

Accepted Article

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To be cited as: Angew. Chem. Int. Ed. 10.1002/anie.201705333 Angew. Chem. 10.1002/ange.201705333

Link to VoR: http://dx.doi.org/10.1002/anie.201705333 http://dx.doi.org/10.1002/ange.201705333

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Photocyclization

DOI: 10.1002/anie.201((will be filled in by the editorial staff))

Visible light photocatalysis of 6π heterocyclization**

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Abstract: Photo-mediated 6π cyclization is a valuable method for the formation of fused heterocyclic systems. Here we demonstrate that irradiation of cyclic 2-aryloxyketones with blue LED light in the presence of an Ir(III) complex leads to efficient and high yielding arylation across a panoply of substrates by energy transfer. 2-Arylthioketones and 2-arylaminoketones also cyclize effectively under these conditions. Quantum calculation demonstrates that the reaction proceeds via conrotatory ring closure in the triplet excited state. Subsequent suprafacial 1,4-hydrogen shift and epimerization leads to the observed cis-fused products.

Six-electron cyclization reactions are of fundamental importance within contemporary synthetic chemistry. Most investigations in this field have focussed on thermal processes, with relatively little work on the corresponding photochemical reactions.^[1] Within this field, photochemical 6π heterocyclization offers a distinct strategic approach to the synthesis of complex heterocyclic systems. Chapman demonstrated that irradiation of N-aryl enamines led to the formation of indolines bearing predominantly trans-stereochemistry across the ring junction (Scheme 1). This reaction, which is isoelectronic with the pentadienyl anion electrocyclization,^[2] was proposed to occur through excited state electrocyclization followed by a suprafacial 1,4-hydrogen shift.^[3] A related transformation was disclosed by Schultz, who reported that photocyclization of 2-aryloxyketones and 2-arylthioketones could be achieved with pyrex-filtered UV irradiation to yield fused dihydrobenzofurans and dihydrobenzothiophenes respectively.^[4-6] This reaction offers a diastereoselective route to cis-fused heterocycles useful in a range of synthetic endeavours, which we exploited in a recent total synthesis of morphine.^[7] Although the Schultz photocyclization reaction was the key stereodefining step in our total synthesis, the reactivity of the products under high intensity UV light and the sensitivity of conversion to varying substitution on the aromatic ring motivated us to find an alternative method to achieve this valuable transformation. In principle, visible light photoredox catalysis^[8] or triplet energy

• This work: visible light mediated 6π photocyclization • This work: visible light mediated 6π

Previous work: indoline synthesis (Chapman) and dihydrobenzofuran synthesis (Schultz)

Scheme 1. Previous work and approach to visible light mediated 6π cyclization

transfer^[9] from an appropriately activated sensitizer could both offe solutions to this problem. In considering the feasibility of these tw approaches, we rationalized that the estimated reduction potential of cyclic aryloxyketones ($E_{1/2} \approx -2.2$ V vs SCE) lie outside of th reducing ability of most excited state photocatalysts.^[10] In contras the triplet energy of cyclic aryloxyketones is ≈ 60 kcal mol⁻¹, whic is of a similar magnitude to the triplet energies of some excited stat iridium photocatalysts.^[11] This principle has been elegantly applie to the energy transfer mediated [2+2] cycloaddition of olefins^[12] an other processes.^[13] Consequently, we prepared a test 2 aryloxyketone substrate **1a** through treatment of the epoxide derive from 3-methylcyclohexenone with phenol in the presence c potassium carbonate in acetonitrile,^[14] and examined its reactivity i the presence of a range of photocatalysts under irradiation with blu LED light (Table 1).^[15]

Table 1. Optimization: photocyclization of 2-aryloxyketones



	Entry	Catalyst	Conversion	Yield
Dr Niels Münster, Nicholas A. Parker, Lucy van Dijk, Prof. Dr Robert S. Paton, Prof. Dr Martin D. Smith	1	Ru(bpy) ₃ Cl ₂	0%	-
Chemistry Research Laboratory	2	Ru(phen) ₃ Cl ₂	0%	- 1
University of Oxford	3	[lr(dtbbpy)(ppy) ₂]PF ₆	<5%	trace
12 Mansfield Road, Oxford, OX1 3TA (UK)	4	<i>fac</i> -Ir(ppy)₃	45%	44%
E-mail: robert.paton@chem.ox.ac.uk; martin.smith@chem.ox.ac.uk	5	[Ir(dF(CF ₃)ppy) ₂ (dtbbpy)]PF ₆	80%	77%
Homepage: http://msmith.cnem.ox.ac.uk	6	lr(Fppy) ₃	100%	95%

[**] The ERC has provided financial support (grant agreement no. 259056). We are grateful to the Deutsche Forschungsgemeinschaft (MU 3987/1-1) for a fellowship (to N.M.), the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/ L015838/1) for studentships (to N.A.P. and L.V.D.) and to John Jolliffe for help with X-ray crystallography.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201xxxxxx.



