible-light. Compound **577** (300 mg, 1.00 mmol), *N*-benzyl maleimide (374 mg, 2.00 mmol), 2,2'-diBrTX (19 mg, 0.05 mmol) and DCM (20 mL) were used and stirred at r.t. for 2 hours. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20 to 60/40) to give the title compound (204 mg, 42%) as a colourless oil.

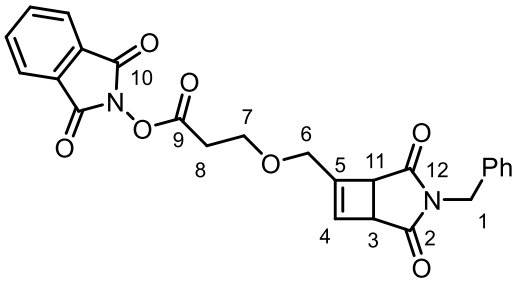
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 – 7.86 (2H, m, 2 x **Ar**-H), 7.86 – 7.75 (2H, m, 2 x **Ar**-H), 7.38 – 7.29 (5H, m, 5 x **Ar**-H), 6.20 (1H, td, *J* = 1.5, 1.0 Hz, C**4**-H), 4.64 (2H, s, C**1**-H_2), 3.77 (1H, dt, *J* = 3.0, 1.0 Hz, C**13**-H), 3.66 (1H, ddt, *J* = 4.0, 3.0, 1.5 Hz, C**3**-H), 2.24 (2H, s, C**6**-H_2), 1.76 – 1.61 (4H, m, C**7**-H_2, C**8**-H_2), 1.40 (3H, s, C**10**-H_3), 1.40 (3H, s, C**10**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 175.4 (C**2**), 174.4 (C**14**), 173.6 (C**11**), 162.1 (C**12**), 153.3 (C**5**) 136.0 (**Ar**), 134.7 (**Ar**), 130.0 (**Ar**), 128.6 (**Ar**), 128.4 (**Ar**), 127.8 (**Ar**), 123.9 (**Ar**), 48.6 (C**13**), 44.0 (C**3**), 42.0 (C**1**), 40.1 (C**7**), 30.0 (C**6**), 25.2 (C**10**), 25.0 (C**10**), 21.3 (C**8**).

IR *vmax*/cm-1: 3703 (w), 2980 (w), 1780 (w), 1742 (s), 1702 (s), 1390 (w), 1054 (m), 1033 (m), 1014 (m), 697 (m).

HRMS (ESI) m/z calcd for $C_{28}H_{26}N_2NaO_6$ [$(M+Na)^+$] 509.1683, found 509.1692.

1,3-Dioxoisoindolin-2-yl 3-((3-benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)methoxy)propanoate **615**



General Procedure 3 – Visible-Light. Compound **609** (205 mg, 0.75 mmol), *N*-benzyl maleimide (94 mg, 0.5 mmol), 2,2'-diBrTX (9 mg, 0.025 mmol) and DCM (5.0 mL) were used. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20 to 60/40) to give the title compound (136 mg, 59%) as a colourless oil.

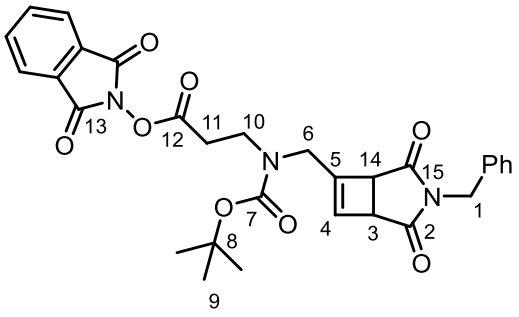
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 – 7.86 (2H, m, 2 x **Ar**-H), 7.86 – 7.79 (2H, m, 2 x **Ar**-H), 7.39 – 7.29 (5H, m, 5 x **Ar**-H), 6.40 (1H, td, *J* = 1.5, 1.0 Hz, C**4**-H), 4.70 – 4.58 (2H, m, C**1**-H_2), 4.13 – 4.10 (2H, m, C**6**-H_2), 3.86 – 3.83 (1H, m, C**11**-H), 3.80 (2H, dt, *J* = 6.5, 5.5 Hz, C**7**-H_2), 3.74 (1H, ddd, *J* = 3.0, 2.0, 1.0 Hz, C**3**-H), 2.93 (2H, ddd, *J* = 6.5, 5.5, 5.0 Hz, C**8**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.7 (C**2**), 173.9 (C**12**), 167.7 (C**9**), 161.9 (C**10**), 148.8 (C**5**), 135.9 (**Ar**), 134.9 (**Ar**), 132.6 (C**4**), 128.9 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 127.9 (**Ar**), 124.1 (**Ar**), 67.2 (C**6**), 65.5 (C**7**), 47.5 (C**11**), 44.7 (C**3**), 42.2 (C**1**), 32.2 (C**8**).

IR *vmax*/cm-1: 3063 (w), 2927 (w), 1816 (w), 1787 (m), 1740 (s), 1696 (s), 1378 (m), 1348 (m), 1134 (m), 877 (m), 731 (m), 695 (s).

HRMS (ESI) m/z calcd for $C_{25}H_{21}N_2O_7$ [$(M+H)^+$] 461.1343, found 461.1342.

1,3-Dioxoisoindolin-2-yl 3-(N-((3-benzyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)methyl)pivalamido)propanoate **616**



General Procedure 3 – Visible-light. Compound **612** (168 mg, 0.45 mmol), *N*-benzyl maleimide (56 mg, 0.30 mmol), 2,2'-diBrTX (11 mg, 0.03 mmol) and DCM (3 mL) were used. Flash column chromatography (petroleum ether/ethyl acetate: 80/20 to 60/40) gave the title compound (97 mg, 58%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.88 – 7.77 (2H, m, 2 x **Ar**-H), 7.77 – 7.68 (2H, m, 2 x **Ar**-H), 7.29 – 7.18 (5H, m, 5 x **Ar**-H), 6.15 (1H, s, C**4**-H), 4.60 – 4.44 (2H, m, C**1**-H_2), 4.01 – 3.80 (2H, m, C**10**-H_2), 3.70 – 3.57 (2H, m, C**6**-H_2), 3.45 – 3.25 (2H, m, C**11**-H_2), 2.93 – 2.66 (2H, m), 1.47 – 1.31 (10H, m).

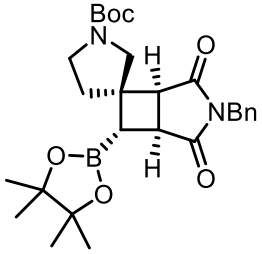
^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.6 (C**2**), 173.3 (C**15**), 168.5 (C**13**), 168.0 (C**7**), 161.8 (C**12**), 154.9 (C**5**), 149.4 (**Ar**), 135.8 (**Ar**), 134.9 (**Ar**), 131.6 (**Ar**), 128.9 (C**4**), 128.7 (**Ar**), 127.9 (**Ar**), 124.1 (**Ar**), 80.9 (C**8**), 47.8 (C**6**), 47.3 (C**10**), 46.7 (C**14**), 44.1 (C**3**), 43.3 (C**1**), 30.8 (C**11**), 28.4 (C**9**).

IR *vmax*/cm-1: 3666 (w), 2977 (m), 2906 (m), 1787 (m), 1741 (s), 1695 (s), 1466 (w), 1365 (m), 1164 (s), 1078 (s), 877 (m), 695 (s).

HRMS (ESI) m/z calcd for $C_{30}H_{29}N_3NaO_8$ [$(M+Na)^+$] 582.1847, found 582.1840.

Mp ($CHCl_3$): 61 – 64 °C

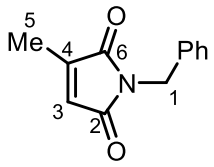
tert-Butyl (1*S**,5*S**,6*R**,7*S**)-3-benzyl-2,4-dioxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azaspiro[bicyclo[3.2.0]heptane-6,3'-pyrrolidine]-1'-carboxylate **618**



General Procedure 5 – Decarboxylation of *N*-Acyloxy Phthalimide. Compound **616** (14 mg, 0.025 mmol), DIPEA (13 µL, 0.075 mmol), B_2cat_2 (24 mg, 0.10 mmol), 2,2'diBrTX (1.0 mg, 0.003 mmol) and DCM (5 mL) were used. Purification *via* flash column chromatography (acetone/hexane: 10/90) gave the title compound as a mixture compounds.

HRMS (ESI) m/z calcd for $C_{27}H_{37}BN_2NaO_6$ [$(M+Na)^+$] 519.2637, found 519.2621.

1-Benzyl-3-methyl-1*H*-pyrrole-2,5-dione **644**



To a round-bottomed flask, a solution of citraconic anhydride (900 µL, 10 mmol), benzyl amine (1.09 mL, 10 mmol) and acetic acid (15 mL) was made. The solution was heated to reflux, and the reaction was followed by ^{1}H NMR. After 3 hours the reaction was completed and the solvent was concentrated *in vacuo* and the crude material was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (1.72 g, 86%) as a colourless solid.

