Organic Letters

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Letter

Visible-Light-Enabled Paternò–Büchi Reaction via Triplet Energy Transfer for the Synthesis of Oxetanes

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02316

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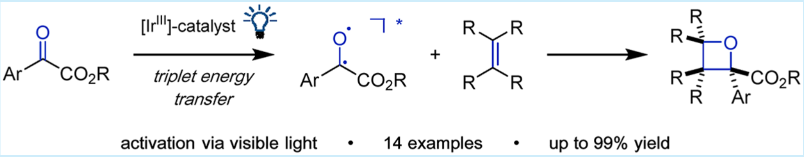


ABSTRACT: One of the most efficient ways to synthesize oxetanes is the light-enabled [2 + 2] cycloaddition reaction of carbonyls and alkenes, referred to as the Paternò–Büchi reaction. The reaction conditions for this transformation typically require the use of high energy UV light to excite the carbonyl, limiting the applications, safety, and scalability. We herein report the development of a visible-light-mediated Paternò–Büchi reaction protocol that relies on triplet energy transfer from an iridium-based photocatalyst to the carbonyl substrates. This mode of activation is demonstrated for a variety of aryl glyoxylates and negates the need for both visible-light-absorbing carbonyl starting materials and UV light to enable access to a variety of functionalized oxetanes in up to 99% yield.

Oxetanes are four-membered oxygen-containing heterocycles that have emerged as important scaffolds in drug design and development over the past decade. The incorporation of oxetanes into active pharmaceuticals is particularly attractive and was shown to have a positive impact on their physiochemical and biochemical properties.[1] Specifically, these four-membered heterocycles profoundly impact the aqueous solubility, lipophilicity, metabolic stability, and conformational preference of molecules, lending themselves as alternative scaffolds for geminal dimethyl substituents or carbonyl groups.[2] Several strategies for the synthesis of functionalized oxetanes have been advanced including intramolecular etherification via nucleophilic substitution (**1**),[3] epoxide ring opening and closing (**2**),[4] ring contraction of carbohydrates (**3**),[5] and electrophilic halocyclization of alcohols (**4**)[6] (Figure 1A). Arguably, while each of these methods offer unique benefits to oxetane synthesis, the direct light-induced [2 + 2] cycloaddition between carbonyls and alkenes (**5**) represents a highly efficient method and the most direct approach toward these heterocycles. These [2 + 2] cycloadditions are referred to as Paternò–Büchi reactions and allow for a variety of substitution about the heterocycle and a convergent synthesis, while requiring minimal prefunctionalization.[7]

Traditionally, the Paternò–Büchi reaction proceeds via an excitation of the carbonyl moiety (**6**) under UV light irradiation (**7**), which then engages from either the singlet or triplet excited state with an alkene (**8**) to form an oxetane (**9**) (Figure 1B). Recent advances in Paternò–Büchi reactions have lent themselves to the synthesis of new and structurally complex oxetanes, but still require the use of high-energy UV

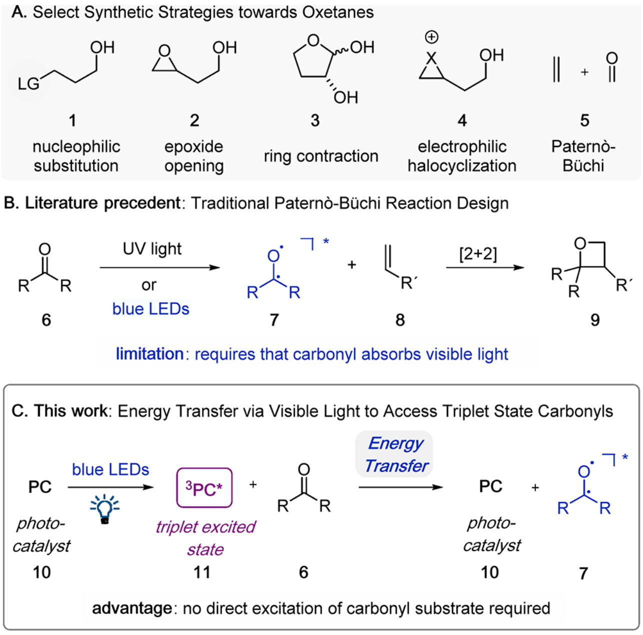


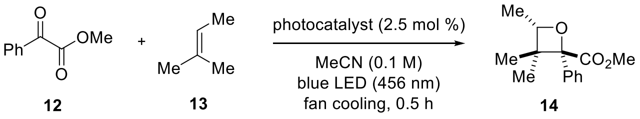
Figure 1. (A) Select strategies to access oxetanes. (B) Traditional Paternò–Büchi reaction design. (C) Proposed energy transfer mechanism for excitation of carbonyls.

