

## Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions

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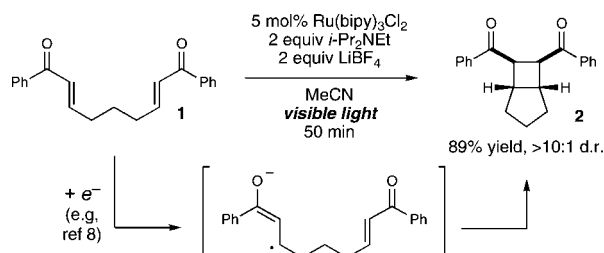
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As early as 1912,<sup>1</sup> Ciamician recognized that light had the potential to serve as an inexpensive, abundant, renewable, and nonpolluting reagent for chemical synthesis. But despite the interest of the increasingly environmentally conscious chemical community,<sup>2</sup> photochemical syntheses have enjoyed only limited application on industrial scales.<sup>3</sup> One fundamental obstacle is the inability of most common organic molecules to absorb the wavelengths of visible light that are most abundant in the solar spectrum. Efficient organic photochemical reactions typically require high-intensity UV light generated in specialized photoreactors, which limits their scalability and compromises the benefits of utilizing direct solar radiation. Thus, the development of new strategies for efficient visible light photocatalysis of synthetic transformations is a particularly important goal.

Research aimed at harnessing solar energy to address global energy needs has benefited from the rich visible light photochemistry of many inorganic and organometallic compounds.<sup>4</sup> In particular, the photochemistry of Ru(bipy)<sub>3</sub><sup>2+</sup> has been especially well studied.<sup>5</sup> Irradiation of this chromophore with visible light ( $\lambda_{\text{max}} = 452 \text{ nm}$ ) produces a photoexcited state (Ru(bipy)<sub>3</sub><sup>2+\*</sup>) that is a powerful photoredox catalyst capable of either oxidizing or reducing a variety of organic and inorganic quenchers. Given the relatively long lifetime of this photoexcited state ( $\sim 600 \text{ ns}$ ), the high quantum efficiency of its formation, and the exceptional chemical stability of its ground-state precursors, derivatives of Ru(bipy)<sub>3</sub><sup>2+</sup> have been extensively exploited in the design of systems for the conversion of solar energy, either directly into electrical current or into fuel by photoreduction of water and CO<sub>2</sub>.<sup>5a</sup> Nevertheless, only a few examples of synthetically useful transformations catalyzed by Ru(bipy)<sub>3</sub><sup>2+</sup> have been reported to date.<sup>6,7</sup>

We elected to study the [2+2] cycloaddition of bis(enone) **1** as an initial goal for our investigations into visible light photocatalysis (Scheme 1). Krische has reported that cobalt<sup>8a,b</sup> and copper<sup>8c</sup> catalyzed [2+2] cyclizations of bis(enones) are initiated by one-electron reduction of the enone. The intermediacy of a radical anion in these processes is corroborated by the formation of identical [2+2] cycloadducts upon cathodic<sup>8d</sup> and homogeneous<sup>8c</sup> one-electron reduction. We speculated that a photoreductant generated by irradiation of Ru(bipy)<sub>3</sub><sup>2+</sup> could also initiate the desired cycloaddition.

## Scheme 1

Table 1. Visible Light Photocatalysis of Enone Cycloadditions<sup>a</sup>

entry <sup>a</sup>	substrate	cycloadduct	time	yield <sup>b</sup>	dr <sup>b</sup>
1	R = Ph		50 min	89%	>10:1
2	R = 4-MeOPh		20 min	98%	10:1
3	R = 4-ClPh		10 min	96%	>10:1
4	R = 2-furyl		30 min	89%	>10:1
5	R = Me		22 h	0%	--
6	R = OEt		17 h	0%	--
7	X = O		10 min	90%	5:1
8	X = CMe <sub>2</sub>		10 min	68%	4:1
9			2 h	54%	6:1
10	R = Me		75 min	85%	>10:1
11	R = OEt		45 min	88%	>10:1
12	R = NEt <sub>2</sub>		30 min	74%	>10:1
13			1 h	84%	10:1
14 <sup>c</sup>	R = Ph		2 h	82%	>10:1
15 <sup>c</sup>	R = 4-ClPh		1 h	93%	>10:1

<sup>a</sup> Reactions conducted using Ru(bipy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O (5 mol%), LiBF<sub>4</sub> (2 equiv), and *i*-Pr<sub>2</sub>NEt (2 equiv) in degassed MeCN (0.1 M) under irradiation by a 275 W floodlight at a distance of 20 cm. <sup>b</sup> Isolated yields and diastereomer ratios are averaged from two reproducible experiments. <sup>c</sup> Molar ratios for intermolecular dimerizations calculated with respect to theoretical yield of product (e.g., 2.5 mol% catalyst with respect to enone).

To our delight, we found that bis(enone) **1** undergoes efficient cyclization upon visible light irradiation using 5 mol% Ru(bipy)<sub>3</sub>Cl<sub>2</sub> with LiBF<sub>4</sub> and *i*-Pr<sub>2</sub>NEt as additives (Scheme 1). The *meso* diastereomer of cyclobutane-containing bicyclic dione **2** is produced with excellent stereoselectivity. Importantly, the light source used in this procedure is a standard 275 W floodlight; no specialized high-pressure UV photolysis apparatus is required.