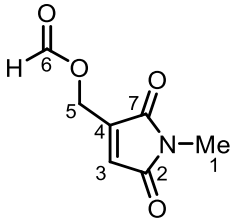
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.53 – 6.91 (5H, m, 5 x **Ar**-H), 6.35 (1H, q, *J* = 2.0 Hz, C**3**-H), 4.68 (2H, s, C**1**-H_2), 2.10 (3H, d, *J* = 2.0 Hz, C**5**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.5 (C**2**), 170.5 (C**6**), 145.8 (C**4**), 136.5 (**Ar**), 128.7 (C**3**), 128.4 (**Ar**), 127.8 (**Ar**), 127.4 (**Ar**), 41.5 (C**1**), 11.0 (C**5**).

IR *vmax*/cm^{-1}: 2926 (w), 1774 (w), 1700 (s), 1640 (m), 1433 (s), 1394 (m), 1358 (m), 1324 (m), 1128 (w), 1070 (w), 959 (s), 849 (s), 725 (s).

HRMS (ESI) m/z calcd for $C_{12}H_{11}NNaO_2$ [$(M+Na)^+$] 224.0682, found 224.0687.

(1-Methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)methyl formate **646**



To a round-bottomed flask, a solution of citraconic anhydride (900 µL, 10 mmol), methyl amine hydrochloride (670 mg, 10 mmol) and formic acid (15 mL) was made. The solution was heated to reflux, and the reaction was followed by ^{1}H NMR. After 48 hours, selenium dioxide (1.22 g, 11 mmol) was added and the solution was left to stir over 16 hours at reflux. After 18 hours, the reaction had not gone to completion but had ceased converting starting material. The solution was filtered through celite to remove selenium solids and the solvent was concentrated *in vacuo* to give the crude material. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10) gave the title compound (439 mg, 26%) as a colourless crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.08 (1H, t, *J* = 1.0 Hz, C**6**-H), 6.48 (1H, t, *J* = 2.0 Hz, C**3**-H), 5.02 (2H, dd, *J* = 2.0, 1.0 Hz, C**5**-H_2), 2.96 (3H, s, C**1**-H_3).

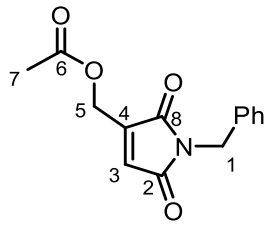
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.7 (C**7**), 169.6 (C**2**), 159.8 (C**6**), 143.0 (C**4**), 128.5 (C**3**), 56.8 (C**5**), 23.9 (C**1**).

IR *vmax*/cm^{-1}: 3098 (w), 1770 (w), 1702 (s), 1695 (s), 1443 (m), 1181 (m), 1149 (m), 872 (m), 682 (m).

HRMS (ESI) m/z calcd for $C_7H_7NNaO_4$ [$(M+Na)^+$] 192.0267, found 192.0263.

Mp ($CHCl_3$): 70 – 73 °C

(1-Benzyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)methyl acetate **650**



To a round-bottomed flask, a solution of citraconic anhydride (900 µL, 10 mmol), benzyl amine (1.09 mL, 10 mmol) and acetic acid (15 mL) was made. The solution was heated to reflux, and the reaction was followed by ^{1}H NMR. After 3 hours, selenium dioxide (1.22 g, 11 mmol) was added and the solution was left to stir over 16 hours at reflux. The solution was filtered through celite to remove selenium solids and the solvent was concentrated *in vacuo* to give the crude material. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10) gave the title compound (573 mg, 23%) as a yellow crystalline solid. Compound **644** was recovered in a 41% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.25 (5H, m, 5 x **Ar**-H), 6.53 (1 H, t, *J* 2.0, C**3**-H), 5.00 (2 H, d, *J* 2.0, C**5**-H_2), 4.69 (2 H, s, C**1**-H_2), 2.17 (3 H, s, C**7**-H_3).

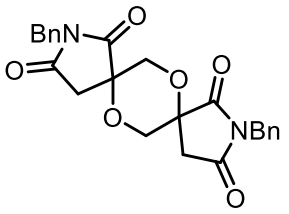
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.0 (C**8**), 169.5 (C**6**), 169.3 (C**2**), 143.7 (C**4**), 136.0 (**Ar**), 128.7 (C**3**), 128.5 (**Ar**), 128.1 (**Ar**), 127.9 (**Ar**), 57.4 (C**5**), 41.6 (C**1**), 20.6 (C**7**).

IR *vmax*/cm^{-1}: 2937 (w), 1745 (s), 1699 (s), 1436 (M), 1403 (m), 1217 (s), 1122 (m), 1066 (m), 1044 (m), 857 (s), 703 (s).

HRMS (ESI) m/z calcd for $C_{14}H_{13}NNaO_4$ [$(M+Na)^+$] 282.0737, found 282.0745.

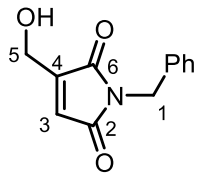
Mp ($CHCl_3$): 69 – 71 °C

2,10-Dibenzyl-6,13-dioxa-2,10-diazadispiro[4.2.48.25]tetradecane-1,3,9,11-tetraone **656**



LRMS (ESI) m/z calcd for $C_{24}H_{22}N_2NaO_6$ [$(M+Na)^+$] 457.3, found 457.3.

1-Benzyl-3-(hydroxymethyl)-1*H*-pyrrole-2,5-dione **657**



To a round-bottomed flask, compound **650** (3.00 g, 17.70 mmol), *p*-toluene sulfonic acid (336 mg, 1.77 mmol) and methanol (177 mL, 0.1 M) were added. The solution was heated to 50°C and stirred for 16 hours. The solvent was concentrated *in vacuo* and the crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) to give the title compound (2.42 g, 96%) as a clear colourless oil.

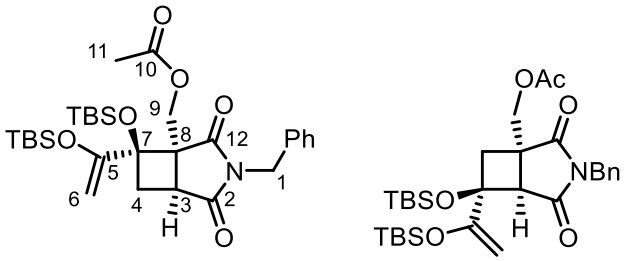
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 – 7.15 (5H, m, 5 x **Ar**-H), 6.46 (1H, t, *J* = 2.0 Hz, C**3**-H), 4.58 (2H, s, C**1**-H_2), 4.52 (2H, d, *J* = 2.0 Hz, C**5**-H_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.4 (C**6**), 170.0 (C**2**), 148.1 (C**4**), 136.1 (**Ar**), 128.7 (C**3**), 128.4 (**Ar**), 127.9 (**Ar**), 126.7 (**Ar**), 57.3 (C**5**), 41.5 (C**1**).

IR *vmax*/cm^{-1}: 3459 (br), 3032 (w), 2936 (w), 1695 (s), 1497 (m), 1435 (s), 1398 (s), 1350 (m), 1206 (m), 1124 (m), 1047 (m), 1071 (m).

HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3$ [$(M+H)^+$] 218.0733, found 218.0734.

((1*R**,5*S**,7*R**)-3-Benzyl-7-((tert-butyldimethylsilyl)oxy)-7-(1-((tert-butyldimethylsilyl)oxy)vinyl)-2,4-dioxo-3-azabicyclo[3.2.0]heptan-1-yl)methyl acetate **665**



2:1

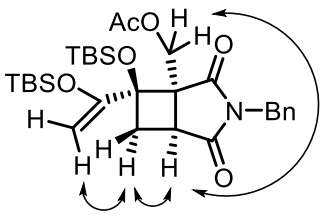
General Procedure 3 – Visible-light. Compound **650** (41 mg, 0.16 mmol), 2,2,7,7-tetramethyl-4,5-dimethylene-3,6-dioxa-2,7-disilaoctane (77 mg, 0.24 mmol), 2,2'-diBrTX (3 mg, 0.008 mmol) and DCM (1.6 mL) were used. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10) gave the title compound (12 mg, 13%) as a colourless cloudy oil.

^{1}H NMR (500 MHz, cdcl$_3$) δ_H 7.39 – 7.20 (5H, m, 5 x **Ar**-H), 4.77 (1H, d, *J* = 14.0 Hz, C**1**-HH), 4.63 (1H, d, *J* = 14.5 Hz, C**1**-HH), 4.57 (1H, d, *J* = 2.5 Hz, C**6**-HH), 4.52 – 4.49 (1H, m, C**9**-HH), 4.36 – 4.34 (1H, m, C**6**-HH), 4.31 (1H, d, *J* = 11.0 Hz, C**9**-HH), 3.18 (1H, dd, *J* = 13.0, 10.5 Hz, C**4**-HH), 2.86 (1H, dd, *J* = 10.5, 4.5 Hz, C**3**-H), 2.17 (1H, dd, *J* = 13.0, 4.5 Hz, C**4**-HH), 1.76 (3H, s, C**11**-H$_3$), 1.00 – 0.95 (18H, m, 2 x **Si^{t}Bu**-H), 0.30 – 0.26 (12H, m, 2 x **SiMe$_2$**-H).

