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A new atom-transfer radical cyclization (ATRC) mediated by photocatalytically-generated aminyl radicals that do not have an α-C–H bond

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A photocatalytic method for the synthesis of sp^3-rich bicyclic *O,O*- and *N,O*-iodoacetals from enol ethers and Boc-protected enamines has been developed. The simple procedure uses catalytic eosin (EY·Na$_2$), a green solvent system (EtOH/water) and blue LED irradiation. The photocatalytic step involves radical cyclisation with halogen atom relocation mediated by aminyl radicals that do not have an α-C–H bond.

Photocatalysis dominates synthetic organic chemistry at the moment.[1] The explosion of interest in developing new photocatalytic synthetic methods is often attributed to the mild and/or sustainable nature of the reaction conditions employed which suit modern requirements for greener technologies (for example; the use of visible spectrum light rather than heat as the source of energy, the compatibility with green solvents such as ethanol and the absence of a need for protecting groups are all positive features widely seen in photocatalytic methods).[2] However, the real power of photocatalysis lies in the diverse range of reaction modes that are accessible.[1,3] A single photocatalyst can be harnessed across a spectrum of different reactivities, from energy transfer reactions through redox chemistry to hydrogen/halogen atom abstractions (HAT/XAT), dependent simply on minor adjustments either to the nature of the substrate or to the components of the reaction mix. If we take as an illustrative example the organic photocatalyst eosin Y,[1d,3] which has been the focus of our recent work;[4] photoactivated eosin Y can act as either an energy transfer agent (common, particularly for the generation of singlet oxygen),[5] as a direct hydrogen atom transfer agent (relatively rare),[6] as an reductant[3,7] or as a oxidant[8] (common, especially with amines as sacrificial electron donors[4,9,10]). For a cheap, (precious) metal-free catalyst, used in very low amounts, this reaction mode versatility only adds to its overall attractiveness. However, the flip side to this argument is that, with so many possibilities available, and, in order to continue expanding the toolbox further, we need to develop a much deeper understanding of how each photocatalyst will behave across a wide range of situations and design new reactions with care. In the study described herein, we show how a small change in the nature of the amine employed in a reaction drives a significant switch in mechanism to yield a different set of products, and, moreover, the new work also reveals that aminyl radical can act as direct halogen atom transfer agents even when they do not have an α-C–H bond (Scheme 1).

In 2020, Leonori's group published a seminal paper which demonstrated how α-aminoalkyl radicals could be generated under very mild photocatalytic conditions and then used to mediate halogen atom transfers (XATs).[9] This work offered a highly effective new way to access alkyl radicals from organic halides, and, because the oxidation of amines is relatively facile, a good range of photocatalysts could be used in these transformations (including metal-free organic photocatalysts).[4,10] We used this concept to develop a mild eosin-mediated methodology for the synthesis of (poly)cyclic *O,O*- and *N,O*-acetals.[4a] During screening and mechanistic investigations for this new method, we began to observe the formation of products bearing an iodide in a relocated position under certain circumstances; more specifically, when certain amines that did not have a C–H bond alpha to the amino group were used where we had expected no reaction to occur. The second example in Scheme 1 illustrates this observation. Since an iodide functionality represents a very useful handle for further transformations and because it was unclear why these products were forming we initiated a new project to investigate the transformation.

Our investigation began with reaction component and condition screening to identify an optimal protocol. Full details of the screenings for photocatalyst, amine and solvent are reported in the SI. From these screenings, favoured protocols were developed which used eosin (EY·Na$_2$, 5 mol%) in an EtOH : water mix (4 : 1, 0.1 M) with either 2,2,6,6-tetramethylpiperidine (TMP), *tert*-butylamine (TBA) or ammonia as the amine of choice.

