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Visible light photocatalysis of intramolecular radical cation Diels–Alder cycloadditions

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Abstract

Intramolecular radical cation Diels–Alder reactions can be conducted under photocatalytic conditions using visible light irradiation. The photocatalyst system involves the use of a $\text{Ru}(\text{bpy})_3^{2+}$ chromophore and methyl viologen as a co-oxidant. These reactions enable the cycloaddition of substrates whose thermal Diels–Alder cycloadditions are electronically mismatched and thus require forcing conditions. Nevertheless, the radical cation cycloadditions can be conducted on gram scale using ambient sunlight as the only source of irradiation.

Diels–Alder cycloadditions have long been recognized as important chemical transformations for the synthesis of structurally complex organic molecules. Intramolecular Diels–Alder (IMDA) reactions, in particular, can provide extraordinarily efficient routes to construct complex polycyclic ring systems from significantly less complex polyene precursors. These reactions are powerful because they result in the formation of two new carbon–carbon bonds and multiple stereocenters, often with excellent diastereocontrol. As a result, IMDA reactions have been the subject of numerous studies that have been extensively reviewed in the literature.¹

The rates of Diels–Alder cycloadditions are fastest when the reaction partners are electronically well matched; typically, reasonable reaction times are observed when electron-deficient dienophiles react with electron-rich dienes. Diels–Alder cycloadditions can be dramatically accelerated by Lewis or Bronsted acid catalysis,² but the presence of a Lewis basic activating group on the dienophile is required for successful implementation of this strategy. An alternative but underutilized approach is the radical cation Diels–Alder cycloaddition, in which a one-electron oxidation of an electron-rich dienophile generates an intrinsically electron-deficient alkene radical cation that can undergo rapid [4+2] cycloaddition with an electron-rich diene partner.³ The requisite radical cations have been generated by both chemical⁴ and photoinduced⁵ one-electron oxidation.

For the past several years, our group has been investigating the chemistry of radical cations generated by visible light photocatalysis.⁶ These reactions exploit the reactivity of photoactive transition metal complexes that enable the use of visible light instead of conventional high-energy UV sources.^{7,8} Recently, we described a highly efficient method for photocatalysis of intermolecular radical cation Diels–Alder cycloadditions of electron-rich alkenes.^{6b} This system features low loadings of a strongly oxidizing $\text{Ru}(\text{bpz})_3^{2+}$

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photocatalyst⁹ and the ability to use any number of convenient sources of visible light including ambient sunlight. Given that the pioneering studies of radical cation Diels–Alder cycloadditions by Bauld and others demonstrated that radical cation Diels–Alder reactions are efficient in both inter- and intramolecular contexts,¹⁰ we wondered if we could demonstrate that radical cation mediated intramolecular Diels–Alder reactions could also be achieved by visible light photocatalysis.

To test this idea, we synthesized and probed the Diels–Alder reactivity of model substrate **1** (Scheme 1). As expected, the thermal Diels–Alder cycloaddition of **1** required high temperatures and long reaction times; after 24 h at 130 °C, we were able to isolate 80% yield of Diels–Alder cycloadduct **2** as a 3:1 mixture of diastereomers favoring the *exo* diastereomer. The forcing conditions required to drive this reaction to completion are consistent with the electronically mismatched nature of Diels–Alder cycloadditions between an electron-rich diene and electron-rich dienophile. On the other hand, Bauld has shown that the radical cation generated by oxidation of **1** with triarylammonium radical salts undergoes rapid, high-yielding Diels–Alder cycloaddition at 0 °C.¹¹

We were surprised, therefore, to observe that the conditions we had optimized for visible light photocatalysis of intermolecular Diels–Alder reactions^{6b} failed to translate to the intramolecular context (Scheme 2). Irradiation of **1** with a 23 W compact fluorescent light bulb in the presence of 0.5 mol% Ru(bpz)₃(BARF)₂ (**3**•(BARF)₂) resulted in complete consumption of the substrate in 2 h, but the expected Diels–Alder cycloadduct was formed in only 35% combined yield (3:1 *endo:exo*). The remainder of the material was a complex mixture of unidentified products that could not be separated by flash chromatography. Speculating that the poor yield was attributable to the strongly oxidizing conditions of Ru(bpz)₃²⁺-photocatalyzed reactions, we also attempted the intramolecular Diels–Alder reaction of **4** under conditions we had initially reported for [2+2] cycloadditions of tethered bis(styrenes).^{6a} We had previously found that these conditions were less successful for intermolecular radical cation Diels–Alder reactions; however, irradiation of **4** in the presence of 5 mol% Ru(bpy)₃(PF₆)₂ (**4**•(PF₆)₂) and 15 mol% methyl viologen (**5**•(PF₆)₂) provided the desired intramolecular cycloadduct in 89% yield and good *endo* diastereoselectivity after just 1.5 h.

