UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

SCHOOL OF CHEMISTRY

Studies on Aminocyclobutenone Rearrangements

and a New C-H Activation Annulation Reaction Leading to *N*-Heterocycles

by

WEI SUN

Thesis for the Degree of Doctor of Philosophy

April 2017

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

SCHOOL OF CHEMISTRY

Doctor of Philosophy

STUDIES ON AMINOCYCLOBUTENONE REARRANGEMENTS

AND A NEW C-H ACTIVATION ANNULATION REACTION LEADING TO *N*-HETEROCYCLES

By WEI SUN

This thesis describes study of aminocyclobutenone rearrangements. Thermal and photo rearrangements of cyclobutenones have become established as useful methods for the synthesis of quinones, naphthoquinones and furanones, some of which show useful biological activity. Though widely used, little is known about the behaviour of aminocyclobutenones. Herein, thermolyses and photolyses of aminocyclobutenones under continuous flow were studied in depth. DFT calculations were employed to bring greater understanding to our experimental results and identify new avenues for study.

In this work we also introduce a novel metal-free C-H activation and annulation reaction which could lead to *N*-heterocycles. Experimental work and DFT calculations were performed to understand the nature of this unusual reaction. We also delineated the regioselectivity and diastereoselectivity of this reaction.

A new rearrangement of cyclobutenones leading to 2-oxobut-3-enamides at low temperature has also been introduced. This new rearrangement offers a short and efficient route to synthesise highly substituted furans.

Table of Contents

DECLARATION OF AUTHORSHIP

I, Wei Sun declare that this thesis entitled “Studies on Aminocyclobutenone Rearrangements and a New C-H Activation Annulation Reaction Leading to *N*-Heterocycles” and the work presented in it are my own and have 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. None of this work has been published before submission.

Signed:

Date: .....

Acknowledgements

Firstly, I would like to thank Professor David Harrowven for giving me the opportunity to undertake this project under his supervision at the University of Southampton. I am extremely grateful for all the meetings, discussions and guidance you have given over the last three years.

I would also thank the InterReg IVa program for their one year funding and the University of Southampton for additional support.

Thanks must be given to everyone in Harrowven lab, Mubina, Theo, Zeshan, Marc, Majdouline, Thomas, Faisal, Fiona, Lawrence, Dharyl, Rebecca, Li, Jason, Mehtap, David, Chong and Joe. In particular, to Mubina and Zeshan, you two lead me into the "magic world" of squarates. Majdouline, it's my pleasure to be your neighbour. Thank you for all your suggestion and help, it made my work much easier. Thomas, interesting catalysts, keyboards and teaaaaaa! Faisal, I really enjoy our discussions about our chemistry. Dharyl, you make my PhD full of laugh and Chinese lunch again? Rebecca, thank you for your help on my poor English. I will also thank everyone in the Linclau, Brown and Whitby labs, Zhong, Xiang, Aqeel, Azam, Xiao Ping……

Special thanks to all the support staff, particularly, to Dr. Neil Wells for all the NMR services, to Dr. John Langley, Julie Herniman and Sarah Clark for the MS service and Dr. Mark Light for the X-ray results. Also thanks to the guys in stores, Keith and Marc, for your unlimited petrol and acetone.

Thanks to all my friends in China for your encouragement and support. Also, to my former work place Beijing Institute for Drug Control, those 4 years of work experiences helped me a lot during my PhD.

Finally I wish to thank my parents for their support and encouragement. And to my wife, Xinyi Cui, thank you for all your patience, encouragement and support during these 3 years, without you I could not do it.

Wei Sun 2017

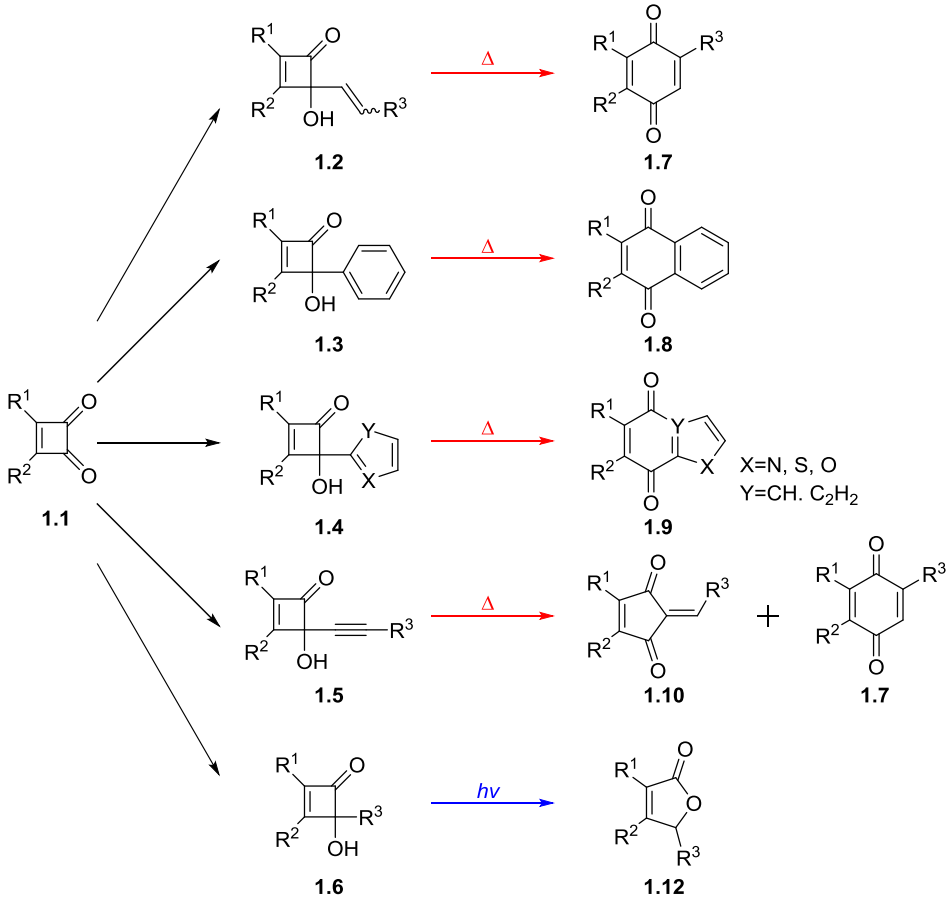
Abbreviations

Å	angstrom	EWG	electron withdrawing group
app.	apparent	g	gram(s)
Ac	acetyl	h	hour(s)
Ar	aryl	HOMO	highest occupied molecular orbital
aq.	aqueous	HPLC	high-performance liquid chromatography
B3LYP	Becke, three-parameter, Lee-Yang-Parr	HRMS	high resolution mass spectrometry
Bn	benzyl	Hz	Hertz
bp	Boiling point	*i*-	iso
br	broad	IEF	integral equation formalism
Bu	butyl	IRC	intrinsic reaction coordinate calculation
Bu_2O	dibutyl ether	*J*	coupling constant
°C	degrees centigrade	*k*	kilo
cal	calories	LDA	lithium diisopropylamide
CCSD(T)	Coupled-Cluster Singles Doubles and Non-iterative Triples Correction method	LiHMDS	lithium hexamethyldisilazide
cm^{-1}	wavenumber	LRMS	Low resolution mass spectrometry
Δ	heat or delta	LUMO	lowest unoccupied molecular orbital
d	doublet / deuterated	m	medium / multiplet / milli
d.r.	diastereomeric ratio	*m*-	meta
DCM	dichloromethane	m/z	mass / charge ratio
DFT	density functional theory	m062x	Minnesota functional 06
DIPA	diisopropylamine	Me	methyl
DMF	*N*,*N*-dimethylformamide	MeOH	methanol
DMP	Dess-Martin periodinane	mg	milligram (s)
DMSO	dimethylsulfoxide	mL	millilitre (s)
E(2)	stabilization energy from NBO analysis	mol	mol (s)
EDG	electron donating group	MOM	methoxymethyl ether
ESI	electrospray ionisation	*n*-	normal
Et	ethyl	NBO	natural bond orbital
Et_2O	diethyl ether	NMR	nuclear magnetic resonance
EtOAc	ethyl acetate	*o*-	orthodox

[O]	oxidation	*tert*	tertiary
p-	para	TBAF	*tetra*-^{n}butylammonium fluoride
PCM	polarizable continuum model	TEA	triethylamine
Pet	petroleum ether	Tf	triflate
PG	protecting group	TFA	trifluoroacetic acid
Ph	phenyl	TFAA	trifluoroacetic anhydride
ppm	parts per million	THF	tetrahydrofuran
Pr	propyl	THP	tetrahydropyran
q	quartet	TLC	thin layer chromatography
rel-	Relative Configuration	TMS	trimethylsilyl
RT	room temperature	trityl	triphenylmethyl
s	singlet	Ts	tosyl
sat.	saturated	TS	transition state
sxt	sextet	UV	ultraviolet
SOMO	singly occupied molecular orbital	ν_{max}	absorption maxima
t	triplet	w	weak
t-	tertiary	W	watt

Chapter 1: Introduction

Substituted cyclobutenones have gained attention as precursors to highly substituted quinones **1.7**, naphthoquinones **1.8**, heteroaromatics **1.9**, cyclopentenediones **1.10** and furanones **1.12** through thermal or photochemical rearrangement (**Scheme 1.1**). Pioneering work by Moore, Liebeskind and their research associates will be introduced in this chapter. Additionally, the Harrowven group has worked on rearrangements of cyclobutenone for more than 10 years and published a number of important papers. A summary of the group's work on cyclobutenones will also be reviewed in this chapter along with a selection of natural product total syntheses that utilise the methodology.

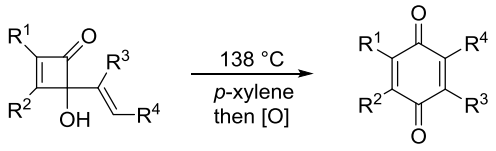


Scheme 1.1: Principle rearrangement pathways of substituted cyclobutenones.

1.1 Thermolyses of 4-vinyl(aryl)cyclobutenones

Thermal rearrangements of 4-vinylcyclobutenones **1.2** and 4-arylcyclobutenones **1.3** have gained attention as they give access to highly substituted quinones **1.7** and naphthoquinones **1.8** respectively.[1-7] These reactions show excellent regioselectivity and usually proceed in good to

excellent yield. Thus, thermolyses of 4-vinylcyclobutenones **1.2a-g** conducted in *p*-xylene at reflux (138 °C), followed by oxidation by air, afforded the substituted quinones **1.7a-g** in high yield (**Table 1.1**).

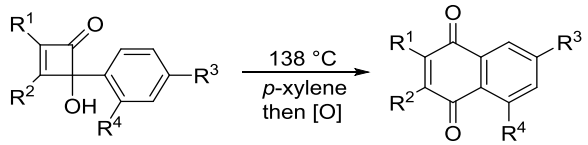


1.2 **1.7**

1.2	*R^1 =*	*R^2 =*	*R^3 =*	*R^4 =*	*Yield 1.7 (%)*
a	Ph	MeO	^{n}Bu	H	87
b	Ph	EtO	Ph	H	71
c	-C≡C-Ph	Me	^{n}Bu	H	80
d	^{n}Bu	Me	^{n}Bu	H	83
e	MeO	MeO	CH_2TMS	H	89
f	MeO	MeO	H	Me	84
g	MeO	MeO	Me	Me	67

Table 1.1: Rearrangement of 4-vinylcyclobutenones **1.2**.

The same result was obtained following thermolyses of 4-arylcyclobutenones **1.3a-g** which gave naphthoquinones **1.8a-g** in high yield (**Table 1.2**).



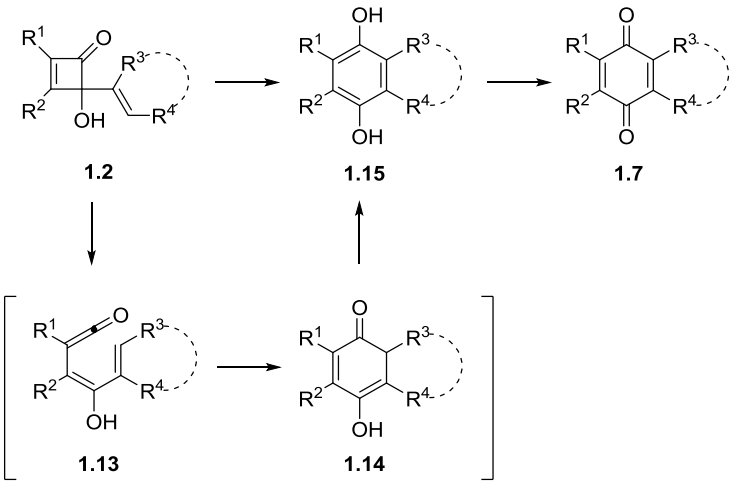
1.3 **1.8**

1.3	*R^1 =*	*R^2 =*	*R^3 =*	*R^4 =*	*Yield 1.8 (%)*
a	MeO	MeO	H	H	73
b	MeO	MeO	Me	H	87
c	MeO	MeO	OMe	H	80
d	MeO	MeO	H	Me	76
e	MeO	MeO	H	OMe	80
f	Me	MeO	H	MeO	66
g	Me	MeO	Ph	H	91

Table 1.2: Rearrangement of 4-arylcyclobutenones **1.3**.

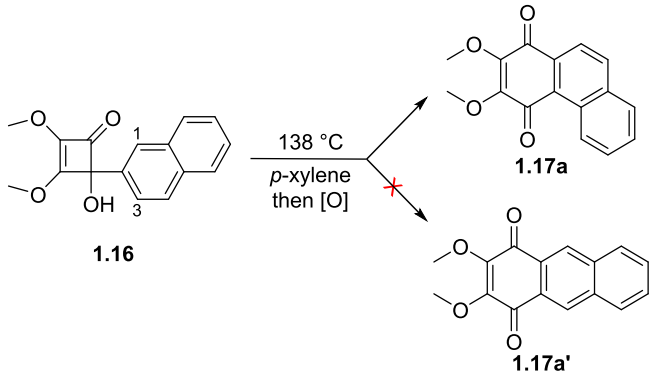
Moore *et al.* first described a mechanism for the reaction in which an electrocyclic ring opening of cyclobutenone **1.2** to form (*Z*)-vinylketene **1.13** was followed by a 6π-electrocyclic ring closure to

1.14. This intermediate then underwent tautomerisation to hydroquinone **1.15** which was oxidised to quinone **1.7** (or **1.8**) by air[8] or through the action of DMP[9] (**Scheme 1.2**).



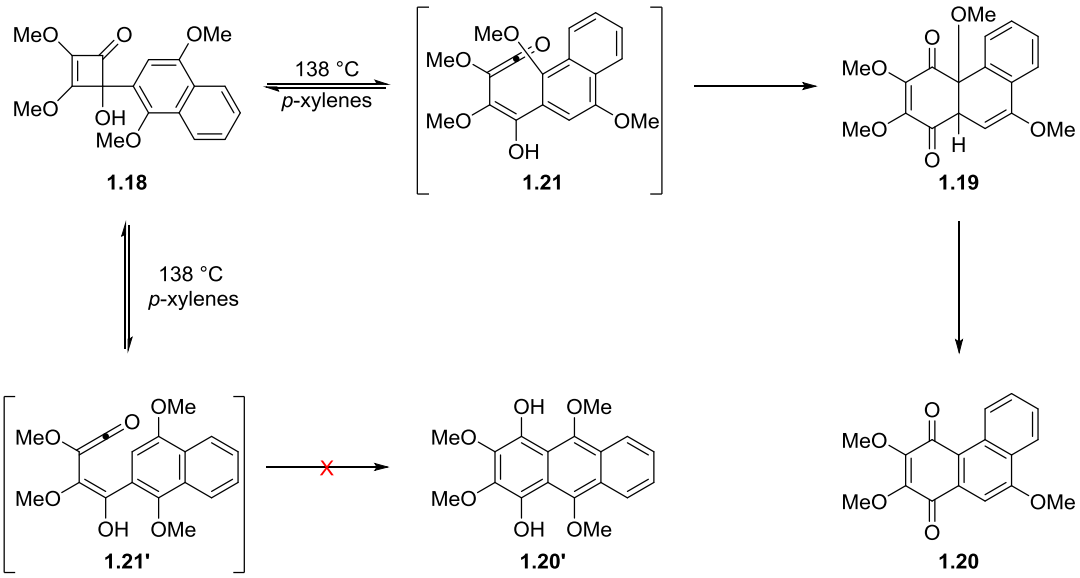
Scheme 1.2: Mechanism of the thermal rearrangement of 4-vinylcyclobutenones **1.2** (and 4-arylcyclobutenones **1.3**).

Interestingly, the rearrangement of 4-naphthylcyclobutenone **1.16** could form polyromantic quinones **1.17a** or **1.17a'** *via* ring closure at the C1 and C3 centres of the naphthalene respectively. However, only the unsymmetrical phenanthraquinone **1.17a** was isolated (**Scheme 1.3**). As electrophilic addition to C1 of naphthalene is favoured over addition of C3, the result indicated that the electrophilic character of the (*Z*)-vinylketene played a key role in the rearrangement of cyclobutenones.



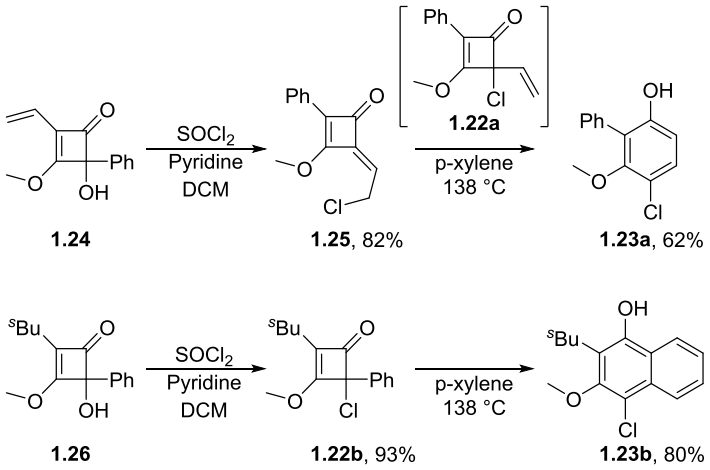
Scheme 1.3: Rearrangement of 4-naphthylcyclobutenone **1.16**.

This hypothesis was confirmed by the rearrangement of cyclobutenone **1.18** which, by analogous ring closure formed cyclohexanedione **1.19** and 1,4-phenanthrenedione **1.20** (**Scheme 1.4**). The reaction underwent selective ring closure to the substituted proximal carbon *via* (*Z*)-vinylketene **1.21** to form 1,4-phenanthrenedione **1.20** after loss of methanol.[10]



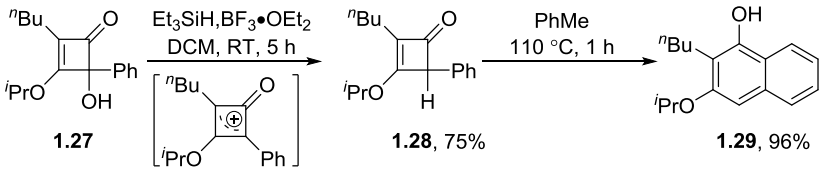
Scheme 1.4: Rearrangement of napthylcyclobutenone **1.18** to phenanthrenedione **1.20**

Thermolyses of 4-chloro-4-(vinyl/aryl)cyclobutenones **1.22** also showed a similar outcome leading to highly substituted chlorophenols **1.23**. Although 4-chloro-4-vinylcyclobutenone **1.22a** could not be formed directly, it is presumed to be an intermediate in the thermolysis of cyclobutenone **1.25** leading to chlorophenol **1.23a**. Similarly, thermolysis of cyclobutenone **1.22b** under reflux in *p*-xylene led to chloronaphthol **1.23b** in high yield (**Scheme 1.5**).[11]



Scheme 1.5: Preparation and rearrangement of 4-chlorocyclobutenones **1.22**.

4-Aryl-4-hydroxycyclobutenone **1.27** can be reduced to 4-arylcyclobutenone **1.28** by exposure to triethylsilane in the presence of $BF_3{\cdot}OEt_2$. On thermolysis in toluene it gave naphthol **1.29** in nearly quantitative yield (**Scheme 1.6**).[12]

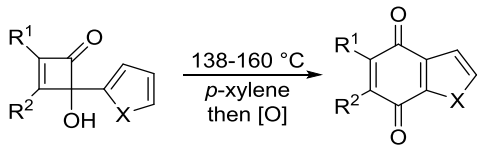


1.27 **1.28**, 75% **1.29**, 96%

Scheme 1.6: Rearrangement of 4-chlorocyclobutenone **1.28**.

1.2 Thermolyses of heteroaromatic cyclobutenones

Such thermal rearrangements have been extended to an array of heteroaromatic cyclobutenone derivatives. Thermal rearrangement of thiophene, furan and pyrrole substituted cyclobutenones **1.30a-f** have been found to give heterocyclic quinones **1.31a-f** in a selectivity way (**Table 1.3**).[5,10,13]

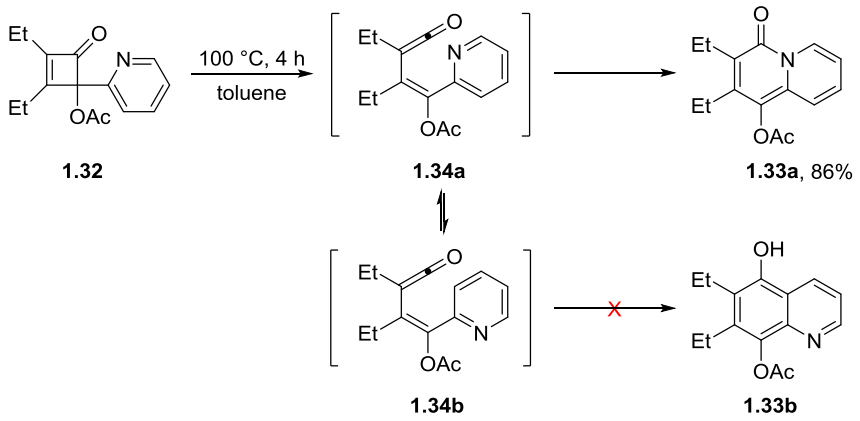


1.30 **1.31**

1.30	*R^1 =*	*R^2 =*	*X =*	*Yield 1.31 (%)*
a	OMe	OMe	S	84
b	^{n}Bu	OMe	O	91
c	OMe	OMe	O	93
d	Ph	OMe	NCH_3	93
e	Me	OMe	NTs	60
f	OMe	^{n}Bu	O	94

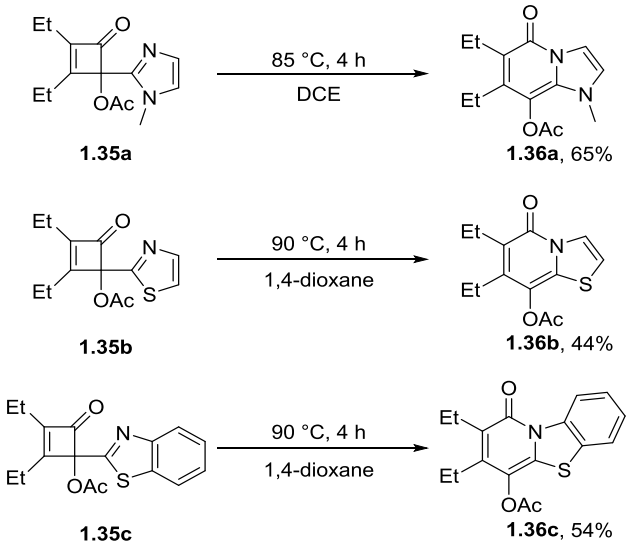
Table 1.3: Thermal rearrangements of cyclobutenones **1.30**.

This rearrangement was further expanded by Liebeskind *et al.* to include pyridines and related azaheteroaromatic ring system.[6] Thermolysis of 4-pyridinecyclobutenone **1.32** was achieved at a relatively low temperature (100 °C) with high regioselectivity to form quinolizin-4-one **1.33** in 86% yield (**Scheme 1.7**). In this reaction the (*Z*)-vinylketene intermediate favoured cyclisation at the electron-rich nitrogen atom to form quinolizin-4-one **1.33a** rather than at the carbon to form quinoline **1.33b**.



Scheme 1.7: Thermolysis of 4-pyridinecyclobutenone **1.32**.

This methodology was then applied to other azaheterocyclobutenones **1.35**. In all the examples, cyclisation occurred towards the proximal nitrogen atom. Notably, as in the thermolyses of pyridine substituted cyclobutenones, all these reactions could be achieved at lower temperatures than for the corresponding arylcyclobutenones (**Scheme 1.8**).

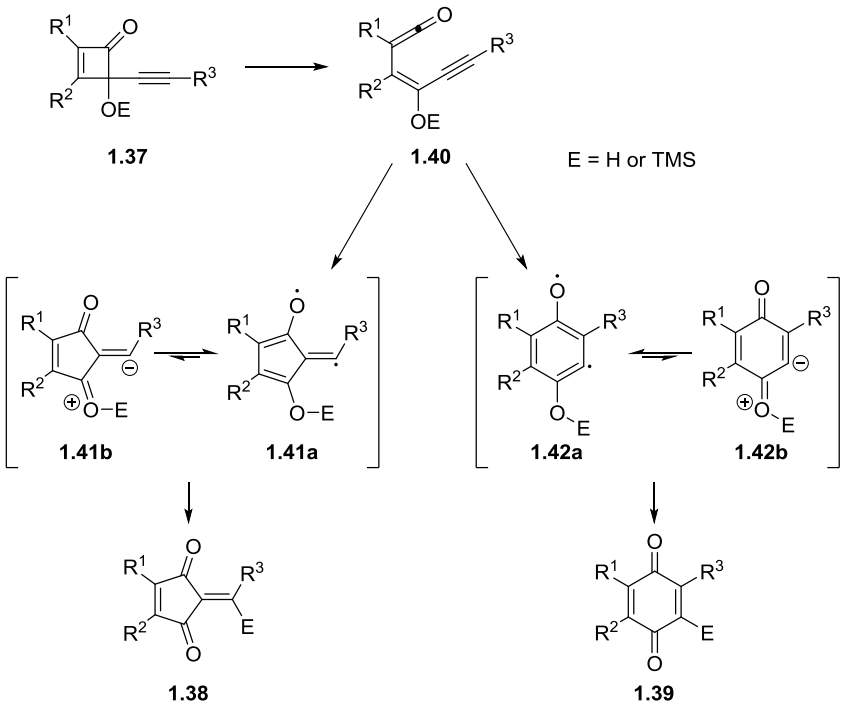


Scheme 1.8: Thermolyses of azaheterocyclobutenones **1.35**.

1.3 Thermolyses of 4-alkynylcyclobutenones

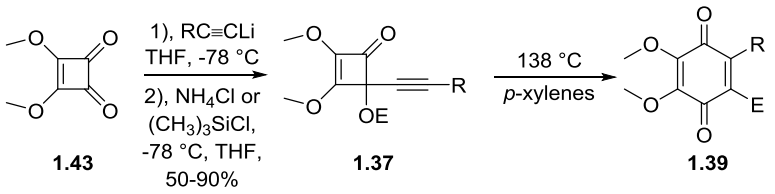
Thermolyses of 4-alkynylcyclobutenones **1.37** to cyclopentenediones **1.38** or quinones **1.39** in a selective way was studied by both the Moore and Liebeskind research teams.[14-19] Thus, 4-alkynylcyclobutenone **1.37** undergoes an electrocyclic ring opening to (*Z*)-vinylketene **1.40** on heating, which then closes to generate zwitterionic intermediates **1.41b** and **1.42b**, which are in equilibrium with their diradical orbital isomers **1.41a** and **1.42a**.[20] These then form cyclopentenedione **1.38** or quinone **1.39** *via* an intramolecular transfer of a proton/hydrogen atom, trimethylsilyl group or allyl group.

Early mechanistic postulates were in line with computational studies and trapping experiments, which indicated that the reaction occurred *via* diradical intermediates rather than zwitterions. A more detailed analysis by Harrowven *et al.* has led to a fuller understanding of the reaction *(vide infra)*. [20,21]



Scheme 1.9: The thermal rearrangement of 4-alkynylcyclobutenones **1.37**.

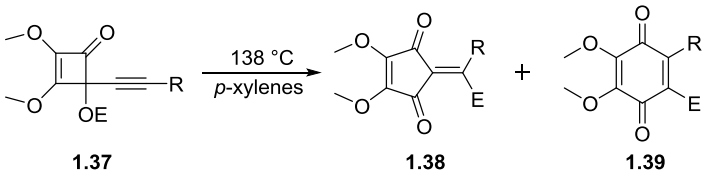
Selectivity in this reaction was studied by subjecting 4-alkynylcyclobutenones **1.37** with various alkynyl residues (R^3) to thermolyses.[22] The precursors were synthesised from cyclobutenedione **1.43** by treatment with the appropriate lithium acetylide followed by quenching with sat. ammonium chloride or trimethylsilyl chloride respectively. Thermolyses of cyclobutenones **1.37a-h** in *p*-xylene at 138 °C gave quinones **1.39a-h** in an acceptable yield (**Table 1.4**).



1.37	*R =*	*E =*	*Yield 1.39 (%)*
a	H	H	48
b	H	TMS	75
c	^{n}Bu	H	78
d	^{n}Bu	TMS	75
e	CH_2OTHP	H	47
f	CH_2OTHP	TMS	41
g	$CH_2C_6H_5$	H	71
h	$CH_2C_6H_5$	TMS	74

Table 1.4: Thermolysis of 4-alkynyl cyclobutenones **1.37a-h**.

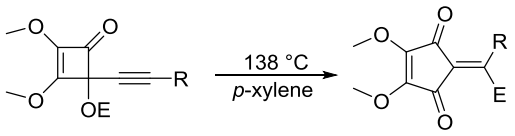
In the above examples, a strong preference for quinone formation was observed with an alkyl, proton or benzyl residue on the alkyne moiety. However, when the alkynyl substituent was an alkoxy, phenyl or TMS group **1.37i-m**, a mixture of quinone **1.39** and cyclopentenedione **1.38** was obtained (**Table 1.5**).



1.37	*R =*	*E =*	*Yield 1.38 (%)*	*Yield 1.39 (%)*
i	C_6H_5	H	21	46
j	C_6H_5	TMS	52	13
k	OC_2H_5	H	25	50
l	OC_2H_5	TMS	23	55
m	TMS	H	41	5

Table 1.5: Thermolyses of 4-alkynylcyclobutenones **1.37i-m**.

Indeed, when the alkynyl substituent was ester or vinyl ether, only cyclopentenediones **1.38** was observed after thermolysis (**Table 1.6**).



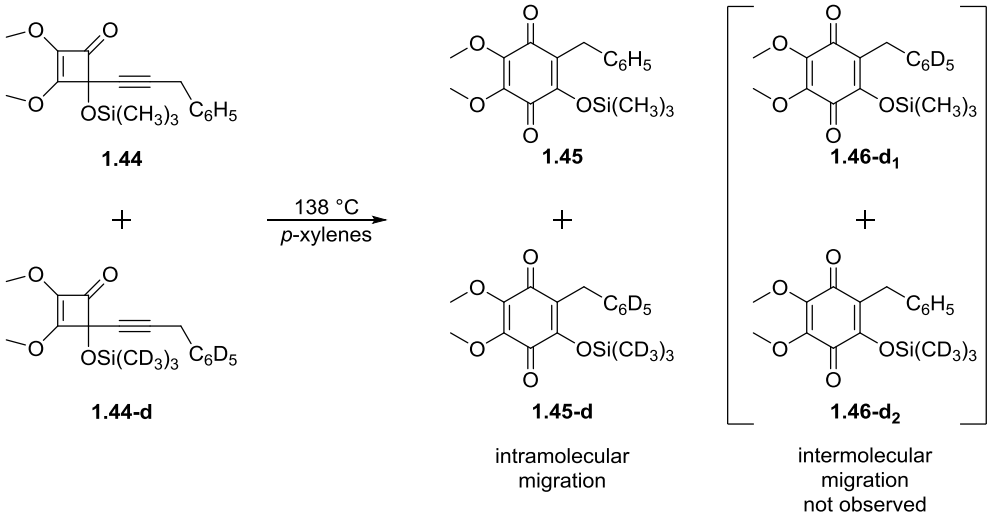
1.37 **1.38**

1.37	*R =*	*E =*	*Yield 1.38 (%)*
n	$CO_2C_2H_5$	H	66
o	$CO_2C_2H_5$	TMS	33
p	$CH{=}CHOCH_3$	H	49

Table 1.6: Thermolyses of 4-alkynylcyclobutenones **1.37n-p**.

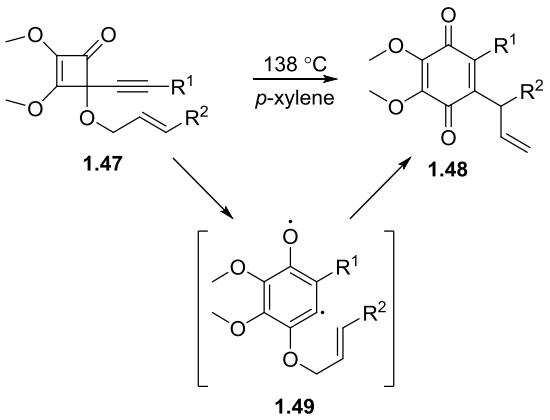
All these results indicated that selectivity in the thermolysis of 4-alkynylcyclobutenone was mainly dictated by the nature of the alkynyl substituent. Moore noted that with a radical-stabilizing group on the alkyne, the reaction favoured cyclopentenedione formation, while alkyl substituent favoured quinone formation. The proposed mechanism was consistent with the results obtained as a radical stabilising group would lower the energy to form diradical intermediate **1.41a**.

To establish whether migration of the oxygen substituent E in **1.41a** and **1.42a** to the carbon radical was an intramolecular or intermolecular process, Moore *et al.* performed the thermolyses of a 1:1 mixture of silyl ether cyclobutenone **1.44** and its deuterated analogue **1.44-d** in refluxing *p*-xylene.[22] No intermolecular migration products **1.46** were observed in the resulting product mixture with ^{1}H NMR analysis showing it to be a 1:1 mixture of quinones **1.45** and **1.45-d**. These results suggested that the diradical intermediate induced intramolecular migration of the TMS group to give the corresponding quinone **1.45**.



Scheme 1.10: Thermolyses of a 1:1 mixture of cyclobutenone **1.44** and its deuterated analogue **1.44-d**.

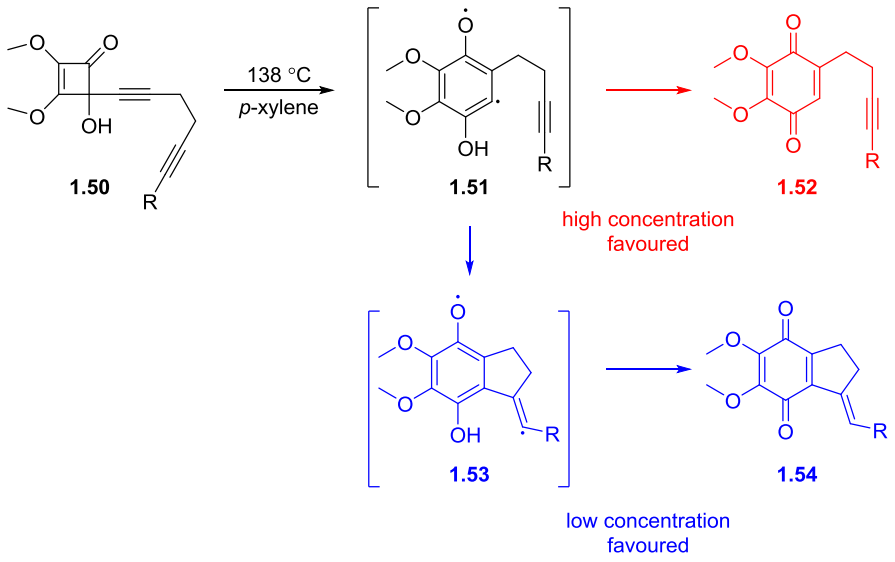
Subsequently, thermolyses of cyclobutenones **1.47** were reported to afford the corresponding quinones **1.48** in moderate yield (**Table 1.7**). These reactions indicated that allyl group migration also occurred to the *C*-radical *via* diradical intermediate **1.49**.



1.47	*R^1 =*	*R^2 =*	*Yield 1.48 (%)*
a	H	H	60
b	$CH_2C_6H_5$	H	76
c	$CH_2C_6H_5$	CH_3	54

Table 1.7: Thermolyses of cyclobutenones **1.47**.

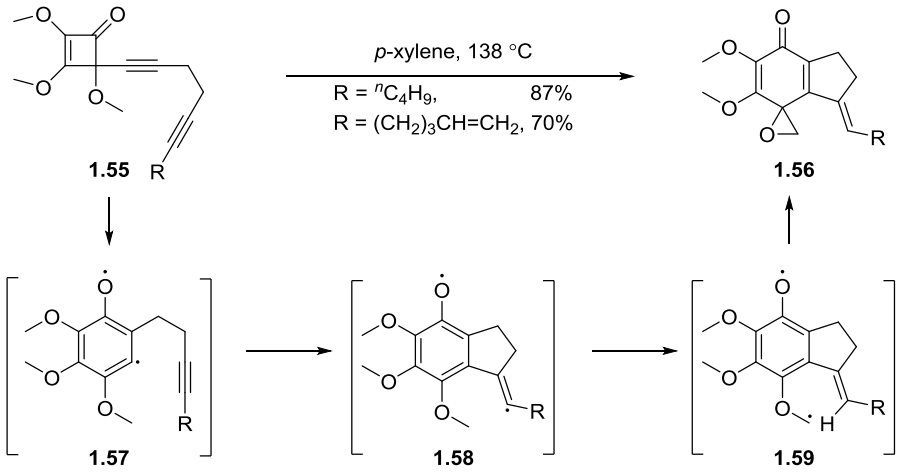
Further studies revealed that the thermolyses of some cyclobutenones was concentration dependent.[23,24] Thus, rearrangement of cyclobutenone **1.50a** in refluxing toluene gave the annulation product **1.54a** in a 23:1 ratio with quinone **1.52a** at a very low concentration (3.86×10^{-3} M). By contrast, thermolysis of **1.50a** at a higher concentration (1.2 M) gave quinone **1.52a** as the major product in a 7:1 ratio with **1.54a**. Similarly, thermolysis of cyclobutenone **1.50b** gave only annulation product **1.54b** in 57% yield at high dilution (2.43×10^{-3} M) but gave a 1:1 mixture of quinones **1.52b** and **1.54b** at 1 M concentration (**Table 1.8**). Moore suggested that the formation of annulation product **1.54** arose from a 5-*exo*-dig cyclisation of the diradical intermediate **1.51** to the alkyne residue giving diradical **1.53**, which then abstracted a hydrogen atom from the proximal hydroxyl group to afford **1.54**. In comparison, quinone **1.52** was formed from diradical **1.51** directly by H-atom abstraction. As the yield of quinone **1.52** was highly depended on intermediate concentration, Moore claimed that diradical **1.51** led to quinone **1.52** *via* an intermolecular rather than an intramolecular H-atom transfer process.



1.50	*R =*	*Concentration (M)*	*Ratio 1.52:1.54*	*Overall yield (%)*
a	$^{n}C_4H_9$	3.9×10^{-3}	1:23	84
		1.2	7:1	70
b	$(CH_2)_3CH=CH_2$	2.4×10^{-3}	only **1.54b**	57
		1.0	1:1	77

Table 1.8: Concentration dependent thermolyses of cyclobutenone **1.50a** and **1.50b**.

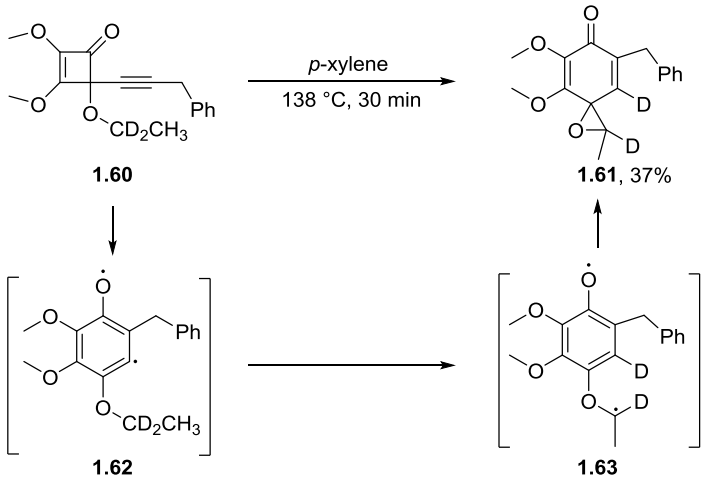
In a related study,[23] thermolyses of the protected cyclobutenones **1.55** led to the annulated spiroepoxycyclohexadienones **1.56** in good yield. The reaction was explained by formation of diradical **1.57**, which underwent a 5-*exo*-dig radical cyclisation to form diradical **1.58**. The resulting vinyl radical then abstracted an H-atom from the proximal methoxy group to form diradical **1.59** which underwent cyclisation to form spiroepoxycyclohexadienones **1.56**.



Scheme 1.11: Thermolyses of protected cyclobutenones **1.55**.

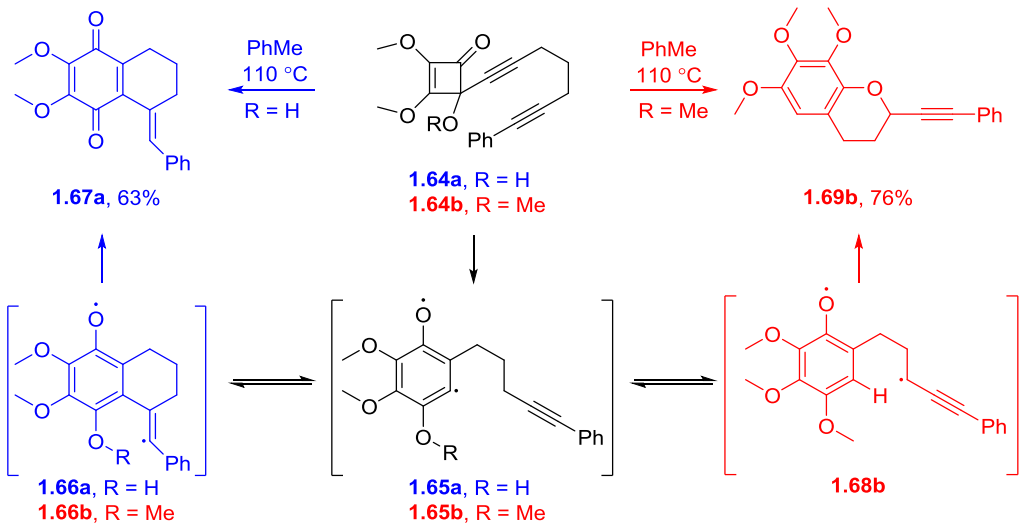
A similar deuterated analogue **1.60** gave spiroepoxide **1.61** at reflux in *p*-xylene (**Scheme 1.12**).[22] In this case the reaction first formed diradical **1.62**, which then abstracted a D-atom from the

proximal methylene group leading to diradical **1.63**. The result indicated that D-atom abstraction from the ethereal carbon was more facile than H-atom abstraction from the methyl.



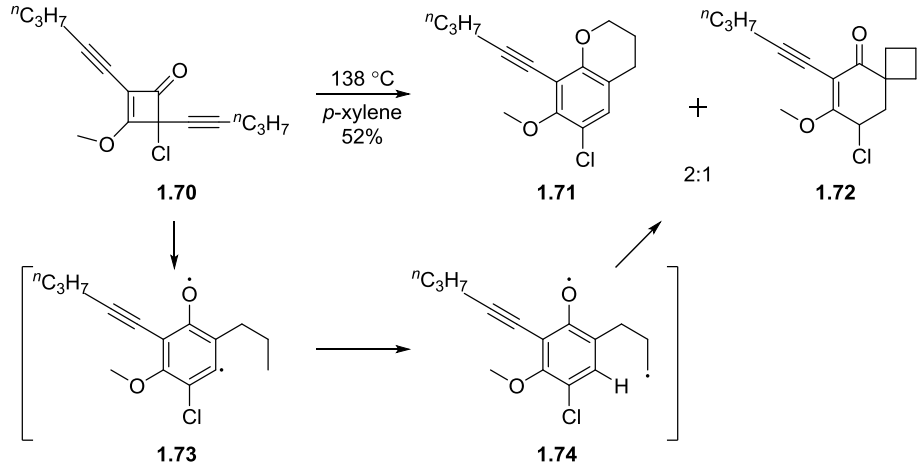
Scheme 1.12: Thermolysis of protected cyclobutenone **1.60**.

The outcome of the thermolysis of cyclobutenone can also be manipulated by protecting the hydroxyl group as this stops the H atom shift from the hydroxyl group to the carbon centred radical. This was demonstrated in the thermolyses of cyclobutenones **1.64a** and **1.64b** with **1.64a** gave the quinone **1.67a** while **1.64b** provided chromanol **1.69b**. The reaction pathways for both the protected and unprotected cyclobutenones proceed *via* diradical intermediates **1.65**, which can then undergo a 6-*exo*-dig cyclisation to form a new diradical **1.66**. If R = H, then abstraction of an H atom from the proximal hydroxyl group affords quinone **1.67a**. However, when R = Me, this abstraction cannot take place so that diradical intermediate **1.66b** reverts back to **1.65b**. H-atom abstraction from the proximal propargylic centre then leads to diradical intermediate **1.68b** which forms chromanol **1.69b** by radical cyclisation (**Scheme 1.13**).



Scheme 1.13: Effect of OH protection on the thermolyses of cyclobutenone **1.63**.

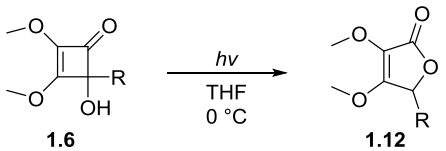
Moore *et al.* then extended these studies on intramolecular radical shifts from *C*- to *C*-.[11] Thermolysis of 4-alkynylcyclobutenone **1.70** was reported to form a 2:1 mixture of benzopyran **1.71** and spirocycle **1.72** (**Scheme 1.14**). In this case, the aryl radical in diradical intermediate **1.73** shifts to the terminal carbon on the propyl chain to afford the new diradical intermediate **1.74**. Diradical **1.74** then undergoes ring closure at two different positions to give benzopyran **1.71** and spirocycle **1.72**.



Scheme 1.14: Radical shift in the thermolysis of cyclobutenone **1.70**.

1.4 Photolyses of cyclobutenones

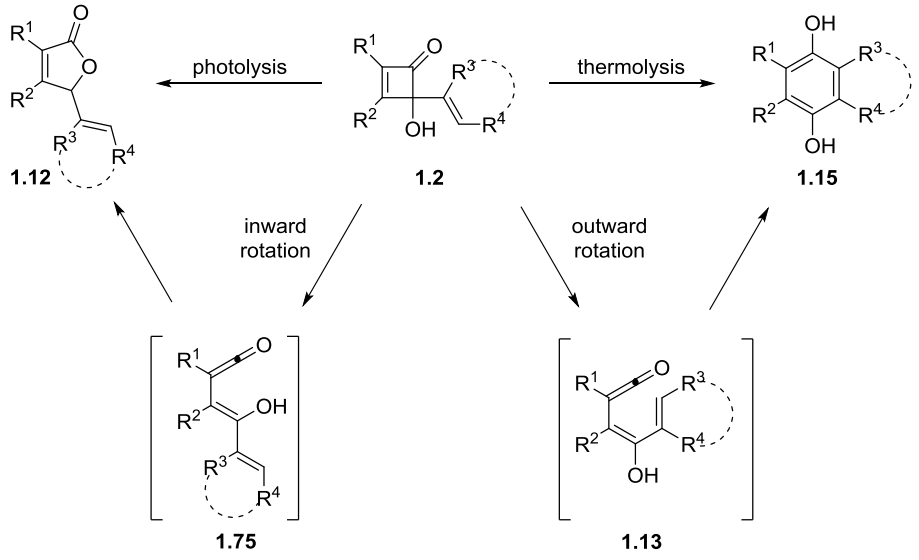
The photolysis of cyclobutenone was first investigated by Moore *et al.*[22,25] Using a Quartz reactor and a 400 W medium-pressure Hanovia lamp to trigger the ring-opening process. The reaction time was dependent on the cyclobutenone substituents and ranged from 1 to 6 h. The yield of the 5*H*-furanones **1.12** produced was low (25-60%) because of the poor stability of the 5*H*-furanone **1.12** under the reaction conditions (**Table 1.9**).



1.6	*R =*	*Yield 1.12 (%)*
a	phenyl	27
b	phenylethynyl	28
c	^{t}Bu	39
d	2-methoxyphenyl	51
e	2-furanyl	60
f	2-thiophenyl	37

Table 1.9: Photolyses of cyclobutenones **1.6a-f**.

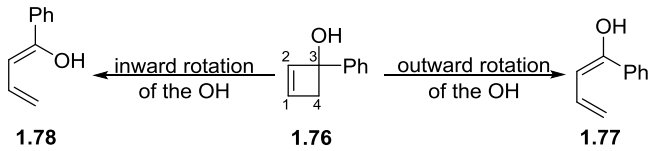
Photolyses of cyclobutenones showed a different rearrangement pathway comparing with their thermolyses. Thus, while thermolysis of cyclobutenone **1.2** led to the formation of quinone **1.15** *via* an outward rotation of the hydroxyl group to give vinylketene **1.13**, its photolysis proceeded *via* an inward rotation of the hydroxyl group to form vinylketene **1.75** which then afforded furanone **1.12** by cyclisation between the ketene and the hydroxyl group (**Scheme 1.6**).



Scheme 1.15: Photolysis and thermolysis of cyclobutenone.

Houk *et al.* performed a computational study to investigate the selectivity of inward rotation *vs.* outward rotation of substituent in the ring opening of cyclobutenones (**Scheme 1.16**).[26-29] They discovered that outward rotation of the OH group (**1.77**) was favoured when a π-donor substituent was located on one the saturated carbon centres. The selectivity was explained by the donor orbital mixing with the LUMO of the breaking bond, resulting in a lowering of the reactions activation energy. For inward rotation, the interaction of the donor orbital to the distorted LUMO

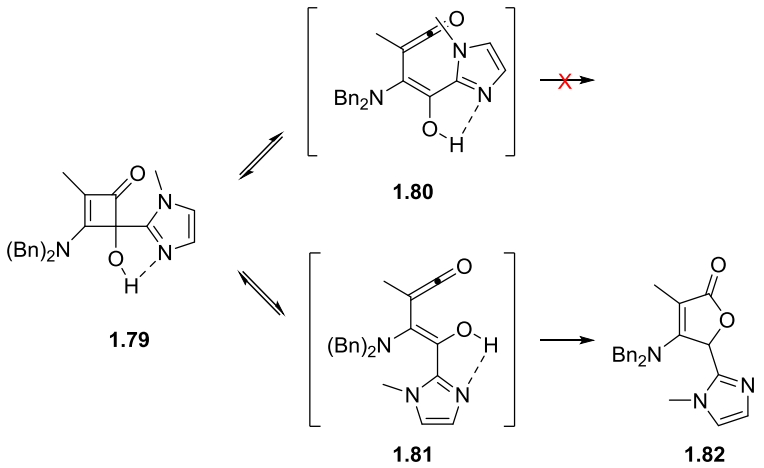
was much less as the signs of the neighbouring lobes of the atomic orbitals were opposite. Harrowven group probed the study further on the DFT calculations of the selectivity in the ring opening step (*vide infra*).



Scheme 1.16: Rotation of the OH group inwards (to **1.78**) *or* outwards (to **1.77**).

1.5 Thermolyses of cyclobutenones to form furanones

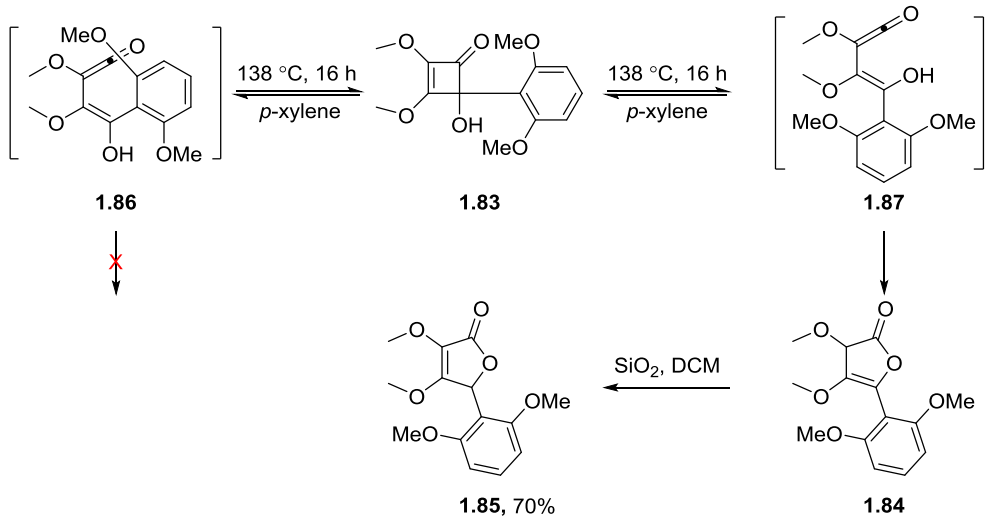
As discussed previously, the thermolyses of vinyl-, aryl- and alkynyl-cyclobutenones generally give rise to quinone. However, a few cases of furanone formations on thermolyses have been reported. For example, Liebeskind *et al.* reported that thermolysis of cyclobutenone **1.79** led to furanone **1.82** as the only product in quantitative yield.[30] This was rationalized by hydrogen bonding between the hydroxyl group and the proximal nitrogen in (*Z*)-vinylketene **1.80**, preventing free rotation of the imidazole. The steric hindrance between the amino group and the ketene moiety then stopped the cyclisation pathway leading to a quinone. Consequently, (*Z*)-vinylketene **1.80** reversed back to cyclobutenone **1.79** and formed (*E*)-vinylketene **1.81** instead, which could form furanone **1.82** by cyclisation (**Scheme 1.17**).



Scheme 1.17: Unexpected thermolysis of cyclobutenone **1.79**.

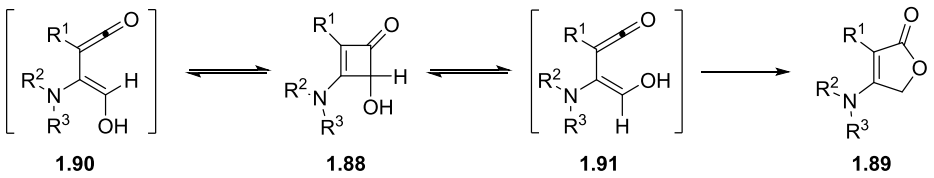
A similar example was reported by Moore *et al.* with the thermolysis of cyclobutenone **1.83** giving a 2:1 mixture of the butenolides **1.84** and **1.85** in 89% yield.[10] The furanone **1.85** was also obtained as the exclusive isomer in 70% yield upon treatment of the crude mixture with silica gel (**Scheme 1.18**). In this reaction, the ring closure pathway from (*Z*)-vinylketene **1.86** to quinone

was blocked by steric hindrance so reversed to form (*E*)-vinylketene **1.87**, which then underwent cyclisation to afford furanone **1.84** and furanone **1.85**.



Scheme 1.18: Unexpected thermolysis of cyclobutenone **1.83**.

Wang *et al.* found that thermolyses of 4-hydroxycyclobutenones **1.88** afforded furanones **1.89** (**Table 1.10**).[31] They suggested that the electrocyclic ring opening of cyclobutenone **1.88** to form (*Z*)-vinylketene **1.90** and (*E*)-vinylketene **1.91** was reversible. However, as no cyclisation could occur with the (*Z*)-vinylketene **1.90**, the reaction proceeded exclusively *via* the (*E*)-vinylketene **1.91** leading to furanone **1.89**.



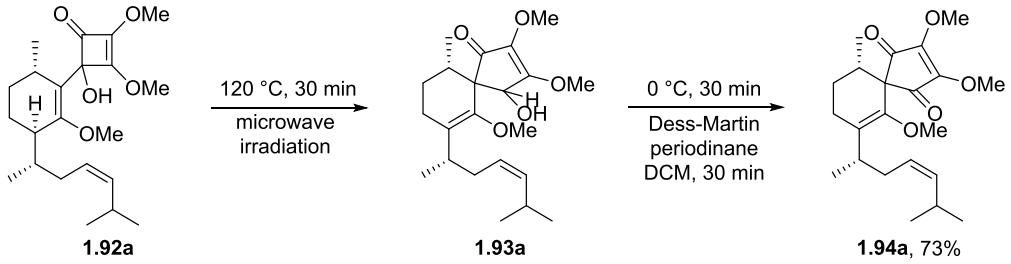
1.88	***R₁ =***	***R₂ (R₃=H) or R₂R₃***	***Time (h)***	***Yield 1.89 (%)***
a	Ph	H	4	84
b	Ph	3-$CH_3C_6H_4CH_2$	2	82
c	Ph	^{n}Bu	2.5	68
d	^{n}Bu	3-$CF_3C_6H_4CH_2$	3	51
e	^{n}Bu	$(CH_2)_5$	4	61
f	^{n}Bu	4-$FC_6H_4CH_2$	2.5	69
g	H	3-$FC_6H_4CH_2$	0.25	72
h	H	^{n}Bu	2.5	74
i	H	4-$ClC_6H_4CH_2$	0.5	94

Table 1.10: Rearrangement of 4-hydroxycyclobutenones **1.88**.

1.6 Studies on cyclobutenone rearrangements in the Harrowven group

1.6.1 Thermal rearrangement of cyclobutenones to form spirocycles

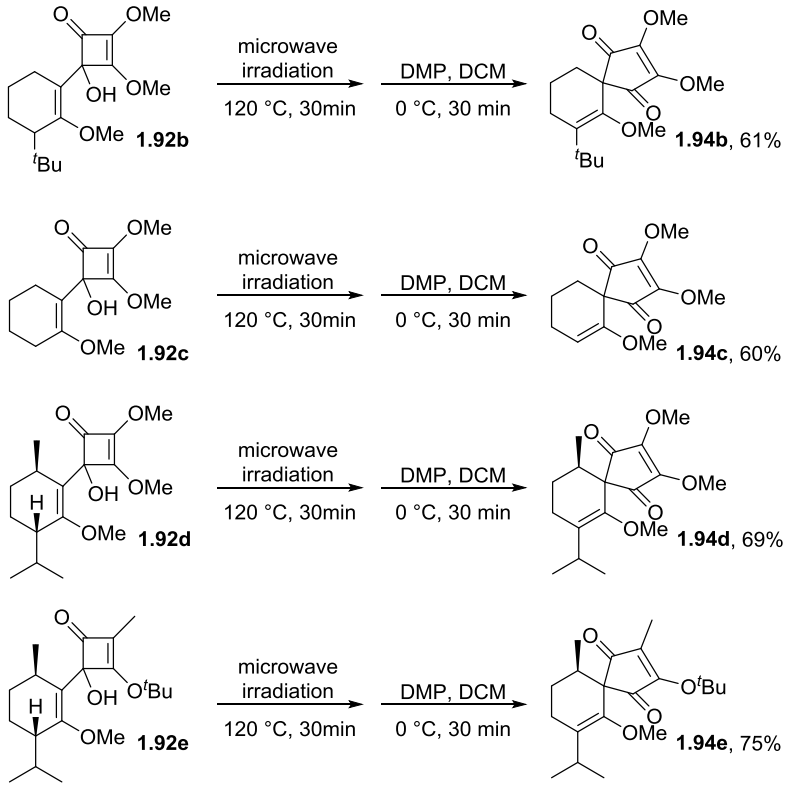
Harrowven *et al.* observed that a different rearrangement pathway was available to 4-vinylcyclobutenones that was distinct from the typical one described by Moore (**Section 1.1**).[9] Thus, the thermolysis of cyclobutenone **1.92** by microwave irradiation failed to yield the anticipated quinone but formed instead a diastereomeric mixture of spirocycle **1.93**, which could be oxidised to cyclopentenedione **1.94** by DMP (**Scheme 1.19**).[9]



1.92a **1.93a** **1.94a**, 73%

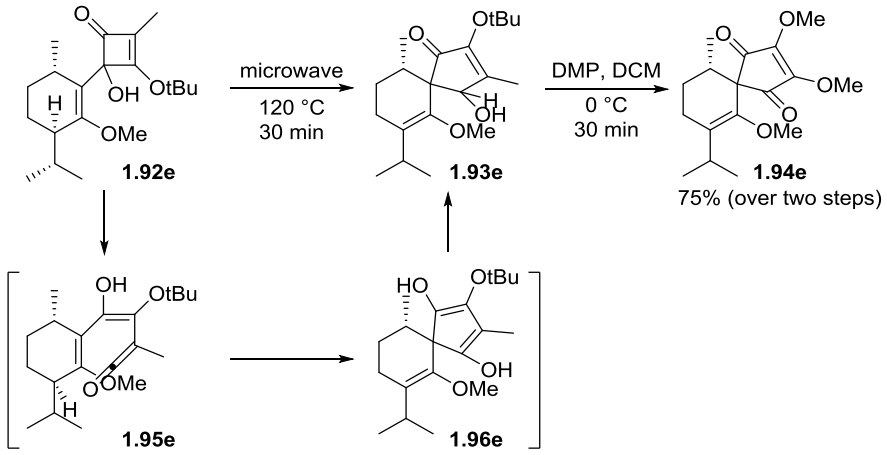
Scheme 1.19: Thermal rearrangement of cyclobutenone **1.92a**.

Following this observation, a series of related cyclobutenones **1.92b-e** containing vinyl ethers were prepared and subjected to thermolysis (**Scheme 1.20**). In all cases cyclopentenediones were formed in high yield.



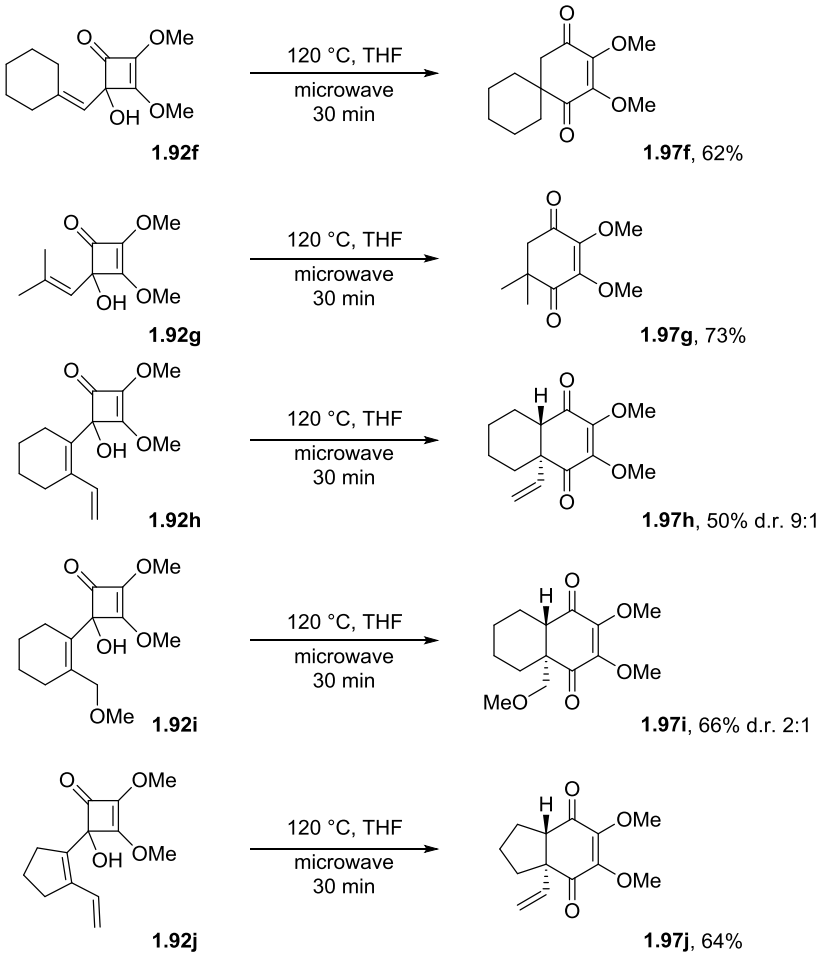
Scheme 1.20: Thermal rearrangement of (alkoxyvinyl)cyclobutenones **1.92b-e**.

It was suggested that the switch in the reaction course was caused by the nature of the substituent on the vinyl analogs. The reaction first undergoes an electrocyclic ring opening to form (*Z*)-vinylketene **1.95e.** At the ring closure step, when the distal carbon bears an electron donating group (*e.g*. MeO), the cyclisation proceeds *via* an ene-reaction leading to spirocyclic **1.94e** (**Scheme 1.21**).



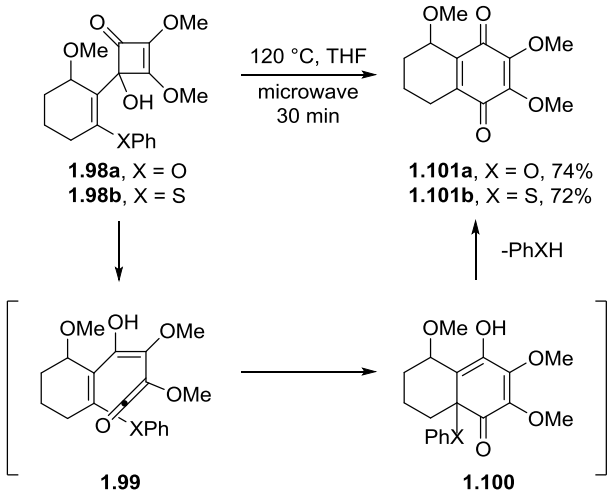
Scheme 1.21: Mechanism for thermolysis of (alkoxyvinyl)cyclobutenone **1.92e**.

Harrowven *et al.* then examined a series of vinylcyclobutenones **1.92f-j** bearing two substituents on the distal carbon of the vinyl group. In each case thermolysis led to a cyclohex-2-en-1,4-dione **1.97** as the product (**Scheme 1.22**). These results demonstrated that it was electronic factor that controlled the outcome of thermolysis of vinylcyclobutenone.



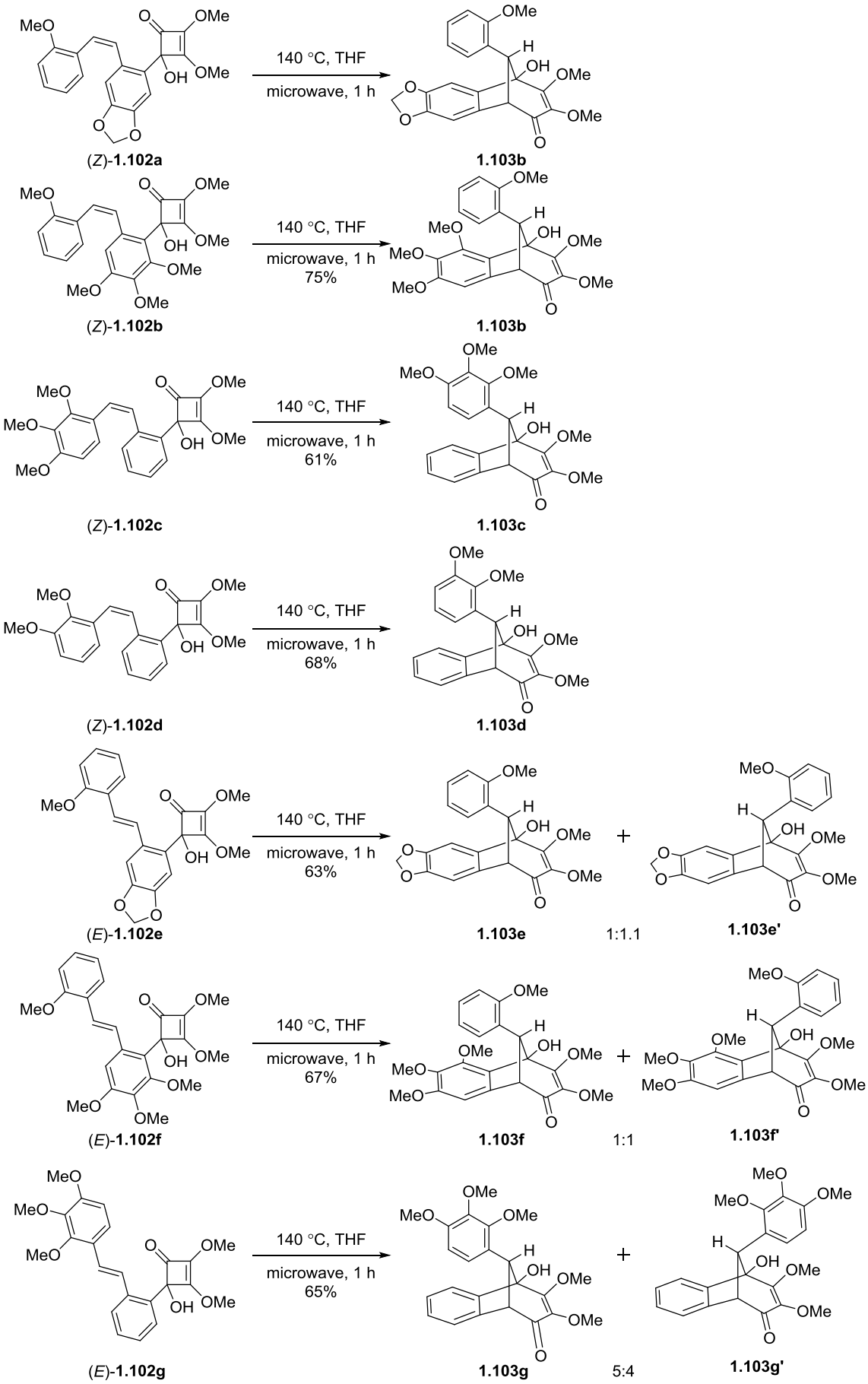
Scheme 1.22: Thermal rearrangement of vinylcyclobutenones **1.91f-j**.

Further evidence for this effect was obtained by the thermolyses of vinylcyclobutenones **1.98a** and **1.98b**. In contrast to the previous results (**Scheme 1.20)**, both of these reactions gave quinones (**1.101a** and **1.101b**) as the only product. Thus, by attenuating the electron density of the vinyl substituent, the selectivity could be switched from spirocycle formation to quinone formation (**Scheme 1.23**).

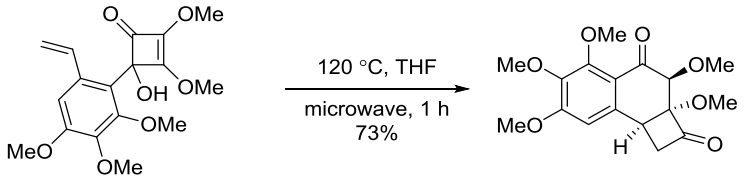


Scheme 1.23: Mechanism for thermolyses of (alkoxyvinyl)cyclobutenones **1.98a** and vinylsulfide **1.98b**.

This method was expanded further to the rearrangement of (*Z*)-4-(*o*-styryl)-cyclobutenones **1.102a-d** which gave benzobicyclo[3.2.1]octenones **1.103a-d** as single diastereoisomers. By contrast, thermolyses of the isomeric (*E*)-4-(*o*-styryl)-cyclobutenones **1.102e-g** gave rise to diastereomeric mixtures of **1.103** and **1.103'** (**Scheme 1.24**). Thermolysis of 4-(*o*-styryl)-cyclobutenone **1.102h** gave benzobicyclo[4.2.0]octenone **1.104h** as the primary product (**Scheme 1.25**).



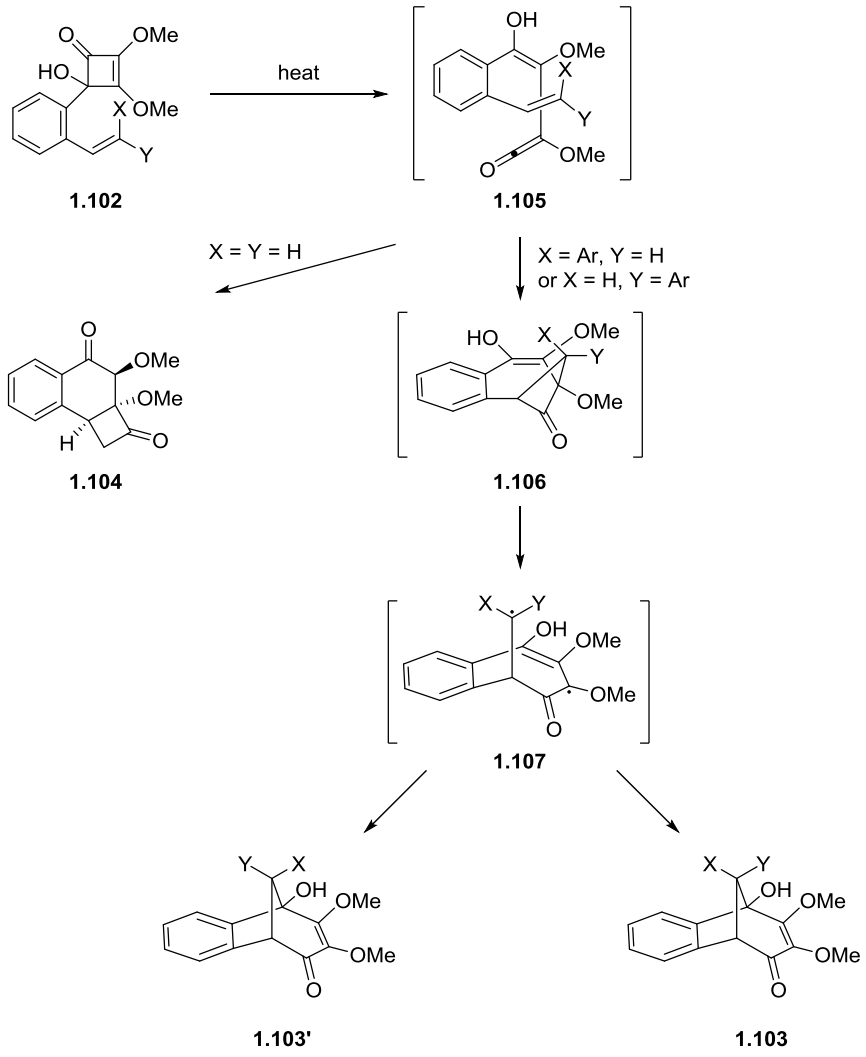
Scheme 1.24: Thermolyses of (Z/E)-4-(*o*-styryl)-cyclobutenones **1.102a-g**.



1.102h **1.104h**, d.r. 6 : 1

Scheme 1.25: Thermolysis of 4-(*o*-styryl)-cyclobutenone **1.102h**

These results were explained by the fact that 4-(*o*-styryl)-cyclobutenone first forms ketene **1.105** by electrocyclic ring opening, which then undergoes an intramolecular [2+2] cycloaddition to give **1.104**. However, when the styrene carries an aromatic substituent (X or Y = Ar), ketene **1.105** follows a different regiochemical course to give intermediate **1.106**. The weak cyclobutane C-C bond is then broken to form diradical intermediate **1.107**, which undergoes cyclisation to the corresponding benzobicyclo[3.2.1]octenones **1.103** (X = Ar, Y = H) as a single diastereoisomer or a diastereoisomeric mixture of **1.103** and **1.103'** (X= H, Y = Ar) (**Scheme 1.26**).



1.102 **1.105** **1.104** **1.106** **1.107** **1.103'** **1.103**

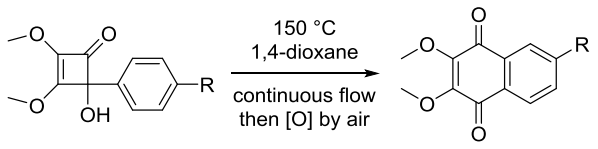
Scheme 1.26: Mechanism of thermolyses of 4-(*o*-styryl)-cyclobutenones **1.102**.

1.6.2 Flow chemistry in rearrangement of cyclobutenones

Harrowven *et al.* were the first to apply the flow chemistry technique to the rearrangement of cyclobutenones.[21,32] Flow chemistry showed significant advantages compared with the traditional batch method.[33,34] In particular, the flow system allowed them to achieve greater uniform of the reaction temperature. Moreover it provided the ability to handle wide extremes in reaction conditions could cope with rapid exotherms and provided a simple means to heat a solvent beyond its usual boiling point.

1.6.2.1 Thermal flow reaction of cyclobutenones

In batch, thermolyses of cyclobutenones were usually conducted in *p*-xylene at reflux for 2 – 10 h (**Section 1.1**, **1.2** and **1.3**). However, when conducted using the flow system, it was possible to employ 1,4-dioxane (bp: 101 °C) as the solvent, even at a temperature of 150 °C, to induce the thermolyses of cyclobutenones **1.108** in a near-quantitative yield in shorter reaction times (**Table 1.11**).



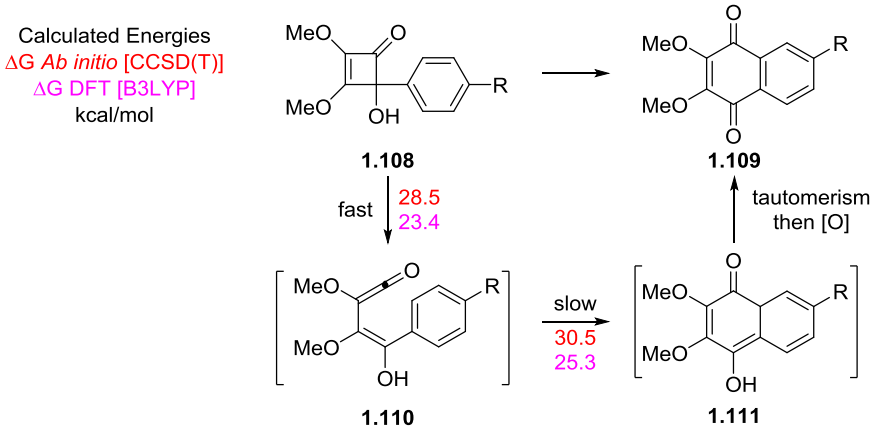
1.108 **1.109**

1.108	***R_1 =***	***Reaction time (h)***	***Yield 1.109 (%)***	***$K \times 10^{-4} (s^{-1})$***	***$LogK_x/K_0$***
a	H	0.5	99	14.9	0
b	Me	2	94	13.1	-0.06
c	TMS	2	94	12.1	-0.09
d	^{t}Bu	2	94	10.2	-0.16
e	Ph	3	95	8.2	-0.26
f	CON*i*Pr$_2$	1.5	84	8.0	-0.27
g	OMe	4	94	6.6	-0.35
h	F	4	92	4.6	-0.51
i	CF_3	4	93	4.4	-0.53

Table 1.11: Rearrangements of cyclobutenones **1.107** under continuous flow.

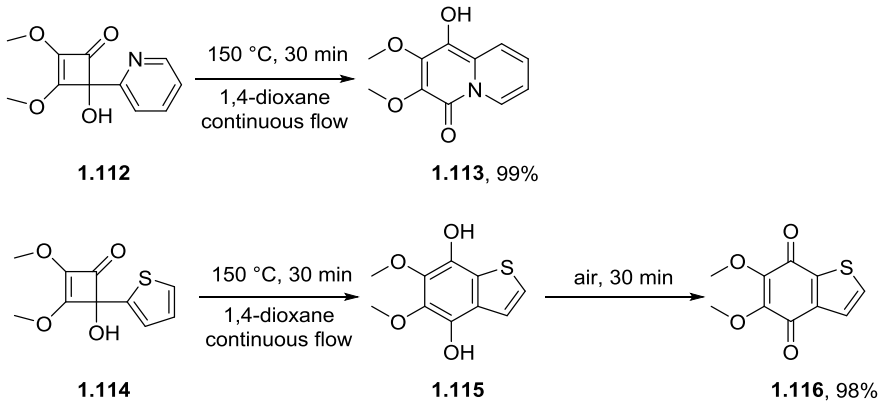
The near quantitative yield attained in this thermal flow reaction made it possible to calculate the reaction rate constant by conducting the reaction at various residence times. All these reactions showed first order rate kinetics and this allowed a Hammett relationship ($\log K_x/K_0 = \rho\sigma$)[35] to be determined in order to understand the nature of these substituent effects and ascertain the rate determining step.

The Hammett plots showed no correlation to σ_p and σ_R and a poor correlation to σ_m (R^2 = 0.69169).[36-38] However, it gave a reasonable correlation to σ_I (R^2 = 0.85842).[39] Greatest deviation was shown by substrates with large substituents (^{t}Bu, TMS, CF_3), suggesting a significant steric component. Thus, correlation was corrected by the inclusion of a small steric correction factor (6% E_s) and this led to an excellent correlation (R^2 = 0.98895).[40-42] The correlation observed with the σ_I parameter set suggested the inductive effect of substituents had an influence on the ease of forming the new σ-bond between the arene and the carbonyl (**1.110** → **1.111**) and that this was the rate determining step. This result was supported by DFT and *Ab initio* calculation when computational studies showed the highest energy barrier for the reaction was for the ring closure step (**Scheme 1.27**).



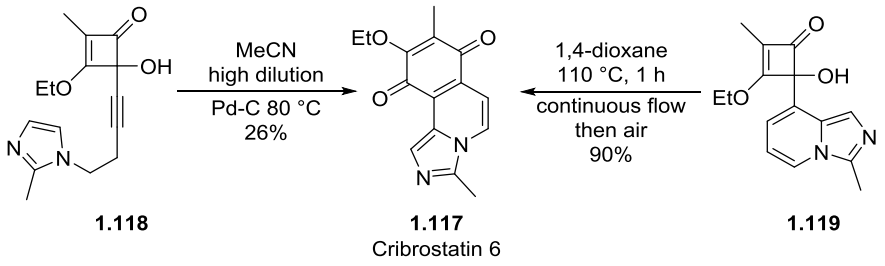
Scheme 1.27: Mechanism for thermolysis of cyclobutenone **1.108**.

The thermal rearrangement of heteroarylcyclobutenones **1.112** and **1.114** under continuous flow was also investigated and proceeded in high yield. Both electron-rich (thiophene) and electron-poor (pyridine) systems were examined (**Scheme 1.28**). Compared with the batch reactions in **Section 1.2**, thermolyses of heteroarylcyclobutenones under continuous flow all showed an increase yield to near quantitative.



Scheme 1.28: Thermolyses of heteroarylcyclobutenones under continuous flow.

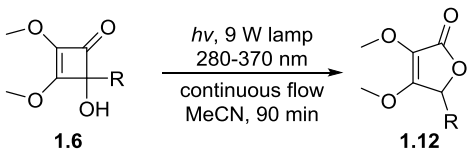
The high yield achieved for thermal rearrangements under continuous flow prompted them to apply the methodology in a total synthesis of cribrostatin 6. Cribrostatin 6 (**1.117**) was first identified by Pettit *et al*. who showed that it exhibited useful anti-neoplastic and anti-microbial activity.[43] At the time the shortest route to cribrostatin 6 was reported by Knueppel and Martin, using the thermolysis of 4-alkynylcyclobutenone **1.118** as a key step, albeit low yielding (26%). Harrowven *et al.* recognised that thermolysis of a heteroarylcyclobutenone **1.119** would offer greater efficiency (**Scheme 1.29**). To that end, thermolysis of **1.119** under continuous flow gave cribrostatin 6 **1.117** in 90% yield.



Scheme 1.29: Key steps in two total syntheses of cribrostatin 6 **1.117**.

1.6.2.2 Photo flow reaction of cyclobutenones

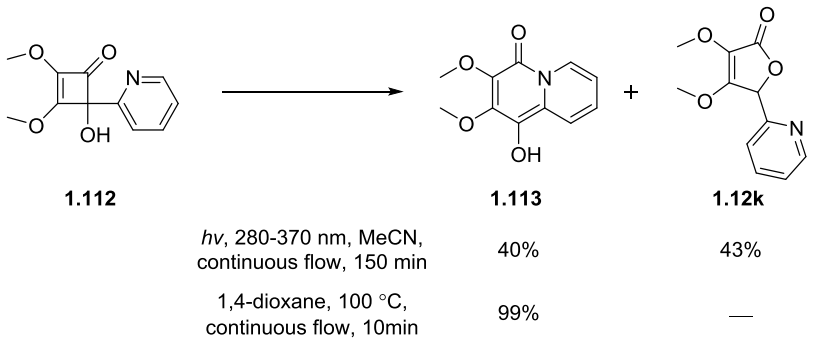
Harrowven *et al.* also found that flow-photochemistry could be used to good effect in the photolyses of cyclobutenones.[32] In **Section 1.4**, photolyses of cyclobutenones showed a low yield of 25-60%. However, by using an in house flow photochemical reactor and a low-energy light bulb, these furanones **1.12** were given in near quantitative yield (**Table 1.12**).



1.6	*R =*	*Yield 1.12 (%)*	*Lit. yield 1.12 (%)*
a	Ph	99	27
b	phenylethynyl	95	28
c	^{t}Bu	96	39
d	*o*-$MeOC_6H_4$	97	51
g	^{n}Bu	95	/
h	*p*-$Me_3SiC_6H_4$	93	/
i	*p*-$^{t}BuC_6H_4$	92	/
j	3-Pyridyl	94	/

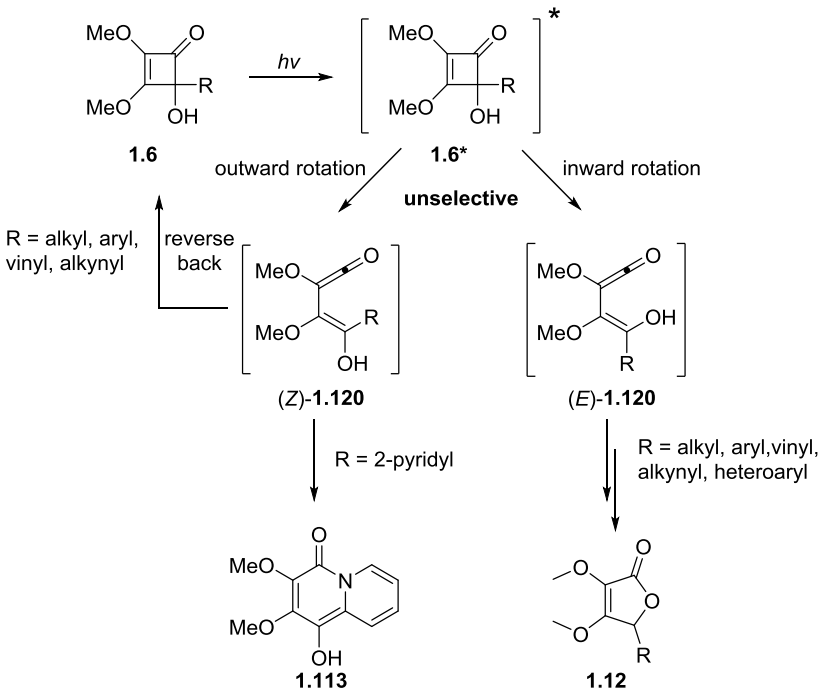
Table 1.12: Photolyses of cyclobutenones **1.6** under continuous flow.

Photolysis of 2-pyridylcyclobutenone **1.112** gave an anomalous result in that it afforded a mixture of furanone **1.12k** and quinolizinone **1.113** in roughly equal amounts (**Scheme 1.30**). Quinolizinone **1.113** was also obtained from thermolysis of 2-pyridylcyclobutenone **1.6k** in a near quantitative yield.



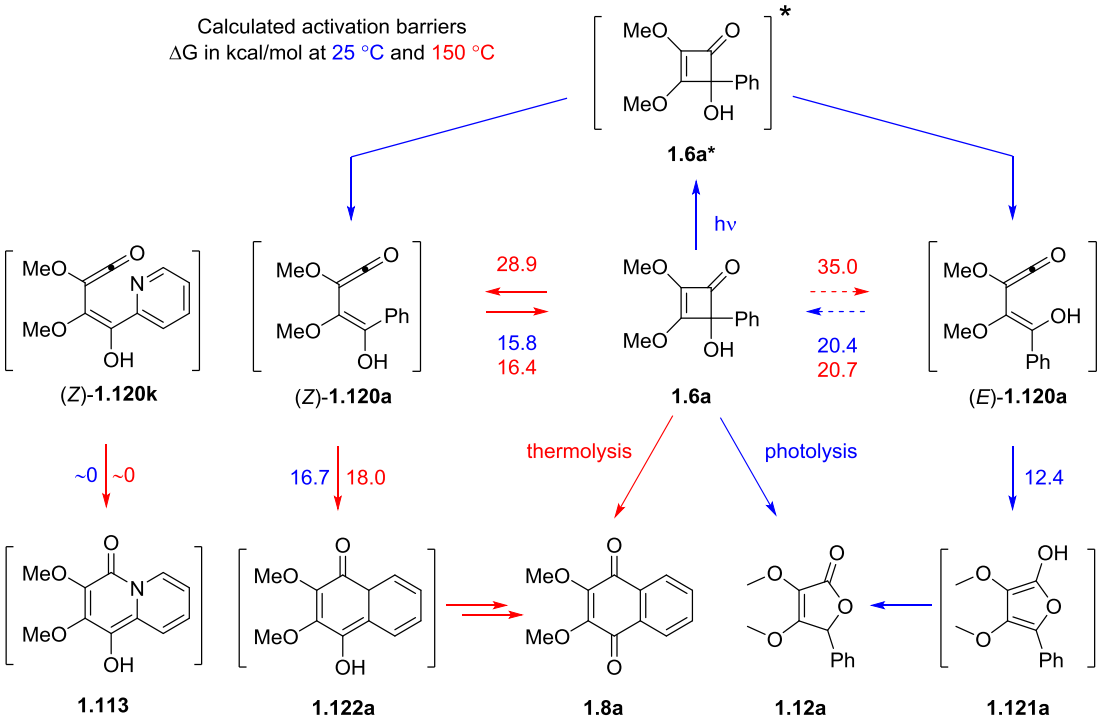
Scheme 1.30: Photolysis and thermolysis of cyclobutenone **1.112.**

This result cast doubt on the idea that the photolysis of cyclobutenone proceeded *via* torquoselective ring opening and cyclisation to a furanone. Instead, the result suggested that under UV irradiation, cyclobutenone **1.6** was excited from a ground state to a high energy excited state **1.6***, which then collapsed unselectively to give a mixture of (*Z*)- and (*E*)-vinylketenes **1.120**. For (*Z*)-vinylketene (*Z*)-**1.120k** (where R = 2-pyridyl) the ring closure step showed a very low energy barrier to form quinone **1.113**. By contrast, other (Z)-vinylketenes **1.120** (where R = alkyl, aryl, vinyl or alkynyl) showed a high energy barrier for the related ring closure steps so that the vinylketene reversed back to starting material **1.6**. In all cases, the corresponding (*E*)-vinylketene ((*E*)-**1.120**) underwent ring closure leading to furanone **1.12** *via* a low energy pathway (**Scheme 1.31**).



Scheme 1.31: Revised mechanism for the photochemical rearrangement of cyclobutenones **1.6**.

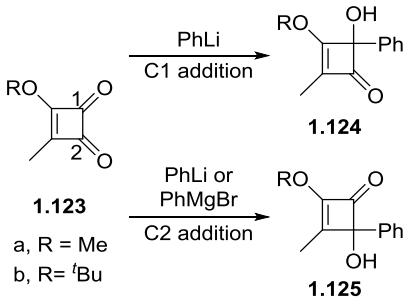
These results were confirmed by DFT calculations on the thermolysis or photolysis of cyclobutenone **1.6a**. In this case the energy barrier for the 6π-electrocyclic ring closure of vinylketene (*Z*)-**1.120a** was 16.7 kcal/mol ((*Z*)-**1.120a** → **1.122a**) and exceeded that for 4π-electrocyclic ring closure (15.8 kcal/mol) ((*Z*)-**1.120a** → **1.6a**). For vinylketene (*E*)-**1.120a**, the energy barrier for returning back to cyclobutenone **1.6a** was 20.4 kcal/mol ((*E*)-**1.120a** → **1.6a**), higher than the cyclisation pathway to form furanone **1.12a** (12.4 kcal/mol) ((*E*)-**1.120a** → **1.121a**). In contrast, thermolysis of cyclobutenone **1.6a** showed a much higher energy barrier to form (*E*)-**1.120a** (35.0 kcal/mol) than (*Z*)-**1.120a** (28.9 kcal/mol) at 150 °C. Additional calculations on 2-pyridionecyclobutenone **1.112** showed no energy barrier for the ring closure step from (*Z*)-**1.120k** to **1.113**, hence in this reaction (*Z*)-**1.120k** did not reverse back to starting material **1.112** (**Scheme 1.32**).



Scheme 1.32: Energy barriers in the rearrangement of cyclobutenone **1.6a** and ring closure of vinylketene (*Z*)-**1.120k**. Calculated at B3LYP/6-311G(d,p).

1.6.3 Organoytterbium additions to cyclobutenediones and subsequent rearrangements

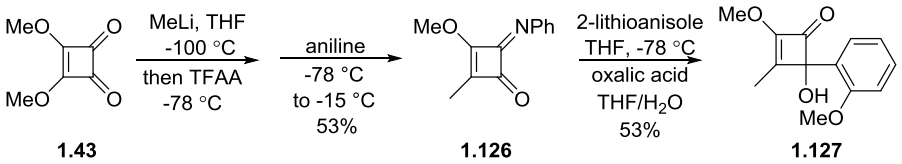
The rearrangement of substituted cyclobutenones has been recognized as a valuable method for the synthesis of quinones, cyclopentenediones and furanones. To prepare substituted cyclobutenones, organolithium or Grignard regents are generally added to cyclobutenediones. Importantly, the different reactivity of the C1 and C2 carbonyl groups in unsymmetrical cyclobutenediones makes selective addition possible. 3-Methyl-4-alkoxycyclobutenediones **1.123**, for example, shows a strong preference for addition to the C1 carbonyl as the C2 carbonyl is a vinylogous ester (**Table 1.13**).



1.123	*R =*	*Reaction condition*	*Yield 1.124 (%)*	*Yield 1.125 (%)*
a	Me	PhLi, THF, –78 °C	76	/
b	^{t}Bu	PhLi, THF, –78 °C	48	41
b	^{t}Bu	PhMgBr, THF, –78 °C	22	67

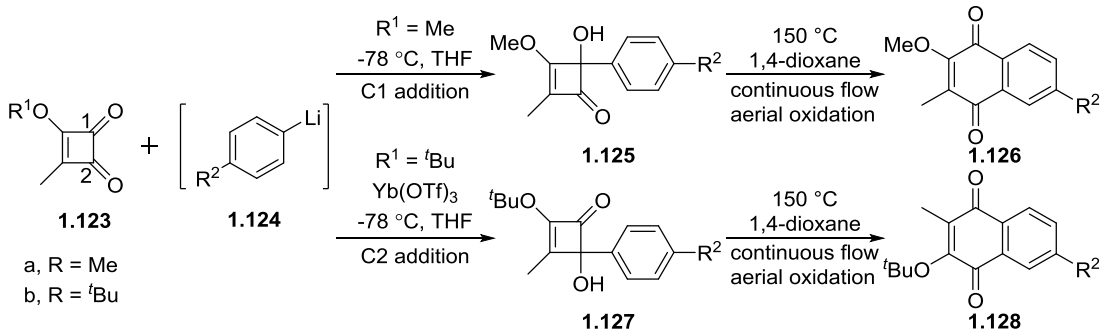
Table 1.13: Regioselectivity in the addition of cyclobutenones **1.123**.

Trost *et al.* and Moore *et al.* used a capricious protecting group strategy to obtain a different regioselectivity.[44] Thus, imine-protected cyclobutenone **1.126** was obtained from cyclobutenedione **1.43** in 53% yield. The addition of an aromatic nucleophile and *in situ* acid catalysed removed of the imine protecting group gave the C2 addition product **1.127** in 53% yield. The low yield could be attributed to the poor stability of cyclobutenone **1.127** under acid conditions (**Scheme 1.33**).



Scheme 1.33: Preparation of C2 addition cyclobutenone **1.127**.

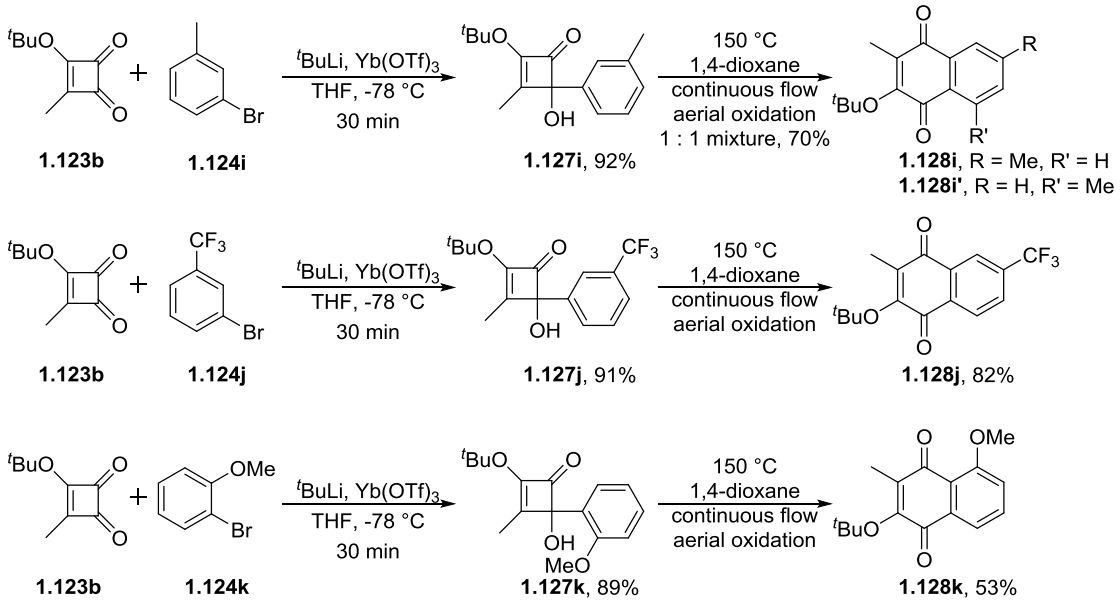
Harrowven *et al.* reported a general method for the formation of C2 addition products such as **1.127** through the use of organoytterbium reagents in these addition reaction together with a bulky alkoxy protecting group for the enol in cyclobutenone **1.123** (**Table 1.14**).[45] A series of *para*-substituted aromatic additions were tested. All organoytterbium additions to **1.123b** (R = ^{t}Bu) resulted in C2 addition products whereas organolithium additions to **1.123a** (R = Me) gave C1 addition products.



entry	*R^1 =*	*R^2 =*	*Yield 1.125 (%)*	*Yield 1.126 (%)*	*Yield 1.127 (%)*	*Yield 1.128 (%)*
a	Me	H	76	91	/	/
b	^{t}Bu	H	/	/	92	78
c	Me	Me	89	94	/	/
d	^{t}Bu	Me	/	/	96	65
e	Me	OMe	74	70	/	/
f	^{t}Bu	OMe	/	/	98	75
g	Me	CF_3	74	78	/	/
h	^{t}Bu	CF_3	/	/	94	87

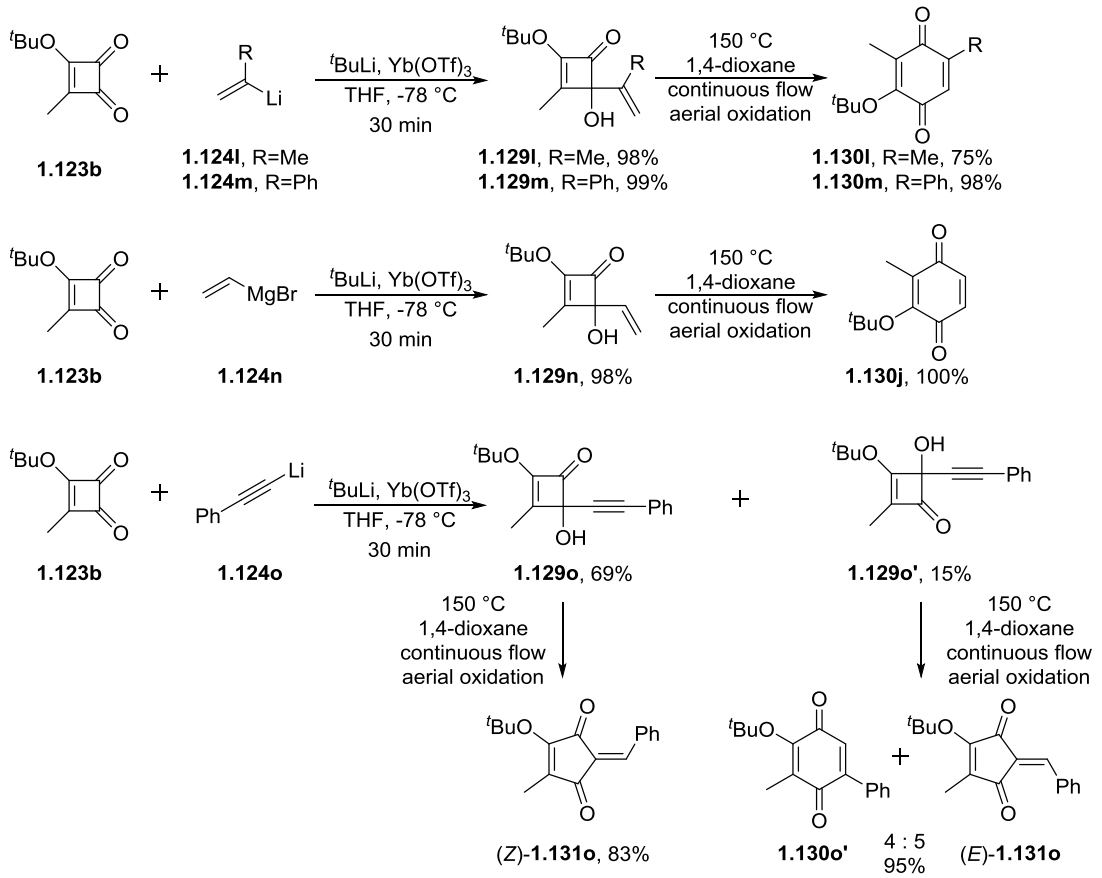
Table 1.14: Organolithium and organoytterbium additions to cyclobutenedione **1.123** and following rearrangement.

This method was then tested on *ortho*- and *meta*- substituted arenes. All of the reactions with cyclobutenone **1.123b** gave the C2 addition products **1.127** in a high yield with the resulting thermolyses affording the corresponding quinones **1.128** (**Scheme 1.34**).



Scheme 1.34: Further organoytterbium addition reactions to cyclobutenedione **1.123b**.

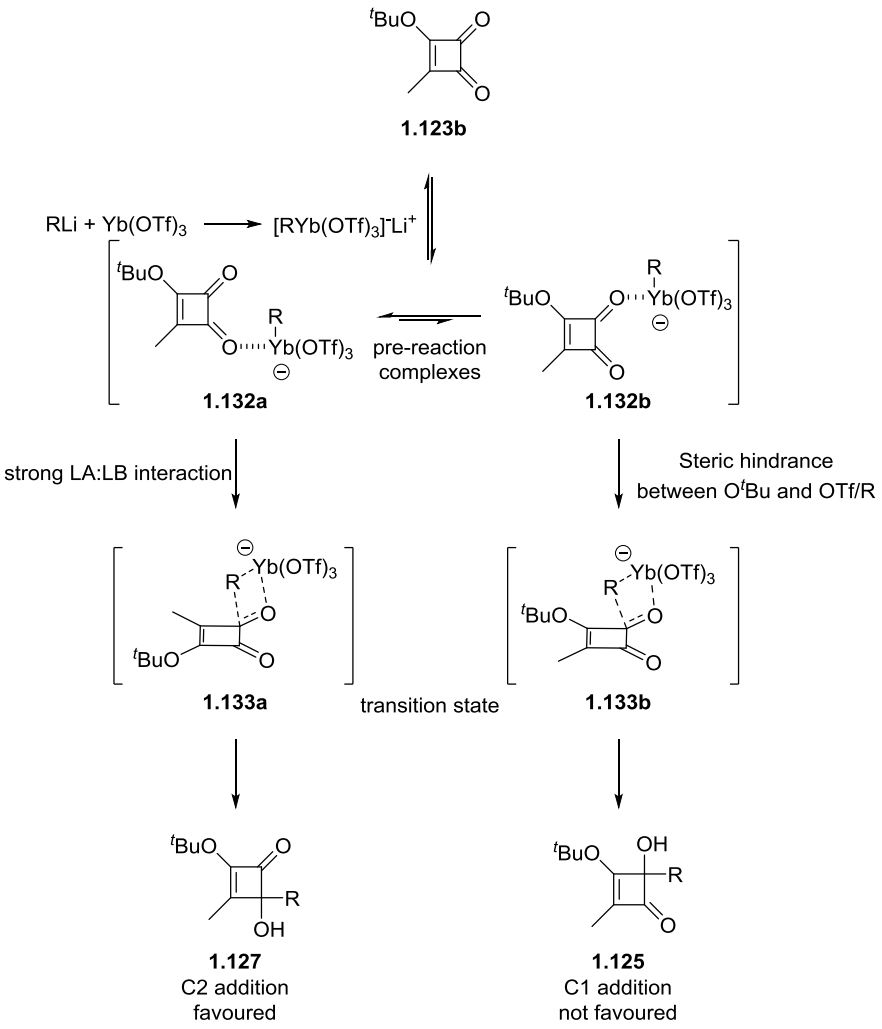
This methodology was then expanded to vinyl and alkynylytterbium complexes. The vinylytterbium addition reaction showed good regioselectivity towards C2 addition giving cyclobutenones **1.129l-n** in near quantitative yield. Each gave the corresponding quinones **1.130l-n** on thermolyses under flow. The alkynylytterbium addition with **1.124o** was poorer, giving a 4.6 : 1 mixture of C2 addition product **1.129o** and C1 addition product **1.129o'** on reaction with cyclobutenedione **1.123b**. Thermolysis of **1.129o** gave cyclobutenedione (*Z*)-**1.131o** in 83% yield. By contrast, thermolysis of **1.129o'** gave a 4:5 mixture of quinone **1.130o'** and cyclobutenedione (*Z*)-**1.131o** in combined 95% yield (**Scheme 1.35**).



Scheme 1.35: Ytterbium reactions on vinyl, alkynyl reagents.

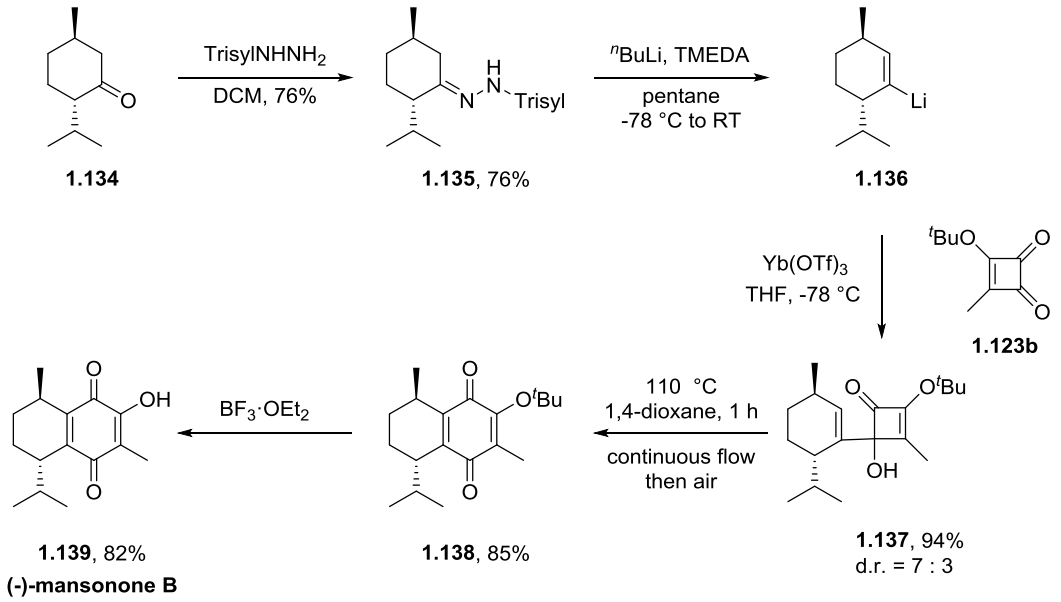
Harrowven *et al.* explained that the selectivity of the organoytterbium addition was due to two factors. Thus, when an organoytterbium reagent is added to cyclobutenedione **1.123**, it first forms a pre-reaction complex **1.132a** or **1.132b**. The carbonyl of the vinylogous ester, C2, is more electron rich than the ketonic C1 carbonyl, hence pre-reaction complex **1.132a** is more favoured than **1.132b**. DFT calculation confirmed this as the Gibbs energy of **1.132a** was 2.5 kcal/mol lower than **1.132b**. Additionally, a steric interaction in transition state **1.133b** between the triflate ligands (or the R residue) and the ^{t}BuO residue increases the energy barrier for C1 addition. This is greatest for the ^{t}Bu group where DFT calculation showed the energy barrier in transition state **1.133b** was 2 kcal/mol higher than in transition state **1.133a**. In conclusion, these two factors tip

the balance in favour of C2 addition of organoytterbium reagents to cyclobutenedione **1.123b** (**Scheme 1.36**).



Scheme 1.36: Explanation of the regioselectivity observed in organoytterbium additions to cyclobutenedione **1.125b**.

Having established that aryl- and vinyl- ytterbium reagents could give C2 additions to cyclobutenedione **1.123b**, Harrowven *et al.* demonstrated the value of the method with a short and highly efficient route to (–)-mansonone B **1.139** (**Scheme 1.37**). The synthesis started from (–)-menthone **1.134**, from which the required vinyllithium reagent **1.136** was formed by a Shapiro reaction. Transmetallation with ytterbium triflate next gave the corresponding vinylytterbium intermediate which, on addition to cyclobutenedione **1.123b**, gave the C2 adduct cyclobutenone **1.137** as a 7:3 diastereomeric mixture. Thermolysis of the mixture **1.137** under continuous flow at 110 °C with concomitant aerial oxidation gave the quinone **1.138** in 85% yield. Finally, deprotection of the enol by $BF_3{\cdot}OEt_2$ afforded the desired product (–)-mansonone B **1.139** in 82% yield.



Scheme 1.37: Total synthesis of (–)-mansonone B **1.139** by using an organoytterbium reagent.

1.6.4 DFT calculations on the rearrangement of cyclobutenones

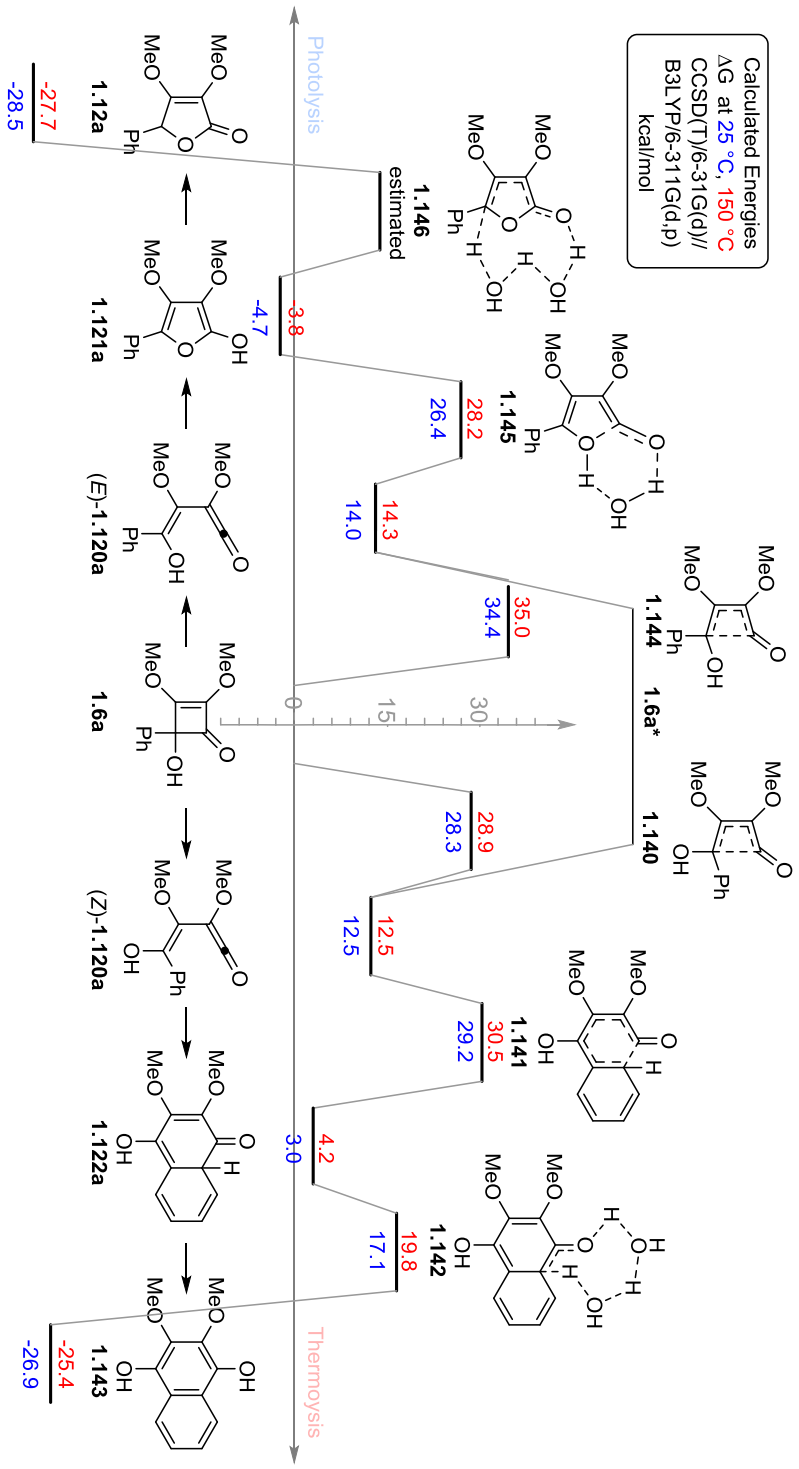
In order to investigate the rearrangements of cyclobutenones more thoroughly, several computational studies were performed to understand the reaction mechanism and selectivity observed.[46] Various functions and basis sets were first examined to establish a suitable method for energy calculations in this system. It was determined that CCSD(T) gave the most accurate results but was computationally expensive to apply.[47] The B3LYP functional[48,49] showed an accurate result in geometry calculations when using the 6-311G(d,p) basis set but was not appropriate for gaining a quantitative picture.[50,51] Nevertheless, it was able to provide qualitative trends for such reactions. The M062X functional[52] with the 6-311+G(d,p) basis set also gave reasonably accurate results with a much lower computational demand than CCSD(T), and was therefore considered to be an appropriate method to use.

Calculation results by both the B3LYP/6-311G(d,p) method and the CCSD(T)/6-31G(d) method suggested that ring closure was the rate determining step in arylcyclobutenones rearrangements, which was consistent with the experimental results obtained by Hammett analysis (**Section 1.6.2.1**). However, the B3LYP function result showed a much lower energy barrier than the CCSD(T) method. Rates calculated from B3LYP/6-311G(d,p) predicted a rate constant of 0.72 s^{-1} for the rearrangement of cyclobutenone **1.6a** to **1.143**, which was more than 500 times faster than that obtained experimentally (0.0015 s^{-1}). Whereas the CCSD(T)/6-31G(d) method predicted a rate constant of 0.0016 s^{-1} which was in excellent agreement with the experimental result (**Table 1.15**).

Energy barrier (kcal/mol)			
Method at 150 °C	***Ring opening step 1.6a → (Z)-1.120a***	***Ring closure step (Z)-1.120a → 1.122a***	***Rate constant (s^{-1})***
ΔG (B3LYP/6-311G(d,p))	23.4	25.3	0.72
ΔG (CCSD(T)/6-31G(d))	28.9	30.5	0.0016
Exp.	/	/	0.0015

Table 1.15: Energy barriers for the ring opening and ring closure steps in the thermolysis of cyclobutenone **1.140**.

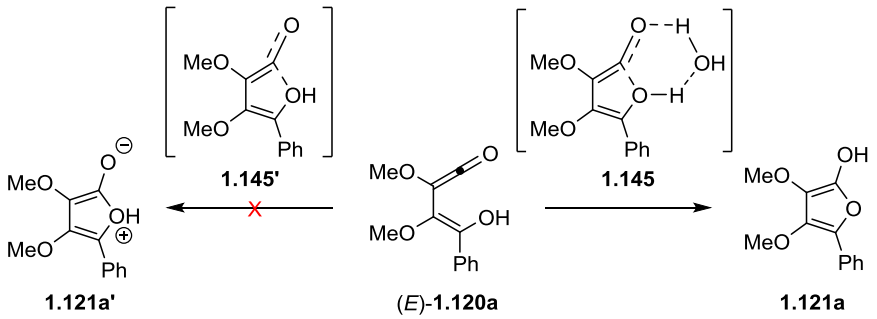
From the calculation results a full energy diagram of the rearrangement of cyclobutenone **1.6a** was obtained. For the thermal rearrangement of cyclobutenone **1.6a**, the ring opening transition state **1.140** showed a much lower energy barrier (28.3 kcal/mol) than transition state **1.144** (34.4 kcal/mol), showing that (*Z*)-vinylketene (*Z*)-**1.120a** was favoured over (*E*)-vinylketene (*Z*)-**1.120a**. The subsequent ring closing transition state **1.141** gave an energy barrier of 30.5 kcal/mol, which was higher than that for the ring opening transition state **1.140** but still lower than transition state **1.144**. These results predicted that the thermal rearrangement would afford quinone **1.143** as the final product and that ring closure was the rate determining step, in line with the experimental results. For the photo rearrangement we assume that there is no selectivity in the ring opening step to form ketenes (*Z*)**-1.120a** and (*E*)-**1.120a** as the excited intermediate **1.6a*** has sufficient energy to transcend both transition state **1.140** and **1.144**. However, for (Z)-vinylketene (*Z*)**-1.120a**, transition state **1.141** showed a higher energy barrier than transition state **1.140**, indicating that it would reverse back to cyclobutenone **1.6a**. The ring closure transition step from (*E*)-vinylketene (*E*)**-1.120a** to furan **1.121a** showed a much lower barrier than that required for reversal indicating that furanone **1.12a** would be the product from photolysis, which was again consistent with the experimental result (**Scheme 1.38**).



Scheme 1.38: Energy diagram for rearrangement of cyclobutenone **1.6a**.

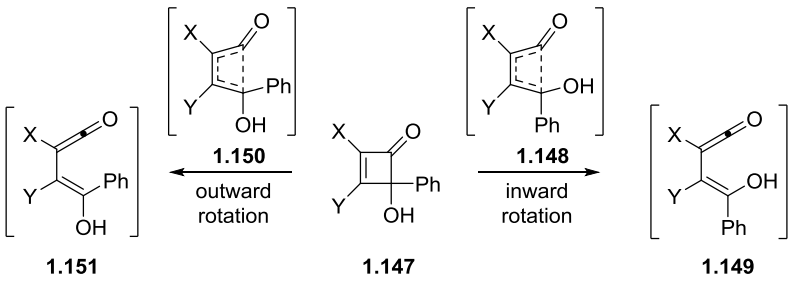
Attention next turned to the mechanism of the ring closure step from (*E*)-vinylketene (*E*)-**1.120a** to furanol **1.121a** (**Scheme 1.39**). It had been assumed that this proceeded *via* an intramolecular cyclisation *via* transition state **1.145'** to form zwitterion **1.121a'**. However, all attempts to calculate the ground state for the zwitterionic intermediate **1.121a'** failed and converged to the intermediate (*E*)-**1.120a**. Consequently intermediate **1.121a'** does not appear to be an intermediate in this reaction pathway. Subsequently, calculations revealed that cyclisation could

be catalysed by water with the reaction proceeding *via* a six-membered cyclic transition state **1.145** with a low energy barrier.



Scheme 1.39: Possible mechanism for the cyclisation of ketene (*E*)-**1.120a** to furanol **1.121a**.

The ring opening step was then thoroughly investigated. A series of 35 arylcyclobutenones with various substituents were analysed to determine the influence of substituents (X and Y) on the ring opening step (**Table 1.16**). All showed an energy difference between the transition state **1.148** and **1.150** of between 4-10 kcal/mol. These results showed how substituents could affect torquoselectivity in the ring opening step of thermolysis of cyclobutenone, and that in most cases this effect would provide the quinone as the major product in thermal rearrangement of arylcyclobutenones.



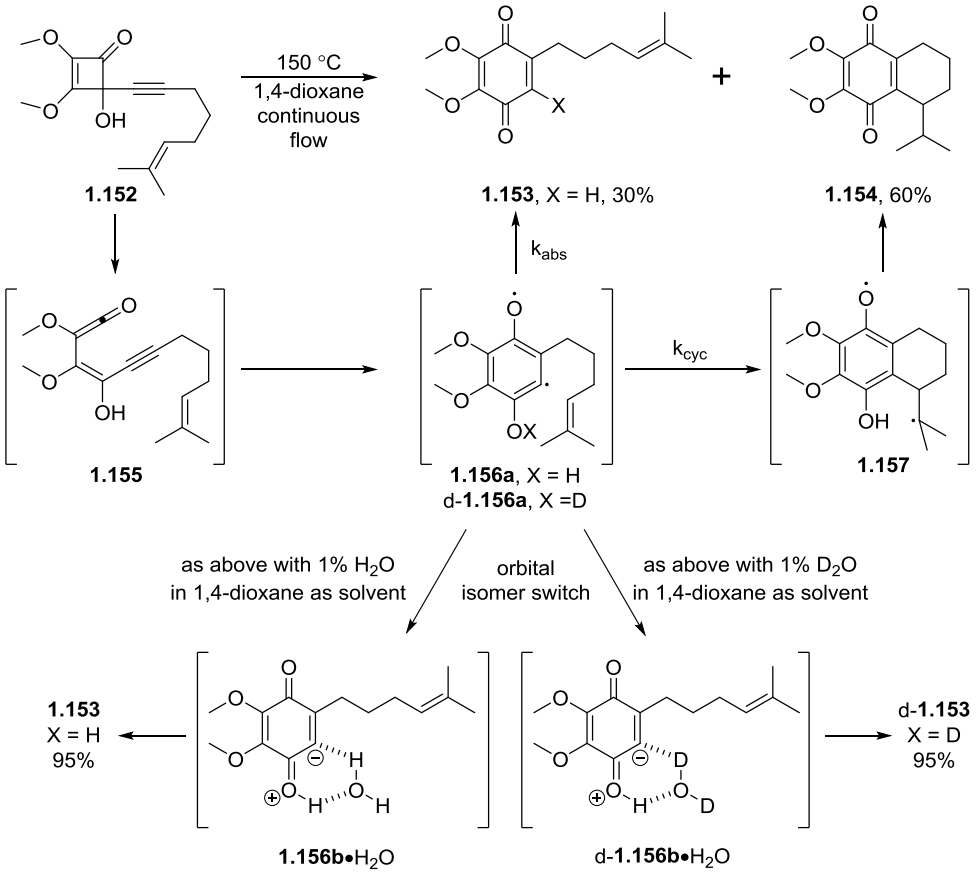
1.147	*X =*	*Y =*	*Barrier height (kcal/mol)*		
			$E_{1.148}$	$E_{1.150}$	$\Delta E_{1.148\text{-}1.150}$
a	NO_2	H	13.4	19.69	6.2
b	F	H	14.4	26.1	11.7
c	H	NO_2	14.8	21.8	6.9
d	H	F	15.8	20.2	4.4
e	CN	CN	16.8	23.6	6.8
f	CF_3	CF_3	17.1	24.1	6.9
g	F	F	17.2	21.3	4.2
h	CF_3	H	17.3	23.9	6.6
i	H	CF_3	17.3	24.2	6.9
j	OH	OH	21.9	27.1	5.0
k	OMe	OMe	21.6	27.1	5.5

Table 1.16: Examples of DFT calculations on torquoselectivity in the thermal ring opening of arylcyclobutenones **1.147**.

1.6.5 Orbital isomerisation in thermolyses of alkynylcyclobutenones

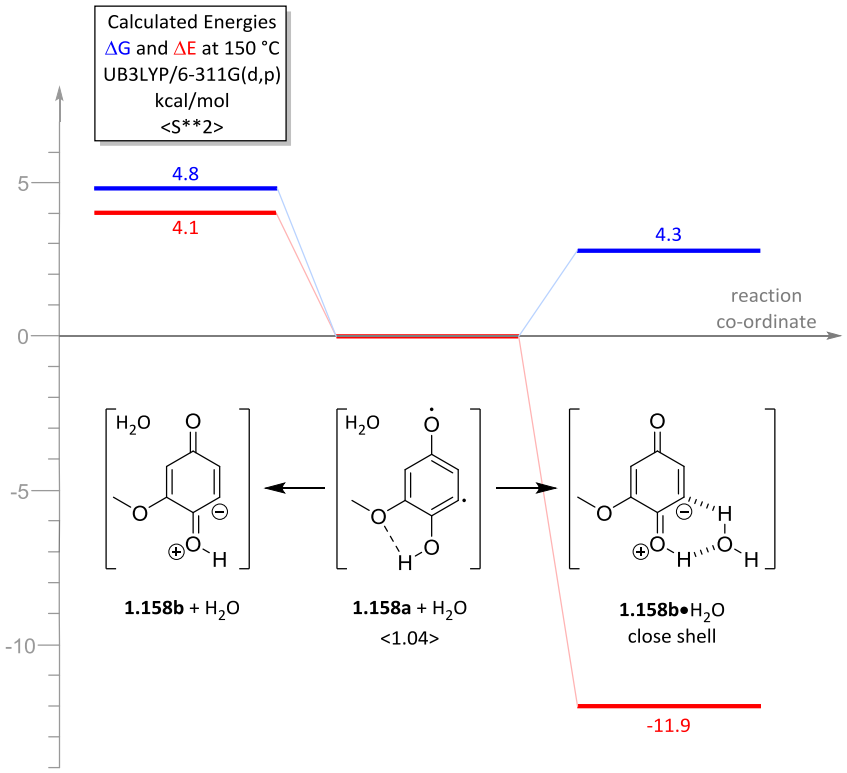
Harrowven *et al.* also found that the Moore rearrangement of alkynylcyclobutenone **1.152** gave a mixture of quinones **1.153** (30%) and **1.154** (60%) (**Scheme 1.40**).[20] As previously discussed (**Section 1.3**), the reaction first formed the diradical intermediate **1.156a**, which could either form quinone **1.153** directly by H-atom abstraction or give the new diradical intermediate **1.157** *via* a 6-exo-dig cyclisation to the alkene residue. Diradical **1.157** could then abstract an H-atom from the proximal phenol to give quinone **1.154**. They planned to slow down the H-atom abstraction step from **1.156a** to **1.153** by exploiting the deuterium isotope effect, as deuterium-atom abstraction from **1.156a** to **1.153** would be much slower than H-atom abstraction, but the rate of cyclisation leading to diradical **1.157** would be unchanged. Consequently, it should be possible to increase the yield of **1.157** by adding D_2O as a cosolvent for the reaction. However, instead of promoting the cyclisation pathway to form quinone, only quinone d-**1.153** was isolated in 98% yield. A similar reaction using aqueous 1,4-dioxane only gave quinone **1.153** in 95% yield. These results suggested

the reaction proceeded *via* the zwitterionic orbital isomer **1.156b**, in which a rapid O – C proton shift was catalysed by water (*i.e. via* **1.156b**·H_2O or **1.156b**·D_2O).



Scheme 1.40: An orbital isomer switch promoted by H_2O (or D_2O) diverts the course of the reaction towards the quinone **1.153** (or [D]-**1.153**).

DFT calculations were conducted to confirm the hypothesis at UB3LYP/6-311G(d,p) level. The analysis showed the ΔE value for the diradical **1.158a** was 4.1 kcal/mol lower than that for the zwitterionic isomer **1.158b**. However, when a molecule of water was included in the model, the zwitterion **1.158b**·H_2O was favoured over **1.158a** + H_2O by 11.9 kcal/mol due to the hydrogen bonding. Importantly, **1.158b**·H_2O showed no spin contamination, confirmed its closed-shell structure (**Scheme 1.41**).



Scheme 1.41: Computational study reveals an orbital isomer switch triggered by water.

Moreover, optimization of the diradical intermediate **1.159a** and its hydrated zwitterionic orbital isomer **1.159b**·H_2O revealed the most stable geometries for each. As expected, diradical **1.159a** showed a planar arene. By contrast, **1.159b**·H_2O had a significant pucker in its ring (151.5°) (**Figure 1.1**).

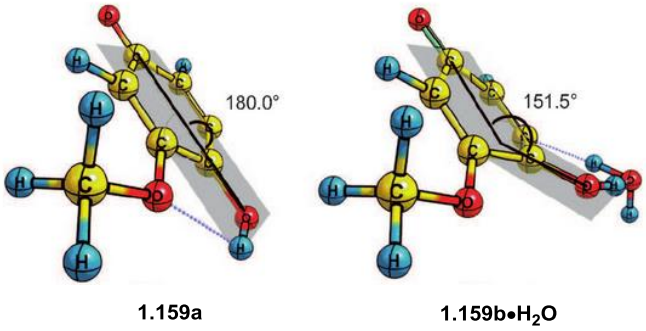
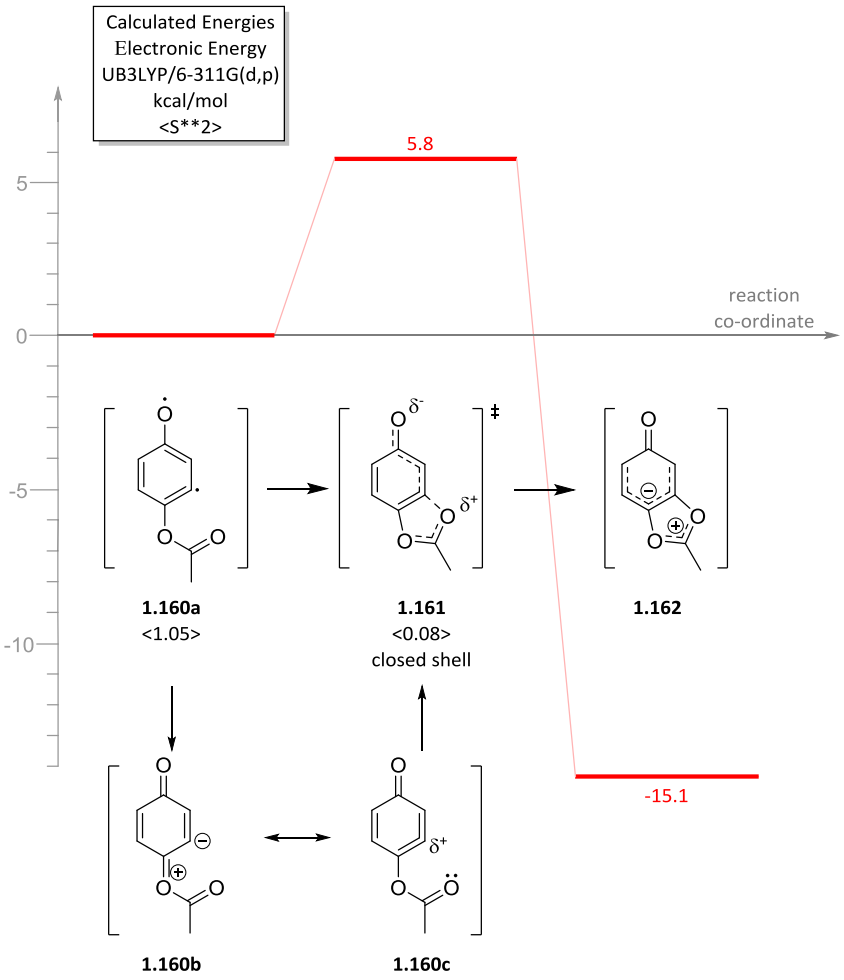


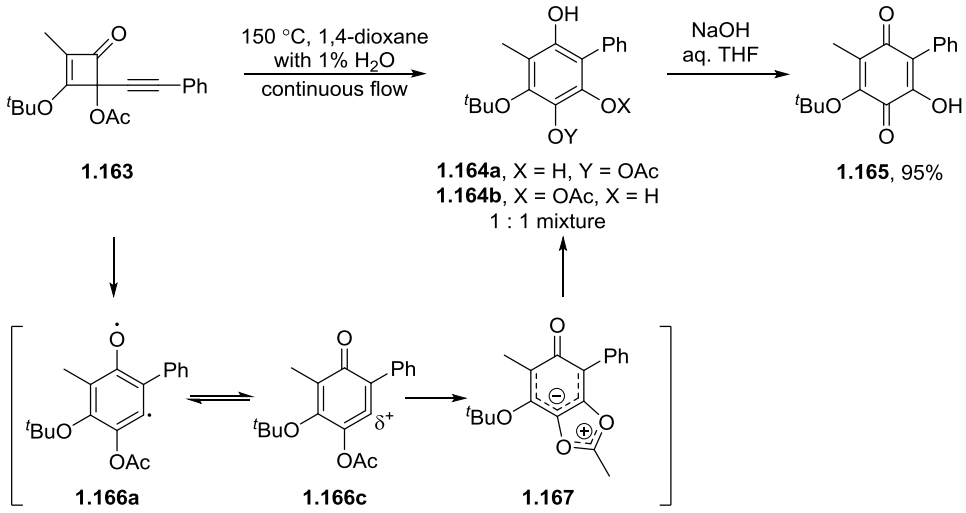
Figure 1.1: A computational study reveals a planarity diradical **1.159a** and the pronounced puckering zwitterion **1.159b**·H_2O.

