

Endoperoxide Synthesis by Photocatalytic Aerobic [2 + 2 + 2] Cycloadditions

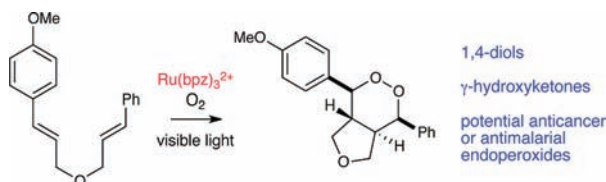
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ABSTRACT



Structurally novel endoperoxides can be synthesized by the photocatalytic cyclotrimerization of bis(styrene) substrates with molecular oxygen. The optimal catalyst for this process is $\text{Ru}(\text{bpz})_3^{2+}$, which is a markedly more efficient catalyst for these photooxygenation reactions than conventional organic photosensitizers. The 1,2-dioxolane products are amenable to synthetic manipulation and can be easily processed to 1,4-diols and γ -hydroxyketones. An initial screen of the biological activity of these compounds reveals promising inhibition of cancer cell growth.

A number of endoperoxides from both natural and synthetic sources have been identified as promising anti-malarial, anticancer, and antiviral agents.¹ Many studies of the mechanism of action of these remarkable compounds suggest that the endoperoxide moiety is the key pharmacophore; homolytic cleavage of the oxygen–oxygen bond by endogenous reductants produces free radicals that are believed to be responsible for the biological activity of this

class of compounds.² In addition, fragmentation reactions of 1,2-dioxanes provide access to 1,4-diols, γ -ketoalcohols, and similar substitution patterns that are difficult to assemble using standard enolate chemistry.³ As a result of both the biological activity and synthetic utility of this class of compounds, there has been considerable interest in the development of methods for the synthesis of structurally novel 1,2-dioxanes.⁴

We recently reported that polypyridyl ruthenium(II) photocatalysts can generate radical cations from olefins upon irradiation with visible light, and we showed that

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(1) For recent reviews of the biological activity of endoperoxides, see: (a) Casteel, D. A. *Nat. Prod. Rep.* **1992**, *9*, 289–312. (b) Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55–73. (c) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601–636. (d) Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425–448. (e) Posner, G. H.; D'Angelo, J.; O'Neill, P. M.; Mercer, A. *Expert Opin. Ther. Pat.* **2006**, *16*, 1665–1672. (f) Dembitsky, V. M. *Eur. J. Med. Chem.* **2008**, *43*, 223–251. (g) Hencken, C. P.; Kalinda, A. S.; Solomon, A.; D'Angelo, J. G. *Amu. Rep. Med. Chem.* **2009**, *44*, 359–378.

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(4) Selected examples: (a) Porter, N. A.; Funk, M. O.; Gilmore, D.; Isaac, R.; Nixon, J. *J. Am. Chem. Soc.* **1976**, *98*, 6000–6005. (b) Porter, N. A.; Gilmore, D. W. *J. Am. Chem. Soc.* **1977**, *99*, 3503–3504. (c) Porter, N. A.; Roe, A. N.; McPhail, A. T. *J. Am. Chem. Soc.* **1980**, *102*, 7574–7576. (d) Xu, X.-X.; Dong, H.-Q. *J. Org. Chem.* **1995**, *60*, 3039–3044. (e) O'Neill, P. M.; Searle, N. L.; Raynes, K. J.; Maggs, J. L.; Ward, S. A.; Storr, R. C.; Park, B. K.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 6065–6068. (f) Ghorai, P.; Dussault, P. H.; Hu, C. *Org. Lett.* **2008**, *10*, 2401–2404. (g) Harris, J. R.; Waetzig, S. R.; Woerpel, K. A. *Org. Lett.* **2009**, *11*, 3290–3293. (h) Gemma, S.; Marti, F.; Gabellieri, E.; Campiani, G.; Novellino, E.; Butini, S. *Tetrahedron Lett.* **2009**, *50*, 5719–5722.

