

**A radical–polar crossover approach to complex nitrogen heterocycles  
*via* the triplet state**

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

**Doctor of Philosophy**

of the

**University of Oxford**

*by*

Zachariah Lockhart

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In memory of John Eric Riordan,  
who instilled in me  
a love of chemistry,  
and whose gentleness  
was evident to all.



*“He is able to deal gently with those who are ignorant and are going astray ...”*

Hebrews 5:2a (NIV)



## Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between February 2018 and April 2023 under the supervision of Professor Martin D. Smith. The dissertation is a product of my own work and includes no results obtained through collaboration, except where specifically stated in the text.

Parts of this work have been described in an article under peer review for publication in a journal.<sup>1</sup>



Zachariah Lockhart





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Thank you, Pearse, Kate, Dani and Charlie, for so warmly welcoming me into 109 Howard Street after the first lockdown – and Dani and Charlie again for receiving me into 7 Earl Street several lockdowns (and false finishes) later. Your friendship has been a great source of joy over the past few years.

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## Abbreviations

1, <i>x</i> -[H]	1, <i>x</i> -hydrogen shift
1e	one-electron
2e	two-electron
4CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
$\nu$	frequency
A	energy acceptor
Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
APCI	atmospheric-pressure chemical ionisation
aq.	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bpin	pinacolboranyl
C( <i>sp</i> <sup>3</sup> )	<i>sp</i> <sup>3</sup> -hybridised carbon
°C	degrees Celsius
CASSCF	complete active space self-consistent field
<i>con</i>	conrotatory
COSY	correlation spectroscopy
COT	1,3,5,7-cyclooctatetraene
Cy	cyclohexyl
D	deuterium
d	doublet
d.r.	diastereomeric ratio
(1,2-)DCE	1,2-dichloroethane
DFT	density functional theory
DIPEA	diisopropylethylamine

( <i>N,N</i> -)DMF	<i>N,N</i> -dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
e	electron
( <i>E</i> )	entgegen
e.r.	enantiomeric ratio
E <sup>+</sup>	electrophile
E1	unimolecular elimination
<i>E</i> <sub>1/2</sub>	half-wave potential
E2	bimolecular elimination
<i>endo</i>	endocyclic
<i>ent</i>	enantioenriched
EnT	(Dexter) energy transfer
eq.	equivalent
ESI	electrospray ionisation
Et	ethyl
<i>E</i> <sub>T</sub>	triplet energy
EWG	electron-withdrawing group
<i>exo</i>	exocyclic
<i>fac</i> -Ir(dFppy) <sub>3</sub>	tris[3,5-difluoro-2-(2-pyridinyl)phenyl]iridium(III) (facial)
<i>fac</i> -Ir(ppy) <sub>3</sub>	tris[2-phenylpyridinato-C <sup>2</sup> , <i>N</i> ]iridium(III) (facial)
FTIR	Fourier transform infrared
G	Gibbs free energy
G	gram
h	Planck's constant or hour
HAT	hydrogen-atom transfer
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation
HOMO	highest occupied molecular orbital
HRMS	high-resolution mass spectrometry

HSQC	heteronuclear single-quantum coherence
Hz	hertz
IR	infrared
IRC	intrinsic reaction coordinate
[Ir(dtbbpy)(ppy) <sub>2</sub> ]PF <sub>6</sub>	[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine- <i>N</i> 1, <i>N</i> 1']bis[2-(2-pyridinyl- <i>N</i> )phenyl-C]iridium(III) hexafluorophosphate
ISC	intersystem crossing
IUPAC	International Union of Pure and Applied Chemistry
J.A.	Jay Ahuja
kcal	kilocalorie
KIE	kinetic isotope effect
L	litre
λ	wavelength
LED	light-emitting diode
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet or (with prefix) metre
M.V.P.	Mihai Viorel Popescu
Me	methyl
MECP	minimum energy crossing point
Mes	mesityl
min	minute
mol	mole
MP	melting point
Ms	methanesulfonyl (mesyl)
NBO	natural bond orbital analysis
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -Bu	normal butyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy

NuY	nucleophile
[O]	oxidant
O.S.	Owen Smith
PE	petroleum ether
Ph	phenyl
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
q	quartet
R, R', etc.	generic group or other substituent as specified
r.t.	room temperature
<i>rac</i>	racemic
RPC	radical-polar crossover
s	singlet
S <sub>0</sub>	singlet ground state
S <sub>1</sub>	first excited singlet state
SET	single-electron transfer
t	triplet
T <sub>1</sub>	first excited triplet state
<i>t</i> -Bu or <i>tert</i> -Bu	tertiary butyl
Tf	trifluoromethanesulfonyl (triflyl)
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TosMIC	<i>para</i> -toluenesulfonyl isocyanide
<i>trig</i>	trigonal
( <i>p</i> -)Ts	<i>para</i> -toluenesulfonyl
TS	transition state
UV	ultraviolet
UV–vis	ultraviolet–visible
WBO	Wiberg bond order
X	halogen or other substituent as specified

(Z)

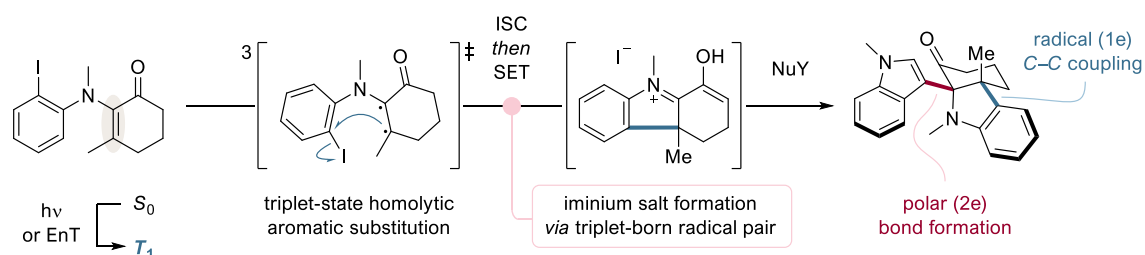
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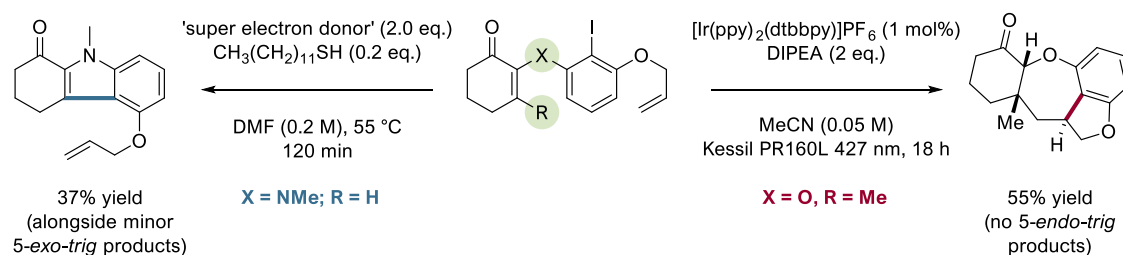


## Abstract

This thesis centres on the development and mechanistic study of a photochemical ‘radical–polar crossover’ method for the synthesis of natural product-like heterocyclic compounds from *N*-(2-iodoaryl) enaminone substrates. The transformation originates from an excited triplet state and involves a transition from diradical to ionic reactivity enabled by an iodine radical, liberated during a homolytic aromatic substitution step, functioning as a single-electron oxidant. In contrast to other ‘eliminative’ photocyclisations – which generally assemble planar, aromatic scaffolds – the primary photoproduct of this reaction is an iminium salt that can be intercepted by a variety of two-electron nucleophiles to generate densely functionalised, C(*sp*<sup>3</sup>)-rich indoline frameworks.



A brief study on the cyclisation of aryl radicals is also described. The main finding of this work is that, where there is a choice between 5-*exo-trig* cyclisation onto one alkene functional group and 5-*endo-trig* cyclisation onto another, certain aryl radical intermediates undergo the latter, formally Baldwin-disfavoured process. Through careful modification of the radical precursor, this inherent 5-*endo-trig* bias can be overridden, triggering a 5-*exo-trig*/7-*endo-trig* cascade cyclisation that rapidly assembles a complex, oxepane-containing tetracyclic molecule.





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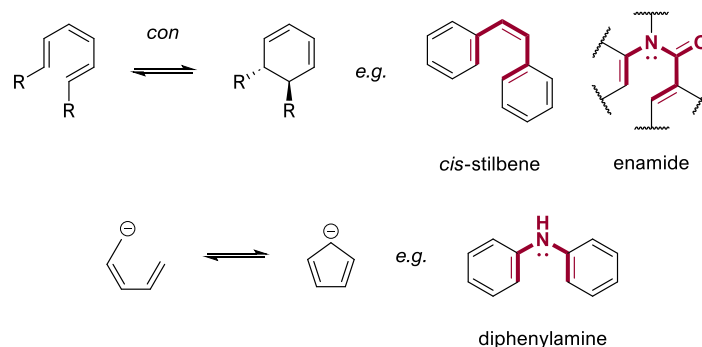
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## Chapter 1 – Introduction to photochemical six-electron cyclisations

Photocyclisations of conjugated  $6\pi$  systems represent a versatile strategy for the synthesis of structurally diverse carbo- and heterocyclic compounds. Huisgen<sup>2</sup> proposed two broad categories for reactions of this type (Scheme 1): those based on the hexatriene–cyclohexadiene electrocycloisatation (such as the photocyclisation of *cis*-stilbenes<sup>3</sup> and various ‘enamide’ compounds<sup>4,5</sup>) or those isoelectronic with the pentadienyl anion electrocycloisatation (such as the photocyclisation of diphenylamine<sup>6</sup>).



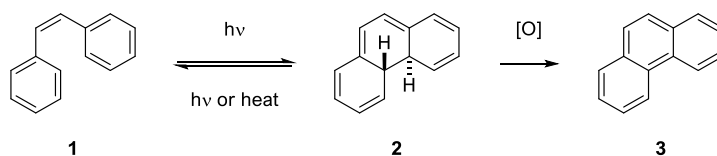
**Scheme 1.** Representative examples (with conjugated  $6\pi$  systems highlighted in red) of photochemical six-electron cyclisations analogous to the hexatriene and pentadienyl anion electrocycloisatations.

The section to follow discusses synthetic and mechanistic aspects of both classes of reaction, with an emphasis on examples that proceed with the loss of a leaving group (so-called ‘eliminate’ photocyclisations) as well as those that assemble five-membered heterocyclic compounds. Some of these reactions are *not* pericyclic processes;<sup>7</sup> nevertheless, the Huisgen ‘electrocycloisatation’ classification is used as a convenient means to compare related photochemical transformations.

### Reactions based on the hexatriene–cyclohexadiene electrocycloisatation

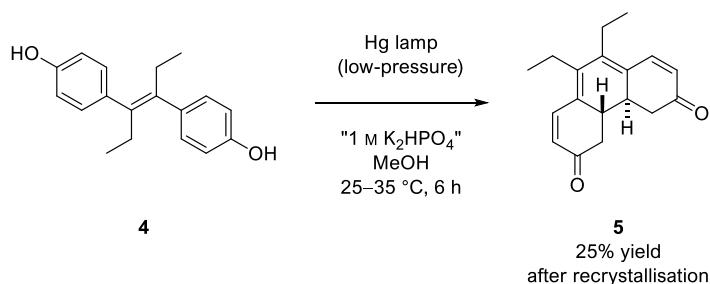
#### Stilbene photocyclisations

*cis*-Stilbene (**1**) undergoes a thermally and photochemically reversible cyclisation upon irradiation with ultraviolet (UV) light to form *trans*-4*a*,4*b*-dihydrophenanthrene (**2**) (Scheme 2).<sup>3</sup> In the presence of an oxidant, such as oxygen or iodine, this intermediate can be irreversibly transformed to phenanthrene, **3**, likely *via* a radical chain process involving consecutive hydrogen atom transfers, producing hydrogen peroxide or hydrogen iodide as a by-product depending on the oxidant used. In the strict absence of oxidants, photostationary mixtures of the unstable dihydrophenanthrene intermediate and starting material are formed, whose composition depends on the wavelength of the incident light.



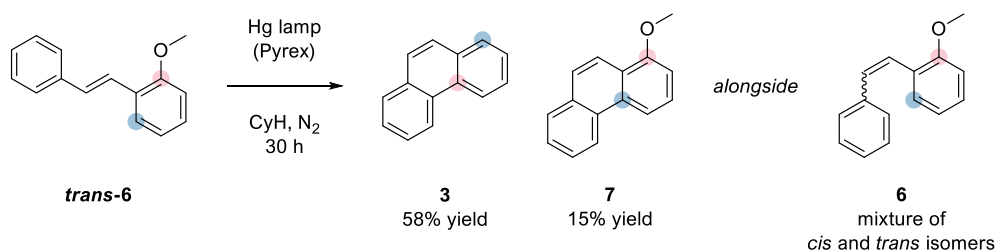
**Scheme 2.** Oxidative photocyclisation of *cis*-stilbene (**1**) to phenanthrene (**3**).

Irradiation of *cis*-stilbene in the presence of triplet sensitisers under conditions that ensure selective excitation of the sensitiser does not lead to dihydrophenanthrene formation.<sup>3,8</sup> Likewise, azulene (a known quencher of stilbene triplet states) does not inhibit dihydrophenanthrene formation upon irradiation of stilbene solutions. These results suggest that the photocyclisation of *cis*-stilbene does not involve a triplet state but most likely proceeds *via* the molecule's first singlet excited state. Further evidence for an excited-state mechanism (as opposed to a hot ground-state reaction) is the formation of dihydrophenanthrene intermediates with *trans*-stereochemistry, suggested by the isolation of **5** from the photochemical reaction of **4** (Scheme 3),<sup>9</sup> which is consistent with orbital symmetry rules.<sup>10</sup>



**Scheme 3.** The isolation of a stable dihydrophenanthrene intermediate, **5**, with *trans*-stereochemistry from the reaction of **4** supports the involvement of an excited singlet state in *cis*-stilbene photocyclisations.

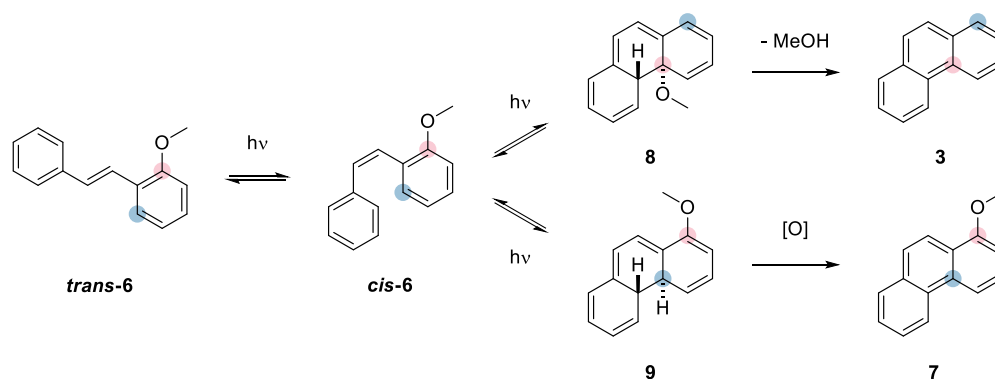
Certain stilbene substrates undergo photocyclisation with loss of a suitably placed leaving group, obviating the need for an external oxidant. One example of such an 'eliminative' photocyclisation is the UV-mediated reaction of *trans*-1-methoxy-2-styrylbenzene (*trans*-**6**) reported by Giles and Sargent (Scheme 4).<sup>11,12</sup> Irradiation of this substrate in deoxygenated cyclohexane using a 500 W medium-pressure mercury lamp gave phenanthrene (**3**) as the major product (58% yield) alongside unconverted starting material (as a mixture of geometric isomers) and a minor amount (15% yield) of 1-methoxyphenanthrene (**7**).



**Scheme 4.** 'Eliminative' photocyclisation of 1-methoxy-2-styrylbenzene, **6**.

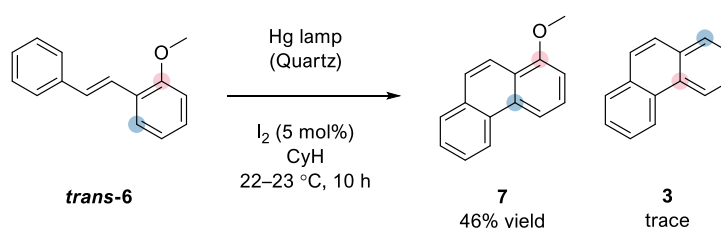


The major product of this reaction, **3**, was thought to arise from elimination of methanol from a dihydrophenanthrene intermediate, **8**, formed by  $6\pi$  electrocyclication following photochemical alkene isomerisation. Oxidation (presumably by adventitious molecular oxygen) of the alternative electrocyclication product, 1-methoxy-4a,4b-dihydrophenanthrene (**9**), meanwhile could account for the formation of **7** in a minor quantity (Scheme 5).



**Scheme 5.** Mechanistic rationale for the formation of **3** and **7** during the photoreaction of stilbene **6**.

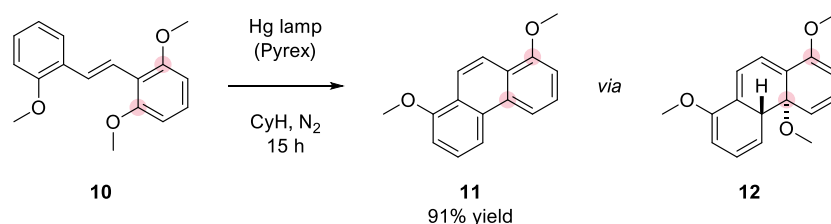
Irradiation of the same substrate in the presence of a catalytic quantity of iodine was previously shown by Wood and Mallory to generate 1-methoxyphenanthrene, **7**, as the major product; only a trace amount of the elimination product, **3**, was detected by IR spectroscopic analysis of the crude reaction mixture under these oxidative conditions.<sup>13</sup> Thus, the regioselectivity of this transformation appears to depend on the relative rates at which the initially (and reversibly) formed photochemical intermediates **8** and **9** are irreversibly transformed to phenanthrene products by oxidation or elimination, respectively, with the latter process being favoured by the rigorous exclusion of oxygen and other oxidants.



**Scheme 6.** Photocyclisation of *trans*-1-methoxy-2-styrylbenzene, **trans-6**, in the presence of iodine leads to oxidation product **7** in preference to elimination product **3**.

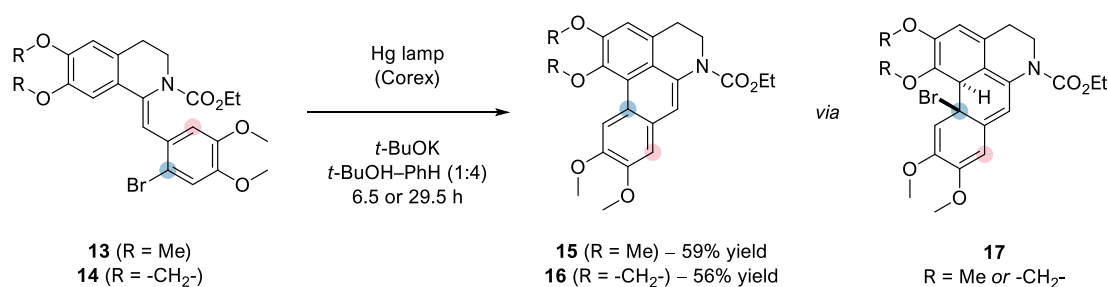
Benefitting from the absence of an alternative oxidative cyclisation pathway, *bis-ortho*-methoxy stilbene substrates, exemplified by **10**, undergo non-oxidative, eliminative photocyclisation in high yields upon irradiation in deaerated cyclohexane solution (Scheme 7).<sup>11</sup> The photocyclisation of **10** proceeds in 91% yield under these conditions and likely proceeds *via* phenanthrene intermediate **12**, from which elimination of methanol (observed by gas chromatographic analysis of the

photolysate) occurs thermally to form the extended aromatic ring system present in the final product, phenanthrene **11**.



**Scheme 7.** Preventing oxidative cyclisation through *bis-ortho*-substitution leads to a high-yielding eliminative photocyclisation.

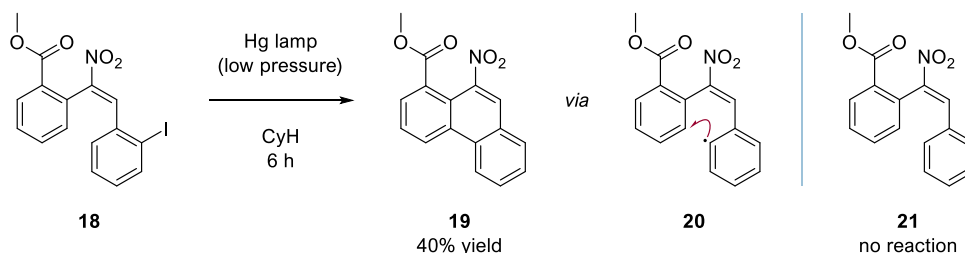
*ortho*-Halogen atoms are also effective leaving groups in stilbene photocyclisations. Cava and co-workers demonstrated that, upon Corex-filtered irradiation in the presence of potassium *tert*-butoxide in *tert*-butanol–benzene (4:1 v/v), *ortho*-bromo stilbenes **13** and **14** undergo eliminative photocyclisation to form phenanthrene derivatives **15** and **16** as single regioisomers in yields of 59 and 56%, respectively (Scheme 8).<sup>14</sup> The phenanthrene products could be elaborated into two aporphine alkaloids – namely, glaucine and dicentrine – highlighting the applicability of eliminative photocyclisations to the synthesis of natural products. A mechanism involving bimolecular elimination (E2) of HBr from photochemical intermediate **17**, promoted by the strong, bulky potassium *tert*-butoxide base, was proposed. In support of such a mechanism is the diminished photocyclisation yield – 24% from *ortho*-bromo stilbene **13** – observed when the reaction was performed in methanolic calcium carbonate, which the authors attribute to the preponderance of a unimolecular elimination (E1) process under these conditions.<sup>15</sup>



**Scheme 8.** An E2 elimination from the photochemically generated dihydrophenanthrene intermediate **17** was proposed by Cava and co-workers to account for the formation of phenanthrene products **15** and **16** from **13** and **14**, respectively, in the presence of potassium *tert*-butoxide.

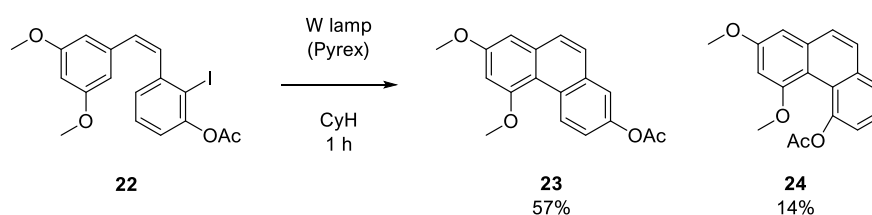
An alternative mechanism for the eliminative photocyclisation of *ortho*-halogen-substituted stilbenes involves the cyclisation of an aryl radical formed by homolysis of the carbon–halogen bond. The regioselective cyclisation of nitrostilbene **18**, which contains an *ortho*-iodine substituent, upon direct irradiation with light from a low-pressure mercury lamp was hypothesised to proceed *via* an aryl radical intermediate (**20**), considering the failure of its non-iodinated analogue, **21**, to undergo oxidative photocyclisation under the same irradiation conditions (the latter compound

might have been expected undergo oxidative photocyclisation *via* an electrocyclic mechanism) (Scheme 9).<sup>16</sup>



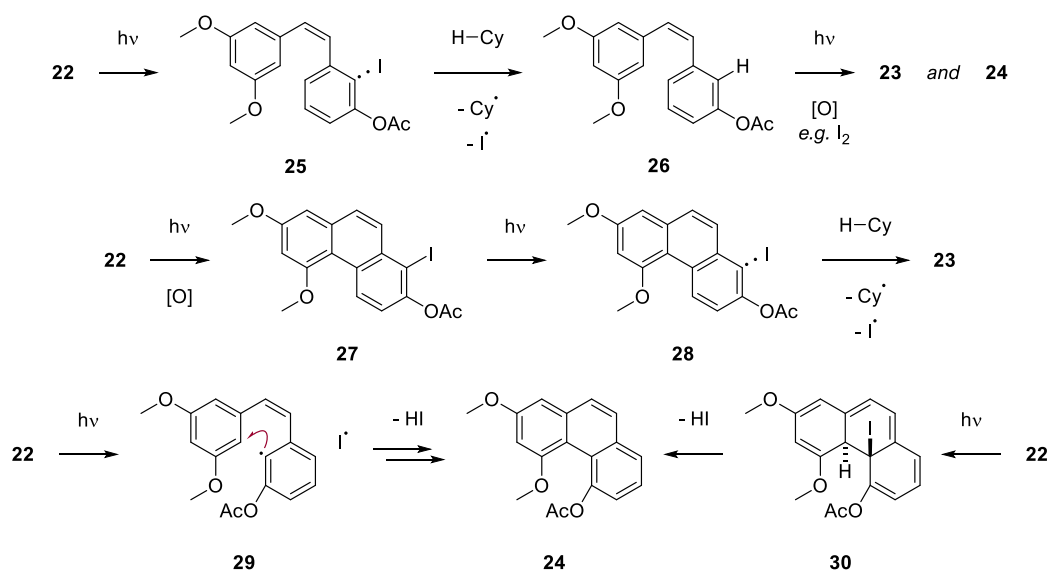
**Scheme 9.** An aryl radical (**20**) is formed and cyclises to give **19** upon photochemical stimulation of nitrostilbene **18**.

The mechanisms of other eliminative photocyclisations of *ortho*-iodo stilbenes are less clear. Irradiation of *meta*-acetoxystilbene **22** with UV light, for instance, leads to **23** and **24** – two regioisomeric phenanthrene products in which the *ortho*-iodine substituent present in the starting material has been lost – in yields of 57 and 14% respectively (Scheme 10).<sup>17</sup>



**Scheme 10.** *ortho*-Iodo stilbene **22** cyclises to give a mixture of regioisomeric products upon irradiation with light from a tungsten lamp.

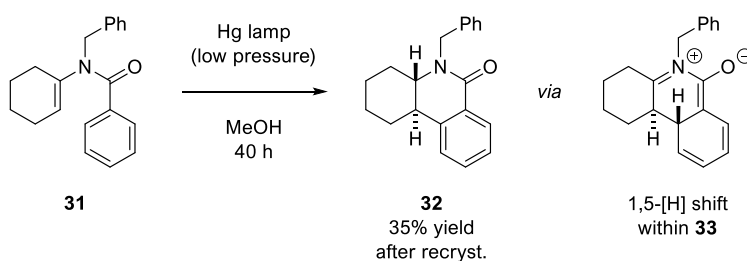
The simplest mechanism that accounts for this result is that both products arise from an oxidative photocyclisation of stilbene **26**, formed by homolysis of the C–I bond in **22** followed by hydrogen abstraction from solvent *via* aryl radical **25**, with the iodine by-product of the initial photolysis step potentially serving as the external oxidant for the subsequent photocyclisation (Scheme 11). Alternatively, or in parallel to the aforementioned pathway, an oxidative photocyclisation of iodostilbene **22** to **27** followed by hydrodehalogenation *via* **28** could account for the formation of the major product, **28**. Two additional pathways leading to the minor product, **24**, are possible from iodostilbene **22**: cyclisation of homolytically generated aryl radical **29** and re-aromatisation of the resulting intermediate; or non-oxidative electrocyclisation followed by elimination of HI from dihydrophenanthrene **30**.



**Scheme 11.** Plausible mechanisms accounting for the formation of **23** and **24** from *ortho*-iodo stilbene **22**.

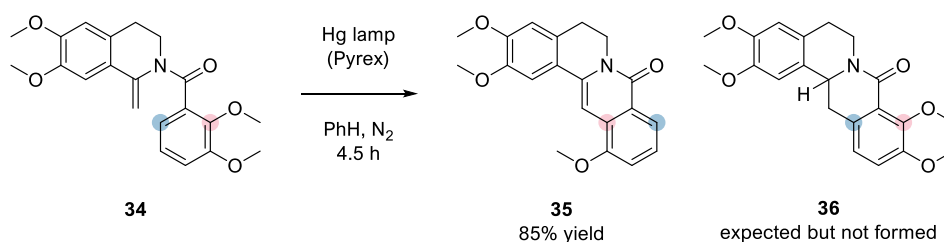
## Enamide photocyclisations

Non-oxidative photocyclisations are more common with enamides, resulting in six-membered lactams *via* stabilised zwitterionic intermediates.<sup>4</sup> For example, Ninomaya and co-workers reported that irradiation in dilute methanol solution leads to *trans*-fused lactam **32** from *N*-benzoyl enamine **31** in 35% yield after recrystallisation; this product likely results from a suprafacial 1,5-hydrogen shift following  $6\pi$  electrocyclicisation (Scheme 12).<sup>18</sup>



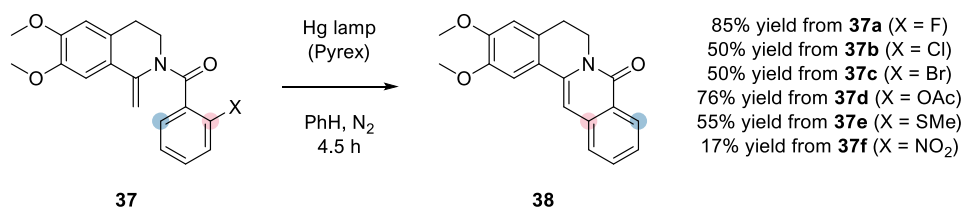
**Scheme 12.** *N*-Benzoyl enamine **31** undergoes a non-oxidative photocyclisation to *trans*-fused lactam **32**, likely *via* zwitterion **33**.

As with *cis*-stilbene photocyclisations, *ortho*-substituents can also direct the regiochemical course of enamide photocyclisations. Irradiation of *N*-benzoyl enamine **34** in benzene solution under a nitrogen atmosphere affords phenanthridone **35** as the sole product in 85% yield (Scheme 13); isomerisation product **36**, which might have been anticipated to form *via* a 1,5-hydrogen shift, was not observed.<sup>19,20</sup>



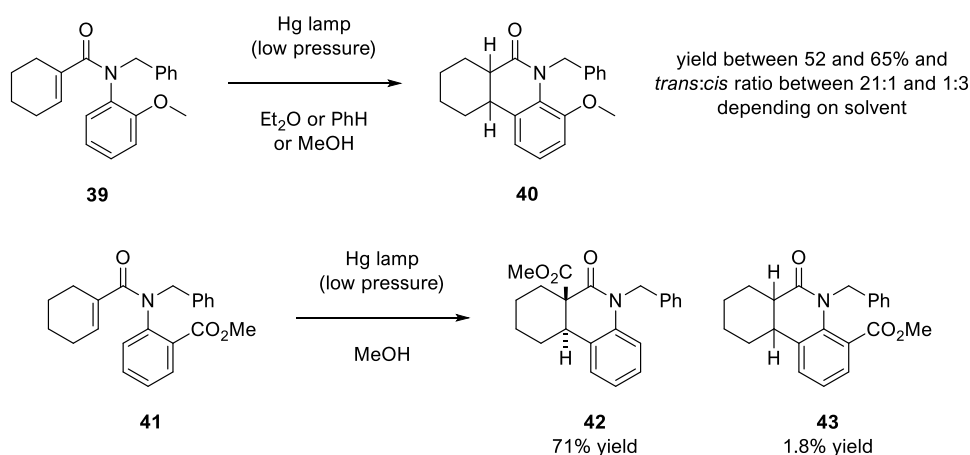
**Scheme 13.** Irradiation of an *ortho*-methoxy-substituted *N*-benzoyl enamine substrate, **34** leads exclusively to elimination product **35**.

*N*-Benzoyl enamine substrates containing fluorine, chlorine and bromine atoms at one of the two available sites of cyclisation (**37a–c**) undergo cyclisation with loss of the halogen atom, being transformed to phenanthridone **38** in yields of 85, 50 and 50%, respectively, upon photochemical stimulation (Scheme 14); the fact that **38** is obtained in highest yield from *ortho*-fluorinated substrate **37a** suggests, on the basis of relative bond strengths, that an aryl radical-based mechanism is not operative under these conditions.<sup>19</sup> Eliminative photocyclisation to the same product (likely *via* dihydrophenanthrene-type intermediate) also occurs for substrates bearing *ortho*-acetoxy (**37d**) and -methanesulfanyl (**37e**) groups in moderate to very good yields; likewise, **37f** leads to **38** with elimination of the elements of HNO<sub>2</sub>, albeit in a low yield of 17%.



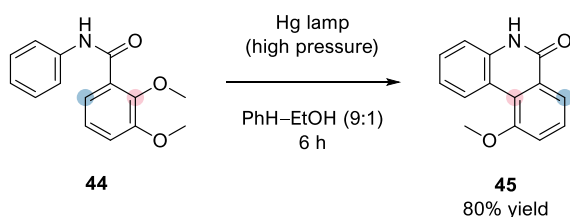
**Scheme 14.** A range of *ortho*-substituents groups can induce eliminative photocyclisation from *N*-benzoyl enamine **37**.

Six-membered lactams can also be prepared photochemically from *N*-alkenoyl and -benzoyl *anilide* substrates. In contrast to the above *ortho*-methoxy-substituted *N*-benzoyl enamine example, *N*-alkenoyl anilide **39** cyclised at the unsubstituted *ortho*-position upon irradiation with 254 nm light in ethereal solution to afford **40** in 21:1 d.r. in favour of the *trans* isomer and an unspecified yield between 52 and 65%.<sup>21</sup> Conversely, when irradiated in methanol solution, *N*-acyl anilide **41** predominantly underwent photocyclisation with migration of the *ortho*-carboxymethyl group, forming **42** with *trans*-stereochemistry in 71% yield alongside only a minor quantity (1.8%) of the alternative lactam product, **43**, as a mixture of *cis*- and *trans*-isomers.<sup>22</sup>



**Scheme 15.** *N*-Acyl anilides also undergo photocyclisation with both retention (as in the reaction to form **40**) and migration (as in the reaction to form **41**) of *ortho*-substituents.

In a related reaction, photocyclisation to **45** occurred cleanly in 80% yield with loss of the *ortho*-methoxy substituent when *N*-benzanilide **44** was irradiated for 6 h in a 9:1 (v/v) mixture of benzene and ethanol (Scheme 16).<sup>23</sup>

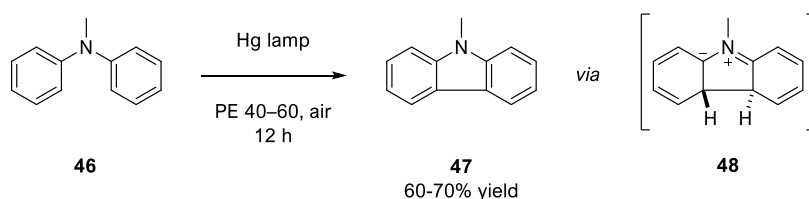


**Scheme 16.** Lactam **45** was formed in 80% yield as a single regioisomer when *ortho*-methoxy-substituted *N*-acyl anilide **44** was subjected to ultraviolet light.

## Heteroatom-containing systems isoelectronic with the pentadienyl anion

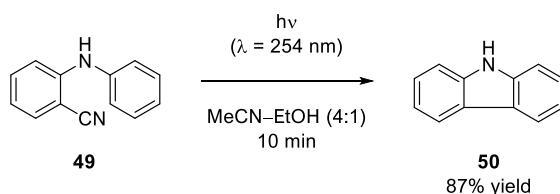
### Diaryl amines, ethers and thioethers

*N*-Methyldiphenylamine, **46**, undergoes an oxidative photocyclisation upon irradiation with UV light in hydrocarbon solvent, affording *N*-methylcarbazole, **47**, in 60–70% yield (Scheme 17).<sup>24</sup> Flash photolysis studies reveal that the reaction of **46** proceeds *via* a singlet zwitterionic intermediate, **48**, formed by conrotatory ring-closure from an excited state. This unstable intermediate can revert thermally or photochemically to starting material in a process reminiscent of the cyclopentadienyl anion electrocyclic ring-opening. Ultimately, however, **48** is transformed to the carbazole product by reaction with oxygen or, in deaerated solutions, by disproportionation.<sup>6,25</sup>



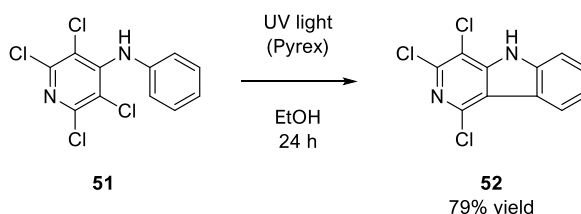
**Scheme 17.** Irradiation of **46** in the presence of air leads to carbazole formation *via* an electrocyclic mechanism.

Eliminative photocyclisations of related substrates generating five-membered heterocycles are known. Carbazole (**50**) was produced in 87% yield when *N*-phenylanthranilonitrile (**49**) was exposed to 254 nm light in a 4:1 (v/v) mixture of acetonitrile and ethanol (Scheme 18).<sup>26</sup>



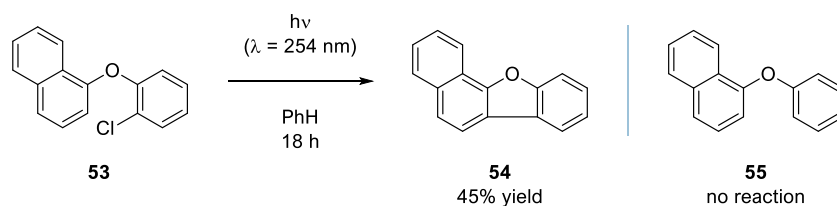
**Scheme 18.** *N*-Phenylanthranilonitrile, **49**, undergoes photocyclisation with loss of HCN upon irradiation with short-wavelength light.

Likewise, the 4-aminophenyl-substituted polyhalogenopyridine compound **51** cyclises with loss of HCl to afford **52** in 79% yield upon Pyrex-filtered irradiation in ethanol solution (Scheme 19).<sup>27</sup>



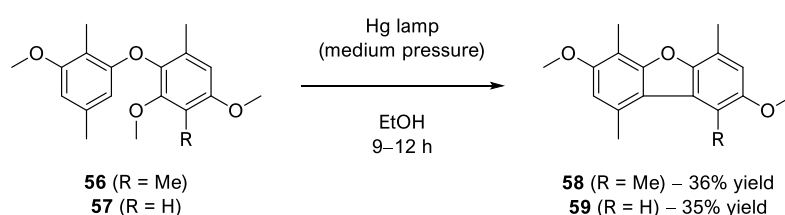
**Scheme 19.** Eliminative photocyclisation of 4-aminophenyl-substituted pyridine **52**.

Diaryl ethers typically rearrange, rather than cyclise, upon photoexcitation.<sup>28</sup> Photocyclisation can be induced in compounds of this class, however, through the incorporation of *ortho*-halogen leaving groups. For example, whereas naphthyl ether **55** failed to react upon irradiation with 254 nm light in benzene solution, a chloro-substituted analogue, **53**, underwent clean photocyclisation under the same conditions, affording naphtho[1,2-*b*]benzofuran, **54**, in 45% yield (alongside unreacted starting material) after an irradiation time of 18 hours (Scheme 20).<sup>29</sup> While little work has been done to uncover the mechanism of this reaction, it likely proceeds *via* an aryl radical.



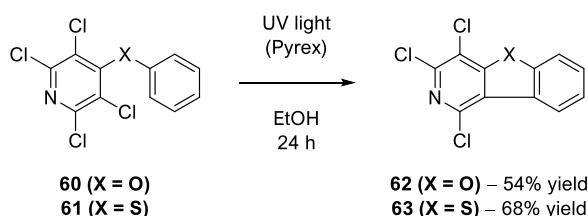
**Scheme 20.** An *ortho*-halogen substituent is necessary to induce photocyclisation in naphthyl phenyl ether substrates, implicating an aryl radical-based mechanism.

*ortho*-Methoxy-substituted diaryl ethers **56** and **57**, in which the alternative site of cyclisation has been blocked through methyl substitution, are transformed upon irradiation in ethanol solution to benzofurans **58** and **59** in yields of 36 and 35%, respectively.<sup>30</sup>



**Scheme 21.** Other eliminative photocyclisations of diaryl ethers may proceed via electrocyclic mechanisms, as suggested by the successful reactions of *ortho*-methoxy-substituted substrates **56** and **57**.

Similarly, diaryl ether **60** and its thioether analogue, **61**, undergo eliminative photocyclisation, likely *via* an aryl radical-based mechanism, affording benzo(thio)furans **62** and **63** in 54 and 68% yields, respectively.<sup>27</sup>

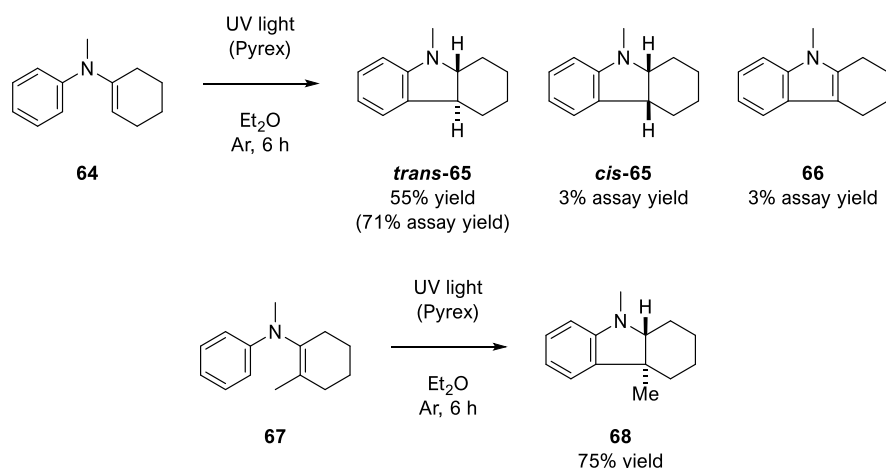


**Scheme 22.** 4-Aryloxy- and 4-arylthioether-substituted polyhalogenopyridines **60** and **61** both undergo moderately high-yielding eliminative photocyclisations.

### N-Aryl enamines and aryl vinyl (thio)ethers

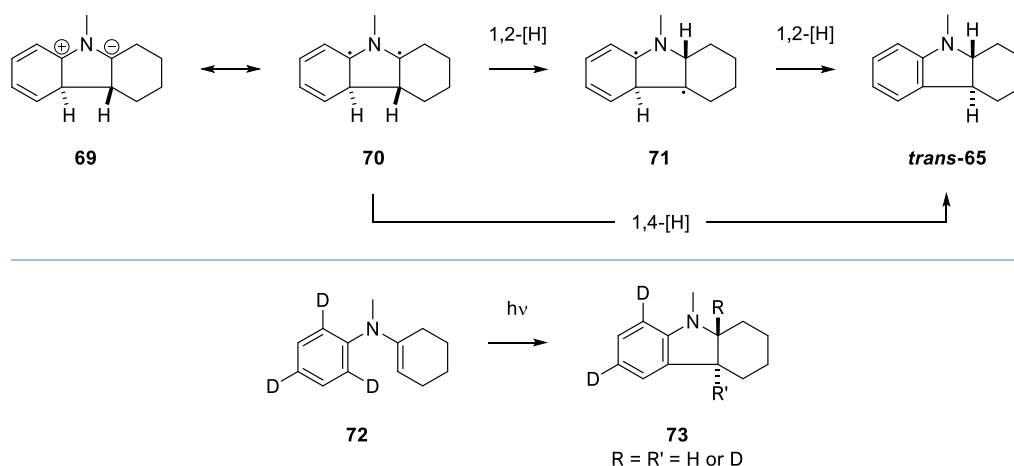
Chapman and co-workers demonstrated that *N*-aryl enamines undergo non-oxidative photocyclisation when irradiated with Pyrex-filtered UV light in deaerated ethereal solution.<sup>31</sup> For cyclic enamine **64**, these conditions led to the formation of *trans*-**65** in an assay yield of 71% (55% isolated yield) alongside a minor amount of its *cis*-isomer. Substrates with enamine  $\beta$ -substituents also undergo efficient photocyclisation, as shown by the formation of indoline **68** from **67** in 75% yield under the same conditions; a single-crystal X-ray structure of a dibrominated derivative of **68** confirmed its *trans*-stereochemistry.<sup>32</sup>





**Scheme 23.** Alicyclic *N*-aryl enamines **64** and **67** are photochemically transformed to (predominantly if not exclusively *trans*-fused) indoline products.

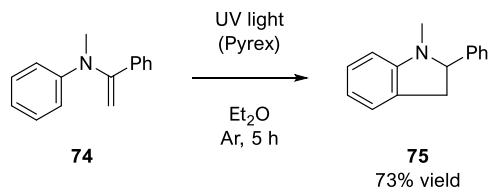
Conrotatory ring-closure from an excited state to form an intermediate that could be viewed as either a zwitterion (**69**) or singlet diradical (**70**) followed by a 1,4-hydrogen shift and/or two sequential 1,2-hydrogen shifts would account for the formation of *trans*-**65** as the major product of the photochemical reaction of **64** (Scheme 24). Photocyclisation of a deuterium-labelled substrate, **72**, led to deuterium incorporation at both carbon atoms of the newly formed ring junction in indoline **73**, indicating that, for this substrate, product formation arises from a combination of 1,4- and 1,2-hydrogen shift processes (although it was not possible to quantify deuterium incorporation at either position, except to say that global incorporation was greater than 89%).<sup>33</sup>



**Scheme 24.** A mechanism involving a combination of 1,2- and 1,4-hydrogen shift processes is suggested by the isolation of **73** with deuterium incorporation at both carbon atoms of the ring juncture from the photochemical reaction of **72**.

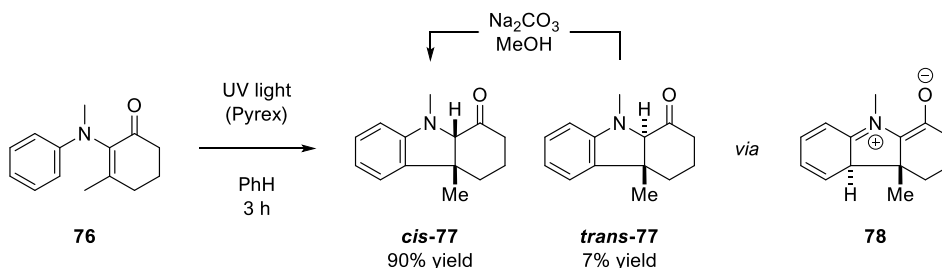
Enamines derived from acyclic ketones are also viable substrates for photocyclisation: when irradiated for 5 h in diethyl ether in the absence of oxygen,  $\alpha$ -(*N*-methylanilino)styrene, **74**, underwent smooth photocyclisation to form **75** in 73% yield (Scheme 25).<sup>31,33</sup> The transformation can be sensitised by xanthone ( $E_T = 74 \text{ kcal mol}^{-1}$ ) and Michler's ketone ( $E_T = 61 \text{ kcal mol}^{-1}$ ),

demonstrating that a reaction from the triplet state is possible; however, the failure of 1,3-cyclohexadiene to quench product formation upon direct irradiation of **74** suggests that the reaction of this and related compounds could proceed *via* an excited singlet state in the absence of a sensitiser (alternatively, the reactive triplet state is very short-lived).



**Scheme 25.**  $\alpha$ -(*N*-methylanilino)styrene **74** undergoes non-oxidative photocyclisation to indoline **75** in 73% when exposed to Pyrex-filtered UV light in ethereal solution.

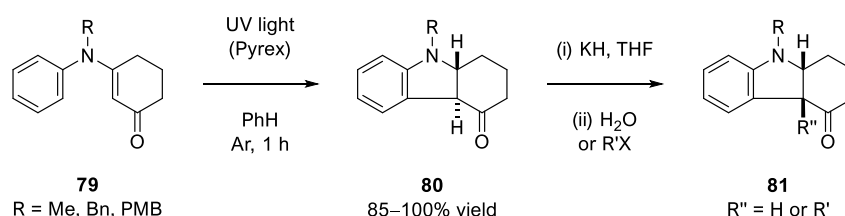
Building on Chapman's pioneering work, Schultz and colleagues extensively explored the photochemistry of *N*-aryl enamines conjugated with a carbonyl group.<sup>34</sup>  $\alpha$ -Enaminone **76** undergoes isomerisation upon direct irradiation with Pyrex-filtered UV light in degassed benzene solution, forming *cis*-**77** in 90% yield alongside its *trans*-fused isomer in 7% yield after an irradiation time of 3 hours (Scheme 26); it was shown that the latter compound could be transformed in a subsequent step to the former by treatment with sodium carbonate in methanol.<sup>35</sup> Enaminones such as **76** possess several advantages as cyclisation precursors over *N*-aryl enamines without carbonyl substitution. Firstly, the cross-conjugated alkene chromophore absorbs at longer wavelengths, enabling the use of less energetic UV light and thus minimising secondary photoreactions of the indoline products. Secondly, the presence of a carbonyl group is thought to stabilise the intermediate zwitterion, **78**, by resonance. Enolate formation following an initial suprafacial 1,4-hydrogen shift likewise provides a mechanism for the formation of *cis*-fused indoline products with high levels of stereocontrol.



**Scheme 26.** Schultz reported that enamines with carbonyl substitution (termed enaminones) isomerise upon Pyrex-filtered irradiation in benzene solution; the carbonyl group is thought to stabilise the putative zwitterionic intermediate, **78**, and facilitates epimerisation of the minor *trans*-isomer in a subsequent step.

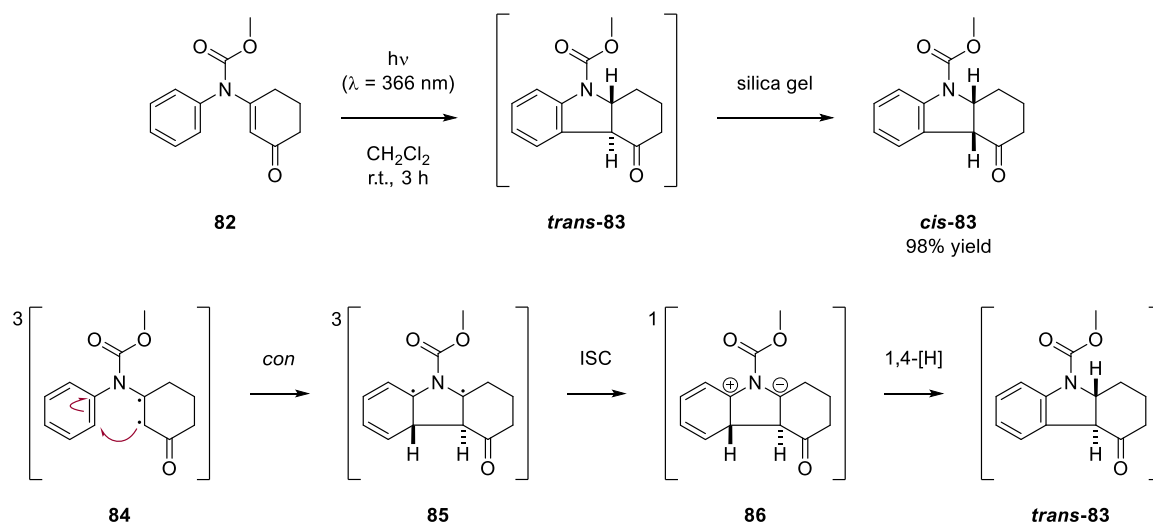
Gramain *et al.* reported the  $6\pi$  photocyclisation of tertiary *N*-alkyl-*N*-aryl- $\beta$ -enaminones **79**.<sup>36</sup> In contrast to the Schultz system, in which the carbonyl group is substituted at the enamine  $\alpha$ -position, these compounds cyclise upon Pyrex-filtered irradiation in degassed benzene to form *trans*- (rather

than *cis*-) fused products (Scheme 27). The indoline products (**80**) of these reactions (formed in yields ranging from 85 to 100%) are unstable, being prone to oxidation, but can be isolated following their transformation to *cis*-fused derivatives (**81**) through deprotonation with potassium hydride in THF and quenching of the resulting enolate with either water (as a proton source) or various alkylating agents.



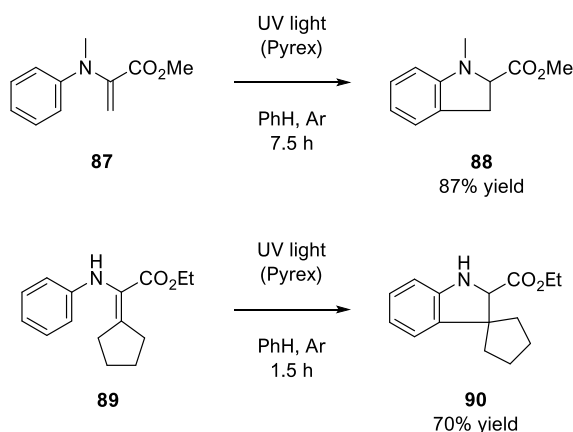
**Scheme 27.** Enamine substrates, **79**, bearing carbonyl substituents at the β-position are also viable photocyclisation substrates, giving rise to *trans*-fused heterocycles, **80**, which could be transformed in a subsequent step to more stable *cis*-fused derivatives, **81**.

The Bach group showed more recently that analogous substrates bearing *N*-alkoxycarbonyl groups instead of *N*-alkyl groups cyclise upon direct irradiation with 366 nm light in dichloromethane solution to form *trans*-fused indoline products that undergo epimerisation in contact with silica (Scheme 28).<sup>37</sup> Thus, while analysis of the crude product by <sup>1</sup>H NMR spectroscopy revealed the exclusive formation of *trans*-**83** from **82**, purification of this material by silica gel chromatography led to isolation of the *cis*-isomer exclusively. Deuterium labelling and triplet quenching experiments, as well as the results of DFT modelling, implicate a mechanism for the photocyclisation of tertiary *N*-alkoxycarbonyl-*N*-aryl-β-enaminone **82** involving conrotatory cyclisation in the triplet state followed by a suprafacial 1,4-hydrogen shift from singlet zwitterion **86**, in line with previous analyses of related systems.



**Scheme 28.** Incorporation of an *N*-alkoxycarbonyl group enables the isolation of ‘dihydroindole’ products from *N*-aryl- $\beta$ -enaminone photocyclisations without an intermediary enolate functionalisation step (cf. Gramain).

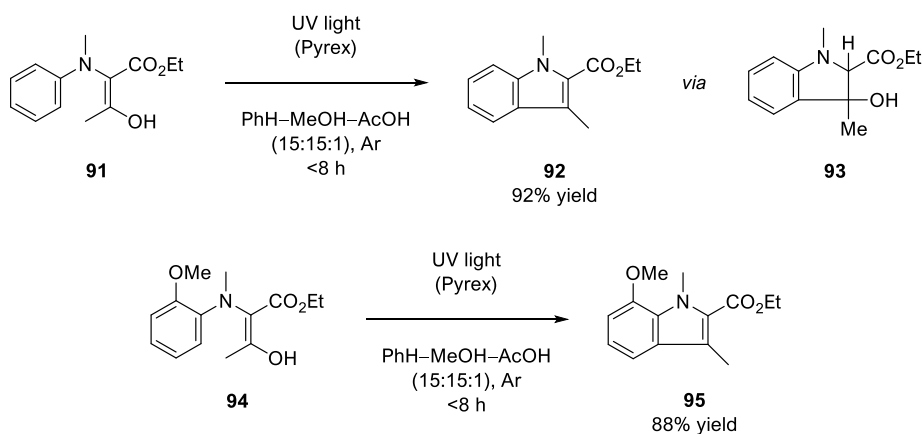
$\alpha$ -Carbonyl substituents are also tolerated in photocyclisations of acyclic *N*-aryl enamines.<sup>38</sup> For example, enamine **87**, derived from the *N*-methylaniline and methyl 2-oxopropanoate, is transformed to indoline **88** in 87% yield upon Pyrex-filtered irradiation in degassed benzene solution over a period of 7.5 hours (Scheme 29). Moreover, these irradiation conditions are applicable to the synthesis of spirocyclic indolines such as **90**, which was produced in a yield of 70% from **89**, demonstrating that *N*-aryl enamine photocyclisations are not limited to tertiary (that is, *N*-alkylated) substrates.



**Scheme 29.** Non-oxidative photocyclisations of *acyclic* enamine substrates bearing carbonyl substituents are also possible.

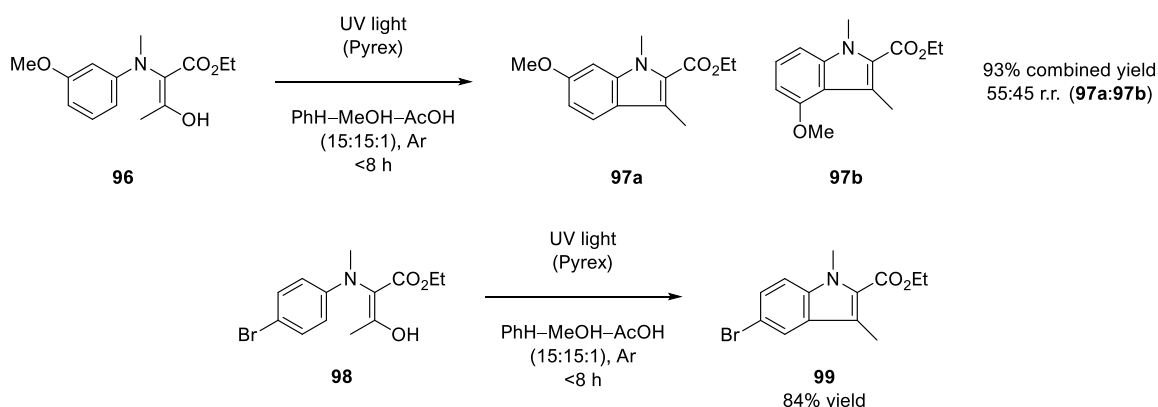
A related transformation is the photochemical cyclisation of ethyl 2-(methyl(phenyl)amino)-3-oxobutanoate, **91**, in an argon-saturated mixture of benzene, methanol and acetic acid (15:15:1 v/v).<sup>39</sup> Excitation of the enol tautomer of this compound leads to the formation of 3-hydroxyindoline **93** via a pentadienyl anion-like electrocycloisation; this intermediate

(which can be isolated in excellent yield when the same substrate is irradiated in a mixture of *n*-pentane and sodium carbonate) undergoes acid-mediated dehydration *in situ*, affording indole **92** in a yield of 92% (Scheme 30). Notably, an analogue containing an *ortho*-methoxy substituent cyclises in 88% yield without elimination of methanol; this photochemical behaviour contrasts that of some *ortho*-methoxy-substituted stilbene derivatives and enamides, for which eliminative photocyclisations have been observed, as discussed previously.



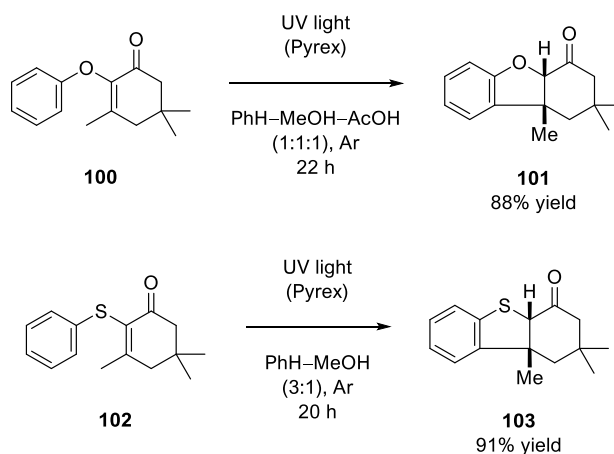
**Scheme 30.** Enol **91** is transformed upon irradiation in the presence of acid to **92** via hydroxyindoline **93**; *ortho*-methoxy-substituents are retained in photocyclisations of this substrate class, as illustrated by the formation of **95** in 88% yield from **94** under the standard reaction conditions.

The reaction of a *meta*-methoxy-substituted substrate, **96**, is also illustrative, highlighting an issue common to many *N*-aryl enamine photocyclisations, which is that regioselectivity with respect to *meta*-substituents on the aromatic ring is generally poor: **97a** and **97b** were obtained from **96** as a 55:45 mixture of regioisomers, albeit in a high combined yield of 93% (Scheme 31).<sup>39</sup> Another noteworthy example is the photocyclisation of *para*-bromo substrate **98**, which proceeds cleanly and in high yield (84%) under the same conditions to form **99**, in which the photolabile C–Br bond has been retained.



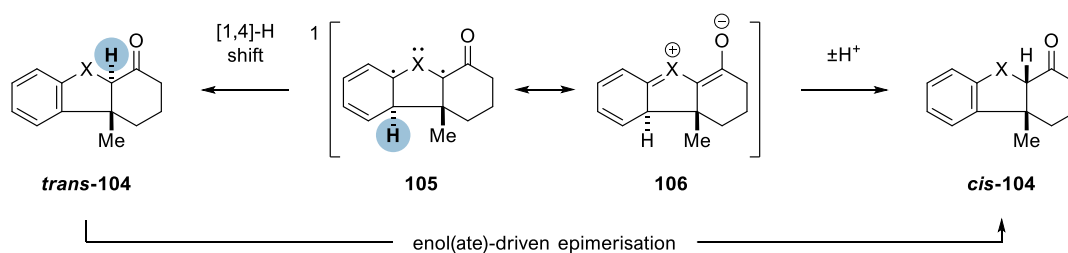
**Scheme 31.** Photocyclisation proceeds smoothly for *meta*-methoxy (**96**) and *para*-bromo (**98**) substrates, although the product is formed as a mixture of regioisomers in the former case.

Schultz and co-workers found that, like their aniline-derived counterparts, 2-aryloxy- and 2-arylthiocyclohexenones also undergo efficient photocyclisation.<sup>40,41</sup> Thus, *cis*-fused heterocycles **101** and **103** were formed in yields of 88% and 91%, respectively, upon irradiation of compounds **100** and **102** with Pyrex-filtered light in benzene mixtures containing acetic acid and/or methanol (Scheme 32).



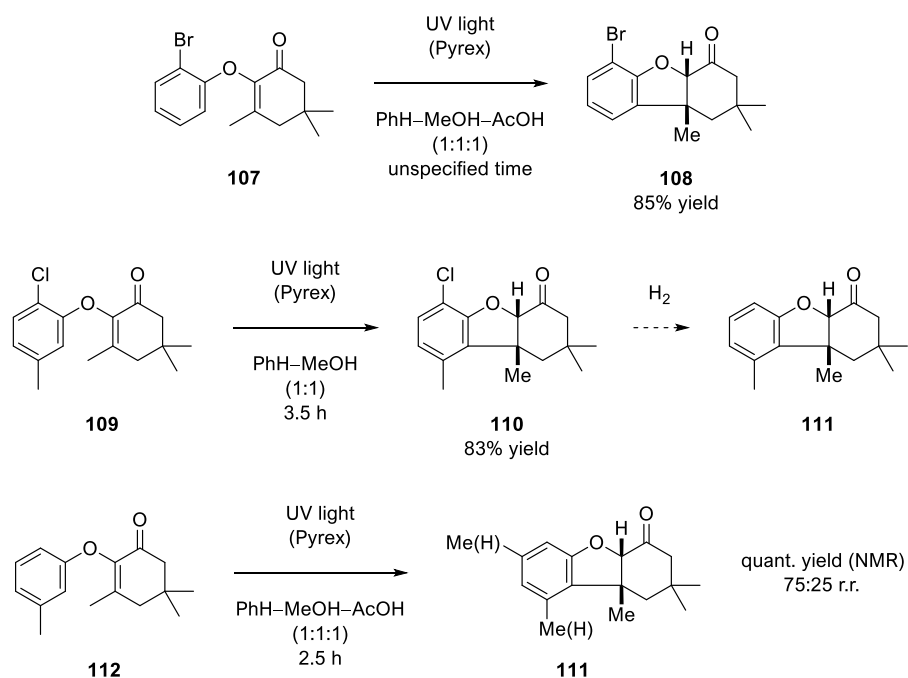
**Scheme 32.** Non-oxidative photocyclisations of archetypal 2-aryloxy- and 2-arylthiocyclohexenone substrates reported by Schultz and co-workers.

These reactions likely proceed *via* conrotatory ring-closure from an excited state, leading to zwitterion (**106**), which could also be viewed<sup>42</sup> as a singlet diradical (**105**) (Scheme 33). In the presence of a protic solvent, such as methanol, this intermediate (stabilised by conjugation with the carbonyl group) is thought to be transformed to product through a series of intermolecular proton transfer events; in the absence of a proton source, a thermally allowed, suprafacial 1,4-hydrogen shift followed by epimerisation would account for the formation of *cis*-fused products (mixtures of *cis*- and *trans*-isomers were isolated from photoreactions performed in pure benzene solution).



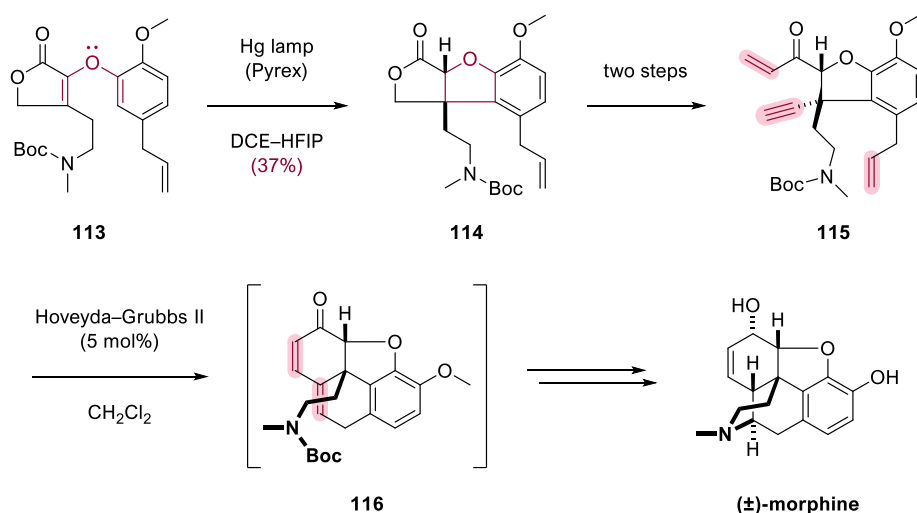
**Scheme 33.** Possible mechanisms accounting for the formation of *trans*-fused products in photocyclisations of 2-aryloxy- and 2-arylthiocyclohexenones.

The UV-mediated photocyclisation of 2-aryloxy- and 2-arylthiocyclohexenones is high-yielding across a range of substrates, with both electron-donating and -withdrawing substituents on the aromatic nucleus being well tolerated. Of particular note is the successful reaction of *ortho*-bromo substrate **107**, which occurs exclusively at the unsubstituted *ortho*-position, affording isomerisation product **108** in 85% yield (Scheme 34).<sup>34</sup> Considering the feasibility of reductively cleaving the carbon–halogen bond in a subsequent step, it was proposed that *ortho*-halogen substituents could be strategically employed as temporary ‘blocking’ groups to control the regioselectivity of 2-aryloxyketone photocyclisations with respect to arene *meta*-substituents. For instance, 2-chloro-5-methylphenyl substrate was shown to form **110** as the sole product in **83%** yield; reduction of this compound would provide access to dihydrobenzofuran **111** as a single regioisomer. By contrast, the same compound was formed as an inseparable 75:25 mixture of regioisomers whenever the corresponding substrate without a chlorine substituent, **112**, was subjected to similar photocyclisation conditions.<sup>40</sup>



**Scheme 34.** 2-Aryloxycyclohexenone substrates cyclise upon Pyrex-filtered irradiation without loss of *ortho*-bromine or -chlorine substituents, enabling control over the regiochemical outcome of the reaction with respect to a *meta*-substituent.

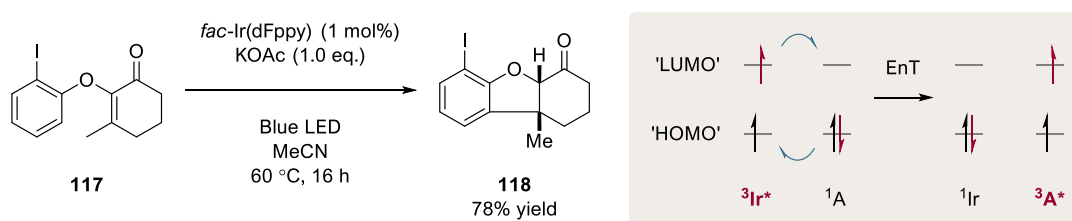
In 2016, Smith and co-workers reported a concise total synthesis of *rac*-morphine in which a Schultz-type photochemical  $6\pi$  electrocyclisation of butenolide **113** was employed as the key stereodefining step (Scheme 35).<sup>43</sup> This compound underwent photocyclisation upon Pyrex-filtered irradiation in a mixture of 1,2-dichloroethane and hexafluoroisopropanol to form *cis*-fused benzofuran derivative **114** in 37% yield. A ruthenium-catalysed ene-yne-ene metathesis cascade cyclisation of **115**, obtained in two steps from the photocyclisation product, subsequently assembled the tetracyclic morphine core (**116**) in a highly step- and atom-economic manner.



**Scheme 35.** Final stages of Smith's total synthesis of *rac*-morphine, including a Schultz-type aryl vinyl ether photocyclisation.



The low yield of the photocyclisation of **114** in Smith's morphine synthesis prompted a search by the same group for milder conditions to promote this class of reaction. To this end, it was found that the photochemical isomerisation of 2-aryloxy-, 2-arylthio- and 2-arylamino ketones reported originally by Schultz can be mediated by *visible* light, if used in combination with an iridium photocatalyst.<sup>44</sup> The mildness of the photocatalytic approach is highlighted by the clean isomerisation of 2-aryloxyketone **117** to **118** in 78% yield, which proceeds with retention of the weak carbon–iodine bond (Scheme 36). Thus, an *ortho*-iodine substituent can be used as blocking group for 2-aryloxyketone photocyclisations under these conditions. Essential to the success of this strategy was the selection of a photocatalyst – *fac*-Ir(dFppy)<sub>3</sub> ( $E_T = 60.1 \text{ kcal mol}^{-1}$ ) – with a similar triplet energy to the enone substrate ( $E_T \approx 60 \text{ kcal mol}^{-1}$  for 2-aryloxycyclohexenone-based substrates), implicating a mechanism involving Dexter energy transfer from the triplet-state photocatalyst ( $^3\text{Ir}^*$ ) to the ground-state substrate ( $^1\text{A}$ ).<sup>45</sup>



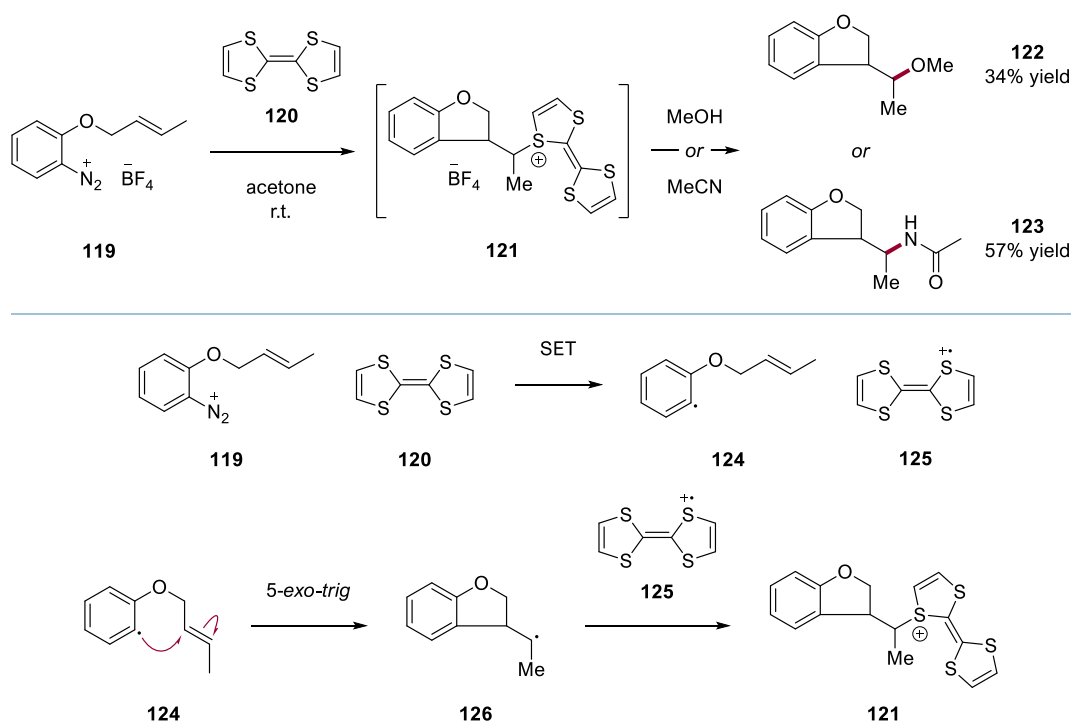
**Scheme 36.** Energy transfer from an excited iridium sensitiser enables the use of visible light to promote the isomerisation of 2-aryloxycyclohexenones such as **117** and related substrates.



## Chapter 2 – A radical–polar crossover approach to complex nitrogen heterocycles *via* the triplet state

### Introduction to radical–polar crossover reactions

In 1993, Murphy and co-workers reported that treating diazonium tetrafluoroborate **119** with a stoichiometric amount of tetrathiafulvalene (**120**) in acetone at room temperature led to a sulfonium salt, **121**, that could be isolated and transformed in a subsequent step to *O*-methyl ether **122** in 34% yield through reaction with methanol or to acetamide **123** in 57% yield through reaction with acetonitrile (Scheme 37).<sup>46</sup> A mechanism involving both radical (one-electron) and polar (two-electron) bond-forming processes was proposed, in which an initial 5-*exo-trig* cyclisation of aryl radical **124** – generated by single-electron reduction of diazonium salt **119** by **120** – is followed by a radical combination step between the cyclised radical, **126**, and tetrathiafulvalene radical cation, **125**. The latter step affords the electrophilic sulfonium species, **121**, that subsequently undergoes solvolysis *via* a polar mechanism.

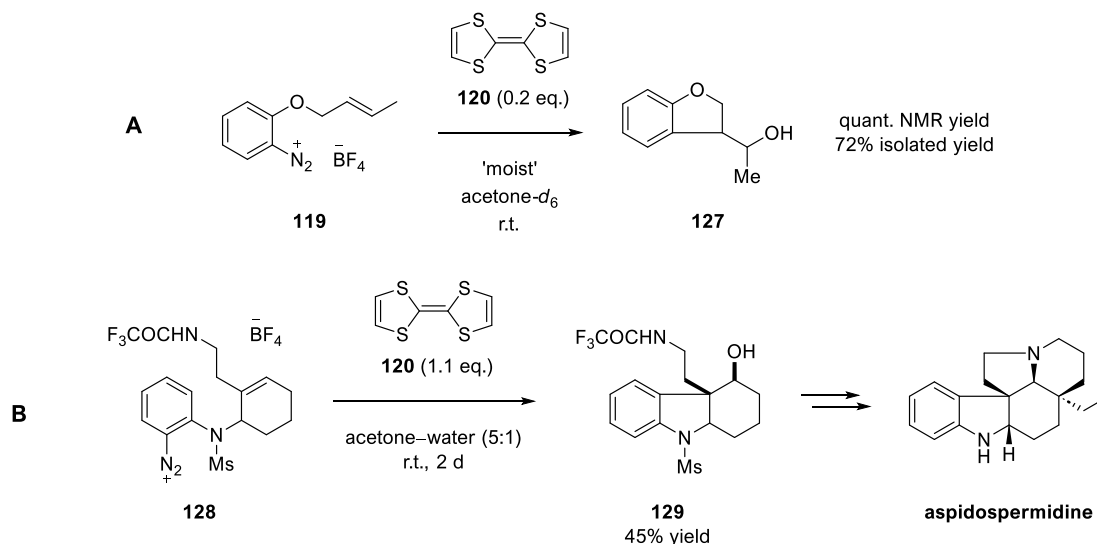


**Scheme 37.** Treating diazonium tetrafluoroborate **119** with tetrathiafulvalene leads to nucleophilic trapping products **122** or **123** *via* a sulfonium species, **121**, generated through a radical recombination step.

It was further shown that the reaction – described by the authors as a ‘radical–polar crossover’ reaction – could be made catalytic in tetrathiafulvalene; thus, the same diazonium salt, **119**, was transformed quantitatively to alcohol **127** when treated with 0.2 equivalents of tetrathiafulvalene in ‘moist’ acetone (Scheme 38A).<sup>\*</sup> Since this initial discovery, the Murphy group has extensively

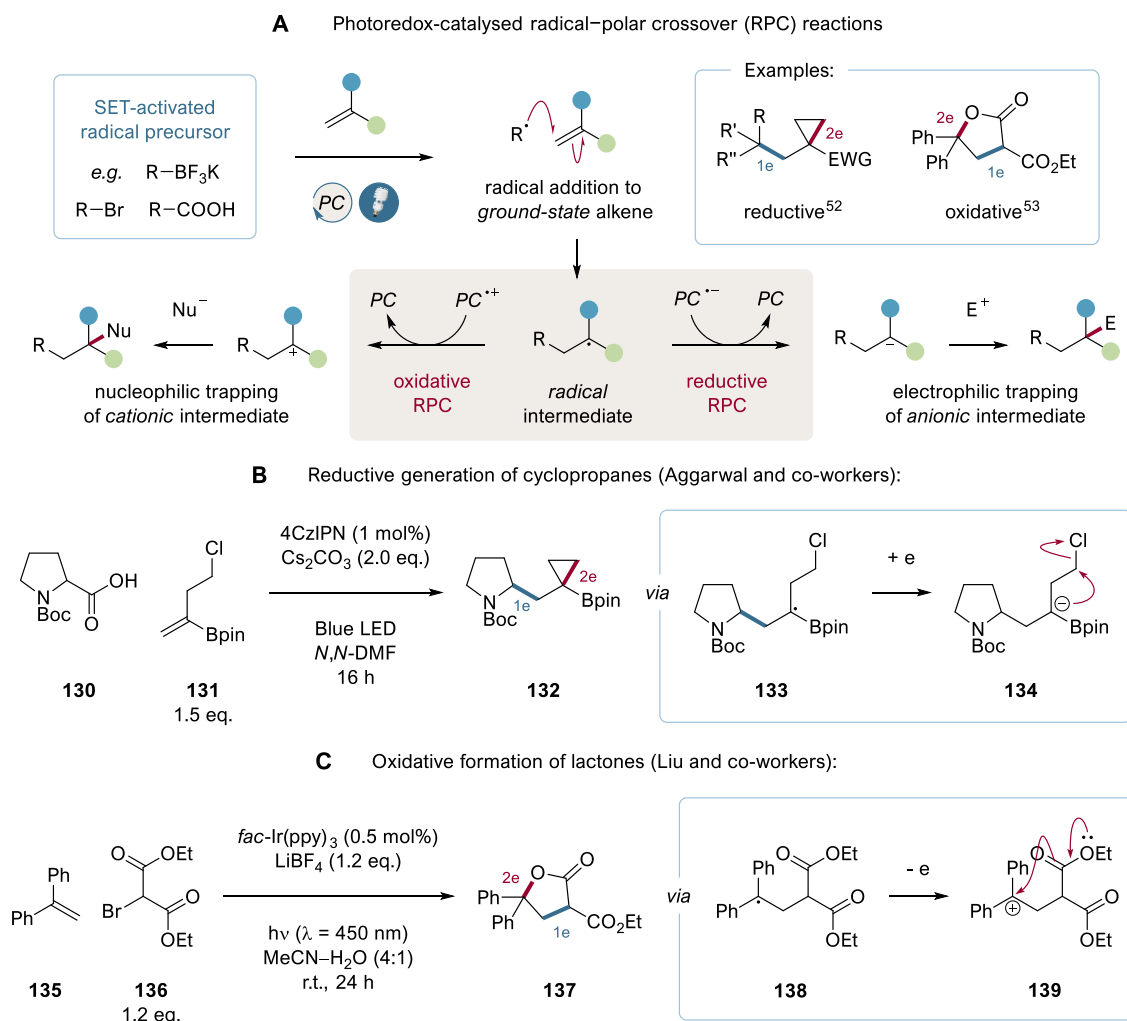
<sup>\*</sup> The exact water content of the reaction solvent was not specified in the Murphy group’s original report.

shown that this (thermal) strategy for initiating a radical mechanism and subsequently diverting its course to a polar manifold (using a single reagent in catalytic amounts) is applicable to a range of synthetic endeavours,<sup>47</sup> including the total synthesis of natural products such as *rac*-aspidospermidine (Scheme 38B).<sup>48</sup>



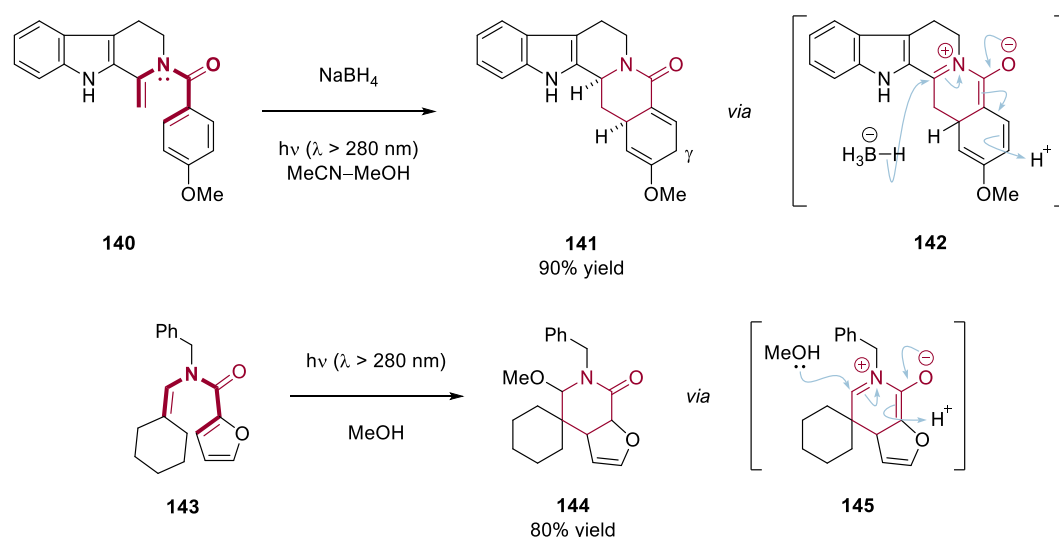
**Scheme 38. (A)** The tetrathiafulvalene reagent is regenerated following the nucleophilic substitution step, enabling its use in catalytic quantities in the reaction of diazonium tetrafluoroborate **119**. **(B)** A tetrathiafulvalene-promoted radical–polar crossover reaction of **128** afforded alcohol **129** in 45% yield as a single diastereomer, which was subsequently transformed to aspidospermidine.

A wide range of transformations incorporating radical–polar crossover is also possible under photoredox catalysis.<sup>49–51</sup> Mechanistically, a typical reaction of this type involves addition of radicals (generated by single-electron oxidation or reduction of suitably activated precursors such as alkyl halides, carboxylic acids or trifluoroborate salts) to an alkene substrate, producing an open-shell intermediate that undergoes a subsequent single-electron transfer event involving the photocatalyst (Scheme 39A). Both anionic and cationic intermediates can be generated and productively intercepted in this way. For example, Aggarwal and co-workers developed a modular synthesis of cyclopropanes (such as **132** from alkyl carboxylic acid **130** and vinyl boronic ester **131**) enabled by a *reductive* radical–polar crossover event; in this reaction, an anionic cyclisation (of **134**) is induced upon single-electron reduction of an intermediate (**133**) arising from radical addition to the alkene substrate (Scheme 39B).<sup>52</sup> By contrast, the Liu group showed that *oxidative* radical–polar crossover is possible from radical intermediate **138** – generated through the addition of a malonyl radical to 1,1-diphenylethylene – leading to a cation, **139**, that cyclises to form lactone **137** (Scheme 39C).<sup>53</sup>



**Scheme 39. (A)** Photochemical radical–polar crossover (RPC) reactions enabled by electron-transfer catalysis. Radical addition to an alkene is a common elementary step in reactions of this type, leading to radical intermediates that can undergo single-electron oxidation or reduction to form cationic or anionic products, respectively. **(B)** Cyclopropane formation triggered by single-electron transfer to radical intermediate **133** demonstrates reductive radical–polar crossover. **(C)** Carbocation **139**, formed upon single-electron oxidation of **138** following radical addition to 1,1-diphenylethylene, cyclises to form lactone **137**, exemplifying oxidative radical–polar crossover.

