



[3+2] Photooxygenation of aryl cyclopropanes via visible light photocatalysis



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ABSTRACT

We report that $\text{Ru}(\text{bpz})_3^{2+}$ is an excellent sensitizer for the photooxygenation of aryl cyclopropanes upon irradiation with visible light. The effectiveness of this photocatalyst enables the synthesis of a range of five-membered endoperoxides in excellent yield with quite low (0.5 mol %) catalyst loadings even when standard household light sources are utilized.

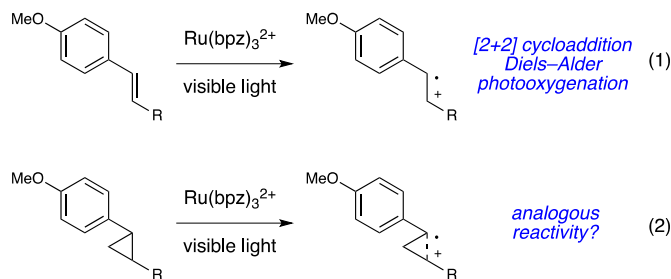
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1. Introduction

Cyclic peroxides are the characteristic pharmacophores of a class of biologically active compounds that exhibit a range of potent antibacterial, anticancer, and antimalarial activities.¹ Five-membered endoperoxides, in particular, have also been valued as synthetic intermediates because of the ease with which their O–O bonds can be reductively cleaved to afford 1,3-diols.² Many methods for the preparation of five-membered endoperoxides involve sequences that require pre-installation of the reactive peroxide moiety,³ which often limits the scope and yield of the reaction. An attractive alternative strategy involves the ring-expanding reaction of cyclopropanes with molecular oxygen. Vinylcyclopropanes can be induced to undergo this transformation upon reaction with phenylthiyl or phenylselenenyl radicals,⁴ although the requirement for a vinyl substituent represents a significant limitation on the generality of this process. An arguably more general method is the photooxygenation of aryl cyclopropanes, originally developed by Mizuno and Otsuji,⁵ which is commonly catalyzed by organic PET sensitizers such as 9,10-dicyanoanthracene (DCA, **2**).

For the past several years, our research group has been developing methods that exploit the remarkable photoredox properties of transition metal polypyridyl complexes to perform

a variety of synthetically useful radical ion processes.^{6,7} We have found that electron-deficient bipyrazyl and bipyrimidyl complex of Ru(II) in particular are excellent catalysts for the photochemical one-electron oxidation of electron-rich styrenes (Eq. 1), which has enabled us to develop a suite of synthetically useful reactions of the resulting radical cations.^{8,9} Recognizing that the chemistry of cyclopropanes can often offer homologous reactivity to that of olefins, we have become interested in exploring radical cation reactions of electron-rich cyclopropanes (Eq. 2). Zheng recently demonstrated that $\text{Ru}(\text{bpz})_3^{2+}$ (**1**) is an effective visible light photocatalyst for the [3+2] cycloaddition of amine-substituted cyclopropanes with a variety of alkenes.¹⁰ In this manuscript, we demonstrate that $\text{Ru}(\text{bpz})_3^{2+}$ also catalyzes aerobic photooxygenation of electron-rich aryl cyclopropanes upon irradiation with visible light and is a markedly more effective catalyst for this transformation than DCA (Scheme 1).



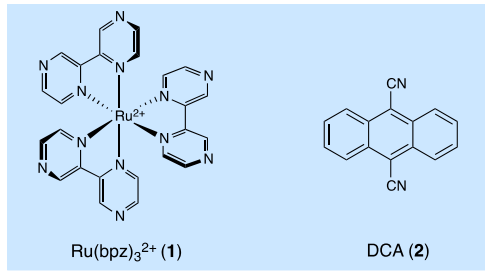
Scheme 1.

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2. Results and discussion

We began our initial investigations by examining the reaction of 1-(*p*-methoxyphenyl)-2-phenylcyclopropane (**3a**) under conditions based upon those we had developed for the synthesis of six-membered endoperoxides by aerobic [2+2+2] cycloaddition.¹¹ Thus, irradiation of a solution of **3a** in MeNO₂ with a 23 W compact fluorescent light bulb (CFL) in the presence of 0.5 mol % Ru(bpz)₃(PF₆)₂ under an atmosphere of O₂ afforded 16% yield of the expected endoperoxide **4a** (Table 1, entry 1); this compound was isolated as a 3:1 mixture of *syn* to *anti* diastereomers. While the reaction was much less efficient under an atmosphere of air in place of oxygen (entry 2), the yield could be easily improved to synthetically useful levels by conducting the reaction under 2 atm of oxygen (entry 3). We attempted the same reaction using 10 mol % of DCA as a sensitizer and observed no formation of **4a** (entry 4), indicating that Ru(bpz)₃²⁺ is indeed a more effective visible light photocatalyst for this transformation. Nitromethane proved to be essential in this reaction; other solvents resulted in dramatically diminished reactivity (entries 5–8). However, a 1:1 mixture of MeNO₂ and toluene allowed us to conduct the reaction at –30 °C, which resulted in a modest improvement of both the *syn/anti* ratio