Following that study another diradical intermediate **1.160** was examined computationally. DFT calculations revealed that a low energy cyclisation pathway (**1.161**) leading to zwitterion **1.162** was available to this intermediate. The transition state **1.161** showed a puckered closed-shell structure, consistent with the reaction proceeding *via* orbital isomer **1.160b/c** (**Scheme 1.42**).



Scheme 1.42: Computational study reveals an orbital isomer switch on a new ring closing pathway.

This result was confirmed by experiment in that the thermolysis of the cyclobutenone acetate **1.163** in aqueous 1,4-dioxane led to a 1 : 1 mixture of the acetates **1.164a** and **1.164b** in near quantitative yield (**Scheme 1.43**). This provided compelling evidence for the zwitterion intermediate **1.167** and implicated that the orbital isomer **1.166b/c** had significant cyclohexatrienone character.

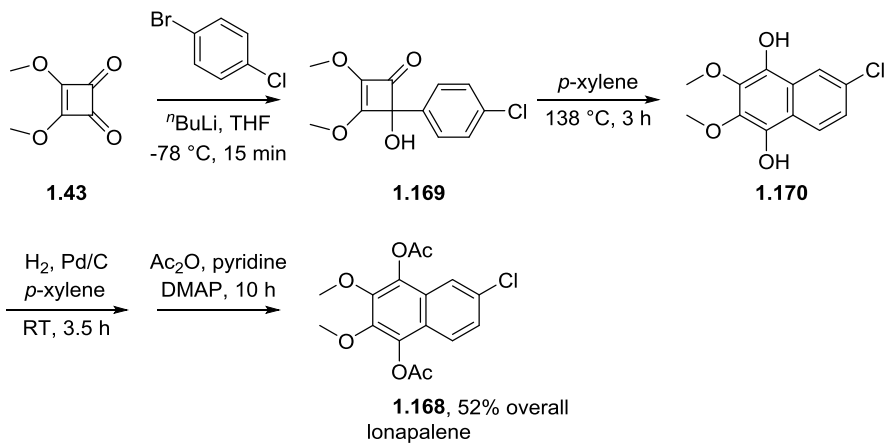


Scheme 1.43: Thermolysis of cyclobutenone **1.169** in aqueous 1,4-dioxane.

In conclusion, Harrowven *et al.*'s work demonstrated that the aryl radical centre in such diradical intermediate can act as radicals (*e.g.* **1.156a**), anions (*e.g.* **1.156b**) or electrophiles (*e.g.* **1.166c**) through its orbital isomerisation.

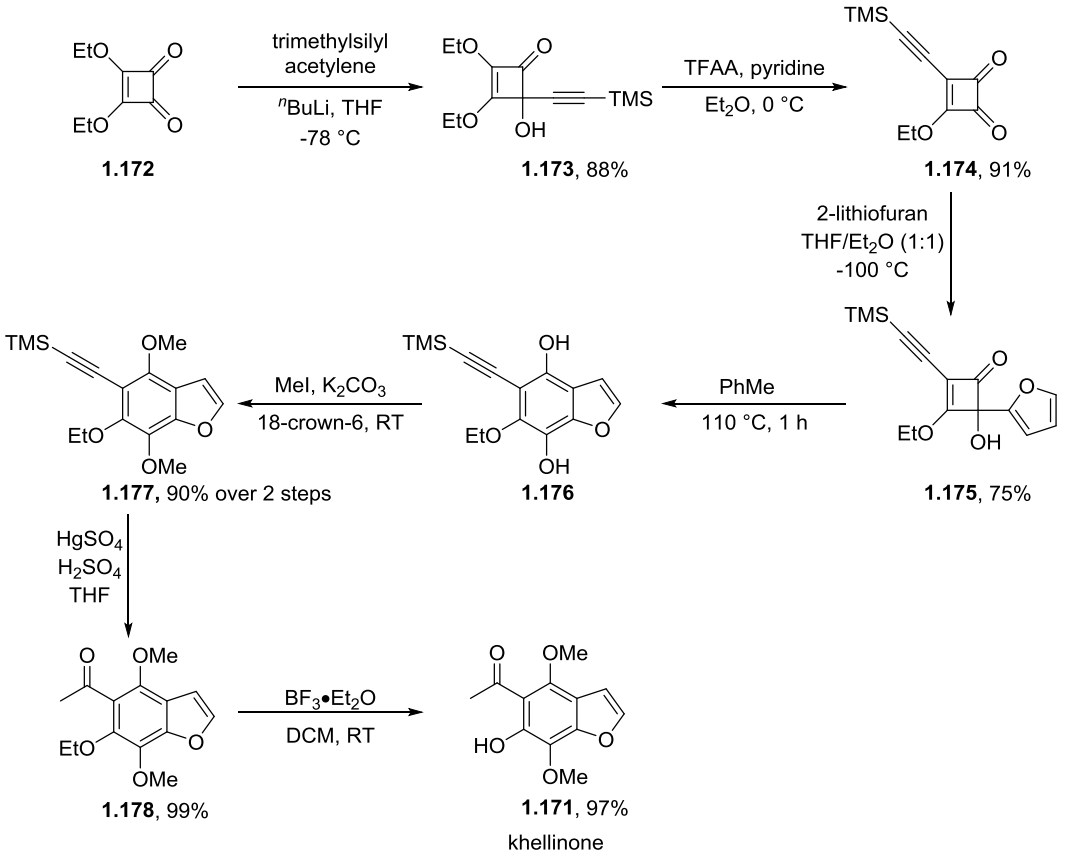
1.7 Synthesis of natural products from cyclobutenones

The rearrangement of cyclobutenones has proven especially valuable in the total synthesis of natural products with quinone or naphthoquinone subunits.[53,54] Moore *et al.* were the first to report their use in total synthesis with the development of a route to lonapalene[55] **1.168** (a selective 5-lipoxygenase inhibitor used as an antipsoriatic drug).[8] Their synthesis started with the lithiation of 4-bromochlorobenzene followed by addition of the resulting aryllithium to cyclobutenedione **1.43** to give cyclobutenone **1.169**. The crude product mixture was then subjected to thermolysis to form hydroquinone **1.170**, which was then acetylated in the presence of acetic anhydride to give lonapalene **1.168** in 52% overall yield (**Scheme 1.44**).



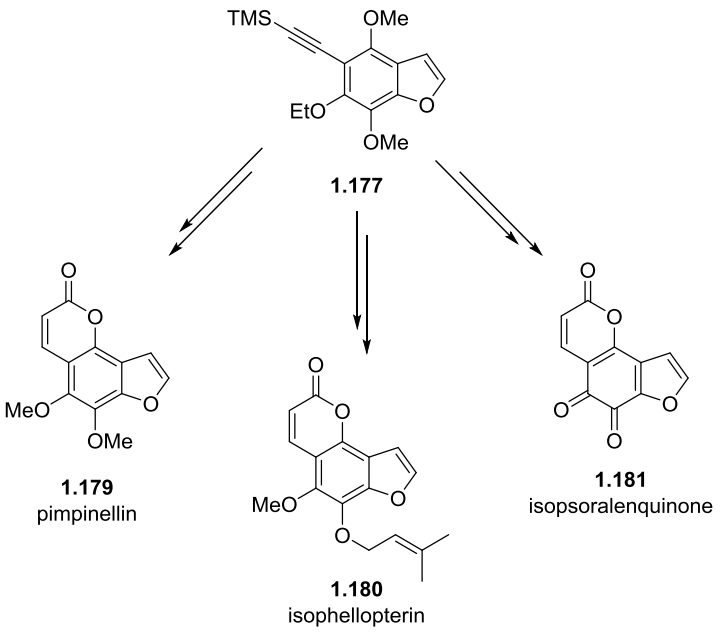
Scheme 1.44: Total synthesis of lonapalene **1.168**.

Moore *et al.* also reported a total synthesis of khellinone **1.171** in seven steps from cyclobutenedione **1.172** (**Scheme 1.45**).[56] Their synthesis started with the addition of lithiated trimethylsilylacetylene to cyclobutenedione **1.172** leading to cyclobutenone **1.173**, which was then dehydrated to cyclobutenedione **1.174** in the presence of TFAA. Addition of 2-lithofuran to cyclobutenone **1.174** next gave substituted cyclobutenone **1.175**, which was subjected to thermolysis to form hydroquinone **1.176**. Hydroquinone **1.176** was protected as its dimethyl ether **1.177** then $HgSO_4$ was used to hydrate the alkyne to form an acetyl side chain giving hydroquinone **1.178**. Finally, selective deprotection of the ethoxy residue afforded khellinone **1.171** in 97% yield.



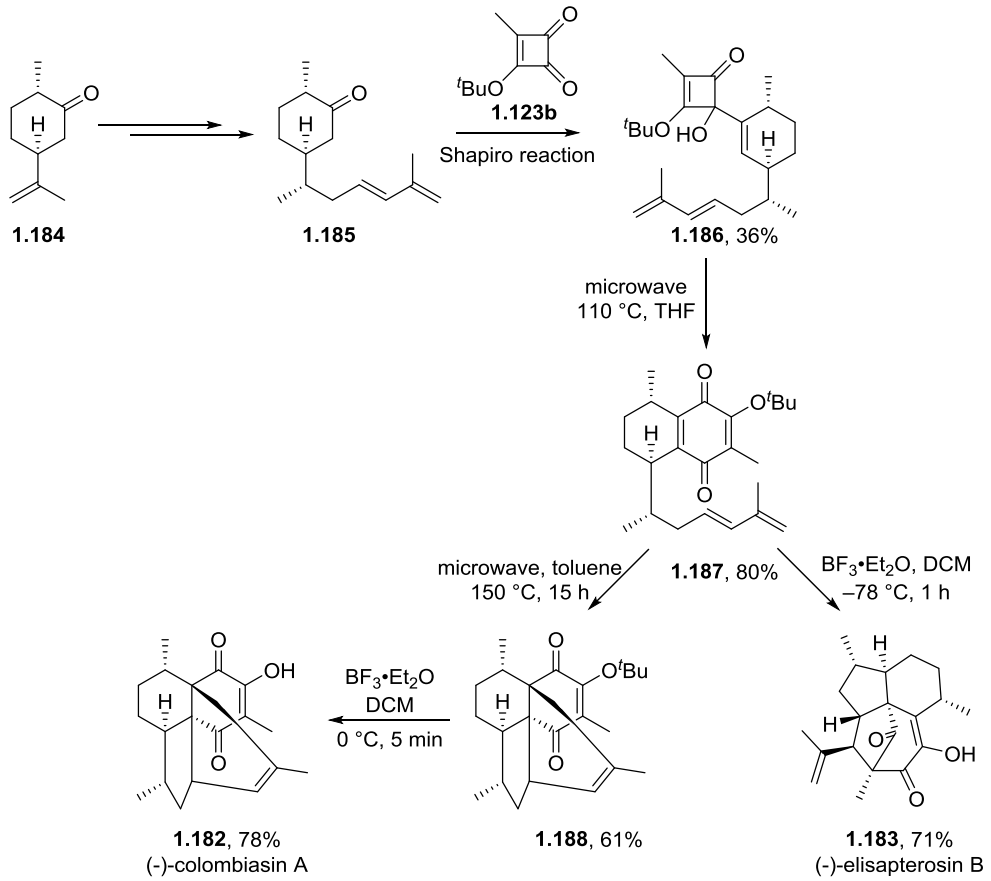
Scheme 1.45: Total synthesis of khellinone **1.171**.

Benzofuran **1.177** also proved to be a valuable precursor in the total syntheses of pimpinellin **1.179**, isophellopterin **1.180** and isopsoralenquinone **1.181** (**Scheme 1.46**).[57]



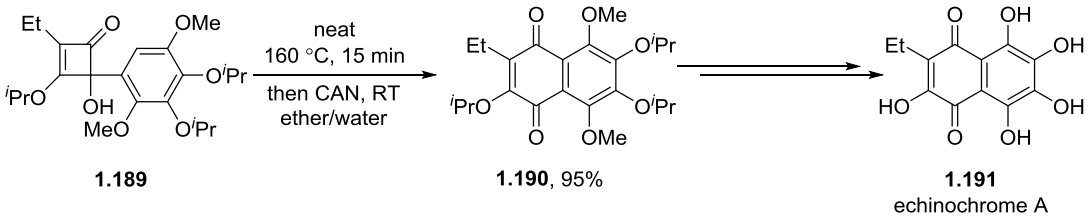
Scheme 1.46: Total synthesis of other natural products from intermediate **1.177**

Harrowven *et al.* published a short and highly efficient route for the synthesis of (–)-colombiasin A **1.182** and (–)-elisapterosin B **1.183** in which the thermolysis of a cyclobutenone featured as a key step.[8] They planned to get access to both natural products from the same intermediate, vinylcyclobutenone **1.186**, which was synthesised from (–)-dihydrocarvone **1.184** in eight steps. A Shapiro reaction with (*E*)-dienone **1.185** facilitated its coupling with cyclobutenone **1.123b** and gave vinylcyclobutenone **1.186**. It then underwent thermolysis to form quinone **1.187** in 80% yield. Treatment of quinone **1.187** with $BF_3{\cdot}OEt_2$ induced both deprotection of the ^{t}butyl ether and an intramolecular [5+2] cycloaddition to give (–)-elisapterosin B **1.183**. Moreover, heating quinone **1.187** to 150 °C in toluene in the dark by microwave irradiation triggered an intramolecular Diels-Alder reaction to **1.188**, which gave (–)-colombiasin A **1.182** on deprotection (**Scheme 1.47**).

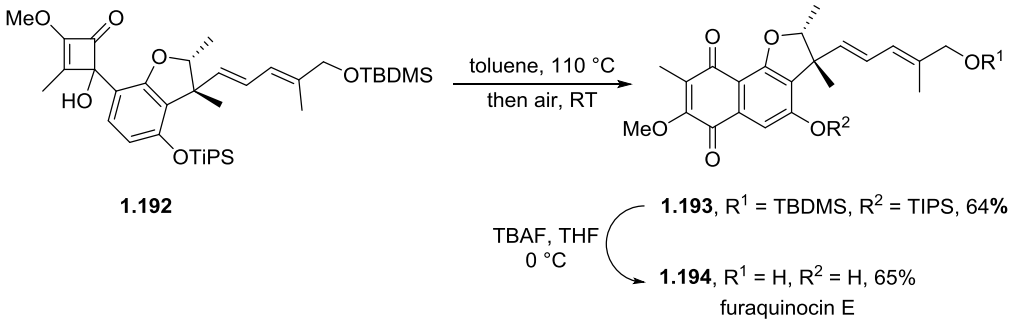


Scheme 1.47: Total synthesis of (–)-colombiasin A **1.182** and (–)-elisapterosin B **1.183**.

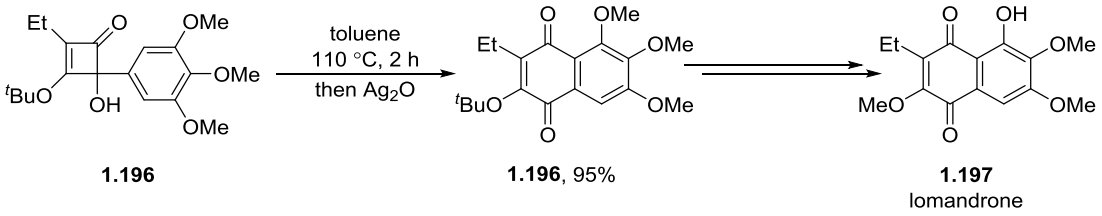
Thermolyses of 4-arylcyclobutenones to form naphthoquinones have been used as the key step in total synthesis of echinochrome A[58] **1.191** (**Scheme 1.48**), furaquinocin E[59] **1.194** (**Scheme 1.49**), lomandrone[60] **1.197** (**Scheme 1.50**) and (–)-thespesone **1.200**[61] (**Scheme 1.51**).



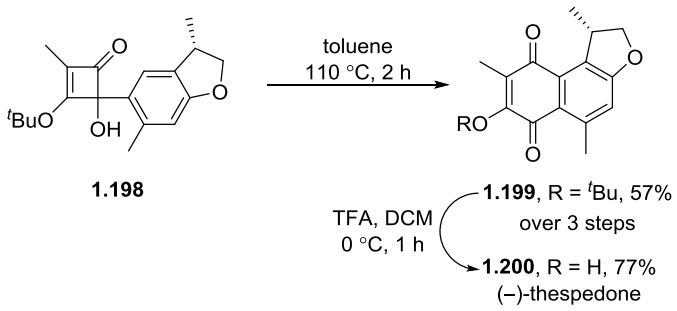
Scheme 1.48: Key step in the total synthesis of echinochrome A **1.191**.



Scheme 1.49: Key step in the total synthesis of furaquinocin E **1.194**.

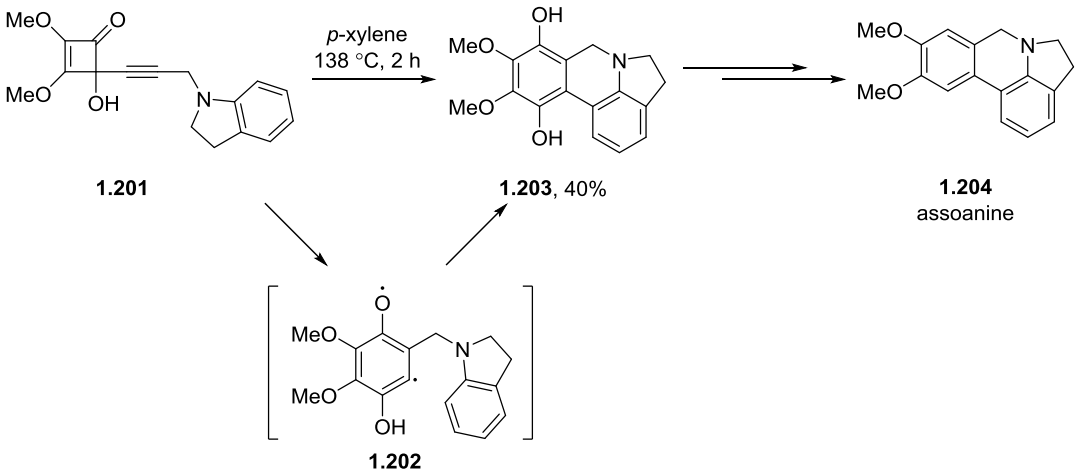


Scheme 1.50: Key step in the total synthesis of lomandrone **1.197**.

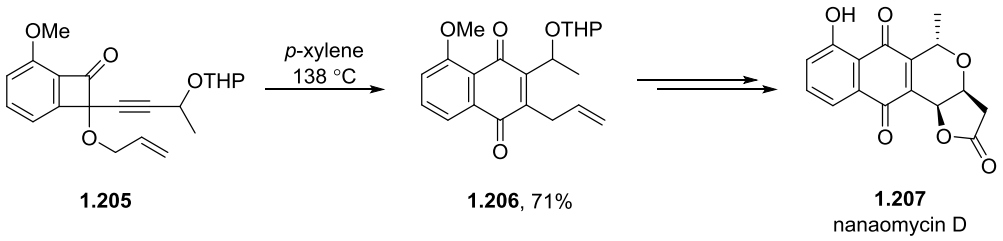


Scheme 1.51: Key step in the total synthesis of (–)-thespesone **1.200**.

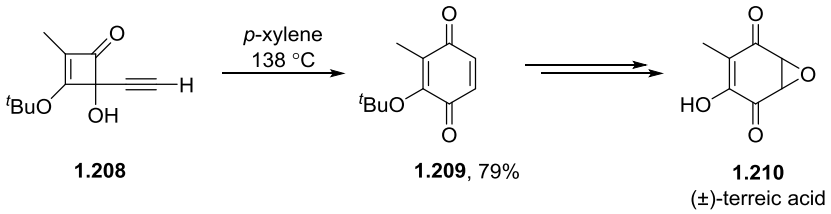
Thermolyses of 4-alkynylcyclobutenones to form quinones have also been used in total synthesis. Natural products synthesized using this methodology include assoanine[62] **1.204** (**Scheme 1.52**), (±)-nanaomycin D **1.207**[63] (**Scheme 1.53**), (±)-terreic acid[64] **1.210** (**Scheme 1.54**) and (±)-isoperezone[64] **1.213** (**Scheme 1.55**).



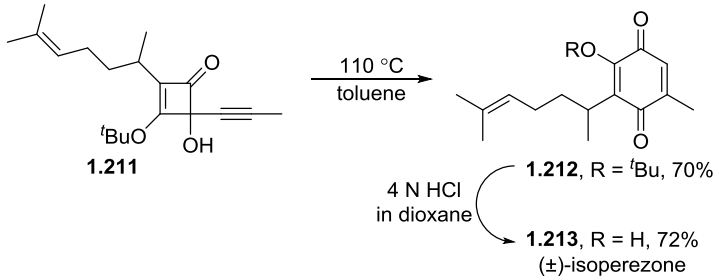
Scheme 1.52: Key step in the total synthesis of assoanine **1.204**.



Scheme 1.53: Key step in the total synthesis of nanaomycin D **1.207**.



Scheme 1.54: Key step in the total synthesis of (±)-terreic acid **1.210**.



Scheme 1.55: Key step in the total synthesis of (±)-isoperezone **1.213**.

Chapter 2: Method

2.1 Thermal rearrangement

Thermal rearrangements of cyclobutenones are usually conducted in *p*-xylene or toluene under reflux for several hours. Harrowven *et al.* have shown that significant advantages are offered when using flow chemistry instead of the batch reaction including higher yields, shorter reaction times and the ability to heat a solvent beyond its usual boiling point (**Section 1.6.2**).[21] In this work, because of the higher temperatures required (150-220 °C), normal batch reactions in toluene or *p*-xylene become unsuitable. The Vapourtec R4/R2+ flow system allows solvent to be heated under pressure, thereby allowing temperature above their normal boiling point readily available (**Figure 2.1**).[65]

Figure 2.1: Vapourtec R4/R2^{+} device.

The Vapourtec R2 pumping module contains a self-calibrating dual pumping system and injection loop. It affords two methods for sample loading. Firstly, the sample loop can be pre-loaded with filtrated reagent/substrate allowing software control the loading process automatically. This method is suitable for volumes of 1 – 20 mL. Alternatively, the filtrated reagent/substrate can be pumped directly into the reactor. There is no volume limit for this method but it requires a manual switch of the pump from reagent to solvent when the reagent finishes loading (**Figure 2.2**).

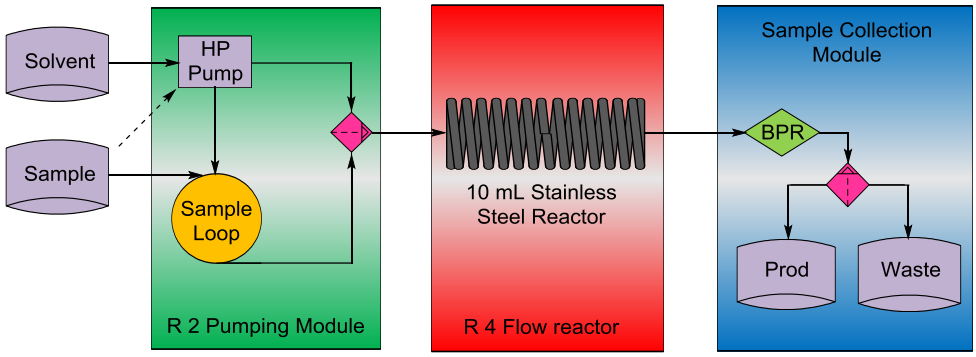


Figure 2.2: Processing for the flow system.

The Vapourtec R4 reactor module can support four temperature zones. The first three zones can be set at a temperature between RT and 150 °C and the fourth one can be set between RT to 220 °C (when used with a high temperature reactor) (**Figure 2.3**). The control software and the probe can tightly maintain the temperature to less than ±1 °C.

Figure 2.3: High temperature reactor.

In line back pressure regulators (BPR) maintain the solvents in liquid form when heated above their boiling point, which can lead to an increase in the system pressure up to 35 bar. In turn, some solvents with moderate boiling point such as 1,4-dioxane (b.p. 101 °C) can be used in a high temperature reaction (150 °C, 3.7 bar required; 220 °C, 15.2 bar required). The final switcher can automatically collect the product solution, which can also be controlled by the software.

2.2 Photo rearrangement

Photolysis of cyclobutenone was first carried out in an immersion well reactor (**Figure 2.4**) with a high-pressure mercury vapour lamp. The principle problem with this system is its poor applicability for small and large-scale photochemical synthesis. Consequently photolyses of cyclobutenones generally gave products in a low yield (**Section 1.4**).

Figure 2.4: Typical photochemical reactor.

The Harrowven and Whitby groups designed a new photoreactor inspired by the work of Booker-Milburn, Berry and co-workers (**Figure 2.5**).[32,66,67] The first layer of the reactor is PFAA tubing which is wrapped around a cylindrical quartz tube. The PFAA tubing has an internal volume of 28 mL and is next covered with aluminium foil to assist heat transfer and protect the user from strong UV radiation. The outside layer is condenser tubing through which cold water is passed as a secondary coolant. The set-up used 9 W bulbs supplied by OSRAM and Philips spanning various wavelengths (wavelengths in **Appendix B**). Connecting the UV-reactor to the Vapourtec R2 module affords control over the flow rate and the residence time *via* the flow systems computer.

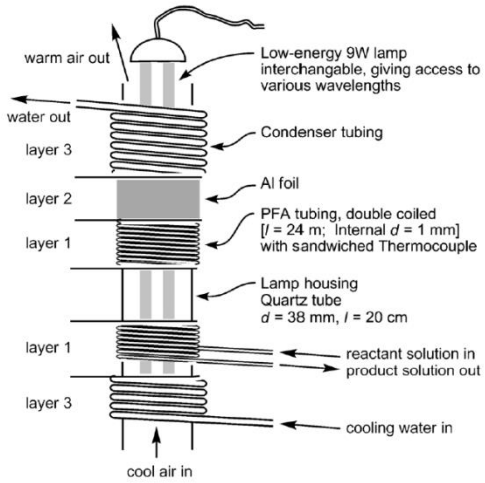


Figure 2.5: Photochemical reactor designed by the Harrowven and Whitby groups.

2.3 DFT calculation method

All DFT calculations were carried out with the Gaussian 09W C.01 or Gaussian 09 A.02 (IRIDIS) program.[68] In **Section 1.6.4** previous computational chemistry studies on the rearrangement of cyclobutenones were summarised. They showed how the B3LYP methods been previously used to

great effect in providing qualitative trends in the rearrangement of cyclobutenones. They also showed that the M062X functional was able to provide more accurate energy.

In this work, the M062X level of theory was employed whenever the accurate energy calculation was warranted. The B3LYP method was used instead when qualitative trends were sufficient, e.g. to predict the selectivity. The geometries of all intermediate species were optimised and confirmed by the absence of imaginary frequencies. The transition states were found by relaxed scans of the bond distance between atoms directly involved and checked by the existence of a single imaginary frequency corresponding to their reaction coordinates. For an open shell system, unrestricted methods (UB3LYP and UM062X) were used.

2.3.1 Functionals

The B3LYP (Becke, three-parameter, Lee-Yang-Parr) functional is one of the most popular hybrid functional. This exchange-correlation functional is based on Becke's hybrid functional and mixed with a fractional of the exact exchange from Hartree-Fock and introduces three empirical parameters. The B3LYP functional, as one of the first DFT methods to show a significant improvement over the Hartree-Fock method, is widely used. It usually yields comparable results to other methods but is much faster. With a 6-31(d) or larger basis set, it can usually afford acceptable result for most of systems. However, for some energy related calculations, the B3LYP functional fails to give accurate results.

Minnesota functionals are a group of approximate exchange-correlation energy functionals developed by Truhlar *et al.* at the University of Minnesota. The M062X functional is a global hybrid functional with 54% Hartree-Fock exchange. It has been shown to be the top performer in DFT calculations for main group thermochemistry and kinetics. Using the M062X functional, big basis sets are normally required.

2.3.2 Basis Sets

In this work, split valence basis sets were utilized in all DFT calculations. Split valance basis sets are characterized by the number of functions allocated to each valence orbitals. 6-31G is one of the popular double zeta basis sets proposed by Pople *et al.*[69] The number 6 in this basis set is the number of primitive Gaussians describing each core atomic orbital basis function. The number 31 represents the valence orbitals which are composed of two basis functions (3 and 1 primitive Gaussian function in each). The G stands for Gaussian type basis functions. 6-311G is the famous triple zeta basis sets which split the valence orbitals into three basis functions (3, 1 and 1 primitive

Gaussian function in each). Further flexibility of basis set towards better performance is achieved by the addition of polarization functions and diffuse functions.

Split valence basis set is limited as it does not allow a change to the orbitals shape.[70] As a consequent, a polarized basis set is utilized by adding orbitals with an angular momentum on each atom. Polarization functions are important to describe bonds because they provide the flexibility needed to describe regions between bonded atoms. The 6-31G(d) basis set is formed by adding a d polarization function to all the heavy atoms (non-hydrogen atoms) whereas 6-311G(d,p) is formed from the 6-311G basis set by addition of d polarization functions to all non-hydrogen atoms and p polarization functions to hydrogen atoms.

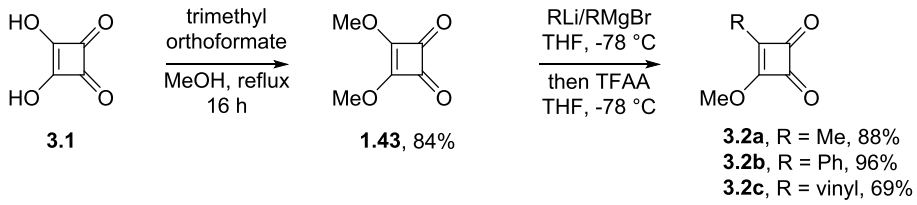
To properly described the electron density of the anions, lone pairs and excited states, diffuse functions are required.[71] They allow orbitals to relax and occupy a large region of space to improve the description of weakly bonded electrons. The addition of diffusion functions to non-hydrogen atoms in 6-311G(d,p) basis set is represented by addition of a "+", as in the 6-311+G(d,p) basis set.

Chapter 3: Thermolyses of Aminocyclobutenones

Although cyclobutenone rearrangements have been widely used since they were introduced by Moore and Liebeskind, little is known about the behaviour of aminocyclobutenones. The potential products given, aminoquinones, aminonaphthoquinones and aminofuranones, are widely used in chemical and pharmaceutical research, and have been employed as intermediates in the total synthesis of natural products.[72-76] Therefore, we have good reason to focus our attention on the thermolyses and photolyses of such substrates.

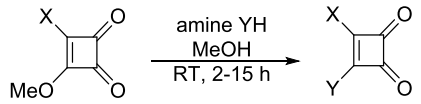
3.1 Synthesis of aminocyclobutenediones

Our investigation began with the synthesis of various aminocyclobutenediones **3.4**, which were each prepared in three steps from commercially available 3,4-dihydroxycyclobut-3-ene-1,2-dione **3.1** (squaric acid). Squaric acid **3.1** was first converted into 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43** by esterification with MeOH and trimethyl orthoformate.[77] Addition of the appropriate organolithium or Grignard reagent to **1.43** followed by treatment with TFAA then afforded cyclobutenediones **3.2a-c**.[57,78,79]



Scheme 3.1: Preparation of cyclobutenediones **3.2a-c**.

Amino substituted cyclobutenediones **3.3a-m** were then obtained by nucleophilic substitution of the methoxy residue by the requisite amines using cyclobutenediones **1.43** or **3.2a-c** (**Table 3.1**).[31,80-82]



1.43 or **3.2a-c** **3.3**

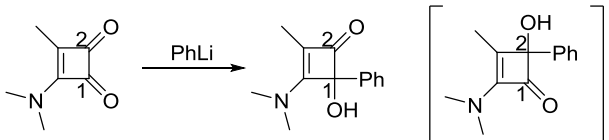
3.3	*X =*	*YH =*	*Yield (%)*
a	Me	Me_2NH	85
b	Me	Et_2NH	85
c	Me	piperidine	85
d	Me	pyrrolidine	86
e	Me	azepane	93
f	Me	Bn_2NH	56
g	Me	isopropylamine	99
h	Me	*N*-methylaniline	84
i	Me	$MeNH_2$	91
j	Ph	Me_2NH	97
k	OMe	Me_2NH	85
l	NMe_2	Me_2NH	30
m	vinyl	Me_2NH	90

Table 3.1: Preparation of aminocyclobutenediones **3.3a-m**.

3.2 Synthesis of substituted aminocyclobutenone

3.2.1 Organolithium addition reactions

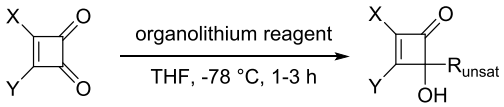
Organolithium additions to aminocyclobutenediones **3.3** all showed a strong preference for nucleophilic addition to the C1 carbonyl (**3.4a**) rather than the carbonyl (C2 carbonyl) conjugated to the amine group (**3.5a**) (**Scheme 3.2**).



3.3a **3.4a** **3.5a** not observed

Scheme 3.2: Selectivity in the organolithium addition reaction.

Thus, treatment of aminocyclobutenediones **3.3a-m** with a variety of organolithium reagents afforded substituted aminocyclobutenones **3.4a-r** in 40-87% yield (**Table 3.2**).

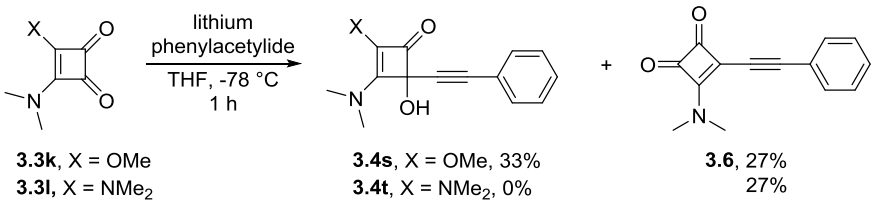


3.3 **3.4**

3.4	***X =***	***Y =***	***R_{unsat} =***	***Yield (%)***
a	Me	NMe_2	Ph	87
b	vinyl	NMe_2	Ph	54
c	Me	NHMe	Ph	74
d	Me	NPhMe	Ph	93
e	Me	NMe_2	phenylethynyl	70
f	Me	NEt_2	phenylethynyl	81
g	Me	piperidinyl	phenylethynyl	81
h	Me	pyrrolidinyl	phenylethynyl	85
i	Me	azepanyl	phenylethynyl	76
j	Me	NBn_2	phenylethynyl	77
k	Ph	NMe_2	phenylethynyl	83
l	Me	isopropylamino	phenylethynyl	40
m	Me	NMe_2	pentynyl	80
n	Me	NMe_2	(trimethylsilyl)ethynyl	83
o	Me	NMe_2	3-methylbut-3-enynyl	75
p	Me	NMe_2	ethoxyethynyl	70
q	Me	NMe_2	ethynylpropionate	59
r	Me	NEt_2	ethynylpropionate	100

Table 3.2: Synthesis of substituted aminocyclobutenones **3.4a-r**.

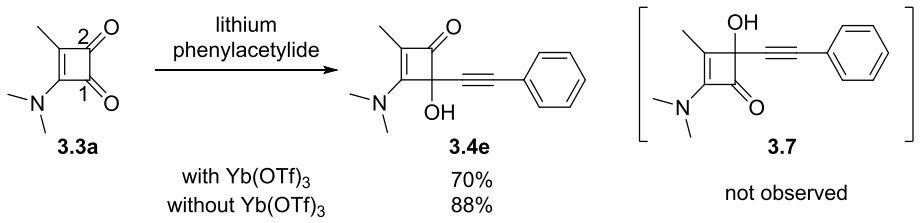
The attempted synthesis of substituted aminocyclobutenones **3.4s** and **3.4t** was unsuccessful due to their instability. Indeed, these each gave the elimination product **3.6** in significant quantity (**Scheme 3.3**).



Scheme 3.3: Elimination of substituted aminocyclobutenones **3.4s** and **3.4t**.

3.2.2 Organoytterbium addition reaction

Harrowven *et al*. described how organoytterbium reagents could be used to change the selectivity of addition reactions to *tert*-butoxy-4-methycyclobutene-1,2-dione **1.123b** (see **Section 1.6.3**). Therefore we decided to investigate the organoytterbium addition to aminocyclobutenedione **3.3a**. In this case only the C1 addition product **3.4e** was observed as the steric clash between the ytterbium complex and the amine residue was insufficient to bias the reaction toward C2 addition (**Scheme 3.4**).



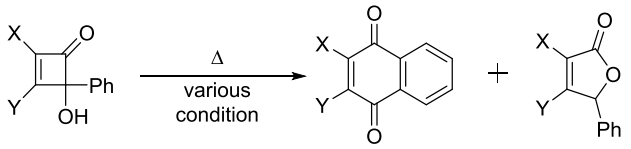
Scheme 3.4: Selectivity of organoytterbium addition reaction.

3.3 Thermal rearrangement of aminocyclobutenones

Generally, thermal rearrangements of cyclobutenones are conducted at reflux. However, the use of a flow device, as in this study, can provide significant advantages including stabilisation of thermal exotherms and enable the heating of solvents above their normal boiling point (see **Section 2.1**).

3.3.1 Result of thermal flow reactions

Preliminary investigations on the thermolyses of substituted aminocyclobutenones **3.4a-d** were conducted in 1,4-dioxane by using a Vapourtec R4/R2^{+} flow device over 1-2 h. Surprisingly, we found that (dimethylamino)cyclobutenones **3.4a** and **3.4b** favoured formation of furanone **3.9** in contrast to all reported examples of phenylcyclobutenone rearrangements (*e.g.* **3.4a'-g'**→**3.8a'-g'**), including its lower homolog **3.4c** and the phenylmethylamino analogue **3.4d** (**Table 3.3**).

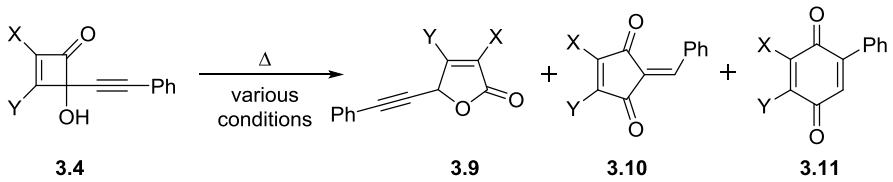


3.4 **3.8** **3.9**

3.4	***X =***	***Y=***	***Yield 3.8 (%)***	***Yield 3.9 (%)***
a' [10]	OMe	OMe	73%	–
b' [83]	O^{i}Pr	O^{i}Pr	40%	–
c' [45]	O^{t}Bu	Me	78%	–
d' [84]	CF_3	O^{i}Pr	73%	–
e' [15]	Me	Me	87%	–
f' [45]	Me	OMe	91%	–
g' [3]	Me	Ph	90%	–
a	Me	NMe_2	–	91%
b	Vinyl	NMe_2	–	79%
c	Me	NHMe	73%	–
d	Me	NPhMe	76%	–

Table 3.3 : Thermal rearrangement of arylcyclobutenones.

To explore the generality of that finding we next examined the thermolyses of alkynylcyclobutenones. To the best of our knowledge, no precedent existed for their thermal rearrangements to furanones as reactions typically give cyclopentenediones akin to **3.10** and/or benzoquinones akin to **3.11** (*e.g.* reported examples of thermolyses of cyclobutenones **3.4h'-l'**). Notably, while thermolysis of (isopropylamino)-cyclobutenone **3.4l** gave a complex product mixture, the related aminocyclobutenones **3.4e-k** gave furanones **3.9e-k** respectively (**Table 3.4**).

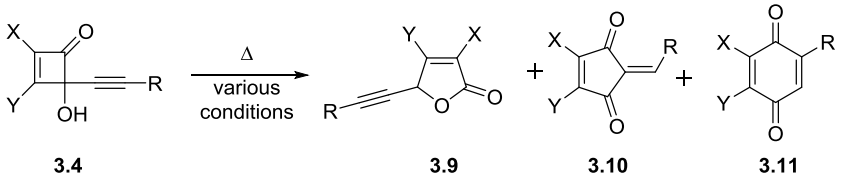


3.4 **3.9** **3.10** **3.11**

3.4	***X=***	***Y=***	***Yield 3.9 (%)***	***Yield 3.10 (%)***	***Yield 3.11 (%)***
h' [22]	OMe	OMe	–	46	21
i' [45]	O^{t}Bu	Me	–	83	–
j' [45]	Me	OMe	–	52	40
k' [20]	Me	O^{t}Bu	–	36	51
l' [22]	OEt	Ph	–	46	–
e	Me	NMe_2	49	–	–
f	Me	NEt_2	61	–	–
g	Me	piperidinyl	57	–	–
h	Me	pyrrolidinyl	70	–	–
i	Me	azepanyl	51	–	–
j	Me	NBn_2	67	–	–
k	Ph	NMe_2	67	–	–
l	Me	isopropylamino	complex product mixture		

Table 3.4 : Dichotomous thermal rearrangements of alkynylcyclobutenones.

The additional examples collated in **Table 3.5** show the thermolyses of alkynylcyclobutenones with different alkyne residues. All of the literature examples favoured benzoquinone formation (**3.11**) while all but one of our aminocyclobutenones favoured furanone formation (**3.9**). Exceptional reactivity was displayed by alkynyl ether **3.4p**, which gave cyclopentenedione **3.10** as the product.

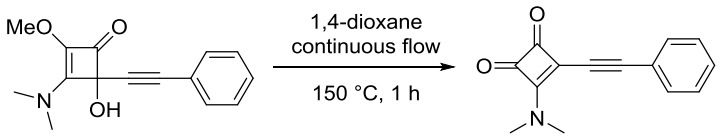


3.4 **3.9** **3.10** **3.11**

3.4	*X =*	*Y=*	*R=*	*Yield 3.9(%)*	*Yield 3.10 (%)*	*Yield 3.11 (%)*
m' [85]	Me	O^{i}Pr	H	–	–	85
n' [64]	Me	O^{t}Bu	TMS	–	–	69
o ' [64]	Me	O^{t}Bu	H	–	–	79
p' [3]	Me	Ph	^{n}Bu	–	–	80
q' [22]	OMe	OMe	H	–	–	72
r' [86]	O^{t}Bu	OMe	CH_2SiMe_3	–	–	75
s' [87]	OMe	OMe	CD_3	–	–	55
m	Me	NMe_2	$^{n}C_3H_7$	83	–	–
n	Me	NMe_2	TMS	75	–	–
o	Me	NMe_2	$^{i}C_3H_5$	73	–	–
p	Me	NMe_2	OEt	–	61	–

Table 3.5: Representative examples of thermolyses of alkynylcyclobutenones.

Attempted thermal rearrangement of aminocyclobutenone **3.4s** failed to give rearrangement due to its poor stability. Rather, it gave elimination product **3.6**, which was also observed as a side product during its synthesis (**Scheme 3.5**).



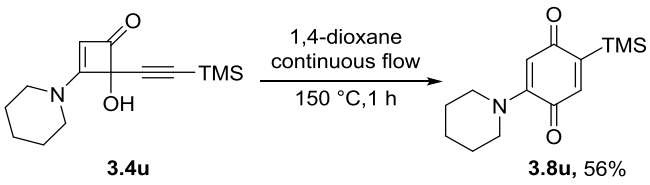
3.4s **3.6**,73%

Scheme 3.5: Elimination of aminocyclobutenone **3.4s** under flow.

Thermolyses of aminocyclobutenones **3.4q** and **3.4r** were also investigated but each gave an unusual outcome. Consequently, the new reaction pathway discovered will be discussed in detail in **Chapter 4**.

3.3.2 Selectivity in the thermal rearrangement of aminocyclobutenones

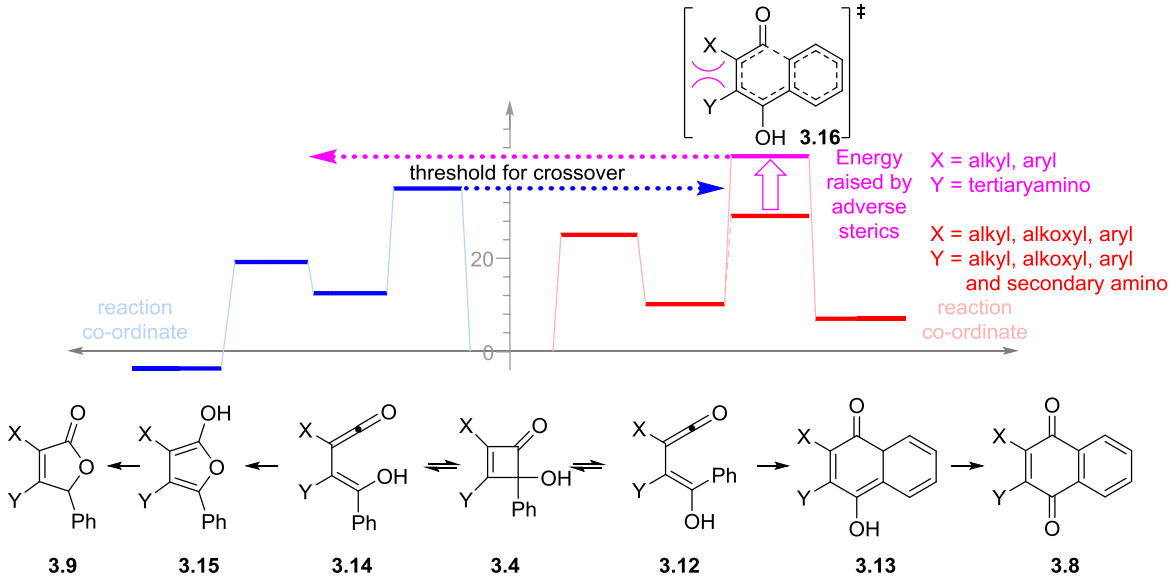
As showed in **Section 3.3.1**, most of the tertiary aminocyclobutenones showed a preference for furanone formation over quinone or cyclopentenedione formation. However, secondary aminocyclobutenones showed the reverse selectivity, providing quinones and/or cyclopentenediones rather than furanones! It had been observed previously in the Harrowven group that aminocyclobutenone **3.4u** formed naphthoquinone **3.8u** when subjected to thermolysis (**Scheme 3.6**). From these results we began to wonder if the size of the C3 and C4 substituents was an important factor in determining selectivity. "Expected" outcomes had been observed with secondary amino groups and with tertiary amino groups when flanked by an unsubstituted carbon centre. In stark contrast, when a tertiary amino residue was flanked by an alkyl or aryl residue, furanone formation was observed, suggesting that steric buttressing might be involved in determining the outcome of thermolyses of cyclobutenones.



3.4u **3.8u**, 56%

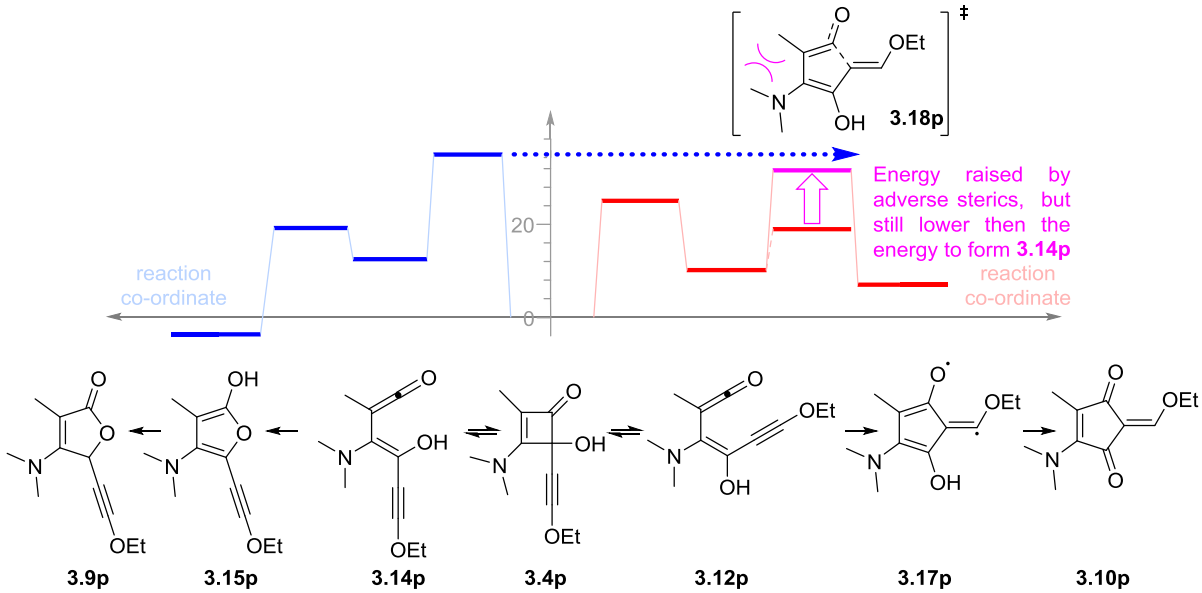
Scheme 3.6: Thermal rearrangement of aminocyclobutenone **3.4u**.

As a result of these observations, it seems that the reason for the different selectivity observed is a significant increase in the energy barrier for ring closure of the vinylketene **3.12** to ketone **3.13**. Indeed, once that energy barrier is raised above that for ring opening to form vinylketene **3.14**, the reaction will favour formation 5*H*-furanone **3.9** (pink pathway, **Scheme 3.7**).



Scheme 3.7: Plausible mechanism for the thermolysis of aminocyclobutenone **3.4** to form furanone **3.9**.

We also found that thermolysis of aminocyclobutenone **3.4p** formed cyclopentenedione **3.10p** instead of furanone **3.9p**. In that case the alkynylcyclobutenone proceeded *via* transition state **3.18p** leading to a cyclopentenedione diradical (**3.12p** → **3.17p**). The proximal ether function is a good radical stabilising group so is able to stabilize the diradical intermediate in the ring closure step, leading to a decrease in the energy barrier of the transition state. This result indicated that a decrease in the energy barrier for ring closure of the vinylketene **3.12p** leads to a change in selectivity from 5*H*-furanone to cyclopentenedione formation (**Scheme 3.8**).



Scheme 3.8: Plausible mechanism for the thermolysis of cyclobutenone **3.4p** to form cyclopentenedione **3.10p**.

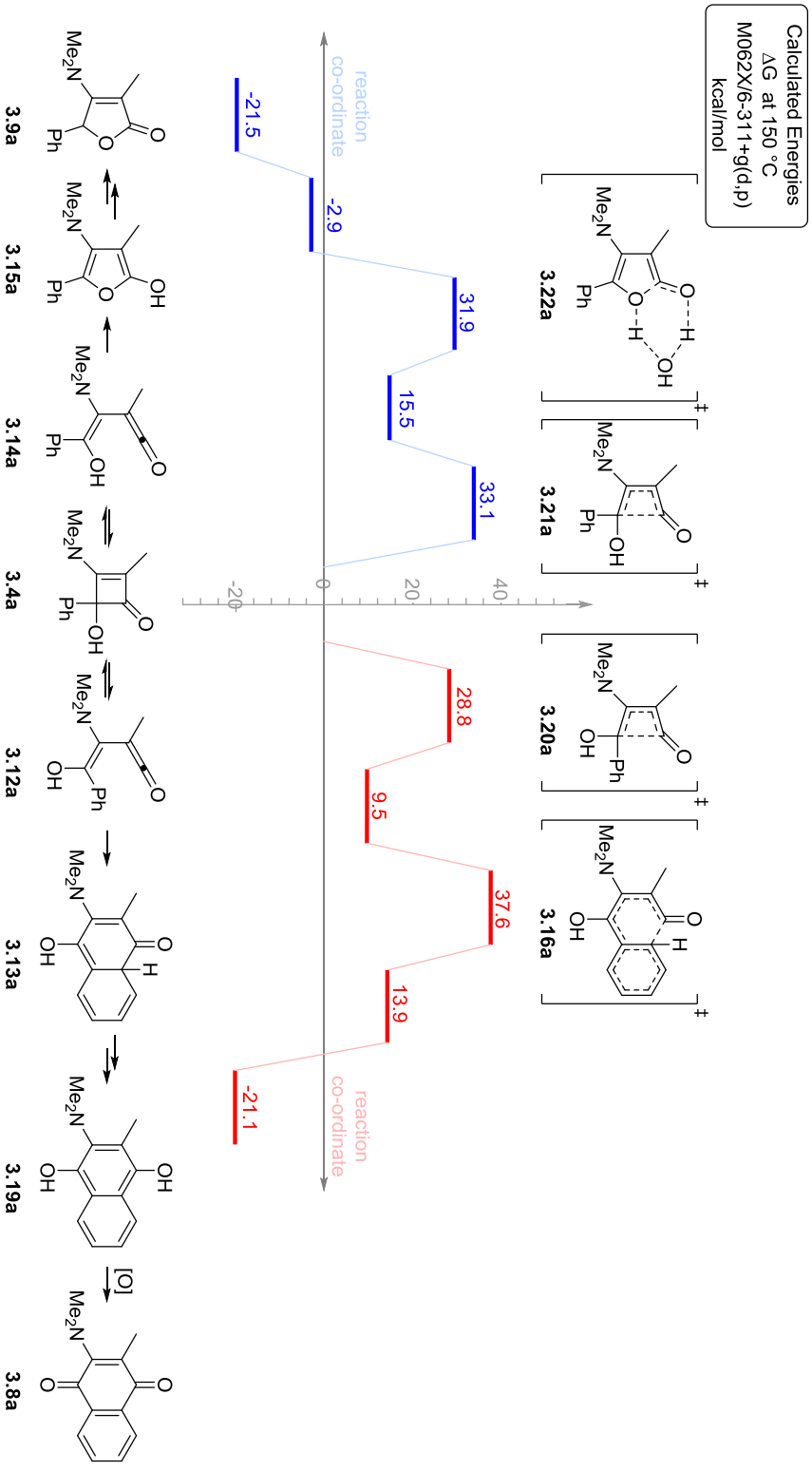
3.4 DFT calculations on thermolyses of aminocyclobutenones

To confirm the proposed explanation of the findings obtained from the thermolyses of aminocyclobutenones, the course of the reaction was modelled at the M062X/6-311+G(d,p), B3LYP/6-311G(d,p) and B3LYP/6-31G(d) levels using the Gaussian 09 program.

3.4.1 DFT calculations on thermolysis of aminoarylcyclobutenone

We began a computational investigation by examining the proposed ring opening and cyclisation pathways for the thermolysis of aminocyclobutenone **3.4a**. In this case, the energy barrier to form (*Z*)-vinylketene **3.12a** was 28.8 kcal/mol, which was lower than the energy barrier to form (*E*)-vinylketene **3.14a** (33.1 kcal/mol), suggesting that ring opening *via* outward rotation of the hydroxyl group to form (*Z*)-vinylketene **3.12a** was favoured. However, for (*Z*)-vinylketene **3.12a**, the transition state for ring closure to ketone **3.13a** showed a high energy barrier, which was higher than that required to reverse back to the starting material **3.4a** (37.6 kcal/mol *vs.* 28.8 kcal/mol) and on to the furanone **3.9a** (**Scheme 3.9**). Thus, by shifting the highest energy barrier

from the ring opening transition state **3.21a** to the (*Z*)-vinylketene ring closure transition state **3.16a** (37.6 kcal/mol *vs.* 33.1 kcal/mol), the reaction outcome also shifts to 5*H*-furanone formation (**3.9a**).



Scheme 3.9: Energy diagram for aminocyclobutenone **3.4a**.
Calculated at M062X/6-311+G(d,p), temperature=423.15 K.

The ring opening pathway to form (*Z*)-vinylketene **3.12a** was first examined by NBO analysis. Conformational screening for the lowest energy conformation of the starting material **3.4a** shows there is no hydrogen bond between the hydroxyl group and amino group (**Figure 3.1**). The distance for the C1-C4 bond is 1.583 Å, indicating a weak C-C bond. The dihedral angle of 178.5° for C2-C3-N-C5 and the Second Order Perturbation analysis with Natural Bond Orbital (E(2)-NBO) both reveal that the lone pair of electrons on nitrogen interacts with the π* orbital (C2-C3). These analyses indicate that the amino group is conjugated with the cyclobutenone π-system.

Analysis of the transition state **3.20a** shows that the conformation of the amino and hydroxyl groups is different to those in starting material **3.4a** (**Figure 3.1**). In this step the C1-C4 σ bond and the C2-C3 π bond are broken to form the two new π bonds between C1-C2 and C3-C4. The transition state geometry is reached when the C1-C4 distance is 2.229 Å. The hydrogen of the hydroxyl group points towards the amino group but there is still no hydrogen bond between them. In this case, the lone pair of electrons on nitrogen interacts with the π* orbital (C3-C4).

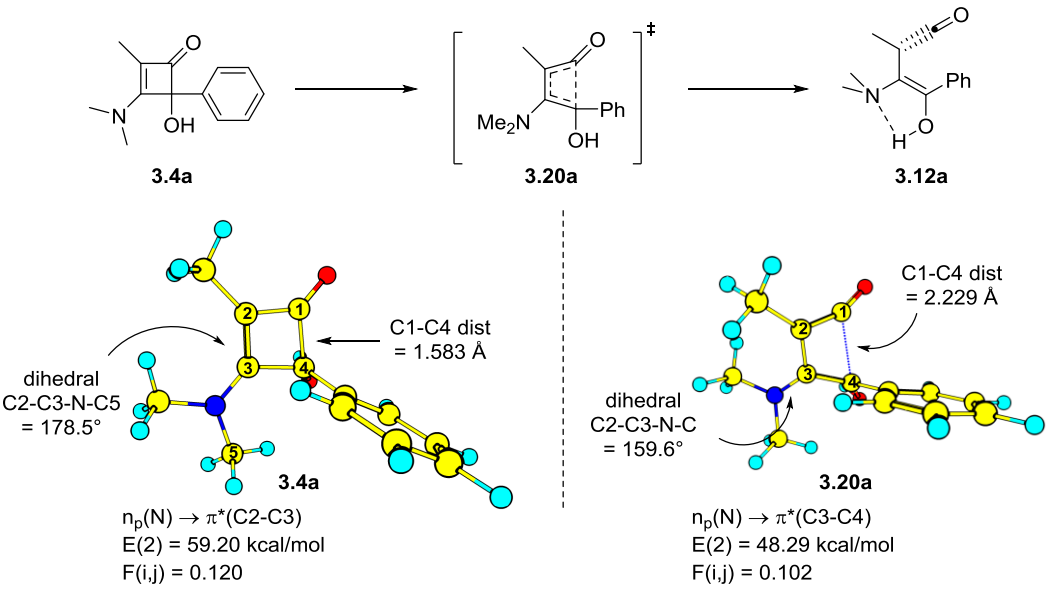


Figure 3.1: Geometry of the lowest energy conformation of aminocyclobutenone **3.4a** and TS **3.20a**. Geometry and NBO at B3LYP/6-311G(d,p).

In the ring closure step, (*Z*)-vinylketene **3.12a** undergoes ring closure with the proximal arene to form the ketone intermediate **3.13a**. In (*Z*)-vinylketene **3.12a**, hydrogen bonding is evident between the amino and hydroxyl group as the N-H distance is short at 1.945 Å and the N-H-O angle is 122.7° (**Figure 3.2**). Moreover, the hybrid atomic orbitals of the nitrogen change from sp^2 hybridization to sp^3 hybridization and the amino group is no longer conjugated with the C3-C4 π bond.

In transition state **3.16a**, the hydrogen bond between the hydroxyl and amino groups is preserved but has a slightly longer H-N distance (1.98 Å) (**Figure 3.2**). The hybrid atomic orbital of the nitrogen atom still exhibits sp^3 hybridization. Importantly, in the transition state **3.16a**, two of the hydrogen atoms on the C2 methyl group are close to hydrogen atoms on the dimethylamine group with interatomic distances of 2.25 Å and 2.08 Å respectively.

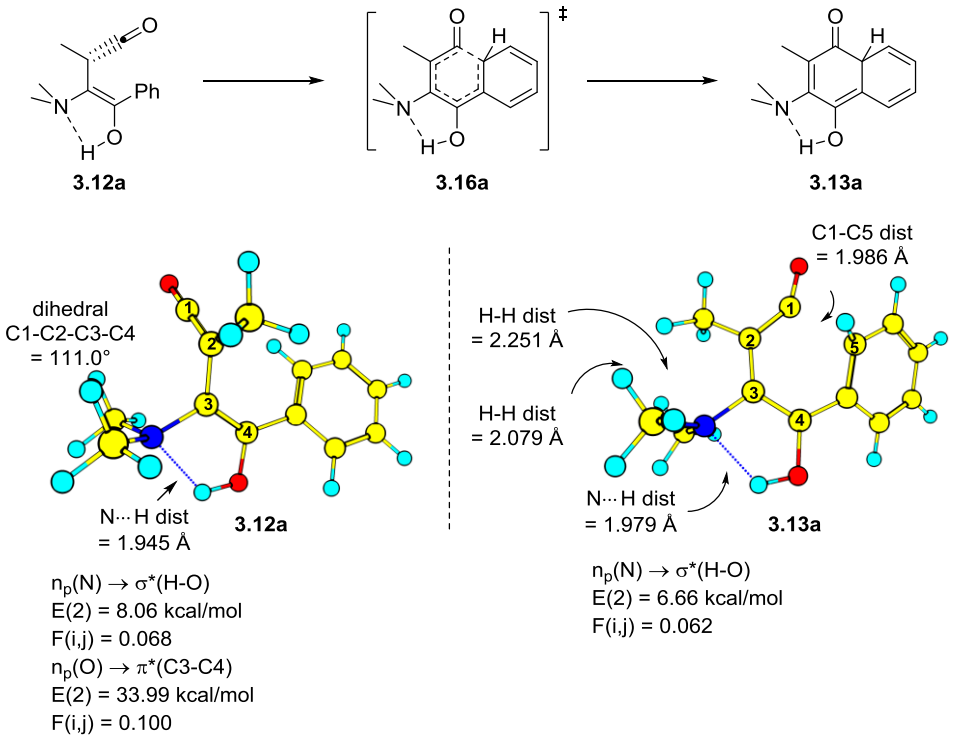


Figure 3.2: Geometry of the lowest energy conformation (*Z*)-vinylketene **3.12a** and TS **3.13a**. Geometry and NBO at B3LYP/6-311G(d,p).

For electrocyclic closure of vinylketene intermediate **3.12a** to reach transition state **3.16a**, the C2 and C3 substituents must rotate toward one another. When one or both are bulky residues, steric interactions are severe and the activation energy increases significantly (**Figure 3.3**).

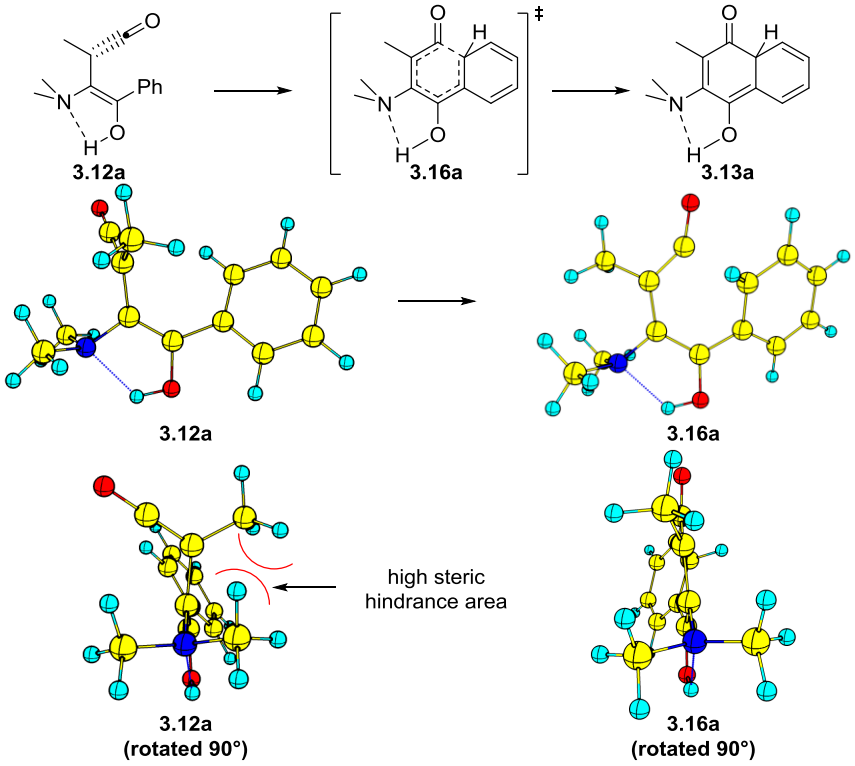


Figure 3.3: Steric influences in the ring closure of (Z)-vinylketene **3.12a**.

In contrast, ring closure of vinylketene **3.12f'**, with a methoxy residue at C3 instead of amino residue, shows no such steric hindrance (**Figure 3.4**). Consequently, transition state **3.16f'** requires an energy of 23.8 kcal/mol, much less than the energy required for the transition state **3.16a** (37.6 kcal/mol).

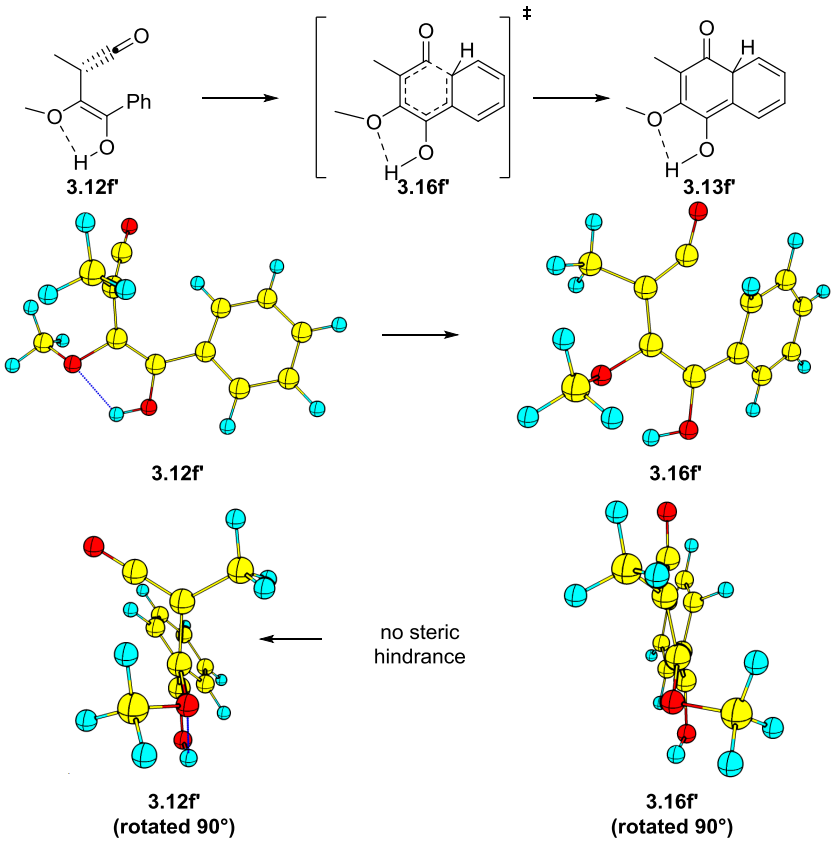


Figure 3.4: Ring closure of (Z)-vinylketene **3.12f'** to **3.16f'**.

In ketone **3.13a**, the N-H distance is 1.98 Å, suggesting that the hydrogen bond is still present. Meanwhile, the shortest H-H distances between the C2 methyl group and C3 dimethylamine group are 2.25 Å and 2.08 Å, indicating high steric hindrance (**Figure 3.5**).

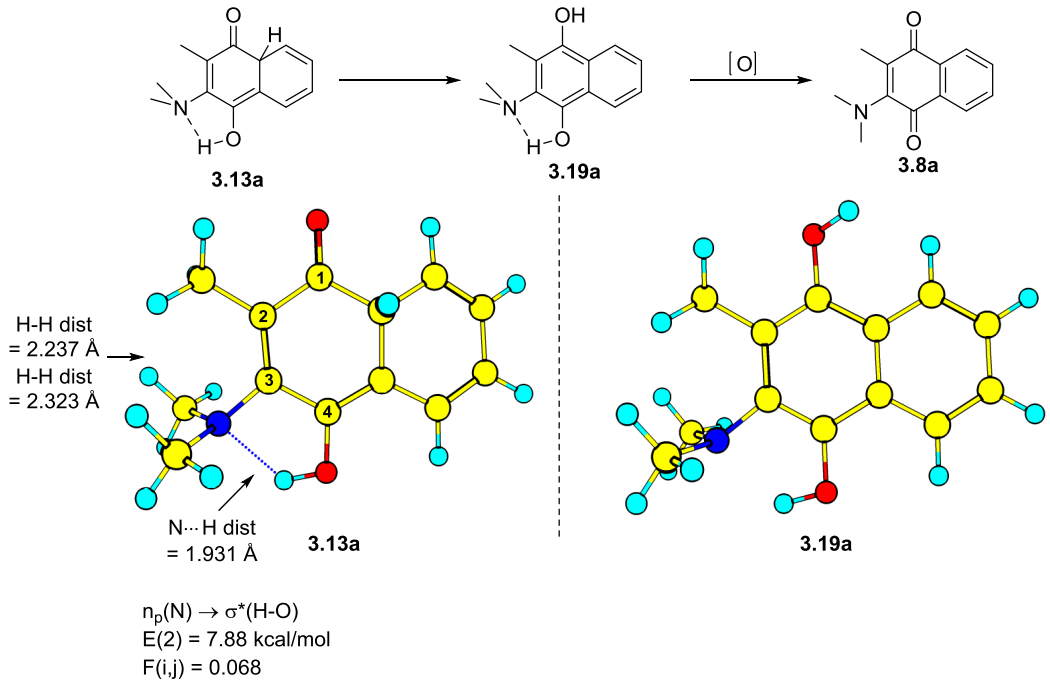


Figure 3.5: Geometry of the lowest energy conformation of ketone **3.12a** and **TS 3.19a**.
Geometry and NBO at B3LYP/6-311G(d,p).

As noted in previous work, the thermodynamic driving force for this reaction comes in the next step, where ketone **3.13a** undergoes tautomerization to hydroquinone **3.19a** *via* a water assisted proton shift. This step is reasoned to have a much lower energy barrier when compared to the previous two steps. Therefore we did not calculate the energy barrier for this transition state.

We next examined the competing pathway, leading to furanone formation. In this case, inward rotation of the hydroxyl group proceeds *via* a similar geometry to that for its outward rotation but with the movement of the hydroxyl and phenyl groups reversed. The breaking C1-C4 bond length is 2.240 Å in transition state **3.21a**, slightly longer than that observed in transition state **3.20a** (2.229 Å) (**Figures 3.6** and **3.1**).

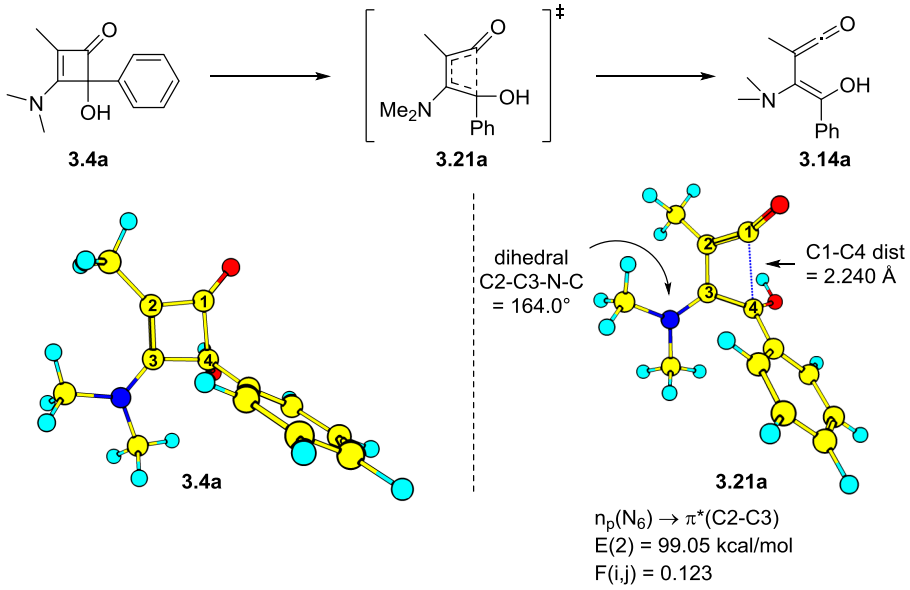


Figure 3.6: Geometry of the lowest energy conformation of aminocyclobutenone **3.4a** and TS **3.21a**. Geometry and NBO at B3LYP/6-311G(d,p).

In (*E*)-vinylketene **3.14a**, no hydrogen bonding is possible between the amine and hydroxyl group (**Figure 3.7**). The dihedral angle C1-C2-C3-C4 is 2.7° and the interaction of the π orbital (C1-C2) with the π* orbital (C3-C4) is 14.37 kcal/mol, which implies conjugation between them. The dihedral angle of C3-N-C6-C7 is 150.1°, also suggesting significant sp^3 hybridisation of the nitrogen atom. The lone pair of electrons on N interacts strongly with the proximal σ* orbital (C2-C3) with a contribution of 10.22 kcal/mol for this interaction. The distance of C1 and O9 is 2.467 Å and the lone pair of electron on O9 shows a 4.42 kcal/mol interaction energy with the π* orbital (C1-O8).

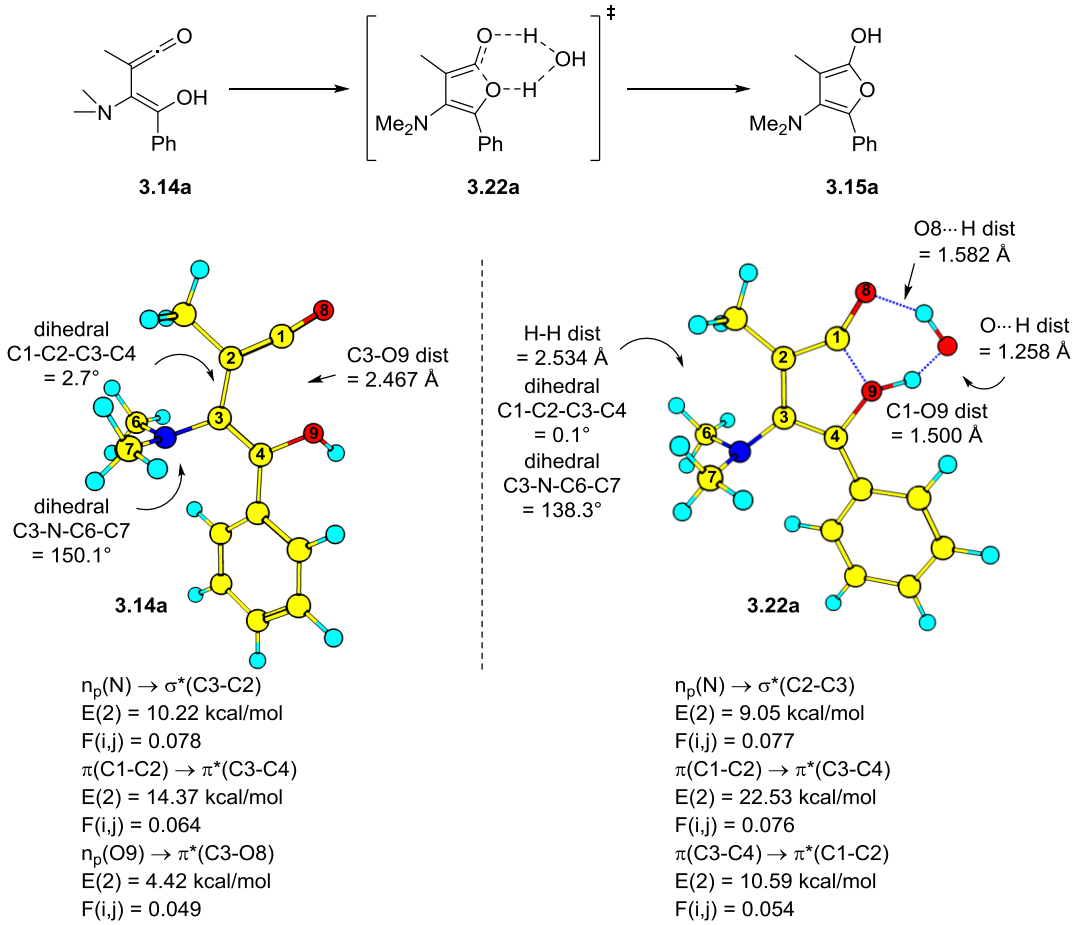
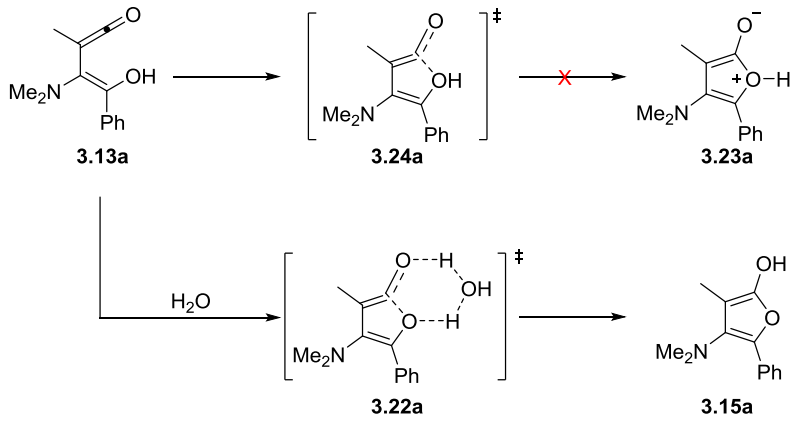


Figure 3.7: Geometry of the lowest energy conformation of (*E*)-vinylketene **3.14a** and TS **3.22a**. Geometry and NBO at B3LYP/6-311G(d,p).

As observed in previous work, the ring closure step showed that the zwitterion **3.23a** was unlikely to exist (**Section 1.6.4**). This indicated a key role for water in the ring closure step (**Scheme 3.10**).



Scheme 3.10: Potential transition state for ring closure of **3.13a**.

In the postulated ring closure transition state **3.22a** (**Figure 3.7**), the distance of C1 and O9 is 1.500 Å. The NBO analysis shows that the 5 membered ring (C1, C2, C3, C4, O9) was close to being a fully constituted furan ring. The dihedral angle for C3-C4 to the phenyl ring is 15.5°. It also showed strong interaction energies of 15.51 and 16.64 kcal/mol to the aromatic π system (*ipso* to *ortho* and *ortho*'), indicating strong conjugation between the furan and benzene rings. As with intermediate **3.13**, the lone pair of electrons on the nitrogen atom interacts with the σ* orbital (C2-C3) rather than the π* orbital (C2-C3).

Furanol **3.15a** was obtained following the cyclisation step. Analysis shows that the furanol ring was conjugated with the benzene ring (**Figure 3.8**). Meanwhile the nitrogen atom shows sp^3 hybridisation with the interaction energy between the lone pair of electrons on nitrogen and σ* (C2-C3) calculated to be 10.44 kcal/mol. Tautomerization of **3.15a** to 5*H*-furanone **3.9a** can be assumed to have a low energy barrier *via* a water assisted proton shift. We did not deem it necessary to calculate the energy barrier for this transition state as all indicators showed that it was not rate determining.

In 5*H*-furanone **3.9a**, the nitrogen atom shows sp^2 hybridisation with a high degree of conjugation with the π* orbital (C2-C3) (**Figure 3.8**). The different hybridisation of the amino group in furanol **3.15a** and furanone **3.9a** can be attributed to steric hindrance in furanol **3.15a** between the amino group and the aromatic group, which forces the amino group to be sp^3 hybridised.

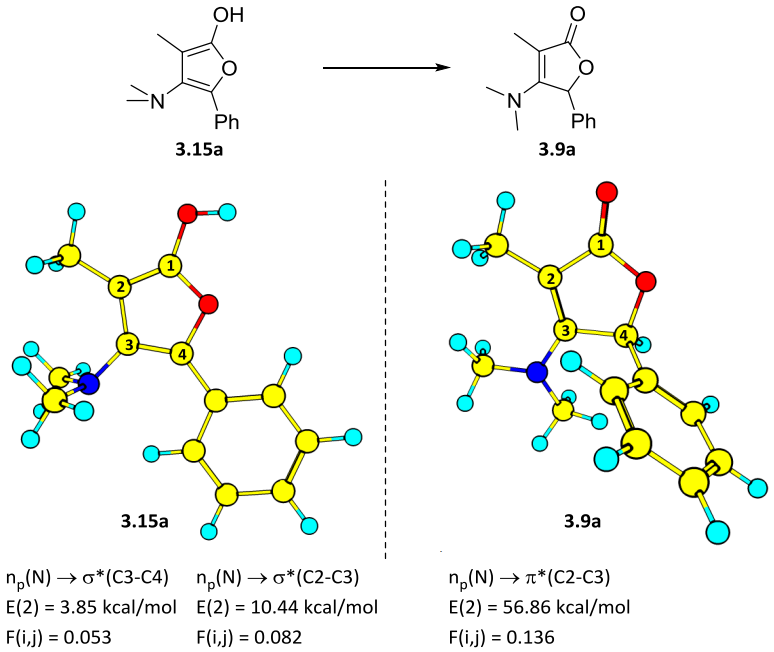
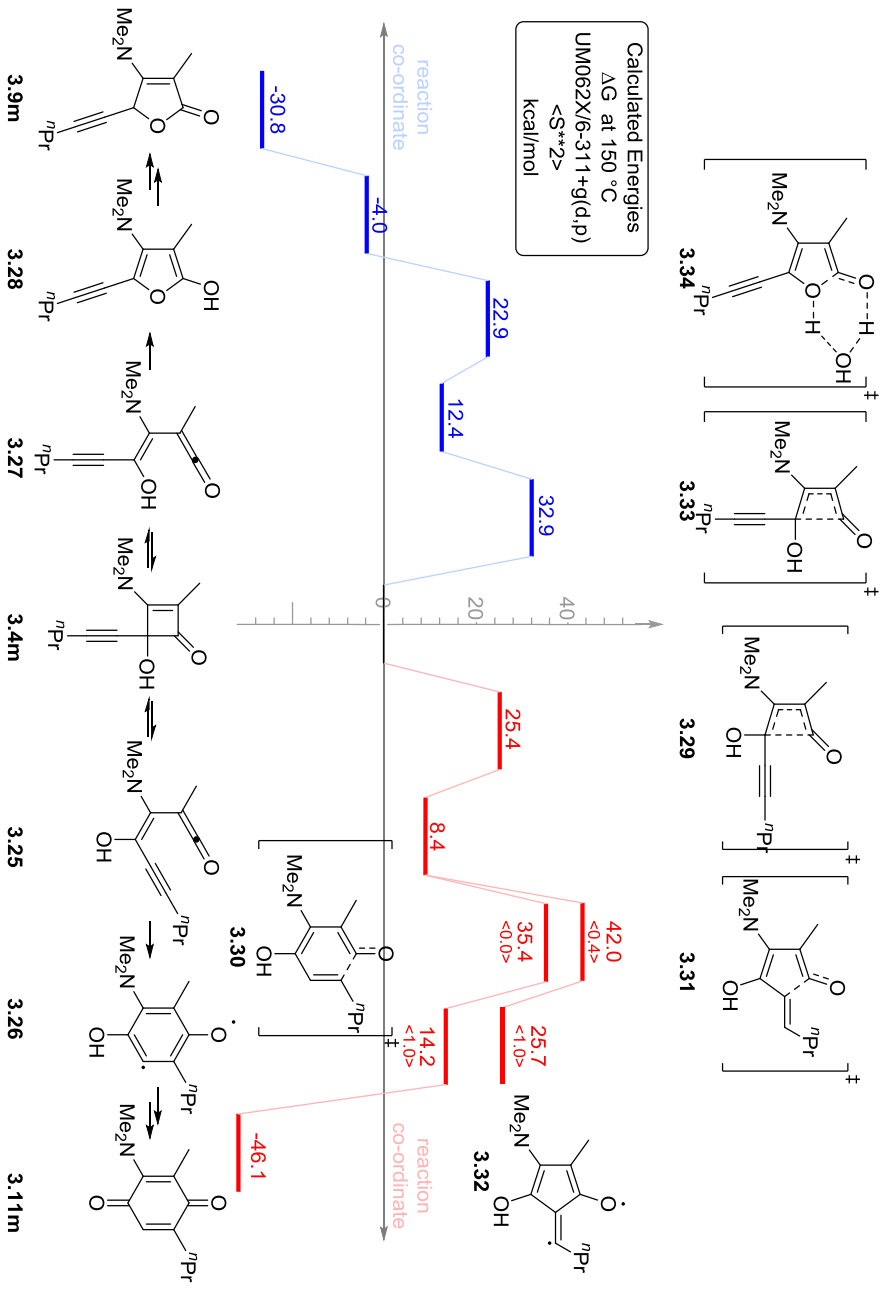


Figure 3.8: Geometry of the lowest energy conformation of furanol **3.15a** and 5*H*-furanone **3.9a**. Geometry and NBO at B3LYP/6-311G(d,p).

In conclusion, Gibbs free energy values were determined for all of the low-energy conformations. These were calculated at 150 °C to provide a useful insight into the thermolysis of aminoarylcyclobutenone **3.4a**. The highest energy barrier on the reaction coordinate was for ring closure of (*Z*)-vinylketene **3.12a** to ketone **3.13a**, which had a barrier of 37.2 kcal/mol. This was 2.5 kcal/mol higher than the competing ring opening leading to (*E*)-vinylketene **3.14a**. Consequently, calculations predicted 5*H*-furanone formation in line with our experimental findings. Importantly, the significant increase in the energy barrier of transition state **3.16a** was caused by steric hindrance between the C2 methyl group and the C3 dimethylamine group.

3.4.2 DFT calculations on thermolysis of aminoalkynylcyclobutenone

In turn, we calculated the energies of the ring opening and cyclisation pathways for thermolysis of aminoalkynylcyclobutenone **3.4m**. The ring opening step again favoured formation of (*Z*)-vinylketene **3.25** (25.4 kcal/mol) over (*E*)-vinylketene **3.27** (32.9 kcal/mol). Examination of the ring closure of (*Z*)-vinylketene **3.25** showed that it proceeded *via* a diradical pathway. The energy barrier for the transition state leading to quinone diradical **3.26** was 35.4 kcal/mol while that to form cyclopentenedione diradical **3.32** was 42.0 kcal/mol. Both of these modes of (*Z*)-vinylketene ring closure showed a higher energy barrier than that for the ring opening transition state **3.33**. Therefore, as observed previously, calculations correctly predicted that 5*H*-furanone **3.9m** would be formed as the sole product of the reaction (**Scheme 3.11**).



Scheme 3.11: Energy diagram for aminocyclobutenone **3.4m**.

Calculated at UM062X/6311+G(d,p), temperature=423.15 K.

NBO analysis of the ring opening of cyclobutenone **3.4m** to (*Z*)-vinylketene **3.25** was first performed. Aminocyclobutenone **3.4m** shows many similarities with **3.4a** (**Section 3.4.1**) in that the dimethylamino group was strongly conjugated to the cyclobutenone ring. Transition state **3.29** with inward rotation of the hydroxyl residue, again, proved similar to the analogous cyclobutenone **3.20a** (**Figures 3.9** and **3.1**).

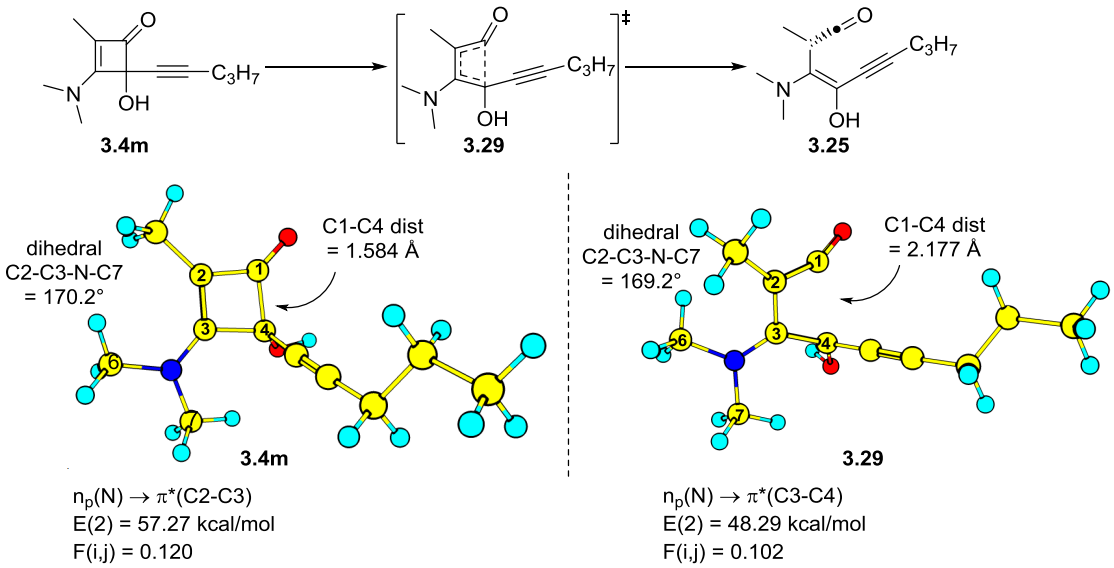


Figure 3.9: Geometry of the lowest energy conformation of aminocyclobutenone **3.4m** and TS **3.29**. Geometry and NBO at B3LYP/6-311G(d,p).

In (*Z*)-vinylketene **3.25**, the dihedral angle for C1-C2-C3-C4 was 51.5°, substantially less than that observed in the transition state for **3.12a** (111°) (**Figures 3.10** and **3.2**). The N-H distance is 2.021 Å, also indicated a weaker hydrogen bond compare to that in **3.12a**.

In transition state **3.30**, spin contamination (s**2) is 0, indicating a closed shell transition state. Notably, the N-H distance is 2.079 Å and the interaction energy is 4.24 kcal/mol, all suggesting moderate hydrogen bonding. The nitrogen atom is sp^3 hybridization and shows a tetrahedral geometry (**Figure 3.10**). As a consequence, the two methyl groups on N are close to the C2 methyl group causing significant steric hindrance.

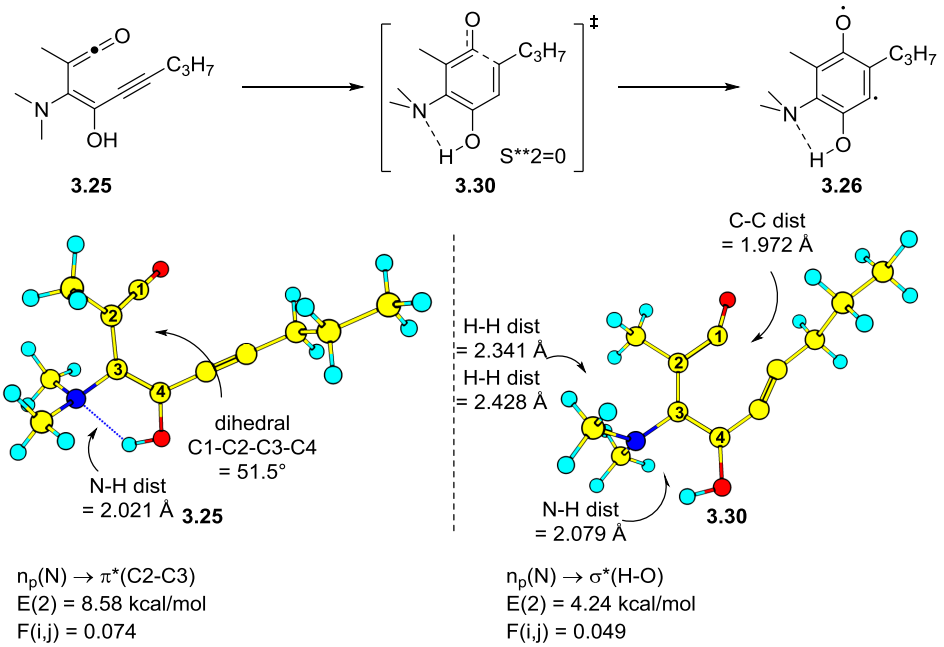


Figure 3.10: Geometry of the lowest energy conformation of (*Z*)-vinylketene **3.25** and TS **3.30**. Geometry and NBO at UB3LYP/6-311G(d,p).

As with our previous study, for (*Z*)-vinylketene **3.25** to reach transition state **3.30**, the C2 methyl group needs to overcome the high steric hindrance imparted by the dimethylamino group at C3 (**Figure 3.11**). As a result, transition state **3.30** showed a high energy barrier.

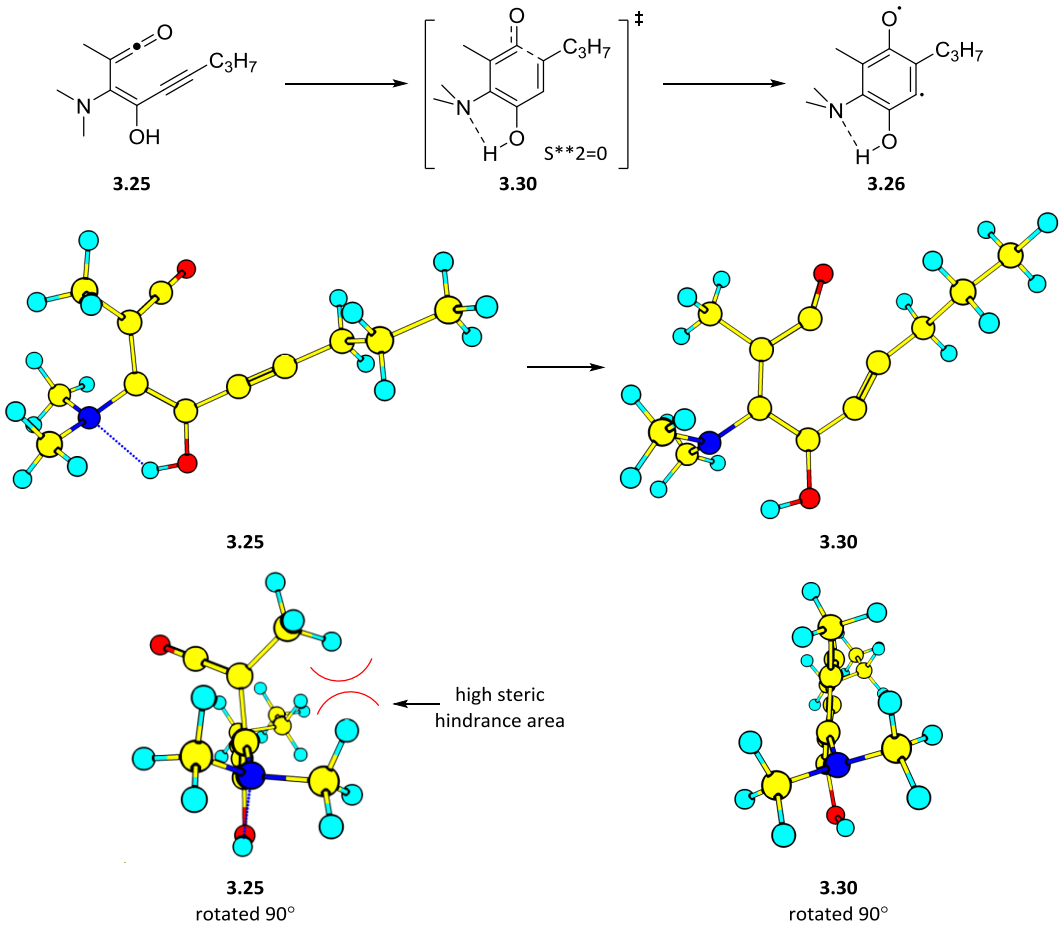


Figure 3.11: Steric effect at (*Z*)-vinylketene **3.25** and ring closure transition state **3.30**.

In diradical **3.26**, spin contamination is 1, indicating an open shell singlet diradical structure. Hydrogen bonding is still present. Additionally the closest H-H distances between the C2 methyl group and the C3 dimethylamino group are 2.25 Å and 2.08 Å, again showing severe steric hindrance (**Figure 3.12**).

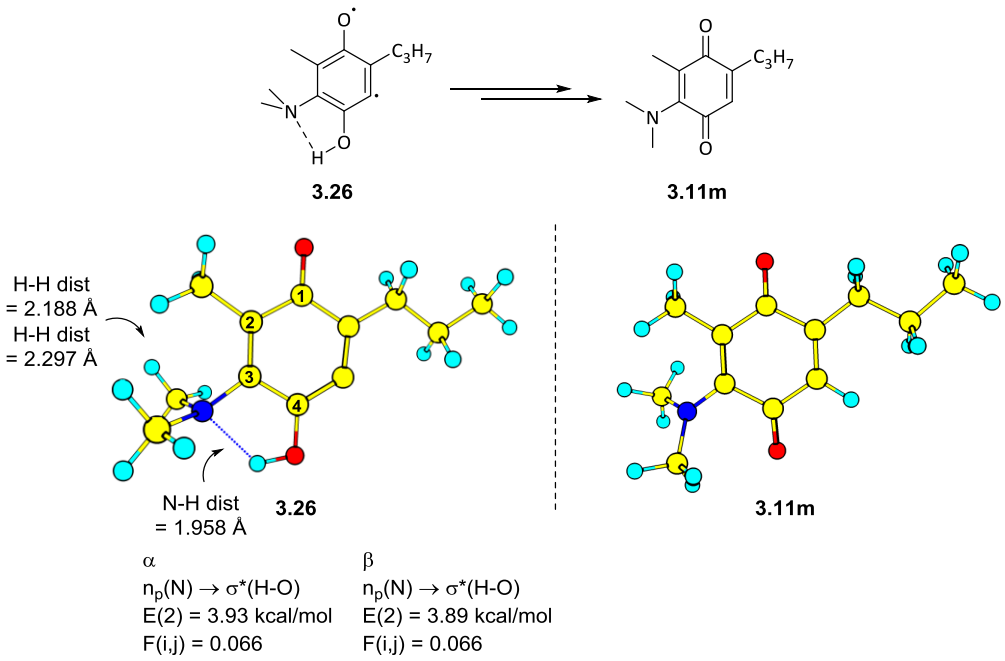


Figure 3.12: Geometry of the lowest energy conformation of diradical **3.26** and quinone **3.11m**. Geometry and NBO at UB3LYP/6-311G(d,p).

In transition state **3.33**, with inward rotation of the hydroxyl group, the nitrogen lone pair of electrons is stabilized by p-π conjugation of N to both C2-C3 and C3-C4 (**Figure 3.13**).

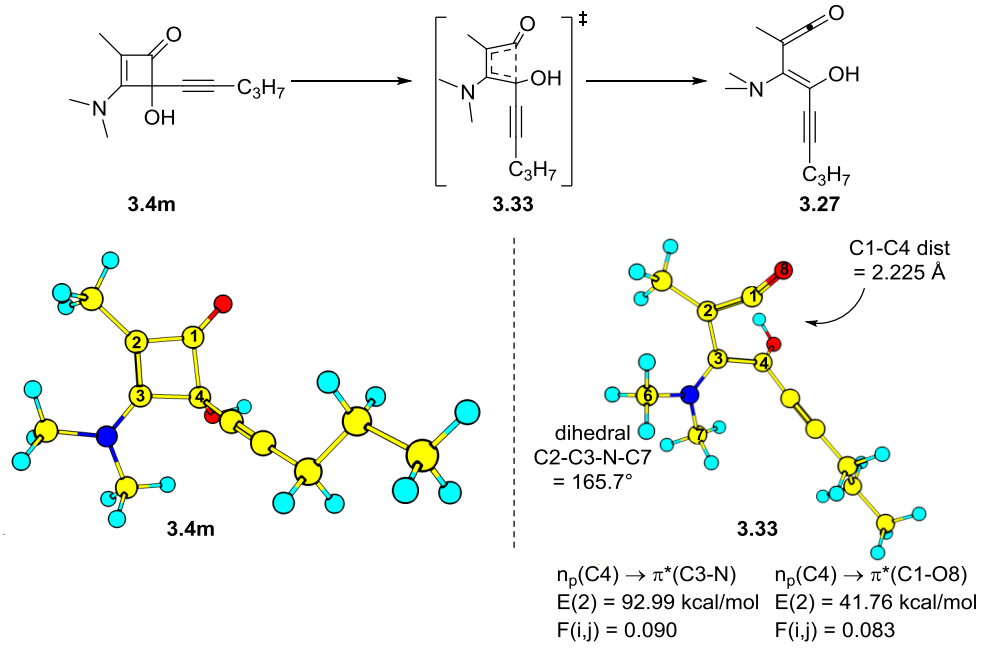


Figure 3.13: Geometry of the lowest energy conformation of TS **3.33**. Geometry and NBO at B3LYP/6-311G(d,p).

In (*E*)-vinylketene **3.27**, the lone pair of electrons on nitrogen interacts with the σ* orbital (C2-C3), indicating an sp^3 hybridisation. By contrast, in transition state **3.34**, the nitrogen shows an sp^2 hybridisation with an interaction to the π* orbital (C2-C3) (**Figure 3.14**).

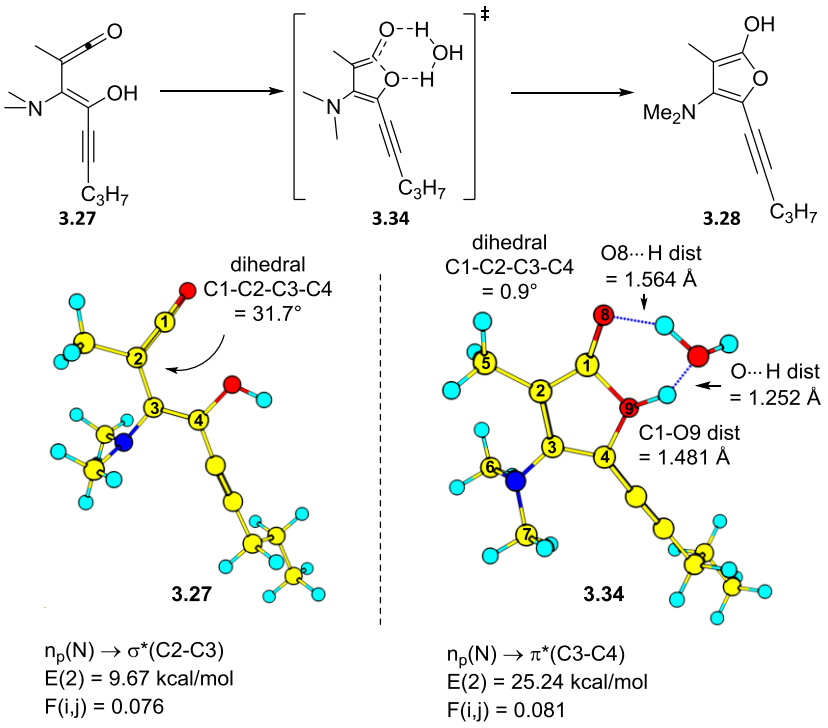


Figure 3.14: Geometry of the lowest energy conformation of (*E*)-vinylketene **3.27** and TS **3.34**. Geometry and NBO at B3LYP/6-311G(d,p).

Furanone **3.28** also shows conjugation between the lone pair of electrons on nitrogen and the furan ring (**Figure 3.15**). Tautomerization of **3.28** gives furanone **3.9m** *via* a water assisted proton shift.

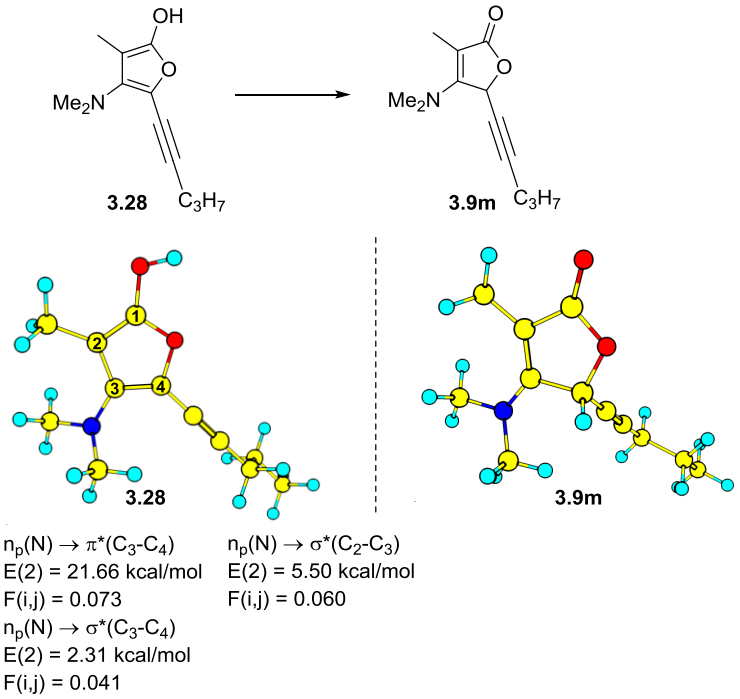


Figure 3.15: Geometry of the lowest energy conformation of furanol **3.28** and furanone **3.9m**. Geometry and NBO at B3LYP/6-311G(d,p)

The different hybridisation of the nitrogen atom in the alkynyl substituted furanol (**3.28**) and the aryl substituted furanol (**3.15a**) is caused by steric hindrance between the amino group and the aromatic group, which forces the nitrogen atom to be sp^3 hybridised in **3.15a** (**Figure 3.16**).

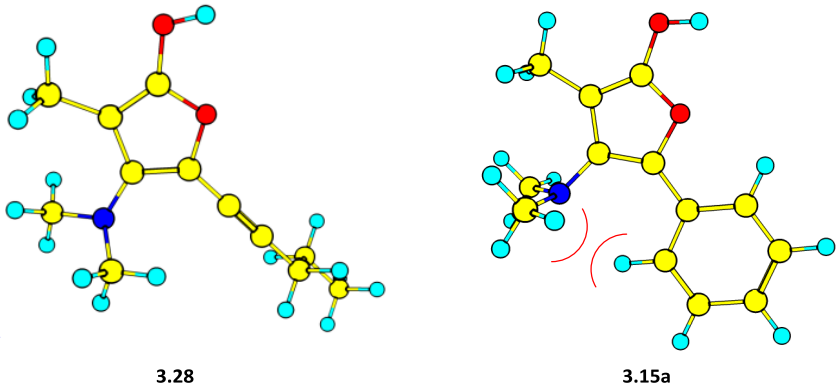


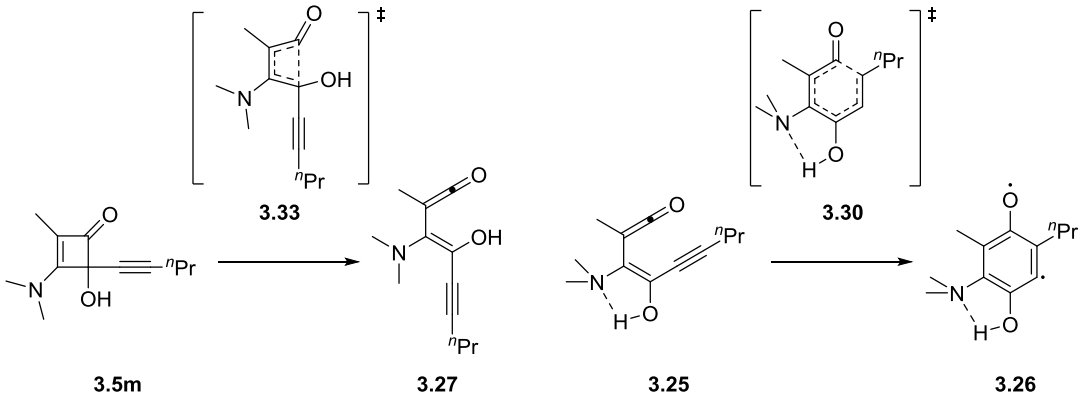
Figure 3.16: sp^3 Hybridisation of the amino group in **3.28** and **3.15a.**

In conclusion, DFT calculations for the thermal rearrangement of alkynyl substituted aminocyclobutenone have established that the change in selectivity from quinone to furanone formation is due to an increase in the energy for electrocyclic ring closure. NBO analysis suggested this was caused by steric hindrance between the C2 methyl group and the C3 amine group.

3.4.3 Solvent effects

In **Schemes 3.9** and **3.11**, the calculation results relate to reactions in the gas phase. In order to determine the influence of solvents on the rearrangement, DFT calculations were next performed in the presence of a solvent by placing the substrate in a cavity within the solvent reaction field. Here we used the Polarizable Continuum Model and the integral equation formalism variant (IEFPCM). Calculations examined the energies of transition states **3.30** and **3.33** as these presented the highest energy barrier in each pathway (**Section 1.1.2**).

According to the results (**Table 3.6**), gas phase calculations underestimated energy barriers for both transition states **3.30** and **3.33**. They also underestimated the ΔΔG between the two transition states. When considering the solvent effect, reactions in MeCN and DMSO displayed the highest selectivity (highest ΔΔG) while those in 1,4-dioxane and *p*-xylene had a lower energy barrier to form the furanol intermediate **3.28**. From this we concluded that the reaction should occur at a lower temperature or require a shorter reaction time in those solvents. Moreover, although all solvents examined showed variations in the energy barriers, none changed the selectivity of the reaction (all showed a positive ΔΔG).

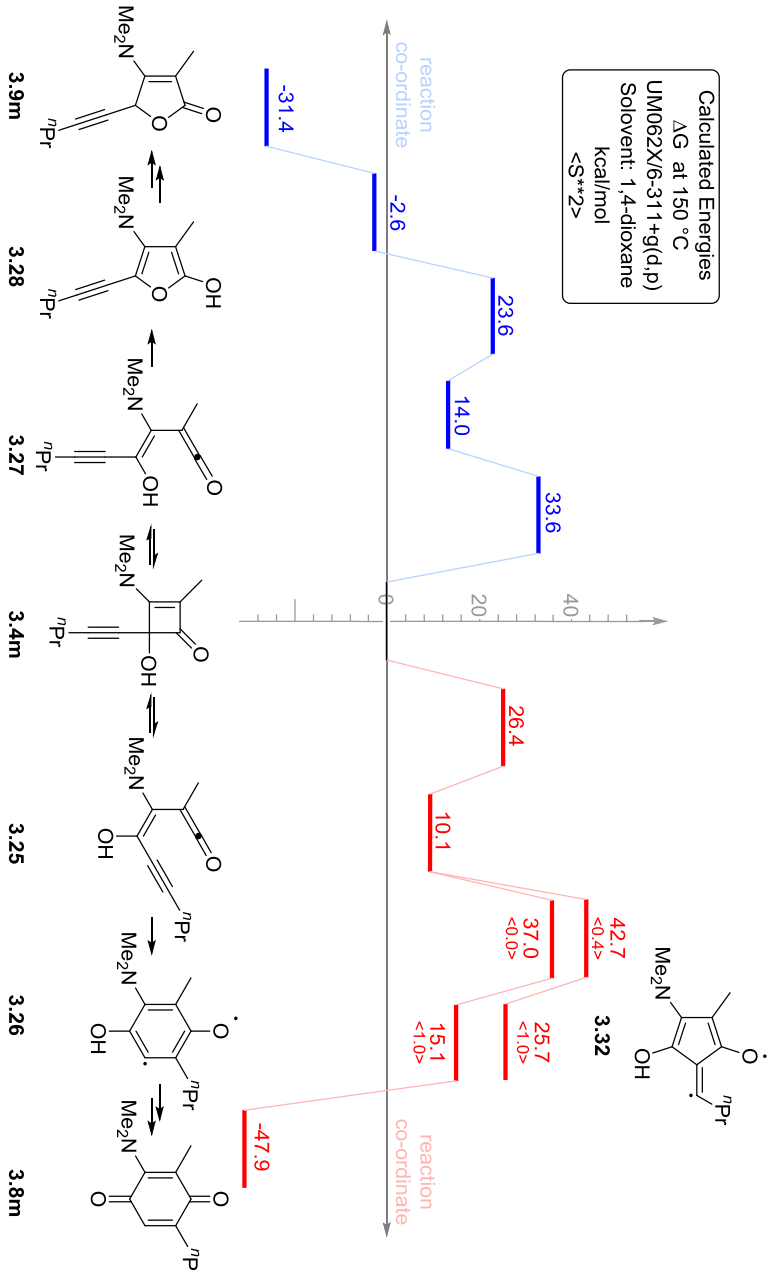


solvent	$\Delta G_{3.33}$ *(kcal/mol)*	$\Delta G_{3.30}$ *(kcal/mol)*	$\Delta\Delta G_{3.30\text{-}3.33}$ *(kcal/mol)*
Gas phase	29.1	31.8	2.7
1,4-dioxane	29.2	33.4	4.2
MeCN	30.5	36.3	5.8
DMSO	30.5	36.3	5.8
p-xylene	29.2	33.4	4.2

Table 3.6: DFT calculation with different solvents.

Calculated at UB3LYP/6-311G(d,p), scrf=IEFPCM=1,4dioxane, temperature=423.15k.

Following that initial assessment we performed a highly accurate calculation considering the solvent effect for the thermal rearrangement of aminocyclobutenone **3.4m**. The result is summarised in **Scheme 3.12**.

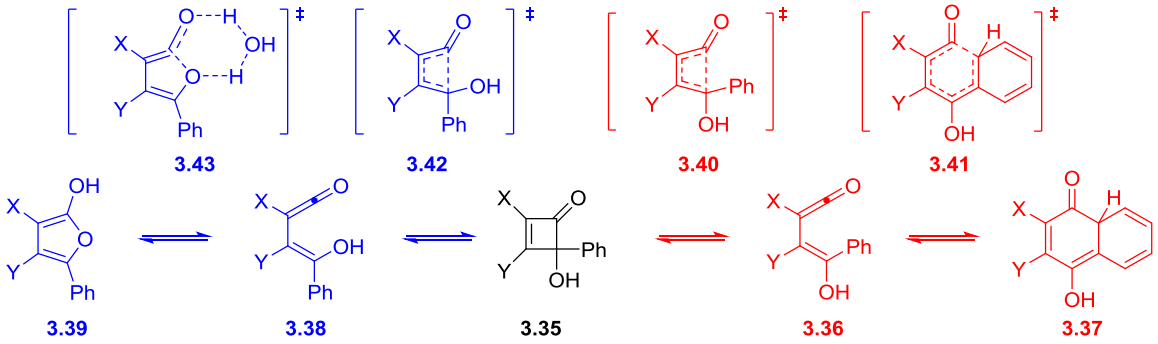


Scheme 3.12: Energy diagram for the rearrangement of aminocyclobutenone **3.4m** in 1,4-dioxane at 150 °C. Calculated at UM062X/6-311+G(d,p), scrf=IEFPCM=1,4-dioxane, temperature=423.15 K.

3.4.4 Selectivity study

As discussed in **Sections 3.4.1** and **3.4.2**, the different outcomes observed for thermolyses of aminocyclobutenones were caused by a change in the highest energy barrier from the ring opening transition state **3.42** to the ring closure transition state **3.41** (**Table 3.7**). This switch was caused by steric buttressing between the C2 and C3 substituents of the cyclobutenone. To

understand more about the selectivity, Gibbs energies for the ring opening transition states **3.40** and **3.42**, and the ring closing transition state **3.41** were calculated for fourteen 3-amino-4-arylcyclobutenones containing a variety of substituents. The results of these calculations are shown in **Table 3.7** and are also summarised in **Graphs 3.1** and **3.2**, where a plot of the energy barrier for inward versus outward rotation (of the hydroxyl group), and of furanone versus quinone formation are summarised.



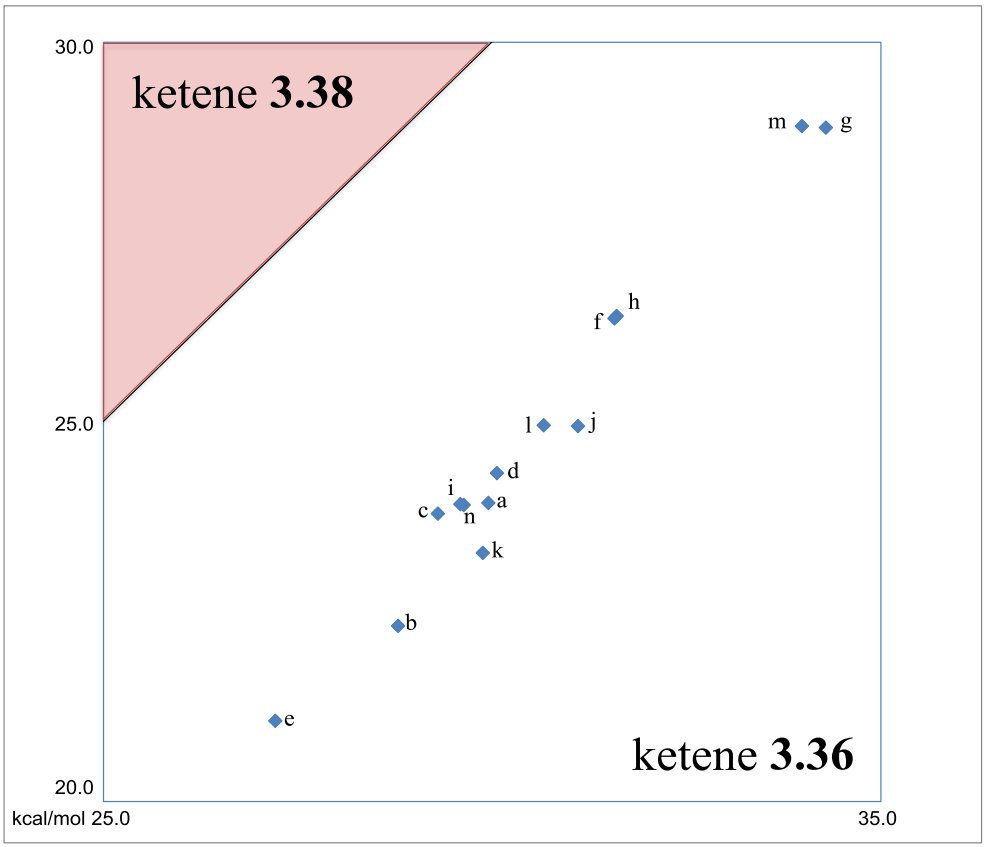
3.35	*X*	*Y*	$\Delta\Delta G_{3.42-3.40}$	$\Delta\Delta G_{3.42-3.41}$	*Predict result*	*Experimental result*
a	methyl	$N(Me)_2$	6.0	-3.2	5*H*-furanone	5*H*-furanone
b	H	$N(Me)_2$	6.5	2.9	quinone	quinone
c	Ph	$N(Me)_2$	5.5	-6.3	5*H*-furanone	5*H*-furanone
d	CF_3	$N(Me)_2$	5.7	-4.5	5*H*-furanone	/
e	Nitro	$N(Me)_2$	6.1	-6.2	5*H*-furanone	/
f	F	$N(Me)_2$	5.2	1.0	quinone	/
g	OH	$N(Me)_2$	5.4	1.9	quinone	/
h	alkynyl	$N(Me)_2$	5.2	-1.1	5*H*-furanone	5*H*-furanone
i	TMS	$N(Me)_2$	5.7	-8.5	5*H*-furanone	/
j	ethyl	$N(Me)_2$	6.1	-2.4	5*H*-furanone	/
k	methyl	methylaniline	6.6	1.5	quinone	quinone
l	methyl	NHMe	5.7	1.3	quinone	quinone
m	methyl	NH_2	6.0	3.7	quinone	/
n	methyl	pyrrol	5.7	8.2	quinone	/

Table 3.7: DFT calculations with 14 kinds of aminocyclobutenones.

Calculated at B3LYP/6-31G(d) at 423.15 K.

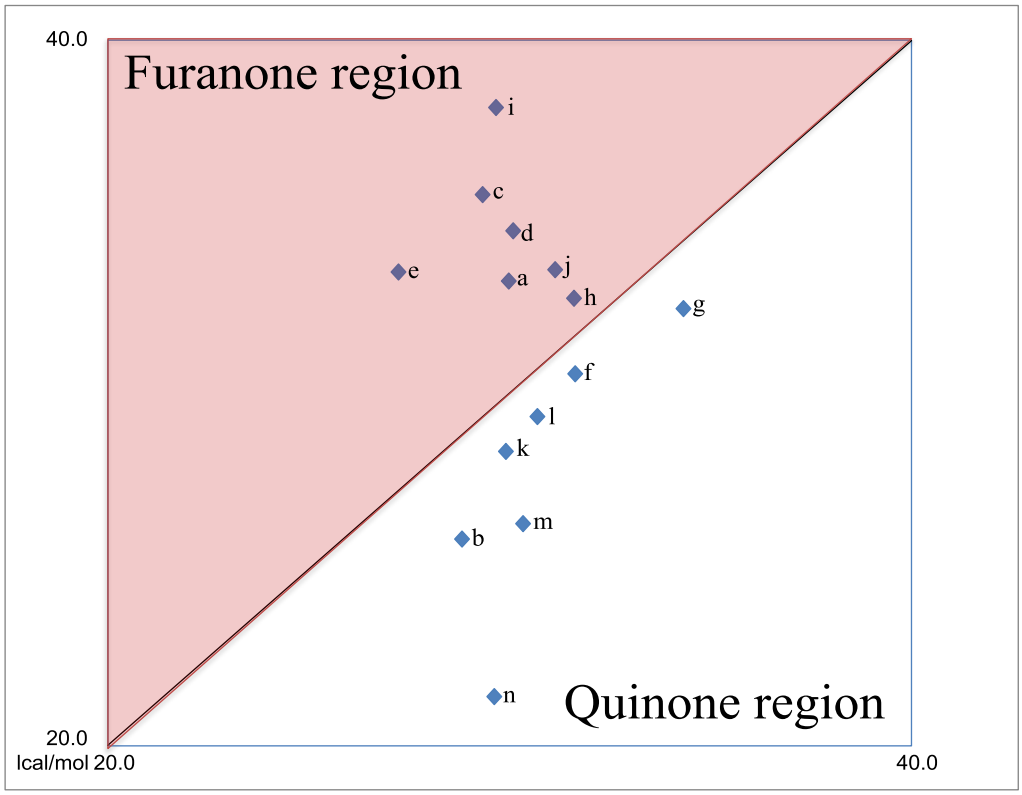
In **Graph 3.1**, DFT calculation showed that in the ring opening step, all 14 aminocyclobutenones favoured outward rotation of the hydroxyl residue to form a vinylketene **3.36** rather than inward rotation of the hydroxyl residue to form vinylketene **3.38**. The energy difference ($\Delta\Delta G_{3.42-3.40}$) in

each case was around 5-7 kcal/mol. The torquoselectivity predicted matched the results of previous work from the Harrowven group and others.



Graph 3.1: Graphical representation of results shown in **Table 3.7**. The line separates the molecules favouring inward and outward rotation of the hydroxyl group in the ring open step.

When considering the energy barrier for the ring closing transition state **3.41**, the preference for a final product emerges (**Graph 3.2**). Although the result showed both 5*H*-furanone and quinone formation, certain trends can be established. These support our theory that the energy barrier in the rearrangement is shifted from the transition state to form vinylketene **3.38** to the transition state leading to ring closure of vinylketene **3.36**.



Graph 3.2: Graphical representation of results shown in **Table 3.7**. The line separates the molecules favouring furanone formation and quinone formation.

Our primary conclusions are:

1. In the thermolyses of aminocyclobutenones, the ring opening step favours outward rotation of the hydroxyl group over its inward rotation. As such torquoselectivity in the ring opening step is consistent with the thermolyses of other 4-hydroxycyclobutenones.

2. Some aminocyclobutenones showed a high energy for the transition state leading to ring closure *via* vinylketene **3.36**. When the energy of this step exceeds that for the transition state with inward rotation of the hydroxyl group, the thermal rearrangement will switch from forming quinone formation to furanone formation.

3. When C3 bears a dimethylamine group, selectivity in these reactions is influenced by the substituent at C2. Aminocyclobutenones in **3.35d-f** all have an electron withdrawing group at C2 but did not give the same outcome. This indicates that selectivity is not determined by electronic effects. Considering **3.35b**, **3.35f** and **3.35g**, which all favour quinone formation, each bears a small group at C2 (H, F and OH). Thus it can be postulated that steric buttressing between C2 and C3 determines the reaction outcome.

4. In **3.35k-n**, all of which have a small (or less steric hindrance) amino group at C3, the energy barrier for ring closure *via* vinylketene **3.36** is low. As a consequence, all are predicted to favour the quinone formation (**Figure 3.17**). This too demonstrates the importance of steric buttressing between C2 and C3 in determining the reaction outcome.

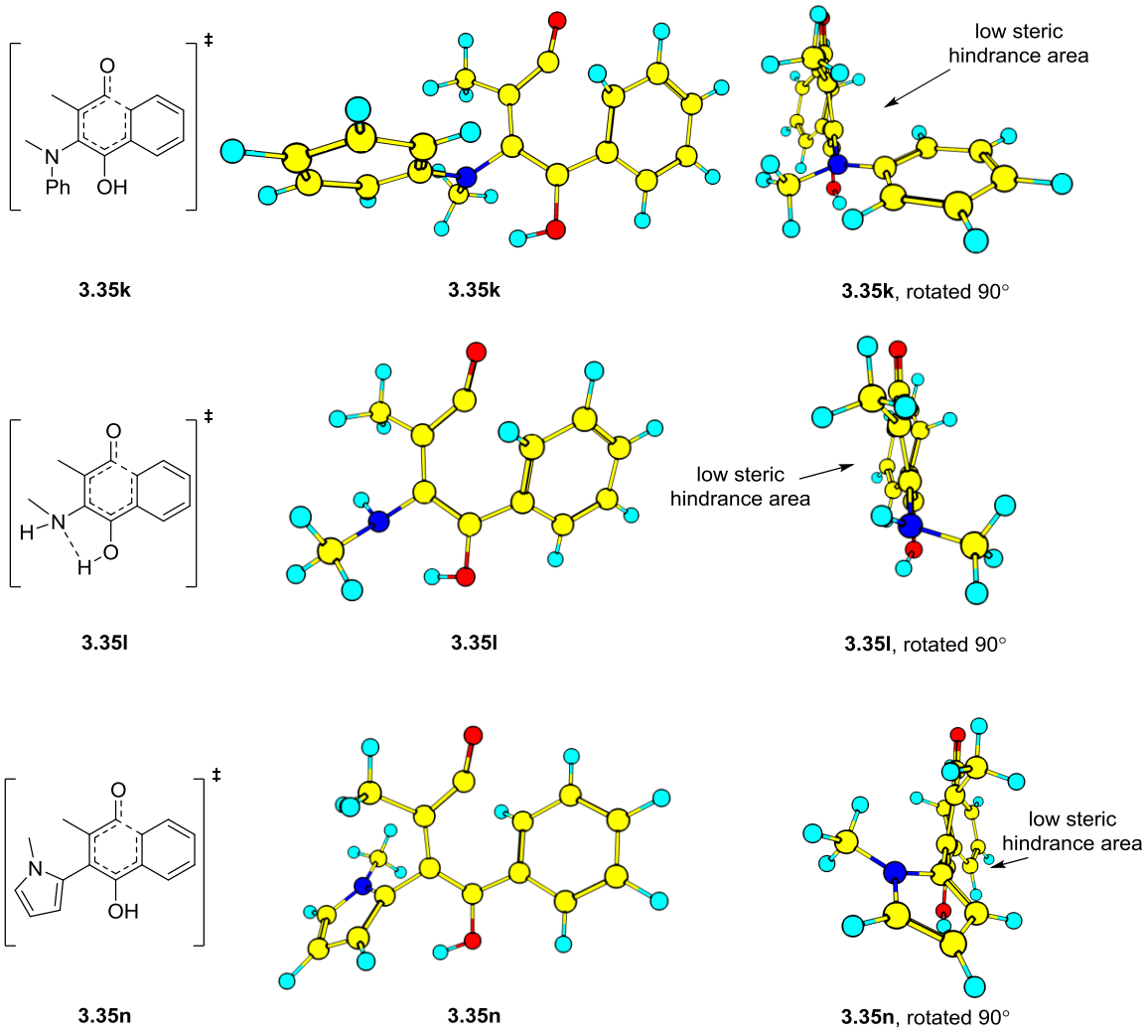


Figure 3.17: Low steric hindrance area in TS **3.35k**, **l**, **n**.

Notably, thermolyses of aminocyclobutenones **3.35a, b**, **c**, **h**, **k** and **3.35l** have been performed experimentally and all gave the selectivity predicted by DFT calculation.

3.4.5 Conclusions

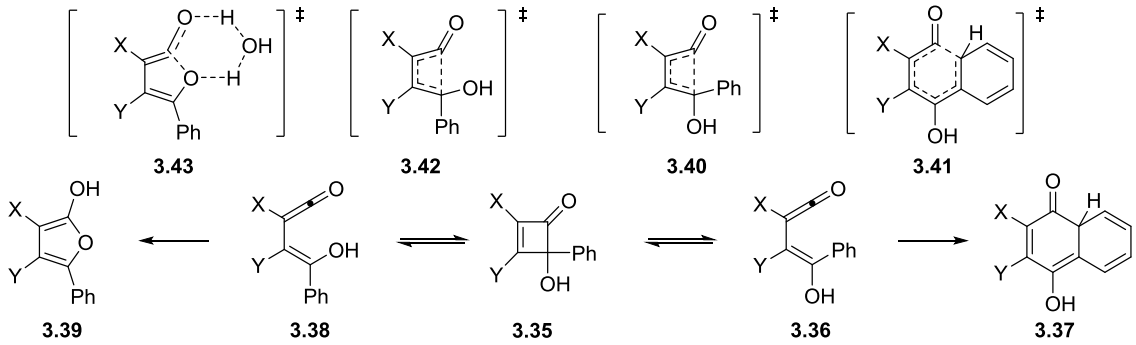
The DFT calculation results suggest that steric buttressing of the C2 and C3 substituents dictates the outcome of thermolyses of aminocyclobutenones. Dialkylamino substituents push reactions toward furanone formation while smaller amino substituents proceed *via* classical Moore rearrangement pathways leading to quinone or cyclopentenedione formation.

3.5 Thermolyses of ^{t}butylcyclobutenones

Having established that steric buttressing can change the course of thermolyses of aminocyclobutenones, we decided to probe the effect further by investigating the thermolyses of ^{t}butylcyclobutenones, as these should also display the steric buttressing effect.

3.5.1 DFT calculations on thermolyses of ^{t}butylcyclobutenones

Firstly, DFT calculations were performed to determine the highest energy barrier for both quinone and 5*H*-furanone formation (**Table 3.8**). Pleasingly, all five of the models examined showed a strong preference for the formation of a 5*H*-furanone as the final product.