Received: July 11, 2020

light.[7] This prerequisite for UV light is often associated with challenges in the scalability of these transformations and significant safety concerns due to possible UV radiation exposure. Despite these drawbacks, complementary visible-light-induced processes are significantly less advanced, although the milder reaction conditions are expected to significantly increase the functional group tolerance, scalability, and safety of these Paternò−Büchi reactions. Importantly, two successful examples of these [2 + 2] cycloadditions relying on visible light irradiation have recently been reported by the groups of Dell'Amico and Ouyang.[8,9]

Although an important advancement, these reactions are inherently limited to starting materials that exhibit the required photophysical features for direct excitation (Figure 1B). We envisioned that a potentially more general synthetic approach to visible-light-enabled Paternò−Büchi reactions could rely on utilizing a photocatalyst (**10**) to be the primary excited state species in solution to ultimately generate the desired excited state carbonyl (**7**) via triplet energy transfer (Figure 1C). In related efforts, our lab has recently demonstrated that triplet energy transfer can efficiently activate functionalized imines to enable the synthesis of similarly strained four-membered nitrogen-containing heterocycles in aza Paternò−Büchi reactions.[10] This transformation relies on a visible-light-absorbing iridium photocatalyst to access the corresponding excited state of the substrate via triplet energy transfer. We envisioned a similar design principle to be applicable to carbonyl activation in a visible-light enabled Paternò−Büchi reaction protocol.[11] In this reaction platform, the photocatalyst (**10**) is expected to absorb visible light, resulting in population of the triplet excited state (**11**), followed by subsequent energy transfer to the carbonyl (**6**), producing the reactive triplet energy state (**7**) allowing for efficient Paternò−Büchi reactions (Figure 1C). Importantly, this mode of activation negates the need for visible-light-absorbing carbonyls, instead requiring that their triplet energy (E_T) lies close enough to that of the photocatalyst. Based on their low triplet energy (approximately 60 kcal mol^{-1}), we hypothesized that glyoxylate derivatives could be a good starting point for the development of a visible-light-enabled Paternò−Büchi reaction relying on triplet energy transfer.[12]

Our initial investigations into the development of a mild protocol for visible-light-enabled Paternò−Büchi reactions was focused on methyl benzoylformate (**12**), due to its superior stability compared to other glyoxylate substrates. Specifically, Norrish type II reactivity is a known competing reaction path for glyoxylate substrates under irradiation with UV light (see Supporting Information for details).[13] When glyoxylate **12** and alkene **13** were converted with catalytic amounts of [Ir(dF(Me)ppy)$_2$(dtbbpy)]PF$_6$ upon irradiation with 456 nm light in acetonitrile for 0.5 h, the formation of oxetane **14** was observed in 72% yield (entry 1, Figure 2). A selection of photocatalysts varying in their triplet energies was subsequently evaluated (entries 2−6, Figure 2). Ultimately, photocatalyst **15** was identified as optimal due to its established reactivity and high yield of oxetane **14** (entry 2, Figure 2), while photocatalysts of similar triplet energies compared to **15** were found equally sufficient in catalyzing the transformation. Importantly, catalysts of lower triplet energy failed to provide the desired oxetane product **14**, which is consistent with a reaction mechanism relying on an energy transfer mechanism (entries 4−6, Figure 2). Subsequent efforts focused on additional reaction optimization, including varying the solvent, catalyst loading, and alkene equivalents (see Supporting Information for additional details). The reaction was determined to proceed in good yields of up to 75% relying on 1,2-dichloroethane, methylene chloride, acetone, toluene, ethyl acetate, methanol, and acetonitrile as reaction solvent. Catalyst loadings as low as 0.5 mol % of **15** and equimolar amounts of alkene **13** proved to be sufficient in forming oxetane **14** in up to 70% yield.