Table 1
Optimization of photooxygenation of **1**



Entry	O ₂	Solvent	T (°C)	Yield ^a (%)	<i>syn/anti</i> ^b
1	15 psi	MeNO ₂	23	16	3:1
2	Air	MeNO ₂	23	3	3:1
3	30 psi	MeNO ₂	23	90	4:1
4 ^c	30 psi	MeNO ₂	23	0	—
5	30 psi	MeCN	23	36	4:1
6	30 psi	Acetone	23	2	—
7	30 psi	Toluene	23	0	—
8	30 psi	DMSO	23	0	—
9 ^d	30 psi	1:1 MeNO ₂ /toluene	–30	99	5:1
10 ^{d,e}	30 psi	1:1 MeNO ₂ /toluene	–30	0	—
11 ^{d,f}	30 psi	1:1 MeNO ₂ /toluene	–30	0	—

^a Yields determined by ¹H NMR spectroscopy using an internal standard unless otherwise noted.

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

^c Using 10 mol % of 9,10-dicyanoanthracene (DCA) as photosensitizer in place of Ru(bpz)₃(PF₆)₂.

^d Reaction time: 3 h.

^e Reaction conducted in the dark.

^f Reaction conducted without Ru(bpz)₃²⁺.

and the yield of the reaction (entry 9). Control experiments under these conditions showed that no reaction occurred in the absence of light or of Ru(bpz)₃²⁺, confirming the necessity of photoexcited Ru(II) in order for this transformation to occur.

Experiments probing the scope of this reaction are summarized in Table 2. Mizuno and Otsuji's proposal for the mechanism of the

DCA-sensitized photooxygenation of cyclopropanes⁵ suggests that this reaction is initiated by one-electron oxidation of the substrate to afford the corresponding radical cation. In line with this expectation, no endoperoxide is formed from unsubstituted 1,2-diphenylcyclopropane (entry 2), even after long reaction times. We similarly observed no reaction using a cyclopropane substrate bearing one 3-methoxyphenyl substituent (entry 3). The analogous 2-methoxy-substituted substrate underwent photooxygenation, but at a significantly slower rate than the

Table 2
Scope of the photooxygenation reaction^a

Entry	substrate	Product	Time (h)	Yield ^b (%)	<i>syn/anti</i> ^c
1	3a R=4-OMe	4a	3	99	5:1
2	3b R=H	4b	48	0	—
3	3c R=3-OMe	4c	48	0	—
4 ^d	3d R=2-OMe	4d	48	47	5:1
5	3e R=4-OH	4e	1	78	>10:1
6	3f R=4-OTIPS	4f	3	95	4:1
7	3g R=4-NH ₂	4g	1	70	>10:1
8	3h R=4-NHBoc	4h	3	93	5:1
9	3i R=2,4-OMe	4i	1	99	10:1
10 ^d	3j R=3,4-OMe	4j	24	77	5:1
11	3k R=2,4-OMe	4k	1	98	6:1
12	3l R=4-OMe	4l	1	99	9:1
13	3m R=4-Me	4m	1	98	10:1
14	3n R=4-Br	4n	1	99	9:1
15	3o R=4-Cl	4o	1	98	10:1
16	3p R=3-Cl	4p	1	97	>10:1
17	3q R=2-Cl	4q	1	99	10:1
18	3r R=4-CF ₃	4r	1	98	10:1
19	3s R=2-CF ₃	4s	1	94	>10:1
20	3t	4t	1	75	6:1
21	3u	4u	24	98	1:1
22	3v	4v	1	96	10:1
23	3w	4w	1	99	6:1
24	3x	4x	12	94	—

^a Unless otherwise noted, reactions were conducted in 1:1 MeNO₂/toluene using 0.5 mol % Ru(bpz)₃²⁺, 30 psi O₂, and a 23 W CFL bulb.

^b Values represent the averaged isolated yields from two reproducible experiments.

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

^d Reaction conducted using 5 mol % Ru(bpz)₃(PF₆)₂.

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