4-π-Photocyclisation of Troponoids – Scope and Applications

by

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I, Jack Lowe, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work. Many of the ideas in this thesis were the product of discussion with my supervisor Dr Susannah Coote. Any section of this thesis which has been published will be clearly identified.

Abstract

This thesis describes the synthesis of novel [3.2.0]bicycles via 4-π-photocyclisation of tropone and its 2-substituted derivatives.

Chapter 1 provides a bibliographic overview of the literature pertaining to the synthesis of cyclobutenes, with a particular emphasis on the 4-π-photocyclisation of cyclic 1,3-butadienes.

Chapter 2 investigates the optimisation and gram-scale synthesis of phototropone via 4-π-photocyclisation of tropone·BF_3 in a batch photoreactor. The phototropone product obtained was subjected to a wide variety of reactions to yield novel small-molecule building blocks.

Chapter 3 describes the synthesis of 2-substituted tropones by known literature procedures as well as custom syntheses. The 2-substituted tropones obtained were irradiated both in the presence and absence of $BF_3{\cdot}OEt_2$ to obtain a series of novel [3.2.0]bicycles, and valuable insights into the substituent effects on this reaction were gleaned.

Chapter 4 provides overall conclusions from **Chapters 2** and **3**, as well as ideas for potential future work.

Chapter 5 describes the experimental details and characterisation of novel compounds described in this thesis.

Acknowledgements

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Contents

List of Abbreviations and Acronyms

°	degrees
Δ	heat
λ_{max}	absorption maximum
δ	chemical shift
μ**L**	microlitres
2D	two-dimensional
3D	three-dimensional
Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
APCI	atmospheric pressure chemical ionisation
Aq	aqueous
Ar	unspecified aryl group
ATR	attenuated total reflection
BBN	9-borabicyclo[3.3.1]nonane
BCH	bicyclo[3.2.0]hepta-3,6-dien-2-one
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bpy	2,2'-bipyridine
br	broad
Bu	butyl
CAS	complete active space
CAT	chloramine T
COS	combinatorial-oriented synthesis

COSY correlation spectroscopy

Cy cyclohexyl

d doublet

D dimensional

d.r diastereomeric ratio

Da daltons

DCM dichloromethane

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DFT density functional theory

DMAD dimethyl acetylenedicarboxylate

DMA dimethyl acetamide

DME dimethoxyethane

DMAP 4-dimethylaminopyridine

DMF dimethylformamide

DMP Dess-Martin periodinane

DMSO dimethylsulfoxide

DOS diversity-oriented synthesis

dppf 1,1'-bis(diphenylphosphino)ferrocene

E unspecified electrophile

ee enantiomeric excess

Eq equivalents

ESI electrospray ionisation

Et ethyl

EWG electron-withdrawing group

FDA Food and Drug Administration

GABA γ-aminobutyric acid

GC-MS gas chromatography-mass spectrometry

h Planck's constant (6.626×10^{-34} Js)

HetAr unspecified heteroaryl group

HFIP 1,1,1,3,3,3-Hexafluoroisopropanol

HMBC	heteronuclear multiple-bond coherence
HOMO	highest occupied molecular orbital
hr(s)	hour(s)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
i*-*Pr	*iso*-propyl
IR	infrared
ISC	intersystem crossing
J	coupling constant
LA	Lewis acid
LED	light-emitting diode
logP	octanol-water partition coefficient
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar
***m*-CPBA**	*meta*-chloroperoxybenzoic acid
m/z	mass/charge
MC-SCF	multiconfigurational self consistent field
Me	methyl
MECI	minimum energy conical intersection
MFSDA	methyl fluorosulfonyldifluoroacetate
MIDA	methyliminodiacetic acid
mins	minutes
mL	millilitre
M	molar
mM	millimolar
mmol	millimole
mp	melting point
MS	mass spectrometry

MW molecular weight

n.r not reported

NBS *N*-bromosuccinimide

NIS *N*-iodosuccinimide

nm nanometres

NMO *N*-methylmorpholine *N*-oxide

NMR nuclear magnetic resonance

Nu unspecified nucleophile

Ns Nosyl

***p*-Tol** *para*-tolyl

PCA photocycloaddition

PCC pyridinium chlorochromate

PDC pyridinium dichromate

PG unspecified protecting group

Ph phenyl

PKR Pauson-Khand reaction

PMI principal moment of inertia

ppm parts per million

ppy 2-phenylpyridine

q quartet

q quartet

R unspecified group

Rf retention factor

ROM ring-opening metathesis

r.t. room temperature

s singlet

S_NAr nucleophilic aromatic substitution

SCF self-consistent field

SOC spin orbit coupling

t triplet

t	tertiary
TBACl	tetra-*n*-butylammonium chloride
TBAF	tetra-*n*-butylammonium fluoride
TBAOH	tetra-*n*-butylammonium hydroxide
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
TD-DFT	time-dependant density functional theory
Tf	triflate
TFA	trifluoroacetic acid
tfacac	trifluoroacetoacetonoate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
TOS	target-oriented synthesis
Ts	4-toluenesulfonyl (tosyl)
UV-Vis	ultraviolet-visible
v	frequency
w/v	weight/volume
w/w	weight/weight

Chapter 1

Introduction

1.1 The Importance of sp^3-Rich Compounds

Small molecule compounds, defined as molecules with a low molecular weight (MW < 1000 Da) that may modulate biological processes, are an indispensable resource to the medicinal community as drug-like molecules[1,2] and as agents to explore the functions of proteins.[3,4] Ideally, one would like to find a small molecule that modulates the process of every known human protein, to build up an exact picture of biological processes in the body, which is often referred to as 'chemical genetics'.[5] As the number of possible stable small molecules is estimated to be between 10^{63}–10^{200} within certain boundaries,[6] significant resources are put into their development and study. Indeed, whilst biologically active molecules make up a fraction of this total space,[5] there is no definitive way of determining *a priori* whether or not a small molecule may fit in this category. Nonetheless, Lipinski and co-workers described several parameters that may determine the usefulness of a small molecule drug, in particular, orally active drugs.[7] They are as follows:

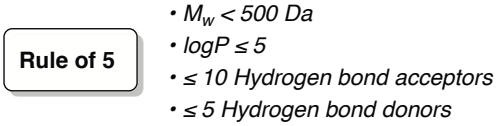


Figure 1.1: Lipinski's Rule of Five

Those drugs taken orally are generally favoured by medicinal practitioners due to ease of administration, safety and patient compliance.[8] It is important to note that not all drugs stick to the rules outlined above,[9] and as such, many caveats have been introduced since. For example, Veber and co-workers showed that from studying the properties of 1100 drug candidates at GlaxoSmithKline, those with 10 or fewer rotatable bonds, and a lower polar surface area led to enhanced oral bioavailability in rats.[10] Later, Lovering and co-workers described the importance of molecular complexity within drug candidates,[11] defining molecular complexity as the fraction of sp^3 centres in the molecule, (Equation 1.1).

$$Fsp^3 = \frac{number\ of\ sp^3\ carbons}{total\ number\ of\ carbons} \tag{1.1}$$

In general, as the number of sp^3 carbons in a drug candidate increases, so do other desirable physiochemical properties, including improved solubility, metabolic stability and selectivity for drug targets.[12] In a follow-up publication, Lovering also showed that an increase in Fsp^3 generally increases the selectivity of a drug candidate by reducing off-target effects,[13] which is one of the main contributors to toxicity.[14] Three-dimensional molecules exhibit lower lipophilicity compared to their two-dimensional counterparts, which is desirable due to its decrease in toxicity, one of the leading causes of attrition in drug clinical trials.[15] Furthermore, Macdonald and co-workers suggested that a successful drug molecule contain no more than three aromatic rings. In addition to enhanced physiochemical parameters, increasing the saturation content of a drug candidate is an effective way of introducing greater structural and shape diversity to a compound without drastically increasing its molecular weight.[11] Considering that protein receptors in the body consist of complex three-dimensional shapes, it is intuitive that full utilisation of this space would lead to higher potency. Providing saturated analogues of aromatic rings is thus an ongoing goal of synthetic organic chemistry.[16]

Medicinal chemists often rely on the screening of large compound libraries derived from combinatorial oriented synthesis against molecular targets to discover

biologically active hits; they must rely on robust, well-known methodologies to deliver these. As such, out of the myriad of reaction types known, only a select few are routinely used,[17,18] namely: amide couplings, Boc group (de)protection, hydrolyses, S_NAr and Suzuki-Miyaura cross-couplings, (in particular, *para-para* couplings).[17] This is hardly surprising considering the pressure to deliver large chemical libraries in a timely fashion, and it is not always in medicinal chemist's best interests to pursue novel, state-of-the-art reaction types, which are a riskier allocation of valuable resources.[19,20] These reactions are often performed around a single core scaffold, and simply changing the appendages around it does not drastically alter the overall structural diversity of the compound library.[21] This reliance on using robust methodologies, in particular, Suzuki-Miyaura cross-couplings between sp^2-sp^2 systems, has led to a large percentage of drugs on the market being largely planar, and as such the area of chemical space that these compounds occupy is quite small. This is best visualised by a principal moment of intertia (PMI) plot of the current FDA drugs approved, which represents the shape diversity of a compound library across three descriptors: linear, disc-like and spherical (Figure 1.3).[22] Generally, there is a bias towards disk-like and rod-like compounds in this library. In order to activate biological targets previously deemed 'undruggable',[4] it is important that compound libraries shift away from high-quantity combinatorial libraries that only interrogate a thin slice of chemical space, and focus efforts on producing smaller, high-quality libraries with higher sp^3 content.

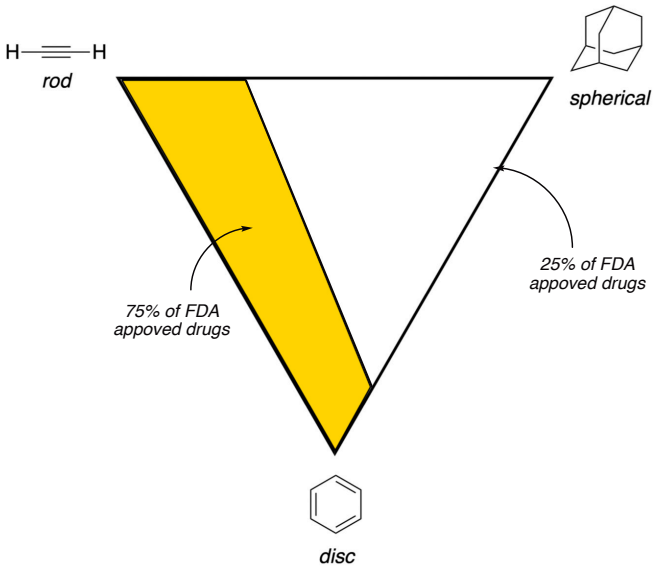


Figure 1.2

1.2 Diversity-Oriented Synthesis

Diversity-oriented synthesis (DOS), first introduced by Schreiber,[3] has emerged as a powerful tool to combat this underpopulation of potentially biologically relevant areas of chemical space, while target oriented synthesis (TOS) aims to generate a single compound, typically a natural product with promising biological activity. On the other hand, combinatorial- and diversity-oriented synthesis (COS and DOS) aim to generate compound libraries, with the former aiming to generate as large a library as possible, and the latter a library as diverse as possible.[23] When describing the diversity of a library or selection of molecules, this is usually taken to mean four different descriptors: appendage, stereochemical, functional and skeletal.[21,24] Those compound libraries bearing higher skeletal diversity typically fare better in terms of biological hit rates, but are harder to obtain than the other three criteria.[25] The generation of skeletal diversity within DOS libraries may be split into two general approaches – the substrate (folding processes) or reagent-based (differentiating processes). The former approach involves subjecting a small collection of substrates containing pre-encoded skeletal information to a common set of conditions, resulting in a wide range of different scaffolds. The latter often starts with the synthesis of a

highly functionalised common intermediate, or with pluripotent functional groups, and subjects it to a various reagents and reaction conditions to yield a series of structurally diverse compounds (Figure 1.3).

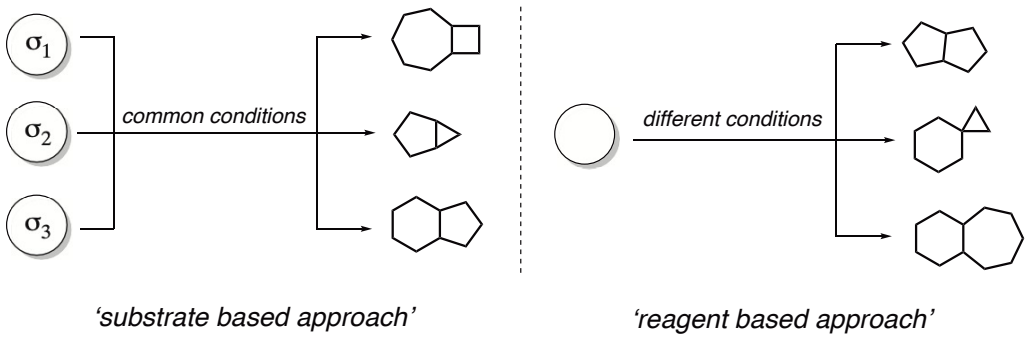
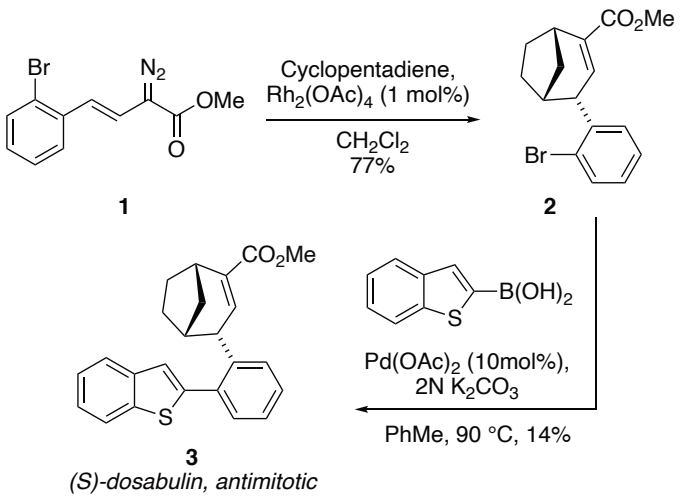


Figure 1.3

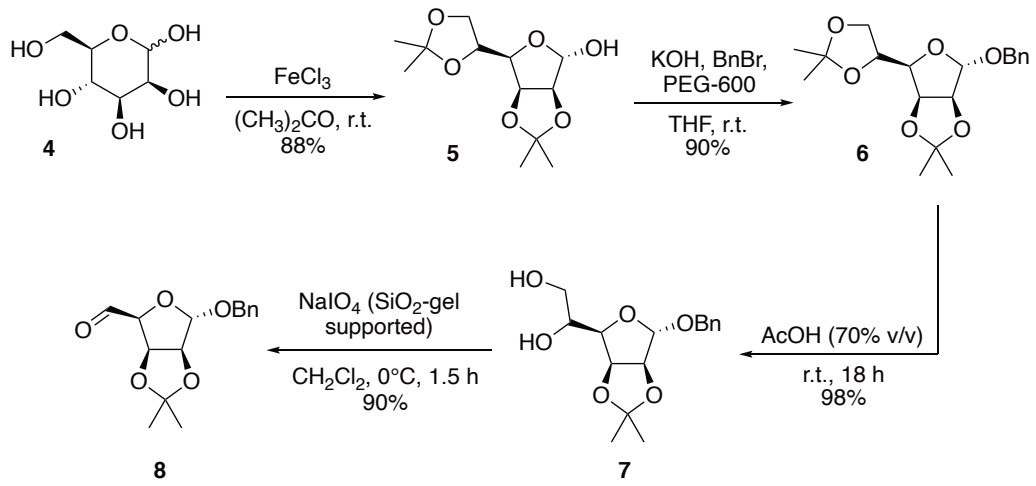
Whilst the size of compound libraries generated by DOS strategies is often small, they explore wider areas of chemical space than can be accessed via a combinatorial approach. In fact, one of the most notable stories in DOS was the identification of the antimitotic (*S*)-Dosabulin (**3**) from a DOS library of only 35 compounds, starting from diazo compound **1** (Scheme 1.1).[26]



Scheme 1.1

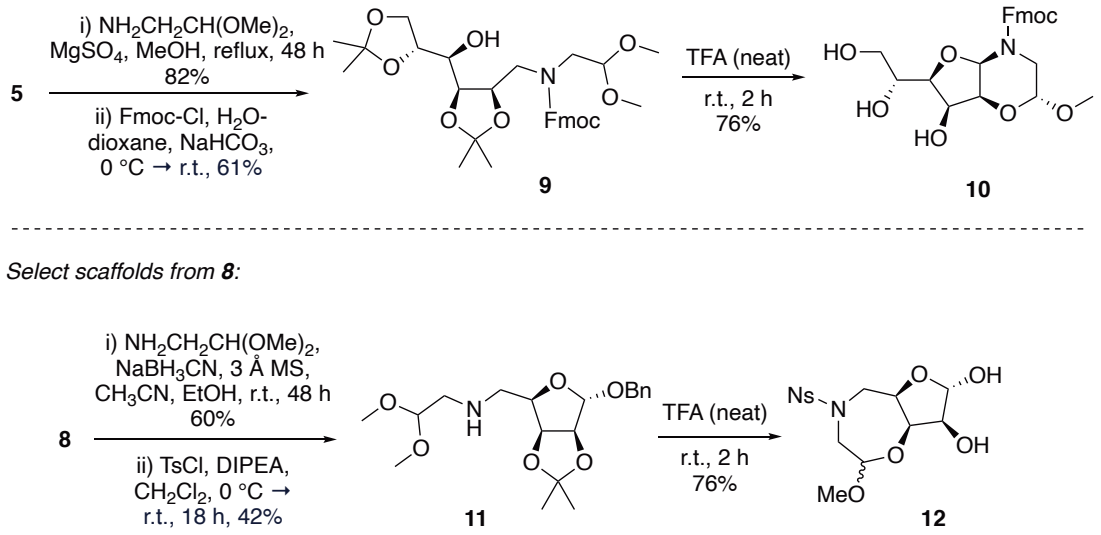
Despite its inception over thirty years ago, the synthesis of DOS libraries remains an active area of research. Chen *et al.* first described the transformation of D-mannose to di-isopropilidene-D-mannose **5** and benzyl-isopropylidene lyxaric aldehyde **8**, in good yields (Scheme 1.2).[27]

*Construction of building blocks **5** and **8** from **4**:*



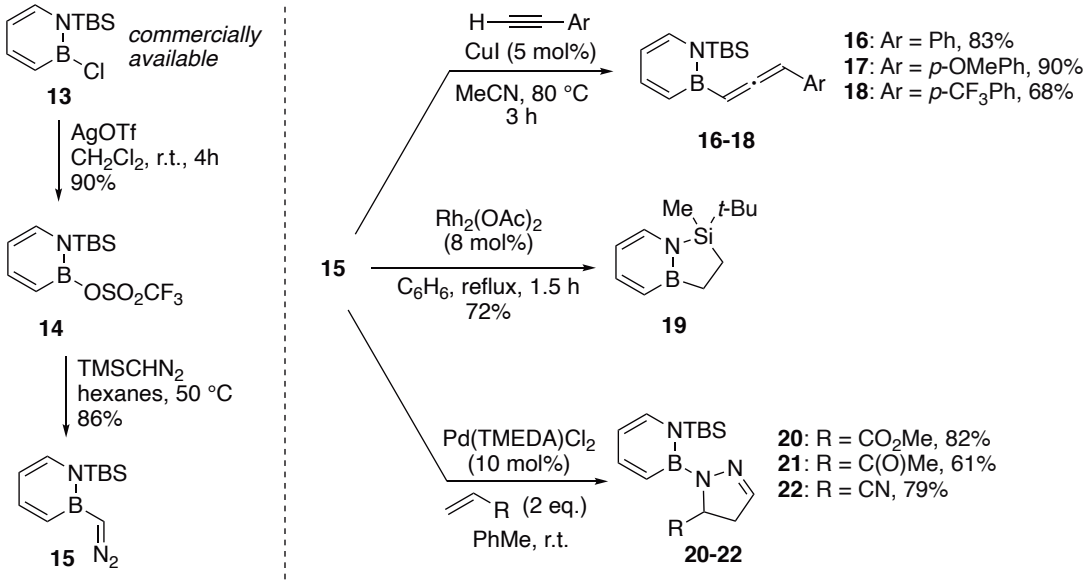
Scheme 1.2

Later, Lenci and co-workers later investigated the potential of these intermediates as starting points for DOS, and were able to isolate a wide range of skeletally diverse polyhydroxylated scaffolds (20 examples) within three steps of either **5** or **8** – scaffolds **9**-**12** are given as representative examples (Scheme 1.3). Finally, PMI analysis against various FDA-approved drugs and natural products further highlighted **4** as a powerful building block in the synthesis of diverse building blocks.



Scheme 1.3

Similarly, Liu *et al.* synthesised a novel α-boryl diazo compound (**15** via a two step procedure from 1,2-azaborine **13** (Scheme 1.4). The resulting compound was amenable to Grubbs metathesis, C-H activation, [3+2] cycloaddition, esterification and halogenation/coupling to yield several diverse compounds – compounds **16**-**22** are given as representative examples.[28]



Scheme 1.4

From looking at these studies, it is clear that DOS is a powerful method in the creation of structurally diverse compound libraries, from readily accessible material by applications of known and robust transformations. The incorporation of these libraries into biological screening and drug discovery campaigns may elucidate previously unchartered biological processes.

1.3 Four-Membered Carbocycles

The high ring strain of the cyclobutane motif (**23**, Figure 1.4), calculated to be between 26–28 kcal/mol,[29] lends itself to reactivity similar to cyclopropane, including its propensity to undergo a number of ring opening reactions.[30] In addition to this, due to its unique 'puckered' three-dimensional shape, the cyclobutane motif is of great interest to medicinal chemists,[31,30] and its inclusion into drug candidates often improves their overall rigidity, metabolic stability, and solubility.[31] Whilst relatively rare in nature, it may be found in several marine and plant natural products that display promising biological activity[32–34] and has thus found its way into several

approved drugs in the market. Hence, the design and synthesis of cyclobutanes is a thriving area of research.

23 **24**

Figure 1.4

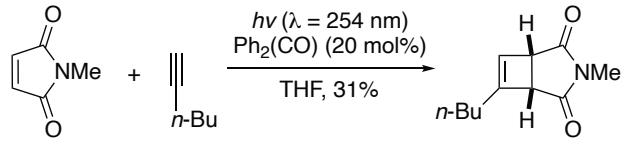
Although significantly more reactive, the cyclobutene motif (**24**) has received considerably less attention in the literature; this is surprising, considering the applications of cyclobutenes as reactive intermediates,[35–37] not least as precursors to cyclobutanes.[38–40] A brief overview of the various synthetic methods to access them is therefore necessary.

1.4 Synthesis of Cyclobutenes

1.4.1 [2+2] Cycloadditions

1.4.1.1 Photochemical

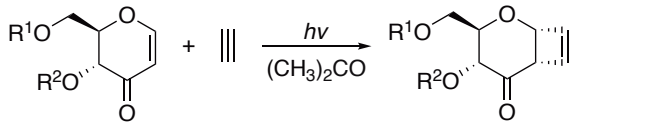
Whilst [2+2] photocycloadditions (PCA) between olefin pairs are more commonly reported,[41] there are several examples of alkynes and alkenes undergoing this reaction. Childs and Johnson first reported the [2+2] PCA of an alkyne and an alkene in 1967 (Scheme 1.4).[42] Thus, irradiation of *N*-methylmaleimide **25** and hex-1-yne **26** in the presence of catalytic amounts of a benzophenone afforded cyclobutene derivative **27** in 31% yield (Scheme 1.5).



25 **26** **27**

Scheme 1.5

Nakayama and co-workers reported the [2+2] PCA between acetylene and D-glycal derivatives (**28** and **29**) to afford cyclobutene derivatives **30** and **31** in good yields (75 and 81%, respectively) (Scheme 1.6). Here, [2+2] PCA took place exclusively on the less hindered side to yield the products as single stereoisomers.[43]

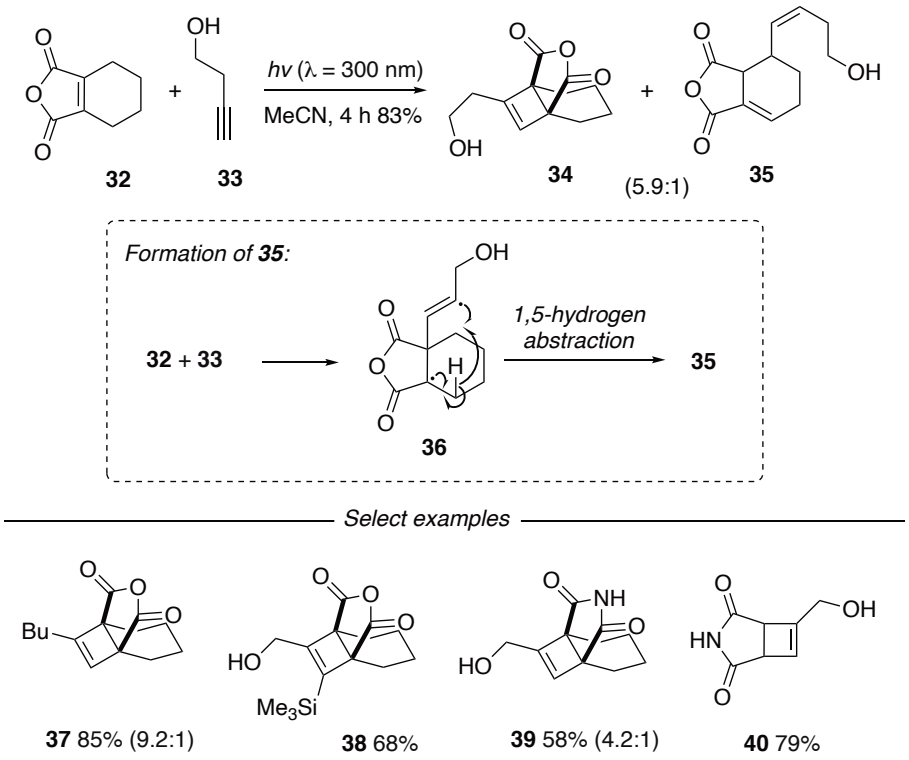


28: $R_1 = R_2 = C(CH_3)_2$
29: $R_1 = CPh_3$, R_2 = Ac

30: $R_1 = R_2 = C(CH_3)_2$, 81%
31: $R_1 = CPh_3$, R_2 = Ac, 75%

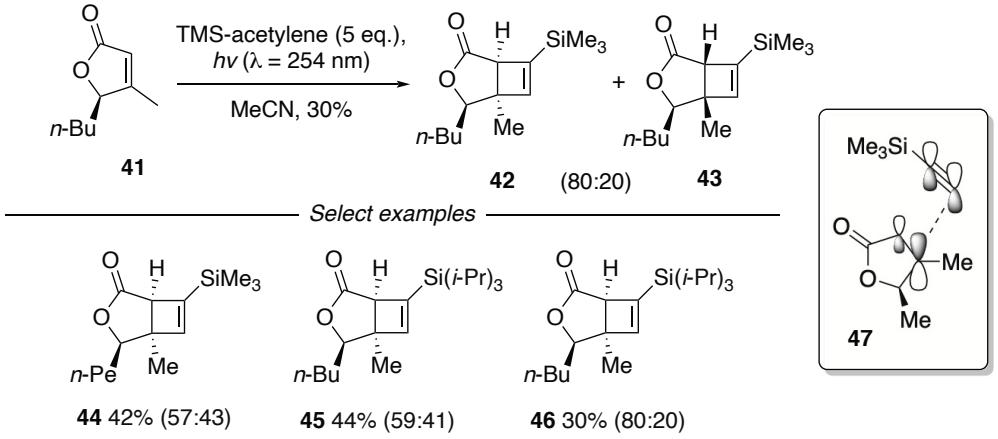
Scheme 1.6: R^1 = H, R^2 = Ac

Booker-Milburn and co-workers reported the [2+2] PCA between tetrahydrophthalic anhydride/imides with various substituted alkynols to yield [2+2] photocycloaddition adducts **31**, **37**-**40** (Scheme 1.7).[44] Pleasingly, these were obtained in remarkably short reaction times (one to eight hours) and in overall good yields (42-90%). In several cases, a rearrangement product (**35**) was obtained alongside the expected [2+2] PCA product. The formation of this minor constituent may be rationalised via a transannular 1,5-hydrogen atom abstraction from the initially formed triplet biradical intermediate **36**, (boxed, Scheme 1.7).



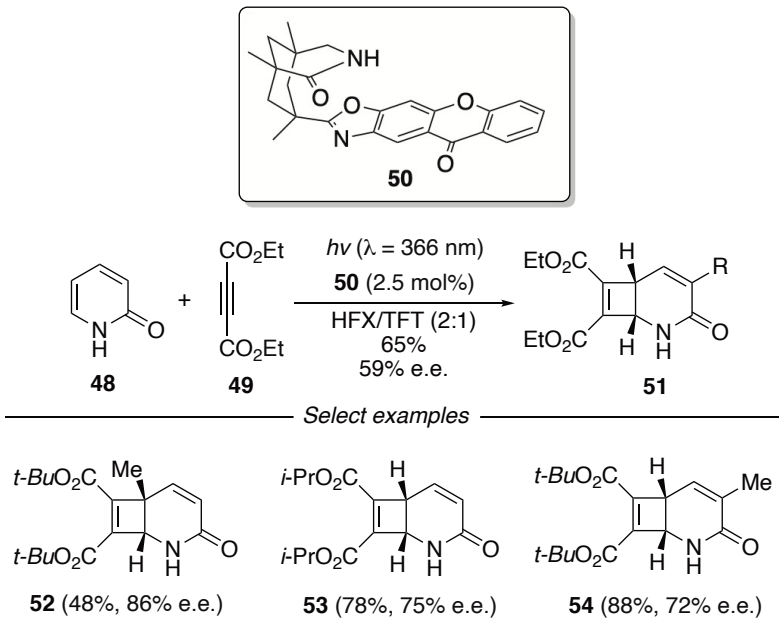
Scheme 1.7: (major:minor)

D'Annibale and co-workers reported the [2+2] PCA between 2(5*H*)-furanones and trialkylsilylacetylenes with excellent regioselectivity, leading to head-to-head products as the sole isomers (Scheme 1.8).[45] The excellent regioselectivity observed may be explained by intermediate **47** (boxed) – here, the position of the methyl group prevents a suprafacial approach.



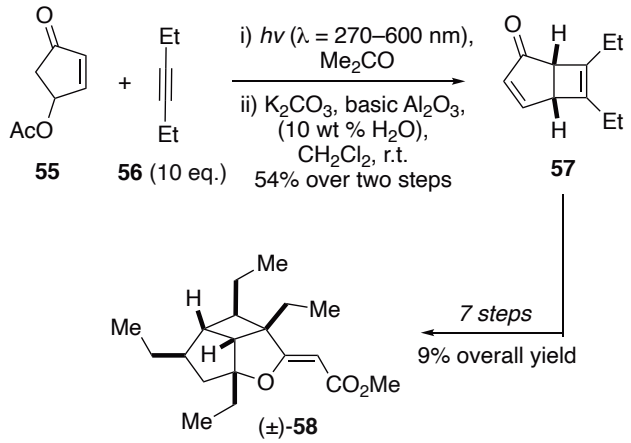
Scheme 1.8: (*syn*:*anti*)

Bach and Marcello-Maturi demonstrated the first catalytic enantioselective [2+2] PCA using a chiral triplet sensitiser **50**. Irradiation of 2-pyridones and acetylenedicarboxylates in the presence of **50** afforded cyclobutene derivatives **51**-**54** in good yields and excellent enantioselectivites (Scheme 1.9). Furthermore, the amount of triplet sensitiser **50** required was extremely low (2.5 mol%).



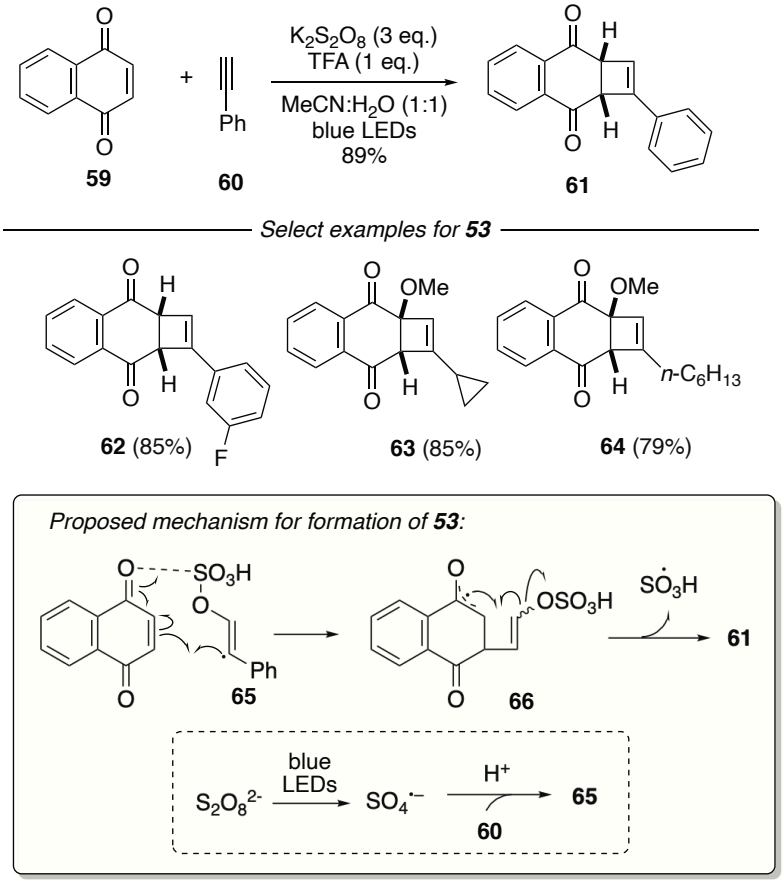
Scheme 1.9

(±)-Hippolachnin A (**58**) is a marine polyketide with promising pharmacological activity. The Carrerira group first achieved its racemic total synthesis in 2015, from [3.2.0]bicycle **57**, accessed via [2+2] PCA between cyclopentenone derivative **55** and hex-1-yne **56**, followed subsequent elimination of the acetate group (Scheme 1.10).[46] In 7 further steps, (±)-**58** was obtained in 9% overall yield (Scheme 1.10).



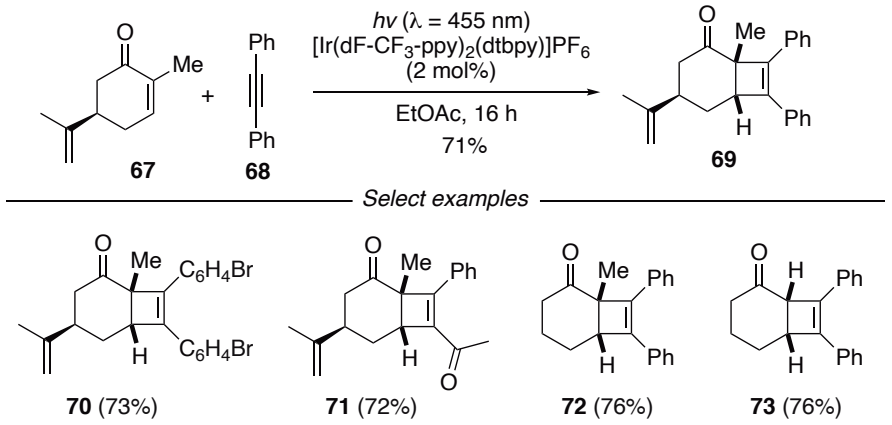
Scheme 1.10

In order to avoid the use of harsh UV light, which may lead to the decomposition of products and undesirable side reactions, several groups have focussed on performing these reactions using visible light. The visible light mediated [2+2] PCA between 1,4-napthoquinones and alkynes using TFA and $K_2S_2O_8$ has been reported by Ali Shah and co-workers, to give cyclobutene derivatives **61**-**64** in good yields (Scheme 1.11).[47] The authors proposed a mechanism detailing the formation of **61**, based on a previous study by Wille[48] involving homolysis of the persulfate anion to the SO_4 radical, followed by generation of vinyl radical **65**. Attack of **65** to **59** is assisted by coordination of the sulfur atom to the ketone, leading to intermediate **66**. Formation of the cyclobutene ring to yield the cyclobutene product **61** is accompanied by loss of the $\cdot SO_3H$ radical.



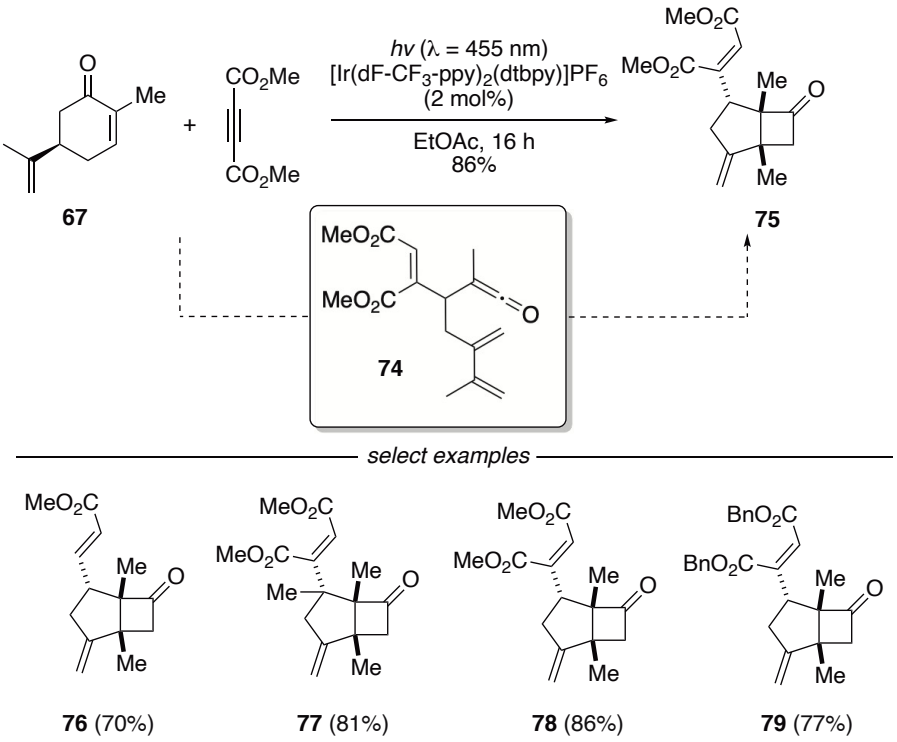
Scheme 1.11

The design and synthesis of enhanced triplet sensitisers has enabled previously unsuccessful [2+2] PCAs,[49] including those between alkynes and alkenes. The Glorius group reported the visible light mediated photocatalysed reaction between alkynes and enones and acetylenes in the presence of an iridium photocatalyst to yield cyclobutenes **69**-**73** in good yields (Scheme 1.12).[50]



Scheme 1.12

Interestingly, when carvone **67** was irradiated with various electron-deficient alkynes a novel reaction pathway was discovered, giving [3.2.0]bicycles **75**-**79** in good yields (Scheme 1.13). The authors proposed ketene **74** as a key intermediate.

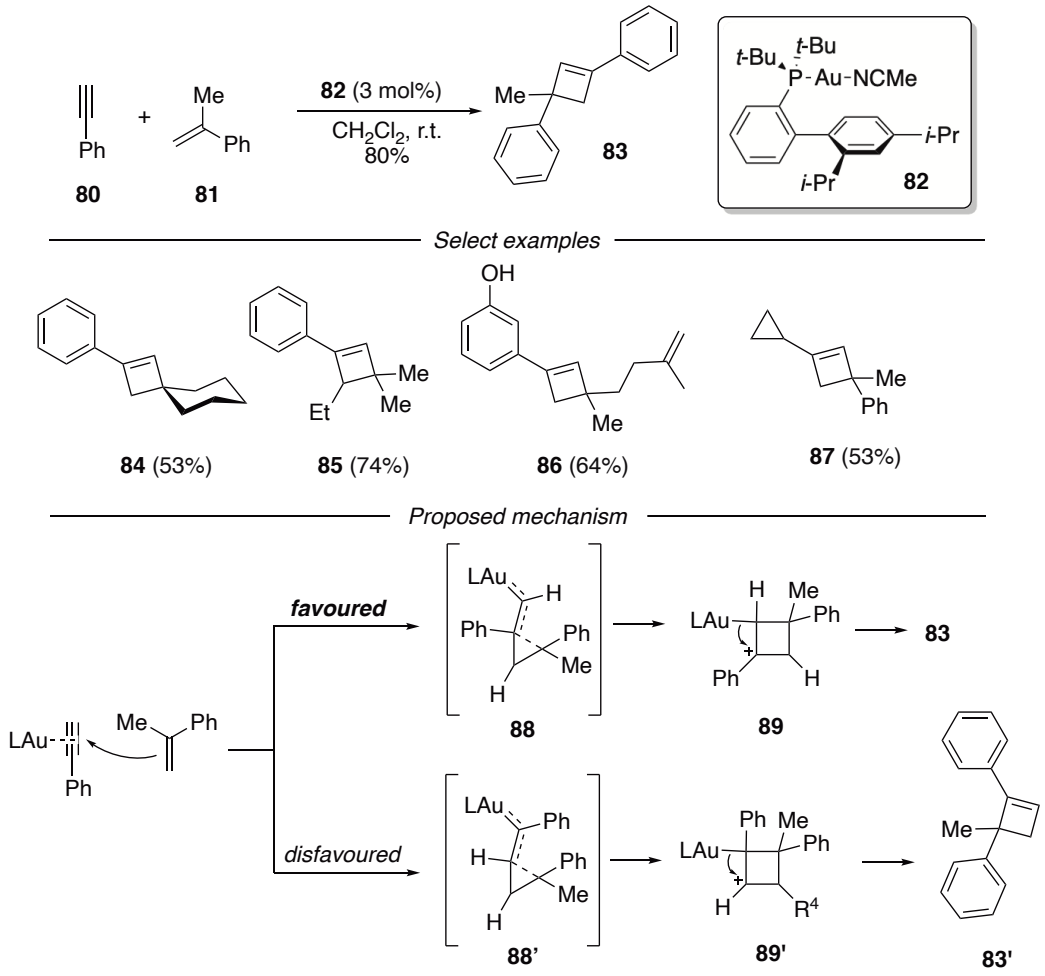


Scheme 1.13

Although there are many publications concerning intramolecular [2+2] PCA between olefins,[41,51] including enantioselective variants,[52] examples involving tethered alkynes/alkanes are quite limited.[53,54] and often are accompanied alongside many side products.

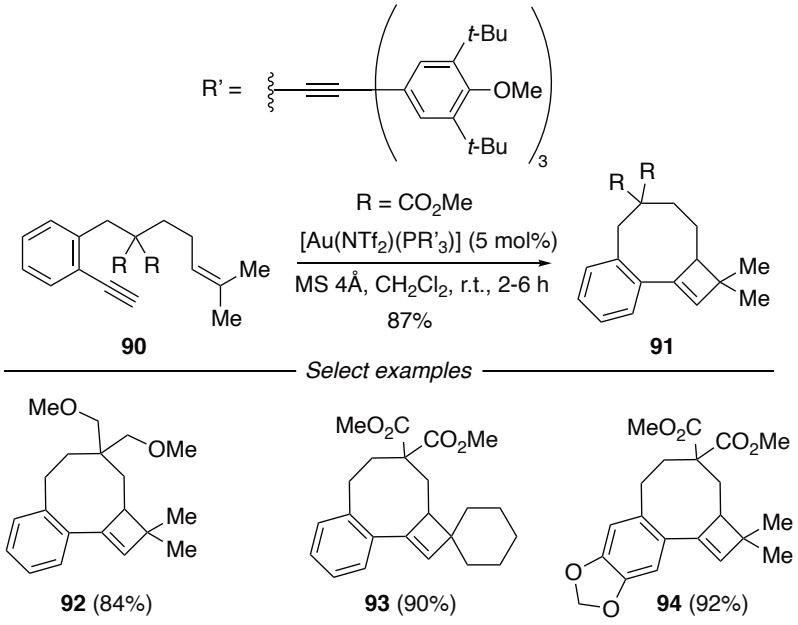
1.4.1.2 Metal and Lewis Acid Catalysis

Whilst thermal [2+2] cycloadditions are forbidden according to the Woodward-Hoffmann rules, they can be achieved by transition metal or Lewis acid catalysis. For example, Echavarren and Lopez-Carrillo reported the first example of an intermolecular gold-catalysed [2+2] cycloaddition between terminal alkynes and alkenes to yield cyclobutene derivatives **83**-**87** in excellent regioselectivities (Scheme 1.14).[55] The use of catalyst **82**, possessing bulky ligands at the Au(I) metal centre, was crucial for successful reaction. It was proposed that the formation of **74** proceeds via formation of cations **80/80'** through cyclopropyl gold intermediates **88/88'**. The excellent regioselectivites obtained were rationalised by faster formation of intermediate **88** over **88'**.



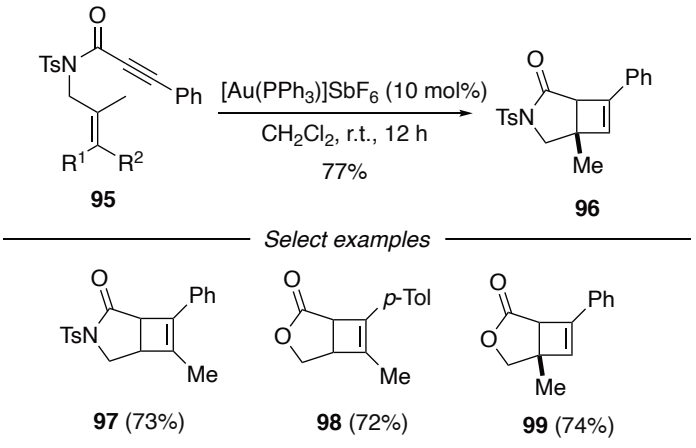
Scheme 1.14

Intramolecular variants of gold-catalysed [2+2] cycloadditions have also been reported – for example, Sawamura and co-workers described the gold-catalysed intramolecular [2+2] cycloaddition of enynes to afford cyclobutene-fused eight-membered carbocycles **91**-**94** in good yields (74–92%) (Scheme 1.15).[56]



Scheme 1.15

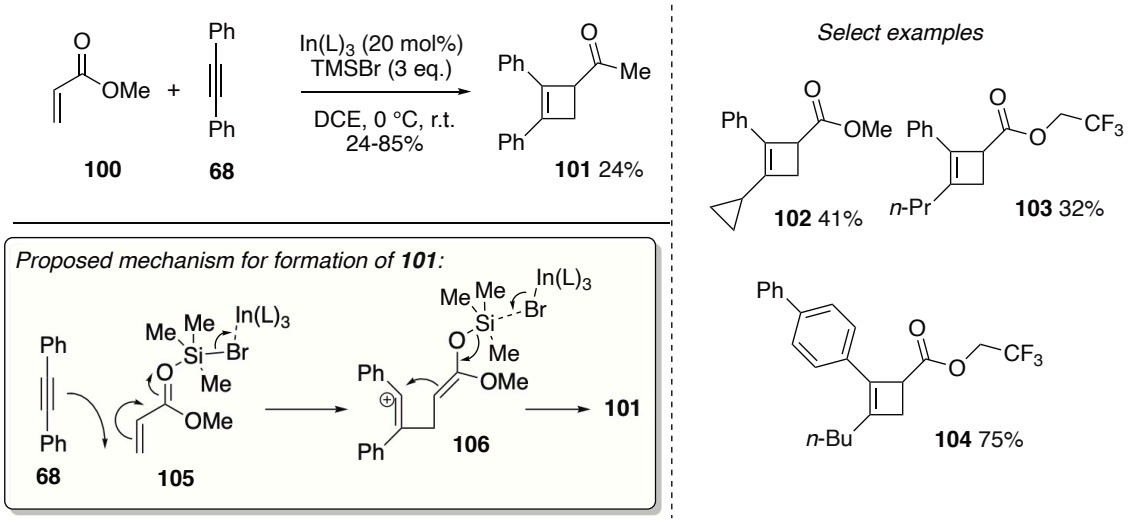
Lactam – or lactone-fused cyclobutenes can also be formed when a heteroatom is present in the tether.[57] Thus, reaction of 1,6-enynes in the presence of a gold catalyst bearing bulky ligands afforded lactones and lactams **96**-**99** in good yield (Scheme 1.16).



Scheme 1.16

In a similar vein, metal-catalysed [2+2] cycloaddition between other 1,5-,[58] 1,6-,[59] 1,7-,[60] and 1,9-enynes to yield the corresponding polycycle have been reported. Indeed, a variety of other transition metal catalysts may be employed in these reactions, including rhodium,[61] rhenium,[62] ruthenium,[63,64] iridium,[65] and silver[66] to generate cyclobutene derivatives in excellent stereo-, regio- and chemoselectivity. However, the requirement for electron-rich alkenes, electron-deficient alkynes and often expensive metal catalysts limit the scope of these reaction types. Variants utilising abundant earth metals such as nickel,[67,68] copper,[69] cobalt[70] and iron[71] have been reported, but still suffer similar issues in terms of substrate scope and practicality as other metal-catalysed systems.

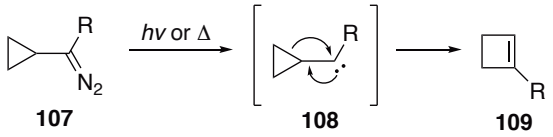
Lewis acids may be utilised instead of metal catalysts – for example, Loh and co-workers developed a combined Lewis acid-catalysed [2+2] cycloaddition between aryl alkynes and acrylates, employing trimethylsilyl bromide and $In(tfacac)_3$ in the synthesis of densely functionalised cyclobutene **101**–**104** (Scheme 1.17).[72] The authors proposed carbocation **106** as a potential intermediate in the reaction.



Scheme 1.17: L = tfacac.

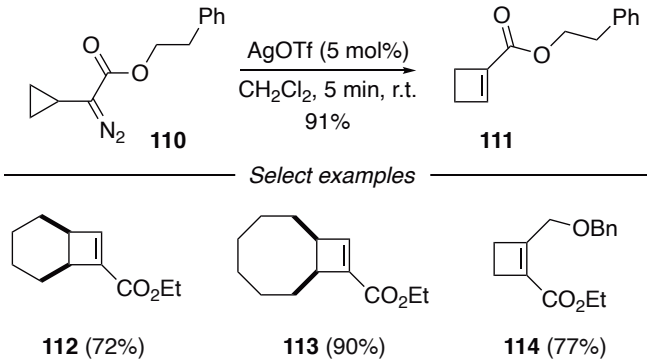
1.4.2 Ring Expansions

Cyclopropyl diazo compounds **107** are able to undergo thermal[73] and photochemical[74] decomposition to afford cyclopropyl carbenes (**108**), which undergo ring expansion to yield cyclobutenes **109**, although often in poor yields (Scheme 1.18).



Scheme 1.18: R = H, CO_2Me

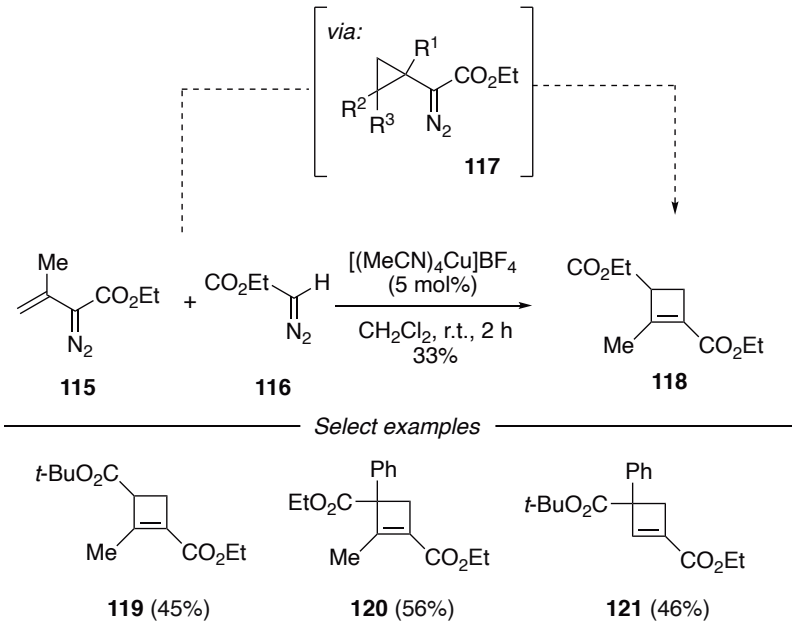
In 2008, Tang and co-workers reported the first metal-catalysed decomposition of cyclopropyl diazo compounds, using either rhodium, copper, or silver complexes as the catalyst. The reaction proceeded in a highly chemoselective fashion to yield the cyclobutenes **111**-**114** as the sole products (Scheme 1.19).[75]



Scheme 1.19

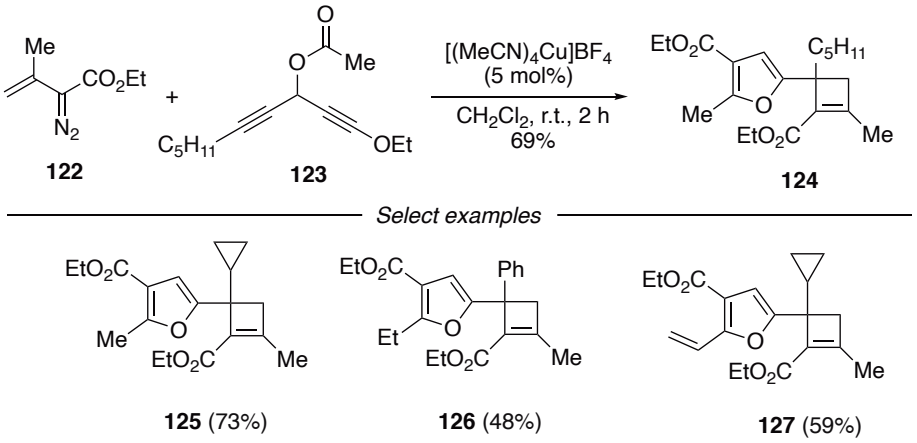
Later, Barluenga and co-workers reported a copper-catalysed formal [3+1] cycloaddition between vinyldiazoacetates and diazo electron deficient azo compounds compounds, to yield functionalised cyclobutenes **118-121** (Scheme 1.20).[76] Here,

the carbenoid formed from **105** is formed preferentially, which undergoes insertion to yield cyclopropyldiazoacetate ester **108** in which carbenoid formation and subsequent bond cleavage occurs yields **107**.



Scheme 1.20

Additionally, application of these conditions to mixtures of bispropargylic esters and vinyl diazocarboxylates led to the formation of furanyl-substituted cyclobutenes **124**-**127** via a cascade process (Scheme 1.21).

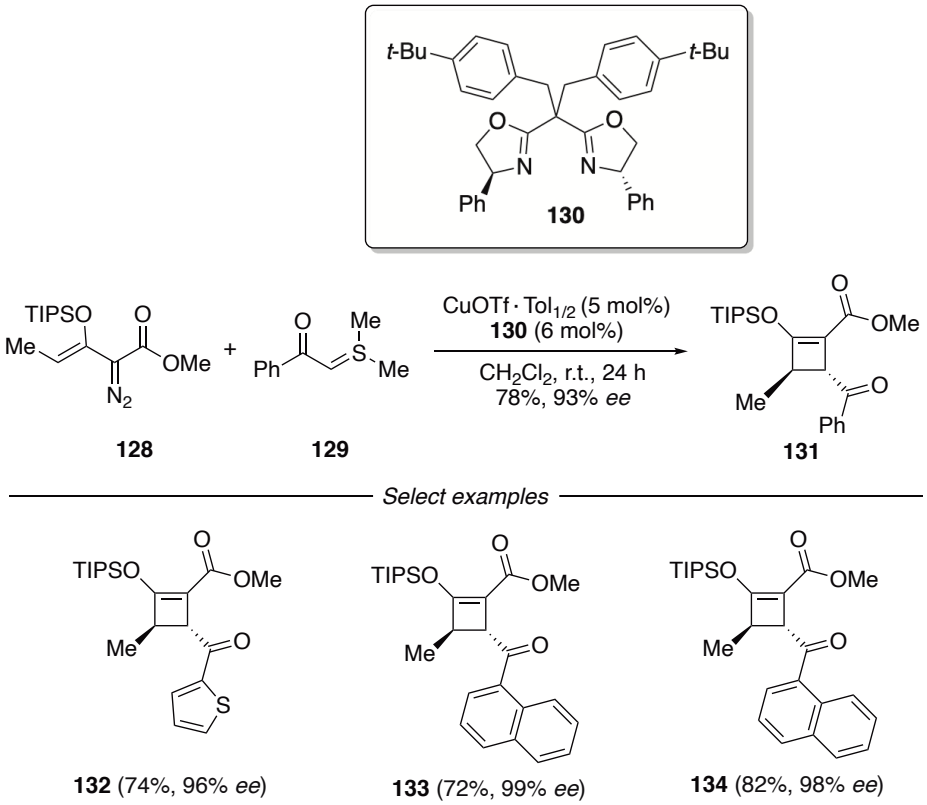


Scheme 1.21

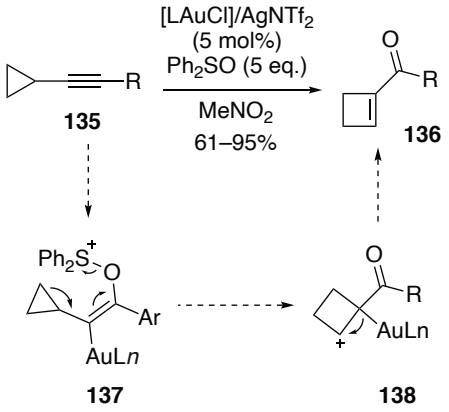
Doyle and co-workers applied a similar methodology to β-triisopropylsilyl enoldiazo compounds and sulfur ylides to afford cyclobutenes **131**-**134** in the presence of catalytic copper (Scheme 1.22).[77] The authors were able to perform the reaction asymmetrically by use of ligand **130** to afford the product cyclobutenes in high enantioselectivities (70–99% ee).