With optimum conditions in hand, we next sought to explore the scope of the reaction. Beginning with iodoacetals

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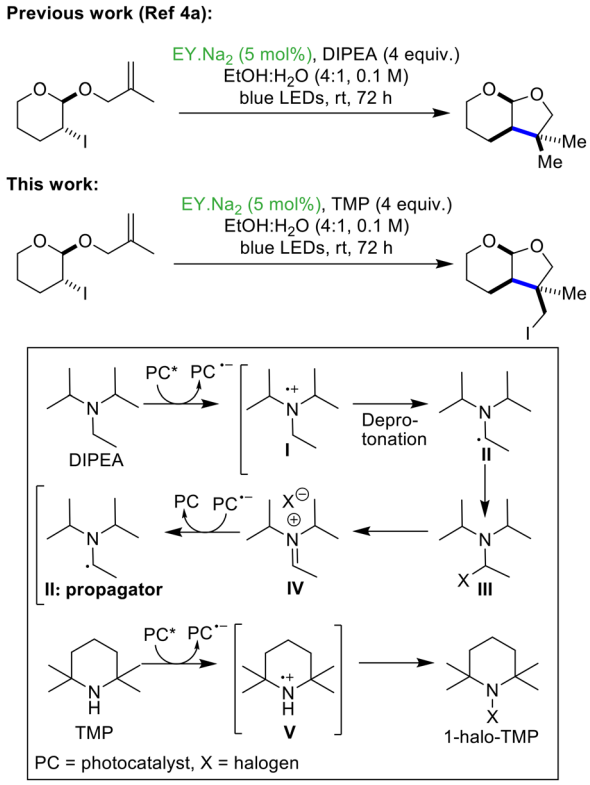


Scheme 1 Example demonstrating how a small change in the nature of the amine employed leads to a switch in reaction mechanism and a different set of products.

