Cyclization–endoperoxidation cascade reactions of dienes mediated by a pyrylium photoredox catalyst
Nathan J. Gesmundo and David A. Nicewicz*

Abstract
Triarylpyrylium salts were employed as single electron photooxidants to catalyze a cyclization–endoperoxidation cascade of dienes. The transformation is presumed to proceed via the intermediacy of diene cation radicals. The nature of the diene component was investigated in this context to determine the structural requirements necessary for successful reactivity. Several unique endoperoxide structures were synthesized in yields up to 79%.

Introduction
Endoperoxides are a structurally unique class of naturally-occurring compounds that feature a reactive cyclic peroxide moiety of varying ring sizes (Figure 1). The lability of the endocyclic peroxide O–O bond engenders these compounds with a range of important biological functions, most notably, antimalarial and antitumor activity (e.g., artemisinin, yingzhaosu A and merulin C) [1–4]. From a synthetic standpoint, the installation of the endoperoxide moiety presents a significant challenge due to its susceptibility to reduction and for this reason, is ideally introduced late-stage in target-oriented synthesis. Additionally, many endoperoxide natural products possess architecturally complex frameworks (e.g., artemisinin, yingzhaosu A, muurolan-4,7-peroxide) [5] that pose significant synthetic challenges. Classical approaches to the introduction of cyclic peroxides typically rely on cycloadditions of alkenes and dienes with singlet oxygen. However, ene processes can often compete, leading to complex mixtures of hydroperoxide adducts [1,6-8]. More recently, cyclization reactions of hydroperoxides with pendant alkenes or alkynes have been developed. Selected examples include Pd(II)-catalyzed hydroalkoxylation reactions of unsaturated hydroperoxides [9], Au(I)-catalyzed endoperoxidation of alkynes [10] and Brønsted acid-catalyzed enantioselective acetalization/oxa-Michael addition cascade reactions of peroxynitrols [11].

While these extant methods are effective at installing the endoperoxide functional group, our interest lay in developing strate-
Figure 1: Selected examples of endoperoxide-containing natural products.

Figure 1: Selected examples of endoperoxide-containing natural products.

Miyashi:

\[
\begin{align*}
\text{Ar} & = 4-(\text{MeO})\text{C}_6\text{H}_4 \\
\text{Ar} & = 4-(\text{MeO})\text{C}_6\text{H}_4
\end{align*}
\]

\[
\begin{align*}
\text{MeCN, rt, 1 atm O}_2 \\
\text{hv}
\end{align*}
\]

\[
\begin{align*}
72\% \text{ yield}
\end{align*}
\]

Yoon:

\[
\begin{align*}
\text{Ar} & = 4-(\text{MeO})\text{C}_6\text{H}_4 \\
\text{Ar} & = 4-(\text{MeO})\text{C}_6\text{H}_4
\end{align*}
\]

\[
\begin{align*}
\text{MeNO}_2 \text{O}_2 \text{Pr} \text{O}_2 \\
\text{hv}
\end{align*}
\]

\[
\begin{align*}
92\% \text{ yield; 6:1 dr}
\end{align*}
\]

Scheme 1: Endoperoxide formation via cation radicals. In both examples, single electron oxidation is followed quickly by cyclization to form stabilized distonic cation radical intermediates. The distonic intermediates are trapped by O2 and furnish the shown bicyclic products after reduction.
6-endo). Herein is reported an organocatalytic photoredox-mediated strategy for the endoperoxidation of 1,5-dienes using ¹⁸O₂ to rapidly generate complex endoperoxide frameworks.

Results and Discussion

Reaction optimization

We began our investigation into endoperoxidation conditions with diene 2a as the substrate as it contained both a styrene and an aliphatic alkene. Using catalyst 1c in DCM at −41 °C under irradiation with 470 nm LEDs afforded endoperoxide 3a in 40% yield after 5 hours (Table 1, entry 1). The observed endoperoxide was attributed to a 5-exo cyclization mode of the diene cation radical followed by capture of molecular oxygen. The use of acetonitrile as solvent gave none of the desired adducts (Table 1, entry 2). Further improvement of the chemical yield of 3a was realized by increasing the reaction concentration

![Scheme 2: Diversification strategy for endoperoxide synthesis by single electron transfer. $E_{\text{red}}$ vs SCE [20].](image)

**Table 1: Reaction Optimization and Control Experiments.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions$^a$</th>
<th>Conversion</th>
<th>Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 mol % 1c, 0.01 M DCM, −41 °C</td>
<td>100%</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>2 mol % 1c, 0.01 M MeCN, −41 °C</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>2 mol % 1c, 0.02 M DCM, −41 °C</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>4</td>
<td>1 mol % 1c, 0.05 M DCM, −41 °C</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>5</td>
<td>0.7 mol % 1c, 0.07 M DCM, −41 °C</td>
<td>100%</td>
<td>70%</td>
</tr>
<tr>
<td>6$^c$</td>
<td>Excluding O₂</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>Excluding hv</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>Excluding catalyst 1c</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>9</td>
<td>9-Mes-10-Me-Acr-BF$_4$ in place of 1c</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>10$^d$</td>
<td>Rose Bengal in place of 1c</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

