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Singlet Oxygen Generation from a Water-Soluble Hypervalent Iodine(V) Reagent AIBX and H_2O_2: An Access to Artemisinin

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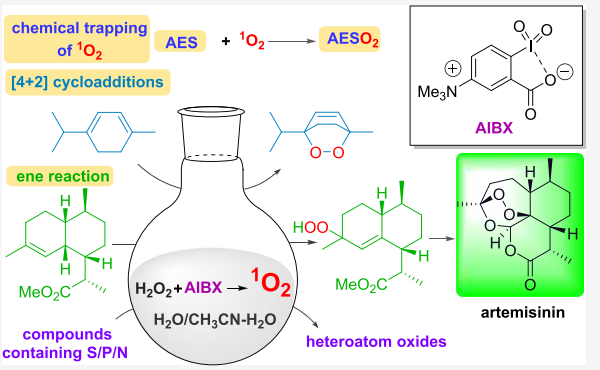
ABSTRACT: Herein, we report an efficient method for the chemical generation of $^1O_2$ by treatment of H_2O_2 with AIBX, a highly water-soluble, bench-stable, recyclable hypervalent iodine(V) reagent developed by our group. The generation of $^1O_2$ was confirmed by the following results: (1) capture of $^1O_2$ with the sodium salt of anthracene-9,10-bis(ethanesulfonate) produced the corresponding endoperoxide and (2) TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) produced by the oxidation of 2,2,6,6-tetramethylpiperidine with $^1O_2$ generated using the AIBX/H_2O_2 system was detected by electron spin resonance spectroscopy. To illustrate the potential utility of this method for organic synthesis, we used the AIBX/H_2O_2 system to perform typical reactions of $^1O_2$: [2 + 2]/[4 + 2] cycloadditions, Schenck ene reactions, and heteroatom oxidation reactions, which afforded the corresponding products in high yields. Moreover, we used the method to synthesize the antimalarial drug artemisinin. Finally, we demonstrated that AIBX could be regenerated after the reaction by means of a workup involving extraction and removal of water to obtain a precursor of AIBX, which could then be re-oxidized.



INTRODUCTION

Singlet oxygen, $^1O_2(^1\Delta_g)$, is the lowest excited electronic state of molecular oxygen (22.4 kcal/mol above the triplet oxygen [$^3O_2$], which is the ground state). Singlet oxygen participates in reactions that distinguish it from $^3O_2$, including [2 + 2]/[4 + 2] cycloadditions, Schenck ene reactions, and oxidation reactions of various heteroatoms.[1] As an important active oxygen species and synthetic reagent, $^1O_2$ is still at the forefront of research due to its unique reactivity,[2] and it has been widely used for photodynamic therapy of tumors,[3] wastewater treatment,[4] and organic synthesis of natural products including withanolide A and pandamarine and pharmaceuticals such as milbemycin E, the antibiotic (±)-PS-5, and the antimalarial drug artemisinin.[5]

$^1O_2$ is typically generated by dye-sensitized photooxidation of $^3O_2$ (Scheme 1a),[6] but scaling up this process for industrial use is not a simple task.[7] Therefore, chemical methods for generating $^1O_2$ without light have been developed as alternatives to the photochemical method.[8] The first chemical method to be reported, in the early 1960s, involves the oxidation of H_2O_2 with NaOCl (Scheme 1b).[9] Subsequently, methods for disproportionation of H_2O_2 to afford $^1O_2$ with catalysis by transition-metal ions such as Cr^{VI}, Ti^{IV}, Mo^{VI}, or La^{III} were developed.[10] Moreover, $^1O_2$ formation has also been observed in reactions of ozone with amines, sulfides, phenols, and nucleophilic anions (NO_2^-, N_3^-, Br^-, Cl^-, and CN^-; Scheme 1c).[11] Other reported chemical sources of $^1O_2$ include peroxides ($KHSO_5$,[12] $CaO_2{\cdot}2H_2O_2$,[13] K_3CrO_8,[14] Na_2MoO_8,[15] arene endoperoxides,[16] peracids,[17] cholesterol hydroperoxide,[18] and dimethyldioxirane [DMDO][19]) and triphenylphosphite ozonide[20] (Scheme 1d). However, because many peroxides and the ozonide are thermally unstable, the development of a safe, practical, efficient chemical method for generating $^1O_2$ would be desirable for both laboratory and industrial applications.

We reasoned that the combination of H_2O_2 and a hypervalent iodine reagent might be useful for this purpose. Hypervalent iodine reagents have drawn considerable attention not only because of their richly varied reactivity but also because they are stable, easy to handle, and environmentally benign.[21] In a previously reported work, H_2O_2 has been used in combination with a hypervalent iodine reagent, either $PhIO_2$ or $PhI(OCOCF_3)_2$, for the generation of $^1O_2$.[22] However, the yields of $^1O_2$ (46% and 55%, respectively) are only moderate, which limits the synthetic utility of these combinations. Because the moderate yield of $^1O_2$ obtained from H_2O_2/$PhIO_2$ might be due to the poor water solubility of $PhIO_2$ in aqueous H_2O_2, we speculated that the yield could be improved

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Scheme 1. Existing Methods for Generation of Singlet Oxygen

(a) The dye-sensitized photooxidation of triplet oxygen ($^3O_2$)

Sens $\xrightarrow{h\nu}$ ^{1}(Sens*) $\longrightarrow$ ^{3}(Sens*) $\xrightarrow{^3O_2}$ $^1O_2$ + Sens

Sensitizer (Sens): methylene blue, rose bengal, hematoporphyrin, eosin yellow, riboflavin, erythrosin B, etc.

