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Alloxan-Catalyzed Biomimetic Oxidations with Hydrogen Peroxide or Molecular Oxygen

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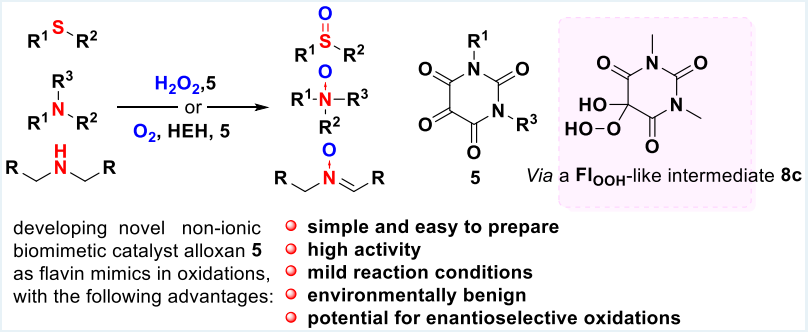
Supporting Information



ABSTRACT: Inspired by biological flavin catalysis, the nonionic alloxan derivatives were applied as the biomimetic catalysts for various oxidations, catalyzing oxidations of sulfides and amines with hydrogen peroxide or molecular oxygen under mild conditions with high yields in a short time. The whole catalytic cycle has been verified to be a biomimetic approach through the formation of the alloxan hydroperoxide reactive intermediate. Additionally, encouraging asymmetric catalytic results have been obtained with an easily prepared chiral alloxan in a sulfoxidation reaction.

KEYWORDS: *biomimetic oxidation, alloxan, aerobic oxidation, asymmetric oxidation, sulfide, amine*

Oxidation reactions are of fundamental importance in nature and are key transformations in organic synthesis.[1] In response to the current need to develop an environmentally benign and efficient technology, biomimetic catalytic oxidations that mimic the functions of enzymes would be one of the most attractive approaches.[1,2] Flavin-dependent monooxygenases (**FMO**), as a kind of widely existing redox enzymes containing cofactor flavin adenine dinucleotide (**FAD**), are responsible for the oxidation of various substrates via the activation of molecular oxygen and transfer of one oxygen atom to the substrate (Figure 1A).[3] The active species responsible for these oxidations has been established as the enzyme-bound hydroperoxyflavin ($\mathbf{Fl_{OOH}}$).[3b,c,4] As shown in Figure 1A, two plausible reaction pathways are depicted,[2a,5] depending on the terminal oxidant: (1) the direct addition of H_2O_2[6] to the $C_{(4a)}$-iminium cation oxidized flavin ($\mathbf{Fl_{ox}}$); (2) the reduction of $\mathbf{Fl_{ox}}$ or **FAD** with **NADH** (or **NADPH**) and subsequent incorporation of O_2.[3c,5,7] The thus-formed $\mathbf{Fl_{OOH}}$ undergoes monooxygenation of a substrate (**S**) to give the oxidized product (**SO**) and hydroxyflavin ($\mathbf{Fl_{OH}}$).

Because of the advantage of biomimetic catalysis, various oxidations with H_2O_2 or O_2 mediated by flavin catalysts have been reported,[2a,8] including sulfoxidation[9] and amine oxidation,[5,10] among others.[4c,7,11] All of them could proceed under mild conditions with low catalyst loading. Despite the diversity of the reported flavin catalysts, almost all of them are conjugated to a polycyclic aromatic skeleton,[2a] such as alloxazinium catalysts **1**[9c,12] and isoalloxazinium catalysts **2**[6] (Figure 1B). Furthermore, the necessity of the complicated skeleton makes it difficult to introduce chirality to the catalyst, resulting in limited studies on flavin-catalyzed asymmetric oxidation, such as asymmetric sulfoxidation[2b,13] and Baeyer−Villiger oxidation[14] with H_2O_2. To simplify the structure of flavinium salts, the Cibulka group prepared a series of simple electron-deficient aza-arenium salts **3** by removing all but the central pyrazinium ring in alloxazine (Figure 1C).[15] As the simplified version of flavin catalyst, **3** exhibited good catalytic activity in sulfoxidation with H_2O_2, whereas it had almost no activity in the O_2 system. Hence, to develop a novel and simple nonionic flavin mimic which could be activated with both H_2O_2 and O_2 is significant and challenging.

