University of Southampton

FACULTY OF ENGINEERING AND PHYSICAL SCIENCES

SCHOOL OF CHEMISTRY

THE DISCOVERY AND INVESTIGATION OF NOVEL REARRANGEMENTS OF CYCLOBUTENEDIONES TRIGGERED BY NUCLEOPHILIC ADDITION

by

Ryan Mark Bennett

Thesis for the Degree of Doctor of Philosophy

September 2021

University of Southampton

Abstract

FACULTY OF ENGINEERING AND PHYSICAL SCIENCES

SCHOOL OF CHEMISTRY

Doctor of Philosophy

THE DISCOVERY AND INVESTIGATION OF NOVEL REARRANGEMENTS OF CYCLOBUTENEDIONES TRIGGERED BY NUCLEOPHILIC ADDITION

by

Ryan Mark Bennett

This thesis entails the discovery and investigation of two new modes of cyclobutenedione rearrangement. The rearrangement of cyclobutenones has been well established in the past and has proven to be a robust method for the synthesis of a wide variety of substrates *e.g.* quinones and furanones. This has also been extended to the synthesis of a number of natural products and biologically active compounds. Despite this, the rearrangement of cyclobutenediones is less prominent. Herein is described two new modes of this class of rearrangements.

Firstly, the investigation into the rearrangement of cyclobutenediones upon treatment with lithium amides is described. This method has been studied and a wide substrate scope featuring cyclobutenediones bearing alkyl, ether and amine residues has been examined. This new rearrangement has been tested using a variety of lithium amides and has been extended to offer an efficient route to tetra-substituted furans.

The rearrangement of diarylcyclobutenediones to diarylanhydrides and fused polyaromatic anhydrides has also been developed. This method involves photolysis under continuous flow using a segmented system allowing the introduction of oxygen bubbles to facilitate oxidation. Again, a wide substrate scope was examined featuring substituted aromatics and heteroaromatics leading to anhydrides in good to excellent yields.

Table of Contents

Research Thesis: Declaration of Authorship

Print name: RYAN MARK BENNETT

Title of thesis: “Novel Rearrangements of Cyclobutenediones Triggered by Nucleophilic Addition”

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published as:- ‘A new mode of cyclobutenedione ring opening for the synthesis of 2-oxobut-3-enamides and tetrasubstituted furans’
   R. M. Bennett, W. Sun, D. C. Wilson, M. E. Light, D. C. Harrowven, *Chem. Commun*., 2021, **57**, 5694-5697

Signature: ..... Date: .....

Acknowledgements

I would first like to thank Professor David Harrowven for allowing me to study within his brilliant group and supervising me throughout my time at the University of Southampton. Your advice both professionally and personally has provided me with the means to carry on throughout the troubling times that have occurred over my four years.

I would also like to thank both the Interreg LabFact program and the EPSRC funding program to allow me to study for my PhD.

My massive thanks are next given to everybody in the Harrowven and Linclau labs, namely Wei Sun, Luke, Morgan, Mariana, Diego, Hannah, Simon, James, Will, Lawrence, Kristina, Ed and Oli. Wei Sun, your advice and guidance has been crucial for getting me through and your dry sense of humour has been a massive help when times were tough. Luke, your constant arguing of your point with Wei Sun has brought many laughs to everyone and your love of climbing managed to prove even Chemistry can be interesting in comparison! Morgan, as fume hood neighbours we shared many a gossip and chat which always helped those long column days. James and Will, thanks for making my times in the lab surreal by inventing random games to play and pondering thoughts that appear to be plucked from absolutely nowhere! Ed, my little protégé, you have a lot to learn but cheers for always putting a smile on my face by being as posh as humanly possible. Mariana and Diego, you two are definitely honorary Harrowven group members and thanks for the amazing times we have had over the years. Hannah and Simon, cheers for being such fun and always having a good chat whenever I popped by. Kristina, I will get you to try more green tea in the future! And of course Lawrence, Hot Tuna will permanently be etched into my brain as will the many nights shared at the Frog.

Thanks also go to the support staff, namely to Dr Neil Wells for any questions and upkeep of the NMR services, Dr John Langley and Ms Julie Herniman for the MS services and Dr Mark Light for your X-ray services. Of course Mark and Keith must get a massive thanks for your hilarious chats when popping down to stores for another bottle of solvent.

Finally, I must thank my parents for your constant support and understanding throughout my PhD (even though you have no idea what I do). You have been my constant motivation to get through this and I can’t thank you enough.

Abbreviations

aq.	aqueous	Me	methyl
app.	apparent	min	minute
Ar	aryl	mol	mole (s)
Bu	butyl	MOM	Methoxymethyl ether
br	broad	MP	melting point
Δ	heat	*n*-	normal
DCM	dichloromethane	NBS	*N*-bromosuccinimide
°C	Degrees Celcius	NMR	nuclear magnetic resonance
DIPA	Diisopropylamine	[O]	oxidation
DMSO	dimethyl sulfoxide	*o*-	*ortho*
EI	electron impact ionisation	*p*-	*para*
equiv.	equivalent	Ph	phenyl
ESI	electrospray ionisation	Pr	propyl
Et	ethyl	Py	pyridyl
g	gram(s)	R	organic residue
h	hour	RT	room temperature
hv	ultraviolet light	s	strong/singlet
HRMS	high resolution mass spectrometry	sat.	saturated (aqueous solution)
Hz	hertz	*t*-	*tertiary*
IR	infra-red	TBAF	tetra-^{n}butylammonium fluoride
i-	*iso*	THF	tetrahydrofuran
J	coupling constant	TFAA	trifluoroacetic anhydride
LC-MS	liquid chromatography mass spectrometry	TIPS	triisopropylsilyl
LDA	lithium diisopropylamide	TLC	thin layer chromatography
LiHMDS	Lithium hexamethyldisilazide	TMS	trimethylsilyl
M	milli/medium/multiplet	UV	ultraviolet
m-	*meta*	w	weak

Chapter 1: Introduction to cyclobutenediones

1.1 Background and history

Cyclobutenediones are a versatile class of molecules with a great potential for functionalisation. They have been used successfully in both the biological and pharmaceutical fields to form a wide variety of complex structures. Similarly, total syntheses originating from simple cyclobutenedione starting materials are common, with the majority of these being used to form a quinone core within a natural product (Figure 1.1).[1–8]

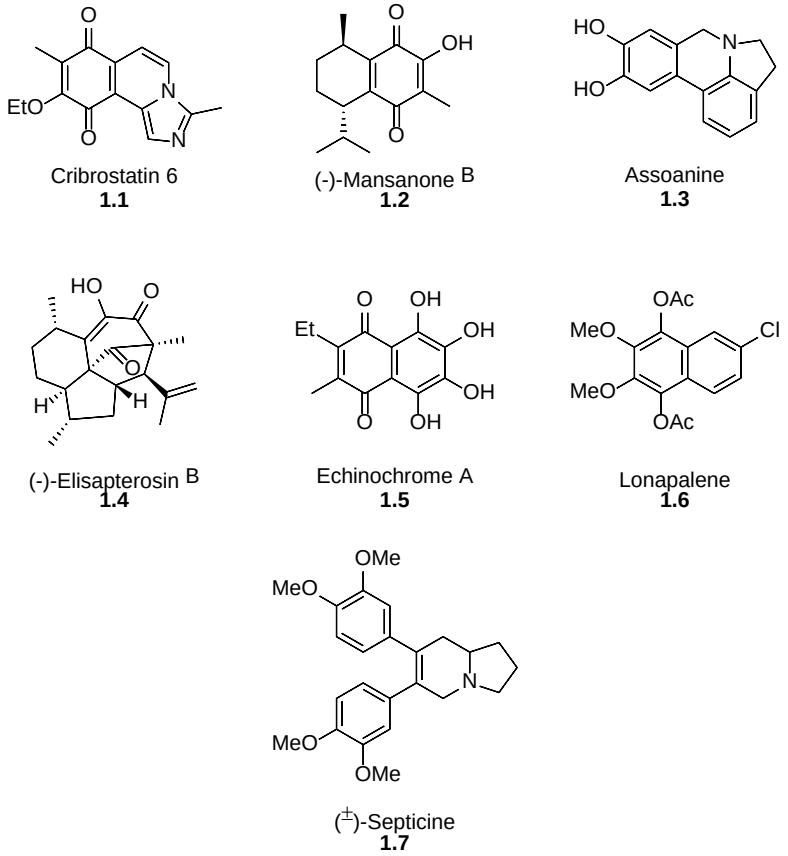
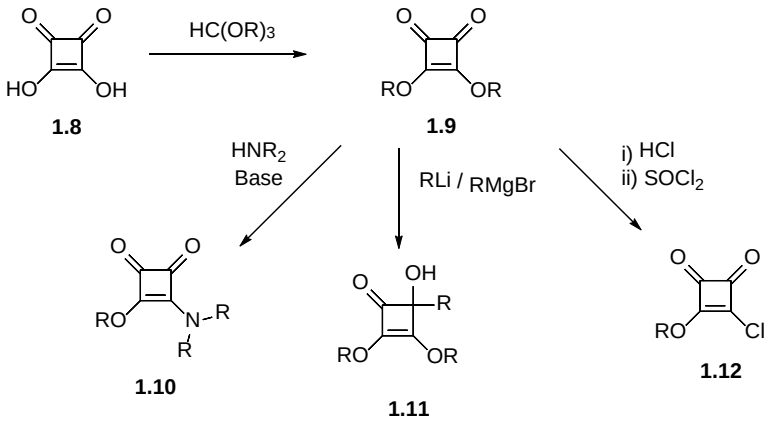


Figure 1.1: Some of the many natural products synthesised from cyclobutenediones

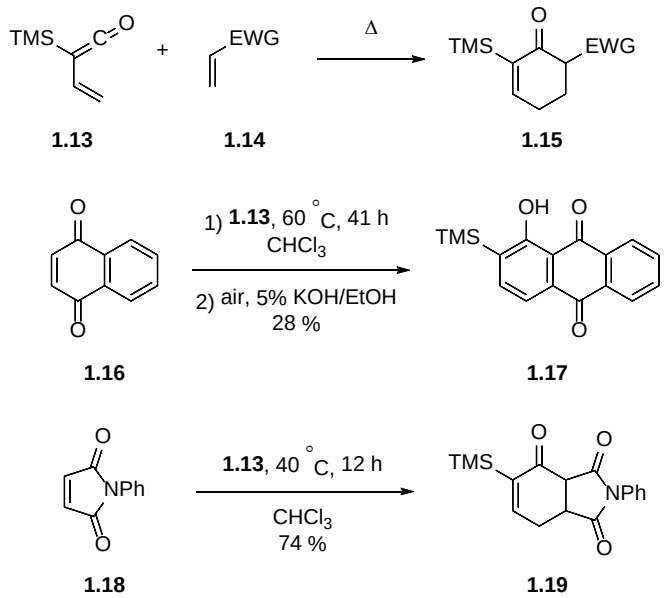
A quinone unit can be formed through the thermal rearrangement of various substituted cyclobutenones. In turn, these are prepared by nucleophilic additions to squarates **1.9** derived by esterification of squaric acid (3,4-dihydroxycyclobut-3-ene-1,2-dione), **1.8**, a readily available starting material. Squarates **1.9** provide opportunities for substitution by, for example, replacement of an ether group with an amino group, whilst also allowing

nucleophilic additions to one or both carbonyls with hard nucleophiles such as Grignard and organolithium reagents (Scheme 1.1).



Scheme 1.**1**: Common transformations of cyclobutenediones

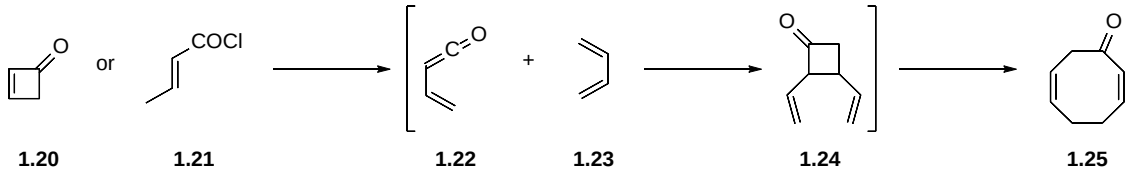
In the early 1980's, Danheiser *et al*. observed that vinylketenes would react with olefins yielding [4 + 2]-cycloaddition products *via* Diels-Alder type reactions. Originally this was conducted with (trimethylsilyl)vinylketenes and electron-poor olefins leading to cyclohexanones and phenols (Scheme 1.2).[9]



Scheme 1.2: Original work conducted by Danheiser *et al.* utilising ketene cycloadditions

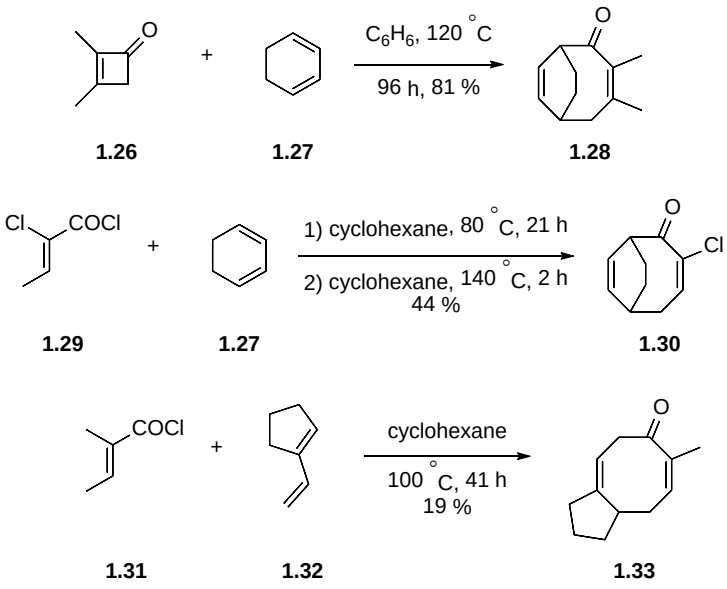
Danheiser *et al.* later expanded the scope to form 8-membered ring systems *via* formal [4 + 4] cycloadditions.[10] It was proposed that initial formation of vinylketene **1.22** was followed by a [2 + 2] cycloaddition with diene **1.23** forming cyclobutanone **1.24**. This then undergoes a [3,3] sigmatropic rearrangement to form cyclooctadiene **1.25**. The reaction

between vinylketenes and 1,3-dienes was found to produce highly functionalised cyclooctadiene derivatives in moderate yields with the vinylketene being generated *in situ via* 1,4-dehydrohalogenation of α,β-unsaturated acid chlorides or the electrocyclic ring opening of cyclobutenones (Scheme 1.3).



Scheme 1.3: Synthesis of 8-membered carbocycles by Danheiser *et al.*

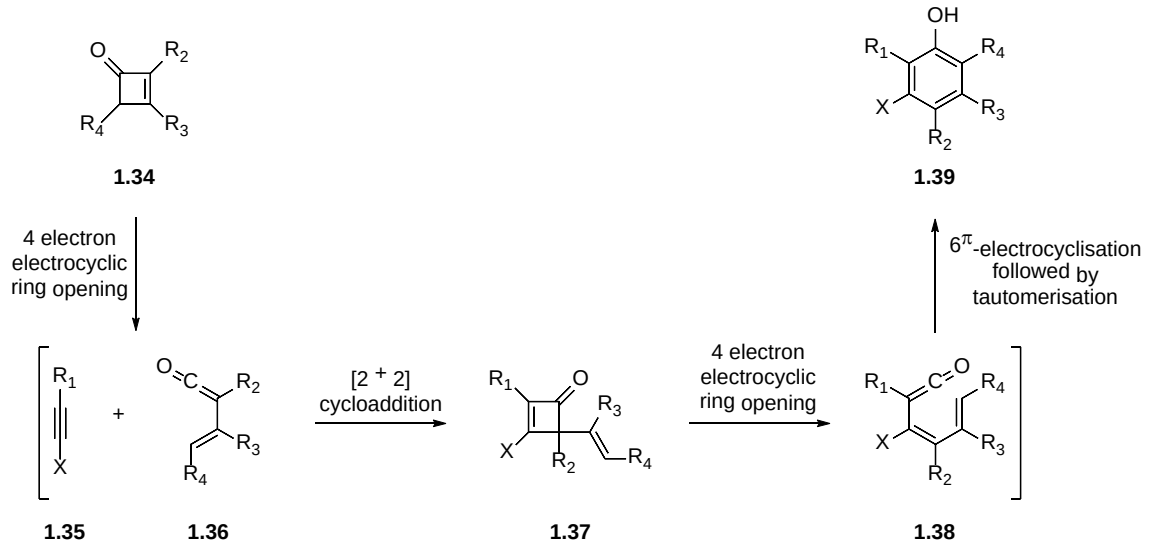
Initial formation of vinylketene **1.22** was followed by reaction with ketenophilic diene **1.23** forming divinylcyclobutanone **1.24** which, to relieve ring strain at the elevated temperature, would undergo a [3,3] sigmatropic rearrangement producing cyclooctadienone **1.26**. Expanding upon this, a variety of vinylketenes were examined, producing an array of substituted carbocycles when reacted with various 1,3-dienes (Scheme 1.4).



Scheme 1.4: Expansion of the [4 + 4] annulation with vinylketenes

Danheiser *et al.* furthered their research in this area by reacting substituted cyclobutenones with heterosubsituted alkynes to form highly functionalised phenols (Scheme 1.5).[11] It was observed that reversible, electrocyclic ring opening of cyclobutenone **1.34** to form vinylketene **1.36** was followed by [2 + 2] cycloaddition with ketenophilic alkyne **1.35** to produce 2-vinylcyclobutenone **1.37**. Further electrocyclic cleavage then formed

dienylketene **1.38** which underwent a 6π electrocyclisation to yield phenol **1.40** after tautomerisation.

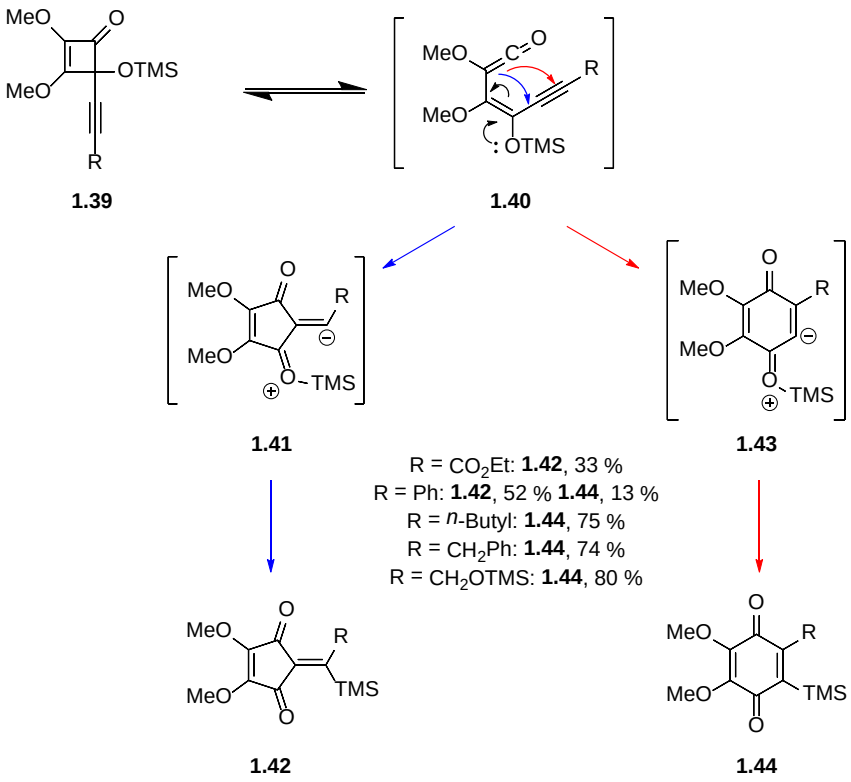


Scheme 1.5: Reaction pathway leading to highly substituted phenols

1.2 Introduction to the Moore Rearrangement

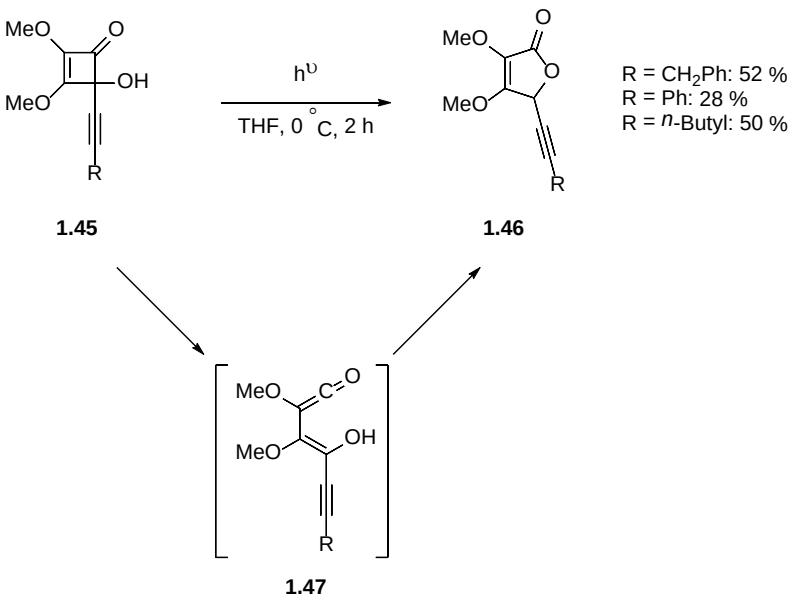
1.2.1 Rearrangement of 4-alkynylcyclobutenones

In 1985, Moore *et al.* uncovered a novel rearrangement involving alkynylcyclobutenones.[12] Upon thermolysis, it was observed that cyclobutenone **1.39** would form a mixture of products namely quinone **1.44** and cyclopentenedione **1.42** (Scheme 1.6).



Scheme 1.6: Rearrangement of 2-alkynylcyclobutenones observed by Moore *et al.*

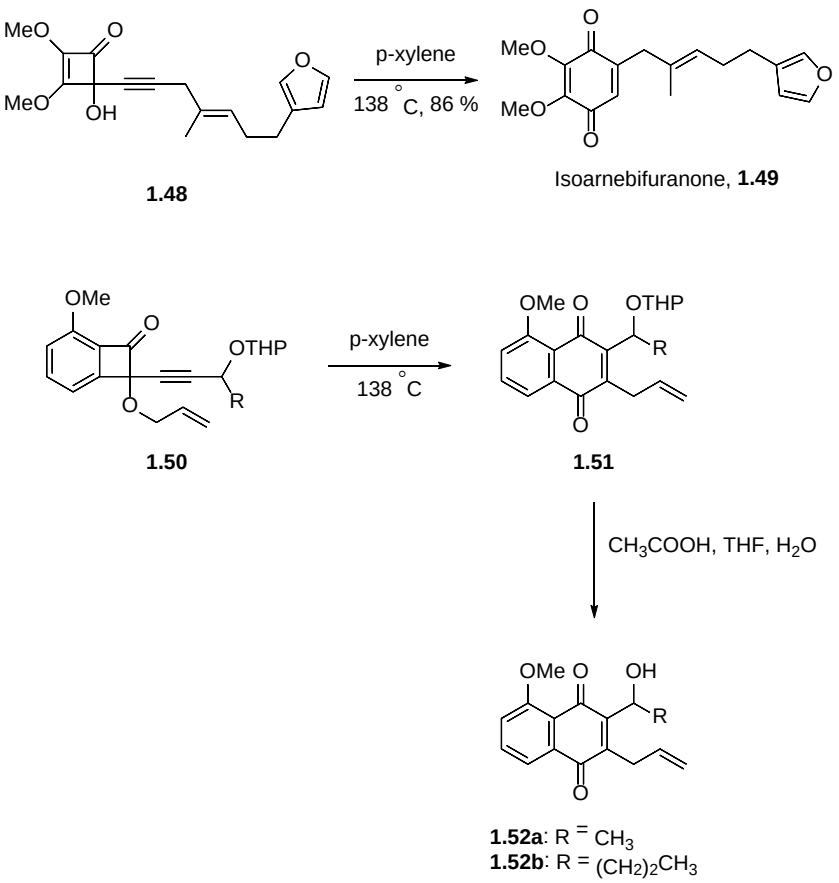
Moore *et al*. envisaged that cyclobutenone **1.39** first undergoes a 4π-electrocyclic ring opening forming ketene **1.40**, which then has two ring closure pathways that can be undertaken, respectively producing zwitterionic species **1.41** and **1.43**. Subsequently, these formed cyclopentenedione **1.42** and quinone **1.44** respectively by intramolecular silyl group migration. The likelihood of each pathway was dictated by the electronic characteristics of the terminal substituent, R, of the alkyne, such that electron-withdrawing groups (esters) favour formation of cyclopentenediones **1.42** whilst electron-donating groups (ethers) favour the creation of quinones **1.44**. This work was later expanded upon by Moore *et al.* to include a larger variety of alkynyl substituents and cyclobutenones bearing alkyl and aryl moieties.[13] In addition to the aforementioned quinone and cyclopentenedione products, it was observed that upon photolysis of cyclobutenones **1.45**, 5*H*-furanones **1.46** were formed in modest yield (Scheme 1.7). It was hypothesised that outward rotation of the 4-hydroxyl group was dominant on thermolysis while inward rotation of the hydroxyl group to ketene **1.47** occurred under photolysis through quartz from a 450 W Hanovia lamp allowing ring closure to furanone **1.46**.



Scheme 1.7: Photolysis of alkynylcyclobutenones to form furanones

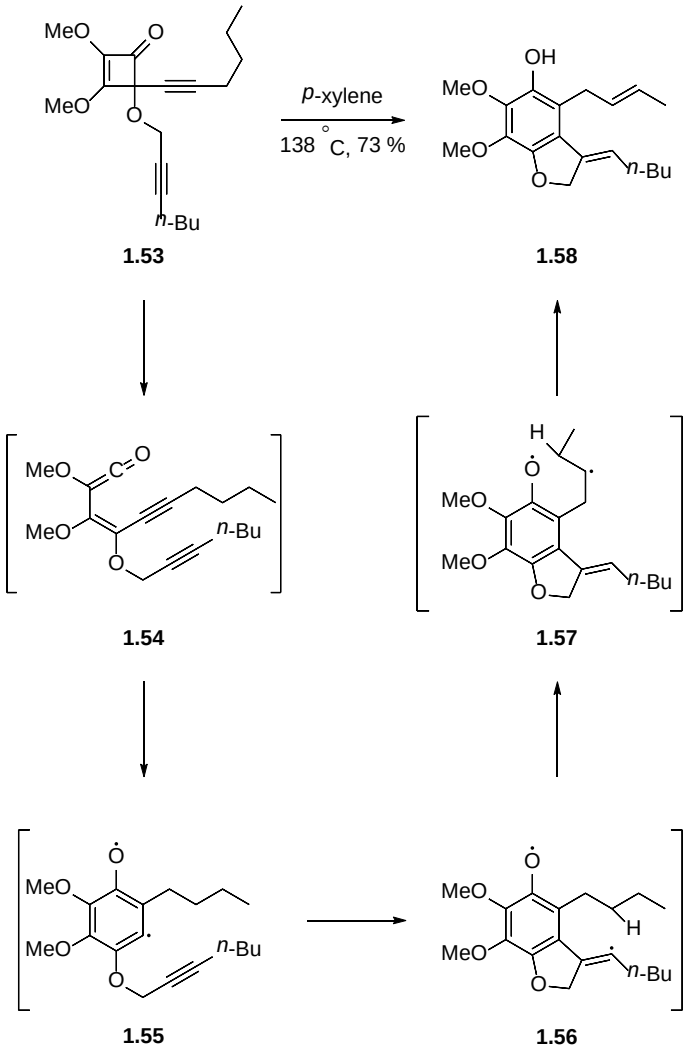
1.2.2 Rearrangement of cyclobutenones bearing protected alcohols

In 1989, Moore *et al*. reported the synthesis of isoarnebifuranone, an isomer of natural product arnebifuranone, and a precursor to natural products nanaomycin D and deoxyfrenolicin.[14] The production of isoarnebifuranone employed the thermolysis of alkynylcyclobutenone **1.48**, formed from a multi-step synthesis from 3-(2-bromoethyl)furan, and proceeded to give the target quinone **1.49** in an impressive 86 % yield (Scheme 1.8). This demonstrated the reliability of this class of reactions and was extended to the synthesis of natural product precursors **1.52a** and **1.52b**.



Scheme 1.8: Synthesis of isoarnebifuranone and nanaomycin D and deoxyfrenolicin precursors

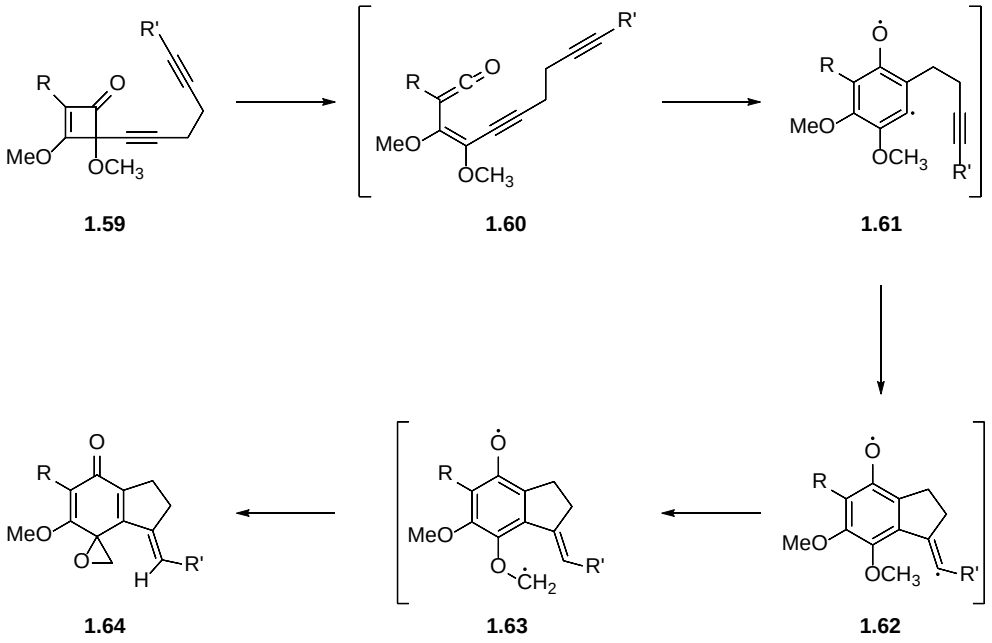
In the early 1990's Moore *et al.* reported the formation of methylenebenzofurans by the thermal rearrangement of alkynylcyclobutenones.[15] For example the thermolysis of alkynylethers **1.53** triggered a cascade radical reaction leading to the formation of methylenebenzofurans **1.58** (Scheme 1.9). The reaction was presumed to begin with the formation of conjugated ketene **1.54** by electrocyclic ring opening of **1.53**. Subsequent ring closure to diradical **1.55** was followed by a 5-*exo*-*dig* cyclisation forming diradical **1.56**. H-atom abstraction to **1.57**, and then furan **1.58**, competed the sequence.



Scheme 1.9: Formation of methylenebenzofurans

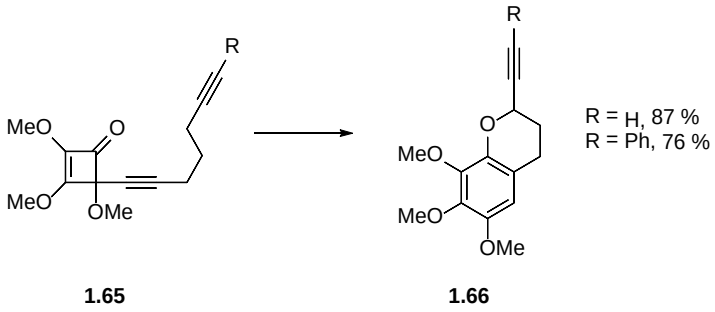
1.2.3 Rearrangement of cyclobutenones featuring diyne substituents

Moore *et al.* then expanded the scope of the reactions involving cyclobutenones bearing protected alcohols by uncovering a series of cascade reactions leading to spiroepoxides, epoxides and annulated quinones.[16] It was observed that on thermolysis cyclobutenone **1.59** undergoes a 4π-electrocyclic ring opening to form vinylketene **1.60** which then undergoes cyclisation to form diradical intermediate **1.61**. The reactive ring-based radical then undergoes addition to the proximal alkyne leading to vinyl radical **1.62**. An H-atom abstraction from the adjacent methyl group follows forming diradical **1.63**, a precursor to spiroepoxide **1.64**. Yields for this sequence were moderate to very good depending upon the substituent at the alkyne terminus. The lowest yield was 54 % when the alkyne substituent was a proton while the highest was an impressive 91 % when the alkyne bore a phenyl residue (Scheme 1.10).



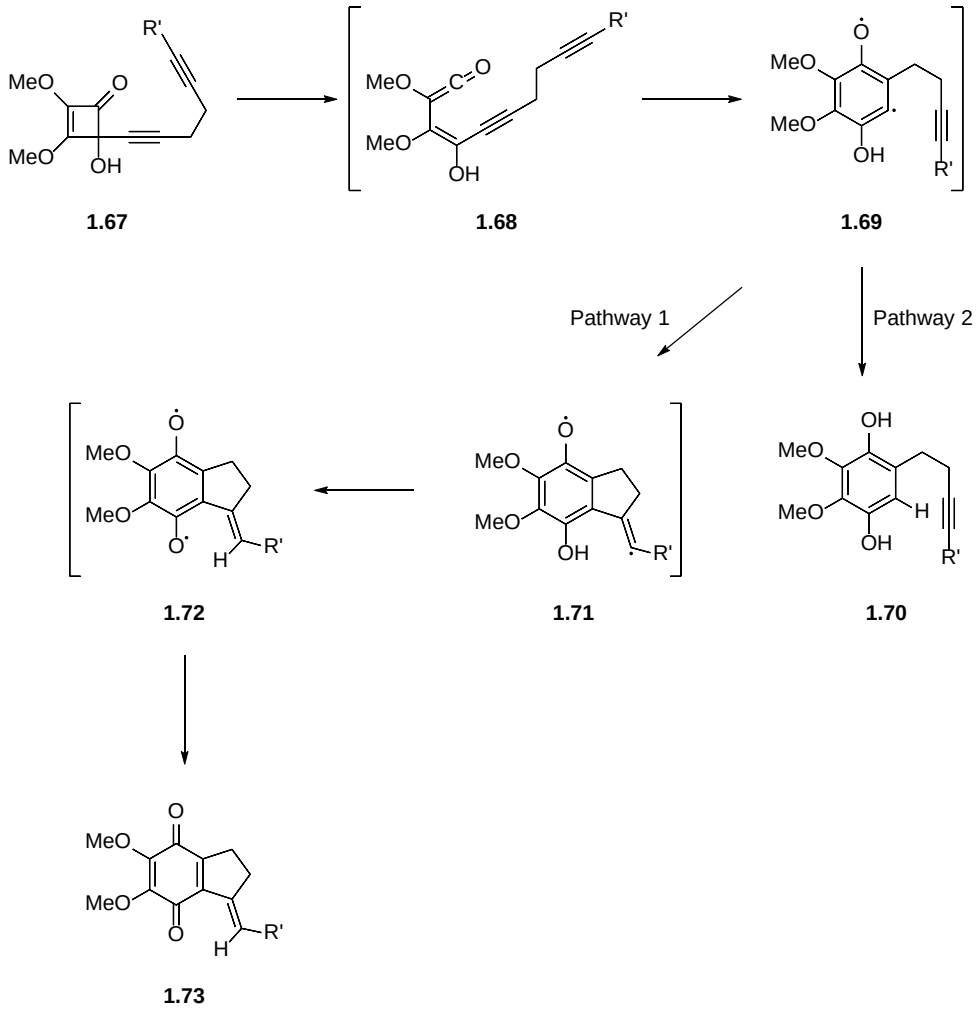
Scheme 1.10: Radical cascade to form annulated spiroepoxides

It was also found that diyne **1.65** gave dihydrobenzopyran **1.66** (Scheme 1.11). This was rationalized as being formed *via* diradical generation and tandem cyclisation.



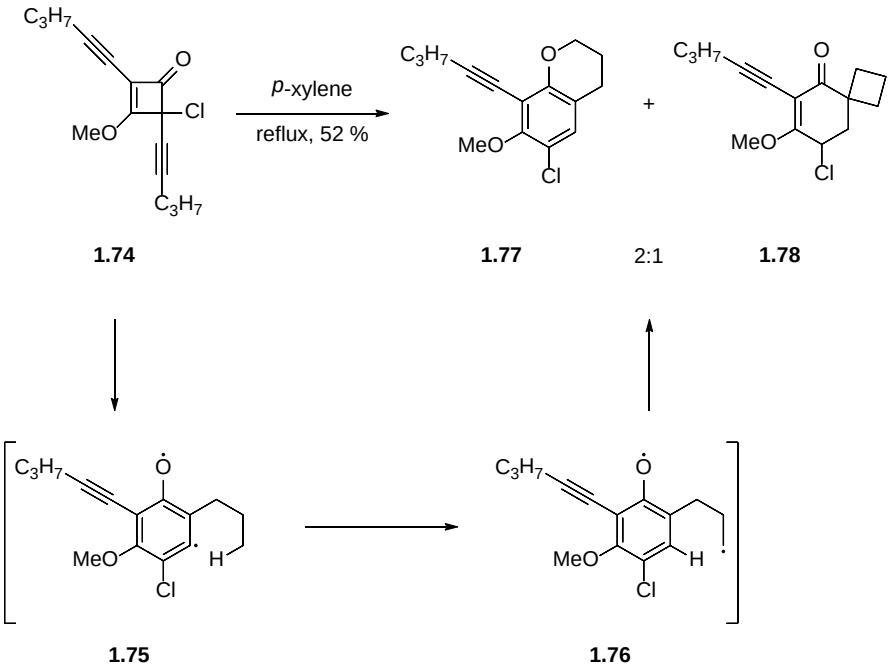
Scheme 1.11: Formation of epoxides by extension to a diyne side-chain

Should the 4-methoxy group of cyclobutenones **1.59** be replaced with a 4-hydroxyl group, as in **1.67**, Moore witnessed a mixture of quinone products rather than epoxides (Scheme 1.12). If the concentration was high (1.20 M), the reaction gave a 1:7 ratio of **1.73** and **1.70** respectively. In contrast, at high dilution (3.86×10^{-3} M), the annulated quinone **1.73** was predominantly formed in a ratio of 23:1 with hydroquinone **1.70**. This concentration dependence was rationalised by suggesting that diradical **1.69** favoured intermolecular H-abstraction rather than intramolecular cyclisation at high concentration.



Scheme 1.12: Concentration dependent quinone formation

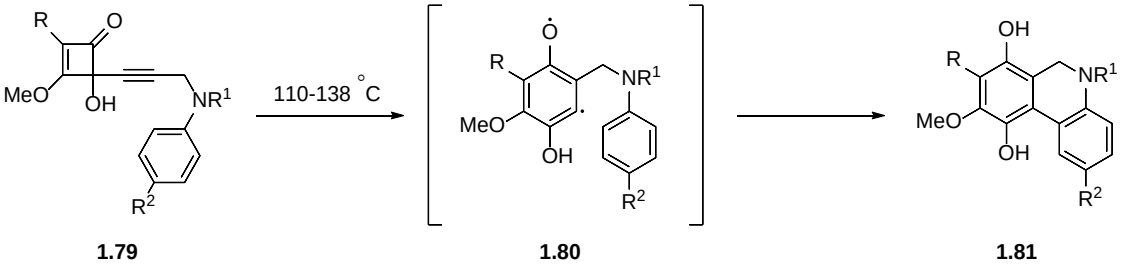
In a related study, Moore *et al*. observed the formation of pyrans and spirocycles as a result of intramolecular radical cyclisations.[17] Upon thermolysis of 4-alkynyl-4-chlorocyclobutenone **1.74**, a 2:1 mixture of benzopyran **1.77** and spirocycle **1.78** was produced prompting further investigation (Scheme 1.13). It was proposed that upon formation of diradical **1.75**, the aryl radical performs an H-atom abstraction leading to propyl radical **1.76**. This then has the possibility of undergoing ring closure at two positions, *O*- or *C*-, affording benzopyran **1.77** or spirocycle **1.78** respectively.



Scheme 1.13: Intramolecular radical cyclisations from 4-alkynyl-4-chlorocyclobutenones

1.2.4 Rearrangement of cyclobutenones bearing nitrogen-containing alkynes

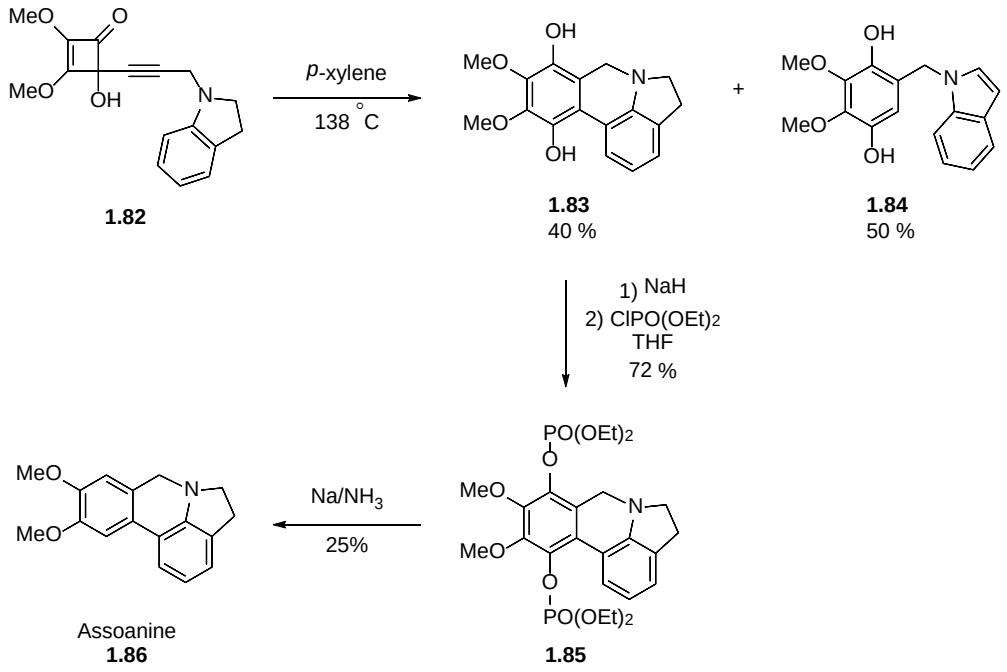
Furthering the scope of this rearrangement, Moore *et al.* reported rearrangements of 4-alkynylcyclobutenones bearing nitrogen-containing alkynes.[7] The thermolysis of this class of compounds produced *N*-heterocyclic ring systems including piperidinoquinones and benzophenanthridines (Scheme 1.14) and ultimately led to a total synthesis of assoanine, a naturally occurring pyrrolophenanthridine.



R	R^1	R^2	Yield % **1.81**
OMe	*n*-Bu	H	65
OMe	allyl	H	63
OMe	tBoc	H	70
OMe	4-pentenyl	H	70

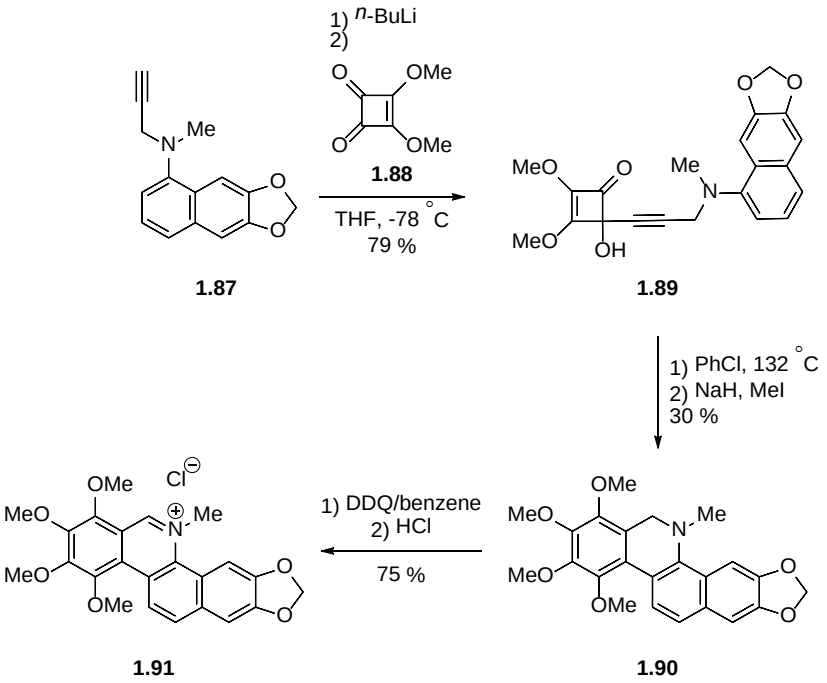
Scheme 1.14: Thermal rearrangement to phenanthridinediols

In order to modify this to synthesise assoanine **1.86**, *N*-propargyl indoline was coupled to dimethyl squarate to form cyclobutenone **1.82**. This adduct was then thermolysed in refluxing *p*-xylene for 2 h to form a mixture of annulated hydroquinone **1.83** and by-product **1.84**. This by-product was suggested to arise from the intramolecular H-atom abstraction of the diradical species, leading to the indole containing product. The diol was then converted to phosphate **1.85** followed by reduction using sodium in ammonia to produce the target natural product, assoanine **1.86** (Scheme 1.15).



Scheme 1.15: Synthesis of natural product, assoanine **1.86**

This method was extended by Moore *et al*. to annulated systems including benzophenanthridines and benzophenanthridinium ions (Scheme 1.16).[18] By coupling naphthalene bearing amine residue **1.87** with cyclobutenedione **1.88**, adduct **1.89** was produced in good yield. Thermolysis of **1.89** then furnished benzophenanthridines precursor **1.90** which was successfully converted to benzophenanthridinium salt **1.91** on treatment with DDQ and HCl.



Scheme 1.15: Formation of benzophenanthridines and their corresponding benzophenanthridinium salts

These heteroaromatic ring systems are commonly found within natural products, including the alkaloids chelilutine **1.92** and chelerythrine **1.93**, that display significant anti-tumour activity (Figure 1.2).[19,20]

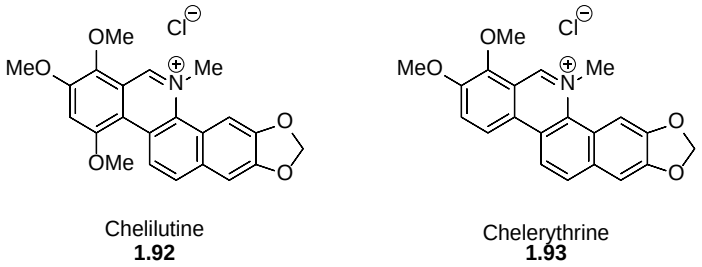
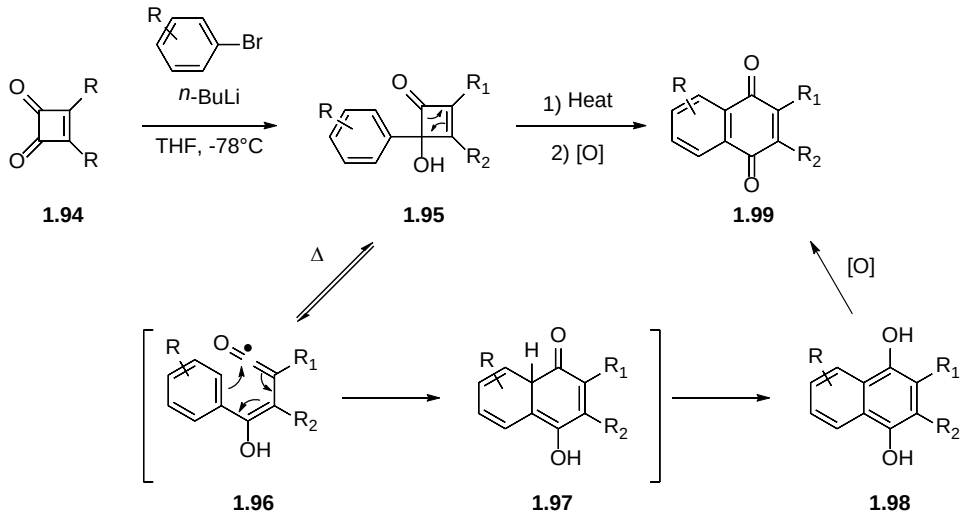


Figure 1.2: Naturally occurring alkaloids featuring the benzophenanthridinium core

1.2.5 Rearrangement of cyclobutenones bearing arene substituents

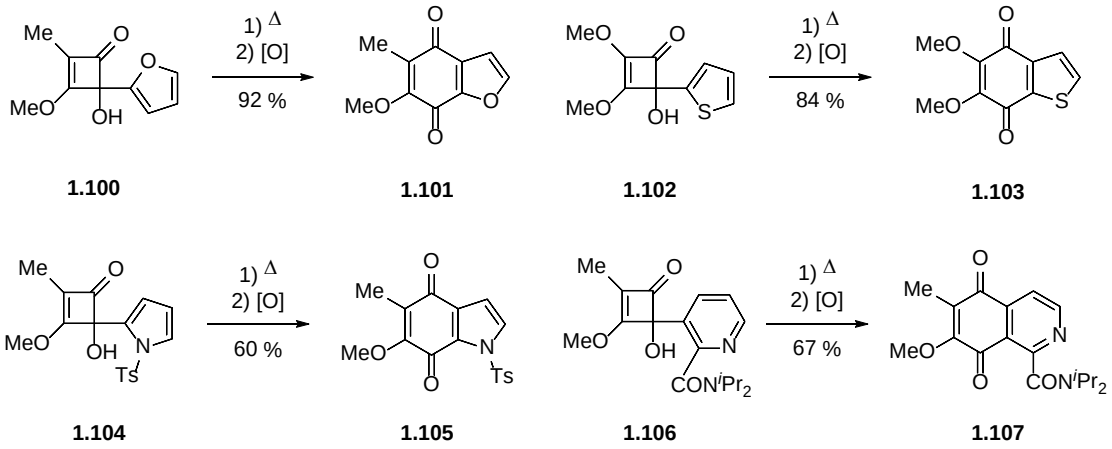
In the late 1980's, Moore and Liebeskind each described methods to synthesise annulated quinones from cyclobutenediones in high yields.[21,22] Cyclobutenones **1.95**, when exposed to thermolysis, initially provide annulated hydroquinones **1.98** which, following an oxidative work-up, yielded the respective naphthoquinones **1.99** (Scheme 1.16). This was proven to be a valuable and reliable method of synthesising these fused ring systems based on the high yields and simple reaction conditions. Upon thermolysis, the strained cyclobutenone ring opens to form the corresponding vinylketene **1.96** which then

undergoes a 6π-electrocyclic ring closure with the aryl substituent forming adduct **1.97**. This tautomerises to the more stable hydroquinone **1.98** which, after oxidative work-up, yields naphthoquinone **1.99**.



Scheme 1.16: General example of Moore's rearrangement of modified cyclobutenediones

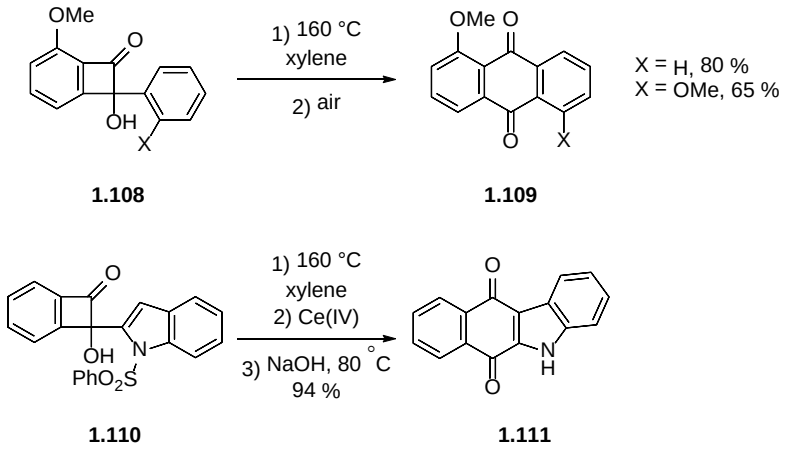
Furthermore, this was also proven to be effective in the formation of fused heteroaromatic ring systems, such as oxygenated benzofurans, benzothiophenes and indoles, with equally impressive yields (Scheme 1.17).



Scheme 1.17: Rearrangement of cyclobutenones bearing heteroaromatic residues

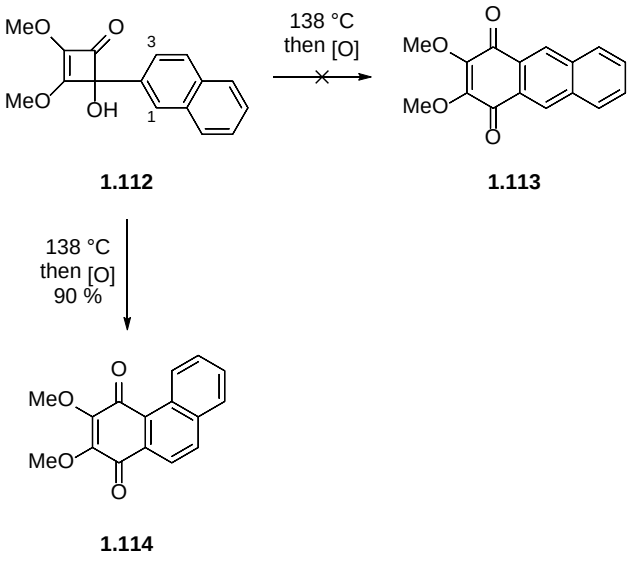
1.2.6 Rearrangement to extended polyaromatic systems

In 1986, Liebeskind *et al*. extended the method to synthesise anthraquinones **1.109** and polyaromatics **1.111** from benzocyclobutenones (Scheme 1.18).[22]



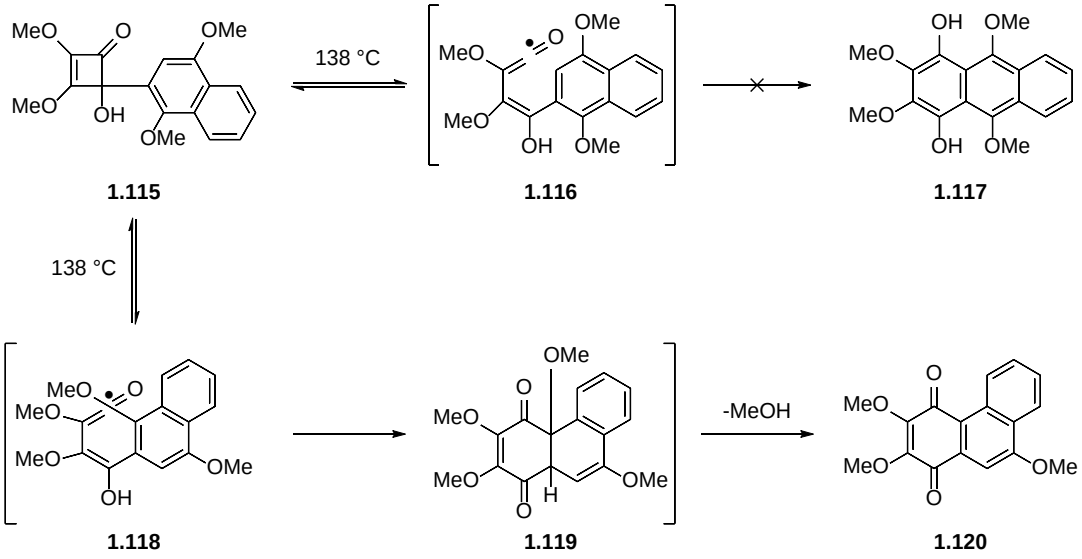
Scheme 1.18: Approach by Liebeskind *et al.* to extended polyaromatics

This methodology was extended by Moore *et al.* to include a 2-naphthyl substituent that formed phenanthrenedione **1.114** (Scheme 1.19).[21] It was envisaged that thermolysis of cyclobutenone **1.112** could form either phenanthraquinone **1.113** or anthraquinone **1.114** by cyclisation at C-1 or C-3 respectively. Despite this, only phenanthraquinone **1.114** was isolated indicating that electrophilic addition to C-1 was favoured.



Scheme 1.19: Thermolysis of cyclobutenone **1.112** to phenanthraquinone **1.114**

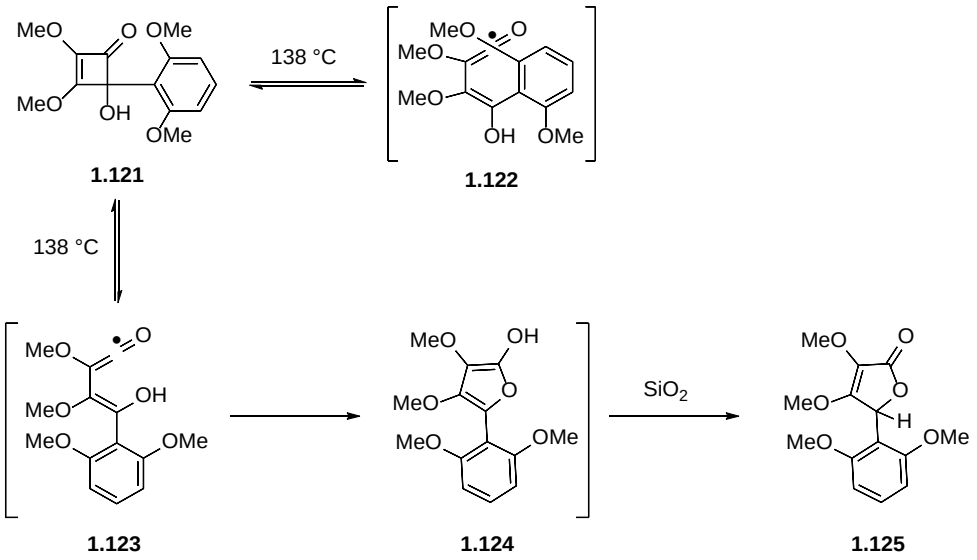
This was also observed with the thermolysis of cyclobutenone **1.115** which did not yield the expected linear anthraquinone **1.117** but instead produced phenanthraquinone **1.120** as the major product (Scheme 1.20). This confirmed that the electrophilic character of the ketene formed upon thermolysis influences the reaction pathway in the rearrangement of cyclobutenones.



Scheme 1.20: Unexpected formation of phenanthraquinone **1.120** from cyclobutenone **1.115**

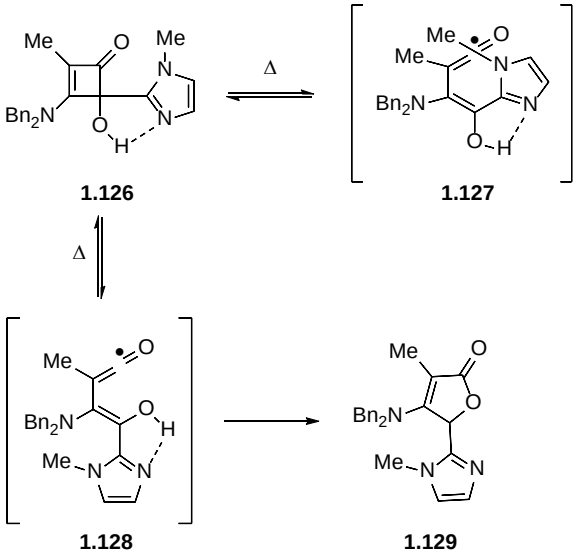
1.2.7 Rearrangement of cyclobutenones to furanones

Interestingly it was also observed by Moore *et al.* that when cyclobutenone **1.121** was subjected to thermolysis, it resulted in the formation of butenolide **1.125**. In this case, inward rotation of the hydroxyl group led to ketene **1.123** which spontaneously collapsed to the furanone **1.124** (Scheme 1.21). This change in torquoselectivity can be attributed to the steric clash between the ketene and the *ortho*-methoxy group of the arene residue raising the barrier for cyclisation.



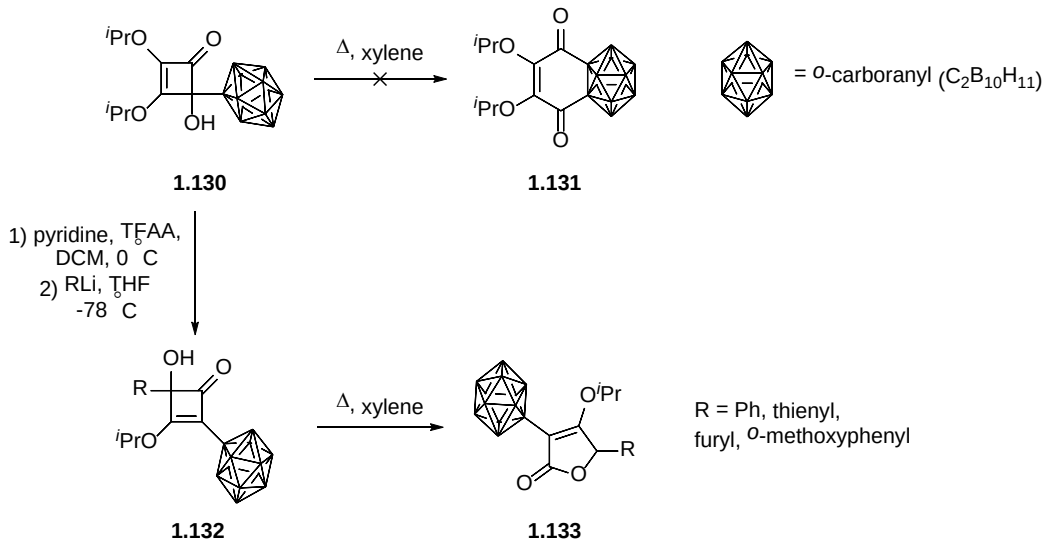
Scheme 1.21: Formation of furanone **1.125** by thermolysis of cyclobutenone **1.121**

This unexpected case of butenolide formation has also been reported by Liebeskind *et al.*[23] During the synthesis of pyridones from cyclobutenones bearing azaheteroaryl residues, it was observed that, when cyclobutenone **1.126** was subjected to thermolysis, furanone **1.129** was produced in quantitative yield (Scheme 1.22). This was explained by the imine nitrogen of the imidazole forming a hydrogen bond with the hydroxyl group of (*Z*)-vinylketene **1.127**, preventing rotation to allow cyclisation. This intermediate would then reverse back to cyclobutenone **1.126** allowing formation of (*E*)-vinylketene **1.128** and cyclisation to furanone **1.129**.



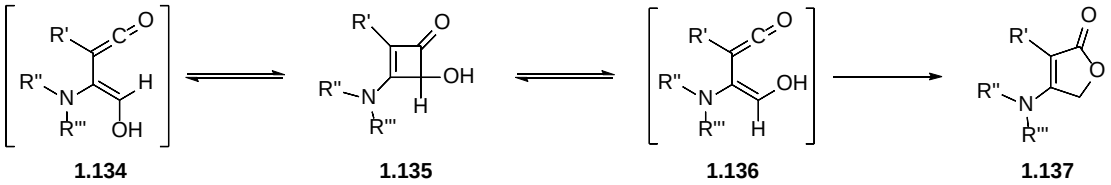
Scheme 1.22: Furanone formation from cyclobutenone **1.126**

Liebeskind *et al.* also reported furanone formation when attempting to synthesise carboranoquinones.[24] Thus, when cyclobutenone **1.130** was subjected to thermolysis it returned the starting material rather than the carborane substituted quinone **1.131** (Scheme 1.23). Cyclobutenones **1.132** were then synthesised and, when exposed to thermolysis, the products given were the corresponding butenolides **1.132**.



Scheme 1.23: Formation of carborane-substituted furanones

Production of furanones *via* thermolyses of cyclobutenones was also reported by Wang *et al.* in 2001.[25] It was observed that upon refluxing a solution of 4-hydroxycyclobutenone **1.135** in *p*-xylene in the presence of TFA, furanones **1.137** were exclusively produced (Scheme 1.24). It was suggested that this was caused by the reversible electrocyclic ring opening of **1.135** to (*E*)-vinylketene **1.136** and (Z)-vinylketene **1.134**. However, as no cyclisation could occur within the (*Z*)-vinylketene furanones **1.137** were formed as the sole product. This was repeated with various amino residues bearing alkyl and benzyl groups and various cyclobutenone substituent leading to yields of between 51-94 % upon thermolysis.

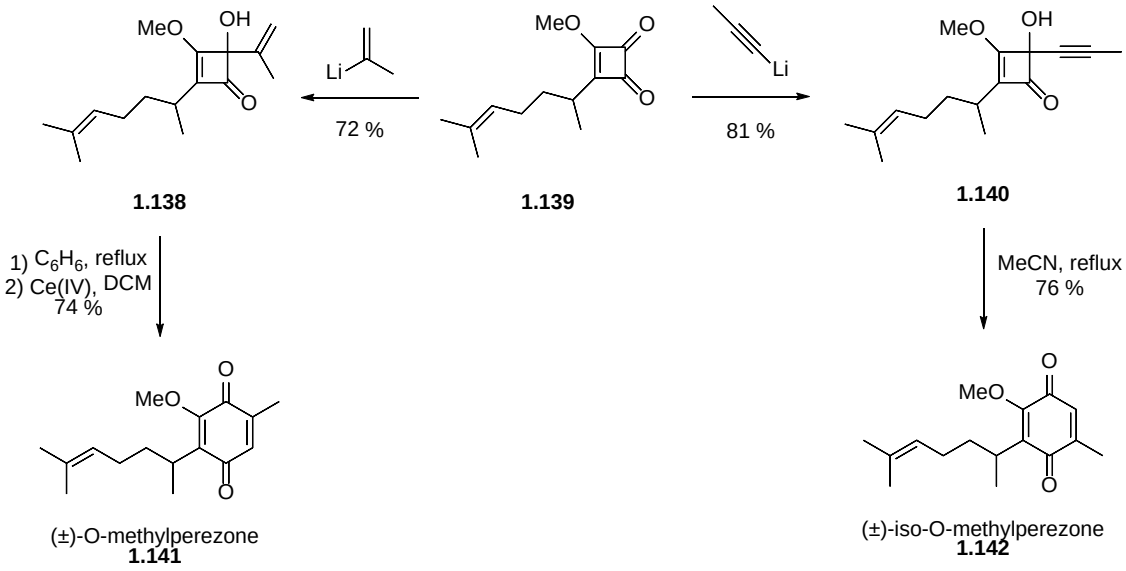


Scheme 1.24: Furanone formation by Wang *et al.*

1.2.8 Rearrangement of cyclobutenones bearing vinyl substituents

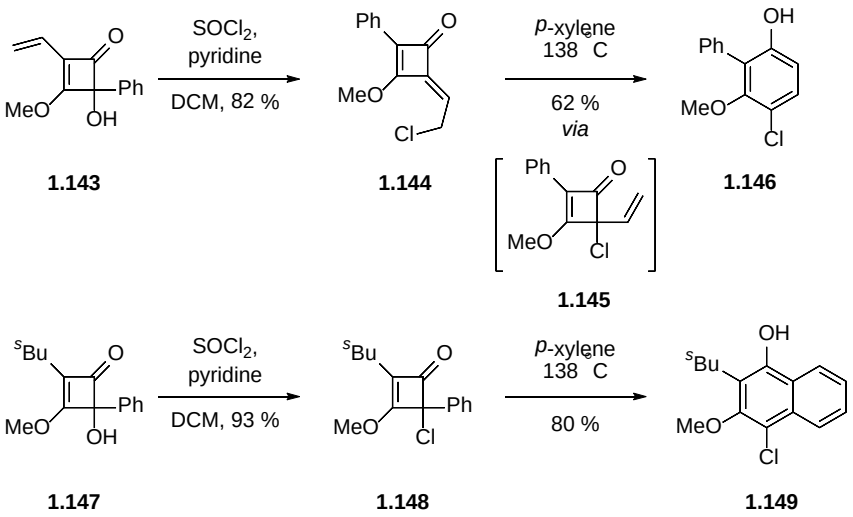
It was also observed that cyclobutenones bearing vinyl residues rearranged in a similar way to those bearing aryl substituents. In 1989, Moore *et al.* reported a complimentary reaction to those involving alkynylcyclobutenone rearrangements when he demonstrated that vinylcyclobutenone **1.138** and alkynylcyclobutenone **1.140** would rearrange in a similar

manner to form the regioisomeric natural products (±)-*O*-methylperezone **1.141** and (±)-*iso*-*O*-methylperezone **1.142** respectively (Scheme 1.25).