Table 1 outlines the experiments conducted to probe the scope of the intramolecular radical cation Diels–Alder reaction under these conditions. A variety of substrates bearing three-carbon tethers transformed smoothly into the desired cycloadducts (entries 1–3). Reactions of substrates with four-carbon tethers, on the other hand, did not give appreciable amounts of product (entry 4). The styrene moiety also tolerated significant substitution. Although the aryl group required an electron-donating group to facilitate generation of the corresponding radical cation, this group could be at either the *ortho* or *para* position (entries 1 and 5), and additional electron-donating and withdrawing groups were both tolerated at other positions of the ring (entries 6 and 7). Other electron-rich olefins such as 2-vinylfurans¹² also successfully initiated the reaction (entry 8). The diene moiety also tolerated substitution at various positions (entry 9), including at an internal position that results in the formation of a quaternary carbon stereocenter at the ring junction (entry 10). The monosubstituted diene substrate, however, gave a complex mixture of products from which the Diels–Alder product could not be isolated (entry 11). Finally, disubstitution of the diene terminus with geminal methyl groups resulted in the formation of the [2+2] cycloadduct rather than the desired Diels–Alder cycloadduct (entry 12), underscoring the fact that both [2+2] and [4+2] pericyclic reactivity is accessible using radical cation methods.

Reactions using transition metal photocatalysts can be extremely efficient and easily scalable. Indeed, as a demonstration of the scalability of the photocatalytic intramolecular

Diels–Alder, we conducted the cycloaddition of **1** on gram scale. As an additional challenge to the system, we conducted the reaction in a laboratory window using ambient sunlight as the source of irradiation instead of the standard 23 W compact fluorescent light bulb used in small-scale reactions. Nevertheless, the reaction proceeded to completion in 3 h, and cycloadduct **2** could be isolated in 80% yield and 8:1 *endo:exo* selectivity. (Scheme 3)

In conclusion, visible light photocatalysis offers a useful and operationally simple method to construct polycyclic Diels–Alder products under conditions that are significantly milder than those required to promote the corresponding electronically mismatched thermal cycloadditions. Notably, cycloadditions of the styrenyl substrates examined in this study are not amenable to acceleration by conventional Lewis or Brønsted acid catalysis. Photocatalytic radical cation Diels–Alder cycloadditions are thus a useful complementary approach to the catalysis of this important class of reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Thermal cycloaddition of electronically mismatched Diels-Alder substrate **1**.

Scheme 2.
 Comparison of photocatalyst systems for radical cation IMDA.

Scheme 3.
Large-scale photoreaction in ambient sunlight.

Table 1

Scope studies on intramolecular photocatalytic radical cation Diels–Alder cycloadditions.^a

entry	substrate	product	time	yield ^b (<i>endo:exo</i>)
1			1.5 h	89% (8:1)
2			5 h	74% (3:1)
3			8 h	65% (5:1)
4		-	24 h	0%
5			24 h	23% (>10:1)
6			18 h	75% (2:1)
7			24 h	58% (>10:1)
8			16 h	40% (7:1)
9			7 h	72% (2:1)
10			4 h	90% (>10:1)
11		-	2 h	0%

entry	substrate	product	time	yield ^b (<i>endo:exo</i>)
12			20 h	55%

^aReactions conducted by irradiating a solution of 1 equiv of substrate, 0.05 equiv of **4**•(PF₆)₂, 0.15 equiv of **5**•(PF₆)₂, and 2 wt. equiv of MgSO₄ in degassed MeNO₂ in front of a 23 W household compact fluorescent light bulb. See Supporting Information for details.

^bIsolated yields. Diastereomer ratios determined by ¹H NMR analysis of the unpurified reaction mixture.