Finally, the Liu group reported the gold-catalysed oxidative ring expansion of cyclopropyl arylalkynes **135** in the presence of diphenyl sulfoxide to yield acyl cyclobutenones **136** (Scheme 1.23).[78] On the basis of cross-over experiments, the authors proposed the intermediacy of the cationic intermediate **138** formed through α-carbonylcarbenoid intermediate **137**.

Indeed, the routes discussed above can often provide cyclobutene derivatives in high yields, but there are several drawbacks that are commonly observed among them. [2+2] PCAs are hampered by narrow substrate scopes, and the products themselves are often UV active, leading to secondary photorearrangements that complicate the reactions. In the case of metal-catalysed [2+2] cycloadditions, the substrate scopes are limited, often only being performed on a handful of similar substrates. Additionally, the metal catalysts required for these transformations are



Scheme 1.22



Scheme 1.23: R = Aryl, L = P(*t*-Bu)$_2$(*o*-biphenyl).

expensive, which may limit their applications outside of small scale syntheses. For the case of intramolecular [2+2] cycloadditions, the yields of cyclobutene products are often low due to competing side reactions that complicate the product profile.

1.5 4-π-Photocyclisation

The last, and perhaps most under-utilised method to generate cyclobutenes is via 4-π-photocyclisation of 1,3-butadienes (Figure 1.5).

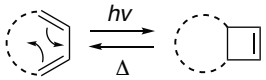


Figure 1.5

1.5.1 Theoretical Aspects

Electrocyclisation reactions are a subclass of pericyclic rearrangements that take place on conjugated π-systems in which one π-bond is converted to a new σ-bond. The reverse case is also possible and is usually referred to as electrocyclic ring opening (Figure 1.5). As four π electrons take part in the reaction, this process is referred to as a '4-π-electrocyclisation'. The stereospecifity of electrocyclic reactions is governed by the number of π-electrons involved in the reaction, and whether the reaction is induced thermally (from the ground state) or photochemically (from an excited state). This is summarised by the Woodward-Hoffmann rules given in Table 1.1, where conrotatory and disrotatory describe the substituents on the alkene termini rotating either in the same or opposite directions, respectively. The rules stated in Table 1.1 can be derived via an analysis of the Frontier Molecular Orbitals (FMO) (Figure 1.6). Thus, the thermal reaction starts from the HOMO, and conrotatory motion allows ring closure, giving the *trans* isomer. Upon excitation, the former LUMO becomes occupied (i.e. the new HOMO) and disrotatory rotation results in the *cis* isomer.

# of π electrons	Δ	*hv*
4n	Conrotatory	Disrotatory
4n+2	Disrotatory	Conrotatory

Table 1.1

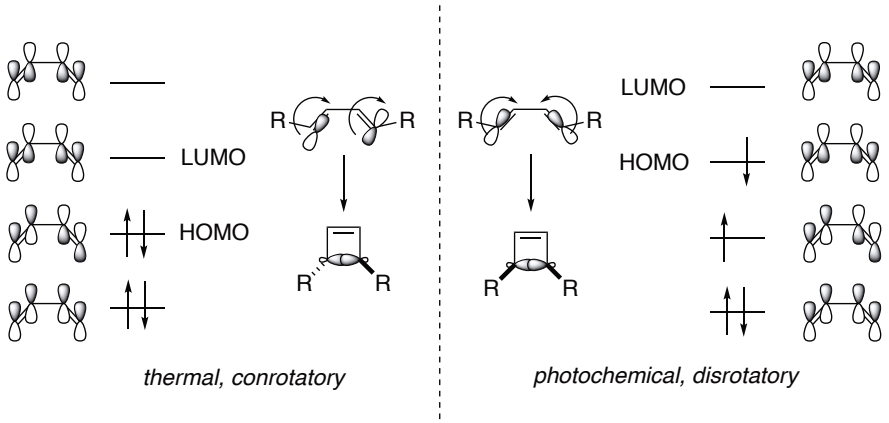


Figure 1.6

All electrocyclisations are theoretically reversible, but whilst a thermal 4-π-electrocyclisation can in principle take place on butadiene, such a process would involve a significant increase in strain energy and would thus be unlikely. Photochemical 4-π-electrocyclisations, or 4-π-photocyclisations, are more likely to occur, as the conjugated diene starting materials absorb at longer wavelengths than their unconjugated products, so it is often possible to drive the cyclisation to completion (Figure 1.7).

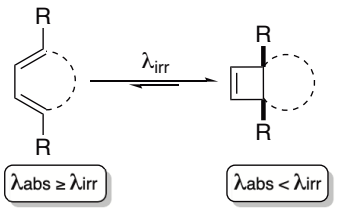


Figure 1.7

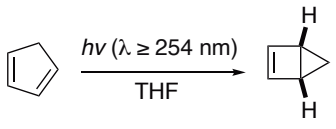
Whilst the 4-π-photocyclisation of acyclic dienes is theoretically possible, the overall efficiency of this process is hampered by competing *E*/*Z* photoisomerisation, as well as the requirement for the diene to take on a *Z*-configuration. Thus, 4-π-photocyclisations are significantly more likely to occur in small- to medium-ring systems where these requirements are met.

1.5.2 Substrate Scope

The literature pertaining to 4-π-photocylisation will be discussed, in order of increasing ring size; where applicable, the applications of the bicyclic photoproducts will also be discussed.

1.5.2.1 Five-Membered Rings

The 4-π-photocyclisation of cyclopentadiene **139** was first achieved by van Tamelen and co-workers in 1966 (Scheme 1.24).[79] Irradiation (λ = 254 nm) of **139** in cold ethanol led to 10% conversion after one to two hours. The reaction was later performed on a larger scale by Baldwin and co-workers to afford a 2–5% solution of **140** in tetrahydrofuran.[80] The authors state that due to the lability of **140** towards acid, all contact with water, hydroxylic solvents and acids must be avoided. Whilst **140** is stable in anhydrous THF at –78 °C indefinitely, it is also known to detonate spontaneously.



139 **140**

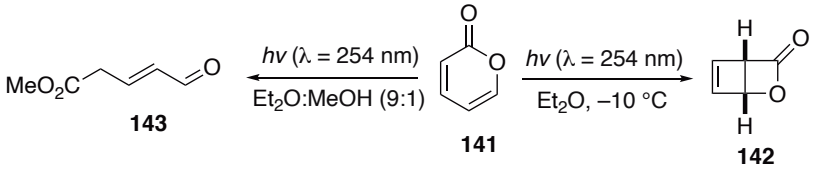
Scheme 1.24

The photochemistry of five-membered heterocycles including furan, thiophene

and pyrrole derivatives is quite complex. Indeed, 4-π-photocyclisation may occur alongside other products, but the [2.1.0]bicycles obtained are unstable and undergo a host of secondary transformations.[81]

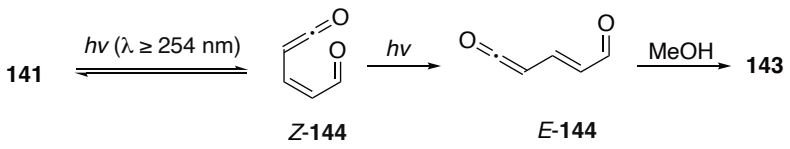
1.5.2.2 Six-Membered Rings

2-Pyrone **141** exhibits complex behaviour upon irradiation, with a range of photoproducts possible, depending on the conditions employed and identity of substituents around the ring (Scheme 1.25). Corey and Streith first performed the irradiation of **141** in diethyl ether to yield the bicyclic product **142**, via 4-π-photocyclisation (Scheme 5).[82] Interestingly, irradiation in methanolic solutions (9:1 diethyl ether:methanol) resulted instead in ring opening to yield a 4-methylacetonylcrotonate product **143**.



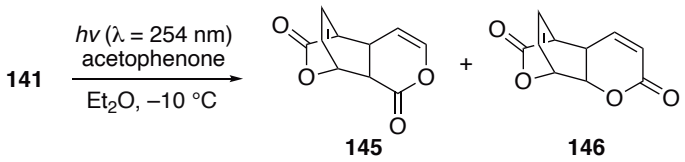
Scheme 1.25

As **143** formed in the presence of methanol, this suggests that the 6π ring-opening occurs via ketene intermediate **144**, which is trapped by an equivalent of methanol (Scheme 1.26). The reaction between **141** and **144** is reversible, and 6-π-electrocyclisation may return **141**.[83]



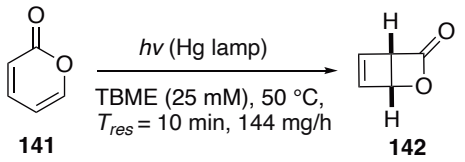
Scheme 1.26

In contrast, irradiation of **141** in benzene formed a mixture of the [2+4] dimers (**145** and **146**, respectively), although no yield for either was reported. No evidence of the 4-π-photocyclisation (**142**) or ring opened product (**143**) was observed (Scheme 1.27). As irradiation of methanolic solutions of **141** gave **145** and **146** in the presence of acetophenone, a triplet sensitiser, this indicates that this dimerisation process likely proceeds via an excited triplet state.[84]



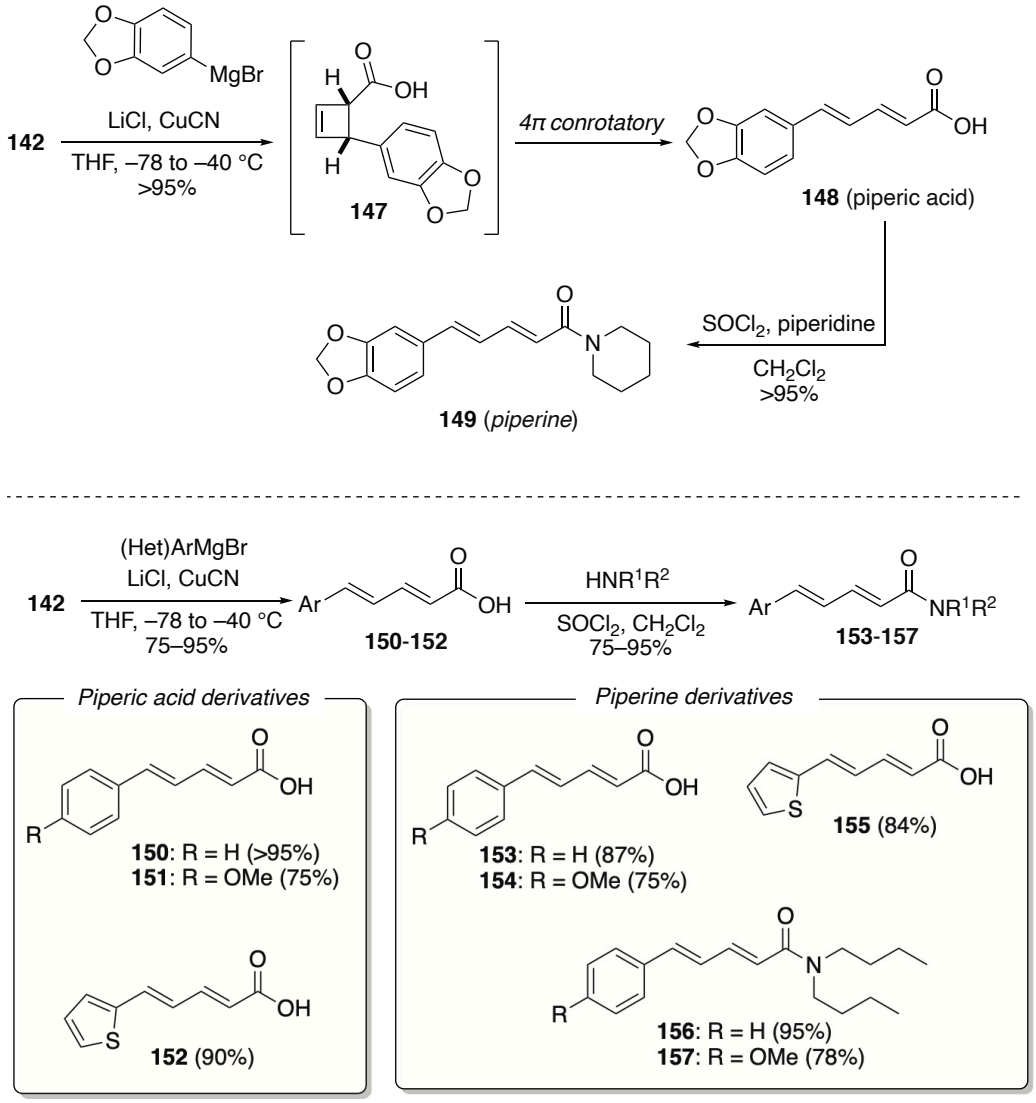
Scheme 1.27

The Maulide group provided an efficient synthesis of bicycle **142** on a multi-gram scale by use of a flow photoreactor (Scheme 1.28).[85]



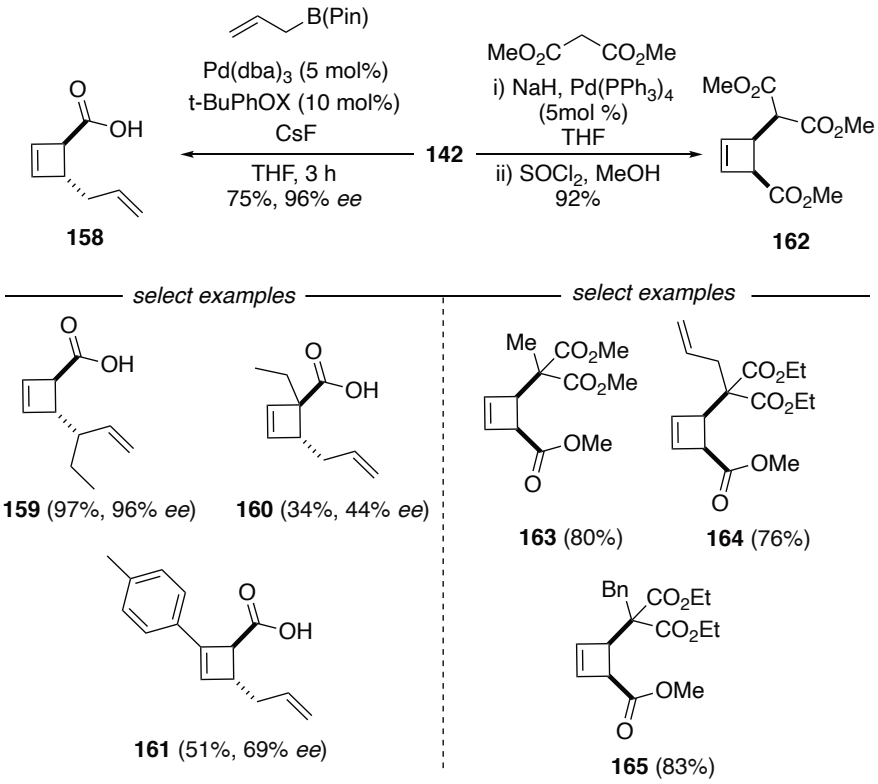
Scheme 1.28

In subsequent publications, the same group detailed the applications of **142**, in the synthesis of piperine (149) (Scheme 1.29).[86] Thus, ring opening of the β-lactam motif via addition of 1,3-benzodioxlemagensium bromide yielded cyclobutene (**147**), which immediately underwent stereoselective *retro*-4-π-electrocyclisation to form the open chain form (**148**). Reaction of **148** with piperidine and thionyl chloride afforded **149**.Other piperic acid (**150**-**152**) and piperine derivatives (**153**-**157**) could be obtained by reaction of **142** with the appropriate Grignard reagent and amine.



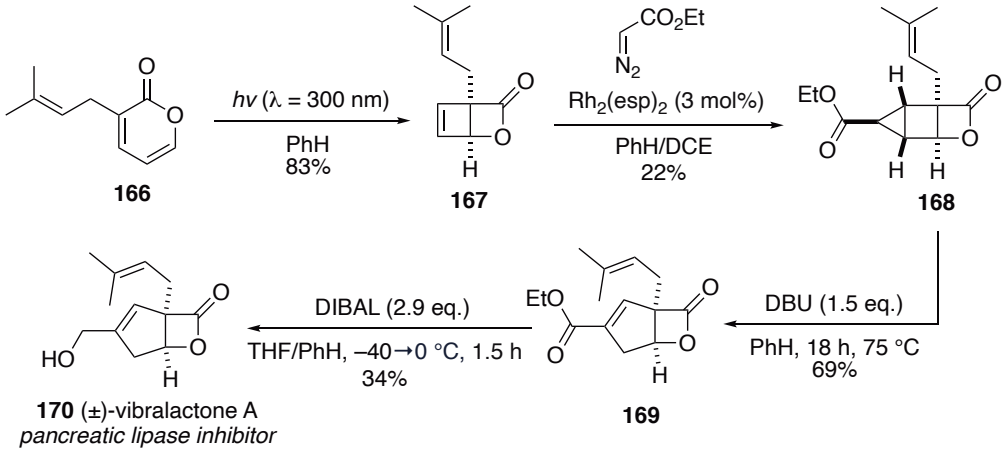
Scheme 1.29

In addition to the ring-opening products, other ring-openings of the β-lactone motif that are not immediately followed by *retro*-4-π-electrocyclisation have been reported. Thus, various enantioselective palladium-catalysed allylations with allyl boronic pinacol esters were also possible to afford cyclobutene derivatives **159**-**161** in good yields and enantioselectivities. In addition, palladium catalysed alkylation of **142** with electron deficient esters afforded a series of novel cyclobutene derivatives (**163**-**165**) in good yields (Scheme 1.30).[87]



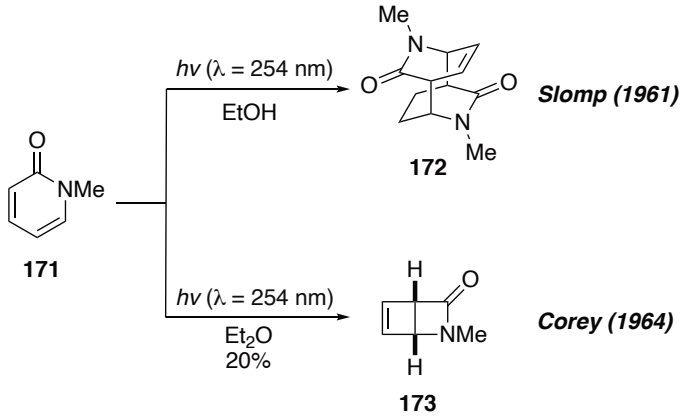
Scheme 1.30

Starting from prenylated 2-pyrone derivative **166**, bicycle **167** could be obtained in high yields (83%) upon irradiation at 300 nm in toluene (Scheme 1.31).[88] A short sequence of subsequent steps (3) afforded (±)-vibralactone A **170** in 5% overall yield.



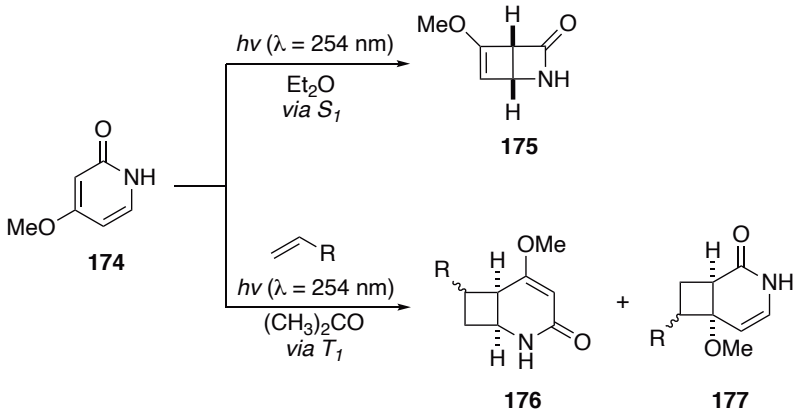
Scheme 1.31

Upon irradiation of an ethanolic solution of *N*-N-methyl-2-pyridone **171**, a dimer (**172**) was obtained via [4+4] PCA, rather than the expected 4-π-photocyclisation product **173** (Figure 1.32), although no yield was reported.[89] Later, Corey and Streith demonstrated that upon changing the reaction solvent to diethyl ether, **172** could be obtained in low yields.[90]



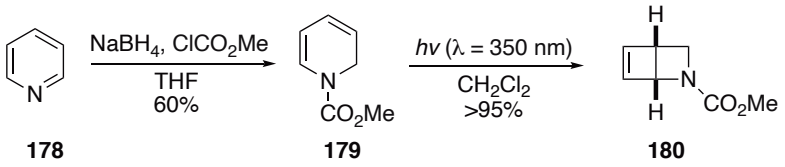
Scheme 1.32

Kaneko *et al.* reported successful 4-π-photocyclisation of 4-alkoxy substituted 2-pyridone **174** in an unspecified yield, with no dimerisation occurring. Additionally, the [2+2] cycloaddition of **174** with various olefins was also investigated. It was found that using acetone as the solvent resulted in successful cycloadditions, and any other solvent to the formation of bicycle **175**. Due to acetone's ability to act as a triplet sensitiser, it is likely that the photocycloaddition reactions to yield dimers **176** and **177** occur in the T_1 state, and that the 4-π-photocyclisation reaction will occur in the S_1 state (Scheme 1.33). The bicyclic photoproducts **173** and **175** are much more attractive for use in synthesis compared to their lactone analouges (e.g., **130**), which are typically much more unstable and pyrophoric.[91]



Scheme 1.33: R = Me_2, CH_2OAc, CO_2Me, CN.

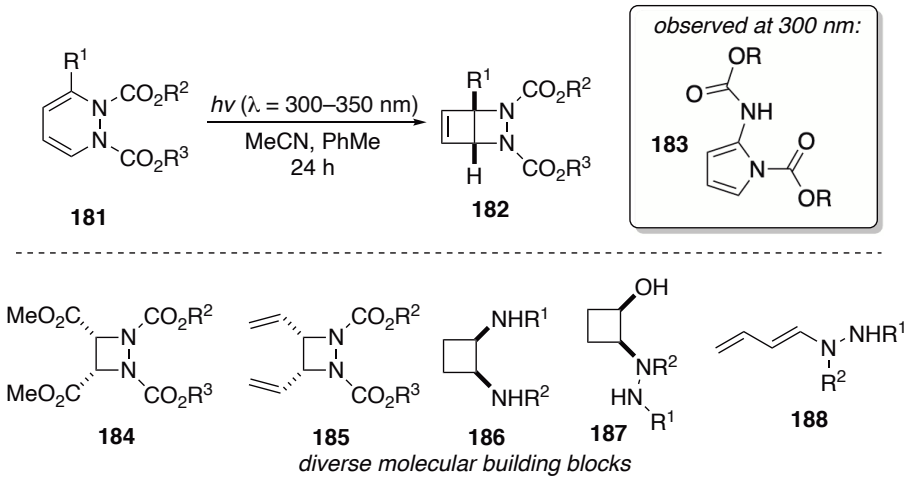
1,2-Dihydropyridines are potentially valuable intermediates in the synthesis of biologically important molecules – however, owing to their reactivity, would not likely survive a multiple-step synthesis to more complex molecules. The [2.2.0]bicyclic photoproducts (i.e., **180**) are much more stable compared to the parent 1,2-dihydropyridine compounds, which may act as 'masked' 1,2-dihydropyridines in such synthetic methodologies.[92] The 1,2-dihydropyridine **179** was obtained in 60% yield by Fowler, by reduction of a pyridinium ion with sodium borohydride. The photochemistry of this compound was investigated by irradiating in methylene chloride, which resulted in nearly complete consumption of the dihydropyridine starting material to give the bicyclic azetidine **180** (Scheme 1.34).[93]



Scheme 1.34

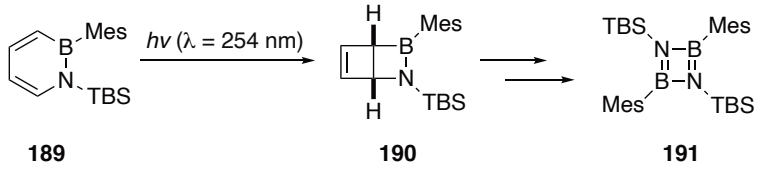
The Coote group recently published a detailed report on the 4-π-photocyclisation of 1,2-dihydropyridazine derivatives (**181**) (Scheme 1.35).[94] Thus, irradiation of **181** at

300 nm for several hours led to the expected bicyclic photoproducts **182**, although concomitant formation of an aminopyrrole side product **183** was also observed. After further optimisation of the reaction parameters, the formation of **183** could be suppressed by performing the reaction at longer wavelengths (λ = 350 nm), although longer reaction times (24-48 hours) were required for full conversion. The bicyclic 1,2-diazetidines obtained were useful synthetic intermediates, and were amenable to several transformations, including Ru(IV)-catalysed oxidative cleavage, olefin metathesis and SmI_2 cleavage of the N-N bond to yield derivatives **184**–**188**.



Scheme 1.35: R^1 = H, CO_2Me, R^2 = alkyl, R^3 = alkyl

Azaborane **175** undergoes 4-π-photocyclisation upon irradiation at 254 nm to yield its Dewar isomer **176**, which upon extended irradiation, cycloreversion occurs to yield novel 4-membered ring **177** (Scheme 1.36).[95] As the initial 4-π-photocyclisation reaction is thermally reversible, this system has potential applications within solar thermal fuels.

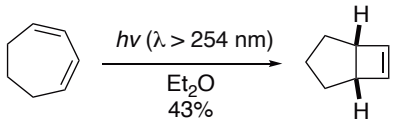


189 190 191

Scheme 1.36

1.5.2.3 Seven-Membered Rings

Several examples of 1,3-cycloheptadienes undergoing 4-π-photocyclisation have been reported. This reaction was first reported by Dauben, in which [3.2.0]bicycle **193** could be isolated from cycloheptadi-1,3-ene (**192**) in moderate yield after irradiation (λ = 254 nm) in diethyl ether (Scheme 1.37).[96]

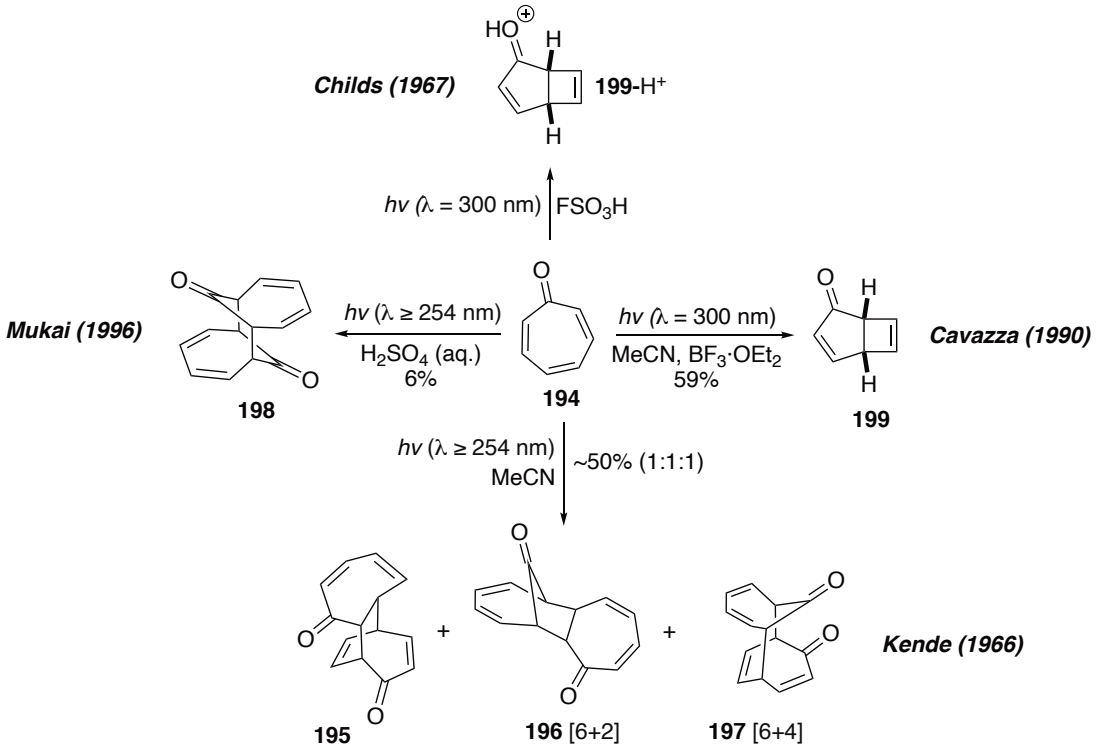


192 **193**

Scheme 1.37

The photochemistry of tropone (**194**) depends strongly on the reaction conditions, with a variety of photoproducts possible (Scheme 1.38). Thus, upon irradiation of (**125**) in acetonitrile, mixtures of the [6+4], [6+2] and [4+2] dimers (**195**-**197**) were obtained,[97] and small quantities of the [6+6] dimer (**198**) obtained in neutral or acidic aqueous media.[98] Later, Childs and Taguchi reported the first instance of **194** undergoing 4-π-photocyclisation, whereby protonated **199** was observed upon irradiation in methanesulfonic acid, although this was only performed as an NMR experiment.[42] This reaction was repeated by Kende and co-workers on a gram scale during studies to improve the [6+6] dimerisation of **198**, forming **199** as the sole product, although no yield was reported.[99] Finally, the 4-π-photocyclisation of **199** in the presence of $BF_3{\cdot}OEt_2$ was reported by Cavazza and co-workers to furnish **199** in 59% after 30 minutes of irradiation.[100] It was suggested that the lowest excited

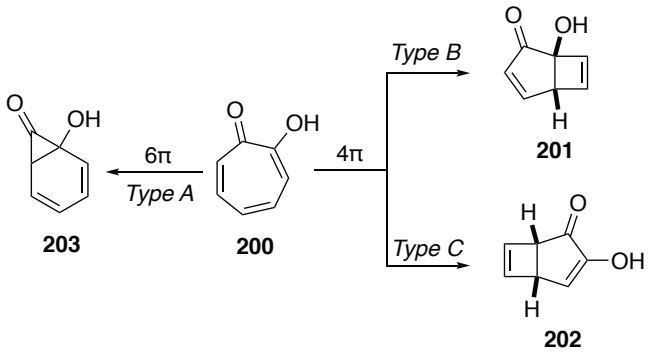
state of protonated **194** (or when **194** is complexed to a Lewis acid), corresponds to a π-π* transition that enables productive 4-π-photocyclisation, whereas in the absence of acid, the lowest excited state of **194** corresponds to a prohibited n-π* transition from which 4-π-photocyclisation does not occur.



Scheme 1.38

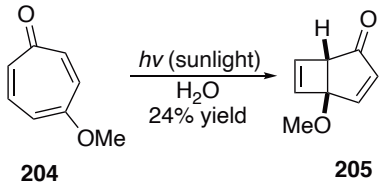
Tropolones – tropones bearing a hydroxy substituent at any point on the ring – display markedly different behaviour upon irradiation to **194**. Theoretically, there are two possible products that may arise from 4-π-photocyclisation of tropolones, depending on which of the double bonds take part in the reaction. Thus, for **200**, Chapman and Pasto provided nomenclature to classify these reactions – a 'Type B' photoreaction is one in which the new σ-bond is formed to the carbon atom bearing an oxygen substituent (**201**), and a 'Type C' cyclisation in the alternate case (**202**, Scheme 1.39). Type A photoreactivity, a 6-π-photocyclisation to give norcaradienone

intermediate **203** en route to phenolic or aldehyde products, is rarely observed in troponoid photochemistry but much more prevalent in cycloheptatrienes.[101]



Scheme 1.39

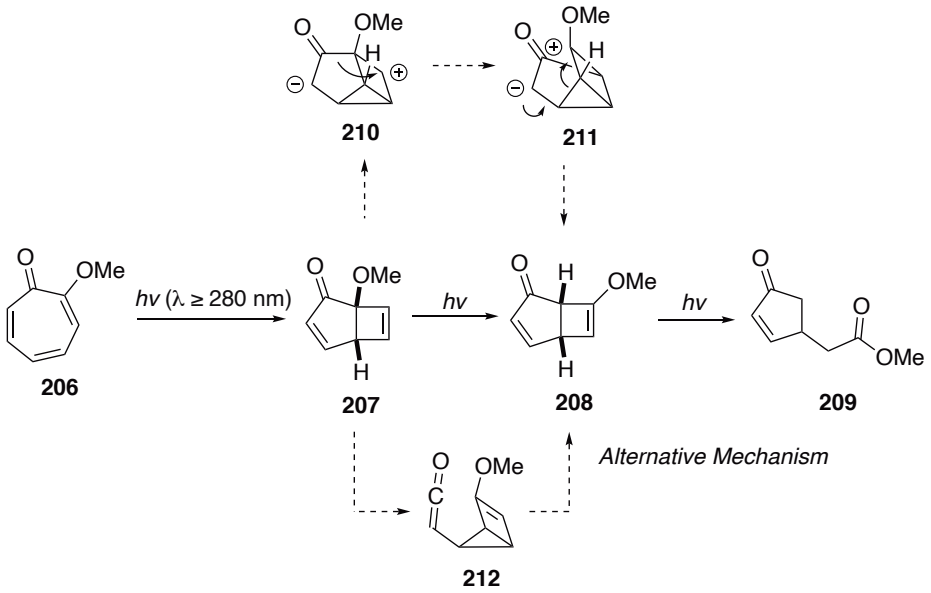
Thus, Chapman and Pasto reported the 4-π-photocyclisation of a simple monocyclic tropolone – upon irradiation of dilute aqueous solutions containing **204** in direct sunlight (8 days), bicycle **205** could be obtained in low yield (24%), with poor conversions (76% based on recovered starting material) (Scheme 1.40).[102,103]



Scheme 1.40

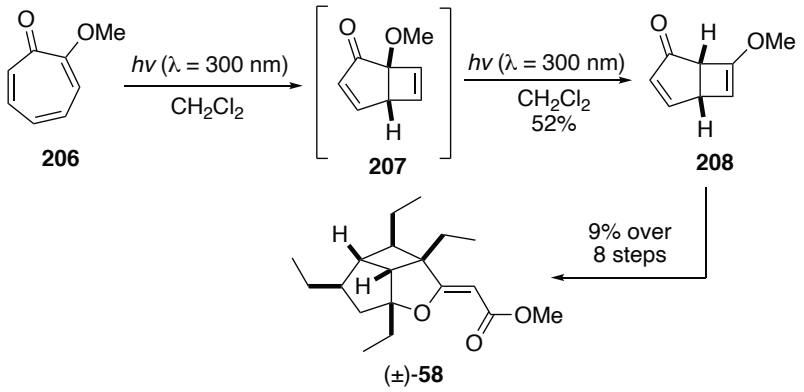
The photochemistry of the methyl ether of **200**, **206**, was explored extensively by Dauben and Chapman, in separate publications (Scheme 1.41). In aqueous and methanolic solutions giving rise to a complex mixture of products.[104] The [3.2.0]bicycle **207** arising from 4-π-photocyclisation underwent a rearrangement upon prolonged irradiation to yield rearranged [3.2.0]bicycle **208** and further solvolysis to yield cyclopentenone **209**. With the support of several alkyl-substituted

tropolone methyl ethers, a mechanism accounting for the formation of **207** was proposed: i) [2+2] photocycloaddition between the enone and cyclobutene double bond and sigma bond migration to yield intermediates **210** and **211** best represented in their zwitterionic forms, followed by another σ-bond migration reformation of the enone and cyclobutene double bond.[105] Later, the same group identified a band at 2118 cm^{-1} in the infrared spectroscopy of the reaction mixture at low temperatures (–180 °C) which is in the region expected for a ketene (2100 cm^{-1}),[106] leading to the proposal of ketene **212** as a potential intermediate in this reaction.[107,108] The photochemical reactivity of other tropones bearing a range of substituents will be discussed in Chapter 3.



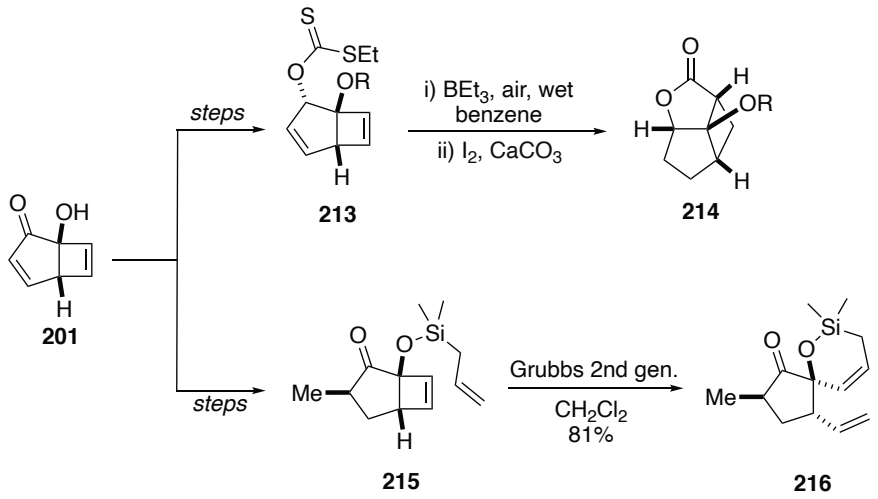
Scheme 1.41

The unique rearrangement of **207** to **208** was exploited by the Trauner group in their synthesis of (±)-Hippolachnin A (**58**, Scheme 1.42).[109] Thus, **208** could be isolated in moderate yield after irradiation of a thin film of **206** for 18 hours. In eight subsequent steps, (±)-**58** was isolated in 5% overall yield, representing its most efficient synthesis to date.



Scheme 1.42

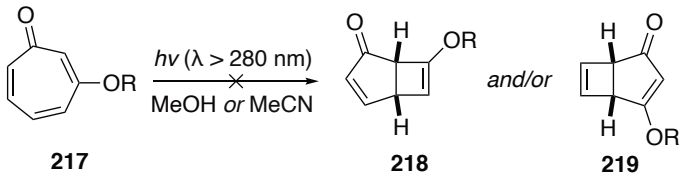
Wulff and co-workers further demonstrated the synthetic utility of **201**, obtained in good yield via irradiation of a thin film of **200**, wherein it was able to be converted to a series of novel lactones (**214**), through xanthate **213** (Scheme 1.43).[110] In a separate publication, the same group were able to access silyloxy spirocycle **216** in good yield from **201**.[111]



Scheme 1.43

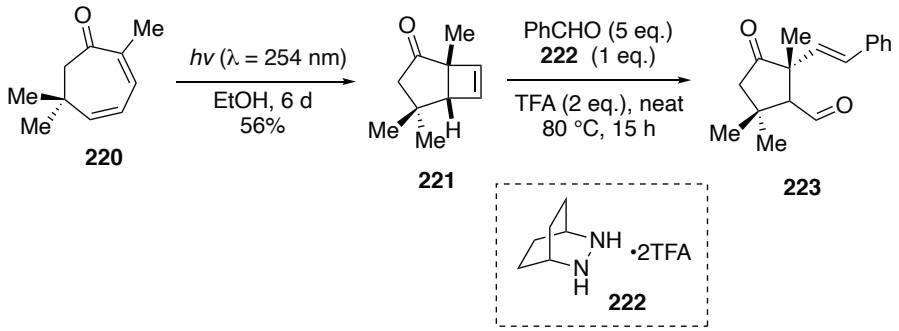
The third possible isomer of tropolone (**217**) is photostable and can be be recovered unchanged upon irradiation with 300 nm light, with neither **218** or **219** observed

(Scheme 1.44).



Scheme 1.44: R = H, Me.

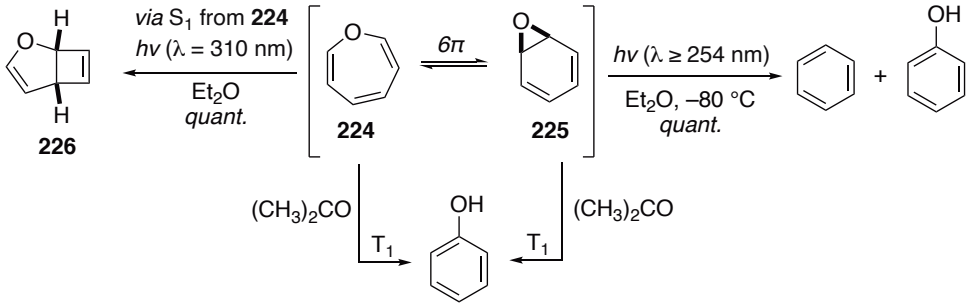
From looking at these three isomeric tropolone ethers, it is clear that the position of the hydroxyl substituent can have a significant effect on the photochemical behaviour of the substrate. The 4-π-photocyclisations of dihydrotropones have also been explored. For example, eucarvone (**220**) underwent 4-π-photocyclisation upon irradiation (λ = 254 nm) in ethanol to yield the corresponding [3.2.0]bicycle **221** in moderate yield, which was converted to densely functionalised cyclopentenone **223** via ring-opening carbonyl-olefin metathesis (ROCOM) (Scheme 1.45).[112]



Scheme 1.45

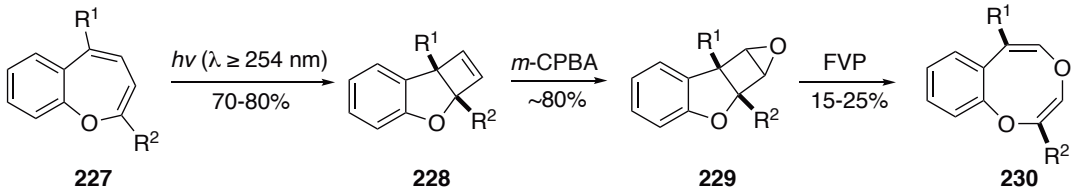
Heterocyclic seven-membered rings are also known to undergo 4-π-photocyclisation. Oxepine (**224**) and benzene oxide (**225**) exist in equilibrium with one another through a 6-π-electrocyclisation (Scheme 1.46). By careful selection of the reaction conditions, onte isomer may be favoured over the other, enabling the exploration of their respective photochemistry. Thus, irradiation (λ = 310 nm) of **212** in diethyl

ether led to 4-π-photocyclisation product **226** in quantitative yield.[113] Alternatively irradiation (λ 254 nm) at –80 °C led to significantly lower yields of **226** isolated, as well as benzene and phenol as photoproducts – these are assumed to arise primarily from isomer **225**. Performing the reaction using acetone as a solvent triplet sensitiser led to phenol being formed as the sole product, indicating a potential triplet pathway.



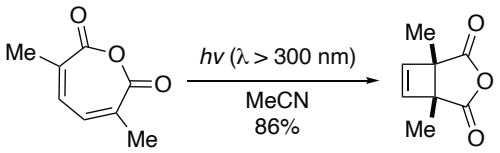
Scheme 1.46

Tsuchiya and co-workers described the 4-π-photocyclisation of several substituted benzoxepines (**227**) to afford tricycles **228** good yields, en route to 1,4-benzodioxicines **230** (Scheme 1.47).[114] Thus, epoxidation of **228** with *m*-CPBA and subsequent flash vacuum pyrolysis afforded the desired products **230**.



Scheme 1.47: R^1 = H, Me; R^2= H, Me

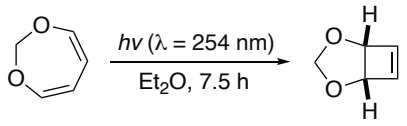
Muconic acid anhydride (**231**) underwent clean photoisomerisation upon irradiation in acetonitrile to yield bicycle 232 in good yield (86%) (Scheme 1.48).[115]



231 232

Scheme 1.48

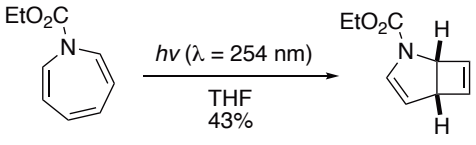
Similarly, 1,3-dioxepine **233** could be converted to its bicyclic isomer **234** upon irradiation (λ = 254 nm) in diethyl ether, although no yield was reported (Scheme 1.49).[116]



233 234

Scheme 1.49

Upon irradiation at 254 nm, azepine derivative **235** underwent isomerisation to its [3.2.0]bicyclic isomer **236** in moderate yield (43%) (Scheme 1.50). However, long irradiation times (2–3 days) were necessary for complete conversion of **223**.

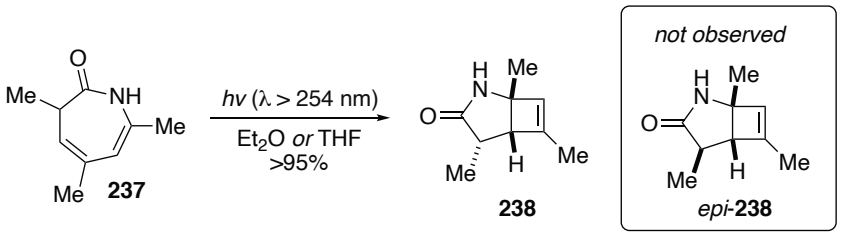


235 236

Scheme 1.50

The photochemistry of 3H-azepinone derivatives has been studied by various groups. Thus, Paquette[117] and Chapman[118], at the same time, reported the 4-π-

photocyclisation of dihydroazepinone **237** to yield bicycles **238** as the sole product in good yields and excellent stereoselectivity (Scheme 1.51).

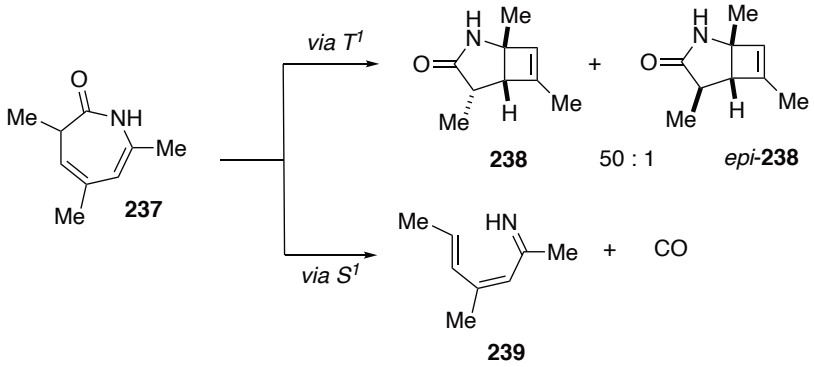


Scheme 1.51: R = H, Me.

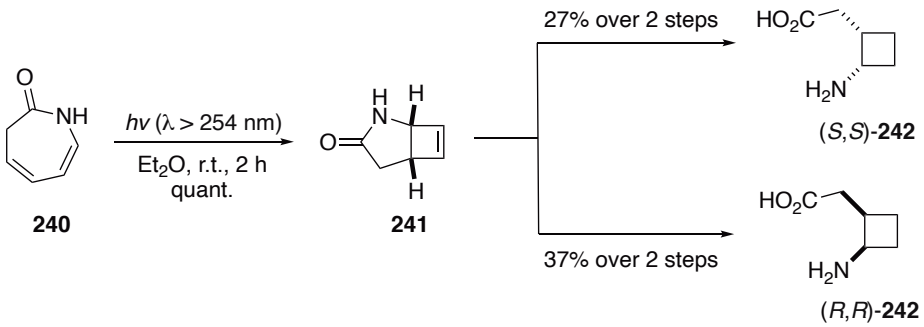
A later study by Pavlik and Seymour suggested that the photochemistry of **237** was more complex than previously suggested.[119] Thus, on the basis of GC-MS data performed on the crude photolysis product upon irradiation in diethyl ether, the authors suggest a 50:1 ratio of diastereoisomers **238**:*epi*-**238** (Scheme 1.52). Changing the solvent to methanol led to a marked decrease in both yield and stereoselectivity. Alternatively, irradiation in the presence of acetophenone, or by performing the reaction in acetone, gave the bicyclic products (**238**). On the other hand, irradiation in the presence of molecular oxygen (a triplet quencher), gave rise to acyclic imine **239** as the major product, through photodecarbonylation. These results suggest that 4-π-photocyclisation occurs from a triplet excited state, and the latter reaction a singlet excited state.

Later, Aitken and co-workers described various derivatisations of bicycle **229**, obtained in quantitative yield from irradiation of **228** in diethyl ether at 254 nm, including chiral resolution and further manipulations en route to both enantiomers of GABA analogue **230** in enantiopure forms (Scheme 1.53).[120]

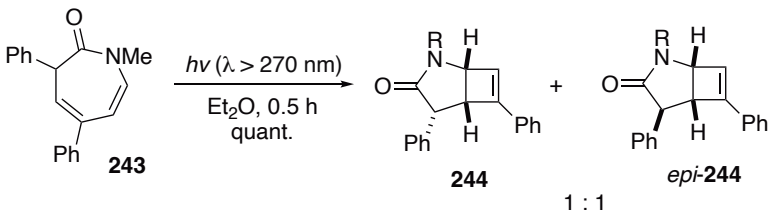
Substitution of **240** with phenyl rings leads (**243**) to a marked decrease in stereoselectivity, affording diastereomers **244** and *epi*-**244** in a 1:1 ratio (Scheme 1.54).[121]



Scheme 1.52: R = H, Me.

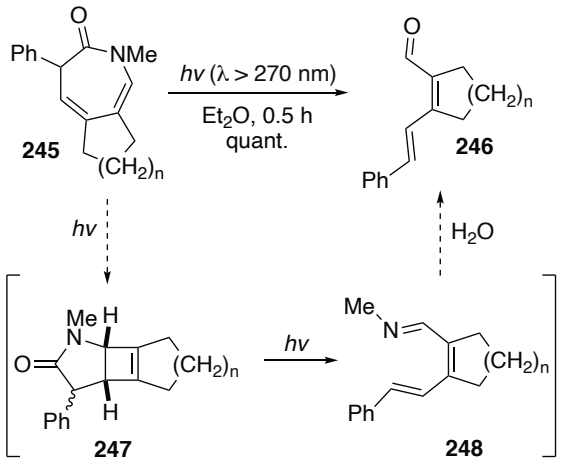


Scheme 1.53



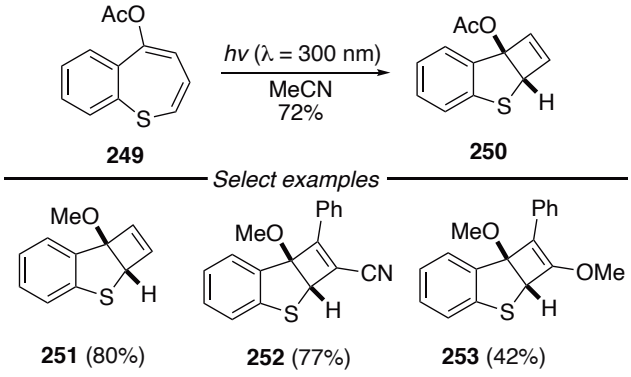
Scheme 1.54

Alkyl annulated 3H-azepinones (**245**) yielded ring–opened products **246** – this presumably occurs via an initial 4-π-photocyclisation to yield tricycle **247** which undergo decarbonylation and hydrolysis to yield aldehyde **248** (Scheme 1.55).



Scheme 1.55: n = 1–4.

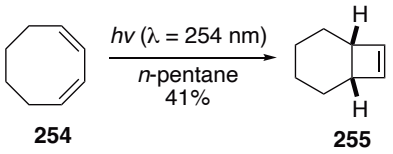
The photochemistry of thiepines and related compounds is quite limited. Hofmann and co-workers detailed the photochemistry of benzothiepines **249** in two separate publications.[122,123] The corresponding bicycles (**250**-**253**) could be obtained selectively in good yields upon irradiation in acetonitrile at 300 nm (Scheme 1.56).



Scheme 1.56

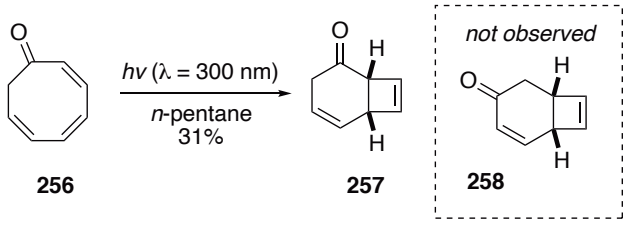
1.5.2.4 Eight-Membered Rings

Dauben and Cargill first reported the 4-π-photocyclisation of an eight-membered carbocycle – irradiation at 254 nm of 1,3-octadiene **254** in diethyl ether, to afford the corresponding [4.2.0]bicycle **255** in moderate yield (41%) (Scheme 1.57).[124]



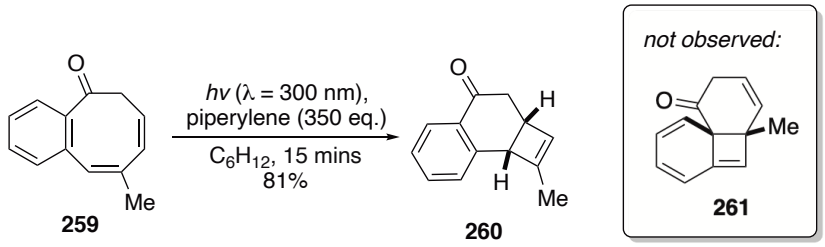
Scheme 1.57

Later, Buchi and Burgess reported the 4-π-photocyclisation of cyclooctatrienone **256** upon irradiation at 254 nm in *n*-pentane for 21 days, to yield [4.2.0]bicycle **257** in moderate yield (31%) (Scheme 1.58).[125] **257** was found to slowly isomerise back to **256** at 0 °C, making its purification and storage difficult. The other potential regioisomer **258** was not observed.



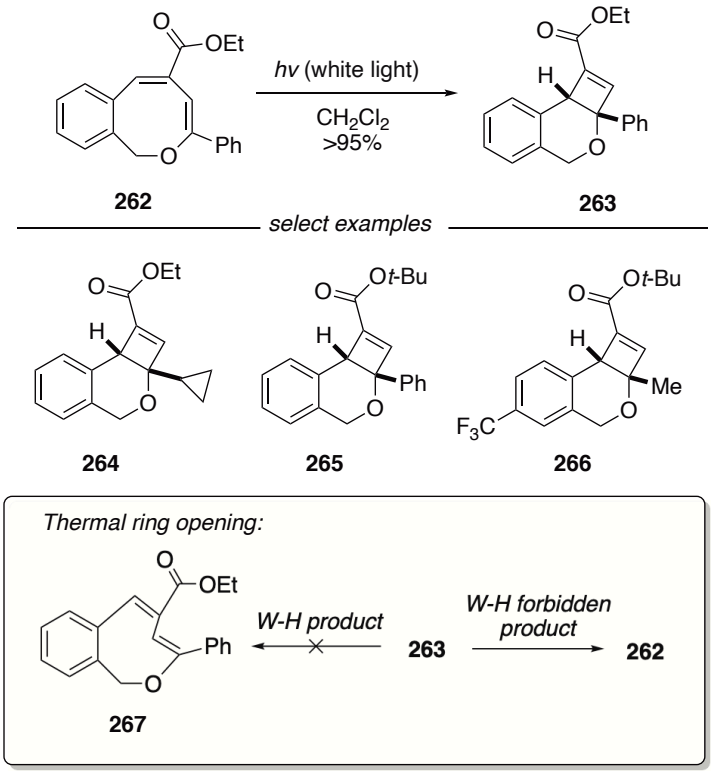
Scheme 1.58

Later, the photochemistry of benzoctatrienone **259** was explored by McKay and co-workers.[126] Thus, irradiation of **259** with Pyrex-filtered light gave tricycle **260** in good yield (81%). The use of excess piperylene as a triplet quencher was required to suppress side-reactions occurring from the triplet state (Scheme 1.59).



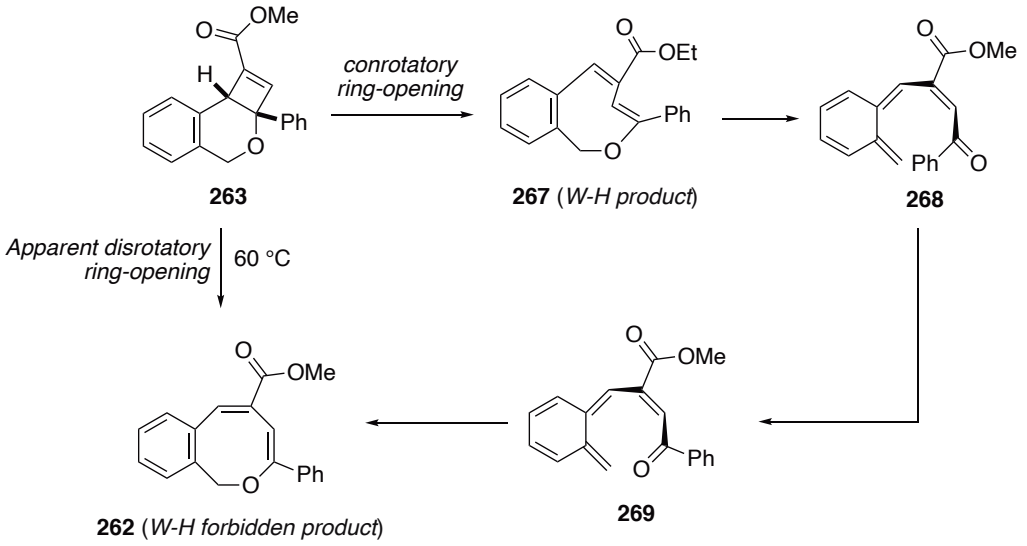
Scheme 1.59

Finally, the de Bruin group published the first application of a 4-π-photocyclisation in a photothermal switch.[127] Thus, 1*H*-2-benzo[c]oxocins (e.g. **262**) could be converted to dihydro-4H-cyclobuta[c]isochromenes **263–266** in excellent yields upon irradiation using visible light (Scheme 1.60). Remarkably, the product obtained from thermal ring-opening is the Woodward-Hoffman forbidden product **263**, and not the expected product obtained from conrotatory ring closure (**267**).



Scheme 1.60

On the basis of density functional theory DFT calculations, the authors suggested that the thermal formation of **262** is in fact preceded by **267** which rearranges through **268** and **269** to return **262** (Scheme 1.61).