Scheme 1.25: Regioisomeric control by varying cyclobutenone starting materials

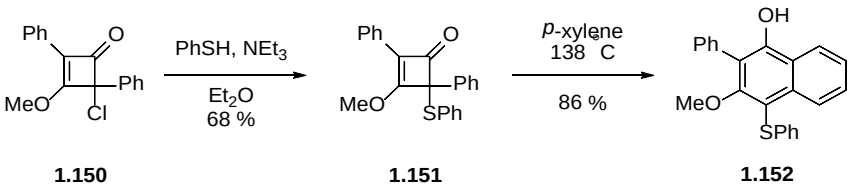
This methodology has since been used to produce a vast array of useful precursors, natural products and synthetically valuable quinone containing molecules.[26–28] Thermolyses of 4-vinyl/arylcyclobutenones bearing a 4-chloro substituent were observed to undergo rearrangements to highly substituted chlorophenols.[17] Moore and Xu firstly prepared cyclobutenone **1.144** *via* treatment of cyclobutenone **1.143** with $SOCl_2$ and pyridine before thermolysis yielded chlorophenol **1.146** (Scheme 1.26). It was presumed that the rearrangement occurred *via* rearrangement of chloride **1.144** to intermediate **1.145**. The more stable 4-chlorocyclobutenone **1.148** was also prepared and on thermolysis formed chloronaphthol **1.149** in good yield.



Scheme 1.26: Formation of chlorophenols and chloronaphthols

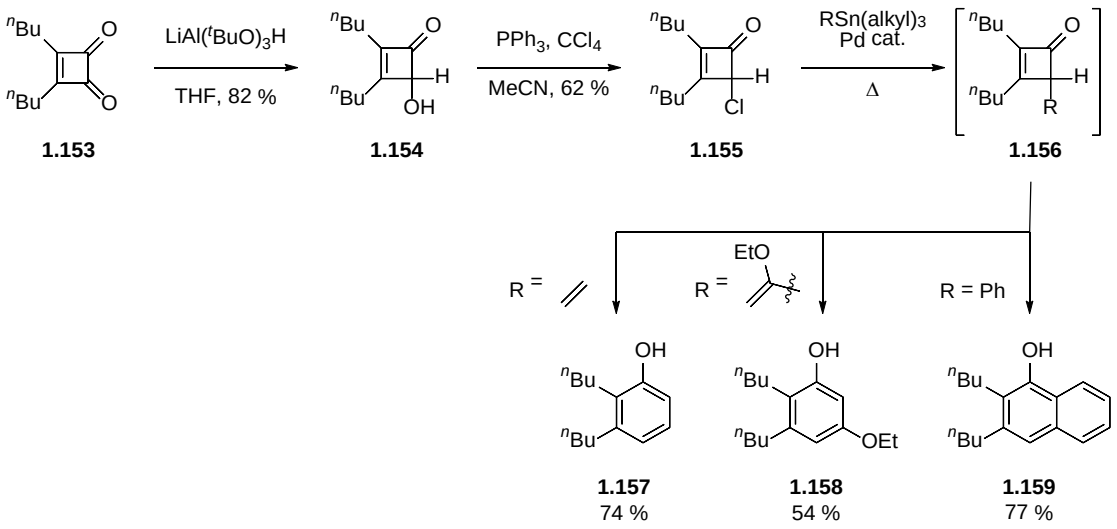
1.2.9 Functionalisation using 4-chloro-substituted cyclobutenones

Moore and Xu also demonstrated that the 4-chloro-substituent could be substituted by a variety of nucleophiles such as thiols and ethers (Scheme 1.27).[17]



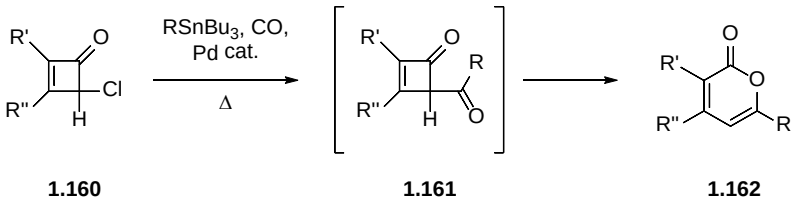
Scheme 1.27: Substitution of the 4-chloro substituent to form substituted phenols

Liebeskind *et al.* furthered this methodology by developing alternative routes to highly substituted phenols *via* thermolysis of cyclobutenones **1.156** (Scheme 1.28).[29] Preparation of these began with reduction of cyclobutenedione **1.153** before chlorination with PPh_3/CCl_4 furnished adduct **1.155**. Palladium-catalysed cross-couplings with various organostannanes followed by subsequent thermolysis yielded the corresponding phenols in moderate yields. This methodology was then extended to the formation of benzo- and dibenzo-furans as well as benzo- and dibenzo-thiophenes.[30]



Scheme 1.28: Phenol synthesis by palladium-catalysed cross-coupling

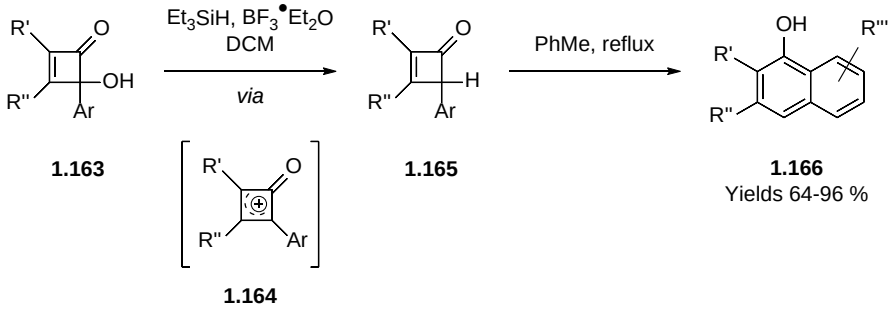
The scope of this rearrangement was also extended to the synthesis of pyrones.[31] When conducting the palladium-catalysed cross-coupling of chlorocyclobutenone **1.160** and an organostannane in the presence of CO, pyrones **1.162** were formed in good yields (Scheme 1.29).



R	R'	R''	Yield **1.162** %
Ph	^{n}Bu	^{n}Bu	86
Ph	Me	Ph	78
p-ClPh	Et	Et	84
p-MeOPh	Et	Et	80
2-furyl	Me	^{i}PrO	89
2-propenyl	Et	Et	65

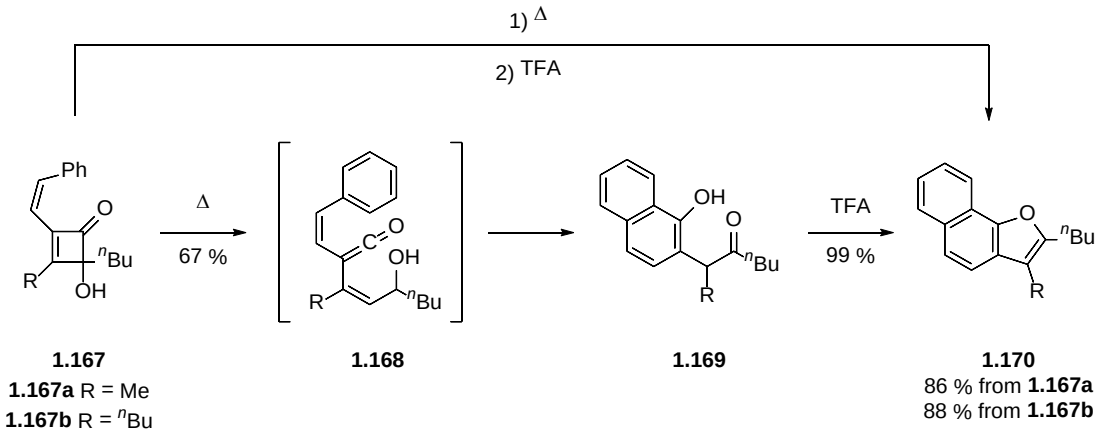
Scheme 1.29: Palladium-catalysed carbonylation to pyrones

A synthesis of substituted phenols was also reported by Moore and Turnbull in 1995.[32] They described the reduction of cyclobutenones **1.163** to cyclobutenones **1.165** by treatment with Et_3SiH in the presence of $BF_3 \bullet Et_2O$ and their subsequent thermolysis to naphthols **1.166** in good to excellent yield (Scheme 1.30).



Scheme 1.30: Synthesis of naphthols by Moore and Turnbull

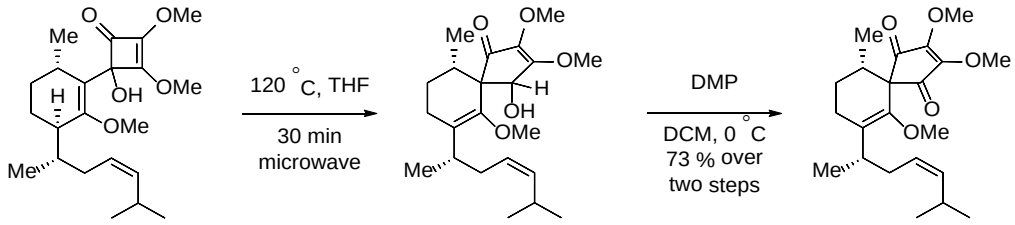
In 1996, Moore *et al.* reported the formation of annulated furans by thermolysis of 4-alkylcyclobutenones **1.167**.[33] Due to the lack of compatible group at the C-4 position, typical thermal rearrangements are prohibited. Consequently, thermal ring expansion to ketene **1.168** is followed by cyclisation to the proximal arene leading to naphthols **1.169**. If TFA is added, furan **1.170** is formed (Scheme 1.31). Of note is that that only (*Z*)-vinylketene **1.168** can perform the 6π-electrocyclisation. In the aforementioned case, the initial stereochemistry of the alkene is irrelevant as the (*E*)- and (*Z*)-isomers are in equilibrium.



Scheme 1.31: Synthesis of annulated furans from 4-alkylcyclobutenones

1.2.10 Rearrangement of cyclobutenones to spirocycles and cycloalkane ring systems

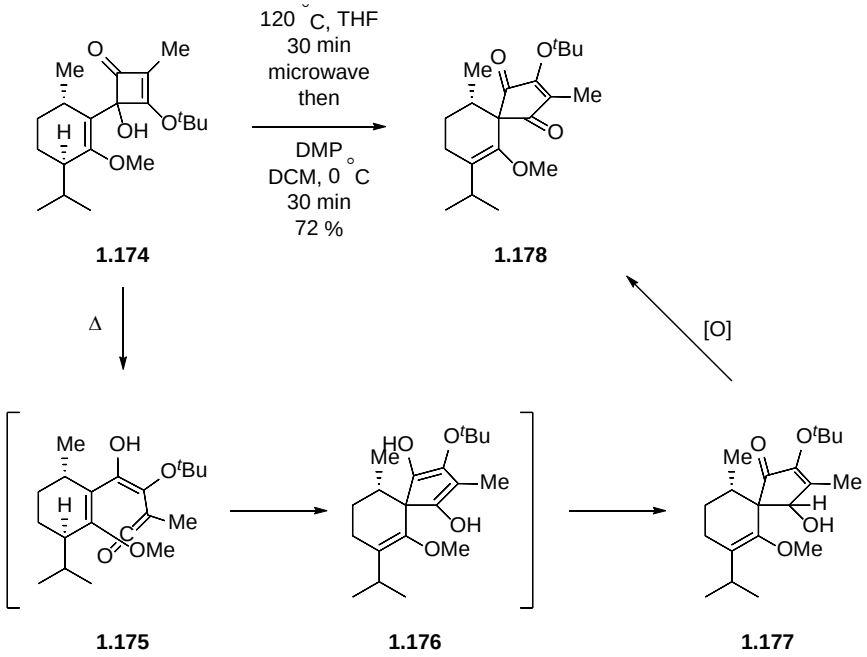
Harrowven *et al.* later observed a series of dichotomous rearrangement pathways of 4-vinylcyclobutenones.[34] When a leaving group was incorporated within the vinyl residue of cyclobutenone **1.171**, instead of the anticipated quinone being produced upon thermolysis a mixture of two diastereoisomers of cyclopenteneone **1.172** and cyclopentenedione **1.173** were observed that produced the latter in good yield on oxidation (Scheme 1.32).



1.171 **1.172** **1.173**

Scheme 1.32: Unexpected spirocycle formation on thermolysis of cyclobutenone **1.171**

A series of related cyclobutenones were then subjected to analogous conditions and all were observed to produce cyclopentenediones in high yields. The mechanistic course of this rearrangement was suggested to occur *via* electrocyclic ring opening to ketene **1.175** followed by a carbonyl-ene reaction to form spirocycle **1.176**. Tautomerisation to **1.177** followed by oxidation then produced the observed cyclopentenedione (Scheme 1.33).

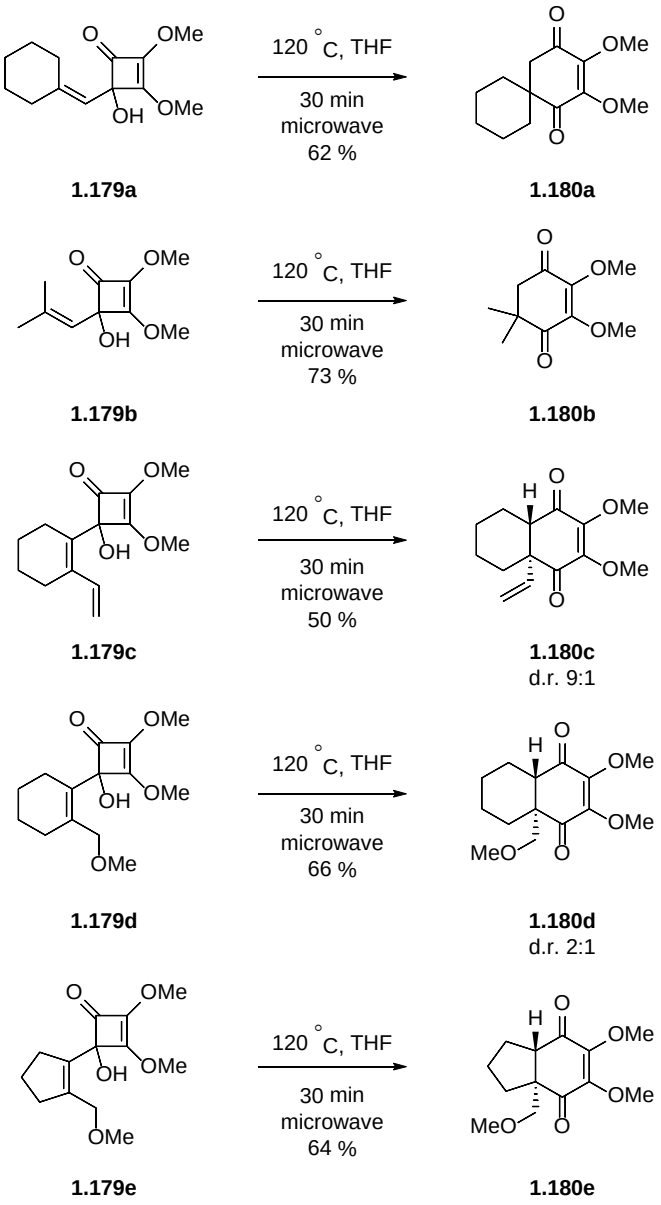


1.174 **1.178**

1.175 **1.176** **1.177**

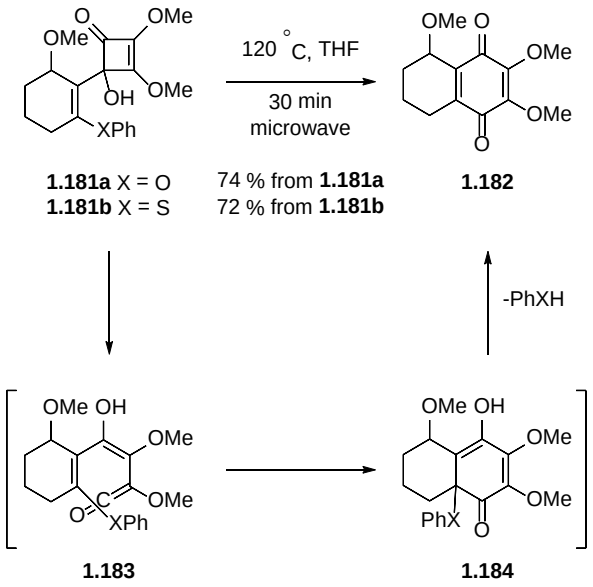
Scheme 1.33: Proposed mechanism of spirocycle formation from vinylcyclobutenone **1.174**

To further investigate the factors affecting the cyclisation of the ketene intermediate, substrates bearing vinyl residues featuring two alkyl groups on the distal carbon were prepared. Thermolysis of each of these substrates produced cyclohexenediones **1.180** in good yield indicating it was an electronic factor influencing the rearrangement (Scheme 1.34).



Scheme 1.34: Formation of cyclohexenediones

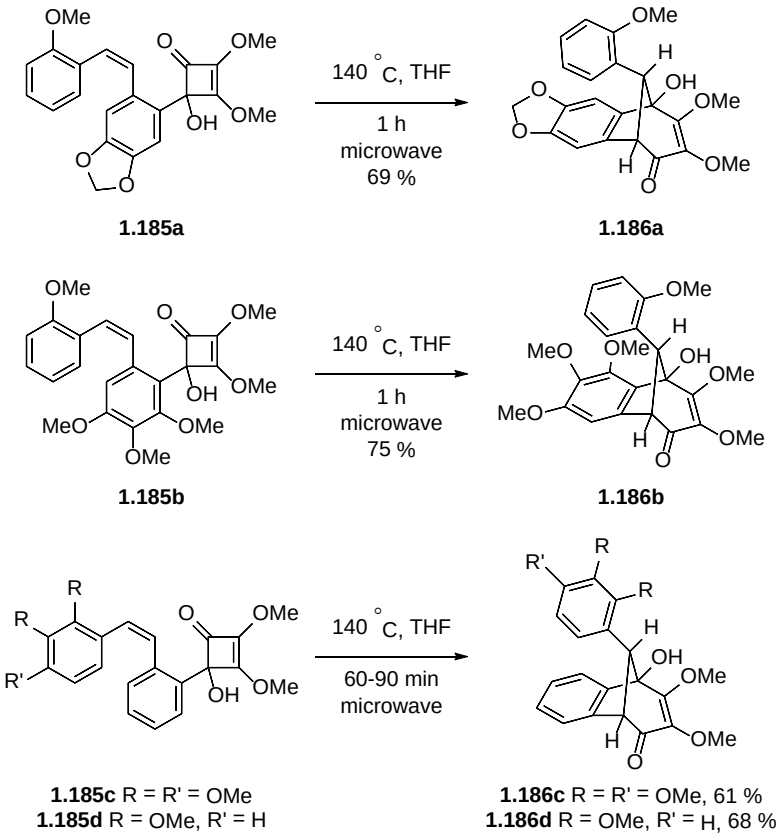
The influence of electronic factors on the mode of cyclisation was further evidenced by the thermolysis of cyclobutenones **1.181a** and **1.181b**. In contrast to the thermolysis of vinyl ether **1.174**, both gave quinone **1.182** in good yield (Scheme 1.35). This demonstrated the ability to alter the reaction pathway from spirocycle to quinone formation by attenuating electron density in the pendant vinyl residue.



Scheme 1.35: Domino reactions observed upon thermolysis of cyclobutenone **1.181**

1.2.11 Rearrangement of cyclobutenones bearing styrene residues

The scope of the Moore rearrangement was then extended to include 4-(*o*-styryl)cyclobutenones which were observed to produce benzobicyclo[3.2.1]octenones in good yield (Scheme 1.36).[34] While thermolyses of (*Z*)-4-(*o*-styryl)cyclobutenones **1.185a-d** were shown to give single diastereoisomers **1.186a-d**, the analogous reaction of the (*E*)-isomers produced diastereomeric mixtures.



1.185a → **1.186a**

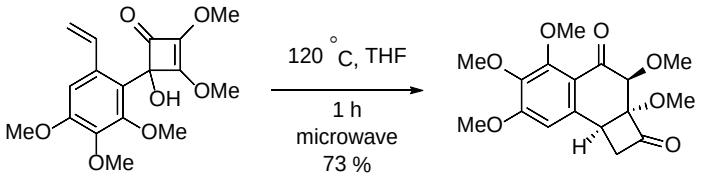
1.185b → **1.186b**

1.185c R = R' = OMe
1.185d R = OMe, R' = H

1.186c R = R' = OMe, 61 %
1.186d R = OMe, R' = H, 68 %

Scheme 1.36: Formation of benzobicyclo[3.2.1]octenones from (*Z*)-4-(*o*-styryl)cyclobutenones

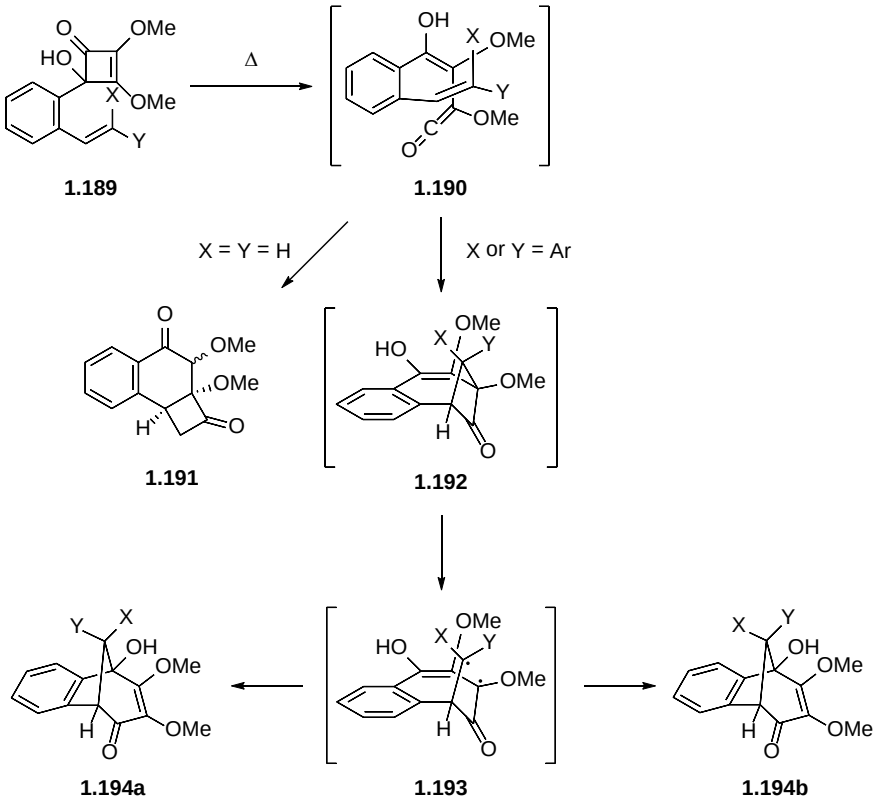
This rearrangement occurred *via* a different pathway in the case of 4-styrylcyclobutenone **1.187** which formed the [2+2] cycloadduct **1.188** (Scheme 1.37).



1.187 → **1.188**
d.r. 6:1

Scheme 1.37: Rearrangement of cyclobutenone **1.187** to benzobicyclo[4.2.0]octenone **1.188**

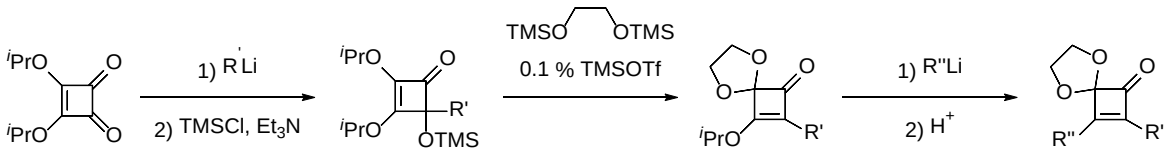
It was proposed that these reactions begin with electrocyclic ring opening of cyclobutenone **1.189** to ketene **1.190** followed by a [2+2] cycloaddition (Scheme 1.38). For styrenes, this leads to dione **1.191** whereas for stilbenes (X or Y = Ar), ketene **1.190** proceeds via a different course leading to intermediate **1.192**. Formation of diradical **1.193** *via* ring opening then occurs followed by cyclisation to produce benzobicyclo[3.2.1]octenones **1.194a** and **1.194b**.



Scheme 1.38: Proposed mechanism of thermolyses of 4-(*o*-styryl)cyclobutenones

1.3 Using protection chemistry to influence regiochemistry in cyclobutenediones

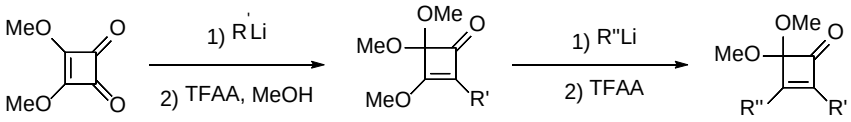
To date, there have been many cases of utilising protection chemistry to control the regiochemical course of nucleophilic additions to cyclobutenediones. In 1990, Liebeskind and Wirtz reported the use of acetal protection to control addition of organolithiums to cyclobutenediones.[35] Acetals **1.197** were produced by treatment of silyl ethers **1.196** with ethylene glycol *bis*-(trimethylsilyl)ether and trimethylsilyl triflate in good yields (Scheme 1.39). Treatment with a variety of organolithiums followed by mild hydrolysis yielded exclusively cyclobutenedione monoacetals **1.198** in excellent yields without further deprotection of the acetal moiety. This method was later demonstrated to tolerate cuprate additions.[36]



1.195 **1.196** **1.197** **1.198**

Scheme 1.39: Regiocontrolled addition using acetal protection

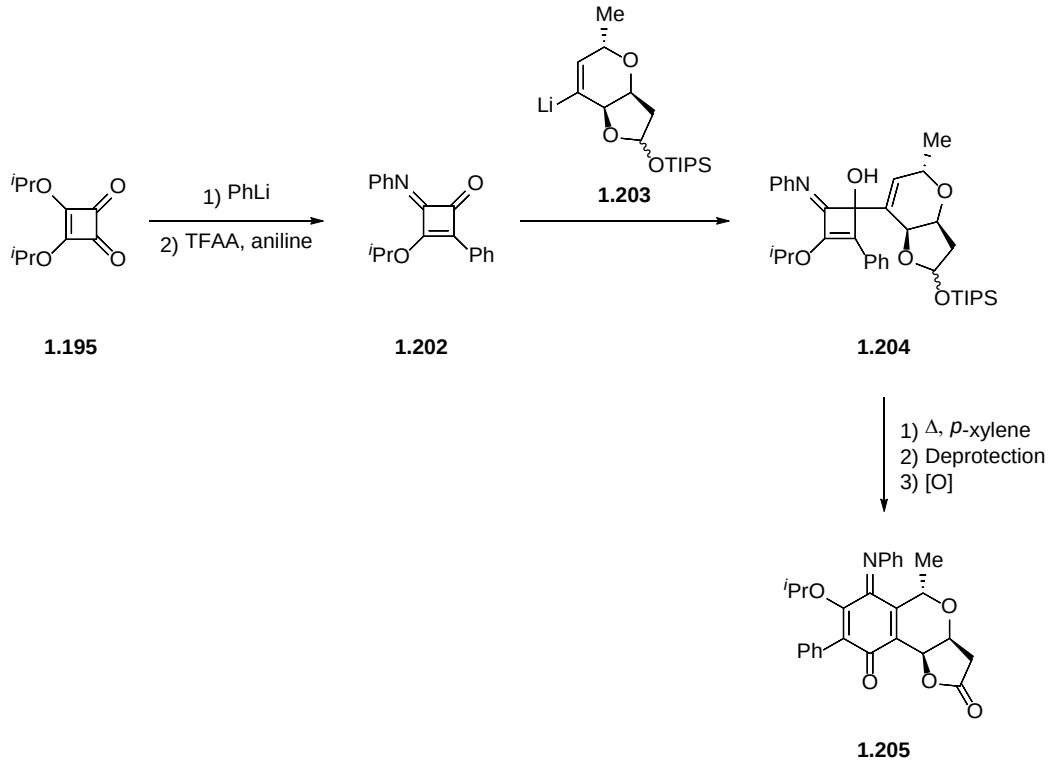
A similar approach was undertaken by Moore in 1992 using dimethyl acetals.[37] A one-pot addition/protection procedure was developed involving organolithium addition followed by methanolysis giving acetals **1.200** (Scheme 1.40). A second organolithium was then added before treatment with TFAA yielded the cyclobutenedione monoacetals **1.201** in good yield.



1.199 **1.200** **1.201**

Scheme 1.40: One-pot protection method used by Moore *et al.*

When investigating the synthesis of isochromanquinones, Moore *et al.* developed a new protecting group strategy in the form of iminocyclobutenone **1.202**.[38] This proved as effective as acetal protection however it was also noteworthy in that it could be converted to iminoquinone **1.205**, a previously unreported transformation within the field of cyclobutenone rearrangements (Scheme 1.41). This methodology has since been used by Trost *et al*. in the total synthesis of furaquinocins, a class of natural products that display antibiotic properties.[39]



Scheme 1.41: Use of iminocyclobutenones to control regioselectivity and iminoquinone formation

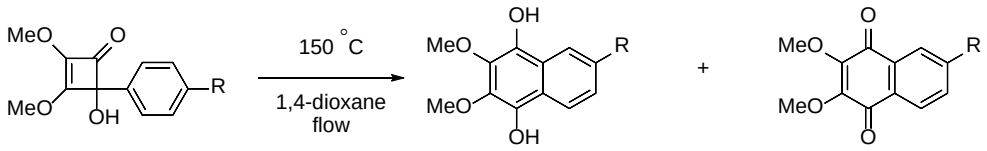
1.4 Recent developments in cyclobutenone rearrangements

In the recent past there have been many reported uses of cyclobutenone rearrangements including variations on the Moore rearrangement and its use in natural product total synthesis.

1.4.1 The effect of flow chemistry on the Moore rearrangement

Traditionally, thermal rearrangements of cyclobutenones were conducted in refluxing *p*-xylene for long reactions times. In 2011, Harrowven *et al.* utilised flow systems to improve this dramatically.[2] By employing 1,4-dioxane as a solvent, it was possible to heat the substrates to 150 °C resulting in drastically shorter reaction times and near quantitative yields (Table 1.1).

Table 1.1: Thermal rearrangement of 4-arylcyclobutenones under flow

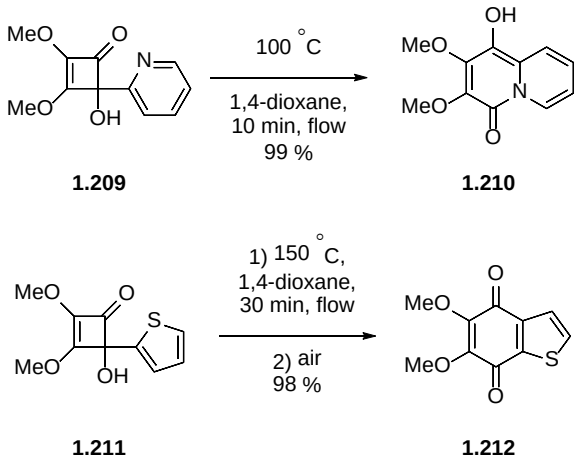


1.206 **1.207** **1.208**

1.206	R	Reaction time h	Yield **1.208** %
a	H	0.5	99
b	Me	2	94
c	$SiMe_3$	2	94
d	^{t}Bu	2	94
e	Ph	3	95
f	CON^iPr_2	1.5	84
g	OMe	4	94
h	F	4	92
i	CF_3	4	93

air

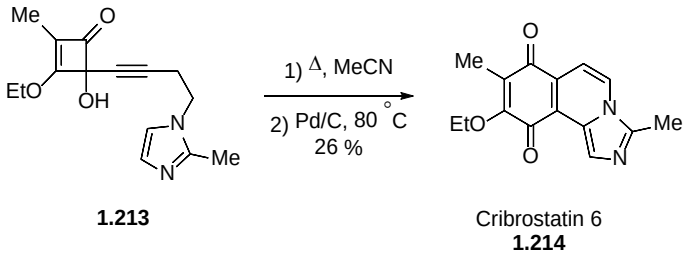
This vast improvement was also displayed when heteroarylcyclobutenones **1.209** and **1.211** were subjected to thermolysis under flow (Scheme 1.42). By examining both electron-rich (thiophene) and electron-poor (pyridine) heteroaryl residues, the near quantitative yields proved the generality of the method.



Scheme 1.42: Thermal flow rearrangements of heteroarylcyclobutenones

Building upon the improved yields they had achieved when employing continuous thermal flow, Harrowven *et al*. chose to develop a synthetic route to cribrostatin 6, an isoquinolinedione isolated from the blue marine sponge *Cribrochalina* which displays potent antimicrobial, anti-tumour and antineoplastic activity.[40] Originally isolated by Pettit

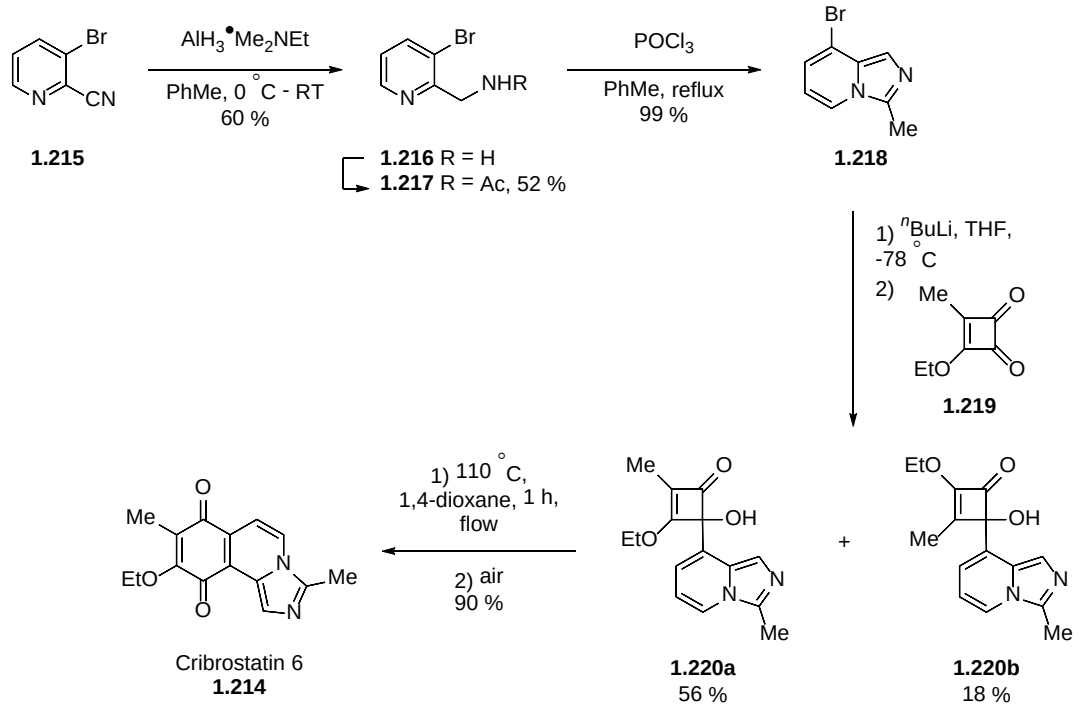
et al., a total synthesis of cribrostatin 6 was reported in 2007 by Knueppel and Martin involving thermal rearrangement of 4-alkynylcyclobutenone **1.213** followed by dehydrogenation by Pd/C furnishing the desired product **1.214** in a 14.1 % overall yield over 5 total steps (Scheme 1.43).[1,41]



1.213 Cribrostatin 6 **1.214**

Scheme 1.43: Key rearrangement to cribrostatin 6 **1.214**

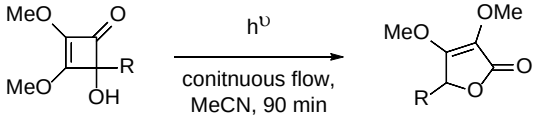
Due to the many pathways thermal rearrangements of 4-alkynylcyclobutenones can proceed by, Harrowven *et al*. set out to develop a more efficient *via* rearrangement of 4-arylcyclobutenone **1.220a** (Scheme 1.44). To that end, nitrile **1.215** was converted to amide **1.217** by reduction with alane and subsequent acylation. Cyclisation using $POCl_3$ then yielded imidazopyridine **1.218** in near-quantitative yield before coupling with cyclobutenedione **1.219** furnished adduct **1.220a** (alongside regioisomer **1.220b**). Thermolysis under flow followed by aerial oxidation then gave cribrostatin 6 **1.214** in an impressive 90 % yield.



Scheme 1.44: Synthetic route to cribrostatin 6 **1.214** by Harrowven *et al*.

Various analogues have since been synthesised using this reaction sequence by varying the substituents of cyclobutenedione **1.219** in the hope of increasing potency as anti-tumour agents.[42]

Recently, Harrowven *et al.* revisited the photochemical rearrangement of cyclobutenones to furanones using a photochemical flow reactor based on a design by Booker-Milburn *et al*.[43,44] Importantly, this system allowed a variety of light sources to be used. Their studies allowed near quantitative yields of furanone **1.222** to be achieved (Scheme 1.45) and also exposed an anomaly.



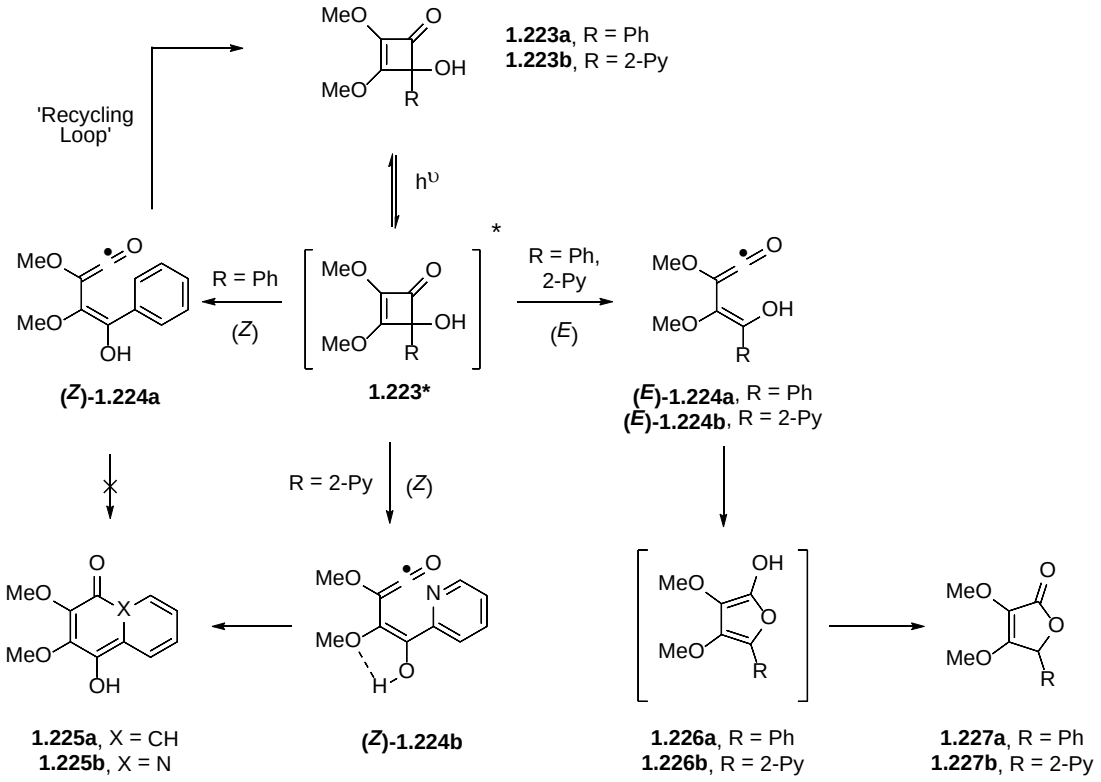
1.221 **1.222**

R	Yield **1.222** %
Ph	99
^{n}Bu	95
^{t}Bu	96
Ph-CC	95
2-MeOPh	97
4-Me$_3$SiPh	93
4-^{t}BuPh	92
3-pyridyl	94

Scheme 1.45: Continuous flow preparation of furanones **1.222**

Thus, photolysis of (2-pyridyl)-cyclobutenone **1.223b** led to a 1:1 mixture of furanone **1.227b** and quinolizinone **1.225b** casting doubt on the suggestion that this was a torquoselective process. Rather it indicated that a mixture of (*E*) and (*Z*)-vinylketenes were initially formed (Scheme 1.46). Computational modelling was performed using substituted cyclobutenones bearing the phenyl (**1.223a**) and 2-pyridyl (**1.223b**) residues to shed some light on this postulate. These showed that for **(*Z*)-1.224a**, the energy barrier for 6π-electrocyclic ring closure leading to **1.225a** was higher than that for 4π-ring closure to the starting material **1.123a**. By contrast, cyclisation of **(*E*)-1.224a** to furan **1.226a** was spontaneous explaining why this was formed as the sole product of the reaction. In the case of the 2-pyridyl compound adduct **1.223b**, closure of **(*E*)-1.224b** and **(*Z*)-1.224b** were both spontaneous leading to the observed mixture of furanone and quinolizinone products.

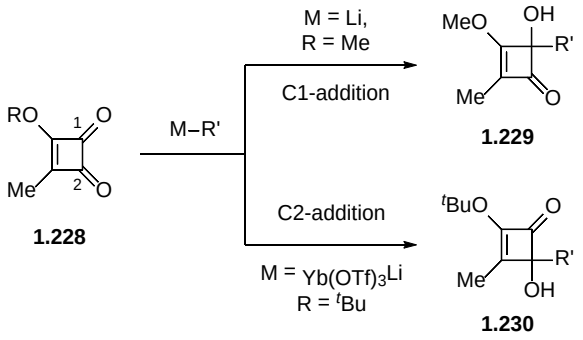
This computational modelling thus gave an extremely plausible reasoning behind the experimental results observed.



Scheme 1.46: Photolysis reaction mechanism postulated by Harrowven *et al.*

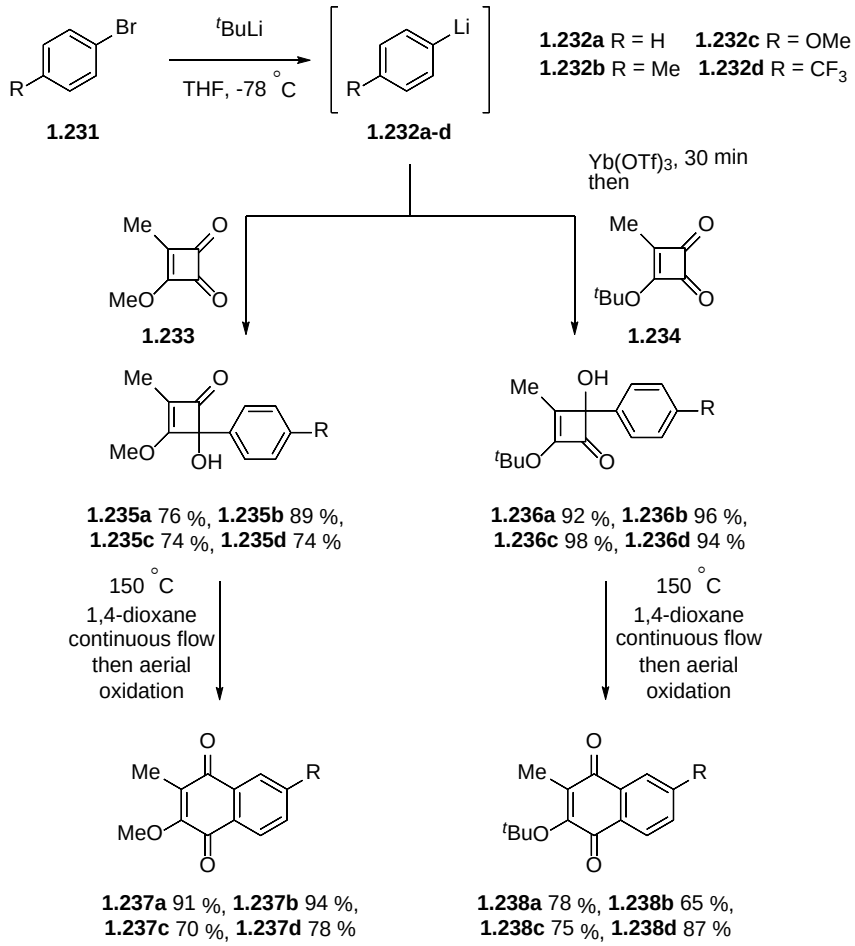
1.4.2 Manipulation of regiochemistry using ytterbium

In 2013, Harrowven *et al*. demonstrated the ability to alter nucleophilic additions upon cyclobutenediones through the use of ytterbium transmetallation.[6] As previously mentioned, nucleophiles will typically insert into the C1 position of 3-alkyl-4-alkoxy-cyclobutenediones, *e.g.* **1.228**, as it is the more reactive carbonyl. However through transmetallation of the organolithium with ytterbium triflate and the introduction of a bulky *tert*-butoxy at C4, nucleophilic addition occurs at the C2 position (Scheme 1.47).



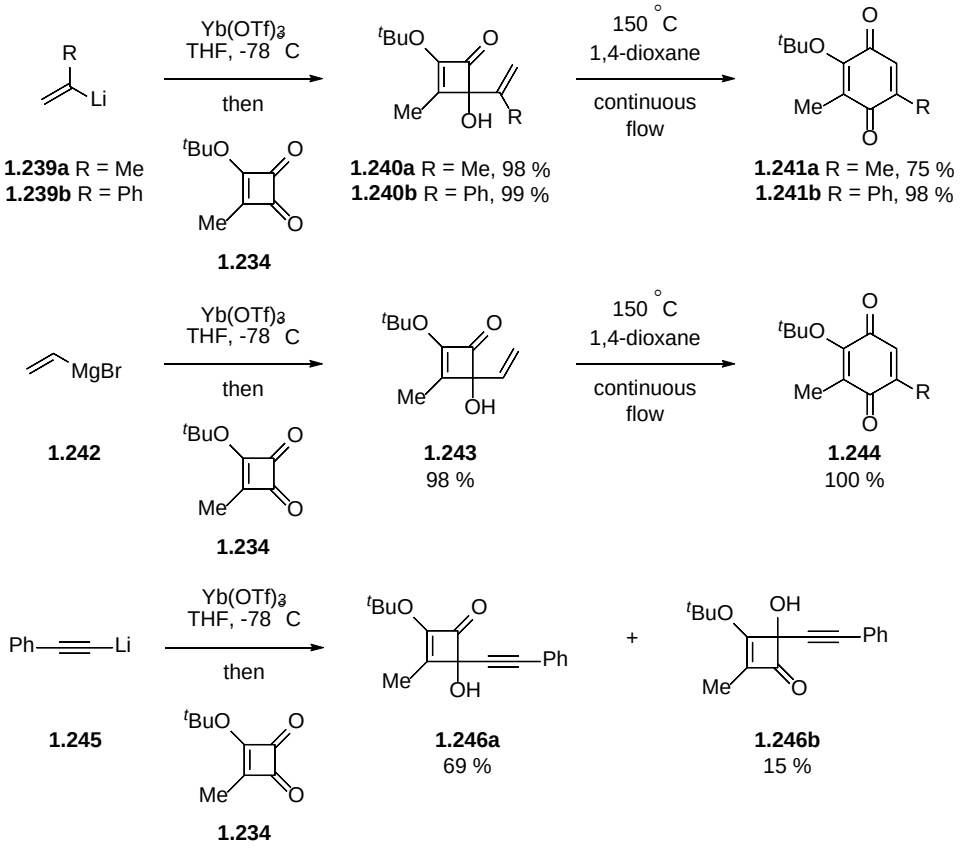
Scheme 1.47: Regioselectivity of organoytterbium reagents contrary to organolithiums

The scope of this dichotomous reactivity was extended to an array of aryllithium reagents (Scheme 1.48). In each case, the organoytterbium intermediate added to the vinylogous ester carbonyl of cyclobutenedione **1.234** and gave the corresponding cyclobutenone in near quantitative yield. This was in stark contrast to the addition of the corresponding organolithium reagent to cyclobutenedione **1.233** where addition to the other carbonyl predominated.



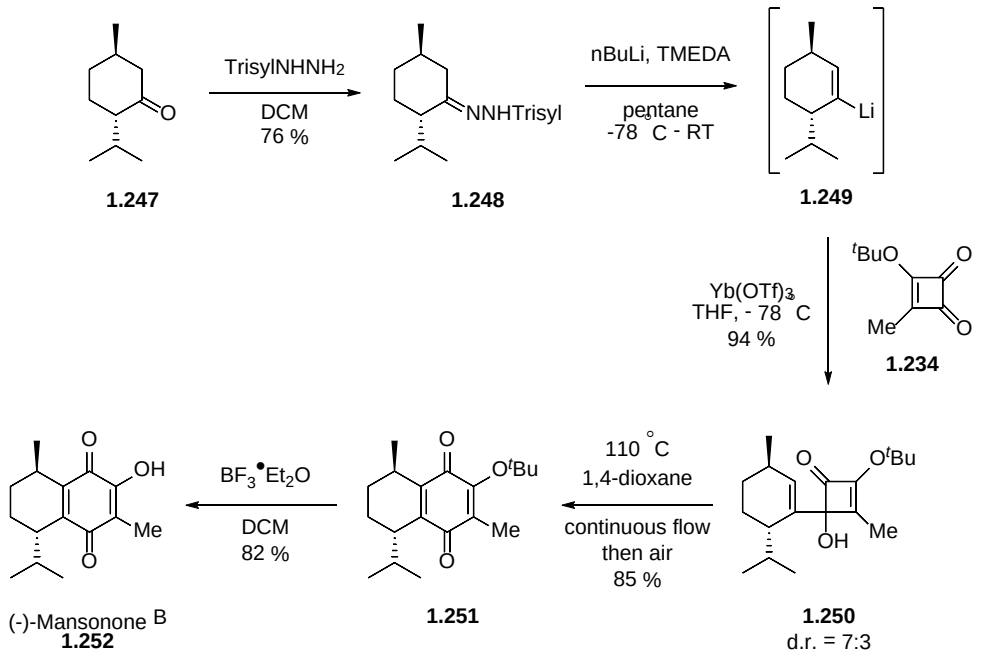
Scheme 1.48: Comparison of treatment with organolithium and organoytterbium species

Building upon this success, the substrate scope was expanded to include arenes bearing *ortho*- and *para*-substituents and to vinyl and alkynylytterbium complexes. While organoytterbium complexes derived from vinyllithiums and Grignard reagents also displayed the excellent regioselectivity previously observed, alkynylytterbium complexes proved less selective (Scheme 1.49). Indeed, when cyclobutenone **1.234** was treated with alkynylytterbium derived from phenylacetylene **1.245**, it produced a 1:4.6 ratio of the addition products **1.246b** and **1.246a** respectively.



Scheme 1.49: Comparison of different organoytterbium complexes additions

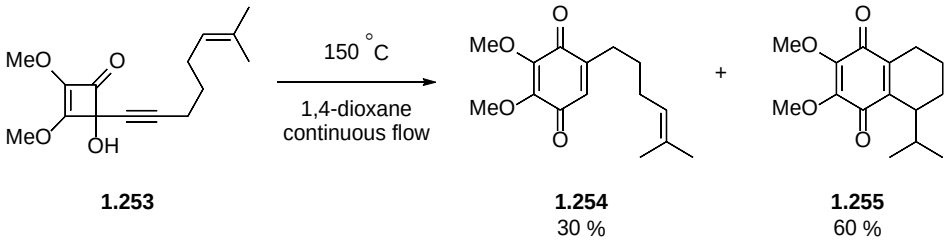
To demonstrate the potential of this reaction, Harrowven *et al.* developed a highly efficient route to (-)-mansonone B, a naturally occurring terpenoid isolated from *Mansonia altissima* (Scheme 1.50).[45] This class of quinones has since been proven to exhibit antimicrobial and herbicidal properties.[46] The route began with (-)-menthone **1.247** from which the required vinyllithium reagent **1.249** was produced *via* a Shapiro reaction. Transmetallation with ytterbium triflate and subsequent coupling to cyclobutenedione **1.234** gave cyclobutenone **1.250** which, following thermolysis under flow and aerial oxidation, yielded precursor **1.251**. This was readily converted to the target quinone **1.252** following deprotection by $BF_3 \bullet Et_2O$.



Scheme 1.50: Synthetic route to (-)-mansonone B **1.252** developed by Harrowven *et al.*

1.4.3 Mechanistic studies of the rearrangement of alkyne-substituted cyclobutenones

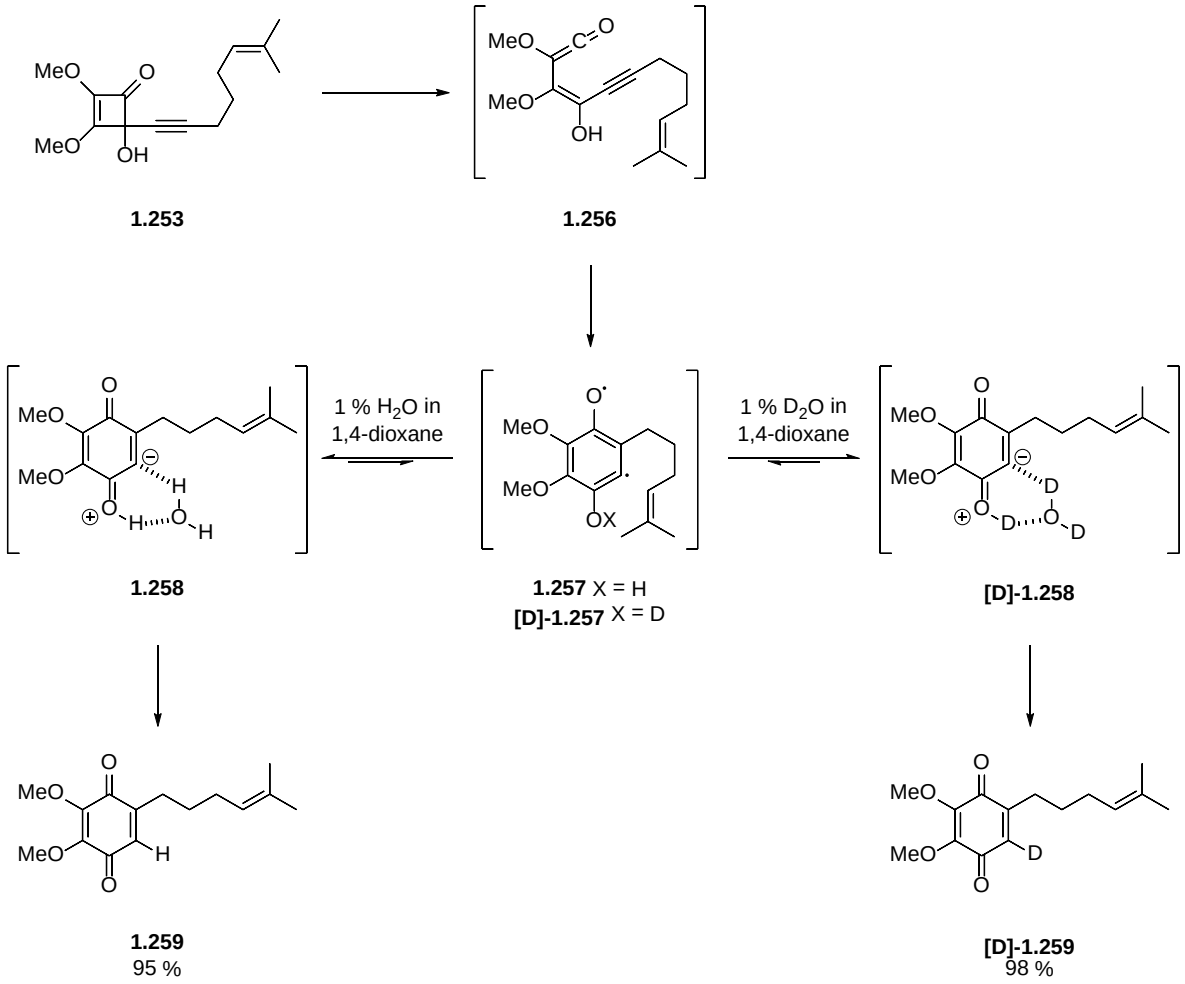
In 2015, Harrowven *et al*. set out to further investigate the Moore rearrangement of alkynylcyclobutenones.[47] When attempting to synthesise bicyclic quinone **1.255** from cyclobutenone **1.253**, quinone **1.254** was also produced in significant yield, which was presumed to result from H-atom abstraction (Scheme 1.51).



Scheme 1.51: Synthesis of bicyclic quinone **1.255** and by-product **1.254**

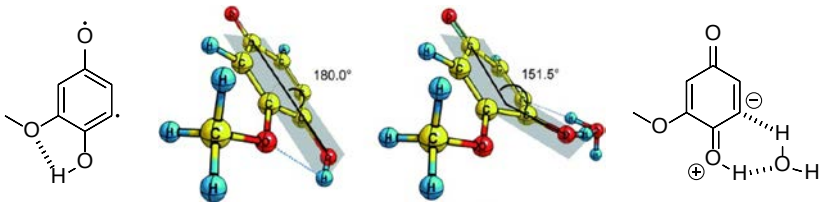
In an attempt to bias the reaction towards the production of **1.255**, 1,4-dioxane doped with 1 % D_2O was used with the rationale that the deuterium-isotope effect would cause D-atom abstraction from the phenol in **[D]-1.257** to be much slower than H-atom abstraction from the phenol in **1.257**, thereby promoting cyclisation to the proximal alkene (Scheme 1.52). In the event, adding D_2O had the opposite effect and shut down the radical cyclisation pathway completely such that the only product given was **[D]-1.259**. The reaction was then

reattempted with 1,4-dioxane doped with 1 % H_2O and a similar outcome was observed producing **1.259** in 95 % yield.



Scheme 1.52: Orbital isomer switch promoted by H_2O/D_2O doping

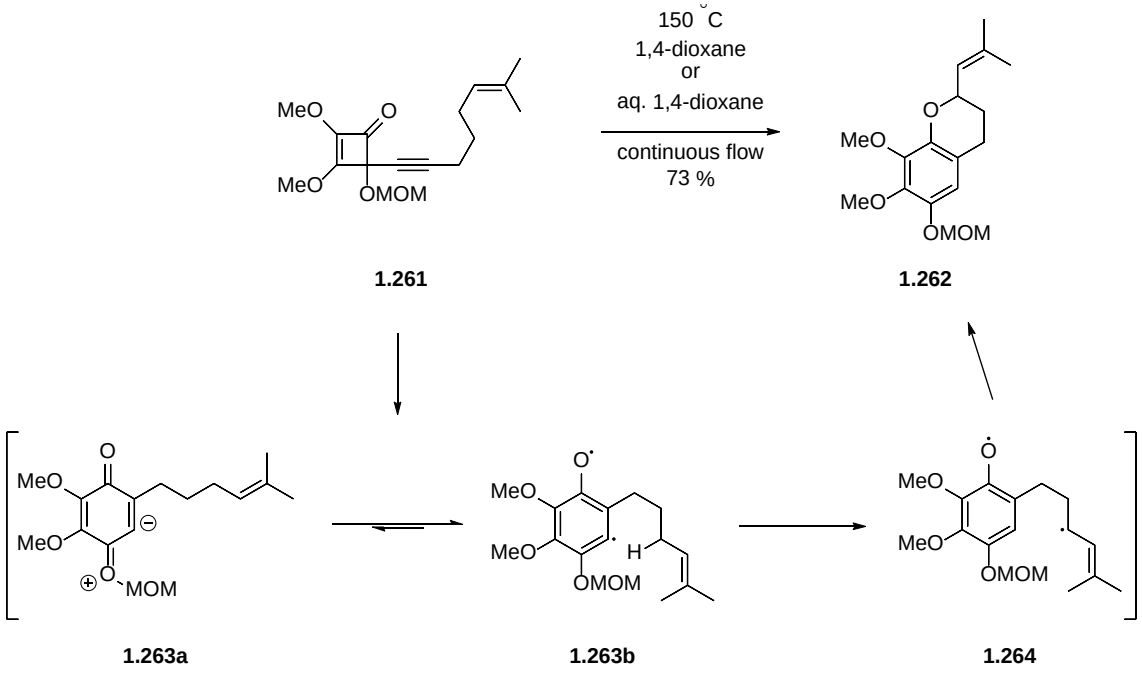
These results indicated that the zwitterionic orbital isomer **1.258** was favoured in the presence of water and catalysed *O* to *C* proton transfer. DFT calculations supported this hypothesis, indicating a favourability for hydrated zwitterion **1.260b** over diradical species **1.260a** of 11.9 kcalmol^{-1} (Figure 1.3). Interestingly, the geometry of the hydrated zwitterionic orbital isomer **1.260b** was puckered by approximately 30 ° while the diradical orbital isomer **1.260a** had a near planar geometry. This puckering also indicated that the zwitterionic orbital isomer had significant cyclohexatrienone character.



1.260a **1.260b**

Figure 1.3: Ring puckering observed by hydrated zwitterion **1.260b**

The importance of hydrogen bonding in **1.258** was experimentally proven using MOM-protected cyclobutenone **1.261** (Scheme 1.53). Its thermolysis in both 1,4-dioxane and aqueous 1,4-dioxane provided benzopyran **1.262** in 73 % yield indicating a reaction pathway favouring diradical intermediate **1.263b**.

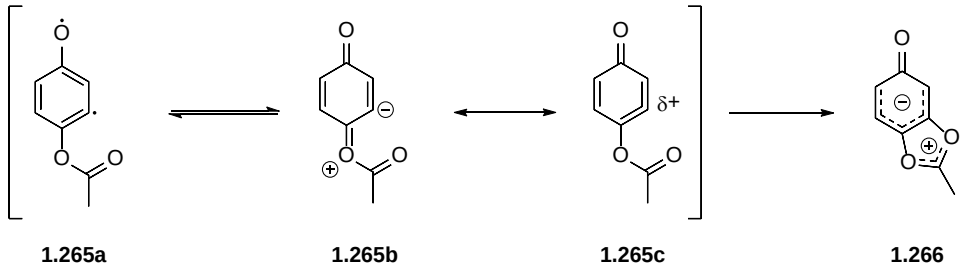


1.261 **1.262**

1.263a **1.263b** **1.264**

Scheme 1.53: Use of MOM-protecting group to influence the reaction pathway

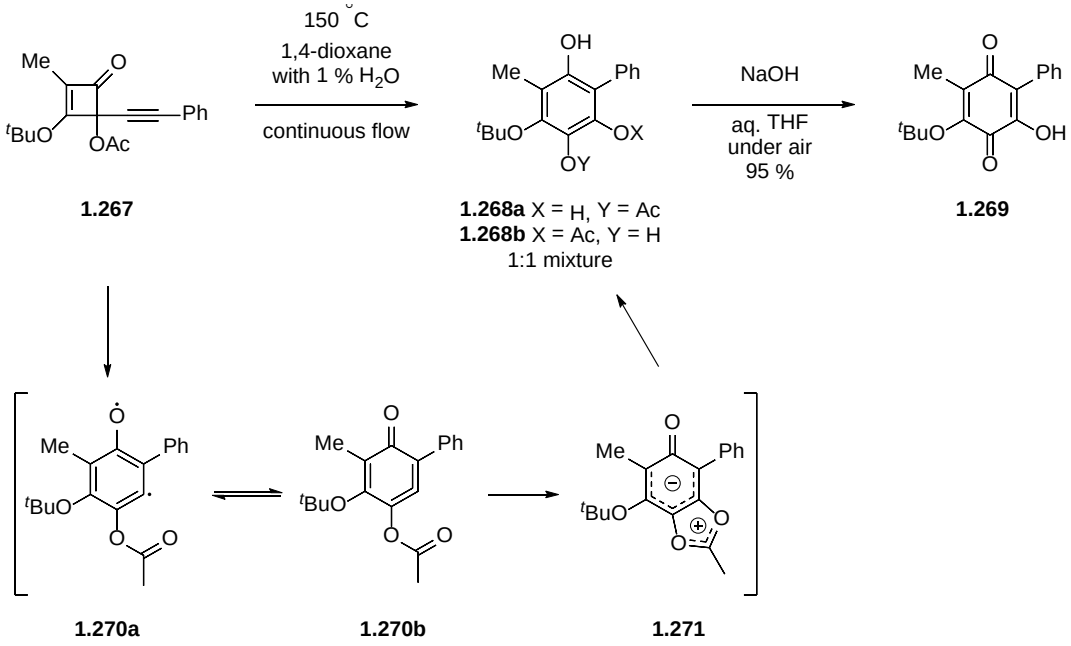
The ring-puckering observed in **1.260b** led Harrowven *et al*. to examine whether its cyclohexatrienone character could also be exploited. To that end, DFT calculations were performed to determine whether diradical **1.265a** might undergo cyclisation to zwitterion **1.266** *via* its orbital isomer **1.265b/c**. These predicted a low energy barrier for the formation of zwitterion **1.266** and a closed-shell transition state consistent with the reaction occurring *via* an orbital isomer switch (Scheme 1.54).



1.265a **1.265b** **1.265c** **1.266**

Scheme 1.54: Cyclisation of acetate **1.265** to zwitterion **1.266**

To support this experimentally, acetate **1.267** was subjected to thermolysis in 1,4-dioxane doped with 1 % H_2O and gave a 1:1 mixture of acetates **1.268a** and **1.268b** in near quantitative yield (Scheme 1.55). This allowed efficient syntheses of tetrasubstituted quinones and demonstrated that the diradical formed as a result of thermolysis of 4-alkynylcyclobutenones can simultaneously act as a radical (*e.g.* **1.263b**), an anion (*e.g.* **1.258**) or an electrophile (*e.g.* **1.271**).



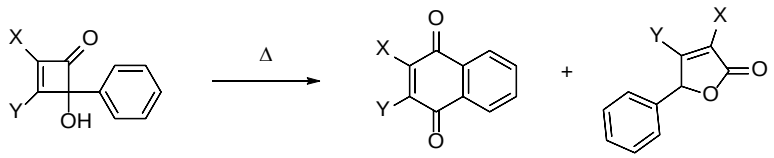
1.267 **1.268a** X = H, Y = Ac; **1.268b** X = Ac, Y = H, 1:1 mixture **1.269**

1.270a **1.270b** **1.271**

Scheme 1.55: Experimental evidence of cyclohexatrienone character of **1.270b**

1.4.4 Anomalous behaviour of cyclobutenones bearing sterically demanding residues

In 2017, Harrowven *et al*. reported an anomaly in the rearrangement of 4-arylcyclobutenones **1.272** when the substrates bore a bulky substituent.[48] Thermolysis of cyclobutenone **1.272** produced furanone **1.274** as opposed to the expected benzoquinone **1.273** prompting an investigation into this anomalous result (Scheme 1.56).

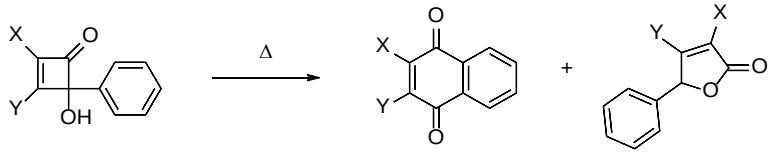


1.272 **1.273** **1.274**

1.272	X	Y	**1.273**	**1.274**
a	OMe	OMe	73 %	-
b	O^{t}Bu	Me	78 %	-
c	Me	NMe_2	-	92 %

Scheme 1.56: Anomalous furanone formation

In order to prove that the influence of 3°-amino substituents were comparable to those of bulky carbon substituents, cyclobutenones bearing *tert*-butyl residues were subjected to thermolysis (Scheme 1.57). As expected, all produced the corresponding furanones **1.274** rather than benzoquinone products **1.273** given in a classic Moore rearrangement.

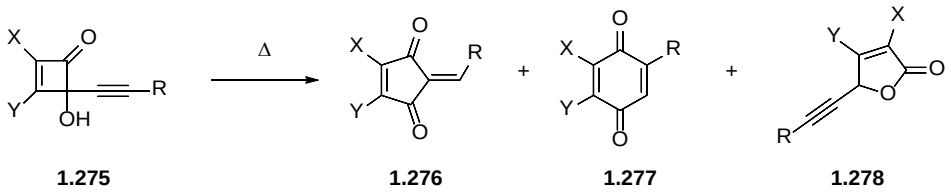


1.272 **1.273** **1.274**

1.272	X	Y	**1.273**	**1.274**
d	Me	OMe	91 %	-
e	^{t}Bu	OMe	-	99 %
f	Me	NHMe	73 %	-
g	^{t}Bu	NHMe	-	87 %

Scheme 1.57: Effect of *tert*-butyl substituents upon thermolysis

These observations were confirmed by DFT calculations which demonstrated that despite the initial higher energy barrier for outward rotation of the hydroxyl group (*ca.* 6 kcalmol^{-1}), this was still lower than the activation energy required to complete 6π-electrocyclisation due to severe steric interactions between substituents X and Y. This was then extended to cyclobutenones bearing alkynyl substituents for which no previous precedent for thermal rearrangement to furanones had been reported (Scheme 1.58). As predicted, the introduction of a 3°-amine substituent biased the reaction towards formation of furanones **1.278** over cyclopentenediones **1.276** or quinones **1.277**.