Alloxans **5**, as a kind of widely used intermediate to construct the flavinium salts,[10b,11e,16] have elicited our interest because of their special vicinal tricarbonyl structures (Figure 1D). Its central carbonyl group (C_5-) vicinally substituted by two electron-withdrawing amide groups could be a highly

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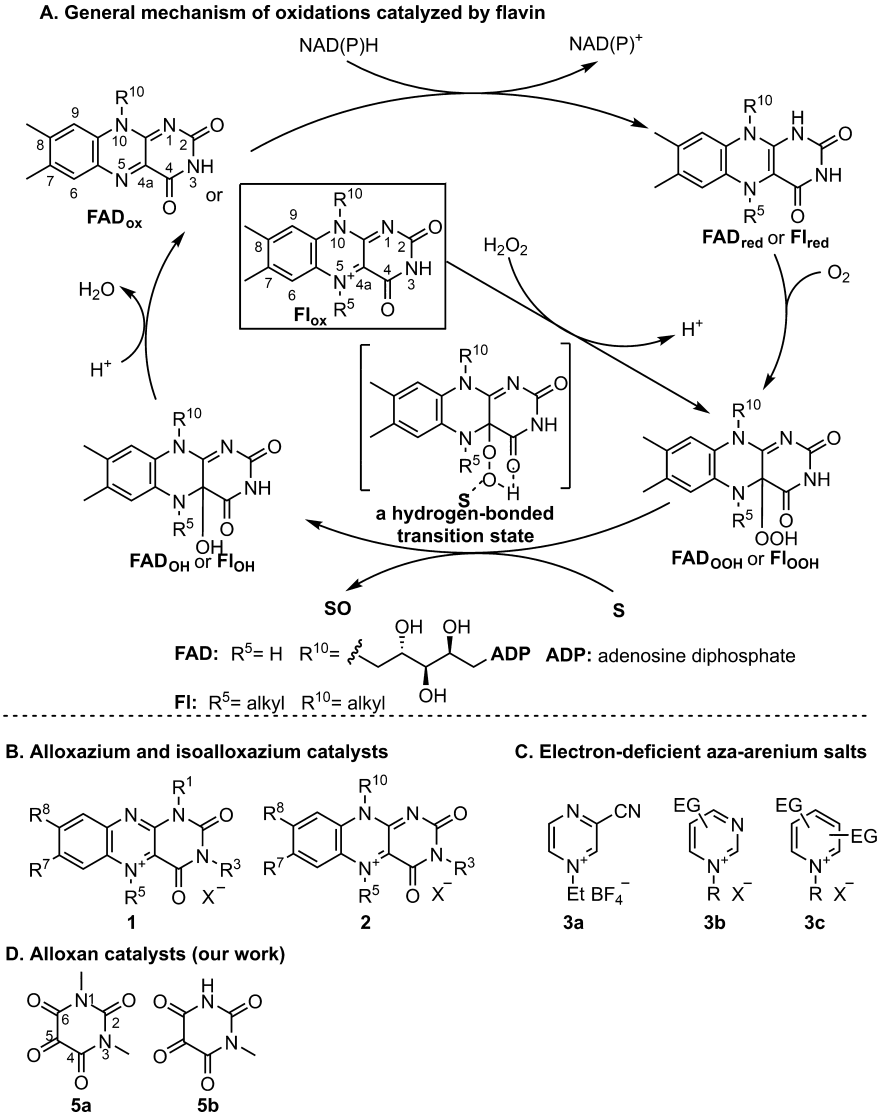

Figure 1. Simplification of flavin catalysts for oxidations.

reactive electrophilic site.[17] We speculated the carbonyl group was similar to the active site of flavin ($C_{(4a)}$-iminium), which could be attacked by H_2O_2 to yield the $\mathbf{Fl}_{\mathbf{OOH}}$-like hydroperoxy intermediate (Figure 1A). This idea led us to explore the possibility of using alloxan derivatives as the novel candidates to mimic the alloxazinium skeletons of flavin.

