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Organophotocatalytic carbo-heterofunctionalization of unactivated olefins with pendant nucleophiles†

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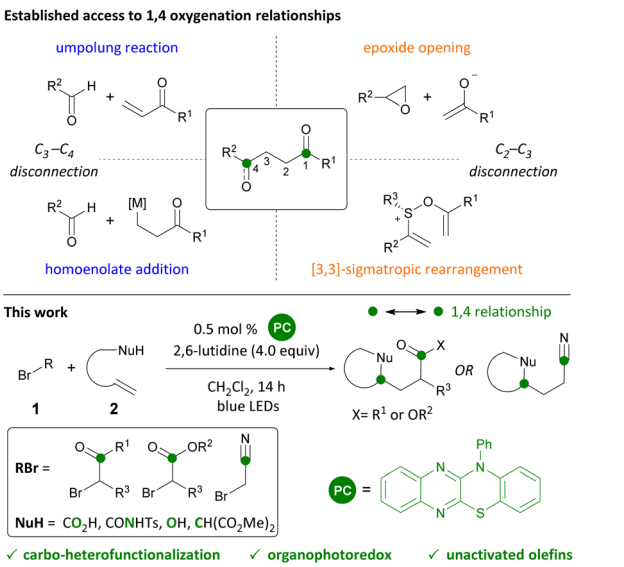
We report the difunctionalization of unactivated, terminal olefins through intermolecular addition of α-bromoketones, -esters, and -nitriles followed by formation of 4- to 6-membered heterocycles with pendant nucleophiles. The reaction can be conducted with alcohols, acids, and sulfonamides as nucleophiles furnishing products bearing 1,4 functional group relationships that offer various handles for further manipulation. Salient features of the transformations are the use of 0.5 mol% of a benzothiazinoquinoxaline organophotoredox catalyst and their robustness with respect to air and moisture. Mechanistic investigations are carried out and a catalytic cycle for the reaction is proposed.

Introduction

1,4 Functional group relationships are found as motifs in a range of natural products, pharmaceuticals, and polymers.[1] New methods to access these motifs constitute valuable additions to the synthetic toolkit. While 1,3 and 1,5 relationships (consonant) are attainable through transformations such as aldol, Michael, and Mannich reactions, 1,2 and 1,4 relationships (dissonant) require the use of alternative methods.[2] Synthetic strategies to generate dissonant relationships include the use of 3-membered rings (epoxide or cyclopropane opening),[3] Umpolung reactions,[4] homoenolates,[5] sulfonium [3,3]-sigmatropic rearrangements,[6] and radical additions[7] (Scheme 1). Photoredox catalysis has emerged as a convenient way of generating radicals and effecting their subsequent transformation to cations and anions with attendant reactivity.[8] Herein, we report the organophotocatalytic carbo-heterofunctionalization of unactivated olefins under visible-light irradiation (Scheme 1). Products readily accessed through this transformation include γ-acyloxy esters, ketones, and nitriles that are akin to homoaldol addition products and the reaction can be conveniently carried out in the presence of oxygen and moisture.

Carbo-oxygenations of olefins involving activated bromides and *O*-nucleophiles have been reported in the presence of Pd, Cu, and Fe complexes.[9] These transformations have focused on fluorinated alkyl bromides and activated alkenes such as styrenes. With the advent of photoredox catalysis, methods involving Ir photocatalysts have been investigated (Scheme 2).[10]

Early studies by Liu focused on the addition of bromoacetic acid esters over styrenes furnishing γ-lactones. Later work by Xia and Han employed styrenes and doubly activated alkyl bromides to furnish tetrahydrofurans, -pyrans, and lactones. The direct photocatalytic carbofunctionalization of unactivated olefins with alkyl bromides stands out as a desirable transformation for investigation. However, the challenge of using unactivated olefins is their attenuated reactivity as illustrated by



Scheme 1 Synthesis of 1,4 oxygenation motifs. Carbo-functionalizations of unactivated olefins.