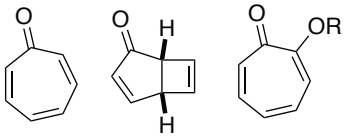
Scheme 1.61

1.6 Conclusions

Clearly, the 4-π-photocyclisation of both carbocyclic and heterocyclic dienes is an efficient method in the synthesis of uncommon [2.2.0], [3.2.0] and [4.2.0]bicyclic cyclobutene products. Nevertheless, for each substrate class, there are relatively few examples, and these photocyclisations (and their versatile products) have been generally underexploited in synthesis. Of these examples, [3.2.0]bicycles derived from tropones, despite having enormous synthetic potential, have been particularly underutilised in synthesis. With improvements in flow technology in the past several years,[128] these reactions are now ever-more feasible on larger scales to meet the needs of drug-discovery campaigns.

In particular, **199** itself – the product of 4-π-photocyclisation of **194** – possesses both an electron deficient enone and a highly strained electron rich cyclobutene, but

has received virtually no attention, in contrast to the product of 4-π-photocyclisation of **200** and its derivatives.



194 **199** **200**: R = H
206: R = Me

Figure 1.8

References

[1] Ngo, H. X.; Garneau-Tsodikova, S. *MedChemComm* **2018,** *9,* 757–758.

[2] Zhong, L.; Li, Y.; Xiong, L.; Wang, W.; Wu, M.; Yuan, T.; Yang, W.; Tian, C.; Miao, Z.; Wang, T.; Yang, S. *Signal Transduct. Target. Ther.* **2021,** *6,* 201.

[3] Schreiber, S. L. *Science* **2000,** *287,* 1964–1969.

[4] O' Connor, C. J.; Beckmann, H. S. G.; Spring, D. R. *Chem. Soc. Rev.* **2012,** *41,* 4444–4456.

[5] Dobson, C. M. *Nature* **2004,** *432,* 824–828.

[6] Reymond, J.-L.; van Deursen, R.; Blum, L. C.; Ruddigkeit, L. *MedChemComm* **2010,** *1,* 30–38.

[7] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **1997,** *23,* 3–25.

[8] Alqahtani, M. S.; Kazi, M.; Alsenaidy, M. A.; Ahmad, M. Z. *Front. Pharmacol.* **2021,** *12,* 1–21.

[9] Doak, B. C.; Kihlberg, J. *Expert Opin. Drug Discov.* **2017,** *12,* 115–119.

[10] Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002,** *45,* 2615–2623.

[11] Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009,** *52,* 6752–6756.

[12] Hamilton, D. J.; Beemsterboer, M.; Carter, C. M.; Elsayed, J.; Huiberts, R. E. M.; Klein, H. F.; O'Brien, P.; de Esch, I. J. P.; Wijtmans, M. *ChemMedChem* **2022,** *17,* e202200113.

[13] Lovering, F. *Medchemcomm* **2013,** *4,* 515.

[14] Schreiber, S. L. *Proc. Natl. Acad. Sci. U. S. A.* **2011,** *108,* 6699–6702.

[15] Ritchie, T. J.; Macdonald, S. J. F. *Drug Discov. Today* **2009,** *14,* 1011–1020.

[16] Roche, S. P.; Porco, Jr, J. A. *Angew. Chem. Int. Ed Engl.* **2011,** *50,* 4068–4093.

[17] Brown, D. G.; Gagnon, M. M.; Boström, J. *J. Med. Chem.* **2015,** *58,* 2390–2405.

[18] Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011,** *54,* 3451–3479.

[19] Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem. Int. Ed Engl.* **2010,** *49*, 8082–8091.

[20] Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, 3rd, W. F.; Schenck, R. J.; Trippe, A. J.; CAS Registry, *J. Org. Chem.* **2008,** *73*, 4443–4451.

[21] Galloway, W. R. J. D.; Bender, A.; Welch, M.; Spring, D. R. *Chem. Commun. (Camb.)* **2009,** 2446–2462.

[22] Sauer, W. H. B.; Schwarz, M. K. *J. Chem. Inf. Comput. Sci.* **2003,** *43*, 987–1003.

[23] Spring, D. R. *Org. Biomol. Chem.* **2003,** *1*, 3867.

[24] Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* **2010,** *1*, 80.

[25] Kim, Y.-K.; Arai, M. A.; Arai, T.; Lamenzo, J. O.; Dean, 3rd, E. F.; Patterson, N.; Clemons, P. A.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004,** *126*, 14740–14745.

[26] Ibbeson, B. M.; Laraia, L.; Alza, E.; O' Connor, C. J.; Tan, Y. S.; Davies, H. M. L.; McKenzie, G.; Venkitaraman, A. R.; Spring, D. R. *Nat. Commun.* **2014,** *5*, 1–8.

[27] Chen, F.-E.; Zhao, J.-F.; Xiong, F.-J.; Xie, B.; Zhang, P. *Carbohydrate Research* **2007,** *342*, 2461–2464.

[28] Liu, Y.; Puig de la Bellacasa, R.; Li, B.; Cuenca, A. B.; Liu, S.-Y. *J. Am. Chem. Soc.* **2021,** *143*, 14059–14064.

[29] Rablen, P. R. *Chemistry* **2020,** *2*, 347–360.

[30] Li, J.; Gao, K.; Bian, M.; Ding, H. *Org. Chem. Front.* **2020,** *7*, 136–154.

[31] van der Kolk, M. R.; Janssen, M. A. C. H.; Rutjes, F. P. J. T.; Blanco-Ania, D. *ChemMedChem* **2022,** *17*,.

[32] Dembitsky, V. M. *Phytomedicine* **2014,** *21*, 1559–1581.

[33] Sergeiko, A.; Poroikov, V. V.; Hanus, L. O.; Dembitsky, V. M. *Open Med. Chem. J.* **2008,** *2*, 26–37.

[34] Fan, Y.-Y.; Gao, X.-H.; Yue, J.-M. *Sci. China Chem.* **2016,** *59*, 1126–1141.

[35] Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed Engl.* **2011,** *50,* 7740–7752.

[36] Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003,** *103,* 1449–1483.

[37] Misale, A.; Niyomchon, S.; Maulide, N. *Acc. Chem. Res.* **2016,** *49,* 2444–2458.

[38] Deeprose, M. J.; Lowe, M.; Noble, A.; Booker-Milburn, K. I.; Aggarwal, V. K. *Org. Lett.* **2022,** *24,* 137–141.

[39] Goetzke, F. W.; Sidera, M.; Fletcher, S. P. *Chem. Sci.* **2021,** *13,* 236–240.

[40] Liang, Z.; Wang, L.; Wang, Y.; Wang, L.; Chong, Q.; Meng, F. *J. Am. Chem. Soc.* **2023,** *145,* 3588–3598.

[41] Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. *Chem. Rev.* **2016,** *116,* 9748–9815.

[42] Childs, R. F.; Johnson, A. W. *J. Chem. Soc.* **1967,** 874.

[43] Matsui, T.; Morooka, T.; Nakayama, M. *Bull. Chem. Soc. Jpn.* **1987,** *60,* 417–419.

[44] Booker-Milburn, K. I.; Cowell, J. K.; Sharpe, A.; Jiménez, F. D. *Chem. Commun.* **1996,** 249–251.

[45] D'Annibale, A.; D'Auria, M.; Mancini, G.; Pace, A. D.; Racioppi, R. *Eur. J. Org. Chem.* **2011,** *2012,* 785–791.

[46] Ruider, S. A.; Sandmeier, T.; Carreira, E. M. *Angew. Chem. Int. Ed Engl.* **2015,** *54,* 2378–2382.

[47] Sultan, S.; Bhat, M.-U.-S.; Rizvi, M. A.; Shah, B. A. *J. Org. Chem.* **2019,** *84,* 8948–8958.

[48] Wille, U. *Organic Letters* **2000,** *2,* 3485–3488.

[49] Elliott, L. D.; Kayal, S.; George, M. W.; Booker-Milburn, K. *J. Am. Chem. Soc.* **2020,** *142,* 14947–14956.

[50] Strieth-Kalthoff, F.; Henkel, C.; Teders, M.; Kahnt, A.; Knolle, W.; Gómez-Suárez, A.; Dirian, K.; Alex, W.; Bergander, K.; Daniliuc, C. G.; Abel, B.; Guldi, D. M.; Glorius, F. *Chem* **2019,** *5,* 2183–2194.

[51] Zhao, J.; Brosmer, J. L.; Tang, Q.; Yang, Z.; Houk, K. N.; Diaconescu, P. L.; Kwon, O. *J. Am. Chem. Soc.* **2017,** *139,* 9807–9810.

[52] Rigotti, T.; Schwinger, D. P.; Graßl, R.; Jandl, C.; Bach, T. *Chem. Sci.* **2022,** *13,* 2378–2384.

[53] Gerber, P.; Keese, R. *Tetrahedron Letters* **1992,** *33,* 3987–3988.

[54] Mancini, I.; Cavazza, M.; Guella, G.; Pietra, F. *J. Chem. Soc., Perkin Trans.* **1994,** 2181.

[55] López-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010,** *132,* 9292–9294.

[56] Iwai, T.; Ueno, M.; Okochi, H.; Sawamura, M. *Adv. Synth. Catal.* **2018,** *360,* 670–675.

[57] Lee, Y. T.; Kang, Y. K.; Chung, Y. K. *J. Org. Chem.* **2009,** *74,* 7922–7934.

[58] Debleds, O.; Campagne, J.-M. *J. Am. Chem. Soc.* **2008,** *130,* 1562–1563.

[59] Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005,** *127,* 8244–8245.

[60] Saltó, J.; Biosca, M.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2022,** *364,* 3682–3689.

[61] Sakai, K.; Kochi, T.; Kakiuchi, F. *Org. Lett.* **2013,** *15,* 1024–1027.

[62] Kuninobu, Y.; Yu, P.; Takai, K. *Chem. Lett.* **2007,** *36,* 1162–1163.

[63] Mitsudo, T.-A.; Kokuryo, K.; Takegami, Y. *J. Chem. Soc. Chem. Commun.* **1976,** 722.

[64] Mitsudo, T.-A.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem. Int. Ed. Engl.* **1994,** *33,* 580–581.

[65] Fan, B.-M.; Li, X.-J.; Peng, F.-Z.; Zhang, H.-B.; Chan, A. S. C.; Shao, Z.-H. *Org. Lett.* **2010,** *12,* 304–306.

[66] Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004,** *126,* 7442–7443.

[67] Nishimura, A.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2012,** *134,* 15692–15695.

[68] Cañellas, S.; Montgomery, J.; Pericàs, M. À. *J. Am. Chem. Soc.* **2018,** *140,* 17349–17355.

[69] Li, H.; Hsung, R. P.; DeKorver, K. A.; Wei, Y. *Org. Lett.* **2010,** *12,* 3780–3783.

[70] Parsutkar, M. M.; Pagar, V. V.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2019,** *141,* 15367–15377.

[71] Rosenblum, M.; Scheck, D. *Organometallics* **1982,** *1,* 397–399.

[72] Shen, L.; Zhao, K.; Doitomi, K.; Ganguly, R.; Li, Y.-X.; Shen, Z.-L.; Hirao, H.; Loh, T.-P. *J. Am. Chem. Soc.* **2017,** *139,* 13570–13578.

[73] Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1960,** *82,* 1002–1003.

[74] Gallucci, R. R.; Jones, Jr, M. *J. Am. Chem. Soc.* **1976,** *98,* 7704–7711.

[75] Xu, H.; Zhang, W.; Shu, D.; Werness, J. B.; Tang, W. *Angew. Chem.* **2008,** *120,* 9065–9068.

[76] Barluenga, J.; Riesgo, L.; López, L. A.; Rubio, E.; Tomás, M. *Angew. Chem. Int. Ed Engl.* **2009,** *48,* 7569–7572.

[77] Deng, Y.; Massey, L. A.; Zavalij, P. Y.; Doyle, M. P. *Angew. Chem. Int. Ed Engl.* **2017,** *56,* 7479–7483.

[78] Li, C.-W.; Pati, K.; Lin, G.-Y.; Sohel, S. M. A.; Hung, H.-H.; Liu, R.-S. *Angew. Chem. Int. Ed Engl.* **2010,** *49,* 9891–9894.

[79] Brauman, J. I.; Ellis, L. E.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1966,** *88,* 846–848.

[80] A. Harry Andrist, J. E. B.; Robert K. Pinschmidt, J. *Org. Synth.* **1976,** *55,* 15.

[81] Rendall, W. A.; Torres, M.; Lown, E. N.; Strausz, O. P. *Rev. Chem. Intermed.* **1986,** *6,* 335–364.

[82] Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964,** *86,* 950–951.

[83] Pirkle, W. H.; McKendry, L. H. *J. Am. Chem. Soc.* **1969,** *91,* 1179–1186.

[84] Pirkle, W. H.; McKendry, L. H. *Tetrahedron Lett.* **1968,** *9,* 5279–5282.

[85] Williams, J. D.; Otake, Y.; Coussanes, G.; Saridakis, I.; Maulide, N.; Kappe, C. O. *ChemPhotoChem* **2019,** *3,* 229–232.

[86] Maulide, N.; Bauer, A.; Nam, J.-H. *Synlett* **2019,** *30,* 413–416.

[87] Misale, A.; Niyomchon, S.; Maulide, N. *Acc. Chem. Res.* **2016,** *49,* 2444–2458.

[88] Nistanaki, S. K.; Boralsky, L. A.; Pan, R. D.; Nelson, H. M. *Angew. Chem. Int. Ed Engl.* **2019,** *58,* 1724–1726.

[89] Slomp, G.; MacKellar, F. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1961,** *83,* 4472–4473.

[90] Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964,** *86,* 950–951.

[91] Chapman, O. L.; Hoganson, E. D. *J. Am. Chem. Soc.* **1964,** *86,* 498–500.

[92] Beeken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979,** *101,* 6677–6682.

[93] Fowler, F. W. *J. Org. Chem.* **1972,** *37,* 1321–1323.

[94] Britten, T. K.; Kemmitt, P. D.; Halcovitch, N. R.; Coote, S. C. *Org. Lett.* **2019,** *21,* 9232–9235.

[95] Edel, K.; Yang, X.; Ishibashi, J. S. A.; Lamm, A. N.; Maichle-Mössmer, C.; Giustra, Z. X.; Liu, S.-Y.; Bettinger, H. F. *Angew. Chem. Int. Ed Engl.* **2018,** *57,* 5296–5300.

[96] Dauben, W. G.; Cargill, R. L. *Tetrahedron* **1961,** *12,* 186–189.

[97] Kende, A. S. *J. Am. Chem. Soc.* **1966,** *88,* 5026–5027.

[98] Mukai, T.; Tezuka, T.; Akasaki, Y. *J. Am. Chem. Soc.* **1966,** *88,* 5025–5026.

[99] Reingold, I. D.; Kwong, K. S.; Menard, M. M. *J. Org. Chem.* **1989,** *54,* 708–710.

[100] Cavazza, M.; Zandomeneghi, M.; Pietra, F. *J. Chem. Soc. Chem. Commun.* **1990,** 1336.

[101] Jansen, H.; Slootweg, J. C.; Lammertsma, K. *Beilstein J. Org. Chem.* **2011,** *7,* 1713–1721.

[102] Chapman, O. L.; Pasto, D. J. *J. Am. Chem. Soc.* **1958,** *80,* 6685–6686.

[103] Chapman, O. L.; Pasto, D. J. *J. Am. Chem. Soc.* **1960,** *82,* 3642–3648.

[104] Dauben, W. G.; Koch, K.; Chapman, O. L.; Smith, S. L. *J. Am. Chem. Soc.* **1961,** *83,* 1768–1769.

[105] Dauben, W. G.; Koch, K.; Smith, S. L.; Chapman, O. L. *J. Am. Chem. Soc.* **1963,** *85,* 2616–2621.

[106] McAllister, M. A.; Tidwell, T. T. *Can. J. Chem.* **1994,** *72,* 882–887.

[107] Chapman, O. L.; Lassila, J. D. *J. Am. Chem. Soc.* **1968,** *90,* 2449–2450.

[108] Day, A. C.; Ledlie, M. A. *J. Chem. Soc. D* **1970,** *0,* 1265b–1266.

[109] Winter, N.; Trauner, D. *J. Am. Chem. Soc.* **2017,** *139,* 11706–11709.

[110] Davy, J. A.; Mason, J. W.; Moreau, B.; Wulff, J. E. *J. Org. Chem.* **2012,** *77,* 6332–6339.

[111] Davy, J. A.; Moreau, B.; Oliver, A. G.; Wulff, J. E. *Tetrahedron* **2015,** *71,* 2643–2657.

[112] Holl, M. G.; Lambert, T. H. *ACS Catal.* **2022,** *12,* 4813–4817.

[113] Holovka, J. M.; Gardner, P. D. *J. Am. Chem. Soc.* **1967,** *89,* 6390–6391.

[114] Kurita, J.; Yamada, S.; Sakai, H.; Tsuchiya, T. *J. Chem. Soc. Chem. Commun.* **1985,** 1254.

[115] Brodbeck, H.; Bourgin, D.; Neier, R. *Tetrahedron Lett.* **1986,** *27,* 343–344.

[116] Keana, J. F. W.; Morse, R. H. *Tetrahedron Lett.* **1976,** *17,* 2113–2114.

[117] Paquette, L. A. *J. Am. Chem. Soc.* **1964,** *86,* 500–503.

[118] Chapman, O. L.; Hoganson, E. D. *J. Am. Chem. Soc.* **1964,** *86,* 498–500.

[119] Pavlik, J. W.; Seymour, C. A. *Tetrahedron Lett.* **1977,** *18,* 2555–2558.

[120] Awada, H.; Robin, S.; Guillot, R.; Yazbeck, O.; Naoufal, D.; Jaber, N.; Hachem, A.; Aitken, D. J. *European J. Org. Chem.* **2014,** *2014,* 7148–7155.

[121] Knobloch, K.; Koch, J.; Keller, M.; Eberbach, W. *European J. Org. Chem.* **2005,** *2005,* 2715–2733.

[122] Hofmann, H.; Gaube, H. *Justus Liebigs Ann. Chem.* **1977,** *1977,* 1874–1887.

[123] Hofmann, H.; Djafari, H. *Liebigs Ann. Chem.* **1987,** *1987,* 505–507.

[124] Dauben, W. G.; Cargill, R. L. *J. Org. Chem.* **1962,** *27,* 1910–1910.

[125] Buchi, G.; Burgess, E. M. *J. Am. Chem. Soc.* **1962,** *84,* 3104–3109.

[126] Bender, C. O.; Bengtson, D. L.; Dolman, D.; McKay, R. T. *Can. J. Chem.* **1994,** *72,* 1556–1564.

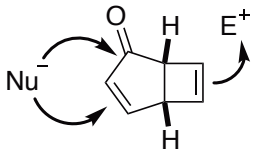
[127] Zhou, M.; Mathew, S.; de Bruin, B. *J. Am. Chem. Soc.* **2023,** *145,* 645–657.

[128] Politano, F.; Oksdath-Mansilla, G. *Org. Process Res. Dev.* **2018,** *22*, 1045–1062.

Chapter 2

Synthesis and Reactions of Phototropone

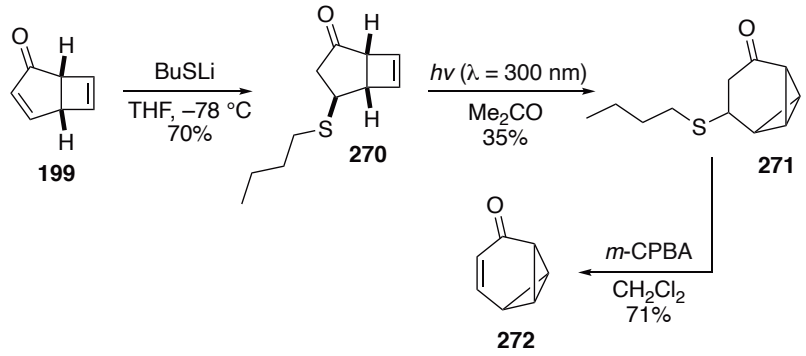
Possessing both a strained electron-rich cyclobutene ring and an electron-deficient enone, the phototropone (bicyclo[3.2.0]hepta-3,6-dien-2-one; BCH) scaffold **199** appears ripe for derivatisation, with electrophilic additions to the cyclobutene and nucleophilic additions to the enone easily imagined (Figure 2.1).



199

Figure 2.1

However, **199** itself has barely been explored in this way, despite its synthetic potential. Indeed, only one reaction of **199** has previously been reported – the 1,4-addition of *n*-butanethiol to give thioether **270**, which was amenable to a subsequent photochemical transformation to give tropovalene precursor **271**.[1] Treatment of **271** with *m*-CPBA afforded **272** in good yield (Scheme 2.1).



Scheme 2.1

In contrast, the applications of phototropolones (**201**, **207**, Figure 2.2) have been extensively explored by Trauner[2] and Wulff[3,4] and these molecules have proved themselves useful synthetic intermediates. However, reactions of the core BCH motif (**199**) have been underreported, most likely due to difficulties in accessing the parent compound in appreciable amounts. Thus, ready access to **199** would allow a full investigation into its synthetic potential.

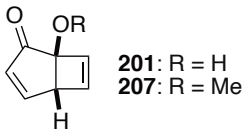
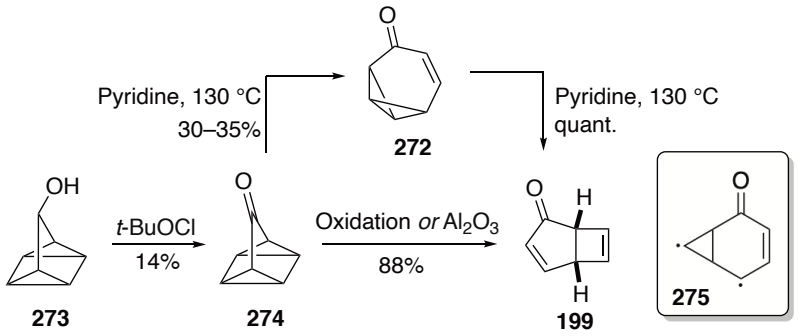


Figure 2.2

2.1 Background

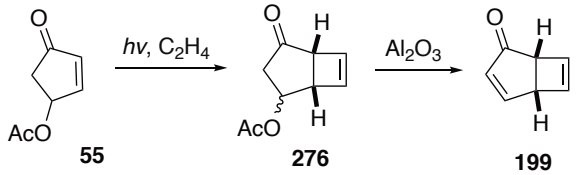
A number of synthetic approaches to phototropone **199** have been reported. Story and Farenholtz first described the rearrangement of quadricyclanone **274**, generated from quadricyclanol **273** in low yields, under oxidative conditions or upon reaction with either neutral or acidic alumina to yield the **199** (Scheme 2.2).[5] Later, Prinzbach and co-workers reported the synthesis of tropovalene (**272**) from **274**, which yielded **199** in quantitative yield after heating in pyridine at reflux for several days.[6] With

the help of several deuterium labelling studies, Murata and co-workers suggested the intermediacy of biradical intermediate **275** in the transformation of **274** to **199**.[7] Whilst these transformations provide **199** in excellent yield, the inefficient syntheses of **273** and **274** render them impractical on larger scales.



Scheme 2.2

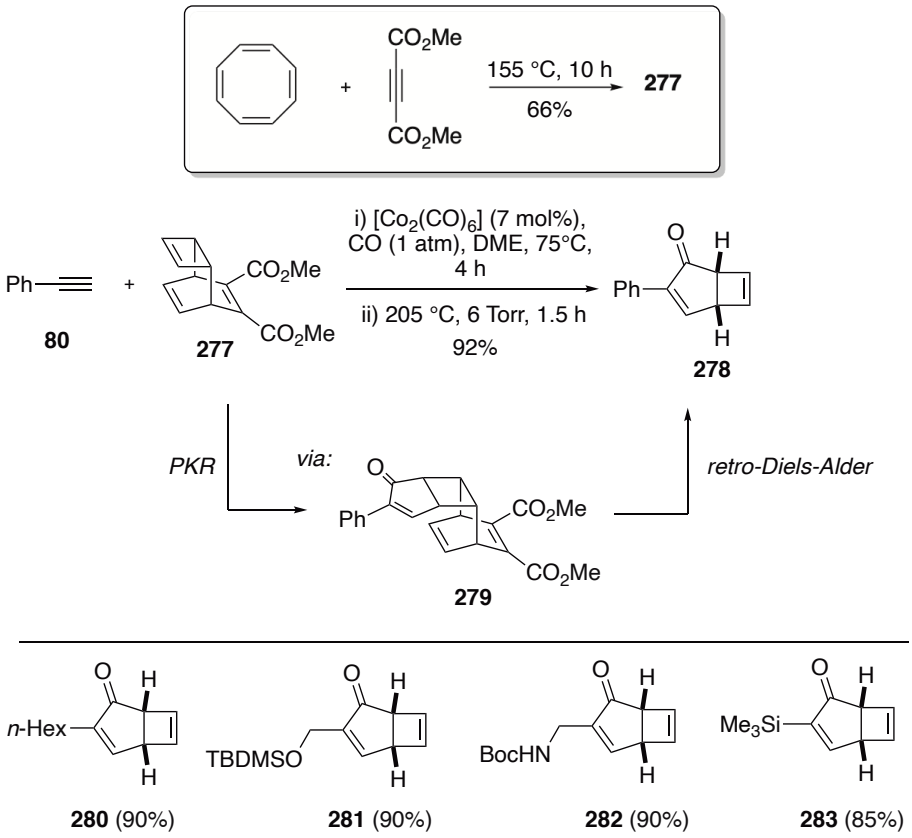
Cavazza and Zandomeneghi reported the [2+2] photocycloaddition of enone **46** with acetylene, followed by acetate elimination of adduct **255** to give **199** in moderate overall yield (Scheme 2.3).[8] Much like **261** and **263**, enone **46** is not commercially available and is only accessible via a multistep synthesis. In addition, the safety issues associated with employing large quantities of acetylene gas prohibit performing this reaction on a multi-gram scale.



Scheme 2.3

Approaches to substituted phototropones (other than naturally occuring examples) are scarce. Gibson and co-workers reported the Pauson-Khand reaction (PKR)

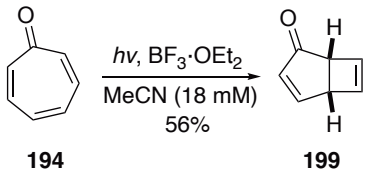
between phenylacetylene and diester **277**, which was synthesised from cyclooctatetrene and dimethyl acetylenedicarboxylate (Scheme 2.4).[9] Retro-Diels-Alder of the obtained adduct **279** gave [3.2.0]bicycle **278** in good yields, with bicycles **280**-**283** being generated under similar conditions. Whilst it presents a promising route to substituted BCH's, the number of substrates reported in the route is quite small, and the harsh conditions required render this impractical on larger scales. Additionally, the synthesis of **199** itself would require the use of acetylene gas, which in addition to the safety concerns, may not work well in this reaction.



Scheme 2.4

A particularly concise route to **199** would consist of the 4-π-photocyclisation of **194**, which is commercially available, described in Chapter 1 (Scheme 1.38).[10] It is surprising that this reaction has not been well-developed, particularly in comparison

to the corresponding reactions of tropolones and tropolone ethers, described in Chapter 1.



194 **199**

Scheme 2.5

To conclude, whilst several strategies to obtain **199** exist, many require starting materials that are not commercially available, often requiring lengthy multistep syntheses. Other synthetic approaches are limited to substituted versions of phototropone, and cannot be applied to the parent compound. Considering the commercial availability of **194**, the high atom economy of its 4-π-photocyclisation process, and the potential for facile scale-up on an industrial scale using flow photoreactors, it is surprising that the 4-π-photocyclisation of **194** has not previously been investigated in detail.

2.2 Proposed Research

The 4-π-photocyclisation of **194** will be first explored in a batch photoreactor, optimising a variety of reaction parameters including, solvent, wavelength, concentration and Lewis acid. With an optimised set of conditions in hand, attention will be turned to scale-up in a batch photoreactor, to obtain multi-gram quantities of **199**. Optimisation using a flow photoreactor will also be attempted. Next, **199** will be subjected to various reaction conditions, to access a diverse library of novel small-molecule building blocks, with a view to generate skeletal diversity (Figure 2.3). A wide variety of reactions will be tested, including chemoselective epoxidations/aziridinations, cycloadditions, regioselective additions and cross-couplings.

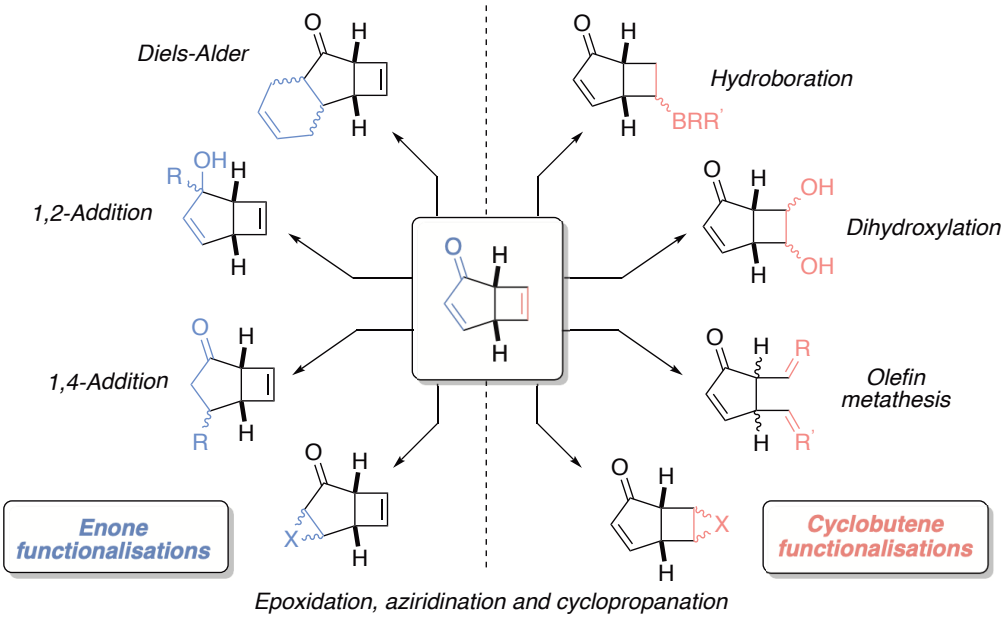


Figure 2.3

2.3 Results and Discussion

The work detailed in this section has been published in part as: Lowe, J. P.; Halcovitch N. R.; Coote S. C. *J. Org. Chem.* **2023**, *88*, 9514–9517.[11]

2.3.1 Optimisation of Tropone Photocyclisation

The transformation of **194** to **199** (Scheme 2.5) was originally performed on a small scale (<1 mmol),[10] and as large quantities of **199** were required for derivatisation studies, scale up was thus required. Optimisation of a set of conditions in batch was planned, followed by investigation of the reaction in flow. The Rayonet batch photoreactor used for this reaction has a large central space in which a carousel resides, that can hold either 18 x 20 mL or 12 x 60 mL tubes – thus, if latter is chosen, a maximum volume of reaction mixture that can be processed is 720 mL (Figure 2.4). The reactor also comes with a variety of lamps at different wavelengths (λ = 254, 300, 350, 365, 419 and 525 nm).

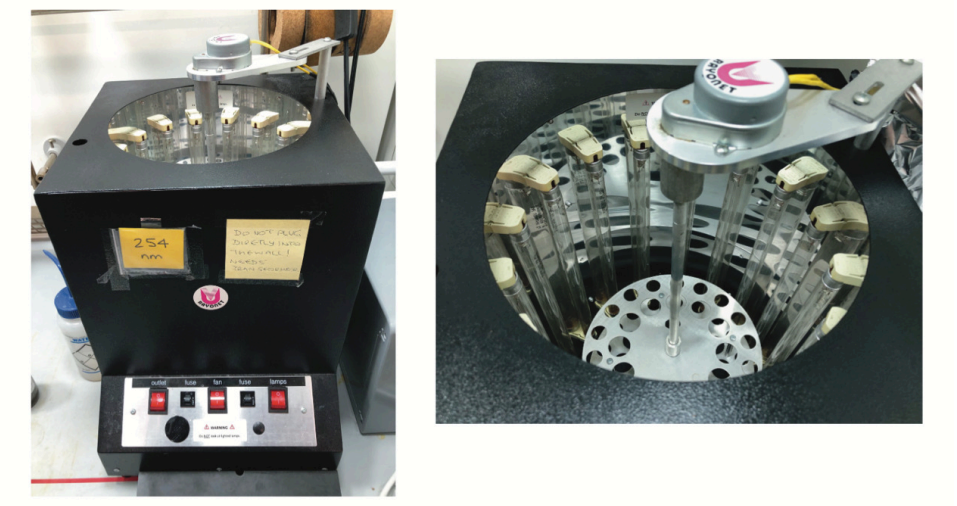


Figure 2.4

The initial conditions used were adapted from the conditions Cavazza and co-workers used for the 4-π-photocyclisation of **194**.[10] Here, the authors stated the use of a low-pressure mercury lamp, which includes all wavelengths at 254 nm and above, using acetonitrile (20 mM) as the solvent. To determine the optimal irradiation wavelength, a UV/Vis spectrum of **194**·BF_3 in acetonitrile was obtained (Figure 2.5). The UV/Vis spectrum displayed a sharp λ_{max} at 224 nm (n→π*), and smaller peaks at 316 and 274 nm, both corresponding to a π→π* transition. In view of the high energy of λ_{max}, the excited state resulting in 4-π-photocyclisation most likely corresponds to the band at 316 nm, thus 300 nm lamps were selected to begin the optimisation.

Typically, photoreactions must be performed at low concentrations (10–100 mM), in order to suppress competing photodimerisation and polymerisation, as well as to improve the overall efficiency of the reaction. Hence, under the initial conditions optimised in the batch reactor (entry 1, table 2.1), complete disappearance of **194** was noted after one and a half hours, as was appearance of a new product, which was assumed to be **199**, which was observed via ^{1}H NMR spectroscopy, using solvent suppression in undeuterated acetonitrile (Figure 2.6).

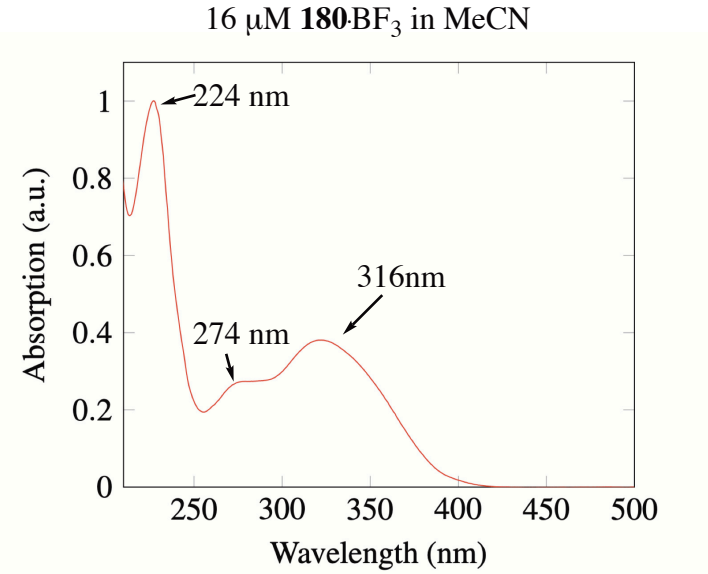


Figure 2.5

However, on removal of the reaction solvent, only trace amounts of **199** could be isolated. Surprisingly, **199** is significantly more volatile than **194** and was co-evaporating with acetonitrile solvent upon its removal from the reaction mixture. Hence, an alternative solvent with a lower boiling point that delivered the same conversion as acetonitrile was sought. Of the reaction solvents screened, most (including diethyl ether, *tert*-butyl methyl ether, methanol and pentane) were incompatible with **194**·BF_3 due to solubility issues, unless at extremely low concentrations (1-5 mM), which severely limited the amount of reaction material that could be processed. Fortunately, acetone and dichloromethane were able to solubilise **194**·BF_3 up to higher concentrations (>100 mM). However, the absorption peak at 316 nm thought to be responsible for 4-π-photocyclisation was below the cut-off wavelength of acetone (λ = 330 nm). Additionally, the use of acetone as solvent may sensitise the triplet state upon excitation, leading to undesired side reactions, and use of this solvent was hence avoided, leaving dichloromethane as the only suitable solvent available to perform the reaction. Gratifyingly, the reaction proceeded in dichloromethane, with full conversion being obtained after two hours of irradiation, and phototropone could be isolated in good yield (entry 2). However, the ^{1}H NMR

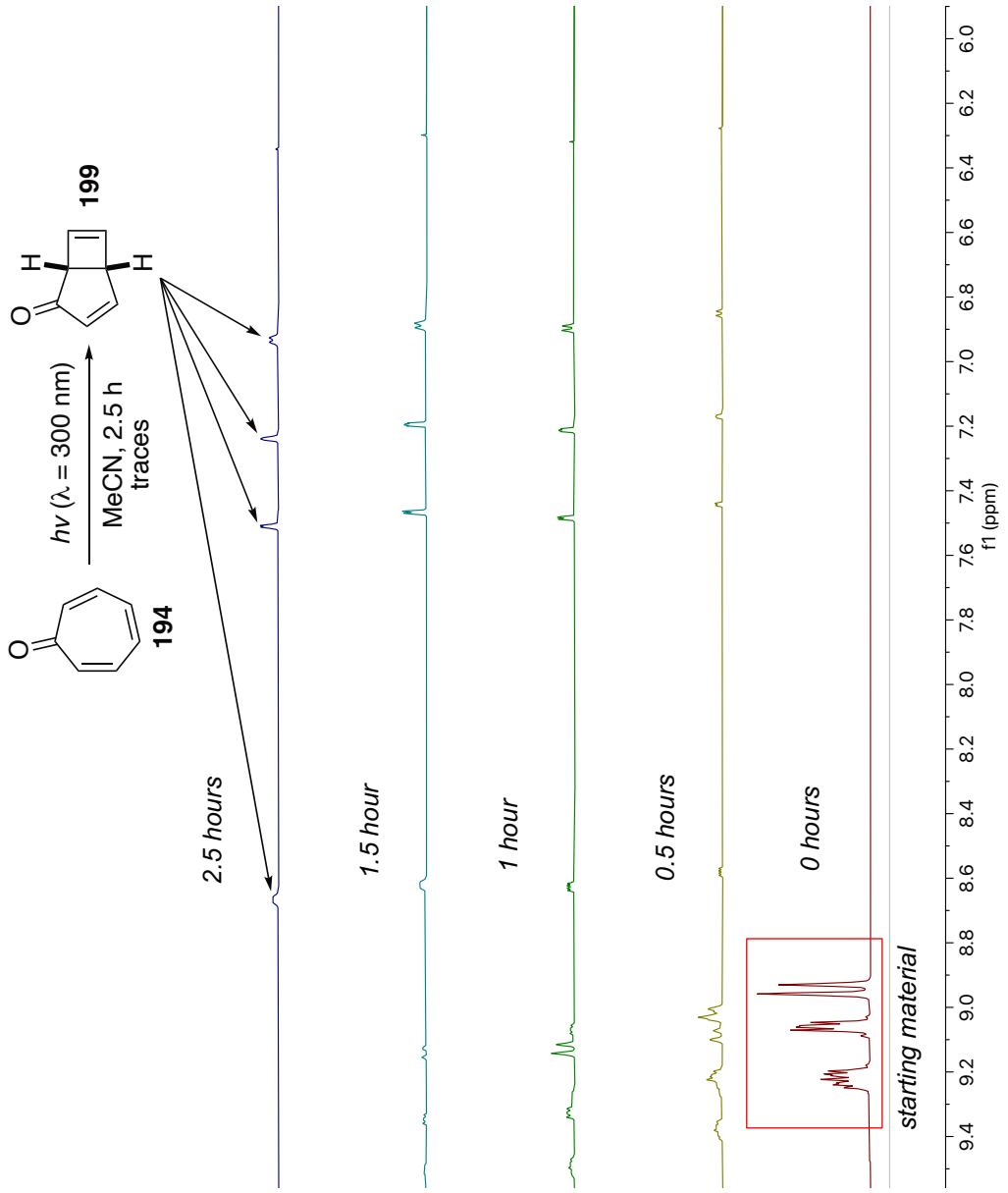

O
194
hv (λ = 300 nm)
MeCN, 2.5 h
traces
O
H
H
199
2.5 hours
1.5 hour
1 hour
0.5 hours
0 hours
starting material
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
f1 (ppm)

Figure 2.6

spectrum of the reaction mixture obtained via solvent suppression showed the presence of unspecified degradation material. As the product was volatile, the use of a high vaccuum to remove excess solvent was avoided, usually leading to trace quantities of dichloromethane being left over in the product.

Next, other parameters of the reaction were optimised before attempting scale-up. Performing the irradiation at other wavelengths gave inferior results – for example, at 254 nm, rapid consumption of starting material was observed, but alongside significant decomposition occuring (entry 4). Conversely, at 350 nm the reaction was significantly slower, generating only traces of **199** after extended irradiation, whereas no product was observed at 419 nm (entries 5 and 6). Additionally, other Lewis acids (including aluminium(III) chloride and scandium(III) triflate) gave significantly poorer results than $BF_3{\cdot}OEt_2$ (entries 7 and 8). Whilst higher concentrations were more attractive due to higher volumes of material being processed, significantly longer reaction times were required at 50 and 100 mM, and full consumption of **199** was not observed in these examples (entries 9 and 10). The complete drop off in photoreactivity observed at higher concentrations was attributed to the formation of a thin film of degradation material collecting on the inside of the reactor vessels, reflecting any incoming light. The reaction was significantly slower employing catalytic amounts of $BF_3{\cdot}OEt_2$ (20 mol %) (entry 11), and considering that this reagent is inexpensive, stoichiometric quantities were maintained.

To determine the involvement of triplet states in the acid mediated transformation of **194** to **199**, triplet quenching experiments were carried out. Thus, performing the reaction in the presence of 20 equivalents of cyclooctatetraene, or in the presence of oxygen (achieved by enriching sample with compressed air prior to reaction) led to no significant decrease in conversion when compared to a control sample, indicating that it is unlikely that this reaction takes place via a triplet state.

180 185

Entry	Solvent	λ (nm)	Lewis acid	Conc. (mM)	Time (h)[a]	Yield (%)[b]
1	MeCN	300	$BF_3{\cdot}OEt_2$	25	2	traces
2	**CH_2Cl_2**	**300**	**$BF_3{\cdot}OEt_2$**	**25**	**2.5**	**88**
3[c]	CH_2Cl_2	300	$BF_3{\cdot}OEt_2$	25	4	61
4	CH_2Cl_2	254	$BF_3{\cdot}OEt_2$	25	1	11
5	CH_2Cl_2	350	$BF_3{\cdot}OEt_2$	25	18	traces
6	CH_2Cl_2	419	$BF_3{\cdot}OEt_2$	25	24	0
7	CH_2Cl_2	300	$AlCl_3$	25	4	7
8	CH_2Cl_2	300	$ScOTf_3$	25	18	0
9	CH_2Cl_2	300	$BF_3{\cdot}OEt_2$	50	4.5	48
10	CH_2Cl_2	300	$BF_3{\cdot}OEt_2$	100	6	41
11	CH_2Cl_2	300	$BF_3{\cdot}OEt_2$[d]	25	6	41

Table 2.1: [a] Time taken for complete consumption of starting material by ^{1}H NMR spectroscopy, or if the reaction was found to not proceed any further. [b] Isolated yield after column chromatography. [c] 18 mmol scale. [d] 20 mol% $BF_3{\cdot}OEt_2$.

With an optimised set of conditions in hand, scale-up of this reaction could be performed. Thus, 0.61 g of **199** could be isolated from 1.1 g of **194** in a Rayonet batch photoreactor in just under three hours in a single run, although multiple batches could be combined for purification. This represents a 27% decrease in yield from the reaction on a 1 mmol scale, and is most likely due to the longer reaction times leading to more degradation occurring.

Next, scale up in a Vaportec E-series flow photoreactor (Figure 2.7) was attempted, in order to access larger quantities of **199**. Here, a solution of **199**·BF_3 could be pumped through the reactor and a small amount of the reaction solution (10 mL) could be exposed to the light source at a given time. The actual volume of reaction solvent exposed irradiated at a given time is much smaller than in batch reactors (10 mL, as opposed to 720 mL), which drastically reduces any fire or explosion risk. Additionally, shorter residence times would lead to less degradation occurring, and thus improved yields. The light source used in the flow reactor is a medium pressure mercury lamp, which emits all wavelengths between 220-600 nm – this may be used in conjunction with filters to give narrower wavelengths of light. For this reaction, a pyrex filter was chosen, which would block undesirable higher energy wavelengths under 280 nm[12] that would likely lead to decomposition of material. However, reaction was unsuccessful due to the rapid formation of degradation material that coated the inside of the reactor tubing, thereby blocking incoming light and causing a drastic cut off in conversion. In addition, the use of BF_3·OEt_2 in the flow reactor was a concern, due to the potential for damage to the tubing as a result of exposure to the Lewis acid, and due to cleaning of the tubing potentially being difficult to achieve. As a result, the reaction was run routinely in the batch reactor and the optimisation in flow was not pursued.

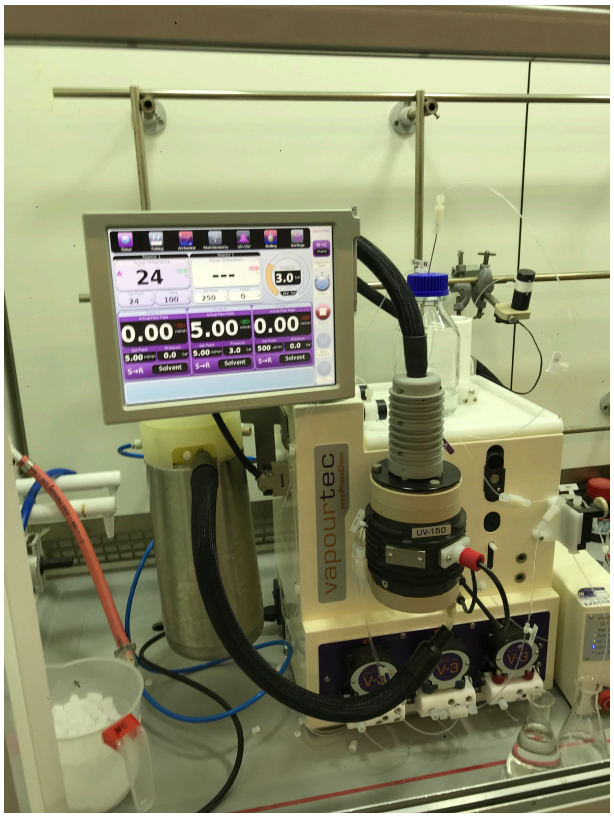


Figure 2.7: Vaportec E-series flow photoreactor.

In summary, an efficient, multigram route to **185** via 4-π-photocyclisation of **130**·BF_3 was developed. With multigram quantities of **180** available, attention was turned to its manipulations in the context of diversity oriented synthesis.

2.3.2 Derivatisations of Phototropone

2.3.2.1 Synthesis and Reactions of Tricycles

It was envisaged that epoxidation, aziridination or cyclopropanation of **199** would give rise to either the corresponding [4.2.0.$0^{2,4}$] or [3.3.0.$0^{2,4}$]tricycle depending on the reaction conditions used (Figure 2.8). The products obtained could themselves provide a useful starting point for further elaboration, including through ring opening and ring expansion.

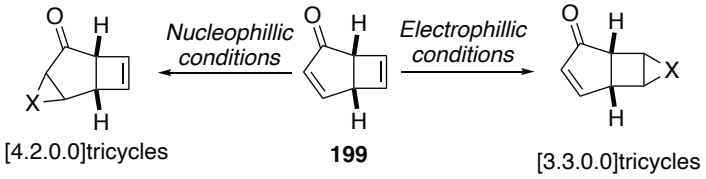
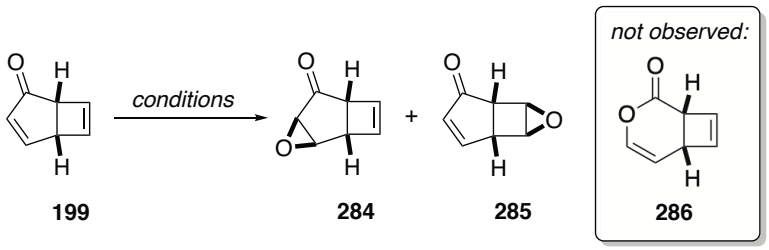


Figure 2.8

First, a variety of epoxidation conditions was investigated, in an attempt to selectively epoxidise either the cyclobutene or the enone (Table 2.2). Indeed, nucleophilic epoxidation with the hydroperoxide anion, generated in situ by treatment of hydrogen peroxide with potassium hydroxide, afforded **284** as the sole product in good yield (74%). Pleasingly, **284** was obtained as a single diastereomer, and did not require further purification after work-up. Maintaining a low reaction concentration (0.03 M) was particularly important in achieving good yields, as an increase in concentration (0.3 M) led to a marked decrease in yield of **284** (15%) and a significant increase in the amount of decomposition material.



Entry	Conditions	Time (h)	Yield 284 (%)	Yield 285 (%)
1	H_2O_2, KOH, MeOH	0.2	15	0
2	**H_2O_2, KOH, MeOH** [a]	**0.2**	**74**	**0**
3	*m*-CPBA (1 eq.), CH_2Cl_2	48	0	42
4	*m*-CPBA (2 eq.), CH_2Cl_2	48	0	58
5	*m*-CPBA (3 eq.), CH_2Cl_2	48	0	7
6	***m*-CPBA (2 eq.), $NaHCO_3$ (1 eq.) CH_2Cl_2**	**48**	0	**66**
7	Oxone (2 eq.), $NaHCO_3$ (2 eq.), MeCN	24	0	0

Table 2.2: [a] Performed at 0.03 M.

The excellent diastereoselectivity obtained is best illustrated in Figure 2.9. Steric hindrance by the cyclobutene motif blocks attack of the hydroperoxide nucleophile on the bottom face of the enone, compared to the less bulky hydrogen substituents.

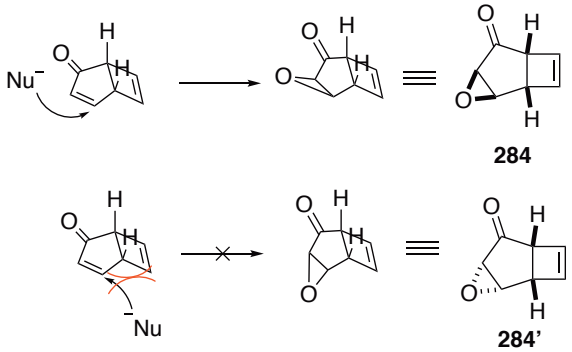
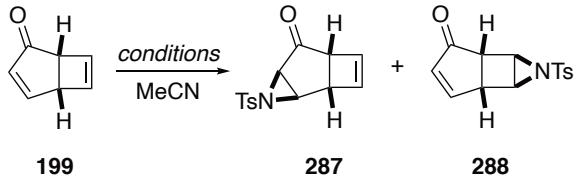


Figure 2.9

Electrophilic epoxidation on the cyclobutene moiety was next targeted, and initial attempts employing one equivalent of *m*-CPBA gave a complex mixture of products, with epoxide **285** being obtained in moderate yields (42%). Using two equivalents of *m*-CPBA followed by addition of $NaHCO_3$ to neutralise the benzoic acid by-product gave **285** exclusively after 48 hours of stirring at room temperature in good yield (66%). Purification on deactivated silica (1% NEt_3) was essential to avoid loss of product material. Whilst lactone **286** was a possible side product arising from a competing Baeyer-Villiger reaction, its formation was not observed, likely due to the cyclobutene double bond being significantly more reactive. Other epoxidising agents, including $NaHCO_3$/Oxone^{TM} did not furnish **286**.

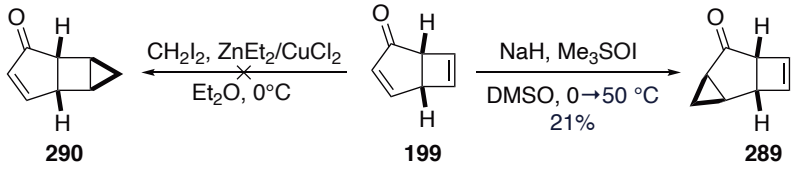
Encouraged by the excellent chemoselectivity obtained in the epoxidation reactions, attention was turned to similar chemoselective syntheses of aziridines **287** and **288** (Table 2.3). Application of the copper-catalysed electrophilic aziridination conditions using Chloramine T trihydrate and phenyltrimethylammonium tribromide, developed by Sharpless and co-workers,[13] yielded none of the expected aziridine (**288**) after 48 hours. Instead, slow reaction on the enone moiety took place, yielding **287** in trace quantities. Attempts to drive the reaction towards **288** by heating the reaction mixture (80 °C) instead led to decomposition and neither isomer was observed. Interestingly, copper(II)–catalysed reaction of N-tosyliminobenzyliodinane ,[14] conditions typically employed in electrophilic aziridination reactions, instead reacted preferentially on the enone double bond, giving aziridine **287** as a single diastereomer in moderate yields. Next, metal–free aziridination using N-tosyliminobenzyliodinane, catalysed by a I_2/KI system to generate *N*,*N*-diiodotosylamide as the active reagent *in situ* was attempted, but led to no addition on either of the double bonds.[15]



Entry	Conditions	Yield 287 (%)	Yield 288 (%)
1	CAT·3H_2O, PTAB, r.t., 24	traces	0
2	CAT·3H_2O, PTAB, 80 °C, 24	0	0
3	PhI=NTs (2 eq.) $Cu(OTf)_2$ (10 mol%), r.t., 48	44	0
4	PhI=NTs (2 eq.), I_2, KI, r.t., 24	0	0

Table 2.3: CAT = Chloramine T., PhI=NTs = N-tosyliminobenzyliodinane.

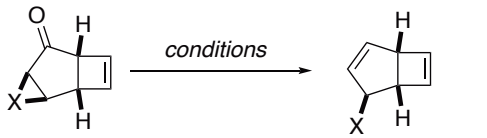
Corey-Chaykovsky cyclopropanation[16] afforded cyclopropane **289** in excellent diastereoselectivity, albeit it poor yields (21%) (Scheme 2.6), which may be attributed to loss of product material upon removal of the reaction solvent, as **289** is expected to have similar volatility to **299** Simmons-Smith cyclopropanation[17] was attempted, but failed to give any of the corresponding cyclopropane **290** upon reaction – this is surprising, considering the electron rich nature of the cyclobutene double bond.



Scheme 2.6

With several tricycles in hand, their derivatisations were also explored. The Wharton reaction is a reduction of an α,β-epoxy ketone to yield allylic alcohols, with stereochemical retention with respect to the epoxide.[18] Subjecting epoxide **284** to the initial Wharton conditions gave alcohol **291** in excellent diastereoselectivity, although in low yields (Table 2.4, entry 1). **291** is expected to have similar volatility to **199**, although performing the work-up with low boiling point solvents (CH_2Cl_2

and Et_2O) did not improve the yield. Next, the instability of **291** towards acid was considered. Using sub-stoichiometric quantities of acetic acid did little to improve the yield (entry 3) and using Amberlite™ IRC-120(H) resin as the acid source led to only trace quantities of product after extended reaction times (entry 4). A variant of the Wharton reaction employing basic conditions was next attempted, using hydrazine sulfate and triethylamine (entry 5), which failed to furnish **291**. Finally, the method of Masaji and co-workers[19] was attempted and gave significantly better results than the previous entries (entry 6). Aziridine **287** was also subjected to the above conditions, but only reacted under the initial conditions to give allylic sulfonamide **292** in low yields.



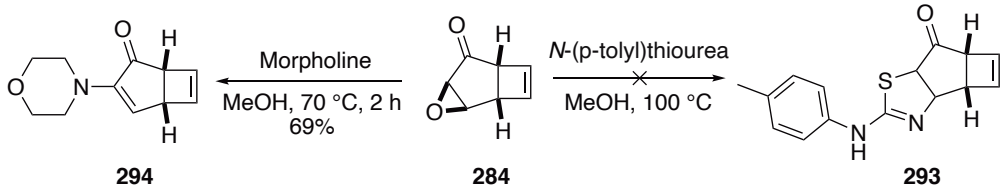
284/287

291: X = O
292: X = NTs

Entry	X	Conditions	Solvent	Time (h)	Yield (%)
1	O	H_2NNH_2 (1 eq.), AcOH (1 eq.)	EtOH	0.25	17
2	O	H_2NNH_2 (1 eq.), AcOH (1 eq.)	MeOH	0.25	15
3	O	H_2NNH_2 (1 eq.), AcOH (0.1 eq.)	MeOH	0.25	15
4	O	H_2NNH_2 (1 eq.), Amberlite	MeOH	24	traces
5	O	Hydrazine sulfate, NEt_3	CH_2Cl_2	48	0
6	O	H_2NNH_2 (1.5 eq.), AcOH (1.5 eq.), NEt_3 (1.25 eq.)	MeCN	0.25	57
7	NTs	H_2NNH_2 (1 eq.) /AcOH (0.1 eq.)	MeOH	0.25	19

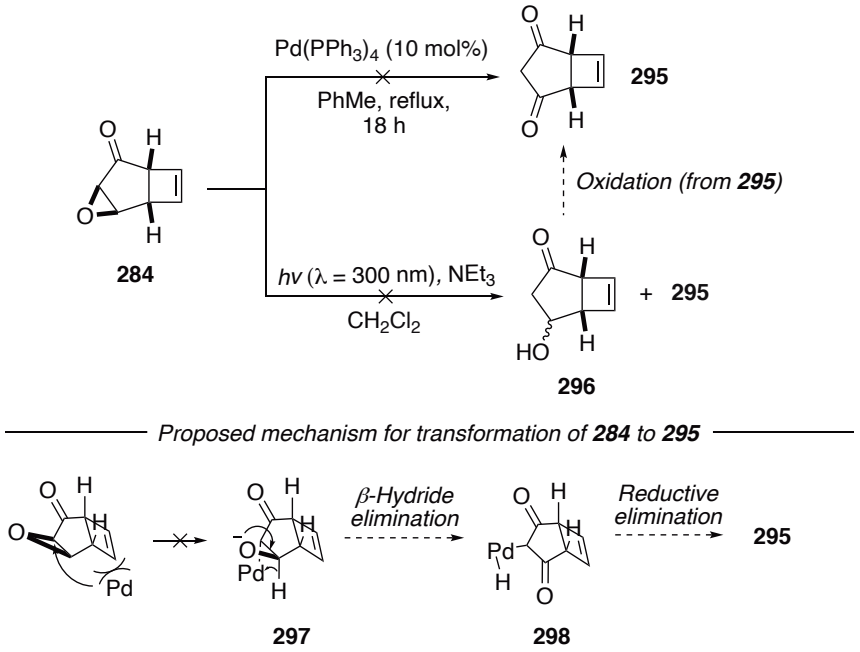
Table 2.4

Other reactions of epoxide **284** were next targeted (Scheme 2.7). Reaction of **264** with *N*-(*p*-tolyl)thiourea at elevated temperatures (100 °C) to yield thiazole **293** gave a complex mixture of products. Similar reaction at lower temperatures (r.t., 60 °C) returned only starting material. Morpholine derivative **294** could be isolated from reaction of **284** and morpholine in good yield (69%).