Therefore, we first investigated the catalytic ability of alloxan derivatives in sulfoxidation reaction using thioanisole **6a** as substrate and H_2O_2 as oxidant (Table 1).[6] The *N,N′*-dimethylalloxan **5a** did not promote the reaction in methanol, which is a commonly used solvent for the flavin-catalyzed oxidation reactions[6] (Table 1, entry 1). As an alternative, another reported solvent 2,2,2-trifluoroethanol (TFEA) was tested,[5,14] and it showed remarkable catalytic activity, albeit with obvious background reaction (Table 1, entry 2). To our delight, after the solvents were screened, significant catalytic activity was exhibited in CH_2Cl_2, for the nearly quantitative conversion of **6a** within 60 min with almost no background reaction observed (Table 1, entry 3). The reaction efficiency could be further improved by adding $MgSO_4$ to remove water, which is present in aqueous hydrogen peroxide and also formed as a byproduct after the reaction.[18] Thus, the reaction time was shortened from 60 min to just 20 min (Table 1, entries 3 and 4). To further evaluate the effect of the substitution, various N-substituted alloxan derivatives (**5b**−**5f**) were synthesized[19] for investigation (Table 1 and Schemes S1−S3). Under the optimized reaction conditions, we found the catalytic activity of N,N′-disubstituted alloxan (**5a**) is higher than the monosubstituted one (**5b**), and **5b** gave the better result than the nonsubstituted one (**5c**) (Table 1, entries 4−6). However, when replaced the two methyl of **5a** with ethyl (**5d**) or benzyl groups (**5e**), the corresponding catalytic ability slightly decreased, probably because of the steric effect (Table 1, entries 4, 7, and 8). When we replaced the carbonyl group at the 5-position of **5a** with an oxime (**5f**), the catalyst was deactivated, revealing that the 5-position group was essential for the catalytic activity (Table 1, entry 9).

To show the catalytic activity of alloxan catalyst more directly, we compared **5a** with the reported flavin mimic **1a**[9c,12,16d,20] and pyrazinium salt **3a**[15a] in the sulfoxidation reaction with H_2O_2. As shown in Figure 2, under their optimized reaction conditions, **5a** afforded the best catalytic efficiency, which catalyzed the sulfoxidation of thioanisole **6a** with more than 90% conversion in 10 min. Therefore, **5a** was

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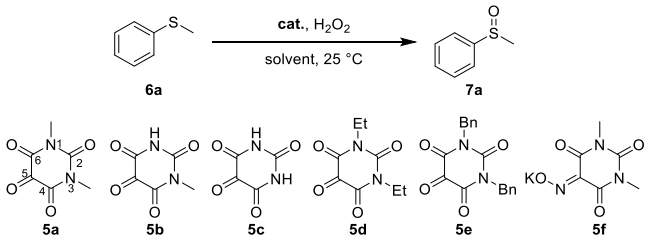
Table 1. Optimization for Alloxan-Catalyzed Model Sulfoxidation with H_2O_2[a]



entry	cat.	solvent	conv. (%)[b]	yield (%)[c]
1[d]	**5a**	MeOH	<1	<1
2	**5a**	TFEA	100	99 (70)[e]
3[d]	**5a**	CH_2Cl_2	98	97
4[f]	**5a**	CH_2Cl_2	100	99
5[f]	**5b**	CH_2Cl_2	96	95
6[f]	**5c**	CH_2Cl_2	27	26
7[f]	**5d**	CH_2Cl_2	97	96
8[f]	**5e**	CH_2Cl_2	93	92
9[f]	**5f**	CH_2Cl_2	1	<1

[a]Reaction conditions: **6a** (0.05 mmol), H_2O_2 (0.06 mmol), **5** (5 mol %), solvent (1 mL), 25 °C, 60 min; the blank conversion is less than 5%. [b]Conversions are determined by ^{1}H NMR. [c]Isolated yields. [d]The blank conversion is less than 1%. [e]70% blank conversion. [f]$MgSO_4$ (100 mg), 20 min.

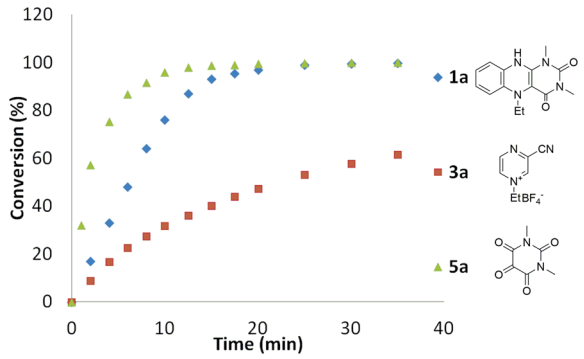


Figure 2. Course of the oxidation of thioanisole with H_2O_2 catalyzed by alloxan. Conditions of **5a**: **6a** (0.05 mmol), H_2O_2 (0.06 mmol), **5a** (5 mol %), $MgSO_4$ (100 mg), CH_2Cl_2 (1 mL), 25 °C. Conditions of **3a** or **1a**: **6a** (0.5 mmol), H_2O_2 (0.75 mmol), **3a** or **1a** (5 mol %), MeOH (1 mL), 25 °C, in the air. **1a** should be activated to form the active $\mathbf{1a}_{OOH}$.[20]

used as the catalyst for the subsequent research because of its outstanding catalytic ability.