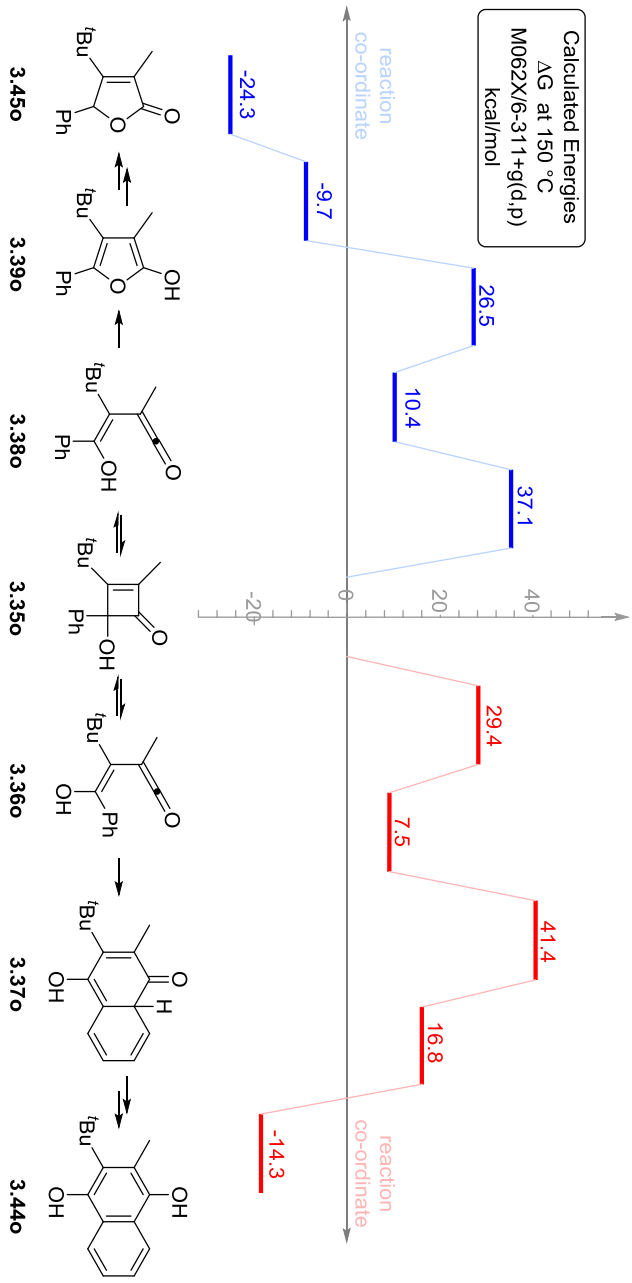


3.35	*X*	*Y*	$\Delta\Delta G_{3.42-3.40}$	$\Delta\Delta G_{3.42-3.41}$	*result*
o	Me	^{t}Bu	7.4	-3.0	5*H*-furanone
b	^{t}Bu	Me	6.5	-2.1	5*H*-furanone
q	^{t}Bu	MeO	1.2	-3.3	5*H*-furanone
r	^{t}Bu	NHPh	5.5	-9.8	5*H*-furanone
s	^{t}Bu	NHMe	5.1	-12.9	5*H*-furanone

Table 3.8: DFT calculations on the thermolyses of 5 different ^{t}butylcyclobutenones.

Calculated at B3LYP/6-31G(d) at 423.15K.

The full pathway for thermolysis of ^{t}butylcyclobutenone **3.35o** was also calculated. The energy profile it exhibited (**Scheme 3.13**) was similar to that of aminocyclobutenone **3.4** (**Scheme 3.6**), in that the ring closure transition state from vinylketene **3.36o** to quinone **3.37o** presented the highest energy barrier. The result suggested that the steric impact of the ^{t}butyl group would increase the energy barrier of ring closure *via* vinylketene **3.36o** to such an extent that we would expect its thermolysis to favour formation of 5*H*-furanone **3.45o** (**Scheme 3.13**).

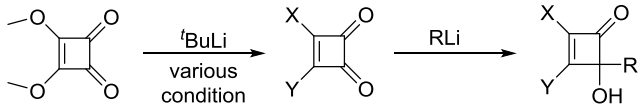


Scheme 3.13: Energy diagram for thermolysis of ^{t}butylcyclobutenone **3.35o**.

M062X/6-311+G(d,p), temperature=423.15K

3.5.2 Thermolyses of ^{t}butylarylcyclobutenones

Next, these results were tested experimentally. Firstly a series of ^{t}butylcyclobutenones were prepared, each was then subjected to thermolysis under continuous flow at 180 °C (**Table 3.9**).

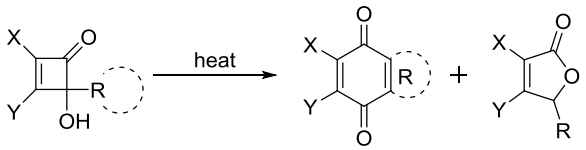


3.2 **3.46** **3.47**

	X	***Y***	***R***	***Yield 3.46 (%)***	***Yield 3.47 (%)***
a	Me	^{t}Bu	Ph	63	*
b	^{t}Bu	MeO	Ph	89	87
c	^{t}Bu	NHMe	Ph	73 (two steps)	78
d	^{t}Bu	MeO	3-pyridinyl	89	80
e	^{t}Bu	MeO	Furanyl	89	82
* ^{t}Butylcyclobutenone **3.39a** was isolated as an inseparable mixture of regioisomers due to poor selectivity during the addition of PhLi. The mixture was taken through to the following reaction.					

Table 3.9: Preparation of ^{t}butylcyclobutenones **3.46** and **3.47**.

Importantly, while the thermolyses of methyl(methoxyl)cyclobutenones **3.50a'-e'** each led to quinones **3.48a'**-**e'**, these analogous ^{t}butylcyclobutenones **3.50a-e** all favoured 5*H*-furanone formation (**Table 3.10**). The results support our theory that steric hindrance between the C2 and C3 substituents can change the selectivity of thermal cyclobutenone rearrangements from quinone formation to 5*H*-furanone formation.



3.47 **3.48** **3.49**

3.47	*X*	*Y*	*R*	*Yield 3.48 (%)*	*Yield 3.49 (%)*
a	Me	^{t}Bu	Ph	/	61*
a' [15]	Me	Me	Ph	87	/
b	^{t}Bu	MeO	Ph	/	100
b' [45]	Me	MeO	Ph	91	/
c	^{t}Bu	MeNH	Ph	/	87
c'	Me	MeNH	Ph	73	/
d	^{t}Bu	MeO	3-Pyridinyl	/	88
d' [32]	MeO	MeO	3-Pyridinyl	40**	23
e	^{t}Bu	MeO	Furanyl	/	91
e' [88]	Me	MeO	Furanyl	98	/

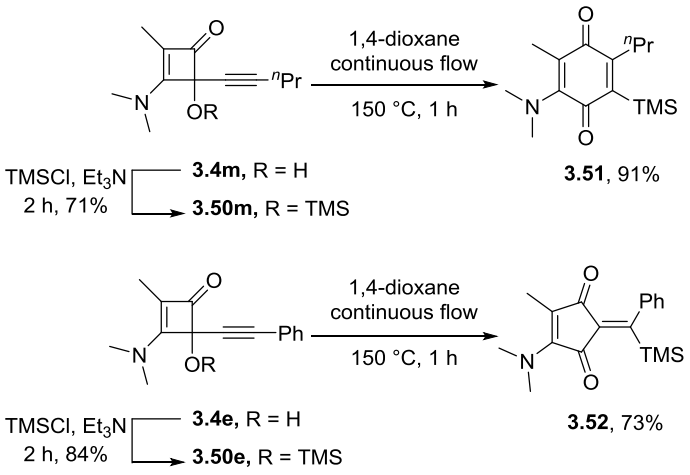
* The modest yield was largely due to contamination of the starting material with *ca.* 20% of a regioisomer
** Yield of **3.51d'** was reported as a mixture of quinone and hydroquinone

Table 3.10: Thermolyses of cyclobutenones **3.47a-e** and **3.47a'-e'**.

3.6 Special cases in the thermolyses of aminocyclobutenones

3.6.1 Thermolyses of protected aminocyclobutenones

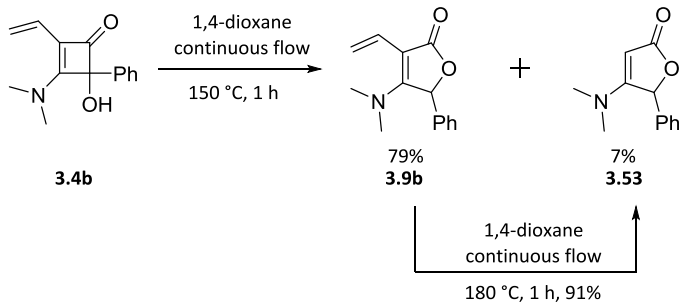
Having demonstrated the wide impact of steric buttressing on cyclobutenone rearrangements, we next sought to examine the thermolysis of aminocyclobutenone in which the C4 hydroxyl residue is protected. Pathways for furanone formation should be shut down by such protection. TMS protected aminocyclobutenones **3.50e** and **3.50m** were each obtained by treatment of the respective aminocyclobutenones **3.4e** and **3.4m** with TMSCl and Et_3N. Each was then subjected to thermolysis under flow. As expected, thermolysis of protected aminocyclobutenone **3.50m** gave quinone **3.51m** while aminocyclobutenone **3.50e** gave cyclopentenedione **3.52e** as the primary product (**Scheme 3.14**).



Scheme 3.14: Thermolyses of protected aminocyclobutenones **3.50m** and **3.50e**.

3.6.2 Thermal elimination of a vinyl substituted furanone

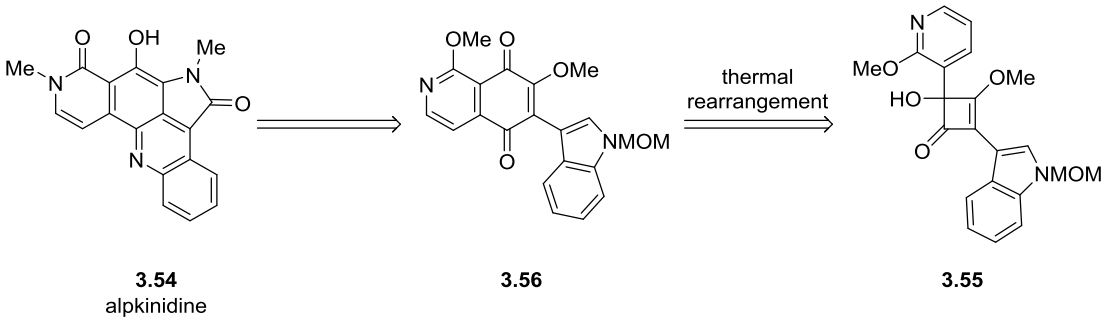
In the thermolysis of aminocyclobutenone **3.4b**, elimination product **3.53** was isolated as an unexpected by-product. Further studies showed that it was also obtained in high yield by heating vinyl substituted furanone **3.9b** at 180 °C under continuous flow for 1 h (**Scheme 3.15**). The mechanism of this curious fragmentation reaction is unclear.



Scheme 3.15: Thermal rearrangement of **3.4b** and **3.9b**.

3.7 Selectivity in thermolysis of cyclobutenone to form alpkinidine

Contemporaneously, studies within the Harrowven group were directed towards the synthesis of alpkinidine **3.54** *via* thermal rearrangement of cyclobutenone **3.55** (**Scheme 3.16**). When this process was examined, they noticed that thermolysis of cyclobutenone **3.55** gave a mixture of quinone **3.56** and furanone **3.57** (**Scheme 3.17**).

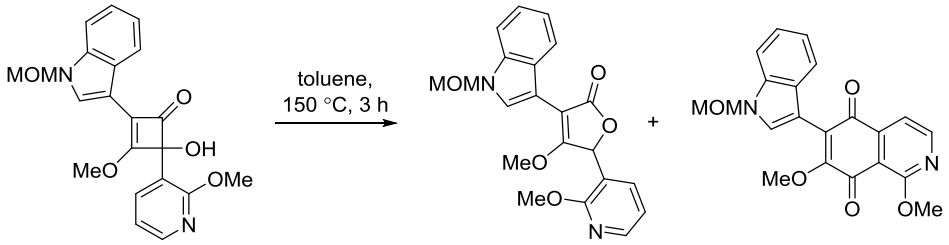


3.54
alpkinidine

3.56

3.55

Scheme 3.16: A new route for the total synthesis of alpkinidine *via* thermolysis of cyclobutenone.



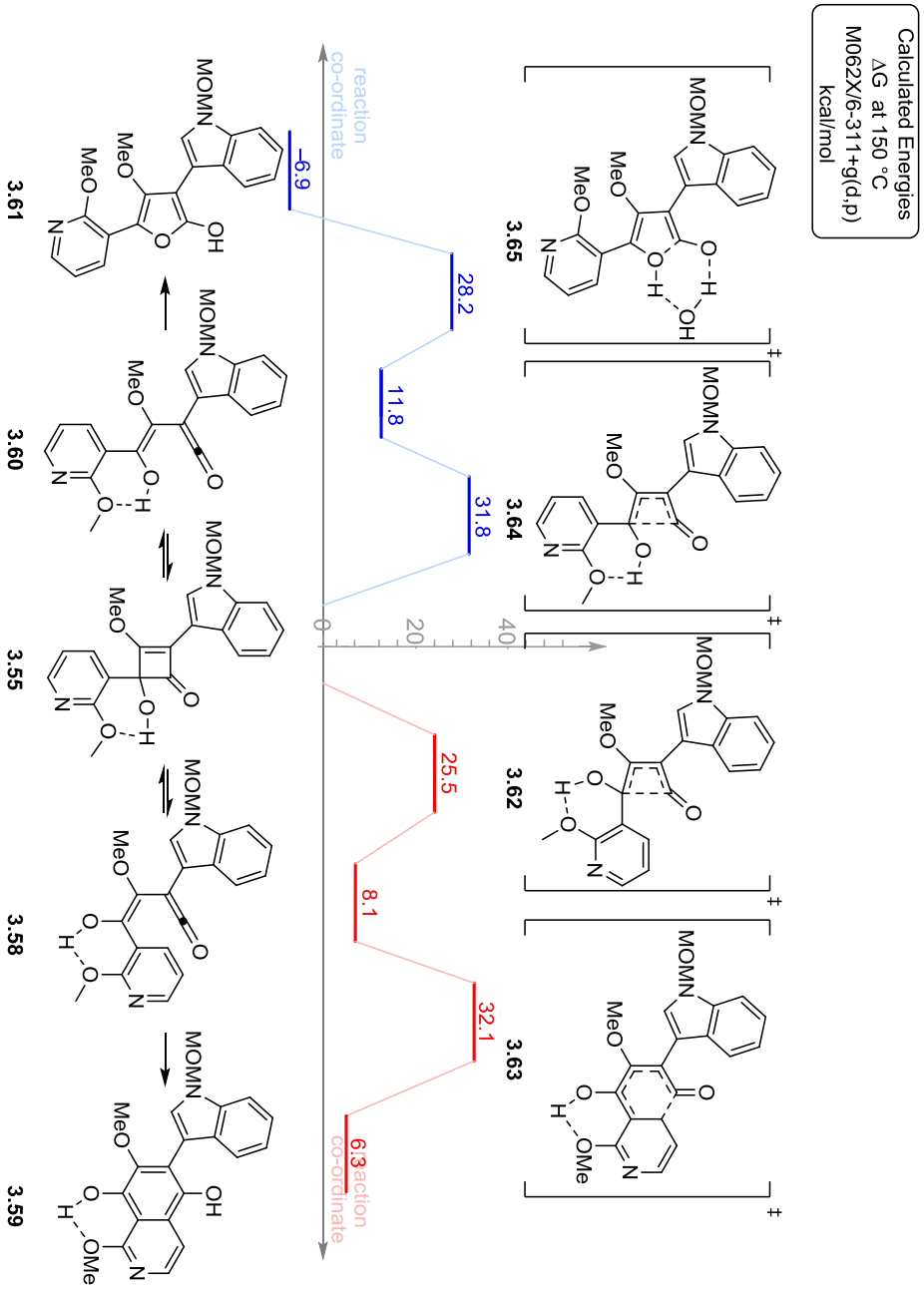
3.55

3.57, 25%

3.56, 29%

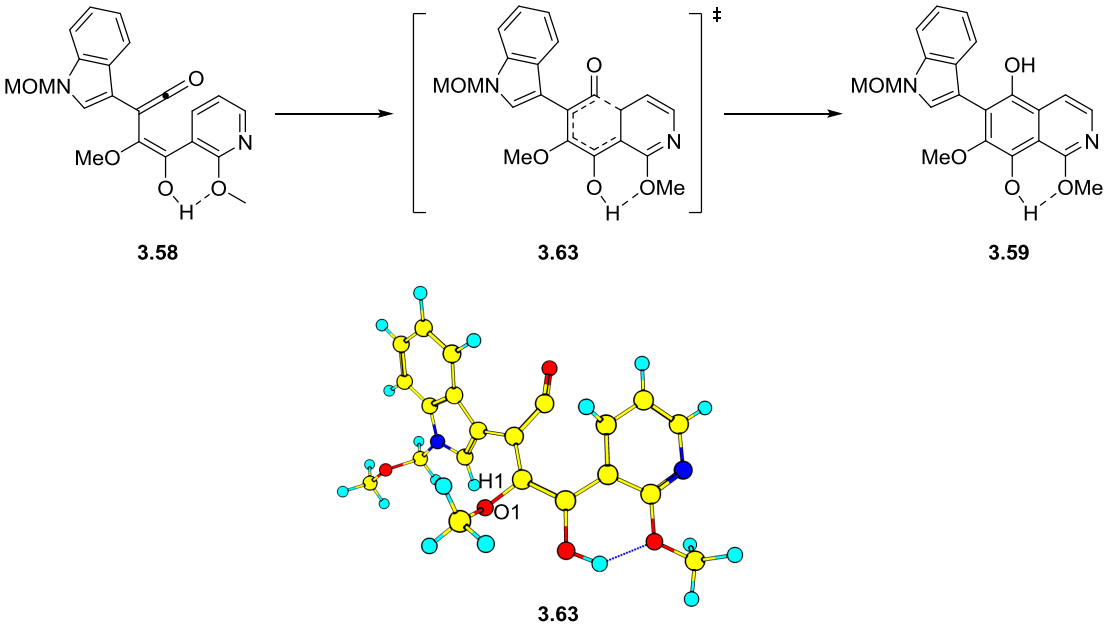
Scheme 3.17: Thermolysis of cyclobutenone **3.55**.

To understand the anomalous formation of furanone **3.57**, DFT calculations were performed for the thermolysis of cyclobutenone **3.55** (**Scheme 3.18**). Notably, in this reaction, ring opening *via* inward rotation of the hydroxyl group (transition state **3.64**) and ring closure *via* transition state **3.63** showed energy barriers of 31.8 kcal/mol and 32.1 kcal/mol respectively, implicating these as the rate determining steps. Moreover, the small energy difference between them (0.3 kcal/mol) was in line with the poor selectivity observed experimentally for this reaction.



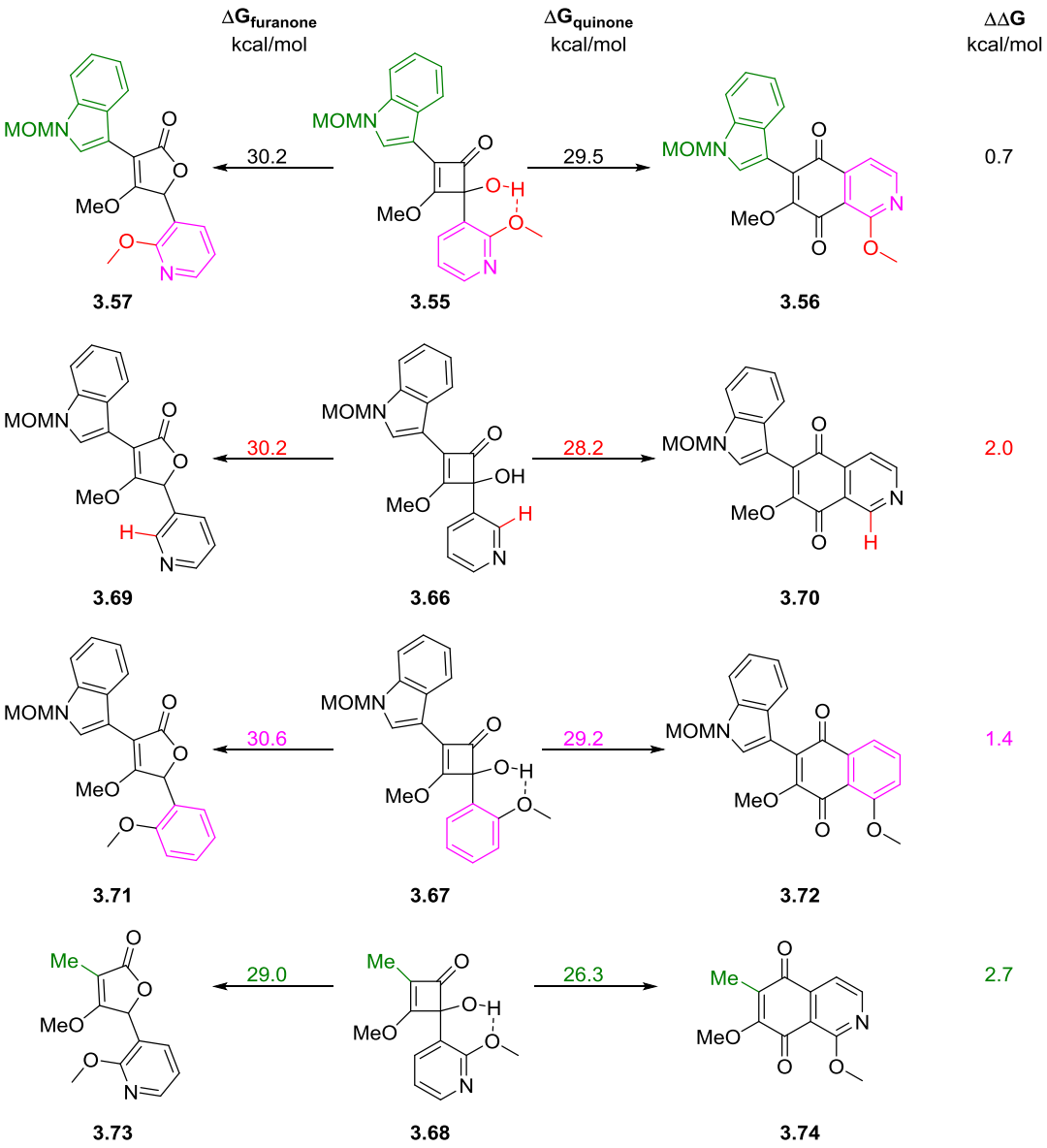
Scheme 3.18: Energy diagram in thermolysis for cyclobutenone **3.58**. M062X/6-311+G(d,p), scrf=IEFPCM=1,4-dioxane, temperature=423.15 K, opt=tight, int=ultrafine

NBO analysis of transition state **3.63** showed hydrogen bonding between the hydroxyl group and the methoxy substituent on the pyridine residue. Moreover, in transition state **3.63**, the hydrogen atom at C2 of the indole (H1) was close to the oxygen atom of the vinyl ether (O1), causing a significant steric barrier (**Scheme 3.19**).



Scheme 3.19: NBO analysis of the lowest energy formation of transition state **3.63**. B3LYP/6-311G(d,p)

To better understand which factors (hydrogen bonding or steric buttressing) were responsible for the poor selectivity, DFT calculations were performed on three analogous (**3.66**–**3.68**). These provide us with the means to compare the impact of different structural features on each pathway (**Scheme 3.20**).



Scheme 3.20: DFT calculations on **3.55** and analogous **3.66**–**3.68**.

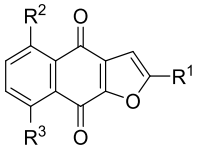
B3LYP/6-311G(d,p), scrf=IEFPCM=1,4-dioxane, temperature=423.15 K

Analog **3.66**, which lacked a methoxy substituent on the pyridine ring, showed a bigger ΔΔG (2.0 kcal/mol) than **3.55** (0.8 kcal/mol), indicating that hydrogen bonding between the hydroxyl group and methoxy group on pyridine retards quinone formation **3.70**. In analog **3.67**, where the pyridine is replaced by a phenyl residue, a slight increase in the energy difference (1.4 kcal/mol) was predicted indicating that the 3-pyridinyl residue also retards quinone formation (**3.72**), albeit to a less extent (**Section 3.5.2**). Notably, in analog **3.68**, where the indole residue is substituted for a methyl group, energy barriers for both pathways were reduced significantly. Moreover, the energy difference between them was greatest (2.7 kcal/mol), suggesting that steric buttressing between the indole and methoxy residue in transition state **3.63** was the principle cause of the poor selectivity observed.

3.8 Exemplification of aminocyclobutenone rearrangement

3.8.1 Heterocycle-fused quinones and naphthoquinones

Heterocycle-fused quinones and naphthoquinones have gained attention in recent years due to the range of biological activities they display, such as furonaphthoquinones, indonaphthoquinones, indolequinone and thionaphthoquinones. For example, furonaphthoquinones **3.75a-j** have been isolated from the Southern and Central American trees *Tabebuia cassinoides* (Lam.) DC. (Bignonisceae), *Tabebuia avellanedae*, *Crescentia cujete, L. achyrantifolia* and *Radermachera sinica*.[89-94] Each has been studied in biological screens and exhibited antileukemic activity, cytotoxic activity against KB, K562 and P388 cells (tumour cell) and *in vitro* antiprotozoan activity against *Trypanosoma cruzi*. Some of the crude extracts have been used as herbal medicines (Pau d'Arco, lp'e Roxo, Lapacho and Taheebo) due to their anticancer, antifungal, antibacterial and anti-inflammatory properties (**Table 3.11**).[95]



3.75

3.75	***R*^{1}**	***R*^{2}**	***R*^{3}**
a	$COCH_3$	H	H
b	$COCH_3$	OH	H
c	$COCH_3$	H	OH
d	$CH(OH)CH_3$	H	H
e	$CH(OH)CH_3$	OH	H
f	$CH(OH)CH_3$	H	OH
g	H	OH	H
h	H	H	OH
i	Et	H	H
j	$C(Me)=CH_2$	H	H

Table 3.11: Furanaphthoquinones **3.75** family.

Indonaphthoquinones **3.76** and indolequinones **3.77** are important heterocycles since they display a wide array of bioactivities including anticancer, cytotoxic and antibiotic activities. Indolequinones **3.78** and **3.79** have also found use in prodrug systems as they can release target drugs by bioreduction to hypoxia, which is a feature of several diseases, including cancer and rheumatoid arthritis.[96-98] Additionally, they were found as a core structure in various drugs and

biologically active compounds, such as mitomycin C[99] **3.80**, BE10988[100] **3.81**, (+)-terreusinone[101] **3.82** and EO9 (apaziquone)[102,103] **3.83** (**Table 3.12**). Since each can bind to multiple receptors with high affinity, indoles are considered to be privileged structures in medicinal chemistry.

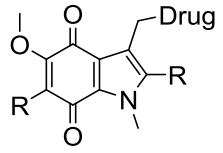
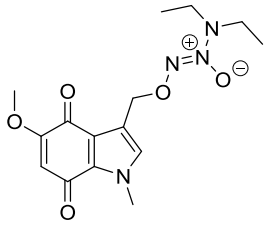
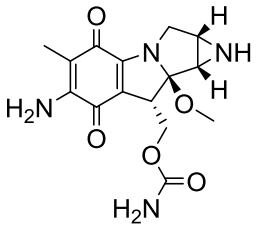
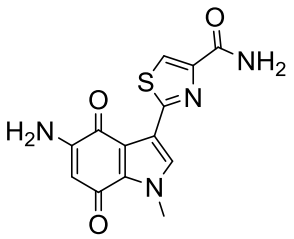
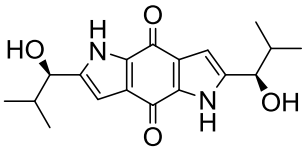
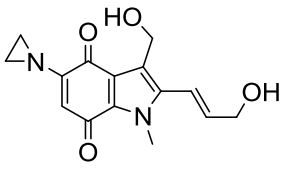
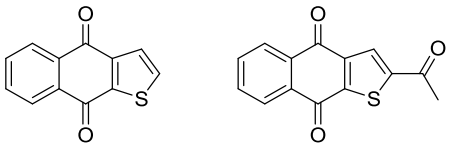
	structure	***Name***	***Bio activities***
3.78		/	anticancer prodrug (targeting NQ01, DT-diaphorase)
3.79		INDQ/NO	nitric oxide prodrug
3.80		mitomycin C	antitumor activity
3.81		BE10988	Inhibitor of topoisomerase
3.82		(+)-terreusinone	UV-A protecting properties
3.83		EQ9	DT-diaphorase-cytotoxicity

Table 3.12: Indonaphthoquinones or indolequinones compound **3.78**-**3.83**.

Studies on thionaphthoquinones **3.84a** and **3.84b** have also ungoverned cytotoxic activity against KB cells with a low ED_{50} value (**Scheme 3.21**).[104]



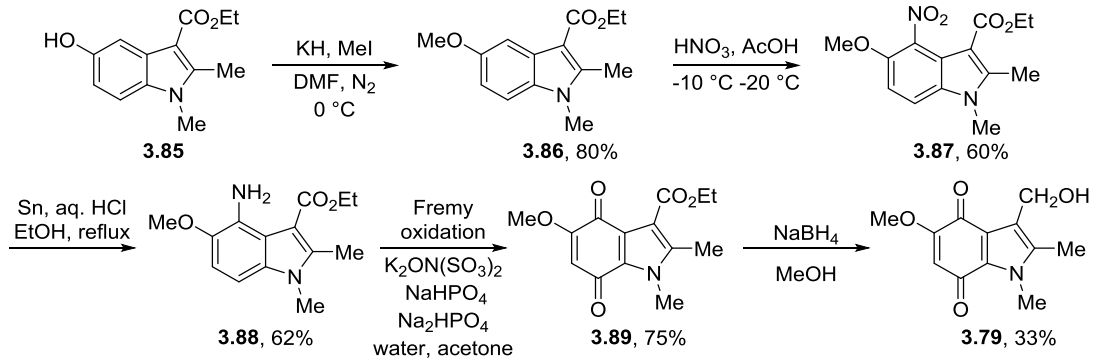
3.84a **3.84b**

Scheme 3.21: Thionaphthoquinones **3.84a** and **3.84b**.

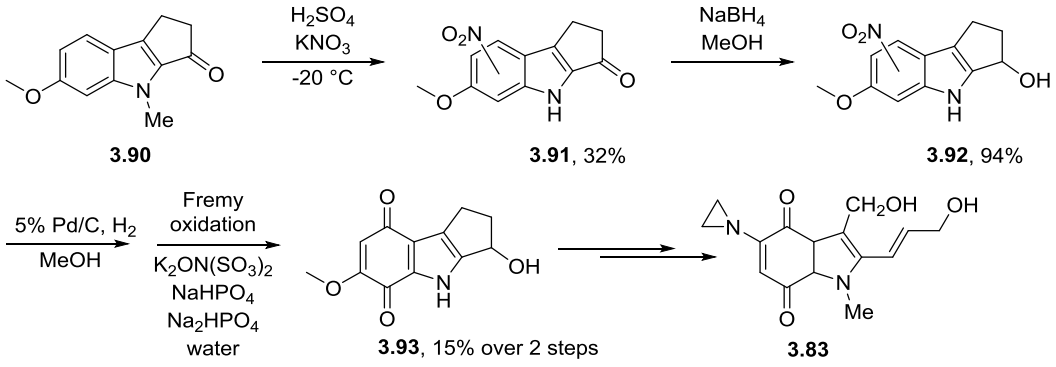
Despite their therapeutic potential, their synthesis has proven difficult due to the complexity of the naphthoquinone units. Therefore, it is worth developing effective methods for the synthesis and derivatization of heterocycle-fused quinones and naphthoquinones.

3.8.2 Former route

As mentioned, despite their therapeutic potential, a survey of the literature revealed that very few efficient and general methods have been reported to prepare both heterocycle-fused quinones and naphthoquinones.[105,106] First, oxidation of indoles was developed as an extension to a conventional method. For example, Threadgill *et al*. reported a synthesis of prodrug **3.79** by Fremy oxidation to form indolequinone (**Scheme 3.22**).[98] Xing *et al.* also used the same oxidation in their synthesis of EQ9 **3.83** (**Scheme 3.23**).[102] However, due to the harsh conditions employed there was little functional group tolerance and a low yield for the key step was observed.

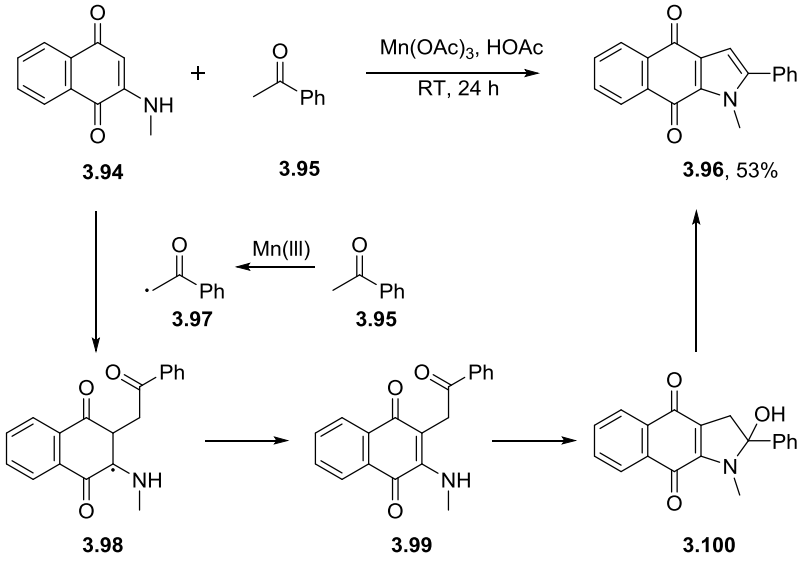


Scheme 3.22: Synthesis of prodrug **3.79**.



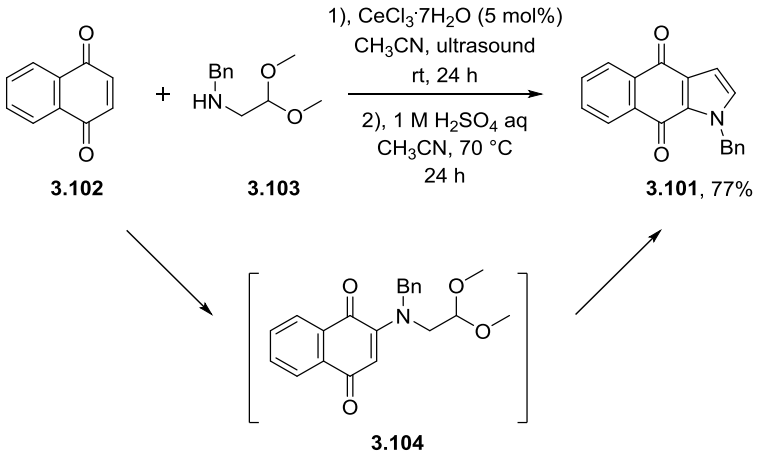
Scheme 3.23: Synthesis of EQ9 **3.83**.

In 2001, Lin *et al.* reported a route to 2-amino-1,4-naphthoquinone **3.96** using a manganese(III) initiated oxidative free radical addition reaction.[107] They suggested that the reaction began with a manganese(lll) acetate facilitated oxidation of acetophenone **3.95** to form radical intermediate **3.97**, followed by intermolecular addition to form **3.98** and oxidation to **3.99**. Finally, this intermediate underwent self-condensation to produce indolequinone **3.96** in 53% yield (**Scheme 3.24**).



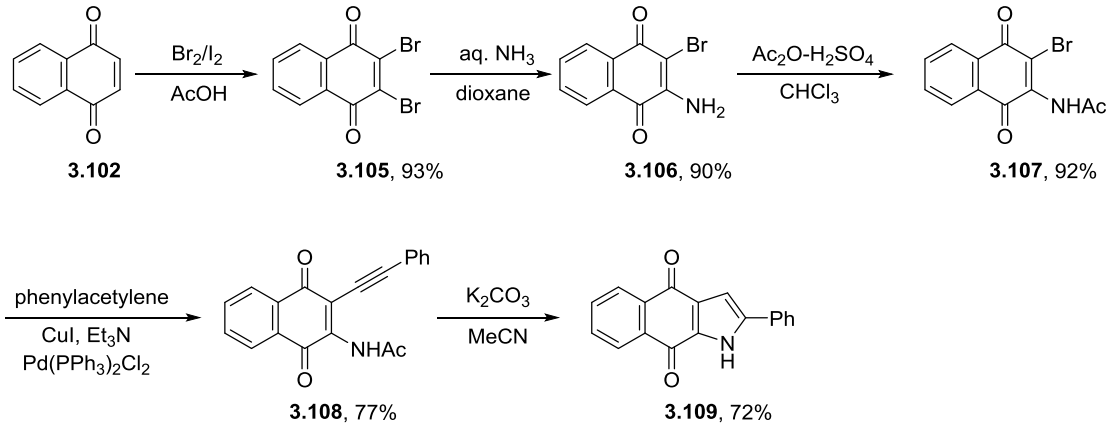
Scheme 3.24: Lin's procedure to form indolequinone **3.96**.

Recently, Mito *et al.* published a one-pot synthesis of indonaphthoquinone **3.101** from 1,4-naphthoquinone **3.102** with α-aminoacetals **3.103** (**Scheme 3.25**).[108] The first step was the amination of naphthoquinone **3.102** with $CeCl_3 \cdot 7H_2O$ as catalyst to form intermediate **3.104**. Treatment with H_2SO_4 at 70 °C then resulted in ring closure to indonaphthoquinone **3.101**. Again the reaction showed little functional group tolerance due to the use of strong acid at an elevated temperature.



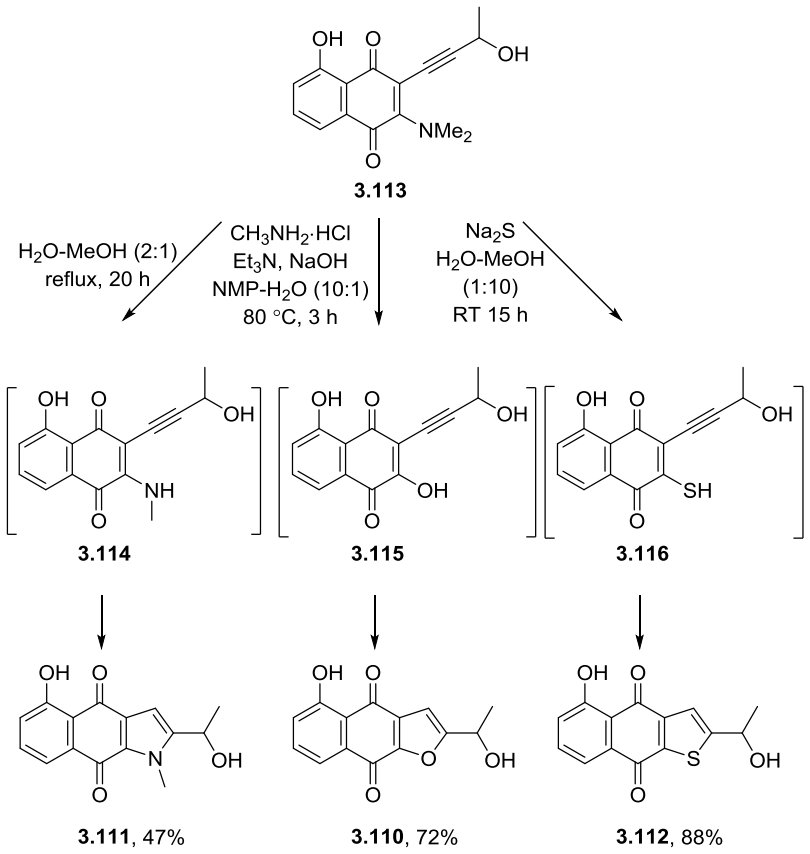
Scheme 3.25: One-pot synthesis to indonaphthoquinone **3.101**.

Shvartsberg *et al.* developed a highly efficient and mild way to make indonaphthoquinone by the intramolecular cyclisation of *ortho*-alkynylarylamines and amides.[109] Thus, the bromination of naphthoquinone **3.102** gave dibromonaphthoquinone **3.105**, then amination and protection yielded precursor **3.107**. A Sonogashira coupling with phenylacetylene next gave *ortho*-alkynylarylamine **3.108**, which underwent cyclisation to indonaphthoquinone **3.109** on heating in MeCN with K_2CO_3 (**Scheme 3.26**).



Scheme 3.26: Sonogashira coupling and cyclisation to form indonaphthoquinone **3.109**.

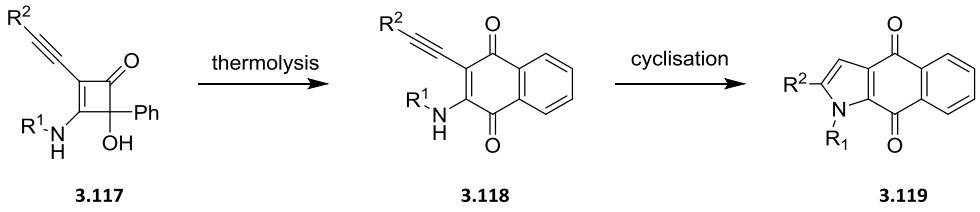
Based on Shvartsberg's work, Iida *et al.* reported a method to synthesise furonaphthoquinone **3.110**, indonaphthonone **3.111** and thionaphthoquinone **3.110** by cyclisation of *ortho*-alkynylarylamines **3.113** (**Scheme 3.27**).[110] The dimethylamino group of **3.113** can be easily replaced with hydroxide, secondary amino or sulfide groups to form intermediates **3.114**, **3.115** and **3.116**, which then cyclized to form the corresponding heterocycle-fused naphthoquinone. This method provides a mild and easily modifiable pathway for the synthesis of such naphthoquinones from alkynylaminonaphthoquinone **3.113**.



Scheme 3.27: Synthesis of hetero-fused naphthoquinones from alkynyl substituted aminoquinone.

3.8.3 Our approach

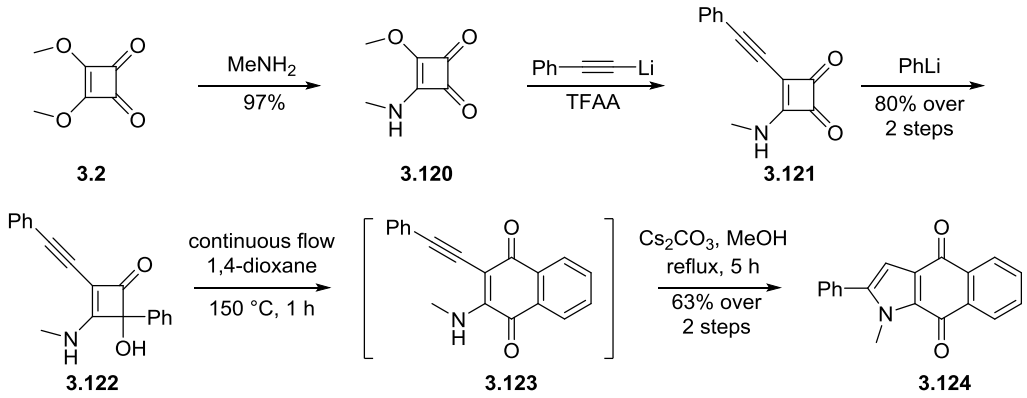
All previous syntheses have required either the use of forcing reaction conditions (acid and heating) or heavy metals. Thus, a protocol that was more benign environmentally would be a significant advantage. To that end, we have developed a new route to prepare heterocycle-fused naphthoquinone **3.119** from a commercially available cyclobutenedione (**Scheme 3.28**). In Section **3.3** we noted that thermolysis of a secondary-aminocyclobutenone resulted in quinone formation. It was therefore postulated that cyclobutenone **3.117** would give quinone **3.118** *via* thermal rearrangement, and that this could give access to indonaphthoquinone **3.119** by cyclisation.



Scheme 3.28: Our route to make indonaphthoquinone **3.119**

Our synthesis began with the amination of 1,3-dimethoxycyclobutenedione **3.2** to obtain amino-cyclobutenone **3.120** in 97% yield. Treatment with lithiated phenylacetylene and TFAA then afforded the aminocyclobutenedione **3.121.** Further treatment with PhLi next provided

arylcyclobutenone **3.122**, which on thermolysis under continuous flow gave quinone **3.123** as a dark red oil. This was then dissolved in MeOH and treated with Cs_2CO_3 at reflux for 5 h to successfully give indonaphthoquinone **3.124** in 63% yield (**Scheme 3.29**).

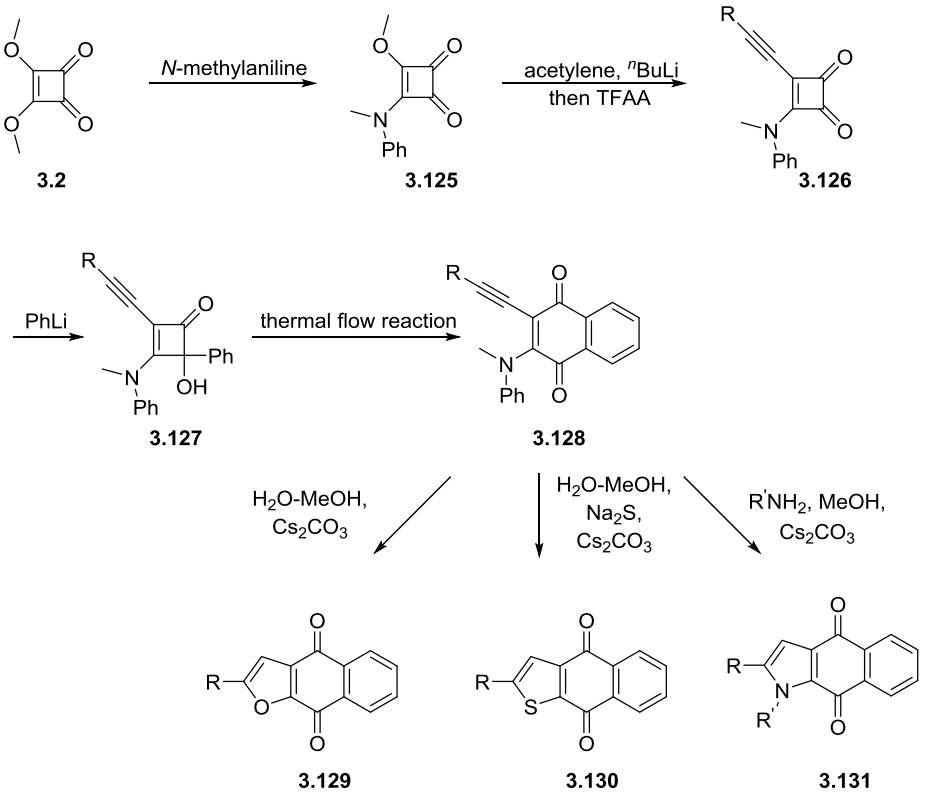


Scheme 3.29: synthesis the indonaphthoquinone **3.124**.

This short, high yielding synthesis requires minimal purification as intermediates can easily be obtained by trituration with Et_2O. Indeed, only the final indonaphthoquinone **3.124** required purification by column chromatography.

3.8.4 Future work

Following on from this work, we plan to probe the methodology further to synthesise furonaphthoquinones and thionaphthoquinones. We plan to proceed *via* anilinecyclobutenone **3.127** as this would be expected to form naphthoquinone **3.128** on thermolysis due to low steric hindrance bwtween the C2 and C3 residue. Treatment with different additives could then be used to access various heterocycle-fused naphthoquinones such as **3.129**, **3.130**, and **3.131** by an addition-elimination sequence followed by cyclisation (**Scheme 3.30**).



3.2 **3.125** **3.126** **3.127** **3.128** **3.129** **3.130** **3.131**

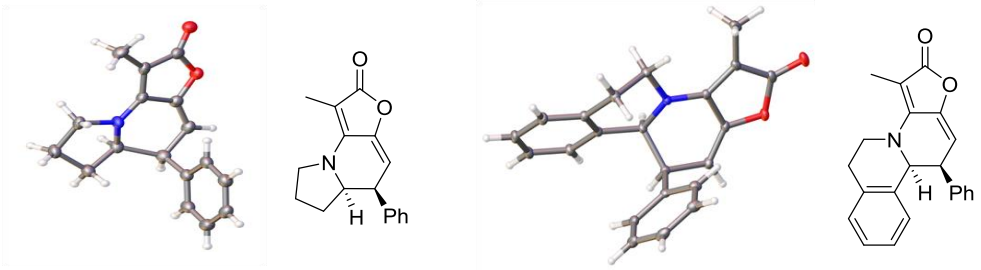
Scheme 3.30: Route to prepare several of hetero-fused naphthoquinones.

3.9 Conclusion

Thermolyses of tertiary aminocyclobutenones have been shown to form 5*H*-furanones in many systems. DFT calculations suggest that this switch in course from a classical Moore rearrangement pathway is caused by steric buttressing, which leads to a significant increase in the energy barrier for ring closure *via* a vinylketene intermediate. This was confirmed by further computational studies and experimental work on the rearrangement of ^{t}butylcyclobutenones. Therefore, for the thermolysis of cyclobutenone, steric buttressing between substituents at C2 and C3 can change the course of reaction from quinone or cyclopentenedione formation to 5*H*-furanone formation.

Chapter 4: Thermal C-H Activation Reaction

In **Chapter 3** we showed how thermolyses of aminocyclobutenones resulted in 5*H*-furanones as adverse steric interactions diverted such reactions away from classical Moore rearrangement pathways. In this chapter we would discuss our discovery of a new C-H activation reaction to transform those furanones into dihydrofuropyridinones (**Figure 4.1**).

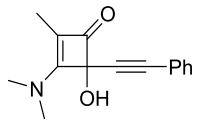
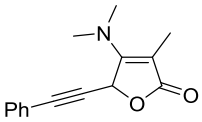
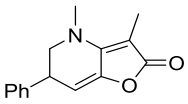
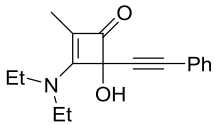
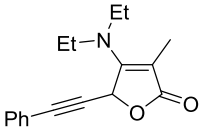
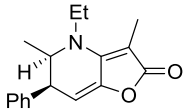
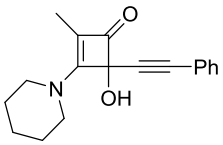
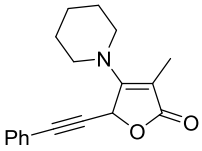
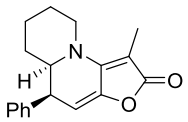
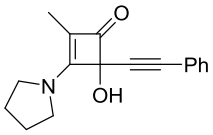
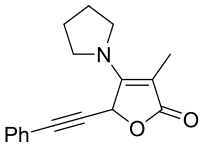
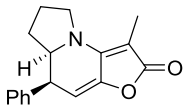
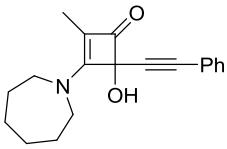
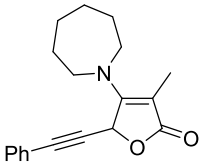
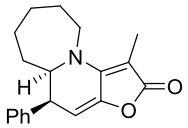
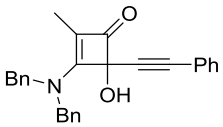
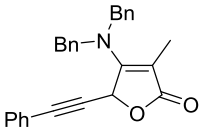
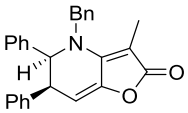
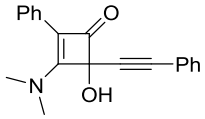
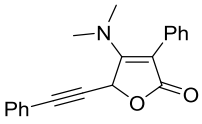
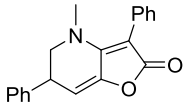
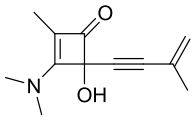
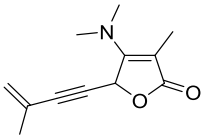
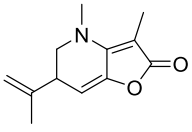


4.1h **4.26f**

Figure 4.1: X-ray diffraction structure of dihydrofuropyridinones **4.1h** and **4.26f**.

4.1 Thermal rearrangements of furanones

During the scoping phase of the aforementioned programme we found the optimisation of alkynylcyclobutenone rearrangements particularly challenging due, in part, to the formation of a persistent by-product, dihydrofuropyridinone **4.1** (**Table 4.1**).

Starting material	*Major product*	*By-product (Major stereoisomer drawn)*
 **3.4e**	 **3.9e**, 49%	 **4.1e**, 10%
 **3.4f**	 **3.9f**, 61%	 **4.1f***, 15%
 **3.4g**	 **3.9g**, 70%	 **4.1g***, 10%
 **3.4h**	 **3.9h**, 57%	 **4.1h***, 21%
 **3.4i**	 **3.9i**, 51%	 **4.1i***, 11%
 **3.4j**	 **3.9j**, 67%	 **4.1j***, 25%
 **3.4k**	 **3.9k**, 67%	 **4.1k**, 14%
 **3.4o**	 **3.9o**, 73%	 **4.1o**, 5%

*d.r. could not be determined from the crude ^{1}H-NMR spectrum due to the low yield of **4.1**

Table 4.1: Thermolyses of aminocyclobutenones **3.4e**-**o**.

To understand the nature of the formation of dihydrofuropyridinones **4.1**, further thermal flow reactions of aminocyclobutenone **3.4e** were run at different temperatures (**Figure 4.2**). The ratio of the two products given was determined by ^{1}H-NMR as the 5*H*-furanone **3.9e** presented a characteristic singlet at ~5.4 ppm while the dihydrofuropyridinone **4.1e** showed a characteristic doublet at ~5.5 ppm (**Table 4.2**).

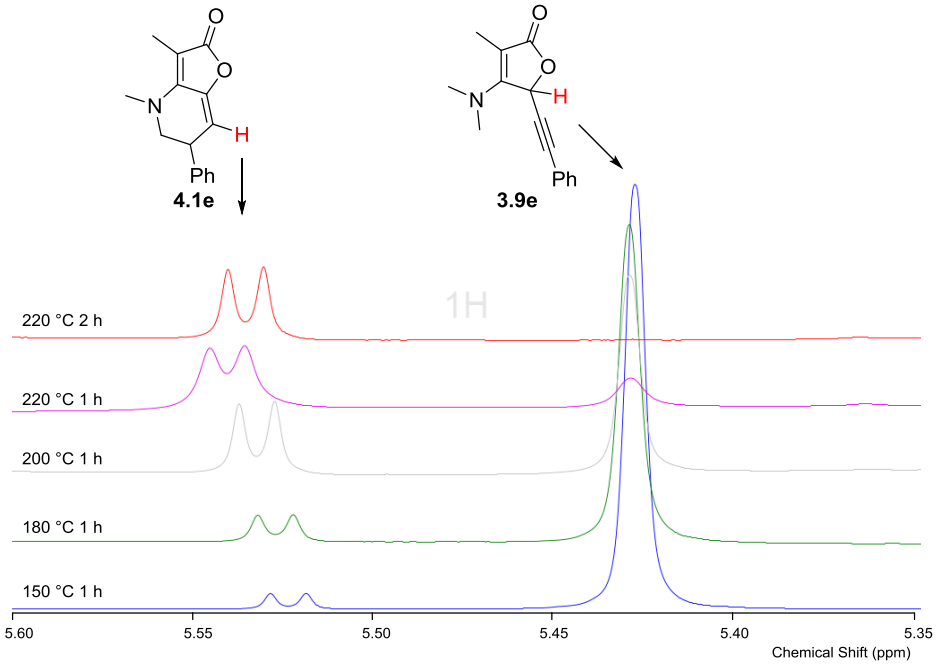


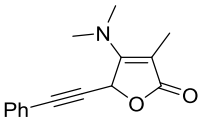
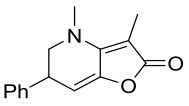
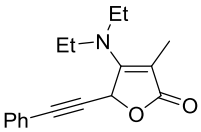
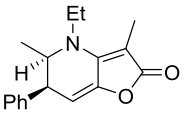
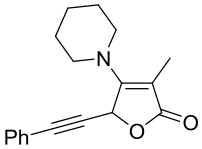
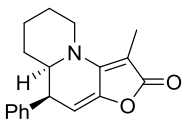
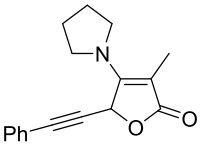
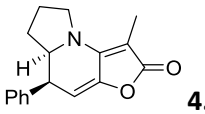
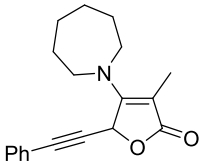
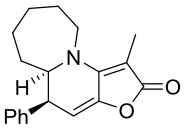
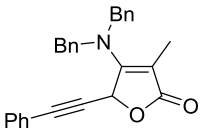
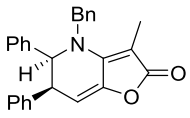
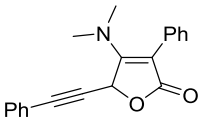
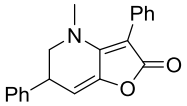
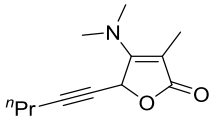
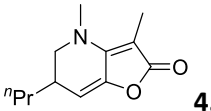
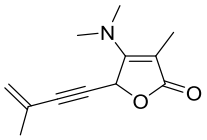
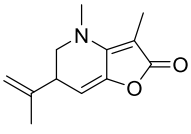
Figure 4.2: Detail from the ^{1}H-NMR spectra for thermolysis of aminocyclobutenone **3.9e** at different temperatures.

Entry	***Temperature (℃)***	***Time (h)***	***Conversion* 3.9e : 4.1e***
1	120	1	Start material recovered
2	150	1	22:1
3	180	1	9:1
4	200	1	2:1
5	220	1	0.3:1
6	220	2	Only **4.1e** observed
*ratios determined by ^{1}H-NMR analysis on crude product mixtures			

Table 4.2: Effects of different temperatures on the thermolysis of aminocyclobutenone **3.4e**.

With the increasing of temperature, the singlet peak corresponding to the 5*H*-furanone **3.9e** reduced while the doublet peak from dihydrofuropyridinone **4.1e** increased significantly. The result suggested that an increase of temperature favoured formation of dihydrofuropyridinone **4.1e** rather than 5*H*-furanone **3.9e**. As no furanone **3.9e** was detected at the higher temperature, it seemed highly likely that the dihydrofuropyridinone **4.1e** could be derived from 5*H*-furanone **3.9e**.

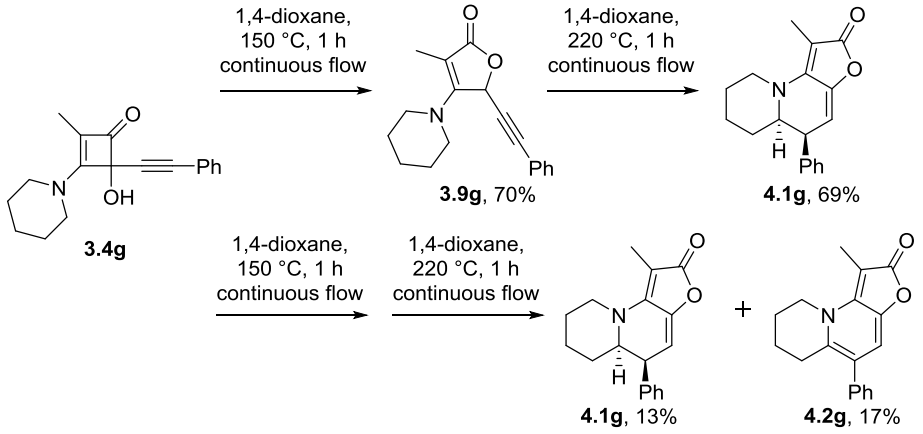
Indeed, when furanone **3.9e** in 1,4-dioxane was heated at 220 °C under continuous flow for a residence time of 2 h, it gave dihydrofuropyridinone **4.1e** in 83% yield. The scope of the reaction was next explored by heating various 5*H*-furanones **3.9** at 220 °C in 1,4-dioxane under continuous flow. On each occasion dihydrofuropyridinone **4.1** was given in good to excellent yield. As expected, analogues bearing an *N*,*N*-dimethylamino residue gave rise to a single dihydrofuropyridinone (**4.1e**, **4.1k**, **4.1m** and **4.1o**) while higher homologues and those bearing cyclic 3°-amines (**4.1f–j**) displayed useful diastereoselectivity (**Table 4.3**). These striking observations indicated that we had uncovered a new thermolysis reaction that transforms 5*H*-furanone **3.9** to dihydrofuropyridinones **4.1** *via* a metal-free CH-activation of the 3°-amino residue.

Starting material	*Product Major stereoisomer drawn*	*Reaction conditions*	*Yield 4.1 (%)*
 **3.9e**	 **4.1e**	**220 °C, 2 h continuous flow**	**83%**
 **3.9f**	 **4.3f**	**220 °C, 2 h continuous flow**	**80% d.r. * = 4 : 1**
 **3.9g**	 **4.1g**	**220 °C, 1 h continuous flow**	**69% d.r. * = 16 : 1**
 **3.9h**	 **4.1h**	**220 °C, 1 h continuous flow**	**86% d.r. * = 25:1**
 **3.9i**	 **4.1i**	**220 °C, 1 h continuous flow**	**79% d.r. * = 7 : 1**
 **3.9j**	 **4.1j**	**220 °C, 1 h continuous flow**	**76% d.r. * = 6 : 1**
 **3.9k**	 **4.1k**	**220 °C, 1 h continuous flow**	**76%**
 **3.9m**	 **4.1m**	**220 °C, 4 h (2 × 2 h) continuous flow**	**67% (+ 3.9m 7%)**
 **3.9o**	 **4.1o**	**220 °C, 2 h continuous flow**	**76%**

*d.r. determined by ^{1}H-NMR analysis on crude product mixtures

Table 4.3: Thermolyses of 5*H*-furanones **4.3a-i.**

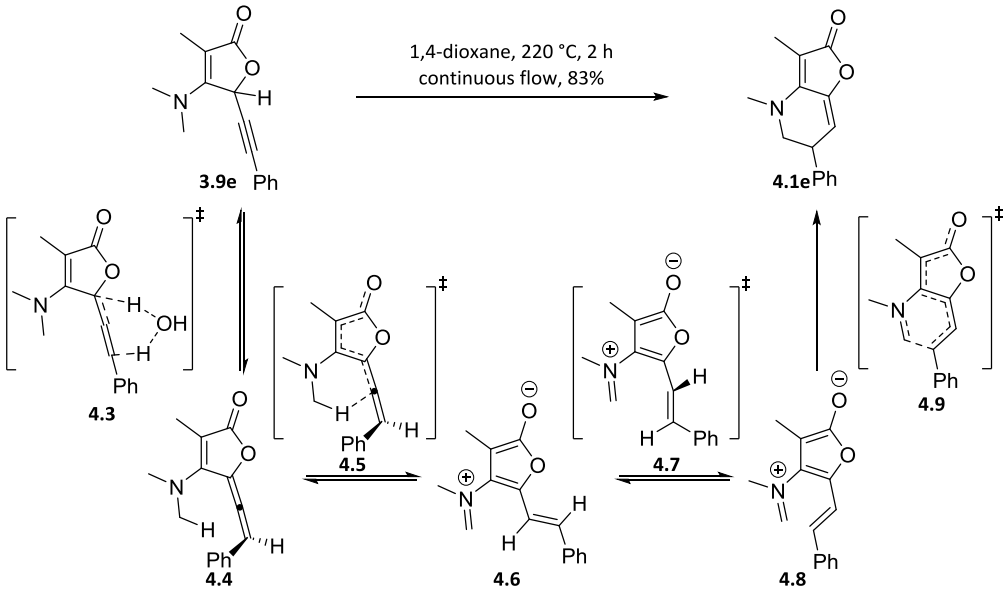
Notably, for the conversion of cyclobutenone **3.4g** to dihydrofuropyridinone **4.1g**, a higher yield was attained when the reaction was conducted in stages (i.e. heating at 150 °C, isolating furanone **3.9g** then heating at 220 °C) rather than as a continuous process (heating at 150 °C for 1 h then at 220 °C for 1 h). The appearance of furopyridinone **4.2g** as a by-product in these continuous processes suggests that some loss of product **4.1g** may be due to its oxidation (**Scheme 4.1**).



Scheme 4.1: Thermolysis of aminocyclobutenone **3.4g**.

4.2 Mechanism

The previous result suggested that a C-H activation of the amine had occurred due to its proximity to the alkyne group and this had induced formation of the dihydrofuropyridinones **4.1.** A plausible mechanism for the rearrangement was outlined below (**Scheme 4.2**).

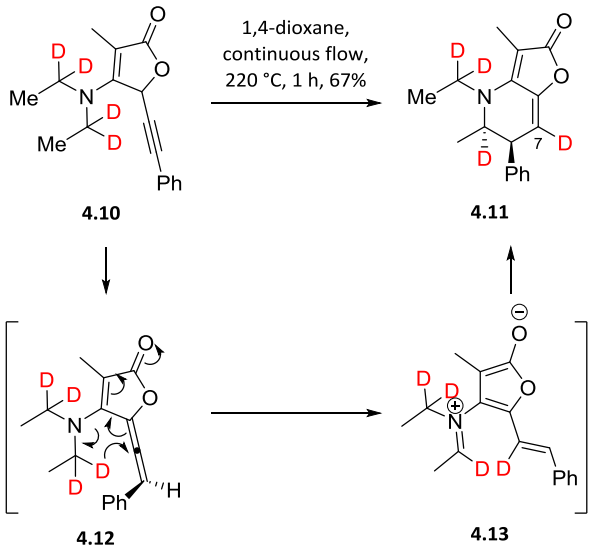


Scheme 4.2: Plausible mechanism for the rearrangement of 5*H*-furanone **3.9e** to dihydrofuropyridinone **4.1e**.

We presume that the rearrangement first involves a 1,3-hydride shift in the alkynyl chain to form allene **4.4**. This step can be catalysed by trace water in the solvent *via* formation of a hydrogen-bonded bridge between the reacting centres (transition state **4.3**). Then a 1,5-hydride shift can be envisioned leading to the zwitterion **4.6**, which rotates to reactive conformer **4.8**. Finally, zwitterion **4.8** undergoes a ring closure by electro-cyclisation to afford the dihydrofuropyridinone **4.1e**.

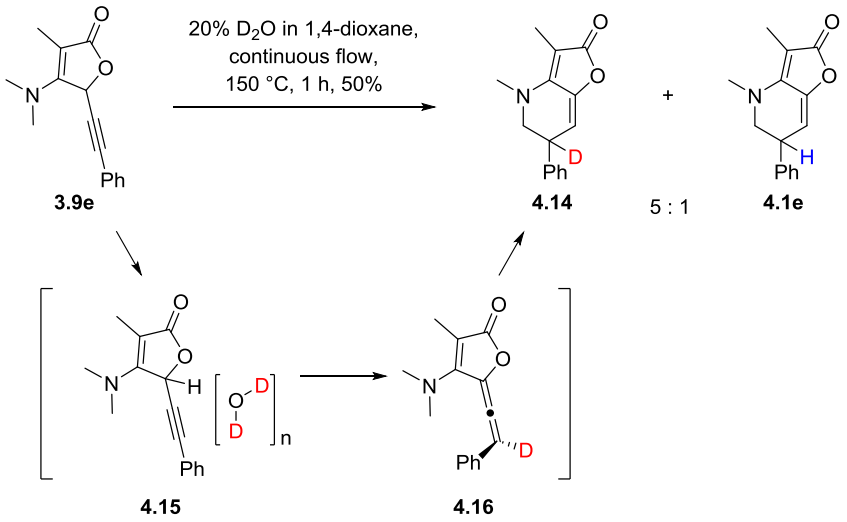
4.3 Deuterium labelling study

To better understand the mechanistic course of the reaction, two isotope labeling experiments were conducted. Firstly, tetradeuterated aminofuranone **4.10** was thermolysed at 220 °C for 2 h under continuous flow to give tetradeuterated dihydrofuropyridinone **4.11** in 67% yield. Pleasingly, the isotope pattern observed in the product was consistent with our proposed mechanism (**Scheme 4.3**).



Scheme 4.3: Deuterium labelling study of aminofuranone **4.10**.

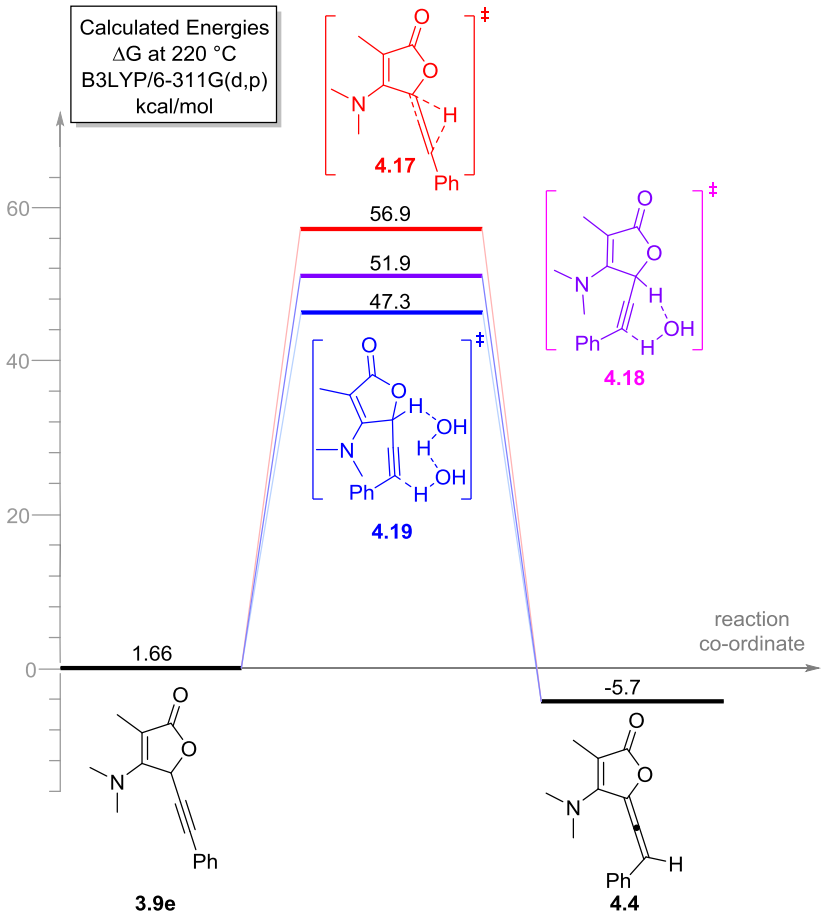
We also effected the thermolysis of aminofuranone **3.9e** in 1,4-dioxane doped with 20% D_2O. This produced mono-deuterated dihydrofuropyridinone **4.14** as the major product, thereby confirming a role for water in the alkyne to allene isomerisation step (**Scheme 4.4**).



Scheme 4.4: Deuterium labelling study of aminofuranone **3.9j**.

4.4 Computational study on the C-H activation reaction

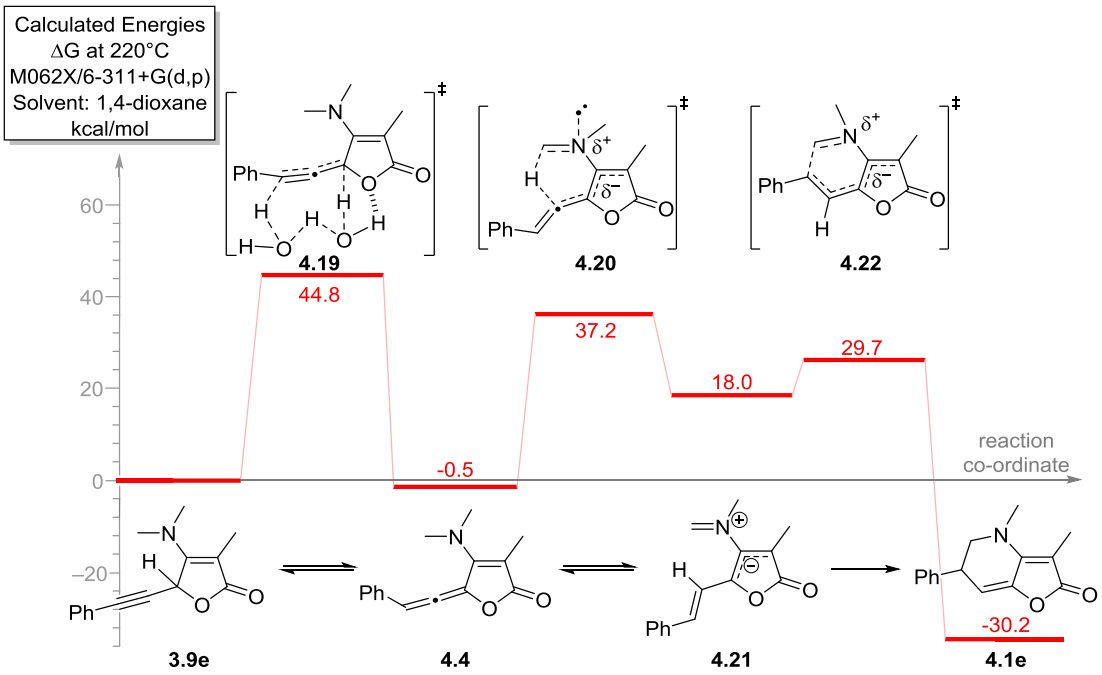
DFT calculations were next performed to assess whether our proposed mechanism for the rearrangement was reasonable (**Scheme 4.2**). First, we tried to determine how the 1,3-hydride shift step proceeded (**3.9e** → **4.4**). According to Woodward-Hoffmann rules, a 1,3-hydride shift is antarafacial, which, although symmetry allowed, is impossible geometrically due to the Möbius topology required in the transition state. Meanwhile, an anti-Woodward-Hoffmann suprafacial hydride shift would require an extremely high energy to proceed. Indeed the energy barrier to effect the isomerisation of alkyne **3.9e** to allene **4.4** was determined to be 56.9 kcal/mol even at 220 °C. Further calculations were performed by considering a water bridged transition state (**Scheme 4.5**). The transition state containing two bridging H_2O molecules (**4.19)** gave the lowest energy barrier at 47.3 kcal/mol, which was nearly 10 kcal/mol lower than transition state **4.17**. Other transition states containing more water molecules or with solvent (1,4-dioxane) are possible but until now no reasonable transition state structure has been found. Additionally, H-tunnelling was not considered in these calculations. Though this is normally associated with low temperature reactions, it could still decrease the energy required in the 1,3-hydride shift. Notwithstanding these factors, we presume that the 1,3-hydride shift step proceeds with water assisting the process akin to that depicted in transition state **4.19** (or **4.18**).



Scheme 4.5: Energy diagram for the 1,3-hydride shift. B3LYP/6-311G(d,p), temperature=493.15 K.

DFT calculations were then performed for the full reaction (**Scheme 4.6**). To achieve an accurate depiction of the new annulation reaction, solvent effects were considered by applying the IEF-PCM model. Optimization with a tight convergence and an ultrafine integral were employed to ensure adequate convergence and reliability of frequencies.

DFT calculations predicted a reaction pathway similar to our postulated mechanism (**Scheme 4.2**). Specifically, DFT calculations implied that zwitterion **4.21** formed **4.1e** in a single step via bond rotation and ring closure (transition state **4.22**) rather than in two stages *via* transition states **4.7** and **4.9**. The 1,5-hydride transfer (**4.4** → [**4.20**] → **4.21**) was found to have a higher energy barrier than the bond rotation and ring closure step (**4.21** → [**4.22**] → **4.1e**) with both being lower than that required for the rate-limiting alkyne to allene isomerisation (**3.9e** → [**4.19**] → **4.4**). In the bond rotation transition state **4.22**, the alkene bond rotated from *transoid* to *cisoid* and in the process underwent spontaneous ring closure to form the dihydrofuropyridinone **4.1e**. Notably, the calculated barrier for the reaction was also consistent with that implicated by experiment.



Scheme 4.6: Energy diagram for thermal rearrangement of furanone **3.9e**.

M062X/6-311+G(d,p), temperature=493.15K, scrf=IEFPCM=1,4-dioxane, opt=tight, int=ultrafine

The whole reaction process (**3.9e** → **4.1e**) was also examined by NBO analysis. Conformational screening of the lowest energy conformation of the starting material **3.9e** shows a high interaction energy between the lone pair of electrons on nitrogen and the π* orbital (C2-C3), which implied a strong conjugation between the amino group and the furanone ring (**Figure 4.3**).

In transition state **4.19**, the alkyne chain C4-C5-C6 and the two water molecules constitutes an eight membered ring transition state. NBO analysis shows the C4-H10 bond is weaken by the interaction with the π* orbital (C2-C3) and the π* orbital (C5-C6). In this transition state, the amino residue is still conjugated with the furanone ring (**Figure 4.3**).

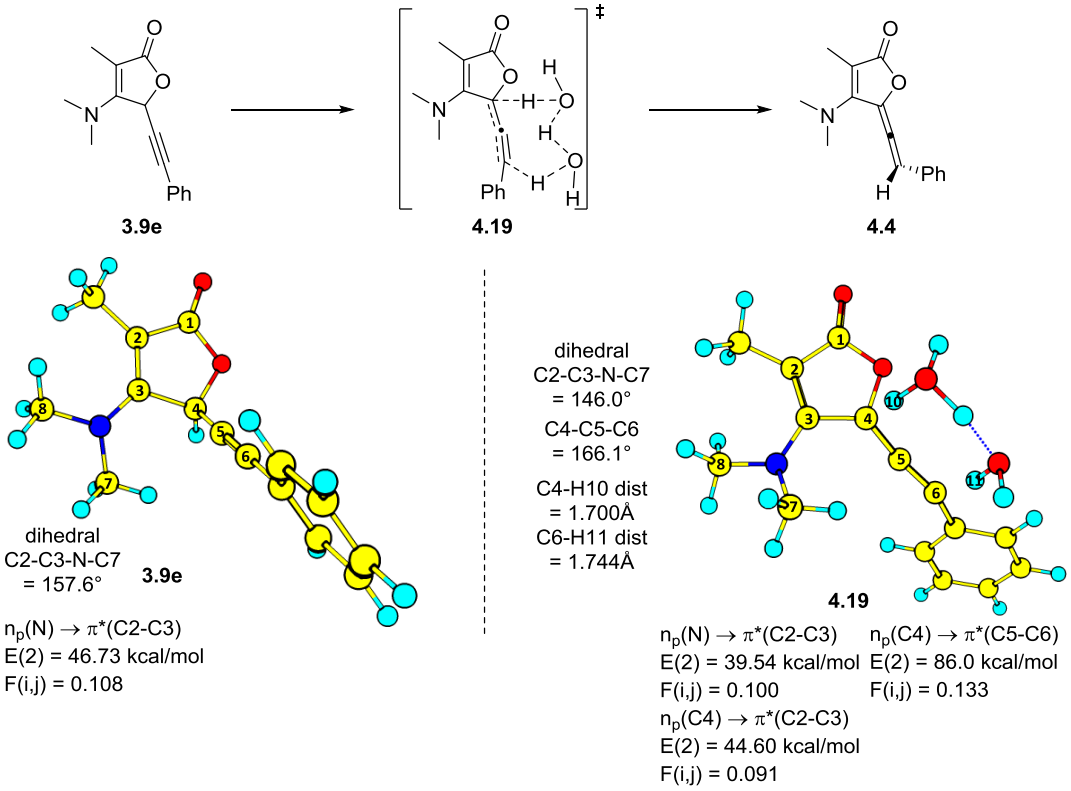


Figure 4.3: Geometry of the lowest energy conformation of furanone **3.9e** and TS **4.19**.

Geometry and NBO at B3LYP/6-311G(d,p)

Allene **4.4** shows a high positive charge associated with the central carbon (C5) and the amino group still shows significant conjugation to the furanone ring (**Figure 4.4**).

In transition state **4.20**, a hydride moves from C7 to C5 in the allene moiety. The interaction energy between the lone pair of electrons on N and the breaking C7-H9 anti-bond is 8.61 kcal/mol, indicating that the lone pair of electrons on N was a key driving force behind this hydride shift. Indeed, its 'lone pair' is aligned anti to the breaking CH bond. The forming C5-H9 σ bond showed a strong interaction with π* orbital from either C4-C5 or C5-C6, providing another driving force for this hydride shift. Moreover, the breaking C7-H9 bond distance is 1.492 Å while the new C5-H9 distance is 1.274 Å, indicating a late transition state (**Figure 4.4**).

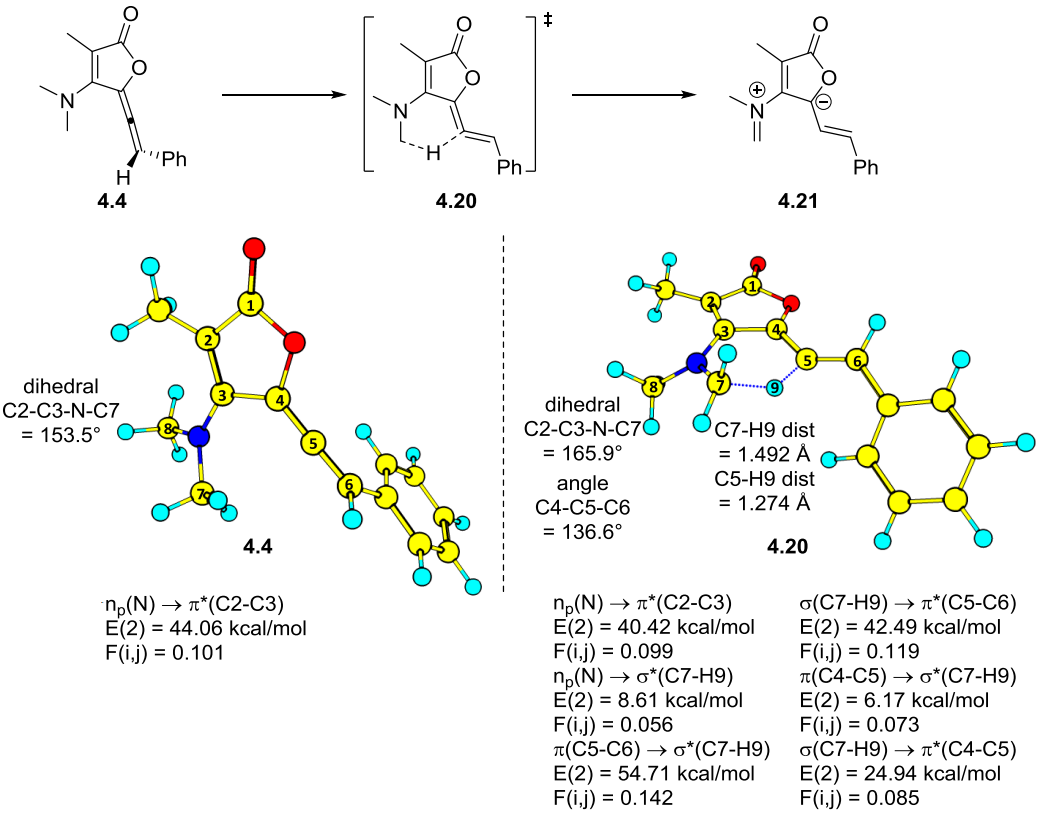


Figure 4.4: Geometry of the lowest energy conformation of allene intermediate **4.4** and TS **4.20**.

Geometry and NBO at B3LYP/6-311G(d,p)

After the 1,5-hydride shift, intermediate **4.21** is formed as a zwitterion. The negative charge is primary located on C4, which is stabilized by both the C2-C3 double bond and the C5-C6 double bond as evidence by the high interaction energies (70.94 kcal/mol and 44.91 kcal/mol) (**Figure 4.5**). The new iminium intermediate shows only weak conjugation with the C2-C3 bond with a small interaction energy to π* orbital (C2-C3). The C4-C5 bond next rotated to allow the C5-C6 double bond to come close to the iminium group N-C7.

In this transition state (**4.22**), conjugation between the furanone ring and the C5-C6 alkene is broken. Consequently, NBO analysis suggests that the pair of electrons is largely located at C2, stabilized by the adjacent carbonyl group C1-O11 and double bond C3-C4 (**Figure 4.5**). IRC of transition state **4.22** suggests that the ring closure step between the iminium and C5-C6 will happen spontaneously without any further transition state. As a result, transition state **4.22** will give the final product directly.

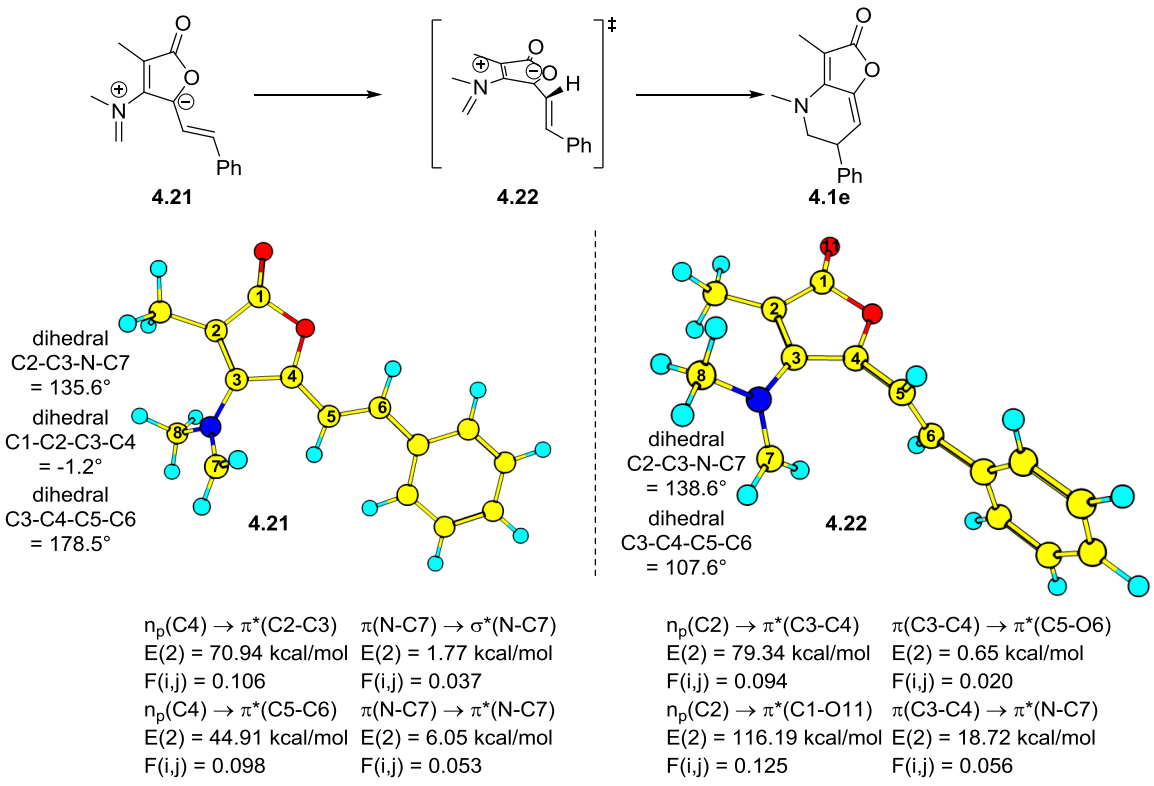


Figure 4.5: Geometry of the lowest energy conformation of intermediate **4.21** and TS **4.22**.

Geometry and NBO at B3LYP/6-311G(d,p)

In the dihydrofuropyridinone product **4.1e**, the lone pair of electrons on nitrogen exhibits very strong conjugation to the furanone ring, indicating a sp^2 hybridised nitrogen (Figure **4.6**).

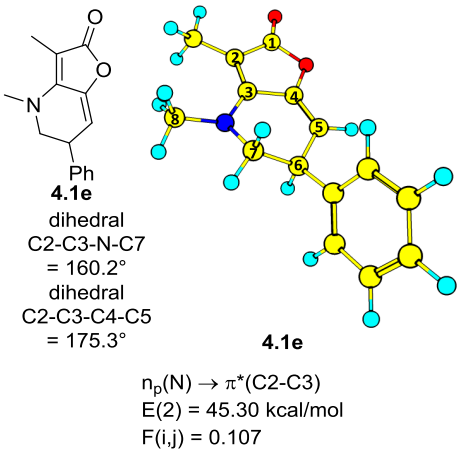


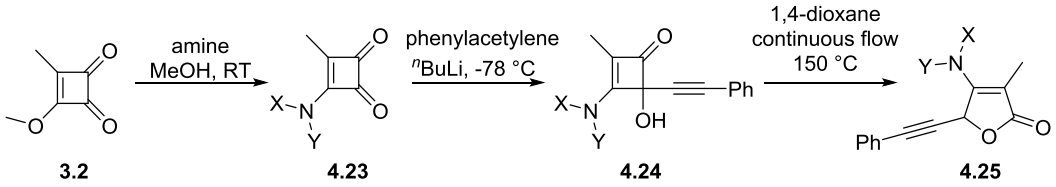
Figure 4.6: Geometry of the lowest energy conformation of product **4.1e**.

Geometry and NBO at B3LYP/6-311G(d,p)

In conclusion, DFT calculations showed that there were three steps in the new annulation sequence: a water catalysed 1,3-hydride shift; a 1,5-hydride shift and a final concomitant bond rotation with ring closure step. All three showed a high energy barrier compared with the energy required for thermal rearrangement of amino cyclobutenones, which explained the high temperature requirement for the new C-H activation and annulation sequence.

4.5 Regioselectivity in the thermal C-H activation reaction

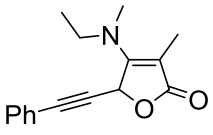
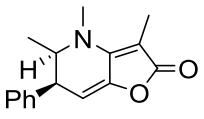
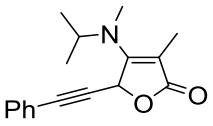
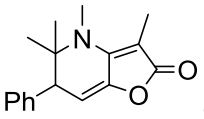
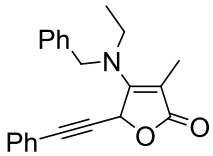
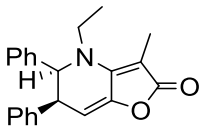
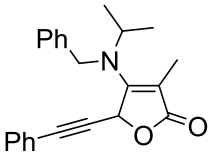
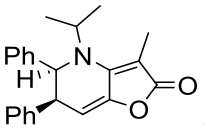
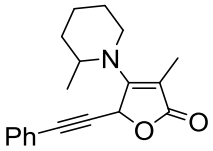
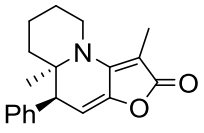
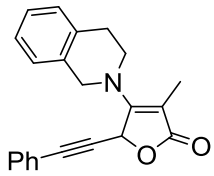
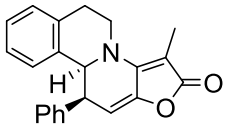
To probe the mechanism of the unusual C-H activation reaction further we decided to examine cases where the amine residues were different. These unsymmetrical furanones **4.25** were synthesized using the same method as described in **Section 3**.1. In these reactions, dihydrofuropyridinones **4.26** were found as by-products (**Table 4.4**).



	X =	*Y=*	*Yield 4.23 (%)*	*Yield 4.24 (%)*	*Yield 4.25 (%)*	*Yield 4.26 (%)*
a	Me	Et	100	93	71	/
b	Me	^{i}Pr	92	92	72	11
c	Et	Bn	91	78	40	37
d	^{i}Pr	Bn	90	82	82	11
e	2-methylpiperidine		57	83	65	22
f	1,2,3,4-tetrahydro-isoquinoline		97	81	50	19

Table 4.4: Synthesis of unsymmetrical furanone **4.25**.

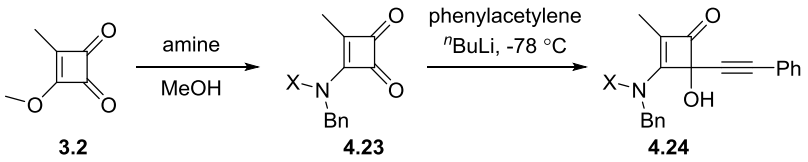
The resulting furanones **4.25** were subjected to thermal flow reaction at 220 °C for 1 h and all gave dihydrofuropyridinones **4.26** as the principle product in a high yield and with excellent regioselectivity (**Table 4.5**). In each case the newly created ring was formed to the amine residue bearing the weakest C-H bond with insertion following the sequence: Bn > 3°-alkyl > 2°-alkyl > 1°-alkyl > Me.

Starting material	*Product. Major stereoisomer drawn*	*Reaction conditions*	*Yield 4.24 (%)*
 **4.25a**	 **4.26a**	**220 °C, 2 h continuous flow**	**78% d.r. = 5 : 2**
 **4.25b**	 **4.26b**	**220 °C, 2 h continuous flow**	**75%**
 **4.25c**	 **4.26c**	**220 °C, 1 h continuous flow**	**78% d.r. = 4 : 1**
 **4.25d**	 **4.26d**	**220 °C, 1 h continuous flow**	**77% d.r. > 25 : 1**
 **4.25e**	 **4.26e**	**220 °C, 1 h continuous flow**	**79% d.r. = 15 : 1**
 **4.25f**	 **4.26f**	**220 °C, 1 h continuous flow**	**80% d.r. = 10 : 3**

*d.r. detected from the crude ^{1}H-NMR

Table 4.5: Thermolyses of furanones **4.21**.

Then, a series of differentially substituted dibenzylamino-analogues **4.23g-k** were synthesised by the same method (**Table 4.6**).

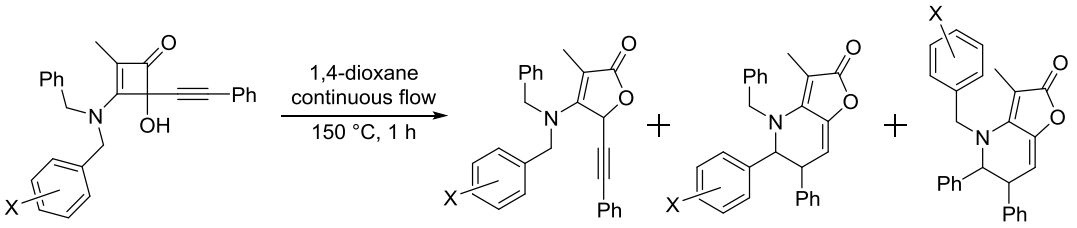


3.2 **4.23** **4.24**

	X =	***Yield 4.23 (%)***	***Yield 4.24 (%)***
g	2,4,6-trimethoxybenzyl	80	88
h	4-methoxybenzyl	100	80
i	4-fluorobenzyl	96	86
j	3-fluorobenzyl	97	87
k	4-nitrobenzyl	70	100

Table 4.6: Synthesis of aminocyclobutenones **4.23** and **4.34**.

Thermolyses of these aminocyclobutenones **4.24g-k** were conducted under flow at 150 °C for 1 h. Reactions afforded a complex mixture of products that were difficult to separate by column chromatography. We therefore assessed the regioselectivity of the dihydrofuropyridinones products **4.26** and **4.27** by ^{1}H-NMR as each showed a characteristic doublet at ~5.5 ppm region **(Table 4.7)**. Attribution of each of the doublets was confirmed by H-H cosy, HSQC and HMBC NMR. Though some exhibited reasonable regioselectivity (up to 6 : 1) and diastereoselectivity (up to 6 : 1), all gave rise to complex isomeric mixtures that were not amenable to separation by column chromatography and HPLC.



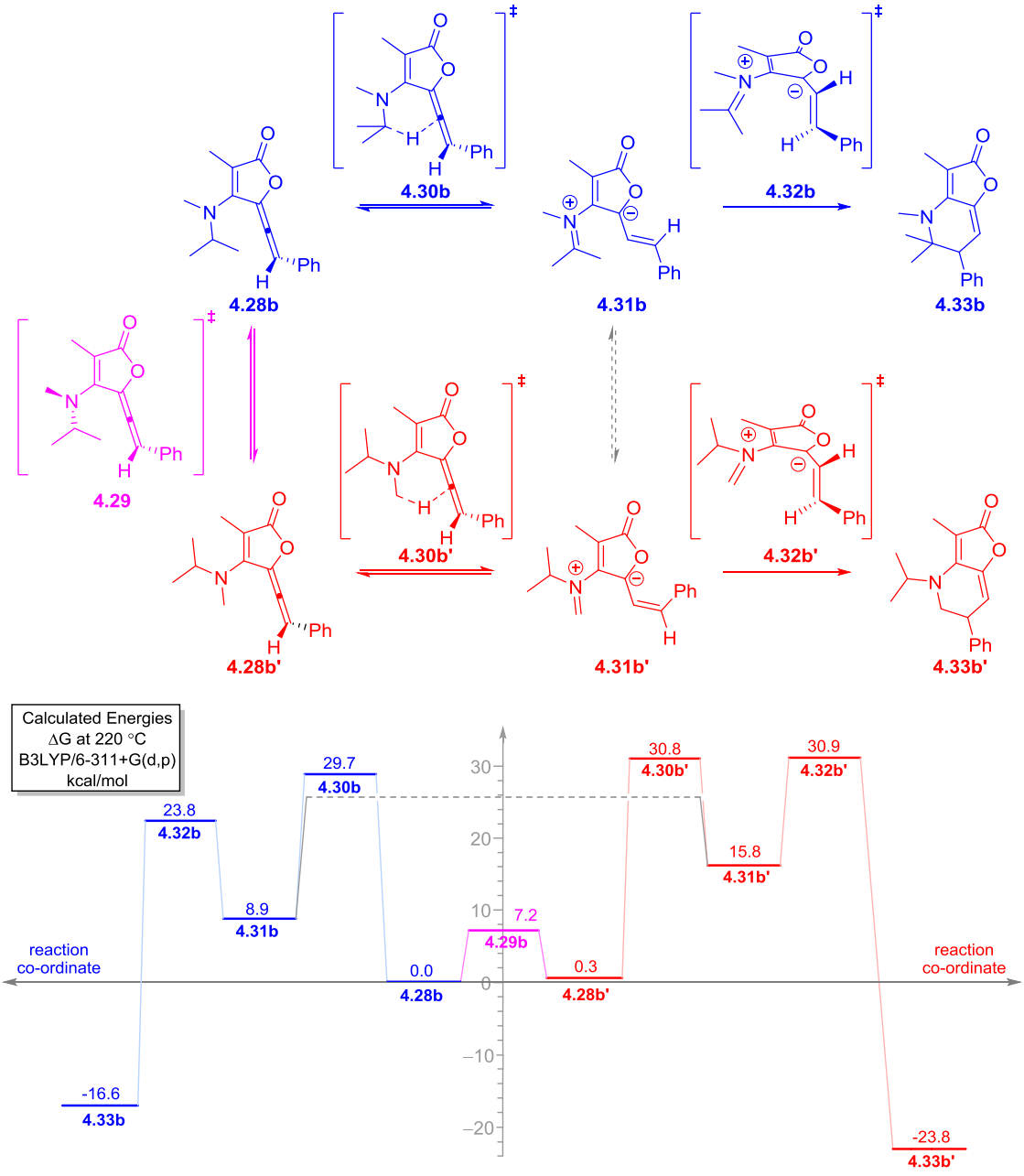
4.24 **4.25** **4.26** **4.27**

4.24	**Yield 4.25 %**	**Total yield of 4.26 & 4.27 %**	**Product ratio* 4.26 : 4.27**
g	66	16	6 : 1
h	53	33	1 : 1
i	60	17	7 : 1
j	59	15	1 : 1
k	65	20	3 : 1
* determined by ^{1}H-NMR analysis on crude product mixtures			

Table 4.7: Result of thermolysis of aminocyclobutenone **4.24g-k**.

To determine the nature of regioselectivity in the new thermal CH-activation reaction, further DFT calculations were conducted (**Scheme 4.7**). Since the 1,3-hydride shift step occurs on the alkynyl chain and has no impact on the regioselectivity, we started our calculations from the allene intermediate **4.28b** and the rotamer **4.28b'**, which can interconvert *via* transition state **4.29** with a low energy barrier (7.2 kcal/mol). In the 1,5-hydride shift step, both pathways showed a high energy barrier with transition state **4.30b** (29.7 kcal/mol) being 1.1 kcal/mol lower than transition state **4.30b'** (30.8 kcal/mol), suggesting that at this step intermediate **4.30b** will be favoured. Intermediate **4.31b** showed a significantly lower energy (8.9 kcal/mol) than the corresponding intermediate **4.31b'** (15.8 kcal/mol), which can be attributed to the fact that 2-propaniminium is more stable than methaniminium. For the same reason, the ring closure transition state **4.32b** showed a lower energy (23.8 kcal/mol) than transition state **4.32b'** (30.9 kcal/mol). In fact, transition state **4.32b'** showed the highest energy barrier in the rearrangement (30.9 kcal/mol).

Moreover, although a suprafacial 1,3-hydride shift (**4.31b** ⇋ **4.31b'**) is forbidden by Woodward-Hoffman rules, a few studies have revealed that it can happen *via* a water bridge, solvent bridge or even between two molecules at a modest temperature. Therefore there would be a plausible pathway by which intermediate **4.31b'** can be transformed into **4.31b** *via* a 1,3-hydride shift at a relatively low temperature.



Scheme 4.7: Energy diagram for the thermal annulation reaction of allene **4.28b**.

In conclusion, DFT analysis of the two pathways available for the rearrangement of an unsymmetrical furanone **4.25b**, found that the regiochemical course was determined by three factors.

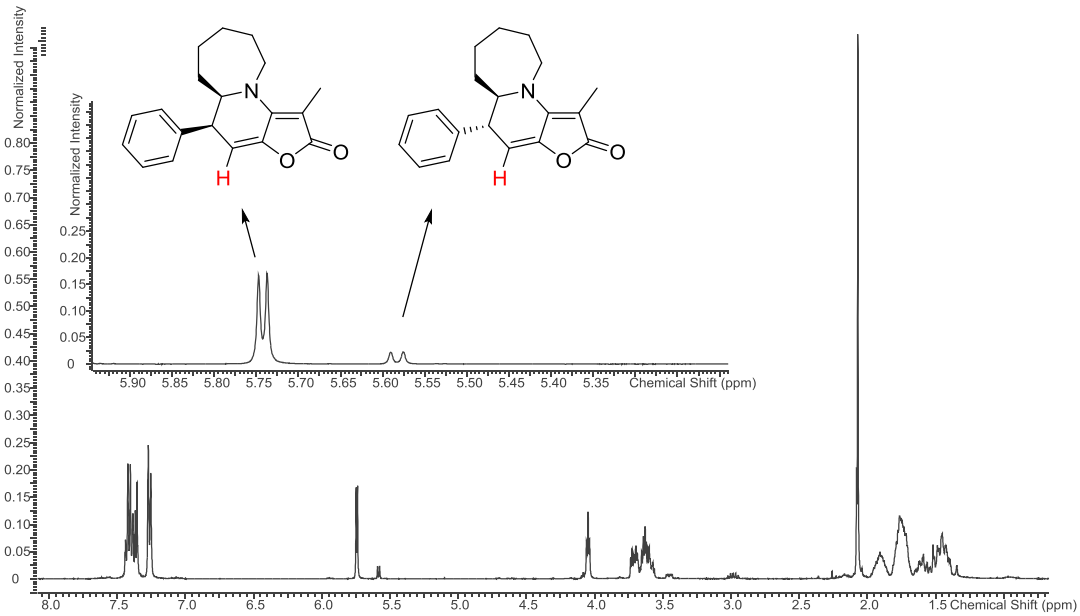
1. In the 1,5-hydride shift step, transfer occurs from the nitrogen substituent with the weaker C-H bond (**4.30**) as this has a lower energy barrier than hydride transfer from the substituent with the stronger C-H bond (**4.30b'**).
2. Formation of a stable iminium group can significantly decrease the energy barriers for formation of intermediate **4.31** and transition state **4.32**.

3. Interconversion of intermediates **4.31** and **4.31'** is implicated by the high energy differences between them and may contribute to the high regioselectivity exhibited.

The results attained by DFT calculation matched our experimental observations for the thermal C-H annulation of unsymmetrical 4-aminofuranones, where cyclisation to the amine residue bearing the weakest CH bond was favoured.

4.6 Stereoselectivity in the Thermal C-H activation reaction

In Sections **4.3** and **4.5**, it was noticed that some of the thermal annulation reactions of 4-aminofuranones (**4.1f-j**, **4.26a** and **4.26c-f**) gave a mixture of diastereoisomers with high stereoselectivity. The two diastereoisomers can be easily seen in the ^{1}H-NMR spectrum as each gives rise to a doublet at ~5.5 ppm (**Scheme 3.23**).



Scheme 4.8: Crude ^{1}H-NMR of the thermolysis of furanone **4.1i**.

From analyses by X-ray diffraction (Figure **4.10**) and by comparison of the coupling constant in the ^{1}H-NMR spectrum, the major diastereoisomer was confirmed as the *cis*-dihydrofuropyridinone **4.34** and the minor one as the *trans*-dihydrofuropyridinone **4.35** (**Scheme 4.9**).

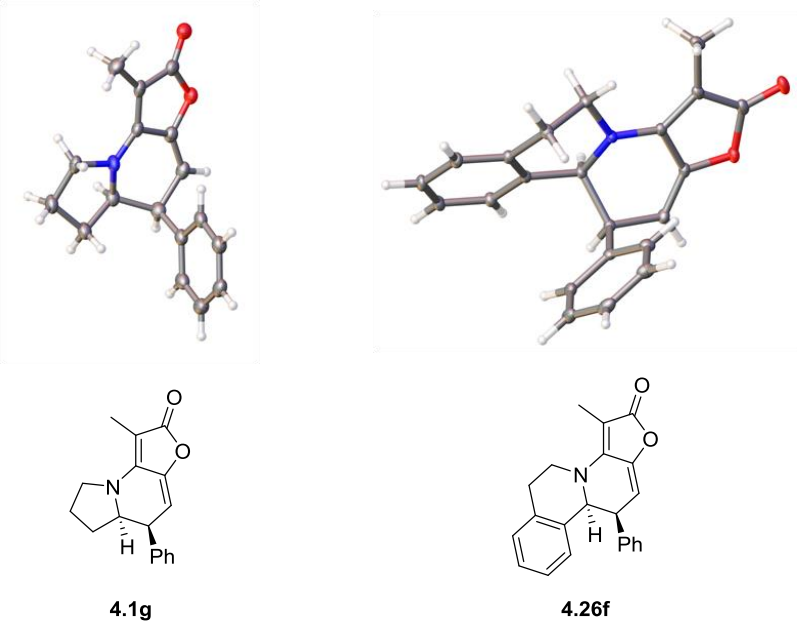
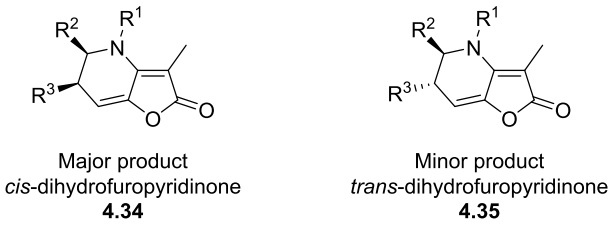
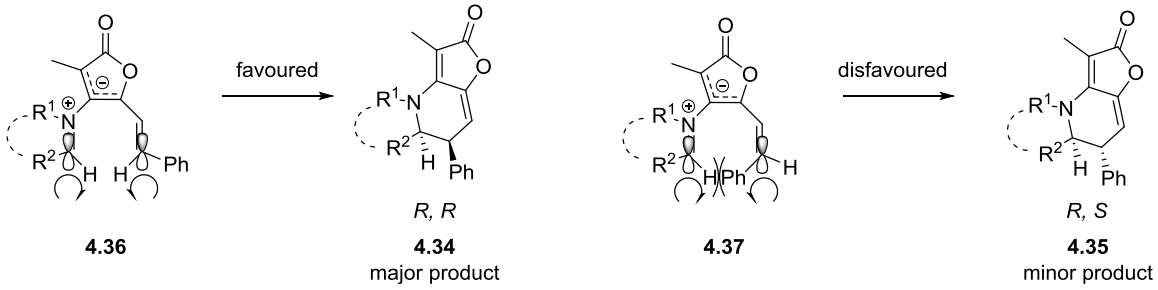


Figure 4.7: X-ray crystal structure for the major diastereoisomer in **4.1g** and **4.26f**.



Scheme 4.9: Diastereoselectivity of the annulation reaction.

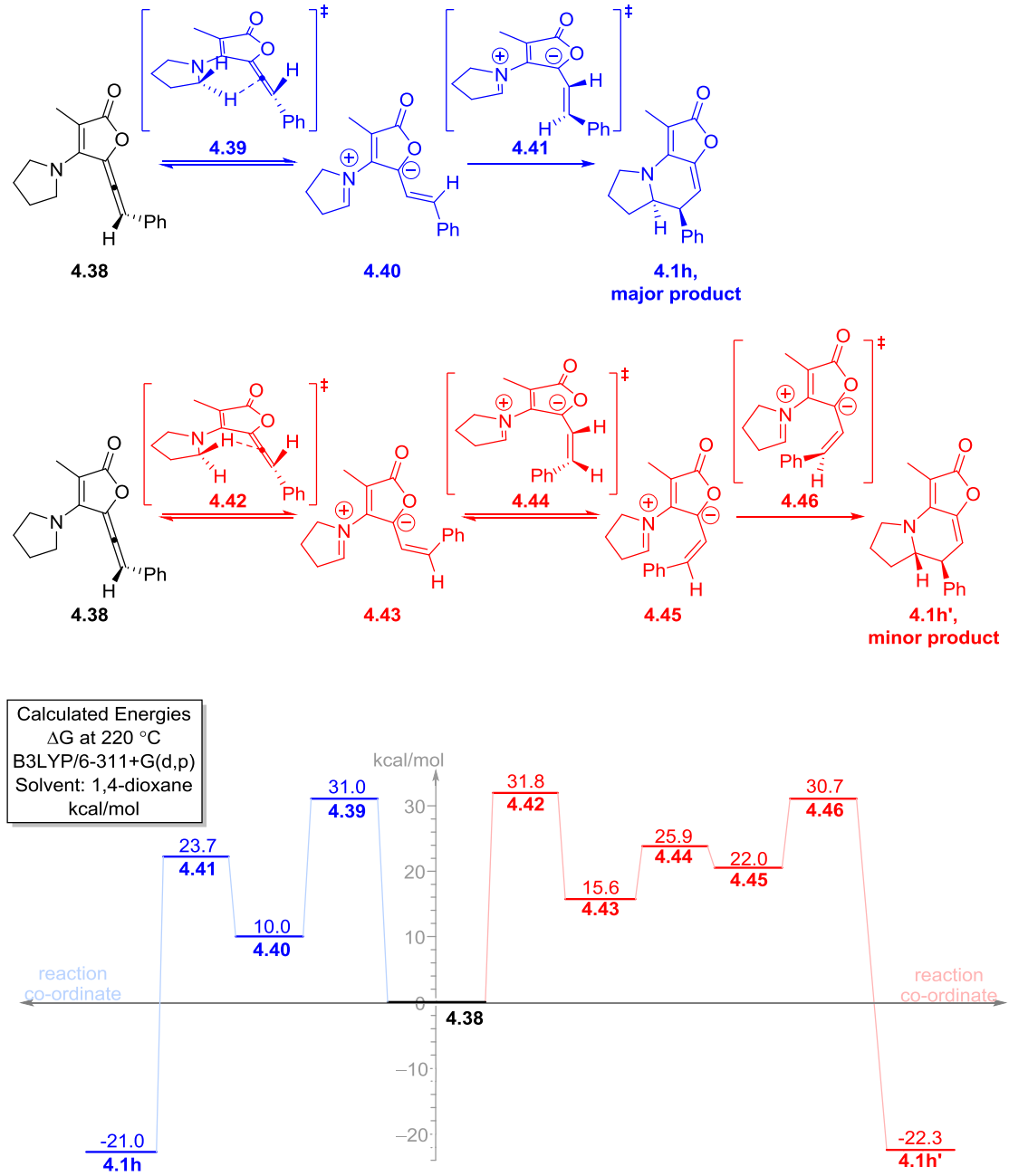
The stereochemistry of the dihydrofuropyridinone is determined in the final electrocyclisation step, which follows the Woodward-Hoffmann rules. For example, in the thermolysis of furanone **4.1g**, the intermediate **4.36** could undergo a disrotatory ring closure leading to either the *rel*-(*R, R*) or *rel*-(*R, S*) product depending on the conformation of the intermediate. In intermediate **4.37**, the additional steric hindrance imparted by the phenyl group makes this ring closure less favoured than the one in **4.34**. Thus the *rel*-(*R, R*) product will be obtained as the major product, which was confirmed experimentally (**Scheme 4.10**).



Scheme 4.10: Diastereoselectivity selectivity according to Woodward-Hoffman rules.

Moreover, DFT calculations were performed to understand the origin of the diastereoselectivity. Again, as the 1,3-hydride shift step to form the allene has no impact on diastereoselectivity, we started our calculations from allene **4.38**.

In the 1,5-hydride shift step, the hydride could migrate to the allene *via* two different pathways. In transition state **4.39**, the hydride migrates to the alkene on the same side as the phenyl group to give *trans*-intermediate **4.40**. Alternatively, in transition state **4.42** the hydride migrates to the allene on the opposite side as the phenyl group to give *cis*-intermediate **4.43**. For this step, transition state **4.39** showed a slightly lower energy barrier than transition state **4.42** (31.0 kcal/mol *vs* 31.8 kcal/mol). The energy difference here is caused by steric buttressing between the phenyl residue and the furanone residue. Intermediate **4.40** then underwent a bond rotation *via* transition state **4.41** with spontaneously ring closure to *cis*-product **4.1h**. However, bond rotation of intermediate **4.43** gave a new intermediate **4.45**, which then underwent a high energy ring closure *via* transition state **4.46** to form product **4.1h'**. The high energy barrier was caused by steric hindrance between the phenyl group and the amino group, which prevents spontaneous ring closure to **4.1h'** (**Scheme 4.11**).



Scheme 4.11: Energy diagram of the thermolysis of allene **4.36**.

In **Section 4.3** and **4.4** we noted that the rate determining step in this rearrangement was established as the first 1,3-hydride shift. Herein we need to consider how kinetic effects impact on diastereoselectivity. The DFT calculations presented in **Scheme 4.11** suggest the highest energy barrier for rearrangement is for the 1,5-hydride shift. Therefore, an accurate calculation was performed is consider the solvation effect on this step using the IEF-PCM model to compare rate constants (**Table 4.8**).

TS	*Method*	*Rate Constant s^{-1}*
4.39	B3LYP/6-311g(d,p)	0.27168
4.39	M062X/6-311+g(d,p)	0.00121
4.42	B3LYP/6-311g(d,p)	0.11579
4.42	M062X/6-311+g(d,p)	0.00029

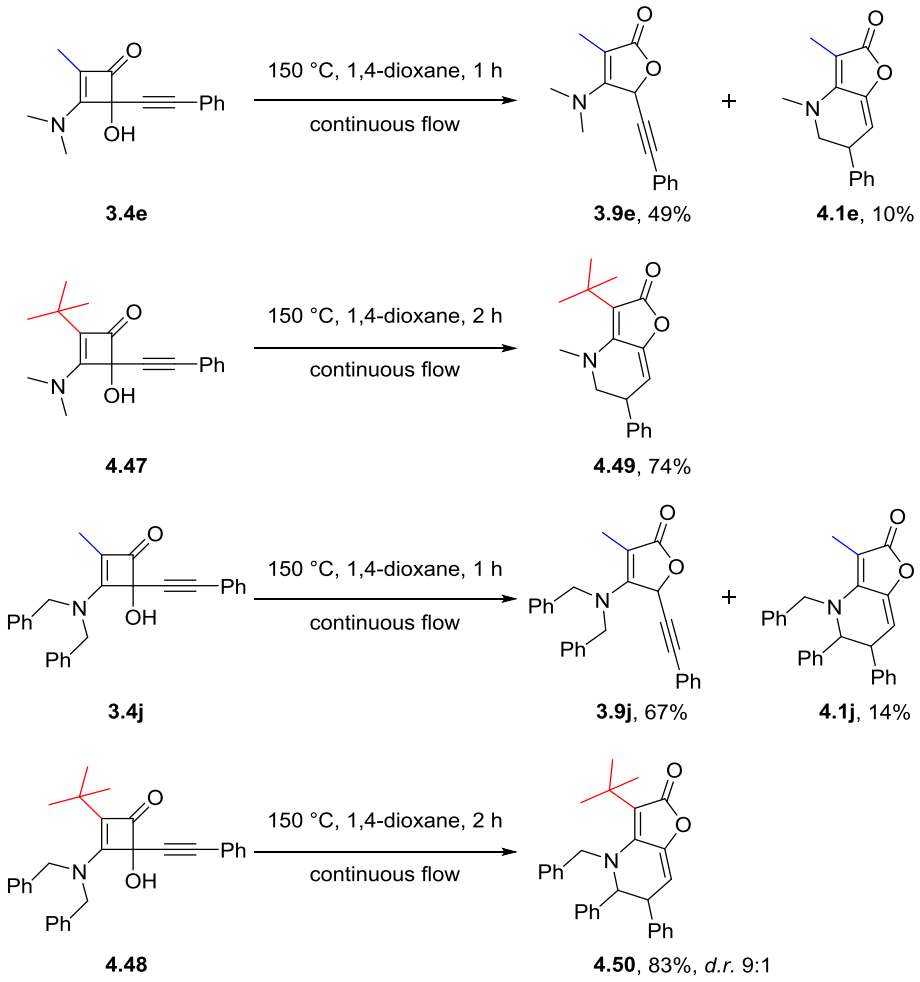
Table 4.8: Kinetic effect at 1,5-hydride shift step.

We found that the B3LYP functional significantly overestimated the rate constant for the 1,5-hydride shift step. It showed the rate constant of transition state **4.39** to be twice as fast as transition state **4.42**. When applying the M062X function with the 6-311+G(d,p) basis set, it gave a smaller rate constant and a fivefold difference in the rate constant between transition state **4.39** and **4.42** (0.00121 s^{-1} vs 0.00029 s^{-1}), which matches the experiment result.

In conclusion, diastereoselectivity in the new annulation reaction is controlled by either thermos-dynamic or kinetic effects. Thermodynamically, the highest energy barrier is for the 1,5-hydride shift step and the transition state **4.39** (**4.38** → **4.1h**) shows a lower energy barrier than transition state **4.42** (**4.38** → **4.1h'**). Moreover, the latter pathway requires an additional step to trigger ring closure, in contrast to the spontaneous ring closure leading to **4.1h**. The difference is caused by steric hindrance between the phenyl residue and the amino residue in transition state **4.46**. Kinetically, the rate constant for reaction *via* transition state **4.39** is around 5 times faster than *via* transition state **4.42**, which can be attributed to steric buttressing between the phenyl residue and the furanone residue in transition state **4.42** and intermediate **4.43**. Consequently, both thermodynamic and kinetic effects correctly predict the formation of dihydrofuropyridinone **4.1h** as the major product.

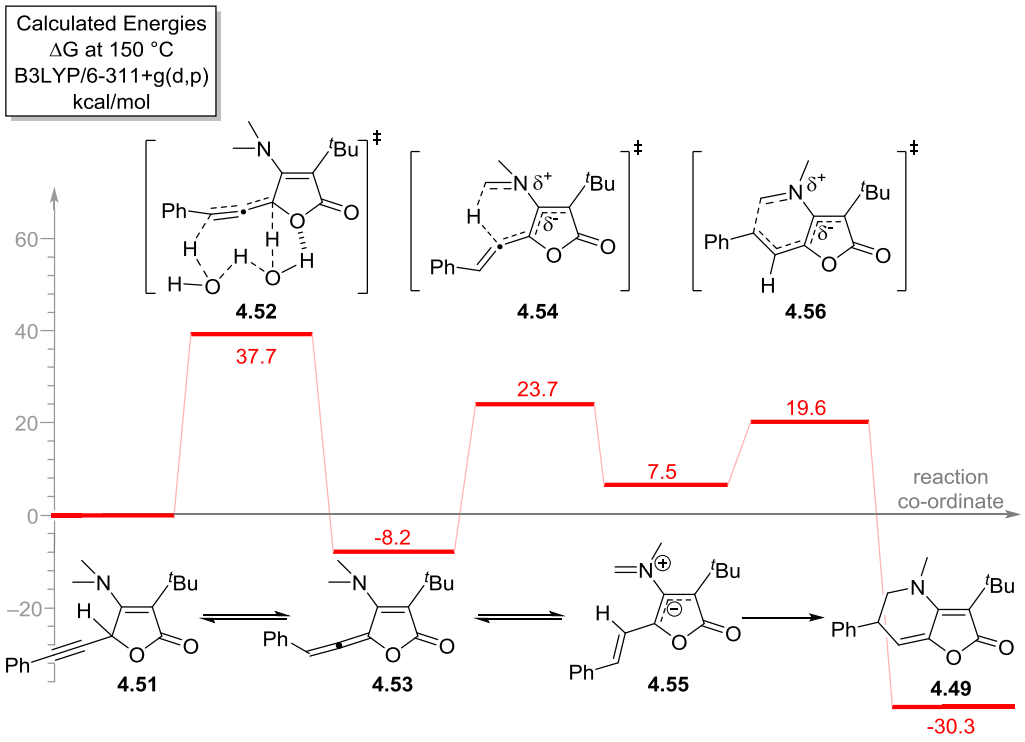
4.7 Steric effect in thermal rearrangement of aminofuranones

In **Chapter 3** we saw how steric buttressing could change selectivity in thermal rearrangements of cyclobutenones. Surprisingly, steric buttressing effect was also observed in the thermal C-H activation reaction which can lead to a significant decrease in the temperature required to effect the reaction. For example, thermolyses of ^{t}butylaminocyclobutenones **4.47** and **4.48** gave dihydrofuropyridinones **4.49** and **4.50** in a high yield when the corresponding methyl substituted cyclobutenones **3.4e** and **3.4j** gave the corresponding furanones **3.9e** and **3.9j** as the major products at the same temperature (**Scheme 4.12**).



Scheme 4.12: Thermolyses of ^{t}butylfuranones **4.47** and **4.48**.

To understand the impact of steric buttressing in the thermal C-H activation reaction, DFT calculations were again performed to obtain the energy diagram for the reaction (**Scheme 4.13**). These showed that the ^{t}butyl group reduced the energy barrier for each transition state allowing the reaction to run to completion at a much lower temperature.



Scheme 4.13: Energy diagram of the thermal C-H activation reaction of furanone **4.51**.

An NBO analysis was conducted on the starting furanone **4.51** (**Figure 4.8**). It showed that steric hindrance between the ^{t}butyl group and the dimethylamino group weakened conjugation of the latter to the furanone ring. The interaction energy for the lone pair of electrons on N to the π* orbital (C2-C3) is 19.4 kcal/mol, lower than in **4.3a** (46.7 kcal/mol). A charge distribution study based on Mulliken population shows that C4 in **4.3a** is significantly more negative than the C4 in **4.51** (–0.105 vs. –0.017) (**Figure 4.9**).

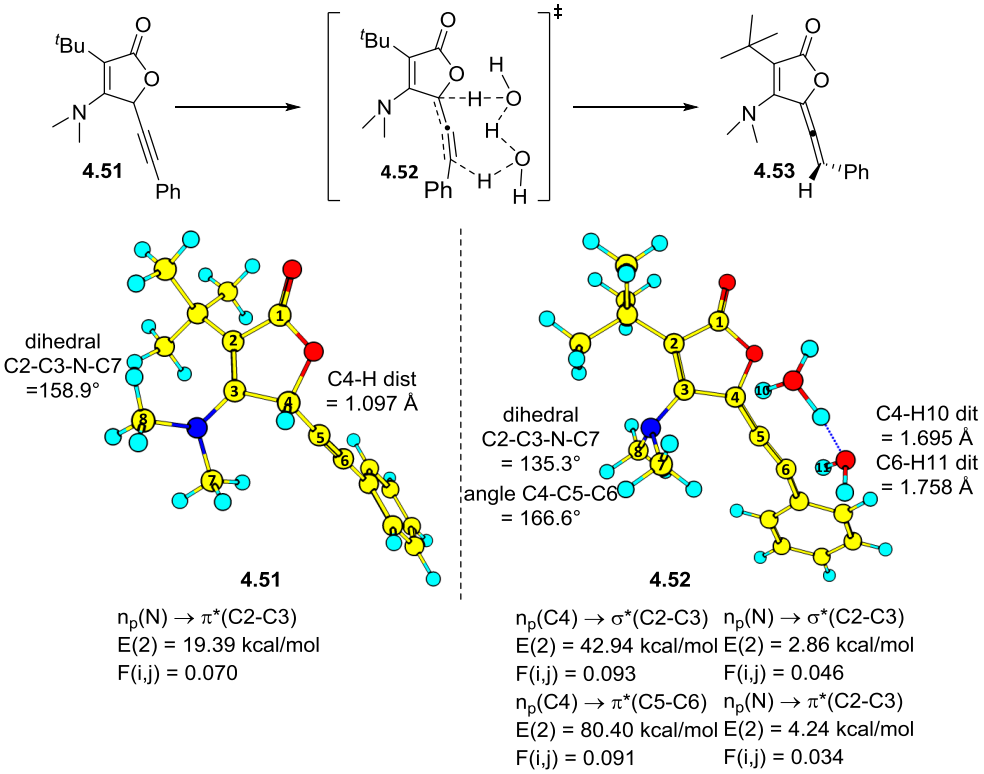


Figure 4.8: Geometry of the lowest energy conformation of start material **4.51** and TS **4.52.**

Geometry and NBO at B3LYP/6-311G(d,p)

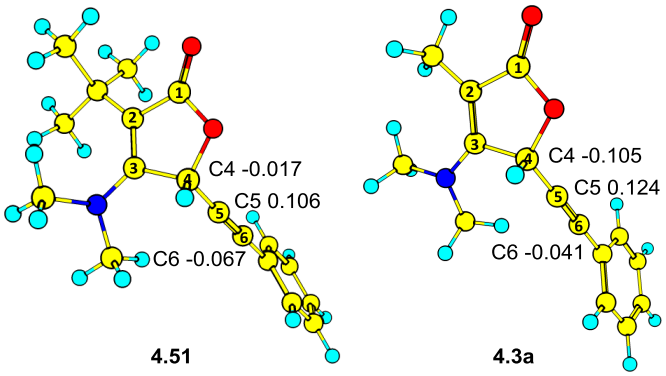


Figure 4.9: Charge distribution in **4.51** an **4.3a** based on Mulliken population at B3LYP/6-311G(d,p).

In transition state **4.52**, the amino group is not conjugated with the furanone ring and the N atom approached to sp^3 hybridization, meaning that electron density in the furanone ring (C1-C2-C3-C4-O) is less than in transition state **4.19** (**Figures 4.8** and **4.3**). Moreover, in transition state **4.19** the N-C3-C2-C1-O chain shows vinylogous carbamate character whereas in **4.52** it is more akin to an unsaturated ester. This makes the C4-H10 bond more acidic in **4.52** and easier to break than the corresponding bond in **4.19**. Consequently, transition state **4.52** shows a relatively low energy barrier leading to a decrease in the temperature required for the C-H activation reaction.

Allene **4.53** also reveals sp^3 hybridization of its nitrogen atom and virtually no conjugation with the furanone ring. As with **4.51** and **4.53**, steric buttressing weakens conjugation between the amino group and the furanone ring in transition state **4.54**. Indeed, the C7-H9 bond is nearly broken in the transition state as the forming C5-H9 bond is stabilized by interaction with π* (C4-C5) and π* (C5-C6). The interaction energies between σ orbital (C5-H9), π* orbital (C4-C5) and π* orbital (C5-C6) are much higher than those observed in transition state **4.20** such that **4.54** has a lower energy barrier (**Figures 4.10** and **4.4**).

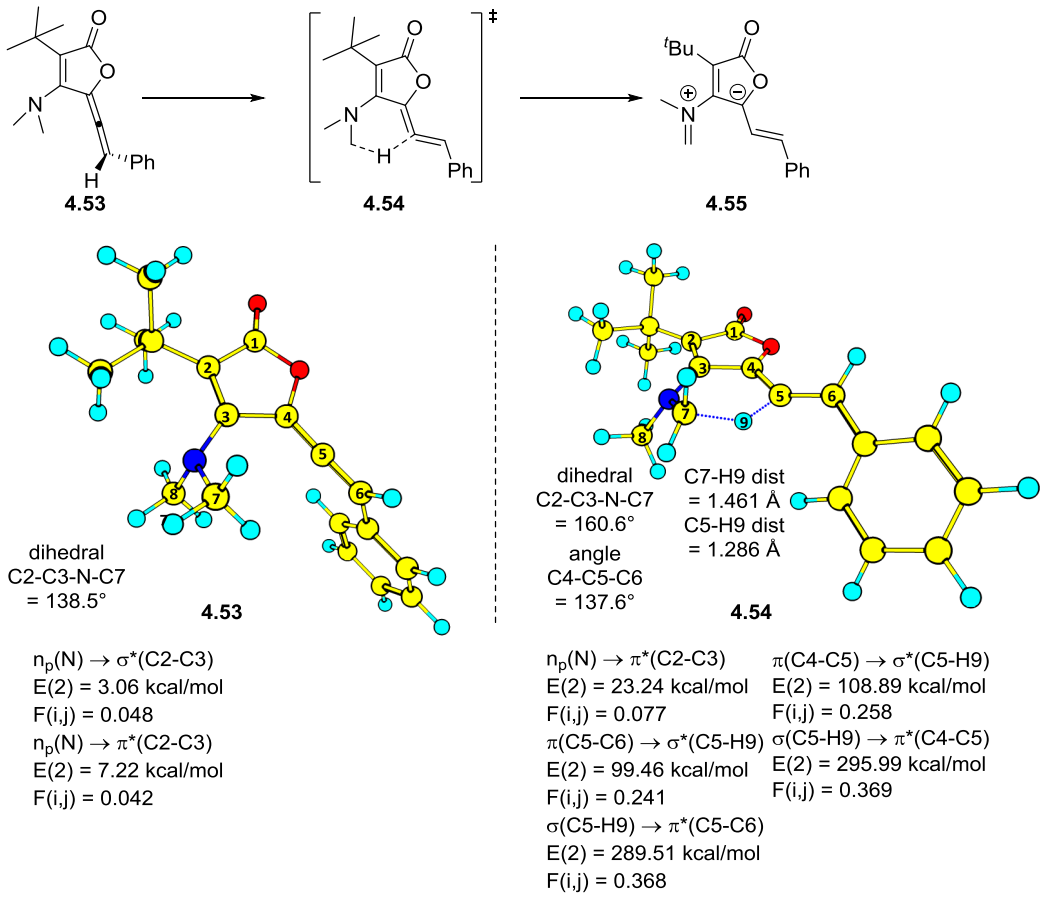


Figure 4.10: Geometry of the lowest energy conformation of intermediate **4.53** and TS **4.54**.

Geometry and NBO at B3LYP/6-311G(d,p)

In intermediate **4.55** (**Figure 4.11**), steric buttressing with the ^{t}butyl group caused the amino group to rotate so out of conjugation with the furanone ring (dihedral C2-C3-N-C7 = 125.9°). As a result, the furanone ring can better stabilize a pair of electrons on C4, thus decreasing the energy for zwitterion formation. The bond rotation transition state **4.56** is similar to that for the corresponding C2-methyl analogue **4.22** (**Figure 4.5**) with the pair of electrons preferentially located on C2 of the furanone ring.