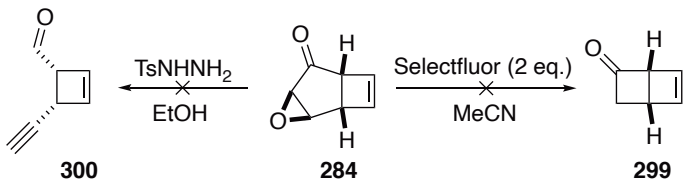
Scheme 2.7

Symmetrical diketone **295** was initially identified as an interesting target in this study, with potential for further derivatisation. Palladium-catalysed isomerisation of **284** to yield **295** was attempted, but failed to react under the conditions applied (Scheme 2.8). In the original publication,[20] a mechanism involving a back-side displacement of the Pd(0) catalyst, followed by hydride shift and reductive elimination to yield the diketone product was put forward, although in this case, such a mechanism is hindered by the cyclobutene group. The 1,3-hydroxyketone **296** was identified as a potential precursor to **295**, which might be accessed via a photoinduced single electron transfer mechanism, by irradiating **284** at 254 nm in the presence of triethylamine. Unfortunately, significant degradation occurred, and at longer wavelengths (300 nm), **284** was recovered unchanged.



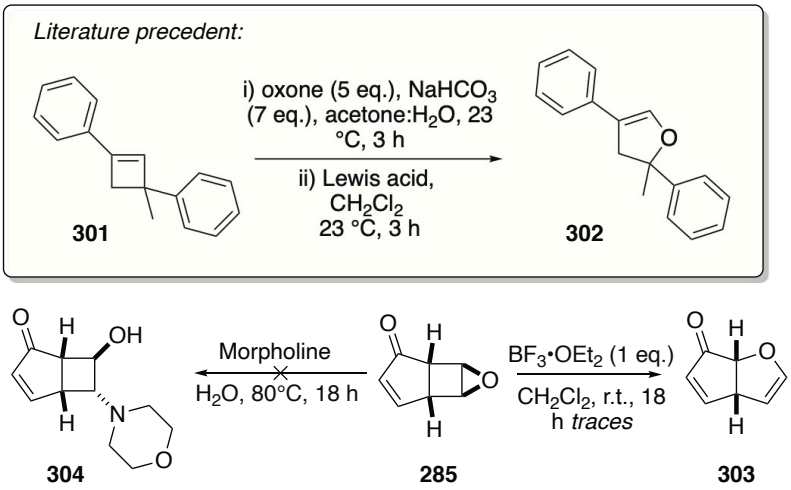
Scheme 2.8

Products with diverse structures from **199** were attractive, as product libraries with higher degrees of skeletal diversity generally have an increased number of potential biological binding targets. To that end, Selectfluor™ mediated cleavage, as reported by Liu and co-workers[21] to give the [2.2.0]bicycle **299** was attempted, but yielded none of the desired product (Scheme 2.9). This reaction is most likely unfavourable, as **299** possesses significantly high ring strain. Next, Eschenmoser fragmentation[22,23] of **284** to give enynal **300** only yielded complex mixtures of products upon reaction, with no peaks indicating the presence of an aldehyde or terminal alkyne group in the ^{1}H NMR spectrum of the crude material.



Scheme 2.9

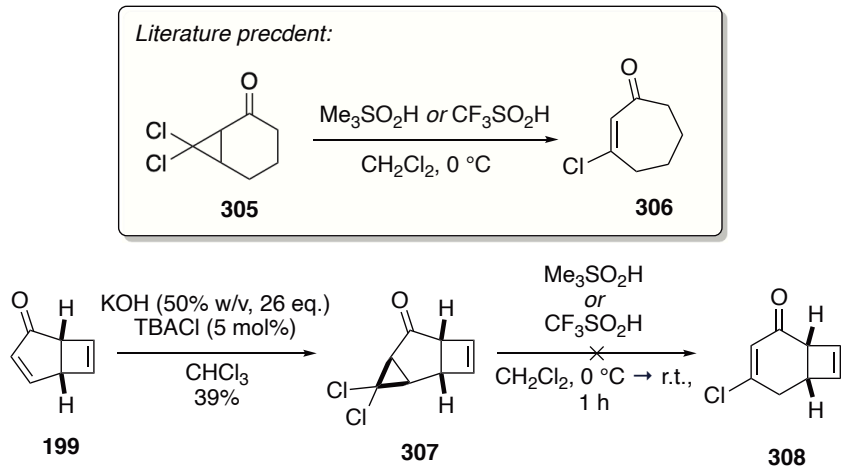
Epoxide **285** was itself subjected to several other sets of conditions. Taking inspiration by work by Echavarren and co-workers, whereby cyclobutenes (**301**) could be converted to furan derivatives (**302**) (Scheme 2.10, boxed),[24] it was envisaged that **285** could undergo a similar rearrangement to yield dihydrofuran **303** – this transformation is particularly attractive, as it involves rearrangement to generate a distinctly new scaffold. Indeed, traces of a rearrangement product were observed on treatment of **285** with one equivalent of $BF_3{\cdot}OEt_2$ although poor conversions (<10%) were observed. Leaving the reaction to stir at room temperature overnight, as well as heating of this mixture, led to large amounts of degradation occuring and no **303** could be isolated. Treatment of **285** with substoichiometric amounts of $BF_3{\cdot}OEt_2$ (10-50 mol%) as well as other Lewis acids ($Cu(OTf)_2$, ZnI_2) gave similarly poor conversions. Next, attempts at ring opening with morpholine to give **304** were unsuccessful, furnishing a complex mixture of products.



Scheme 2.10

Inspired by Banwell's synthesis of 3-substituted tropones, in which dichlorocyclopropane **305** could undergo acid-catalysed ring expansion to tetrahydrotropone derivative **306**,[25] a similar rearrangement was sought for **307**. Thus, conversion of **199** to chlorocyclopropane **307** was achieved in moderate yields (39%) via reac-

tion with dichlorocarbene, generated from chloroform in strongly basic conditions (Scheme 2.11). Next, **307** was treated with with either methanesulfonic acid or trifluoromethanesulfonic acid, although did not furnish **308** after 24 hours of stirring at room temperature.

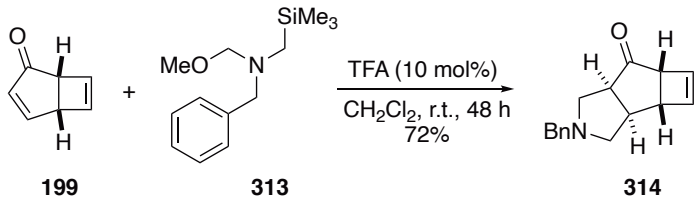


Scheme 2.11

It was envisaged that tricyclic ketone **310** could be formed by Diels-Alder reaction of **199** with Danishefsky's diene **309**, followed by treatment of the intermediate product **311** with dilute aqueous acid. However, reaction of **199** with three equivalents of **309** gave none of the desired product (Table 2.5, entry 1). Attempting forcing conditions at elevated temperatures and extended reaction times also led to none of the desired product (entry 1). Concerned that the immiscibility of dichloromethane and aqueous acid were leading to the lack of reactivity in the second step, the reaction was instead performed in ethanol, which was chosen over methanol to aid work-up. However, the reaction was entirely suppressed (entry 3). Attempts at performing the reaction in water or in the absence of solvent were similarly unsuccessful. Next, a one-step procedure to **310** was investigated, using a large excess of **309** and stoichiometric quantities of $BF_3{\cdot}OEt_2$. Gratifyingly, tricycle **310** was obtained, albeit in poor yields (entry 5) and alongside an inseparable impurity identified as isomer **312**. As this impurity was not present in the crude material and only appeared after purification

by flash column chromatography on silica gel, other stationary phases were explored. Pleasingly, performing the purification on neutral alumina entirely suppressed formation of this impurity and homogenous samples of **310** could be obtained in low yield (32%), although the reaction did not go to completion. Concerned with the instability of product **310** towards $BF_3{\cdot}OEt_2$, substoichiometric amounts of the Lewis acid were investigated, but gave poor conversion and yield (entry 7). A high boiling point solvent (toluene) was used in an attempt to force the reaction, but led mainly to degradation (entry 5). Finally, a large excess of **309** (5 eq.) was used, giving **310** in a moderate yield of 42%, although alongside significant starting material.

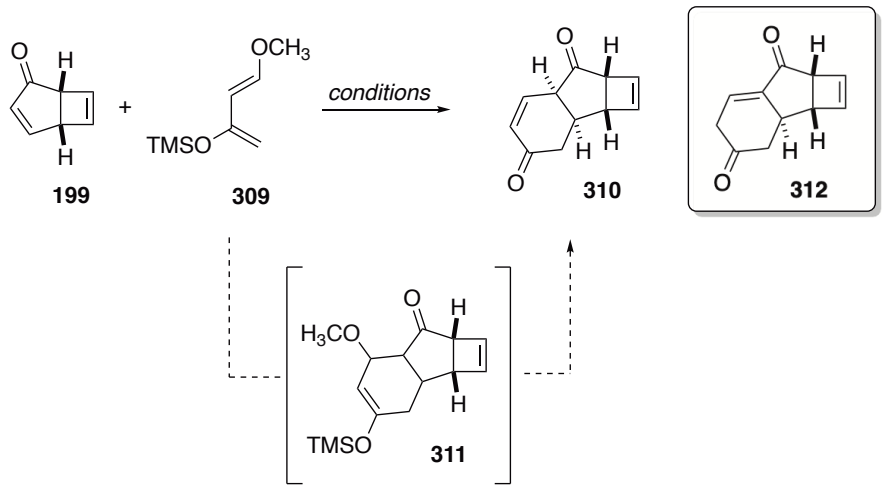
Attention was next turned to other cycloadditions. Thus, tricyclic amine **314** could be synthesised by [3+2] cycloaddition between *N*-benzylamine ylide generated *in situ* by treatment of *N*-benzyl-*N*-(methoxymethyl)- *N*-trimethylsilylmethylamine (**313**) with TFA, as a single diastereomer in good yield (72%) (Scheme 2.12). Several equivalents of **313** (5) were necessary for even modest conversions. Heating of the reaction mixture (40 °C) led to poor conversions and decomposition, with **292** obtained in poor yields alongside significant degradation material, presumably due to thermal decomposition of **313**.



199 **313** **314**

Scheme 2.12

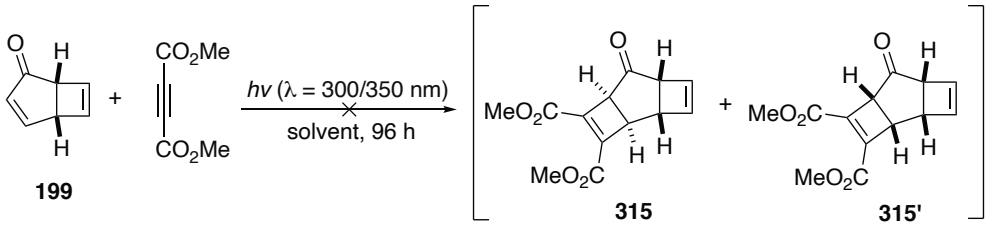
Photochemical cycloadditions were also investigated. Firstly, a [2+2] photocycloaddition between DMAD and **199** was attempted to yield either **315** or **315'** (Scheme 2.13). Unfortunately, no reaction took place in acetonitrile at either 300 or 350 nm after using 20 equivalents of DMAD and extended reaction times. Performing the re-



Entry	Conditions	Solvent	Temp (°C)	Time (h)	Yield (%)
1	i) **287** (3 eq.) ii) HCl[a]	CH_2Cl_2	r.t.	1	-
2	i) **287** (3 eq.) ii) HCl[a]	CH_2Cl_2	40	18	-
3	i) **287** (3 eq.) ii) HCl[a]	EtOH	r.t.	18	-
4	i) **287** (3 eq.) ii) HCl[a]	-	r.t.	18	-
5	**287** (2 eq.), $BF_3{\cdot}OEt_2$ (1.1 eq.)	PhMe	110	3	10
6	**287** (2 eq.), $BF_3{\cdot}OEt_2$ (1.1 eq.)	CH_2Cl_2	r.t.	18	32
7	**287** (2 eq.), $BF_3{\cdot}OEt_2$ (0.5 eq.)	CH_2Cl_2	r.t.	18	18
8	**287** (5 eq.), $BF_3{\cdot}OEt_2$ (1.1 eq.)	CH_2Cl_2	r.t.	18	42

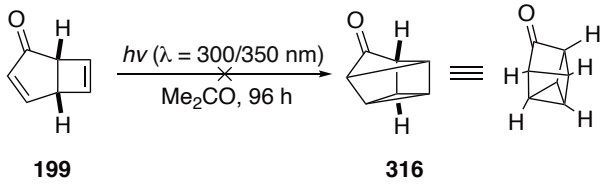
Table 2.5: [a]1M aqueous.

action in acetone, in the hopes of sensitising the reaction, was similarly unsuccessful. Unfortunately, time constraints limited the exploration of other triplet sensitisers.



Scheme 2.13

Finally, in a similar vein, an intramolecular [2+2] PCA between the enone and cyclobutene double bond of **185** to yield **295** was attempted, but only starting material could be recovered unchanged (Scheme 2.14).

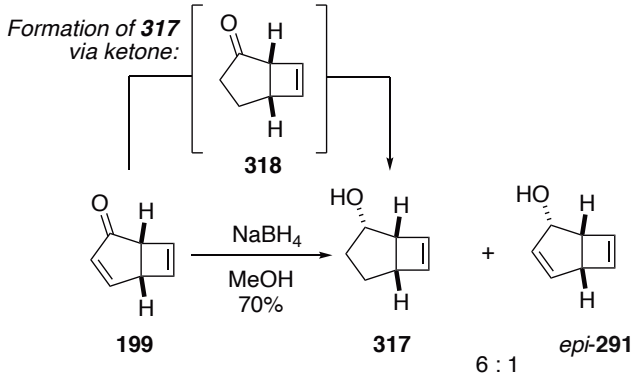


Scheme 2.14

2.3.2.2 Regioselective Additions

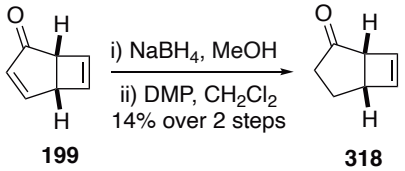
Initial attempts at reduction of **199** with sodium borohydride gave the globally reduced alcohol **317** as the major product, alongside small quantities of allyl alcohol *epi*-**291**, the epimer of the **291** (Scheme 2.15). Evidently, 1,4-addition to yield ketone **318** is the favoured pathway, which further reacts with another hydride equivalent to furnish **317**. The use of substoichiometric quantities of sodium borohydride (0.5 eq.) led to poor conversion, and in any case, suppression of the formation of **317** was not observed. Lowering of the reaction temperature (–20 °C) did not alter the ratio

of **317**:*epi*-**291**. The use of L-Selectride, a soft reducing agent that should attack in a 1,4-fashion, furnished a complex mixture of products upon reaction at room temperature and at –78 °C, and starting material was recovered unchanged.



Scheme 2.15

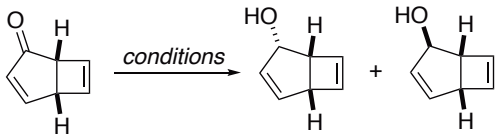
Regioselective reduction of the enone double bond was abandoned, and an alternative strategy to **199** via oxidation of **317** was pursued instead. Indeed, global reduction of **199** and treatment of the crude mixture with Dess-Martin periodinane furnished **318** (Scheme 2.16), although in poor overall yields (14% over two steps). Furthermore, **318** turned out to be quite unstable and decomposed to non-specific degradation material even when stored at –20 °C.



Scheme 2.16

Luche reduction of **199** gave a 7:5 mixture of *epi*-**291** and **291** in good yield (Table 2.6, entry 1). Separation of the diastereomers was difficult due to them having near-identical R_f values, although homogenous samples of *epi*-**291** could be obtained

by repeated flash column chromatography for characterisation. Reaction at –20 °C led to a slight increase in diastereoselectivity (entry 2), but lower temperatures (–40 and –78 °C) led to prohibitively slow reaction times (entries 3 and 4). Finally, DIBAL-H was employed, and a drastically improved diastereoselectivity of 3:1 was obtained, in 62% yield.

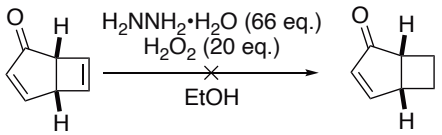


199 *epi*-**291** **291**

Entry	Conditions	Solvent	Yield (%)	d.r. (*epi*-291:291)[a]
1	$CeCl_3 \cdot H_2O$, $NaBH_4$, 0 °C	MeOH	60	1:1.4
2	$CeCl_3 \cdot H_2O$, $NaBH_4$, –20 °C	MeOH	62	1:1.8
3	$CeCl_3 \cdot H_2O$, $NaBH_4$, –78 °C	MeOH	traces	-
4	DIBAL-H	THF	62	1:3

Table 2.6: [a] Determined from comparison of product peaks in crude ^{1}H NMR spectrum.

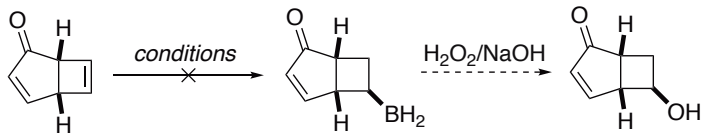
Selective reduction of the cyclobutene double bond was also desirable, as cyclobutanes are ubiquitous in pharmaceutically active compounds.[26] However, reduction of **199** with diimide (generated from oxidation of hydrazine with peroxide) gave a complex mixture of products and cyclobutane **319** was not isolated (Scheme 2.17). The exploration of other chemoselective hydrogenation protocols, including the use a H-Cube flow reactor, was not possible due to time constraints.



199 **319**

Scheme 2.17

A hydroboration/oxidation sequence to alcohol **321** was expected to be facile due to the electron rich nature of the cyclobutene double bond. Reaction of **130** with two equivalents of BH_3·THF at room temperature led to none of the desired product(s) (one regioisomer shown for clarity), and starting material was recovered unchanged (Table 2.7, entry 1). Thus, the reaction was repeated under increasingly forcing conditions, including heating at 75 and 100 °C (performed in a sealed microwave vessel) for extended periods of time (entries 2 and 3). Unfortunately, even under these forcing conditions, hydroboration to yield **320** did not take place, and starting material was recovered unchanged.

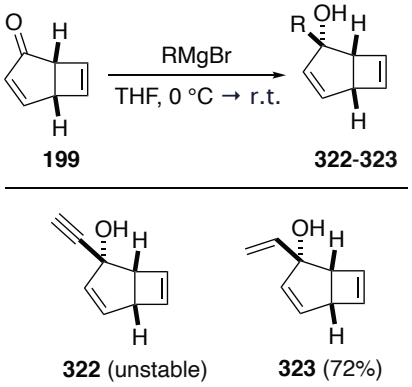


199 **320** **321**

Entry	Conditions	Yield 320 (%)
1	BH_3·THF (2 eq.), THF, r.t., 48 h	0
2	BH_3·THF (2 eq.), THF, 75 °C, 48 h	0
3	BH_3·THF (2 eq.), THF, 100 °C, 48 h	0

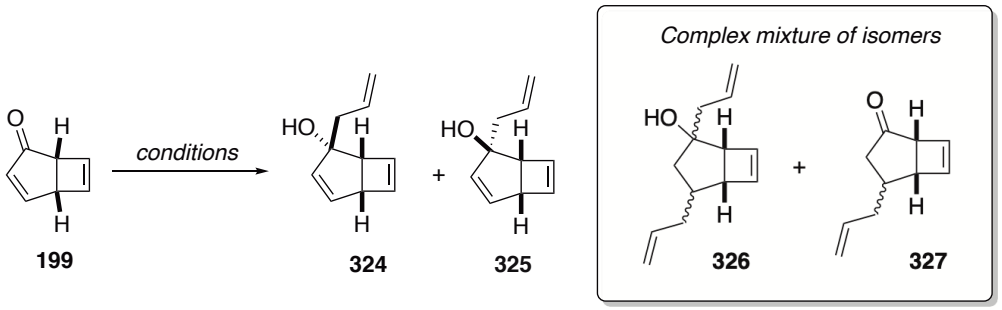
Table 2.7

Nucleophilic addition of Grignard reagents were next examined. Addition of ethynylmagnesium bromide afforded the propargylic alcohol **322** in moderate yield and excellent diastereoselectivity (Scheme 2.18). However, this product decomposed rapidly even when stored under argon at 0 °C, and thus ^{13}C NMR and HRMS data could not be collected. In a similar fashion, alcohol **323** was obtained in good yield (72%) and excellent diastereoselectivity (dr 20:1) from vinylmagnesium bromide. These products obtained contain useful functional handles for further derivitisation, but unfortunately, the instability of **322** precludes its storage.



Scheme 2.18

The reaction of **199** with allylmagnesium bromide gave a complex mixture of products (Table 2.8). In this case, alcohol **324** was obtained in low yield alongside traces of **325**) with the conjugate addition products **326** and **327** being identified as side products. This is hardly surprising, considering the high reactivity of allylmagnesium bromide.[27] The addition of cerium(III) chloride drastically did not alter this selectivity, although this strategy is often used to promote 1,2-addition over 1,4-addition.

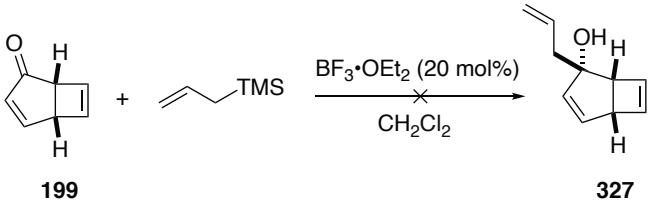


Entry	Conditions	Yield 324(%)	Yield 325(%)
1	AllylMgBr (2 eq.), THF, 0 °C	10	traces
2	AllylMgBr (2 eq.), –78 C, $CeCl_3$ (2 eq.)	9	traces

Table 2.8

Hosomi-Sakurai reaction of **199** and allyltrimethylsilane to yield **327** was identified as an alternative strategy, although only starting material could be recovered upon

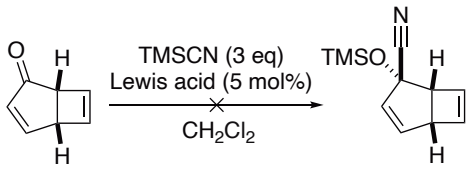
reaction of **199** allyl trimethylsilane and equimolar $BF_3 \cdot OEt_2$ (Scheme 2.19).



199 **327**

Scheme 2.19

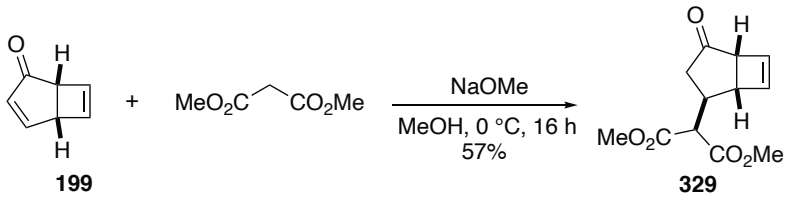
The addition of trimethylsilylcyanide both in the presence and absence of catalytic Lewis acids (ZnI_2, $BF_3 \cdot OEt_2$) led to complex mixtures of products, and it was assumed that the cyanohydrin **328** is unstable (Scheme 2.20).



199 **328**

Scheme 2.20

Finally, **199** was amenable to Michael addition of the carbanion generated from dimethyl malonate to give **329** as a single diastereomer in good yield (Scheme 2.21).

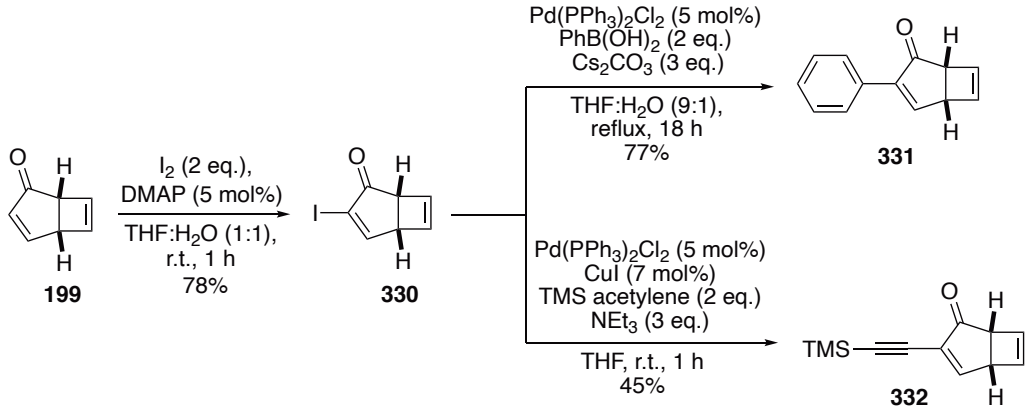


199 **329**

Scheme 2.21

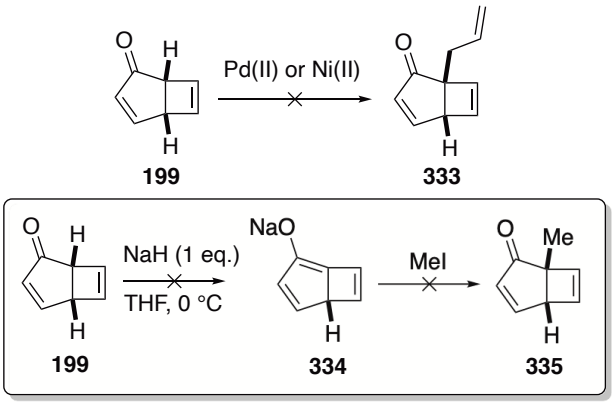
2.3.2.3 Coupling Reactions

Installation of a halogen in the α-position of the enone would potentially allow cross-coupling at this position to access substituted phototropones. Thus, addition of I_2 in the presence of catalytic DMAP gave α-iodo derivative **330** in good yield (78%) (Scheme 2.22). **330** was amenable to palladium cross-couplings, including Suzuki and Sonagashira variants to yield **331** and **332** in good yields (77 and 45%, respectively).



Scheme 2.22

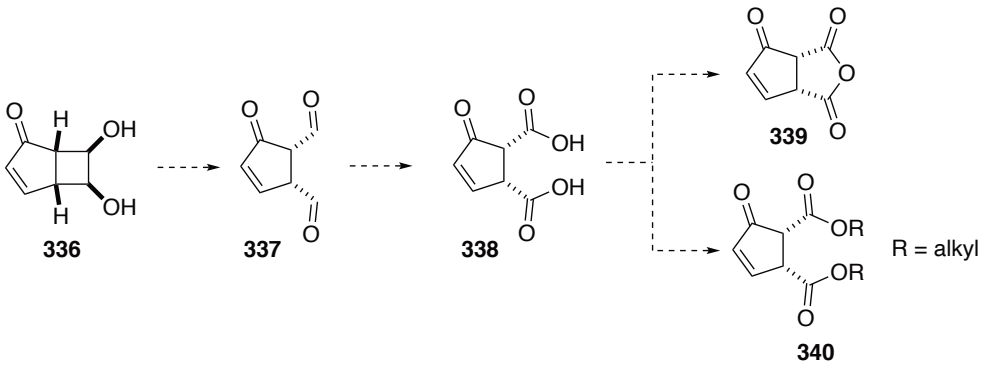
Other substitution reactions were also explored. Palladium-catalysed Tsuji-Trost allylation to **333** was unsuccessful, as well as the nickel(II)-catalysed alternative (Scheme 2.23). This may be attributed to enolate anion **312** being highly unfavoured due to ring strain. Attempts at generating this enolate by reaction with sodium hydride and trapping it with methyl iodide were also unsuccessful (Scheme 2.23, boxed).



Scheme 2.23

2.3.2.4 Cyclobutene Cleavage

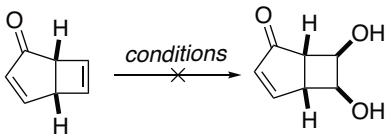
syn-Diol **336** would be a particularly useful intermediate en route to highly oxygenated, structurally diverse compounds (**337**–**340**, Scheme 2.24). For example, sodium periodate cleavage and further oxidation would yield dialdehyde **337** and diacid **338**. Diacid **338** could be cyclised to give anhydride **339** or coupled with various alcohols to give esters **340**. Thus, reaction with various MO_4 species (M = Os, Ru, KMn) was attempted.



Scheme 2.24

To that end, **199** was reacted with 5 mol% OsO_4, with NMO as a co-oxidant, resulting in a complex mixture of products, with none of the desired dihydroxylated product

336 observed in the crude material (Table 2.9, entry 1). Attempting to reduce the amount of decomposition occurring, the reaction was repeated at a series of lower catalyst loadings (2.5 and 1 mol%) (entries 2 and 3). Complex mixtures of products were still observed at lower catalyst loadings, alongside recovered starting material, and at extremely low catalyst loadings (0.5 and 0.1 mol%), starting material was recovered unchanged after extended reaction times (24-48 h) (entries 5–7). Cold basic $KMnO_4$ was next employed, but much like the previous attempts, a complex mixture of products was obtained upon reaction (entry 8). As a stoichiometric amount of $KMnO_4$ is required for this reaction, investigating substoichiometric quantities was not possible. From these results, it was apparent that the reaction of **199** with OsO_4 or $KMnO_4$ failed to deliver the desired outcomes.



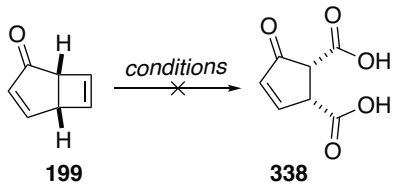
199 **336**

Entry	Conditions	Solvent	Yield 314 (%)
1	OsO_4 (5 mol%), NMO, r.t.	TBME:H_2O (1:1)	0
2	OsO_4 (2.5 mol%), NMO, r.t.	TBME:H_2O (1:1)	0
3	OsO_4 (1 mol%), NMO, r.t.	TBME:H_2O (1:1)	0
4	OsO_4 (0.5 mol%), NMO, r.t.	TBME:H_2O (1:1)	0
5	OsO_4 (0.1 mol%), NMO, r.t.	TBME	0
6	OsO_4 (0.1 mol%), NMO, r.t.	Acetone (0.7 M)	0
7	OsO_4 (0.1 mol%), NMO, r.t.	Acetone (0.02 M)	0
8	$KMnO_4$ (1.1 eq), KOH (aq.), 0 °C	CH_2Cl_2:H_2O (1:1)	0

Table 2.9

Thus, attention was turned to dihydroxylation and subsequent cleavage using RuO_4. In this reaction, the reactive RuO_4 reagent is generated as a transient species from a Ru(II) or Ru(III) source, such as RuO_2 or $RuCl_3$. Sodium periodate is used as the re-oxidant in this reaction, which would cause concomitant cleavage of the obtained

syn-diol to yield dialdehyde **337**, which would undergo further oxidation to yield dicarboxylic acid **338**. Several parameters had to be investigated, including solvent choice, ruthenium source, number of equivalents of $NaIO_4$, temperature and reaction times. The initial conditions employed 10 mol% of RuO_2 and four equivalents of sodium periodate in ethyl acetate (Table 2.10, entry 1). Thus, after stirring for 24 hours, starting material was recovered in 26% yield alongside some decomposition material. However, it is uncertain whether the low mass recovery of **199** can be attributed to its co-evaporation upon removal of the reaction solvent, or from conversion under the reaction conditions. Possessing both a relatively low molecular weight (MW = 170.12 g/mol) and two carboxylic acid groups, it was hypothesised that **338** was remaining in the aqueous layer after work-up, although solvent suppression ^{1}H NMR spectroscopy of the aqueous layer indicated no presence of **338**. The number of equivalents of re-oxidant used can have a profound impact on the reaction outcome[28] and was hence increased to six and eight equivalents (entries 2 and 3), which again led to none of the observed product after 24 hours of stirring at room temperature. Concerned with the formation of Ru·x**338** complexes leading to a loss of catalytic activity, the Sharpless modification[29] was considered, employing an equivalent amount of acetonitrile, but again gave none of the desired products (entries 4 and 5). Changing the ruthenium source to $RuCl_3$ led to no change in reactivity, yet its use was maintained in subsequent attempts as it was available in greater quantities in the laboratory. The classic examples of ruthenium oxidative cleavage employ carbon tetrachloride in the reaction mix ture – considering its use paramount to the success of the reaction, a final attempt using this solvent was performed, although this also failed, as well as other chlorinated solvents (entries 8-10).

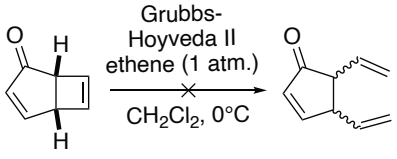


199 338

Entry	Conditions	Solvent	Yield (%)
1	RuO_2 (10%), $NaIO_4$ (4 eq.), r.t., 24 h	EtOAc	0
2	RuO_2 (10%), $NaIO_4$ (6 eq.), r.t., 24 h	EtOAc	0
3	RuO_2 (10%), $NaIO_4$ (8 eq.), r.t., 24 h	EtOAc	0
4	RuO_2, $NaIO_4$ (8 eq.), r.t., 24 h	EtOAc/MeCN/H_2O	0
5	$RuCl_3$, $NaIO_4$ (8 eq.), r.t., 24 h	EtOAc/MeCN/H_2O	0
6	$RuCl_3$, $NaIO_4$ (8 eq.), r.t., 24 h	TCE/MeCN/H_2O	0
7	$RuCl_3$, $NaIO_4$ (8 eq.), r.t., 24 h	DCE/MeCN/H_2O	0
8	$RuCl_3$, $NaIO_4$ (8 eq.), r.t., 24 h	DCE	0
9	$RuCl_3$, $NaIO_4$ (8 eq.), r.t., 24 h	EtOAc/MeCN/H_2O	0
10	$RuCl_3$ (10%), $NaIO_4$ (8 eq.), r.t.	CCl_4/MeCN/H_2O	0

Table 2.10

Finally, Grubbs metathesis with ethene gas was attempted. Indeed, full consumption of starting material was observed after 15 minutes of reaction but gave a highly complex mixture of products, and **341** was not generated (Scheme 2.25).



199 341

Scheme 2.25

2.4 Conclusions

Whilst routes to **199** have been previously reported, most are undesirable due to safety concerns or require complex multistep syntheses of starting materials. The

4-π-photocyclisation of **194** to **199** in the presence of a Lewis acid was identified as a viable strategy, due to the commercial availability of **194**, the high atom economy of the process, mild conditions, and potential for scale-up in flow photoreactors. Various reaction parameters were tested, including solvent, irradiation wavelength, concentration, and Lewis acid used. The solvent choice was limited, as adducts of **194** with Lewis acids were insoluble in most solvents employed, limiting the choice to dichloromethane. Nevertheless, good yields of **199** could be obtained in just under two hours upon irradiation of **199**·BF_3 in a Rayonet batch photoreactor. Attempts to scale the reaction up in a Vapourtec E-Series flow photoreactor were met with considerable difficulty, due to the deposition of degradation material which blocked the reactor tubing. With multigram quantities of **199** in hand, attention was turned to its derivatisations in the context of diversity-oriented synthesis. Gratifyingly, **199** was amenable to a wide range of transformations on the enone moiety including Diels-Alder reaction, 1,2- and 1,4-additions, epoxidations, aziridinations and cyclopropanations. In total, 17 novel small molecule building blocks could be accessed in this study, with 14 directly accessible from **185**.

Whilst the cyclobutene motif was predicted to be highly reactive, only a limited number of reactions attempted were successful. For example, hydroboration under various conditions failed to give the corresponding borane, and electrophilic aziridination preferentially reacted on the enone double bond. Dihydroxylation and oxidative cleavage of the obtained products were similarly unsuccessful. This lack of reactivity was unprecedented, and further investigation, including computational studies, is required to understand these anomalous results.

References

[1] Wakabayashi, S.; Saito, N.; Sugihara, Y.; Sugimura, T.; Murata, I. *Synth. Commun.* **1995,** *25,* 2019–2027.

[2] Winter, N.; Trauner, D. *J. Am. Chem. Soc.* **2017,** *139,* 11706–11709.

[3] Davy, J. A.; Mason, J. W.; Moreau, B.; Wulff, J. E. *J. Org. Chem.* **2012,** *77,* 6332–6339.

[4] Davy, J. A.; Moreau, B.; Oliver, A. G.; Wulff, J. E. *Tetrahedron* **2015,** *71,* 2643–2657.

[5] Story, P. R.; Fahrenholtz, S. R. *J. Am. Chem. Soc.* **1964,** *86,* 1270–1271.

[6] Prinzbach, H.; Babsch, H.; Fritz, H. *Tetrahedron Lett.* **1976,** *17,* 2129–2132.

[7] Sugihara, Y.; Sugimura, T.; Saito, N.; Murata, I. *J. Chem. Soc. Chem. Commun.* **1989,** 537.

[8] Zandomeneghi, M.; Cavazza, M.; Pietra, F. *J. Am. Chem. Soc.* **1984,** *106,* 7261–7262.

[9] Gibson, S. E.; Mainolfi, N.; Kalindjian, S. B.; Wright, P. T. *Angew. Chem. Int. Ed Engl.* **2004,** *43,* 5680–5682.

[10] Cavazza, M.; Zandomeneghi, M.; Pietra, F. *J. Chem. Soc. Chem. Commun.* **1990,** 1336.

[11] Lowe, J. P.; Halcovitch, N. R.; Coote, S. C. *J. Org. Chem.* **2023,** *88,* 9514–9517.

[12] Lukes, P.; Clupek, M.; Babicky, V.; Sunka, P. *Plasma Sources Sci. Technol.* **2008,** *17,* 024012.

[13] Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999,** *1,* 783–786.

[14] Gillespie, K. "N-tosyliminobenzyliodinane - PhINTs from Iodobenzene diacetate", 2001.

[15] Kiyokawa, K.; Kosaka, T.; Minakata, S. *Org. Lett.* **2013,** *15,* 4858–4861.

[16] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965,** *87,* 1353–1364.

[17] Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958,** *80,* 5323–5324.

[18] Wharton, P.; Bohlen, D. *J. Org. Chem.* **1961,** *26,* 3615–3616.

[19] Tamiya, M.; Isaka, N.; Kitazawa, T.; Hasegawa, A.; Ishizawa, K.; Ikeda, M.; Kawada, S.; Ishiguro, M. *Bull. Chem. Soc. Jpn.* **2019,** *92,* 1474–1494.

[20] Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980,** *102,* 2095–2096.

[21] Wang, H.; Ren, S.; Zhang, J.; Zhang, W.; Liu, Y. *J. Org. Chem.* **2015,** *80,* 6856–6863.

[22] Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim Acta.* **1967,** *50,* 708–713.

[23] Schreiber, J.; Felix, D.; Eschenmoser, A.; Winter, M.; Gautschi, F.; Schulte-Elte, K. H.; Sundt, E.; Ohloff, G.; Kalovoda, J.; Kaufmann, H.; Wieland, P.; Anner, G. *Helv. Chim. Acta.* **1967,** *50,* 2101–2108.

[24] de Orbe, M. E.; Echavarren, A. M. *Eur. J. Org. Chem.* **2018,** *2018,* 2740–2752.

[25] Banwell, M. G. *J. Chem. Soc. Chem. Commun.* **1982,** 847.

[26] van der Kolk, M. R.; Janssen, M. A. C. H.; Rutjes, F. P. J. T.; Blanco-Ania, D. *ChemMedChem* **2022,** *17,* e202200020.

[27] Bartolo, N. D.; Woerpel, K. A. *J. Org. Chem.* **2018,** *83,* 10197–10206.

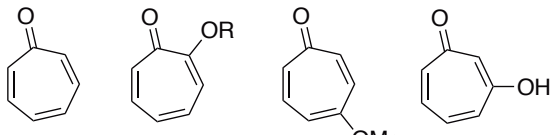
[28] Piccialli, V. *Molecules* **2014,** *19,* 6534–6582.

[29] Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981,** *46,* 3936–3938.

Chapter 3

Synthesis and Photochemistry of 2-Substituted Tropones

In addition to tropone (**194**) and tropolones (**200**, **204**, **206**, **217**) (Figure 3.1) themselves, the photochemistry of other substituted tropones (troponoids) has also been studied. As for tropones, 4-π-photocyclisation of substituted tropones gives [3.2.0]bicycles, this time substituted versions of the parent compound. The nature and type of substituent on the tropone core affects the behaviour of the troponoid upon irradiation, and other photochemical and photophysical processes other than 4-π-photocyclisation compete effectively in some cases. Previous work in the area is summarised in this section, encompassing both naturally occurring troponoids and synthetic troponoids, with a focus on the 4-π-photocyclisation of troponoids to give [3.2.0]bicyclic products.



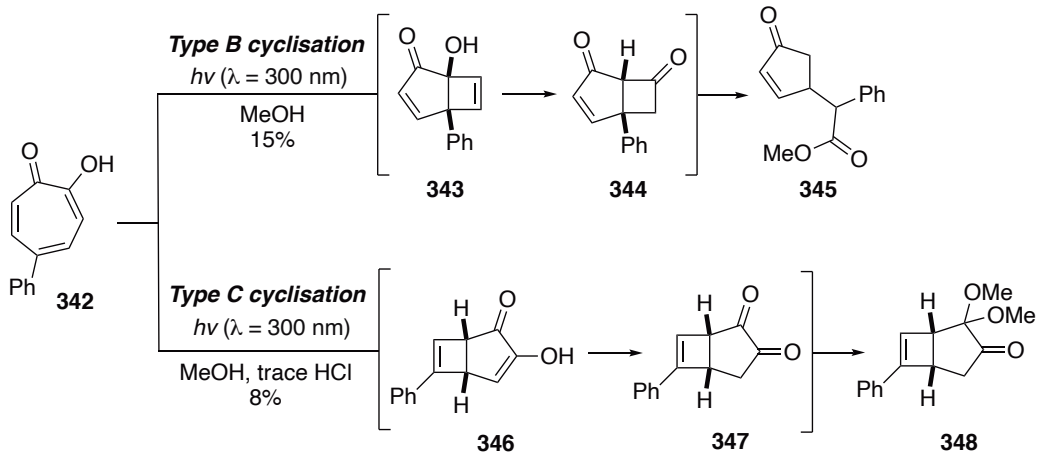
194 **200**: R = H, **204**: R = Me **206** **217**

Figure 3.1

3.1 Background

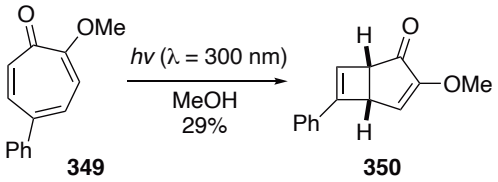
3.1.1 Tropolone derivatives

As discussed in Chapter 1, the photochemistry of the tropolones differ markedly depending on the position of the hydroxyl group. A range of other substituted tropolone derivatives has also been studied, with the findings further demonstrating that the effect of substituents can have a profound role in the outcome of these photoreactions. For example, Mukai and Miyashi reported a variety of different outcomes for 5-substituted tropolones and their methyl ethers.[1] Irradiation of 5-phenyltropolone (**342**) gave rise to a complex mixture of products upon irradiation at 300 nm in methanol (Scheme 3.1). Thus, ester **345** was isolated in 15% yield, presumably from an initial type B photocyclisation (**343**) followed by rearrangement (**344**) and solvolysis, similar to **200** and **204**. Surprisingly, acetal **348** could be obtained in low yields from irradiation of **320** in methanol containing trace quantities of hydrochloric acid. Here, the mode of photocyclisation is switched to type C cyclisation to initially yield product **346**, which then undergoes tautomerisation to α,β-diketone **347** that further reacts with two equivalents of methanol to furnish **348**.



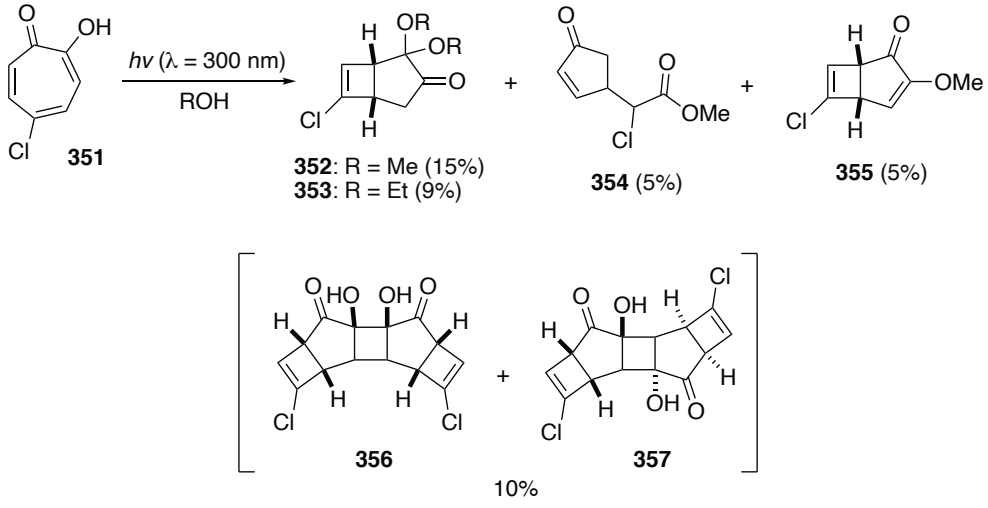
Scheme 3.1

For the methyl ether of **342**, **349**, the product arising from a type C photocyclisation (**350**) was isolated as the sole photoproduct in low yields (29%) after 70 hours of irradiation, alongside significant amounts of recovered starting material (61%) (Scheme 3.2).



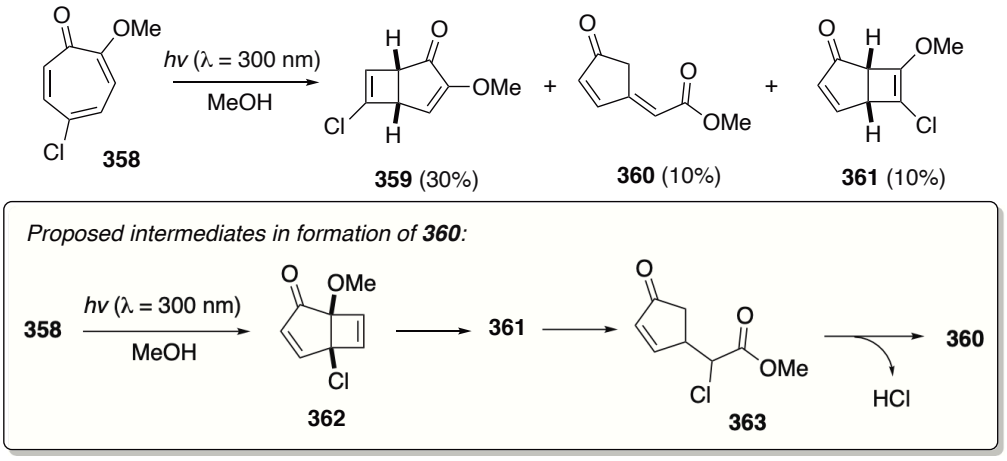
Scheme 3.2

The photochemistry of 5-chlorotropolone (**351**) was also explored by the same group, exhibiting similar behaviour upon irradiation to **342** (Scheme 3.3).[2] Thus, irradiation of **351** in protic solvents gave acetals **352** and **353** (R = Me, 15, R = Et: 9%) arising from a Type C photocyclisation, and cyclopentenone **354** in low yield (4%). Whilst a similar product profile was obtained upon irradiation in ethanol mixtures of the head-to-head (**356**) and head-to-tail (**357**) [2+2] PCA products were also obtained in low yield (10%).



Scheme 3.3: R = Me, Et.

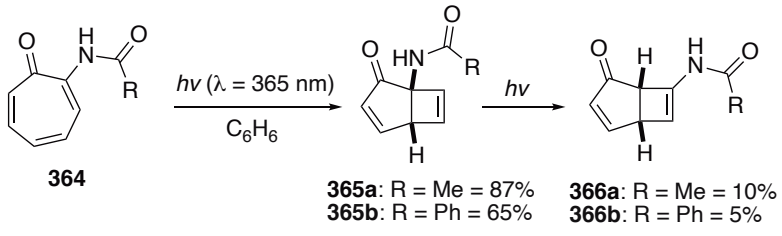
Under similar conditions, 5-chlorotropolone methyl ether (**358**) gave bicycle **359** resulting from a Type C photocyclisation as the major product (Scheme 3.4). **366** presumably arises from elimination of hydrogen chloride from the solvolysis product of **361**, which in turn arises from a Type B photocyclisation (**362**).



Scheme 3.4

3.1.2 2-Aminotropones

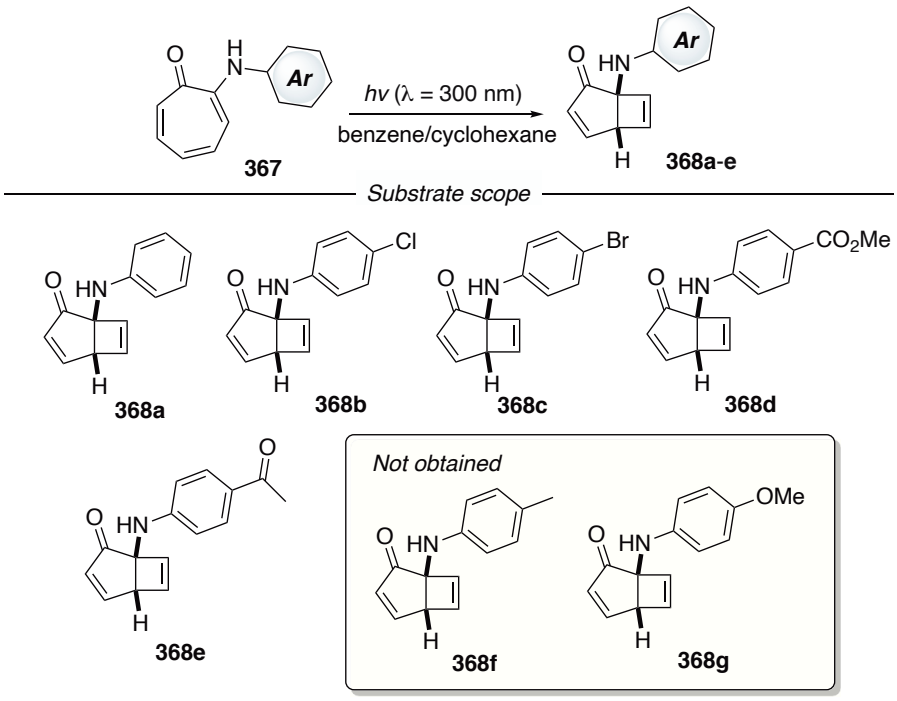
Mukai and Kimura detailed the photoreactivity of a range of *N*-substituted amionotropones (Scheme 3.5).[3] 2-Amidotropones **364** showed similar photoreactivty to tropolone, yielding bicyclic products **365a**-**b** in good yields, which formed their rearranged products **366a**-**b** upon extended irradiation (Scheme 3.5).



Scheme 3.5

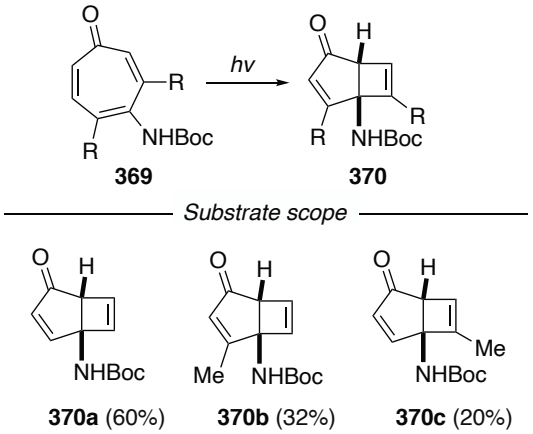
2-Anilinotropone (**346**) underwent 4-π-photocyclisation in aprotic solvents such as

benzene or cyclohexane to afford the corresponding [3.2.0]bicycle (**3**47)in moderate yields, but not in protic solvents such as ethanol (Scheme 3.6). Substituent effects at the *para* position of were also explored under similar conditions, and [3.2.0]bicyles **348**-**351** could be obtained with electron-withdrawing groups, although no yields were reported. Conversely, the expected products **352** and **353** from electron-donating *para* groups (Me, OMe) were not obtained, and starting material was recovered unchanged.



Scheme 3.6

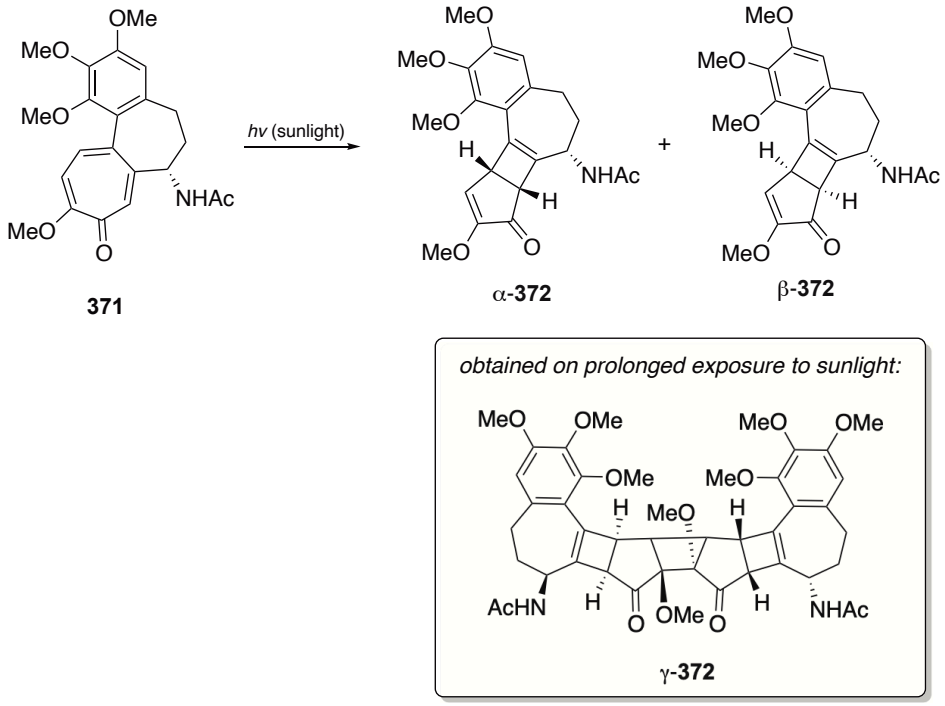
A small range of 4-aminotropones **354** (R = Me, H) has also been investigated, and these substrates react similarly to γ-tropolone to afford [3.2.0]bicycles **355**–**357** in moderate yields (20–60%).[4] In these cases, the addition of a methyl group in the 3- or 5-position did not have a significant influence on the outcome of the reaction.