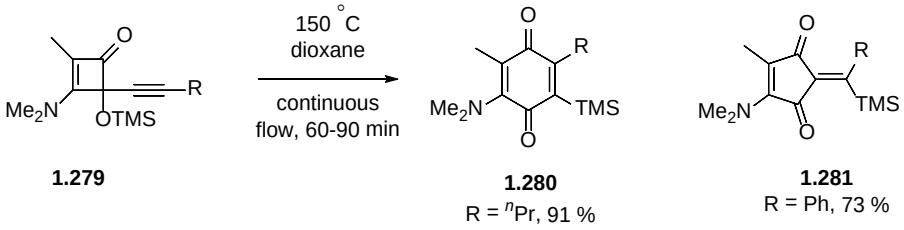


1.275 **1.276** **1.277** **1.278**

1.275	X	Y	R	**1.276**	**1.277**	**1.278**
a	OMe	OMe	Ph	46 %	21 %	-
b	Me	NEt_2	Ph	-	-	60 %
c	Me	NMe_2	$SiMe_3$	-	-	67 %
d	Me	NMe_2	^{n}Pr	-	-	83 %

Scheme 1.58: Effect of steric buttressing on alkynylcyclobutenone rearrangements

It was then noted that this dichotomous pathway could be shut down and the traditional pathway restored by protection of the 4-hydroxyl substituent. Introduction of a trimethylsilyl substituent provided a simple means to form quinone **1.280** or cyclopentenedione **1.281** over the previously observed furanones (Scheme 1.59).



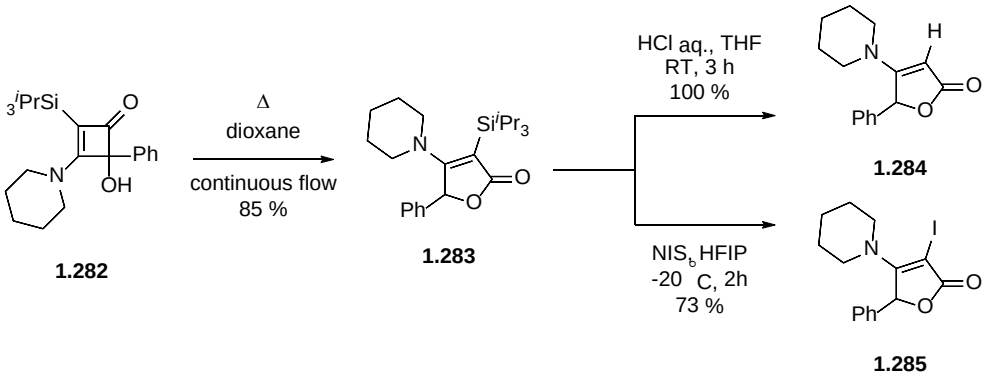
1.279

1.280
R = ^{n}Pr, 91 %

1.281
R = Ph, 73 %

Scheme 1.59: Shutting down the formation of furanones by alcohol protection

Finally, cyclobutenones bearing a triisopropylsilyl substituent (e.g. **1.282**) were synthesised in the hope of using this as a bulky proton or a halogen surrogate leading to formation of furanones **1.283** (Scheme 1.60).



1.282

1.283

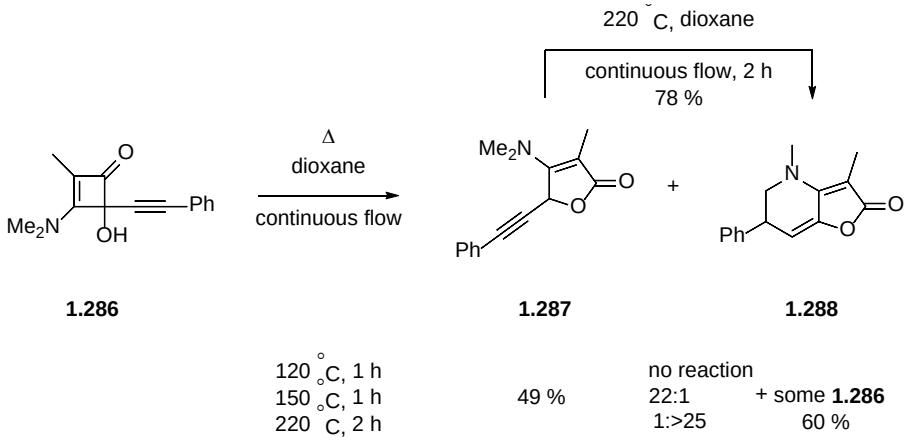
1.284

1.285

Scheme 1.60: Use of the triisopropylsilyl moiety as a bulky proton or halogen surrogate

1.4.5 Further rearrangement of furanones to extended ring systems

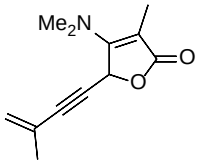
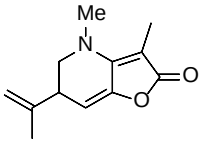
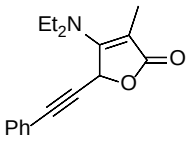
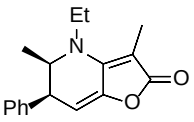
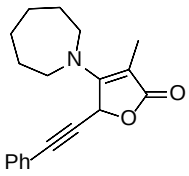
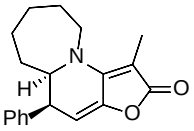
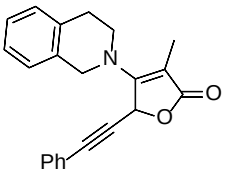
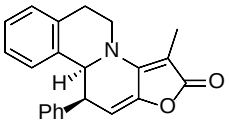
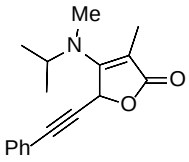
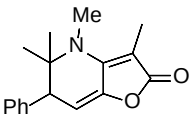
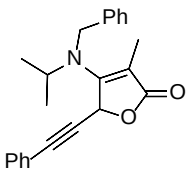
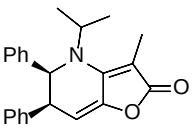
Harrowven *et al.* furthered the scope of this study by extension to an unknown rearrangement of aminocyclobutenones to dihydrofuropyridinones *via* a thermally induced hydride transfer.[49] It was observed that thermolysis of aminocyclobutenone **1.286** was sensitive to both reaction time and temperature (Scheme 1.61). Thus, when thermolysis was conducted at 150 °C for 1 h furanone **1.287** was the major product whilst at elevated temperatures and prolonged reaction times formation of dihydrofuropyridinone **1.288** dominated.



Scheme 1.61: Formation of previously unobserved dihydrofuropyridinone **1.288**

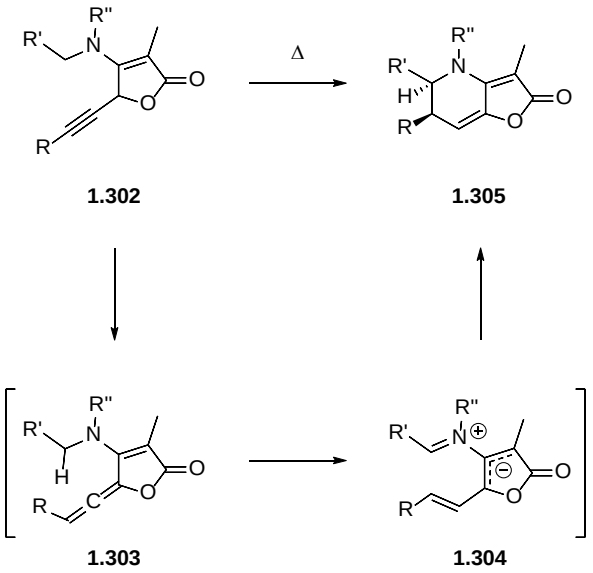
A variety of cyclobutenones bearing different 3°-amines were synthesised and tested under continuous flow producing dihydrofuropyridinones in good to excellent yields (Table 1.2). Amine substituents bearing extended alkyl chains were found to produce products with useful diastereoselectivity while differentially substituted amine residues displayed excellent regioselectivity. In each example, the new ring system was formed to the amino residue bearing the weakest CH bond following the sequence of Bn > 3°-alkyl > 2°-alkyl > 1°-alkyl > Me.

Table 1.2: Extension of scope of the dihydrofuropyridinone synthesis

Starting material	Product, Yield, dr	Conditions
 **1.289**	 **1.290**, 76 %	220 °C, dioxane, 2 h
 **1.291**	 **1.292**, 82 %, d.r. 4:1	220 °C, dioxane, 2 h
 **1.293**	 **1.294** 79 %, d.r. 7:1	220 °C, dioxane, 1 h
 **1.295**	 **1.296** 76 %, d.r. 10:3	220 °C, dioxane, 1 h
 **1.298**	 **1.299** 75 %	220 °C, dioxane, 2 h
 **1.300**	 **1.301** 79 %, d.r. 25:1	220 °C, dioxane, 1 h

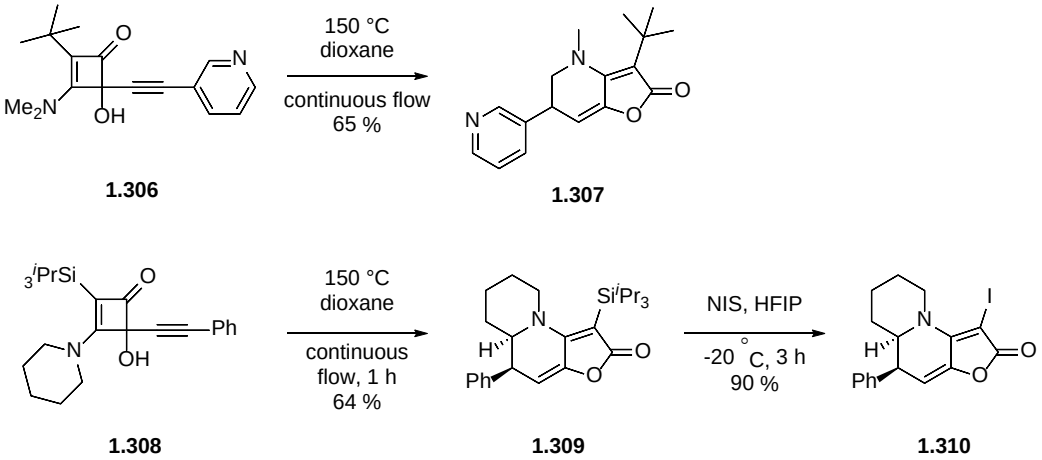
To rationalise the formation of these products, isotope labelling studies and DFT calculations were undertaken. These indicated that the reaction began with isomerisation of alkyne **1.302** to allene **1.303** by water catalysed proton transfer. Hydride transfer to

zwitterion **1.304** was followed by a disrotary 6π-electrocyclisation to produce dihydrofuropyridinone **1.305** (Scheme 1.62).



Scheme 1.62: Alkyne to allene isomerisation leading to dihydrofuropyridinone **1.305**

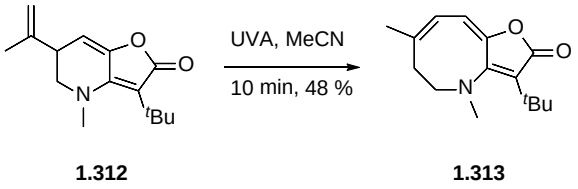
Notably, the thermolysis of cyclobutenones bearing bulkier substituents proceeded directly to dihydrofuropyridinones at 150 °C, bypassing the furanone intermediates (Scheme 1.63). This was observed in multiple examples where substrates carried triisopropylsilyl or *tert*-butyl residues, further enhancing the practicality of this reaction pathway.



Scheme 1.63: Direct dihydrofuropyridinone formation due to sterically demanding residues

More recently, Harrowven *et al.* have extended this methodology further for the formation of azocines and benzoazocines.[50] They found that the thermal rearrangement of aminocyclobutenones to furopyridinones could be followed by exposure of the product,

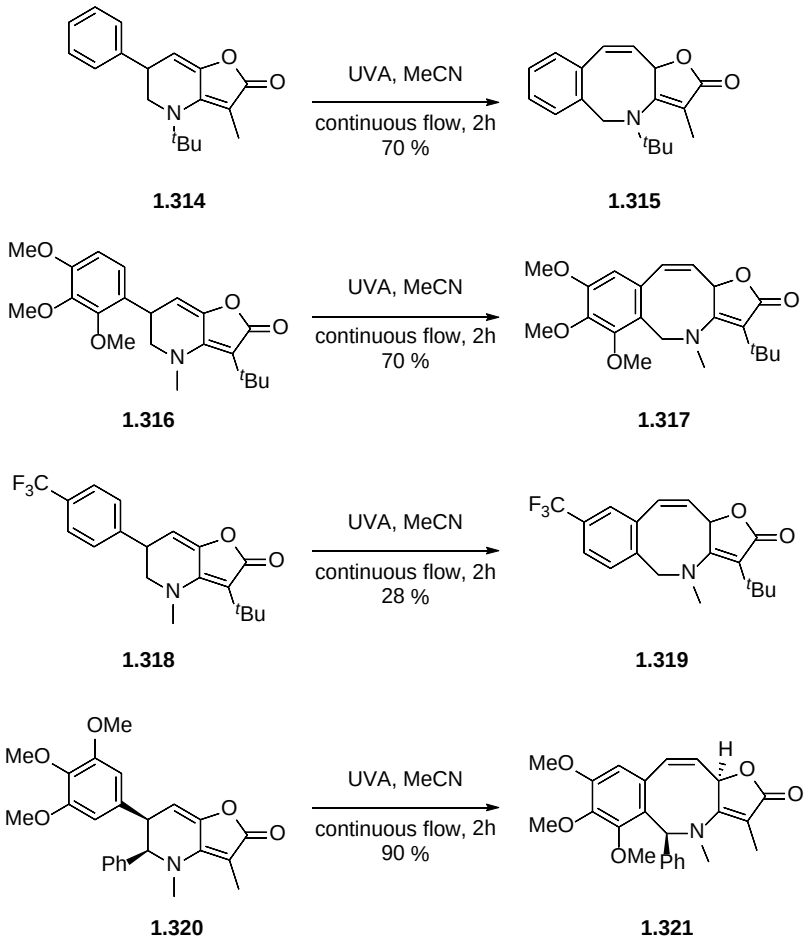
e.g. **1.311**, to UVA irradiation under continuous flow to produce a furoazocine*, e.g.* **1.312**, in moderate yield (Scheme 1.64).



1.312 **1.313**

Scheme 1.64: Formation of furoazocine **1.313** from furopyridinone **1.312**

The photolysis of furopyridinones bearing aryl residues was then studied, with photolysis of systems such as **1.314** giving benzoazocines **1.315** in moderate to good yield. One exception noted was with the electron deficient arene **1.318** where the yield of **1.319** decreased to 28 % (Scheme 1.65). Substrates containing two aryl residues (*e.g.* **1.320**) were also shown to form benzoazocines as single diastereoisomers in high yield.



1.314 **1.315**

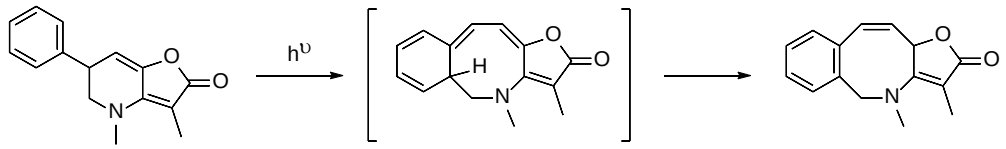
1.316 **1.317**

1.318 **1.319**

1.320 **1.321**

Scheme 1.65: Examples of benzoazocine formation from furopyridinones

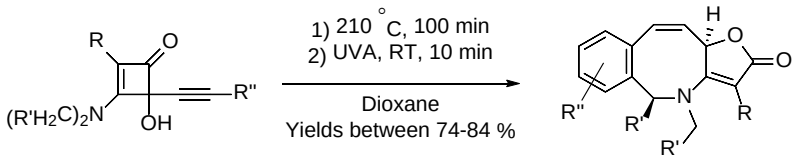
DFT calculations indicated that photolysis to the singlet excited state of furopyridinone **1.322** could be followed by direct relaxation to azocine **1.323** via a [1,3]-sigmatropic rearrangement. A thermally allowed [1,5]-sigmatropic H-shift then formed benzoazocine **1.324** (Scheme 1.66).



1.322 **1.323** **1.324**

Scheme 1.66: Mechanistic formation of benzoazocine **1.324**

To further this methodology, it was shown that benzoazocines **1.326** could be formed directly from alkynylcyclobutenones **1.325** by sequencing thermal and photochemical steps under flow. Thus, by subjecting a solution of **1.325** to thermolysis (210 °C, 100 min) then irradiating the resulting solution directly with UVA (6 x 1.7 W LEDs, 10 min), benzoazocines **1.326** could be produced directly in high yields.



1.325 **1.326**

Scheme 1.67: Preparation of benzoazocines using sequential thermal and photochemical flow methods

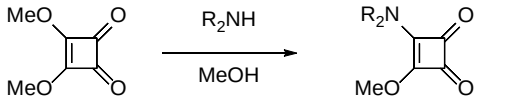
As demonstrated throughout this chapter, cyclobutenones contain the capability to produce structures with a large array of chemical complexity utilising relatively simple reaction conditions. Herein will be described two previously undiscovered rearrangements of cyclobutenediones which have been examined and tested using a wide variety of substrates and reaction conditions.

Chapter 2 Ring opening of cyclobutenediones to 2-oxobut-3-enamides

As previously described in Chapter 1, cyclobutenones are highly versatile substrates with the capability to be transformed into a vast array of complex structural moieties using robust and highly proven methods. Traditionally, cyclobutenones bearing C4-substituents are prepared in high yields by treatment of cyclobutenediones with organolithium reagents. Typically, this will be a carbon-based nucleophile and, to the best of our knowledge, this has not been attempted using lithium amides. Thus, it was decided to investigate the addition of lithium amides to cyclobutenediones which, in this event, led to the discovery of a new mode of cyclobutenedione ring opening producing 2-oxobut-3-enamides. This dichotomous behaviour will be discussed and developed in the following chapter.

2.1 Initial discovery

Within the Harrowven group, previous research into the rearrangements of aminocyclobutenediones required the preparation of 3-amino-4-methoxycyclobutenediones **2.2** by the addition of amines to dimethyl squarate **2.1** (Scheme 2.1). Though this method worked well for many substrates it did not extend to amines that were sterically demanding which generally returned the starting materials, *e.g.* dimethyl squarate **2.1** and diisopropylamine.

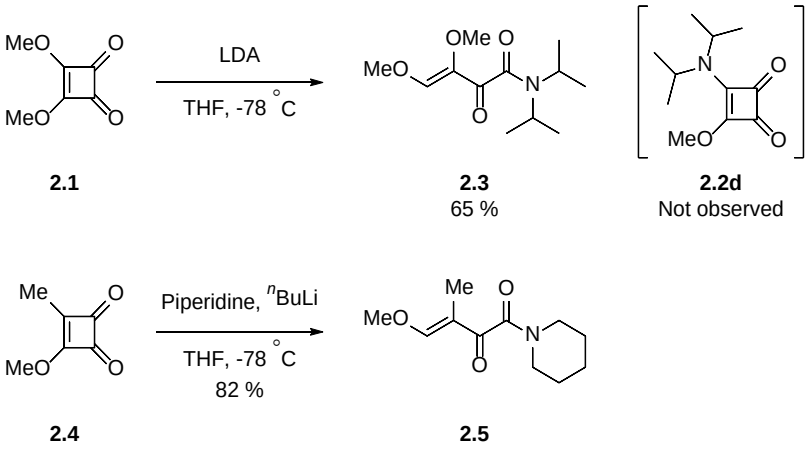


2.1

2.2a R = Me, 91 %
2.2b R = $(CH_2)_4$' 85 %
2.2c R = Et, 89 %
2.2d R = ^{i}Pr, 0 %

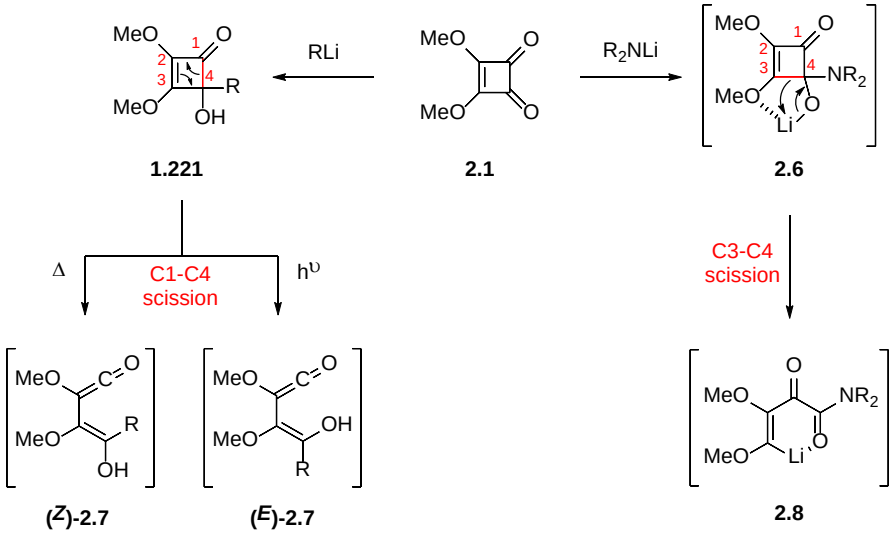
Scheme 2.1: Preparation of aminocyclobutenediones

To improve the nucleophilicity of the amine, a switch to using LDA as the nucleophile was made. This did not produce the expected aminocyclobutenedione **2.2d** but instead gave (*Z*)-2-oxobut-3-enamide **2.3** in 65 % isolated yield, prompting this investigation (Scheme 2.2). The rearrangement had also been observed once before within the group when cyclobutenedione **2.4** and lithium piperidide produced (*E*)-2-oxobut-4-enamide **2.5** in 82 % yield.[51]



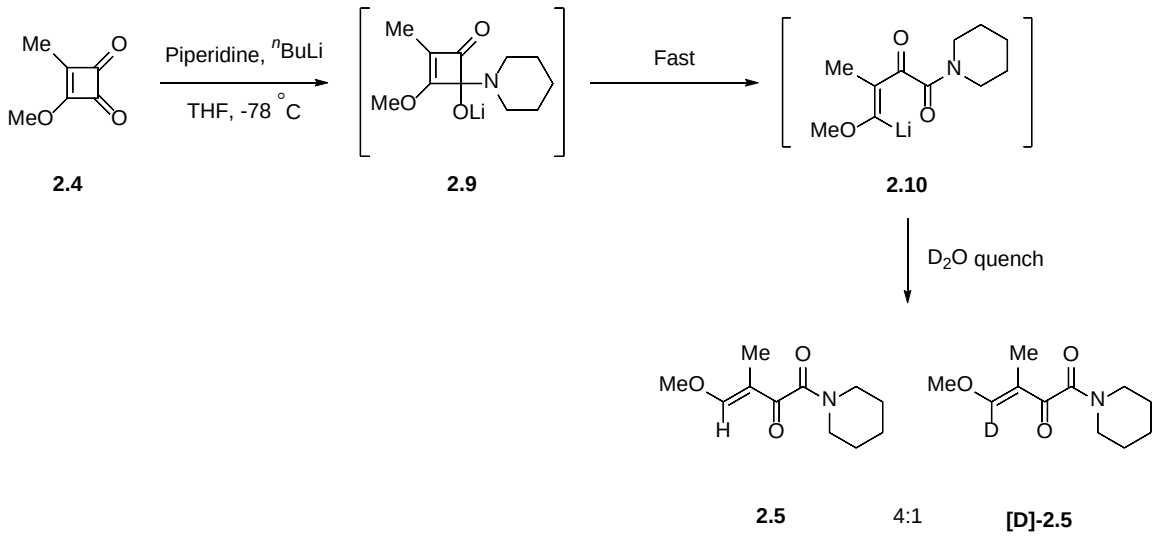
Scheme 2.2: Unexpected formation of 2-oxobut-3-enamides

Traditionally, rearrangement of cyclobutenones such as **1.221** occurs *via* scission of the C1-C4 bond upon thermolysis or photolysis (Scheme 2.3). However, the aforementioned examples indicated that addition of a lithium amide induced scission of the C3-C4 bond of adduct **2.6** forming vinyllithium **2.8**.



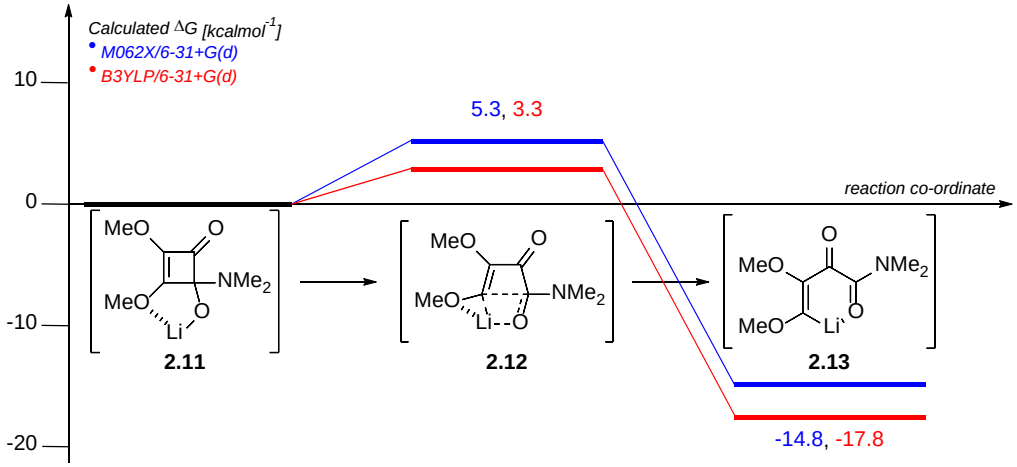
Scheme 2.3: Contrasting bond scission observed on addition of lithium amides

Further investigation was then undertaken into this previously unobserved reactivity to lithium amides by Dr Wei Sun in the Harrowven group. It was noted that upon quenching the reaction of cyclobutenedione **2.4** and lithium piperidide with D_2O at -78 °C, a 4:1 mixture of protonated product **2.5** and deuterated product **[D]-2.5** was formed (Scheme 2.4). This indicated the formation of anion **2.10** was fast and irreversible at -78 °C.



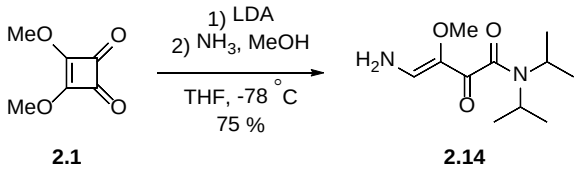
Scheme 2.4: Addition of lithium piperidide followed by deuterium quench

DFT calculations performed by Dr Wei Sun for adduct **2.11** indicated that there was a very low energy barrier for ring scission *via* transition state **2.12** (Scheme 2.5). The following formation of anion **2.13** is also accompanied by a large decrease in energy indicating a facile *O*- to *C*-lithium transfer due to relief of ring-strain and strong co-ordination between the newly formed amide and the proximal vinyllithium. These results supported the observations that the reaction occurs at -78 °C and that formation of anion **2.13** is irreversible at this temperature.



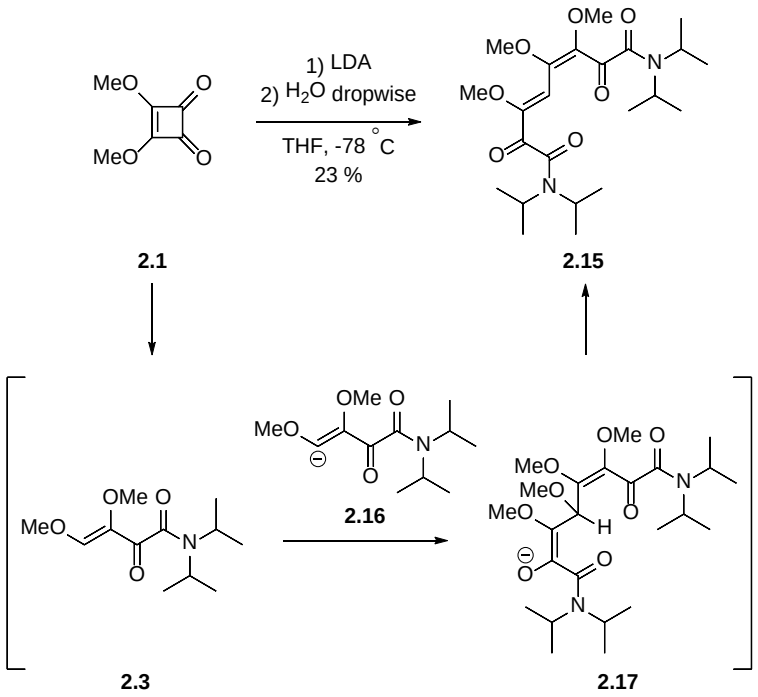
Scheme 2.5: DFT calculations performed by Dr Wei Sun concerning ring opening with lithium dimethylamide

Due to the presence of the α,β-unsaturated carbonyl moiety, the potential for Michael additions to occur was examined. It was observed that, upon treatment of cyclobutenedione **2.1** with LDA followed by a quench using ammonia in methanol, amine **2.14** was produced in good yield (Scheme 2.6).



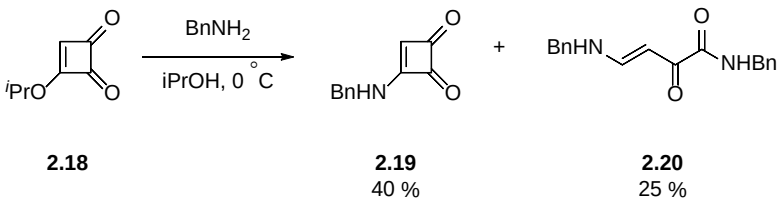
Scheme 2.6: Formation of terminal amines using an ammoniacal quench

Notably, if the reaction was quenched by dropwise addition of water at -78 °C, dimer **2.15** was formed in low yield (Scheme 2.7).



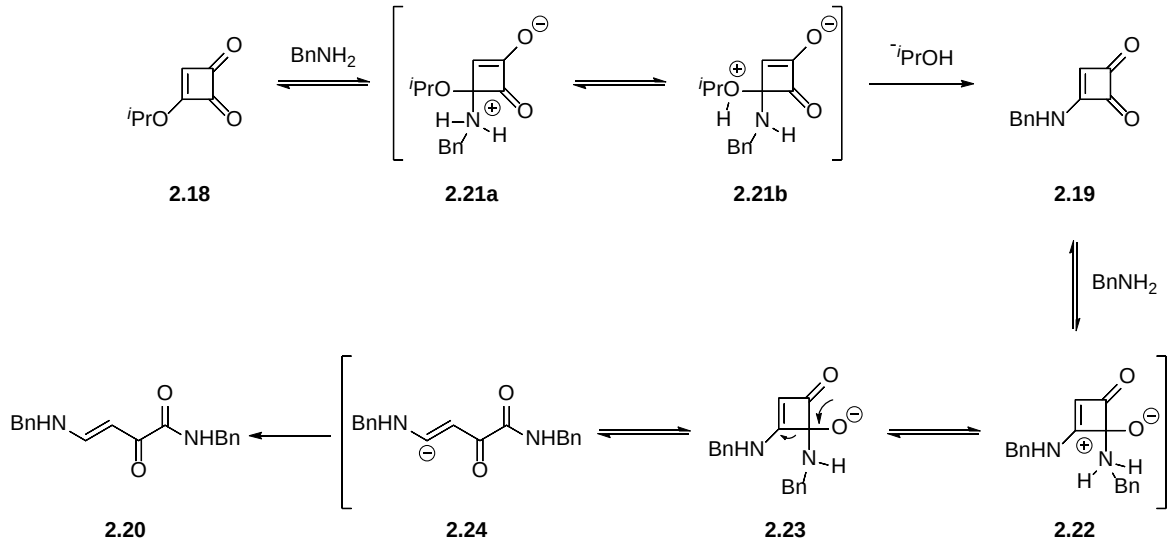
Scheme 2.7: Dimerization of **2.3** to form **2.15**

Interestingly, a single example of C3-C4 ring scission had also been observed by Dr Dharyl Wilson during addition of benzylamine to cyclobutenedione **2.18** (Scheme 2.8).[51] While the expected cyclobutenedione **2.19** was produced in 40 % yield, 2-oxobut-3-enamide **2.20** was a significant by-product formed in 25 % yield. However, efforts to bias the reaction towards formation of **2.20** by the addition of excess benzylamine had no noticeable impact on the yield.



Scheme 2.8: Unexpected fragmentation of cyclobutenedione **2.18** to 2-oxobut-3-enamide **2.20**

It was proposed by Dr Wilson that the reaction began with addition of benzylamine to cyclobutenedione **2.18** to give zwitterion **2.21a**, and that was followed by proton transfer to the adjacent ether giving zwitterion **2.21b**. Loss of isopropanol then produces cyclobutenedione **2.19** which, after a second addition of benzylamine, gives zwitterion **2.22**. Proton loss followed by ring opening of **2.23** then yields anion **2.24** which upon quenching produces 2-oxobut-3-enamide **2.20** (Scheme 2.9).



Scheme 2.9: Proposed mechanism of ring opening upon amine addition to cyclobutenedione **2.18**

2.2 Aims and objectives

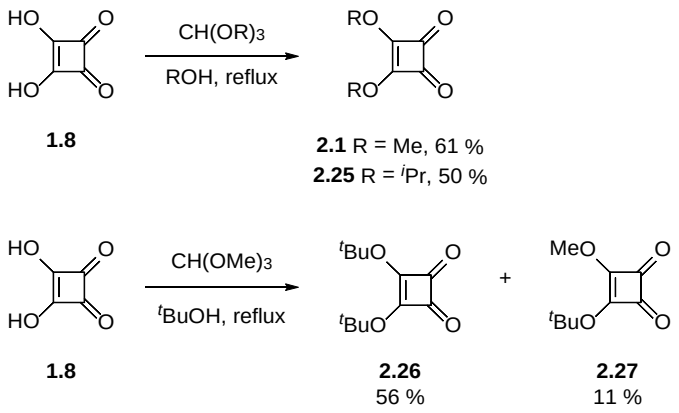
As previously described, a new mode of cyclobutenedione ring opening had been uncovered within the Harrowven group however, very few substrates had been examined. Thus, we sought to develop this chemistry further by investigating the scope of this rearrangement and the potential to extend the method by further functionalisation of the intermediate 4-lithio-2-oxobut-3-enamides.

2.3 Results and Discussion

2.3.1 Formation of 2-oxobut-3-enamides from bis-alkoxycyclobutenediones

Our initial studies began with an investigation into the effect of increasing steric bulk in the cyclobutenedione. To that end, preparation of various squarates from squaric acid **1.8** was undertaken on a multi-gram scale using literature methods (Scheme 2.10).[2,42,52] Dimethyl and diisopropyl squarates **2.1** and **2.25** were synthesised in good yield through

esterification of squaric acid **1.8** using the respective orthoformate as a drying agent. The synthesis of di-*tert*-butyl squarate **2.26** used trimethyl orthoformate as a drying agent but required distillation from the reaction of the methanol and methyl formate generated *in-situ* to minimise formation of unwanted by-products. Despite this, mixed ester **2.27** was produced as a by-product in low yield.



Scheme 2.10: Preparation of cyclobutenedione starting materials

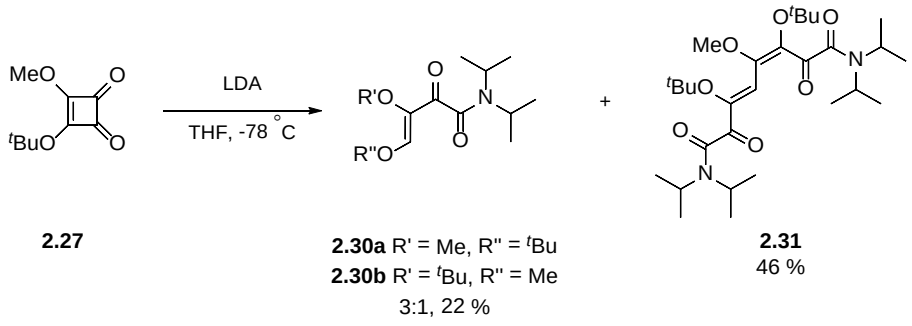
To demonstrate the effect of sterics, cyclobutenediones **2.25** and **2.26** were treated with LDA and each formed the expected 2-oxobut-3-enamides, **2.28** and **2.29** respectively, after 2 h albeit in low yield with starting material also recovered. The reaction time was increased to 8 h and promisingly, the yields of **2.28** and **2.29** increased to 61 and 56 % respectively (Scheme 2.11).

2.X	Reaction time, h	2.X, Yield
2.25	2	**2.28**, 50 % + **2.25**' 12 %
2.25	8	**2.28**, 61 %
2.26	2	**2.29**, 40 % + **2.26,** 21 %
2.26	8	**2.29**, 56 %

Scheme 2.11: Effect of sterics on ring opening with LDA

Notably, no dimer formation was observed within these reactions. This implies that increasing the steric bulk of the alkoxy residues of the cyclobutenediones not only slows the ring opening but also decreases the likelihood of Michael addition occurring within the products. However, this side reaction was observed when treating cyclobutenedione **2.27** with LDA where a 3:1 mixture of regioisomers **2.30a**/**b** was formed alongside dimer **2.31** in significant yield (Scheme 2.12). It was speculated that the high steric demand of the *tert*-

butoxy residue made the vinylogous ester carbonyl more ketone-like due to poorer resonance with the etheric *O* lone pair. This then increases the reactivity of the enone towards Michael addition of nucleophiles.



2.27

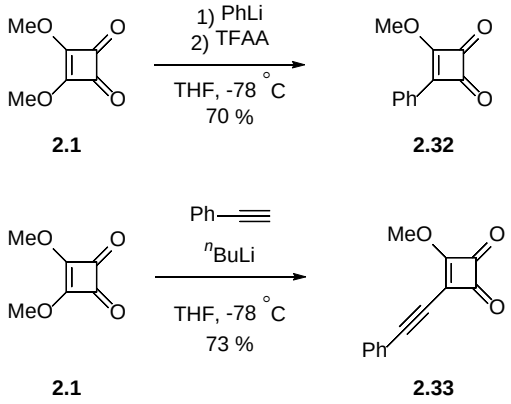
2.30a R' = Me, R'' = ^{t}Bu
2.30b R' = ^{t}Bu, R'' = Me
3:1, 22 %

2.31
46 %

Scheme 2.12: LDA addition to cyclobutenedione **2.27**

2.3.2 Functionalisation of cyclobutenediones prior to lithium amide addition

To extend the scope of the reaction to cyclobutenediones bearing aryl and alkynyl substituents, cyclobutenediones **2.32** and **2.33** were synthesised in high yields by treatment of cyclobutenedione **2.1** with the corresponding organolithium followed by addition of TFAA (Scheme 2.13).



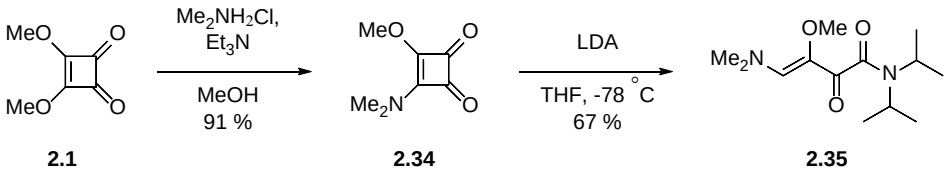
2.1 **2.32**

2.1 **2.33**

Scheme 2.13: Preparation of aryl- and alkynylcyclobutenediones

Disappointingly, the reactions of cyclobutenediones **2.32** and **2.33** with LDA ended in failure leading to either degradation or recovery of the starting material respectively. This prompted further investigation into the effect of substituents upon the ring opening. To that end, aminocyclobutenedione **2.34** was prepared from squarate **2.1** and treated with LDA (Scheme 2.14). Pleasingly, this produced 2-oxobut-3-enamide **2.35** in good yield and

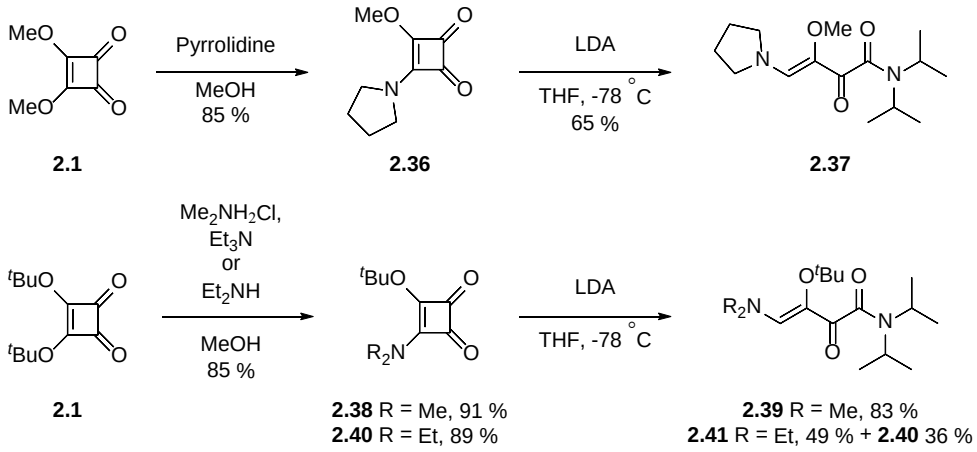
showed excellent regioselectivity attributed to preferential addition of LDA to the vinylogous ester carbonyl over the vinylogous amide carbonyl.



2.1 **2.34** **2.35**

Scheme 2.14: Ring opening of aminocyclobutenedione **2.34** to 2-oxobut-3-enamide **2.35**

The reaction was then repeated by treatment of the analogous cyclobutenedione **2.36** with LDA yielding 2-oxobut-3-enamide **2.37** in similarly good yield. Synthesis of cyclobutenediones bearing bulkier alkoxy and amino residues was then undertaken to further examine the effects of sterics on the ring opening. In the case of cyclobutenedione **2.38**, treatment with LDA produced 2-oxobut-3-enamide **2.39** in an excellent 83 % yield while treatment of bulkier analogue **2.40** proved more sluggish producing 2-oxobut-3-enamide **2.41** in 49 % yield alongside recovered starting material (36 %) (Scheme 2.15).



2.1 **2.36** **2.37**

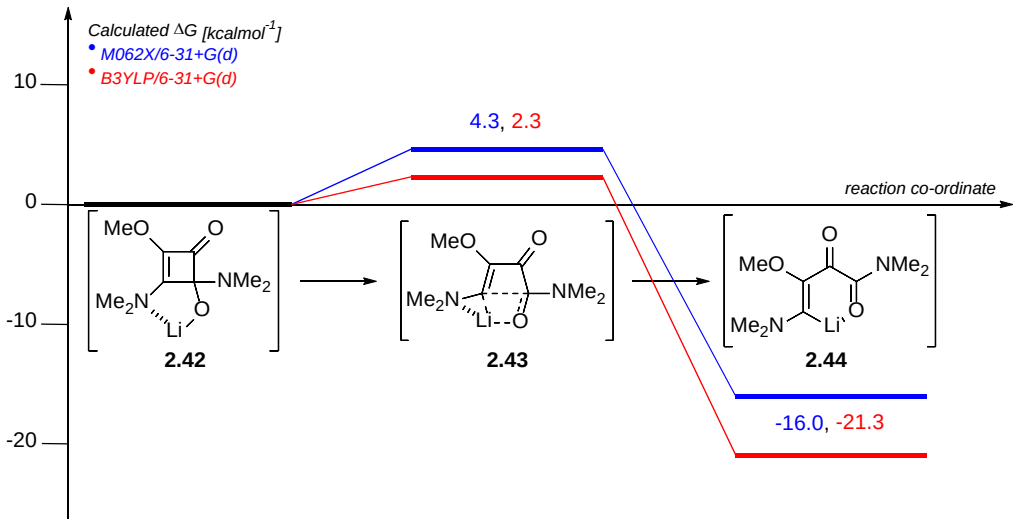
2.1

2.38 R = Me, 91 %
2.40 R = Et, 89 %

2.39 R = Me, 83 %
2.41 R = Et, 49 % + **2.40** 36 %

Scheme 2.15: Formation of 2-oxobut-3-enamides from various aminocyclobutenediones

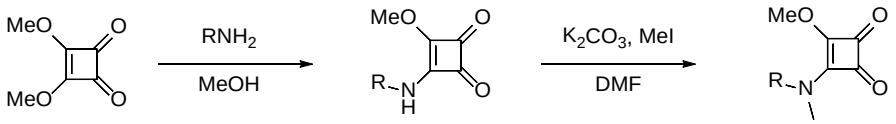
DFT analysis of adduct **2.42** was performed by Dr Wei Sun which indicated that ring scission of aminocyclobutenones occurred *via* a similarly low energy pathway as adduct **2.11**, albeit with a slightly lower energy barrier and a greater energy decrease upon formation of complex **2.44** (Scheme 2.16).



Scheme 2.16: DFT analysis of ring scission within adduct **2.42**

2.3.3 Ring opening of cyclobutenediones featuring aniline and benzylamine residues

The substrate scope was next extended to cyclobutenediones containing amines bearing aromatic residues. These were prepared in good yields from treatment of cyclobutenedione **2.1** with the corresponding aniline followed by methylation of the newly formed vinylogous amide using K_2CO_3 and MeI in DMF (Scheme 2.17). Benzylamine derivative **2.51** was also prepared in a similar fashion. It was hypothesised that compounds **2.45**-**51** would all present as different rotamers due to containing nitrogen substituents bearing two different groups. However, this was only displayed by cyclobutenedione **2.51**. It was theorised that the benzylamine moiety present in **2.51** restricted the rotation between states to such a degree that both rotamers were apparent during NMR analysis. Contrary to this, cyclobutenediones **2.45-50** all appeared as single rotamers, indicating that rotation of the aniline moiety is faster than the NMR timescale leading to an average of the rotamers being observed during analysis.

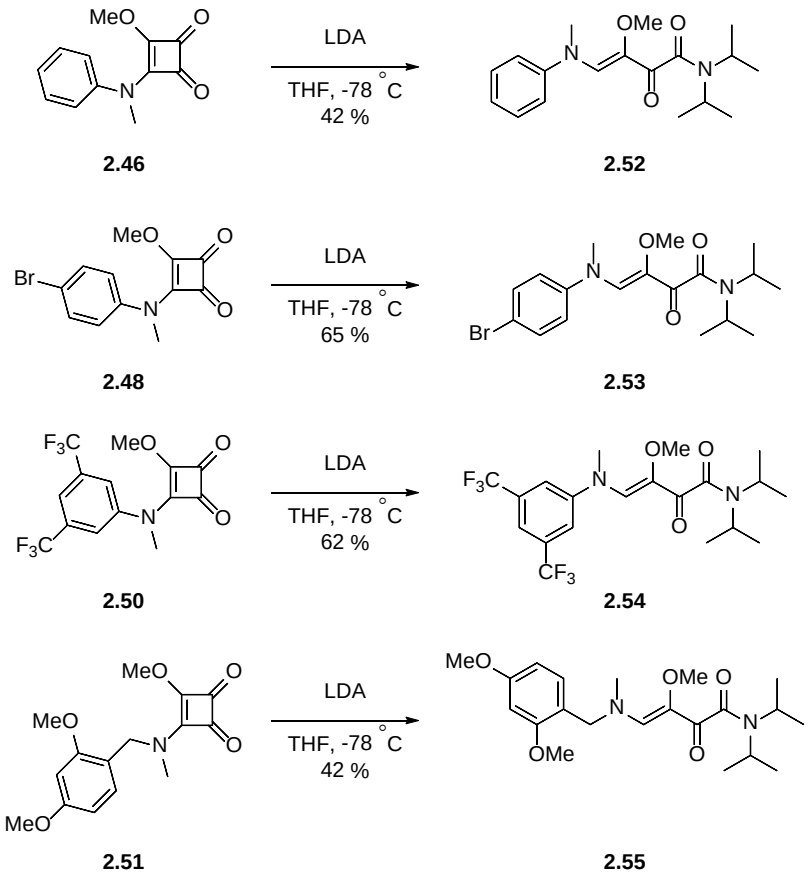


2.1 **2.X** **2.Y**

R	**2.X**, Yield	**2.Y**, Yield
Phenyl	**2.45**, 91 %	**2.46**, 85 %
4-Bromophenyl	**2.47**, 79 %	**2.48**, 80 %
3,5-Bis(trifluoromethyl)phenyl	**2.49**, 64 %	**2.50**, 83 %
2,4-Dimethoxylbenzyl	**2.51**, 79 % over two steps	

Scheme 2.17: Preparation of cyclobutenediones bearing various amino residues

To our delight, treatment of cyclobutenedione **2.46** with LDA gave 2-oxobut-3-enamide **2.52**, albeit in a comparatively low yield of 42 % (Scheme 2.18). Moreover, when cyclobutenediones **2.48** and **2.50** were subjected to analogous conditions, 2-oxobut-3-enamides **2.53** and **2.54** were produced in higher yields of 65 % and 62 % respectively. Treatment of benzylamine derivative **2.51** also gave 2-oxobut-3-enamide **2.55** in 42 % yield.



2.46 **2.52**

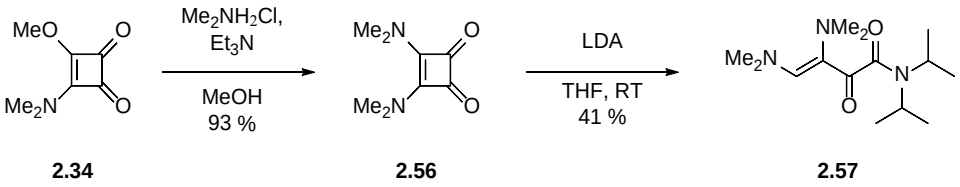
2.48 **2.53**

2.50 **2.54**

2.51 **2.55**

Scheme 2.18: Formation of 2-oxobut-3-enamides from aminocyclobutenediones bearing aryl residues

To examine the effect of *bis*-amino groups upon the ring opening, cyclobutenedione **2.56** was prepared and treated with LDA (Scheme 2.19). Initially the reaction was conducted at -78 °C however no noticeable formation of the expected product **2.57** was observed due to the insolubility of the substrate in THF at that temperature. Pleasingly, when the reaction was repeated at room temperature, 2-oxobut-3-enamide **2.57** was produced in 41 % yield.

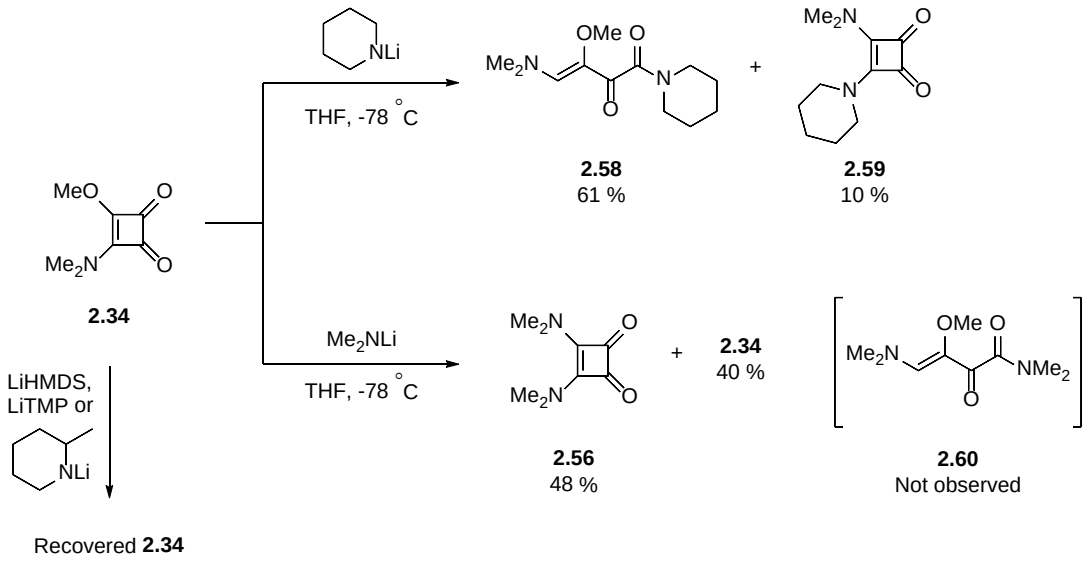


2.34 **2.56** **2.57**

Scheme 2.19: Ring opening of *bis*-aminocyclobutenedione **2.55**

2.3.4 Effect of increasing sterics of lithium amides on the ring opening of cyclobutenediones

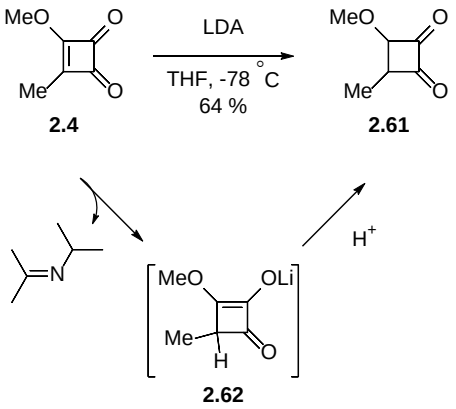
Steric influences on the ring opening were next examined with respect to the lithium amide. Aminocyclobutenedione **2.35** was chosen as a model substrate and its treatment with a variety of lithium amides was carried out exposing some further subtleties of the reaction (Scheme 2.20). As observed previously, treatment with LDA produced 2-oxobut-3-enamide **2.35** in 67 % yield. Similarly, lithium piperidide produced 2-oxobut-3-enamide **2.58** in 61 % yield along with cyclobutenedione **2.59** as a minor product (10 % yield). The effect of increasing steric demand was then examined through the treatment of cyclobutenedione **2.34** with lithium *bis*-(trimethylsilyl)amide. While its addition was accompanied by a change of colour, on quenching only starting material was recovered. The reaction was then reattempted with lithium tetramethylpiperidide and lithium 2-methylpiperidide and in each case starting material was recovered. Our focus then shifted to the use of lithium amides with a lower steric demand, *e.g.* lithium dimethylamide. In this case, treatment of cyclobutenedione **2.34** also failed to give the expected 2-oxobut-3-enamide **2.60**, providing instead the substitution product, *bis*-aminocyclobutenedione **2.56**.



Scheme 2.20: Effect of altering steric demand of lithium amides

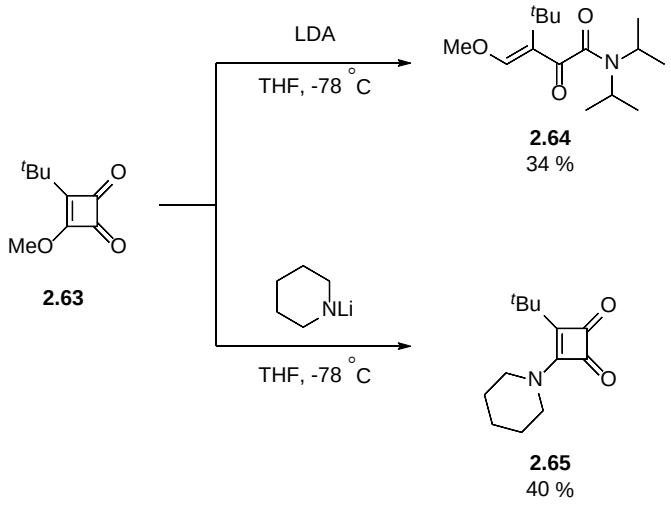
2.3.5 Reaction of lithium amides with cyclobutenediones bearing alkyl residues

The effect of lithium amides upon alkyl substituted cyclobutenediones was next examined. Treatment of cyclobutenedione **2.4** with lithium piperidide had been shown to cause ring opening to 2-oxobut-3-enamide **2.5** and thus addition of LDA to **2.4** was investigated and led to a surprising result (Scheme 2.21). It was observed that reduction of cyclobutenedione **2.4** to cyclobutanedione **2.61** was the primary outcome rather than ring opening *via* nucleophilic addition! It is presumed that reduction occurs *via* a mechanism akin to the Meerwein-Ponndorf-Verley reduction.[53,54] Thus, initial co-ordination of the lithium amide to cyclobutenedione **2.4** is followed by hydride transfer to give enolate **2.62**. On quenching, cyclobutanedione **2.61** is produced which proved to be highly sensitive to degradation at room temperature.



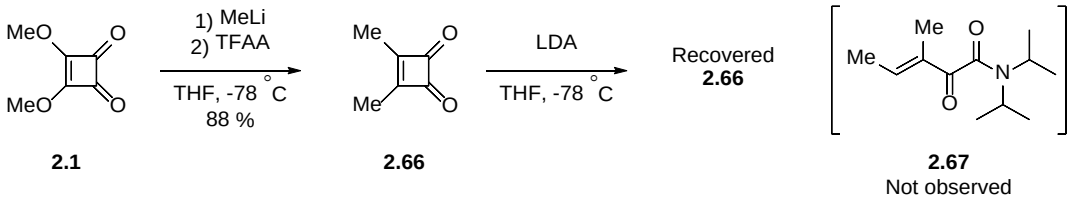
Scheme 2.21: Unexpected reduction observed upon treatment of cyclobutenedione **2.4** with LDA

To expand the scope of this rearrangement of alkyl-substituted cyclobutenediones, *tert*-butyl derivative **2.63** was prepared and treated with various lithium amides (Scheme 2.22). While addition of LDA gave the expected 2-oxobut-3-enamide **2.64**, substitution dominated upon treatment with lithium piperidide leading to cyclobutenedione **2.65**. It was theorised that this observed change in reactivity was caused by the decreased steric bulk of lithium piperidide compared to lithium diisopropylamide causing a shift to Michael addition in contrast to the expected ring opening.



Scheme 2.22: Comparative treatment of cyclobutenedione **2.63** with varying lithium amides

Dimethylcyclobutenedione **2.66** was next produced in order to examine whether the reaction could proceed in the absence of heteroatom stabilisation of the lithiated complex upon addition of LDA (Scheme 2.23). As expected, only starting material was recovered as opposed to formation 2-oxobut-3-enamide **2.67** indicating the necessity of a heteroatom residue at the C3 position prior to ring opening.



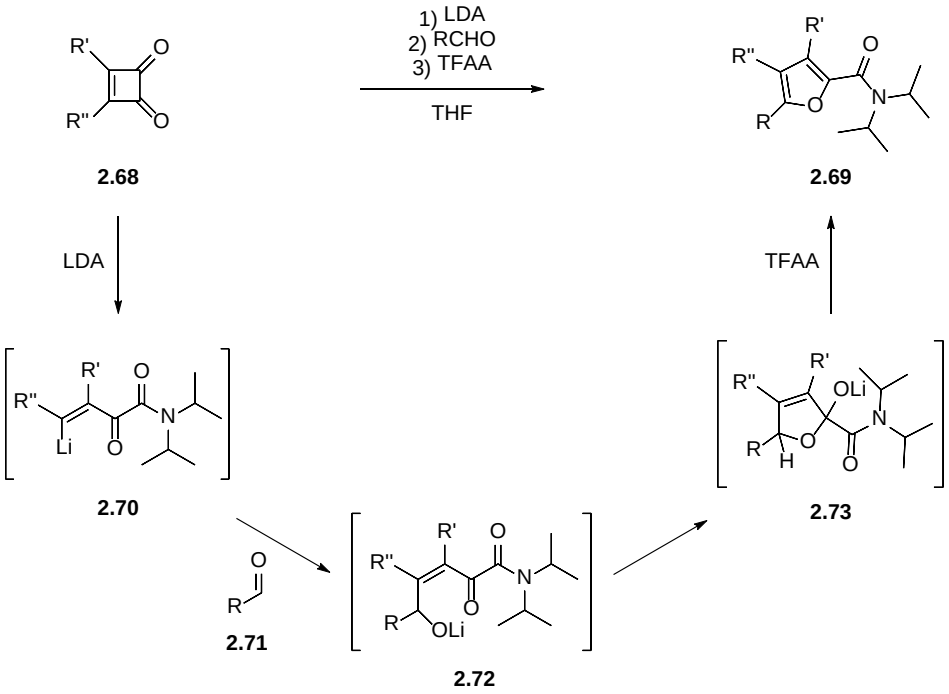
Scheme 2.23: Treatment of dimethylcyclobutenedione **2.66** with LDA

The reluctance of cyclobutenedione **2.66** to form oxobutenamide **2.67** indicates that a heteroatom on position C3 is preferred for ring opening to occur. This was further reinforced by the consistent formation of oxobutenamides from cyclobutenediones bearing amine or ether residues at C3, *e.g.* **2.34** to **2.35**. Lithium diisopropylamide may also

display altered reactivity due to the presence of two methyl groups in **2.66**, reverting back to behaving as a traditional base in contrast to its observed nucleophilicity thus far.

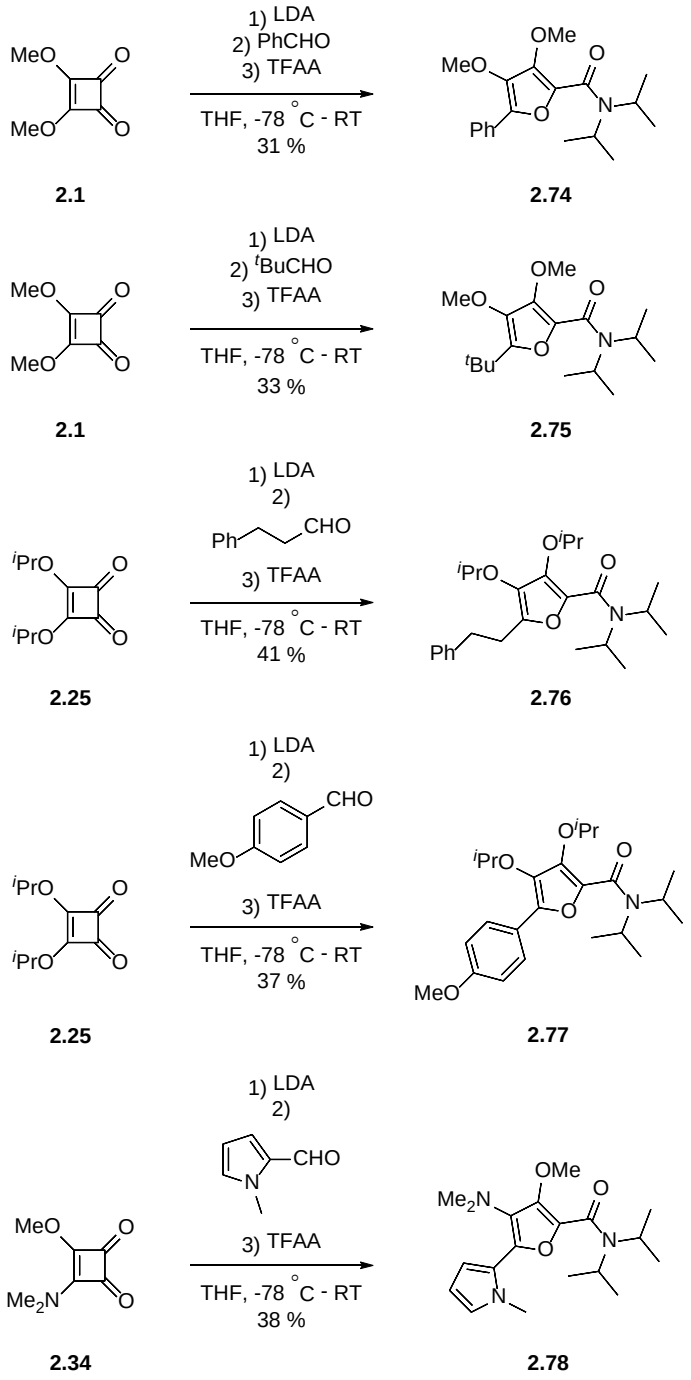
2.3.6 Further functionalisation of the 2-oxobut-3-enamides

To further extend this ring opening sequence, it was hypothesised that quenching the vinyllithium intermediate with an aldehyde had the potential to form tetrasubstituted furans (Scheme 2.24). It was envisaged that treatment of a cyclobutenedione **2.68** with LDA would give a vinyllithium **2.70** that could subsequently undergo nucleophilic addition to aldehyde **2.71** to form adduct **2.72**. Following intramolecular cyclisation to alkoxide **2.73** and dehydration induced by work-up with TFAA, furan **2.69** would be given.



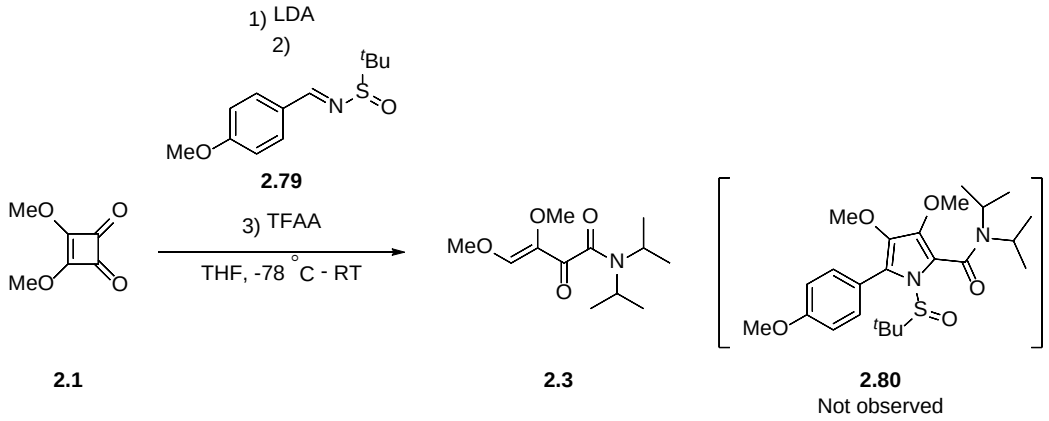
Scheme 2.24: Hypothesised formation of tetrasubstituted furans from 2-oxobut-3-enamides

To examine this theory, cyclobutenedione **2.1** was treated sequentially with LDA, benzaldehyde and TFAA. To our delight, furan **2.74** was given in a modest 31 % yield prompting us to investigate further extension of this sequence using different aldehydes and cyclobutenediones (Scheme 2.25). Of note is the difficulty of preparing such electron rich furans due to their increased reactivity when compared to furan.[55,56]



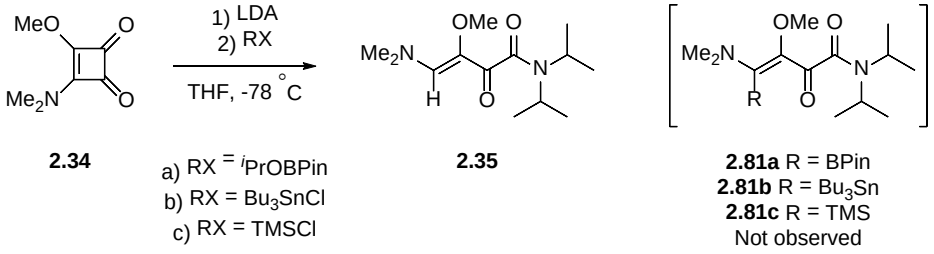
Scheme 2.25: Preparation of furans from cyclobutenediones

This sequence was also attempted using sulfinimine **2.79** in place of an aldehyde in the hope of synthesising pyrrole **2.80** (Scheme 2.26). Sadly, this reaction failed to yield any observable pyrrole product within the crude mixture and instead produced 2-oxobut-3-enamide **2.3** indicating premature quenching as opposed to nucleophilic addition on imine **2.79**.



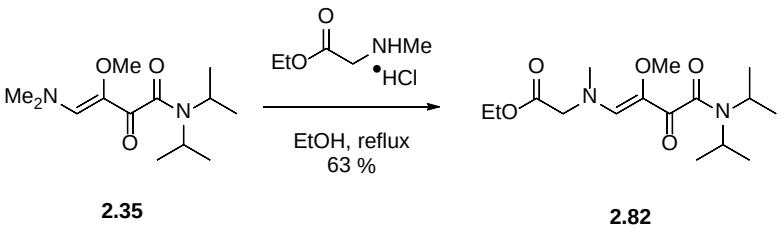
Scheme 2.26: Attempted pyrrole formation using sulfinimine **2.79**

The intermediacy of the vinyllithium species formed upon addition of LDA prompted the investigation of different electrophilic quenches in the hope of preparing alkenes bearing trialkyltin or borane residues. To examine this theory, cyclobutenedione **2.34** was treated with LDA followed by addition of the respective electrophile. 2-isoproxy-4,4,5,5-tetramethyl-1,3,2-dioxaborlane and tributyltin chloride were tested in the hope of preparing substrates with the potential for further functionalisation through the use of palladium cross-coupling reactions along with addition of trimethylsilyl chloride to prepare silicone-containing adducts (Scheme 2.27). Unfortunately, only 2-oxobut-3-enamide **2.35** was observed within the crude reaction mixtures suggesting that the products **2.81a-c** were protodemetallated on aqueous work-up or favoured quenching by a proton source over reaction with the added electrophile.