Entry	Photocatalyst	E_T (kcal mol^{-1})	Yield (%)[a]
1	[Ir(dF(Me)ppy)$_2$(dtbbpy)]PF$_6$	60.2	72
2	[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (**15**)	60.1	73
3	[Ir(dFppy)$_2$(dtbbpy)]PF$_6$	57.1	75
4	[Ir(Fppy)$_2$(dtbbpy)]PF$_6$	53.3	41
5	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	49.2	4
6	[Ru(bpy)$_3$](PF$_6$)$_2$	46.9	0

Figure 2. Evaluation of photocatalysts in visible-light-enabled Paternò−Büchi reactions. Reactions were performed with **12** (0.05 mmol), alkene **13** (10 equiv), and photocatalyst (2.5 mol %) in MeCN (0.1 M) under blue LED irradiation (465 nm) at ambient temperature (fan cooling) for 0.5 h. [a]Yield determined by quantitative ^{1}H NMR analysis from the crude mixture using an internal standard.

Next, we set out to investigate the scope of this visible-light-enabled Paternò−Büchi reaction (Figure 3). Specifically, a variety of aryl glyoxylates and different alkene reaction partners were investigated upon their ability to undergo the desired transformation. Methyl, ethyl, adamantyl, and *tert*-butyl esters all provided good to excellent yields of oxetanes **16**−**19** of up to 99%. Interestingly, direct irradiation of ethyl benzoylformate without photocatalyst or alkene showed complete decomposition. We were pleased to see that, under our standard conditions, rapid conversion to oxetane **17** was observed (see Supporting Information for details). Additionally, both electron-donating and -withdrawing groups on the aromatic ring resulted in the formation of the desired oxetane products. The anisole derivative **21** was obtained in 72% yield, while the electron-withdrawing *para*-nitrile provided oxetane **20** in 66% yield. Interestingly, an additional ester present on the aromatic ring was tolerated under the optimal reaction conditions as shown in the formation of oxetane **22** in 91% yield. Furthermore, the *para*-bromo aromatic glyoxylate was evaluated and proceeded in 77% yield to result in oxetane **23**. Further efforts centered on the investigation of alkene reaction partners showed that di-, tri-, and tetrasubstituted alkenes undergo the desired transformation providing oxetanes **14** and **24**−**28** in yields ranging from 46% to 83%. Specifically, cyclohexene as an alkene partner successfully formed the bicyclic oxetane **25** in a good yield of 65%. Moreover, aromatic alkenes like benzofuran and furan gave the cycloadducts **26** and **27** in 64% and 46% yield, respectively. Additionally, an acyclic vinyl ether was able to provide oxetane **28** in 68% yield.

Mechanistic investigations were subsequently initiated to gain additional insights into the controlling features of this visible-light-enabled Paternò−Büchi reaction. Specifically, we were interested in investigating the difference between a possible direct excitation of the carbonyl and our proposed triplet energy transfer process. When glyoxylate **12** and alkene **13** were irradiated with UV-A light, the formation of oxetane

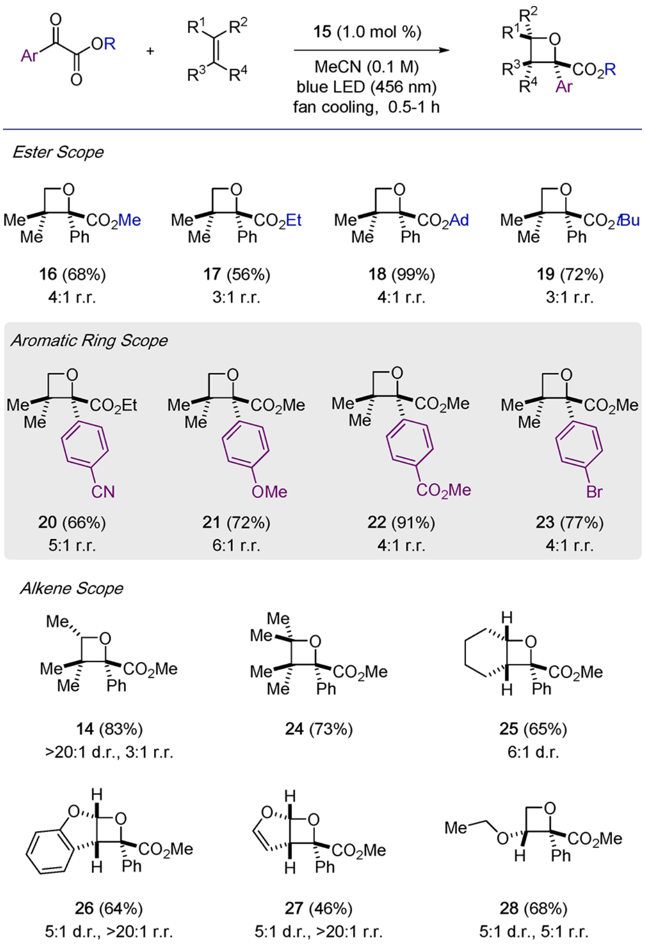
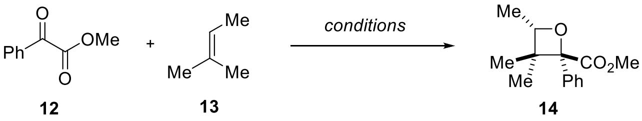