Scheme 3.7

3.1.3 Colchicine and Colchicine Derivatives

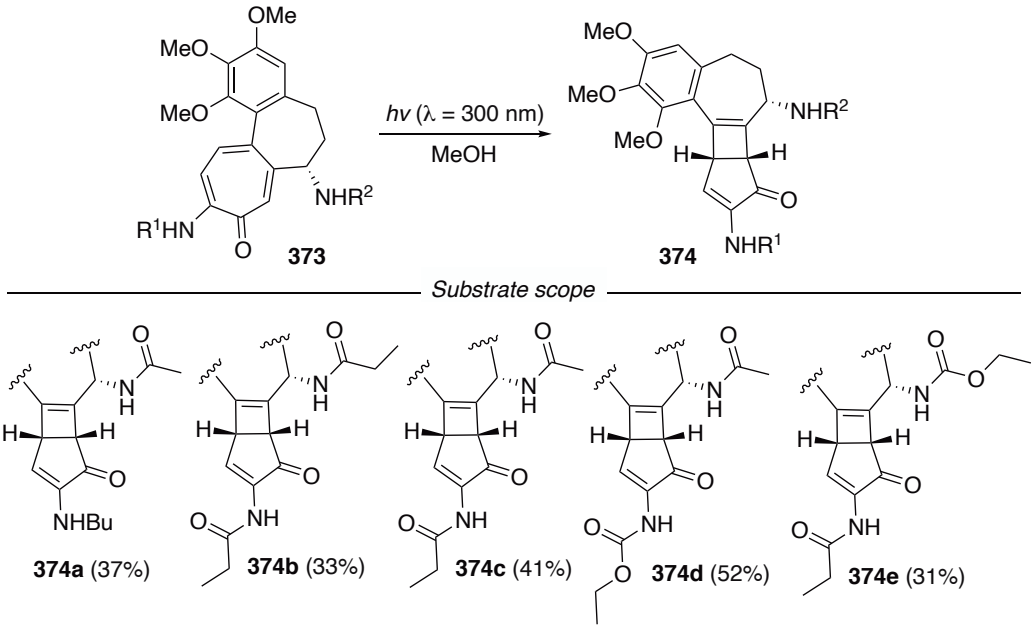
Upon exposure to sunlight for several weeks, (–)-colchicine (**371**), a naturally occuring product isolated from *Colchicum autumnale* containing the α-tropolone moiety, was reported to undergo conversion into three different photoproducts: α-, β-, and γ-luminocolchicine (**372**), in a roughly 4:3:2 ratio (Scheme 3.8).[5] However, Forbes reported significantly higher amounts of β-**372** to be obtained, in an approximate 1:16:1 ratio. The difference in product profiles obtained is likely due to the difficulty in repeating such a long reaction effectively, where actual irradiation times are expected to differ significantly. The structures of α- and β-**372** were determined separately by Chapman, Forbes and Gardener, and result from 4-π-photocyclisation and are diastereoisomers of one another.[6] Later, Chapman assigned the structure of γ-**372**, which was a head-to-head photodimer formed from two equivalents of β-**372**.[7]



Scheme 3.8

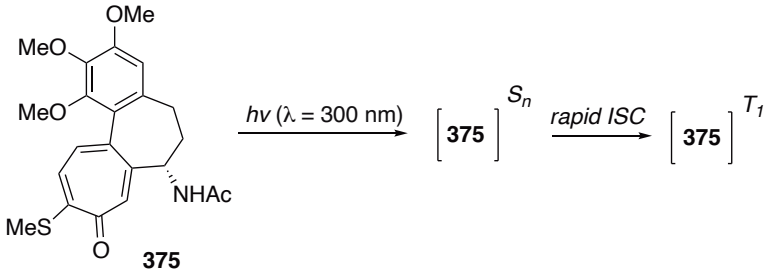
Later, a range of aminocolchicine (**373**) were irradiated in methanol to yield the diastereomerically pure 4-π-cyclisation products **374a**-**e** in moderate yields (31–52%) (Scheme 3.9) – in all cases, Type C reactivity was observed, as for colchicine itself under similar irradiation conditions.

Mechanistic studies on the 4-π-photocyclisation of troponoid species have focussed on the photophysics of **371** and its derivatives including thiocolchicine (**375**) via computational and femotosecond transient spectroscopy studies.[8] Thus, based on these, D'Auria and co-workers proposed that the isomerisation of **371** involves disrotatory ring closure on the S_1 hypersurface, and that no triplet states are involved in the reaction. This is in agreement with triplet quenching studies by Croteau and Leblanc, whereby irradiation of (±)-**371**, **200** and **204** in the presence of various triplet quenchers (2,3-bornanedione, riboflavin, fluorescein or eosin Y) led to none of the corresponding 4-π-photocyclisation products.[9] Surprisingly, thiocolchicine (**375**) does not undergo cyclisation, and the authors proposed that efficient intersystem



Scheme 3.9

crossing to the triplet state occurred immediately after population of the singlet excited state, which resulted in unproductive decay back to the ground state (Scheme 3.10).

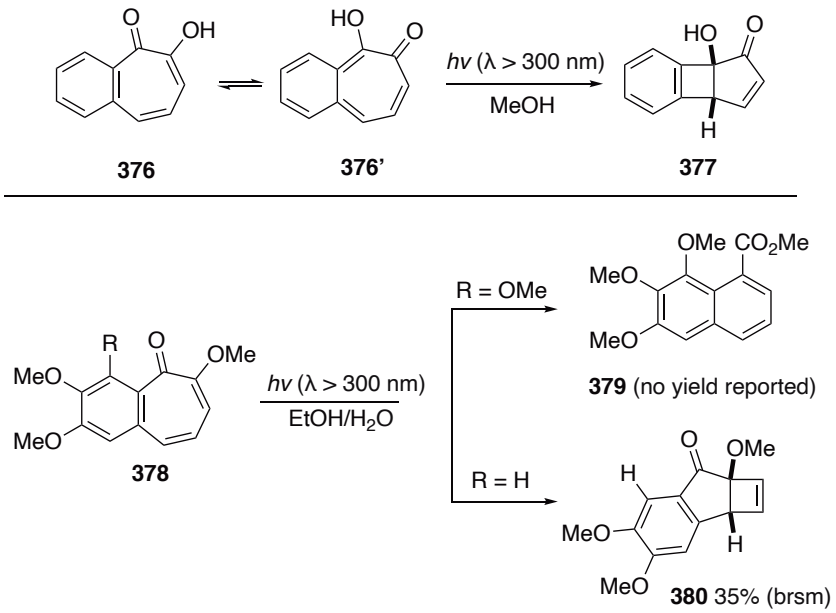


Scheme 3.10

3.1.4 (Hetero)Aryl-Fused Troponoids

The photochemistry of 6,7-benzotropolones (**376**, **378**) has also been explored. Thus, irradiation of benzotropolone **376** gave **377**, through tautomer **376'**, although no yield was reported.[10] Tetramethyl purpurogallin ether (**378**, R = OMe) underwent 6-π-photocyclisation and subsequent ring opening to afford ester **379**[11] whereas

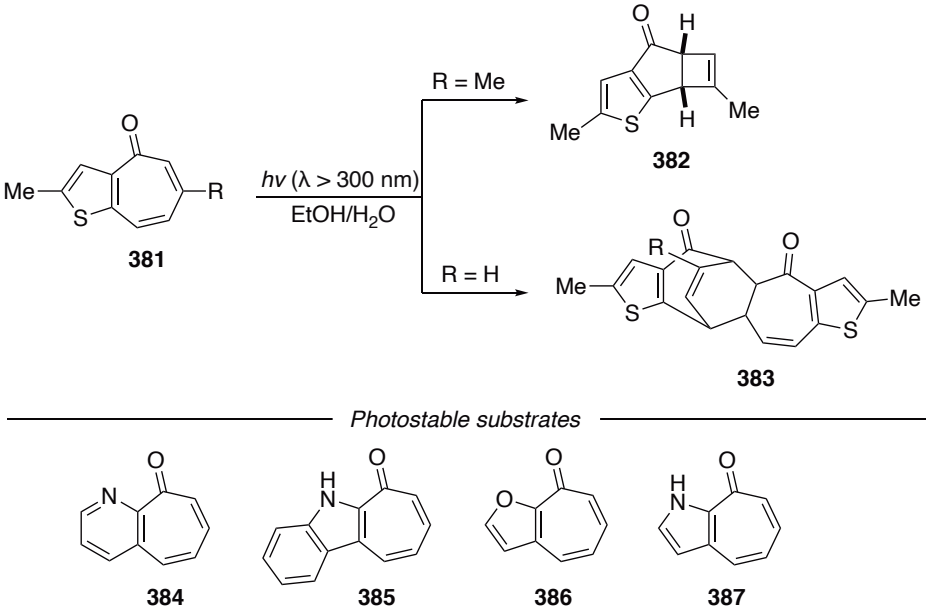
its closely related derivative underwent (**378**, R = H) 4-π-photocyclisation to yield tricycle **380** (Scheme 3.11).[12,13]



Scheme 3.11

The vast majority of heterocycle-fused tropones including pyridine-, indole-, furan- and pyrrole fused tropones were photostable (**384**-**387**) and did not react under the conditions attempted. However, thiophene derivative (**381** R = Me) did undergo 4-π-photocyclization to yield **382**, otherwise dimerisation occurred to yield **383** when R = H (Scheme 3.12).

From looking at these examples, the nature of substituents around the tropone core may have a profound impact on its photochemical behaviour. Whilst many such examples exist, there has been no systematic study of this reaction. Additionally, those tropones bearing oxygen or nitrogen substituents at the 2-position may undergo secondary rearrangements as discussed in Chapter 1. In addition, competing photochemical/photophysical processes may complicate the product profiles.



Scheme 3.12

3.2 Project Aims

This section of work aims to explore the substituent effects of troponoid 4-π-photocyclisation. The effects of substituents at the 2-position will first be explored, owing to the sizeable body of literature pertaining to their synthesis, and their ease of access from commercially available starting materials (Figure 3.2).

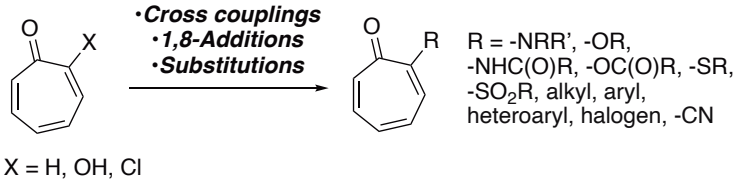


Figure 3.2

With access to the requisite substrates established, their behaviour upon irradiation across a variety of different reaction conditions including solvent, wavelength and concentration will be explored, and reactions will be discussed by their substituent type. As there are two possible cyclisation modes, depending on which of the double bonds take part in the reaction, a general idea of substituent effects on this

may help predict the reactivity of new substrates. In these cases where mixtures of regioisomers are obtained, attempts to improve the regioselectivity by variation of the reaction conditions will be attempted (Figure 3.1).

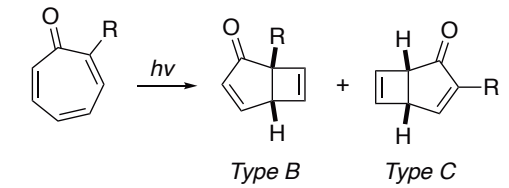


Figure 3.3

3.3 Results and Discussion

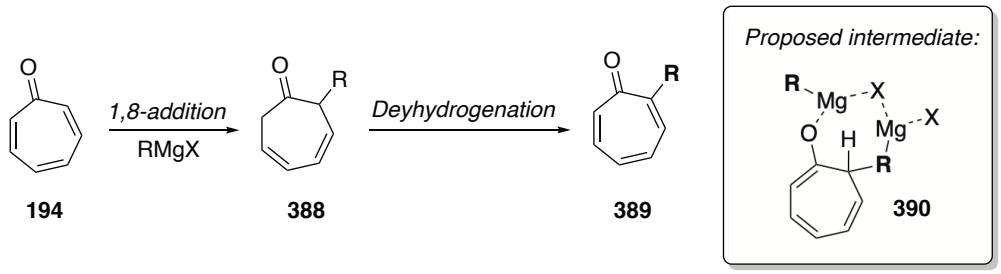
In order to carry out the planned investigation into the photochemistry of 2-substituted tropones, it was first necessary to synthesise a range of 2-tropones, as only a very small range of substituted tropones are available commercially. This work is described in the next section, with a variety of synthetic approaches being investigated.

3.3.1 Synthesis of 2-Substituted Tropones

It was envisaged that commercially available tropones (X = H, OH, Cl) could undergo a variety of different reaction types including 1,8-additions, cross-couplings, and substitutions, to generate a diverse pool of 2-substituted tropones. Using these approaches, a wide range of 2-substituted tropones was targeted, and the reactions will be discussed according to reaction type.

3.3.1.1 Synthesis of 2-Substituted Tropones via 1,8-Additions

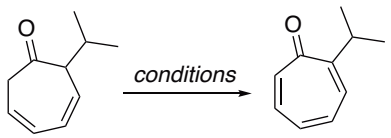
A route to 2-alkyltropones (**389**) was first investigated. Tropone (**194**) is known to undergo 1,8-addition upon reaction with two equivalents of Grignard reagent to yield the corresponding dihydrotropone **388** (Scheme 3.13).[14,15] Two equivalents of the Grignard reagent are presumably required so that coordination of one magnesium centre stabilises the intermediate **390** (Scheme 3.13, boxed). Due to this stabilisation, addition of the alkyl group to the 7-position is thus preferable to other positions on the ring. Subsequent dehydrogenation of these species would return the 2-substituted tropone nucleus. Pleasingly, several alkyl Grignard reagents (R = Me, *i*-Pr, Bu, cy-Hex, Bn) underwent successful 1,8-addition to **104** to yield dihydrotropones **388** in good to excellent yields (95–99%), and were sufficiently pure by ^{1}H NMR spectroscopy. In fact, attempted purification by flash column chromatography (SiO_2, neutral alumina) led to a significant reduction in the yields of **388**, and so were used without further purification in the subsequent oxidation step.



Scheme 3.13

With several 2-alkyl-2,7-dihydrotropones (**388**) in hand, attention was turned to their transformations to 2-alkyltropones. In Nozoe's original publication, SeO_2 in 1,4-dioxane at reflux was used as the dehydrogenating conditions, although application of these conditions to **388a** (R = *i*-Pr) led to **389a** being obtained in disappointingly low yield (14%). Considering the toxic and malodorous nature of SeO_2, as well as the low yield obtained, a different set of conditions for scale-up were was sought. Thus, reaction of **388a** with DDQ/NEt_3, a common set of conditions used

for rearomatization reactions, did not result in any formation of the desired product. The use of hypervalent iodine reagents in the dehydrogenation step, popularised by Niccolau,[16] also did not result in any formation of **389a** (entries 2 and 3). Finally, iodine in ethanol at reflux was next attempted, and **389a** could be isolated in an improved yield of 22%. A short optimisation identified 2 equivalents of iodine in methanol at reflux for 18 hours as the optimal set of conditions, obtaining **389a** in 28% yield.

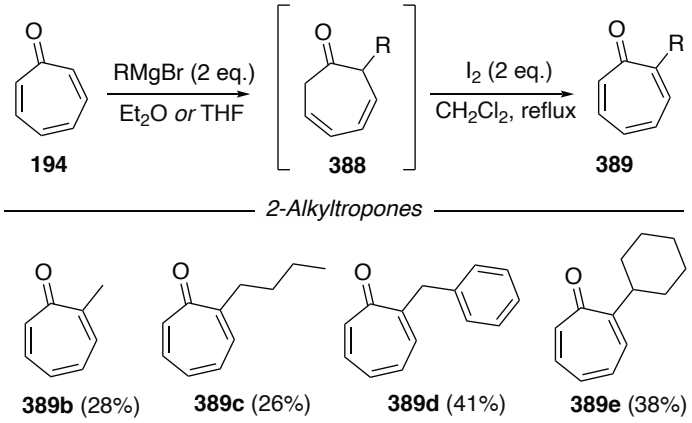


388a **389a**

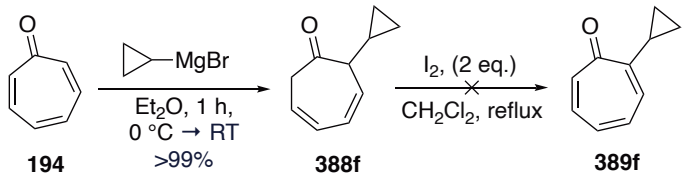
Entry	Conditions	Yield (%)
1	SeO_2, 1,4-dioxane, reflux	14
2	PhIOAc, 1,4-dioxane	0
3	Koser's reagent, PhMe	0
4	DDQ/NEt_3	0
5	I_2, EtOH, reflux	1
6	I_2, MeOH, reflux	28
7	I_2, CH_2Cl_2, reflux	17

Table 3.1

The other alkyltropones (**389b–e**) were synthesised using this optimised procedure in similar yields (28–37%). Whilst 1,8-addition of cyclopropylmagnesium bromide to **194** was successful (**388f**), transformation to its corresponding tropone (**389f**) furnished a complex mixture of products upon reaction and could not be isolated (Scheme 3.15).

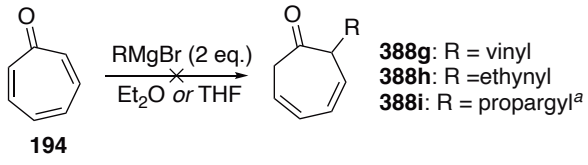


Scheme 3.14



Scheme 3.15

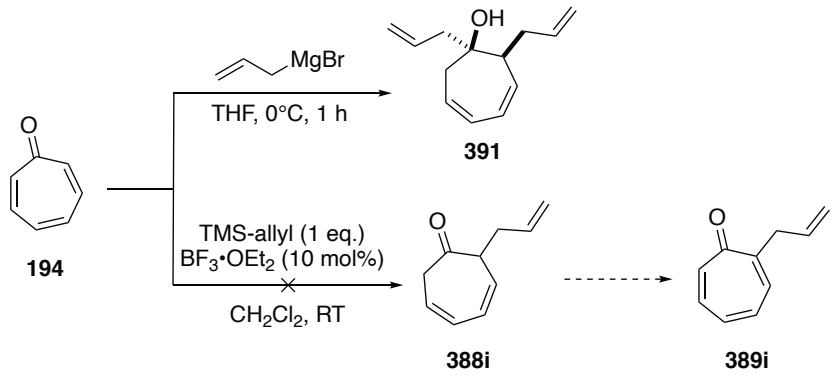
Other Grignard reagents were also employed under the same reaction conditions in an attempt to install other substituents (**388g–i**, R = vinyl, ethynyl and propargyl). Unfortunately, the nucleophilic addition step failed to generate the desired product, and instead returned complex mixtures of products upon completion of the reaction (Scheme 3.16). Thus, installation of the these groups could not be achieved under these conditions.



Scheme 3.16: [a] Reaction performed in the presence of catalytic $Hg(OAc)_2$.

Attempts at installing an allyl group via this methodology led to a complex mixture of products, with diallylated product **391** identified as the major constituent (21%)

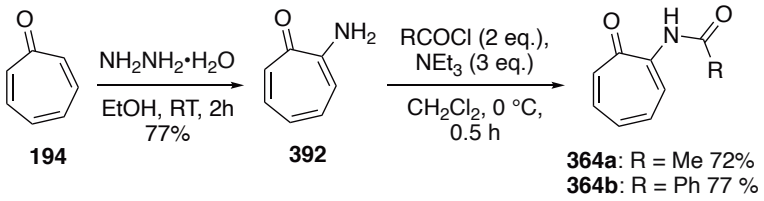
(Scheme 3.17). As two equivalents of the Grignard reagent are usually employed for 1,8-addition to occur, diallylation was unavoidable, but reducing the equivalents of allylmagnesium bromide did not lead to the desired mono-addition – diallylation was still observed. Allylmagnesium bromide is known to be much more reactive than other Grignard reagents, often exhibiting low selectivity in additions to carbonyl compounds and unsaturated carbonyl compounds.[17] Thus, it is likely that this particular addition reaction would be very difficult to optimise effectively using this reagent. Thus, other methods for the addition of an allyl group were considered. Hosomi-Sakurai type reaction to dihydrotropone **388i**,[18] followed by a dehydrogenation step similar to that employed for the 2-alkyltropones was identified as a potential alternative, where diallylation could be avoided by employing only one equivalent of the allylating reagent. However, no reaction took place, and starting material was recovered unchanged, and **389i** could not be isolated under these conditions.



Scheme 3.17

2-Aminotropone (**392**) could be isolated in good yield upon reaction of tropone and hydrazine monohydrate, and benefitted from purification by recrystallisation rather than flash column chromatography. However, **396** was found to decompose rapidly in air and storage under an inert atmosphere was necessary (Scheme 3.18). **396** could be further derivatised to amides **341a** and **341b** in good yields (72 and 77%,

respectively) upon reaction with the corresponding acyl/aroyl chloride.

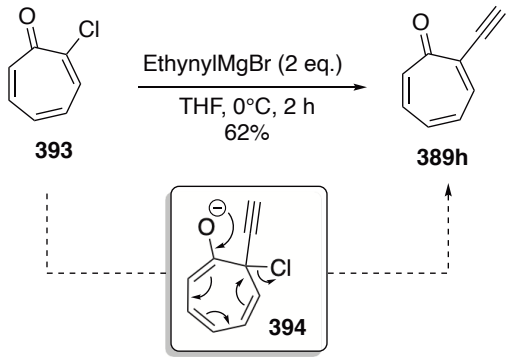


Scheme 3.18

In summary, a range of 2-alkyltropones and 2-amino/amidotropones has been prepared from tropone itself through nucleophilic addition followed by oxidation to regenerate the tropone nucleus. Unfortunately, attempts to prepare vinyl-, allyl-, ethynyl- and propargyl-substituted tropones using the same approach were unsuccessful, due either to poor selectivity in the addition of the nucleophile to tropone, or lack of reactivity.

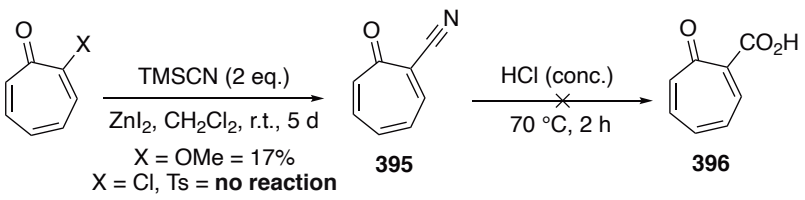
A related approach was next pursued, in which nucleophilic 1,8-addition to tropones bearing a leaving group was targeted. Subsequent elimination of the leaving group then allows regeneration of the tropone core. Bickel and co-workers reported the 1,8-addition of alkyl and phenyl Grignard reagents to **393**, followed by heating of the resulting dihydrotropone to eliminate hydrogen chloride and return the tropone nucleus. Thus, attempting this reaction with alkyl Grignard reagents and **393** led to none of the 2,7-dihydrotropone forming, and starting material was recovered unchanged after 24 hours of stirring. However, by reacting **397** with ethynyl magnesium bromide, **389h** was obtained directly in good yield (62%) (Scheme 3.19). It is proposed that intermediate **394** spontaneously eliminates one equivalent of hydrogen chloride under the reaction conditions to form the more stable conjugated system in **389h**. Temperature control and the rate of addition of the Grignard reagent were particularly important for achieving good yields; the best result was obtained

by performing the reaction at 0 °C, adding the Grignard reagent dropwise over the course of half an hour, and stirring the reaction at 0 °C for a further two hours, obtaining **389h** in 62% yield.



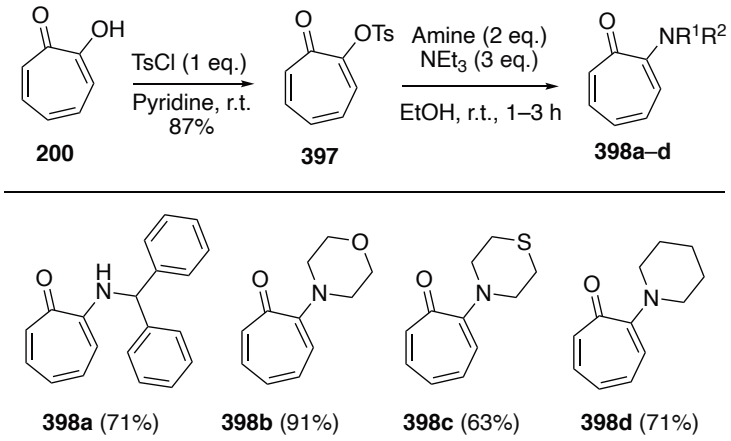
Scheme 3.19

The reaction of **393** with allylmagnesium bromide was also attempted, instead obtaining an unidentifiable product assumed to arise from ring-contraction. A similar reaction using 2-methoxytropone (**204**) (synthesised from a literature procedure in 84% yield) gave the same result. TMSCN may also react with **204** in a 1,8-fashion to yield 2-cyanotropone (**395**) (Scheme 3.20).[19] Thus, repeating the procedure reported by Katsuhiro and Hisashi afforded **395** in low yield (17%). Other leaving groups, (X = Cl, OTs) did not furnish **395** under the same conditions. Heating at reflux in CH_2Cl_2, or even in neat TMSCN did not significantly improve the yield either. Finally, heating of **395** in concentrated hydrochloric acid did not reveal the expected carboxylic acid derivative **396**.[20]



Scheme 3.20

2-Tosyloxytropone (**397**), synthesised in good yields via a literature procedure,[21] proved to be a useful intermediate in the synthesis of 2-aminotropones (Scheme 3.21). Thus, by reaction of **397** with the corresponding amines, 2-aminotropone derivatives (**398a–d**), were obtained in good yields (63–91%). However, using diethylamine as the amine source was unsuccessful, and its substitution of **397** could not be observed, even at elevated temperatures (79 °C). As the photochemistry of several 2-anilinotropones (Scheme 3.6) have already been reported elsewhere,[22] their synthesis was not pursued.



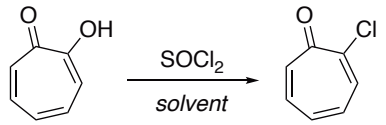
Scheme 3.21

In summary, the use of tropone precursors bearing a leaving group in the 2-position allowed access to 2-ethynyltropone (**389h**), 2-cyanotropone (**395**) and four new 2-aminotropones (**398a**-**d**) through an addition-elimination sequence.

3.3.1.2 Synthesis of 2-Substituted Tropones via Cross-Coupling

2-Chlorotropone (**393**) was identified as a key intermediate to access other 2-substituted tropones, and whilst commercially bought material was available in the laboratory, much larger quantities (10–20 g) were required for further transformations. Doering and Knox first achieved the synthesis of **393** in excellent yields by heating **200** and thionyl chloride in benzene at reflux.[23] Considering the car-

cinogenic nature of benzene, toluene was identified as a safer alternative. Under these modified conditions, **393** was obtained in 7% yield, which was significantly lower than the literature yield (86%), although could be improved by performing the reaction at lower concentrations (entries 1 and 2, Table 3.2).[24] As **200** is known to be hygroscopic, it was considered that trace water in our starting material may be leading to decomposition of thionyl chloride. However, when using thionyl chloride as both solvent and reagent (entry 4), only traces of product were isolated. Finally, it was considered that the use of benzene as the solvent was paramount for successful transformation, but no significant increase in yield was observed with its use (37%) (entry 3). However, through various attempts at this transformation, in addition to commercially bought material, sufficient quantities of **393** were garnered.



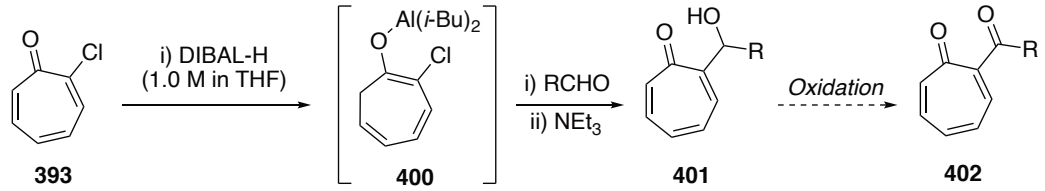
200 **393**

Entry	Solvent	Temp (°C)	Yield (%)
1	PhMe (0.33 M)	110	7
2	PhMe	110	33
3	Benzene	70	37
4	$SOCl_2$	100	traces

Table 3.2

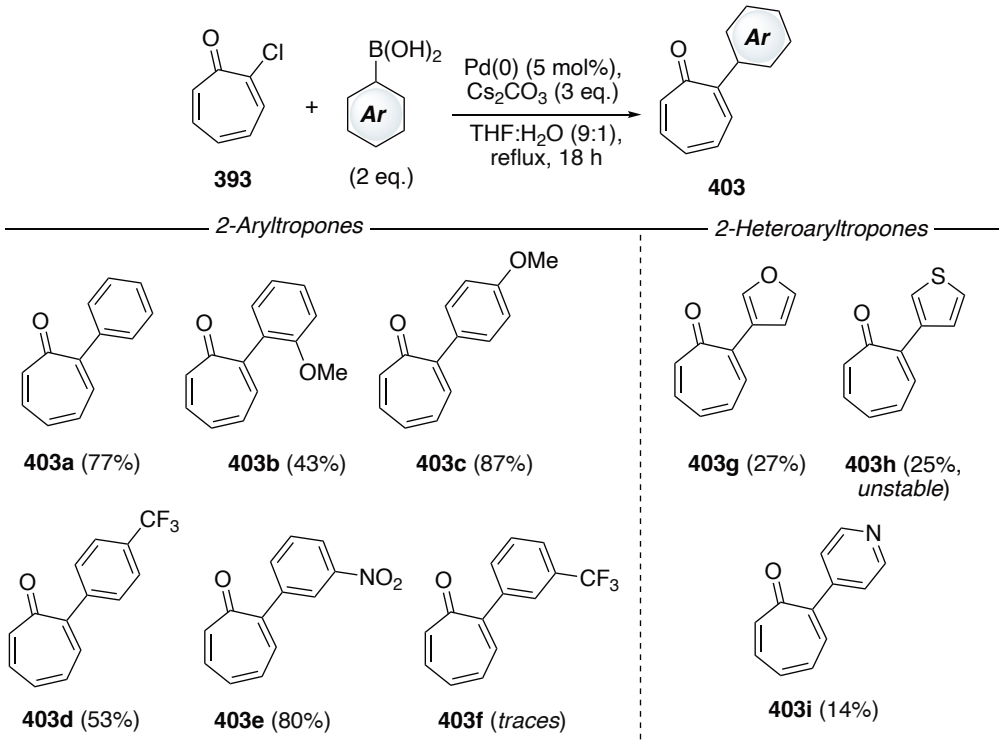
The synthesis of 2-aroyl and 2-acyltropones (**399**) was attempted starting from **393** using conditions reported by Nitta and co-workers (Scheme 3.22).[25] Whilst the tropone nucleus is generally resistant to electrophilic attack, an umpolung strategy was employed to generate enolate **400**, which may then undergo an aldol-type reaction with aldehydes to give **401**. The alcohols obtained (**401**) would generate acyl substituted tropones (**402**) upon subsequent oxidation. However, none of the expected alcohols **401** were observed upon following the protocol as described in Nitta's original publication, and complex mixtures were obtained after reaction with

various aldehydes (R = Et, *p*-C_6H_4Cl, *p*-$C_6H_4NO_2$, *p*-C_6H_4CN), alongside large quantities of starting material. Thus, investigation into this route was abandoned.



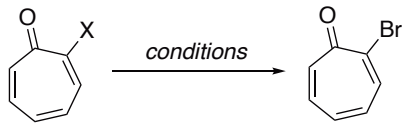
Scheme 3.22: R = Et, *p*-C_6H_4Cl, *p*-$C_6H_4NO_2$, *p*-C_6H_4CN.

Next, attention was turned to the synthesis of 2-aryltropones via Suzuki-Miyaura coupling. Application of Suzuki cross-coupling conditions developed by Ononye and co-workers gave 2-aryltropones **403a–f** in moderate to good yields (43–87%), with no modifications required (Scheme 3.23).[26] However, **403f** was unstable, and fully decomposed in 12 hours under ambient conditions, hence it was deemed unsuitable as a substrate for photochemical studies. 2-Heteroaryltropones **403g–403i** could be synthesised under these conditions, although in poorer yields (14–27%). **403i** was unstable under ambient conditions and was deemed unsuitable for photochemical studies. In a similar vein, Suzuki-Miyaura coupling of **393** with other non-aryl boronic acids including cyclopropyl boronic acid, allyl boronic acid MIDA ester and allenyl boronic acid were unsuccessful in generating the desired products.



Scheme 3.23

2-Bromotropone (**404**) was next targeted, as it was hoped it would be a more useful coupling partner where **393** failed. Cavazza and co-workers have reported the synthesis of **404** by heating of **397** with lithium bromide salt in methanol with catalytic $BF_3{\cdot}OEt_2$.[27] Similarly, this transformation was also achieved by reaction of **397** and lithium halides in in ionic liquids.[28] However, poor yields of **404** were obtained (12%) under the first set of conditions, and considering the expense of the ionic liquid required in the latter, a different set of reaction conditions was sought (Table 3.3, entry 1). Stirring **200** with either one equivalent of PBr_3 in PhMe (1.0 M) or in PBr_3 led only to unchanged starting material (entries 2 and 3). As bromination of tropone with neat bromine would lead to undesired over-brominated products,[29] *N*-bromosuccinimide was identified as a potential brominating agent. After a short optimisation of the reaction parameters (entries 4–5) five equivalents of NBS in DMF gave the best results (45% yield) (entry 5).

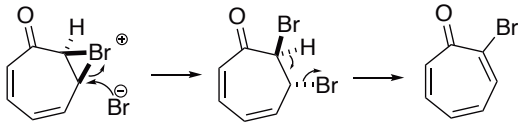


404

Entry	X	Conditions	Yield (%)
1	OTs	$BF_3{\cdot}OEt_2$, LiBr, toluene, reflux	14
2	OH	PBr_3, PhMe, rt	0
3	OH	PBr_3, RT	0
4	H	NBS (2 eq.), MeCN, reflux	23
5	H	NBS (2 eq.) DMF, reflux	45

Table 3.3

It is proposed that the reaction proceeds via bromonium ion **405**, which is ring-opened by bromine cation to give the corresponding dibromide **421**, whereby elimination of hydrogen bromide returns the double bond to yield **419** (Scheme 3.24). **194** was reacted in a similar fashion with *N*-iodosuccinimide (NIS), but corresponding iodo derivative was not observed — considering the potential instability of this product, further attempts at its synthesis were abandoned. The amount of **404** was limited, and therefore its use in reactions was limited to when reaction with other coupling partners were unsuccessful.

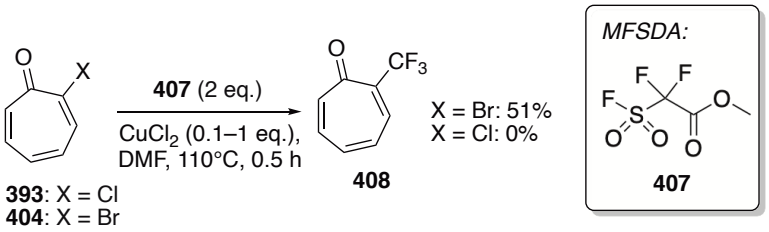


405 **406** **404**

Scheme 3.24

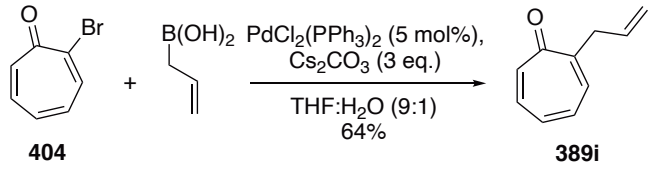
Installation of a trifluoromethyl (-CF_3) group, using MFSDA[30] (**407**) as the trifluoromethylating agent, turned out to be quite trivial (Scheme 3.25). Thus, using **404** as the coupling partner yielded 2-trifluoromethyltropone (**408**) in good yield (55%) after 30 minutes of stirring at reflux (Scheme 3.24). However, attempts to

react **393** with one equivalent of **407** and a catalytic amount of copper(II) in boiling DMF returned only **393**. Attempting to force the reaction to completion by using a 1:1 ratio of Cu(II):**407**, which in theory would generate the active $CuCF_3$ reagent stoichiometrically, was similarly unsuccessful.



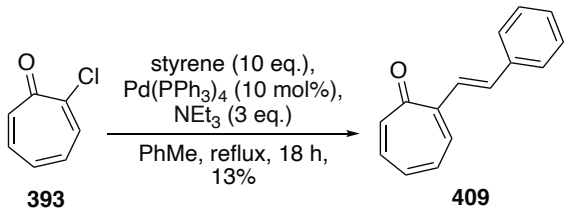
Scheme 3.25

Although introduction of an allyl group via 1,8-addition/dehydrogenation sequence was unsuccessful, **389i** was obtained in moderate yields (51%) by Suzuki-Miyaura cross coupling of the corresponding boronic acid with 404 (Scheme 3.26).



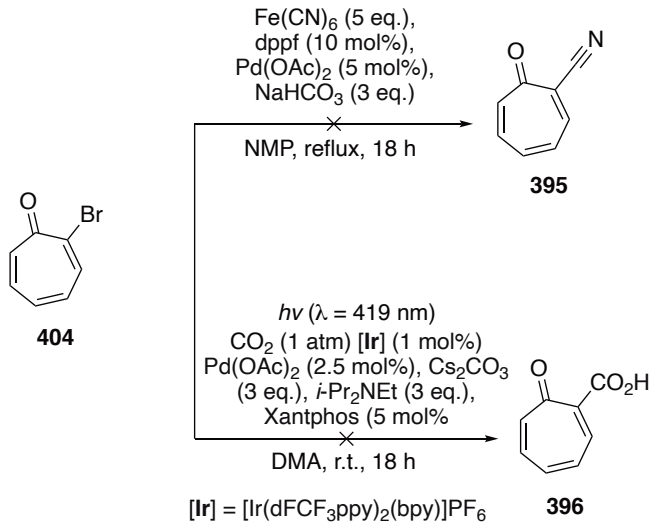
Scheme 3.26

Other cross coupling conditions were also tried. Heck coupling between **404** and 10 equivalents of styrene gave **409** , albeit in poor yields (13%) (Scheme 3.27).



Scheme 3.27

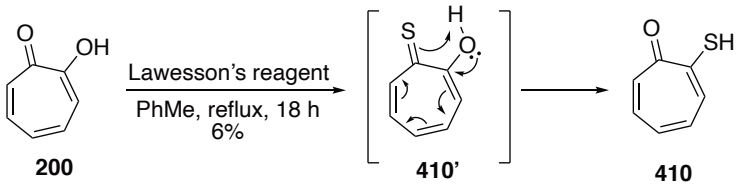
Finally, palladium-catalysed cyanation[31] towards **395** from **404** was attempted, but no product material was obtained after 18 hours of heating at reflux (Scheme 3.28). Similarly, Ir/Pd photoredox catalysis[32] to install a carboxylic acid (**396**) under an atmosphere of carbon dioxide was attempted, but was also unsuccessful (Scheme 3.28).



Scheme 3.28

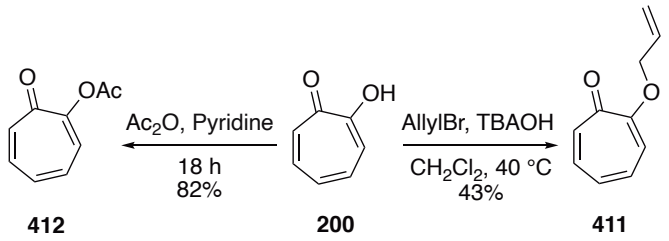
3.3.1.3 Miscellaneous Syntheses

It was envisaged that 2-mercaptotropone (**410**) could be accessed via reaction of **200** with Lawesson's reagent, whereby tautomerisation to the thiol form (**410'**) would take place rapidly to yield **410**. Indeed, reaction of **200** with two equivalents of Lawessons reagent gave **410**, albeit in poor yield (6% yield) (Scheme 3.29).



Scheme 3.29

Finally, following literature procedures, tropolone derivatives **411**[33] and **412**[34] could be isolated in good yields (Scheme 3.29).



Scheme 3.30

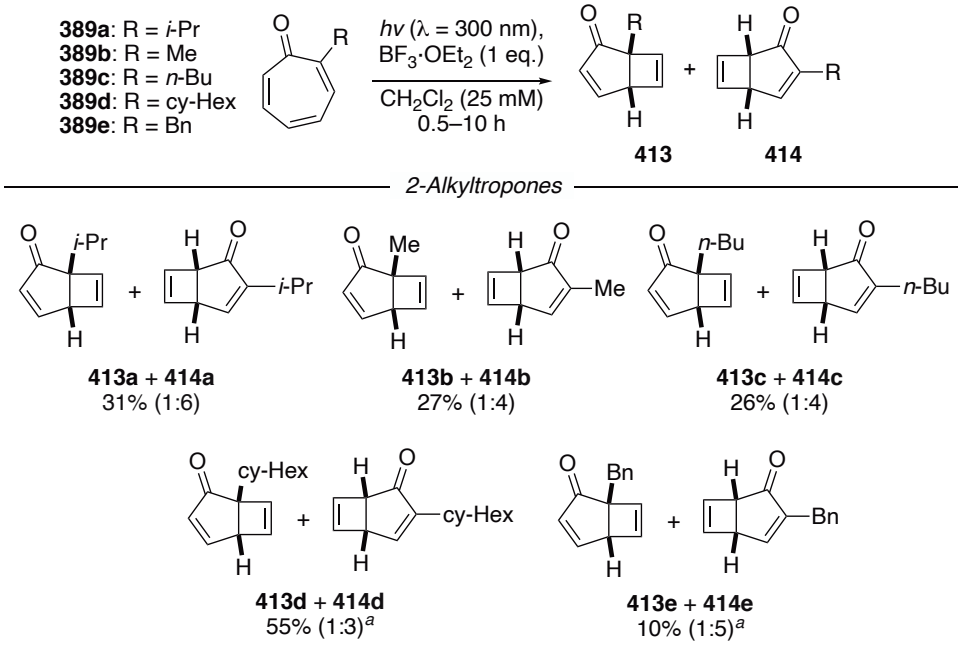
In summary, various approaches were tested for the introduction of substituents at the 2 position on tropone, including nucleophilic addition to tropone, followed by oxidation, addition-elimination sequences on tropones bearing a leaving group at the 2 position, and cross-coupling approaches. Whilst some of these reactions were more successful than others, the focus was on generating a range of 2-substituted tropones to enable a photochemical study. Therefore, further optimisation of poorly-performing reactions was not prioritised if enough material was obtained to continue with the photochemical study.

3.3.2 Photochemistry of 2-Substituted Tropones

With a range of 2-substituted tropones in hand, attention was turned to their photochemistry. For the sake of convenience, the nomenclature outlined by Chapman and Pasto to describe the outcome of tropolone photoreactions will be used in this section. Thus, those photoproducts bearing the substituent on the bond-forming carbon are referred to as the type B isomer, and for the alternate case will be type C. All reactions were performed in a Rayonet batch photoreactor, using a similar set up as described for the transformation of **194** to **199**.

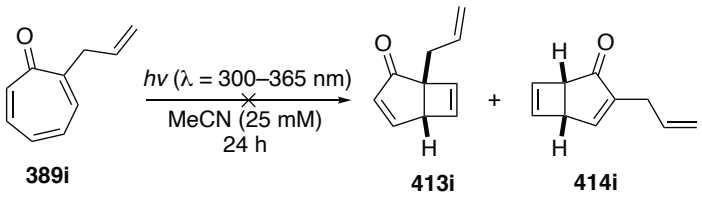
3.3.2.1 Alkyl Substituents

Alkyltropones **389a**-**e**, **389i** were subjected to the conditions optimised for tropone **180** in Chapter 2, to give the bicyclic photoproducts as mixtures of regioisomers **413a**–**e** and **414a**–**e** in low to moderate yields (10–55%).[35] Similar to **180**, irradiation in the absence of $BF_3{\cdot}OEt_2$, led to starting material being recovered largely unchanged.



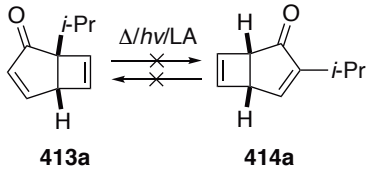
Scheme 3.31: [a] Performed in MeCN.

Although 2-allyltropone (**389i**) was consumed under these conditions, no peaks corresponding to **438** or **439** were observed by ^{1}H NMR spectroscopy in the crude material – instead large quantities of non-specific degradation were obtained (Scheme 3.32). Considering the use of 300 nm light causes this decomposition, lower energy longer wavelengths (λ = 350, 365 nm) reactions were attempted, but **395** failed to react under these conditions.



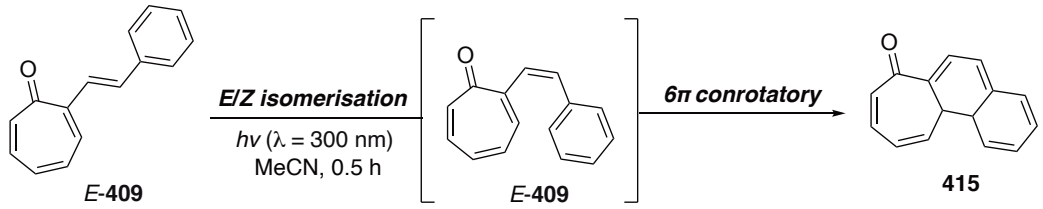
Scheme 3.32

The type C isomers were formed as the favoured product in these examples, and upon increasing the size of the alkyl group, led to larger quantities of the type B isomer. The mixtures obtained were often inseparable by column chromatography, hence another optimisation study was performed in order to alter the product distribution. To that end, a mixture of **413a** and **414a** obtained after irradiation of **389a** was subjected to mild heating (50 °C), irradiation at 300 nm and stirring with one molar equivalent of $BF_3{\cdot}OEt_2$, none of which led to any change in the distribution of products by ^{1}H NMR spectroscopy (Scheme 3.33). Potential interconversion between the two isomers under the reaction conditions therefore seems unlikely. Next, the parameters of the reaction were investigated. The reaction solvent was limited to acetonitrile and dichloromethane due to similar solubility issues of the **389a**$\cdot BF_3$ complex in other solvents. Irradiation in acetonitrile led to similar conversions, but no significant difference in the ratio of **413a**:**414a**. Finally, irradiation of **389a** at 254 nm in a quartz vessel led to regioisomer **414a** being obtained exclusively, albeit in low yields (7%). The lack of regioisomer **413a** most likely arises from its rapid decomposition at 254 nm, rather than a selective formation of **414a**.



Scheme 3.33

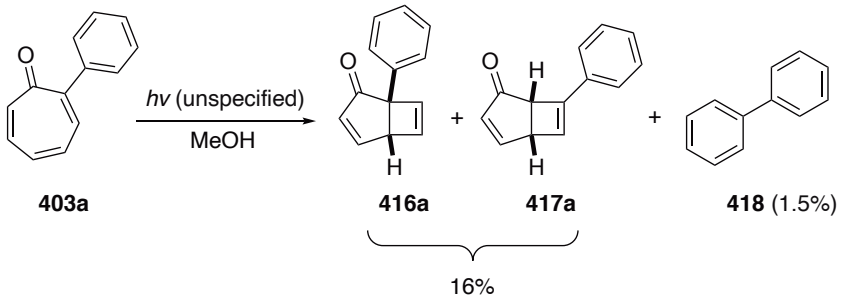
From **409**, no [3.2.0]bicycle was formed, and instead another reaction took place, likely a competing 6-π-photocyclisation preceded by *E*/*Z* isomerisation to give tricycle **440** (Scheme 3.34). However, due to the very limited quantities of the starting material, this product was only observed in NMR studies, and further work is required to isolate and fully characterise the product.



Scheme 3.34

3.3.2.2 (Hetero)Aryl Substituents

2-Phenyltropone (**410a**) is known to undergo slow 4-π-photocyclisation in neutral media to **416a**, followed by a similar rearrangement upon extended irradiation as seen in tropolone systems to yield rearranged [3.2.0]bicycle **417a** (Scheme 3.34).[2] In addition, biphenyl (**418**) may be obtained in low quantities from a competing type A cyclisation.



Scheme 3.35

Indeed, slow cyclisation to yield **416a** occurred upon irradiation of **410a** in acetonitrile at 300 nm, along with the concomitant rearranged product **417a**, which were inseparable by flash column chromatography. Another optimisation study was carried out to investigate whether reaction times could be decreased or not, and if suppression of the secondary rearrangement was possible. Reactions in methanol, acetonitrile, and dichloromethane all gave comparable yields, with methanol performing slightly better in terms of secondary product suppression (Table 3.4, entries 1–3). Reactions in diethyl ether and TBME only furnished traces of **416a** and **417a** after 24 hours of irradiation (entries 4 and 5) whereas no reaction occurred in toluene. Another theory which required examination was that formation of **416a** proceeds via a triplet pathway, and that a slow rate of intersystem crossing to the triplet state was responsible for the slow rate of reaction observed. Performing the irradiation in acetone, as both reaction solvent and as a triplet sensitiser led to no product formation — thus, a potential triplet pathway seem unlikely. Methanol was selected as the optimal solvent for this reaction. Next, decreasing the concentration to 10 and 5 mM (entries 7 and 8) led to a slight increase in reaction times, although more degradation occurred at lower concentrations. Finally, the choice of wavelength was altered. As seen in Figure 3.3, the UV/Vis spectrum contains two distinct peaks at 224, 318 and a small peak at 360 nm, although it is unclear whether the latter real or may be attributed to noise.

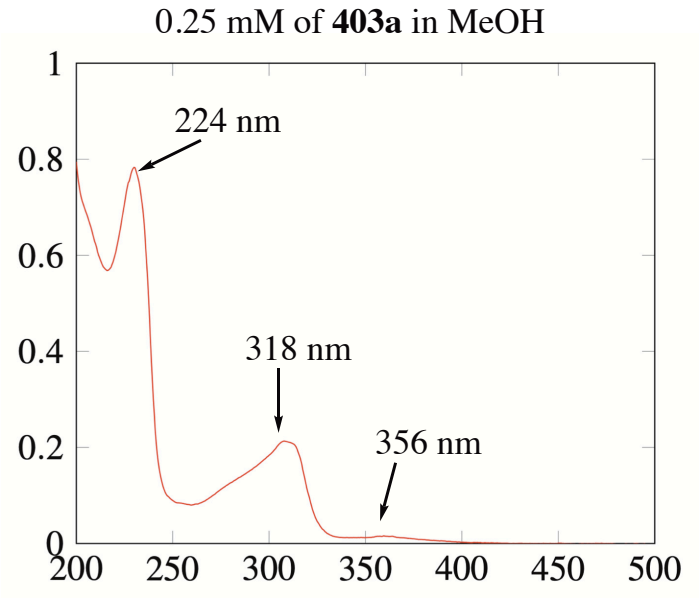
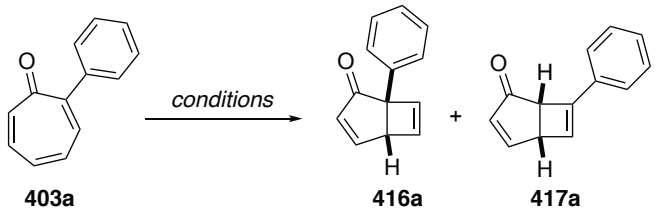


Figure 3.4

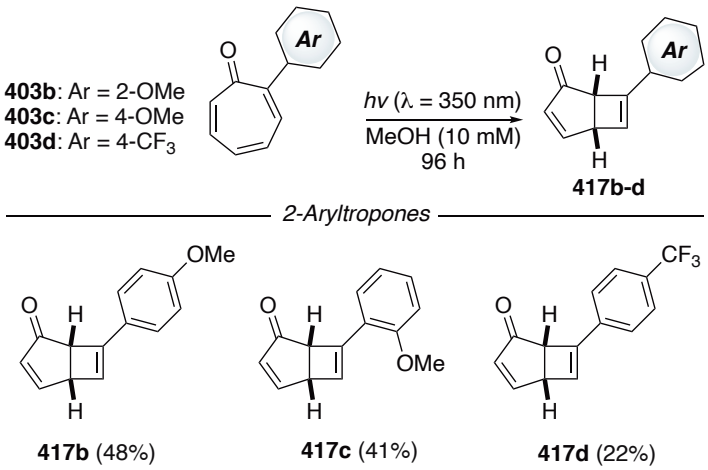
Changing to shorter wavelengths (254 nm) led to no 4-π-photocyclisation occurring, and at 350 nm, the reaction was found to proceed at a slightly faster rate, leading to an improved yield of 27% for **416a** and **417a** (entry 10). Even after optimisation, concomitant formation of **417a** was unavoidable if the reaction was allowed to fully react. Hence, it was decided to allow the side reaction to occur, and it was possible to isolate **417a** in 46% yield after 96 hours of irradiation, with no starting material present in the crude ^{1}H NMR spectrum. It should be noted however, that the very slow reaction and requirement for very dilute solutions does limit the amount of material that can be processed.

Electron-donating substituents on the phenyl ring did not influence the yield or reaction time significantly (*o*- and *p*-methoxy groups, **411**–**412**). A *p*-trifluoromethyl substituent (**414**) gave poorer results (Scheme 3.36).



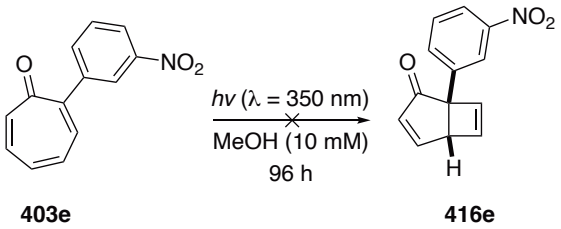
Entry	Solvent	λ (nm)	Conc. (mM)	Time (h)	Yield (%) (**416a**:**417a**)[a]
1	MeOH	300	25	24	14 (6:1)
2	MeCN	300	25	24	13 (4:1)
3	DCM	300	25	24	8 (4:1)
4	Et_2O	300	25	24	traces
5	TBME	300	25	24	traces
6	PhMe	300	25	24	0
7	MeOH	300	5	24	13 (6:1)
8	MeOH	254	10	24	0
9	MeOH	350	10	24	27 (4:1)
10	MeOH	365	10	24	traces
11	MeOH	350	10	96	46[b]

Table 3.4: [a] Calculated by comparison of product peaks in crude ^{1}H NMR spectrum. [b] **417a** obtained as sole regioisomer.



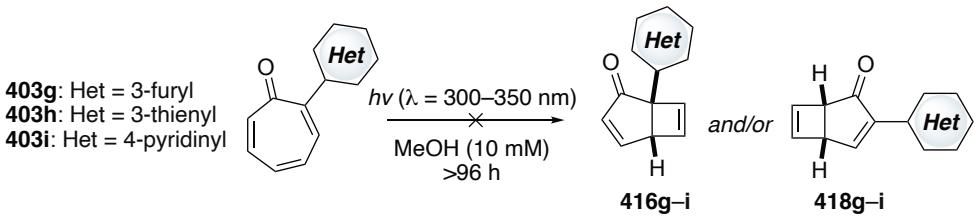
Scheme 3.36

Next, an *m*-nitro group (**403e**) did not result in any 4-π-photocyclisation, most likely due to excitation of the NO_2 group, resulting in decomposition (Scheme 3.37).



Scheme 3.37

Whilst heteroaryl species **403g–i** absorb light at around 350 nm, no 4-π-photocyclisation occurred under the optimised conditions for **403a**, and instead returned starting material in all three cases (Scheme 3.38). Longer wavelengths (λ = 365–419 nm) were also unsuccessful at generating the desired products.

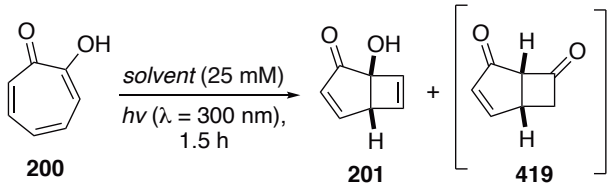


Scheme 3.38

3.3.2.3 Tropolone and Tropolone Derivatives

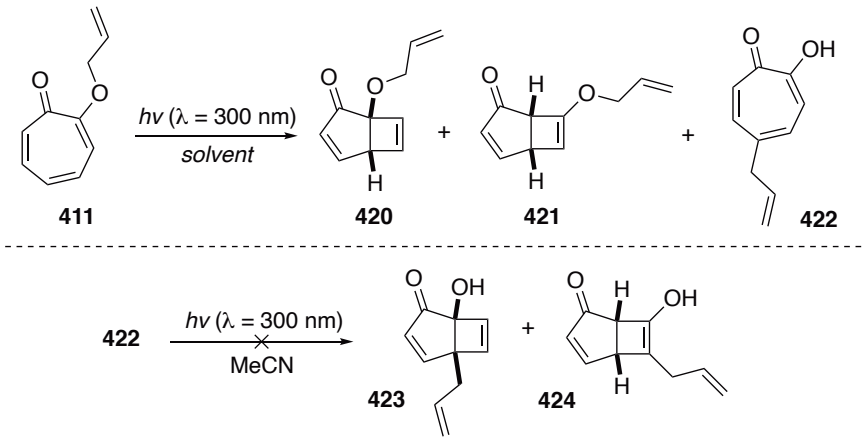
The photoreactivity of tropolones and tropolone ethers in the absence of a Lewis acid have been investigated previously. Generally, the first formed photoproduct will undergo rearrangement under the irradiation conditions resulting in a second photoproduct. Whilst homogenous samples of the initial type B photoproduct may be obtained by simple extension of the reaction time to ensure **200** is fully converted,

obtaining pure **201** is more challenging, and has only been demonstrated on a small scale. Further investigation into the suppression of **419** formation is thus required. After comparison of the crude products obtained after irradiation of **200** at 300 nm in various solvents by ^{1}H NMR spectroscopy, it was found that secondary rearrangement from **201** was most suppressed when using TBME as the solvent (Scheme 3.39). This may be attributed to a slight bathochromic shift to longer wavelengths than in other solvents. Performing the reaction at longer wavelength (λ= 350 nm) increased the rate of **201** formation, whereas shorter wavelengths (λ = 254 nm) led to significant degradation alongside cyclisation.



Scheme 3.39

For allyl ether **411**, a competing 1,5-allyl shift leading to 5-allyltropolone **422** as the major product, occurred on the same timescale as 4-π-photocyclisation (Scheme 3.40). After a short solvent screen (MeCN, MeOH), methanol showed the best activity in suppressing formation of **422**, resulting in **420** being formed as the major product. The inadvertent formation of **422** also allowed insight into the reactivity of a 5-substituted tropolone. Upon prolonged irradiation of the reaction mixtures, neither photoproduct **423** nor **424** were observed, and again when pure samples of **422** were irradiated in acetonitrile at 300 nm.

