JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Radical Cation Diels–Alder Cycloadditions by Visible Light Photocatalysis

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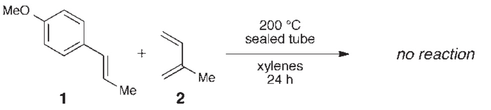
Supporting Information

ABSTRACT: Ruthenium(II) polypyridyl complexes promote the efficient radical cation Diels–Alder cycloaddition of electron-rich dienophiles upon irradiation with visible light. These reactions enable facile [4 + 2] cycloadditions that would be electronically mismatched under thermal conditions. Key to the success of this methodology is the availability of ligand-modified ruthenium complexes that enable rational tuning of the electrochemical properties of the catalyst without significantly perturbing the overall photophysical properties of the system.

The Diels–Alder reaction ranks among the most important carbon–carbon bond-forming reactions in the repertoire of synthetic organic chemistry.[1] Factors governing the rate, stereoselectivity, and catalysis of this powerful transformation have been extensively studied and are well-understood. In particular, the reaction rate is generally synthetically useful only when an electron-rich component (typically the diene) engages an electron-deficient reaction partner (typically the dienophile). Electronically mismatched Diels–Alder reactions between two electron-rich components require more forcing conditions and significantly longer reaction times.

On the other hand, the radical cations of electron-rich olefins undergo exceptionally facile [4 + 2] cycloadditions with electron-rich dienes. These radical cation Diels–Alder reactions can occur with high regio-, stereo-, and chemoselectivity and often occur at rates several orders of magnitude greater than thermal cycloaddition of the corresponding neutral species.[2] The requisite radical cations are most commonly generated using either one-electron chemical oxidants such as aminium salts[2a–c,3] or photoinitiated electron transfer (PET) with an organic photosensitizer.[4] Both approaches require somewhat high loadings of the oxidant or photosensitizer, and the photochemical methods generally call for the use of high-intensity xenon lamps. In this communication, we report a highly efficient and operationally facile protocol for radical cation Diels–Alder cycloaddition that utilizes low loadings of a ruthenium photosensitizer and visible light irradiation (eq 2).



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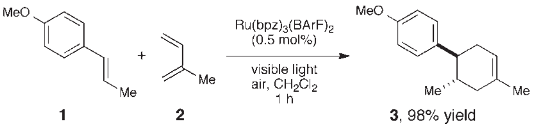

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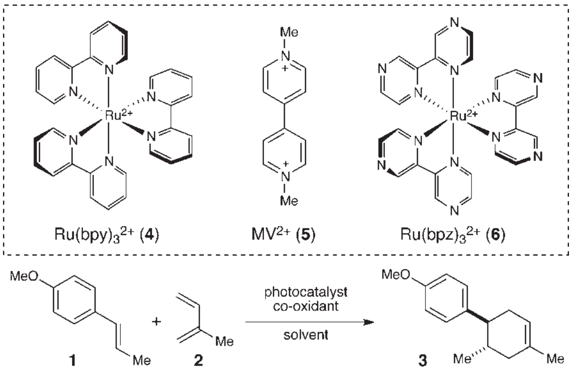
Table 1. Optimization of the Conditions for the Radical Cation Diels–Alder Cycloaddition



entry	catalyst (mol %)	co-oxidant (amount)	diene (equiv)	solvent	time	yield (%)[a]
1[b]	$Ru(bpy)_3(PF_6)_2$ (5)	$MV(PF_6)$ (15 mol %)	10	$MeNO_2$	1 h	98
2[b]	$Ru(bpy)_3(PF_6)_2$ (1)	$MV(PF_6)$ (3 mol %)	10	$MeNO_2$	1 h	25
3[b]	$Ru(bpy)_3(PF_6)_2$ (1)	air (1 atm)	10	$MeNO_2$	1 h	0
4[b]	$Ru(bpz)_3(PF_6)_2$ (1)	air (1 atm)	10	$MeNO_2$	1 h	78
5[b]	$Ru(bpz)_3(PF_6)_2$ (1)	air (1 atm)	3	$MeNO_2$	1 h	76
6[b]	$Ru(bpz)_3(BArF)_2$ (1)	air (1 atm)	3	$MeNO_2$	30 min	83
7[b]	$Ru(bpz)_3(BArF)_2$ (1)	air (1 atm)	3	CH_2Cl_2	30 min	85
8	$Ru(bpz)_3(BArF)_2$ (1)	air (1 atm)	3	CH_2Cl_2	30 min	92
9	$Ru(bpz)_3(BArF)_2$ (0.5)	air (1 atm)	3	CH_2Cl_2	1 h	98[c]

[a] Yields were determined by ^1H NMR analysis using CH_2Br_2 as an internal standard, unless otherwise noted. [b] Conducted in the presence of 200 wt % $MgSO_4$. [c] Isolated yield.