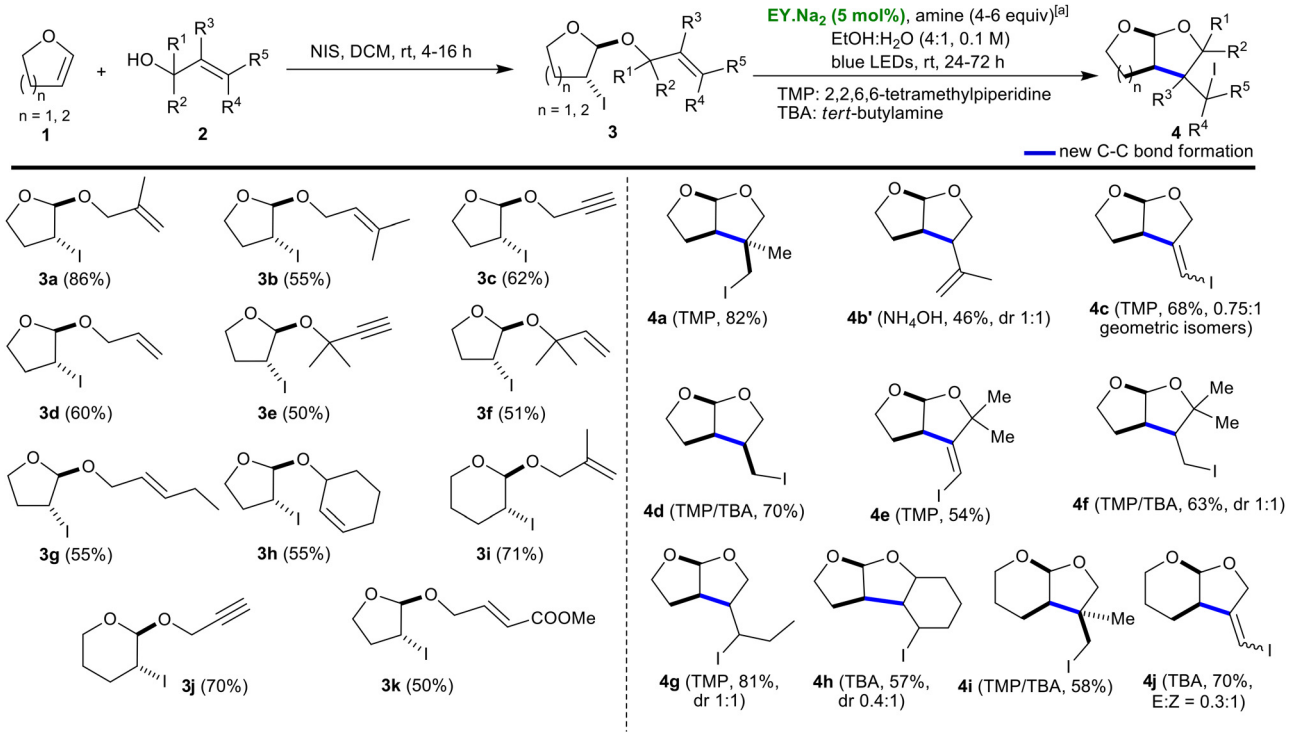
related to the substrate which had first led us to observe the novel reaction, we synthesised a range of new substrates for testing (**3a–k**, Table 1). The products of the first photocatalysed reactions (**3** → **4**) would be rigid *O*,*O*-bicyclic acetals that are important pharmacophores and medicinal chemistry targets.[4a] The Stork–Ueno cyclisation has been used to access analogous cyclic acetals;[4a,11,12] however, the original Stork–Ueno reaction and many of its variants suffer from drawbacks, such as; a requirement for (toxic, stoichiometric[12b,c] or precious[12e]) metal-based reagents (*e.g.* tributyl tin hydride[11] or iridium catalysis[12e]) and/or harsh reaction conditions (*e.g.* UV light[12a]). Our methodology is advantageous because as well as being mild and affording the iodo-handle to facilitate further manipulations, it uses small amounts of a metal-free catalyst and is done with visible spectrum light in a green solvent system (ethanol-water). In general, following irradiation with blue LEDs for between 24 and 72 h, we saw that the products of a 5-*exo* cyclisation/XAT sequence were formed with good yields (54–82%, Table 1). The relative stereochemistry for products **4a**, **4d**, **4e**, **4i** and **4j** was established through NOE experiments. If the allylic alcohol **2** was replaced with a homoallylic alcohol, the resulting substrates were slow to react with conversions of approximately 30% seen after days of being subjected to the photocatalytic conditions; thus, it can be concluded that while 6-*exo* cyclisations using this method do occur, they are much slower to yield the desired products. A second interesting observation is that the substrate **3i** is converted to product **4i** much more slowly than its close analogue **3a** (as seen when these reactions were monitored by ^{1}H NMR). Acyclic iodoacetals gave either no conversion (with NH_4OH) or very low conversions (with TMP). In the case of **4b′**, it is likely that the initially formed tertiary iodide undergoes an elimination reaction under the conditions employed; this extra step would also explain the lower yield. Finally, when the double bond included in the substrate was electron deficient as in **3k**, the reaction was sluggish and yielded the cyclised product without the iodide. This product is likely a result of either the radical adjacent to the ester group (after 5-*exo* cyclisation) being directly reduced by the photocatalyst radical anion ($EY^{\bullet -}$)[13] or the α-iodoester product being reduced by the photocatalyst radical anion ($EY^{\bullet -}$); thus, the normal reaction cycle is disturbed (see; SI).

Next, the scope of the reaction was expanded by employing Boc-protected enamine **1c** as the initial substrate (Table 2). The previously developed conditions were applied and first iodoalkoxy pyrrolidines **5** were obtained (yields 61–73%), then, following application of the photocatalytic protocol, Boc-protected *N*,*O*-acetals **6** were isolated in high yield (65–86%). Ammonia was the amine base of choice for all these substrates **5**. Products **6** were then deprotected using a standard trifluoroacetic acid (TFA) protocol to give *N*,*O*-acetals **7** (73–76%) with simplified ^{1}H NMR spectra in comparison to the Boc-protected acetals where restricted bond rotation had led to complex spectra. The relative stereochemistry for *N*,*O*-acetal **7a** was established by NOE. As further proof of the simplicity of this chemistry and the ease with which it can be implemented, we were able to combine the steps and convert the protocol into a versatile one pot procedure for the synthesis of *O*,*O*- or *O*,*N*-acetals from dihydro-furans/pyrroles (Scheme 2 and SI).

