

[2+2] Cycloadditions by Oxidative Visible Light Photocatalysis

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Cyclobutanes are prominent structural features of many bioactive natural products.¹ Arguably the most straightforward method for the preparation of cyclobutane rings is the [2+2] photocycloaddition of olefins, and the utility of this prototypical photochemical reaction has been demonstrated in numerous synthetic applications.² Nevertheless, the requirement for irradiation with high energy UV light is a disadvantage of this reaction in terms of the cost, scalability, and environmental impact of the methodology.³ We recently reported a new approach to [2+2] enone cycloadditions catalyzed by Ru(bpy)₃Cl₂ upon irradiation with low-intensity visible light.⁴ Several other groups⁵ have also recently become interested in similar strategies for utilizing the well-studied photoredox properties of metal polypyridyl complexes⁶ in various synthetically useful transformations.

Notably, each of the methods recently developed by us,⁴ MacMillan,^{5a,b} Stephenson,^{5c–e} and Akita^{5f} has taken advantage of a reductive quenching photoredox cycle (Figure 1, Path A). In our method for [2+2] cycloaddition of enones, for example, the photoexcited state (Ru*(bpy)₃²⁺), generated upon visible light irradiation of the photocatalyst, abstracts an electron from a relatively electron-rich tertiary amine base (*i*-Pr₂NEt); the resulting Ru(bpy)₃³⁺ complex is a strong reductant that reduces an aryl enone to the key radical anion intermediate involved in the [2+2] cycloaddition. This mechanism implies that a fundamental limitation of our strategy is the requirement for an alkene that is sufficiently electron-deficient to undergo efficient one-electron reduction by Ru(bpy)₃³⁺; indeed, electron-rich olefins (e.g., styrenes) do not react under the conditions we previously reported.

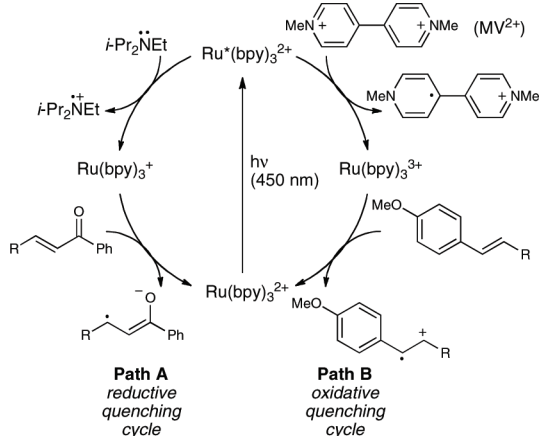


Figure 1. Reductive and oxidative photocatalytic cycles.

We therefore became interested in designing a complementary method for photooxidative electron transfer catalysis that could engage electron-rich olefins in productive [2+2] cycloadditions. Our design plan draws upon two well-established precedents. First, electron-rich olefins are known to participate in [2+2] cycloadditions upon one-electron oxidation to afford the corre-

sponding radical cations. This reactivity was first described by Ledwith⁷ in 1969 and has subsequently been shown to be accessible both by chemical oxidants and by photoinduced electron transfer with organic sensitizers.⁸ Second, the photochemistry of Ru(bpy)₃²⁺ has been extensively investigated for solar energy applications,^{6a} and the most well-studied among these systems rely on an oxidative quenching cycle (Figure 1, Path B) in which Ru*(bpy)₃²⁺ reacts with an electron acceptor (e.g., methyl viologen, MV²⁺).⁹ The resulting oxidized Ru(bpy)₃³⁺ complex is turned over by one-electron reduction using a sacrificial electron-rich organic species such as a tertiary amine base.

Given these precedents, it seemed logical that the photogenerated Ru(bpy)₃³⁺ complex generated upon visible light irradiation of Ru(bpy)₃²⁺ in the presence of MV²⁺ should also oxidize electron-rich styrenes, affording a radical cation that would undergo subsequent [2+2] cycloaddition. Indeed, under optimized conditions, bis(styrene) **1** undergoes efficient intramolecular cycloaddition upon irradiation in the presence of 5 mol % Ru(bpy)₃²⁺ and 15 mol % MV²⁺, affording cyclobutane **2** in 89% yield with excellent diastereoselectivity. As with our previously described Ru(bpy)₃²⁺-catalyzed reactions, this transformation can be conducted using a standard household light bulb and does not require specialized photochemical equipment.