(b) The reaction of hydrogen peroxide with hypochlorite

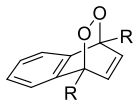
H_2O_2 + ClO^- $\longrightarrow$ $^1O_2$ + H_2O + Cl^-

(c) The reaction of ozone with various substrates

O_3 + S $\longrightarrow$ $^1O_2$

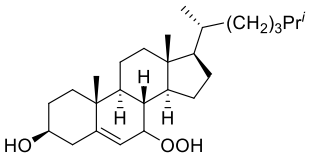
Substrates (S): amines, sulfides, phenols and nucleophilic anions (NO_2^-, N_3^-, Br^-, Cl^- and CN^-), etc.

(d) Other chemical sources of $^1O_2$

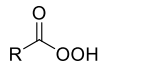


R = Me, CH_2OH, $(CH_2)_2COO^-$, $CH_2SO_3^-$, etc.

arene endoperoxides



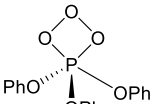
cholesterol hydroperoxide



R = Me, *m*-ClC_6H_4, etc.

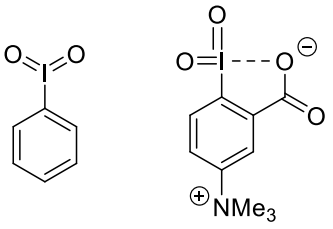
peracids

DMDO



triphenylphosphite ozonide

by using a more water-soluble hypervalent iodine reagent, such as AIBX (Figure 1), a bench-stable, recyclable zwitterionic



$PhIO_2$ **AIBX**

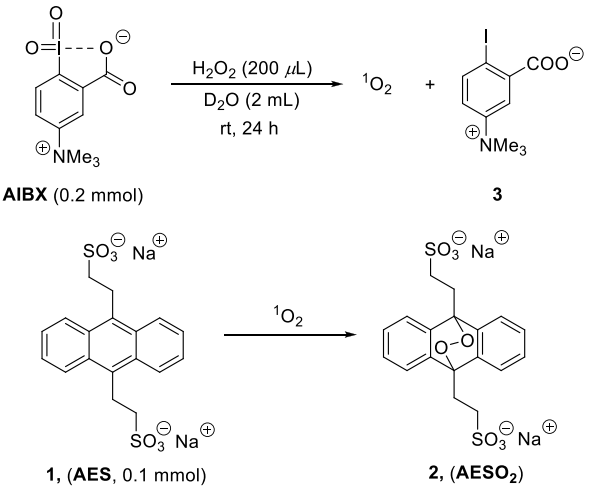
Figure 1. Structures of $PhIO_2$ and AIBX.

pseudocyclic iodylarene that we reported in 2011.[23] AIBX, which is air- and moisture-stable and can be stored at ambient temperature for at least 3 months without decomposition, bears a carboxylate anion and a trimethylammonium cation at the *ortho* and *para* positions of the phenyl ring, respectively, which make this compound highly water-soluble (up to 0.38 M at room temperature). Herein, we report that treatment of aqueous H_2O_2 with AIBX is an efficient method for the chemical generation of $^1O_2$.

RESULTS AND DISCUSSION

To observe $^1O_2$ formation in the AIBX/aq. H_2O_2 system, we trapped $^1O_2$ with the sodium salt of anthracene-9,10-bis(ethanesulfonate) (AES, **1**),[22a] a water-soluble compound that undergoes a rapid [4 + 2] cycloaddition reaction with all available $^1O_2$ to yield the corresponding stable endoperoxide ($AESO_2$, **2**; Scheme 2).[2g,16,18]

Scheme 2. Generation and Trapping of Singlet Oxygen



The formation of $AESO_2$ can be easily monitored by means of ^1H and $^{13}C\{^1H\}$ NMR spectroscopy (Figures 2 and 3). Comparison with the NMR spectrum of an authentic sample of $AESO_2$[24] showed that the AES in a reaction mixture containing AIBX and H_2O_2 was completely converted into $AESO_2$ and that the AIBX was reduced to 2-iodo-5-(trimethylammonio)benzoate (**3**, Scheme 2). Moreover, when we used electron spin resonance (ESR) spectroscopy to analyze an AIBX/H_2O_2 reaction mixture containing 2,2,6,6-tetramethylpiperidine (TEMP) as a spin trap agent,[25] we observed the characteristic 1:1:1 three-line signal of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) with a hyperfine coupling constant (a_N) of 16.6 G (Figure 4), which is identical to the value reported in the literature.[26] The formation of $AESO_2$ and ESR detection of TEMPO unambiguously demonstrated that $^1O_2$ was generated from the AIBX/H_2O_2 system.

Encouraged by these results, we next investigated the influence of the amount of H_2O_2 on the yield of $^1O_2$ using the yield of $AESO_2$ as a metric (Table 1). When the amount of 50% H_2O_2 was 100 μL (19.5 mol/L, 1.95 mmol), the yield of $AESO_2$ was 36% (entry 1). Increasing the amount to 200 μL (3.9 mmol) resulted in a similar yield (35%, entry 2), but as the amount was increased further, the $AESO_2$ yield increased substantially, reaching a maximum of 91% at 600 μL (entries 3−6). However, increasing the amount further (to 700 μL, 13.65 mmol) slightly decreased the yield (to 85%, entry 7). Therefore, the optimal amount of 50% H_2O_2 (600 μL, 11.7 mmol, entry 6) was used in subsequent experiments.

We also screened the following other water-soluble hypervalent iodine reagents: PISA, HTIB, AIBA, PIBS, IBX-SO_3K, and *m*IBX (Scheme 3). Singlet oxygen was not detected when PISA or HTIB was used. In contrast, the other reagents did generate $^1O_2$, but the yields were low or moderate.