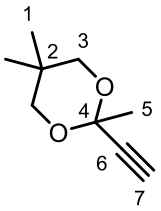
^{13}C NMR (125 MHz, $CDCl_3$) δ_C 178.7 (C**2**), 174.7 (C**12**), 170.3 (C**10**), 156.5 (C**5**), 136.1 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 127.7 (**Ar**), 91.6 (C**6**), 77.6 (C**7**), 62.5 (C**9**), 58.0 (C**8**), 42.6 (C**1**), 35.5 (C**3**), 34.2 (C**4**), 25.8 (**Si^{t}Bu**), 25.7 (**Si^{t}Bu**), 20.4 (C**11**), 18.1 (**SiMe$_2$**), 18.0 (**SiMe$_2$**).

IR *vmax*/cm-1: 2953 (m), 2930 (m), 2857 (m), 1748 (m), 1707 (s), 1390 (m), 1253 (m), 1227 (s), 1145 (m), 1038 (m), 833 (s), 777 (s), 698 (s).

HRMS (ESI) m/z calcd for $C_{30}H_{48}NO_6Si_2$ $[(M+H)^+]$ 574.3015, found 574.3016.



2-Ethynyl-2,5,5-trimethyl-1,3-dioxane **715**



To a round bottomed flask, a solution of 3-butyne-2-one (5.00 mL, 64 mmol), neopentyl glycol (7.30 g, 70 mmol), *p*-toluene sulfonic acid (500 mg, 10% w/w), DCM (32 mL) and calcium sulphate (10.00 g) was made and stirred at 50°C for 16 hours. The solvent was concentrated *in vacuo* and the mixture was diluted in diethyl ether (100 mL) and washed with $NaHCO_3$ (100 mL). The organic extracts were dried over $MgSO_4$ and the filtrate was concentrated *in vacuo* [*caution: product sublimes*] to give the title compound (6.60 g, 67%) as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.94 (2H, ddt, *J* = 11.0, 1.8, 1.0 Hz, C**3**-$\underline{H_2}$), 3.44 (2H, dt, *J* = 11.5, 1.5 Hz, C**3**-$\underline{H_2}$), 2.60 (1H, s, C**7**-$\underline{H}$), 1.69 (3H, s, C**5**), 1.20 (3H, s, C**1**-$\underline{H_3}$), 0.78 (3H, s, C**1**-$\underline{H_3}$).

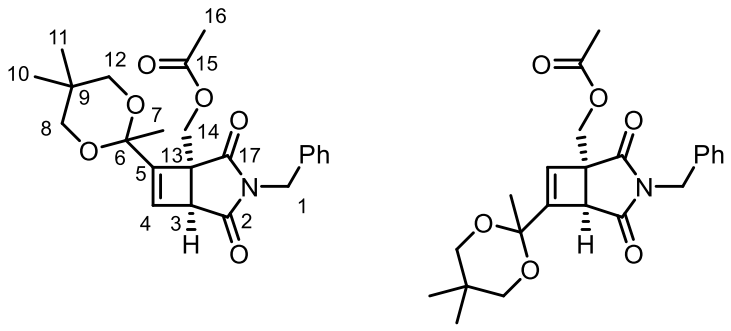
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 93.4 (C**4**), 80.0 (C**6**), 73.6 (C**7**), 72.8 (C**3**), 29.7 (C**2**), 28.9 (C**5**), 22.9 (C**1**), 21.8 (C**1**).

IR *vmax*/cm-1: 3236 (m), 2958 (w), 2871 (w), 2105 (w), 1718 (w), 1470 (w), 1374 (w), 1154 (s), 1066 (s), 1009 (s), 858 (s), 706 (s).

HRMS (ESI) m/z calcd for $C_9H_{15}O_2$ [$(M+H)^+$] 155.1067, found 155.1063.

Mp ($CHCl_3$): 58-60 °C

((1*S**,5*S**)-3-Benzyl-2,4-dioxo-7-(2,5,5-trimethyl-1,3-dioxan-2-yl)-3-azabicyclo[3.2.0]hept-6-en-1-yl)methyl acetate **716**



1.3:1

General Procedure 3 – Visible-light. Compound **650** (480 mg, 1.85 mmol), compound **715** (571 mg, 3.70 mmol), 2,2'diBrTX (34 mg, 0.09 mmol) and DCM (19 mL) was used and irradiated for 2 hours. The

crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) gave the title compound (505 mg, 66%) as a colourless oil.

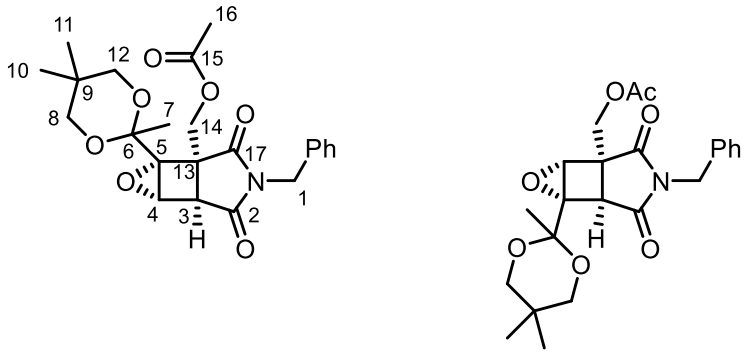
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*mixture of regioisomers reported*) 7.41 – 7.28 (5H, m, 5 x **Ar**-H), 6.50 – 6.27 (1H, m, C**4**-H), 4.81 – 4.38 (4H, m, C**1**-H_2, C**14**-H_2), 3.64 – 3.24 (5H, m, C**8**-H_2, C**12**-H_2, C**3**-H), 2.06 – 1.95 (3H, m C**16**-H_3), 1.35 (3H, s, C**7**-H_3), 1.14 – 1.03 (3H, m, C**10**-H_3), 0.77 – 0.60 (3H, m, C**11**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*mixture of regioisomers reported*) 174.1 (C**2**), 173.7 (C**2**'), 173.2 (C**17**), 172.3 (C**17**'), 170.3 (C**15**), 170.3 (C**15**'), 151.5 (C**5**), 151.4 (C**4**'), 141.3 (**Ar**), 135.6 (**Ar**), 135.5 (**Ar**), 134.3 (**Ar**), 134.1 (**Ar**), 128.6 (C**4**), 128.6 (C**5**'), 128.4 (**Ar**), 128.0 (**Ar**), 127.9 (**Ar**), 96.2 (C**6**), 96.1 (C**6**'), 72.3 (C**8**), 72.1 (C**8**'), 71.9 (C**12**), 71.9 (C**12**), 62.2 (C**14**), 62.1 (C**14**'), 49.8 (C**13**), 47.0 (C**13**'), 42.3(C**1**), 42.3(C**1**'), 29.9 (C**9**), 29.8 (C**9**'), 26.2 (C**7**), 24.9 (C**7**), 22.3 (C**10**'), 22.2 (C**11**), 22.1 (C**10**), 22.0 (C**11**'), 20.6 (C**16**), 20.6 (C**16**').

IR *vmax*/cm-1: 2954 (w), 2970 (w), 1745 (m), 1702 (s), 1387 (m), 1227 (s), 1175 (s), 1037 (m), 859 (w), 700 (m).

HRMS (ESI) m/z calcd for $C_{23}H_{27}NNaO_6$ [$(M+Na)^+$] 436.1731, found 436.1727.

((1*R**,2*R**,4*S**,5*R**)-7-Benzyl-6,8-dioxo-2-(2,5,5-trimethyl-1,3-dioxan-2-yl)-3-oxa-7-azatricyclo[3.3.0.02,4]octan-1-yl)methyl acetate **718**



To a round bottomed flask, compound **716** (200 mg, 0.48 mmol), *m*-CPBA (77%, 163 mg, 0.73 mmol) and chloroform (1.0 mL) were added and stirred at reflux for 16 hours. The solution was diluted in ethyl acetate (10 mL) washed with $NaHCO_3$ (3 x 10 mL) and organic extracts dried over $MgSO_4$, filtered and the solvent was concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 80/20) gave the title compound (62 mg, 30%) as a colourless oil.