The scope of application of *N,N′*-dimethylalloxan **5a** for the oxidations of a variety of sulfides and amines with H_2O_2 was examined (Scheme 1). Using 5 mol % of **5a**, complete conversion of almost all of the tested substrates was achieved within 30 min (Scheme S5). In the sulfoxidation reaction, a broad range of sulfides were investigated under the optimized conditions. In general, aryl methyl sulfides with both electron-donating (**6a**–**6e**) and electron-withdrawing (**6f**–**6i**) substituents were converted to the corresponding sulfoxides in high yields, while the former provide a faster reaction rate. It is important to note that electron-poor substrate *p*-nitrothioanisole (**6g**), which did not work well in the reported heteroarenium-catalyzed oxidation,[15] could be quickly oxidized by alloxan **5a** to the corresponding product in 94% yield. Furthermore, excellent reactivity was preserved even when varying a *p*-, *m*-, and *o*-bromo substituent on the aromatic ring (**6f**, **6h**, and **6i**). Besides, aromatic thioethers with larger alkyl groups (**6j**–**6m**) instead of methyl could also be well oxidized, and the simple dialkyl thioether (**6o**) and diaryl thioether (**6n**) were also easily oxidized. Remarkably, disulfides (**6p** and **6q**) and nitrogen sulfide (**6r**) were transformed to the corresponding monosulfoxides selectively; among them, aldehyde-derived 1,3-dithiane **6q** gave good diastereoselectivity (d.r. > 95:5). As a practical example, this method was used to quickly obtain the nonsteroidal anti-inflammatory drug Modafinil (**7s**) in a quantitative yield, thus avoiding the use of noble metal catalysts. Similar to the oxidations catalyzed by flavinium salts,[6,10b] various representative amines were also chosen as the substrates in our oxidative system. The oxidative transformation of tertiary amines to *N*-oxides (**7t** and **7u**) and that of secondary amine to nitrone (**7v**) could also be performed quickly and cleanly.

Since it has been reported that alloxan could catalyze the epoxidation of the alkene with Oxone by in situ formation of dioxirane intermediate **8a**[21] (Figure 3A), we designed the experiments to validate whether our system also proceeds through the similar mechanism (Table S2). When Oxone was replaced with H_2O_2 as the oxidant, the disappearance of catalytic activity of **5a** in the epoxidation of *trans*-stilbene with H_2O_2 denied the formation of the dioxirane intermediate **8a** in our system (Figure 3A and Table S2). Therefore, we speculated that the flavin-like catalytic pathway could be more likely in our systems, namely through oxidizing substrates with a hydroperoxy intermediate.[6,22] Thus, in situ NMR studies were conducted. As starting material, *N,N′*-dimethylalloxan has proven to be the mixture of its monohydrate **8b** and unhydrate **5a** (Scheme S8 and Figures S1 and S2), which could readily be converted into **8b** in the presence of water, with characteristic peaks at 3.22 and 5.9 ppm in ^{1}H NMR, as well as 85 ppm in ^{13}C NMR (step 1, Figure 3B). After treatment of **8b** with 1.2 equiv of aqueous H_2O_2, the observation of typical hydroxy hydroperoxide group signals[23] (^{1}H NMR spectrum at 6.2 and 11.2 ppm, ^{13}C NMR spectrum at 93 ppm) indicated the formation of a $\mathbf{Fl}_{OOH}$-like intermediate **8c** in this system (step 2, Figure 3B), which was also confirmed by UPLC-HRMS (Scheme S10 and Figure S5). After that, **6a** was added into the above mixture to verify the activity of **8c** in sulfoxidation (Figure 3C). Five minutes later, the appearance of the expected product **7a**, accompanied by the disappearance of **8c** and reappearance of **8b** (step 2 and 3, Figure 3C), further confirmed **8c** as the active intermediate in our cycle.

On the basis of the above results, it could be concluded that the alloxan molecule successfully mimics the function of flavin to form hydroperoxy intermediate with H_2O_2 for the oxidation reaction. In addition to using H_2O_2 as an oxidant, the reduced flavin could also catalyze oxidation reactions with O_2 through forming the reactive intermediate (Figure 1A).[2a] Inspired by this, we continued our research on alloxan-catalyzed aerobic oxidations. In the O_2 system, we also used the sulfoxidation of **6a** as the template reaction. As illustrated in Figure 1A, reducing reagent (**ZH**), which corresponds to **NAD(P)H**,[3b] is required for the flavin-catalyzed oxidation using O_2 as oxidant. After preliminary screening of several commonly used reducing reagents[7] (Table 2, entries 1–4), we found that the expected product could be obtained using catlyst **5a** and Hantzsch ester (**HEH**) in 1 atm of O_2 (entry 4). Then, we investigated the solvent effects on this aerobic sulfoxidation (Table S1).