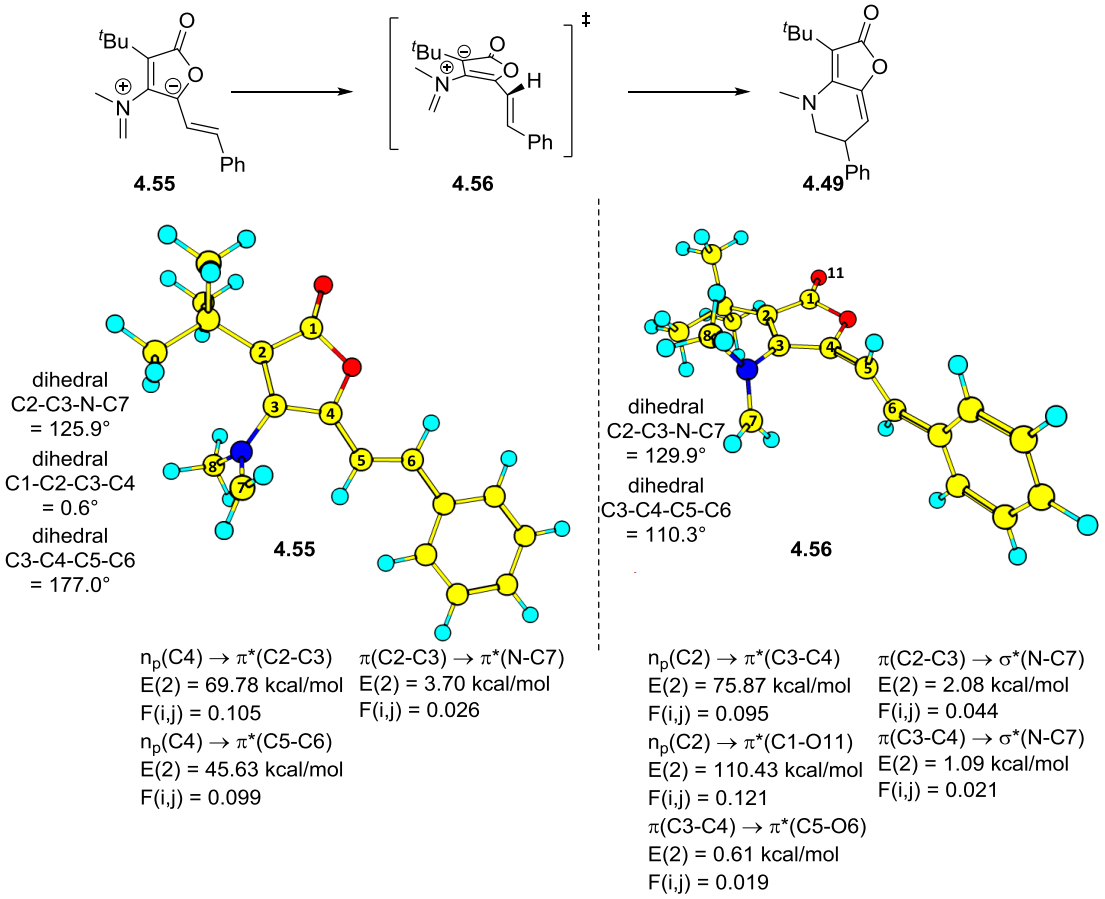


Figure 4.11: Geometry of the lowest energy conformation of intermediate **4.55** and TS **4.56**.

Geometry and NBO at B3LYP/6-311g(d,p)

In the final product, dihydrofuropyridinone **4.49**, steric buttressing between the ^{t}butyl and N-Me group (C8) residues weaken conjugation between the N lone pair and the furanone ring. The dihedral angle for C3-N-C7-C8 is 155.8°, which implies near sp^3 hybridisation of the nitrogen centre. Meanwhile the interaction energy for the N lone pair to π* orbital (C2-C3) is 15.78 kcal/mol, just one third of that calculated for **4.1e** (**Figures 4.12** and **4.6**).

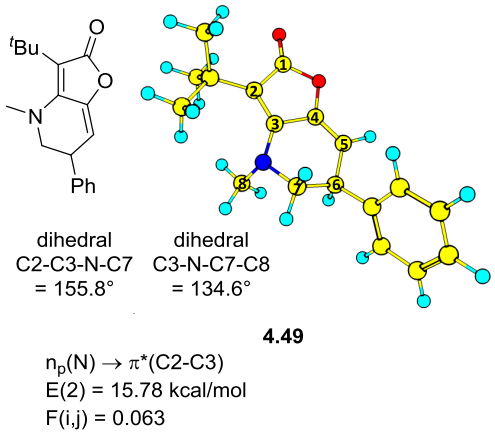


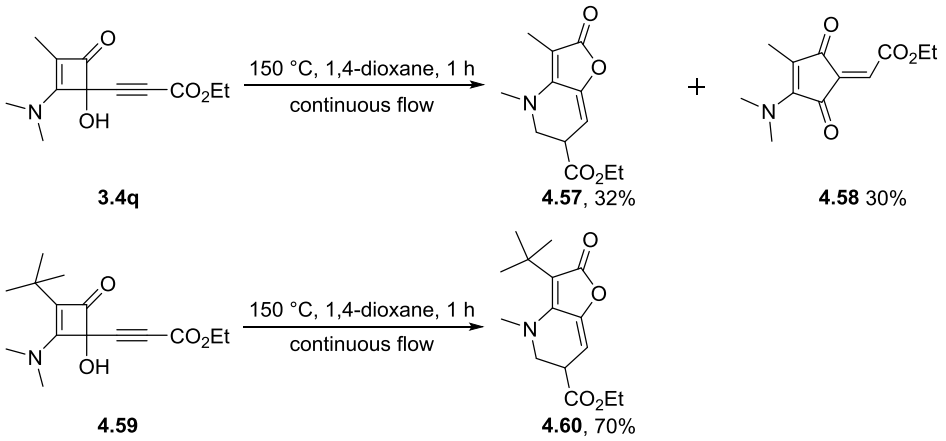
Figure 4.12: Geometry of the lowest energy conformation of product **4.49**.

Geometry and NBO at B3LYP/6-311G(d,p)

In conclusion, steric hindrance between the ^{t}butyl group and the amino group forces the latter to rotate out of conjugation with the furanone ring. As a consequence, the furanone ring is relatively electron poor and better able to stabilize the negative charge of the zwitterion. This decreases energy barriers at each step, allowing the C-H activation reaction to occur at a much lower temperature.

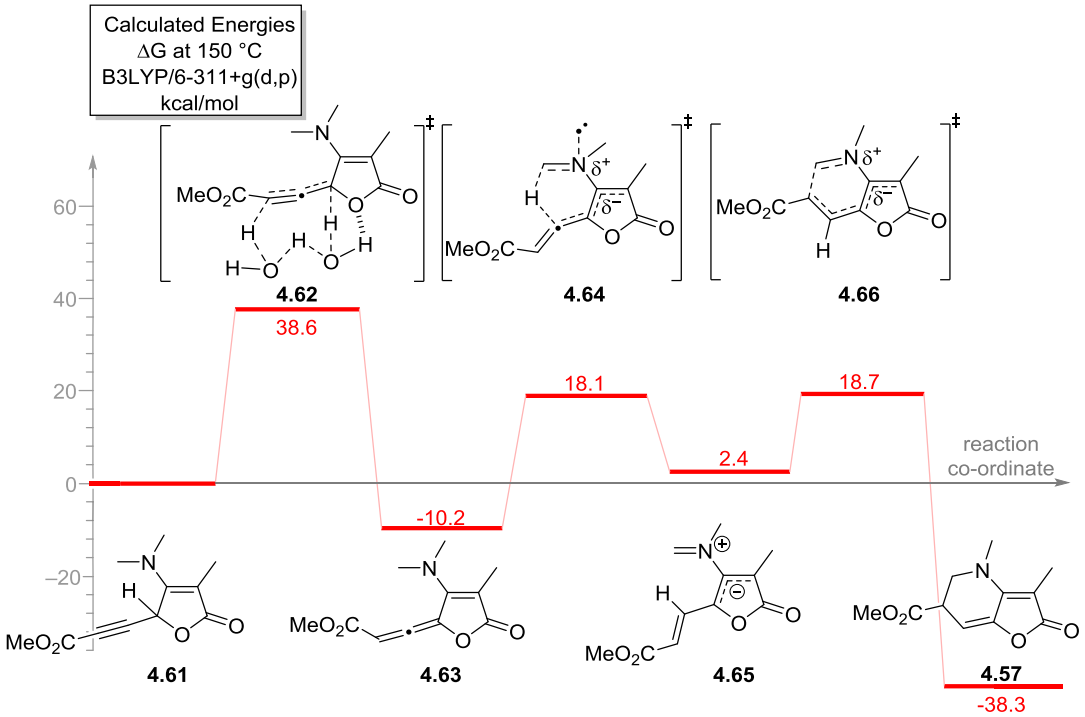
4.8 Thermal rearrangement of ester substituted aminocyclobutenone

Thermolyses of aminocyclobutenones **3.4q** and **4.59** bearing an alkyl ester residue gave surprising outcomes as they produced dihydrofuropyridinones **4.57** and **4.60** after a relatively short reaction time at a low temperature (**Scheme 4.14**). Cyclobutenone **3.4q** also gave cyclopentenedione **4.58** as a significant product due to poor regioselectivity in the step leading to furanone formation (**Section 3.3.2**).



Scheme 4.14: Thermolyses of ester substituted aminocyclobutenones **4.57** and **4.60**.

To understand why aminocyclobutenones **3.4q** and **4.59** were transformed into dihydrofuropyridinones at a relatively low temperature (150 °C), an energy diagram was calculated for the rearrangement of furanone **4.61** to dihydrofuropyridinone **4.57** (**Scheme 4.15**). Comparing the outcome with the energy diagram in **Scheme 4.6**, it can be seen that transition states **4.62**, **4.64** and **4.66** all showed a lower energy barrier than the corresponding transition state for the phenyl substituted furanone **3.9e** (**Section 4.4**), accounting for the lower temperature for rearrangement.



Scheme 4.15: Energy diagram for thermolysis of furanone **4.61**.

Geometry and NBO at B3LYP/6-311G(d,p)

NBO analysis was conducted for the 1,3-hydride shift transition state **4.62** and it shows that the amino group is strongly conjugated with the furanone ring (**Figure 4.13**). Moreover, as the ester residue is a strong electron withdrawing group, the C4-H10 bond is made more acidic. Consequently, the 1,3-hydride shift transition state **4.62** shows a much lower energy barrier compared with the corresponding transition state **4.19** in **Section 4.4**.

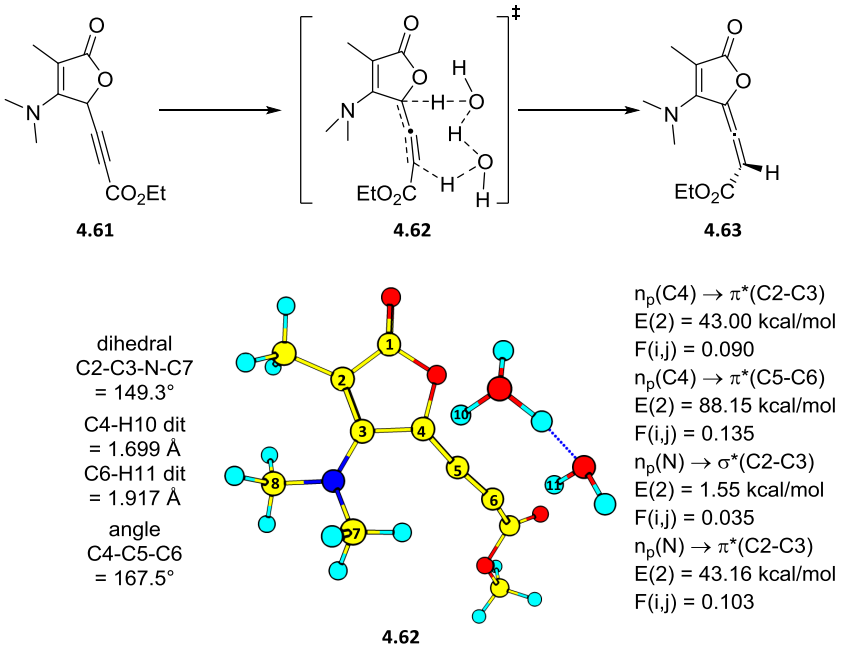


Figure 4.13: Geometry of the lowest energy conformation of TS **4.62**.

Geometry and NBO at B3LYP/6-311G(d,p)

In transition state **4.64** (**Figure 4.14**), both the interaction between σ orbital (C7-H9) and π* orbital (C4-C5) and between π orbital (C4-C5) and σ* orbital (C7-H9) showed a higher interaction energy than that observed for the comparable transition state **4.20** (**Figure 4.4**). The reduced energy barrier for transition state **4.64** can be attributed to the stabilising effect of the electron withdrawing ester group on the allene.

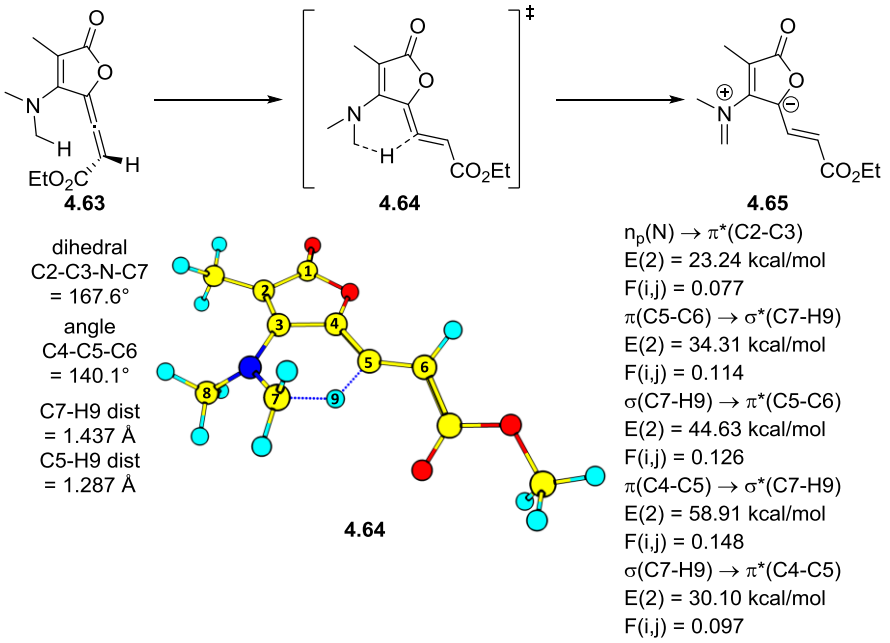


Figure 4.14: Geometry of the lowest energy conformation of TS **4.64**.

Geometry and NBO at B3LYP/6-311G(d,p)

The bond rotation transition state **4.66** proved to be similar to that observed previously **4.22** (**Figures 4.15** and **4.5**).

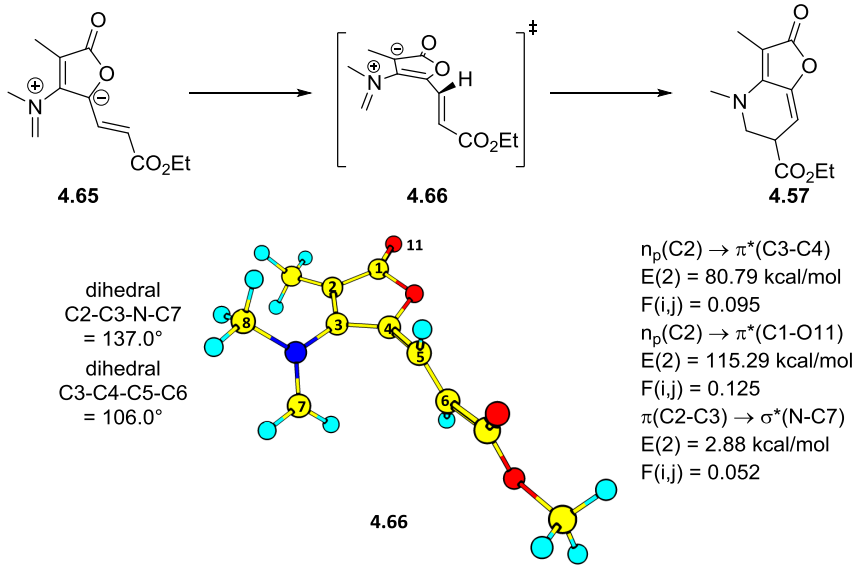
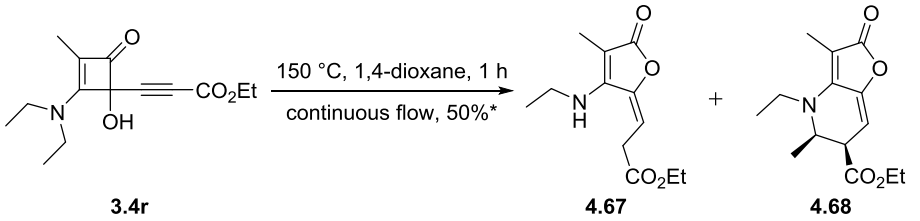


Figure 4.15: Geometry of the lowest energy conformation of TS **4.66**.

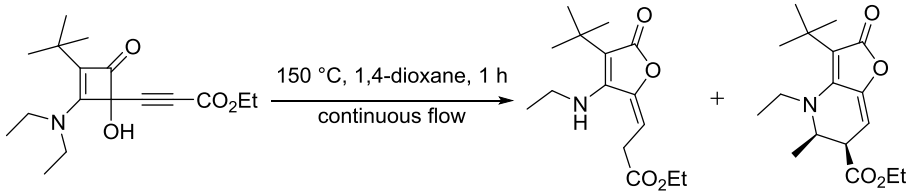
Geometry and NBO at B3LYP/6-311G(d,p)

In conclusion, an electron withdrawing substituent on the alkyne can significantly decrease the energy barrier for the C-H activation reaction by stabilizing the developing anion during zwitterion formation. Consequently, thermal C-H activation reaction can occur at a lower temperature (150°) than is observed with alkynes bearing aromatic or alkyl substituents.

However, these rearrangements are prone to side reactions. For example, in the thermolysis of diethylaminocyclobutenone **3.4r**, a new furanone **4.67** was obtained in low yield. A similar outcome was also given by diethylaminocyclobutenone **4.69** which gave furanone **4.70** as the major product together with dihydrofuropyridinone **4.71** (**Scheme 4.16**).

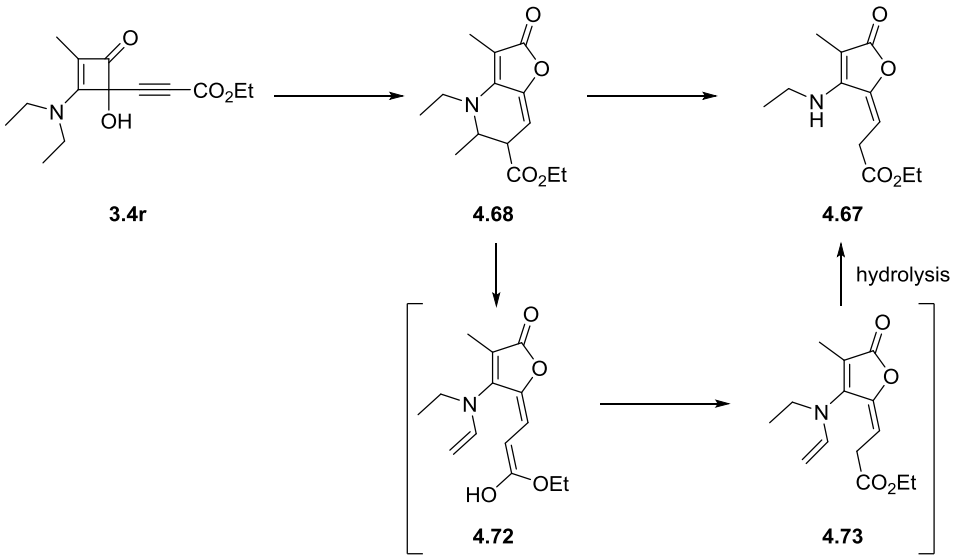


* furanone **4.67** and dihydrofuropyridinone **4.68** cannot be seperated by HPLC. A 5:1:3 mixture (major diastereoisomer **4.68** : minor diastereoisomer **4.68** : **4.67**) was seperated in ~ 50% yield.



Scheme 4.16: Thermolyses of aminocyclobutenones **3.4r** and **4.69**.

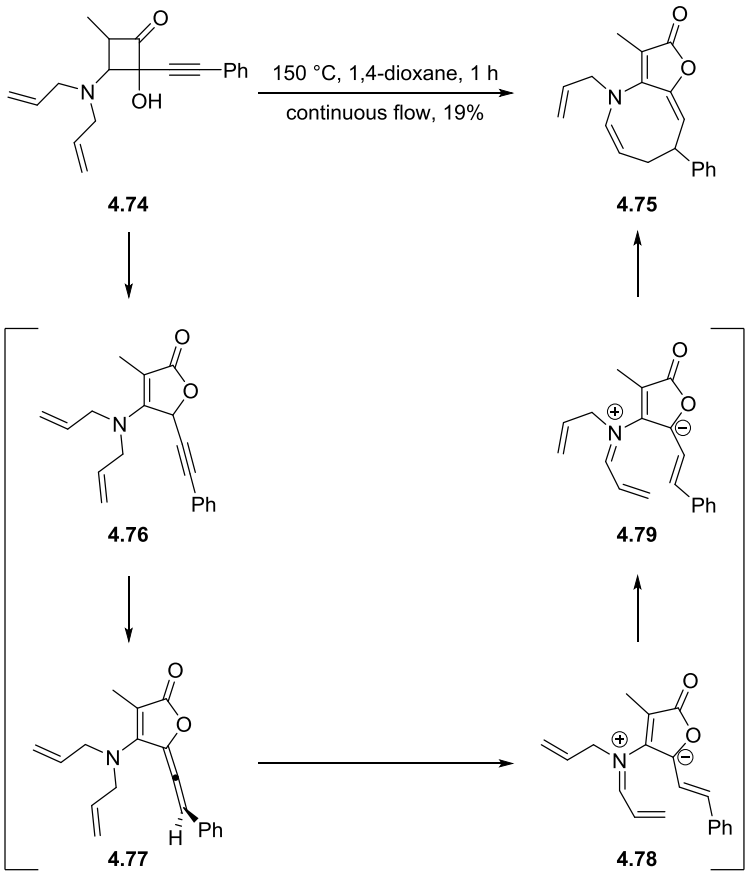
From our previous work, we had expected aminocyclobutenone **3.4r** to form dihydrofuropyridinone **4.68**. In this case we suspect that it is formed but then gives a new rearrangement leading to enamine **4.72**. Tautomerism to **4.73** followed by loss of the vinyl group by hydrolysis then affords furanone **4.67** as the product (**Scheme 4.17**).



Scheme 4.17: Plausible mechanism for the rearrangement from **3.4r** to **4.67**.

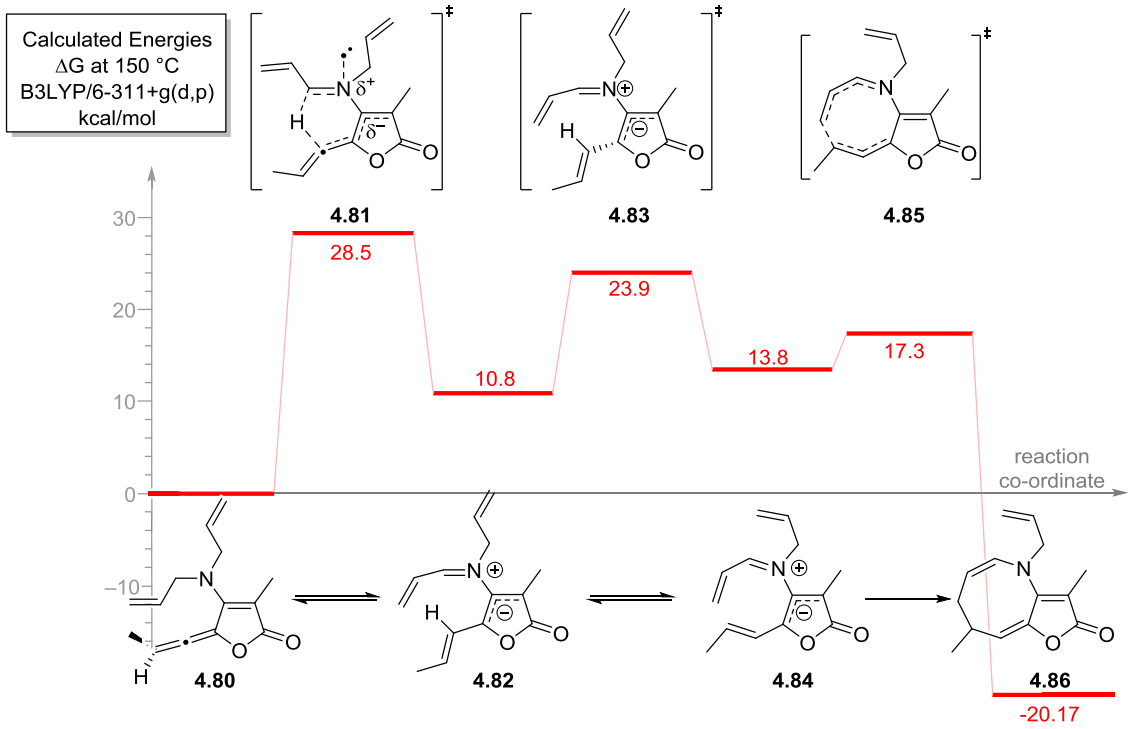
4.9 Thermal rearrangement to form dihydrofuroazocinone

Thermolysis of diallylaminocyclobutenone **4.74** also gave an unexpected outcome in that it produced furoazocinone **4.75**. Although the yield was low due to the presence of many by-products, the reaction revealed its potential to make an 8 membered ring, which is usually considered to be difficult (**Scheme 4.18**).



Scheme 4.18: Thermolysis of diallylaminocyclobutenone **4.76**

Our postulated mechanism was outlined in **Scheme 4.18**, DFT calculations were then performed to ensure that it was reasonable and to obtain an energy diagram for a simplified analogue **4.80** (**Scheme 4.19**). We noticed that the hydride shift step (**4.80** → **4.83**) and bond rotation step (**4.83** → **4.85**) followed a similar pathway to all of the related examples discussed previously. However, in the ring closing step (**4.84** → **4.86**), an 8 membered ring transition state leading to furoazocinone compound **4.86** by sigmatropic ring closure was energetically favoured.



Scheme 4.19: Energy diagram of thermolysis of furanone **4.80**.

NBO analysis of transition state **4.85** shows a well matched HOMO that obeyed Woodward-Hoffmann rules. Here the new bond was formed by conrotatory ring closure (**Figure 4.16**).

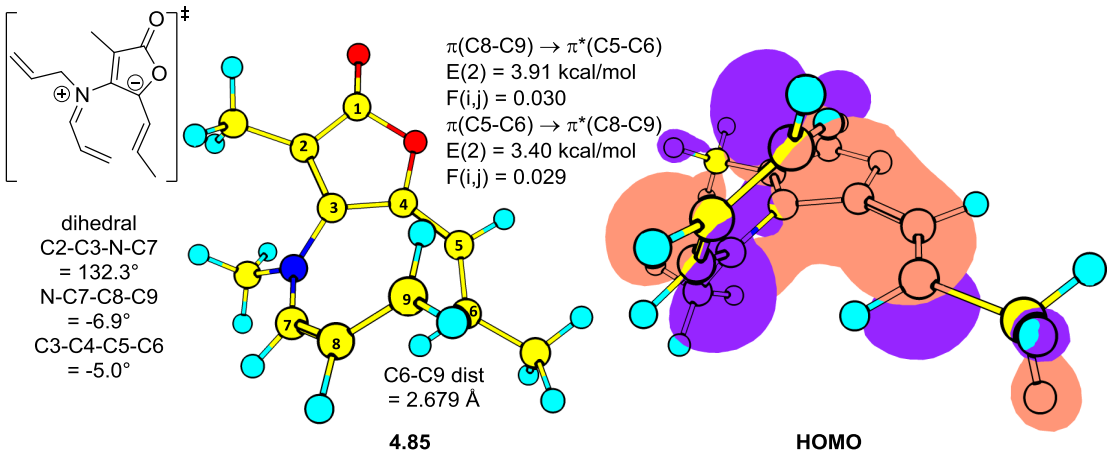


Figure 4.16: Geometry of the lowest energy conformation of TS **4.85**.

Geometry and NBO at B3LYP/6-311G(d,p)

In the furoazocinone product **4.86**, the 8 membered ring is highly twisted. Conjugation of the N lone pair and the furanone ring is observed and showed a 19.5 kcal/mol interaction energy (**Figure 4.17**).

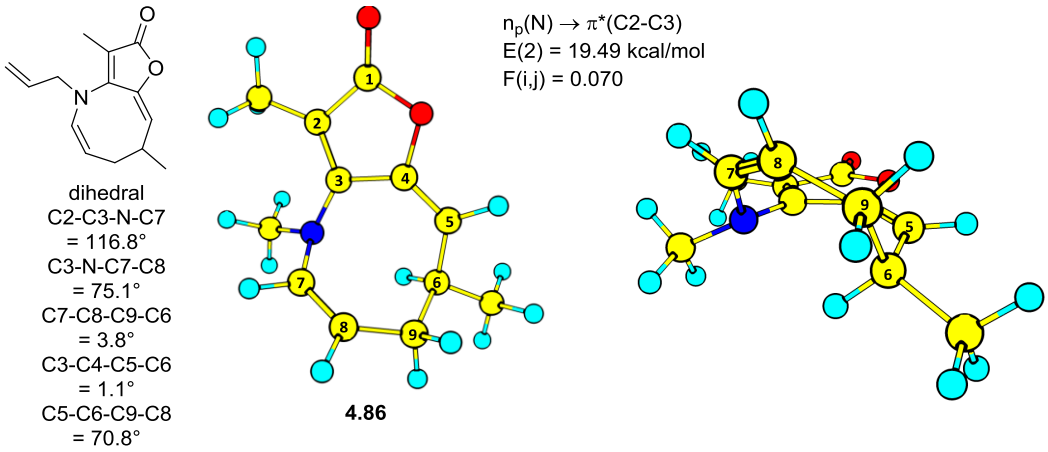
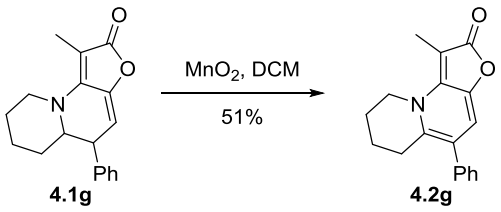


Figure 4.17: Geometry of the lowest energy conformation of **4.86.**

Geometry and NBO at B3LYP/6-311G(d,p)

4.10 Oxidation of dihydrofuropyridinone

Once when performing the thermolysis of furanone **3.9g**, a sudden loss of system pressure occurred causing the dihydrofuropyridinone **4.1g** to crash out in the stainless steel tubing, which then overheated. A complex mixture was formed that included furopyridinone **4.2g**. This result suggests that an oxidation reaction from dihydrofuropyridinone to furopyridinone was possible. Indeed, treatment of dihydrofuropyridinone **4.1g** with MnO_2 afford the furopyridinone **4.2g** in 51% yield (**Scheme 4.20**).

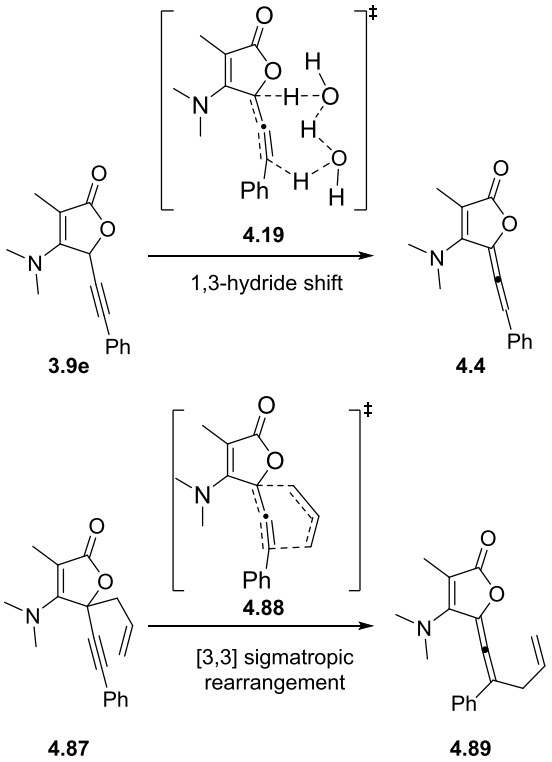


4.1g **4.2g**

Scheme 4.20: Oxidation reaction of duhydrofuropyridinone **4.1g**.

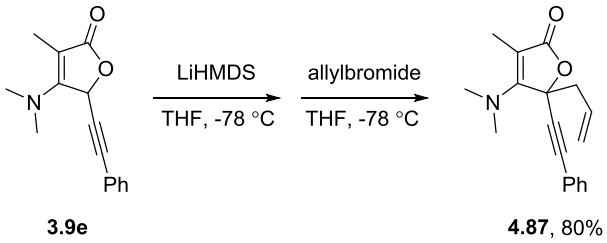
4.11 Thermal rearrangement of substituted furanone

In **Section 4.4** we observed that the 1,3-hydride shift step was the highest energy step and thus constituted the rate determining step in the CH-activation reaction. To decrease the temperature required for the reaction, we tried to design a model that could form the allene by a sigmatropic shift rather than a 1,3-hydride shift (**Scheme 4.21**).



Scheme 4.21: [3,3] Sigmatropic rearrangement to form allene **4.88**.

Allyl substituted furanone **4.87** was thus prepared from furanone **3.9e** by deprotonation by LiHMDS and treatment with allylbromide (**Scheme 4.22**). Unfortunately, thermolysis of furanone **4.87** at 220 °C returned only starting material. When the temperature was increased to 250 °C, decomposition occurred and the reaction gave a complex product mixture containing none of the expected product (detection by crude MS and ^{1}HNMR of the crude reaction mixture).



Scheme 4.22: Preparation of the substituted furanone **4.87**.

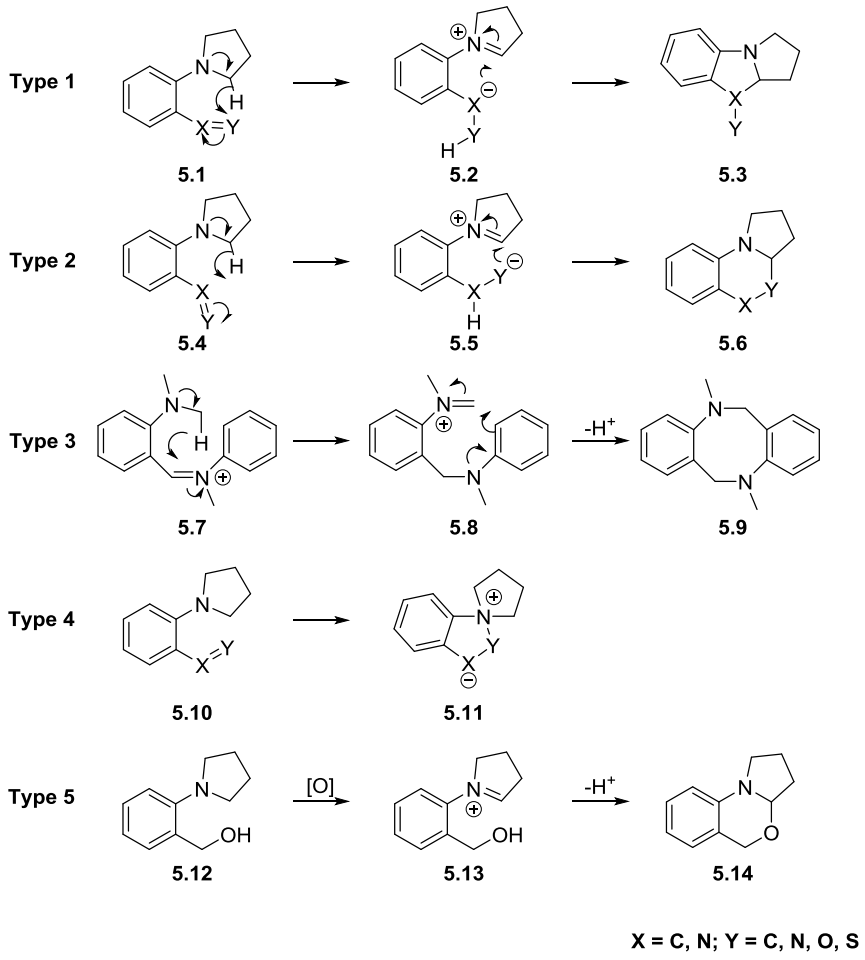
4.12 Conclusion

Our investigation uncovered a new thermal C-H activation and annulation sequence to transform aminofuranones to dihydrofuropyridinones. The reaction showed high regioselectivity and good diastereoselectivity.

Chapter 5: A New Type of *tert*-Amino Effect Reaction

5.1 Introduction of *tert*-amino effect

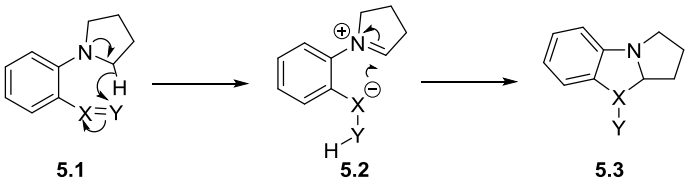
The *tert*-amino effect has largely been developed as a method for the synthesis of saturated nitrogen heterocyclic ring system.[111] The first example was reported by Pinnow in 1895.[112] Generally, the *tert*-amino effect starts with a hydride shift from a dialkylaniline to an electron poor centre in an *ortho* substituent. This sets up a cyclisation of the resulting dipolar intermediate leading to a heterocycle. *tert*-Amino effect reactions were classified into five types by Meth-Cohn and Suschitzky according to the nature of the donor and acceptor (**Scheme 5.1**).[113-115] Recently some further examples of the reaction have been reported, all of which fall into one of these five reaction types.



Scheme 5.1: 5 types of *tert*-amino-effect reaction.

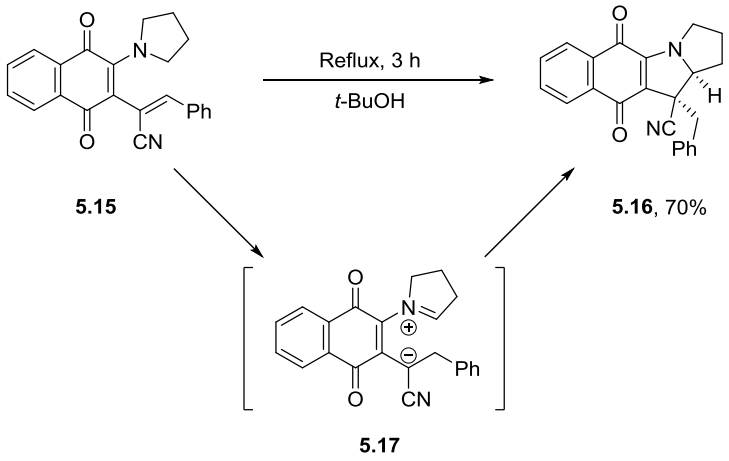
5.1.1 Type 1: Forming five-membered rings

In Type 1 *tert*-amino effect reactions, an initial 1,6-hydride shift forms a zwitterion **5.2**, which then undergoes cyclisation leading to 5-membered heterocyclic product **5.3** (**Scheme 5.2**).

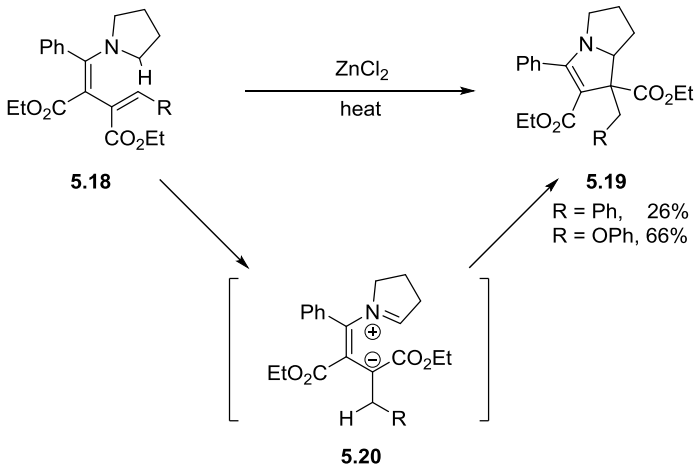


Scheme 5.2: The Type 1 *tert*-amino effect reactions.

When X=Y is C=C, an electron withdrawing group such as a nitrile (**Scheme 5.3**)[116] or ester group (**Scheme 5.4**)[117,118] is required to stabilize the anionic centre in the zwitterion.

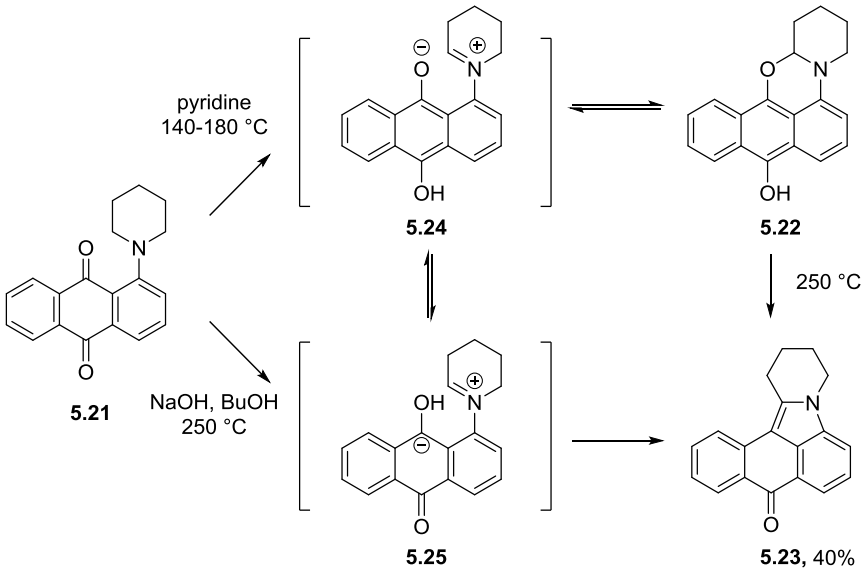


Scheme 5.3: An example of the Type 1 *tert*-amino effect reaction.



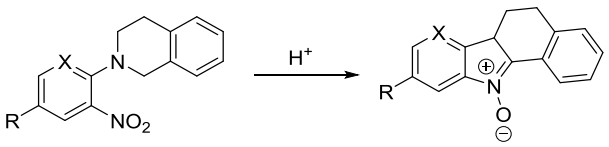
Scheme 5.4: A further example of the Type 1 *tert*-amino effect reaction.

When X=Y is C=O or C=N, the hydride shift can occur without an attached electron withdrawing substituent due to the electronegativity of oxygen and nitrogen (**Scheme 5.5**).[119]

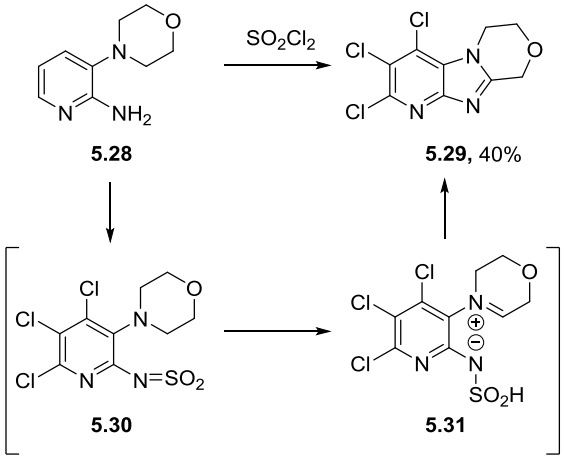


Scheme 5.5: A further example of the Type 1 *tert*-amino effect reaction.

When X=Y is N=O or N=S, the cyclisation can often be realised under mild conditions due to the electron deficient nature of these group (**Schemes 5.6** and **5.7**).[120,121]



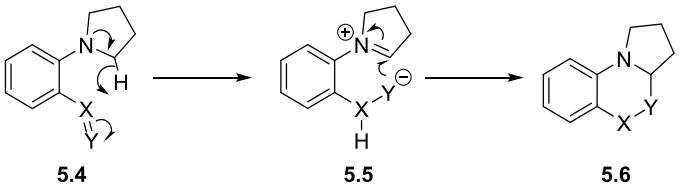
Scheme 5.6: A further example of the Type 1 *tert*-amino effect reaction.



Scheme 5.7: A further example of the Type 1 *tert*-amino effect reaction.

5.1.2 Type 2: Forming six-membered rings

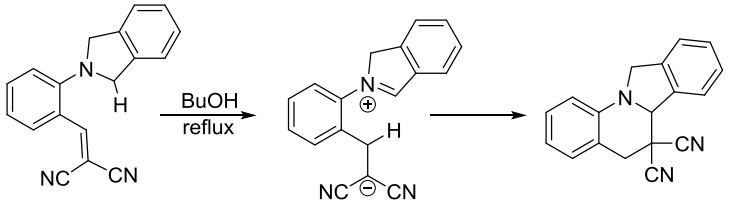
In Type 2 *tert*-amino effect reactions, a 1,5-hydride shift occurs leading to a zwitterion. Subsequently, ring closure leads to a 6 membered ring. Polarisation of the acceptor is required such that the X group becomes the hydride acceptor (**Scheme 5.8**).[122-125]



5.4 **5.5** **5.6**

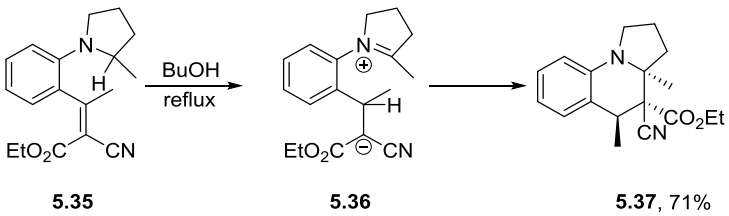
Scheme 5.8: Type 2 *tert*-amino effect reactions.

When X=Y is a C=C bond, the forming anion is not stabilized by the aromatic ring so requires stabilisation by electron withdrawing groups. Conjugation to two nitriles (**Scheme 5.9**)[126] or a nitrile and an ester group is typically required (**Scheme 5.10**).[127]



5.32 **5.33** **5.34**, 78%

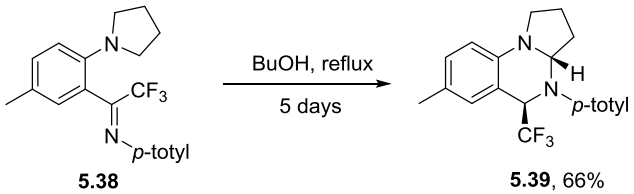
Scheme 5.9: An example of the Type 2 of *tert*-amino effect reaction.



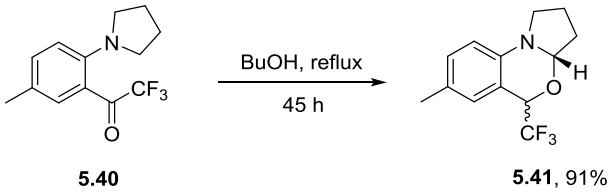
5.35 **5.36** **5.37**, 71%

Scheme 5.10: A further example of the Type 2 *tert*-amino effect reaction.

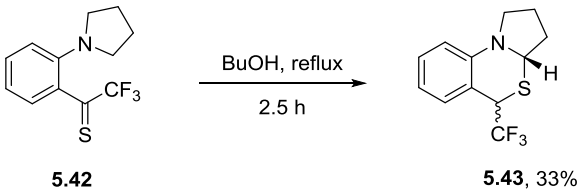
There are also a few examples of Type 2 *tert*-amino effect reactions where X=Y is C=N,[128] C=O,[111] C=S[128] or N=N[129] (**Schemes 5.11**, **5.12**, **5.13** and **5.14**). In comparison to Type 1 reactions, these require more and/or stronger electron withdrawing groups to stabilize the anionic centre in the intermediate.



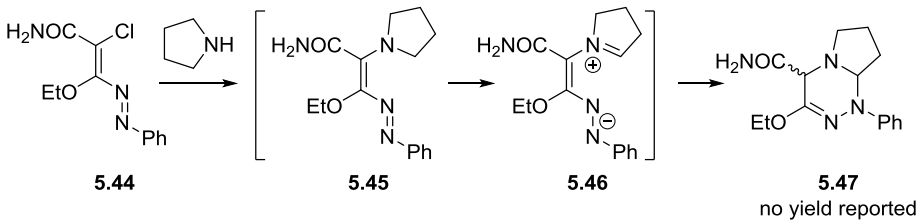
Scheme 5.11: A further example of the Type 2 *tert*-amino effect reaction.



Scheme 5.12: A further example of the Type 2 *tert*-amino effect reaction.



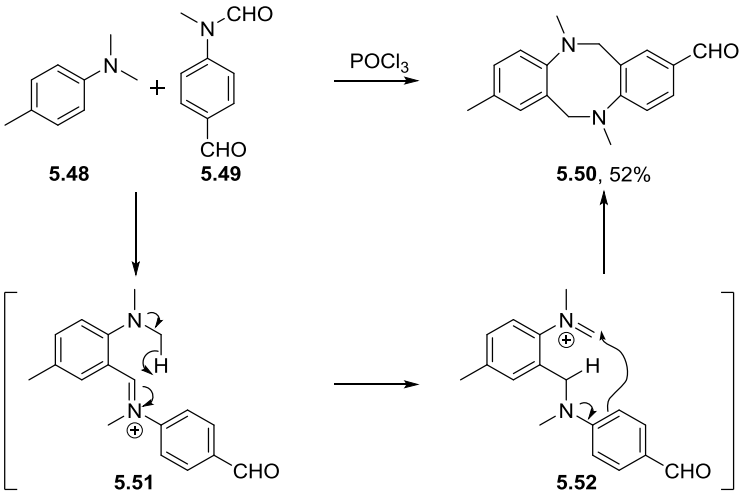
Scheme 5.13: A further example of the Type 2 *tert*-amino effect reaction.



Scheme 5.14: A further example of the Type 2 *tert*-amino effect reaction.

5.1.3 Type 3: Forming rings containing more than six-members

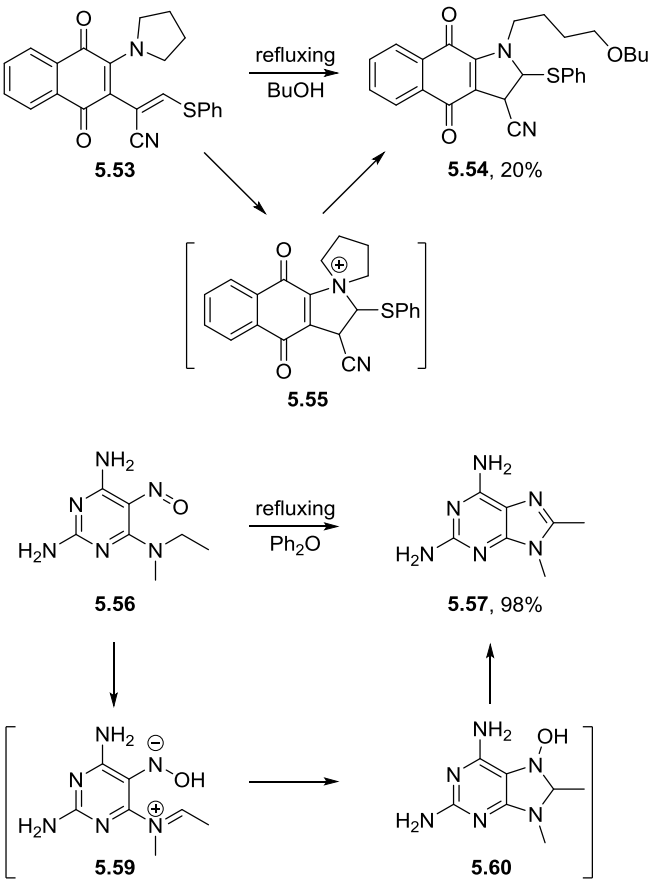
In Type 3 *tert*-amino effect reactions, rings of more than 6 atoms can be formed. One example published by Meth-Cohn *et al.* showed how an eight membered ring could be formed via iminium salt **5.51** by hydride transfer and ring closure (**Scheme 5.15**).[130]



Scheme 5.15: An example of the third type of *tert*-amino effect reaction.

5.1.4 Type 4: Reactions on *tert*-amino nitrogen

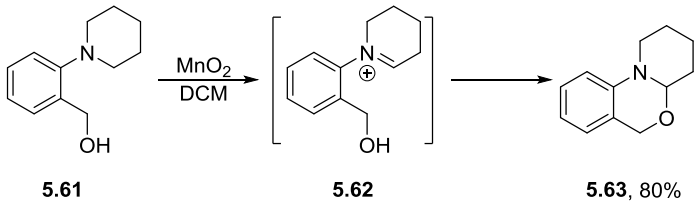
The Type 4 *tert*-amino effect reactions result in products derived by the nucleophilic addition of nitrogen to a proximal group. The lone pair of electrons on nitrogen directly attacks an electrophilic centre to form the new bond (**5.53** → **5.54)**. Alternatively, it may capture the electrophilic centre following zwitterion formation (**5.56** → **5.57)** (**Scheme 5.16**).[131-133]



Scheme 5.16: Examples of the Type 4 *tert*-amino effect reactions.

5.1.5 Type 5: Forming *ortho*-iminium salts

Type 5 *tert*-amino effect reactions begin with oxidation of the amine to an iminium salt, which is then captured to form a heterocyclic ring (**Scheme 5.17**).[134]

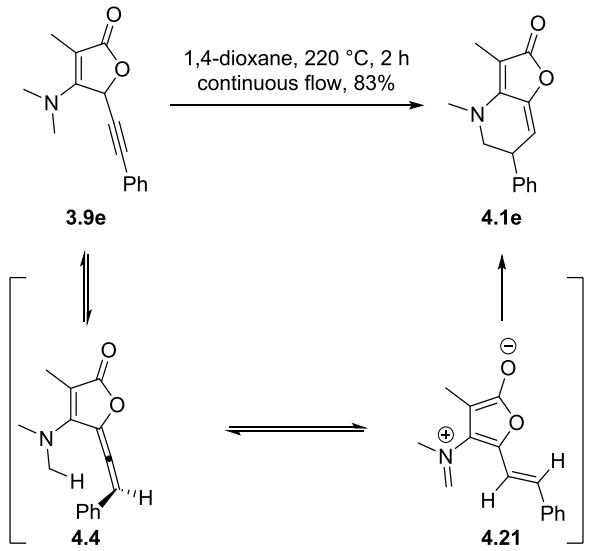


5.61 **5.62** **5.63**, 80%

Scheme 5.17: An example of Type 5 *tert*-amino effect reaction.

5.2 A new type of *tert*-amino effect reaction

In **Chapter 4** we described a new annulation reaction in which an aminofuranone was transformed into a dihydrofuropyridinone. Importantly, this constituted a new type of *tert*-amino effect reaction (**Scheme 5.18**). In this reaction, the *tert*iary amine group acted as the hydride donor and the allene group as the hydride acceptor to give zwitterion **4.21**. In this case the negative charge is stabilized by extensive conjugation. The resulting alkene then rotates towards the iminium group to induce spontaneous ring closure to form dihydrofuropyridinone **4.1e**.



3.9e **4.1e**

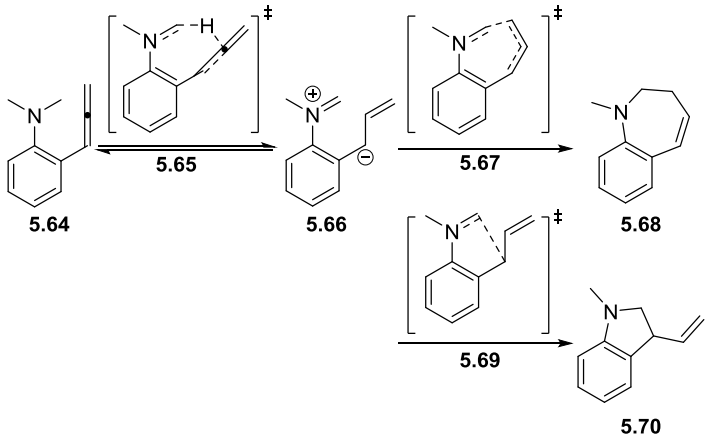
4.4 **4.21**

Scheme 5.18: Mechanism for the thermolysis of furanone **3.9e.**

Following on from this, we tried to extend the method to other systems to further exemplify this new type of *tert*-amino effect reaction.

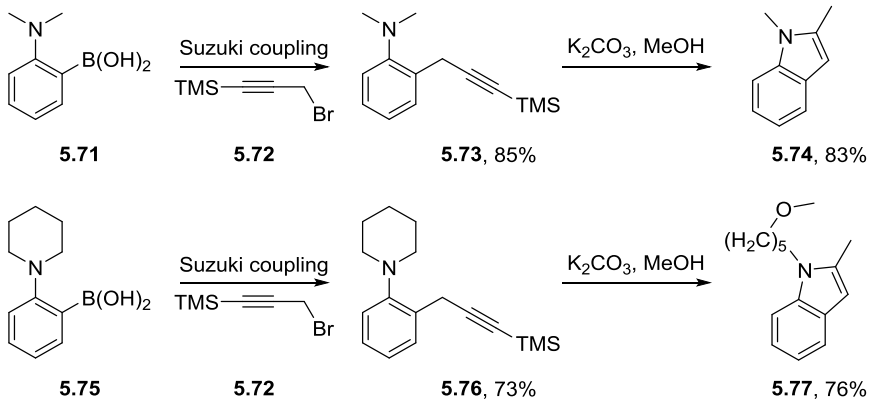
5.3 *tert*-Amino effect reaction of *ortho*-alleneanilline

Our first plan was to design an *ortho*-allenylanilline system and test its possible rearrangement to **5.68** or **5.70** (**Scheme 5.19**).



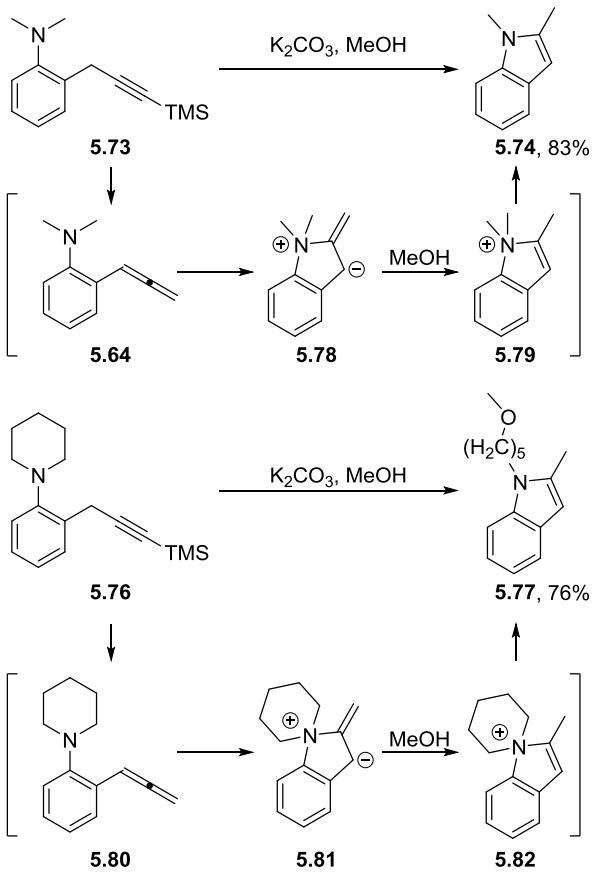
Scheme 5.19: Possible rearrangement of allenylaniline **5.64**.

Our preparation of the starting material started with a Suzuki coupling of boronic acids **5.71** and **5.75** with propargyl bromide **5.72** to form alkynylanilines **5.73** and **5.76**. There have been a few reported examples that TMS-alkynes being isomerised to terminal allenes under basic conditions.[135,136] However, in our studies, treating alkynylanilines **5.73** and **5.76** with K_2CO_3 in MeOH at RT overnight, led to indoles **5.74** and **5.77** in high yield (**Scheme 5.20**).



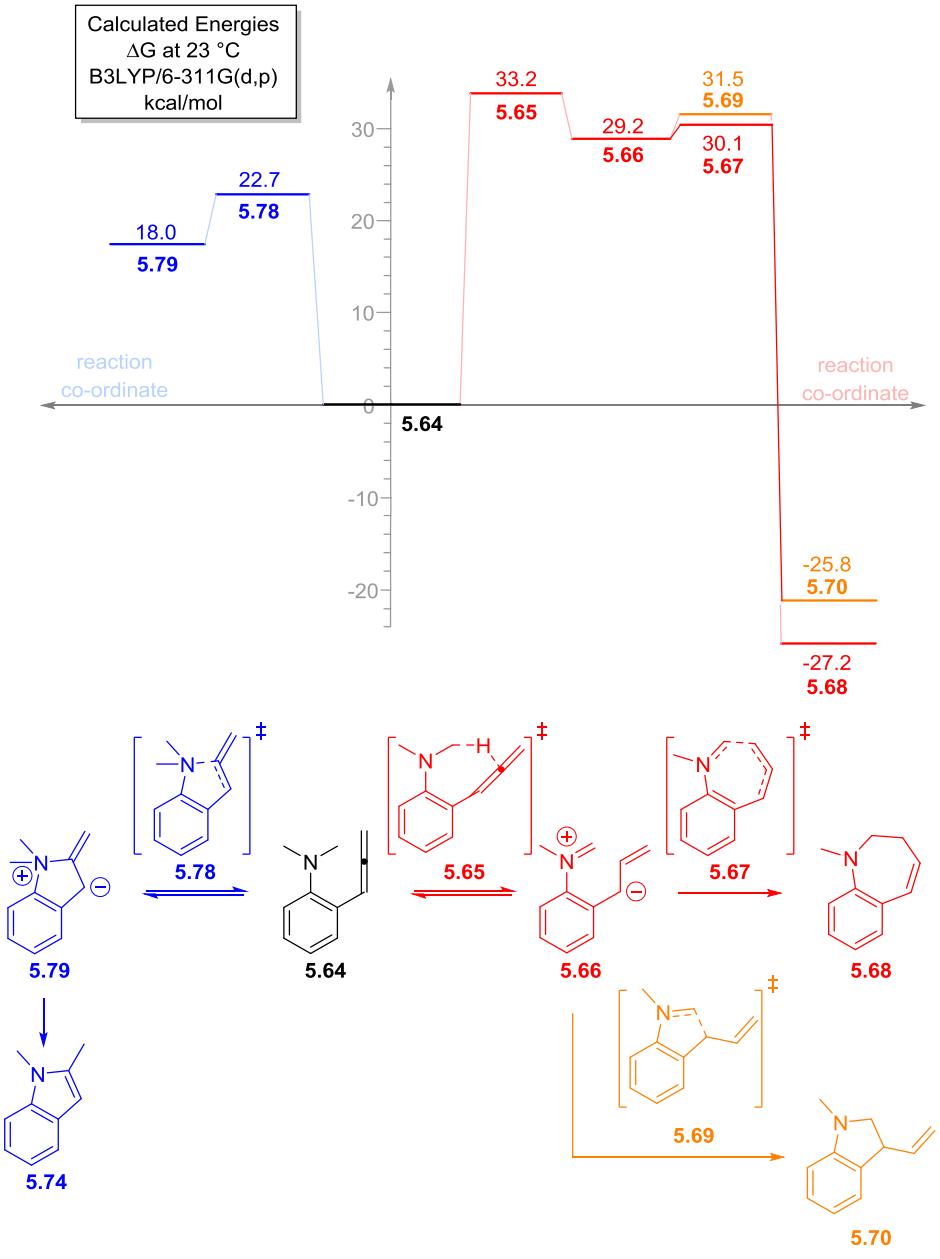
Scheme 5.20: An unexpected reaction to form indoline **5.74** and **5.77**.

Our explanation for these outcomes is that they proceed *via* formation of allenes **5.64** and **5.80**, but then undergo a Type 4 *tert*-amino effect reaction, in which the nitrogen adds to the proximal allene to form a zwitterion (**5.78** and **5.81**). This is then quenched by MeOH to form the corresponding indole (**5.74** and **5.77**) (**Scheme 5.21**).



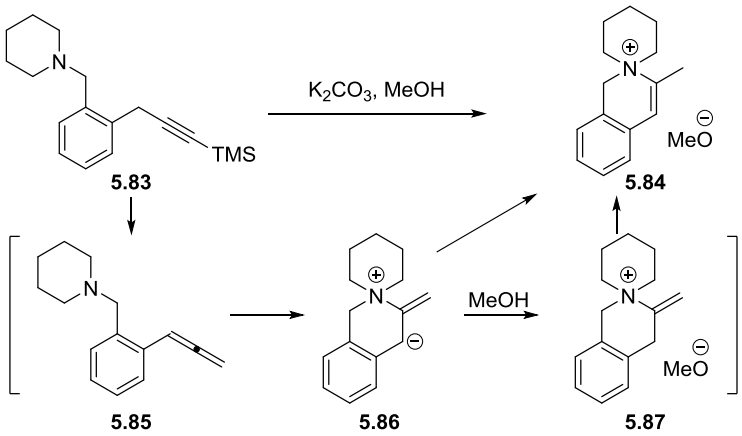
Scheme 5.21: The mechanism of rearrangement of **5.73** and **5.76**.

Following these observations, DFT calculations were performed to establish an energy profile for the reaction (**Scheme 5.22**). The hydride shift step (**5.64** → **5.66**) gave the highest energy barrier (33.2 kcal/mol). The ring closing transition states **5.67** and **5.69** also showed a high energy barrier with that for 7 membered ring closure being slightly lower than that for 5 membered ring closure. Importantly, the Type 4 *tert*-amino effect reaction pathway *via* transition state **5.78** showed the lowest energy barrier (22.7 kcal/mol) leading to zwitterion **5.79**.



Scheme 5.22: Energy diagram for the possible *tert*-amino effect reactions of aminoallene **5.64**.

We also tried to make *ortho*-allenebenzylpiperidine **5.83** but again, the Type 4 *tert*-amino effect reaction occurred to give ammonium salt **5.84** as the major product (**Scheme 5.23**).



Scheme 5.23: Rearrangement of **5.83** to give the ammonium salt **5.84**.

5.4 *tert*-Amino effect reaction of 4-alleneisoindoline

Having found that our new *tert*-amino effect reaction was outpaced by a classical Type 4 process, we designed a new amino allene systems (4-allenylisoindoline **5.88**) in which the nitrogen was fixed in a ring to keep it away from the allene group (**Figure 5.1**).

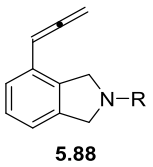
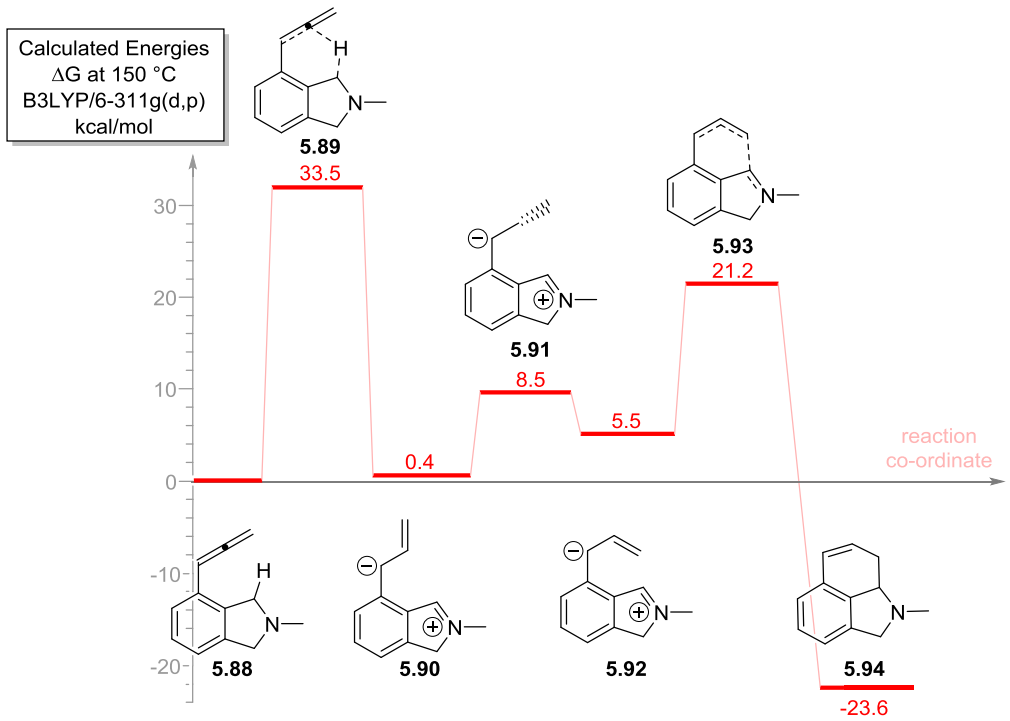


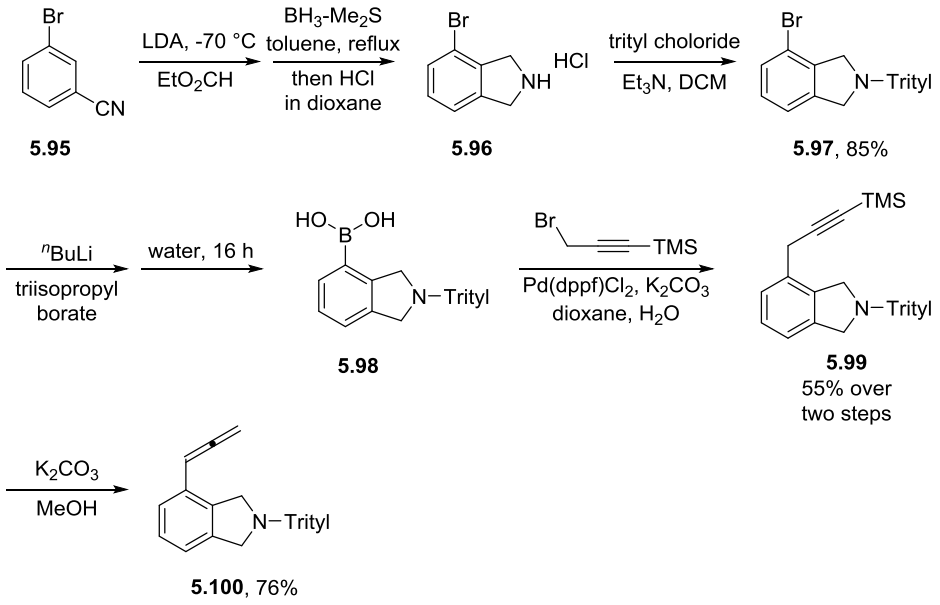
Figure 5.1: 4-Allenylisoindoline **5.88**.

A DFT calculation was first performed to test that the energy barrier for the desired reaction was reasonable and less than that for side-reactions (**Scheme 5.24**). Geometrically, the nitrogen in 4-allenylisoindoline **5.88** could not add to the allene directly ensuring that that pathway was stopped. In the energy diagram, the 1,5-hydride shift transition state **5.89** showed the highest energy barrier (33.5 kcal/mol) at 150 °C and gave zwitterion **5.90**. Following this the alkene rotated towards the iminium group *via* a bond rotation transition state **5.91** (8.5 kcal/mol). Finally zwitterion **5.92** closed to afford the final compound **5.94** *via* transition state **5.93** (21.1 kcal/mol).



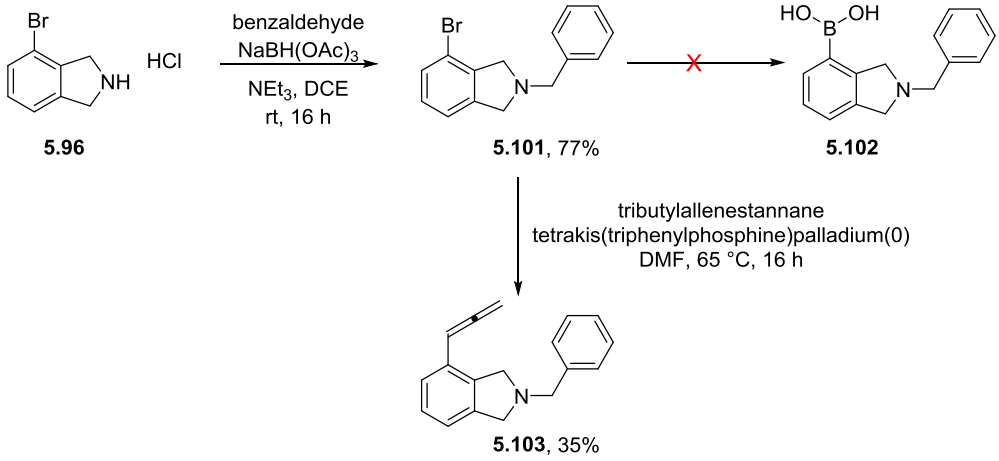
Scheme 5.24: Energy diagram of the thermolysis of 4-alleneisoindoline **5.88**.

Having confirmed that the new type *tert*-amino effect reaction was plausible by DFT calculation, we began the synthesis of 4-allenylisoindoline **5.100**. We first prepared bromoisoindoline HCl salt **5.96** from 3-bromobenzonitrile **5.95** using a literature protocol.[137] Bromoisoindoline HCl salt **5.96** was then protected by tritylation under basic conditions in DCM to give protected bromoisoindoline **5.97** in 85% yield. It was then treated with ^{n}BuLi and triisopropyl borate to give, after hydrolysis by water, boronic acid **5.98**. A Suzuki-Miyaura coupling was then employed on crude **5.98** to give the 4-alkynylisoindoline **5.99** in 55%* yield over two steps. Finally the TMS group was removed to form the terminal alkyne, which spontaneously underwent tautomerization to give 4-allenylisoindoline **5.100** in 76%* yield (**Scheme 5.25**). (*Note: the yields reported for **5.97** and **5.100** are not accurate due to the presence of ca. 10% of an inseparable impurity)



Scheme 5.25: Synthesis of trityl protected 4-alleneisoindoline **5.100**.

We also synthesized the benzyl protected 4-bromoindoline **5.101** from 4-bromoisoindoline salt **5.96** in 75% yield by using benzaldehyde and $NaBH(OAc)_3$ in dichloroethane. Many borylation methods were tried but all showed protodeborolation and no desired product **5.102** could be obtained. Consequently a Stille coupling was used to form the benzyl protected 4-allenylisoindoline **5.103** by coupling bromide **5.101** with tributylallenylstannane using catalytic tetrakis(triphenylphosphine)palladium(0) (**Scheme 5.26**).



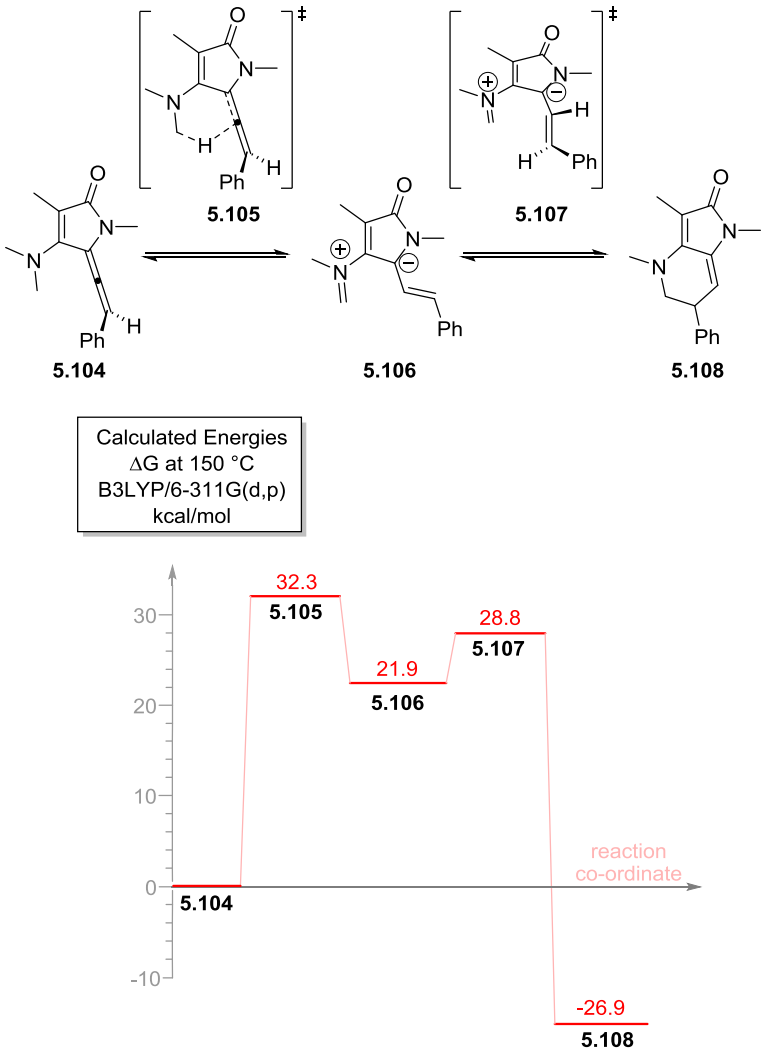
Scheme 5.26: Synthesis of benzyl protected 4-alleneisoindoline **5.103**.

Unfortunately, due to time contracts, the thermolyses of 4-allenylisoindoline **5.100** and **5.103** could not be studied in detail. Preliminary results showed that *N*-deprotection was more facile than the desired ring closure at high temperature.

5.5 DFT calculations on the new type of *tert*-amino effect reactions

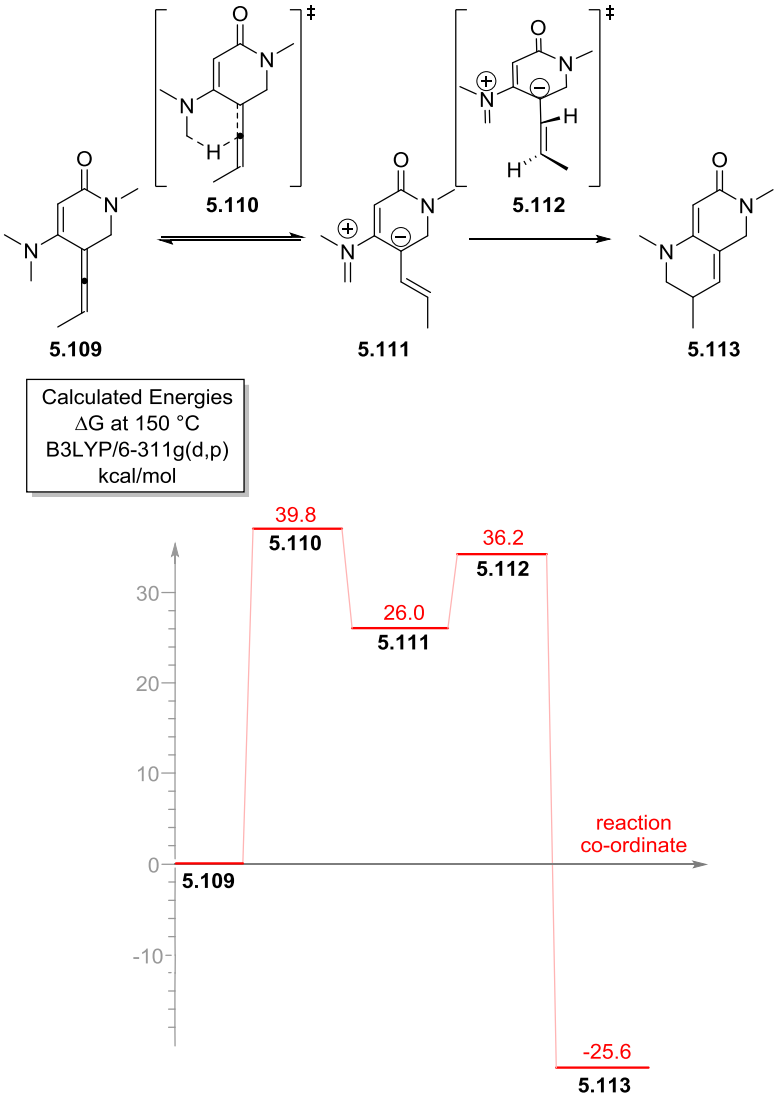
We also modelled other possible *tert*-amino effect reaction by DFT calculation. In this chapter we chose to use the B3LYP functional and 6-311G(d,p) basis set to perform these calculations as they would give reasonably accurate results at low computational cost. Considering the stability issue for some models at a high temperature, DFT calculations assumed that the reactions were performed at 150 °C.

Pyrrolone **5.104** was first examined due to the similarity of its structure to furanone **3.9e** in **Chapter 4**. In this reaction the 1,5-hydride shift transition state **5.105** showed the highest energy barrier at 32.3 kcal/mol at 150 °C, which was similar to the energy barrier for the successful rearrangement of **4.4** to **4.21** *via* corresponding transition state **4.20** (**Scheme 4.6**). Following bond rotation, ring closure *via* **5.107** showed an energy barrier of 28.8 kcal/mol (**Scheme 5.27**).



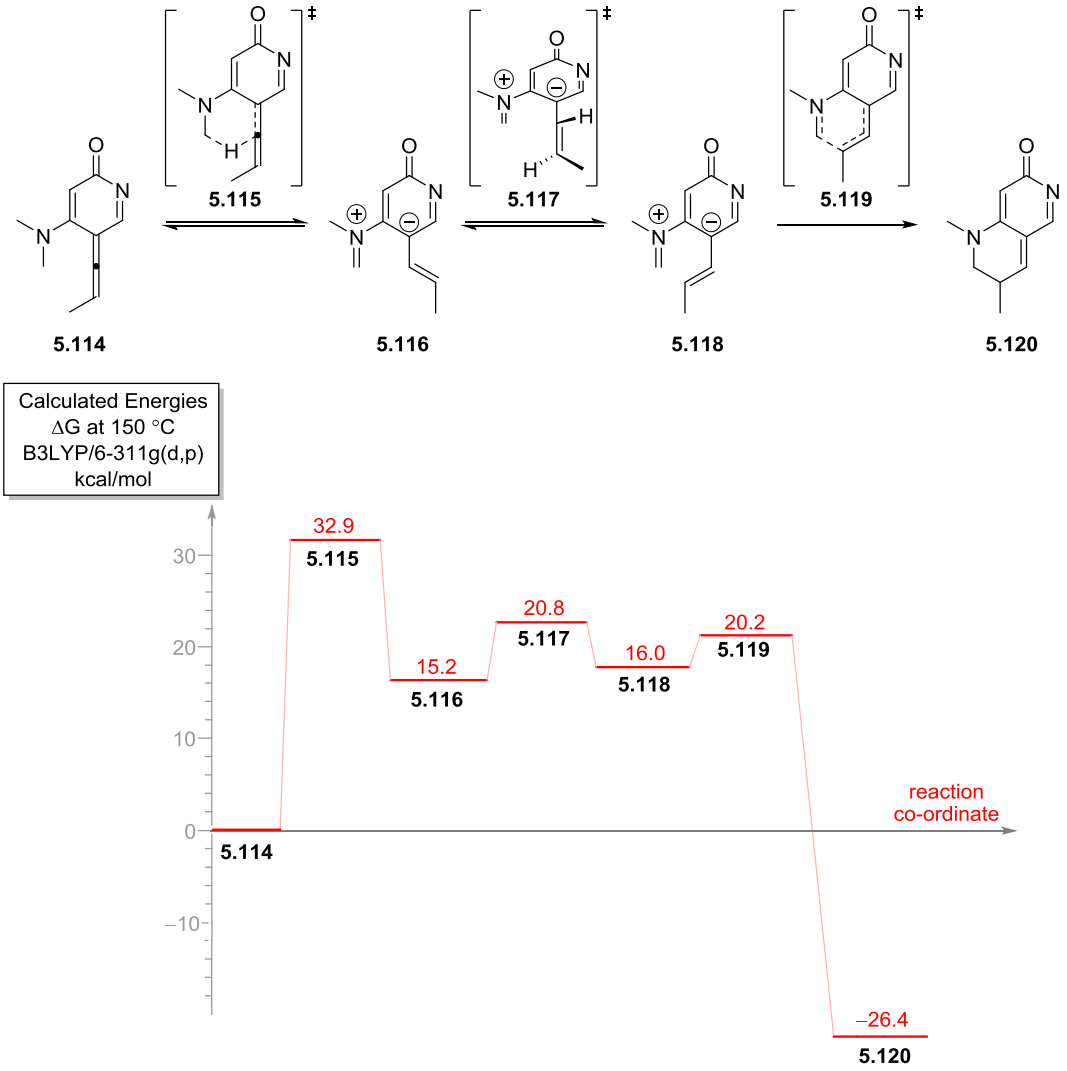
Scheme 5.27: Energy diagram of the *tert*-amino effect reaction of pyrrolone **5.104**.

Dihydropyridinone **5.109** was then examined. The 1,5-hydride shift transition state **5.110** showed a relatively high energy barrier at 39.8 kcal/mol. Intermediate **5.111** was also a high energy species because the anion can only be stabilized by conjugation to the α,β-unsaturated amide and does not lead to generation of an aromatic system. Consequently, the bond rotation and ring closure transition state **5.112** showed a high energy barrier (36.2 kcal/mol) to give product **5.113** (**Scheme 5.29**).



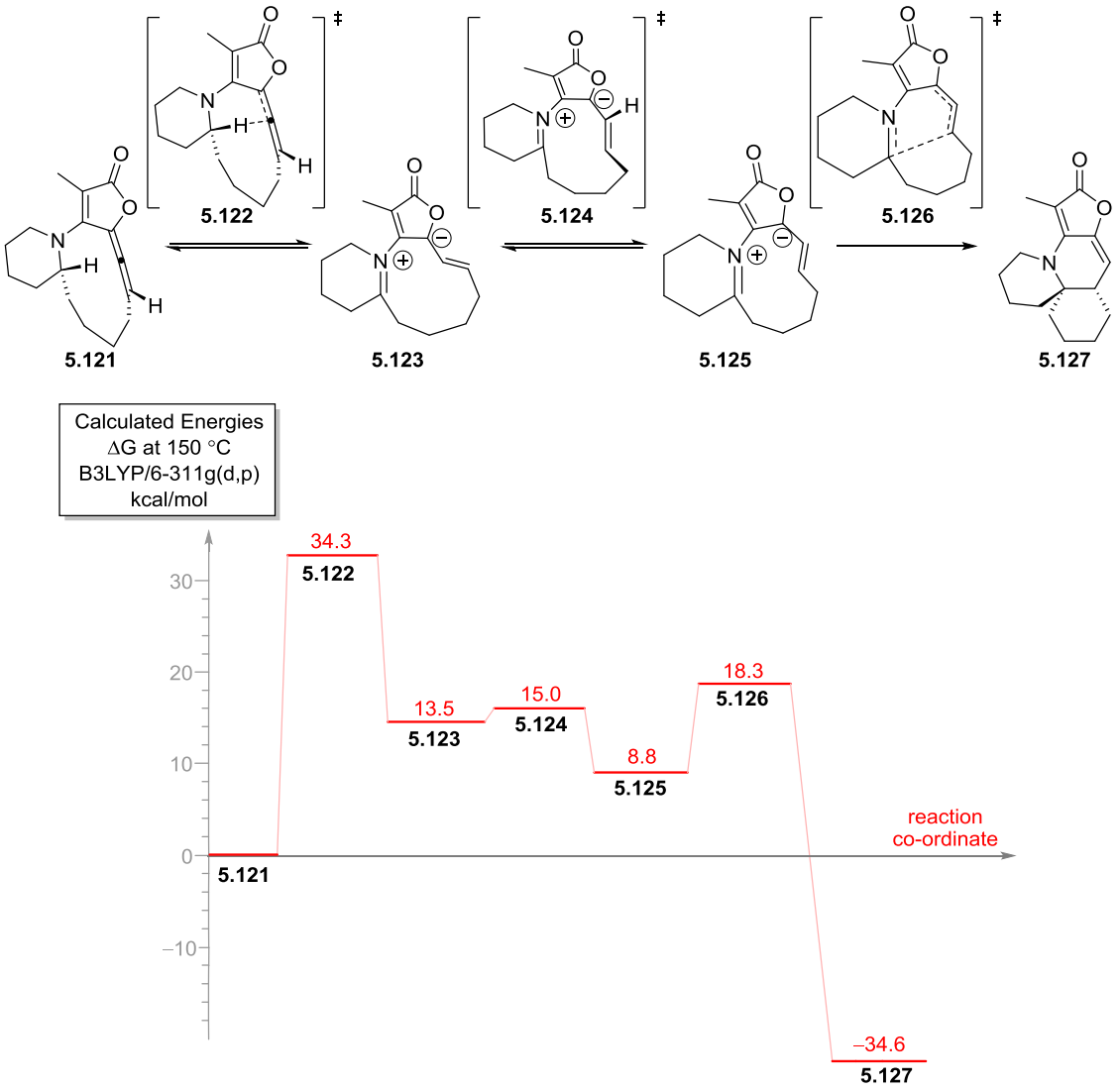
Scheme 5.28: Energy diagram of the *tert*-amino-effect reaction of dihydropyridinone **5.109**.

DFT calculations on pyridinone **5.114** showed a different result in comparison to **5.109**. The 1,5-hydride shift *via* **5.115** showed the highest energy barrier at 32.9 kcal/mol. The energies for both the bond rotation transition state **5.117** and ring closure transition state **5.119** were similar at around 20 kcal/mol. Comparing the energy diagram for rearrangement of pyridinone **5.114** (**Scheme 5.29**) with dihydropyridinone **5.109** (**Schemes 5.28**), the energy barrier presented by each transition state and intermediate in the former is decreased due to the aromatic character displayed by intermediates **5.116** and **5.118**.



Scheme 5.29: Energy diagram of the *tert*-amino effect reaction of pyridinone **5.114**.

Finally we examined furanone **5.121**, in which the amino group is connected to the allene group by virtue of being within a macrocycle. As observed previously, the 1,5-hydride shift step showed the highest energy barrier at 34.9 kcal/mol. The subsequent bond rotation transition state **5.124** and ring closure transition state **5.126** each showed a low energy barrier of less than 20 kcal/mol. Calculations thus predict that the reaction would give spirofuranone **5.127** as the main product (**Scheme 5.31**).



Scheme 5.30: Energy diagram of the *tert*-amino effect reaction of furanone **5.121**.

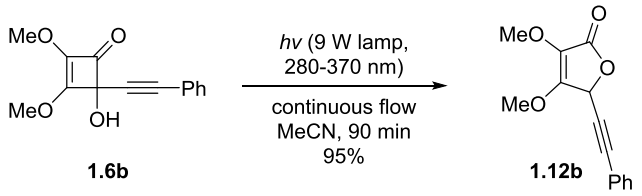
In conclusion, these DFT calculation results suggest that the new type of *tert*-amino effect reaction discovered could work for a range of system at 150 °C or a higher temperature. The highest energy barrier in this type reaction is likely to be for the 1,5-hydride shift step.

5.6 Conclusion and future work

The thermal annulation reactions described in Chapter 4 represent a new type of *tert*-amino-effect reaction. In this type of reaction, the amino group donates a hydride from the α-position to a proximal allene to form a dipolar intermediate. After rotation of the resulting allyl anion, ring closure occurred forming a new ring system. This reaction had been demonstrated in a series thermal annulations transforming aminofuranones into dihydrofuropyridinones. We prepared a series of 4-allenylisoindolines to extend the scope of the reaction to new aromatic ring systems but this requires further work.

Chapter 6: Photolyses of Aminocyclobutenones

Following our success in establishing some new and unusual thermal rearrangements of aminocyclobutenones, we next examined whether each could be triggered photochemically. According to the previous work, 5*H*-furanone are obtained on photolysis of cyclobutenone such as **1.6b** (**Scheme 6.1**).



Scheme 6.1: Published result of photolysis of cyclobutenone **1.6b**.

6.1 Photo rearrangement of aminocyclobutenones

Our investigation of the photolysis of aminocyclobutenones began with an examination of the UV-visible spectrum of aminocyclobutenone **3.4e**, 5*H*-furanone **3.9e** and dihydrofuropyridinone **4.1e** (prepared in **Chapter 3** and **Chapter 4**), in the belief that this could help us to choose a suitable lamp for irradiation (**Figure 6.1**).

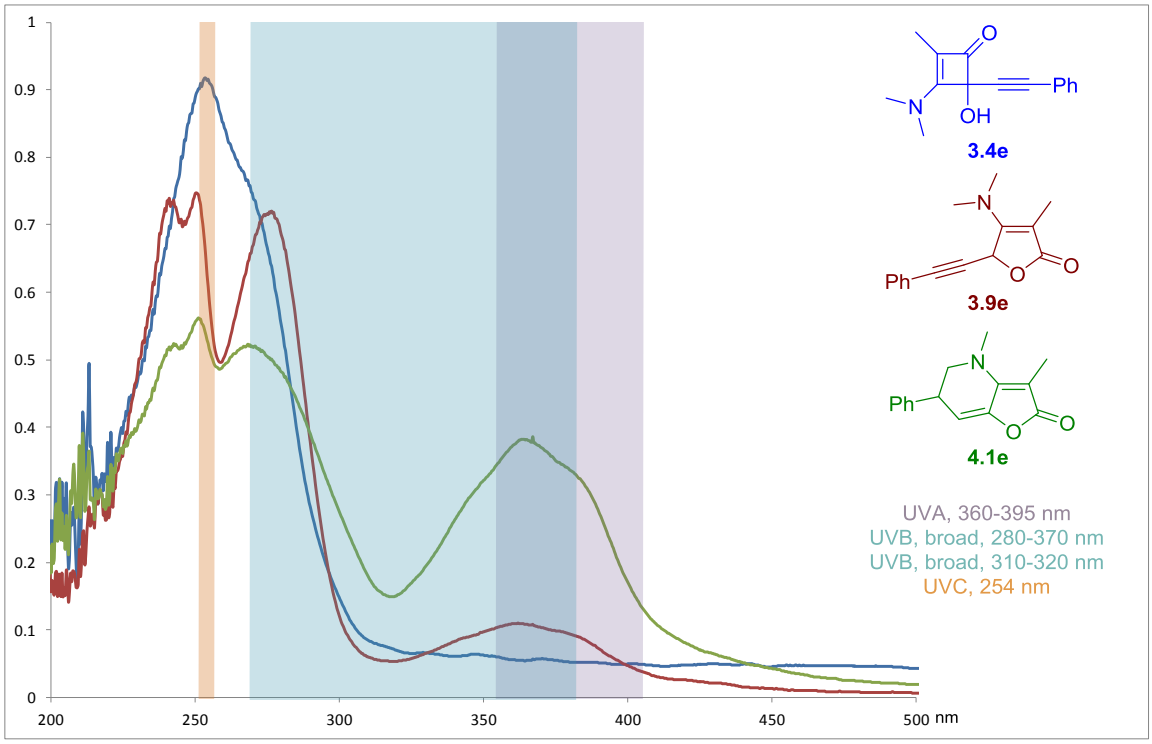
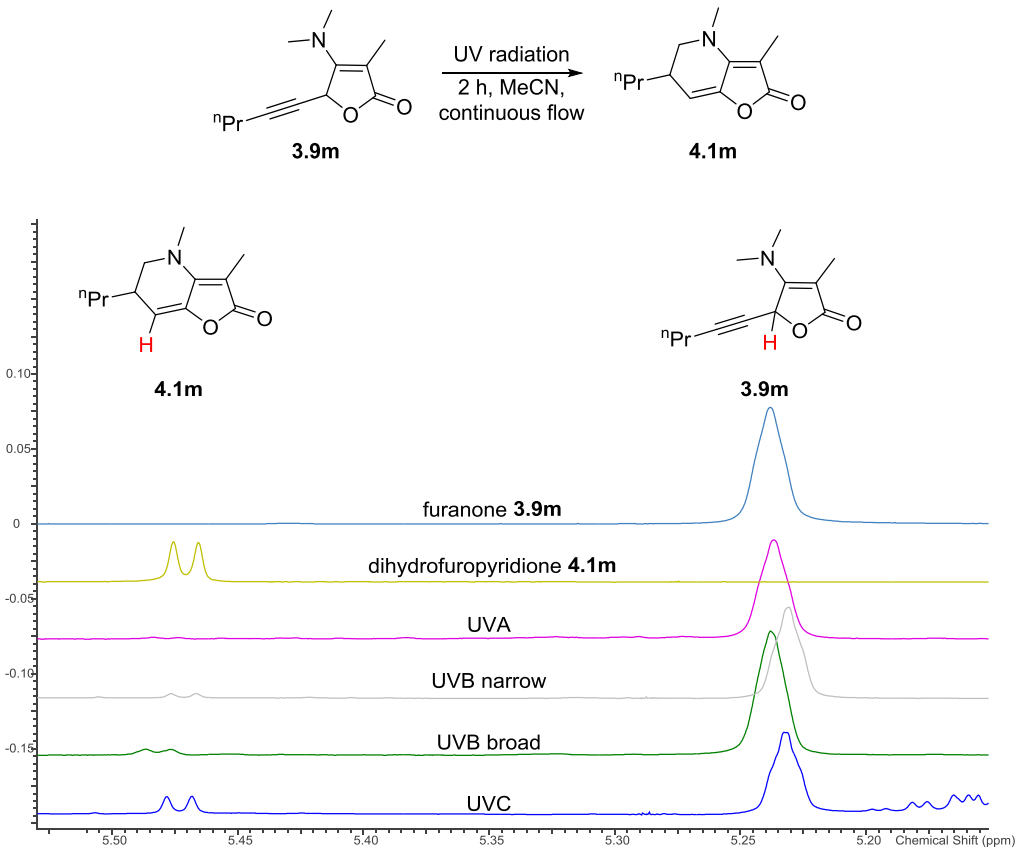


Figure 6.1: UV-visible spectrum of aminocyclobutenone **3.4e**, furanone **3.9e** and dihydrofuropyridinone **4.1e** and the range of wavelengths of UV lamps.

Cyclobutenone **3.4e** gave a UV absorption bands with λ_{max} = 254 and 270 nm, suggesting the use of a UVB lamp (280-340 nm), or a UVC lamp (254 nm) to trigger the reaction. Furanone **3.9e** showed three strong absorptions (λ_{max} = 240, 250 and 280 nm) and a weaker broad absorption (λ_{max} = 360 nm), which were in the range of UVC, UVB broad and UVA lamps respectively. However, the product, dihydrofuropyridinone **4.1e** gave a similar UV absorption to furanone **3.9e**, suggesting that UV radiation might also cause some further photochemical reactions of the product.

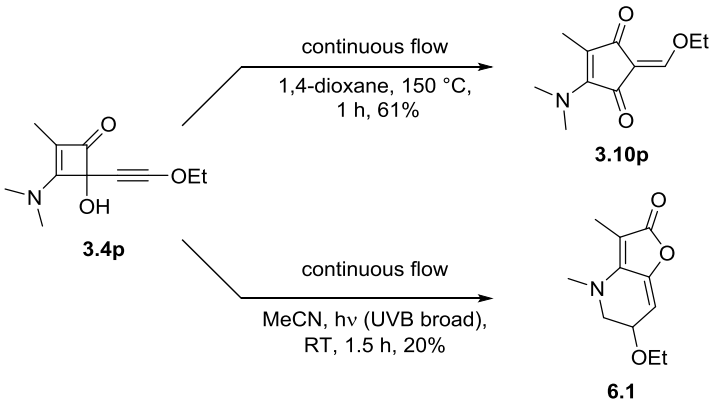
Aminocyclobutenone **3.4m** and furanone **3.9m** were next subjected to irradiation in our flow system by using different UV lamps. When using a UVA lamp, both substrates gave only starting materials. By contrast, use of UVB and UVC lamps gave rise to complex product mixtures with more than ten products detected by UPLC-MS. Also, none of these products could be separated in a pure form by flash column chromatography. This was disappointing considering the good behaviour of these compounds in our previous studies. Consequently, ^{1}H-NMR analysis of the crude product mixture formed on photolysis of furanone **3.9m** under irradiation by different UV lamps were compared in order to better understand the result of these reactions **(Scheme 5.2).**



Scheme 6.2: ^{1}H-NMR of photolysis of furanone **3.9m**.

In all case, furanone **3.9m** could be identified by a singlet at δ_H = 5.25 ppm and dihydrofuropyridinone **4.1m** could be identified by a doublet at δ_H = 5.48 ppm. Photolysis using UVB broad and UVB narrow lamps gave similar results in that most of the starting material **3.9m** remained after 2 h and the ratio of dihydrofuropyridinone **4.1m** to furanone **3.9m** was in 1 : 25. When using a UVC lamp, the ratio of dihydrofuropyridinone **4.1m** and furanone **3.9m** was 1 : 6 while under the UVA irradiation, furanone **3.9m** gave only a hint of the dihydrofuropyridinone **4.1m** after 2 h. However, the UVB broad, UVB narrow and UVC reactions all showed a complex result in both ^{1}H NMR and HPLC-MS analyses.

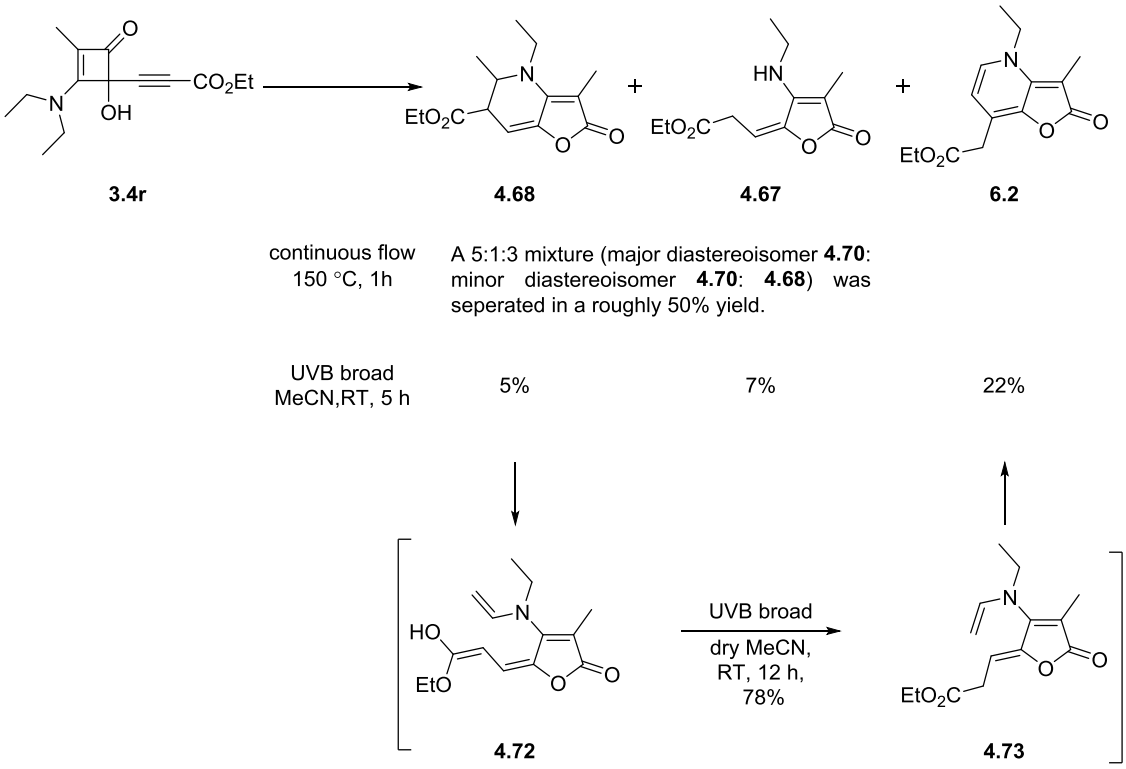
We have examined the photolyses of several aminocyclobutenones using the photo-flow system and most have given rise to complex product mixtures that were not worth the further analysis. An important example was aminocyclobutenone **3.4p** (**Scheme 6.3**). Its thermolysis led to cyclopentenedione **3.10p** in a selective way and no dihydrofuropyridinone **6.1** could be detected. However, under photolysis using a broad wavelength UVB lamp it gave a complex mixture that included dihydrofuropyridinone **6.1** in 20% yield. No cyclopentenedione **3.10p** was detected.



Scheme 6.3: Thermal and photo rearrangement of aminocyclobutenone **3.4p**.

6.2 Photolysis of an ester substituted diethylaminocyclobutenone

In **Section 4.8**, we discussed a new rearrangement of aminocyclobutenones **3.4r** in which the expected product **4.68** lost a vinyl group to form a new furanone **4.67** (**Scheme 4.16**). In the photolysis of aminocyclobutenone **3.4r**, the same furanone **4.67** was observed together with a new furopyridinone **6.2** (**Scheme 6.4**). Further study showed that the photolysis of dihydrofuropyridinone **4.68** in dry acetonitrile under argon gave furopyridinone **6.2** in 78% yield. This result suggests that **4.68** first undergoes ring opening to form intermediate **4.72**, which then tautomerizes to **4.73**. Intermediate **4.73** undergoes a ring closure reaction to form the new furopyridinone **6.2**.



Scheme 6.4: Thermolysis and photolysis of ester substituted diethylaminocyclobutenone **4.68**.

6.3 Conclusion

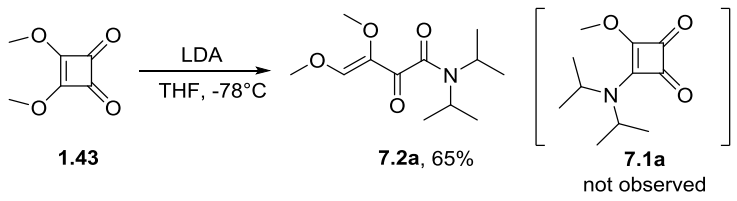
Photolyses of aminocyclobutenones can lead to furanones and/or dihydrofuropyridinones. However, as these products are not stable under UV radiation, all of the flow-photo rearrangements gave rise to complex product mixtures with products formed in low yield. This is in stark contrast to the results attained by thermolyses of aminolcyclobutenones. Photo rearrangement did uncover some new rearrangement pathways.

Chapter 7: Formation of 2-oxobut-3-enamides from Cyclobutenediones

Previously, 4-hydroxy-4-arylcyclobutenones and 4-hydroxy-4-alkynylcyclobutenone have been obtained in high yield by the addition of an organolithium reagent to a cyclobutenedione. However, to the best of our knowledge, the addition of lithium amides to cyclobutenedione has not been reported. Therefore we decided to see if they could be used to substituted alkoxides to introduce amine residues. Surprisingly, from these reactions we did not obtain any aminocyclobutenones but instead generated a 2-oxobut-3-enamides. In this chapter we examine the new rearrangement of cyclobutenones to 2-oxobut-3-enamide in more detail.

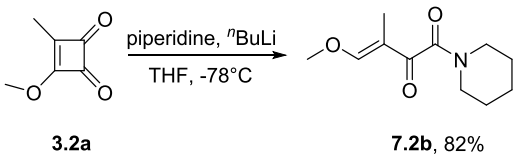
7.1 Rearrangement of 4-aminocyclobutenone anions to 2-oxobut-3-enamide

When trying to synthesize aminocyclobutenedione **7.1a** from LDA and 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43**, none of that product was obtained. Instead, (*Z*)-*N*,*N*-diisopropyl-3,4-dimethoxy-2-oxobut-3-enamide **7.2a** was isolated as the sole identifiable product (**Scheme 7.1**). This result implicated the discovery of a new mode of cyclobutenone ring opening reaction.



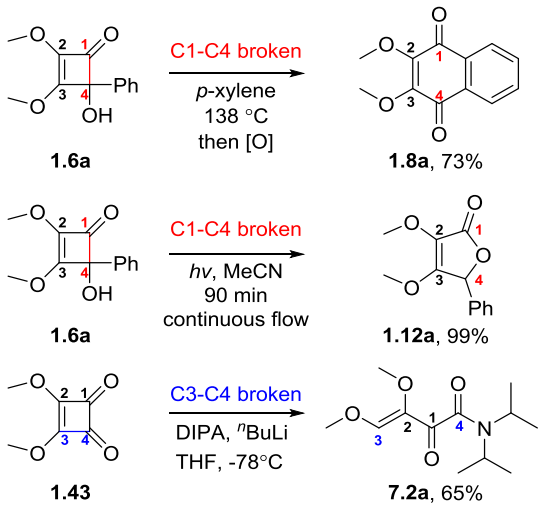
Scheme 7.1: Lithium amide addition and rearrangement to form 2-oxobut-3-enamide **7.2a**.

This result was replicated for the reaction between 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **3.2a** and lithium piperidide, where (*E*)-4-methoxy-3-methyl-1-(piperidin-1-yl)but-3-ene-1,2-dione **7.2b** was obtained (**Scheme 7.2**).



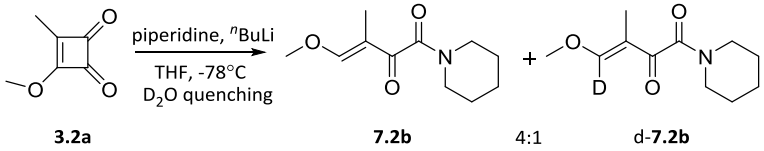
Scheme 7.2: Lithium amide addition and rearrangement to form 2-oxobut-3-enamide **7.2b**

Normally rearrangement of cyclobutenone **1.6** occurs on heating or exposure to UV irradiation and leads to scission of the C1-C4 bond to form quinone **1.8** or furanone **1.12** (**Section 1.1** and **Section 1.6.2**). However, in this case, it is the C3-C4 bond that breaks on exposure to a lithium amide at –78 °C to form a 2-oxobut-3-enamide **7.2** (**Scheme 7.3**).

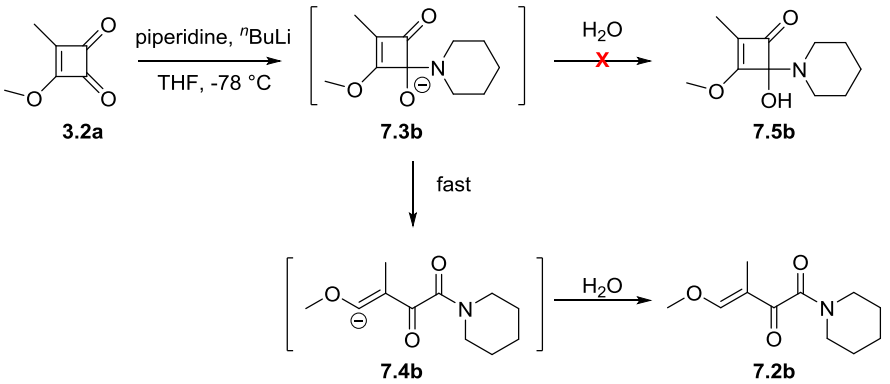


Scheme 7.3: Different pathways for rearrangement of cyclobutenones to form quinone **1.8**, furanone **1.12** and 2-oxobut-3-enamide **7.2**.

Notably, when using D_2O to quench the reaction at –78 °C, a 4:1 mixture of the protonated product **7.2b** and deuterated product d-**7.2b** was obtained (**Scheme 7.4**). This suggested that the formation of 2-oxobut-3-enamide anion **7.4b** occurred at –78 °C and was fast and irreversible. Therefore, when a water quench was used, 2-oxobut-3-enamide **7.2b** was formed as the only product (**Scheme 7.5**).



Scheme 7.4: Deuterium labelling reaction of rearrangement of **3.2a**.



Scheme 7.5: Plausible mechanism to form 2-oxobut-3-enamide **7.2**.

7.2 DFT calculations on the novel rearrangement.

To confirm the viability of this mechanism, NBO analysis of 4-hydroxycyclobutenone **7.5c** was performed (**Figure 7.1**). In cyclobutenone **7.5c**, the bond distance of C1-C4 is 1.586 Å, which implies that it is a weaker σ bond than the C3-C4 (1.528 Å). Moreover no transition state for ring opening could be found that involved breaking the C3-C4 bond. This confirmed that the rearrangement could not occur *via* cyclobutenone **7.5c**.

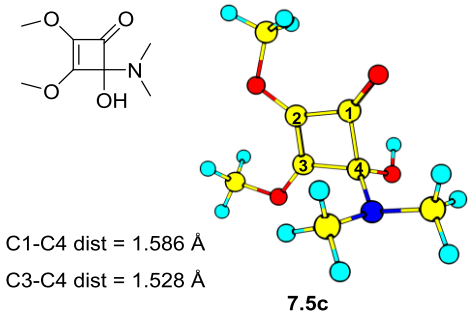
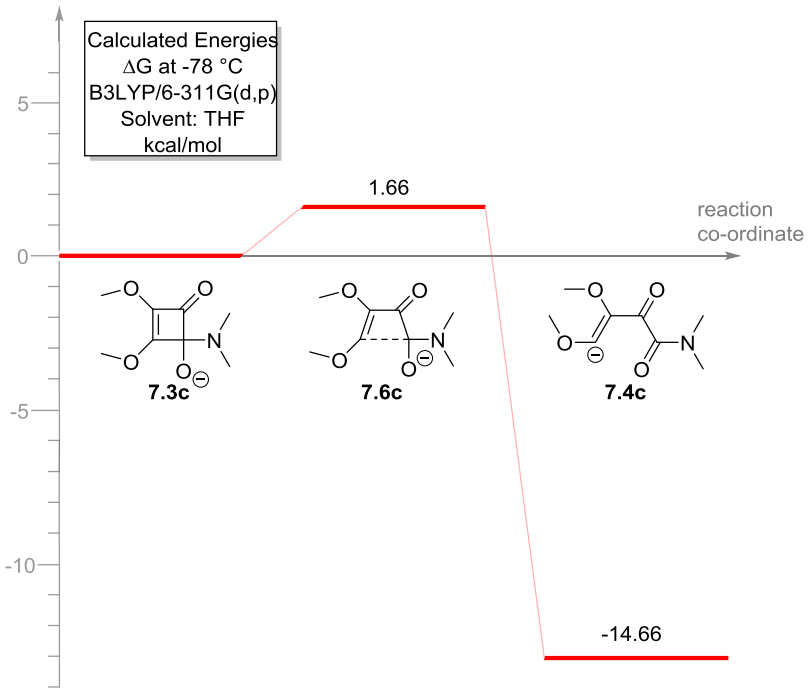


Figure 7.1: Geometry of the lowest energy conformation of cyclobutenone **7.5c**.
Geometry and NBO at B3LYP/6-31G(d).

Following this we modified the possible reaction pathway from cyclobutenone anion **7.3c** to 2-oxobut-3-enamide anion **7.4c** *via* transition state **7.6c** (**Scheme 7.6**). These gave a very low energy barrier (1.66 kcal/mol) for the ring opening transition state **7.6c**, which supports our experimental result that the reaction occurred at –78 °C. Moreover, the energy of the 2-oxobut-3-enamide anion **7.4c** is 14.66 kcal/mol lower than the starting alkoxide **7.3c**, meaning that it is more favoured than the starting alkoxide **7.3c** and the reaction could be considered irreversible at –78 °C.



Scheme 7.6: Energy diagram of rearrangement of cyclobutenone anion **7.3c**

B3LYP/6-311G(d,p), scrf=IEFPCM=THF, temperature=195.15K

NBO analysis was then conducted to understand the nature of this rearrangement. In **7.3c**, the interaction energy of the lone pair of electrons on O6 and σ* orbital (C-N) was 24.34 kcal/mol, which implies strong conjugation (**Figure 7.2**). It also shows a high interaction energy (19.74 kcal/mol) due to interaction of the lone pair of electrons on O6 and σ* orbital (C3-C4).

In transition state **7.6c**, the C3-C4 bond is broken and the bond distance increases to 1.89 Å (**Figure 7.2**). The lone pairs of electrons on O5 and N both show a significant interaction with σ* orbital (C3-C4). The dihedral angle O-C-N-C is –41.9°, while the interaction energy of the lone pair of electrons of O5 and σ* orbital (C-N) is 22.59 kcal/mol, suggesting an amide formation.

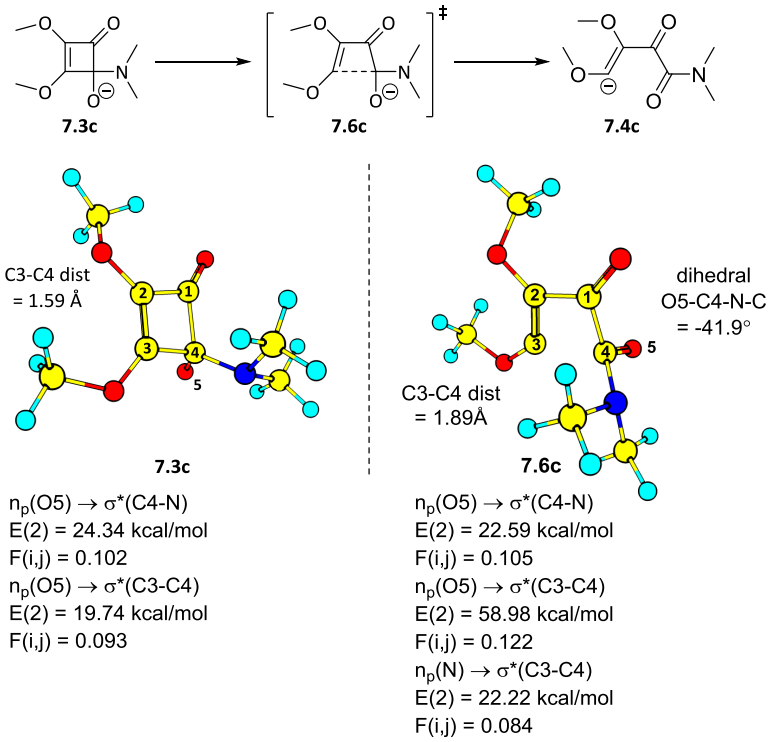


Figure 7.2: Geometry of the lowest energy conformation of cyclobutenone anion **7.3c** and transition state **7.6c**.

Geometry and NBO at B3LYP/6-311G(d,p), scrf=IEFPCM=THF.

Product **7.4c** shows a highly conjugated α,β-unsaturated carbonyl structure. NBO analysis shows that the negative charge is now located on C3 and stabilized by interaction with the σ* orbital (C2-O). The amide group also contributes significantly to the stability of **7.4c**, dramatically lowering its energy (**Figure 7.3**).

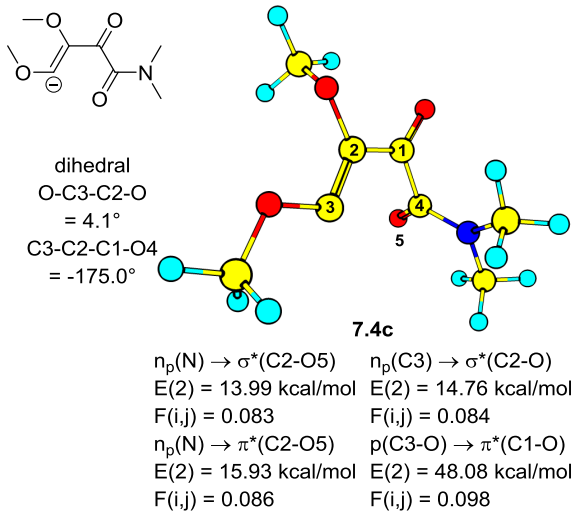
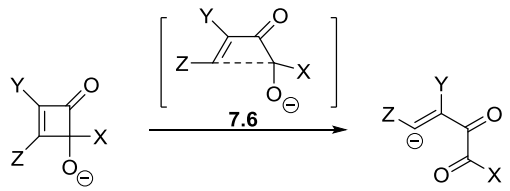


Figure 7.3: Geometry of the lowest energy conformation of product **7.4c**.

Geometry and NBO at B3LYP/6-311G(d,p), scrf=IEFPCM=THF

Having discovered this new mode of cyclobutenedione ring opening, we decided to ascertain whether other lithium nucleophiles could also trigger the rearrangement (**Table 7.1**). To do so, we examined various cyclobutenone anions by DFT calculation of the Gibbs energies for both the transition states **7.6** and the resulting anions **7.4**. When the nucleophiles were a lithium amide or alkoxide (**7.3c**, **d**, **g-j**), carbanion formations (**7.4c**, **d**, **g-j**) were always favoured due to the thermodynamic stability of the amide or ester residues. When aryl anions were added (**7.3e** and **f**), these reactions showed high energy transition states (**7.6e** and **7.6f)**, which prevented the reaction from occurring at –78 °C. Cyclobutenone formation (**7.3k**) was exclusively favoured when a sulfonyl anion was added. In this case its inability to form a stable, conjugated π-system raised the energy of the product **7.4k** significantly.



7.3 **7.4**

7.3	***solvent***	***X =***	***Y =***	***Z =***	$\Delta G_{7.6}$ ***(kcal/mol)***	$\Delta G_{7.4}$ ***(kcal/mol)***
c	THF	$N(Me)_2$	MeO	MeO	1.6	-12.6
d	THF	$N(Me)_2$	Me	MeO	4.0	-4.3
e	THF	*p*-DMAPh	Me	MeO	6.3	-1.9
f	THF	Ph	Me	MeO	7.6	-1.6
g	THF	MeO	MeO	MeO	5.0	-3.3
h	THF	$N(Me)_2$	Me	$N(Me)_2$	5.8	-2.6
i	THF	$N(Me)_2$	H	$N(Me)_2$	4.5	-9.2
j	THF	MeO	Me	MeO	5.7	-4.2
k	THF	MeS	Me	MeO	11.5	10.8

Table 7.1: DFT calculation on the rearrangement of cyclobutenone alkoxides **7.3**.

B3LYP/6-31G(d), temperature=195.15k, scrf=IEFPCM=THF

As the starting material, product and transition state were all anions, it seemed likely that solvent effects might play a significant role in this reaction. Consequently we examined the reaction in different solvents and compared the result (**Table 7.2**).

solvent	*ε = (20°)*	$\Delta G_{7.6}$ *(kcal/mol)*	$\Delta G_{7.4}$ *(kcal/mol)*
gas phase	/	2.4	-7.7
hexane	1.88	3.7	-6.1
Toluene	2.38	4.2	-5.6
THF	7.58	5.7	-4.2
DCM	8.93	5.9	-3.9
MeOH	32.70	6.7	-2.5
DMSO	46.68	6.8	-2.4

Table 7.2: Solvent effects in the new rearrangement of **7.4j**.
B3LYP/6-31G(d), temperature=195.15 K, scrf=IEFPCM=solvent

It is known that when the solvent effect is not considered (gas phase reaction), DFT calculations underestimate the Gibbs energy for the transition state leading to ring opening and overestimates the energy difference between the starting material and product. In these reactions, non-polar solvents (small ε) gave a low energy barrier for the rearrangement and a high energy difference between the starting material and product. Comparatively, a polar solvent (large ε) gave a higher energy barrier for the reaction and a lower energy difference between the starting material and product. The ΔΔG values were next compared between a solvent based reaction and a gas phase reaction for the starting material **7.3**, product **7.4** and transition state **7.6** (**Figure 7.4**). All of the calculated Gibbs energies decreased due to solvent effects. ΔΔG for product **7.6** showed the largest decrease. In this case ΔΔG increased with increasing solvent polarity. Hence a polar solvent would be expected to give a higher energy barrier for the transition state and a lower energy difference between starting material and product. Consequently, we would expect the rearrangement to favour non-polar solvents where we might employ a lower reaction temperature and achieve greater selectivity.

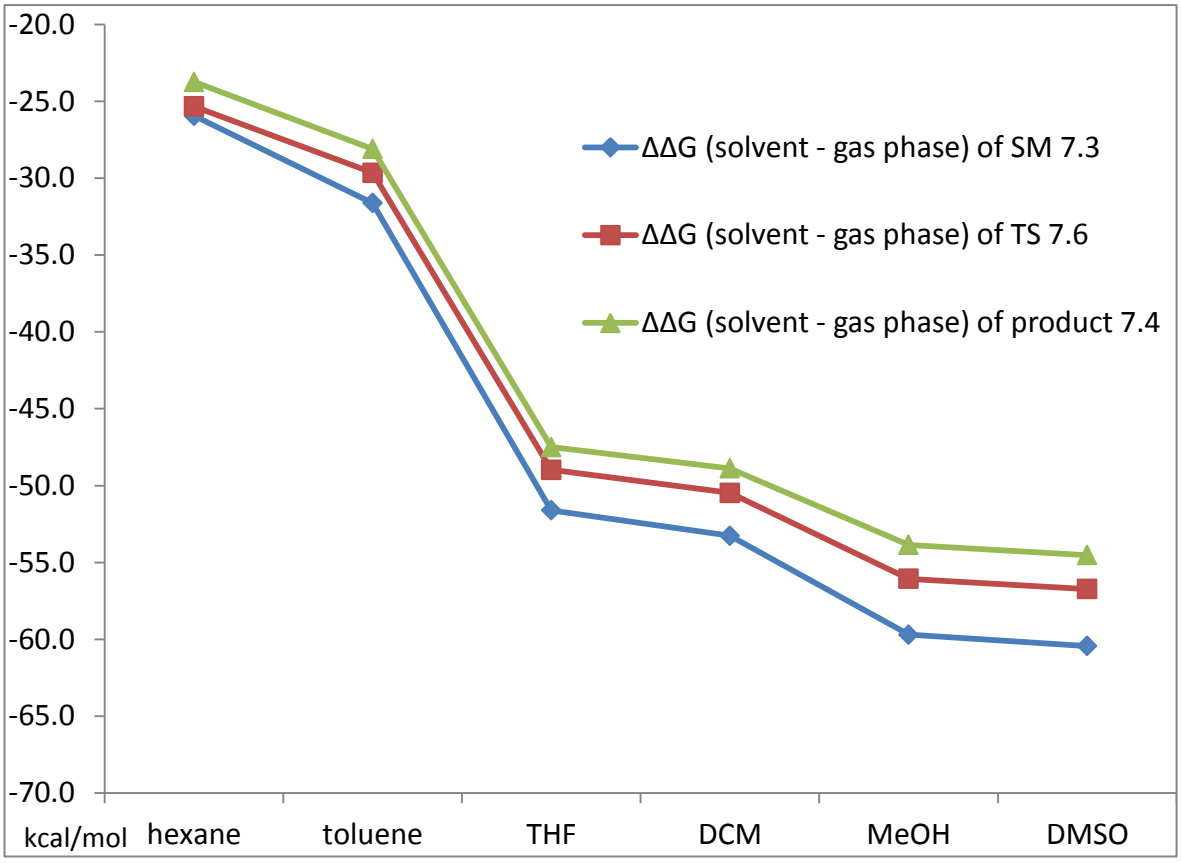
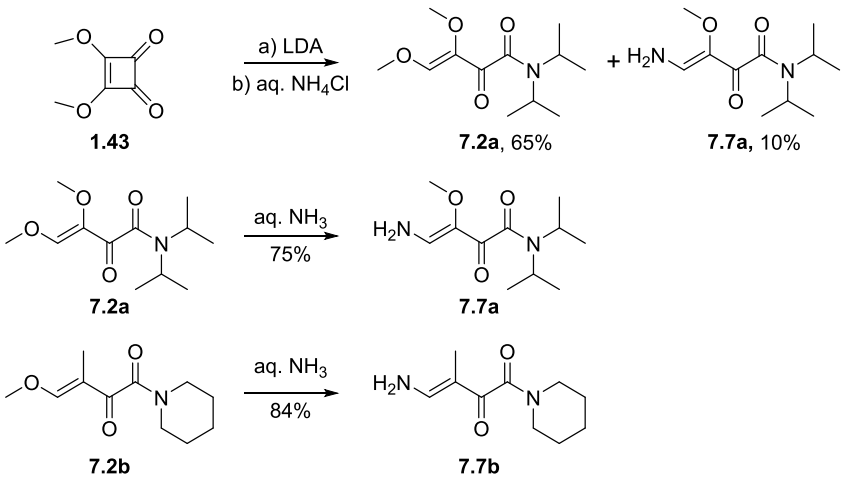


Figure 7.4: $\Delta\Delta G_{solvent\text{-}gas\ phase}$ of six solvents. B3LYP/6-31G(d), temperature=195.15K, scrf=IEFPCM=solvent.

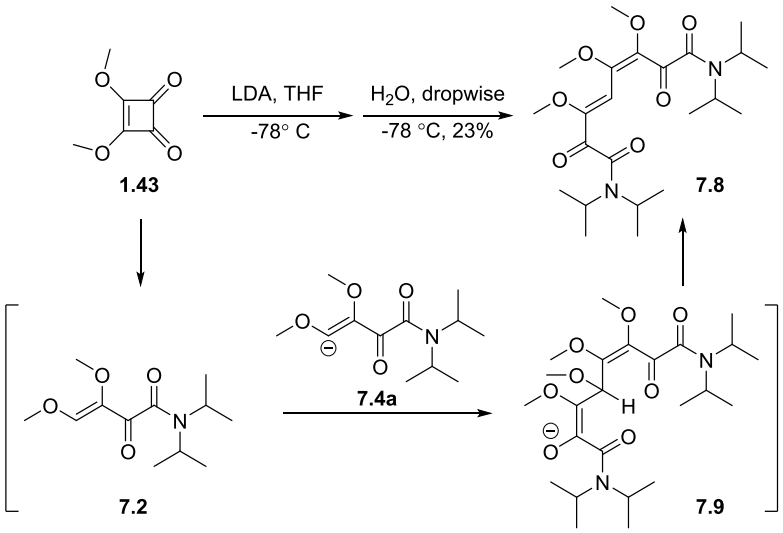
7.3 Michael addition on 2-oxobut-3-enamide compound

Since the 2-oxobut-3-enamide compound contained an α,β-unsaturated carbonyl unit, it has the potential to be Michael acceptor. Indeed, this was observed when reactions were quenched with aq. NH_4Cl, leading to 2-oxobut-3-enamide **7.7a**. Further studies confirmed that treatment of 2-oxobut-3-enamides **7.2a** and **7.2b** with aqueous ammonia gave **7.7a** and **7.7b** respectively in a high yield (**Scheme 7.7**).



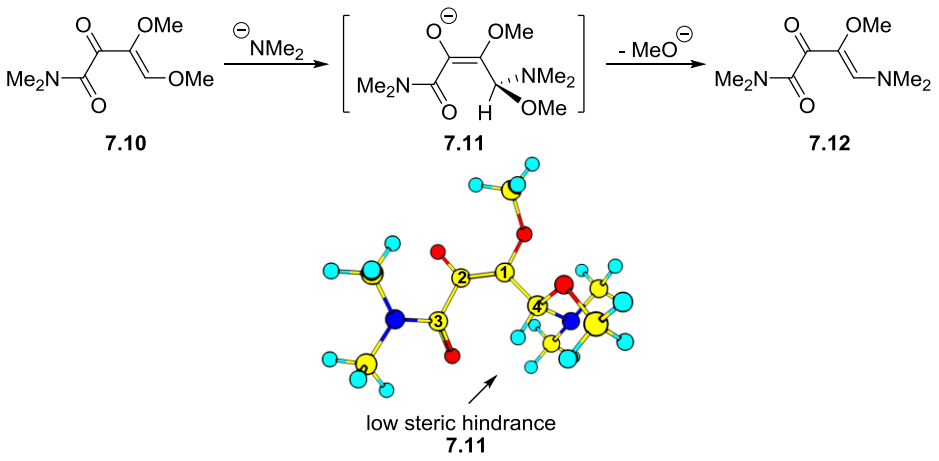
Scheme 7.7: Michael addition and elimination reactions of 2-oxobut-3-enamides **7.2**.

Moreover, when the organolithium addition reaction of **7.2a** was quenched with water at –78 °C, dimer **7.8** was formed in 23% yield (**Scheme 7.8**).



Scheme 7.8: Michael addition to form dimer **7.8**

All the Michael addition products gave the same geometric isomer *via* rotamer **7.11** (**Scheme 7.9**). It displayed the least steric hindrance as none of the large groups clash. Scans of the dihedral angle C2-C1-C4-H were also performed and supported this result (**Figure 7.5**). Consequently, only product **7.12** was formed in this reaction.



Scheme 7.9: Selectivity in Michael addition.