To illustrate the potential synthetic utility of the present method, we investigated [2 + 2]/[4 + 2] cycloaddition reactions and heteroatom oxidation reactions of $^1O_2$ generated from the AIBX/H_2O_2 system (method A, Table 2). A mixed solvent consisting of CH_3CN and H_2O was used to increase the solubility of the organic substrates. Reaction of 2,2′-bi(adamantanylidene) (**4**) afforded the corresponding per-

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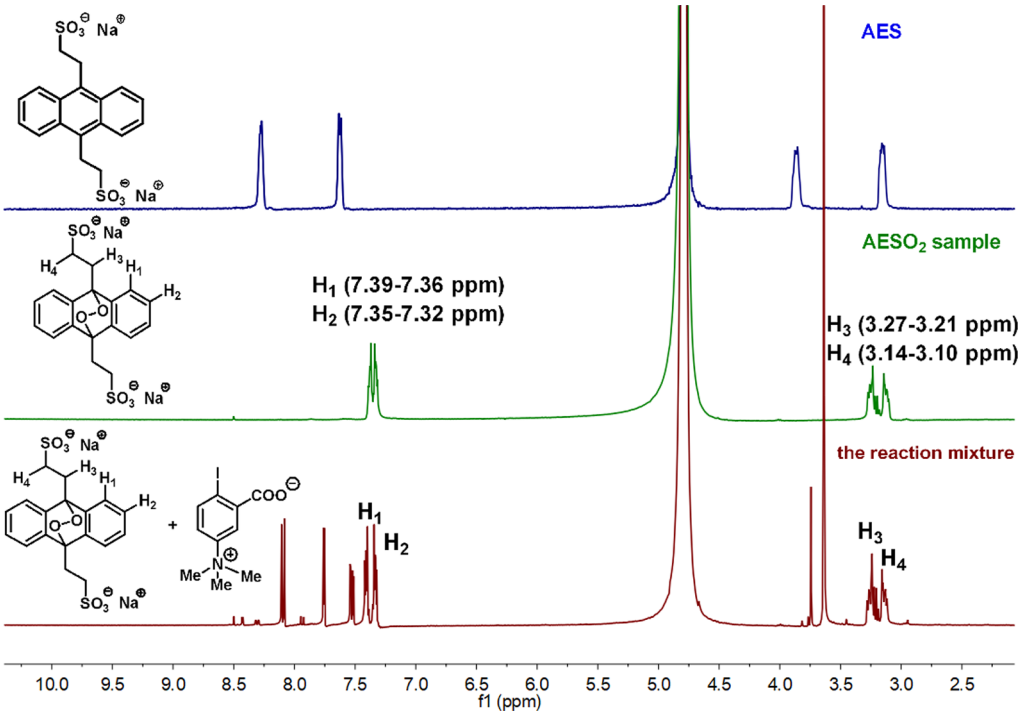

Figure 2. ^{1}H NMR spectra of AES, an authentic $AESO_2$ sample, and an AIBX/H_2O_2/AES mixture.

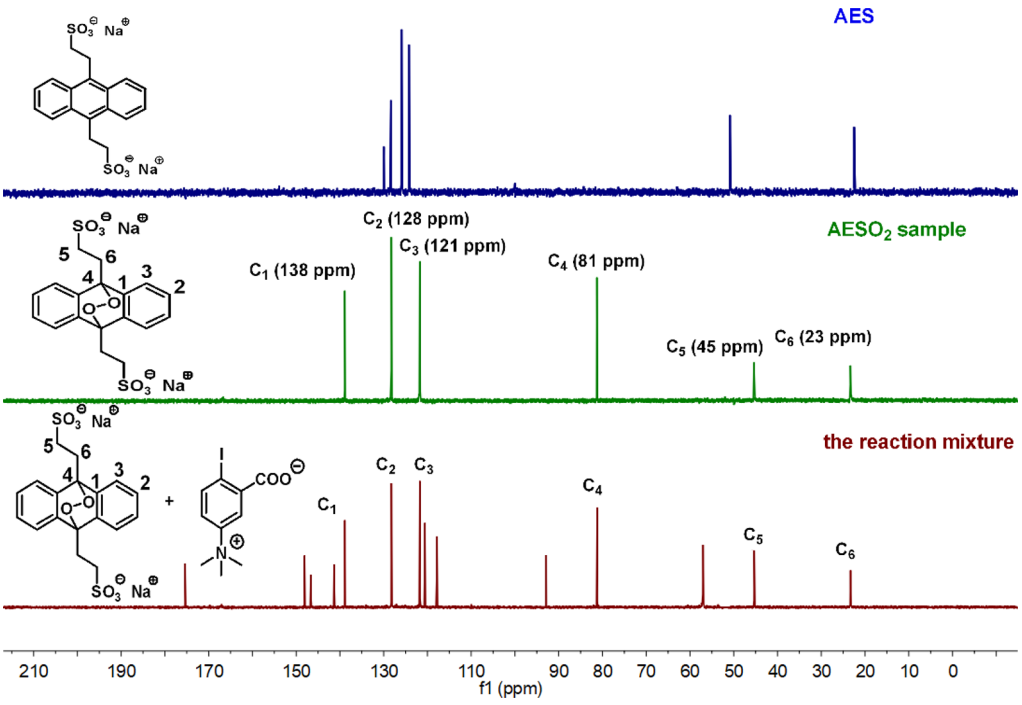

Figure 3. $^{13}C\{^{1}H\}$ spectra of AES, an authentic $AESO_2$ sample, and an AIBX/H_2O_2/AES mixture.