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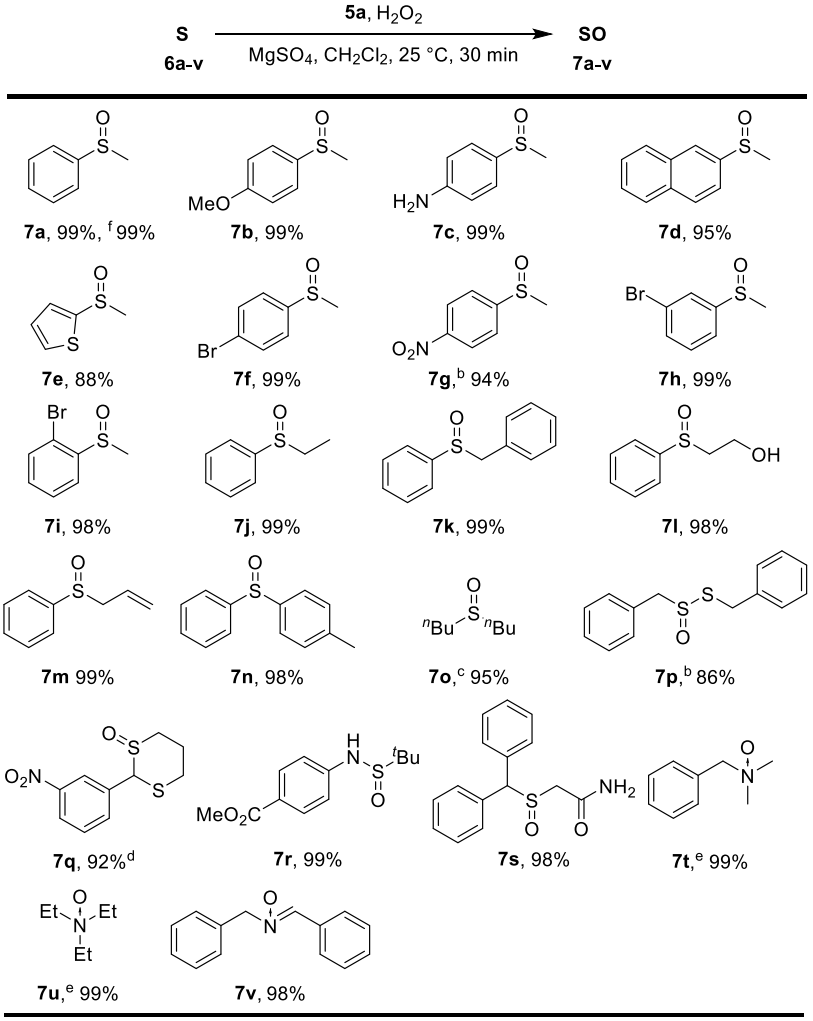
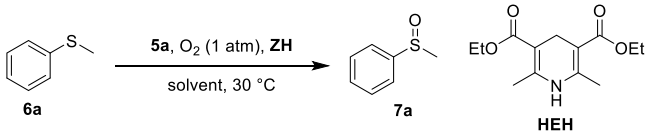
Scheme 1. Alloxan-Catalyzed Oxidation of Various Substrates with H_2O_2[a]



[a]Isolated yields. **S** (0.05 mmol), H_2O_2 (0.06 mmol), **5a** (5 mol %), $MgSO_4$ (100 mg), CH_2Cl_2 (1 mL), 25 °C, 30 min. [b]**5a**, 120 min. [c]20 min. [d]d.r. > 95:5. [e]Na_2SO_4 (100 mg). [f]Performed at 10 mmol scales of **6a** in 20 min (Scheme S7).

Table 2. Optimization for Alloxan-Catalyzed Model Sulfoxidation with O_2[a]



entry	ZH	solvent	conv. (%)[b]	yield (%)[c]
1[d]	$N_2H_4{\cdot}H_2O$	TFEA	<2	<2
2[d]	Zn	TFEA	<2	<2
3[d]	HCOONa	TFEA	<2	<2
4	**HEH**	TFEA	68	67
5	**HEH**	$CHCl_3$	94	93
6[e]	**HEH**	$CHCl_3$	65	62
7[f]	**HEH**	$CHCl_3$	95	94

[a]Reaction conditions: **6a** (0.05 mmol), O_2 (1 atm, balloon), **5a** (20 mol %, which is higher than that of H_2O_2 system because of the degradation of the catalyst, shown in Table S1), **ZH** (0.075 mmol), solvent (1 mL), 30 °C, 60 min; the blank conversion is less than 5%. [b]Conversions are determined by ^1H NMR. [c]Isolated yields. [d]The blank conversion is less than 2%. [e]Air, 24 h. [f]14 W white LED.