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[a] Reaction conditions: 1a (0.05 mmol), KOAc (1.0 equiv.), catalyst (1 mol.%),

12 W blue LED, MeCN ([1a] = 0.05 mol dm⁻³), 60 °C, 16 h. Conversion and

Ruthenium(II) catalysts proved to be ineffective (entries 1 and 2),^[16] and hence we examined photocatalysts with significantly higher

yields measured by ¹H NMR spectroscopy vs internal standard.





Table 2. Scope of triplet energy transfer mediated 6π heterocyclization. Reaction conditions: 0.3 mmol enone, 0.01 equiv. Ir(Fppy)₃, 1 equiv. KOAc, 12 W blue LED, MeCN ([enone] = 0.05 M); reaction time 16 h. Yields are for isolated material. d.r. (diastereoisomeric ratio) determined by ¹H NMR spectroscopy. Positions around the benzofuran core are indicated in red numerals. [‡]Reaction time 72 h. ^{*}Reaction time 36 h. ^aReaction conducted in the presence of 8-methylquinoline (0.2 equiv.); reaction time 2-7 h. ^bReaction conducted using NaOAc (1 equiv.) in EtOAc; reaction time 40 h. Numbers in parentheses indicate yields calculated on the basis of recovered starting material. r.r. (regioisomeric ratio) determined by ¹H NMR spectroscopy; minor regioisomer is indicated by parentheses.

triplet energies. $[Ir(dtbbpy)(ppy)_2]PF_6$ (entry 3)^[17] afforded a trace of product, but we observed significant reactivity with *fac*-Ir(ppy)₃leading to **2** in 44% yield (entry 4). Significantly higher conversion was observed with $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (80%)

yield), and $Ir(Fppy)_3$ gave complete conversion and a 94% yield of **2**; only the *cis*-dihydrobenzofuran isomer was isolated under these reaction conditions.^[18] Addition of triplet quenchers (TEMPO or 1,1-diphenylethylene) inhibited the reaction entirely and only