oxide **5** in 79% yield via a [2 + 2] cycloaddition (entry 1), and reactions of 1,3-cyclohexadiene (**6**) and α-terpinene (**8**) gave the endoperoxide products **7** and **9**[27] in 62 and 87% yields, respectively, via [4 + 2] cycloadditions (entries 2 and 3). Endoperoxide **11** could be obtained from the relatively low reactivity of diphenylanthracene (**10**), but the yield was 50% because conversion of **10** was only moderate (55%, entry 4). However, the electron-deficient substrate tropone (**12**) gave disappointing results (entry 5). 1,3-Diphenylisobenzofuran (**14**) was oxidized to 1,2-dibenzoylbenzene (**15**) in 84% yield via [4 + 2] cycloaddition and subsequent ring opening (entry 6). Similarly, 2,5-dimethyl furan (**16**) was converted to (*E*)-3-hexene-2,5-dione (**17**) in 50% overall yield via reduction of the hydroperoxyl intermediate with PPh_3 (entry 7).[10f] Dearomatization of mesitol (**18**) was achieved in 40% yield (entry 8). The oxygenation of 1-methyltryptophan derivative **20** provided a 27% yield of 3-hydroxypyrroloindole derivative **21**, which is an important intermediate in the synthesis of the potent anthelmintic natural product CJ-12663 (entry 9).[28] Phosphorus- and sulfur-containing compounds could be oxidized with

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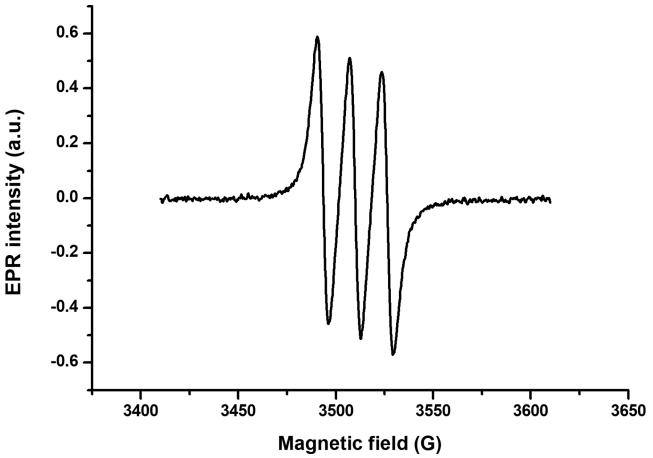


Figure 4. ESR spectra of TEMPO from the oxidation of TEMP with the AIBX/aq. H_2O_2 system.

Table 1. Influence of the Amount of 50% H_2O_2 on the Yield of Singlet Oxygen

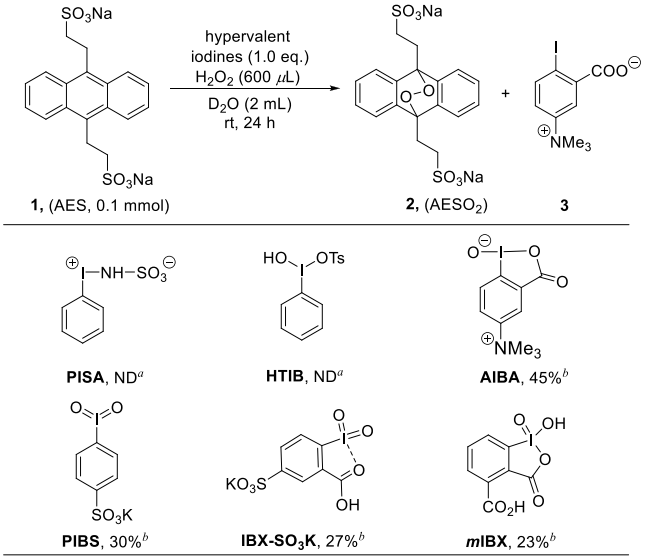
1, (AES, 0.1 mmol) **2**, ($AESO_2$)

entry	volume of 50% H_2O_2 (μL)	yield of $AESO_2$ (%)[a]
1	100	36
2	200	35
3	300	53
4	400	65
5	500	72
6	600	91
7	700	85

[a]Determined by ^{1}H NMR spectroscopy.

the AIBX/H_2O_2 system. For example, oxidation of PPh_3 (**22**) afforded triphenylphosphine oxide (**23**) in a quantitative yield (entry 10), and oxidation of Fmoc-L-Met-OMe (**24**) gave a 1:3.88 mixture of sulfoxide **25** and sulfone **26**. When 6.0 equiv of AIBX was used instead of 2 equiv, the oxidation products were obtained in a quantitative yield, and the ratio of **25** and **26** was 1:10.7 (entry 11); that is, the yield of sulfone **26** increased as the amount of AIBX was increased. Finally, we carried out a Schenck ene reaction of $^1O_2$ and dihydroartemisinic methyl ester (**27**) (for details, see Table S1 of the Supporting Information), which smoothly gave tertiary hydroperoxide **28** in 48% yield (data not shown). The yield of **28** was determined by ^{1}H NMR spectroscopy, owing to the selective degradation of the hydroperoxide; the characteristic peak was identical to that previously reported.[29] In an attempt to improve the yield of **28**, we replaced AIBX with *m*AIBX, an isomer bearing a trimethylammonium cation at the *meta*-position of the phenyl ring (Figure 5; for details on the synthesis of AIBX and *m*AIBX, see the Supporting Information), and were pleased to find that the yield of **28** increased to 66% (entry 12). To increase the consumption of

Scheme 3. Screening of Other Water-Soluble Hypervalent Iodine Reagents



[a]ND = $^1O_2$ was not detected. [b]Yield of $^1O_2$ was determined by ^{1}H NMR spectroscopy.

ester **27**, we increased the amount of *m*AIBX to 8 equiv and found that **28** could be obtained in 77% yield (entry 13).