All reactions carried out in oxygen-saturated solvents unless otherwise noted. $^a$−41 °C found to be the optimum temperature during initial substrate/reaction optimization. $^b$Yields with respect to (Me₃Si)₂O-¹H NMR internal standard. $^c$Reaction carried out under N₂ atmosphere in DCM. $^d$Reaction carried out in oxygen saturated MeOH at room temperature using a white flood lamp.
Scheme 3: Proposed mechanism for endoperoxide synthesis from tethered dienes.

We invoke a mechanism similar to that proposed by Miyashi [12] and Yoon [15] in their respective transformations (Scheme 3). Following excitation of triarylpyrylium tetrafluoroborate catalyst 1, one-electron oxidation of the 1,5-diene substrate produces localized cation radical intermediate 4 and pyranyl radical 1•. Cyclization of diene cation radical 4 then forms stabilized distonic cation radical intermediate 5, which is intercepted by O2 to form 6. Single electron reduction, either from 1• to regenerate active catalyst 1 or from another substrate equivalent in a chain process, forms the desired bicyclic endoperoxide.

DFT calculations suggest that the formation of the initial distonic cation radical 5 is exothermic by approximately 3 kcal/mol relative to cation radical 4 [27]. Superficially, this is rationalized by the increased substitution on 5 relative to 4. In addition, the majority of the spin density on 5 is located on the isoprenyl group (DFT-5, Scheme 3). This may be fortuitous as...
stereoselectivity in the oxygen addition step is irrelevant, whereas the opposite scenario involving a benzylic radical intermediate would require a stereospecific addition of oxygen to the same face of the cyclopentane system as the isoprenyl cation in order for endoperoxide formation to occur.

With optimized conditions identified, we sought to examine the scope of the reaction with respect to the diene structure. Miyashi’s 1,5-diene (2b; $E_{1/2}^{Ox} = 1.22$ V vs SCE [12]) afforded a 50% yield of the expected endoperoxide along with ~5% of a 1,4-dione, presumably from double oxidative cleavage of the 1,5-diene (Table 2, entry 1). Unfortunately, attempts to move away from 2b to less electron-rich dienes such as 2c, 2d and 2e (Table 1, entries 2–4), failed to produce any of the desired endoperoxide products and mainly oxidative cleavage adducts were observed.

Given the lack of reactivity of this alkene substitution pattern, we turned our attention to the investigation of diene structures similar to successful endoperoxidation substrate 2a. Removal of

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Expected adduct</th>
<th>Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>66%</td>
</tr>
<tr>
<td>6</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>$\text{R}^2$-$\text{R}^3$-$\text{R}^4$-$\text{R}^5$</td>
<td>32%</td>
</tr>
</tbody>
</table>

$^a$photoredox catalyst (0.7–2 mol %) $\text{1 atm O}_2$ 470 nm LEDs

Table 2: Diene structure investigation for endoperoxidation cascade.
the geminal dimethyl group (2f) resulted in significantly diminished yields of the endoperoxide adduct, likely due to the lack of a Thorpe–Ingold effect present in 2a. These experiments also demonstrated that the electron-rich arene was necessary for reactivity (cf. 2e and 2f; Table 2, entries 4 and 6). The importance of the electron-rich arene may lie in the necessary distonic cation radical intermediate: the electron-rich arene may provide greater stability to the distonic intermediate formed after 5-exo-trig cyclization, ultimately ensuring it remains to intercept oxygen. A further survey of the styrene component supported this hypothesis. While electron-rich styrenes gave modest amounts of product formation (2f, 2g and 2i; Table 2, entries 6, 7 and 9), styrenes with either weakly donating (4-Me; Table 2, entry 10) or even withdrawing (4-Cl; Table 2, entry 11) functionality furnished none of the expected endoperoxides. In these cases, oxidative degradation was observed as was the case with the highly oxidizable 2-furyl group (Table 2, entry 12). Interestingly, 3,4-dimethoxystyrene-substituted diene 2h also gave none of the desired adduct, which we attributed to lack of charge density on the alkene [28,29].
We next investigated the endoperoxidation cascade by replacing the isoprenyl substituent with a variety of other alkenes. A pendant styrene afforded the desired endoperoxide adduct in 68% yield, albeit with no diastereocntrol (2m, 1:1 dr; Table 3, entry 1). A diene bearing a tetrasubstituted alkene (2n) was reactive in this context, giving polycyclic endoperoxide 3n in 64% yield (6.5:1 dr). The use of 1,2-, 1,1-dialkyl as well as monoalkyl-substituted alkenes appeared to completely disfavor