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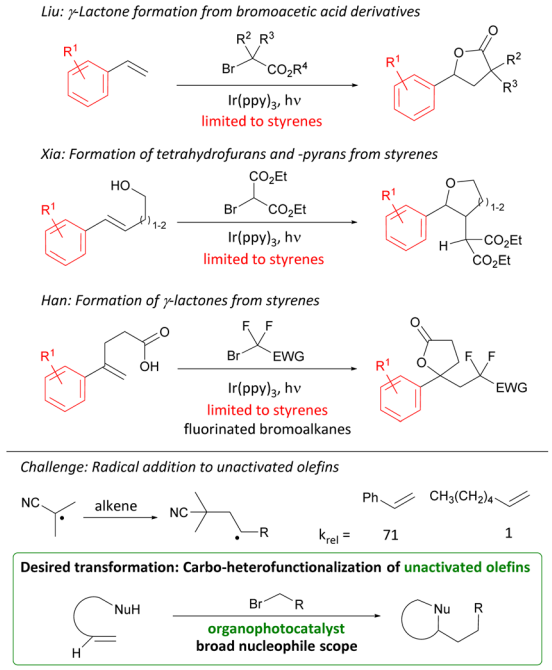


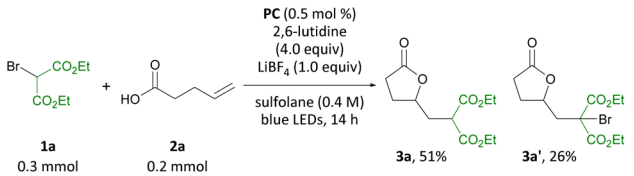
Scheme 2 Previous photocatalytic alkene difunctionalization reactions, challenge, and targeted transformation.

the rate of radical addition to styrenes *vs.* terminal olefins (Scheme 2).[11]

Results and discussion

Guided by our interest in olefin functionalizations and, more recently, organophotocatalysis, we examined pent-4-enoic acid as part of a study on olefin cyclopropanation reactions.[8d] When pent-4-enoic acid was subjected to blue-light irradiation in the presence of benzothiazinoquinoxaline catalyst **PC**, 2,6-lutidine, $LiBF_4$ and diethyl bromomalonate in sulfolane, no cyclopropane product was isolated. Instead, γ-lactone **3a** was isolated along with a second related product **3a′** (Scheme 3). Intrigued by this result, we set out to investigate the carbo-heterofunctionalization of unactivated olefins under organophotocatalytic conditions to access lactone **3a** and related products.

On the basis of our earlier mechanistic work, we hypothesize side product **3a′** is formed through bromide exchange between **3a** and excess bromomalonate **1a** in the presence of Li^+.[8d] Gratifyingly, in the absence of $LiBF_4$ under otherwise identical conditions formation of **3a′** was not observed, and **3a** was

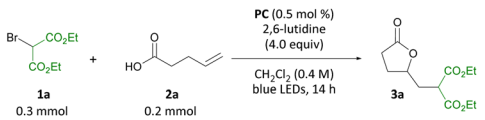


Scheme 3 Initial result.

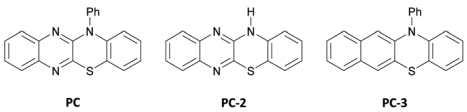
produced in 82% yield (Table 1, entry 2). Further optimization studies (see ESI†) revealed that a combination of 0.5 mol% **PC**, 4.0 equiv. 2,6-lutidine, and 1.5 equiv. diethyl bromomalonate in CH_2Cl_2 is optimal for the transformation reported (entry 3). Related photocatalysts **PC-2** and **PC-3** were also able to effect the transformation, albeit in lower yields (entries 4 and 5). In the absence of photocatalyst or light, no reaction was observed, and only 7% product were obtained in the absence of 2,6-lutidine (entries 6–8). No benefit was observed for the reaction carried out under argon atmosphere and in degassed, anhydrous solvent (entry 9). Indeed, an outstanding feature of this transformation is its air and moisture tolerance, which is in contrast to previous methods carried out under argon.[10a,c] An identical yield was obtained when the reaction was irradiated using a commercial Kessil light (see ESI†).