For comparison, substrates were also subjected to the conventional H_2O_2/NaOCl method (method B, Table 2). It was found that only for two substrates **16** and **18**, method B could give better yields than method A. For substrates **8**, **12**, and **22**, these two methods yielded equal results. It was worth noting that the remaining seven substrates performed much better when using the current combination of AIBX/H_2O_2. Notably, another two methods were also tried to synthesize the product **28**. Reaction of **27** with $KHSO_5$, a water-soluble inorganic peroxide that decomposes to generate $^1O_2$, gave no detectable **28**; instead, a complex mixture was obtained, owing to the strong acidity of the aqueous $KHSO_5$ solution. **28** was produced in 29% yield with the combination of the hypervalent iodine(III) reagent $PhI(OCOCF_3)_2$ and H_2O_2; the yield of recovered **27** was 52%.[22c] These results demonstrate the superiority of our method to the other three methods.

To demonstrate the synthetic utility of the AIBX/H_2O_2 system, we used it in the key step of a synthesis of the antimalarial drug artemisinin (**29**, Scheme 4).,[7b,c,30,31] Specifically, the ester **27** was prepared from dihydroartemisinic acid (DHAA), and then a Schenck ene reaction of $^1O_2$ and **27** gave the crude hydroperoxide **28** in 77% yield after extraction and concentration. Treatment of **28** with trifluoroacetic acid under a balloon of O_2 afforded a 70% yield of artemisinin. The overall yield was 51%, which is higher than that reported for the established photochemical method.[7c]

We also investigated the regeneration of AIBX (Figure 6). Upon completion of the oxidation of PPh_3 with the AIBX/H_2O_2 system, any remaining AIBX was reduced to **3** by addition of saturated aqueous sodium sulfite. Extraction of the reaction mixture with EtOAc removed the triphenylphosphine oxide, leaving **3** in the aqueous phase, owing to its high water solubility. Evaporation of H_2O afforded **3** in 95% yield. Finally, AIBX could then be obtained in 91% yield by oxidation of the recovered **3** with dimethyldioxirane, which was reduced to acetone.

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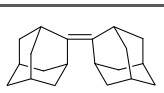
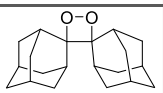
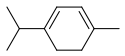
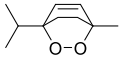
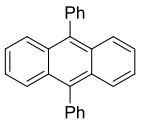
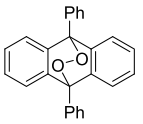
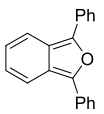
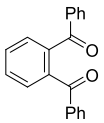
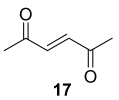
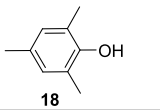
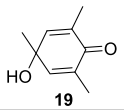
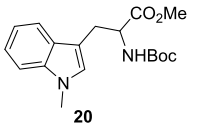
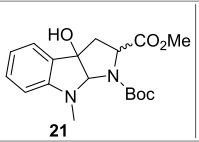
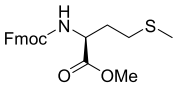
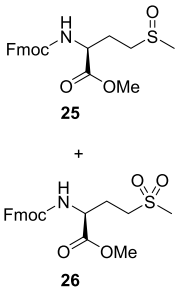
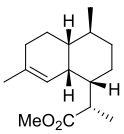
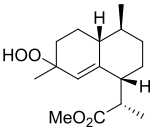
Table 2. Substrate Scope[a]

Substrate (0.2 mmol) → method A: AIBX (2 eq.), H_2O_2 (600 μL), CH_3CN/H_2O (4 mL, V/V=1:1), rt; method B: NaClO (90 μL), H_2O_2 (600 μL), CH_3CN/H_2O (4 mL, V/V=1:1), rt → Product(s)

entry	substrate	product(s)	time (h)	yield (%)[b] method A	yield (%)[b] method B
1	 **4**	 **5**	48	79	0
2	 **6**	 **7**	12	62[c]	20
3	 **8**	 **9**	7	87	90
4	 **10**	 **11**	48	50[d]	0
5	 **12**	 **13**	48	trace	trace
6	 **14**	 **15**	48	84[d]	8
7[e]	 **16**	 **17**	12	50	84
8	 **18**	 **19**	36	40[f]	91
9	 **20**	 **21**	72	27[g]	0
10	PPh_3 **22**	$O{=}PPh_3$ **23**	0.5	quant.; 95[h]	quant.
11[i]	 **24**	 **25** + **26**	7	8.5% of **25** and 91.5% of **26**; 85[h]	trace
12	 **27**	 **28**	48	66[j,k]	0
13	**27**	**28**	48	77[k,l]	0

[a]Method A: AIBX (2 equiv), 50% H_2O_2 (600 μL), 4 mL of 3:1 (v/v) $MeCN/H_2O$, rt. Method B: NaClO (90 μL), 50% H_2O_2 (600 μL) in 4 mL of 3:1 (v/v) $MeCN/H_2O$, rt. [b]Isolated yields. [c]Performed in 1:1 (v/v) diglyme/H_2O for 7 h. [d]Performed with 4 equiv of AIBX and 300 μL of 50% H_2O_2 in 3:1 (v/v) THF/H_2O for 48 h. [e]Performed in 3:1 (v/v) MeOH/H_2O for 12 h. [f]Performed with 6 equiv of AIBX and 300 μL of 50% H_2O_2 in 3:1 (v/v) CH_3CN/tetraborate buffer (pH 9.18) for 36 h. [g]Performed with 8 equiv of AIBX and 300 μL of 50% H_2O_2 in 3:1 (v/v) CH_3CN/tetraborate buffer for 72 h. [h]Yield of the recovered substrate in the absence of H_2O_2. [i]Performed with 6.0 equiv of AIBX for 7 h. [j]Performed with 4.0 equiv of *m*AIBX in 3:1 (v/v) CH_3CN/tetraborate buffer for 48 h. [k]Determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [l]Performed with 8.0 equiv of *m*AIBX in 3:1 (v/v) CH_3CN/tetraborate buffer for 48 h.