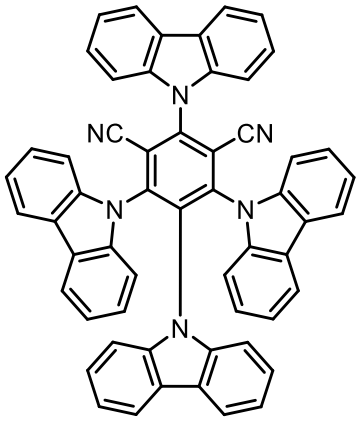
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*mixture of regioisomers reported*) 7.38 – 7.21 (5H, m, 5 x **Ar**-H), 4.81 – 4.15 (5H, m, C**1**-H_2, C**14**-H_2, C**3**-H), 3.50 – 3.03 (5H, m, C**8**-H_2, C**12**-H_2, C**4**-H), 1.85 (3H, d, *J* = 12.5 Hz, C**16**-H_3), 1.37 – 1.19 (3H, m, C**7**-H_3), 1.01 – 0.80 (3H, m, C**10**-H_3), 0.70 (3H, s, C**11**-H_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*mixture of regioisomers reported*) 173.6 (C**2**), 172.8 (C**2**'), 171.9 (C**17**), 171.3 (C**17**'), 170.2 (C**15**), 170.1 (C**15**'), 135.4 (**Ar**), 135.4 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 127.8 (**Ar**), 95.8 (C**6**), 95.1 (C**6**'), 70.7 (C**8**), 70.5 (C**8**'), 70.5 (C**12** + C**12**'), 68.2, 66.4, 61.5 (C**14**), 61.0 (C**14**'), 58.6 (C**5**), 58.5 (C**5**'), 58.2 (C**4**), 56.7 (C**4**'), 50.9 (C**13**), 50.6 (C**13**'), 42.8 (C**1**), 42.8 (C**1**'), 29.9 (C**9**), 29.9 (C**9**'), 23.1 (C**10**), 22.8 (C**10**'), 22.5 (C**11**), 22.4 (C**11**'), 20.6 (C**16**), 20.4 (C**16**'), 17.1 (C**7**), 15.8 (C**7**').

IR *vmax*/cm-1: 2956 (w), 2971 (w), 1744 (m), 1706 (s), 1393 (m), 1230 (s), 1039 (m), 880 (w), 700 (m).

HRMS (ESI) m/z calcd for $C_{23}H_{27}NNaO_7$ [$(M+Na)^+$] 452.1680, found 452.1677.

1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene **S1**

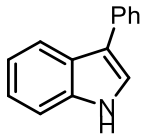


In a flame dried, dual necked, round bottomed flask, a solution of carbazole (1.67 g, 10 mmol), and THF (40 mL) was cooled to 0°C and sodium hydride was added slowly. The solution was stirred at r.t. for 30 mins. 2,4,5,6-Tetrafluoroisophthalonitrile was added and the solution was stirred at r.t. for 16 hrs. On completion of the reaction, the solution was washed with water and ethanol. The product was recrystallised in hexane/DCM to give the title compound (1.18 g, 75%) as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.22 (1H, d, *J* = 8.0 Hz, **Ar**-H), 7.75 – 7.65 (4H, m, 4 x **Ar**-H), 7.49 (1H, ddd, *J* = 8.0, 6.5, 1.5 Hz, **Ar**-H), 7.33 (1H, d, *J* = 7.5 Hz, **Ar**-H), 7.22 (2H, dd, *J* = 7.0, 2.0 Hz, 2 x **Ar**-H), 7.08 (4H, tt, *J* = 7.5, 6.0 Hz, 4 x **Ar**-H), 6.82 (2H, t, *J* = 7.5 Hz, 2 x **Ar**-H), 6.63 (1H, t, *J* = 7.5 Hz, **Ar**-H).[37]

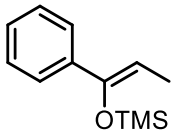
All recorded data match literature values.

3-Phenyl-1H-indole **S2**



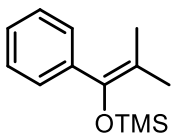
To a round bottomed flask, phenylacetaldehyde (1.13 mL, 10.17 mmol) and phenylhydrazine (1 mL, 37.4 mmol) was added and stirred at r.t. for 1 hour followed by heating to 100 °C for 30 mins. A solution of $ZnCl_2$ (2.5 g, 18.31 mmol) in ethanol (10 mL) was added to the reaction mixture and stirred at 100 °C for 1 hour. After cooling, the reaction mixture was filtered and the solvent was concentrated *in vacuo*. The crude product was washed with 1 M HCl soln (10 mL) and extracted with DCM (3 x 10 mL). The combined organic extracts were combined and dried over $MgSO_4$ to give the title compound (1.11 g, 57%) as an orange solid. The crude product was used in the next step with no further purification.[178]

(*Z*)-Trimethyl((1-phenylprop-1-en-1-yl)oxy)silane **S3**



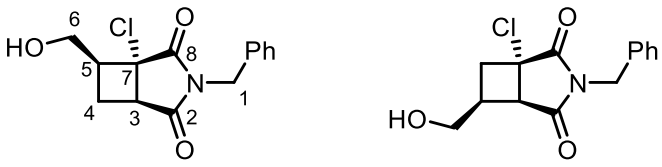
To a flame-dried dual-necked round bottomed flask, propiophenone (1.0 mL, 7.53 mmol), NaI (129 mg, 9.34 mmol), triethylamine (1.29 mL, 9.34 mmol) and acetonitrile (9.3 mL) were added under a nitrogen atmosphere at r.t.. To this, TMSCl (1.17 mL, 9.34 mmol) was added dropwise over 5 mins. A white precipitate was formed on addition. The mixture was left to stir for 1 hour. At 0°C, cold pentane (20 mL) and cold water (20 mL) was added. The aqueous layer was extracted with pentane (2 x 20 mL) and the organic layers were washed with NH_4Cl (*sat.* aqueous, 2 x 10 mL). The organic layers were dried over $MgSO_4$ and the solvent was removed to give the title compound. The crude product was used in the next step without further purification.

Trimethyl((2-methyl-1-phenylprop-1-en-1-yl)oxy)silane **S4**



To a flame-dried dual-necked round bottomed flask, 2-methyl-1-phenylpropan-1-one (1.0 mL, 6.67 mmol), NaI (119 mg, 8.27 mmol), triethylamine (1.15 mL, 8.27 mmol) and acetonitrile (8.3 mL) were added under a nitrogen atmosphere at r.t.. To this, TMSCl (1.03 mL, 8.27 mmol) was added dropwise over 5 mins. A white precipitate was formed on addition. The mixture was left to stir for 1 hour. At 0 °C, cold pentane (20 mL) and cold water (20 mL) was added. The aqueous layer was extracted with pentane (2 x 20 mL) and the organic layers were washed with NH_4Cl (*sat.* aqueous, 2 x 10 mL). The organic layers were dried over $MgSO_4$ and the solvent was removed to give the title compound. The crude product was used in the next step without further purification.

(1*S**,5*R**,7*S**)-3-Benzyl-1-chloro-7-(hydroxymethyl)-3-azabicyclo[3.2.0]heptane-2,4-dione **S5**



3:1

General Procedure 3 – Batch. Crude **350** (16.9 mmol) was used and irradiated for 90 mins.

General Procedure 4. The crude product from the previous step (11.83 mmol) was used and the reaction was heated to 60 °C until completion. Purification*via via* flash column chromatography (petrol/ethyl acetate: 80/20 to 75/25) gave the title compound (1.00 g, 20%) as a yellow oil.

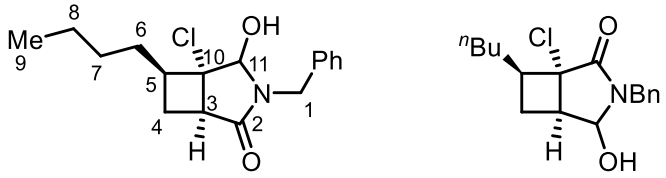
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.38 – 7.20 (5H, m, **Ar**-H x5), 4.78 – 4.55 (2H, m, C**1**-H_2), 3.70 (1H, dd, *J* = 12.0, 4.0 Hz, C**6**-HH), 3.35 (1 H, dd, *J* 12.0, 7.0 Hz, C**6**-HH), 3.31 – 3.26 (1H, m, C**3**-H), 3.11 (1 H, dddd, *J* 10.5, 8.0, 7.0, 4.0 Hz, C**5**-H), 2.72 – 2.56 (1 H, m, C**4**-HH), 1.79 (1 H, ddd, *J* = 12.5, 8.0, 6.0 Hz, C**4**-HH).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 175.2 (C**2**), 174.7 (C**8**), 135.0 (**Ar**), 128.8 (**Ar**), 128.7 (**Ar**), 128.3 (**Ar**), 61.0 (C**7**), 60.7 (C**6**), 47.6 (C**5**), 44.7 (C**3**), 43.2 (C**1**), 21.7 (C**4**).

IR *vmax*/cm^{-1}: 3476 (br), 2950 (w), 1779 (w), 1706 (s), 1389 (m), 1180 (w), 700 (m).

HRMS (ESI) m/z calcd for $C_{14}H_{14}ClNNaO_3$ $[(M+Na)^+]$ 302.0554, found 302.0554.

(1*R**,5*S**,6*R**)-3-Benzyl-6-butyl-5-chloro-4-hydroxy-3-azabicyclo[3.2.0]heptan-2-one **S6**



7:1

A solution of **360** (100 mg, 0.33 mmol) and $NaBH_4$ (19 mg, 0.50 mmol) in ethanol (1.5 mL) and water (1.0 mL) was stirred at 40 °C for 16 hours. The solution was diluted with ethyl acetate (20 mL) and washed with 1 M aqueous HCl (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was concentrated *in vacuo*. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 90/10) gave the title compound (21 mg, 24%) as a colourless solid.