It has also been shown that the (singlet) zwitterionic intermediates formed in some photochemical  $6\pi$  electrocyclisations – which typically undergo intramolecular hydrogen transfer processes – can be intercepted with two-electron nucleophiles under certain conditions (Scheme 40). When irradiated with Pyrex-filtered UV light in the presence of methanolic sodium borohydride, for example, *N*-benzoyl enamine **140** was cleanly transformed to enol ether **141** in 90% yield, which could be hydrolysed in a subsequent step and elaborated to yohimbine and other indole alkaloids.<sup>54,55</sup> It was proposed that the reaction proceeds *via* the concomitant protonation and reduction of zwitterion **142**. In a related transformation, Gramain *et al.* suggested that methanol reacts with zwitterionic intermediate **145**, formed upon Pyrex-filtered irradiation of *N*-acyl enamine **143**, to afford a spirocyclic nucleophilic trapping product, **144**, in 80% yield.<sup>56</sup>



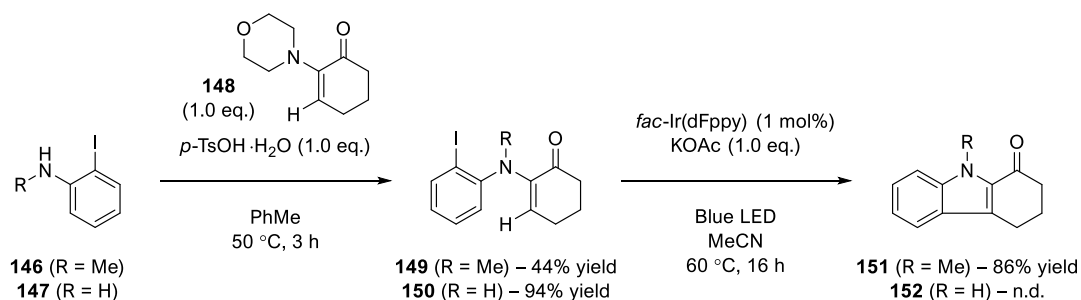
**Scheme 40.** Intercepting the zwitterionic intermediates of photochemical  $6\pi$  electrocyclisations.

While they do not strictly involve a transition from *radical* to polar reactivity, owing to the pericyclic nature of the photochemical step,  $6\pi$  photocyclisations of this type represent a complementary strategy to the use of photoredox catalysts for photochemically generating ionic intermediates from alkene substrates.

### Discovery of an eliminative *N*-aryl enaminone photocyclisation

While eliminative photocyclisations of stilbenes and enamides are well-studied, and in some cases the zwitterionic intermediates of photochemical  $6\pi$  electrocyclisations have been shown to react with external nucleophiles, there are, to our knowledge, few examples of reactions mediated by a *triplet* excited state that involve a transition from (di)radical to polar reactivity. In this chapter, we describe the development and mechanistic study of a photocyclisation reaction in which such a transition appears to occur, enabling the rapid assembly of molecular complexity through the generation (and subsequent thermal trapping) of an iminium electrophile.

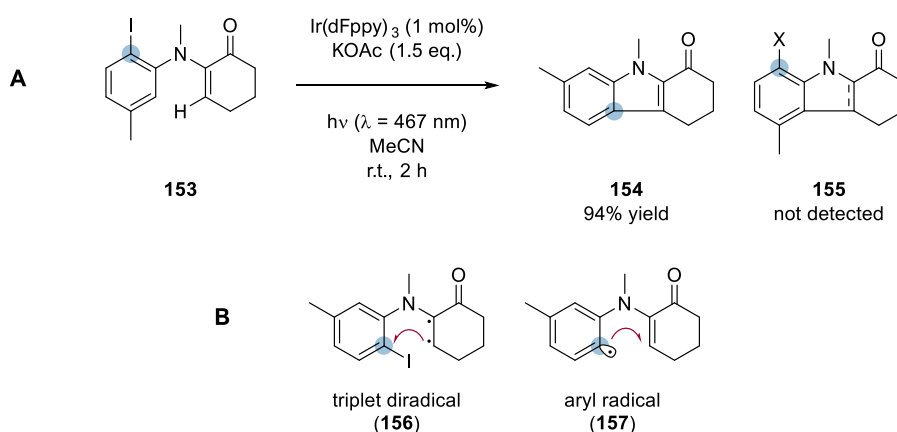
The initial discovery was made when *N*-aryl enaminone **149** – synthesised in 44% yield *via* the transamination<sup>57</sup> of morpholine enamine **148** with *N*-methyl-2-iodoaniline (**146**) – was irradiated in acetonitrile solution with light from a blue LED strip in the presence of a catalytic amount of *fac*-Ir(dFppy)<sub>3</sub> (Scheme 41). Unexpectedly, this reaction gave indole **151**, in which the *ortho*-iodine substituent present in the starting material had been lost, as the exclusive product in a yield of 86%. *N*-Substitution is necessary for the successful photocyclisation of this class of substrate, as illustrated by the failure of secondary *N*-aryl enaminone **150** (synthesised in 94% yield from morpholine enamine **147**) to react under the same conditions.



**Scheme 41.** Initial observation of eliminative photocyclisation behaviour with a tertiary *N*-aryl enaminone substrate, **149**, bearing an *ortho*-iodine substituent.

### Iminium hypothesis and reaction design

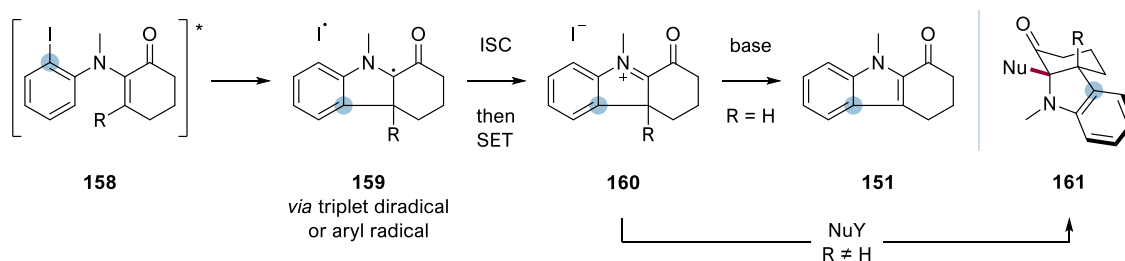
To determine whether C–I bond cleavage was directly responsible for product formation in the example described above (as opposed to occurring in a secondary photoreaction of some initially formed iodine-containing product), a substrate, **153**, containing a 5-methyl substituent was synthesised. Upon sensitised irradiation with 467 nm light in acetonitrile solution, this compound again underwent clean photocyclisation with loss of the iodine substituent, producing **154** as a single regioisomer in 94% yield; alternative ‘*ipso*-H’ diradical cyclisation products, such as **155**, were not observed (Scheme 42A).<sup>58</sup> The regioselectivity\* observed in this eliminative photocyclisation was thought to implicate a mechanism involving either the *ipso*-I cyclisation<sup>59,60</sup> of an alkene triplet diradical (**156**) or the 5-*endo-trig* cyclisation<sup>61</sup> of a homolytically generated aryl radical (**157**) (Scheme 42B).



**Scheme 42.** (A) Photocyclisation of **153** occurred with high regioselectivity with respect to the *meta*-methyl substituent. (B) Cyclisation of a triplet diradical (**156**) or an aryl radical intermediate (**157**) could account for the observed regioselectivity.

\* The term ‘regioselectivity’ is used here to describe the ‘direction’ of cyclisation – that is, the preference for bond formation to occur at one *ortho*-carbon atom over the other – in line with IUPAC recommendations.<sup>62</sup>

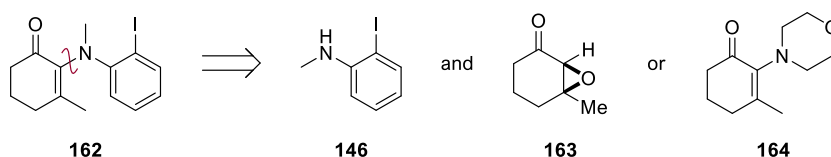
Whether mediated by an aryl radical or triplet diradical, it was hypothesised that the eliminative photocyclisation of *N*-aryl enaminones represented generally as **158** would proceed initially *via* radical pair **159**; this could be expected to form an iminium iodide salt **160** upon intersystem crossing and single-electron transfer (Scheme 43). The deprotonation of such an intermediate would account for the fused indole products (e.g. **151**) obtained previously (in the presence of a base) from the photochemical reaction of substrates containing a hydrogen atom at the enone  $\beta$ -position. If, therefore, aromatisation was prevented by the presence of a *non-hydrogen* substituent at this position, it should be possible to intercept the putative iminium intermediate through a thermal nucleophilic trapping event, enabling the construction of complex molecular architectures **161**. To test this hypothesis, a substrate bearing a methyl substituent at the  $\beta$ -position of the enone was targeted for synthesis.



**Scheme 43.** Iminium hypothesis and reaction design.

### Initial attempts to synthesise a substrate, **162**, bearing a $\beta$ -methyl substituent

It was envisaged that  $\beta$ -methyl substrate **162** could be obtained in one step through the condensation of epoxide **163** derived from 3-methyl-2-cyclohexenone and the corresponding secondary aniline (**146**) (Scheme 44). Another possible synthesis of **162** from 2-iodo-*N*-methylaniline (**146**) would involve the reaction of the latter with morpholine enamine **164**.



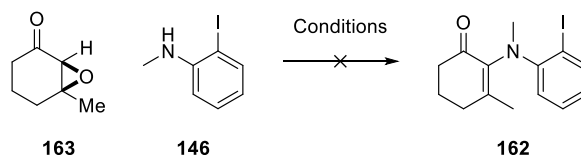
**Scheme 44.** Retrosynthetic analysis of **162** from 2-iodo-*N*-methylaniline (**146**) and 3-methyl-2-cyclohexen-1-one or 3-methylcyclohexane-1,2-dione derivatives **163** or **164**.

Heating *N*-methyl-2-iodoaniline (**146**) and epoxide **163** in a 3:1 (v/v) mixture of methanol and water to reflux – conditions employed successfully by Münster *et al.* to synthesise related substrates without *ortho*-substituents<sup>44</sup> – led to clean recovery of the starting materials (Table 1, entry 1); it is hypothesised that the failure of this reaction is due to steric hindrance imposed by the large *ortho*-iodine substituent. The use of copper(II) triflate<sup>63</sup> (entries 2 and 3) and lithium bromide<sup>63</sup> (entry 4) as Lewis acid catalysts, as well as performing the reaction in a fluorinated alcohol solvent



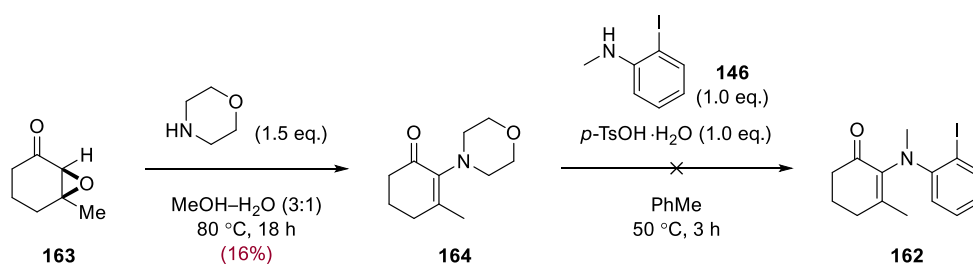
system<sup>64</sup> (entry 5) and in the presence of alumina<sup>65</sup> (entry 6), also gave no reaction, desired or otherwise.

**Table 1.** Conditions explored for the condensation of *N*-methyl-2-iodoaniline (**146**) with epoxide **163**.



Entry	Conditions
1	<b>163</b> (1.0 eq.), (1.2 eq.), MeOH–H <sub>2</sub> O (3:1 v/v) (0.42 M), reflux.
2	<b>163</b> (1.0 eq.), <b>146</b> (1.2 eq.), Cu(OTf) <sub>2</sub> (10 mol%), Et <sub>2</sub> O (0.2 M), r.t.
3	<b>163</b> (1.0 eq.), <b>146</b> (1.2 eq.), Cu(OTf) <sub>2</sub> (10 mol%), MeCN (0.2 M), 80 °C.
4	<b>163</b> (1.0 eq.), <b>146</b> (1.2 eq.), LiBr (10 mol%), neat, r.t.
5	<b>163</b> (1.0 eq.), <b>146</b> (1.2 eq.), HFIP (0.5 M), reflux.
6	<b>163</b> (1.0 eq.), <b>146</b> (1.2 eq.), aluminium oxide (6 g per mmol of <b>163</b> ), THF (0.1 M) reflux.

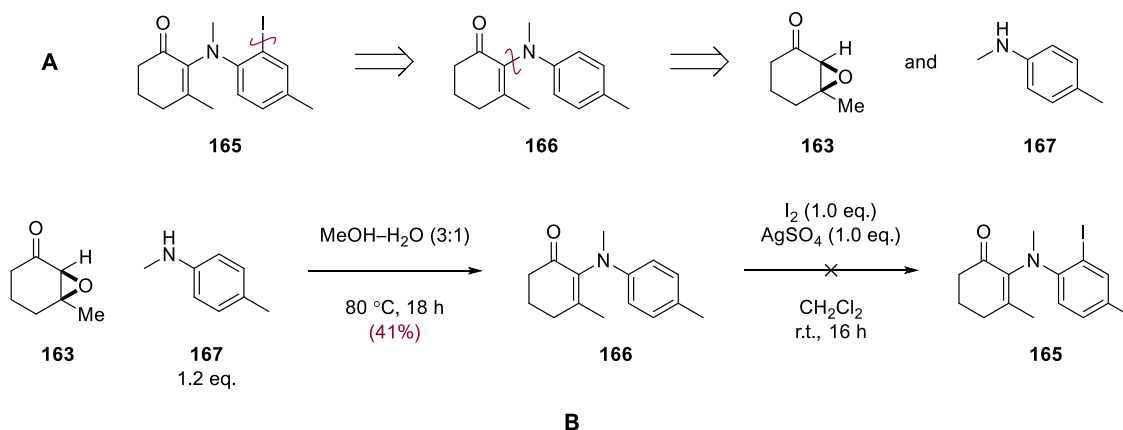
Morpholine enamine **164** was synthesised in 16% yield through condensation of epoxide **163** with morpholine (Scheme 45). Subjecting this compound and *N*-methyl-2-iodoaniline to the conditions described above for the acid-mediated transamination of its  $\beta$ -hydrogen analogue, however, resulted in no observable chemical change.



**Scheme 45.** Unsuccessful synthesis of  $\beta$ -methyl enaminone **162** via the acid-mediated transamination of morpholine enamine **164** with secondary aniline **146**.

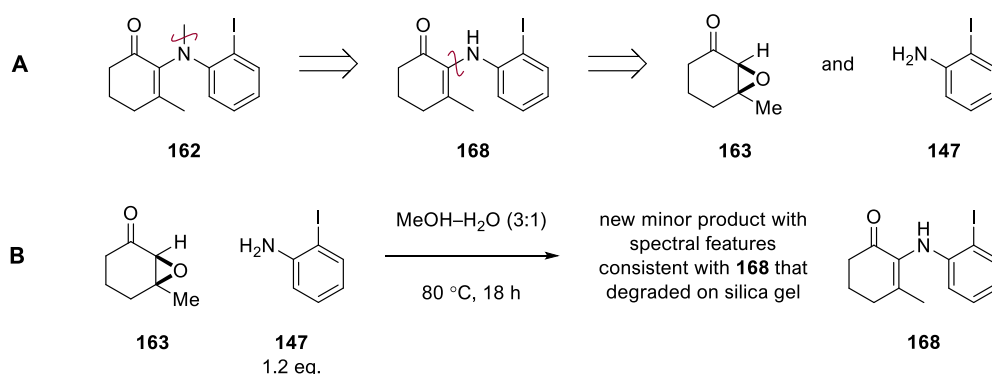
The likelihood that the large *ortho*-iodine atom was adversely affecting the reactions of *N*-methyl-2-iodoaniline led us to consider installing this substituent at a later stage of the synthesis of  $\beta$ -methyl analogues such as **162**. One implementation of this strategy would be the *ortho*-iodination of enaminone **166**, in which the *para*-position has been blocked through methyl substitution (Scheme 46A). Reaction of epoxide **163** with *N*,4-dimethylaniline (**167**) under

conditions that had previously failed when *N*-methyl-2-iodoaniline was used as the nucleophile gave enaminone **166** in 41% yield; no reaction was observed, however, when this compound was treated with iodine and silver sulfate in dichloromethane (Scheme 46B).\*



**Scheme 46. (A)** Retrosynthesis of **165** involving late-stage incorporation of the *ortho*-iodine substituent. **(B)** Mixing **166**, synthesised in one step from epoxide **163** and *N*,4-dimethylaniline (**167**), with iodine and silver sulfate in dichloromethane at room temperature led to recovery of starting material.

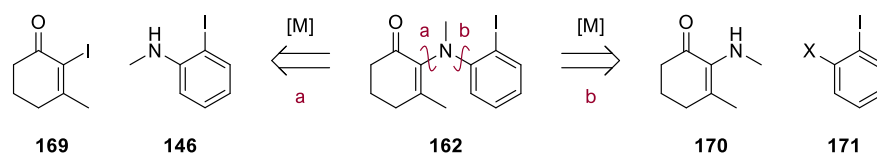
An alternative plan to incorporate the *N*-methyl substituent at a late stage in the synthesis of **162** was devised (Scheme 47A); it was hypothesised that, as a result of its less hindered nitrogen atom, 2-iodoaniline might be a more effective nucleophile than 2-iodo-*N*-methylaniline in the ring-opening of epoxide **163**. An attempt to synthesise secondary enaminone **168** from epoxide **163** *via* this route gave a minor quantity of a new product with spectral features consistent with **168**; this compound, however, degraded on silica gel, precluding its full characterisation (Scheme 47B). The low conversion of starting materials and difficulty in isolating the product under these conditions led us to abandon this route.



**Scheme 47. (A)** Retrosynthesis of **162** involving late-stage incorporation of the *N*-methyl substituent. **(B)** The reaction of epoxide **163** and 2-iodoaniline (**147**) gave a small amount of a new product that degraded on silica gel and could not be fully characterised but is tentatively assigned as **168**.

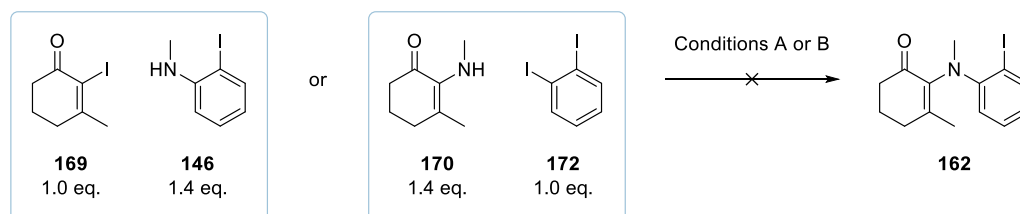
\* These conditions have since been shown to readily effect the *para*-iodination of related compounds (see below).

Having failed to prepare **162** *via* condensation reactions, we considered other C–N bond-forming strategies (Scheme 48). In principle, a transition metal-catalysed cross-coupling reaction between iodoenone **169** and *N*-methyl-2-iodoaniline (**146**) (disconnection a) or between secondary enaminone **170** and some 2-iodophenyl derivative, **171**, (disconnection b) could make for an expedient synthesis of the required substrate.



**Scheme 48.** Retrosynthetic strategies exploring the use of metal-catalysed C–N cross-coupling reactions to synthesise **162**. For example, X = I, B(OH)<sub>2</sub>, *etc.*

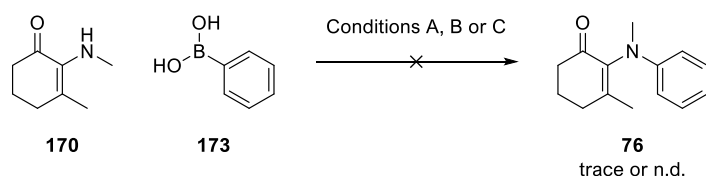
Palladium catalysis was initially explored for both disconnections. Under two sets of conditions recommended by Buchwald and co-workers<sup>65</sup> for the cross-coupling of secondary amine nucleophiles with aryl halides employing the dialkylbiaryl phosphine ligand RuPhos, neither the use of *N*-methyl-2-iodoaniline together with iodoenone **169** nor the reaction of secondary enaminone **170** and 1,2-diiodobenzene (**172**) was successful in delivering the desired tertiary enaminone product, with large recoveries of starting materials and only trace amounts of side-products being observed instead.



**Scheme 49.** Attempted syntheses of **162** from iodoenone **169** or secondary *N*-methyl enaminone **170**, both derived from 3-methyl-2-cyclohexenone, through palladium-catalysed Buchwald–Hartwig cross-coupling.

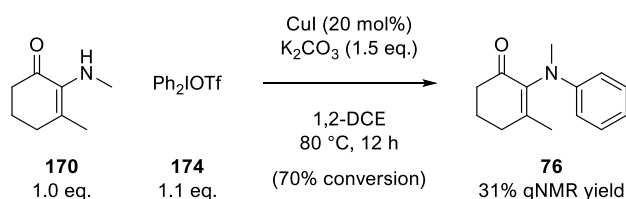
*Conditions A:* Pd(OAc)<sub>2</sub> (5 mol%), RuPhos (10 mol%), Cs<sub>2</sub>CO<sub>3</sub> (1.4 eq.), PhMe, 110 °C. *Conditions B:* Pd(OAc)<sub>2</sub> (5 mol%), RuPhos (10 mol%), *t*-BuONa (1.4 eq.), 1,4-dioxane, 100 °C.

Disconnection b could potentially be achieved under copper catalysis through a Chan–Lam-type coupling of secondary enaminone **170** with an appropriate aryl boronic acid. To explore this idea, we attempted the reaction of **170** with phenyl boronic acid (**173**) using copper(II) acetate in combination with triethylamine or boric acid additives, as recommended by Watson and co-workers,<sup>65</sup> in the presence of 4 Å molecular sieves (Scheme 50). Under these conditions, however, only trace quantities of the desired product could be observed; hydrolysis of enaminone **170** occurred predominantly instead.



**Scheme 50.** Attempted Chan-Lam coupling of secondary *N*-alkyl enaminone **170** with phenyl boronic acid (**173**). *Conditions A:* **173** (1.0 eq.), **170** (2.0 eq.), Cu(OAc)<sub>2</sub> (1.0 eq.), B(OH)<sub>3</sub> (2.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> (0.25 M), 4 Å molecular sieves (100 mg/mmol of **173**), room temperature. *Conditions B:* **173** (1.0 eq.), **170** (2.0 eq.), Cu(OAc)<sub>2</sub> (1.0 eq.), B(OH)<sub>3</sub> (2.0 eq.), MeCN (0.25 M), 4 Å molecular sieves (100 mg/mmol of **173**), 80 °C. *Conditions C:* **173** (2.0 eq.), **170** (1.0 eq.), Cu(OAc)<sub>2</sub> (1.0 eq.), Et<sub>3</sub>N (2.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> (0.25 M), 4 Å molecular sieves (100 mg/mmol of **170**), room temperature.

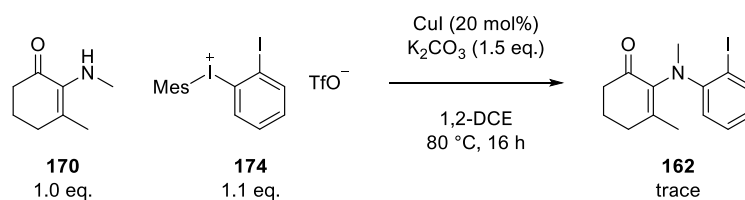
A brief study was also performed to explore the feasibility of using diaryliodonium reagents to synthesise the β-methyl substrate through the direct arylation of secondary enaminone **170** under copper catalysis (Scheme 51).<sup>65</sup> Promisingly, an NMR yield of 31% was obtained for tertiary enaminone **76** when **170** was reacted with diphenyliodonium triflate (**174**) in the presence of copper(I) iodide\* and potassium carbonate in 1,2-dichloroethane at 80 °C.



**Scheme 51.** A model reaction in which secondary enaminone **170** was reacted with diphenyliodonium triflate **174** under copper catalysis afforded the desired *N*-arylation product, **76**, in an NMR yield of 31%.

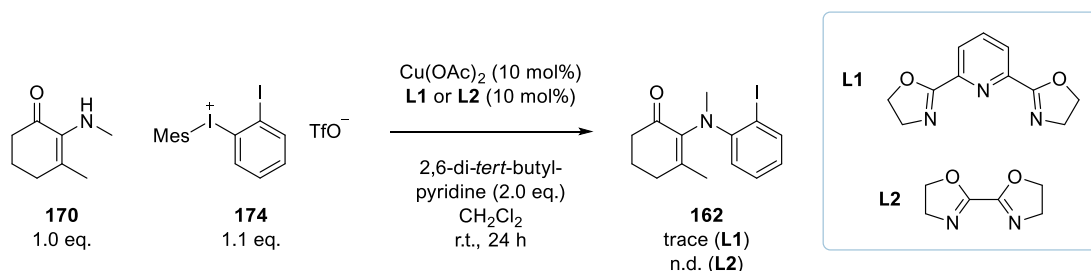
Under the same conditions, however, mesityl iodonium triflate **174** (see Chapter 4 for full synthetic details) failed to deliver **162** in non-trace quantities from secondary enaminone **170** (Scheme 52). The desired product was also not detected in the end-of-reaction mixture when other solvent and base combinations (e.g., potassium carbonate in acetonitrile, sodium carbonate in ethyl acetate, and sodium carbonate in 1,4-dioxane) were employed under otherwise identical conditions.

\* No product formation was observed in the absence of this copper salt.



**Scheme 52.** Only a trace amount of the desired enaminone product, **162**, was detected in the crude product mixture when secondary enaminone **170** was reacted with mesityl iodonium triflate **174** under copper catalysis.

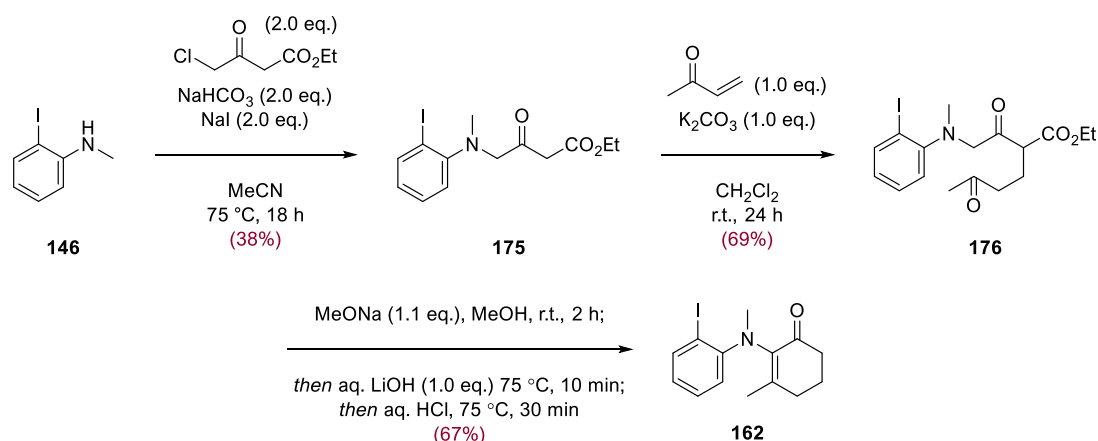
Likewise, ligated copper(II) catalysts<sup>66</sup> were unsuccessful in promoting the desired *N*-arylation reaction between secondary enaminone **170** and mesityl iodonium triflate **174** (Scheme 53).



**Scheme 53.** Trace quantities at most of **162** were detected in the crude product mixtures of reactions between secondary enaminone **170** and mesityl iodonium triflate **174** performed in the presence of bis(oxazoline)-ligated copper catalysts.

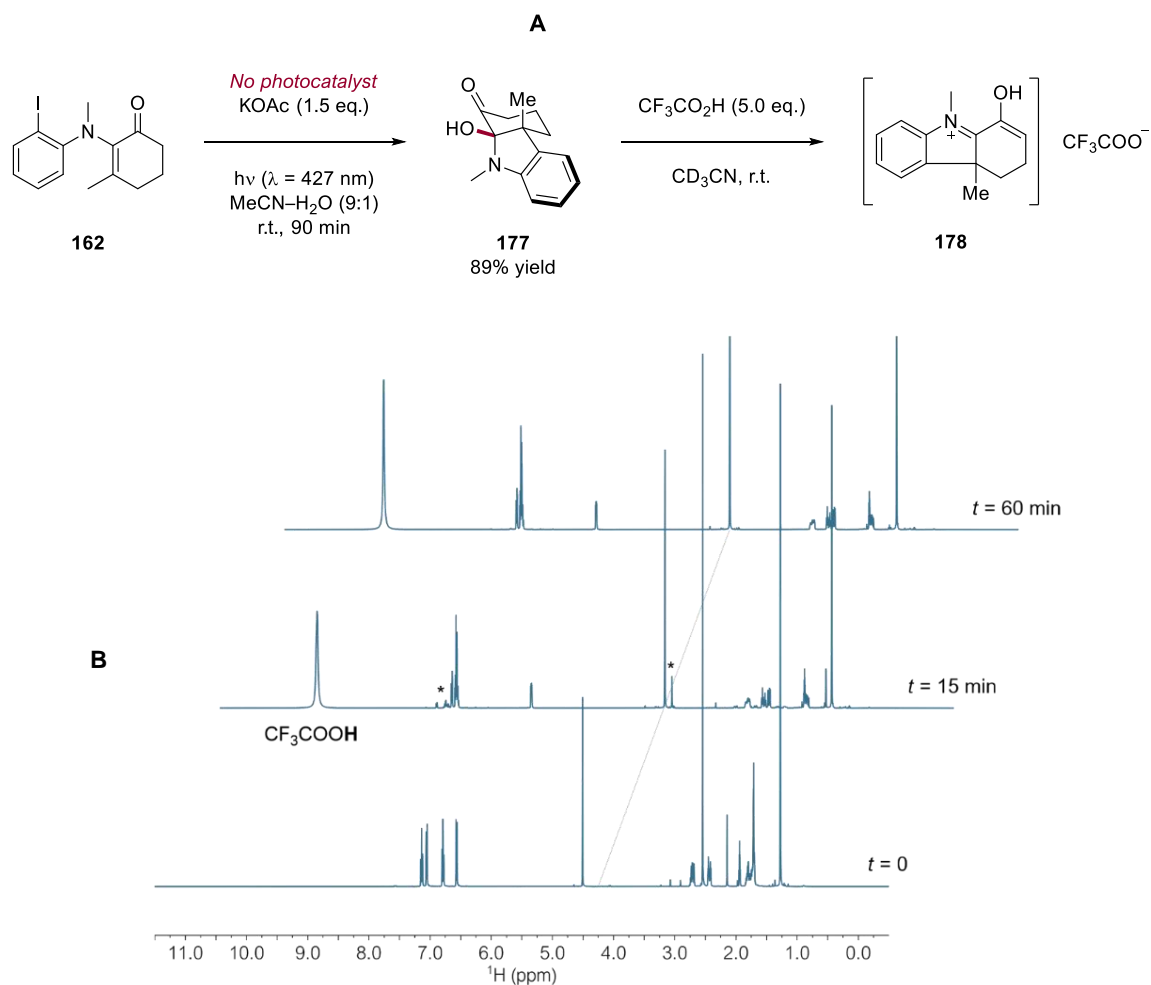
## Successful synthesis of $\beta$ -methyl substrate **162** and preliminary investigations into its photochemical reactivity

Confronted with the failure of more direct synthetic routes,  $\beta$ -methyl substrate **162** was ultimately prepared *via* a three-step Michael–aldol sequence from 2-iodo-*N*-methylaniline (**146**) (Scheme 54).<sup>67</sup> Reaction of **46** with ethyl 4-chloroacetoacetate in acetonitrile at 75 °C under Finkelstein conditions in the presence of sodium hydrogencarbonate and sodium iodide afforded aminoketone **175** in a moderate yield of 38%; subsequently treating this compound with methyl vinyl ketone and potassium carbonate in dichloromethane at room temperature gave a 69% yield of the corresponding Michael adduct, **176**. Aldol cyclisation–dehydration followed by ester hydrolysis and thermal decarboxylation was then accomplished in a one-pot fashion, furnishing the desired enaminone **162** in a yield of 67%.



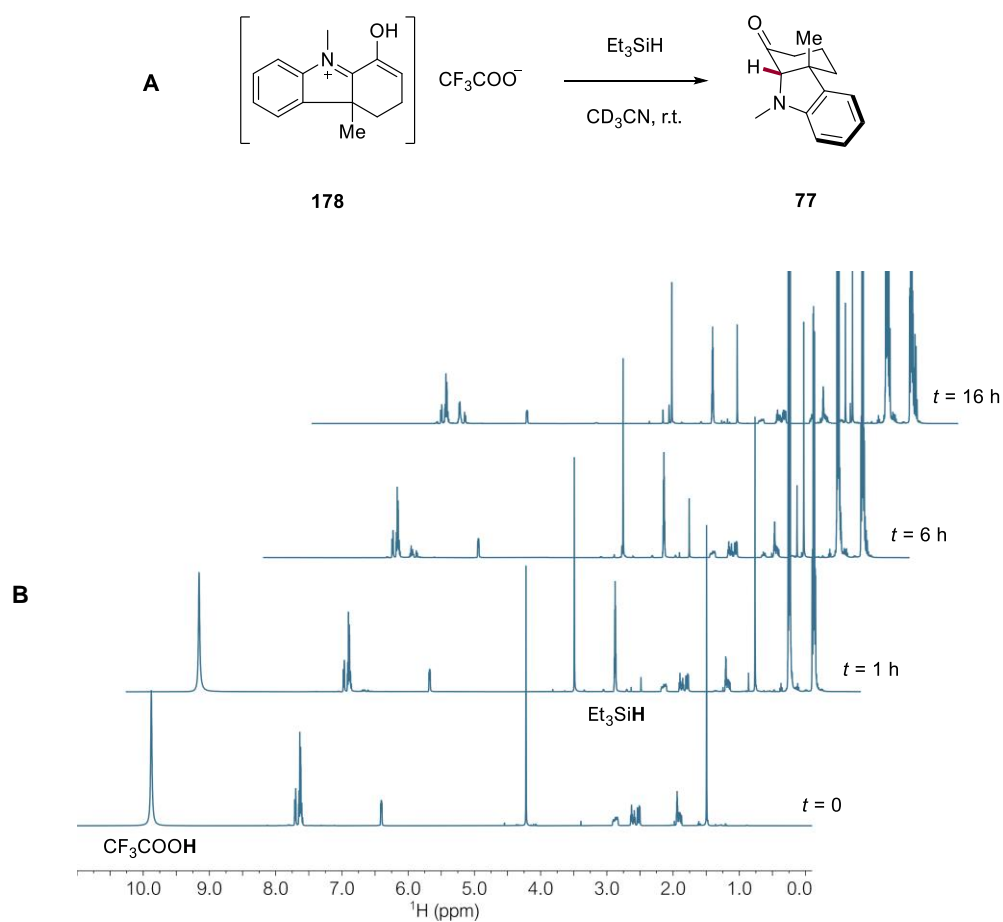
**Scheme 54.** Synthesis of  $\beta$ -methyl substrate **162** via a Michael–aldol sequence.

When irradiated with 427 nm light in aqueous acetonitrile solution in the absence of photocatalyst and presence of potassium acetate, this compound (which absorbs weakly at wavelengths above 400 nm) yielded hemiaminal **177** in a yield of 89%, in line with our hypothesis that an iminium salt is the primary photoproduct of the reaction (Figure 1A). This putative intermediate was formally generated with a trifluoroacetate counterion by treating a solution of hemiaminal **177** in CD<sub>3</sub>CN with 5.0 equivalents of trifluoroacetic acid at room temperature. Proton NMR spectra recorded at time intervals, *t*, after the addition of acid revealed quantitative conversion of the starting material to a new compound within 60 min; this compound was characterised fully by <sup>1</sup>H and <sup>13</sup>C spectroscopy as enol iminium trifluoroacetate **178** (Figure 1B).



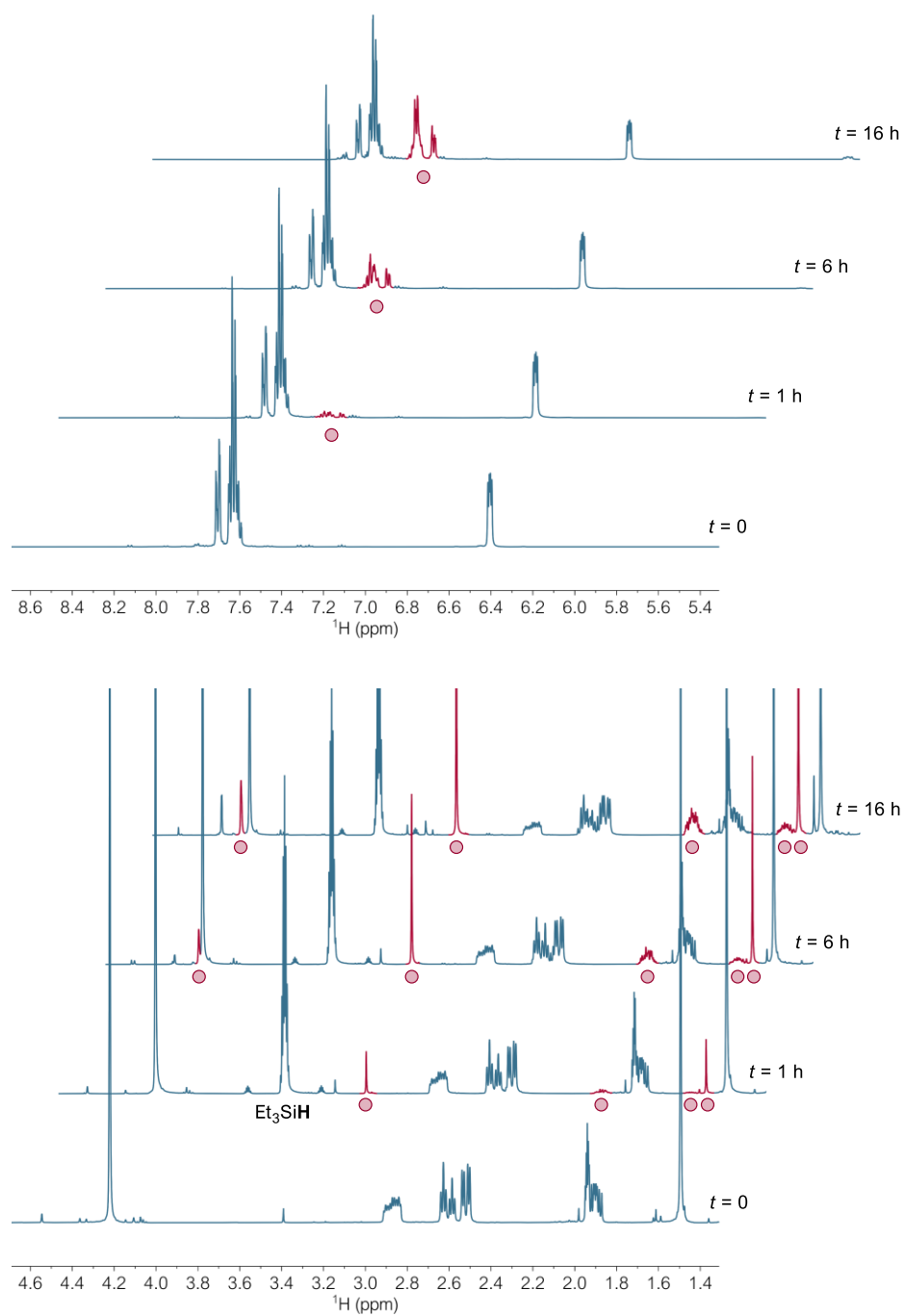
**Figure 1. (A)** Photochemical formation of hemiaminal **177** from  $\beta$ -methyl substrate **162** and its acid-mediated conversion to an enol species, **178**. **(B)** Stacked  $^1\text{H}$  NMR spectra showing the conversion of hemiaminal **177** to **178** in  $\text{CD}_3\text{CN}$  at time intervals,  $t$ , after addition of trifluoroacetic acid. A grey line has been added to assist the reader in distinguishing signals around 4.25 ppm. Signals marked with an asterisk (\*) on the spectrum recorded at  $t = 15$  min may correspond to the keto tautomer of the iminium trifluoroacetate salt, potentially observed fleetingly under these conditions prior to chemical equilibration.

To assess whether this enol iminium intermediate could be intercepted by an external nucleophile *via* a non-photochemical mechanism, the above solution of iminium trifluoroacetate **178** was treated with 3.0 equivalents of triethylsilane in the dark and analysed at regular intervals by  $^1\text{H}$  NMR spectroscopy (Figures 2 and 3). This resulted in the slow accumulation of an iminium reduction product, **77**, demonstrating the viability of a *thermal* iminium trapping event in the photochemical reaction of *N*-aryl enaminone **162** in the presence of triethylsilane, and pointing to the possibility of intercepting the same with intermediate with other two-electron nucleophiles.



**Figure 2. (A)** Reduction of enol trifluoroacetate **178** *in situ* with triethylsilane. **(B)** Stacked  $^1\text{H}$  NMR spectra of enol iminium trifluoroacetate **178**, formed by treating hemiaminal **177** with trifluoroacetic acid in  $\text{CD}_3\text{CN}$ , at time intervals,  $t$ , after addition of the reducing agent.





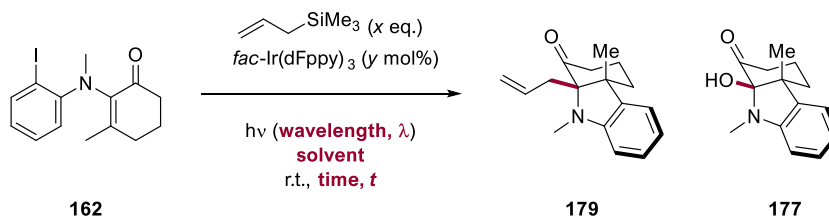
**Figure 3.** Expanded views of stacked  $^1\text{H}$  NMR spectra of enol iminium trifluoroacetate **178** in  $\text{CD}_3\text{CN}$  at time intervals,  $t$ , after addition of triethylsilane. Signals corresponding to indoline **77** are highlighted in red and marked with a red circle.

## Photochemical reactivity of $\beta$ -methyl substrate **162** in the presence of various nucleophiles

With preliminary evidence that the iminium salt formed in the photocyclisation of  $\beta$ -methyl substrate **162** could be productively intercepted with external nucleophiles, we proceeded to examine the scope of the reaction with respect to the nucleophilic trapping agent.

A catalytic quantity of iridium sensitiser was initially employed in screening reactions with allyltrimethylsilane. In acetonitrile solution, the desired allylated product, **179**, was formed in 50% yield (with 32% recovered starting material) after an irradiation period of 3 h when 3.0 equivalents of this nucleophile and 1 mol% of *fac*-Ir(dFppy)<sub>3</sub> were used in combination with 440 nm light in a photoreaction of **162** (Table 2, entry 1). Under otherwise identical conditions, *N,N*-dimethylformamide resulted in a 64% yield of **179** with full conversion of starting material (entry 2), while dimethyl sulfoxide (used in deuterated form for analytical convenience) gave predominantly hemiaminal **177** in a yield of 54%, with only trace amounts of **179** observed in the crude product mixture by <sup>1</sup>H NMR spectroscopy (entry 3). The use of methanol as solvent afforded **179** as the major product, albeit in a lower yield (34%) than before (entry 4). Having observed previously that an iridium sensitiser is not required to induce photocyclisation of **162** with blue light, the reaction was performed under the conditions reported in entry 1 except without *fac*-Ir(dFppy)<sub>3</sub> (entry 5). This led to a slower reaction (48% conversion after an irradiation period of 6 h) but similar levels of selectivity (defined here as the ratio of desired product yield to starting material conversion). Encouraged by this result, we proceeded without *fac*-Ir(dFppy)<sub>3</sub>. Not only would sensitiser-free conditions represent a more cost-effective and sustainable process, but they would also avoid any potential compatibility issues between the photocatalyst and electron-rich amine product of the reaction (or between the photocatalyst and nucleophile in other reactions). Improvements in yield were observed upon switching to 9:1 (v/v) mixtures of acetonitrile and water or methanol: after 6 h, the former combination led to full conversion of the starting material and a 62% yield of **179** (entry 6), while the latter resulted in a starting material conversion of 76% and 59% yield of desired product (entry 7). Increasing the dose of nucleophile to 5.0 equivalents and irradiating for 16 h in methanolic acetonitrile produced **179** in 62% yield after full starting material conversion (entry 8). The use of 2,2,2-trifluoethanol (TFE) as the polar additive (entry 9) produced the necessary improvement in selectivity, delivering the same product in 71% yield with starting material still present in the end-of-reaction mixture (86% conversion). The reaction could be driven to near-completion (95% conversion) with an attendant increase in product yield (to 85%) through the use of shorter-wavelength light (427 nm) in only 6 h (entry 10). 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was also an effective polar additive, leading to full conversion of starting material and producing **179** in 78% yield (entry 11) under otherwise identical conditions.

**Table 2.** Optimisation of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of allyltrimethylsilane.



Entry	$x$ / eq.	$y$ / mol%	Solvent	$\lambda$ / nm	$t$ / h	Conversion <sup>a</sup> of <b>162</b> / %	Yield of <b>179</b> / %
1 <sup>b</sup>	3.0	1	MeCN	440	3	68	50
2 <sup>b</sup>	3.0	1	DMF	440	3	>95	64
3 <sup>b</sup>	3.0	1	DMSO- $d_6$	440	3	>95	trace <sup>c</sup>
4 <sup>b</sup>	3.0	1	MeOH	440	3	94	34
5 <sup>b,d</sup>	3.0	0	MeCN	440	6	48	33
6 <sup>b,d</sup>	3.0	0	MeCN–H <sub>2</sub> O (9:1)	440	6	>95	62
7 <sup>b,d</sup>	3.0	0	MeCN–MeOH (9:1)	440	6	76	59
8 <sup>b,d</sup>	5.0	0	MeCN–MeOH (9:1)	440	16	>95	63
9 <sup>b,d</sup>	5.0	0	MeCN–TFE (9:1)	440	16	86	71
10 <sup>b,d</sup>	5.0	0	MeCN–TFE (9:1)	427	6	95	85
11 <sup>b,d</sup>	5.0	0	MeCN–HFIP (9:1)	427	6	>95	78
12 <sup>b,d</sup>	3.0	0	MeCN–TFE (9:1)	427	16	>95	80
13 <sup>e</sup>	3.0	0	MeCN–TFE (9:1)	427	18	– <sup>f</sup>	69% <sup>g</sup>
14 <sup>e</sup>	3.0	0	MeCN–HFIP (9:1)	427	18	– <sup>f</sup>	80% <sup>g</sup>

<sup>a</sup>Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

<sup>b</sup> Reaction conditions (unless otherwise stated): **162** (0.1 mmol), allyltrimethylsilane (0.3 or 0.5 mmol), *fac*-Ir(dFppy)<sub>3</sub> (0 or 1  $\mu$ mol), solvent (0.05 M), 1 x Kessil PR160(L) 440 or 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* without quenching the HI by-product.

<sup>c</sup> Hemiaminal **177** was formed as the major product in an NMR yield of 54%.

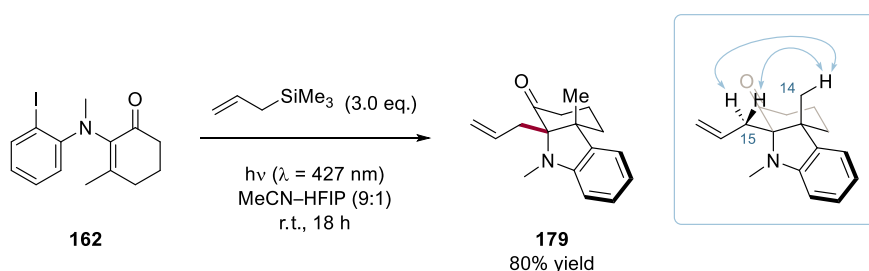
<sup>d</sup> The end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

<sup>e</sup> Reaction conditions: **162** (0.3 mmol), allyltrimethylsilane (0.9 mmol), solvent (0.05 M), 2 x Kessil PR160L 427 nm LED lamps, r.t., 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (2.0 mL) in one portion.

<sup>f</sup> Not determined.

<sup>g</sup> Isolated yield after flash column chromatography on silica gel.

Simultaneously restoring the original nucleophile dose of 3.0 equivalents and extending the irradiation period to 16 h (entry 12) led to a small reduction in yield to 80%, which was deemed tolerable. On a preparative (0.3 mmol) scale, these conditions led to the isolation of **179** in a lower-than-expected yield of 69% (entry 13); fortunately, this could be increased to 80% through the replacement of TFE with HFIP (entry 14). The *cis*-stereochemistry of the product (formed as a single diastereomer) was confirmed by nuclear Overhauser effect spectroscopy (Scheme 55).

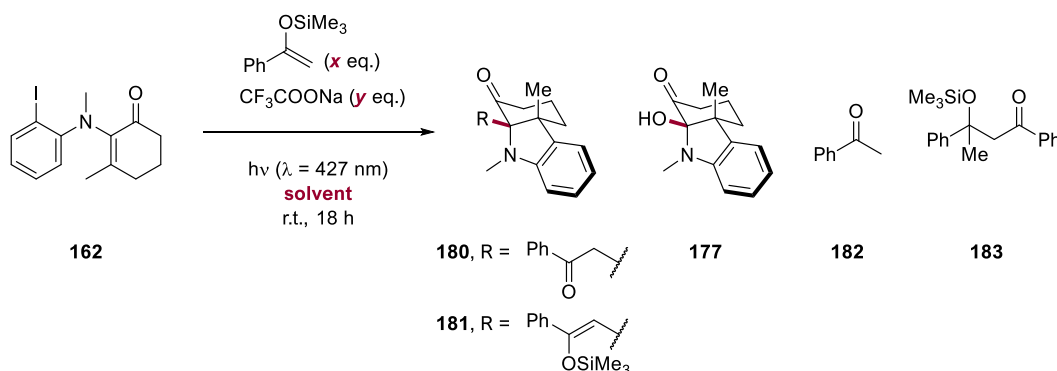


**Scheme 55.** Optimised conditions for the photocyclisation of **162** in the presence of allyltrimethylsilane on 0.3 mmol scale. The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to through-space couplings H14↔H15 and H14↔H15' (arbitrary numbering as found in experimental section) indicates the formation of the *cis*-diastereomer of **179** shown.

Next, the trimethylsilyl enol ether derived from acetophenone was investigated as a nucleophile in the photocyclisation–cation trapping cascade (Table 3). Initial attempts to achieve this reaction in a range of polar solvent systems (entries 1–5) failed to deliver any of the desired product, **180**; instead, mixtures of hemiaminal **177** and acetophenone (**182**) (or, in the case of acetonitrile, a Mukaiyama aldol product, **183**, derived from acetophenone, whose spectroscopic data has been reported in the literature<sup>68</sup>) were observed in the crude photolysates by <sup>1</sup>H NMR spectroscopy in varying proportions after quenching with triethylamine. It was hypothesised that buffering the HI by-product of the photochemical step might ameliorate the problem of nucleophile hydrolysis observed in these reactions. To this end, it was found that sodium trifluoroacetate provided an optimal balance between promoting the desired nucleophilic trapping event and preventing mere hydrolysis of the iminium iodide intermediate (that is, preventing the formation of hemiaminal **177** as the major product). Thus, in the presence of 3.0 equivalents of nucleophile and 1.0 equivalent of sodium trifluoroacetate, 1,4-diketone product **180** was formed for the first time in a yield of 26%, alongside 7% of a related structure that is (in the absence of full characterisation data) assigned tentatively as the trimethylsilylenol ether, **181**, derived from the desired product (entry 6). These two compounds were formed in yields of 10 and 27%, respectively, when the nucleophile dose was increased to 5.0 equivalents and the reaction performed under otherwise identical conditions (entry 7). Reasoning that the triethylamine base added at the end of the reaction (to neutralise the acidic reaction medium prior to its concentration *in vacuo* for analysis) was likely promoting the formation of **181** (or some isomer of this compound), the reaction was repeated and the (presumed) trimethylsilyl iodide by-product quenched by stirring with methanol; this gave **180** in a yield of

29% without detection of the undesired side-product (entry 8). Reactions were performed in an acetonitrile–hexafluoroisopropanol mixture (entry 9) and *N,N*-dimethylformamide (entry 10), both leading to the formation of desired product in lower yields, before anhydrous nitromethane was identified as the optimal solvent, delivering **180** in 49% yield on an analytical (0.1 mmol) scale in the presence of both 3.0 and 5.0 equivalents of the nucleophile (entries 11 and 12).

**Table 3.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of 1-phenyl-1-trimethylsiloxyethylene.



Entry	<i>x</i> / eq.	<i>y</i> / eq.	Solvent	Conversion / %	Yield of <b>180</b> ( <b>181</b> <sup>a</sup> ) / %	Yield of <b>177</b> / %	Yield of <b>182</b> / %
1 <sup>b,c</sup>	3.0	0	MeCN	82	n.d. <sup>d</sup> (n.d.)	trace	n.d. <sup>e</sup>
2 <sup>b,c</sup>	3.0	0	MeCN–HFIP (9:1)	>95	n.d. (n.d.)	– <sup>f</sup>	98
3 <sup>b,c</sup>	3.0	0	MeCN–TFE (9:1)	81	n.d. (n.d.)	45	108
4 <sup>b,c</sup>	3.0	0	MeCN–H <sub>2</sub> O (9:1)	>95	n.d. (n.d.)	55	– <sup>g</sup>
5 <sup>b,c</sup>	3.0	0	DMF	85	n.d. (n.d.)	trace	49
6 <sup>b,h</sup>	3.0	1.0	MeCN	94	26 (7)	trace	32

<sup>a</sup> The <sup>1</sup>H NMR data of this compound has been assigned tentatively by analogy to that of the desired product **180**.

<sup>b</sup> Reaction conditions (unless otherwise stated): **162** (0.1 mmol), 1-phenyl-1-trimethylsiloxyethylene (0.3 or 0.5 mmol), additive (0 or 0.3 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

<sup>c</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against 1,3,5-trimethoxybenzene (0.33 eq.).

<sup>d</sup> Not detected.

<sup>e</sup> The Mukaiyama aldol product **183** derived from acetophenone was formed in an NMR yield of 50%.

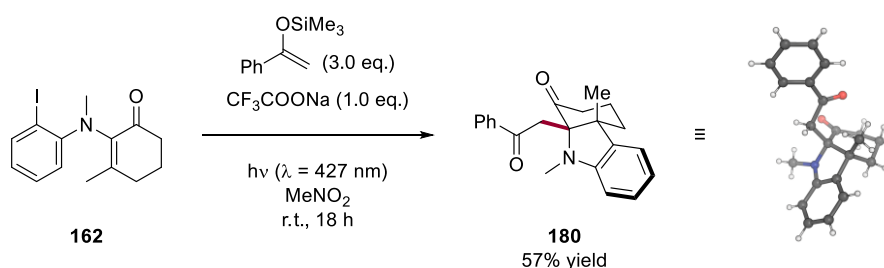
<sup>f</sup> A complex mixture of products was obtained in which hemiaminal **11** was present in major amounts; signal overlap made accurate integration of <sup>1</sup>H resonances corresponding to this compound impossible.

<sup>g</sup> Acetophenone (**182**) was formed in relatively large quantities; <sup>1</sup>H resonances corresponding to this compound, however, could not be accurately integrated within TopSpin.

<sup>h</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.).

7 <sup>b,h</sup>	5.0	1.0	MeCN	94	10 (27)	trace	7
8 <sup>b,h,i</sup>	3.0	1.0	MeCN	93	29 (n.d.)	n.d.	184
9 <sup>b,h,i</sup>	3.0	1.0	MeCN–HFIP (9:1)	91	19 (n.d.)	n.d.	123
10 <sup>b,h,i</sup>	3.0	1.0	DMF	94	15 (n.d.)	n.d.	46
11 <sup>b,h,i</sup>	3.0	1.0	MeNO <sub>2</sub>	93	49 (n.d.)	n.d.	74
12 <sup>b,h,i</sup>	5.0	1.0	MeNO <sub>2</sub>	95	49 (n.d.)	n.d.	265

On a 0.3 mmol scale, the 1,4-diketone product of this reaction (**180**) was isolated in a yield of 57% as a single diastereomer; the *cis*-stereochemistry of the ring junction was confirmed through both 2D NOESY and X-ray crystallography (Scheme 56).

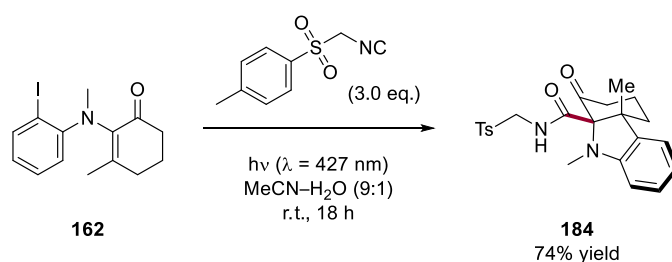


**Scheme 56.** Sodium trifluoroacetate is required to promote the formation of **180** when **162** is irradiated in the presence of 1-phenyl-1-trimethylsiloxyethylene. Single-crystal X-ray diffraction studies performed by Owen Smith (O.S.) and nOe analysis (not shown) confirm the *cis*-stereochemistry of the product, **180**.

*para*-Toluenesulfonyl isocyanide (TosMIC) was also found to be an effective nucleophile.<sup>†</sup> Thus, irradiating substrate **162** in the presence of 3.0 equivalents of this reagent in a 9:1 (v/v) mixture of acetonitrile and water gave  $\gamma$ -ketoamide **184** in 74% yield *via* a nucleophilic trapping–hydrolysis sequence (Scheme 57).

<sup>i</sup> The end-of-reaction mixture was concentrated *in vacuo* after adding MeOH (2.0 mL) and stirring at r.t. for 30 min.

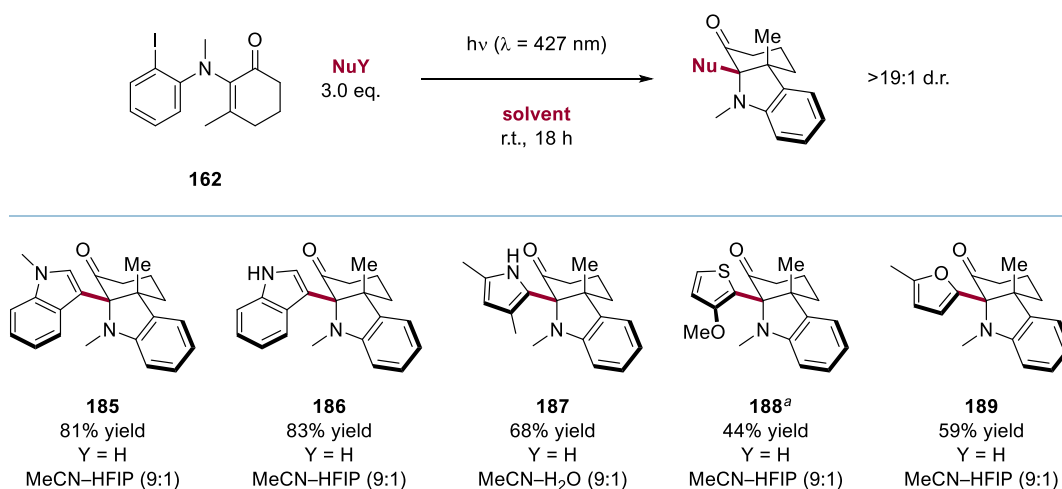
<sup>†</sup>The identification of optimal reaction conditions for other nucleophiles was generally more straightforward, with mixtures of acetonitrile and polar protic solvents being favoured. Only salient features of reaction optimisation are thus discussed from here onward; a fuller account in tabular form is provided in Appendix A.



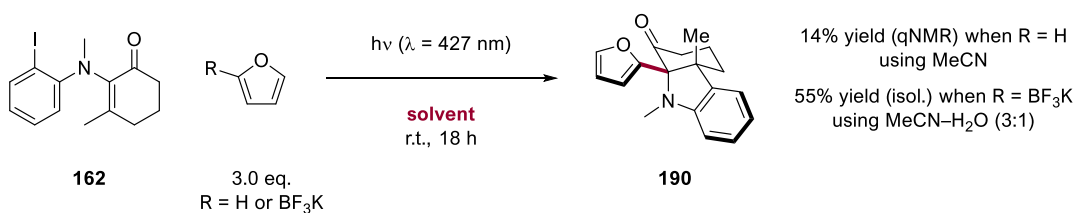
**Scheme 57.** Reaction to form ketonamide **184** from  $\beta$ -methyl substrate **162** and TosMIC.

A range of electron-rich heterocycles can be used to intercept the cationic photoproduct of the reaction (Table 4). Photoreactions performed in the presence of 1-methylindole, 1*H*-indole and 2,4-dimethylpyrrole gave the expected nucleophilic trapping products **185**, **186** and **187** in yields of 81, 83 and 68%, respectively, all as single diastereomers with *cis*-stereochemistry. Electron-rich 3-methoxythiophene was also effective, leading to **188** in a moderate yield of 44%, as was 2-methylfuran, which produced **189** in 59% yield.

**Table 4.** Scope of the radical–polar crossover reaction of **162** with respect to heterocyclic nucleophiles. All yields isolated.

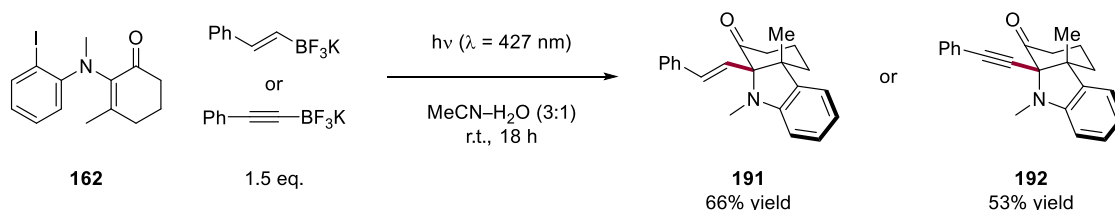


A screening reaction with furan as the nucleophile in acetonitrile led to the corresponding indoline product, **190**, in a dramatically lower yield (*ca.* 14% measured by quantitative <sup>1</sup>H NMR spectroscopy) than that observed with 2-methylfuran (Scheme 58). Studies by Mayr and co-workers<sup>69</sup> delineating the activating effects of trifluoroborate substitution on a range of  $\pi$ -nucleophiles (including furan) led us to consider the use of potassium furan-2-trifluoroborate to achieve the same reaction. It was found that a rigorously degassed 3:1 (v/v) mixture of acetonitrile and water provided the optimal reaction medium for this nucleophile, delivering **190** in a yield of 55% on a preparative scale when 3.0 equivalents of the reagent were used.



**Scheme 58.** Furan-containing compound **190** was formed in a low NMR yield of 14% when **162** was irradiated in acetonitrile solution in the presence of furan; an isolated yield of 55% was obtained for the same product when potassium furan-2-trifluoroborate was used as the nucleophile in aqueous acetonitrile.

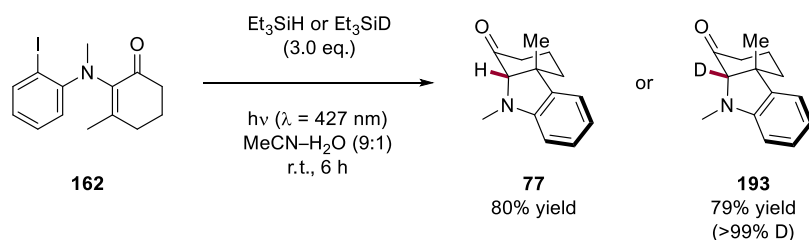
Petasis borono-Mannich-type reactions<sup>70,71</sup> could also be achieved using potassium *trans*-styryltrifluoroborate and potassium (phenylethynyl)trifluoroborate, leading to the formal addition of alkenes (to afford **191**) and alkynes (to give **192**) in yields of 66% and 53%, respectively, on a 0.3 mmol scale when 1.5 equivalents of the nucleophile were used (Scheme 59). Screening reactions on an analytical, 0.1 mmol scale revealed an unusual relationship between product yield and nucleophile dose for the former reaction. Whereas **191** was obtained in 67% yield on this scale when 1.5 equivalents of nucleophile were used, a lower yield of 44% was obtained when a larger dose of 2.0 equivalents was used; when the reagent dose was further increased to 3.0 equivalents, *none* of the desired product was formed (see Appendix X). Potassium thiophene-2-trifluoroborate (at doses of 1.5 and 3.0 equivalents) and 4-methoxyphenyltrifluoroborate (at a dose of 3.0 equivalents) both failed to deliver the corresponding iminium trapping product in reactions of **162** performed in a 3:1 (v/v) acetonitrile–water mixture. Similar scope limitations have been noted by Lee *et al.* in reactions of organocatalytically-generated  $\alpha,\beta$ -unsaturated iminium electrophiles with trifluoroborate-activated  $\pi$ -nucleophiles.<sup>72,73</sup>



**Scheme 59.** Potassium *trans*-styryltrifluoroborate and (phenylethynyl)trifluoroborate salts are effective nucleophiles in the radical–polar crossover reaction of  $\beta$ -methyl substrate **162**, leading to alkene- and alkyne-containing products **191** and **192**.

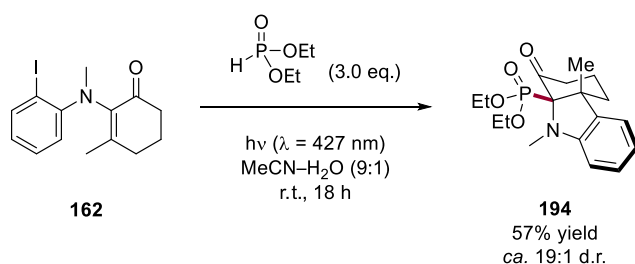
It was possible to reduce the iminium intermediate using hydrosilane reagents. Indoline **77** was obtained in isolated yield of 80% when **162** was irradiated in the presence of triethylsilane (Scheme 60). A deuterated analogue (**193**) of this compound was generated in 79% with high levels of deuterium incorporation (>99%) using triethylsilane-*d* under otherwise identical reaction conditions.





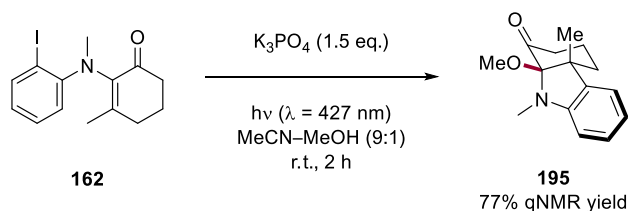
**Scheme 60.** Triethylsilane and its deuterated analogue lead to iminium reduction products **77** and **193** with high levels of deuterium incorporation in the latter case.

We were able to isolate aminophosphonate **194** in 57% yield by irradiating **162** in the presence of diethylphosphite. When the reaction was performed in a 9:1 (v/v) mixture of acetonitrile and water, **194** was formed and isolated as the major component of a mixture containing a compound with near-identical NMR spectroscopic features, assumed to be the corresponding *trans*-isomer, in a molar ratio between 20:1 and 19:1 estimated from relative integrations of  $^{31}\text{P}$  resonances (Scheme 61). Prior screening reactions (see Appendix A) revealed a strong dependence of the ratio between these two products on solvent polarity; the *trans*-fused iminium trapping product was not observed for any nucleophile other than diethylphosphite.



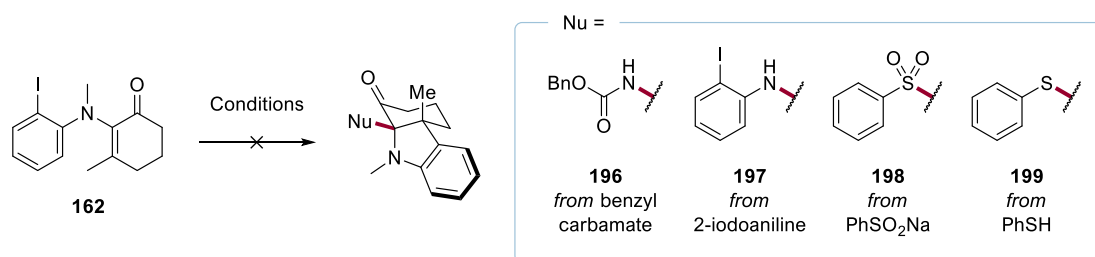
**Scheme 61.** The use of diethyl phosphite as the nucleophilic component yields aminophosphonate **194**.

Methanol is also a proficient trapping agent in the presence of potassium phosphate, affording **195** in a yield of 77% measured by  $^1\text{H}$  NMR spectroscopy; the *O*-methyl hemiaminal ether product could not be cleanly isolated, however, owing to its instability on silica and alumina gels.



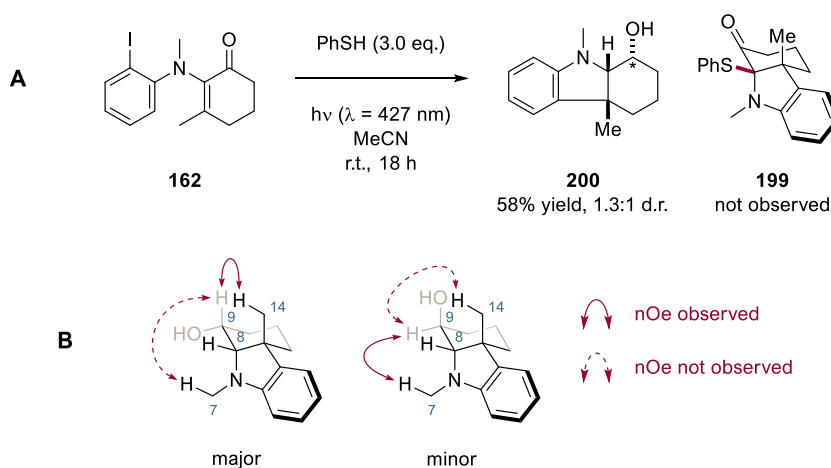
**Scheme 62.** Irradiation of **162** in the presence of methanol and potassium phosphate leads to the formation of *O*-methyl hemiaminal ether **195**.

Nucleophiles that were unsuccessfully employed in the cascade include benzyl carbamate, 2-iodoaniline, sodium benzenesulfinate and thiophenol (Scheme 63).



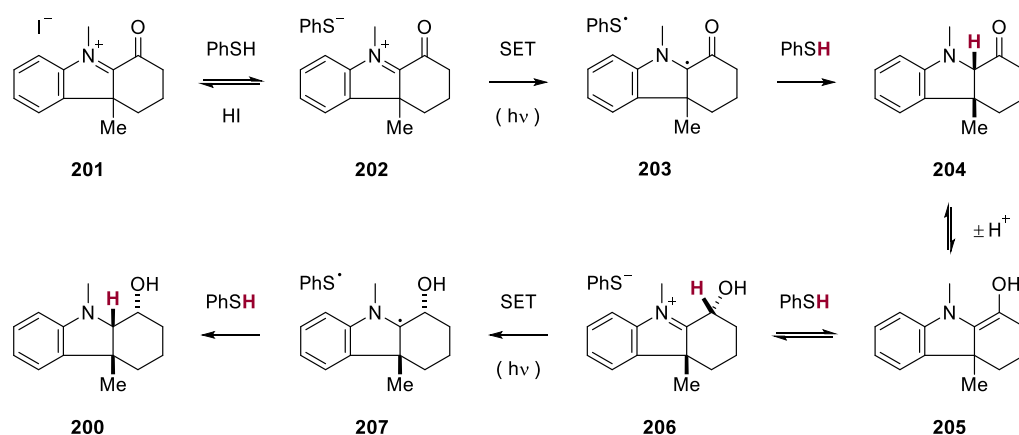
**Scheme 63.** Nucleophiles that failed to deliver the expected nucleophilic trapping product in the radical–polar crossover reaction of  $\beta$ -methyl substrate **162**. Conditions:  $h\nu$  ( $\lambda = 427$  nm), MeCN, r.t., 18 h.

While the expected nucleophilic trapping product was not formed when **162** was irradiated in the presence of thiophenol, an alternative compound of interest, indoline **200**, was generated in a yield of 58% as a 1.3:1 mixture of diastereomers, differing only in the configuration at C9 (Scheme 64).



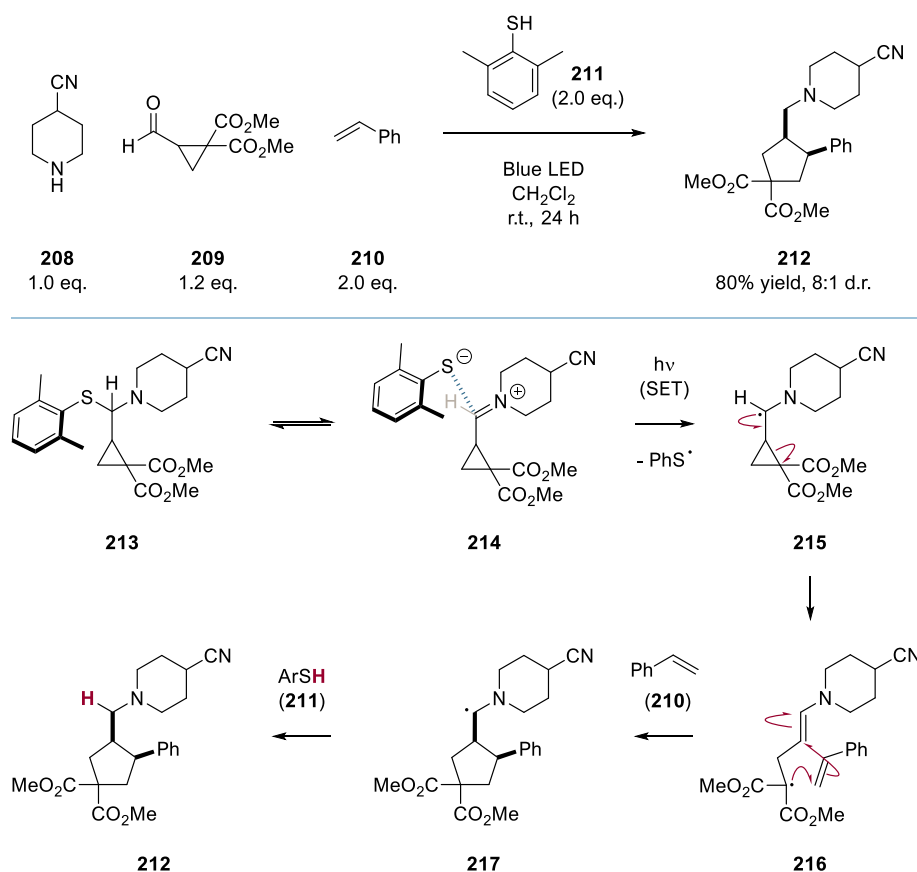
**Scheme 64. (A)** Irradiating **162** in the presence of thiophenol resulted in the formation of indoline **200** as a mixture of diastereomers; the expected nucleophilic trapping product, **199**, was not observed. **(B)** NOESY analysis confirms that the major diastereomer is the C9-epimer shown.

A possible mechanism for the thiol-mediated generation of indoline **200** is depicted in Scheme 65. The key mechanistic step is thought to be the formation of an  $\alpha$ -amino radical, **203**, via single-electron transfer within iminium thiolate salt **202**; the latter intermediate could arise from counterion metathesis of the initially formed iminium iodide salt, **201**. In the presence of excess amounts of thiophenol,  $\alpha$ -amino radical **203** would likely abstract a hydrogen atom from the thiol reagent, which possesses a weak S–H bond. This hydrogen-atom transfer (HAT) process would give rise to indoline **204**, which – through protonation of its enol form, **205**, by thiophenol – could generate another iminium thiolate species, **206**. Single-electron transfer within this ion pair would result in a second  $\alpha$ -amino radical intermediate, **207**, which could be reduced in a subsequent step by another molecule of thiophenol.



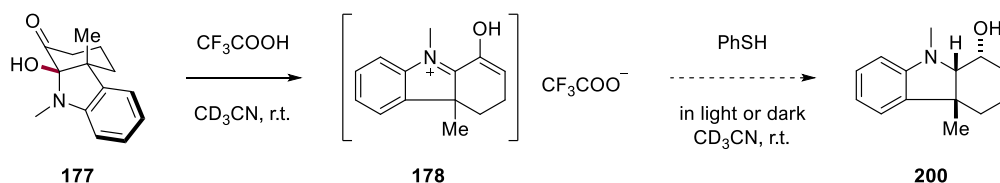
**Scheme 65.** Mechanistic rationale for the formation of indoline **200** from iminium iodide **201** in the presence of thiophenol.

While it is likely that iminium iodide **201** is the primary photoproduct of the reaction, it is not clear whether light is necessary for the subsequent reduction of this intermediate by thiophenol. It is possible, for example, that the single-electron transfer events within iminium thiolate salts **202** and **206** proposed above are photochemically induced. The Gaunt group recently demonstrated that, under visible-light irradiation, an aromatic thiol, **211**, promotes a reductive three-component reaction between secondary amines, cyclopropanecarboxaldehydes and alkenes (Scheme 66).<sup>74</sup> Experimental and theoretical studies indicate that the reaction (for instance, between **208**, **209** and **210**) likely occurs *via* the direct excitation of an iminium thiolate charge-transfer complex. Photoinduced electron transfer within ion pair **214** (believed to exist in low concentration in equilibrium with its corresponding *N,S*-thiohemiacetal, **213**) gives rise to  $\alpha$ -amino radical **215**, which undergoes  $\beta$ -scission to form radical intermediate **216**. This homoallylic radical species reacts with the alkene component in a formal [3+2]-cycloaddition, generating  $\alpha$ -amino radical **217**, which is reduced by a second molecule of the aromatic thiol, **211**, to afford the observed product **212** in 80% yield and 8:1 d.r.



**Scheme 66.** Visible-light-mediated three-component reaction proceeding *via* single-electron transfer within an iminium thiolate charge-transfer complex reported by Gaunt and co-workers.

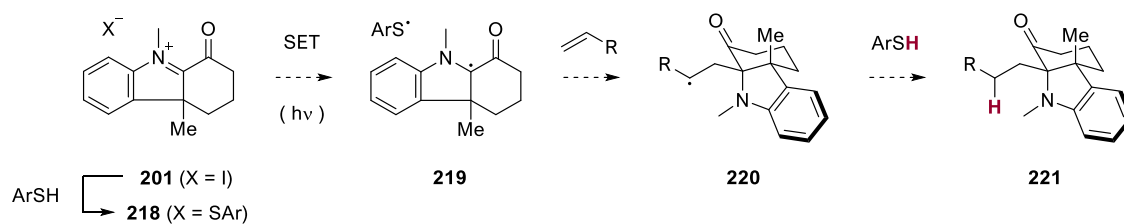
Future work should focus on identifying the conditions necessary for iminium ion reduction in our system. Subjecting iminium trifluoroacetate **178**, formed by treating hemiaminal **177** with trifluoroacetic acid as described previously, to excess thiophenol in the dark and in the presence of light would indicate whether the reduction of the iminium cation is photochemical (Scheme 67).



**Scheme 67.** The light-dependence of thiol-mediated iminium reduction could be determined by treating iminium trifluoroacetate **178** with thiophenol in the presence and absence of light.

In the future, the reactivity observed in the presence of thiophenol could be leveraged to expand the scope of coupling partners for our photochemical cascade reaction. For instance, instead of trapping the initially formed iminium iodide salt with a two-electron nucleophile, it might be possible to intercept the putative  $\alpha$ -amino radical resulting from thiol-mediated iminium ion reduction with an alkene, in a similar manner to Gaunt and co-workers (Scheme 68). In this reaction, HAT from the

aromatic thiol reagent to the alkyl radical, **220**, resulting from alkene radical addition would furnish C-alkylated indoline derivatives, **221**.

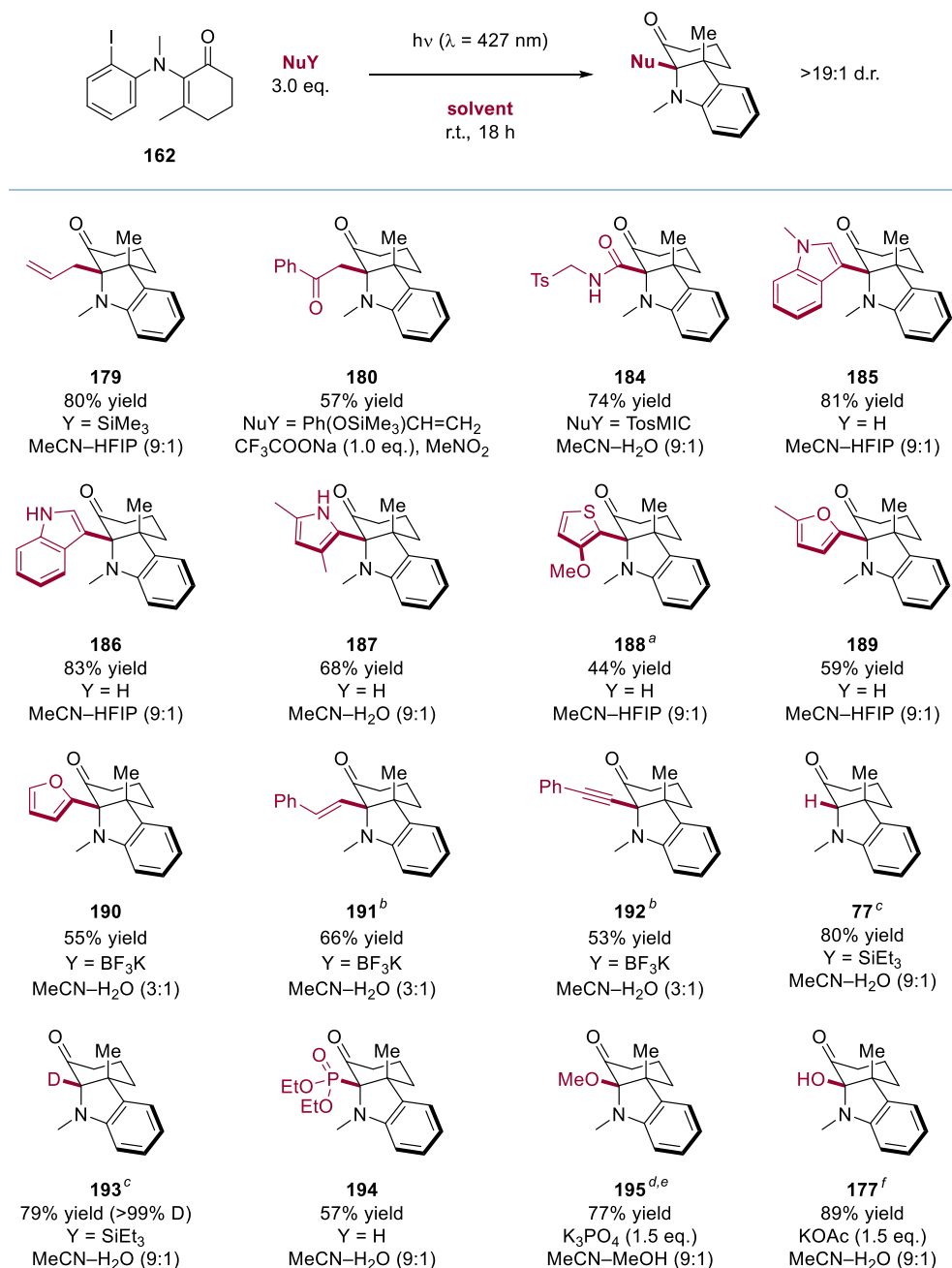


**Scheme 68.** Future work exploring the potential for  $\alpha$ -amino radical functionalisation enabled by thiol-mediated reduction of iminium iodide **201**.

### Summary of nucleophile scope studies

A summary of the compounds prepared upon photochemical activation of  $\beta$ -methyl substrate **162** in the presence of various nucleophiles is presented in Table 5.

**Table 5.** Scope of the photocyclisation–cation trapping cascade with respect to the nucleophilic coupling partner using  $\beta$ -methyl substrate **162**. Reaction conditions (unless otherwise stated): **162** (0.3 mmol, 1.0 eq.), NuY (0.9 mmol, 3.0 eq.), solvent(s) (v/v) (0.05 M), room temperature (r.t.), 2 x Kessil PR160L 427 nm lamps, 18 h.