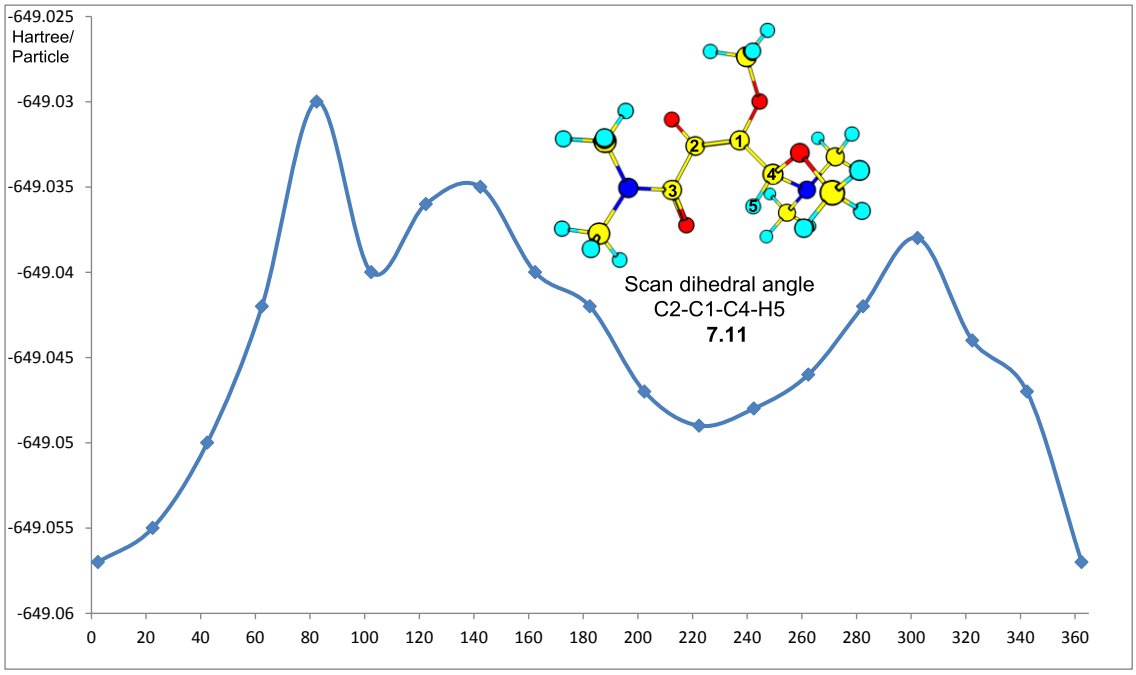
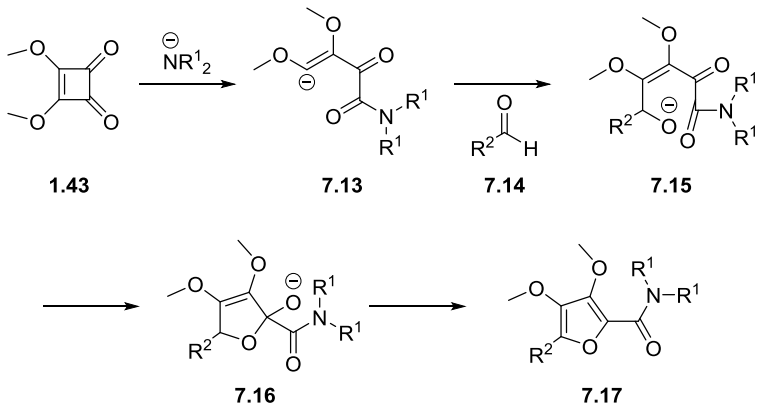


Figure 7.5: Scan of the influence of dihedral angle C2-C1-C4-H5 in **7.11** using B3LYP/6-31G(d).

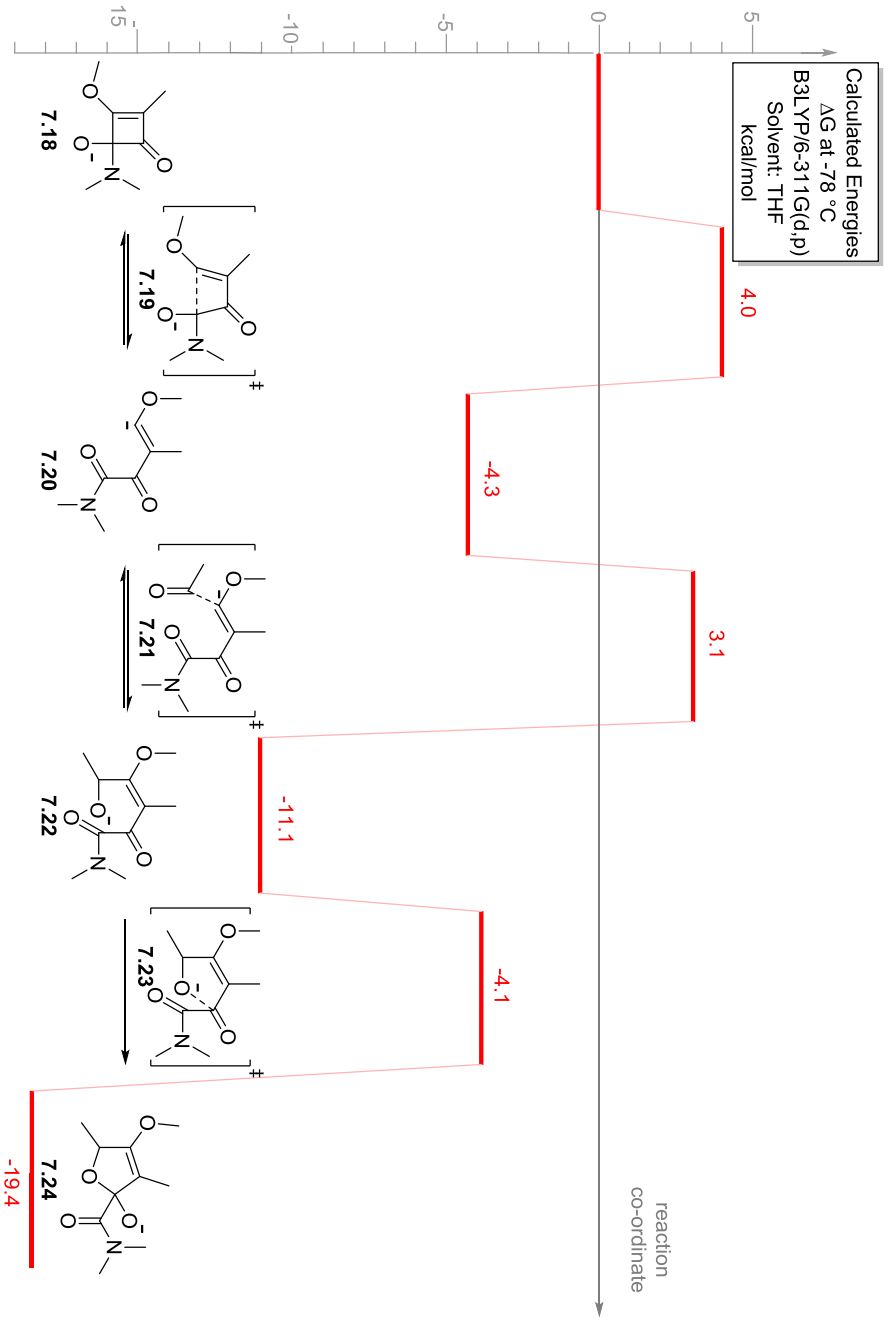
7.4 Conclusion and Future Work

A new mode of cyclobutenedione scission has been discovered resulting in an enamide. Though time constraints prevented us from examining the reaction fully, it appears to offer many new opportunities. For example, we postulate that the rearrangement could be used to prepare highly substituted furans (**Scheme 7.10**). Nucleophilic addition of the enamide anion to an aldehyde **7.14** would generate alkoxide **7.15**, which can then cyclise to furanol **7.16**. Dehydration would then give furan **7.17** as the final product. Thus, highly substituted furans could be easily synthesised from the simple and cheap starting materials **1.43** and **7.14**.



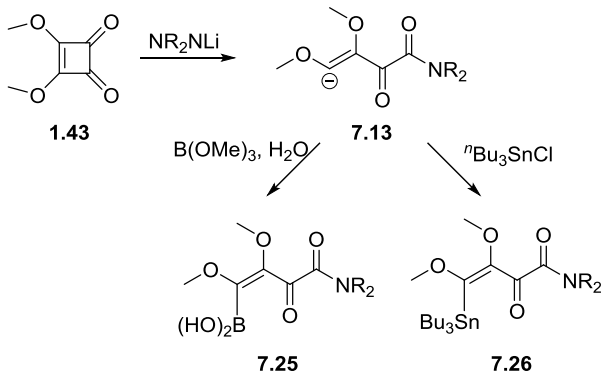
Scheme 7.10: Future plan to make furan from cyclobutenone.

DFT calculations for this transformation indicate a moderate energy barrier for addition at –78 °C, suggesting that the plan is plausible (**Scheme 7.11**).



Scheme 7.11: DFT calculations for the rearrangement of cyclobutenone alkoxide **7.18**. B3LYP/6-311G(d,p), temperature=195.15K, scrf=IEFPCM=THF.

Moreover, the 2-oxobut-3-enamide anions could be transformed to boronic acids or organotin compounds, thus facilitating palladium catalysed cross couplings using Suzuki and Stille reactions (**Scheme 7.12**).



Scheme 7.12: Future plans to make organotin compounds and boronic acids from cyclobutenone **1.43**.

Chapter 8: Experimental

8.1 General experimental techniques

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

Infrared Spectra: Infrared spectra were recorded neat as thin films or as solid compressions using a Nicolet 380 Laboratory FT-IR spectrometer or a Nicolet iS5 Laboratory FT-IR spectrometer. Absorption maxima (υ_{max}) are expressed as s, strong; m, medium; w, weak or br, broad and are quoted in wavenumbers (cm^{-1}).

NMR Spectra: Proton (^{1}H) and carbon (^{13}C) spectra were recorded on a Bruker AVIIIHD 400 (400/100 MHz) or a Bruker AVIIIHD 500 (500/125 MHz) spectrometer at 298 K unless stated otherwise. Experiments were carried out in deuterated chloroform ($CDCl_3$) unless otherwise stated, supplied by Sigma Aldrich and stored over dried K_2CO_3 to neutralise trace acidity. Chemical shifts were reported in parts per million (ppm) downfield of tetramethylsilane with residual solvent as the internal standard. Assignments were made on the basis of chemical shifts, coupling constants, DEPT-135, COSY, HMQC and comparison with literature values where available. Resonances are depicted as s (singlet), d (doublet), t (triplet), q (quartet), sxt (sextet), sept (septet), m (multiplet), br (broad) and app (apparent). 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 (Bruker Daltonics, Bremen, Germany) 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 (0.1% formic acid) over five min. Spectra were recorded using positive/negative ion electrospray ionization as specified and were calculated to four decimal places from the molecular formula. All samples were analyzed and recorded by Ms. Julie Herniman at the University of Southampton.

Low Resolution Mass Spectrometry was carried out using electrospray ionisation on a directly injected WATERS quadrupole MSD using ESI+ with MeOH/acetonitrile as solvent. *m/z* values were reported with their respective abundances.

X-ray data were recorded by Dr. Mark Light at the UK National Crystallography Service, University of Southampton using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at 100 K.

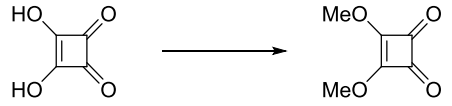
Chromatography: Thin layer chromatography was carried out on Merck Silica Gel 60 Å F 254 0.2 mm plates, which were visualised under fluorescence UV (254 nm) followed by staining with iodine and/or aqueous 1% $KMnO_4$, methanolic H_2SO_4 or methanolic vanillin. Column chromatography was carried out under slight positive pressure using silica gel with the stated solvent system. Preparative TLC was carried out on Analtech Inc silica gel F 254 plates, which were visualised under fluorescence UV (254 nm and/or 326 nm).

HPLC: Preparative High Performance Liquid Chromatography was carried out using a Macherey-Nagel VP 250/10 NUCLEODUR 100-5 column (250 × 10 mm at 5 mL/min).

Solvents and Reagents: Reagents that were commercially available were purchased and used without further purification unless stated otherwise. THF was distilled from sodium benzophenone ketyl under argon. Toluene was distilled from sodium under argon. All air sensitive reactions were carried out under argon using flame or oven dried apparatus.

8.2 Experimental procedures for Chapter 3

3,4-dimethoxycyclobut-3-ene-1,2-dione (1.43)



3.1
$C_4H_2O_4$
Mol Wt:114.06

1.43
$C_6H_6O_4$
Mol Wt:142.11

To a solution of 3,4-dihydroxycyclobut-3-ene-1,2-dione **3.1** (10.0 g, 87.7 mmol) in MeOH (100 mL) was added trimethylorthoformate (20 mL, 179 mmol). The mixture was refluxed for 16 h and cooled to RT. The solution was concentrated under reduced pressure and purified by column chromatography (10–50% EtOAc/Pet) to afford the title compound (10.5 g, 73.9 mmol, 84%) as a white solid.

Data is consistent with literature.[77]

MP 55–56 °C (Lit. 52–54°C (EA/Pet)).

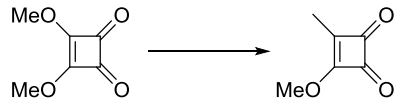
FT-IR (ν_{max}, $CHCl_3$) 2962 (br), 1810 (m), 1726 (s), 1592 (s), 1475 (s), 1425 (m), 1350 (s), 1209 (w), 1105 (m), 1081 (m), 1028 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 4.36 (6 H, s, 2 × OC**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 189.1 (**C**), 184.4 (**C**), 60.9 (2 × O**C**H$_3$) ppm.

LRMS (ESI+) 165 ([M+Na]$^+$, 30%), 184 ([M+MeCN+H]$^+$, 100%).

3-methoxy-4-methylcyclobut-3-ene-1,2-dione (3.2a)



1.43
$C_6H_6O_4$
Mol Wt:142.11

3.2a
$C_6H_6O_3$
Mol Wt:126.11

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43** (1167 mg, 8.22 mmol) in THF (80 mL) at –78 °C was added MeLi (1.66 M in Et_2O, 4.95 mL, 8.22 mmol) dropwise. After stirring at –78 °C for 1 h, TFAA (1.37 mL, 9.86 mmol) was added dropwise. After 20 min the resulting solution was quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by recrystallisation (Et_2O) to afford the title compound (908 mg, 7.21 mmol, 88%) as a white solid.

Data is consistent with literature.[57]

MP 50–52 °C (Et_2O) (Lit. 49–50 °C (Et_2O/hexane)).

FT-IR (ν_{max}, $CHCl_3$) 2966 (w), 1747 (s), 1589 (s), 1497 (m), 1450 (s), 1373 (s), 1322 (m), 1026 (m) cm^{-1}.

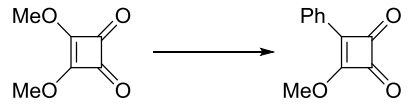
δ_H (400 MHz, $CDCl_3$) 4.42 (3 H, s, OC**H**$_3$)

2.22 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 199.2 (**C**), 195.4 (**C**), 193.8 (**C**), 180.3 (**C**), 60.9 (O**C**H$_3$), 9.5 (**C**H$_3$) ppm.

LRMS (ESI+) 168 ([M+H+MeCN]$^+$, 100%).

3-methoxy-4-phenylcyclobut-3-ene-1,2-dione (3.2b)



1.43
$C_6H_6O_4$
Mol Wt:142.11

3.2b
$C_{11}H_8O_3$
Mol Wt:188.05

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43** (284 mg, 2.00 mmol) in THF (50 mL) at –78 °C was added PhLi (1.89 M in Bu_2O, 1.16 mL, 2.19 mmol) dropwise. After stirring at –78 °C for 1 h, TFAA (0.33 mL, 2.20 mmol) was added dropwise. After 20 min the resulting solution was quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–25% EtOAc/cyclohexane) to afford the title compound (369 mg, 1.90 mmol, 96%) as a yellow solid.

Data is consistent with literature.[57]

MP 149–150 °C (EtOAc /cyclohexane) (Lit. 149–151°C (DCM/hexane)).

FT-IR (ν_{max}, $CHCl_3$) 3074 (w), 3020 (w), 2962 (w), 1846 (w), 1784 (s), 1740 (s), 1236 (s), 1600 (s), 1591 (s), 1497 (m), 1446 (s), 1369 (s), 1321 (m), 1215 (m), 1038 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 8.05–8.03 (2 H, m, 2 × Ar**H**)

7.57–7.49 (3 H, m, 3 × Ar**H**)

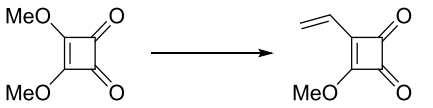
4.61 (3 H, s, OC**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 194.8 (**C**), 192.7 (**C**), 192.4 (**C**), 173.9 (**C**), 132.8 (**C**H), 129.1 (**C**H), 127.8 (**C**H), 127.6 (**C**), 61.7 (O**C**H$_3$) ppm.

LRMS (ESI+) 189 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 211.0367, $C_{11}H_8NaO_3$ $[M+Na]^+$ requires 211.0366.

3-methoxy-4-vinylcyclobut-3-ene-1,2-dione (3.2c)



1.43
$C_6H_6O_4$
Mol Wt:142.11

3.2c
$C_7H_6O_3$
Mol Wt:138.03

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43** (1418 mg, 10.0 mmol) in THF (80 mL) at –78 °C was added vinylmagnesium bromide solution (1.0 M in THF, 12.0 mL, 12.0 mmol) dropwise. After stirring at –78 °C for 1 h, TFAA (1.67 mL, 12.0 mmol) was added dropwise. After 20 min the resulting solution was quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (20–50% EtOAc/cyclohexane) to afford the title compound (954 mg, 6.91 mmol, 69%) as a yellow oil.

Data is consistent with literature.[138]

FT-IR (ν_{max}, $CHCl_3$) 1780 (s), 1742 (s), 1617 (m), 1569 (m), 1459 (m), 1397 (m), 1359 (m), 1348 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 6.50 (1 H, dd, *J* = 17.5, 10.9 Hz, C**H**)

6.28 (1 H, dd, *J* = 17.5, 1.6 Hz, C**H**H)

5.69 (1 H, dd, *J* = 10.8, 1.7 Hz, CH**H**)

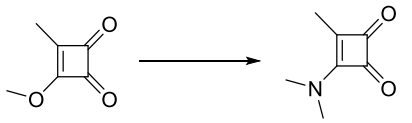
4.30 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 194.4 (**C**), 192.7 (**C**), 192.1 (**C**), 172.4 (**C**), 128.2 (**C**H_2), 121.9 (**C**H), 61.2 (**C**H_3) ppm.

LRMS (ESI+) 139 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 139.0389, $C_7H_7O_3$ $[M+H]^+$ requires 139.0390.

3-(Dimethylamino)-4-methylcyclobutene-1,2-dione (3.3a)



3.2a
$C_6H_6O_3$
Mol Wt: 126.1

3.3a
$C_7H_9NO_2$
Mol Wt: 139.2

A solution of dimethylamine hydrochloride (67 mg, 0.82 mmol) and Et_3N (0.12 mL, 0.82 mmol) in MeOH (10 mL) was added to a solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **3.2a** (103 mg, 0.82 mmol) in MeOH (40 mL). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (0–5% MeOH/EtOAc) to afford the title compound (97 mg, 0.70 mmol, 85%) as a white solid.

MP 128–129 °C.

FT-IR (ν_{max}, $CHCl_3$) 2939 (br), 1778 (s), 1728 (s), 1616 (vs), 1411 (m), 1234 (m), 1064 (s), 979 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 3.32 (3 H, s, NC**H**$_3$),

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

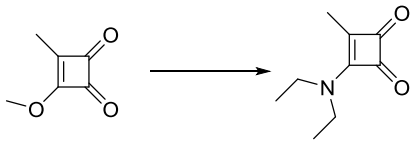
2.22 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 192.7 (**C**), 191.4 (**C**), 183.1 (**C**), 166.3 (**C**), 39.7 (**C**H$_3$), 38.9 (**C**H$_3$), 10.3 (**C**H$_3$) ppm.

LRMS (ESI+) 162 ($[M+Na]^+$, 100%), 203 ($[M+MeCN+Na]^+$, 60%).

HRMS (ESI+) Found 140.0706, $C_7H_{10}NO_2$ $[M+H]^+$ requires 140.0706.

3-(diethylamino)-4-methylcyclobutene-1,2-dione (3.3b)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

3.3b
$C_9H_{13}NO_2$
Mol Wt: 168.10

A solution of diethylamine hydrochloride (132 mg, 1.20 mmol) and TEA (0.10 mL, 1.20 mmol) in MeOH (10 mL) was added to a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (150 mg, 1.20 mmol) in MeOH (40 mL). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (20–60% acetone/cyclohexane) to afford the title compound (170 mg, 1.01 mmol, 85%) as a pale yellow oil.

Data is consistent with literature.[139]

FT-IR (ν_{max}, $CHCl_3$) 2973 (br), 2939 (w), 1774 (s), 1727 (s), 1581 (vs), 1438 (s), 1365 (m), 1296 (s), 1211 (m), 1061 (s), 949 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 3.64 (2 H, q, *J* = 7.2 Hz, NC**H**$_2$)

3.36 (2 H, q, *J* = 7.2 Hz, NC**H**$_2$)

2.15 (3 H, s, C**H**$_3$)

1.18 (3 H, t, *J* = 7.3 Hz, $CH_2C\mathbf{H}_3$)

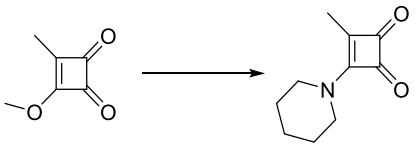
1.13 (3 H, t, *J* = 7.2 Hz, $CH_2C\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 192.8 (**C**), 191.3 (**C**), 182.0 (**C**), 165.7 (**C**), 44.4 (**C**H_2), 44.1 (**C**H_2), 14.4 (**C**H_3), 14.1 (**C**H_3), 10.2 (**C**H_3) ppm.

LRMS (ESI+) 168 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 168.1019, $C_9H_{14}NO_2$ $[M+H]^+$ requires 168.1019.

4-methyl-3-(piperidin-1-yl)cyclobutene-1,2-dione (3.3c)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

3.3c
$C_{10}H_{13}NO_2$
Mol Wt: 179.10

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (380 mg, 3.01 mmol) in MeOH (50 mL) at RT was added piperidine (0.30 mL, 3.01 mmol). After stirring at RT for 3 h the solution was concentrated under reduced pressure and purified by column chromatography (30–70% EtOAc/hexane) to afford the title compound (460 mg, 2.57 mmol, 85%) as a yellow solid.

MP 118–120 °C.

FT-IR (ν_{max}, $CHCl_3$) 3007 (w), 2947 (w), 2860 (w), 1778 (m), 1728 (m), 1595 (s), 1444 (m), 1375 (w), 1282 (m), 1238 (w), 1059 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 3.79 (2 H, br t, *J* = 5.2 Hz, 2 × NC**H**H)

3.49–3.42 (2 H, m, 2 × NCH**H**)

2.15 (3 H, s, C**H**$_3$)

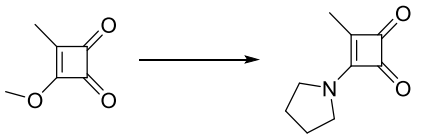
1.65–1.58 (6 H, m, 3 × C**H**$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 192.9 (**C**), 191.2 (**C**), 180.9 (**C**), 165.4 (**C**), 48.9 (**C**H_2), 47.7 (**C**H_2), 25.7 (**C**H_2), 25.6 (**C**H_2), 23.1 (**C**H_2), 10.5 (**C**H_3) ppm.

LRMS (ESI+) 180 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 180.1019, $C_{10}H_{14}NO_2$ $[M+H]^+$ requires 180.1019.

4-methyl-3-(pyrrolidin-1-yl)cyclobutene-1,2-dione (3.3d)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

3.3d
$C_9H_{11}NO_2$
Mol Wt: 165.08

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (252 mg, 2.00 mmol) in MeOH (50 mL) at RT was added pyrrolidine (0.16 mL, 2.00 mmol). After stirring at RT for 3 h the solution was concentrated under reduced pressure and purified by column chromatography (EtOAc) to afford the title compound (285 mg, 1.72 mmol, 86%) as a yellow solid.

MP 125–126 °C (EA/cyclohexane) .

FT-IR (ν_{max}, $CHCl_3$) 2977 (br), 2881 (w), 1780 (m), 1724 (m), 1595 (vs), 1481 (w), 1429 (s), 1346 (m), 1217 (w), 1068 (s), 1033 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 3.82 (2 H, app. t, *J* = 6.7 Hz, 2 × NC**H**H)

3.63 (2 H, app. t, *J* = 6.8 Hz, 2 × NCH**H**)

2.24 (3 H, s, C$\mathbf{H}_3$)

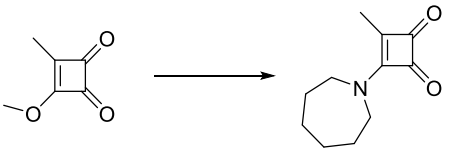
2.10–1.84 (4 H, m, 2 × C$\mathbf{H}_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 193.2 (**C**), 191.7 (**C**), 180.9 (**C**), 166.8 (**C**), 49.0 (**C**H_2), 48.4 (**C**H_2), 25.0 (**C**H_2), 24.7 (**C**H_2), 10.0 (**C**H_3) ppm.

LRMS (ESI+) 166 ($[M+H]^+$, 100%), 353 ($[2M+Na]^+$, 30%).

HRMS (ESI+) Found 166.0864, $C_9H_{12}NO_2$ $[M+H]^+$ requires 166.0863.

3-(azepan-1-yl)-4-methylcyclobutene-1,2-dione (3.3e)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

3.3e
$C_{11}H_{15}NO_2$
Mol Wt: 193.12

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (126 mg, 1.00 mmol) in MeOH (50 mL) at RT was added azepane (0.12 mL, 1.00 mmol). After stirring at RT for 3 h the solution was concentrated under reduced pressure and purified by column chromatography (20–70% acetone/cyclohexane) to afford the title compound (180 mg, 0.93 mmol, 93%) as a yellow solid.

MP 130–132 °C.

FT-IR (ν_{max}, $CHCl_3$) 3232 (br), 2973 (m), 2927 (m), 2360 (w), 1782 (s), 1720 (s), 1573 (s), 1427 (s), 1157 (s), 1060 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 3.92–3.86 (2 H, m, 2 × NC**H**H)

3.64–3.52 (2 H, m, 2 × NCH**H**)

2.27 (3 H, s, CH_3)

1.84–1.73 (4 H, m, 2 × C**H**$_2$)

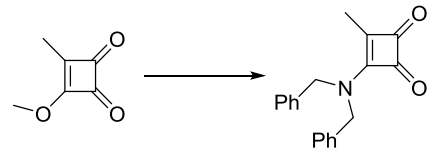
1.69–1.55 (4 H, m, 2 × C**H**$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 193.1 (**C**), 191.7 (**C**), 182.8 (**C**), 166.1 (**C**), 50.9 (**C**H_2), 49.9 (**C**H_2), 29.1 (**C**H_2), 28.2 (**C**H_2), 27.2 (**C**H_2), 26.3 (**C**H_2), 10.7 (**C**H_3) ppm.

LRMS (ESI+) 194 ($[M+H]^+$, 100%), 387 ($[2M+H]^+$, 40%).

HRMS (ESI+) Found 194.1174, $C_{11}H_{16}NO_2$ $[M+H]^+$ requires 194.1176.

3-(dibenzylamino)-4-methylcyclobutene-1,2-dione (3.3f)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

3.3f
$C_{19}H_{17}NO_2$
Mol Wt: 291.13

To a cooled (0 °C) solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (126 mg, 1.00 mmol) in MeOH (50 mL) was added dibenzylamine (0.20 mL, 1.04 mmol). After stirring at 0 °C for 2 h the solution was warmed to RT and after a further 2 h was concentrated under reduced pressure and purified by column chromatography (EtOAc) to afford the title compound (160 mg, 0.55 mmol, 55%) as a pale yellow oil.

Data is consistent with literature.[4]

FT-IR (ν_{max}, $CHCl_3$) 2928 (m), 2854 (m), 1761 (s), 1731 (s), 1643 (w), 1581 (vs), 1430 (s), 1357 (w), 1269 (s), 1172 (w), 1064 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.43–7.31 (6 H, m, 6 × Ar**H**)

7.26–7.16 (4 H, m, 4 × Ar**H**)

4.86 (2 H, s, C**H**$_2$)

4.50 (2 H, s, C**H**$_2$)

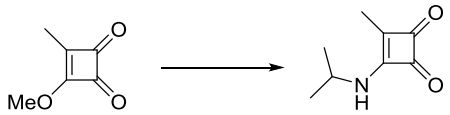
2.20 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 192.8 (**C**), 191.6 (**C**), 183.5 (**C**), 167.2 (**C**), 134.6 (**C**), 134.3 (**C**), 129.1 (2 × **C**H), 128.9 (2 × **C**H), 128.5 (2 × **C**H), 128.3 (2 × **C**H), 126.8 (2 × **C**H), 52.2 (**C**H_2), 52.0 (**C**H_2), 10.5 (**C**H_3) ppm.

LRMS (ESI+) 292 ($[M+H]^+$, 30%), 583 ($[2M+H]^+$, 100%).

HRMS (ESI+) Found 292.1328, $C_{19}H_{18}NO_2$ $[M+H]^+$ requires 292.1332.

3-(isopropylamino)-4-methylcyclobut-3-ene-1,2-dione (**3.3g**)



3.2a
$C_6H_6O_3$
Mol Wt:126.11

3.3g
$C_8H_{11}NO_2$
Mol Wt:153.08

To a solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **3.2a** (126 mg, 1.00 mmol) in MeOH (50 mL) was added isopropylamine (0.09 mL, 1.00 mmol). After stirring at RT for 3 h the solution was concentrated under reduced pressure and purified by column chromatography (20% acetone/DCM) to afford the title compound (151 mg, 0.99 mmol, 99%) as a white solid.

MP 81–83 °C.

FT-IR (ν_{max}, $CHCl_3$) 3234 (br), 2973 (w), 1782 (s), 1722 (s), 1575 (vs), 1429 (m), 1317 (w), 1159 (m), 1060 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) Major rotamer:

6.80 (1 H, br d, *J* = 6.1 Hz, N**H**)

3.91–3.84 (1 H, m, C**H**)

2.31 (3 H, s, C$\mathbf{H}_3$)

1.36 (6 H, d, *J* = 6.5 Hz, 2 × C$\mathbf{H}_3$) ppm.

Minor rotamer:

6.64 (1 H, br d, *J* = 6.5 Hz, N**H**)

4.47–4.35 (1 H, m, C**H**)

2.12 (3 H, s, C$\mathbf{H}_3$)

1.30 (6 H, d, *J* = 6.5 Hz, 2 × C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) Major rotamer:

193.7 (**C**), 192.2 (**C**), 182.4 (**C**), 166.7 (**C**), 47.4 (**C**H), 23.4 (2 × **C**H_3), 10.8 (**C**H_3) ppm.

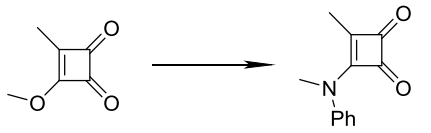
Minor rotamer

192.9 (**C**), 192.3 (**C**), 184.0 (**C**), 168.4 (**C**), 47.3 (**C**H), 23.8 (2 × **C**H_3), 9.5 (**C**H_3) ppm.

LRMS (ESI+) 154 ($[M+H]^+$, 100%), 176 ($[M+Na]^+$, 20%).

HRMS Found 154.0865, $C_8H_{12}NO_2$ $[M+H]^+$ requires 154.0863.

3-methyl-4-(methyl(phenyl)amino)cyclobut-3-ene-1,2-dione (3.3h)



3.2a
$C_9H_{12}O_3$
Mol Wt: 169.08

3.3h
$C_{12}H_{11}NO_2$
Mol Wt: 201.08

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (400 mg, 2.36 mmol) in MeOH (40 mL) was added *N*-methylaniline (0.26 mL, 2.40 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (40–70% EtOAc/Pet) to afford the title compound (401 mg, 2.00 mmol, 84%) as a white solid.

MP 103–104 °C.

FT-IR (ν_{max}, $CHCl_3$) 2942 (br), 1779 (s), 1727 (s), 1720 (s), 1608 (s), 1567 (s), 1455 (m), 1429 (m), 1379 (m), 1034 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.52–7.38 (3 H, m, 3 × Ar**H**)

7.29–7.24 (2 H, m, 2 × Ar**H**)

3.77 (3 H, s, NC**H**$_3$)

1.63 (3 H, s, C**H**$_3$) ppm

with additional signals attributed to the minor rotamer at

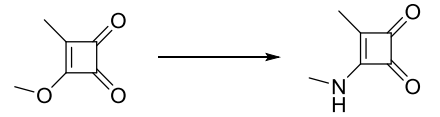
1.68 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 193.1 (**C**), 192.9 (**C**), 183.2 (**C**), 169.5 (**C**), 142.2 (**C**), 129.8 (**C**H), 128.5 (**C**H), 125.1 (**C**H), 40.2 (**C**H_3), 10.7 (**C**H_3) ppm.

LRMS (ESI+) 202 ($[M+H]^+$, 100%), 224 ($[M+Na]^+$, 40%).

HRMS (ESI+) Found 202.0866, $C_{12}H_{12}NO_2$ $[M+H]^+$ requires 202.0863.

3-methyl-4-(methylamino)cyclobut-3-ene-1,2-dione (3.3i)



3.2a
$C_6H_6O_3$
Mol Wt: 126.1

3.3i
$C_6H_7NO_2$
Mol Wt: 125.05

A solution of methylamine hydrochloride (440 mg, 6.52 mmol) and TEA (0.9 mL, 6.46 mmol) in MeOH (10 mL) was added to a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (627 mg, 4.98 mmol) in MeOH (40 mL). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (60–90% EtOAc/Pet) to afford the title compound (550 mg, 4.40 mmol, 88%) as a white solid.

MP 178–179 °C (Et_2O).

FT-IR (ν_{max}, $CHCl_3$) 3138 (br), 2952 (br), 1702 (s), 1587 (s), 1506 (s), 1475 (s), 1397 (s), 1255 (m), 1174 (s), 1150 (s) cm^{-1}.

δ_H (400 MHz, D_2O) major rotamer:

3.18 (3 H, s, C**H**$_3$)

2.31 (3 H, s, C**H**$_3$) ppm.

minor rotamer:

3.23 (3 H, s, C**H**$_3$)

2.09 (3 H, s, C**H**$_3$) ppm.

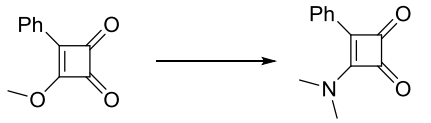
δ_C (100 MHz, D_2O) major rotamer: 194.4 (**C**), 192.2 (**C**), 184.5 (**C**), 189.3 (**C**), 30.5 (**C**H_3), 10.0 (**C**H_3) ppm.

minor rotamer: 194.1 (**C**), 192.6 (**C**), 185.1 (**C**), 168.3 (**C**), 30.9 (**C**H_3), 8.7 (**C**H_3) ppm.

LRMS (ESI+) 251 ($[2M+H]^+$, 100%), 273 ($[2M+Na]^+$, 90%).

HRMS (ESI+) Found 126.0555, $C_6H_8NO_2$ $[M+H]^+$ requires 126.0550.

3-(dimethylamino)-4-phenyl-cyclobutene-1,2-dione (3.3j)



3.2b
$C_{11}H_8O_3$
Mol Wt: 188.05

3.3j
$C_{12}H_{11}NO_2$
Mol Wt: 201.08

To a solution of dimethylamine hydrochloride (81 mg, 1.01 mmol) in MeOH (10 mL) was added TEA (0.07 mL, 1.00 mmol). After 10 min the solution was added to a solution of 3-methoxy-4-phenylcyclobutene-1,2-dione **3.2b** (192 mg, 1.02 mmol) in MeOH (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then stirred at RT for 3 h. The solution was concentrated under reduced pressure and purified by column chromatography (EtOAc) to give the title compound (196 mg, 0.97 mmol, 97%) as a pale yellow solid.

MP 120–122 °C

FT-IR (ν_{max}, $CHCl_3$) 2931 (br), 1762 (s), 1731 (s), 1597 (vs), 1434 (m), 1404 (s), 1227 (s), 1122 (m), 1103 (m), 1026 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.60–7.59 (2 H, m, 2 × Ar**H**)

7.49–7.36 (3 H, m, 3 × Ar**H**)

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

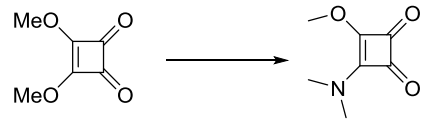
3.17 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 192.5 (**C**), 188.8 (**C**), 180.1 (**C**), 164.1 (**C**), 129.7 (**C**H), 128.7 (**C**H), 128.5 (**C**), 127.7 (**C**H), 41.9 (**C**H_3), 39.6 (**C**H_3) ppm.

LRMS (ESI+) 202 ($[M+H]^+$, 100%), 224 ($[M+Na]^+$, 80%).

HRMS (ESI+) Found 202.0862, $C_{12}H_{12}NO_2$ $[M+H]^+$ requires 202.0863.

3-(dimthylamino)-4-methoxycyclobut-3-ene-1,2-dione (3.3k)



1.43
$C_6H_6O_4$
Mol Wt:142.11

3.3k
$C_7H_9NO_3$
Mol Wt:155.15

To a solution of dimethylamine hydrochloride (570 mg, 7.04 mmol) in MeOH (10 mL) was added TEA (0.98 mL, 7.04 mmol). The solution was stirred at RT for 10 min and added into a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43** (1000 mg, 7.04 mmol) in MeOH (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then stirred at RT for 16 h. The solution was concentrated under reduced pressure and purified by column chromatography (EtOAc) to afford the title compound (930 mg, 6.00 mmol, 85%) as a white solid.

MP 135–137 °C.

FT-IR (ν_{max}, $CHCl_3$) 2929 (br), 1791 (w), 1697 (m), 1614 (s), 1491 (s), 1388 (s), 1274 (m), 1182 (w), 1072 (w), 1028 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 4.28 (3 H, s, OC**H**$_3$)

3.24 (3 H, s, C**H**$_3$)

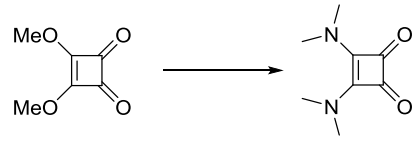
3.06 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 186.6 (**C**), 182.1 (**C**), 176.2 (**C**), 171.7 (**C**), 60.1 (O**C**H_3), 39.1 (**C**H_3), 38.4 (**C**H_3) ppm.

LRMS (ESI+) 156 ($[M+H]^+$, 100%), 178 ($[M+Na]^+$, 20%).

HRMS (ESI+) Found 156.0652, $C_7H_{10}NO_3$ $[M+H]^+$ requires 156.0655.

3,4-bis(dimethylamino)cyclobut-3-ene-1,2-dione (3.3l)



1.43
$C_6H_6O_4$
Mol Wt:142.11

3.3l
$C_8H_{12}N_2O_2$
Mol Wt:168.19

To a solution of dimethylamine hydrochloride (1.14 g, 14.08 mmol) in MeOH (10 mL) was added TEA (1.96 mL, 14.08 mmol). The solution was stirred at RT for 10 min and added into a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43** (1000 mg, 7.04 mmol) in MeOH (40 mL). After stirring at RT for 16 h the resulting solution was concentrated under reduced pressure and purified by column chromatography (0–10% MeOH/EtOAc) to afford the title compound (0.36 g, 2.14 mmol, 30%) as a white solid.

MP 222–223 °C.

FT-IR (ν_{max}, $CHCl_3$) 2927 (br), 2015(w), 1772 (w), 1654 (m), 1585 (m), 1540 (s), 1521(s), 1456 (s), 1394 (s), 1186 (m) cm^{-1}.

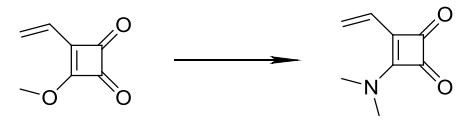
δ_H (400 MHz, $CDCl_3$) 3.19 (12 H, s, 2 × N(C**H**$_3$)$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 183.6 (**C**), 168.8 (**C**), 41.3 (N(**C**H$_3$)$_2$) ppm.

LRMS (ESI+) 169 ($[M+H]^+$, 100%), 337 ($[2M+H]^+$, 80%).

HRMS (ESI+) Found 169.0970, $C_8H_{13}N_2O_2$ $[M+H]^+$ requires 169.0972.

3-(dimethylamino)-4-vinylcyclobut-3-ene-1,2-dione (3.3m)



3.2c
$C_7H_6O_3$
Mol Wt: 138.03

3.3m
$C_8H_9NO_2$
Mol Wt: 151.06

To a solution of dimethylamine hydrochloride (475 g, 5.83 mmol) in MeOH (10 mL) was added TEA (0.81 mL, 5.83 mmol). The solution was stirred at RT for 10 min and added into a solution of 3-methoxy-4-vinylcyclobut-3-ene-1,2-dione **3.2c** (690 mg, 4.86 mmol) in MeOH (40 mL). After stirring at RT for 16 h the resulting solution was concentrated under reduced pressure and

purified by column chromatography (10–40% acetone/DCM) to afford the title compound (660 mg, 4.37 mmol, 90%) as a yellow solid.

MP 133–134 °C.

FT-IR (ν_{max}, $CHCl_3$) 3473 (br), 2927 (w), 1765 (m), 1724 (m), 1607 (s), 1414 (m), 1250 (m), 1140 (m), 1067 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 6.71 (1 H, dd, *J* = 17.1, 10.5 Hz, C**H**)

6.60 (1 H, dd, *J* = 17.1, 2.0 Hz, C**H**H)

5.67 (1 H, dd, *J* = 10.6, 2.1 Hz, CH**H**)

3.46 (3 H, s, C$\mathbf{H}_3$)

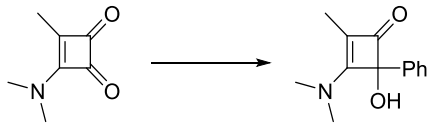
3.22 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 191.8 (**C**), 188.9 (**C**), 178.2 (**C**), 161.7 (**C**), 124.7 (**C**H_2), 123.3 (**C**H), 39.8 (**C**H_3), 39.4 (**C**H_3) ppm.

LRMS (ESI+) 152 ($[M+H]^+$, 100%), 174 ($[M+Na]^+$, 20%).

HRMS (ESI+) Found 152.0709, $C_8H_{10}NO_2$ $[M+H]^+$ requires 152.0706.

3-(dimethylamino)-4-hydroxy-2-methyl-4-phenylcyclobut-2-enone (3.4a)



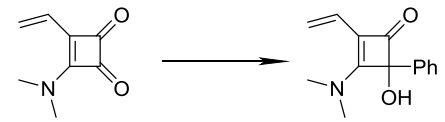
3.3a
$C_7H_9NO_2$
Mol Wt 139.15

3.4a
$C_{13}H_{15}NO_2$
Mol Wt 217.26

To a solution of 3-(dimethylamino)-4-methylcyclobut-3-ene-1,2-dione **3.3a** (140 mg, 1.01 mmol) in THF (50 mL) at –78 °C was added PhLi (1.89 M in Bu_2O, 0.69 mL, 1.30 mmol) dropwise. The solution was stirred at –78 °C for 1 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (Et_2O then 60% acetone/cyclohexane) to afford the title compound (190 mg, 0.87 mmol, 87%) as a white solid.

MP	Decomposed over 154 °C.
FT-IR (ν_{max}, $CHCl_3$)	3020 (br), 1745 (w), 1576 (s), 1448 (w), 1414 (m), 1271 (w), 1215 (m), 1170 (w), 1151 (w), 1040 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.42–7.40 (2 H, m, Ar**H**)
	7.29–7.25 (2 H, m, Ar**H**)
	7.20–7.17 (1 H, m, Ar**H**)
	5.67 (H, br s, O**H**)
	3.08 (3 H, s, C**H**$_3$)
	2.76 (3 H, s, C**H**$_3$)
	1.79 (3 H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	187.9 (**C**), 171.6 (**C**), 138.2 (**C**), 127.8 (**C**H), 126.9 (**C**H), 125.3 (**C**H), 114.0 (**C**), 90.3 (**C**), 39.6 (**C**H_3), 39.1 (**C**H_3), 7.1 (**C**H_3) ppm.
LRMS (ESI+)	218 ($[M+H]^+$, 100%), 240 ($[M+Na]^+$, 20%).
HRMS (ESI+)	Found 218.1177, $C_{13}H_{16}NO_2$ $[M+H]^+$ requires 218.1176.

3-(dimethylamino)-4-hydroxy-4-phenyl-2-vinylcyclobut-2-en-1-one (3.4b)



3.3m
$C_8H_9NO_2$
Mol Wt: 151.06

3.4b
$C_{14}H_{15}NO_2$
Mol Wt: 229.11

To a solution of 3-(dimethylamino)-4-vinylcyclobut-3-ene-1,2-dione **3.3m** (188 mg, 1.25 mmol) in THF (50 mL) at –78 °C was added PhLi (1.89 M in Bu_2O, 0.86 mL, 1.63 mmol) dropwise. The solution was stirred at –78 °C for 1 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–25% acetone/DCM) to afford the title compound (155 mg, 0.68 mmol, 54%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3300 (br), 1730 (m), 1621 (s), 1579 (s), 1417 (m), 1267 (w), 1169 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.48–7.45 (2 H, m, 2 × Ar**H**)

7.35 (2 H, d, *J* = 7.5 Hz, 2 × Ar**H**)

7.29–7.26 (1 H, m, Ar**H**)

6.30 (1 H, dd, *J* = 17.4, 11.3 Hz, C**H**)

5.91 (1 H, dd, *J* = 17.4, 2.1 Hz, C**H**H)

5.25 (1 H, dd, *J* = 11.3, 2.1 Hz, CH**H**)

4.70 (1 H, s, O**H**)

3.22 (3 H, s, C$\mathbf{H}_3$)

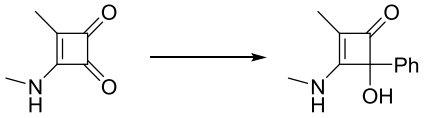
2.92 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 185.6 (**C**), 167.8 (**C**), 137.7 (**C**), 128.4 (**C**H), 127.6 (**C**H), 125.6 (**C**H), 123.6 (**C**H), 117.9 (**C**), 117.8 (**C**H_2), 91.4 (**C**), 40.6 (**C**H_3), 40.6 (**C**H_3) ppm.

LRMS (ESI+) 230 ($[M+H]^+$, 100%), 252 ($[M+Na]^+$, 30%).

HRMS (ESI+) Found 230.1177, $C_{14}H_{16}NO_2$ $[M+H]^+$ requires 230.1176.

4-hydroxy-2-methyl-3-(methylamino)-4-phenylcyclobut-2-en-1-one (3.4c)



3.3i
$C_6H_7NO_2$
Mol Wt 125.05

3.4c
$C_{12}H_{13}NO_2$
Mol Wt 203.09

To a solution of 3-(methylamino)-4-methylcyclobutene-1,2-dione **3.3i** (434 mg, 3.47 mmol) in THF (50 mL) at –78 °C was added PhLi (1.89 M in Bu_2O, 4.6 mL, 8.69 mmol) dropwise. The solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined,

dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (Et_2O) to afford the title compound (635 mg, 3.13 mmol, 89%) as an off white solid.

MP Decomposed over 187 °C.

FT-IR (ν_{max}, $CHCl_3$) 3160 (br), 2928 (w), 2858 (w), 1747 (m), 1567 (vs), 1516 (s), 1396 (s), 1192 (m), 1006 (m) cm^{-1}.

δ_H (400 MHz, DMSO-d6) Major rotamer

7.84 (1 H, m, N**H**)

7.40–7.21 (5 H, m, 5 × Ar**H**)

6.37 (1 H, s, O**H**)

2.63 (3 H, d, *J* = 4.9 Hz, C**H**$_3$)

1.56 (3 H, s, C**H**$_3$) ppm.

Minor rotamer

7.84 (1 H, m, N**H**)

7.40–7.21 (5 H, m, 5 × Ar**H**)

6.16 (1 H, s, O**H**)

2.98 (3 H, d, *J* = 4.9 Hz, C**H**$_3$)

1.76 (3 H, s, C**H**$_3$) ppm.

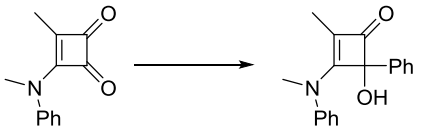
δ_C (100 MHz, DMSO-d6) Major rotamer: 186.4 (**C**), 172.3 (**C**), 139.9 (**C**), 128.0 (**C**H), 126.8 (**C**H), 125.7 (**C**H), 113.3 (**C**), 90.9 (**C**), 30.2 (**C**H$_3$), 6.2 (**C**H$_3$) ppm.

Minor rotamer: 187.6 (**C**), 172.0 (**C**), 138.6 (**C**), 127.8 (**C**H), 126.9 (**C**H), 125.3 (**C**H), 112.3 (**C**), 90.6 (**C**), 30.5 (**C**H$_3$), 7.0 (**C**H$_3$) ppm.

LRMS (ESI+) 204 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 204.1023, $C_{12}H_{14}NO_2$ $[M+H]^+$ requires 204.1023.

4-hydroxy-2-methyl-3-(methyl(phenyl)amino)-4-phenylcyclobut-2-en-1-one (3.4d)



3.3h
$C_{12}H_{11}NO_2$
Mol Wt 201.08

3.4d
$C_{18}H_{17}NO_2$
Mol Wt 279.13

To a solution of 3-(methyl(phenyl)amino)-4-methylcyclobut-3-ene-1,2-dione **3.3h** (303 mg, 1.51 mmol) in THF (50 mL) at –78 °C was added PhLi (1.9 M in Bu_2O, 1.1 mL, 2.09 mmol) dropwise. The solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (Et_2O) to afford the title compound (309 mg, 1.11 mmol, 74%) as a white solid.

MP Decomposed over 150 °C.

FT-IR (ν_{max}, $CHCl_3$) 3272 (br), 2952 (w), 1738 (m), 1562 (vs), 1493 (m), 1448 (m), 1409 (m), 1284 (w), 1183 (w), 1024 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.56 (2 H, br s, 2 × Ar**H**)

7.45–7.37 (4 H, m, 4 × Ar**H**)

7.35–7.28 (4 H, m, 4 × Ar**H**)

5.36 (1 H, br s, O**H**)

3.24 (3 H, s, C$\mathbf{H}_3$)

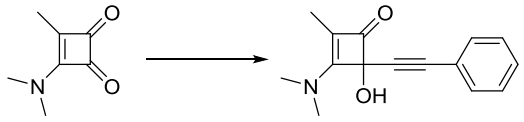
1.24 (3 H, br s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 189.1 (**C**), 143.8 (**C**), 138.3 (**C**), 129.2 (**C**H), 128.4 (**C**H), 127.5 (**C**H), 127.4 (**C**H), 125.6 (**C**H), 125.5 (**C**H), 118.0 (**C**), 91.8 (**C**), 40.9 (**C**H_3), 7.6 (**C**H_3) ppm.

LRMS (ESI+) 280 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 280.1331, $C_{18}H_{18}NO_2$ $[M+H]^+$ requires 280.1332.

3-(Dimethylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-enone (3.4e)



3.3a
$C_7H_9NO_2$
Mol Wt 139.15

3.4e
$C_{15}H_{15}NO_2$
Mol Wt 241.29

To a solution of phenylacetylene (0.07 mL, 0.65 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.27 mL, 0.65 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-dimethylamino-4-methylcyclobutene-1,2-dione **3.3a** (68 mg, 0.49 mmol) in THF (10 mL) at –78 °C. After a further 50 min sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (70–100% EtOAc/hexane) to afford the title compound (83 mg, 0.34 mmol, 70%) as a white solid.

MP Decomposed over 120 °C.

FT-IR (ν_{max}, $CHCl_3$) 3234 (br), 2927 (w), 1786 (w), 1749 (w), 1575 (vs), 1488 (m), 1410 (s), 1267 (m), 1137 (m), 1080 (m), 1068 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.44–7.41 (2H, m, 2 × ArH)

7.28–7.25 (3H, m, 3 × ArH)

5.34 (H, br s, OH)

3.29 (3 H, s, NCH_3)

3.17 (3 H, s, NCH_3)

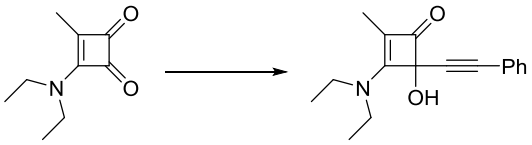
1.77 (3 H, s, CH_3) ppm.

δ_C (100 MHz, $CDCl_3$) 184.8 (**C**), 170.1 (**C**), 131.8 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 121.3 (**C**), 114.5 (**C**), 87.9 (**C**), 85.1 (**C**), 81.6 (**C**), 40.1 (**C**H_3), 39.4 (**C**H_3), 7.7 (**C**H_3) ppm.

LRMS (ESI+) 242 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 242.1180, $C_{15}H_{16}NO_2$ $[M+H]^+$ requires 242.1176.

3-(Diethylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-enone (3.4f)



3.3b
$C_9H_{14}NO_2$
Mol Wt 167.10

3.4f
$C_{17}H_{19}NO_2$
Mol Wt 269.15

To a solution of phenylacetylene (0.14 mL, 1.25 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.53 mL, 1.27 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-(diethylamino)-4-methylcyclobutene-1,2-dione **3.3b** (161 mg, 0.96 mmol) in THF (40 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–30% acetone/DCM) to afford the title compound (208 mg, 0.78 mmol, 81%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3234 (br), 2978 (w), 1745 (w), 1564 (vs), 1144 (m), 1296 (m), 1217 (w), 1161 (w), 1140 (w), 1078 (m), 1009 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.45–7.42 (2 H, m, 2 × Ar**H**)

7.30–7.23 (3 H, m, 3 × Ar**H**)

5.79 (1 H, s, O**H**)

3.81 (1 H, dq, *J* = 14.3 Hz, 7.2 Hz, C**H**H)

3.61 (1 H, dq, *J* = 14.1 Hz, 7.1 Hz, CH**H**)

3.48–3.38 (2 H, m, C$\mathbf{H}_2$),

1.77 (3 H, s, C$\mathbf{H}_3$)

1.37 (3 H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$)

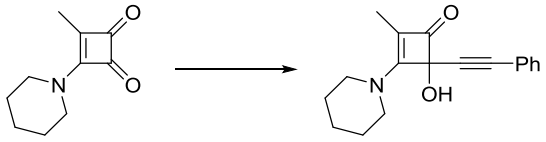
1.29 (3 H, t, *J* = 7.2 Hz, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 184.9 (**C**), 169.7 (**C**), 131.7 (**C**H), 128.2 (**C**H), 127.9 (**C**H), 122.5 (**C**), 113.4 (**C**), 87.4 (**C**), 85.6 (**C**), 81.6 (**C**), 45.2 (**C**H_2), 43.3 (**C**H_2), 14.1 (**C**H_3), 13.9 (**C**H_3), 7.5 (**C**H_3) ppm.

LRMS (ESI+) 270 ($[M+H]^+$, 100%), 539 ($[2M+H]^+$, 60%).

HRMS (ESI+) Found 270.1487, $C_{17}H_{20}NO_2$ $[M+H]^+$ requires 270.1489.

4-Hydroxy-2-methyl-4-(phenylethynyl)-3-(piperidin-1-yl)-cyclobut-2-enone (3.4g)



3.3c
$C_{10}H_{13}NO_2$
Mol Wt 179.10

3.4g
$C_{18}H_{19}NO_2$
Mol Wt 281.14

To a solution of phenylacetylene (0.07 mL, 0.49 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.20 mL, 0.48 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 4-methyl-3-(piperidin-1-yl)-cyclobutene-1,2-dione **3.3c** (68 mg, 0.38 mmol) in THF (50 mL) at –78 °C. After a further 90 min sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (50–70% EtOAc/cyclohexane) to afford the title compound (83 mg, 0.31 mmol, 81%) as a yellow solid.

MP Decomposed over 120 °C.

FT-IR (ν_{max}, $CHCl_3$) 3232 (br), 2939 (w), 2858 (w), 2360 (w), 1747 (m), 1564 (vs), 1442 (s), 1282 (s), 1083 (s), 1012 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.48–7.41 (2 H, m, 2 × Ar**H**)

7.36–7.28 (3 H, m, 3 × Ar**H**)

3.81–3.47 (4 H, m, 2 × NC**H**$_2$)

1.78 (3 H, s, C**H**$_3$)

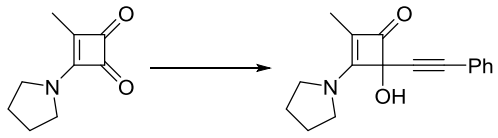
1.73 (6 H, br s, 3 × C**H**$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 183.8 (**C**), 168.1 (**C**), 132.2 (**C**H), 128.9 (**C**H), 128.5 (**C**H), 122.6 (**C**), 114.1 (**C**), 88.5 (**C**), 85.2 (**C**), 82.2 (**C**), 50.2 (**C**H$_2$), 49.0 (**C**H$_2$), 26.3 (**C**H$_2$), 26.1 (**C**H$_2$), 24.0 (**C**H$_2$), 8.4 (**C**H$_3$) ppm.

LRMS (ESI+) 282 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 282.1489, $C_{18}H_{20}NO_2$ $[M+H]^+$ requires 282.1489.

4-Hydroxy-2-methyl-4-(phenylethynyl)-3-(piperidin-1-yl)-cyclobut-2-enone (3.4h)



3.3d
$C_9H_{11}NO_2$
Mol Wt 165.08

3.4h
$C_{17}H_{17}NO_2$
Mol Wt 267.13

To a solution of phenylacetylene (0.16 mL, 1.45 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.60 mL, 1.44 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 4-methyl-3-(pyrrolidin-1-yl)-cyclobutene-1,2-dione **3.3d** (180 mg, 1.09 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–10% acetone/DCM) to afford the title compound (250 mg, 0.94 mmol, 85%) as a yellow solid.

MP Decomposed over 120 °C.

FT-IR (ν_{max}, $CHCl_3$) 3234 (br), 2975 (w), 2875 (w), 1749 (w), 1566 (vs), 1488 (w), 1450 (s), 1350 (m), 1248 (w), 1128 (w), 1083 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.40–7.33 (2 H, m, 2 × Ar**H**)

7.23–7.14 (3 H, m, 3 × Ar**H**)

5.92 (1 H, s, O**H**)

3.90–3.80 (1 H, m, C**H**H)

3.77–3.67 (1 H, m, C**H**H)

3.59–3.49 (2 H, m, 2 × CH**H**)

1.99–1.85 (4 H, m, 2 × C**H**$_2$)

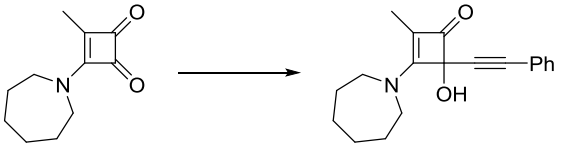
1.69 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 185.6 (**C**), 167.5 (**C**), 131.8 (**C**H), 128.3 (**C**H), 128.1 (**C**H), 122.6 (**C**), 115.0 (**C**), 87.6 (**C**), 85.7 (**C**), 81.8 (**C**), 48.6 (**C**H_2), 48.2 (**C**H_2), 25.5 (**C**H_2), 25.0 (**C**H_2), 7.3 (**C**H_3) ppm.

LRMS (ESI+) 268 ($[M+H]^+$, 100%), 535 ($[2M+H]^+$, 40%).

HRMS (ESI+) Found 268.1337, $C_{17}H_{18}NO_2$ $[M+H]^+$ requires 268.1332.

3-(Azepan-1-yl)-4-hydroxy-2-methyl-4-(phenylethynyl)-cyclobut-2-enone (3.4i)



3.3e
$C_{11}H_{15}NO_2$
Mol Wt 193.12

3.4i
$C_{19}H_{21}NO_2$
Mol Wt 295.16

To a solution of phenylacetylene (0.14 mL, 1.26 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.54 mL, 1.30 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-(azepan-1-yl)-4-methyl-cyclobutene-1,2-dione **3.3e** (193 mg, 1.00 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–10% acetone/DCM) to afford the title compound (225 mg, 0.76 mmol, 76%) as a yellow solid.

MP Decomposed over 120 °C.

FT-IR (ν_{max}, $CHCl_3$) 2919 (s), 2850 (m), 2160 (m), 2017 (m), 1731 (m), 1597 (m), 1457 (m), 1286 (w), 1076 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.47–7.40 (2 H, m, 2 × Ar**H**)

7.33–7.27 (3 H, m, 3 × Ar**H**)

3.92 (1 H, s, O**H**)

3.89 (1 H, m, NC**H**H)

3.74 (1 H, m, NCH**H**)

3.67–3.47 (2 H, m, NC**H**$_2$)

1.98–1.87 (2 H, m, 2 × C**H**H)

1.85–1.77 (2 H, m, 2 × C**H**H)

1.80 (3 H, s, C**H**$_3$)

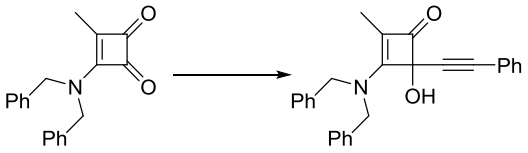
1.72–1.63 (4 H, m, 4 × CH**H**) ppm.

δ_C (100 MHz, $CDCl_3$) 183.5 (**C**), 168.8 (**C**), 131.5 (**C**H), 128.3 (**C**H), 127.9 (**C**H), 121.9 (**C**), 114.1 (**C**), 88.0 (**C**), 84.8 (**C**), 81.8 (**C**), 50.8 (**C**H$_2$), 49.9 (**C**H$_2$), 28.4 (**C**H$_2$), 28.2 (**C**H$_2$), 27.7 (**C**H$_2$), 25.7 (**C**H$_2$), 7.6 (**C**H$_3$) ppm.

LRMS (ESI+) 296 ([M+H]$^+$, 70%), 591 ([2M+H]$^+$, 100%).

HRMS (ESI+) Found 296.1648, $C_{19}H_{22}NO_2$ [M+H]$^+$ requires 296.1645.

3-(Dibenzylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)-cyclobut-2-enone (3.4j)



3.3f
$C_{19}H_{18}NO_2$
Mol Wt 291.13

3.4j
$C_{27}H_{23}NO_2$
Mol Wt 393.18

To a solution of phenylacetylene (0.10 mL, 0.90 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.38 mL, 0.90 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-(dibenzylamino)-4-methylcyclobutene-1,2-dione **3.3f** (200 mg, 0.69 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–30% acetone/cyclohexane) to afford the title compound (210 mg, 1.53 mmol, 77%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2924 (s), 2160 (m), 2017 (m), 1597 (s), 1454 (s), 1376 (w), 1261 (m), 1080 (m), 1026 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.58–7.08 (15 H, m, 15 × Ar**H**)

5.52 (1 H, s, O**H**)

4.84 (1 H, d, *J* = 15.1 Hz, C**H**H)

4.74 (1 H, d, *J* = 15.1 Hz, CH**H**)

4.48 (1 H, d, *J* = 16.0 Hz, C**H**H)

4.36 (1 H, d, *J* = 16.0 Hz, CH**H**)

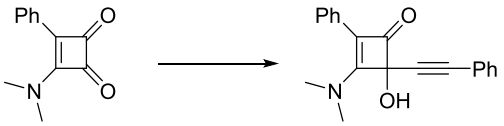
1.72 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 185.2 (**C**), 170.9 (**C**), 135.4 (**C**), 135.0 (**C**), 131.8 (**C**H), 129.1 (**C**H), 128.8 (**C**H), 128.7 (**C**H), 128.5 (**C**H), 128.1 (**C**H), 128.0 (**C**H), 126.9 (**C**H), 122.2 (**C**), 114.7 (**C**), 85.9 (**C**), 85.2 (**C**), 82.2 (**C**), 53.8 (**C**H_2), 51.0 (**C**H_2), 7.6 (**C**H_3) ppm.

LRMS (ESI+) 394 ($[M+H]^+$, 100%), 787 ($[2M+H]^+$, 40%).

HRMS (ESI+) Found 416.1613, $C_{27}H_{23}NaNO_2$ $[M+Na]^+$ requires 416.1621.

3-(Dimethylamino)-4-hydroxy-2-phenyl-4-(phenylethynyl)-cyclobut-2-enone (3.4k)



3.3j
$C_{12}H_{11}NO_2$
Mol Wt 201.08

3.4k
$C_{20}H_{17}NO_2$
Mol Wt 303.13

To a solution of phenylacetylene (0.07 mL, 0.65 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.27 mL, 0.65 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-(dimethylamino)-4-phenylcyclobutene-1,2-dione **3.3j** (100 mg, 0.50 mmol) in THF (20 mL) at –78 °C. After a further 90 min sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–50% acetone/cyclohexane) to afford the title compound (131 mg, 0.42 mmol, 83%) as a yellow solid.

MP Decomposed over 130 °C.

FT-IR (ν_{max}, $CHCl_3$) 3062 (br), 2939 (m), 1735 (m), 1607 (s), 1585 (vs), 1412 (s), 1234 (m), 1165 (m), 1095 (m), 1072 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.48–7.39 (4 H, m, 4 × Ar**H**)

7.35–7.21 (6 H, m, 6 × Ar**H**)

5.29 (1 H, s, O**H**)

3.42 (3 H, s, C$\mathbf{H}_3$)

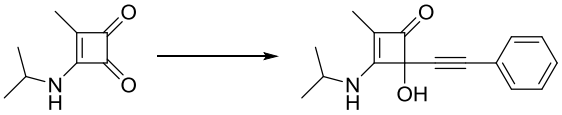
3.12 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 182.5 (**C**), 167.4 (**C**), 131.8 (**C**H), 129.8 (**C**), 128.6 (**C**H), 128.5 (**C**H), 128.2 (**C**H), 128.1 (**C**H), 127.0 (**C**H), 122.2 (**C**), 118.2 (**C**), 88.5 (**C**), 84.6 (**C**), 82.8 (**C**), 41.1 (**C**H_3), 40.6 (**C**H_3) ppm.

LRMS (ESI+) 304 ($[M+H]^+$, 100%), 607 ($[2M+H]^+$, 80%).

HRMS (ESI+) Found 304.1335, $C_{20}H_{18}NO_2$ $[M+H]^+$ requires 304.1332.

4-hydroxy-3-(isopropylamino)-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (3.4l)



3.3g
$C_8H_{11}NO_2$
Mol Wt 153.08

3.4l
$C_{16}H_{17}NO_2$
Mol Wt 255.13

To a solution of phenylacetylene (0.29 mL, 2.64 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 1.1 mL, 2.64 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of 3-(isopropyl(methyl)amino)-4-methylcyclobutene-1,2-dione **3.3g** (153 mg, 1.00 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–25% acetone/DCM) to afford the title compound (103 mg, 0.4 mmol, 40%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3216 (br), 2970 (br), 1761 (w), 1574 (s), 1466 (w), 1446 (m), 1122 (m), 1080 (m) cm^{-1}.

δ_H (400 MHz, major rotamer:

Methanol-d4) 7.44–7.40 (2 H, m, 2 × Ar**H**)

7.36–7.32 (3 H, m, 3 × Ar**H**)

4.23 (1 H, sept, *J* = 6.5 Hz, C**H**)

1.09 (3 H, s, C**H**$_3$)

1.10 (6 H, br d, *J* = 6.5 Hz, CH(C**H**$_3$)$_2$) ppm.

minor rotamer:

7.44–7.40 (2 H, m, 2 × Ar**H**)

7.36–7.32 (3 H, m, 3 × Ar**H**)

4.87 (1 H, sept, *J* = 5.9 Hz, C**H**)

1.76 (3 H, s, C**H**$_3$)

1.37 (6 H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$) ppm.

δ_C (100 MHz, Methanol-d4)

major rotamer:

187.1 (**C**), 173.4 (**C**), 132.7 (**C**H), 130.3 (**C**H), 129.7 (**C**H), 123.7 (**C**), 115.2 (**C**), 88.6 (**C**), 86.4 (**C**), 82.7 (**C**), 49.3 (**C**H), 31.1 (**C**H$_3$), 23.7 (**C**H$_3$), 6.2 (**C**H$_3$) ppm.

minor rotamer:

188.5 (**C**), 172.2 (**C**), 132.8 (**C**H), 129.9 (**C**H), 129.6 (**C**H), 123.9 (**C**), 114.5 (**C**), 87.7 (**C**), 86.0 (**C**), 79.6 (**C**), 48.2 (**C**H), 29.7 (**C**H$_3$), 24.3 (**C**H$_3$), 7.8 (**C**H$_3$) ppm.

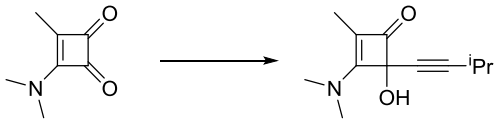
LRMS (ESI+)

256 ([M+H]$^+$, 100%), 511 ([2M+H]$^+$, 60%).

HRMS (ESI+)

Found 256.1330, $C_{16}H_{18}NO_2$ [M+H]$^+$ requires 256.1332.

3-(Dimethylamino)-4-hydroxy-2-methyl-4-(pent-1-yn-1-yl)cyclobut-2-enone (3.4m)



3.3a
$C_7H_9NO_2$
Mol Wt:139.2

3.4m
$C_{12}H_{17}NO_2$
Mol Wt:207.1

Experimental

To a solution of pent-1-yne (0.17 mL, 1.74 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexane, 0.75 mL, 1.73 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-dimethylamino-4-methylcyclobutene-1,2-dione **3.3a** (186 mg, 1.39 mmol) in THF (20 mL) at –78 °C. After a further 4 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–20% acetone/DCM) to afford the title compound (210 mg, 1.01 mmol, 75%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3245 (br), 2962 (w), 1783 (w), 1749 (m), 1570 (vs), 1410 (s), 1269 (m), 1192 (w), 1130 (m), 1024 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 4.71 (1H, s, O**H**),

3.22 (3 H, s, NC**H**$_3$),

3.14 (3 H, s, NC**H**$_3$),

2.19 (2 H, t, *J* = 7.1 Hz, C**H**$_2$),

1.73 (3 H, s, C**H**$_3$),

1.51 (2 H, m, C**H**$_2$),

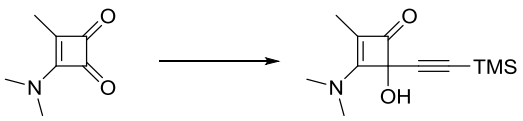
0.94 (3 H, t, *J* = 7.4 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 185.0 (**C**), 170.1 (**C**), 113.8 (**C**), 88.8 (**C**), 81.1 (**C**), 75.8 (**C**), 39.6 (**C**H_3), 39.1 (**C**H_3), 21.5 (**C**H_2), 20.6 (**C**H_2), 13.1 (**C**H_3), 7.2 (**C**H_3) ppm.

LRMS (ESI+) 208 ($[M+H]^+$, 100%), 415 ($[2M+H]^+$, 30%).

HRMS (ESI+) Found 208.1332, $C_{12}H_{18}NO_2$ [M+H]+ requires 208.1332.

3-(dimethylamino)-4-hydroxy-2-methyl-4-((trimethylsilyl)ethynyl)cyclobut-2-en-1-one (3.4n)



3.3a
$C_7H_9NO_2$
Mol Wt 139.15

3.4n
$C_{12}H_{19}NO_2Si$
Mol Wt 237.12

To a solution of ethynyltrimethylsilane (0.18 mL, 1.30 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexane, 0.56 mL, 1.29 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of 3-dimethylamino-4-methylcyclobutene-1,2-dione **3.3a** (139 mg, 1.00 mmol) in THF (20 mL) at –78 °C. After a further 4 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–40% acetone/DCM) to afford the title compound (207 mg, 0.87 mmol, 87%) as a yellow solid.

MP Decomposed over 147 °C.

FT-IR (ν_{max}, $CHCl_3$) 3200 (br), 2957 (w), 1750 (w), 1573 (s), 1411 (m), 1249 (m), 1109 (m), 841 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 4.46 (H, br s, O**H**)

3.19 (3 H, s, NC**H**$_3$)

3.13 (3 H, s, NC**H**$_3$)

1.71 (3 H, s, C**H**$_3$)

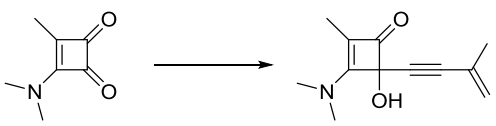
0.11 (9 H, s, Si(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 184.4 (**C**), 170.0 (**C**), 114.8 (**C**), 100.9 (**C**), 93.0 (**C**), 81.6 (**C**), 39.9(**C**H$_3$), 39.4 (**C**H$_3$), 7.6 (**C**H$_3$), -0.33 (Si(**C**H$_3$)$_3$)ppm.

LRMS (ESI+) 238 ([M+H]$^+$, 100%), 260 ([M+Na]$^+$, 30%).

HRMS (ESI+) Found 238.1261, $C_{12}H_{20}NO_2Si$ [M+H]$^+$ requires 238.1258.

3-(Dimethylamino)-4-hydroxy-2-methyl-4-(3-methylbut-3-en-1-yn-1-yl)cyclobut-2-enone (3.4o)



3.3a
$C_7H_9NO_2$
Mol Wt 139.15

3.4o
$C_{12}H_{15}NO_2$
Mol Wt 205.11

To a solution of 2-methylbut-1-en-3-yne (0.17 mL, 1.74 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.75 mL, 1.74 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-dimethylamino-4-methylcyclobutene-1,2-dione **3.3a** (186 mg, 1.39

mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–30% acetone/DCM) to afford the title compound (221 mg, 1.07 mmol, 80%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3234 (br), 2922 (w), 1749 (m), 1570 (vs), 1410 (s), 1271 (m), 1117 (m), 1024 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.29 (1 H, m, C**H**H)

5.21 (1 H, m, CH**H**)

5.10 (1 H, s, O**H**)

3.23 (3 H, s, NC**H**$_3$)

3.16 (3 H, s, NC**H**$_3$)

1.85 (3 H, s, C**H**$_3$)

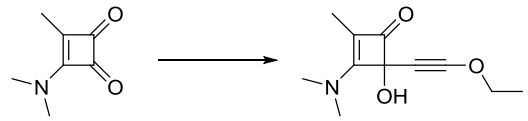
1.74 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 184.4 (**C**), 169.8 (**C**), 125.7 (**C**), 122.3 (**C**H$_2$), 114.1 (**C**), 88.8 (**C**), 83.6 (**C**), 81.2 (**C**), 39.6 (**C**H$_3$), 39.1 (**C**H$_3$), 22.8 (**C**H$_3$), 7.3 (**C**H$_3$) ppm.

LRMS (ESI+) 206 ($[M+H]^+$, 100%), 433 ($[2M+Na]^+$, 20%).

HRMS (ESI+) Found 206.1177, $C_{12}H_{16}NO_2$ $[M+H]^+$ requires 206.1176.

3-(Dimethylamino)-4-(ethoxyethynyl)-4-hydroxy-2-methyl-cyclobut-2-enone (3.4p)



3.3a
$C_7H_9NO_2$
Mol Wt 139.15

3.4p
$C_{11}H_{15}NO_3$
Mol Wt 209.11

To a solution of ethoxyethyne (0.33 mL, 1.87 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexane, 0.80 mL, 1.87 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-dimethylamino-4-methylcyclobutene-1,2-dione **3.3a** (200 mg, 1.44 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to

RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–25% acetone/DCM) to afford the title compound (211 mg, 1.01 mmol, 70%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3215 (br), 2927 (br), 2256 (s), 1749 (m), 1572 (s), 1410 (m), 1267 (m), 1161 (m), 1134 (m), 1030 (s), 1018 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.57 (1 H, s, O**H**)

3.95 (2 H, q, *J* = 7.1 Hz, C**H**$_2$)

3.07 (3 H, s, C**H**$_3$)

2.99 (3 H, s, C**H**$_3$)

1.55 (3 H, s, C**H**$_3$)

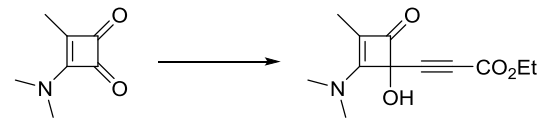
1.18 (3 H, t, *J* = 7.1 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 186.4 (**C**), 171.0 (**C**), 112.4 (**C**), 95.8 (**C**), 80.3 (**C**), 74.5 (**C**H_2), 39.4 (**C**H_3), 39.0 (**C**H_3), 34.6 (**C**), 13.9 (**C**H_3), 7.0 (**C**H_3) ppm.

LRMS (ESI+) 210 ($[M+H]^+$, 100%), 419 ($[2M+H]^+$, 20%).

HRMS (ESI+) Found 210.1129, $C_{11}H_{16}NO_3$ $[M+H]^+$ requires 210.1125.

Ethyl 3-(2-(dimethylamino)-1-hydroxy-3-methyl-4-oxocyclobut-2-en-1-yl)propiolate (3.4q)



3.3a
$C_7H_9NO_2$
Mol Wt 139.15

3.4q
$C_{12}H_{15}NO_4$
Mol Wt 237.25

To a solution of ethyl propiolate (0.20 mL, 1.97 mmol) in THF (10 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexane, 0.86 mL, 1.98 mmol) dropwise. The solution was stirred at –78 °C for 5 min and added *via* cannula to a solution of 3-methoxy-4-methyl cyclobut-3-ene-1,2-dione **3.3a** (190 mg, 1.37 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred at –78 °C for 5 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$,

concentrated under reduced pressure and purified by column chromatography (10–50% acetone/cyclohexane) to afford the title compound (193 mg, 0.81 mmol, 59%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3218 (br), 2933 (br), 2233 (w), 1753 (w), 1507 (s), 1576 (Vs), 1412 (s), 1242 (s), 1140 (m), 1020 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 6.16 (1 H, br, O**H**)

4.18 (2 H, q, *J* = 7.2 Hz, C**H**$_2$)

3.21 (3 H, S, C**H**$_3$)

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

1.72 (3 H,s,C**H**$_3$)

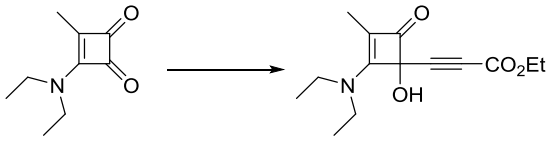
1.25 (3 H, t, *J* = 7.2 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 182.3 (**C**), 168.8 (**C**), 153.2 (**C**), 115.3 (**C**), 83.0 (**C**), 80.8 (**C**), 78.7 (**C**), 62.1 (**C**H$_2$), 40.2 (**C**H$_3$), 39.5 (**C**H$_3$), 13.9 (**C**H$_3$), 7.6 (**C**H$_3$) ppm.

LRMS (ESI+) 238 ($[M+H]^+$, 100%), 475 ($[2M+H]^+$, 40%).

HRMS (ESI+) Found 238.1076, $C_{12}H_{16}NO_4$ $[M+H]^+$ requires 238.1074.

ethyl 3-(2-(diethylamino)-1-hydroxy-3-methyl-4-oxocyclobut-2-en-1-yl)propiolate (3.4r)



3.3b
$C_9H_{13}NO_2$
Mol Wt 167.09

3.4r
$C_{14}H_{19}NO_4$
Mol Wt 265.13

To a solution of ethyl propiolate (0.18 mL, 1.77 mmol) in THF (10 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexane, 0.78 mL, 1.79 mmol) dropwise. The solution was stirred at –78 °C for 10 min. A solution of 3-(diethylamino)-4-methylcyclobut-3-ene-1,2-dione **3.3b** (200 mg, 1.20 mmol) in THF (20 mL) at –78 °C was adde into the reaction mixture *via* cannulation. The resulting solution was stirred at –78 °C for 3 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography

(10–50% acetone/cyclohexane) to afford the title compound (3.6 mg, 1.36 mmol, 100%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3205 (br), 2979 (w), 2230 (w), 1748 (w). 1707 (m), 1562 (s), 1446 (m), 1365 (w), 1247 (s), 1215 (m) 1140 (m), 1019 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 6.28 (1 H, s, O**H**)

4.11 (2 H, q, *J* = 7.1 Hz, C**H**$_2$)

3.58 (1 H, app sxt, *J* = 7.1 Hz, CH**H**)

3.45 (1 H, app sxt, *J* = 7.1 Hz, C**H**H)

3.35 (2 H, q, *J* = 7.3 Hz, C**H**$_2$)

1.64 (3 H, s, C**H**$_3$)

1.25-1.14 (9 H, m, 3 × C**H**$_3$) ppm.

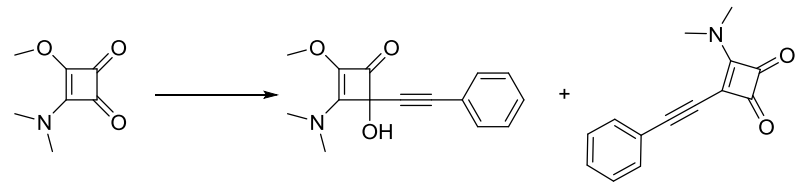
δ_C (100 MHz, $CDCl_3$) 182.2 (**C**), 168.1 (**C**), 153.0 (**C**), 114.3 (**C**), 83.2 (**C**), 80.8 (**C**), 78.3 (**C**), 61.8 (**C**H_2), 45.4 (**C**H_2), 43.3 (**C**H_2), 14.0 (**C**H_3), 13.7 (**C**H_3), 13.5 (**C**H_3), 7.4 (**C**H_3) ppm.

LRMS (ESI+) 266 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 266.1393, $C_{14}H_{20}NO_4$ $[M+H]^+$ requires 266.1387.

3-(dimethylamino)-4-hydroxy-2-methoxy-4-(phenylethynyl)cyclobut-2-enone (3.4s)

3-(dimethylamino)-4-(phenylethynyl)cyclobut-3-ene-1,2-dione (3.6)



3.3k
$C_7H_9NO_3$
Mol Wt 155.06

3.4s
$C_{15}H_{15}NO_3$
Mol Wt 257.11

3.6
$C_{14}H_{11}NO_2$
Mol Wt 225.08

To a solution of phenylacetylene (0.14 mL, 1.28 mmol) in DCM (25 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.54 mL, 1.30 mmol) dropwise. The solution was stirred at –78 °C for 10 min and added *via* cannula to a solution of 3-(dimethylamino)-4-methoxycyclobut-3-ene-1,2-dione **3.3k**

(155 mg, 1 mmol) in DCM (40 mL) at –78 °C. The resulting solution was stirred at –78 °C for 3 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The mixture was purified by column chromatography (30% EA/hexane) to afford **3.4s** (86 mg, 0.33 mmol, 33%) as a yellow solid, then afford **3.6** (60 mg, 0.27 mmol, 27%) as a yellow solid.

3.4s

Due to the extremely poor stability of cyclobutenone **3.4s**, only IR, ^{1}H-NMR and ^{13}C-NMR datas were collected.

FT-IR (ν_{max}, $CHCl_3$) 2929 (br), 1782 (m), 1743 (s), 1629 (vs), 1490 (m), 1442 (m), 1398 (m), 1303 (w), 1110 (m), 1031 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.49–7.42 (2 H, m, 2 × Ar**H**)

7.30–7.24 (3 H, m, 3 × Ar**H**)

5.68 (H, s, O**H**)

3.94 (3 H, s, OC**H**$_3$)

3.23 (3 H,s, C**H**$_3$)

3.13 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.8 (**C**), 158.9 (**C**), 131.7 (**C**H), 128.7 (**C**H), 128.3 (**C**H), 127.9 (**C**), 122.2 (**C**), 87.2 (**C**), 85.1 (**C**), 77.4 (**C**), 58.5 (O**C**H$_3$), 39.3 (2 × C**H**$_3$) ppm.

3.6

MP 136-137 °C (DCM/hexane) .

FT-IR (ν_{max}, $CHCl_3$) 2927 (br), 1755 (s), 1731 (s), 1623 (s), 1298 (m), 1186 (m), 1022 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.55–7.46 (2 H, m, 2 × Ar**H**)

7.45–7.33 (3 H, m, 3 × Ar**H**)

3.47 (3 H, s, C**H**$_3$)

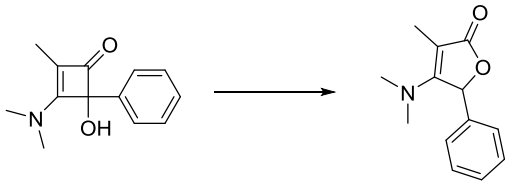
3.46 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 194.3 (**C**), 187.4 (**C**), 180.0 (**C**), 147.0 (**C**), 131.4 (**C**H), 129.8 (**C**H), 128.6 (**C**H), 121.8 (**C**), 114.4 (**C**), 40.18 (**C**H_3), 39.56 (**C**H_3) ppm (one **C** not observed).

LRMS (ESI+) 226 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 226.0858, $C_{14}H_{12}NO_2$ $[M+H]^+$ requires 226.0863.

4-(dimethylamino)-3-methyl-5-phenylfuran-2(5H)-one (3.9a)



3.4a
$C_{13}H_{15}NO_2$
Mol Wt 217.26

3.9a
$C_{13}H_{15}NO_2$
Mol Wt 217.26

Cyclobutenone **3.4a** (100 mg, 0.46 mmol) in 1,4-dioxane (10 mL) was heated at 180 °C in stainless steel tubing under continuous flow for a residence time of 2 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/ cyclohexane) to afford the title compound (92 mg, 0.41 mmol, 92%) as a yellow solid.

MP 148–149 °C.

FT-IR (ν_{max}, $CHCl_3$) 2925 (br), 1720 (s), 1608 (s), 1489 (w), 1456 (w), 1406 (s), 1313 (m), 1296 (m), 1078 (m), 1016 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.37–7.31 (3 H, m, 3 × Ar**H**)

7.29–7.25 (2 H, m, 2 × Ar**H**)

5.56 (H, s, C**H**)

2.86 (6 H, s, N(C**H**$_3$)$_2$)

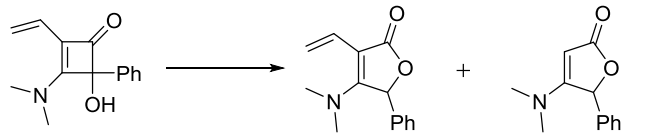
2.06 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.7 (**C**), 163.8 (**C**), 135.8 (**C**), 129.2 (**C**H), 128.9 (**C**H), 127.7 (**C**H), 90.5 (**C**), 79.1 (**C**H), 40.7 (2 × C**H**$_3$), 9.8 (**C**H_3) ppm.

LRMS (ESI+) 218 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 218.1179, $C_{13}H_{16}NO_2$ $[M+H]^+$ requires 218.1176.

4-(dimethylamino)-5-phenyl-3-vinylfuran-2(5H)-one (3.9b)



3.4b
$C_{14}H_{15}NO_2$
Mol Wt: 229.11

3.9b
$C_{14}H_{15}NO_2$
Mol Wt: 229.11

3.53
$C_{12}H_{13}NO_2$
Mol Wt: 203.09

Cyclobutenone **3.4b** (150 mg, 0.66 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (60–100% Et_2O/cyclohexane) to afford firstly the title compound (119 mg, 0.52 mmol, 79%) as a yellow oil, then the eliminated furanone **3.53** (10 mg, 0.05 mmol, 7%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2925 (w), 1715 (s), 1609 (s), 1455 (m), 1318 (m), 1163 (m), 1011 (m), cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.40–7.36 (3 H, m, 3 × Ar**H**)

7.33–7.29 (2 H, m, 2 × Ar**H**)

6.70 (1 H, dd, *J* = 17.3, 11.6 Hz, C**H**)

6.00 (1 H, dd, *J* = 17.4, 2.1 Hz, C**H**H)

5.62 (1 H, s, C**H**)

5.26 (1 H, dd, *J* = 11.5, 2.2 Hz, CH**H**)

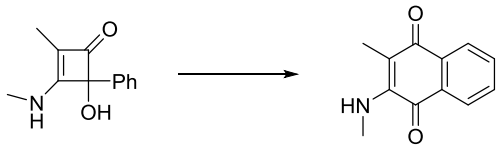
2.96 (6 H, s, N(C$\mathbf{H}_3$)$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.7 (**C**), 163.3 (**C**), 135.7 (**C**), 129.5 (**C**H), 129.2 (**C**H), 127.8 (**C**H), 125.6 (**C**H), 115.4 (**C**H_2), 95.4 (**C**), 78.7 (**C**H), 42.1 (2 × **C**H_3) ppm.

LRMS (ESI+) 230 ($[M+H]^+$, 100%), 252 ($[M+Na]^+$, 40%).

HRMS (ESI+) Found 230.1174, $C_{14}H_{16}NO_2$ $[M+H]^+$ requires 230.1176.

2-methyl-3-(methylamino)naphthalene-1,4-dione (3.8c)



3.4c
$C_{12}H_{13}NO_2$
Mol Wt 203.09

3.8c
$C_{12}H_{11}NO_2$
Mol Wt 201.08

4-hydroxy-2-methyl-3-methylamino-4-phenylcyclobut-2-en-1-one **3.4c** (200 mg, 0.99 mmol) in tetraethylene glycol dimethyl ether (10 mL) was stirred at 160 °C for 5 h under argon then cooled to RT and stirred at RT for 1 h under air. The reaction mixture was diluted by H_2O (50 mL) then extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 300 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The mixture was purified by column chromatography (10–30% Et_2O/Pet) to afford the title compound (145 mg, 0.72 mmol, 73%) as a dark red solid.

MP 128–129 °C (Et_2O/Pet).

FT-IR (ν_{max}, $CHCl_3$) 3365 (br), 2921 (br), 1715 (w), 1667 (m), 1598 (m), 1562 (s), 1514 (s), 1467 (s), 1340 (s), 1278 (s), 1086 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 8.08 (1 H, dd, *J* = 7.7, 1.0 Hz, Ar**H**)

7.98 (1 H, dd, *J* = 7.6, 1.0 Hz, Ar**H**)

7.67 (1 H, td, *J* = 7.6, 1.3 Hz, Ar**H**)

7.57 (1 H, td, *J* = 7.6, 1.3 Hz, Ar**H**)

5.81 (1 H, br s, N**H**)

3.24 (3 H, d, *J* = 5.0 Hz, C**H**$_3$)

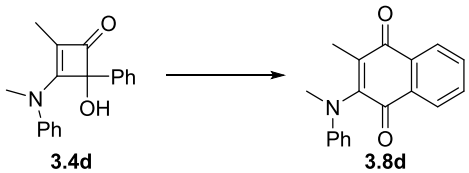
2.28 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 183.6 (**C**), 182.5 (**C**), 146.9 (**C**), 134.3 (**C**H), 133.5 (**C**), 131.7 (**C**H), 130.2 (**C**), 126.2 (**C**H), 125.9 (**C**H), 112.0 (**C**), 32.9 (**C**H$_3$), 10.9 (**C**H$_3$) ppm.

LRMS (ESI+) 202 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 202.0861, $C_{12}H_{12}NO_2$ $[M+H]^+$ requires 202.0863.

2-methyl-3-(methyl(phenyl)amino)naphthalene-1,4-dione (3.8d)



3.4d
$C_{18}H_{17}NO_2$
Mol Wt 279.13

3.8d
$C_{18}H_{15}NO_2$
Mol Wt 277.11

Cyclobutenone **3.4d** (80 mg, 0.29 mmol) in 1,4-dioxane (5 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–50% Et_2O/petrol) to afford the title compound (69 mg, 0.25 mmol, 86%) as a purple solid.

MP 143–144 °C.

FT-IR (ν_{max}, $CHCl_3$) 2924 (w), 1666 (s), 1649 (m), 1595 (s), 1576 (m), 1497 (s), 1332 (m), 1285 (s), 1264 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 8.14 (1 H, m, Ar**H**)

8.06 (1 H, m, Ar**H**)

7.76–7.70 (2 H, m, 2 × Ar**H**)

7.27–7.24 (2 H, m, 2 × Ar**H**)

6.87 (1 H, t, *J* = 7.3 Hz, Ar**H**)

6.75 (2 H, d, *J* = 8.0 Hz, Ar**H**)

3.32 (3 H, s, C$\mathbf{H}_3$)

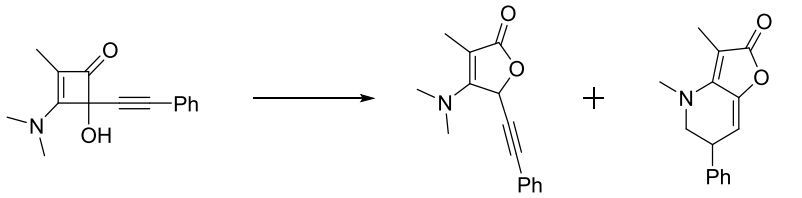
2.06 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 185.7 (**C**), 182.0 (**C**), 148.9 (**C**), 147.1 (**C**), 141.6 (**C**), 133.6 (**C**H), 133.5 (**C**H), 132.4 (**C**), 132.1 (**C**), 129.2 (**C**H), 126.6 (**C**H), 126.3 (**C**H), 119.4 (**C**H), 114.6 (**C**H), 38.8 (**C**H_3), 12.9 (**C**H_3) ppm.

LRMS (ESI+) 278 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 278.1180, $C_{18}H_{16}NO_2$ $[M+H]^+$ requires 278.1176.

4-(Dimethylamino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (3.9e)



3.4e
$C_{15}H_{15}NO_2$
Mol Wt: 241.12

3.9e
$C_{15}H_{15}NO_2$
Mol Wt: 241.12

4.1e
$C_{15}H_{15}NO_2$
Mol Wt: 241.12

Cyclobutenone **3.4e** (75 mg, 0.31 mmol) in 1,4-dioxane (5 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–100% EtOAc/hexane) to afford firstly dihydrofuropyridinone **4.1e** (7 mg, 0.03 mmol, 10%) as a yellow oil, then the title compound (37 mg, 0.15 mmol, 49%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2976 (br), 1734 (s), 1614 (s), 1489 (w), 1443 (m), 1381 (w), 1317 (w), 1290 (w), 1213 (w), 1173 (w), 1112 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.48–7.44 (2 H, m, 2 × Ar**H**)

7.37–7.31 (3 H, m, 3 × Ar**H**)

5.50 (1H, s, C**H**)

3.20 (6 H, s, N(C**H**$_3$)$_2$)

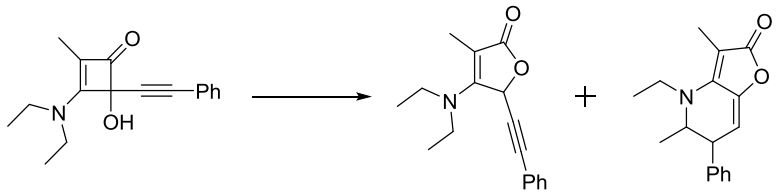
2.02 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.2 (**C**), 161.7 (**C**), 131.7 (**C**H), 129.1 (**C**H), 128.3 (**C**H), 121.4 (**C**), 88.9 (**C**), 87.2 (**C**), 81.9 (**C**), 67.0 (**C**H), 40.8 (2 × **C**H$_3$), 9.8 (**C**H$_3$) ppm.

LRMS (ESI+) 242 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 242.1172, $C_{15}H_{16}NO_2$ $[M+H]^+$ requires 242.1176.

4-(Diethylamino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (3.9f)



3.4f
$C_{17}H_{19}NO_2$
Mol Wt: 269.15

3.9f
$C_{17}H_{19}NO_2$
Mol Wt: 269.15

4.1f
$C_{17}H_{19}NO_2$
Mol Wt: 269.15

Cyclobutenone **3.4f** (120 mg, 0.45 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford firstly dihydrofuropyridinone **4.1f** (20 mg, 0.07 mmol, 15%) as a yellow solid, then the title compound (73 mg, 0.27 mmol, 60%) as a yellow solid.

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 2975 (br), 2929 (br), 1731 (s), 1604 (s), 1436 (m), 1319 (w), 1266 (m), 1070 (m), 1029 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.41–7.39 (2 H, m, 2 × Ar**H**)

7.30–7.25 (3 H, m, 3 × Ar**H**)

5.47 (1H, s, C**H**)

3.53–3.34 (4 H, m, 2 × C**H**$_2$)

1.92 (3 H, s, C**H**$_3$)

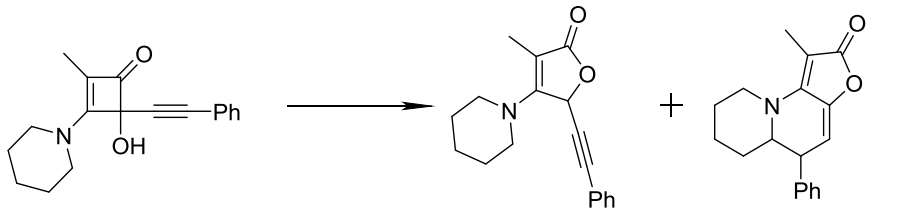
1.21 (6 H, t, *J* = 7.1 Hz, 2 × C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.2 (**C**), 160.5 (**C**), 131.5 (**C**H), 128.9 (**C**H), 128.2 (**C**H), 121.3 (**C**), 87.3 (**C**), 86.7 (**C**), 82.5 (**C**), 66.7 (**C**H), 43.9 (2 × **C**H_2) 14.0 (2 × **C**H_3), 9.7 (**C**H_3) ppm.

LRMS (ESI+) 270 ($[M+H]^+$, 100%), 292 ($[M+Na]^+$, 40%).

HRMS (ESI+) Found 270.1486, $C_{17}H_{20}NO_2$ $[M+H]^+$ requires 270.1489.

3-Methyl-5-(phenylethynyl)-4-(piperidin-1-yl)furan-2(5H)-one (3.9g)



3.4g
$C_{18}H_{19}NO_2$
Mol Wt: 281.15

3.9g
$C_{18}H_{19}NO_2$
Mol Wt: 281.15

4.1g
$C_{18}H_{19}NO_2$
Mol Wt: 281.15

Cyclobutenone **3.4g** (230 mg, 0.82 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford firstly dihydrofuropyridinone **4.1g** (41 mg, 0.15 mmol, 18%) as a yellow solid, then the title product (130 mg, 0.46 mmol, 57%) as a yellow solid .

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 2937 (br), 2656 (br), 1731 (s), 1614 (s), 1442 (m), 1294 (m), 1076 (m), 1018 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.41–7.49 (2 H, m, 2 × Ar**H**)

7.30–7.39 (3 H, m, 3 × Ar**H**)

5.51 (1 H, s, C**H**)

3.55 (4 H, br s, 2 × C$\mathbf{H}_2$)

1.97 (3 H, s, C$\mathbf{H}_3$)

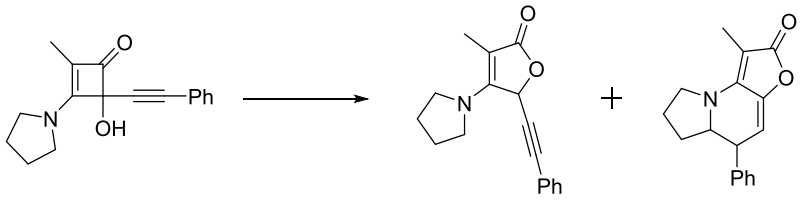
1.66–1.76 (6 H, m, 3 × C$\mathbf{H}_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.4 (**C**), 160.7 (**C**), 131.8 (**C**H), 129.1 (**C**H), 128.4 (**C**H), 121.6 (**C**), 88.4 (**C**), 87.0 (**C**), 82.5 (**C**), 66.9 (**C**H), 49.4 (2 × **C**H_2), 26.1 (2 × **C**H_2), 24.1 (**C**H_2), 10.5 (**C**H_3) ppm.

LRMS (ESI+) 282 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 282.1492, $C_{18}H_{20}NO_2$ $[M+H]^+$ requires 282.1489.

3-Methyl-5-(phenylethynyl)-4-(pyrrolidin-1-yl)furan-2(5H)-one (3.9h)



3.4h
$C_{17}H_{17}NO_2$
Mol Wt: 267.13

3.9h
$C_{17}H_{17}NO_2$
Mol Wt: 267.13

4.1h
$C_{17}H_{17}NO_2$
Mol Wt: 267.13

Cyclobutenone **3.4h** (100 mg, 0.37 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford firstly dihydrofuropyridinone **4.1h** (10 mg, 0.04 mmol, 10%) as a yellow solid, then the title compound (70 mg, 0.26 mmol, 70%) as a yellow solid.

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 2973 (br), 2873 (w), 1731 (s), 1616 (s), 1489 (w), 1435 (s), 1367 (w), 1290 (w), 1089 (w), 1070 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.44–7.41 (2 H, m, 2 × Ar**H**)

7.34–7.30 (3 H, m, 3 × Ar**H**)

5.49 (1 H, s, C**H**)

3.84–3.77 (2 H, m, 2 × NC**H**H)

3.60 (2 H, br s, 2 × NCH**H**)

2.05–1.90 (4 H, m, 2 × C$\mathbf{H}_2$)

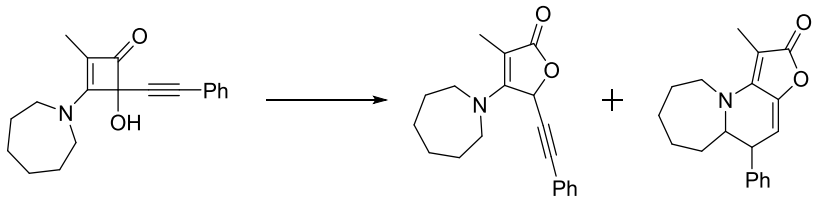
1.99 (3 H, m, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.3 (**C**), 159.6 (**C**), 131.8 (**C**H), 129.1 (**C**H), 128.3 (**C**H), 121.5 (**C**), 88.1 (**C**), 87.3 (**C**), 82.0 (**C**), 67.1 (**C**H), 49.1 (2 × **C**H_2), 25.2 (2 × **C**H_2), 9.0 (**C**H_3) ppm.

LRMS (ESI+) 268 ($[M+H]^+$, 100%), 557($[2M+Na]^+$, 60%).

HRMS (ESI+) Found 268.1330, $C_{17}H_{18}NO_2$ $[M+H]^+$ requires 268.1332.

4-(Azepan-1-yl)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (3.9i)



3.4i
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

3.9i
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

4.1i
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

Cyclobutenone **3.4i** (197 mg, 0.67 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford firstly dihydrofuropyridinone **4.1i** (21 mg, 0.07 mmol, 11%) as a yellow oil, then the title compound (100 mg, 0.34 mmol, 51%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2924 (br), 2874 (w), 1731 (s), 1616 (vs), 1489 (w), 1435 (s), 1290 (m), 1089 (w), 1070 (m), 1027 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.46–7.42 (2 H, m, 2 × Ar**H**)

7.37–7.31 (3 H, m, 3 × Ar**H**)

5.52 (1 H, s, C**H**)

3.63 (4 H, app. t, *J* = 6.0 Hz, 2 × NC$\mathbf{H}_2$)

2.00 (3 H, s, C$\mathbf{H}_3$)

1.87–1.78 (4 H, m, 2 × C$\mathbf{H}_2$)

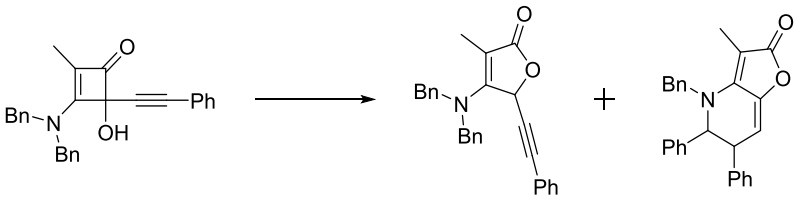
1.74–1.60 (4 H, m, 2 × C$\mathbf{H}_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.4 (**C**), 161.0 (**C**), 131.8 (**C**H), 129.1 (**C**H), 128.4 (**C**H), 121.6 (**C**), 87.4 (**C**), 87.2 (**C**), 82.7 (**C**), 66.8 (**C**H), 50.8 (2 × **C**H_2), 29.3 (2 × **C**H_2), 26.8 (2 × **C**H_2), 10.1 (**C**H_3) ppm.

LRMS (ESI+) 296 ($[M+H]^+$, 80%), 591 ($[2M+H]^+$, 100%).

HRMS (ESI+) Found 318.1463, $C_{19}H_{21}NO_2Na$ $[M+Na]^+$ requires 318.1465.

4-(Dibenzylamino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (3.9j)



3.4j
$C_{27}H_{23}NO_2$
Mol Wt: 393.17

3.9j
$C_{27}H_{23}NO_2$
Mol Wt: 393.17

4.1j
$C_{27}H_{23}NO_2$
Mol Wt: 393.17

Cyclobutenone **3.4j** (180 mg, 0.46 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (30–70% Et_2O/cyclohexane) to afford firstly dihydrofuropyridinone **4.1j** (45 mg, 0.11 mmol, 25%) as a yellow oil, then the title compound (122 mg, 0.31 mmol, 67%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3031 (br), 2919 (br), 1735 (s), 1616 (s), 1493 (m), 1431 (s), 1288 (m), 1076 (m), 1041 (m), 1014 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.36–7.26 (11 H, m, 11 × Ar**H**)

7.24–7.19 (4 H, m, 4 × Ar**H**)

5.60 (1 H, s, C**H**)

4.81 (2 H, d, *J* = 16.5 Hz, 2 × PhC**H**H)

4.44 (2 H, d, *J* = 16.5 Hz, 2 × PhCH**H**)

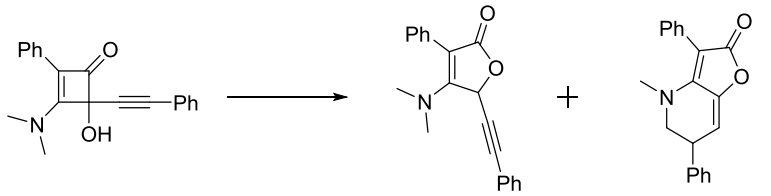
1.92 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.0 (**C**), 161.5 (**C**), 136.4 (**C**), 131.7 (**C**H), 129.1 (**C**H), 129.0 (**C**H), 128.3 (**C**H), 127.8 (**C**H), 126.7 (**C**H), 121.2 (**C**), 90.1 (**C**), 87.9 (**C**), 82.2 (**C**), 67.3 (**C**H), 53.0 (2 × **C**H_2), 9.9 (**C**H_3) ppm.

LRMS (ESI+) 394 ($[M+H]^+$, 100%), 787 ($[2M+H]^+$, 40%).

HRMS (ESI+) Found 394.1813, $C_{27}H_{24}NO_2$ $[M+H]^+$ requires 394.1802.

4-(Dimethylamino)-3-phenyl-5-(phenylethynyl)furan-2(5H)-one (3.9k)



3.4k
$C_{20}H_{17}NO_2$
Mol Wt: 303.13

3.9k
$C_{20}H_{17}NO_2$
Mol Wt: 303.13

4.1k
$C_{20}H_{17}NO_2$
Mol Wt: 303.13

Cyclobutenone **3.4k** (150 mg, 0.50 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–70% Et_2O/cyclohexane) to afford firstly dihydrofuropyridinone **4.1k** (21 mg, 0.07 mmol, 14%) as a yellow solid, then the title compound (100 mg, 0.33 mmol, 67%) as a yellow solid.

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 2920 (br), 2850 (w), 1747 (s), 1620 (s), 1597 (m), 1508 (w), 1454 (w), 1415 (w), 1323 (m), 1068 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.51–7.47 (2 H, m, 2 × Ar**H**)

7.40–7.30 (8 H, m, 8 × Ar**H**)

5.71 (1 H, s, C**H**)

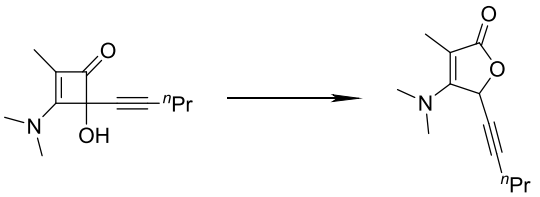
2.98 (6 H, s, 2 × C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 173.2 (**C**), 161.5 (**C**), 132.2 (**C**), 131.8 (**C**H), 131.0 (**C**H), 129.2 (**C**H), 128.4 (**C**H), 127.8 (**C**H), 127.1 (**C**H), 121.4 (**C**), 95.7 (**C**), 87.8 (**C**), 81.7 (**C**), 67.1 (**C**H), 41.7 (2 × C**H**$_3$) ppm.

LRMS (ESI+) 304 ($[M+H]^+$, 100%), 629 ($[2M+Na]^+$, 100%).

HRMS (ESI+) Found 304.1334, $C_{20}H_{18}NO_2$ $[M+H]^+$ requires 304.1332.

4-(Dimethylamino)-3-methyl-5-(pent-1-yn-1-yl)furan-2(5H)-one (3.9m)



3.4m
$C_{12}H_{17}NO_2$
Mol Wt: 207.13

3.9m
$C_{12}H_{17}NO_2$
Mol Wt: 207.13

Cyclobutenone **3.4m** (120 mg, 0.58 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–100% Et_2O/cyclohexane) to afford the title compound (100 mg, 0.48 mmol, 83%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2958 (br), 2870 (m), 1724 (w), 1666 (w), 1641 (w), 1581 (m), 1520 (m), 1486 (m), 1448 (m), 1294 (m), 1195 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.21 (1 H, s, C**H**)

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

2.17 (2 H, t, *J* = 7.0 Hz, C**H**$_2$)

1.92 (3 H, s, C**H**$_3$)

1.50 (2 H, app sxt, *J* = 7.2 Hz, C**H**$_2$)

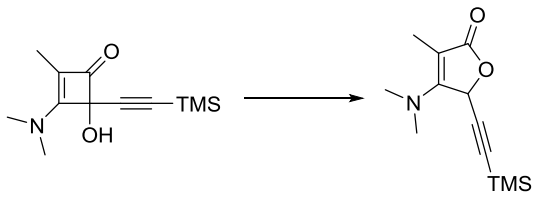
0.93 (3 H, t, *J* = 7.3 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.3 (**C**), 162.2 (**C**), 88.5 (**C**), 88.4 (**C**), 73.4 (**C**), 66.8 (**C**H), 40.7 (**C**H$_3$), 21.5 (**C**H$_2$), 20.6 (**C**H$_2$), 13.3 (2 × **C**H$_3$), 9.7 (**C**H$_3$) ppm.

LRMS (ESI+) 208 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 208.1330, $C_{12}H_{18}NO_2$ $[M+H]^+$ requires 208.1332.

4-(dimethylamino)-3-methyl-5-((trimethylsilyl)ethynyl)furan-2(5H)-one (3.9n)



3.4n
$C_{12}H_{19}NO_2Si$
Mol Wt 237.12

3.9n
$C_{12}H_{19}NO_2Si$
Mol Wt 237.12

Cyclobutenone **3.4n** (120 mg, 0.5 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–80% Et_2O/cyclohexane) to afford the title compound (80 mg, 0.34 mmol, 75%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2958 (br), 1733 (s), 1620 (s), 1408 (m), 1295 (m), 1250 (m), 1076 (m), 1044 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.23 (1H, s, C**H**)

3.12 (6 H, s, N(C**H**$_3$)$_2$)

1.94 (3 H, s, C**H**$_3$)

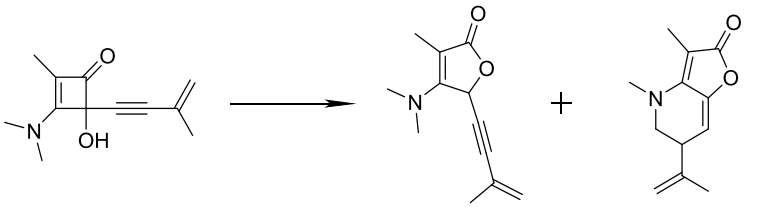
0.15 (9 H, s, Si(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.2 (**C**), 161.5 (**C**), 97.4 (**C**), 93.3 (**C**), 88.6 (**C**), 66.8 (**C**H), 40.8(2 × **C**H$_3$), 9.8 (**C**H$_3$), –0.56 (Si(**C**H$_3$)$_3$)ppm.

LRMS (ESI+) 238 ($[M+H]^+$, 100%), 475 ($[2M+H]^+$, 50%).

HRMS (ESI+) Found 238.1258, $C_{12}H_{20}NO_2Si$ $[M+H]^+$ requires 238.1258.

4-(Dimethylamino)-3-methyl-5-(3-methylbut-3-en-1-yn-1-yl)furan-2(5H)-one (3.9o)



3.4o
$C_{12}H_{15}NO_2$
Mol Wt: 205.11

3.9o
$C_{12}H_{15}NO_2$
Mol Wt: 205.11

4.1o
$C_{12}H_{15}NO_2$
Mol Wt: 205.11

Cyclobutenone **3.4o** (210 mg, 1.02 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1.5 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–100% Et_2O/cyclohexane) to afford firstly dihydrofuropyridinone **4.1o** (19 mg, 0.10 mmol, 10%) as a yellow oil, then the title compound (153 mg, 0.75 mmol, 73%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2960 (w), 2931 (br), 2871 (w), 1726 (s), 1605 (s), 1456 (w), 1404 (m), 1296 (m), 1084 (m), 1031 (m), 1014 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.36 (1 H, s, C**H**)

5.32 (1 H, br s, C**H**H)

5.28 (1 H, m, CH**H**)

3.13 (6 H, s, N(C**H**$_3$)$_2$)

1.95 (3 H, s, C**H**$_3$)

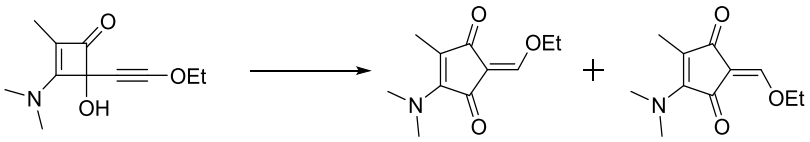
1.86 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.2 (**C**), 161.7 (**C**), 125.4 (**C**), 123.6 (**C**H_2), 88.7 (**C**), 88.3 (**C**), 80.9 (**C**), 66.8 (**C**H), 40.8 (2 × **C**H_3), 22.8 (**C**H_3), 9.7 (**C**H_3) ppm.

LRMS (ESI+) 206 ($[M+H]^+$, 100%), 228 ($[M+Na]^+$, 50%).

HRMS (ESI+) Found 206.1176, $C_{12}H_{16}NO_2$ $[M+H]^+$ requires 206.1176.

(*E*/*Z*)-4-(Dimethylamino)-2-(ethoxymethylene)-5-methylcyclopent-4-ene-1,3-dione (3.10p)



3.4p
$C_{11}H_{15}NO_3$
Mol Wt: 209.11

(*E*)-**3.10p**
$C_{11}H_{15}NO_3$
Mol Wt: 209.11

(*Z*)-**3.10p**
$C_{11}H_{15}NO_3$
Mol Wt: 209.11

Cyclobutenone **3.4p** (100 mg, 0.48 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford the title compound (61 mg, 0.29 mmol, 61%) as a yellow oil and an inseparable 1 : 1 mixture of geometric isomers.

FT-IR (ν_{max}, $CHCl_3$) 2925 (m), 1716 (w), 1639 (s), 1581 (s), 1436 (w), 1396 (m), 1230 (w), 1207 (w), 1065 (m), 1022 (s), 966 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.11 (1 H, s, C**H**)

7.08 (1 H, s, C**H**)

4.24 (2 H, q, *J* = 7.1 Hz, C$\mathbf{H}_2$)

4.24 (2 H, q, *J* = 7.1 Hz, C$\mathbf{H}_2$)

3.31 (3 H + 3 H, s, N(C$\mathbf{H}_3$)$_2$)

3.29 (3 H + 3 H, s, N(C$\mathbf{H}_3$)$_2$)

2.13 (3 H, s, C$\mathbf{H}_3$)

2.12 (3 H, s, C$\mathbf{H}_3$)

1.42 (3 H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$)

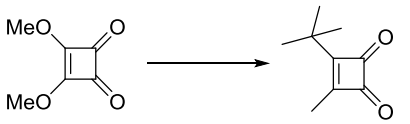
1.41 (3 H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 191.3 (**C**), 190.5 (**C**), 188.8 (**C**), 188.4 (**C**), 156.1 (**C**), 154.8 (**C**), 153.8 (**C**H), 153.7 (**C**H), 121.8 (**C**), 119.3 (**C**), 109.9 (**C**), 109.5 (**C**), 72.87 (**C**H_2), 72.85 (**C**H_2), 41.83 (**C**H_3), 41.75 (**C**H_3), 31.6 (**C**H_3), 30.9 (**C**H_3), 15.38 (**C**H_3), 15.35 (**C**H_3), 9.9(**C**H_3), 9.7 (**C**H_3) ppm.

LRMS (ESI+) 210 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 210.1121, $C_{11}H_{16}NO_3$ $[M+H]^+$ requires 210.1125.

3-(*tert*-butyl)-4-methylcyclobut-3-ene-1,2-dione (3.46a)



1.43
$C_6H_6O_4$
Mol Wt:142.03

3.46a
$C_9H_{12}O_2$
Mol Wt:152.08

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43** (350 mg, 2.46 mmol) in THF (50 mL) at –78 °C was added MeLi (1.6 M in Et_2O, 1.9 mL, 3.04 mmol) dropwise. The mixture was stirred at –78 °C for 1 hour and then ^{t}BuLi (1.7 M in pentane, 2.0 mL, 3.40 mmol) was added dropwise. After stirring at –78 °C for 30 min TFAA (0.87 mL, 6.22 mmol) was added dropwise. After 20 min the reaction mixture was quenched with sat. NH_4Cl (20 mL). The solution was warmed to RT then the aqueous phase separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–40% EA/petrol) to afford the title compound (270 mg, 1.8 mmol, 67%) as a brown oil.

FT-IR (ν_{max}, $CHCl_3$) 2959 (br), 1788 (s), 1762 (s), 1366 (m), 1209 (m), 1171 (m), 1024 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 2.29 (3 H, s, C**H**$_3$)

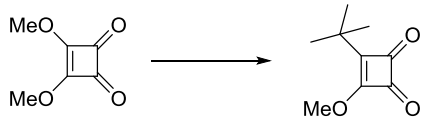
1.25 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 209.2 (**C**), 200.1 (**C**), 198.3 (**C**), 196.0 (**C**), 35.5 (**C**), 27.1 (C(**C**H$_3$)$_3$), 11.6 (**C**H$_3$) ppm.

LRMS (ESI+) 153 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 153.0909, $C_9H_{13}O_2$ $[M+H]^+$ requires 153.0910.

3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione (3.46b)



1.43
$C_6H_6O_4$
Mol Wt:142.03

3.46b
$C_9H_{12}O_3$
Mol Wt:168.08

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43** (350 mg, 2.46 mmol) in THF (50 mL) at –78 °C was added ^{t}BuLi (1.7 M in pentane, 1.6 mL, 2.71 mmol) dropwise. After stirring at –78 °C for 30 min TFAA (0.41 mL, 2.95 mmol) was added dropwise. After stirring at –78 °C for 2 h the resulting solution was quenched with sat. NH_4Cl (20 mL). The solution was warmed to RT then the aqueous phase separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/petrol) to afford the title compound (398 mg, 2.2 mmol, 89%) as a yellow oil.

Data is consistent with literature.[57]

FT-IR (ν_{max}, $CHCl_3$) 2971 (br), 1790 (s), 1761 (s), 1735 (m), 1585 (vs), 1481 (m), 1398 (w), 1356 (s), 1217 (w), 1049 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 4.38 (3 H, s, OC**H**$_3$)

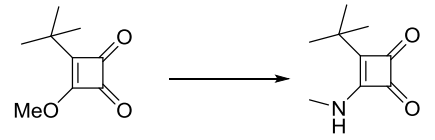
1.26 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 197.3 (**C**), 194.8 (**C**), 194.7 (**C**), 191.0 (**C**), 61.3 (**C**H$_3$), 34.5 (**C**), 27.2 (C(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 169 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 169.0858, $C_9H_{13}O_3$ $[M+H]^+$ requires 169.0859.

3-(*tert*-butyl)-4-(methylamino)cyclobut-3-ene-1,2-dione (3.46c)



1.43
$C_9H_{12}O_3$
Mol Wt:168.08

3.46c
$C_9H_{13}NO_2$
Mol Wt:167.09

A solution of methylamine hydrochloride (216 mg, 3.19 mmol) and TEA (0.45 mL, 3.25 mmol) in MeOH (10 mL) was added to a solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **3.49b** (410 mg, 2.44 mmol) in MeOH (40 mL). After stirring at –78 °C for 2 h the resulting solution was concentrated under reduced pressure and purified by column chromatography (50–80% EtOAc/Pet) to afford the title compound (350 mg, 2.10 mmol, 86%) as a white solid.

MP 194–195 °C.

FT-IR (ν_{max}, $CHCl_3$) 3170 (br), 2962 (m), 1786 (s), 1722 (s), 1584 (s), 1484 (m), 1404 (m), 1243 (m), 1168 (m) cm^{-1}.

δ_H (400 MHz, DMSO-d6) 8.59 (1 H, br s, N**H**)

3.15 (3 H, d, *J* = 4.9 Hz, C**H**$_3$)

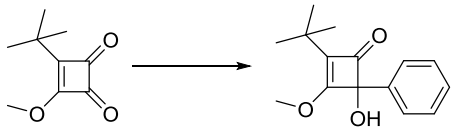
1.24 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, DMSO-d6) 195.6 (**C**), 189.5 (**C**), 181.4 (**C**), 178.0 (**C**), 33.3 (**C**H$_3$), 30.7 (C), 27.0 (C(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 168 ([M+H]$^+$, 100%), 335 ([2M+H]$^+$, 30%).

HRMS (ESI+) Found 168.1017, $C_9H_{14}NO_2$ [M+H]$^+$ requires 168.1019.

2-(*tert*-butyl)-4-hydroxy-3-methoxy-4-phenylcyclobut-2-en-1-one (3.47b)



3.46b
$C_9H_{12}O_3$
Mol Wt:168.08

3.47b
$C_{15}H_{18}O_3$
Mol Wt:246.13

To a solution of 2-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **3.46b** (340 mg, 2.02 mmol) in THF (50 mL) at –78 °C was added PhLi (1.9 M in Bu_2O, 1.3 mL, 2.47 mmol) dropwise. The solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–50% EtOAc/Pet) afforded the title product (390 mg, 1.58 mmol, 78%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3398 (br), 2952 (m), 1745 (s), 1630 (m), 1448 (w), 1365 (w), 1187 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.50–7.44 (2 H, m, 2 × Ar**H**)

7.40–7.34 (2 H, m, 2 × Ar**H**)

7.32–7.29 (1 H, m, 1 × Ar**H**)

5.41 (1 H, br s, O**H**)

3.84 (3 H, s, C$\mathbf{H}_3$)

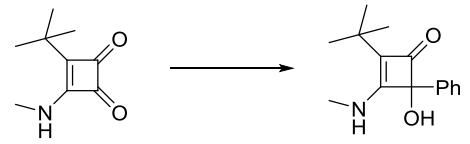
1.27 (9 H, s, C(C$\mathbf{H}_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 189.9 (**C**), 180.2 (**C**), 137.5 (**C**), 137.4 (**C**), 128.6 (**C**H), 127.8 (**C**H), 125.4 (**C**H), 92.1 (**C**), 59.5 (**C**H_3), 31.2 (**C**), 28.2 (C(**C**H_3)$_3$) ppm.

LRMS (ESI+) 247 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 247.1333, $C_{15}H_{18}O_3$ $[M+H]^+$ requires 247.1329.

2-(*tert*-butyl)-4-hydroxy-3-(methylamino)-4-phenylcyclobut-2-en-1-one (3.47c)



3.46c
$C_9H_{13}NO_2$
Mol Wt:167.09

3.47c
$C_{15}H_{19}NO_2$
Mol Wt: 245.14

To a solution of 3-(*tert*-butyl)-4-(methylamino)cyclobut-3-ene-1,2-dione **3.46c** (300 mg, 1.8 mmol) in THF (50 mL) at –78 °C was added PhLi (1.9 M in Bu_2O, 2.4 mL, 4.56 mmol) dropwise. The solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by recrytalisation (Et_2O) to afford the title compound (343 mg, 1.4 mmol, 78%) as a white solid.

MP Decomposed over 175 °C.

FT-IR (ν_{max}, $CHCl_3$) 3310 (br), 2955 (w), 1737 (w), 1537 (s), 1394 (m), 1265 (m), 1141 (m), 1032 (m), 996 (m) cm^{-1}.

δ_H (400 MHz, DMSO-d6) 7.42 (1 H, s, Ar**H**)

7.37–7.33 (4 H, m, 3 × Ar**H** + N**H**)

7.24 (1 H, s, Ar**H**)

6.36 (1 H, s, O**H**)

2.59 (3 H, d, *J* = 4.8 Hz, C**H**$_3$)

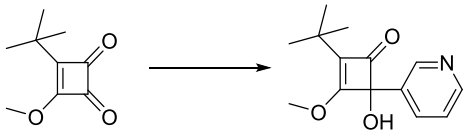
1.18 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, DMSO-d6) 184.9 (**C**), 168.9 (**C**), 140.2 (**C**), 128.1 (**C**H), 126.7 (**C**H), 125.9 (**C**), 125.2 (**C**H), 90.3 (**C**), 30.6 (**C**H$_3$), 30.5 (**C**), 28.6 (C(**C**H$_3$)$_3$)ppm.

LRMS (ESI+) 246 ($[M+H]^+$, 100%), 268 ($[M+Na]^+$, 20%).

HRMS (ESI+) Found 246.1490 $[M+H]^+$, $C_{15}H_{20}NO_2$ requires 246.1489.

2-(*tert*-butyl)-4-hydroxy-3-methoxy-4-(pyridin-3-yl)cyclobut-2-en-1-one (3.47d)



3.46c
$C_9H_{12}O_3$
Mol Wt: 168.08

3.47d
$C_{14}H_{17}NO_3$
Mol Wt: 247.12

To a solution of 3-bromopyridine (0.3 mL, 3.11 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 1.25 mL, 3.13 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of 2-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **3.46c** (403 mg, 2.40 mmol) in THF (50 mL) at –78 °C. The solution was stirred at –78 °C for 1 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (20–50% EtOAc/Pet) to afford the title compound (207 mg, 0.84 mmol, 35%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2955 (w), 1751 (m), 1610 (s), 1479 (m), 1344 (s), 1224 (w), 1014 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 8.66 (1 H, d, *J* = 1.7 Hz, Ar**H**)

8.45 (1 H, dd, *J* = 4.9, 1.6 Hz, Ar**H**)

7.86 (1 H, dt, *J* = 8.0, 1.9 Hz, Ar**H**)

7.71 (1 H, s, O**H**)

7.31 (1 H, dd, *J* = 8.0, 4.9 Hz, Ar**H**)

3.82 (3 H, s, C**H**$_3$)

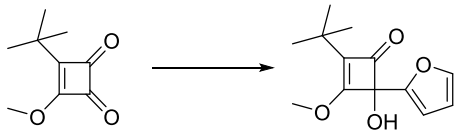
1.13 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 188.7 (**C**), 179.4 (**C**), 148.2 (**C**H), 146.4 (**C**H), 138.0 (**C**), 134.1 (**C**), 134.0 (**C**H), 123.6 (**C**H), 90.9 (**C**), 59.3 (**C**H$_3$), 31.1 (**C**), 28.0 (C(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 248 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 248.1283 $[M+H]^+$, $C_{14}H_{18}NO_3$ requires 248.1281.

2-(*tert*-butyl)-4-(furan-2-yl)-4-hydroxy-3-methoxycyclobut-2-en-1-one (3.47e)



3.46c
$C_9H_{12}O_3$
Mol Wt: 168.08

3.47e
$C_{13}H_{16}O_4$
Mol Wt: 236.10

To a solution of 2-bromofuran (0.14 mL, 1.55 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 0.62 mL, 1.55 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of 2-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **3.46c** (200 mg, 1.19 mmol) in THF (50 mL) at –78 °C. The solution was stirred at –78 °C for 1 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–50% EtOAc/Pet) to afford the title compound (249 mg, 1.05 mmol, 89%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3325 (br), 2956 (w), 1747 (m), 1609 (s), 1481 (m), 1349 (s), 1153 (m), 1006 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.37 (1 H, dd, *J* = 1.8, 0.8 Hz, Ar**H**)

6.45 (1 H, dd, *J* = 3.3, 0.7 Hz, Ar**H**)

6.37 (1 H, dt, *J* = 3.3, 1.8 Hz, Ar**H**)

5.30 (1 H, br s, O**H**)

3.96 (3 H, s, C$\mathbf{H}_3$)

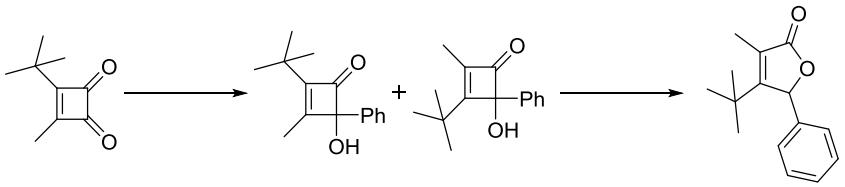
1.21 (9 H, s, C(C$\mathbf{H}_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 188.5 (**C**), 179.6 (**C**), 150.5 (**C**H), 142.5 (**C**H), 137.8 (**C**), 111.0 (**C**H), 108.1 (**C**H), 88.6 (**C**), 59.4 (**C**H_3), 31.2 (**C**), 28.0 (C(**C**H_3)$_3$) ppm.

LRMS (ESI+) 237 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 237.1124 $[M+H]^+$, $C_{13}H_{17}O_3$ requires 237.1121.

4-(*tert*-butyl)-3-methyl-5-phenylfuran-2(5H)-on (3.49a)



3.46a
$C_9H_{12}O_2$
Mol Wt:152.08

3.47a^1

3.47a^2

3.49a
$C_{15}H_{18}O_2$
Mol Wt:230.12

To a solution of 3-(*tert*-butyl)-4-methylcyclobut-3-ene-1,2-dione **3.46a** (250 mg, 1.64 mmol) in THF (50 mL) at –78 °C was added PhLi (1.9 M in Bu_2O, 1.0 mL, 1.90 mmol) dropwise. The solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give an inseparable 2 : 1 mixture of 2-(*tert*-butyl)-4-hydroxy-3-methyl-4-phenylcyclobut-2-en-1-one **3.47a^1** and 3-(*tert*-butyl)-4-hydroxy-2-methyl-4-phenylcyclobut-2-en-1-one **3.47a^2**.

The mixture was dissolved in 1,4-dioxane (10 mL) and heated at 170 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/Pet) to afford **3.49a** (252 mg, 1.09 mmol, 67% over two steps) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2956 (br), 1740 (vs), 1455 (m), 1294 (m), 1143 (m), 1019 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.41-7.35 (3 H, m, 3 × Ar**H**)

7.22-7.17 (2 H, m, 2 × Ar**H**)

5.41 (1 H, s, C**H**)

1.93 (3 H, s, C$\mathbf{H}_3$)

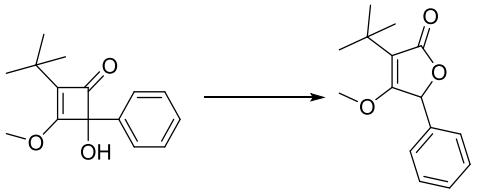
1.40 (9 H, s, C(C$\mathbf{H}_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 173.3 (**C**), 156.1 (**C**), 135.3 (**C**), 132.9 (**C**), 129.2 (**C**H), 128.9 (**C**H), 127.1 (**C**H), 84.5 (**C**H), 33.3 (**C**), 23.3 (C(**C**H$_3$)$_3$), 14.0 (**C**H$_3$) .

LRMS (ESI+) 231 ([M+H]$^+$, 100%).

HRMS (ESI+) Found 231.1383, $C_{15}H_{19}O_2$ [M+H]$^+$ requires 231.1380.