We recently reported that the [2 + 2] photocycloadditions of electron-rich olefins can be conducted upon visible light irradiation in the presence of catalytic $Ru(bpy)_3^{2+}$ and methyl viologen (MV^{2+}).[5–7] This reaction involves oxidative quenching of the $Ru^*(bpy)_3^{2+}$ photoexcited state with MV^{2+} to afford an oxidized $Ru(bpy)_3^{3+}$ complex that is sufficiently oxidizing (+1.3 V vs SCE) to convert a variety of electron-rich styrenes to the corresponding radical cations. Given the facility of this approach, we speculated that other reactions known to involve radical cation intermediates, including the Diels–Alder cycloaddition, might also be amenable to visible light photocatalysis under similar conditions.

Received: October 4, 2011
Published: October 27, 2011

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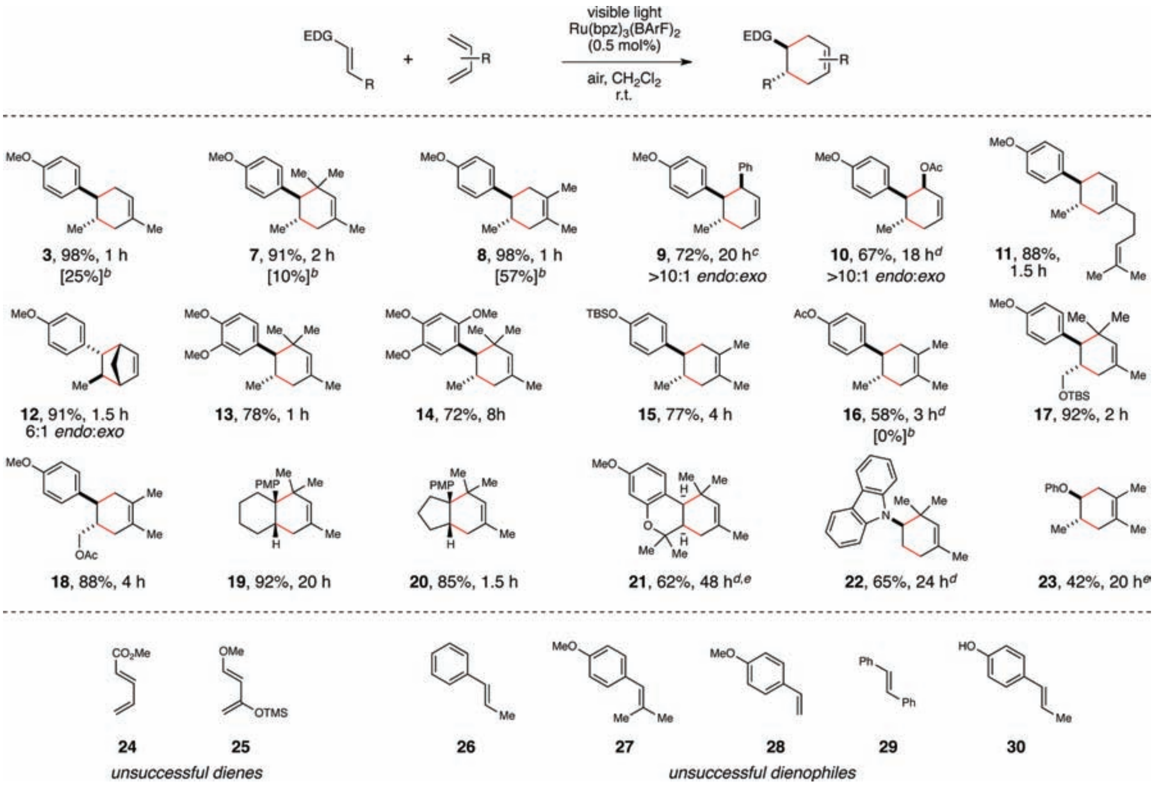
Chart 1. Scope of the Radical Cation Diels−Alder Cycloaddition[a]



[a]Conditions, unless otherwise noted: 0.5 mol % Ru(bpz)$_3$(BArF)$_2$, 3 equiv of diene, CH$_2$Cl$_2$, irradiated with a 23 W compact fluorescent bulb. [b]Yields in brackets are for the same time point using the following conditions: 5 mol % Ru(bpy)$_3$(PF$_6$)$_2$, 15 mol % MV(PF$_6$)$_2$, MgSO$_4$, MeNO$_2$. [c]Using 2 equiv of diene. [d]Using 3 mol % Ru(bpz)$_3$(BArF)$_2$. [e]The yield was determined by ^{1}H NMR analysis using CH$_2$Br$_2$ as an internal standard.