Figure 3. Evaluation of the substrate scope of visible-light-enabled Paternò–Büchi reactions. Reactions were performed with glyoxylate substrate (0.1 mmol), alkene (1.5 equiv), and **15** (1.0 mol %) in MeCN (0.1 M) under blue LED irradiation (456 nm) at ambient temperature (fan cooling) for 0.5–1 h; diastereomer ratios (d.r.) and regioisomer ratios (r.r.) were determined by ^{1}H NMR analysis of the crude reaction mixture; isolated yields provided.

14 was observed in 25% yield after 0.5 h (entry 1, Figure 4). We also tried directly irradiating the glyoxylate substrate **12** with visible light; however, at 456 nm, no product formation was observed within 0.5 h of irradiation (entry 2, Figure 4). After 16 h at 456 nm, a 25% yield of oxetane **14** was observed (entry 3, Figure 4). Upon heating **12** and **13**, without photocatalyst and light no reactivity was observed (entry 5, Figure 4). These results suggest that the reactivity observed under our optimal reaction conditions (entry 4, Figure 4) does not stem from direct excitation of the carbonyl, and instead indicate that the photocatalyst has a significant impact on the reactivity by greatly accelerating the desired transformation. Demonstration of this reactivity suggests that other carbonyls which do not absorb visible light will be able to be sensitized with visible light in combination with a suitable photocatalyst, given that the triplet energy is low enough for an energetically favorable energy transfer process. Furthermore, a Stern–Volmer quenching study was completed which showed a quenching interaction between glyoxylate **12** and photocatalyst (**15**) (see Supporting Information for details). We postulate that a photoredox process is unlikely under the optimized reaction conditions, as the excited state redox potentials of **15** ($\mathrm{Ir}^{\mathrm{III}*/\mathrm{II}}$ = +1.21 V versus SCE; Ir $^{\mathrm{IV}/\mathrm{III}*}$ = −0.89 V versus SCE) are not expected to be sufficient for an effective oxidation or reduction of glyoxylate **12** (E_{red} = −1.16 V versus SCE; E_{red} = −1.75 V versus SCE; see Supporting Information for additional details).[14]

Based on these combined results, we propose a triplet energy transfer mechanism to be operative under our optimal reaction conditions for Paternò–Büchi reactions in which the carbonyl triplet state (^{3}**12***) is accessible via energy transfer from an excited state photocatalyst (Figure 5). The observed regioselectivity indicates the *C–O* bond formation occurs first to give the stabilized biradical, which can then recombine to form the oxetane product **14**.



Entry	Photocatalyst	Wavelength (nm)	Time (h)	Yield (%)[a]
1	no photocatalyst	365	0.5	25
2	no photocatalyst	456	0.5	<5
3	no photocatalyst	456	16	25
4	photocatalyst (**15**)	456	0.5	73
5	no photocatalyst	dark (50 °C)	16	<5

Figure 4. Mechanistic control experiments of visible-light-enabled Paternò–Büchi reactions. Reactions were performed with **12** (0.05 mmol), alkene **13** (10 equiv), and if indicated photocatalyst (2.5 mol %) in MeCN (0.1 M) under blue LED (465 nm) or UV-A (365 nm) irradiation at ambient temperature (fan cooling) for 0.5–16 h. [a]Yield determined by quantitative ^{1}H NMR analysis from the crude mixture using an internal standard.