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Observed product</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td><img src="2m.png" alt="" /></td>
<td><img src="3m.png" alt="" /></td>
<td>68%, 1:1 d.r.</td>
</tr>
<tr>
<td>2c</td>
<td><img src="2n.png" alt="" /></td>
<td><img src="3n.png" alt="" /></td>
<td>64%, 6.5:1 d.r.</td>
</tr>
<tr>
<td>3d</td>
<td><img src="2o.png" alt="" /></td>
<td><img src="3o.png" alt="" /></td>
<td>36%</td>
</tr>
<tr>
<td>4d</td>
<td><img src="2p.png" alt="" /></td>
<td><img src="3p.png" alt="" /></td>
<td>37%</td>
</tr>
<tr>
<td>5d</td>
<td><img src="2q.png" alt="" /></td>
<td><img src="3q.png" alt="" /></td>
<td>27%</td>
</tr>
<tr>
<td>6e</td>
<td><img src="2r.png" alt="" /></td>
<td>–</td>
<td>0%</td>
</tr>
<tr>
<td>7e</td>
<td><img src="2s.png" alt="" /></td>
<td>–</td>
<td>0%</td>
</tr>
</tbody>
</table>

Reactions carried out in oxygen-saturated solvents. aAverage of two isolated yields. b1:1 mixture of separable diastereomers. c6.5:1 mixture of inseparable diastereomers. Presumed major diastereomer shown. dDesired endoperoxide never observed. eMultiple conditions tested, no productive chemistry observed.
the endoperoxidation pathway and resulted in the unexpected isolation of α-allyl ketones (Table 3, entries 3–5) in modest yields. Based on the Miyashi precedent, the formation of these adducts can be rationalized by invoking a formal [3,3]-rearrangement of the initial cation radical intermediate. The competing 6-endo cyclization mode and formation of distonic cation radical 9 ultimately provides access to the more stabilized cation radical 10, which undergoes oxidative cleavage to afford the corresponding α-allyl ketones (Scheme 4). In the absence of the geminal dimethyl group (2r, 2s), neither the Cope-like reactivity or the endoperoxidation was observed (Table 3, entries 6 and 7).

Lastly, we elected to explore cyclization modes similar to the Yoon work under the developed conditions. Diene 2t was anticipated to undergo 6-exo-trig cyclization to form the necessary distonic cation radical intermediate (Table 4, entry 1). The expected trioxabicyclo[3.3.1]nonane product was formed, albeit

Table 4: Other cyclization modes and substrate designs.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Desired product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image" alt="Substrate 2t" /></td>
<td><img src="image" alt="Desired product 3t" /></td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 2u" /></td>
<td><img src="image" alt="Desired product 3u" /></td>
<td>79%, 5.7:1 d.r.</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 2v" /></td>
<td><img src="image" alt="Desired product 3v" /></td>
<td>&lt;5%</td>
</tr>
<tr>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image" alt="Substrate 2w" /></td>
<td><img src="image" alt="Desired product 3w" /></td>
<td>0%</td>
</tr>
</tbody>
</table>

Reactions carried out in oxygen-saturated dichloromethane. <sup>a</sup>Average of two isolated yields. <sup>b</sup>Carried out in 0.4 M DCE after solvent and concentration optimization. <sup>c</sup>Catalysts 1a or 1b were also tested but failed to furnish the endoperoxide.
in low yields (16%), where the remainder of the mass balance was attributed to oxidative degradation.

Bis(styrene) 2u afforded the identical fused 1,2-dioxane observed in Yoon’s report in 79% yield (5.7:1 dr). Tethered trisubstituted aliphatic alkene substrate 2v, along with bis(styrene) substrate 2w were unfortunately unsuccessful, producing neither of the desired fused 1,2-dioxane products in appreciable amounts. Degradation pathways were dominant for 2v and mainly unreacted starting material was observed 2w.

Conclusion
In the presence of an organic single electron photooxidant, a variety of dienes were demonstrated to undergo a cyclization/endoperoxidation cascade sequence to form 1,2-dioxanes. Requirements for successful diene reactivity are the presence of an oxidizable olefin and an alkene that can efficiently react with the putative alkene cation radical to form a more stable distonic cation radical. If available, a Cope-like pathway can compete and suppress endoperoxide formation. With these parameters in mind, this reaction could provide a platform for the discovery of novel biologically-active endoperoxides.

Supporting Information
Supporting Information File 1
Experimental procedures and characterization data.
[http://www.beilstein-journals.org/bjoc/content/ supplementary/1860-5397-10-128-S1.pdf]

Supporting Information File 2
X-ray data.
[http://www.beilstein-journals.org/bjoc/content/ supplementary/1860-5397-10-128-S2.pdf]

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References
27. Gaussian 09. Revision D.01; Gaussian, Inc.: Wallingford CT, 2013.
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