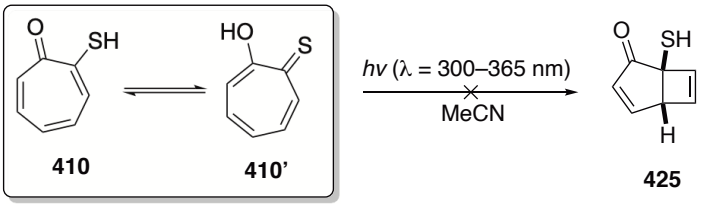


Entry	Solvent	Yield 420 (%)	Yield 421 (%)	Yield 422 (%)
1	MeCN	7	traces	30
2	MeOH	45	traces	traces

Table 3.5

3.3.2.4 Thiotropolone

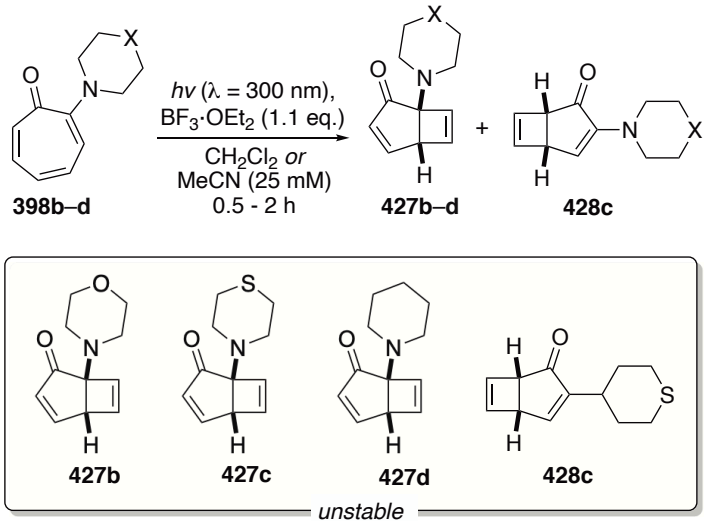
Thiol **410** was irradiated at a variety of different wavelengths (λ = 300–365 nm) but did not undergo cyclisation (Scheme 3.40). This lack of reactivity can either be attributed to tautomer **410'** being favoured in equilibrium, which does not undergo cyclisation when irradiated, or from a fast intersystem crossing upon excitation to the triplet state that eventually leads to decay back to starting material.[8]



Scheme 3.40

3.3.2.5 2-Aminotropones

2-Aminotropone (**392**) was able to undergo 4-π-photocyclisation, being fully converted to bicycle **426** in just under three hours (Figure 3.5). Despite clean conversion being observed by ^{1}H NMR spectroscopy using solvent suppression, the product was unstable upon concentration and hence could not be isolated and fully characterised. Whilst irradiation of solutions of 2-aminotropones **398a–d** did not afford bicyclic isomers, their reactivity could be switched in the presence of $BF_3{\cdot}OEt_2$ exclusively, although benzhydryl derivative **398a** did not react under either set of conditions (Scheme 3.41). However, much like **392**, whilst formation of bicycles **398b–d** was observed by ^{1}H NMR spectroscopy of the reaction mixture these products could not be isolated on removal of the reaction solvent. For **398c**, small quantities of the type C isomer were also obtained (Figure 3.4). Although unlikely due to their significantly higher molecular weight, it was considered that **b**-**d** and **428** were co-evaporating with the reaction solvent, as seen in **199**. These [3.2.0]bicycles containing an amino group were similarly unstable under ambient conditions, hence purification and isolation was abandoned.



Scheme 3.41

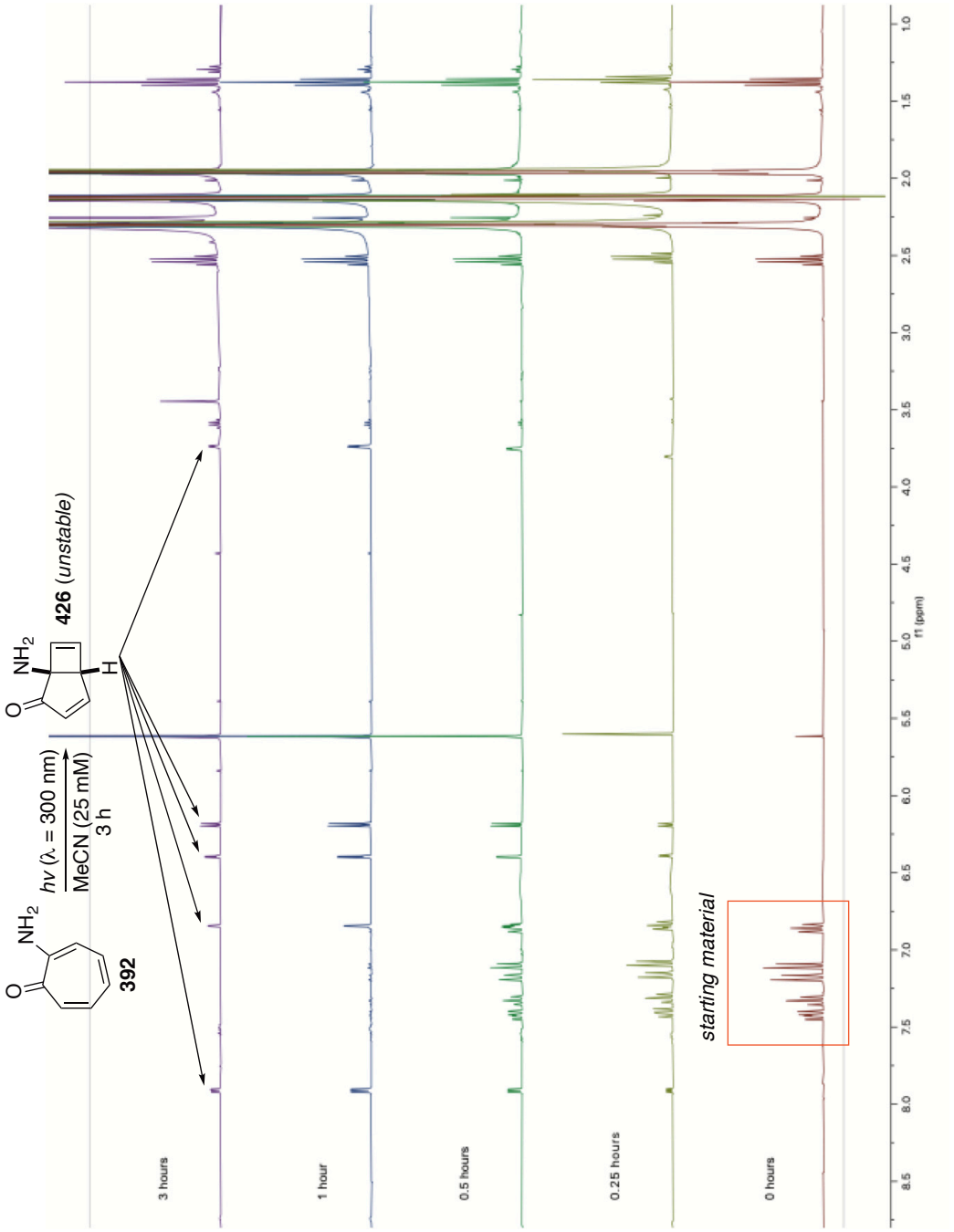

NH2
O
392
hν (λ = 300 nm)
MeCN (25 mM)
3 h
NH2
O
H
426 (unstable)
3 hours
1 hour
0.5 hours
0.25 hours
0 hours
starting material
f1 (ppm)

Figure 3.5

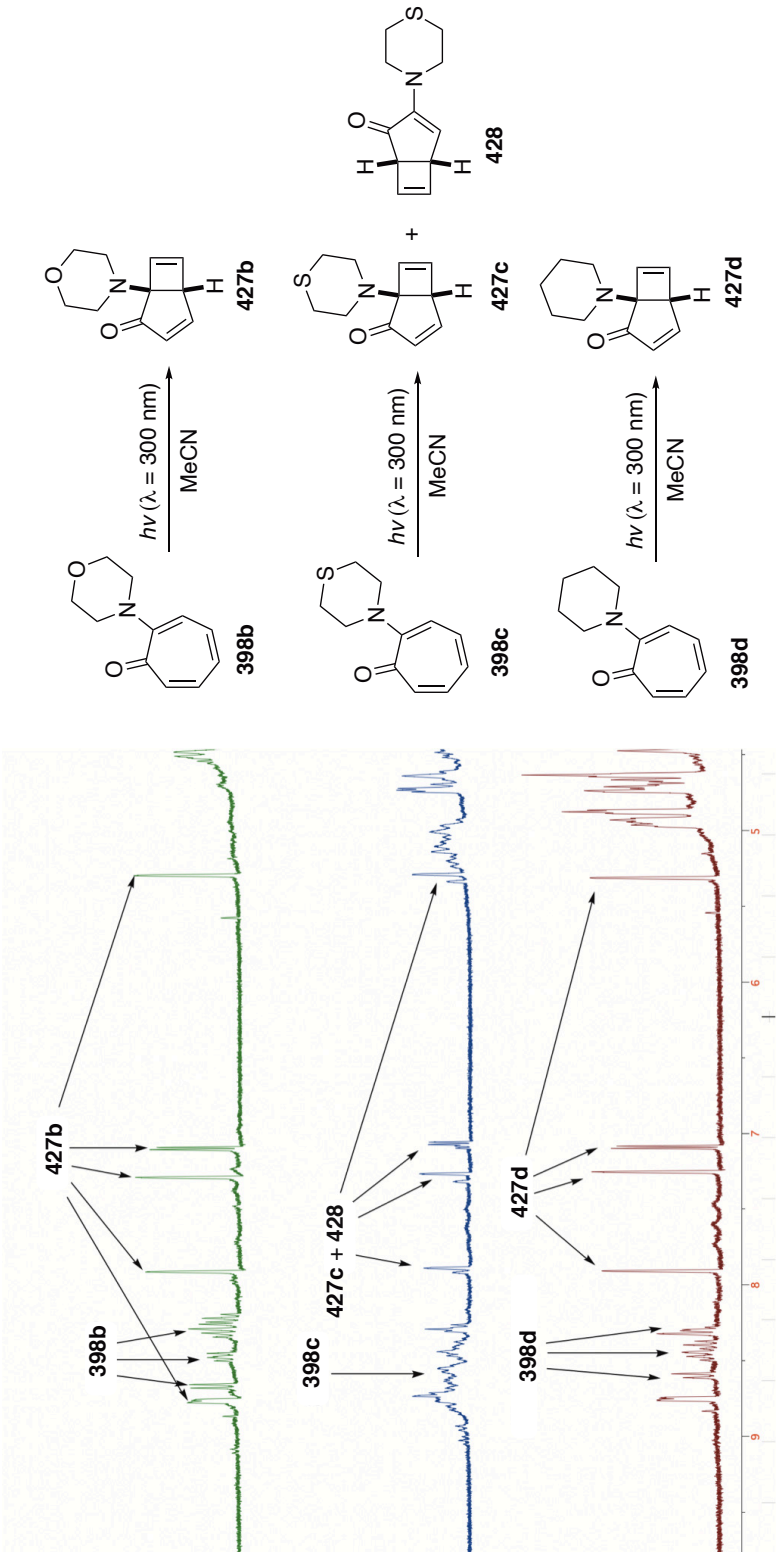
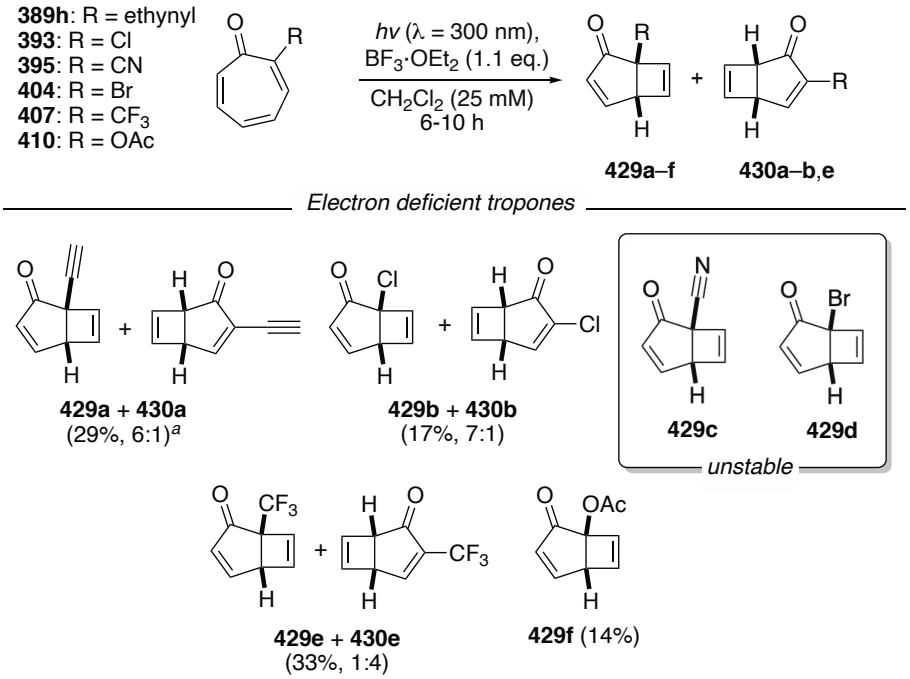

hν (λ = 300 nm)
MeCN
398b
427b
398c
427c
428
398d
427d
427b
398b
427c + 428
398c
427d
398d

Figure 3.6

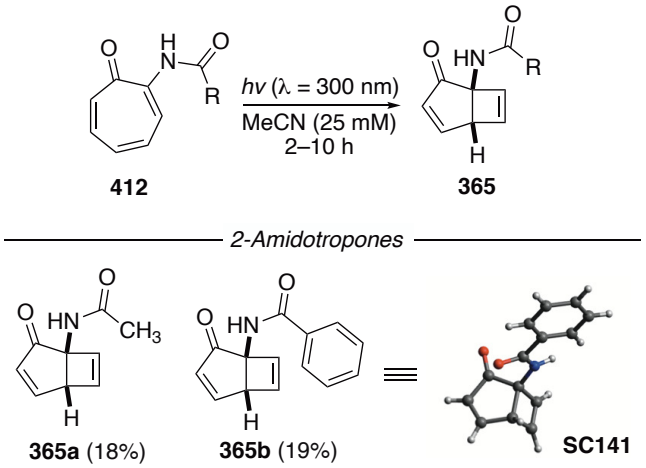
3.3.2.6 Electron-Deficient Troponoids

Several tropones bearing electron-withdrawing/conjugating species were next examined. Thus, tropones **389h**, **393**, **395** , **404**, **407** and **410** were subjected to the conditions found for **194** (Scheme 3.42). Generally, longer reaction times were required (6–10 hours) to afford the [3.2.0]bicycles in low to moderate yields. For tropones **389h**, **393** and **407**, mixtures of regioisomers were formed – in these cases, the minor constituents were not formed in large enough quantities to obtain sufficient quality data, and hence only data for the major constituents are reported. The irradiation of **389h** benefitted from irradiation at lower concentration (10 mM), as significant fouling of the reaction vessel occurred at 25 mM which led to a drastic cut-off in conversion. Whilst formation of **429c** and **429d** was observed *in situ* by ^{1}H NMR spectroscopy of the reaction mixture, significant decomposition occurred, and the corresponding products could not be isolated. Irradiation of **395** and **404** at lower energy, longer wavelengths (λ = 350 nm) led to similar decomposition, hence it was assumed that these products are unstable under ambient conditions, and their isolation and characterisation was abandoned. In the case of **429d**, it is likely that the bromine substituent, as a heavy atom, will increase the rate of intersystem crossing from the singlet to the triplet excited state due to significant spin-orbit coupling. As these 4-π-photocyclisation are thought to be singlet-mediated, the bromine substituent may well interfere with the desired reaction, leading to poor yields of the phototropone product, as observed.



Scheme 3.42: [a] Performed at 10 mM.

2-Amidotropones **412** are known to undergo regioselective 4-π-photocyclisation to yield bicycles **365a**–**b** as crystalline solids, in addition to their rearranged products **365a**-**b** (Scheme 3.43). Indeed, performing the irradiation of **412** led to bicycles **342** and **343**, which were stable indefinitely at room temperature, air, and ambient light, as opposed to products **427** and **428**. Gratifyingly, crystals of **365b** of suitable quality could be grown for X-ray diffraction studies, providing unambiguous evidence for the [3.2.0]bicycloheptadienone motif obtained in this reaction, and for others in the series.



Scheme 3.43

3.3.3 Computational Studies

It was hoped that an understanding of the transformation of **200** to **201** could be gained by studying the reaction computationally.

3.3.3.1 Conical Intersections

A conical intersection is a point where two or more adiabatic energy surfaces are degenerate and the non-adiabatic coupling tends to infinity.[36] Here, ultrafast radiationless decay from the upper state to a lower state is possible, often occuring within one vibrational period. The degeneracy of the conical intersection point may be lifted by movement in the direction of the branching plane, which comprise two vectors – the difference of energy gradient vectors of the two intersecting electronic energy states g and the non-adiabatic coupling vector h. Movement in this plane gives rise to the characteristic double cone that lends itself to 'conical intersection' (Figure 3.7). Conical intersections are ubiquitous in polyatomic systems. In such systems, they are not single points, but multidimensional seams, and are responsible for mediating many photochemical and photophysical processes. Minima on these seams, referred to as minimum energy conical intersections (MECI) can be calculated using a variety of available quantum chemistry codes, including Gaussian-09,[37] GAMESS,[38] Molcas and OpenMolcas.[39]

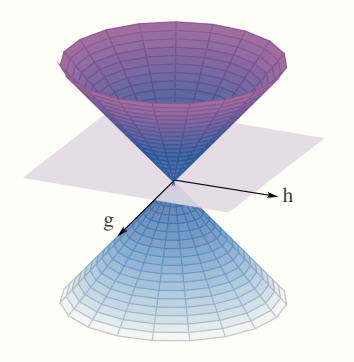


Figure 3.7

Of the multitude of methods available to calculate the properties of conical intersections in polyatomic systems, multireference methods often provide the most accurate results.[40] Arguably the most widely used of these are multiconfigurational self consistent (MC-SCF), in particular, the complete active space self consistent field variant (CASSCF). Here, the orbitals of a particular system are separated into three subsets – the inactive (or frozen), active, and virtual spaces. Within the active space, the full configuration interaction (FCI) problem is solved, capturing static correlation energy that is pertinent in the study of excited states (Figure 3.8). However, CASSCF is limited only to moderate sized systems (18 electrons in 18 orbitals is generally considered by most to be the upper size-limit)[41], and also fails to capture the dynamic correlation energy contribution to the overall energy, and hence a correction is often made using multireference pertubation theory (MRPT) methods, such as complete active space pertubation theory (CASPT2)[42] and n-electron valence state pertubation theory (NEVPT2).[43] Thus, the combined MCSCF/MRPT approach is a useful strategy for the calculation of conical intersections in small to medium sized polyatomic systems, and is often used as benchmark for which other computational methods are compared to.[44] As such, there exists an astronomical number of these methods being employed in the elucidation of photochemical mechanistic pathways.[45–49] Indeed, single reference methods, including time-dependant density functional (TDDFT) and its spin flip variant (SF-TD-DFT)[50] have been utilised in such studies, but often give inconsistent and inaccurate results and are thus unreliable.[51]

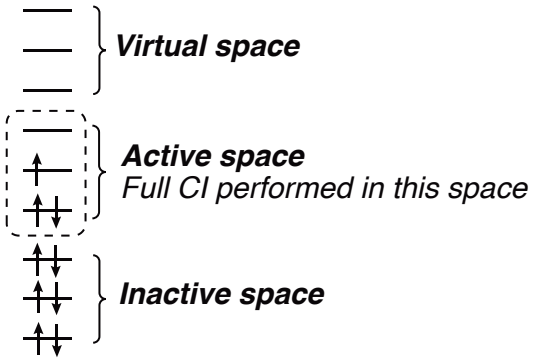


Figure 3.8

An MECI between an excited state and the ground state of **200** that corresponds to 4-π-photocyclisation was sought. The complete active space self consistent field (CASSCF) method, in conjunction with second order pertubation theory was used for this study, which is the one of the most frequently used quantum chemical approaches for excited states.[52,53] The active space was composed of the three C=C π/π^* orbitals, and the two lone pairs, leading to a CASSCF(10,8) calculation, starting from a geometry calculated at the CAM-B3LYP/cc-pvdz level of theory.[†] Due to limitations in computing resources, a larger active space was not feasible, although in theory would give more accurate energies. However, the active space selected was deemed a suitable size for this study. Steer and co-workers[54] identified the the four lowest excited singlets of **200** in condensed media. Thus, the S_1 and S_4 states relate to a π-π^* transition and an n-π^* transition, with reasonable oscillator strengths, and S_2 and S_3 relate to two other π-π^* transitions, with smaller oscillator strengths. Given its large oscillator strength, and based on Kasha's rule that photochemical reactions are more likely to take place from the first excited state,[55] the search for a conical intersections was limited to the first excited state. Indeed, excitation Starting from the ground state geometry, a conical intersection on the first excited state was sought. The branching plane updating method implemented in GAMESS was used in this search. A conical intersection with distorted planarity was found

[†]Coordinates for structures detailed in this section are available for download from GitHub: https://github.com/jack-lowe/phototropolone_coordinates

(**200-MECI-1**, Figure 3.9), which most likely results in reformation of starting material at the ground state. Thus, the molecule was manually distorted along the reaction coordinate and a new search was begun from this structures, maintaining the CASSCF(10,8) active space. Pleasingly, another MECI possessing significant distortion along the reaction coordinate was discovered (**200-MECI-2**).

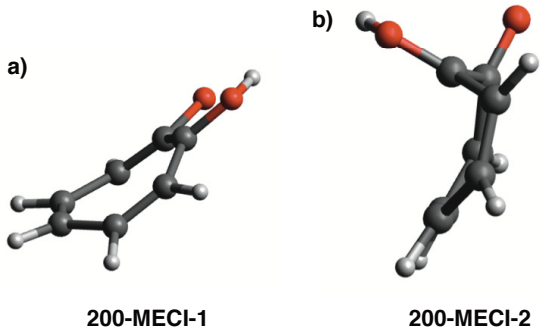


Figure 3.9

A linear interpolation of internal coordinates (LIIC) plot from tropolone, through **MECI-200-2** to **201** was calculated at the CASSCF(10,8)-cc-pvdz/CASPT2 level of theory, averaged over the lowest four singlet states. Whilst 0.05 eV lower than the S_1 Franck-Condon point, it is precluded by a barrier of around 0.5 eV, which is expected to be overcome at room temperature. Attempts at locating a transition state for this barrier were unsuccessful. Thus, a plausible mechanism resulting in formation of **201** is summarised in Figure 3.10. Excitation to the first excited singlet state takes place to the FC geometry on S_1. Here, the excited state may decay via two pathways – i) unproductive decay through **200-MECI-1** takes place to return starting material, or ii) the barrier precluding **200-MECI-2** is overcome, and decay through this conical intersection results in photoproduct formation. More sophisticated computational approaches, such as investigation into non-adiabatic dynamics using SHARC,[56] are required to gain a better understanding of the photodynamics of this system,

but are out of the scope of this study. Nevertheless, a more detailed understanding of the transformation of **200** to **201** was gleaned, and will provide the basis into investigations into other tropone systems, as well as the possible development of enantioselective variants.

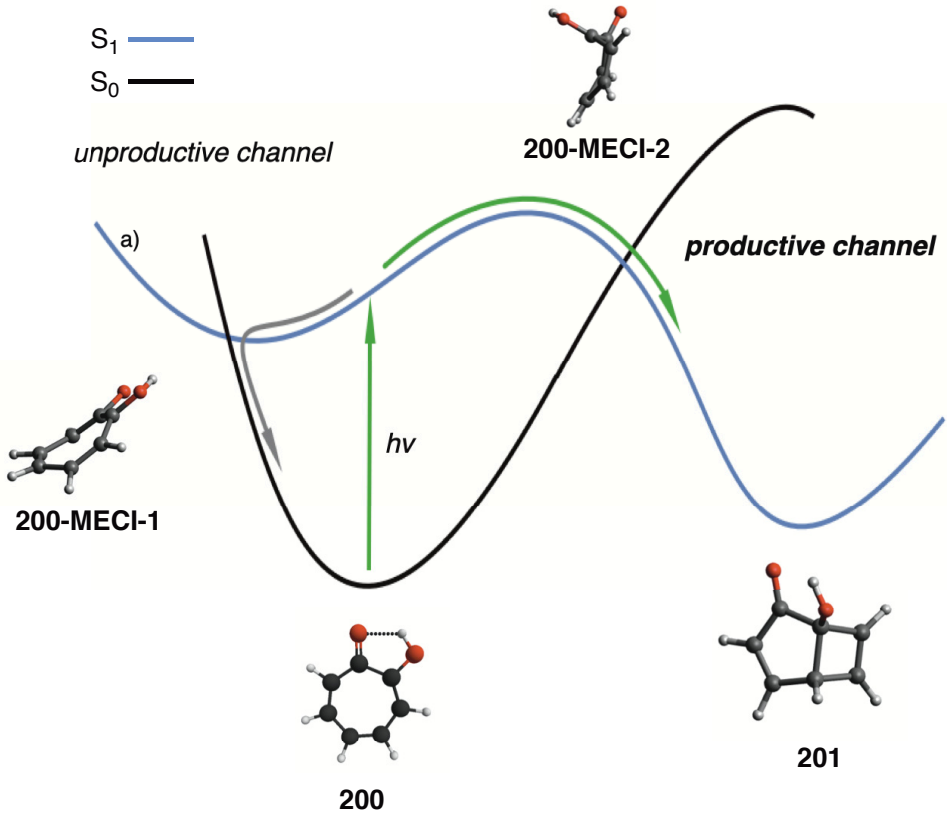


Figure 3.10

3.4 Conclusions

The photoreactivity of a series of tropones bearing a range of different substituents at the 2-position were investigated, after their synthesis from various precursors. The identity of the substituent was found to heavily influence the photoreactivity of the tropone substrate. For example, 2-alkyltropones produced mixtures of regioisomers in low to moderate yields upon irradiation using the conditions optimised for tropone (Chapter 2), with a bias towards the type C regiosomer. These mixtures were difficult to separate, and reoptimisation studies to improve the yields and regioselectivities were unsuccessful. Under similar conditions, aryl-substituted tropones were photostable and did not undergo rearrangement. Performing the irradiations in the absence of $BF_3{\cdot}OEt_2$ led to slow photoisomerisation occurring, alongside rearrangement products. There were no observable acceleratory effects when various substitution patterns were explored. The photochemistry of **188** was explored in the laboratory, obtaining improved selectivity for the initially formed photoproduct from previous studies. Aditionally, the transformation of **200** to **201** was explored computationally, gaining insight into the reaction pathway. 2-Aminotropones were able to undergo photocyclisation, but the products were unstable upon concentration and could not be isolated. Finally, the photochemistry of several tropones bearing electron-withdrawing groups was examined, obtaining several novel [3.2.0]bicycles.

In total, 19 [3.2.0]bicyclic compounds could be isolated out of 28 tropone starting materials using a Rayonet batch photoreactor, 15 of which were novel. No obvious trends could be identified across the different functionalities of 2-substituted tropones despite a wide variety of optimisation attempts.

References

[1] Mukai, T.; Miyashi, T. *Tetrahedron* **1967,** *23,* 1613–1620.

[2] Mukai, T.; Shishido, T. *J. Org. Chem.* **1967,** *32,* 2744–2749.

[3] Mukai, T.; Kimura, M. *Tetrahedron Lett.* **1970,** *11,* 717–720.

[4] Carreño, M. C.; Sanz-Cuesta, M. J.; Ribagorda, M. *Chem. Commun.* **2005,** 1007–1009.

[5] Grewe, R.; Wulf, W. *Chem. Ber.* **1951,** *84,* 621–625.

[6] Forbes, E. J. *J. Chem. Soc.* **1955,** *0,* 3864–3870.

[7] Chapman, O. L.; Smith, H. G. *J. Am. Chem. Soc.* **1961,** *83,* 3914–3916.

[8] Bussotti, L.; Cacelli, I.; D'Auria, M.; Foggi, P.; Lesma, G.; Silvani, A.; Villani, V. *J. Phys. Chem. A* **2003,** *107,* 9079–9085.

[9] Croteau, R.; Leblanc, R. M. *Photochem. Photobiol.* **1978,** *28,* 33–38.

[10] Collington, E. W.; Jones, G. *J. Chem. Soc.* **1969,** *0,* 2656–2661.

[11] Forbes, E. J.; Ripley, R. A. *J. Chem. Soc.* **1959,** 2770.

[12] Forbes, E. J.; Griffiths, J. *J. Chem. Soc.* **1966,** *0,* 2072–2075.

[13] Forbes, E. J.; Griffiths, J.; Ripley, R. A. *J. Chem. Soc.* **1968,** 1149.

[14] Chapman, O. L.; Pasto, D. J.; Griswold, A. A. *J. Am. Chem. Soc.* **1962,** *84,* 1213–1219.

[15] Nozoe, T.; Mukai, T.; Tezuka, T. *Bull. Chem. Soc. Jpn.* **1961,** *34,* 619–622.

[16] Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002,** *124,* 2245–2258.

[17] Bartolo, N. D.; Woerpel, K. A. *J. Org. Chem.* **2018,** *83,* 10197–10206.

[18] Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976,** *5,* 941–942.

[19] Saito, K.; Kojima, H. *Bull. Chem. Soc. Jpn.* **1985,** *58,* 1918–1921.

[20] Asao, T.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* **1966,** *39,* 2538–2541.

[21] Ohtsu, K.; Hayami, R.; Sagawa, T.; Tsukada, S.; Yamamoto, K.; Gunji, T. *Tetrahedron* **2019,** *75,* 130658.

[22] Mukai, T.; Kimura, M. *Tetrahedron Lett.* **1970,** *11,* 717–720.

[23] von E. Doering, W.; Hiskey, C. F. *J. Am. Chem. Soc* **1952,** *74,* 5688–5693.

[24] Li, M.; Wang, D.-H. *Org. Lett.* **2021,** *23,* 6638–6641.

[25] Miyano, H.; Nitta, M. *Tetrahedron Lett.* **1988,** *29,* 4723–4726.

[26] Ononye, S. N.; VanHeyst, M. D.; Oblak, E. Z.; Zhou, W.; Ammar, M.; Anderson, A. C.; Wright, D. L. *ACS Med. Chem. Lett.* **2013,** *4,* 757–761.

[27] Cavazza, M.; Pietra, F. *Synth. Commun.* **1997,** *27,* 3405–3413.

[28] Cavazza, M.; Pietra, F. *Tetrahedron Lett.* **2004,** *45,* 3633–3634.

[29] Mukai, T. *Bull. Chem. Soc. Jpn.* **1958,** *31,* 846–852.

[30] Clarke, S. L.; McGlacken, G. P. *Chemistry* **2017,** *23,* 1219–1230.

[31] Zhang, X.; Zhang, F.; Li, X.; Lu, M.-Z.; Meng, X.; Huang, L.; Luo, H. *Org. Lett.* **2022,** *24,* 5029–5033.

[32] Shimomaki, K.; Murata, K.; Martin, R.; Iwasawa, N. *J. Am. Chem. Soc.* **2017,** *139,* 9467–9470.

[33] Kumar, N. R.; Agrawal, A. R.; Choudhury, A.; Zade, S. S. *J. Org. Chem.* **2020,** *85,* 9029–9041.

[34] Lyons, D. J. M.; Empel, C.; Pace, D. P.; Dinh, A. H.; Mai, B. K.; Koenigs, R. M.; Nguyen, T. V. *ACS Catal.* **2020,** *10,* 12596–12606.

[35] Cavazza, M.; Cimiraglia, R.; Persico, M.; Zandomeneghi, M.; Pietra, F. *J. Photochem. Photobiol. A* **1991,** *61,* 329–342.

[36] Yarkony, D. R. *J. Phys. Chem. A* **2001,** *105,* 6277–6293.

[37] Frisch, M. J. *et al.* "Gaussian~16 Revision C.01", 2016 Gaussian Inc. Wallingford CT.

[38] Barca, G. M. J. *et al. J. Phys. Chem.* **2020,** *152,* 154102.

[39] Aquilante, F. *et al. J. Phys. Chem.* **2020,** *152,* 214117.

[40] Park, J. W.; Al-Saadon, R.; MacLeod, M. K.; Shiozaki, T.; Vlaisavljevich, B. *Chem. Rev.* **2020,** *120,* 5878–5909.

[41] Townsend, J.; Kirkland, J. K.; Vogiatzis, K. D. Post-Hartree-Fock methods: configuration interaction, many-body perturbation theory, coupled-cluster theory. In *Mathematical Physics in Theoretical Chemistry*; Elsevier: 2019.

[42] Serrano-Andrés, L.; Merchán, M.; Lindh, R. *J. Chem. Phys.* **2005,** *122,*.

[43] Angeli, C.; Cimiraglia, R.; Evangelisti, S.; Leininger, T.; Malrieu, J.-P. *J. Chem. Phys.* **2001,** *114,* 10252–10264.

[44] Hill, N. S.; Coote, M. L. A comparison of methods for theoretical photochemistry: Applications, successes and challenges. In *Annu. Rep. Comput. Chem.*; Elsevier: 2019.

[45] Su, M.-D. *RSC Advances* **2017,** *7,* 9975–9980.

[46] Soto, J.; Otero, J. C.; Avila, F. J.; Peláez, D. *Phys. Chem. Chem. Phys.* **2019,** *21,* 2389–2396.

[47] Hammer, N.; Christensen, M. L.; Chen, Y.; Naharro, D.; Liu, F.; Jørgensen, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **2020,** *142,* 6030–6035.

[48] Peschel, M. T.; Kabaciński, P.; Schwinger, D. P.; Thyrhaug, E.; Cerullo, G.; Bach, T.; Hauer, J.; Vivie-Riedle, R. *Angew. Chemie. Int. Ed.* **2021,** *60,* 10155–10163.

[49] Jeremias, N.; Peschel, M. T.; Jaschke, C.; de Vivie-Riedle, R.; Bach, T. *J. Org. Chem.* **2022,** *88,* 6294–6303.

[50] Winslow, M.; Cross, W. B.; Robinson, D. *J. Chem. Theory Comput.* **2020,** *16,* 3253–3263.

[51] Levine, B. G.; Ko, C.; Quenneville, J.; MartÍnez, T. J. *Mol. Phys.* **2006,** *104,* 1039–1051.

[52] Schmidt, M. W.; Gordon, M. S. *Ann. Rev. Phys. Chem.* **1998,** *49,* 233–266.

[53] Lewin, M. *J. Mat. Chem.* **2008,** *44,* 967–980.

[54] Shoute, L. C. T.; MacKenzie, V. J.; Falk, K. J.; Sinha, H. K.; Warsylewicz, A.; Steer, R. P. *Phys. Chem. Chem. Phys.* **2000,** *2,* 1–9.

[55] Kasha, M. *Discuss. Faraday. Soc.* **1950,** *9,* 14.

[56] Mai, S.; Marquetand, P.; González, L. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2018,** *8,*.

Chapter 4

Conclusions and Future Work

4.1 Chapter 2

The 4-π-photocyclisation of tropone (**194**) was carried at 300 nm in acetonitrile in the presence of $BF_3{\cdot}OEt_2$, following a literature procedure and was found to give considerably lower yields than expected. This was attributed to the phototropone product (**199**) being significantly more volatile than its parent compound, and it was co-evaporating with the acetonitrile solvent upon its removal. This could be avoided by performing the reaction in a solvent with a lower boiling point. Whilst the **194**$\cdot BF_3$ complex was insoluble in most solvents screened, it was soluble in dichloromethane, giving similar conversions to acetonitrile. Other parameters of the reaction, including Lewis acid used and concentration were examined, but the initial conditions selected were maintained. Higher substrate concentrations were avoided, as this led to a thin film of degradation material collecting on the inside of the reactor tubes, slowing down the reaction significantly. A similar issue was also found upon attempting the reaction in a flow photoreactor, and was hence avoided. Nevertheless, multigram quantities of phototropone (**199**) could be isolated in under three hours by use of a batch photoreactor.

199 proved to be a useful synthetic intermediate. Epoxidation of either double bond could take place with excellent selectively by choice of epoxidising agent, to afford either epoxide (**284** or **285**) as a single diastereomer. Epoxide **284** itself

could be converted to several novel derivatives itself, including allylic alcohol **291** and morpholine derivative **294**. Surprisingly, reaction of **199** with PhI=NTs, which was expected to react on the more electron rich cyclobutene double bond instead reacted on the enone double bond to afford aziridine **287** in moderate yield and excellent diastereoselectivity. Similarly, reaction of **199** with the Chloramine T/PTAB system developed by Sharpless and co-workers was unsuccessful in aziridinating the cyclobutene double bond, instead affording **287** in trace quantities. Whilst Corey-Chaycovsky cyclopropanation afforded cyclopropane **289** in low yield, Simmons-Smith cyclopropanation was unsuccessful in generating the desired product. Diels-Alder reaction with Danishefsky's diene and [3+2] cycloaddition with *N*-benzylazomethine ylide afforded tricycles **310** and **314** in moderate yields. Photochemical cycloadditions, including an intramolecular variant between the cylobutene and enone double bond, were unsuccessful.

Regioselective additions to the enone moiety in **199** were next attempted. Reduction with sodium borohydride afforded the globally reduced alcohol **317** in moderate yields. This alcohol could be oxidised to ketone **318** in moderate yields, although this product was unstable and decomposed even when stored at –20 °C. Addition of ethynyl- and vinylmagnesium bromide gave allylic alcohols **322** and **323** in 33% and 72% yield respectively, both in excellent diastereoselectivity, although the former was unstable even when stored at –20 °C. Conversely, reaction with allylmagnesium bromide was complicated by a competing 1,4-addition, which gave a complicated mixture of products. Addition of cerium(III) chloride, to promote 1,2-addition, were unsuccessful. Michael addition with the carbanion generated from dimethyl malonate and sodium methoxide afforded **329** as a single diastereomer. α-Iodination was possible, and further cross-couplings (Suzuki-Miyaura and Sonagashira) from **330** were realised.

Whilst oxidative cleavage of the cyclobutene double bond was expected to be facile in view of its highly strained nature, this was not possible, even under forcing

conditions. Similarly, OsO_4 dihydroxylation to yield *syn*-diol **336** was not possible. Other metal catalysed oxidative cleavage systems ($KMnO_4$ and RuO_4) were similarly unsuccessful. Finally, Grubbs metathesis with ethylene gas afforded a complex mixture of products.

Overall, a convenient access to multigram quantities of **199** has been established. In addition, the synthetic potential of **199** as a precursor to a wide variety of derivatives was demonstrated with a variety of successful derivatisations developed.

4.2 Chapter 3

Next, the 4-π-photocyclisation of several 2-substituted tropones was investigated. A series of 2-substituted tropones could synthesied via 1,8-additions and metal catalysed cross coupling reactions, in varying yields. The synthesis of 2-ethynyltropone (**389h**) proved challenging, with several routes tried, although it could be synthesised by 1,8-addition of the corresponding Grignard reagent to **393**, which underwent spontaneous elimination of hydrogen chloride.The synthesis of **389i** was similarly challenging, with the 1,8-addition strategy applied to other alkyltropones unsuccessful, resulting in double addition products. Repetition of a literature procedure towards **395** gave poor yields (21%), although this method afforded enough product for further photochemical studies. **393** was a useful coupling partner in several Suzuki-Miyaura cross-coupling reactions between aryl- and heteroaryl boronic acids. Tosylate **397** proved to be a useful synthetic intermediate en route to substituted amines (**398a**–**d**), which were isolated in good yields with no column chromatography required. Application of Cavazza's conditions towards bromo- derivative **404** from **397** gave the desired product, but in extremely poor yields. Thus, bromination of **194** with NBS was identified as a better alternative, and **404** could be isolated in 45% yield. This material was only available in small quantities, so it was only used when other coupling partners failed. **404** was a useful intermediate en route to **407**, which was isolated via copper-catalysed coupling with MFSDA. Additionally, **404** underwent Suzuki-Miyaura cross-coupling with allyl boronic acid to afford **389i** in

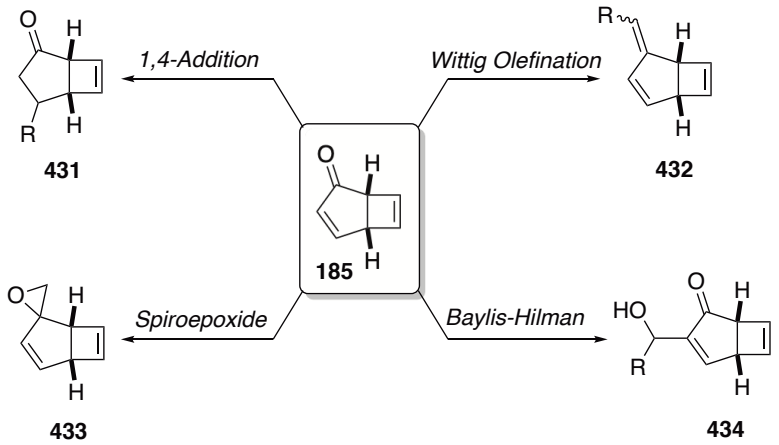
moderate yields.

With a range of 2-substituted tropones in hand, attention was turned to their photochemistry. 2-Alkyltropones (**389a–e**) reacted using the conditions established for **194**, with no reaction observed in the absence of Lewis acid. Mixtures of regioisomers were observed, resulting from competing modes of 4π-photocyclisation. **389i** did not afford bicyclic photoproducts upon irradiation, and instead gave large quantities of decomposition material. 2-Aryltropones (**403a–d**) showed similar reactivity to tropolone upon irradiation, and the addition of a Lewis acid prevented 4-π-photocyclisation from occurring. Significantly longer reaction times ($\sim$96 hours) were required for full conversion, whereby rearrangement could not be avoided. The presence of groups on the aryl ring did not lead to any noticeable acceleratory effects. On the other hand, 2-heteroaryltropones (**403g–i**) did not react under a variety of conditions tried, most likely due to a competing photophysical process. 2-Aminotropone **392** underwent clean 4-π-photocyclisation in acetonitrile, although the product was unstable and could not be isolated. Addition of cyclic amine substituents altered the reactivity such that $BF_3{\cdot}OEt_2$ was required for reaction, and although regioselective photoisomerisation occurred slowly to afford bicycles **427a–428c** and **428**, these could not be isolated.

4.3 Future Work

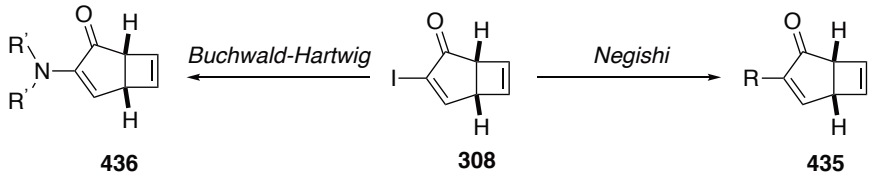
Whilst sufficient quantities of **199** could be isolated by batch reaction, further optimisation in flow photoreactors could provide significantly larger quantities of material for downstream applications that what can be obtained using batch photoreactors. Commercial flow photoreactors may not be the best choice for this reaction, as the corrosive nature of $BF_3{\cdot}OEt_2$ will likely cause damage to the reactor tubing. However, a falling film flow reactor might well be worth pursuing, since it can be constructed from glass components.

There are still many reactions that were either unsuccessful or unattempted on the enone moiety, which could provide access to other derivatives. For example, reactions with Gilman reagents (**431**), Wittig olefination (**432**), synthesis of vinyl spiro epoxides (**433**), or Baylis-Hilman reaction (**434**) (Scheme 4.1).



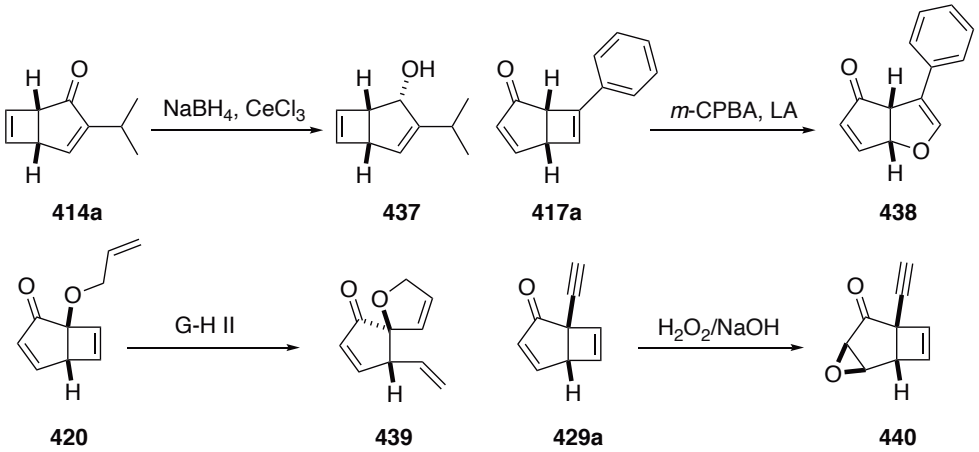
Scheme 4.1

Those derivatives of **199** that displayed synthetic utility themselves, may also be further exploited – for example, other variants of palladium-catalysed cross-couplings from α-iodo derivative **308**, including Negishi and Buchwald-Hartwig couplings (Scheme 4.2).



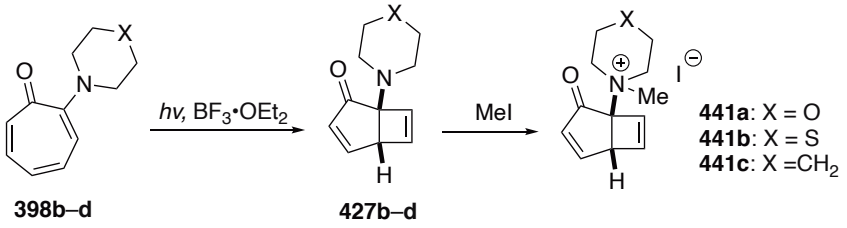
Scheme 4.2: LA = Lewis acid.

Although the cyclobutene moiety was expected to be highly reactive, it failed to react under a variety of conditions. Further work, potentially including computational studies, is required to understand this anomalous lack of reactivity. Finally, the phototropone derivatives obtained in Chapter 3 could also be subjected to a similar derivitisation study as for **199**, to give highly functionalised derivatives, e.g. **437**–**440** (Scheme 4.3).



Scheme 4.3: LA = Lewis acid.

Whilst the 4-π-photocyclisation of 2-aminotropones **398b**–**d** proceeded cleanly, the products obtained could not be isolated. However, *in situ* trapping of the formed photoproducts to yield the photoproducts as salts instead may improve their isolation and handling (Scheme 4.4).



Scheme 4.4

The design and synthesis of other 2-substituted tropones could provide more insights into the scope this reaction. For example, other heteroatom containing species, vinyl- (**442**), acyl- (**443**), carboxyl- (**444**) tropones, and other heteroatom groups (**445**-**446**) (Figure 4.1).

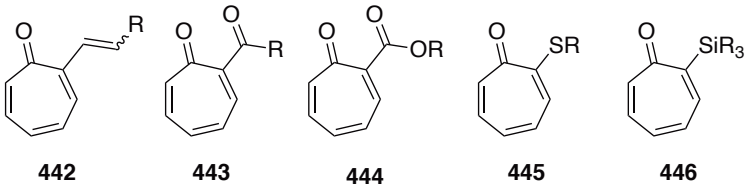
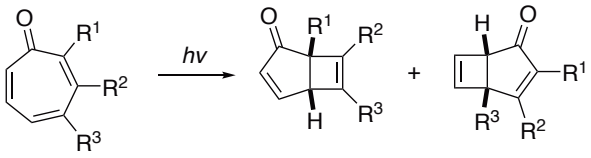


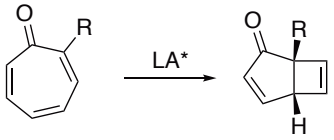
Figure 4.1: R = H, alkyl, aryl.

The position of a substituent is also known to drastically alter the outcomes of these reactions – for example, the position of the hydroxyl group in the three isomers of tropolone. Thus, similar studies could explore the effects of these substituents developed in this study, but at different positions around the ring (Scheme 4.5). Similarly, the photochemistry of other, more complex polysubstituted tropones could be explored, which would lead to highly substituted [3.2.0]bicycles. Further, detailed computational work is expected to give greater understanding of the scope and limitations of these reactions, with the ultimate goal of being able to predict with confidence the likelihood of a given tropolone undergoing 4-π-photocyclisation and the photocyclisation mode of unsymmetrical tropone substrates.



Scheme 4.5

Finally, performing these reactions enantioselectively would be a desirable goal. One particular strategy may employ chiral Lewis acid catalysis, although this is expected to be extremely challenging (Scheme 4.6). Computational studies are expected to be particularly useful here.



Scheme 4.6: LA* = Chiral Lewis acid. One enantiomer and regioisomer shown for clarity.

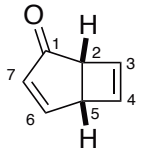
Chapter 5

Experimental

All solvents and reagents were purchased from Sigma Aldrich, Acros Organics, TCI Chemicals, Fisher Scientific, Alfa Aesar or Fluorochem. All reactions were carried out under dry inert conditions unless stated otherwise, and dry solvents were purchased from Acros Organics equipped with AcroSealTM. Reactions were monitored by thin layer chromatography (TLC) or by ^{1}H NMR spectroscopy (with solvent suppression). Photochemical reactions were carried out in a Rayonet RPR-100 Photochemical Batch photoreactor. Analytical TLC was carried out on pre-coated aluminium-backed TLC plates (silica gel 60 F254) from VWR and visualised by UV light (λ = 254 nm) or stained with potassium permanganate and heated as developing agent. Flash chromatography on silica gel was performed with silica gel from VWR (40-63 microns). ^{1}H, ^{13}C and ^{19}F NMR spectroscopic data were collected on a Bruker-400 MHz instrument and chemical shifts are reported in parts per million (δ) calibrated to residual undeuterated solvent as internal reference ($CHCl_3$) at δH 7.26 ppm and δC 77.0 ppm). The following abbreviations are used to describe the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and a = apparent. Coupling constants (J) are given in Hertz. Assignment of the signals in 1H and ^{13}C NMR spectra was achieved using 2D-NMR techniques (COSY, HSQC and HMBC). When using ^{1}H NMR to monitor the reaction progress, solvent suppression was used to suppress the signal arising from the nondeuterated solvent. Infrared (IR) spectra were recorded on an Agilent Technologies Cary 630 **FTIR** spectrometer. High resolution mass spectrometry data were recorded using

electron spray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer.

Bicyclo[3.2.0]hepta-3,6-dien-1-one 199



Six Pyrex tubes containing **194** (0.18 g, 1.74 mmol) and $BF_3{\cdot}OEt_2$ (0.21 mL, 1.75 mmol) in anhydrous CH_2Cl_2 (60 mL) were purged with argon for 30 minutes, before being irradiated (λ = 300 nm) at room temperature for three hours. The reaction mixture was concentrated under reduced pressure (500 mbar, bath temperature at 30 °C) to yield the crude product. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 99:1 $\rightarrow$ 4:1] as the eluent afforded **199** (0.66 g, 2.07 mmol, 61%) as a yellow oil.

$\boldsymbol{R_f}$ (CH_2Cl_2) = 0.47.

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.64 (dd, *J* = 5.8, 2.6 Hz, 1H, **H6**), 6.53 (dd, *J* = 2.6, 1.2 Hz, 1H, **H3**), 6.34 (dd, *J* = 2.6, 1.3 Hz, 1H, **H4**), 6.06 (dd, *J* = 5.8, 0.9 Hz, 1H, **H7**), 3.93 (dd, *J* = 3.5, 1.2 Hz, 1H, **H2**), 3.48-3.41 (m, **H5**).

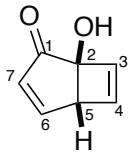
^{13}C NMR (101 MHz, $CDCl_3$); δ 206.3 (**C1**), 162.6 (**C6**), 143.1 (**C3**), 137.0 (**C4**), 134.5 (**C7**), 53.2 (**C5**), 50.6 (**C2**).

FTIR. neat. (ATR) ν (cm^{-1}); 3054, 2946, 1690 (C=O).

HRMS (APCI); *m*/*z* calculated for: C_7H_6O $[M+H]^+$ 107.0491, found 107.0489.

N.B. product is volatile and should not be subected to high vacuum.

2-Hydroxybicyclo[3.2.0]hepta-3,6-dien-1-one 189



A solution of **200** (61 mg, 0.5 mmol) in TBME (10 mL) was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for six hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 1:1] afforded **201** (35 mg, 0.28 mmol, 57%) as an orange oil.

R_f (CH_2Cl_2) = 0.55

^{1}H NMR (400 MHz, $CDCl_3$); δH 7.69 (1H, dd, *J* = 6.4, 2.5 Hz, **H6**), 6.74 (1H, d, *J*= 2.9 Hz, **H4**), 6.30 (1H, d, *J* = 2.9 Hz, **H3**), 6.12 (1H, d, *J* = 6.4, **H7**), 3.80 (d, *J* = 2.5, 1H, **H5**).

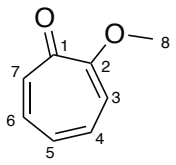
^{13}C NMR (101 MHz, $CDCl_3$); δ 206.9 (**C1**), 162.1 (**C6**), 145.9 (**C4**), 138.1 (**C3**), 132.1 (**C7**), 81.2 (**C2**), 57.6 (**C5**).

FTIR (ATR) ν (cm^{-1}); 3375 (O-H), 3052, 2939, 1695 (C=O).

HRMS (APCI); *m/z* calculated for: $C_7H_6O_2$ $[M+H]^+$ 123.0441, found 123.0442.

The spectroscopic data are consistent with those reported previously, although some report a broad singlet at 5.30 ppm due to the OH peak, which was not apparent in our spectra.[1]

2-Methoxycyclohepta-2,4,6-trien-1-one 206



Potassium carbonate (3.38 g, 24.5 mmol) and dimethyl sulfate (1.18 mL, 12.4 mmol)

were added to a stirred solution of **200** (1.00 g, 8.18 mmol) in 9:1 acetone-water (7.5 mL) at room temperature under argon. The reaction mixture was heated at reflux for three hours, then allowed to cool to room temperature and stirred for a further 17 hours at room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was taken up in distilled water (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, CH_2Cl_2:MeOH, 19:1] afforded **206** (0.93g, 6.87 mmol, 84%) as a yellow oil that solidified to a waxy beige solid after standing at room temperature for several days.

$\boldsymbol{R_f}$ (CH_2Cl_2:MeOH, 19:1) = baseline

mp = 25°C

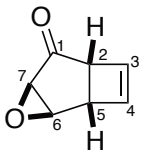
^{1}H NMR (300 MHz, $CDCl_3$); δ 7.23-7.17 (m, 2H, **H4** + **H6**), 7.05 (ddat, J = 10.8, 9.9, 1.0 Hz, 1H, **H5**), 6.93-6.75 (m, 1H, **H3**), 6.71 (dat, J = 9.9, 0.7 Hz, 1H, **H7**), 3.91 (s, 3H, **H8**).

^{13}C NMR (100 MHz, $CDCl_3$); 180.5 (**C1**), 165.4 (**C2**), 136.9 (**C6**), 136.6 (**C4**), 132.7 (**C5**), 127.9 (**C3**), 112.3 (**C7**), 56.2 (**C8**).

FTIR (ATR) ν (cm^{-1}); 3011, 2940, 1623 (C=O).

HRMS (APCI); m/z calculated for: $C_8H_8O_2$ $[M+H]^+$ 137.0597, found 137.0600.

(*1S*,*2R*,*4R*,*6R*)-3-Oxatricyclo[4.2.0.02,4]oct-7-en-5-one 284



An aqueous 2 M solution of NaOH (1.5 mL, 3.0 mmol) was added dropwise to a stirred solution of **199** (318 mg, 3 mmol) and H_2O_2 (50% w/w in H_2O, 0.73 mL, 8.97 mmol) in MeOH (50 mL) at –20°C under argon, and the resulting solution was stirred at 20 °C for 15 minutes. The reaction mixture was diluted with H_2O (30 mL)

and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give epoxide **284** (272 mg, 2.2 mmol, 74%) as a colourless oil.

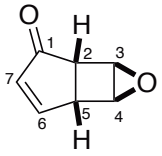
R_f (CH_2Cl_2) = 0.63.

^{1}H NMR (400 MHz, $CDCl_3$); δ 6.31 (dd, *J* = 2.6, 0.8 Hz, 1H, **H4**), 6.14 (dd, *J* = 2.6, 1.5 Hz, 1H, **H3**), 3.89 (atd, *J* = 1.5, 0.5 Hz, 1H, **H7**), 3.57 (ddd, *J* = 2.6, 1.4, 0.8 Hz, 1H, **H5**), 3.41 (atd, *J* = 1.5, 0.5 Hz, 1H, **H6**), 3.34 (ddd, *J* = 2.6, 1.5, 0.5 Hz, 1H, **H2**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 203.6 (**C1**), 139.1 (**C3**), 137.2 (**C4**), 58.9 (**C6**), 55.2 (**C7**), 50.9 (**C5**), 46.0 (**C2**).

FTIR. (ATR) ν (cm^{-1}); 3423, 2920, 2851, 1727 (C=O).

(*1R*,*2S*,*4R*,*5S*)-3-Oxatricyclo[4.2.0.02,4]oct-7-en-5-one 285



To a stirred solution of **199** (106 mg, 1.00 mmol) in anhydrous dichloromethane (2 mL) at 0 °C was added *m*-CPBA (516 mg, 3.00 mmol) portionwise. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 24 hours, before being diluted with saturated aqueous $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2:NEt_3, 4:1:0.01] afforded **284** (40 mg, 0.33 mmol, 33%) as a colourless oil.

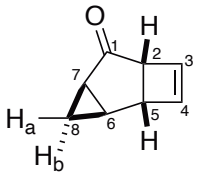
R_f (Pentane:CH_2Cl_2, 4:1) = 0.19.

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.60 (dd, *J* = 5.8, 2.9, 1H, **H6**), 6.39 (dat, *J* = 5.8, 0.7, 1H, **H7**), 4.10 (dd, *J* = 2.9, 2.1 Hz, 1H, **H3**), 3.93 (dd, *J* = 2.9, 2.1 Hz, 1H, **H4**), 3.47 (aqd, *J* = 2.9, 0.7 Hz, 1H, **H5**), 3.01 (at, *J* = 2.9 Hz, 1H, **H2**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 204.6 (**C1**), 160.1 (**C6**), 138.6 (**C7**), 60.5 (**C3**), 55.9 (**C4**), 54.5 (**C2**), 52.4 (**C5**).

FTIR. (ATR) ν (cm^{-1}); 3060, 2959, 1764, 1697 (C=O).