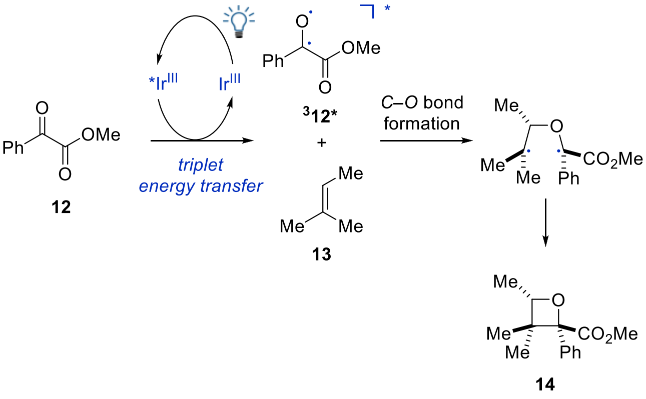


Figure 5. Proposed triplet energy transfer mechanism for the synthesis of oxetane **14**.

We herein report the development of a visible-light-mediated Paternò–Büchi reaction between carbonyls and alkenes relying on triplet energy transfer. Importantly, the reaction is greatly accelerated in the presence of a suitable photocatalyst and demonstrates the capability of visible-light-absorbing photocatalysts to efficiently transfer energy to carbonyls. This reaction platform further expands the toolbox for medicinal chemists interested in modulating drug properties through the incorporation of functionalized oxetanes, as this method negates the need for UV light and proceeds rapidly under the optimized reaction conditions.

https://dx.doi.org/10.1021/acs.orglett.0c02316

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02316.

Experimental details and spectroscopic data for all new reactants and products (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the University of Michigan Office of Research and the NIH/National Institute of General Medical Sciences (R01-GM118644) for financial support. C.S.S. thanks the David and Lucile Packard Foundation, the Alfred P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation. K.A.R. thanks the National Science Foundation for a Graduate Research Fellowship.

REFERENCES

(1) Bull, J. A.; Davis, O. A.; Doran, R.; Morgan, K. F. Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry. *Chem. Rev.* **2016**, *116*, 12150−12233.

(2) (a) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. Oxetanes in Drug Discovery: Structural and Synthetic Insights. *J. Med. Chem.* **2010**, *53*, 3227−3246. (b) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. Oxetanes as Versatile Elements in Drug Discovery and Synthesis. *Angew. Chem. Int. Ed.* **2010**, *49*, 9052−9067.

(3) For examples of intramolecular etherification: (a) Picard, P.; Leclercq, D.; Bats, J.-P.; Moulines, J. An Efficient One-Pot Synthesis of Oxetanes from 1,3-Diols. *Synthesis* **1981**, 550−551. (b) Servrin, M.; Krief, A. Regioselective and [C,C] Connective Routes to Oxetane and Tetrahydrofuranes. *Tetrahedron Lett.* **1980**, *21*, 585−586.

(4) For examples of epoxide opening and closing: Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. Reaction of Dimethyloxosulfonium Methylide with Epoxides. Preparation of Oxetanes. *J. Org. Chem.* **1983**, *48*, 5133−5134.

(5) For examples of carbohydrate contraction: (a) Jenkinson, S. F.; Fleet, G. W. J. Oxetanes from the Ring Contraction of α-Triflates from γ-Lactones: Oxetane Nucleosides and Oxetane Amino Acids. *Chimia* **2011**, *65*, 71−75. (b) Austin, G. N.; Fleet, G. W. J.; Peach, J. M.; Prout, K.; Son, J. C. Chiral Oxetanes from Sugar Lactones: Synthesis of Derivatives of 3,5-Anhydro-1,2-O-Isopropylidine-α-D-Glucuronic Acid and of 3,5-Anhydro-1,2-O-Isopropylidine-β-L-Iduronic Acid. *Tetrahedron Lett.* **1987**, *28*, 4741−4744.

