Photoredox Catalysis

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Photooxidizing Chromium Catalysts for Promoting Radical Cation Cycloadditions**

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Abstract: *The photooxidizing capabilities of selected Cr^{III} complexes for promoting radical cation cycloadditions are described. These complexes have sufficiently long-lived excited states to oxidize electron-rich alkenes, thereby initiating [4+2] processes. These metal species augment the spectrum of catalysts explored in photoredox systems, as they feature unique properties that can result in differential reactivity from the more commonly employed ruthenium or iridium catalysts.*

Over the past several years, photoredox catalysis has arisen as a powerful tool in organic synthesis for its ability to form C–C bonds.[1] A light-generated excited-state metal complex can act as an oxidant or reductant, yielding unconventional radical intermediates from organic substrates through single-electron transfer. An advantage of photocatalysis is its utilization of a simple energy source (i.e., light) to initiate these valuable transformations. Despite this benefit, the photocatalysts most commonly employed in these processes are complexes of ruthenium and iridium, two of the most rare and expensive transition metals. In contrast, examples of the use of first-row metal photocatalysts for synthetic applications are sparse; in 1987, Kern and Sauvage reported the application of $[Cu(dap)_2]^+$ in the reductive couplings of benzylic halides.[2,3] More recent investigations of Cu^I photocatalysis—primarily in reductive processes—have been described,[4,5] yet reports are relatively few, and to our knowledge no analogous disclosures of metal-catalyzed oxidative systems exist. The discovery and employment of photoredox catalysts based on alternative, earth-abundant, first-row transition metals for synthetic organic transformations would be a major advance. Moreover, the potential for photocatalyst development with different reactive properties may enable the downstream development of transformations optimal for these catalyst systems. Herein, we report the realization of this goal in the discovery of photooxidizing chromium-catalyzed Diels–Alder cycloadditions that proceed via radical cation intermediates (Figure 1).

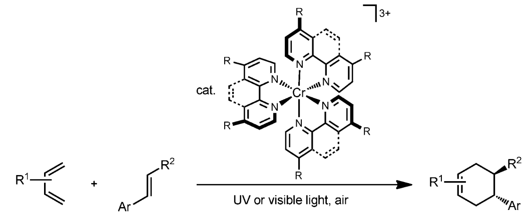

Figure 1. Photooxidizing Cr^{III}-catalyzed cycloadditions.

The judicious use of Ru and Ir photoredox catalysts for promoting organic transformations, based on their inherent oxidative or reductive demands, is well appreciated. Select examples of prevailing Ru and Ir catalysts are shown in Figure 2. With regard to first-row metals, the photooxidizing properties of dipyridyl and phenanthrolinyl chromium(III) complexes were reported by Serpone, Hoffman, and coworkers over 30 years ago.[6] One of us with Damrauer and coworkers had further investigated the oxidizing properties of these homoleptic and related homo- and heteroleptic complexes, with specific examples also shown in Figure 2.[7] Ground-state Cr^{III} complexes are generally substitution inert, and these specific species absorb strongly in the ultraviolet region ($\pi \rightarrow \pi^*$), with weaker absorptions in the near-UV (NUV) and visible regions (charge-transfer).[8] The excited state lifetimes (τ_{obs}^*) of the Cr^{III} species are substantially longer than those of the common Ru/Ir photocatalysts, with values up to 304 and 425 μs for complexes **3** and **4**, respectively. The oxidizing capabilities of these species are also unique and intriguing. Excited-state reduction potentials for the conventional metal photocatalysts range from $+0.31$ V (vs. SCE)[9] for *fac*-$Ir(ppy)_3$ to $+1.45$ V for the photooxidizing $[Ru(bpz)_3]^{2+}$.[1] The Cr^{III} complexes feature comparatively higher excited state reduction potentials, ranging from $+1.40$ to $+1.84$ V, nearing the potentials of select strong organic photosensitizers (e.g., pyrilium/acridinium salts; $E_{1/2}$ generally $> +2.0$ V).[10] Overall, these data indicate that the Cr^{III} complexes may serve as reactive oxidizing alternatives to the more commonly utilized photocatalysts of rare metals.