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starting material was isolated, consistent with an energy transfer mechanism.^[19] With a working substrate synthesis and cyclization procedure in hand, we examined the scope and limitations of this visible light mediated process (Table 2). We initially explored cyclization of cyclohexenone substrates with different substituents on the aromatic ring. Substituents in the 6-position were well tolerated including alkyl groups (3, 90%) and halogens (difluoroderivative 4, 87%; chloro-5, 89%; bromo- 6 92%; iodo- 7, 78%). Substrates bearing electron-donating groups such as 8 and 9 both cyclize effectively; in these cases the competing [2+2] cycloaddition is likely disfavoured by geometrical constraints precluding close approach of the enone and allyl groups. Introducing 7-substitution does not have any deleterious effects on the reaction, and tetracycle 10 can be produced in 93% yield. meta-Substituents on cyclohexenone-derived aryloxy substrates generally cyclize to give regioisomeric ratios in which the 7-isomer is the minor product: 9/7methyl 11 (91% combined yield, ratio 2.2:1) and 9/7 dimethylamino 12 (68% combined yield, ratio 2.3:1). It is worth noting that electron rich substrates efficiently cyclize to products such as 12 in high yields; under high intensity UV irradiation this cyclization does not proceed.^[4e] Symmetrical disubstituted substrates cyclize effectively whether electron donating (13, 94% yield) or electron withdrawing (14, 92% yield). A similar trend is observed with groups in the 8position: pyridine 15 (76% yield), and both electron withdrawing groups (aldehyde 16, 75% yield; ester 17, 95% yield; nitrile 18, 86% yield) and electron donating groups (methoxy 19, 90% yield; benzyloxy 20, 95% yield; amide 21, 90% yield; thioalkyl 22, 88% yield; alkyl 23, 91% yield) are tolerated without incident. Using an isophorone-derived substrate bearing a gem-dialkyl substituent on the cyclohexane ring^[4c] does not affect the reaction significantly, and the product 24 an be isolated in 95% yield. Variation in the β position of the cyclohexenone is also possible: ethyl 25 (93% yield) and isopropyl 26 (80% yield; 15:1 d.r.) groups can be accommodated at the all-carbon quaternary stereocentre without reduction in overall yield. Extension to a derivative of progesterone was also possible, yielding 27 in 84% yield (d.r. 4:1). Cyclization of substrates bearing hydrogen in the β -position of the enone is possible, though these are more challenging substrates and can undergo competing oxidation to benzofurans. This can be circumvented somewhat by performing the reaction in the presence of 8-methylquinoline. Under these conditions cyclization to afford 28 occurred in 88% yield, and introduction of groups around the aromatic ring of this template was well tolerated as exemplified by 8-methyl 29 (87% yield) and 8-phenyl 30 (80% yield) products. Introduction of an electron withdrawing group (31, 87% yield), halogens (32, 76% yield and 33, 56% yield), or an electron-donating group (34, 85% yield) in this position did not affect the efficacy of the procedure. The cis-stereochemistry at the ring junction was confirmed by single crystal X-ray diffraction of 2, 3, 22 and 28.^[20] We also examined the photocyclization of aryloxycyclopentenones, which were significantly more challenging to work with than the corresponding cyclohexenones. In general, longer reaction times are required and the process is sensitive to the presence of electron withdrawing groups on the aromatic ring, but high yielding transformations can be achieved. Thus 35 can be generated in high vield (87%) as a single diastereoisomer. Halogens can be tolerated in the 6-position on the aromatic ring (chloro- 36, 36% yield; bromo- 37 65% yield iodo- 38, 45% yield). In contrast to the cyclohexenone series, meta-substituents on aryloxy substrates generally cyclize to give regioisomeric ratios in which the 7-isomer is the major product (9/7-dimethylamino 39; 67% combined yield, ratio 1:1.6). Other electron donating substituents in the 8-position on the aromatic ring are similarly effective: 8-methoxy 40 (83% vield) and 8-methyl 41 (86% vield). Electron withdrawing groups are particularly challenging (8-formyl 42, 23% yield and ester 43, 38% yield), leading to lower conversions and yields. The fused pyridine 44 can be generated in 52% yield. Variation in the β position of the cyclopentanone is also remarkably well tolerated: ethyl 45 (86% yield), benzyl 46 (71% yield) and cyclohexyl 47 (86% yield) groups can be installed at the fully substituted centre without issue. The cis-stereochemistry at the ring junction was confirmed by single crystal X-ray diffraction of 40. Cyclization of 2-arylthioketones and 2-arylaminoketones is also effective under these conditions. Dihydrothiophenes can be be formed in high yields, to form both six (49, 91% yield) and five-membered fused ring systems (50, 87% yield). In a related process, N-methylated 2arylaminoketones cyclize to afford dihydroindoles in good yields i both five and six ring series (51, 77% yield; 52, 84% yield Different N-substituents are tolerated without incident a exemplified by N-allyl 53 (52% yield) and N-benzyl 54 (88% yield derivatives. This approach can also be extended to generate fuse tetracylic systems such as 55 (77% yield) by cyclization of tetrahydroquinoline substrate. In general, the cyclization procedur is highly effective and demonstrates remarkable insensitivity t substitution, particularly in the cyclohexenone series. The scalabilit of this process is demonstrated by a 5.00 mmol reaction (1.01 g) t generate 2, which proceeds in 92% yield with a photocatalys loading of 0.05 mol%. A series of chemo-and diastereoselectiv derivatizations were also performed on this compound.^[15] In ou hands the reaction was also insensitive to the presence of moisture However, several substrates possessed distinct reactivity or wer surprisingly unreactive under these reaction conditions (Scheme 2) Substrate 56, which contains an $\alpha,\beta,\gamma,\delta$ -unsaturated ketone undergoes efficient intermolecular [2+2] cycloaddition (71% yield rather than the arylation reaction to afford cyclobutane 57, in whic stereochemistry was confirmed by single crystal X-ray diffractior This is consistent with previous observations on the rate of [2+2 cycloadditions versus the arylation reaction.^[21]