Examination of common solvents indicated that the reaction worked well in both polar and nonpolar solvents (Table S1), in which $CHCl_3$ provided the best yield (entry 5). Importantly, the oxidation under the air atmosphere also proceeded smoothly by prolonging the reaction time (entry 6). However, the reaction could not be promoted by light (entry 7 and Table S1).

Under the optimal conditions of the O_2 system (Scheme S6), some representative substrates were studied and are shown in Scheme 2. At 30 °C, almost complete conversion of all the tested substrates could be achieved within 60 min, including various aryl thioethers (**6a**, **6b**, **6f**, **6g**, **6e**, **6j**, and **6m**), alkyl thioether (**6o**), disulfide (**6p**), nitrogen sulfide (**6r**), and tertiary amines (**6t** and **6u**).

After investigation of the substrate scope of alloxan-catalyzed aerobic oxidation, the in situ NMR experiments were conducted to study the reaction mechanism of this O_2 system. As shown in Figure 4 (for details, see Scheme S9 and Figures S3 and S4), when **HEH** was added into CD_3CN solution of catalyst (**5a**/**8b**) under Ar atmosphere, the signals of **8b** at 3.22 and 85 ppm disappeared, replaced by the appearance of new signals at 3.19, 5.0, and 70 ppm, which were assigned to groups

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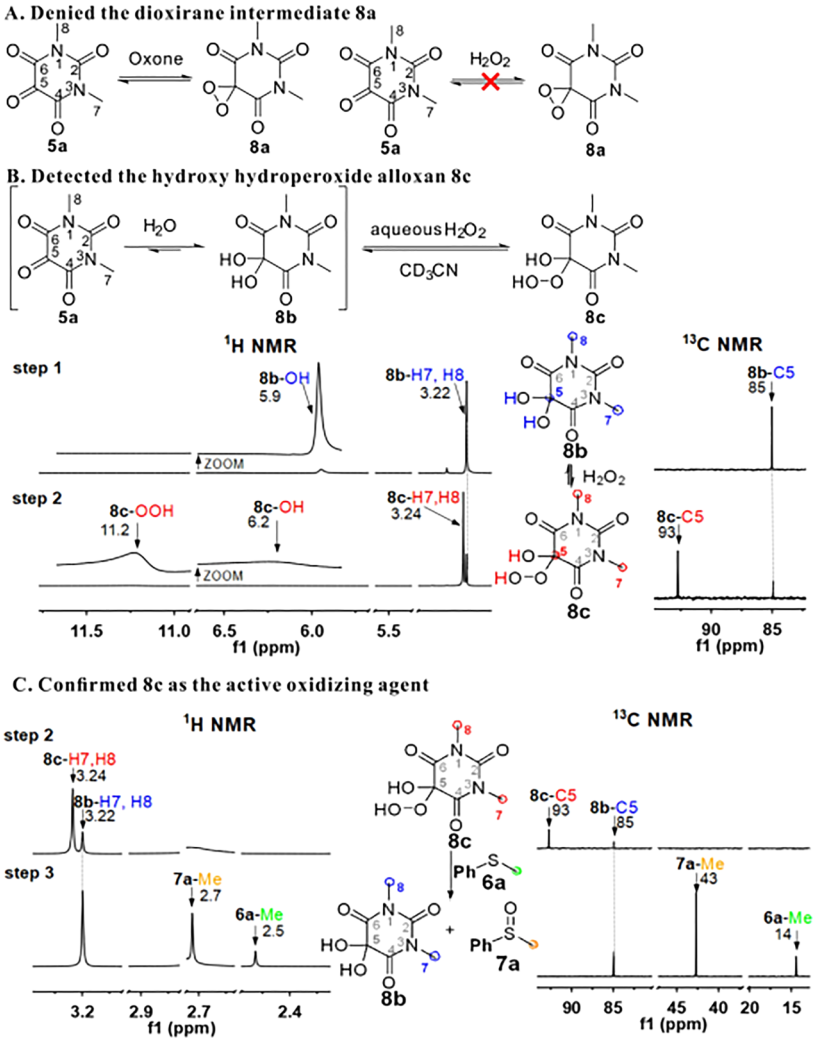
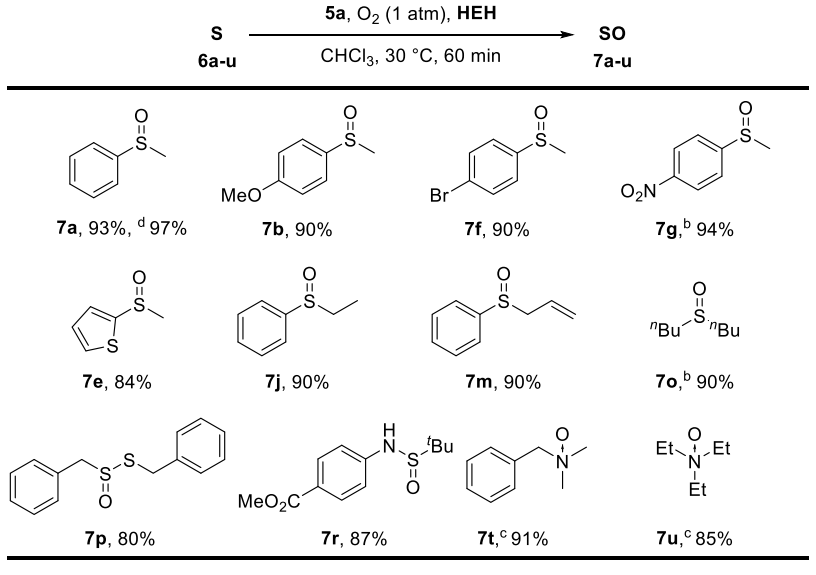