Scheme 2.27: Attempted further functionalisation of 2-oxobut-3-enamides using electrophilic quenches

Finally, the potential to perform amine exchange reactions upon 2-oxobut-3-enamide **2.35** to extend the functionality of this substrate was examined. Utilising a method developed by Gupton *et al.*, 2-oxobut-3-enamide **2.35** was heated under reflux in ethanol with sarcosine ethyl ester hydrochloride yielding sarcosine derivative **2.82** in good yield (Scheme 2.28).[57]



2.35 **2.82**

Scheme 2.28: Amine exchange of 2-oxobut-3-enamide **2.35**

This reaction sequence has the potential to introduce greater functionality on the oxobutenamide substrate through the use of mild reaction conditions. As observed within derivative **2.82** the introduction of amino acid residues is facile, thus expanding the generality of this ring opening sequence into the ever-growing field of medicinal chemistry.

2.4 Conclusions

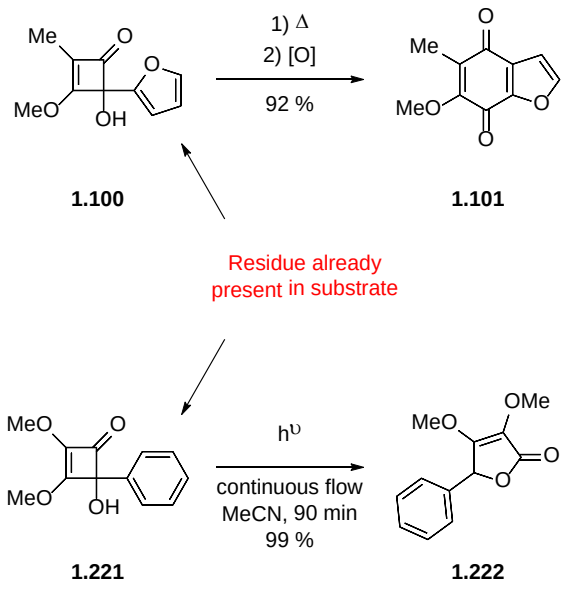
In conclusion, a new mode of cyclobutenedione ring opening has been observed upon treatment with lithium amides resulting in 2-oxobut-3-enamides. A wide variety of cyclobutenediones have been examined alongside the use of a range of lithium amides resulting in a large substrate scope. The reaction has been shown to proceed *via* a vinyllithium species which has been utilised to produce highly substituted, electron-rich furans that are difficult to synthesise by conventional methods due to their high reactivity. Our scoping of the reaction has exposed some limitations. Outcomes such as reduction to alkylcyclobutanediones and substitution reactions have been found to compete in some cases. The work conducted within this Chapter has contributed to a research paper published in Chemical Communications entitled “A new mode of cyclobutenedione ring opening for the synthesis of 2-oxobut-3-enamides and tetrasubstituted furans”.[51]

Chapter 3 Preparation of anhydrides upon photolysis of cyclobutenediones

3.1 Previous work

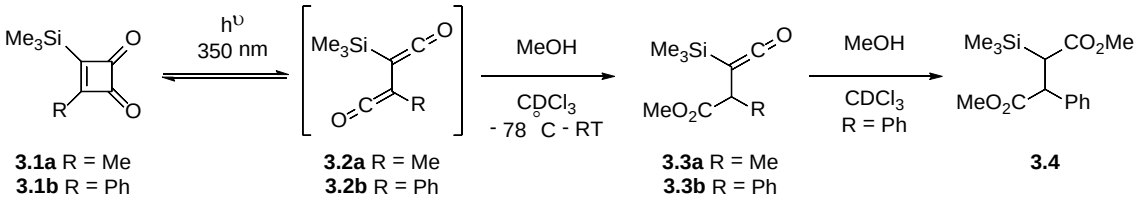
3.1.1 Introduction to the formation of fused anhydrides

As summarised in Chapter 1, the Moore rearrangement of cyclobutenones is a highly versatile method for the preparation of a large number of cyclic compounds (*e.g.* quinones, cyclopentenediones, phenols etc.). These also require a substrate to contain a suitable substituent in the C4 position that, upon subjecting to those reaction conditions, allows ring closure (Scheme 3.1).



Scheme 3.1: Examples of the rearrangement of cyclobutenones

While literature surrounding cyclobutenone rearrangements is prominent, work regarding the ring opening of cyclobutenediones is less so. The majority of these studies consist of the formation of *bis*-ketenes upon irradiation. For instance, Tidwell *et al.* studied the reactivity of unsymmetrical *bis*-ketenes 3**.2** produced from cyclobutenediones **3.1** (Scheme 3.2).[58]



3.1a R = Me
3.1b R = Ph

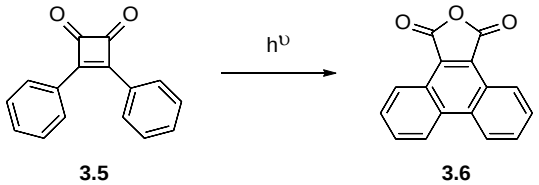
3.2a R = Me
3.2b R = Ph

3.3a R = Me
3.3b R = Ph

3.4

Scheme 3.2: Formation of *bis*-ketenes upon irradiation of unsymmetrical cyclobutenediones

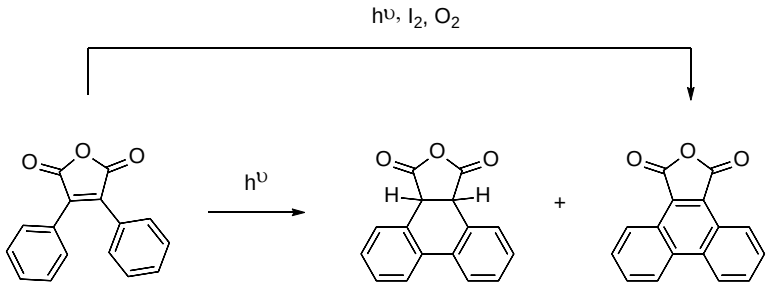
However in 1968, Bird described the rearrangement of cyclobutenedione **3.5** to anhydride **3.6** on photolysis.[59] Unfortunately, no experimental details were given and only one example of the reaction was provided (Scheme 3.3).[59]



3.5 **3.6**

Scheme 3.3: Photolysis of cyclobutenedione **3.5** to anhydride **3.6** by Bird

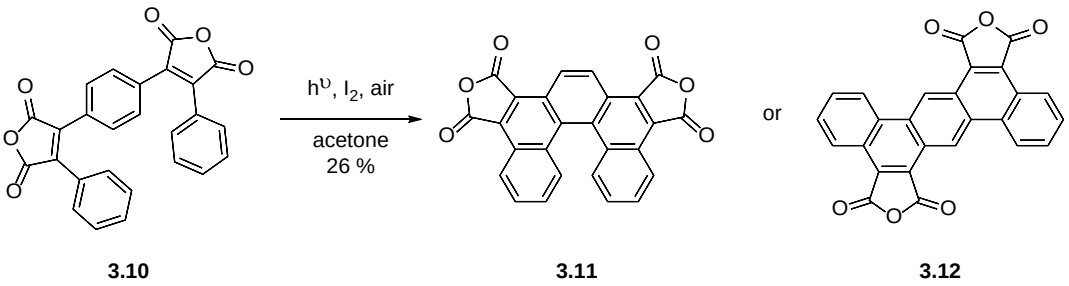
This product has also been observed upon photolysis of diphenylmaleic anhydride **3.7** by Fields *et al*. when investigating the formation of photodimers from aryl-substituted maleic anhydrides.[60] Upon photolysis of anhydride **3.7**, fused anhydride **3.6** was produced alongside its dihydro derivative **3.9** (Scheme 3.4). When the reaction was repeated in the presence of iodine and oxygen, anhydride **3.6** was given as the sole product.



3.7 **3.9** **3.6**

Scheme 3.4: Irradiation of anhydride **3.7** to fused anhydride **3.6** and its dihydro derivative **3.9**

This was then extended to the irradiation of *bis*-anhydride **3.10** which produced either polyaromatic **3.11** or **3.12** (Scheme 3.5).



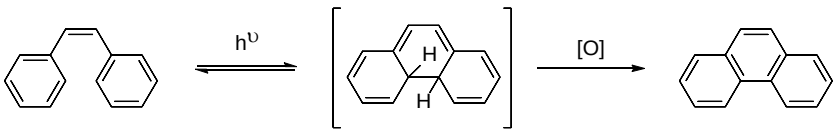
3.10 **3.11** **3.12**

Scheme 3.5: Photolysis of *bis*-anhydride **3.10** by Fields *et al.*

The yield of this reaction was substantially improved by Frimer *et al*. who observed that using the Katz propylene oxide modification the yield of the major product could be improved from 25-30 % to 88 % with a small amount of the minor isomer (<5 %).[61] While Fields *et al.* suggested that the major product of this reaction was the planar isomer **3.12**, this was proven to be false by Frimer *et al.* who were able to show by X-ray crystallography that it was in fact the helical *bis*-anhydride **3.11**.

3.1.2 Photocyclisation of diarylethylenes

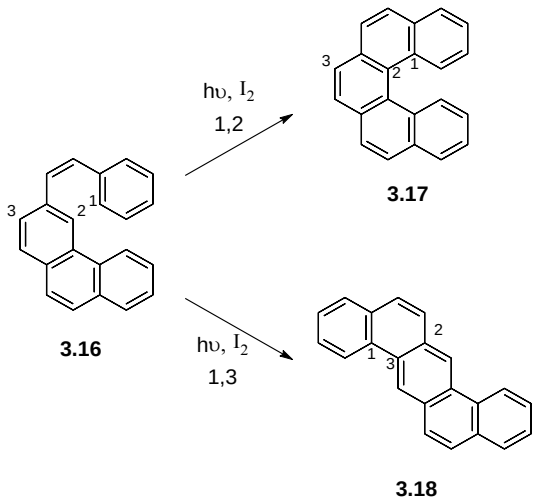
The photocyclisation of the diarylethylene moiety present within anhydride **3.7** was founded upon the photocyclisation of substituted stilbenes to phenanthrenes, originally described by Wood and Mallory (Scheme 3.6).[62,63]



3.13 **3.14** **3.15**

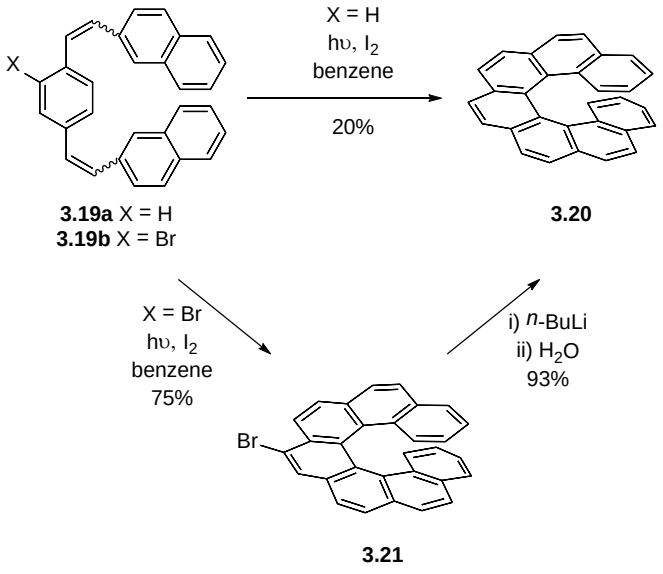
Scheme 3.6: Photocyclisation of stilbenes

This cyclisation has also been extended to the formation of helicenes allowing a variety of these to be prepared from readily accessible diarylethylenes merely by subjecting them to photolysis in the presence of iodine (Scheme 3.7).[64] There are drawbacks to this method however as cyclisation may occur to either *ortho* position of the central arene leading to helicenes **3.17** and the corresponding planar polyaromatic **3.18**. It has also been suggested that the HI produced as a by-product of the reaction can promote formation of other by-products, thereby limiting the yield of the desired helicene.[65]



Scheme 3.7: Competitive cyclisation during photolysis of stilbenes

To combat these difficulties in regioselectivity, Katz *et al.* developed an efficient method to form the desired helicene involving bromine-directed photocyclistion. Thus, while precursor **3.19a** gave helicene **3.20** in 20% yield on irradiation, photocyclisation of **3.19b** produced helicene **3.21** in 75% yield with no contaminations from the planar regioisomer (Scheme 3.8).[66]



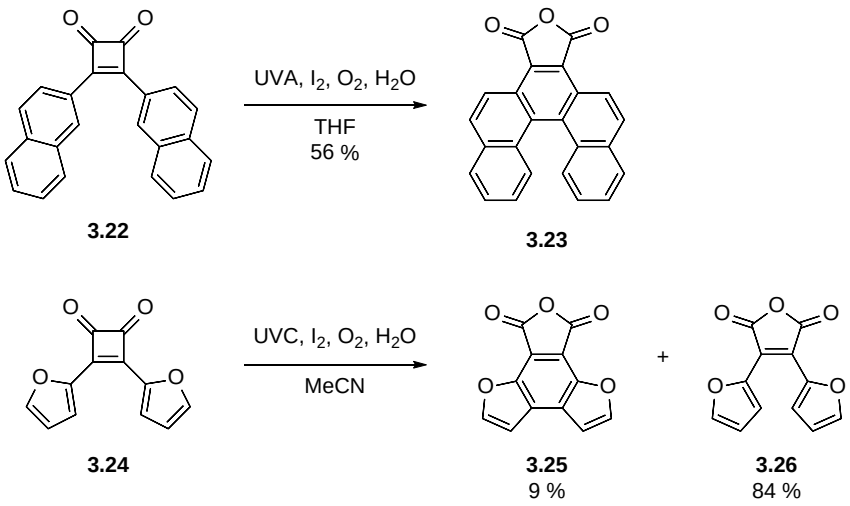
Scheme 3.8: Effect of bromine atom introduction in helicene formation

As mentioned previously, in order to solve the issue regarding HI reduction, Katz and co-workers used a stoichiometric amount of iodine with an excess of propylene oxide. This led to increased product yields and higher purities with every helicene they produced.[65]

While the photocyclisation to form helicenes is a relatively facile method, it generally requires that the reactions are performed on very dilute samples to reduce the chance of photodimerisation. Consequently, scale-up remains problematic.

3.1.3 Previous observations within the Harrowven group

Within the Harrowven group, it was observed that the ring opening and photocyclisation observed by Bird could be repeated using flow photochemistry (Scheme 3.3). During studies on the photochemistry of cyclobutenedione **3.5**, it was observed that phenanthrene **3.6** was produced as a minor component. This was achieved by UVC irradiation of an acetonitrile solution of cyclobutenedione **3.5** when using a segmented flow system with air. Further studies also revealed that helicene **3.23** could be produced by UVA irradiation of cyclobutenedione **3.22** in the presence of oxygen, water and stoichiometric quantities of iodine (Scheme 3.9). It was noted that the cyclobutenedione **3.22** was insoluble in acetonitrile and thus THF was used. Despite this change, helicene **3.23** too proved insoluble in THF leading to its precipitation within the photoreactor. This transformation was also given by cyclobutenedione **3.24** leading to both fused anhydride **3.25** and anhydride **3.26**.



Scheme 3.9: Photochemical transformations of cyclobutenediones observed within the Harrowven group

3.2 Aims and objectives

Using the initial observation by Bird and those within the Harrowven group as a starting point, we sought to develop an improved methodology for the photochemical

transformation of diarylcyclobutenediones to fused polyaromatic anhydrides (Scheme **3.3**). Should this approach be successful, the scope of the reaction would be delineated further with cyclobutenediones bearing substituted arenes and heteroaromatics.

3.3 Methodology for photochemical rearrangement

We hypothesised that the ideal methodology would entail the use of flow photochemistry as it offered an array of benefits over the traditional immersion well method such as the increased productivity and more efficient irradiation of the reaction medium.[67,68] To that end, the reactions carried out within this chapter were conducted using a flow photochemical reactor originally inspired by Booker-Milburn *et al.*[47,69] This reactor consists of a coil of fluorinated ethylene-propylene (FEP) tubing wrapped around a quartz cylinder with an internal volume of 110 mL (Figure 3.1). An additional coil of condenser tubing then surrounds this to enable water cooling of the reactor to keep internal temperatures low. The entire reactor is then wrapped with aluminium foil primarily to protect the user from harmful UV irradiation when in use. The required 36 W UV lamp was then placed within the quartz cylinder attached to an external ballast allowing for uniform irradiation of the reaction medium.

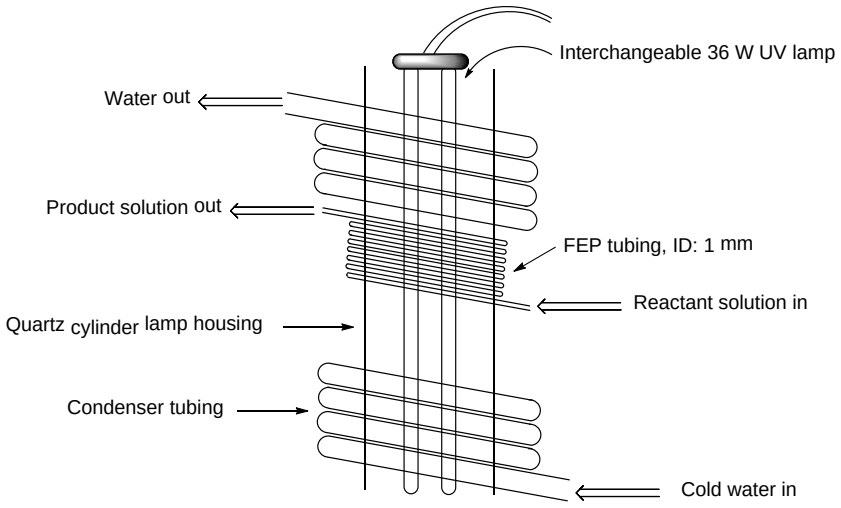


Figure 3.1: Schematic of photochemical reactor

The reactant solution was introduced into the reactor *via* a peristaltic pump allowing the programming of a specific flow rate. The use of a T-piece allows a second continuous flow of gas (air or oxygen) which creates bubbles within the reaction solution, increasing gas-liquid phase mixing (Figure 3.2).

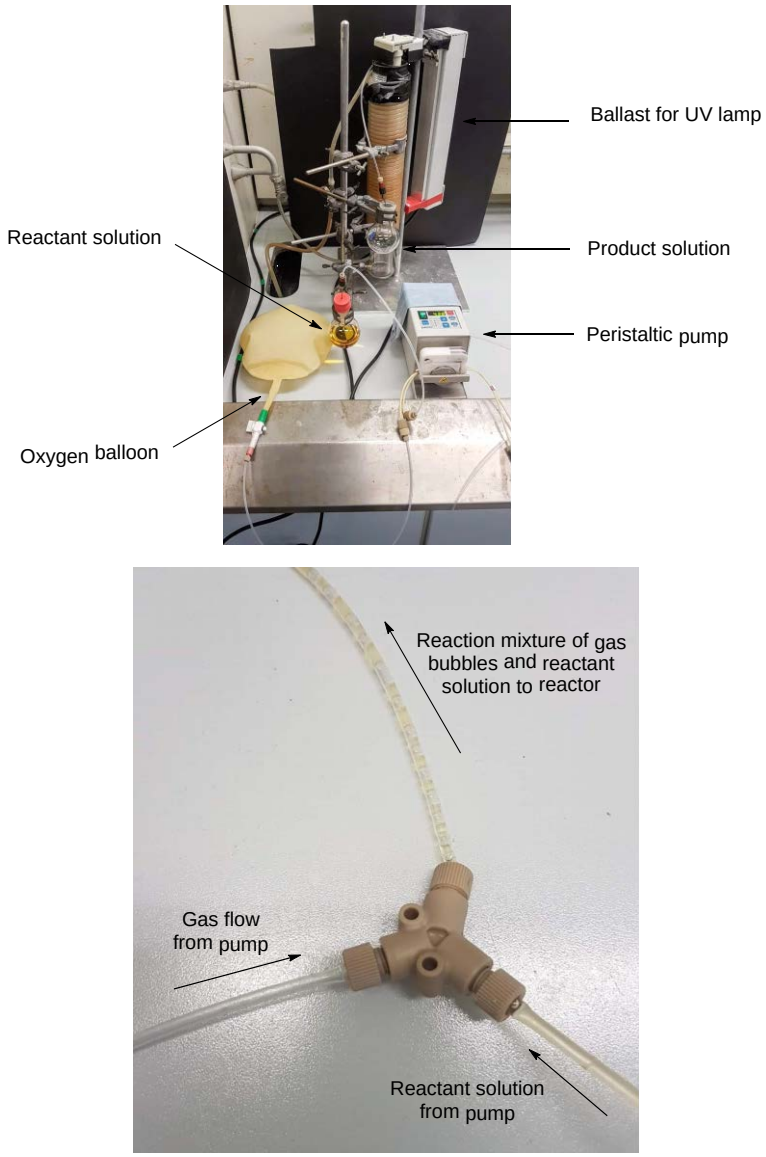


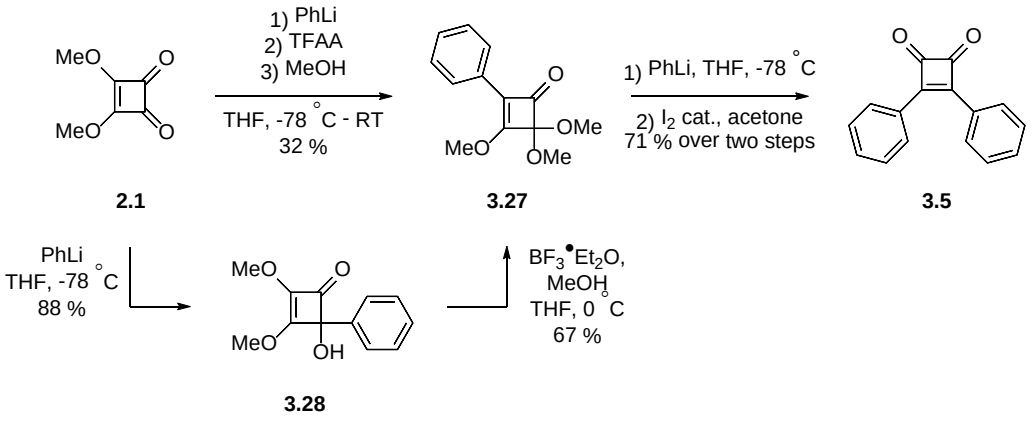
Figure 3.2: Photochemical reactor (above) and T-piece used to introduce gas bubbles (below)

3.4 Results and Discussion

3.4.1 Preparation of diarylcyclobutenediones

To examine the optimal conditions for the photocyclisation of cyclobutenedione **3.5**, a synthesis based upon protection methods used by Moore *et al.* was derived (Scheme 3.10).[70] Initially, the sequence began with the addition of phenyllithium to cyclobutenedione **2.1** followed by addition of TFAA and methanol to give acetal **3.27**. Due to the sensitivity of acetal **3.27** to purification by column chromatography, the yield for this step was very low when compared to the literature and thus an alternative method was sought. Addition of phenyllithium to cyclobutenedione **2.1** gave cyclobutenone **3.28** in high

yield which was then converted to acetal **3.27** in good yield using methods developed by Moore *et al.*[37] A second addition of phenyllithium to acetal **3.27** followed by deprotection then produced cyclobutenedione **3.5** in good yield. Deprotection using conc. HCl was initially tested however an alternative method using catalytic iodine led to shorter reaction times and a greater yield of **3.5**.[71] Sun *et al.* observed that addition of catalytic iodine to acetals in acetone decreases the reaction time from 24 hours to mere minutes and avoids the use of harsh reaction conditions.

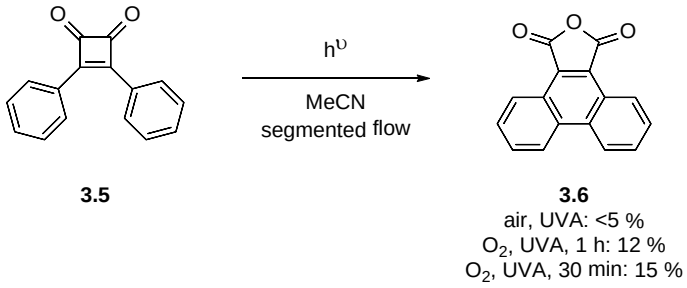


Scheme 3.10: Preparation of cyclobutenedione **3.5**

3.4.2 Photolysis studies

With a robust synthesis of cyclobutenedione **3.5** in hand, the focus was then diverted to the photochemical rearrangement of **3.5** to anhydride **3.6**.[59] Due to the lack of an experimental procedure, the initial examination began with the use of the flow photoreactor fitted with a 36 W UVA lamp (Scheme 3.11). The reaction was conducted using a 0.2 M solution of cyclobutenedione **3.5** in acetonitrile due to the observations noted previously regarding the low solubility of the product in the solvent. Irradiation of this solution within the photoreactor under a flow segmented with air for 30 min provided a crude mixture that contained a low amount of anhydride **3.6** (<5 %) and a large quantity of unreacted starting material (as determined by ^{1}H NMR). The reaction was repeated for 1 hour and gave a similar result. Thus, our focus shifted to the replacement of air with oxygen within the photoreactor to facilitate the oxidation reaction. Once the dual channel set-up was fitted with an oxygen balloon, the test solution of cyclobutenedione **3.5** was irradiated for 1 hour leading to an increased production of anhydride **3.6** (≈12 % after purification) alongside the observation of a large amount of broad aromatic residues within the ^{1}H NMR.

It was hypothesised that this could be due to over-irradiation. However, repeating the reaction over 30 minutes produced a similar product yield of 15 % for **3.6**. With over-irradiation ruled out as an issue, it was suggested that an additional oxidant to facilitate the oxidation to anhydride **3.6** could be beneficial.

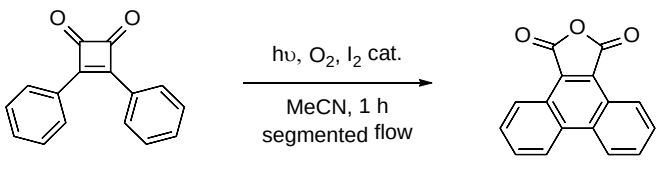


3.5

3.6
air, UVA: <5 %
O_2, UVA, 1 h: 12 %
O_2, UVA, 30 min: 15 %

Scheme 3.11: Initial photochemical studies of cyclobutenedione **3.5**

Due to the previously mentioned use of Katz photochemical methods for the synthesis of a wide array of polyaromatic syntheses (Chapter 3.1.1) and its use in the syntheses of fused anhydrides within the Harrowven group (Chapter 3.1.3), the use of iodine was investigated. To our delight, addition of catalytic iodine increased the yield of anhydride **3.6** dramatically from 12-15 % to 88 % when used in conjunction with oxygen bubbles (Scheme 3.12). Of note was the decreased solubility of anhydride **3.6** over cyclobutenedione **3.5** in acetonitrile which caused large precipitates to form within the reactor. This was overcome by using a THF flush to purge the reactor of precipitated product ahead of its next use. This insolubility had the advantage of facilitating product purification as only a wash with cold acetonitrile was needed to yield clean samples of anhydride **3.6**. It was also observed that addition of water was unnecessary for the reaction to occur, possibly due to residual water within the acetonitrile used and its formation as a by-product of the oxidation. The use of UVB broad and UVC lamps was also examined leading to similarly high yields of anhydride **3.6** being obtained (85 and 79 % respectively).



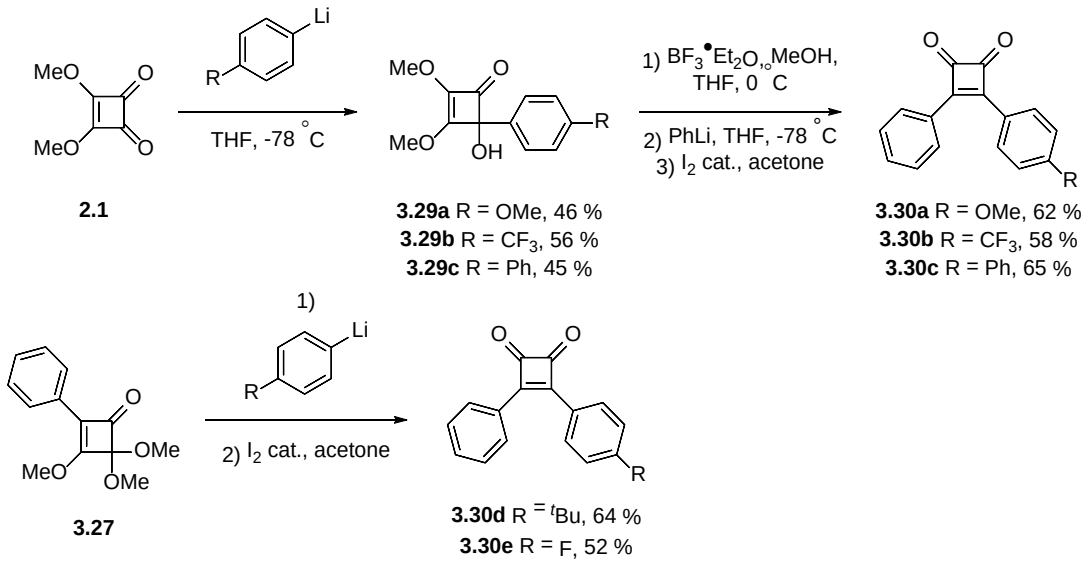
3.5

3.6
UVA: 88 %
UVB: 85 %
UVC: 79 %

Scheme 3.12: Increased yield of anhydride **3.6** upon addition of catalytic iodine

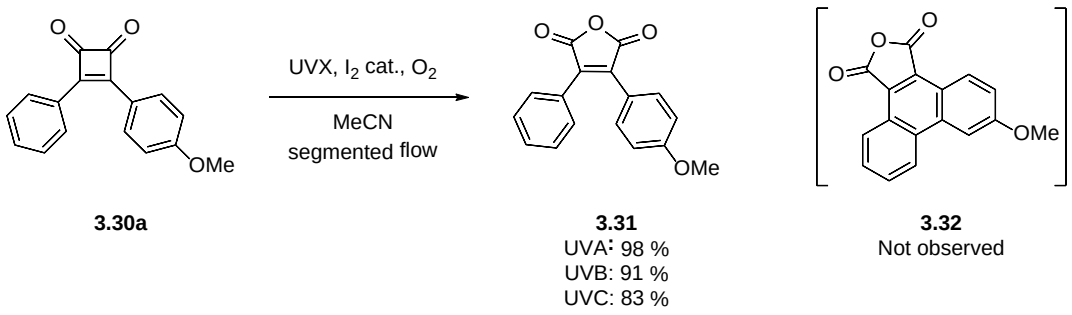
3.4.3 Expansion of substrate scope – 2, 3 and 4-substituted arene systems

With the successful formation of anhydride **3.6** in high yields, the focus was next diverted to the formation of functionalised phenanthrenes. Initially substitution at the 4 position of the aryl residues was investigated and thus cyclobutenediones **3.30a-e** were produced. Syntheses of cyclobutenediones **3.30a-c** began in a similar manner to that of cyclobutenedione **3.5** with the addition of a 4-substituted aryllithium to cyclobutenedione **2.1** yielding cyclobutenones **3.29a-c** in good yields. These were then converted to cyclobutenediones **3.30a-c** in 3 sequenced steps which lowered product loss due to degradation through purification (Scheme 3.13). Alongside this, acetal **3.27** was treated with 4-fluoro-1-lithiobenzene and 4-*tert*-butyl-1-lithiobenzene followed by deprotection using catalytic iodine, to yield cyclobutenediones **3.30d** and **3.30e** in 64 % and 52 % yields respectively.



Scheme 3.13: Synthesis of 4-substitutedarylcyclobutenediones **3.30a-e**

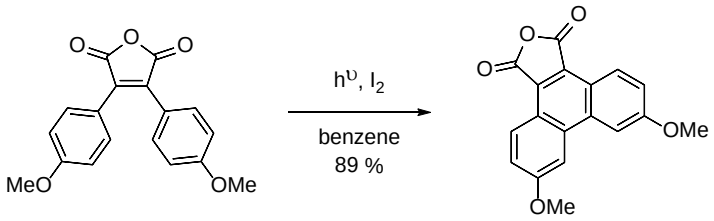
To examine the effects of 4-substitution on the photochemical transformation, a 0.2 M solution of cyclobutenedione **3.30a** and 0.1 equivalents of iodine in acetonitrile was segmented with oxygen and passed through the flow photochemical reactor while under irradiation from a 36 W UVA lamp for 1 hour (Scheme 3.14). Unexpectedly, only anhydride **3.31** was isolated in near quantitative yield with no observable phenanthrene **3.32**. The reaction was therefore repeated using 36 W UVB narrow and UVC lamps yielding similar results although of note was the significantly lower yield observed when using UVC irradiation.



3.30a | **3.31** UVA: 98 %, UVB: 91 %, UVC: 83 % | **3.32** Not observed

Scheme 3.14: Irradiation of cyclobutenedione **3.30a**

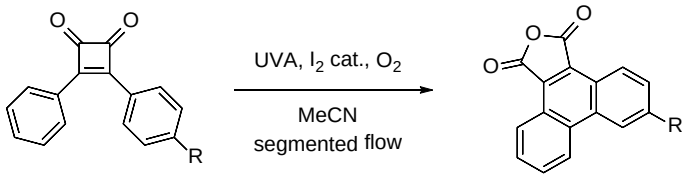
Interestingly, this reluctance of anhydride **3.31** to undergo further photocyclisation is unexpected when compared to the analogous reaction conducted by Reis *et al.* who observed successful formation of phenanthrene **3.34** from anhydride **3.33** (Scheme 3.15).[72] This reaction however utilised irradiation from a 450 W Hg lamp for 12 hours and 50 equivalents of molecular iodine indicating a strong hesitation of anhydride **3.33** to undergo photocyclisation.



3.33 | **3.34**

Scheme 3.15: Synthesis of phenanthrene **3.34** by Reis *et al.*

The irradiation of cyclobutenediones **3.30b** and **3.30d** was next examined. Pleasingly, treatment of acetonitrile solutions of **3.30b** and **3.30d** with UVA irradiation under flow and segmented with oxygen, gave phenanthrenes **3.35** and **3.36** in 92 % and 61 % respectively (Scheme 3.16).

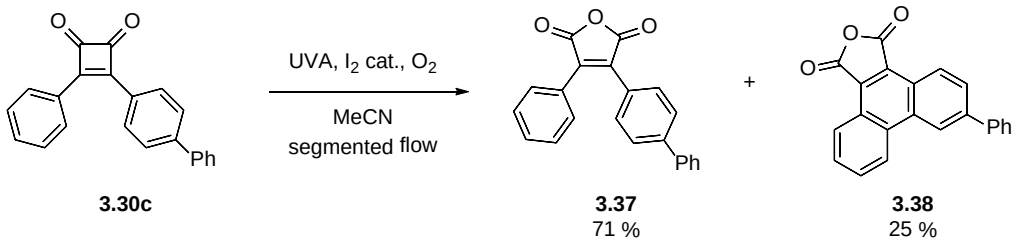


3.30b R = CF_3
3.30d R = ^{t}Bu

3.35 R = CF_3, 92 %
3.36 R = ^{t}Bu, 61 %

Scheme 3.16: Formation of phenanthrenes **3.35** and **3.36**

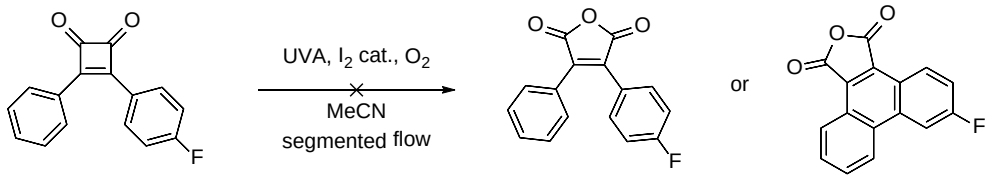
Interestingly, when cyclobutenedione **3.30c** was subjected to the aforementioned conditions, both anhydride **3.37** and phenanthrene **3.38** were produced in an approximate 3:1 ratio respectively (Scheme 3.17).



3.30c **3.37** 71 % **3.38** 25 %

Scheme 3.17: UVA irradiation of cyclobutenedione **3.30c**

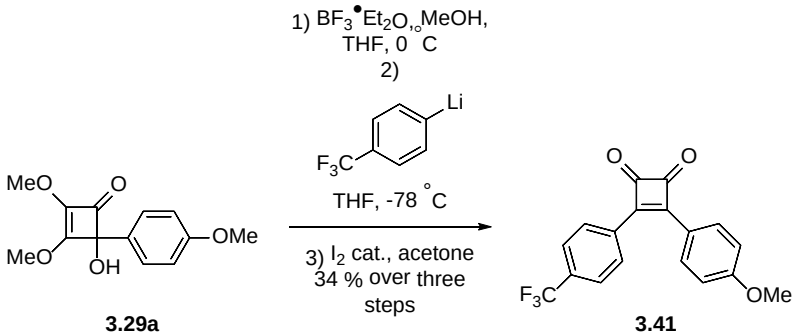
Cyclobutenedione **3.30e** was also subjected to these reaction conditions but failed to give any identifiable products within the crude reaction mixture, producing only broad peaks in the aromatic region of the ^{1}H NMR spectrum (Scheme 3.18).



3.30e **3.39** **3.40**

Scheme 3.18: Failed irradiation of cyclobutenedione **3.30e**

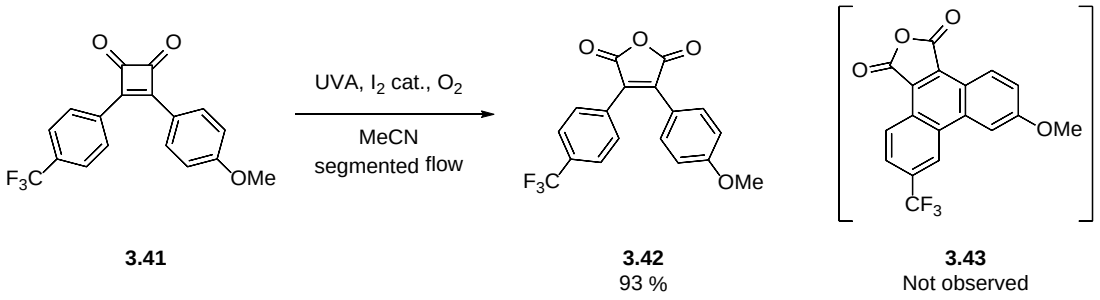
Due to the successful photocyclisation of cyclobutenedione **3.30b**, it was envisioned that the introduction of a 4-trifluoromethyl onto the second arene of cyclobutenedione **3.30a** would have the potential to induce phenanthrene formation. To that end, cyclobutenedione **3.41** was produced by treatment of cyclobutenone **3.29a** with BF_3•Et_2O and methanol followed by addition of (4-(trifluoromethyl)phenyl)lithium and subsequent deprotection (Scheme 3.19).



3.29a **3.41**

Scheme 3.19: Synthesis of cyclobutenedione **3.41**

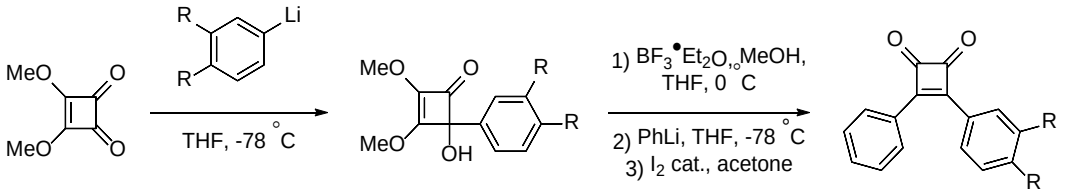
The formation of phenanthrene **3.43** was then attempted using UVA irradiation of cyclobutenedione **3.41** under segmented flow with oxygen. In this case only anhydride **3.42** was produced in near quantitative yield (Scheme 3.20).



3.41 | **3.42** 93 % | **3.43** Not observed

Scheme 3.20: Attempted formation of phenanthrene **3.43**

The effect of introducing an electron-donating substituent into the 3- and 4-position of one of the arenes was next examined. 3,4-Dimethoxy- and methylenedioxycyclobutenediones **3.45a** and **3.45b** were produced respectively from cyclobutenedione **2.1** in moderate yields using the previously described procedures (Scheme 3.21).



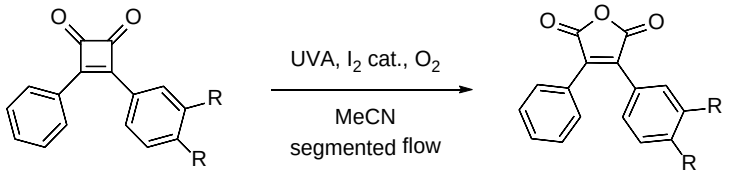
2.1

3.44a R = OMe, 73 %
3.44b R = OCH_2O, 71 %

3.45a R = OMe, 57 %
3.45b R = OCH_2O, 51 %

Scheme 3.21: Synthesis of cyclobutenediones **3.45a** and **3.45b**

Upon UVA irradiation of cyclobutenediones **3.45a** and **3.45b** under a segmented flow with oxygen, anhydrides **3.46a** and **3.46b** were produced respectively in near quantitative yields (Scheme 3.22). This led us to postulate that introduction of strongly electron-donating residues onto the cyclobutenedione decreases the possibility for further photocyclisation following anhydride formation.

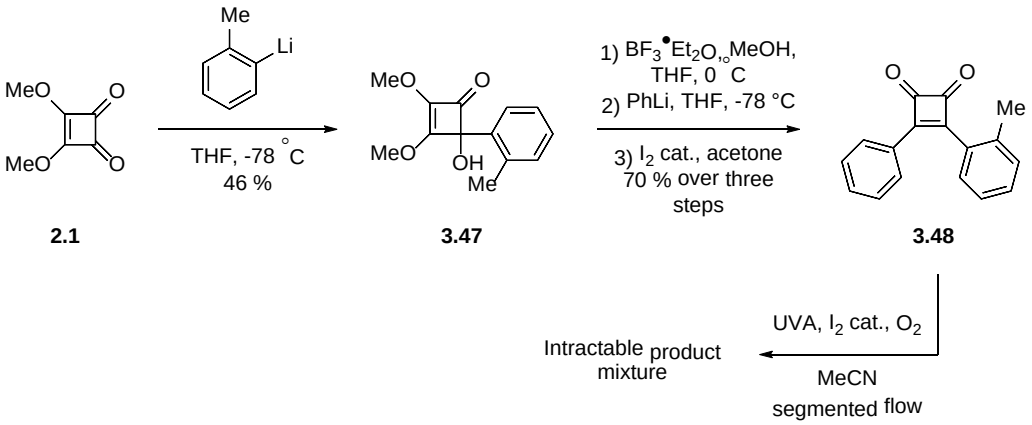


3.45a R = OMe
3.45b R = OCH_2O

3.46a R = OMe, 96 %
3.46b R = OCH_2O, 99 %

Scheme 3.22: Photochemical transformation of cyclobutenediones **3.45a** and **3.45b**

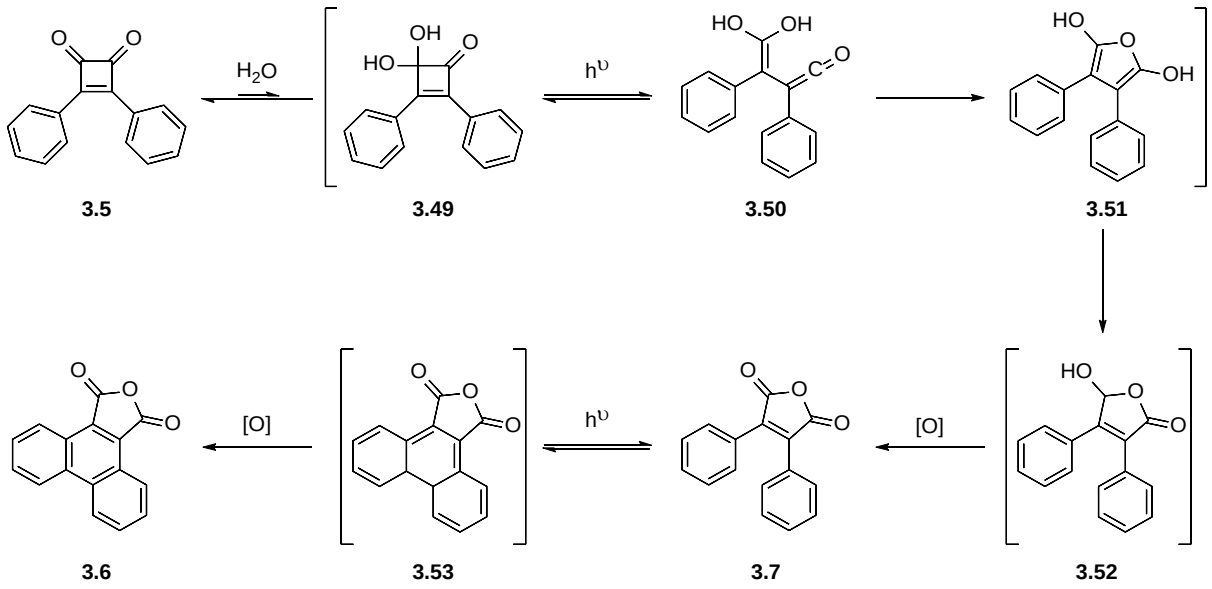
An example of *ortho*-substitution was also tested in the form of 2-tolylcyclobutenedione **3.48**. However, this failed to produce any observable product and instead gave rise to an intractable product mixture upon irradiation (Scheme 3.23).



Scheme 3.23: Attempted anhydride formation from cyclobutenedione **3.48**

3.4.4 Proposed mechanism for anhydride formation

As observed during the photolysis of cyclobutenedione **3.30a**, anhydride **3.31** was the only product formed. Thus, it is realistic to propose that the formation of diaryl anhydrides is an intermediate step in the formation of the fused polyaromatic anhydrides. This was also demonstrated in the photolysis of cyclobutenedione **3.30c** in which both the diaryl and fused phenanthrene anhydrides, **3.37** and **3.38** respectively, were produced. It was therefore speculated that given an increased reaction time all of anhydride **3.37** would be converted to phenanthrene **3.38** when in the presence of iodine and oxygen. Consequently, we hypothesised the following mechanism for the formation of anhydride **3.7** and then fused system **3.6** (Scheme 3.24).



3.5 **3.49** **3.50** **3.51**

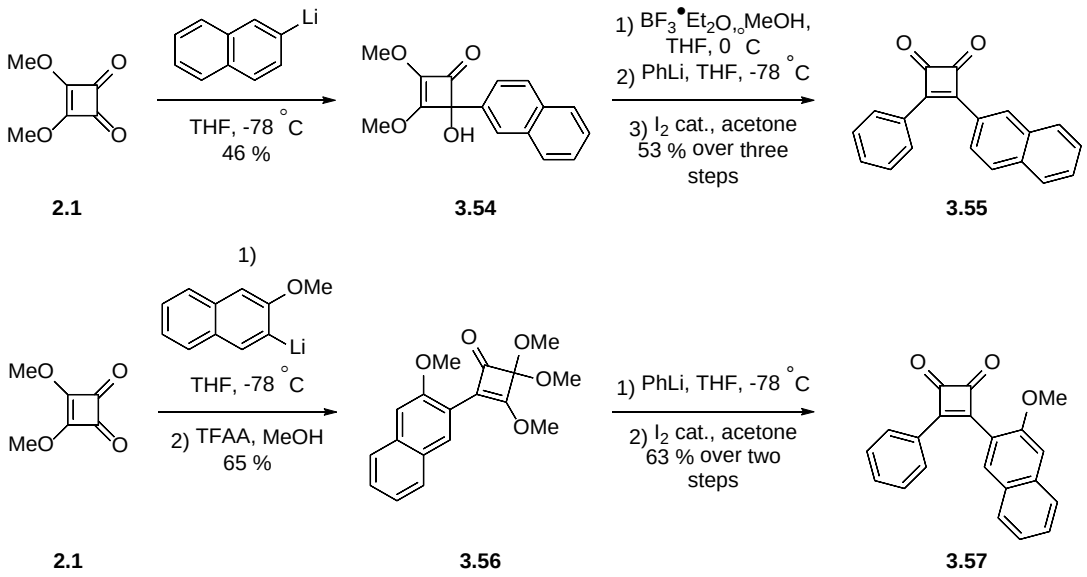
3.6 **3.53** **3.7** **3.52**

Scheme 3.24: Proposed mechanism for the formation of anhydride **3.7** and subsequently phenanthrene **3.6**

We postulate that the mechanistic course of the reaction begins with hydration of cyclobutenedione **3.5** to diol **3.49** followed by electrocyclic ring opening to vinylketene **3.50** triggered by photolysis. Ring closure to furan **3.51** is followed by tautomerisation to furanone **3.52** which is then oxidised to anhydride **3.7**. Photocyclisation then gives **3.53** which undergoes further oxidation to phenanthrene **3.6**. It has been observed that this photocyclisation step is accelerated when the arenes bear electron-withdrawing substituents which further supports the observation that the incorporation of the trifluoromethyl group leads to near quantitative yields of phenanthrene **3.35** while cyclobutenediones bearing electron-donating alkoxy groups fail to cyclise within the reaction times attempted within this research programme.[63]

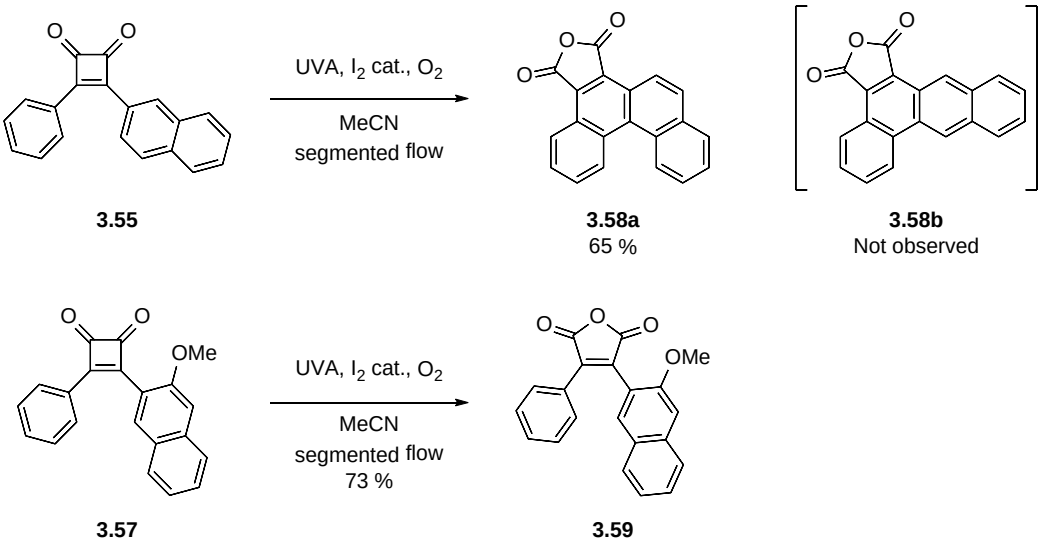
3.4.5 Expansion of substrate scope – attempted synthesis of helical systems

After successfully producing several anhydride systems, some of which contained fused phenanthrene residues, the scope was shifted to the synthesis of helical systems as an extension of the previously observed formation of helicene **3.23**. To that end, cyclobutenediones **3.55** and **3.57** were synthesised bearing naphthalene residues, the hypothesis being that ring closure to the proximal arene would give [4]helicene containing anhydrides (Scheme 3.25).



Scheme 3.25: Synthesis of naphthalene-bearing cyclobutenediones **3.55** and **3.57**

Pleasingly, photolysis of cyclobutenedione **3.55** in the presence of oxygen gave fused anhydride **3.58a** in 65 % yield with no observation of regioisomer **3.58b** (Scheme 3.26). However, as observed with cyclobutenediones bearing arenes containing alkoxy groups, irradiation of cyclobutenedione **3.57** yielded only anhydride **3.59** in 73 % yield as the sole identifiable product.

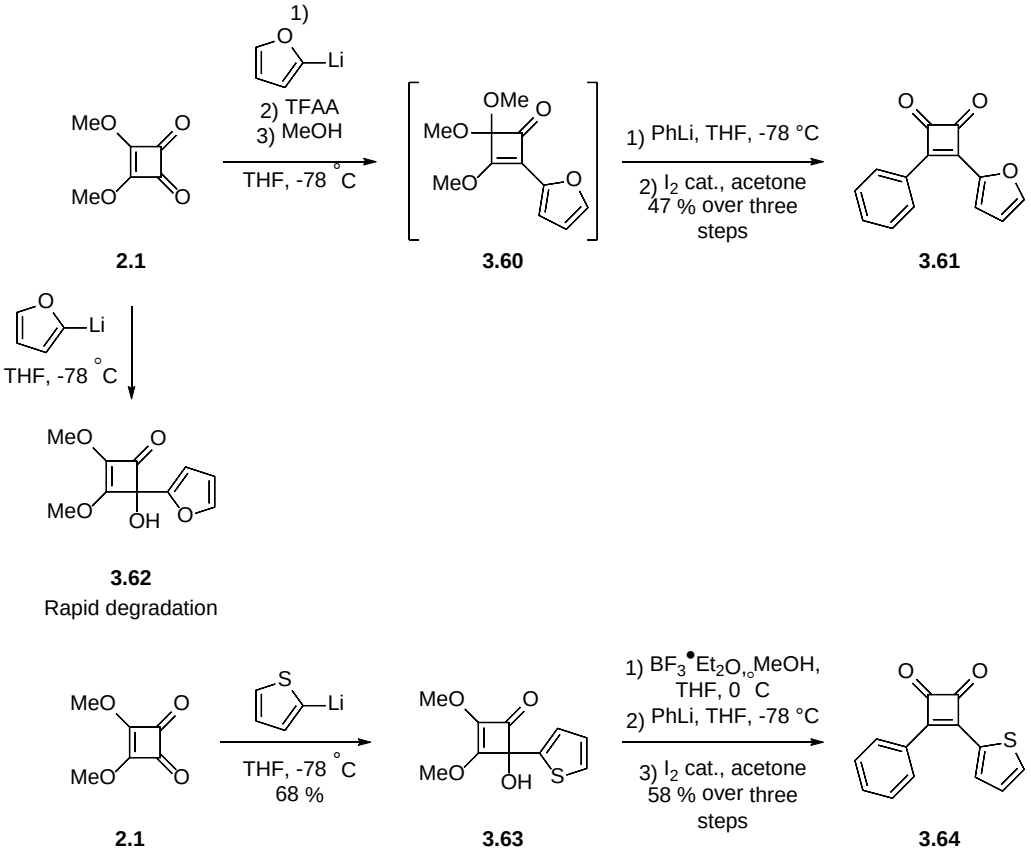


Scheme 3.26: Irradiation of cyclobutenediones bearing naphthalene residues

3.4.6 Expansion of substrate scope – incorporation of heteroaromatics

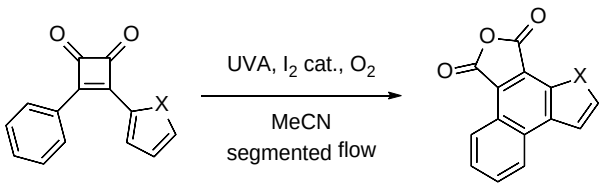
To extend the scope of this rearrangement further, the focus shifted to the incorporation of heteroaromatic residues onto the cyclobutenedione. Initially, a synthesis for

cyclobutenedione **3.61** which bears a furan residue was sought. The preparation of cyclobutenone **3.62** was attempted however this proved to be incredibly unstable, degrading over the course of 48 hours even when kept within the freezer. Thus, the synthesis of cyclobutenedione **3.61** was reattempted using an alternative pathway beginning with preparation of acetal **3.60** followed by addition of phenyllithium to the crude reaction mixture and subsequent deprotection (Scheme 3.27). Alongside this, the analogous cyclobutenedione **3.64** containing a thiophene residue was also prepared from cyclobutenedione **2.1**.



Scheme 3.27: Synthesis of cyclobutenediones bearing furan and thiophene residues

Pleasingly, once cyclobutenediones **3.61** and **3.64** were subjected to the optimised reaction conditions used thus far, fused polyaromatics **3.65** and **3.66** were produced in 34 % and 61 % respectively (Scheme 3.28). In the case of furan containing substrate **3.61**, formation of polyaromatic **3.65** was accompanied by a large amount of decomposition resulting in a black solution exiting the reactor as opposed to the yellow/orange solutions observed up to this point. This can be attributed to the increased reactivity demonstrated by furan containing compounds. Both **3.65** and **3.66** also demonstrated much lower solubility within most organic solvents than the fused systems previously synthesised.

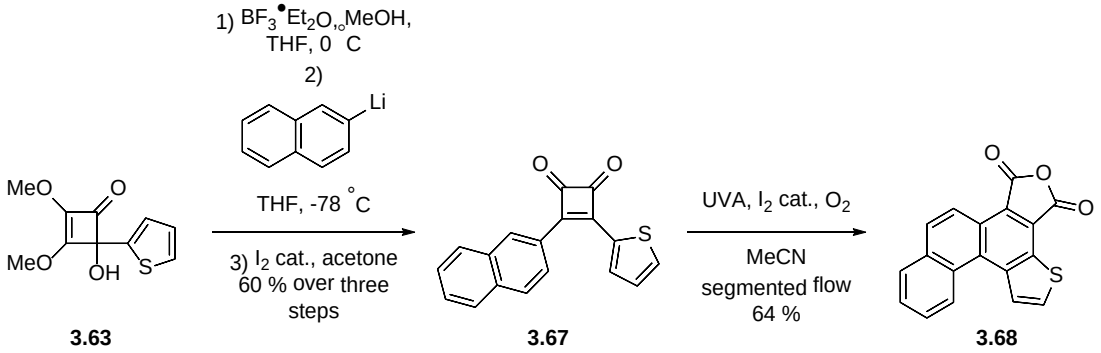


3.61 X = O
3.64 X = S

3.65 X = O, 34 %
3.66 X = S, 61 %

Scheme 3.28: Formation of fused heteroaromatic systems **3.65** and **3.66**

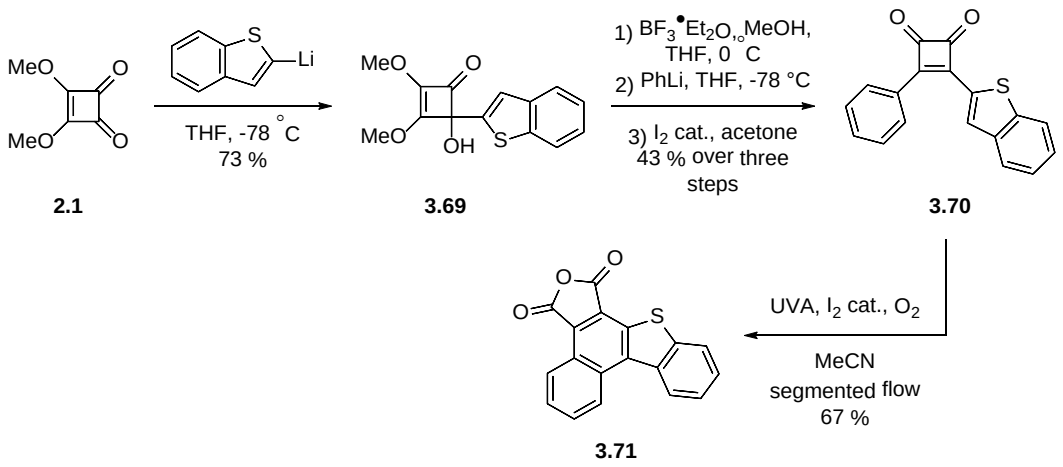
With the successful formation of fused thiophene **3.66** and [4]-helicene **3.58a**, it was predicted that cyclobutenedione **3.67** would prove a prime candidate for the photochemical oxidative cyclisation method we had developed. Thus, cyclobutenedione **3.67** was produced from cyclobutenone **3.63** in good yield and pleasingly gave **3.68** in 64 % yield with no observable regioisomer when irradiated using the aforementioned methods (Scheme 3.29).



3.63 **3.67** **3.68**

Scheme 3.29: Formation of fused polyaromatic **3.68** from cyclobutenedione **3.67**

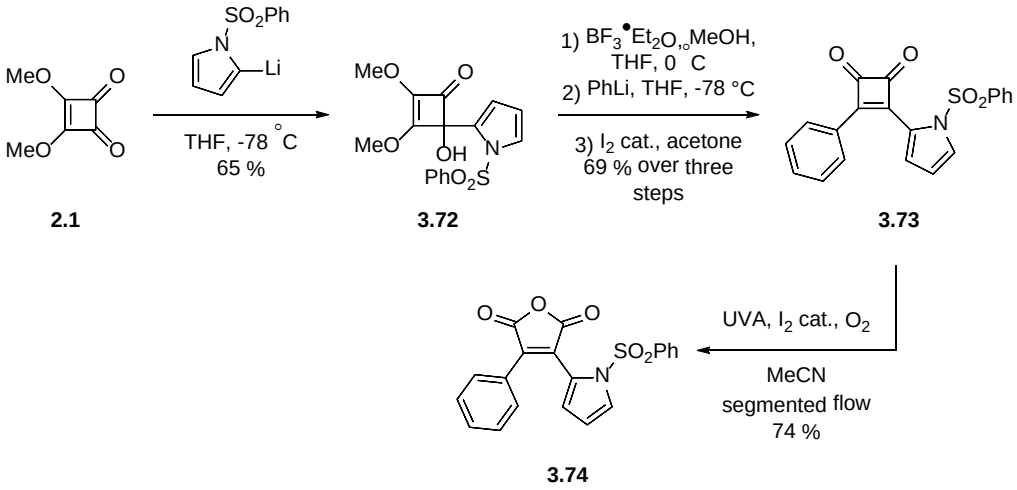
The focus next shifted to the incorporation of a benzo[*b*]thiophene residue to form fused polyaromatics. Thus, cyclobutenedione **3.70** was produced from cyclobutenone **3.69**, which in turn was derived from cyclobutenedione **2.1** (Scheme 3.30). Cyclobutenedione **3.70** was then irradiated using segmented flow with oxygen to give fused polyaromatic **3.71** in 67 % yield.



2.1 **3.69** **3.70** **3.71**

Scheme 3.30: Formation of cyclobutenedione **3.70** and subsequent photolysis to polyaromatic **3.71**

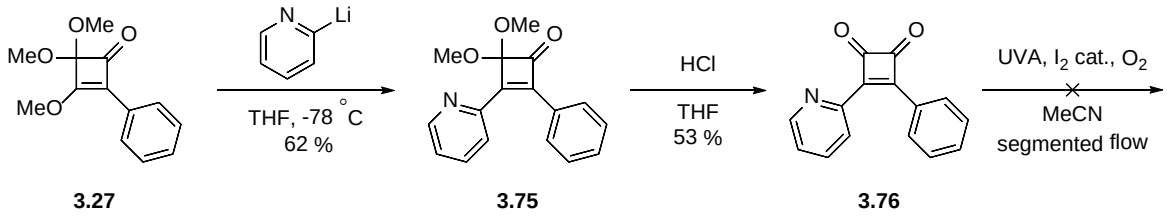
The substrate focus was then shifted to nitrogen-containing heterocycles which began with the synthesis of pyrrole-containing cyclobutenedione **3.73** (Scheme 3.31). Interestingly, once cyclobutenedione **3.73** was subjected to photolysis, only anhydride **3.74** was isolated. That no fused polyaromatic product was observed within the crude reaction mixture indicated a reluctance for anhydride **3.74** to undergo ring closure.



2.1 **3.72** **3.73** **3.74**

Scheme 3.31: Formation and subsequent photolysis of cyclobutenedione **3.73** to anhydride **3.74**

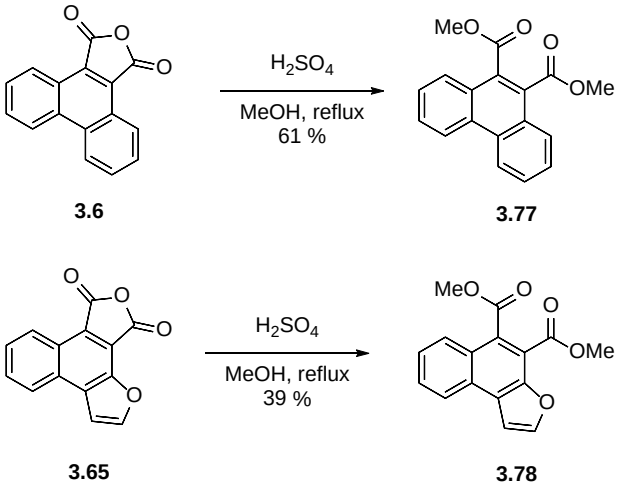
The effect of incorporating a pyridine residue was then undertaken beginning with the production of cyclobutenedione **3.76**. Interestingly, acetal **3.75** proved resistant to deprotection using catalytic iodine in acetone and thus the traditional deprotection method of treatment with conc. HCl was used (Scheme 3.32). Unfortunately, cyclobutenedione **3.76** proved intolerant to irradiation yielding a black crude mixture comprised of baseline material.



Scheme 3.32: Attempted photolysis of cyclobutenedione **3.76**

3.4.7 Further functionalisation – anhydride ring opening

With the segmented flow methods using oxygen proving successful, efforts were next shifted to functionalisation of the products given. It was observed that when methanol solutions of fused anhydrides **3.6** and **3.65** were subjected to reflux in the presence of sulfuric acid, the corresponding dimethyl esters **3.77** and **3.78** were produced in moderate to good yields (Scheme 3.33).



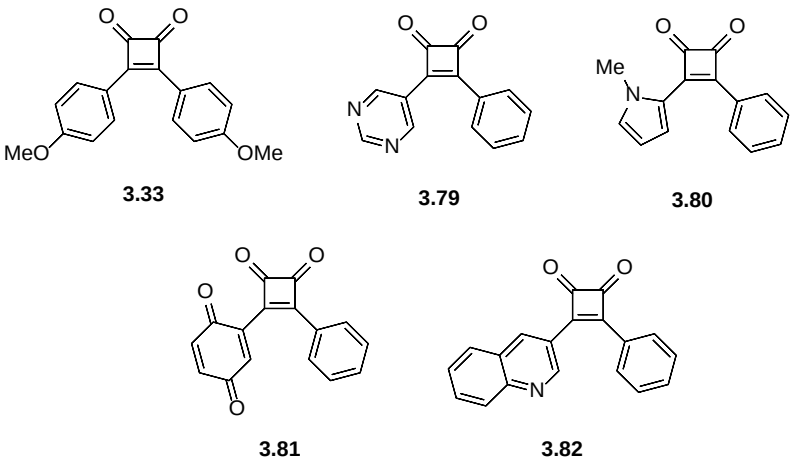
Scheme 3.33: Anhydride ring opening of polyaromatics **3.6** and **3.65**

3.5 Conclusions and future work

In conclusion, the rearrangement of diarylcyclobutenediones to diarylanhydrides and fused polyaromatic anhydrides has been developed and shown to have a wide substrate scope. The use of segmented flow to facilitate oxidation with oxygen gas was of particular note as it allowed for the facile generation of a vast array of polyaromatic ring systems in good yield while maintaining short reaction times and a low chemical waste stream. The work described within this Chapter has contributed to a research paper being drafted that is entitled “Syntheses of diaryl and fused polyaromatic maleic anhydrides from

cyclobutenediones by photochemical ring expansion, cyclisation and oxidation under segmented flow". With anhydrides and polyaromatics proving to be extremely interesting molecules within the field of electronics and light emission, the substrates synthesised within this study have huge potential as scaffolds in materials chemistry research.[73–75]

Time constraints invoked by the COVID-19 pandemic have limited the number of substrates that could be tested. However, should the scope for this rearrangement be expanded, cyclobutenediones bearing two functionalised arene residues (*e.g.* cyclobutenedione **3.33**) should be further tested and compared against the literature method described previously.[72] The effect of alternative arenes and heterocyclic residues (*e.g.* pyrimidines, *N*-methyl pyrroles, quinones, quinolines) could also be examined (Figure 3.3) as could their derivatization to form fused maleimides.



3.33 **3.79** **3.80**

3.81 **3.82**

Figure 3.3: Possible substrates to examine using this photochemical transformation

Chapter 4 Experimental

4.1 General experimental procedures

NMR Spectra: Proton (^{1}H) and carbon (^{13}C) were recorded on a Bruker AVIIIHD 400 (400/100 MHz respectively) spectrometer at 298 K. Spectra were obtained from samples dissolved in deuterated chloroform ($CDCl_3$) supplied by Sigma Aldrich. Chemical shifts were reported in units of parts per million (ppm) downfield of tetramethylsilane with residual solvent as the internal standard. Resonances are depicted as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), sept (septet), m (multiplet) and br (broad). Coupling constants (*J*) are given in Hz and are rounded to the nearest 0.1 Hz.

High Resolution Mass Spectrometry was carried out using a MaXis mass spectrometer equipped with a time of flight (TOF) analyser. Samples were introduced to the mass spectrometer via a Dionex Ultimate 3000 autosampler and uHPLC pump using a gradient of 20% to 100% acetonitrile (0.2% formic acid) over 5 min. Spectra were recorded using positive/negative ion electrospray as specified and were calculated to four decimal places from the molecular formula. All samples were analysed and recorded by Ms Julie Herniman at the University of Southampton.