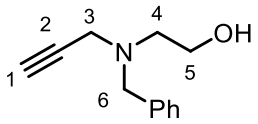
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.38 – 7.27 (5H, m, 5 x **Ar**-H), 5.01 (1H, d, *J* = 14.5 Hz, C**1**-HH), 4.64 (1H, d, *J* = 9.0 Hz, C**11**-H), 4.21 (1H, d, *J* = 14.5 Hz, C**1**-HH), 2.82 (1H, dd, *J* = 9.5, 7.5 Hz, C**3**-H), 2.79 – 2.69 (1H, m, C**5**-H), 2.59 (1H, d, *J* = 9.0 Hz, OH), 2.41 (1H, dd, *J* = 12.0, 10.0, C**4**-HH), 1.75 (1H, tdd, *J* = 8.0, 3.5, 1.5 Hz, C**6**-HH), 1.44 – 1.17 (5H, m, C**6**-HH, C**7**-H_2, C**8**-H_2), 0.91 – 0.85 (4H, m, C**4**-H, C**9**-H_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 169.8 (C**2**), 136.2 (**Ar**), 128.9 (**Ar**), 128.8 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.0 (**Ar**), 84.6 (C**11**), 64.6 (C**10**), 46.5 (C**3**), 46.2 (C**5**), 44.4 (C**1**), 31.1 (C**6**), 28.8 (C**7**), 26.1 (C**4**), 22.5 (C**8**), 14.0 (C**9**).

IR *vmax*/cm^{-1}: 3384 (br), 2927 (m), 2858 (w), 1680 (s), 1454 (m), 1072 (m).

HRMS (ESI) m/z calcd for $C_{17}H_{23}ClNO_2$ [$(M+H)^+$] 308.1412, found 308.1412.

2-(Benzyl(prop-2-yn-1-yl)amino)ethan-1-ol **S7**



Benzyl aminoethanol (4.2 mL, 30 mmol) was added dropwise to compound **515** (2 g, 15 mmol) in a round bottomed flask and stirred at 80°C for 2 hours. Flash column chromatography of the solution (petroleum ether/ethyl acetate: 50/50) gave the title compound (2.42 g, 85%) as a clear colourless oil.

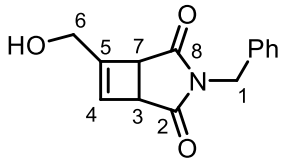
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 – 7.29 (5H, m, 5 x **Ar**), 3.74 (2H, s, C**6**-H_2), 3.69 (2H, dd, *J* = 11.0, 6.0 Hz, C**4**-H_2), 3.38 (2H, d, *J* = 2.5 Hz, C**3**-H_2), 2.89 – 2.80 (2H, m, C**5**-H_2), 2.29 (1H, t, *J* = 2.5 Hz, C**1**-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 129.2 (**Ar**), 128.5 (**Ar**), 127.5 (**Ar**), 73.6 (C**2**), 58.4 (C**6**), 58.3 (C**1**), 57.5 (C**4**), 54.9 (C**5**), 41.3 (C**3**).

IR *vmax*/cm^{-1}: 3290 (br), 2882 (w), 1453 (w), 1051 (m), 908 (w).

HRMS (ESI) m/z calcd for $C_{12}H_{16}NO$ [$(M+H)^+$] 190.1232, found 190.1226.

3-Benzyl-6-(hydroxymethyl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione **S8**



General Procedure 3 – Batch. Benzyl maleimide (1 g, 5.34 mmol), propargyl alcohol (0.47 mL, 8 mmol) and ITX (13 mg, 0.05 mmol) were used. The reaction was exposed to UVA irradiation for 90 mins. The crude product was purified *via* flash column chromatography (petroleum ether/ethyl acetate: 60/40) to give the title compound (1.11 g, 85%) as a yellow oil.

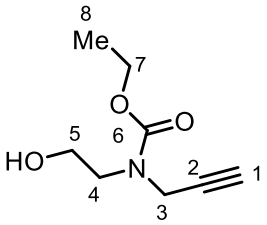
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.14 (5H, m, 5 x **Ar**-H), 6.20 (1H, td, *J* = 1.5, 1.0 Hz, C**4**-H), 4.53 (2H, s, C**1**-H_2), 4.13 (2H, d, *J* = 2.5 Hz, C**6**-H_2), 3.73 (1H, dt, *J* = 3.0, 1.0 Hz, C**7**-H), 3.61 (1H, dtd, *J* = 3.0, 2.0, 1.0 Hz, C**3**-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.6 (C**2**), 174.4 (C**8**), 151.5 (C**5**), 135.7 (**Ar**), 130.5 (C**4**), 128.7 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 59.4 (C**6**), 47.3 (C**7**), 44.2 (C**3**), 42.3 (C**1**).

IR *vmax*/cm^{-1}: 3485 (br), 3065 (w), 1689 (s), 1390 (m), 1166 (m), 1028 (w), 845 (w).

HRMS (ESI) m/z calcd for $C_{14}H_{13}NNaO_3$ [$(M+Na)^+$] 266.0793, found 266.0780.

Ethyl (2-hydroxyethyl)(prop-2-yn-1-yl)carbamate **S9**



A solution of compound **515** (100 mg, 0.53 mmol) and dry DCM (1 mL, 2 mL/mmol) was made in a round bottomed flask under an N_2 atmosphere. To this, ethyl chloroformate (101 µL, 1.06 mmol) was added and the solution was stirred at r.t. for 16 hours. The product was purified *via* flash column

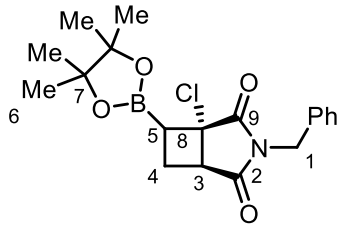
chromatography (petroleum ether/ethyl acetate: 70/30) to give the title compound (62 mg, 35%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (2H, s,), 4.28 – 4.12 (7H, m,), 3.68 (t, *J* = 5.7 Hz, 2H), 2.26 (t, *J* = 2.5 Hz, 1H), 1.37 – 1.26 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (C**6**), 79.0 (C**2**), 64.2, 62.0, 37.3, 14.4 (d, *J* = 31.8 Hz).

IR *vmax*/cm^{-1}: 3286 (br), 2962 (w), 1697 (s), 1468 (w), 1236 (s), 1138 (m), 1010 (m), 770 (m).

(1*S**,5*R**)-3-Benzyl-1-chloro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-azabicyclo[3.2.0]heptane-2,4-dione **S10**



mix of regio- and diastereoisomers

General Procedure 3 – Batch. Using crude **350** (3.38 mmol), ITX (10 mg, 0.04 mmol), and vinylboronic acid pinacol ester (954 µL, 5.64 mmol). The reaction was exposed to UVA irradiation for 90 minutes. Purification *via* flash column chromatography (petroleum ether/ethyl acetate: 95/5 to 90/10) gave the title compound (759 mg, 54%) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H (*major regioisomer reported*) 7.48 – 7.19 (5H, m, 5 x **Ar**-H), 4.85 – 4.61 (2H, m, C**1**-H_2), 3.56 – 3.43 (1H, m, C**3**-H), 2.87 – 2.62 (2H, m, C**4**-HH, C**5**-H), 1.94 (1H, ddd, *J* = 12.0, 9.5, 5.0 Hz, C**4**-HH), 1.34 – 1.17 (12H, m, 4 x C**6**-H_3).

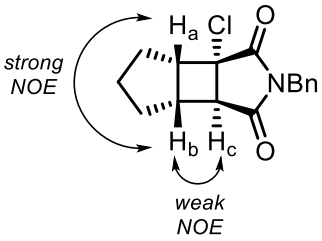
^{13}C NMR (125 MHz, $CDCl_3$) δ_C (*major regioisomer reported*) 175.6 (C**2**), 175.0 (C**9**), 135.3 (**Ar**), 128.8 (**Ar**), 128.7 (**Ar**), 128.7 (**Ar**), 128.1 (**Ar**), 128.0 (**Ar**), 84.7 (C**7**), 61.1 (C**8**), 48.7 (C**3**), 43.0 (C**1**), 34.5 (C**5**), 24.9 (C**6**), 21.9 (C**4**).

IR *vmax*/cm^{-1}: 2979 (w), 1711 (s), 1429 (w), 1373 (s), 1336 (s), 1138 (s), 850 (m), 697 (s).

