

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

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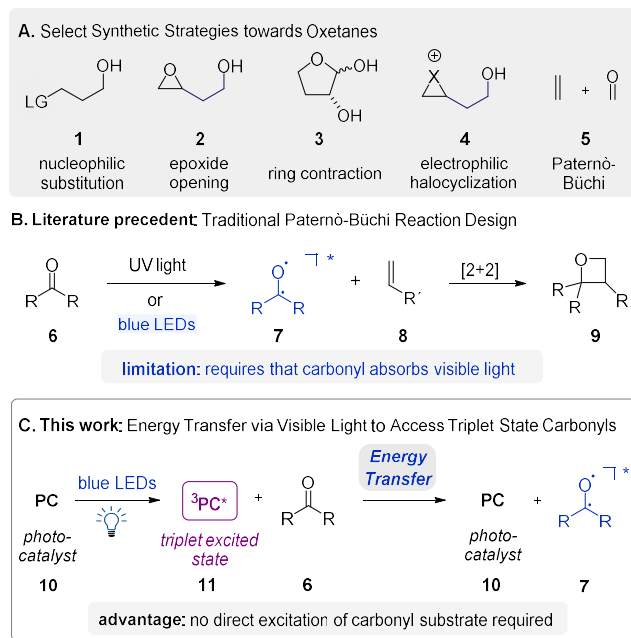
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Supporting Information Placeholder

**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 or 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 physicochemical and biochemical properties.<sup>1</sup> 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.<sup>2</sup> Several strategies for the synthesis of functionalized oxetanes have been advanced including intramolecular etherification via nucleophilic substitution (1)<sup>3</sup>, epoxide ring opening and closing (2)<sup>4</sup>, ring contraction of carbohydrates (3)<sup>5</sup>, and electrophilic halocyclization of alcohols (4)<sup>6</sup> (Fig. 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 towards 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.<sup>7</sup>

Traditionally, the Paternò-Büchi reaction proceeds via an excitation of the carbonyl moiety (6) under UV-light irradiation to subsequently engage with an alkene from the singlet or triplet excited state (7), which then engages with an alkene (8) to form oxetane 9 (Fig. 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-light.<sup>7</sup> 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

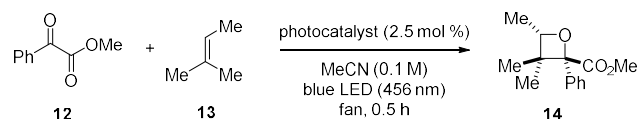


**Figure 1.** A. Select strategies to access oxetanes. B. Traditional Paternò-Büchi reaction design. C. Proposed energy transfer mechanism for excitation of carbonyls.

conditions are expected to significantly increase 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.<sup>8-9</sup>

Although an important advancement, these reactions are typically dependent on substrates such as benzophenones and dicarbonyls, which absorb light in the near-UV or visible light region. Consequently, this approach is inherently limited to starting materials that incorporate either of the required photophysical features (Fig. 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 (Fig. 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.<sup>10</sup> This transformation relies on a visible light-absorbing iridium photocatalyst to access the corresponding excited state of the substrate via triplet energy transfer, which cannot undergo direct excitation with visible light. We envisioned a similar reaction design principle to be applicable to carbonyl activation in a visible-light enabled Paternò-Büchi reaction protocol. In this reaction platform, the photocatalyst (**10**) is expected to absorb visible light and undergo excitation to its triplet state (**11**), while subsequent energy transfer to the carbonyl (**6**) will attain the reactive triplet energy state (**7**) required for efficient Paternò-Büchi reactions (Fig. 1C). Importantly, this mode of activation negates the need for visible light absorbing carbonyls, albeit requiring that their triplet energy lies close enough to that of the photocatalyst. Based on their low triplet energy (approximately 60 kcal mol<sup>-1</sup>), we hypothesized that glyoxylate derivatives could be a good starting point for the development of a visible light-enabled Paternò-Büchi reaction relying on energy transfer.<sup>11</sup>