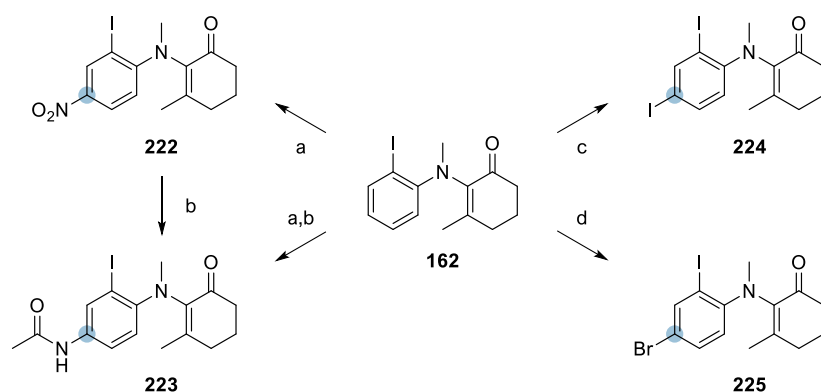


<sup>a</sup> 5.0 eq. NuY. <sup>b</sup> 1.5 eq. NuY. <sup>c</sup> 6 h reaction time. <sup>d</sup> This compound was isolated and characterized without chromatographic purification owing to its instability on silica and alumina gels; the reported yield was measured for a 0.1 mmol-scale reaction by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate. <sup>e</sup> 2 h reaction time. <sup>f</sup> 90 min reaction time.

## Synthesis of alternative photochemical substrates

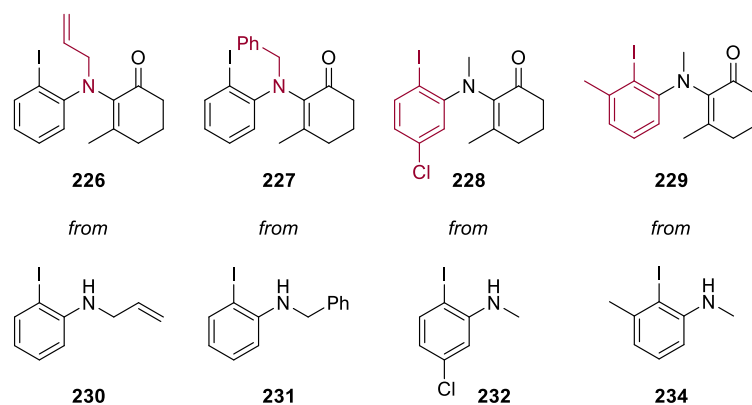
Having explored the scope of the reaction of  $\beta$ -methyl substrate **162** with respect to external nucleophiles, we decided to investigate whether structural modifications to this prototypical substrate were tolerated. Analogous compounds with different *N*-alkyl, aromatic and enone  $\beta$ -substituents were thus synthesised for testing.

Substrate **162** could be readily transformed to a range of *para*-substituted analogues (Scheme 69). Nitration of this compound under Menke conditions<sup>75</sup> afforded *para*-nitro analogue **222** in a moderate yield of 28%; reduction and *N*-acetylation gave the corresponding acetamide, **223**, in 55% yield over two steps. Reaction of **162** with iodine in the presence of silver sulfate gave *para*-iodo substrate **224** in 63% yield, while *N*-bromosuccinimide (NBS) effectively installed the *para*-bromo substituent in **225** (45% yield).



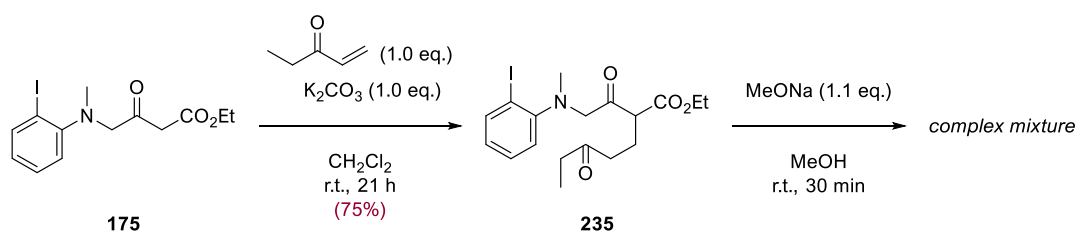
**Scheme 69.** Synthesis of *para*-substituted analogues of  $\beta$ -methyl substrate **162**. Conditions: (a)  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  (1.0 eq.),  $\text{Ac}_2\text{O}$ - $\text{AcOH}$  (1:1 v/v) (0.5 M), 1 h, 28% yield; (b) (i) Fe (10 eq.),  $\text{EtOH}$ - $\text{AcOH}$  (2:1 v/v) (0.1 M), 60 °C, 2 h; (ii)  $\text{Ac}_2\text{O}$  (ca. 3.0 eq.),  $\text{CH}_2\text{Cl}_2$  (ca. 0.1 M), r.t., 2 h, 55% yield over two steps; (c)  $\text{I}_2$  (1.1 eq.),  $\text{Ag}_2\text{SO}_4$  (1.1 eq.),  $\text{CH}_2\text{Cl}_2$  (0.2 M), r.t., 3 h, 63% yield.; (d) NBS (1.05 eq.), MeCN (0.1 M), r.t., 1 h, then NBS (0.1 eq.), 3 h, 45% yield.

*N*-Allyl (**226**), *N*-benzyl (**227**), 5-chloro (**228**) and 3-methyl (**229**) substrates were assembled *via* the Michael–aldol route described above (Scheme 70); for full synthetic details, see Chapter 4.



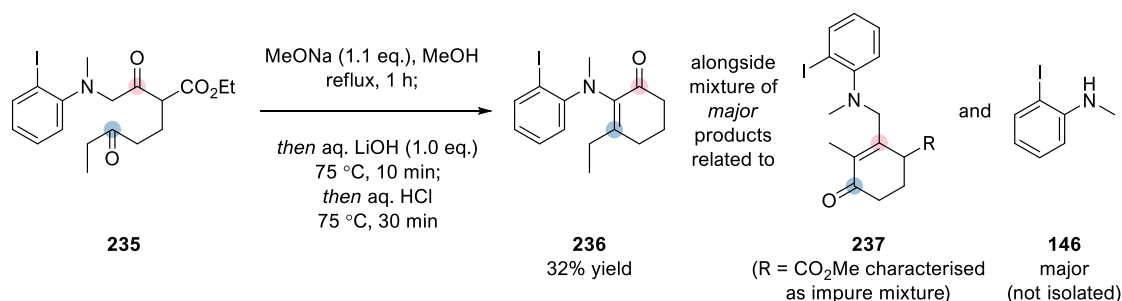
**Scheme 70.** Alternative substrates synthesised *via* a Michael–aldol sequence.

An initial attempt to synthesise enaminone **236**, a substrate bearing a  $\beta$ -ethyl group, using the same strategy failed at the aldol stage. Subjecting 1,5-diketone **235**, formed in 75% yield by the Michael addition of aminoketone **175** to ethyl vinyl ketone, to methanolic sodium methoxide at room temperature (conditions that had been used previously without incident) gave a complex mixture of products after a reaction time of only 30 minutes (Scheme 71).



**Scheme 71.** A complex mixture of products was obtained when **235**, formed through Michael addition of aminoketone **175** to ethyl vinyl ketone, was treated with methanolic sodium methoxide at room temperature.

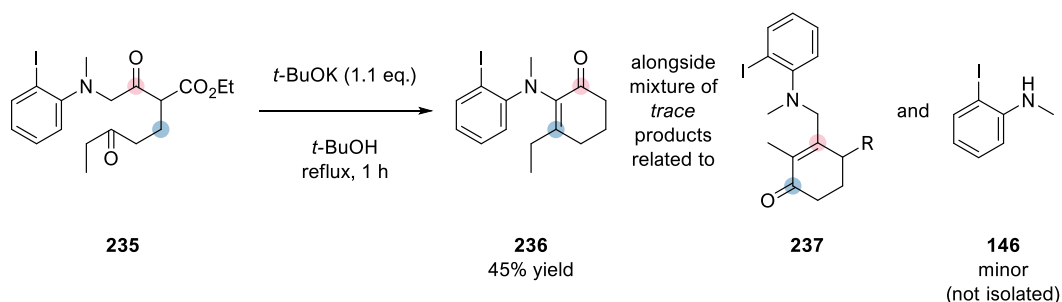
Treating **235** with sodium methoxide in refluxing methanol and then subjecting the resulting mixture to the standard hydrolysis–decarboxylation sequence gave a more tractable mixture of products, from which the desired aldol product, **236**, was isolated in 32% yield alongside an alternative aldol product, **237** ( $R = CO_2Me$ ), in an approximate yield of 12% (Scheme 72). The latter compound was formed in a major amount but isolated (and characterised) in impure form, precluding the accurate determination of its yield. One other product with a structure related to **237** was formed, also in a major amount; this compound (which was observed in the crude product mixture but not isolated and thus not fully characterised) could correspond to **237** ( $R = CO_2H$ ) or **237** ( $R = H$ ) – that is, the product of hydrolysis (in the case of the former) or decarboxylation (in the case of the latter) of **237** ( $R = CO_2Me$ ). Analysis of the crude product mixture by  $^1H$  NMR spectroscopy revealed that the two structures related to **237** were together formed in roughly equal proportion to the desired aldol product; 2-iodo-*N*-methylaniline (**146**) was also observed to have formed but was not isolated.



**Scheme 72.** The desired enaminone substrate, **236**, was obtained alongside major amounts of the undesired aldol product, **237**, and 2-iodo-*N*-methylaniline (**146**) following a hydrolysis–decarboxylation sequence when Michael adduct **235** was treated with sodium methoxide in refluxing methanol.



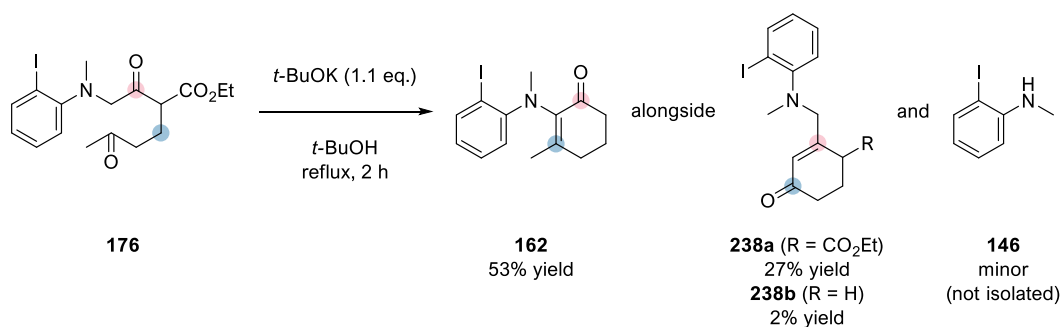
Although the yield of **236** was sufficient to deliver material for the evaluation of its photochemical reactivity, the formation of the alternative aldol regioisomer (or derivatives, **237**, thereof) in major quantities under the action of sodium methoxide prompted a search for more selective conditions. Potassium *tert*-butoxide in refluxing *tert*-butanol was subsequently found to promote the desired cyclisation of **235** with concomitant loss of the carboxyethyl group to form **236** in 45% yield after 1 h, with only trace quantities of undesired aldol products, **237**, and a minor amount of **146** observed in the crude product mixture by  $^1\text{H}$  NMR spectroscopy (Scheme 73).



**Scheme 73.** Treating Michael adduct **235** with potassium *tert*-butoxide afforded the desired enaminone substrate, **236**, in a yield of 45%, with only traces of products arising from the alternative aldol cyclisation mode, **237**, being detected in the crude product mixture.

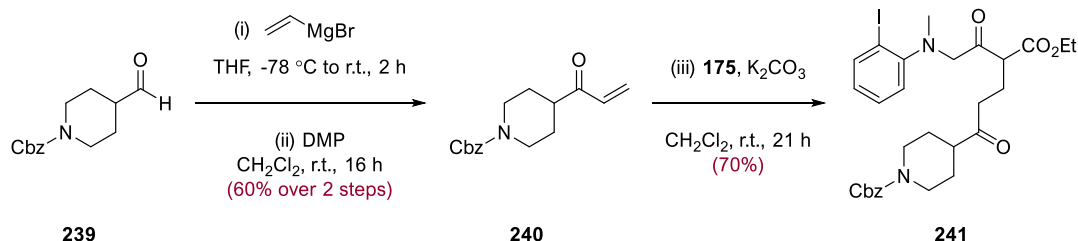
The bulky *tert*-butoxide base was also effective\* in inducing cyclisation of the aldol precursor, **176**, derived from methyl vinyl ketone. In this case, the desired aldol product, **162**, was obtained in 53% yield, alongside **146** in a minor amount and an inseparable mixture of undesired aldol products, **238a** (R = CO<sub>2</sub>Et, 27% yield) and **238b** (R = H, 2%), which had not formed in appreciable quantities (if at all) when sodium methoxide was used as the base (Scheme 74).

\* Earlier attempts to induce cyclisation of *N*-allyl (**325**) and *N*-benzyl (**327**) aldol precursors (see Chapter 4 for structures and synthetic details) using potassium *tert*-butoxide led to minor or trace quantities of the desired enaminone products; instead, compounds tentatively assigned as arising from the alternative aldol cyclisation mode were obtained under these conditions. In the absence of detailed comparative studies, it anecdotally appears that the use of a bulkier *tert*-butoxide base is effective for the synthesis of enaminones with  $\beta$ -substituents spanning a range of sizes, provided a small *N*-alkyl substituent (e.g. *N*-methyl) is used. In contrast, a less hindered base such as sodium methoxide is likely to be more effective when substrates bearing larger *N*-alkyl substituents are desired.



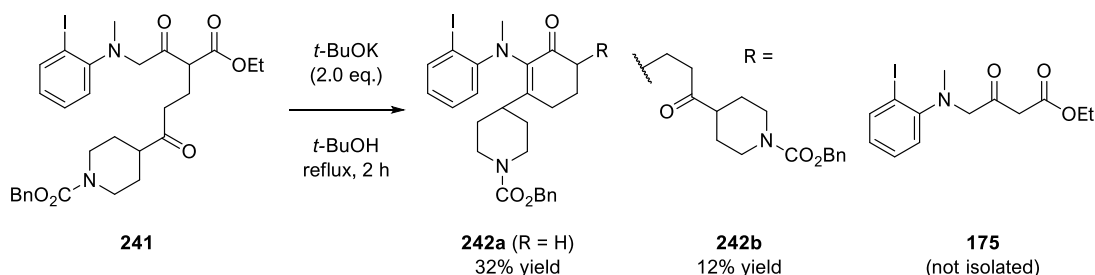
**Scheme 74.** In contrast to the behaviour observed for Michael adduct **235** (derived from ethyl vinyl ketone) under the same conditions, the aldol precursor, **176**, derived from methyl vinyl ketone gave a mixture of aldol products, **162** and **238**, when treated with potassium *tert*-butoxide. Yields of **238a** and **238b** were estimated from relative integrations of alkenyl protons of isolated material (an inseparable mixture).

In addition to  $\beta$ -ethyl substrate **236**, a substrate, **242a**, bearing a *branched* alkyl substituent at the enone  $\beta$ -position was synthesised. Addition of vinyl magnesium bromide to aldehyde **239** followed by oxidation of the resulting allylic alcohol with Dess–Martin periodinane (DMP) delivered vinyl ketone **240** in 60% over two steps; this compound was reacted with aminoketone **175** immediately after its chromatographic purification to deliver 1,5-diketone **241** in 70% yield under the standard conditions for Michael addition (Scheme 75).



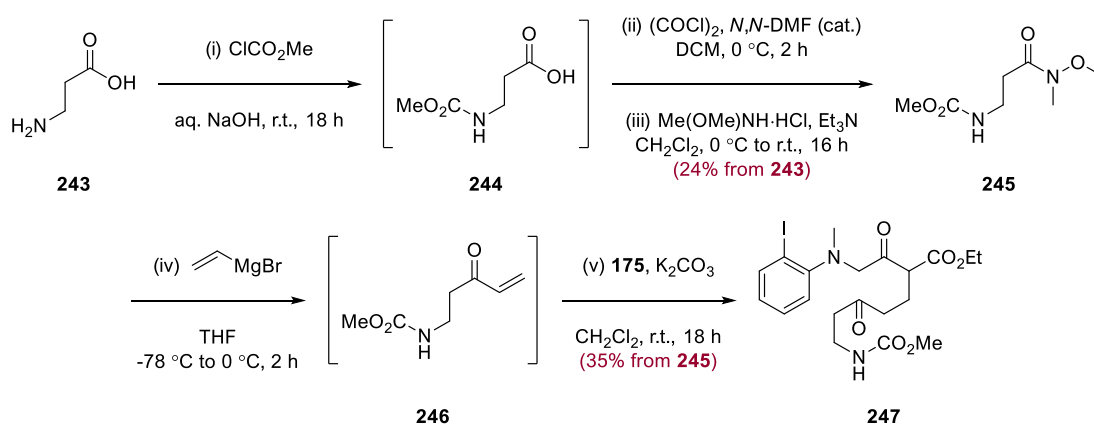
**Scheme 75.** Synthesis of 1,5-diketone **241** en route to *N*-acylpiperidinyl substrate **242a**.

Treating **241** with potassium *tert*-butoxide in refluxing *tert*-butanol afforded the desired  $\gamma$ -branched enaminone product, **242a**, in 32% yield, alongside an over-reaction product, **242b**, in 12% yield and aminoketone **175** whose formation under these basic conditions presumably involves a retro-Michael reaction of the 1,5-diketone starting material (Scheme 76). Alternative aldol cyclisation products were not observed under these conditions.



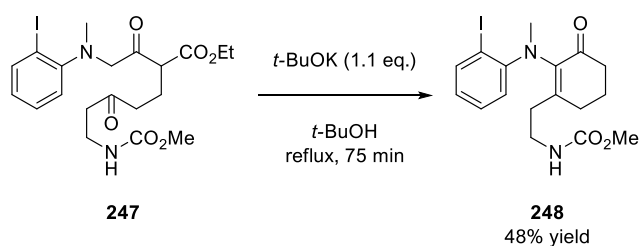
**Scheme 76.** Aldol condensation of 1,5-diketone **241**, leading to desired enaminone substrate **242a** alongside an over-reaction product, **242b**.

As well as varying the steric bulk at the enone  $\beta$ -position, we sought to explore the possibility of intercepting the iminium salt intermediate intramolecularly with a nucleophilic group tethered through the enone  $\beta$ -position. To this end, aldol precursor **247** was synthesised in five steps from  $\beta$ -alanine (**243**) (Scheme 77). Introducing a methyl carbamate protecting group under Schotten–Baumann conditions (to afford **244**) followed by acid chloride formation and reaction with *in situ*-generated *N,O*-dimethylhydroxylamine delivered Weinreb amide **245** in 24% yield over three steps. This material was subjected to a Grignard reaction with vinylmagnesium bromide, the crude product of which (**246**) was immediately dissolved in dichloromethane and reacted with aminoketone **175** in the presence of potassium carbonate to afford the corresponding Michael adduct, **247**, in 35% yield over two steps.



**Scheme 77.** Synthesis of 1,5-diketone **247**, the immediate precursor to a substrate, **248**, containing a tethered carbamate group.

Cyclisation of 1,5-diketone **247** to enaminone **248** proceeded smoothly under the action of potassium *tert*-butoxide, without formation of alternative aldol products, in a yield of 48% (Scheme 78).



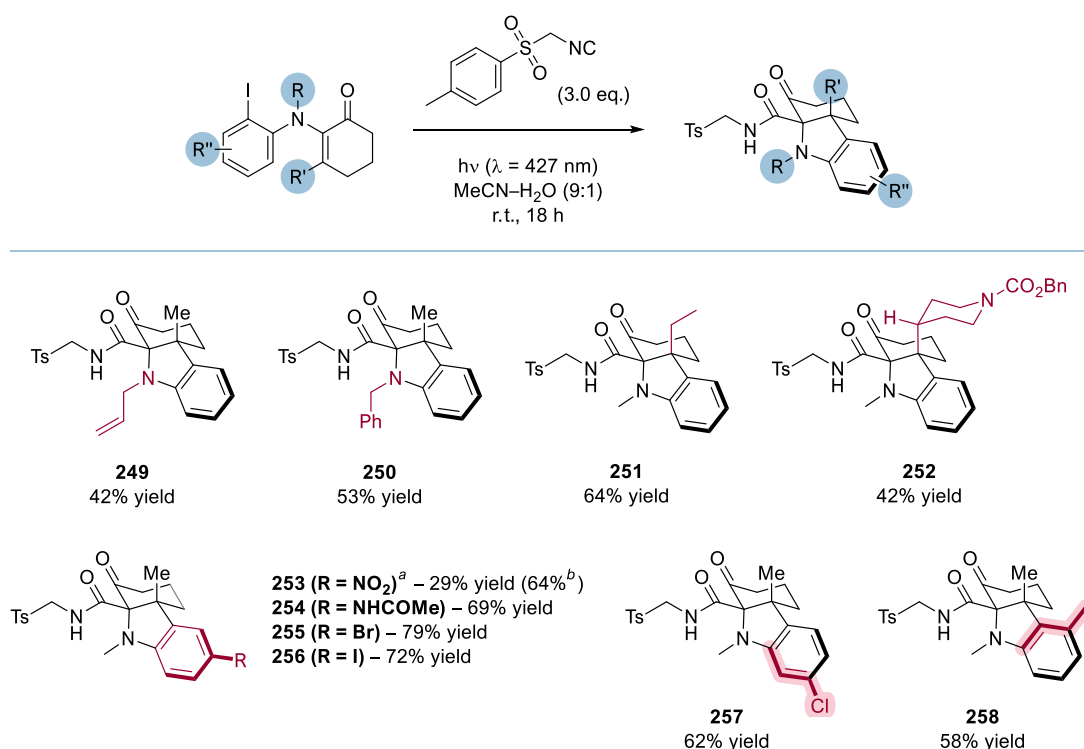
**Scheme 78.** Aldol condensation of **247** to form substrate **248**, which bears a carbamate group tethered through the  $\beta$ -position of the enone.

### Photochemical reactivity of alternative substrates

With the exception of tethered carbamate **248**, the various substrates were irradiated in aqueous acetonitrile in the presence of 3.0 equivalents of TosMIC over a period of 18 h (Table 6). TosMIC was selected as the nucleophile because of the high-yielding reaction it gave previously with

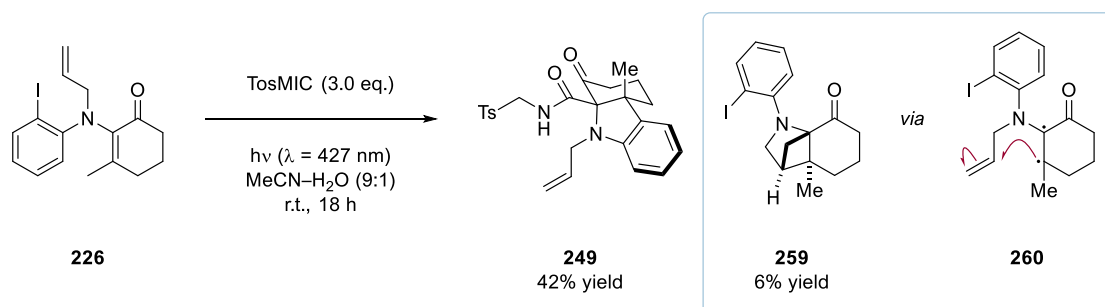
$\beta$ -methyl substrate **162** and the ease with which the ketoamide product of this reaction could be isolated by silica gel flash chromatography. It was found that the selected modifications to the prototypical substrate, **162**, were all tolerated. Substrates bearing *N*-allyl (**226**) and *N*-benzyl (**227**) substituents underwent efficient photocyclisation – affording the corresponding iminium trapping products **249** and **250** in yields of 42% and 53%, respectively – as did substrates with bulkier substituents at the enone  $\beta$ -position: **251** was obtained in 64% yield from  $\beta$ -ethyl substrate **236**, while *N*-acylpiperidine **252** was formed in a lower yield of 42% from the corresponding  $\gamma$ -branched substrate, **242a**. Introducing a *para*-nitro group led to a slower reaction: a low yield of 29% (64% brsm) was obtained for **253** alongside substantial amounts of starting material (**222**), despite performing the reaction over a longer irradiation period (21 h) and in the presence of a larger dose (5.0 equivalents) of TosMIC. Substrates bearing *para*-*N*-acetyl, -bromo and -iodo groups, in contrast, all cyclised effectively, leading to the desired ketoamide products **254**, **255** and **256**, respectively, in yields of 69, 79 and 72%. The formation of **257** and **258** in yields of 62 and 58%, respectively, from substrates bearing 5-chloro (**228**) and 3-methyl (**229**) substituents on the aromatic ring highlights the regioselectivity of the transformation: products arising from *ipso*-H cyclisation were formed, if at all, in trace quantities that could not be isolated on a 0.3 mmol reaction scale.

**Table 6.** Scope of the radical–polar crossover reaction with respect to substrate modifications using TosMIC as the nucleophile (all yields based on isolated material).



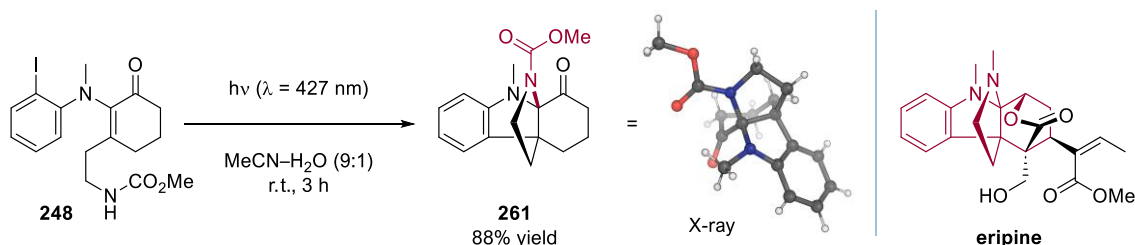
<sup>a</sup> 5.0 equivalents of TosMIC and a reaction time of 21 h were used. <sup>b</sup> Yield based on recovered starting material (brsm).

An intramolecular [2+2]-photocycloadduct, **259**, was formed in 6% yield as a side-product in the (uncatalysed) reaction of *N*-allyl substrate **226** (Scheme 79). Since the [2+2]-photocycloaddition of enones is known to proceed *via* a stepwise triplet-state mechanism, this result provides additional evidence to that described below for the involvement of a triplet excited state in the reaction of **226** and related compounds when performed in the absence of a sensitiser.<sup>76,77</sup>



**Scheme 79.** A [2+2]-cycloaddition competes with radical–polar crossover in the unsensitised photoreaction of *N*-allyl substrate **226**, suggesting a common triplet diradical intermediate (**260**) to both pathways.

When irradiated in a 9:1 (v/v) mixture of acetonitrile and water, tethered carbamate **248** was cleanly transformed in 88% yield to bridged tetracycle, **261** (Scheme 80). Single-crystal X-ray diffraction confirmed the structure of this compound, which contains the core of a range of akuammiline natural products, including eripine.<sup>78</sup>



**Scheme 80.** An iminium ion cyclization provides access to the tetracyclic core of akuammiline alkaloids.

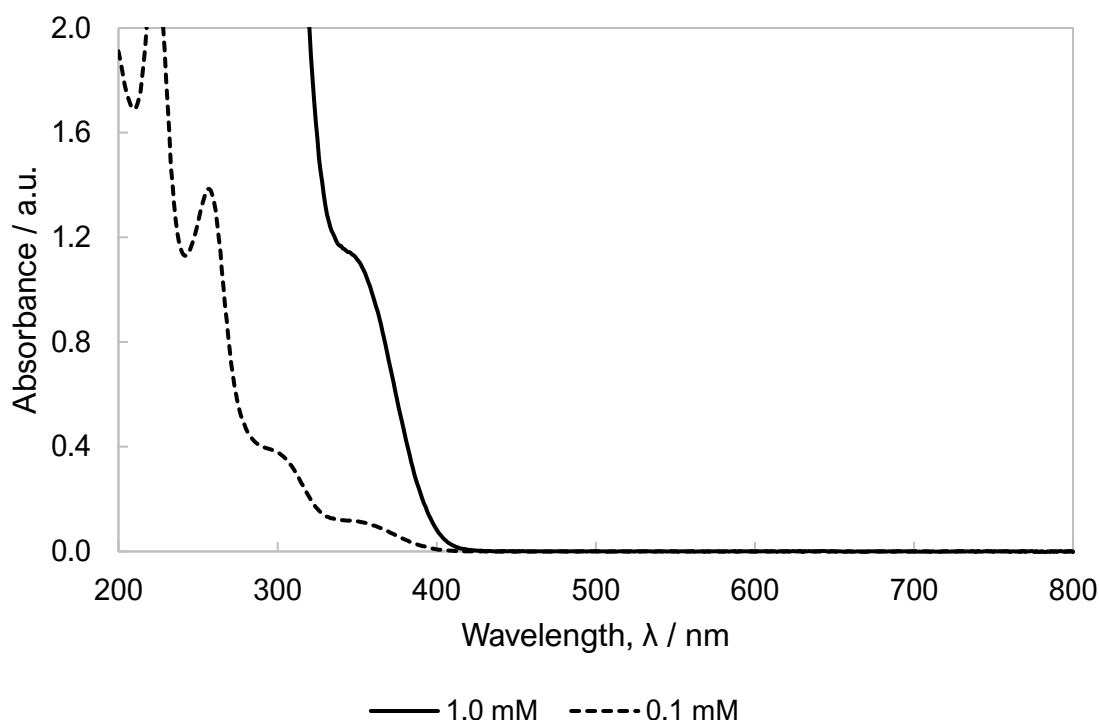
## Mechanistic studies

To understand the source of regioselectivity observed in the reaction, we conducted a range of experimental and theoretical mechanistic investigations, beginning with studies to probe the involvement of a triplet excited state.

## Absorption spectroscopy

In line with previous analyses of structurally related enones,<sup>37,79,80</sup> the low intensity absorption band observed at *ca.* 345 nm in acetonitrile solution by ultraviolet–visible (UV–vis) spectroscopy for  $\beta$ -methyl substrate **162** was assigned to an electronic transition from the molecule's ground state to its lowest lying  $^1n\pi^*$  ( $S_1$ ) state (Figure 4). For cyclic  $\alpha,\beta$ -enones, intersystem crossing from this state to the triplet manifold (or internal conversion from this state to the electronic ground state) is

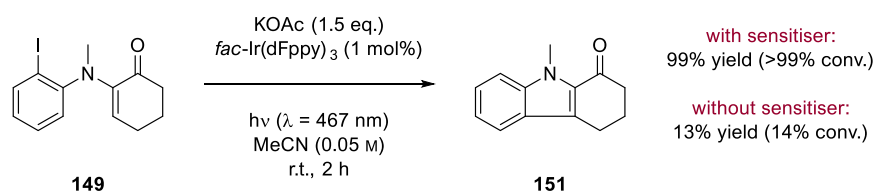
generally considered to be fast<sup>81</sup> relative to chemical reactions originating from the excited singlet state, particularly for transitions involving a change in molecular orbital type (such as the  $^3\pi\pi^* \leftarrow ^1n\pi^*$  transition available to excited-state enones) as predicted by El Sayed's rules<sup>82</sup>. Thus, we propose that the visible-light-mediated reaction of *N*-(2-iodoaryl) enaminones proceeds, like other enamine photocyclisations,<sup>83,84</sup> *via* triplet intermediates.



**Figure 4.** UV-vis absorption profile of  $\beta$ -methyl substrate **162**.

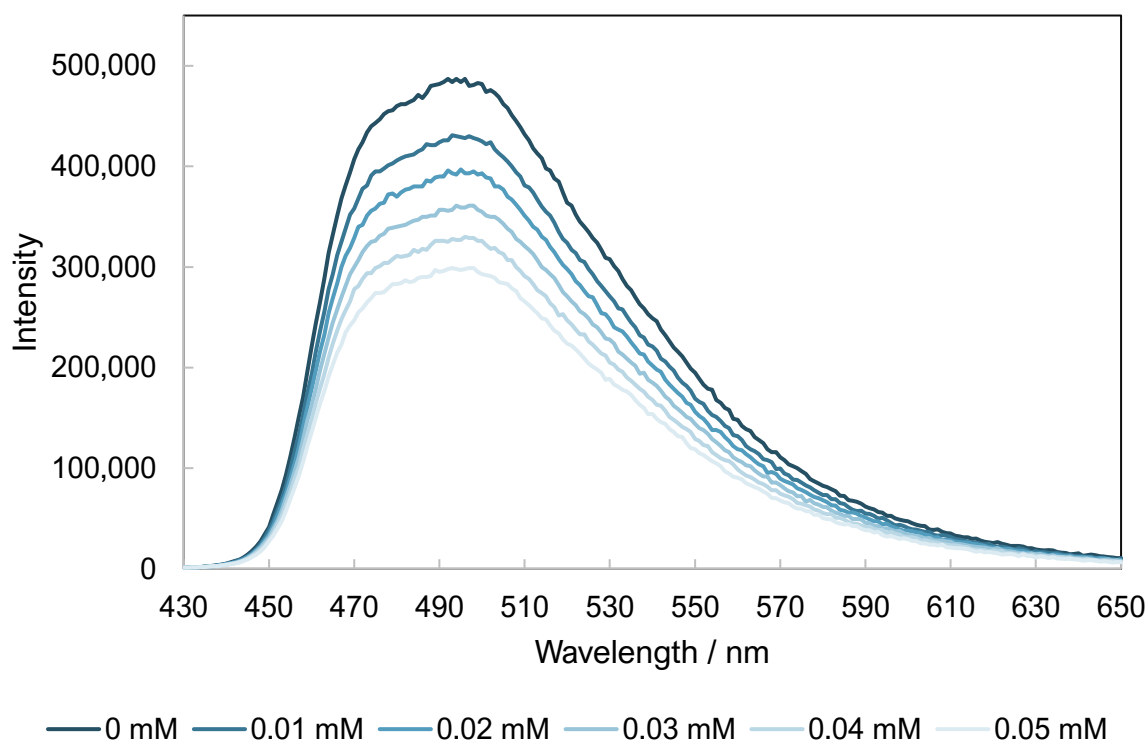
### Triplet sensitisation

Our proposal that the reaction proceeds *via* the triplet state is consistent with the observation of a dramatic rate acceleration for the photocyclisation of **149** in the presence of catalytic *fac*-Ir(dFppy)<sub>3</sub> (Scheme 81). Full conversion of the starting material and a 99% NMR yield of **151** was obtained when **149** was irradiated in acetonitrile solution for 2 h in the presence of potassium acetate and 1 mol% of the iridium sensitiser. In the sensitiser's absence, a conversion of only 14% was observed after the same reaction time.



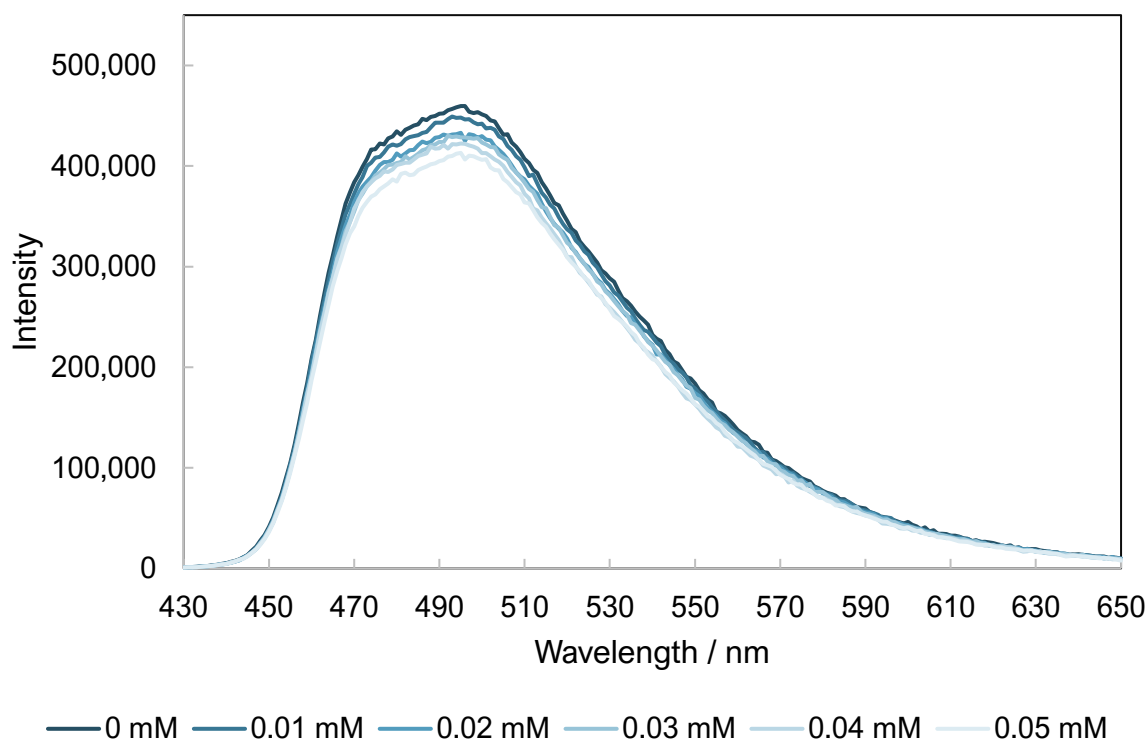
**Scheme 81.** Photocyclisation of **149** in the presence and absence of an iridium photocatalyst. Yields and conversions were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate.

To confirm that an interaction between substrate **149** and the excited photocatalyst is responsible for the rate acceleration, Stern–Volmer constants were obtained for the quenching of *fac*-Ir(dFppy)<sub>3</sub> in acetonitrile by substrate **149** and tetra-*n*-butylammonium acetate.\* This was achieved by recording emission spectra for a degassed 5 μM acetonitrile solution of *fac*-Ir(dFppy)<sub>3</sub> in the presence of different concentrations of substrate **149** at an excitation wavelength of 420 nm (Figure 5); this procedure was repeated with tetra-*n*-butylammonium acetate in place of **149** (Figure 6).



**Figure 5.** Emission spectra recorded for a 5 μM solution of *fac*-[Ir(dFppy)<sub>3</sub>] in the presence of different concentrations of substrate **149** in acetonitrile solution. Excitation wavelength = 420 nm.

\* Tetra-*n*-butylammonium acetate was used instead of potassium acetate, owing to the former salt's higher solubility in acetonitrile.

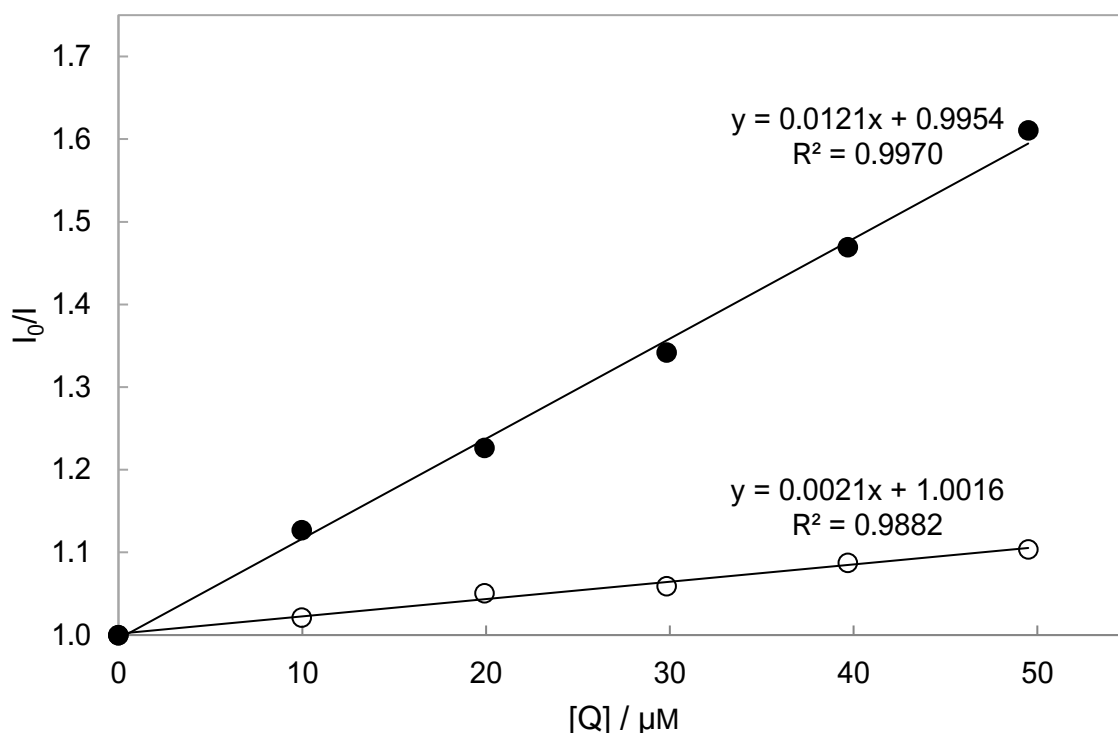


**Figure 6.** Emission spectra recorded for a 5  $\mu\text{M}$  solution of *fac*-[Ir(dFppy)<sub>3</sub>] in the presence of different concentrations of tetra-*n*-butylammonium acetate, (*n*-Bu)<sub>4</sub>NOAc, in acetonitrile solution. Excitation wavelength = 420 nm.

Linear plots of  $I^0/I$  vs. concentration of quencher, [Q], were obtained for both **149** (Figure 7, closed/solid dots) and tetra-*n*-butylammonium acetate (Figure 7, open dots); from the slopes of these lines, the Stern–Volmer constants,  $K_{SV}$ , for the two compounds were calculated as  $1.2 \times 10^4 \text{ M}^{-1}$  and  $2.1 \times 10^3 \text{ M}^{-1}$ , respectively, according to the equation:

$$\frac{I^0}{I} = 1 + K_{SV}[Q]$$





**Figure 7.** Stern–Volmer plot for the phosphorescence quenching of *fac*-[Ir(dFppy)<sub>3</sub>] in the presence of quencher, Q, in acetonitrile solution, where Q is substrate **149** (●) or (*n*-Bu)<sub>4</sub>NOAc (○).  $I_0$  is the intensity of emission in the absence of quencher;  $I$  is the same quantity in the presence of different concentrations of Q.

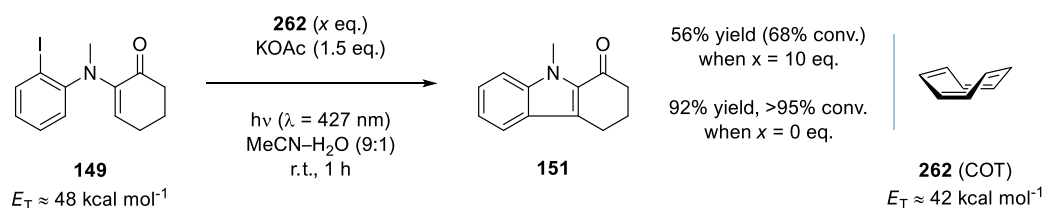
Emission spectroscopy therefore confirms that the emissive triplet state of *fac*-Ir(dFppy)<sub>3</sub> reached upon excitation with 420 nm light is efficiently quenched by substrate **149**. In contrast, (*n*-Bu)<sub>4</sub>NOAc is a relatively inefficient quencher. As a result, the rate acceleration observed in the presence of *fac*-Ir(dFppy)<sub>3</sub> for the photocyclisation of **149** likely arises from an interaction between the substrate and excited photocatalyst, rather than an interaction between the acetate base and excited photocatalyst. To examine the feasibility of a mechanism of catalysis involving single-electron transfer (that is, a photoredox-catalysed mechanism) occurring in the presence of *fac*-Ir(dFppy)<sub>3</sub>, the ground-state reduction and oxidation potentials of substrate **149** were measured in acetonitrile by square-wave voltammetry. Values of +1.10 V and -2.04 V, respectively, *vs.* SCE were obtained for the half-wave oxidation and reduction potentials of this compound;<sup>85</sup> these values lie outside of both the oxidising ( $E_{1/2}(\text{Ir}^{\text{III}*}/\text{Ir}^{\text{II}}) = +0.39$  V *vs.* SCE) and reducing ( $E_{1/2}(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}*}) = -1.23$  V *vs.* SCE) capabilities of the excited-state photocatalyst,<sup>86</sup> implicating triplet energy transfer as the likely mode of catalysis, in light of the substrate's low triplet energy ( $E_{\text{T}} \approx 48$  kcal mol<sup>-1</sup>) relative to that of the apparent triplet donor, *fac*-Ir(dFppy)<sub>3</sub> ( $E_{\text{T}} = 60.1$  kcal mol<sup>-1</sup>).

### Triplet quenching

Attempts to probe the formation of a triplet state in the *absence* of photocatalyst using known triplet quenchers were hampered by the low triplet energies of the substrates, calculated for substrates **149**

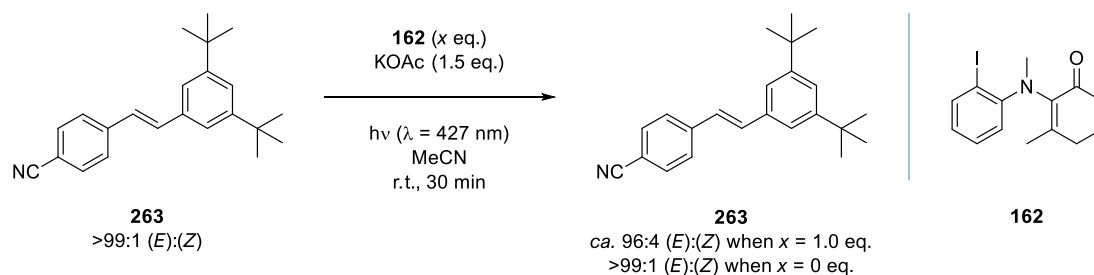
and **162** as *ca.* 48 kcal mol<sup>-1</sup>, both. Compounds that might be expected to quench these triplet states (that is, compounds with triplet energies lower than *ca.* 48 kcal mol<sup>-1</sup>) either absorbed (or could not be separated from impurities that absorbed) in the same range of wavelengths as the substrate and/or were insoluble in the polar aprotic reaction medium; both effects would effectively shield the substrate from the incident light, leading to a reduced reaction rate regardless of the state multiplicity of the reaction.

For instance, an attempt was made to record the difference in photocyclisation rate for substrate **149** in the presence and absence of 1,3,5,7-cyclooctatetraene (COT), which has an estimated triplet energy of *ca.* 42 kcal mol<sup>-1</sup>.<sup>87</sup> Indeed, a substantially lower yield of **151** and lower conversion of starting material was obtained when the reaction was performed in the presence of 10 equivalents of this putative quencher (Scheme 82). These data must be interpreted with caution, however, since the batch of COT used contained a deeply coloured impurity, which co-distilled with the polyene. It is likely, therefore, that the rate difference observed in the presence of this additive does *not* reflect triplet-state quenching, but rather arises from a mere ‘sunscreen’ effect.



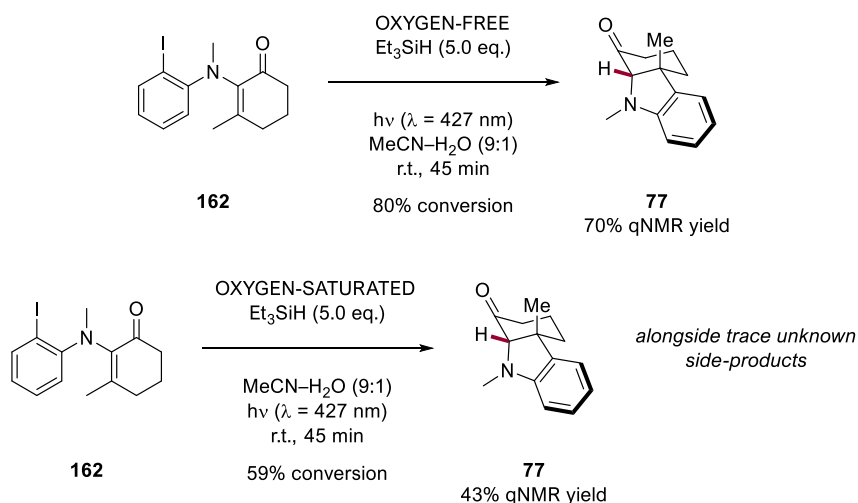
**Scheme 82.** The addition of 10 equivalents of cyclooctatetraene (**262**) leads to reduction in rate for the photocyclisation of **149**, likely through a ‘sunscreen’ effect.

Other molecules that were considered as potential triplet quenchers but gave inconclusive results were Ni(acac)<sub>2</sub> and Cu(acac)<sub>2</sub> (both of which were insoluble in acetonitrile),<sup>88</sup> anthracene (also insoluble in acetonitrile), and acridine (which contained a coloured impurity and whose presence led to precipitate formation during a photoreaction performed in aqueous acetonitrile).<sup>89</sup> An attempt was also made to use a stilbene derivative, **263**, to report on triplet-state formation upon the direct excitation of  $\beta$ -methyl substrate **162** (Scheme 83). It was hypothesised that, if the triplet state of the latter compound was populated during its photochemical reaction, it might sensitise the isomerisation of co-added (*E*)-**263** (which, by analogy to related compounds,<sup>90</sup> is thought to have a triplet energy of *ca.* 47 kcal mol<sup>-1</sup>) to (*Z*)-**263**. While the (*E*)-stilbene derivative did absorb very weakly in the same region as the enaminone substrate, a small change in (*E*):(*Z*) ratio (from >99:1 to 96:4) was observed when **263** was irradiated with 427 nm light for 30 min in the presence and absence of enaminone **162** that was not observed in the absence of the latter compound. This effect, albeit minor, suggests that a triplet state is indeed populated upon direct irradiation of enaminone **162** in the absence of a sensitizer.



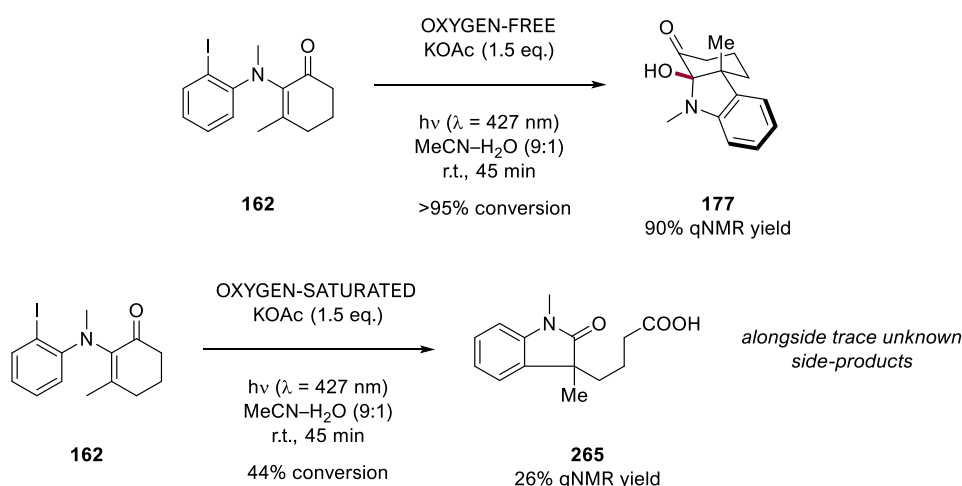
**Scheme 83.** Irradiation of (*E*)-stilbene **263** in the presence of 1.0 equivalent of  $\beta$ -methyl substrate **162** led to a small degree of alkene isomerisation, which did not occur in the absence of **162**.

Additionally, it was possible to observe a lower rate of reaction (alongside the formation of oxidative degradation products) in the presence of oxygen for  $\beta$ -methyl substrate **162** under two sets of conditions. In the presence of triethylsilane, irradiation of **162** in a rigorously degassed acetonitrile–water mixture gave 80% conversion of starting material and a 70% yield of indoline **77**, both measured by quantitative  $^1\text{H}$  NMR spectroscopy against dimethyl terephthalate, after an irradiation period of 45 min (Scheme 84). In contrast, whenever the reaction was repeated with oxygen-sparging of the medium prior to irradiation, the same product was obtained in a diminished yield of 43% alongside trace unknown side-products and a larger recovery of starting material (59% conversion).



**Scheme 84.** Photochemical reaction of  $\beta$ -methyl substrate **162** in the presence of triethylsilane with and without oxygen-sparging of the reaction medium prior to irradiation.

Irradiating **162** in the presence of potassium acetate likewise gave markedly different results depending on the oxygen content of the reaction mixture. When rigorously degassed, the expected hemiaminal product, **177**, was obtained in an NMR yield of 90% with no starting material recovery after an irradiation period of 45 min (Scheme 85); whereas, when saturated with oxygen, a ring-opened oxidation product, **265**, derived from hemiaminal **177** (not observed) was formed (26% NMR yield) alongside trace unknown side-products and a substantial amount of starting material (44% conversion).

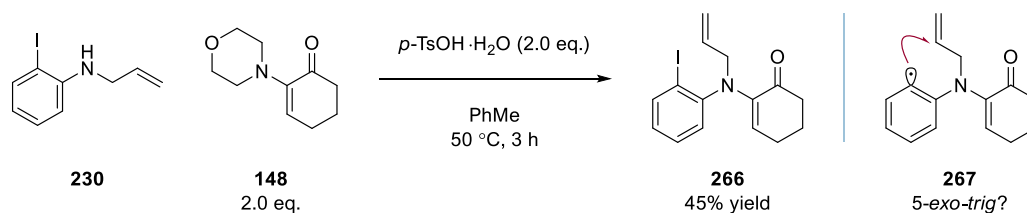


**Scheme 85.** Photochemical reaction of  $\beta$ -methyl substrate **162** in the presence of potassium acetate with and without oxygen-sparging prior to irradiation.

While oxygen is known to quench both singlet and triplet excited states,<sup>91</sup> it has been postulated<sup>92</sup> that states of sufficiently long lifetime as to observe fluorescence are required to observe any substantial rate decrease upon oxygen sparging for reactions mediated by an excited singlet state. Thus, the absence of fluorescence upon exciting a degassed 100  $\mu\text{M}$  acetonitrile solution of **162** at 350 nm (the approximate position of longest-wavelength absorption band of the molecule) in a spectrofluorometer suggests that the lower rates of reaction for **162** in the presence of oxygen arise from quenching of a reactive triplet state.<sup>93</sup>

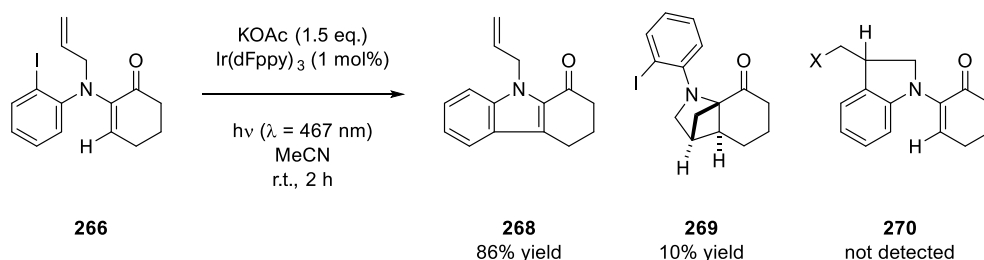
### Radical clock study

While evidence for a triplet-state mechanism was mounting, the question of whether the reaction proceeded *via* the cyclisation of an aryl radical or an alkene triplet diradical had not been addressed. Considering that aryl halides are widely used as precursors to the former intermediate under photochemical activation, and that *N*-aryl enaminones<sup>44</sup> and related compounds<sup>83</sup> without iodine substituents are thought to isomerise *via* the latter, both mechanistic possibilities seemed plausible. To investigate the formation of an aryl radical, *N*-allyl substrate **266** was synthesised; it was hypothesised that if an aryl radical did form under photochemical activation of this compound, it should be possible to identify products from a 5-*exo-trig* aryl radical cyclisation in the crude photolysate (Scheme 86).



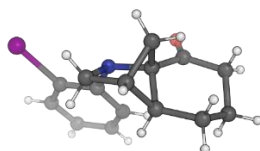
**Scheme 86.** Synthesis of *N*-allyl substrate **266**. The putative aryl radical (**267**) resulting from C–I bond homolysis could be expected to undergo a 5-*exo-trig* cyclisation onto the pendent radical acceptor.

When irradiated in acetonitrile solution with 467 nm light in the presence of potassium acetate and *fac*-Ir(dFppy)<sub>3</sub>, *N*-allyl substrate **266** underwent efficient photocyclisation to give indole **268** in 86% yield alongside a single side-product, **269**, in 10% yield (Scheme 87). No other products could be identified by analysis of the crude product mixture by either <sup>1</sup>H NMR spectroscopy or thin-layer chromatography. The absence of **270** (X = H or I), or any other products that might be expected to form as a result of an aryl radical 5-*exo-trig* cyclisation, suggests that homolysis of the C–I bond to form an aryl radical does *not* occur upon photochemical activation of this substrate.



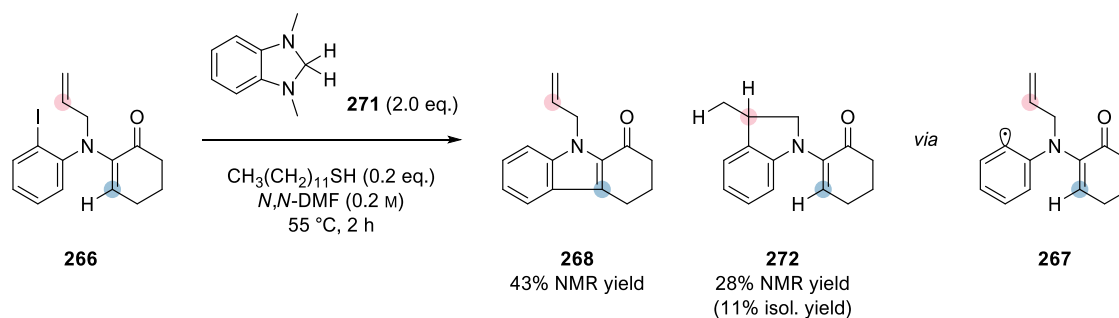
**Scheme 87.** The photochemical reaction of *N*-allyl substrate **266** undermines a mechanism involving the cyclisation of an aryl radical. X = H or I.

Together with the absence of aryl radical 5-*exo-trig* products, the formation of [2+2]-cycloadduct **269** in which the carbon–iodine bond present in the starting material has been preserved (see Figure 8 for a crystal structure) as the sole side-product of the sensitised photoreaction of **266** suggests that the triplet state formed by energy transfer between the excited sensitiser and substrate is *not* dissociative but instead displays diradical reactivity.



**Figure 8.** Single-crystal X-ray structure of bridged cyclobutane **269**.

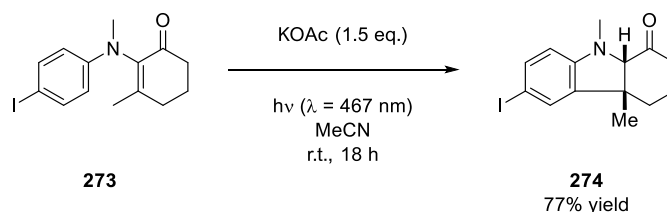
To conclusively rule out the possibility of an aryl radical being formed *via* a competing dissociative reaction channel in the excited state, we subjected *N*-allyl substrate **266** to conditions reported by Murphy and co-workers for the thermal generation of aryl radicals from aryl halides (Scheme 88).<sup>94</sup> These conditions gave a mixture of cyclisation products: indole **268**, which ostensibly arises from 5-*endo-trig* cyclisation of the putative aryl radical followed by oxidation *in situ*, and indoline **272**, which corresponds to a reductive aryl radical 5-*exo-trig* cyclisation product, in 43% and 28% yields, respectively, measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate. This result demonstrates that 5-*exo-trig* cyclisation is a viable reaction pathway available to aryl radical **267**. Thus, the failure to observe 5-*exo-trig* cyclisation products related to **272** in the *photochemical* reaction of *N*-allyl substrate **266** is likely a result of the same aryl radical intermediate not forming under these conditions, rather than the cyclisation mode itself being unfeasible.



**Scheme 88.** Treating *N*-allyl substrate **266** with a neutral organic super electron donor (**271**) gave a mixture of products ostensibly arising from 5-*endo*- (**268**) and 5-*exo-trig* (**272**) cyclisation of aryl radical **267**.

### Photochemical reactivity of an ‘iodo-displaced’ substrate

An additional result that can be interpreted as refuting an aryl radical-based mechanism is the clean isomerisation (a known triplet process<sup>44</sup>) of *N*-aryl enaminone **273** to *cis*-indoline **274** in 77% yield under photochemical activation (Scheme 89); no other non-trace products could be identified in the crude product mixture of this reaction by <sup>1</sup>H NMR spectroscopy. This result demonstrates that mere substitution of the aromatic ring with an iodine substituent is not sufficient to divert the photochemical path of excited-state *N*-aryl enaminones from isomerisation; rather, C–I bond rupture only occurs when the leaving group is situated at an aromatic carbon available to attack by the putative diradical intermediate. The finding also points away from alternative mechanisms involving the formation of charge-transfer complexes, which might in this case have been expected to give rise to *des*-iodo derivatives of either the starting material or product.



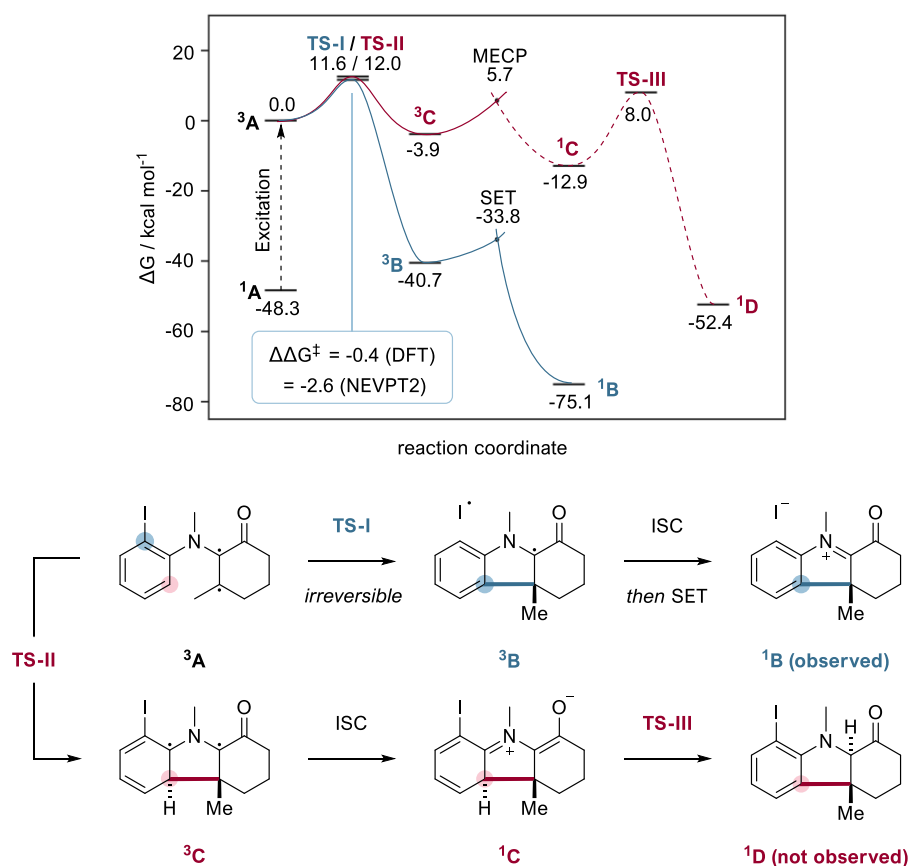
**Scheme 89.** *para*-Iodinated substrate **273** undergoes isomerisation rather than radical–polar crossover.

### Computational studies and the possibility of a minor *ipso*-H cyclisation pathway

The section below summarises computational studies performed by Mihai V. Popescu (M.V.P.), which have been detailed elsewhere.<sup>1,95</sup>

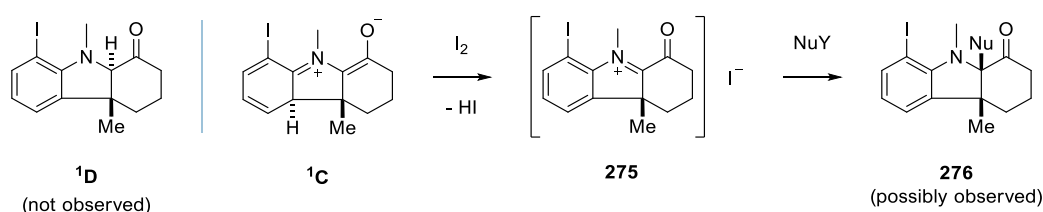
The reaction mechanism was studied using Density Functional Theory (DFT) at the M06-2X-D3/def2-QZVPP(SMD=MeCN)//M06-2X-D3/def2-TZVP(SMD=MeCN) level of theory (Figure 9). Substrate **162** (here denoted as <sup>1</sup>**A** and <sup>3</sup>**A** in its ground and first triplet excited states, respectively) was found to have an adiabatic triplet energy of 48.3 kcal mol<sup>-1</sup>. Triplet diradical <sup>3</sup>**A**, obtained upon intersystem crossing from an excited singlet state or by triplet energy transfer to <sup>1</sup>**A** from an appropriate sensitiser, may undergo conrotatory ring-closure *via* two regioisomeric

transition structures. DFT predicts, across multiple levels of theory, that cyclisation onto the iodine-bearing carbon (that is, '*ipso*-I' cyclisation) leading *via* **TS-I** to radical pair **<sup>3</sup>B** is preferred to the alternative '*ipso*-H' cyclisation pathway, which would lead *via* **TS-II** to **<sup>3</sup>C**. At the level of theory used to model the entire reaction coordinate, the predicted magnitude of this selectivity is modest, corresponding to a  $\Delta\Delta G^\ddagger$  value of  $-0.4$  kcal mol<sup>-1</sup>; however, a considerably larger  $\Delta\Delta G^\ddagger$  value of  $-2.6$  kcal mol<sup>-1</sup> was predicted using the complete active space self-consistent field (CASSCF) method with perturbative treatment (NEVPT2:CASSCF(10,10)/Def2-TZVP(SMD=MeCN)). The favoured *ipso*-I cyclisation pathway is predicted to be irreversible and highly exergonic by 40.7 kcal mol<sup>-1</sup>, delivering the experimentally observed iminium iodide product, **<sup>1</sup>B**, through intersystem crossing of radical pair **<sup>3</sup>B** (accelerated by localisation of one of the spins on a heavy iodine atom) followed by single-electron transfer ( $\Delta G^\ddagger = 6.9$  kcal mol<sup>-1</sup>). Cyclisation *via* **TS-II** would give **<sup>3</sup>C**, which lies 3.9 kcal mol<sup>-1</sup> below **<sup>3</sup>A** in energy. Subsequent intersystem crossing of this intermediate to yield a singlet zwitterionic species, **<sup>1</sup>C**, through a minimum energy crossing point (MECP) at 5.7 kcal mol<sup>-1</sup> (that is, 9.6 kcal mol<sup>-1</sup> above **<sup>3</sup>C**) followed by an intramolecular hydrogen transfer process (**TS-III**,  $\Delta G^\ddagger = 20.9$  kcal mol<sup>-1</sup>) could be expected to produce **<sup>1</sup>D**.



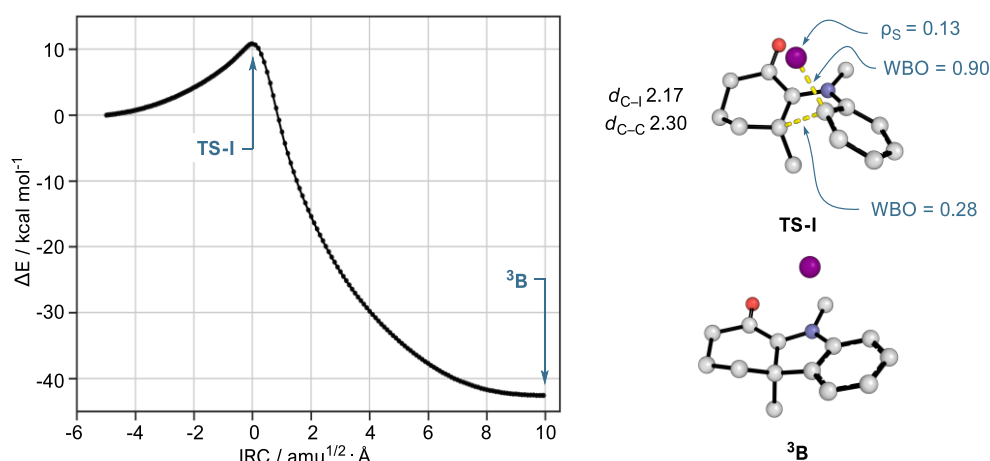
**Figure 9.** Computed reaction profile with *ipso*-I and *ipso*-H cyclisation pathways shown in blue and red, respectively.

While neither **1D** nor any isomeric structure was ever detected experimentally, trace side-products with similar  $^1\text{H}$  NMR spectral features to the major, ‘*ipso*-I’ nucleophilic trapping products were occasionally observed in crude product mixtures, whose formation could be indicative of a very minor competing pathway involving *ipso*-H cyclisation *via* **TS-II**. Since they were formed in very small quantities (if at all), these products were never isolated and left uncharacterised; however, the presence of low-field aromatic proton signals corresponding to these products is suggestive of a general structure, **276**, in which the C–I bond present in the starting material has been retained. Such compounds could form *via* oxidation of zwitterion **1C** by trace iodine in the reaction mixture, which could be expected to accumulate during reactions in which the HI by-product is not sequestered (Scheme 90).



**Scheme 90.** Structures tentatively assigned as **276** were observed in trace quantities in some crude photolysates, suggestive of a minor *ipso*-H cyclisation pathway in which zwitterionic intermediate **1C** is irreversibly transformed to iminium iodide **275** through oxidation by trace iodine.

Intrinsic reaction coordinate (IRC) calculations performed from **TS-I** suggest that *ipso*-I cyclisation does not proceed *via* a stable  $\sigma$ -intermediate, with natural bond orbital analysis (NBO) indicating an early transition state in which the C–I bond has been partially broken (Figure 10).

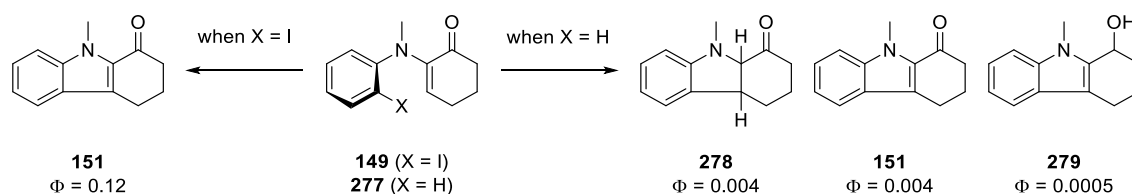


**Figure 10.** Intrinsic reaction coordinate calculations from **TS-I** implicating a concerted substitution process. Wiberg bond orders (WBO) of 0.28 and 0.90, respectively, were calculated for the forming C–C and breaking C–I bonds, while the natural spin density ( $\rho_s$ ) on iodine was found to be 0.13.



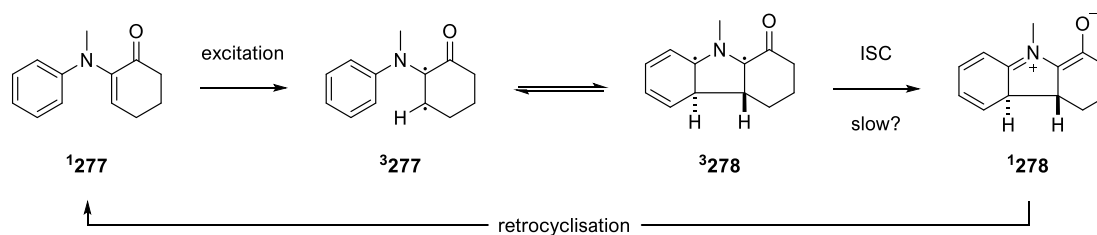
## Quantum yield and $^{13}\text{C}$ kinetic isotope effect (KIE) studies

Quantum yield experiments reveal substantially different photocyclisation efficiencies for **149** and a non-iodinated analogue, **277**. For the former compound, a quantum yield of 0.12 for the sole product, **151**, was measured at an irradiation wavelength of 405 nm; whereas, for the latter, three photocyclisation products – **278**, **151** and **279** – were formed in quantum yields adding to 0.0085 under the same conditions (Scheme 91).



**Scheme 91.** Quantum yields of reaction obtained at 405 nm for iodinated (**149**) and non-iodinated (**277**) substrates, revealing a 14-fold increase in photocyclisation efficiency upon introducing an *ortho*-iodine substituent. Conditions: KOAc (1.5 eq.),  $h\nu$  ( $\lambda = 405$  nm), MeCN (0.05 M), 25 °C.

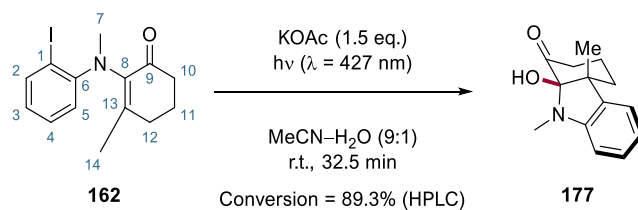
The occurrence of radical chain reactions cannot be unambiguously excluded on the basis of these results;<sup>96</sup> however, considering the moderate quantum yield of 0.12 obtained for **151** in the photochemical reaction of substrate **149**, it is unlikely that a long-lived radical chain process constitutes the dominant pathway under these conditions. The larger quantum yield of reaction observed for **149** may reflect a more efficient ISC event leading to the reactive triplet state when an iodine atom is present,<sup>97</sup> although the heavy atom itself is not in the conjugation path of the enone chromophore. An alternative hypothesis to explain the difference in reaction efficiency is that *ipso*-I cyclisation in the triplet state – despite having a lower predicted barrier than the corresponding *ipso*-H cyclisation pathway for  $\beta$ -methyl substrate **162** – is not the sole selectivity-determining step in the eliminative photocyclisation of *ortho*-iodinated substrates. In such an event, the lower quantum yield observed for non-iodinated substrate **277** could reflect reversibility along the *ipso*-H pathway, a possibility suggested by the large calculated MECP value for the intersystem crossing of *ipso*-H-cyclised intermediate  $^3\text{C}$  to  $^1\text{C}$  described above (Scheme 92). That is, it is possible in the case of **277** that intersystem crossing (a spin-forbidden process) from  $^3\text{278}$  to  $^1\text{278}$  following cyclisation in the triplet state is *slow* relative to retrocyclisation to triplet-state starting material,  $^3\text{277}$ ; in other words, the ring-closure of  $^3\text{277}$  to  $^3\text{278}$  could be reversible. Retrocyclisation could also occur from a singlet zwitterionic intermediate<sup>83</sup> such as  $^1\text{278}$  following a non-limiting intersystem crossing event, providing an alternative mechanism for recycling the starting material that might also explain the lower quantum yield of reaction observed in the absence of an iodine leaving group.



**Scheme 92.** Speculative mechanisms invoking the possibility of reversibility along the *ipso*-H cyclisation pathway that might explain the substantially lower photocyclisation efficiency of non-iodinated substrate **277**.

A small but observable  $^{13}\text{C}$  kinetic isotope effect (KIE) value of 1.013(5) measured at natural abundance<sup>98</sup> for the iodinated carbon atom in a single high-conversion photoreaction of **162** is qualitatively consistent with a mechanism in which C–I bond rupture occurs in the first irreversible photochemical step (see Table 7 for a summary of  $^{13}\text{C}$  KIE measurements). The magnitude of this observed KIE, however, is significantly lower than the 1.051 value predicted computationally for this carbon assuming *ipso*-I cyclisation alone is selectivity-determining. Kuan and Singleton have previously noted lower-than-expected KIE values for two photoredox-catalysed enone [2+2]-cycloaddition reactions.<sup>99</sup> It was suggested that a slow (reversible) electron transfer process occurring prior to, and in competition with, the key (irreversible) radical anion cycloaddition step (assumed originally to be the *sole* selectivity-determining step) was responsible for this discrepancy. The possibility that a similar effect is operative in our system – that is, that a single high-barrier irreversible bond-forming process does not exclusively determine product selectivity – warrants further investigation in future studies.<sup>100</sup>

**Table 7.**  $^{13}\text{C}$  KIE effects measured in a high-conversion photoreaction of **162** alongside theoretical values predicted assuming *ipso*-I or *ipso*-H cyclisation is selectivity-determining.



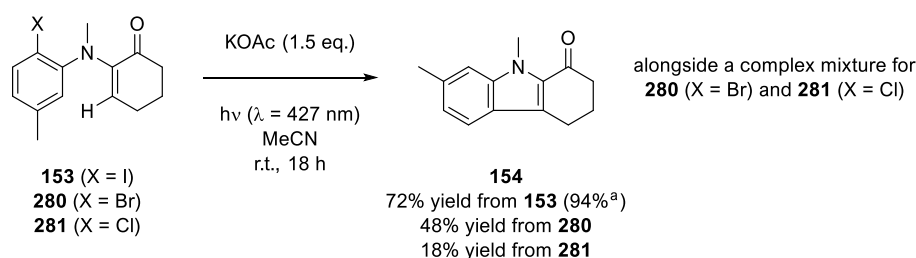
Carbon	$^{13}\text{C}$ KIE (expt.)	$^{13}\text{C}$ KIE (calc. for <b>TS-I</b> )	$^{13}\text{C}$ KIE (calc. for <b>TS-II</b> )
9	1.004(2)	0.998	0.998
13	1.003(1)	1.009	1.019
6	0.997(2)	1.002	1.002
2	1.001(5)	1.007	1.006
8	1.001(2)	1.000	0.998
4	0.997(3)	1.004	1.007
3	0.997(2)	1.004	1.004
5	0.999(2)	1.004	1.043
<b>1</b>	<b>1.013(5)</b>	<b>1.051</b>	<b>1.004</b>
7	<sup>a</sup>	1.000	1.000
10	0.996(3)	1.000	1.000
12	0.999(2)	1.000	0.999
11	1.000 (assumed)	1.001	1.000
14	0.996(5)	0.999	0.998

<sup>a</sup> Not determined; overlap with DMSO solvent signal led to over-estimation of this integral.

## Investigation of alternative leaving groups

One consequence of the homolytic aromatic substitution mechanism described above is that substrates bearing leaving groups other than iodine should also undergo eliminative photocyclisation; that is, the success of the radical–polar crossover reaction should not depend on the presence of a photolabile C–I bond to achieve regioselective cyclisation *via* the generation of an aryl radical.

To explore this idea, we initially compared the photocyclisation efficiency of substrates containing different *ortho*-halogen substituents; substrates **153**, **280** and **281** (all containing an aromatic methyl group to probe the regiochemical course of the reaction) were therefore synthesised and separately irradiated with 427 nm light in acetonitrile solution in the presence of potassium acetate (Scheme 93).



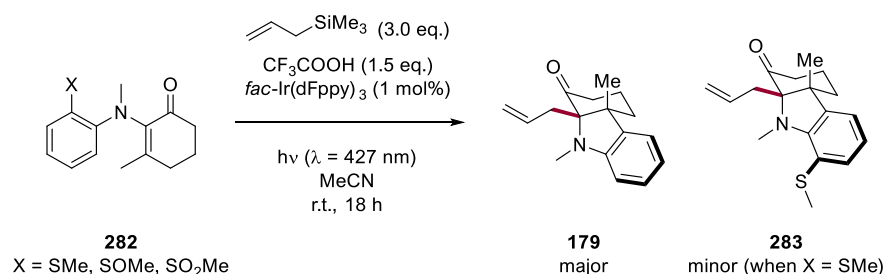
**Scheme 93.** Halogen leaving group study. Yields were measured by quantitative  $^1\text{H}$  NMR spectroscopy against dimethyl terephthalate for 0.1 mmol-scale photoreactions. <sup>a</sup> Isolated yield from a 0.3 mmol reaction performed in the presence of *fac*-Ir(dFppy)<sub>3</sub> and 467 nm light for 2 h under otherwise identical conditions.

Within this compound series and under these reaction conditions, the yield of the eliminative photocyclisation product, indole **154**, appears to correlate inversely with the strength of the carbon–halogen bond present in the starting material. Thus, chloro substrate **281** gave **154** in a low yield of 18%, alongside a complex mixture of side-products that could not be cleanly resolved.\* Indole **154** was formed in a larger yield of 48% from bromo substrate **280**, albeit still alongside considerable amounts of (unidentified) side-products. Finally, the parent iodine-containing compound, **153**, cyclised with minimal side-product formation to **154** in 72% yield (though this value is notably lower than the 94% isolated yield obtained when the same reaction was performed on a 0.3 mmol scale in the presence of a photocatalyst using 467 nm light). In the absence of characterisation data for the reaction side-products, it is not possible to draw firm conclusions about regioselectivity or other aspects of the reaction mechanism from these results. Nevertheless, the preliminary data

\* Repeating the photocyclisation of chloro substrate **281** in the presence of *fac*-Ir(dFppy)<sub>3</sub> in either MeCN or MeCN–H<sub>2</sub>O (9:1 v/v) led to extremely complex product mixtures containing only trace quantities of indole **154**. The photocatalytic generation of chlorine radicals (which are known to be extremely reactive toward C–H bonds) from KCl, one of the presumed by-products of *ipso*-Cl photocyclisation in the presence of KOAc, could account for the intractable product distributions obtained when **281** was irradiated in the presence of a photocatalyst.

reported here appear to suggest that alternative reaction pathways (e.g. *ipso*-H cyclisation) begin to at least compete with, if not outcompete, *ipso*-X cyclisation in the triplet state when the iodine substituent in **153** is replaced with bromine or chlorine atoms.

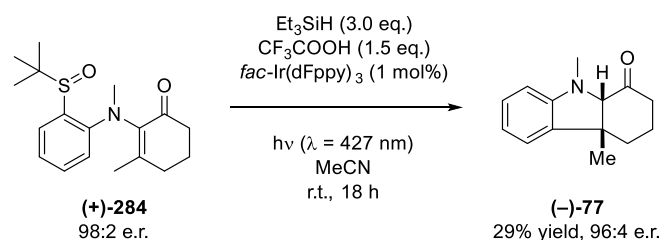
A more comprehensive investigation of alternative leaving groups was carried out by Jay Ahuja (J.A.).<sup>101</sup> This undergraduate member of the Smith group showed that enaminones **282** bearing *ortho*-sulfanyl, -sulfinyl and -sulfonyl substituents undergo predominantly or exclusively eliminative photocyclisation upon sensitised irradiation in acetonitrile solution (Scheme 94). In the presence of allyltrimethylsilane and trifluoroacetic acid, this process yields **179**, in which the *ortho*-substituent has been lost, as the sole (non-trace) product when SMe or SO<sub>2</sub>Me leaving groups are used. In the reaction of *ortho*-SMe-substituted substrate (i.e., when X = SMe), the same product, **179**, is formed in major quantities alongside a minor, formally oxidised ‘non-eliminative’ product, **283**.



**Scheme 94.** Sulfur-based leaving group study performed by J.A.

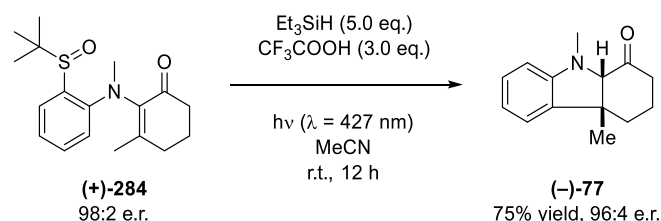
Encouraged by the successful reaction of *ortho*-sulfinyl-substituted substrate **282** (X = SOMe), and inspired by recent reports of radical Smiles-type rearrangements by the Nevado group<sup>102</sup> and others<sup>103</sup>, J.A. demonstrated that the same and related compounds prepared in enantioenriched form undergo photocyclisation with transfer of chirality from sulfur to carbon. Irradiation, for example, of *tert*-butyl sulfoxide (+)-**284** (98:2 e.r.) in acetonitrile solution in the presence of triethylsilane, trifluoroacetic acid\* and an iridium sensitiser was shown to afford iminium reduction product (–)-**77** in 29% yield and an e.r. of 96:4 (Scheme 95).

\* In a supplementary study performed by the present author, it was found that camphorsulfonic and aqueous tetrafluoroboric acids were also effective additives in a related reaction of *tert*-butyl sulfoxide **284** in which allyltrimethylsilane was used as the nucleophile, though the latter acid led to diminished enantioselectivities.



**Scheme 95.** Enantioselective visible-light-mediated cyclisation of **(+)-284** involving the loss of a sulfur-based leaving group developed by J.A.