Scheme 1. Photooxidative [2+2] Cycloaddition

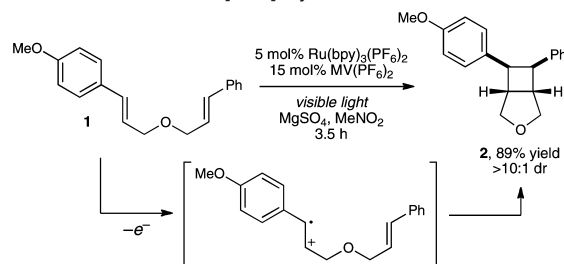


Table 1. Modification of Experimental Parameters

entry	variation from optimized conditions	yield ^a
1	No change	89% ^b
2 ^c	Conventional photolysis (Xe arc lamp, no Ru)	0%
3	No light	0%
4	No Ru(bpy) ₃ ²⁺	0%
5	No MV ²⁺	0%
6	1,4-Dinitrobenzene instead of MV ²⁺	13%
7	1,4-Benzoquinone instead of MV ²⁺	14%
8	1 atm of O ₂ instead of MV ²⁺	0%
9	MeCN instead of MeNO ₂	36%
10	Acetone instead of MeNO ₂	11%
11	DMSO or DMF instead of MeNO ₂	0%
12	No MgSO ₄	73%

^a Yields determined by ¹H NMR spectroscopy using an internal standard, unless noted. ^b Isolated yield. ^c A solution of **1** in MeNO₂ was irradiated with a xenon arc lamp for 3.5 h.

Table 1 summarizes the importance of each of the experimental parameters to the efficiency of the reaction. First, we observe no cycloaddition upon irradiation of **1** with UV light under conventional photolytic conditions (entry 2). This result suggests that the reaction does not involve direct photoexcitation of the styrenic substrate. The observation that visible light, $\text{Ru}(\text{bpy})_3^{2+}$, and MV^{2+} are each required for successful cycloaddition (entries 3–5) is instead consistent with the photoinduced one-electron oxidation mechanism that we have proposed. Other known oxidative quenchers of $\text{Ru}^*(\text{bpy})_3^{2+}$ such as nitroarenes and quinones¹⁰ also promote cycloaddition but were not as effective as MV^{2+} (entries 6 and 7). Oxygen was an ineffective co-oxidant (entry 8).¹¹ We observed a pronounced solvent dependency on the efficiency of the reaction (entries 9–11); reactions conducted in MeCN and acetone produced poorer yields of the cycloadduct than those using MeNO_2 , and we observed no conversion at all in more polar solvents such as DMSO and DMF. Finally, the reaction showed a modest sensitivity to adventitious water, and we found that the addition of MgSO_4 provided slightly higher and more reproducible yields (entry 12).

Experiments probing the scope of [2+2] cycloadditions using the $\text{Ru}(\text{bpy})_3^{2+}/\text{MV}^{2+}$ system are outlined in Table 2. In most cases, we found that 1 mol % of the Ru photocatalyst is sufficient for successful cycloaddition. Our mechanistic design plan is validated by the observation that at least one styrene must bear an electron-donating substituent at the *para* or *ortho* position (entries 1 and 2); *meta*-substituted and unsubstituted styrenes are presumably not electron-rich enough to undergo one-electron oxidation to afford the key radical cation intermediate (entries 3 and 4).¹² However, a number of electron-donating *para* substituents are effective activators of the styrene (entries 5–6), and the presence of an electron-withdrawing substituent at the *meta* position does not seem to significantly decrease the efficiency of the cycloaddition (entry 7). Aliphatic olefins are not suitable reaction partners (entry 8). On the other hand, both electron-rich and electron-poor styrenes react smoothly with the photogenerated radical cation (entries 9–11). Substituents at the α -position of the styrene are tolerated (entry 10), which enables access to all-carbon quaternary stereocenters on the cyclobutane framework, although β -substituents significantly retard the rate of reaction. Substituents on the tether are also tolerated, and these modifications can induce good levels of facial selectivity in the cycloaddition (entries 11 and 12, 5:1 and 7:1 d.r., respectively). The identity of the tether seems to be critical; while both oxygen and nitrogen-containing tethers give good yields (entry 13), we have been unable to identify all-carbon tethers that promote efficient cycloaddition, and intermolecular cycloadditions are impractically slow.