3-(*tert*-butyl)-4-methoxy-5-phenylfuran-2(5H)-one (3.49b)



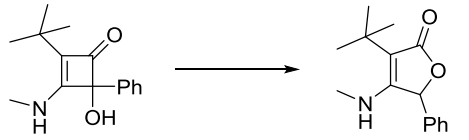
3.47b
$C_{15}H_{18}O_3$
Mol Wt:246.13

3.49b
$C_{15}H_{18}O_3$
Mol Wt:246.13

Cyclobutenone **3.47b** (200 mg, 0.87 mmol) in 1,4-dioxane (10 mL) was heated at 170 °C in stainless steel tubing under continuous flow for a residence time of 1 hour. The resulting solution was concentrated under reduced pressure and purified by column chromatography (60% Et_2O/Pet) to afford the title compound as a yellow solid (198 mg, 0.87 mmol, 100%)

MP	113 °C (Et_2O/Pet)
FT-IR (ν_{max}, $CHCl_3$)	2954 (br), 1737 (s), 1643 (s), 1456 (m), 1348 (m), 1303 (m), 1241 (w) cm^{-1}
δ_H (400 MHz, $CDCl_3$)	7.41–7.38 (3 H, m, 3 × Ar**H**)
	7.33–7.30 (2 H, m, 2 × Ar**H**)
	5.70 (1 H, s, C**H**)
	3.56 (3 H, s, C**H**$_3$)
	1.35 (9 H, s, C(C**H**$_3$)$_3$) ppm
δ_C (100 MHz, $CDCl_3$)	172.2 (**C**), 171.9 (**C**), 134.2 (**C**), 129.7 (**C**H), 129.3 (**C**H), 127.7 (**C**H), 112.4 (**C**), 77.0 (**C**H), 57.5 (**C**H$_3$), 31.6 (**C**), 28.8 (C(**C**H$_3$)$_3$)
LRMS (ESI+)	247 ($[M+H]^+$, 100%), 269 ($[M+Na]^+$, 40%).
HRMS (ESI+)	Found 247.1331, $C_{15}H_{19}O_3$ $[M+H]^+$ requires 247.1329

3-(*tert*-butyl)-4-(methylamino)-5-phenylfuran-2(5H)-one (3.49c)



3.47c
$C_{15}H_{19}NO_2$
Mol Wt: 245.14

3.49c
$C_{15}H_{19}NO_2$
Mol Wt: 245.14

A mixture of 2-(*tert*-butyl)-4-hydroxy-3-(methylamino)-4-phenylcyclobut-2-en-1-one **3.47c** (200 mg, 0.82 mmol) in tetraethylene glycol dimethyl ether (10 mL) was stirred at 180 °C for 2 h under argon then cooled to RT. The reaction mixture was diluted by H_2O (50 mL) then extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 300 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The mixture was purified by column chromatography (10–30% Et_2O/Pet) to afford the title compound as a yellow oil (174 mg, 0.71 mmol, 87%).

FT-IR (ν_{max}, $CHCl_3$) 3400 (br), 2953 (m), 1715 (s), 1603 (s), 1455 (m), 1396 (m), 1307 (m), 1036 (m), 997 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.39–7.35 (3 H, m, 3 × Ar**H**)

7.33–7.29 (2 H, m, 2 × Ar**H**)

5.57 (1 H, s, C**H**)

5.06 (1 H, br d, *J* = 4.0 Hz, N**H**)

2.55 (3 H, d, *J* = 5.3 Hz, C$\mathbf{H}_3$)

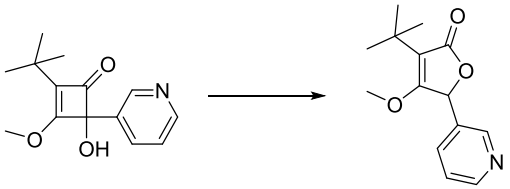
1.40 (9 H, s, C(C$\mathbf{H}_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 173.4 (**C**), 162.7 (**C**), 135.7 (**C**), 129.4 (**C**H), 129.0 (**C**H), 127.8 (**C**), 101.7 (**C**H), 77.3 (**C**H), 31.7 (**C**), 31.1 (**C**H_3), 29.3 (C(**C**H_3)$_3$) ppm.

LRMS (ESI+) 246 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 246.1495 $[M+H]^+$, $C_{15}H_{20}NO_2$ requires 246.1489.

3-(*tert*-butyl)-4-methoxy-5-(pyridin-3-yl)furan-2(5H)-one (3.49d)



3.47d
$C_{14}H_{17}NO_3$
Mol Wt: 247.12

3.49d
$C_{14}H_{17}NO_3$
Mol Wt: 247.12

Cyclobutenone **3.47d** (150 mg, 0.61 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (60–100% Et_2O/petrol) to afford the title compound (119 mg, 0.48 mmol, 80%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2954 (w), 1743 (s), 1645 (s), 1457 (w), 1342 (s), 1245 (m), 1032 (m), 997 (m) cm^{-1}

δ_H (400 MHz, $CDCl_3$) 8.64 (1 H, dd, *J* = 4.8, 1.6 Hz, Ar**H**)

8.61 (1 H, d, *J* = 1.8 Hz, Ar**H**)

7.58 (1 H, dt, *J* = 8.0, 2.0 Hz, Ar**H**)

7.35 (1 H, dt, *J* = 7.8, 4.8 Hz, Ar**H**)

5.78 (1 H, s, C**H**)

3.58 (3 H, s, C$\mathbf{H}_3$)

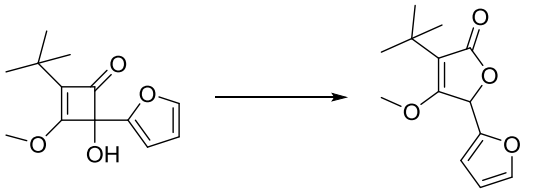
1.32 (9 H, s, C(C$\mathbf{H}_3$)$_3$) ppm

δ_C (100 MHz, $CDCl_3$) 171.7 (**C**), 171.1 (**C**), 151.1 (**C**H), 149.5 (**C**H), 135.0 (**C**H), 130.4 (**C**), 124.3 (**C**H), 113.5 (**C**), 74.5 (**C**H), 57.7 (**C**H_3), 31.8 (**C**), 28.9 (C(**C**H_3)$_3$) ppm

LRMS (ESI+) 248 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 248.1280 $[M+H]^+$, $C_{14}H_{18}NO_3$ requires 248.1281

4-(*tert*-butyl)-3-methoxy-[2,2'-bifuran]-5(2H)-one (3.49e)



3.47e
$C_{13}H_{16}O_4$
Mol Wt: 236.10

3.49e
$C_{13}H_{16}O_4$
Mol Wt: 236.10

Cyclobutenone **3.47e** (150 mg, 0.64 mmol) in 1,4-dioxane (10 mL) was heated at 170 °C in stainless steel tubing under continuous flow for a residence time of 1 hour. The resulting solution was concentrated under reduced pressure and purified by column chromatography (40–80% Et_2O/Pet) to afford the title compound (147mg, 0.62 mmol, 98%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2954 (m), 1746 (s), 1651 (s), 1459 (m), 1344 (s), 1294 (m), 1248 (m) 1030 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.47 (1 H, dd, *J* = 1.8, 0.7 Hz, Ar**H**)

6.48 (1 H, dd, *J* = 3.2, 0.5 Hz, Ar**H**)

6.43 (1 H, dd, *J* = 3.3, 1.7 Hz, Ar**H**)

5.80 (1 H, s, C**H**)

3.65 (3 H, s, C$\mathbf{H}_3$)

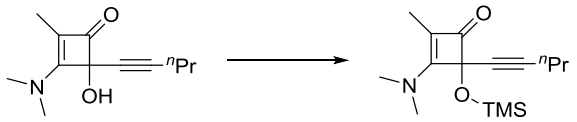
1.33 (9 H, s, C(C$\mathbf{H}_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 171.8 (**C**), 169.3 (**C**), 147.2 (**C**), 143.9 (**C**H), 112.9 (**C**), 111.0 (**C**H), 110.7 (**C**H), 69.6 (**C**H), 57.3 (**C**H_3), 31.7 (**C**), 28.8 (C(**C**H_3)$_3$) ppm.

LRMS (ESI+) 237 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 237.1124, $C_{13}H_{17}O_4$ $[M+H]^+$ requires 237.1121.

3-(Dimethylamino)-2-methyl-4-(pent-1-yn-1-yl)-4-((trimethylsilyl)oxy)cyclobut-2-enone (**3.50m**)



3.4m
$C_{12}H_{17}NO_2$
Mol Wt 207.13

3.50m
$C_{15}H_{25}NO_2Si$
Mol Wt 279.17

To a solution of aminocyclobutenone **3.4m** (330 mg, 1.5 mmol) and TEA (0.25 mL, 1.80 mmol) in THF (50 mL) at 0 °C was added chlorotrimethylsilane (0.23 mL, 1.8 mmol) dropwise. After 2 h sat. NH_4Cl (10 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–30% DCM/Pet) to afford the title compound (310 mg, 1.1 mmol, 71%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2956 (br), 1759 (m), 1597 (vs), 1488 (w), 1412 (m), 1250 (m), 1176 (w), 1139 (m), 1090 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 3.16 (3 H, s, C**H**$_3$)

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

2.21 (2 H, t, *J* = 7.2 Hz, C**H**$_2$)

1.73 (3 H, s, C**H**$_3$)

1.53 (2 H, sxt, *J* = 7.2 Hz, C**H**$_2$)

0.96 (3 H, t, *J* = 7.4 Hz, C**H**$_3$)

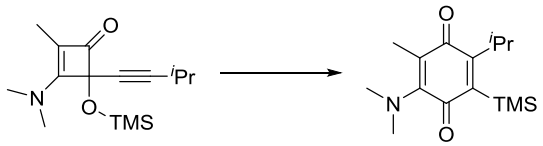
0.22 (9 H, s, Si(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 184.1 (**C**), 170.2 (**C**), 114.0 (**C**), 89.5 (**C**), 82.8 (**C**), 77.2 (**C**), 39.5 (**C**H$_3$), 39.4 (**C**H$_3$), 21.8 (**C**H$_2$), 21.0 (**C**H$_2$), 13.5 (**C**H$_3$), 7.6 (**C**H$_3$), 1.3 (C(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 280 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 280.1732, $C_{15}H_{26}NO_2Si$ $[M+H]^+$ requires 280.1727.

2-(Dimethylamino)-3-methyl-5-propyl-6-(trimethylsilyl)cyclohexa-2,5-diene-1,4-dione (3.51)



3.50m
$C_{15}H_{25}NO_2Si$
Mol Wt 279.17

3.51
$C_{15}H_{25}NO_2Si$
Mol Wt 279.17

Aminocyclobutenone **3.50m** (150 mg, 0.54 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (0–5% Et_2O/petrol) to afford the title compound (137 mg, 0.49 mmol, 91%) as a dark red oil.

FT-IR (ν_{max}, $CHCl_3$) 2950 (br), 1709 (m), 1655 (s), 1610 (s), 1594 (s), 1572 (s), 1398 (m), 1296 (m), 1245 (m), 1203 (w), 1093 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 2.98 (6 H, s, N(C**H**$_3$)$_2$)

2.49–2.45 (2 H, m, C**H**$_2$)

1.97 (3 H, s, C**H**$_3$)

1.47–1.38 (2 H, m, C**H**$_2$)

0.97 (3 H, t, *J* = 7.3 Hz, C**H**$_3$)

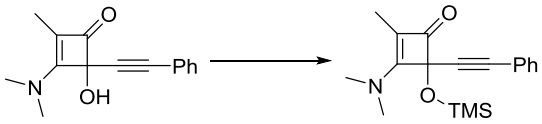
0.29 (9 H, s, Si(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 191.1 (**C**), 186.9 (**C**), 157.0 (**C**), 152.6 (**C**), 144.0 (**C**), 121.1 (**C**), 43.5 (**C**H$_3$), 31.4 (**C**H$_2$), 24.5 (**C**H$_2$), 14.4 (**C**H$_3$), 12.7 (**C**H$_3$), 1.2 (Si(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 280 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 280.1721, $C_{15}H_{26}NO_2Si$ $[M+H]^+$ requires 280.1727.

3-(Dimethylamino)-2-methyl-4-(phenylethynyl)-4-((trimethylsilyl)oxy)cyclobut-2-enone (3.50e)



3.4e
$C_{15}H_{15}NO_2$
Mol Wt 241.11

3.50e
$C_{18}H_{23}NO_2Si$
Mol Wt 313.15

To a solution of aminocyclobutenone **3.4e** (180 mg, 0.75 mmol) and TEA (0.13 mL, 0.9 mmol) in THF (50 mL) at 0 °C was added chlorotrimethylsilane (0.11 mL, 0.87 mmol) dropwise. After 2 h sat. NH_4Cl (10 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–30% DCM/petrol) to afford the title compound (200 mg, 0.63 mmol, 84%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2962 (br), 1761 (w), 1597 (vs), 1412 (m), 1248 (m), 1211 (w), 1130 (m), 1049 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.41–7.36 (2 H, m, 2 × Ar**H**)

7.28–7.24 (3 H, m, 3 × Ar**H**)

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

3.12 (3 H, s, C**H**$_3$)

1,73 (3 H, s, C**H**$_3$)

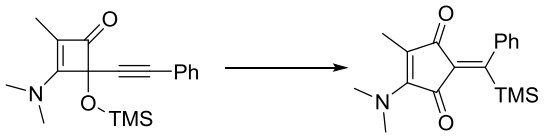
0.25 (9 H, s, Si(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 183.1 (**C**), 169.6 (**C**), 131.5 (**C**H), 128.5 (**C**H), 128.2 (**C**H), 122.3 (**C**), 114.4 (**C**), 88.4 (**C**), 86.0 (**C**), 83.0 (**C**), 39.6 (**C**H$_3$), 39.4 (**C**H$_3$), 7.6 (**C**H$_3$), 1.2 (Si(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 314 ($[M+H]^+$, 100%), 336 ($[M+Na]^+$, 100%).

HRMS (ESI+) Found 314.1575, $C_{18}H_{24}NO_2Si$ $[M+H]^+$ requires 314.1571.

(*Z*/*E*)-4-(Dimethylamino)-5-methyl-2-(phenyl(trimethylsilyl)methylene)cyclopent-4-ene-1,3-dione (3.52)



3.50e
$C_{18}H_{23}NO_2Si$
Mol Wt 313.15

3.52
$C_{18}H_{23}NO_2Si$
Mol Wt 313.15

Aminocyclobutenone **3.50e** (120 mg, 0.38 mmol) in 1,4-dioxane (10 mL) was heated at 160 °C in stainless steel tubing under continuous flow for a residence time of 1.5 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (0–10% Et_2O/Pet) to afford the title compound (87 mg, 0.28 mmol, 73%) as a yellow solid.

MP 153–155 °C.

FT-IR (ν_{max}, $CHCl_3$) 2960 (br), 1759 (w), 1595 (s), 1412 (m), 1248 (m), 1130 (m), 1049 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.33–7.29 (2 H, m, 2 × Ar**H**)

7.22 (1 H, m, Ar**H**)

6.89–6.87 (2 H, m, 2 × Ar**H**)

3.36 (6 H, s, N(C**H**$_3$)$_2$)

2.09 (3 H, s, C**H**$_3$)

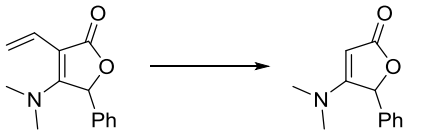
0.12 (9 H, s, Si(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 191.4 (**C**), 188.2 (**C**), 159.9 (**C**), 156.3 (**C**), 142.7 (**C**), 135.9 (**C**), 127.4 (**C**H), 127.1 (**C**), 125.7 (**C**H), 124.9 (**C**H), 41.9 (**C**H$_3$), 10.0 (**C**H$_3$), –0.5 (Si(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 314 ([M+H]$^+$, 100%), 336 ([M+Na]$^+$, 70%).

HRMS (ESI+) Found 314.1572, $C_{18}H_{24}NO_2Si$ [M+H]$^+$ requires 314.1571.

4-(dimethylamino)-5-phenylfuran-2(5H)-one (3.53)



3.9b
$C_{14}H_{15}NO_2$
Mol Wt: 229.11

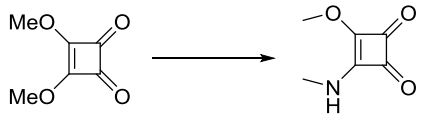
3.53
$C_{12}H_{13}NO_2$
Mol Wt: 203.09

Furanone **3.9b** (90 mg, 0.39 mmol) in 1,4-dioxane (5 mL) was heated at 180 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (80–100% Et_2O/cyclohexane) to afford title compound (78 mg, 0.38 mmol, 96%) as a yellow solid.

Data is consistent with literature.[140]

MP	145–146 °C.
FT-IR (ν_{max}, $CHCl_3$)	3486 (br), 2926 (w), 1715 (s), 1609 (s), 1408 (m), 1318 (m), 1163 (m), 1011 (m) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.39–7.36 (3 H, m, 3 × Ar**H**)
	7.32–7.31 (2 H, m, 2 × Ar**H**)
	5.72 (1 H, s, C**H**)
	4.77 (1 H, s, C**H**)
	2.78 (6 H, br s, N(C**H**$_3$)$_2$) ppm.
δ_C (100 MHz, $CDCl_3$)	174.0 (**C**), 170.2 (**C**), 135.0 (**C**), 129.5 (**C**H), 129.1 (**C**H), 127.8 (**C**H), 82.8 (**C**H), 80.1 (**C**H), 40.4 (br s, **C**H$_3$), 40.0 (br s, **C**H$_3$) ppm.
LRMS (ESI+)	204 ($[M+H]^+$, 100%), 226 ($[M+Na]^+$, 60%).
HRMS (ESI+)	Found 204.1021, $C_{12}H_{14}NO_2$ $[M+H]^+$ requires 204.1019.

3-methoxy-4-(methylamino)cyclobut-3-ene-1,2-dione (3.120)



1.43
$C_6H_6O_4$
Mol Wt:142.11

3.120
$C_6H_7NO_3$
Mol Wt:141.04

To a solution of methylamine hydrochloride (140 mg, 2.07 mmol) in MeOH (10 mL) was added TEA (0.3 mL, 2.13 mmol). The solution was stirred at RT for 10 min and added into a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione **1.43** (300 mg, 2.11 mmol) in MeOH (40 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour and then stirred at RT for 16 h. The solution was concentrated under reduced pressure and purified by column chromatography (EA) to afford the product as a white solid (291 mg, 2.06 mmol, 97%).

Data is consistent with literature.[141]

MP 190–191 °C.

FT-IR (ν_{max}, $CHCl_3$) 3150 (w), 2951 (w), 1801 (w), 1704 (m), 1595 (s), 1506 (s), 1413 (s), 1399(s), 1177 (m), 1050 (m) cm^{-1}.

δ_H (400 MHz, DMSO-d6) Major rotamer

8.59 (1 H, s, N**H**)

4.28 (3 H, s, OC**H**$_3$)

2.94 (3 H, s, NC**H**$_3$) ppm.

Minor rotamer

8.38 (1 H, s, N**H**)

4.26 (3 H, s, OC**H**$_3$)

3.09 (3 H, s, NC**H**$_3$) ppm.

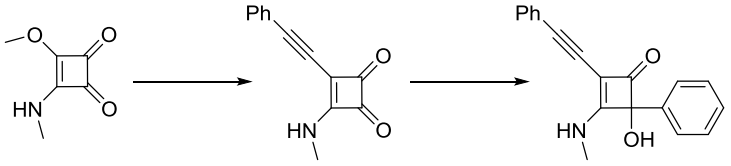
δ_C (100 MHz, DMSO-d6) Major rotamer: 189.3 (**C**), 182.3 (**C**), 177.2 (**C**), 172.9 (**C**), 60.1 (O**C**H$_3$), 30.4 (N**C**H$_3$) ppm.

Minor rotamer: 189.8 (**C**), 182.1 (**C**), 177.4 (**C**), 172.3 (**C**), 59.8 (O**C**H$_3$), 30.2 (N**C**H$_3$) ppm.

LRMS (ESI+) 164 ([M+Na]$^+$, 100%).

HRMS (ESI+) Found 142.0495, $C_6H_8NO_3$ [M+H]$^+$ requires 142.0499.

4-hydroxy-3-(methylamino)-4-phenyl-2-(phenylethynyl)cyclobut-2-en-1-one (3.122)



3.120
$C_6H_7NO_2$
Mol Wt: 141.04

3.121
$C_{13}H_9NO_2$
Mol Wt: 211.06

3.122
$C_{19}H_{15}NO_2$
Mol Wt: 289.11

To a solution of Phenylacetylene (0.29 mL, 2.64 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 1.0 mL, 2.50 mmol) dropwise. The solution was stirred at –78 °C for 10 min and added *via* cannula to a solution of 3-methoxy-4-(methylamino)cyclobut-3-ene-1,2-dione **3.120** (282 mg, 2.00 mmol) in THF (50 mL) at –78 °C. After stirring at –78 °C for 1 hour, TFAA (1.37 mL, 9.86 mmol) was added dropwise. After 20 min the result mixture was quenched with sat. NH_4Cl then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude **3.121** as a yellow solid.

To a solution of **3.121** in THF (50 mL) at –78 °C was added PhLi (1.89 M in Bu_2O, 1.4 mL, 2.65 mmol) dropwise. The solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by recrytalization (Et_2O) to afford the title compound (390 mg, 1.35 mmol, 68%) as a yellow solid.

MP Decomposed over 148 °C.

FT-IR (ν_{max}, $CHCl_3$) 3445 (br), 2959 (w), 1714 (s), 1597 (m), 1564 (m), 1486 (m), 1448 (m), 1394 (s), 1255 (s), 1220 (s),1140 (s) cm^{-1}.

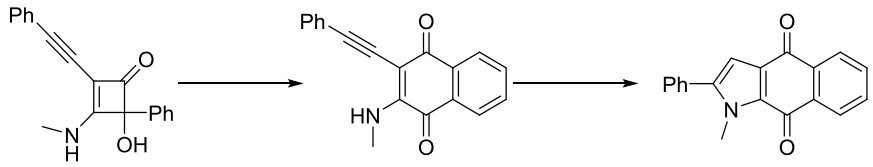
δ_H (400 MHz, DMSO-d6) Major rotamer

8.93 (1 H, m, N**H**)

7.48-7.28 (10 H, m, 10 × Ar**H**)

	6.72 (H, s, O**H**) ppm.
	3.21 (3 H, d, *J* = 4.8 Hz, C**H**$_3$) ppm
	Minor rotamer
	9.01 (1 H, m, N**H**)
	7.48–7.28 (10 H, m, 10 × Ar**H**)
	6.91 (H, s, O**H**)
	2.74 (3 H, d, *J* = 4.8 Hz, C**H**$_3$) ppm.
	With the addition peak at 3.32 ppm contribute to H_2O
δ_C (100 MHz, DMSO-d6)	Major rotamer:
	185.8 (**C**), 174.0 (**C**), 138.1 (**C**), 130.8 (**C**H), 128.7 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 127.5 (**C**H), 125.6 (**C**H), 122.8 (**C**), 96.8 (**C**), 91.7 (**C**), 91.3 (**C**), 80.1 (**C**), 31.0 (**C**H$_3$) ppm.
	Minor rotamer:
	185.0 (**C**), 174.1 (**C**), 138.2 (**C**), 130.9 (**C**H), 128.7 (**C**H), 128.2 (**C**H), 128.1 (**C**H), 127.5 (**C**H), 125.2 (**C**H), 122.9 (**C**), 98.0 (**C**), 91.9 (**C**), 89.8 (**C**), 79.2 (**C**), 30.9 (**C**H$_3$) ppm.
LRMS (ESI+)	290 ([M+H]$^+$, 100%).
HRMS (ESI+)	Found 290.1168, $C_{19}H_{16}NO_2$ [M+H]$^+$ requires 290.1176.

1-methyl-2-phenyl-1H-benzo[f]indole-4,9-dione (3.124)



3.122
$C_{19}H_{15}NO_2$
Mol Wt: 289.11

3.123
$C_{19}H_{13}NO_2$
Mol Wt:287.09

3.124
$C_{19}H_{13}NO_2$
Mol Wt:287.09

Cyclobutenone **3.122** (233 mg, 0.81 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 90 min. The resulting solution was concentrated under reduced to afford the crude **3.123** as a red oil.

To a solution of the former **3.123** in MeOH (30 mL) was added $CsCO_3$ (156 mg, 0.81 mmol). The result mixture was refluxed for 5 h and cooled to RT. The solution was concentrated under reduced pressure and purified by column chromatography (20%–70% Et_2O/Pet) to afford the title compound (145 mg, 0.51 mmol, 65%) as a yellow solid.

Data is consistent with literature.[107]

MP 150–151 °C. (153–154 °C lit.)

FT-IR (ν_{max}, $CHCl_3$) 3064 (br), 2952 (br), 1650 (s), 1595 (m), 1587 (m), 1481 (m), 1464 (m), 1437 (m), 1403 (m), 1244 (s), 1148 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 8.21–8.17 (2 H, m, 2 × Ar**H**)

7.73–7.66 (2 H, m, 2 × Ar**H**)

7.55–7.45 (5 H, m, 5 × Ar**H**)

6.82 (1 H, s, C**H**)

4.07 (3 H, s, NC**H**$_3$) ppm.

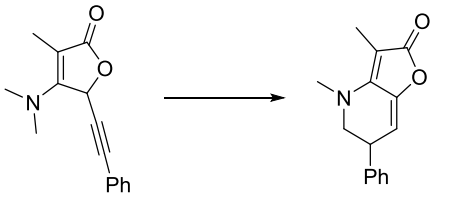
δ_C (100 MHz, $CDCl_3$) 181.1 (**C**), 176.2 (**C**), 143.9 (**C**), 134.3 (**C**), 133.6 (**C**), 133.1 (**C**H), 133.0 (**C**H), 131.5 (**C**), 130.3 (**C**), 129.3 (**C**H), 129.1 (**C**H), 128.8 (**C**H), 128.4 (**C**), 126.5 (**C**H), 126.4 (**C**H), 108.4 (**C**H), 34.7 (O**C**H$_3$) ppm.

LRMS (ESI+) 288 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 288.1020, $C_{19}H_{14}NO_2$ $[M+H]^+$ requires 288.1019.

8.3 Experimental procedures for Chapter 4

3,4-Dimethyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.1e)



3.9e
$C_{15}H_{15}NO_2$
Mol Wt: 241.12

4.1e
$C_{15}H_{15}NO_2$
Mol Wt: 241.12

Furanone **3.9e** (30 mg, 0.12 mmol) in 1,4-dioxane (5 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 2 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–100% EtOAc/hexane) to afford the title compound (25 mg, 0.10 mmol, 83%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2924 (br), 1743 (s), 1689 (w), 1614 (s), 1490 (w), 1452 (m), 1416 (m), 1317 (m), 1292 (m), 1203 (m), 1027 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.39–7.25 (5 H, m, 5 × Ar**H**)

5.63 (1 H, d, *J* = 3.9 Hz, C**H**)

3.90 (1 H, ddd, *J* = 8.4, 6.0, 4.0 Hz, PhC**H**)

3.43 (1 H, dd, *J* = 11.9, 6.0 Hz, NC**H**H)

3.17 (1 H, dd, *J* = 11.9, 8.6 Hz, NCH**H**)

3.14 (3 H, s, NC$\mathbf{H}_3$)

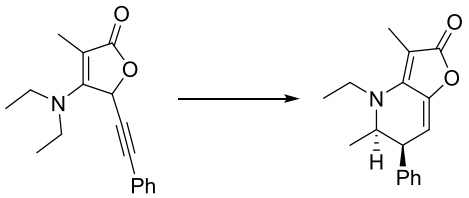
2.03 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.1 (**C**), 151.3 (**C**), 145.6 (**C**), 140.9 (**C**), 128.8 (**C**H), 127.7 (**C**H), 127.5 (**C**H), 104.1 (**C**H), 90.5 (**C**), 56.0 (**C**H_2), 39.8 (**C**H_3), 39.1 (**C**H), 8.5 (**C**H_3) ppm.

LRMS (ESI+) 242 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 242.1182, $C_{15}H_{16}NO_2$ $[M+H]^+$ requires 242.1176.

rel-(5R,6S)-4-Ethyl-3,5-dimethyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.1f)



3.9f
$C_{17}H_{19}NO_2$
Mol Wt: 269.15

4.1f
$C_{17}H_{19}NO_2$
Mol Wt: 269.15

Furanone **3.9f** (40 mg, 0.19 mmol) in 1,4-dioxane (5 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 2 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford the title compound (41 mg, 0.15 mmol, 80%) as a 4 : 1 mixture of diastereoisomers. The major diastereoisomer was separated by HPLC (15% EtOAc/hexane) for analysis.

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 2971 (w), 2929 (w), 2873 (w), 1743 (s), 1606 (s), 1490 (w), 1448 (m), 1378 (w), 1297 (m), 1236 (w), 1216 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.34–7.27 (3 H, m, 3 × Ar**H**)

7.17–7.14 (2 H, m, 2 × Ar**H**)

5.50 (1 H, d, *J* = 6.0 Hz, C**H**)

3.66 (1 H, dq, *J* = 14.5, 7.2 Hz, NC**H**H)

3.49 (1 H, dd, *J* = 6.1, 1.7 Hz, PhC**H**)

3.43 (1 H, br q, *J* = 6.6 Hz, NC**H**)

3.15 (1 H, dq, *J* = 14.4, 7.2 Hz, NCH**H**)

1.99 (3 H, s, C**H**$_3$)

1.40 (3 H, d, *J* = 6.7, C**H**$_3$)

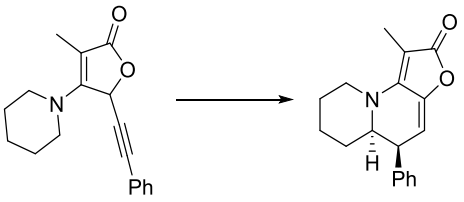
0.92 (3 H, t, *J* = 7.2, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.8 (**C**), 148.9 (**C**), 145.4 (**C**), 141.5 (**C**), 129.0 (**C**H), 127.9 (**C**H), 127.7 (**C**H), 100.7 (**C**H), 88.3 (**C**), 60.8 (**C**H), 45.6 (**C**H), 44.2 (**C**H_2), 10.1 (**C**H_3), 14.7 (**C**H_3), 9.2 (**C**H_3) ppm.

LRMS (ESI+) 270 ($[M+H]^+$, 100%), 561 ($[2M+Na]^+$, 30%).

HRMS (ESI+) Found 270.1486, $C_{17}H_{20}NO_2$ $[M+H]^+$ requires 270.1489.

rel-(5S,5aR)-1-Methyl-5-phenyl-3a,5a,6,7,8,9-hexahydro-2H-furo[2,3-c]quinolizin-2-one (4.1g)



3.9g
$C_{18}H_{19}NO_2$
Mol Wt: 281.15

4.1g
$C_{18}H_{19}NO_2$
Mol Wt: 281.15

Furanone **3.9g** (100 mg, 0.36 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford the title compound (69mg, 0.25 mmol, 69%) as a yellow solid and a 16 : 1 mixture of diastereoisomers .

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 2923 (br), 1734 (s), 1616 (s), 1437 (m), 1357 (w), 1290 (w), 1090 (w), 1030 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.43–7.35 (3 H, m, 3 × Ar**H**)

7.27–7.24 (2 H, m, 2 × Ar**H**)

5.74 (1 H, d, *J* = 4.4 Hz, C**H**)

4.23 (1 H, m, C**H**)

3.97 (1 H, app. t, *J* = 5.0 Hz, C**H**H)

3.51 (1 H, ddd, *J* = 10.9, 5.9, 3.6 Hz, C**H**)

3.12 (1 H, td, *J* = 12.8, 3.0 Hz, CH**H**)

2.12 (3 H, s, C**H**$_3$)

1.83 (1 H, m, C**H**H)

1.73 (1 H, m, C**H**H)

1.60–1.30 (4 H, m, C**H**H + 3 × CH**H**) ppm.

with additional signals attributed to the minor stereoisomer:

5.58 (1 H, d, *J* = 4.3 Hz, C**H**)

3.54 (1 H, obscured ddd, C**H**)

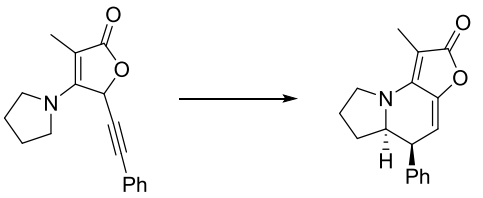
2.12 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.2 (**C**), 151.3 (**C**), 144.7 (**C**), 138.4 (**C**), 128.9 (**C**H), 128.5 (**C**H), 127.3 (**C**H), 104.1 (**C**H), 92.3 (**C**), 62.1 (**C**H), 49.3 (**C**H_2), 44.2 (**C**H), 26.7 (**C**H_2), 24.4 (**C**H_2), 23.7 (**C**H_2), 9.6 (**C**H_3) ppm.

LRMS (ESI+) 282 ($[M+H]^+$, 100%), 585 ($[2M+H]^+$, 60%).

HRMS (ESI+) Found 282.1488, $C_{18}H_{20}NO_2$ $[M+H]^+$ requires 282.1489.

rel-(5S,5aR)-1-Methyl-5-phenyl-5a,6,7,8-tetrahydrofuro[3,2-e]indolizin-2(5H)-one (4.1h)



3.9h
$C_{17}H_{17}NO_2$
Mol Wt: 267.13

4.1h
$C_{17}H_{17}NO_2$
Mol Wt: 267.13

Furanone **3.9h** (60 mg, 0.22 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford the title compound (51 mg, 0.19 mmol, 86%) as a 25 : 1 mixture of diastereoisomers. The major diastereoisomer was separated by HPLC (15% EtOAc/hexane) for analysis

MP 151–153 °C (Et_2O/Pet).

FT-IR (ν_{max}, $CHCl_3$) 2970 (m), 2871 (w), 1749 (s), 1624 (s), 1454 (w), 1319 (s), 1276 (w), 1197 (w), 760 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.33–7.25 (3 H, m, 3 × Ar**H**)

7.08–7.05 (2 H, m, 2 × Ar**H**)

5.64 (1 H, d, *J* = 6.2 Hz, C**H**)

3.94 (1 H, dt, *J* = 10.4 Hz, 5.4 Hz, CH**H**)

3.79–3.69 (2 H, m, 2 × C**H**)

3.48 (1 H, dt, *J* = 10.0 Hz, 7.8 Hz, C**H**H)

2.01 (3 H, s, C**H**$_3$)

1.92–1.72 (3 H, m, 2 × C**H**H + CH**H**)

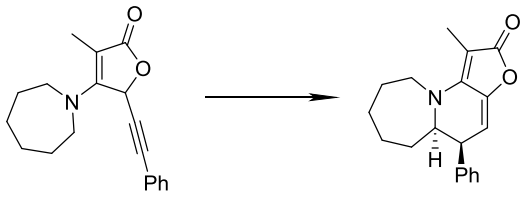
1.10 (1 H, m, CH**H**) ppm.

δ_C (100 MHz, $CDCl_3$) 172.3 (**C**), 149.9 (**C**), 145.8 (**C**), 137.1 (**C**), 129.0 (**C**H), 128.5 (**C**H), 127.5 (**C**H), 103.6 (**C**H), 88.0 (**C**), 61.4 (**C**H), 46.4 (**C**H$_2$), 42.1 (**C**H), 27.3 (**C**H$_2$), 23.6 (**C**H$_2$), 7.6 (**C**H$_3$) ppm.

LRMS (ESI+) 268 ([M+H]$^+$, 100%), 557 ([2M+Na]$^+$, 30%).

HRMS (ESI+) Found 268.1335, $C_{17}H_{18}NO_2$ [M+H]$^+$ requires 268.1332.

rel-(5S,5aR)-1-Methyl-5-phenyl-5a,6,7,8,9,10-hexahydrofuro[2',3':5,6]pyrido[1,2-a]azepin-2(5H)-one (4.1i)



3.9i
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

4.1i
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

Furanone **3.9i** (80 mg, 0.27 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford the title compound (63 mg, 0.21 mmol, 79%) as a yellow solid and a 7 : 1 mixture of diastereoisomers.

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 2970 (br), 2871 (w), 1749 (s), 1624 (vs), 1454 (m), 1319 (m), 1276 (w), 1197 (w), 1018 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.39–7.37 (3 H, m, 3 × Ar**H**)

7.22–7.15 (2 H, m, 2 × Ar**H**)

5.66 (1 H, d, *J* = 4.0 Hz, C**H**)

3.96 (1 H, app. t, *J* = 4.4 Hz, C**H**)

3.62 (1 H, m, C**H**)

3.58–3.50 (2 H, m, C**H**$_2$)

1.99 (3 H, s, C**H**$_3$)

1.87–1.31 (8 H, m, 4 × C**H**$_2$) ppm.

with additional signals attributed to the minor stereoisomer:

5.50 (1 H, d, *J* = 6.0 Hz, C**H**)

3.37 (1 H, dd, *J* = 10.5, 4.2 Hz, C**H**)

2.90 (1 H, dt, *J* = 15.1, 7.7 Hz, C**H**)

2.27–2.25 (1 H, m, C**H**) ppm.

δ_C (100 MHz, $CDCl_3$) 172.5 (**C**), 151.3 (**C**), 145.8 (**C**), 138.3 (**C**), 128.6 (**C**H), 128.6 (**C**H), 127.4 (**C**H), 103.7 (**C**H), 88.7 (**C**), 64.7 (**C**H), 49.7 (**C**H$_2$), 44.9 (**C**H), 30.9 (**C**H$_2$), 28.2 (**C**H$_2$), 27.4 (**C**H$_2$), 26.5 (**C**H$_2$), 8.8 (**C**H$_3$) ppm.

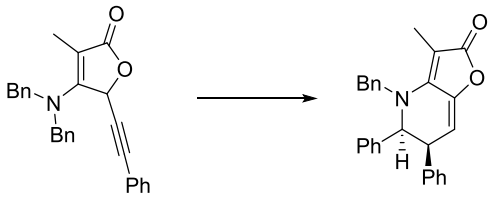
with additional signals attributed to the minor stereoisomer at:

149.3 (**C**), 144.7 (**C**), 141.5 (**C**), 128.8 (**C**H), 127.5 (**C**H), 101.2 (**C**H), 87.7 (**C**), 65.8 (**C**H), 50.8 (**C**H$_2$), 44.8 (**C**H), 34.1 (**C**H$_2$), 31.1 (**C**H$_2$), 30.3 (**C**H$_2$), 26.4 (**C**H$_2$), 25.3 (**C**H$_2$), 15.3 (**C**H$_3$) ppm.

LRMS (ESI+) 296 ($[M+H]^+$, 100%), 318 ($[M+Na]^+$, 70%).

HRMS (ESI+) Found 318.1462, $C_{19}H_{21}NO_2Na$ $[M+Na]^+$ requires 318.1465.

rel-(5S,6S)-4-Benzyl-5,6-diphenyl-3-methyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.1j)



3.9j
$C_{27}H_{23}NO_2$
Mol Wt: 393.17

4.1j
$C_{27}H_{23}NO_2$
Mol Wt: 393.17

Furanone **3.9j** (100 mg, 0.25 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (30–70% Et_2O/cyclohexane) to afford the title compound (76 mg, 0.19 mmol, 76%) as a 6 : 1 mixture of diastereoisomers. The major diastereoisomer was separated by HPLC (15% EtOAc/hexane) for analysis.

FT-IR (ν_{max}, $CHCl_3$) 3062 (m), 2928 (m), 1754 (s), 1616 (s), 1492 (w), 1450 (m), 1296 (m), 1076 (w), 1033 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.40–7.29 (6 H, m, 6 × Ar**H**)

7.24–7.09 (7 H, m, 7 × Ar**H**)

6.85–6.81 (2 H, m, 2 × Ar**H**)

5.54 (1 H, d, *J* = 5.9 Hz, C**H**)

5.02 (1 H, d, *J* = 16.0 Hz, NC**H**H)

4.31 (1 H, d, *J* = 2.2 Hz, NC**H**)

3.96 (1 H, d, *J* = 16.1 Hz, NCH**H**)

3.88 (1 H, dd, *J* = 5.8, 2.3 Hz, PhC**H**)

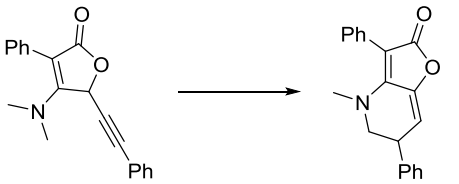
2.02 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.0 (**C**), 150.0 (**C**), 145.1 (**C**), 140.8 (**C**), 139.9 (**C**), 135.8 (**C**), 128.6 (**C**H), 128.4 (**C**H), 128.3 (**C**H), 127.8 (**C**H), 127.5 (**C**H), 127.2 (**C**H), 126.6 (**C**H), 126.2 (**C**H), 99.9 (**C**H), 88.9 (**C**), 67.5 (**C**H), 52.3 (**C**H_2), 47.0 (**C**H), 8.9 (**C**H_3) ppm.

LRMS (ESI+) 394 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 394.1800, $C_{27}H_{24}NO_2$ $[M+H]^+$ requires 394.1802.

4-Methyl-3,6-diphenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.1k)



3.9k
$C_{20}H_{17}NO_2$
Mol Wt 303.13

4.1k
$C_{20}H_{17}NO_2$
Mol Wt 303.13

Furanone **3.9k** (50 mg, 0.17 mmol) in 1,4-dioxane (5 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–50% Et_2O/cyclohexane) to afford the title compound (38 mg, 0.13 mmol, 76%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3012 (w), 2924 (br), 1732 (s), 1620 (vs), 1597 (s), 1504 (m), 1488 (m), 1442 (m), 1404 (m), 1288 (m), 1261 (m), 1149 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.42–7.27 (10 H, m, 10 × Ar**H**)

5.78 (1 H, d, *J* = 3.8 Hz, C**H**)

3.98 (1 H, ddd, *J* = 11.3, 6.2, 3.9 Hz, C**H**)

3.51 (1 H, dd, *J* = 12.1, 6.2 Hz, C**H**H)

3.27 (1 H, dd, *J* = 12.1, 8.9 Hz, CH**H**)

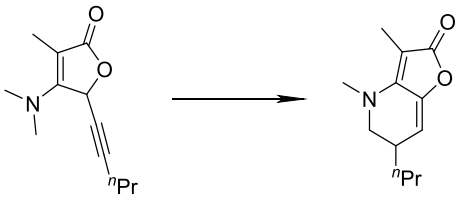
2.77 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 170.2 (**C**), 150.8 (**C**), 145.4 (**C**), 140.7 (**C**), 131.1 (**C**), 130.9 (**C**H), 129.0 (**C**H), 127.9 (**C**H), 127.7 (**C**H), 127.6 (**C**H), 127.4 (**C**H), 105.3 (**C**H), 96.2 (**C**), 57.9 (**C**H_2), 40.2 (**C**H), 39.7 (**C**H_3) ppm.

LRMS (ESI+) 304 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 304.1336, $C_{20}H_{18}NO_2$ $[M+H]^+$ requires 304.1332.

3,4-Dimethyl-6-propyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.1m)



3.9m
$C_{12}H_{17}NO_2$
Mol Wt: 207.13

4.1m
$C_{12}H_{17}NO_2$
Mol Wt: 207.13

Furanone **3.9m** (90 mg, 0.44 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 4 h (2 × 2h). The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford the title compound (61 mg, 0.29 mmol, 67%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2958 (m), 2927 (w), 2871 (w), 1749 (s), 1622 (s), 1456 (w), 1417 (w), 1297 (m), 1209 (w), 1095 (w), 1032 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.50 (1 H, d, *J* = 3.9 Hz, C**H**)

3.23 (1 H, dd, *J* = 11.7 Hz, 5.7 Hz, NC**H**H)

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

2.95 (1 H, dd, *J* = 11.7, 8.1 Hz, NCH**H**)

2.59 (1 H, m, C**H**)

1.99 (3 H, s, C**H**$_3$)

1.47–1.37 (4 H, m, 2 × C**H**$_2$)

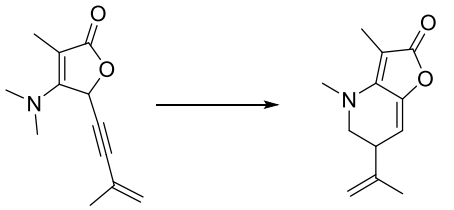
0.94 (3 H, t, *J* = 18.1 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.3 (**C**), 151.7 (**C**), 144.6 (**C**), 105.4 (**C**H), 89.9 (**C**), 55.9 (**C**H$_2$), 39.2 (**C**H$_3$), 35.4 (**C**H$_2$), 33.0 (**C**H), 19.9 (**C**H$_2$), 14.0 (**C**H$_3$), 8.8 (**C**H$_3$) ppm.

LRMS (ESI+) 208 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 208.1332, $C_{12}H_{18}NO_2$ $[M+H]^+$ requires 208.1332.

3,4-Dimethyl-6-(propen-2-yl)-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.1o)



3.9o
$C_{12}H_{15}NO_2$
Mol Wt: 205.11

4.1o
$C_{12}H_{15}NO_2$
Mol Wt: 205.11

Furanone **3.9o** (130 mg, 0.63 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 2 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford the title compound (99 mg, 0.48 mmol, 76%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2966 (w), 2917 (m), 1749 (s), 1689 (w), 1622 (s), 1446 (w), 1415 (w), 1296 (m), 1201 (w), 1034 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.48 (1 H, d, *J* = 4.0 Hz, C**H**)

4.91 (1 H, quin, *J* = 1.4 Hz, C**H**H)

4.86 (1 H, m, CH**H**)

3.31 (1 H, dd, *J* = 11.3, 5.9 Hz, NC**H**H)

3.24 (1 H, ddd, *J* = 7.2, 5.9, 4.0 Hz, C**H**)

3.16 (3 H, s, C**H**$_3$)

3.11 (1 H, dd, *J* = 11.4, 7.2 Hz, NCH**H**)

2.00 (3 H, s, C**H**$_3$)

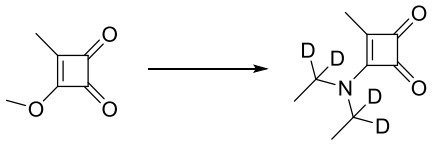
1.78 (3 H, m, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.5 (**C**), 151.6 (**C**), 145.5 (**C**), 144.4 (**C**), 113.7 (**C**H_2), 103.8 (**C**H), 90.5 (**C**), 55.2 (**C**H_2), 41.1 (**C**H), 39.5 (**C**H_3), 21.1 (**C**H_3), 9.1 (**C**H_3) ppm

LRMS (ESI+) 206 ($[M+H]^+$, 100%), 228 ($[M+Na]^+$, 40%).

HRMS (ESI+) Found 206.1178, $C_{12}H_{16}NO_2$ $[M+H]^+$ requires 206.1176.

4-methyl-3-(1,1,1',1'-tetradeuterodiethyl)amino-cyclobutene-1,2-dione (d-3.3b)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

d-**3.3b**
$C_9H_9D_4NO_2$
Mol Wt: 171.12

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (276 mg, 2.19 mmol) in MeOH (40 mL) at RT was added (1,1,1',1'-tetradeutero-diethyl)amine (574 mg, 2.00 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (EtOAc) to afford the title compound (337 mg, 1.97 mmol, 90%) as colourless oil.

FT-IR (ν_{max}, $CHCl_3$) 2973 (w), 2935 (w), 1778 (s), 1728 (w), 1577 (s), 1425 (m), 1217 (w), 1157 (m), 1122 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 2.16 (3 H, s, C**H**$_3$)

1.18 (3 H, s, C**H**$_3$)

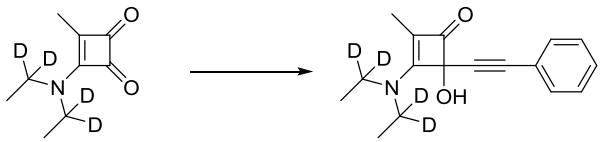
1.13 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 193.2 (**C**), 191.6 (**C**), 182.3 (**C**), 166.0 (**C**), 44.6–43.2 (m, 2 × **C**D_2), 14.5 (**C**H_3), 14.2 (**C**H_3), 10.5 (**C**H_3) ppm.

LRMS (ESI+) 172 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 172.1272, $C_9H_{10}D_4NO_2$ $[M+H]^+$ requires 172.1270.

4-hydroxy-2-methyl-4-(phenylethynyl)-3-(1,1,1',1'-tetradeuterodiethyl)amino-cyclobut-2-enone (d-3.4f)



d-**3.3b**
$C_9H_9D_4NO_2$
Mol Wt 171.12

d-**3.4f**
$C_{17}H_{15}D_4NO_2$
Mol Wt 273.17

To a solution of phenylacetylene (0.14 mL, 1.26 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.66 mL, 1.58 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of cyclobutene-1,2-dione d-**3.3b** (200 mg, 1.17 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (30–80% EtOAc/cyclohexane) to afford the title compound (230 mg, 0.84 mmol, 55%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3234 (br), 1745 (w), 1566 (s), 1448 (w), 1159 (w), 1091 (w), 1014 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.45–7.43 (2 H, m, 2 × Ar**H**)

7.34–7.29 (3 H, m, 3 × Ar**H**)

3.84 (1 H, s, O**H**)

1.79 (3 H, s, C$\mathbf{H}_3$)

1.36 (3 H, s, C$\mathbf{H}_3$)

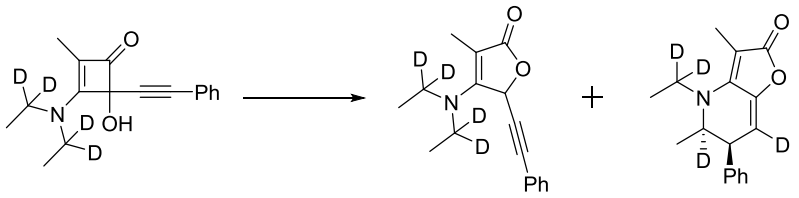
1.30 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 183.6 (**C**), 169.0 (**C**), 131.8 (**C**H), 128.7 (**C**H), 128.2 (**C**H), 122.1 (**C**), 114.3 (**C**), 88.4 (**C**), 84.7 (**C**), 81.8 (**C**), 14.0 (**C**H_3), 13.8 (**C**H_3), 7.8 (**C**H_3) ppm [**C**D_2 not observed].

LRMS (ESI+) 274 ($[M+H]^+$, 100%), 547 ($[2M+H]^+$, 40%).

HRMS (ESI+) Found 274.1740, $C_{17}H_{16}D_4NO_2$ $[M+H]^+$ requires 274.1745.

3-Methyl-5-(phenylethynyl)-4-(1,1,1',1'-tetradeuterodiethyl)amino-5H-furan-2-one (4.10)



d-**3.4f**
$C_{17}H_{15}D_4NO_2$
Mol Wt: 273.17

4.10
$C_{17}H_{15}D_4NO_2$
Mol Wt: 273.17

4.11
$C_{17}H_{15}D_4NO_2$
Mol Wt: 273.17

Cyclobutenone d-**3.4f** (120 mg, 0.45 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford firstly dihydrofuropyridinone **4.11** (18 mg, 0.07 mmol, 15%) as a yellow solid, then the title compound **4.10** (60 mg, 0.23 mmol, 50%) as a yellow solid.

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 2971 (m), 2931 (m), 2872 (w), 1736 (s), 1610 (s), 1491 (w), 1421 (m), 1375 (w), 1297 (w), 1218 (w), 1162 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.45–7.41 (2 H, m, 2 × Ar**H**)

7.35–7.30 (3 H, m, 3 × Ar**H**)

5.50 (1 H, s, C**H**)

1.96 (3 H, s, C$\mathbf{H}_3$)

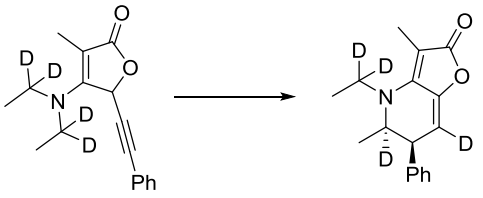
1.24 (6 H, s, 2 × C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.4 (**C**), 160.6 (**C**), 131.7 (**C**H), 129.1 (**C**H), 128.4 (**C**H), 121.5 (**C**), 87.7 (**C**), 86.9 (**C**), 82.6 (**C**), 66.9 (**C**H), 43.4 (m, 2 × **C**D_2), 13.9 (**C**H_3), 9.8 (**C**H_3) ppm.

LRMS (ESI+) 274 ($[M+H]^+$, 100%), 569 ($[2M+Na]^+$, 40%).

HRMS (ESI+) Found 274.1748, $C_{17}H_{16}D_4NO_2$ $[M+H]^+$ requires 274.1740.

rel-(5R,6S)-5,7-Bisdeutero-4-(1,1-bisdeuteroethyl)-3,5-dimethyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.11)



4.10
$C_{17}H_{15}D_4NO_2$
Mol Wt: 273.17

4.11
$C_{17}H_{15}D_4NO_2$
Mol Wt: 273.17

Furanone **4.10** (61 mg, 0.22 mmol) in 1,4-dioxane (5 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 2 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford the title compound (40 mg, 0.15 mmol, 67%) as a yellow solid and 5 : 1 mixture of diastereoisomers (the major diastereoisomer was separated by HPLC (15% EtOAc/hexane) for analysis and gave a yellow solid.), then recovered **4.10** (13 mg, 0.05 mmol, 21%).

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 2968 (w), 2927 (w), 2868 (w), 1743 (s), 1599 (s), 1490 (w), 1439 (m), 1379 (w), 1286 (m), 1219 (w), 1168 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.34–7.24 (3 H, m, 3 × Ar**H**)

7.18–7.14 (2 H, m, 2 × Ar**H**)

3.48 (1 H, s, C**H**)

1.99 (3 H, s, C$\mathbf{H}_3$)

1.39 (3 H, s, C$\mathbf{H}_3$)

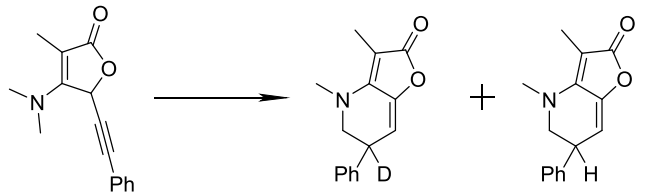
0.90 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.8 (**C**), 148.9 (**C**), 145.3 (**C**), 141.5 (**C**), 129.0 (**C**H), 127.9 (**C**H), 127.7 (**C**H), 100.4 (1:1:1 t, *J* = 25.7 Hz, **C**D), 88.2 (**C**), 60.3 (1:1:1 t, *J* = 22.0 Hz, **C**D), 45.4 (**C**H), 43.7–43.3 (m, **C**D_2), 20.0 (**C**H_3), 14.4 (**C**H_3), 9.2 (**C**H_3) ppm.

LRMS (ESI+) 274 ($[M+H]^+$, 100%), 569 ($[2M+Na]^+$, 30%).

HRMS (ESI+) Found 274.1747, $C_{17}H_{16}D_4NO_2$ $[M+H]^+$ requires 274.1740.

6-Deutero-3,4-dimethyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.14)



3.9e
$C_{15}H_{15}NO_2$
Mol Wt: 241.11

4.14
$C_{15}H_{14}DNO_2$
Mol Wt: 242.12

4.1e
$C_{15}H_{15}NO_2$
Mol Wt: 241.11

Furanone **3.9e** (160 mg, 0.61 mmol) in a mixture of dioxane (8 mL) and D_2O (2 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford firstly the title compound (61 mg, 0.23 mmol, 38%) as a yellow oil and 5 : 1 mixture with isotopomer then recovered **3.9e** (81 mg, 0.31 mmol, 50%).

FT-IR (ν_{max}, $CHCl_3$) 2925 (br), 2871 (w), 1747 (s), 1620 (s), 1490 (w), 1446 (w), 1415 (w), 1302 (m), 1091 (w), 1035 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.39–7.25 (5 H, m, 5 × Ar**H**)

5.63 (1 H, s, C**H**)

3.45 (1 H, d, *J* = 11.7 Hz, NC**H**H)

3.19 (1 H, d, *J* = 11.9 Hz, NCH**H**)

3.15 (3 H, s, C$\mathbf{H}_3$)

2.05 (3 H, s, C$\mathbf{H}_3$) ppm.

with additional signals attributed to **4.1e** at

5.64 (1 H, obscured d, PhC**H**)

3.90 (1 H, m, C**H**) ppm.

δ_C (100 MHz, $CDCl_3$) 172.1 (**C**), 151.3 (**C**), 145.6 (**C**), 140.8 (**C**), 128.8 (**C**H), 127.7 (**C**H), 127.5 (**C**H), 104.0 (**C**H), 90.5 (**C**), 58.0 (**C**H_2), 39.4 (1:1:1 t, *J* = 19.8 Hz, **C**D), 39.1 (**C**H_3), 8.8 (**C**H_3) ppm.

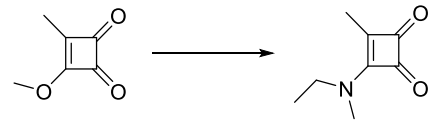
with additional signals attributed to **4.1e** at

104.1 (**C**H), 58.1 (**C**H_2), 39.8 (**C**H) ppm.

LRMS (ESI+) 243 ($[M+H]^+$, 100%), 265 ($[M+Na]^+$, 40%),

HRMS (ESI+) Found 243.1237, $C_{15}H_{15}DNO_2$ $[M+H]^+$ requires 243.1238.

3-(ethyl(methyl)amino)-4-methylcyclobut-3-ene-1,2-dione (4.23a)



3.2a
$C_6H_6O_3$
Mol Wt: 126.1

4.23a
$C_8H_{11}NO_2$
Mol Wt: 153.09

To a solution of 3-methoxy-4-methylcyclo-butene-1,2-dione **3.2a** (330 mg, 2.62 mmol) in MeOH (40 mL) at RT was added *N*-ethylmethylamine (0.23 mL, 2.68 mmol). After stirring at RT for 4 h the solution was concentrated under reduced pressure to afford the title compound (407 mg, 2.66 mmol, 100%) as a yellow oil without any purification.

FT-IR (ν_{max}, $CHCl_3$) 3493 (br), 2973 (br), 1774 (s), 1724 (s), 1587 (vs), 1411 (s), 1298 (m), 1217 (m), 1058 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

3.56 (2 H, q, *J* = 7.1 Hz, C**H**$_2$)

3.02 (3 H, s, C**H**$_3$)

2.08 (3 H, s, C**H**$_3$)

1.04 (3 H, t, *J* = 7.0 Hz, C**H**$_3$) ppm.

minor rotamer:

3.27 (2 H, q, *J* = 7.3 Hz, C**H**$_2$)

3.16 (3 H, s, C**H**$_3$)

2.05 (3 H, s, C**H**$_3$)

1.10 (3 H, t, *J* = 7.3 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

192.8 (**C**), 190.9 (**C**), 182.4 (**C**), 166.2 (**C**), 46.2 (**C**H$_2$), 36.3 (**C**H$_3$), 13.0

(**C**H_3), 10.0 (**C**H_3) ppm.

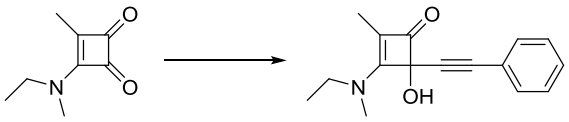
minor rotamer:

192.3 (**C**), 191.0 (**C**), 181.9 (**C**), 165.5 (**C**), 47.1 (**C**H_2), 35.6 (**C**H_3), 12.6 (**C**H_3), 9.9 (**C**H_3) ppm.

LRMS (ESI+) 154 ($[M+H]^+$, 100%), 176 ($[M+Na]^+$, 40%),

HRMS (ESI+) Found 154.0867, $C_8H_{12}NO_2$ $[M+H]^+$ requires 154.0863.

4-Hydroxy-3-(isopropyl(methyl)amino)-2-methyl-4-(phenylethynyl)-cyclobut-2-enone (4.24a)



4.23a
$C_8H_{12}NO_2$
Mol Wt 159.09

4.24a
$C_{16}H_{17}NO_2$
Mol Wt 255.13

To a solution of phenylacetylene (0.28 mL, 2.55 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 1.1 mL, 2.75 mmol) dropwise. After 20 min the solution was added *via* cannula to a solution of 3-(ethyl(methyl)amino)-4-methylcyclobut-3-ene-1,2-dione **4.23a** (300 mg, 1.88 mmol) in THF (40 mL) at –78 °C. After a further 3 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–15% acetone/DCM) to afford the title compound **1k** (473 mg, 1.58 mmol, 93%) as a white solid.

MP Decomposed over 120 °C.

FT-IR (ν_{max}, $CHCl_3$) 3238 (br), 2973 (w), 1742 (m), 1568 (vs), 1489 (w), 1442 (w), 1414 (m), 1300 (m), 1140 (w), 1083 (m), 1024 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

7.45–7.41 (2 H, m, 2 × Ar**H**)

7.30–7.23 (3 H, m, 3 × Ar**H**)

5.36 (1 H, br s, O**H**)

3.80 (1 H, dq, *J* = 14.1 Hz, 7.1 Hz, C**H**H)

3.56 (1 H, dq, *J* = 14.1 Hz, 7.1 Hz, CH**H**)

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

1.78 (3 H, s, C**H**$_3$)

1.35 (3 H, t, *J* = 7.2 Hz, C**H**$_3$) ppm.

minor rotamer:

7.45–7.41 (2 H, m, 2 × Ar**H**)

7.30–7.23 (3 H, m, 3 × Ar**H**)

5.36 (1 H, br s, O**H**)

3.43 (2 H, q, *J* = 7.2 Hz, C**H**$_2$)

3.30 (3 H, s, C**H**$_3$)

1.75 (3 H, s, C**H**$_3$)

1.29 (3 H, t, *J* = 7.3 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

184.9 (**C**), 170.2 (**C**), 131.7 (**C**H), 128.3 (**C**H), 128.0 (**C**H), 122.4 (**C**), 114.2 (**C**), 87.5 (**C**), 85.3 (**C**), 81.5 (**C**), 48.0 (**C**H$_2$), 36.1 (**C**H$_3$), 13.0 (**C**H$_3$), 7.7 (**C**H$_3$) ppm.

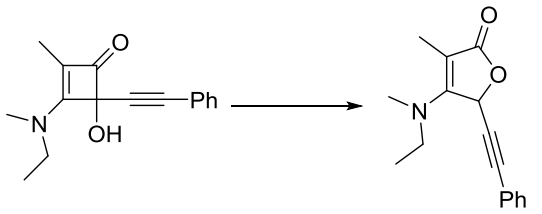
minor rotamer:

184.8 (**C**), 169.2 (**C**), 131.8 (**C**H), 128.3 (**C**H), 128.3 (**C**H), 122.4 (**C**), 113.9 (**C**), 87.8 (**C**), 85.2 (**C**), 81.9 (**C**), 47.0 (**C**H$_2$), 37.1 (**C**H$_3$), 13.1 (**C**H$_3$), 7.6 (**C**H$_3$) ppm.

LRMS (ESI+) 256 ([M+H]$^+$, 100%),

HRMS (ESI+) Found 256.1334, $C_{16}H_{18}NO_2$ [M+H]$^+$ requires 256.1332.

4-(ethyl(methyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25a)



4.24a
$C_{16}H_{17}NO_2$
Mol Wt: 255.13

4.25a
$C_{16}H_{17}NO_2$
Mol Wt: 255.13

Cyclobutenone **4.24a** (150 mg, 1 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–80% Et_2O/Pet) to afford the title compound (107 mg, 0.71 mmol, 71%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2927 (br), 1732 (s), 1612 (s), 1412 (m), 1296 (m), 1072 (m), 1032 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.43–7.39 (2 H, m, 2 × Ar**H**)

7.36–7.28 (3 H, m, 3 × Ar**H**)

5.47 (1 H, s, C**H**)

3.50–3.41 (2 H, m, C**H**$_2$)

3.14 (3 H, s, C**H**$_3$)

1.96 (3 H, s, C**H**$_3$)

1.23 (3 H, t, *J* = 7.1 Hz, C**H**$_3$) ppm.

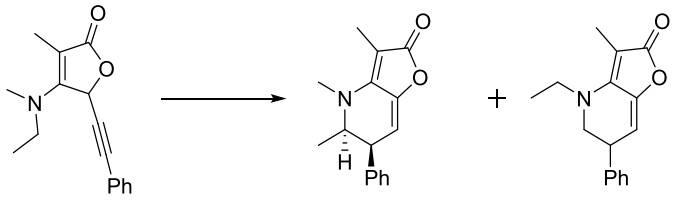
δ_C (100 MHz, $CDCl_3$) 175.2 (**C**), 161.1 (**C**), 131.6 (**C**H), 129.0 (**C**H), 128.3 (**C**H), 121.4 (**C**), 88.1 (**C**), 87.0 (**C**), 82.2 (**C**), 66.8 (**C**H), 47.4 (**C**H_2), 37.7 (**C**H_3), 13.2 (**C**H_3), 9.7 (**C**H_3) ppm.

LRMS (ESI+) 256 ($[M+H]^+$, 100%), 533 ($[2M+Na]^+$, 40%).

HRMS (ESI+) Found 256.1339, $C_{16}H_{18}NO_2$ $[M+H]^+$ requires 256.1332.

3,4,5-Trimethyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.26a);

4-Ethyl-3-methyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one (4.26a')



4.25a
$C_{16}H_{17}NO_2$
Mol Wt: 255.13

4.26a
$C_{16}H_{17}NO_2$
Mol Wt: 255.13

4.26a'
$C_{16}H_{17}NO_2$
Mol Wt: 255.13

Furanone **4.25a** (80 mg, 0.31 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (5–30% Et_2O/Pet) to afford firstly 4-Ethyl-3-methyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one **4.26a'** (13 mg, 0.05 mmol, 17%) as a yellow oil, then 3,4,5-Trimethyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4*H*)-one **4.26a** (63 mg, 0.25 mmol, 79%) as a yellow oil and a 5 : 2 mixture of diastereoisomers. The diastereoisomers were partially separated by HPLC (15% EtOAc/hexane) for analysis.

4,5-dimethyl-3,6-diphenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26a)

major rel-(5S,6R)-diastereoisomer

FT-IR (ν_{max}, $CHCl_3$) 2970 (br), 1747 (s), 1616 (s), 1415 (w), 1294 (m), 1253 (w), 1079 (m), 1031 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.37–7.29 (3 H, m, 3 × Ar**H**)

7.24–7.18 (2 H, m, 2 × Ar**H**)

5.50 (1 H, d, *J* = 6.1 Hz, C**H**)

3.48 (1 H, br d, *J* = 6.1 Hz, C**H**)

3.31 (1 H, br q, *J* = 6.2 Hz, C**H**)

3.10 (3 H, s, C$\mathbf{H}_3$)

2.04 (3 H, s, C$\mathbf{H}_3$)

1.38 (3 H, d, *J* = 6.6 Hz, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.3 (**C**), 149.6 (**C**), 144.5 (**C**), 141.5 (**C**), 128.8 (**C**H), 127.4 (**C**H),

127.4 (**C**H), 100.6 (**C**H), 90.1 (**C**), 62.9 (**C**H), 45.4 (**C**H), 37.6 (**C**H_3), 18.1 (**C**H_3), 8.8 (**C**H_3) ppm.

LRMS (ESI+) 256 ($[M+H]^+$, 100%), 278 ($[M+Na]^+$, 50%).

HRMS (ESI+) Found 256.1328, $C_{16}H_{18}NO_2$ $[M+H]^+$ requires 256.1332.

minor rel-(5R,6R)-diastereoisomer

FT-IR (ν_{max}, $CHCl_3$) 2970 (br), 1749 (s), 1618 (s), 1456 (w), 1294 (w), 1083 (w), 997 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.38–7.29 (3 H, m, 3 × Ar**H**)

7.25–7.21 (2 H, m, 2 × Ar**H**)

5.62 (1 H, d, *J* = 3.1 Hz, C**H**)

4.19 (1 H, dd, *J* = 5.8 Hz, 3.0 Hz, C**H**)

3.45 (1 H, app quin, *J* = 6.2 Hz, C**H**)

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

2.05 (3 H, s, C**H**$_3$)

0.86 (3 H, d, *J* = 6.6 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.7 (**C**), 150.7 (**C**), 145.8 (**C**), 139.4 (**C**), 129.0 (**C**H), 128.9 (**C**H), 127.7 (**C**H), 102.3 (**C**H), 91.3 (**C**), 61.8 (**C**H), 44.9 (**C**H), 37.5 (**C**H_3), 11.7 (**C**H_3), 9.2 (**C**H_3) ppm.

LRMS (ESI+) 256 ($[M+H]^+$, 100%), 533 ($[2M+Na]^+$, 20%).

HRMS (ESI+) Found 256.1332, $C_{16}H_{18}NO_2$ $[M+H]^+$ requires 256.1332.

4-ethyl-3-methyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26a')

FT-IR (ν_{max}, $CHCl_3$) 2973 (br), 1751 (s), 1618 (s), 1454 (w), 1299 (m), 1033 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.38–7.24 (5 H, m, 5 × Ar**H**)

5.63 (1 H, d, *J* = 3.8 Hz, C**H**)

3.88 (1 H, m, C**H**)

3.53–3.39 (3 H, m, C**H**H + CH_2)

3.22 (1 H, dd, *J* =11.9 Hz, 8.5 Hz, CH**H**)

2.00 (3 H, s, C$\mathbf{H}_3$)

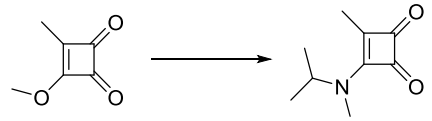
1.16 (3 H, t, *J* = 7.2 Hz, C$\mathbf{H}_3$) .

δ_C (100 MHz, $CDCl_3$) 171.9 (**C**), 149.9 (**C**), 145.6 (**C**), 140.6 (**C**), 128.5 (**C**H), 127.4 (**C**H), 127.2 (**C**H), 103.7 (**C**H), 88.7 (**C**), 54.8 (**C**H_2), 45.5 (**C**H_2), 39.5 (**C**H), 12.7 (**C**H_3), 8.5 (**C**H_3) ppm.

LRMS (ESI+) 256 ($[M+H]^+$, 100%), 533 ($[2M+Na]^+$, 30%).

HRMS (ESI+) Found 256.1333, $C_{16}H_{18}NO_2$ $[M+H]^+$ requires 256.1332.

3-(isopropyl(methyl)amino)-4-methylcyclobutene-1,2-dione (4.23b)



3.2a
$C_6H_6O_3$
Mol Wt: 126.1

4.23b
$C_9H_{13}NO_2$
Mol Wt: 167.10

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (330 mg, 2.60 mmol) in MeOH (50 mL) at RT was added *N*-isopropylmethylamine (0.27 mL, 2.60 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (70%–90% EtOAc/cyclohexane) to afford the title compound (400 mg, 2.40 mmol, 92%) as a white solid.

MP 113–114 °C.

FT-IR (ν_{max}, $CHCl_3$) 2979 (br), 1778 (s), 1728 (s), 1585 (vs), 1413 (s), 1213 (m), 1134 (m), 1058 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

4.98 (1 H, sept, *J* = 6.7 Hz, C**H**)

3.08 (3 H, s, NC$\mathbf{H}_3$)

2.31 (3 H, s, C$\mathbf{H}_3$)

1.25 (6 H, d, *J* = 6.7 Hz, (C**H**$_3$)$_2$CH) ppm.

minor rotamer:

4.06 (1 H, sept, *J* = 6.7 Hz, C**H**)

3.28 (3 H, s, NC**H**$_3$)

2.28 (3 H, s, C**H**$_3$)

1.31 (6 H, d, *J* = 6.7 Hz, (C**H**$_3$)$_2$CH) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

193.5 (**C**), 191.6 (**C**), 183.1 (**C**), 166.4 (**C**), 50.7 (**C**H), 30.2 (**C**H$_3$), 20.0 (2 × **C**H$_3$), 10.8 (**C**H$_3$) ppm.

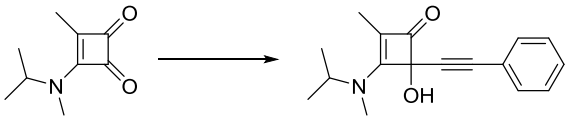
minor rotamer:

192.8 (**C**), 191.6 (**C**), 182.5 (**C**), 165.7 (**C**), 51.9 (**C**H), 29.3 (**C**H$_3$), 19.7 (2 × **C**H$_3$), 11.0 (**C**H$_3$) ppm.

LRMS (ESI+) 168 ([M+H]$^+$, 100%), 334 ([2M+H]$^+$, 70%),

HRMS (ESI+) Found 168.1018, $C_9H_{14}NO_2$ [M+H]$^+$ requires 168.1019.

4-Hydroxy-3-(isopropyl(methyl)amino)-2-methyl-4-(phenylethynyl)-cyclobut-2-enone (4.24b)



4.23b
$C_9H_{13}NO_2$
Mol Wt 167.10

4.24b
$C_{17}H_{19}NO_2$
Mol Wt 269.14

To a solution of phenylacetylene (0.26 mL, 2.37 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 1.01 mL, 2.42 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-(isopropyl(methyl)amino)-4-methylcyclobutene-1,2-dione **4.23b** (290 mg, 1.74 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–25% acetone/DCM) to afford the title compound (432 mg, 1.61 mmol, 92%) as a yellow solid.

MP Decomposed over 110 °C.

FT-IR (ν_{max}, $CHCl_3$) 3010 (br), 1749 (w), 1591 (s), 1567 (vs), 1489 (w), 1452 (m), 1265 (w), 1215 (w), 1131 (w), 1083 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

7.45–7.40 (2 H, m, 2 × Ar**H**)

7.29–7.24 (3 H, m, 3 × Ar**H**)

4.56 (1 H, sept, *J* = 6.6 Hz, C**H**)

4.50 (1 H, br s, O**H**)

3.03 (3 H, s, C$\mathbf{H}_3$)

1.80 (3 H, s, C$\mathbf{H}_3$)

1.35–1.26 (6 H, m, CH(C$\mathbf{H}_3$)$_2$) ppm.

minor rotamer:

7.45–7.40 (2 H, m, 2 × Ar**H**)

7.29–7.24 (3 H, m, 3 × Ar**H**)

4.09 (1 H, sept, *J* = 6.7 Hz, C**H**)

3.16 (3 H, s, C$\mathbf{H}_3$)

1.77 (3 H, s, C$\mathbf{H}_3$)

1.35–1.26 (6 H, m, CH(C$\mathbf{H}_3$)$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

184.2 (**C**), 169.7 (**C**), 131.80 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 122.4 (**C**), 114.2 (**C**), 87.7 (**C**), 85.2 (**C**), 81.8 (**C**), 52.5 (**C**H), 29.7 (**C**H_3), 19.9 (**C**H_3), 7.9 (**C**H_3) ppm.

minor rotamer:

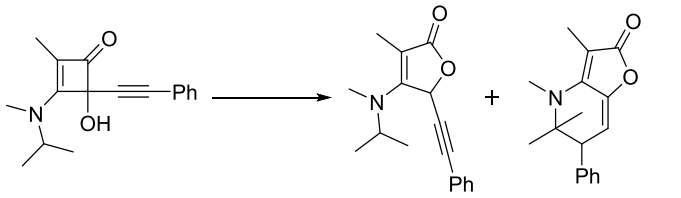
184.4 (**C**), 169.2 (**C**), 131.84 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 122.4 (**C**), 114.0 (**C**), 88.2 (**C**), 85.1 (**C**), 82.0 (**C**), 51.0 (**C**H), 30.1 (**C**H_3), 19.6

(**C**H_3), 8.0 (**C**H_3) ppm.

LRMS (ESI+) 270 ([M+H]$^+$, 90%), 539 ([2M+H]$^+$, 100%),

HRMS (ESI+) Found 270.1493, $C_{17}H_{20}NO_2$ [M+H]$^+$ requires 270.1489.

4-(isopropyl-(methyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25b)



4.24b
$C_{17}H_{19}NO_2$
Mol Wt: 269.14

4.25b
$C_{17}H_{19}NO_2$
Mol Wt: 269.14

4.26b
$C_{17}H_{19}NO_2$
Mol Wt: 269.14

Aminocyclobutenone **4.24b** (280 mg, 1.04 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–80% Et_2O/cyclohexane) to afford firstly dihydrofuropyridinone **4.26b** (31 mg, 0.11 mmol, 11%) as a yellow oil, then the title compound (201 mg, 0.73 mmol, 72%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2964 (m), 1732 (s), 1606 (s), 1488 (w), 1444 (w), 1414 (m), 1290 (m) 1120 (m), 1072 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.44–7.39 (2 H, m, 2 × Ar**H**)

7.34–7.28 (3 H, m, 3 × Ar**H**)

5.51 (1 H, s, C**H**)

4.18 (1 H, app. sept, *J* = 6.6 Hz, C**H**)

3.02 (3 H, s, C**H**$_3$)

2.00 (3 H, s, C**H**$_3$)

1.28 (3 H, d, *J* = 6.5 Hz, C**H**$_3$)

1.23 (3 H, d, *J* = 6.6 Hz, C**H**$_3$) ppm.

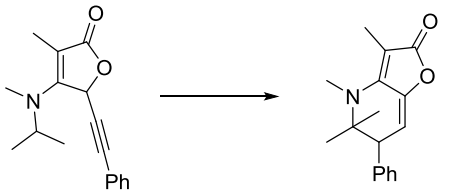
δ_C (100 MHz, $CDCl_3$) 175.4 (**C**), 161.6 (**C**), 131.7 (**C**H), 129.0 (**C**H), 128.3 (**C**H), 121.5 (**C**), 88.4 (**C**), 86.9 (**C**), 82.5 (**C**), 67.0 (**C**H), 50.8 (**C**H), 30.4 (**C**H_3), 19.98

(**C**H_3), 19.95 (**C**H_3), 10.3 (**C**H_3) ppm.

LRMS (ESI+) 270 ([M+H]$^+$, 100%), 561 ([2M+Na]$^+$, 60%).

HRMS (ESI+) Found 270.1484, $C_{17}H_{20}NO_2$ [M+H]$^+$ requires 270.1489.

3,4,5,5-Tetramethyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26b)



4.25b
$C_{17}H_{19}NO_2$
Mol Wt: 269.14

4.26b
$C_{17}H_{19}NO_2$
Mol Wt: 269.14

Furanone **4.25b** (150 mg, 0.53 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 2 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–80% Et_2O/cyclohexane) to afford the title compound (113 mg, 0.40 mmol, 75%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2929 (m), 1734 (s), 1616 (s), 1508 (s), 1434 (m), 1415 (m), 1221 (m), 1155 (w), 1089 (m), 752 (s), 692 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.30–7.26 (3 H, m, 3 × Ar**H**)

7.16–7.14 (2 H, m, 2 × Ar**H**)

5.56 (1 H, d, *J* = 5.6 Hz, C**H**)

3.41 (1 H, d, *J* = 5.6 Hz, C**H**)

3.07 (3 H, s, C**H**$_3$)

2.09 (3 H, s, C**H**$_3$)

1.40 (3 H, s, C**H**$_3$)

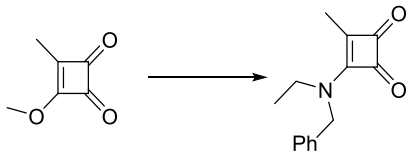
0.99 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.4 (**C**), 151.4 (**C**), 144.1 (**C**), 138.8 (**C**), 129.3 (**C**H), 128.3 (**C**H), 127.5 (**C**H), 104.1 (**C**H), 91.1 (**C**), 60.1 (**C**), 51.3 (**C**H), 31.4 (**C**H_3), 25.1 (**C**H_3), 24.0 (**C**H_3), 9.6 (**C**H_3) ppm.

LRMS (ESI+) 270 ([M+H]$^+$, 100%), 561 ([2M+Na]$^+$, 40%),

HRMS (ESI+) Found 270.1485, $C_{17}H_{20}NO_2$ [M+H]$^+$ requires 270.1489.

3-(benzyl(ethyl)amino)-4-methylcyclo-butene-1,2-dione (4.23c)



3.2a
$C_6H_6O_3$
Mol Wt: 126.1

4.23c
$C_{14}H_{15}NO_2$
Mol Wt: 229.11

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (252 mg, 2.00 mmol) in MeOH (50 mL) at RT was added *N*-benzylethylamine (0.30 mL, 2.00 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (70%–90% EtOAc/cyclohexane) to afford the title compound (415 mg, 1.81 mmol, 91%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3230 (br), 1745 (w), 1564 (vs), 1489 (w), 1442 (m), 1363 (w), 1295 (w), 1261 (w), 1145 (w), 1114 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

7.40–7.19 (5 H, m, 5 × Ar**H**)

4.92 (2 H, s, C**H**$_2$)

3.37 (2 H, q, *J* = 7.2 Hz, C**H**$_2$)

2.30 (3 H, s, C**H**$_3$)

1.20 (3 H, t, *J* = 7 Hz, C**H**$_3$) ppm.

minor rotamer

7.40–7.19 (5 H, m, 5 × Ar**H**)

4.63 (2 H, s, C**H**$_2$)

3.78 (2 H, q, *J* = 7.2 Hz, C**H**$_2$)

2.16 (3 H, s, C**H**$_3$)

1.20 (3 H, t, *J* = 7.2 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

193.0 (**C**), 191.4 (**C**), 182.3 (**C**), 166.0 (**C**), 135.0 (**C**H), 128.6 (**C**H), 128.0 (**C**H), 126.3 (**C**), 52.1 (**C**H$_2$), 43.9 (**C**H$_2$), 13.4 (**C**H$_3$), 10.3 (**C**H$_3$) ppm.

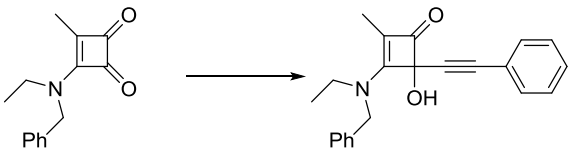
minor rotamer:

192.3 (**C**), 191.5 (**C**), 183.3 (**C**), 166.5 (**C**), 134.8 (**C**H), 128.9 (**C**H), 128.1 (**C**H), 126.3 (**C**), 52.9 (**C**H$_2$), 44.5 (**C**H$_2$), 14.0 (**C**H$_3$), 10.2 (**C**H$_3$) ppm.

LRMS (ESI+) 230 ($[M+H]^+$, 100%), 459 ($[M+H]^+$, 90%).

HRMS (ESI+) Found 230.1174, $C_{14}H_{16}NO_2$ $[M+H]^+$ requires 230.1176.

3-(Benzyl(ethyl)amino)-4-hydroxy-2-methyl-4-(phenylethynyl)-cyclobut-2-enone (4.24c)



4.23c
$C_{14}H_{15}NO_2$
Mol Wt 229.11

4.24c
$C_{22}H_{21}NO_2$
Mol Wt 331.16

To a solution of phenylacetylene (0.20 mL, 1.82 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexane, 0.86 mL, 1.98 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-(benzyl(ethyl)amino)-4-methylcyclobutene-1,2-dione **4.23c** (300 mg, 1.31 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–30% acetone/DCM) to afford the title compound (338 mg, 1.02 mmol, 78%) as a yellow solid.

MP Decomposed over 110 °C.

FT-IR (ν_{max}, $CHCl_3$) 3230 (br), 2973 (w), 1745 (m), 1564 (s), 1442 (m), 1363 (w), 1296 (w), 1261 (w), 1145 (w), 1080 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

7.48–7.43 (2 H, m, 2 × Ar**H**)

7.41–7.21 (8 H, m, 8 × Ar**H**)

4.91 (1 H, d, *J* = 15.3 Hz, PhC**H**H)

4.76 (1 H, d, *J* = 15.3 Hz, PhCH**H**)

3.37 (1 H, dq, *J* = 14.3, 7.0 Hz, C**H**H)

3.29 (1 H, dq, *J* = 14.3, 7.2 Hz, CH**H**)

1.82 (3 H, s, C$\mathbf{H}_3$)

1.19 (3 H, t, J = 7.2 Hz, C$\mathbf{H}_3$) ppm.

minor rotamer:

7.48–7.43 (2 H, m, 2 × Ar**H**)

7.41–7.21 (8 H, m, 8 × Ar**H**)

4.63 (2 H, s, C$\mathbf{H}_2$)

3.88 (1 H, br s, O**H**)

3.78 (1 H, dq, *J* = 14.3, 7.0 Hz, C**H**H)

3.64 (1 H, dq, *J* = 14.2, 6.9 Hz, CH**H**)

1.66 (3 H, s, C$\mathbf{H}_3$)

1.34 (3 H, t, *J* = 7.2 Hz, C$\mathbf{H}_3$) ppm.

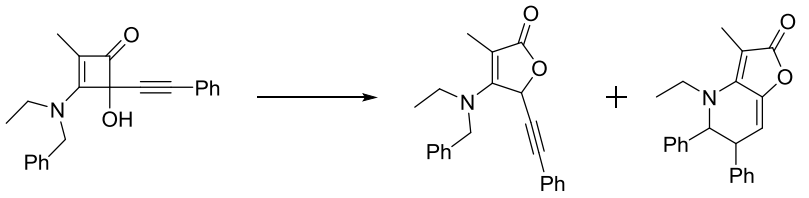
δ_C (100 MHz, $CDCl_3$) Reported as the mixture of two rotamers:

184.5 (**C**), 184.4 (**C**), 170.5 (**C**), 169.4 (**C**), 136.1 (**C**), 135.6 (**C**), 131.9 (**C**H), 131.8 (**C**H), 129.1 (**C**H), 128.7 (**C**H), 128.5 (**C**H), 128.5 (**C**H), 128.2 (**C**H), 128.2 (**C**H), 128.1 (**C**H), 128.0 (**C**H), 126.6 (**C**H), 126.6 (**C**H), 122.3 (**C**), 122.2 (**C**), 114.9 (**C**), 114.4 (**C**), 88.7 (**C**), 88.2 (**C**), 85.1 (**C**), 85.0 (**C**), 82.2 (**C**), 82.1 (**C**), 54.1 (**C**H_2), 51.9 (**C**H_2), 45.8 (**C**H_2), 43.2 (**C**H_2), 13.6 (**C**H_3), 13.5 (**C**H_3), 7.8 (**C**H_3), 7.6 (**C**H_3) ppm.

LRMS (ESI+) 332 ($[M+H]^+$, 100%), 685 ($[2M+Na]^+$, 40%).

HRMS (ESI+) Found 332.1643, $C_{22}H_{22}NO_2$ $[M+H]^+$ requires 332.1645.

4-(benzyl(ethyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25c)



4.24c
$C_{22}H_{21}NO_2$
Mol Wt: 331.16

4.25c
$C_{22}H_{21}NO_2$
Mol Wt: 331.16

4.26c
$C_{22}H_{21}NO_2$
Mol Wt: 331.16

Aminocyclobutenone **4.24c** (200 mg, 0.60 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–60% Et_2O/cyclohexane) to afford firstly the dihydrofuro[3,2-b]pyridin-2(4H)-one **4.26c** (73 mg, 0.22 mmol, 37%) as a yellow oil, then the title compound (80 mg, 0.24 mmol, 40%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2929 (m), 1734 (s), 1616 (s), 1616 (s), 1491 (w), 1435 (m), 1290 (m), 1092 (m), 1076 (m), 1033 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.38–7.29 (10 H, m, 10 × Ar**H**)

5.58 (1 H, s, C**H**)

4.82 (1 H, d, *J* = 16.6 Hz, C**H**H)

4.59 (1 H, d, *J* = 16.5 Hz, CH**H**)

3.61–3.37 (2 H, m, C$\mathbf{H_2}$)

1.95 (3 H, s, C$\mathbf{H_3}$)

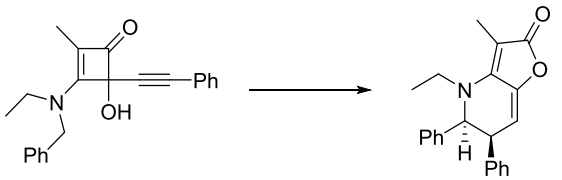
1.25 (3 H, t, *J* = 7.2 Hz, C$\mathbf{H_3}$) ppm.

δ_C (100 MHz, $CDCl_3$) 174.9 (**C**), 160.7 (**C**), 136.7 (**C**), 131.4 (**C**H), 128.8 (**C**H), 128.6 (**C**H), 128.0 (**C**H), 127.4 (**C**H), 126.3 (**C**H), 121.0 (**C**), 88.9 (**C**), 87.1 (**C**), 82.1 (**C**), 66.8 (**C**H), 52.3 (**C**H_2), 44.6 (**C**H_2), 13.4 (**C**H_3), 9.5 (**C**H_3) ppm.

LRMS (ESI+) 332 ($[M+H]^+$, 100%), 663 ($[2M+H]^+$, 50%), 685 ($[2M+Na]^+$, 50%).

HRMS (ESI+) Found 332.1653, $C_{22}H_{22}NO_2$ $[M+H]^+$ requires 332.1645.

rel-(5S,6S)-5,6-Diphenyl-4-ethyl-3-methyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26c)



4.25c
$C_{22}H_{21}NO_2$
Mol Wt: 331.16

4.26c
$C_{22}H_{21}NO_2$
Mol Wt: 331.16

Aminocyclobutenone **4.25c** (170 mg, 0.51 mmol) in 1,4-dioxane (10 mL) was heated at 200 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–60% Et_2O/cyclohexane) to afford the title compound (132 mg, 0.40 mmol, 78%) as a yellow oil and a 4 : 1 mixture of diastereoisomers. The major diastereoisomer was separated by HPLC (15% EtOAc/hexane) for analysis.

FT-IR (ν_{max}, $CHCl_3$) 3025 (m), 2929 (m), 1747 (s), 1693 (w), 1608 (s), 1492 (w), 1448 (m), 1298 (m), 1028 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.39–7.30 (6 H, m, 6 × Ar**H**)

7.25–7.20 (4 H, m, 4 × Ar**H**)

5.45 (1 H, d, *J* = 5.6 Hz, C**H**)

4.33 (1 H, d, *J* = 2.9 Hz, C**H**)

3.84 (1 H, dd, *J* = 5.6 Hz, 3.1 Hz, C**H**)

3.69 (1 H, dq, *J* = 14.6 Hz, 7.2 Hz, C**H**H)

3.00 (1 H, dq, *J* = 14.6 Hz, 7.2 Hz, CH**H**)

2.09 (3 H, s, C$\mathbf{H}_3$)

0.94 (3 H, t, *J* = 7.2 Hz, C$\mathbf{H}_3$) ppm.

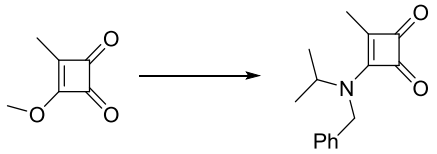
δ_C (100 MHz, $CDCl_3$) 172.1 (**C**), 149.3 (**C**), 144.9 (**C**), 141.1 (**C**), 140.5 (**C**), 128.5 (**C**H), 127.7 (**C**H), 127.4 (**C**H), 127.3 (**C**H), 126.1 (**C**H), 100.4 (**C**H), 87.8 (**C**), 66.0

(**C**H), 47.4 (**C**H), 44.1 (**C**H_2), 13.4 (**C**H_3), 8.8 (**C**H_3) ppm.

LRMS (ESI+) 332 ($[M+H]^+$, 90%), 685 ($[2M+Na]^+$, 100%).

HRMS (ESI+) Found 332.1648, $C_{22}H_{22}NO_2$ $[M+H]^+$ requires 332.1645.

3-(benzyl(isopropyl)amino)-4-methylcyclobut-3-ene-1,2-dione (4.23d)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

4.23d
$C_{15}H_{17}NO_2$
Mol Wt: 243.13

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (253 mg, 2.01 mmol) in MeOH (40 mL) at RT was added *N*-isopropylbenzylamine (0.33 mL, 1.97 mmol). After stirring at RT for 4 h the solution was concentrated under reduced pressure and purified by column chromatography (EtOAc) to afford the title compound (459 mg, 1.80 mmol, 90%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2975 (br), 1778 (s), 1726 (s), 1573 (vs), 1431 (s), 1348 (w), 1169 (m), 1047 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

7.36–7.29 (2 H, m, 2 × Ar**H**)

7.25–7.13 (3 H, m, 3 × Ar**H**)

4.97 (1 H, sept, *J* = 6.9 Hz, C**H**)

4.61 (2 H, s, C**H**$_2$)

1.93 (3 H, s, C**H**$_3$)

1.21 (6 H, d, *J* = 6.9 Hz, 2 × C**H**$_3$) ppm.

minor rotamer:

7.36–7.29 (2 H, m, 2 × Ar**H**)

7.25–7.13 (3 H, m, 3 × Ar**H**)

4.94 (2 H, s, C**H**$_2$)

4.05 (1 H, sept, *J* = 6.7 Hz, C**H**)

2.31 (3 H, s, C**H**$_3$)

1.15 (6 H, d, *J* = 6.9 Hz, 2 × C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

192.5 (**C**), 191.8 (**C**), 184.0 (**C**), 167.7 (**C**), 137.4 (**C**), 129.0 (**C**H), 127.7 (**C**H), 126.0 (**C**H), 51.9 (**C**H), 48.3 (**C**H$_2$), 21.0 (2 × **C**H$_3$), 10.2 (**C**H$_3$) ppm.

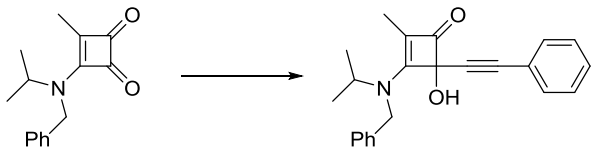
minor rotamer:

193.3 (**C**), 191.7 (**C**), 183.0 (**C**), 164.4 (**C**), 136.8 (**C**), 128.6 (**C**H), 127.2 (**C**H), 126.0 (**C**H) 53.1 (**C**H), 48.3 (**C**H$_2$), 21.0 (2 × **C**H$_3$), 11.2 (**C**H$_3$) ppm.

LRMS (ESI+) 244 ([M+H]$^+$, 100%), 509 ([2M+Na]$^+$, 30%),

HRMS (ESI+) Found 244.1333, $C_{15}H_{18}NO_2$ [M+H]$^+$ requires 244.1332.

3-(Benzyl(isopropyl)amino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-enone (4.24d)



4.23d
$C_{15}H_{17}NO_2$
Mol Wt 243.13

4.24d
$C_{23}H_{23}NO_2$
Mol Wt 345.184

To a solution of phenylacetylene (0.28 mL, 2.5 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 1.0 mL, 2.50 mmol) dropwise. After 20 min the solution was added *via* cannula to a solution of 3-(benzyl(isopropyl)amino)-4-methylcyclobut-3-ene-1,2-dione **4.23d** (452 mg, 1.86 mmol) in THF (40 mL) at –78 °C. After a further 4 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–15% acetone/DCM) to afford the title compound (533 mg, 1.54 mmol, 82%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3212 (br), 1743 (m), 1556 (s), 1435 (m), 1348 (w), 1174 (w), 1155

(w), 1083 (w), 1012 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer

7.49–7.44 (2 H, m, 2 × Ar**H**)

7.36–7.23 (8 H, m, 8 × Ar**H**)

5.67 (1 H, br s, O**H**)

4.81 (1 H, sept, *J* = 6.1 Hz, C**H**)

4.59 (2 H, s, C$\mathbf{H}_2$)

1.44 (3 H, s, C$\mathbf{H}_3$)

1.28 (3 H, d, *J* = 6.7 Hz, C$\mathbf{H}_3$)

1.25 (3 H, d, *J* = 6.7 Hz, C$\mathbf{H}_3$) ppm.

minor rotamer:

7.49–7.44 (2 H, m, 2 × Ar**H**)

7.36–7.23 (8 H, m, 8 × Ar**H**)

5.67 (1 H, br s, O**H**)

4.77 (2 H, s, C$\mathbf{H}_2$)

4.09 (1 H, sept, *J* = 6.7 Hz, C**H**)

1.84 (3 H, s, C$\mathbf{H}_3$)

1.20 (3 H, d, *J* = 6.7 Hz, C$\mathbf{H}_3$)

1.12 (3 H, d, *J* = 6.7 Hz, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

185.4 (**C**), 171.2 (**C**), 138.0 (**C**), 131.7 (**C**H), 128.8 (**C**H), 128.3 (**C**H), 128.0 (**C**H), 127.2 (**C**H), 125.6 (**C**H), 122.5 (**C**), 114.9 (**C**), 87.6 (**C**), 85.5 (**C**), 81.8 (**C**), 53.3 (**C**H), 46.8 (**C**H_2), 21.1 (**C**H_3), 20.9 (**C**H_3), 7.1 (**C**H_3) ppm.

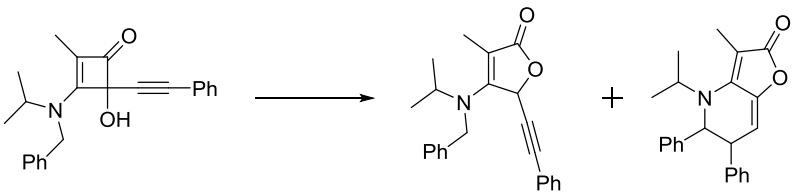
minor rotamer:

185.5 (**C**), 170.4 (**C**), 137.7 (**C**), 131.7 (**C**H), 128.2 (**C**H), 127.9 (**C**H), 127.8 (**C**H), 127.3 (**C**H), 125.6 (**C**H), 122.2 (**C**), 114.2 (**C**), 88.2 (**C**), 85.3 (**C**), 82.2 (**C**), 52.2 (**C**H), 50.8 (**C**H_2), 21.4 (**C**H_3), 20.8 (**C**H_3), 8.3 (**C**H_3) ppm.

LRMS (ESI+) 346 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 346.1807, $C_{23}H_{24}NO_2$ $[M+H]^+$ requires 346.1802.

4-(benzyl(isopropyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25d)



4.24d
$C_{23}H_{23}NO_2$
Mol Wt: 345.18

4.25d
$C_{23}H_{23}NO_2$
Mol Wt: 345.18

4.26d
$C_{23}H_{23}NO_2$
Mol Wt: 345.18

Aminocyclobutenone **4.24d** (180 mg, 0.52 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/Pet) to afford firstly the dihydrofuropyridinone **4.26d** (21 mg, 0.06 mmol, 11%) as a yellow oil, then the title compound (145 mg, 0.42 mmol, 81%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2964 (br), 1732 (s), 1604 (s), 1444 (m), 1427 (s), 1348 (m), 1286 (w), 1172 (w), 1074 (m), 1037 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.47–7.44 (2 H, m, 2 × Ar**H**)

7.38–7.32 (5 H, m, 5 × Ar**H**)

7.27–7.23 (3 H, m, 3 × Ar**H**)

5.53 (1 H, s, C**H**)

4.82 (1 H, d, *J* = 17.9 Hz, C**H**H)

4.49 (1 H, d, *J* = 17.7 Hz, CH**H**)

4.32 (1 H, sept, *J* = 6.6 Hz, C**H**)

1.79 (3 H, s, C**H**$_3$)

1.27 (3 H, d, *J* = 6.6 Hz, C**H**$_3$)

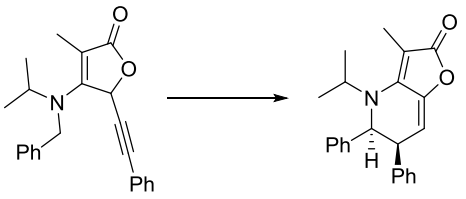
1.24 (3 H, d, *J* = 6.6 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.3 (**C**), 161.6 (**C**), 138.9 (**C**), 131.7 (**C**H), 129.2 (**C**H), 128.8 (**C**H), 128.4 (**C**H), 127.2 (**C**H), 125.6 (**C**H), 121.4 (**C**), 90.3 (**C**), 87.2 (**C**), 82.6 (**C**), 67.2 (**C**H), 52.1 (**C**H), 46.2 (**C**H$_2$), 21.3 (**C**H$_3$), 20.8 (**C**H$_3$), 9.8 (**C**H$_3$) ppm.

LRMS (ESI+) 346 ([M+H]$^+$, 100%), 713 ([2M+Na]$^+$, 50%),

HRMS (ESI+) Found 346.1793, $C_{23}H_{24}NO_2$ [M+H]$^+$ requires 346.1802.

rel-(5S,6S)-4-Isopropyl-3-methyl-5,6-diphenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26d)



4.25d
$C_{23}H_{23}NO_2$
Mol Wt: 345.18

4.26d
$C_{23}H_{23}NO_2$
Mol Wt: 345.18

Furanone **4.25d** (100 mg, 0.29 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–40% Et_2O/Pet) to afford the title compound (79 mg, 0.23 mmol, 77%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2971 (br), 1747 (s), 1693 (w), 1599 (s), 1446 (m), 1308 (m), 1276 (w), 1232 (w), 1035 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.41–7.28 (10 H, m, 10 × Ar**H**)

5.33 (1 H, d, J = 6.1 Hz, C**H**)

4.45 (1 H, br s, C**H**)

4.26 (1 H, sept, *J* = 6.7 Hz, C**H**)

3.75 (1 H, d, *J* = 6.0 Hz, C**H**)

2.06 (3 H, s, C**H**$_3$)

0.81 (3 H, d, *J* = 6.9 Hz, C**H**$_3$)

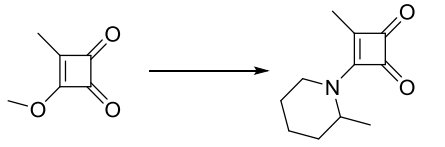
0.66 (3 H, d, *J* = 6.5 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.7 (**C**), 150.0 (**C**), 146.1 (**C**), 143.3 (**C**), 140.9 (**C**), 128.8 (**C**H), 128.7 (**C**H), 127.8 (**C**H), 127.7 (**C**H), 127.6 (**C**H), 125.8 (**C**H), 99.3 (**C**H), 87.5 (**C**), 61.5 (**C**H), 49.8 (**C**H), 47.8 (**C**H), 21.3 (**C**H$_3$), 20.4 (**C**H$_3$), 9.5 (**C**H$_3$) ppm.

LRMS (ESI+) 346 ([M+H]$^+$, 100%), 713 ([2M+Na]$^+$, 30%).

HRMS (ESI+) Found 346.1791, $C_{23}H_{24}NO_2$ [M+H]$^+$ requires 346.1802.

3-methyl-4-(2-methylpiperidin-1-yl)cyclobut-3-ene-1,2-dione (4.23e)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

4.23e
$C_{11}H_{15}NO_2$
Mol Wt: 193.11

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (268 mg, 2.13 mmol) in MeOH (40 mL) at RT was added 2-methylpiperidine (0.25 mL, 2.13 mmol). After stirring at RT for 4 h the solution was concentrated under reduced pressure and purified by column chromatography (EtOAc) to afford the title compound (230 mg, 1.19 mmol, 57%) as a yellow solid.

MP 86–87 °C.

FT-IR (ν_{max}, $CHCl_3$) 2941 (br), 2862 (br), 1774 (s), 1724 (s), 1579 (vs), 1440 (s), 1280 (m), 1060 (m), 1035 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

4.48 (1 H, br dd, *J* = 13.5 Hz, 2.8 Hz, NC**H**H)

4.03 (1 H, m, NC**H**)

3.17 (1 H, td, *J* = 13.2 Hz, 2.9 Hz, NCH**H**)

2.18 (3 H, s, C**H**$_3$)

1.82–1.44 (6 H, m, 3 × C**H**$_2$)

1.29 (3 H, d, *J* = 7.0 Hz, C**H**$_3$) ppm.

minor rotamer:

4.95–4.89 (1 H, m, NC**H**)

3.62–3.54 (1 H, m, C**H**H)

3.38 (1H, td, *J* = 13.1 Hz, 2.9 Hz, NCH**H**)

2.17 (3 H, s, C**H**$_3$)

1.82–1.44 (6 H, m, 3 × C**H**$_2$)

1.24 (3 H, d, *J* = 7.0 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

193.3 (**C**), 191.3 (**C**), 181.1 (**C**), 165.3 (**C**), 51.4 (**C**H), 41.9 (**C**H$_2$), 29.7 (**C**H$_2$), 25.4 (**C**H$_2$), 17.5 (**C**H$_2$), 16.5 (**C**H$_3$), 10.6 (**C**H$_3$) ppm.

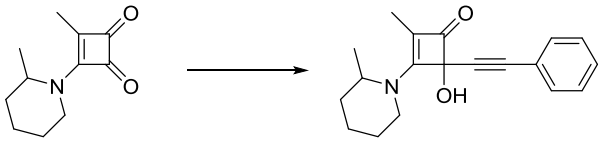
minor rotamer:

192.9 (**C**), 191.3 (**C**), 181.2 (**C**), 165.7 (**C**), 50.1 (**C**H), 43.1 (**C**H$_2$), 29.8 (**C**H$_2$), 25.5 (**C**H$_2$), 17.4 (**C**H$_2$), 16.7 (**C**H$_3$), 10.8 (**C**H$_3$) ppm.

LRMS (ESI+) 194 ($[M+H]^+$, 100%), 387 ($[2M+H]^+$, 30%).

HRMS (ESI+) Found 194.1178, $C_{11}H_{16}NO_2$ $[M+H]^+$ requires 194.1178.

4-Hydroxy-2-methyl-3-(2-methylpiperidin-1-yl)-4-(phenylethynyl)cyclobut-2-enone (4.24e) 256



4.23e
$C_{11}H_{15}NO_2$
Mol Wt: 193.11

4.24e
$C_{19}H_{22}NO_2$
Mol Wt 295.16

To a solution of phenylacetylene (0.19 mL, 1.68 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 0.67 mL, 1.68 mmol) dropwise. After 20 min the solution was added *via* cannula to a cooled solution of 3-methyl-4-(2-methylpiperidin-1-yl)cyclobut-3-ene-1,2-dione **4.23e** (250 mg, 1.29 mmol) in THF (40 mL) at –78 °C. After a further 3 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–10% acetone/DCM) to afford the title compound (310 mg, 1.07 mmol, 83%) as a yellow oil and 1 : 1 mixture of diastereoisomer.

FT-IR (ν_{max}, $CHCl_3$) 3234 (br), 2942 (w), 1142 (w), 1556 (vs), 1442 (m), 1282 (m), 1184 (w), 1134 (m), 1089 (w), 1020 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) each diastereoisomer exhibited rotamers in a ca. 2 : 1 ratio.

^{1}H-NMR was reported as a mixture.

7.41–7.34 (4 H, m, 2 × Ar**H**)

7.24–7.16 (6 H, m, 3 × Ar**H**)

6.04–5.88 (2H, m, OH)

4.68–4.54 (1 H, m, NC**H**)

4.14–4.01 (2 H, m, NC**H** + NC**H**H)

3.69–3.57 (1 H, m, NC**H**H)

3.39–3.25 (2 H, m, 2 × NCH**H**)

1.97–1.78 (2 H, m, 2 × C**H**H)

1.75–1.50 (10 H, m, 10 × C**H**H & CH**H**)

1.69 (6 H, s, 2 × C**H**$_3$)

1.41–1.27 (6 H, m, 2 × C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) each diastereoisomer exhibited rotamers.

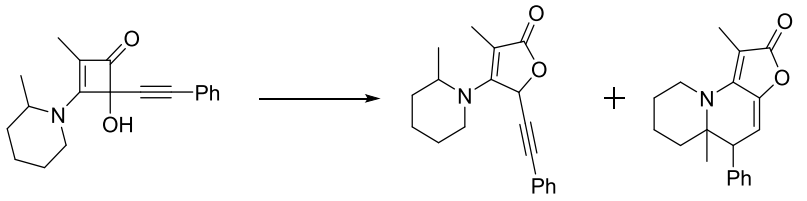
^{13}C-NMR was reported as a mixture.

185.0, 184.6 and 184.5 (**C**), 168.9, 168.6 and 168.5 (**C**), 131.6 and 131.5 (**C**H), 128.1 (**C**H), 127.8 (**C**H), 122.5 and 122.4 (**C**), 112.9, 112.8 and 112.6 (**C**), 87.3, 87.2, 87.0 and 87.0 (**C**), 85.5 and 85.3 (**C**), 81.6 and 81.2 (**C**), 53.8, 52.1, 51.7 and 50.6 (**C**H), 43.6, 43.4, 42.7 and 42.6 (**C**H_2), 30.1, 29.9, 29.8 and 29.5 (**C**H_2), 25.7, 25.5 and 25.3 (**C**H_2), 17.8 and 17.7 (**C**H_2), 16.6, 16.3 and 15.8 (**C**H_3), 7.9, 7.8 and 7.7 (**C**H_3) ppm.

LRMS (ESI+) 296 ($[M+H]^+$, 100%), 591 ($[2M+H]^+$, 70%),

HRMS (ESI+) Found 296.1647, $C_{19}H_{22}NO_2$ $[M+H]^+$ requires 296.1645.

3-methyl-4-(2-methylpiperidin-1-yl)-5-(phenylethynyl)furan-2(5H)-one (4.25e)



4.24e
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

4.25e
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

4.26e
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

The diastereoisomeric mixture of aminocyclobutenone **4.24e** (253 mg, 0.85 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/petrol) to afford firstly the title compound **4.26e** (57 mg, 0.19 mmol, 22%) as a yellow oil, then the title compound (164 mg, 0.55 mmol, 65%) as a yellow oil and 1 : 1 mixture of diastereoisomers. The diastereoisomers were separated by HPLC (15% EtOAc/hexane) for analysis.

The first diastereoisomer exhibited

FT-IR (ν_{max}, $CHCl_3$) 2937 (br), 1734 (s), 1608 (s), 1429 (m), 1288 (m), 1080 (m), 1032 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.45–7.42 (2 H, m, 2 × Ar**H**)

7.35–7.30 (3 H, m, 3 × Ar**H**)

5.51 (1 H, s, C**H**)

4.29 (1 H, m, C**H**)

3.70 (1 H, br d, *J* = 12.4 Hz, C**H**H)

3.27 (1 H, br dd, *J* = 12.8, 2.7 Hz, CH**H**)

1.96 (3 H, s, C$\mathbf{H}_3$)

1.90–1.54 (6 H, m, 3 × C$\mathbf{H}_2$)

1.29 (3 H, d, *J* = 6.9 Hz, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.2 (**C**), 160.9 (**C**), 131.4 (**C**H), 128.7 (**C**H), 128.1 (**C**H), 121.3 (**C**), 88.9 (**C**), 86.6 (**C**), 82.1 (**C**), 66.7 (**C**H), 50.0 (**C**H), 43.0 (**C**H_2), 29.7 (**C**H_2), 25.7 (**C**H_2), 17.7 (**C**H_2), 15.7 (**C**H_3), 10.3 (**C**H_3) ppm.

LRMS (ESI+) 296 $[M+H]^+$.

HRMS (ESI+) Found 296.1648, $C_{19}H_{22}NO_2$ $[M+H]^+$ requires 296.1645.

The second diastereoisomer exhibited

FT-IR (ν_{max}, $CHCl_3$) 2937 (br), 1732 (s), 1606 (s), 1437 (m), 1292 (m), 1082 (m), 1032 (m); cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.45–7.42 (2 H, m, 2 × Ar**H**)

7.35–7.30 (3 H, m, 3 × Ar**H**)

5.51 (1 H, s, C**H**)

4.29 (1 H, m, C**H**)

3.75 (1 H, br d, *J* = 13.5 Hz, C**H**H)

3.25 (1 H, m, CH**H**)

1.98 (3 H, s, C$\mathbf{H}_3$)

1.90–1.57 (6 H, m, 3 × C$\mathbf{H}_2$)

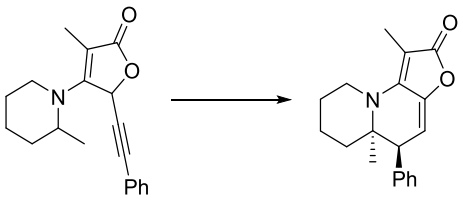
1.37 (3 H, d, *J* = 6.9 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.8 (**C**), 161.0 (**C**), 132.1 (**C**H), 129.4 (**C**H), 128.7 (**C**H), 121.9 (**C**), 87.8 (**C**), 87.1 (**C**), 83.1 (**C**), 67.3 (**C**H), 50.8 (**C**H), 43.1 (**C**H$_2$), 30.6 (**C**H$_2$), 26.4 (**C**H$_2$), 18.7 (**C**H$_2$), 16.7 (**C**H$_3$), 10.7 (**C**H$_3$) ppm.

LRMS (ESI+) 296 ([M+H]$^+$, 100%), 613 ([M+H]$^+$, 30%).

HRMS (ESI+) Found 296.1653, $C_{19}H_{22}NO_2$ [M+H]$^+$ requires 296.1645.

rel-(5S,5aR)-1,5a-Dimethyl-5-phenyl-5,5a,6,7,8,9-hexahydro-2H-furo[2,3-c]quinolizin-2-one (4.26e)



4.25e
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

4.26e
$C_{19}H_{21}NO_2$
Mol Wt: 295.16

The diastereoisomeric mixture of 5H-furanones **4.25e** (80 mg, 0.27 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–50% Et_2O/Pet) to afford the title compound (63 mg, 0.21 mmol, 79%) as a yellow oil and a 15 : 1 mixture of diastereoisomers. The major diastereoisomers was separated by HPLC (15% EtOAc/hexane) as a yellow solid.

MP 251–252 °C.

FT-IR (ν_{max}, $CHCl_3$) 2947 (br), 1743 (s), 1695 (m), 1593 (s), 1493 (w), 1429 (m), 1326 (m), 1288 (w), 1269 (w), 1240 (m), 1186 (w), 1143 (m), 1054 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.33–7.28 (3 H, m, 3 × Ar**H**)

7.15–7.13 (2 H, m, 2 × Ar**H**)

5.61 (1 H, d, *J* = 6.4 Hz, C**H**)

3.99 (1 H, m, C**H**H)

3.32 (1 H, d, *J* = 6.2 Hz, PhC**H**)

3.23 (1 H, td, *J* = 12.9 Hz, 3.4 Hz, CH**H**)

2.09 (3 H, s, C**H**$_3$)

1.71 (1 H, m, C**H**H)

1.54 (1 H, m, C**H**H)

1.44 (3 H, s, C**H**$_3$)

1.27-1.23 (3 H, m, 3 × CH**H**)

1.16 (1 H, m, C**H**H) ppm.

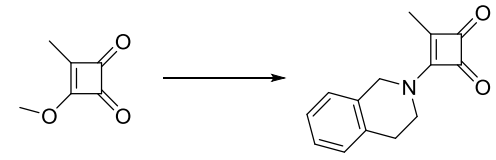
N.O.E. (500MHz,$CDCl_3$) Irradiation of the signal at δ = 3.32 (PhC**H**) ppm led to enhancement at δ = 7.15–7.13 (ArH), 5.61 (=C**H**), 1.44 (N-C-C**H**$_3$) and 1.25 (C-CH**H**) ppm.

δ_C (100 MHz, $CDCl_3$) 172.4 (**C**), 161.1 (**C**), 143.6 (**C**), 138.6 (**C**), 129.4 (**C**H), 128.4 (**C**H), 127.5 (**C**H), 104.4 (**C**H), 92.7 (**C**), 58.9 (**C**), 51.8 (**C**H), 44.3 (**C**H$_2$), 34.7 (**C**H$_2$), 24.4 (**C**H$_2$), 21.1 (**C**H$_3$), 19.2 (**C**H$_2$), 10.1 (**C**H$_3$) ppm.

LRMS (ESI+) 296 ($[M+H]^+$, 100%), 318 ($[M+Na]^+$, 100%).

HRMS (ESI+) Found 296.1648, $C_{19}H_{22}NO_2$ $[M+H]^+$ requires 296.1645.

3-(3,4-dihydroisoquinolin-2(1H)-yl)-4-methylcyclobutene-1,2-dione (4.23f)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

4.23f
$C_{14}H_{13}NO_2$
Mol Wt: 227.10

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (142 mg, 1.13 mmol) in MeOH (50 mL) at RT was added 1,2,3,4-tetrahydroisoquinoline (0.14 mL, 1.13 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (20%–60% acetone/cyclohexane) to afford the title compound (250 mg, 1.10 mmol, 97%) as a yellow solid.

MP 161–162 °C.

FT-IR (ν_{max}, $CHCl_3$) 2915 (br), 1778 (s), 1724 (s), 1592 (vs), 1573 (vs), 1497 (m), 1435 (s), 1300 (m), 1261 (s), 1072 (m), 1049 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

7.24–7.10 (4 H, m, 4 × Ar**H**)

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

4.18 (2 H, t, *J* = 5.9 Hz, NC**H**$_2$CH$_2$)

2.98 (2 H, t, *J* = 5.9 Hz, NCH$_2$C**H**$_2$)

2.35 (3 H, s, C**H**$_3$) ppm.

minor rotamer:

7.24–7.10 (4 H, m, 4 × Ar**H**)

5.08 (2 H, s, NC**H**$_2$)

3.85 (2 H, t, *J* = 6.2 Hz, NC**H**$_2$CH$_2$)

3.04 (2 H, t, *J* = 6.2 Hz, NCH$_2$C**H**$_2$)

2.32 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

193.1 (**C**), 191.8 (**C**), 182.2 (**C**), 167.1 (**C**), 133.4 (**C**), 132.2 (**C**), 129.4 (**C**H), 127.6 (**C**H), 127.2 (**C**H), 126.2 (**C**H), 49.2 (**C**H$_2$), 46.1 (**C**H$_2$), 29.2 (**C**H$_2$), 11.1 (**C**H$_3$) ppm.

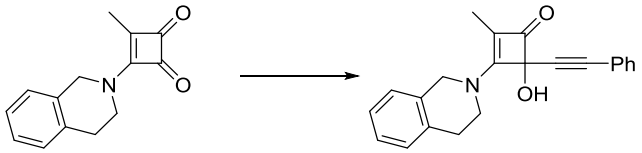
minor rotamer:

193.3 (**C**), 191.7 (**C**), 182.1 (**C**), 166.5 (**C**), 132.9 (**C**), 130.4 (**C**), 128.9 (**C**H), 127.6 (**C**H), 127.1 (**C**H), 126.3 (**C**H), 48.3 (**C**H$_2$), 44.6 (**C**H$_2$), 28.7 (**C**H$_2$), 11.0 (**C**H$_3$) ppm.

LRMS (ESI+) 228 ($[M+H]^+$, 100%), 455 ($[2M+H]^+$, 100%).

HRMS (ESI+) Found 228.1017, $C_{14}H_{14}NO_2$ $[M+H]^+$ requires 228.1019.

4-Hydroxy-2-methyl-4-(phenylethynyl)-3-(1,2,3,4-tetrahydroisoquinolin-2-yl)-cyclobut-2-enone (4.24f)



4.23f
$C_{14}H_{13}NO_2$
Mol Wt 227.10

4.24f
$C_{22}H_{19}NO_2$
Mol Wt 329.15

To a solution of phenylacetylene (0.13 mL, 1.15 mol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexane, 0.50 mL, 1.15 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 4-methyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-cyclobutene-1,2-dione **4.23f** (200 mg, 0.88 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–30% acetone/DCM) to afford the title compound (235 mg, 0.71 mmol, 81%) as a yellow solid.

MP Decomposed over 120 °C.

FT-IR (ν_{max}, $CHCl_3$) 3010 (br), 1749 (w), 1591 (s), 1567 (vs), 1489 (w), 1452 (m), 1265 (w), 1215 (w), 1131 (w), 1083 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) major rotamer:

7.42–7.07 (9 H, m, 9 × Ar**H**)

6.26 (1 H, s, O**H**)

4.79–4.70 (2 H, m, NC**H**$_2$)

4.14–3.91 (2 H, m, NC**H**$_2$CH$_2$)

3.10–2.98 (2 H, m, NCH$_2$C**H**$_2$)

1.83 (3 H, s, C**H**$_3$) ppm.

minor rotamer:

7.42–7.07 (9 H, m, 9 × Ar**H**)

6.26 (1 H, s, O**H**)

5.03–4.93 (2 H, m, NC**H**$_2$)

3.84–3.73 (2 H, m, NC**H**$_2$CH$_2$)

3.10–2.98 (2 H, m, NCH$_2$C**H**$_2$)

1.81 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) major rotamer:

185.3 (**C**), 169.2 (**C**), 133.9 (**C**), 131.9 (**C**H), 131.3 (**C**), 129.2 (**C**H), 128.5 (**C**H), 128.2 (**C**H), 127.1 (**C**H), 126.6 (**C**H), 126.1 (**C**H), 122.5 (**C**), 114.6 (**C**), 87.8 (**C**), 85.5 (**C**), 81.7 (**C**), 49.0 (**C**H$_2$), 46.1 (**C**H$_2$), 29.1 (**C**H$_2$), 8.1 (**C**H$_3$) ppm.

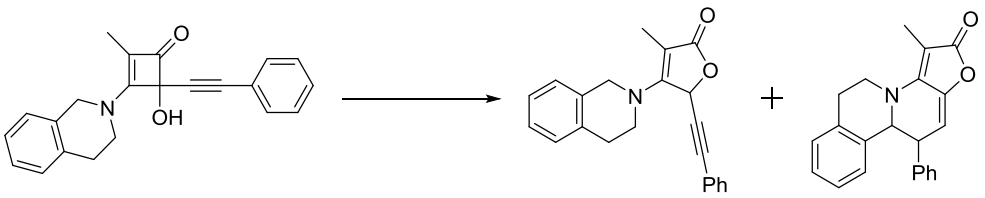
minor rotamer:

185.4 (**C**), 169.1 (**C**), 133.4 (**C**), 132.7 (**C**H), 131.9 (**C**), 128.6 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 127.1 (**C**H), 126.8 (**C**H), 126.3 (**C**H), 122.4 (**C**), 114.5 (**C**), 88.2 (**C**), 85.4 (**C**), 81.8 (**C**), 49.2 (**C**H$_2$), 45.4 (**C**H$_2$), 28.7 (**C**H$_2$), 8.1 (**C**H$_3$) ppm.

LRMS (ESI+) 330 ([M+H]$^+$, 100%).

HRMS (ESI+) Found 330.1484, $C_{22}H_{20}NO_2$ [M+H]$^+$ requires 330.1489.

4-(3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25f)



4.24f
$C_{22}H_{19}NO_2$
Mol Wt 329.39

4.25f
$C_{22}H_{19}NO_2$
Mol Wt 329.39

4.26f
$C_{22}H_{19}NO_2$
Mol Wt 329.39

Cyclobutenone **4.24f** (160 mg, 0.49 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 hour. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford firstly the title compound **4.26f** as a yellow solid (80 mg, 0.24 mmol, 50%) and afford the title compound **4.25f** as a yellow solid (30 mg, 0.09 mmol, 19%).

MP Decomposed over 140 °C.

FT-IR (ν_{max}, $CHCl_3$) 3025 (w), 2922 (br), 1749 (s), 1618 (s), 1491(w), 1448 (m), 1335 (w), 1302 (w), 1186 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.37–7.10 (9 H, m, 9 × Ar**H**)

5.64 (1 H, s, C**H**)

4.85 (1 H, d, *J* = 16.1 Hz, C**H**H)

4.79 (1 H, d, *J* = 16.1 Hz, CH**H**)

3.93 (1 H, dd, *J* = 13.1, 5.6 Hz, C**H**H)

3.76 (1 H, ddd, *J* = 13.0, 8.1, 4.5 Hz, CH**H**)

3.07 (1 H, m, C**H**H)

2.96 (1 H, dt, *J* = 16.0, 5.61 Hz, CH**H**)

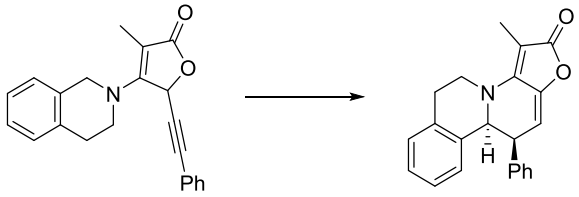
2.08 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.1 (**C**), 160.5 (**C**), 133.7 (**C**), 132.4 (**C**), 131.7 (**C**H), 129.1 (**C**H), 128.8 (**C**H), 128.3 (**C**H), 127.0 (**C**H), 126.6 (**C**H), 126.0 (**C**H), 121.3 (**C**), 89.6 (**C**), 87.5 (**C**), 82.1 (**C**), 66.9 (**C**H), 50.0 (**C**H_2), 46.0 (**C**H_2), 28.9 (**C**H_2), 10.3 (**C**H_3) ppm.

LRMS (ESI+) 330 ($[M+H]^+$, 100%), 352 ($[M+Na]^+$, 40%).

HRMS (ESI+) Found 330.1495, $C_{22}H_{20}NO_2$ $[M+H]^+$ requires 330.1494.

rel-(10bS,11S)-3-Methyl-11-phenyl-5,6,10b,11-tetrahydro-2H-furo[2',3':5,6]pyrido[2,1-a]isoquinolin-2-one (4.26f)



4.25f
$C_{22}H_{19}NO_2$
Mol Wt 329.39

4.26f
$C_{22}H_{19}NO_2$
Mol Wt 329.39

Furanone **4.25f** (50 mg, 0.15 mmol) in 1,4-dioxane (10 mL) was heated at 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford the title compound (38 mg, 0.12 mmol, 80%) as a yellow solid and a 10 : 3 mixture of diastereoisomers. Recrystalization (Et_2O/Pet) gave the major diastereoisomer as a yellow solid.

MP Decomposed over 140 °C (Et_2O/Pet).

FT-IR (ν_{max}, $CHCl_3$) 3020 (br), 2927 (br), 1734 (s), 1616 (s), 1486 (w), 1442 (m), 1290 (m), 1091 (w), 1076 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.33–7.29 (2 H, m, 2 × Ar**H**)

7.15–7.08 (2 H, m, 2 × Ar**H**)

7.05–7.01 (2 H, m, 2 × Ar**H**)

6.86 (1H, d, *J* = 7.6 Hz, Ar**H**)

6.76–6.65 (2 H, m, 2 × Ar**H**)

5.85 (1 H, d, *J* = 6.4 Hz, C**H**)

5.15 (1 H, d, *J* = 4.2 Hz, C**H**)

4.09 (1 H, ddd, *J* = 11.6, 4.8, 2.1 Hz, C**H**H)

3.88 (1 H, dd, *J* = 6.4, 4.3 Hz, C**H**)

3.39 (1 H, td, *J* = 12.0, 2.7 Hz, CH**H**)

2.41 (1 H, dt, *J* = 15.3, 2.3 Hz, C**H**H)

2.12 (1 H, obscured, CH**H**)

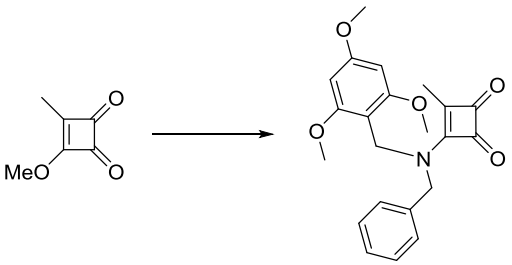
2.10 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 172.5 (**C**), 152.1 (**C**), 146.3 (**C**), 135.3 (**C**), 135.1 (**C**), 133.4 (**C**), 129.5 (**C**H), 128.5 (**C**H), 127.9 (**C**H), 127.7 (**C**H), 127.2 (**C**H), 127.0 (**C**H), 126.9 (**C**H), 106.0 (**C**H), 90.7 (**C**), 61.4 (**C**H), 46.7 (**C**H), 44.0 (**C**H$_2$), 29.2 (**C**H$_2$), 9.3 (**C**H$_3$) ppm.

LRMS (ESI+) 330 ([M+H]$^+$, 100%), 681 ([2M+Na]$^+$, 80%).

HRMS (ESI+) Found 330.1490, $C_{22}H_{20}NO_2$ [M+H]$^+$ requires 330.1494.

3-(benzyl(2,4,6-trimethoxybenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione (4.23g)



3.2a
$C_6H_6O_3$
Mol Wt:126.11

4.23g
$C_{22}H_{23}NO_5$
Mol Wt: 381.43

To a solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **3.2a** (252 mg, 2.00 mmol) in MeOH (50 mL) was added *N*-benzyl-1-(2,4,6-trimethoxyphenyl)methanamine (574 mg, 2.02 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (0–3% acetone/DCM) to afford the title compound (607 mg, 1.59 mmol, 80%) as yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2943 (br), 1780 (m), 1728 (m), 1591 (vs), 1454 (m), 1438 (m), 1205 (w), 1151 (m), 1126 (m), 1056 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) Major rotamer

7.35–7.29 (3 H, m, 3 × Ar**H**)

7.22–7.20 (2 H, m, 2 × Ar**H**)

6.11 (2 H, s, 2 × Ar**H**)

4.68 (2 H, s, C**H**$_2$)

4.58 (2 H, s, C**H**$_2$)

3.84 (3 H, s, OC**H**$_3$)

3.74 (6 H, s, 2 × OC**H**$_3$)

2.44 (3 H, s, C**H**$_3$) ppm.

Minor rotamer

7.35–7.29 (3 H, m, 3 × Ar**H**)

7.10 (2 H, d, *J* = 7.0 Hz, 2 × Ar**H**)

6.06 (2 H, s, 2 × Ar**H**)

5.01 (2 H, s, C**H**$_2$)

4.42 (2 H, s, C**H**$_2$)

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

3.71 (6 H, s, 2 × OC**H**$_3$)

2.10 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) Major rotamer

193.3 (**C**), 191.9 (**C**), 183.6 (**C**), 167.3 (**C**), 165.1 (**C**), 162.1 (**C**), 159.9 (**C**), 136.3 (**C**), 128.7 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 101.9 (**C**), 90.3 (**C**H), 55.5 (O**C**H$_3$), 55.3 (O**C**H$_3$), 50.5 (**C**H$_2$), 42.3 (**C**H$_2$), 11.3 (**C**H$_3$) ppm.

Minor rotamer

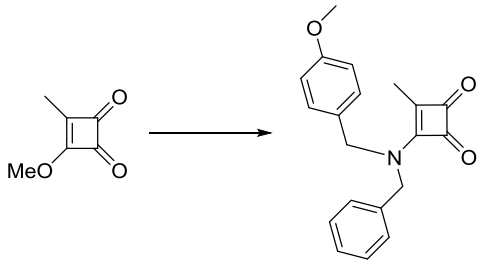
192.6 (**C**), 192.2 (**C**), 184.7 (**C**), 164.8 (**C**), 165.1 (**C**), 161.9 (**C**), 160.2 (**C**), 136.3 (**C**), 128.7 (**C**H), 127.8 (**C**H), 126.3 (**C**H), 103.2 (**C**), 90.3

(**C**H), 55.4 (O**C**H_3), 55.3 (O**C**H_3), 51.9 (**C**H_2), 42.1 (**C**H_2), 10.5 (**C**H_3) ppm.

LRMS (ESI+) 382 ([M+H]$^+$, 100%), 763 ([2M+H]$^+$, 80%).

HRMS (ESI+) Found 382.1649, $C_{22}H_{24}NO_5$ [M+H]$^+$ requires 382.1649.

3-(benzyl(4-methoxybenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione (4.23h)



3.2a
$C_6H_6O_3$
Mol Wt:126.11

4.23h
$C_{20}H_{19}NO_3$
Mol Wt: 321.38

To a solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **3.2a** (320 mg, 2.54 mmol) in MeOH (50 mL) was added *N*-benzyl-1-(4-methoxyphenyl)methanamine (578 mg, 2.54 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (EA) to afford the title compound (835 mg, 2.60 mmol, 100%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2933 (br), 1780 (s), 1730 (s), 1591 (s), 1577 (s), 1510 (s), 1440 (m), 1363 (w), 1241 (s), 1176 (m), 1066 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.43–7.35 (3 H, m, 3 × Ar**H**)

7.24 (1 H, m, Ar**H**)

7.17 (2 H, d, *J* = 8.3 Hz, 2 × Ar**H**)

7.09 (1 H, d, *J* = 8.6 Hz, Ar**H**)

6.89 (2 H, d, *J* = 8.6, Ar**H**)

4.81 (2 H, s, C**H**$_2$)

4.48 (2 H, s, C**H**$_2$)

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

2.20 (3 H, s, C**H**$_3$) ppm.

with additional signals attributed to the minor rotamer at:

6.94 (2 H, d, *J* = 8.6, Ar**H**)

4.84 (2 H, s, C**H**$_2$)

4.42 (2 H, s, C**H**$_2$)

3.83 (3 H, s, OC**H**$_3$)

2.25 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 191.7 (**C**), 183.5 (**C**), 167.0 (**C**), 159.7 (**C**), 134.5 (**C**), 130.1 (**C**H), 129.3 (**C**H), 129.0 (**C**H), 128.5 (**C**H), 126.9 (**C**H), 126.7 (**C**), 114.3 (**C**H), 55.27 (O**C**H$_3$), 52.0 (**C**H$_2$), 51.6 (**C**H$_2$), 10.6 (**C**H$_3$) ppm.