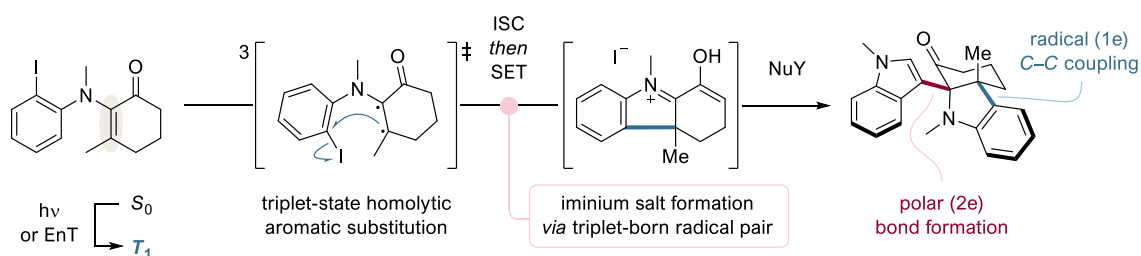
Successive rounds of reaction optimisation by the present author identified that a higher yield of 75% could be obtained for this reaction (without deterioration in the enantioselectivity of the overall process) by removing the iridium photocatalyst and making slight adjustments to the doses of acid and nucleophile (Scheme 96). One possible reason for the higher yield in the absence of  $\text{fac-Ir(dFppy)}_3$  is that the electron-rich amine product is prone to oxidative degradation under the action of the photocatalyst.



**Scheme 96.** Optimised reaction conditions for the enantioselective photocyclisation of **(+)-284**.

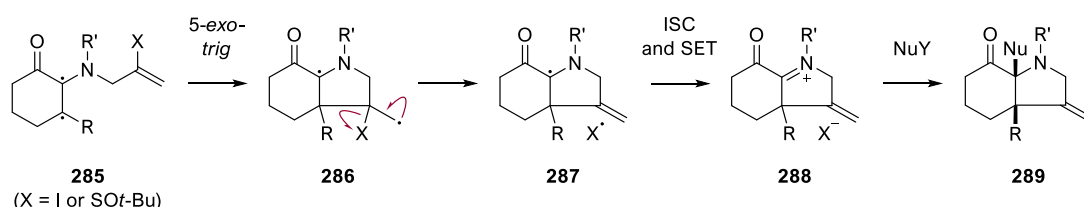
## Conclusions and future directions of radical–polar crossover work

We have discovered that certain *N*-(2-iodoaryl) enaminones undergo eliminative photocyclisation to form a stabilised iminium salt. This intermediate can be intercepted by a variety of two-electron nucleophiles in both an inter- and intramolecular fashion, enabling the assembly of complex molecular architectures, including the tetracyclic core of akuammiline natural products. Experimental mechanistic investigations indicate that the reaction proceeds *via* the regioselective cyclisation of an alkene triplet diradical rather than a mechanism involving the homolytic generation of an aryl radical. Quantum calculations performed by M.V.P. corroborate such a mechanism, suggesting that the key *ipso*-I cyclisation step is preferred to *ipso*-H cyclisation on the basis of its lower activation energy, occurring irreversibly without formation of a discrete radical  $\sigma$ -intermediate; single-electron transfer and intersystem crossing within the resulting radical pair leads to the primary iminium salt photoproduct, representing a transition from radical to ionic reactivity *via* the triplet state (Scheme 97). The intermediacy of an alkene diradical is significant as it enables an enantioselective variant of the reaction through the use of an *ortho*-sulfinyl substituent in place of iodine as a traceless chiral auxiliary.



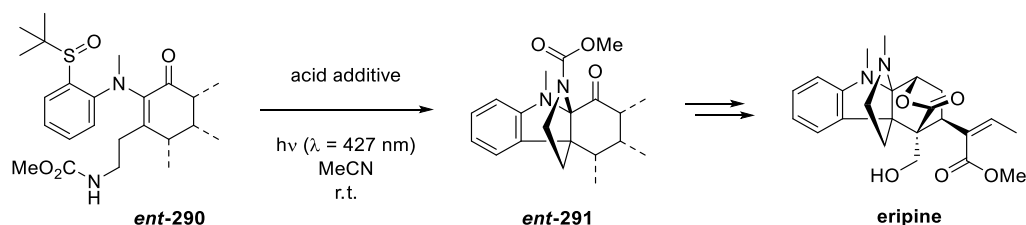
**Scheme 97.** A transition from diradical to ionic reactivity is enabled by a homolytic aromatic substitution mechanism.

Other triplet-state reactions incorporating radical–polar crossover events enabled by a homolytic aromatic (or vinylic) substitution mechanism should be explored in the future. It is possible, for example, that the course of certain [2+2]-photocycloadditions could be diverted from isomerisation through the elimination of a suitably placed leaving group (Scheme 98). In the presence of a sulfinyl group, this could provide a means for not only inducing radical–polar crossover but also controlling the absolute stereochemistry of the products.<sup>104</sup>



**Scheme 98.** Proposed future work exploring homolytic *vinylic* substitution leading to radical–polar crossover and/or S-to-C chirality transfer.

The eliminative photocyclisation of *ortho*-sulfinyl-substituted substrates could also be applied to the enantioselective synthesis of alkaloid natural products such as eripine (Scheme 99). This endeavour would probably require the development of new strategies for synthesising more highly decorated substrates (**290**) or for functionalising the tetracyclic core (**291**) following photocyclisation.



**Scheme 99.** Eliminative photocyclisation with chirality transfer from sulfur to carbon could enable an enantioselective synthesis of akuammiline natural products.

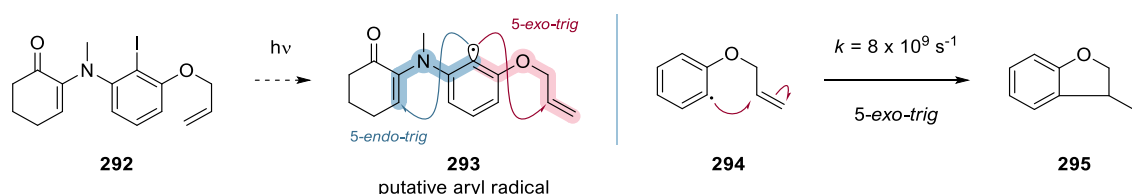




## Chapter 3 – A study on the cyclisation of aryl radicals

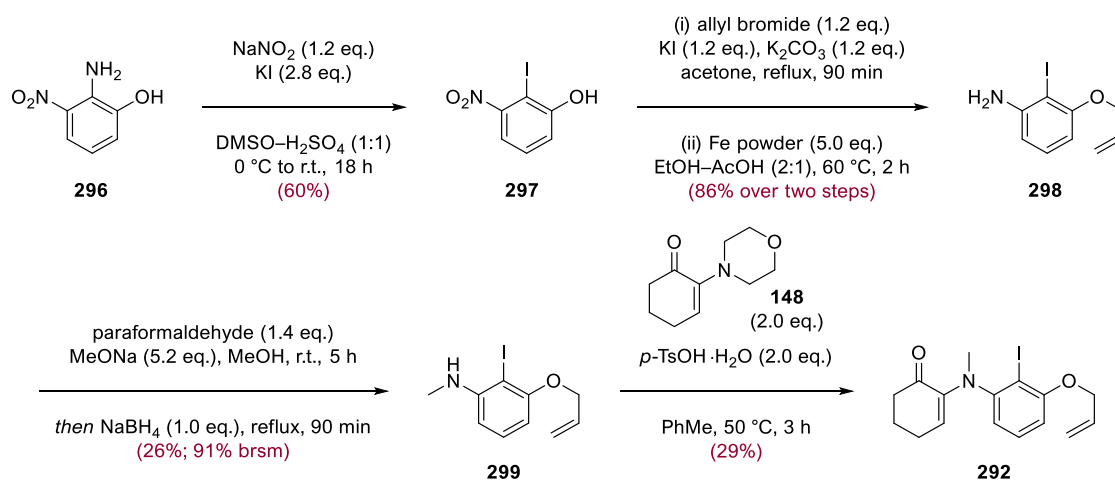
### Synthesis and photochemical reactivity of an *O*-allylated substrate, **292**

As part of our efforts to exclude an aryl radical-based mechanism for the reaction described in the previous chapter, we synthesised and studied the photochemical behaviour of a substrate, **292**, containing an aromatic *O*-allyl substituent (Scheme 100). As with the related *N*-allyl substrate, **266**, the pendent alkene functional group in **292** was intended to report on aryl radical generation by “trapping” the putative intermediate in a 5-*exo-trig* cyclisation. Related processes have been calibrated as radical clocks and are known to be extremely fast, with unimolecular rate constants in the order of  $10^9 \text{ s}^{-1}$ .<sup>105</sup>



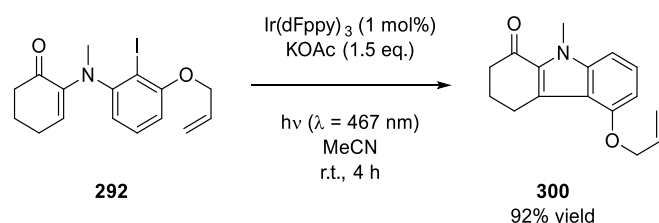
**Scheme 100.** The formation of 5-*exo-trig* cyclisation products arising from aryl radical **293** should indicate whether or not C–I bond homolysis occurs when *O*-allyl substrate **292** is photochemically excited.

Substrate **292** was synthesised from 2-amino-3-nitrophenol (**296**) in five steps (Scheme 101). Diazotisation–iodination of **296** using sodium nitrite and potassium iodide in an acidic reaction medium gave nitrophenol **297**, in 60% yield; this compound was transformed in 86% yield over two steps to aniline **298** by reaction with allyl bromide under Finkelstein conditions followed by an iron-mediated reduction of the nitro group. Transamination of morpholine enamine **148** with aniline **299**, formed in 26% yield (91% brsm) by the reductive amination of **298** with paraformaldehyde, then delivered *O*-allyl substrate in a moderate yield of 29%.



**Scheme 101.** Synthesis of an *O*-allylated substrate, **292**.

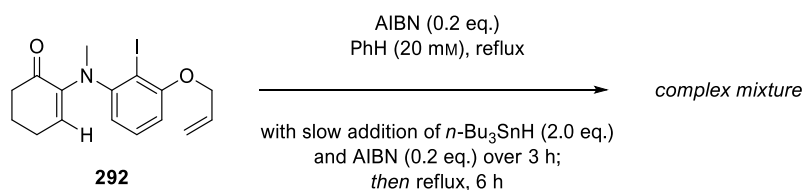
Irradiation of **292** in acetonitrile solution with 467 nm light in the presence of *fac*-Ir(dFppy)<sub>3</sub> and potassium acetate afforded indole **300** in 92% yield as a single regioisomer without side-product formation (Scheme 102). The absence of products arising from an aryl radical 5-*exo-trig* cyclisation is of particular note, being consistent with our earlier proposal that the photocyclisation of *N*-(2-iodoaryl) enaminones such as **292** proceeds *via* the cyclisation of an alkene triplet diradical.



**Scheme 102.** Radical clock experiment with O-allyl substrate **292**.

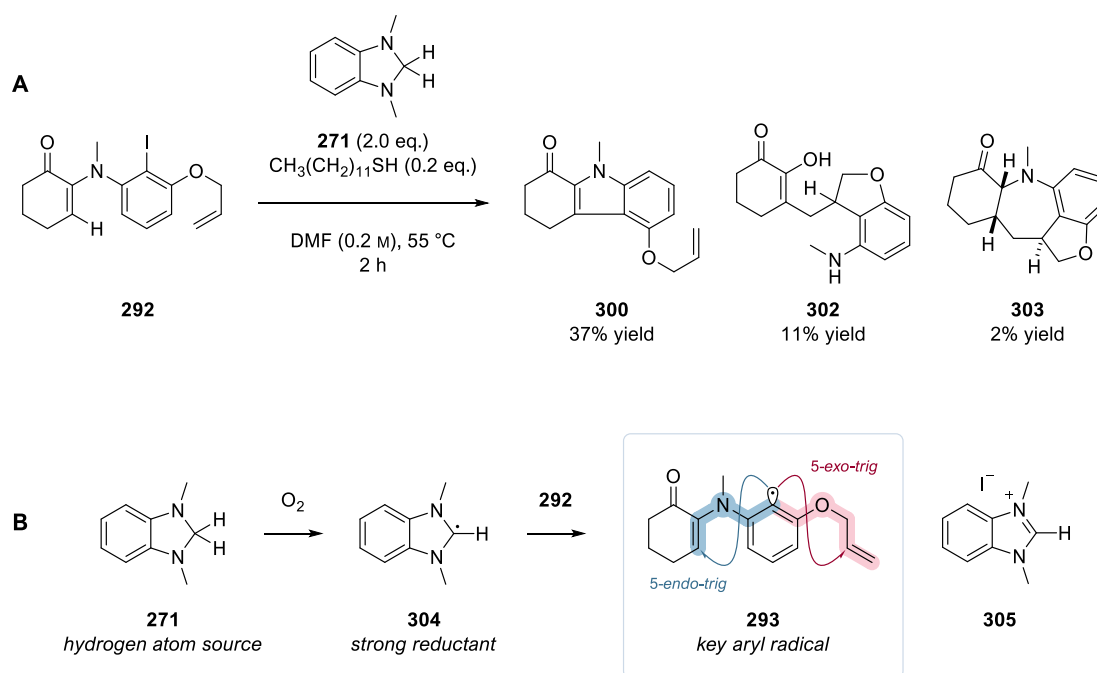
### Subjecting **292** to thermal conditions for aryl radical generation

As a control experiment, we sought to verify that the 5-*exo-trig* cyclisation under consideration was viable when the putative aryl radical was generated thermally. An initial attempt to induce a reductive cyclisation of **292** using tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile (AIBN) in dilute, refluxing benzene solution gave a complex mixture of products that were left uncharacterised (Scheme 103).



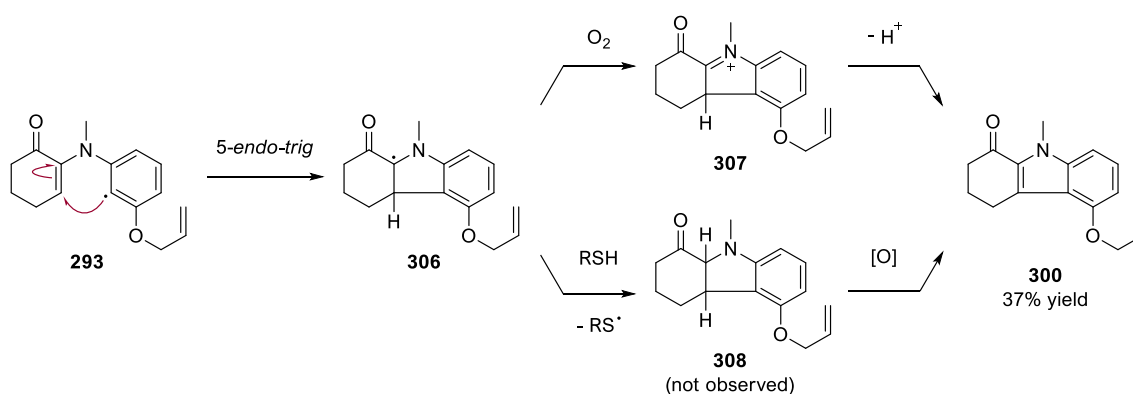
**Scheme 103.** Attempted cyclisation of O-allyl substrate **292** using tri-*n*-butyltin hydride as a hydrogen atom source and AIBN as initiator.

Heating **292** in the presence of dihydrobenzimidazole **271** and dodecanethiol at 55 °C in *N,N*-dimethylformamide gave a cleaner product distribution (Scheme 104A).<sup>94</sup> Indole **300** was formed as the major product in 37% yield under these conditions alongside two minor products: 1,2-diketone **302** in 11% yield and fused tetracycle **303** in 2% yield. An additional compound present in the crude product mixture could not be isolated despite extensive chromatographic efforts; this compound, however, was formed in only minor quantities. Non-specific degradation is therefore thought to account for the mass imbalance.



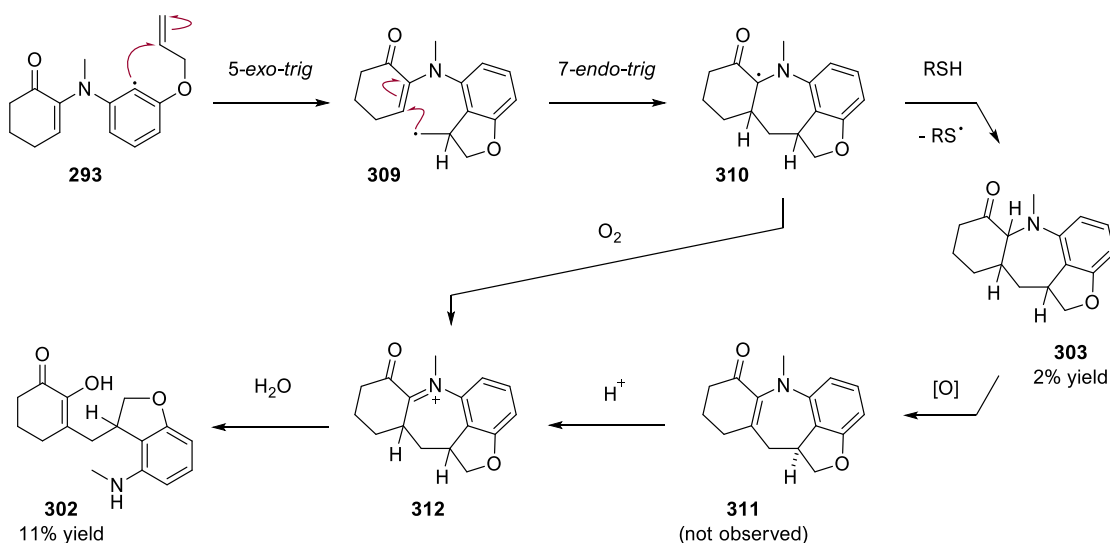
**Scheme 104. (A)** Subjecting **292** to thermal conditions for aryl radical generation led to a mixture of products, of which indole **300** was the major component. **(B)** Proposed mechanism for the generation of the putative key aryl radical intermediate, **293**, involving aerobic oxidation of dihydrobenzimidazole **271** and single-electron transfer between the resulting radical, **304**, and aryl iodide starting material, **292**.

All three products of the reductive cyclisation of **292** ostensibly arise from either the 5-*endo*- or 5-*exo-trig* cyclisation of aryl radical **293**, which is likely formed by single-electron reduction of the starting material by a radical species, **304**, derived from the dihydrobenzimidazole reagent (Scheme 104B). While less common than other cyclisation modes, 5-*endo-trig* radical cyclisations are well studied, particularly in the context of five-membered nitrogen heterocycle synthesis.<sup>106</sup> Indole **300** could form under the above conditions *via* an  $\alpha$ -amino radical, **306**, formed by such a process; direct oxidation of this intermediate followed by deprotonation of the resulting iminium cation (**307**) or hydrogen atom transfer from 1-dodecanethiol (or dihydrobenzimidazole **271**) followed by *in situ* oxidation of the resulting indoline product (**308**) would account for the formation of the formally oxidised indole product (Scheme 105).



**Scheme 105.** Possible mechanisms for the formation of **300** via a 5-endo-trig cyclisation of aryl radical **293**.

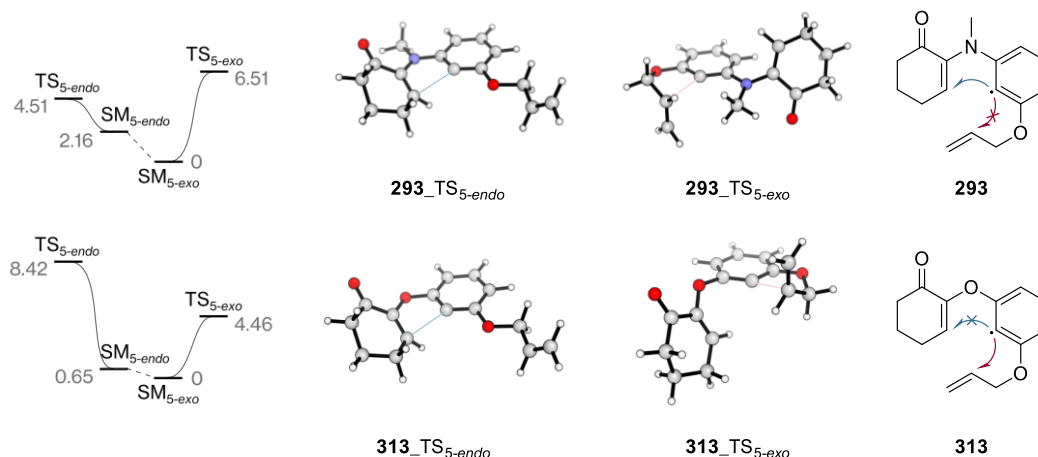
Mechanisms for the formation of **302** and **303** in the reductive cyclisation of aryl iodide **292** are proposed in Scheme 106. Both proceed via a 5-exo-trig/7-endo-trig cascade cyclisation of aryl radical **293**, generating  $\alpha$ -amino radical **310**. Reduction of this intermediate by the thiol reagent would lead to tetracycle **303**, isolated in 2% yield, while two reaction sequences from **310** could account for the formation of **302** in 11% yield: either tetracycle **303** is oxidised *in situ*, forming enaminone **311**, which then undergoes hydrolysis upon protonation via iminium cation **312**; or, the latter intermediate is formed by direct oxidation of  $\alpha$ -amino radical **310**. (Interestingly, no products arising from the reduction of radical intermediate **309** were observed/isolated.)



**Scheme 106.** Possible mechanisms for the formation of **302** and **303** from aryl radical **293** in the presence of oxygen and a thiol reductant.

The formation of 5-exo-trig cyclisation products **302** and **303** when **292** was reduced using dihydrobenzimidazole **271** validates our hypothesis that an aryl radical was *not* formed upon sensitised irradiation of the same compound with visible light; that is, the former, thermally induced reaction of **292** serves as positive control for the latter radical clock experiment performed under photochemical conditions.

While Baldwin's rules<sup>107,108</sup> chiefly describe the expected *regiochemical* outcomes of intramolecular addition reactions (for instance, predicting that the 4-*exo-trig* cyclisation of a given radical is generally preferable to 5-*endo-trig* cyclisation onto *the same functional group*), it is noteworthy that a formally disfavoured cyclisation mode (that is, a 5-*endo-trig* cyclisation) appears in the case of aryl radical **293** to outcompete an alternative 5-*exo-trig* pathway (which is known in related systems to be extremely fast). DFT calculations (B3LYP/6-31G) performed by M.V.P. confirm that the 5-*endo-trig* cyclisation of aryl radical **293** formed by single-electron reduction of *O*-allyl substrate **292** is indeed kinetically favoured under Curtin–Hammett control (Figure 11A). It is hypothesised that a thermodynamic factor contributes to the lower 5-*endo-trig* barrier: the captodative radical resulting from 5-*endo-trig* cyclisation would be substantially more stable than the primary alkyl radical generated by 5-*exo-trig* cyclisation, leading to an earlier transition state for the former process.<sup>109</sup> Moreover, it is possible that the 5-*exo-trig* cyclisation transition state (**293**\_TS<sub>5-*exo*</sub>) is destabilised by a steric clash between the *O*-allyl radical acceptor and adjacent *N*-methyl group. Modelling of a related substrate in which the *N*-methyl linker of **292** has been replaced by an oxygen atom revealed that the cyclisation selectivity should be reversed in this system, with the 5-*exo-trig* cyclisation of aryl radical **313** being favoured by *ca.* 4.0 kcal mol<sup>-1</sup>; this difference could reflect either relief of strain in the 5-*exo-trig* transition state or a less stable 5-*endo-trig* radical cyclisation product.

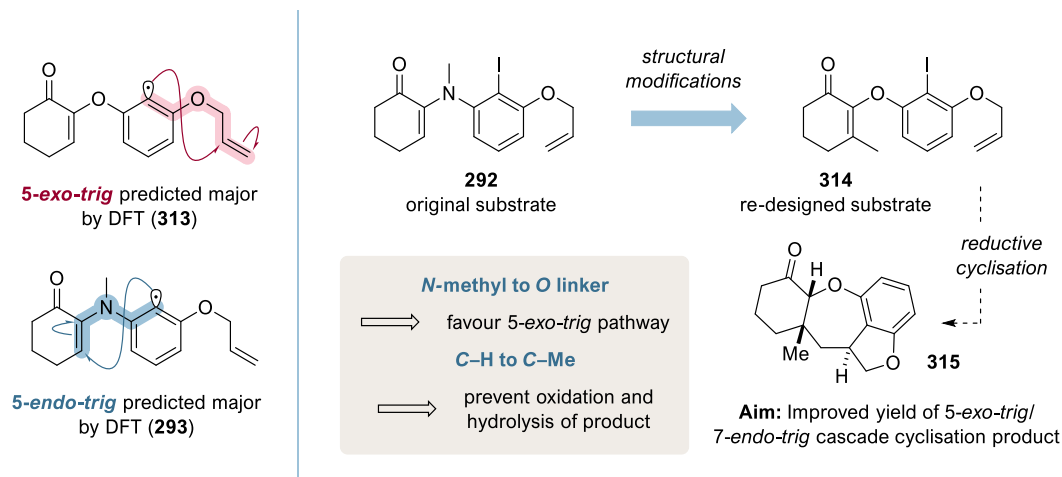


**Figure 11.** DFT modelling by M.V.P. suggests that the 5-*endo-trig* selectivity observed for aryl radical **293** should be reversed in its oxygen-bridged analogue **313**.

### Development of a novel aryl radical cascade cyclisation

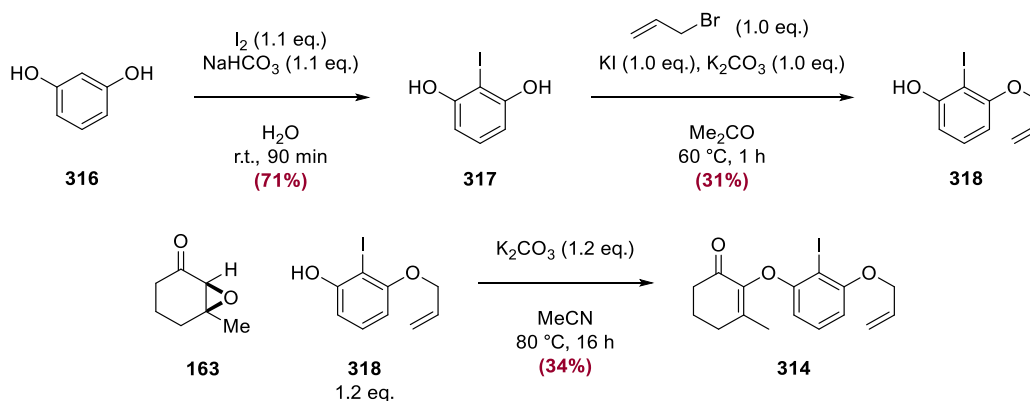
We were intrigued by the structural features of tetracycle **303**, isolated in a very low yield of 2% from the reduction of **292**, that appears to arise from an aryl radical 5-*exo-trig*/7-*endo-trig* cascade cyclisation. We sought to improve the efficiency of this process, initially by modifying the structure of the aryl iodide starting material (Figure 12). Considering the results of DFT modelling described above, it was hypothesised that replacing the original *N*-methyl linker with an oxygen atom would

promote the initial 5-*exo-trig* cyclisation step. It was also thought that introducing a methyl substituent at the enone  $\beta$ -position might avoid *in situ* oxidation (leading to hydrolytic ring-opening) of the 7-membered cyclic product, which had been postulated to occur with the original *N*-linked substrate, **292**. Thus, 2-aryloxycyclohexeneone **314** was targeted for synthesis.



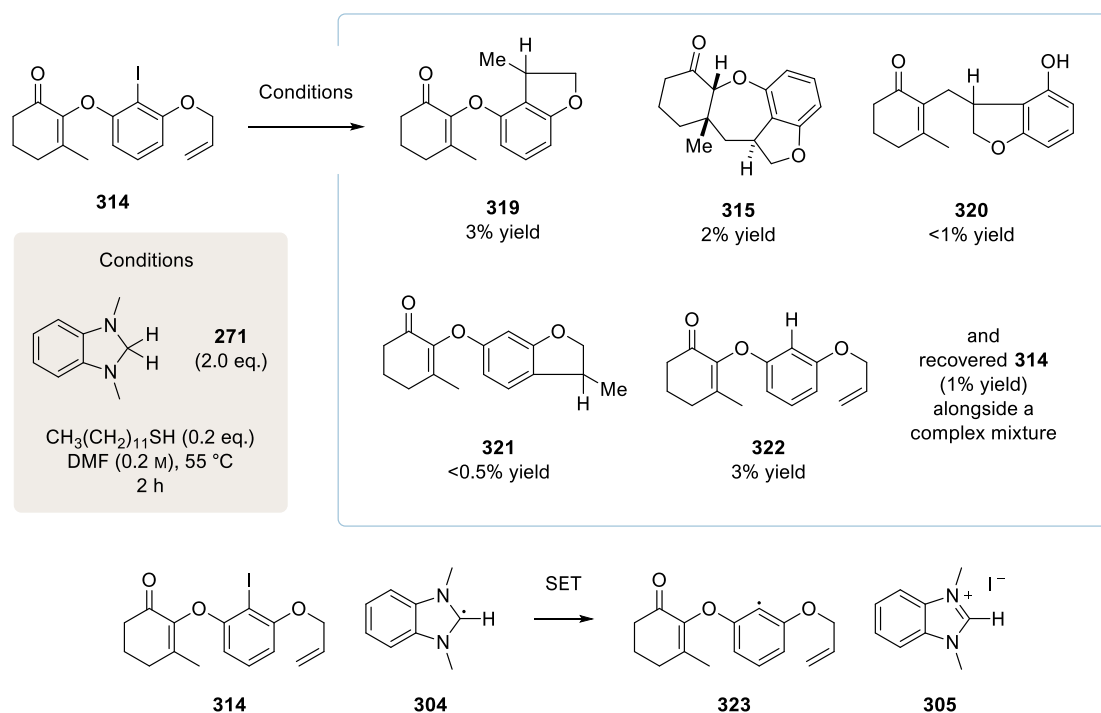
**Figure 12.** Design of a radical cascade cyclisation precursor, **314**, guided by DFT studies performed by M.V.P.

Reaction of phenol **318**, obtained in 71% yield over two steps from resorcinol (**316**), with 2,3-epoxycyclohexanone (**163**) under basic conditions delivered the target compound, **314**, in 34% yield (Scheme 107).



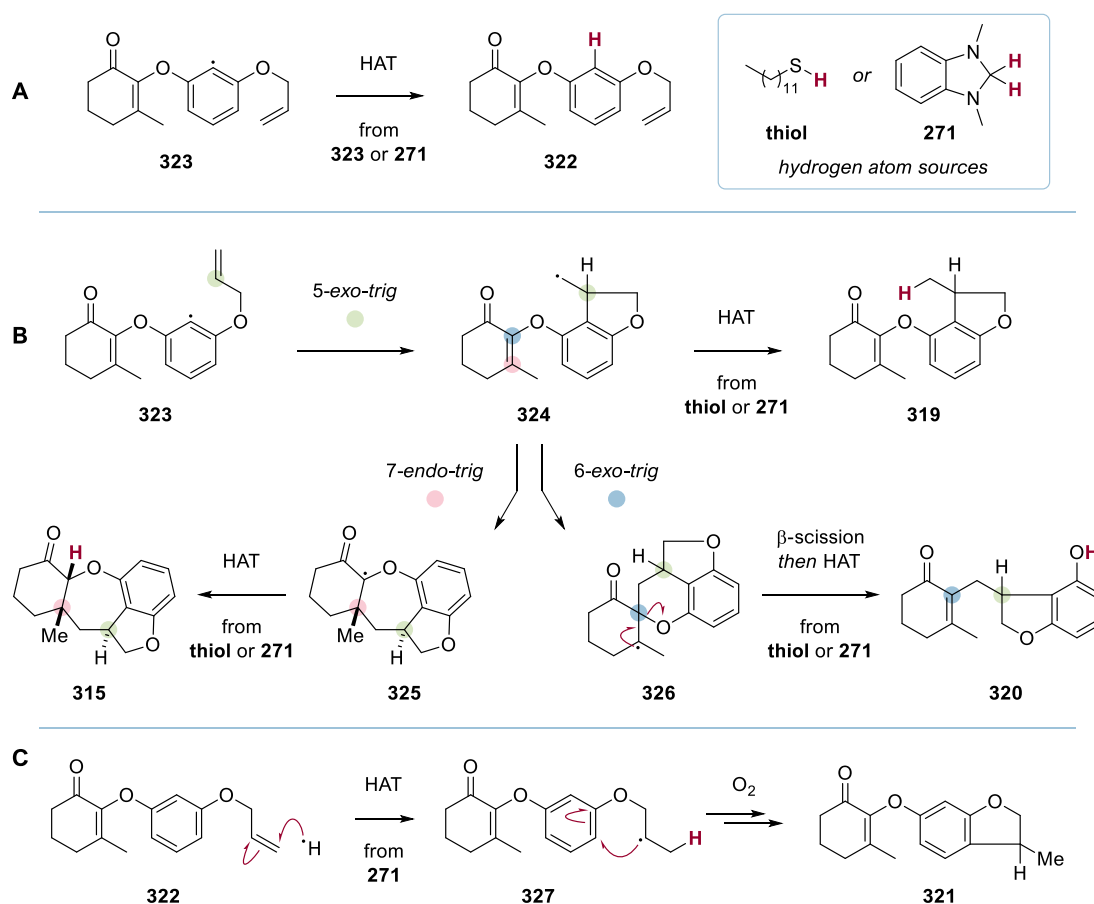
**Scheme 107.** Synthesis of an O-linked analogue, **314**, of the original radical clock substrate bearing a methyl substituent at the enone  $\beta$ -position.

Subjecting 2-aryloxycyclohexenone **314** to Murphy's reductive cyclisation conditions led to a complex mixture of products, from which five compounds arising from a common aryl radical intermediate, **313**, could be isolated in low yields (Scheme 108).



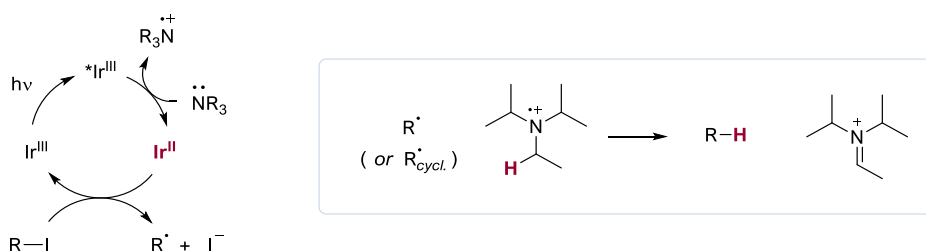
**Scheme 108.** Subjecting 2-aryloxycyclohexenone **314** to Murphy's reductive cyclization conditions led to a complex mixture, from which several 5-*exo-trig* cyclization products could be isolated in low yields. All yields correspond to isolated yields of TLC-purified products. The presumed mechanism for the formation of the key aryl radical intermediate, **323**, involves SET between aryl iodide **314** and radical **304** followed by mesolytic cleavage of the C–I bond.

Hydrodehalogenated starting material **321** presumably arises under these conditions from hydrogen atom transfer from 1-dodecanethiol ('thiol') or the dihydrobenzimidazole **271** to aryl radical **323** (Scheme 109A). Compounds **315**, **319** and **320**, on the other hand, arise from 5-*exo-trig* cyclisation of the same radical intermediate; reduction of the initially formed primary alkyl radical **324** by **323.5** or **271** delivers dihydrobenzofuran **319**, while 7-*endo-trig* or 6-*exo-trig* cyclisation of **324** followed by hydrogen atom transfer leads to **315** or **320**, respectively, *via* an intervening  $\beta$ -scission event for the latter compound (Scheme 109B). The mechanism by which **321** forms is less clear but possibly involves the oxidative cyclisation of a secondary alkyl radical, **327**, formed by the (formal) addition of a hydrogen radical to the alkene functional group in **322** (Scheme 109C).



**Scheme 109.** Proposed mechanisms for the formation of **315**, **319**, **321** and **322** during the reaction of 2-aryloxycyclohexenone **314** and super electron donor **271** in the presence of dodecanethiol ('thiol').

In light of the very low isolated yields obtained in the above reaction, we sought milder conditions for generating the key aryl radical intermediate that might lead to a cleaner product distribution. Conditions for the photocatalytic reduction (or reductive cyclisation) of organyl iodides reported Kim *et al.* seemed applicable to our system.<sup>110</sup> The proposed mechanism of this transformation involves reductive quenching of an excited iridium(III) complex to generate an iridium(II) species capable of reducing the iodine-containing compound; hydrogen atom transfer between the free radical (or some cyclised derivative of this species) and amine radical cation resulting from these electron transfer processes then delivers the final product (Scheme 110).



**Scheme 110.** Mechanism reported by Kim *et al.* for the photocatalytic reduction (or reductive cyclisation) of organyl iodides.



Gratifyingly, the optimal conditions developed by Kim *et al.* were effective in generating the desired tetracyclic product, **315**, from **314** in an NMR yield of 51% yield on a 0.1 mmol scale; this was accompanied by the formation of **322**, presumably arising from premature reduction of the aryl radical intermediate, in an undetermined amount (Table 8, entry 1). (A control experiment performed in the absence of photocatalyst and reductive quencher led to recovery of starting material.) An attempt to minimise the formation of this side-product by decreasing the reaction concentration, [**314**], from 0.05 M to 0.02 M was unsuccessful, leading to a dramatically lower yield (17%) of the desired product (entry 2). Lowering the dose of reductive quencher to 2.0 equivalents led to an improvement in the yield of **315** to 64% (entry 3); a cleaner product distribution was also obtained, enabling the determination of the yield of side product (12% against dimethyl terephthalate). Performing the reaction at a higher concentration (0.1 M) with 2.0 equivalents of amine caused the yield of **315** to decrease and the yield of side-product to increase (entry 4). The conditions described in entry 3 were therefore repeated on a larger scale (entry 4); the major product, **315**, of this reaction was isolated in 56% yield (63% brsm), with single-crystal X-ray diffraction studies confirming the formation of the *syn,anti*-diastereomer shown (Figure 13).

**Table 8.** Reductive cyclisation of 2-aryloxycyclohexenone **314** under photoredox catalysis.

Entry	<i>x</i> / eq.	<i>y</i> / M	Yield of <b>315</b> / %	Yield of <b>322</b> / %
1 <sup>a</sup>	10	0.05	51	- <sup>b</sup>
2 <sup>a</sup>	10	0.02	17	- <sup>b</sup>
3 <sup>a</sup>	2	0.05	64	12
4 <sup>a</sup>	2	0.10	56	24
5 <sup>c</sup>	2	0.05	55% (63% <sup>d</sup> )	- <sup>e</sup>

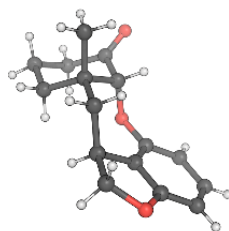
<sup>a</sup> Reaction performed on a 0.1 mmol scale. Yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.).

<sup>b</sup> Not determined. Signal overlap made accurate integration of <sup>1</sup>H resonances corresponding to this compound impossible.

<sup>c</sup> Reaction performed on a 0.3 mmol scale. Yields correspond to isolated material.

<sup>d</sup> Yield based on recovered starting material.

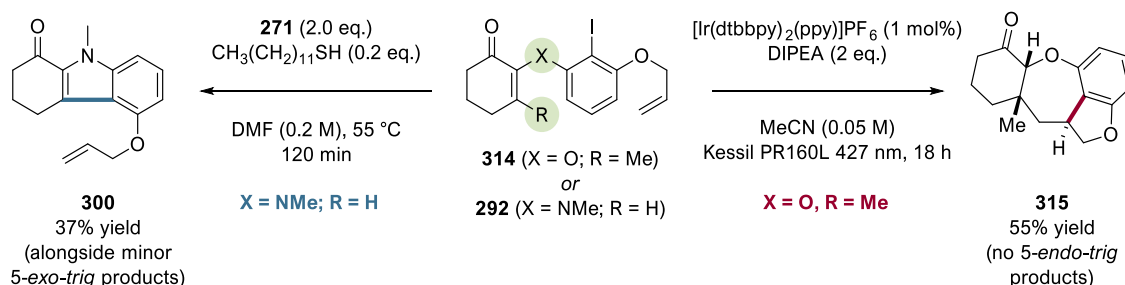
<sup>e</sup> **322** was present in the crude product mixture; a solution of this material was isolated but spilled prior to yield determination.



**Figure 13.** Single-crystal X-ray structure of tetracycle **315**.

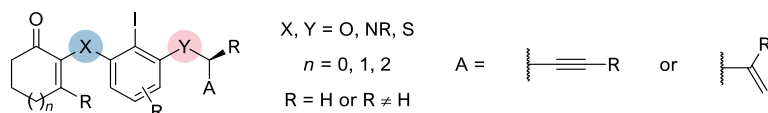
## Conclusions and future directions of aryl radical work

We have shown that two structurally related aryl iodide starting materials cyclise to skeletally distinct heterocyclic products under conditions for aryl halide reduction (Scheme 111). The aryl radical formed upon single-electron reduction of *N*-methyl-containing compound **292** with a neutral organic super electron donor undergoes a formally Baldwin-disfavoured *5-endo-trig* cyclisation in preference to (though not to the exclusion of) an alternative *5-exo-trig* process involving the pendent *O*-allyl group. Subjecting an analogous substrate, **314**, containing an oxygen bridging atom in place of the *N*-methyl linker in **292** to the same reaction conditions led to the formation of a complex mixture of products, from which tetracycle **315** (thought to arise from a cascade process involving an initial aryl radical *5-exo-trig* cyclisation) could be isolated in very low yield. Photocatalytic conditions for aryl halide reduction gave a considerably higher yield (55%, 63% brsm) of the same product without detection of aryl radical *5-endo-trig* cyclisation products.



**Scheme 111.** Summary of aryl radical clock experiments.

Future work should explore the scope of this radical cascade cyclisation with respect to the pendent radical acceptor and other substrate modifications (Figure 14), and potentially apply the complex,  $\text{C}(\text{sp}^3)$ -rich heterocyclic products to probe compound development.



**Figure 14.** Proposed future work exploring the scope of the radical cascade cyclisation with respect to substrate modifications.

## Chapter 4 – Experimental details

### General information

#### Compound names and atom numbers

Systematic names for all compounds were generated in ChemDraw Professional (version 22); the atom-numbering scheme used for NMR assignment is *arbitrary* and does not follow any particular convention. Compounds not explicitly described in Chapters 2 and 3 are given numbers prefixed by the letter 'S' here.

#### Solvents, reagents and light sources

Anhydrous acetonitrile, tetrahydrofuran and 1,4-dioxane were obtained using an MBraun SPS-5 solvent purifier. Water was purified using a PURELAB Chorus 1 Complete system. Other solvents and reagents were used directly as received from commercial suppliers or prepared according to literature procedures as specified.

A reactor consisting of 12 W blue LED strips wrapped around the inside of a 260 x 160 mm metal tin was used for several photoreactions. The internal temperature of the reactor (*ca.* 60 °C after equilibration) was monitored using a glass thermometer. Reactions conducted in this photoreactor were performed in glass screw-capped vials placed 3 cm away from the lights and stirred magnetically. Irradiation was otherwise achieved using Kessil® PR160L 427 nm or PR160 467 nm LED lamps.

#### Chromatography

Flash column chromatography was performed on Geduran Si 60 for column chromatography (40-63 µm particle size) or Millipore Aluminium oxide 90 standardised for column chromatographic adsorption analysis according to Brockmann (basic, activity stage I).

Thin-layer chromatography was performed on Supelco TLC Silica gel 60 F<sub>254</sub> or Alugram Alox N / UV<sub>254</sub> pre-coated (0.2 mm) aluminium plates. Visualisation was achieved under ultraviolet (UV) light ( $\lambda_{\text{max}} = 254 \text{ nm}$ ) or by staining with aqueous potassium permanganate or ethanolic vanillin solutions.

Chiral HPLC was performed on a Dionex Ultimate 3000 system comprising a Dionex LPG-3400SD pump, WPS-3000SL autosampler, TCC-3000SD column compartment fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm  $\phi$  x 25 cm) and corresponding guard column (0.4 cm  $\phi$  x 1 cm), and a DAD-3000 diode array detector. Reverse-phase HPLC was performed using an Agilent InfinityLab Poroshell 120 EC-C18 column (dimensions: 0.3 cm  $\phi$  x 10 cm) on an otherwise identical system. Wavelengths ( $\lambda$ ) are reported in nm, retention times ( $\tau_R$ ) in minutes (min), temperatures (T) in °C, and solvent flow rates in mL min<sup>-1</sup>.

## Nuclear magnetic resonance spectroscopy

Unless otherwise stated, nuclear magnetic resonance (NMR) spectra were acquired at 298 K on Bruker Avance spectrometers and referenced to residual non-deuterated solvent signals. Mnova (version 14) or TopSpin (version 4) was used for processing and viewing NMR data. Chemical shifts ( $\delta$ ) are quoted in parts per million (ppm) and coupling constants ( $J$ ) in Hertz (Hz).  $^1\text{H}$  NMR spectra are reported as follows:  $\delta$  / ppm (number of protons, multiplicity, coupling constant  $J$  / Hz [where appropriate], atom assignment). Multiplicity is abbreviated as follows: s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet. Where signals are not fully resolved but two-dimensional experiments unambiguously identify the regions of multiplet corresponding to particular hydrogens, this is indicated with a subscript denoting the portion of the multiplet. For example,  $\text{H3}_{\text{RHS}}$  would indicate that the right-hand side of the multiplet corresponds to H3.  $^{13}\text{C}$  NMR spectra are reported as follows:  $\delta$  / ppm (atom assignment). Two-dimensional (e.g. COSY, HSQC, HMBC and NOESY) experiments were used to assign  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all novel compounds. Where  $^1\text{H}$  signals overlap, the number of protons quoted for a given spectral range was determined through multiplicity-edited HSQC analysis; similarly, coincident  $^{13}\text{C}$  signals were identified through HSQC and HMBC correlations.

## Infrared spectroscopy

Fourier transform infrared (FTIR) spectra were recorded as thin films on a Tensor 27 FTIR spectrometer equipped with a diamond attenuated total reflectance (ATR) absorption module. Only selected maximum absorbances ( $\nu_{\text{max}}$ ) of the most intense peaks are reported ( $\text{cm}^{-1}$ ).

## High-resolution mass spectrometry

High-resolution mass spectrometry (HRMS) was performed on Bruker MicroTOF or Waters Micromass GCT / BioAccord instruments under electrospray ionisation (ESI) or atmospheric-pressure chemical ionisation (APCI) conditions.

## Melting points

Melting points (MP) were determined using a Reichert melting point apparatus and are uncorrected.

## Polarimetry

Optical rotations were measured at the sodium D-line (589 nm) using a SCHMIDT+HAENSCH UniPol 2020 polarimeter containing a cell of path length,  $l$ , 1 dm at 25 °C. Specific rotations are reported in degrees for concentrations ( $c$ ) in  $\text{g } 100 \text{ mL}^{-1}$ ; the calculation thus includes a correction factor of 100. Reported values are the average of eight readings.

## Absorption spectroscopy

Absorption spectra were acquired at 298 K using an Agilent Cary 60 UV–vis spectrophotometer.

## Emission spectroscopy

Emission spectra were acquired at 298 K using an Edinburgh Instruments FS5 spectrofluorometer equipped with a xenon arc lamp (providing an excitation range of 230–1000 nm), a thermostatic sample holder (SC-20) and an R13456 PMT detector (200–950 nm spectral coverage, Hamamatsu), operating Fluoracle® software.

## Crystallography

Single-crystal X-ray diffraction studies were conducted by Owen A. Smith or by the Oxford Chemical Crystallography Service on a (Rigaku) Oxford Diffraction/Agilent Supernovae A diffractometer (Cu-K $\alpha$  radiation,  $\lambda = 1.54184$  Å) equipped with a graphite monochromator, within the Department of Chemistry at the University of Oxford. Samples were mounted in perfluoropoly-ethyl ether oil and cooled to 150 K during the data collection process by a Crysostream<sup>111</sup> N<sub>2</sub> open-flow cooling device. The raw frame data was integrated and reduced using CrysalisPro. CRYSTALS<sup>112,113</sup> was used to obtain an *ab initio* solution using SuperFlip<sup>114</sup> embedded within CRYSTALS and for structure refinement.

## Details of aryl radical computational modelling (Chapter 3)

Density functional theory (DFT) calculations were performed by Mihai Viorel Popescu (M.V.P.).

The hybrid density functional B3LYP<sup>115</sup> was used in combination with the 6-31G<sup>116–121</sup> basis set to optimize the geometries of all stationary points. Vibrational frequency calculations were performed to verify that stationary points were either minima or first-order saddle points on the potential energy surface, and to calculate thermal corrections to Gibbs free energies at 298.15 K (25 °C).

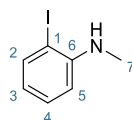
In order to calculate Gibbs free energies of the different reaction steps along the pathways, a correction for the change in standard state from gas phase at 1 atm to a 1 M solution was applied to all the individual calculations. Furthermore, in all the individual calculations, quasi-harmonic (QHA) vibrational corrections were applied to entropies using a frequency cut-off value of 100.0 cm<sup>-1</sup>, as proposed by Grimme.<sup>122</sup> These thermodynamic corrections were calculated and automatically applied using GoodVibes.<sup>123</sup>

Gaussian 09 A.02<sup>124</sup> was used for geometry optimizations, while PyMol<sup>125</sup> was used to create molecular graphics.

A radical–polar crossover approach to complex nitrogen heterocycles via the triplet state (Chapter 2)

Synthesis of  $\beta$ -hydrogen, *ortho*-iodinated substrates **149** and **150**

2-Iodo-*N*-methylaniline, **146**



*n*-Butyllithium in hexanes (8.8 mL, 2.5 M, 22 mmol, 1.1 eq.) was added over 30 min *via* syringe pump to a stirred, -78 °C solution of 2-iodoaniline (4.38 g, 20.0 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (40 mL, 0.5 M) under an argon atmosphere. Methyl iodide (1.4 mL, 3.2 g, 22 mmol, 1.1 eq.) was added in one portion after complete addition of the organometallic reagent. After a further 5 min at -78 °C, the acetone–dry ice bath was replaced with a tepid water bath, and the reaction mixture was allowed to warm to room temperature over a period of 2 h. Ammonium chloride solution (sat. aq., 40 mL) was added, followed by diethyl ether (40 mL). The layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 40 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10% dichloromethane in pentane) to afford **146** (3.26 g, 14.0 mmol, 70%) as a pale-yellow oil. The spectral data matched that previously reported in the literature.<sup>126</sup>

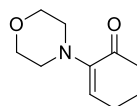
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.67 (1H, dt, *J* 7.8, 1.4, H2), 7.30–7.21 (1H, m, H4), 6.57 (1H, dd, *J* 8.2, 1.5, H5), 6.51–6.42 (1H, m, H3), 4.21 (1H, br s, NH), 2.89 (3H, d, *J* 5.1, H7).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 148.3 (C6), 139.0 (C2), 129.6 (C4), 118.6 (C3), 110.1 (C5), 85.3 (C1), 31.1 (C7).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3406 (br), 1593, 1510, 1456, 1316, 1169, 1073, 1005, 743, 648.

HRMS (ESI)  $m/z$  calcd. for C<sub>7</sub>H<sub>9</sub>IN [M+H]<sup>+</sup>: 233.9774; found: 233.9771.

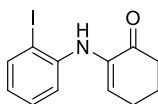
2-Morpholinocyclohex-2-en-1-one, **148**



This compound was prepared according to a literature procedure.<sup>127</sup> A mixture of cyclohexane-1,2-dione (2.24 g, 20.0 mmol, 1.0 eq.) and morpholine (2.2 mL, 2.2 g, 25 mmol, 1.3 eq.) in toluene (50 mL, 0.4 M) were heated to reflux under Dean–Stark conditions for 12 h. After cooling to room temperature, the orange liquid thus obtained was decanted from the viscous brown



2-(phenylamino)cyclohex-2-en-1-one, **150**



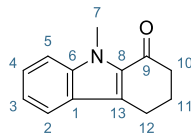
This compound was prepared according to a literature procedure.<sup>57</sup> 2-Iodoaniline (**147**) (437 mg, 2.00 mmol, 1.0 eq.), morpholine enamine **148** (362 mg, 2.00 mmol, 1.0 eq.) and *para*-toluenesulfonic acid monohydrate (380 mg, 2.00 mmol, 1.0 eq.) were heated to 50 °C in toluene (10 mL, 0.2 M) for 3 h. The reaction was cooled to room temperature and diluted with ethyl acetate (20 mL). The solution was washed with sodium hydrogencarbonate (sat. aq., 3 x 10 mL) followed by brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 5 to 10% diethyl ether in pentane) to afford **150** (585 mg, 1.87 mmol, 94%) as a white solid. The spectral data matched that previously reported in the literature.<sup>57</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.79 (1H, dd, *J* 7.9, 1.4), 7.24 (1H, ddd, *J* 8.2, 6.8, 1.3), 7.21 (1H, dd, *J* 8.2, 2.0), 6.65 (1H, ddd, *J* 7.9, 3.7, 2.0), 6.55 (1H, br s), 6.35 (1H, t, *J* 4.8), 2.59 (2H, dd, *J* 7.2, 6.1), 2.48–2.43 (2H, m), 2.08–2.00 (2H, m).



## Photochemical reactivity of $\beta$ -hydrogen, *ortho*-iodinated substrate **149**

### 9-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one, **151**



*Procedure for a reaction performed in the presence of photocatalyst using a blue LED strip (initial discovery):*

Enaminone **149** (60 mg, 0.18 mmol, 1.0 eq.), *fac*-Ir(dFppy)<sub>3</sub> (1.4 mg, 1.8  $\mu$ mol, 1 mol%) and potassium acetate (18 mg, 0.18 mmol, 1.0 eq.) were charged to a 7 mL screw-capped glass vial equipped with a magnetic stir bar. The vial was sealed with a septum and then evacuated and back-filled with argon three times. Argon-sparged acetonitrile (3.7 mL, 0.05 M) was added *via* syringe to the vial, and the septum was replaced with a screw cap under an atmosphere of argon. The vial was placed *ca.* 3 cm from the LED strip in the photoreactor described above, and the reaction mixture was stirred under constant irradiation with blue light for 16 h. The reaction mixture was concentrated *in vacuo*, and the crude residue was loaded directly onto silica gel and purified by flash column chromatography (silica gel, gradient elution 10 to 20% diethyl ether in pentane) to afford indole **151** (31 mg, 0.16 mmol, 85%) as an off-white solid.

*Procedure for a reaction performed without photocatalyst using 427 nm light:*

Enaminone **149** (98.2 mg, 0.300 mmol, 1.0 eq.) and potassium acetate (44.2 mg, 0.450 mmol, 1.5 eq.) were dissolved in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with two Kessil PR160L 427 nm LED lamps (each positioned *ca.* 3 cm from the flask and directed toward it) for 2 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in pentane) to afford indole **151** (55.3 mg, 0.278 mmol, 92%) as an off-white solid.

The spectral data matched that previously reported in the literature.<sup>129</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.66 (1H, dt, *J* 8.1, 1.0, H2), 7.41 (1H, ddd, *J* 8.0, 6.7, 1.1, H4), 7.35 (1H, dt, *J* 8.6, 1.0, H5), 7.15 (1H, ddd, *J* 8.0, 6.8, 1.1, H3), 4.08 (3H, s, H7), 3.02 (2H, t, *J* 6.1, H12), 2.65 (2H, dd, *J* 7.2, 5.7, H10), 2.22 (2H, quint, *J* 6.2, H11).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 192.4 (C9), 139.8 (C6), 130.6 (C8), 129.3 (C13), 126.8 (C4), 124.8 (C1), 121.4 (C2), 120.1 (C3), 110.4 (C5), 40.1 (C10), 31.6 (C7), 24.9 (C11), 22.0 (C12).

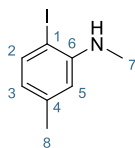
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1656, 1532, 1472, 1432, 1381, 1233, 1188, 1079, 934, 744.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{14}\text{ON}$   $[\text{M}+\text{H}]^+$ : 200.10699; found: 200.10708.

MP 93–94 °C.

## Synthesis and photochemical reactivity of 5-methyl substrate **153**

### 2-Iodo-*N*,5-dimethylaniline, **328**



*n*-Butyllithium in hexanes (7.0 mL, 1.6 M, 11 mmol, 1.1 eq.) was added over 30 min *via* syringe pump to a stirred, -78 °C solution of 2-iodo-5-methylaniline (2.33 g, 10.0 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (20 mL, 0.5 M) under an argon atmosphere. Methyl iodide (0.68 mL, 1.6 g, 11 mmol, 1.1 eq.) was added in one portion after complete addition of the organometallic reagent. After a further 5 min at -78 °C, the acetone–dry ice bath was replaced with a tepid water bath, and the reaction mixture was allowed to warm to room temperature over a period of 2 h. Ammonium chloride solution (sat. aq., 20 mL) was added, followed by diethyl ether (20 mL). The layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10% dichloromethane in pentane) to afford **328** (1.37 g, 5.54 mmol, 55%) as an off-white solid. The spectral data matched that previously reported in the literature.<sup>130</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.52 (1H, d, *J* 7.9, H2), 6.40 (1H, d, *J* 2.0, H5), 6.31 (1H, dd, *J* 8.0, 2.0, H3), 4.16 (1H, br s, NH), 2.89 (3H, s, H7), 2.30 (3H, s, H8).

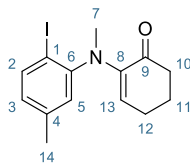
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 148.1 (C6), 139.7 (C4), 138.6 (C2), 119.7 (C3), 111.1 (C5), 81.4 (C1), 31.1 (C7), 21.6 (C8).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3406 (br), 1592, 1576, 1509, 1404, 1304, 1188, 1004, 839, 789.

HRMS (ESI) *m/z* calcd. for C<sub>8</sub>H<sub>11</sub>IN [M+H]<sup>+</sup>: 247.9931; found: 247.9927.

MP 44–45 °C.

### 2-((2-Iodo-5-methylphenyl)(methyl)amino)cyclohex-2-en-1-one, **153**



Aniline **328** (618 mg, 2.50 mmol, 1.0 eq.), morpholine enamine **148** (453 mg, 2.50 mmol, 1.0 eq.) and *para*-toluenesulfonic acid monohydrate (476 mg, 2.50 mmol, 1.0 eq.) were heated to 50 °C in

toluene (12.5 mL, 0.2 M) for 3 h. The reaction was cooled to room temperature and diluted with ethyl acetate (25 mL). The solution was washed with sodium hydrogencarbonate (sat. aq., 3 x 12.5 mL) followed by brine (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on alumina gel (gradient elution from 5 to 10% ethyl acetate in pentane) to afford **153** (379 mg, 1.11 mmol, 44%) as a viscous yellow oil, which turned over slowly upon storage at -18 °C to a buff solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.68 (1H, d, *J* 8.0, H2), 6.77 (1H, dd, *J* 2.1, 0.8, H5), 6.62 (1H, ddd, *J* 8.1, 2.1, 0.8, H3), 6.01 (1H, t, *J* 4.6, H13), 2.91 (3H, s, H7), 2.51–2.40 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.25 (3H, s, H14), 2.07–1.96 (2H, m, H11).

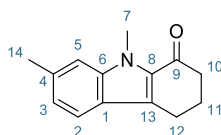
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 195.6 (C9), 151.6 (C6), 145.3 (C8), 139.9 (C2), 139.1 (C4), 128.9 (C13), 127.0 (C3), 124.6 (C5), 93.9 (C1), 40.6 (C7), 39.7 (C10), 25.7 (C12), 23.0 (C11), 21.1 (C14).

FTIR (neat) ν/cm<sup>-1</sup> = 1686, 1612, 1468, 1366, 1306, 1188, 1110, 1055, 1015, 806.

HRMS (ESI) *m/z* calcd. for C<sub>14</sub>H<sub>17</sub>ONi [M+H]<sup>+</sup>: 342.0349; found: 342.0349.

MP 56–58 °C.

#### 7,9-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one, **154**



Enaminone **153** (102.4 mg, 0.300 mmol, 1.0 eq.), *fac*-Ir(dFppy)<sub>3</sub> (2.3 mg, 3.0 μmol, 1 mol%) and potassium acetate (44.2 mg, 0.450 mmol, 1.5 eq.) were charged to a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum and then evacuated and back-filled with argon three times. Argon-sparged acetonitrile (6.0 mL, 0.05 M) was added *via* syringe. The reaction mixture was stirred under constant irradiation with a single Kessil PR160 467 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 2 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in pentane) to afford indole **154** (60.2 mg, 0.282 mmol, 94%) as an off-white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.53 (1H, d, *J* 8.2, H2), 7.12 (1H, app. s, H5), 6.98 (1H, dd, *J* 8.2, 1.4, H3), 4.04 (3H, s, H7), 2.99 (2H, t, *J* 6.1, H12), 2.63 (2H, dd, *J* 7.1, 5.7, H10), 2.51 (3H, s, H14), 2.20 (2H, quint, *J* 6.3, H11).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 192.1 (C9), 140.3 (C6), 137.2 (C4), 130.3 (C8), 129.5 (C13), 122.8 (C1), 122.3 (C3), 121.1 (C2), 110.0 (C5), 40.0 (C10), 31.6 (C7), 24.9 (C11), 22.5 (C14), 22.0 (C12).

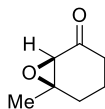
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1656, 1622, 1532, 1475, 1259, 1181, 1080, 940, 800, 733.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{16}\text{NO}$   $[\text{M}+\text{H}]^+$ : 214.1226; found: 214.1224.

MP 62–63 °C.

## Compounds relevant to initial attempts to synthesise $\beta$ -methyl substrate **162**

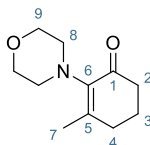
### 6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one, **163**



This compound was prepared according to a literature procedure.<sup>131</sup> To a stirred solution of 3-methyl-2-cyclohexenone (2.20 g, 20.0 mmol, 1.0 eq.) and aqueous hydrogen peroxide (35.5–36.5% w/w, 5.2 mL, 2.0 g, 60 mmol, 3.0 eq.) in methanol (20 mL, 1.0 M) was added sodium hydroxide (3 M aq., 1.3 mL, 3.9 mmol, 0.2 eq.) dropwise by syringe, with ice-bath cooling, ensuring the internal reaction temperature stayed below 10 °C throughout the addition. After complete addition of the base, the reaction mixture was allowed to warm to room temperature over 2 h. The reaction mixture was then added to a mixture of brine (sat. aq., 50 mL) and ice (*ca.* 50 mL) in a separating funnel. The aqueous phase was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford **163** (2.02 g, 16.0 mmol, 80%) as a colourless oil. The spectral data matched that previously reported in the literature.<sup>132</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.08 (1H, s), 2.53–2.44 (1H, m), 2.17–2.09 (1H, m), 2.09–1.81 (3H, m), 1.69–1.59 (1H, m), 1.45 (3H, s).

### 3-Methyl-2-morpholinocyclohex-2-en-1-one, **164**



6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one (**163**) (631 mg, 5.00 mmol, 1.0 eq.) and morpholine (0.66 mL, 0.66 g, 7.5 mmol, 1.5 eq.) were dissolved in a 3:1 (v/v) mixture of methanol (9 mL) and water (3 mL) (*ca.* 0.4 M) in a two-necked round-bottomed flask equipped with a magnetic stir bar and condenser. The resulting mixture was sparged with argon for 15 min before being heated to reflux with stirring. After 18 h, the reaction mixture was poured onto water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (sat. aq., 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 25% ethyl acetate in pentane) to afford **164** (157 mg, 0.804 mmol, 16%) as an orange oil.

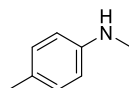
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.72–3.62 (4H, m, H9), 2.96–2.89 (4H, m, H8), 2.41–2.30 (4H, m, H2 & H4), 2.01 (3H, t, *J* 0.8, H7), 1.94–1.83 (2H, m, H3).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 198.1 (C1), 156.3 (C6), 143.1 (C5), 68.0 (C9), 50.5 (C8), 39.7 (C2), 32.3 (C4), 22.3 (C3), 19.9 (C7).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1667, 1453, 1374, 1259, 1163, 1113, 1046, 940, 850, 677.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{18}\text{O}_2\text{N}$   $[\text{M}+\text{H}]^+$ : 196.1332; found: 196.1332.

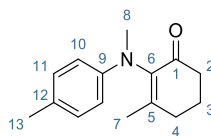
### *N*,4-Dimethylaniline, **167**



This compound was prepared according to a literature procedure.<sup>133</sup> Sodium methoxide (30 wt% in methanol, 9.4 mL, 2.8 g, 52 mmol, 5.2 eq.) and paraformaldehyde (420 mg, 14.0 mmol, 1.4 eq.) were successively added to a solution of *para*-toluidine (1.07 g, 9.99 mmol, 1.0 eq.) in methanol (20 mL, 0.5 M). The resulting suspension was stirred at room temperature for 5 h. Sodium borohydride (378 mg, 10.0 mmol, 1.0 eq.) was then added in one portion, and the reaction mixture was heated to reflux for 3 h. After this time, the reaction mixture was cooled to room temperature and quenched by the addition of sodium hydroxide (1 M aq., 20 mL). The resulting mixture was transferred to a separating funnel using water (20 mL) and ethyl acetate (20 mL). After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 5 to 10% ethyl acetate in pentane) to afford **167** (924 mg, 7.63 mmol, 76%) as a yellow oil. The spectral data matched that previously reported in the literature.<sup>134</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.09–7.01 (2H, m), 6.63–6.55 (2H, m), 3.55 (1H, s), 2.85 (3H, s), 2.29 (3H, s).

### 3-Methyl-2-(methyl(*p*-tolyl)amino)cyclohex-2-en-1-one, **166**



This compound was prepared by analogy to a literature procedure.<sup>44</sup> 6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one (**163**) (771 mg, 6.11 mmol, 1.0 eq.) and secondary aniline **167** (889 mg, 7.34 mmol, 1.2 eq.) were dissolved in a 3:1 (v/v) mixture of methanol (11.0 mL) and water (3.7 mL) (0.42 M) in a two-necked round-bottomed flask equipped with a magnetic stir bar and condenser. The resulting mixture was sparged with argon for 15 min before being heated to reflux with stirring. After 18 h, the reaction mixture was poured onto water (20 mL)

and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (sat. aq., 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 10 to 20% ethyl acetate in pentane) to afford **166** (581 mg, 2.53 mmol, 42%) as a viscous orange oil.

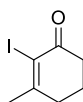
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.02–6.96 (2H, m, H11), 6.50–6.43 (2H, m, H10), 3.01 (3H, s, H8), 2.57–2.45 (4H, m, H4<sub>LHS</sub> & H2<sub>RHS</sub>), 2.23 (3H, s, H8), 2.13–2.00 (2H, m, H3), 1.89 (3H, d, *J* 0.9, H7).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 196.2 (C1), 158.5 (C5), 146.3 (C9), 140.0 (C6), 129.7 (C11), 125.7 (C12), 111.7 (C10), 39.0 (C2), 38.0 (C8), 32.3 (C4), 22.2 (C3), 20.4 (C13), 20.2 (C7).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1677, 1614, 1516, 1376, 1288, 1226, 1179, 1115, 925, 804.

HRMS (ESI) *m/z* calcd. for C<sub>15</sub>H<sub>20</sub>ON [M+H]<sup>+</sup>: 230.1539; found: 230.1540.

#### 2-Iodo-3-methylcyclohex-2-en-1-one, **169**

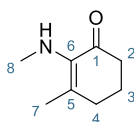


This compound was prepared according to a literature procedure.<sup>135</sup> To a solution of iodine (508 mg, 2.00 mmol, 1.0 eq.) in dichloromethane (2.0 mL, 1.0 M) was added pyridine (0.40 mL, 0.39 g, 4.9 mmol, 2.5 eq.) and phenyliodine(III) bis(trifluoroacetate) (PIFA) (860 mg, 2.00 mmol, 1.0 eq.). The resulting mixture was stirred at room temperature for 15 min before adding 3-methyl-2-cyclohexenone (0.23 mL, 0.22 g, 2.0 mmol, 1.0 eq.) in one portion. After stirring for an additional 16 h, the reaction mixture was quenched by the addition of sodium hydrogencarbonate (sat. aq., 5 mL). The resulting mixture was transferred to a separating funnel using water (10 mL) and ethyl acetate (10 mL). After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional ethyl acetate (2 x 5 mL). The combined organic extracts were washed successively with sodium thiosulfate (10 mL) and brine (sat. aq., 10 mL) before being dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in pentane) to afford **169** (400 mg, 1.69 mmol, 85%) as an orange-yellow oil. The spectral data matched that previously reported in the literature.<sup>136</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 2.64–2.57 (2H, m), 2.57–2.51 (2H, m), 2.26 (3H, t, *J* 0.9), 2.02–1.94 (2H, m).



### 3-Methyl-2-(methylamino)cyclohex-2-en-1-one, **170**



6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one (**163**) (1.00 g, 7.93 mmol, 1.0 eq.) was dissolved in a 3:1 (v/v) mixture of methanol (12 mL) and aqueous methylamine (40 wt%, 4 mL) in a round-bottomed flask equipped with a magnetic stir bar and condenser and heated to reflux with stirring. After 3 h, the reaction mixture was poured onto water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (sat. aq., 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 25 to 50% ethyl acetate in pentane) to afford **170** (298 mg, 2.14 mmol, 27%) as an orange oil.

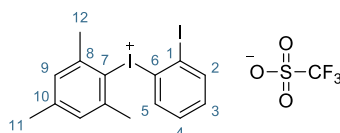
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.94 (1H, br s), 2.58 (3H, s, H8), 2.44–2.32 (4H, m, H2<sub>LHS</sub> & H4<sub>RHS</sub>), 1.95–1.85 (2H, m, H3), 1.94 (3H, t, *J* 1.2).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 196.2 (C1), 141.8 & 137.8 (C5 & C6), 37.0 (C2), 35.5 (C8), 32.3 (C4), 22.0 (C3), 20.1 (C7).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3352, 1664, 1634, 1491, 1373, 1298, 1178, 1134, 924, 764.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_8\text{H}_{13}\text{NONa}$  [ $\text{M}+\text{Na}$ ] $^+$ : 162.0889; found: 162.0884.

### (2-iodophenyl)(mesityl)iodonium trifluoromethanesulfonate, **174**



This compound was prepared by analogy to a literature procedure.<sup>137</sup> Boron trifluoride diethyl etherate (0.20 mL, 0.23 g, 1.6 mmol, 1.1 eq.) was added dropwise to a stirred, 0 °C solution of (2-iodophenyl)boronic acid<sup>138</sup> (355 mg, 1.43 mmol, 1.0 eq.) in dichloromethane (18 mL). After stirring at this temperature for 10 min, a solution of mesityl- $\lambda^3$ -iodanediyl diacetate<sup>139</sup> (574 mg, 1.58 mmol, 1.1 eq.) in dichloromethane (4.2 mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to room temperature over 2 h. Sodium tetrafluoroborate (*ca.* 10 g) in water (15 mL) was then added, and the resulting mixture was stirred vigorously for 30 min before being extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. A white solid was collected and dried by suction filtration following trituration of the crude residue with diethyl ether. This material (*ca.* 0.54 g) was dissolved in anhydrous acetonitrile (4 mL); the resulting solution was

cooled to 0 °C, and trimethylsilyl trifluoromethanesulfonate (0.28 mL, 0.34 g, 1.5 mmol) was added dropwise with stirring. The reaction mixture was allowed to warm to room temperature over 16 h before being concentrated *in vacuo*. Trituration of the crude residue with diethyl ether and filtration afforded **174** (553 mg, 0.924 mmol, 65% over two steps) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.91 (1H, dd,  $J$  7.7, 1.6, H2), 7.36 (1H, td,  $J$  7.8, 1.6, H4), 7.29 (1H, td,  $J$  7.6, 1.5, H3), 7.22 (2H, s, H9), 6.69 (1H, dd,  $J$  8.1, 1.5, H5), 2.61 (6H, s, H12), 2.41 (3H, s, H11).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 145.6 (C10), 142.9 (C8), 141.2 (C2), 132.9 (C3), 131.9 (C4), 131.1 (C9), 130.7 (C5), 124.1 (C7), 121.7 (C6), 120.5 (q,  $^1J_{\text{CF}}$  319.7,  $^-\text{OSO}_2\text{CF}_3$ ), 99.1 (C1), 27.3 (C12), 21.4 (C11).

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  = -78.3 ( $^-\text{OSO}_2\text{CF}_3$ ).

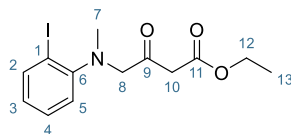
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1440, 1279, 1242, 1162, 1028, 979, 913, 758, 737, 637.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{15}\text{I}_2 \text{M}^+$ : 448.9258; found: 448.9242.

MP not determined.

## Synthesis of $\beta$ -methyl substrate **162** via a Michael–aldol sequence

### Ethyl 4-((2-iodophenyl)(methyl)amino)-3-oxobutanoate, **175**



This compound was prepared by analogy to a literature procedure.<sup>140</sup> To a stirred mixture of **146** (2.43 g, 10.4 mmol, 1.0 eq.), sodium hydrogencarbonate (1.75 g, 20.8 mmol, 2.0 eq.) and sodium iodide (3.13 g, 20.9 mmol, 2.0 eq.) in acetonitrile (21 mL, 0.5 M) at room temperature was added ethyl 4-chloroacetoacetate (95% w/w, 3.0 mL, 21 mmol, 2.0 eq.) in one portion. The reaction mixture was heated to 75 °C for 18 h with stirring. After this time, the reaction mixture was allowed to cool to room temperature before adding triethylamine (4.4 mL, 3.2 g, 32 mmol, 3.0 eq.) in one portion and stirring for a further 30 min. The reaction mixture was concentrated *in vacuo*, and the crude residue thus obtained was dissolved in ethyl acetate (40 mL) and washed successively with sodium thiosulfate (sat. aq., 20 mL) and water (20 mL). The aqueous washings were extracted with ethyl acetate (2 x 40 mL), and the combined organic extracts were subjected to a final wash with brine (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified twice by flash column chromatography (silica gel, 5% ethyl acetate in pentane; then, silica gel, dichloromethane) to afford **175** (1.44 g, 3.99 mmol, 38%) as a viscous pale-yellow oil.

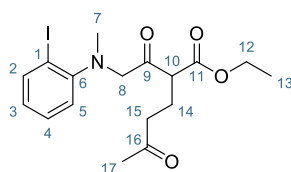
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.84 (1H, dd, *J* 7.9, 1.5, H2), 7.31 (1H, ddd, *J* 8.0, 7.3, 1.5, H4), 7.14 (1H, dd, *J* 8.0, 1.6, H5), 6.81 (1H, ddd, *J* 7.8, 7.3, 1.6, H3), 4.17 (2H, q, *J* 7.1, H12), 3.90 (2H, s, H8), 3.65 (2H, s, H10), 2.79 (3H, s, H7), 1.25 (3H, t, *J* 7.1, H13).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 202.0 (C9), 167.5 (C11), 153.0 (C6), 140.3 (C2), 129.4 (C4), 126.1 (C3), 122.6 (C5), 97.4 (C1), 66.0 (C8), 61.5 (C12), 46.6 (C10), 43.2 (C7), 14.2 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1746, 1721, 1472, 1315, 1228, 1182, 1032, 1015, 950, 760.

HRMS (ESI) *m/z* calcd. for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>NINa [M+Na]<sup>+</sup>: 384.00671; found: 384.00665.

### Ethyl 2-(*N*-(2-iodophenyl)-*N*-methylglycyl)-5-oxohexanoate, **176**



Aminoketone **175** (2.34 g, 6.48 mmol, 1.0 eq.) was dissolved in dichloromethane (13 mL, 0.5 M). Potassium carbonate (895 mg, 6.48 mmol, 1.0 eq.) was added in one portion followed by freshly

distilled methyl vinyl ketone (0.54 mL, 0.46 g, 6.5 mmol, 1.0 eq.). The reaction mixture was stirred for 24 h at room temperature before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 2 to 5% ethyl acetate in dichloromethane) to afford **176** (1.93 g, 4.48 mmol, 69%) as a viscous orange-yellow oil.

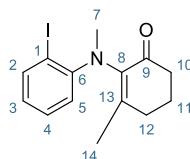
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.82 (1H, dd,  $J$  7.9, 1.5, H2), 7.34–7.25 (1H, m, H4), 7.15 (1H, dd,  $J$  8.0, 1.5, H5), 6.78 (1H, td,  $J$  7.6, 1.5, H3), 4.13 (2H, q,  $J$  7.1, H12), 4.02 (1H, d,  $J$  17.5, H8), 3.96 (1H, d,  $J$  17.5, H8'), 3.84 (1H, t,  $J$  7.0, H10), 2.81 (3H, s, H7), 2.44 (2H, app. td,  $J$  7.1, 1.5, H15), 2.11–2.00 (2H, m, H14), 2.08 (3H, s, H17), 1.20 (3H, t,  $J$  7.1, H13).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 207.6 (C16), 203.4 (C9), 169.3 (C11), 153.0 (C6), 140.3 (C2), 129.2 (C4), 125.9 (C3), 122.7 (C5), 97.1 (C1), 65.2 (C8), 61.6 (C12), 53.8 (C10), 42.8 (C7), 40.7 (C15), 23.0 (C17), 21.7 (C14), 14.2 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1744, 1716, 1580, 1472, 1369, 1182, 1162, 1015, 858, 760.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{22}\text{O}_4\text{NINa}$   $[\text{M}+\text{Na}]^+$ : 454.04857; found: 454.04777.

#### 2-((2-Iodophenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **162**



Sodium methoxide (30 wt% in methanol, 0.81 mL, 0.24 g, 4.4 mmol, 1.1 eq.) was added in one portion to a stirred, argon-sparged solution of diketone **176** (1.70 g, 3.94 mmol, 1.0 eq.) in methanol (40 mL, 0.1 M) at room temperature. The reaction mixture was stirred at this temperature for a further 2 h before adding a solution of lithium hydroxide monohydrate (165 mg, 3.93 mmol, 1.0 eq.) in water (20 mL) and heating to 75 °C. After 10 min, the reaction mixture was cooled to room temperature and acidified to *ca.* pH 2 with HCl (1 M aq., *ca.* 20 mL). The reaction mixture was heated to 75 °C for a further 30 min before cooling to room temperature, adding water (40 mL) and extracting with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 20 to 30% diethyl ether in pentane) to afford **162** (896 mg, 2.63 mmol, 67%) as a pale-yellow solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.72 (1H, dd,  $J$  7.8, 1.6, H2), 7.31–7.22 (1H, m, H4), 7.03 (1H, dd,  $J$  8.2, 1.5, H5), 6.57 (1H, ddd,  $J$  7.8, 7.2, 1.5, H3), 3.05 (3H, s, H7), 2.53–2.41 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.09–1.98 (2H, m, H11), 1.76 (3H, t,  $J$  1.0, H14).

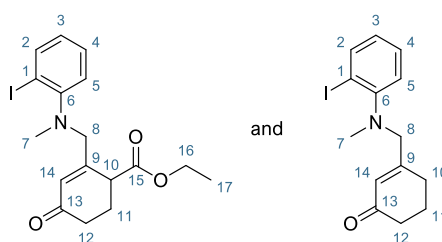
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 196.5 (C9), 154.7 (C13), 151.7 (C6), 141.2 (C2), 140.6 (C8), 128.8 (C4), 122.3 (C3), 120.0 (C5), 87.5 (C1), 40.6 (C7), 38.7 (C10), 32.9 (C12), 21.9 (C11), 21.4 (C14).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1674, 1580, 1472, 1317, 1207, 1115, 1060, 1008, 928, 753.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{16}\text{ONa}$   $[\text{M}+\text{Na}]^+$ : 364.01688; found: 364.01705.

MP 50–51°C.

Ethyl 2-(((2-iodophenyl)(methyl)amino)methyl)-4-oxocyclohex-2-ene-1-carboxylate, **283a**, and 3-(((2-iodophenyl)(methyl)amino)methyl)cyclohex-2-en-1-one, **283b**



A solution of diketone **176** (2.92 g, 6.75 mmol, 1.0 eq.) in *tert*-butanol (68 mL, 0.1 M) was sparged with argon for 15 min before adding potassium *tert*-butoxide (833 mg, 7.42 mmol, 1.1 eq.) in one portion under an argon atmosphere (the solution was gently heated using a tepid water bath during the sparging process to prevent freezing of the solvent). The reaction mixture was heated to reflux with stirring for 2 h. The reaction mixture was cooled to room temperature and quenched by the addition of ammonium chloride (sat. aq., 100 mL). The resulting mixture was transferred to a separating funnel using water (100 mL) and diethyl ether (100 mL). After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (sat. aq., 100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 20 to 40% diethyl ether in pentane) to afford an inseparable mixture (797 mg) of compounds **238a** and **238b** in an approximate molar ratio of 92:8 (estimated from relative integrations of  $^1\text{H}$  signals corresponding to H14, corresponding to approximate yields of 27 and 2%, respectively) as a viscous yellow oil, alongside **162** (1.23 g, 3.60 mmol, 53%) as a pale-yellow solid.

NMR data are reported for **238a** only; **238b**, whose assignment is supported by the HRMS data below, possessed near-identical NMR spectroscopic features to **238a**.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.84 (1H, dd,  $J$  7.9, 1.6, H2), 7.34–7.27 (1H, m, H4), 7.10 (1H, dd,  $J$  8.0, 1.6, H5), 6.81 (1H, td,  $J$  7.6, 1.5, H3), 6.30 (1H, d,  $J$  1.6, H14), 4.22–4.11 (2H, m, H16),

3.92–3.84 (1H, m, H8), 3.73–3.62 (2H, m, H8'<sub>LHS</sub> & H10<sub>RHS</sub>), 2.63 (3H, s, H7), 2.61–2.48 (1H, m, H12), 2.47–2.35 (2H, m, H11<sub>LHS</sub> & H12'<sub>RHS</sub>), 2.21–2.08 (1H, m, H11'), 1.23 (3H, t, *J* 7.1, H17).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 198.8 (C13), 171.4 (C15), 157.2 (C9), 153.7 (C6), 140.3 (C2), 129.3 (C4), 128.9 (C14), 126.2 (C3), 122.4 (C5), 98.5 (C1), 61.5(4) & 61.5(1) (C8 & C16), 43.0 (C7), 42.2 (C10), 35.0 (C12), 26.4 (C11), 14.3 (C17).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1727, 1674, 1472, 1242, 1183, 1042, 1015, 940, 763, 724.

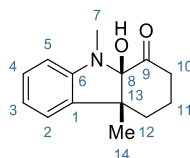
HRMS (ESI)  $m/z$  calcd. for C<sub>17</sub>H<sub>20</sub>INO<sub>3</sub> [M+H]<sup>+</sup>: 414.0561; found: 414.0559;  $m/z$  calcd. for C<sub>14</sub>H<sub>16</sub>INO [M+H]<sup>+</sup>: 342.0349; found: 342.0352.

Photochemical reactivity of  $\beta$ -methyl substrate **162** in the presence of various nucleophiles (nucleophile scope)

#### General Procedure A

Enaminone **162** (102.4 mg, 0.300 mmol, 1.0 eq.) and (if non-volatile) the appropriate nucleophile (3.0 eq., unless otherwise stated) and/or basic additive were charged to a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the flask was evacuated and back-filled with argon three times. Solvent(s) and nucleophile (if volatile), both argon-sparged, were added *via* syringe. The reaction mixture was stirred under constant irradiation with two Kessil PR160L 427 nm LED lamps (each positioned *ca.* 3 cm from the flask and directed toward it) for the specified time, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Triethylamine (2.0 mL) was added to the reaction mixture at the end of the irradiation period, and the resulting mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography to afford the corresponding indoline product.

(4a*R*,9a*R*)-9a-Hydroxy-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **177**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture was degassed by three freeze–pump–thaw cycles prior to irradiation; also, no triethylamine was added at the end of the reaction. Irradiation was performed in the presence of potassium acetate (44.2 mg, 0.450 mmol, 1.5 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) over a period of 90 min. Flash column chromatography on silica gel (gradient elution from 5 to 10% ethyl acetate in pentane) yielded **177** (61.6 mg, 0.266 mmol, 89%) as an off-white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 7.14 (1H, td, *J* 7.6, 1.3, H4), 7.06 (1H, dd, *J* 7.3, 1.3, H2), 6.79 (1H, td, *J* 7.4, 1.0, H3), 6.57 (1H, d, *J* 7.8, H5), 4.51 (1H, s, OH), 2.77–2.66 (1H, m, H10), 2.54 (3H, s, H7), 2.47–2.39 (1H, m, H10'), 1.86–1.66 (4H, m, H11<sub>LHS</sub>, H11'<sub>LHS</sub>, H12<sub>RHS</sub> & H12'<sub>RHS</sub>), 1.27 (3H, s, H14).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  = 211.1 (C9), 150.5 (C6), 138.1 (C1), 128.7 (C4), 122.0 (C2), 119.8 (C3), 108.5 (C5), 98.1 (C8), 54.1 (C13), 40.0 (C12), 38.1 (C10), 28.7 (C7), 21.9 (C11), 18.1 (C14).