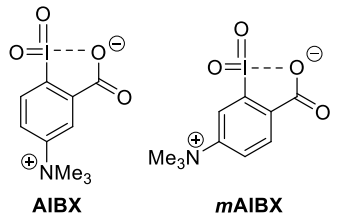
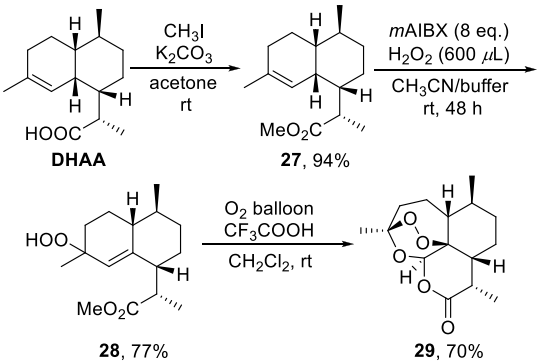


Figure 5. Structures of AIBX and *m*AIBX.

CONCLUSIONS

In summary, we have developed an efficient and practical method for chemical generation of $^1O_2$ by treatment of H_2O_2 with AIBX, a highly water-soluble, bench-stable, recyclable

Scheme 4. Synthesis of Artemisinin (29)



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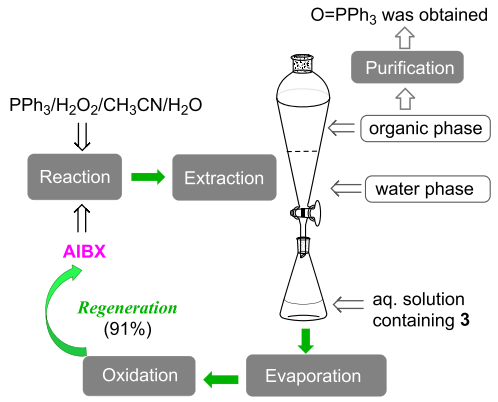

Figure 6. Procedure for AIBX regeneration.

hypervalent iodine(V) reagent. The formation of $^1O_2$ from this system was confirmed by chemical trapping of $^1O_2$ with AES and by ESR detection of TEMPO generated by the oxidation of TEMP by $^1O_2$. In addition, the $^1O_2$ generated with the AIBX/H_2O_2 system was used to carry out three typical reactions: [2 + 2]/[4 + 2] cycloaddition reactions to afford endoperoxides, oxidation of heteroatomic compounds to afford heteroatom oxides, and a Schenck ene reaction to afford an allylic hydroperoxide. Moreover, we used the method for the synthesis of the antimalarial drug artemisinin. Finally, AIBX could be efficiently regenerated by means of a simple workup and re-oxidation with dimethyldioxirane. Our findings demonstrate that the AIBX/H_2O_2 system is an attractive chemical source of $^1O_2$.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an air atmosphere without any special protections. Distilled CH_3CN, diglyme THF, and deionized water were used as solvents. Some known chemicals (**4**, **6**, **8**, **10**, **12**, **14**, **16**, and **18**) were available from commercial suppliers. Known compounds (**1**,[22a] **13**,[7d] **20**,[28] **24**,[32] and **27**[29]) were synthesized using the reported procedures and were identified by comparison of their NMR spectra with literature data. The ^1H NMR spectra were recorded at 400 MHz and the $^{13}C\{^1H\}$ NMR spectra were measured at 100 MHz using a Bruker AV 400 as a spectrometer; $CDCl_3$ was used as the solvent. The ^1H NMR spectra are reported as follows: chemical shift in ppm (δ) relative to the chemical shift of $CDCl_3$ at 7.26 ppm, multiplicities, coupling constants (Hz), and integration values. The $^{13}C\{^1H\}$ NMR spectra are reported in ppm (δ) relative to the central line of $CDCl_3$ triplet at 77.00 ppm. The IR spectra were recorded with a Fourier transform IR Bruker EQUINOX55 spectrometer in KBr pellets. High-resolution mass spectroscopy (HRMS) was performed with a high-resolution electrospray ionization Fourier transform ion cyclotron resonance mass spectrometer (Varian 7.0T). ESR measurements were performed with a Bruker E580-10/12 instrument.

Trapping of $^1O_2$ with AES. To a solution of AES (47.4 mg, 0.1 mmol) and AIBX (67.4 mg, 0.2 mmol) in D_2O (2 mL) was added 50% H_2O_2 (19.5 mol/L, 200 μL) dropwise at room temperature. The reaction mixture was stirred for 24 h and monitored by ^1H NMR.

Preparation of the Authentic $AESO_2$ Sample. To a solution of AES (23 mg, 0.05 mmol) and 5.84% NaClO (20 μL) in D_2O (2 mL) was added 50% H_2O_2 (19.5 mol/L, 10 μL) dropwise at room temperature. The reaction mixture was stirred for 30 min, and then 0.5 mL of the reaction mixture was placed in an NMR tube for ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopy.