To start, we directed our attention toward radical-cation-mediated Diels–Alder cycloadditions, which are initiated by single-electron oxidation of the dienophile. Bauld and co-

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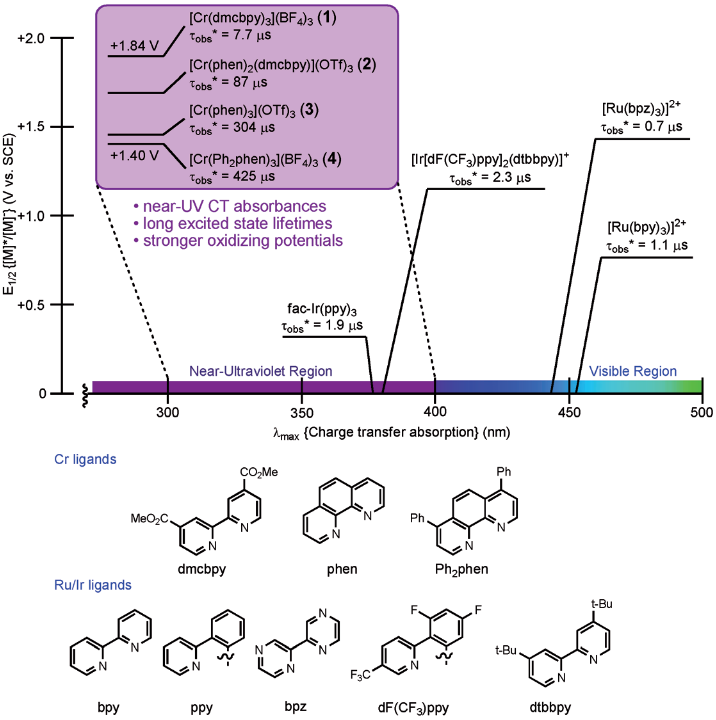


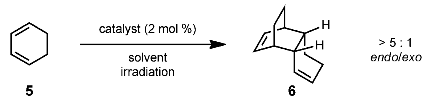
Figure 2. Photochemical properties of selected catalysts.[1,6]

workers originally described the [4+2] dimerization of 1,3-cyclohexadiene promoted by a catalytic radical cation aminium salt, tris(4-bromophenyl)aminium hexachloridoantimonate.[11] In addition to this seminal report, other promotion systems have been disclosed, including photosensitized electron transfer,[12] polymer-supported aminiums,[13] and zeolites.[14] More recently, the visible-light-promoted, $[Ru(bpz)_3]^{2+}$-catalyzed radical cation Diels–Alder reaction was described by Yoon and co-workers.[15] We were interested in establishing the competency of Cr^{III} catalysis for two specific reasons. First, calculations indicate that these cycloadditions are essentially barrierless compared to their neutral reaction counterparts.[16] And second, because these reactions can proceed through radical propagation,[17] an external oxidant to regenerate the Cr^{III} ground state should not necessarily be required, thereby minimizing reaction variables. Taking these aspects into account, we anticipated that if the Cr^{III} complexes were to successfully perform a single-electron oxidation of the organic substrate, product formation would likely occur.

Our analysis of this transformation is depicted in Table 1. Irradiating a solution of 1,3-cyclohexadiene (**5**, $E_{1/2} = +1.53$ V[19]) and a catalytic amount of $[Cr(dmcbpy)_3](BF_4)_3$ (**1**) in dichloromethane with 300–419 nm light (i.e., predominantly NUV),[18] afforded the bicyclic adduct (**6**), albeit in low yield (entry 1). Acetonitrile was somewhat more effective, but a dramatic increase in yield was observed using nitromethane as the solvent (entry 5).[20] Less photooxidizing Cr catalysts were also effective for this transformation (entries 6–8), although the conversions and/or yields were decreased relative to the use of complex **1**. Lower catalyst loadings marginally benefited reactivity (entry 9). Control experiments confirmed that catalyst and light were both required (entries 10–13). Ru complexes were also evaluated for this transformation using visible light (standard light bulb); indeed, the strongly oxidizing $[Ru(bpz)_3]^{2+}$ induced the cycloaddition in nitromethane. Notably, however, the use of the Cr catalyst system led to a demonstrably improved yield using the same visible light irradiation (entry 17).[21] Crucially, these experiments validated that catalysts based on first row metals could be used in photooxidizing transformations.