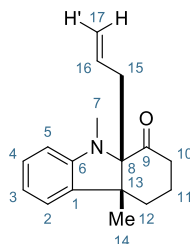
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ OH is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3485, 1711, 1607, 1479, 1275, 1124, 1106, 1070, 1007, 735.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{18}\text{NO}_2$   $[\text{M}+\text{H}]^+$ : 232.1332; found: 232.1329;  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}_2\text{Na}$   $[\text{M}+\text{Na}]^+$ : 254.1152; found: 254.1148.

MP not determined; sample decomposed upon heating at some temperature below 100 °C.

(4a*R*,9a*S*)-9a-Allyl-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **179**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A. Irradiation was performed in the presence of allyltrimethylsilane (0.14 mL, 0.10 g, 0.88 mmol, 2.9 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and hexafluoroisopropanol (0.6 mL) (0.05 M) over a period of 18 h. Flash column chromatography on silica gel (eluent: 2% ethyl acetate in pentane) yielded **179** (61.5 mg, 0.241 mmol, 80%) as a light brown oil.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 7.01 (1H, td,  $J$  7.6, 1.3, H4), 6.92 (1H, dd,  $J$  7.3, 1.3, H2), 6.59 (1H, td,  $J$  7.4, 1.0, H3), 6.38 (1H, d,  $J$  7.7, H5), 5.62 (1H, ddt,  $J$  17.2, 10.2, 7.1, H16), 5.16 (1H, dq,  $J$  16.9, 1.7, H17), 4.98 (1H, dq,  $J$  10.0, 1.5, H17'), 2.82 (3H, s, H7), 2.77 (1H, ddt,  $J$  15.5, 7.0, 1.6, H15), 2.56 (1H, ddt,  $J$  15.5, 7.2, 1.4, H15'), 2.32 (1H, ddd,  $J$  14.5, 11.1, 6.2, H10), 2.21 (1H, dddd,  $J$  14.4, 5.4, 3.7, 1.4, H10'), 2.00–1.90 (1H, m, H12), 1.81–1.65 (2H, m, H12' <sub>LHS</sub> & H11 <sub>RHS</sub>), 1.58–1.42 (1H, m, H11'), 1.19 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 213.9 (C9), 150.7 (C6), 134.3 (C16), 134.0 (C1), 127.8 (C4), 120.6 (C2), 118.1 (C17), 117.1 (C3), 105.0 (C5), 79.6 (C8), 51.7 (C13), 39.2 (C10), 34.1 (C12), 33.4 (C15), 30.5 (C7), 23.1 (C14), 20.8 (C11).

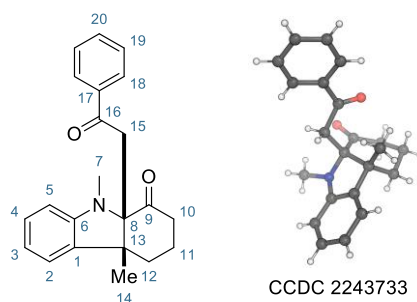
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to  $\text{H14} \leftrightarrow \text{H15}$ ,  $\text{H14} \leftrightarrow \text{H15}'$  and  $\text{H14} \leftrightarrow \text{H16}$  is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1706, 1605, 1488, 1370, 1305, 1120, 1021, 916, 871, 739.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{22}\text{NO}$   $[\text{M}+\text{H}]^+$ : 256.1696; found: 256.1692.



(4a*R*,9a*S*)-4a,9-Dimethyl-9a-(2-oxo-2-phenylethyl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **180**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture was degassed by three freeze–pump–thaw cycles prior to irradiation. Irradiation was performed in the presence of 1-phenyl-1-trimethylsilyloxyethylene<sup>141</sup> (173 mg, 0.899 mmol, 3.0 eq.) and sodium trifluoroacetate (40.8 mg, 0.300 mmol, 1.0 eq.) in nitromethane solution (6.0 mL, 0.05 M) over a period of 18 h. Instead of adding triethylamine at the end of the irradiation period, the reaction mixture was diluted with methanol (6.0 mL) and stirred for 30 min at room temperature before concentrating *in vacuo*. Flash column chromatography on silica gel (gradient elution from 50 to 100% dichloromethane in pentane) yielded **180** (56.7 mg, 0.170 mmol, 57%) as a pale green solid. Diffraction-quality crystals were grown by vapour diffusion of cyclohexane into a solution of the product in tetrahydrofuran followed by slow evaporation of the resulting mixture.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 8.09–7.98 (2H, m, H18), 7.71–7.61 (1H, m, H20), 7.59–7.49 (2H, m, H19), 7.03 (1H, td, *J* 7.6, 1.3, H4), 6.96 (1H, dd, *J* 7.3, 1.3, H2), 6.62 (1H, td, *J* 7.4, 1.0, H3), 6.47–6.34 (1H, m, H5), 3.89 (1H, d, *J* 18.4, H15), 3.70 (1H, d, *J* 18.4, H15'), 2.64 (3H, s, H7), 2.52–2.40 (1H, m, H10), 2.19 (1H, dt, *J* 15.1, 5.6, H10'), 2.07–1.90 (2H, m, H12 & H12'), 1.89–1.76 (1H, m, H11), 1.53–1.37 (1H, m, H11'), 1.18 (3H, s, H14).

<sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 207.6 (C9), 198.6 (C16), 149.9 (C6), 136.2 (C17), 134.4 (C1), 133.5 (C20), 128.8 (C19), 128.1 (C18), 127.7 (C4), 121.2 (C2), 117.3 (C3), 105.9 (C5), 77.7 (C8), 51.2 (C13), 39.2 (C15), 37.4 (C10), 33.2 (C12), 29.6 (C7), 25.0 (C14), 20.7 (C11).

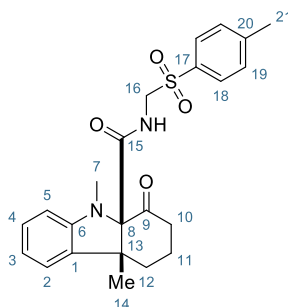
The stereochemistry of this compound was confirmed through single-crystal X-ray diffraction (CCDC 2243733). The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14↔H15 and H14↔H15' is also consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1699, 1684, 1602, 1488, 1449, 1348, 1307, 1217, 1021, 742.

HRMS (ESI)  $m/z$  calcd. for C<sub>22</sub>H<sub>24</sub>O<sub>2</sub>N [M+H]<sup>+</sup>: 334.1802; found: 334.1801.

MP 93–95 °C.

(4b*R*,8a*S*)-4b,9-Dimethyl-8-oxo-*N*-(tosylmethyl)-4b,5,6,7,8,9-hexahydro-8a*H*-carbazole-8a-carboxamide, **184**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture was degassed by three freeze–pump–thaw cycles prior to irradiation. Irradiation was performed in the presence of *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) over a period of 18 h. Flash column chromatography on silica gel (gradient elution from 20 to 30% ethyl acetate in pentane) yielded **184** (94.1 mg, 0.221 mmol, 74%) as an off-white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.83–7.74 (2H, m, H18), 7.47 (1H, t, *J* 6.9, NH), 7.35 (2H, d, *J* 8.1, H19), 7.16 (1H, td, *J* 7.6, 1.3, H4), 6.90 (1H, dd, *J* 7.4, 1.3, H2), 6.81 (1H, td, *J* 7.4, 1.0, H3), 6.54 (1H, d, *J* 7.8, H5), 4.91 (1H, dd, *J* 14.1, 7.5, H16), 4.59 (1H, dd, *J* 14.1, 6.1, H16'), 3.00 (3H, s, H7), 2.60 (1H, ddd, *J* 15.5, 11.2, 7.2, H10), 2.44 (3H, s, H21), 2.17 (1H, dddd, *J* 15.5, 6.2, 3.6, 1.3, H10'), 2.07 (1H, dtd, *J* 14.3, 3.8, 1.4, H12), 1.93 (1H, ddd, *J* 14.3, 13.0, 4.1, H12'), 1.85–1.72 (1H, m, H11), 1.62–1.47 (1H, m, H11'), 1.08 (3H, s, H14).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 209.7 (C9), 168.6 (C15), 150.0 (C6), 145.7 (C20), 134.2 (C17), 132.7 (C1), 130.2 (C19), 128.8 (C18), 128.7 (C4), 121.4 (C2), 120.0 (C3), 108.1 (C5), 85.3 (C8), 60.0 (C16), 52.6 (C13), 40.1 (C10), 34.5 (C7), 32.3 (C12), 27.2 (C14), 21.8 (C21), 20.1 (C11).

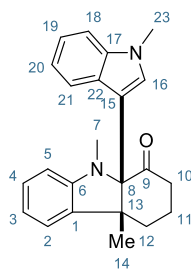
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14↔NH and H14↔H18 (weak) is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat) ν/cm<sup>−1</sup> = 3341, 1716, 1677, 1482, 1322, 1290, 1145, 1086, 745, 668.

HRMS (ESI) *m/z* calcd. for C<sub>23</sub>H<sub>27</sub>O<sub>4</sub>N<sub>2</sub>S [M+H]<sup>+</sup>: 427.1686; found: 427.1684.

MP 148–150 °C.

(4a*R*,9a*R*)-4a,9-Dimethyl-9a-(1-methyl-1*H*-indol-3-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **185**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A. Irradiation was performed in the presence of 1-methylindole (112  $\mu$ L, 118 mg, 0.897 mmol, 3.0 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and hexafluoroisopropanol (0.6 mL) (0.05 M) over a period of 18 h. Flash column chromatography on alumina gel (gradient elution from 5 to 25% dichloromethane in pentane) yielded **185** (83.9 mg, 0.244 mmol, 81%) as a peach-coloured solid.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 7.43–7.38 (1H, m, H18), 7.36 (1H, d,  $J$  8.1, H21), 7.31 (1H, s, H16), 7.16–7.06 (2H, m, H19<sub>LHS</sub> & H4<sub>RHS</sub>), 6.99 (1H, dd,  $J$  7.2, 1.3, H2), 6.95 (1H, ddd,  $J$  8.1, 7.0, 1.1, H20), 6.67 (1H, td,  $J$  7.4, 1.0, H3), 6.51 (1H, d,  $J$  7.7, H5), 3.78 (3H, s, H23), 2.79–2.66 (1H, m, H10), 2.72 (3H, s, H7), 2.39–2.27 (1H, m, H10'), 2.09–1.98 (1H, m, H12), 1.93–1.74 (2H, m, H11<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.68–1.51 (1H, m, H11'), 0.84 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 212.0\* (C9), 150.2 (C6), 136.6 (C17), 133.8 (C1), 129.3 (C16), 127.9 (C4), 127.5 (C22), 121.6 (C2 & C21, coincident), 121.0 (C19), 119.1 (C20), 117.3 (C3), 109.7 (C18), 108.8 (C15), 105.6 (C5), 81.9 (C8), 52.7 (C13), 39.7 (C10), 32.5 (C23), 32.1 (C12), 31.8 (C7), 27.1 (C14), 20.0 (C11).

The observation of a transient nuclear Overhauser effect (nOe) by 1D NOESY for H21 upon selective inversion of H14 is consistent with the formation of the *cis*-diastereomer shown.

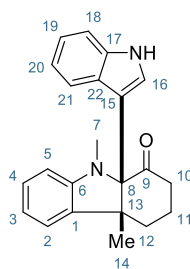
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1707, 1604, 1488, 1371, 1305, 1020, 911, 739.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 345.1961; found: 345.1954.

MP 163–165  $^{\circ}\text{C}$ .

\* Identified through HMBC correlations.

(4a*R*,9a*R*)-9a-(1*H*-Indol-3-yl)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one,  
**186**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A. Irradiation was performed in the presence of indole (105.4 mg, 0.900 mmol, 3.0 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and hexafluoroisopropanol (0.6 mL) (0.05 M) over a period of 18 h. Flash column chromatography on alumina gel (gradient elution from 20 to 100% dichloromethane in pentane) yielded **186** (82.6 mg, 0.250 mmol, 83%) as an off-white solid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 11.20 (1H, s, NH), 7.38 (1H, dt, *J* 8.1, 0.9, H18), 7.33 (1H, d, *J* 8.1, H21), 7.27–7.21 (1H, m, H16), 7.10 (1H, td, *J* 7.7, 1.3, H4), 7.05 (1H, ddd, *J* 8.1, 7.0, 1.2, H19), 6.99 (1H, dd, *J* 7.2, 1.3, H2), 6.91 (1H, ddd, *J* 8.1, 6.9, 1.1, H20), 6.66 (1H, td, *J* 7.4, 1.0, H3), 6.51 (1H, d, *J* 7.7, H5), 2.81–2.60 (1H, m, H10), 2.72 (3H, m, H7), 2.38–2.27 (1H, m, H10'), 2.10–1.96 (1H, m, H12), 1.93–1.75 (2H, m, H11<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.69–1.52 (1H, m, H11'), 0.84 (3H, s, H14).

<sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 212.2 (C9), 150.2 (C6), 136.2 (C17), 134.0 (C1), 127.9 (C4), 127.1 (C22), 125.0 (C16), 121.6 (C2), 121.4 (C21), 120.8 (C19), 118.9 (C20), 117.2 (C3), 111.5 (C18), 109.7 (C15), 105.5 (C5), 81.9 (C8), 52.7 (C13), 39.6 (C10), 32.3 (C12), 31.7 (C7), 27.0 (C14), 19.9 (C11).

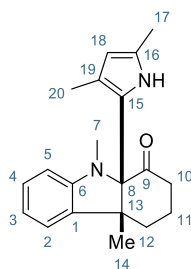
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ H21 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3406 (br), 1701, 1604, 1489, 1457, 1421, 1305, 1021, 912, 743.

HRMS (ESI)  $m/z$  calcd. for C<sub>22</sub>H<sub>23</sub>ON<sub>2</sub> [M+H]<sup>+</sup>: 331.1805; found: 331.1802.

MP 189–191 °C.

(4a*R*,9a*R*)-9a-(3,5-Dimethyl-1*H*-pyrrol-2-yl)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **187**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture was degassed by three freeze–pump–thaw cycles prior to irradiation. Irradiation was performed in the presence of 2,4-dimethylpyrrole (93  $\mu$ L, 86 mg, 0.90 mmol, 3.0 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) over a period of 18 h. Flash column chromatography on alumina gel (gradient elution from 25 to 50% dichloromethane in pentane) yielded **187** (63.0 mg, 0.204 mmol, 68%) as an extremely viscous brown oil.

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 9.78 (1H, s, NH), 7.08 (1H, td,  $J$  7.6, 1.3, H4), 6.99 (1H, dd,  $J$  7.2, 1.3, H2), 6.66 (1H, td,  $J$  7.4, 1.0, H3), 6.46 (1H, d,  $J$  7.7, H5), 5.48 (1H, d,  $J$  2.8, H18), 2.55 (3H, s, H7), 2.30 (1H, ddd,  $J$  16.6, 8.5, 6.0, H10), 2.11–1.89 (2H, m, H10'<sub>LHS</sub> & H12<sub>RHS</sub>), 2.10 (3H, s, H17), 1.86–1.67 (2H, m, H12'<sub>LHS</sub> & H11<sub>RHS</sub>), 1.76 (3H, s, H20), 1.61–1.45 (1H, m, H11'), 0.76 (3H, s, H14).

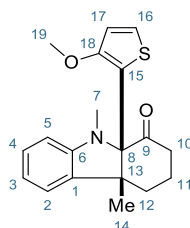
$^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  = 206.3 (C9), 149.5 (C6), 134.5 (C1), 127.8 (C4), 125.0 (C16), 121.9 (C2), 120.5 (C15 or C19), 117.4 (C3), 115.2 (C15 or C19), 108.6 (C18), 105.7 (C5), 80.6 (C8), 52.4 (C13), 36.1 (C10), 32.5 (C12), 30.3 (C7), 26.9 (C14), 18.3 (C11), 12.8 (C20), 12.6 (C17).

The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ NH and H14 $\leftrightarrow$ H20 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3396 (br), 1699, 1603, 1490, 1449, 1306, 1209, 1022, 788, 741.

HRMS (ESI)  $m/z$  calcd. for C<sub>20</sub>H<sub>25</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 309.1961; found: 309.1958.

(4a*R*,9a*S*)-9a-(3-Methoxythiophen-2-yl)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **188**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A. Irradiation was performed in the presence of 3-methoxythiophene (0.15 mL, 0.17 g, 1.5 mmol, 5.0 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and hexafluoroisopropanol (0.6 mL) (0.05 M) over a period of 18 h. Flash column chromatography on alumina gel (eluent: 25% dichloromethane in pentane) yielded **188** (42.8 mg, 0.131 mmol, 44%) as a pale pink solid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 7.34 (1H, dd, *J* 5.5, 0.8, H16), 7.09 (1H, td, *J* 7.6, 1.2, H4), 7.05–6.99 (2H, m, H17<sub>LHS</sub> & H2<sub>RHS</sub>), 6.72 (1H, td, *J* 7.4, 1.0, H3), 6.51 (1H, d, *J* 7.8, H5), 3.67 (3H, s, H19), 2.66 (3H, s, H7), 2.40 (1H, ddd, *J* 16.9, 8.3, 6.9, H10), 2.09 (1H, ddd, *J* 16.9, 8.9, 5.5, H10'), 2.03–1.93 (2H, m, H12 & H12'), 1.83–1.68 (1H, m, H11), 1.52 (1H, m, H11'), 0.91 (3H, s, H14).

<sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 205.3 (C9), 154.0 (C18), 149.4 (C6), 134.5 (C1), 127.9 (C4), 123.0 (C16), 121.9 (C2), 119.5 (C15), 118.4 (C3), 117.7 (C17), 106.5 (C5), 80.1 (C8), 58.2 (C19), 52.0 (C13), 36.5 (C10), 32.4 (C12), 31.6 (C7), 26.7 (C14), 18.3 (C11).

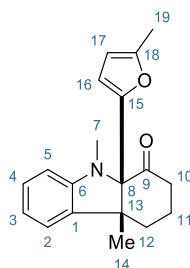
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ H19 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1710, 1603, 1555, 1487, 1381, 1304, 1239, 1063, 1022, 742.

HRMS (ESI) *m/z* calcd. for C<sub>19</sub>H<sub>22</sub>O<sub>2</sub>NS [M+H]<sup>+</sup>: 328.1366; found: 328.1367.

MP 78–80 °C.

(4a*R*,9a*R*)-4a,9-Dimethyl-9a-(5-methylfuran-2-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **189**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A. Irradiation was performed in the presence of 2-methylfuran (82  $\mu$ L, 75 mg, 0.91 mmol, 3.0 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and hexafluoroisopropanol (0.6 mL) (0.05 M) over a period of 18 h. Flash column chromatography on alumina gel (gradient elution from 2 to 10% diethyl ether in pentane yielded **189** (51.9 mg, 0.176 mmol, 59%) as a pale-yellow solid.

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 7.07 (1H, td,  $J$  7.6, 1.3, H4), 6.98 (1H, dd,  $J$  7.3, 1.3, H2), 6.66 (1H, td,  $J$  7.4, 1.0, H3), 6.48 (1H, d,  $J$  7.8, H5), 6.27 (1H, d,  $J$  3.2, H16), 6.13–6.06 (1H, m, H17), 2.81 (3H, s, H7), 2.75–2.62 (1H, m, H10), 2.34–2.23 (1H, m, H10'), 2.25 (3H, s, H19), 2.20–2.09 (1H, m, H12), 1.93–1.77 (2H, m, H11<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.60–1.44 (1H, m, H11'), 0.89 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  = 211.2 (C9), 151.5 (C18), 150.0 (C6), 147.9 (C15), 132.9 (C1), 127.9 (C4), 121.2 (C2), 117.7 (C3), 110.8 (C16), 106.3 (C17), 105.9 (C5), 81.5 (C8), 53.0 (C13), 39.9 (C10), 32.3 (C12), 31.8 (C7), 26.1 (C14), 20.5 (C11), 13.3 (C19).

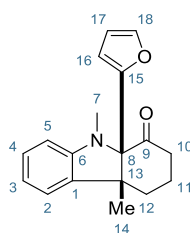
The observation of a transient nuclear Overhauser effect (nOe) by 1D NOESY for H16 upon selective inversion of H14 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1718, 1606, 1486, 1457, 1363, 1304, 1120, 1022, 786, 740.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{22}\text{O}_2\text{N}$   $[\text{M}+\text{H}]^+$ : 296.1645; found: 296.1647.

MP 71–73  $^{\circ}\text{C}$ .

(4a*R*,9a*R*)-9a-(Furan-2-yl)-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **190**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture was degassed by three freeze–pump–thaw cycles prior to irradiation. Irradiation was performed in the presence of potassium 2-furantrifluoroborate<sup>142</sup> (156.6 mg, 0.900 mmol, 3.0 eq.) in a 3:1 (v/v) mixture of acetonitrile (4.5 mL) and water (1.5 mL) (0.05 M) over a period of 18 h. Flash column chromatography on silica gel (gradient elution from 2 to 5% ethyl acetate in pentane) yielded **190** (46.1 mg, 0.164 mmol, 55%) as a peach-coloured solid.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 7.69 (1H, dd,  $J$  1.8, 0.8, H18), 7.08 (1H, td,  $J$  7.6, 1.3, H4), 6.99 (1H, dd,  $J$  7.3, 1.2, H2), 6.67 (1H, td,  $J$  7.4, 1.0, H3), 6.55–6.47 (2H, m, H5<sub>LHS</sub> & H17<sub>RHS</sub>), 6.44 (1H, dd,  $J$  3.3, 0.8, H16), 2.78 (3H, s, H7), 2.66 (1H, ddd,  $J$  15.1, 10.9, 6.7, H10), 2.34 (1H, dddd,  $J$  15.2, 5.5, 3.9, 1.6, H10'), 2.17–2.06 (1H, m, H12), 1.92–1.74 (2H, m, H11<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.63–1.48 (1H, m, H11'), 0.87 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 210.6 (C9), 150.1 & 150.0 (C6 & C15), 142.9 (C18), 133.2 (C1), 128.0 (C4), 121.3 (C2), 117.8 (C3), 110.3 (C17), 110.1 (C16), 106.0 (C5), 81.3 (C8), 53.2 (C13), 39.6 (C10), 32.9 (C12), 31.8 (C7), 25.7 (C14), 20.2 (C11).

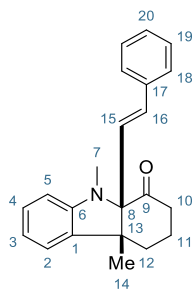
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ H16 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1716, 1605, 1485, 1363, 1304, 1207, 1153, 1020, 858, 739.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{20}\text{O}_2\text{N}$   $[\text{M}+\text{H}]^+$ : 282.1489; found: 282.1488.

MP 79–81 °C.

(4a*R*,9a*S*)-4a,9-Dimethyl-9a-((*E*)-styryl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one,  
**191**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture was degassed by three freeze–pump–thaw cycles prior to irradiation. Irradiation was performed in the presence of potassium *trans*-styryltrifluoroborate (94.5 mg, 0.450 mmol, 1.5 eq.) in a 3:1 (v/v) mixture of acetonitrile (4.5 mL) and water (1.5 mL) (0.05 M) over a period of 18 h. Flash column chromatography on silica gel (gradient elution from 2.5 to 5% ethyl acetate in pentane) yielded **191** (62.5 mg, 0.197 mmol, 66%) as a viscous yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 7.59–7.52 (2H, m, H18), 7.42–7.32 (2H, m, H19), 7.31–7.25 (1H, m, H20), 7.06 (1H, td,  $J$  7.6, 1.3, H4), 6.96 (1H, dd,  $J$  7.3, 1.3, H2), 6.64 (1H, td,  $J$  7.4, 1.0,



H3), 6.51\* (2H, app. s, H15 & H16), 6.48 (1H, dd,  $J$  7.8, 0.8, H5), 2.87 (3H, s, H7), 2.78–2.63 (1H, m, H10), 2.25–2.09 (2H, m, H10'\_{LHS} & H12\_{RHS}), 1.90–1.78 (2H, m, H11\_{LHS} & H12'\_{RHS}), 1.59–1.41 (1H, m, H11'), 1.12 (3H, s, H14).

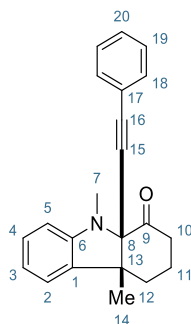
$^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  = 214.3 (C9), 150.5 (C6), 136.2 (C17), 133.5 (C16), 133.2 (C1), 128.6 (C19), 128.0 (C20), 127.9 (C4), 126.6 (C18), 123.9 (C15), 121.0 (C2), 117.3 (C3), 105.8 (C5), 83.7 (C8), 53.7 (C13), 39.6 (C10), 32.4 (C12), 31.6 (C7), 25.9 (C14), 21.5 (C11).

The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ H15/16 (signals coincident) is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1715, 1606, 1486, 1368, 1306, 1125, 976, 913, 742, 694.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{22}\text{H}_{24}\text{ON}$   $[\text{M}+\text{H}]^+$ : 318.1852; found: 318.1852.

(4a*R*,9a*S*)-4a,9-Dimethyl-9a-(phenylethynyl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **192**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture was degassed by three freeze–pump–thaw cycles prior to irradiation. Irradiation was performed in the presence of potassium (2-phenylethynyl)trifluoroborate<sup>143</sup> (93.6 mg, 0.450 mmol, 1.5 eq.) in a 3:1 (v/v) mixture of acetonitrile (4.5 mL) and water (1.5 mL) (0.05 M) over a period of 18 h. Flash column chromatography on silica gel (eluent: 5% ethyl acetate in pentane) yielded **192** (49.7 mg, 0.158 mmol, 53%) as a viscous orange oil.

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 7.51–7.45 (2H, m, H18), 7.44–7.35 (3H, m, H19 & H20), 7.09 (1H, td,  $J$  7.6, 1.3, H4), 7.07–7.01 (1H, m, H2), 6.70 (1H, td,  $J$  7.4, 1.0, H3), 6.55 (1H, d,  $J$  7.5, H5), 2.90 (3H, s, H7), 2.68–2.56 (1H, m, H10), 2.38 (1H, ddd,  $J$  14.6, 5.7, 4.2, H10'), 2.07 (1H,

\* While splitting was not observed under these conditions, it is assumed that H15 and H16 are indeed spin-coupled; the singlet appearance of this signal is likely the result of a pronounced roofing effect between two near-isochronous doublets.

ddt,  $J$  12.5, 5.9, 2.0, H12), 1.93–1.80 (2H, m, H11<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.59 (1H, m, H11'), 1.40 (3H, s, H14).

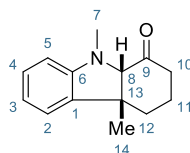
$^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  = 208.1 (C9), 149.4 (C6), 133.9 (C1), 131.6 (C18), 129.1 (C20), 128.7 (C19), 128.1 (C4), 121.5 (C17), 121.2 (C2), 118.3 (C3), 107.1 (C5), 89.6 (C16), 83.3 (C15), 79.6 (C8), 53.7 (C13), 37.7 (C10), 33.6 (C12), 31.3 (C7), 24.7 (C14), 21.4 (C11).

The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ H18 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1726, 1607, 1484, 1449, 1306, 1118, 1021, 756, 741, 691.

HRMS (ESI)  $m/z$  calcd. for C<sub>22</sub>H<sub>22</sub>ON [M+H]<sup>+</sup>: 316.1696; found: 316.1696.

(4a*R*,9a*S*)-4a,9-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **77**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture (excluding nucleophile) was degassed by three freeze–pump–thaw cycles prior to irradiation (the nucleophile was deoxygenated separately by sparging with argon before being added to the degassed reaction mixture). Irradiation was performed in the presence of triethylsilane (0.14 mL, 0.10 g, 0.88 mmol, 2.9 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) over a period of 6 h. Flash column chromatography on silica gel (gradient elution from 2.5 to 5% ethyl acetate in pentane) yielded **77** (51.8 mg, 0.241 mmol, 80%) as a viscous colourless oil.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data for this have been reported elsewhere in CDCl<sub>3</sub>.<sup>44</sup>

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 7.08 (1H, td,  $J$  7.6, 1.3, H4), 7.04 (1H, dd,  $J$  7.3, 1.3, H2), 6.72 (1H, td,  $J$  7.4, 1.0, H3), 6.60 (1H, d,  $J$  7.8, H5), 3.12 (1H, d,  $J$  1.1, H8), 2.65 (3H, s, H7), 2.58–2.48 (1H, m, H10), 2.31–2.20 (1H, m, H10'), 1.79–1.66 (3H, m, H11<sub>LHS</sub>, H11'<sub>LHS</sub> & H12<sub>RHS</sub>), 1.66–1.54 (1H, m, H12'), 1.32 (3H, s, H14).

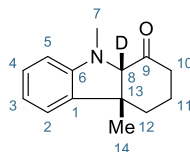
$^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  = 210.9 (C9), 151.0 (C6), 137.3 (C1), 127.7 (C4), 121.2 (C2), 118.6 (C3), 108.0 (C5), 81.0 (C8), 48.2 (C13), 37.7 (C10), 35.5 (C12), 34.7 (C7), 24.5 (C14), 20.7 (C11).

The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H8 $\leftrightarrow$ H14 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1713, 1605, 1483, 1453, 1309, 1259, 1140, 1022, 977, 743.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{18}\text{NO}$   $[\text{M}+\text{H}]^+$ : 216.1383; found: 216.1382.

(4a*R*,9a*S*)-4a,9-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one-9a-*d*, **193**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture (excluding nucleophile) was degassed by three freeze–pump–thaw cycles prior to irradiation (the nucleophile was added after this process *without* argon-sparging). Irradiation was performed in the presence of triethyl(silane-*d*) (0.14 mL, 0.10 g, 0.88 mmol, 2.9 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) over a period of 6 h. Flash column chromatography on silica gel (gradient elution from 2.5 to 5% ethyl acetate in pentane) yielded **193** (51.4 mg, 0.238 mmol, 79%, >99%  $\text{D}^*$ ) as a viscous pale-yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 7.08 (1H, td,  $J$  7.6, 1.3, H4), 7.04 (1H, dd,  $J$  7.3, 1.2, H2), 6.72 (1H, td,  $J$  7.4, 1.0, H3), 6.60 (1H, d,  $J$  7.8, H5), 2.65 (3H, s, H7), 2.59–2.49 (1H, m, H10), 2.31–2.19 (1H, m, H10'), 1.78–1.65 (3H, m, H11<sub>LHS</sub>, H11'<sub>LHS</sub> & H12<sub>RHS</sub>), 1.65–1.55 (1H, m, H12'), 1.32 (3H, s, H14).

$^2\text{H}$  NMR (92 MHz,  $\text{DMSO}-h_6$ )  $\delta^\dagger$  = 3.06 (s).

$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 210.9 (C9), 151.1 (C6), 137.3 (C1), 127.7 (C4), 121.2 (C2), 118.6 (C3), 108.0 (C5), 80.5 (1:1:1 t,  $^1J_{\text{CD}}$  21.5, C8), 48.1 (C13), 37.7 (C10), 35.5 (C12), 34.6 (C7), 24.4 (C14), 20.7 (C11).

The stereochemistry of this compound was assigned by analogy to that of its non-deuterated analogue, **77**.

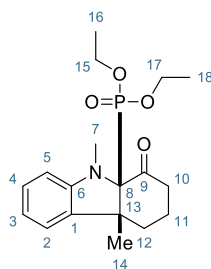
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1709, 1605, 1481, 1453, 1349, 1302, 1126, 1021, 932, 743.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{17}^2\text{HNO}$   $[\text{M}+\text{H}]^+$ : 217.1446; found: 217.1443.

\* Deuterium incorporation was estimated by HRMS; no signal corresponding to H8 was observed by  $^1\text{H}$  NMR spectroscopy.

† The  $^2\text{H}$  NMR spectrum was referenced to the triplet corresponding to  $\text{DMSO}-d_1$  observed at natural abundance; a deuterium chemical shift of 2.50 ppm was assumed for this signal.

Diethyl ((4*bR*,8*aR*)-4*b*,9-dimethyl-8-oxo-4*b*,5,6,7,8,9-hexahydro-8*aH*-carbazol-8*a*-yl)phosphonate, **194**



This compound was prepared from **162** (102.4 mg, 0.300 mmol, 1.0 eq.) according to General Procedure A, except that the reaction mixture was degassed by three freeze–pump–thaw cycles prior to irradiation. Irradiation was performed in the presence of diethylphosphite (116  $\mu$ L, 124 mg, 0.900 mmol, 3.0 eq.) in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) over a period of 18 h. Flash column chromatography on silica gel (eluent: 50% ethyl acetate in pentane) yielded **194** (60.0 mg, 0.171 mmol, 57%) as a viscous yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 7.03 (1H, td,  $J$  7.6, 1.3, H4), 6.92 (1H, dd,  $J$  7.3, 1.3, H2), 6.62 (1H, td,  $J$  7.4, 1.0, H3), 6.46 (1H, d,  $J$  7.8, H5), 4.25–4.05 (4H, m, H15, H15', H17 & H17'), 3.08 (3H, s, H7), 2.81–2.69 (1H, m, H10), 2.34–2.10 (3H, m, H12<sub>LHS</sub>, H12'<sub>LHS</sub> & H10'<sub>RHS</sub>), 1.99–1.87 (1H, m, H11), 1.43–1.31 (1H, m, H11'), 1.32–1.22 (6H, m, H16 & H18), 1.30 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 210.6 (d,  $^2J_{\text{CP}}$  9.6, C9), 150.3 (d,  $^3J_{\text{CP}}$  13.0, C6), 131.9 (d,  $^3J_{\text{CP}}$  14.1, C1), 127.9 (C4), 120.3 (C2), 117.6 (C3), 106.0 (C5), 84.7 (d,  $^1J_{\text{CP}}$  153.7, C8), 62.4 (d,  $^2J_{\text{CP}}$  7.2, C15 or C17), 62.3 (d,  $^2J_{\text{CP}}$  7.5, C15 or C17), 54.7 (d,  $^2J_{\text{CP}}$  1.8, C13), 40.1 (C10), 33.0 (C7), 30.9 (C12), 27.2 (d,  $^3J_{\text{CP}}$  5.4, C14), 22.8 (C11), 16.2\* (d,  $^3J_{\text{CP}}$  ca. 6, C16 or C18), 16.1\* (d,  $^3J_{\text{CP}}$  ca. 6, C16 or C18).

$^{31}\text{P}$  NMR (162 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 26.7 (minor), 19.4 (major).

The observation of transient nuclear Overhauser effect (nOe) enhancements by 1D NOESY for H15/H15'/H17 /H17' (signals coincident) upon selective inversion of H14 is consistent with the formation of the *cis*-fused heterocycle shown as the major diastereomer. This compound was formed and isolated as the major component of a mixture containing a compound with near-identical NMR spectroscopic features, assumed to be the corresponding *trans*-isomer, in a molar ratio between 20:1 and 19:1 (estimated from relative integrations of  $^{31}\text{P}$  resonances). Screening reactions performed during reaction optimisation (see below) revealed a strong

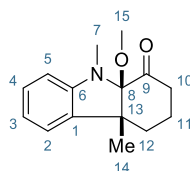
\* Overlap of these signals makes accurate determination of their  $J$  values difficult; approximate values are thus reported.

dependence of the ratio of these two products on solvent polarity; the *trans*-fused iminium trapping product was not observed for any nucleophile other than diethylphosphite.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1720, 1605, 1484, 1458, 1304, 1245, 1048, 1022, 965, 742.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{27}\text{NO}_4\text{P}$   $[\text{M}+\text{H}]^+$ : 352.1672; found: 352.1665.

(4a*R*,9a*R*)-9a-Methoxy-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **195**



This compound was isolated and characterised without chromatographic purification owing to its instability on silica and alumina gels. Enaminone **162** (34.1 mg, 0.0999 mmol, 1.0 eq.) and potassium phosphate (31.8 mg, 0.150 mmol, 1.5 eq.) were charged to a flame-dried Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the flask was evacuated and back-filled with argon three times. Anhydrous acetonitrile (1.8 mL; obtained from the solvent purification system described above) and methanol (0.2 mL; dried over 3 Å molecular sieves and filtered through a 0.2 µm PTFE syringe filter prior to use) (0.05 M), both argon-sparged, were added *via* syringe. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 2 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask, after which time the reaction mixture was concentrated *in vacuo*. The analytical data below were collected using a  $\text{CDCl}_3$  solution of the resulting material, which contained predominantly indoline **195** alongside trace unknown side-products. A near-identical experiment was performed in parallel, differing only in that dimethyl terephthalate was added to the reaction mixture at the end of the irradiation period as a solution in acetonitrile (25.0 mM, 1.0 mL, 0.25 mmol, 0.25 eq.). The resulting mixture was concentrated *in vacuo*, and the crude residue was dissolved in  $\text{CDCl}_3$  for analysis by quantitative  $^1\text{H}$  NMR spectroscopy. The NMR yield of indoline **195** measured against dimethyl terephthalate for this reaction was 77%.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.18 (1H, td,  $J$  7.6, 1.2, H4), 7.00 (1H, dd,  $J$  7.3, 1.3, H2), 6.80 (1H, td,  $J$  7.4, 1.0, H3), 6.49 (1H, d,  $J$  7.7, H5), 2.98 (3H, s, H15), 2.81 (3H, s, H7), 2.57–2.39 (2H, m, H10 & H10'), 1.73–1.60 (4H, m, H12<sub>LHS</sub>, H12'<sub>LHS</sub>, H11<sub>RHS</sub> & H11'<sub>RHS</sub>), 1.42 (3H, s, H14).

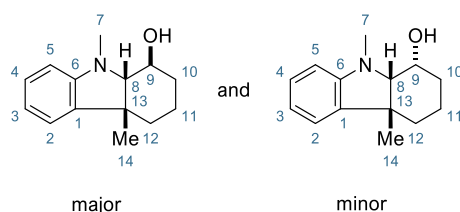
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 206.9 (C9), 149.4 (C6), 135.7 (C1), 128.4 (C4), 120.7 (C2), 118.9 (C3), 104.8 (C5), 100.1 (C8), 53.0(0) & 52.9(6) (C13 & C15), 41.4 (C12), 38.9 (C10), 29.3 (C7), 19.5 (C11), 18.9 (C14).

The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ H15 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1723, 1606, 1490, 1372, 1307, 1085, 1016, 929, 866, 741.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{20}\text{NO}_2$   $[\text{M}+\text{H}]^+$ : 246.1489; found: 246.1478;  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{Na}$   $[\text{M}+\text{Na}]^+$ : 268.1308; found: 268.1296.

(1*S*,4*aR*,9*aS*)-4*a*,9-dimethyl-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-carbazol-1-ol and  
(1*R*,4*aR*,9*aS*)-4*a*,9-dimethyl-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-carbazol-1-ol, **200**



Enaminone **162** (34.1 mg, 0.0999 mmol, 1.0 eq.) and thiophenol (31  $\mu\text{L}$ , 33 mg, 0.30 mmol, 3.0 eq.) were dissolved in acetonitrile (2.0 mL, 0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. Argon-sparged triethylsilane (31  $\mu\text{L}$ , 58 mg, 0.50 mol, 5.0 eq.) was added *via* syringe. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 18 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Triethylamine (2.0 mL) was added to the reaction mixture at the end of the irradiation period, and the resulting mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, dichloromethane) to afford **200** (12.5 mg, 0.0575 mmol, 58%, 1.3:1.0 d.r.) as a colourless oil.

Major:

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta^*$  = 7.14–7.10 (1H, m, H4), 6.99–6.95 (1H, m, H2), 6.77–6.73 (1H, m, H3), 6.60 (1H, d,  $J$  7.8, H5), 4.10–4.05 (1H, m, H9), 3.07 (1H, d,  $J$  3.9, H8), 2.94 (3H, s, H7), 1.93–1.86 (1H, m, H10), 1.70–1.60 (2H, m, H10'<sub>LHS</sub> & H11<sub>RHS</sub>), 1.56–1.47 (2H, m, H12<sub>LHS</sub> & H11'<sub>RHS</sub>), 1.46–1.40 (1H, m, H12'), 1.34 (3H, s, H14).

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  = 152.4 (C6), 139.2(2) (C1), 127.6 (C4), 121.1 (C2), 118.7 (C3), 108.6 (C5), 76.4 (C8), 69.3 (C9), 43.9 (C13), 37.1 (C7), 34.1 (C12), 27.7 (C10), 24.7 (C14), 18.8 (C11).

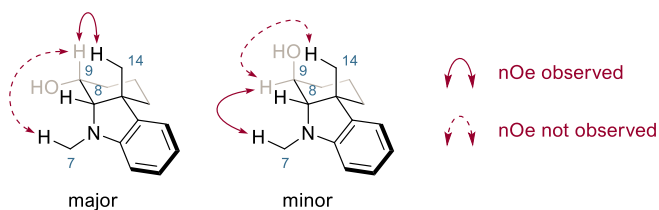
\* Chemical shift ranges and integrations reported for diastereotopic methylene signals were obtained indirectly using multiplicity-edited HSQC and HMBC data.

Minor:

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.12–7.08 (1H, m, H4), 6.99–6.95 (1H, m, H2), 6.75–6.70 (1H, m, H3), 6.53 (1H, d,  $J$  7.8, H5), 4.10–4.05 (1H, m, H9), 2.89 (1H, d,  $J$  4.0, H8), 2.84 (3H, s, H7), 1.81–1.72 (2H, m, H10<sub>LHS</sub> & H11<sub>RHS</sub>), 1.63–1.51 (3H, m, H12<sub>LHS</sub>, H10'<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.42 (3H, s, H14), 1.35–1.29 (1H, m, H11').

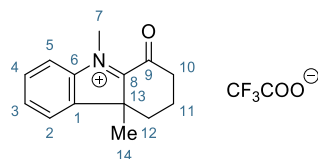
$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  = 151.2 (C6), 139.2(4) (C1), 127.5 (C4), 120.9 (C2), 118.4 (C3), 108.1 (C5), 77.9 (C8), 68.4 (C9), 43.0 (C13), 35.4 (C12), 35.1 (C7), 30.2 (C10), 25.7 (C14), 16.9 (C11).

The observation of strong nuclear Overhauser effect (nOe) correlations corresponding to H8 $\leftrightarrow$ H14 in both diastereomers, H9 $\leftrightarrow$ H14 in the major diastereomer only, and H7 $\leftrightarrow$ H9 in the minor diastereomer only is indicative of the relative stereochemistry depicted for each isomer.



FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3390 (br), 1605, 1483, 1457, 1300, 1251, 1133, 1056, 1022, 741.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{20}\text{ON}$   $[\text{M}+\text{H}]^+$ : 218.1539; found: 218.1539.

4a,9-Dimethyl-1-oxo-2,3,4,4a-tetrahydro-1*H*-carbazol-9-ium 2,2,2-trifluoroacetate, **178**

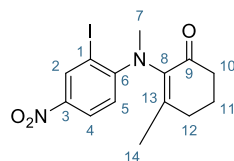
<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN) δ = 7.73–7.67 (1H, m, H5), 7.67–7.57 (3H, m, H2, H3 & H4), 6.40 (1H, dd, *J* 6.1, 3.3, H10), 4.22 (3H, s, H7), 2.93–2.81 (1H, m, H11), 2.61 (1H, dtd, *J* 20.8, 6.0, 1.3, H11'), 2.52 (1H, ddt, *J* 13.5, 5.1, 0.9, H12), 1.94–1.85 (1H, m, H12'), 1.49 (3H, s, H14).

<sup>13</sup>C NMR (126 MHz, CD<sub>3</sub>CN) δ 180.3 (C8), 159.4 (q, <sup>2</sup>J<sub>CF</sub> 39.7, CF<sub>3</sub>CCOO<sup>-</sup>), 144.3 (C6), 142.8 (C9), 142.0 (C1), 131.5 (C10), 130.9 (C3), 130.5 (C2 or C4), 124.2 (C2 or C4), 116.3 (q, <sup>1</sup>J<sub>CF</sub> 286.4, CF<sub>3</sub>CCOO<sup>-</sup>), 116.2 (C5), 53.9 (C13), 37.1 (C7), 31.9 (C12), 24.1 (C11), 22.5 (C14).



## Synthesis of *para*-nitro and *para*-*N*-acetyl substrates **222** and **223**

### 2-((2-Iodo-4-nitrophenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **222**



Copper(II) nitrate trihydrate (483 mg, 2.00 mmol, 1.0 eq.) was added in one portion to **162** (682 mg, 2.00 mmol, 1.0 eq.) dissolved in a 1:1 (v/v) mixture of acetic anhydride (2.0 mL) and glacial acetic acid (2.0 mL) (0.5 M) at room temperature. After sonicating for 2 min, the reaction mixture was stirred at room temperature for 1 h before being added dropwise to a mixture of sodium hydrogencarbonate (*ca.* 6 g) in water (100 mL) with vigorous stirring. The resulting mixture was transferred to a separating funnel using ethyl acetate (50 mL) and a small volume of water. After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (sat. aq., 75 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* (residual acetic anhydride was azeotropically removed with toluene). The crude residue was purified by flash column chromatography (silica gel, 1% ethyl acetate in dichloromethane) to afford **222** (220 mg, 0.570 mmol, 28%) as an extremely viscous orange-brown oil, which turned over slowly upon storage at -18 °C to an orange solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.61 (1H, d, *J* 2.7, H2), 8.15 (1H, dd, *J* 9.2, 2.7, H4), 6.95 (1H, d, *J* 9.2, H5), 3.11 (3H, s, H7), 2.52 (4H, app. t, *J* 6.4, H10 & H12), 2.13–2.02 (2H, m, H11), 1.82 (3H, s, H14).

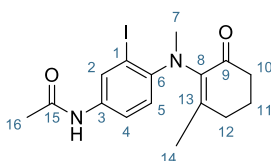
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 195.0 (C9), 156.8 & 156.7 (C6 & C13), 140.4 (C3), 139.6 (C8), 138.0 (C2), 124.9 (C4), 116.4 (C5), 80.8 (C1), 41.5 (C7), 37.9 (C10), 32.6 (C12), 21.7 (C11 & C14, coincident).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1674, 1576, 1498, 1320, 1307, 1264, 1208, 1114, 748, 727.

HRMS (APCI) *m/z* calcd. for C<sub>14</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub>I [M+H]<sup>+</sup>: 387.0200; found: 387.0200.

MP 85–87 °C.

### *N*-(3-Iodo-4-(methyl(2-methyl-6-oxocyclohex-1-en-1-yl)amino)phenyl)acetamide, **223**



Nitro compound **222** (182 mg, 0.471 mmol, 1.0 eq.) was dissolved in a 2:1 (v/v) mixture of ethanol (3.2 mL) and glacial acetic acid (1.6 mL) (0.1 M). Iron powder (263 mg, 4.71 mmol, 10 eq.) was added slowly in portions at room temperature with stirring before heating the mixture to 60 °C for 2 h. After this time, the reaction mixture was cooled to room temperature and added slowly by dropping funnel to a mixture of sodium hydrogencarbonate (*ca.* 3 g) in water (50 mL) with vigorous stirring. The neutralised reaction mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (75 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was dissolved in dichloromethane (4.8 mL) along with acetic anhydride (0.13 mL, 0.14 g, 1.4 mmol). The reaction mixture was stirred at room temperature for 2 h before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 25% ethyl acetate in dichloromethane) to afford **223** (104 mg, 0.261 mmol, 55% over two steps from **222**) as a light brown foam solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.84 (1H, d, *J* 2.5, H2), 7.62 (1H, br s, NH), 7.38 (1H, dd, *J* 8.8, 2.5, H4), 6.93 (1H, d, *J* 8.8, H5), 3.02 (3H, s, H7), 2.52–2.39 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.09 (3H, s, H16), 2.07–1.97 (2H, m, H11), 1.77 (3H, s, H14).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 196.9 (C9), 168.4 (C15), 155.2 (C13), 148.4 (C6), 140.6 (C8), 132.6 (C2), 132.3 (C3), 121.2 (C4), 120.0 (C5), 87.4 (C1), 40.8 (C7), 38.8 (C10), 33.0 (C12), 24.4 (C16), 21.9 (C11), 21.6 (C14).

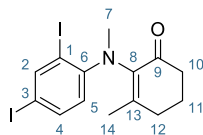
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3307 (br), 1664, 1592, 1520, 1487, 1384, 1310, 1290, 1117, 731.

HRMS (ESI) *m/z* calcd. for C<sub>16</sub>H<sub>19</sub>O<sub>2</sub>N<sub>2</sub>INa [M+Na]<sup>+</sup>: 421.0383; found: 421.0378.

MP 64–68 °C (ambiguous phase transition owing to foam nature of solid).

## Synthesis of *para*-iodo substrate **224**

### 2-((2,4-Diiodophenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **224**



To a solution of **162** (341 mg, 0.999 mmol, 1.0 eq.) in dichloromethane (5 mL, 0.2 M) at room temperature was added iodine (279 mg, 1.10 mmol, 1.1 eq.) and silver sulfate (343 mg, 1.10 mmol, 1.1 eq.) with vigorous stirring. After 3 h, the reaction mixture was filtered through celite, and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 25% diethyl ether in pentane) to afford **224** (292 mg, 0.668 mmol, 63%) as a pale-yellow solid.

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.99 (1H, d,  $J$  2.1, H2), 7.51 (1H, dd,  $J$  8.7, 2.1, H4), 6.77 (1H, d,  $J$  8.6, H5), 3.01 (3H, s, H7), 2.50–2.43 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.02 (2H, quint, H11), 1.79 (3H, s, H14).

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  = 196.1 (C9), 155.4 (C13), 151.7 (C6), 148.3 (C2), 140.2 (C8), 137.5 (C4), 121.5 (C5), 87.9 & 83.3 (C1 & C3), 40.7 (C7), 38.6 (C10), 32.9 (C12), 21.9 (C11), 21.6 (C14).

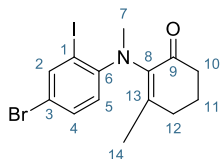
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1673, 1563, 1465, 1375, 1290, 1202, 1118, 1013, 807, 730.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{15}\text{NINa}$   $[\text{M}+\text{Na}]^+$ : 489.9135; found: 489.9135.

MP 89–90 °C.

## Synthesis of *para*-bromo substrate **225**

### 2-((4-Bromo-2-iodophenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **225**



*N*-Bromosuccinimide (187 mg, 1.05 mmol, 1.05 eq.) was added in one portion to a stirred solution of **162** (341 mg, 0.999 mmol, 1.0 eq.) in acetonitrile (10 mL, 0.1 M) at room temperature. The reaction mixture was stirred for 1 h at this temperature before charging additional *N*-bromosuccinimide (18 mg, 0.10 mmol, 0.1 eq.). After stirring for a further 3 h, the reaction mixture was concentrated *in vacuo*, and the crude residue thus obtained was dissolved in ethyl acetate (10 mL) and washed with sodium hydrogencarbonate (sat. aq., 2 x 5 mL) and brine (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 30 to 40% diethyl ether in pentane) to afford **225** (189 mg, 0.450 mmol, 45%) as a pale-yellow solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.82 (1H, d,  $J$  2.3, H2), 7.35 (1H, dd,  $J$  8.7, 2.4, H4), 6.89 (1H, d,  $J$  8.8, H5), 3.02 (3H, s, H7), 2.51–2.42 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.08–1.97 (2H, m, H11), 1.80 (3H, t,  $J$  0.9, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 196.2 (C9), 155.4 (C13), 151.1 (C6), 142.7 (C2), 140.3 (C8), 131.6 (C4), 120.9 (C5), 113.2 (C3), 87.3 (C1), 40.8 (C7), 38.6 (C10), 32.9 (C12), 21.9 (C11), 21.6 (C14).

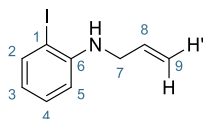
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1674, 1468, 1375, 1290, 1203, 1118, 1018, 913, 802, 743.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{16}\text{ON}^{79}\text{BrI}$  ( $\text{C}_{14}\text{H}_{16}\text{ON}^{81}\text{BrI}$ )  $[\text{M}+\text{H}]^+$ : 419.9454 (421.9434); found: 419.9454 (421.9432).

MP 87–88 °C

## Synthesis of *N*-allyl substrate **226**

### *N*-Allyl-2-iodoaniline, **230**



To a stirred mixture of 2-iodoaniline (4.38 g, 20.0 mmol, 1.0 eq.) and potassium carbonate (3.04 g, 22.0 mmol, 1.1 eq.) in *N,N*-dimethylformamide (40 mL, 0.5 M) was added allyl bromide (1.9 mL, 2.7 g, 22 mmol, 1.1 eq.) in one portion at room temperature. After 18 h, the reaction mixture was diluted with ethyl acetate (40 mL) and washed sequentially with water (3 x 40 mL) and brine (40 mL). The combined aqueous extracts were back-extracted with ethyl acetate (40 mL); the resulting organic layer was washed sequentially with water (3 x 40 mL) and brine (40 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 5 to 10% dichloromethane in pentane) to afford **230** (2.52 g, 9.72 mmol, 49%) as a colourless oil. The spectral data matched that previously reported in the literature.<sup>144</sup>

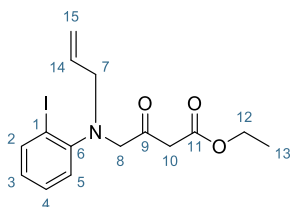
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.68 (1H, dd, *J* 7.8, 1.5, H2), 7.21 (1H, ddd, *J* 8.5, 7.3, 1.5, H4), 6.57 (1H, dd, *J* 8.2, 1.5, H5), 6.46 (1H, td, *J* 7.5, 1.5, H3), 5.97 (1H, ddt, *J* 17.2, 10.3, 5.1, H8), 5.31 (1H, dq, *J* 17.2, 1.7, H9), 5.22 (1H, dq, *J* 10.3, 1.5, H9'), 4.45–4.23 (1H, br m, NH), 3.84 (2H, tt, *J* 5.5, 1.7, H7).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 147.1 (C6), 139.1 (C2), 134.7 (C8), 129.5 (C4), 118.9 (C3), 116.6 (C9), 111.0 (C5), 85.5 (C1), 46.7 (C7).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3395 (br), 1590, 1505, 1452, 1316, 1287, 1164, 1004, 920, 741.

HRMS (ESI)  $m/z$  calcd. for C<sub>9</sub>H<sub>11</sub>NI [M+H]<sup>+</sup>: 259.9931; found: 259.9933.

### Ethyl 4-(allyl(2-iodophenyl)amino)-3-oxobutanoate, **324**



This compound was prepared by analogy to a literature procedure.<sup>140</sup> To a stirred mixture of **230** (2.35 g, 9.07 mmol, 1.0 eq.), sodium hydrogencarbonate (1.52 g, 18.1 mmol, 2.0 eq.) and sodium iodide (2.72 g, 18.1 mmol, 2.0 eq.) in acetonitrile (18 mL, 0.5 M) at room temperature was added ethyl 4-chloroacetoacetate (95% w/w, 2.6 mL, 18 mmol, 2.0 eq.) in one portion. The reaction mixture was heated to 75 °C for 18 h with stirring. After this time, the reaction mixture was allowed

to cool to room temperature before adding triethylamine (3.8 mL, 2.8 g, 2.7 mmol, 3.0 eq.) in one portion and stirring for a further 30 min. The reaction mixture was concentrated *in vacuo*, and the crude residue thus obtained was dissolved in ethyl acetate (40 mL) and washed successively with sodium thiosulfate (sat. aq., 20 mL) and water (20 mL). The aqueous washings were extracted with ethyl acetate (2 x 40 mL), and the combined organic extracts were subjected to a final wash with brine (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 2 to 10% ethyl acetate in pentane) to afford **324** (874 mg, 2.26 mmol, 25%) as a viscous yellow oil.

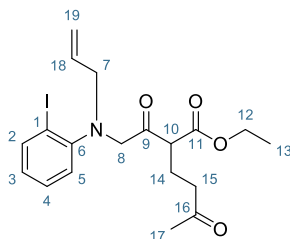
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.85 (1H, dd,  $J$  7.9, 1.5, H2), 7.29 (1H, ddd,  $J$  7.9, 7.3, 1.5, H4), 7.13 (1H, dd,  $J$  8.0, 1.6, H5), 6.82 (1H, ddd,  $J$  7.9, 7.3, 1.6, H3), 5.90 (1H, ddt,  $J$  16.8, 10.1, 6.6, H14), 5.27–5.16 (2H, m, H15), 4.14 (2H, q,  $J$  7.1, H12), 3.96 (2H, s, H8), 3.68 (2H, dt,  $J$  6.5, 1.3, H7), 3.52 (2H, s, H10), 1.23 (3H, t,  $J$  7.2, H13).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 202.5 (C9), 167.4 (C11), 151.2 (C6), 140.4 (C2), 133.9 (C14), 129.2 (C4), 126.4 (C3), 124.3 (C5), 119.5 (C15), 98.9 (C1), 61.9 (C8), 61.4 (C12), 58.5 (C7), 46.7 (C10), 14.2 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1744, 1720, 1469, 1315, 1220, 1033, 1014, 928, 761, 724.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{19}\text{O}_3\text{NI}$   $[\text{M}+\text{H}]^+$ : 388.0404; found: 388.0401.

#### Ethyl 2-(*N*-allyl-*N*-(2-iodophenyl)glycyl)-5-oxohexanoate, **325**



Aminoketone **324** (874 mg, 2.26 mmol, 1.0 eq.) was dissolved in dichloromethane (4.5 mL, 0.5 M). Potassium carbonate (312 mg, 2.26 mmol, 1.0 eq.) was added in one portion followed by freshly distilled methyl vinyl ketone (0.19 mL, 0.16 g, 2.3 mmol, 1.0 eq.). The reaction mixture was stirred for 21 h at room temperature before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 1.25 to 5% ethyl acetate in dichloromethane) to afford **325** (891 mg, 1.95 mmol, 86%) as a viscous orange-yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.84 (1H, dd,  $J$  7.9, 1.5, H2), 7.32–7.23 (1H, m, H4), 7.15 (1H, dd,  $J$  8.0, 1.6, H5), 6.80 (1H, td,  $J$  7.6, 1.6, H3), 5.90 (1H, ddt,  $J$  16.7, 10.1, 6.5, H18), 5.27–5.15 (2H, m, H19), 4.09 (2H, q,  $J$  7.1, H12), 4.05 (2H, app. s, H8), 3.82–3.73 (2H, m, H10<sub>LHS</sub> & H7<sub>RHS</sub>),

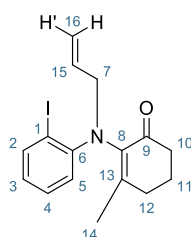
3.66 (1H, ddt, *J* 14.4, 6.7, 1.3, H7'), 2.29 (2H, t, *J* 7.3, H15), 2.04 (3H, s, H17), 2.06–1.91 (2H, m, H14), 1.17 (3H, t, *J* 7.1, H13).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 207.5 (C16), 204.3 (C9), 169.2 (C11), 151.2 (C6), 140.3 (C2), 134.3 (C18), 129.0 (C4), 126.2 (C3), 124.6 (C5), 119.2 (C19), 98.8 (C1), 61.5 (C12), 61.0 (C8), 58.1 (C7), 53.6 (C10), 40.6 (C15), 29.9 (C17), 21.5 (C14), 14.1 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1743, 1716, 1469, 1368, 1212, 1161, 1014, 931, 762, 723.

HRMS (ESI) *m/z* calcd. for C<sub>19</sub>H<sub>24</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup>: 480.0642; found: 480.0636.

## 2-(Allyl(2-iodophenyl)amino)-3-methylcyclohex-2-en-1-one, **226**



Sodium methoxide (30 wt% in methanol, 0.40 mL, 0.12 g, 2.2 mmol, 1.1 eq.) was added in one portion to a stirred, argon-sparged solution of diketone **325** (901 mg, 1.97 mmol, 1.0 eq.) in methanol (20 mL, 0.1 M) at room temperature. The reaction mixture was stirred at this temperature for a further 2 h before adding a solution of lithium hydroxide monohydrate (83 mg, 2.0 mmol, 1.0 eq.) in water (10 mL) and heating to 75 °C. After 10 min, the reaction mixture was cooled to room temperature and acidified to *ca.* pH 2 with HCl (1 M aq., *ca.* 10 mL). The reaction mixture was heated to 75 °C for a further 30 min before cooling to room temperature, adding water (20 mL) and extracting with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 10 to 20% diethyl ether in pentane) to afford **226** (511 mg, 1.39 mmol, 71%) as a pale-yellow solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.75 (1H, dd, *J* 7.9, 1.6, H2), 7.20 (1H, ddd, *J* 8.2, 7.2, 1.6, H4), 7.03 (1H, dd, *J* 8.2, 1.6, H5), 6.61 (1H, ddd, *J* 7.8, 7.2, 1.5, H3), 5.95 (1H, ddt, *J* 17.3, 10.2, 6.2, H15), 5.14 (1H, dq, *J* 17.2, 1.7, H16), 5.08 (1H, dq, *J* 10.2, 1.4, H16'), 4.13 (2H, dt, *J* 6.2, 1.5, H7), 2.52–2.40 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.05–1.94 (2H, m, H11), 1.78 (3H, t, *J* 0.9, H14)

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 197.1 (C9), 155.8 (C13), 150.9 (C6), 141.0 (C2), 139.4 (C8), 135.7 (C15), 128.8 (C4), 123.5 (C3), 123.3 (C5), 117.5 (C16), 91.4 (C1), 55.1 (C7), 39.0 (C10), 33.0 (C12), 22.0 (C11), 21.7 (C14).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1672, 1579, 1469, 1432, 1193, 1170, 1011, 925, 758, 732.

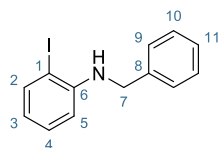
HRMS (ESI)  $m/z$  calcd. for  $C_{16}H_{19}INO$   $[M+H]^+$ : 368.0506; found: 368.0500.

MP 65–66 °C



## Synthesis of *N*-benzyl substrate **227**

### *N*-benzyl-2-iodoaniline, **231**



This compound was prepared according to a literature procedure.<sup>145</sup> Sodium cyanoborohydride (754 mg, 12.0 mmol, 1.2 eq.) was added in portions to a stirred mixture of 2-iodoaniline (2.19 g, 10.0 mmol, 1.0 eq.), benzaldehyde (1.2 mL, 1.3 g, 12 mmol, 1.2 eq.) and zinc chloride (1.64 g, 12.0 mmol, 1.2 eq.) in methanol (50 mL, 0.2 M) at room temperature. A condenser was attached to the flask, and the reaction mixture was heated to reflux. After 2 h, the reaction mixture was cooled to room temperature and quenched by the addition of sodium hydroxide (1 M aq., 50 mL). The resulting mixture was transferred to a separating funnel using water (25 mL) and diethyl ether (50 mL). After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 25 mL). The combined organic extracts were washed with brine (sat. aq., 50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10% pentane in dichloromethane) to afford **231** (2.71 g, 8.77 mmol, 88%) as a yellow oil. The spectral data matched that previously reported in the literature.<sup>146</sup>

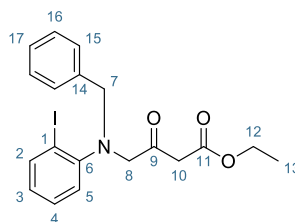
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.71 (1H, dd, *J* 7.8, 1.5, H<sub>2</sub>), 7.44–7.27 (5H, m, H<sub>9LHS</sub>, H<sub>10LHS</sub> & H<sub>11RHS</sub>), 7.22–7.14 (1H, m, H<sub>4</sub>), 6.57 (1H, dd, *J* 8.2, 1.5, H<sub>5</sub>), 6.48 (1H, ddd, *J* 7.8, 7.3, 1.5, H<sub>3</sub>), 4.66 (1H, br t, *J* 5.6, NH), 4.43 (2H, d, *J* 5.6, H<sub>7</sub>).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 147.2 (C<sub>6</sub>), 139.1 (C<sub>2</sub>), 138.8 (C<sub>8</sub>), 129.6 (C<sub>4</sub>), 128.8 (C<sub>10</sub>), 127.4 (C<sub>11</sub>), 127.3 (C<sub>9</sub>), 119.0 (C<sub>3</sub>), 111.1 (C<sub>5</sub>), 85.4 (C<sub>1</sub>), 48.5 (C<sub>7</sub>).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3403 (br), 1590, 1505, 1450, 1425, 1319, 1295, 1005, 741, 697.

HRMS (ESI)  $m/z$  calcd. for C<sub>13</sub>H<sub>13</sub>NI [M+H]<sup>+</sup>: 310.0087; found: 310.0085.

### Ethyl 4-(benzyl(2-iodophenyl)amino)-3-oxobutanoate, **326**



This compound was prepared by analogy to a literature procedure.<sup>140</sup> To a stirred mixture of **231** (4.31 g, 13.9 mmol, 1.0 eq.), sodium hydrogencarbonate (2.34 g, 27.9 mmol, 2.0 eq.) and sodium

iodide (4.18 g, 27.9 mmol, 2.0 eq.) in acetonitrile (28 mL, 0.5 M) at room temperature was added ethyl 4-chloroacetoacetate (95% w/w, 4.0 mL, 28 mmol, 2.0 eq.) in one portion. The reaction mixture was heated to 75 °C for 18 h with stirring. After this time, the reaction mixture was allowed to cool to room temperature, before adding triethylamine (5.8 mL, 4.2 g, 42 mmol, 3.0 eq.) in one portion and stirring for a further 30 min. The reaction mixture was concentrated *in vacuo*, and the crude residue thus obtained was dissolved in ethyl acetate (60 mL) and washed successively with sodium thiosulfate (sat. aq., 30 mL) and water (30 mL). The aqueous washings were extracted with ethyl acetate (2 x 60 mL), and the combined organic extracts were subjected to a final wash with brine (90 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified twice by flash column chromatography (silica gel, 10% ethyl acetate in pentane; then, silica gel, dichloromethane) to afford **326** (1.74 g, 3.98 mmol, 29%) as a viscous yellow oil.

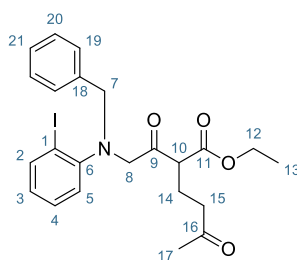
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.87 (1H, dd,  $J$  7.9, 1.5, H2), 7.41–7.21 (6H, m, H4, H15, H16 & H17), 7.17 (1H, dd,  $J$  8.1, 1.6, H5), 6.82 (1H, td,  $J$  7.5, 1.6, H3), 4.30 (2H, s, H7), 4.11 (2H, q,  $J$  7.1, H12), 3.91 (2H, s, H8), 3.43 (2H, s, H10), 1.19 (3H, t,  $J$  7.1, H13).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 201.9 (C9), 167.1 (C11), 151.1 (C6), 140.3 (C2), 136.9 (C14), 129.3 (C15), 129.1 (C4), 128.5 (C16), 127.8 (C17), 126.5 (C3), 125.1 (C5), 98.6 (C1), 61.7 (C8), 61.4 (C12), 58.8 (C7), 46.8 (C10), 14.2 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1746, 1721, 1469, 1314, 1031, 1014, 763, 738, 721, 700.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{21}\text{O}_3\text{NI}$   $[\text{M}+\text{H}]^+$ : 438.0561; found: 438.0561.

Ethyl 2-(*N*-benzyl-*N*-(2-iodophenyl)glycyl)-5-oxohexanoate, **327**



Aminoketone **326** (1.13 g, 2.58 mmol, 1.0 eq.) was dissolved in dichloromethane (5.2 mL, 0.5 M). Potassium carbonate (357 mg, 2.58 mmol, 1.0 eq.) was added in one portion followed by freshly distilled methyl vinyl ketone (0.22 mL, 0.19 g, 2.6 mmol, 1.0 eq.). The reaction mixture was stirred for 21 h at room temperature before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 5% ethyl acetate in dichloromethane) to afford **327** (1.04 g, 2.05 mmol, 79%) as a viscous pale-yellow oil.

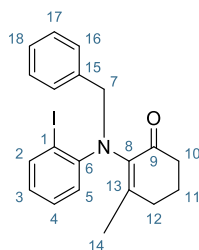
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.86 (1H, dd,  $J$  7.9, 1.4, H2), 7.44–7.36 (2H, m, H19), 7.35–7.20 (5H, m, H4, H5<sub>RHS</sub>, H20 & H21), 6.81 (1H, ddd,  $J$  7.8, 7.0, 1.8, H3), 4.40 (1H, d,  $J$  13.9, H7), 4.30 (1H, d,  $J$  13.9, H7'), 4.08–3.98 (3H, m, H8 & H12), 3.94 (1H, d,  $J$  17.9, H8'), 3.67 (1H, t,  $J$  7.1, H10), 2.26 (2H, t,  $J$  7.3, H15), 2.03 (3H, s, H17), 2.03–1.84 (2H, m, H14), 1.10 (3H, t,  $J$  7.1, H13).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 207.5 (C16), 204.1 (C9), 169.0 (C11), 151.2 (C6), 140.2 (C2), 137.3 (C18), 129.2 (C19), 129.0 (C4), 128.5 (C20), 127.7 (C21), 126.3 (C3), 125.4 (C5), 98.6 (C1), 61.5 (C12), 60.8 (C8), 58.4 (C7), 53.9 (C10), 40.5 (C15), 29.9 (C17), 21.6 (C14), 14.1 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1743, 1716, 1469, 1369, 1206, 1160, 1015, 763, 721, 699.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{27}\text{O}_4\text{NI}$   $[\text{M}+\text{H}]^+$ : 508.0979; found: 508.0986.

## 2-(Benzyl(2-iodophenyl)amino)-3-methylcyclohex-2-en-1-one, **227**



Sodium methoxide (30 wt% in methanol, 0.75 mL, 0.22 g, 4.0 mmol, 1.1 eq.) was added in one portion to a stirred, argon-sparged solution of diketone **327** (1.85 g, 3.65 mmol, 1.0 eq.) in methanol (36 mL, 0.1 M) at room temperature. The reaction mixture was stirred at this temperature for a further 2 h before adding a solution of lithium hydroxide monohydrate (153 mg, 3.65 mmol, 1.0 eq.) in water (18 mL) and heating to 75 °C. After 10 min, the reaction mixture was cooled to room temperature and acidified to *ca.* pH 2 with HCl (1 M aq., *ca.* 18 mL). The reaction mixture was heated to 75 °C for a further 30 min before cooling to room temperature, adding water (40 mL) and extracting with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 10 to 20% diethyl ether in pentane) to afford **227** (586 mg, 1.40 mmol, 39%) as a viscous yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.78 (1H, dd,  $J$  7.9, 1.5, H2), 7.47–7.40 (2H, m, H16), 7.30–7.22 (2H, m, H17), 7.22–7.12 (2H, m, H18<sub>LHS</sub> & H4<sub>RHS</sub>), 7.07 (1H, dd,  $J$  8.2, 1.6, H5), 6.63 (1H, ddd,  $J$  7.9, 7.1, 1.6, H3), 4.73 (2H, s, H7), 2.38–2.28 (4H, m, H12<sub>LHS</sub> & H10<sub>RHS</sub>), 1.93–1.83 (2H, m, H11), 1.81 (3H, t,  $J$  1.0, H14).

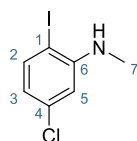
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 197.6 (C9), 155.5 (C13), 150.5 (C6), 140.9 (C2), 140.1 (C8), 138.5 (C15), 128.9 (C4), 128.6 (C16), 128.2 (C17), 127.0 (C18), 124.6 (C5), 124.1 (C3), 92.9 (C1), 55.9 (C7), 39.0 (C10), 33.0 (C12), 22.0 (C11), 21.5 (C14).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1673, 1579, 1465, 1432, 1165, 1011, 928, 760, 726, 698.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{20}\text{H}_{20}\text{ONa}$   $[\text{M}+\text{Na}]^+$ : 440.0482; found: 440.0480.

## Synthesis of 5-chloro substrate **228**

### 5-Chloro-2-iodo-*N*-methylaniline, **232**



*n*-Butyllithium in hexanes (8.8 mL, 2.5 M, 22 mmol, 1 eq.) was added over 30 min *via* syringe pump to a stirred, -78 °C solution of 5-chloro-2-iodoaniline (5.07 g, 20.0 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (40 mL, 0.5 M) under an argon atmosphere. Methyl iodide (1.4 mL, 3.2 g, 22 mmol, 1.1 eq.) was added in one portion after complete addition of the organometallic reagent. After a further 5 min at -78 °C, the acetone–dry ice bath was replaced with a tepid water bath, and the reaction mixture was allowed to warm to room temperature over a period of 2 h. Ammonium chloride solution (sat. aq., 40 mL) was added, followed by diethyl ether (40 mL). The layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 40 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 5 to 10% dichloromethane in pentane) to afford **232** (2.38 g, 8.90 mmol, 44%) as a yellow oil.

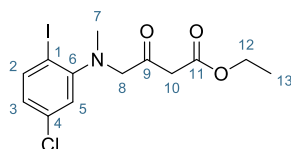
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.53 (1H, d, *J* 8.3, H2), 6.51 (1H, d, *J* 2.3, H5), 6.45 (1H, dd, *J* 8.3, 2.4, H3), 4.28 (1H, br s, NH), 2.88 (3H, d, *J* 5.1, H7).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 149.2 (C6), 139.4 (C2), 135.8 (C4), 118.4 (C3), 110.0 (C5), 82.0 (C1), 31.0 (C7).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3405 (br), 1584, 1506, 1399, 1284, 1094, 1003, 880, 830, 783.

HRMS (APCI) *m/z* calcd. for C<sub>7</sub>H<sub>8</sub>NCI<sup>+</sup> [M+H]<sup>+</sup>: 267.9384; found: 267.9385.

### Ethyl 4-((5-chloro-2-iodophenyl)(methyl)amino)-3-oxobutanoate, **328**



This compound was prepared by analogy to a literature procedure.<sup>140</sup> To a stirred mixture of **232** (1.75 g, 6.54 mmol, 1.0 eq.), sodium hydrogencarbonate (1.10 g, 13.1 mmol, 2.0 eq.) and sodium iodide (1.96 g, 13.1 mmol, 2.0 eq.) in acetonitrile (13 mL, 0.5 M) at 75 °C was added ethyl 4-chloroacetoacetate (95% w/w, 1.9 mL, 13 mmol, 2.0 eq.) over 30 min *via* syringe pump. After heating for a further 12 h, the reaction mixture was concentrated *in vacuo*, and the crude residue thus obtained was dissolved in ethyl acetate (30 mL) and washed successively with sodium

thiosulfate (sat. aq., 15 mL) and water (15 mL). The aqueous washings were extracted with ethyl acetate (2 x 30 mL), and the combined organic extracts were subjected to a final wash with brine (45 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution 10 to 20% diethyl ether in pentane) to afford **328** (670 mg, 1.69 mmol, 26%) as a viscous yellow oil.

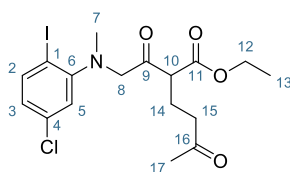
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.73 (1H, d,  $J$  8.4, H2), 7.12 (1H, d,  $J$  2.4, H5), 6.80 (1H, dd,  $J$  8.4, 2.4, H3), 4.18 (2H, q,  $J$  7.1, H12), 3.94 (2H, s, H8), 3.59 (2H, s, H10), 2.81 (3H, s, H7), 1.26 (3H, t,  $J$  7.1, H13).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 201.0 (C9), 167.2 (C11), 154.2 (C6), 140.9 (C2), 135.3 (C4), 126.0 (C3), 123.2 (C5), 93.8 (C1), 65.5 (C8), 61.6 (C12), 46.6 (C10), 42.7 (C7), 14.2 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1745, 1721, 1457, 1315, 1228, 1185, 1098, 1032, 1016, 805.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{16}\text{ClINO}_3$   $[\text{M}+\text{H}]^+$ : 395.9858; found: 395.9857.

Ethyl 2-(*N*-(5-chloro-2-iodophenyl)-*N*-methylglycyl)-5-oxohexanoate, **329**



Aminoketone **328** (1.03 g, 2.60 mmol, 1.0 eq.) was dissolved in dichloromethane (5.2 mL, 0.5 M). Potassium carbonate (360 mg, 2.60 mmol, 1.0 eq.) was added in one portion followed by freshly distilled methyl vinyl ketone (0.22 mL, 0.18 g, 2.6 mmol, 1.0 eq.). The reaction mixture was stirred for 24 h at room temperature before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 20% ethyl acetate in pentane) to afford **329** (807 mg, 1.73 mmol, 67%) as a viscous yellow oil.

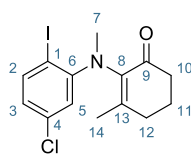
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.70 (1H, d,  $J$  8.4, H2), 7.12 (1H, d,  $J$  2.4, H5), 6.78 (1H, dd,  $J$  8.4, 2.4, H3), 4.14 (2H, q,  $J$  7.1, H12), 4.07 (1H, d,  $J$  18.0, H8), 3.99 (1H, d,  $J$  18.0, H8'), 3.73 (1H, t,  $J$  7.0, H10), 2.83 (3H, s, H7), 2.47 (2H, t,  $J$  7.1, H15), 2.13–2.02 (2H, m, H14), 2.10 (3H, s, H17), 1.22 (3H, t,  $J$  7.1, H13).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 207.6 (C16), 202.6 (C9), 169.2 (C11), 154.2 (C6), 140.9 (C2), 135.1 (C4), 125.7 (C3), 123.2 (C5), 93.4 (C1), 64.7 (C8), 61.7 (C12), 54.1 (C10), 42.3 (C7), 40.6 (C15), 30.0 (C17), 21.7 (C14), 14.2 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1744, 1716, 1571, 1457, 1368, 1187, 1161, 1099, 1014, 805.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{22}\text{O}_4\text{NCI}$   $[\text{M}+\text{H}]^+$ : 466.0277; found: 466.0277.

2-((5-Chloro-2-iodophenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **228**



Sodium methoxide (30 wt% in methanol, 0.33 mL, 0.096 g, 1.8 mmol, 1.1 eq.) was added in one portion to a stirred, argon-sparged solution of diketone **329** (749 mg, 1.61 mmol, 1.0 eq.) in methanol (16 mL, 0.1 M) at room temperature. The reaction mixture was stirred at this temperature for a further 2 h before adding a solution of lithium hydroxide monohydrate (68 mg, 1.6 mmol, 1.0 eq.) in water (8 mL) and heating to 75 °C. After 10 min, the reaction mixture was cooled to room temperature and acidified to *ca.* pH 2 with HCl (1 M aq., *ca.* 8 mL). The reaction mixture was heated to 75 °C for a further 30 min before cooling to room temperature, adding water (20 mL) and extracting with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified three times by flash column chromatography (silica gel, 20% diethyl ether in pentane; then, silica gel, dichloromethane; then, silica gel, 20% tetrahydrofuran in pentane) to afford **228** (253 mg, 0.674 mmol, 42%) as a pale-yellow solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.60 (1H, d, *J* 8.4, H2), 6.97 (1H, d, *J* 2.4, H5), 6.56 (1H, dd, *J* 8.4, 2.4, H3), 3.03 (3H, s, H7), 2.53–2.42 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.09–1.98 (2H, m, H11), 1.79 (3H, t, *J* 0.9, H14).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 196.0 (C9), 155.4 (C13), 152.8 (C6), 142.0 (C2), 140.1 (C8), 135.0 (C4), 122.2 (C3), 119.7 (C5), 83.6 (C1), 40.8 (C7), 38.5 (C10), 32.9 (C12), 21.8 (C11), 21.5 (C14).

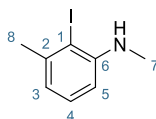
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1675, 1570, 1467, 1393, 1373, 1203, 1109, 1005, 930, 792.

HRMS (ESI) *m/z* calcd. for C<sub>14</sub>H<sub>16</sub>ONClI [M+H]<sup>+</sup>: 375.9960; found: 375.9961.

MP 81–83 °C.

## Synthesis of 3-methyl substrate **229**

### 2-Iodo-*N*,3-dimethylaniline, **234**



2-Iodo-3-nitrotoluene (5.00 g, 19.0 mmol, 1.0 eq.) was dissolved in a 2:1 (v/v) mixture of ethanol (64 mL) and glacial acetic acid (32 mL) (0.2 M). Iron powder (10.6 g, 190 mmol, 10 eq.) was added slowly in portions at room temperature with stirring before heating the mixture to 60 °C for 2 h. After this time, the reaction mixture was cooled to room temperature and added slowly by dropping funnel to a mixture of sodium hydrogencarbonate (50 g) in water (500 mL) with vigorous stirring. The neutralised reaction mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was dissolved in anhydrous tetrahydrofuran (38 mL, 0.5 M) under an argon atmosphere, and the resulting solution was cooled to –78 °C in an acetone–dry ice bath and stirred magnetically. *n*-Butyllithium in hexanes (8.2 mL, 2.5 M in hexanes, 21 mmol) was added dropwise *via* syringe pump over 30 min to the reaction mixture. Methyl iodide (1.3 mL, 3.0 g, 21 mmol) was added in one portion after complete addition of the organometallic reagent. After a further 5 min at –78 °C, the acetone–dry ice bath was replaced with a tepid water bath, and the reaction mixture was allowed to warm to room temperature over 2 h. Ammonium chloride solution (sat. aq., 40 mL) was added, followed by diethyl ether (40 mL). The layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 40 mL). The combined organic extracts were washed with brine (sat. aq., 80 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 1% diethyl ether in pentane) to afford **234** (4.10 g, 16.6 mmol, 87% over two steps) as a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.13 (1H, t, *J* 7.7, H4), 6.68–6.61 (1H, m, H3), 6.43–6.36 (1H, m, H5), 4.39 (1H, br s, NH), 2.90 (3H, d, *J* 5.0, H7), 2.44 (3H, s, H8).

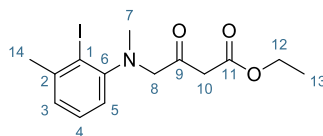
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 148.6 (C6), 142.3 (C2), 128.9 (C4), 118.7 (C3), 107.4 (C5), 92.6 (C1), 31.4 (C7), 29.7 (C8).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3407 (br), 1587, 1503, 1468, 1319, 1281, 1159, 1002, 764, 703.

HRMS (ESI) *m/z* calcd. for C<sub>8</sub>H<sub>11</sub>IN [M+H]<sup>+</sup>: 247.9931; found: 247.9929.



### Ethyl 4-((2-iodo-3-methylphenyl)(methyl)amino)-3-oxobutanoate, **330**



This compound was prepared by analogy to a literature procedure.<sup>140</sup> To a stirred mixture of **234** (3.97 g, 16.1 mmol, 1.0 eq.), sodium hydrogencarbonate (2.70 g, 32.1 mmol, 2.0 eq.) and sodium iodide (4.82 g, 32.2 mmol, 2.0 eq.) in acetonitrile (32 mL, 0.5 M) at room temperature was added ethyl 4-chloroacetoacetate (95% w/w, 4.6 mL, 32 mmol, 2.0 eq.) in one portion. The reaction mixture was heated to 75 °C for 18 h with stirring. After this time, the reaction mixture was allowed to cool to room temperature before adding triethylamine (6.7 mL, 4.9 g, 48 mmol, 3.0 eq.) in one portion and stirring for a further 30 min. The reaction mixture was concentrated *in vacuo*, and the crude residue thus obtained was dissolved in ethyl acetate (60 mL) and washed successively with sodium thiosulfate (sat. aq., 30 mL) and water (30 mL). The aqueous washings were extracted with ethyl acetate (2 x 60 mL), and the combined organic extracts were subjected to a final wash with brine (90 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified twice by flash column chromatography (silica gel, 5% ethyl acetate in pentane; then, silica gel, dichloromethane) to afford **330** (2.47 g, 6.58 mmol, 41%) as a viscous yellow oil.