Figure 3. Mechanism studies for **5a**-catalyzed sulfoxidation with H_2O_2. **Step 1**: 0.05 mmol **8b** in 0.5 mL CD_3CN; **Step 2**: 0.06 mmol aqueous H_2O_2 was added into **step 1**, for 60 min; **Step 3**: 0.075 mmol **6a** was added into **step 2**, for 5 min.

Scheme 2. Alloxan-Catalyzed Oxidation of Various Substrates with O_2[a]



[a]Isolated yields. **S** (0.05 mmol), O_2 (1 atm, balloon), **5a** (20 mol %), **HEH** (0.075 mmol), $CHCl_3$ (1 mL), 30 °C, 60 min. [b]TFEA (1 mL), $MgSO_4$ (100 mg). [c]MeCN (1 mL). [d]Performed at 10 mmol scales of **6a** in 120 min (Scheme S7).

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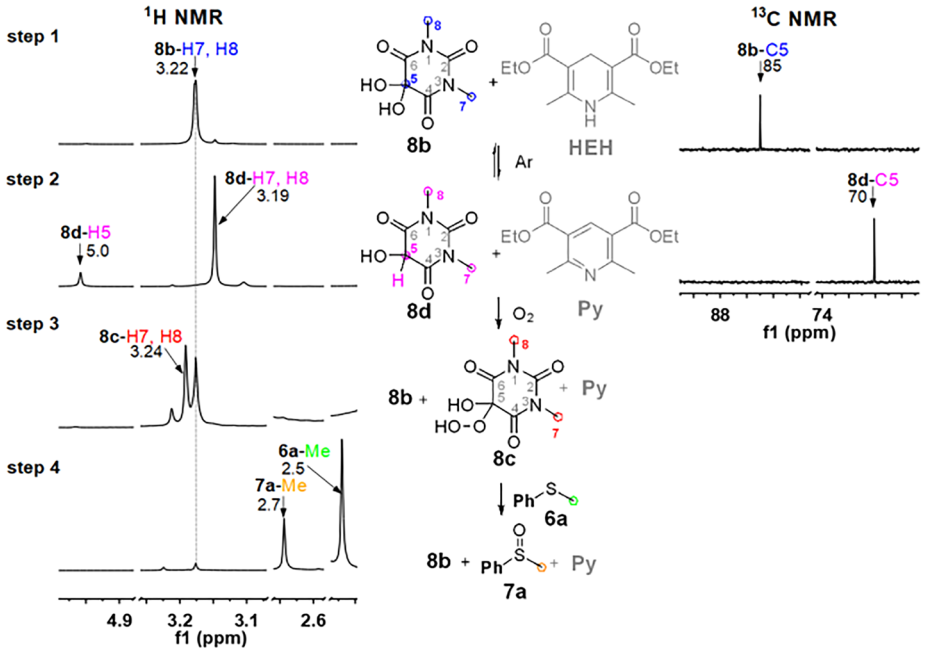


Figure 4. Partial typical peaks of the in situ NMR spectra in sulfoxidation with O_2. **Step 1**: under Ar atmosphere, 0.025 mmol *N,N′*-dimethylalloxan (mixture of **5a** and **8a**) and 0.03 mmol **HEH** in 0.5 mL CD_3CN; **Step 2**: **step 1** stayed for 48 h; **Step 3**: displaced **step 2** with O_2, for 30 min; **Step 4**: 0.05 mmol **6a** was added into **step 3**, for 60 min.