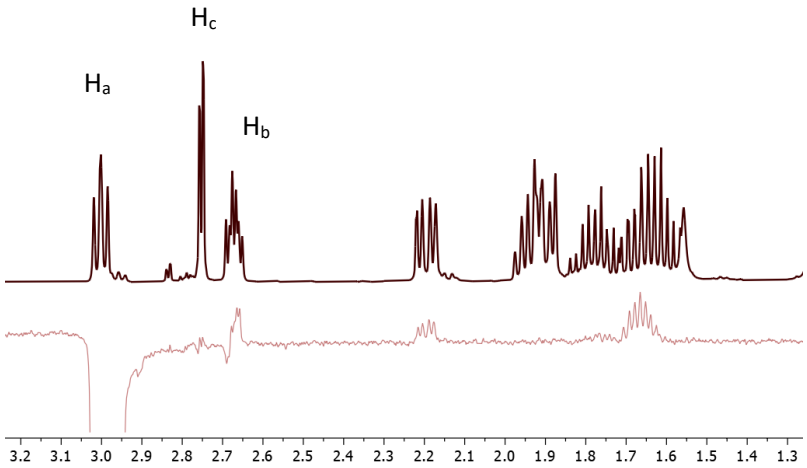
HRMS (ESI) m/z calcd for $C_{19}H_{23}BClNNaO_4$ $[(M+Na)^+]$ 398.1304, found 398.1321.