Our investigation commenced with an exploration of the reaction between anethole (**1**) and isoprene (**2**). As expected, this electronically mismatched Diels−Alder cycloaddition does not proceed upon thermal activation (200 °C, 24 h; eq 1). Nevertheless, we found that the photocatalytic conditions we had developed for intramolecular [2 + 2] cycloaddition of electron-rich styrenes[5] translated smoothly to this [4 + 2] process. Cycloadduct **3** was formed in 98% yield after just 1 h of irradiation with a household 23 W compact fluorescent light bulb at ambient temperature (Table 1, entry 1).

Despite this promising preliminary result, the scope of the Ru(bpy)$_3^{2+}$/MV^{2+} catalyst system proved to be quite limited. Reactions involving sterically demanding dienes or less electron-rich dienophiles required much longer reaction times or higher catalyst loadings to achieve synthetically useful yields (*vide infra*). Also, the photocatalyst and MV^{2+} loadings (5 and 15 mol %, respectively) were relatively high, and lower loadings resulted in significant loss of efficiency (Table 1, entry 2). Thus, it became clear that the development of a robust and efficient protocol for the radical cation Diels−Alder reaction would require a more reactive catalyst system for oxidative photocatalysis.

We speculated that rapid back electron transfer from the reduced viologen quencher (MV$^+$) to the dienophile radical cation might be reducing the efficiency of the desired cycloaddition.[8] To slow the rate of back electron transfer, we first replaced MV^{2+} with air as an irreversible co-oxidant for this process (Table 1, entry 3), without success. The observed lack of reactivity is consistent with the propensity of oxygen to quench Ru*(bpy)$_3^{2+}$ by net energy transfer rather than by oxidative quenching;[9] the key Ru(bpy)$_3^{3+}$ photooxidant required for one-electron oxidation of **1**[10] would not be expected to be efficiently formed under air. On the other hand, numerous ligand-modified variants of Ru(bpy)$_3^{2+}$ are known,[11] and the effect of these modifications on the photophysical and electrochemical properties of the complex have been studied in detail. In particular, the tris(bipyrazyl) analogue, Ru(bpz)$_3^{2+}$ (**6**),[12] possesses an excited state oxidation potential (+1.4 V vs SCE) sufficient to directly oxidize **1** without the need for a co-oxidant.

Indeed, irradiation of **1** and **2** under air in the presence of 1 mol % Ru(bpz)$_3$(PF$_6$)$_2$ [**6**·(PF$_6$)$_2$] produced [4 + 2] cycloadduct **3** in good yield (Table 1, entry 4). Using this catalyst, we found that the concentration of the diene could be lowered to 3 equiv relative to **1** without an adverse effect on the yield (entry 5). We also investigated the effect of various counteranions. The BArF complex of the catalyst afforded marginally higher yields, and its greater solubility enabled us to conduct the cycloaddition in less polar solvents such as CH$_2$Cl$_2$ (entries 6 and 7). We discovered that under these conditions MgSO$_4$ had a deleterious effect and that the yield improved when no desiccant was added (entry 8). Finally, we observed that the Diels−Alder cycloaddition remained high-yielding when the loading of **6**·(BArF)$_2$ was reduced to 0.5 mol % (entry 9).

The scope studies outlined in Chart 1 demonstrate that this optimized protocol for the radical cation Diels−Alder reaction is quite general. A variety of substituted dienes proved to be successful reaction partners, including sterically bulky (**7**), aryl- and