Entry	Photocatalyst	$E_T$ (kcal mol <sup>-1</sup> )	Yield (%) <sup>a</sup>
1	[Ir(dF(Me)ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	60.2	72
2	[Ir(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub> ( <b>15</b> )	60.1	73
3	[Ir(dFppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	57.1	75
4	[Ir(Fppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	53.3	41
5	[Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	49.2	4
6	[Ru(bpy) <sub>3</sub> ](PF <sub>6</sub> ) <sub>2</sub>	46.9	0

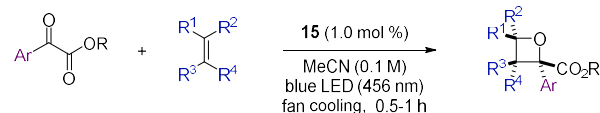
**Conditions:** Reactions were performed with **12** (0.05 mmol), alkene **13** (10 equiv.), and photocatalyst (2.5 mol %) in MeCN (0.1 M) under blue LED irradiation (456 nm) at ambient temperature (fan cooling) for 0.5 h. <sup>a</sup>Yield determined by quantitative <sup>1</sup>H NMR analysis from the crude mixture using an internal standard.

**Table 1.** Evaluation of photocatalysts in visible light-enabled Paternò-Büchi reactions.

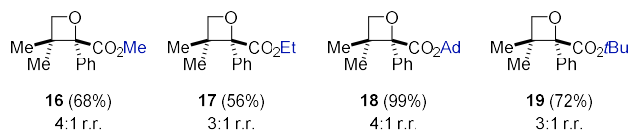
Our initial investigations into the development of a mild protocol for visible light-enabled Paternò-Büchi reactions was focused on methyl benzoylformate (**12**), due to its superior stability compared to other glyoxylate substrates. Specifically, Norrish type II reactivity is a known competing reaction path for glyoxylate substrates under irradiation with UV-light (see Supporting Information for details).<sup>12</sup> When glyoxylate **12** and alkene **13** were converted with catalytic amounts of [Ir(dF(Me)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> upon irradiation with 456 nm light in acetonitrile for 30 minutes, the formation of oxetane **14** was observed in 72% yield (entry 1, Table 1). A selection of photocatalysts varying in their triplet energies was subsequently evaluated (entries 2-6, Table 1). Ultimately, photocatalyst **15** was identified as optimal due to its commercial availability and high yield of oxetane **14** observed (entry 2, Table 1), while photocatalysts of similar triplet energies compared to **15** were found equally sufficient in catalyzing the transformation.

Importantly, catalysts of lower triplet energy ( $E_T$ ) failed to provide the desired oxetane product **14**, which is consistent with a reaction mechanism relying on an energy transfer mechanism (entries 4-6, Table 1). 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.

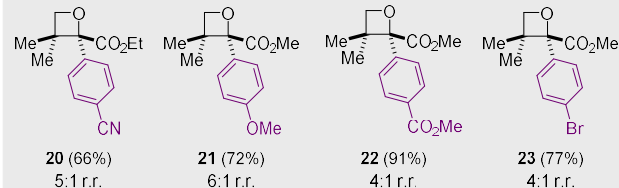
Next, we set out to investigate the scope of this visible light-enabled Paternò-Büchi reaction (Table 2). Specifically, a variety of aryl glyoxylates and different alkene reaction partners were investigated upon their ability to undergo the desired transformation. Methyl, ethyl, adamantyl, and *tert*-butyl esters all provided good to excellent yields of oxetanes **16-19**



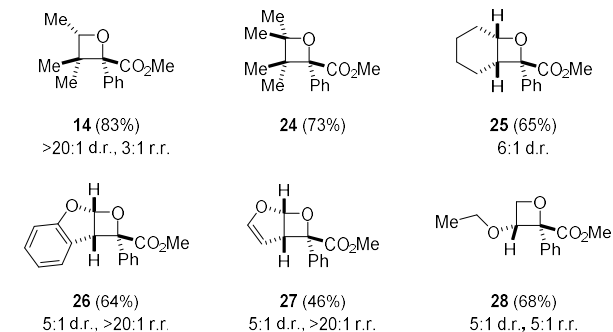
#### Ester Scope



#### Aromatic Ring Scope



#### Alkene Scope

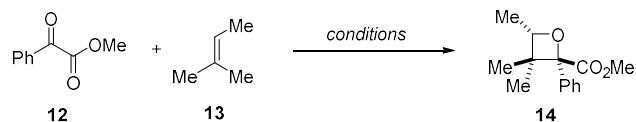


**Conditions:** Reactions were performed with glyoxylate substrate (0.1 mmol), alkene (1.5 equiv.), and **15** (1.0 mol %) in MeCN (0.1 M) under blue LED irradiation (456 nm) at ambient temperature (fan cooling) for 0.5-1 h; diastereomer ratios (d.r.) and regioisomer ratios (r.r.) were determined by <sup>1</sup>H NMR analysis of the crude reaction mixture; isolated yields provided.