With the optimized conditions in hand, the substrate scope of the carbo-lactonization of pent-4-enoic acid was investigated (Scheme 4).[12] The transformation was amenable to a range of activated alkyl bromides. Acetoacetate derived γ-lactones **3b** to **3d** were accessed from the corresponding bromides **1b** to **1d** in 70–80% yield. Substituted α-bromo-β-ketoesters were also tolerated with Et and i-Pr derivatives **1e** and **1f** furnishing **3e** and **3f** in 84 and 85% yield, respectively. Phenethyl ketone **1g** provided lactone **3g** in 74% yield and *tert*-butyl ketone **1h** produced **3h** in 38% yield. The 1 : 1 d.r. observed in this transformation can be attributed to epimerization of C_α-H of the β-ketoester group, which we have previously shown to exchange in the presence of 2,6-lutidine.[8d] 3-Bromobutanone **1i** gave ketone **3i** in 66% yield. α-Bromo ethyl acetate and α-bromo acetonitrile were shown to be suitable coupling partners in the reaction giving access to ester **3j** and nitrile **3k** in 68 and 85% yield, respectively. A variety of substituted bromoacetophenones

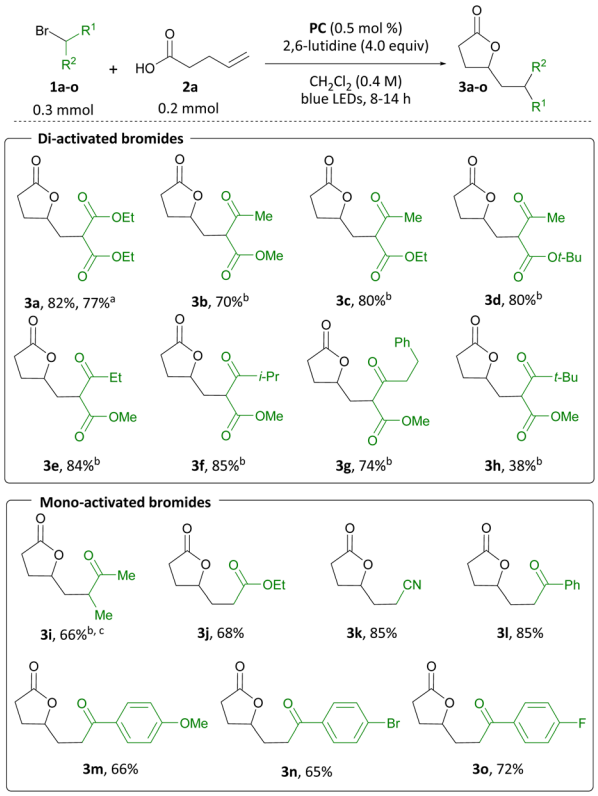
Table 1 Optimization of reaction conditions[a]



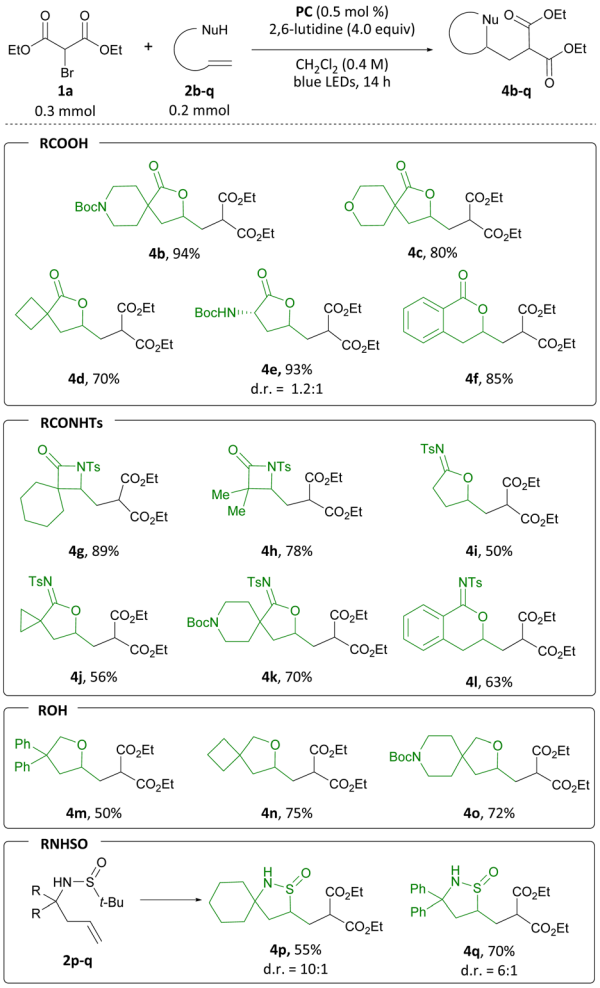
Entry	Change from standard conditions	Yield[b] (%)
1	Sulfolane instead of CH_2Cl_2 1.0 equiv. $LiBF_4$	51
2	Sulfolane instead of CH_2Cl_2	82
3	—	**93**
4	**PC-2**	80
5	**PC-3**	83
6	In the dark, 40 °C	0
7	Without photocatalyst	0
8	Without 2,6-lutidine	7
9	Under Ar; degassed, dry solvent	90



[a] Reaction temperature rises to 40 °C. [b] Yields obtained by ^1H NMR (1,3,5-mesitylene as internal standard).