(6) For examples of halocyclization: (a) Ehlinger, E.; Magnus, P. Silicon in Synthesis. 10. The (Trimethylsilyl)allyl Anion: A β-Acyl Anion Equivalent for the Conversion of Aldehydes and Ketones into γ-Lactones. *J. Am. Chem. Soc.* **1980**, *102*, 5004−5011. (b) Manabe, S.; Nishino, C. Stereochemistry of cis-Clerodane Diterpenes. *Tetrahedron* **1986**, *42*, 3461−3470.

(7) Paternò−Büchi: (a) Paternò, E.; Chieffi, G. Synthesis in Organic Chemistry Using Light. Note II. Compounds of Unsaturated Hydrocarbons with Aldehydes and Ketones. *Gazz. Chim. Ital.* **1909**, *39*, 341. (b) Büchi, G.; Inman, C. G.; Lipinsky, E. S. Light-Catalyzed Organic Reactions. I. The Reaction of Carbonyl Compounds with 2-methyl-2-butene in the Presence of Ultraviolet Light. *J. Am. Chem. Soc.* **1954**, *76*, 4327. (c) Bach, T. Stereoselective Intermolecular [2 + 2]-Photocycloaddition Reactions and Their Application in Synthesis. *Synthesis* **1998**, *1998*, 683−703. (d) Abe, M. Recent Progress Regarding Regio-, Site-, and Stereoselective Formation of Oxetanes in Paterno-Buchi Reactions. *J. Chin. Chem. Soc.* **2008**, *55*, 479−486. (e) D'Auria, M.; Racioppi, R. Oxetane Synthesis Through the Paternò-Büchi Reaction. *Molecules* **2013**, *18*, 11384−11428.

(8) Mateos, J.; Vega-Peñaloza, A.; Franceschi, P.; Rigodanza, F.; Andreetta, P.; Companyó, X.; Pelosi, G.; Bonchio, M.; Dell'Amico, L. A Visible-Light Paternò-Büchi Dearomatisation Process Towards the Construction of Oxeto-Indolic Polycycles. *Chem. Sci.* **2020**, *11*, 6532−6538.

(9) Li, H. F.; Cao, W.; Ma, X.; Xie, X.; Xia, Y.; Ouyang, Z. Visible-Light-Driven [2 + 2] Photocycloadditions between Benzophenone and C═C Bonds in Unsaturated Lipids. *J. Am. Chem. Soc.* **2020**, *142*, 3499−3505.

(10) (a) Becker, M. R.; Richardson, A. D.; Schindler, C. S. Functionalized Azetidines Via Visible Light-Enabled Aza Paternò-Büchi Reactions. *Nat. Commun.* **2019**, *10*, 5095. (b) Becker, M. R.; Wearing, E. R.; Schindler, C. S. Synthesis of Azetidines via Visible Light-Mediated Intermolecular [2 + 2] Photocycloaddition. *ChemRxiv* **2020**, DOI: 10.26434/chemrxiv.11832993.v1.

(11) Previously published preprint: Rykaczewski, K. A.; Schindler, C. S. Visible Light-Enabled Paternò−Büchi Reaction via Triplet Energy Transfer for the Synthesis of Oxetanes. *ChemRxiv. Preprint.* **2020**, DOI: 10.26434/chemrxiv.12606377.v2.

(12) Herkstroeter, W. G.; Lamola, A. A.; Hammond, G. S. Mechanisms of Photochemical Reactions in Solution. XXVIII. Values of Triplet Excitation Energies of Selected Sensitizers. *J. Am. Chem. Soc.* **1964**, *86*, 4537−4540.

(13) (a) Hu, S.; Neckers, D. C. Rapid Regio- and Diastereoselective Paternò-Büchi Reaction of Alkyl Phenylglyoxylates. *J. Org. Chem.* **1997**, *62*, 564−567. (b) Hu, S.; Neckers, D. C. Photochemical Reactions of Alkenyl Phenylglyoxylates. *J. Org. Chem.* **1997**, *62*, 6820−6826. (c) Hu, S.; Neckers, D. C. Photochemical Reactions of Alkyl Phenylglyoxylates. *J. Org. Chem.* **1996**, *61*, 6407−6415.

(14) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. Advances in Photocatalysis: A Microreview of Visible Light Mediated Ruthenium and Iridium Catalyzed Organic Transformations. *Org. Process Res. Dev.* **2016**, *20*, 1156−1163.