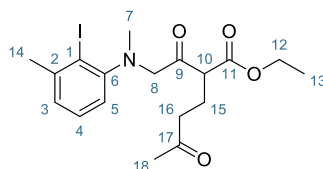
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.18 (1H, t, *J* 7.7, H4), 7.05–6.98 (1H, m, H3), 6.98–6.90 (1H, m, H5), 4.17 (2H, q, *J* 7.2, H12), 3.85 (2H, s, H8), 3.69 (2H, s, H10), 2.75 (3H, s, H7), 2.49 (3H, s, H14), 1.25 (3H, t, *J* 7.1, H13).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 202.2 (C9), 167.6 (C11), 153.7 (C6), 143.8 (C2), 128.7 (C4), 126.3 (C3), 119.8 (C5), 105.6 (C1), 66.5 (C8), 61.4 (C12), 46.6 (C10), 43.8 (C7), 30.0 (C14), 14.2 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1746, 1721, 1464, 1315, 1227, 1183, 1030, 1013, 785, 720.

HRMS (ESI) *m/z* calcd. for C<sub>14</sub>H<sub>19</sub>INO<sub>3</sub> [M+H]<sup>+</sup>: 376.0404; found: 376.0396.

### Ethyl 2-(*N*-(2-iodo-3-methylphenyl)-*N*-methylglycyl)-5-oxohexanoate, **331**



Aminoketone **330** (2.35 g, 6.26 mmol, 1.0 eq.) was dissolved in dichloromethane (12.5 mL, 0.5 M). Potassium carbonate (866 mg, 6.27 mmol, 1.0 eq.) was added in one portion followed by freshly distilled methyl vinyl ketone (0.52 mL, 0.44 g, 6.2 mmol, 1.0 eq.). The reaction mixture was stirred

for 21 h at room temperature before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 20 to 30% ethyl acetate in pentane) to afford **331** (2.45 g, 5.50 mmol, 88%) as a viscous yellow oil.

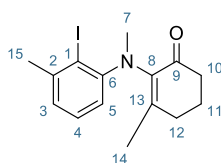
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.17 (1H, t,  $J$  7.7, H4), 7.00 (1H, ddd,  $J$  7.5, 1.5, 0.7, H3), 6.95 (1H, dd,  $J$  7.9, 1.6, H5), 4.13 (2H, q,  $J$  7.1, H12), 4.00–3.86 (3H, m, H8 & H10), 2.77 (3H, s, H7), 2.47 (3H, s, H14), 2.43 (2H, app. td,  $J$  7.0, 1.5, H16), 2.12–2.00 (2H, m, H15), 2.08 (3H, s, H18), 1.20 (3H, t,  $J$  7.1, H13).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 207.6 (C17), 203.7 (C9), 169.4 (C11), 153.6 (C6), 143.7 (C2), 128.6 (C4), 126.0 (C3), 119.9 (C5), 105.5 (C1), 65.7 (C8), 61.5 (C12), 53.7 (C10), 43.4 (C7), 40.7 (C16), 30.0(1) & 29.9(6) (C14 & C18), 21.8 (C15), 14.1 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1744, 1717, 1464, 1369, 1161, 1098, 1013, 860, 787, 720.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{25}\text{INO}_4$   $[\text{M}+\text{H}]^+$ : 446.0823; found: 446.0814.

#### 2-((2-Iodo-3-methylphenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **229**



Sodium methoxide (30 wt% in methanol, 1.06 mL, 0.308 g, 5.70 mmol, 1.1 eq.) was added in one portion to a stirred, argon-sparged solution of diketone **331** (2.31 g, 5.19 mmol, 1.0 eq.) in methanol (52 mL, 0.1 M) at room temperature. The reaction mixture was stirred at this temperature for a further 2 h before adding a solution of lithium hydroxide monohydrate (239 mg, 5.70 mmol, 1.1 eq.) in water (26 mL) and heating to 75 °C. After 10 min, the reaction mixture was cooled to room temperature and acidified to *ca.* pH 2 with HCl (1 M aq., *ca.* 26 mL). The reaction mixture was heated to 75 °C for a further 30 min before cooling to room temperature, adding water (50 mL) and extracting with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 20% diethyl ether in pentane) to afford **229** (1.13 g, 3.18 mmol, 61%) as a cream-coloured solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.13 (1H, dd,  $J$  8.1, 7.3, H4), 6.87 (1H, dd,  $J$  8.2, 1.6, H5), 6.84 (1H, ddd,  $J$  7.3, 1.6, 0.7, H3), 3.08 (3H, s, H7), 2.51–2.39 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.43 (3H, s, H15), 2.06–1.95 (2H, m, H11), 1.76 (3H, t,  $J$  0.9, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 196.8 (C9), 154.1 (C13), 152.8 (C6), 143.2 (C2), 141.2 (C8), 128.2 (C4), 122.9 (C3), 118.9 (C5), 97.3 (C1), 41.2 (C7), 39.0 (C10), 33.1 (C12), 30.7 (C15), 22.0 (C11), 21.5 (C14).

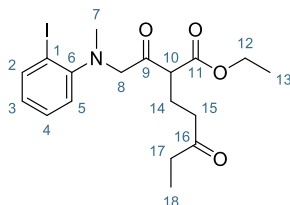
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1675, 1575, 1462, 1290, 1199, 1079, 1007, 937, 777, 731.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{19}\text{INO}$   $[\text{M}+\text{H}]^+$ : 356.0506; found: 356.0503.

MP 90–92 °C.

## Synthesis of $\beta$ -ethyl substrate **236**

### Ethyl 2-(*N*-(2-iodophenyl)-*N*-methylglycyl)-5-oxoheptanoate, **235**



Aminoketone **175** (1.56 g, 4.32 mmol, 1.0 eq.) was dissolved in dichloromethane (8.6 mL, 0.5 M). Potassium carbonate (598 mg, 4.33 mmol, 1.0 eq.) was added in one portion followed by freshly distilled ethyl vinyl ketone (0.43 mL, 0.37 g, 4.4 mmol, 1.0 eq.). The reaction mixture was stirred for 21 h at room temperature before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10 to 20% ethyl acetate in pentane) to afford **235** (1.44 g, 3.23 mmol, 75%) as a viscous pale-yellow oil.

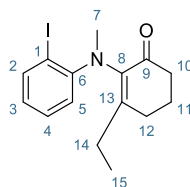
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.79 (1H, dd,  $J$  7.9, 1.5, H2), 7.31–7.24 (1H, m, H4), 7.13 (1H, dd,  $J$  8.1, 1.6, H5), 6.76 (1H, td,  $J$  7.6, 1.6, H3), 4.11 (2H, q,  $J$  7.1, H12), 4.01 (1H, d,  $J$  17.6, H8), 3.95 (1H, d,  $J$  17.5, H8'), 3.82 (1H, t,  $J$  7.0, H10), 2.79 (3H, s, H7), 2.43–2.36 (2H, m, H15), 2.34 (2H, q,  $J$  7.3, H17), 2.12–1.98 (2H, m, H14), 1.18 (3H, t,  $J$  7.1, H13), 0.99 (3H, t,  $J$  7.3, H18).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 210.3 (C16), 203.3 (C9), 169.3 (C11), 152.9 (C6), 140.2 (C2), 129.2 (C4), 125.8 (C3), 122.7 (C5), 97.0 (C1), 65.1 (C8), 61.5 (C12), 53.9 (C10), 42.7 (C7), 39.2 (C15), 35.9 (C17), 21.8 (C14), 14.1 (C13), 7.8 (C18).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1743, 1716, 1471, 1368, 1186, 1115, 1015, 760, 724, 641.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{25}\text{O}_4\text{NI}$   $[\text{M}+\text{H}]^+$ : 446.0823; found: 446.0821.

### 3-Ethyl-2-((2-iodophenyl)(methyl)amino)cyclohex-2-en-1-one, **236**



A solution of diketone **235** (737 mg, 1.66 mmol, 1.0 eq.) in *tert*-butanol (17 mL, 0.1 M) was sparged with argon for 15 min before adding potassium *tert*-butoxide (204 mg, 1.82 mmol, 1.1 eq.) in one portion under an argon atmosphere (the solution was gently heated using a tepid water bath during the sparging process to prevent freezing of the solvent). The reaction mixture was heated to reflux with stirring for 1 h. The reaction mixture was cooled to room temperature and quenched by the addition of ammonium chloride (sat. aq., 40 mL). The resulting mixture was transferred to a

separating funnel using water (40 mL) and diethyl ether (40 mL). After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 40 mL). The combined organic extracts were washed with brine (sat. aq., 80 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified twice by flash column chromatography (silica gel, gradient elution from 10 to 20% diethyl ether in pentane; then, silica gel, dichloromethane) to afford **236** (265 mg, 0.746 mmol, 45%) as a yellow solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.72 (1H, dd,  $J$  7.8, 1.6, H2), 7.24 (1H, ddd,  $J$  8.1, 7.2, 1.6, H4), 7.01 (1H, dd,  $J$  8.2, 1.6, H5), 6.57 (1H, ddd,  $J$  7.8, 7.2, 1.5, H3), 3.07 (3H, s, H7), 2.55–2.47 (2H, m, H10), 2.44 (2H, t,  $J$  6.1, H12), 2.21 (2H, q,  $J$  7.6, H14), 2.10–1.99 (2H, m, H11), 0.85 (3H, t,  $J$  7.6, H15).

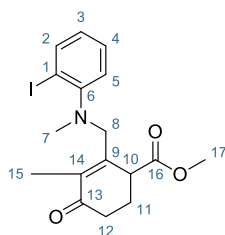
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 197.1 (C9), 159.9 (C13), 152.2 (C6), 141.2 (C2), 140.3 (C8), 128.8 (C4), 122.5 (C3), 120.5 (C5), 88.3 (C1), 41.3 (C7), 39.0 (C10), 29.9 (C12), 27.4 (C14), 22.0 (C11), 10.5 (C15).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1673, 1579, 1471, 1293, 1202, 1114, 1057, 1008, 922, 753.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{18}\text{INO}$   $[\text{M}+\text{H}]^+$ : 356.0506; found: 356.0498.

MP 42–44 °C.

Methyl 2-(((2-iodophenyl)(methyl)amino)methyl)-3-methyl-4-oxocyclohex-2-ene-1-carboxylate, **237** (R =  $\text{CO}_2\text{Me}$ )



Sodium methoxide (30 wt% in methanol, 0.20 mL, 0.058 g, 1.1 mmol, 1.1 eq.) was added in one portion to a stirred, argon-sparged solution of diketone **235** (445 mg, 0.999 mmol, 1.0 eq.) in methanol (10 mL, 0.1 M) at room temperature. The reaction mixture was heated to reflux with stirring for 1 h before adding a solution of lithium hydroxide monohydrate (41.9 mg, 0.999 mmol, 1.0 eq.) in water (5 mL) and heating to 75 °C. After 10 min, the reaction mixture was cooled to room temperature and acidified to *ca.* pH 2 with HCl (1 M aq., *ca.* 5 mL). The reaction mixture was heated to 75 °C for a further 30 min before cooling to room temperature, adding water (10 mL) and extracting with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 20 to 40% diethyl

ether in pentane) to afford an impure mixture containing predominantly **237** (R = CO<sub>2</sub>Me) (47.7 mg, 0.115 mmol, 12% assuming a purity of 100%) as a viscous yellow oil, alongside **236** (114 mg, 32.1 mmol, 32%) as a pale-yellow solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.84 (1H, dd, *J* 7.9, 1.5, H2), 7.31 (1H, td, *J* 7.6, 1.5, H4), 7.13 (1H, dd, *J* 8.0, 1.5, H5), 6.83 (1H, td, *J* 7.6, 1.6, H3), 4.10–4.01 (2H, m, H8 & H10), 3.80–3.72 (1H, m, H8'), 2.61 (3H, s, H7), 2.55–2.33 (3H, m, H12<sub>LHS</sub>, H12'<sub>LHS</sub> & H11<sub>RHS</sub>), 2.13–2.01 (H11'), 1.92 (3H, s, H15).

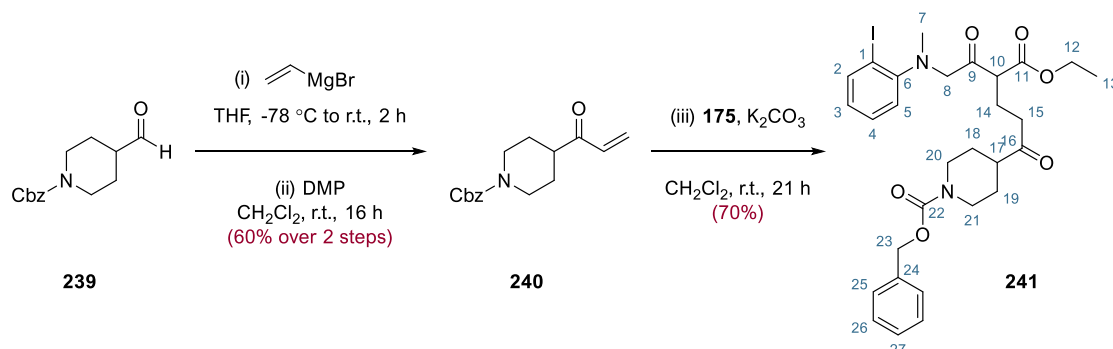
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 198.5 (C13), 172.8 (C16), 153.9 (C6), 150.1 (C9), 140.2 (C2), 134.8 (C14), 129.4 (C4), 126.5 (C3), 122.6 (C5), 98.9 (C1), 57.2 (C8), 52.3 (C17), 43.9 (C7), 42.2 (C10), 34.9 (C12), 26.0 (C11), 11.2 (C15).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1731, 1672, 1473, 1336, 1198, 1173, 1015, 915, 763, 727.

HRMS (ESI) *m/z* calcd. for C<sub>17</sub>H<sub>20</sub>INO<sub>3</sub> [M+H]<sup>+</sup>: 414.0561; found: 414.0553.

## Synthesis of $\beta$ -piperidinyI substrate **242a**

Benzyl 4-(4-(ethoxycarbonyl)-6-((2-iodophenyl)(methyl)amino)-5-oxohexanoyl)piperidine-1-carboxylate, **241**



To a  $-78\text{ }^{\circ}\text{C}$  solution of 1-((benzyloxy)methyl)piperidine-4-carbaldehyde (**239**) (2.47 g, 9.99 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (20 mL, 0.5 M) under an argon atmosphere was added vinylmagnesium bromide (1.0 M in tetrahydrofuran solution, 12 mL, 12 mmol, 1.2 eq.) dropwise *via* syringe pump over 15 min, with stirring. After complete addition of the Grignard reagent, the reaction mixture was allowed to warm to room temperature over 2 h. The reaction mixture was diluted with diethyl ether (20 mL) and quenched by the sequential addition of ammonium chloride (sat. aq., 20 mL) and water (10 mL). The layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was dissolved in dichloromethane (40 mL) and cooled to  $0\text{ }^{\circ}\text{C}$  using an ice–water bath. Dess–Martin periodinane (4.67 g, 11.0 mmol) was added in one portion, and the resulting mixture was stirred for 15 min at  $0\text{ }^{\circ}\text{C}$ . The reaction mixture was allowed to warm to room temperature over 16 h. The reaction mixture was quenched by the addition of sodium thiosulfate (sat. aq., 20 mL) and sodium hydrogencarbonate (sat. aq., 20 mL). The layers were separated, and the organic phase was washed with additional portions of sodium hydrogen carbonate (sat. aq., 2 x 20 mL) followed by brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 25% ethyl acetate in pentane) to afford vinyl ketone **240** (1.64 g, 6.00 mmol, 60% from **239** over two steps) as a viscous colourless oil. A sample of this compound retained for analysis underwent polymerisation on the timescale of minutes–hours, despite being stored in the dark at  $-18\text{ }^{\circ}\text{C}$ , precluding its full characterisation; however, the following  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data, obtained immediately after the compound’s isolation, supports its tentative assignment as the structure shown.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.40–7.28 (5H, m), 6.45 (1H, dd,  $J$ , 17.4, 10.5), 6.29 (1H, dd,  $J$ , 17.4, 1.4), 5.81 (1H, dd,  $J$  10.5, 1.4), 5.13 (2H, s), 4.30–4.08 (2H, br m), 2.92 (2H, br t,  $J$  12.6), 2.78 (1H, tt,  $J$  11.1, 3.8), 1.92–1.72 (2H, br m), 1.68–1.56 (2H, m).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 201.4, 155.3, 136.9, 134.4, 128.8, 128.6, 128.1, 128.0, 67.3, 45.9, 43.5, 27.6.

Vinyl ketone **240** (1.31 g, 4.79 mmol, 1.00 eq.) was dissolved in dichloromethane (5 mL) immediately after its purification and isolation in the preceding step. Potassium carbonate (692 mg, 5.00 mmol, 1.05 eq.) was added in one portion followed by aminoketone **175** (1.81 g, 5.01 mmol, 1.05 eq.) as a solution in dichloromethane (5 mL). The reaction mixture was stirred for 21 h at room temperature before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 30% ethyl acetate in pentane) to afford **241** (2.14 g, 3.37 mmol, 70%) as a viscous yellow oil.

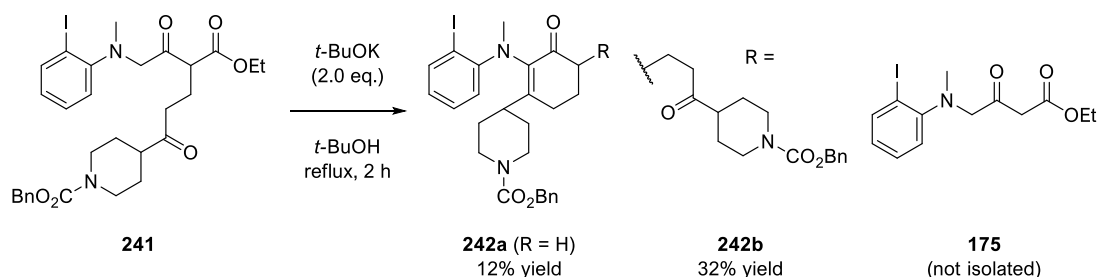
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.73 (1H, dd,  $J$  7.9, 1.4, H2), 7.30–7.18 (6H, m, H25<sub>LHS</sub>, H26<sub>LHS</sub>, H27<sub>RHS</sub> & H4<sub>RHS</sub>), 7.07 (1H, dd,  $J$  8.0, 1.4, H5), 6.70 (1H, td,  $J$  7.7, 1.4, H3), 5.03 (2H, s, H23), 4.20–3.97 (4H, m, H12 & H20/H21), 3.93 (1H, d,  $J$  17.4, H8), 3.88 (1H, d,  $J$  17.3, H8'), 3.78 (1H, t,  $J$  6.9, H10), 2.89–2.63 (2H, m, H20/H21), 2.73 (3H, s, H7), 2.44–2.28 (3H, m, H15<sub>LHS</sub> & H17<sub>RHS</sub>), 2.05–1.92 (2H, m, H14), 1.88–1.52 (2H, m, H18/H19), 1.45–1.35 (2H, m, two of the four protons represented by H18/H19), 1.12 (3H, t,  $J$  7.1, H13).

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  = 210.7 (C16), 203.4 (C9), 169.2 (C11), 155.1 (C22), 152.8 (C6), 140.2 (C2), 136.8 (C24), 129.2 (C4), 128.5 (C25 or C26), 128.0 (C27), 127.9 (C25 or C26), 125.8 (C3), 122.7 (C5), 97.1 (C1), 67.1 (C23), 65.0 (C8), 61.5 (C12), 53.6 (C10), 48.2 (C17), 43.4(0) & 43.3(9) (C20 & C21), 42.8 (C7), 37.5 (C15), 27.4(0) & 27.3(9) (C18 & C19), 21.6 (C14), 14.1 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1743, 1699, 1471, 1434, 1279, 1226, 1132, 1015, 912, 731.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{29}\text{H}_{36}\text{O}_6\text{N}_2\text{I}$   $[\text{M}+\text{H}]^+$ : 635.1613; found: 635.1611.

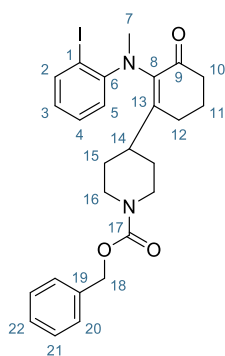
#### Aldol condensation of **241**





A solution of diketone **241** (1.70 g, 2.68 mmol, 1.0 eq.) in *tert*-butanol (27 mL, 0.1 M) was sparged with argon for 15 min before adding potassium *tert*-butoxide (601 mg, 5.36 mmol, 2.0 eq.) in one portion under an argon atmosphere (the solution was gently heated using a tepid water bath during the sparging process to prevent freezing of the solvent). The reaction mixture was heated to reflux with stirring for 2 h. The reaction mixture was cooled to room temperature and quenched by the addition of ammonium chloride (sat. aq., 50 mL). The resulting mixture was transferred to a separating funnel using water (50 mL) and diethyl ether (50 mL). After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (sat. aq., 100 mL) before being dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 20 to 100% diethyl ether in pentane) to afford **242b** (263 mg, 0.322 mmol, 12%) as an off-white foam solid, alongside an impure mixture containing predominantly **242a**; the latter material was further purified by flash column chromatography (silica gel, 5% ethyl acetate in dichloromethane) to afford **242a** (460 mg, 0.845 mmol, 32%) as a yellow foam solid.

Benzyl 4-(2-((2-iodophenyl)(methyl)amino)-3-oxocyclohex-1-en-1-yl)piperidine-1-carboxylate, **242a**



$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 7.71 (1H, dd,  $J$  7.8, 1.6, H<sub>2</sub>), 7.39–7.22 (6H, m, H<sub>20LHS</sub>, H<sub>21LHS</sub>, H<sub>22LHS</sub> & H<sub>4RHS</sub>), 7.01 (1H, dd,  $J$  8.2, 1.5, H<sub>5</sub>), 6.61 (1H, td,  $J$  7.5, 1.5, H<sub>3</sub>), 5.03 (2H, s, H<sub>18</sub>), 3.96 (2H, br d,  $J$  13.0, H<sub>16</sub>), 2.99 (3H, s, H<sub>7</sub>), 2.84 (1H, tt,  $J$  12.1, 3.3, H<sub>14</sub>), 2.54 (2H, br s, H<sub>16'</sub>), 2.47–2.39 (2H, m, H<sub>10</sub>), 2.34–2.26 (2H, m, H<sub>12</sub>), 1.93 (2H, quint,  $J$  6.1, H<sub>11</sub>), 1.31 (2H, qd,  $J$  12.4, 4.0, H<sub>15</sub>), 1.19–1.05 (2H, br m, H<sub>15'</sub>).

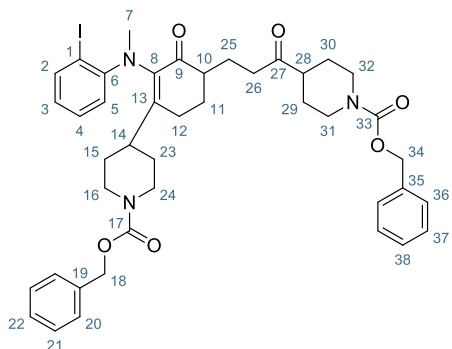
$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 196.1 (C<sub>9</sub>), 159.2 (C<sub>13</sub>), 154.2 (C<sub>17</sub>), 152.1 (C<sub>6</sub>), 140.7 (C<sub>2</sub>), 139.6 (C<sub>8</sub>), 136.9 (C<sub>19</sub>), 128.8 (C<sub>4</sub>), 128.4 (C<sub>20</sub> or C<sub>21</sub>), 127.8 (C<sub>22</sub>), 127.5 (C<sub>20</sub> or C<sub>21</sub>), 122.5 (C<sub>3</sub>), 120.8 (C<sub>5</sub>), 88.6 (C<sub>1</sub>), 66.1 (C<sub>18</sub>), 43.5 (C<sub>16</sub>), 41.0 (C<sub>7</sub>), 38.9 (C<sub>14</sub>), 38.4 (C<sub>10</sub>), 27.6 (C<sub>15</sub>), 25.6 (C<sub>12</sub>), 21.5 (C<sub>11</sub>).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1697, 1678, 1471, 1433, 1229, 1205, 1120, 1010, 755, 698.

HRMS (ESI)  $m/z$  calcd. for  $C_{26}H_{29}IN_2O_3$   $[M+H]^+$ : 545.1296; found: 545.1307.

MP 44–46 °C (ambiguous phase transition owing to foam nature of solid).

Benzyl 4-(3-(4-(1-((benzyloxy)carbonyl)piperidin-4-yl)-3-((2-iodophenyl)(methyl)amino)-2-oxocyclohex-3-en-1-yl)propanoyl)piperidine-1-carboxylate, **242b**



$^1H$  NMR (500 MHz,  $DMSO-d_6$ , 363 K)  $\delta$  = 7.72 (1H, dd,  $J$  7.8, 1.5, H2), 7.40–7.27 (10H, m, H20 to H22 & H36 to H38), 7.25 (1H, ddd,  $J$  8.4, 7.3, 1.6, H4), 6.98 (1H, dd,  $J$  8.2, 1.4, H5), 6.66–6.59 (1H, m, H3), 5.09 (2H, s, H18 or H34), 5.06 (2H, s, H18 or H34), 4.06–3.93 (4H, m, four of the eight protons represented by H16/H24 and H31/H32), 3.02 (3H, s, H7), 3.00–2.88 (3H, m, H14 & two of the eight protons represented by H16/H24 and H31/H32), 2.69–2.53 (5H, m, H26, H26', H28 & two of the eight protons represented by H16/H24 and H31/H32), 2.42–2.27 (3H, m, H10<sub>LHS</sub>, H12 & H12'), 2.08–1.93 (2H, m, H11<sub>LHS</sub> & H25<sub>RHS</sub>), 1.84–1.76 (2H, m, two of the eight protons represented by H15/H23 and H29/H30), 1.75–1.66 (1H, m, H11'), 1.63–1.54 (1H, m, H25'), 1.45–1.25 (5H, m, five of the eight protons represented by H15/H23 and H29/H30), 1.16–1.09 (1H, m, one of the eight protons represented by H15/H23 and H29/H30).

$^{13}C$  NMR (126 MHz,  $DMSO-d_6$ , 363 K)  $\delta$  = 210.9 (C27), 197.5 (C9), 157.8 (C13), 154.0(5) & 153.9(8) (C17 & C33), 151.9 (C6), 140.3 (C2), 139.1 (C8), 136.7 & 136.6 (C19 & C35), 128.3 (C4), 127.8 (C21 & C37, coincident), 127.2 (C22 & C38, coincident), 127.0 & 126.9 (C20 & C36), 122.3 (C3), 121.0 (C5), 88.1 (C1), 65.7(4) & 65.7(2) (C18 & C34), 46.7 (C28), 45.4 (C10), 43.3 & 43.2 (C31 & C32), 42.6 (C16 & C24, coincident), 40.8 (C7), 38.4 (C14), 36.9 (C26), 27.5, 27.4, 26.6(0) & 26.5(8) (C15, C23, C29 & C30), 26.4 (C11), 23.9 (C12), 23.0 (C25).

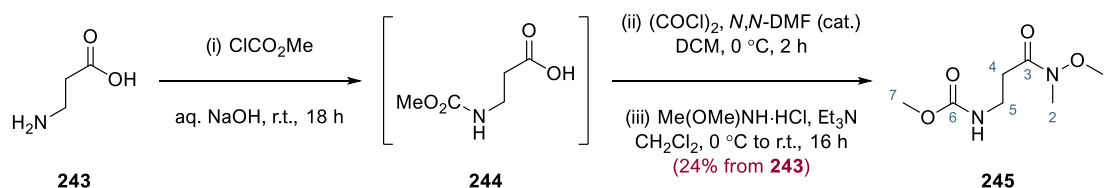
FTIR (neat)  $\nu/cm^{-1}$  = 1696, 1471, 1432, 1277, 1229, 1126, 1012, 911, 730, 698.

HRMS (ESI)  $m/z$  calcd. for  $C_{42}H_{49}O_6N_3I$   $[M+H]^+$ : 818.2661; found: 818.2656.

MP 48–50 °C (ambiguous phase transition owing to foam nature of solid).

## Synthesis of **248**, a substrate bearing a tethered carbamate group

### Methyl (3-(methoxy(methyl)amino)-3-oxopropyl)carbamate, **245**



To a stirred, 0 °C solution of  $\beta$ -alanine (**243**) (2.67 g, 30.0 mmol, 1.0 eq.) in aqueous sodium hydroxide (1 M, 30 mL) were simultaneously added methyl chloroformate (2.3 mL, 2.8 g, 30 mmol, 1.0 eq.) and sodium hydroxide (2 M aq., 15 mL). The reaction mixture was allowed to warm to room temperature over 18 h. Hydrochloric acid (1 M aq., 50 mL) was added slowly with ice-bath cooling, and the resulting aqueous mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (75 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*, affording 2.73 g (18.6 mmol assuming a purity of 100%) of **244** (presumed) as a viscous pale-yellow oil (this material was used directly in next step without characterisation or chromatographic purification). The crude residue was dissolved in dichloromethane (19 mL). Oxalyl chloride (1.8 mL, 2.7 g, 21 mmol) was added in one portion, and the solution was cooled to 0 °C. Two drops of *N,N*-dimethylformamide were added by glass dropping pipette to the reaction mixture with stirring; effervescence was immediately observed. The reaction mixture was stirred for a further 2 h with ice-bath cooling before being concentrated *in vacuo*. The resulting material was re-dissolved in dichloromethane (19 mL). *N,O*-Dimethylhydroxylamine hydrochloride (1.99 g, 20.4 mmol) was added in one portion, and the solution was cooled to 0 °C. Triethylamine (5.8 mL, 4.2 g, 42 mmol) was added dropwise *via* syringe over 5 min; the addition was accompanied by the formation of dense fumes and a white precipitate (additional dichloromethane was necessary to mobilise the slurry that formed). The reaction mixture was allowed to warm to room temperature over 16 h before being diluted with dichloromethane (20 mL) and washed successively with water (20 mL), hydrochloric acid (1 M aq., 20 mL), sodium hydrogencarbonate (sat. aq., 20 mL) and brine (sat. aq., 20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 50% ethyl acetate in dichloromethane) to afford **245** (1.37 g, 7.20 mmol, 24% over three steps from **S7**) as a pale-yellow oil.

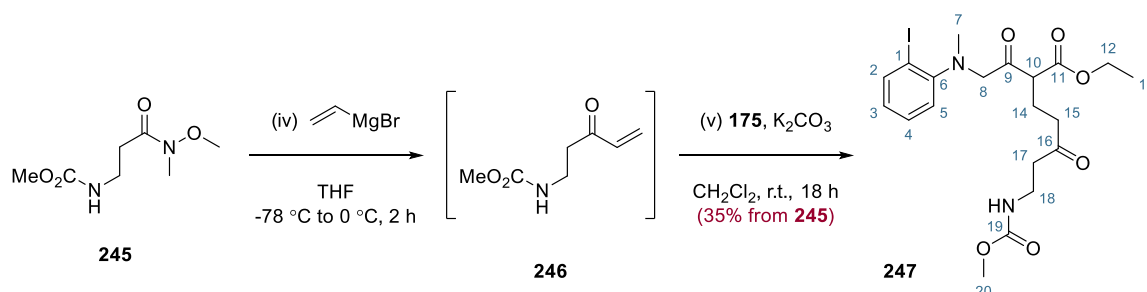
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.42 (1H, br s, NH), 3.65 (3H, s, H1), 3.62 (3H, s, H7), 3.44 (2H, q, *J* 6.0, H5), 3.15 (3H, s, H2), 2.63 (2H, br t, *J* 5.8, H4).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 173.1 (C3), 157.2 (C6), 61.3 (C1), 52.0 (C7), 36.4 (C5), 32.3 (C4), 32.1 (C2).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3337 (br), 1706, 1648, 1533, 1446, 1390, 1267, 1193, 1150, 1010.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_7\text{H}_{15}\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 191.1026; found: 191.1025.

Ethyl 2-(*N*-(2-iodophenyl)-*N*-methylglycyl)-7-((methoxycarbonyl)amino)-5-oxoheptanoate, **247**



To a -78 °C solution of Weinreb amide **245** (1.34 g, 7.05 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (35 mL, 0.2 M) under an argon atmosphere was added a solution of vinylmagnesium bromide (1.0 M in THF, 21 mL, 21 mmol, 3.0 eq.) dropwise *via* syringe pump over 15 min, with stirring. After complete addition of the Grignard reagent, the dry ice–acetone bath was replaced with an ice–water bath, and the reaction mixture was allowed to warm to 0 °C over 2 h. The reaction mixture was added dropwise to hydrochloric acid (1 M aq., 50 mL) with ice-bath cooling. The resulting mixture was transferred to a separating funnel using diethyl ether (50 mL). After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 25 mL). The combined organic extracts were washed with brine (sat. aq., 50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, affording 917 mg (5.83 mmol assuming a purity of 100%) of presumably vinyl ketone **246** as an orange oil (owing to its propensity to polymerise, this material was used directly in next step without characterisation or further purification). The crude residue and aminoketone **175** (1.99 g, 5.51 mmol) were immediately dissolved in dichloromethane (12 mL). Potassium carbonate (762 mg, 5.51 mmol) was added in one portion, and the resulting mixture was stirred for 18 h at room temperature before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 5 to 10% ethyl acetate in dichloromethane) to afford **247** (1.29 g, 2.49 mmol, 35% from **245** over two steps) as a viscous yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.81 (1H, dd,  $J$  7.9, 1.4, H<sub>2</sub>), 7.32–7.26 (1H, m, H<sub>4</sub>), 7.14 (1H, dd,  $J$  8.0, 1.5, H<sub>5</sub>), 6.78 (1H, td,  $J$  7.6, 1.5, H<sub>3</sub>), 5.16 (1H, br s, NH), 4.12 (2H, q,  $J$  7.1, H<sub>12</sub>), 4.00 (1H, d,  $J$  17.4, H<sub>8</sub>), 3.94 (1H, d,  $J$  17.4, H<sub>8'</sub>), 3.85 (1H, t,  $J$  6.9, H<sub>10</sub>), 3.62 (3H, s, H<sub>20</sub>), 3.35 (2H, q,  $J$  5.8, H<sub>18</sub>), 2.80 (3H, s, H<sub>7</sub>), 2.57 (2H, t,  $J$  5.7, H<sub>17</sub>), 2.40 (2H, app. td,  $J$  7.2, 2.8, H<sub>15</sub>), 2.13–1.97 (2H, m, H<sub>14</sub>), 1.19 (3H, t,  $J$  7.1, H<sub>13</sub>).

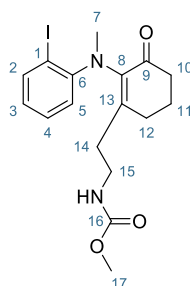
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 208.9 (C16), 203.5 (C9), 169.3 (C11), 157.1 (C19), 152.9 (C6), 140.3 (C2), 129.3 (C4), 125.9 (C3), 122.7 (C5), 97.2 (C1), 65.1 (C8), 61.6 (C12), 53.7 (C10), 52.1 (C20), 43.0 (C7), 42.5 (C17), 40.0 (C15), 35.7 (C18), 21.5 (C14), 14.1 (C13).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3390 (br), 1709, 1579, 1471, 1250, 1190, 1097, 1015, 1015, 761.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{20}\text{H}_{27}\text{IN}_2\text{O}_6$   $[\text{M}+\text{H}]^+$ : 519.0987; found: 519.0978.

Methyl (2-(2-((2-iodophenyl)(methyl)amino)-3-oxocyclohex-1-en-1-yl)ethyl)carbamate,

**248**



A solution of diketone **247** (1.11 g, 2.14 mmol, 1.0 eq.) in *tert*-butanol (21 mL, 0.1 M) was sparged with argon for 15 min before adding potassium *tert*-butoxide (264 mg, 2.35 mmol, 1.1 eq.) in one portion under an argon atmosphere (the solution was gently heated using a tepid water bath during the sparging process to prevent freezing of the solvent). The reaction mixture was heated to reflux with stirring for 75 min. The reaction mixture was cooled to room temperature and quenched by the addition of ammonium chloride (sat. aq., 40 mL). The resulting mixture was transferred to a separating funnel using water (40 mL) and diethyl ether (40 mL). After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 40 mL). The combined organic extracts were washed with brine (sat. aq., 80 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 25 to 50% ethyl acetate in pentane) to afford **248** (441 mg, 1.03 mmol, 48%) as an extremely viscous yellow-brown oil.

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.72 (1H, dd,  $J$  7.8, 1.5, H2), 7.20 (1H, ddd,  $J$  8.7, 7.2, 1.6, H4), 6.96 (1H, dd,  $J$  8.2, 1.5, H5), 6.60 (1H, ddd,  $J$  7.8, 7.2, 1.5, H3), 4.73–4.48 (1H, br m, NH), 3.59 (3H, s, H17), 3.12 (2H, q,  $J$  6.7, H15), 3.05 (3H, s, H7), 2.53–2.48 (2H, m, H10), 2.45 (2H, t,  $J$  6.1, H12), 2.35 (2H, t,  $J$  7.3, H14), 2.01 (2H, quint,  $J$  6.1, H11).

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  = 197.2 (C9), 156.9 (C16), 155.5 (C13), 152.3 (C6), 142.2 (C8), 141.1 (C2), 129.1 (C4), 123.3 (C3), 121.7 (C5), 89.7 (C1), 52.1 (C17), 41.3 (C7), 39.0 (C10), 38.1 (C15), 34.7 (C14), 30.4 (C12), 21.9 (C11).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3333 (br), 1717, 1672, 1579, 1532, 1472, 1434, 1258, 1010, 755.

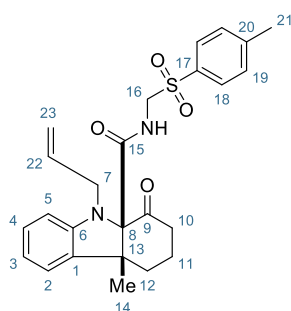
HRMS (ESI)  $m/z$  calcd. for  $C_{17}H_{21}IN_2O_3$   $[M+H]^+$ : 429.0670; found: 429.0665.

## Photochemical reactivity of alternative *N*-aryl enaminone substrates in the presence of TosMIC (substrate scope)

### General Procedure B

The appropriate enaminone substrate (0.300 mmol, 1.0 eq.) and *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) were dissolved in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with two Kessil PR160L 427 nm LED lamps (each positioned *ca.* 3 cm from the flask and directed toward it) for 18 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Triethylamine (2.0 mL) was added to the reaction mixture at the end of the irradiation period, and the resulting mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography to afford the corresponding indoline product.

(4*bR*,8*aS*)-9-Allyl-4*b*-methyl-8-oxo-*N*-(tosylmethyl)-4*b*,5,6,7,8,9-hexahydro-8*aH*-carbazole-8*a*-carboxamide, **249**



This compound was prepared from **226** (110.2 mg, 0.300 mmol, 1.0 eq.) and *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) according to General Procedure B. Flash column chromatography on silica gel (eluent: 25% ethyl acetate in pentane) yielded **229** (57.4 mg, 0.127 mmol, 42%) as a white solid, alongside an impure mixture of compounds containing **259**; the latter material was subjected to preparatory thin-layer chromatography on silica gel (eluent: 25% ethyl acetate in pentane), affording pure **259** (6.2 mg, 0.017 mmol, 6%) as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.80–7.72 (2H, m, H18), 7.43 (1H, t, *J* 6.8, NH), 7.33 (2H, d, *J* 8.0, H19), 7.10 (1H, td, *J* 7.6, 1.2, H4), 6.90 (1H, dd, *J* 7.3, 1.3, H2), 6.80 (1H, td, *J* 7.4, 1.0, H3), 6.48 (1H, d, *J* 7.8, H5), 6.08 (1H, ddt, *J* 17.6, 10.6, 3.6, H22), 5.28–5.15 (2H, m, H23 & H23'), 4.74 (1H, dd, *J* 14.1, 6.7, H16), 4.66 (1H, dd, *J* 14.1, 6.8, H16'), 4.18–4.01 (2H, m, H7 & H7'), 2.88 (1H, td, *J* 13.6, 6.2, H10), 2.43 (3H, s, H21), 2.28–2.19 (1H, m, H10'), 2.19–2.11 (1H, m,

H12), 2.06 (1H, td,  $J$  13.7, 3.9, H12'), 1.92–1.80 (1H, m, H11), 1.55 (1H, qt,  $J$  13.3, 4.2, H11'), 1.13 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 210.9 (C9), 168.3 (C15), 149.1 (C6), 145.6 (C20), 135.9 (C22), 134.2 (C17), 132.1 (C1), 130.2 (C19), 128.8 (C18), 128.5 (C4), 121.1 (C2), 120.0 (C3), 115.1 (C23), 109.0 (C5), 87.5 (C8), 60.0 (C16), 54.0 (C13), 51.2 (C7), 41.1 (C10), 31.2 (C12), 27.2 (C14), 21.8 (C21), 21.6 (C11).

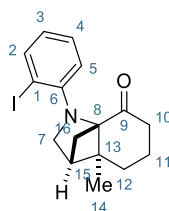
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ NH and H14 $\leftrightarrow$ H18 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3382 (br), 1716, 1680, 1504, 1480, 1326, 1146, 1086, 915, 736.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 453.1843; found: 453.1844.

MP 58–62 °C (unclear phase transition owing to foam nature of solid).

(3*R*,3*aS*,7*aS*)-1-(2-Iodophenyl)-3*a*-methylhexahydro-3,7*a*-methanoindol-7(1*H*)-one, **259**



Isolated from the photoreaction of **226**, as described above.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.80 (1H, dd,  $J$  7.9, 1.5, H2), 7.17–7.08 (1H, m, H4), 6.66 (1H, td,  $J$  7.5, 1.4, H3), 6.44 (1H, d,  $J$  8.1, H5), 4.29 (1H, d,  $J$  8.3, H7), 3.08–3.00 (1H, m, H16), 2.68 (1H, ddd,  $J$  14.3, 12.9, 5.6, H10), 2.62–2.55 (2H, m, H15<sub>LHS</sub> & H7'<sub>RHS</sub>), 2.45–2.27 (2H, m, H12<sub>LHS</sub> & H10'<sub>RHS</sub>), 2.25–2.13 (1H, m, H11), 2.12–1.97 (1H, m, H11'), 1.96 (1H, d,  $J$  8.0, H16'), 1.84–1.74 (1H, m, H12'), 1.17 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 204.1 (C9), 152.1 (C6), 140.4 (C2), 127.5 (C4), 123.5 (C3), 120.6 (C5), 93.3 (C1), 76.9 (C8), 59.5 (C13), 58.1 (C7), 43.8 (C15), 40.9 (C10), 38.2 (C16), 31.5 (C12), 27.5 (C11), 16.6 (C14).

The stereochemistry of this compound was assigned by analogy to that of **269** below.

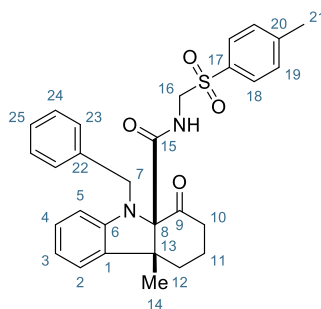
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1704, 1579, 1469, 1433, 1299, 1038, 754, 648.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{19}\text{INO}$   $[\text{M}+\text{H}]^+$ : 368.0506; found: 368.0502.

MP 148–150 °C.



(4*b**R*,8*a**S*)-9-Benzyl-4*b*-methyl-8-oxo-*N*-(tosylmethyl)-4*b*,5,6,7,8,9-hexahydro-8*aH*-carbazole-8*a*-carboxamide, **250**



This compound was prepared from **227** (125.2 mg, 0.300 mmol, 1.0 eq.) and *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) according to General Procedure B. Flash column chromatography on silica gel (gradient elution from 5 to 25% ethyl acetate in pentane) yielded **250** (79.2 mg, 0.158 mmol, 53%) as an off-white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.65–7.57 (2H, m, H18), 7.39–7.23 (7H, m, H24<sub>LHS</sub>, H19<sub>RHS</sub>, H23<sub>RHS</sub> & H25<sub>RHS</sub>), 7.17 (1H, t,  $J$  6.7, NH), 7.04 (1H, td,  $J$  7.7, 1.3, H4), 6.96 (1H, dd,  $J$  7.4, 1.3, H2), 6.83 (1H, td,  $J$  7.4, 1.0, H3), 6.32 (1H, d,  $J$  7.8, H5), 4.69 (2H, s, H7), 4.67 (1H, dd,  $J$  14.1, 7.2, H16), 4.38 (1H, dd,  $J$  14.1, 6.2, H16'), 2.94 (1H, td,  $J$  13.8, 6.3, H10), 2.45 (3H, s, H21), 2.37–2.26 (1H, m, H10'), 2.25–2.16 (1H, m, H12), 2.10 (1H, td,  $J$  13.7, 3.8, H12'), 1.98–1.85 (1H, m, H11), 1.63 (1H, qt,  $J$  13.2, 4.3, H11'), 1.26 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 211.1 (C9), 168.3 (C15), 149.4 (C6), 145.4 (C20), 138.8 (C22), 134.2 (C17), 132.5 (C1), 130.1 (C19), 129.4 (C24), 128.7 (C18), 128.5 (C4), 127.4 (C25), 125.6 (C23), 121.2 (C2), 120.3 (C3), 109.3 (C5), 87.6 (C8), 59.9 (C16), 54.2 (C13), 52.4 (C7), 41.3 (C10), 31.7 (C12), 27.2 (C14), 21.8 (C21), 21.5 (C11).

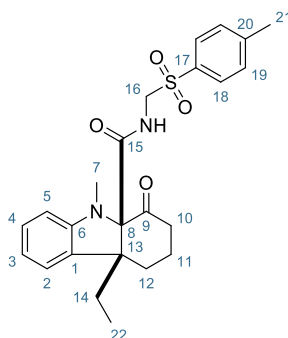
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ NH and H14 $\leftrightarrow$ H18 (weak) is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3395 (br), 1716, 1681, 1601, 1479, 1326, 1145, 1086, 912, 733.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 503.1999; found: 503.1999.

MP 68–72 °C (unclear phase transition owing to foam nature of solid).

(4b*R*,8a*S*)-4b-ethyl-9-methyl-8-oxo-*N*-(tosylmethyl)-4b,5,6,7,8,9-hexahydro-8a*H*-carbazole-8a-carboxamide, **251**



This compound was prepared from **236** (106.6 mg, 0.300 mmol, 1.0 eq.) and *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) according to General Procedure B. Flash column chromatography on silica gel (eluent: 25% ethyl acetate in pentane) yielded **251** (85.1 mg, 0.193 mmol, 64%) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.82–7.76 (2H, m, H18), 7.42 (1H, t,  $J$  6.9, NH), 7.39–7.30 (2H, m, H19), 7.17 (1H, td,  $J$  7.6, 1.4, H4), 6.88 (1H, dd,  $J$  7.3, 1.3, H2), 6.79 (1H, t,  $J$  7.4, H3), 6.56 (1H, d,  $J$  7.8, H5), 4.95 (1H, dd,  $J$  14.2, 7.6, H16), 4.58 (1H, dd,  $J$  14.2, 6.0, H16'), 3.09 (3H, s, H7), 2.69 (1H, ddd,  $J$  14.7, 12.2, 6.5, H10), 2.44 (3H, s, H21), 2.31–2.21 (1H, m, H12), 2.12 (1H, dddd,  $J$  14.6, 5.1, 3.3, 1.5, H10'), 1.90–1.70 (2H, m, H11<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.57–1.43 (2H, m, H11' & H14), 1.33–1.19 (1H, m, H14'), 0.72 (3H, t,  $J$  7.4, H22).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 210.4 (C9), 168.5 (C15), 150.6 (C6), 145.7 (C20), 134.2 (C17), 130.2 (C19), 129.5 (C1), 128.8 (C18), 128.7 (C4), 123.3 (C2), 119.2 (C3), 108.5 (C5), 87.0 (C8), 60.0 (C16), 56.3 (C13), 40.7 (C10), 35.5 (C7), 30.2 (C14), 27.2 (C12), 21.8 (C21), 20.6 (C11), 8.4 (C22).

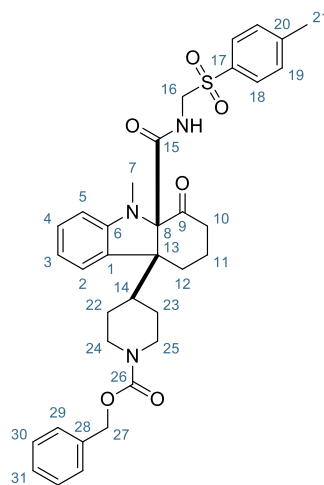
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ NH, H14' $\leftrightarrow$ NH (weak), H14 $\leftrightarrow$ H18 (weak) and H14' $\leftrightarrow$ H18 (weak) is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3351 (br), 1716, 1677, 1603, 1481, 1322, 1145, 1085, 913, 736.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 441.1843; found: 441.1847.

MP 78–80 °C

Benzyl 4-((4a*S*,9a*S*)-9-methyl-1-oxo-9a-((tosylmethyl)carbamoyl)-1,2,3,4,9,9a-hexahydro-4a*H*-carbazol-4a-yl)piperidine-1-carboxylate, **252**



This compound was prepared from **242a** (163.3 mg, 0.300 mmol, 1.0 eq.) and *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) according to General Procedure B. Flash column chromatography on silica gel (eluent: 10% ethyl acetate in dichloromethane) yielded **252** (78.7 mg, 0.125 mmol, 42%) as a green solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.85–7.76 (2H, m, H18), 7.66–7.42 (1H, br m, NH), 7.40–7.23 (7H, m, H19<sub>LHS</sub> & H29 to H31), 7.18 (1H, ddd,  $J$  7.7, 6.5, 2.2, H4), 6.87–6.75 (2H, m, H2<sub>LHS</sub> & H3<sub>RHS</sub>), 6.57 (1H, d,  $J$  7.8, H4), 5.16–4.95 (3H, m, H16<sub>LHS</sub> & H27<sub>RHS</sub>), 4.40–4.31 (1H, m, H16'), 4.26–3.82 (2H, m, two of the four protons represented by H24/H25), 3.05 (3H, s, H7), 2.71–2.47 (3H, m, H10<sub>RHS</sub> & two of the four protons represented by H24/H25), 2.44 (3H, s, H21), 2.24–2.13 (1H, m, H12), 2.08–1.91 (2H, m, H10'<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.91–1.76 (2H, m, H11<sub>LHS</sub> & H14<sub>RHS</sub>), 1.76–1.60 (1H, m, one of the four protons represented by H22/H23), 1.59–1.43 (2H, m, H11'<sub>LHS</sub> & one of the four protons represented by H22/H23), 1.38–1.15 (1H, m, one of the four protons represented by H22/H23), 0.96–0.56 (1H, m, one of the four protons represented by H22/H23).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 209.1 (C9), 168.9 (C15), 155.0 (C26), 151.1 (C6), 145.8 (C20), 136.9 (C28), 134.2 (C17), 130.3 (C19), 129.0 (C4), 128.9 (C1), 128.7 (C18), 128.5 (C29 or C30), 128.0 (C31), 127.9 (C29 or C30), 123.6 (C2), 119.7 (C3), 108.8 (C5), 86.8 (C8), 67.0 (C27), 60.1 (C16), 58.8 (C13), 44.4 & 44.1 (C24 & C25), 42.2 (C14), 39.3 (C10), 35.4 (C7), 28.9 & 27.5 (C22 & C23), 26.4 (C12), 21.9 (C21), 19.8 (C11).

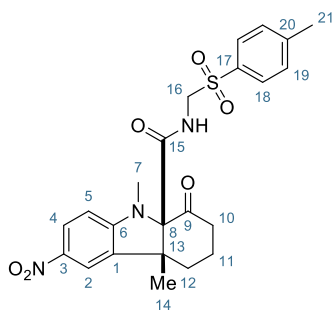
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ NH is consistent with the formation of the *cis*-diastereomer shown; cross-peaks at (7.54 ppm, 1.48 ppm) and (1.48 ppm, 7.54 ppm) on the 2D NOESY spectrum, indicative of a through-space interaction between NH and one of the four protons represented by H22/H23, also support this assignment.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3349 (br), 1682, 1480, 1322, 1285, 1244, 1145, 1086, 912, 733.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{35}\text{H}_{40}\text{O}_6\text{N}_3\text{S}$   $[\text{M}+\text{H}]^+$ : 630.2632; found: 630.2629.

MP not determined; sample underwent an unclear phase transition / decomposed upon heating at *ca.* 100 °C.

(4b*R*,8a*S*)-4b,9-Dimethyl-3-nitro-8-oxo-*N*-(tosylmethyl)-4b,5,6,7,8,9-hexahydro-8a*H*-carbazole-8a-carboxamide, **253**



This compound was prepared from **222** (115.9 mg, 0.300 mmol, 1.0 eq.) according to General Procedure B, except with a larger quantity of TosMIC (292.9 mg, 1.50 mmol, 5.0 eq.) and a longer irradiation time of 21 h. Flash column chromatography on silica gel (gradient elution from 0 to 5% ethyl acetate in dichloromethane) yielded **253** (41.5 mg, 0.0880 mmol, 29%, 64% based on recovered starting material) as a yellow solid, alongside unreacted **222** (63.0 mg, 0.163 mmol) as an extremely viscous orange-brown oil.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 9.11 (1H, t,  $J$  6.5, NH), 8.08 (1H, dd,  $J$  8.8, 2.3, H4), 7.88 (1H, d,  $J$  2.3, H2), 7.79–7.72 (2H, m, H18), 7.48–7.40 (2H, m, H19), 6.63 (1H, d,  $J$  8.9, H5), 4.84 (1H, dd,  $J$  14.1, 6.8, H16), 4.62 (1H, dd,  $J$  14.1, 6.3, H16'), 2.94 (3H, s, H7), 2.67 (1H, ddd,  $J$  15.3, 11.7, 6.2, H10), 2.40 (3H, s, H21), 2.30–2.16 (2H, m, H10' & H12), 1.91–1.79 (2H, m, H11 & H12'), 1.44–1.26 (1H, m, H11'), 1.17 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 208.2 (C9), 167.0 (C15), 155.4 (C6), 144.7 (C20), 138.9 (C3), 135.1 (C17), 134.0 (C1), 129.7 (C19), 128.5 (C18), 126.7 (C4), 117.7 (C2), 105.5 (C5), 85.2 (C8), 60.5 (C16), 51.4 (C13), 39.9 (C10), 33.4 (C7), 32.5 (C12), 26.5 (C14), 21.1 (C21), 19.8 (C11).

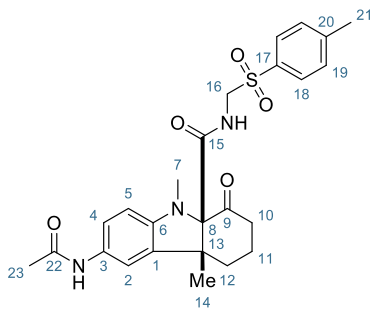
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to  $\text{H14} \leftrightarrow \text{NH}$  and  $\text{H14} \leftrightarrow \text{H18}$  (weak) is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3331 (br), 1681, 1604, 1498, 1379, 1145, 1121, 1086, 1059, 735.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{25}\text{O}_6\text{N}_3\text{NaS}$   $[\text{M}+\text{Na}]^+$ : 494.1356; found: 494.1359.

MP not determined; sample decomposed upon heating at some temperature above 150 °C.

(4*b**R*,8*a**S*)-3-Acetamido-4*b*,9-dimethyl-8-oxo-*N*-(tosylmethyl)-4*b*,5,6,7,8,9-hexahydro-8*aH*-carbazole-8*a*-carboxamide, **254**



This compound was prepared from **223** (119.5 mg, 0.300 mmol, 1.0 eq.) and *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) according to General Procedure B. Flash column chromatography on silica gel (gradient elution from 25 to 50% ethyl acetate in dichloromethane) yielded **254** (100.2 mg, 0.207 mmol, 69%) as a buff solid.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 9.63 (1H, s, R–NH–COCH<sub>3</sub>), 8.95 (1H, t,  $J$  6.7, R–NH–SO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>), 7.77–7.69 (2H, m, H18), 7.48–7.40 (2H, m, H19), 7.24 (1H, dd,  $J$  8.3, 2.1, H4), 7.18 (1H, d,  $J$  2.0, H2), 6.42 (1H, d,  $J$  8.4, H5), 4.84 (1H, dd,  $J$  14.0, 7.0, H16), 4.56 (1H, dd,  $J$  14.0, 6.3, H16'), 2.86 (3H, s, H7), 2.65 (1H, ddd,  $J$  14.6, 12.1, 6.3, H10), 2.40 (3H, s, H21), 2.16–1.99 (2H, m, H10'<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.96 (3H, s, H23), 1.91–1.74 (2H, m, H12'<sub>LHS</sub> & H11'<sub>RHS</sub>), 1.45–1.27 (1H, m, H11'), 1.07 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  = 210.4 (C9), 168.3 (C15), 167.4 (C22), 145.8 (C6), 144.5 (C20), 135.3 (C17), 132.2 (C1), 131.2 (C3), 129.7 (C19), 128.4 (C18), 119.6 (C4), 113.7 (C2), 106.4 (C5), 85.1 (C8), 60.6 (C16), 52.0 (C13), 40.5 (C10), 33.9 (C7), 31.6 (C12), 26.9 (C14), 23.7 (C23), 21.1 (C21), 20.1 (C11).

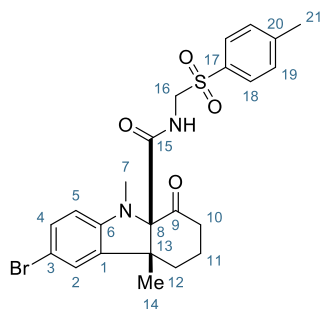
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14↔NH and H14↔H18 is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3352 (br), 1714, 1667, 1553, 1487, 1301, 1144, 1085, 812, 756.

HRMS (ESI)  $m/z$  calcd. for C<sub>25</sub>H<sub>30</sub>N<sub>3</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: 484.1901; found: 484.1898.

MP 104–106 °C.

(4*bR*,8*aS*)-3-Bromo-4*b*,9-dimethyl-8-oxo-*N*-(tosylmethyl)-4*b*,5,6,7,8,9-hexahydro-8*aH*-carbazole-8*a*-carboxamide, **255**



This compound was prepared from **225** (126.0 mg, 0.300 mmol, 1.0 eq.) and *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) according to General Procedure B. Flash column chromatography on silica gel (gradient elution from 20 to 40% ethyl acetate in pentane) yielded **255** (119.7 mg, 0.237 mmol, 79%) as a pale-yellow solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.82–7.71 (2H, m, H18), 7.47 (1H, t,  $J$  6.8, NH), 7.38–7.33 (2H, m, H19), 7.23 (1H, dd,  $J$  8.3, 2.0, H4), 6.97 (1H, d,  $J$  2.0, H2), 6.39 (1H, d,  $J$  8.3, H5), 4.88 (1H, dd,  $J$  14.1, 7.4, H16), 4.61 (1H, dd,  $J$  14.1, 6.3, H16'), 2.98 (3H, s, H7), 2.63 (1H, ddd,  $J$  15.4, 11.6, 7.0, H10), 2.44 (3H, s, H21), 2.22 (1H, dddd,  $J$  15.4, 6.0, 3.4, 1.3, H10'), 2.02 (1H, dtd,  $J$  14.4, 3.9, 1.5, H12), 1.91 (1H, ddd,  $J$  14.4, 12.9, 3.9, H12'), 1.86–1.74 (1H, m, H11), 1.62–1.47 (1H, m, H11'), 1.07 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 209.6 (C9), 168.0 (C15), 149.2 (C6), 145.8 (C20), 135.1 (C1), 134.1 (C17), 131.4 (C4), 130.2 (C19), 128.8 (C18), 124.5 (C2), 111.8 (C3), 109.5 (C5), 85.4 (C8), 60.0 (C16), 52.9 (C13), 40.2 (C10), 34.5 (C7), 32.4 (C12), 27.1 (C14), 21.9 (C21), 20.3 (C11).

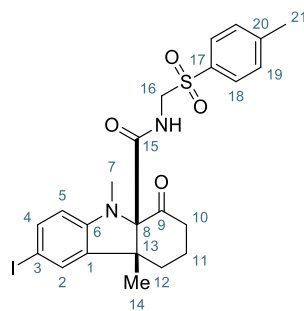
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to  $\text{H14} \leftrightarrow \text{NH}$  and  $\text{H14} \leftrightarrow \text{H18}$  (weak) is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3343 (br), 1715, 1678, 1478, 1322, 1145, 1085, 912, 809, 732.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{26}\text{O}_4\text{N}_2^{79}\text{BrS}$  ( $\text{C}_{23}\text{H}_{26}\text{O}_4\text{N}_2^{81}\text{BrS}$ )  $[\text{M}+\text{H}]^+$ : 505.0791 (507.0771); found: 505.0791 (507.0770).

MP not determined; sample decomposed upon heating at some temperature above 150 °C.

(4*bR*,8*aS*)-3-Iodo-4*b*,9-dimethyl-8-oxo-*N*-(tosylmethyl)-4*b*,5,6,7,8,9-hexahydro-8*aH*-carbazole-8*a*-carboxamide, **256**



This compound was prepared from **224** (140.1 mg, 0.300 mmol, 1.0 eq.) and *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) according to General Procedure B. Flash column chromatography on silica gel (eluent: 25% ethyl acetate in pentane) yielded **256** (118.5 mg, 0.215 mmol, 72%) as an off-white solid.

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 8.98 (1H, t,  $J$  6.6, NH), 7.78–7.70 (2H, m, H18), 7.47–7.40 (2H, m, H19), 7.37 (1H, dd,  $J$  8.1, 1.8, H4), 7.28 (1H, d,  $J$  1.8, H2), 6.35 (1H, d,  $J$  8.2, H5), 4.83 (1H, dd,  $J$  14.0, 6.9, H16), 4.56 (1H, dd,  $J$  14.0, 6.2, H16'), 2.85 (3H, s, H7), 2.66 (1H, ddd,  $J$  15.0, 12.2, 6.3, H10), 2.40 (3H, s, H21), 2.21–2.09 (2H, m, H12<sub>LHS</sub> & H10'<sub>RHS</sub>), 1.90–1.71 (2H, m, H11<sub>LHS</sub> & H12'<sub>RHS</sub>), 1.40–1.25 (1H, m, H11'), 1.08 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  = 209.8 (C9), 167.7 (C15), 149.6 (C6), 144.5 (C20), 136.5 (C4), 135.5 & 135.3 (C1 & C17), 129.7 (C19), 129.4 (C2), 128.4 (C18), 109.2 (C5), 84.9 (C8), 79.5 (C3), 60.6 (C16), 52.1 (C13), 40.3 (C10), 33.6 (C7), 31.6 (C12), 26.7 (C14), 21.1 (C21), 20.2 (C11).

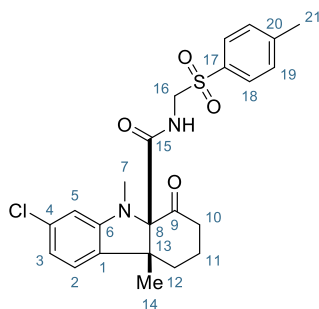
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ NH and H14 $\leftrightarrow$ H18 (weak) is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3347 (br), 1716, 1680, 1478, 1323, 1146, 1086, 913, 811, 736.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{26}\text{IN}_2\text{O}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 553.0653; found: 553.0641.

MP not determined; sample decomposed upon heating at some temperature above 150 °C.

(4b*R*,8a*S*)-2-Chloro-4b,9-dimethyl-8-oxo-*N*-(tosylmethyl)-4b,5,6,7,8,9-hexahydro-8a*H*-carbazole-8a-carboxamide, **257**



This compound was prepared from **228** (112.7 mg, 0.300 mmol, 1.0 eq.) and *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 eq.) according to General Procedure B. Flash column chromatography on silica gel (gradient elution from 20 to 40% ethyl acetate in pentane) yielded **257** (86.4 mg, 0.187 mmol, 62%) as an off-white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.80–7.74 (2H, m, H18), 7.48 (1H, t,  $J$  6.9, NH), 7.38–7.29 (2H, m, H19), 6.83–6.72 (2H, m, H2<sub>LHS</sub> & H3<sub>RHS</sub>), 6.48 (1H, d,  $J$  1.6, H5), 4.87 (1H, dd,  $J$  14.1, 7.3, H16), 4.62 (1H, dd,  $J$  14.1, 6.3, H16'), 2.97 (3H, s, H7), 2.64 (1H, ddd,  $J$  15.4, 11.6, 7.0, H10), 2.44 (3H, s, H21), 2.23 (1H, dddd,  $J$  15.4, 5.9, 3.3, 1.4, H10'), 2.02 (1H, dtd,  $J$  14.4, 3.8, 1.5, H12), 1.91 (1H, ddd,  $J$  14.4, 13.0, 3.9, H12'), 1.85–1.74 (1H, m, H11), 1.61–1.46 (1H, m, H11'), 1.07 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 209.7 (C9), 168.0 (C15), 151.3 (C6), 145.8 (C20), 134.3 (C4), 134.1 (C17), 131.4 (C1), 130.2 (C19), 128.8 (C18), 122.2 (C2), 119.6 (C3), 108.4 (C5), 85.5 (C8), 60.0 (C16), 52.6 (C13), 40.2 (C10), 34.4 (C7), 32.5 (C12), 27.1 (C14), 21.8 (C21), 20.3 (C11).

The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ NH and H14 $\leftrightarrow$ H18 (weak) is consistent with the formation of the *cis*-diastereomer shown.

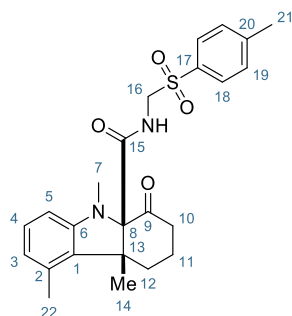
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3340 (br), 1716, 1678, 1481, 1289, 1145, 1085, 902, 813, 732.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{26}\text{O}_4\text{N}_2\text{ClS}$   $[\text{M}+\text{H}]^+$ : 461.1296; found: 461.1296.

MP not determined; sample underwent an unclear phase transition between *ca.* 80–90 °C.



(4*b**R*,8*a**S*)-4,4*b*,9-Trimethyl-8-oxo-*N*-(tosylmethyl)-4*b*,5,6,7,8,9-hexahydro-8*aH*-carbazole-8*a*-carboxamide, **258**



This compound was prepared from **229** (106.6 mg, 0.300 mmol, 1.0 eq.) according to General Procedure B. Flash column chromatography on silica gel (gradient elution from 20 to 40% ethyl acetate in pentane) yielded **258** (76.4 mg, 0.173 mmol, 58%) as an off-white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.84–7.76 (2H, m, H18), 7.48 (1H, t,  $J$  6.9, NH), 7.39–7.33 (2H, m, H19), 7.06 (1H, t,  $J$  7.7, H4), 6.57 (1H, d,  $J$  7.6, H5), 6.42 (1H, d,  $J$  7.8, H3), 4.92 (1H, dd,  $J$  14.2, 7.5, H16), 4.61 (1H, dd,  $J$  14.1, 6.1, H16'), 2.89 (3H, s, H7), 2.50 (1H, dt,  $J$  16.2, 8.3, H10), 2.45 (3H, s, H21), 2.35–2.25 (1H, m, H12), 2.27 (3H, s, H22), 2.06 (1H, ddd,  $J$  15.6, 8.0, 4.4, H10'), 1.96 (1H, ddd,  $J$  14.7, 13.4, 4.6, H12'), 1.84 (1H, m, H11), 1.65–1.51 (1H, m, H11'), 1.13 (3H, s, H14).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 208.7 (C9), 168.6 (C15), 150.3 (C6), 145.7 (C20), 134.3 (C17), 133.3 (C2), 130.2 (C19), 129.3 (C1), 128.8 (C18), 128.6 (C4), 123.4 (C5), 106.5 (C3), 85.5 (C8), 60.0 (C16), 53.5 (C13), 39.0 (C10), 34.4 (C7), 31.5 (C12), 24.1 (C14), 21.9 (C21), 19.8 (C11), 18.5 (C22).

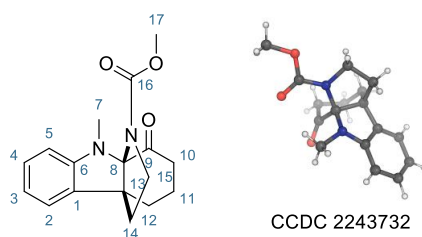
The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H14 $\leftrightarrow$ NH and H14 $\leftrightarrow$ H18 (weak) is consistent with the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3352 (br), 1715, 1677, 1503, 1470, 1323, 1291, 1144, 913, 734.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$   $[\text{M}+\text{H}]^+$ : 441.1843; found: 441.1838.

MP 64–68 °C (unclear phase transition owing to foam nature of solid).

Photochemical reactivity of **248**, a substrate bearing a tethered carbamate group  
Methyl (4b*S*,8a*R*)-9-methyl-8-oxo-5,6,7,8-tetrahydro-9*H*-8a,4b-  
(epiminoethano)carbazole-10-carboxylate, **261**



*N*-Aryl enaminone **248** (128.5 mg, 0.300 mmol, 1.0 eq.) was dissolved in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with two Kessil PR160L 427 nm LED lamps (each positioned *ca.* 3 cm from the flask and directed toward it) for 3 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Triethylamine (2.0 mL) was added to the reaction mixture at the end of the irradiation period, and the resulting mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography on alumina gel (eluent: 20% ethyl acetate in pentane) to afford **261** (79.6 mg, 0.265 mmol, 88%) as a peach-coloured solid. Diffraction-quality crystals were grown by vapour diffusion of *n*-hexane into a solution of the product in dichloromethane.

$^1\text{H}$  NMR (600 MHz,  $\text{CD}_2\text{Cl}_2$ , 298 K)  $\delta$  = 7.13 (1H, td,  $J$  7.7, 1.3, H4), 6.95 (1H, dd,  $J$  7.2, 1.3, H2), 6.66 (1H, t,  $J$  7.4, H3), 6.40 (1H, d,  $J$  7.8, H5), 3.89–3.82\* (1H, br m, H15), 3.70\* (3H, br s, H17), 3.47 (1H, ddd,  $J$  10.8, 8.4, 5.6, H15'), 2.99\* (3H, br s, H7), 2.48 (1H, ddd,  $J$  13.5, 10.1, 6.6, H14), 2.31 (1H, dddd,  $J$  13.5, 5.7, 4.4, 1.1, H14'), 2.12 (1H, ddd,  $J$  12.6, 8.4, 6.9, H14), 2.08–1.92 (3H, m, H11, H12 & H14'), 1.79 (1H, ddd,  $J$  14.2, 11.0, 3.6, H12'), 1.74–1.63 (1H, m, H11').

Cooling of the  $\text{CD}_2\text{Cl}_2$  solution to 253 K (spectra below) resulted in resolution of the broad  $^1\text{H}$  resonances (marked above with an asterisk, \*) into two clear sets of signals, each of which presumably corresponds to different rotational states about the carbamate C–N bond; the two conformers were present in a *ca.* 72:28 ratio at this temperature. As a result of slow chemical exchange at room temperature, it was necessary to collect  $^{13}\text{C}$  NMR data for this compound at low temperature.

$^{13}\text{C}$  NMR (151 MHz,  $\text{CD}_2\text{Cl}_2$ , 253 K)  $\delta$  = 207.4 (C9<sub>B</sub>), 207.2 (C9<sub>A</sub>), 155.7 (C16<sub>A</sub>), 154.8 (C16<sub>B</sub>), 149.7 (C6<sub>B</sub>), 149.6 (C6<sub>A</sub>), 130.4 (C1<sub>B</sub>), 130.3 (C1<sub>A</sub>), 128.9 (C4<sub>A</sub> & C4<sub>B</sub>, coincident), 121.1(3) (C2<sub>B</sub>), 121.1(0) (C2<sub>A</sub>), 117.3 (C3<sub>B</sub>), 117.0 (C3<sub>A</sub>), 105.6 (C5<sub>B</sub>), 105.5 (C5<sub>A</sub>), 95.1 (C8<sub>A</sub>), 94.6 (C8<sub>B</sub>), 64.6 (C13<sub>B</sub>), 62.8 (C13<sub>A</sub>), 52.9 (C17<sub>A</sub>), 52.5 (C17<sub>B</sub>), 47.6 (C15<sub>B</sub>), 47.0 (C15<sub>A</sub>), 38.2 (C14<sub>A</sub>), 37.8 (C10<sub>A</sub>),

37.5 (C10<sub>B</sub>), 36.9 (C14<sub>B</sub>), 31.3 (C7<sub>A</sub>), 30.9(0) (C7<sub>B</sub>), 30.8(5) (C12<sub>B</sub>), 30.3 (C12<sub>A</sub>), 24.0 (C11<sub>A</sub>), 23.8 (C11<sub>B</sub>). (Here, the subscript 'A' denotes signals corresponding to the major component of the rotameric mixture, while 'B' denotes resonances of the minor component.)

The structure of this compound was confirmed through single-crystal X-ray diffraction (CCDC 2243732).

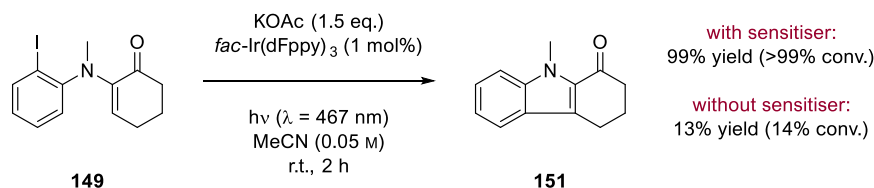
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1729, 1703, 1610, 1487, 1446, 1369, 1198, 1073, 1017, 745.

HRMS (ESI)  $m/z$  calcd. for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 301.1547; found: 301.1409.

MP 110–112 °C.

## Triplet sensitisation

### Experimental procedure

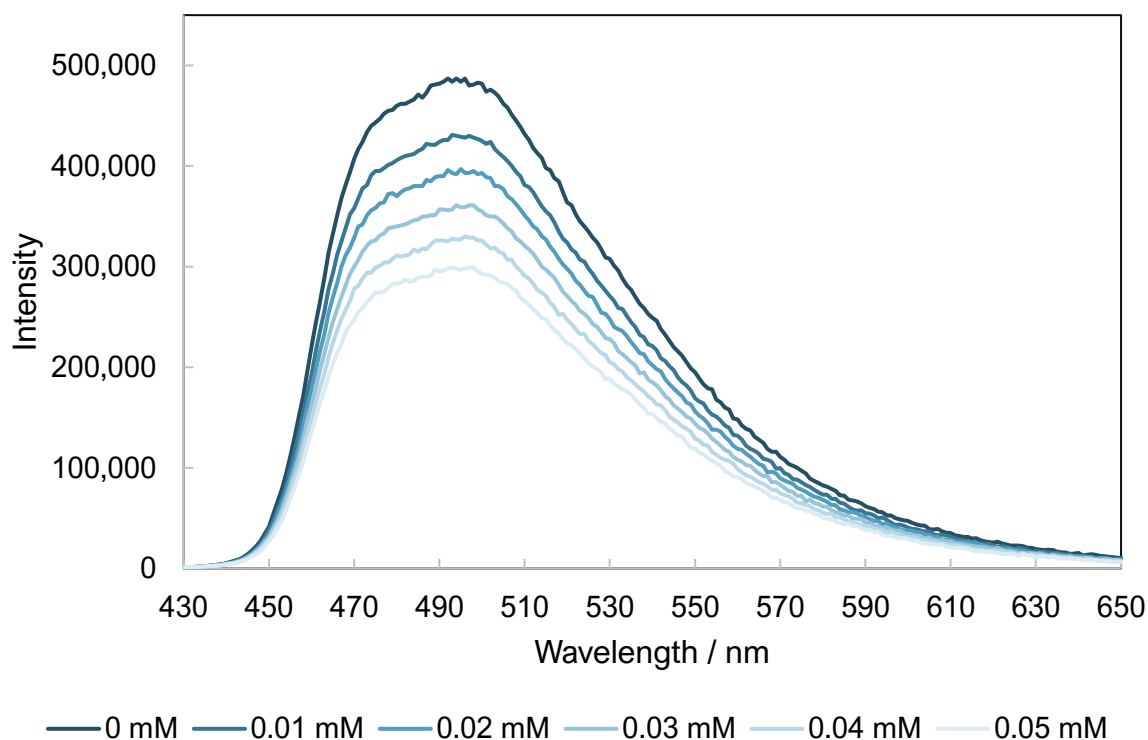


Enaminone **149** (32.7 mg, 0.100 mmol, 1.0 eq.), *fac*-Ir(dFppy)<sub>3</sub> (0.8 mg, 1  $\mu$ mol, 1 mol%) and potassium acetate (14.7 mg, 0.150 mmol, 1.5 eq.) were charged to a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum and then evacuated and back-filled with argon three times. Argon-sparged acetonitrile (2.0 mL, 0.05 M) was added *via* syringe. The reaction mixture was stirred under constant irradiation with a single Kessil PR160 467 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 2 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Dimethyl terephthalate was added at the end of the irradiation period as a solution in acetonitrile (25.0 mM, 1.0 mL, 0.25 mmol, 0.25 eq.). The resulting mixture was concentrated *in vacuo*, and the crude residue was dissolved in CDCl<sub>3</sub> for analysis by quantitative <sup>1</sup>H NMR spectroscopy. The NMR yield of indole **151** measured against dimethyl terephthalate was 99% (full conversion of **149**). A near-identical experiment was performed in parallel, differing only in that *fac*-Ir(dFppy)<sub>3</sub> was excluded; the NMR yield of indole **151** measured against dimethyl terephthalate for this reaction was 13% (14% conversion of **149**).

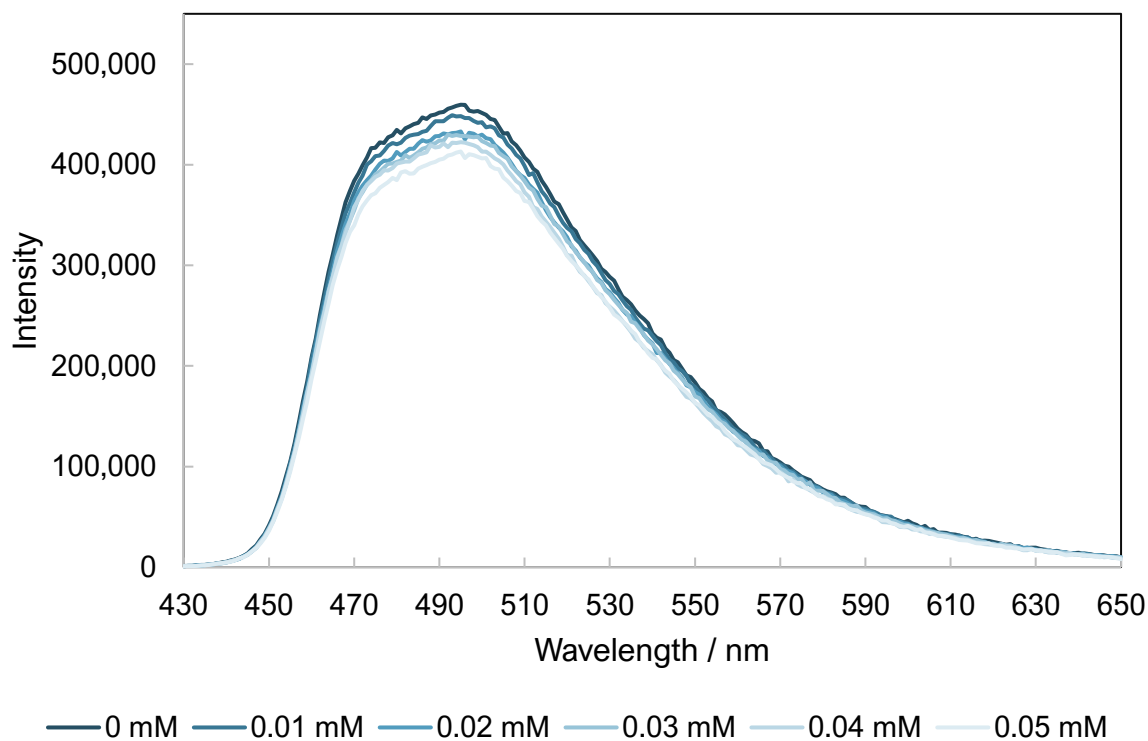
### Stern–Volmer phosphorescence quenching of *fac*-Ir(dFppy)<sub>3</sub> by **149**

Into a 1-cm quartz cuvette was placed 2.5 mL of a 5  $\mu$ M solution of *fac*-[Ir(dFppy)<sub>3</sub>] in anhydrous acetonitrile. The cuvette was sealed with a rubber septum, and the solution was gently sparged with argon for 10 min. A luminescence emission spectrum (excitation wavelength = 420 nm) was measured between 430 and 650 nm. An argon-sparged solution of substrate **149** (5 mM) in anhydrous acetonitrile was added to the above photocatalyst solution in 5  $\mu$ L portions. Fluorescence emission spectra were recorded after each addition (Figure 5). This procedure was repeated using tetra-*n*-butylammonium acetate (dried prior to use by heating to 100 °C under high vacuum for 16 h) in place of **149** as the quencher (Figure 6).

Stern–Volmer quenching constants were calculated as described in the main text.



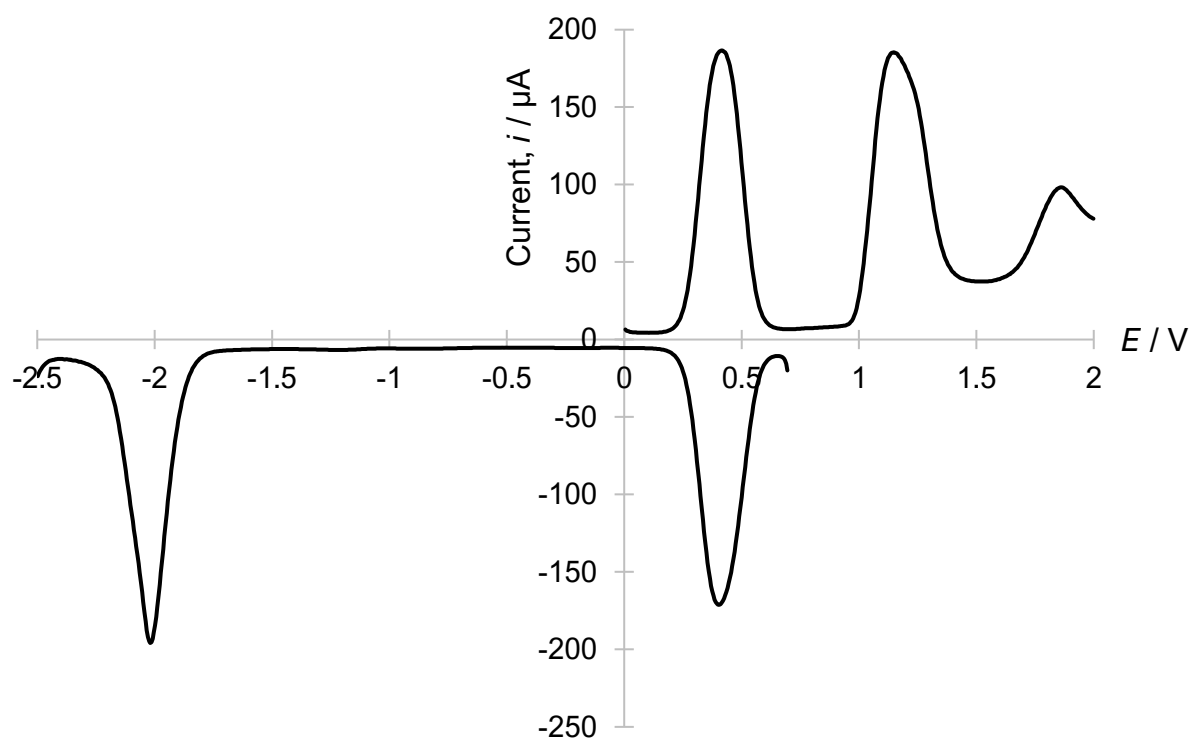
**Figure 5 (reproduced from main text).** Emission spectra recorded for a 5  $\mu\text{M}$  solution of *fac*-[Ir(dFppy)<sub>3</sub>] in the presence of different concentrations of substrate **149** in acetonitrile solution. Excitation at 420 nm.



**Figure 6 (reproduced from main text).** Emission spectra recorded for a 5  $\mu\text{M}$  solution of *fac*-[Ir(dFppy)<sub>3</sub>] in the presence of different concentrations of (*n*-Bu)<sub>4</sub>NOAc in acetonitrile solution. Excitation at 420 nm.