Scheme 4 Substrate scope for the olefin difunctionalization of pent-4-enoic acid with activated alkyl bromides. [a]Reaction carried out on 2.00 mmol scale. [b]d.r. = 1 : 1 by ^{1}H NMR analysis of the unpurified reaction mixture. [c]1.00 mmol of bromide **1i** was used.



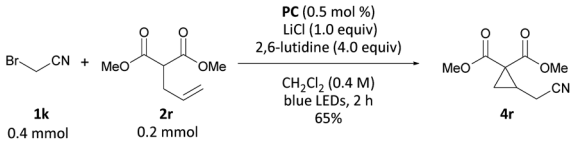
Scheme 5 Substrate scope for the olefin difunctionalization reaction with diethyl bromomalonate.

bearing electron-withdrawing and electron-donating aryl substituents were well tolerated and provided γ-lactones **3l–3o** in 65–85% yield. Thus, it was shown that in this system a single activating group suffices for the reaction to proceed. Finally, it was demonstrated that the reaction may also be carried out on 2.00 mmol scale in comparable yield (**3a** formed in 77% yield). Notably, the use of activated alkyl bromides in this transformation constitutes a valuable example of a bifunctional reagent in synthesis.[13]

Having established the feasibility and generality of the transformation with pent-4-enoic acid, we sought to expand the substrate scope to include more highly substituted carboxylic acids (Scheme 5). A range of α-substituted carboxylic acids were suitable for use in this transformation, furnishing *N*-Boc amine **4b**, spirocyclic ether **4c** and spiro[3.4]lactone **4d** in 94, 80, and 70% yield, respectively. *N*-Boc-protected amino acid **2e** produced **4e** in 93% yield and 1.2 : 1 d.r. Finally, δ-lactone **4f** was accessed from the corresponding carboxylic acid in 85% yield.

To broaden the range of heterocycles accessible through this transformation, we examined additional pendant nucleophiles. Guided by the similar pK_a of carboxylic acids and *N*-acyl sulfonamides, the latter were considered as nucleophiles in the difunctionalization reaction.[14] We examined β,γ-unsaturated *N*-acylsulfonamides first, and when **2g** was subjected to the reaction conditions, β-lactam **4g** was isolated in 89% yield. Analogously, β-lactam **4h** was produced from **2h** in 78% yield. When γ,δ- and δ,ε-unsaturated alkenyl *N*-acyl sulfonamides were employed, *N*-sulfonyl imidates **4i** to **4l** were formed in 50 to 70% yield. Aiming to probe whether this transformation was amenable to less acidic nucleophiles, we considered alcohols next.[15] To this end, tetrahydrofuran **4m** was produced in 50% yield from alcohol **2m**. Spirocyclic ethers **4n** and **4o** were accessed from **2n** and **2o** in 75% and 72% yield, respectively. Finally, inspired by Zhu's work on olefin sulfinylation employing CF_3 radicals,[16] we investigated sulfinamides as potential substrates. Gratifyingly, we could access two heterocyclic isothiazolidine *S*-oxides, **4p** and **4q**, in 55 and 70% yield, respectively. Derivatives of this class of heterocycles have found application in drug discovery research.[17]

Interested in whether this method could be extended to carbon nucleophiles, we subjected dimethyl allyl malonate to a combination of 0.5 mol% **PC**, 2.0 equiv. of bromoacetonitrile, 1.0 equiv. LiCl and 4.00 equiv. of 2,6-lutidine in CH_2Cl_2 under blue-light irradiation. Gratifyingly, formation of cyclopropane **4r** was observed in 65% yield (Scheme 6). LiCl was added to effect soft enolization of the malonate group.



Scheme 6 Reaction of dimethyl allyl malonate with bromoacetonitrile.