(*1R*,*2R*,*4R*,*6R*)-Tricyclo[4.2.0.02,4]oct-7-en-5-one 289



Sodium hydride (80 mg, 2.0 mmol, 60% suspension in mineral oil) was added portionwise to anhydrous DMSO (1 mL) at room temperature, followed by trimethylsulfoxonium iodide (440 mg, 2 mmol). The resulting suspension was stirred at room temperature for one hour. A solution of **199** (212 mg, 2.00 mmol) in anhydrous DMSO (0.2 mL) was added dropwise. The resulting suspension was stirred at 50 °C for one hour before being allowed to cool to room temperature, crushed ice added (~5 g) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield **189** (52 mg, 0.21 mmol, 21%) as a yellow oil.

$\boldsymbol{R_f}$ (4:1 Heptane:EtOAc) = 0.29

^{1}H NMR (400 MHz, $CDCl_3$); δ 6.36 (dd, J = 2.5, 0.5 1H, **H4**), 6.12 (dd, J = 2.6, 1.1 Hz, 1H, **H3**), 3.29 (at, J = 2.5 Hz, 1H, **H5**), 3.19 (brs, 1H, **H2**), 2.03 (m, 1H, **H7**), 1.91 (m, 1H, **H6**), 1.29 (ddd, J = 9.0, 7.3, 4.9 Hz, **H8a**), 0.70 (atd, J = 4.9, 3.4 Hz, 1H, **H8b**).

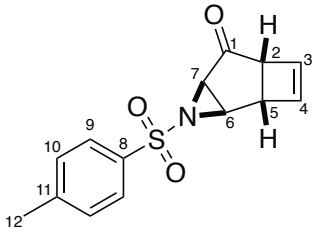
^{13}C NMR (101 MHz, $CDCl_3$); δ 209.9 (**C1**), 142.3 (**C4**), 136.5 (**C3**), 52.1 (**C5**), 46.4 (**C2**), 27.6 (**C6**), 23.5 (**C7**), 12.1 (**C8**).

FTIR. (ATR) ν (cm^{-1}); 3049, 2926, 2994, 1707 (C=O).

HRMS (APCI); *m*/*z* calculated for: C_8H_8O $[M+H]^+$ 121.0648, found 121.0652.

NB The product is volatile and should not be subjected to high vacuum.

(*1S*,*2R*,*4R*,*6R*)-3-(4-Methylbenzenesulfonyl)-3-azatricyclo[4.2.0.02,4]oct-7-en-5-one 287



To a stirred solution of **199** (25 mg, 0.23 mmol) and $CuOTf_2$ (6.0 mg, 0.023 mmol) in MeCN (2 mL) was added Ph=INTs[2] (243 mg, 0.910 mmol) in one portion at room temperature under nitrogen, then stirred at room temperature for 48 hours. The reaction mixture was filtered through Celite, washed with Et_2O (15 mL) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography [SiO_2, 4:1, heptane:EtOAc] afforded **287** (29 mg, 0.11 mmol, 45%) as a light beige oil.

R_f (Hexane-EtOAc, 4:1) = 0.15

mp = 73-77 °C

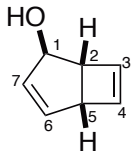
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.81 (d, J = 8.1 Hz, 2H, **H9**), 7.35 (d, J = 8.1 Hz, 2H, **H10**), 6.30 (dd, J = 2.7, 1.1 Hz, 1H, **H3**), 6.09 (dd, J = 2.7, 1.1 Hz, 1H, **H4**), 3.77 (dd, J = 4.4, 1.1 Hz, 1H, **H7**), 3.51 (dd, J = 2.6, 1.1 Hz, 1H, **H2**), 3.38 (dd, J = 4.4, 1.1 Hz, 1H, **H6**), 3.31 (dat, J = 2.6, 1.1 Hz, 1H, **H5**), 2.45 (s, 3H, **H12**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 200.8 (**C1**), 145.4 (**C11**), 139.7 (**C3**), 137.2 (**C4**), 134.4 (**C8**), 130.1 (**C10**), 128.1 (**C9**), 52.7 (**C5**), 46.4 (**C6**), 45.6 (**C2**), 45.2 (**C7**), 21.8 (**C12**).

FTIR. ($CHCl_3$). (ATR) ν (cm^{-1}); 3125, 3058, 2957, 1742 (C=O).

HRMS (APCI); *m*/*z* calculated for: $C_{14}H_{13}NO_3S$ $[M+H]^+$ 276.0689, found 276.0687.

(*1R*,*2R*,*5R*-Bicyclo[3.2.0]hepta-3,6-dien-2-ol 291



Triethylamine (0.14 mL, 1.0 mmol) was added to a stirred solution of hydrazine monohydrate (0.13 mL, 1.0 mmol) in acetonitrile (2.5 mL) at room temperature and the resulting solution stirred at room temperature for 20 minutes. A solution of **284** (94 mg, 0.76 mmol) in acetonitrile (2.5 mL) was added in one portion at room temperature and the resulting solution stirred for a further 20 minutes. Glacial acetic acid (0.065 mL, 1.14 mmol) was then added dropwise at room temperature and the solution stirred for a further five minutes. The reaction mixture was diluted with water (5 mL), the layers sepearted and the aqeuous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 1:1] afforded **291** (48 mg, 0.44 mmol, 59%) as a clear oil.

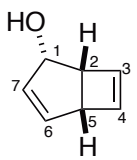
$\boldsymbol{R_f}$ (pentane:CH_2Cl_2) = 0.55.

^{1}H NMR (400 MHz, $CDCl_3$); δ 6.47 (dd, J = 2.6, 1.0 Hz, 1H, **H6**), 6.21-6.19 (m, 2H, **H3** and **H4**), 5.84-5.78 (m, 1H, **H7**), 4.58 (s, 1H, **H1**), 3.82 (aqd, J = 3.6, 1.0 Hz, 1H, **H2**), 3.18 (dat, J = 3.6, 1.0 Hz 1H, **H5**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 148.5 (**C6**), 139.8 (**C3**), 138.6 (**C4**), 133.8 (**C7**), 76.2 (**C1**), 55.1 (**C2**), 55.0 (**C5**).

FTIR. (ATR) ν (cm^{-1}); 3343 (br, OH), 3047, 2924.

(*1R*,*2S*,*5R*)-Bicyclo[3.2.0]hepta-3,6-dien-2-ol *epi*-**291**



A solution of **199** (53 mg, 0.50 mmol) in anhydrous Et_2O was cooled to 0 °C and a DIBAL-H (0.5 mL, 1.0 mmol of a 1.0M solution in THF) was added dropwise over the course of five minutes. The reaction mixture was stirred at 0 °C for 15 minutes. The reaction was quenched by dropwise addition of distilled water (5 mL) at 0 °C, the layers separated and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a 3:1 mixture of *epi*-**291** and **291** (34 mg, 0.31 mmol, 62%) as a colourless oil. Repeated column chromatography of this mixture was performed to obtain analytically pure *epi*-**291** (10 mg, 0.18 mmol, 21%).

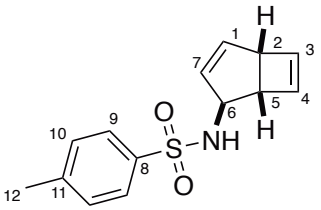
R_f (Pentane:CH_2Cl_2) = 0.55.

^{1}H NMR (400 MHz, $CDCl_3$); δ 6.64 (d, J = 2.6 Hz, 1H, **H4**), 6.18 (at, J = 2.6 Hz, 1H, **H3**), 6.10 (ddd, J = 5.7, 2.4, 1.4 Hz, 1H, **H6**), 5.63 (dd, J = 5.7, 1.8 Hz, 1H, **H7**), 4.80 (d, J = 9.0 Hz, 1H, **H1**), 3.68 (dd, J = 9.0, 2.6 Hz, 1H, **H2**), 3.56 (at, J = 2.6 Hz, 1H, **H5**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 148.9 (**C6**), 137.2 (**C3**), 136.5 (**C4**), 134.4 (**C7**), 74.2 (**C1**), 54.5 (**C2**), 48.7 (**C5**).

FTIR. ($CHCl_3$). (ATR) ν (cm^{-1}); 3343 (br, OH), 3047, 2924.

(*1R*,*2R*,*5R*)-*N*-Bicyclo[3.2.0]hept-3-en-2-yl-4-methylbenzene-1-sulfonamide 292



Glacial acetic acid (0.14 mL, 2.4 mmol) was added dropwise over the course of five minutes to a stirred solution of **287** (150 mg, 0.55 mmol) and hydrazine monohydrate (0.13 mL, 2.7 mmol) in methanol (2 mL) at 0°C and stirred for 5 minutes. Saturated aqueous sodium bicarbonate (5 mL) was added and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$)

and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 7:3] afforded **292** (20 mg, 0.08 mmol, 14%) as orange crystals.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 4:1) = 0.22

mp = 100-103 °C

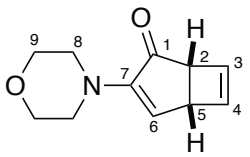
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.78 (d, J = 8.2 Hz, 1H, **H9**), 7.31 (d, J = 8.2 Hz, 1H, **H10**), 6.37 (dd, J = 2.6, 0.6 Hz, 1H, **H3**), 6.06 (d, J = 2.6 Hz, 1H, **H4**), 6.03 (dat, J = 5.6, 2.1 Hz, 1H, **H1**), 5.39-5.35 (m, 1H, **H7**), 4.47 (d, J = 9.3 Hz, 1H -N**H**), 4.24-4.18 (datd, J = 9.3, 4.2, 1.8, 1H, **H6**), 3.71-3.67 (m, 1H, **H2**), 2.93 (dat, J = 4.2, 1.8 Hz, 1H, **H5**), 2.43 (s, 3H, **H12**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 146.9 (**C3**), 143.6 (**C11**), 138.9 (**C1**), 138.5 (**C4**), 138.5 (**C8**), 130.7 (**C7**), 129.9 (**C10**), 127.2 (**C9**), 59.2 (**C6**), 54.8 (**C2**), 52.9 (**C5**), 21.7 (**C12**).

FTIR (ATR) ν (cm^{-1}); 3240 (N-H), 3835, 2953, 2829, 2851

HRMS (APCI); m/z calculated for: $C_{14}H_{15}NO_2S$ $[M-H]^-$ 260.0751, found 260.0751.

3-(Morpholin-4-yl)bicyclo[3.2.0]hepta-3,6-dien-2-one 294



A solution of **284** (122 mg, 1.00 mmol) and morpholine (86 mL, 1.2 mmol) in 3:1 MeOH:H_2O (2 mL) was stirred at 70 °C for four hours. The reaction mixture was diluted with brine (5 mL), the layers separated and the aqueous layer extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **294** (57 mg, 0.29 mmol, 69%) as light-yellow crystals.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 4:1) = 0.14

mp 59-61 °C

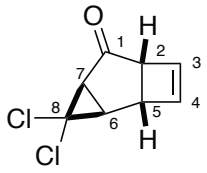
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.58 (dat, *J* = 2.4, 0.6, 1H, **H4**), 6.39 (d, *J* = 2.6' Hz, 1H, **H6**), 6.35 (dd, *J* = 2.4, 1.3 Hz, 1H, **H3**), 3.80 (ddd, *J* = 6.0, 3.7, 2.3 Hz, 4H, **H8**), 3.76 (at, *J* = 2.6 Hz, 1H, **H5**), 3.54 (dd, *J* = 2.6, 1.3 Hz, 1H, **H2**), 3.30-3.22 (m, 2H, **H9**), 2.99-2.91 (m, 2H, **H9**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 202.3 (**C1**), 150.9 (**C7**), 144.8 (**C4**), 136.1 (**C3**), 132.1 (**C6**), 66.7 (**C8**), 53.8 (**C2**), 48.3 (**C9**), 44.9 (**C5**).

FTIR. (ATR) ν (cm^{-1}); 3050, 2967, 2860, 2816, 1686 (C=O).

HRMS (ESI); *m/z* calculated for: $C_{11}H_{13}NO_2$ $[M+H]^+$ 192.1019, found 192.1012.

(*1S*,*2R*,*4R*,*6R*)-3,3-Dichlorotricyclo[4.2.0.02,4]oct-7-en-5-one 307



An aqueous solution of KOH (50% w/v, 5 mL) was added dropwise over the course of ten minutes to a solution of **199** (106 mg, 1.00 mmol) and TBACl (14 mg, 0.050 mmol) in $CHCl_3$ (25 mL) at 0 °C under argon, then stirred at room temperature for five hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL), the organic layer seperated and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 9:1] afforded **307** (75 mg, 0.39 mmol, 39%) as an orange oil.

R_f (4:1 Heptane-EtOAc) = 0.58

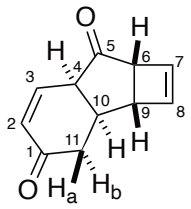
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.39 (dd, *J* = 2.5, 0.9 Hz, 1H, **H4**), 6.08 (dd, *J* = 2.6, 1.0 Hz, 1H, **H3**), 3.55 (at, *J* = 2.5 Hz, 1H, **H5**), 3.29 (dd, *J* = 2.5, 1.0 Hz, 1H, **H2**), 2.74 (dd, *J* = 6.0, 2.5 Hz, 1H, **H6**), 2.68 (dd, *J* = 6.0, 2.1 Hz, 1H, **H7**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 202.3 (**C1**), 140.8 (**C4**), 136.1 (**C3**), 62.1 **C8**, 55.4 (**C2**), 44.5 (**C5**), 44.4 (**C6**), 39.7 (**C7**).

FTIR. (ATR) ν (cm^{-1}); 3444, 3058, 2931, 1723 (C=O)

HRMS (APCI); *m/z* calculated for: $C_8H_6OCl_2$ $[M+H]^+$ 186.9868, found 186.9863.

2aH,2bH,3H,4H,6aH,7H,7aH-Cyclobuta[a]indene-4,7-dione 310



A solution of **199** (106 mg, 1.00 mmol) and Danishefsky's diene (1.00 mL, 5.17 mmol) in CH_2Cl_2 (4 mL) was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (0.12 mL, 1.1 mmol) added in one portion. The reaction mixture was stirred at 0 °C for 24 hours and allowed to warm to room temperature during this time. The reaction was quenched with saturated aqueous sodium bicarbonate (5 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash column chromatography [neutral alumina, heptane:EtOAc, 9:1→1:4] afforded **310** (75 mg, 0.43 mmol, 43%) as a waxy brown solid.

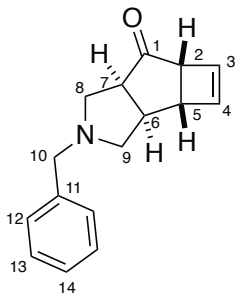
$\boldsymbol{R_f}$ (SiO_2, Heptane-EtOAc, 4:1) = 0.18

^{1}H NMR (400 MHz, $CDCl_3$); δ 6.98 (dd, J = 10.1, 6.5 Hz, 1H, **H3**), 6.42 (dat, J = 2.6, 0.8 Hz, 1H, **H8**), 6.29 (dd, J = 2.6, 1.0 Hz, 1H, **H7**), 6.08 (ddd, J = 10.1, 1.5, 0.9 Hz, 1H, **H2**), 4.02 (at, J = 6.5 Hz, 1H, **H4**), 3.46 (ddd, J = 2.9, 1.9, 1.0 Hz, 1H, **H6**), 3.12 (d, J = 2.9 Hz, 1H, **H9**), 2.89 (ddd, J = 14.2, 6.5, 5.1 Hz, 1H, **H10**), 2.52 (dd, J = 16.1, 5.1 Hz, 1H, **H11a**), 2.10 (dd, J = 16.1, 14.2 Hz, 1H, **H1**1b).

^{13}C NMR (101 MHz, $CDCl_3$); δ 212.0 (**C1**), 197.6 (**C5**), 144.3 (**C3**), 142.2 (**C8**), 138.0 (**C7**), 130.8 (**C2**), 54.8 (**C6**), 47.2 (**C10**), 44.9 (**C4**), 40.5 (**C11**), 34.5 (**C11**).

FTIR. (ATR) ν (cm^{-1}); 3332 (broad), 2850, 1697 (C=O), 1675 (C=O)

9-Benzyl-9-azatricyclo[5.3.0.02,5]dec-3-en-6-one 314



A solution of **199** (106 mg, 1.00 mmol) and and *N*-methoxymethyl-*N*- trimethylsilyl-methyl)benzylamine (1.3 mL, 5.0 mmol) in CH_2Cl_2 (4 mL) was cooled to 0 °C and trifluoroacetic acid (75 μL, 0.20 mmol) added in one portion and allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 48 hours. The reaction was quenched with saturated aqueous sodium bicarbonate (5 mL) the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 9:1→1:4] afforded **314** (172 mg, 0.72 mmol, 72%) as an orange oil.

$\boldsymbol{R_f}$ (SiO_2, Heptane:EtOAc, 9:1) = 0.15

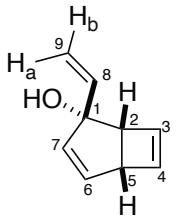
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.36-7.21 (m, 7H, Ar-**H**), 6.41 (d, *J* = 2.6 Hz, 1H, **H4**), 6.08 (dd, *J* = 2.6, 1.0 Hz, 1H, **H3**), 3.63-3.47 (m, 3H, **H10**+**H5**), 3.21-3.14 (m, 2H, **H2** + **H6**), 3.02 (dd, *J* = 9.3, 2.1 Hz, 1H, **H9**), 2.76 (atd, *J* = 7.7, 4.1 Hz, 1H, **H7**), 2.63 (atat, *J* = 7.7, 4.1 Hz, 2H, **H8**), 2.55 (dd, *J* = 9.3, 4.5 Hz, 2H, **H9**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 217.9 (**C1**), 144.5 (**C4**), 138.9 (**C11**), 135.4 (**C3**), 128.6 (Ar-**C**), 128.4 (Ar-**C**), 127.1 (Ar-**C**), 60.5 (**C9**), 59.9 (**C10**), 58.3 (**C8**), 56.5 (**C5**), 51.2 (**C6**), 49.2 (**C2**), 40.1 (**C7**).

FTIR. (ATR) ν (cm^{-1}); 3028, 2927, 2788, 1723 (C=O).

HRMS (APCI); *m/z* calculated for: $C_{16}H_{17}NO$ $[M+H]^+$ 240.1383, found 240.1374.

(*1R*,*2S*,*5R*)-2-Vinylbicyclo[3.2.0]hepta-3,6-dien-2-ol 323



A solution of **199** (106 mg, 1.00 mmol) in THF (1 mL) was added dropwise to a solution of vinylmagnesium bromide (2 mL, 2 mmol) in anhydrous THF (2 mL) at 0 °C and stirred at 0 °C for 0.5 hours. The reaction mixture was quenched by dropwise addition of saturated ammonium chloride (5 mL) at 0 °C and the reaction mixture extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 4:1] afforded **323** (53 mg, 0.39 mmol, 39%) as as colourless oil.

$\boldsymbol{R_f}$ (Heptane-EtOAc, 9:1) = 0.38

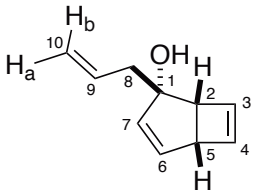
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.63 (dd, J = 2.5, 0.7 Hz, 1H, **H4**), 6.19 (d, J = 2.5 Hz, 1H, **H3**), 6.09 (dd, J = 5.6, 2.6 Hz, 1H, **H6**), 6.06-5.98 (dd, J = 17.2, 10.8 Hz, 1H, **H8**), 5.46 (dd, J = 5.6, 0.7 Hz, 1H, **H7**), 5.15 (dd, J = 17.2, 1.4, 1H, **H9b**), 5.05 (dd, J = 10.8, 1.4 Hz, 1H, **H9a**) 3.65-3.62 (m, 1H, **H5**), 3.43 (dat, J = 3.3, 1.0 Hz, 1H, **H2**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 148.3 (**C4**), 143.6 (**C8**), 137.1 (**C3**), 136.4 (**C6**), 135.9 (**C7**), 112.3 (**C9**), 81.9 (**C1**), 54.6 (**C5**), 54.1 (**C2**).

FTIR (ATR) ν (cm^{-1}); 3416 (O-H, broad), 3050, 2924, 2853, 2359 (C=C), 2338, 1720.

HRMS (APCI); m/z calculated for: $C_9H_{10}O$ $[M+H]^+$ 135.0804, found 135.0805.

(*1R*,*2S*,*5R*)-2-(Prop-2-en-1-yl)bicyclo[3.2.0]hepta-3,6-dien-2-ol 324



A solution of **199** (106 mg, 1.00 mmol) in THF (1 mL) was added dropwise to a solution of allylmagnesium bromide (1.3 mL, 1.0 mmol) in anhydrous THF (2 mL) at 0 °C and stirred at 0 °C for 0.5 hours. The reaction mixture was quenched by dropwise addition of saturated ammonium chloride (5 mL) at 0 °C and the reaction mixture extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 4:1] afforded **324** (16 mg, 0.10 mmol, 9%) as a colourless oil.

$\boldsymbol{R_f}$ (Heptane-EtOAc, 19:1) = 0.17.

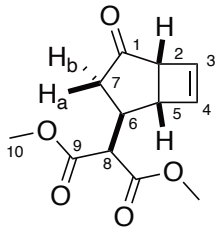
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.23 (d, J = 2.7, 0.7 Hz, 1H, **H4**), 6.17 (d, J = 2.7 Hz, 1H, **H3**), 6.04 (dd, J = 5.7, 2.4 Hz, 1H, **H6**), 5.89-5.80 (m, 1H, **H9**), 5.52 (dd, J = 5.7, 0.7 Hz, **H7**), 5.21-5.09 (m, 2H, **H10**), 3.56-3.55 (m, 1H, **H5**), 3.39 (dt, J = 3.2, 1.0 Hz, 1H, **H2**), 2.39 (dat, J = 7.2, 1.3 Hz, 1H, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 148.2 (**C4**), 137.2 (**C3**), 135.8 (**C6**), 137.0 (**C7**), 132.1 (**C9**), 118.6 (**C10**), 80.7 (**C1**), 54.2 (**C5**), 52.5 (**C2**), 45.9 (**C8**).

FTIR (ATR) ν (cm^{-1}); 3075, 3017, 2976, 2905.

HRMS (APCI); m/z calculated for: $C_{10}H_{10}O$ $[M+H]^+$ 147.0803, found 147.0804.

1,3-Diethyl 2-[(*1R*,*2S*,*5R*)-4-oxobicyclo[3.2.0]hept-6-en-2-yl]propanedioate 329



Dimethyl malonate (0.17 mL, 1.5 mmol) was added to a stirred solution of sodium methoxide (82 mg, 1.5 mmol) in methanol (1 mL) at 0 °C, then allowed to warm to room temperature and stirred at room temperature for one hour. A solution of **199** (106 mg, 1.00 mmol) in methanol (1 mL) was then added dropwise at 0 °C and the solution allowed to warm to room temperature and then stirred at room temperature for 15 hours. The reaction solution was then quenched with brine (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 19:1→9:1] afforded **329** (128 mg, 0.57 mmol, 57%) as a yellow oil.

$\boldsymbol{R_f}$ (Heptane-EtOAc, 4:1) = 0.25

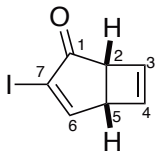
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.37 (dat, J = 2.6, 0.9 Hz, 1H, **H4**), 6.12 (dd, J = 2.6, 1.0 Hz, 1H, **H3**), 3.72 (d, J = 2.1 Hz, 6H, **H10**), 3.44 (d, J = 6.7 Hz, 1H, **H8**), 3.31 (ddd, J = 3.4, 1.8, 1.0 Hz, 1H, **H2**), 3.27 (dd, J = 3.4, 0.9 Hz, 1H, **H5**), 3.20 (ddd, J = 18.6, 9.2, 1.2 Hz, 1H, **H7b**), 2.83 (dddd, J = 9.2, 6.7, 1.5, 0.9 Hz, 1H, **H6**), 2.23-2.15 (dtd, J = 18.6, 1.6, 0.9 Hz 1H, **H7a**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 214.2 (**C1**), 168.7 (**C9**), 168.7 (**C9**), 143.0 (**C3**), 137.2 (**C4**), 55.3 (**C8**), 55.0 (**C2**), 52.8 (**C10**), 52.7 (**C10**), 48.3 (**C5**), 39.2 (**C7**), 33.9 (**C6**).

FTIR. (ATR) ν (cm^{-1}); 3449, 2959, 1718 (C=O).

HRMS (APCI); m/z calculated for: $C_{12}H_{14}O_5$ $[M+H]^+$ 239.0914, found 239.0906.

3-Iodobicyclo[3.2.0]hepta-3,6-dien-1-one 330



A solution of **199** (318 mg, 3.00 mmol), K_2CO_3 (621 mg, 4.50 mmol), DMAP (72 mg, 0.59 mmol) and I2 (1.1 g, 4.5 mmol)) in 1:1 THF-H_2O (30 mL) was stirred at room temperature for 1.5 hours. EtOAc (20 mL) was added and the organic layer was seperated. The organic layer was washed with 1M HCl (10 mL) and saturated aquous $Na_2S_2O_3$ (2 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 4:1] afforded **330** (498 mg, 2.2 mmol, 78%) as an orange oil.

$\boldsymbol{R_f}$ (Hexane-EtOAc, 4:1) = 0.38.

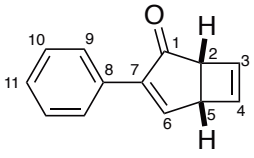
^{1}H NMR (400 MHz, $CDCl_3$); δ 8.01 (d, J = 3.0 Hz, 1H, **H6**), 6.59 (ddd, J = 1.6, 0.9, 0.9 Hz 1H, **H3**), 6.34 (dd, J = 1.6, 0.9 Hz, 1H, **H4**), 4.00 (dddd, J = 3.0, 2.5, 0.9, 0.9 Hz, 1H, **H5**), 3.61 (dddd, J = 2.5, 1.5 Hz, 0.9, 0.9 1H, **H2**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 199.6 (**C1**), 167.8 (**C6**), 143.6 (**C3**), 137.0 (**C4**), 104.0 (**C7**), 52.3 (**C5**), 49.8 (**C2**).

FTIR. ($CHCl_3$). (ATR) ν (cm^{-1}); 2988, 2359, 1707 (C=O).

HRMS (APCI); *m/z* calculated for: C_7H_5OI $[M+H]^+$ 232.9458, found 232.9451.

3-Phenylbicyclo[3.2.0]hepta-3,6-dien-1-one 331



Phenylboronic acid (242 mg, 2.00 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol) and $Pd(PPh_3)4$ (57 mg, 0.050 mmol) were added to a stirred solution of **330** (231 mg, 1.00 mmol)

in THF:H_2O (9:1, 7.5 mL) and heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 10 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concetrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 9:1] afforded **331** (140 mg, 0.77 mmol, 77%) as pale-yellow oil.

R_f (Heptane:EtOAc, 9:1) = 0.33.

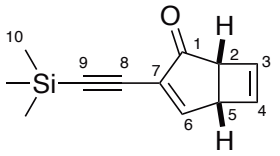
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.76 (d, J = 3.0 Hz, 1H, **H6**), 7.68-7.63 (m, 2H, Ar-**H**), 7.41-7.29 (m, 3H, Ar-**H**), 6.61 (dd, 1H, J = 2.4, 0.5, **H4**), 6.44 (dd, J = 2.4, 1.3 Hz, 1H, **H3**), 3.95 (ddd, J = 3.0, 2.5, 0.5 Hz, 1H, **H5**), 3.69 (dd, J = 2.5, 1.3, 0.5 Hz, 1H, **H2**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 204.0 (**C1**), 156.1 (**C6**), 143.4 (Ar-**C**), 143.2 (**C4**), 137.2 (**C3**), 132.2 (**C7**), 128.6 (Ar-**C**), 128.5 (Ar-**C**), 127.4 (**C9**), 54.9 (**C2**), 47.4 (**C5**).

FTIR. (ATR) ν (cm^{-1}); 3052, 2935, 1692 (C=O)

HRMS (APCI); *m/z* calculated for: $C_{13}H_{10}O$ $[M+H]^+$ 183.0804, found 183.0807.

3-[2-(Trimethylsilyl)ethynyl]bicyclo[3.2.0]hepta-3,6-dien-2-one 332



Trimethylsilylacetylene (95 mL 0.67 mmol), CuI (11 mg, 0.056 mmol) and $PdCl_2(PPh_3)2$ (20 mg, 0.028 mmol) were added to a stirred solution of **330** (231 mg, 1.0 mmol) in anhydrous THF (2.5 mL). The reaction mixture was stirred at 0 °C for one hour. The reaction mixture was allowed to warm to room temperature and HCl (1.0 M, 2 mL) was added. The layers were seperated and the aqueous layer extracted with EtOAc (3 x 10 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concetrated under reduced pressure. Purification by flash

column chromatography [SiO_2, heptane:EtOAc, 9:1] afforded **332** (52 mg, 0.25 mmol, 45%) as a waxy orange solid.

R_f (Heptane-EtOAc, 4:1) = 0.32

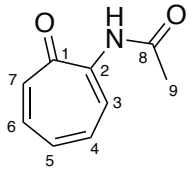
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.74 (d, J = 3.0 Hz, 1H, **H6**), 6.53-6.51 (m, 1H, **H4**), 6.34 (dd, J = 2.4, 1.3 Hz, 1H, **H3**), 3.93-3.88 (m, 1H, **H5**), 3.55 (dd, J = 2.1, 1.3 Hz, 1H, **H2**), 0.22 (s, 9H, **H10**)

^{13}C NMR (101 MHz, $CDCl_3$); δ 201.5 (**C1**), 163.7 (**C6**), 143.0 (**C4**), 137.0 (**C3**), 129.9 (**C7**), 102.1 (**C8**), 95.7 (**C9**), 53.2 (**C2**), 48.4 (**C5**), -0.08 (**C10**).

FTIR. (ATR) ν (cm^{-1}); 3190, 3054, 2957, 2898, 2154 (C≡C), 1705 (C=O).

HRMS (APCI); *m/z* calculated for: $C_{12}H_{14}OSi$ $[M+H]^+$ 203.0887, found 203.0878.

N-(7-Oxocyclohepta-1,3,5-trien-1-yl)acetamide 364a



Acetyl chloride (0.35 mL, 3.0 mmol) was added dropwise to a solution of **392** (121 mg, 1.00 mmol) and triethylamine (0.42 mL, 3.0 mmol) in anyhydrous CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for one hour. The reaction was quenched with distilled water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10mL) dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc. 7:3] afforded **364a** (118 mg, 0.72 mmol, 72%) as yellow needles.

R_f (Heptane:EtOAc, 7:3) = 0.24

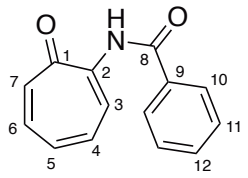
mp = 174-186 °C

^{1}H NMR (400 MHz, $CDCl_3$); δ 9.38 (brs, 1H, -N**H**), 9.00 (dd, J = 10.0, 0.7 Hz, 1H, **H6**), 7.39-7.31 (m, 2H, **H3**+**H4**), 7.29-7.23 (m, 1H, **H7**), 7.05-6.99 (m, 1H, **H5**), 2.28 (s, 3H, **H9**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 179.1 (**C8**), 170.2 (**C1**), 146.9 (**C2**), 137.9 (**C4**), 136.4 (**C3**), 135.9 (**C7**), 130.12 (**C5**), 121.1 (**C6**), 25.7 (**C9**). **FTIR** (ATR) ν (cm^{-1}); 3244 (NH), 1686 (C=O).

HRMS (APCI); *m/z* calculated for: $C_9H_9NO_2$ $[M+H]^+$ 164.0706, found 164.0708.

***N*-(7-Oxocyclohepta-1,3,5-trien-1-yl)benzamide 364b**



Benzoyl chloride (0.35 mL, 3.0 mmol) was added dropwise to a solution of **392** (121 mg, 1.00 mmol) and triethylamine (0.42 mL, 3.0 mmol) in anyhydrous CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for one hour. The reaction was quenched with distilled water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10mL) dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc. 7:3] afforded **364b** (173 mg, 0.77 mmol, 77%) as orange needles.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 7:3) = 0.28

mp = 172-174 °C

^{1}H NMR (400 MHz, $CDCl_3$); δ 10.36 (s, 1H, -N**H**), 9.22 (dd, *J* = 10.0, 0.6 Hz, 1H, **H6**), 8.02-7.98 (m, 2H, Ar-**H**), 7.63-7.57 (m, 1H, Ar-**H**), 7.56-7.49 (m, 2H, Ar-**H**), 7.43 – 7.39 (m, 2H, **H3**+**H4**), 7.34 (t, *J* = 10.0 Hz, 1H, **H7**), 7.12-7.04 (m, 1H, **H5**).

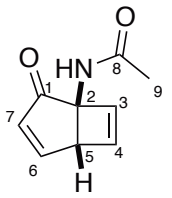
^{13}C NMR (101 MHz, $CDCl_3$); δ 215.0 (**C8**), 179.7 (**C1**), 166.7 (Ar-**C**), 147.4 (**C2**), 138.3 (**C4**), 136.3 (**C3**), 136.2 (**C4**), 134.5 (**C9**), 132.7 (Ar-**C**), 131.0 (**C5**), 129.1 (Ar-**C**), 127.7 (Ar-**C**), 121.5 (**C6**).

FTIR (ATR) ν (cm^{-1}); 3274 (NH), 1677 (C=O).

HRMS (APCI); *m/z* calculated for: $C_{14}H_{11}NO_2$ $[M-H]^-$ 224.0717, found 224.0713.

The spectroscopic data were consistent with those previously reported.[3]

***N*-2-Oxobicyclo[3.2.0]hepta-3,6-dien-1-ylacetamide 365a**



A solution of **364a** (55 mg, 0.34 mmol) in MeCN (14 mL) was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for two hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 4:1] afforded **365a** (10 mg, 0.06 mmol, 18%) as a white solid.

mp = 158-161 °C

$\boldsymbol{R_f}$ (Heptane:EtOAc, 7:3) = 0.28

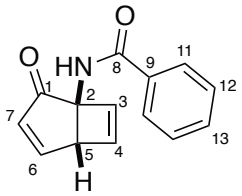
^{1}H NMR (400 MHz, $CDCl_3$); δ 9.39 (brs, -N**H**), 7.64 (dd, *J* = 6.2, 2.7 Hz, 1H, **H6**), 6.82 (dd, *J* = 2.6, 0.9 Hz, 1H, **H4**), 6.24 (d, *J* = 2.6 Hz, 1H, **H3**) 6.16 (d, *J* = 6.2 Hz, 1H, **H7**), 3.95 (d, *J* = 2.7 Hz, 1H, **H5**) 2.01 (s, 3H, **H9**).

^{13}C NMR (101 MHz, $CDCl_3$) 203.1 (**C1**), 169.3 (**C8**), 160.3 (**C6**), 147.7 (**C4**) 135.0 (**C3**) 132.5 (**C7**), 67.0 (**C2**), 56.1 (**C5**), 22.8 (**C9**).

FTIR (ATR) ν (cm^{-1}); 3285 (N-H), 3054, 1705 (C=O).

HRMS (APCI); *m*/*z* calculated for: $C_9H_9NO_2$ $[M+H]^+$ 164.0706, found 164.0709.

***N*-2-Oxobicyclo[3.2.0]hepta-3,6-dien-1-ylbenzamide 365b**



A solution of **364b** (113 mg, 0.500 mmol) in MeCN (20 mL) was purged with

argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for ten hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 4:1] afforded **365b** (22 mg, 0.09 mmol, 19%) as an orange solid.

$\boldsymbol{R_f}$ (4:1 heptane-EtOAc) = 0.22

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.84-7.76 (m, 2H, Ar-**H**), 7.71 (dd, *J* = 6.2, 2.8 Hz, 1H, **H6**), 7.53-7.48 (m, 1H, Ar-**H**), 7.46-7.38 (m, 2H, Ar-**H**), 6.88 (dd, *J* = 2.6, 0.9 Hz, 1H, **H4**), 6.35 (d, *J* = 2.6 Hz, 1H, **H3**), 6.24 (d, *J* = 6.2 Hz, 1H, **H7**), 4.06 (d, *J* = 2.6 Hz, 1H, **H5**).

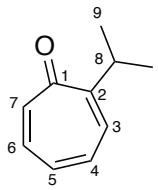
^{13}C NMR (101 MHz, $CDCl_3$); δ 203.3 (**C1**), 166.5 (Ar-**C**), 160.4 (**C6**), 147.9 (**C4**), 134.9 (**C3**), 132.9 (Ar-**C**), 132.5 (**C7**), 132.2 (Ar-**C**), 128.8 (Ar-**C**), 127.4 (Ar-**C**), 67.3 (**C2**), 56.3 (**C5**).

FTIR (ATR) ν (cm^{-1}); 3312, 3055, 1702, 1634 (C=O).

HRMS (APCI); *m/z* calculated for: $C_{14}H_{11}NO_2$ $[M+H]^+$ 226.0863, found 226.0853.

Suitable quality crystals of **343** for X-ray crystallography were grown by slow evaporation of chloroform solvent.

2-Isopropylcyclohepta-2,4,6-trien-1-one 389a



A solution of **194** (1.00 g, 9.40 mmol) in THF (5 mL) was added dropwise to a solution of isopropylmagnesium bromide (11.7 mL, 18.8 mmol of a 1.60 M in THF) at 0 °C under nitrogen. The solution was allowed to warm to room temperature and stirred for a further 30 minutes. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of saturated ammonium chloride (20 mL) and allowed to warm to room temperature. The mixture was extracted with Et_2O (3 x 20

mL), the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude dihydrotropone. The crude dihydrotropone was taken up in MeOH (50 mL), iodine (4.64 g, 18.8 mmol) was added, and the mixture was heated at reflux for two hours. The solution was allowed to return to room temperature and saturated aqueous sodium thiosulfate (20 mL) added in one portion. The mixture was extracted with EtOAc (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1→1:1] afforded **389a** (462 mg, 3.10 mmol, 33%) as a light-yellow oil.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 4:1) = 0.17

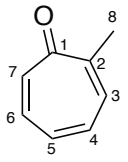
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.17 (d, J = 8.9 Hz, 1H, **H6**), 7.12-7.01 (m, 3H, **H3**+**H4**+**H7**), 6.93-6.85 (m, 1H, **H5**), 3.44 (sept, J = 6.8 Hz, 1H, **H8**), 1.17 (d, J = 6.8 Hz, 6H, **H9**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 187.2 (**C1**), 161.5 (**C2**), 140.6 (**C3**), 135.1 (**C4**), 134.1 (**C7**), 132.5 (**C5**), 132.0 (**C6**), 30.3 (**C8**), 22.6 (**C9**).

FTIR (ATR) ν (cm^{-1}); 2959, 2929, 2870, 1628 (C=O), 1567.

HRMS (APCI); *m/z* calculated for: $C_{10}H_{12}O$ $[M+H]^+$ 149.0961, found 149.0956.

2-Methylcyclohepta-2,4,6-trien-1-one 389b



A solution of **194** (795 mg, 7.50 mmol) in THF (5 mL) was added dropwise to a solution of methylmagnesium chloride (5.0 mL, 15 mmol of a 3.0 M solution in THF) at 0 °C under nitrogen. The solution was allowed to warm to room temperature and stirred for a further 30 minutes. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of saturated ammonium chloride (20 mL) and

allowed to warm to room temperature. The mixture was extracted with Et_2O (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude dihydrotropone. The crude dihydrotropone was taken up in MeOH (50 mL), iodine (3.79 g, 15.0 mmol) added, and the mixture was heated at reflux for two hours. The solution was allowed to return to room temperature and saturated aqueous sodium thiosulfate (20 mL) was added in one portion. The mixture was extracted with EtOAc (3 x 20 mL), the combined organic layers washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1→1:1] afforded 389b (247 mg, 2.10 mmol, 28%) as a green-brown oil.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 4:1) = 0.28

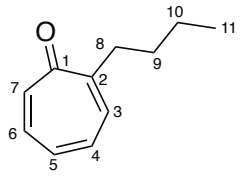
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.34-7.30 (m, 1H, **H6**), 7.15-7.05 (m, 2H, **H3**+**H4**), 6.97-6.87 (m, 2H, **H5**+**H7**), 2.27 (d, J = 0.9 Hz, 3H, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 187.5 (**C1**), 152.6 (**C2**), 140.0 (**C3**), 135.6 (**C4**), 135.26 (**C6**), 133.9 (**C5**), 132.6 (**C7**), 23.0 (**C8**).

FTIR (ATR) ν (cm^{-1}); 3021, 2983, 2950, 2916, 1628 (C=O).

HRMS (APCI); *m/z* calculated for: C_8H_8O $[M+H]^+$ 121.0648, found 121.0654.

2-Butylcyclohepta-2,4,6-trien-1-one 389c



A solution of **194** (1.00 g, 9.40 mmol) in THF (5 mL) was added dropwise to a solution of butyl magnesium bromide (6.2 mL, 6.2 mmol of a 1.0 M solution in THF,) at 0 °C. The solution was allowed to warm to room temperature and stirred for a further 30 minutes. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of saturated ammonium chloride (20 mL) and allowed to warm to

room temperature. The mixture was extracted with Et_2O (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude dihydrotropone. The crude dihydrotropone was taken up in MeOH (50 mL), iodine (4.64 g, 18.8 mmol) was added, and the mixture was heated at reflux for two hours. The solution was allowed to return to room temperature and saturated aqueous sodium thiosulfate (20 mL) was added in one portion. The mixture was extracted with EtOAc (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1→1:1] afforded **389c** (398 mg, 2.40 mmol, 26%) as a brown oil.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 4:1) = 0.34

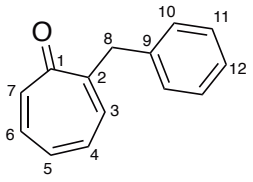
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.26 (m, 1H, **H6**), 7.14-7.01 (m, 2H, **H3**+**H4**), 6.99-6.86 (m, 2H, **H5**+**H7**), 2.69-2.61 (t, J = 7.6, 2H, **H8**), 1.54 (m, 2H, **H9**), 1.44-1.32 (m, 2H, **H10**), 0.93 (t, J = 7.3 Hz, 3H, **H11**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 187.26 (**C1**), 156.41 (**C2**), 140.48 (**C3**), 135.4 (**C4**), 134.80 (**C6**, 133.97 (**C7**), 132.53 (**C5**), 35.45 (**C8**), 25.50 (**C9**), 22.9 (**C10**), 14.1 (**C11**).

FTIR (ATR) ν (cm^{-1}); 2955, 2926, 2858, 1720, 1627, 1569 (C=O).

HRMS (APCI); m/z calculated for: $C_{11}H_{14}O$ $[M+H]^+$ 163.1117, found 163.1115.

2-Benzylcyclohepta-2,4,6-trien-1-one 389d



A solution of **194** (499 mg, 4.7 mmol) in Et_2O (5 mL) was added dropwise to a solution of benzyl magnesium bromide (5.0 mL, 9.4 mmol of a 1.8 M solution in THF) at 0 °C. The solution was allowed to warm to room temperature and stirred

for a further 30 minutes. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of saturated ammonium chloride (20 mL) and allowed to warm to room temperature. The mixture was extracted with Et_2O (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude dihydrotropone (1.0 g, 5.7 mmol). The crude dihydrotropone was taken up in MeOH (50 mL), iodine (2.60 g, 10.1 mmol) was added, and the mixture was heated at reflux for two hours. The solution was allowed to return to room temperature and saturated aqueous sodium thiosulfate (20 mL) was added in one portion. The mixture was extracted with EtOAc (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 9:1→4:1] afforded **389d** (381 mg, 2.10 mmol, 41%) as a brown oil.

$\boldsymbol{R_f}$ (4:1 Heptane:EtOAc) = 0.11

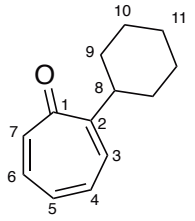
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.36-7.30 (m, 2H, Ar-**H**), 7.30-7.21 (m, 3H, Ar-**H**), 7.15-7.08 (m, 3H, **H3**+**H4**+**H6**), 6.92 (m, 2H, **H5**+**H7**), 4.00 (s, 2H, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 186.8 (**C1**), 154.9 (**C2**), 140.8 (**C6**), 139.2 (**C3**), 135.7 (**C4**), 135.6 (**C9**), 133.8 (**C5**), 132.9 (**C7**), 129.7 (Ar-**C**), 128.7 (Ar-**C**), 126.6 (Ar-**C**), 40.7 (**C8**).

FTIR (ATR) ν (cm^{-1}); 2920, 2849, 1563 (C=O).

HRMS (ESI); *m/z* calculated for: $C_{14}H_{12}O$ [M+H+] 197.0961, found 197.0955.

2-Cyclohexylcyclohepta-2,4,6-trien-1-one 390



A solution of **194** (810 mg, 7.60 mmol) in THF (5 mL) was added dropwise to a

solution of cyclohexyl magnesium bromide[4] (30 mL, 15 mmol of a 0.50 M solution in THF) at 0 °C. The solution was allowed to warm to room temperature and stirred for a further 30 minutes. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of saturated ammonium chloride (20 mL) and allowed to warm to room temperature. The mixture was extracted with Et_2O (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude dihydrotropone. The crude dihydrotropone was taken up in MeOH (50 mL), iodine (3.49 g, 13.8 mmol) was added, and the mixture was heated at reflux for two hours. The solution was allowed to return to room temperature and saturated aqueous sodium thiosulfate (20 mL) added in one portion. The mixture extracted with EtOAc (3 x 20 mL), the combined organic layers washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 9:1→4:1] afforded **389e** (520 mg, 2.7 mmol, 37%) as a brown solid.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 4:1) = 0.55

mp = 54-55 °C

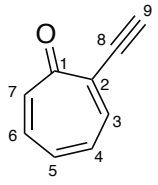
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.15 (d, J = 8.9 Hz, 1H, **H3**), 7.08-7.04 (m, 2H, **H6+H7**), 6.99 (ddt, J = 9.9, 8.9, 1.0 Hz, 1H, **H4**), 6.88 (m, 1H, **H5**), 3.14 (tt, J = 11.9, 2.7 Hz, 1H, **H8**), 1.86-1.70 (m, 5H, **H9+H10**), 1.56-1.36 (m, 2H, **H11**), 1.36-1.12 (m, 3H, **H9+H10**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 187.2 (**C1**), 160.4 (**C2**), 140.5 (**C6**), 135.1 (**C7**), 134.1 (**C4**), 132.6 (**C3**), 132.4 (**C5**), 40.3 (**C8**), 33.3 (**C9**), 26.9 (**C10**), 26.5 (**C11**).

FTIR (ATR) ν (cm^{-1}); 2920, 2849, 1627, 1563 (C=O).

HRMS (ESI); m/z calculated for: $C_{13}H_{16}O$ [M+H$^+$] 189.1274, found 189.1272.

2-Ethynylcyclohepta-2,4,6-trien-1-one 389h



To a solution of **397** (200 mg, 1.40 mmol) in anhydrous THF (5mL) at 0 °C was added ethynyl magnesium bromide (10.8 mL, 2.80 mmol of a 3.86 M solution in THF) dropwise over ten minutes, and the solution stirred at 0 °C for 1.5 h under argon. The reaction was quenched with H_2SO_4 (3 mL of a 1 M solution in H_2O), allowed to warm to room temperature and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 1:1] afforded **398** (96 mg, 0.73 mmol, 52%) as a brown glass.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 1:1) = 0.26

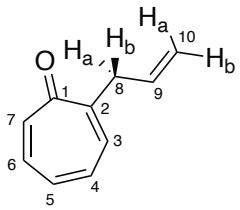
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.61 (dd, J = 8.8, 1.2 Hz, 1H, **H3**), 7.18-7.07 (m, 2H, **H6+H7**), 7.04 (dddd, J = 10.7, 6.0, 3.4, 1.2 Hz, 1H, **H5**), 6.94 (ddt, J = 10.7, 8.8, 1.2 Hz, 1H, **H4**), 3.51 (s, 1H, **H9**)

^{13}C NMR (101 MHz, $CDCl_3$); δ 185.4 (**C1**), 141.2 (**C3**), 141.1 (**C6**), 136.0 (**C2**), 136.0 (**C5**), 135.7 (**C7**), 133.2 (**C4**), 85.6 (**C9**), 82.6 (**C8**).

FTIR (ATR) ν (cm^{-1}); 3220, 3186, 2087 (C≡C), 1623 (C=O).

HRMS (ESI); No mass peak found.

2-(Prop-2-en-1-yl)cyclohepta-2,4,6-trien-1-one 389i



Allylboronic acid (0.37 mL, 2.0 mmol), Cs_2CO_3 (0.958 g, 3.00 mmol) and $PdCl_2(PPh_3)2$ (35 mg, 50 μmol) were added to a stirred solution of **404** (183 mg, 1.00 mmol) in THF:H_2O (9:1, 2 mL) and heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 10 mL). The organic layers were washed with brine (10 mL), dried

($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 7:3] afforded **389i** (94 mg, 0.64 mmol, 64% yield) as an orange oil.

R_f (Heptane:EtOAc, 3:1) = 0.56

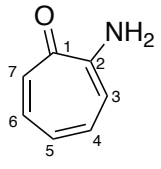
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.23 (dd, J = 8.5, 0.8 Hz, 1H, **H3**), 7.14-7.03 (m, 2H, **H4**+**H5**), 7.00-6.87 (m, 2H, **H6**+**H7**), 5.93 (ddt, J = 17.0, 10.1, 6.8 Hz, 1H, **H9**), 5.18 – 5.06 (m, 2H, **H10**), 3.38 (d, J = 6.8 Hz, 2H, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 186.8 (**C1**), 153.7 (**C2**), 140.6 (**C6**), 135.6 (**C7**), 135.3 (**C9**), 135.1 (**C3**), 133.9 (**C5**), 132.9 (**C4**), 117.5 (**C10**), 39.0 (**C8**).

FTIR (ATR) ν (cm^{-1}); 3017, 1627 (C=O), 1565.

HRMS (APCI); m/z calculated for: $C_{10}H_{10}O$ $[M+H]^+$ 147.0804, found 147.0803.

2-Aminocyclohepta-2,4,6-trien-1-one 392



Hydrazine monohydrate (0.25 mL, 5.0 mmol) was added to a solution of **194** (500 mg, 4.70 mmol) in ethanol (20 mL) under argon and the mixture was stirred at room temperature for two hours under argon. The reaction mixture was concentrated under reduced pressure and then taken up in CH_2Cl_2 (20 mL). The organic layer was washed with water (3 x 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by recrystallisation from hexane afforded **392** (410 mg, 0.48 mmol, 72% yield) as yellow plates.

(Heptane:EtOAc, 7:3) = 0.44

mp = 101-103 °C

^{1}H NMR (400 MHz, $CDCl_3$); δ: 7.30 (ddd, J = 11.5, 8.5, 0.8 Hz, 1H, **H6**), 7.22 (d, J = 11.5, 1H, **H7**), 7.15 (dd, J = 10.1, 0.8, 1H, **H4**), 6.88 (dd, J = 10.1, 0.8 Hz, 1H, **H3**), 6.77 (dd, J = 10.1, 8.5 Hz, 1H, **H5**), 6.01 (brs, -N**H2**).

^{13}C NMR (101 MHz, $CDCl_3$); δ: 176.6 (**C1**), 157.1 (**C2**), 137.2 (**C6**), 136.4 (**C4**), 131.1 (**C7**), 124.3 (**C5**), 112.8 (**C3**).

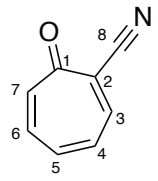
FTIR (ATR) ν (cm^{-1}); 3289 (N-H antisymmetric), 3252 (N-H symmetric), 1593 (C=O).

HRMS (ESI); *m/z* calculated for: $C_{13}H_{11}NO$ $[M+H]^+$ 122.0600, found 122.0606.

2-Aminocyclohepta-2,4,6-trien-1-one rapidly decomposes in air and must be kept in the freezer under an inert atmosphere.

The spectroscopic data were consistent with those previously reported.[5]

2-Cyanocyclohepta-2,4,6-trien-1-one 395



A solution of **204** (250 mg, 1.8 mmol) TMSCN (0.45 mL, 3.7 mmol) and zinc iodide (58 mg, 0.18 mmol) in methylene chloride (18 mL) was stirred at room temperature under argon for 120 h. The mixture was concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 1:4 $\rightarrow$ 1:1] afforded **395** (74 mg, 0.56 mmol, 19%) as an orange solid.

$\boldsymbol{R_f}$ (Hexane:EtOAc, 1:1) = 0.18

mp = 136°C

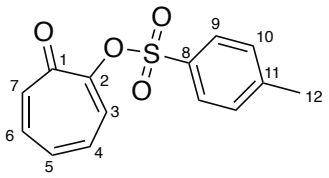
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.72 (d, J = 8.3 Hz, 1H, **H3**), 7.31-7.14 (m, 3H, **H5+H6+H7**), 7.12-6.98 (m, 1H, **H4**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 182.7 (**C1**), 144.1 (**C3**), 143.0 (**C6**), 139.9 (**C5**), 136.4 (**C7**), 132.7 (**C4**), 127.2 (**C2**), 116.9 (**C8**).

FTIR (ATR) ν (cm^{-1}); 3028, 2227 (C≡N), 1623 (C=O).

HRMS (APCI); *m/z* calculated for: C_8H_5NO $[M+H]^+$ 132.0444, found 132.0450.

7-Oxocyclohepta-1,3,5-trien-1-yl 4-methylbenzene-1-sulfonate 397



Tosyl chloride (0.57 g, 4.1 mmol) was added to a stirred solution of **200** (0.50 g, 4.1 mmol) in pyridine (2 mL) at 0 ºC under nitrogen, then stirred at 0 ºC. The reaction was then allowed to warm to room temperature and stirred for a further 18 hours, diluted with water (2 mL) and the resulting white precipitate was collected by filtration. Recrystallisation from hot ethanol yielded **397** (430 mg, 1.9 mmol, 47%) as white needles.

mp = 157–160 ºC

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.92 (ddd, J = 8.5, 3.7, 1.9 Hz, 2H, **H9**), 7.46 (dd, J = 9.7, 1.2 Hz, 1H, **H3**), 7.35 (dd, J = 8.5, 0.6, 2H, **H10**), 7.24-7.18 (ddd, J = 12.2, 7.8, 1.2 Hz, 1H, **H6**), 7.14 (ddd, J = 12.2, 1.2, 1H, **H7**), 7.11-7.05 (1H, m, **H5**), 7.01-6.94 (ddd, J = 9.7, 1.1, 0.3 Hz, 1H, **H4**), 2.45 (s, 3H, **H12**).

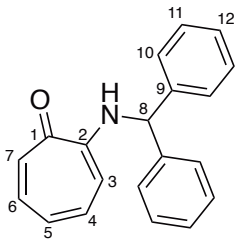
^{13}C NMR (101 MHz, $CDCl_3$); δ 179.9 (**C1**), 155.2 (**C2**), 145.6 (**C8**), 141.4 (**C7**), 136.5 (**C6**), 134.7 (**C5**), 133.6 (**C13**), 131.0 (**C4**), 130.2 (**C3**), 129.8 (**C10**), 128.8 (**C9**), 21.92 (**C12**).

FTIR (ATR) ν (cm^{-1}); 3062, 3039, 2918, 2730, 1628 (C=O).

HRMS (ESI); *m/z* calculated for: $C_{13}H_{10}O_2$ $[M+H]^+$ 277.0529, found 277.0525.

The spectroscopic data were consistent with those previously reported.[6]

2-(Benzhydryl)cyclohepta-2,4,6-trien-1-one 398a



Benzhydrylamine (0.12 mL, 0.70 mmol) was added to a mixture of **397** (100 mg, 0.4 mmol) and triethylamine (0.1 mL, 0.7 mmol) in EtOH (2 mL). The reaction mixture was heated at reflux for one hour, allowed to cool to room temperature and concentrated under reduced pressure. The residue was taken up in distilled water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1→1:1] afforded **398a** (71 mg, 0.50 mmol, 71%) as a yellow solid.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 1:1) = 0.36

mp = 69-71 °C

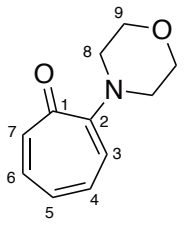
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.71 (d, J = 6.0 Hz, 1H, -N**H**), 7.38-7.24 (m, 11H, Ar-**H** and **H6**), 7.21 (m, 1H, **H3**), 7.07 (at, J = 10.9 Hz, 1H, **H4**) 6.68-6.63 (m, 1H, **H5**), 6.42 (d, J = 10.8 Hz, 1H, **H7**), 5.72 (d, J = 6.0 Hz, 1H, **H8**)

^{13}C NMR (101 MHz, $CDCl_3$); δ 177.2 (**C1**) 154.2 (**C2**), 140.4, 137.3 (**C6**), 136.1 (**C4**), 129.7 (Ar-**C**), 129.0 (**C3**), 127.9 (Ar-**C**), 127.4 (Ar-**C**), 122.9 (**C5**), 110.3 (**C7**), 61.8 (**C8**).

FTIR (ATR) ν (cm^{-1}); 3306, 2115, 1569 (C=O).

HRMS (APCI); *m/z* calculated for: $C_{20}H_{17}NO$ $[M+H]^+$ 288.1383, found 288.1394.

2-(Morpholin-4-yl)cyclohepta-2,4,6-trien-1-one 398b



Morpholine (0.17 mL, 2.0 mmol) was added to a mixture of **397** (276 mg, 1.00 mmol) and triethylamine (0.27 mL, 2.0 mmol) in EtOH (5 mL). The reaction mixture was heated at reflux for one hour, allowed to cool to room temperature and concentrated underreduced pressure. The residue was taken up in distilled water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford **398b** (174 mg, 0.910 mmol, 91%) as an orange solid.