Substrates **3** and **4**, the (*E,Z*) bis(styrenes) isomeric to the model (*E,E*) substrate **1** were also prepared and irradiated with visible light in the presence of $\text{Ru}(\text{bpy})_3^{2+}$ and MV^{2+} (Scheme 2). In both cases, the major product observed is the same *cis* diastereomer obtained from cycloaddition of **1**, indicating that the stereochemical integrity of the olefins is lost over the course of the reaction. To better understand the origins of the stereoconvergency, we monitored the cycloaddition of **4** by GC (see Supporting Information). During the course of this reaction, **4** undergoes isomerization to **1** at a rate competitive with that of cycloaddition. As the reaction proceeds, the ratio of *cis*-**4** to the isomeric *trans* cycloadduct increases from 1:1 at 30 min to 5:1 upon completion of the reaction. We conclude from these studies that the [2+2] cycloaddition step is itself stereospecific, as predicted from previous theoretical and experimental studies of radical cation cyclobutanations¹³ but that the rate of cycloaddition is relatively slow compared to the rate of olefin isomerization. This conclusion is consistent with Bauld's

Table 2. Representative [2+2] Cycloadditions^a

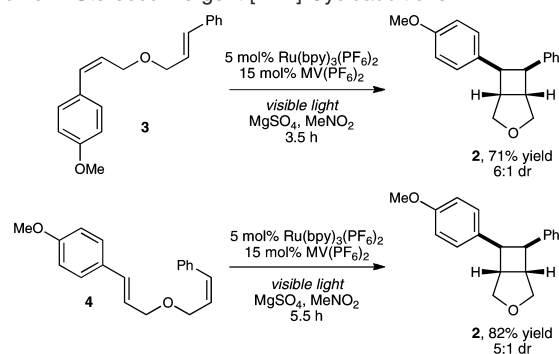
entry	bis(styrene)	cycloadduct	time	yield ^b
1 ^c	$\text{R}^1 = 4\text{-MeOPh}$		3.5 h	88%
2	$\text{R}^1 = 2\text{-MeOPh}$		11 h	73%
3	$\text{R}^1 = 3\text{-MeOPh}$		22 h	0%
4	$\text{R}^1 = \text{Ph}$		22 h	0%
5	$\text{R}^1 = 4\text{-TIPSOPh}$		2.5 h	69%
6 ^c	$\text{R}^1 = 4\text{-HOPh}$		13 h	64%
7	$\text{R} = 3\text{-Br-4-MeOPh}$		8 h	71%
8	$\text{R}^2 = \text{Me}$		22 h	0%
9	$\text{R}^2 = 4\text{-MeOPh}$		2 h	67%
10	$\text{R}^2 = 4\text{-ClPh}$		5 h	92%
11	$\text{R} = 3\text{-FPh}$		5 h	78%
12 ^c			6 h	54%
13 ^d			7 h	69%
14 ^e			6 h	69%
15 ^c			6 h	67%

^a Unless otherwise noted, reactions conducted using 1 mol % $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ and 15 mol % $\text{MV}(\text{PF}_6)_2$. ^b Yields represent the averaged results of two reproducible experiments. ^c Conducted using 5 mol % $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ and 15 mol % $\text{MV}(\text{PF}_6)_2$. ^d 5:1 d.r. ^e 7:1 d.r.

studies of intermolecular [2+2] cycloadditions chemically initiated by an aminium radical cation.^{13a} It is also consistent with the observation that the minor *trans* isomers produced from cycloaddition of **3** and of **4** are different and are consistent with the stereoretentive suprafacial cycloadditions of each of these (*E,Z*) substrates.