Scheme 2. 2-Aryloxyketone substrates with distinct reactivity profiles

β-Aryl substrate **58** and β-cyclopropyl substrate **59** were bot unreactive under the optimized reaction conditions and were re isolated unchanged. To probe the reaction mechanism (Figure 1A and divergent reactivity of some of the substrates investigated, w_v turned to computations (M06-2X+SMD/def2-TZVP).^[22] The calculated energy required to promote cyclohexanone **1a** from singlet (S₀) to π–π* triplet (T₁) state is 58.2 kcal mol⁻¹.^[23] This is well matched with the emissive energy of the Ir(Fppy)₃ catalyst (experimentally 60.1 kcal mol⁻¹).^[11] Triplet excitation of cyclopentenone **1b**, which required longer reaction times, requires an additional 4.1 kcal mol⁻¹ of energy. Substrate **58** forms a more stable triplet state in comparison to **1a** (48.8 kcal mol⁻¹; Figure 1B). However, heterocyclization is kinetically and thermodynamically less favorable: TS_{AB} has a higher barrier and this step is endergonic

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Figure 1. **A** Proposed mechanism of 6π heterocyclization of **1b** to form **35**. **B** M06-2X/def2-TZVP+SMD(EtOAc)//M06-2X/def2-TZVP computed Gibbs energy profil (kcal mol⁻¹) for the cyclization of **1b** to form **35** taking place on singlet and triplet surfaces. ISC = intersystem crossing; TET = triplet energy transfer; MECP minimum energy crossing point; dis = disrotatory; con = conrotatory.

by 3.8 kcal mol⁻¹. The intersystem crossing (ISC) from the triplet states of unreactive substrates 58 and 59 involves smaller changes in energy and in dihedral twisting relative to 1b. This is consistent with more efficient relaxation from the triplet back to the singlet ground state for these substrates. Heterocyclization proceeds via triplet intermediate ³A, which preferentially occurs in a conrotatory fashion (Figure 1B, with several other substrates shown in SI). Conrotatory closure through TSAB, is favoured over disrotatory closure by more than 10 kcal mol⁻¹ (ΔG^{\ddagger} 13.5 kcal mol⁻¹). This preference is consistent with the expectation that a conrotatory 6π electrocyclic TS is Möbius aromatic in the triplet excited state.^[24] However, computed magnetic criteria of aromaticity (NICS, ACID, magnetic susceptibility exaltation) do not show the shielding/cyclic ring current characteristics of a pericyclic reaction (see SI). Ring-closed intermediate ³B lies downhill by 3.5 kcal mol⁻¹ (with a β -phenyl group as in 58, this step is uphill by a similar amount, which may also contribute towards lower reactivity) and must undergo intersystem crossing (ISC) back to the singlet state. Interestingly we find the open-shell singlet structure of ${}^{1}\mathbf{B}$ to be 7 kcal mol⁻¹ more stable than the closed-shell (e.g. ylide) structure. 1B and 3B geometries, along with that of the minimum energy crossing point (MECP) are very similar, which facilitates ISC. The subsequent suprafacial [1,4]-H shift is Woodward-Hoffman allowed in the singlet ground state, with a computed barrier of 14.2 kcal mol⁻¹. Thi sigmatropic rearrangement is extremely exergonic and leads t *trans*-fused **C**. The diastereomeric *cis*-fused product could aris through base-mediated epimerization of **C** – it is *significantly* mor stable by 15.3 kcal mol⁻¹ – or from the non-stereospecifi intermolecular deprotonation/reprotonation of **B**. The extremel large preference (ca. 10 kcal mol⁻¹) for conrotatory closure wa obtained for all substrates and so it is implausible that the *cis*-fuse skeleton is the result of disrotatory cyclization.

In conclusion, we have described an operationally convenier approach to the synthesis of fused dihydrobenzofurans dihydroindoles and dihydrothiophenes using an iridium(III, sensitizer in the presence of visible light to mediate energy transfer. This is a versatile reaction that enables the synthesis of fused heterocyclic ring systems with a wide variety of substituents in good yields. Quantum calculations demonstrate that this reaction proceeds in the triplet state with a large preference for conrotatory ring closure, but without the magnetic characteristics of an electrocyclic mechanism.

Received: ((will be filled in by the editorial staff)) Published online on ((will be filled in by the editorial staff))

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Keywords: visible light • photochemistry • mechanism • energy transfer • catalyst • DFT

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