We set out to examine the mechanism of the transformation reported herein next (Scheme 7). To illuminate the photocatalytic part of the transformation, Stern–Volmer quenching studies were conducted, which revealed strong quenching of the photocatalyst excited state by bromides **1l** and **1a** (Scheme 7A and ESI†). Interestingly, weak Stern–Volmer quenching was also observed for carboxylic acid **2a**, however no quenching was observed for alcohol **2n** (see ESI†). Thus, we suggest that quenching of the photocatalyst by the carboxylic acid group in **2a** is inconsequential for the mechanism of this transformation.

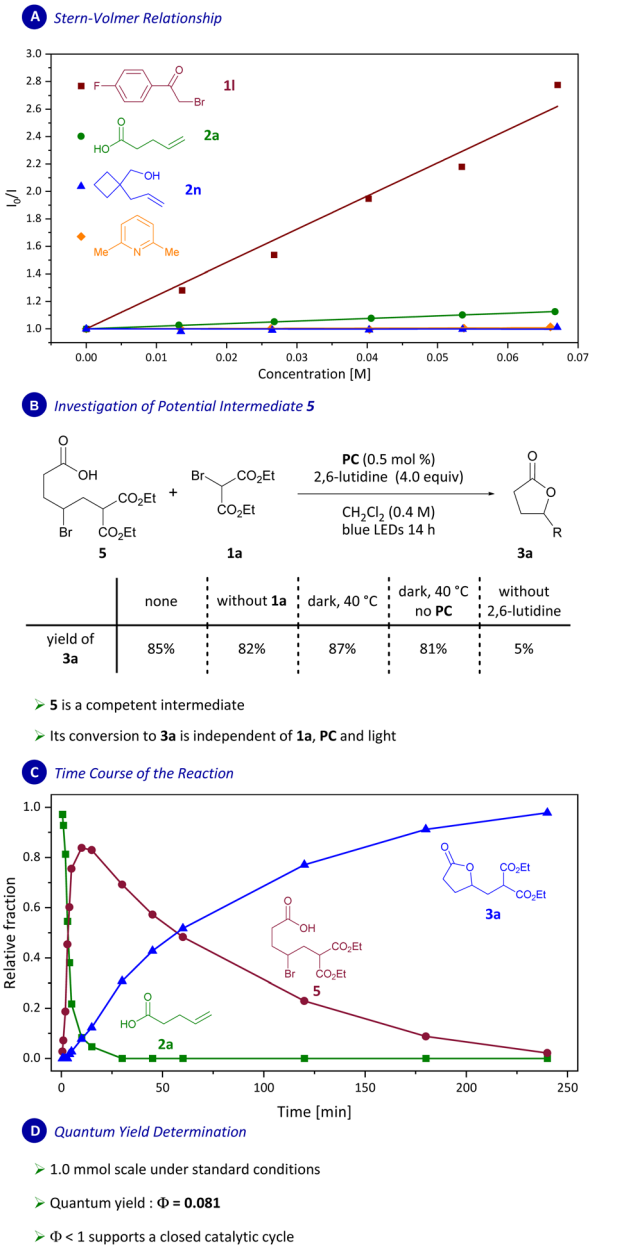
In difunctionalization reactions of styrenes catalyzed by $Ir(ppy)_3$ as photocatalyst, an intermediate benzylic carbocation has been speculated to directly undergo intramolecular trapping.[10a,b] Based on our previous work,[8d] we considered the feasibility of an additional pathway proceeding *via* an *n*-alkyl bromide intermediate. To distinguish between these two options, we designed a set of mechanistic experiments. Consequently, bromide **5** was independently synthesized to assess if it is an intermediate in the transformation reported herein (Scheme 7B and ESI†). When **5** was subjected to the reaction conditions (0.5 mol% **PC**, 4.0 equiv. 2,6-lutidine in CH_2Cl_2 under blue-light irradiation) product **3a** was formed in 85% yield as determined by analysis of ^{1}H NMR spectra (Scheme 7B).

We further demonstrated that the conversion of intermediate **5** to **3a** is independent of irradiation, photocatalyst or bromomalonate **1a** but relies on the presence of 2,6-lutidine. ^{13}C NMR experiments were carried out and are consistent with **2a** being predominantly present in its deprotonated form ($RCOO^-$) under the reaction conditions (4 equiv. of 2,6-lutidine). Thus, we show that **5** could be a relevant intermediate in a catalytic cycle.