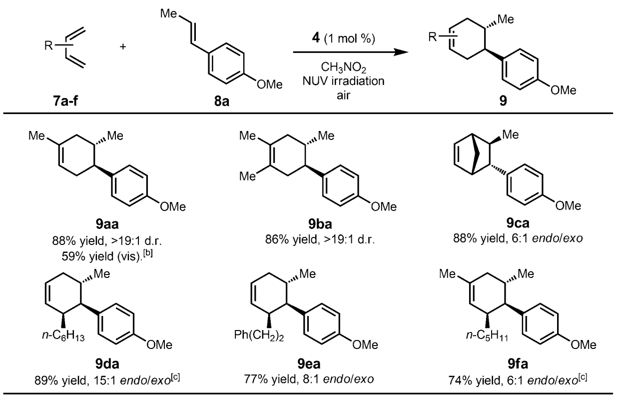
Having established this key proof-of-principle, we sought to expand this reactivity to cross-cycloadditions. We opted to explore simpler systems in which the reactants would have well-defined roles as diene and dienophile. Thus we investigated the cycloaddition of electron-rich dienophiles with dienes that should be relatively more difficult to oxidize. The distinct photooxidation range of the Cr catalysts would ideally discriminate between these two reactants. An evaluation of dienes with *trans*-anethole ($E_{1/2} = +1.11$ V)[19] is presented in Scheme 1. Here, we used a Cr catalyst with lower oxidizing capability ($[Cr(Ph_2phen)_3](BF_4)_3$, **4**) to accentuate selective dienophile oxidation. In accordance with this hypothesis, the cycloaddition of *trans*-anethole with isoprene ($E_{1/2} = +1.98$ V)[19] afforded cyclohexene **9aa** in 88% yield.[22] 2,3-Dimethyl-1,3-butadiene was similarly effective, giving adduct **9ba** in 86% yield. High diastereoselectivities could also be achieved with terminally substituted dienes;

Table 1: [4+2] dimerization of cyclohexadiene.[a]



Entry	Catalyst	Solvent	Irradiation[b]	Time [h]	GC yield [%][c]
1	**1**	CH_2Cl_2	NUV	24	19
2	**1**	CH_3CN	NUV	24	39
3	**1**	CH_3OH	NUV	24	0
4	**1**	THF	NUV	24	0
5	**1**	CH_3NO_2	NUV	24	61 (69[d])
6	**2**	CH_3NO_2	NUV	24	39
7	**3**	CH_3NO_2	NUV	24	36
8	**4**	CH_3NO_2	NUV	24	40
9	**1**[e]	CH_3NO_2	NUV	24	66
10	$CrCl_3$	CH_3NO_2	NUV	24	1
11	–	CH_3NO_2	NUV	24	<1
12	–[f]	CH_3NO_2	NUV	24	<1
13[g]	**1**	CH_3NO_2	None	48	<1
14	$Ru(bpy)_3Cl_2$[h]	CH_2Cl_2	23 W CFL	48	<1
15	$Ru(bpz)_3(PF_6)_2$[e]	CH_2Cl_2	23 W CFL	24	<1
16	$Ru(bpz)_3(PF_6)_2$[e]	CH_3NO_2	23 W CFL	24	21
17	**1**	CH_3NO_2	23 W CFL	24	55