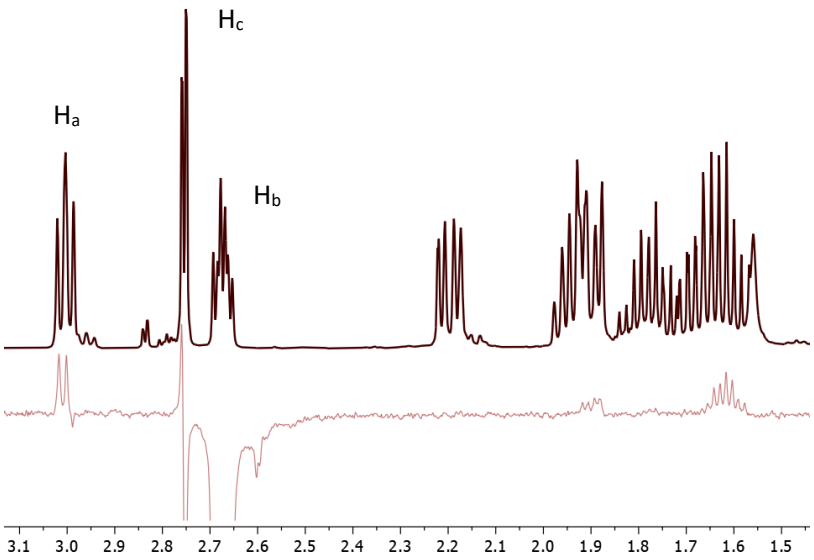
NOE Data

Compound **352**

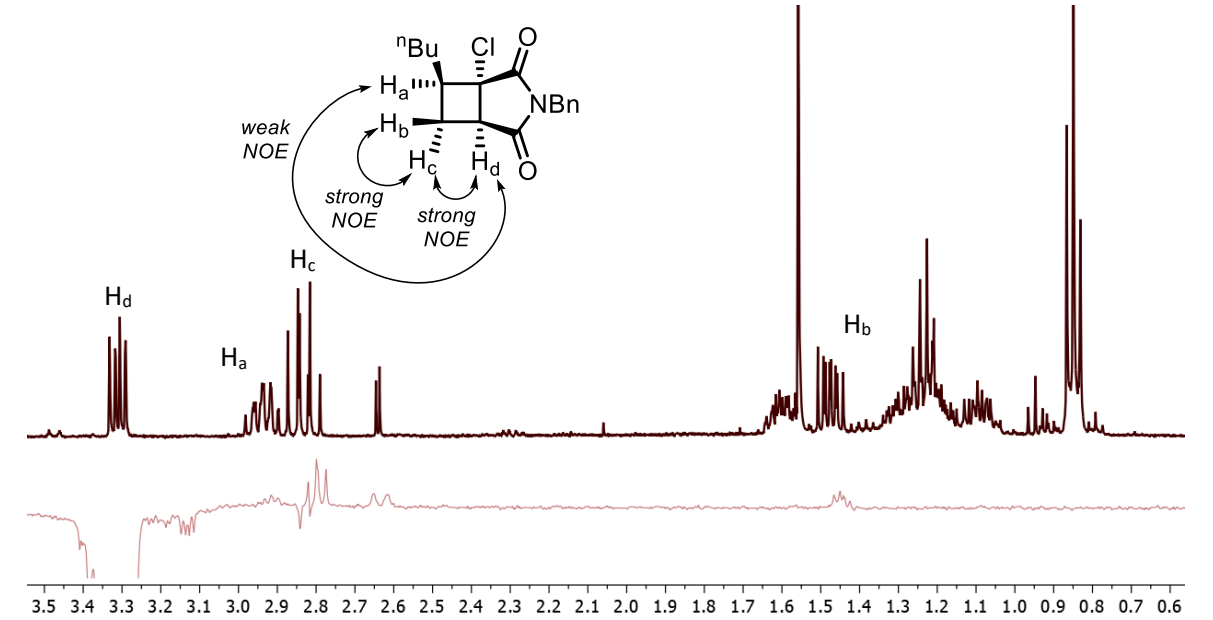


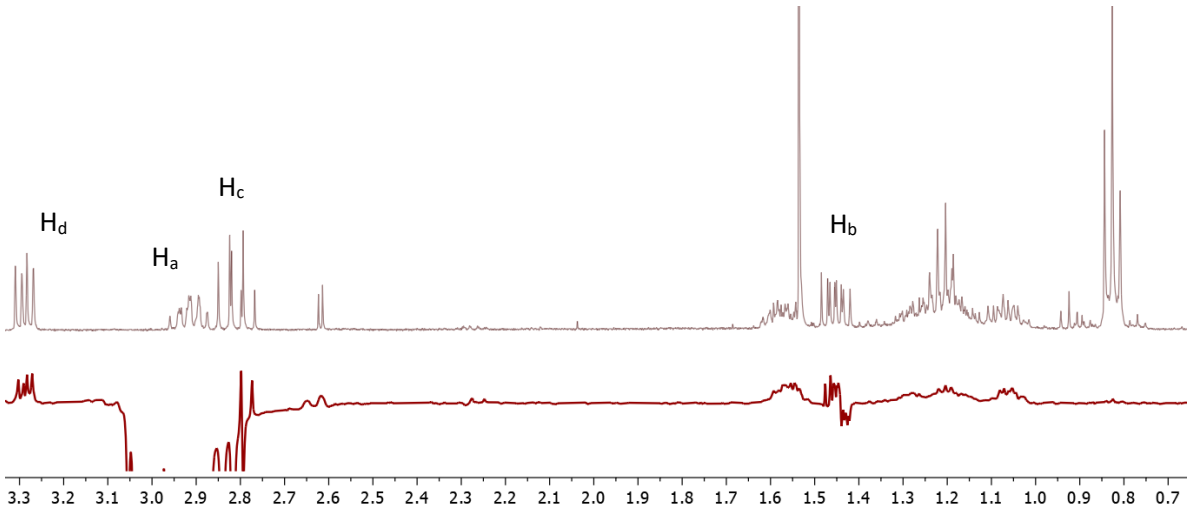
No H_a to H_c correlation



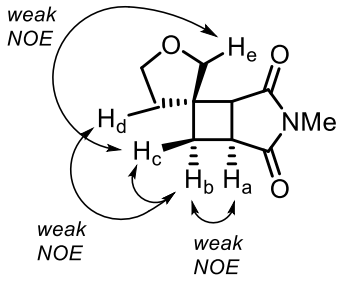


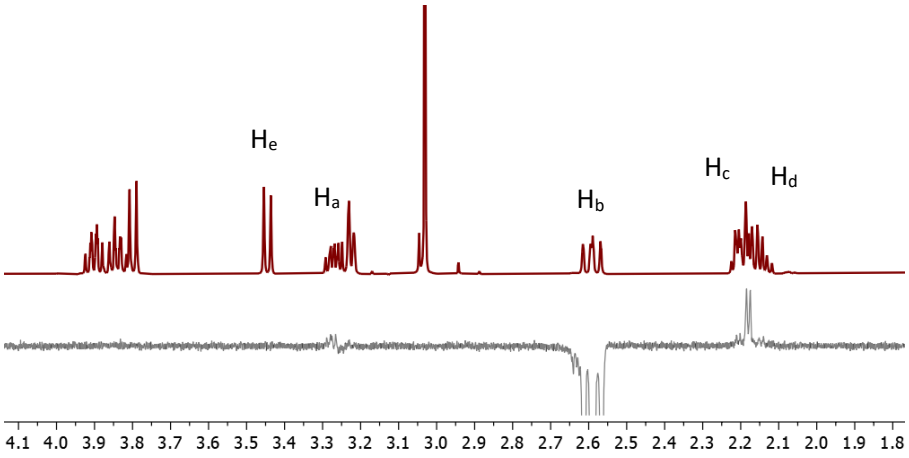
Compound **360**

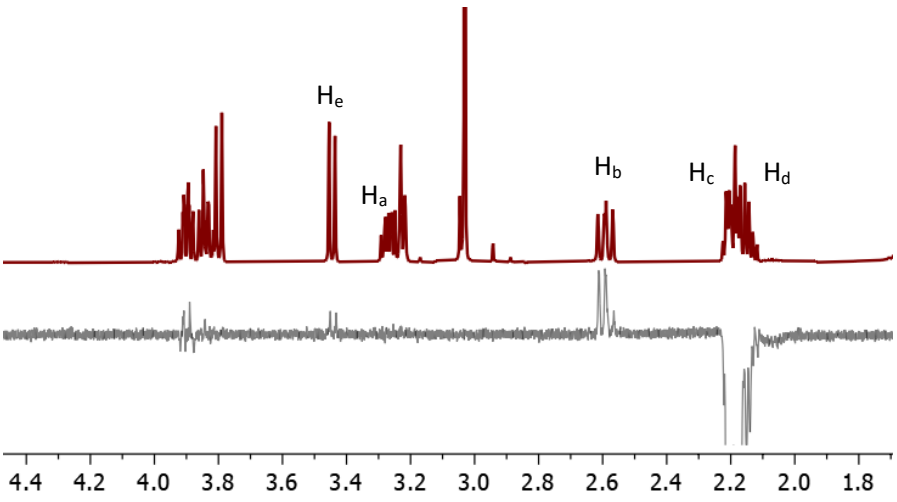


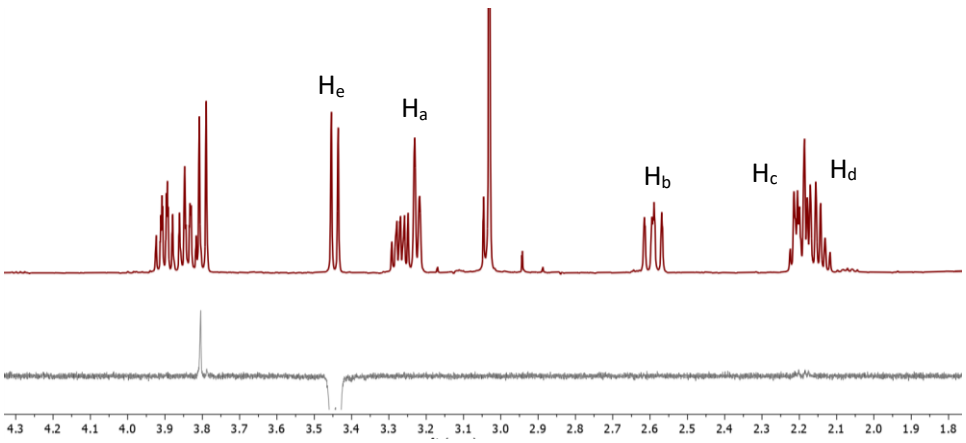


Compound **608**

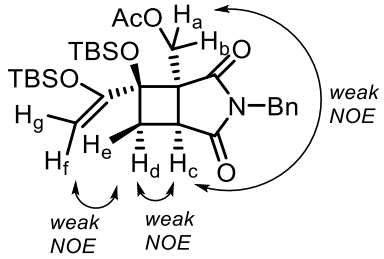


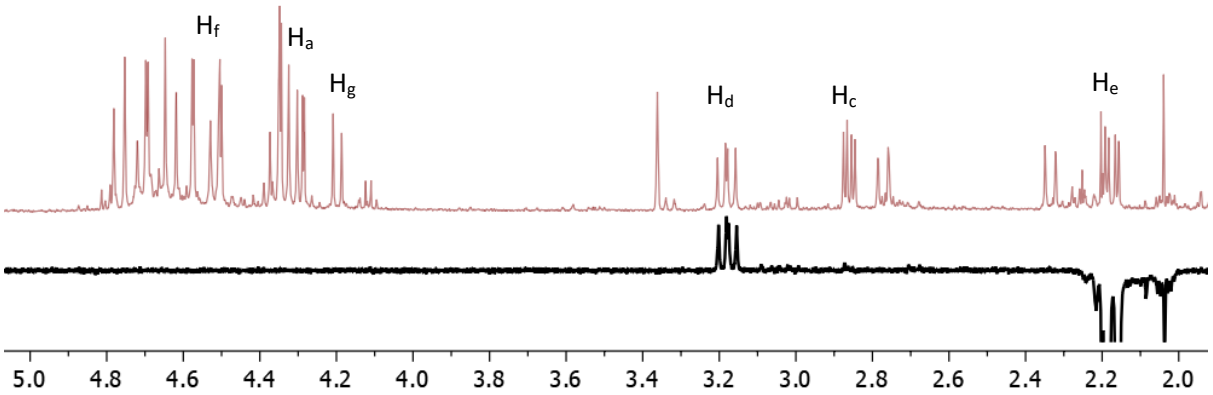


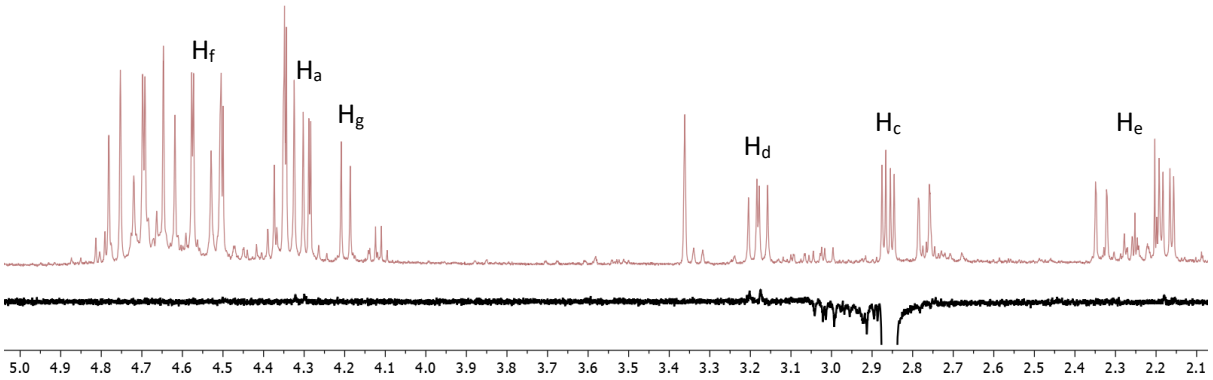


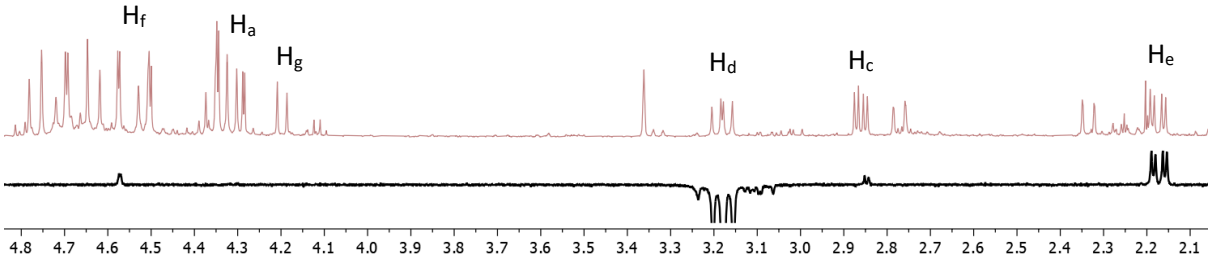


Compound **665**









UV/Vis Spectra

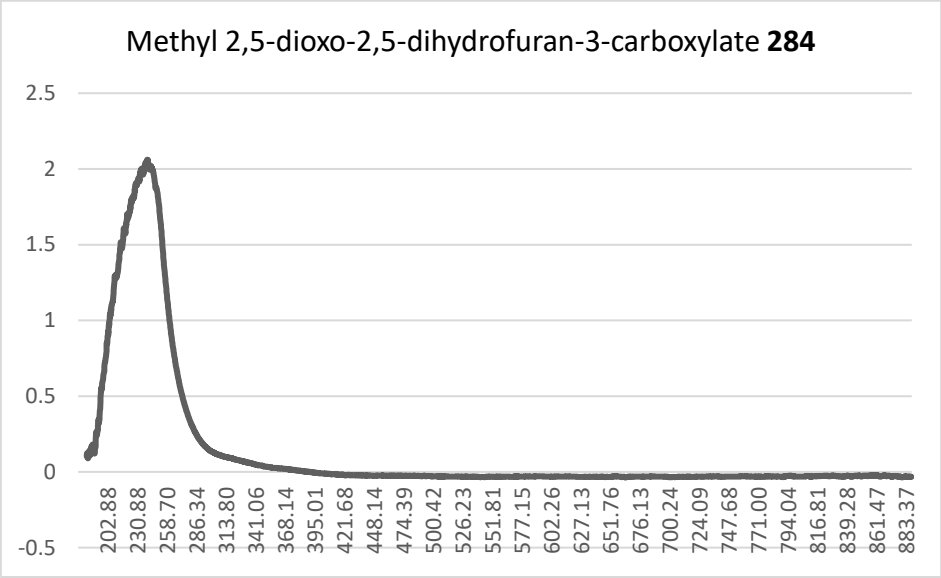


*Figure S3 – UV/Visible-light absorption spectra of compound **284**.*

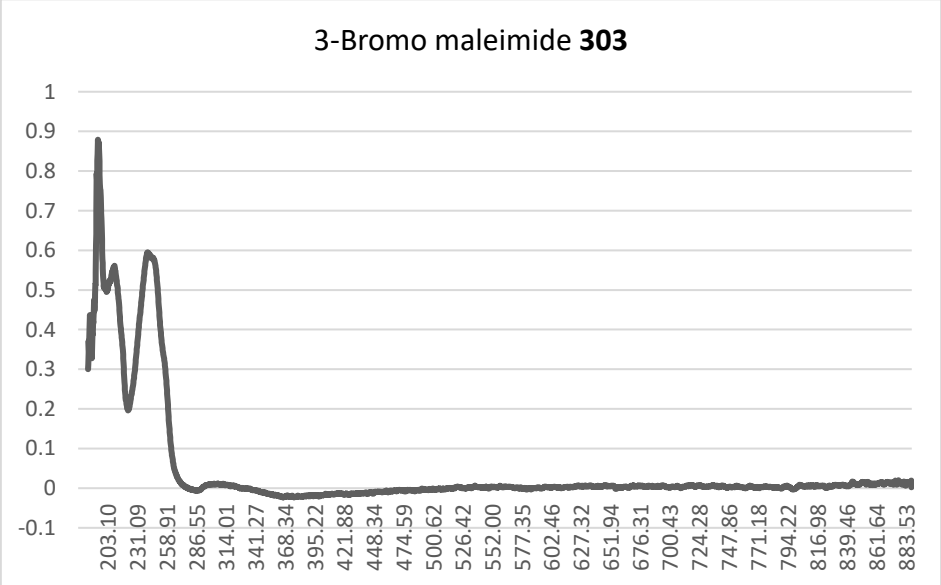


*Figure S4 - UV/Visible-light absorption spectra of compound **303**.*

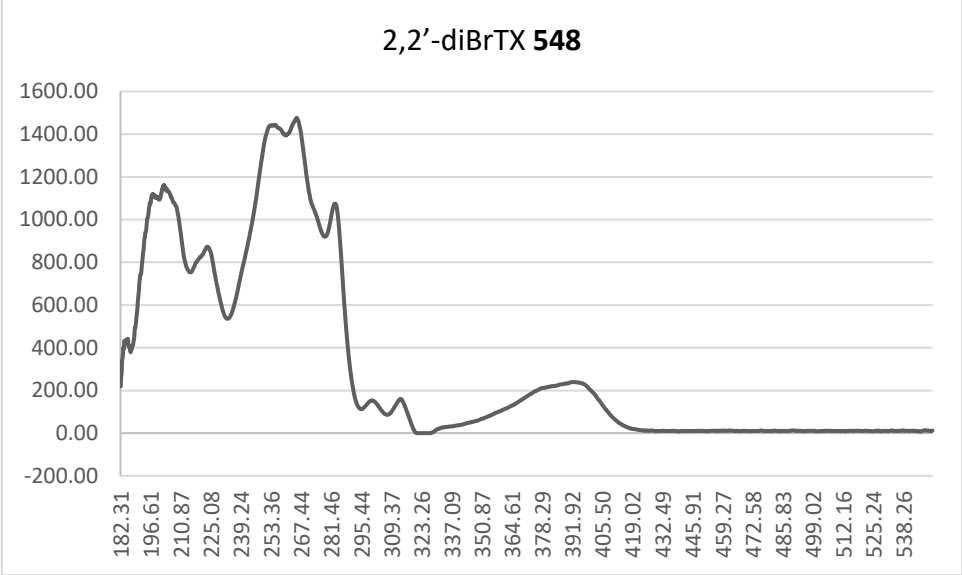


*Figure S5 - UV/Visible-light absorption spectra of compound **548**.*

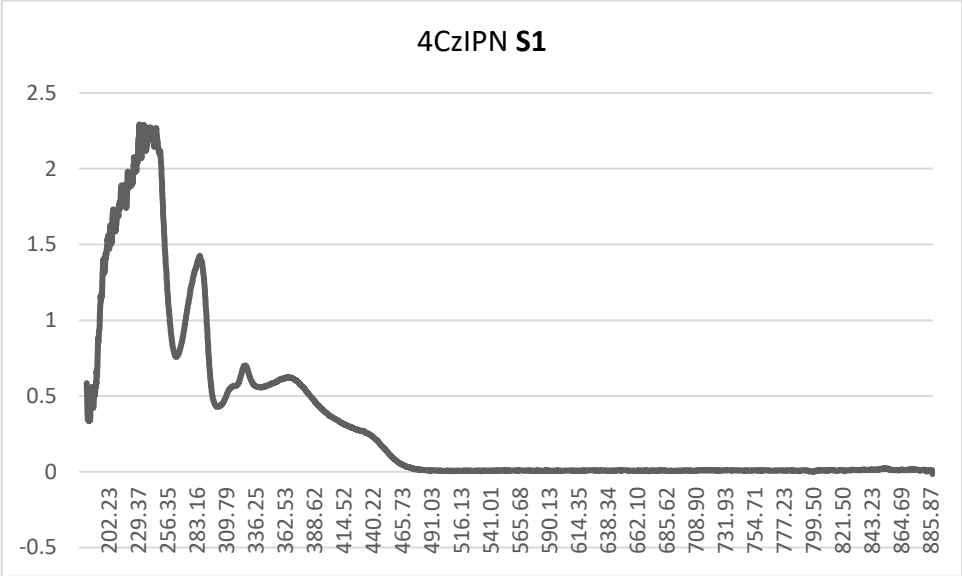


*Figure S6 - UV/Visible-light absorption spectra of compound **S1**.*

Design Of Experiment Data

Dehalogenation/C–H activation

Table S1 - Dechlorinative Functionalisation DOE.

Catalyst (mol%)	**Conc.** (M)	**Reagent** (Equiv)	**amine/ acid ratio**	**Solvent ratio**	**368** (%)	**360** (%)	**Conv** (%)	**363** (%)	**Mass** (%)
5.5	0.3	3	54	50	19	0	100	14	33
1	0.1	5	33	25	0	73	27	0	73
10	0.5	5	33	25	4	77	23	0	81
10	0.1	5	33	75	2	76	24	0	78
1	0.5	5	33	75	4	66	34	0	70
1	0.5	1	75	75	7	22	78	11	40
1	0.5	1	33	25	12	46	54	17	75
10	0.5	1	33	75	9	75	25	0	84
5.5	0.3	3	54	50	11	64	36	0	75
1	0.1	5	75	75	27	18	82	5	50