Thus, the experimental evidence suggests that cycloaddition using the $\text{Ru}(\text{bpy})_3^{2+}/\text{MV}^{2+}$ catalyst system indeed involves a radical

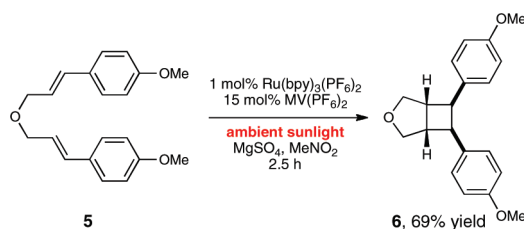
Scheme 2. Stereoconvergent [2+2] Cycloadditions



cationic intermediate whose reactivity is identical to those generated using other methods. Photoinduced electron transfer has previously been used to initiate similar radical cation [2+2] cycloadditions of electron-rich olefins,¹⁴ but these reactions have generally required mercury arc lamps and relatively high loadings of an aromatic nitrile photosensitizer. Consistent with these reports, we find that when the cycloaddition of **1** is conducted using 5 mol % of 9,10-dicyanoanthracene (DCA)^{14b,c} in place of Ru(bpy)₃²⁺, the reaction is considerably slower and produces cyclobutane **2** in only 19% yield after 3.5 h under otherwise identical conditions. The faster reaction rates using Ru(bpy)₃²⁺ may be attributable to its longer excited state lifetime (600 ns vs 15 ns), its larger extinction coefficients (13 000 vs 11 500 M⁻¹ cm⁻¹), and its broader absorption in the visible range compared to DCA.^{6,15}

As in the photoreductive enone cycloaddition we previously reported,⁴ this method for photooxidative cycloaddition does not require the use of any specialized photochemical equipment, and our reactions are typically conducted using a standard household light bulb. To highlight the efficiency of the Ru(bpy)₃²⁺/MV²⁺ system in promoting the radical cation mediated cycloaddition, we conducted the cycloaddition of **5** on a gram scale in a laboratory window using ambient sunlight as the only source of irradiation (Scheme 3). The cycloaddition still proceeded to completion in 2.5 h and provided a nearly identical yield of the cyclobutane product as smaller-scale experiments under more controlled conditions. In addition, the larger-scale reaction was conducted in undistilled nitromethane and without rigorous degassing of the solvent. Thus, these conditions provide a powerful and operationally facile method to perform photochemical cycloadditions using convenient sources of visible light including ambient sunlight.

Scheme 3. Gram-Scale Cycloaddition with Ambient Sunlight



Thus, we have shown that Ru(bpy)₃²⁺ is a powerful photocatalyst for the [2+2] cycloaddition of both electron-rich and electron-deficient olefins. The versatility of this catalyst arises from the ability to access either photooxidative or photoreductive reactivity by choosing the appropriate oxidative or reductive quencher, respectively. In both regimes, the photophysical properties of Ru(bpy)₃²⁺ enable a variety of inexpensive, readily available sources of visible light to be utilized, including sunlight. In addition, there exists a vast wealth of electrochemical literature that describes synthetically useful organic transformations initiated by one-electron redox processes. We expect that photocatalytic systems exploiting the reactivity of Ru(bpy)₃²⁺ should also be able to efficiently promote similar reactivity. The exploration of this reactivity will continue to be a focus of research in our lab.

Acknowledgment. We thank Chris Shaffer and Prof. Robert McMahon for their assistance performing the direct photolysis experiment (Table 1, entry 2). We thank the Sloan Foundation, Beckman Foundation, and Research Corporation for financial support. The NMR facilities at UW-Madison are funded by the NSF (CHE-9208463, CHE-9629688) and NIH (RR08389-01).

Supporting Information Available: Experimental procedures and spectral data for all new compounds are provided. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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JA103934Y