*$AESO_2$ (**2**).*[24] Known compound; ^1H NMR (400 MHz, D_2O) δ 7.39−7.32 (m, 8H), 3.27−3.10 (m, 8H). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 138.9, 128.2, 121.7, 81.3, 45.4, 23.3.

The ESR Measurement. To a solution of TEMP (14 mg, 0.1 mmol) and AIBX (68 mg, 0.2 mmol) in 1:1 (v/v) CH_3CN/H_2O (4 mL) was added 50% H_2O_2 (19.5 mol/L, 600 μL) dropwise at room temperature. The reaction mixture was stirred for 18 h, and then the ESR spectra were measured.

Procedure for Reactions Using the AIBX/Aq. H_2O_2 System. To a solution of the desired substrate (0.2 mmol) and AIBX (0.4 mmol, 135 mg) in 3:1 (v/v) CH_3CN/H_2O (4 mL) was added 50% aqueous H_2O_2 (19.5 mol/L, 600 μL) dropwise at room temperature. The reaction mixture was stirred for 24 h and monitored by TLC. After the substrate was completely consumed, 5 mL of saturated sodium sulfite aqueous solution was added. The reaction mixture was then extracted with dichloromethane (3 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated from the filtrate, and the residue was purified by column chromatography to afford the target product.

*2-Iodo-5-(trimethylammonio)benzoate (**3**).*[23a] Colorless solid, m.p. 193−195 °C; ^1H NMR (400 MHz, D_2O) δ 8.06 (d, J = 8.9 Hz, 1H), 7.71 (d, J = 3.2 Hz, 1H), 7.49 (dd, J = 8.9, 3.3 Hz, 1H), 3.61 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 175.2, 148.2, 146.7, 141.3, 120.6, 117.9, 92.9, 57.0.

*Adamantylideneadamantane 1,2-Dioxetane (**5**).*[33] Colorless solid, 47 mg, 79% yield; m.p. 161−163 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 4H), 2.06−1.49 (m, 24H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 99.9, 95.8, 37.3, 34.6, 32.8, 31.9, 26.7, 26.5.

*2,3-Dioxabicyclo[2.2.2]oct-5-ene (**7**).*[22d] Colorless oil, 14 mg, 62% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (dd, J = 4.4, 3.3 Hz, 2H), 4.69−4.66 (m, 2H), 2.30−2.27 (m, 2H), 1.50−1.47 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 132.2, 70.9, 21.6.

*Ascaridole (**9**).*[22c] Colorless oil, 44 mg, 87% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (d, J = 8.5 Hz, 1H), 6.41 (d, J = 8.5 Hz, 1H), 2.07−1.98 (m, 2H), 1.96−1.89 (m, 1H), 1.53−1.50 (m, 2H), 1.38 (s, 3H), 1.00 (d, J = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 136.3, 133.0, 79.7, 74.3, 32.1, 29.5, 25.6, 21.4, 17.2, 17.1.

*9,10-Diphenyl-9,10-dihydro-9,10-epidioxyanthracene (**11**).*[22d] Colorless solid, 36 mg, 50% yield; m.p. 192−195 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.69 (m, 4H), 7.65−7.61 (m, 4H), 7.56−7.53 (m, 2H), 7.26−7.19 (m, 8H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 140.2, 132.9, 128.3, 128.2, 127.6, 127.5, 123.5, 84.0.

*1,2-Dibenzoylbenzene (**15**).*[22d] Colorless solid, 36 mg, 84% yield; m.p. 145−147 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 4H), 7.62 (s, 4H), 7.52 (t, J = 7.0 Hz, 2H), 7.38 (t, J = 7.6 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.6, 140.0, 137.2, 133.0, 130.3, 129.8, 129.7, 128.3.

*(E)-Hex-3-ene-2,5-dione (**17**).*[10f] Colorless solid, 11 mg, 50% yield; m.p. 75−77 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 2H), 2.37 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.5, 137.8, 28.0.

*4-Hydroxy-2,4,6-trimethylcyclohexa-2,5-dien-1-one (**19**).*[10f] Colorless solid, 12 mg, 40% yield; m.p. 45−47 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 2H), 1.87 (s, 6H), 1.43 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 147.2, 133.4, 67.1, 27.0, 15.8.

*1-(tert-Butyl) 2-Methyl 3a-Hydroxy-8-methyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b] Indole-1,2(2H)-dicarboxylate (**21**).*[28] Colorless oil, 18 mg, 27% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19−7.26 (m, 4H), 6.78 (t, J = 7.2 Hz, 1H), 6.54−6.49 (m, 1H), 5.44 (s, 0.5H), 4.45 (t, J = 9.1 Hz, 1H), 4.18 (s, 0.5H), 3.84−3.82 (m, 2H), 3.67 (s, 0.5H), 3.02 (s, 1.5H), 2.92 (s, 1H), 2.48−2.25 (m, 2H), 1.55−1.46 (m, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.4, 175.9, 154.7, 149.6, 130.1, 129.9, 129.7, 121.9, 118.8, 118.7, 109.9, 108.3, 108.1, 93.4, 93.3, 86.9, 85.9, 81.9, 81.3, 61.1, 53.0, 52.7, 42.4, 35.4, 31.9, 29.7, 28.3, 28.2. HRMS (ESI): m/z calcd for $C_{18}H_{24}N_2O_5$ $[M + Na]^+$: 371.1577; found: 371.1580.

*Triphenylphosphine Oxide (**23**).*[10f] Colorless solid, 56 mg, quantitative yield; m.p. 155−157 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.64 (m, 6H), 7.58−7.52 (m, 3H), 7.50−7.43 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 133.0, 132.1, 132..0, 131.9, 131.9, 128.5, 128.4.