## Voltammetry

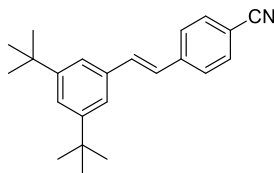
A PalmSens EmStat3 potentiostat, equipped with a glassy carbon working electrode, Pt wire (0.5 mm diameter) counter electrode and leak-free Ag/AgCl (3.4 M KCl) reference electrode, was used for redox measurements. Square-wave voltammograms were acquired with a 5 mV step potential, 100 mV modulation amplitude and 5 Hz frequency, and internally referenced to the  $\text{Fc}^+/\text{Fc}$  couple; an argon-sparged solution of tetra-*n*-butylammonium hexafluorophosphate in acetonitrile (0.1 M, 5 mL) was used as the supporting electrolyte. The half-wave oxidation and reduction potentials of **149** in acetonitrile were measured as +1.10 V and -2.04 V, respectively, vs. SCE (Figure 15).<sup>85</sup>



**Figure 15.** Square-wave voltammogram of substrate **149** in acetonitrile, internally referenced to  $\text{Fc}^+/\text{Fc}$ .

## Triplet quenching

### (*E*)-4-(3,5-Di-*tert*-butylstyryl)benzonitrile, **263**



This compound was prepared by analogy to a literature procedure.<sup>147</sup> Aqueous sodium hydroxide (1.0 M, 3.0 mL, 3.0 mmol, 1.5 eq.) was added in one portion to a stirred, room-temperature solution of (3,5-di-*tert*-butylbenzyl)triphenylphosphonium bromide (1.36 g, 2.49 mmol, 1.25 eq.) in dichloromethane (10 mL, 0.2 M) followed by 4-formylbenzonitrile (262 mg, 2.00 mmol, 1.0 eq.), also in one portion. After stirring for 1 h, the reaction mixture was diluted with dichloromethane (20 mL) and washed once with water (10 mL). The layers were separated, and the aqueous phase was extracted with additional dichloromethane (10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 5% ethyl acetate in pentane) to afford **263** (*ca.* 630 mg, (*E*):(*Z*)  $\approx$  1.2:1) as a viscous colourless oil, which was dissolved together with iodine (50 mg) in *n*-hexane (20 mL) and heated to reflux for 12 h. Ethyl acetate (20 mL) was added after cooling to room temperature to dissolve the solids that had formed during the reaction. The resulting solution was washed successively with sodium thiosulfate (sat. aq., 2 x 10 mL) and brine (20 mL) before being dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford **263** (496 mg, 1.56 mmol, 78% over two steps) as an off-white solid. The spectral data matched that previously reported in the literature.<sup>147</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.67–7.56 (4H, m), 7.42 (1H, t, *J* 1.7), 7.39 (2H, d, *J* 1.7), 7.27 (1H, d, *J* 16.3), 7.09 (1H, d, *J* 16.3), 1.38 (18H, s).

## Procedures for oxygen quenching experiments

### Reactions performed in the presence of triethylsilane:

Enaminone **162** (34.1 mg, 0.0999 mmol, 1.0 eq.) was dissolved in a 9:1 (v/v) mixture of acetonitrile (1.8 mL) and water (0.2 mL) (0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. Argon-sparged triethylsilane (80  $\mu$ L, 58 mg, 0.50 mol, 5.0 eq.) was added *via* syringe. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 45 min, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Dimethyl terephthalate was added at the end of the irradiation period as a solution in acetonitrile (25.0 mM, 1.0 mL, 0.25 mmol, 0.25 eq.). The resulting mixture was concentrated *in vacuo*, and the crude

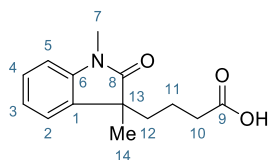


residue was dissolved in CDCl<sub>3</sub> for analysis by quantitative <sup>1</sup>H NMR spectroscopy. The NMR yield of indoline **77** measured against dimethyl terephthalate was 90%; the conversion of **149** was 70%. A near-identical experiment was performed in parallel, differing only in that the reaction mixture was sparged with oxygen prior to irradiation. Analysis of the crude product of this reaction as above by quantitative <sup>1</sup>H NMR spectroscopy revealed the formation of indoline **77** in a yield of 43% measured against dimethyl terephthalate, alongside several trace unknown side-products; the conversion of **162** was 59%.

*Reactions performed in the presence of potassium acetate:*

Enaminone **162** (34.1 mg, 0.0999 mmol, 1.0 eq.) and potassium acetate (14.7 mg, 0.150 mmol, 1.5 eq.) were dissolved in a 9:1 (v/v) mixture of acetonitrile (1.8 mL) and water (0.2 mL) (0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 45 min, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Dimethyl terephthalate was added at the end of the irradiation period as a solution in acetonitrile (25.0 mM, 1.0 mL, 0.25 mmol, 0.25 eq.). The resulting mixture was concentrated *in vacuo*, and the crude residue was dissolved in CDCl<sub>3</sub> for analysis by quantitative <sup>1</sup>H NMR spectroscopy. The NMR yield of hemiaminal **177** measured against dimethyl terephthalate was 90%; the conversion of **162** was >99%. A near-identical experiment was performed in parallel, differing only in that the reaction mixture was sparged with oxygen prior to irradiation. Analysis of the crude product of this reaction as above by quantitative <sup>1</sup>H NMR spectroscopy revealed the formation of oxindole **265** in a yield of 26% measured against dimethyl terephthalate, alongside several trace unknown side-products; the conversion of **162** was 44%. Flash column chromatography on silica gel (gradient elution from 2.5 to 5% ethanol in chloroform) provided an analytical sample of the major product.

4-(1,3-Dimethyl-2-oxoindolin-3-yl)butanoic acid, **265**



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.30–7.24 (1H, m, H4), 7.17 (1H, dd, *J* 7.3, 1.3, H2), 7.07 (1H, td, *J* 7.5, 1.0, H3), 6.84 (1H, dd, *J* 7.8, 0.8, H5), 3.22 (3H, s, H7), 2.27–2.17 (2H, m, H10 & H10'), 1.93 (1H, ddd, *J* 13.4, 11.9, 4.9, H12), 1.80 (1H, ddd, *J* 13.4, 12.0, 4.7, H12'), 1.35 (3H, s, H14), 1.35–1.17 (2H, m, H11 & H11').

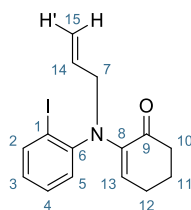
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 180.6 (C8), 177.8 (C9), 143.3 (C6), 133.7 (C1), 128.0 (C4), 122.8 (C3), 122.7 (C2), 108.2 (C5), 48.4 (C13), 37.7 (C12), 33.8 (C10), 26.3 (C7), 24.0 (C14), 19.9 (C11).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3055 (br), 1707 (br), 1612, 1470, 1378, 1179, 1126, 1019, 909, 734.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{17}\text{O}_3\text{NNa}$   $[\text{M}+\text{Na}]^+$ : 270.11006; found: 270.11013.

## Synthesis and photochemical reactivity of *N*-allyl substrate **266**

### 2-(Allyl(2-iodophenyl)amino)cyclohex-2-en-1-one, **266**



Aniline **230** (1.52 g, 5.87 mmol, 1.0 eq.), morpholine enamine **148** (2.13 g, 11.7 mmol, 2.0 eq.) and *para*-toluenesulfonic acid monohydrate (2.23 g, 11.7 mmol, 2.0 eq.) were heated to 50 °C in toluene (14.5 mL, 0.4 M) for 3 h. The reaction was cooled to room temperature and diluted with ethyl acetate (30 mL). The solution was washed with sodium hydrogencarbonate (sat. aq., 3 x 15 mL) followed by brine (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on alumina gel (eluent: 5% ethyl acetate in pentane) to afford **266** (940 mg, 2.66 mmol, 45%) as a viscous yellow oil.

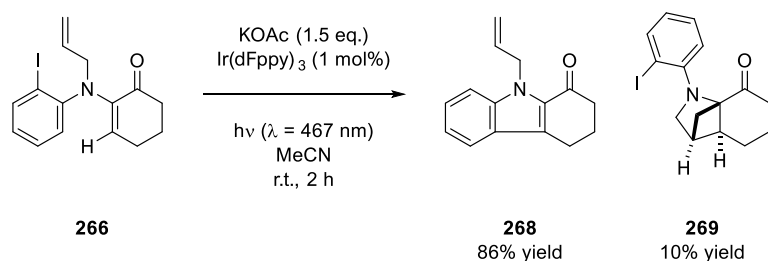
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.83 (1H, dd,  $J$  7.9, 1.5, H2), 7.24 (1H, ddd,  $J$  7.9, 7.2, 1.4, H4), 7.04 (1H, dd,  $J$  8.0, 1.6, H5), 6.78 (1H, ddd,  $J$  7.8, 7.3, 1.6, H3), 5.99 (1H, t,  $J$  4.6, H13), 5.91 (1H, ddt,  $J$  17.3, 10.3, 5.8, H14), 5.16 (1H, dq,  $J$  17.3, 1.6, H15), 5.11 (1H, dq,  $J$  10.3, 1.5, H15'), 4.01 (2H, dt,  $J$  5.9, 1.6, H7), 2.49–2.43 (2H, m, H10), 2.43–2.36 (2H, m, H12), 2.05–1.94 (2H, m, H11).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 195.8 (C9), 150.3 (C6), 143.3 (C8), 140.4 (C2), 135.2 (C14), 131.2 (C13), 128.7 (C4), 125.8 (C3), 125.4 (C5), 117.3 (C15), 98.7 (C1), 54.8 (C7), 39.7 (C10), 25.7 (C12), 22.9 (C11).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1684, 1466, 1193, 1155, 1113, 1016, 919, 891, 763, 732.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{17}\text{INO}$   $[\text{M}+\text{H}]^+$ : 354.0349; found: 354.0347.

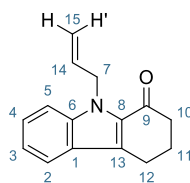
### Photocyclisation of **266**



Enaminone **266** (106.0 mg, 0.300 mmol, 1.0 eq.), *fac*-Ir(dFppy)<sub>3</sub> (2.3 mg, 3.0  $\mu\text{mol}$ , 1 mol%) and potassium acetate (44.2 mg, 0.450 mmol, 1.5 eq.) were charged to a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum and then evacuated and back-filled with

argon three times. Argon-sparged acetonitrile (6.0 mL, 0.05 M) was added *via* syringe. The reaction mixture was stirred under constant irradiation with a single Kessil PR160 467 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 2 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, gradient elution from 5 to 25% ethyl acetate in pentane) to afford indole **268** (57.9 mg, 0.257 mmol, 86%) as a viscous colourless oil, alongside bridged cyclobutane **269** (10.6 mg, 0.0300 mmol, 10%) as an off-white solid.

#### 9-Allyl-2,3,4,9-tetrahydro-1H-carbazol-1-one, **268**



The spectral data matched that previously reported in the literature.<sup>148</sup>

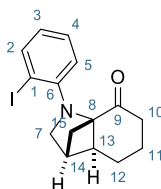
<sup>1</sup>H (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.67 (1H, dt, *J* 8.0, 1.0, H2), 7.43–7.30 (2H, m, H4<sub>LHS</sub> & H5<sub>RHS</sub>), 7.16 (1H, ddd, *J* 8.0, 6.6, 1.3, H3), 5.99 (1H, ddt, *J* 17.1, 10.3, 5.2, H5), 5.23 (2H, dt, *J* 5.2, 1.7, H7), 5.09 (1H, dq, *J* 10.3, 1.5, H15), 4.95 (1H, dq, *J* 17.1, 1.7, H15'), 3.04 (2H, t, *J* 6.1, H12), 2.65 (2H, dd, *J* 7.2, 5.7, H10), 2.23 (2H, quint, *J* 6.3, H11).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 192.0 (C9), 139.3 (C6), 134.2 (C14), 129.9 (C8), 129.8 (C13), 126.8 (C4), 125.1 (C1), 121.5 (C2), 120.3 (C3), 116.2 (C15), 110.9 (C5), 47.0 (C7), 40.1 (C10), 24.9 (C11), 22.0 (C12).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1656, 1534, 1460, 1437, 1380, 1269, 1185, 1090, 929, 745.

HRMS (ESI) *m/z* calcd. for C<sub>15</sub>H<sub>15</sub>NO [M+H]<sup>+</sup>: 226.1226; found: 226.1226.

#### (3*R*,3*aS*,7*aS*)-1-(2-Iodophenyl)hexahydro-3,7*a*-methanoindol-7(1*H*)-one, **269**



Broad signals on the <sup>1</sup>H NMR spectrum of compound **269** in DMSO-*d*<sub>6</sub> solution at 298 K suggested the presence of two slowly interconverting conformers. Signal coalescence was observed upon heating to 368 K; however, the sample quickly degraded (reverting to *N*-aryl enaminone **266**) at this temperature, precluding the compound's full characterisation. The two conformers were therefore individually characterised at 253 K in CD<sub>2</sub>Cl<sub>2</sub> solution; the <sup>1</sup>H and <sup>13</sup>C NMR data for both

are provided below. Diffraction-quality crystals of **269** were grown by vapour diffusion of cyclohexane into a solution of **269** in tetrahydrofuran followed by slow evaporation of the resulting mixture.

**Major rotamer:**

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ , 253 K)  $\delta^* = 7.82\text{--}7.78$  (1H, m, H2),  $7.17\text{--}7.11$  (1H, m, H4),  $6.70\text{--}6.64$  (1H, m, H3),  $6.45$  (1H, dd,  $J$  8.2, 1.5, H5),  $4.29$  (1H, d,  $J$  8.0, H7),  $3.03$  (1H, dd,  $J$  8.5, 2.8, H15),  $2.73$  (1H, d,  $J$  2.8, H14),  $2.66\text{--}2.61$  (1H, m, H7'),  $2.64\text{--}2.56$  (1H, m, H10),  $2.53\text{--}2.47$  (1H, m, H13),  $2.28$  (1H, dtd,  $J$  12.8, 3.2, 1.3, H10'),  $2.21\text{--}2.15$  (1H, m, H12),  $2.07\text{--}1.94$  (3H, m, H11, H11' & H15'),  $1.81\text{--}1.70$  (1H, m, H12').

$^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ , 253 K)  $\delta = 205.1$  (C9),  $152.7$  (C6),  $140.4$  (C2),  $127.4$  (C4),  $123.4$  (C3),  $120.6$  (C5),  $92.1$  (C1),  $75.2$  (C8),  $61.6$  (C7),  $58.1$  (C13),  $41.6$  (C14),  $40.9$  (C10),  $38.1$  (C15),  $29.1$  (C12),  $24.9$  (C11).

**Minor rotamer:**

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ , 253 K)  $\delta = 7.84\text{--}7.80$  (1H, m, H2),  $7.17\text{--}7.11$  (1H, m, H4),  $6.70\text{--}6.64$  (1H, m, H3),  $6.24$  (1H, dd,  $J$  8.1, 1.5, H5),  $4.42$  (1H, dd,  $J$  7.8, 1.1, H7),  $2.94$  (1H, dt,  $J$  7.8, 2.8, H15),  $2.75$  (1H, d,  $J$  3.3, H14),  $2.66\text{--}2.61$  (1H, m, H7'),  $2.50\text{--}2.44$  (1H, m, H13),  $2.51\text{--}2.42$  (2H, m, H10 & H10'),  $2.19\text{--}2.11$  (2H, m, H11 & H12),  $2.07\text{--}1.94$  (2H, m, H11' & H15'),  $1.94\text{--}1.83$  (1H, m, H12').

$^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ , 253 K)  $\delta = 204.3$  (C9),  $151.4$  (C6),  $140.9$  (C2),  $127.7$  (C4),  $123.6$  (C3),  $119.7$  (C5),  $92.8$  (C1),  $74.1$  (C8),  $61.5$  (C7),  $49.8$  (C13),  $43.2$  (C15),  $41.1$  (C14),  $39.8$  (C10),  $25.1$  (C12),  $24.6$  (C11).

Single-crystal X-ray diffraction confirmed the formation of the regioisomer shown; additionally, the observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to  $\text{H5} \leftrightarrow \text{H13}$  in the minor conformer and  $\text{H5} \leftrightarrow \text{H15'}$  in the major conformer is consistent with this structure.

FTIR (neat)  $\nu/\text{cm}^{-1} = 1706, 1578, 1465, 1433, 1294, 1104, 1012, 947, 872, 753$ .

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{17}\text{INO}$   $[\text{M}+\text{H}]^+$ : 354.0349; found: 354.0345.

MP  $136\text{--}137\text{ }^\circ\text{C}$ .

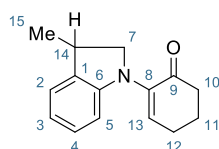
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\* Where signals of the two rotamers overlapped, the chemical shifts and number of protons quoted for a given spectral range were determined through multiplicity-edited HSQC analysis; integration of clearly resolved signals within MestReNova indicates an approximate molar ratio of 3:2 between the two rotamers.

## Reductive cyclisation of *N*-allyl substrate **266**

This reaction was performed under conditions reported by Murphy and co-workers;<sup>94</sup> the dihydrobenzimidazole reagent, **271**, was synthesised according to a literature procedure and stored under argon at -18 °C prior to use.<sup>149</sup> The following compounds were charged sequentially to a 7 mL glass vial equipped with magnetic stir bar: *N*-allyl substrate **4** (106.0 mg, 0.300 mmol, 1.0 eq.), dihydrobenzimidazole **271** (88.9 mg, 0.600, 2.0 eq.) as a solution in *N,N*-dimethylformamide (1.5 mL, 0.2 M), and 1-dodecanethiol (14.5  $\mu$ L, 12.3 mg, 0.0605 mmol, 0.2 eq.). The vial was kept open to air whilst the reaction mixture was heated to 55 °C with stirring. After 2 h, the reaction mixture was poured onto brine (50 mL); the resulting aqueous mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate before adding dimethyl terephthalate as a solution in acetonitrile (25.0 mM, 3.0 mL, 0.75 mmol, 0.25 eq.), concentrating *in vacuo*, and dissolving the resulting crude residue in CDCl<sub>3</sub> for analysis by quantitative <sup>1</sup>H NMR spectroscopy. The NMR yields of indole **268** and indoline **272** measured against dimethyl terephthalate were 43% and 28%, respectively. Flash column chromatographic purification of the crude product mixture on silica gel (eluent: 5% ethyl acetate in pentane) furnished impure samples of **268** and **272**. The former sample was contaminated with the NMR internal standard dimethyl terephthalate but otherwise possessed identical spectral data to that obtained previously for this compound (see above); subsequent attempts to resolve the two components of this mixture by flash column chromatography were unsuccessful. The latter sample containing **272** was successfully purified by flash column chromatography on alumina gel (eluent: 5% ethyl acetate in pentane) to afford **272** (7.5 mg, 32  $\mu$ mol, 11%) as a viscous orange oil. This sample contained a minor (less than *ca.* 5%) impurity, which appears to be structurally related to the starting material, **266**, but whose exact identity is unknown; multiple subsequent chromatographic purification attempts to isolate this contaminant were unsuccessful.

### 2-(3-Methylindolin-1-yl)cyclohex-2-en-1-one, **272**



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.10–7.05 (1H, m, H2), 7.04–6.96 (1H, m, H4), 6.74–6.67 (2H, m, H3 & H13), 6.46–6.33 (1H, m, H5), 3.83 (1H, t, *J* 8.7, H7), 3.47–3.33 (1H, m, H14), 3.27 (1H, t, *J* 8.6, H7'), 2.62–2.54 (2H, m, H10), 2.54–2.46 (2H, m, H12), 2.10–2.02 (2H, m, H11), 1.33 (3H, d, *J* 6.8, H15).

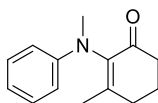
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 196.1 (C9), 148.5 (C6), 141.1 (C8), 135.8 (C1), 134.6 (C13), 127.1 (C4), 123.5 (C2), 118.7 (C3), 109.7 (C5), 61.1 (C7), 39.5 (C10), 35.3 (C14), 25.7 (C12), 23.1 (C11), 19.0 (C15).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1685, 1602, 1484, 1459, 1265, 1231, 1156, 1119, 914, 745.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{18}\text{NO}$   $[\text{M}+\text{H}]^+$ : 228.1383; found: 228.1383.

## Synthesis and photochemical reactivity of an 'iodo-displaced' substrate

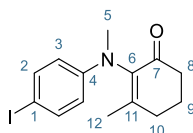
### 3-Methyl-2-(methyl(phenyl)amino)cyclohex-2-en-1-one, **332**



This compound was prepared according to a literature procedure.<sup>44</sup> 6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one (**163**) (631 mg, 5.00 mmol, 1.0 eq.) and *N*-methylaniline (0.65 mL, 0.64 g, 6.0 mmol, 1.2 eq.) in a two-necked round-bottomed flask equipped with a condenser and magnetic stir bar were dissolved in a 3:1 (v/v) mixture of methanol (9 mL) and water (3 mL) (*ca.* 0.4 M). The resulting mixture was sparged with argon for 15 min before being heated to reflux with stirring. After 21 h, the reaction mixture was poured onto water (20 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (sat. aq., 15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 30% diethyl ether in pentane) to afford **332** (369 mg, 1.71 mmol, 34%) as a viscous yellow-brown oil. The spectral data matched that previously reported in the literature.<sup>44</sup>

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.25–7.07 (2H, m), 6.82–6.62 (1H, m), 6.59–6.44 (2H, m), 3.02 (3H, s), 2.62–2.43 (4H, m), 2.24–1.95 (2H, m), 1.88 (3H, s).

### 2-((4-Iodophenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **273**



To a solution of enaminone **332** (365 mg, 1.70 mmol, 1.0 eq.) in dichloromethane (10 mL, *ca.* 0.2 M) at room temperature was added iodine (473 mg, 1.86 mmol, 1.1 eq.) and silver sulfate (581 mg, 1.86 mmol, 1.1 eq.) with vigorous stirring. After 3 h, the reaction mixture was filtered through celite, and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 75% dichloromethane in pentane) to afford **273** (155 mg, 0.453 mmol, 27%) as a viscous green oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.44–7.35 (2H, m, H<sub>2</sub>), 6.36–6.27 (2H, m, H<sub>3</sub>), 2.98 (3H, s, H<sub>5</sub>), 2.58–2.46 (4H, m, H<sub>10LHS</sub> & H<sub>8RHS</sub>), 2.05 (2H, quint, *J* 6.2, H<sub>9</sub>), 1.86 (3H, t, *J* 0.9).

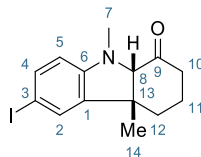
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 195.7 (C<sub>7</sub>), 159.0 (C<sub>11</sub>), 148.1 (C<sub>4</sub>), 139.4 (C<sub>6</sub>), 137.7 (C<sub>2</sub>), 114.2 (C<sub>3</sub>), 77.9 (C<sub>1</sub>), 38.8 (C<sub>8</sub>), 38.0 (C<sub>5</sub>), 32.3 (C<sub>10</sub>), 22.1 (C<sub>9</sub>), 20.2 (C<sub>12</sub>).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1673, 1587, 1489, 1354, 1342, 1290, 1226, 1117, 925, 808.



HRMS (ESI)  $m/z$  calcd. for  $C_{14}H_{17}ONI$   $[M+H]^+$ : 342.0349; found: 342.0348.

(4a*R*,9a*S*)-6-Iodo-4a,9-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **274**



Enaminone **273** (34.1 mg, 0.0999 mmol, 1.0 eq.) and potassium acetate (14.7 mg, 0.150 mmol, 1.5 eq.) were dissolved in acetonitrile (2.0 mL, 0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with a single Kessil PR160 467 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 18 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, gradient elution from 5 to 10% ethyl acetate in pentane) to afford indoline **274** (26.3 mg, 0.0771 mmol, 77%) as a viscous colourless oil.

$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.41 (1H, dd,  $J$  8.2, 1.8, H4), 7.23 (1H, d,  $J$  1.8, H2), 6.33 (1H, d,  $J$  8.2, H5), 3.17 (1H, s, H8), 2.68 (3H, s, H7), 2.69–2.57 (1H, m, H10), 2.32 (1H, dt,  $J$  15.5, 5.7, H10'), 1.94–1.70 (3H, m, H11, H11' & H12), 1.64–1.54 (1H, m, H12'), 1.36 (3H, s, H14).

$^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  = 211.1 (C9), 151.3 (C6), 140.4 (C1), 136.8 (C4), 130.4 (C2), 110.5 (C5), 81.5 (C8), 80.1 (C3), 48.7 (C13), 38.0 (C10), 36.3 (C12), 34.8 (C7), 24.7 (C14), 21.1 (C11).

The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to  $H8 \leftrightarrow H14$  is consistent with the formation of the *cis*-diastereomer shown.

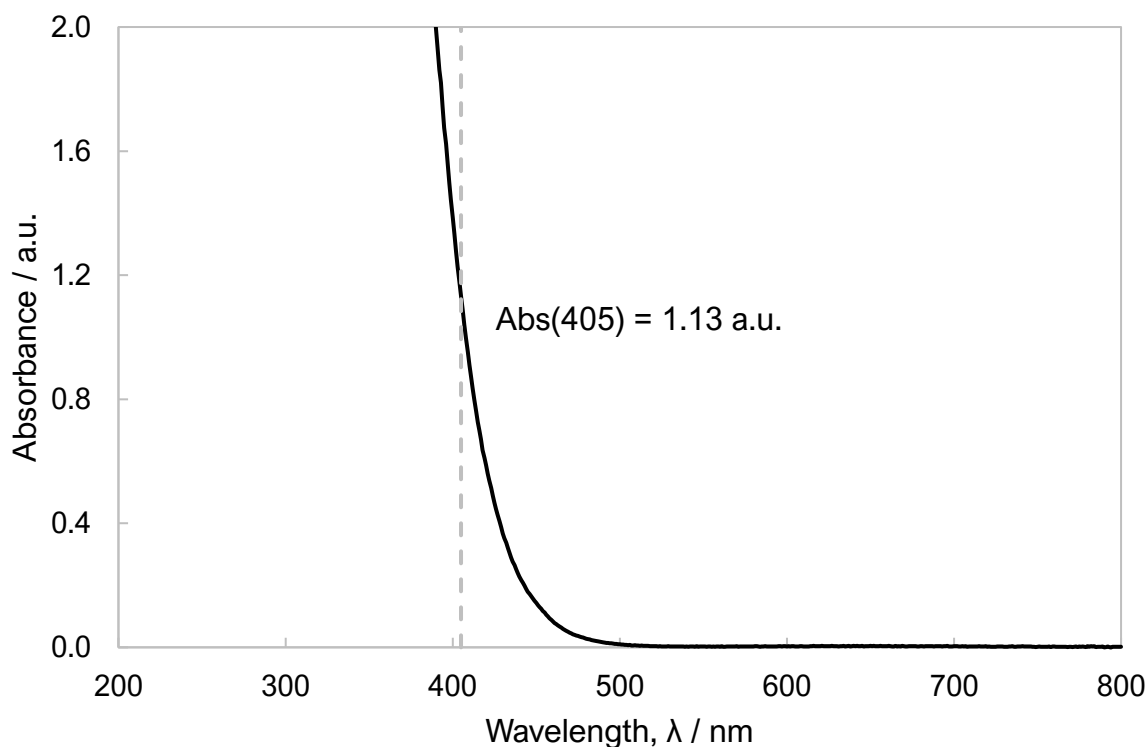
FTIR (neat)  $\nu/cm^{-1}$  = 1713, 1595, 1477, 1453, 1257, 1231, 1069, 908, 805, 734.

HRMS (ESI)  $m/z$  calcd. for  $C_{14}H_{17}INO$   $[M+H]^+$ : 342.0349; found: 342.0345.

### Chemical actinometry<sup>150</sup>

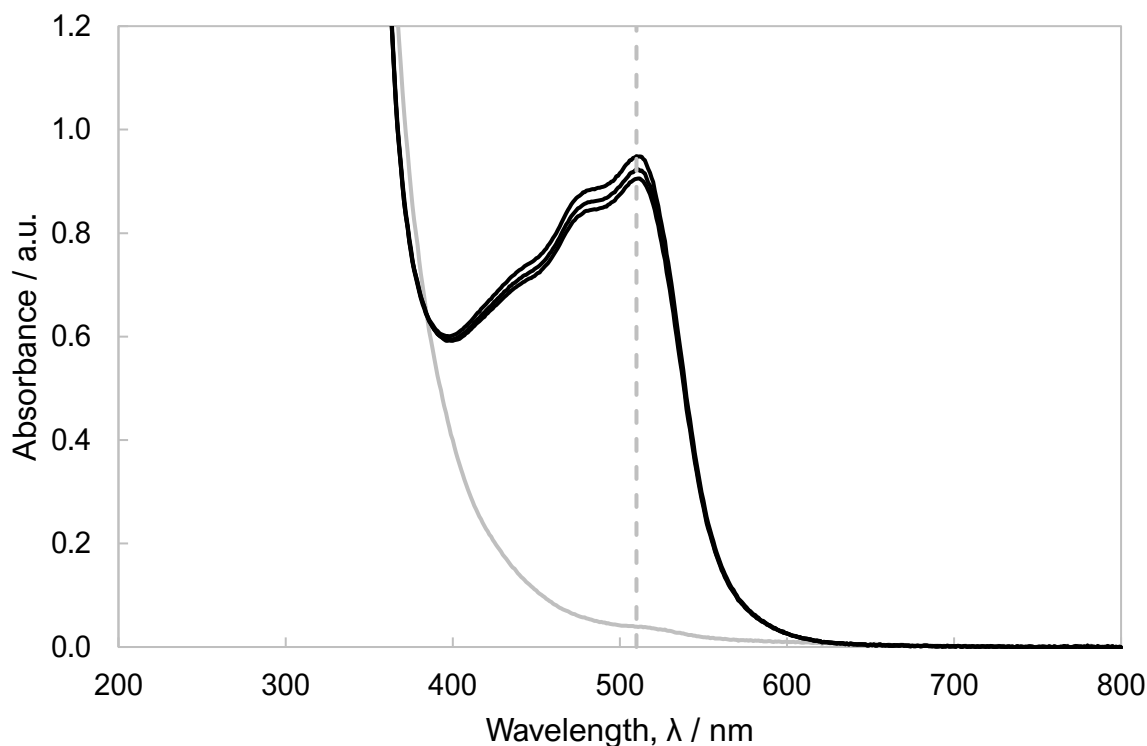
A Thorlabs M405L4 405 nm (1000 mW min.) mounted LED equipped with a liquid light guide was used for quantum yield measurements. The photon flux of this light source was determined by ferrioxalate actinometry, as described below. An Agilent Cary 60 UV-vis spectrophotometer was used for all absorption measurements.

A 0.0060 M solution of potassium ferrioxalate was prepared by dissolving 147.4 mg (0.300 mmol) of  $\text{K}_3[\text{Fe}(\text{C}_2\text{O}_4)_3] \cdot 3\text{H}_2\text{O}$  in 50 mL of 0.05 M aqueous  $\text{H}_2\text{SO}_4$  and stored in the dark. The absorbance of this solution at 405 nm (the irradiation wavelength) was measured as 1.13 a.u. (Figure 16).



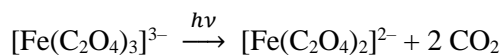
**Figure 16.** UV-vis absorption profile of the potassium ferrioxalate solution used for chemical actinometry.

Three 3.0 mL samples of the above ferrioxalate solution were placed in quartz cuvettes and irradiated with stirring for 8.0 s. An identical control sample was kept in the dark. After irradiation, 0.30 mL aliquots of each sample were transferred to vials containing 1.35 mL of a buffered, 0.1% solution of 1,10-phenanthroline (prepared by dissolving 100.0 mg of 1,10-phenanthroline and 13.56 g of sodium acetate in 100 mL of 0.5 M aqueous  $\text{H}_2\text{SO}_4$ ) and 1.35 mL of distilled water. The resulting solutions were stored in the dark for 1 h before being analysed by UV-vis spectroscopy (Figure 17). The irradiation conditions were selected to ensure that (i) the conversion of ferrioxalate did not exceed 15% and (ii) the absorbances of the final  $[\text{Fe}(\text{phen})_3]^{2+}$  solutions were within the range 0.5–1.0.



**Figure 17.** UV-vis absorption profiles of three samples of ferrioxalate solution after irradiation and complexation with 1,10-phenanthroline (black traces) and one control sample (grey trace).

The quantum yield of reaction,  $\Phi_R$ , for the photoreduction of the ferrioxalate anion (Scheme 112) was determined by Alegria *et al.* to be 1.14 at 405 nm.<sup>151</sup>



**Scheme 112.** Photoreduction of the ferrioxalate anion.

The photon flux,  $f$ , of the 405 nm LED was calculated using the following equation:

$$f = \frac{n(\text{Fe}^{2+})}{\Phi_R t (1 - 10^{-A})}$$

where  $n(\text{Fe}^{2+})$  is the number of moles of  $\text{Fe}^{2+}$  formed during the irradiation period,  $\Phi_R$  is the quantum yield for ferrioxalate photoreduction at the irradiation wavelength (1.14 at 405 nm),  $t$  is the irradiation time in s (8.0 s),  $A$  is the absorbance of the 0.0060 M ferrioxalate solution at the irradiation wavelength (1.13 a.u. at 405 nm).

The amount in mol of  $\text{Fe}^{2+}$  formed during the irradiation period,  $n(\text{Fe}^{2+})$ , was calculated for each sample using the following equation:

$$n(\text{Fe}^{2+}) = \frac{V_1 V_3 \Delta A_{510}}{V_2 \varepsilon_{510} l}$$

where  $V_1$  is the volume of ferrioxalate solution placed in the cuvette prior to irradiation in L,  $V_2$  is the volume of the aliquot taken for complexation in L,  $V_3$  is the final volume of the complexation solution in L,  $\Delta A_{510}$  is the difference in absorbance between the irradiated and dark samples at 510 nm after complexation with 1,10-phenanthroline,  $\varepsilon_{510}$  is the molar attenuation coefficient of  $[\text{Fe}(\text{phen})_3]^{2+}$  at 510 nm ( $11,100 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ ), and  $l$  is the optical path length, in cm, of the cuvette.

The values of  $n(\text{Fe}^{2+})$  and  $f$  calculated for each sample are presented in Table 9.

**Table 9.** Summary of results of ferrioxalate actinometry.

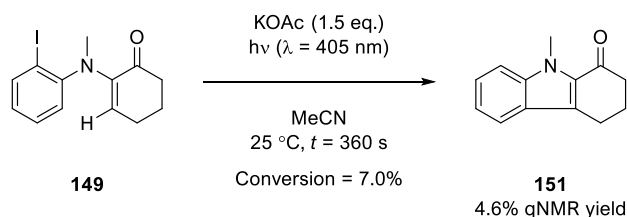
Sample	$A_{510}$ / a.u.	$\Delta A_{510}$ / a.u.	$n(\text{Fe}^{2+})$ / mol	$f$ / einsteins $\cdot\text{s}^{-1}$
Dark	0.039	0	-	-
Sample 1	0.949	0.910	$2.46 \times 10^{-6}$	$2.91 \times 10^{-7}$
Sample 2	0.905	0.866	$2.34 \times 10^{-6}$	$2.77 \times 10^{-7}$
Sample 3	0.923	0.884	$2.39 \times 10^{-6}$	$2.83 \times 10^{-7}$
		AVERAGE	$2.40 \times 10^{-6}$	$2.84 \times 10^{-7}$

An average value of  $2.84 \times 10^{-7}$  einsteins $\cdot\text{s}^{-1}$  was obtained for the photon flux,  $f$ , of the 405 nm LED.

## Determination of the quantum yield of reaction for $\beta$ -hydrogen, *ortho*-iodinated substrate **149**

### Experimental procedure

Substrate **149** (49.1 mg, 0.150 mmol, 1.0 eq.) and potassium acetate (22.1 mg, 0.225 mmol, 1.5 eq.) were charged to a 1 cm quartz cuvette equipped with a magnetic stir bar followed by argon-sparged acetonitrile (3.0 mL, 0.05 M). The resulting mixture was gently sparged with argon for 5 min before sealing the cuvette with a rubber septum under an argon atmosphere. The reaction mixture was irradiated with continuous stirring using the calibrated light source for 360 s at 25 °C inside the sample chamber of an Agilent Cary 60 spectrophotometer equipped with a Peltier temperature control accessory. After irradiation, the reaction mixture was transferred to a round-bottomed flask containing dimethyl terephthalate (7.3 mg, 0.038 mmol, 0.25 eq.) and concentrated *in vacuo*. The crude residue was dissolved in CDCl<sub>3</sub> for analysis by quantitative <sup>1</sup>H NMR spectroscopy. The NMR yield of **151** measured against dimethyl terephthalate was 4.6%. The conversion of starting material was measured to be 7.0% (Scheme 113).



**Scheme 113.** Product distribution obtained from the photocyclisation of *ortho*-iodinated substrate **40** after irradiation for 360 s using the calibrated light source.

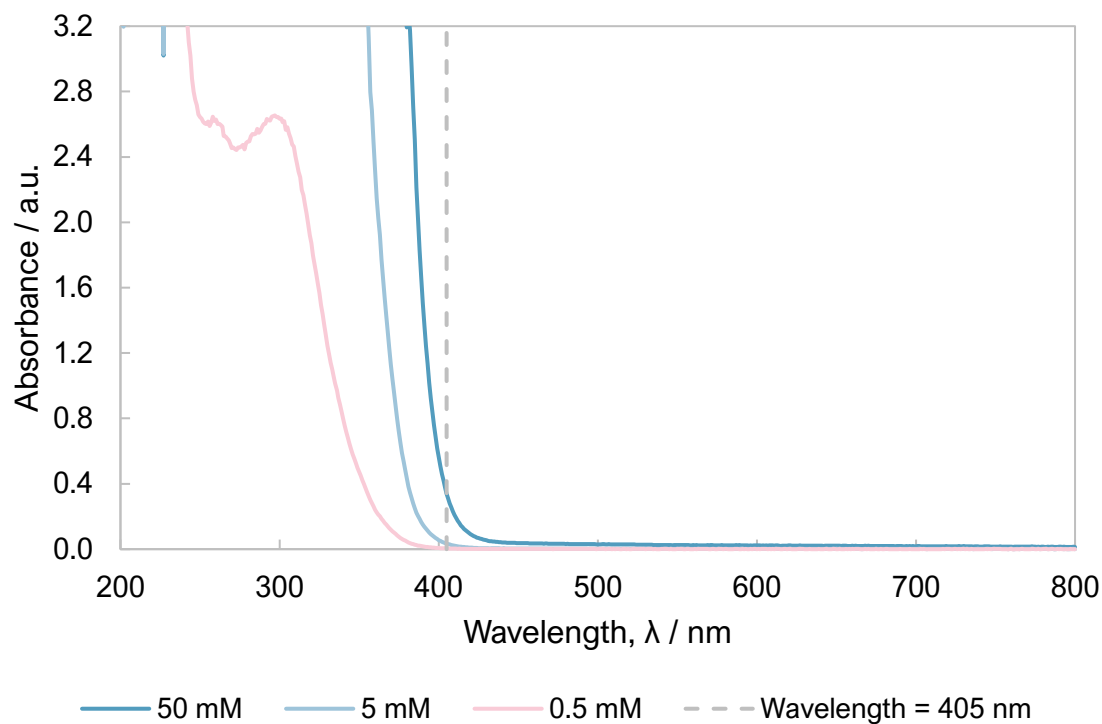
### Calculation

The quantum yield was determined using the following equation:

$$\Phi_R = \frac{\text{moles of product formed}}{ft(1 - 10^{-A})}$$

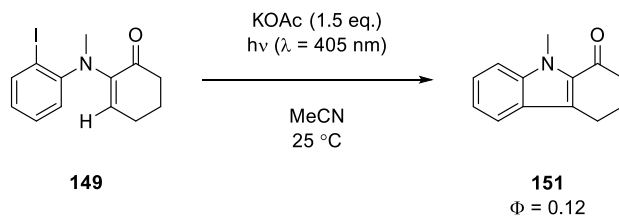
where  $f$  is the photon flux of the light source, in einsteins·s<sup>-1</sup>, determined by ferrioxalate actinometry,  $t$  is the irradiation time in s,  $A$  is the absorbance of a 0.05 M solution of the substrate in acetonitrile and  $(1 - 10^{-A})$  is the fraction of light absorbed by the substrate.

The absorbance at 405 nm of a 50 mM acetonitrile solution of **149** was measured to be 0.341 a.u. (Figure 18). The irradiation time was chosen to ensure that the conversion of **149** did not exceed 15%.



**Figure 18.** UV-vis absorption profiles of *ortho*-iodinated substrate **40** at different concentrations in acetonitrile.

The quantum yield of **151** at 405 nm was calculated as 0.12 (Scheme 114).



**Scheme 114.** Photocyclisation of *ortho*-iodinated substrate **149** with fractional quantum yield of reaction.

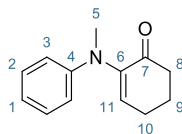
The calculation of the quantum yield of **151** at 405 nm is provided below:

$$\phi_R = \frac{\text{moles of product formed}}{f t (1 - 10^{-A})}$$

$$= \frac{0.046 \times 1.50 \times 10^{-4} \text{ mol}}{2.84 \times 10^{-7} \text{ mol s}^{-1} \times 360 \text{ s} \times (1 - 10^{-0.341})} = 0.12$$

## Synthesis and photochemical reactivity of $\beta$ -hydrogen, *ortho*-unsubstituted substrate **277**

### 2-(Methyl(phenyl)amino)cyclohex-2-en-1-one, **277**



*N*-Methylaniline (0.27 mL, 0.27 g, 2.5 mmol, 1.0 eq.), morpholine enamine **148** (453 mg, 2.50 mmol, 1.0 eq.) and *para*-toluenesulfonic acid monohydrate (476 mg, 2.50 mmol, 1.0 eq.) were heated to 50 °C in toluene (12.5 mL, 0.2 M) for 3 h. The reaction was cooled to room temperature and diluted with ethyl acetate (25 mL). The solution was washed with sodium hydrogencarbonate (sat. aq., 3 x 12.5 mL) followed by brine (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on alumina gel (gradient elution from 5 to 10% ethyl acetate in pentane) to afford **277** (232 mg, 1.15 mmol, 46%) as a viscous yellow oil. The spectral data matched that previously reported in the literature.<sup>58</sup>

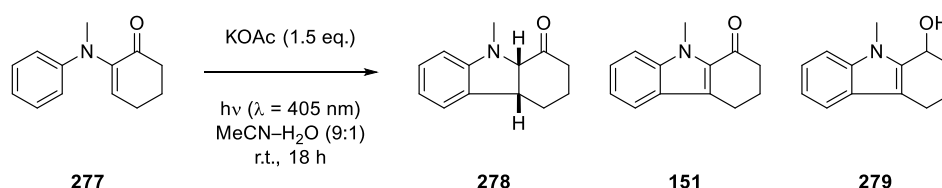
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.24–7.14 (2H, m, H<sub>2</sub>), 6.83–6.66 (4H, m, H<sub>1LHS</sub>, H<sub>11LHS</sub> & H<sub>3RHS</sub>), 3.07 (3H, s, H<sub>5</sub>), 2.60–2.48 (4H, m, H<sub>8LHS</sub> & H<sub>10RHS</sub>), 2.14–2.03 (2H, m, H<sub>9</sub>).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 196.6 (C<sub>7</sub>), 149.1 & 144.8 (C<sub>4</sub> & C<sub>6</sub>), 143.2 (C<sub>11</sub>), 129.0 (C<sub>2</sub>), 118.5 (C<sub>1</sub>), 114.9 (C<sub>3</sub>), 39.6 (C<sub>5</sub>), 39.5 (C<sub>8</sub>), 26.1 (C<sub>10</sub>), 23.0 (C<sub>9</sub>).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1685, 1598, 1500, 1326, 1215, 1110, 903, 750, 693, 640.

HRMS (ESI)  $m/z$  calcd. for C<sub>13</sub>H<sub>16</sub>NO [M+H]<sup>+</sup>: 202.1226; found: 202.1223.

### Photocyclisation of **277**



### Analytical-scale reaction:

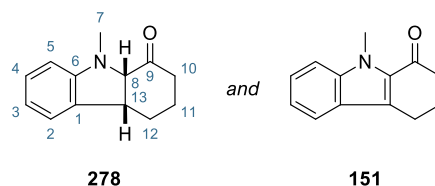
Enaminone **277** (20.1 mg, 0.0999 mmol, 1.0 eq.) and potassium acetate (14.7 mg, 0.150 mmol, 1.5 eq.) were dissolved in a 9:1 (v/v) mixture of acetonitrile (1.8 mL) and water (0.2 mL) (0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 18 h, with cooling to ambient temperature being achieved

using a strong jet of nitrogen gas directed at the flask. Dimethyl terephthalate was added at the end of the irradiation period as a solution in acetonitrile (25.0 mM, 1.0 mL, 0.25 mmol, 0.25 eq.). The resulting mixture was concentrated *in vacuo*, and the crude residue was dissolved in CDCl<sub>3</sub> for analysis by quantitative <sup>1</sup>H NMR spectroscopy. The NMR yields of indoline **278**, indole **151** and indole **279** measured against dimethyl terephthalate were 21%, 45% and 13%, respectively.

*Preparative-scale reaction:*

Enaminone **277** (60.4 mg, 0.300 mmol, 1.0 eq.) and potassium acetate (44.2 mg, 0.450 mmol, 1.5 eq.) were dissolved in a 9:1 (v/v) mixture of acetonitrile (5.4 mL) and water (0.6 mL) (0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with two Kessil PR160L 427 nm LED lamps (each positioned *ca.* 3 cm from the flask and directed toward it) for 18 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, gradient elution 5 to 20% ethyl acetate in pentane) to afford a *ca.* 2:3 mixture (estimated from relative integrations of <sup>1</sup>H resonances) of indole **151** and indoline **278** (25.9 mg, corresponding to isolated yields of *ca.* 26% and 17%, respectively), alongside an impure sample of indole **279**; the latter material was subjected to further flash column chromatographic purification (silica gel, dichloromethane), affording pure **279** (6.5 mg, 0.032 mmol, 11%) as a white solid.

(4*aR*,9*aS*)-9-Methyl-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-carbazol-1-one, **278**, and 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one, **151**



Indoline **278** was characterised as a mixture with **151**. <sup>1</sup>H and <sup>13</sup>C NMR data corresponding to the former compound are reported individually below; the NMR spectral data of **151** matched that obtained previously.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.19–7.12 (1H, m, H4), 7.11–7.05 (1H, m, H2), 6.82–6.73 (1H, m, H3), 6.57 (1H, d, *J* 7.9, H5), 3.58 (1H, td, *J* 8.2, 5.7, H13), 3.48 (1H, d, *J* 8.4, H8), 2.74 (3H, s, H7), 2.66–2.55 (1H, m, H10), 2.47–2.36 (1H, m, H10'), 2.03–1.87 (2H, m, H11<sub>LHS</sub> & H12<sub>RHS</sub>), 1.82–1.58 (2H, m, H11'<sub>LHS</sub> & H12'<sub>RHS</sub>).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 211.3 (C9), 152.0 (C6), 133.2 (C1), 128.2 (C4), 123.4 (C2), 119.1 (C3), 108.5 (C5), 74.2 (C8), 44.4 (C13), 38.7 (C10), 35.1 (C7), 29.3 (C12), 22.4 (C11).

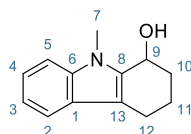


The observation of a transient (negative) nOe enhancement by 1D NOESY for H13 upon selective inversion of H8 suggests the formation of the *cis*-diastereomer shown.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1711, 1657, 1607, 1482, 1314, 1251, 1123, 934, 827, 743.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{14}\text{NO}$   $[\text{M}+\text{H}]^+$ : 200.1070; found: 200.1070;  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{16}\text{NO}$   $[\text{M}+\text{H}]^+$ : 202.1226; found: 202.1224.

**9-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol, 279**



The spectral data matched that previously reported in the literature.<sup>58</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.53 (1H, app. d,  $J$  7.9, H2), 7.31 (1H, app. d,  $J$  8.2, H5), 7.28–7.20 (1H, m, H4), 7.10 (1H, ddd,  $J$  8.0, 6.9, 1.1, H3), 4.95 (1H, dt,  $J$  7.7, 3.6, H9), 3.78 (3H, s, H7), 2.87 (1H, dt,  $J$  15.8, 4.2, H12), 2.68–2.56 (1H, m, H12'), 2.18–2.08 (1H, m, H10), 2.08–1.86 (3H, m, H10'LHS, H11RHS & H11'RHS), 1.67 (1H, br d,  $J$  8.1, OH).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 137.5 (C6), 135.7 (C8), 126.4 (C1), 122.3 (C4), 119.1 & 119.0 (C2 & C3), 112.1 (C13), 109.2 (C5), 62.1 (C9), 33.4 (C10), 29.6 (C7), 21.3 (C12), 18.7 (C11).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3323 (br), 1471, 1378, 1247, 1195, 1154, 1068, 995, 926, 738.

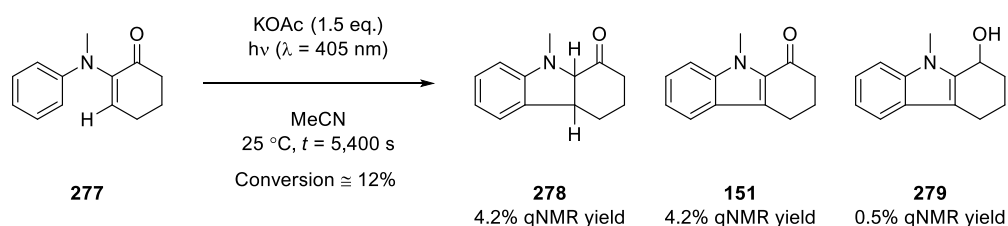
HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{16}\text{NO}$   $[\text{M}+\text{H}]^+$ : 202.1226; found: 202.1226.

MP 94–96 °C.

## Determination of the quantum yield of reaction for $\beta$ -hydrogen, *ortho*-unsubstituted substrate **277**

### Experimental procedure

Substrate **277** (30.2 mg, 0.150 mmol, 1.0 eq.) and potassium acetate (22.1 mg, 0.225 mmol, 1.5 eq.) were charged to a 1 cm quartz cuvette equipped with a magnetic stir bar followed by argon-sparged acetonitrile (3.0 mL, 0.05 M). The resulting mixture was gently sparged with argon for 5 min before sealing the cuvette with a rubber septum under an argon atmosphere. The reaction mixture was irradiated with continuous stirring using the calibrated light source for 5,400 s at 25 °C inside the sample chamber of an Agilent Cary 60 spectrophotometer equipped with a Peltier temperature control accessory. After irradiation, the reaction mixture was transferred to a round-bottomed flask containing dimethyl terephthalate (7.3 mg, 0.038 mmol, 0.25 eq.) and concentrated *in vacuo*. The crude residue was dissolved in CDCl<sub>3</sub> for analysis by quantitative <sup>1</sup>H NMR spectroscopy. The NMR yields of **278**, **151** and **279** measured against dimethyl terephthalate were 4.2, 4.2 and 0.5%, respectively. The conversion of starting material was estimated to be *ca.* 12% (signal overlap prevented accurate integration of <sup>1</sup>H resonances corresponding to the starting material) (Scheme 115).



**Scheme 115.** Product distribution obtained from the photocyclisation of *ortho*-unsubstituted substrate **277** after irradiation for 5,400 s using the calibrated light source.

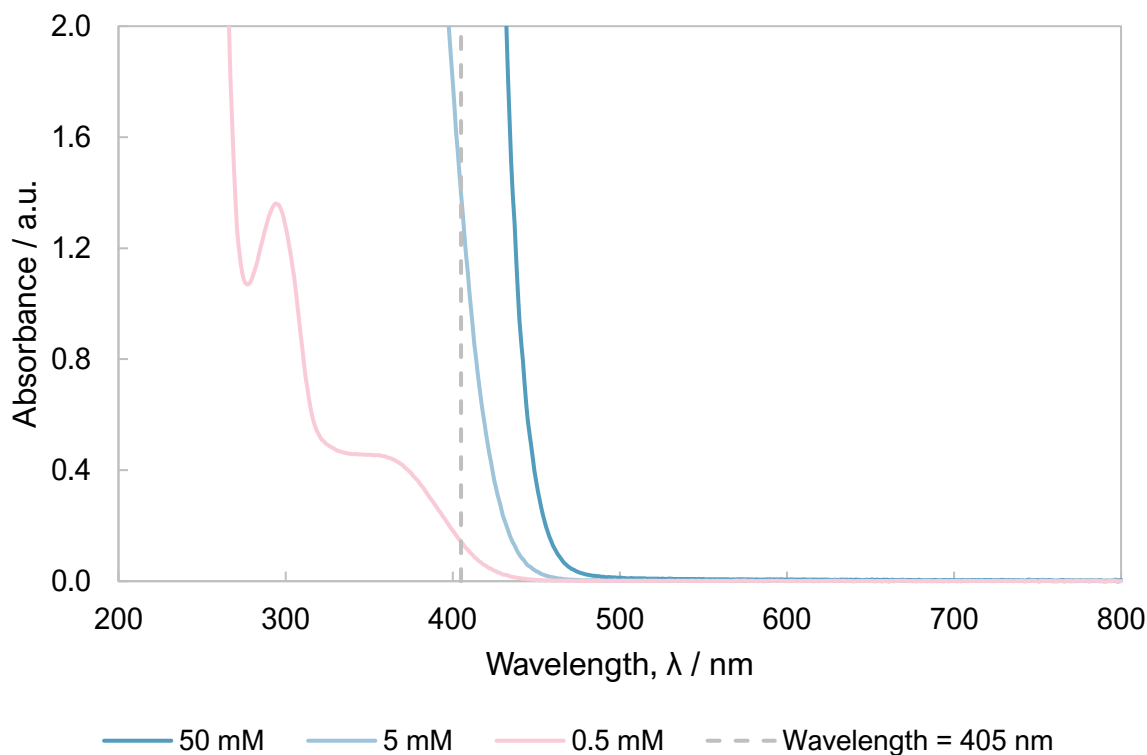
### Calculation

The quantum yields of each product were determined using the following equation:

$$\phi_R = \frac{\text{moles of product formed}}{ft(1 - 10^{-A})}$$

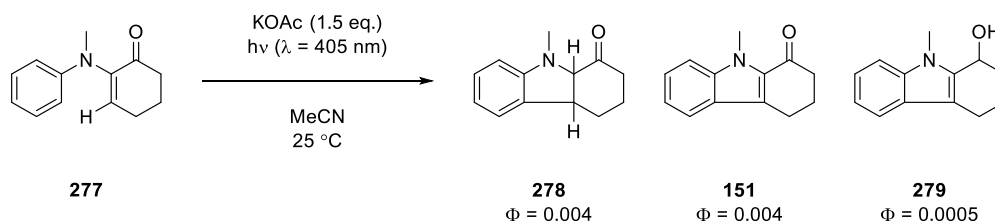
where  $f$  is the photon flux of the light source, in einsteins·s<sup>-1</sup>, determined by ferrioxalate actinometry,  $t$  is the irradiation time in s,  $A$  is the absorbance of a 0.05 M solution of the substrate in acetonitrile and  $(1 - 10^{-A})$  is the fraction of light absorbed by the substrate.

The absorbance at 405 nm of a 50 mM acetonitrile solution of **277** was measured to be in excess of 2 arbitrary units (Figure 19), meaning that virtually all incident light is absorbed by the analyte under the irradiation conditions, i.e.  $(1 - 10^{-A}) \cong 1$ . The irradiation time was chosen to ensure that the conversion of **277** did not exceed 15%.



**Figure 19.** UV-vis absorption profiles of *ortho*-unsubstituted substrate **277** at different concentrations in acetonitrile.

The quantum yields of **278**, **151** and **279** at 405 nm were calculated as 0.004, 0.004 and 0.0005, respectively (Scheme 116).

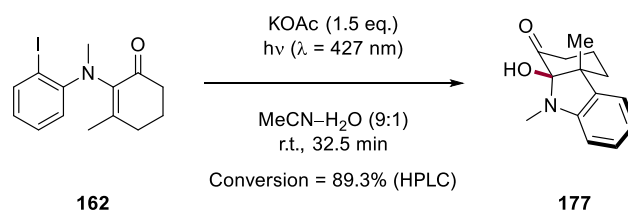


**Scheme 116.** Photocyclisation of *ortho*-unsubstituted substrate **277** with fractional quantum yields of reaction.

The calculation of the quantum yield of **278** at 405 nm is provided below as an example.

$$\begin{aligned}\phi_R &= \frac{\text{moles of product formed}}{ft(1 - 10^{-A})} \\ &= \frac{0.042 \times 1.50 \times 10^{-4} \text{ mol}}{2.84 \times 10^{-7} \text{ mol s}^{-1} \times 5,400 \text{ s} \times (1 - 10^{-2})} = 0.004\end{aligned}$$

## Measurement of $^{13}\text{C}$ kinetic isotope effects (KIEs) at natural abundance<sup>98</sup>



### Procedure for high-conversion photoreaction of **10** and NMR sample preparation

Enaminone **162** (341 mg, 1.00 mmol, 1.0 eq.) and potassium acetate (147 mg, 1.50 mmol, 1.5 eq.) were charged to a Schlenk tube equipped with a magnetic stir bar. The reaction vessel was sealed with a septum and evacuated and backfilled with argon three times. The contents of the flask were dissolved in a mixture of acetonitrile and water (20 mL, 9:1 v/v, 0.05 M) that had been previously degassed by three freeze-pump-thaw cycles. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it), with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Irradiation was stopped periodically and aliquots of the reaction mixture were taken for reverse-phase HPLC analysis (see below for calibration plots and further details): after an irradiation time of 32.5 min, the conversion of **162** and yield of **177** were measured as 89.3% and 86.1%, respectively, against 1,3,5-trimethoxybenzene. The reaction mixture was concentrated *in vacuo*, and the resulting crude residue was purified twice by flash column chromatography (silica gel, gradient elution from 5 to 10% ethyl acetate in pentane; then, silica gel, dichloromethane) to afford 34.8 mg of impure starting material; additional purification by flash column chromatography on alumina gel (gradient elution from 5 to 10% ethyl acetate in pentane) yielded analytically pure **162** (29.0 mg, corresponding to a recovery yield of *ca.* 9%\*), which was dissolved in DMSO-*d*<sub>6</sub> (0.45 mL) for analysis by quantitative  $^{13}\text{C}$  NMR spectroscopy. A ‘standard’ NMR sample was prepared by dissolving 34.8 mg of unfractionated starting material (that is, material from the same batch as that used for the photoreaction above, but which had not been itself subjected to the photochemical reaction conditions) in DMSO-*d*<sub>6</sub> (0.45 mL) and analysed under the same NMR conditions as the fractionated material (see below for full details of spectral acquisition and processing).

### Calibration of HPLC instrument for quantitative analysis

Calibration plots for starting material and product were obtained by reverse-phase HPLC analysis of stock solutions containing a fixed concentration of 1,3,5-trimethoxybenzene (1.0 mM) alongside **162** and **177** in concentrations ranging from 0.05 to 1.0 mM in acetonitrile (Figure 20). HPLC:

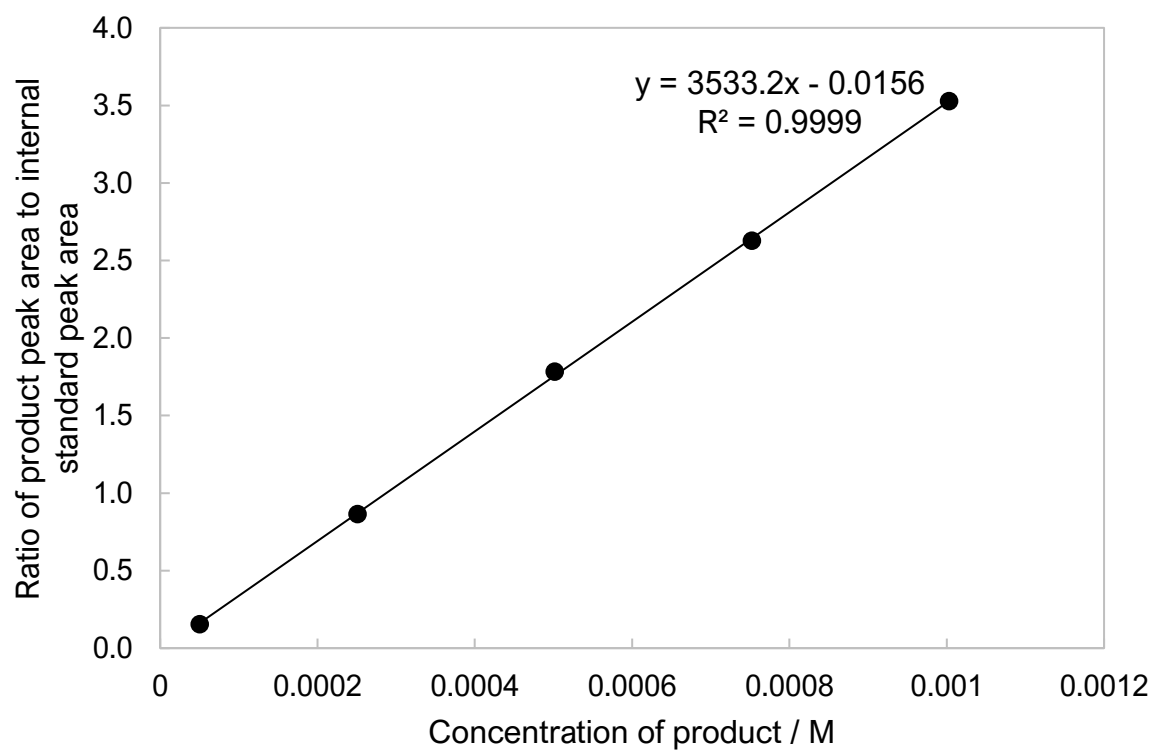
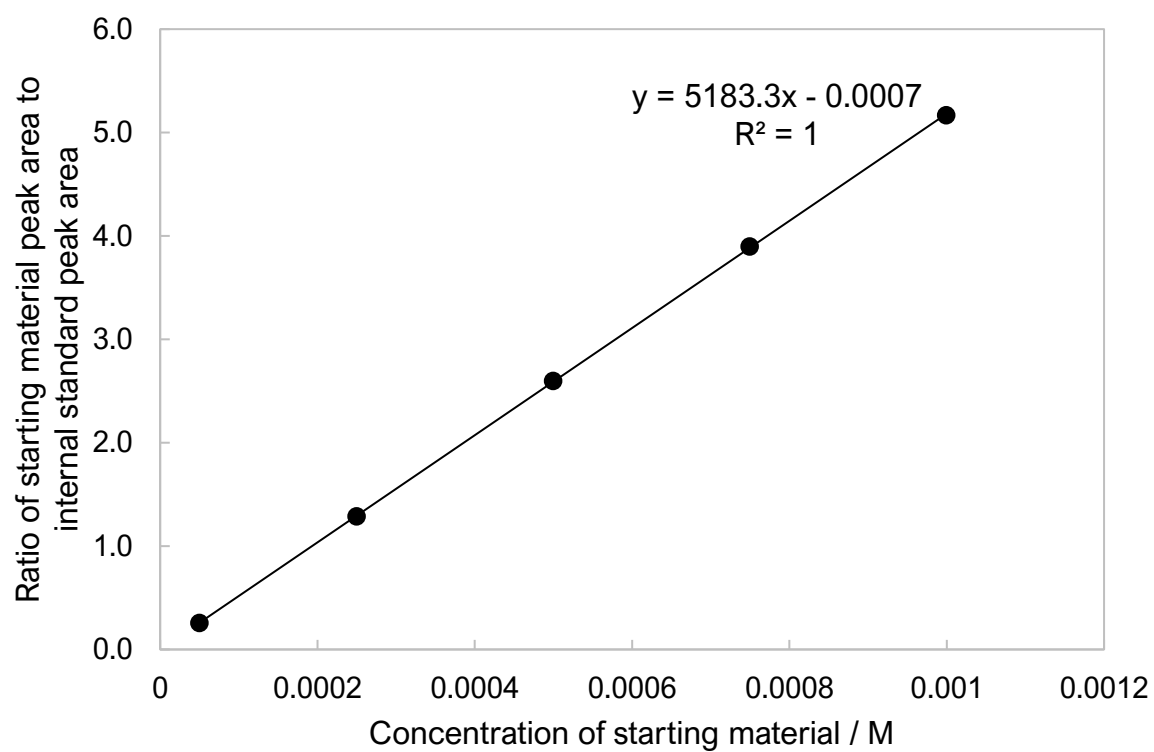
\* Material losses upon transfer in DMSO-*d*<sub>6</sub> solution prior to the final chromatographic purification step account, at least in part, for the recovery yield of starting material being lower than the 10.7% value measured by HPLC.

(InfinityLab Poroshell 120 EC-C18, gradient elution from 5 (t = 0) to 40 (t = 0.25 min) to 90% (t = 9.00 min) acetonitrile in water, 0.4 mL min<sup>-1</sup>, T = 40 °C,  $\lambda$  = 242 nm);  $\tau_R$  (internal standard) = 6.61 min,  $\tau_R$  (product) = 7.60 min,  $\tau_R$  (starting material) = 8.95 min.

Samples of the reaction mixture were prepared for HPLC analysis as follows. A 0.2 mL aliquot of the reaction mixture (reaction concentration: 50 mM) was taken using a 1.0 mL gastight syringe and added to a 10 mL volumetric flask containing 1.0 mL of a 10 mM acetonitrile solution of 1,3,5-trimethoxybenzene. The final volume of the solution was adjusted to 10 mL using acetonitrile, and analysed directly by HPLC according to the instrument method described above. (Final concentration of 1,3,5-trimethoxybenzene = 1.0 mM; theoretical maximum concentration of analyte [i.e., starting material or product] = 1.0 mM.) Conversion and yield data obtained in this way are presented in Table 10 for the high-conversion, 1 mmol-scale photochemical reaction of **162** described above.

**Table 10.** Time-course conversion and yield data for a high-conversion, 1 mmol-scale photochemical reaction of **162** obtained by reverse-phase HPLC analysis of the reaction mixture.

Aliquot	Reaction time / min	Starting material peak area / internal standard peak area	Conversion of starting material / %	Product peak area / internal standard peak area	Yield of product / %
1	27.5	0.90743	82.5	2.79431	79.5
2	32.5	0.55249	89.3	3.02623	86.1



**Figure 20.** HPLC calibration plots for starting material and product.

### Spectral acquisition and processing

Quantitative  $^{13}\text{C}$  spectra were acquired in triplicate for both the fractionated and unfractionated samples of starting material at 150.92 MHz on a two-channel Bruker AVIII HD 600 spectrometer equipped with a dedicated 5 mm BB-F/ $^1\text{H}$  Prodigy  $\text{N}_2$  cryoprobe, with inverse-gated decoupling (WALTZ-16) and a  $90^\circ$  pulse angle. 512 scans were collected in each experiment, with a relaxation delay of 40 s between pulses. (Longitudinal relaxation,  $T_1$ , rates were determined by the inversion-recovery method; the largest  $T_1$  value was measured as 5.8 s.) 65,536 data points were collected for each free induction decay (FID); Fourier transform was performed after zero-filling to 1,048,576 points and applying an exponential multiply (EM) window function with line-broadening of 1.0 Hz. The spectra were manually phased before applying an automatic fifth-order polynomial baseline correction. Integrals were measured across a  $\pm 15$  Hz region centred on each  $^{13}\text{C}$  resonance. Peak integrals obtained across three NMR experiments for the fractionated and unfractionated samples of starting material are summarised in **Tables 11** and **12**, respectively. (The peak integral of C11 was set to a value of 100 in each spectrum; all NMR data were processed within TopSpin.)

**Table 11.**  $^{13}\text{C}$  integrations of fractionated starting material ('Sample').

Carbon	Spectrum 1	Spectrum 2	Spectrum 3	Mean, IntSample	Standard, deviation, $\Delta\text{IntSample}$
9	100.02	100.0178	99.6191	99.88563	0.18847
13	100.683	101.4565	100.8986	101.01270	0.32592
6	98.8187	98.9748	99.4667	99.08673	0.27613
2	98.3434	100.1907	98.7541	99.09607	0.79197
8	97.4085	97.6995	97.387	97.49833	0.14252
4	99.36	100.5302	99.2467	99.71230	0.58019
3	98.3826	98.7288	97.876	98.32913	0.35020
5	99.9195	100.8145	100.4939	100.40930	0.37025
1	104.4437	105.6502	104.1324	104.74210	0.65458
7	100.7269	100.1074	99.5986	100.14430	0.46136
10	99.009	100.0778	99.9495	99.67877	0.47648
12	98.6101	98.6623	99.227	98.83313	0.27932
11	100	100	100	100.00000	0.00000
14	100.6442	101.4602	100.569	100.89113	0.40356



**Table 12.**  $^{13}\text{C}$  integrations of unfractionated starting material ('Standard').

Carbon	Spectrum 1	Spectrum 2	Spectrum 3	Mean, IntStandard	Standard, deviation, $\Delta$ IntStandard
9	99.5945	98.5165	98.6651	98.92537	0.47702
13	100.1709	100.3107	100.3332	100.27160	0.07180
6	100.0999	99.3911	99.5586	99.68320	0.30248
2	99.5083	97.9123	99.5152	98.97860	0.75399
8	96.9525	96.9607	97.7754	97.22953	0.38600
4	100.8249	99.9011	100.6887	100.47157	0.40720
3	99.4712	98.9464	98.4515	98.95637	0.41635
5	101.0133	100.4006	100.5768	100.66357	0.25755
1	102.749	100.6106	101.7447	101.70143	0.87353
7	98.3125	98.1294	98.2952	98.24570	0.08254
10	101.0797	99.8887	100.9318	100.63340	0.53003
12	99.3137	98.3771	99.3468	99.01253	0.44952
11	100	100	100	100	0
14	103.2152	101.0224	101.2193	101.81897	0.99055

### Calculation of $^{13}\text{C}$ KIE values

$^{13}\text{C}$  KIEs were calculated for each  $^{13}\text{C}$  resonance using the following equation

$$KIE = \frac{\ln(1 - F)}{\ln\left[\frac{R}{R_0}(1 - F)\right]} \quad (1)$$

where  $F$  corresponds to fractional conversion of starting material measured by HPLC and  $R/R_0$  is the signal's mean integration, obtained across three identical NMR experiments, in the recovered sample of starting material (i.e. 'IntSample') divided by its corresponding value in the unfractionated material (i.e. 'IntStandard'). The error in this quantity,  $\Delta(R/R_0)$ , was calculated according to the following equation

$$\Delta\left(\frac{R}{R_0}\right) = \frac{R}{R_0} \sqrt{\left(\frac{\Delta\text{IntSample}}{\text{IntSample}}\right)^2 + \left(\frac{\Delta\text{IntStandard}}{\text{IntStandard}}\right)^2} \quad (2)$$

The errors associated with the KIE measurements were calculated using the following equations

$$\Delta KIE = KIE \sqrt{\left(\frac{\Delta KIE_R}{KIE}\right)^2 + \left(\frac{\Delta KIE_F}{KIE}\right)^2} \quad (3)$$

$$\Delta KIE_R = \frac{-\ln(1 - F)}{\frac{R}{R_0} \ln^2\left[\frac{R}{R_0}(1 - F)\right]} \Delta\left(\frac{R}{R_0}\right) \quad (4)$$

$$\Delta KIE_F = \frac{-\ln\frac{R}{R_0}}{(1 - F) \ln^2\left[\frac{R}{R_0}(1 - F)\right]} \Delta F \quad (5)$$

where  $\Delta KIE_R$  and  $\Delta KIE_F$  are the uncertainties in calculated KIEs due to  $\Delta(R/R_0)$  and  $\Delta F$ , respectively. The error in the HPLC measurement of fractional conversion,  $\Delta F$ , was assumed to be 0.01 (that is, 1.0%).

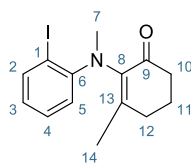
$R/R_0$  and  $^{13}\text{C}$  KIE values are presented with their associated errors for all  $^{13}\text{C}$  starting material resonances in Tables 13 and 14, respectively. These data are further summarised in Table 15.

**Table 13.** R/R<sub>0</sub> values and their associated errors for all starting material <sup>13</sup>C resonances.

Carbon	IntSample	IntStandard	R/R <sub>0</sub>	Δ(R/R <sub>0</sub> )
9	99.88563333	98.92536667	1.009706981	0.005228
13	101.0127	100.2716	1.007390926	0.003329
6	99.08673333	99.6832	0.994016377	0.004095
2	99.09606667	98.9786	1.001186789	0.011054
8	97.49833333	97.22953333	1.002764592	0.004242
4	99.7123	100.4715667	0.99244297	0.007037
3	98.32913333	98.95636667	0.993661516	0.005477
5	100.4093	100.6635667	0.997474094	0.004477
1	104.7421	101.7014333	1.029897973	0.01094
7	100.1443	98.2457	1.019325019	0.004773
10	99.67876667	100.6334	0.990513753	0.007045
12	98.83313333	99.01253333	0.998188108	0.005338
11	100	100	1	0
14	100.8911333	101.8189667	0.990887421	0.010423

**Table 14.** Calculated  $^{13}\text{C}$  KIE values and their associated errors for all starting material  $^{13}\text{C}$  resonances.

Carbon	KIE	$\Delta\text{KIE}_\text{R}$	$\Delta\text{KIE}_\text{F}$	$\Delta\text{KIE}$
9	1.004336110	0.002334326	-0.000182369	0.002341439
13	1.003301922	0.001486888	-0.000138730	0.001493346
6	0.997324901	0.001831470	0.000111724	0.001834875
2	1.000530374	0.004939716	-0.000022222	0.004939766
8	1.001235390	0.001895418	-0.000051798	0.001896126
4	0.996621190	0.003147769	0.000141015	0.003150926
3	0.997166199	0.002449703	0.000118334	0.002452560
5	0.998870953	0.002001308	0.000047227	0.002001865
1	1.013342012	0.004874841	-0.000566173	0.004907609
7	1.008628284	0.002129221	-0.000364441	0.002160185
10	0.995758175	0.003151967	0.000176880	0.003156927
12	0.999190139	0.002386222	0.000033887	0.002386463
11	1	0	0.00000000	0
14	0.995925346	0.004662892	0.000169937	0.004665988

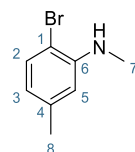
**Table 15.** Summary of  $^{13}\text{C}$  KIE results.

Carbon	$^{13}\text{C}$ KIE (expt.)	$^{13}\text{C}$ KIE (calc. for TS-I)	$^{13}\text{C}$ KIE (calc. for TS-II)
9	1.004(2)	0.998	0.998
13	1.003(1)	1.009	1.019
6	0.997(2)	1.002	1.002
2	1.001(5)	1.007	1.006
8	1.001(2)	1.000	0.998
4	0.997(3)	1.004	1.007
3	0.997(2)	1.004	1.004
5	0.999(2)	1.004	1.043
<b>1</b>	<b>1.013(5)</b>	<b>1.051</b>	<b>1.004</b>
7	<sup>a</sup>	1.000	1.000
10	0.996(3)	1.000	1.000
12	0.999(2)	1.000	0.999
11	1.000 (assumed)	1.001	1.000
14	0.996(5)	0.999	0.998
<sup>a</sup> Not determined; overlap with DMSO solvent signal led to over-estimation of this integral.			

Theoretical KIEs were calculated at the M06-2X-D3/Def2-TZVP(SMD=MeCN) level of theory using the Kinisot python package.<sup>152</sup>

## Synthesis and photochemical reactivity of substrates bearing alternative halogen leaving groups

### 2-Bromo-*N*,5-dimethylaniline, **333**



A solution of *n*-butyllithium in hexanes (7.0 mL, 1.6 M, 11 mmol, 1.1 eq.) was added over 30 min *via* syringe pump to a stirred, -78 °C solution of 2-bromo-5-methylaniline (1.86 g, 10.0 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (20 mL, 0.5 M) under an argon atmosphere. Methyl iodide (0.68 mL, 11 mmol, 1.1 eq.) was added in one portion after complete addition of the organometallic reagent. After a further 5 min at -78 °C, the acetone–dry ice bath was replaced with a tepid water bath, and the reaction mixture was allowed to warm to room temperature over a period of 2 h. Ammonium chloride solution (sat. aq., 20 mL) was added, followed by diethyl ether (20 mL). The layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10% dichloromethane in pentane) to afford **333** (1.05 g, 5.25 mmol, 52%) as a pale-yellow oil. The spectral data matched that previously reported in the literature.<sup>153</sup>

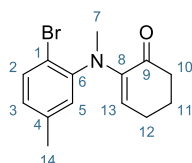
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.29 (1H, d, *J* 7.9, H2), 6.45 (1H, d, *J* 2.0, H5), 6.41 (1H, dd, *J* 7.9, 2.0, H3), 4.29 (1H, br s, NH), 2.89 (3H, s, H7), 2.30 (3H, s, H8).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 145.7 (C6), 138.7 (C4), 132.0 (C2), 118.6 (C3), 111.7 (C5), 106.5 (C1), 30.7 (C7), 21.6 (C8).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3423 (br), 1599, 1511, 1406, 1308, 1188, 1078, 1018, 839, 789.

HRMS (ESI)  $m/z$  calcd. for C<sub>8</sub>H<sub>11</sub>BrN [M+H]<sup>+</sup>: 200.0069; found: 200.0068.

### 2-((2-Bromo-5-methylphenyl)(methyl)amino)cyclohex-2-en-1-one, **280**



Aniline **333** (500 mg, 2.50 mmol, 1.0 eq.), morpholine enamine **148** (453 mg, 2.50 mmol, 1.0 eq.) and *para*-toluenesulfonic acid monohydrate (476 mg, 2.50 mmol, 1.0 eq.) were heated to 50 °C in toluene (12.5 mL, 0.2 M) for 3 h. The reaction was cooled to room temperature and diluted with

ethyl acetate (25 mL). The solution was washed with sodium hydrogencarbonate (sat. aq., 3 x 12.5 mL), followed by brine (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on alumina gel (gradient elution from 5 to 10% ethyl acetate in pentane) to afford **280** (337 mg, 1.15 mmol, 46%) as a viscous yellow oil, which turned over to a pale-yellow solid upon storage at -18 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.39 (1H, d, *J* 8.0, H2), 6.79 (1H, dd, *J* 2.0, 0.8, H5), 6.76–6.70 (1H, m, H3), 6.05 (1H, t, *J* 4.6, H13), 2.95 (3H, s, H7), 2.52–2.40 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.25 (3H, s, H14), 2.06–1.96 (2H, m, H11).

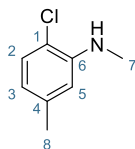
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 195.6 (C9), 148.3 (C6), 145.2 (C8), 138.0 (C4), 133.5 (C2), 129.6 (C13), 126.1 (C3), 124.8 (C5), 116.8 (C1), 40.2 (C7), 39.6 (C10), 25.7 (C12), 23.1 (C11), 21.1 (C14).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1687, 1480, 1309, 1215, 1162, 1111, 1056, 1027, 936, 805.

HRMS (ESI) *m/z* calcd. for C<sub>14</sub>H<sub>17</sub>ONBr [M+H]<sup>+</sup>: 294.0488; found: 294.0488.

MP 48–50 °C.

### 2-Chloro-*N*,5-dimethylaniline, **334**



A solution of *n*-butyllithium in hexanes (7.0 mL, 1.6 M, 11 mmol, 1.1 eq.) was added over 30 min *via* syringe pump to a stirred, -78 °C solution of 2-iodo-5-methylaniline (1.42 g, 10.0 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (20 mL, 0.5 M) under an argon atmosphere. Methyl iodide (0.68 mL, 11 mmol, 1.1 eq.) was added in one portion after complete addition of the organometallic reagent. After a further 5 min at -78 °C, the acetone–dry ice bath was replaced with a tepid water bath, and the reaction mixture was allowed to warm to room temperature over a period of 2 h. Ammonium chloride solution (sat. aq., 20 mL) was added, followed by diethyl ether (20 mL). The layers were separated, and the aqueous phase was extracted with additional diethyl ether (2 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10% dichloromethane in pentane) to afford **334** (880 mg, 5.65 mmol, 56%) as a pale-yellow oil.

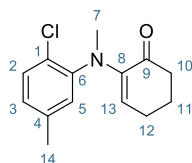
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.18–7.09 (1H, m, H2), 6.53–6.42 (2H, m, H5<sub>LHS</sub> & H3<sub>RHS</sub>), 4.29 (1H, br s, NH), 2.90 (3H, d,  $J$  5.2, H7), 2.32 (3H, s, H8).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 144.8 (C6), 137.9 (C4), 128.7 (C2), 117.9 (C3), 116.3 (C1), 111.6 (C5), 30.5 (C7), 21.6 (C8).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3433 (br), 1603, 1515, 1409, 1310, 1187, 1082, 1039, 841, 791.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_8\text{H}_{11}\text{ClN}$   $[\text{M}+\text{H}]^+$ : 156.0575; found: 156.0573.

2-((2-Chloro-5-methylphenyl)(methyl)amino)cyclohex-2-en-1-one, **281**



Aniline **334** (389 mg, 2.50 mmol, 1.0 eq.), morpholine enamine **148** (453 mg, 2.50 mmol, 1.0 eq.) and *para*-toluenesulfonic acid monohydrate (476 mg, 2.50 mmol, 1.0 eq.) were heated to 50 °C in toluene (12.5 mL, 0.2 M) for 3 h. The reaction was cooled to room temperature and diluted with ethyl acetate (25 mL). The solution was washed with sodium hydrogencarbonate (sat. aq., 3 x 12.5 mL), followed by brine (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on alumina gel (gradient elution from 5 to 10% ethyl acetate in pentane) to afford **281** (256 mg, 1.03 mmol, 41%) as a viscous pale-green oil, which turned over to a pale green solid upon storage at -18 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.23–7.16 (1H, m, H2), 6.83–6.75 (2H, m, H3 & H5), 6.08 (1H, t,  $J$  4.6, H13), 2.96 (3H, s, H7), 2.52–2.40 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.27 (3H, s, H14), 2.06–1.95 (2H, m, H11).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 195.6 (C9), 146.8 (C6), 145.2 (C8), 137.3 (C4), 130.3 (C2), 129.8 (C13), 126.2 (C1), 125.4 & 124.3 (C3 & C5), 40.0 (C7), 39.6 (C10), 25.7 (C12), 23.1 (C11), 21.1 (C14).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1686, 1485, 1311, 1216, 1114, 1062, 1040, 938, 865, 807.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{17}\text{ONCl}$   $[\text{M}+\text{H}]^+$ : 250.0993; found: 250.0993.

MP 48–49 °C.

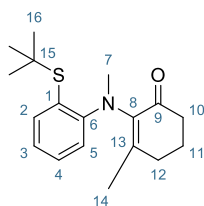


General procedure for 0.1 mmol-scale photocyclisation of substrates **153**, **280** and **281** in the absence of photocatalyst

Enaminone **153**, **280** or **281** (34.1 mg, 29.4 mg or 25.0 mg, respectively, 0.10 mmol, 1.0 eq.) and potassium acetate (14.7 mg, 0.15 mmol, 1.5 eq.) were charged to a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum and then evacuated and back-filled with argon three times. Acetonitrile (2.0 mL, 0.05 M) was added *via* syringe, and the resulting mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 18 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Dimethyl terephthalate was added at the end of the irradiation period as a solution in acetonitrile (25.0 mM, 1.0 mL, 0.25 mmol, 0.25 eq.). The resulting mixture was concentrated *in vacuo*, and the crude residue was dissolved in CDCl<sub>3</sub> for analysis by quantitative <sup>1</sup>H NMR spectroscopy. The NMR yields of indole **154** from **153**, **280** and **281**, measured against dimethyl terephthalate, were 72%, 48% and 18%, respectively.

## Synthesis and photochemical reactivity of ( $\pm$ )- and (+)-**284**, substrates bearing an *ortho*-sulfinyl group

### 2-((2-(*tert*-Butylthio)phenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **335**



This compound was prepared by analogy to a literature procedure.<sup>154</sup> Aryl iodide **162** (341 mg, 0.999 mmol, 1.0 eq.), Pd<sub>2</sub>(dba)<sub>3</sub> (22.9 mg, 25.0  $\mu$ mol, 2.5 mol%) and Xantphos (28.9 mg, 49.9  $\mu$ mol, 5.0 mol%) were added to a microwave vial equipped with a magnetic stir bar. The vial was sealed with a septum cap, and evacuated and backfilled with argon three times. Argon-sparged anhydrous 1,4-dioxane (2.0 mL, 0.5 M) was added to the vial *via* syringe, followed by *N,N*-diisopropylethylamine (0.35 mL, 0.26 g, 2.0 mmol, 2.0 eq.) and 2-methyl-2-propanethiol (0.15 mL, 0.12 g, 1.3 mmol, 1.3 eq.). The reaction mixture was heated to 110 °C for 18 h with continuous stirring. After this time, the reaction mixture was allowed to cool to room temperature before being concentrated *in vacuo*. The crude residue was purified twice by flash column chromatography (silica gel, 75% dichloromethane in pentane; then, silica gel, 5 to 10% ethyl acetate in pentane) to afford **335** (140 mg, 0.461 mmol, 46%) as a viscous yellow oil.