Table 1 summarizes experiments probing the [2+2] cycloadditions of a series of structurally varied enones under these optimized conditions.<sup>9</sup> Symmetrical aryl bis(enones) bearing electron-donating and -withdrawing substituents are excellent substrates for cycloadd-

dition, as are heteroaryl enones (entries 1–4). On the other hand, aliphatic enones and enoates do not cyclize (entries 5 and 6), a result we attribute to their more negative reduction potential<sup>10</sup> and the difficulty of generating the corresponding radical anions. A variety of tethering groups are also tolerated in this transformation (entries 7–9). Thus, the general reactivity trends we observe are similar to those reported by Krische,<sup>8</sup> although we were delighted to discover that the efficiency of the photocatalytic process is higher, and harder-to-reduce enones that fail to undergo cycloaddition upon cathodic or stoichiometric reduction are still excellent substrates for our new methodology (e.g., entry 2).

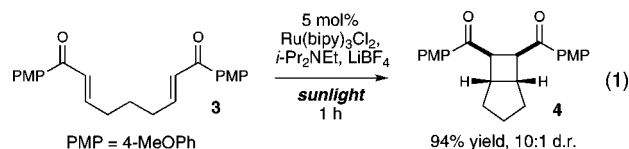
We also investigated cycloadditions of unsymmetrical enones under our optimized conditions. Here, too, the presence of one aryl enone appears to be a strict requirement. However, a variety of  $\alpha,\beta$ -unsaturated carbonyl compounds are suitable reaction partners, including aliphatic ketones, esters, and amides (entries 10–12). The reaction is also successful using  $\alpha$ -substituted enoate acceptors (entry 13), which enables the diastereoselective introduction of an all-carbon quaternary stereocenter on the cyclobutane framework. Finally, intermolecular dimerizations of untethered enones also proceed smoothly (entries 14 and 15) to afford the *rac* isomer of the products, in contrast to the intramolecular reactions.

Control experiments verify the necessity of each component of the reaction protocol. We observe no consumption of **1** when the reaction is conducted in the dark or in the absence of  $\text{Ru}(\text{bipy})_3\text{Cl}_2$ . This indicates that the reaction is indeed initiated by photoexcitation of the ruthenium catalyst. We also observe no reaction in the absence of *i*-Pr<sub>2</sub>NEt, even upon extended irradiation with higher catalyst loadings (5 h, 20 mol%  $\text{Ru}(\text{bipy})_3\text{Cl}_2$ ). This suggests that cycloaddition is not directly initiated by the photoexcited  $\text{Ru}(\text{bipy})_3^{2+*}$  state but rather that the catalytically relevant reductant is a  $\text{Ru}(\text{bipy})_3^+$  species formed upon reductive quenching by the amine.<sup>11,12</sup> Lastly, we find that no reaction occurs in the absence of  $\text{LiBF}_4$ .  $\text{Ru}(\text{bipy})_3\text{Cl}_2$  is sparingly soluble in dry acetonitrile; the addition of  $\text{LiBF}_4$  produces a homogeneous reaction mixture, presumably due to the increased solubility of  $\text{Ru}(\text{bipy})_3(\text{BF}_4)_2$ . The lithium cation is also essential for successful cycloaddition; replacement of the  $\text{LiBF}_4$  additive with either  $\text{Bu}_4\text{N}^+\text{BF}_4^-$  or  $\text{NaBF}_4$  results in a homogeneous reaction mixture but leads to no observable consumption of enone **1**. This suggests that the lithium cation functions as a Lewis acid in this reaction and likely activates the enone toward one-electron reduction.<sup>13</sup>

These data are consistent with the mechanism outlined in Scheme 2. Photoexcitation of  $\text{Ru}(\text{bipy})_3^{2+}$  with visible light results in a photoexcited state ( $\text{Ru}(\text{bipy})_3^{2+*}$ ) that can undergo reductive quenching by *i*-Pr<sub>2</sub>NEt. The resulting  $\text{Ru}(\text{bipy})_3^+$  complex is a powerful reducing agent that can transfer an electron to the lithium-activated enone, initiating the [2+2] cycloaddition and regenerating the  $\text{Ru}^{2+}$  photocatalyst.

As a demonstration of the operational facility of this visible light driven photocatalytic process, we performed the cyclization of bis(enone) **3** on a gram scale using the ambient sunlight in a

laboratory window as the only source of irradiation (eq 1). As expected, this reaction was less efficient than those using the higher-intensity floodlight. Nevertheless, the sunlight-driven reaction proceeded to completion in 1 h and gave 94% yield of *cis*-dione **4** with excellent diastereoselectivity. Thus, our method indeed constitutes a practical strategy for the direct use of sunlight in organic synthesis.



In summary, we have demonstrated that  $\text{Ru}(\text{bipy})_3\text{Cl}_2$  is a very efficient photocatalyst for the formal [2+2] cycloaddition of enones. This approach to effecting visible light photocatalysis has enormous potential for the development of new reaction protocols with reduced environmental impact, and efforts to develop new photocatalyzed synthetic methods are the focus of continuing studies in our laboratory.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds (PDF) and crystallographic data for Table 1, entry 15 (CIF) are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## Scheme 2