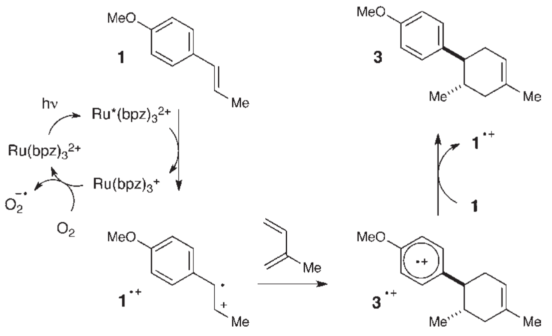
Table 2. Control and Comparison Studies for Cycloaddition of 1 and 2 (eq 2)

entry	conditions	time	yield (%)
1	standard conditions	1 h	98
2	no $Ru(bpz)_3(PF_6)_2$	1 h	0
3	no light	1 h	0
4	ambient sunlight instead of fluorescent lamp	1 h	98
5	no air (under N_2)	1 h	46
6	Rose Bengal instead of $Ru(bpz)_3^{2+}$	1 h	0
7	9,10-dicyanoanthracene instead of $Ru(bpz)_3^{2+}$	1 h	0
8	triphenylpyrilium·BF_4 instead of $Ru(bpz)_3^{2+}$	1 h	28

heteroatom-substituted (**9** and **10**), and cyclic dienes (**12**), and in cases where diastereoselectivity is an issue, the cycloaddition exhibits a high *endo* selectivity (**9**, **10**, and **12**). Electron-deficient dienes such as **24** failed to produce cycloadduct, demonstrating that moderately electron-rich dienes are required because of the electron deficiency of the radical cationic dienophile. Danishefsky's diene (**25**) also failed to undergo [4 + 2] cycloaddition, presumably as a result of competitive, unproductive oxidation of this highly electron-rich diene. The dienophile also tolerates significant structural modification, including multiple alkoxy groups (**13** and **14**) or other protected oxygen substituents (**15** and **16**). Substitution at the allylic position is tolerated (**17** and **18**), and a variety of cyclic electron-rich styrenes are suitable dienophiles in the cycloaddition (**19**−**21**). We also found that the scope of the reaction is not limited to styrenes; other electron-rich olefins such as enamines (**22**) and vinyl ethers (**23**) also undergo cycloaddition under these conditions. However, several key limitations remain to be addressed. Styrenes lacking electron-donating *para* or *ortho* substitutents (**26**) do not react, presumably because of the greater difficulty of oxidizing these substrates. β,β-Disubstituted styrenes (**27**) and stilbenes (**29**) also are not suitable dienophiles. Finally, unprotected phenols (**30**) undergo competitive oxidative decomposition rather than productive cycloaddition. Nevertheless, within these constraints, the scope of the radical cation Diels−Alder cylcoaddition under these conditions is quite broad.

Control and comparison experiments probing the reaction conditions are summarized in Table 2. Both $Ru(bpz)_3^{2+}$ and a light source are required for cycloaddition (entries 2 and 3), consistent with a photocatalytic process. However, a variety of visible light sources are suitable, including ambient sunlight (entry 4). Reactions conducted in degassed solvents in the absence of air produce the cycloadduct but do not proceed to completion (entry 5). We reason from this observation that a chain propagation mechanism is operative, as suggested by Ledwith's studies of radical cation cycloadditions,[13] and that the role of oxygen is to facilitate catalyst turnover from the photogenerated $Ru(bpz)_3^{+}$ complex to the resting $Ru(bpz)_3^{2+}$ state. Reactions conducted with Rose Bengal in place of the ruthenium photocatalyst (entry 6) did not produce cycloadduct, suggesting that the radical cation Diels−Alder reaction is not mediated by singlet oxygen. Finally, we also observed significantly diminished reactivity using the organic photosensitizers most commonly reported for promoting radical cation Diels−Alder reactions. No conversion occurred when the photocatalyst was replaced with 9,10-dicyanoanthracene (entry 7), and only 28% yield was obtained using triphenylpyrilium·BF_4 (entry 8). Thus, the conditions reported in this paper are uniquely well suited to the promotion of this radical cation cycloaddition under visible light irradiation.