$\boldsymbol{R_f}$ (Heptane:EtOAc, 1:1) = 0.34

mp = 69-70 °C

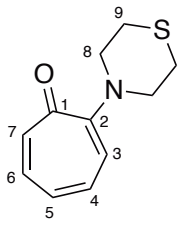
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.11 (m, 2H, **H4+H6**), 6.72-6.65 (m, 3H, **H3+H5+H7**), 3.92-3.83 (m, 4H, **H9**), 3.37-3.28 (m, 4H, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 182.8 (**C1**), 159.8 (**C2**), 136.2 (**C3/C4**), 135.6 (**C6**), 133.7 (**C3/C4**), 126.9 (**C5**), 118.9 (**C7**), 66.9 (**C9**), 49.3 (**C8**).

FTIR (ATR) ν (cm^{-1}); 2961, 2829, 1850, 1616 (C=O), 1562.

HRMS (ESI); *m/z* calculated for: $C_{11}H_{13}NO_2$ $[M+H]^+$ 192.1019, found 192.1014.

2-(Thiomorpholin-4-yl)cyclohepta-2,4,6-trien-1-one 398c



Thiomorpholine (0.20 mL, 2.0 mmol) was added to a mixture of **397** (276 mg, 1.00 mmol) and triethylamine (0.27 mL, 2.0 mmol) in EtOH (5 mL). The reaction mixture was heated at reflux for one hour, allowed to cool to room temperature and concentrated under reduced pressure. The residue was taken up in distilled water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford **398c** (130 mg, 0.63 mmol, 63%) as a dark orange solid.

R_f (Heptane:EtOAc, 1:1) = 0.23

mp = 70-71 °C

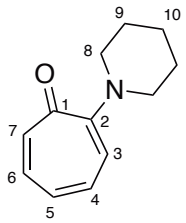
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.13-7.07 (ddd, J = 12.0, 8.0, 1.2 Hz, 1H, **H6**), 7.01 (m, 2H, **H3**+**H4**), 6.74-6.64 (m, 2H, **H5**+**H7**), 3.65-3.59 (m, 4H, **H9**), 2.82-2.75 (m, 4H, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 183.0 (**C1**), 160.2 (**C2**), 136.2 (C3/C4), 135.6 (**C6**), 133.7 (C3/C4), 126.8 (**C5**), 119.7 (**C7**), 52.0 (**C9**), 47.5 (**C8**).

FTIR (ATR) ν (cm^{-1}); 2947, 2104, 1610 (C=O), 1549.

HRMS (APCI); *m/z* calculated for: $C_{11}H_{13}NOS$ $[M+H]^+$ 208.0791, found 208.0782.

2-(Piperidin-1-yl)cyclohepta-2,4,6-trien-1-one 398d



Piperidine (0.17 mL, 2.0 mmol) was added to a mixture of **397** (276 mg, 1.00 mmol) and triethylamine (0.27 mL, 2.0 mmol) in EtOH (5 mL). The reaction mixture was heated at reflux for one hour, allowed to cool to room temperature and concentrated under reduced pressure. The residue was taken up in distilled water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford

398d (134 mg, 0.910 mmol, 71%) as an orange oil.

R_f (Heptane:EtOAc, 1:1) = 0.22

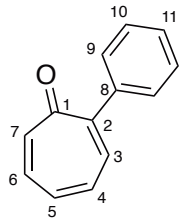
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.09-7.02 (m, 1H, **H6**) 7.02-6.95 (m, 2H, **H3**+**H4**) 6.69 (d, J = 10.3 Hz, 1H, **H7**), 6.65-6.58 (m, 1H, **H5**), 3.36-3.27 (m, 4H, **H8**), 1.78-1.61 (m, 6H, **H9**+**10**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 183.0 (**C1**), 160.71 (**C2**), 135.32 (**C6**), 134.94, 133.9 , 125.34 (**C5**), 118.3 (**C7**), 50.5 (**C8**), 26.1 (**C9**), 24.8 (**C10**).

FTIR (ATR) ν (cm^{-1}); 2935, 2855, 2804, 1612 (C=O).

HRMS (APCI); *m/z* calculated for: $C_{12}H_{15}NO$ $[M+H]^+$ 190.1226, found 190.1232.

2-Phenylcyclohepta-2,4,6-trien-1-one 403a



Phenylboronic acid (1.7 g, 7.1 mmol), Cs_2CO_3 (9.1 g, 28 mmol) and $Pd(PPh_3)4$ (0.8 g, 0.7 mmol) were added to a stirred solution of **393** (1.0 g, 7.1 mmol) in THF:H_2O (9:1, 40 mL) and the resulting mixture was heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 10 mL). The organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 1:1] afforded **403a** (0.99 g, 5.5 mmol, 77% yield) as orange crystals.

R_f (hexane-EtOAc, 1:1) = 0.51

mp = 78-79 °C

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.52-7.45 (m, 2H, **H9**), 7.44-7.37 (m, 4H, **H10**+**H11**+**H6**), 7.19 (ddd, J = 12.1, 1.5, 0.8 Hz, 1H, **H3**), 7.13 (ddd, J = 12.1, 7.3, 1.4 Hz, 1H, **H4**), 7.04 (ddd, J = 10.5, 8.7, 1.5, 0.8 Hz, 1H, **H5**), 6.97 (ddt, J = 10.5,

7.3, 1.3 Hz, 1H, **H7**).

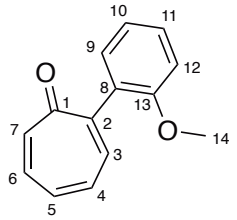
^{13}C NMR (101 MHz, $CDCl_3$); δ: 186.5 (**C1**), 152.6 (**C2**), 142.2 (**C3**), 139.9 (**C8**), 136.4 (**C6**), 135.2 (**C4**), 133.7 (**C5**), 133.2 (**C7**), 129.2 (**C9**), 128.4 (**C11**), 128.09 (**C10**).

FTIR (ATR) ν (cm^{-1}); 2920 (C-H), 1625 (C=O).

HRMS (ESI); *m/z* calculated for: $C_{13}H_{11}O$ $[M+H]^+$ 183.0804, found 183.0803.

The spectroscopic data were consistent with those previously reported.[7]

2-(2-Methoxyphenyl)cyclohepta-2,4,6-trien-1-one 403b



2-Methoxyphenylboronic acid (106 mg, 0.698 mmol), Cs_2CO_3 (456 mg, 1.39 mmol) and $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol) were added to a stirred solution of **393** (50 mg, 0.35 mmol) in THF:H_2O (9:1, 2 mL) and the resulting mixture was heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concetrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 1:1] afforded **403b** (32 mg, 0.41 mmol, 43%) as an orange solid.

$\boldsymbol{R_f}$ (Hexane-EtOAc, 1:1) = 0.27

mp = 71-74 °C

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.35 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 1H, Ar-**H**), 7.29 (dd, *J* = 8.3, 1.5 Hz, 2H, Ar-**H**), 7.23 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-**H**), 7.12 (m, 2H, **H3**+**H6**), 7.03-6.96 (m, 2H, **H4**+**H5**), 6.96-6.90 (m, 2H, **H7**+Ar-**H**), 3.78 (s, 3H, **H14**).

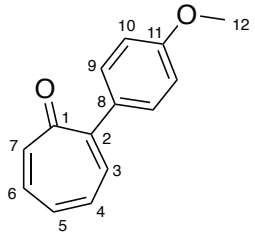
^{13}C NMR (101 MHz, $CDCl_3$); δ 186.7 (**C1**), 156.3 (**C2**), 151.4 (**C8**), 141.2 (**C6**),

136.4 (Ar-**C**), 134.9 (**C3**), 133.7 (Ar-**C**), 133.3 (**C4**), 130.6 (Ar-**C**), 130.3 (Ar-**C**), 129.75 (**C9**), 121.0 (**C5**), 111.3 (Ar-**C**), 55.9 (**C14**).

FTIR (ATR) ν (cm^{-1}); 3011, 2961, 2933, 2834, 1630 (C=O).

HRMS (ESI); *m/z* calculated for: $C_{14}H_{12}O_2$ $[M+H]^+$ 213.0910, found 213.0901.

2-(4-Methoxyphenyl)cyclohepta-2,4,6-trien-1-one 403c



4-Methoxyphenylboronic acid (106 mg, 0.698 mmol), Cs_2CO_3 (456 mg, 1.39 mmol) and $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol) were added to a stirred solution of **393** (50 mg, 0.35 mmol) in THF:H_2O (9:1, 2 mL) and the resulting mixture was heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 1:1] afforded **403c** (75 mg, 0.31 mmol, 87%) as an orange solid.

$\boldsymbol{R_f}$ (Hexane-EtOAc, 1:1) = 0.51

mp = 47-49 °C

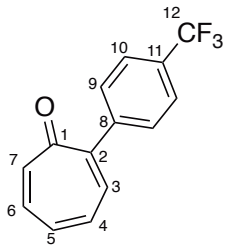
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.52-7.46 (m, 2H, Ar-**H**), 7.35 (dd, *J* = 8.9, 1.0 Hz, 1H, **H3**), 7.17 (ddd, *J* = 12.1, 1.4, 0.8 Hz, 1H, **H6**), 7.11 (ddd, *J* = 12.1, 7.4, 1.4 Hz, 1H, **H7**), 7.02 (dddd, *J* = 9.7, 8.9, 1.4, 0.8 Hz, 1H, **H4**), 6.97-6.90 (m, 3H, Ar-**H**+**H5**), 3.84 (s, 3H, **H11**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 186.8 (**C1**), 160.1 (**C2**), 152.1 (Ar-**C**), 142.1 (**C6**), 135.9 (**C3**), 135.2 (**C7**), 133.8 (**C4**), 132.8 (**C5**), 132.4 (Ar-**C**), 130.8 (Ar-**C**), 113.7 (Ar-**C**), 55.5 (**C12**).

FTIR (ATR) ν (cm^{-1}); 3060, 3017, 2942, 2907, 2832, 1602 (C=O).

HRMS (ESI); *m/z* calculated for: $C_{14}H_{12}O_2$ $[M+H]^+$ 213.0910, found 213.0903.

2-[4-(Trifluoromethyl)phenyl]cyclohepta-2,4,6-trien-1-one 403d



2-(4-Trifluoromethyl)phenylboronic acid (132 mg, 0.7 mmol), Cs_2CO_3 (456 mg, 1.40 mmol) and $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol) were added to a stirred solution of **393** (50 mg, 0.35 mmol) in THF:H_2O (9:1, 2 mL) and the resulting mixture heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 1:1] afforded **403d** (47 mg, 0.19 mmol, 53%) as a tan solid.

$\boldsymbol{R_f}$ (hexane-EtOAc, 1:4) = 0.37

mp = 73-77 °C

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.66 (d, J = 8.2 Hz, 1H, Ar-**H**), 7.58 (d, J = 8.2 Hz, 1H, Ar-**H**), 7.40-7.33 (m, 1H, **H3**), 7.21-7.17 (m, 2H, **H5+H6**), 7.11-6.99 (m, 2H, **H4+H7**).

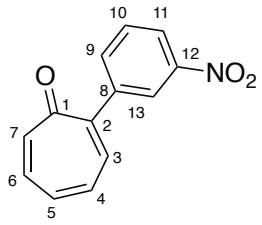
^{13}C NMR (101 MHz, $CDCl_3$); δ 186.2 (**C1**), 151.4 (**C2**), 143.5 (Ar-**C**), 142.9 (**C6**), 137.2 (**C3**), 135.8 (**C5**), 134.3 (**C4**), 133.8 (**C7**), 129.64 (Ar-**C**), 125.3 (Ar-**C**), 124.1 (q, J = 272 Hz, **C12**).

^{19}F NMR (376 MHz, $CDCl_3$); δ -62.67.

FTIR (ATR) ν (cm^{-1}); 3017, 2943, 1629, 1569 (C=O).

HRMS (APCI); Target mass not found.

2-(3-Nitrophenyl)cyclohepta-2,4,6-trien-1-one 403e



3-Nitrophenylboronic acid (120 mg, 0.70 mmol), Cs_2CO_3 (456 mg, 1.40 mmol) and $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol) were added to a stirred solution of **393** (50 mg, 0.35 mmol) in THF:H_2O (9:1, 2 mL) and the resulting mixture was heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 1:1] afforded **403e** (64 mg, 0.3 mmol, 80%) as a tan solid.

$\boldsymbol{R_f}$ (Hexane-EtOAc, 1:1) = 0.51

mp = 101-103 °C (decomposed).

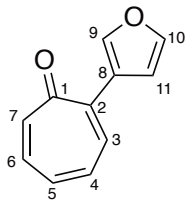
^{1}H NMR (400 MHz, $CDCl_3$); δ 8.33 (t, J = 1.7 Hz, 1H, Ar-**H**), 8.21 (ddd, J = 7.9, 2.1, 0.8 Hz, 1H, Ar-**H**), 7.83 (ddd, J = 7.9, 1.7, 1.0 Hz, Hz, 1H, Ar-**H**), 7.56 (t, J = 8.0 Hz, 1H, Ar-**H**), 7.41 (m, 1H, **H6**), 7.22-7.18 (m, 2H, **H3**+**H4**), 7.09-7.04 (m, 2H, **H5**+**H7**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 185.7 (**C1**), 150.1 (**C2**), 148.3 (Ar-**C**) 143.9 (**C3**), 141.3 (Ar-**C**), 137.4 (**C6**), 135.9 (**C4**), 134.6 (**C5**), 133.5 (**C7**), 135.5 (Ar-**C**), 129.0 (Ar-**C**), 124.5 (Ar-**C**), 123.3 (Ar-**C**).

FTIR (ATR) ν (cm^{-1}); 3060, 3017, 2942, 2907, 2832, 1602 (C=O).

HRMS (ESI); m/z calculated for: $C_{14}H_{12}O_2$ $[M+H]^+$ 213.0910, found 213.0903.

2-Furanylcyclohepta-2,4,6-trien-1-one 403g



3-Furanylboronic acid MIDA ester (802 mg, 3.60 mmol), Cs_2CO_3 (2.9 g, 8.9 mmol) and $PdCl_2PPh_3$ (12 mg, 0.017 mmol) were added to a stirred solution of **393** (500 mg, 3.5 mmol) THF:H_2O (9:1, 40 mL) and heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 4:1] afforded **403g** (470 mg, 2.7 mmol, 78%) as a yellow oil.

$\boldsymbol{R_f}$ (Hexane:EtOAc, 1:1) = 0.27

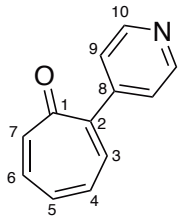
^{1}H NMR (400 MHz, $CDCl_3$); δ 8.66 (d, J = 0.6 Hz, 1H, **H9**), 7.61 (d, J = 9.0 Hz, 1H, **H3**), 7.48 – 7.42 (m, 1H, **H10**), 7.17-7.07 (m, 3H, **H4**+**H6**+**H7**), 6.98 (dddd, J = 10.7, 6.6, 2.5, 0.8 Hz, 1H, **H5**), 6.72 (dd, J = 2.0, 0.6 Hz, 1H, **H11**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 185.4 (**C1**), 146.1 (**C9**), 143.56 (**C2**), 142.6 (**C1**), 140.6 (**C6**), 134.8 (**C7**), 133.6 (**C4**), 133.1 (**C3**), 132.9 (**C5**), 123.1 (**C8**), 109.2 (**C11**).

FTIR (ATR) ν (cm^{-1}); 2961, 2873, 1716, 1740 (C=O).

HRMS (APCI); Target mass not found.

2-Pyridinylcyclohepta-2,4,6-trien-1-one 403i



4-Pyridinylboronic acid MIDA ester (87 mg, 0.36 mmol), Cs_2CO_3 (290 mg, 0.90 mmol) and $PdCl_2PPh_3$ (12 mg, 0.017 mmol) were added to a stirred solution of **393** (50 mg, 0.35 mmol) THF:H_2O (9:1, 4 mL) and heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 5 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 1:9] afforded **403i** (17 mg, 0.11 mmol, 27%) as an orange solid.

$\boldsymbol{R_f}$ (Hexane:EtOAc, 1:1) = 0.05

mp = 89-90 °C

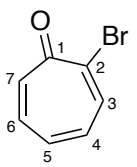
^{1}H NMR (400 MHz, $CDCl_3$); δ 8.64 (dd, J = 4.5, 1.6 Hz, 2H, **H10**), 7.38 (dd, J = 4.5, 1.6 Hz, 2H, **H9**), 7.34-7.31 (m, 1H, **H6**), 7.19-7.15 (m, 1H, **H3**+**H4**), 7.11-6.97 (m, 1H, **H5**+**H7**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 185.7 (**C1**), 149.9 (**C2**), 149.8 (**C10**), 147.7 (**C8**), 143.0 (**C3**), 137.1 (**C6**), 135.8 (**C4**), 134.7 (**C5**), 133.6 (**C7**), 123.8 (**C9**).

FTIR (ATR) ν (cm^{-1}); 3021, 2972, 1567 (C=O).

HRMS (ESI); m/z calculated for: $C_{12}H_9NO$ $[M+H]^+$ 184.0757, found 184.0752.

2-Bromocyclohepta-2,4,6-trien-1-one 404



NBS (1.77 g, 10 mmol) was added portionwise to a solution of **194** (530 mg, 5.00 mmol) in anhydrous DMF (30 mL) and the resulting mixture was heated at reflux for 18 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. The resulting residue was taken up in EtOAc (20 mL) and washed with saturated aqueous sodium thiosulfate (2 x 20 mL), water (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane-EtOAc, 9:1→7:3] afforded **404** (415 mg, 2.26 mmol, 45%) as orange needles.

$\boldsymbol{R_f}$ (7:3 heptane-ethyl acetate) = 0.28

mp = 75 °C

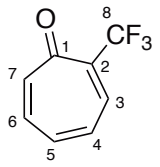
^{1}H NMR (400 MHz, $CDCl_3$); δ 8.09 (dd, J = 9.6, 1.1 Hz, 1H, **H3**), 7.23-7.12 (m, 2H, **H6+H7**), 7.08 (dddd, J = 9.6, 7.3, 2.0, 0.7 Hz, 1H, **H5**), 6.83 (atdd, J = 9.6, 1.1, 0.7 Hz, **H4**)

^{13}C NMR (101 MHz, $CDCl_3$) 180.8 (**C1**), 143.6 (**C2**), 139.3 (**C3**), 137.9 (**C6**), 135.4 (**C7**), 134.4 (**C5**), 131.9 (**C4**)

FTIR (ATR) ν (cm^{-1}); 3026, 1625 (C=O).

HRMS (ESI); m/z calculated for: C_7H_5OBr $[M+H]^+$ 184.9597, found 184.9601.

2-Trifluoromethylcyclohepta-2,4,6-trien-1-one 408



To a stirred suspension of **404** (183 mg, 1.00 mmol) and CuI (19 mg, 0.10 mmol) in dry DMF (5 mL) was added methyl fluorosulfonyldifluoroacetate (**407**) (0.31 mL, 2.5 mmol) in one portion at room temperature. The resulting solution was heated at 90 °C for 1.5 hours. The reaction mixture was allowed to cool to room temperature and then poured into EtOAc (20 mL). The organic layer was washed with water

(10 mL), aqueous 10% LiCl (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1] afforded **408** (91 mg, 0.52 mmol, 52%) as an orange oil.

R_f (1:1 pentane:CH_2Cl_2) = 0.65

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.68-7.62 (m, 1H, H3), 7.18-7.07 (m, 3H, H4–6), 7.06-6.98 (m, 1H, H4).

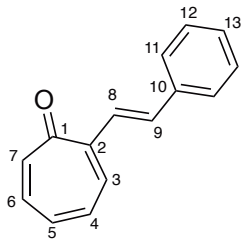
^{13}C NMR (101 MHz, $CDCl_3$); δ 183.2 (**C1**), 143.9 (q, J = 1.8, **C6**), 138.5 (q, J = 26.1, **C2**), 138.1 (), 135.6 (q, *J* = 6.2 Hz, **C3**), 135.5 (**C7**), 135.3 (**C5**), 131.9 (**C4**), 122.3 (q, *J* = 278 Hz, **C8**).

^{19}F NMR (376 MHz, $CDCl_3$); δ -66.4.

FTIR (ATR) ν (cm^{-1}); 1643 (C=O).

HRMS (APCI); *m/z* calculated for: $C_8H_5OF_3$ $[M+H]^+$ 175.0363, found 175.0365.

2-[(1E)-2-Phenylethenyl]cyclohepta-2,4,6-trien-1-one 409



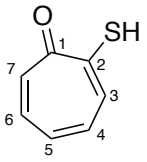
Styrene (40 μL, 0.35 mmol), NEt_3 (0.1 mL, 0.7 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.075 mmol) were added to a stirred solution of **393** (50 mg, 0.35 mmol) in anhydrous PhMe (4 mL) the resulting mixture was heated at reflux for 18 hours under argon. The solution was allowed to cool to room temperature concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 4:1] afforded **409** (10 mg, 0.05 mmol, 13%) as a yellow residue.

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.66-7.57 (m, 4H, **H8**, Ar-**H**), 7.42-7.36 (m, 3H, **H9**, Ar-**H**), 7.34 – 7.30 (m, 1H, **H3**), 7.16-7.14 (m, 2H, **H6** + **H4**), 7.10-7.05 (m, 1H, **H5**), 6.99-6.94 (m, 1H, **H7**).

^{13}C NMR (101 MHz, $CDCl_3$)δ 186.2 (**C1**), 148.5 (**C2**), 140.6 (**C6**), 137.0 (Ar-**C**), 135.3 (**C4**), 134.4 (Ar-**C**), 133.6 (**C5**), 133.1 (**C7**), 132.1 (Ar-**C**), 128.7 (Ar-**C**), 128.6 (**C3**), 127.4 (**C11**), 126.7 (**C8**).

HRMS (APCI); *m*/*z* calculated for: $C_{15}H_{12}O_2$ $[M+H]^+$ 209.0961, found 209.0954.

2-Sulfanylcyclohepta-2,4,6-trien-1-one 410



Lawesson's reagent (6.51 g, 16.1 mmol) was added to a stirred solution of **186** (1.0 g, 8.1 mmol) in toluene (50 mL), and the resulting mixture was heated at reflux overnight. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, 7:3, heptane:EtOAc] afforded **410** (70 mg, 0.50 mmol, 6%) as a red oily solid.

$\boldsymbol{R_f}$ (7:3 heptane:EtOAc) = 0.27

^{1}H NMR (400 MHz, $CDCl_3$); δ 9.93 (s, 1H, -S**H**), 8.54-8.51 (m, 1H, **H3**), 7.45 (dd, J = 11.0, 1.0 Hz, 1H, **H7**), 7.41-7.34 (m, 1H, **H6**), 7.24-7.16 (m, 2H, **H4** + **H5**).

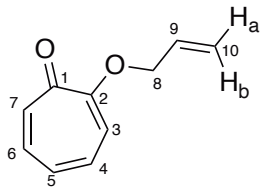
^{13}C NMR (101 MHz, $CDCl_3$); δ 183.44 (**C1**), 174.02 (**C2**), 143.68 (**C3**), 138.12 (**C6**), 134.10 (**C4/C5**), 133.14 (**C4/C5**), 120.62 (**C7**).

FTIR (MeCN) ν (cm^{-1}); 3002, 2944, 2292, 2253.

HRMS (APCI); No mass peak detected.

The spectroscopic data were consistent with those previously reported.[8]

2-(Prop-2-en-1-yloxy)cyclohepta-2,4,6-trien-1-one 411



200 (1.0 g, 8.2 mmol) was added to a stirred solution of TBAOH (1.5 M in H_2O, 5.4 mL, 8.2 mmol) at room temperature, and the resulting suspension stirred at room temperature for one hour. A solution of allyl bromide (0.70 mL, 8.2 mmol) in dichloromethane (40 mL) was then added dropwise over the course of 30 minutes and the resulting solution was heated at reflux for 18 hours. The reaction mixture was allowed to cool to room temperature, diluted with water (40 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, 7:3, CH_2Cl_2:EtOAc] afforded **411** (560 mg, 3.4 mmol, 43%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$); δ 7.17–7.23 (m, 2H, **H4** + **H5**), 7.01-6.93 (m, 1H, **H6**), 6.83-6.76 (m, 1H, **H3**), 6.70 (d, J = 10.8, 1H, **H7**), 6.04-5.93 (m, 1H, **H9**), 5.36 (ddd, J = 17.2, 2.8, 1.6 Hz, **H10b**) , 5.26 (ddd, J = 10.6, 2.8, 1.6 Hz, **H10a**) 4.65-4.60 (m, 2H, **H8**)

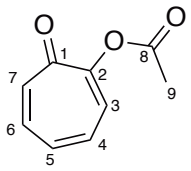
^{13}C NMR (101 MHz, $CDCl_3$); δ 180.4 (**C1**), 164.2 (**C2**), 137.0 (**C6**), 136.3 (**C4**), 132.5 (**C5**), 131.4 (**C9**), 128.0 (**C3**), 118.7 (**C10**), 114.0 (**C7**), 69.8 (**C8**).

FTIR (ATR) ν (cm^{-1}); 2893, 1623 (C=O).

HRMS (APCI); *m/z* calculated for: $C_{10}H_{10}O_2$ $[M+Na]^+$ 163.0730, found 163.0738.

The spectroscopic data were consistent with those previously reported.[9]

7-Oxocyclohepta-1,3,5-trien-1-yl acetate 412



Acetic anhydride (2.00 mL, 29.7 mmol) was added in one portion to a stirred solution of **200** (1.0 g, 8.1 mmol) in anhydrous pyridine (5 mL) at room temperature and the resulting solution was stirred at room temperature for 18 hours. The solvent and excess acetic anhydride were removed under reduced pressure to afford **412** (1.1 g, 6.7 mmol, 82%) as a light beige solid.

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.22 (dd, J = 11.0, 1.2 Hz, 2H, **H4**+**H6**), 7.14 (dd, J = 14.9, 6.1 Hz, 2H, **H3**+**H5**), 7.09-7.02 (m, 1H, **H7**), 2.35 (s, 3H, **H9**).

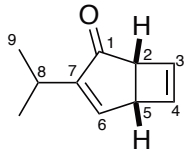
^{13}C NMR (101 MHz, $CDCl_3$); δ 168.35 (**C2**), 134.16 (**C4**), 133.58 (**C5**), 20.84 (**C9**).

FTIR (ATR) ν (cm^{-1}); 3069, 3021, 2931, 1753 (C=O).

HRMS (APCI); *m*/*z* calculated for: $C_9H_8O_3$ $[M+H]^+$ 165.0546, found 165.0551.

The spectroscopic data were consistent with those previously reported.[10]

7-Isopropylbicyclo[3.2.0]hepta-3,6-dien-1-one 413a



To a solution of **386** (33 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (8.6 mL) was added $BF_3{\cdot}OEt_2$ (28 μL, 0.23 mmol) and the resulting solution purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for 2.5 hours and concentrated under reduced pressure. Purification by flash column

chromatography [SiO_2, pentane:CH_2Cl_2, 99:1 → 4:1] afforded a 1:4 mixture of **429** and **434** (9 mg, 0.07 mmol, 27%) as a yellow oil.

Data for mixture:

R_f (1:1 pentane:CH_2Cl_2) = 0.56.

FTIR (ATR) ν (cm^{-1}); 3026, 2957, 2871, 1709 (C=O).

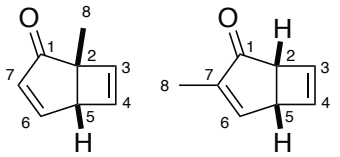
HRMS (ESI); No mass peak found.

NMR data for **434**:

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.22 (dd, *J* = 2.9, 1.3 Hz, 1H, **H6**), 6.55 (dt, *J* = 2.4, 0.6 Hz, 1H, **H4**), 6.35 (dd, *J* = 2.4, 1.7 Hz, 1H, **H3**), 3.81-3.78 (m, 1H, **H5**), 3.51 (dd, *J* = 2.5, 1.7 Hz, 1H, **H2**) 2.57 (qt, *J* = 7.1, 1.3 Hz, 1H, **H8**), 1.07 (dd, *J* = 10.9, 7.1, 6H, **H9**)

^{13}C NMR (101 MHz, $CDCl_3$); δ 206.5 (**C1**), 164.6 (**C7**), 152.8 (**C6**), 143.6 (**C4**), 136.8 (**C3**), 54.2 (**C2**), 47.7 (**C5**), 24.9 (**C8**), 21.3 (**C9**), 21.0 (**C9**).

2-Methylbicyclo[3.2.0]hepta-3,6-dien-1-one 413b and **7-Methylbicyclo[3.2.0]hepta-3,6-dien-1-one 414b**



428 **433**

To a solution of **389b** (202 mg, 1.60 mmol) in anhydrous CH_2Cl_2 was added $BF_3{\cdot}OEt_2$ (0.20 mL, 1.7 mmol) and the resulting solution was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for two hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 99:1 → 4:1] afforded a 1:6 mixture of **413b** and **414b** (64 mg, 0.52 mmol, 31%) as a yellow oil.

R_f (9:1 Heptane-EtOAc) = 0.47.

NMR data for **428**:

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.63 (dd, J = 5.8, 2.8 Hz, 1H, **H6**), 6.52 (dd, J = 2.8, 1.0 Hz, 1H, **H3**), 6.31 (d, J = 2.8 Hz, 1H, **H4**), 6.07 (d, J = 5.8 Hz, 1H, **H7**), 3.56 (dd, J = 2.8, 0.8 Hz, 1H, **H5**), 1.36 (s, 3H, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 204.7 (**C1**), 142.3 (**C4**), 141.2 (**C3**), 141.1 (**C6**), 133.3 (**C7**), 56.7 (**C5**), 29.7 (**C2**), 15.4 (**C8**)

NMR data for **433**:

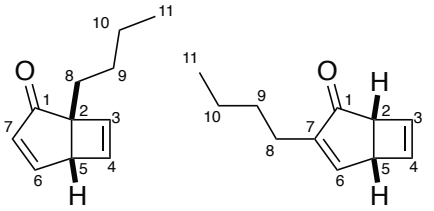
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.28 (dq, J = 2.7, 1.4 Hz, 1H, **H6**), 6.55-6.53 (m, 1H, **H4**), 6.35 (dd, J = 2.5, 1.3 Hz, 1H, **H3**), 3.79 (ddd, J = 3.7, 2.7, 1.1 Hz, 1H, **H5**), 3.51-3.49 (m, 1H, **H2**), 1.74 (d, J = 1.4 Hz, 3H, **H8**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 206.5 (**C1**), 161.5 (**C7**), 156.1 (**C6**), 143.6 (**C4**), 136.9 (**C3**), 53.6 (**C2**), 48.0 (**C5**), 11.0 (**C8**).

FTIR (ATR) ν (cm^{-1}); 3050, 2924, 1688 (C=O).

N.B. products is volatile and should not be subjected to high vacuum.

2-Butylbicyclo[3.2.0]hepta-3,6-dien-1-one 413c and **7-Butylbicyclo[3.2.0]hepta-3,6-dien-1-one 414c**



430 **435**

To a solution of **389c** (338 mg, 2.06 mmol) in anhydrous CH_2Cl_2 (82 mL) split across two pyrex tubes was added $BF_3{\cdot}OEt_2$ (0.28 mL, 2.2 mmol) and the resulting solution purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for two hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, CH_2Cl_2] afforded a 4:1 mixture of **430** and **435** (91 mg, 0.60 mmol, 26%) as a yellow oil.

Data for mixture:

R_f (9:1 pentane:CH_2Cl_2) = 0.62.

FTIR (ATR) ν (cm^{-1}); 2955, 2929, 2860, 1692.

HRMS (APCI); *m/z* calculated for: $C_{11}H_{14}O$ $[M+H]^+$ 163.1117, found 163.1114.

NMR data for **413c**:

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.63 (dd, *J* = 5.9, 2.8 Hz, 1H, **H6**), 6.54 (m, 1H, **H4**), 6.29 (d, *J* = 2.6 Hz, 1H, **H3**), 6.08 (d, *J* = 5.9 Hz, 1H, **H7**), 3.63 (dd, *J* = 2.9, 0.8 Hz, 1H, **H5**), 1.89-1.79 (m, 2H, **H8**), 1.41-1.18 (m, 4H, **H9** + **H10**), (m, 3H, **H11**).

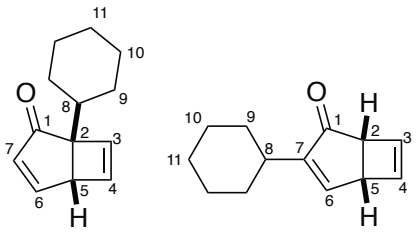
^{13}C NMR (101 MHz, $CDCl_3$); δ 208.8 (**C1**), 161.8 (**C6**), 141.5 (**C4**), 140.5 (**C3**), 134.2 (**C7**), 54.6 (**C5**), 47.1 (**C2**), 30.2 (**C8**), 27.9 (**C9/C10**), 23.1 (**C9/C10**), 21.8 (**C11**).

NMR data for **414c**:

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.24 (dt, *J* = 2.8, 1.4 Hz, 1H, **H6**), 6.55-6.53 (m, 1H, **H4**), 6.34 (dd, *J* = 2.5, 1.3 Hz, 1H, **H3**), 3.80 (td, *J* = 2.8, 1.2 Hz, 1H, **H5**), 3.50-3.49 (m, 1H, **H2**), 2.16-2.08 (m, 2H, **H8**), 1.48-1.38 (m, 2H, **H9**), 1.38-1.27 (m, 2H, **H10**), 0.93-0.84 (m, 3H, **H11**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 206.1 (**C1**), 154.9 (**C6**), 143.6 (**C4**), 136.8(**C3**), 53.8 (**C5**), 47.9(**C2**), 29.7 (**C9**), 25.0 (**C8**), 22.4 (**C10**), 13.9 (**C11**).

3-Cyclohexylbicyclo[3.2.0]hepta-3,6-dien-2-one 389d



431 **436**

To a solution of **389d** (186 mg, 1.00 mmol) in anhydrous MeCN (82 mL) split across two pyrex tubes was added $BF_3{\cdot}OEt_2$ (0.28 mL, 2.2 mmol) and the resulting solution purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300

nm) at room temperature for two hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 19:1] afforded a 1:3 mixture of **413d** and **414d** (105 mg, 0.555 mmol, 55%) as a yellow oil.

Data for mixture:

$\boldsymbol{R_f}$ (9:1 Heptane:EtOAc) = 0.36.

FTIR (ATR) ν (cm^{-1}); 2924, 2851, 1695 (C=O).

HRMS (APCI); *m/z* calculated for: $C_{13}H_{16}O$ $[M+H]^+$ 189.1274, found 189.1276.

NMR data for **413d**:

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.61 (dd, *J* = 5.8, 2.9 Hz, 1H, **H6**), 6.54 (m, 1H, **H3**), 6.31 (d, *J* = 2.6 Hz, 1H, **H4**), 6.06 (d, *J*= 5.8 Hz, 1H, **H7**), 3.70 (d, *J*= 2.8 Hz, 1H, **H5**), 1.95 (tt, *J*= 12.3, 3.7 Hz, 1H, **H8**), 1.78-1.05 (m, 10H, Cy-**H**).

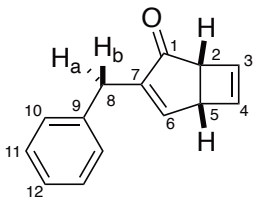
^{13}C NMR (101 MHz, $CDCl_3$); δ 209.3 (**C1**), 61.7 (**C6**), 141.8 (**C3**), 139.5 (**C4**), 134.6 (**C7**), 52.5 (**C5**), 39.3 (**C8**).

NMR data for **414d**:

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.20 (dd, *J* = 2.9, 1.1, 1H, **H6**), 6.53-6.54 (m, 1H, **H4**), 6.34 (dd, *J* = 2.5, 1.3 Hz, 1H, **H3**), 3.78-3.79 (m, 1H, **H5**), 3.49 (dd, *J* = 2.4, 1.3 Hz, **H2**), 2.28-2.21 (m, 1H, **H8**), 1.78-1.05 (m, 10H, Cy-**H**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 205.7 (**C1**), 161.8 (**C7**), 153.5 (**C6**), 143.7 (**C4**), 136.8 (**C3**), 54.1 (**C2**), 47.8 (**C5**), 34.3 (**C8**), 31.9 (Cy-**C**-), 31.5 (Cy-**C**), 26.3 (Cy-**C**).

3-Benzylbicyclo[3.2.0]hepta-3,6-dien-2-one 413e



To a solution of **389** (273 mg, 1.50 mmol) in anhydrous MeCN (60 mL) split across two pyrex tubes was added $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol) and the resulting solution was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300

nm) at room temperature for two hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 7:3] afforded a 1:5 mixture of **437** and **432** (26 mg, 0.13 mmol, 9%) as an orange oil.

Data for mixture:

R_f (7:3 Heptane:EtOAc) = 0.55.

FTIR (ATR) ν (cm^{-1}); 3056, 3028, 2927, 2249, 1692 (C=O).

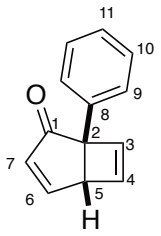
HRMS (APCI); *m/z* calculated for: $C_{14}H_{12}O$ $[M+H]^+$ 197.0961, found 197.0962.

NMR data for **413e**:

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.33-7.14 (m, 5H, Ar-**H**), 7.08 (dt, *J* = 2.9, 1.5 Hz, 1H, **H6**), 6.52-6.51 (m, 1H, **H4**), 6.36 (dd, *J* = 2.4, 1.3 Hz, 1H, **H3**), 3.82-3.78 (m, 1H, **H5**), 3.56 (dd, *J* = 2.2, 1.3 Hz, 1H, **H2**), 3.52 (d, *J* = 15.8 Hz, 1H, **H8a**) 3.46 (d, *J* = 15.8 Hz, 1H, **H8b**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 205.3 (**C1**), 156.4 (**C6**), 146.2 (**C2**), 143.4 (**C4**), 136.7 (**C3**), 129.0 (**C7**), 128.5 (Ar-**C**), 126.4 (Ar-**C**), 126.3 (Ar-**C**), 53.9 (**C2**), 48.0 (**C5**), 31.8 (**C8**).

2-Phenylbicyclo[3.2.0]hepta-3,6-dien-1-one 416a



A solution of **403a** (47 mg, 0.26 mmol) in MeOH (10 mL) was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 350 nm) at room temperature for 24 hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 9:1] afforded **416a** (5 mg, 0.03 mmol, 12%) as a brown oil.

R_f (4:1 Heptane:EtOAc = 0.51).

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.77 (dd, *J* = 5.8, 2.6 Hz, 1H, **H6**), 7.36-7.32 (m,

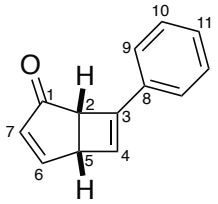
2H, Ar-**H**), 7.28-7.23 (m, 3H, Ar-**H**), 6.75 (dd, *J* = 2.5, 1.1 Hz, 1H, **H4**), 6.65 (d, *J*= 2.5 Hz, 1H, **H3**), 6.23 (d, *J* = 5.8 Hz, 1H, **H7**), 3.97 (d, *J* = 2.6, 1H, **H5**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 206.4 (**C1**), 161.5 (**C6**), 143.4 (**C4**), 138.8 (**C3**), 137.7 (Ar-**C**) 134.3 (**C7**), 128.7 (Ar-**C**), 127.2 (Ar-**C**), 126.9 (Ar-**C**), 64.8 (**C2**), 59.2 (**C5**).

FTIR (ATR) ν (cm^{-1}); 3063, 2916, 2942, 1701 (C=O).

HRMS (APCI); *m*/*z* calculated for: $C_{10}H_{12}O_2$ $[M+H]^+$ 183.0804, found 183.0802.

7-Phenylbicyclo[3.2.0]hepta-3,6-dien-2-one 417a



A solution of **403a** (82 mg, 0.44 mmol) in MeOH (44 mL) was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 350 nm) at room temperature for 96 hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1] afforded **417a** (38 mg, 0.21 mmol, 46%) as a yellow solid.

R_f (4:1 Heptane:EtOAc = 0.51.

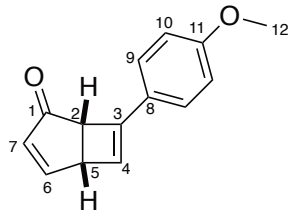
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.72 (dd, *J* = 5.7, 2.7 Hz, 1H, **H6**), 7.60-7.53 (m, 2H, Ar-**H**), 7.35 (m, 2H, Ar-**H**), 7.28 (m, 1H, Ar-**H**), 6.69 (d, *J* = 0.7 Hz, 1H, **H4**), 6.11-6.07 (ddd, *J* = 5.7, 1.0, 0.5 Hz, 1H, **H7**), 3.95 (td, *J* = 2.7, 0.7 Hz, 1H, **H5**), 3.89 (dd, *J* = 2.7, 1.0 Hz, 1H, **H2**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 206.37 (**C1**), 163.20 (**C6**), 147.68 (**C3**), 134.52 (**C7**), 132.88 (Ar-**C**), 131.16 (**C4**), 128.75 (Ar-**C**), 128.63 (Ar-**C**), 125.69 (Ar-**C**), 52.67 (**C2**), 46.58 (**C5**).

FTIR (ATR) ν (cm^{-1}); 2916, 1735 (C=O).

HRMS (APCI); *m*/*z* calculated for: $C_{13}H_{10}O$ $[M+H]^+$ 183.0809, found 183.0804.

7-(4-Methoxyphenyl)bicyclo[3.2.0]hepta-3,6-dien-2-one 417b



A solution of **403b** (75 mg, 0.35 mmol) in MeOH (35 mL) was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 350 nm) at room temperature for 96 hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1] afforded **417b** (11 mg, 0.051 mmol, 48%) as a light beige solid.

$\boldsymbol{R_f}$ (4:1 Heptane:EtOAc = 0.53.

mp = 66-67 °C

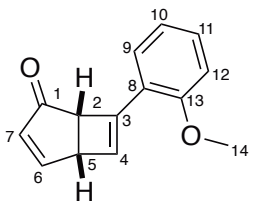
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.72 (dd, *J* = 5.7, 2.7 Hz, 1H, **H6**), 7.60-7.53 (m, 2H, Ar-**H**), 6.69 (d, *J* = 1.2 Hz, 1H, Ar-**H**), 6.52 (d, *J* = 1.2, 1H, **H4**), 6.11-6.07 (d, *J* = 1.1 Hz, 1H, **H7**), 3.95 (td, *J* = 2.7, 1.2 Hz, 1H, **H5**), 3.89 (dd, *J* = 2.7, 0.7 Hz, 1H, **H2**), 3.84 (s, 1H, H12).

^{13}C NMR (101 MHz, $CDCl_3$); δ 206.6 (**C1**), 163.5 (**C6**), 159.9 (Ar-**C**), 147.0 (**C3**), 134.2 (**C7**), 128.3 (**C4**), 127.1 (Ar-**C**), 125.8 (Ar-**C**), 113.9 (Ar-**C**), 55.3 (A**C12**), 52.6 (**C2**), 46.3 (**C5**).

FTIR (ATR) ν (cm^{-1}); 3418, 3004, 1710 (C=O).

HRMS (APCI); *m*/*z* calculated for: $C_{14}H_{12}O_2$ $[M+H]^+$ 213.0982, found 213.0908.

7-(2-Methoxyphenyl)bicyclo[3.2.0]hepta-3,6-dien-2-one 417c



A solution of **403c** (27 mg, 0.13 mmol) in MeOH (25 mL) was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 350 nm) at room temperature for 96 hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1] afforded **417c** (11 mg, 0.052 mmol, 41%) as a light beige solid.

R_f (4:1 Heptane:EtOAc = 0.52.

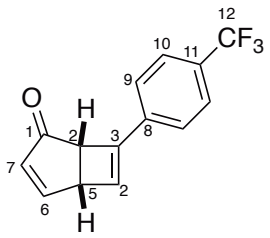
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.73 (dd, *J* = 5.8, 2.7 Hz, 1H, **H6**), 7.70 (dd, *J* = 7.6, 1.3 Hz, 1H, Ar-**H**), 7.28-7.21 (dd, *J* = 7.6, 1.9, 2H, Ar-**H**), 7.03-6.96 (m, 1H, Ar-**H**), 6.85 (dd, *J* = 8.3, 0.7 Hz, 1H, Ar-**H**), 6.74 (d, *J* = 1.1 Hz, 1H, **H4**), 6.08-6.06 (d, *J* = 5.8 Hz, 1H, **H7**), 3.98-3.95 (m, 1H, **H5**), 3.92-3.90 (m, 1H, **H2**), 3.87 (s, 3H, **H14**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 206.7 (**C1**), 163.5 (**C6**), 158.2 (Ar-**C**), 143.8 (**C3**), 135.6 (**C4**), 134.0 (**C7**), 129.6 (Ar-**C**), 128.8 (Ar-**C**), 121.6 (Ar-**C**), 120.5 (Ar-**C**), 110.2 (Ar-**C**), 55.1 (**C14**), 53.00 (**C2**), 47.5 (**C5**).

FTIR (ATR) ν (cm^{-1}); 3418, 3004, 1710 (C=O).

HRMS (APCI); Not received at time of submission.

2-[4-(Trifluoromethyl)phenyl]cyclohepta-2,4,6-trien-1-one 403d



A solution of **403d** (98 mg, 0.39 mmol) in MeOH (39 mL) was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 350 nm) at room temperature for 96 hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1] afforded **417d** (22 mg, 0.087 mmol, 22%) as a dark brown resin.

R_f (4:1 Heptane:EtOAc = 0.36).

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.72 (dd, *J* = 5.8, 2.7 Hz, 1H, **H6**), 7.68–7.56 (m,

ArH), 6.83 (d, *J* = 1.0 Hz, 1H, **H4**), 6.11 (d, *J* = 5.8 Hz, 1H, **H7**), 4.00-3.97 (m, 1H, **H2**), 3.90 (dd, *J* = 2.7, 1.0 Hz, 1H, **H5**).

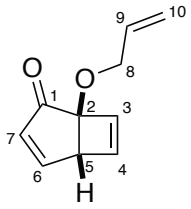
^{13}C NMR (101 MHz, $CDCl_3$); δ 205.6 (**C1**), 162.6 (**C6**), 146.3 (**C4**), 134.6 (**C7**), 134.0 (**C4**), 130.5 (Ar-C), 125.8 (Ar-**C**), 125.5 (q, *J* = 4.1 Hz, Ar-**C**), 122.7 (**C8**), 120.3 (q, *J* = 232 Hz, **C**F_3) 52.4 (**C5**), 46.6 (**C2**).

^{19}F NMR (376 MHz, $CDCl_3$); δ -62.70.

FTIR (ATR) ν (cm^{-1}); 3058, 2935, 1694 (C=O).

HRMS (APCI); *m/z* calculated for: $C_{14}H_9OF_3$ $[M+H]^+$ 251.0678, found 251.0690.

1-(Prop-2-en-1-yloxy)bicyclo[3.2.0]hepta-3,6-dien-2-one 420



***R*$_f$** (4:1 Heptane:EtOAc = 0.45).

A solution of **411** (40 mg, 0.25 mmol) in MeOH (10 mL) was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for two hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, hexane:EtOAc, 4:1] afforded **420** (16 mg, 0.28 mmol, 41%) as a light beige oil.

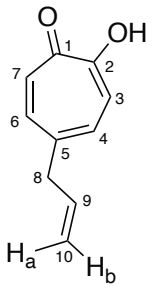
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.62 (dd, *J* = 6.3, 3.0 Hz, 1H, **H6**), 6.77 (dd, *J* = 2.5, 0.9 Hz, 1H, **H4**), 6.38 (d, *J* = 2.5 Hz, 1H, **H3**), 6.13 (d, *J* = 6.3 Hz, 1H, **H7**), 6.08–5.86 (m, 1H, **H9**), 5.30 (dq, *J* = 17.2, 1.5, 1H, **H10a**), 5.17 (dq, *J* = 10.4, 1.5 Hz, 1H, **H10b**), 4.19 (ddt, *J* = 12.3, 5.6, 1.4 Hz, 1H, **H8**), 4.10 (ddt, *J* = 12.3, 5.6, 1.4 Hz, 1H, **H8**), 3.88 (dt, *J* = 2.8, 0.9 Hz, 1H, **H5**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 204.5 (**C1**), 165.0 (**C6**), 146.2 (**C4**), 136.5 (**C3**), 134.6 (**C9**), 133.3 (**C7**), 117.3 (**C10**), 85.4 (**C2**), 67.9 (**C8**), 54.3 (**C5**).

FTIR (ATR) ν (cm^{-1}); 3401, 2957, 2924, 1712 (C=O).

HRMS *m/z* calculated for: $C_{10}H_{10}O2$ $[M+H]^+$ 163.0753, found 163.0754.

2-Hydroxy-4-(prop-2-en-1-yl)cyclohepta-2,4,6-trien-1-one 422



A solution of **411** (54 mg, 0.37 mmol) in MeCN (60 mL) was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for 2 hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, heptane:EtOAc, 4:1] afforded **422** (16 mg, 0.11 mmol, 30%) as a dark green residue.

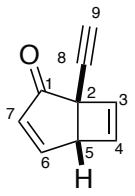
$\boldsymbol{R_f}$ (4:1 Heptane:EtOAc = 0.76).

^{1}H NMR (400 MHz, $CDCl_3$); δ 6.77 (ddd, *J* = 17.4, 10.8, 1.3 Hz, 1H, **H9**), 6.71-6.65 (m, 1H, **H6**), 6.42 (dd, *J* = 17.4, 1.8 Hz, 1H, **H10a**), 6.25-6.18 (m, 2H, **H3**+**H4**), 5.82 (dd, *J* = 10.8, 1.8 Hz, 1H, **H10b**), 5.65-5.58 (m, 1H, **H7**), 3.00 (d, *J* = 6.7, 1H **H8**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 193.3 (**C1**), 176.7 (**C2**), 129.4 (**C9**), 128.7 (**C4**), 127.8 (**C10**), 125.22 (**C3**), 124.9 (**C6**), 120.8 (**C7**), 111.0 (**C5**), 40.8 (**C8**).

FTIR (ATR) ν (cm^{-1}); 3418, 3060, 2933, 2864, 1707 (C=O).

Ethynylbicyclo[3.2.0]hepta-3,6-dien-1-one 429a



To a solution of **389h** (72 mg, 0.55 mmol) in anhydrous CH_2Cl_2 (55 mL) was added $BF_3{\cdot}OEt_2$ (0.075 mL, 0.62 mmol) and the resulting solution was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for six hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 1:1] afforded **429a** (14 mg, 0.11 mmol, 19%) as a light brown oil. Contained a small quantity of **430a** (<5%) that could not be removed.

R_f (19:1 Pentane:CH_2Cl_2 = 0.11).

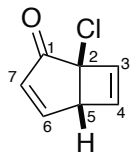
^{1}H NMR (400 MHz, $CDCl_3$); δ 7.66 (dd, *J* = 5.9, 2.8 Hz, 1H, **H6**), 6.68-6.61 (m, 1H, **H4**), 6.36 (d, *J* = 2.4 Hz, 1H, **H3**), 6.11 (d, *J* = 5.9 Hz, 1H, **H7**), 4.03 (d, *J* = 2.8 Hz, 1H, **H5**), 2.40 (s, 1H, **H9**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 201.1 (**C1**, 164.3 (**C6**, 161.0 (**C8**, 144.1 (**C4**, 137.9 (**C3**, 132.9 (**C7**), 73.0 (**C9**), 57.6 (**C5**), 52.5 (**C2**).

FTIR (ATR) ν (cm^{-1}); 3270, 3062, 2361 (C≡C), 1701 (C=O)

HRMS (ESI); No mass peak found.

2-Chlorobicyclo[3.2.0]hepta-3,6-dien-1-one 429a



To a solution of **393** (210 mg, 1.5 mmol) in anhydrous CH_2Cl_2 (60 mL) was added $BF_3{\cdot}OEt_2$ (62 μL, 0.51 mmol) and the resulting solution purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for three hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 19:1] afforded **429b** (31 mg, 0.2 mmol, 15%) as a light brown oil. Contained a small quantity of **430b** (<5%) that could not be removed.

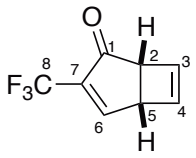
R_f (19:1 Pentane:CH_2Cl_2 = 0.15).

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.67 (dd, J = 6.1, 2.7 Hz, 1H, **H6**), 6.75 (dd, J = 2.6, 0.9 Hz, 1H, **H4**), 6.32 (d, J = 2.6 Hz, 1H, **H3**), 6.20-6.19 (d, J = 6.1 Hz, 1H, **H7**), 4.00 (dt, J = 2.7, 0.9 Hz, 1H, **H5**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 199.4 (**C1**, 160.2 (**C6**, 144.8 (**C4**), 137.2 (**C3**), 132.6 (**C7**, 66.0 (**C5**, 60.0 (**C2**).

HRMS (APCI); *m/z* calculated for: C_7H_5OCl $[M+H]^-$ 141.0102, found 141.0099.

3-(Trifluoromethyl)bicyclo[3.2.0]hepta-3,6-dien-2-one 429e



To a solution of **407** (55 mg, 0.31 mmol) in anhydrous CH_2Cl_2 (25 mL) was added $BF_3{\cdot}OEt_2$ (39 μL, 0.31 mmol) and the resulting solution was purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for four hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 1:1] afforded textbf429e (21 mg, 0.11 mmol, 31%) as an orange oil. Contained a small quantity of **430e** (<5%) that could not be removed.

$\boldsymbol{R_f}$ (19:1 Pentane:CH_2Cl_2) = 0.47.

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.99 (dq, J = 3.0, 1.4 Hz, 1H, **H6**), 6.55 (ddd = 2.8, 1.2, 0.8, 1H, **H4**), 6.39 (dd, J = 2.4, 1.4 Hz, 1H, **H3**), 4.01 (tt, J = 3.0, 1.5 Hz, 1H, **H5**), 3.67 (dd, J = 2.0, 1.6 Hz, 1H, **H2**).

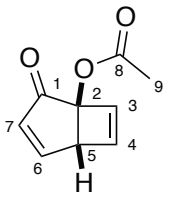
^{13}C NMR (101 MHz, $CDCl_3$); δ 197.8 (**C1**), 162.1 (q, J = 4.3, C8), 142.5 (**C4**), 136.0 (**C3**), 136.4, 120.9, 55.0 (**C2**), 48.0 (**C5**).

^{19}F NMR (376 MHz, $CDCl_3$); δ -65.52.

FTIR (ATR) ν (cm^{-1}); 3065, 2955, 1712 (C=O), 1634.

HRMS (APCI); *m/z* calculated for: $C_8H_5OF_3$ $[M-H]^-$ 173.0220, found 173.0219.

2-Oxobicyclo[3.2.0]hepta-3,6-dien-1-yl acetate 429f



To a solution of **410** (164 mg, 1.00 mmol) in anhydrous CH_2Cl_2 (30 mL) was added $BF_3{\cdot}OEt_2$ (0.1 mL, 1 mmol) and the resulting solution purged with argon for ten minutes. The reaction mixture was irradiated (λ = 300 nm) at room temperature for three hours and concentrated under reduced pressure. Purification by flash column chromatography [SiO_2, pentane:CH_2Cl_2, 1:1] afforded **429f** (24 mg, 0.10 mmol, 14%) as a colourless oil.

$\boldsymbol{R_f}$ (19:1 Pentane:CH_2Cl_2) = 0.27.

^{1}H NMR (400 MHz, $CDCl_3$); δ 7.61 (dd, *J* = 6.3, 2.8 Hz, 1H, **H6**), 6.82 (dd, *J* = 2.6, 0.8 Hz, 1H, **H4**), 6.31 (d, *J* = 2.6 Hz, 1H, **H3**), 6.15 (d, *J* = 6.3 Hz, 1H, **H7**), 3.87 (d, *J* = 2.8 Hz, 1H, **H5**), 2.10 (s, 3H, **H9**).

^{13}C NMR (101 MHz, $CDCl_3$); δ 201.1 (**C1**), 169.3 (**C8**), 159.4 (**C6**), 147.7 (**C4**), 134.7 (**C3**), 132.3 (**C7**), 82.9 (**C2**), 55.4 (**C5**), 20.4 (**C9**).

References

[1] Davy, J. A.; Moreau, B.; Oliver, A. G.; Wulff, J. E. *Tetrahedron* **2015,** *71,* 2643–2657.

[2] Gillespie, K. "N-tosyliminobenzyliodinane - PhINTs from Iodobenzene diacetate", 2001.

[3] Li, K.; Mu, H.; Kang, X.; Jian, Z. *Macromolecules* **2022,** *55,* 2533–2541.

[4] Saito, F. *Angew. Chem. Int. Ed.* **2022,** *61,*.

[5] Ohtsu, K.; Hayami, R.; Sagawa, T.; Tsukada, S.; Yamamoto, K.; Gunji, T. *Tetrahedron* **2019,** *75,* 130658.

[6] Murfin, L. C.; Weber, M.; Park, S. J.; Kim, W. T.; Lopez-Alled, C. M.; McMullin, C. L.; Pradaux-Caggiano, F.; Lyall, C. L.; Kociok-Köhn, G.; Wenk, J.; Bull, S. D.; Yoon, J.; Kim, H. M.; James, T. D.; Lewis, S. E. *J. Am. Chem. Soc.* **2019,** *141,* 19389–19396.

[7] Ononye, S. N.; VanHeyst, M. D.; Oblak, E. Z.; Zhou, W.; Ammar, M.; Anderson, A. C.; Wright, D. L. *ACS Med. Chem. Lett.* **2013,** *4,* 757–761.

[8] Cao, F.; Orth, C.; Donlin, M. J.; Adegboyega, P.; Meyers, M. J.; Murelli, R. P.; Elagawany, M.; Elgendy, B.; Tavis, J. E. *ACS Omega* **2018,** *3,* 15125–15133.

[9] Kumar, N. R.; Agrawal, A. R.; Zade, S. S. *Chem. Eur. J.* **2019,** *25,* 14064–14071.

[10] Lyons, D. J. M.; Empel, C.; Pace, D. P.; Dinh, A. H.; Mai, B. K.; Koenigs, R. M.; Nguyen, T. V. *ACS Catal.* **2020,** *10,* 12596–12606.