Low Resolution Mass Spectrometry was carried out using either electrospray ionisation or electron ionisation as stated. ESI mass spectra were recorded using a Waters TQD mass spectrometer equipped with a triple quadrupole analyser. EI spectra were measured on a Thermo Trace GC-MS equipped with a single quadrupole analyser*m/z* values were reported with their respective abundances.

Infrared Spectra were recorded neat as solid compressions using a Nicolet 380 Laboratory FT-IR spectrometer. Absorption maxima (ν_{max}) are expressed as s (strong), m (medium), w (weak) and/or br (broad) and are quoted in wavenumbers (cm^{-1}).

Melting points were recorded on an Electrothermal IA9100 digital melting point apparatus and are uncorrected.

Thin Layer Chromatography were carried out on Merck Silica Gel 60Å F 254 0.2 mm plates, which were visualised under fluorescence UV (254 nm) followed by staining with aqueous

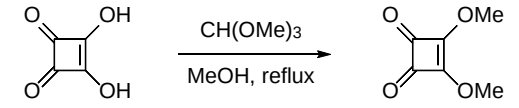
1% $KMnO_4$. Column chromatography was carried out using silica with the stated solvent system.

Solvents and reagents that were commercially available were used as purchased. THF was distilled from sodium benzophenone ketyl under argon. All moisture sensitive reactions were carried out under argon atmosphere using flame dried apparatus.

Crystallisations to obtain melting points and X-ray structures were performed as follows. The title compound was dissolved in the polar solvent stated followed by partial submersion of the vial containing the compound solution in a larger vial containing the co-solvent stated. This container was then sealed and left to allow crystals to form. The solvent was removed and the crystals dried *in vacuo* prior to analysis.

4.2 Experimental procedures for Chapter 2

3,4-Dimethoxycyclobut-3-ene-1,2-dione (2.1)



1.8
$C_4H_2O_4$
Mol Wt: 114.06

2.1
$C_6H_6O_4$
Mol Wt: 142.11

A suspension of 3,4-dihydroxycyclobut-3-ene-1,2-dione (5.00 g, 43.8 mmol) and trimethyl orthoformate (14.4 mL, 131.4 mmol) in MeOH (90 mL) was heated at reflux for 60 h. The reaction mixture was cooled to RT and concentrated *in vacuo* to a blue oil. Purification by column chromatography (10–40 % ethyl acetate/petroleum ether) gave the title compound (3.78 g, 26.5 mmol, 61 %) as white crystals.

Data consistent with literature[2]

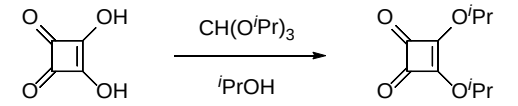
MP: 52–53 °C (diethyl ether)

δ_H (400 MHz, $CDCl_3$): 4.38 (s, 6H, 2 x OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 189.0 (2 x **C**), 184.3 (2 x **C**), 60.8 (2 x O**C**H_3)

LC-MS (ESI^+): 165 (51 %, $[M + Na]^+$).

3,4-Bis(1-methylethoxy)-3-cyclobut-3-ene-1,2-dione (2.25)



1.8
$C_4H_2O_4$
Mol Wt: 114.06

2.25
$C_{10}H_{14}O_4$
Mol Wt: 198.22

A suspension of 3,4-dihydroxycyclobut-3-ene-1,2-dione (5.20 g, 45.7 mmol) and triisopropyl orthoformate (29.3 mL, 131.4 mmol) in IPA (90 mL) was heated at reflux for 60 h. The reaction was cooled to RT then concentrated *in vacuo* to a red oil. Purification by column chromatography (10–20 % ethyl acetate/petroleum ether) gave the title compound (4.54 g, 22.9 mmol, 50 %) as an off-white solid.

Data consistent with literature[76]

MP: 42–43 °C (diethyl ether)

δ_H (400 MHz, $CDCl_3$): 5.35 (sept, J = 6.2 Hz, 2H, 2 x OC**H**$(CH_3)_2$)

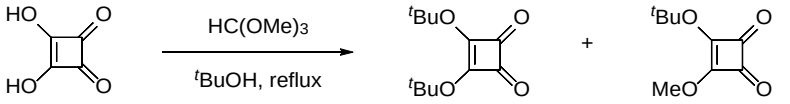
1.46 (d, J = 6.2 Hz, 12H, 2 x OCH(C**H**$_3)_2$)

δ_C (100 MHz, $CDCl_3$): 189.2 (2 x **C**), 184.1 (2 x **C**), 78.9 (2 x **OCH**$(CH_3)_2$), 22.8 (2 x OCH(**C**$H_3)_2$)

LC-MS (ESI^+): 199 (86 %, $[M + H]^+$).

3,4-Di-*tert*-butoxycyclobut-3-ene-1,2-dione (2.26)

3-(*Tert*-butoxy)-4-methoxycyclobut-3-ene-1,2-dione (2.27)



1.8
$C_4H_2O_4$
Mol Wt: 114.06

2.26
$C_{12}H_{18}O_4$
Mol Wt: 226.27

2.27
$C_9H_{12}O_4$
Mol Wt: 184.19

To a solution of 3,4-dihydroxycyclobut-3-ene-1,2-dione (2.28 g, 20.0 mmol) in ^{t}BuOH (80 mL) at reflux was added trimethyl orthoformate (26.5 mL, 250 mmol) over 30 min. MeOH was removed *via* short-path distillation before being concentrated *in vacuo* after 18 h at reflux. Purification by column chromatography (5–10 % ethyl acetate/hexane) afforded firstly

cyclobutenedione **2.26** (2.54 g, 11.2 mmol, 56 %) as a white solid followed by cyclobutenedione **2.27** (206 mg, 1.12 mmol, 11 %) as a white solid.

3,4-Di-*tert*-butoxycyclobut-3-ene-1,2-dione (**2.26**)

Data consistent with literature[42]

MP: 100–102 °C (ethyl acetate/hexane)

δ_H (400 MHz, $CDCl_3$): 1.61 (s, 18H, 2 x OC($C\mathbf{H}_3$)$_3$)

δ_C (100 MHz, $CDCl_3$): 188.6 (2 x **C**), 186.3 (2 x **C**), 87.0 (2 x O**C**(CH_3)$_3$), 28.6 (2 x OC(**C**H_3)$_3$)

LC-MS (ESI^+): 227 (61 %, $[M + Na]^+$), 227 (13 %, $[M + H]^+$).

3-(*Tert*-butoxy)-4-methoxycyclobut-3-ene-1,2-dione (**2.27**)

Data consistent with literature[42]

MP: 94–95 °C (ethyl acetate/hexane)

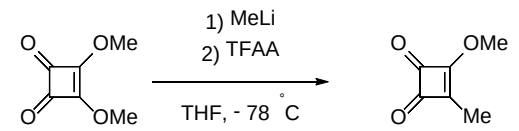
δ_H (400 MHz, $CDCl_3$): 4.40 (s, 3H, OC$\mathbf{H}_3$)

1.60 (s, 9H, OC($C\mathbf{H}_3$)$_3$)

δ_C (100 MHz, $CDCl_3$): 189.5 (**C**), 188.5 (**C**), 185.7 (**C**), 184.7 (**C**), 87.4 (O**C**(CH_3)$_3$), 60.8 (O**C**H_3), 28.6 (OC(**C**H_3)$_3$)

LC-MS (ESI^+): 207 (76 %, $[M + Na]^+$), 185 (8 %, $[M + H]^+$).

3-Methoxy-4-methylcyclobut-3-ene-1,2-dione (2.4)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.4
$C_6H_6O_3$
Mol Wt: 126.11

To a solution of cyclobutenedione **2.1** (1.10 g, 7.74 mmol) in THF (50 mL) at - 78 °C was added a solution of methyllithium (1.6 M in diethyl ether, 5.32 mL, 8.51 mmol) in THF (30 mL) dropwise *via* cannula. TFAA (1.42 mL, 10.06 mmol) was added after 90 min followed by sat. $NaHCO_3$ (30 mL) after 60 min and subsequent warming to RT. The aqueous phase

was separated and extracted with DCM (3x50 mL) then the organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was recrystallised (diethyl ether) to yield the title compound (618 mg, 4.90 mmol, 63 %) as a yellow, crystalline solid.

Data consistent with literature[77]

MP: 47-49 °C (diethyl ether)

δ_H (400 MHz, $CDCl_3$): 4.42 (s, 3H, OC**H**$_3$)

2.21 (s, 3H, C**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 199.3 (**C**), 195.9 (**C**), 193.4 (**C**), 180.1 (**C**), 60.9 (O**C**H_3), 9.5 (**C**H_3)

LC-MS (ESI^+): 127 (100 %, $[M + H]^+$).

3-Methoxy-4-methylcyclobut-3-ene-1,2-dione (2.66)

2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.66
$C_6H_6O_2$
Mol Wt: 110.11

To a solution of cyclobutenedione **2.1** (711 g, 5.00 mmol) in THF (100 mL) at - 78 °C was added methyllithium (1.6 M in diethyl ether, 9.40 mL, 15.0 mmol) followed after 3 h by TFAA (1.60 mL, 11.50 mmol). After 2 h, water (50 mL) was added and the solution warmed to RT. The aqueous phase was separated and extracted with DCM (3x60 mL) then the organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a red oil. Purification by column chromatography (30 % ethyl acetate/petroleum ether) gave the title compound (489 mg, 4.44 mmol, 88 %) as a yellow oil.

Data consistent with literature[6]

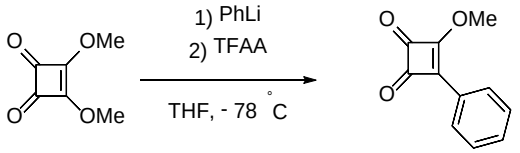
ν_{max}, (neat): 1764 (s), 1605 (s), 1433 (w), 1383 (m), 1308 (w), 1183 (m), 1019 (m), 911 (w), 754 (w), 680 (w)

δ_H (400 MHz, $CDCl_3$): 2.34 (s, 6H, 2 x C**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 199.9 (2 x **C**), 199.3 (2 x **C**), 10.9 (2 x **C**H_3)

LC-MS (ESI^+): 133 (2 %, $[M + Na]^+$), 111 (77 %, $[M + H]^+$).

3-Methoxy-4-phenylcyclobut-3-ene-1,2-dione (2.32)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.32
$C_{11}H_8O_3$
Mol Wt: 188.18

To a solution of cyclobutenedione **2.1** (800 mg, 5.63 mmol) in THF (40 mL) at - 78 °C was added phenyllithium (1.9 M in dibutyl ether, 3.85 mL, 7.32 mmol) followed after 90 min by TFAA (1.42 mL, 10.06 mmol). After 2 h sat. NH_4Cl (20 mL) was added and the solution warmed to RT before the aqueous phase was separated and extracted with DCM (3x50 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5-10 % ethyl acetate/petroleum ether) gave the title compound (744 mg, 3.96 mmol, 70 %) as a yellow, crystalline solid.

Data consistent with literature[78]

MP: 149-150 °C (diethyl ether)

δ_H (400 MHz, $CDCl_3$): 8.04-7.99 (m, 2H, 2 x Ar**H**)

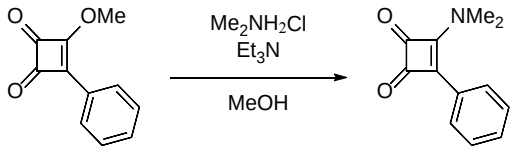
7.56-7.45 (m, 3H, 3 x Ar**H**)

4.59 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 194.8 (**C**), 192.7 (**C**), 192.3 (**C**), 173.7 (**C**), 132.7 (**C**H), 129.1 (2 x **C**H), 127.7 (2 x **C**H), 127.5 (**C**), 61.7 (O**C**H_3)

LC-MS (ESI^+): 189 (100 %, $[M + H]^+$).

3-(Dimethylamino)-4-phenylcyclobut-3-ene-1,2-dione (2.83)



2.32
$C_{11}H_8O_3$
Mol Wt: 188.18

2.83
$C_{12}H_{11}NO_2$
Mol Wt: 201.23

To a solution of cyclobutenedione **2.32** (345 mg, 1.83 mmol) in methanol (40 mL) was added Me_2NH_2Cl (194 mg, 2.38 mmol) followed by triethylamine (0.33 mL, 2.38 mmol). After 3 h the solution was concentrated *in vacuo* to an orange solid. Purification by column chromatography (50-60 % ethyl acetate/petroleum ether) gave the title compound (328 mg, 1.63 mmol, 89 %) as a yellow, crystalline solid.

MP: Dec. 115 °C

ν_{max}, (neat): 2934 (w), 1784 (s), 1765 (s), 1731 (s), 1606 (s), 1506 (w), 1435 (m), 1408 (s), 1230 (m), 1124 (w)

δ_H (400 MHz, $CDCl_3$): 7.60-7.54 (m, 2H, 2 x Ar**H**)

7.49-7.43 (m, 2H, 2 x Ar**H**)

7.43-7.37 (m, 1H, Ar**H**)

3.52 (s, 3H, $(CH_3)N(C\mathbf{H}_3)$)

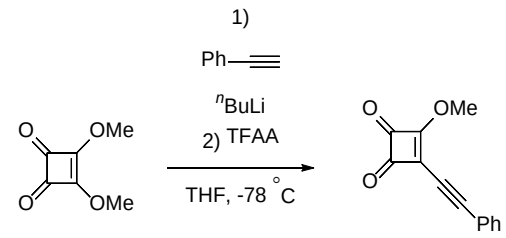
3.18 (s, 3H, $(C\mathbf{H}_3)N(CH_3)$)

δ_C (100 MHz, $CDCl_3$): 192.5 (**C**), 188.8 (**C**), 180.1 (**C**), 164.1 (**C**), 129.7 (**C**H), 128.7 (2 x **C**H), 128.5 (**C**), 127.7 (2 x **C**H), 41.7 $(CH_3)N(\mathbf{C}H_3)$, 39.7 $(\mathbf{C}H_3)N(CH_3)$

LC-MS (ESI^+): 224 (33 %, $[M + Na]^+$), 202 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{12}H_{11}NNaO_2$ $[M + Na]^+$ calculated 224.0682, observed 224.0687, $C_{12}H_{12}NO_2$ $[M + H]^+$ calculated 202.0863, observed 202.0869.

3-Methoxy-4-(phenylethynyl)cyclobut-3-ene-1,2-dione (2.33)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.33
$C_{13}H_8O_3$
Mol Wt: 212.20

To a solution of phenylacetylene (0.70 mL, 6.33 mmol) in THF (30 mL) at - 78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.03 mL, 5.06 mmol). After 30 min, this solution was added via cannula to a solution of cyclobutenedione **2.1** (600 mg, 4.22 mmol) in THF (50 mL) at -78 °C. After 90 min, TFAA (0.89 mL, 6.33 mmol) was added followed after 2 h by sat. $NaHCO_3$ (20 mL) and subsequent warming to RT. The aqueous phase was separated and extracted with DCM (3x40 mL) and the organic phases combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (10-20 % ethyl acetate/petroleum ether) gave the title compound (651 mg, 3.06 mmol, 73 %) as a yellow, crystalline solid.

Data consistent with literature[78]

MP: 141-142 °C (diethyl ether)

δ_H (400 MHz, $CDCl_3$): 7.60-7.53 (m, 2H, 2 x Ar**H**)

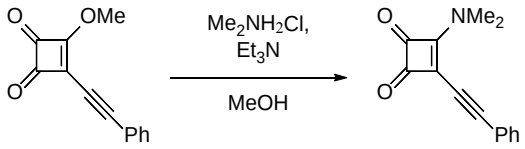
7.50-7.38 (m, 3H, 3 x Ar**H**)

4.54 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 196.1 (**C**), 194.5 (**C**), 190.3 (**C**), 161.1 (**C**), 132.0 (2 x **C**H), 130.8 (**C**H), 128.7 (2 x **C**H), 120.8 (**C**), 119.2 (**C**), 75.1 (**C**), 61.9 (O**C**H$_3$)

LC-MS (ESI^+): 213 (100 %, $[M + H]^+$).

3-(Dimethylamino)-4-(phenylethynyl)cyclobut-3-ene-1,2-dione (2.84)



2.33
$C_{13}H_8O_3$
Mol Wt: 212.20

2.84
$C_{14}H_{11}NO_2$
Mol Wt: 225.25

To a solution of cyclobutenedione **2.33** (400 mg, 1.89 mmol) in methanol (30 mL) was added Me_2NH_2Cl (169 mg, 2.07 mmol) followed by triethylamine (0.29 mL, 2.07 mmol). After 2 h the solution was concentrated *in vacuo* to an orange solid. Purification by column chromatography (40-60 % ethyl acetate/petroleum ether) gave the title compound (379 mg, 1.68 mmol, 89 %) as a yellow solid.

MP: Dec. 128 °C

ν_{max}, (neat): 2981 (m), 1784 (s), 1773 (s), 1735 (s), 1629 (s), 1598 (m), 1498 (m), 1446 (w), 1410 (m), 1239 (w)

δ_H (400 MHz, $CDCl_3$): 7.52-7.47 (m, 2H, 2 x Ar**H**)

7.43-7.32 (m, 3H, 3 x Ar**H**)

3.45 (s, 3H, $(CH_3)N(C\mathbf{H}_3)$)

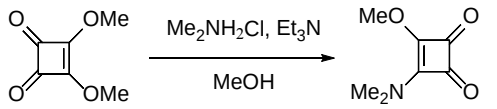
3.44 (s, 3H, $(C\mathbf{H}_3)N(CH_3)$)

δ_C (100 MHz, $CDCl_3$): 194.3 (**C**), 187.4 (**C**), 180.0 (**C**), 146.9 (**C**), 131.4 (2 x **C**H), 129.8 (**C**H), 128.6 (2 x **C**H), 121.8 (**C**), 114.3 (**C**), 77.4 (**C**), 40.1 $(CH_3)N(\mathbf{C}H_3)$, 39.5 $(\mathbf{C}H_3)N(CH_3)$

LC-MS (ESI^+): 248 (35 %, $[M + Na]^+$), 226 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{14}H_{11}NNaO_2$ $[M + Na]^+$ calculated 248.0682, observed 248.0686, $C_{14}H_{12}NO_2$ $[M + H]^+$ calculated 226.0863, observed 226.0865.

3-(Dimethylamino)-4-methoxycyclobut-3-ene-1,2-dione (2.34)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.34
$C_7H_9NO_3$
Mol Wt: 155.15

To a solution of cyclobutenedione **2.1** (500 mg, 3.51 mmol) in methanol (80 mL) was added Me_2NH_2Cl (286 mg, 3.51 mmol) followed by triethylamine (0.49 mL, 3.51 mmol). The solution was stirred for 2 h before being concentrated *in vacuo* to a yellow solid. Purification by column chromatography (60–80 % ethyl acetate/petroleum ether) gave the title compound (496 mg, 3.19 mmol, 91 %) as a white solid.

MP: 142-143 °C (ethyl acetate/hexane)

ν_{max}, (film): 2941 (br), 2358 (br), 1801 (m), 1700 (s), 1609 (s), 1497 (s), 1417 (m), 1393 (s), 1277 (m), 1187 (m)

δ_H (400 MHz, $CDCl_3$): 4.37 (s, 3H, OC**H**$_3$)

3.32 (s, 3H, (C**H**$_3$)N(CH_3))

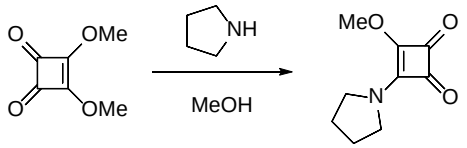
3.13 (s, 3H, (CH_3)N(C**H**$_3$))

δ_C (100 MHz, $CDCl_3$): 188.8 (**C**), 182.4 (**C**), 176.4 (**C**), 171.9 (**C**), 60.4 (O**C**H_3), 39.2 ((**C**H_3)N(CH_3)), 38.7 ((CH_3)N(**C**H_3))

LR-MS (ESI^+): 156 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_7H_9NNaO_3$ $[M + Na]^+$ calculated 178.0475, observed 178.0478.

3-Methoxy-4-(pyrrolidin-1-yl)cyclobut-3-ene-1,2-dione (2.36)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.36
$C_9H_{11}NO_3$
Mol Wt: 181.19

To a solution of cyclobutenedione **2.1** (500 mg, 3.51 mmol) in methanol (80 mL) was added pyrrolidine (0.29 mL, 3.51 mmol). The solution was stirred for 3 h before being concentrated *in vacuo* to a yellow solid. Purification by column chromatography (60 % ethyl acetate/petroleum ether) gave the title compound (540 mg, 2.98 mmol, 85 %) as a white solid.

MP: 139-141 °C (diethyl ether/petroleum ether)

ν_{max} (film): 2981 (br), 2885 (m), 2359 (br), 1792 (m), 1703 (s), 1649 (s), 1593 (w), 1489 (s), 1462 (s), 1405 (s)

δ_H (400 MHz, $CDCl_3$): 4.36 (s, 3H, OC**H**$_3$)

3.88-3.75 (m, 2H, 2×NC**H**H)

3.65-3.53 (m, 2H, 2×NCH**H**)

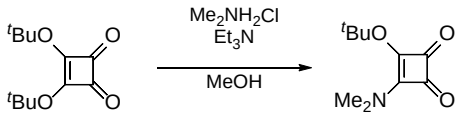
2.01-1.93 (m, 4H, 2 x C**H**$_2$)

δ_C (100 MHz, $CDCl_3$): 189.0 (**C**), 182.7 (**C**), 177.1 (**C**), 170.0 (**C**), 60.1 (O**C**H$_3$), 48.6 (**C**H$_2$), 48.5 (**C**H$_2$), 25.1 (**C**H$_2$), 24.8 (**C**H$_2$)

LR-MS (ESI^+): 182 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_9H_{12}NO_3$ $[M + H]^+$ calculated 182.0812, observed 182.0814.

3-(*Tert*-butoxy)-4-(dimethylamino)cyclobut-3-ene-1,2-dione (2.38)



2.26
$C_{12}H_{18}O_4$
Mol Wt: 226.27

2.38
$C_{10}H_{15}NO_3$
Mol Wt: 197.23

To a solution of cyclobutenedione **2.26** (679 mg, 3.00 mmol) in methanol (40 mL) was added Me_2NH_2Cl (245 mg, 3.00 mmol) followed by triethylamine (0.42 mL, 3.00 mmol). The solution was stirred for 24 h before being concentrated *in vacuo* to a yellow solid. Purification by column chromatography (20–50 % ethyl acetate/petroleum ether) afforded the title compound (496 mg, 3.19 mmol, 91 %) as a white solid.

MP: 129–130 °C (diethyl ether/hexane)

ν_{max} (film): 2952 (w), 2924 (w), 2852 (w), 1772 (m), 1663 (s), 1557 (s), 1522 (s), 1461 (w), 1445 (m), 1412 (s)

δ_H (400 MHz, $CDCl_3$): 3.34 (s, 3H, (C**H**$_3$)N(CH$_3$))

3.19 (s, 3H, (CH$_3$)N(C**H**$_3$))

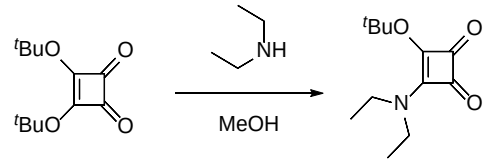
1.60 (s, 9H, OC(C**H**$_3$)$_3$)

δ_C (100 MHz, $CDCl_3$): 189.5 (**C**), 180.9 (**C**), 176.3 (**C**), 173.4 (**C**), 85.3 (O**C**(CH$_3$)$_3$), 39.0 ((**C**H$_3$)N(CH$_3$)), 38.8 ((CH$_3$)N(**C**H$_3$)), 28.8 (OC(**C**H$_3$)$_3$)

LR-MS (ESI^+): 220 (100 %, $[M + Na]^+$), 198 (45 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{10}H_{15}NNaO_3$ $[M + Na]^+$ calculated 220.0944, observed 220.0942, $C_{10}H_{16}NO_3$ $[M + H]^+$ calculated 198.1125, observed 198.1122.

3-(*Tert*-butoxy)-4-(diethylamino)cyclobut-3-ene-1,2-dione (2.40)



2.26
$C_{12}H_{18}O_4$
Mol Wt: 226.27

2.40
$C_{12}H_{19}NO_3$
Mol Wt: 225.29

To a solution of cyclobutenedione **2.26** (905 mg, 4.00 mmol) in methanol (70 mL) was added diethylamine (0.41 mL, 4.00 mmol). After 3 h, the solution was concentrated *in vacuo* and the crude material purified by column chromatography (10–20 % ethyl acetate/petroleum ether) to give the title compound (799 mg, 3.54 mmol, 89 %) as an off-white solid.

MP: 61–63 °C (diethyl ether)

ν_{max} (film): 2976 (m), 2360 (w), 1796 (m), 1704 (s), 1592 (s), 1426 (s), 1397 (w), 1371 (m), 1306 (s), 1270 (w)

δ_H (400 MHz, $CDCl_3$): 3.68 (q, *J*=7.2 Hz, 2H, C**H**$_2$)

3.45 (q, *J*=7.2 Hz, 2H, C**H**$_2$)

1.55 (s, 9H, OC(C**H**$_3$)$_3$)

1.194 (t, *J*=7.2 Hz, 3H, C**H**$_3$)

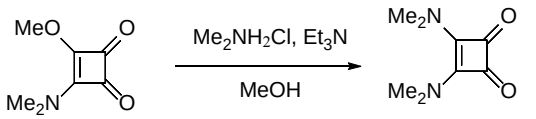
1.189 (t, *J*=7.2 Hz, 3H, C**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 189.4 (**C**), 180.7 (**C**), 176.2 (**C**), 172.7 (**C**), 84.9 (O**C**(CH$_3$)$_3$), 44.1 (**C**H$_2$), 43.6 (**C**H$_2$), 28.6 (OC(**C**H$_3$)$_3$), 14.5 (**C**H$_3$), 14.4 (**C**H$_3$)

LR-MS (ESI^+): 248 (73 %, $[M + Na]^+$), 226 (4 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{12}H_{19}NNaO_3$ $[M + Na]^+$ calculated 248.1257, observed 248.1259, $C_{12}H_{20}NO_3$ $[M + H]^+$ calculated 226.1438, observed 226.1441.

3,4-Bis(dimethylamino)cyclobut-3-ene-1,2-dione (2.56)



2.34
$C_7H_9NO_3$
Mol Wt: 155.15

2.56
$C_8H_{12}N_2O_2$
Mol Wt: 168.20

To a solution of cyclobutenedione **2.34** (310 mg, 2.00 mmol) in MeOH (35 mL) was added Me_2NH_2Cl (326 mg, 4.00 mmol) followed by triethylamine (0.56 mL, 4.00 mmol). After 18 h, the solution was concentrated *in vacuo* to a yellow solid before subsequent purification by column chromatography (0–10 % MeOH/ethyl acetate) to yield cyclobutenedione **2.56** (312 mg, 1.86 mmol, 93 %) as a white solid.

Data consistent with literature[79]

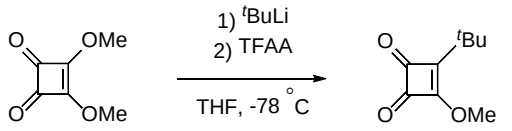
MP: 219–220 °C (diethyl ether)

δ_H (400 MHz, $CDCl_3$): 3.25 (s, 12H, 2 x N(C**H**$_3$)$_2$)

δ_C (100 MHz, $CDCl_3$): 183.9, (2 x **C**) 169.1 (2 x **C**), 41.4 (2 x N(**C**H$_3$)$_2$)

LC-MS (ESI^+): 191 (22 %, $[M + Na]^+$), 169 (100 %, $[M + H]^+$).

3-(*Tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione (2.63)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.63
$C_9H_{12}O_3$
Mol Wt: 168.19

To a solution of cyclobutenedione **2.1** (1.10 g, 7.74 mmol) in THF (50 mL) at - 78 °C was added a solution of ^{t}butyllithium (1.7 M in pentane, 5.01 mL, 8.51 mmol) in THF (50 mL) dropwise *via* cannula. TFAA (1.42 mL, 10.06 mmol) was added after 90 min followed by sat. NH4Cl (50 mL) after a further 60 min. The reaction mixture was warmed to RT before being diluted with water (100 mL). The aqueous phase was separated and extracted with DCM (3x100 mL) then the organic phases were combined, dried over $MgSO_4$ and concentrated

in vacuo. Purification by column chromatography (5–15 % ethyl acetate/hexane) yielded the title compound (1037 mg, 6.17 mmol, 80 %) as a yellow oil.

Data consistent with literature[78]

ν_{max} (film): 2966 (m), 2871 (w), 1790 (s), 1760 (s), 1736 (s), 1584 (s), 1482 (m), 1460 (m), 1398 (m), 1356 (s)

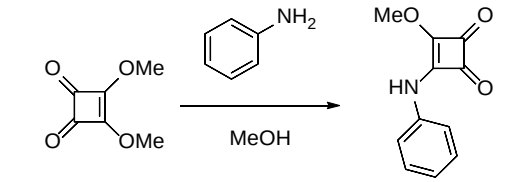
δ_H (400 MHz, $CDCl_3$): 4.43 (s, 3H, OC**H**$_3$)

1.31 (s, 9H, C(C**H**$_3$)$_3$)

δ_C (100 MHz, $CDCl_3$): 197.5 (**C**), 195.6 (**C**), 193.8 (**C**), 190.7 (**C**), 61.3 (O**C**H_3), 34.4 (**C**$(CH_3)_3$), 27.0 (C(**C**H_3)$_3$)

LR-MS (ESI^+): 169 (100 %, $[M + H]^+$).

3-Methoxy-4-(phenylamino)cyclobut-3-ene-1,2-dione (2.45)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.45
$C_{11}H_9NO_3$
Mol Wt: 203.20

To a solution of cyclobutenedione **2.1** (1.42 g, 10.00 mmol) in methanol (50 mL) was added aniline (0.91 mL, 10.0 mmol). The solution was stirred for 24 h before being concentrated *in vacuo* to yield the title compound (1.85 g, 9.11 mmol, 91 %) as a pale, yellow solid.

Data consistent with literature[80]

MP: Dec. 204 °C

δ_H (400 MHz, DMSO-d_6): 10.75 (br s, 1H, N**H**)

7.35 (app d, *J*=4.9 Hz, 4H, 4 x Ar**H**)

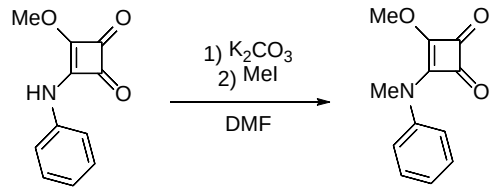
7.11 (app dt, *J*=8.6, 4.2 Hz, 1H, Ar**H**)

4.38 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, DMSO-d_6): 188.1 (**C**), 183.9 (**C**), 178.6 (**C**), 169.2 (**C**), 137.9 (**C**), 129.1 (2 x **C**H), 124.0 (**C**H), 119.6 (2 x **C**H), 60.5 (O**C**H_3)

LR-MS (ESI^+): 226 (15 %, $[M + Na]^+$), 204 (100 %, $[M + H]^+$).

3-Methoxy-4-(methyl(phenyl)amino)cyclobut-3-ene-1,2-dione (2.46)



2.45
$C_{11}H_9NO_3$
Mol Wt: 203.20

2.46
$C_{12}H_{11}NO_3$
Mol Wt: 217.22

To a solution of cyclobutenedione **2.45** (609 mg, 3.00 mmol) in DMF (15 mL) was added K_2CO_3 (621 mg, 4.50 mmol) followed after 30 min by MeI (0.37 mL, 6.00 mmol). The solution was stirred for 24 h before water (15 mL) was added. The aqueous phase was extracted with ethyl acetate (3x90 mL) and the organic phases were combined and washed with water (3x270 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (30 % ethyl acetate/petroleum ether) yielded the title compound (555 mg, 2.56 mmol, 85 %) as a pale, yellow solid.

MP: 157–159 °C (DCM/hexane)

ν_{max} (neat): 2946 (w), 1795 (m), 1712 (m), 1608 (s), 1579 (s), 1485 (s), 1455 (m), 1422 (m), 1382 (s), 1296 (m)

δ_H (400 MHz, $CDCl_3$): 7.45-7.38 (m, 2H, 2 x Ar**H**)

7.30 (m, 1H, Ar**H**)

7.20-7.14 (m, 2H, 2 x Ar**H**)

4.35 (br s, 3H, OC**H**$_3$)

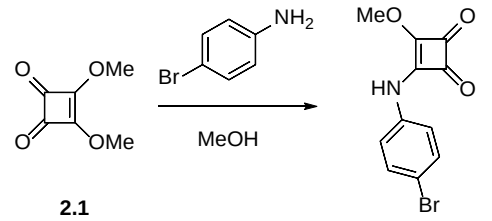
3.73 (br s, 3H, NC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 184.4 (**C**), 177.8 (**C**), 141.4 (**C**), 129.0 (2 x **C**H), 127.0 (**C**H), 123.0 (2 x **C**H), 60.6 (O**C**H_3), 39.3 (N**C**H_3), two **C** coincident or not observed

LR-MS (ESI^+): 240 (51 %, $[M + Na]^+$), 218 (100 %, $[M + H]^+$)

HR-MS (ESI$^+$): $C_{12}H_{11}NNaO_3$ [M + Na]$^+$ calculated 240.0631, observed 240.0633, $C_{12}H_{12}NO_3$ [M + H]$^+$ calculated 218.0812, observed 218.0814.

3-((4-Bromophenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (2.47)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.47
$C_{11}H_8BrNO_3$
Mol Wt: 282.09

To a solution of cyclobutenedione **2.1** (711 mg, 5.00 mmol) in methanol (25 mL) was added 4-bromoaniline (946 mg, 5.50 mmol). The solution was stirred for 24 h before being concentrated *in vacuo* to an orange solid. Purification by column chromatography (40-100 % ethyl acetate/petroleum ether) gave the title compound (1121 mg, 3.97 mmol, 79 %) as an off-white solid.

MP: Dec. 233 °C

ν_{max} (neat): 3243 (w), 3190 (w), 3095 (w), 2988 (br), 1794 (m), 1703 (m), 1609 (s), 1566 (s), 1511 (s), 1494 (m)

δ_H (400 MHz, DMSO-d_6): 10.81 (br s, 1H, N**H**)

7.56-7.50 (m, 2H, 2 x Ar**H**)

7.31 (br d, *J*=8.6 Hz, 2H, 2 x Ar**H**)

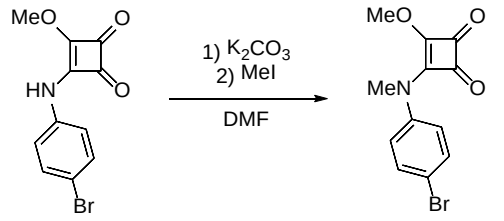
4.38 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, DMSO-d_6): 184.0 (C), 179.0 (**C**), 178.9 (**C**), 169.0 (**C**), 137.4 (**C**), 131.9 (2 x **C**H), 121.5 (2 x **C**H), 116.1 (**C**), 60.6 (O**C**H$_3$)

LR-MS (ESI$^+$): 284 (54 %, [M + H]$^+$, ^{81}Br), 282 (66 %, [M + H]$^+$, ^{79}Br)

HR-MS (ESI$^+$): $C_{11}H_9BrNO_3$ [M + H]$^+$ calculated 281.9760, observed 281.9755.

3-((4-Bromophenyl)(methyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (2.48)



2.47
$C_{11}H_8BrNO_3$
Mol Wt: 282.09

2.48
$C_{12}H_{10}BrNO_3$
Mol Wt: 296.12

To a solution of cyclobutenedione **2.47** (846 mg, 3.00 mmol) in DMF (15 mL) was added K_2CO_3 (621 mg, 4.50 mmol) followed after 30 min by MeI (0.37 mL, 6.00 mmol). The solution was stirred for 24 h before water (15 mL) was added. The aqueous phase was extracted with ethyl acetate (3x90 mL) and the organic phases were combined and washed with water (3x270 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Trituration by diethyl ether gave the title compound (713 mg, 2.41 mmol, 80 %) as a pale, yellow powder.

MP: 201–202 °C (DCM/hexane)

ν_{max} (neat): 2970 (br), 2360 (w), 1796 (s), 1712 (s), 1591 (s), 1570 (s), 1473 (s), 1427 (m), 1406 (m), 1362 (s)

δ_H (400 MHz, DMSO-d_6): 7.66-7.55 (m, 2H, 2 x Ar**H**)

7.35-7.24 (m, 2H, 2 x Ar**H**)

4.29 (s, 3H, OC**H**$_3$)

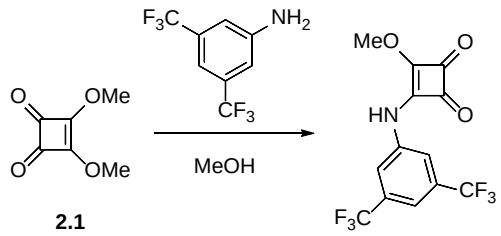
3.60 (s, 3H, NC**H**$_3$)

δ_C (100 MHz, DMSO-d_6): 184.0 (**C**), 178.2 (**C**), 170.2 (**C**), 140.7 (**C**), 131.5 (2 x **C**H), 125.2 (2 x **C**H), 118.9 (**C**), 60.6 (O**C**H$_3$), 38.7 (N**C**H$_3$), one **C** coincident or not observed

LR-MS (ESI$^+$): 298 (90 %, $[M + H]^+$, ^{81}Br), 296 (100 %, $[M + H]^+$, ^{79}Br)

HR-MS (ESI$^+$): $C_{12}H_{10}BrNNaO_3$ $[M + Na]^+$ calculated 317.9736, observed 317.9734, $C_{12}H_{11}BrNO_3$ $[M + H]^+$ calculated 295.9917, observed 295.9914.

3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (2.49)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.49
$C_{13}H_7F_6NO_3$
Mol Wt: 339.19

To a solution of cyclobutenedione **2.1** (711 mg, 5.00 mmol) in methanol (25 mL) was added 3,5-bis(trifluoromethyl)aniline (0.78 mL, 5.00 mmol). The solution was stirred for 48 h before being concentrated *in vacuo* to a yellow solid. Purification by column chromatography (20 % ethyl acetate/petroleum ether) gave the title compound (1091 mg, 3.21 mmol, 64 %) as a pale yellow solid.

MP: Dec. 193 °C

ν_{max} (neat): 3101 (w), 2972 (br), 1796 (w), 1735 (w), 1698 (m), 1629 (w), 1586 (s), 1534 (m), 1473 (m), 1373 (s)

δ_H (400 MHz, DMSO-d_6): 11.19 (br s, 1H, N**H**)

8.02 (app s, 2H, 2 x Ar**H**)

7.74 (br s, 1H, Ar**H**)

4.40 (s, 3H, OC**H**$_3$)

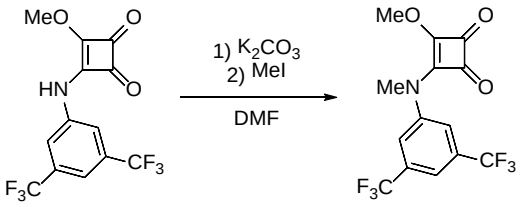
δ_C (100 MHz, DMSO-d_6): 187.4 (**C**), 184.5 (**C**), 179.9 (**C**), 169.1 (**C**), 140.2 (**C**), 131.2 (q, *J*=33.0 Hz, 2 x **C**CF_3), 123.1 (q, *J*=272.9 Hz, 2 x **C**F_3), 119.2 (app d, *J*=3.7 Hz, 2 x **C**H), 116.2 (app t, *J*=3.7 Hz, **C**H), 60.9 (**C**H_3)

δ_F (376MHz, DMSO-d_6): -61.96 (s, 6F, 2 x CF_3)

LR-MS (ESI^+): 340 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{13}H_7F_6NNaO_3$ $[M + Na]^+$ calculated 362.0222, observed 362.0220, $C_{13}H_8F_6NO_3$ $[M + H]^+$ calculated 340.0403, observed 340.0399.

3-((3,5-Bis(trifluoromethyl)phenyl)(methyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (2.50)



2.49
$C_{13}H_7F_6NO_3$
Mol Wt: 339.19

2.50
$C_{14}H_9F_6NO_3$
Mol Wt: 353.22

To a solution of cyclobutenedione **2.49** (1020 mg, 3.00 mmol) in DMF (15 mL) was added K_2CO_3 (621 mg, 4.50 mmol) followed after 30 min by MeI (0.37 mL, 6.00 mmol). The solution was stirred for 24 h before water (15 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 90 mL) and the organic phases were combined and washed with water (3x270 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to a yellow solid. Purification by column chromatography (15–20 % ethyl acetate/petroleum ether) gave the title compound (880 mg, 2.49 mmol, 83 %) as a pale yellow solid.

MP: 95–96 °C (diethyl ether)

ν_{max} (neat): 2988 (br), 2901 (br), 1796 (m), 1723 (m), 1572 (s), 1491 (s), 1460 (m), 1422 (w), 1392 (s), 1373 (s)

δ_H (400 MHz, $CDCl_3$): 7.76 (br s, 1H, Ar**H**)

7.59 (app s, 2H, 2 x Ar**H**)

4.41 (s, 3H, OC**H**$_3$)

3.80 (s, 3H, NC**H**$_3$)

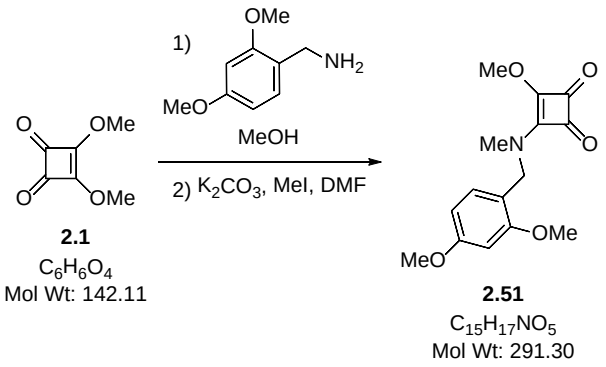
δ_C (100 MHz, $CDCl_3$): 187.4 (**C**), 184.9 (**C**), 178.8 (**C**), 170.3 (**C**), 142.3 (**C**), 132.5 (q, *J*=33.8 Hz, 2x **C**CF_3), 122.7 (q, *J*=237.1 Hz, 2 x **C**F_3), 122.3 (app d, *J*=3.6 Hz, 2 x **C**H), 119.7 (sept, *J*=3.7 Hz, **C**H), 61.0 (O**C**H_3), 38.5 (N**C**H_3)

δ_F (376MHz, $CDCl_3$): -63.38 (s, 6F, 2 x CF_3)

LR-MS (ESI^+): 354 (100 %, $[M + H]^+$)

HR-MS (ESI$^+$): $C_{14}H_9F_6NNaO_3$ [M + Na]$^+$ calculated 376.0379, observed 376.0381, $C_{14}H_{10}F_6NO_3$ [M + H]$^+$ calculated 354.0559, observed 354.0560.

3-((2,4-Dimethoxybenzyl)(methyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (2.51)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.51
$C_{15}H_{17}NO_5$
Mol Wt: 291.30

To a solution of cyclobutenedione **2.1** (711 mg, 5.00 mmol) in methanol (40 mL) was added 2,4-dimethoxybenzylamine (0.75 mL, 5.00 mmol). The solution was stirred for 24 h before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in DMF (15 mL) and K_2CO_3 (822 mg, 5.96 mmol) and MeI (0.49 mL, 7.94 mmol) was added sequentially. After 24 h, water (15 mL) was added and the aqueous phase extracted with ethyl acetate (3x30 mL). The organic phases were combined, washed with water (3x90 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (50 % ethyl acetate/petroleum ether) gave the title compound (1121 mg, 3.97 mmol, 79 %) as a yellow oil.

ν_{max} (neat): 3011 (w), 2942 (w), 1799 (m), 1702 (m), 1604 (s), 1492 (s), 1458 (m), 1420 (m), 1398 (s), 1334 (w)

Major rotamer:

δ_H (400 MHz, $CDCl_3$): 7.13 (d, *J*=8.8 Hz, 1H, Ar**H**)

6.48-6.42 (m, 2H, 2 x Ar**H**)

4.79 (s, 2H, C**H**$_2$)

4.36 (s, 3H, OC**H**$_3$)

3.79 (s, 3H, OC**H**$_3$)

3.76 (s, 3H, OC**H**$_3$)

2.96 (s, 3H, NC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 188.7 (**C**), 182.5 (**C**), 175.9 (**C**), 172.1 (**C**), 161.2 (**C**), 159.0 (**C**), 131.6 (**C**H), 115.3 (**C**), 104.3 (**C**H), 98.6 (**C**H) 60.2 (O**C**H$_3$), 55.3 (2 x O**C**H$_3$), 49.6 (**C**H$_2$), 35.8 (N**C**H$_3$)

Minor rotamer:

δ_H (400 MHz, $CDCl_3$): 7.05 (d, *J*=8.9 Hz, 1H, Ar**H**)

6.48-6.42 (m, 2H, 2 x Ar**H**)

4.49 (s, 2H, C**H**$_2$)

4.43 (s, 3H, OC**H**$_3$)

3.81 (s, 3H, OC**H**$_3$)

3.78 (s, 3H, OC**H**$_3$)

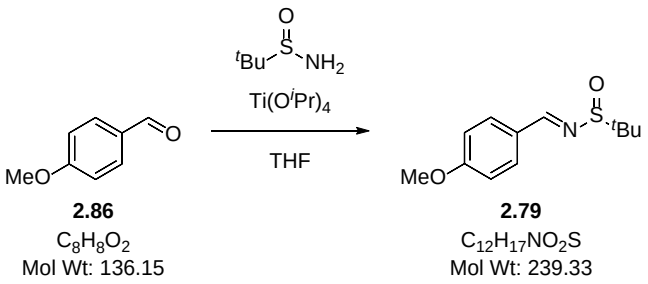
3.15 (s, 3H, NC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 189.0 (**C**), 182.6 (**C**), 176.4 (**C**), 171.8 (**C**), 161.3 (**C**), 159.0 (**C**), 130.9 (**C**H), 114.6 (C), 104.3 (**C**H), 98.6 (**C**H), 60.4 (O**C**H$_3$), 55.3 (2 x O**C**H$_3$), 50.7 (**C**H$_2$), 35.1 (N**C**H$_3$)

LR-MS (ESI^+): 314 (38 %, $[M + Na]^+$) 292 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{15}H_{17}NNaO_5$ $[M + Na]^+$ calculated 314.0999, observed 314.1006, $C_{15}H_{18}NO_5$ $[M + H]^+$ calculated 292.1179, observed 292.1185.

_N_-(4-Methoxybenzylidene)-2-methylpropane-2-sulfinamide (2.79)



2.86
$C_8H_8O_2$
Mol Wt: 136.15

2.79
$C_{12}H_{17}NO_2S$
Mol Wt: 239.33

To a solution of *p*-anisaldehyde (1.22 mL, 10.0 mmol) in THF (20 mL) was added *tert*-butanesulfinamide (1.21 g, 10.0 mmol) followed by $Ti(O^iPr)_4$ (8.88 mL, 30.0 mmol). The solution was stirred for 24 h before brine (20 mL) was added. The resultant suspension was filtered through Celite and washed with ethyl acetate (100 mL). The filtrate was added to water (50 mL) and the aqueous phase extracted with ethyl acetate (3x50 mL) before the organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (5–15 % ethyl acetate/petroleum ether) gave the title compound (2.02 g, 8.44 mmol, 84 %) as a pale yellow liquid that solidified upon standing.

Data consistent with literature[81]

MP: 87–88 °C (diethyl ether)

δ_H (400 MHz, $CDCl_3$): 8.51 (s, 1H, C**H**N)

7.82-7.78 (m, 2H, 2 x Ar**H**)

6.94-7.00 (m, 2H, 2 x Ar**H**)

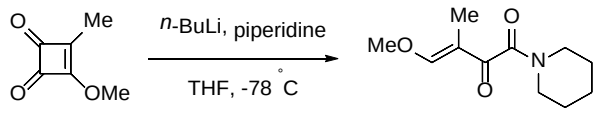
3.87 (s, 3H, OC$\mathbf{H}_3$)

1.25 (s, 9H, C(C$\mathbf{H}_3$)$_3$)

δ_C (100 MHz, $CDCl_3$): 163.0 (**C**), 161.7 (**C**H), 131.2 (2 x **C**H), 127.3 (**C**), 114.3 (2 x **C**H), 57.5 (**C**$(CH_3)_3$), 55.4 (O**C**H_3), 22.5 (C(**C**H_3)$_3$)

LR-MS (ESI^+): 262 (3 %, $[M + Na]^+$), 240 (100 %, $[M + H]^+$).

(*E*)-4-Methoxy-3-methyl-1-(piperidin-1-yl)but-3-ene-1,2-dione (2.5)



2.4
$C_6H_6O_3$
Mol Wt: 126.11

2.5
$C_{11}H_{17}NO_3$
Mol Wt: 211.26

To a solution of piperidine (0.10 mL, 1.05 mmol) in THF (10 mL) at 0 °C was added *n*-butyllithium (2.5M in hexanes, 0.42 mL, 1.05 mmol) dropwise. After 20 min the solution was added *via* cannula to a solution of cyclobutenedione **2.4** (126 mg, 1.0 mmol) in THF (30 mL) at - 78 °C. Water (10 mL) was added after 90 min and the reaction mixture warmed to RT. The aqueous phase was separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (30–80 % ethyl acetate/petroleum ether) gave the title compound (167 mg, 0.79 mmol, 79 %) as a yellow oil.

ν_{max} (film): 3482 (br), 2939 (br), 2858 (m), 1734 (br), 1612 (s), 1446 (m), 1395 (w), 1365 (w), 1314 (w), 1248 (s)

δ_H (400 MHz, $CDCl_3$): 7.16 (d, *J*=1.2 Hz, 1H, C**H**)

3.88 (s, 3H, C**H**$_3$)

3.57 (app t, *J*=5.4 Hz, 2H, C**H**$_2$)

3.21 (app t, *J*=5.4 Hz, 2H, C**H**$_2$)

1.70 (d, *J*=1.1 Hz, 3H, C**H**$_3$)

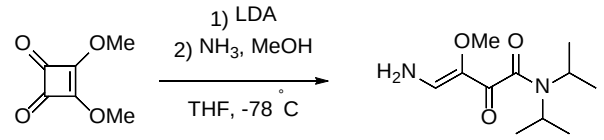
1.67-1.51 (m, 6H, 3 x C**H**$_2$)

δ_C (100 MHz, $CDCl_3$): 192.6 (**C**), 166.0 (**C**), 165.7 (**C**H), 115.1 (**C**), 62.0 (**C**H$_3$), 47.1 (**C**H$_2$), 42.1 (**C**H$_2$), 26.2 (**C**H$_2$), 25.4 (**C**H$_2$), 24.3 (**C**H$_2$), 6.9 (**C**H$_3$)

LR-MS (ESI^+): 212 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{11}H_{18}NO_3$ $[M + H]^+$ calculated 212.1281, observed 212.1283.

(*Z*)-4-Amino-*N,N*-diisopropyl-3-methoxy-2-oxobut-3-enamide (2.14)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.14
$C_{11}H_{20}N_2O_3$
Mol Wt: 228.29

To a solution of DIPA (0.16 mL, 1.11 mmol) in THF (10 mL) at 0 °C was added *n*-butyllithium (2.5 M in hexanes, 0.47 mL, 1.17 mmol) dropwise. After 20 min the solution was added *via* cannula to a solution of cyclobutenedione **2.1** (150 mg, 1.06 mmol) in THF (30 mL) at - 78 °C. Ammonia (7 M in methanol, 10 mL) was added after 2 h and the reaction mixture warmed to RT after 1 h. The aqueous phase was separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow solid. Purification by column chromatography (30–80 % ethyl acetate/petroleum ether) gave the title compound (171 mg, 0.75 mmol, 71 %) as a white solid.

MP: 216-218 °C (ethyl acetate/hexane)

ν_{max} (neat): 3371 (m), 3198 (br), 2982 (br), 2360 (m), 1665 (m), 1628 (s), 1612 (s), 1535 (s), 1469 (m), 1457 (m)

δ_H (400 MHz, DMSO-d_6): 6.98 (br s, 2H, N**H**$_2$)

6.78 (t, *J*=10.8 Hz, 1H, C**H**)

3.70 (spt, *J*=6.5 Hz, 1H, NC**H**(CH$_3$**)**$_2$)

3.51 (s, 3H, OC**H**$_3$)

3.49 (spt, *J*=6.7 Hz, 1H, C**H,** NC**H**(CH$_3$**)**$_2$)

1.35 (d, *J*=6.8 Hz, 6H, NCH(C**H**$_3$**)**$_2$)

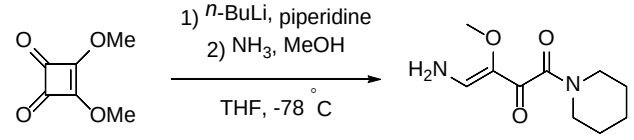
1.10 (d, *J*=6.5 Hz, 6H, NCH(C**H**$_3$**)**$_2$)

δ_C (100 MHz, DMSO-d_6): 183.4 (**C**), 167.6 (**C**), 144.5 (**C**H), 131.4 (**C**), 58.3 (O**C**H$_3$), 49.8 (N**C**H(CH$_3$**)**$_2$), 44.4 (N**C**H(CH$_3$**)**$_2$), 20.0 (NCH(**C**H$_3$**)**$_2$), 19.9 (NCH(**C**H$_3$**)**$_2$)

LR-MS (ESI^+): 229 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{11}H_{20}N_2NaO_3$ $[M + Na]^+$ calculated 251.1366, observed 251.1367.

(*Z*)-4-Amino-3-methoxy-1-(piperidin-1-yl)but-3-ene-1,2-dione (2.85)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.85
$C_{10}H_{16}N_2O_3$
Mol Wt: 212.25

To a solution of DIPA (0.16 mL, 1.11 mmol) in THF (10 mL) at 0 °C was added *n*-butyllithium (2.5 M in hexanes, 0.47 mL, 1.17 mmol) dropwise. After 20 min the solution was added *via* cannula to a solution of cyclobutenedione **2.1** (150 mg, 1.06 mmol) in THF (30 mL) at - 78 °C. Ammonia (7 M in methanol, 10 mL) was added after 2 h and the reaction mixture warmed to RT after 1 h. The aqueous phase was separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow solid. Purification by column chromatography (50-80 % ethyl acetate/hexane) gave the title compound (157 mg, 0.74 mmol, 70 %) as a white solid.

MP: 204-205 °C (ethyl acetate/hexane)

ν_{max} (neat): 3377 (m), 3288 (w), 3236 (w), 2932 (m), 2859 (w), 2360 (w), 1665 (w), 1628 (s), 1610 (s), 1540 (s)

δ_H (400 MHz, DMSO-d_6): 7.19-6.98 (m, 2H, N**H**$_2$)

6.86 (t, *J*=11.3 Hz, 1H, C**H**)

3.52 (s, 3H, OC**H**$_3$)

3.43 (t, *J*=5.6 Hz, 2H, C**H**$_2$)

3.22 (t, *J*=5.6 Hz, 2H, C**H**$_2$)

1.63-1.55 (m, 2H, C**H**$_2$)

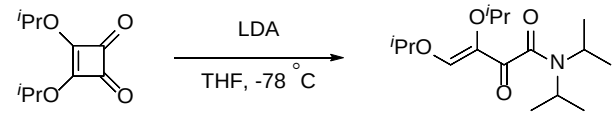
1.52-1.40 (m, 4H, 2 x C**H**$_2$)

δ_C (100 MHz, DMSO-d_6): 183.1 (**C**), 166.2 (**C**), 145.2 (**C**), 131.8 (**C**), 58.4 (O**C**H$_3$), 46.5 (**C**H$_2$), 41.0 (**C**H$_2$), 25.9 (**C**H$_2$), 25.1 (**C**H$_2$), 23.9 (**C**H$_2$)

LR-MS (ESI$^+$): 213 (100 %, $[M + H]^+$)

HR-MS (ESI$^+$): $C_{10}H_{16}N_2NaO_3$ $[M + Na]^+$ calculated 235.1053, observed 235.1052, $C_{10}H_{17}N_2O_3$ $[M + H]^+$ calculated 213.1234, observed 213.1232.

(*Z*)-3,4-Diisopropoxy-*N*,*N*-diisopropyl-2-oxobut-3-enamide (2.28)



2.25
$C_{10}H_{14}O_4$
Mol Wt: 198.22

2.28
$C_{16}H_{29}NO_4$
Mol Wt: 299.41

To a solution of cyclobutenedione **2.25** (198 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added LDA (1.0 M in THF/hexanes, 1.05 mL, 1.05 mmol) followed by water (20 mL) after 8 h. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated in vacuo to a red oil. Purification by column chromatography (20 % ethyl acetate/petroleum ether) gave the title compound (182 mg, 0.61 mmol, 61 %) as a yellow oil.

ν_{max} (film): 2975 (s), 2935 (w), 1619 (s), 1448 (m), 1372 (m), 1347 (m), 1212 (s), 1138 (m), 1098 (s), 1056 (w)

δ_H (400 MHz, $CDCl_3$): 7.05 (s, 1H, C**H**)

4.32 (spt, *J*=6.2 Hz, 1H, C**H**$(CH_3)_2$)

4.20 (spt, *J*=6.2 Hz, 1H, C**H**$(CH_3)_2$)

3.73 (spt, *J*=6.8 Hz, 1H, C**H**$(CH_3)_2$)

3.46 (spt, *J*=6.8 Hz, 1H, C**H**$(CH_3)_2$)

1.47 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3)_2$)

1.33 (d, *J*=6.2 Hz, 6H, CH(C**H**$_3$)$_2$)

1.24 (d, *J*=6.2 Hz, 6H, CH(C**H**$_3$)$_2$)

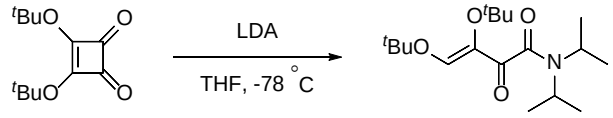
1.17 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3$)$_2$)

δ_C (100 MHz, $CDCl_3$): 189.3 (**C**), 167.1 (**C**), 152.3 (**C**H), 134.6 (**C**), 78.8 (**C**H(CH$_3$)$_2$), 74.4 (**C**H(CH$_3$)$_2$), 50.2 (**C**H(CH$_3$)$_2$), 45.7 (**C**H(CH$_3$)$_2$), 22.3 (CH(**C**H$_3$)$_2$), 22.3 (CH(**C**H$_3$)$_2$), 20.4 (CH(**C**H$_3$)$_2$), 20.0 (CH(**C**H$_3$)$_2$)

LR-MS (ESI^+): 322 (38 %, $[M + Na]^+$), 300 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{16}H_{29}NNaO_4$ $[M + Na]^+$ calculated 322.1989, observed 322.1991, $C_{16}H_{30}NO_4$ $[M + H]^+$ calculated 300.2169, observed 300.2165.

(*Z*)-3,4-Di-*tert*-butoxy-*N*,*N*-diisopropyl-2-oxobut-3-enamide (2.29)



2.26
$C_{12}H_{18}O_4$
Mol Wt: 226.27

2.29
$C_{18}H_{33}NO_4$
Mol Wt: 327.47

To a solution of cyclobutenedione **2.26** (226 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added LDA (1.0 M in THF/hexanes, 1.05 mL, 1.05 mmol) followed by water (20 mL) after 8 h. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a red oil. Purification by column chromatography (10-20 % ethyl acetate/petroleum ether) gave the title compound (184 mg, 0.56 mmol, 56 %) as a yellow oil.

ν_{max} (film): 2975 (br), 2936 (w), 1665 (w), 1613 (s), 1448 (m), 1370 (m), 1349 (w), 1269 (w), 1231 (m), 1216 (w)

δ_H (400 MHz, $CDCl_3$): 7.30 (s, 1H, C**H**)

3.76 (spt, *J*=6.6 Hz, 1H, C**H**(CH$_3$)$_2$)

3.46 (spt, *J*=6.8 Hz, 1H, C**H**(CH$_3$)$_2$)

1.49 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3$)$_2$)

1.38 (s, 9H, C(C**H**$_3$)$_3$), 1.33 (s, 9H, C(C**H**$_3$)$_3$)

1.15 (d, *J*=6.6 Hz, 6H, CH(C**H**$_3$)$_2$)

δ_C (100 MHz, $CDCl_3$): 190.3 (**C**), 167.8 (**C**), 152.5 (br, **C**H), 133.3 (**C**), 81.4 (**C**(CH$_3$)$_3$), 81.2 (**C**(CH$_3$)$_3$), 50.2 (**C**H(CH$_3$)$_2$), 45.7 (**C**H(CH$_3$)$_2$), 28.7 (C(**C**H$_3$)$_3$), 28.0 (C(**C**H$_3$)$_3$), 20.4 (CH(**C**H$_3$)$_2$), 20.1 (CH(**C**H$_3$)$_2$)

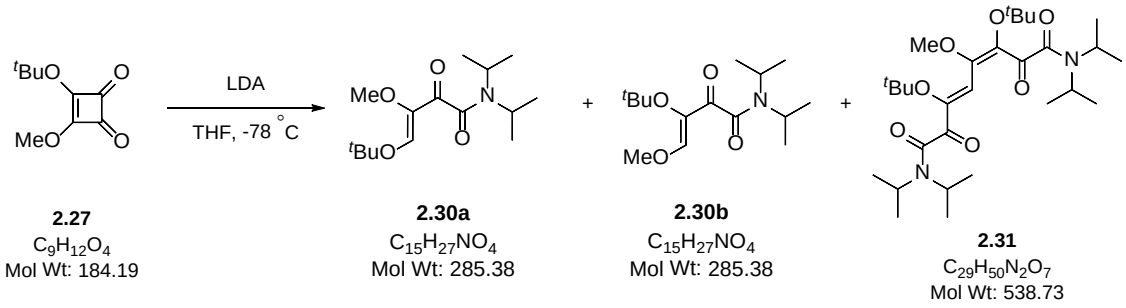
LR-MS (ESI^+): 350 (32 %, $[M + Na]^+$), 328 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{18}H_{33}NNaO_4$ $[M + Na]^+$ calculated 350.2302, observed 350.2311, $C_{18}H_{34}NO_4$ $[M + H]^+$ calculated 328.2482, observed 328.2487.

(*Z*)-4-(*tert*-butoxy)-*N*,*N*-diisopropyl-3-methoxy-2-oxobut-3-enamide (2.30a)

(*Z*)-3-(*tert*-butoxy)-*N*,*N*-diisopropyl-4-methoxy-2-oxobut-3-enamide (2.30b)

(3*Z*,5*Z*)-3,6-Di-tert-butoxy-*N*1,*N*1,*N*8,*N*8-tetraisopropyl-4-methoxy-2,7-dioxoocta-3,5-dienediamide (2.31)



2.27
$C_9H_{12}O_4$
Mol Wt: 184.19

2.30a
$C_{15}H_{27}NO_4$
Mol Wt: 285.38

2.30b
$C_{15}H_{27}NO_4$
Mol Wt: 285.38

2.31
$C_{29}H_{50}N_2O_7$
Mol Wt: 538.73

To a solution of cyclobutenedione **2.27** (184 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added LDA (1.0 M in THF/hexanes, 1.05 mL, 1.05 mmol) followed by water (20 mL) after 2 h. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (15-20 % ethyl acetate/petroleum ether) gave the firstly dimer **2.31** (123 mg, 0.23 mmol, 46 %) as a yellow oil followed by an inseparable mixture of isomers **2.30a** and **2.30b** (62 mg, 0.22 mmol, 22 %) as a pale yellow oil with a ratio of 3:1.

(3*Z*,5*Z*)-3,6-Di-tert-butoxy-*N*1,*N*1,*N*8,*N*8-tetraisopropyl-4-methoxy-2,7-dioxoocta-3,5-dienediamide (**2.31**)

ν_{max} (film): 2976 (s), 2937 (w), 1723 (m), 1645 (s), 1621 (s), 1578 (w), 1449 (m), 1371 (m), 1347 (m), 1319 (w)

δ_H (400 MHz, $CDCl_3$): 7.00 (s, 1H, C**H**)

3.69-3.62 (m, 2H, 2 x C**H**$(CH_3)_2$)

3.60 (s, 3H, OC**H**$_3$)

3.55-3.45 (m, 2H, 2 x C**H**$(CH_3)_2$)

1.51 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3)_2$)

1.50 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3)_2$)

1.38 (s, 9H, C(**C**$H_3)_3$)

1.36 (s, 9H, C(**C**$H_3)_3$)

1.21 (d, *J*=6.6 Hz, 6H, CH(C**H**$_3)_2$)

1.20 (d, *J*=6.6 Hz, 6H, CH(C**H**$_3)_2$)

δ_C (100 MHz, $CDCl_3$): 190.2 (**C**), 188.8 (**C**), 167.3 (**C**), 166.6 (**C**), 157.5 (**C**), 150.2 (**C**), 142.3 (**C**), 123.9 (**C**H), 85.9 (**C**$(CH_3)_3$), 83.7 (**C**$(CH_3)_3$), 60.1 (OCH_3), 50.5 (**C**H$(CH_3)_2$), 50.2 (**C**H$(CH_3)_2$), 46.1 (**C**H$(CH_3)_2$), 45.4 (**C**H$(CH_3)_2$), 29.1 (C(**C**$H_3)_3$), 28.7 (C(**C**$H_3)_3$), 20.5 (CH(**C**$H_3)_2$), 20.4 (CH(**C**$H_3)_2$), 20.3 (CH(**C**$H_3)_2$), 20.2 (CH(**C**$H_3)_2$)

LR-MS (ESI^+): 562 (89 %, $[M + Na]^+$), 539 (2 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{29}H_{50}N_2NaO_7$ $[M + Na]^+$ calculated 561.3510, observed 561.3515.

(*Z*)-4-(*Tert*-butoxy)-*N*,*N*-diisopropyl-3-methoxy-2-oxobut-3-enamide (**2.30a**) and (*Z*)-3-(*tert*-butoxy)-*N*,*N*-diisopropyl-4-methoxy-2-oxobut-3-enamide (**2.30b**)

ν_{max} (film): 2978 (m), 2938 (w), 1622 (s), 1473 (w), 1448 (m), 1369 (m), 1348 (w), 1250 (m), 1146 (s), 1058 (w)

Major isomer:

δ_H (400 MHz, $CDCl_3$): 6.98 (s, 1H, C**H**)

3.88 (s, 3H, OC**H**$_3$)

3.73 (spt, *J*=6.6 Hz, 1H, C**H**(CH$_3$)$_2$)

3.48 (spt, *J*=6.8 Hz, 1H, C**H**(CH$_3$)$_2$)

1.49 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3$)$_2$)

1.34 (s, 9H, C(C**H**$_3$)$_3$)

1.18 (d, *J*=6.6 Hz, 6H, CH(C**H**$_3$)$_2$)

δ_C (100 MHz, $CDCl_3$): 190.0 (**C**), 167.4 (**C**), 158.0 (**C**H), 133.2 (**C**), 81.9 (**C**(CH$_3$)$_3$), 62.3 (O**C**H$_3$), 50.24 (**C**H(CH$_3$)$_2$), 45.8 (**C**H(CH$_3$)$_2$), 28.6 (C(**C**H$_3$)$_3$), 20.4 (CH(**C**H$_3$)$_2$), 20.12 (CH(**C**H$_3$)$_2$)

Minor isomer:

δ_H (400 MHz, $CDCl_3$): 7.20 (s, 1H, C**H**)

3.77 (s, 3H, OCH$_3$)

3.73 (spt, *J*=6.6 Hz, 1H, C**H**(CH$_3$)$_2$)

3.48 (spt, *J*=6.8 Hz, 1H, C**H**(CH$_3$)$_2$)

1.49 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3$)$_2$)

1.41 (s, 9H, C(C**H**$_3$)$_3$)

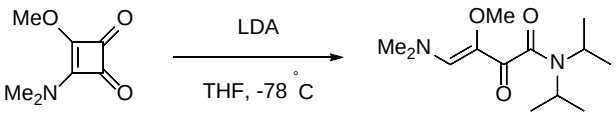
1.19 (br d, *J*=6.6 Hz, 6H, CH(C**H**$_3$)$_2$)

δ_C (100 MHz, $CDCl_3$): 137.3 (**C**), 81.4 (**C**(CH$_3$)$_3$), 60.1 (O**C**H$_3$),), 50.22 (**C**H(CH$_3$)$_2$), 45.7 (**C**H(CH$_3$)$_2$), 28.0 (C(**C**H$_3$)$_3$), 20.5 (CH(**C**H$_3$)$_2$), 20.06 (CH(**C**H$_3$)$_2$), three **C** coincident or not observed

LR-MS (ESI^+): 308 (21 %, $[M + Na]^+$), 286 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{15}H_{27}NNaO_4$ $[M + Na]^+$ calculated 308.1832, observed 308.1835, $C_{15}H_{28}NO_4$ $[M + H]^+$ calculated 286.2013, observed 286.2013.