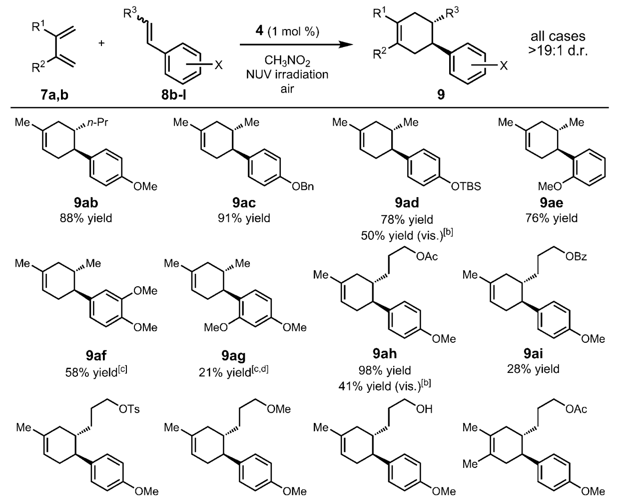
[a] Reactions were set up under air. [b] NUV: Reaction was performed in a photoreactor with light bulbs of 300, 350, and 419 nm wavelengths. 23 W CFL: Reaction was performed in a sealed box with a compact fluorescent light. None: Reaction performed wrapped in foil. [c] Determined using tridecane as the internal standard. [d] Yield of the isolated product (0.500 mmol scale). [e] 1 mol% catalyst loading. [f] Added 6 mol% of dmcbpy ligand. [g] Reaction heated at 40 °C (the measured temperature inside the photoreactor). [h] 5 mol% catalyst loading.



Scheme 1. Diene variation.[a] [a] Reaction conditions: 1 equiv **8a**, 10 equiv diene, 1 mol% cat., 0.10 M CH_3NO_2, set up under air, 300–419 nm light, 24–48 h. [b] Reaction performed with 23 W CFL light. [c] Reaction performed with needle outlet open to air.

these substrates also participated in the cycloaddition to give the corresponding adducts in excellent yields and stereoselectivities. Optimal reactivity was consistently observed under the NUV irradiation mode; visible-light promotion was also effective for these cycloadditions, albeit in lower yield.[23]

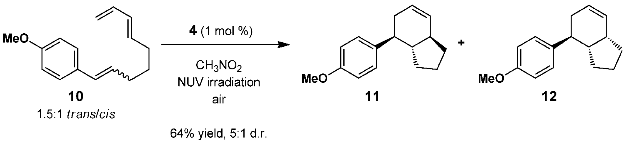
An array of dienophile components were found to be reactive participants in the Cr-catalyzed cycloadditions (Scheme 2). Electron-rich styrene derivatives were the optimal compounds; several were found to be successful reactants with either isoprene or 2,3-dimethyl-1,3-butadiene. Trisubstituted aryl substrates gave lower yields (**9af** and **9ag**), presumably because the radical cation intermediate formed is more stable and thus less reactive. Different functional groups (ethers, esters, sulfonates) were tolerated under the reaction conditions. The difference in yields between adducts **9ah** and **9ai** is revealing; presumably the benzoate is interfering with catalyst excitation, perhaps by competitive light absorption. The results of adducts **9aj**–**9al** are also informative. The positioning of the pendant oxygen atom is such that an electron-withdrawing substituent is critical, as the ether gave diminished yield and the alcohol afforded no product whatsoever. These observations are consistent with a competitive intramolecular donation of the oxygen electron(s) into the putative radical cation intermediate.[24] Also noteworthy, the isomeric ratio of the dienophile had no impact on the outcome of the cycloaddition; *anti*-products were formed exclusively.[25]



Scheme 2. Dienophile variation.[a] [a] Reaction conditions: 1 equiv dienophile, 10 equiv diene, 1 mol% cat., 0.10 M CH_3NO_2, set up under air, 300–419 nm light, 24–48 h. [b] Reaction performed with 23 W CFL light. [c] Reaction mixture bubbled with O_2 prior to sealing. [d] 1.5 mol% catalyst.