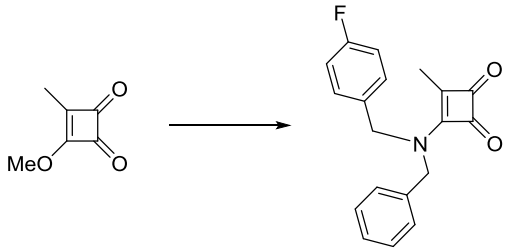
with additional signals attributed to the minor rotamer at:

192.9 (**C**), 183.4 (**C**), 166.8 (**C**), 134.8 (**C**), 128.6 (**C**H), 126.1 (**C**), 114.7 (**C**H), 55.32 (**C**H), 51.8 (**C**H$_2$), 51.7 (**C**H$_2$), 10.8 (**C**H$_3$) ppm.

LRMS (ESI+) 322 ([M+H]$^+$, 100%), 643 ([2M+H]$^+$, 60%).

HRMS (ESI+) Found 322.1433, $C_{20}H_{20}NO_3$ [M+H]$^+$ requires 322.1438.

3-(benzyl(4-fluorobenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione (4.23i)



3.2a
$C_6H_6O_3$
Mol Wt:126.11

4.23i
$C_{19}H_{16}FNO_2$
Mol Wt: 309.34

To a solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **3.2a** (240 mg, 1.90 mmol) in MeOH (20 mL) was added *N*-benzyl-1-(4-fluorophenyl)methanamine (409 mg, 1.91 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column

chromatography (30–80% Et_2O/cyclohexane) to afford the title compound (562 mg, 1.81 mmol, 96%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3012 (br), 1783 (m), 1731 (m), 1708 (m), 1594 (s), 1561 (s), 1486 (m), 1442 (s), 1403 (m), 1253 (m), 1217 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.44-7.37 (3 H, m, 3 × Ar**H**)

7.24–7.21 (2 H, m, 2 × Ar**H**)

7.17–7.04 (4 H, m, 4 × Ar**H**)

4.85 (2 H, s, C**H**$_2$)

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

2.22 (3 H, s, C**H**$_3$) ppm.

with additional signals attributed to the minor rotamer at:

4.86 (2 H, s, C**H**$_2$)

4.47 (2 H, s, C**H**$_2$)

2.23 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) Major rotamer:

192.9 (**C**), 191.66 (**C**), 183.60 (**C**), 167.4 (**C**), 162.7 (**C**, d, $J_{C\text{-}F}$ =248 Hz), 134.3 (**C**), 130.6 (**C**H, d, $J_{C\text{-}F}$ =8 Hz), 130.6-103.5 (obscured **C**), 129.4 (**C**H), 128.6 (**C**H), 126.9 (**C**H), 115.9 (**C**H, d, $J_{C\text{-}F}$ = 21 Hz), 52.3 (**C**H$_2$), 51.4 (**C**H$_2$), 10.7 (**C**H$_3$) ppm.

minor rotamer:

192.8 (**C**), 191.73 (**C**), 183.63 (**C**), 167.0 (**C**), 162.6 (**C**, d, $J_{C\text{-}F}$ =248 Hz), 134.6 (**C**), 130.2 (**C**, d, $J_{C\text{-}F}$ =3 Hz), 129.1 (**C**H), 128.8 (**C**H, d, $J_{C\text{-}F}$ =8 Hz), 128.6 (**C**H), 126.9 (**C**H), 116.4 (**C**H, d, $J_{C\text{-}F}$ = 21 Hz), 52.1 (**C**H$_2$), 51.7 (**C**H$_2$), 10.7 (**C**H$_3$) ppm.

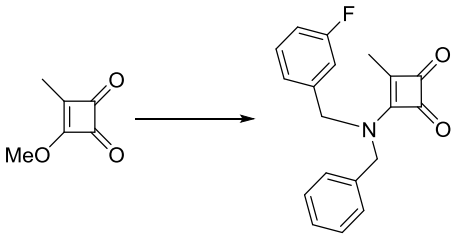
δ_F (376 MHz, $CDCl_3$) Major rotamer: –113.03 (F. m, Ar**F**)

Minor rotamer: –112.92 (F. m, Ar**F**).

LRMS (ESI+) 310 $[M+H]^+$.

HRMS (ESI+) Found 310.1241, $C_{19}H_{17}FNO_2$ $[M+H]^+$ requires 310.1238.

3-(benzyl(3-fluorobenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione (4.23j)



3.2a
$C_6H_6O_3$
Mol Wt:126.11

4.23j
$C_{19}H_{16}FNO_2$
Mol Wt: 309.34

To a solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **3.2a** (300 mg, 2.38 mmol) in MeOH (50 mL) was added *N*-benzyl-1-(3-fluorophenyl)methanamine (510 mg, 2.38 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (0–5% acetone/DCM) to afford the title compound (750 mg, 2.31 mmol, 97%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3230 (br), 1747 (m), 1587 (s), 1566 (vs), 1508 (m), 1442 (m), 1417 (w), 1363 (w), 1223 (w), 1157 (w), 1132 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.44–7.32 (4 H, m, 4 × Ar**H**)

7.25–7.15 (2 H, m, 2 × Ar**H**)

7.10–7.00 (1 H, m, Ar**H**)

6.95–6.90 (1 H, m, Ar**H**)

6.88–6.83 (1 H, m, Ar**H**)

4.86 (2 H, s, C**H**$_2$)

4.51 (2 H, s, C**H**$_2$)

2.23 (3 H, s, C**H**$_3$) ppm.

with additional signals attributed to the minor rotamer at:

4.89 (2 H, s, C**H**$_2$)

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

2.20 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 192.8 (**C**), 191.66 (**C**), 183.7 (**C**), 167.5 (**C**), 163.0 (**C**, d, $J_{C\text{-}F}$ =248 Hz), 137.3 (**C**H, d, $J_{C\text{-}F}$ =7 Hz), 134.2 (**C**), 130.7 (**C**, d, $J_{C\text{-}F}$ =9 Hz), 129.4 (**C**H), 128.6 (**C**H), 126.9 (**C**H), 124.2 (**C**H, d, $J_{C\text{-}F}$ =3 Hz), 115.5 (**C**H, d, $J_{C\text{-}F}$ =21 Hz), 114.0 (**C**H), 52.6 (**C**H$_2$), 51.5 (**C**H$_2$), 10.7 (**C**H$_3$) ppm.

with additional signals attributed to the minor rotamer at:

192.7 (**C**), 191.73 (**C**), 183.8 (**C**), 167.2 (**C**), 163.0 (**C**, d, $J_{C\text{-}F}$ =249 Hz), 137.1 (**C**H, d, $J_{C\text{-}F}$ =7 Hz), 134.5 (**C**), 131.0 (**C**, d, $J_{C\text{-}F}$ =8 Hz), 129.1 (**C**H), 128.6 (**C**H), 126.9 (**C**H), 122.4 (**C**H, d, $J_{C\text{-}F}$ =3 Hz), 115.5 (**C**H, d, $J_{C\text{-}F}$ =22 Hz), 113.8 (**C**H), 52.5 (**C**H$_2$), 51.9 (**C**H$_2$), 10.6 (**C**H$_3$) ppm.

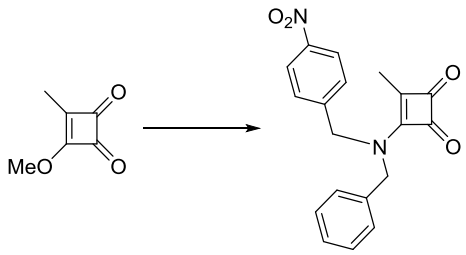
δ_F (376 MHz, $CDCl_3$) Major rotamer: –111.92 (F. s, Ar**F**) ppm;

Minor rotamer: –111.26 (F. s, Ar**F**) ppm.

LRMS (ESI+) 310 ([M+H]$^+$, 100%), 619 ([M+H]$^+$, 20%).

HRMS (ESI+) Found 310.1234, $C_{19}H_{17}FNO_2$ [M+H]$^+$ requires 310.1238.

3-(benzyl(4-nitrobenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione (4.23k)



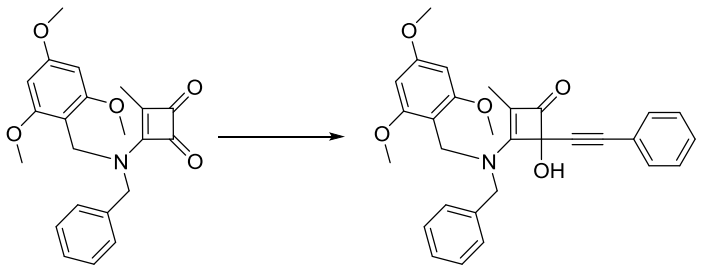
3.2a
$C_6H_6O_3$
Mol Wt:126.11

4.23k
$C_{19}H_{16}N_2O_4$
Mol Wt: 336.35

To a solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **3.2a** (310 mg, 2.46 mmol) in MeOH (50 mL) was added *N*-benzyl-1-(4-nitrophenyl)methanamine (595 mL, 2.47 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (80–100% Et_2O/Pet) to afford the title compound (580 mg, 1.72 mmol, 70%) as a yellow solid.

MP	132–134 °C.
FT-IR (ν_{max}, $CHCl_3$)	2837 (br), 1600 (w), 1514 (s), 1454 (w), 1342 (s), 1107 (w), 850 (w), 736 (w), 698 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	8.24–8.21 (2 H, m, 2 × Ar**H**)
	7.43–7.34 (5 H, m, 5 × Ar**H**)
	7.17–7.15 (2 H, m, 2 × Ar**H**)
	4.99 (2 H, s, C**H**$_2$)
	4.53 (2 H, s, C**H**$_2$)
	2.27 (3 H, s, C**H**$_3$) ppm.
	with additional signals attributed to the minor rotamer at:
	4.92 (2 H, s, C**H**$_2$)
	4.62 (2 H, s, C**H**$_2$)
	2.17 (3 H, s, C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	Major rotamer:
	192.9 (**C**), 191.5 (**C**), 183.8 (**C**), 168.2 (**C**), 147.9 (**C**), 142.1 (**C**), 134.2 (**C**), 129.5 (**C**H), 129.3 (**C**H), 128.8 (**C**H), 127.0 (**C**H), 124.2 (**C**H), 52.9 (**C**H_2), 51.3 (**C**H_2), 10.8 (**C**H_3) ppm.
	Minor rotamer:
	192.5 (**C**), 191.9 (**C**), 184.0 (**C**), 167.4 (**C**), 147.9 (**C**), 142.0 (**C**), 133.8 (**C**), 129.3 (**C**H), 129.2 (**C**H), 128.6 (**C**H), 127.6 (**C**H), 124.5 (**C**H), 53.1 (**C**H_2), 52.0 (**C**H_2), 10.6 (**C**H_3) ppm.
LRMS (ESI+)	337 ($[M+H]^+$, 100%).
HRMS (ESI+)	Found 337.1187, $C_{19}H_{17}N_2O_4$ $[M+H]^+$ requires 337.1183.

3-(benzyl(2,4,6-trimethoxybenzyl)amino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-enone (4.24g)



4.23g
$C_{22}H_{23}NO_5$
Mol Wt: 381.43

4.24g
$C_{30}H_{29}NO_5$
Mol Wt: 483.56

To a solution of phenylacetylene (0.14 mL, 1.26 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.54 mL, 1.26 mmol) dropwise. The solution was stirred at –78 °C for 10 min and added *via* cannula to a solution of 3-(benzyl(2,4,6-trimethoxybenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione **4.23g** (370 mg, 0.97 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–30% acetone/DCM) to afford the title compound (413 mg, 0.85 mmol, 88%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3246 (br), 2939 (w), 1745 (w), 1587 (m), 1564 (Vvs), 1497 (w), 1490 (w), 1462 (m), 1437 (m), 1417 (m), 1340 (w), 1267 (w), 1228 (w), 1203 (w), 1151 (m), 1130 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) Major rotamer:

7.38–7.25 (10 H, m, 10 × Ar**H**)

6.14 (2 H, s, 2 × Ar**H**)

4.73–4.56 (4 H, m, 2 × C**H**$_2$)

3.89 (3 H, s, OC**H**$_3$)

3.74 (6 H, s, 2 × OC**H**$_3$)

2.03 (3 H, s, C**H**$_3$) ppm.

Minor rotamer:

7.38–7.25 (10 H, m, 10 × Ar**H**)

6.09 (2 H, s, 2 × Ar**H**)

5.02 (1 H, d, *J* = 13.9 Hz, C**H**H)

4.95 (1 H, d, *J* = 13.8 Hz, CH**H**)

4.53 (1 H, d, *J* = 16.3 Hz, C**H**H)

4.43 (1 H, d, *J* = 16.5 Hz, CH**H**)

3.85 (3 H, s, OC**H**$_3$)

3.73 (6 H, s, 2 × OC**H**$_3$)

1.70 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) Major rotamer:

184.2 (**C**), 170.6 (**C**), 161.7 (**C**), 160.0 (**C**), 136.4 (**C**), 131.76 (**C**H), 128.0 (**C**H), 127.9 (**C**H), 127.7 (**C**H), 127.12 (**C**H), 126.0 (**C**H), 122.3 (**C**), 114.8 (**C**), 102.61 (**C**), 90.1 (**C**H), 88.1 (**C**), 85.4 (**C**), 82.2 (**C**), 55.34 (O**C**H$_3$), 55.26 (O**C**H$_3$), 52.3 (**C**H$_2$), 41.4 (**C**H$_2$), 8.4 (**C**H$_3$) ppm.

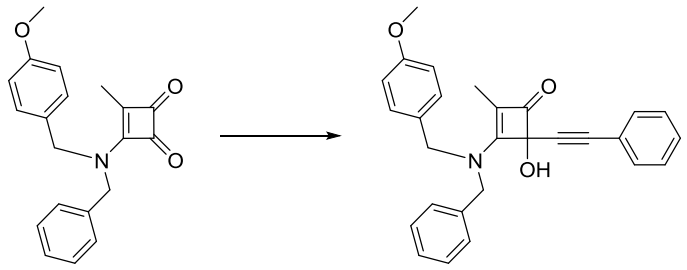
Minor rotamer:

183.9 (**C**), 170.3 (**C**), 161.8 (**C**), 159.9 (**C**), 137.4 (**C**), 131.84 (**C**H), 128.4 (**C**H), 128.3 (**C**H), 128.1 (**C**H), 127.05 (**C**H), 126.0 (**C**H), 122.6 (**C**), 115.3 (**C**), 102.64 (**C**), 90.3 (**C**H), 88.3 (**C**), 85.6 (**C**), 82.4 (**C**), 55.5 (O**C**H$_3$), 55.3 (O**C**H$_3$), 50.9 (**C**H$_2$), 43.3 (**C**H$_2$), 7.5 (**C**H$_3$) ppm.

LRMS (ESI+) 484 ($[M+H]^+$, 100%), 967 ($[2M+H]^+$, 40%).

HRMS (ESI+) Found 484.2117, $C_{30}H_{30}NO_5$ $[M+H]^+$ requires 484.2118.

3-(benzyl(4-methoxybenzyl)amino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-enone (4.24h)



4.23h
$C_{20}H_{19}NO_3$
Mol Wt: 321.38

4.24h
$C_{28}H_{25}NO_3$
Mol Wt: 423.50

To a solution of phenylacetylene (0.18 mL, 1.64 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.69 mL, 1.64 mmol) dropwise. The solution was stirred at –78 °C for 10 min and added *via* cannula to a solution of 3-(benzyl(4-methoxybenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione **4.23g** (403 mg, 1.26 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined , dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–30% acetone/DCM) to afford the title compound as (421 mg, 1.00 mmol, 80%) a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3230 (br), 1747 (m), 1589 (s), 1566 (s), 1512 (s), 1440 (m), 1364 (w), 1244 (m), 1174 (m), 1020 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.42–7.24 (12 H, m, 12 × Ar**H**)

6.83 (2 H, d, *J* = 8.6 Hz, 2 × Ar**H**)

4.87 (1 H, s, O**H**)

4.83–4.69 (2 H, m, C$\mathbf{H}_2$)

4.49–4.31 (2 H, m, C$\mathbf{H}_2$)

3.81 (3 H, s, OC$\mathbf{H}_3$)

1.73 (3 H, s, C$\mathbf{H}_3$) ppm.

with additional signals attributed to the minor rotamer at:

3.83 (3 H, s, OC$\mathbf{H}_3$)

1.78 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) Major rotamer:

184.7 (**C**), 170.4 (**C**), 159.52 (**C**), 135.6 (**C**), 131.9 (**C**H), 130.2 (**C**H), 128.7 (**C**H), 128.6 (**C**H), 128.4 (**C**H), 128.13 (**C**H), 126.9 (**C**H), 122.20 (**C**), 114.8 (**C**), 114.1 (**C**H), 88.8 (**C**), 85.2 (**C**), 82.28 (**C**), 55.29 (O**C**H_3), 53.3 (**C**H_2), 50.7 (**C**H_2), 7.8 (**C**H_3) ppm.

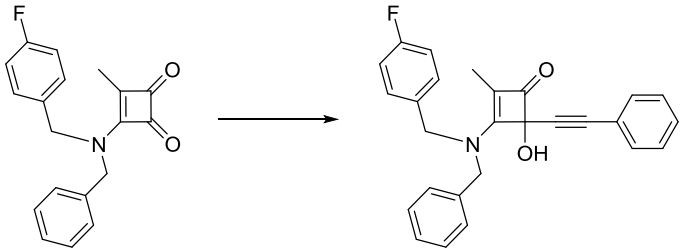
Minor rotamer:

184.7 (**C**=O), 170.4 (**C**), 159.45 (**C**), 135.1 (**C**), 131.9 (**C**H), 129.1 (**C**H), 128.8 (**C**H), 128.6 (**C**H), 128.4 (**C**H), 128.09 (**C**H), 127.2 (**C**H), 122.16 (**C**), 114.7 (**C**), 114.5 (**C**H), 88.8 (**C**), 85.0 (**C**), 82.31 (**C**), 55.31 (O**C**H_3), 53.4 (**C**H_2), 50.5 (**C**H_2), 7.9 (**C**H_3) ppm.

LRMS (ESI+) 424 ($[M+H]^+$, 30%), 847 ($[2M+H]^+$, 100%).

HRMS (ESI+) Found 424.1906, $C_{28}H_{26}NO_3$ $[M+H]^+$ requires 424.1907.

3-(benzyl(4-fluorobenzyl)amino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-enone (4.24i)



4.23i
$C_{19}H_{16}FNO_2$
Mol Wt: 309.34

4.24i
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

To a solution of phenylacetylene (0.2 mL, 1.82 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.86 mL, 2.05 mmol) dropwise. The solution was stirred at –78 °C for 10 min and added *via* cannula to a solution of 3-(benzyl(4-fluorobenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione **4.23i** (400 mg, 1.29 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–30% acetone/DCM) to afford the product (436 mg, 1.06 mmol, 86%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3232 (br), 1747 (m), 1566 (vs), 1508 (s), 1442 (s), 1415 (m), 1261

(m), 1221 (m), 1157 (w), 1130 (w), 1082 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.45–7.19 (12 H, m, 12 × Ar**H**)

7.13–6.99 (2 H, m, 2 × Ar**H**)

5.03 (1 H, br s, O**H**)

4.87–4.69 (2 H, m, C$\mathbf{H}_2$)

4.50–4.84 (2 H, m, C$\mathbf{H}_2$)

1.74 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 184.9 (**C**), 170.6 (**C**), 162.1 (**C**, d, $J_{C\text{-}F}$ =247 Hz), 135.3 (**C**), 134.9 (**C**), 131.8 (**C**H), 130.8 (**C**H, d, $J_{C\text{-}F}$ =3Hz), 130.6 (**C**, d, $J_{C\text{-}F}$ =8 Hz), 129.2 (**C**H), 128.8 (**C**H), 128.6 (**C**H), 128.1 (**C**H), 126.9 (**C**H), 122.1 (**C**), 115.6 (**C**H, d, $J_{C\text{-}F}$ =21 Hz), 88.0 (**C**), 85.1 (**C**), 82.2 (**C**), 53.1 (**C**H_2), 51.0 (**C**H_2), 7.7 (**C**H_3) ppm.

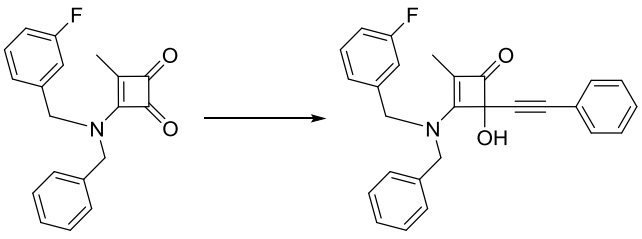
δ_F (376 MHz, $CDCl_3$) Major rotamer: –113.94 (F. m, Ar**F**).

Minor rotamer: –113.92 (F. m, Ar**F**).

LRMS (ESI+) 412 ($[M+H]^+$, 40%), 823 ($[2M+H]^+$, 100%).

HRMS (ESI+) Found 412.1717, $C_{27}H_{23}FNO_2$ $[M+H]^+$ requires 412.1707.

3-(benzyl(3-fluorobenzyl)amino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-enone (4.24j)



4.23j
$C_{19}H_{16}FNO_2$
Mol Wt: 309.34

4.24j
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

To a solution of phenylacetylene (0.11 mL, 1.04 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.44 mL, 1.04 mmol) dropwise. The solution was stirred at –78 °C for 10 min and added *via* cannula to a solution of 3-(benzyl(3-fluorobenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione **4.23j** (250 mg, 0.81 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred at –

78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–30% acetone/DCM) to afford the title compound (290 mg, 0.71 mmol, 87%) as off white oil.

FT-IR (ν_{max}, $CHCl_3$) 3241 (br), 1747 (w), 1572 (s), 1508 (m), 1442 (m), 1417 (w), 1263 (w), 1222 (w), 1157 (w), 1132 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.43–7.19 (12 H, m,12 × Ar**H**)

7.06–6.95 (2 H, m, 2 × Ar**H**)

5.84 (1 H, s, O**H**)

4.82–4.72 (2 H, m, C$\mathbf{H}_2$)

4.55–4.38 (2 H, m, C$\mathbf{H}_2$)

1.75 (3 H, s, C$\mathbf{H}_3$) ppm.

with additional signals attributed to the minor rotamer at:

5.77 (1 H, s, O**H**)

1.72 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 185.4 (**C**), 170.9 (**C**), 163.1 (**C**, d, $J_{C\text{-}F}$ =248 Hz), 138.0 (**C**, d, $J_{C\text{-}F}$ =38 Hz), 135.2 (**C**), 131.76 (**C**H), 130.8 (**C**H, d, $J_{C\text{-}F}$ = 8 Hz), 129.2 (**C**H), 128.8 (**C**H), 128.1 (**C**H), 128.0 (**C**H), 124.3 (**C**H, d, $J_{C\text{-}F}$ = 3 Hz), 122.1 (**C**), 115.7 (**C**H), 115.1 (**C**H, d, $J_{C\text{-}F}$ = 4 Hz), 114.9 (**C**), 113.9 (**C**H), 88.7 (**C**), 85.1 (**C**), 82.1 (**C**), 54.1 (**C**H_2), 51.3 (**C**H_2), 7.61 (**C**H_3) ppm.

with additional signals attributed to the minor rotamer at:

185.4 (**C**), 171.0 (**C**), 163.2 (**C**, d, $J_{C\text{-}F}$ =248 Hz), 138.1 (**C**, d, $J_{C\text{-}F}$ =38 Hz), 134.8 (**C**), 131.80 (**C**H), 130.2 (**C**H, d, $J_{C\text{-}F}$ =8 Hz), 128.8 (**C**H), 128.5 (**C**H), 128.2 (**C**H), 126.9 (**C**H), 122.4 (**C**H, d, $J_{C\text{-}F}$ =4 Hz), 122.2 (**C**), 115.4 (**C**H), 114.9 (**C**H, d, $J_{C\text{-}F}$ = 4 Hz), 114.9 (**C**), 113.7 (**C**H), 88.7 (**C**), 85.1 (**C**), 82.2 (**C**), 53.2 (**C**H_2), 50.5 (**C**H_2), 7.55 (**C**H_3) ppm.

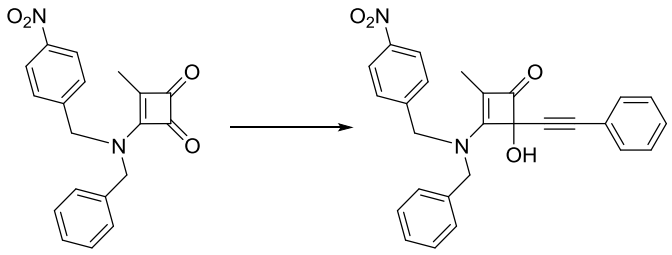
δ_F (376 MHz, $CDCl_3$) Major rotamer: –112.38 (F, dt, *J* = 8.7, 7.0 Hz, Ar**F**).

Minor rotamer: –111.62 (F, dt, *J* = 8.7, 7.0 Hz, Ar**F**).

LRMS (ESI+) 412 ([M+H]$^+$, 100%), 823 ([M+H]$^+$, 40%).

HRMS (ESI+) Found 412.1715, $C_{27}H_{23}FNO_2$ [M+H]$^+$ requires 412.1707.

3-(benzyl(4-nitrobenzyl)amino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-enone (4.24k)



4.23k
$C_{19}H_{16}N_2O_4$
Mol Wt: 336.35

4.24k
$C_{27}H_{22}N_2O_4$
Mol Wt: 438.47

To a solution of phenylacetylene (0.3 mL, 2.85 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexane, 1.15 mL, 2.69 mmol) dropwise. The solution was stirred at –78 °C for 10 min and added *via* cannula to a solution of 3-(benzyl(4-nitrobenzyl)amino)-4-methylcyclobut-3-ene-1,2-dione **4.23k** (510 mg, 1.52 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred at –78 °C for 2 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–25% acetone/DCM) to afford the title compound (711 mg, 1.62 mmol, 100%) as a yellow solid.

MP Decomposed over 120 °C.

FT-IR (ν_{max}, $CHCl_3$) 3244 (br), 2921 (w), 1747 (m), 1568 (s), 1518 (s), 1489 (m), 1441 (m), 1342 (m), 1263 (m), 1174 (w), 1132 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 8.18 (2 H, d, *J* = 8.6 Hz, 2 × Ar**H**)

7.58 (2 H, d, *J* = 8.6 Hz, 2 × Ar**H**)

7.43–7.22 (10 H, m, 10 × Ar**H**)

4.89 (2 H, s, C**H**$_2$)

4.54–4.42 (2 H, m, C**H**$_2$)

1.78 (3 H, s, C**H**$_3$) ppm.

with additional signals attributed to the minor rotamer at:

8.24 (2 H, d, *J* = 8.4 Hz, Ar**H**)

1.68 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 185.3 (**C**), 170.8 (**C**), 148.1 (**C**), 143.1 (**C**), 135.1 (**C**), 132.0 (**C**H), 129.7 (**C**H), 129.3 (**C**H), 128.8 (**C**H), 128.5 (**C**H), 127.9 (**C**H), 127.3 (**C**H), 124.3 (**C**H), 122.1 (**C**), 116.1 (**C**), 89.5 (**C**), 85.0 (**C**), 82.6 (**C**), 53.4 (**C**H_2), 52.4 (**C**H_2), 8.0 (**C**H_3) ppm.

with additional signals attributed to the minor rotamer at:

143.4 (**C**), 134.8 (**C**), 132.2 (**C**), 129.6 (**C**H), 129.2 (**C**H), 129.1 (**C**H), 124.7 (**C**H), 82.7 (**C**), 55.0 (**C**H_2), 51.0 (**C**H_2), 7.93 (**C**H_3) ppm.

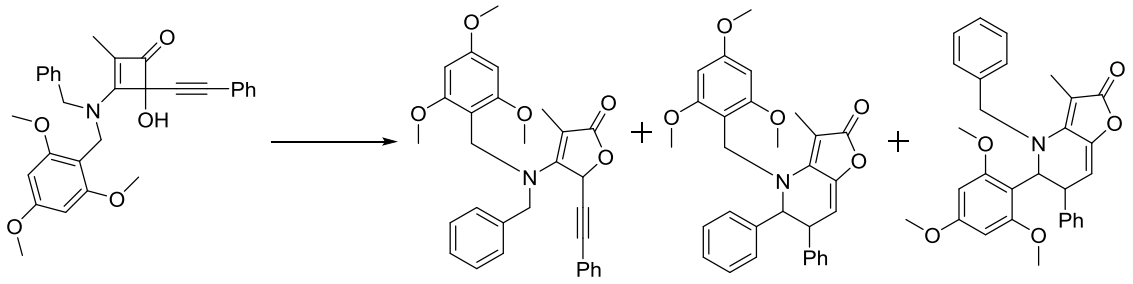
LRMS (ESI+) 439 ([M+H]$^+$, 100%), 877 ([2M+H]$^+$, 80%).

HRMS (ESI+) Found 439.1649, $C_{27}H_{23}N_2O_4$ [M+H]$^+$ requires 439.1652.

4-(benzyl(2,4,6-trimethoxybenzyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25g)

3-methyl-5,6-diphenyl-4-(2,4,6-trimethoxybenzyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26g)

4-benzyl-3-methyl-6-phenyl-5-(2,4,6-trimethoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.27g)



4.24g
$C_{30}H_{29}NO_5$
Mol Wt: 483.55

4.25g
$C_{30}H_{29}NO_5$
Mol Wt: 483.55

4.26g
$C_{30}H_{29}NO_5$
Mol Wt: 483.55

4.27g
$C_{30}H_{29}NO_5$
Mol Wt: 483.55

Cyclobutenone **4.24g** (200 mg, 0.41 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (40–80%

Et_2O/cyclohexane) to afford the title compound **4.25g** (122 mg, 0.27 mmol, 66%) as yellow oil and the title compound **4.26g** and **4.27g** together (6 : 1 mixture by ^{1}H-NMR analysis) (31 mg, 0.07 mmol, 16%) as a yellow oil.

4.25g

FT-IR (ν_{max}, $CHCl_3$) 2929 (br), 1633 (s), 1600 (s), 1522 (w), 1497 (w), 1454 (m), 1319 (w), 1228 (w), 1203 (w), 1149 (m), 1126 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.45–7.40 (2 H, m, 2 × Ar**H**)

7.38–7.29 (4 H, m, 4 × Ar**H**)

7.27–7.25 (4 H, m, 4 × Ar**H**)

6.12 (2 H, s, 2 × Ar**H**)

6.02 (1 H, s, C**H**)

4.82 (1 H, d, *J* = 16.8 Hz, C**H**H)

4.73 (1 H, d, *J* = 14.3 Hz, CH**H**)

4.54 (1 H, d, *J* = 14.3 Hz, C**H**H)

4.30 (1 H, d, *J* = 16.8 Hz, CH**H**)

3.84 (6 H, s, 2 × OC**H**$_3$)

3.75 (3 H, s, OC**H**$_3$)

1.89 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 176.0 (**C**), 163.0 (**C**), 161.5 (**C**), 159.7 (**C**H), 138.4 (**C**H), 131.8 (**C**H), 128.9 (**C**H), 128.4 (**C**H), 128.3 (**C**H), 127.0 (**C**H),126.2 (**C**H), 121.7 (**C**), 104.5 (**C**), 90.3 (**C**H), 88.2 (**C**), 83.2 (**C**), 67.6 (**C**H), 55.4 (O**C**H$_3$), 55.3 (O**C**H$_3$), 50.9 (**C**H$_2$), 43.2 (**C**H$_2$), 9.9 (**C**H$_3$) ppm.

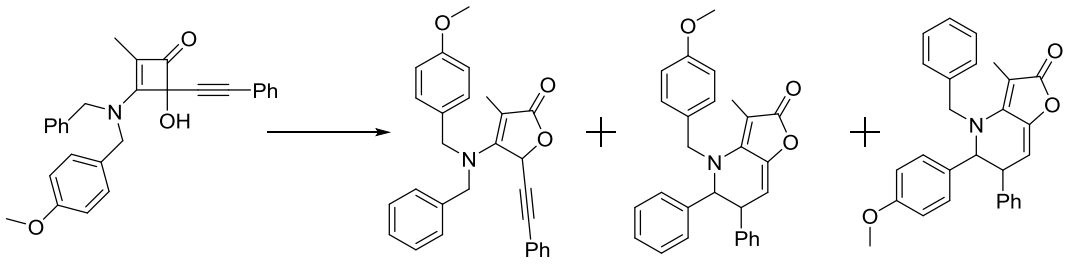
LRMS (ESI+) 484 ($[M+H]^+$, 90%), 989 ($[2M+Na]^+$, 100%).

HRMS (ESI+) Found 484.2129, $C_{30}H_{30}NO_5$ $[M+H]^+$ requires 484.2118.

4-(benzyl(4-methoxybenzyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25h)

3-methyl-5,6-diphenyl-4-(4-methoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26h)

4-benzyl-3-methyl-6-phenyl-5-(4-methoxyphenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.27h)



4.24h
$C_{28}H_{25}NO_3$
Mol Wt: 423.50

4.25h
$C_{28}H_{25}NO_3$
Mol Wt: 423.50

4.26h
$C_{28}H_{25}NO_3$
Mol Wt: 423.50

4.27h
$C_{28}H_{25}NO_3$
Mol Wt: 423.50

Cyclobutenone **4.24h** (200 mg, 0.47 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford the title compound **4.25h** (105 mg, 0.25 mmol, 53%) as a yellow oil and **4.26h** and **4.27h** together (1 : 1 mixture by ^{1}H-NMR analysis) (68 mg, 0.16 mmol, 33%) as a yellow oil.

4.25h

FT-IR (ν_{max}, $CHCl_3$) 3012 (br), 1734 (s), 1612 (s), 1512 (m), 1491 (w), 1435 (m), 1290 (w), 1248 (m), 1174 (w), 1076 (w), 1037 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.39-7.29 (8 H, m, 8 × Ar**H**)

7.26-7.23 (2 H, m, 2 × Ar**H**)

7.17 (2 H, d, *J* = 8.6 Hz, 2 × Ar**H**)

6.90-6.87 (2 H, m, 2 × Ar**H**)

5.65 (H, s, C**H**)

4.82-4.75 (2 H, m, 2 × C**H**$_2$)

4.49-4.40 (2 H, m, 2 × C**H**$_2$)

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

1.97 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.2 (**C**), 161.5 (**C**), 159.3 (**C**), 136.5 (**C**), 131.7 (**C**H), 129.2 (**C**H), 129.0 (**C**H), 128.3 (**C**H), 128.2 (**C**H), 127.8 (**C**H), 126.8 (**C**H), 121.2 (**C**), 114.3 (**C**H), 89.9 (**C**), 87.9 (**C**), 82.2 (**C**), 67.3 (**C**H), 55.2 (**C**H$_3$), 52.6 (**C**H$_2$), 52.5 (**C**H$_2$), 9.9 (**C**H$_3$) ppm.

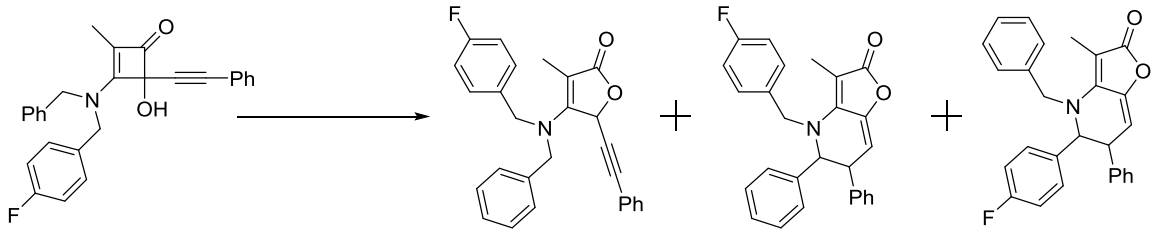
LRMS (ESI+) 424 ([M+H]$^+$, 90%), 847 ([2M+H]$^+$, 100%).

HRMS (ESI+) Found 424.1906, $C_{28}H_{26}NO_3$ [M+H]$^+$ requires 424.1907.

4-(benzyl(4-fluorobenzyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25i)

3-methyl-5,6-diphenyl-4-(4-fluorophenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26i)

4-benzyl-3-methyl-6-phenyl-5-(4-fluorophenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.27i)



4.24i
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

4.25i
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

4.26i
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

4.27i
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

Cyclobutenone **4.24i** (240 mg, 0.58 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford **4.25i** (142 mg, 0.35 mmol, 60%) as a yellow oil and **4.26i** and **4.27i** together (7 : 1 mixture by ^{1}H-NMR analysis) (40 mg, 0.1 mmol, 17%) as a yellow oil.

4.25i

FT-IR (ν_{max}, $CHCl_3$) 3012 (w), 2927 (br), 1731 (s), 1616 (s), 1600 (s), 1508 (s), 1435 (m), 1415 (m), 1292 (br), 1221 (m), 1155 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.33–7.24 (8 H, m, 8 × Ar**H**)

7.20–7.15 (4 H, m, 4 × Ar**H**)

6.98 (2 H, t, *J* = 9 Hz, 2 × Ar**H**)

5.59 (H, s, C**H**)

4.74 (2 H, d, *J* = 16.6 Hz, C$\mathbf{H}_2$)

4.41 (2 H, dd, *J* = 16.5 Hz, 5.3 Hz, C$\mathbf{H}_2$)

1.90 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 174.9 (**C**), 162.3 (**C**, d, $J_{C\text{-}F}$ =248 Hz), 161.3 (**C**), 136.2 (**C**), 132.1 (**C**H, d, $J_{C\text{-}F}$ =3 Hz), 131.7 (**C**H), 129.2 (**C**H), 129.0 (**C**H), 128.6 (**C**, d, $J_{C\text{-}F}$ =8 Hz), 128.3 (**C**H), 127.9 (**C**H), 126.8 (**C**H), 121.1 (**C**), 115.9 (**C**H, d, $J_{C\text{-}F}$ =21 Hz), 90.4 (**C**), 88.0 (**C**), 82.1 (**C**), 67.3 (**C**H), 52.9 (**C**H_2), 52.3 (**C**H_2), 9.9 (**C**H_3) ppm.

δ_F (376 MHz, CDCl3) –114.19 (F, s, Ar**F**) ppm.

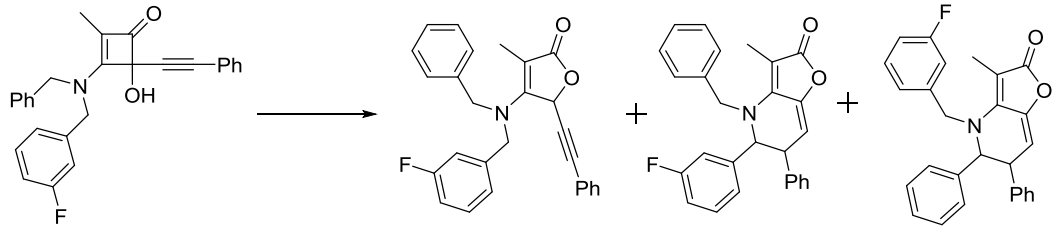
LRMS (ESI+) 412 ($[M+H]^+$, 100%), 845 ($[2M+Na]^+$, 50%).

HRMS (ESI+) Found 412.1718, $C_{27}H_{23}FNO_2$ $[M+H]^+$ requires 412.1707.

4-(benzyl(3-fluorobenzyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25j)

3-methyl-5,6-diphenyl-4-(3-fluorophenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26j)

4-benzyl-3-methyl-6-phenyl-5-(3-fluorophenyl)-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.27j)



4.24j
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

4.25j
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

4.26j
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

4.27j
$C_{27}H_{22}FNO_2$
Mol Wt: 411.47

Cyclobutenone **4.24j** (240 mg, 0.58 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford **4.25j** (142 mg, 0.35 mmol, 60%) as a yellow oil and **4.26j** and **4.27j** together (1 : 1 mixture by ^{1}H-NMR analysis) (40 mg, 0.1 mmol, 17%) as a yellow oil.

4.25j

FT-IR (ν_{max}, $CHCl_3$) 3029 (br), 2924 (br), 1736 (s), 1612 (s), 1489 (m), 1427 (m), 1290 (br), 1250 (w), 1172 (w), 1134 (w), 1078 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.39–7.30 (9 H, m, 9 × Ar**H**)

7.26–7.24 (2 H, m, 2 × Ar**H**)

7.05–6.98 (3 H, m, 3 × Ar**H**)

5.64 (H, s, C**H**)

4.85 (2 H, dd, *J* = 16.6 Hz, 5.6 Hz, C$\mathbf{H}_2$)

4.48 (2 H, dd, *J* = 16.5 Hz, 8.9 Hz, C$\mathbf{H}_2$)

1.95 (3 H, s, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 175.2 (**C**), 163.5 (**C**, d, $J_{C\text{-}F}$ = 248 Hz), 161.5 (**C**), 139.5 (**C**, d, $J_{C\text{-}F}$ = 7 Hz), 136.5 (**C**), 132.1 (CH), 131.0 (**C**H, d, $J_{C\text{-}F}$ = 8 Hz), 129.6 (**C**H), 129.3 (**C**H), 128.7 (**C**H), 128.4 (**C**H), 127.1 (**C**H). 122.6 (**C**H, d, $J_{C\text{-}F}$ = 3 Hz), 121.4 (**C**), 115.2 (**C**H, d, $J_{C\text{-}F}$ = 21 Hz), 114.0 (**C**H, d, $J_{C\text{-}F}$ = 22 Hz), 91.0 (**C**), 88.4 (**C**), 82.3 (**C**), 67.6 (**C**H), 53.6 (**C**H_2), 52.8 (**C**H_2, d, $J_{C\text{-}F}$ = 1 Hz), 10.2 (**C**H_3) ppm.

δ_F (376 MHz, CDCl3) –111.76 (F. s, Ar**F**) ppm.

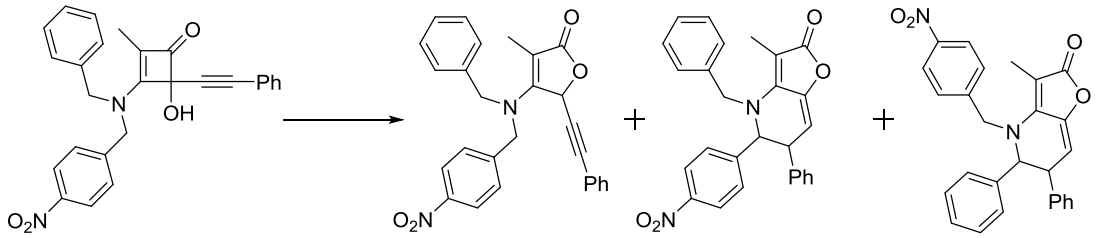
LRMS (ESI+) 412 ($[M+H]^+$, 60%), 823 ($[2M+H]^+$, 100%).

HRMS (ESI+) Found 412.1708, $C_{27}H_{23}FNO_2$ $[M+H]^+$ requires 412.1707.

4-(benzyl(4-nitrobenzyl)amino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.25k)

4-benzyl-3-methyl-5-(4-nitrophenyl)-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.26k)

3-methyl-4-(4-nitrobenzyl)-5,6-diphenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.27k)



4.24k
$C_{27}H_{22}N_2O_4$
Mol Wt: 438.47

4.25k
$C_{27}H_{22}N_2O_4$
Mol Wt: 438.47

4.26k
$C_{27}H_{22}N_2O_4$
Mol Wt: 438.47

4.27k
$C_{27}H_{22}N_2O_4$
Mol Wt: 438.47

Amino cyclobutenone **4.24k** (300 mg, 0.68 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–60% Et_2O/cyclohexane) to afford **4.25k** (191 mg, 0.44 mmol, 65%) as a yellow oil and afford **4.26k** and **4.27k** together (3 : 1 mixture by ^{1}H-NMR analysis) (60 mg, 0.14 mmol, 20%) as a yellow oil.

4.25k

FT-IR (ν_{max}, $CHCl_3$) 3031 (br), 2929 (br), 1740 (s), 1622 (s), 1519 (m), 1491 (w), 1435 (m), 1344(m), 1322 (w), 1091 (w), 1016 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 8.22–8.16 (2 H, m, 2 × Ar**H**)

7.49–7.42 (2 H, m, 2 × Ar**H**)

7.40–7.31 (7 H, m, 7 × Ar**H**)

7.27–7.24 (3 H, m, 3 × Ar**H**)

5.68 (H, s, C**H**)

4.93–4.79 (2 H, m, C$\mathbf{H}_2$)

4.65–4.53 (2 H, m, C$\mathbf{H}_2$)

1.94 (3 H, s, C$\mathbf{H}_3$) ppm.

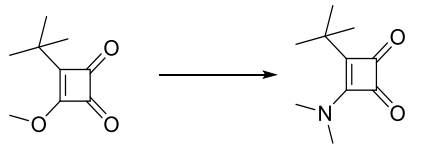
δ_C (100 MHz, $CDCl_3$) 174.3 (**C**), 160.6 (**C**), 147.2 (**C**), 143.8 (**C**), 135.4 (**C**), 131.3 (**C**H), 129.1 (**C**H), 128.9 (**C**H), 128.1 (**C**H), 127.9 (**C**H), 127.2 (**C**H), 126.5 (**C**H),

123.9 (**C**), 120.5 (**C**H), 91.0 (**C**), 88.0 (C), 81.6 (**C**), 67.0 (**C**H), 53.3 (**C**H_2), 52.1 (**C**H_2), 9.5 (**C**H_3) ppm.

LRMS (ESI+) 439 ([M+H]$^+$, 100%), 899 ([2M+Na]$^+$, 30%)

HRMS (ESI+) Found 439.1655, $C_{27}H_{23}N_2O_4$ [M+H]$^+$ requires 439.1652.

3-(*tert*-butyl)-4-(dimethylamino)cyclobut-3-ene-1,2-dione (4.90)



3.46b
$C_9H_{12}O_3$
Mol Wt: 169.08

4.90
$C_{10}H_{15}NO_2$
Mol Wt: 181.12

A solution of dimethylamine hydrochloride (196 mg, 2.40 mmol) and TEA (0.33 mL, 2.37 mmol) in MeOH (10 mL) was added to a solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **3.46b** (362 mg, 2.14 mmol) in MeOH (40 mL). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (EtOAc) to afford the title compound (404 mg, 2.23 mmol, 97%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2971 (br), 1781 (s), 1770 (s), 1720 (s), 1587 (vs), 1479 (w), 1462 (w), 1427 (m), 1406 (m), 1365 (m), 1250 (m), 1169 (s), 1113 (m), 1063 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 3.37 (6 H, br s, N(C**H**$_3$)$_2$)

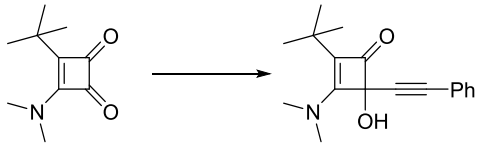
1.40 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 194.3 (**C**), 190.2 (**C**), 181.8 (**C**), 177.4 (**C**), 43.3 (br s, **C**H_3), 40.1 (br s, **C**H_3), 33.8 (**C**), 30.0 (C(**C**H_3)$_3$) ppm.

LRMS (ESI+) 182 ([M+H]$^+$, 100%).

HRMS (ESI+) Found 182.1176, $C_{10}H_{16}NO_2$ [M+H]$^+$ requires 182.1176.

2-(*tert*-butyl)-3-(dimethylamino)-4-hydroxy-4-(phenylethynyl)cyclobut-2-en-1-one (4.47)



4.90
$C_{10}H_{15}NO_2$
Mol Wt: 181.11

4.47
$C_{18}H_{21}NO_2$
Mol Wt: 283.16

To a solution of phenylacetylene (0.23 mL, 2.04 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.85 mL, 2.04 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-(*tert*-butyl)-4-(dimethylamino)cyclobut-3-ene-1,2-dione **4.90** (284 mg, 1.81 mmol) in THF (40 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–40% EtOAc/Pet) to afford the title compound (270 mg, 0.96 mmol, 61%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3219 (br), 2958 (br), 1732 (m), 1568 (vs), 1404 (s), 1363 (m), 1253 (s), 1188 (m), 1140 (m), 1078 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.48–7.44 (2 H, m, 2 × Ar**H**)

7.30–7.24 (3 H, m, 3 × Ar**H**)

4.97 (1 H, s, O**H**)

3.32 (6 H, br s, N(C**H**$_3$)$_2$)

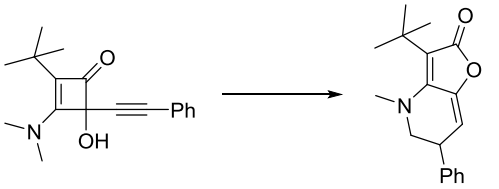
1.30 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 183.1 (**C**), 168.3 (**C**), 131.9 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 126.9 (**C**), 122.5 (**C**), 87.8 (**C**), 85.6 (**C**), 81.5 (**C**), 42.0 (br s, 2 × **C**H$_3$), 31.0 (C(**C**H$_3$)$_3$), 31.0 (**C**) ppm.

LRMS (ESI+) 284 ([M+H]$^+$, 100%).

HRMS (ESI+) Found 284.1651 $C_{18}H_{21}NO_2$ [M+H]$^+$ requires 284.1645.

3-(*tert*-Butyl)-4-methyl-6-phenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.49)



4.47
$C_{18}H_{21}NO_2$
Mol Wt 283.16

4.49
$C_{18}H_{21}NO_2$
Mol Wt 283.16

Cyclobutenone **4.47** (229 mg, 0.81 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 2 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/Pet) to afford the title compound (169 mg, 0.60 mmol, 74%) as yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2955 (br), 1743 (s), 1682 (m), 1578 (s), 1452 (m), 1406 (m), 1329 (m), 1288 (m), 1063 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.40–7.25 (5 H, m, 5 × Ar**H**)

5.71 (1 H, d, *J* = 3.7 Hz, C**H**)

3.88 (1 H, ddd, *J* = 8.8, 5.0, 3.9 Hz, C**H**)

3.42 (1 H, dd, *J* = 13.0, 5.3 Hz, C**H**H)

3.22 (1 H, dd, *J* = 13.0, 8.8 Hz, CH**H**)

3.09 (3 H, s, C$\mathbf{H}_3$)

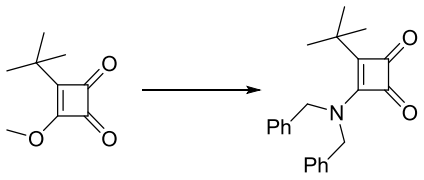
1.43 (9 H, s, C(C$\mathbf{H}_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 169.6 (**C**), 152.7 (**C**), 146.2 (**C**), 141.0 (**C**), 128.8 (**C**H), 127.7 (**C**H), 127.3 (**C**H), 109.1 (**C**), 105.1 (**C**H), 58.7 (**C**H_2), 45.1 (**C**H), 37.9 (**C**H_3), 31.1 (**C**), 30.5 (C(**C**H_3)$_3$) ppm.

LRMS (ESI+) 284 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 284.1652, $C_{18}H_{22}NO_2$ $[M+H]^+$ requires 284.1645.

3-(*tert*-butyl)-4-(dibenzylamino)cyclobut-3-ene-1,2-dione (4.91)



3.46b
$C_9H_{12}O_3$
Mol Wt: 169.08

4.91
$C_{22}H_{23}NO_2$
Mol Wt: 333.17

To a solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **3.46b** (168, 1.00 mmol) in MeOH (50 mL) was added dibenzylamine (0.23 mL, 1.00 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (50–100% DCM/Pet) to afford the title compound (290 mg, 0.88 mmol, 88%) as a yellow solid.

MP 106–107 °C.

FT-IR (ν_{max}, $CHCl_3$) 2966 (br), 1772 (s), 1732 (s), 1570 (vs), 1452 (m), 1363 (m), 1263 (w), 1196 (w), 1116 (w), 1066 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.46–7.33 (6 H, m, 6 × Ar**H**)

7.18–7.16 (4 H, m, 4 × Ar**H**)

4.79 (4 H, br s, 2 × C**H**$_2$)

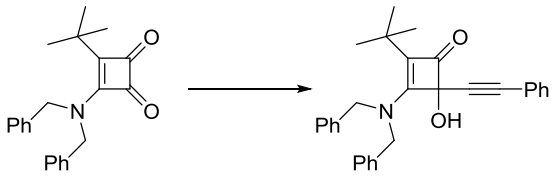
1.40 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 194.4 (**C**), 190.3 (**C**), 182.3 (**C**), 178.1 (**C**), 133.8 (br s, **C**), 129.1 (**C**H), 128.4 (**C**H), 127.8 (br s, **C**H), 54.4 (br s, **C**H$_2$), 51.5 (br s, **C**H$_2$), 34.3 (**C**), 29.6 (C(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 334 ($[M+H]^+$, 100%), 667 ($[2M+H]^+$, 30%).

HRMS (ESI+) Found 334.1811, $C_{22}H_{24}NO_2$ $[M+H]^+$ requires 334.1802.

2-(*tert*-Butyl)-3-(dibenzylamino)-4-hydroxy-4-(phenylethynyl)cyclobut-2-enone (4.48)



4.93
$C_{22}H_{23}NO_2$
Mol Wt 333.18

4.48
$C_{30}H_{29}NO_2$
Mol Wt 435.23

To a solution of phenylacetylene (0.11 mL, 1.00 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.42 mL, 1.01 mmol) dropwise. After 10 min the solution was added *via* cannula to a solution of 3-(*tert*-butyl)-4-(dibenzylamino)cyclobut-3-ene-1,2-dione **4.91** (220 mg, 0.66 mmol) in THF (40 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–20% acetone/DCM) to afford the title compound (210 mg, 0.48 mmol, 73%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2962 (br), 1732 (m), 1589 (s), 1562 (vs), 1495 (w), 1452 (m), 1427 (m), 1363 (w), 1263 (w), 1153 (w), 1126 (w), 1078 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.41–7.20 (15 H, m, 15 × Ar**H**)

5.21 (1 H, br s, O**H**)

4.86 (2 H, br s, C$\mathbf{H}_2$)

4.59 (2 H, br s, C$\mathbf{H}_2$)

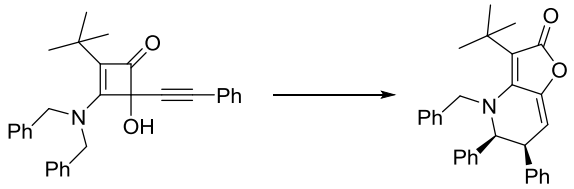
1.30 (9 H, s, C(C$\mathbf{H}_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 183.6 (**C**), 169.4 (**C**), 135.1 (br **C**), 131.9 (**C**H), 128.9 (br **C**H), 128.4 (**C**H), 128.0 (**C**H), 127.8 (br **C**H**),** 126.8 (**C**), 122.3 (**C**), 88.3 (**C**), 85.5 (**C**), 81.9 (**C**), 53.5 (**C**H_2), 31.4 (**C**), 30.4 (C(**C**H_3)$_3$) ppm.

LRMS (ESI+) 436 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 436.2275, $C_{30}H_{30}NO_2$ $[M+H]^+$ requires 436.2271.

rel-(5S,6S)-4-Benzyl-3-(*tert*-butyl)-5,6-diphenyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (4.50)



4.48
$C_{30}H_{29}NO_2$
Mol Wt 435.23

4.50
$C_{30}H_{29}NO_2$
Mol Wt 435.23

Cyclobutenone **4.48** (80 mg, 0.18 mmol) in 1,4-dioxane (5 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/Pet) to afford the title compound (66 mg, 0.15 mmol, 83%) as a yellow oil and 9 : 1 mixture of diastereoisomers. The major diastereoisomer was separated by HPLC (15% EtOAc/hexane) for analysis.

FT-IR (ν_{max}, $CHCl_3$) 3025 (br), 1749 (s), 1689 (m), 1587 (m), 1562 (s), 1495 (w), 1452 (w), 1277 (w), 1220 (w), 1029 (w), 980 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.41–7.34 (3 H, m, 3 × Ar**H**)

7.30–7.24 (3 H, m, 3 × Ar**H**)

7.27–7.24 (2 H, m, 2 × Ar**H**)

7.18–7.11 (3 H, m, 3 × Ar**H**)

7.07–7.01 (2 H, m, 2 × Ar**H**)

6.75 (2 H, d, *J* = 7.3 Hz, 2 × Ar**H**)

5.54 (1 H, d, *J* = 5.9 Hz, C**H**)

4.92 (1 H, d, *J* = 15.5 Hz, C**H**H)

4.28 (1 H, d, *J* = 2.0 Hz, C**H**)

4.11 (1 H, d, *J* = 15.7 Hz, CH**H**)

3.82 (1 H, dd, *J* = 5.9 Hz, 2.2 Hz, C**H**)

1.47 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 169.8 (**C**), 151.5 (**C**), 146.1 (**C**), 141.3 (**C**), 141.1 (**C**), 135.5 (**C**), 128.8

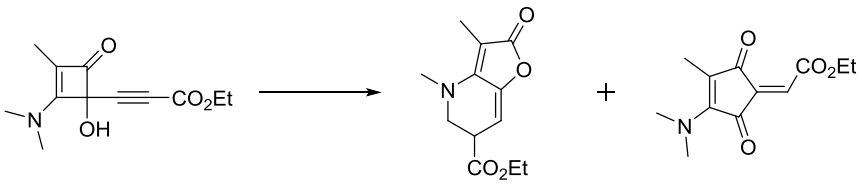
(**C**H), 128.7 (**C**H), 128.4 (**C**H), 128.0 (**C**H), 127.8 (**C**H), 127.5 (**C**H), 127.4 (**C**H), 127.3 (**C**H), 126.5 (**C**H), 105.6 (**C**), 99.8 (**C**H), 66.3 (**C**H), 56.0 (**C**H_2), 45.8 (**C**H), 31.4 (C(**C**H_3)$_3$), 31.3 (**C**) ppm.

LRMS (ESI+) 436 ([M+H]$^+$, 100%), 893 ([2M+Na]$^+$, 30%)

HRMS (ESI+) Found 436.2267, $C_{30}H_{30}NO_2$ [M+H]$^+$ requires 436.2271.

Ethyl 3,4-dimethyl-2-oxo-2,4,5,6-tetrahydrofuro[3,2-b]pyridine-6-carboxylate (4.57)

Ethyl (E/Z)-2-(3-(dimethylamino)-4-methyl-2,5-dioxocyclopent-3-en-1-ylidene)acetate (4.58)



3.4q
$C_{12}H_{15}NO_4$
Mol Wt 237.10

4.57
$C_{12}H_{15}NO_4$
Mol Wt 237.10

4.58
$C_{12}H_{15}NO_4$
Mol Wt 237.10

Cyclobutenone **3.4q** (90 mg, 0.38 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford first **4.58** (27 mg, 0.11 mmol, 30%) as a yellow oil and then afford **4.57** (30 mg, 0.13 mmol, 34%) as an orange oil.

4.57

FT-IR (ν_{max}, $CHCl_3$) 2962 (w), 2926 (br), 1736 (s), 1603 (s), 1448(w), 1412 (m), 1288 (w), 1159 (w), 1028 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.67 (H, d, *J* = 4.4 Hz, C**H**)

4.21 (2 H, br q, *J* = 7.2 Hz, C**H**$_2$)

3.56–3.42 (3 H, m, C**H** + C**H**$_2$)

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

2.00 (3 H, s, C**H**$_3$)

1.29 (3 H, t, *J* = 7.0 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 171.7 (**C**), 170.6 (**C**), 150.7 (**C**), 145.6 (**C**), 98.3 (**C**H), 91.0 (**C**), 61.7 (**C**H_2), 51.4 (**C**H_2), 39.2 (**C**H), 39.0 (**C**H_3), 14.1 (**C**H_3), 8.8 (**C**H_3) ppm.

LRMS (ESI+) 238 ($[M+H]^+$, 100%)

HRMS (ESI+) Found 238.1072, $C_{12}H_{16}NO_4$ $[M+H]^+$ requires 238.1074.

4.58

FT-IR (ν_{max}, $CHCl_3$) 2929 (br), 1720 (s), 1660 (s), 1574 (s), 1400 (m), 1311 (m), 1220 (m), 1025 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) Major isomer

6.58 (1 H, s, C**H**)

4.349 (2 H, q, *J* = 7.2 Hz, C**H**$_2$)

3.39 (6 H, s, N(C**H**$_3$)$_2$)

2.26 (3 H, s, C**H**$_3$)

1.36 (3 H, t, *J* = 7.1 Hz, C**H**$_3$) ppm.

Minor isomer

6.51 (1 H, s, C**H**)

4.347 (2 H, q, *J* = 7.2 Hz, C**H**$_2$)

3.39 (6 H, s, N(C**H**$_3$)$_2$)

2.24 (3 H, s, C**H**$_3$)

1.37 (3 H, t, *J* = 7.0 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) Major isomer:

186.31 (**C**), 186.26 (**C**), 165.6 (**C**), 158.2 (**C**), 135.1 (**C**), 127.4 (**C**), 121.1 (**C**H), 61.5 (**C**H_2), 42.1 (**C**H_3) 14.05 (**C**H_3), 10.9 (**C**H_3) ppm.

Minor isomer:

188.2 (**C**), 185.4 (**C**), 165.9 (**C**), 156.9 (**C**), 129.4 (**C**), 125.5 (**C**), 120.9 (**C**H), 61.7 (**C**H_2), 42.0 (**C**H_3), 14.08 (**C**H_3), 10.7 (**C**H_3) ppm.

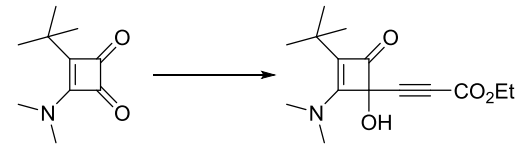
LRMS (ESI+) Minor isomer: 238 ($[M+H]^+$, 100%), 497 ($[2M+Na]^+$, 30%)

Major isomer: 238 ($[M+H]^+$, 100%), 497 ($[2M+Na]^+$, 20%)

HRMS (ESI+) Major isomer: Found 238.1072, $C_{12}H_{16}NO_4$ $[M+H]^+$ requires 238.1074.

Minor isomer: Found 238.1074, $C_{12}H_{16}NO_4$ $[M+H]^+$ requires 238.1074.

Ethyl 3-(3-(*tert*-butyl)-2-(dimethylamino)-1-hydroxy-4-oxocyclobut-2-en-1-yl)propiolate (4.59)



4.90
$C_{10}H_{15}NO_2$
Mol Wt: 181.11

4.59
$C_{15}H_{21}NO_4$
Mol Wt: 279.15

To a solution of ethyl propiolate (0.25 mL, 2.42 mmol) in THF (10 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 0.97 mL, 2.42 mmol) dropwise. The solution was stirred at –78 °C for 5 min and added *via* cannula to a solution of 3-(*tert*-butyl)-4-(dimethylamino)cyclobut-3-ene-1,2-dione **4.90** (190 mg, 1.37 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred at –78 °C for 5 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–50% acetone/cyclohexane) to afford the title compound (453 mg, 1.62 mmol, 94%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3224 (br), 2980 (w), 1709 (s), 1556 (s), 1298 (m), 1251 (s), 1110 (m), 1016 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 6.32 (1 H, br s, O**H**)

4.17 (2 H, q, *J* = 7.1 Hz, C**H**$_2$)

3.24 (6 H, s, 2 × C**H**$_3$)

1.25 (3 H, t, *J* = 7.2 Hz, C**H**$_3$)

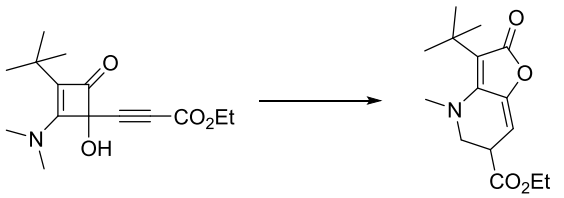
1.22 (9 H, s, C(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 180.9 (**C**), 167.2 (**C**), 153.3 (**C**), 127.5 (**C**), 83.5 (**C**), 80.6 (**C**), 78.5 (**C**), 61.9 (**C**H_2), 42.0 (br s, 2 × **C**H_3), 30.9 (**C**), 30.7 (**C**H_3), 13.9 (C(**C**H_3)$_3$) ppm.

LRMS (ESI+) 280 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 280.1542, $C_{15}H_{22}NO_4$ $[M+H]^+$ requires 280.1543.

Ethyl 3-(*tert*-butyl)-4-methyl-2-oxo-2,4,5,6-tetrahydrofuro[3,2-b]pyridine-6-carboxylate (4.60)



4.59
$C_{15}H_{21}NO_4$
Mol Wt: 279.15

4.60
$C_{15}H_{21}NO_4$
Mol Wt: 279.15

Cyclobutenone **4.59** (213 mg, 0.76 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/cyclohexane) to afford the title compound (150 mg, 0.54 mmol, 70%) as an organge oil.

FT-IR (ν_{max}, $CHCl_3$) 2926 (w), 1732 (s), 1585 (s), 1458 (m), 1365 (m), 1298 (m), 1180 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.67 (1 H, d, *J* = 4.2 Hz, C**H**)

4.17 (2 H, qd, *J* = 7.1, 1.8 Hz, C**H**$_2$)

3.49–3.40 (3 H, m, C**H** + C**H**$_2$)

3.10 (3 H, s, C**H**$_3$)

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

1.25 (3 H, t, *J* = 7.2 Hz, C**H**$_3$) ppm.

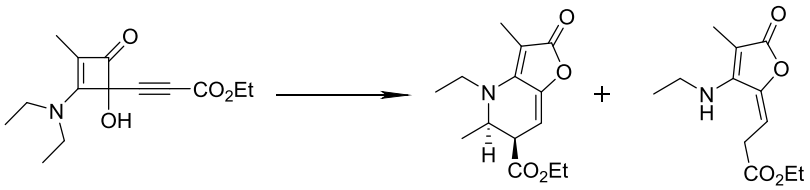
δ_C (100 MHz, $CDCl_3$) 171.1 (**C**), 169.3 (**C**), 152.2 (**C**), 146.2 (**C**), 110.4 (**C**H), 99.5 (**C**), 61.5 (**C**H_2), 51.8 (**C**H_2), 45.2 (**C**H_3), 37.3 (**C**H), 31.2 (**C**), 30.4 (**C**H_3), 14.1 (C(**C**H_3)$_3$) ppm.

LRMS (ESI+) 280 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 280.1543, $C_{15}H_{22}NO_4$ $[M+H]^+$ requires 280.1543.

Ethyl 4-ethyl-3,5-dimethyl-2-oxo-2,4,5,6-tetrahydrofuro[3,2-b]pyridine-6-carboxylate (4.68)

Ethyl (E)-3-(3-(ethylamino)-4-methyl-5-oxofuran-2(5H)-ylidene)propanoate (4.67)



3.4r
$C_{14}H_{19}NO_4$
Mol Wt: 265.13

4.68
$C_{14}H_{19}NO_4$
Mol Wt: 265.13

4.67
$C_{12}H_{17}NO_4$
Mol Wt: 239.12

Furanone **3.4r** (80 mg, 0.30 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 2 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford the title compound (41 mg, yield cannot be calculated) together as an inseparable mixture (Major diastereoisomer **4.68** : minor diastereoisomers **4.68** : **4.67** = 5 : 1 : 3).

FT-IR (ν_{max}, $CHCl_3$) 2922 (w), 1732 (s), 1622 (s), 1310 (m), 1186 (m), 1022 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) Major diastereoisomer

5.48 (1 H, d, *J* = 6.5 Hz, C**H**)

4.25-4.11 (2 H, m, C**H**$_2$)

3.92 (1 H, q, *J* = 6.8 Hz, MeC**H**)

3.72 (1 H, q, *J* = 7.2 Hz, NC**H**H)

3.20 (1 H, q, *J* = 7.1 Hz, NCH**H**)

3.12 (1 H, dd, *J* = 6.6, 1.3 Hz, C**H**)

1.93 (3 H, s, C**H**$_3$)

1.27 (3 H, t, *J* = 6.9, C**H**$_3$)

1.25 (3 H, t, *J* = 6.9, C**H**$_3$)

1.30-1.23 (3 H, m, C**H**$_3$) ppm.

with additional signals attributed to the minor diastereoisomer at

5.63 (1 H, br d, *J* = 2.0 Hz, C**H**)

1.95 (3 H, s, C**H**$_3$)

1.32-1.28 (6 H, m, 6 × C**H**$_3$)

1.13 (3 H, d, *J* = 6.4, C**H**$_3$) ppm.

with additional signals attributed to furanone **4.67**

5.95 (1 H, br s, N**H**)

5.62 (1 H, t, *J* = 9.3, C**H**CH$_2$)

3.28 (2 H, d, *J* = 9.3, CHC**H**$_2$)

2.03 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) Major diastereoisomer:

172.2 (**C**), 171.0 (**C**), 147.9 (**C**), 145.4 (**C**), 95.2 (**C**H), 88.6 (**C**), 61.5 (**C**H$_2$), 53.8 (**C**H), 44.6 (**C**H), 44.1 (**C**H$_2$), 18.6 (**C**H$_3$), 14.7 (**C**H$_3$), 14.2 (**C**H$_3$), 8.8 (**C**H$_3$) ppm.

with additional signals attributed to minor diastereoisomer and furanone **4.67**:

172.3 (**C**), 172.0 (**C**), 170.0 (**C**), 151.7 (**C**), 148.7 (**C**), 148.4 (**C**), 145.1 (**C**), 100.3 (**C**H), 96.7 (**C**H), 89.9 (**C**), 62.0 (**C**), 61.6 (**C**H$_2$), 54.5 (**C**H), 45.0 (**C**H), 44.1 (**C**H$_2$), 39.4 (**C**H$_2$), 31.4 (**C**H$_2$), 15.9 (**C**H$_3$), 15.5 (**C**H$_3$), 14.1 (**C**H$_3$), 13.4 (**C**H$_3$), 9.0, 8.9 (**C**H$_3$), 8.4 (**C**H$_3$) ppm.

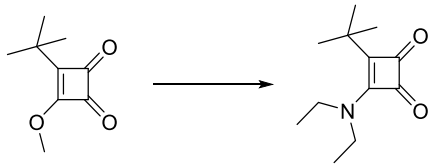
LRMS (ESI+) **4.68**: 266 ($[M+H]^+$, 100%);

4.67: 240 ($[M+H]^+$, 100%), 262 ($[M+Na]^+$, 40%).

HRMS (ESI+) **4.68**: Found 266.1386, $C_{14}H_{20}NO_4$ $[M+H]^+$ requires 266.1397;

4.67: Found 240.1236, $C_{12}H_{18}NO_4$ $[M+H]^+$ requires 240.1230.

3-(*tert*-butyl)-4-(diethylamino)cyclobut-3-ene-1,2-dione (4.92)



3.46b
$C_9H_{12}O_3$
Mol Wt: 168.08

4.92
$C_{12}H_{19}NO_2$
Mol Wt: 209.14

To a solution of 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **3.46b** (856 mg, 5.10 mmol) in MeOH (50 mL) was added diethylamine hydrochloride (665 mg, 6.10 mmol) and Et_3N (0.85 mL, 6.11 mmol). After stirring at RT for 18 h the solution was concentrated under reduced pressure and purified by column chromatography (50–80% EtOAc/Pet) to afford the title compound (900 mg, 4.31 mmol, 86%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2977 (br), 1772 (s), 1722 (s), 1574 (s), 1465 (w), 1300 (m), 1163 (m), 1057 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 3.57 (4 H, br s, 2 × C**H**$_2$)

1.27 (9 H, s, C(C**H**$_3$)$_3$)

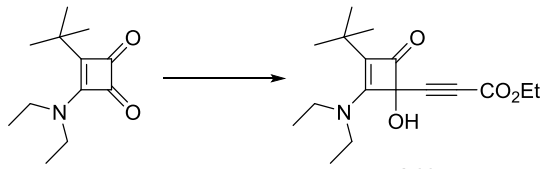
1.15 (6 H, t, *J* = 6.9 Hz, 2 × C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 194.1 (**C**), 189.7 (**C**), 180.2 (**C**), 176.5 (**C**), 46.2 (br s, **C**H$_2$), 43.3 (br s, **C**H$_2$), 33.7 (**C**), 29.1 (C(**C**H$_3$)$_3$), 14.1 (br s, **C**H$_3$), 13.0(br s, **C**H$_3$) ppm.

LRMS (ESI+) 210 ($[M+H]^+$, 100%), 232 ($[M+Na]^+$, 60%).

HRMS (ESI+) Found 210.1489, $C_{12}H_{20}NO_2$ $[M+H]^+$ requires 210.1489.

Ethyl-3-(3-(*tert*-butyl)-2-(diethylamino)-1-hydroxy-4-oxocyclobut-2-en-1-yl)propiolate (4.69)



4.92
$C_{12}H_{19}NO_2$
Mol Wt: 209.14

4.69
$C_{17}H_{25}NO_4$
Mol Wt: 307.18

To a solution of ethyl propiolate (0.55 mL, 5.45 mmol) in THF (10 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 2.18 mL, 5.45 mmol) dropwise. The solution was stirred at –78 °C for 5 min and added *via* cannula to a solution of 3-(*tert*-butyl)-4-(diethylamino)cyclobut-3-ene-1,2-dione **4.92** (876 mg, 4.19 mmol) in THF (20 mL) at –78 °C. The resulting solution was stirred at –78 °C for 5 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–50% acetone/cyclohexane) to afford the title compound (982 mg, 3.21 mmol, 76%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3224 (br), 2980 (w), 1709 (s), 1556 (s), 1298 (m), 1251 (s), 1110 (m), 1016 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 6.14 (1 H, br s, O**H**)

4.18 (2 H, q, *J* = 7.1 Hz, C**H**$_2$)

3.67 (2 H, br s, C**H**$_2$)

3.53 (2 H, sxt, *J* = 7.1 Hz, C**H**$_2$)

1.29 (6 H, t, *J* = 7.1 Hz, 2 × C**H**$_3$)

1.27 (3 H, t, *J* = 7.2 Hz, C**H**$_3$)

1.24 (9 H, s, C(C**H**$_3$)$_3$) ppm.

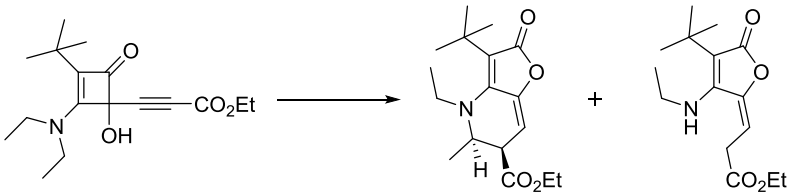
δ_C (100 MHz, $CDCl_3$) 180.4 (**C**), 166.3 (**C**), 153.0 (**C**), 126.3 (**C**), 83.6 (**C**), 80.3 (**C**), 78.0 (**C**), 61.6 (**C**H$_2$), 44.0 (2 × **C**H$_2$), 30.9 (**C**), 29.9 (3 × **C**H$_3$), 13.6 (2 × **C**H$_3$), 12.7 (**C**H$_3$) ppm.

LRMS (ESI+) 308 ($[M+H]^+$, 100%), 330 ($[M+Na]^+$, 100%).

HRMS (ESI+) Found 308.1856, $C_{17}H_{26}NO_4$ $[M+H]^+$ requires 308.1856.

ethyl 3-(*tert*-butyl)-4-ethyl-5-methyl-2-oxo-2,4,5,6-tetrahydrofuro[3,2-b]pyridine-6-carboxylate (4.71)

ethyl (E)-3-(4-(*tert*-butyl)-3-(ethylamino)-5-oxofuran-2(5H)-ylidene)propanoate (4.70)



4.69
$C_{17}H_{25}NO_4$
Mol Wt: 307.18

4.71
$C_{17}H_{25}NO_4$
Mol Wt: 307.18

4.70
$C_{15}H_{23}NO_4$
Mol Wt: 281.16

Furanone **4.69** (300 mg, 0.98 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford first the title compound **4.71** (110 mg, 0.36 mmol, 37%) as a 3:1 mixture of diastereoisomers as a orange oil, then afford the title compound **4.70** (150 mg. 0.53 mmol, 54%) as a yellow oil.

4.71

FT-IR (ν_{max}, $CHCl_3$) 2958 (br), 1732 (s), 1585 (s), 1585 (s), 1365 (m), 1297 (m), 1180 (s), 978 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) Major diastereoisomer

5.46 (1 H, dd, J = 6.2, 0.9 Hz, C**H**)

4.21–4.09 (2 H, m, C**H**$_2$)

3.92 (1 H, q, J = 7.0 Hz, C**H**)

3.53 (1 H, dq, J = 14.1, 7.0 Hz, C**H**H)

3.16 (1 H, dq, J = 14.1, 7.1 Hz, CH**H**)

3.03 (1 H, dq, J = 6.2, 1.0 Hz, C**H**)

1.30 (9 H, s, C(C**H**$_3$)$_3$)

1.28-1.21 (6 H, m, 2 × C**H**$_3$)

1.17 (3 H, t, J = 7.1 Hz, C**H**$_3$) ppm.

Minor diastereoisomer

5.60 (1 H, dd, J = 2.4, 0.9 Hz, C**H**)

4.21–4.09 (2 H, m, C$\mathbf{H}_2$)

3.84 (1 H, dd, J = 5.3, 2.5 Hz, C**H**)

3.66 (1 H, m, C**H**)

3.40 (1 H, dq, J = 14.0, 7.0 Hz, C**H**H)

3.09–3.00 (1 H, m, CH**H**)

1.29 (9 H, s, C(C$\mathbf{H}_3$)$_3$)

1.28-1.21 (6 H, m, 2 × C$\mathbf{H}_3$)

1.10-1.07 (3 H, m, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) Major diastereoisomer:

171.6 (**C**), 169.4 (**C**), 149.6 (**C**), 145.6 (**C**), 110.1 (**C**), 95.6 (**C**H), 61.3 (**C**H$_2$), 51.5 (**C**H), 49.7 (**C**H$_2$), 43.2 (**C**H), 31.0 (**C**), 30.0 (C(**C**H$_3$)$_3$), 21.1 (**C**H$_3$), 14.0 (**C**H$_3$), 13.2 (**C**H$_3$) ppm.

Minor diastereoisomer:

170.7 (**C**), 169.3 (**C**), 150.9 (**C**), 145.2 (**C**), 116.3 (**C**), 98.1 (**C**H), 61.2 (**C**H$_2$), 51.8 (**C**H), 49.7 (**C**H$_2$), 41.0 (**C**H), 31.5 (**C**), 29.3 (C(**C**H$_3$)$_3$), 15.9 (**C**H$_3$), 14.0 (**C**H$_3$), 13.6 (**C**H$_3$) ppm.

LRMS (ESI+) 308 ([M+H]$^+$, 100%), 330 ([M+Na]$^+$, 30%),

HRMS (ESI+) Found 308.1860, $C_{17}H_{26}NO_4$ [M+H]$^+$ requires 308.1856 .

4.70

FT-IR (ν_{max}, $CHCl_3$) 3419 (br), 2960 (w), 1726 (s), 1585 (s), 1306 (m), 1180 (m), 1159 (m), 1251 (s), 1024 (w), 965 (m) cm^{-1}

δ_H (400 MHz, $CDCl_3$) 5.56 (1 H, t, J = 7.1 Hz, C**H**)

4.65 (1 H, br s, N**H**)

4.12 (2 H, q, J = 7.1 Hz, C**H**$_2$)

3.43–3.36 (4 H, m, 2 × C**H**$_2$)

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

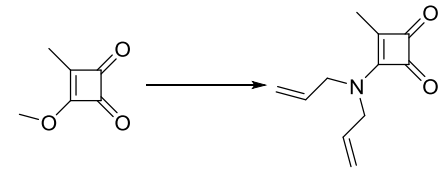
1.28-1.20 (6 H, m, 2 × C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 170.8 (**C**), 168.3 (**C**), 152.2 (**C**), 144.9 (**C**), 105.7 (**C**), 103.5 (**C**H), 60.8 (**C**H$_2$), 41.4 (**C**H$_2$), 31.6 (**C**H$_2$), 29.1 (C(**C**H$_3$)$_3$), 15.7 (**C**H$_3$), 14.0 (**C**H$_3$) ppm. (one **C** mot observed)

LRMS (ESI+) 282 ([M+H]$^+$, 100%), 304 ([M+Na]$^+$, 40%).

HRMS (ESI+) Found 282.1700, $C_{15}H_{24}NO_4$ [M+H]$^+$ requires 282.1700.

3-(diallylamino)-4-methylcyclobut-3-ene-1,2-dione (4.93)



3.2a
$C_6H_6O_3$
Mol Wt: 126.11

4.93
$C_{11}H_{13}NO_2$
Mol Wt: 191.09

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **3.2a** (126 mg, 1.00 mmol) in MeOH (50 mL) at RT was added diallylamine (0.13 mL, 1.00 mmol). After stirring at RT for 2 h the solution was concentrated under reduced pressure and purified by column chromatography (50%–80% EA/Pet) to afford the title compound (170 mg, 0.89 mmol, 89%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2963 (w), 1779 (m), 1730 (m), 1580 (s), 1418 (m), 1268 (m), 1065 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.82 (2 H, m, 2 × C**H**)

5.21–5.35 (4 H, m, 2 × C**H**$_2$)

4.35 (2 H, d, *J* = 6.2 Hz, C**H**$_2$)

4.00 (2 H, app dt, *J* = 5.0, 1.6 Hz, C**H**$_2$)

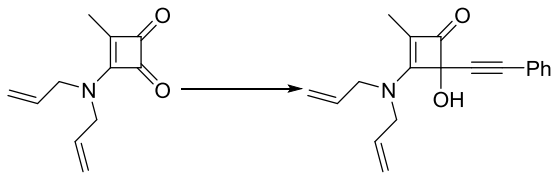
2.24 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 192.6 (**C**), 191.9 (**C**), 183.5 (**C**), 167.0 (**C**), 131.8 (**C**H), 131.2 (**C**H), 120.0 (**C**H_2), 118.6 (**C**H_2), 51.9 (**C**H_2), 51.5 (**C**H_2), 10.5 (**C**H_3) ppm.

LRMS (ESI+) 192 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 192.1019, $C_{11}H_{14}NO_2$ $[M+H]^+$ requires 192.1019.

3-(diallylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (4.74)



4.93
$C_{11}H_{13}NO_2$
Mol Wt 191.09

4.74
$C_{19}H_{19}NO_2$
Mol Wt 293.14

To a solution of phenylacetylene (0.12 mL, 1.06 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexane, 0.45 mL, 1.06 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of 3-(diallylamino)-4-methylcyclobut-3-ene-1,2-dione **4.93** (145 mg, 0.76 mmol) in THF (50 mL) at –78 °C. After a further 90 min sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5%–20% acetone/DCM) to afford the title compound (200 mg, 0.68 mmol, 90%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3222 (br), 1746 (m), 1566 (vs), 1490 (m), 1442 (m), 1273 (m), 1150 (m), 1086 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.47–7.42 (2 H, m, 2 × Ar**H**)

7.35–7.29 (3 H, m, 3 × Ar**H**)

5.97 (1 H, m, C**H**)

5.61 (1 H, m, C**H**)

5.36–5.25 (4 H, m, 2 × C$\mathbf{H}_2$)

4.29 (1 H, dd, *J* = 15.4, 6.0 Hz, C**H**H)

4.17 (1 H, dd, *J* = 15.3, 6.5 Hz, CH**H**)

4.05–3.90 (2 H, m, C**H**$_2$)

3.62 (1 H, s, O**H**)

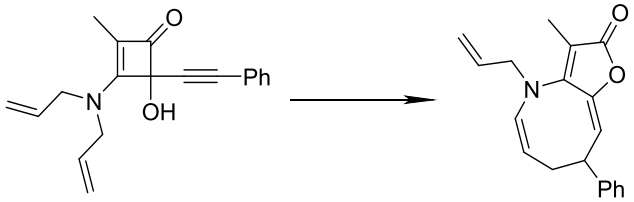
1.76 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 183.7 (**C**), 169.4 (**C**), 132.6 (**C**H), 131.8 (**C**H), 131,7 (**C**H), 128.7 (**C**H), 128.2 (**C**H), 122.1 (**C**), 119.7 (**C**H$_2$), 118.0 (**C**H$_2$), 115.5 (**C**), 88.7 (**C**), 84.6 (**C**), 82.3 (**C**), 53.5 (**C**H$_2$), 50.2 (**C**H$_2$), 7.5 (**C**H$_3$) ppm.

LRMS (ESI+) 294 ([M+H]$^+$, 100%), 609 ([2M+Na]$^+$, 30%).

HRMS (ESI+) Found 294.1490, $C_{19}H_{20}NO_2$ [M+H]$^+$ requires 294.1489.

(5Z,9E)-4-allyl-3-methyl-8-phenyl-7,8-dihydrofuro[3,2-b]azocin-2(4H)-one (4.75)



4.74
$C_{19}H_{19}NO_2$
Mol Wt: 293.14

4.75
$C_{19}H_{19}NO_2$
Mol Wt: 293.14

Cyclobutenone **4.74** (200 mg, 0.68 mmol) in 1,4-dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h then 220 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–100% Et_2O/cyclohexane) to afford the title compound (37 mg, 0.13 mmol, 19%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2926 (w), 1735 (s), 1611 (s), 1441 (m), 1429 (m), 1305 (m), 1286 (m), 1077 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.38–7.29 (5 H, m, 5 × Ar**H**)

6.761 (1 H, s, =C**H**)

6.756 (1 H, s, =C**H**)

5.95 (1 H, m, =C**H**)

5.87 (1 H, dd, *J* = 7.7, 2.7 Hz, PhC**H**)

5.36–5.30 (2 H, m, =C**H**$_2$)

4.62 (1 H, ddd, *J* = 7.8, 6.2, 2.1 Hz, =C**H**)

4.17 (1 H, ddd, *J* = 17.0, 4.8, 1.6 Hz, C**H**H)

4.06 (1 H, ddd, *J* = 17.0, 4.5, 1.8 Hz, CH**H**)

2.46 (1 H, dt, *J* = 16.8, 2.0 Hz, CH**H**)

2.27 (1 H, dd, *J* = 16.9, 6.4 Hz, CH**H**)

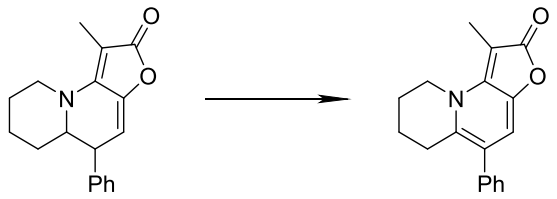
1.47 (3 H, s, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 178.1 (**C**), 137.2 (**C**), 133.1 (**C**H), 130.8 (**C**H), 128.9 (**C**), 128.7 (**C**H), 127.5 (**C**), 127.2 (**C**H), 126.9 (**C**H), 126.2 (**C**H), 117.7 (**C**H$_2$), 113.7 (**C**H), 95.6 (**C**H), 54.6 (**C**H$_2$), 42.6 (**C**), 28.9 (**C**H$_2$), 22.6 (**C**H$_3$) ppm.

LRMS (ESI+) 294 ([M+H]$^+$, 100%), 609 ([2M+Na]$^+$, 20%).

HRMS (ESI+) Found 294.1493, $C_{19}H_{20}NO_2$ [M+H]$^+$ requires 294.1489.

1-methyl-5-phenyl-6,7,8,9-tetrahydro-2H-furo[2,3-c]quinolizin-2-one (4.2g)



4.1g
$C_{18}H_{19}NO_2$
Mol Wt: 281.15

4.2g
$C_{18}H_{17}NO_2$
Mol Wt: 279.13

To a solution of **4.1g** (281 mg, 1 mmol) in DCM (100 mL) was added MnO_2 (1740 mg, 20 mmol). The mixture was stirred at RT for 18 h. The resulting solution was filtered through celite and concentrated under reduced pressure. The crude mixture was purified by column chromatography (20–80% Et_2O/Pet) to afford the title compound (141 mg, 0.51 mmol, 51%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2926 (br), 1706 (s), 1564 (s), 1495 (w), 1442 (w), 1290 (w), 1173 (w), 1044 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.44–7.33 (3 H, m, 3 × Ar**H**)

7.32 (2 H, br d, *J* = 7.0 Hz, 2 × Ar**H**)

6.69 (1 H, s, C**H**)

4.38 (2 H, t, *J* = 6.4 Hz, C$\mathbf{H}_2$)

2.75 (2 H, t, *J* = 6.7 Hz, C$\mathbf{H}_2$)

2.23 (3 H, s, C$\mathbf{H}_3$)

2.08 (2 H, quin, *J* = 6.7 Hz, C$\mathbf{H}_2$)

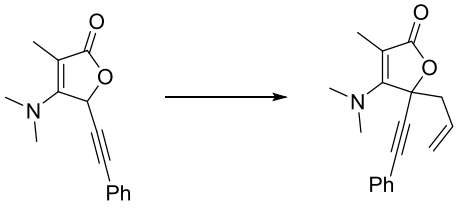
1.79 (2 H, quin, *J* = 6.7 Hz, C$\mathbf{H}_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 171.3 (**C**), 146.2 (**C**), 142.7 (**C**), 138.6 (**C**), 136.3 (**C**), 129.5 (**C**H), 128.6 (**C**H), 127.4 (**C**H), 120.3 (**C**H), 110.1 (**C**), 79.6 (**C**), 47.3 (**C**H_2), 26.0 (**C**H_2), 22.1 (**C**H_2), 18.8 (**C**H_2), 9.9 (**C**H_3) ppm.

LRMS (ESI+) 280 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 280.1331, $C_{18}H_{18}NO_2$ [M+H]+ requires 280.1332.

5-allyl-4-(dimethylamino)-3-methyl-5-(phenylethynyl)furan-2(5H)-one (4.87)



3.9e
$C_{15}H_{15}NO_2$
Mol Wt: 241.12

4.87
$C_{18}H_{19}NO_2$
Mol Wt: 281.14

To a solution of furanone **3.9e** (670 mg, 2.28 mmol) in THF (100 mL) was added LiHMDS solution (1.0 M in THF, 3.6 mL. 3.60 mmol) at –78° C. The solution was stirred at –78° C for 20 min then allyl bromide (0.31 mL, 3.60 mmol) was added. The resulting solution was stirred at –78 °C for 3 h and quenched with sat. NH_4Cl (20 mL) then warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (30–80% EtOAc/Pet) to afford the title compound (500 mg, 1.78 mmol, 78%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2929 (br), 1734 (s), 1616 (s), 1489 (w), 1402 (m), 1304 (m), 1014 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.43–7.41 (2 H, m, 2 × Ar**H**)

7.35–7.31 (3 H, m, 3 × Ar**H**)

5.76 (1 H, app tq, *J* = 9.9, 7.1 Hz, C**H**)

5.20 (1 H, m, C**H**H)

5.17 (1 H, d, *J* = 0.9 Hz CH**H**)

3.25 (6 H, s, 2 × C**H**$_3$)

2.97 (1 H, dd, *J* = 14.6, 6.9 Hz, C**H**H)

2.70 (1 H, dd, *J* = 14.6, 7.4 Hz, CH**H**)

1.99 (3 H, s, C**H**$_3$) ppm.

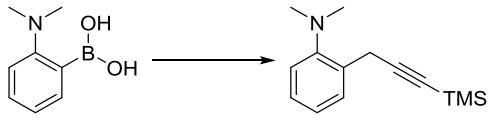
δ_C (100 MHz, $CDCl_3$) 174.0 (**C**), 163.3 (**C**), 131.6 (**C**H), 130.3 (**C**H), 129.0 (**C**H), 128.3 (**C**H), 121.5 (**C**), 119.9 (**C**H_2), 91.3 (**C**), 87.7 (**C**), 84.8 (**C**), 77.3 (**C**), 43.3 (**C**H_2), 41.5 (2 × **C**H_3), 10.3 (**C**H_3) ppm.

LRMS (ESI+) 282 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 282.1294, $C_{18}H_{20}NO_2$ $[M+H]^+$ requires 282.1489.

8.4 Experimental procedures for Chapter 5

***N*,*N*-dimethyl-2-(3-(trimethylsilyl)prop-2-yn-1-yl)aniline (5.73)**



5.71
$C_8H_{12}BNO_2$
Mol Wt: 165.10

5.73
$C_{14}H_{21}NSi$
Mol Wt: 231.14

K_2CO_3 (276 mg, 2.00 mmol), 3-bromo-1-(trimethylsilyl)-1-propyne (0.33 mL, 2.02 mmol) and H_2O (2.0 mL) were added to a solution of (2-(dimethylamino)phenyl)boronic acid (330 mg, 2.00 mmol)

in 1,4-dioxane (8 mL). The resulting mixture was degassed under argon for 15 min, then Pd(dppf)Cl_2 · DCM (163 mg, 0.20 mmol) was added. The reaction mixture was heated at 70 °C under argon for 18 h then cooled to RT. The solution was concentrated under reduced pressure and purified by column chromatography (10–50% Et_2O/Pet) to afford the title compound (393 mg, 1.70 mmol, 85%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2956 (br), 2173 (m), 1598 (m), 1491 (s), 1452 (m), 1248 (s), 1155 (w), 1025 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.70–7.66 (1 H, m, Ar**H**)

7.35–7.30 (1 H, m, Ar**H**)

7.22–7.16 (2 H, m, 2 × Ar**H**)

3.85 (2 H, s, C**H**$_2$)

2.77 (6 H, s, 2 × C**H**$_3$)

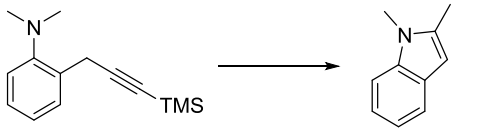
0.32 (9 H, s, Si(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 152.0 (**C**), 131.4 (**C**), 129.5 (**C**H), 127.4 (**C**H), 123.4 (**C**H), 119.1 (**C**H), 105.7 (**C**), 85.9 (**C**), 44.9 (**C**H$_2$), 21.7 (2 × **C**H$_3$), 0.1 (Si(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 232 ([M+H]$^+$, 100%).

HRMS (ESI+) Found 232.1519, $C_{14}H_{22}NSi$ [M+H]$^+$ requires 232.1516.

1,2-dimethyl-1H-indole (5.73)



5.73
$C_{14}H_{21}NSi$
Mol Wt: 231.14

5.74
$C_{10}H_{11}N$
Mol Wt: 145.09

To a solution of *N*,*N*-dimethyl-2-(3-(trimethylsilyl)prop-2-yn-1-yl)aniline **5.70** (231 mg, 1.00 mmol) in MeOH (10 mL) was added K_2CO_3 (276 mg, 2.00 mmol). The resulting mixture was stirred at RT for 18 h. The solution was concentrated under reduced pressure and purified by column

chromatography (40–60% EtOAc/Pet) to afford the title compound (120 mg, 0.83 mmol, 83%) as a yellow oil.

Data is consistent with literature.[142]

δ_H (400 MHz, $CDCl_3$) 7.58 (1 H, d, *J* = 7.7 Hz, Ar**H**)

7.30 (1 H, d, *J* = 8.2 Hz, Ar**H**)

7.21 (1 H, td, *J* = 7.6, 1.2 Hz, Ar**H**)

7.13 (1 H, td, *J* = 7.7, 1.1 Hz, Ar**H**)

6.30 (1 H, br s, C**H**)

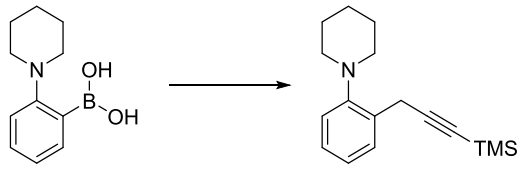
3.69 (3 H, s, C$\mathbf{H}_3$)

2.47 (3 H, d, *J* = 0.9 Hz, C$\mathbf{H}_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 137.3 (**C**), 136.7 (**C**), 127.9 (**C**), 120.4 (**C**H), 119.6 (**C**H), 119.2 (**C**H), 108.7 (**C**H), 99.5 (**C**H), 29.3 (**C**H_3), 12.7 (**C**H_3) ppm.

LRMS (ESI+) 146 ($[M+H]^+$, 40%).

1-(2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)piperidine (5.76)



5.75
$C_{11}H_{16}BNO_2$
Mol Wt: 205.13

5.76
$C_{17}H_{25}NSi$
Mol Wt: 271.18

K_2CO_3 (770 mg, 5.56 mmol), 3-bromo-1-(trimethylsilyl)-1-propyne (0.45 mL, 2.78 mmol) and H_2O (2 mL) were added to a solution of (2-(piperidin-1-yl)phenyl)boronic acid (570 mg, 2.78 mmol) in 1,4-dioxane (25 mL). The resulting mixture was degassed under argon for 15 min, then Pd(dppf)Cl_2 · DCM (227 mg, 0.28 mmol) was added. The reaction mixture was heated at 70 °C for 18 h then cooled to RT. The solution was concentrated under reduced pressure and purified by column chromatography (10–50% Et_2O/Pet) to afford the title compound (550 mg, 2.03 mmol, 73%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2933 (br), 2852 (w), 2804 (w), 2173 (m), 1597 (m), 1489 (s), 1450 (s), 1250 (m), 1218 (s), 1026 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.66 (1 H, dd, *J* = 7.6, 1.2 Hz, Ar**H**)

7.31 (2 H, td, *J* = 7.5, 1.7 Hz, 2 × Ar**H**)

7.17 (1 H, qd, *J* = 7.5, 1.2 Hz, Ar**H**)

3.83 (2 H, s, C$\mathbf{H}_2$)

2.90 (4 H, br t, *J* = 5.1 Hz, 2 × C$\mathbf{H}_2$)

1.79 (4 H, dt, *J* = 10.9, 5.6 Hz, 2 × C$\mathbf{H}_2$)

1.69-1.65 (2 H, m, C$\mathbf{H}_2$)

0.30 (9 H, s, Si(C$\mathbf{H}_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 152.1 (**C**), 131.8 (**C**), 129.2 (**C**H), 127.4 (**C**H), 123.5 (**C**H), 119.7 (**C**H), 105.7 (**C**), 85.8 (**C**), 53.8 (**C**H_2), 26.6 (**C**H_2), 24.3 (**C**H_2), 21.5 (**C**H_2), 0.1 (Si(**C**H_3)$_3$) ppm.

LRMS (ESI+) 272 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 272.1833, $C_{17}H_{26}NSi$ $[M+H]^+$ requires 272.1833.

1-(5-methoxypentyl)-2-methyl-1H-indole (5.77)

5.76
$C_{17}H_{25}NSi$
Mol Wt: 285.19

5.77
$C_{15}H_{21}NO$
Mol Wt: 231.16

To a solution of 1-(2-(3-(trimethylsilyl)prop-2-yn-1-yl)phenyl)piperidine **5.76** (285 mg, 1.00 mmol) in MeOH (10 mL) was added K_2CO_3 (276 mg, 2.00 mmol). The resulting mixture was stirred at RT for 18 h. The solution was concentrated under reduced pressure and purified by column

chromatography (40–60% EtOAc/Pet) to afford the title compound (176 mg, 0.76 mmol, 76%) as a yellow oil*.

FT-IR (ν_{max}, $CHCl_3$) 2929 (br), 1550 (w), 1459 (s), 1399 (s), 1355 (m), 1310 (m), 1115 (s), 1014 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.59 (1 H, d, *J* = 7.6 Hz, Ar**H**)

7.33 (1 H, dd, *J* = 8.1, 0.7 Hz, Ar**H**)

7.20 (1 H, td, *J* = 7.6, 1.2 Hz, Ar**H**)

7.13 (1 H, m, Ar**H**)

6.30 (1 H, t, *J* = 0.8 Hz, C**H**)

4.11 (2 H, t, *J* = 4.1 Hz,, C$\mathbf{H}_2$)

3.42 (2 H, t, *J* = 6.4 Hz,, C$\mathbf{H}_2$)

3.39 (3 H, s, C$\mathbf{H}_3$)

2.48 (3 H, d, *J* = 0.9 Hz, C$\mathbf{H}_3$)

1.87-1.79 (2 H, m, C$\mathbf{H}_2$)

1.71-1.64 (2 H, m, C$\mathbf{H}_2$)

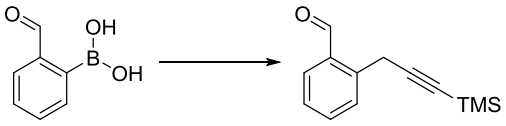
1.53-1.47 (2 H, m, C$\mathbf{H}_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 136.5 (**C**), 136.2 (**C**), 128.0 (**C**), 120.2 (**C**H), 119.6 (**C**H), 119.0 (**C**H), 108.9 (**C**H), 99.8 (**C**H), 72.4 (**C**H_2), 58.5 (**C**H_3), 43.0 (**C**H_2), 30.0 (**C**H_2), 29.3 (**C**H_2), 23.7 (**C**H_2), 12.7 (**C**H_3) ppm.

LRMS (ESI+) 232 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 232.1525, $C_{15}H_{22}NO$ $[M+H]^+$ requires 232.1543.

2-(3-(trimethylsilyl)prop-2-yn-1-yl)benzaldehyde (5.128)



5.129
$C_7H_7BO_3$
Mol Wt: 150.05

5.128
$C_{13}H_{16}OSi$
Mol Wt: 216.10

K_2CO_3 (3670 mg, 26.6 mmol), 3-bromo-1-(trimethylsilyl)-1-propyne (2.5 mL, 14.6 mmol) and H_2O (4.4 mL) were added to a solution of (2-formylphenyl)boronic acid (2000 mg, 13.3 mmol) in toluene (133 mL). The resulting mixture was degassed under argon for 15 min, then Pd(dppf)Cl_2 · DCM (108 mg, 0.13 mmol) was added. The reaction mixture was heated at 70 °C for 18 h then cooled to RT. The solution was concentrated under reduced pressure and purified by column chromatography (10-50% Et_2O/Pet) to afford the title compound (2080 mg, 9.63 mmol, 72%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2958 (w), 2177 (w), 1693 (s), 1250 (s), 1198 (m), 1027 (m), 839(s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 10.17 (1 H, s, C**H**)

7.75 (1 H, dd, *J* = 7.6, 1.5 Hz, Ar**H**)

7.70 (1 H, br d, *J* = 7.7 Hz, Ar**H**)

7.55 (1 H, td, *J* = 7.6, 1.5 Hz, Ar**H**)

7.34 (1 H, t, *J* = 7.3 Hz, Ar**H**)

4.08 (2 H, s, C**H**$_2$)

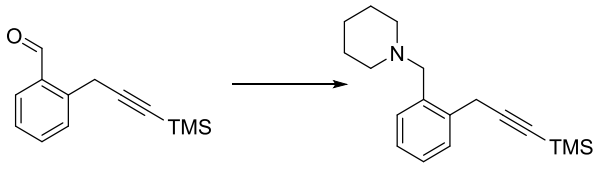
0.18 (9 H, s, Si(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 192.3 (**C**H), 138.1 (**C**), 133.8 (**C**H), 133.2 (**C**H), 133.0 (**C**), 129.6 (**C**H), 127.1 (**C**H), 103.3 (**C**), 88.3 (**C**), 23.8 (**C**H$_2$), -0.1 (Si(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 217 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 217.1043, $C_{13}H_{17}OSi$ $[M+H]^+$ requires 217.1043.

1-(2-(3-(trimethylsilyl)prop-2-yn-1-yl)benzyl)piperidine (5.83)



5.128
$C_{13}H_{16}OSi$
Mol Wt: 216.10

5.83
$C_{18}H_{27}NSi$
Mol Wt: 285.19

To a solution of 2-(3-(trimethylsilyl)prop-2-yn-1-yl)benzaldehyde **5.128** (648 mg, 3.00 mmol) in MeOH (100 mL) was added sodium triacetoxyborohydride (1145 mg, 5.40 mmol) amd piperidine (0.6 mL, 6.08 mmol). The mixture was stirred at RT for 18 h. The solution was concentrated under reduced pressure and purified by column chromatography (20–60% Et_2O/Pet) to afford the title compound (712 mg, 2.50 mmol, 83%) as a brown oil.

FT-IR (ν_{max}, $CHCl_3$) 3392 (br), 2933 (sm), 1662 (m), 1454 (m), 1344 (m), 1118 (w), 1110 (w), 1037 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.56 (1 H, br d, *J* = 7.5 Hz, Ar**H**)

7.33–7.22 (3 H, m, 3 × Ar**H**)

3.92 (2 H, s, C**H**$_2$)

3.49 (2 H, s, C**H**$_2$)

2.39 (4 H, br s, 2 × C**H**$_2$)

1.58 (4 H, br s, 2 × C**H**$_2$)

1.48 (2 H, br s, C**H**$_2$)

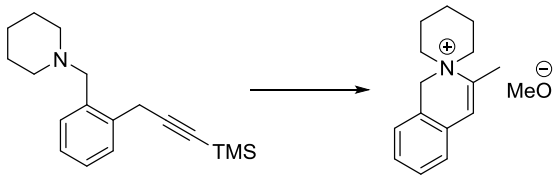
0.26–0.24 (9 H, m, Si(C**H**$_3$)$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 136.4 (**C**), 135.8 (**C**), 130.1 (**C**H), 128.5 (**C**H), 127.3 (**C**H), 126.2 (**C**H), 104.8 (**C**), 87.0 (**C**), 61.8 (**C**H$_2$), 54.6 (**C**H$_2$), 26.1 (2 × **C**H$_2$), 24.5 (**C**H$_2$), 23.4 (2 × **C**H$_2$), 0.1 (Si(**C**H$_3$)$_3$) ppm.

LRMS (ESI+) 286 ($[M+H]^+$, 100%).

HRMS (ESI+) Found 286.1986, $C_{18}H_{28}NSi$ $[M+H]^+$ requires 286.1986.

3-methyl-1H-spiro[isoquinoline-2,1'-piperidin]-2-ium methanolate (5.84)



5.83
$C_{18}H_{27}NSi$
Mol Wt: 285.19

5.84
$C_{16}H_{23}NO$
Mol Wt: 245.18

To a solution of 1-(2-(3-(trimethylsilyl)prop-2-yn-1-yl)benzyl)piperidine **5.83** (285 mg, 1.00 mmol) in MeOH (10 mL) was added K_2CO_3 (276 mg, 2.00 mmol). The mixture was stirred at RT for 18 h. The solution was concentrated under reduced pressure and purified by column chromatography (40–80% EtOAc/Pet) to afford the title compound (208 mg, 0.85 mmol, 85%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3305 (br), 2932 (s), 2851(w), 2801 (w), 1598 (m), 1489 (s), 1450 (s), 1379 (m), 1326 (w), 1225 (s), 1117 (w), 1026 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.79 (1 H, dd, *J* = 7.8, 1.0 Hz, Ar**H**)

7.32 (1 H, dd, *J* = 7.5, 1.0 Hz, Ar**H**)

7.22 (1 H, td, *J* = 7.6, 1.3 Hz, Ar**H**)

7.13 (1 H, td, *J* = 7.5, 1.3 Hz, Ar**H**)

5.76 (1 H, s, C**H**)

3.66 (3 H, s, C$\mathbf{H}_3$)

3.45 (2 H, s, C$\mathbf{H}_2$)

2.42 (4 H, br s, 2 × C$\mathbf{H}_2$)

2.10 (3 H, s, C$\mathbf{H}_3$)

1.63–1.55 (4 H, m, 2 × C$\mathbf{H}_2$)

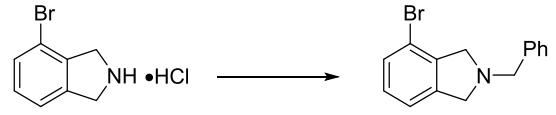
1.50–1.46 (2 H, m, C$\mathbf{H}_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 152.8 (**C**), 135.7 (**C**), 135.4 (**C**), 129.5 (**C**H), 129.2 (**C**H), 126.3 (**C**H), 125.1 (**C**H), 103.6 (**C**H), 61.5 (C$\mathbf{H}_2$), 55.4 (C$\mathbf{H}_3$), 54.6 (2 × C$\mathbf{H}_2$), 26.1 (2 × C$\mathbf{H}_2$), 24.5 (C$\mathbf{H}_2$), 19.0 (C$\mathbf{H}_3$) ppm.

LRMS (ESI+) 214 ([M-MeO$^-$]$^+$, 100%).

HRMS (ESI+) Found 214.1593, $C_{15}H_{20}N$ [M-MeO$^-$]$^+$ requires 214.1590.

2-benzyl-4-bromoisoindoline (5.101)



5.96
C_8H_9BrClN
Mol Wt: 232.96

5.101
$C_{15}H_{14}BrN$
Mol Wt: 287.03

To a solution of 4-bromoisoindoline hydrogen chloride (1045 mg, 4.46 mmol) in dichloroethane (100 mL) was added Et_3N (0.92 mL, 6.68 mmol), benzaldehyde (1.14 mL, 11.14 mmol) and sodium triacetoxyborohydride (2362 mg, 11.14 mmol). The result mixture was stirred at RT for 18 h. The solution was concentrated under reduced pressure and purified by column chromatography (30–60% EtOAc/Pet) to afford the title compound (918 mg, 3.20 mmol, 72%) as a brown oil.

FT-IR (ν_{max}, $CHCl_3$) 2925 (w), 1771 (w), 1674 (m), 1591 (s), 1426 (m), 1398 (m), 1357 (w), 1284 (w), 1072 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.48–7.45 (2 H, m, 2 × Ar**H**)

7.45–7.38 (2 H, m, 2 × Ar**H**)

7.48–7.32 (2 H, m, 2 × Ar**H**)

7.14–7.07 (2 H, m, 2 × Ar**H**)

4.06 (2 H, s, C**H**$_2$)

4.02 (2 H, s, C**H**$_2$)

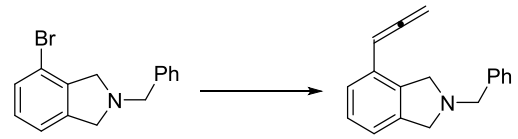
3.95 (2 H, s, C**H**$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 142.1 (**C**), 140.9 (**C**), 138.8 (**C**), 129.9 (**C**H), 128.6 (**C**H), 128.5 (**C**H), 128.4 (**C**H), 127.2 (**C**H), 121.1 (**C**), 117.3 (**C**), 60.0 (**C**H$_2$), 59.8 (**C**H$_2$), 59.7 (**C**H$_2$) ppm.

LRMS (ESI+) 288 ([M(^{79}Br)+H]$^+$, 100%), 290 ([M(^{81}Br)+H]$^+$, ~100%)

HRMS (ESI+) Found 288.0390, $C_{15}H_{15}{}^{79}BrN$ $[M(^{79}Br)+H]^+$ requires 288.0382.

2-benzyl-4-(2-propa-1,2-dien-1-yl)isoindoline (5.103)



5.101
$C_{15}H_{14}BrN$
Mol Wt: 287.03

5.103
$C_{18}H_{17}N$
Mol Wt: 247.14

LiCl (91 mg, 2.17 mmol) and tributyl(propa-1,2-dien-1-yl)stannane (711 mg, 2.20 mmol) were added to a solution of 2-benzyl-4-bromoisoindoline (521 mg, 1.82 mmol) in DMF (6 mL). The resulting mixture was degassed under argon for 15 min, then Tetrakis(triphenylphosphine)-palladium(0) (231 mg, 0.20 mmol) was added. The reaction mixture was heated at 70 °C for 18 h then cooled to RT. The solution was concentrated under reduced pressure and purified by column chromatography (10–60% Et_2O/Pet, 10% K_2CO_3/Silica) to afford the title compound (237 mg, 0.96 mmol, 53%) as a light sensitive brown oil.

FT-IR (ν_{max}, $CHCl_3$) 3290 (m), 3025 (w), 2910 (br), 1906 (w), 1493 (s), 1454 (s), 1117 (m), 1027 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.48–7.30 (5 H, m, 5 × Ar**H**)

7.18 (1 H, s, Ar**H**)

7.17 (1 H, s, Ar**H**)

7.05 (1 H, m, Ar**H**)

6.14 (1 H, t, J = 6.9 Hz, C**H**)

5.13 (2 H, d, J = 6.9 Hz, C**H**$_2$)

4.05 (2 H, s, C**H**$_2$)

3.93 (4 H, s, 2 × C**H**$_2$) ppm.

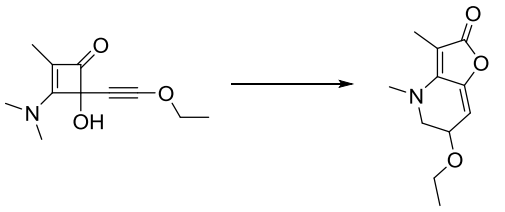
δ_C (100 MHz, $CDCl_3$) 210.8 (**C**), 140.8 (**C**), 139.1 (**C**), 137.8 (**C**), 128.72 (**C**H), 128.67 (**C**), 128.4 (**C**H), 127.12 (**C**H), 127.06 (**C**H), 125.1 (**C**H), 120.7 (**C**H), 91.6 (**C**H), 78.4 (**C**H$_2$), 60.3 (**C**H$_2$), 58.8 (**C**H$_2$), 58.0 (**C**H$_2$) ppm.

LRMS (ESI+) 248 ([M+H]$^+$, 100%).

HRMS (ESI+) Found 248.1434, $C_{18}H_{28}N$ [M+H]$^+$ requires 248.1434.

8.5 Experimental procedures for Chapter 6

6-ethoxy-3,4-dimethyl-5,6-dihydrofuro[3,2-b]pyridin-2(4H)-one (6.1)



3.5p
$C_{11}H_{15}NO_3$
Mol Wt 209.24

6.1
$C_{11}H_{15}NO_3$
Mol Wt 209.24

Cyclobutenone **3.5p** (50 mg, 0.25 mmol) in MeCN (20 mL) was pumped into the photo-reactor (UVB broad lamp) for 90 min. The resulting solution was concentrated under reduced pressure and purified by prep-TLC (Et_2O) to afford the title compound (10 mg, 0.05mmol, 20%) as a yellow oil.

MP 148–149 °C.

FT-IR (ν_{max}, $CHCl_3$) 2973 (br), 2928 (br), 2874 (br), 1751 (s), 1620 (s), 1446 (w), 1417 (w), 1309 (s), 1220 (w), 1086 (m), 1014 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 5.70 (1 H, d, *J* = 5.4 Hz, C**H**)

4.16 (1 H, td, *J* = 4.8 Hz, 2.9 Hz, C**H**)

3.63–3.50 (2 H, m, C**H**$_2$)

3.43 (1 H, dd, *J* = 13.0 Hz, 4.5 Hz, C**H**H)

3.34 (1 H, dd, *J* = 13.1 Hz, 2.3 Hz, CH**H**)

3.22 (3 H, s, C**H**$_3$)

2.01 (3 H, s, C**H**$_3$)

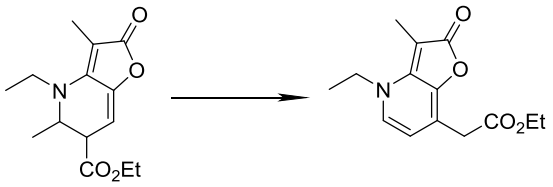
1.22 (3 H, t, *J* = 7.0 Hz, C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 171.3 (**C**), 150.1 (**C**), 147.0 (**C**), 98.7 (**C**H), 90.1 (**C**), 68.6 (**C**H), 63.6 (**C**H_2), 54.8 (**C**H_2), 38.9 (**C**H_3), 15.2 (**C**H_3), 8.5 (**C**H_3) ppm.

LRMS (ESI+) 210 ($[M+H]^+$, 100%), 441 ($[2M+Na]^+$, 30%).

HRMS (ESI+) Found 210.1123, $C_{11}H_{16}NO_3$ $[M+H]^+$requires 210.1123.

Ethyl 2-(4-ethyl-3-methyl-2-oxo-2,4-dihydrofuro[3,2-b]pyridin-7-yl)acetate (6.2)



4.68
$C_{14}H_{19}NO_4$
Mol Wt: 265.13

6.2
$C_{14}H_{17}NO_4$
Mol Wt: 263.12

Dihydrofuropyridinone **4.2g** (100 mg, 0.38 mmol) in dry MeCN (20 mL) was pumped into the photo-reactor (UVB lamp, 280–370 nm) for 4 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford the title compound **6.2** (78 mg, 0.30 mmol, 78%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3465 (br), 2980 (w), 1712 (s), 1577 (s), 1300 (m), 1243 (m), 1179 (m), 1029 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 6.85 (1 H, d, *J* = 7.1 Hz, C**H**)

6.28 (1 H, d, *J* = 7.2 Hz, C**H**)

4.20–4.11 (4 H, m, 2 × C**H**$_2$)

3.66 (2 H, s, C**H**$_2$)

2.14 (3 H, s, C**H**$_3$)

1.47 (3 H, t, *J* = 7.3, C**H**$_3$)

1.26 (3 H, t, *J* = 7.1, C**H**$_3$) ppm.

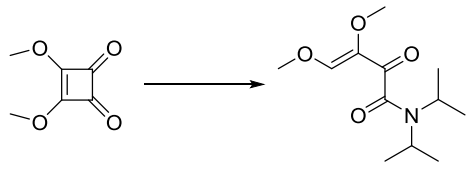
δ_C (100 MHz, $CDCl_3$) 170.7 (**C**), 169.7 (**C**), 145.0 (**C**), 142.9 (**C**), 129.7 (**C**H), 113.7 (**C**), 109.8 (**C**H), 79.8 (**C**), 61.3 (**C**H_2), 48.5 (**C**H_2), 33.4 (**C**H_2), 16.3 (**C**H_3), 14.1 (**C**H_3), 8.7 (**C**H_3) ppm.

LRMS (ESI+) 264 ([M+H]$^+$, 100%).

HRMS (ESI+) Found 264.1235, $C_{14}H_{18}NO_4$ [M+H]$^+$ requires 264.1230.

8.6 Experimental procedures for Chapter 7

(*Z*)-*N*,*N*-diisopropyl-3,4-dimethoxy-2-oxobut-3-enamide (7.2a)



1.43
$C_6H_6O_4$
Mol Wt: 142.03

7.2a
$C_{12}H_{21}NO_4$
Mol Wt: 243.15

To a solution of DIPA (0.29 mL, 2.10 mmol) in THF (20 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexane, 0.84 mL, 2.10 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of cyclobutenedione **1.43** (284 mg, 2.00 mmol) in THF (50 mL) at –78 °C. After a further 2 h H_2O (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (30–80% EtOAc/Pet) to afford the title compound (326 mg, 1.34 mmol, 65%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2974 (br), 1636 (s), 1446 (m), 1371 (m), 1239 (m), 1210 (m), 1139 (m), 1033 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 6.86 (1 H, s, C**H**)

3.89 (3 H, s, C**H**$_3$)

3.73 (3 H, s, C**H**$_3$)

3.68 (1 H, dt, *J* = 13.3, 6.6 Hz, C**H**)

3.46 (1 H, dt, *J* = 13.7, 6.9 Hz, C**H**)

1.44 (6 H, d, *J* = 6.9 Hz, 2 × C**H**$_3$)

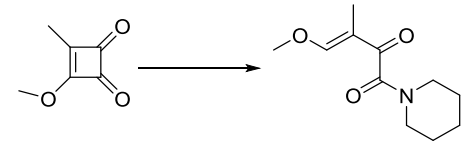
1.16 (6 H, d, *J* = 6.7 Hz, 2 × C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 188.4 (**C**), 166.5 (**C**), 153.4 (**C**), 136.9 (**C**H), 62.5 (**C**H_3), 60.2 (**C**H_3), 50.1 (**C**H), 45.7 (**C**H), 20.4 (2 × **C**H_3), 20.0 (2 × **C**H_3) ppm.

LRMS (ESI+) 244 ($[M+H]^+$, 100%), 266 ($[M+Na]^+$, 30%).

HRMS (ESI+) Found 244.1544, $C_{12}H_{22}NO_4$ $[M+H]^+$requires 244.1543.

(*E*)-4-methoxy-3-methyl-1-(piperidin-1-yl)but-3-ene-1,2-dione (7.2b)



3.2a
$C_6H_6O_3$
Mol Wt: 126.03

7.2b
$C_{11}H_{17}NO_3$
Mol Wt: 211.12

To a solution of piperidine (0.21 mL, 2.12 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 0.84 mL, 2.10 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of 3-methoxy-4-methylcyclobut-3-ene-1,2-dione **3.2a** (252 mg, 2.00 mmol) in THF (50 mL) at –78 °C. After a further 90 min H_2O (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (30–80% EtOAc/Pet) to afford the title compound (345 mg, 1.64 mmol, 82%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 2940 (br), 2858 (br), 1616 (s), 1447 (m), 1250 (s), 1151 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.06 (1 H, app d, *J* = 1.1 Hz, C**H**)

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

3.47 (2 H, t, *J* = 5.6 Hz, C**H**$_2$)

3.11 (2 H, t, *J* = 5.6 Hz, C**H**$_2$)

1.6 (3 H, d, *J* = 1.1 Hz, C**H**$_3$)

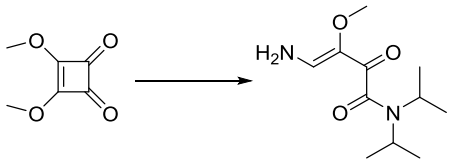
1.57–1.42 (6 H, m, 3 × C**H**$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 192.4 (**C**), 165.7 (**C**), 165.5 (**C**), 114.7 (**C**H), 61.9 (**C**H_3), 46.9 (**C**H_2), 41.8 (**C**H_2), 25.9 (**C**H_2), 25.1 (**C**H_2), 24.0 (**C**H_2) 6.6 (**C**H_3) ppm.

LRMS (ESI+) 212 ([M+H]$^+$, 100%), 234 ([M+Na]$^+$, 50%).

HRMS (ESI+) Found 212.1281, $C_{11}H_{18}NO_3$ [M+H]$^+$ requires 212.1281.

(*Z*)-4-amino-*N*,*N*-diisopropyl-3-methoxy-2-oxobut-3-enamide (7.7a)



1.43
$C_6H_6O_4$
Mol Wt: 142.03

7.7a
$C_{11}H_{20}N_2O_3$
Mol Wt: 228.15

To a solution of dry DIPA (0.29 mL, 2.07 mmol) in THF (20 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexane, 0.84 mL, 2.10 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of cyclobutenedione **1.43** (284 mg, 2.00 mmol) in THF (50 mL) at –78 °C. After a further 2 h ammonia solution (4 M in MeOH, 10 mL) was added a dropwise and the solution was stirred at –78 °C for another 30 min. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (30–80% EtOAc/Pet) to afford the title compound (343 mg, 1.5 mmol, 75%) as a white solid.

MP 215-217 °C (DCM/hexane).

FT-IR (ν_{max}, $CHCl_3$) 3370 (m), 3232 (br), 2928 (br), 1627 (s), 1535 (s), 1444 (m), 1289 (s), 1110 (m), 1032 (s) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 6.99 (1 H, br t, *J* = 9.7 Hz, C**H**)

4.97 (2 H, br d, *J* = 8.2 Hz, N**H**$_2$)

3.86 (1 H, spt, *J* = 6.6 Hz, C**H**)

3.77(1 H, s, C**H**$_3$)

3.47 (1 H, spt, *J* = 6.7 Hz, C**H**)

1.48 (6 H, d, *J* = 6.9 Hz, 2 × C**H**$_3$)

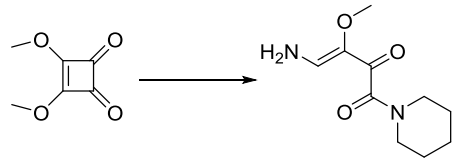
1.19 (6 H, d, *J* = 6.6 Hz, 2 × C**H**$_3$) ppm.

δ_C (100 MHz, $CDCl_3$) 167.5 (**C**H), 133.8 (**C**), 59.3 (**C**H_3), 50.4 (**C**H), 45.7 (**C**H), 20.5 (2 × **C**H_3), 20.2 (2 × **C**H_3) ppm (2 **C** not observed).

LRMS (ESI+) 229 ($[M+H]^+$, 100%), 251 ($[M+Na]^+$, 30%).

HRMS (ESI+) Found 251.1358, $C_{11}H_{20}NaN_2O_3$ $[M+Na]^+$ requires 251.1366.

(*Z*)-4-amino-3-methoxy-1-(piperidin-1-yl)but-3-ene-1,2-dione (7.7b)



1.43
$C_6H_6O_4$
Mol Wt: 142.03

7.7b
$C_{10}H_{16}N_2O_3$
Mol Wt: 212.12

To a solution of piperidine (0.21 mL, 2.12 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexane, 0.84 mL, 2.10 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of cyclobutenedione **3.2a** (252 mg, 1.77 mmol) in THF (50 mL) at –78 °C. After a further 90 min ammonia solution (4 M in MeOH, 10 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (40–80% EtOAc/Pet) to afford the title compound (356 mg, 1.68 mmol, 84%) as a white solid.

MP 205-206 °C (DCM/hexane).

FT-IR (ν_{max}, $CHCl_3$) 3291 (br), 2936 (m), 1658 (m), 1617 (s), 1545 (s), 1444 (m), 1308 (m), 1254 (m), 1060 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.08 (1 H, br t, *J* = 10.6 Hz, C**H**)

5.18 (2 H, br d, *J* = 8.2 Hz, N**H**$_2$)

3.76 (1 H, s, C**H**$_3$)

3.56 (2 H, t, *J* = 5.6 Hz, C**H**$_2$)

3.35 (2 H, t, *J* = 5.5 Hz, C**H**$_2$)

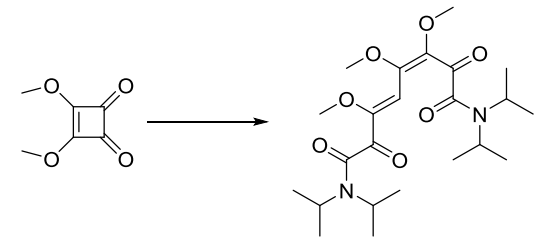
1.70-1.55 (6 H, m, 3 × C**H**$_2$) ppm.

δ_C (100 MHz, $CDCl_3$) 166.1 (**C**), 142.7 (**C**H), 133.9 (**C**), 59.4 (**C**H_3), 47.4 (**C**H_2), 42.2 (**C**H_2), 26.3 (**C**H_2), 25.4 (**C**H_2), 24.4 (**C**H_2) ppm (one **C** not observed).

LRMS (ESI+) 213 ($[M+H]^+$, 100%), 235 ($[M+Na]^+$, 40%).

HRMS (ESI+) Found 213.1240, $C_{10}H_{17}N_2O_3$ $[M+H]^+$ requires 213.1234.

(3*Z*,5*Z*)-*N*1,*N*1,*N*8,*N*8-tetraisopropyl-3,4,6-trimethoxy-2,7-dioxoocta-3,5-dienediamide (7.8)



1.43
$C_6H_6O_4$
Mol Wt: 142.03

7.8
$C_{23}H_{38}N_2O_7$
Mol Wt: 454.27

To a solution of dry DIPA (0.29 mL, 2.07 mmol) in THF (20 mL) at 0 °C was added ^{n}BuLi (2.5 M in hexane, 0.84 mL, 2.10 mmol) dropwise. After 15 min the solution was added *via* cannula to a solution of cyclobutenedione **1.43** (284 mg, 2.00 mmol) in THF (50 mL) at –78 °C. After a further 2 h H_2O (20 mL) was added dropwise and the solution was stirred at –78 °C for another 30 min. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (50–80% EtOAc/ Pet) to afford the title compound (178 mg, 0.39 mmol, 39%) as a yellow oil and **7.2a** (113mg, 0.46 mmol, 23%) as a yellow oil.

FT-IR (ν_{max}, $CHCl_3$) 3370 (br), 3222 (br), 2932 (br), 1665 (m), 1629 (s), 1535 (s), 1456 (m), 1373 (m), 1303 (s), 1290 (s), 1111 (m), 1032 (m) cm^{-1}.

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

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

3.70 (3 H, s, C**H**$_3$)

3.69–3.63 (2 H, m, 2 × C**H**)

3.62 (3 H, s, C**H**$_3$)

3.56–3.44 (2 H, m, 2 × C**H**)

	1.49 (6 H, d, *J* = 6.4 Hz, 2 × C**H**$_3$)
	1.48 (6 H, d, *J* = 6.4 Hz, 2 × C**H**$_3$)
	1.22 (6 H, dd, *J* = 6.6 Hz, 2 × C**H**$_3$)
	1.18 (6 H, dd, *J* = 6.6 Hz, 2 × C**H**$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	187.6 (**C**), 185.8 (**C**), 166.8 (**C**), 165.9 (**C**H), 154.9 (**C**), 153.4 (**C**), 144.7 (**C**), 113.2 (**C**H), 61.1 (**C**H$_3$), 60.1 (**C**H$_3$), 60.0 (**C**H$_3$), 50.4 (**C**H), 50.3 (**C**H), 46.0(**C**H), 45.5(**C**H), 20.32 (2 × **C**H$_3$), 20.30 (2 × **C**H$_3$), 20.1(2 × **C**H$_3$), 19.9 (2 × **C**H$_3$) ppm.
LRMS (ESI+)	423 ([M-MeO$^-$]$^+$, 100%), 455 ([M+H]$^+$, 40%), 477 ([M+Na]$^+$, 60%).
HRMS (ESI+)	Found 477.2564, $C_{23}H_{38}NaN_2O_7$ [M+Na]$^+$ requires 477.2571.

References

(1) Perri, S. T.; Dyke, H. J.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 2032.
(2) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897.
(3) Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896.
(4) Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 1412.
(5) Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345.
(6) Gurski, B.; Liu; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 7737.
(7) Sun, L. J.; Liebeskind, L. S. *J. Org. Chem.* **1995**, *60*, 8194.
(8) Harrowven, D. C.; Pascoe, D. D.; Demurtas, D.; Bourne, H. O. *Angew. Chem.* **2005**, *117*, 1247.
(9) Harrowven, D. C.; Pascoe, D. D.; Guy, I. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 425.
(10) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996.
(11) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 326
(12) Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 644
(13) Perri, S. T.; Foland, L. D.; Decker, O. H.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067.
(14) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.
(15) Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053.
(16) Pollart, D. J.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 5444.
(17) Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990**, *112*, 8612
(18) Ezcurra, J. E.; Karabelas, K.; Moore, H. W. *Tetrahedron* **2005**, *61*, 275
(19) Yin, H.; Dantale, S. W.; Akhmedov, N. G.; Soederberg, B. C. G. *Tetrahedron* **2013**, *69*, 9284.
(20) Gonçalves, T. P.; Mohamed, M.; Whitby, R. J.; Sneddon, H. F.; Harrowven, D. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 4531.
(21) Mohamed, M.; Goncalves, T. P.; Whitby, R. J.; Sneddon, H. F.; Harrowven, D. C. *Chem. Eur. J.* **2011**, *17*, 13698.
(22) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; et al. *J. Am. Chem. Soc.* **1989**, *111*, 975.
(23) Xia, H.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 3765.
(24) Xiong, Y.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 6460.
(25) Perri, S. T.; Foland, L. D.; Moore, H. W. *Tetrahedron Lett.* **1988**, *29*, 3529.
(26) Kirmse, W.; Rondan, N. G.; Houk, K. *J. Am. Chem. Soc.* **1984**, *106*, 7989.
(27) Rondan, N. G.; Houk, K. *J. Am. Chem. Soc.* **1985**, *107*, 2099.
(28) Rudolf, K.; Spellmeyer, D. C.; Houk, K. *J. Org. Chem.* **1987**, *52*, 3708.
(29) Dawson, B. A.; Girard, M.; Kindack, D.; Fillion, J.; Awang, D. V. C. *Magn. Reson. Chem.* **1989**, *27*, 1176.
(30) Birchler, A. G.; Liu, F.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 7737.
(31) Wang, J.; Jiang, X.; Chen, M.; Ge, Z.; Hu, Y.; Hu, H. *J. Chem. Soc. Perkin 1* **2001**, 66.
(32) Harrowven, D. C.; Mohamed, M.; Goncalves, T. P.; Whitby, R. J.; Bolien, D.; Sneddon, H. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 4405.
(33) Jas, G.; Kirschning, A. *Chem. Eur. J.* **2003**, *9*, 5708.
(34) Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8547.
(35) Hammett, L. *Chem. Rev.* **1937**, *17*, 125.
(36) Dubois, J. E.; Ruasse, M. F.; Argile, A. *J. Am. Chem. Soc.* **1984**, *106*, 4840.
(37) Ruasse, M. F.; Argile, A.; Dubois, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 4846.
(38) Lee, I.; Shim, C. S.; Chung, S. Y.; Kim, H. Y.; Lee, H. W. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1919.
(39) Hansch, C.; Leo, A.; Taft, R. *Chem. Rev.* **1991**, *91*, 165.