(*Z*)-4-(Dimethylamino)-*N*,*N*-diisopropyl-3-methoxy-2-oxobut-3-enamide (2.35)



2.34
$C_7H_9NO_3$
Mol Wt: 155.15

2.35
$C_{13}H_{24}N_2O_3$
Mol Wt: 256.35

To a solution of cyclobutenedione **2.34** (155 mg, 1.00 mmol) in THF (40 mL) at - 78 °C was added LDA (2.0 M in THF/ethylbenzene/hexanes, 0.53 mL, 1.05 mmol) followed by water (10 mL) after 90 min. The reaction mixture was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (50–80 % ethyl acetate/petroleum ether) gave the title compound (173 mg, 0.67 mmol, 67 %) as a yellow oil.

ν_{max} (film): 3482 (br), 2970 (m), 2932 (br), 2359 (br), 1654 (w), 1629 (m), 1560 (s), 1445 (m), 1421 (m), 1404 (m)

δ_H (400 MHz, $CDCl_3$): 6.50 (s, 1H, C**H**)

3.88 (spt, *J*=6.6 Hz, 1H, C**H**, NC**H**$(CH_3)_2$)

3.66 (s, 3H, OC**H**$_3$)

3.43 (spt, *J*=6.8 Hz, 1H, C**H**, NC**H**$(CH_3)_2$)

3.11 (s, 6H, N(C**H**$_3)_2$)

1.46 (d, *J*=6.8 Hz, 6H, NCH(C**H**$_3)_2$)

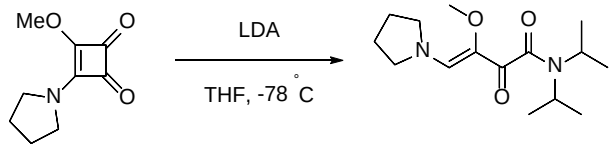
1.16 (d, *J*=6.6 Hz, 6H, NCH(C**H**$_3)_2$)

δ_C (100 MHz, $CDCl_3$): 185.9 (**C**), 168.2 (**C**), 145.7 (**C**H), 131.1 (**C**), 60.5 (O**C**H_3), 50.3 (N**C**H$(CH_3)_2$), 45.5 (N**C**H$(CH_3)_2$), 42.5 (br s, N(**C**$H_3)_2$) 20.5 (NCH(**C**$H_3)_2$), 20.1 (NCH(**C**$H_3)_2$)

LR-MS (ESI^+): 257 (100 %, $[M + H]^+$)

HR-MS (ESI$^+$): $C_{13}H_{24}N_2NaO_3$ [M + Na]$^+$ calculated 279.1679, observed 279.1679, $C_{13}H_{25}N_2O_3$ [M + H]$^+$ calculated 257.1860, observed 257.1862.

(*Z*)-*N*,*N*-Diisopropyl-3-methoxy-2-oxo-4-(pyrrolidin-1-yl)but-3-enamide (2.37)



2.36
$C_9H_{11}NO_3$
Mol Wt: 181.19

2.37
$C_{15}H_{26}N_2O_3$
Mol Wt: 282.38

To a solution of cyclobutenedione **2.36** (181 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added LDA (2.0M in THF/ethylbenzene/hexanes, 0.53 mL, 1.05 mmol) followed by water (10 mL) after 90 min. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (50-80 % ethyl acetate/petroleum ether) gave the title compound (183 mg, 0.65 mmol, 65 %) as a yellow oil.

ν_{max} (film): 3481 (br), 2970 (m), 2875 (br), 2359 (br), 1629 (s), 1565 (s), 1443 (m), 1410 (m), 1365 (m), 1340 (w)

δ_H (400 MHz, $CDCl_3$): 6.76 (s, 1H, C**H**)

3.89 (spt, *J*=6.6 Hz, 1H, C**H**$(CH_3)_2$)

3.65 (s, 3H, OC**H**$_3$)

3.55 (br s, 4H, 2 x C**H**$_2$)

3.41 (spt, *J*=6.8 Hz, 1H, C**H**$(CH_3)_2$)

1.89 (br s, 4H, 2 x C**H**$_2$)

1.44 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3)_2$)

1.14 (d, *J*=6.6 Hz, 6H, CH(C**H**$_3)_2$)

δ_C (100 MHz, $CDCl_3$): 185.3 (**C**), 168.3 (**C**), 142.6 (**C**H), 131.4 (**C**), 61.0 (O**C**H_3), 54.1 (br, 2 x CH_2), 50.2 (**C**H(CH_3)$_2$), 45.5 (**C**H(CH_3)$_2$), 25.1 (br, 2 x CH_2), 20.5 (CH(**C**H_3)$_2$), 20.0 (CH(**C**H_3)$_2$)

LR-MS (ESI^+): 283 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{15}H_{27}N_2O_3$ $[M + H]^+$ calculated 283.2016, observed 283.2020.

(*Z*)-3-(*Tert*-butoxy)-4-(dimethylamino)-*N*,*N*-diisopropyl-2-oxobut-3-enamide (2.39)

2.38
$C_{10}H_{15}NO_3$
Mol Wt: 197.23

2.39
$C_{16}H_{30}N_2O_3$
Mol Wt: 298.43

To a solution of cyclobutenedione **2.38** (100 mg, 0.51 mmol) in THF (20 mL) at -78 °C was added LDA (1.0 M in THF/hexanes, 0.56 mL, 0.56 mmol) followed by water (20 mL) after 2 h. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x20 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (50 % ethyl acetate/petroleum ether) gave the title compound (126 mg, 0.42 mmol, 83 %) as a yellow oil which solidified upon standing.

MP: 112–113 °C (diethyl ether)

ν_{max} (film): 2972 (m), 2932 (m), 1629 (s), 1572 (s), 1445 (m), 1421 (w), 1365 (s), 1279 (s), 1204 (m), 1166 (w)

δ_H (400 MHz, $CDCl_3$): 6.63 (s, 1H, C**H**)

3.88 (spt, *J*=6.6 Hz, 1H, C**H**(CH_3)$_2$)

3.42 (spt, *J*=6.8 Hz, 1H, C**H**(CH_3)$_2$)

3.10 (br s, 6H, N(C**H**$_3$)$_2$),

1.47 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3$)$_2$)

1.32 (s, 9H, C(C**H**$_3$)$_3$)

1.14 (d, *J*=6.6 Hz, 6H, CH(C**H**$_3$)$_2$)

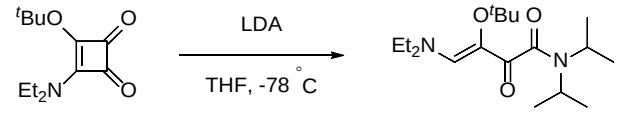
δ_C (100 MHz, $CDCl_3$): 187.9 (**C**), 169.2 (**C**), 148.5 (**C**H), 126.5 (**C**), 80.9 (**C**$(CH_3)_3$), 50.2 (**C**H$(CH_3)_2$), 45.5 (**C**H$(CH_3)_2$), 42.5 (br, N(**C**$H_3)_2$), 28.4 (C(**C**$H_3)_3$), 20.4 (CH(**C**$H_3)_2$), 20.1 (CH(**C**$H_3)_2$)

LR-MS (ESI^+): 321 (14 %, $[M + Na]^+$), 299 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{16}H_{30}N_2NaO_3$ $[M + Na]^+$ calculated 321.2149, observed 321.2151, $C_{16}H_{31}N_2O_3$ $[M + H]^+$ calculated 299.2329, observed 299.2329.

Crystallographic data for **2.39** can be obtained in Appendix A.

(*Z*)-3-(*tert*-Butoxy)-4-(diethylamino)-*N*,*N*-diisopropyl-2-oxobut-3-enamide (2.41)



2.40
$C_{12}H_{19}NO_3$
Mol Wt: 225.29

2.41
$C_{18}H_{34}N_2O_3$
Mol Wt: 326.48

To a solution of DIPA (0.17 mL, 1.20 mmol) in THF (15 mL) at 0 °C, *n*-butyllithium (2.5 M in hexane, 0.48 mL, 1.2 mmol) was added dropwise. After 20 min, the solution was added *via* cannula to a solution of cyclobutenedione **2.40** (225 mg, 1.00 mmol) in THF (15 mL) at -78 °C. Water (10 mL) was added after 90 min and the solution warmed to RT. The aqueous phase was separated and extracted with DCM (3x30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (20–40 % ethyl acetate/petroleum ether) afforded recovered starting material (81 mg, 0.36 mmol, 36 %) as a white solid followed by the title compound (161 mg, 0.49 mmol, 49 %) as a colourless oil.

ν_{max}, (film): 2972 (br), 2934 (w), 2359 (w), 1629 (m), 1569 (s), 1444 (m), 1367 (m), 1307 (w), 1253 (s), 1212 (w)

δ_H (400 MHz, $CDCl_3$): 6.67 (s, 1H, C**H**)

3.87 (spt, *J*=6.6 Hz, 1H, C**H**$(CH_3)_2$)

3.40 (br s, 4H, N(C**H**$_2CH_3)_2$)

3.39 (spt, *J*=6.8 Hz, 1H, C**H**$(CH_3)_2$)

1.45 (d, *J*=6.8 Hz, 6H, 2 x CH(C**H**$_3)_2$)

1.29 (s, 9H, C(C**H**$_3)_3$)

1.12 (br t, 6H, N(CH_2C**H**$_3)_2$)

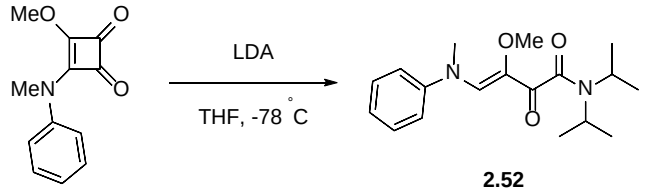
1.11 (d, *J*=6.6 Hz, 6H, CH(C**H**$_3)_2$)

δ_C (100 MHz, $CDCl_3$): 187.8 (**C**), 169.3 (**C**), 146.8 (**C**H), 126.5 (**C**), 81.2 (**C**$(CH_3)_3$), 50.2 (N**C**H$(CH_3)_2$), 45.4 (N**C**H$(CH_3)_2$), 42.7 (br, N(**C**$H_2CH_3)_2$), 28.4 (C(**C**$H_3)_3$), 20.3 (CH(**C**$H_3)_2$), 20.0 (CH(**C**$H_3)_2$), 13.8 (N(CH_2**C**$H_3)_2$)

LR-MS (ESI^+): 327 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{18}H_{34}N_2NaO_3$ $[M + Na]^+$ calculated 349.2462, observed 349.2470, $C_{18}H_{35}N_2O_3$ $[M + H]^+$ calculated 327.2642, observed 327.2649.

(*Z*)-*N*,*N*-Diisopropyl-3-methoxy-4-(methyl(phenyl)amino)-2-oxobut-3-enamide (2.52)



2.46
$C_{12}H_{11}NO_3$
Mol Wt: 217.22

2.52
$C_{18}H_{26}N_2O_3$
Mol Wt: 318.42

To a solution of cyclobutenedione **2.46** (217 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added LDA (2.0M in THF/ethylbenzene/hexanes, 0.60 mL, 1.20 mmol) followed by water (20 mL) after 2 h. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a red oil. Purification by column chromatography (25–30 % ethyl acetate/petroleum ether) yielded the title compound (133 mg, 0.42 mmol, 42 %) as a red oil.

ν_{max} (film): 2969 (m), 2934 (m), 1631 (s), 1605 (m), 1577 (s), 1495 (m), 1445 (m), 1351 (m), 1298 (s), 1273 (m)

δ_H (400 MHz, $CDCl_3$): 7.39-7.31 (m, 2H, 2 x Ar**H**)

7.17-7.11 (m, 3H, 3 x Ar**H**)

7.11 (br s, 1H, C**H**)

3.90 (spt, *J*=6.6 Hz, 1H, C**H**$(CH_3)_2$)

3.73 (br s, 3H, NC$\mathbf{H}_3$)

3.67 (s, 3H, OC$\mathbf{H}_3$)

3.46 (spt, *J*=6.8 Hz, 1H, C**H**$(CH_3)_2$)

1.46 (d, *J*=6.8 Hz, 6H, CH(C$\mathbf{H}_3)_2$)

1.20 (d, *J*=6.6 Hz, 6H, CH(C$\mathbf{H}_3)_2$)

δ_C (100 MHz, $CDCl_3$): 187.9 (**C**), 167.9 (**C**), 146.9 (**C**H), 133.8 (**C**), 129.4 (2 x **C**H), 127.1 (**C**), 124.6 (**C**H), 119.4 (2 x **C**H), 60.9 (br s, **C**H_3), 50.3 (**C**H_3), 45.7 (**C**H$(CH_3)_2$), 37.3 (**C**H$(CH_3)_2$), 20.6 (CH(**C**$H_3)_2$), 20.1 (CH(**C**$H_3)_2$)

LR-MS (ESI^+): 341 (23 %, $[M + Na]^+$), 319 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{18}H_{26}N_2NaO_3$ $[M + Na]^+$ calculated 341.1836, observed 341.1845, $C_{18}H_{27}N_2O_3$ $[M + H]^+$ calculated 319.2016, observed 319.2019.

(*Z*)-4-((4-Bromophenyl)(methyl)amino)-*N*,*N*-diisopropyl-3-methoxy-2-oxobut-3-enamide (2.53)

2.48
$C_{12}H_{10}BrNO_3$
Mol Wt: 296.12

2.53
$C_{18}H_{25}BrN_2O_3$
Mol Wt: 397.31

To a solution of cyclobutenedione **2.48** (296 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added LDA (2.0M in THF/ethylbenzene/hexanes, 0.60 mL, 1.20 mmol) followed by water (20 mL) after 2 h. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and

concentrated *in vacuo* to a red oil. Purification by column chromatography (20–30 % ethyl acetate/petroleum ether) gave the title compound (257 mg, 0.65 mmol, 65 %) as a red solid.

MP: 171-173 °C (DCM/hexane)

ν_{max} (film): 2972 (br), 2935 (br), 1630 (s), 1600 (s), 1572 (s), 1491 (s), 1446 (s), 1446 (m), 1415 (w), 1370 (w)

δ_H (400 MHz, $CDCl_3$): 7.48-7.44 (m, 2H, 2 x Ar**H**)

7.04 (br s, 1H, C**H**)

7.02-6.96 (m, 2H, 2 x Ar**H**)

3.87 (spt, *J*=6.6 Hz, 1H, C**H**$(CH_3)_2$)

3.71 (s, 3H, NC$\mathbf{H}_3$)

3.62 (s, 3H, OC$\mathbf{H}_3$)

3.47 (spt, *J*=6.8 Hz, 1H, C**H**$(CH_3)_2$)

1.46 (d, *J*=6.8 Hz, 6H, CH(C$\mathbf{H}_3)_2$)

1.19 (d, *J*=6.6 Hz, 6H, CH(C$\mathbf{H}_3)_2$)

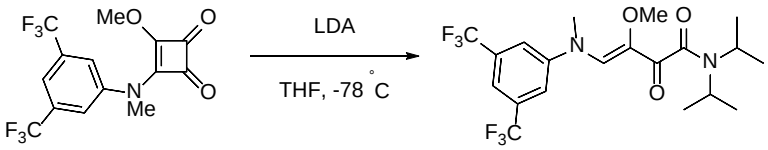
δ_C (100 MHz, $CDCl_3$): 188.0 (**C**), 167.8 (**C**), 145.8 (**C**H), 134.3 (**C**), 132.4 (2 x **C**H), 120.8 (2 x **C**H), 117.4 (**C**), 61.0 (**C**H_3), 50.3 (**C**H_3), 45.7 (**C**H$(CH_3)_2$), 37.4 (**C**H$(CH_3)_2$), 20.6 (CH(**C**$H_3)_2$), 20.1 (CH(**C**$H_3)_2$), one **C** coincident or not observed

LR-MS (ESI^+): 421 (24 %, $[M + Na]^+$, ^{81}Br), 419 (25 %, $[M + Na]^+$, ^{79}Br), 399 (100 %, $[M + H]^+$, ^{81}Br), 397 (90 %, $[M + H]^+$, ^{79}Br)

HR-MS (ESI^+): $C_{18}H_{25}BrN_2NaO_3$ $[M + Na]^+$ calculated 419.0941, observed 419.0940, $C_{18}H_{26}BrN_2O_3$ $[M + H]^+$ calculated 397.1121, observed 397.1118.

Crystallographic data for **2.53** can be obtained within Appendix A.

(*Z*)-4-((3,5-Bis(trifluoromethyl)phenyl)(methyl)amino)-*N*,*N*-diisopropyl-3-methoxy-2-oxobut-3-enamide (2.54)



2.50
$C_{14}H_9F_6NO_3$
Mol Wt: 353.22

2.54
$C_{20}H_{24}F_6N_2O_3$
Mol Wt: 454.41

To a solution of cyclobutenedione **2.50** (353 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added LDA (2.0 M in THF/ethylbenzene/hexanes, 0.60 mL, 1.20 mmol) followed by water (20 mL) after 2 h. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a red oil. Purification by column chromatography (20 % ethyl acetate/petroleum ether) gave the title compound (282 mg, 0.62 mmol, 62 %) as a red oil.

ν_{max} (film): 2976 (br), 1629 (s), 1594 (s), 1473 (w), 1384 (s), 1352 (w), 1277 (s), 1263 (m), 1218 (w), 1185 (s)

δ_H (400 MHz, $CDCl_3$): 7.60 (br s, 1H, Ar**H**)

7.47 (app s, 2H, 2 x Ar**H**)

7.03 (s, 1H, C**H**)

3.86 (spt, *J*=6.7 Hz, 1H, NC**H**$(CH_3)_2$)

3.72 (s, 3H, NC**H**$_3$)

3.69 (s, 3H, OC**H**$_3$)

3.50 (spt, *J*=6.8 Hz, 1H, NC**H**$(CH_3)_2$)

1.48 (d, *J*=6.8 Hz, 6H, NCH(C**H**$_3)_2$)

1.23 (d, *J*=6.7 Hz, 6H, NCH(C**H**$_3)_2$)

δ_C (100 MHz, $CDCl_3$): 188.3 (**C**), 167.2 (**C**), 147.3 (**C**H), 135.9 (**C**), 132.9 (q, *J*=33.8 Hz, 2 x **C**CF_3), 122.9 (q, *J*=272.9 Hz, 2 x **C**F3), 118.1 (app d, *J*=3.7 Hz, 2 x **C**H),

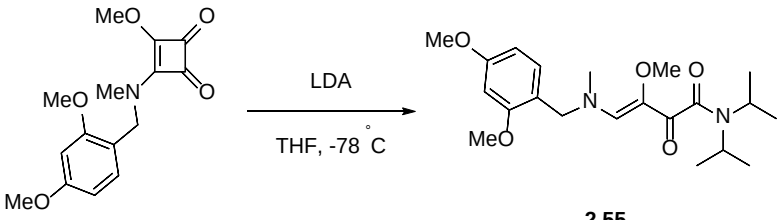
116.9 (app t, *J*=3.7 Hz, **C**H), 60.8 (**C**H_3), 50.4 (N**C**H(CH_3)$_2$), 45.9 (N**C**H(CH_3)$_2$), 37.3 (N**C**H_3), 20.6 (NCH(**C**H_3)$_2$), 20.0 (NCH(**C**H_3)$_2$), one **C** coincident or not observed

δ_F ($CDCl_3$, 376MHz): -63.19 (s, 6F, 2 x C**F**$_3$)

LR-MS (ESI^+): 477 (5 %, $[M + Na]^+$), 455 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{20}H_{24}F_6N_2NaO_3$ $[M + Na]^+$ calculated 477.1583, observed 477.1586, $C_{20}H_{25}F_6N_2O_3$ $[M + H]^+$ calculated 455.1764, observed 455.1763.

(*Z*)-4-((2,4-Dimethoxybenzyl)(methyl)amino)-*N*,*N*-diisopropyl-3-methoxy-2-oxobut-3-enamide (2.55)



2.51
$C_{15}H_{17}NO_5$
Mol Wt: 291.30

2.55
$C_{21}H_{32}N_2O_5$
Mol Wt: 392.50

To a solution of cyclobutenedione **2.51** (291 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added LDA (1.0M in THF, 1.10 mL, 1.10 mmol) followed by water (20 mL) after 2 h. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a red oil. Purification by column chromatography (50–80 % ethyl acetate/petroleum ether) gave the title compound (165 mg, 0.42 mmol, 42 %) as a red oil.

ν_{max} (film): 2935 (m), 2838 (w), 1629 (m), 1613 (s), 1569 (s), 1508 (m), 1441 (m), 1410 (m), 1368 (w), 1288 (s)

δ_H (400 MHz, $CDCl_3$): 7.05 (br d, *J*=8.1 Hz, 1H, Ar**H**)

6.70 (br s, 1H, Ar**H**)

6.46 (s, 1H, C**H**)

6.45 (m, 1H, Ar**H**)

4.44-4.18 (m, 2H, C**H**$_2$)

3.89 (spt, *J*=6.6 Hz, 1H, NC**H**(CH$_3$)$_2$)

3.82 (s, 3H, OC**H**$_3$)

3.80 (s, 3H, OC**H**$_3$)

3.65 (s, 3H, OC**H**$_3$)

3.40 (spt, *J*=6.8 Hz, 1H, NC**H**(CH$_3$)$_2$)

3.15 (br s, 3H, NC**H**$_3$)

1.44 (d, *J*=6.8 Hz, 6H, NCH(C**H**$_3$)$_2$)

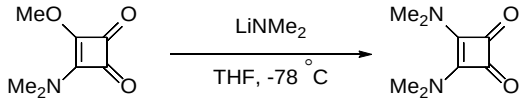
1.12 (d, *J*=6.6 Hz, 6H, NCH(C**H**$_3$)$_2$)

δ_C (100 MHz, $CDCl_3$): 186.0 (**C**), 168.3 (**C**), 161.2 (**C**), 158.9 (**C**), 145.6 (**C**H), 130.9 (**C**), 130.6 (br s, **C**H), 116.0 (br s, **C**), 104.1 (**C**H), 98.7 (**C**H), 60.5 (**C**H$_3$), 55.4 (**C**H$_3$), 55.3 (2 x **C**H$_3$), 50.3 (N**C**H(CH$_3$)$_2$), 45.4 (N**C**H(CH$_3$)$_2$), 20.4 (NCH(**C**H$_3$)$_2$), 20.1 (NCH(**C**H$_3$)$_2$), one **C**H$_2$ coincident or not observed

LR-MS (ESI$^+$): 415 (10 %, [M + Na]$^+$), 393 (100 %, [M + H]$^+$)

HR-MS (ESI$^+$): $C_{21}H_{32}N_2NaO_5$ [M + Na]$^+$ calculated 415.2203, observed 415.2209, $C_{21}H_{33}N_2O_5$ [M + H]$^+$ calculated 393.2384, observed 393.2388.

3,4-Bis(dimethylamino)cyclobut-3-ene-1,2-dione (2.56)



2.34
$C_7H_9NO_3$
Mol Wt: 155.15

2.56
$C_8H_{12}N_2O_2$
Mol Wt: 168.20

To a solution of cyclobutenedione **2.34** (155 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added $LiNMe_2$ (5 wt% in hexanes, 1.80 mL, 1.20 mmol) followed after 3 h by water (20 mL) and subsequent warming to RT. The aqueous phase was extracted with DCM (3x40 mL), the organic phases combined and dried over $MgSO_4$ before being concentrated in vacuo to a yellow solid. Purification by column chromatography (0–10 % MeOH/ethyl acetate)

afforded recovered starting material (61 mg, 0.40 mmol, 40 %) as a white solid followed by the title compound (81 mg, 0.48 mmol, 48 %) as a white solid.

Data consistent with literature[79]

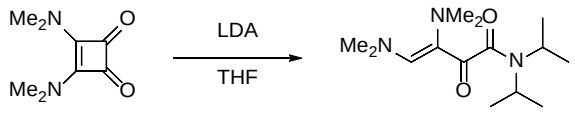
MP: 219–220 °C (diethyl ether)

δ_H (400 MHz, $CDCl_3$): 3.25 (s, 12H, 2 x N(C**H**$_3$)$_2$)

δ_C (100 MHz, $CDCl_3$): 183.9, (2 x **C**) 169.1 (2 x **C**), 41.4 (2 x N(**C**H$_3$)$_2$)

LC-MS (ESI^+): 191 (22 %, $[M + Na]^+$), 169 (100 %, $[M + H]^+$).

(*Z*)-3,4-Bis(dimethylamino)-*N*,*N*-diisopropyl-2-oxobut-3-enamide (2.57)



2.56
$C_8H_{12}N_2O_2$
Mol Wt: 168.20

2.57
$C_{14}H_{27}N_3O_2$
Mol Wt: 269.39

To a solution of cyclobutenedione **2.56** (110 mg, 0.65 mmol) in THF (25 mL) at RT was added LDA (1.0 M in THF/hexanes, 0.72 mL, 0.72 mmol) followed by water (15 mL) after 2 h. The aqueous phase was separated and extracted with DCM (3x20 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to an orange oil. Purification by column chromatography (100 % ethyl acetate) gave the title compound (72 mg, 0.27 mmol, 41 %) as an orange oil.

ν_{max} (film): 2968 (m), 2926 (m), 1631 (s), 1573 (s), 1476 (w), 1443 (m), 1419 (m), 1361 (m), 1350 (w), 1289 (m)

δ_H (400 MHz, $CDCl_3$): 6.61 (br s, 1H, C**H**)

3.90 (spt, *J*=6.7 Hz, 1H, C**H**$(CH_3)_2$)

3.42 (spt, *J*=6.8 Hz, 1H, C**H**$(CH_3)_2$)

3.17 (br s, 6H, N(C**H**$_3$)$_2$)

2.66 (s, 6H, N(C**H**$_3$)$_2$)

1.47 (d, *J*=6.8 Hz, 6H, CH(C**H**$_3$)$_2$)

1.18 (d, *J*=6.7 Hz, 6H, CH(C**H**$_3$)$_2$)

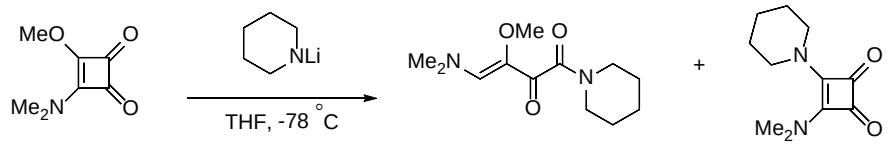
δ_C (100 MHz, $CDCl_3$): 190.2 (**C**), 169.0 (**C**), 152.1 (**C**H), 121.2 (**C**), 50.0 (**C**H(CH$_3$)$_2$), 45.4 (**C**H(CH$_3$)$_2$), 43.2 (N(**C**H$_3$)$_2$), 30.3 (N(**C**H$_3$)$_2$), 20.5 (CH(**C**H$_3$)$_2$), 20.2 (CH(**C**H$_3$)$_2$)

LR-MS (ESI$^+$): 270 (100 %, [M + H]$^+$)

HR-MS (ESI$^+$): $C_{14}H_{27}N_3NaO_2$ [M + Na]$^+$ calculated 292.1995, observed 292.1996, $C_{14}H_{28}N_3O_2$ [M + H]$^+$ calculated 270.2176, observed 270.2174.

(*Z*)-4-(Dimethylamino)-3-methoxy-1-(piperidin-1-yl)but-3-ene-1,2-dione (2.58)

3-(Dimethylamino)-4-(piperidin-1-yl)cyclobut-3-ene-1,2-dione (2.59)



2.34
$C_7H_9NO_3$
Mol Wt: 155.15

2.58
$C_{12}H_{20}N_2O_3$
Mol Wt: 240.30

2.59
$C_{11}H_{16}N_2O_2$
Mol Wt: 208.26

To a solution of lithium piperidide (prepared *in situ* from piperidine (0.11 mL, 1.10 mmol) and *n*-butyllithium (0.44 mL, 1.10 mmol)) in THF (40 mL) at 0 °C was added cyclobutenedione **2.34** (155 mg, 1.00 mmol) followed by subsequent cooling to -78 °C. After 2h, water (20 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x40 mL), the organic phases combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column (90–100 % ethyl acetate/petroleum ether) afforded firstly cyclobutenedione **2.59** (21 mg, 0.10 mmol, 10 %) as a white solid followed by 2-oxobut-3-enamide **2.58** (147 mg, 0.61 mmol, 61 %) as a yellow oil.

3-(Dimethylamino)-4-(piperidin-1-yl)cyclobut-3-ene-1,2-dione (**2.59**)

MP: 138–140 °C (ethyl acetate/hexane)

ν_{max} (film): 3016 (w), 2943 (w), 1786 (w), 1677 (m), 1585 (s), 1522 (s), 1449 (m), 1411 (m), 1304 (w), 1247 (w)

δ_H (400 MHz, $CDCl_3$): 3.64-3.58 (m, 4H, 2 x C**H**$_2$)

3.21 (s, 6H, N(C**H**$_3$)$_2$)

1.71-1.67 (m, 6H, 3 x C**H**$_2$)

δ_C (100 MHz, $CDCl_3$): 184.3 (**C**), 184.3 (**C**), 169.6 (**C**), 168.1 (**C**), 49.9 (2 x **C**H$_2$), 41.0 (N(**C**H$_3$)$_2$), 26.0 (2 x **C**H$_2$), 23.6 (**C**H$_2$)

LR-MS (ESI^+): 231 (15 %, $[M + Na]^+$), 209 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{11}H_{16}N_2NaO_2$ $[M + Na]^+$ calculated 231.1104, observed 231.1106, $C_{11}H_{17}N_2O_2$ $[M + H]^+$ calculated 209.1285, observed 209.1286.

(*Z*)-4-(Dimethylamino)-3-methoxy-1-(piperidin-1-yl)but-3-ene-1,2-dione (**2.58**)

ν_{max} (film): 2936 (br), 2858 (w), 1626 (s), 1563 (s), 1445 (m), 1420 (m), 1404 (m), 1364 (w), 1323 (s), 1282 (w)

δ_H (400 MHz, $CDCl_3$): 6.58 (s, 1H, C**H**)

3.66 (s, 3H, OC**H**$_3$)

3.56-3.52 (m, 2H, 2 x C**H**$_2$)

3.35-3.30 (m, 2H, 2 x C**H**$_2$)

3.12 (s, 6H, N(C**H**$_3$)$_2$)

1.67-1.60 (m, 2H, C**H**$_2$)

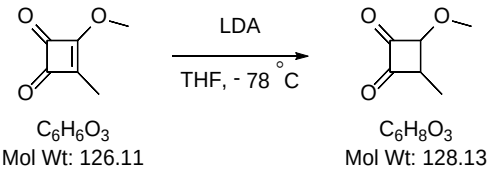
1.60-1.52 (m, 4H, 2 x C**H**$_2$)

δ_C (100 MHz, $CDCl_3$): 185.2 (**C**), 166.8 (**C**), 146.1 (**C**H), 131.6 (**C**), 60.6 (O**C**H$_3$), 47.4 (**C**H$_2$), 42.1 (**C**H$_2$), 41.4 (br, N(**C**H$_3$)$_2$), 26.3 (**C**H$_2$), 25.5 (**C**H$_2$), 24.4 (**C**H$_2$)

LR-MS (ESI^+): 263 (10 %, $[M + Na]^+$), 241 (100 %, $[M + H]^+$)

HR-MS (ESI$^+$): $C_{12}H_{20}N_2NaO_3$ [M + Na]$^+$ calculated 263.1366, observed 263.1369, $C_{12}H_{21}N_2O_3$ [M + H]$^+$ calculated 241.1547, observed 241.1549.

3-Methoxy-4-methylcyclobutane-1,2-dione (2.61)



To a solution of cyclobutenedione **2.4** (187 mg, 1.48 mmol) in THF (50 mL) at -78 °C was added LDA (1 M in THF/hexanes, 1.56 mL, 1.56 mmol) followed after 2 h by water (20 mL) and subsequent warming to RT. The solution was extracted with DCM (3 x 40 mL), organic phases combined, dried over $MgSO_4$ and concentrated to an orange oil. Purification by column chromatography (ethyl acetate) yielded the title compound (113 mg, 0.88 mmol, 60 %) as a sensitive yellow oil.

ν_{max} (film): 2925 (m), 1751 (m), 1616 (s), 1457 (m), 1385 (m), 1341 (s), 1150 (w), 1046 (w), 974 (w) 814 (w)

δ_H (400 MHz, $CDCl_3$): 5.14 (dq, *J*=6.3, 1.8 Hz, 1H, C**H**)

4.17 (s, 3H, OC**H**$_3$)

2.88 (d, *J*=6.3 Hz, 1H, C**H**)

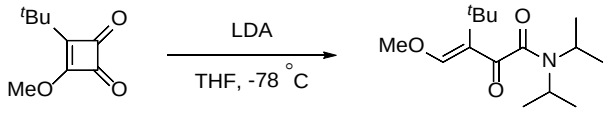
1.70 (d, *J*=1.8 Hz, 3H, C**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 205.1 (**C**), 181.5 (**C**), 81.9 (**C**H), 63.1 (**C**H), 59.7 (O**C**H$_3$), 6.3 (**C**H$_3$)

LR-MS (ESI$^+$): 151 (3 %, [M + Na]$^+$), 129 (100 %, [M + H]$^+$)

HR-MS (ESI$^+$): $C_6H_8NaO_3$ [M + Na]$^+$ calculated 151.0366, observed 151.0361.

(*E*)-*N*,*N*-Diisopropyl-3-(methoxymethylene)-4,4-dimethyl-2-oxopentanamide (2.64)



2.63
$C_9H_{12}O_3$
Mol Wt: 168.19

2.64
$C_{15}H_{27}NO_3$
Mol Wt: 269.39

To a solution of cyclobutenedione **2.63** (168 mg, 1.00 mmol) in THF (40 mL) at -78 °C was added LDA (1.0 M in THF/hexanes, 1.05 mL, 1.05 mmol) followed by water (20 mL) after 2 h. The solution was warmed to RT and the aqueous phase separated and extracted with DCM (3x30 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (10-20 % ethyl acetate/petroleum ether) gave the title compound (92 mg, 0.34 mmol, 34 %) as yellow crystals.

MP: 84–85 °C (diethyl ether)

ν_{max} (film): 2971 (br), 1614 (s), 1446 (m), 1371 (m), 1349 (w), 1273 (s), 1243 (w), 1214 (m), 1140 (m), 1114 (w)

δ_H (400 MHz, $CDCl_3$): 6.91 (s, 1H, C**H**)

3.81 (s, 3H, OC**H**$_3$)

3.70 (spt, *J*=6.6 Hz, 1H, C**H**$(CH_3)_2$)

3.45 (spt, *J*=6.9 Hz, 1H, C**H**$(CH_3)_2$)

1.48 (d, *J*=6.9 Hz, 6H, CH(C**H**$_3)_2$)

1.29 (s, 9H, C(C**H**$_3)_3$)

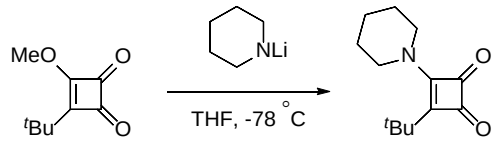
1.19 (d, *J*=6.6 Hz, 6H, CH(C**H**$_3)_2$)

δ_C (100 MHz, $CDCl_3$): 193.7 (**C**), 167.6 (**C**), 165.7 (**C**H), 124.7 (**C**), 62.5 (O**C**H_3), 50.1 (**C**H$(CH_3)_2$), 45.6 (**C**H$(CH_3)_2$), 34.3 (**C**$(CH_3)_3$), 29.7 (C(**C**$H_3)_3$), 20.3 (CH(**C**$H_3)_2$), 20.1 (CH(**C**$H_3)_2$)

LR-MS (ESI^+): 292 (10 %, $[M + Na]^+$), 270 (100 %, $[M + H]^+$)

HR-MS (ESI$^+$): $C_{15}H_{27}NNaO_3$ [M + Na]$^+$ calculated 292.1883, observed 292.1885, $C_{15}H_{28}NO_3$ [M + H]$^+$ calculated 270.2064, observed 270.2063.

3-(*Tert*-butyl)-4-(piperidin-1-yl)cyclobut-3-ene-1,2-dione (2.65)



2.63
$C_9H_{12}O_3$
Mol Wt: 168.19

2.65
$C_{13}H_{19}NO_2$
Mol Wt: 221.30

To a solution of lithium piperidide (prepared *in situ* from piperidine (0.11 mL, 1.05 mmol) and *n*-butyllithium (0.42 mL, 1.05 mmol)) in THF (40 mL) at 0 °C was added cyclobutenedione **2.63** (168 mg, 1.00 mmol) followed by subsequent cooling to -78 °C. After 2 h, water (20 mL) was added and the solution warmed to RT before the phases were separated and the aqueous phase extracted with DCM (3x40 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated to an orange oil. Purification by column chromatography (30–50 % ethyl acetate/petroleum ether) yielded the title compound (88 mg, 0.40 mmol, 40 %) as a yellow oil.

ν_{max} (film): 2940 (s), 2863 (m), 1772 (s), 1721 (m), 1580 (s), 1452 (m), 1413 (w), 1286 (m), 1259 (w), 1191 (m)

δ_H (400 MHz, $CDCl_3$): 3.82 (br s, 4H, 2 x C**H**$_2$)

1.74 (br s, 6H, 3 x C**H**$_2$)

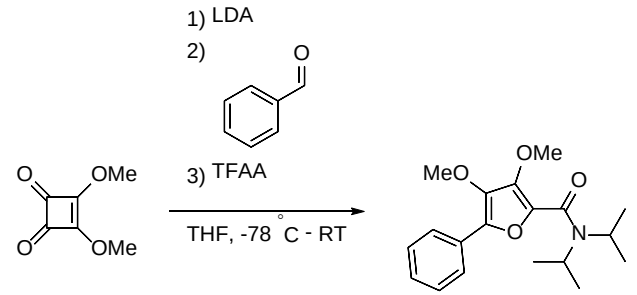
1.40 (s, 9H, C(C**H**$_3$)$_3$)

δ_C (100 MHz, $CDCl_3$): 194.7 (**C**), 189.9 (**C**), 179.8 (**C**), 176.4 (**C**), 49.6 (br, 2 x **C**H$_2$), 33.8 (**C**(CH$_3$)$_3$), 29.5 (C(**C**H$_3$)$_3$), 26.0 (br, 2 x **C**H$_2$), 23.5 (**C**H$_2$)

LR-MS (ESI$^+$): 244 (58 %, [M + Na]$^+$), 222 (100 %, [M + H]$^+$)

HR-MS (ESI$^+$): $C_{13}H_{19}NNaO_2$ [M + Na]$^+$ calculated 244.1308, observed 244.1308, $C_{13}H_{20}NO_2$ [M + H]$^+$ calculated 222.1489, observed 222.1492.

_N_,_N_-Diisopropyl-3,4-dimethoxy-5-phenylfuran-2-carboxamide (2.74)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.74
$C_{19}H_{25}NO_4$
Mol Wt: 331.41

To a solution of cyclobutenedione **2.1** (142 mg, 1.00 mmol) in THF (30 mL) at - 78 °C was added LDA (2.0 M in THF/ethylbenzene/hexanes, 0.55 mL, 1.10 mmol) dropwise followed after 90 min by benzaldehyde (0.12 mL, 1.20 mmol). The reaction mixture was warmed to RT after 30 min then cooled - 78 °C after a further 2 h. TFAA (0.18 mL, 1.20 mmol) was added, followed after 90 min by water (10 mL). After warming to RT the aqueous phase was separated and extracted with DCM (3x20 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to an orange oil. Purification by column chromatography (5–10 % ethyl acetate/petroleum ether) gave the title compound (102 mg, 0.31 mmol, 31 %) as a yellow oil.

ν_{max} (film): 2971 (m), 2936 (w), 2359 (m), 2343 (w), 1623 (s), 1580 (w), 1559 (w), 1465 (s), 1448 (s), 1410 (m)

δ_H (500 MHz, DMSO-d_6, 373 K): 7.73-7.69 (m, 2H, 2 x Ar**H**)

7.47-7.42 (m, 2H, 2 x Ar**H**)

7.32-7.27 (m, 1H, Ar**H**)

3.91 (s, 3H, OC**H**$_3$)

3.90 (s, 3H, OC**H**$_3$)

3.87 (spt, *J*=6.7 Hz, 2H, N(C**H**$(CH_3)_2)_2$)

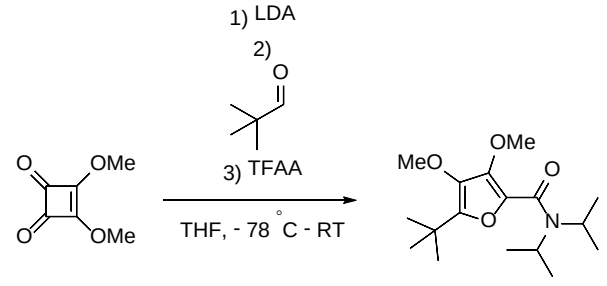
1.35 (d, *J*=6.8 Hz, 12H, N(CH(C**H**$_3)_2)_2$)

δ_C (126 MHz, DMSO-d_6, 373 K): 159.3 (**C**), 142.4 (**C**), 137.1 (**C**), 136.8 (**C**), 131.6 (**C**), 128.9 (**C**), 128.2 (2 x **C**H), 126.8 (**C**H), 122.9 (2 x **C**H), 59.83 (O**C**H_3), 59.80 (O**C**H_3), 47.2 (br, N(**C**H$(CH_3)_2)_2$), 20.1 (N(CH(**C**$H_3)_2)_2$)

LR-MS (ESI^+): 332 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{19}H_{25}NNaO_4$ $[M + Na]^+$ calculated 354.1676, observed 354.1682, $C_{19}H_{26}NO_4$ $[M + H]^+$ calculated 332.1856, observed 332.1863.

5-(*Tert*-butyl)-*N*,*N*-diisopropyl-3,4-dimethoxyfuran-2-carboxamide (2.75)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

2.75
$C_{17}H_{29}NO_4$
Mol Wt: 311.42

To a solution of cyclobutenedione **2.1** (142 mg, 1.00 mmol) in THF (30 mL) at - 78 °C was added LDA (2.0 M in THF/ethylbenzene/hexanes, 0.55 mL, 1.10 mmol) dropwise followed after 90 min by trimethylacetaldehyde (0.14 mL, 1.30 mmol). The reaction mixture was warmed to RT after 30 min then cooled to - 78 °C after a further 2 h. TFAA (0.18 mL, 1.20 mmol) was added, followed after 90 min by water (10 mL). After warming to RT the aqueous phase was separated and extracted with DCM (3x20 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a brown oil. Purification by column chromatography (5-10 % ethyl acetate/petroleum ether) gave the title compound (103 mg, 0.33 mmol, 33 %) as a yellow oil.

ν_{max} (film): 2967 (m), 2934 (w), 1622 (s), 1571 (m), 1483 (w), 1462 (w), 1408 (m), 1369 (m), 1340 (s), 1288 (m)

δ_H (500 MHz, DMSO-d_6, 373 K): 3.82 (s, 3H, OC**H**$_3$)

3.78 (spt, *J*=6.7 Hz, 2H, N(C**H**$(CH_3)_2)_2$)

3.73 (s, 3H, OC**H**$_3$)

1.31 (d, *J*=6.8 Hz, 12H, N(CH(C**H**$_3$)$_2$)$_2$)

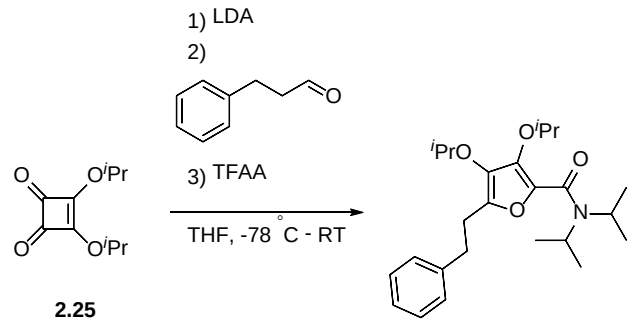
1.28 (s, 9H, C(C**H**$_3$)$_3$)

δ_C (126 MHz, DMSO-d_6, 373 K): 159.6 (**C**), 146.6 (**C**), 142.8 (**C**), 134.6 (**C**), 129.4 (**C**), 60.3 (O**C**H$_3$), 59.4 (O**C**H$_3$), 46.9 (br, N(**C**H(CH$_3$)$_2$)$_2$), 32.0 (**C**(CH$_3$)$_3$), 27.7 (C(**C**H$_3$)$_3$), 20.1 (N(CH(**C**H$_3$)$_2$)$_2$)

LR-MS (ESI$^+$): 312 (100 %, [M + H]$^+$)

HR-MS (ESI$^+$): $C_{17}H_{29}NNaO_4$ [M + Na]$^+$ calculated 334.1989, observed 334.1991, $C_{17}H_{30}NO_4$ [M + H]$^+$ calculated 312.2169, observed 312.2173.

3,4-Diisopropoxy-*N*,*N*-diisopropyl-5-phenethylfuran-2-carboxamide (2.76)



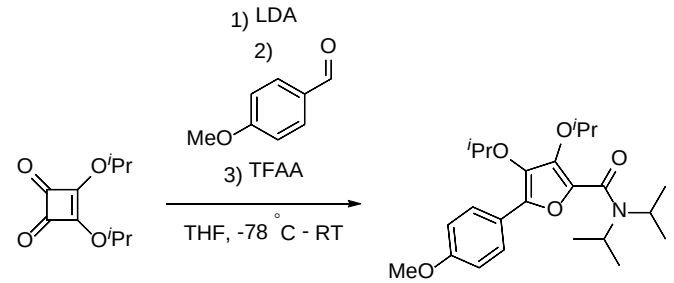
2.25
$C_{10}H_{14}O_4$
Mol Wt: 198.22

2.76
$C_{25}H_{37}NO_4$
Mol Wt: 415.57

To a solution of cyclobutenedione **2.25** (198 mg, 1.00 mmol) in THF (30 mL) at - 78 °C was added LDA (2.0 M in THF/ethylbenzene/hexanes, 0.55 mL, 1.10 mmol) dropwise, followed after 90 min by 3-phenylpropionaldehyde (0.16 mL, 1.20 mmol). The reaction mixture was warmed to RT after 30 min then cooled to - 78 °C after a further 2 h. TFAA (0.18 mL, 1.20 mmol) was added, followed after 90 min by sat. sodium bisulfite solution (10 mL). After warming to RT the aqueous phase was separated and extracted with DCM (3x20 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a brown oil. Purification by column chromatography (5-10 % ethyl acetate/petroleum ether) gave the title compound (170 mg, 0.41 mmol, 41 %) as a yellow oil.

ν_{max}, (film):	2972 (s), 2931 (m), 2360 (w), 1624 (s). 1570 (w), 1497 (w), 1453 (m), 1421 (w), 1371 (s), 1359 (w)
δ_H (500 MHz, DMSO-d_6, 373 K):	7.27-7.22 (m, 2H, 2 x Ar**H**)
	7.20-7.13 (m, 3H, 3 x Ar**H**)
	4.47 (spt, *J*=6.1 Hz, 1H, OC**H**$(CH_3)_2$)
	4.14 (spt, *J*=6.1 Hz, 1H, OC**H**$(CH_3)_2$)
	3.75 (spt, *J*=6.7 Hz, 2H, 2 x C**H,** N(C**H**$(CH_3)_2)_2$)
	2.93-2.87 (m, 2H, C**H**$_2$)
	2.85-2.79 (m, 2H, C**H**$_2$)
	1.28 (d, *J*=6.7 Hz, 12H, N(CH(C**H**$_3)_2)_2$)
	1.20 (d, *J*=6.1 Hz, 6H, OCH(C**H**$_3)_2$)
	1.17 (d, *J*=6.1 Hz, 6H, OCH(C**H**$_3)_2$)
δ_C (126 MHz, DMSO-d_6, 373 K):	159.7 (**C**), 140.9 (**C**), 140.2 (**C**), 139.1 (**C**), 134.7 (**C**), 132.1 (**C**), 127.58 (2 x **C**H), 127.57 (2 x **C**H), 125.3 (**C**H), 74.2 (O**C**H$(CH_3)_2$), 73.8 (O**C**H$(CH_3)_2$), 46.9 (br, N(**C**H$(CH_3)_2)_2$), 32.4 (**C**H$_2$), 26.5 (**C**H$_2$), 21.5 (OCH(**C**H$_3)_2$), 21.2 (OCH(**C**H$_3)_2$), 20.1 (N(CH(**C**H$_3)_2)_2$)
LR-MS (ESI^+):	416 (100 %, $[M + H]^+$)
HR-MS (ESI^+):	$C_{25}H_{37}NNaO_4$ $[M + Na]^+$ calculated 438.2615, observed 438.2621, $C_{25}H_{38}NO_4$ $[M + H]^+$ calculated 416.2795, observed 416.2802.

3,4-Diisopropoxy-*N*,*N*-diisopropyl-5-(4-methoxyphenyl)furan-2-carboxamide (2.77)



2.25
$C_{10}H_{14}O_4$
Mol Wt: 198.22

2.77
$C_{24}H_{35}NO_5$
Mol Wt: 417.55

To a solution of cyclobutenedione **2.25** (198 mg, 1.00 mmol) in THF (30 mL) at - 78 °C was added LDA (2.0 M in THF/ethylbenzene/hexanes, 0.55 mL, 1.10 mmol) dropwise followed after 90 min by *p*-anisaldehyde (0.15 mL, 1.20 mmol). The reaction mixture was warmed to RT after 30 min then cooled to - 78 °C after a further 2 h. TFAA (0.18 mL, 1.20 mmol) was added, followed after 90 min by sat. sodium bisulfite solution (10 mL). After warming to RT the aqueous phase was separated and extracted with DCM (3x20 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (5–10 % ethyl acetate/petroleum ether) gave the title compound (155 mg, 0.37 mmol, 37 %) as a yellow oil.

ν_{max} (film): 2975 (m), 2935 (w), 1621 (s), 1562 (w), 1509 (s), 1456 (s), 1426 (m), 1373 (s), 1336 (m), 1300 (m)

δ_H (500 MHz, DMSO-d_6, 373 K): 7.73-7.67 (m, 2H, 2 x Ar**H**)

7.05-6.99 (m, 2H, 2 x Ar**H**)

4.57 (spt, *J*=6.2 Hz, 1H, OC**H**$(CH_3)_2$)

4.51 (spt, *J*=6.2 Hz, 1H, OC**H**$(CH_3)_2$)

3.85 (spt, *J*=6.7 Hz, 2H, N(C**H**$(CH_3)_2)_2$)

3.81 (s, 3H, OC**H**$_3$)

1.34 (d, *J*=6.7 Hz, 12H, N(CH(C**H**$_3)_2)_2$)

1.29 (d, *J*=6.2 Hz, 6H, OCH(C**H**$_3)_2$)

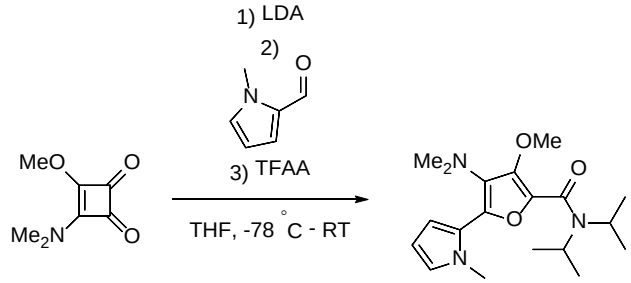
1.27 (d, *J*=6.2 Hz, 6H, OCH(C**H**$_3$)$_2$)

δ_C (126 MHz, DMSO-d_6, 373 K): 159.5 (**C**), 158.3 (**C**), 140.0 (**C**), 138.3 (**C**), 134.3 (**C**), 132.1 (**C**), 124.5 (2 x **C**H), 122.1 (**C**), 113.9 (2 x **C**H), 74.22 (O**C**H(CH$_3$)$_2$), 74.17 (O**C**H(CH$_3$)$_2$), 54.8 (O**C**H$_3$), 47.1 (br, N(**C**H(CH$_3$)$_2$)$_2$), 21.6 (OCH(**C**H$_3$)$_2$), 21.3 (OCH(**C**H$_3$)$_2$), 20.1 (N(CH(**C**H$_3$)$_2$)$_2$)

LR-MS (ESI$^+$): 418 (100 %, [M + H]$^+$)

HR-MS (ESI$^+$): $C_{24}H_{35}NNaO_5$ [M + Na]$^+$ calculated 440.2407, observed 440.2409, $C_{24}H_{36}NO_5$ [M + H]$^+$ calculated 418.2588, observed 418.2596.

4-(Dimethylamino)-*N*,*N*-diisopropyl-3-methoxy-5-(1-methyl-1*H*-pyrrol-2-yl)furan-2-carboxamide (2.78)



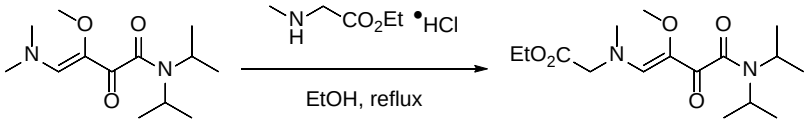
2.34
$C_7H_9NO_3$
Mol Wt: 155.15

2.78
$C_{19}H_{29}N_3O_3$
Mol Wt: 347.46

To a solution of cyclobutenedione **2.34** (155 mg, 1.00 mmol) in THF (30 mL) at - 78 °C was added LDA (2.0 M in THF/ethylbenzene/hexanes, 0.55 mL, 1.10 mmol) dropwise followed after 90 min by *N*-methyl-2-pyrrolecarboxaldehyde (0.13 mL, 1.20 mmol). The reaction mixture was warmed to RT after 30 min the cooled to - 78 °C after a further 2 h. TFAA (0.18 mL, 1.20 mmol) was added followed after 90 min by sat. sodium bisulfite solution (10 mL). After warming to RT the aqueous phase was separated and extracted with DCM (3x20 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (10–15 % ethyl acetate/petroleum ether) gave the title compound (131 mg, 0.38 mmol, 38 %) as a yellow oil.

ν_{max} (film):	2970 (m), 2934 (w), 2791 (w), 2360 (w), 1625 (s), 1527 (w), 1458 (s), 1395 (w), 1370 (m), 1346 (s)
δ_H (500 MHz, DMSO-d_6, 373 K):	6.82 (dd, *J*=2.7, 1.8 Hz, 1H, Ar**H**)
	6.23 (dd, *J*=3.7, 1.7 Hz, 1H, Ar**H**)
	6.07 (dd, *J*=3.6, 2.7 Hz, 1H, Ar**H**)
	3.83 (s, 3H, OC**H**$_3$)
	3.81 (spt, *J*=6.7 Hz, 2H, N(C**H**(CH$_3$)$_2$)$_2$)
	3.56 (s, 3H, NC**H**$_3$)
	2.60 (s, 6H, N(C**H**$_3$)$_2$)
	1.31 (d, *J*=6.8 Hz, 12H, N(CH(C**H**$_3$)$_2$)$_2$)
δ_C (126 MHz, DMSO-d_6, 373 K):	160.0 (**C**), 143.8 (**C**), 132.3 (**C**), 132.2 (**C**), 130.3 (**C**), 123.5 (**C**H), 122.3 (**C**), 111.9 (**C**H), 106.8 (**C**H), 59.5 (O**C**H$_3$), 47.0 (br, N(**C**H(CH$_3$)$_2$)$_2$), 42.1 (N(**C**H$_3$)$_2$), 33.7 (N**C**H$_3$), 20.0 (N(CH(**C**H$_3$)$_2$)$_2$)
LR-MS (ESI$^+$):	348 (100 %, [M + H]$^+$)
HR-MS (ESI$^+$):	$C_{19}H_{29}N_3NaO_3$ [M + Na]$^+$ calculated 370.2101, observed 370.2102, $C_{19}H_{30}N_3O_3$ [M + H]$^+$ calculated 348.2282, observed 348.2290.

Ethyl (*Z*)-*N*-(4-(diisopropylamino)-2-methoxy-3,4-dioxobut-1-en-1-yl)-*N*-methylglycinate (2.82)



2.35
$C_{13}H_{24}N_2O_3$
Mol Wt: 256.35

2.82
$C_{16}H_{28}N_2O_5$
Mol Wt: 328.41

To a solution of amide **2.35** (256 mg, 1.00 mmol) in ethanol (10 mL) was added sarcosine hydrochloride (337 mg, 2.20 mmol) and the mixture heated to reflux for 24 h. The resultant solution was cooled to RT and concentrated *in vacuo* to a red oil. The crude material was dissolved in ethyl acetate (30 mL) and washed with water (3x30 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (80 % ethyl acetate/petroleum ether) yielded the title compound (208 mg, 0.63 mmol, 63 %) as a yellow oil.

ν_{max}, (film): 2973 (w), 2935 (w), 1744 (m), 1630 (s), 1576 (s), 1445 (m), 1408 (m), 1369 (m), 1301 (s), 1249 (w)

δ_H (400 MHz, $CDCl_3$): 6.50 (br s, 1H, C**H**)

4.20 (q, *J*=7.1 Hz, 2H, OC**H**$_2$CH$_3$)

4.12 (br s, 2H, C**H**$_2$)

3.84 (spt, *J*=6.6 Hz, 1H, C**H**(CH$_3$)$_2$)

3.62 (s, 3H, OC**H**$_3$)

3.43 (spt, *J*=6.8 Hz, 1H, C**H**(CH$_3$)$_2$)

3.11 (br s, 3H, NC**H**$_3$)

1.45 (d, *J*=6.8 Hz, 6H, N(CH$_2$C**H**$_3$)$_2$)

1.27 (t, *J*=7.1 Hz, 3H, OCH$_2$C**H**$_3$)

1.16 (d, *J*=6.6 Hz, 6H, N(CH$_2$C**H**$_3$)$_2$)

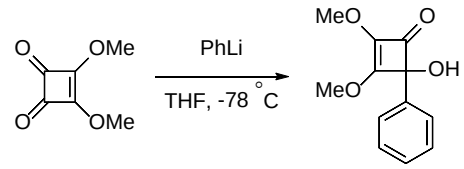
δ_C (100 MHz, $CDCl_3$): 186.4 (**C**), 168.4 (**C**), 167.7 (**C**), 144.8 (**C**H), 132.1 (**C**), 61.4 (O**C**H_2CH_3), 60.4 (**C**H_3), 60.3 (**C**H_3), 54.7 (br, **C**H_2), 50.3 (N**C**H$(CH_3)_2$), 45.5 (N**C**H$(CH_3)_2$), 20.4 (N$(CH_2$**C**$H_3)_2$), 20.1 (N$(CH_2$**C**$H_3)_2$), 14.1 (OCH_2**C**H_3)

LR-MS (ESI^+): 351 (13 %, $[M + Na]^+$), 329 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{16}H_{28}N_2NaO_5$ $[M + Na]^+$ calculated 351.1890, observed 351.1898, $C_{16}H_{29}N_2O_5$ $[M + H]^+$ calculated 329.2071, observed 329.2075.

4.3 Experimental procedures for Chapter 3

4-Hydroxy-2,3-dimethoxy-4-phenylcyclobut-2-en-1-one (3.28)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.28
$C_{12}H_{12}O_4$
Mol Wt: 220.22

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione (1.00 g, 7.04 mmol) in THF (70 mL) at -78 °C was added phenyllithium (1.9 M in dibutyl ether, 4.82 mL, 9.95 mmol) followed after 90 min by sat. NH_4Cl (30 mL) and subsequent warming to RT. The aqueous phase was extracted with DCM (3x50 mL), the organic phases combined, dried over $MgSO_4$ and concentrated to an orange oil. Purification by column chromatography (25–30 % ethyl acetate/petroleum ether) yielded the title compound (1.36 g, 6.18 mmol, 88 %) as a white solid.

Data consistent with literature[2]

MP: 99–101 °C (diethyl ether/hexane)

δ_H (400 MHz, $CDCl_3$): 7.56-7.51 (m, 2H, 2 x Ar**H**)

7.42-7.31 (m, 3H, 3 x Ar**H**)

4.08 (s, 3H, OC**H**$_3$)

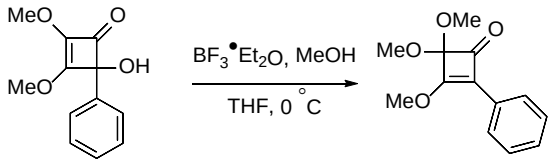
4.02 (s, 3H, OC**H**$_3$)

3.11 (br s, 1H, O**H**)

δ_C (100 MHz, $CDCl_3$): 183.8 (**C**), 165.9 (**C**), 137.1 (**C**), 135.3 (**C**), 128.6 (2 x **C**H), 128.4 (**C**H), 125.8 (2 x **C**H), 87.7 (**C**), 60.3 (**C**H_3), 58.7 (**C**H_3)

LR-MS (ESI^+): 243 (5 %, $[M + Na]^+$), 221 (100 %, $[M + H]^+$).

3,4,4-Trimethoxy-2-phenylcyclobut-2-en-1-one (3.27)



3.28
$C_{12}H_{12}O_4$
Mol Wt: 220.22

3.27
$C_{13}H_{14}O_4$
Mol Wt: 234.25

To a solution of cyclobutenone **3.28** (1.10 g, 5.00 mmol) in THF (40 mL) at 0 °C was added MeOH (0.40 mL, 10.0 mmol) and BF_3•Et_2O (0.74 mL, 6.00 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (20 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x30 mL) and the organic phases combined, washed with brine (50 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. Purification by column chromatography (5-10 % ethyl acetate/petroleum ether) yielded the title compound (788 mg, 3.36 mmol, 67 %) as a colourless oil.

Data consistent with literature[37]

ν_{max} (film): 2947 (w), 2838 (w), 1786 (s), 1753 (s), 1638 (s), 1592 (s), 1497 (s), 1449 (s), 1367 (s), 1338 (m)

δ_H (400 MHz, $CDCl_3$): 7.82-7.78 (m, 2H, 2 x Ar**H**)

7.41-7.36 (m, 2H, 2 x Ar**H**)

7.34-7.29 (m, 1H, Ar**H**)

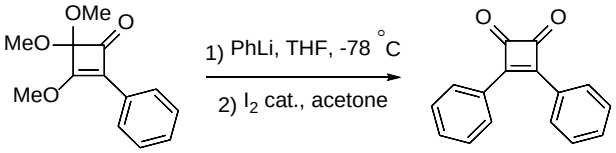
4.26 (s, 3H, OC**H**$_3$)

3.60 (s, 6H, 2 x OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 189.6 (**C**), 180.7 (**C**), 129.2 (**C**), 128.6 (**C**H), 128.5 (2 x **C**H), 128.0 (**C**), 127.1 (2 x **C**H), 115.2 (**C**), 60.2 (O**C**H_3), 53.9 (2 x O**C**H_3)

LR-MS (ESI$^+$): 257 (2 %, [M + Na]$^+$), 235 (4%, [M + H]$^+$).

3,4-Diphenylcyclobut-3-ene-1,2-dione (3.5)



3.27
$C_{13}H_{14}O_4$
Mol Wt: 234.25

3.5
$C_{16}H_{10}O_2$
Mol Wt: 234.25

To a solution of cyclobutenone **3.27** (580 mg, 2.48 mmol) in THF (40 mL) at -78 °C was added phenyllithium (1.9 M in dibutyl ether, 1.56 mL, 2.97 mmol) followed after 90 min by sat. NH_4Cl (30 mL) and subsequent warming to RT. The aqueous phase was extracted with DCM (3 x 50 mL), the organic phases combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude material was then dissolved in acetone (15 mL) and I_2 (63 mg, 0.25 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (25 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (25 mL), water (25 mL) and finally brine (25 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (5–10 % diethyl ether/petroleum ether) yielded the title compound (461 mg, 1.97 mmol, 79 %) as a yellow solid.

Data consistent with literature[82]

MP: 95–97 °C (diethyl ether/hexane)

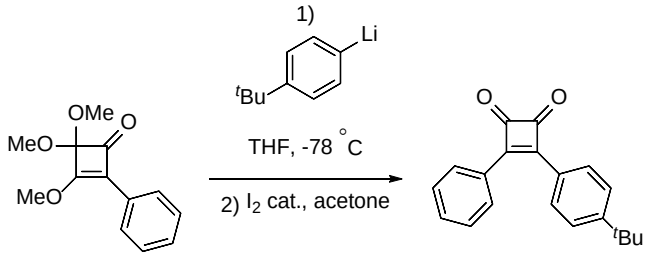
δ_H (400 MHz, $CDCl_3$): 8.12-8.04 (m, 4H, 4 x Ar**H**)

7.66-7.52 (m, 6H, 6 x Ar**H**)

δ_C (100 MHz, $CDCl_3$): 196.1 (2 x **C**), 187.4 (2 x **C**), 133.4 (2 x **C**H), 129.3 (4 x **C**H), 128.2 (4 x **C**H), 128.1 (2 x **C**)

LR-MS (ESI$^+$): 235 (100 %, [M + H]$^+$).

3-(4-(*Tert*-butyl)phenyl)-4-phenylcyclobut-3-ene-1,2-dione (3.30d)



3.27
$C_{13}H_{14}O_4$
Mol Wt: 234.25

3.30d
$C_{20}H_{18}O_2$
Mol Wt: 290.36

To a solution of 1-bromo-4-(*tert*-butyl)benzene (0.30 mL, 1.75 mmol) in THF (20 mL) at -78 °C was added *n*-butylithium (2.5 M in hexanes, 0.70 mL, 1.75 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenone **3.27** (342 mg, 1.46 mmol) in THF (20 mL) at -78 °C followed after 90 min by addition of sat. NH_4Cl (30 mL) and subsequent warming to RT. The aqueous phase was extracted with DCM (3x40 mL), the organic phases combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude material was then dissolved in acetone (20 mL) and I_2 (37 mg, 0.15 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (25 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (25 mL), water (25 mL) and finally brine (25 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange oil. Purification by column chromatography (1–2 % ethyl acetate/cyclohexane) yielded the title compound (271 mg, 0.93 mmol, 64 %) as an orange oil.

ν_{max} (neat): 2963 (m), 1778 (s), 1768 (s), 1603 (s), 1578 (m), 1509 (w), 1447 (w), 1411 (w), 1350 (s), 1314 (w)

δ_H (400 MHz, $CDCl_3$): 8.12-8.08 (m, 2H, 2 x Ar**H**)

8.08-8.04 (m, 2H, 2 x Ar**H**)

7.62-7.54 (m, 5H, 5 x Ar**H**)

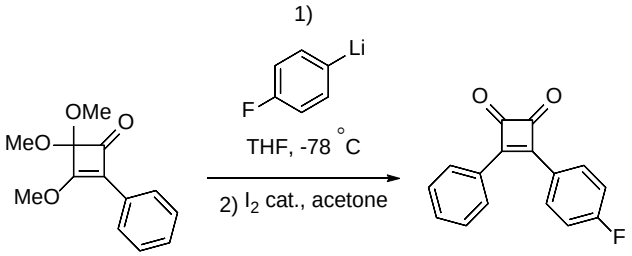
1.39 (s, 9H, C(C**H**$_3$)$_3$)

δ_C (100 MHz, $CDCl_3$): 196.5 (**C**), 196.2 (**C**), 187.3 (**C**), 186.7 (**C**), 157.6 (**C**), 133.1 (**C**H), 129.2 (2 x **C**H), 128.4 (**C**), 128.2 (2 x **C**H), 128.1 (2 x **C**H), 126.3 (2 x **C**H), 125.4 (**C**), 35.4 (**C**(CH$_3$)$_3$), 31.0 (C(**C**H$_3$)$_3$)

LR-MS (ESI$^+$): 291 (100 %, $[M + H]^+$)

HR-MS (EI): $C_{20}H_{18}O_2$ $[M]^{+\bullet}$ calculated 290.1307, observed 290.1302.

3-(4-Fluorophenyl)-4-phenylcyclobut-3-ene-1,2-dione (3.30e)



3.27
$C_{13}H_{14}O_4$
Mol Wt: 234.25

3.30e
$C_{16}H_9FO_2$
Mol Wt: 252.24

To a solution of 1-bromo-4-fluorobenzene (0.20 mL, 1.80 mmol) in THF (20 mL) at -78 °C was added *n*-butylithium (2.5 M in hexanes, 0.72 mL, 1.80 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenone **3.27** (351 mg, 1.50 mmol) in THF (20 mL) at -78 °C followed after 90 min by addition of sat. NH_4Cl (30 mL) and subsequent warming to RT. The aqueous phase was extracted with DCM (3x40 mL), the organic phases combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude material was then dissolved in acetone (20 mL) and I_2 (38 mg, 0.15 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (25 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (25 mL), water (25 mL) and finally brine (25 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange oil. Purification by column chromatography (2-3 % ethyl acetate/cyclohexane) yielded the title compound (197 mg, 0.78 mmol, 52 %) as a yellow solid.