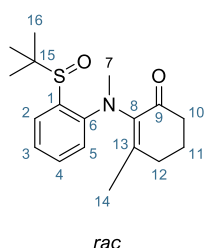
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.36 (1H, dd, *J* 7.6, 1.7, H2), 7.30–7.25 (1H, m, H4), 6.98 (1H, dd, *J* 8.3, 1.3, H5), 6.76 (1H, td, *J* 7.4, 1.3, H3), 3.02 (3H, s, H7), 2.51 (2H, t, *J* 6.7, H10), 2.33 (2H, t, *J* 6.1, H12), 2.03 (2H, quint, *J* 6.2, H11), 1.44 (3H, s, H14), 1.13 (9H, s, H16).

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  = 196.3 (C9), 155.1 (C6), 149.1 (C13), 143.7 (C8), 140.1 (C2), 130.0 (C4), 121.1 (C1), 118.9 (C3), 116.3 (C5), 47.4 (C15), 39.2 (C10), 39.1 (C7), 32.9 (C12), 30.4 (C16), 21.8 (C11), 20.3 (C14).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1682, 1583, 1473, 1378, 1323, 1213, 1168, 1122, 930, 757.

HRMS (ESI) *m/z* calcd. for C<sub>18</sub>H<sub>26</sub>NOS [M+H]<sup>+</sup>: 304.1730; found: 304.1728.

### ( $\pm$ )-2-((2-(*tert*-Butylsulfinyl)phenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, ( $\pm$ )-**284**



This compound was prepared by analogy to a literature procedure.<sup>155</sup> Thioether **335** (47.0 mg, 0.155 mmol, 1.0 eq.) was dissolved in ethanol (1.6 mL, 0.1 M) in a 7 mL vial equipped with a magnetic stir bar. Sodium tungstate dihydrate (10.2 mg, 0.0309 mmol, 0.2 eq.) was added in one portion to the solution, followed by hydrogen peroxide solution (34.5–36.5% w/w aq., 68  $\mu$ L, 0.78 mmol, 5.0 eq.) in one portion *via* micropipette, and the vial was sealed with a screw cap. The reaction mixture was heated to 50 °C for 4.5 h with continuous stirring. After this time, the reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, 50% ethyl acetate in dichloromethane) to afford racemic sulfoxide ( $\pm$ )-**284** (45.8 mg, 0.143 mmol, 93%) as a white solid. This material was used as a racemic standard for chiral HPLC analyses of enantioenriched material (see below).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.70 (1H, dd, *J* 7.8, 1.7, H2), 7.43–7.34 (1H, m, H4), 7.04 (1H, dd, *J* 8.3, 1.1, H5), 7.00 (1H, ddd, *J* 8.1, 7.3, 1.1, H3), 2.98 (3H, s, H7), 2.62–2.52 (1H, m, H10), 2.52–2.31 (3H, m, H10<sub>LHS</sub>, H12<sub>RHS</sub> & H12'<sub>RHS</sub>), 2.18–1.90 (2H, m, H11 & H11'), 1.52 (3H, s, H14), 1.07 (9H, s, H16).

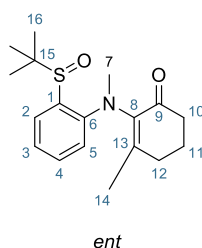
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 196.6 (C9), 154.0 (C13), 150.3 (C6), 142.5 (C8), 132.1 (C4), 129.0 (C1), 127.2 (C2), 120.0 (C3), 117.6 (C5), 57.7 (C15), 39.1 (C10), 38.6 (C7), 33.5 (C12), 22.7 (C16), 21.5 (C11), 20.6 (C14).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1676, 1587, 1475, 1292, 1175, 1118, 1046, 1027, 930, 763.

HRMS (ESI) *m/z* calcd. for C<sub>18</sub>H<sub>25</sub>NO<sub>2</sub>SNa [M+Na]<sup>+</sup>: 342.1498; found: 342.1499.

MP 109–110 °C.

(+)-2-((2-(*tert*-Butylsulfinyl)phenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **(+)-284**



This compound was prepared by analogy to a literature procedure.<sup>156</sup> Dichloromethane (1.5 mL) was added under an argon atmosphere to (+)-diethyl L-tartrate (190 mg, 0.921 mmol, 2.0 eq.) in a septum-sealed 10 mL microwave vial equipped with a magnetic stir bar. The resulting solution was sparged with argon for 2 min before adding titanium isopropoxide (0.14 mL, 0.13 g, 0.47 mmol, 1.0 eq.) and water (8.3  $\mu$ L, 8.3 mg, 0.46 mmol, 1.0 eq.) sequentially *via* syringe under continuous and vigorous stirring. The resulting mixture was sparged with argon for an additional 2 min. An argon-sparged solution of thioether **335** (140 mg, 0.461 mmol, 1.0 eq.) in dichloromethane

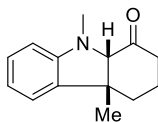
(3.0 mL) was added to the mixture *via* syringe. The vial was cooled to  $-20^{\circ}\text{C}$  using a Polar Bear Plus Crystal. *tert*-Butyl hydroperoxide (0.18 mL, 5.0–6.0 M in decane, *ca.* 0.90 mmol, *ca.* 2.0 eq.) was added *via* syringe, and the resulting mixture was vigorously stirred at  $-20^{\circ}\text{C}$  for 21 h. After this time, water (83  $\mu\text{L}$ , 4.6 mmol, 10 eq.) was added *via* syringe to the reaction mixture. Stirring was continued for 10 min at  $-20^{\circ}\text{C}$  before allowing the quenched reaction mixture to warm to room temperature over 20 min. The reaction mixture was diluted with dichloromethane and filtered through a short plug of basic alumina (*ca.* 5 g). The filtrate (*ca.* 50 mL in volume) was washed successively with sodium hydroxide solution (1 M aq., 3 x 25 mL) and brine (sat. aq., 50 mL) before being dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 50% ethyl acetate in dichloromethane) to afford enantioenriched sulfoxide (+)-**284** (110 mg, 0.344 mmol, 75%, 98:2 e.r.) as a white solid.

The spectral data of this compound matched that of the racemate reported above.

Chiral HPLC: (Chiralpak IG-3, 40% ethanol, 60% *n*-hexane,  $1.0\text{ mL min}^{-1}$ ,  $\lambda = 210\text{ nm}$ );  $\tau_{\text{R}}$  (minor) = 6.6 min,  $\tau_{\text{R}}$  (major) = 8.0 min; e.r. 98:2.

$[\alpha]_{\text{D}}^{25} +318^{\circ}$  ( $c = 1.0$ ,  $\text{CDCl}_3$ )

( $\pm$ )-(4a*R*,9a*S*)-4a,9-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, ( $\pm$ )-**77**, from ( $\pm$ )-**284**

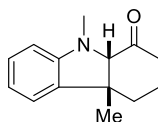


*rac*

Racemic *ortho*-sulfinyl substrate ( $\pm$ )-**284** (31.9 mg, 0.0999 mmol, 1.0 eq.) was charged to a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum and then evacuated and back-filled with argon three times. Acetonitrile (2.0 mL, 0.05 M), triethylsilane (80  $\mu\text{L}$ , 58 mg, 0.50 mmol, 5.0 eq.) and trifluoroacetic acid (23  $\mu\text{L}$ , 34 mg, 0.30 mmol, 3.0 eq.), all argon-sparged, were added successively *via* (micro)syringe. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 12 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Triethylamine (0.7 mL) was added to the reaction mixture at the end of the irradiation period, and the resulting mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 5% ethyl acetate in pentane) to afford racemic ( $\pm$ )-**77** (15.5 mg, 0.0720 mmol, 72%) as a viscous colourless oil. This material

(whose spectral data matched that reported for the same compound above) was used as a racemic standard for chiral HPLC analyses of enantioenriched material (see below).

(–)-(4a*R*,9a*S*)-4a,9-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, (–)-**77**, from (+)-**284**



*ent*

Enantioenriched *ortho*-sulfinyl substrate (+)-**284** (31.9 mg, 0.0999 mmol, 1.0 eq.) was charged to a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum and then evacuated and back-filled with argon three times. Acetonitrile (2.0 mL, 0.05 M), triethylsilane (80  $\mu$ L, 58 mg, 0.50 mmol, 5.0 eq.) and trifluoroacetic acid (23  $\mu$ L, 34 mg, 0.30 mmol, 3.0 eq.), all argon-sparged, were added successively *via* (micro)syringe. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 12 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Triethylamine (0.7 mL) was added to the reaction mixture at the end of the irradiation period, and the resulting mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 5% ethyl acetate in pentane) to afford enantioenriched (–)-**77** (16.1 mg, 0.0748 mmol, 75%) as a viscous colourless oil.

The spectral data of this compound matched that of the racemate reported above.

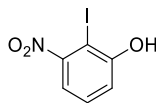
Chiral HPLC: (Chiralpak IA, 10% dichloromethane, 90% *n*-hexane, 1.0 mL min<sup>–1</sup>,  $\lambda$  = 249 nm);  $\tau_R$  (minor) = 7.7 min,  $\tau_R$  (major) = 8.46 min; e.r. 96:4.

$[\alpha]_D^{25}$  –153° (*c* = 1.0, CDCl<sub>3</sub>)

## A study on the cyclisation of aryl radicals (Chapter 3)

### Synthesis and photochemical reactivity of O-allyl substrate **292**

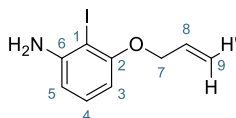
#### 2-Iodo-3-nitrophenol, **296**



This compound was prepared according to a literature procedure.<sup>157</sup> To a three-necked 500 mL round-bottomed flask equipped with a magnetic stir bar and glass thermometer was added 2-amino-3-nitrophenol (6.17 g, 40.0 mmol, 1.0 eq.). Dimethyl sulfoxide (100 mL) and aqueous sulfuric acid (30% v/v, 100 mL). The resulting suspension was heated to 50 °C for 1 h to dissolve the starting material before being cooled to 0 °C in an ice bath. A solution of sodium nitrite (3.86 g, 55.9 mmol, 1.4 eq.) in water (15 mL) was added slowly by dropping funnel over 30 min followed by a solution of potassium iodide (18.6 g, 112 mmol, 2.8 eq.) in water (30 mL), again over 30 min by dropping funnel, ensuring that an internal reaction temperature between 0 and 5 °C was maintained throughout both additions. The reaction mixture was stirred with ice-bath cooling for a further 2 h before being allowed to warm to room temperature overnight. After a further 16 h, the reaction mixture was diluted with diethyl ether (200 mL) and washed sequentially with sodium thiosulfate (sat. aq., 2 x 50 mL), water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 20 to 50% ethyl acetate in pentane) to afford **296** (6.33 g, 23.9 mmol, 60%) as an orange solid. The spectral data matched that previously reported in the literature.<sup>158</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.43 (1H, dd, *J* 8.0), 7.37 (1H, t, *J* 8.0), 7.23 (1H, dd, *J* 8.1, 1.6), 6.01 (1H, br s).

#### 3-(Allyloxy)-2-iodoaniline, **298**



A mixture of **297** (6.28 g, 23.7 mmol, 1.0 eq.), allyl bromide (2.5 mL, 3.5 g, 29 mmol, 1.2 eq.), potassium carbonate (3.93 g, 28.4 mmol, 1.2 eq.) and potassium iodide (4.72 g, 28.4 mmol, 1.2 eq.) in acetone (95 mL, 0.25 M) were heated to reflux for 90 min. After cooling to room temperature, the solids were removed by filtration through celite, and the filtrate was concentrated *in vacuo*. The resulting orange-yellow solid was dissolved in a 2:1 (v/v) mixture of ethanol (80 mL) and glacial acetic acid (40 mL). Iron powder (6.62 g, 119 mmol) was added slowly in portions at room temperature with stirring before heating the mixture to 60 °C for 2 h. After this time, the reaction

mixture was cooled to room temperature and added slowly by dropping funnel to a mixture of sodium hydrogencarbonate (*ca.* 75 g) in water (500 mL) with vigorous stirring. The neutralised reaction mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10 to 20% diethyl ether in pentane) to afford **298** (5.58 g, 20.4 mmol, 86% over two steps) as a peach-coloured oil.

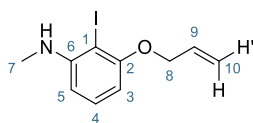
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.05 (1H, t,  $J$  8.0, H4), 6.41 (1H, dd,  $J$  8.0, 1.2, H5), 6.20 (1H, dd,  $J$  8.1, 1.2, H3), 6.06 (1H, ddt,  $J$  17.2, 10.6, 4.8, H8), 5.53 (1H, dq,  $J$  17.3, 1.7, H9), 5.30 (1H, dq,  $J$  10.6, 1.6, H9'), 4.57 (2H, dt,  $J$  4.8, 1.7, H7), 4.22 (2H, br s,  $\text{NH}_2$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  = 158.0 (C2), 148.6 (C6), 133.0 (C8), 129.6 (C4), 117.4 (C9), 108.0 (C5), 102.0 (C3), 76.8 (C1), 69.8 (C7).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3466 (br), 3371 (br), 1613, 1467, 1263, 1134, 1033, 1012, 927, 763.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_9\text{H}_{11}\text{INO}$   $[\text{M}+\text{H}]^+$ : 275.9880; found: 275.9869.

### 3-(Allyloxy)-2-iodo-*N*-methylaniline, **299**



This compound was prepared by analogy to a literature procedure.<sup>158</sup> Sodium methoxide (30 wt% in methanol, 9.4 mL, 2.8 g, 52 mmol, 5.2 eq.) and paraformaldehyde (420 mg, 14.0 mmol, 1.4 eq.) were successively added to a solution of **298** (2.75 g, 10.0 mmol, 1.0 eq.) in methanol (20 mL, 0.5 M). The resulting suspension was stirred at room temperature for 5 h. Sodium borohydride (378 mg, 10.0 mmol, 1.0 eq.) was then added in one portion, and the reaction mixture was heated to reflux for 3 h. After this time, the reaction mixture was cooled to room temperature and quenched by the addition of sodium hydroxide (1 M aq., 20 mL). The resulting mixture was transferred to a separating funnel using water (20 mL) and ethyl acetate (20 mL). After thorough mixing, the layers were separated, and the aqueous phase was extracted with additional ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 5 to 20% diethyl ether in pentane) to afford **299** (740 mg, 2.57 mmol, 26%, 91% brsm) as a pale-yellow oil alongside residual starting material (**298**) (1.97 g, 7.16 mmol) as an orange-yellow oil.

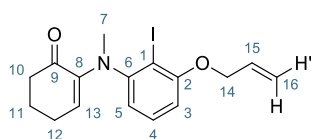
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.15 (1H, t,  $J$  8.1, H4), 6.27–6.21 (2H, m, H5<sub>LHS</sub> & H3<sub>RHS</sub>), 6.07 (1H, ddt,  $J$  17.3, 10.6, 4.8, H9), 5.53 (1H, dq,  $J$  17.3, 1.7, H10), 5.29 (1H, dq,  $J$  10.6, 1.6, H10'), 4.59 (2H, dt,  $J$  4.8, 1.7, H8), 4.41 (1H, br s, NH), 2.90 (3H, s, H7).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 157.8 (C2), 149.9 (C6), 133.1 (C9), 129.8 (C4), 117.4 (C10), 103.7 (C5), 101.6 (C3), 77.1 (C1), 69.8 (C8), 31.3 (C7).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3402 (br), 1598, 1506, 1469, 1428, 1261, 1164, 1008, 926, 757.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{10}\text{H}_{13}\text{ONI}$   $[\text{M}+\text{H}]^+$ : 290.00363; found: 290.00351.

## 2-((3-(Allyloxy)-2-iodophenyl)(methyl)amino)cyclohex-2-en-1-one, **292**



This compound was prepared by analogy to a literature procedure.<sup>159</sup> Aniline **299** (740 mg, 2.56 mmol, 1.0 eq.), morpholine enamine **148** (700 mg, 3.86 mmol, 1.5 eq.), and *para*-toluenesulfonic acid monohydrate (735 mg, 3.86 mmol, 1.5 eq.) were heated to 50 °C in toluene (10 mL, *ca.* 0.26 M) for 3 h. The reaction was cooled to room temperature and diluted with ethyl acetate (20 mL). The solution was washed with sodium hydrogencarbonate (sat. aq., 3 x 10 mL) followed by brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on *alumina* gel (gradient elution from 5 to 10 to 20% ethyl acetate in pentane) followed by flash column chromatography on *silica* gel (20% ethyl acetate in pentane) to afford **292** (283 mg, 0.738 mmol, 29%) as a viscous pale-yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.06 (1H, t,  $J$  8.0, H4), 6.63 (1H, dd,  $J$  7.9, 1.3, H5), 6.56 (1H, dd,  $J$  8.2, 1.3, H3), 6.07 (1H, ddt,  $J$  17.2, 10.6, 4.8, H15), 6.01 (1H, t,  $J$  4.6, H13), 5.56 (1H, dq,  $J$  17.2, 1.7, H16), 5.30 (1H, dq,  $J$  10.6, 1.5, H16'), 4.59 (2H, dt,  $J$  4.8, 1.7, H14), 2.93 (3H, s, H7), 2.48–2.39 (4H, m, H10<sub>LHS</sub> & H12<sub>RHS</sub>), 2.04–1.97 (2H, m, H11).

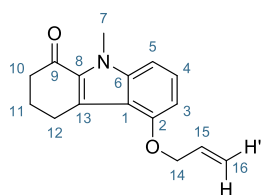
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 195.6 (C9), 158.7 (C2), 153.7 (C6), 145.4 (C8), 132.8 (C15), 129.3 (C4), 129.0 (C13), 117.6 (C16), 116.6 (C5), 108.5 (C3), 90.6 (C1), 70.0 (C14), 40.6 (C7), 39.7 (C10), 25.7 (C12), 23.0 (C11).

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{19}\text{INO}_2$   $[\text{M}+\text{H}]^+$ : 384.0455; found: 384.0457.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1684, 1581, 1453, 1366, 1265, 1062, 1019, 925, 783, 716.



5-(Allyloxy)-9-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one, **300**



Enaminone **292** (115 mg, 0.300 mmol, 1.0 eq.), *fac*-Ir(dFppy)<sub>3</sub> (2.3 mg, 3.0 μmol, 1 mol%) and potassium acetate (44.2 mg, 0.450 mmol, 1.5 eq.) were charged to a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum and then evacuated and back-filled with argon three times. Anhydrous acetonitrile (6.0 mL, 0.05 M) was added *via* syringe, and the resulting mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with a single Kessil PR160 467 nm LED lamp (positioned *ca.* 3 cm from the flask and directed toward it) for 4 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in pentane) to afford **300** (70.5 mg, 0.276 mmol, 92%) as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.25 (1H, dd, *J* 8.4, 7.7, H4), 6.90 (1H, d, *J* 8.4, H5), 6.44 (1H, d, *J* 7.8, H3), 6.13 (1H, ddt, *J* 17.3, 10.3, 5.1, H15), 5.49 (1H, dq, *J* 17.2, 1.7, H16), 5.32 (1H, dq, *J* 10.5, 1.5, H16'), 4.65 (2H, dt, *J* 5.1, 1.6, H14), 4.03 (3H, s, H7), 3.27 (2H, t, *J* 6.1, H12), 2.60 (2H, dd, *J* 7.3, 5.7, H10), 2.18 (2H, quint, *J* 6.3, H11).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 192.1 (C9), 155.6 (C2), 141.4 (C6), 133.4 (C15), 130.0 (C13), 129.7 (C8), 127.6 (C4), 117.3 (C16), 115.9 (C1), 103.2 (C5), 100.4 (C5), 68.7 (C14), 39.8 (C10), 32.0 (C7), 25.1 (C11), 24.1 (C12).

FTIR (neat) ν/cm<sup>−1</sup> = 1644, 1610, 1573, 1426, 1370, 1273, 1140, 1037, 930, 735.

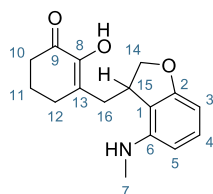
HRMS (ESI) *m/z* calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>N [M+H]<sup>+</sup>: 256.13321; found: 256.13318.

MP 107–109°C.

## Reductive cyclisation of O-allyl substrate **292** mediated by Murphy's super electron donor

This reaction was performed under conditions reported by Murphy and co-workers; the dihydrobenzimidazole reagent, **271**, was synthesised according to a literature procedure and stored under argon at -18 °C prior to use. Compound **292** (115 mg, 0.300 mmol, 1.0 eq.), 1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazole (**271**) (88.9 mg, 0.600 mmol, 2.0 eq.) and 1-dodecanethiol (14.5  $\mu$ L, 12.3 mg, 0.0605 mmol, 0.2 eq.) were dissolved in *N,N*-dimethylformamide (1.5 mL, 0.2 M). The vial was kept open to air whilst the reaction mixture was heated to 55 °C with stirring. After 2 h, the reaction mixture was poured onto brine (50 mL); the resulting aqueous mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 10 to 50 to 75% diethyl ether in pentane) to afford **300** (28.3 mg, 0.111 mmol, 37%) as a pale-yellow solid, alongside an impure mixture of compounds that was resolved by flash column chromatography (silica gel, gradient elution from 1 to 2.5% ethyl acetate in dichloromethane) to afford **302** (9.3 mg, 0.034 mmol, 11%) as an off-white solid and **303** (1.2 mg, 4.7  $\mu$ mol, 2%) as a thin white film. The spectral data of **300** matched that reported for this compound above. Full characterisation data for novel compounds **302** and **303** are provided below.

### 2-Hydroxy-3-((4-(methylamino)-2,3-dihydrobenzofuran-3-yl)methyl)cyclohex-2-en-1-one, **302**



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.06 (1H, t, *J* 8.0, H4), 6.26 (1H, br s, OH), 6.25 (1H, d, *J* 7.9, H5), 6.20 (1H, d, *J* 8.1, H3), 4.49–4.42 (1H, m, H14), 4.39 (1H, dd, *J* 8.9, 2.6, H14'), 3.99 (1H, br s, NH), 3.58–3.50 (1H, m, H15), 2.89 (3H, s, H7), 2.78 (1H, dd, *J* 13.4, 3.5, H16), 2.53–2.46 (2H, m, H10), 2.37–2.27 (3H, m, H12<sub>LHS</sub> & H16'<sub>RHS</sub>), 2.01–1.91 (2H, m, H11).

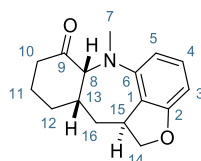
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 194.4 (C9), 160.2 (C2), 146.3 (C6), 144.6 (C8), 132.5 (C13), 129.9 (C4), 113.5 (C1), 102.9 (C3), 99.6 (C5), 76.7 (C14), 39.5 (C15), 35.9 (C10), 34.5 (C16), 30.8 (C7), 30.2 (C12), 22.7 (C11).

FTIR (neat)  $\nu$ /cm<sup>-1</sup> = 3409 (br), 1669, 1645, 1617, 1479, 1382, 1248, 1210, 1151, 774.

HRMS (ESI) *m/z* calcd. for C<sub>16</sub>H<sub>20</sub>O<sub>3</sub>N [M+H]<sup>+</sup>: 274.1437; found: 274.1438.

MP 141–143 °C.

(6a*R*,10a*S*,11a*S*)-6-Methyl-6,6a,8,9,10,10a,11,11a-octahydrobenzo[*f*]benzofuro[4,3-*bc*]azepin-7(1*H*)-one, **303**



$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.07 (1H, t,  $J$  8.0, H4), 6.51 (1H, d,  $J$  8.2, H5), 6.33 (1H, d,  $J$  7.9, H3), 4.69 (1H, t,  $J$  9.0, H14), 4.02 (1H, d,  $J$  4.4, H8), 3.99 (1H, dd,  $J$  9.9, 8.7, H14'), 3.47–3.39 (1H, m, H15), 2.99 (3H, s, H7), 2.75–2.68 (1H, m, H13), 2.40–2.35 (1H, m, H10), 2.33–2.26 (1H, m, H10'), 2.11 (1H, app tt,  $J$  13.8, 4.0, H12), 2.04–1.95 (1H, m, H12'), 1.95–1.88 (1H, m, H11), 1.88–1.78 (1H, m, H11'), 1.68–1.63 (1H, m, H16), 1.36 (1H, q,  $J$  12.5, H16').

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  = 208.7 (C9), 160.3 (C2), 148.6 (C6), 128.9 (C4), 118.2 (C1), 109.7 (C5), 101.5 (C3), 76.2 (C14), 76.0 (C8), 44.7 (C13), 43.5 (C7), 42.8 (C15), 41.9 (C10), 33.7 (C12 & C16), 21.7 (C11).

The observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to  $\text{H8} \leftrightarrow \text{H13}$  is indicative of *cis* stereochemistry at the C8–C13 ring junction, while the absence of nOe correlations corresponding to  $\text{H13} \leftrightarrow \text{H15}$  or  $\text{H8} \leftrightarrow \text{H15}$  suggests the formation of the C15 epimer shown.

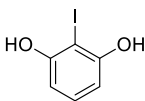
FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1719, 1608, 1591, 1493, 1450, 1125, 1057, 990, 771, 729.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{20}\text{O}_2\text{N}$   $[\text{M}+\text{H}]^+$ : 258.1489; found: 258.1489.

The amorphous nature of the solid obtained, and its small quantity, precluded the determination of a melting point for this compound.

## Synthesis of 2-aryloxycyclohexenone **314**

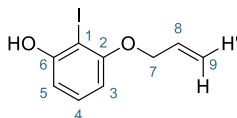
### 2-Iodobenzene-1,3-diol, **317**



This compound was prepared according to a literature procedure.<sup>160</sup> To a room-temperature solution of resorcinol (**316**) (2.20 g, 20.0 mmol, 1.0 eq.) in water (20 mL, 1.0 M) was added iodine (5.43 g, 21.4 mmol, 1.07 eq.) followed by sodium hydrogencarbonate (1.86 g, 22.1 mmol, 1.11 eq.) in portions. The reaction mixture was stirred at room temperature for 90 min. Sodium thiosulfate (sat. aq., 20 mL) was added, and the resulting aqueous mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10 to 20% ethyl acetate in pentane) to afford **317** (3.37 g, 14.3 mmol, 71%) as a white solid. The spectral data matched that previously reported in the literature.<sup>160</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.11 (1H, t, *J* 8.1), 6.56 (2H, d, *J* 8.1), 5.27 (2H, s).

### 3-(Allyloxy)-2-iodophenol, **318**



A mixture of **317** (3.31 g, 14.0 mmol, 1.0 eq.), allyl bromide (1.2 mL, 1.7 g, 14 mmol, 1.0 eq.), potassium carbonate (1.94 g, 14.0 mmol, 1.0 eq.) and potassium iodide (2.33 g, 14.0 mmol, 1.0 eq.) in acetone (56 mL, 0.25 M) was heated to reflux for 1 h. After cooling to room temperature, the solids were removed by filtration through celite, and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in pentane) to afford **318** (1.21 g, 4.38 mmol, 31%) as a pale-yellow oil.

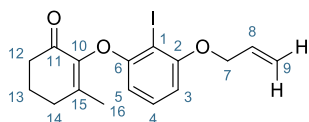
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.16 (1H, t, *J* 8.2, H4), 6.67 (1H, dd, *J* 8.2, 1.2, H3 or H5), 6.38 (1H, dd, *J* 8.2, 1.1, H3 or H5), 6.06 (1H, ddt, *J* 17.2, 10.6, 4.9, H8), 5.52 (1H, dq, *J* 17.2, 1.7, H9), 5.47 (1H, br s, OH), 5.31 (1H, dq, *J* 10.6, 1.5, H9'), 4.59 (2H, dt, *J* 4.9, 1.6, H7).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 157.9 (C2), 156.4 (C6), 132.7 (C8), 130.2 (C4), 117.7 (C9), 108.1 & 104.5 (C3 & C5), 78.9 (C1), 70.0 (C7).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3466 (br), 1586, 1452, 1317, 1264, 1194, 1060, 1043, 927, 766.

HRMS (ESI) *m/z* calcd. for C<sub>9</sub>H<sub>8</sub>O<sub>2</sub>I [M-H]<sup>+</sup>: 274.95745; found: 274.95716.

2-(3-(Allyloxy)-2-iodophenoxy)-3-methylcyclohex-2-en-1-one, **314**



This compound was prepared by analogy to a literature procedure.<sup>44</sup> 6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one (**163**) (252 mg, 2.00 mmol, 1.0 eq.), phenol **318** (662 mg, 2.40 mmol, 1.2 eq.), potassium carbonate (331 mg, 2.40 mmol, 1.2 eq.) and anhydrous acetonitrile (8.0 mL, 0.25 M) were charged to a round-bottomed flask equipped with a magnetic stir bar and condenser. The reaction mixture was heated to reflux with stirring for 16 h before being cooled to room temperature and poured onto aqueous sodium hydroxide (1 M, 20 mL) in a separating funnel, where the aqueous phase was subsequently extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified twice by flash column chromatography (silica gel, 25% ethyl acetate in pentane; then, silica gel, dichloromethane) to afford **314** (262 mg, 0.682 mmol, 34%) as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.08 (1H, t, *J* 8.3, H4), 6.46 (1H, dd, *J* 8.2, 1.2, H3 or H5), 6.15 (1H, dd, *J* 8.2, 1.1, H3 or H5), 6.07 (1H, ddt, *J* 17.3, 10.6, 4.9, H8), 5.54 (1H, dq, *J* 17.3, 1.6, H9), 5.31 (1H, dq, *J* 10.6, 1.5, H9'), 4.61 (1H, dt, *J* 4.8, 1.7, H7), 2.58–2.50 (4H, m, H12 & H14), 2.12–2.04 (2H, m, H13), 1.92 (3H, s, H16).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 192.2 (C11), 159.0 (C2), 157.9 (C6), 148.9 (C15), 144.9 (C10), 132.8 (C8), 129.4 (C4), 117.6 (C9), 106.2 & 106.0 (C3 & C5), 78.3 (C1), 70.1 (C7), 38.5 (C12), 31.8 (C14), 22.2 (C13), 18.2 (C16).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1682, 1585, 1452, 1240, 1147, 1133, 1060, 1022, 928, 767.

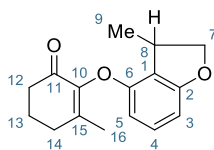
HRMS (ESI) *m/z* calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>3</sub>I [M+H]<sup>+</sup>: 385.03061; found: 385.03021.

MP 68–69°C.

## Reductive cyclisation of 2-aryloxycyclohexenone **314** mediated by Murphy's super electron donor

This reaction was performed under conditions reported by Murphy and co-workers; the dihydrobenzimidazole reagent, **271**, was synthesised according to a literature procedure and stored under argon at -18 °C prior to use. Compound **314** (115 mg, 0.299 mmol, 1.0 eq.), 1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazole (**271**) (88.9 mg, 0.600 mmol, 2.0 eq.) and 1-dodecanethiol (14.5  $\mu$ L, 12.3 mg, 0.0605 mmol, 0.2 eq.) were dissolved in *N,N*-dimethylformamide (1.5 mL, 0.2 M). The vial was kept open to air whilst the reaction mixture was heated to 55 °C with stirring. After 2 h, the reaction mixture was poured onto brine (50 mL); the resulting aqueous mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, gradient elution from 0 to 5 to 100% ethyl acetate in dichloromethane) followed by preparatory thin-layer chromatography (eluent: 25% ethyl acetate in pentane) of pooled fractions yielded analytical samples of the following compounds, all in small quantities as thin white films or viscous colourless oils coating the walls of their glass containers.

### 3-Methyl-2-((3-methyl-2,3-dihydrobenzofuran-4-yl)oxy)cyclohex-2-en-1-one, **319**



Yield: 2.3 mg, 8.9  $\mu$ mol, 3%

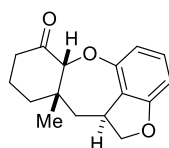
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.92 (1H, t,  $J$  8.1, H4), 6.43 (1H, d,  $J$  8.0, H3), 6.03 (1H, d,  $J$  8.2, H5), 4.67 (1H, t,  $J$  8.7, H7), 4.18 (1H, dd,  $J$  8.6, 5.2, H7'), 3.78–3.70 (1H, m, H8), 2.58–2.49 (4H, m, H14<sub>LHS</sub> & H12<sub>RHS</sub>), 2.08 (2H, quint,  $J$  6.5, H13), 1.92 (3H, s, H16), 1.42 (3H, d,  $J$  6.9, H9).

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  = 192.7 (C11), 161.7 (C2), 154.8 (C6), 148.4 (C15), 144.3 (C10), 128.9 (C4), 119.0 (C1), 104.7 (C5), 103.7 (C3), 79.2 (C7), 38.6 (C12), 35.5 (C8), 31.8 (C14), 22.3 (C13), 19.2 (C16), 18.0 (C9).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1686, 1605, 1478, 1457, 1256, 1234, 1147, 1037, 1007, 775.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$ : 259.1329; found: 259.1329.

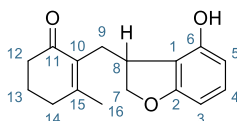
(6a*R*,10a*S*,11a*S*)-10a-methyl-8,9,10,10a,11,11a-hexahydro-1*H*-benzo[6,7]oxepino[4,3,2-*cd*]benzofuran-7(6a*H*)-one, **315**



Yield: 1.4 mg, 1.8  $\mu$ mol, 2%

The spectral data matched that reported for this compound below.

2-((4-Hydroxy-2,3-dihydrobenzofuran-3-yl)methyl)-3-methylcyclohex-2-en-1-one, **320**



Yield: 0.7 mg, 2.7  $\mu$ mol, 1%

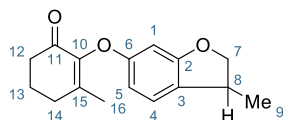
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.07 (1H, br s, OH), 7.02 (1H, t,  $J$  8.0, H4), 6.47 (1H, d,  $J$  8.1, H5), 6.36 (1H, d,  $J$  8.0, H3), 4.51 (1H, t,  $J$  8.7, H7), 4.31 (1H, dd,  $J$  8.8, 3.4, H7'), 3.34–3.27 (1H, m, H8), 2.71–2.65 (1H, m, H9), 2.54 (1H, dd,  $J$  14.5, 8.0, H9'), 2.51–2.47 (2H, m, H12), 2.44–2.39 (2H, m, H14), 2.03 (3H, s, H16), 2.02–1.97 (2H, m, H13).

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  = 201.3 (C11), 160.5 (C2), 158.4 (C15), 154.2 (C6), 134.4 (C10), 129.8 (C4), 116.2 (C1), 109.0 (C5), 101.4 (C3), 78.4 (C7), 40.9 (C8), 37.6 (C12), 33.0 (C14), 31.7 (C9), 22.2 & 22.0 (C13 & C16).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 3270 (br), 1644, 1624, 1461, 1382, 1239, 1018, 945, 776, 649.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$ : 259.1329; found: 259.1329.

3-Methyl-2-((3-methyl-2,3-dihydrobenzofuran-6-yl)oxy)cyclohex-2-en-1-one, **321**



Yield: 0.3 mg, 1.2  $\mu$ mol, <0.5%

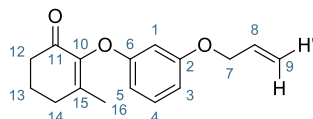
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.98 (1H, dd,  $J$  8.1, 0.8, H4), 6.39 (1H, dd,  $J$  8.1, 2.3, H5), 6.27 (1H, d,  $J$  2.2, H1), 4.67 (1H, t,  $J$  8.7, H7), 4.06 (1H, dd,  $J$  8.4, 7.4, H7'), 3.50–3.41 (1H, m, H8), 2.56–2.49 (4H, m, H12<sub>LHS</sub> & H14<sub>RHS</sub>), 2.06 (2H, quint,  $J$  6.4, H13), 1.90 (3H, s, H16), 1.28 (3H, d,  $J$  6.8, H9).

$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  = 193.0 (C11), 161.1 (C2), 158.3 (C6), 148.7 (C15), 144.5 (C10), 125.6 (C3), 124.0 (C4), 107.0 (C5), 96.9 (C1), 79.6 (C7), 38.6 (C12), 36.0 (C8), 31.8 (C14), 22.2 (C13), 19.6 (C9), 18.1 (C16).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1686, 1618, 1491, 1330, 1268, 1194, 1155, 1092, 980, 762.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$ : 259.1329; found: 259.1328.

**2-(3-(Allyloxy)phenoxy)-3-methylcyclohex-2-en-1-one, 322**



Yield: 2.6 mg, 0.010 mmol, 3%

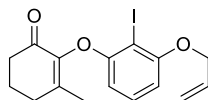
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.17–7.09 (1H, m, H4), 6.53 (1H, ddd,  $J$  8.3, 2.3, 1.0, H3 or H5), 6.48–6.40 (2H, m, H1 & H3 or H5), 6.04 (1H, ddt,  $J$  17.3, 10.6, 5.4, H8), 5.40 (1H, dq,  $J$  17.2, 1.6, H9), 5.28 (1H, dq,  $J$  10.5, 1.4, H9'), 4.50 (2H, dt,  $J$  5.4, 1.5, H7), 2.58–2.49 (4H, m, H12 & H14), 2.07 (2H, quint,  $J$  6.3, H13), 1.90 (3H, t,  $J$  0.9, H16).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta^*$  = 192.8 (C11), 159.9 (C2), 148.6 (C15), 144.1 (C10), 133.3 (C8), 130.0 (C4), 117.9 (C9), 107.7, 107.3 & 102.1 (C1, C3 & C5), 77.3 (C1), 69.0 (C7), 38.4 (C12), 31.7 (C14), 22.1 (C13), 18.0 (C16).

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1685, 1603, 1489, 1262, 1196, 1153, 1033, 915, 736, 668.

HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$ : 259.1329; found: 259.1313.

**2-(3-(Allyloxy)-2-iodophenoxy)-3-methylcyclohex-2-en-1-one, 314**



Yield: 1.5 mg, 3.9 mmol, 1%

The spectral data matched that reported for this compound above.

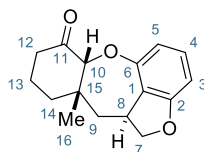
\* Chemical shifts were identified through HSQC and HMBC correlations; no signal corresponding to C6 could be identified at the sample concentration employed.



## Reductive cyclisation of **314** under photoredox catalysis

This reaction was performed under conditions reported by Kim *et al.*<sup>110</sup> 2-Aryloxycyclohexenone **314** (115.3 mg, 0.300 mmol, 1.0 eq), [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> (2.7 mg, 3.0 μmol, 1.0 mol%) and *N,N*-diisopropylethylamine (105 μL, 77.9 mg, 0.603 mmol, 2.0 eq.) were dissolved in anhydrous acetonitrile (6.0 mL, 0.05 M) in a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the reaction mixture was degassed by three freeze–pump–thaw cycles. The reaction mixture was stirred under constant irradiation with a single Kessil PR160L 427 nm LED lamp set to 25% intensity (positioned *ca.* 3 cm from the flask and directed toward it) for 18 h, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (silica gel, gradient elution from 5 to 10% ethyl acetate in pentane) to afford **315** (42.6 mg, 0.165 mmol, 55%) as a white solid. Diffraction-quality crystals of **315** were grown by vapour diffusion of petroleum ether 40–60 into a solution of the product in chloroform (or by vapour diffusion of *n*-hexane into a solution of the product in ethyl acetate).

(6a*R*,10a*S*,11a*S*)-10a-Methyl-8,9,10,10a,11,11a-hexahydro-1*H*-benzo[6,7]oxepino[4,3,2-*cd*]benzofuran-7(6a*H*)-one, **315**



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.05–6.96 (1H, m, H4), 6.56–6.43 (2H, m, H3 & H5), 4.74 (1H, t, *J* 8.9, H7), 4.02 (1H, t, *J* 9.2, H7'), 3.97–3.83 (1H, m, H8), 3.71 (1H, s, H10), 2.93 (1H, td, *J* 13.5, 7.9, H12), 2.64–2.42 (1H, m, H14), 2.35–2.20 (1H, m, H12'), 2.08–1.96 (1H, m, H13), 1.96–1.77 (2H, m, H13'<sub>LHS</sub> & H11<sub>RHS</sub>), 1.56–1.44 (1H, m, H11'), 1.34–1.16 (1H, m, H14'), 0.90 (3H, s, H16).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 207.0 (C11), 161.1 (C2), 156.1 (C6), 129.5 (C4), 122.0 (C1), 112.4 (C5), 105.4 (C3), 91.9 (C10), 77.2 (C7), 44.6 (C9), 42.2 (C15), 37.5 (C8), 36.6 (C12), 28.0 (C14), 23.4 (C16), 21.3 (C13).

The stereochemistry of this compound was confirmed through single-crystal X-ray diffraction (see Appendix C); the observation of nuclear Overhauser effect (nOe) correlations by 2D NOESY corresponding to H10↔H16 is also indicative of *cis* stereochemistry at the C10–C15 ring junction.

FTIR (neat)  $\nu/\text{cm}^{-1}$  = 1728, 1605, 1455, 1256, 1223, 1048, 1017, 960, 775, 725.

HRMS (ESI)  $m/z$  calcd. for C<sub>16</sub>H<sub>19</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 259.13287; found: 259.13294.

MP 142–144°C.



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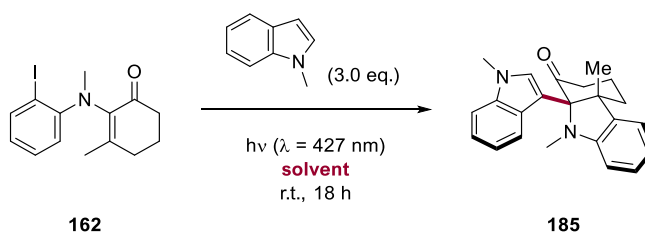
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## Appendix A – Optimisation data for the photocyclisation of $\beta$ -methyl substrate **162** in the presence of various nucleophiles

**Table 16.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of 1-methylindole.



Entry	Solvent	Conversion <sup>a</sup> / %	Yield of <b>185</b> / %
1 <sup>b</sup> ,	MeCN–TFE (9:1)	87	70
2 <sup>b</sup>	MeCN–MeOH (9:1)	94	80
3 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	86	75
4 <sup>b,c</sup>	MeCN–AcOH (9:1)	93	76
5 <sup>b</sup>	MeCN–HFIP (9:1)	>95%	85

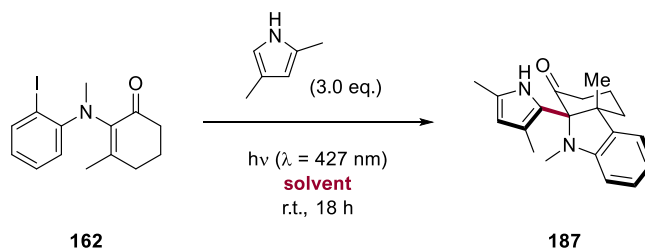
<sup>a</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

<sup>b</sup> Reaction conditions (unless otherwise stated): **162** (0.1 mmol), 1-methylindole (0.3 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

<sup>c</sup> The end-of-reaction mixture was concentrated *in vacuo* without quenching the HI by-product.

6 <sup>b,c</sup>	MeCN–HFIP (9:1)	>95%	84
7 <sup>d</sup>	MeCN–HFIP (9:1)	– <sup>e</sup>	81 <sup>f</sup>

**Table 17.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of 2,4-dimethyl-1*H*-pyrrole.



Entry	Solvent	Conversion <sup>a</sup> / %	Yield of <b>187</b> / %
1 <sup>b</sup>	MeCN–HFIP (9:1)	>95	65
2 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	>95	69
3 <sup>b</sup>	MeCN–TFE (9:1)	>95	61

<sup>d</sup> Reaction conditions: **162** (0.3 mmol), 1-methylindole (0.9 mmol), solvent(s) (0.05 M), 2 x Kessil PR160L 427 nm LED lamps, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (2.0 mL) in one portion.

<sup>e</sup> Not determined.

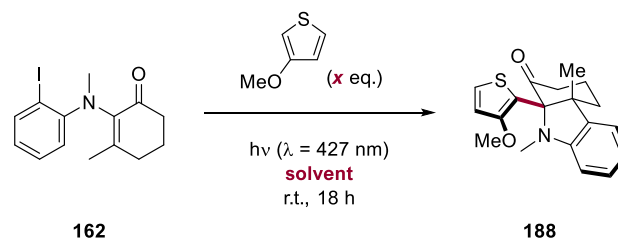
<sup>f</sup> Isolated yield after flash column chromatography on alumina gel.

<sup>a</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

<sup>b</sup> Reaction conditions: **162** (0.1 mmol), 2,4-dimethyl-1*H*-pyrrole (0.3 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

4 <sup>c</sup>	MeCN–H <sub>2</sub> O (9:1)	– <sup>d</sup>	68 <sup>c</sup>
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**Table 18.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of 3-methoxythiophene.



Entry	Solvent	<i>x</i> / eq.	Conversion <sup>a</sup> / %	Yield of <b>188</b> / %
1 <sup>b</sup>	MeCN	3.0	72	30
2 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	3.0	>95	28
3 <sup>b</sup>	MeCN–TFE (9:1)	3.0	92	34
4 <sup>b</sup>	MeCN–HFIP (9:1)	3.0	92	35

<sup>c</sup> Reaction conditions: **162** (0.3 mmol), 2,4-dimethyl-1*H*-pyrrole (0.9 mmol), MeCN–H<sub>2</sub>O (9:1) (0.05 M), 2 x Kessil PR160L 427 nm LED lamps, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (2.0 mL) in one portion.

<sup>d</sup> Not determined.

<sup>e</sup> Isolated yield after flash column chromatography on alumina gel.

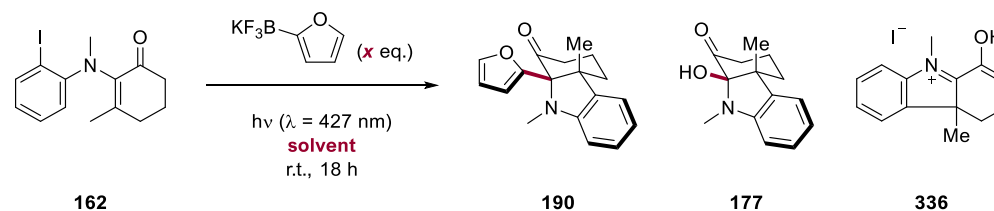
<sup>a</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

<sup>b</sup> Reaction conditions: **162** (0.1 mmol), 3-methoxythiophene (0.3 or 0.5 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.



4 <sup>b</sup>	MeCN–HFIP (9:1)	91	56
5 <sup>c</sup>	MeCN–HFIP (9:1)	– <sup>d</sup>	59 <sup>e</sup>

**Table 20.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of potassium furan-2-trifluoroborate.



Entry	Solvent	$x$ / eq.	Conversion <sup>a</sup> / %	Yield of <b>190</b> / %	Yield of hemiaminal <b>177</b> / %	Yield of <b>336</b> / %
1 <sup>b</sup>	MeCN	3.0	>95	31	n.d. <sup>c</sup>	n.d.
2 <sup>b</sup>	MeNO <sub>2</sub>	3.0	>95	40	n.d.	n.d.

<sup>c</sup> Reaction conditions: **162** (0.3 mmol), 2-methylfuran (0.9 mmol), MeCN–HFIP (9:1) (0.05 M), 2 x Kessil PR160L 427 nm LED lamps, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (2.0 mL) in one portion.

<sup>d</sup> Not determined.

<sup>e</sup> Isolated yield after flash column chromatography on alumina gel.

<sup>a</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

<sup>b</sup> Reaction conditions (unless otherwise stated): **162** (0.1 mmol), potassium furan-2-trifluoroborate (0.15, 0.3 or 0.5 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

<sup>c</sup> Not detected.

3 <sup>b,d</sup>	MeNO <sub>2</sub>	3.0	>95	40	n.d.	n.d.
4 <sup>b</sup>	MeCN–MeOH (9:1)	3.0	>95	44	7	n.d.
5 <sup>b</sup>	MeCN–TFE (9:1)	3.0	>95	35	n.d.	n.d.
6 <sup>b</sup>	MeCN–HFIP (9:1)	3.0	>95	<i>ca.</i> 30–40 <sup>e</sup>	trace	n.d.
7 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	3.0	>95	59	10	trace
8 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	5.0	>95	38	12	trace
9 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	1.5	>95	52	17	trace
10 <sup>b,f</sup>	MeCN–H <sub>2</sub> O (9:1)	1.5	>95	53	14	trace
11 <sup>b</sup>	MeCN–H <sub>2</sub> O (19:1)	1.5	>95	44	19	trace
12 <sup>b</sup>	MeCN–H <sub>2</sub> O (3:1)	1.5	>95	45	11	15
13 <sup>b</sup>	MeCN–H <sub>2</sub> O (3:1)	3.0	>95	64	16	6
14 <sup>b</sup>	MeCN–H <sub>2</sub> O (1:1)	1.5	>95	35	10	21

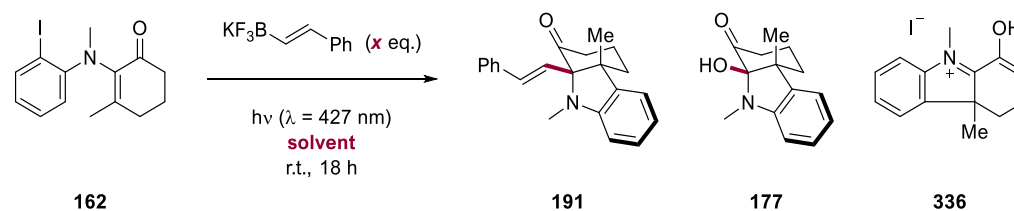
<sup>d</sup> Reaction performed in the presence of CF<sub>3</sub>COONa (1.0 eq.).

<sup>e</sup> Signal overlap made accurate integration of <sup>1</sup>H resonances corresponding to this compound impossible.

<sup>f</sup> Reaction concentration, [**162**] = 0.1 M.

15 <sup>b</sup>	MeCN–H <sub>2</sub> O (1:1)	3.0	>95	51	trace	8
16 <sup>g</sup>	MeCN–H <sub>2</sub> O (3:1)	3.0	– <sup>h</sup>	55 <sup>i</sup>	–	–

**Table 21.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **10** in the presence of potassium *trans*-styryltrifluoroborate.



Entry	Solvent	<i>x</i> / eq.	Conversion <sup>a</sup> / %	Yield of <b>191</b> / %	Yield of hemiaminal <b>177</b> / %	Yield of <b>336</b> / %
1 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	1.5	>95	53	trace	n.d. <sup>c</sup>
2 <sup>b</sup>	MeCN–H <sub>2</sub> O (3:1)	1.5	>95	67	n.d.	n.d.

<sup>g</sup> Reaction conditions: **162** (0.3 mmol), potassium furan-2-trifluoroborate (0.9 mmol), MeCN–H<sub>2</sub>O (3:1) (0.05 M), 2 x Kessil PR160L 427 nm LED lamps, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (2.0 mL) in one portion.

<sup>h</sup> Not determined.

<sup>i</sup> Isolated yield after flash column chromatography on silica gel.

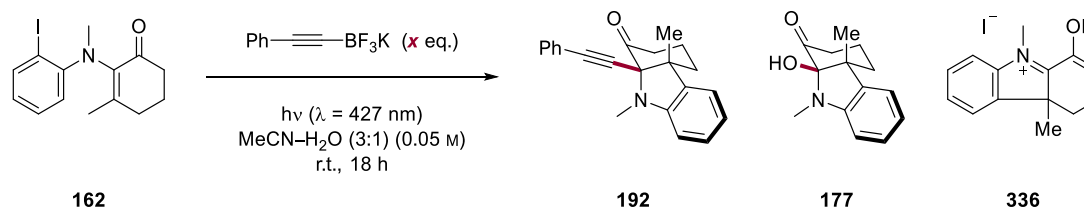
<sup>a</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

<sup>b</sup> Reaction conditions: **162** (0.1 mmol), potassium *trans*-styryltrifluoroborate (0.15, 0.2 or 0.3 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

<sup>c</sup> Not detected.

3 <sup>b</sup>	MeCN–H <sub>2</sub> O (1:1)	1.5	>95	<50 <sup>d</sup>	n.d.	n.d.
4 <sup>b</sup>	MeCN–H <sub>2</sub> O (3:1)	2.0	>95	44	38	n.d.
5 <sup>b</sup>	MeCN–H <sub>2</sub> O (3:1)	3.0	>95	n.d.	77	n.d.
6 <sup>e</sup>	MeCN–H <sub>2</sub> O (3:1)	1.5	- <sup>f</sup>	66 <sup>g</sup>	-	-

**Table 22.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of potassium (phenylethynyl)trifluoroborate.



Entry	Solvent	$x$ / eq.	Conversion <sup>a</sup> / %	Yield of <b>192</b> / %	Yield of hemiaminal <b>177</b> / %	Yield of <b>336</b> / %
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<sup>d</sup> Signal overlap made accurate integration of <sup>1</sup>H resonances corresponding to this compound impossible; the quoted value represents an upper bound estimate.

<sup>e</sup> Reaction conditions: **162** (0.3 mmol), potassium *trans*-styryltrifluoroborate (0.45 mmol), MeCN–H<sub>2</sub>O (3:1) (0.05 M), 2 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (2.0 mL) in one portion.

<sup>f</sup> Not determined.

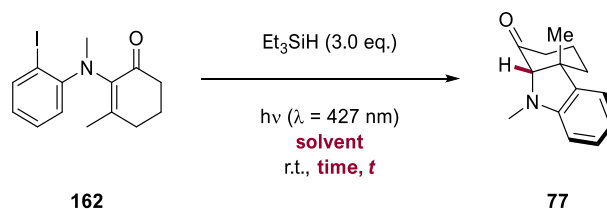
<sup>g</sup> Isolated yield after flash column chromatography on silica gel.

<sup>a</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.



1 <sup>b</sup>	MeCN–H <sub>2</sub> O (3:1)	1.5	90	51	n.d. <sup>c</sup>	n.d.
2 <sup>b</sup>	MeCN–H <sub>2</sub> O (3:1)	3.0	90	51	n.d.	n.d.
3 <sup>d</sup>	MeCN–H <sub>2</sub> O (3:1)	1.5	– <sup>e</sup>	53 <sup>f</sup>	–	–

**Table 23.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of triethylsilane.



Entry	Solvent	<i>t</i> / h	Conversion <sup>a</sup> / %	Yield of <b>77</b> / %
1 <sup>b</sup>	MeCN–HFIP (9:1)	3	>95	84

<sup>b</sup> Reaction conditions: **162** (0.1 mmol), potassium (phenylethynyl)trifluoroborate (0.15 or 0.3 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

<sup>c</sup> Not detected.

<sup>d</sup> Reaction conditions: **162** (0.3 mmol), potassium (phenylethynyl)trifluoroborate (0.45 mmol), MeCN–H<sub>2</sub>O (3:1) (0.05 M), 2 x Kessil PR160L 427 nm LED lamps, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (2.0 mL) in one portion.

<sup>e</sup> Not determined.

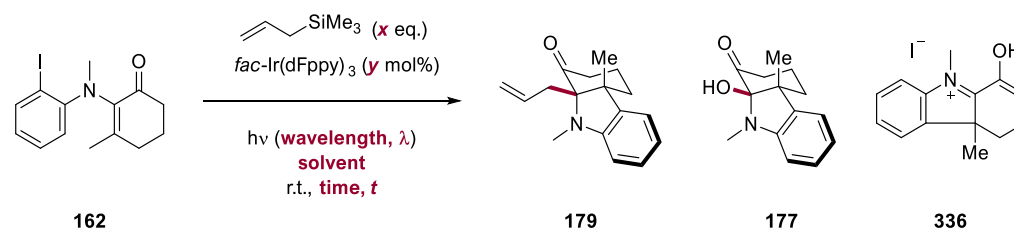
<sup>f</sup> Isolated yield after flash column chromatography on silica gel.

<sup>a</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

<sup>b</sup> Reaction conditions: **162** (0.1 mmol), triethylsilane (0.3 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., 3 h; the end-of-reaction mixture concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

2 <sup>b</sup>	MeCN–TFE (9:1)	3	>95	84 <sup>b</sup>
3 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	3	>95	87 <sup>b</sup>
4 <sup>c</sup>	MeCN–H <sub>2</sub> O (9:1)	6	– <sup>d</sup>	80 <sup>e</sup>

**Table 24.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of allyltrimethylsilane.



Entry	<i>x</i> / eq.	<i>y</i> / mol%	$\lambda$ / nm	Solvent	<i>t</i> / h	Conversion <sup>a</sup> / %	Yield of <b>179</b> / %
1 <sup>b</sup>	3.0	1	440	MeCN	3	68	50
2 <sup>b</sup>	3.0	1	440	DMF	3	>95	64

<sup>c</sup> Reaction conditions: **162** (0.3 mmol), triethylsilane (0.9 mmol), MeCN–H<sub>2</sub>O (9:1) (0.05 M), 2 x Kessil PR160L 427 nm LED lamps, r.t., 6 h; the end-of-reaction mixture concentrated *in vacuo* after adding Et<sub>3</sub>N (2.0 mL) in one portion.

<sup>d</sup> Not determined.

<sup>e</sup> Isolated yield after flash column chromatography on silica gel.

<sup>a</sup> Yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

<sup>b</sup> Reaction conditions (unless otherwise stated): **10** (0.1 mmol), allyltrimethylsilane (0.3 or 0.5 mmol), *fac*-Ir(dFppy)<sub>3</sub> (0 or 1 μmol), solvent(s) (0.05 M), 1 x Kessil PR160L (or PR160) 440 or 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* without quenching the HI by-product.

3 <sup>b</sup>	3.0	1	440	DMSO- <i>d</i> <sub>6</sub>	3	>95	trace <sup>c</sup>
4 <sup>b</sup>	3.0	1	440	MeOH	3	94	34
5 <sup>b</sup>	3.0	1	440	DMF–H <sub>2</sub> O (9:1)	3	>95	n.d. <sup>d,e</sup>
6 <sup>b</sup>	3.0	1	440	MeCN–H <sub>2</sub> O (9:1)	3	94	70
7 <sup>b</sup>	3.0	1	440	MeCN–MeOH	3	92	69
8 <sup>b,f</sup>	3.0	0	440	MeCN	6	48	33
9 <sup>b,f</sup>	3.0	0	440	Me <sub>2</sub> CO	6	53	19
10 <sup>b,f</sup>	3.0	0	440	DCM	6	54	22
11 <sup>b,f</sup>	3.0	0	440	DCM–MeOH (9:1)	6	69	45
12 <sup>b,f</sup>	3.0	0	440	EtOAc	6	56	8

<sup>c</sup> Hemiaminal **177** was formed as the major product in an NMR yield of 54%.

<sup>d</sup> Not detected.

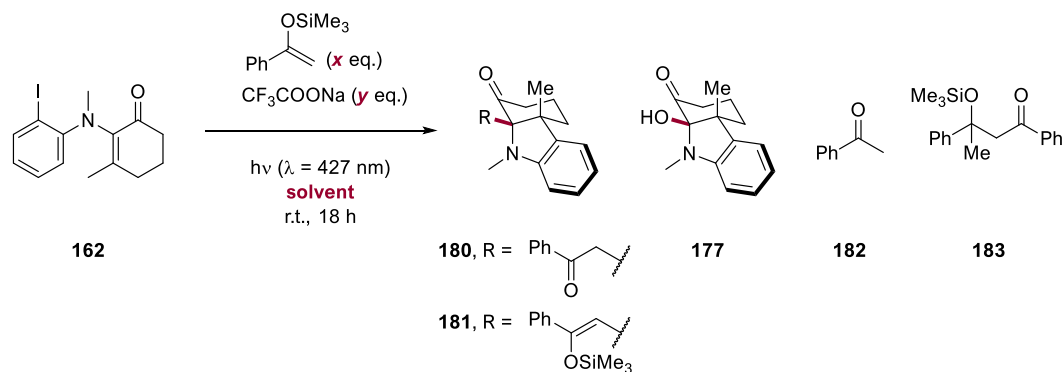
<sup>e</sup> Hemiaminal **177** and iminium iodide **336** were obtained as the major products of this reaction.

<sup>f</sup> The end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

13 <sup>b,f</sup>	3.0	0	440	MeCN–H <sub>2</sub> O (9:1)	6	>95	62
14 <sup>b,f</sup>	3.0	0	440	MeCN–MeOH (9:1)	6	76	59
15 <sup>b,f</sup>	5.0	0	440	MeCN–MeOH (9:1)	16	>95	63
16 <sup>b,f</sup>	5.0	0	440	MeCN–TFE (9:1)	16	86	71
17 <sup>b,f</sup>	5.0	0	427	MeCN–TFE (9:1)	6	95	85
18 <sup>b,f</sup>	5.0	0	427	MeCN–HFIP (9:1)	6	>95	78
19 <sup>b,f</sup>	3.0	0	427	MeCN–TFE (9:1)	16	>95	80

20 <sup>g</sup>	3.0	0	427	MeCN–TFE (9:1)	18	– <sup>h</sup>	69% <sup>i</sup>
21 <sup>g</sup>	3.0	0	427	MeCN–HFIP (9:1)	18	– <sup>h</sup>	80% <sup>i</sup>

**Table 25.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of 1-phenyl-1-trimethylsiloxyethylene.



<sup>g</sup> Reaction conditions: **162** (0.3 mmol), allyltrimethylsilane (0.9 mmol), solvent(s) (0.05 M), 2 x Kessil PR160L 427 nm LED lamps, r.t., 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding  $\text{Et}_3\text{N}$  (2.0 mL) in one portion.

<sup>h</sup> Not determined.

<sup>i</sup> Isolated yield after flash column chromatography on silica gel.

Entry	<i>x</i> / eq.	Additive ( <i>y</i> / eq.)	Solvent	Conversion / %	Yield of <b>180</b> (yield of <b>181</b> <sup>a</sup> ) / %	Yield of hemiaminal <b>177</b> / %	Yield of acetophenone, <b>182</b> / %
1 <sup>b,c</sup>	3.0	none	MeCN	82	n.d. <sup>d</sup> (n.d.)	trace	n.d. <sup>e</sup>
2 <sup>b,c</sup>	3.0	none	MeCN–HFIP (9:1)	>95	n.d. (n.d.)	– <sup>f</sup>	98
3 <sup>b,c</sup>	3.0	none	MeCN–TFE (9:1)	81	n.d. (n.d.)	45	108
4 <sup>b,c</sup>	3.0	none	MeCN–H <sub>2</sub> O (9:1)	>95	n.d. (n.d.)	55	– <sup>g</sup>
5 <sup>b,c</sup>	3.0	none	DMF	85	n.d. (n.d.)	trace	49

<sup>a</sup> The <sup>1</sup>H NMR data of this compound has been assigned tentatively by analogy to that of the desired product **24**.

<sup>b</sup> Reaction conditions (unless otherwise stated): **162** (0.1 mmol), 1-phenyl-1-trimethylsiloxyethylene (0.3 or 0.5 mmol), additive (0 or 0.3 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

<sup>c</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against 1,3,5-trimethoxybenzene (0.33 eq.).

<sup>d</sup> Not detected.

<sup>e</sup> The Mukaiyama aldol product **183** derived from acetophenone was formed in an NMR yield of 50%.

<sup>f</sup> A complex mixture of products was obtained in which hemiaminal **177** was present in major amounts; signal overlap made accurate integration of <sup>1</sup>H resonances corresponding to this compound impossible.

<sup>g</sup> Acetophenone (**182**) was formed in relatively large quantities; <sup>1</sup>H resonances corresponding to this compound, however, could not be accurately integrated within TopSpin.

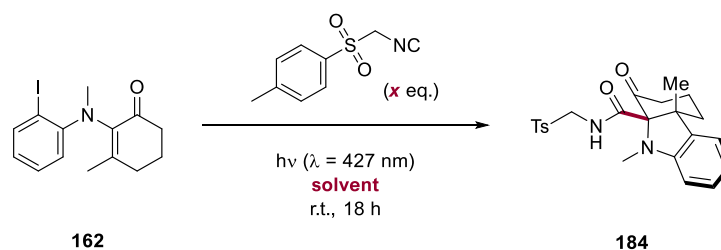
6 <sup>b,h</sup>	3.0	CF <sub>3</sub> COONa (1.0)	MeCN	94	26 (7)	trace	32
7 <sup>b,h</sup>	5.0	CF <sub>3</sub> COONa (1.0)	MeCN	94	10 (27)	trace	7
8 <sup>b,h,i</sup>	3.0	CF <sub>3</sub> COONa (1.0)	MeCN	93	29 (n.d.)	n.d.	184
9 <sup>b,h,i</sup>	3.0	CF <sub>3</sub> COONa (1.0)	MeCN–HFIP (9:1)	91	19 (n.d.)	n.d.	123
10 <sup>b,h,i</sup>	3.0	CF <sub>3</sub> COONa (1.0)	DMF	94	15 (n.d.)	n.d.	46
11 <sup>b,h,i</sup>	3.0	CF <sub>3</sub> COONa (1.0)	MeNO <sub>2</sub>	93	49 (n.d.)	n.d.	74
12 <sup>b,h,i</sup>	5.0	CF <sub>3</sub> COONa (1.0)	MeNO <sub>2</sub>	95	49 (n.d.)	n.d.	265

<sup>h</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.).

<sup>i</sup> The end-of-reaction mixture was concentrated *in vacuo* after adding MeOH (2.0 mL) and stirring at r.t. for 30 min.

13 <sup>j</sup>	3.0	CF <sub>3</sub> COONa (1.0)	MeNO <sub>2</sub>	- <sup>k</sup>	57 <sup>l</sup>	-	-
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**Table 26.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of *para*-toluenesulfonylmethyl isocyanide.



Entry	Solvent	<i>x</i> / eq.	Conversion <sup>a</sup> / %	Yield of <b>184</b> / %
1 <sup>b</sup>	MeCN	3.0	77	25
2 <sup>b</sup>	MeCN–HFIP (9:1)	3.0	88	33

<sup>j</sup> Reaction conditions: **162** (0.3 mmol), 1-phenyl-1-trimethylsiloxyethylene (0.9 mmol), CF<sub>3</sub>COONa (0.3 mmol), MeNO<sub>2</sub> (0.05 M), 2 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding MeOH (6.0 mL) and stirring at r.t. for 30 min.

<sup>k</sup> Not determined.

<sup>l</sup> Isolated yield after flash column chromatography on silica gel.

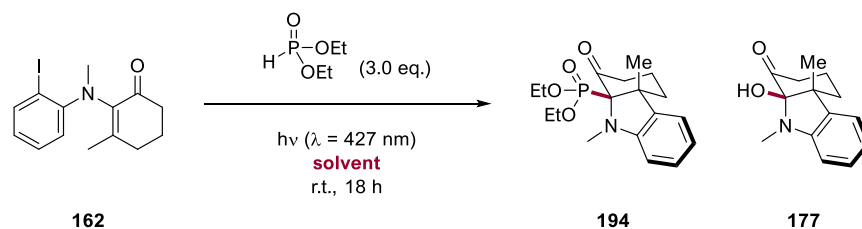
<sup>a</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

<sup>b</sup> Reaction conditions: **162** (0.1 mmol), *para*-toluenesulfonylmethyl isocyanide (0.3 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.



3 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	5.0	>95	58
4 <sup>b</sup>	MeCN–H <sub>2</sub> O (19:1)	3.0	83	33
5 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	3.0	>95	56
6 <sup>c</sup>	MeCN–H <sub>2</sub> O (9:1)	3.0	– <sup>d</sup>	74% <sup>e</sup>

**Table 27.** Screening of conditions for the photocyclisation of  $\beta$ -methyl substrate **162** in the presence of diethyl phosphonate.



Entry	Solvent	Conversion <sup>a</sup> / %	Yield of <b>194</b> / %	Diastereomeric ratio (d.r.) of <b>194</b>	Yield of hemiaminal <b>177</b> / %
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<sup>c</sup> Reaction conditions: **162** (0.3 mmol), *para*-toluenesulfonylmethyl isocyanide (0.9 mmol), MeCN–H<sub>2</sub>O (9:1) (0.05 M), 2 x Kessil PR160L 427 nm LED lamps, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (2.0 mL) in one portion.

<sup>d</sup> Not determined.

<sup>e</sup> Isolated yield after flash column chromatography on silica gel.

<sup>a</sup> Conversions and yields were measured by quantitative <sup>1</sup>H NMR spectroscopy against dimethyl terephthalate (0.25 eq.) unless otherwise stated.

1 <sup>b</sup>	MeCN	>95	40	1.0 : 2.1	26
2 <sup>b</sup>	MeCN–TFE (9:1)	>95	48	1.0 : 1.4	20
3 <sup>b</sup>	MeCN–HFIP (9:1)	>95	49	1.0 : 2.1	16
4 <sup>b</sup>	MeCN–H <sub>2</sub> O (9:1)	>95	53	>19.0 : 1.0	19
5 <sup>b</sup>	MeCN–H <sub>2</sub> O (3:1)	>95	31	>19.0 : 1.0	30
6 <sup>b</sup>	MeCN–H <sub>2</sub> O (19:1)	>95	75	4.0 : 1.0	7
7 <sup>c</sup>	MeCN–H <sub>2</sub> O (9:1)	- <sup>d</sup>	57 <sup>e</sup>	>19.0 : 1.0	-

<sup>b</sup> Reaction conditions: **162** (0.1 mmol), diethyl phosphonate (0.3 mmol), solvent(s) (0.05 M), 1 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

<sup>c</sup> Reaction conditions: **162** (0.3 mmol), diethyl phosphonate (0.9 mmol), MeCN–H<sub>2</sub>O (9:1) (0.05 M), 2 x Kessil PR160L 427 nm LED lamp, r.t., Ar, 18 h; the end-of-reaction mixture was concentrated *in vacuo* after adding Et<sub>3</sub>N (0.7 mL) in one portion.

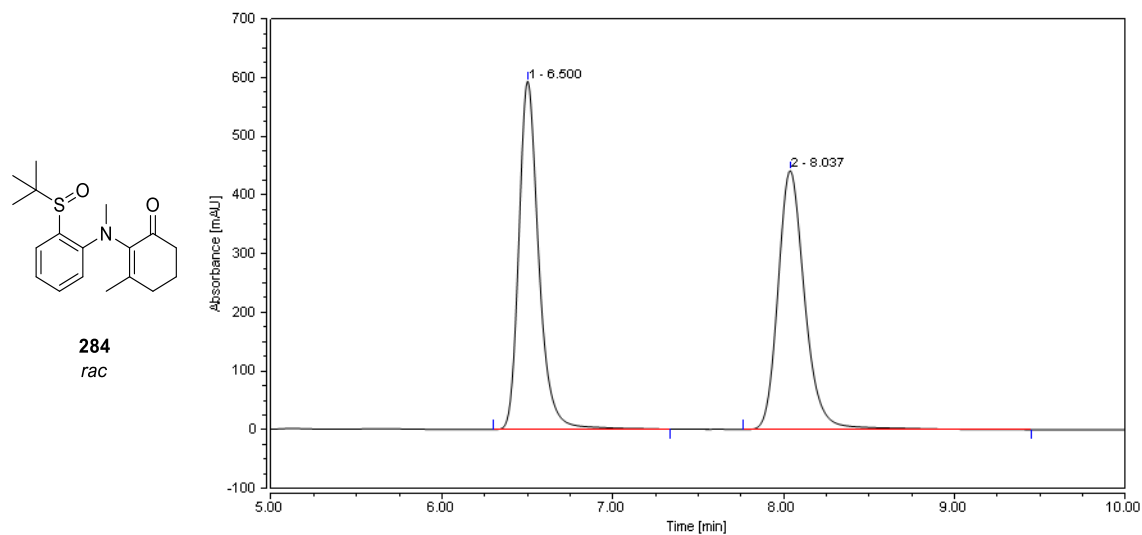
<sup>d</sup> Not determined.

<sup>e</sup> Isolated yield after flash column chromatography on silica gel.

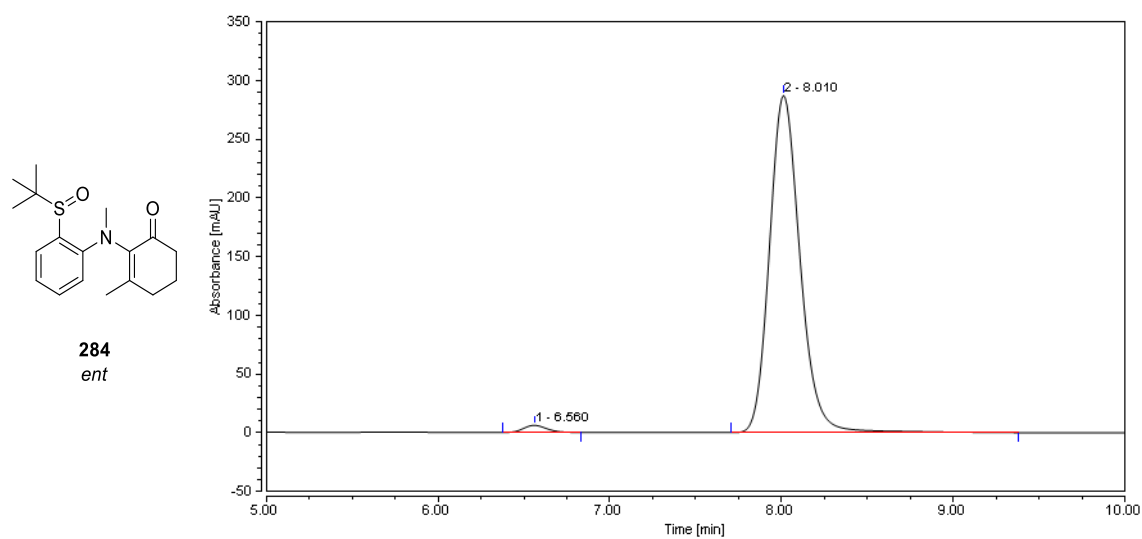
## Appendix B – HPLC traces

2-((2-(*tert*-Butylsulfinyl)phenyl)(methyl)amino)-3-methylcyclohex-2-en-1-one, **284**

Chiral HPLC: (Chiralpak IG-3, 40% ethanol, 60% *n*-hexane, 1.0 mL min<sup>-1</sup>,  $\lambda$  = 210 nm);  $\tau_R$  (minor) = 6.6 min,  $\tau_R$  (major) = 8.0 min.



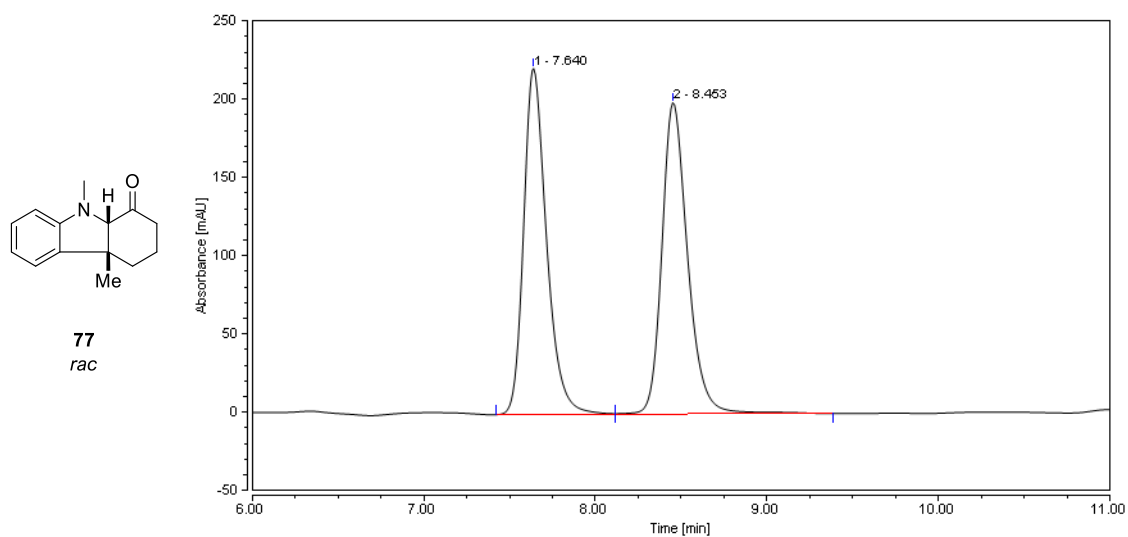
Peak	Retention time / min	Area / mAU*min	Height / mAU	Relative area / %
1	6.500	80.233	592.866	49.96
2	8.037	80.369	441.396	50.04
Total		160.602	1034.262	100.00



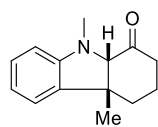
Peak	Retention Time (min)	Area (mAU*min)	Height (mAU)	Relative Area (%)
1	6.560	0.946	6.106	1.57
2	8.010	59.290	287.268	98.43
Total		60.236	293.375	100.00

**(4a*R*,9a*S*)-4a,9-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-1-one, **21****

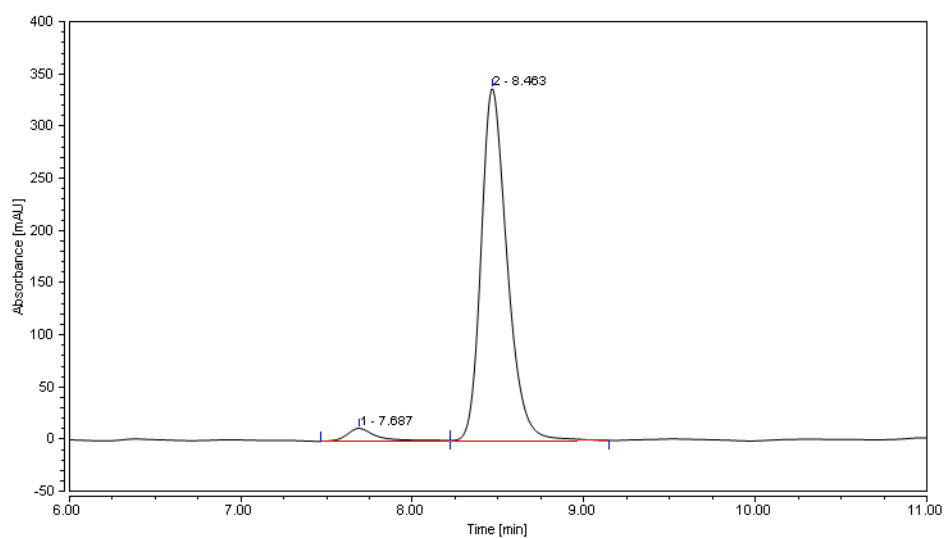
Chiral HPLC: (Chiralpak IA, 10% dichloromethane, 90% *n*-hexane, 1.0 mL min<sup>-1</sup>, λ = 249 nm); τ<sub>R</sub> (minor) = 7.7 min, τ<sub>R</sub> (major) = 8.5 min.



Peak	Retention Time (min)	Area (mAU*min)	Height (mAU)	Relative Area (%)
1	7.640	34.151	221.177	49.66
2	8.453	34.616	199.116	50.34
Total		68.766	420.293	100.00



**77**  
*ent*



Peak	Retention Time (min)	Area (mAU*min)	Height (mAU)	Relative Area (%)
1	7.687	2.507	12.328	4.05
2	8.463	59.339	337.906	95.95
Total		61.846	350.324	100.00

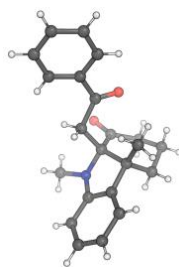




Goodness-of-fit on $F^2$	0.9983
Final R indices [ $I > 2\sigma(I)$ ]	$R_1 = 0.0275$ , $wR_2 = 0.0715$
R indices (all data)	$R_1 = 0.0288$ , $wR_2 = 0.0731$



(4*aR*,9*aS*)-4*a*,9-Dimethyl-9*a*-(2-oxo-2-phenylethyl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-carbazol-1-one, **180**

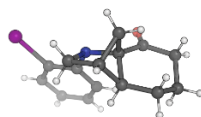


Colourless plates of diffraction quality were grown by vapour diffusion of cyclohexane into a solution of the product in tetrahydrofuran followed by slow evaporation of the resulting mixture.

Identification code	CCDC 2243733 (036OS21)	
Empirical formula	C <sub>22</sub> H <sub>23</sub> NO <sub>2</sub>	
Formula weight	333.43	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P 1	
Unit cell dimensions	a = 9.8591(2) Å	α = 90°
	b = 12.4725(3) Å	β = 90°
	c = 14.9150(4) Å	γ = 90°
Volume	1732.29(7) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.278 Mg/m <sup>3</sup>	
Absorption coefficient	0.641 mm <sup>-1</sup>	
Crystal size	0.02 x 0.06 x 0.55 mm <sup>3</sup>	
Theta range for data collection	4.652 to 76.646°.	
Index ranges	-12 ≤ h ≤ 12, -14 ≤ k ≤ 15, -18 ≤ l ≤ 18	
Reflections collected	41172	
Independent reflections	7210 [R(int) = 0.0560]	
Completeness to theta = 74.347°	99.7%	
Absorption correction	Multi-scan	

Refinement method	Full-matrix least-squares on $F^2$
Goodness-of-fit on $F^2$	1.0051
Final R indices [ $I > 2\sigma(I)$ ]	$R1 = 0.0428$ , $wR2 = 0.1076$
R indices (all data)	$R1 = 0.0506$ , $wR2 = 0.1146$

(3*R*,3*aS*,7*aS*)-1-(2-Iodophenyl)hexahydro-3,7*a*-methanoindol-7(1*H*)-one, **269**



Identification code	7589 (Service)	
Empirical formula	C <sub>15</sub> H <sub>16</sub> INO	
Formula weight	353.20	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	
Unit cell dimensions	a = 7.1717(2) Å	α = 90°
	b = 8.1811(2) Å	β = 90°
	c = 22.4777(6) Å	γ = 90°
Volume	1318.82(6) Å <sup>3</sup>	
Z	4	
Density (calculated) 1	1.779 Mg/m <sup>3</sup>	
Absorption coefficient	18.967 mm <sup>-1</sup>	
F(000)	696	
Crystal size	0.07 x 0.05 x 0.04 mm <sup>3</sup>	
Theta range for data collection	3.933 to 76.365°	
Index ranges	-9 ≤ h ≤ 8, -10 ≤ k ≤ 10, -28 ≤ l ≤ 24	
Reflections collected	29434	
Independent reflections	2741 [R(int) = 0.066]	
Completeness to theta = 74.170°	99.7%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.47 and 0.02	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	2730 / 0 / 164	
Goodness-of-fit on F <sup>2</sup>	0.9952	
Final R indices [I > 2σ(I)]	R1 = 0.0838, wR2 = 0.1866	

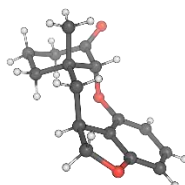
R indices (all data)

$R1 = 0.0843$ ,  $wR2 = 0.1879$

Largest diff. peak and hole

2.68 and -1.26 e.Å<sup>-3</sup>

(6*aR*,10*aS*,11*aS*)-10*a*-Methyl-8,9,10,10*a*,11,11*a*-hexahydro-1*H*-benzo[6,7]oxepino[4,3,2-*cd*]benzofuran-7(6*aH*)-one, **315**



Identification code	6984 (Service)
Empirical formula	C <sub>16</sub> H <sub>18</sub> O <sub>3</sub>
Formula weight	258.32
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 11.0322(3) Å      α = 90° b = 7.6536(2) Å      β = 100.309(2)° c = 15.3156(3) Å      γ = 90°
Volume	1272.31(5) Å <sup>3</sup>
Z	4
Density (calculated) 1	1.348 Mg/m <sup>3</sup>
Absorption coefficient	0.743 mm <sup>-1</sup>
F(000)	552
Crystal size	0.28 x 0.20 x 0.03 mm <sup>3</sup>
Theta range for data collection	4.073 to 76.464°
Index ranges	-12 ≤ h ≤ 13, -8 ≤ k ≤ 9, -19 ≤ l ≤ 17
Reflections collected	6581
Independent reflections	2647 [R(int) = 0.021]
Completeness to theta = 74.170°	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.80
Refinement method	Full-matrix least-squares on F <sup>2</sup>

Data / restraints / parameters	2647 / 0 / 172
Goodness-of-fit on $F^2$	1.0056
Final R indices [ $I > 2\sigma(I)$ ]	$R_1 = 0.0383$ , $wR_2 = 0.0954$
R indices (all data)	$R_1 = 0.0413$ , $wR_2 = 0.0991$
Largest diff. peak and hole	0.31 and -0.19 e. $\text{\AA}^{-3}$