To illustrate how readily the iodo-handle present in the products of this new methodology can seamlessly facilitate further manipulations, we developed another one pot procedure incorporating an additional photocatalytic step (Scheme 3). More specifically, we were able to convert iodo-*O*,*O*-acetal **3a** directly into ester **8a** *via* inclusion of a photocatalytic Giese reaction at the end of the one pot sequence. The ester product **8a** was formed in a 53% yield which is remarkable given the complexity of the sequence.

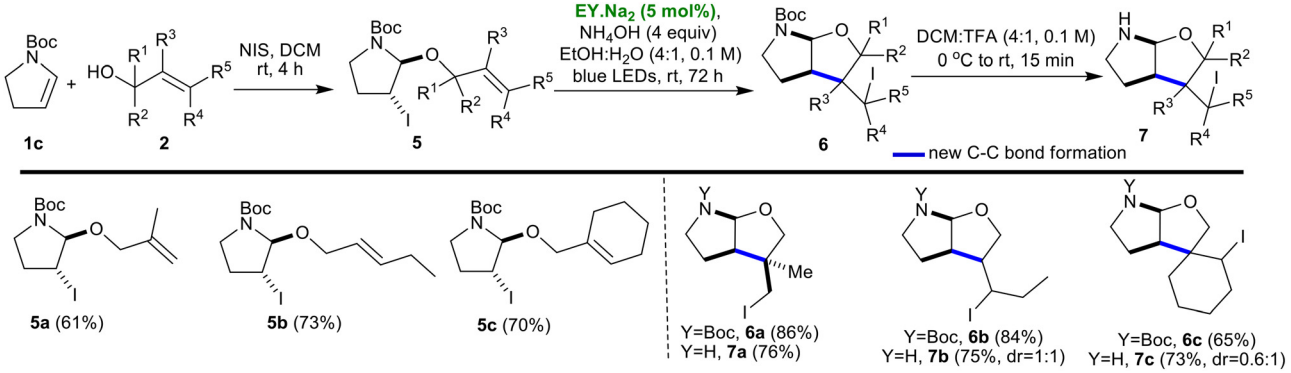
On the basis of these results as well as control and emission quenching experiments, which are presented in full in the SI, we have derived a possible mechanism (Scheme 4). The control experiments confirm that the blue light, photocatalyst and amine are all necessary for the reaction to occur. The Stern–Volmer plots, derived from the emission quenching experiments, suggest that it is the amine that quenches the excited state of the photocatalyst at a substantially higher rate than the substrates (either **3a** or **5a**). Thus, the cycle begins with the amine quenching the excited state of the photocatalyst (EY^* → $EY^{\bullet -}$). The resulting amino radical cation **V** could abstract the iodine atom (activated by the adjacent oxygen, **3** or **5** → **VI**). It is well-known that amino radical cations can abstract hydrogen atoms,[14] but reported halogen atom abstractions mediated by amines are dominated by the α-amino alkyl radical chemistry described earlier[4,9,10] and XAT by the radical cation of amines without an α-C–H bond has not previously been harnessed.

Table 1 Synthesis of iodo-*O*,*O*-acetals **3** which were then subjected to the new photocatalytic protocol to give XAT products **4**



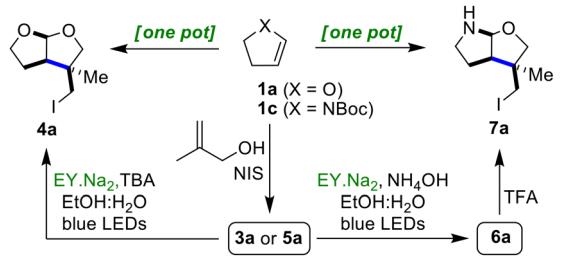
[a] Amine giving the highest yield in each case is shown in the table; details for other amines are given in the SI.