these intermediates could undergo intramolecular [2 + 2] cycloadditions to afford cyclobutane products.^{5–7} In the course of exploring this reaction, we observed that irradiation of bis(styrene) **1** in the presence of a tris(bipyrazyl) ruthenium(II) complex (Ru(bpz)₃(PF₆)₂, **2**•(PF₆)₂)^{8,9} under an atmosphere of oxygen produced the expected [2 + 2] cycloadduct **3** as well as a byproduct that we identified as endoperoxide **4** (Scheme 1). Intrigued by this result, we initiated an investigation to optimize the reaction conditions for production of **4**.

We reasoned that we should be able to partition the reaction toward the [2 + 2 + 2] product by increasing the concentration of oxygen. Indeed, by increasing the pressure of oxygen to 4 atm, we were able to improve the ratio of **4** to **3** to 2.8:1 (Table 1, entries 2 and 3). Next, we found that lowering the reaction concentration led to improved yields of the desired endoperoxide to 77% (entry 5). We also investigated the effect of temperature on the reaction and discovered that lowering the reaction temperature to 5 °C completely suppressed formation of the [2 + 2] cycloadduct without noticeably affecting the rate of endoperoxide formation (entry 6). At this concentration and temperature, we further found that the catalyst loading could be lowered to 0.5 mol % without adverse effect (entry 7). We also attempted the same reaction using the tris(bipyridyl) complex Ru(bpy)₃²⁺ instead of Ru(bpz)₃²⁺ and observed no reaction, indicating that the identity of the bipyrazyl ligands is critical to the success of the reaction (entry 8).

The scope of the photocatalytic endoperoxide synthesis using **2**•(PF₆)₂ is summarized in Table 2. An examination of substituent effects (entries 1–6) revealed that the presence of an electron-donating substituent at the *ortho* or *para* position of one of the styrenes is required for successful reaction. As in the case of the [2 + 2] cycloadditions we previously reported, we suspect that one-electron oxidation of the styrene is the initial step of this process; the failure of less electron-rich substrates such as unsubstituted or *m*-methoxy-substituted styrenes to initiate cycloaddition is consistent with this hypothesis (entries 2 and 4).

Scheme 1

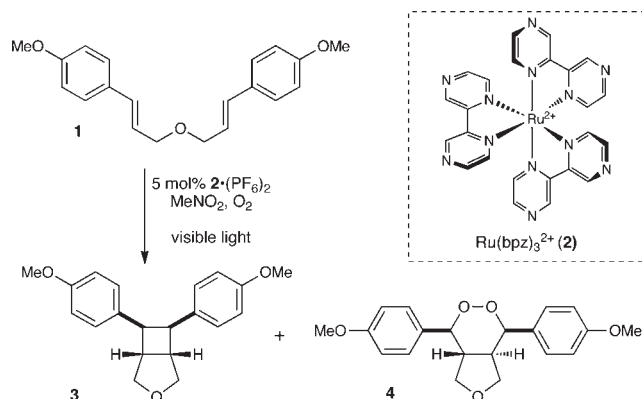


Table 1. Optimization and Control Studies^a

entry	catalyst (mol %)	O ₂ (atm)	concn (M)	temp (°C)	yield (3/4) ^b
1 ^c	Ru(bpz) ₃ (PF ₆) ₂ (5)	1	0.1	23	29%/30%
2 ^c	Ru(bpz) ₃ (PF ₆) ₂ (5)	3	0.1	23	22%/35%
3 ^c	Ru(bpz) ₃ (PF ₆) ₂ (5)	4	0.1	23	16%/44%
4 ^c	Ru(bpz) ₃ (PF ₆) ₂ (5)	4	0.05	23	16%/49%
5	Ru(bpz) ₃ (PF ₆) ₂ (5)	4	0.02	23	11%/77%
6	Ru(bpz) ₃ (PF ₆) ₂ (5)	4	0.02	5	<5%/79%
7	Ru(bpz)₃(PF₆)₂ (0.5)	4	0.02	5	<5%/75% ^d
8	Ru(bpy) ₃ (PF ₆) ₂ (0.5)	4	0.02	5	<5%/<5%
9	tetraphenylporphyrin (5)	4	0.02	5	<5%/<5%
10	9,10-dicyanoanthracene (5)	4	0.02	5	<5%/<5%
11	triphenylpyrylium•BF ₄ (5)	4	0.02	5	<5%/20%