MP: 167-168 °C (diethyl ether/hexane)

δ_H (400 MHz, $CDCl_3$): 8.20-8.13 (m, 2H, 2 x Ar**H**)

8.07-8.03 (m, 2H, 2 x Ar**H**)

7.66-7.55 (m, 3H, 3 x Ar**H**)

7.29-7.23 (m, 2H, 2 x Ar**H**)

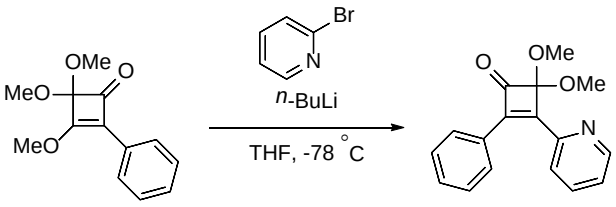
δ_C (100 MHz, $CDCl_3$): 196.0 (**C**), 195.7 (**C**), 187.2 (**C**), 185.9 (**C**), 165.6 (d, *J*=256.8 Hz, **C**F), 133.4 (**C**H), 130.9 (d, *J*=9.5 Hz, 2 x **C**H), 129.4 (2 x **C**H), 128.1 (2 x **C**H), 128.0 (**C**), 124.6 (d, *J*=2.9 Hz, **C**), 116.8 (d, *J*=22.0 Hz, 2 x **C**H)

δ_F (376 MHz, $CDCl_3$): -102.84 (s, 1F)

LR-MS (ESI^+): 275 (2 %, $[M + Na]^+$), 253 (79 %, $[M + H]^+$)

HR-MS (EI): $C_{16}H_9FO_2$ $[M]^{+\bullet}$ calculated 252.0587, observed 252.0579.

4,4-Dimethoxy-2-phenyl-3-(pyridin-2-yl)cyclobut-2-en-1-one (3.75)



3.27
$C_{13}H_{14}O_4$
Mol Wt: 234.25

3.75
$C_{17}H_{15}NO_3$
Mol Wt: 281.31

To a solution of 2-bromopyridine (0.17 mL, 1.79 mmol) in THF (20 mL) at -78 °C was added *n*-butylithium (2.5 M in hexanes, 0.72 mL, 1.79 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenone **3.27** (350 mg, 1.49 mmol) in THF (20 mL) at -78 °C followed after 90 min by addition of sat. NH_4Cl (30 mL) and subsequent warming to RT. The aqueous phase was extracted with DCM (3x40 mL), the organic phases combined, dried over $MgSO_4$ and concentrated *in vacuo* to a brown oil. Purification by column chromatography (5–10 % ethyl acetate/cyclohexane) yielded the title compound (259 mg, 0.92 mmol, 62 %) as a brown oil.

ν_{max} (film): 3059 (w). 2943 (w), 2836 (w), 1751 (s), 1579 (w), 1495 (w), 1449 (w), 1429 (w), 1354 (m), 1299 (w)

δ_H (400 MHz, $CDCl_3$): 8.88 (ddd, *J*=4.8, 1.9, 1.1 Hz, 1H, Ar**H**)

8.59-8.56 (m, 2H, 2 x Ar**H**)

8.04 (app dt, *J*=7.9, 1.1 Hz, 1H, Ar**H**)

7.83 (ddd, *J*=7.9, 7.7, 1.9 Hz, 1H, Ar**H**)

7.49-7.45 (m, 3H, 3 x Ar**H**)

7.38 (ddd, *J*=7.7, 4.8, 1.1 Hz, 1H, Ar**H**)

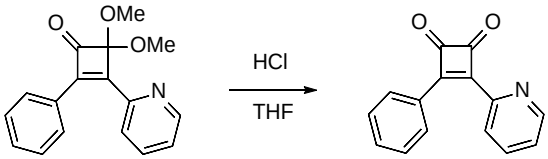
3.59 (s, 6H, 2 x OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 194.6 (**C**), 168.0 (**C**), 150.8 (**C**), 150.4 (**C**H), 149.4 (**C**), 136.8 (**C**H), 130.8 (**C**H), 130.2 (2 x **C**H), 128.6 (**C**), 128.3 (2 x **C**H), 125.7 (**C**H), 125.1 (**C**H), 116.9 (**C**), 53.9 (2 x O**C**H_3)

LR-MS (ESI^+): 304 (3 %, $[M + Na]^+$), 282 (1 %, $[M + H]^+$), 250 (100 % [M – MeOH + $H]^+$)

HR-MS (ESI^+): $C_{17}H_{15}NNaO_3$ $[M + Na]^+$ calculated 304.0944, observed 304.0947.

3-Phenyl-4-(pyridin-2-yl)cyclobut-3-ene-1,2-dione (3.76)



3.75
$C_{17}H_{15}NO_3$
Mol Wt: 281.31

3.76
$C_{15}H_9NO_2$
Mol Wt: 235.24

To a solution of cyclobutenone **3.75** (190 mg, 0.68 mmol) in THF (20 mL) was added conc. HCl (1.0 mL). After 24 h, the reaction was neutralised upon addition of sat. $NaHCO_3$ and water (10 mL) was added. The aqueous phase was extracted with DCM (3x20mL), the organic phases combined, dried over $MgSO_4$ and concentrated *in vacuo* to a brown oil. Purification by column chromatography (5 % ethyl acetate/cyclohexane) yielded the title compound (84 mg, 0.36 mmol, 53 %) as a brown solid.

MP: Dec. 155 °C

ν_{max} (film): 2981 (w), 1785 (s), 1753 (s), 1597 (w), 1570 (s), 1541 (s), 1467 (m), 1449 (m), 1429 (m), 1351 (s)

δ_H (400 MHz, $CDCl_3$): 9.06-9.02 (m, 2H, 2 x Ar**H**)

8.97 (ddd, *J*=4.7, 1.8, 1.0 Hz, 1H, Ar**H**)

8.58 (app dt, *J*=7.8, 1.0 Hz, 1H, Ar**H**)

7.97 (app td, *J*=7.8, 1.8 Hz, 1H, Ar**H**)

7.70-7.65 (m, 1H, Ar**H**)

7.63-7.58 (m, 2H, 2 x Ar**H**)

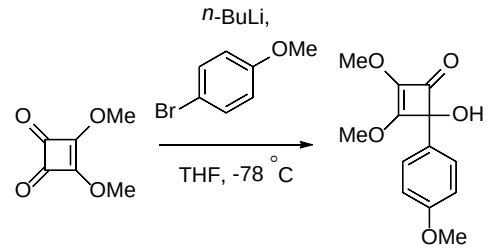
7.51 (ddd, *J*=7.6, 4.7, 1.2 Hz, 1H, Ar**H**)

δ_C (100 MHz, $CDCl_3$): 197.3 (**C**), 195.7 (**C**), 189.1 (**C**), 184.8 (**C**), 150.5 (**C**H), 147.8 (**C**), 137.1 (**C**H), 134.6 (**C**H), 131.6 (2 x **C**H), 128.9 (2 x **C**H), 128.7 (**C**), 126.7 (**C**H), 126.5 (**C**H)

LR-MS (ESI^+): 236 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{15}H_9NNaO_2$ $[M + Na]^+$ calculated 258.0525, observed 258.0531.

4-Hydroxy-2,3-dimethoxy-4-(4-methoxyphenyl)cyclobut-2-en-1-one (3.29a)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.29a
$C_{13}H_{14}O_5$
Mol Wt: 250.25

To a solution of 4-bromoanisole (1.06 mL, 8.45 mmol) in THF (50 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 3.24 mL, 8.10 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (1.00 g, 7.04 mmol) in THF (30 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before the aqueous phase was extracted with DCM (3x50 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to an orange oil. Purification by column chromatography (20–30 % ethyl acetate/petroleum ether) yielded the title compound (817 mg, 3.26 mmol, 46 %) as a yellow solid.

Data consistent with literature[2]

MP: 96-97 °C (diethyl ether/hexane)

δ_H (400 MHz, $CDCl_3$): 7.44-7.39 (m, 2H, 2 x Ar**H**)

6.90-6.85 (m, 2H, 2 x Ar**H**)

4.03 (s, 3H, OC**H**$_3$)

3.98 (s, 3H, OC**H**$_3$)

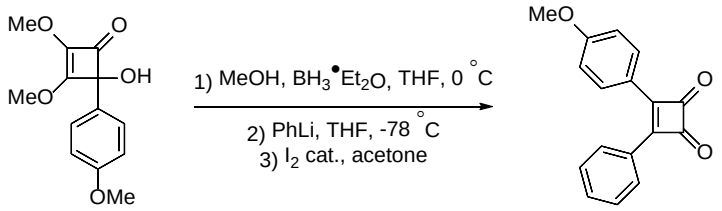
3.96 (br s, 1H, O**H**)

3.79 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 184.7 (**C**), 166.6 (**C**), 159.5 (**C**), 135.0 (**C**), 129.3 (**C**), 127.1 (2 x **C**H), 113.9 (2 x **C**H), 87.2 (**C**), 60.1 (O**C**H$_3$), 58.6 (O**C**H$_3$), 55.2 (O**C**H$_3$)

LR-MS (ESI^+): 273 (12 %, $[M + Na]^+$), 251 (85 %, $[M + H]^+$).

3-(4-Methoxyphenyl)-4-phenylcyclobut-3-ene-1,2-dione (3.30a)



3.29a
$C_{13}H_{14}O_5$
Mol Wt: 250.25

3.30a
$C_{17}H_{12}O_3$
Mol Wt: 264.28

To a solution of cyclobutenone **3.29a** (500 mg, 2.00 mmol) in THF (20 mL) at 0 °C was added MeOH (0.16 mL, 4.0 mmol) and BF_3•Et_2O (0.30 mL, 2.40 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (10 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x15 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in THF (20 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 1.37 mL, 2.60 mmol) was added. After 90 min, sat. NH_4Cl (10 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x15 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to an orange oil. The crude material was then dissolved in acetone (10 mL) and I_2 (51 mg, 0.20 mmol) was added. After 30 min, the solution was concentrated and diethyl ether (15 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (15 mL), water (15 mL) and finally brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (5–10 % ethyl acetate/petroleum ether) yielded the title compound (327 mg, 1.24 mmol, 62 %) as a yellow solid.

MP: 137-138 °C (ethyl acetate/hexane)

ν_{max} (film): 3063 (w), 3023 (w), 2938 (w), 2842 (w), 1750 (s), 1598 (s), 1563 (s), 1508 (s), 1485 (s), 1460 (m)

δ_H (400 MHz, $CDCl_3$): 8.18-8.13 (m, 2H, 2 x Ar**H**)

8.07-8.02 (m, 2H, 2 x Ar**H**)

7.62-7.53 (m, 3H, 3 x Ar**H**)

7.07-7.02 (m, 2H, 2 x Ar**H**)

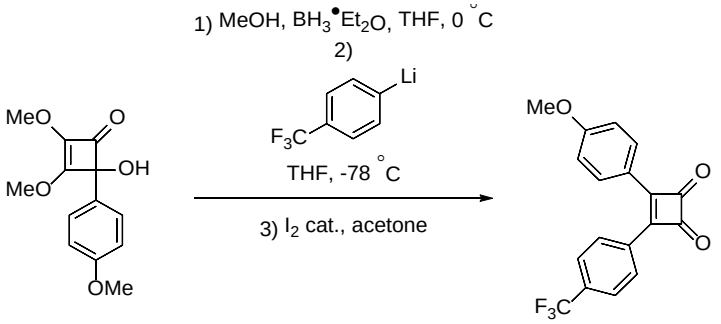
3.92 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 196.7 (**C**), 195.7 (**C**), 186.4 (**C**), 185.2 (**C**), 164.0 (**C**), 132.7 (**C**H), 130.7 (2 x **C**H), 129.2 (2 x **C**H), 128.5 (**C**), 127.9 (2 x **C**H), 120.9 (**C**), 114.8 (2 x **C**H), 55.6 (O**C**H$_3$)

LR-MS (ESI^+): 265 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{19}H_{20}NaO_5$ $[M + 2MeOH + Na]^+$ calculated 351.1203, observed 351.1202.

3-(4-Methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)cyclobut-3-ene-1,2-dione (3.41)



3.30a
$C_{13}H_{14}O_5$
Mol Wt: 250.25

3.41
$C_{18}H_{11}F_3O_3$
Mol Wt: 332.28

To a solution of cyclobutenone **3.30a** (930 mg, 3.72 mmol) in THF (40 mL) at 0 °C was added MeOH (0.29 mL, 7.44 mmol) and BF_3•Et_2O (0.58 mL, 4.46 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (20 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude

material was dissolved in THF (40 mL) and cooled to -78 °C before a solution of (4-(trifluoromethyl)phenyl)lithium (prepared *in-situ* by addition of *n*-butyllithium (1.94 mL, 4.84 mmol) to 4-bromobenzotrifluoride (0.68 mL, 4.84 mmol) in THF (40 mL) at -78 °C) was added *via* cannula. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a brown oil. The crude material was then dissolved in acetone (40 mL) and I_2 (94 mg, 0.37 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (30 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (30 mL), water (30 mL) and finally brine (40 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (5 % ethyl acetate/hexane) yielded the title compound (416 mg, 1.25 mmol, 34 %) as a yellow solid.

MP: 128-129 °C (diethyl ether/hexane)

ν_{max} (film): 2941 (w), 2845 (w), 1782 (s), 1762 (s), 1741 (m), 1685 (w), 1598 (s), 1578 (s), 1561 (s), 1512 (w)

δ_H (400 MHz, $CDCl_3$): 8.16-8.10 (m, 4H, 4 x Ar**H**)

7.85-7.81 (m, 2H, 2 x Ar**H**)

7.08-7.04 (m, 2H, 2 x Ar**H**)

3.94 (s, 3H, OC**H**$_3$)

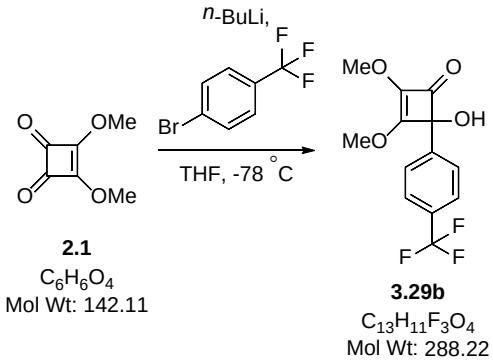
δ_C (100 MHz, $CDCl_3$): 196.4 (**C**), 194.8 (**C**), 187.5 (**C**), 183.1 (**C**), 164.6 (**C**), 133.7 (q, *J*=33.0 Hz, **C**), 131.7 (**C**), 131.0 (2 x **C**H), 128.1 (2 x **C**H), 126.2 (q, *J*=3.8 Hz, 2 x **C**H), 123.5 (q, *J*=272.7 Hz, **C**F_3), 120.5 (**C**), 115.1 (2 x **C**H), 55.7 (O**C**H_3)

δ_F (376 MHz, $CDCl_3$): -63.44 (s, C**F**3)

LR-MS (ESI^+): 333 (100 %, $[M + H]^+$)

HR-MS (ESI$^+$): $C_{20}H_{19}F_3NaO_5$ [M + 2MeOH + Na]$^+$ calculated 419.1077, observed 419.1079, $C_{20}H_{20}F_3O_5$ [M + 2MeOH + H]$^+$ calculated 397.1257, observed 397.1257.

4-Hydroxy-2,3-dimethoxy-4-(4-(trifluoromethyl)phenyl)cyclobut-2-en-1-one (3.29b)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.29b
$C_{13}H_{11}F_3O_4$
Mol Wt: 288.22

To a solution of 4-bromobenzotrifluoride (0.73 mL, 5.20 mmol) in THF (50 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.07 mL, 5.18 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (10 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before being extracted with DCM (3x50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to an orange oil. Purification by column chromatography (15–20 % ethyl acetate/cyclohexane) yielded the title compound (724 mg, 2.51 mmol, 56 %) as a pale, yellow solid.

Data consistent with literature[2]

MP: 180-181 °C (diethyl ether/hexane)

δ_H (400 MHz, $CDCl_3$): 7.64 (app s, 4H, 4 x Ar**H**)

4.09 (s, 3H, OC**H**$_3$)

4.03 (s, 3H, OC**H**$_3$)

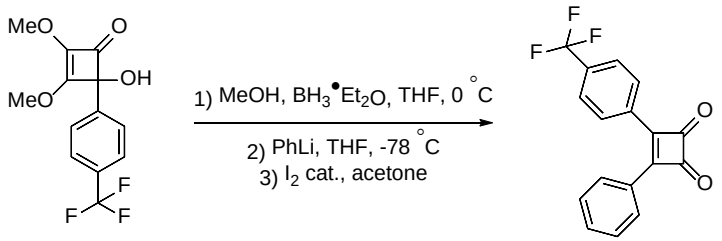
3.40 (br s, 1H, O**H**)

δ_C (100 MHz, $CDCl_3$): 183.0 (**C**), 165.5 (**C**), 141.0 (**C**), 135.7 (**C**), 130.5 (q, *J*=33.0 Hz, **C**), 126.4 (2 x **C**H), 125.6 (q, *J*=4.2 Hz, 2 x **C**H), 124.0 (q, *J*=272.2 Hz, **C**F$_3$), 87.4 (**C**), 60.4 (O**C**H$_3$), 58.8 (O**C**H$_3$)

δ_F (376 MHz, $CDCl_3$): -62.91 (s, C**F**3)

LR-MS (ESI^+): 289 (100 %, $[M + H]^+$).

3-Phenyl-4-(4-(trifluoromethyl)phenyl)cyclobut-3-ene-1,2-dione (3.30b)



3.29b
$C_{13}H_{11}F_3O_4$
Mol Wt: 288.22

3.30b
$C_{17}H_9F_3O_2$
Mol Wt: 302.25

To a solution of cyclobutenone **3.29b** (260 mg, 0.90 mmol) in THF (15 mL) at 0 °C was added MeOH (0.07 mL, 1.80 mmol) and BF_3•Et_2O (0.14 mL, 1.08 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (10 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x15 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in THF (15 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 0.61 mL, 1.17 mmol) was added. After 90 min, sat. NH_4Cl (10 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x15 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to an orange oil. The crude material was then dissolved in acetone (10 mL) and I_2 (23 mg, 0.09 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (15 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (15 mL), water (15 mL) and finally brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (2 % ethyl acetate/cyclohexane) yielded the title compound (157 mg, 0.52 mmol, 58 %) as a yellow solid.

MP: 107–109 °C (diethyl ether)

ν_{max} (film): 2981 (m), 2989 (w), 1782 (s), 1762 (s), 1744 (s), 1595 (m), 1568 (m), 1508 (w), 1486 (w), 1449 (w)

δ_H (400 MHz, $CDCl_3$): 8.16 (dd, *J*=8.8, 0.7 Hz, 2H, 2 x Ar**H**)

8.09-8.05 (m, 2H, 2 x Ar**H**)

7.83 (dd, *J*=8.8, 0.7 Hz, 2H, 2 x Ar**H**)

7.69-7.63 (m, 1H, Ar**H**)

7.62-7.56 (m, 2H, 2 x Ar**H**)

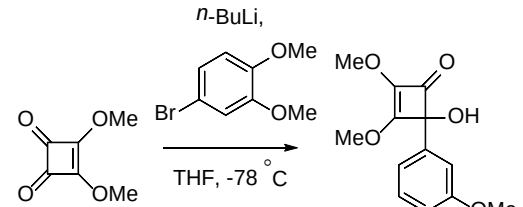
δ_C (100 MHz, $CDCl_3$): 195.8 (**C**), 195.2 (**C**), 188.9 (**C**), 185.7 (**C**), 134.1 (**C**H), 131.2 (**C**), 129.6 (2 x **C**H), 128.4 (2 x **C**H), 128.3 (2 x **C**H), 127.7 (**C**), 126.3 (q, *J*=3.3 Hz, 2 x **C**H), two **C** coincident or not observed

δ_F (376 MHz, $CDCl_3$): -63.53 (s, C**F**$_3$)

LR-MS (ESI^+): 325 (7 %, $[M + Na]^+$), 303 (96 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{19}H_{17}F_3NaO_4$ $[M + 2MeOH + Na]^+$ calculated 389.0971, observed 389.0971, $C_{18}H_{14}F_3O_3$ $[M + MeOH + H]^+$ calculated 335.0890, observed 335.0888.

4-(3,4-Dimethoxyphenyl)-4-hydroxy-2,3-dimethoxycyclobut-2-en-1-one (3.44a)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.44a
$C_{14}H_{16}O_6$
Mol Wt: 280.28

To a solution of 4-bromoveratrole (0.75 mL, 5.18 mmol) in THF (40 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.07 mL, 5.18 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (20 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before the aqueous phase was extracted with DCM (3x40 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (20–30 % ethyl acetate/hexane) yielded the title compound (923 mg, 3.29 mmol, 73 %) as a pale, yellow oil.

ν_{max} (film): 2964 (w), 1783 (s), 1761 (m), 1729 (s), 1589 (s), 1513 (s), 1468 (m), 1453 (m), 1433 (s), 1351 (s)

δ_H (400 MHz, DMSO-d_6): 7.00 (d, *J*=2.1 Hz, 1H, Ar**H**)

6.95 (d, *J*=8.3 Hz, 1H, Ar**H**)

6.89 (dd, *J*=8.3, 2.1 Hz, 1H, Ar**H**)

6.61 (s, 1H, O**H**)

3.93 (s, 3H, OC**H**$_3$)

3.91 (s, 3H, OC**H**$_3$)

3.75 (s, 3H, OC**H**$_3$)

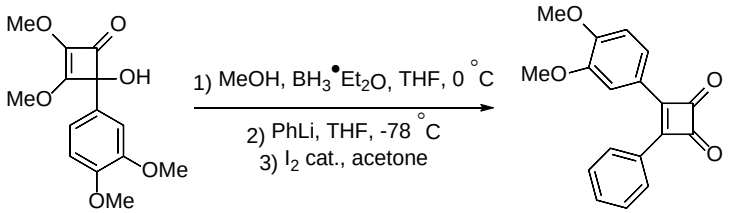
3.75 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, DMSO-d_6): 184.8 (**C**), 166.9 (**C**), 148.6 (**C**), 148.3 (**C**), 134.5 (**C**), 130.7 (**C**), 117.8 (**C**H), 111.6 (**C**H), 109.5 (**C**H), 86.8 (**C**), 59.8 (O**C**H$_3$), 58.3 (O**C**H$_3$), 55.5 (O**C**H$_3$), 55.4 (O**C**H$_3$)

LR-MS (ESI$^+$): 303 (14 %, $[M + Na]^+$), 281 (66 %, $[M + H]^+$)

HR-MS (ESI$^+$): $C_{14}H_{16}NaO_6$ $[M + Na]^+$ calculated 303.0839, observed 303.0841.

3-(3,4-Dimethoxyphenyl)-4-phenylcyclobut-3-ene-1,2-dione (3.45a)



3.44a
$C_{14}H_{16}O_6$
Mol Wt: 280.28

3.45a
$C_{18}H_{14}O_4$
Mol Wt: 294.31

To a solution of cyclobutenone **3.44a** (850 mg, 3.03 mmol) in THF (30 mL) at 0 °C was added MeOH (0.24 mL, 6.06 mmol) and BF_3•Et_2O (0.48 mL, 3.64 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (20 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x30 mL) and the organic phases combined, washed with brine

(40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in THF (30 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 2.07 mL, 3.94 mmol) was added. After 90 min, sat. NH_4Cl (20 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to an orange oil. The crude material was then dissolved in acetone (30 mL) and I_2 (77 mg, 0.30 mmol) was added. After 30 min, the solution was concentrated and diethyl ether (30 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (15 mL), water (15 mL) and finally brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (10 % ethyl acetate/hexane) yielded the title compound (512 mg, 1.74 mmol, 57 %) as a yellow solid.

MP: 181-183 °C (DCM/hexane)

ν_{max} (film): 2937 (w), 2839 (w), 1775 (s), 1653 (w), 1595 (s), 1577 (m), 1512 (s), 1487 (s), 1463 (m), 1447 (m)

δ_H (400 MHz, $CDCl_3$): 8.10-8.04 (m, 2H, 2 x Ar**H**)

7.88 (dd, *J*=8.4, 2.0 Hz, 1H, Ar**H**)

7.66 (d, *J*=2.0 Hz, 1H, Ar**H**)

7.63-7.54 (m, 3H, 3 x Ar**H**)

7.01 (d, *J*=8.4 Hz, 1H, Ar**H**)

4.00 (s, 3H, OC$\mathbf{H}_3$)

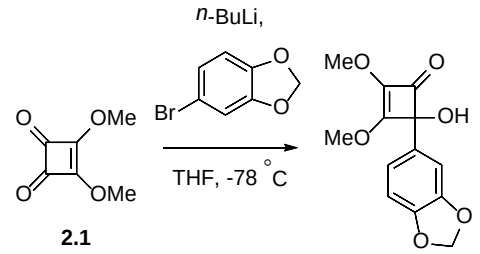
3.90 (s, 3H, OC$\mathbf{H}_3$)

δ_C (100 MHz, $CDCl_3$): 196.7 (**C**), 195.6 (**C**), 186.4 (**C**), 185.3 (**C**), 153.8 (**C**), 149.3 (**C**), 132.8 (**C**H), 129.2 (2 x **C**H), 128.5 (**C**), 128.0 (2 x **C**H), 123.4 (**C**H), 121.0 (**C**), 111.3 (**C**H), 110.6 (**C**H), 56.2 (O**C**H_3), 56.0 (O**C**H_3)

LR-MS (ESI^+): 295 (100 %, $[M + H]^+$)

HR-MS (ESI$^+$): $C_{20}H_{22}NaO_6$ [M + 2MeOH + Na]$^+$ calculated 381.1309, observed 389.1317, $C_{19}H_{19}O_5$ [M + MeOH + H]$^+$ calculated 327.1227, observed 327.1232.

4-(Benzo[*d*][1,3]dioxol-5-yl)-4-hydroxy-2,3-dimethoxycyclobut-2-en-1-one (3.44b)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.44b
$C_{13}H_{12}O_6$
Mol Wt: 264.23

To a solution of 1,2-(methylenedioxy)-4-bromobenzene (0.62 mL, 5.18 mmol) in THF (40 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.07 mL, 5.18 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (20 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before the aqueous phase was extracted with DCM (3x40 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to an orange oil. Purification by column chromatography (15–25 % ethyl acetate/hexane) yielded the title compound (847 mg, 3.21 mmol, 71 %) as a yellow oil.

ν_{max} (film): 2958 (m), 2901 (m), 1779 (s), 1739 (s), 1636 (m), 1616 (m), 1586 (s), 1498 (s), 1455 (s), 1362 (s)

δ_H (400 MHz, DMSO-d_6): 6.95 (dd, *J*=1.5, 0.7 Hz, 1H, Ar**H**)

6.902 (d, *J*=0.7 Hz, 1H, Ar**H**)

6.896 (d, *J*=1.5 Hz, 1H, Ar**H**)

6.64 (br s, 1H, O**H**)

6.02-6.01 (m, 2H, OC**H**$_2$O)

3.95 (s, 3H, OC**H**$_3$)

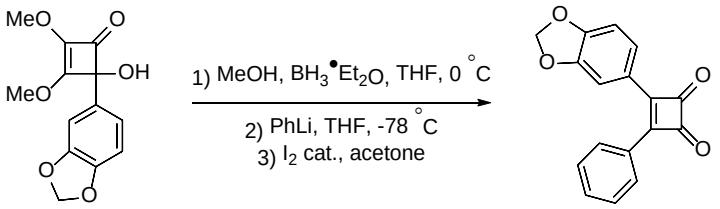
3.91 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, DMSO-d_6): 184.7 (**C**), 166.8 (**C**), 147.4 (**C**), 146.7 (**C**), 134.6 (**C**), 132.3 (**C**), 119.0 (**C**H), 108.1 (**C**H), 106.2 (**C**H), 101.1 (O**C**H_2O), 86.8 (**C**), 59.8 (O**C**H_3), 58.3 (O**C**H_3)

LR-MS (ESI^+): 287 (2 %, $[M + Na]^+$), 265 (66 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{13}H_{12}NaO_6$ $[M + Na]^+$ calculated 287.0526, observed 287.0533.

3-(Benzo[*d*][1,3]dioxol-5-yl)-4-phenylcyclobut-3-ene-1,2-dione (3.45b)



3.44b
$C_{13}H_{12}O_6$
Mol Wt: 264.23

3.45b
$C_{17}H_{10}O_4$
Mol Wt: 278.26

To a solution of cyclobutenone **3.44b** (710 mg, 2.69 mmol) in THF (30 mL) at 0 °C was added MeOH (0.21 mL, 5.37 mmol) and BF_3•Et_2O (0.42 mL, 3.22 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (20 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in THF (30 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 1.84 mL, 3.49 mmol) was added. After 90 min, sat. NH_4Cl (20 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to an orange oil. The crude material was then dissolved in acetone (30 mL) and I_2 (69 mg, 0.27 mmol) was added. After 30 min, the solution was concentrated and diethyl ether (30 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (15 mL), water (15 mL) and finally brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (5-10 % ethyl acetate/hexane) yielded the title compound (382 mg, 1.37 mmol, 51 %) as a yellow solid.

MP: 147-149 °C (diethyl ether/hexane)

ν_{max} (film): 2907 (w), 1772 (s), 1599 (w), 1567 (m), 1504 (m), 1477 (s), 1448 (s), 1436 (m), 1364 (s), 1335 (s)

δ_H (400 MHz, $CDCl_3$): 8.05-8.00 (m, 2H, 2 x Ar**H**)

7.86 (dd, *J*=8.2, 1.7 Hz, 1H, Ar**H**)

7.55 (d, *J*=1.7 Hz, 1H, Ar**H**)

7.62-7.54 (m, 3H, 3 x Ar**H**)

6.98 (d, *J*=8.2 Hz, 1H, Ar**H**)

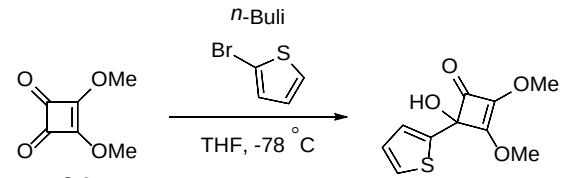
6.11 (s, 2H, OC**H**$_2$O)

δ_C (100 MHz, $CDCl_3$): 196.3 (**C**), 195.6 (**C**), 186.2 (**C**), 185.5 (**C**), 152.3 (**C**), 148.4 (**C**), 132.9 (**C**H), 129.3 (2 x **C**H), 128.3 (**C**), 128.0 (2 x **C**H), 125.1 (**C**H), 122.2 (**C**), 109.3 (**C**H), 107.6 (**C**H), 102.1 (O**C**H_2O)

LR-MS (ESI^+): 279 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{19}H_{18}NaO_6$ $[M + 2MeOH + Na]^+$ calculated 365.0996, observed 365.0994, $C_{17}H_{10}NaO_4$ $[M + Na]^+$ calculated 301.0471, observed 301.0467, $C_{17}H_{11}O_4$ $[M + H]^+$ calculated 279.0652, observed 279.0645.

4-Hydroxy-2,3-dimethoxy-4-(thiophen-2-yl)cyclobut-2-en-1-one (3.63)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.63
$C_{10}H_{10}O_4S$
Mol Wt: 226.25

To a solution of 2-bromothiophene (0.50 mL, 5.20 mmol) in THF (50 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.07 mL, 5.18 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (30 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before being extracted with DCM (3x50 mL). The combined organic phases were dried over

$MgSO_4$ and concentrated in vacuo to an orange oil. Purification by column chromatography (20–25 % ethyl acetate/hexane) yielded the title compound (692 mg, 3.06 mmol, 68 %) as a pale, yellow solid.

Data consistent with literature[2]

MP: 64-66 °C (diethyl ether/hexane)

δ_H (400 MHz, $CDCl_3$): 7.31 (dd, *J*=5.1, 1.2 Hz, 1H, Ar**H**)

7.09 (dd, *J*=3.6, 1.2 Hz, 1H, Ar**H**)

7.00 (dd, *J*=5.1, 3.6 Hz, 1H, Ar**H**)

4.09 (s, 3H, OC**H**$_3$)

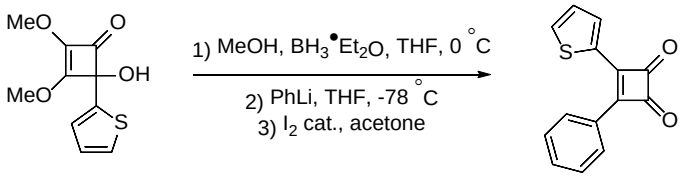
4.05 (br s, 1H, O**H**)

4.00 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 183.4 (**C**), 166.3 (**C**), 140.9 (**C**), 135.1 (**C**), 127.2 (**C**H), 126.1 (**C**H), 124.9 (**C**H), 85.6 (**C**), 60.2 (O**C**H$_3$), 58.7 (O**C**H$_3$)

LR-MS (ESI$^+$): 249 (7 %, $[M + Na]^+$), 227 (85 %, $[M + H]^+$).

3-Phenyl-4-(thiophen-2-yl)cyclobut-3-ene-1,2-dione (3.64)



3.63
$C_{10}H_{10}O_4S$
Mol Wt: 226.25

3.64
$C_{14}H_8O_2S$
Mol Wt: 240.28

To a solution of cyclobutenone **3.63** (300 mg, 1.33 mmol) in THF (20 mL) at 0 °C was added MeOH (0.11 mL, 2.66 mmol) and BF_3•Et_2O (0.20 mL, 1.59 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (10 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x20 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in THF (20 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 0.91 mL, 1.73 mmol) was added. After 90 min, sat. NH_4Cl (15 mL) was added

and the solution warmed to RT. The aqueous phase was extracted with DCM (3x20 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to an orange oil. The crude material was then dissolved in acetone (15 mL) and I_2 (34 mg, 0.13 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (20 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (20 mL), water (20 mL) and finally brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (3-5 % ethyl acetate/cyclohexane) yielded the title compound (186 mg, 0.77 mmol, 58 %) as a yellow solid.

MP: 129–131 °C (diethyl ether/hexane)

ν_{max} (film): 3086 (w), 2981 (m), 1773 (s), 1744 (s), 1596 (m), 1556 (s), 1499 (m), 1473 (m), 1447 (m), 1406 (s)

δ_H (400 MHz, $CDCl_3$): 8.41 (dd, *J*=3.9, 1.1 Hz, 1H, Ar**H**)

8.27-8.21 (m, 2H, 2 x Ar**H**)

7.92 (dd, *J*=5.1, 1.1 Hz, 1H, Ar**H**)

7.66-7.58 (m, 3H, 3 x Ar**H**)

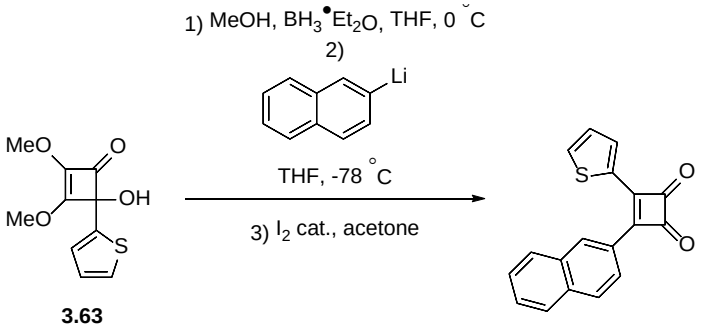
7.37 (dd, *J*=5.1, 3.9 Hz, 1H, Ar**H**)

δ_C (100 MHz, $CDCl_3$): 194.7 (**C**), 194.4 (**C**), 181.9 (**C**), 178.7 (**C**), 135.2 (**C**H), 134.4 (**C**H), 133.2 (**C**H), 129.28 (2 x **C**H), 129.26 (**C**H), 129.2 (**C**), 128.4 (2 x **C**H), 128.3 (**C**)

LR-MS (ESI^+): 263 (4 %, $[M + Na]^+$), 241 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{16}H_{16}NaO_4S$ $[M + 2MeOH + Na]^+$ calculated 327.0662, observed 327.0664, $C_{15}H_{13}O_3S$ $[M + MeOH + H]^+$ calculated 273.0580, observed 273.0577.

3-(Naphthalen-2-yl)-4-(thiophen-2-yl)cyclobut-3-ene-1,2-dione (3.67)



3.63
$C_{10}H_{10}O_4S$
Mol Wt: 226.25

3.67
$C_{18}H_{10}O_2S$
Mol Wt: 290.34

To a solution of cyclobutenone **3.63** (235 mg, 1.04 mmol) in THF (20 mL) at 0 °C was added MeOH (0.09 mL, 2.08 mmol) and BF_3•Et_2O (0.16 mL, 2.08 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (10 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x20 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a brown oil. The crude material was dissolved in THF (15 mL) and cooled to -78 °C before naphthalen-2-yllithium (prepared *in-situ* by addition of *n*-butyllithium (0.50 mL, 1.24 mmol) to 2-bromonaphthalene (258 mg, 1.24 mmol)) in THF (15 mL) at -78 °C was added *via* cannula. After 90 min, sat. NH_4Cl (15 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x20 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to an orange oil. The crude material was then dissolved in acetone (15 mL) and I_2 (25 mg, 0.10 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (20 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (20 mL), water (20 mL) and finally brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (3-5 % ethyl acetate/hexane) yielded the title compound (182 mg, 0.63 mmol, 60 %) as a yellow solid.

MP: Dec. 164 °C

ν_{max} (film): 2971 (w), 1765 (s), 1653 (w), 1625 (w), 1558 (m), 1507 (w), 1490 (w), 1463 (w), 1408 (m), 1390 (w)

δ_H (400 MHz, $CDCl_3$): 8.86 (d, *J*=1.7 Hz, 1H, Ar**H**)

8.45 (dd, *J*=3.9, 1.2 Hz, 1H, Ar**H**)

8.22 (dd, *J*=8.6, 1.7 Hz, 1H, Ar**H**)

8.03 (app d, *J*=8.2 Hz, 2H, 2 x Ar**H**)

7.94 (dd, *J*=5.0, 1.2 Hz, 1H, Ar**H**)

7.93 (m, 1H, Ar**H**)

7.70-7.59 (m, 2H, 2 x Ar**H**)

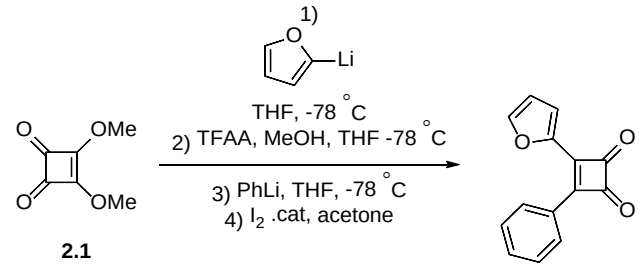
7.39 (dd, *J*=5.0, 3.9 Hz, 1H, Ar**H**)

δ_C (100 MHz, $CDCl_3$): 194.67 (**C**), 194.66 (**C**), 181.7 (**C**), 178.5 (**C**), 135.3 (**C**), 135.1 (**C**H), 134.4 (**C**H), 132.9 (**C**), 130.2 (**C**H), 129.6 (**C**H), 129.4 (**C**), 129.3 (**C**H), 129.1 (**C**H), 129.0 (**C**H), 128.0 (**C**H), 127.3 (**C**H), 125.6 (**C**), 123.9 (**C**H)

LR-MS (ESI^+): 291 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{20}H_{18}NaO_4S$ $[M + 2MeOH + Na]^+$ calculated 377.0818, observed 377.0818, $C_{19}H_{15}O_3S$ $[M + MeOH + H]^+$ calculated 323.0736, observed 323.0732.

3-(Furan-2-yl)-4-phenylcyclobut-3-ene-1,2-dione (3.61)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.61
$C_{14}H_8O_3$
Mol Wt: 224.22

To a solution of furan (0.49 mL, 6.75 mmol) in THF (40 mL) at -78 °C was added *n*-butyllithium (2.70 mL, 6.75 mmol) followed by subsequent warming to RT. After 4 h, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (20 mL) at -78 °C. After 90 min, TFAA (0.81 mL, 5.85 mmol) was added followed after 90 min by methanol (10 mL) and subsequent warming to RT. After 30 min, water (30 mL) was added and the aqueous phase was extracted with DCM (3x30 mL). The organic phases were combined, washed with brine (30 mL) and dried over $MgSO_4$ before being

concentrated *in vacuo* to a dark oil. The crude material was dissolved in THF (40 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 3.08 mL, 5.85 mmol) was added. After 90 min, sat. NH_4Cl (15 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a brown oil. The crude material was then dissolved in acetone (30 mL) and I_2 (114 mg, 0.45 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (40 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (30 mL), water (30 mL) and finally brine (40 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to a brown solid. Purification by column chromatography (5-10 % ethyl acetate/hexane) yielded the title compound (474 mg, 2.12 mmol, 47 %) as a yellow solid.

MP: 157–159 °C (diethyl ether/hexane)

ν_{max} (film): 3148 (w), 2981 (w), 1769 (s), 1589 (s), 1535 (w), 1523 (m), 1489 (m), 1443 (s), 1385 (m), 1374 (m)

δ_H (400 MHz, $CDCl_3$): 8.56-8.52 (m, 2H, 2 x Ar**H**)

7.99 (dd, *J*=1.8, 0.7 Hz, 1H, Ar**H**)

7.86 (dd, *J*=3.7, 0.7 Hz, 1H, Ar**H**)

7.66-7.57 (m, 3H, 3 x Ar**H**)

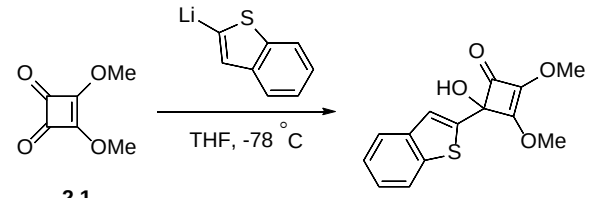
6.81 (dd, *J*=3.7, 1.8 Hz, 1H, Ar**H**)

δ_C (100 MHz, $CDCl_3$): 194.4 (**C**), 193.0 (**C**), 179.6 (**C**), 171.4 (**C**), 149.1 (**C**H), 144.2 (**C**), 133.5 (**C**H), 129.9 (2 x **C**H), 129.2 (2 x **C**H), 128.4 (**C**), 121.9 (**C**H), 114.0 (**C**H)

LR-MS (ESI^+): 225 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{16}H_{16}NaO_5$ $[M + 2MeOH + Na]^+$ calculated 311.0890, observed 311.0890, $C_{14}H_8NaO_3$ $[M + Na]^+$ calculated 247.0366, observed 247.0365.

4-(Benzo[*b*]thiophen-2-yl)-4-hydroxy-2,3-dimethoxycyclobut-2-en-1-one (3.69)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.69
$C_{14}H_{12}O_4S$
Mol Wt: 276.31

To a solution of benzo[*b*]thiophene (695 mg, 5.20 mmol) in THF (40 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.07 mL, 5.18 mmol). After 2 h, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (20 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before being extracted with DCM (3x50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to an orange oil. Purification by column chromatography (15–25 % ethyl acetate/hexane) yielded the title compound (911 mg, 3.30 mmol, 73 %) as a yellow solid.

MP: Dec. 164 °C

ν_{max} (film): 3380 (br), 3058 (w), 2944 (w), 2859 (w), 1771 (s), 1608 (s), 1464 (s), 1432 (s), 1342 (s), 1304 (s)

δ_H (400 MHz, DMSO-d_6): 7.93 (m, 1H, Ar**H**)

7.81 (m, 1H, Ar**H**)

7.38 (d, *J*=0.6 Hz, 1H, Ar**H**)

7.39-7.30 (m, 2H, 2 x Ar**H**)

7.18 (s, 1H, O**H**)

4.02 (s, 3H, OC$\mathbf{H}_3$)

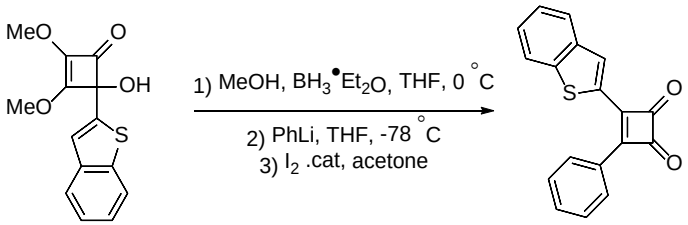
3.95 (s, 3H, OC$\mathbf{H}_3$)

δ_C (100 MHz, DMSO-d_6): 183.1 (**C**), 166.4 (**C**), 143.9 (**C**), 139.6 (**C**), 139.2 (**C**), 134.7 (**C**), 124.4 (**C**H), 124.2 (**C**H), 123.6 (**C**H), 122.4 (**C**H), 120.8 (**C**H), 85.7 (**C**), 60.1 (O**C**H_3), 58.5 (O**C**H_3)

LR-MS (ESI^+): 299 (2 %, $[M + Na]^+$), 277 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{15}H_{16}NaO_5S$ $[M + MeOH + Na]^+$ calculated 331.0611, observed 331.0608, $C_{14}H_{12}NaO_4S$ $[M + Na]^+$ calculated 299.0349, observed 299.0347.

3-(Benzo[*b*]thiophen-2-yl)-4-phenylcyclobut-3-ene-1,2-dione (3.70)



3.69
$C_{14}H_{12}O_4S$
Mol Wt: 276.31

3.70
$C_{18}H_{10}O_2S$
Mol Wt: 290.34

To a solution of cyclobutenone **3.69** (524 mg, 1.90 mmol) in THF (30 mL) at 0 °C was added MeOH (0.15 mL, 3.80 mmol) and BF_3•Et_2O (0.30 mL, 2.28 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (20 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in THF (30 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 1.30 mL, 2.47 mmol) was added. After 90 min, sat. NH_4Cl (25 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a brown oil. The crude material was then dissolved in acetone (25 mL) and I_2 (48 mg, 0.19 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (30 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (30 mL), water (30 mL) and finally brine (40 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (3-5 % ethyl acetate/cyclohexane) yielded the title compound (237 mg, 0.82 mmol, 43 %) as a yellow solid.

MP: Dec. 165 °C

ν_{max} (film): 2971 (s), 2901 (s), 1769 (s), 1599 (w), 1566 (m), 1500 (m), 1482 (w), 1447 (w), 1417 (w), 1394 (w)

δ_H (400 MHz, $CDCl_3$): 8.72 (d, *J*=0.7 Hz, 1H, Ar**H**)

8.33-8.28 (m, 2H, 2 x Ar**H**)

8.02 (m, 1H, Ar**H**)

7.95 (m, 1H, Ar**H**)

7.69-7.62 (m, 3H, 3 x Ar**H**)

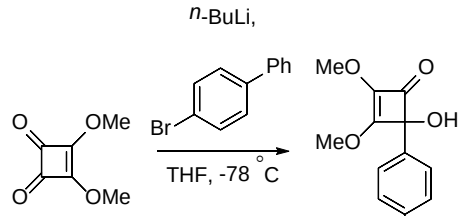
7.57-7.48 (m, 2H, 2 x Ar**H**)

δ_C (100 MHz, $CDCl_3$): 194.7 (**C**), 194.5 (**C**), 183.3 (**C**), 179.3 (**C**), 142.7 (**C**), 138.8 (**C**), 133.5 (**C**H), 132.4 (**C**H), 129.3 (2 x **C**H), 128.7 (2 x **C**H), 128.6 (**C**), 128.2 (**C**H), 128.1 (**C**), 126.1 (**C**H), 125.7 (**C**H), 122.5 (**C**H)

LR-MS (ESI^+): 291 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{20}H_{18}NaO_4S$ $[M + 2MeOH + Na]^+$ calculated 377.0818, observed 377.0819.

4-([1,1'-Biphenyl]-4-yl)-4-hydroxy-2,3-dimethoxycyclobut-2-en-1-one (3.29c)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.29c
$C_{18}H_{16}O_4$
Mol Wt: 296.32

To a solution of 4-bromobiphenyl (1.21 g, 5.20 mmol) in THF (50 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.07 mL, 5.18 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (10 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before being extracted with DCM (3x50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to a brown oil. Purification by column chromatography (15–20 % ethyl acetate/hexane) yielded the title compound (601 mg, 2.03 mmol, 45 %) as a white solid.

Data consistent with literature[2]

MP: 170–171 °C (ethyl acetate/hexane)

δ_H (400 MHz, $CDCl_3$): 7.64-7.56 (m, 6H, 6 x Ar**H**)

7.48-7.42 (m, 2H, 2 x Ar**H**)

7.36 (m, 1H, Ar**H**)

4.13 (s, 3H, OC**H**$_3$)

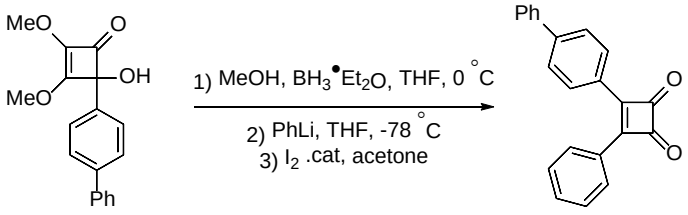
4.06 (s, 3H, OC**H**$_3$)

2.72 (s, 1H, O**H**)

δ_C (100 MHz, $CDCl_3$): 183.5 (**C**), 165.7 (**C**), 141.4 (**C**), 140.6 (**C**), 136.0 (**C**), 135.5 (**C**), 128.8 (2 x **C**H), 127.50 (**C**H), 127.46 (2 x **C**H), 127.1 (2 x **C**H), 126.3 (2 x **C**H), 87.6 (**C**), 60.4 (O**C**H$_3$), 58.7 (O**C**H$_3$)

LR-MS (ESI^+): 319 (9 %, $[M + Na]^+$), 297 (100 %, $[M + H]^+$).

3-([1,1'-Biphenyl]-4-yl)-4-phenylcyclobut-3-ene-1,2-dione (3.30c)



3.29c
$C_{18}H_{16}O_4$
Mol Wt: 296.32

3.30c
$C_{22}H_{14}O_2$
Mol Wt: 310.35

To a solution of cyclobutenone **3.29c** (460 mg, 1.55 mmol) in THF (20 mL) at 0 °C was added MeOH (0.13 mL, 3.10 mmol) and BF_3•Et_2O (0.23 mL, 1.86 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (15 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x20 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in THF (20 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 1.06 mL, 2.02 mmol) was added. After 90 min, sat. NH_4Cl (15 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x20 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before

being concentrated *in vacuo* to a brown oil. The crude material was then dissolved in acetone (20 mL) and I_2 (41 mg, 0.16 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (20 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (20 mL), water (20 mL) and finally brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (2-4 % ethyl acetate/hexane) yielded the title compound (314 mg, 1.01 mmol, 65 %) as a yellow solid.

MP: 148–149 °C (diethyl ether/hexane)

ν_{max} (film): 3093 (w), 2981 (s), 2889 (w), 1773 (s), 1745 (s), 1597 (m), 1559 (s), 1499 (w), 1474 (m), 1406 (s)

δ_H (400 MHz, $CDCl_3$): 8.22-8.18 (m, 2H, 2 x Ar**H**)

8.14-8.10 (m, 2H, 2 x Ar**H**)

7.81-7.78 (m, 2H, 2 x Ar**H**)

7.70-7.66 (m, 2H, 2 x Ar**H**)

7.66-7.56 (m, 3H, 3 x Ar**H**)

7.54-7.49 (m, 2H, 2 x Ar**H**)

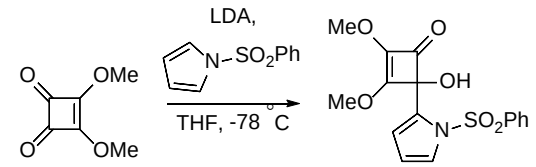
7.45 (m, 1H, Ar**H**)

δ_C (100 MHz, $CDCl_3$): 196.3 (**C**), 196.0 (**C**), 187.1 (**C**), 186.9 (**C**), 146.2 (**C**), 139.5 (**C**), 133.3 (**C**H), 129.3 (2 x **C**H), 129.1 (2 x **C**H), 128.8 (2 x **C**H), 128.6 (**C**H), 128.31 (**C**), 128.25 (2 x **C**H), 127.9 (2 x **C**H), 127.2 (2 x **C**H), 126.9 (**C**)

LR-MS (ESI^+): 311 (100 %, $[M + H]^+$)

HR-MS (ESI^+): $C_{24}H_{22}NaO_4$ $[M + 2MeOH + Na]^+$ calculated 397.1410, observed 397.1414, $C_{23}H_{19}O_3$ $[M + MeOH + H]^+$ calculated 343.1329, observed 343.1326.

4-Hydroxy-2,3-dimethoxy-4-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)cyclobut-2-en-1-one (3.72)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.72
$C_{16}H_{15}NO_6S$
Mol Wt: 349.36

To a solution of *N*-benzenesulfonyl pyrrole (1.07 g, 5.18 mmol) in THF (40 mL) at -78 °C was added LDA (1.0 M in THF, 5.18 mL, 5.18 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (20 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before being extracted with DCM (3x50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (15–25 % ethyl acetate/hexane) yielded the title compound (1021 mg, 2.92 mmol, 65 %) as an off-white solid.

MP: Dec. 127 °C

ν_{max} (film): 3401 (m), 2980 (w), 1773 (w), 1608 (s), 1471 (m), 1449 (w), 1429 (w), 1374 (s), 1350 (s), 1275 (w)

δ_H (400 MHz, $CDCl_3$): 8.00-7.95 (m, 2H, 2 x Ar**H**)

7.61 (m, 1H, Ar**H**)

7.55-7.49 (m, 2H, 2 x Ar**H**)

7.21 (dd, *J*=3.4, 1.7 Hz, 1H, Ar**H**)

6.40 (dd, *J*=3.5, 1.7 Hz, 1H, Ar**H**)

6.25 (dd, *J*=3.5, 3.4 Hz, 1H, Ar**H**)

5.11 (s, 1H, O**H**)

4.11 (s, 3H, OC**H**$_3$)

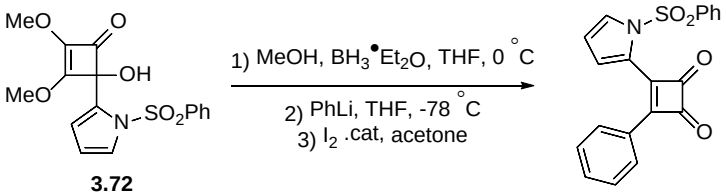
3.98 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 181.7 (**C**), 164.1 (**C**), 139.1 (**C**), 134.3 (**C**), 134.0 (**C**H), 132.7 (**C**), 129.2 (2 x **C**H), 127.1 (2 x **C**H), 125.5 (**C**H), 115.2 (**C**H), 112.3 (**C**H), 84.0 (**C**), 60.4 (O**C**H_3), 58.6 (O**C**H_3)

LR-MS (ESI^+): 372 (58 %, $[M + Na]^+$), 350 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{16}H_{15}NNaO_6S$ $[M + Na]^+$ calculated 372.0512, observed 372.0516, $C_{16}H_{16}NO_6S$ $[M + H]^+$ calculated 350.0693, observed 350.0693.

3-Phenyl-4-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)cyclobut-3-ene-1,2-dione (3.73)



3.72
$C_{16}H_{15}NO_6S$
Mol Wt: 349.36

3.73
$C_{20}H_{13}NO_4S$
Mol Wt: 363.39

To a solution of cyclobutenone **3.72** (873 mg, 2.50 mmol) in THF (30 mL) at 0 °C was added MeOH (0.20 mL, 5.00 mmol) and BF_3•Et_2O (0.39 mL, 3.00 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (20 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in THF (30 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 1.71 mL, 3.25 mmol) was added. After 90 min, sat. NH_4Cl (25 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x30 mL) and the organic phases combined, washed with brine (30 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow solid. The crude material was then dissolved in acetone (30 mL) and I_2 (63 mg, 0.25 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (30 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (30 mL), water (30 mL) and finally brine (30 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (5-10 % ethyl acetate/hexane) yielded the title compound (627 mg, 1.73 mmol, 69 %) as a yellow solid.

MP: Dec. 147 °C

ν_{max} (neat): 3149 (w), 2981 (w), 1790 (s), 1770 (s), 1581 (s), 1535 (m), 1488 (w), 1444 (s), 1385 (s), 1374 (s)

δ_H (400 MHz, $CDCl_3$): 8.12-8.08 (m, 2H, 2 x Ar**H**)

7.79-7.75 (m, 2H, 2 x Ar**H**)

7.63-7.58 (m, 2H, 2 x Ar**H**)

7.56 (dd, *J*=3.2, 1.5 Hz, 1H, Ar**H**)

7.53-7.44 (m, 4H, 4 x Ar**H**)

6.88 (dd, *J*=3.5, 1.5 Hz, 1H, Ar**H**)

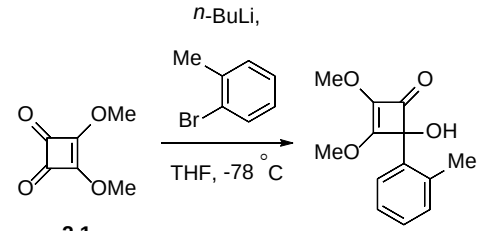
6.55 (dd, *J*=3.5, 3.2 Hz, 1H, Ar**H**)

δ_C (100 MHz, $CDCl_3$): 195.9 (**C**), 193.5 (**C**), 186.8 (**C**), 179.7 (**C**), 137.7 (**C**), 134.5 (**C**H), 134.0 (**C**H), 129.4 (2 x **C**H), 129.3 (**C**H), 129.1 (br, 4 x **C**H) , 128.3 (**C**), 127.0 (**C**H), 123.3 (**C**), 121.1 (**C**H), 115.8 (**C**H)

LR-MS (ESI^+): 386 (73 %, $[M + H]^+$), 364 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{20}H_{14}NO_4S$ $[M + H]^+$ calculated 364.0638, observed 364.0635

4-Hydroxy-2,3-dimethoxy-4-(*o*-tolyl)cyclobut-2-en-1-one (3.47)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.47
$C_{13}H_{14}O_4$
Mol Wt: 234.25

To a solution of 2-bromotoluene (0.62 mL, 5.18 mmol) in THF (40 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.07 mL, 5.18 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (20 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before being extracted with DCM (3x50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography

(15 % ethyl acetate/hexane) yielded the title compound (481 mg, 2.05 mmol, 46 %) as a white solid.

Data consistent with literature[83]

MP: 98-99 °C (diethyl ether/hexane)

δ_H (400 MHz, $CDCl_3$): 7.44 (dd, *J*=7.7, 1.3 Hz, 1H, Ar**H**)

7.26-7.20 (m, 2H, 2 x Ar**H**)

7.15 (m, 1H, Ar**H**)

4.21 (s, 3H, OC**H**$_3$)

4.01 (s, 3H, OC**H**$_3$)

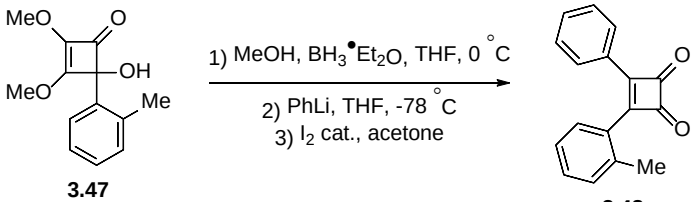
2.69 (s, 1H, O**H**)

2.64 (s, 3H, C**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 184.3 (**C**), 166.7 (**C**), 137.7 (**C**), 135.9 (**C**), 134.5 (**C**), 131.9 (**C**H), 128.7 (**C**H), 126.7 (**C**H), 125.6 (**C**H), 89.1 (**C**), 60.5 (O**C**H$_3$), 58.6 (O**C**H$_3$), 20.8 (**C**H$_3$)

LR-MS (ESI^+): 257 (2 %, $[M + Na]^+$), 235 (100 %, $[M + H]^+$)

3-Phenyl-4-(*o*-tolyl)cyclobut-3-ene-1,2-dione (3.48)



3.47
$C_{13}H_{14}O_4$
Mol Wt: 234.25

3.48
$C_{17}H_{12}O_2$
Mol Wt: 248.28

To a solution of cyclobutenone **3.47** (210 mg, 0.90 mmol) in THF (20 mL) at 0 °C was added MeOH (0.07 mL, 1.80 mmol) and BF_3•Et_2O (0.14 mL, 1.08 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (10 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x20 mL) and the organic phases combined, washed with brine (30 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude

material was dissolved in THF (20 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 0.62 mL, 1.17 mmol) was added. After 90 min, sat. NH_4Cl (15 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x30 mL) and the organic phases combined, washed with brine (30 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow solid. The crude material was then dissolved in acetone (15 mL) and I_2 (23 mg, 0.09 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (15 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (15 mL), water (15 mL) and finally brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to a yellow solid. Purification by column chromatography (1-2 % ethyl acetate/hexane) yielded the title compound (156 mg, 0.63 mmol, 70 %) as a yellow solid.

MP: 85–87 °C (diethyl ether/hexane)

ν_{max} (neat): 1778 (s), 1764 (s), 1599 (m), 1577 (m), 1569 (m), 1477 (w), 1448 (w), 1386 (w), 1346 (m), 1318 (w)

δ_H (400 MHz, $CDCl_3$): 8.01-7.94 (m, 2H, 2 x Ar**H**)

7.59 (m, 1H, Ar**H**)

7.52-7.45 (m, 4H, 4 x Ar**H**)

7.41 (m, 1H, Ar**H**)

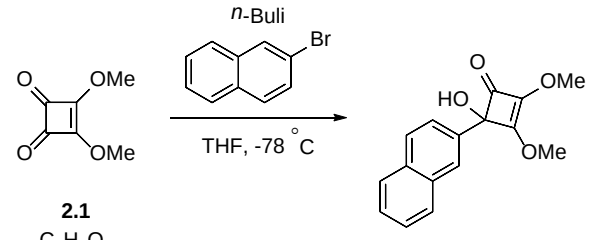
7.36 (m, 1H, Ar**H**)

2.32 (s, 3H, C**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 196.5 (**C**), 195.8 (**C**), 192.0 (**C**), 188.9 (**C**), 136.4 (**C**), 133.9 (**C**H), 131.5 (**C**H), 131.3 (**C**H), 129.3 (2 x **C**H), 128.8 (2 x **C**H), 128.3 (**C**), 128.2 (**C**), 127.2 (**C**H), 126.2 (**C**H), 20.6 (**C**H$_3$)

LR-MS (ESI^+): 249 (100 %, $[M + H]^+$).

4-Hydroxy-2,3-dimethoxy-4-(naphthalen-2-yl)cyclobut-2-en-1-one (3.54)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.54
$C_{16}H_{14}O_4$
Mol Wt: 270.28

To a solution of 2-bromonaphthalene (1.12 g, 5.40 mmol) in THF (50 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.07 mL, 5.18 mmol). After 30 min, this solution was added *via* cannula to a solution of cyclobutenedione **2.1** (639 mg, 4.50 mmol) in THF (30 mL) at -78 °C. After 90 min, sat. NH_4Cl (30 mL) was added and the solution warmed to RT before being extracted with DCM (3x50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to an orange oil. Purification by column chromatography (20–25 % ethyl acetate/hexane) yielded the title compound (572 mg, 2.12 mmol, 47 %) as an off-white solid.

Data consistent with literature[83]

MP: 97-99 °C (diethyl ether/hexane)

δ_H (400 MHz, $CDCl_3$): 8.03 (br d, *J*=1.7 Hz, 1H, Ar**H**)

7.81 (br d, *J*=8.7 Hz, 1H, Ar**H**)

7.84-7.80 (m, 2H, 2 x Ar**H**)

7.59 (dd, *J*=8.7, 1.7 Hz, 1H, Ar**H**)

7.52-7.46 (m, 2H, 2 x Ar**H**)

4.34 (s, 1H, O**H**)

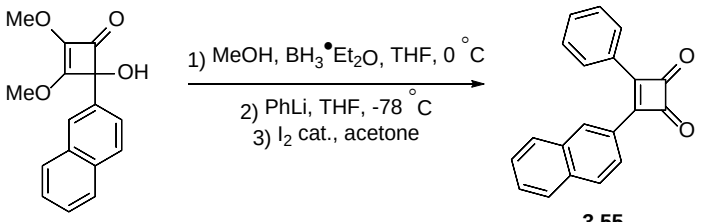
4.08 (s, 3H, OC**H**$_3$)

4.05 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 184.2 (**C**), 166.4 (**C**), 135.3 (**C**), 134.6 (**C**), 133.1 (**C**), 133.0 (**C**), 128.3 (**C**H), 128.2 (**C**H), 127.6 (**C**H), 126.25 (**C**H), 126.22 (**C**H), 125.2 (**C**H), 123.4 (**C**H), 87.8 (**C**), 60.2 (O**C**H_3), 58.6 (O**C**H_3)

LR-MS (ESI^+): 293 (4 %, $[M + Na]^+$), 271 (90 %, $[M + H]^+$).

3-(Naphthalen-2-yl)-4-phenylcyclobut-3-ene-1,2-dione (3.55)



3.54
$C_{16}H_{14}O_4$
Mol Wt: 270.28

3.55
$C_{20}H_{12}O_2$
Mol Wt: 284.31

To a solution of cyclobutenone **3.54** (350 mg, 1.29 mmol) in THF (15 mL) at 0 °C was added MeOH (0.10 mL, 2.59 mmol) and BF_3•Et_2O (0.19 mL, 1.55 mmol). After 3 h, the reaction was quenched upon addition of sat. $NaHCO_3$ (15 mL) and warmed to RT. The aqueous phase was extracted with Et_2O (3x20 mL) and the organic phases combined, washed with brine (25 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a yellow oil. The crude material was dissolved in THF (15 mL) and cooled to -78 °C before phenyllithium (1.9 M in dibutyl ether, 0.88 mL, 1.68 mmol) was added. After 90 min, sat. NH_4Cl (15 mL) was added and the solution warmed to RT. The aqueous phase was extracted with DCM (3x20 mL) and the organic phases combined, washed with brine (20 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to an orange oil. The crude material was then dissolved in acetone (20 mL) and I_2 (33 mg, 0.13 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (20 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (20 mL), water (20 mL) and finally brine (20 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (1 % ethyl acetate/hexane) yielded the title compound (194 mg, 0.68 mmol, 53 %) as a yellow solid.

MP: 155-157 °C (DCM/hexane)

ν_{max} (neat): 3057 (w), 1772 (s). 1625 (w), 1599 (m), 1559 (m), 1490 (w), 1465 (w), 1448 (w), 1387 (w), 1344 (s)

δ_H (400 MHz, $CDCl_3$): 8.77 (d, *J*=0.9 Hz, 1H, Ar**H**)

8.15-8.11 (m, 2H, 2 x Ar**H**)

8.03-7.95 (m, 3H, 3 x Ar**H**)

7.91 (dd, *J*=8.3, 0.9 Hz, 1H, Ar**H**)

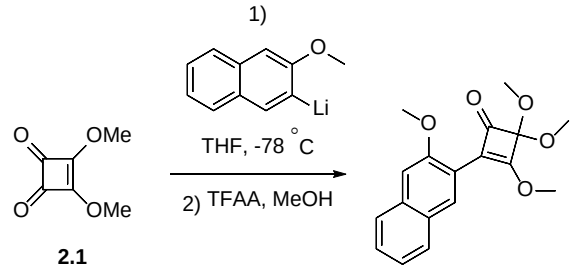
7.69-7.56 (m, 5H, 5 x Ar**H**)

δ_C (100 MHz, $CDCl_3$): 196.4 (**C**), 196.1 (**C**), 187.3 (**C**), 187.2 (**C**), 135.4 (**C**), 133.3 (**C**H), 132.9 (**C**), 130.2 (**C**H), 129.7 (**C**H), 129.3 (2 x **C**H), 129.15 (**C**H), 129.10 (**C**H), 128.3 (2 x **C**H), 128.0 (**C**H), 127.3 (**C**H), 125.5 (**C**), 123.5 (**C**H), one **C** coincident or not observed

LR-MS (ESI^+): 307 (6 %, $[M + Na]^+$), 285 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{22}H_{20}NaO_4$ $[M + 2MeOH + Na]^+$ calculated 371.1254, observed 371.1259, $C_{21}H_{17}O_3$ $[M + MeOH + H]^+$ calculated 317.1175, observed 317.1175.

3,4,4-Trimethoxy-2-(3-methoxynaphthalen-2-yl)cyclobut-2-en-1-one (3.56)



2.1
$C_6H_6O_4$
Mol Wt: 142.11

3.56
$C_{18}H_{18}O_5$
Mol Wt: 314.34

To a solution of 2-methoxynaphthalene (949 mg, 6.00 mmol) in THF (50 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 2.40 mL, 6.00 mmol). The solution was warmed to RT for 3 h before being added *via* cannula to a solution of cyclobutenedione **2.1** (711 mg, 5.00 mmol) in THF (30 mL) at -78 °C. After 2 h, TFAA (0.90 mL, 6.50 mmol) was added followed after 2 h by methanol (10 mL) and subsequent warming to RT. Water (40 mL) was added and the aqueous extracted with DCM (3x50 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to an orange oil. Purification by column

chromatography (20–30 % ethyl acetate/hexane) yielded the title compound (1021 mg, 3.25 mmol, 65 %) as a yellow oil.