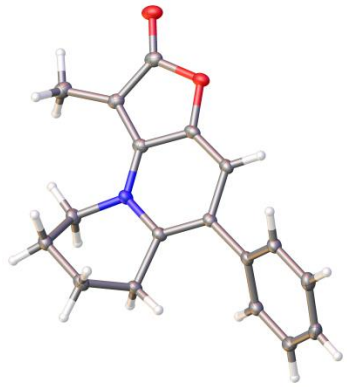
(40) Taft Jr, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 2729.
(41) Taft Jr, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 3120.
(42) Taft Jr, R. W. *J. Am. Chem. Soc.* **1953**, *75*, 4538.
(43) Pettit, R. K.; Fakoury, B. R.; Knight, J. C.; Weber, C. A.; Pettit, G. R.; Cage, G. D.; Pon, S. *J. Med. Microbiol.* **2004**, *53*, 61.
(44) Oppermann, G.; Stranberg, M.; Moore, H. W.; Schaumann, E.; Adiwidjaja, G. *Synthesis* **2010**, 2027.
(45) Packard, E.; Pascoe, D. D.; Maddaluno, J.; Goncalves, T. P.; Harrowven, D. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 13076.
(46) Gonçalves, T. P. PhD Thesis, Univeristy of Southampton **2014**, 61.
(47) Kümmel, H. G. *Recent Progress in Many-Body Theories* **2002**, p 334.
(48) Becke, A. D. *J. chem. Phys.* **1993**, *98*, 5648.
(49) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(50) Musch, P. W.; Remenyi, C.; Helten, H.; Engels, B. *J. Am. Chem. Soc.* **2002**, *124*, 1823.
(51) Schreiner, P. R.; Bui, B. H. *Eur. J. Org. Chem.* **2006**, 1162.
(52) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
(53) Hergueta, A. R.; Moore, H. W. *J. Org. Chem.* **1999**, *64*, 5979.
(54) Tiedemann, R.; Heileman, M. J.; Moore, H. W.; Schaumann, E. *J. Org. Chem.* **1999**, *64*, 2170.
(55) Perri, S. T.; Moore, H. W. *Tetrahedron Lett.* **1987**, *28*.
(56) Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 3491.
(57) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477.
(58) Peña-Cabrera, E.; Liebeskind, L. S. *J. Org. Chem.* **2002**, *67*, 1689.
(59) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155.
(60) Kwan, H. L.; Moore, H. W. *Tetrahedron Lett.* **1993**, *34*, 235.
(61) Breyer, S.; Effenberger-Neidnicht, K.; Schobert, R. *J. Org. Chem.* **2010**, *75*, 6214.
(62) Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 9168.
(63) Winters, M. P.; Stranberg, M.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 7572.
(64) Enhsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 1177.
(65) Vapourtec R4/R2+ devices can be purchased from Vapourtec Ltd., Place Farm, Suffolk, IP31 1NQ; http://www.vapourtec.co.uk
(66) Knueppel, D.; Martin, S. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 2569.
(67) Hook, B. D.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. *J. Org. Chem.* **2005**, *70*, 7558.
(68) Gaussian 09, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.
(69) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. chem. Phys.* **1969**, *51*, 2657.
(70) Hariharan, P. C.; Pople, J. A. *Theor. Chem. Acc.* **1973**, *28*, 213.
(71) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. chem. Phys.* **1980**, *72*, 650.

(72) Schlessinger, R. H.; Mjalli, A. M.; Adams, A. D.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 2992.
(73) Nishide, K.; Aramata, A.; Kamanaka, T.; Inoue, T. *Tetrahedron* **1994**, *50*, 8337.
(74) Schlessinger, R. H.; Pettus, T. R.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1994**, *59*, 3246.
(75) Schlessinger, R.; Li, Y.-J. *J. Am. Chem. Soc.* **1996**, *118*, 3301.
(76) Dankwardt, S. M.; Dankwardt, J. W.; Schlessinger, R. H. *Tetrahedron Lett.* **1998**, *39*, 4971.
(77) Liu, H.; Tomooka, C. S.; Moore, H. W. *Synth. Commun.* **1997**, *27*, 2177.
(78) Kraus, J. L. *Tetrahedron Lett.* **1985**, *26*, 1867.
(79) Xu, S.; Yerxa, B. R.; Sullivan, R. W.; Moore, H. W. *Tetrahedron Lett.* **1991**, *32*, 1129.
(80) Lim, N. C.; Morton, M. D.; Jenkins, H. A.; Brueckner, C. *J. Org. Chem.* **2003**, *68*, 9233.
(81) Onaran, M. B.; Comeau, A. B.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 10792.
(82) Lopez, C.; Vega, M.; Sanna, E.; Rotger, C.; Costa, A. *RSC Advances* **2013**, *3*, 7249.
(83) Yucel, B.; Sanli, B.; Soylemez, H.; Yilmaz, I. *Tetrahedron* **2011**, *67*, 1406.
(84) Yamamoto; Kurohara; Shibuya, *Chem. Commun.* **2015**, *51*, 16357.
(85) Hill-Cousins, J. T.; Pop, I.-A.; Pileio, G.; Stevanato, G.; Håkansson, P. r.; Roy, S. S.; Levitt, M. H.; Brown, L. J.; Brown, R. C. *Org. Lett.* **2015**, *17*, 2150.
(86) Karabelas, K.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 5372.
(87) Boullais, C.; Rannou, C.; Réveillère, E.; Mioskowski, C. *Eur. J. Org. Chem.* **2000**, *2000*, 723.
(88) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. *J. Org. Chem.* **1986**, *51*, 3065.
(89) Lee, Y. R.; Kim, B. S. *Synth. Commun.* **2001**, *31*, 381.
(90) Rao, M. M.; Kingston, D. G. *J. Nat. Prod.* **1982**, *45*, 600.
(91) Heltzel, C. E.; Gunatilaka, A. L.; Glass, T. E.; Kingston, D. G.; Hoffmann, G.; Johnson, R. K. *J. Nat. Prod.* **1993**, *56*, 1500.
(92) Ribeiro-Rodrigues, R.; Dos Santos, W.; Oliveira, A.; Snieckus, V.; Zani, C.; Romanha, A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1509.
(93) Inoue, K.; Chen, C.-C.; Inouye, H.; Kuriyama, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2764.
(94) Ian, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1085.
(95) Müller, K.; Sellmer, A.; Wiegrebe, W. *J. Nat. Prod.* **1999**, *62*, 1134.
(96) Sharma, K.; Iyer, A.; Sengupta, K.; Chakrapani, H. *Org. Lett.* **2013**, *15*, 2636.
(97) Schäfer, A.; Burstein, E. S.; Olsson, R. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1944.
(98) Ferrer, S.; Naughton, D. P.; Threadgill, M. D. *Tetrahedron* **2003**, *59*, 3445.
(99) Vyas, D.; Chiang, Y.; Benigni, D.; Doyle, T. *J. Org. Chem.* **1987**, *52*, 5601.
(100) Moody, C. J.; Swann, E. *Tetrahedron Lett.* **1993**, *34*, 1987.
(101) Wang, C.; Sperry, J. *Tetrahedron* **2013**, *69*, 4563.
(102) Skibo, E. B.; Xing, C.; Dorr, R. T. *J. Med. Chem.* **2001**, *44*, 3545.
(103) Phillips, R. M.; Hendriks, H. R.; Peters, G. J. *Br. J. Pharmacol.* **2013**, *168*, 11.
(104) Lee, K.-H.; Kuo, S.-C.; Google Patents: 2002.
(105) Godbole; Ranade; Joseph; Paradkar *Synth. Commun.* **2000**, *30*, 2951.
(106) Wu, C.; Johnson, R. K.; Mattern, M. R.; Wong, J. C.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 963.
(107) Wu, Y.-L.; Chuang, C.-P.; Lin, P.-Y. *Tetrahedron* **2001**, *57*, 5543.
(108) Luu, Q. H.; Guerra, J. D.; Castañeda, C. M.; Martinez, M. A.; Saunders, J.; Garcia, B. A.; Gonzales, B. V.; Aidunuthula, A. R.; Mito, S. *Tetrahedron Lett.* **2016**, *57*, 2253.
(109) Shvartsberg, M.; Kolodina, E.; Lebedeva, N.; Fedenok, L. *Russ. Chem. Bull.* **2012**, *61*, 582.
(110) Ueda, K.; Yamashita, M.; Sakaguchi, K.; Tokuda, H.; Iida, A. *Chem. Pharm. Bull.* **2013**, *61*, 648.
(111) Dijksman, W.; Verboom, W.; Reinhoudt, D.; Hale, C.; Harkema, S.; van Hummel, G. *Tetrahedron Lett.* **1984**, *25*, 2025.

(112) Pinnow, J.; Müller, E. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 149.
(113) Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1996**, *65*, 1.
(114) Meth-Cohn, O.; Taylor, D. L. *J. Chem. Soc., Chem. Commun.* **1995**, 1463.
(115) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211.
(116) Verboom, W.; Reinhoudt, D.; Lammerink, B.; Orlemans, E.; van Veggel, F.; Lelieveld, P. *Anti-Cancer Drug Des.* **1987**, *2*, 271.
(117) Reinhoudt, D.; Geevers, J.; Trompenaars, W. *Tetrahedron Lett.* **1978**, *19*, 1351.
(118) Reinhoudt, D. N.; Visser, G. W.; Verboom, W.; Benders, P. H.; Pennings, M. L. *J. Am. Chem. Soc.* **1983**, *105*, 4775.
(119) Denisov, V. Y.; Anishina, L.; Fokin, E. *Chem. Heterocycl. Compd.* **1975**, *11*, 1161.
(120) Andrew Hedley, K.; Stanforth, S. P. *J. Heterocycl. Chem.* **1995**, *32*, 529.
(121) Martin, J.; Meth-Cohn, O.; Suschitzky, H. *Tetrahedron Lett.* **1973**, *14*, 4495.
(122) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2008**, *11*, 129.
(123) Mátyus, P.; Földi, Á.; Ludányi, K.; Bényei, A. *Synlett* **2010**, *2010*, 2109.
(124) Povalyakhina, M. A.; Pozharskii, A. F.; Dyablo, O. V.; Ozeryanskii, V. A.; Ryabtsova, O. V. *Mendeleev Commun.* **2010**, *20*, 36.
(125) Pozharskii, A. F.; Povalyakhina, M. A.; Degtyarev, A. V.; Ryabtsova, O. V.; Ozeryanskii, V. A.; Dyablo, O. V.; Tkachuk, A. V.; Kazheva, O. N.; Chekhlov, A. N.; Dyachenko, O. A. *Org. Biomol. Chem.* **2011**, *9*, 1887.
(126) Nijhuis, W.; Leus, G.; Egberink, R.; Verboom, W.; Reinhoudt, D. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 172.
(127) Kelderman, E.; Noorlander‐Bunt, H.; Verboom, W.; Reinhoudt, D.; van Eerden, J. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 115.
(128) Verboom, W.; Hamzink, M.; Reinhoudt, D.; Visser, R. *Tetrahedron Lett.* **1984**, *25*, 4309.
(129) Schmitz, E.; Lutze, G.; Kirschke, K.; Hübner, P. *Bull. Soc. Chim. Belg.* **1992**, *101*, 61.
(130) Meth-Cohn, O.; Taylor, D. L. *J. Chem. Soc., Chem. Commun.* **1995**, 1463.
(131) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2008**, *74*, 419.
(132) del Carmen Ruiz Ruiz, M.; Vasella, A. *Helv. Chim. Acta* **2011**, *94*, 785.
(133) Orlemans, E. O. M.; Lammerink, B. H. M.; Veggel, F. C. J. M. v.; Verboom, W.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1988**, *53*, 2278.
(134) Kienzle, F. *Tetrahedron Lett.* **1983**, *24*, 2213.
(135) Blanco, B.; Sedes, A.; Peon; Lamb, H.; Hawkins, A. R.; Castedo, L.; Gonzalez-Bello, C. *Org. Biomol. Chem.* **2012**, *10*, 3662.
(136) Li, M.; Datta, S.; Barber, D. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 6350.
(137) Kong, J.; Chen, C.-Y.; Balsells-Padros, J.; Cao, Y.; Dunn, R. F.; Dolman, S. J.; Janey, J.; Li, H.; Zacuto, M. J. *J. Org. Chem.* **2012**, *77*, 3820.
(138) MacDougall, J. M.; Moore, H. W. *J. Org. Chem.* **1997**, *62,* 4554.
(139) Bellus, D.; Martin, P.; Sauter, H.; Winkler, T. *Helv. Chim. Acta* **1980**, *63*, 1130.
(140) Ganiek, M. A.; Becker, M. R.; Ketels, M.; Knochel, P. *Org. Lett.* **2016**, *18*, 828.
(141) Young; Durant; Emmett; Ganellin; Graham; Mitchell; Prain; Roantree *J. Med. Chem.* **1986**, *29*, 44.
(142) Taylor, J. E.; Jones, M. D.; Williams, J. M.; Bull, S. D. *Org. Lett.* **2010**, *12*, 5740.

Appendix A X-ray Structure

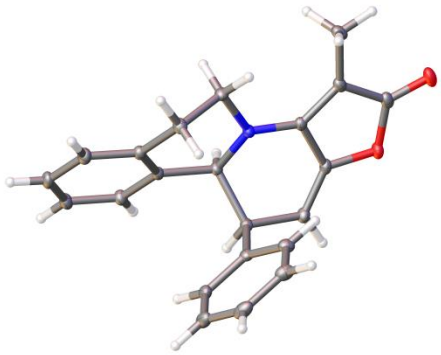
Details of X-ray Crystal Structure Determination for **4.1g**



Compound	**2014sot0040**	V/Å^3	1365.53(9)
Formula	$C_{18}H_{17}NO_2$	Z	4
$D_{calc.}$/ g cm^{-3}	1.359	Z'	1
μ /mm^{-1}	0.089	Theta $_{min}$/°	3.165
Formula Weight	279.32	Theta $_{max}$/°	30.507
Colour	clear pale yellow	Measured Refl.	19263
Shape	plate	Independent Refl.	4154
Max Size/mm	0.210	Reflections Used	3082
Mid Size/mm	0.030	R_{int}	0.0349
Min Size/mm	0.010	Parameters	191
T/K	100(2)	Restraints	0
Crystal System	monoclinic	Largest Peak	0.811
Space Group	$P2_1/c$	Deepest Hole	-0.243
a/Å	13.2699(5)	GooF	1.020
b/Å	7.2099(2)	wR_2 (all data)	0.1487
c/Å	15.4324(6)	wR_2	0.1352
α/°	90	R_1 (all data)	0.0791
β/°	112.354(5)	R_1	0.0546
γ/°	90		

Appendix A

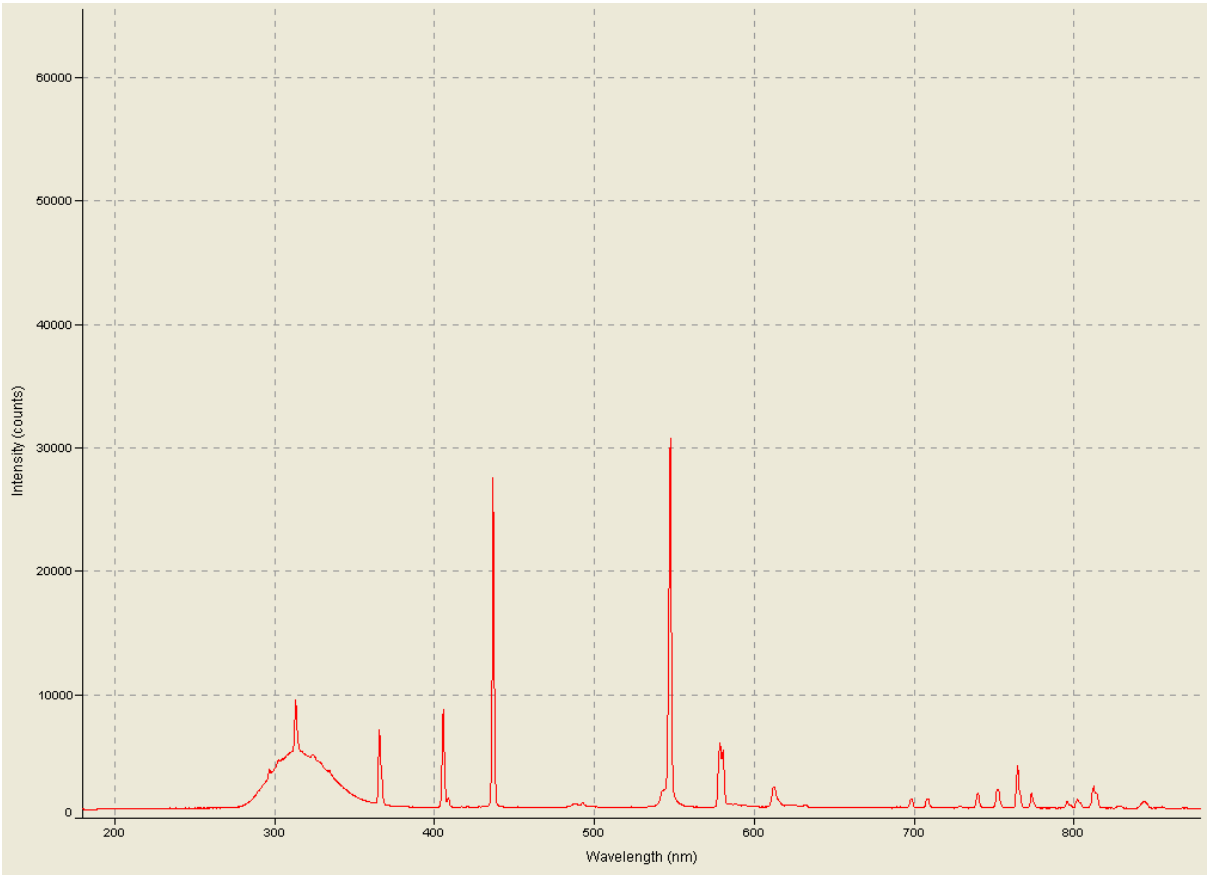
Details of X-ray Crystal Structure Determination for **4.26f**



Compound	**2014sot0031**	V/Å^3	1609.91(10)
Formula	$C_{22}H_{19}NO_2$	*Z*	4
$D_{calc.}$/ g cm^{-3}	1.359	*Z'*	1.000
μ /mm^{-1}	0.087	Theta $_{min}$/°	3.164
Formula Weight	329.38	Theta $_{max}$/°	30.508
Colour	clear colourless	Measured Refl.	22517
Shape	Prism	Independent Refl.	4905
Max Size/mm	0.500	Reflections Used	4066
Mid Size/mm	0.300	R_{int}	0.0260
Min Size/mm	0.200	Parameters	227
T/K	120	Restraints	0
Crystal System	monoclinic	Largest Peak	0.326
Space Group	$P2_1/n$	Deepest Hole	-0.229
a/Å	10.9967(4)	GooF	1.056
b/Å	12.6400(4)	wR_2 (all data)	0.1062
c/Å	11.6768(4)	wR_2	0.1013
α/°	90	R_1 (all data)	0.0493
β/°	97.296(2)	R_1	0.0398
γ/°	90		

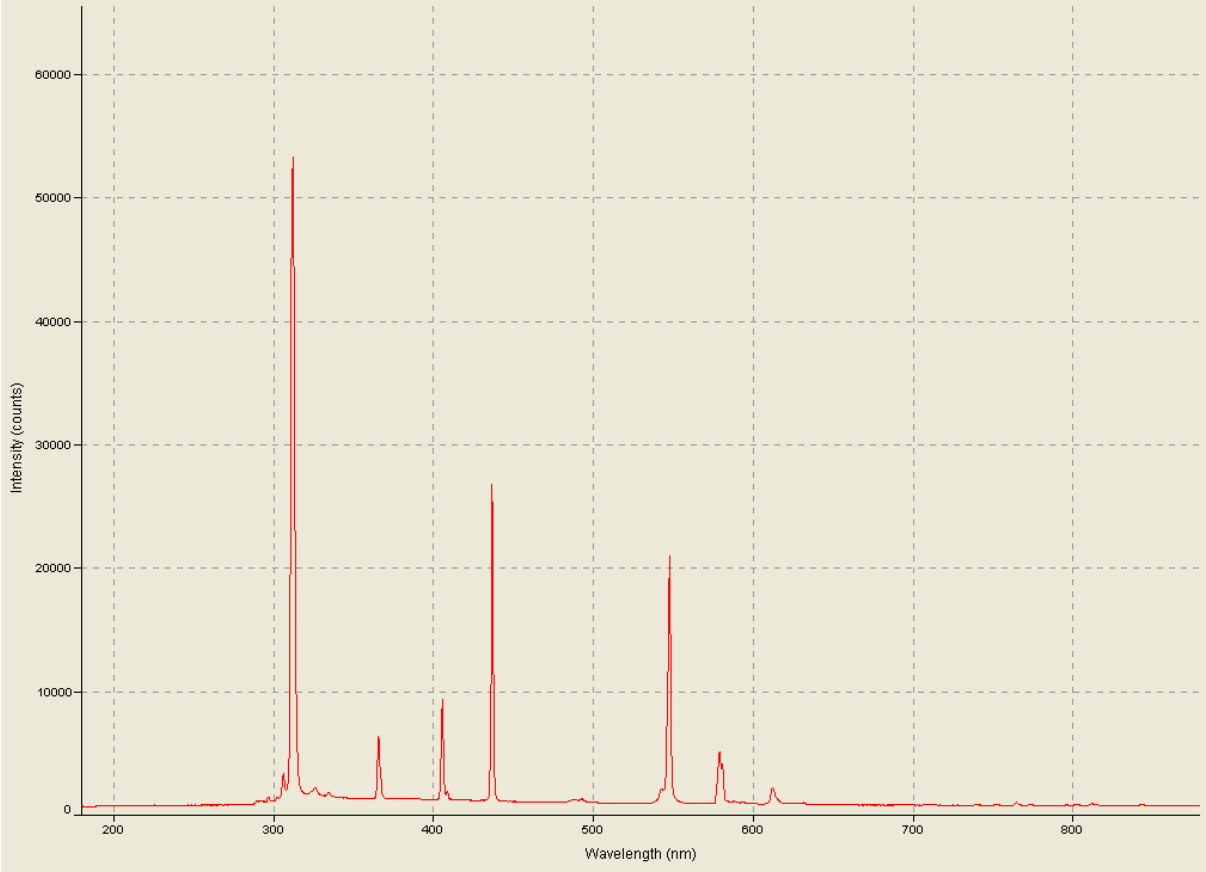
Appendix B Wavelengths of UV Lamps

Philips UVB Broad (280 – 370 nm); PL-S 9W/12/2P

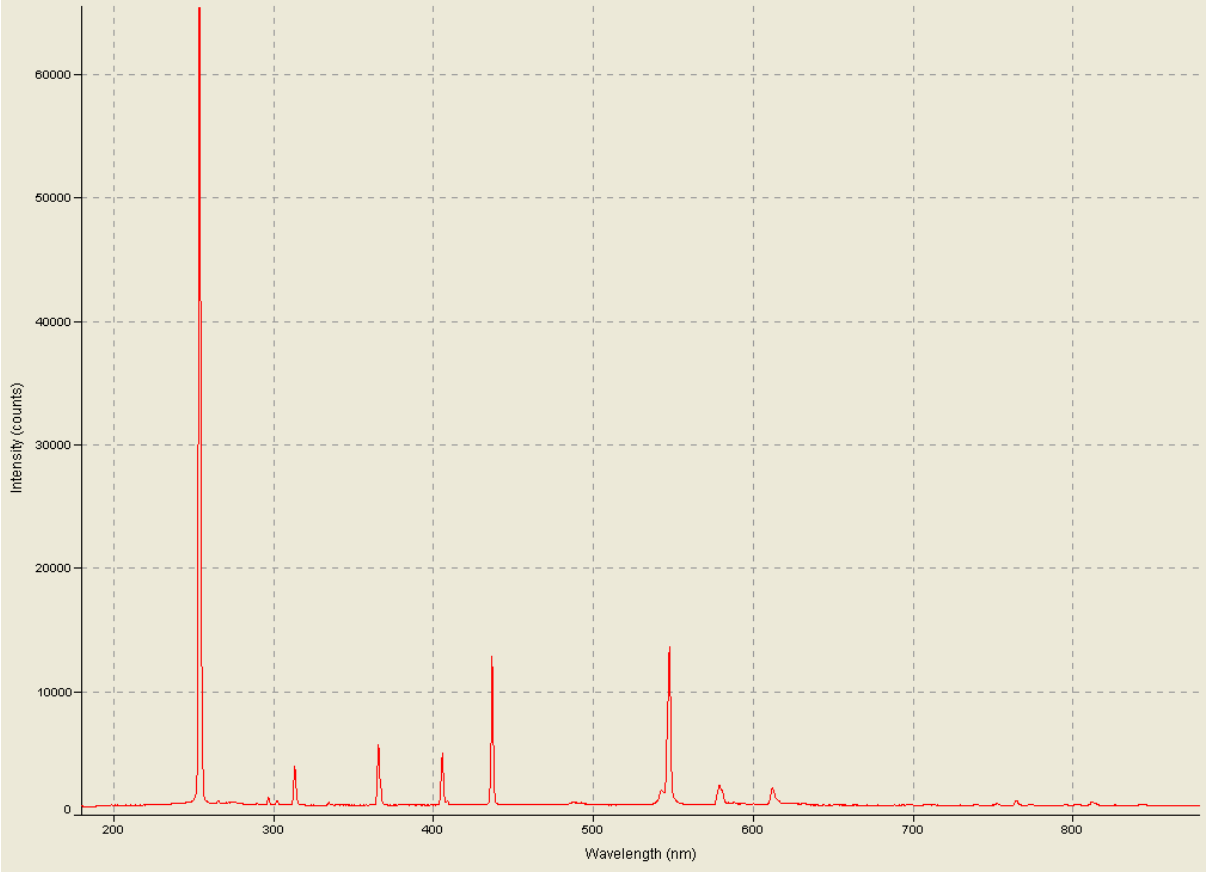


Appendix B

Philips UVB Narrow (310 – 320 nm); PL-S 9W/01/2P

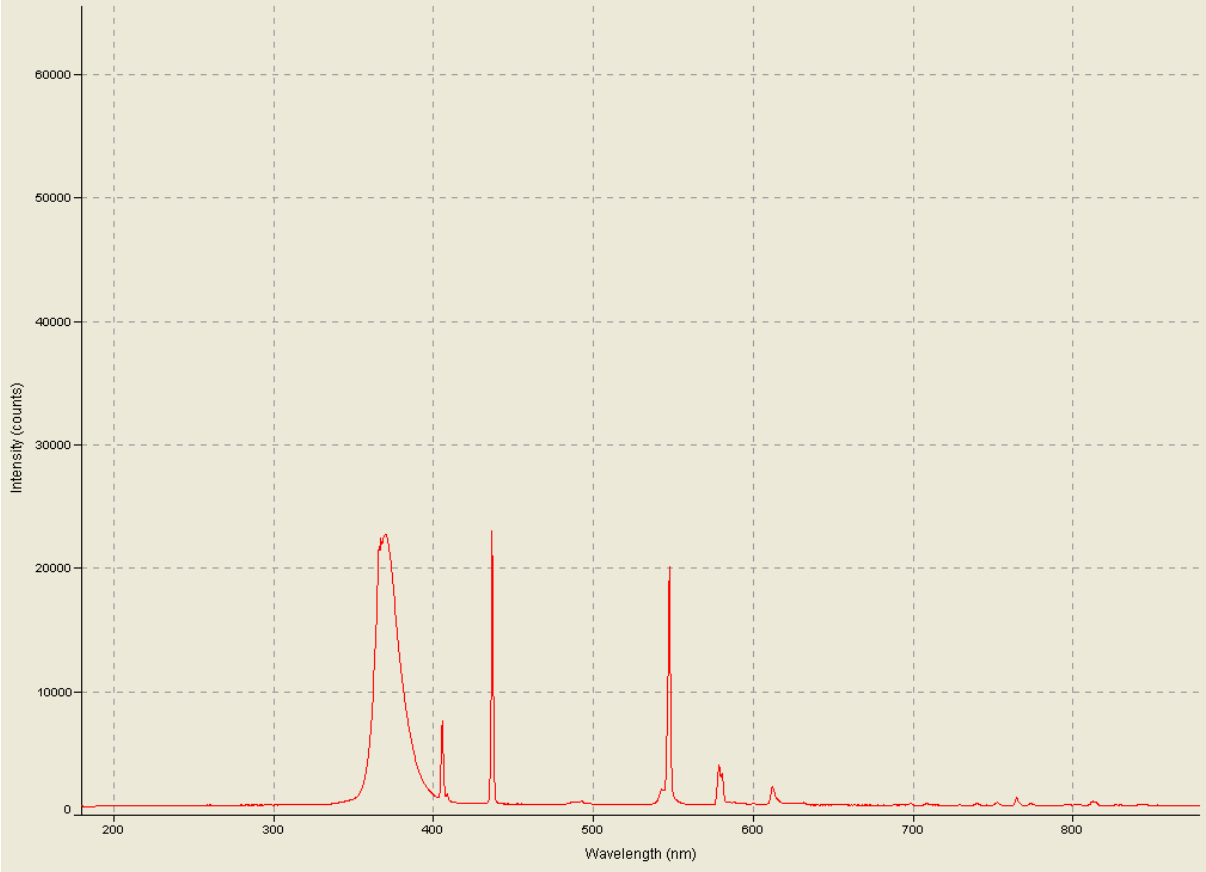


OSRAM UVC (254 nm); HNS S 92, GCF9Ds/G23/Se/OF



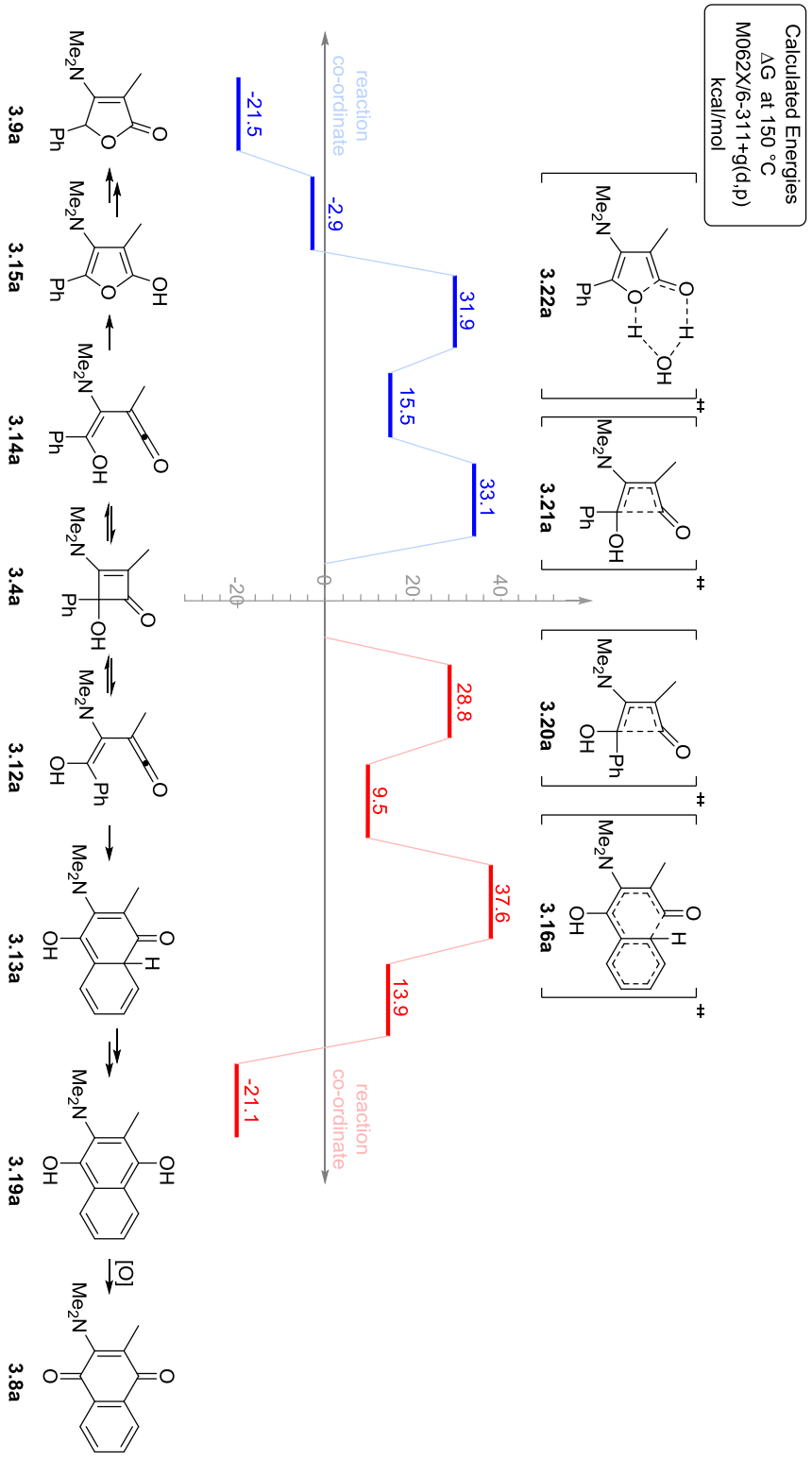
Appendix B

Philips UVA (360 – 395 nm); PL-S/9W/10/2P



Appendix C DFT Calculation Results

For the Thermal Rearrangement of Cyclobutenone **3.4a**



Scheme 3.9: Energy diagram for aminocyclobutenone **3.4a**.

Calculated at M062X/6-311+G(d,p), temperature=423.15 K.

3.4a				3.20a				3.12a			
E + ZPE = –709.214628				**E + ZPE = –709.171001**				**E + ZPE = –709.198365**			
E + thermal energies = –709.184717				**E + thermal energies = –709.140982**				**E + thermal energies = –709.168457**			
E + thermal enthalpies = –709.183377				**E + thermal enthalpies = –709.139642**				**E + thermal enthalpies = –709.167116**			
G = –709.286364				**G = –709.242913**				**G = –709.271165**			
Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)			
C	-1.915647000	-0.851246000	-0.485550000	C	1.232203000	1.345763000	0.082004000	C	-1.105480000	1.019284000	0.557034000
C	-1.331960000	0.214583000	0.170944000	C	1.278956000	-0.076280000	-0.047696000	C	-1.058094000	-0.354454000	-0.023137000
C	-0.146424000	-0.579858000	0.712772000	C	0.103383000	-0.639693000	0.505194000	C	-1.601658000	1.995608000	-0.168544000
C	-0.902003000	-1.759788000	0.012547000	C	0.417460000	1.434241000	1.169096000	C	-0.596459000	1.293384000	1.959351000
C	-3.105940000	-1.098753000	-1.353252000	C	1.783767000	2.439392000	-0.790786000	N	-2.263715000	-1.137873000	-0.140872000
N	-1.589627000	1.509571000	0.355659000	N	2.392855000	-0.786207000	-0.368097000	C	-3.159377000	-0.639830000	-1.182864000
C	-0.631788000	2.373630000	1.031432000	C	2.304327000	-2.170456000	-0.801720000	C	-2.965006000	-1.265076000	1.135348000
C	-2.690670000	2.168064000	-0.323384000	C	3.712852000	-0.186996000	-0.384490000	O	-2.032604000	2.857860000	-0.815703000
O	-0.694135000	-2.946960000	0.000768000	O	-0.079948000	1.847396000	2.141168000	O	0.049635000	-2.317865000	-0.646627000
O	-0.055811000	-0.660658000	2.117560000	O	0.199683000	-1.823274000	1.229444000	H	-1.132016000	0.673399000	2.682546000
H	-4.046644000	-0.937181000	-0.819637000	H	2.219947000	1.996582000	-1.688599000	H	0.468364000	1.051755000	2.020459000
H	-3.107960000	-0.465626000	-2.244473000	H	0.990885000	3.118597000	-1.111990000	H	-0.727279000	2.339695000	2.239742000
H	-3.087380000	-2.139432000	-1.681228000	H	2.555276000	3.031704000	-0.292183000	H	-3.982881000	-1.344698000	-1.316969000
H	-1.175669000	3.092559000	1.648233000	H	2.716825000	-2.853411000	-0.051318000	H	-3.587062000	0.342155000	-0.928221000
H	0.013681000	1.777198000	1.673373000	H	1.264074000	-2.435026000	-0.978738000	H	-2.613472000	-0.555897000	-2.123521000
H	-0.016616000	2.918009000	0.306733000	H	2.867714000	-2.293406000	-1.731464000	H	-2.285409000	-1.677707000	1.883101000
H	-3.394777000	1.425446000	-0.692453000	H	3.706800000	0.730279000	0.203316000	H	-3.346132000	-0.297778000	1.495105000
H	-3.209990000	2.830436000	0.373207000	H	4.433160000	-0.881049000	0.058363000	H	-3.809014000	-1.947350000	1.014832000
H	-2.326815000	2.765115000	-1.167066000	H	4.042913000	0.044095000	-1.403989000	H	-0.895765000	-2.551661000	-0.608525000
H	-0.647432000	-1.354700000	2.423483000	H	0.936163000	-1.747820000	1.842847000	C	0.086851000	-1.006990000	-0.312622000
C	1.198729000	-0.206232000	0.136115000	C	-1.264053000	-0.384929000	0.020146000	C	1.459743000	-0.463239000	-0.234478000
C	2.364351000	-0.396673000	0.875812000	C	-2.349974000	-0.823839000	0.786593000	C	1.773344000	0.832311000	-0.651019000
C	1.291814000	0.313137000	-1.157464000	C	-1.526156000	0.266521000	-1.194947000	C	2.475972000	-1.284504000	0.262334000
C	3.602260000	-0.069342000	0.330628000	C	-3.654674000	-0.597044000	0.362325000	C	3.075459000	1.306243000	-0.543421000
H	2.291012000	-0.797099000	1.878236000	H	-2.159853000	-1.343908000	1.716563000	H	1.002104000	1.462391000	-1.074397000
C	2.528254000	0.640995000	-1.699020000	C	-2.829117000	0.498960000	-1.607424000	C	3.775103000	-0.805380000	0.374422000
H	0.391340000	0.456473000	-1.746391000	H	-0.698299000	0.582942000	-1.820009000	H	2.235654000	-2.298845000	0.556489000
C	3.689236000	0.451306000	-0.955172000	C	-3.904396000	0.070157000	-0.830636000	C	4.077772000	0.492905000	-0.023827000
H	4.502173000	-0.224263000	0.914382000	H	-4.480981000	-0.941633000	0.973467000	H	3.309204000	2.310707000	-0.875845000
H	2.586548000	1.042179000	-2.704074000	H	-3.008561000	1.001853000	-2.550874000	H	4.552858000	-1.448678000	0.768477000
H	4.654219000	0.705894000	-1.377017000	H	-4.921406000	0.245894000	-1.159567000	H	5.091585000	0.866092000	0.059994000
Full Hessian at M062X/6–311+G(d,p) Frequencies:				Full Hessian at M062X/6–311+G(d,p) Frequencies:				Full Hessian at M062X/6–311+G(d,p) Frequencies:			
37.6595	53.4491	69.7621		-280.5284	51.3067	64.4288		32.0903	41.7842	44.864	
79.3794	85.6591	121.8426		66.7236	75.1344	83.9787		76.9683	103.329	109.5036	
150.3764	176.7932	202.9349		99.8285	124.8280	169.0650		133.0726	144.626	179.8009	
208.3126	232.1054	239.3218		175.6934	191.3234	210.5156		210.3978	238.8087	255.3218	
248.0285	266.1986	295.2701		245.2370	253.4293	299.0643		282.9075	297.3228	302.9133	
320.0066	356.5223	383.9652		312.0569	358.0362	373.3705		355.8336	375.2703	415.7108	
414.1808	440.5995	488.2456		378.9486	414.2471	415.9388		440.8484	469.9174	537.7607	
502.0757	587.5768	630.9392		495.3676	510.7131	554.5978		551.5907	577.0947	611.6678	
680.5302	685.5235	712.8665		618.2782	630.1222	655.0944		629.6177	677.4031	693.7303	
736.6308	765.5721	792.5858		679.9049	712.1292	719.4677		715.1893	739.5831	762.1976	
871.6780	882.9846	895.1811		779.4844	863.5321	867.3004		803.0350	853.1983	877.1790	
950.9061	993.2644	1008.8105		889.4644	933.8766	998.5259		940.5064	959.8957	1011.5547	
1015.3957	1021.3306	1023.9025		1002.4935	1012.9246	1014.1359		1011.8377	1022.0580	1025.5103	
1055.6737	1062.7547	1077.0598		1048.7904	1056.2925	1071.7847		1046.4582	1062.2676	1066.2215	
1094.8962	1117.0668	1122.0704		1094.6150	1111.5030	1127.1396		1071.9687	1114.9881	1117.7030	
1168.3384	1177.3966	1179.9218		1144.3942	1163.3869	1176.0276		1167.9590	1180.2631	1190.5450	
1209.6091	1228.5012	1245.4072		1203.1631	1228.8941	1292.6243		1208.8581	1243.5548	1252.1761	
1288.7950	1316.1828	1329.2108		1313.9177	1320.6798	1343.9878		1297.6654	1324.6359	1338.3880	
1354.5826	1367.8132	1409.5737		1351.7931	1393.2047	1411.4037		1355.2041	1399.5268	1403.6576	
1450.8940	1468.1398	1485.5418		1451.1750	1465.6473	1482.2174		1415.9275	1435.9217	1467.5442	
1489.0783	1493.4578	1500.9751		1486.1679	1490.1423	1494.1543		1479.3771	1488.1594	1488.6989	
1502.1519	1506.2357	1507.6926		1503.7312	1511.3340	1516.0013		1500.6125	1506.3330	1511.7662	
1540.2326	1547.9491	1664.1223		1531.8477	1539.4506	1605.8806		1525.8877	1543.7186	1657.0757	
1683.3474	1707.6741	1879.3696		1648.9672	1676.9431	2099.8119		1683.5091	1725.8434	2232.6788	
3032.5233	3035.1793	3047.0610		3030.0635	3034.1401	3043.3684		2994.1440	3009.9427	3037.2101	
3098.4012	3103.6853	3109.1493		3088.0291	3096.6612	3108.8724		3091.3633	3093.6338	3107.4875	
3138.6873	3162.7127	3174.7495		3128.3561	3161.4711	3171.9757		3126.5905	3136.6127	3139.2862	
3182.1588	3187.7759	3188.6480		3177.9927	3185.3214	3194.7012		3185.6462	3194.6983	3206.4364	
3202.3490	3226.0311	3893.5022		3205.1586	3217.1533	3895.2594		3215.4303	3217.9945	3659.9923	
3.16a				**3.13a**				**3.19a**			
E + ZPE = –709.159888				**E + ZPE = –709.196861**				**E + ZPE = –709.253116**			
E + thermal energies = –709.131499				**E + thermal energies = –709.168435**				**E + thermal energies = –709.224475**			
E + thermal enthalpies = –709.130159				**E + thermal enthalpies = –709.167095**				**E + thermal enthalpies = –709.223135**			
G = –709.227118				**G = –709.264233**				**G = –709.319933**			
Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)			
C	0.935010000	1.220349000	0.042421000	C	-0.965825000	1.176994000	0.065372000	C	-0.880055000	1.162814000	0.015334000
C	1.147056000	-0.190805000	-0.130445000	C	-1.201913000	-0.158858000	-0.011033000	C	-1.189533000	-0.228185000	-0.034528000
C	-0.283683000	1.859119000	-0.070205000	C	0.435780000	1.654944000	0.075295000	C	0.441183000	1.546552000	0.029585000
C	1.997744000	2.109458000	0.666185000	C	-2.026555000	2.241187000	0.073456000	C	-1.956846000	2.215265000	0.047798000
N	2.470156000	-0.756466000	-0.057132000	N	-2.490713000	-0.762439000	-0.139088000	N	-2.516676000	-0.774289000	-0.068725000
C	3.154715000	-0.705155000	1.232359000	C	-3.433234000	-0.191756000	-1.095569000	C	-3.381931000	-0.338658000	-1.158009000
C	3.328095000	-0.461436000	-1.198111000	C	-3.095040000	-1.115858000	1.145092000	C	-3.191947000	-0.846268000	1.223300000
O	-0.779981000	2.934683000	-0.110799000	O	0.708270000	2.827368000	-0.075086000	O	-0.478239000	-2.491942000	-0.071533000
O	0.496803000	-2.475415000	-0.262033000	O	-0.478192000	-2.442293000	-0.228404000	H	-2.273251000	2.484676000	-0.964440000
H	2.125381000	1.927000000	1.736799000	H	-2.353548000	2.501672000	-0.937524000	H	-2.835695000	1.872849000	0.591947000

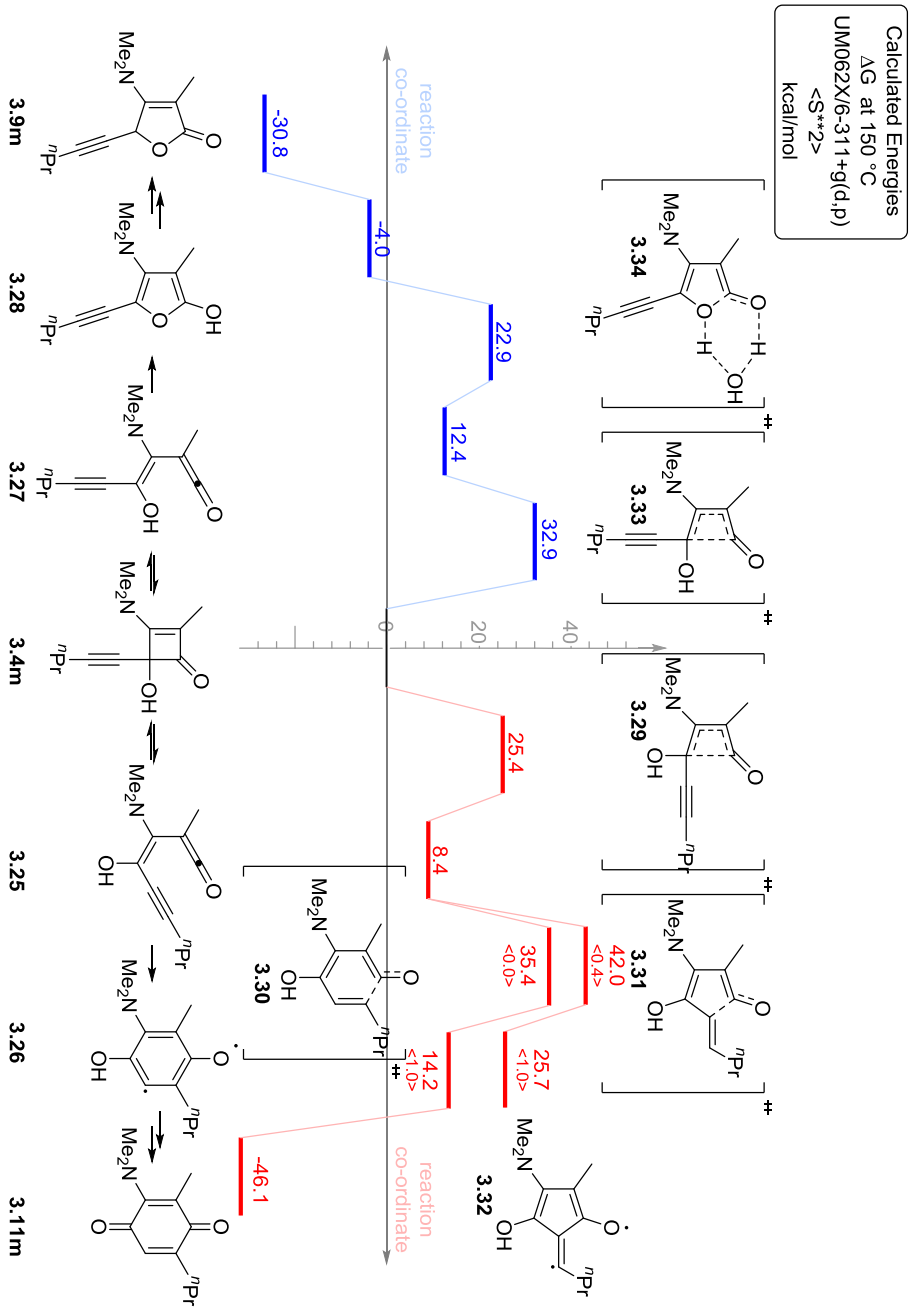
H	2.961928000	1.953556000	0.181801000	H	-2.899317000	1.927400000	0.645748000	H	-1.579228000	3.119247000	0.522555000
H	1.724030000	3.155770000	0.531460000	H	-1.615075000	3.146959000	0.517876000	H	-4.164077000	-1.087473000	-1.309820000
H	3.861895000	-1.537422000	1.290326000	H	-4.118355000	-0.980931000	-1.415216000	H	-3.868893000	0.627135000	-0.972032000
H	3.712486000	0.224135000	1.397076000	H	-4.028566000	0.632140000	-0.687387000	H	-2.795561000	-0.263318000	-2.074589000
H	2.422092000	-0.820492000	2.032699000	H	-2.889724000	0.165818000	-1.970354000	H	-2.507836000	-1.261208000	1.965219000
H	2.781680000	-0.659585000	-2.121174000	H	-2.371546000	-1.662072000	1.753456000	H	-3.546574000	0.128873000	1.584766000
H	3.684880000	0.577302000	-1.220884000	H	-3.425485000	-0.229808000	1.704108000	H	-4.055839000	-1.510698000	1.137440000
H	4.199606000	-1.120156000	-1.164312000	H	-3.958243000	-1.761004000	0.967266000	H	-1.444478000	-2.523178000	-0.175569000
H	1.466744000	-2.479335000	-0.186878000	H	-1.424765000	-2.414845000	-0.448017000	C	-0.183362000	-1.170476000	-0.034852000
C	0.167604000	-1.155916000	-0.263379000	C	-0.120005000	-1.149840000	-0.031977000	C	1.181323000	-0.787449000	-0.006378000
C	-1.212243000	-0.827774000	-0.207034000	C	1.176962000	-0.794858000	0.100861000	C	1.500145000	0.595552000	0.002249000
C	-1.601130000	0.481080000	-0.586368000	C	1.508166000	0.636172000	0.415417000	C	2.218566000	-1.750435000	-0.011352000
C	-2.180361000	-1.714963000	0.312402000	C	2.266061000	-1.738971000	-0.001663000	C	2.869879000	0.966908000	-0.023357000
C	-2.934389000	0.913390000	-0.352761000	C	2.892895000	1.043240000	0.006079000	C	3.531598000	-1.357968000	-0.014256000
H	-1.102133000	0.871394000	-1.481993000	H	1.482321000	0.711008000	1.526164000	H	1.947043000	-2.798692000	-0.015787000
C	-3.464155000	-1.272079000	0.521635000	C	3.537901000	-1.305240000	-0.120579000	C	3.858196000	0.016093000	-0.026780000
H	-1.882704000	-2.723980000	0.568327000	H	2.024357000	-2.794437000	-0.031508000	H	3.153552000	2.012579000	-0.072385000
C	-3.841561000	0.058090000	0.212098000	C	3.839466000	0.119999000	-0.200123000	H	4.322425000	-2.098193000	-0.018017000
H	-3.205671000	1.929620000	-0.615057000	H	3.088807000	2.105758000	-0.068037000	H	4.897686000	0.321384000	-0.051533000
H	-4.198730000	-1.945173000	0.948827000	H	4.347814000	-2.017771000	-0.221252000	O	0.716801000	2.892954000	0.045730000
H	-4.853364000	0.388332000	0.412787000	H	4.847731000	0.423651000	-0.457555000	H	1.555664000	3.045467000	0.487202000
Full Hessian at M062X/6–311+G(d,p) Frequencies:				Full Hessian at M062X/6–311+G(d,p) Frequencies:				Full Hessian at M062X/6–311+G(d,p) Frequencies:				
-623.2293	52.5075	68.4705		45.7019	72.4311	92.9142		58.2402	83.6963	102.3116		
97.4008	121.7874	178.0241		109.2755	160.2657	181.2675		145.3096	165.8086	182.9619		
183.4084	203.8500	206.0203		200.9934	212.9433	230.6706		191.1871	219.6275	235.6077		
236.4346	241.8671	250.4375		243.235	274.9925	300.7482		242.6525	255.6820	290.4016		
280.1741	316.6592	322.3977		310.3554	347.4422	370.1227		303.0483	325.7801	356.9972		
341.2031	360.4194	396.3235		397.1613	411.1035	425.0466		373.0179	411.3160	428.4462		
420.8497	458.3714	465.7898		437.0634	457.1196	521.4174		442.8528	469.3340	475.3011		
552.9878	560.1021	576.5184		539.7298	578.5238	625.0549		517.9586	574.9723	598.9695		
616.9203	636.313	667.3921		655.2446	664.1842	691.8924		657.2730	667.7381	676.6001		
686.9003	731.6996	758.0687		736.9474	772.3315	814.0165		682.1828	729.5082	778.0949		
787.2554	848.4808	881.3444		830.4556	846.5974	875.5583		795.7337	833.4711	861.2402		
898.5625	950.1856	994.9262		946.3829	994.5562	1003.5282		874.7261	976.5290	989.3304		
1012.2142	1025.3293	1042.3999		1010.1533	1015.4439	1042.1255		1013.6499	1016.7072	1049.7828		
1046.4501	1063.0629	1078.5133		1064.6287	1079.8749	1083.6011		1063.6260	1078.8237	1084.5650		
1086.3909	1090.5614	1119.8178		1104.2891	1120.1797	1153.8930		1125.7631	1127.4105	1151.5736		
1160.4449	1178.1405	1182.5990		1175.4534	1180.6856	1181.6029		1181.3352	1187.8727	1207.9993		
1191.3215	1233.6602	1260.6262		1224.3552	1239.4118	1256.1544		1230.2707	1261.1012	1273.7338		
1295.2401	1316.6113	1328.9856		1279.5962	1331.0704	1336.5360		1293.8429	1316.8963	1363.5013		
1365.5727	1407.7164	1415.8907		1372.1674	1400.7889	1419.9708		1408.9795	1421.2991	1441.4605		
1443.9087	1458.4193	1465.1685		1429.3948	1444.5707	1461.7013		1446.0671	1452.3652	1471.4317		
1474.5246	1488.3340	1494.2419		1473.9791	1483.8518	1490.0867		1482.7060	1486.8917	1494.2796		
1497.3214	1512.1140	1518.0699		1495.0918	1506.7760	1517.6166		1497.7783	1510.3889	1514.2925		
1536.6809	1543.2887	1581.3646		1540.5984	1612.1405	1657.9643		1520.8810	1540.7064	1568.0710		
1633.0482	1673.9951	1940.4017		1709.5325	1736.4858	1784.9274		1658.1647	1677.9545	1717.0499		
3015.8764	3024.0296	3031.0405		2891.3192	3014.8267	3029.5273		3014.3439	3027.5350	3056.9563		
3051.9238	3084.0085	3092.7961		3055.4016	3091.5049	3095.2558		3085.1117	3097.6821	3129.1412		
3123.6753	3135.3023	3141.1405		3126.6902	3130.3849	3144.2156		3140.6491	3142.3866	3164.4616		
3153.2398	3190.1748	3204.4861		3160.5373	3187.9293	3199.5642		3177.9304	3184.7119	3206.7778		
3215.1762	3224.3556	3679.6457		3213.5706	3218.9892	3688.8839		3226.8522	3693.2972	3914.4350		
3.21a				**3.14a**				**3.22a**				
E + ZPE = –709.162832				**E + ZPE = –709.188557**				**E + ZPE = –785.588514**				
E + thermal energies = –709.133042				**E + thermal energies = –709.158195**				**E + thermal energies = –785.556783**				
E + thermal enthalpies = –709.131702				**E + thermal enthalpies = –709.156855**				**E + thermal enthalpies = –785.555443**				
G = –709.233627				**G = –709.261712**				**G = –785.661631**				
Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)				
C	2.351813000	-0.547782000	0.081837000	C	2.406263000	-0.221837000	-0.080262000	C	-2.252854000	-0.029367000	0.040621000
C	1.216205000	0.201432000	-0.372314000	C	0.990790000	0.203557000	-0.045701000	C	-0.996667000	-0.741595000	-0.044173000
C	0.120842000	-0.685987000	-0.570404000	C	2.795593000	-1.487982000	-0.087643000	C	-1.984735000	1.309643000	0.153832000
C	1.646008000	-1.490773000	0.767604000	C	3.540369000	0.789303000	-0.137416000	C	-3.658452000	-0.552690000	0.071558000
C	3.833778000	-0.335492000	-0.059726000	N	0.664151000	1.556685000	0.232088000	N	-0.808644000	-2.133047000	-0.131828000
N	1.140280000	1.558078000	-0.350501000	C	1.046650000	2.578076000	-0.724663000	C	-1.835272000	-2.897799000	-0.819585000
C	0.093630000	2.283667000	-1.046404000	C	0.756340000	1.963010000	1.622009000	C	-0.352176000	-2.765978000	1.100120000
C	1.977053000	2.362096000	0.521739000	O	3.268088000	-2.544094000	-0.084268000	O	-2.576033000	2.401626000	0.192941000
O	1.396312000	-2.315705000	1.558775000	O	0.354275000	-2.008249000	-0.239994000	O	-0.511713000	1.408246000	0.217042000
O	0.165866000	-1.695271000	-1.531524000	H	3.549877000	1.322297000	-1.090907000	H	-3.966275000	-1.006562000	-0.873882000
H	4.014882000	0.428395000	-0.818813000	H	3.446330000	1.522520000	0.665308000	H	-3.797796000	-1.295684000	0.860907000
H	4.303394000	-0.008590000	0.872278000	H	4.505910000	0.295898000	-0.021310000	H	-4.333597000	0.279935000	0.275432000
H	4.336305000	-1.249280000	-0.382127000	H	0.301593000	3.381906000	-0.710472000	H	-1.404601000	-3.851634000	-1.134590000
H	0.536540000	3.152815000	-1.540896000	H	2.027706000	3.030904000	-0.523473000	H	-2.714173000	-3.110339000	-0.195957000
H	-0.365422000	1.640527000	-1.794981000	H	1.064972000	2.148696000	-1.728136000	H	-2.156368000	-2.359428000	-1.711392000
H	-0.686829000	2.625204000	-0.356257000	H	0.289498000	1.204614000	2.251769000	H	0.498134000	-2.219845000	1.510030000
H	2.590383000	1.716625000	1.147444000	H	1.789786000	2.118911000	1.969692000	H	-1.146458000	-2.808189000	1.860207000
H	2.627818000	3.025278000	-0.056890000	H	0.210950000	2.901498000	1.754808000	H	-0.030807000	-3.786412000	0.876826000
H	1.346309000	2.980139000	1.171215000	H	-0.300701000	-2.504499000	-0.740788000	H	-0.221655000	2.420835000	-0.193903000
H	1.087369000	-1.873692000	-1.742008000	C	-0.014989000	-0.684979000	-0.166927000	C	0.052552000	0.131694000	0.014967000
C	-1.254583000	-0.352096000	-0.186232000	C	-1.464929000	-0.416159000	-0.114896000	C	1.495283000	0.045352000	-0.002392000
C	-2.349667000	-0.848592000	-0.903771000	C	-2.301379000	-1.340838000	0.522591000	C	2.285108000	1.138603000	0.391812000
C	-1.498717000	0.424850000	0.956312000	C	-2.044784000	0.703160000	-0.725521000	C	2.145459000	-1.124761000	-0.434981000
C	-3.647426000	-0.548180000	-0.505813000	C	-3.677844000	-1.144433000	0.565504000	C	3.671421000	1.063245000	0.353034000
H	-2.168103000	-1.470757000	-1.770534000	H	-1.865337000	-2.204108000	1.013376000	H	1.816196000	2.047100000	0.753273000
C	-2.794968000	0.724893000	1.347504000	C	-3.418254000	0.894834000	-0.681735000	C	3.530135000	-1.188275000	-0.465764000
H	-0.659630000	0.775734000	1.550126000	H	-1.411624000	1.412836000	-1.240426000	H	1.548810000	-1.968639000	-0.757287000
C	-3.877804000	0.242638000	0.614717000	C	-4.241137000	-0.025126000	-0.034607000	C	4.305017000	-0.098630000	-0.073594000
H	-4.484341000	-0.938053000	-1.073729000	H	-4.307457000	-1.865006000	1.073972000	H	4.258888000	1.918635000	0.666381000
H	-2.964395000	1.321292000	2.236574000	H	-3.852537000	1.762767000	-1.163959000	H	4.010761000	-2.098394000	-0.806074000
H	-4.890649000	0.471584000	0.923805000	H	-5.313058000	0.129196000	-0.004374000	H	5.386189000	-0.156203000	-0.098913000

		O -0.491338000 3.658042000 -0.440564000 H -0.409852000 3.957415000 -1.350986000 H -1.473136000 3.488767000 -0.225363000
Full Hessian at M062X/6–311+G(d,p) Frequencies: -396.3464 46.8132 64.0462 65.9782 94.5274 106.2255 134.9708 139.2924 173.0512 192.3850 218.3842 230.4722 243.0531 253.4053 284.8810 321.5499 328.3438 368.1615 401.1851 415.1191 421.0900 490.2001 510.9672 565.5205 610.3585 629.8851 654.9570 682.5845 695.4750 709.8896 788.1575 841.5492 859.5955 901.1817 937.3455 982.3750 996.5576 1012.6148 1016.0211 1052.3765 1059.0869 1085.0421 1092.0649 1107.6585 1126.6852 1133.5380 1170.1292 1174.3814 1196.4162 1225.7564 1292.3343 1300.9386 1312.9861 1333.6402 1348.1237 1402.5802 1421.4210 1448.5426 1460.0097 1480.4527 1486.2352 1491.1377 1496.6656 1501.5130 1507.7393 1515.8002 1524.1870 1541.6451 1596.8623 1650.1845 1674.0746 2087.2549 3029.3080 3041.3940 3043.5032 3090.7839 3096.8858 3108.0963 3137.3713 3160.8395 3163.5102 3176.1070 3182.9585 3183.3847 3203.7455 3210.8484 3891.7380	Full Hessian at M062X/6–311+G(d,p) Frequencies: 13.7109 53.8661 56.1637 88.0155 101.0141 150.7468 168.2719 176.0556 191.2722 210.0864 228.6869 237.5966 273.0443 293.7893 298.2573 326.8385 343.6558 371.4307 387.0147 418.0141 450.3648 520.8930 543.9438 577.9778 599.8677 631.1085 651.8988 706.7041 717.0418 732.5355 792.4326 833.4035 873.1844 946.0012 954.3588 1007.1106 1012.8450 1017.2066 1022.4436 1050.8364 1060.1461 1082.3966 1098.0154 1113.7870 1121.1689 1150.2278 1168.0941 1178.3423 1206.6269 1233.9525 1265.9064 1280.2036 1317.2116 1347.1375 1351.8763 1374.5574 1409.7330 1423.9748 1442.6184 1470.5362 1483.5161 1484.2829 1488.7427 1501.7055 1505.6319 1522.0176 1536.3546 1537.5400 1645.3355 1673.0314 1735.0597 2217.0182 2987.2091 3006.1923 3058.8144 3066.0241 3084.9310 3131.2814 3132.1176 3142.3086 3150.2575 3197.3592 3204.0391 3213.7959 3225.8302 3244.5078 3874.8072	Full Hessian at M062X/6–311+G(d,p) Frequencies: -528.2268 35.7740 52.4263 67.5753 80.4272 98.7640 104.4678 155.4073 185.0183 206.6471 213.5086 232.0049 263.6223 275.8949 293.8778 309.4503 328.2691 334.4429 383.7101 413.7172 423.8497 461.9303 478.3214 501.9697 524.4947 557.5559 621.3165 629.3669 665.7989 690.3086 698.2902 714.2803 731.8319 775.0202 779.6666 867.1888 913.7786 931.8439 938.6248 962.7034 1005.0673 1006.5951 1012.2144 1022.3713 1064.4808 1067.5747 1075.6860 1082.3191 1109.2067 1118.2369 1122.1434 1165.9320 1172.3283 1177.6576 1214.0188 1265.8142 1279.6433 1300.0940 1322.6671 1342.2292 1360.7620 1396.4172 1433.8746 1440.1688 1459.4325 1478.2129 1487.6357 1489.7755 1493.6647 1499.5238 1512.3794 1519.7924 1530.6450 1540.6283 1586.3745 1636.0423 1664.4348 1678.9865 1794.2729 1904.3022 2886.0333 2994.5875 3013.7657 3047.7758 3086.5315 3088.5036 3107.7574 3132.5721 3134.7986 3145.3558 3179.6661 3183.1417 3199.1347 3213.0007 3225.4166 3925.7787
3.15a	**3.9a**	
E + ZPE = –709.221767 **E + thermal energies = –709.192856** **E + thermal enthalpies = –709.191516** **G = –709.291048**	**E + ZPE = –709.253116** **E + thermal energies = –709.224475** **E + thermal enthalpies = –709.223135** **G = –709.319933**	
Geometry at M062X/6–311+G(d,p) C -0.036925000 -0.443529000 -0.067655000 C 1.041203000 0.398241000 -0.080962000 C 2.238002000 -0.420899000 -0.041294000 C 1.764055000 -1.688310000 -0.014860000 O 0.424858000 -1.744753000 -0.019521000 O 2.420274000 -2.857666000 0.009960000 N 0.952936000 1.807406000 -0.071086000 C 3.681289000 -0.027785000 0.018791000 H 4.021608000 0.434111000 -0.910957000 H 3.866267000 0.679258000 0.830740000 H 4.292605000 -0.913542000 0.197901000 C 0.748601000 2.373094000 1.257398000 H 1.636414000 2.265762000 1.899736000 H 0.517934000 3.437073000 1.160720000 H -0.095231000 1.878482000 1.741203000 C 1.970366000 2.511690000 -0.835059000 H 1.623342000 3.530133000 -1.026539000 H 2.938746000 2.575354000 -0.318620000 H 2.114865000 2.014651000 -1.795155000 C -1.481786000 -0.267288000 -0.064812000 C -2.324548000 -1.373602000 0.110060000 C -2.060991000 0.997835000 -0.246681000 C -3.704056000 -1.218482000 0.108880000 H -1.890860000 -2.356314000 0.245941000 C -3.441869000 1.141900000 -0.248120000 H -1.418261000 1.854388000 -0.402682000 C -4.272008000 0.039360000 -0.068071000 H -4.339038000 -2.085857000 0.247302000 H -3.873434000 2.125617000 -0.393932000 H -5.348662000 0.159163000 -0.067109000 H 1.794102000 -3.564120000 0.199852000	Geometry at M062X/6–311+G(d,p) C -0.880055000 1.162814000 0.015334000 C -1.189533000 -0.228185000 -0.034528000 C 0.441183000 1.546552000 0.029585000 C -1.956846000 2.215265000 0.047798000 N -2.516676000 -0.774289000 -0.068725000 C -3.381931000 -0.338658000 -1.158009000 C -3.191947000 -0.846268000 1.223300000 O -0.478239000 -2.491942000 -0.071533000 H -2.273251000 2.484676000 -0.964440000 H -2.835695000 1.872849000 0.591947000 H -1.579228000 3.119247000 0.522555000 H -4.164077000 -1.087473000 -1.309820000 H -3.868893000 0.627135000 -0.972032000 H -2.795561000 -0.263318000 -2.074589000 H -2.507836000 -1.261208000 1.965219000 H -3.546574000 0.128873000 1.584766000 H -4.055839000 -1.510698000 1.137440000 H -1.444478000 -2.523178000 -0.175569000 C -0.183362000 -1.170476000 -0.034852000 C 1.181323000 -0.787449000 -0.006378000 C 1.500145000 0.595552000 0.002249000 C 2.218566000 -1.750435000 -0.011352000 C 2.869879000 0.966908000 -0.023357000 C 3.531598000 -1.357968000 -0.014256000 H 1.947043000 -2.798692000 -0.015787000 C 3.858196000 0.016093000 -0.026780000 H 3.153552000 2.012579000 -0.072385000 H 4.322425000 -2.098193000 -0.018017000 H 4.897686000 0.321384000 -0.051533000 O 0.716801000 2.892954000 0.045730000 H 1.555664000 3.045467000 0.487202000	
Full Hessian at M062X/6–311+G(d,p) Frequencies: 30.5726 71.1838 85.9844 107.5559 114.6269 179.0815 189.4908 206.6379 222.5770 235.1564 237.7960 265.5630 292.4574 310.5553 318.7741 329.8740 375.3923 390.5145 414.7811 460.9308 534.6704 565.4627 630.1505 652.7907 667.3984 695.7051 712.0527	Full Hessian at M062X/6–311+G(d,p) Frequencies: 58.2402 83.6963 102.3116 145.3096 165.8086 182.9619 191.1871 219.6275 235.6077 242.6525 255.6820 290.4016 303.0483 325.7801 356.9972 373.0179 411.3160 428.4462 442.8528 469.3340 475.3011 517.9586 574.9723 598.9695 657.2730 667.7381 676.6001	

713.4082	741.3237	787.5053	682.1828	729.5082	778.0949	
847.4395	875.2709	950.9565	795.7337	833.4711	861.2402	
963.5947	995.9383	1006.0372	874.7261	976.5290	989.3304	
1015.6699	1024.1549	1063.8795	1013.6499	1016.7072	1049.7828	
1071.3706	1084.6540	1107.9344	1063.6260	1078.8237	1084.5650	
1111.7712	1118.5739	1134.0357	1125.7631	1127.4105	1151.5736	
1171.2868	1178.7994	1181.2366	1181.3352	1187.8727	1207.9993	
1209.6964	1252.1896	1267.4506	1230.2707	1261.1012	1273.7338	
1301.3543	1324.9643	1354.0876	1293.8429	1316.8963	1363.5013	
1357.6550	1403.6000	1431.8877	1408.9795	1421.2991	1441.4605	
1445.5370	1465.4174	1480.6071	1446.0671	1452.3652	1471.4317	
1486.1062	1491.6379	1493.2015	1482.7060	1486.8917	1494.2796	
1501.5128	1508.2438	1515.8880	1497.7783	1510.3889	1514.2925	
1536.9107	1545.6871	1640.8013	1520.8810	1540.7064	1568.0710	
1666.1106	1682.2287	1754.0349	1658.1647	1677.9545	1717.0499	
2986.5023	3006.1117	3049.0517	3014.3439	3027.5350	3056.9563	
3084.3928	3085.9802	3112.6894	3085.1117	3097.6821	3129.1412	
3130.1493	3140.2350	3142.5705	3140.6491	3142.3866	3164.4616	
3174.9059	3193.4064	3203.2518	3177.9304	3184.7119	3206.7778	
3215.8168	3228.4693	3893.1167	3226.8522	3693.2972	3914.4350	

Appendix C

For the Thermal Rearrangement of Cyclobutenone **3.4m**



Scheme 3.11: Energy diagram for aminocyclobutenone **3.4m**.

Calculated at UM062X/6311+G(d,p), temperature=423.15 K.

3.4m				**3.29**				**3.25**			
E + ZPE = –672.236266				**E + ZPE = –672.196978**				**E + ZPE = –672.223156**			
E + thermal energies = –672.203807				**E + thermal energies = –672.164791**				**E + thermal energies = –672.190773**			
E + thermal enthalpies = –672.202467				**E + thermal enthalpies = –672.163451**				**E + thermal enthalpies = –672.189433**			
G = –672.314408				**G = –672.273907**				**G = –672.300951**			
Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)			
C	1.921748000	1.125913000	-0.530438000	C	1.602897000	1.233159000	-0.452127000	C	-1.237172000	1.208397000	0.249627000
C	1.639617000	-0.145705000	-0.075437000	C	1.536642000	-0.142079000	-0.099350000	C	-1.491774000	-0.217429000	-0.043054000
C	0.536962000	0.278950000	0.879691000	C	0.486657000	-0.325506000	0.843367000	C	-0.484923000	1.879202000	-0.598580000
C	0.935857000	1.700867000	0.358003000	C	1.031106000	1.775102000	0.663596000	C	-1.757354000	1.883620000	1.501730000
C	2.857661000	1.763342000	-1.503421000	C	2.060045000	1.915262000	-1.711839000	N	-2.826320000	-0.745386000	-0.011071000
N	2.075692000	-1.384447000	-0.307752000	N	2.461150000	-1.075124000	-0.408361000	C	-3.801022000	0.061055000	-0.735437000
C	1.670387000	-2.500741000	0.533456000	C	2.202272000	-2.491161000	-0.208993000	C	-3.293502000	-1.124818000	1.323785000
C	3.213050000	-1.617411000	-1.179393000	C	3.803329000	-0.719482000	-0.831517000	O	0.186911000	2.466665000	-1.336114000
O	0.553743000	2.795467000	0.684164000	O	0.768723000	2.575217000	1.471926000	O	-0.828874000	-2.373511000	-0.731183000
O	0.871183000	0.025356000	2.229811000	O	0.738747000	-1.237155000	1.867203000	H	-2.848342000	1.948586000	1.497905000
H	3.895814000	1.471452000	-1.326848000	H	1.326905000	2.653796000	-2.040814000	H	-1.451544000	1.318442000	2.385913000
H	2.604779000	1.518473000	-2.538835000	H	3.019822000	2.425418000	-1.592313000	H	-1.365991000	2.897614000	1.593353000

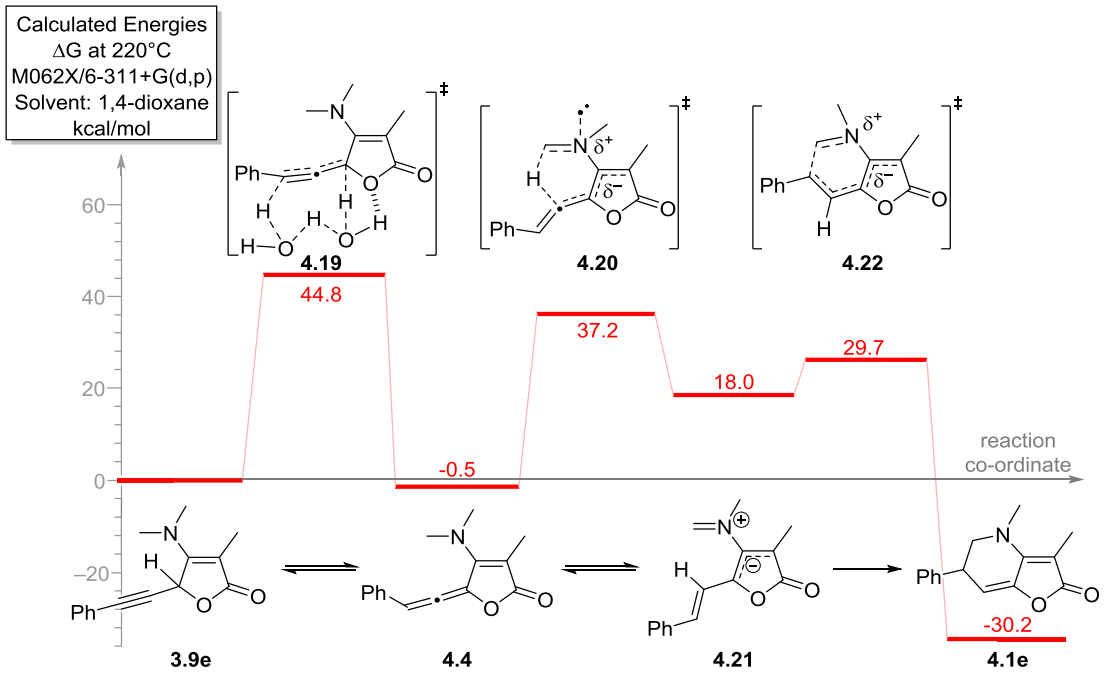
H	2.790080000	2.846900000	-1.393504000	H	2.162527000	1.175421000	-2.508329000	H	-4.738713000	-0.494358000	-0.805373000
H	2.488924000	-2.791248000	1.200519000	H	2.606463000	-2.843322000	0.744604000	H	-4.003810000	1.025197000	-0.247145000
H	0.810791000	-2.219811000	1.137554000	H	1.129354000	-2.671285000	-0.219597000	H	-3.434401000	0.255696000	-1.743723000
H	1.405479000	-3.353426000	-0.096186000	H	2.664202000	-3.047655000	-1.028293000	H	-2.524950000	-1.720007000	1.818905000
H	3.283906000	-0.822039000	-1.918861000	H	3.974526000	0.341404000	-0.657695000	H	-3.529649000	-0.257675000	1.955399000
H	4.146593000	-1.661067000	-0.607173000	H	4.531542000	-1.288339000	-0.245710000	H	-4.196273000	-1.732874000	1.226053000
H	3.077474000	-2.567644000	-1.699868000	H	3.962578000	-0.940748000	-1.892062000	H	-1.800997000	-2.400671000	-0.731352000
H	0.358343000	0.634274000	2.772486000	H	-0.101175000	-1.483268000	2.263579000	C	-0.523383000	-1.097291000	-0.389354000
C	-0.812954000	-0.168449000	0.538721000	C	-0.881086000	-0.057708000	0.559796000	C	0.864485000	-0.770200000	-0.442931000
C	-1.930700000	-0.515273000	0.257826000	C	-2.067254000	0.137796000	0.430766000	C	2.028304000	-0.468142000	-0.509255000
C	-3.300691000	-0.883704000	-0.094400000	C	-3.494728000	0.372683000	0.222822000	C	3.441489000	-0.104126000	-0.553201000
H	-3.758200000	-1.412193000	0.748408000	H	-3.630339000	1.374586000	-0.199409000	H	3.915886000	-0.622533000	-1.392811000
H	-3.278264000	-1.589447000	-0.931394000	H	-3.999316000	0.381948000	1.195224000	H	3.523768000	0.968323000	-0.758641000
C	-4.160402000	0.332497000	-0.468751000	C	-4.161898000	-0.663605000	-0.692438000	C	4.183320000	-0.442811000	0.748275000
H	-3.683863000	0.858107000	-1.299908000	H	-4.020666000	-1.658122000	-0.260680000	H	4.086103000	-1.514198000	0.940847000
H	-4.173655000	1.027206000	0.374575000	H	-3.647005000	-0.664100000	-1.656758000	H	3.692614000	0.072368000	1.578042000
C	-5.580525000	-0.079367000	-0.842748000	C	-5.647485000	-0.374603000	-0.884068000	C	5.654434000	-0.047089000	0.672619000
H	-6.185950000	0.789176000	-1.107191000	H	-5.799519000	0.612892000	-1.327973000	H	5.762505000	1.026625000	0.498124000
H	-5.578647000	-0.759286000	-1.698762000	H	-6.113675000	-1.111527000	-1.540455000	H	6.177384000	-0.290125000	1.599040000
H	-6.072909000	-0.590399000	-0.011201000	H	-6.177026000	-0.394874000	0.072086000	H	6.158940000	-0.570144000	-0.143998000
Full Hessian at M062X/6–311+G(d,p) Frequencies:				Full Hessian at M062X/6–311+G(d,p) Frequencies:				Full Hessian at M062X/6–311+G(d,p) Frequencies:				
20.0244	38.3644	54.9706		-292.3190	19.2911	40.3034		18.5713	32.4304	58.6639		
65.6396	72.7880	87.6415		61.6145	83.6181	92.2672		62.0627	72.4062	94.1679		
107.4885	129.5486	139.3584		101.8058	113.5625	115.8015		111.4216	121.5946	155.7907		
155.2405	176.6165	197.2127		138.1812	179.7498	200.5920		182.7681	195.5577	217.2212		
216.4706	236.8762	254.0222		217.8494	230.0654	240.0392		225.6656	242.9913	244.0343		
258.4070	289.4309	294.1506		261.1953	266.0437	283.5152		268.6327	281.3328	292.5208		
318.7155	339.9561	365.1217		318.0793	329.0295	339.4034		331.9850	345.2304	391.4764		
388.2502	432.4350	491.0647		373.0572	381.8887	413.6665		439.8040	466.9147	523.4897		
541.2330	582.7457	613.0781		482.1121	526.3234	576.1330		548.6772	571.6558	590.0569		
688.2277	740.5881	756.2823		603.2529	621.9909	670.5628		629.5729	685.7842	702.7645		
767.5374	859.5588	872.6862		720.3065	739.2798	844.5041		744.4323	746.6379	835.4671		
887.3903	910.3841	987.7376		870.0398	889.4119	908.8231		873.1473	907.0843	936.7655		
1014.2750	1050.0549	1052.5927		995.8077	1032.0050	1059.8306		1006.3720	1053.5945	1059.8014		
1068.2180	1097.7792	1121.6369		1069.1672	1094.2906	1121.2637		1066.8550	1074.5758	1118.6219		
1123.1131	1125.5495	1169.2289		1122.1572	1127.4274	1140.4770		1120.8061	1125.2420	1129.2370		
1175.3166	1197.8436	1232.2538		1164.5180	1232.5266	1261.9820		1184.6977	1250.7926	1260.6232		
1262.1566	1293.8571	1306.5831		1272.6930	1306.7688	1315.3399		1262.2746	1287.9927	1306.9995		
1308.0866	1329.1247	1363.5086		1326.4711	1331.7519	1388.3185		1326.5053	1341.1447	1385.6627		
1391.9769	1405.6989	1419.4896		1405.1925	1417.9517	1421.3484		1401.6442	1415.1246	1420.2274		
1450.8954	1473.8230	1476.6789		1449.5561	1465.5828	1470.9061		1429.8249	1438.7847	1469.4566		
1484.4011	1489.2841	1498.4988		1486.9552	1494.2852	1496.8648		1477.3433	1481.9093	1488.9568		
1498.7786	1500.5190	1506.2733		1497.2292	1504.6119	1506.8723		1500.4628	1500.6410	1504.7926		
1509.2335	1512.0704	1513.3290		1509.5973	1511.5639	1519.0426		1506.9466	1513.8786	1519.3610		
1553.1486	1714.0461	1886.5472		1546.1789	1629.0130	2098.2033		1523.0211	1705.0716	2239.8412		
2377.5452	3037.9697	3041.0129		2335.0606	3031.8776	3040.3943		2374.8468	3009.0139	3018.8814		
3044.9833	3046.5694	3054.4064		3046.9750	3047.2704	3053.0340		3048.3277	3049.8776	3051.3268		
3072.3364	3082.8765	3107.4101		3063.2359	3079.1250	3088.8122		3071.5687	3088.4097	3088.6908		
3109.4129	3110.1832	3111.4948		3104.7315	3111.7947	3119.7049		3095.3638	3111.3137	3113.0422		
3131.5698	3134.9705	3142.7820		3123.0438	3131.2127	3135.8341		3127.9890	3134.7242	3136.0337		
3167.3387	3195.6945	3870.5791		3164.4108	3164.5649	3910.8483		3139.6192	3141.4572	3686.0100		
3.30				**3.26**				**3.33**				
E + ZPE = –672.187099 **E + thermal energies = –672.156750** **E + thermal enthalpies = –672.155410** **G = –672.257952** **S**2 = 0**				**E + ZPE = –672.220061** **E + thermal energies = –672.189682** **E + thermal enthalpies = –672.188342** **G = –672.291753** **S**2 = 1.0491**				**E + ZPE = –672.184845** **E + thermal energies = –672.152483** **E + thermal enthalpies = –672.151143** **G = –672.261948**				
Geometry at UM062X/6–311+G(d,p)				Geometry at UM062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)				
C	-0.706557000	1.000015000	-0.159965000	C	-0.923179000	1.065124000	0.022464000	C	-2.722598000	-0.383506000	-0.031634000
C	-1.490260000	-0.174188000	-0.103403000	C	-1.394348000	-0.225179000	-0.018847000	C	-1.502069000	0.289074000	0.301902000
C	0.688119000	0.995922000	-0.195546000	C	0.524903000	1.318844000	-0.001412000	C	-0.508067000	-0.691641000	0.599689000
C	-1.306899000	2.389204000	-0.180187000	C	-1.805781000	2.276927000	0.076227000	C	-2.151990000	-1.498600000	-0.570607000
N	-2.867058000	-0.208591000	0.259565000	N	-2.768241000	-0.639222000	-0.047192000	C	-4.168091000	0.016270000	0.083457000
C	-3.796068000	-0.301390000	-0.863621000	C	-3.592488000	-0.076055000	-1.113400000	N	-1.260599000	1.597922000	0.069273000
C	-3.322220000	0.672338000	1.327892000	C	-3.422384000	-0.638147000	1.260703000	C	-0.114414000	2.285482000	0.639076000
O	1.548934000	1.784175000	-0.440952000	O	0.974327000	2.470857000	0.023307000	C	-2.084439000	2.382398000	-0.834264000
O	-1.544414000	-2.564931000	0.220351000	O	-0.962680000	-2.564609000	-0.170061000	O	-2.037098000	-2.462692000	-1.222516000
H	-0.642149000	3.062012000	-0.724791000	H	-2.029260000	2.637853000	-0.933090000	O	-0.605794000	-1.561374000	1.690085000
H	-2.268682000	2.371772000	-0.695103000	H	-2.748376000	2.075442000	0.581878000	H	-4.241331000	0.926361000	0.682148000
H	-1.462851000	2.808455000	0.817593000	H	-1.281381000	3.080923000	0.591507000	H	-4.630034000	0.207771000	-0.888898000
H	-4.776219000	-0.611408000	-0.493585000	H	-4.473660000	-0.708295000	-1.246155000	H	-4.753975000	-0.756053000	0.585332000
H	-3.909688000	0.657215000	-1.389404000	H	-3.930978000	0.946050000	-0.906504000	H	-0.435199000	3.270986000	0.987762000
H	-3.437228000	-1.047884000	-1.573332000	H	-3.024318000	-0.074311000	-2.044163000	H	0.274251000	1.717165000	1.481477000
H	-2.529357000	0.785869000	2.067465000	H	-2.796801000	-1.168783000	1.980447000	H	0.686137000	2.407466000	-0.097849000
H	-3.620439000	1.666243000	0.973509000	H	-3.610735000	0.373360000	1.643372000	H	-2.711277000	1.721517000	-1.430439000
H	-4.186323000	0.212794000	1.814635000	H	-4.378336000	-1.160557000	1.179515000	H	-2.720261000	3.086508000	-0.287128000
H	-2.396805000	-2.253038000	0.566425000	H	-1.931313000	-2.442691000	-0.234495000	H	-1.439724000	2.952236000	-1.509551000
C	-0.904596000	-1.433886000	-0.175253000	C	-0.481795000	-1.325681000	-0.072564000	H	-1.536665000	-1.747119000	1.847268000
C	0.461753000	-1.372580000	-0.313137000	C	0.882561000	-1.061720000	-0.048052000	C	0.833834000	-0.521357000	0.156444000
C	1.528979000	-0.727141000	-0.259963000	C	1.443907000	0.164696000	-0.022094000	C	1.951711000	-0.394349000	-0.281628000
C	2.970749000	-0.588923000	-0.548757000	C	2.918898000	0.433744000	0.005720000	C	3.317833000	-0.257417000	-0.781747000
H	3.095667000	0.170554000	-1.325471000	H	3.136994000	1.052194000	0.883970000	H	3.580653000	-1.150772000	-1.358895000
H	3.330442000	-1.542553000	-0.944758000	H	3.164503000	1.068979000	-0.853268000	H	3.361130000	0.585444000	-1.480306000
C	3.776340000	-0.188125000	0.693456000	C	3.778092000	-0.826520000	0.007164000	C	4.348659000	-0.050244000	0.337260000
H	3.647654000	-0.954838000	1.462248000	H	3.539809000	-1.426530000	-0.876990000	H	4.080499000	0.845695000	0.903692000
H	3.365398000	0.743250000	1.089170000	H	3.516316000	-1.440191000	0.875102000	H	4.285513000	-0.891018000	1.032559000
C	5.254448000	-0.014006000	0.359576000	C	5.268097000	-0.498753000	0.030040000	C	5.763803000	0.075453000	-0.218166000

H	5.828390000	0.262931000	1.245467000	H	5.875326000	-1.405785000	0.031835000	H	6.492509000	0.219456000	0.581321000
H	5.679720000	-0.938784000	-0.039814000	H	5.550877000	0.092893000	-0.844533000	H	6.047273000	-0.823567000	-0.771585000
H	5.392998000	0.770154000	-0.388950000	H	5.526950000	0.080349000	0.920252000	H	5.842807000	0.925616000	-0.901051000
Full Hessian at UM062X/6–311+G(d,p) Frequencies:				Full Hessian at UM062X/6–311+G(d,p) Frequencies:				Full Hessian at M062X/6–311+G(d,p) Frequencies:			
-559.9466	45.8348	59.8915		35.6148	58.0248	89.3360		-403.2911	32.2207	42.7285	
73.1258	98.6007	108.0021		99.1514	104.2317	118.3122		43.2997	78.5749	81.4759	
144.4553	176.0633	200.5150		153.3614	166.2499	179.3299		112.3926	112.5951	123.9828	
210.5524	226.8378	248.9429		199.4280	223.6740	235.7900		128.1261	168.5309	171.4586	
253.5605	263.9940	274.4692		256.3961	268.8248	300.5929		202.9713	228.0652	240.1399	
301.9637	306.6792	329.2499		306.4630	316.2555	349.0426		245.1710	251.1590	272.9524	
335.8297	367.2074	393.1208		399.8933	410.2875	422.3264		289.5588	304.9263	362.0157	
409.5598	458.4306	510.1638		482.4734	500.2980	555.7017		384.0945	402.7979	460.5013	
519.5580	578.4661	596.9246		612.0389	672.1380	692.1418		484.1627	490.6125	571.6596	
619.8036	628.3149	659.1642		709.6486	744.2852	764.7899		624.9410	630.8465	677.3093	
736.6700	753.0367	869.5333		781.5213	874.4390	885.8329		698.0532	743.0514	832.5301	
879.3654	916.4375	953.5695		912.4831	980.1867	990.8909		874.8689	893.2882	912.9680	
1002.7032	1059.9481	1065.2484		1042.8223	1069.4046	1075.2862		979.2619	1046.6199	1056.2256	
1078.9969	1085.0613	1121.7517		1084.8243	1117.4892	1118.1502		1072.4811	1092.5025	1122.4770	
1124.1596	1127.8707	1138.8336		1124.0227	1135.2768	1182.0500		1124.5449	1126.4483	1129.5075	
1178.2689	1219.5473	1260.7015		1199.4543	1212.4598	1256.5821		1165.3851	1208.7694	1265.5395	
1273.0063	1301.9853	1313.2983		1259.7370	1314.6669	1335.1655		1286.7600	1299.6847	1313.1119	
1341.8408	1346.1346	1396.2322		1337.0644	1357.3555	1413.1729		1318.7625	1333.5185	1391.1240	
1420.2261	1420.9211	1438.6083		1414.3587	1424.8391	1441.0531		1403.2943	1418.3950	1421.4707	
1448.6065	1468.9747	1476.8771		1448.0816	1463.2181	1473.2375		1447.4191	1462.3112	1474.6782	
1487.4949	1491.9735	1497.4190		1481.1386	1481.6069	1491.4783		1482.5021	1491.2068	1495.8138	
1501.7724	1509.1009	1509.8159		1498.7073	1500.0607	1509.6022		1496.9948	1503.4499	1506.1980	
1512.6436	1514.9121	1533.6739		1509.6871	1512.1391	1513.1110		1507.9191	1511.4819	1513.7813	
1537.8548	1546.3519	1864.7207		1525.6424	1553.3670	1580.7280		1523.6143	1607.2934	2089.8874	
2083.6921	3007.6260	3023.3800		1660.4631	3017.8887	3028.1058		2351.0757	3032.8814	3042.3277	
3049.2512	3057.4546	3075.6162		3051.3802	3052.2951	3060.0096		3044.7677	3048.4041	3049.0930	
3085.7126	3090.6821	3094.7130		3064.8871	3077.1026	3091.9623		3069.2805	3080.1862	3092.5623	
3114.4426	3116.6263	3127.6406		3095.5126	3100.9499	3131.5555		3104.4109	3105.1679	3114.3626	
3132.7378	3141.6787	3144.4011		3132.7462	3135.1967	3140.0728		3126.1369	3133.2267	3135.4914	
3147.5777	3152.1699	3731.4865		3144.3224	3177.8480	3583.9132		3160.2533	3170.1452	3892.5067	
3.27				**3.34**				**3.28**			
E + ZPE = –672.216017				**E + ZPE = –748.617871**				**E + ZPE = –672.245371**			
E + thermal energies = –672.183014				**E + thermal energies = –748.584010**				**E + thermal energies = –672.213935**			
E + thermal enthalpies = –672.181674				**E + thermal enthalpies = –748.582670**				**E + thermal enthalpies = –672.212594**			
G = –672.294642				**G = –748.695515**				**G = –672.320795**			
Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)				Geometry at M062X/6–311+G(d,p)			
C	-2.714543000	-0.254614000	-0.011959000	C	0.290265000	0.108579000	-0.136700000	C	0.335626000	-0.551015000	0.164640000
C	-1.295126000	0.157617000	-0.066700000	C	1.309821000	-0.809539000	-0.086784000	C	1.297613000	0.402623000	-0.043233000
C	-3.018847000	-1.446368000	0.462815000	C	2.558966000	-0.152443000	0.205966000	C	2.564871000	-0.289564000	-0.165547000
C	-3.812405000	0.619958000	-0.584211000	C	2.332215000	1.192851000	0.315721000	C	2.236871000	-1.598413000	-0.019054000
N	-0.934002000	1.492352000	0.253397000	O	0.879944000	1.366072000	0.171973000	O	0.933707000	-1.801834000	0.189957000
C	-1.471482000	2.004669000	1.500365000	O	2.976247000	2.251462000	0.421533000	O	3.023551000	-2.683398000	-0.036065000
C	-0.959592000	2.448699000	-0.842556000	N	1.224335000	-2.172615000	-0.341454000	N	1.032278000	1.774247000	-0.108984000
O	-3.302406000	-2.482782000	0.889491000	C	3.934628000	-0.741875000	0.166725000	C	3.963304000	0.226494000	-0.322984000
O	-0.643541000	-1.984429000	-0.787886000	H	4.263034000	-1.133857000	1.134292000	H	4.132111000	0.689221000	-1.297534000
H	-3.854333000	1.586461000	-0.078631000	H	3.977625000	-1.555530000	-0.561630000	H	4.204400000	0.963560000	0.445604000
H	-3.635919000	0.799419000	-1.647929000	H	4.649258000	0.027358000	-0.131817000	H	4.664722000	-0.603039000	-0.222681000
H	-4.788831000	0.146057000	-0.476798000	C	-0.004272000	-2.663851000	-0.942209000	C	0.516853000	2.384979000	1.108289000
H	-0.909819000	2.898415000	1.783650000	H	0.174844000	-3.677494000	-1.306577000	H	1.303749000	2.520899000	1.866374000
H	-2.537205000	2.275950000	1.450078000	H	-0.841602000	-2.688236000	-0.231525000	H	0.098702000	3.364097000	0.864007000
H	-1.344222000	1.257533000	2.284440000	H	-0.281546000	-2.031523000	-1.785108000	H	-0.276679000	1.768808000	1.528816000
H	-0.486741000	2.004371000	-1.719031000	C	1.709379000	-3.045379000	0.721472000	C	1.988633000	2.607198000	-0.811359000
H	-1.975400000	2.775752000	-1.114076000	H	0.975699000	-3.127638000	1.536671000	H	1.499504000	3.546968000	-1.078408000
H	-0.384200000	3.332904000	-0.555348000	H	1.887694000	-4.041108000	0.310539000	H	2.881557000	2.847746000	-0.215614000
H	0.154719000	-2.435583000	-1.073484000	H	2.641791000	-2.667315000	1.133890000	H	2.298670000	2.115823000	-1.733624000
C	-0.318365000	-0.700222000	-0.424616000	H	0.703167000	2.397398000	-0.272750000	H	2.489278000	-3.457008000	0.173750000
C	1.063329000	-0.347500000	-0.466917000	C	-1.102036000	0.097028000	-0.295956000	C	-1.056630000	-0.461241000	0.337156000
C	2.245593000	-0.123607000	-0.547259000	C	-2.301387000	0.133616000	-0.447183000	C	-2.247539000	-0.335349000	0.488966000
C	3.678554000	0.157606000	-0.592143000	C	-3.754399000	0.148809000	-0.595912000	C	-3.693553000	-0.181135000	0.625231000
H	4.089382000	-0.217361000	-1.535619000	H	-4.047101000	1.027375000	-1.181759000	H	-4.069942000	-0.934496000	1.325634000
H	3.825785000	1.242639000	-0.596970000	H	-4.052294000	-0.723298000	-1.189041000	H	-3.902224000	0.793570000	1.080238000
C	4.446241000	-0.461105000	0.585552000	C	-4.513500000	0.144362000	0.738714000	C	-4.445400000	-0.295917000	-0.708744000
H	4.284762000	-1.542143000	0.583681000	H	-4.205022000	1.015080000	1.323328000	H	-4.237865000	-1.275590000	-1.146892000
H	4.024254000	-0.081454000	1.519421000	H	-4.216451000	-0.738389000	1.310874000	H	-4.047325000	0.448937000	-1.402395000
C	5.937055000	-0.147443000	0.508855000	C	-6.023983000	0.156765000	0.525494000	C	-5.947446000	-0.103342000	-0.524945000
H	6.112031000	0.931159000	0.534728000	H	-6.559162000	0.154700000	1.476464000	H	-6.477064000	-0.193312000	-1.474863000
H	6.477617000	-0.594643000	1.344680000	H	-6.333317000	1.045363000	-0.031262000	H	-6.357525000	-0.850387000	0.159848000
H	6.371231000	-0.534394000	-0.416784000	H	-6.345854000	-0.720487000	-0.042064000	H	-6.167303000	0.884423000	-0.111006000
				O	1.103558000	3.580206000	-0.575724000				
				H	0.717472000	4.293316000	-0.058787000				
				H	2.029242000	3.357118000	-0.201890000				
Full Hessian at M062X/6–311+G(d,p) Frequencies:				Full Hessian at M062X/6–311+G(d,p) Frequencies:				Full Hessian at M062X/6–311+G(d,p) Frequencies:			
26.6131	33.6775	39.7456		-572.4154	31.8964	38.1963		23.6959	45.7256	52.8254	
68.4598	71.2360	95.2006		56.8279	70.9538	84.3229		60.2213	96.6917	99.2910	
98.5287	127.7200	159.4221		103.6592	106.2785	122.2841		130.0053	164.8687	177.0645	
184.0556	188.3961	202.7622		144.0874	196.6663	207.1463		195.4198	220.3119	245.5471	
214.0059	226.4702	245.5601		236.2356	243.2335	255.7943		247.5101	256.3601	278.7795	
255.9009	276.7484	284.4656		271.6005	280.3619	291.2017		284.8621	298.6881	326.2892	
306.429	322.8157	351.4520		313.1975	341.5386	356.0437		353.2838	359.5720	365.3075	
369.0729	431.8029	452.9361		370.8849	409.4232	445.3985		437.7349	472.1242	487.7631	

517.4643 552.9834 569.4847 578.9584 658.9987 695.7676 747.4342 750.4088 818.3806 874.3754 903.4538 943.3486 1002.4765 1049.4411 1059.1159 1082.0069 1083.4401 1118.9536 1119.7002 1126.2361 1129.1384 1173.3284 1236.5690 1263.8512 1270.1691 1288.6559 1305.0632 1329.1974 1341.6283 1373.1294 1391.8150 1409.6941 1417.1680 1424.1633 1445.9709 1475.0699 1476.6722 1485.9725 1489.3998 1498.9424 1502.8801 1503.8820 1506.3578 1512.9213 1521.3820 1528.5627 1735.3673 2241.7564 2361.0162 2989.5529 2997.2077 3047.9884 3050.1234 3051.2584 3069.2685 3087.8920 3089.1181 3095.4366 3108.5405 3116.3593 3128.1189 3132.2589 3137.7717 3144.6194 3150.5162 3920.9429	457.9309 488.1806 490.0234 537.2159 556.0866 564.3466 623.6707 687.3688 697.0675 732.5231 750.9018 769.3432 877.2026 884.9977 902.4368 943.1768 992.7743 1008.6713 1047.7462 1062.2913 1070.0019 1089.7717 1094.5923 1121.5134 1127.5781 1128.2254 1147.5982 1179.7401 1268.8244 1268.8854 1277.9649 1310.9873 1330.8994 1334.8758 1354.5557 1387.1404 1399.4224 1418.5365 1436.7073 1452.5230 1468.6936 1473.0460 1486.2382 1496.4340 1499.5210 1500.6546 1503.6994 1506.3979 1509.8154 1513.0506 1517.9863 1539.0299 1596.6879 1661.9071 1789.2565 1897.6110 2336.3706 2835.4388 3006.2506 3009.2150 3036.3188 3050.0499 3053.4579 3076.3939 3085.7112 3095.2558 3096.4718 3108.0068 3110.2421 3123.7725 3128.3004 3132.1948 3155.9221 3191.5641 3921.7703	552.4170 580.4088 666.0118 697.1416 708.0047 730.9906 745.0747 843.9921 874.0576 901.4170 964.5640 998.7462 1059.0210 1065.9265 1082.2163 1088.6168 1119.9472 1123.1715 1124.4433 1127.0827 1168.6896 1176.2939 1247.7548 1263.7089 1280.0672 1303.0407 1311.9530 1328.5064 1353.2961 1390.3343 1413.8683 1417.0957 1437.6409 1445.6934 1467.3634 1471.0342 1487.2614 1489.6640 1498.9513 1499.3915 1502.6414 1506.9096 1512.9037 1513.1070 1519.4206 1542.3873 1646.9686 1745.5318 2352.7970 2992.8021 3005.3656 3045.6814 3047.5765 3056.8525 3071.0383 3081.1598 3085.4867 3087.8331 3106.8555 3121.4419 3126.2867 3131.9092 3136.5918 3140.9228 3147.6600 3887.0543
3.31	**3.32**	
E + ZPE = –672.174721 **E + thermal energies = –672.143611** **E + thermal enthalpies = –672.142271** **G = –672.247464** **S**2 = 0.4181**	**E + ZPE = –672.198567** **E + thermal energies = –672.167493** **E + thermal enthalpies = –672.166153** **G = –672.273425** **S**2 = 1.0387**	
Geometry at UM062X/6–311+G(d,p) C -0.945417000 1.177306000 -0.174003000 C -1.514785000 -0.127869000 -0.083422000 C 0.410195000 1.118399000 -0.510089000 C -1.531667000 2.461331000 0.349050000 N -2.873899000 -0.449329000 0.029729000 C -3.849928000 0.542028000 -0.393882000 C -3.260565000 -1.151435000 1.252783000 O 1.306704000 1.847159000 -0.799258000 O -0.916389000 -2.444821000 -0.424681000 H -2.018654000 2.318869000 1.317827000 H -0.738943000 3.199602000 0.473684000 H -2.267149000 2.887045000 -0.339852000 H -4.790397000 0.031363000 -0.612762000 H -4.045383000 1.305787000 0.370419000 H -3.502166000 1.030031000 -1.304191000 H -2.533420000 -1.929197000 1.484503000 H -3.323311000 -0.463903000 2.107669000 H -4.238733000 -1.614492000 1.105791000 H -1.822806000 -2.456657000 -0.762977000 C -0.590863000 -1.146148000 -0.207213000 C 0.742845000 -0.670988000 -0.339153000 C 1.976829000 -0.931566000 -0.408251000 C 4.331979000 -0.530693000 0.355552000 H 5.314968000 -0.281499000 -0.053109000 H 4.406276000 -1.531788000 0.788848000 C 3.934755000 0.482749000 1.424456000 H 2.963403000 0.226899000 1.855292000 H 4.667539000 0.513933000 2.232657000 H 3.851491000 1.483953000 0.994344000 C 3.324966000 -0.556205000 -0.802552000 H 3.247533000 0.444993000 -1.261388000 H 3.654483000 -1.239787000 -1.592994000	Geometry at UM062X/6–311+G(d,p) C -1.004648000 1.114483000 -0.112763000 C -1.610233000 -0.152588000 0.050438000 C 0.423089000 0.914034000 -0.299565000 C -1.626794000 2.468116000 -0.103062000 N -2.971767000 -0.513353000 0.255332000 C -3.758704000 -0.472843000 -0.978940000 C -3.625342000 0.214811000 1.340528000 O 1.284401000 1.763577000 -0.475587000 O -0.912064000 -2.456039000 0.123419000 H -1.891038000 2.781401000 0.912853000 H -0.910497000 3.189880000 -0.498826000 H -2.538021000 2.503855000 -0.705542000 H -4.740355000 -0.913041000 -0.790694000 H -3.900813000 0.552128000 -1.350084000 H -3.256276000 -1.055481000 -1.752158000 H -2.989124000 0.195033000 2.225847000 H -3.839740000 1.260654000 1.081223000 H -4.569422000 -0.279750000 1.579091000 H -1.859539000 -2.519719000 0.331473000 C -0.658693000 -1.158598000 -0.015913000 C 0.657862000 -0.587951000 -0.248081000 C 3.826252000 -0.167466000 0.692500000 H 3.817437000 -0.956780000 1.449173000 H 3.192392000 0.645372000 1.053948000 C 5.248427000 0.333881000 0.463734000 H 5.258928000 1.140778000 -0.272927000 H 5.681274000 0.718804000 1.388908000 H 5.895623000 -0.467315000 0.097251000 C 3.208422000 -0.708233000 -0.610139000 H 3.184066000 0.099582000 -1.353987000 H 3.829450000 -1.516405000 -1.010705000 C 1.830249000 -1.171951000 -0.404540000	
Full Hessian at UM062X/6–311+G(d,p) Frequencies: -1508.6852 37.2745 48.6025 73.2804 83.5982 103.7504 116.1107 151.1828 172.881 197.6887 215.2467 226.5355 247.7290 271.6463 274.4579 292.0417 301.0113 313.1067 319.4877 356.4087 363.6879 383.5103 415.4703 488.3220 503.4895 512.2902 559.1454 604.6947 657.3960 698.0668 719.1472 770.3143 828.8278 844.2261 900.5054 934.1438 987.8460 1032.1181 1052.2427 1063.6625 1079.4369 1088.1503 1105.1821 1125.6067 1151.9386 1178.8969 1217.5256 1238.5312 1266.6836 1279.0383 1283.5944 1345.1244 1351.4103 1367.8902 1415.6605 1417.4876 1422.5605 1432.7460 1450.8265 1468.1081	Full Hessian at UM062X/6–311+G(d,p) Frequencies: 13.1045 42.7463 56.6218 67.3701 110.3846 121.4692 145.3033 169.5546 180.0219 195.0698 230.4831 237.3221 242.1941 254.5516 268.8949 273.5844 296.3786 320.9597 378.2225 398.1484 412.9810 498.0974 512.2463 538.2723 557.3717 606.7004 669.9455 723.6988 732.1762 748.2538 761.4122 845.1325 864.7766 896.7659 975.7172 982.6612 1031.0580 1059.7156 1065.9925 1075.0524 1084.9788 1099.3933 1118.6694 1122.3852 1135.6073 1193.9142 1235.5716 1247.3702 1252.5965 1289.8820 1295.8899 1323.5772 1370.5112 1373.2323 1404.8605 1410.2261 1444.4842 1450.3240 1453.7228 1473.9969	

1484.6659	1490.5576	1491.9810	1486.0480	1490.5956	1491.2952	
1500.8882	1502.9021	1503.4225	1492.6820	1504.6824	1506.0933	
1511.9785	1512.4938	1515.0654	1506.6689	1509.4927	1516.6361	
1529.5450	1583.5894	1863.4712	1526.1261	1598.4393	1697.4856	
1946.8653	2980.0764	3010.4147	1787.7912	3004.7761	3018.6213	
3025.0033	3044.6480	3049.8139	3024.5562	3039.7334	3042.2517	
3053.1782	3066.9972	3095.9600	3056.2485	3067.6746	3097.0824	
3096.3920	3107.0607	3107.9626	3099.2354	3101.5597	3102.2116	
3119.7250	3128.8839	3144.5455	3124.0749	3131.7512	3142.0100	
3147.8608	3155.2365	3790.7041	3151.7780	3152.6227	3724.7612	

For the Thermal Rearrangement of Furanone **3.9e**



Scheme 4.6: Energy diagram for thermal rearrangement of furanone **3.9e**.

M062X/6-311+G(d,p), temperature=493.15K, scrf=IEFPCM=1,4-dioxane, opt=tight, int=ultrafine

3.9e				**4.19**				**4.4**			
E + ZPE = – 785.382913 **E + thermal energies = – 785.340846** **E + thermal enthalpies = – 785.339284** **G = – 785.481771**				**E + ZPE = – 938.142608** **E + thermal energies = – 938.090550** **E + thermal enthalpies = – 938.088988** **G = – 938.253449**				**E + ZPE = – 785.387378** **E + thermal energies = – 785.345273** **E + thermal enthalpies = – 785.343711** **G = – 785.482554**			
Geometry at M062X/6–311G+(d,p)				Geometry at M062X/6–311G+(d,p)				Geometry at M062X/6–311G+(d,p)			
C	2.079771000	0.428119000	-0.204350000	C	2.071668000	0.609607000	-0.112510000	C	-1.936683000	0.419158000	-0.157125000
C	2.978311000	-0.381761000	0.412629000	C	3.207416000	0.143994000	-0.743396000	C	-3.034479000	-0.278664000	0.263985000
C	2.728715000	-1.746809000	-0.045985000	C	2.922473000	-1.195165000	-1.207922000	C	-2.771404000	-1.688710000	0.042749000
O	1.691529000	-1.756501000	-0.945459000	O	1.634142000	-1.528046000	-0.861488000	O	-1.505887000	-1.834678000	-0.508075000
O	3.303239000	-2.762352000	0.238178000	O	3.634945000	-2.002953000	-1.767150000	O	-3.462575000	-2.651603000	0.234736000
N	1.836155000	1.758542000	-0.111908000	N	1.808552000	1.837817000	0.454183000	C	-4.377756000	0.168875000	0.751127000
C	4.098624000	-0.142033000	1.382446000	C	4.580972000	0.710894000	-0.960280000	H	-4.410301000	0.300237000	1.836283000
H	4.706448000	0.720866000	1.113165000	H	4.617813000	1.419791000	-1.792459000	H	-4.681873000	1.105482000	0.282723000
H	3.734373000	-0.003174000	2.403657000	H	4.979338000	1.205211000	-0.074613000	H	-5.112070000	-0.597114000	0.497170000
H	4.739959000	-1.024168000	1.383844000	H	5.245364000	-0.116688000	-1.214325000	C	-0.941343000	-0.582778000	-0.621004000
C	2.687419000	2.591989000	0.723089000	C	2.823320000	2.875683000	0.380038000	C	0.300235000	-0.432655000	-1.003947000
H	3.636370000	2.832626000	0.229555000	H	2.342607000	3.838527000	0.561027000	C	2.704338000	-0.239532000	-0.467287000
H	2.159443000	3.522381000	0.932674000	H	3.617147000	2.741541000	1.126570000	C	3.980915000	-0.048525000	-1.000100000
H	2.887609000	2.092786000	1.667841000	H	3.263646000	2.897042000	-0.613812000	C	2.556243000	-0.369306000	0.918055000
C	1.182137000	2.467065000	-1.206130000	C	1.044862000	1.880997000	1.694093000	C	5.092382000	0.013306000	-0.165555000
H	0.742417000	3.383439000	-0.812489000	H	1.668828000	1.604577000	2.556427000	H	4.101684000	0.049723000	-2.073661000
H	1.896572000	2.731698000	-1.995417000	H	0.678313000	2.897467000	1.845699000	C	3.664845000	-0.307344000	1.748934000
H	0.376399000	1.872930000	-1.631466000	H	0.184748000	1.217500000	1.647305000	H	1.566918000	-0.525432000	1.334781000
C	1.195106000	-0.437055000	-1.100939000	C	1.072430000	-0.439235000	-0.162457000	C	4.936904000	-0.115187000	1.209962000
H	1.315958000	-0.156234000	-2.152322000	H	1.272578000	-1.305385000	1.416172000	H	6.077973000	0.160574000	-0.590659000
C	-0.219439000	-0.367551000	-0.728973000	C	-0.296137000	-0.312705000	-0.183416000	H	3.540848000	-0.412306000	2.820181000
C	-1.383533000	-0.291474000	-0.433216000	C	-1.522124000	-0.304975000	-0.011644000	H	5.801163000	-0.069165000	1.861624000
C	-2.766967000	-0.205103000	-0.068133000	C	-2.893122000	0.010447000	-0.311031000	C	1.544337000	-0.292860000	-1.378124000
C	-3.759118000	-0.204784000	-1.055747000	C	-3.352329000	1.333342000	-0.218543000	H	1.759447000	-0.189497000	-2.441204000
C	-3.133686000	-0.122021000	1.280509000	C	-3.801287000	-0.999823000	-0.660072000	N	-1.692744000	1.748694000	-0.130134000
C	-5.097738000	-0.120564000	-0.696175000	C	-4.683351000	1.632631000	-0.477144000	C	-2.405730000	2.628408000	0.783725000
H	-3.471072000	-0.274657000	-2.097537000	H	-2.653724000	2.117780000	0.047992000	H	-2.851607000	2.050399000	1.589369000
C	-4.474515000	-0.039469000	1.631949000	C	-5.127872000	-0.687885000	-0.928385000	H	-1.690465000	3.328044000	1.223004000
H	-2.362143000	-0.126643000	2.040602000	H	-3.453970000	-2.024059000	-0.730108000	H	-3.185021000	3.203326000	0.273969000
C	-5.457840000	-0.037915000	0.646241000	C	-5.577631000	0.626548000	-0.834902000	C	-0.662544000	2.385196000	-0.936182000
H	-5.861272000	-0.122324000	-1.464606000	H	-5.022297000	2.659663000	-0.406611000	H	-0.996250000	3.396833000	-1.174125000
H	-4.752613000	0.022130000	2.677101000	H	-5.814621000	-1.477507000	-1.209991000	H	0.294343000	2.445365000	-0.406574000
H	-6.503161000	0.025562000	0.923725000	H	-6.613892000	0.864971000	-1.040812000	H	-0.519443000	1.846619000	-1.870512000
				O	1.169991000	-1.948029000	2.195155000				
				H	1.584477000	-2.780511000	1.934310000				
				H	-0.060910000	-1.999568000	2.300283000				
				O	-1.222462000	-1.908470000	2.239358000				
				H	-1.634247000	-1.524991000	3.023165000				
				H	-1.409730000	-1.306227000	1.422930000				
Full Hessian at M062X/6–311G+(d,p) Frequencies:				Full Hessian at M062X/6–311G+(d,p) Frequencies:				Full Hessian at M062X/6–311G+(d,p) Frequencies:			
4.3242	28.035	34.3059		-639.3152	18.8131	29.7491		26.0167	33.0715	37.0342	
57.5756	89.0232	104.2565		30.7308	33.4530	43.9802		66.8716	80.3994	123.6502	

119.2178	141.9907	167.6806
193.8979	222.3058	226.9278
264.7637	274.3893	301.4669
315.7284	347.5042	393.5116
409.1748	422.8652	458.0647
520.6847	556.9382	562.4610
582.9990	619.0019	634.9546
664.4713	706.8868	706.9313
764.7151	773.3966	784.0436
822.0012	871.4055	899.4573
955.5319	979.6720	1009.2404
1009.4979	1017.8411	1027.4623
1060.3701	1061.4112	1088.7644
1098.1573	1108.9732	1114.1890
1126.5290	1131.3073	1162.4274
1179.1798	1193.9549	1200.8466
1282.6570	1290.1532	1309.1180
1325.4561	1331.0826	1348.1198
1372.4719	1411.1023	1451.4620
1453.0240	1483.4394	1483.6078
1486.8642	1498.5700	1505.4851
1507.7751	1515.5802	1536.7759
1539.8263	1643.9283	1672.9396
1708.1292	1851.6806	2380.9929
3031.4242	3038.4495	3067.3260
3071.6643	3130.4138	3131.4424
3135.0498	3162.0795	3178.7812
3190.2937	3205.3302	3213.5594
3220.3122	3227.5734	3232.3871

55.1285	75.5593	77.6931
99.5651	128.3279	157.8733
178.2499	200.3545	206.3329
223.4575	243.2226	258.6280
280.9678	300.8808	303.4617
363.0469	383.8182	390.3071
409.1005	411.1360	439.0118
452.7020	472.0628	522.8804
533.4264	554.9741	555.9654
590.8924	614.6203	633.7757
654.5952	673.5249	687.8619
708.2818	722.6963	751.1364
774.2651	781.2464	808.0374
866.1819	870.7314	909.0457
935.3428	968.0309	1003.1626
1007.2426	1012.5836	1018.2589
1018.6352	1057.9921	1061.0931
1088.0750	1107.0865	1116.7627
1121.6489	1140.2901	1168.4915
1174.6402	1190.1765	1203.4252
1264.7602	1286.1883	1301.5955
1321.3322	1348.1357	1405.6477
1434.4387	1449.0005	1460.8475
1480.3054	1481.1184	1484.5238
1493.4725	1498.9687	1504.9756
1511.1025	1517.5836	1532.0149
1541.1791	1573.6336	1628.2941
1635.7246	1661.3234	1666.4270
1767.0404	1782.8557	2121.2321
2550.6602	2834.3364	3003.4259
3020.3885	3058.7835	3115.9576
3117.0302	3123.9882	3154.7815
3180.3142	3184.2834	3200.1140
3205.1108	3214.5101	3218.8425
3228.5069	3861.0513	3871.6248

128.8227	149.5490	187.7390
192.2963	213.2719	253.4329
255.6260	278.6764	295.3906
303.5517	347.9386	380.7938
405.7600	413.4697	469.2218
487.3937	533.5712	543.7505
595.0114	629.5300	664.6371
679.9695	694.4695	708.4822
728.7973	756.8445	773.4321
832.4787	869.4804	892.3024
895.4636	956.4346	968.1494
1009.4108	1016.7008	1026.1347
1031.6197	1059.6935	1060.5311
1079.9433	1096.2536	1113.0729
1129.8207	1151.8223	1155.7172
1177.2634	1201.8200	1225.3092
1240.7581	1264.1790	1304.7085
1326.2134	1335.8759	1353.9986
1412.1871	1451.3569	1454.8329
1464.5077	1480.0773	1492.4929
1496.9554	1501.1267	1508.8518
1511.5457	1513.4763	1540.5045
1549.3630	1654.0776	1672.9663
1692.0298	1849.7457	2080.4018
3044.4132	3050.2341	3061.5903
3108.4787	3120.9395	3125.9234
3142.4873	3154.6111	3172.7146
3188.0637	3196.8218	3199.0004
3209.2351	3218.4272	3228.1488

4.20	**4.21**	**4.22**
E + ZPE = – 785.331348 **E + thermal energies = – 785.290615** **E + thermal enthalpies = – 785.289054** **G = – 785.422530**	**E + ZPE = – 785.358481** **E + thermal energies = – 785.316632** **E + thermal enthalpies = – 785.315070** **G = – 785.453078**	**E + ZPE = – 785.342331** **E + thermal energies = – 785.301684** **E + thermal enthalpies = – 785.300122** **G = – 785.434364**

Geometry at M062X/6–311G+(d,p)

C	-2.083198000	0.387194000	-0.304923000
C	-3.300841000	-0.172146000	0.021736000
C	-3.037184000	-1.550781000	0.317737000
O	-1.633407000	-1.767302000	0.188400000
O	-3.744284000	-2.473859000	0.629362000
C	-4.675681000	0.417010000	0.054469000
H	-4.835541000	1.082526000	0.907878000
H	-4.893406000	0.978684000	-0.857265000
H	-5.400943000	-0.394202000	0.130529000
C	-1.059735000	-0.619687000	-0.211317000
C	0.285171000	-0.379190000	-0.255090000
C	2.754940000	-0.541439000	-0.130780000
C	3.897394000	-1.147527000	-0.675017000
C	2.929452000	0.540083000	0.747668000
C	5.167392000	-0.681014000	-0.366301000
H	3.777550000	-1.988380000	-1.349842000
C	4.201228000	1.009106000	1.049571000
H	2.064268000	0.995635000	1.216287000
C	5.325571000	0.403310000	0.493958000
H	6.036987000	-1.162572000	-0.797774000
H	4.317828000	1.842035000	1.733138000
H	6.316722000	0.767008000	0.736587000
C	1.433549000	-1.034117000	-0.500409000
H	1.387421000	-1.951316000	-1.082079000
N	-1.690165000	1.690372000	-0.439645000
C	-2.412156000	2.715076000	0.317728000
H	-2.622758000	2.346067000	1.322289000
H	-1.795019000	3.609591000	0.369271000
H	-3.350841000	2.960888000	-0.180321000
C	-0.457627000	1.933499000	-0.987416000
H	-0.037698000	2.910173000	-0.778123000
H	0.342660000	0.893720000	-0.289746000
H	-0.264197000	1.530570000	-1.975100000

Full Hessian at M062X/6–311G+(d,p)
Frequencies:

-1238.3863	37.7878	43.6549
51.0125	86.3456	104.4570
129.2478	146.2528	155.2322
159.9880	220.0670	234.7058
249.6616	298.2282	319.9377
348.0500	353.0863	412.7032
416.7032	498.8731	511.4948
520.3984	557.5088	572.9218
601.3036	629.9911	682.4601
693.3392	703.0784	712.9422

Geometry at M062X/6–311G+(d,p)

C	3.251693000	-0.485494000	-0.036902000
C	2.165500000	0.382705000	0.148614000
C	0.967736000	-0.324212000	0.143077000
O	1.274269000	-1.630192000	-0.004232000
C	2.684721000	-1.783789000	-0.104409000
O	3.154031000	-2.902381000	-0.196357000
N	2.198079000	1.790589000	0.204854000
C	3.042722000	2.473945000	-0.790545000
C	1.517890000	2.450336000	1.080107000
C	-0.388904000	0.105585000	0.084321000
C	-1.448422000	-0.732936000	0.072229000
C	-2.851595000	-0.336838000	-0.014969000
C	-3.843465000	-1.302437000	0.213636000
C	-5.192608000	-0.976311000	0.158775000
C	-5.586809000	0.326315000	-0.131708000
C	-4.614621000	1.295508000	-0.374033000
C	-3.267069000	0.969418000	-0.321705000
C	4.724398000	-0.228484000	-0.009854000
H	4.086903000	2.283542000	-0.547843000
H	2.816131000	2.057044000	-1.769664000
H	2.838225000	3.541198000	-0.758618000
H	1.472386000	3.529305000	1.010458000
H	1.007109000	1.907319000	1.863119000
H	-0.544618000	1.180674000	0.057343000
H	-1.252962000	-1.797765000	0.156632000
H	-3.542700000	-2.319355000	0.442049000
H	-5.937833000	-1.741494000	0.342175000
H	-6.638104000	0.583440000	-0.177734000
H	-4.911293000	2.309654000	-0.615854000
H	-2.532018000	1.735396000	-0.540548000
H	5.237371000	-1.176537000	0.160167000
H	5.010899000	0.451361000	0.798725000
H	5.110542000	0.182807000	-0.949480000

Full Hessian at M062X/6–311G+(d,p)
Frequencies:

15.1871	43.6169	49.0425
68.7127	97.5188	110.2337
141.2597	155.1100	171.4957
181.9959	223.8951	244.7571
253.7534	277.1131	292.8660
344.6132	378.4270	411.2148
445.7140	467.3356	501.6758
535.9670	562.3171	601.1039
629.7533	639.6396	668.5654
691.5018	702.5090	711.6422

Geometry at M062X/6–311G+(d,p)

C	2.077444000	0.390167000	-0.073776000
C	3.313739000	-0.307358000	-0.081131000
C	2.975203000	-1.668405000	0.007150000
O	1.544500000	-1.734590000	0.116367000
O	3.604815000	-2.716039000	-0.023629000
C	4.699354000	0.187067000	-0.356445000
H	4.727065000	0.904903000	-1.183465000
H	5.180701000	0.656202000	0.509952000
H	5.319007000	-0.664794000	-0.642782000
C	1.030527000	-0.490682000	0.056900000
C	-0.385759000	-0.290351000	0.405868000
C	-1.376383000	-0.387325000	-0.485385000
H	-1.114827000	-0.569548000	-1.526027000
N	1.885678000	1.786124000	-0.012417000
C	0.962219000	2.381003000	-0.682797000
H	-0.611201000	-0.100756000	1.455209000
H	0.393944000	1.813554000	-1.405366000
C	-2.815804000	-0.260424000	-0.202893000
C	-3.692802000	-0.024273000	-1.266627000
C	-3.343947000	-0.366448000	1.089777000
C	-5.056837000	0.131276000	-1.046554000
H	-3.297829000	0.038316000	-2.275249000
C	-4.705681000	-0.212583000	1.310157000
H	-2.691057000	-0.594280000	1.924067000
C	-5.566810000	0.041473000	0.244098000
H	-5.720644000	0.315835000	-1.882732000
H	-5.100450000	-0.304187000	2.315064000
H	-6.629895000	0.155084000	0.419222000
H	0.768902000	3.429974000	-0.500420000
C	2.782276000	2.531089000	0.888324000
H	3.779854000	2.540927000	0.452410000
H	2.409963000	3.546149000	1.002439000
H	2.811752000	2.009409000	1.842705000

Full Hessian at M062X/6–311G+(d,p)
Frequencies:

-153.6833	24.7921	40.6304
49.9474	77.2020	103.5888
147.5205	158.7873	162.3771
186.1613	188.4606	226.8152
244.3101	269.7072	290.1326
329.9437	398.6022	410.5293
416.2520	458.3340	509.2115
515.6361	560.9961	600.5377
622.5691	630.4513	673.4099
686.4514	707.3759	716.3105

739.6954 750.3135 752.2496 775.7363 845.1906 855.7230 867.3557 915.3362 941.6942 965.1003 1003.9422 1012.5286 1019.9883 1021.0925 1049.2170 1061.3226 1061.9875 1099.8657 1114.3300 1145.0572 1158.1208 1175.0319 1177.6645 1203.1703 1225.7899 1244.0155 1281.9474 1318.0020 1327.5626 1343.8865 1354.5673 1408.6548 1420.7342 1444.8954 1456.1336 1476.4861 1477.7666 1492.9853 1495.3039 1505.7189 1521.5084 1531.6166 1547.4422 1609.3518 1643.2828 1654.8123 1670.3023 1778.9558 1827.3312 3051.7441 3078.0283 3107.6890 3146.9616 3151.3405 3153.4568 3171.6206 3184.6401 3196.1754 3198.7345 3209.3379 3215.7272 3227.6544 3257.2951	738.5176 747.1016 769.3854 855.8020 856.5567 873.0126 924.6569 935.2819 952.3919 964.3655 995.9427 1000.1659 1011.5425 1012.8402 1016.3115 1042.6116 1061.0847 1061.7966 1110.9459 1123.0788 1141.3971 1157.2646 1175.3358 1202.9965 1232.6891 1278.8086 1306.1850 1321.2223 1339.8434 1356.1348 1382.1980 1391.5645 1417.6388 1444.5852 1457.9720 1474.3470 1484.5875 1486.7273 1494.8916 1513.4306 1529.8943 1550.1146 1567.9199 1639.1945 1660.5369 1681.2214 1696.9275 1771.5261 3029.7291 3079.9060 3100.9607 3136.2797 3175.6668 3183.6177 3190.3882 3193.1226 3195.9738 3199.7779 3207.1476 3210.3478 3215.9624 3226.8221 3312.6004	740.2333 748.3802 774.2085 837.2168 867.0016 874.2019 887.4951 948.9462 951.8042 988.2293 1000.8529 1007.7304 1010.8097 1016.3035 1025.5546 1042.6210 1061.9241 1062.5830 1112.7847 1126.5155 1146.0267 1159.5759 1177.8589 1205.5533 1232.8555 1284.6463 1310.0640 1321.7435 1335.2096 1345.3292 1362.1248 1374.4486 1415.0658 1447.4381 1457.5103 1476.4249 1486.8130 1488.3698 1492.6531 1513.6785 1532.6475 1538.4252 1585.1359 1649.4724 1674.5489 1713.9165 1735.6376 1758.8226 3021.4159 3068.2216 3101.7995 3132.0735 3133.8163 3164.3095 3188.8954 3190.9623 3195.6656 3204.7431 3207.9656 3211.9707 3219.6683 3228.8101 3318.3463
4.1e		
E + ZPE = – 785.441445 **E + thermal energies = – 785.401906** **E + thermal enthalpies = – 785.400344** **G = – 785.529971**		
Geometry at M062X/6–311G+(d,p) C 3.124072000 0.148923000 0.109130000 C 1.796235000 0.388710000 -0.076952000 C 1.142299000 -0.899190000 -0.348496000 O 2.076079000 -1.891892000 -0.298555000 C 3.305803000 -1.296018000 -0.030378000 O 4.296199000 -1.964493000 0.059188000 N 1.028888000 1.511950000 -0.102843000 C 1.575246000 2.752033000 0.426562000 C -0.402439000 1.306979000 0.143489000 C -0.140229000 -1.043427000 -0.658768000 C -1.000175000 0.194047000 -0.727612000 C -2.432353000 -0.050993000 -0.297468000 C -3.485023000 0.560705000 -0.977205000 C -4.800156000 0.378858000 -0.559715000 C -5.075988000 -0.419343000 0.545700000 C -4.031262000 -1.033504000 1.230681000 C -2.718007000 -0.849380000 0.811565000 C 4.307057000 1.027416000 0.378844000 H 1.656073000 2.724998000 1.520363000 H 2.558332000 2.937302000 -0.001038000 H 0.917783000 3.573239000 0.142488000 H -0.916806000 2.246005000 -0.066617000 H -0.567640000 1.059122000 1.202786000 H -0.554500000 -2.011488000 -0.915295000 H -1.013148000 0.543822000 -1.767801000 H -3.273254000 1.179128000 -1.843819000 H -5.608414000 0.856370000 -1.100943000 H -6.099408000 -0.565469000 0.869850000 H -4.239297000 -1.659317000 2.090515000 H -1.906254000 -1.333255000 1.345909000 H 5.163463000 0.392438000 0.608058000 H 4.142865000 1.694984000 1.225427000 H 4.569267000 1.634654000 -0.491304000		
Full Hessian at M062X/6–311G+(d,p) Frequencies: 32.2299 43.6005 71.3386 87.5683 133.0828 147.4044 156.5606 202.4223 233.9724 245.9415 261.9539 268.1634 301.3267 303.6981 319.7249 402.8327 413.6157 458.1406 488.6758 515.9616 561.2997 587.7812 612.1717 630.8053 650.3252 688.6243 720.4059 724.8918 741.8533 757.2825 785.4917 859.4894 873.8932 879.0792 907.4176 947.3752 949.5938 1001.0483 1008.8521 1017.4836 1021.0337 1025.9232 1059.9696 1061.1547 1068.8237 1088.1053 1111.7584 1123.3172 1139.4688 1152.6826 1175.6512 1202.9234 1221.0193 1230.0170 1241.1384 1284.5030 1301.0460 1316.4903 1325.6019 1345.0719 1359.7677 1370.3985 1403.4194 1413.9235 1454.9801 1483.4682 1489.7404 1493.5945 1497.0440 1504.1072 1510.7222 1530.1923		

1538.5384	1656.3321	1676.9631		
1702.0085	1781.1353	1864.8285		
3005.9664	3032.2767	3039.3553		
3065.1952	3125.1674	3130.0176		
3135.3115	3154.9619	3181.4183		
3188.8844	3190.6285	3206.4696		
3215.3803	3220.2431	3226.7300		