^a Reactions were conducted in a 135 mL glass pressure vessel and irradiated for 30 min with a 200 W incandescent light bulb unless otherwise noted. ^b Yields determined by ¹H NMR spectroscopy using an internal standard, unless noted. ^c Irradiated for 2 h. ^d Isolated yield.

Significant variation of the substitution pattern, however, is possible; electron-withdrawing halogen substituents are tolerated at the *meta* position, and other electron-donating moieties such as silyloxy and carbamate can be used to activate the styrene (entries 7–9). The reacting partner cannot be an aliphatic olefin (entry 10), but olefins tolerated in this role include styrenes bearing both electron-donating and -withdrawing substituents as well as enynes (entries 11–14). Substitution on the α-position of the olefin is also tolerated (entry 15), although β-substitution results in lower yield and poorer diastereoselectivity. Finally, while we were unable to use these conditions to conduct efficient photooxidation of untethered styrenes, a

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(6) For recent reviews of transition metal photoredox catalysis, see: (a) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785–9789. (b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527–532. (c) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102–113. (d) Teplý, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859–917.

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(9) We recently reported radical cation Diels–Alder cycloadditions catalyzed by Ru(bpz)₃²⁺. See: Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350–19353.

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variety of tethering groups can be used in this process (entries 16–18).

Table 2. Scope of the Endoperoxide Synthesis^a

entry	substrate	product	time	yield ^b	dr ^b
1	R ¹ = 4-MeOC ₆ H ₄ (PMP)	R ² = Ph	30 min	92%	6:1
2	R ¹ = 3-MeOC ₆ H ₄	R ² = Ph	24 h	0%	--
3 ^c	R ¹ = 2-MeOC ₆ H ₄	R ² = Ph	24 h	45%	10:1
4	R ¹ = Ph	R ² = Ph	24 h	0%	--
5	R ¹ = 2,4-(MeO) ₂ C ₆ H ₃	R ² = Ph	2 h	58%	4:1
6	R ¹ = 3,4-(MeO) ₂ C ₆ H ₃	R ² = Ph	1 h	91%	7:1
7 ^c	R ¹ = 3-Br-4-MeOC ₆ H ₃	R ² = Ph	12 h	65%	8:1
8	4-TIPSO-C ₆ H ₄	R ² = Ph	2 h	75%	10:1
9	4-BocNH-C ₆ H ₄	R ² = Ph	30 min	96%	6:1
10	R ¹ = PMP	R ² = Me	24 h	<5%	--
11	R ¹ = PMP	R ² = PMP	30 min	75%	>10:1
12	R ¹ = PMP	R ² = 2-CF ₃ C ₆ H ₄	2 h	82%	4:1
13	R ¹ = PMP	R ² = 4-ClC ₆ H ₄	2 h	86%	5:1
14	R ¹ = PMP	R ² = -C≡C-Ph	2 h	82%	2:1
15 ^c			2 h	81%	>10:1
16	X = NTs		2 h	73%	>10:1
17	X = C(CO ₂ Et) ₂		2 h	92%	>10:1
18	X = CH ₂		2 h	80%	>10:1