Scheme 1. Proposed Mechanism



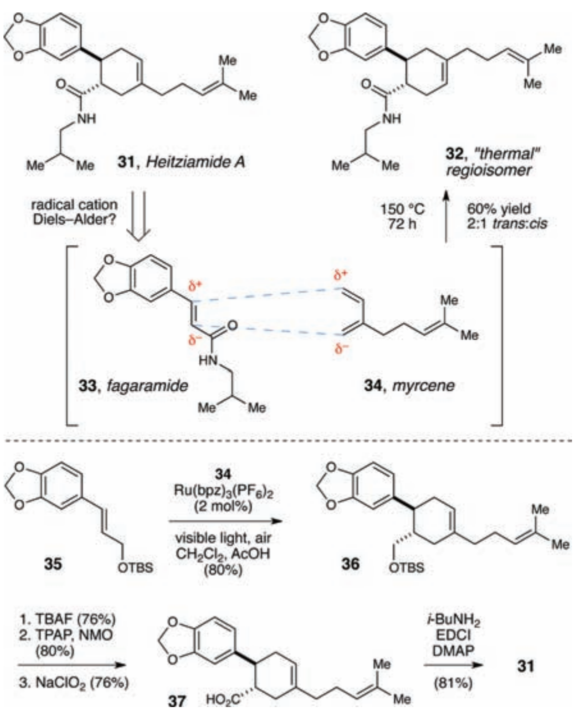
On the basis of these observations, we propose the mechanism outlined in Scheme 1. The $Ru(bpz)_3^{2+}$ chromophore undergoes a metal-to-ligand charge transfer (MLCT) transition in the visible range (λ_{max} = 440 nm), which produces a redox-active photoexcited state, $Ru^*(bpz)_3^{2+}$, whose oxidation potential (+1.4 V vs SCE) is sufficiently positive to oxidize **1** (+1.1 V). The resulting radical cation $\mathbf{1}^{\bullet+}$ is activated toward [4 + 2] cycloaddition to afford the radical cation Diels−Alder product $\mathbf{3}^{\bullet+}$, which can abstract an electron from another equivalent of **1** in a chain-propagation step. Oxygen turns over the reduced $Ru(bpz)_3^{+}$ complex to the photoactive $Ru(bpz)_3^{2+}$ state, which may then initiate additional radical cation chains.

Synthetically, the radical cation Diels−Alder process is best understood as an umpolung process that reverses both the intrinsic electronic character of the electron-rich dienophile and the overall regiochemical preference of the cycloaddition.[14] Given this analysis, we became intrigued by the structure of heitziamide A (**31**), an amide natural product isolated as a racemate from the medicinal shrub *Fagara heitzii*.[15] This compound almost certainly arises from a Diels−Alder cycloaddition between *trans*-fagaramide (**33**), another amide endogenous to *F. heitzii*,[15] and the monoterpene myrcene (**34**). However, the polarization of the diene and dienophile π bonds suggests that the regiochemistry expected from the thermal Diels−Alder reaction would afford the isomeric cycloadduct **32**. Indeed, heating **33** with 20 equiv of neat diene **34** at 150 °C for 72 h afforded a 60% yield of the unnatural regioisomer **32** without any trace of natural heitziamide A (Scheme 2).

On the other hand, as a result of its umpolung reactivity, the intrinsic regiochemical preference of a radical cation in the Diels−Alder reaction is opposite that of the corresponding neutral dienophile. Indeed, the natural regiochemistry of heitziamide A is produced upon irradiation of styrene **35** and myrcene in the presence of 2 mol % $Ru(bpz)_3(PF_6)_2$.[16] No trace of the unnatural regioisomer could be observed by ^{1}H NMR analysis of the unpurified reaction mixture. The regiochemistry was confirmed by deprotection of the silyl ether and oxidation[17] followed by an EDC coupling of the resulting carboxylic acid (**37**) with isobutylamine to afford a compound whose spectral properties were identical to those of natural heitziamide A.

In summary, we have developed a robust protocol for radical cation Diels−Alder cycloadditions using visible light photocatalysis. These reactions feature low catalyst loadings and short reaction times and are conducted open to the atmosphere. In contrast to previously reported photocatalytic radical cation Diels−Alder processes, this method does not require the use of specialized photochemical equipment and can be conducted

Scheme 2. Synthetic Studies on Heitziamide A



using a variety of convenient visible light sources, including ambient sunlight. Thus, we have developed an extremely convenient strategy for promoting electronically mismatched Diels–Alder cycloadditions between electron-rich coupling partners that would otherwise be difficult to accomplish. Further demonstrations of the applicability of this reaction in synthesis are under development in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This paper is dedicated to Prof. Howard Zimmerman in celebration of his career and his many contributions to photochemistry. This research was conducted using funds from the ACS PRF (49817-ND1), NIH (GM095666), Sloan Foundation, Beckman Foundation, and Research Corporation. The NMR facilities at UW-Madison are funded by the NSF (CHE-9208463, CHE-9629688) and NIH (RR08389-01, RR13866-01).

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(14) The regiochemistry of the cycloadducts in Chart 1 is consistent with polarization of the dienophile as shown for structure $\mathbf{1}^{\bullet+}$ (Scheme 1). The umpolung polarization of alkene radical cations has been exploited in synthetic applications by Moeller. For an excellent, concise account, see: Moeller, K. D. *Synlett* **2009**, 1208.

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