10	0.1	1	33	25	4	82	18	0	86
10	0.5	5	75	75	44	0	100	10	54
1	0.5	5	75	25	19	15	85	10	44
10	0.1	5	75	25	25	0	100	7	32
10	0.5	1	75	25	11	0	100	22	33
1	0.1	1	75	25	13	0	100	23	36
5.5	0.3	3	54	50	21	59	41	0	80
1	0.1	1	33	75	10	72	28	0	82
10	0.1	1	75	75	17	0	100	36	53
1	0.5	5	33	75	12	22	78	0	34

Decarboxylation/Cyclisation/Borylation DOE

Table S2 - 1st Run.

						Results				
Compound (mg)	**B_2cat_2** (mg)	**DIPEA** (µL)	**DCM** (mL)	**PhMe** (mL)	**Scale** (mmol)	**575** (%)	**574** (%)	**533** (%)	**512** (%)	**Mass** (%)
12	12	4	5	0	0.025	34	0	11	2	47
29	45	22	3.75	1.25	0.063	0	15	32	7	54
29	45	22	3.75	1.25	0.063	0	16	39	8	63
47	48	52	5	0	0.100	13	16	33	9	71
12	12	13	2.5	2.5	0.025	0	0	5	75	80
47	95	52	2.5	2.5	0.100	9	13	25	0	47
29	45	22	3.75	1.25	0.063	0	13	31	10	54
47	95	17	5	0	0.100	15	24	34	4	77
12	24	4	2.5	2.5	0.025	0	6	26	0	32
47	48	17	2.5	2.5	0.100	21	14	32	4	71
12	24	13	5	0	0.025	0	17	48	22	87

Table S3 - 2nd Run.

				Results				
B_2cat_2 (mg)	**DIPEA** (µL)	**DCM** (mL)	**Scale** (mmol)	**575** (%)	**574** (%)	**533** (%)	**512** (%)	**Mass** (%)
12	2	5	0.013	28	4	25	4	61
18	2	5	0.013	15	6	22	1	44
21	3	5	0.018	36	1	16	3	56
32	4	5	0.023	14	3	21	4	42
22	4	5	0.023	15	8	35	3	61
21	3	5	0.018	10	5	26	2	43

Table S4 - 3rd Run.

				Results				
B_2cat_2 (mg)	**DIPEA** (µL)	**DCM** (mL)	**Scale** (mmol)	**575** (%)	**574** (%)	**533** (%)	**512** (%)	**Mass** (%)
26	19	5	0.110	29	6	6	17	58
95	35	5	0.200	31	18	22	7	78
55	27	5	0.155	23	14	29	19	85
52	19	5	0.110	29	31	32	8	100
55	27	5	0.155	19	14	28	19	80
48	35	5	0.200	19	7	12	26	64

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