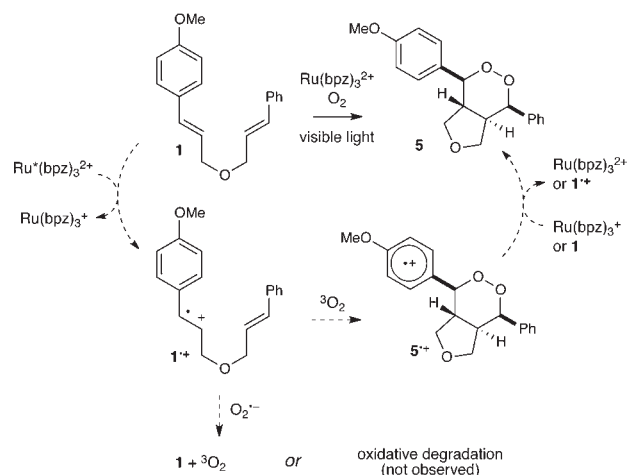
^a Unless otherwise noted, reactions were conducted using 0.5 mol % Ru(bpz)₃(PF₆)₂ in a glass pressure vessel and irradiated with a 200 W incandescent light bulb. ^b Yields and diastereomer ratios represent the averaged results of two reproducible experiments. ^c Conducted using 2 mol % Ru(bpz)₃(PF₆)₂.

The photochemical synthesis of 1,2-endoperoxides by [2 + 2 + 2] aerobic cycloaddition of olefins is most commonly achieved by irradiation of 1,1-diarylethenes in the presence of oxygen and 9,10-dicyanoanthracene (DCA) as a photosensitizer.¹⁰ The mechanism is believed to involve photoinduced one-electron oxidation of the alkene to the corresponding radical cation (e.g., **1** to **1**^{•+}, Scheme 2). This reactive intermediate undergoes [2 + 2 + 2] cycloaddition with triplet oxygen to afford an endoperoxide radical cation (**5**^{•+}) that gives the 1,2-dioxolane product (**5**) upon reduction by either the reduced sensitizer or another equivalent of substrate.^{10g} The scope of the [2 + 2 + 2] cycloaddition, however, is quite limited when DCA is used as a photosensitizer, and only extremely electron-rich 1,1-disubstituted styrenes (e.g., 1,1-bis(*p*-methoxyphenyl)ethylene) have been shown to give good yields of 1,2-dioxolane. This has been attributed to the ability of DCA to sensitize the formation of superoxide radical.¹¹ The formation of this reactive oxygen species is problematic

(11) In accord with this hypothesis, Mattay has reported that triphenylpyrylium tetrafluoroborate (TPT), which cannot form superoxide, is a more effective photosensitizer for photooxidation of 1,1-diphenylethylene than DCA, although the reported yield was still modest. See: Mattay, J.; Vondenhof, M.; Denig, R. *Chem. Ber.* **1989**, *122*, 951–958.

because (1) superoxide reacts with alkene radical cations to produce oxidative cleavage products,^{10b,12} which are the main products when less electron-rich olefins are utilized, and (2) competitive quenching of the photosensitizer by oxygen reduces the efficiency of the desired cycloaddition by decreasing the rate of formation of the key alkene radical cation.

Scheme 2. Proposed Mechanism for Endoperoxide Formation



Compared to standard organic photosensitizers, Ru(bpz)₃²⁺ is a superior photocatalyst for the formation of endoperoxides and significantly extends the scope of this reaction. Table 1, entries 9–11 show that the photooxygenation of **1** using tetraphenylporphyrin or DCA is not successful and that the yield of photooxidation is dramatically reduced using triphenylpyrylium tetrafluoroborate (TPT) even when the catalyst loading is increased to 5 mol %. We attribute these observations to several factors. (1) The homoleptic bipyrazyl complex Ru(bpz)₃²⁺ is significantly more electron-deficient than Ru(bpy)₃²⁺. Thus, its photoexcited state, Ru*(bpz)₃²⁺ (+1.4 V vs SCE), can oxidize **1** (+1.1 V) readily to generate the key radical cation intermediate, while Ru*(bpy)₃²⁺ (+0.8 V) cannot. (2) The observation that tetraphenylporphyrin fails to generate any of the desired endoperoxide suggests that singlet oxygen is not involved in the formation of endoperoxide **5**. (3) Like photoexcited TPT*, Ru*(bpz)₃²⁺ does not generate superoxide that might lead to oxidative cleavage of the olefin.¹¹ (4) Ruthenium polypyridyl complexes possess a longer excited state lifetime than common organic PET sensitizers. For example, the excited state lifetime of *TPT is only 3 ns,¹³ while the lifetime of Ru*(bpz)₃²⁺ has been reported to be 740 ns in MeCN.¹⁴

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(16) See the Supporting Information for details about these screening studies.