*Methyl (2S)-2-[[(9H-Fluoren-9-ylmethoxy)carbonyl]amino]-4-(methylsulfinyl)butanoate (**25**).* Colorless solid, 6.8 mg, 8.5% yield; m.p. 157−159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5

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Hz, 2H), 7.59 (d, J = 6.7 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.33 (td, J = 7.0, 2.5 Hz, 2H), 5.49 (d, J = 6.6 Hz, 1H), 4.45 (d, J = 6.3 Hz, 3H), 4.22 (t, J = 6.6 Hz, 1H), 3.79 (s, 3H), 3.08 (d, J = 45.0 Hz, 2H), 2.92 (s, 3H), 2.47 (s, 1H), 2.21 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.3, 156.0, 143.7, 143.5, 141.3, 127.8, 127.1, 125.0, 120.1, 67.1, 53.0, 52.4, 51.0, 47.1, 40.8, 25.6; IR (KBr) ν = 3332, 2957, 2926, 1721, 1527, 1447, 1295, 1264, 1220, 1130, 1048, 965, 797, 740 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{23}NO_5S$ $[M + Na]^+$: 424.1189; found: 424.1193.

*Methyl (2S)-2-[[(9H-Fluoren-9-ylmethoxy)carbonyl]amino]-4-(methylsulfonyl)butanoate (**26**).* Colorless solid, 76.3 mg, 91.5% yield; m.p. 57−59 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.60 (s, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 5.71 (dd, J = 36.5, 7.1 Hz, 1H), 4.51−4.41 (m, 3H), 4.22 (t, J = 6.6 Hz, 1H), 3.78 (s, 3H), 2.89−2.62 (m, 2H), 2.57 (s, 3H), 2.46−2.33 (m, 1H), 2.29−2.06 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.7, 156.0, 143.7, 143.6, 141.3, 127.7, 127.0, 125.0, 120.0, 67.0, 53.0, 52.7, 50.2, 47.1, 38.5, 26.1; IR (KBr) ν = 3238, 2952, 2923, 1719, 1536, 1446, 1260, 1216, 1036, 739 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{23}NO_6S$ $[M + Na]^+$: 440.1138; found: 440.1142.

General Procedure for the Synthesis of the Crude Hydroperoxide 28. To a solution of **27** (0.2 mmol) and AIBX (135 mg, 0.4 mmol) in 3:1 (v/v) CH_3CN/tetraborate buffer (4 mL) was added 50% H_2O_2 (19.5 mol/L, 600 μL) dropwise at room temperature. After the reaction mixture was stirred for 24 h, another portion of AIBX (135 mg, 0.4 mmol) was added, and the reaction mixture was stirred for an additional 24 h. Upon completion of the reaction, 5 mL of H_2O was added, and the resulting mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and CH_2Cl_2 was removed at 30 °C on a rotary evaporator to afford crude hydroperoxide **28** as a colorless, sticky, oily residue. ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 1H), 3.67 (s, 3H), 2.54−2.46 (m, 2H), 2.02−1.74 (m, 3H), 1.69−1.50 (m, 6H), 1.46−1.36 (m, 1H), 1.25 (dd, J = 10.9, 3.1 Hz, 2H), 1.13 (d, J = 6.9 Hz, 3H), 1.07 (dd, J = 12.5, 3.1 Hz, 1H), 0.94 (dd, J = 12.0, 3.3 Hz, 1H), 0.86 (d, J = 6.5 Hz, 3H).

General Procedure for the Synthesis of Artemisinin (29). To a solution of the crude hydroperoxide **28** in dichloromethane (5 mL) was added CF_3CO_2H (600 μL). The solution was stirred at room temperature under a balloon of O_2 for 2 days. The solvent was evaporated, and the residue was purified by column chromatography to afford artemisinin (**29**).

*Artemisinin (**29**).*[10f] Colorless solid, 31 mg, 70% yield; m.p. 153−154 °C; $[\alpha]_D^{27}$: +60.2 (c = 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (s, 1H), 3.40 (m, 1H), 2.43 (td, J = 13.5, 3.7 Hz, 1H), 2.07−1.98 (m, 2H), 1.90−1.87 (m, 1H), 1.80−1.73 (m, 2H), 1.58 (s, 1H), 1.52−1.34 (m, 6H),1.20 (d, J = 7.3, 3H), 1.11−1.03 (m, 2H), 1.00 (d, J = 6.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.0, 105.3, 93.6, 79.4, 49.9, 44.8, 37.5, 35.8, 33.5, 32.8, 25.1, 24.7, 23.3, 19.7, 12.5; HRMS (ESI): m/z calcd for $C_{15}H_{23}O_5$ $[M + H]^+$: 283.1540; found: 283.1545.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00596.

Optimization of Schenck ene reaction conditions, ^1H and $^{13}C\{^1H\}$ NMR spectra, and HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(27) When we performed the [4 + 2] cycloaddition reaction of α-terpinene **8** with 30% H_2O_2 and AIBX in 4 mL of MeCN/H_2O, the reaction proceeded smoothly, and the corresponding endoperoxide **9** was obtained in 60% yield. In comparison, the yield of the endoperoxide **9** was 65% with 50% H_2O_2, slightly higher than that of 30% H_2O_2. To obtain higher yields of the oxidation reactions

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mediated by $^1O_2$ and to improve the utilization efficiency of the reaction vessel in the future practical use, 50% H_2O_2 was thoroughly used in our work. Also, 50% H_2O_2 was also often used in the oxidation reaction, which has been reported in many literature.

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