**Table 2.** Evaluation of the substrate scope of visible light-enabled Paternò-Büchi reactions.

of up to 99%. Additionally, both electron-donating groups and electron-withdrawing groups on the aromatic ring result 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 and showed that di-, tri-, and tetrasubstituted aliphatic alkenes undergo the desired transformation providing oxetanes **14** and **24–28** in yields ranging from 46–83%. Specifically, cyclohexene as an alkene partner successfully formed the bicyclic oxetane **25** in 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.



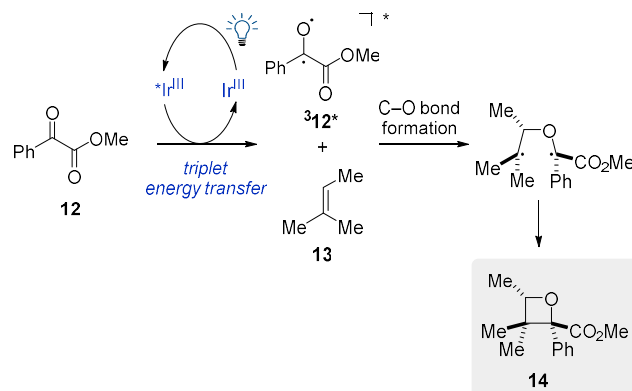
Entry	Photocatalyst	Wavelength (nm)	Time (h)	Yield (%) <sup>a</sup>
1	no photocatalyst	365	0.5	25
2	no photocatalyst	456	0.5	<5
3	no photocatalyst	456	16	25
4	photocatalyst ( <b>15</b> )	456	0.5	73
5	no photocatalyst	dark (50 °C)	16	<5

**Conditions:** Reactions were performed with **12** (0.05 mmol), alkene **13** (10 equiv.), and if indicated photocatalyst **15** (0.25 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. <sup>a</sup>Yield determined by quantitative <sup>1</sup>H NMR analysis from the crude mixture using an internal standard.

**Table 3.** Mechanistic control experiments of visible light-enabled Paternò-Büchi reactions.

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 **14** was observed in 25% yield after 0.5 hours (entry 1, Table 3). We also tried directly irradiating the glyoxylate substrate **12** with visible light, however at 456 nm, no product formation was observed within 3 hours of irradiation. After 16 h at 456 nm, 25% yield of oxetane **14** was observed (entry 2, Table 3). Upon heating **12** and **13**, without photocatalyst and light no reactivity was observed (entry 5, Table 3). These results suggest that the reactivity observed under our optimal reaction conditions (entry 4, Table 3), is not stemming from direct excitation of the carbonyl, and instead indicates 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, although a low triplet energy is required. Furthermore, a Stern-Volmer quenching study unambiguously showed that glyoxylate **12** productively quenches the 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** ( $\text{Ir}^{\text{III}/\text{II}} = +1.21$  V versus SCE;  $\text{Ir}^{\text{IV}/\text{III}} = -0.89$  V versus SCE) are not expected to be sufficient for an effective oxidation or reduction of glyoxylate **12** ( $E_{\text{red}} = -1.16$  V versus SCE;  $E_{\text{red}} = -1.75$  V versus SCE, see Supporting Information for additional details).<sup>13</sup> 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 is accessible via energy transfer from an excited state photocatalyst (Figure 2).



**Figure 2.** 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.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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

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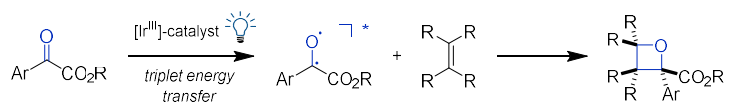
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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activation via visible light • 14 examples • up to 99% yield

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