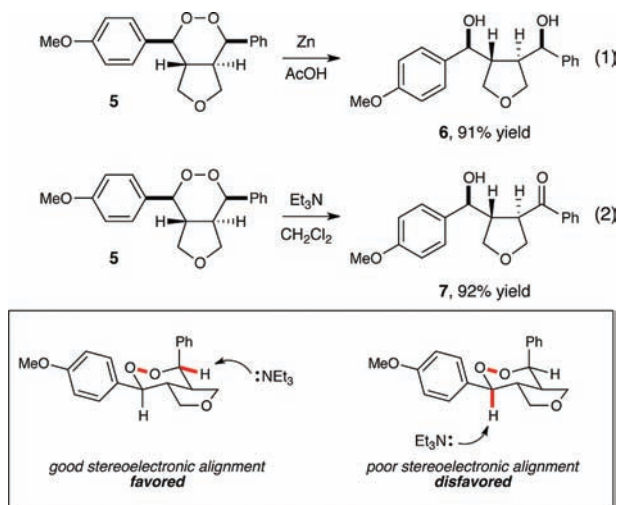


Figure 1. Origin of regioselectivity in Kornblum–DeLaMare rearrangement of **5**.

In addition to their biological activity, endoperoxide structures are valuable as versatile synthetic intermediates. When endoperoxide **5** is treated with zinc metal in acetic acid, the O–O bond undergoes reductive cleavage in high yields to afford 1,4-diol **6**, which retains all four contiguous stereocenters set in the photooxygenation reaction (Figure 1, eq 1). When **5** is treated with triethylamine, the endoperoxide undergoes a highly regioselective Kornblum–DeLaMare rearrangement¹⁵ to afford γ -hydroxyketone **7** (eq 2). We attribute the high selectivity to better stereoelectronic overlap between the equatorial C–H bond and the O–O σ^* antibonding orbital (Figure 1). Thus, the products of this new photocatalytic process enable the construction of stereochemically well-defined 1,4-diols as well as γ -hydroxyketones that are difficult to assemble using alternate methods.

Finally, the endoperoxides synthesized in this study have not previously been accessible using other synthetic methods, and we speculated that they might have biological activity consistent with that of other endoperoxides. As an initial exploration of their potential activity, a selection of the compounds reported in Table 2 were assayed for cytotoxicity in human prostate cancer cell lines (Du145). Indeed, these novel endoperoxides exhibited a range of IC_{50} values, varying from $> 100 \mu\text{M}$ for the least potent members (Table 2, entries 1, 5, and 11) to $4.6 \mu\text{M}$ for the most potent (entry 14).¹⁶ We believe, therefore, that this method provides an attractive approach to the production of endoperoxide structures whose biological activity profiles have yet to be fully explored.

In summary, $\text{Ru}(\text{bpz})_3^{2+}$ is an excellent photocatalyst for the synthesis of endoperoxides by [2 + 2 + 2] aerobic photooxygenation of α,ω -dienes and is considerably more effective than organic photosensitizers that have commonly been utilized for photooxygenation. This reaction can rapidly generate structurally complex endoperoxides that cannot be synthesized by other means from relatively simple bis(styrene) starting materials. We expect this method will be useful in the discovery of potential antimalarial and anticancer compounds, and we are now initiating a program aimed at studying this possibility in greater detail.

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

The authors declare no competing financial interest.