Table 2 Synthesis of iodo-*N*,*O*-acetals **5** which were then subjected to the new photocatalytic protocol to give XAT products **6**

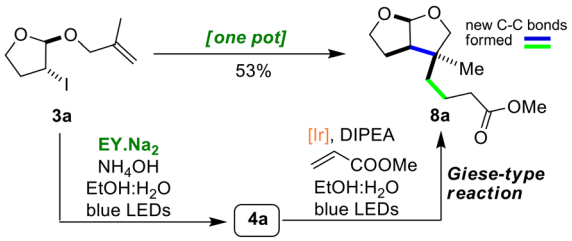


Following deprotonation, the *N*-iodo-amine (*e.g.* 1-iodo-TMP) would result, while, at the same time the substrate would undergo 5-*exo* cyclisation (**VI** → **VII**). The alkyl radical present in **VII** could then abstract the iodine atom from the iodo-amine to complete the halogen atom transfer (**VII** → **4** or **6**). The so-formed *N*-centred radical **VIII** could act as a radical chain propagator. This mechanism is supported further by the regular observation of 1-iodo-TMP in crude reaction spectra. A small change to the sequencing of the initiation step cannot be ruled out (namely, **V** + TMP → **VIII** and then **VIII** + **3**/**5** → **VI** and iodo-TMP). This sequencing alternative does not change the overall proposed radical chain process and is more consistent with the philicity matching of the XAT process. Further experiments and mechanistic detail are discussed in the SI.

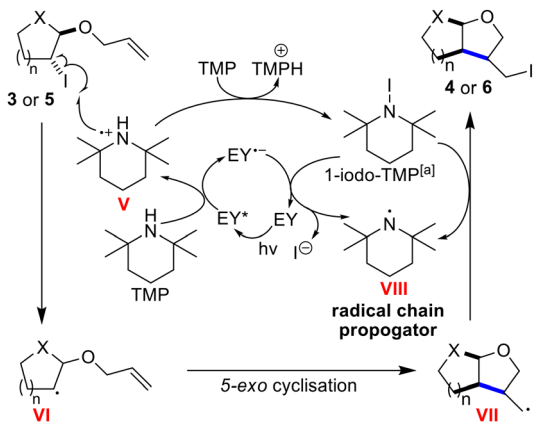
In conclusion, not only have we developed a simple green procedure to synthesise frequently targeted pharmacophores with a useful handle for further modifications (namely, sp^3-rich bicyclic *O*,*O*- and *N*,*O*-iodoacetals), but in so-doing we have shown that amines bearing no α-C–H bond can act as direct halogen atom relocation agents. In the reaction sequence, an activated iodine (one that is adjacent to a heteroatom) is transferred from the substrate to the product *via* the



Scheme 2 One pot procedure for the synthesis of *O,O*- and *N,O*-acetals (of type **4** and **7**) from dihydro-furan/pyrroles of type **1**.



Scheme 3 One pot procedure for the synthesis of ester **8a** from iodo-*O,O*-acetal **3a** by incorporation of a photocatalytic Giese-type reaction.



[a] 1-iodo-TMP observed by ^{1}H NMR and HRMS

Scheme 4 Proposed mechanism for transformation of iodoacetals **3** or **5** into bicyclic acetals **4** or **6**.

photocatalytically-generated aminyl radical and its corresponding 1-iodo-amine.

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Conflicts of interest

There are no conflicts to declare.

Data availability

Data supporting the findings of this study is available within the article and supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6cc00427j.

Raw data (*e.g.* NMR raw data files) is held by the University of Crete and can be shared upon request.

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