It should be mentioned that executing these types of reactions is more nuanced than a simple matching of the reduction potentials of the alkene and the photocatalyst. A cycloaddition between 1,3-cyclohexadiene with *trans*-anethole ($E_{1/2} = +1.53$ V and $+1.11$ V, respectively) afforded a 1:1 mixture of the adduct and unreacted dienophile, with the remainder diene dimer **6**.[26] This product distribution can be readily explained by known kinetic data: the rate of 1,3-cyclohexadiene reacting with the radical cation of itself is faster than the rate of it reacting with the radical cation of *trans*-anethole.[27,28]

Intramolecular cycloadditions were also investigated (Scheme 3). Examples of intramolecular radical cation Diels–Alder reactions have been described;[29] curiously, most reported cases employ 1,4-disubstituted dienes. The few examples of monosubstituted dienes, including those with Ru catalysis, resulted in complex mixtures, some containing both [2+2] and [4+2] cycloadducts.[29b,c] Using Cr catalytic conditions, however, monosubstituted diene **10** underwent the [4+2] intramolecular cycloaddition in 64% yield and synthetically useful d.r., with no [2+2] cycloadduct detected. As in the intermolecular cases, no product formation was observed in the absence of catalyst or light. The success of this process again underscores the importance of alternative catalyst development.



Scheme 3. Intramolecular cycloaddition.

Our proposed mechanism for this cycloaddition, illustrated for *trans*-anethole with isoprene (Figure 3), is somewhat consistent with Yoon's photocatalyzed process and aligned with prior findings.[15,30] Excitation of the Cr^{III} catalyst generates a species capable of oxidizing the dienophile. The resulting radical cation ($\mathbf{8a}^{+\bullet}$) undergoes the cycloaddition to generate intermediate $\mathbf{9aa}^{+\bullet}$. At this point, two possibilities exist. Electron transfer with another equivalent of *trans*-anethole affords the product and propagates the process. Alternatively, the adduct is produced by oxidation of the intermediate Cr^{II}, in turn regenerating the ground-state catalyst. Reaction progress is arrested when irradiation is cut off, indicating that this latter pathway is likely predom-

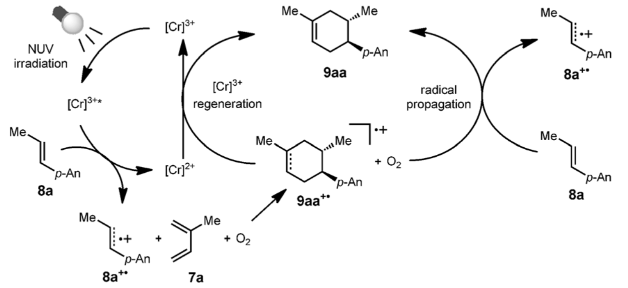


Figure 3. Proposed mechanism.

inant.[26] An additional observation to note is that oxygen was required for reactivity,[31] which was not the case for the Ru-catalyzed system. It is curious how oxygen may be facilitating this specific process. It should not be directly involved in enabling more efficient catalyst turnover;[32] instead, it may be stabilizing specific intermediates on the reaction pathway (e.g., **8a**$^{+\bullet}$ or **9aa**$^{+\bullet}$).[33] More studies are necessary to establish the feasibility of potential mechanistic pathways and the critical role of oxygen.

The arena of light-activated catalysis for synthetic transformations has reached a truly exciting period of innovation, yet it remains confined by the limitations associated with relatively few catalyst options. To our knowledge, this work represents the first report of Cr$^{\text{III}}$ complexes being applied as photocatalysts in organic synthesis. Not only does this effort demonstrate the viability of catalyst design predicated on first-row transition metals, but it also validates the notion that differential reactivity can be discovered through this area of investigation. Current efforts are dedicated toward the development of additional catalyst systems based on earth-abundant metals and further synthetic applications, and these will be reported in due course.

Keywords: chromium · cycloaddition · oxidation · photocatalysis · radical cations

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[20] The beneficial effect of nitromethane is likely in part attributable to effective solvation of both the catalyst and substrate.

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[22] A trace amount of an isoprene dimer (limonene) was detected.

[23] The cycloaddition was also tested using the individual NUV wavelength lights separately. Reactions using irradiation from either the 300 or 350 nm bulbs did not proceed to completion, but the reaction using the 419 nm bulb did indeed consume the starting material. Cycloadduct **9aa** was formed in 73% yield. See the Supporting Information for experimental details.

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[26] See the Supporting Information for experimental details.

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