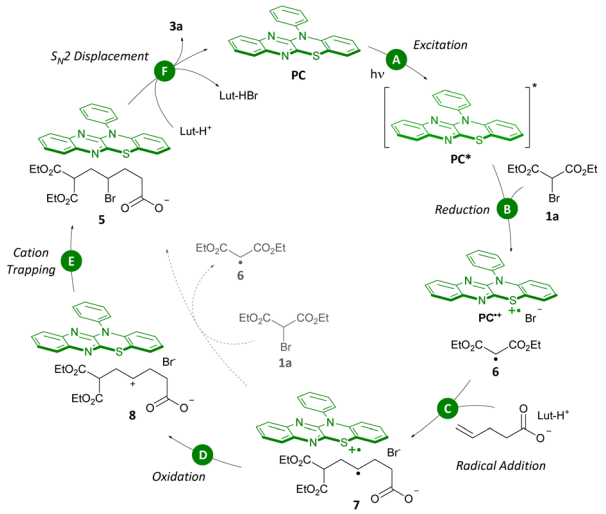
To determine if **5** is, in fact, a kinetically competent intermediate, time-series experiments were carried out next (Scheme 7C). In the experiments we observed rapid accumulation of a species early on ($t < 30$ min) which was then consumed during the remainder of the reaction time with concomitant formation of product **3a**. The initially formed species was isolated and identified as **5**, providing support for its role as an intermediate in this transformation.

Certain photocatalytic radical additions to olefins have been postulated to proceed *via* radical-chain mechanisms.[18] To distinguish between such a mechanism and one that involves a closed catalytic cycle, the quantum yield for the transformation was measured and determined as $\Phi = 0.081$ (Scheme 7D and ESI†). A low quantum yield of 8.1% supports a closed catalytic cycle and leads us to disfavor mechanisms involving a radical-chain process.[18,19]

Together, all of these experiments have guided us to propose a catalytic cycle (Scheme 8). At the outset, **PC** absorbs a photon in the blue-light range ($\lambda_{max,abs} = 420$ nm, Step A) leading to the photocatalyst in the excited state (**PC***). Reduction of bromomalonate **1a** by **PC*** forms a stabilized α-malonyl radical **6** (Step B).[8c,d,15] Radical addition to the unactivated olefin prefentially



Scheme 7 Mechanistic investigations: (A) Stern–Volmer relationship study between **PC** and reagents. (B) Reaction of putative intermediate **5** under reaction conditions and in the absence of light, photocatalyst, base or **1a**. Yields were determined by analysis of ^{1}H NMR spectra of the unpurified reaction mixture with 1,3,5-mesitylene as internal standard. R = $CH_2CH(CO_2Et)_2$. (C) Time course of the reaction (ratio determined by ^{1}H NMR). (D) Quantum yield determination.



Scheme 8 Proposed catalytic cycle. Lut = 2,6-lutidine.

takes place to furnish the more substituted, and thus more stable, secondary carbon radical **7** (Step C). Subsequent oxidation of **7** (ref. 20) by oxidized photocatalyst **PC**$^{\bullet+}$ leads to formation of secondary carbocation **8** which is trapped by Br^- (Steps D and E).[12,21] S_N2 displacement of the alkyl bromide in **5** by the pendant nucleophile leads to formation of product **3a** (Step F). It is worth noting that the accumulation of intermediate **5** identifies S_N2 displacement as the rate-determining step in the carbo-functionalization reaction.

Conclusion

We have developed a carbo-heterofunctionalization reaction of unactivated olefins under organophotocatalytic conditions. In addition to the formation of a new C–C bond, the transformation gives access to a variety of saturated heterocycles including tetrahydrofurans, lactones, and cyclic imidates, all displaying 1,4 functional group relationships. The method was then extended to include cyclization *via* nitrogen and sulfur groups to furnish products that feature β-lactams and isothiazolidine *S*-oxides. Mechanistic investigations were carried out, which identified key intermediates and the rate-determining step. In employing a benzothiazinoquinoxaline we highlight the utility of these photocatalysts. Investigations into further transformations unlocked by this class of catalysts may expand the synthetic toolkit and provide access to novel and exciting synthetic building blocks.

Data availability

Data supporting this article have been uploaded as ESI.†

Author contributions

D. M. F. and E. M. C. conceived the project. D. M. F., M. F., W. M. A., and H. L. conducted the investigations under supervision of E. M. C., D. M. F. and M. F. contributed equally. D. M. F., W. M. A., H. L., and E. M. C. wrote the manuscript. All authors contributed to the revision of the manuscript and have approved the final version.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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