ν_{max} (neat): 2988 (m), 2901 (m), 1826 (m), 1758 (s), 1617 (w), 1505 (m), 1485 (m), 1447 (m), 1361 (m), 1342 (m)

δ_H (400 MHz, $CDCl_3$): 8.13 (br s, 1H, Ar**H**)

7.79 (dd, *J*=8.1, 0.7 Hz, 1H, Ar**H**)

7.71 (dd, *J*=8.1, 0.7 Hz, 1H, Ar**H**)

7.44 (ddd, *J*=8.1, 6.9, 1.3 Hz, 1H, Ar**H**)

7.34 (ddd, *J*=8.1, 6.9, 1.3 Hz, 1H, Ar**H**)

7.13 (br s, 1H, Ar**H**)

4.19 (s, 3H, OC**H**$_3$)

3.95 (s, 3H, OC**H**$_3$)

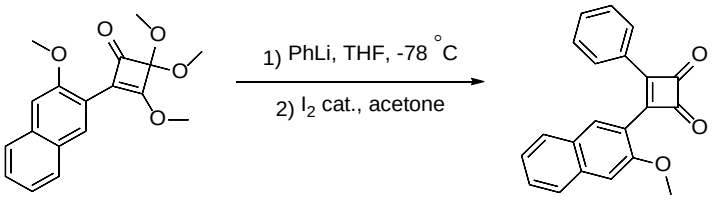
3.65 (s, 6H, 2 x OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 189.3 (**C**), 181.4 (**C**), 154.7 (**C**), 134.5 (**C**), 129.8 (**C**H), 128.2 (**C**), 128.0 (**C**H), 127.0 (**C**H), 126.7 (**C**), 126.3 (**C**H), 124.0 (**C**H), 118.4 (**C**), 114.0 (**C**), 105.6 (**C**H), 60.1 (O**C**H$_3$), 55.5 (O**C**H$_3$), 53.7 (2 x O**C**H$_3$)

LR-MS (ESI^+): 337 (27 %, $[M + Na]^+$), 315 (100 %, $[M + H]^+$),
283 (53 %, $[M – MeOH + H]^+$)

HRMS (ESI^+): $C_{18}H_{18}NaO_5$ $[M + Na]^+$ calculated 337.1046, observed 337.1055, $C_{17}H_{15}O_4$ $[M - MeOH + H]^+$ calculated 283.0965, observed 283.0967.

3-(3-Methoxynaphthalen-2-yl)-4-phenylcyclobut-3-ene-1,2-dione (3.57)



3.56
$C_{18}H_{18}O_5$
Mol Wt: 314.34

3.57
$C_{21}H_{14}O_3$
Mol Wt: 314.34

To a solution of cyclobutenone **3.56** (460 mg, 1.46 mmol) in THF (30 mL) at -78 °C was added phenyllithium (1.9 M in dibutyl ether, 1.00 mL, 1.90 mmol) followed after 90 min by sat. NH_4Cl (20 mL) was added and subsequent warming to RT. The aqueous phase was extracted with DCM (3x30 mL) and the organic phases combined, washed with brine (40 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to a brown oil. The crude material was then dissolved in acetone (25 mL) and I_2 (38 mg, 0.15 mmol) was added. After 30 min, the solution was concentrated *in vacuo* and diethyl ether (30 mL) was added. The organic phase was washed sequentially with sat. $Na_2S_2O_3$ (30 mL), water (30 mL) and finally brine (40 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to an orange solid. Purification by column chromatography (3-5 % ethyl acetate/hexane) yielded the title compound (289 mg, 0.92 mmol, 63 %) as a yellow solid.

MP: 231-233 °C (DCM/hexane)

ν_{max} (neat): 2980 (w), 1774 (s), 1760 (s), 1628 (w), 1597 (m), 1575 (m), 1566 (m), 1505 (w), 1492 (w), 1470 (w)

δ_H (400 MHz, $CDCl_3$): 8.45 (br s, 1H, Ar**H**)

7.93 (br dd, *J*=8.2, 0.6 Hz, 1H, Ar**H**)

7.91-7.87 (m, 2H, 2 x Ar**H**)

7.81 (br dd, *J*=8.3, 0.6 Hz, 1H, Ar**H**)

7.62-7.56 (m, 2H, 2 x Ar**H**)

7.51-7.47 (m, 2H, 2 x Ar**H**)

7.45 (ddd, *J*=8.2, 7.0, 1.1 Hz, 1H, Ar**H**)

7.27 (br s, 1H, Ar**H**)

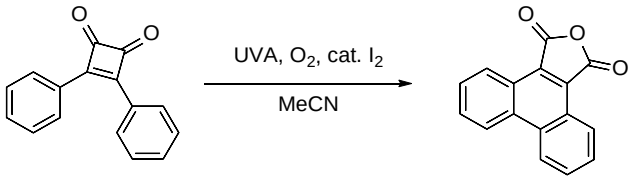
3.71 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 196.6 (**C**), 188.9 (**C**), 185.3 (**C**), 181.6 (**C**), 133.0 (**C**H), 131.0 (**C**H), 129.4 (**C**), 129.3 (2 x **C**H), 129.2 (**C**H), 129.0 (**C**H), 128.4 (2 x **C**H), 128.0 (**C**), 126.6 (**C**H), 124.9 (**C**H), 124.2 (**C**), 123.2 (**C**), 119.2 (**C**), 106.4 (**C**H), 55.0 (O**C**H_3)

LR-MS (ESI^+): 337 (3 %, $[M + Na]^+$), 315 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{23}H_{22}NaO_5$ $[M + 2MeOH + Na]^+$ calculated 401.1359, observed 401.1365, $C_{22}H_{19}O_4$ $[M + MeOH + H]^+$ calculated 347.1278, observed 347.1280.

Phenanthrene-9,10-dicarboxylic anhydride (3.6)



3.5
$C_{16}H_{10}O_2$
Mol Wt: 234.25

3.6
$C_{16}H_8O_3$
Mol Wt: 248.24

A solution of cyclobutenedione **3.5** (141 mg, 0.60 mmol) and I_2 (15 mg, 0.06 mmol) in acetonitrile (30 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid which was washed with cold acetonitrile (50 mL) to yield the title compound (131 mg, 0.53 mmol, 88 %) as a yellow solid.

Data consistent with literature[84]

MP: Stable to 300 °C

δ_H (400 MHz, $CDCl_3$): 9.04 (br dd, *J*=8.1, 0.9 Hz, 2H, 2 x Ar**H**)

8.82 (br d, *J*=8.4 Hz, 2H, 2 x Ar**H**)

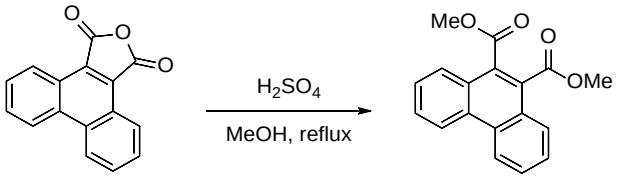
7.95 (ddd, *J*=8.4, 7.1, 1.4 Hz, 2H, 2 x Ar**H**)

7.87 (ddd, *J*=8.1, 7.1, 1.4 Hz, 2H, 2 x Ar**H**)

δ_C (100 MHz, $CDCl_3$): 157.1 (2 x **C**), 131.0 (2 x **C**), 129.7 (2 x **C**H), 129.3 (2 x **C**), 129.1 (2 x **C**H), 126.4 (2 x **C**H), 123.5 (2 x **C**H), two **C** coincident or not observed

LR-MS (ESI^+): 249 (41 %, $[M + H]^+$).

Dimethyl phenanthrene-9,10-dicarboxylate (3.77)



3.6
$C_{16}H_8O_3$
Mol Wt: 248.24

3.77
$C_{18}H_{14}O_4$
Mol Wt: 294.31

To a suspension of anhydride **3.6** (149 mg, 0.60 mmol) in methanol (30 mL) was added H_2SO_4 (conc. 0.15 mL) before being heated to reflux for 30 h. The resultant solution was cooled to RT and concentrated *in vacuo* to an orange solid. Purification by column chromatography (10 % diethyl ether/hexane) yielded the title compound (108 mg, 0.37 mmol, 61 %) as a pale, yellow solid.

Data consistent with literature[85]

MP: 131–133 °C (diethyl ether/hexane)

δ_H (400 MHz, $CDCl_3$): 8.73 (ddd, *J*=8.3, 1.1, 0.6 Hz, 2H, 2 x Ar**H**)

8.18 (ddd, *J*=8.4, 1.3, 0.6 Hz, 2H, 2 x Ar**H**)

7.76 (ddd, *J*=8.4, 7.0, 1.3 Hz, 2H, 2 x Ar**H**)

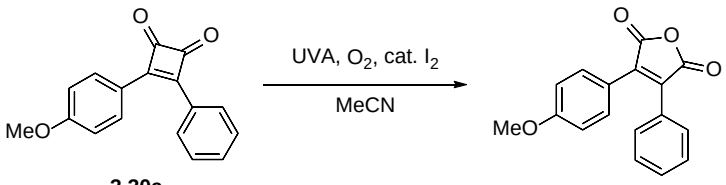
7.68 (ddd, *J*=8.3, 7.0, 1.1 Hz, 2H, 2 x Ar**H**)

4.05 (s, 6H, 2 x OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 168.3 (2 x **C**), 131.0 (2 x **C**), 129.8 (2 x **C**), 128.5 (2 x **C**H), 127.7 (2 x **C**H), 127.0 (2 x **C**), 126.9 (2 x **C**H), 122.9 (2 x **C**H), 52.8 (2 x O**C**H_3)

LR-MS (ESI^+): 317 (52 %, $[M + Na]^+$), 295 (11 %, $[M + Na]^+$).

3-(4-Methoxyphenyl)-4-phenylmaleic anhydride (3.31)



3.30a
$C_{17}H_{12}O_3$
Mol Wt: 264.28

3.31
$C_{17}H_{12}O_4$
Mol Wt: 280.28

A solution of cyclobutenedione **3.30a** (106 mg, 0.40 mmol) and I_2 (10 mg, 0.04 mmol) in acetonitrile (20 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to yield the title compound (110 mg, 0.39 mmol, 98 %) as an orange solid.

MP: 148–150 °C (diethyl ether/hexane)

ν_{max} (film): 2937 (w), 2841 (w), 1827 (m), 1756 (s), 1602 (s), 1513 (m), 1493 (w), 1446 (w), 1423 (w), 1353 (m)

δ_H (400 MHz, $CDCl_3$): 7.60-7.53 (m, 4H, 4 x Ar**H**)

7.49-7.40 (m, 3H, 3 x Ar**H**)

6.93-6.88 (m, 2H, 2 x Ar**H**)

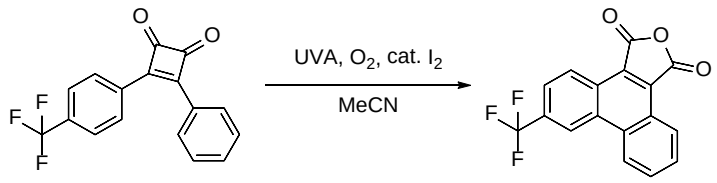
3.85 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 165.2 (**C**), 165.0 (**C**), 162.0 (**C**), 137.8 (**C**), 135.7 (**C**), 131.7 (2 x **C**H), 130.7 (**C**H), 129.5 (2 x **C**H), 128.9 (2 x **C**H), 127.7 (**C**), 119.4 (**C**), 114.4 (2 x **C**H), 55.4 (O**C**H$_3$)

LR-MS (ESI^+): 281 (100 %, $[M + H]^+$)

HRMS (EI): $C_{17}H_{12}O_4$ $[M]^{+\bullet}$ calculated 280.0736, observed 280.0732.

6-(Trifluoromethyl)phenanthrene-9,10-dicarboxylic anhydride (3.35)



3.30b
$C_{17}H_9F_3O_2$
Mol Wt: 302.25

3.35
$C_{17}H_7F_3O_3$
Mol Wt: 316.24

A solution of cyclobutenedione **3.30b** (60 mg, 0.20 mmol) and I_2 (5 mg, 0.02 mmol) in acetonitrile (10 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid which was washed with cold acetonitrile (30 mL) to yield the title compound (58 mg, 0.18 mmol, 92 %) as a white solid.

MP: 225–226 °C (DCM)

ν_{max} (neat): 2923 (w), 1843 (m), 1811 (w), 1577 (s), 1624 (w), 1606 (w), 1567 (w), 1521 (w), 1454 (w), 1417 (m)

δ_H (400 MHz, $CDCl_3$): 9.15 (d, *J*=8.6 Hz, 1H, Ar**H**)

9.07 (br dd, *J*=8.1, 1.1 Hz, 1H, Ar**H**)

9.05 (br s, 1H, Ar**H**)

8.84 (br d, *J*=8.2 Hz, 1H, Ar**H**)

8.06 (dd, *J*=8.6, 1.6 Hz, 1H, Ar**H**)

8.03 (ddd, *J*=8.6, 7.1, 1.6 Hz, 1H, Ar**H**)

7.95 (ddd, *J*=8.2, 7.1, 1.1 Hz, 1H, Ar**H**)

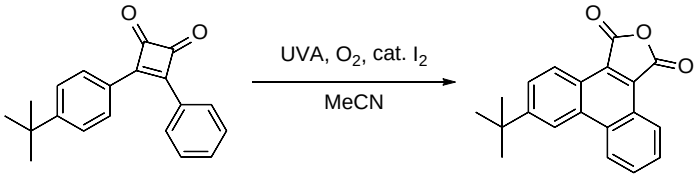
δ_C (100 MHz, $CDCl_3$): 163.01 (**C**), 162.97 (**C**), 133.9 (**C**), 133.7 (**C**), 132.5 (**C**), 132.2 (**C**), 131.8 (**C**H), 130.1 (**C**H), 129.1 (q, *J*=288.3 Hz, **C**F_3), 127.4 (**C**H), 126.7 (**C**H), 126.6 (**C**), 125.1 (q, *J*=3.3 Hz, **C**H), 123.7 (**C**H), 122.4 (**C**), 120.9 (q, *J*=4.2 Hz, **C**H), one **C** coincident or not observed

δ_F (376 MHz, $CDCl_3$): -62.81 (s, C**F**$_3$)

LR-MS (EI): 316 (43 %, $[M]^{+\bullet}$)

HRMS (EI): $C_{17}H_7F_3O_3$ $[M]^{+\bullet}$ calculated 316.0342, observed 316.0342.

6-(*Tert*-butyl)phenanthrene-9,10-dicarboxylic anhydride (3.36)



3.30d
$C_{20}H_{18}O_2$
Mol Wt: 290.36

3.36
$C_{20}H_{16}O_3$
Mol Wt: 304.35

A solution of cyclobutenedione **3.30d** (116 mg, 0.40 mmol) and I_2 (10 mg, 0.04 mmol) in acetonitrile (20 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid which was washed with cold acetonitrile (40 mL) to yield the title compound (74 mg, 0.24 mmol, 61 %) as a yellow solid.

MP: 256–257 °C (DCM)

ν_{max} (neat): 2965 (m), 1840 (m), 1772 (s), 1629 (w), 1619 (w), 1564 (w), 1513 (m), 1477 (w), 1448 (m), 1419 (m)

δ_H (400 MHz, $CDCl_3$): 8.98 (ddd, *J*=8.1, 1.5, 0.6 Hz, 1H, Ar**H**)

8.92 (dd, *J*=8.5, 0.5 Hz, 1H, Ar**H**)

8.82 (app dt, *J*=8.5, 0.5 Hz, 1H, Ar**H**)

8.77 (br d, *J*=1.8 Hz, 1H, Ar**H**)

7.96-7.90 (m, 2H, 2 x Ar**H**)

7.84 (ddd, *J*=8.1, 7.0, 1.1 Hz, 1H, Ar**H**)

1.54 (s, 9H, C(C**H**$_3$)$_3$)

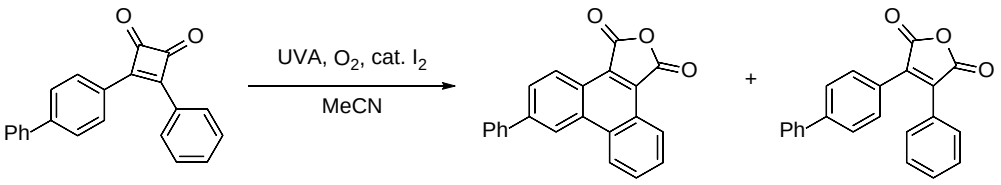
δ_C (100 MHz, $CDCl_3$): 163.74 (**C**), 163.70 (**C**), 154.6 (**C**), 134.2 (**C**), 134.1 (**C**), 130.6 (**C**H), 128.9 (**C**H), 128.4 (**C**), 127.7 (**C**H), 127.5 (**C**), 126.4 (**C**H), 126.0 (**C**H), 125.0 (**C**), 123.4 (**C**H), 122.7 (**C**), 119.2 (**C**H), 35.8 (**C**$(CH_3)_3$), 31.3 (C(**C**$H_3)_3$)

LR-MS (EI): 304 (31 %, $[M]^{+\bullet}$), 289 (100 %, $[M - CH_3]^{+\bullet}$)

HRMS (EI): $C_{20}H_{16}O_3$ $[M]^{+\bullet}$ calculated 304.1094, observed 304.1094, $C_{19}H_{13}O_3$ $[M - CH_3]^{+\bullet}$ calculated 289.0859, observed 289.0858.

6-Phenylphenanthrene-9,10-dicarboxylic anhydride (3.38)

3-([1,1'-Biphenyl]-4-yl)-4-phenylmaleic anhydride (3.37)



3.30c
$C_{22}H_{14}O_2$
Mol Wt: 310.35

3.38
$C_{22}H_{12}O_3$
Mol Wt: 324.34

3.37
$C_{22}H_{14}O_3$
Mol Wt: 326.35

A solution of cyclobutenedione **3.30c** (124 mg, 0.40 mmol) and I_2 (10 mg, 0.04 mmol) in acetonitrile (20 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid which was washed with cold acetonitrile (40 mL) to yield phenanthrene **3.38** (32 mg, 0.10 mmol, 25 %) as a yellow solid. The resultant filtrate was concentrated *in vacuo* followed by purification *via* column chromatography (5 % diethyl ether/petroleum ether) to yield anhydride **3.37** (93 mg, 0.28 mmol, 71 %) as an orange solid.

6-Phenylphenanthrene-9,10-dicarboxylic anhydride (**3.38**)

MP: 255–256 °C (DCM)

ν_{max} (neat): 2981 (w), 1841 (s), 1812 (m), 1768 (s), 1628 (m), 1615 (m), 1601 (m), 1578 (w), 1511 (m), 1497 (m)

δ_H (400 MHz, $CDCl_3$): 9.08 (d, *J*=8.5 Hz, 1H, Ar**H**)

9.04 (dd, *J*=8.1, 1.0 Hz, 1H, Ar**H**)

8.97 (d, *J*=1.6 Hz, 1H, Ar**H**)

8.89 (br d, *J*=8.4 Hz, 1H, Ar**H**)

8.11 (dd, *J*=8.5, 1.6 Hz, 1H, Ar**H**)

7.96 (ddd, *J*=8.4, 7.0, 1.5 Hz, 1H, Ar**H**)

7.89 (ddd, *J*=8.1, 7.0, 1.5 Hz, 1H)

7.86-7.81 (m, 2H, 2 x Ar**H**)

7.63-7.58 (m, 2H, 2 x Ar**H**)

7.52 (m, 1H, Ar**H**)

δ_C (100 MHz, $CDCl_3$): 163.6 (**C**), 163.5 (**C**), 143.9 (**C**), 140.2 (**C**), 134.6 (**C**), 134.1 (**C**), 130.9 (br, 2 x **C**H), 129.2 (2 x **C**H), 128.6 (br, 2 x **C**H), 128.4 (**C**), 128.0 (**C**), 127.8 (2 x **C**H), 126.8 (**C**H), 126.5 (**C**H), 125.1 (**C**), 123.8 (**C**), 123.5 (**C**H), 121.7 (**C**H)

LR-MS (ESI^+): 325 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{23}H_{16}NaO_4$ $[M + MeOH + Na]^+$ calculated 379.0941, observed 379.0942

3-([1,1'-biphenyl]-4-yl)-4-phenylmaleic anhydride (**3.37**)

MP: 159–161 °C (DCM/hexane)

ν_{max} (film): 2988 (m), 2901 (m), 1827 (w), 1760 (s), 1604 (w), 1577 (w), 1500 (w), 1447 (w), 1406 (w), 1394 (w)

δ_H (400 MHz, $CDCl_3$): 7.70-7.56 (m, 8H, 8 x Ar**H**)

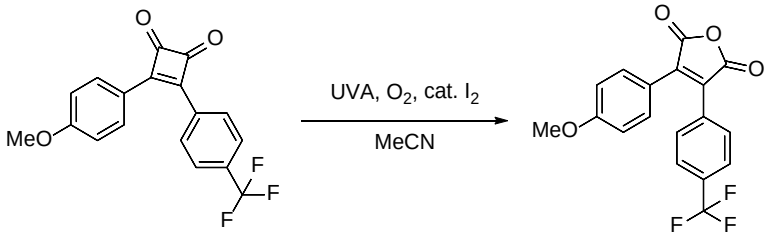
7.53-7.38 (m, 6H, 6 x Ar**H**)

δ_C (100 MHz, $CDCl_3$): 164.9 (**C**), 164.8 (**C**), 143.9 (**C**), 139.6 (**C**), 137.8 (**C**), 137.7 (**C**), 131.1 (**C**H), 130.2 (2 x **C**H), 129.7 (2 x **C**H), 129.01 (2 x **C**H), 128.99 (2 x **C**H), 128.3 (**C**H), 127.5 (2 x **C**H), 127.3 (**C**), 127.1 (2 x **C**H), 126.0 (**C**)

LR-MS (ESI^+): 327 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{23}H_{18}NaO_4$ $[M + MeOH + Na]^+$ calculated 381.1097, observed 381.1101.

3-(4-Methoxyphenyl)-4-(4-(trifluomethyl)phenyl)maleic anhydride (3.42)



3.41
$C_{18}H_{11}F_3O_3$
Mol Wt: 332.28

3.42
$C_{18}H_{11}F_3O_4$
Mol Wt: 348.28

A solution of cyclobutenedione **3.41** (100 mg, 0.30 mmol) and I_2 (7.5 mg, 0.03 mmol) in acetonitrile (15 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange oil. Purification by column chromatography (5–10 % ethyl acetate/hexane) yielded the title compound (93 mg, 0.28 mmol, 93 %) as a yellow oil.

ν_{max} (film): 2939 (w), 1829 (w), 1764 (s), 1603 (m), 1508 (m), 1464 (w), 1411 (w), 1354 (w), 1324 (s), 1261 (s)

δ_H (400 MHz, $CDCl_3$): 7.69 (app s, 4H, 4 x Ar**H**)

7.59-7.54 (m, 2H, 2 x Ar**H**)

6.95-6.91 (m, 2H, 2 x Ar**H**)

3.87 (s, 3H, OC**H**$_3$)

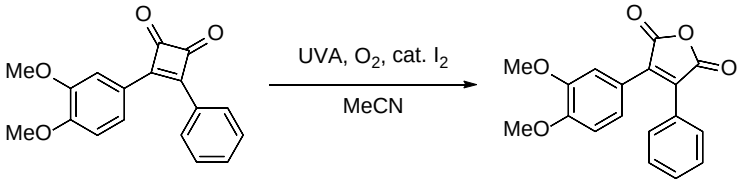
δ_C (100 MHz, $CDCl_3$): 164.7 (**C**), 164.6 (**C**), 162.5 (**C**), 139.4 (**C**), 133.7 (**C**), 132.4 (q, *J*=33.0 Hz, **C**), 131.9 (2 x **C**H), 131.3 (q, *J*=1.5 Hz, **C**), 129.9 (2 x **C**H), 125.9 (q, *J*=3.9 Hz, 2 x **C**H), 123.6 (q, *J*=272.9 Hz, **C**F_3), 118.9 (**C**), 114.7 (2 x **C**H), 55.5 (O**C**H_3)

δ_F (376 MHz, $CDCl_3$): -63.35 ppm (s, 3F, C**F**$_3$)

LR-MS (ESI^+): 349 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{19}H_{15}F_3NaO_5$ $[M + MeOH + Na]^+$ calculated 403.0764, observed 403.0768.

3-(3,4-Dimethoxyphenyl)-4-phenylmaleic anhydride (3.46a)



3.45a
$C_{18}H_{14}O_4$
Mol Wt: 294.31

3.46a
$C_{18}H_{14}O_5$
Mol Wt: 310.31

A solution of cyclobutenedione **3.45a** (88 mg, 0.30 mmol) and I_2 (7.5 mg, 0.03 mmol) in acetonitrile (30 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange oil. Purification by column chromatography (10 % ethyl acetate/hexane) yielded the title compound (89 mg, 0.29 mmol, 96 %) as a yellow oil.

ν_{max} (film): 2937 (w), 1825 (w), 1757 (s), 1599 (m), 1518 (s), 1494 (w), 1464 (w), 1423 (w), 1356 (m), 1257 (s)

δ_H (400 MHz, $CDCl_3$): 7.59-7.54 (m, 2H, 2 x Ar**H**)

7.50-7.42 (m, 3H, 3 x Ar**H**)

7.38 (dd, *J*=8.6, 2.1 Hz, 1H, Ar**H**)

7.03 (d, *J*=2.1 Hz, 1H, Ar**H**)

6.89 (d, *J*=8.6 Hz, 1H, Ar**H**)

3.93 (s, 3H, OC**H**$_3$)

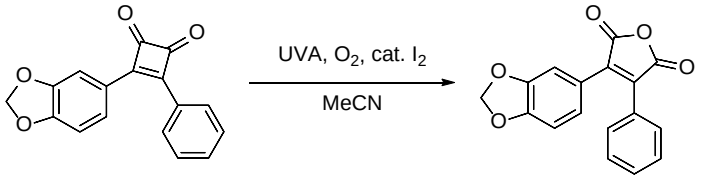
3.64 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 165.1 (**C**), 165.0 (**C**), 151.8 (**C**), 148.9 (**C**), 137.8 (**C**), 135.8 (**C**), 130.8 (**C**H), 129.6 (2 x **C**H), 128.9 (2 x **C**H), 127.8 (**C**), 124.2 (**C**H), 119.6 (**C**), 112.2 (**C**H), 111.1 (**C**H), 56.0 (O**C**H$_3$), 55.7 (O**C**H$_3$)

LR-MS (ESI^+): 311 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{18}H_{14}NaO_5$ $[M + Na]^+$ calculated 333.0733, observed 333.0736.

3-(Benzo[*d*][1,3]dioxol-5-yl)-4-phenylmaleic anhydride (3.46b)



3.45b
$C_{17}H_{10}O_4$
Mol Wt: 278.26

3.46b
$C_{17}H_{10}O_5$
Mol Wt: 294.26

A solution of cyclobutenedione **3.45b** (83 mg, 0.30 mmol) and I_2 (7.5 mg, 0.03 mmol) in acetonitrile (15 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange oil. Purification by column chromatography (10 % ethyl acetate/hexane) yielded the title compound (87 mg, 0.30 mmol, 99 %) as an orange oil.

ν_{max} (film): 2988 (m), 2901 (m), 1826 (m), 1758 (s), 1617 (w), 1505 (m), 1485 (m), 1447 (m), 1361 (m), 1342 (m)

δ_H (400 MHz, $CDCl_3$): 7.57-7.53 (m, 2H, 2 x Ar**H**)

7.50-7.41 (m, 3H, 3 x Ar**H**)

7.21 (dd, *J*=8.2, 1.8 Hz, 1H, Ar**H**)

7.00 (d, *J*=1.8 Hz, 1H, Ar**H**)

6.84 (d, *J*=8.2 Hz, 1H, Ar**H**)

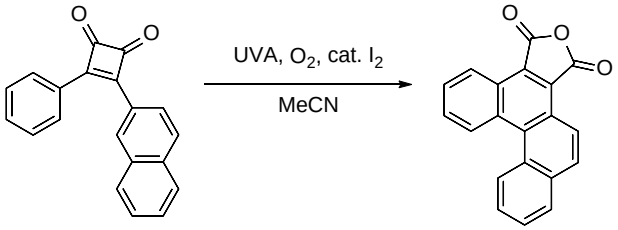
6.03 (s, 2H, OC**H**$_2$O)

δ_C (100 MHz, $CDCl_3$): 164.9 (**C**), 164.8 (**C**), 150.3 (**C**), 148.1 (**C**), 137.6 (**C**), 136.3 (**C**), 130.9 (**C**H), 129.5 (2 x **C**H), 129.0 (2 x **C**H), 127.4 (**C**), 125.5 (**C**H), 120.8 (**C**), 109.5 (**C**H), 108.9 (**C**H), 101.8 (O**C**H$_2$O)

LR-MS (ESI^+): 295 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{17}H_{10}NaO_5$ $[M + Na]^+$ calculated 317.0420, observed 317.0423.

Benzo[3,4]phenanthro[1,2-*c*]furan-1,3-dione (3.58a)



3.55
$C_{20}H_{12}O_2$
Mol Wt: 284.31

3.58a
$C_{20}H_{10}O_3$
Mol Wt: 298.30

A solution of cyclobutenedione **3.55** (114 mg, 0.40 mmol) and I_2 (10 mg, 0.04 mmol) in acetonitrile (40 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid which was washed with cold acetonitrile (40 mL) to yield the title compound (78 mg, 0.26 mmol, 65 %) as a yellow solid.

MP: 261-262 °C (DCM)

ν_{max} (neat): 1839 (m), 1769 (s), 1748 (s), 1629 (w), 1601 (w), 1554 (w), 1508 (w), 1495 (m), 1447 (w), 1417 (w)

δ_H (400 MHz, $CDCl_3$): 9.17 (m, 1H, Ar**H**)

9.13 (m, 1H, Ar**H**)

9.04 (m, 1H, Ar**H**)

8.93 (d, *J*=8.8 Hz, 1H, Ar**H**)

8.14 (br d, *J*=8.8 Hz, 1H, Ar**H**)

8.13 (m, 1H, Ar**H**)

7.97-7.88 (m, 2H, 2 x Ar**H**)

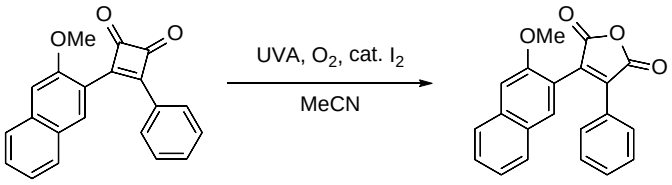
7.83-7.75 (m, 2H, 2 x Ar**H**)

δ_C (100 MHz, $CDCl_3$): 179.5 (**C**), 163.4 (**C**), 134.8 (**C**), 130.5 (**C**H), 130.1 (**C**H), 129.5 (**C**), 129.2 (**C**H), 129.0 (**C**H), 128.9 (**C**H), 128.7 (**C**H), 128.4 (**C**H), 127.5 (**C**), 127.3 (**C**H), 127.2 (**C**), 126.5 (**C**), 126.2 (**C**), 125.8 (**C**H), 124.7 (**C**), 121.5 (**C**H), one **C** coincident or not observed

LR-MS (ESI^+): 299 (45 %, $[M + H]^+$)

HRMS (ESI^+): $C_{21}H_{14}NaO_4$ $[M + MeOH + Na]^+$ calculated 353.0784, observed 353.0782, $C_{20}H_{11}O_3$ $[M + H]^+$ calculated 299.0703, observed 299.0698.

3-(3-Methoxynaphthalen-2-yl)-4-phenylmaleic anhydride (3.59)



3.57
$C_{21}H_{14}O_3$
Mol Wt: 314.34

3.59
$C_{21}H_{14}O_4$
Mol Wt: 330.34

A solution of cyclobutenedione **3.57** (94 mg, 0.30 mmol) and I_2 (7.5 mg, 0.03 mmol) in acetonitrile (100 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid. Trituration with diethyl ether yielded the title compound (72 mg, 0.22 mmol, 73 %) as a yellow solid.

MP: 207-209 °C (DCM)

ν_{max} (film): 2981 (s), 2889 (m), 1782 (w), 1759 (s), 1625 (w), 1595 (m), 1571 (m), 1497 (w), 1472 (w), 1448 (m)

δ_H (400 MHz, $CDCl_3$): 7.95 (s, 1H, Ar**H**)

7.82 (dd, *J*=8.1, 0.7 Hz, 1H, Ar**H**)

7.77 (dd, *J*=8.3, 0.7 Hz, 1H, Ar**H**)

7.58-7.51 (m, 3H, 3 x Ar**H**)

7.45-7.38 (m, 2H, 2 x Ar**H**)

7.36-7.30 (m, 2H, 2 x Ar**H**)

7.16 (s, 1H, Ar**H**)

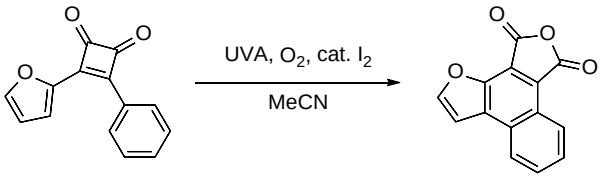
3.53 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 165.0 (**C**), 164.8 (**C**), 154.2 (**C**), 139.8 (**C**), 135.9 (**C**), 135.5 (**C**), 131.8 (**C**H), 130.9 (**C**H), 129.0 (2 x **C**H), 128.8 (**C**), 128.6 (**C**H), 128.5 (2 x **C**H), 128.2 (**C**H), 126.6 (**C**H), 124.6 (**C**H), 118.5 (**C**), 106.6 (**C**H), 55.1 (O**C**H_3), one **C** coincident or not observed

LR-MS (ESI^+): 331 (100 %, $[M + H]^+$)

HRMS (ESI^+): $C_{22}H_{18}NaO_5$ $[M + MeOH + Na]^+$ calculated 385.1046, observed 385.1054.

Naphtho[2,1-*b*:3,4-*c*']difuran-8,10-dione (3.65)



3.61
$C_{14}H_8O_3$
Mol Wt: 224.22

3.65
$C_{14}H_6O_4$
Mol Wt: 238.20

A solution of cyclobutenedione **3.61** (90 mg, 0.40 mmol) and I_2 (10 mg, 0.04 mmol) in acetonitrile (20 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid which was washed with cold acetonitrile (40 mL) to yield the title compound (32 mg, 0.14 mmol, 34 %) as an orange solid.

MP: Dec. 250 °C

ν_{max} (neat): 3149 (w), 3127 (w), 2981 (w), 1838 (m), 1826 (m), 1772 (s), 1623 (w), 1603 (w), 1581 (w), 1506 (m)

δ_H (400 MHz, DCM-d_2): 8.96 (app dq, *J*=8.3, 0.7 Hz, 1H, Ar**H**)

8.34 (m, 1H, Ar**H**)

8.18 (d, *J*=2.1 Hz, 1H, Ar**H**)

7.90 (ddd, *J*=8.3, 7.0, 1.6 Hz, 1H, Ar**H**)

7.84 (ddd, *J*=8.4, 7.0, 1.6 Hz, 1H, Ar**H**)

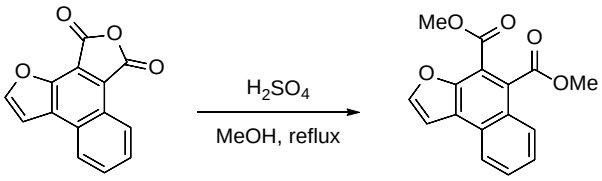
7.52 (d, *J*=2.1 Hz, 1H, Ar**H**)

δ_C (100 MHz, DCM-d_2): 164.1 (**C**), 161.3 (**C**), 150.7 (**C**H), 144.6 (**C**), 133.3 (**C**), 132.1 (**C**), 131.1 (**C**H), 129.3 (**C**H), 126.4 (**C**H), 125.8 (**C**), 125.1 (**C**H), 124.6 (**C**), 118.1 (**C**), 107.4 (**C**H)

LR-MS (EI): 238 (47 %, $[M]^{+\bullet}$)

HRMS (EI): $C_{14}H_6O_4$ $[M]^{+\bullet}$ calculated 238.0261, observed 238.0258.

Dimethyl naphtho[2,1-*b*]furan-4,5-dicarboxylate (3.78)



3.65
$C_{14}H_6O_4$
Mol Wt: 238.20

3.78
$C_{16}H_{12}O_5$
Mol Wt: 284.27

To a suspension of anhydride **3.65** (30 mg, 0.13 mmol) in methanol (10 mL) was added H_2SO_4 (conc. 0.05 mL) before being heated to reflux for 24 h. The resultant solution was cooled to RT and concentrated *in vacuo* to a dark oil. Purification by column chromatography (10 % ethyl acetate/petroleum ether) yielded the title compound (14 mg, 0.05 mmol, 39 %) as a pale, yellow oil.

ν_{max} (film): 2952 (w), 1727 (s), 1623 (w), 1575 (w), 1517 (w), 1459 (m), 1434 (m), 1352 (w), 1286 (s), 1242 (s)

δ_H (400 MHz, $CDCl_3$): 8.18 (ddd, *J*=8.5, 1.3, 1.2 Hz, 1H, Ar**H**)

8.08 (ddd, *J*=8.2, 1.3, 1.2 Hz, 1H, Ar**H**)

7.93 (d, *J*=2.1 Hz, 1H, Ar**H**)

7.71 (ddd, *J*=8.2, 7.0, 1.2 Hz, 1H, Ar**H**)

7.60 (ddd, *J*=8.5, 7.0, 1.3 Hz, 1H, Ar**H**)

7.33 (d, *J*=2.1 Hz, 1H, Ar**H**)

4.08 (s, 3H, OC**H**$_3$)

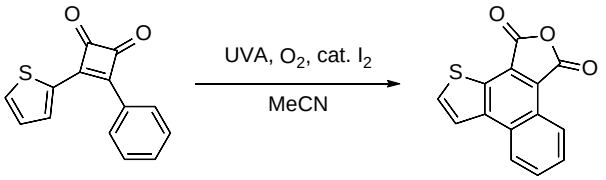
4.07 (s, 3H, OC**H**$_3$)

δ_C (100 MHz, $CDCl_3$): 168.8 (**C**), 165.1 (**C**), 148.1 (**C**), 146.6 (**C**H), 130.7 (**C**), 129.2 (**C**), 128.6 (**C**H), 127.0 (**C**H), 126.6 (**C**), 126.3 (**C**H), 125.7 (**C**), 123.7 (**C**H), 115.3 (**C**), 105.6 (**C**H), 53.0 (O**C**H_3), 52.9 (O**C**H_3)

LR-MS (ESI^+): 307 (37 %, $[M + Na]^+$), 285 (4 %, $[M + Na]^+$), 253 (100 % $[M – MeOH + H]^+$)

HRMS (ESI^+): $C_{16}H_{12}NaO_5$ $[M + Na]^+$ calculated 307.0577, observed 307.0583, $C_{15}H_9O_4$ $[M – MeOH + H]^+$ calculated 253.0495, observed 253.0501.

Thieno[2',3':3,4]naphtho[1,2-*c*]furan-8,10-dione (3.66)



3.64
$C_{14}H_8O_2S$
Mol Wt: 240.28

3.66
$C_{14}H_6O_3S$
Mol Wt: 254.26

A solution of cyclobutenedione **3.64** (96 mg, 0.40 mmol) and I_2 (10 mg, 0.04 mmol) in acetonitrile (20 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid which was washed with cold acetonitrile (40 mL) to yield the title compound (62 mg, 0.24 mmol, 61 %) as a yellow solid.

MP: Stable to 300 °C

ν_{max} (neat): 3113 (w), 2981 (w), 1834 (m), 1818 (m), 1765 (s), 1618 (m), 1555 (w), 1521 (m), 1466 (m), 1440 (m)

δ_H (400 MHz, $CDCl_3$): 8.99 (ddd, *J*=8.1, 1.5, 0.6 Hz, 1H, Ar**H**)

8.52 (ddd, *J*=8.3, 1.3, 0.6 Hz, 1H, Ar**H**)

8.18 (d, *J*=5.4 Hz, 1H, Ar**H**)

8.12 (d, *J*=5.4 Hz, 1H, Ar**H**)

7.91 (ddd, *J*=8.3, 7.0, 1.5 Hz, 1H, Ar**H**)

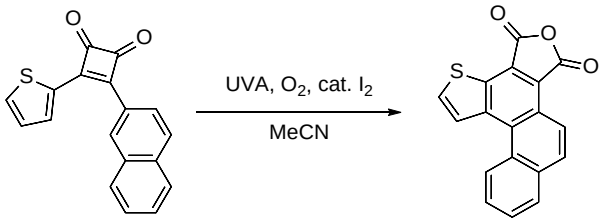
7.85 (ddd, *J*=8.1, 7.0, 1.3 Hz, 1H, Ar**H**)

δ_C (100 MHz, $CDCl_3$): 167.2 (**C**), 166.3 (**C**), 153.7 (**C**), 143.8 (**C**), 141.6 (**C**), 138.3 (**C**), 134.4 (**C**H), 130.6 (**C**H), 128.9 (**C**H), 126.0 (**C**H), 125.6 (**C**), 124.8 (**C**H), 122.4 (**C**H), 118.3 (**C**)

LR-MS (EI): 254 (50 %, $[M]^{+\bullet}$)

HRMS (EI): $C_{14}H_6O_3S$ $[M]^{+\bullet}$ calculated 254.0032, observed 254.0032.

Thieno[2',3':3,4]phenanthro[1,2-c]furan-1,3-dione (3.68)



3.67
$C_{18}H_{10}O_2S$
Mol Wt: 290.34

3.68
$C_{18}H_8O_3S$
Mol Wt: 304.32

A solution of cyclobutenedione **3.67** (50 mg, 0.17 mmol) and I_2 (4.3 mg, 0.02 mmol) in acetonitrile (17.2 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid which was washed with cold acetonitrile (30 mL) to yield the title compound (33 mg, 0.11 mmol, 64 %) as a yellow solid.

MP: Dec. 256 °C

ν_{max} (neat): 3099 (w), 1832 (m), 1754 (s), 1623 (w), 1601 (w), 1559 (w), 1528 (w), 1471 (w), 1442 (w), 1379 (w)

δ_H (400 MHz, DCM-d_2): 9.15 (m, 1H, Ar**H**)

8.89 (d, *J*=8.9 Hz, 1H, Ar**H**)

8.79 (dd, *J*=5.6, 0.6 Hz, 1H, Ar**H**)

8.27 (d, *J*=5.6 Hz, 1H, Ar**H**)

8.119 (d, *J*=8.9 Hz, 1H, Ar**H)**

8.118 (m, 1H, Ar**H**)

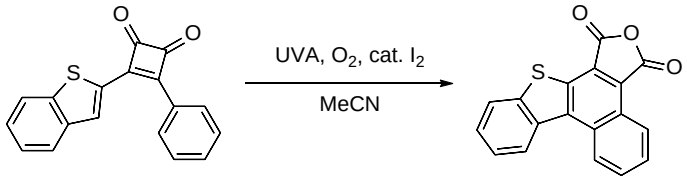
7.89-7.80 (m, 2H, 2 x Ar**H**)

δ_C (100 MHz, DCM-d_2): 164.7 (**C**), 164.3 (**C**), 145.5 (**C**), 143.5 (**C**), 143.1 (**C**), 135.2 (**C**H), 134.6 (**C**), 132.3 (**C**), 131.1 (**C**H), 130.2 (**C**), 129.9 (**C**H), 129.2, 128.4 (**C**H), 127.6 (**C**H), 126.8 (**C**), 126.7 (**C**H), 124.3 (**C**), 122.3 (**C**H)

LR-MS (ESI^+): 305 (65 %, $[M + H]^+$)

HRMS (EI): $C_{18}H_9O_3S$ $[M + H]^+$ calculated 305.0267, observed 305.0266.

Benzo[4',5']thieno[2',3':3,4]naphtho[1,2-*c*]furan-1,3-dione (3.71)



3.70
$C_{18}H_{10}O_2S$
Mol Wt: 290.34

3.71
$C_{18}H_8O_3S$
Mol Wt: 304.32

A solution of cyclobutenedione **3.70** (116 mg, 0.40 mmol) and I_2 (10 mg, 0.04 mmol) in acetonitrile (40 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to an orange solid which was washed with cold acetonitrile (40 mL) to yield the title compound (82 mg, 0.27 mmol, 67 %) as a yellow solid.

MP: Dec. 269 °C

ν_{max} (neat): 1828 (m), 1768 (s), 1618 (w), 1589 (w), 1546 (m), 1522 (w), 1449 (m), 1438 (m), 1422 (w), 1365 (w)

δ_H (400 MHz, DCM-d_2): 9.19 (br d, *J*=8.7 Hz, 1H, Ar**H**)

9.05 (app dq, *J*=8.3, 0.9 Hz, 1H, Ar**H**)

8.96 (dd, *J*=7.6, 1.5 Hz, 1H, Ar**H**)

8.17 (m, 1H, Ar**H**)

8.02 (ddd, *J*=8.7, 7.0, 1.5 Hz, 1H, Ar**H**)

7.90 (ddd, *J*=8.3, 7.0, 0.9 Hz, 1H, Ar**H**)

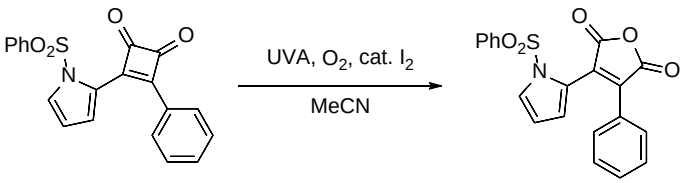
7.78-7.67 (m, 2H, 2 x Ar**H**)

δ_C (100 MHz, DCM-d_2): 163.7 (**C**), 163.5 (**C**), 143.4 (**C**), 138.2 (**C**), 135.2 (**C**), 134.3 (**C**), 131.7 (C), 131.4 (**C**), 129.1 (C), 128.5 (C), 127.0 (**C**), 126.9 (C), 126.6 (C), 126.5 (**C**), 126.4 (C), 124.9 (C), 124.5 (C), 122.1 (**C**)

LR-MS (ESI^+): 305 (21 %, $[M + H]^+$)

HRMS (ESI^+): $C_{18}H_9O_3S$ $[M + H]^+$ calculated 305.0267, observed 305.0267.

3-Phenyl-4-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)maleic anhydride (3.74)



3.73
$C_{20}H_{13}NO_4S$
Mol Wt: 363.39

3.74
$C_{20}H_{13}NO_5S$
Mol Wt: 379.39

A solution of cyclobutenedione **3.73** (145 mg, 0.40 mmol) and I_2 (10 mg, 0.04 mmol) in acetonitrile (20 mL) was passed through the photoflow reactor fitted with a 36 W UVA lamp under a positive pressure of O_2 for a residence time of 1 h. The resultant solution was concentrated *in vacuo* to a brown oil. Purification by column chromatography (10 % ethyl acetate/hexane) yielded the title compound (112 mg, 0.30 mmol, 74 %) as an orange solid.

MP: 141–143 °C (diethyl ether/hexane)

ν_{max} (film): 2922 (w), 1826 (w), 1766 (s), 1647 (w), 1599 (w), 1541 (w), 1507 (w), 1464 (w), 1448 (m), 1372 (m)

δ_H (400 MHz, $CDCl_3$): 7.77-7.74 (m, 2H, 2 x Ar**H**)

7.61-7.53 (m, 3H, 3 x Ar**H**)

7.47-7.41 (m, 4H, 4 x Ar**H**)

7.36-7.31 (m, 2H, 2 x Ar**H**)

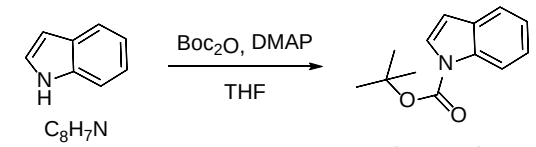
6.46-6.42 (m, 2H, 2 x Ar**H**)

δ_C (100 MHz, $CDCl_3$): 164.3 (**C**), 163.8 (**C**), 141.0 (**C**), 137.9 (**C**), 134.4 (**C**H), 131.7 (**C**H), 130.8 (**C**), 129.8 (2 x **C**H), 129.4 (2 x **C**H), 128.7 (2 x **C**H), 127.11 (**C**), 127.08 (2 x **C**H), 126.3 (**C**H), 120.9 (**C**), 119.3 (**C**H), 114.2 (**C**H)

LR-MS (ESI^+): 380 (38 %, $[M + H]^+$)

HRMS (ESI^+): $C_{21}H_{17}NNaO_6S$ $[M + MeOH + Na]^+$ calculated 434.0669, observed 434.0669, $C_{20}H_{13}NNaO_5S$ $[M + Na]^+$ calculated 402.0407, observed 402.0402, $C_{20}H_{14}NO_5S$ $[M + H]^+$ calculated 380.0587, observed 380.0583.

***Tert*-butyl 1*H*-indole-1-carboxylate (3.79)**



C_8H_7N
Mol Wt: 117.15

$C_{13}H_{15}NO_2$
Mol Wt: 217.27

To a solution of indole (1.75 g, 14.9 mmol) in THF (20 mL) was added di-*tert*-butyl dicarbonate (3.90 g, 17.85 mmol) and DMAP (250 mg, 2.25 mmol). After 4 h the solution was concentrated *in vacuo* and purification by column chromatography (5 % ethyl acetate/hexane) yielded the title compound (3.22 g, 14.8 mmol, 99 %) as a colourless oil.

Data consistent with literature[86]

ν_{max} (neat): 2978 (w), 1730 (s), 1607 (w), 1533 (w), 1474 (m), 1450 (s), 1379 (s), 1369 (s), 1345 (s), 1328 (s)

δ_H (400 MHz, $CDCl_3$): 8.18 (br d, *J*=8.1 Hz, 1H, Ar**H**)

7.63 (d, *J*=3.7 Hz, 1H, Ar**H**)

7.59 (ddd, *J*=7.8, 1.2, 0.7 Hz, 1H, Ar**H**)

7.34 (ddd, *J*=8.1, 7.2, 1.2 Hz, 1H, Ar**H**)

7.25 (ddd, *J*=7.8, 7.2, 1.0 Hz, 1H, Ar**H**)

6.60 (dd, *J*=3.7, 0.7 Hz, 1H, Ar**H**)

1.70 (s, 9H, $C(C\mathbf{H}_3)_3$)

δ_C (100 MHz, $CDCl_3$): 149.8 (**C**), 135.1 (**C**), 130.5 (**C**), 125.8 (**C**H), 124.1 (**C**H), 122.6 (**C**H), 120.9 (**C**H), 115.1 (**C**H), 107.2 (**C**H), 83.6 ($\mathbf{C}(CH_3)_3$), 28.2 ($C(\mathbf{C}H_3)_3$)

LR-MS (ESI^+): 218 (5 %, $[M + H]^+$).

Chapter 5 References

1 D. Knueppel and S. F. Martin, *Angew. Chem. Int. Ed Engl.*, 2009, **48**, 2569–2571.

2 M. Mohamed, T. P. Gonçalves, R. J. Whitby, H. F. Sneddon and D. C. Harrowven, *Chem. – Eur. J.*, 2011, **17**, 13698–13705.

3 B. R. Yerxa, K. Yang and H. W. Moore, *Tetrahedron*, 1994, **50**, 6173–6180.

4 D. C. Harrowven, D. D. Pascoe, D. Demurtas and H. O. Bourne, *Angew. Chem.*, 2005, **117**, 1247–1248.

5 S. T. Perri and H. W. Moore, *Tetrahedron Lett.*, 1987, **28**, 4507–4510.

6 E. Packard, D. D. Pascoe, J. Maddaluno, T. P. Gonçalves and D. C. Harrowven, *Angew. Chem. Int. Ed.*, 2013, **52**, 13076–13079.

7 Y. Xiong and H. W. Moore, *J. Org. Chem.*, 1996, **61**, 9168–9177.

8 E. Peña-Cabrera and L. S. Liebeskind, *J. Org. Chem.*, 2002, **67**, 1689–1691.

9 R. L. Danheiser and H. Sard, *J. Org. Chem.*, 1980, **45**, 4810–4812.

10 R. L. Danheiser, S. K. Gee and H. Sard, *J. Am. Chem. Soc.*, 1982, **104**, 7670–7672.

11 R. L. Danheiser and S. K. Gee, *J. Org. Chem.*, 1984, **49**, 1672–1674.

12 J. O. Karlsson, Nghi V. Nguyen, L. D. Foland and H. W. Moore, *J. Am. Chem. Soc.*, 1985, **107**, 3392–3393.

13 L. D. Foland, J. O. Karlsson, S. T. Perri, R. Schwabe, S. L. Xu, S. Patil and H. W. Moore, *J. Am. Chem. Soc.*, 1989, **111**, 975–989.

14 L. D. Foland, O. H. W. Decker and H. W. Moore, *J. Am. Chem. Soc.*, 1989, **111**, 989–995.

15 S. L. Xu, M. Taing and H. W. Moore, *J. Org. Chem.*, 1991, **56**, 6104–6109.

16 H. Xia and H. W. Moore, *J. Org. Chem.*, 1992, **57**, 3765–3766.

17 S. L. Xu and H. W. Moore, *J. Org. Chem.*, 1992, **57**, 326–338.

18 A. R. Hergueta and H. W. Moore, *J. Org. Chem.*, 1999, **64**, 5979–5983.

19 T. Nakanishi, M. Suzuki, A. Saimoto and T. Kabasawa, *J. Nat. Prod.*, 1999, **62**, 864–867.

20 F.-J. Cao, R. Yang, C. Lv, Q. Ma, M. Lei, H.-L. Geng and L. Zhou, *Eur. J. Pharm. Sci.*, 2015, **67**, 45–54.

21 H. W. Moore and S. T. Perri, *J. Org. Chem.*, 1988, **53**, 996–1003.

22 L. S. Liebeskind, S. Iyer and C. F. Jewell, *J. Org. Chem.*, 1986, **51**, 3065–3067.

23 A. G. Birchler, F. Liu and L. S. Liebeskind, *J. Org. Chem.*, 1994, **59**, 7737–7745.

24 N. M. Goudgaon, J. Shi and R. F. Schinazi, *Tetrahedron Lett.*, 1998, **39**, 1869–1872.

25 J. Wang, X. Jiang, M. Chen, Z. Ge, Y. Hu and H. Hu, *J. Chem. Soc. Perkin Trans. 1*, 2001, 66–71.

26 H. Liu, L. M. Gayo, R. W. Sullivan, A. Y. H. Choi and H. W. Moore, *J. Org. Chem.*, 1994, **59**, 3284–3288.

27 L. S. Liebeskind, K. L. Granberg and J. Zhang, *J. Org. Chem.*, 1992, **57**, 4345–4352.

28 S. Xu, B. R. Yerxa, R. W. Sullivan and H. W. Moore, *Tetrahedron Lett.*, 1991, **32**, 1129–1132.

29 D. J. Krysan, A. Gurski and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1992, **114**, 1412–1418.

30 L. S. Liebeskind and J. Wang, *J. Org. Chem.*, 1993, **58**, 3550–3556.

31 L. S. Liebeskind and J. Wang, *Tetrahedron*, 1993, **49**, 5461–5470.

32 P. Turnbull and H. W. Moore, *J. Org. Chem.*, 1995, **60**, 644–649.

33 P. Turnbull, M. J. Heileman and H. W. Moore, *J. Org. Chem.*, 1996, **61**, 2584–2585.

34 D. C. Harrowven, D. D. Pascoe and I. L. Guy, *Angew. Chem. Int. Ed.*, 2007, **46**, 425–428.

35 L. S. Liebeskind and K. R. Wirtz, *J. Org. Chem.*, 1990, **55**, 5350–5358.

36 A. Gurski and L. S. Liebskind, *J. Am. Chem. Soc.*, 1993, **115**, 6101–6108.

37 L. M. Gayo, M. P. Winters and H. W. Moore, *J. Org. Chem.*, 1992, **57**, 6896–6899.

38 M. P. Winters, M. Stranberg and H. W. Moore, *J. Org. Chem.*, 1994, **59**, 7572–7574.

39 B. M. Trost, O. R. Thiel and H.-C. Tsui, *J. Am. Chem. Soc.*, 2003, **125**, 13155–13164.

40 M. T. Hoyt, R. Palchaudhuri and P. J. Hergenrother, *Invest. New Drugs*, 2011, **29**, 562–573.

41 R. K. Pettit, B. R. Fakoury, J. C. Knight, C. A. Weber, G. R. Pettit, G. D. Cage and S. Pon, *J. Med. Microbiol.*, 2004, **53**, 61–65.

42 D. J. Asby, M. G. Radigois, D. C. Wilson, F. Cuda, C. L. L. Chai, A. Chen, A. S. Bienemann, M. E. Light, D. C. Harrowven and A. Tavassoli, *Org. Biomol. Chem.*, 2016, **14**, 9322–9330.

43 D. C. Harrowven, M. Mohamed, T. P. Gonçalves, R. J. Whitby, D. Bolien and H. F. Sneddon, *Angew. Chem. Int. Ed.*, 2012, **51**, 4405–4408.

44 B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry and K. I. Booker-Milburn, *J. Org. Chem.*, 2005, **70**, 7558–7564.

45 G. B. M. Bettòlo, C. G. Casinovi and C. Galeffi, *Tetrahedron Lett.*, 1965, **6**, 4857–4864.

46 R. Mongkol and W. Chavasiri, *J. Integr. Agric.*, 2016, **15**, 2795–2802.

47 T. P. Gonçalves, M. Mohamed, R. J. Whitby, H. F. Sneddon and D. C. Harrowven, *Angew. Chem. Int. Ed.*, 2015, **54**, 4531–4534.

48 W. Sun, D. C. Wilson and D. C. Harrowven, *Synthesis*, 2017, **49**, 3091–3106.

49 W. Sun, D. C. Wilson, M. E. Light and D. C. Harrowven, *Org. Lett.*, 2018, **20**, 4346–4349.

50 M. A. Manning, W. Sun, M. E. Light and D. C. Harrowven, *Chem. Commun.*, 2021, **57**, 4556–4559.

51 R. M. Bennett, W. Sun, D. C. Wilson, M. E. Light and D. C. Harrowven, *Chem. Commun.*, 2021, **57**, 5694–5697.

52 H. Liu, C. S. Tomooka and H. W. Moore, *Synth. Commun.*, 1997, **27**, 2177–2180.

53 C. Kowalski, X. Creary, A. J. Rollin and M. C. Burke, *J. Org. Chem.*, 1978, **43**, 2601–2608.

54 M. Majewski and D. M. Gleave, *J. Organomet. Chem.*, 1994, **470**, 1–16.

55 P. X. Iten, A. A. Hofmann and C. H. Eugster, *Helv. Chim. Acta*, 1978, **61**, 430–443.

56 G. H. Hakimelahi, M. L. Jain, T. W. Ly, I.-C. Chen, K. S. Ethiraj, J. R. Hwu and A. A. Moshfegh, *J. Org. Chem.*, 2001, **66**, 7067–7071.

57 J. T. Gupton, E. Crawford, M. Mahoney, E. Clark, W. Curry, A. Lane, A. Shimozono, V. Moore-Stoll, K. Elofson, W. Juekun, M. Newton, S. Yeudall, E. Jaekle, R. Kanters and J. A. Sikorski, *Tetrahedron*, 2018, **74**, 7408–7420.

58 A. D. Allen, W.-Y. Lai, J. Ma and T. T. Tidwell, *J. Am. Chem. Soc.*, 1994, **116**, 2625–2626.

59 C. W. Bird, *Chem. Commun. Lond.*, 1968, 1537a–1537a.

60 E. K. Fields, S. J. Behrend, S. Meyerson, M. L. Winzenburg, B. R. Ortega and H. K. Hall, *J. Org. Chem.*, 1990, **55**, 5165–5170.

61 A. A. Frimer, J. D. Kinder, W. J. Youngs and M. A. B. Meador, *J. Org. Chem.*, 1995, **60**, 1658–1664.

62 C. S. Wood and F. B. Mallory, *J. Org. Chem.*, 1964, **29**, 3373–3377.

63 F. B. Mallory, C. S. Wood and J. T. Gordon, *J. Am. Chem. Soc.*, 1964, **86**, 3094–3102.

64 M. Flammang-Barbieux, J. Nasielski and R. H. Martin, *Tetrahedron Lett.*, 1967, **8**, 743–744.

65 L. Liu, B. Yang, T. J. Katz and M. K. Poindexter, *J. Org. Chem.*, 1991, **56**, 3769–3775.

66 A. Sudhakar and T. J. Katz, *Tetrahedron Lett.*, 1986, **27**, 2231–2234.

67 L. D. Elliott, J. P. Knowles, P. J. Koovits, K. G. Maskill, M. J. Ralph, G. Lejeune, L. J. Edwards, R. I. Robinson, I. R. Clemens, B. Cox, D. D. Pascoe, G. Koch, M. Eberle, M. B. Berry and K. I. Booker-Milburn, *Chem. – Eur. J.*, 2014, **20**, 15226–15232.

68 J. P. Knowles, L. D. Elliott and K. I. Booker-Milburn, *Beilstein J. Org. Chem.*, 2012, **8**, 2025–2052.

69 B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry and K. I. Booker-Milburn, *J. Org. Chem.*, 2005, **70**, 7558–7564.

70 M. J. Heileman and H. W. Moore, *Tetrahedron Lett.*, 1998, **39**, 3643–3646.

71 J. Sun, Y. Dong, L. Cao, X. Wang, S. Wang and Y. Hu, *J. Org. Chem.*, 2004, **69**, 8932–8934.

72 I. F. Reis, L. S. Foltran, M. H. Lauer, M. H. Gehlen, R. L. Drekener and C. R. D. Correia, *J. Fluoresc.*, 2021, **31**, 1417–1424.

73 X. Mei, J. Wang, Z. Zhou, S. Wu, L. Huang, Z. Lin and Q. Ling, *J. Mater. Chem. C*, 2017, **5**, 2135–2141.

74 W. Hua, Z. Liu, L. Duan, G. Dong, Y. Qiu, B. Zhang, D. Cui, X. Tao, N. Cheng and Y. Liu, *RSC Adv.*, 2014, **5**, 75–84.

75 W. Delaunay, R. Szűcs, S. Pascal, A. Mocanu, P.-A. Bouit, L. Nyulászi and M. Hissler, *Dalton Trans.*, 2016, **45**, 1896–1903.

76 L. S. Liebeskind, R. W. Fengl, K. R. Wirtz and T. T. Shawe, *J. Org. Chem.*, 1988, **53**, 2482–2488.

77 Y. An, Y. Wang and X. Hu, *Eur. J. Org. Chem.*, 2014, **2014**, 3715–3718.

78 M. W. Reed, D. J. Pollart, S. T. Perri, L. D. Foland and H. W. Moore, *J. Org. Chem.*, 1988, **53**, 2477–2482.

79 N. Fu, A. D. Allen, S. Kobayashi, T. T. Tidwell, S. Vukovic, S. Arumugam, V. V. Popik and M. Mishima, *J. Org. Chem.*, 2007, **72**, 1951–1956.

80 D. Jagleniec, M. Wilczek and J. Romański, *Molecules*, 2021, **26**, 2751.

81 M. Elsherbini and T. Wirth, *Tetrahedron*, 2018, **74**, 3101–3106.

82 M. Periasamy, M. Beesu and D. Shyam Raj, *J. Organomet. Chem.*, 2008, **693**, 2843–2846.

83 H. W. Moore and S. T. Perri, *J. Org. Chem.*, 1988, **53**, 996–1003.

84 M. V. Sulleiro, S. Quiroga, D. Peña, D. Pérez, E. Guitián, A. Criado and M. Prato, *Chem. Commun.*, 2018, **54**, 2086–2089.

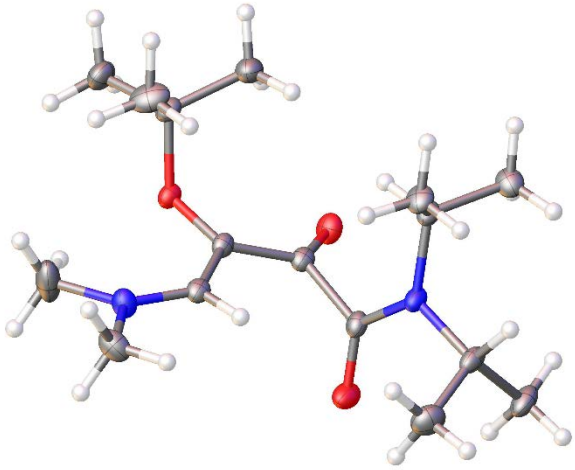
85 F. Jafarpour, H. Hazrati and S. Nouraldinmousa, *Org. Lett.*, 2013, **15**, 3816–3819.

86 Z.-L. Yan, W.-L. Chen, Y.-R. Gao, S. Mao, Y.-L. Zhang and Y.-Q. Wang, *Adv. Synth. Catal.*, 2014, **356**, 1085–1092.

Appendix A Crystallographic data

Crystallographic data of **2.39**

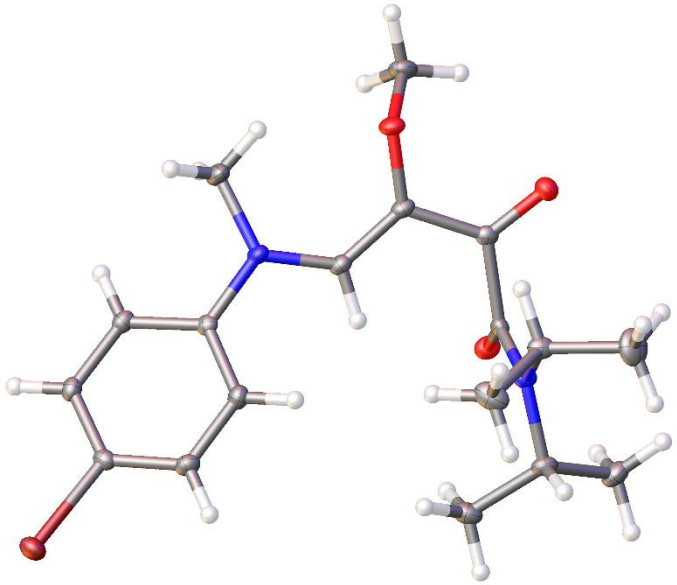
X-ray ID: 2020sot0037_R1_100K CCDC: 2059384



Formula	$C_{16}H_{30}N_2O_3$	Wavelength/Å	0.71073
$D_{calc.}$/ g cm^{-3}	1.137	Radiation type	Mo K$_\alpha$
μ/mm^{-1}	0.078	Θ_{min}/°	2.076
Formula Weight	298.42	Θ_{max}/°	28.497
Colour	clear colourless	Measured Refl's.	19535
Shape	prism	Indep't Refl's	4390
Size/mm^3	0.33×0.10×0.04	Refl's I≥2 σ(I)	3425
T/K	100(2)	R_{int}	0.0885
Crystal System	triclinic	Parameters	199
Space Group	P-1	Restraints	0
a/Å	6.0189(3)	Largest Peak	0.438
b/Å	10.6268(6)	Deepest Hole	-0.261
c/Å	14.7651(6)	GooF	1.050
α/°	70.260(4)	wR_2 (all data)	0.1367
β/°	88.043(4)	wR_2	0.1290
γ/°	78.758(4)	R_1 (all data)	0.0634
V/Å^3	871.33(8)	R_1	0.0482
Z	2	Wavelength/Å	0.71073
Z'	1	Radiation type	Mo K$_\alpha$

Crystallographic data for **2.53**

X-ray ID: 2020sot0020_K1_100K CCDC: 2042398



Formula	$C_{18}H_{25}BrN_2O_3$	Wavelength/Å	0.71073
$D_{calc.}$/ g cm^{-3}	1.443	Radiation type	Mo K_α
μ/mm^{-1}	2.266	Θ_{min}/°	3.031
Formula Weight	397.31	Θ_{max}/°	32.239
Colour	clear colourless	Measured Refl's.	29540
Shape	(cut) plate	Indep't Refl's	6123
Size/mm^3	0.14×0.07×0.04	Refl's I≥2 σ(I)	5061
T/K	100(2)	R_{int}	0.0390
Crystal System	monoclinic	Parameters	223
Space Group	$P2_1/c$	Restraints	0
a/Å	14.7511(2)	Largest Peak	0.541
b/Å	10.26090(10)	Deepest Hole	-0.405
c/Å	12.1428(2)	GooF	1.056
α/°	90	wR_2 (all data)	0.0801
β/°	95.8170(10)	wR_2	0.0751
γ/°	90	R_1 (all data)	0.0516
V/Å^3	1828.46(4)	R_1	0.0380
Z	4		
Z'	1		