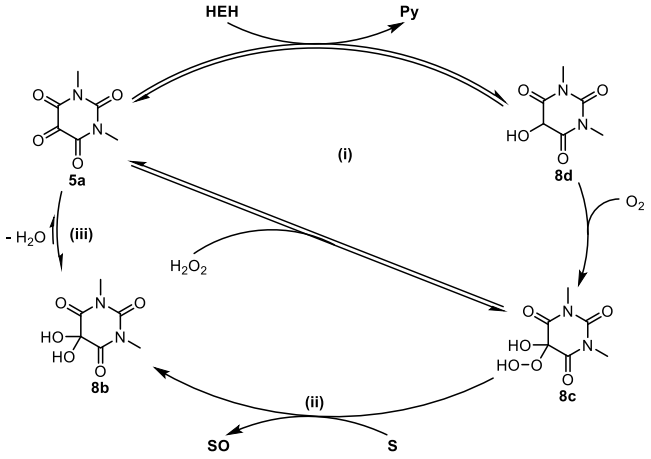
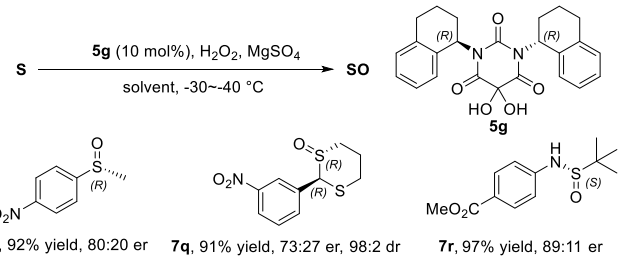


Figure 5. A proposed mechanism of oxidations catalyzed by alloxan.

of $\mathbf{Fl}_{red}$-like intermediate **8d** (step 1 and step 2, Figure 4).[24] However, once the above mixture was treated with O_2, **8d** signal at 3.19 ppm immediately disappeared, accompanied by observation of two additional signals at 3.22 and 3.24 ppm, corresponding to the methyl of **8b** and **8c**, respectively (step 3, Figure 4). The resulting mixture was then directly utilized to oxidize thioanisole **6a**, affording the corresponding product **7a** which indicated **8c** to be a shared active intermediate for both H_2O_2 and O_2 systems (step 4, Figure 4).

According to the above mechanism studies, the proposed pathway of oxidations catalyzed by alloxan is depicted in Figure 5: (i) Forming alloxan hydroperoxide **8c** as active oxygen-transfer species; (ii) Oxidizing the substrate (**S**) to yield alloxan monohydrate **8b**; (iii) Dehydrating to recycle catalyst **5a**. For the O_2 system, a reduced intermediate **8d** could be obtained with **HEH** and then be oxidized with O_2 to generate the key intermediate **8c**. Compared with the already known flavinium-catalyzed oxidation mechanism (Figure 1 A),[2a] the obvious distinction of our catalytic system is that the catalytic active site became a carbonyl group but not an iminium cation, thus yielding the different active intermediates including hydroxy alloxan **8d** and alloxan hydroperoxide **8c** instead of enamine flavin $\mathbf{Fl}_{red}$ and hydroperoxide flavin $\mathbf{Fl}_{OOH}$.

Scheme 3. Preliminary Investigations on Asymmetric Sulfoxidation with H_2O_2[a]



[a]Isolated yields, the ee of **7** were determined by chiral HPLC analysis and their absolute configurations were determined by comparison of the reported literature.[25]

Owing to the high activity and simple structure of alloxan catalyst, a chiral alloxan **5g** was prepared to verify its application in asymmetric catalysis. Unlike the complicated procedure for the preparation of chiral alloxazinium catalysts,[2b,13,14] the synthesis of **5g** could be accomplished easily according to the literature method,[21] which only needs three steps in total (Scheme S4). When applied to the oxidation reactions, the chiral catalyst **5g** afforded encouraging results: the common aryl thioether (**6g**), 1,3-dithiane (**6q**), and nitrogen sulfide (**6r**) could be converted to their corresponding target products in high yields with good diastereoselectivity as well as moderate enantioselectivities (Scheme 3 and Scheme S11), thus revealing the great potential of chiral alloxans in catalytic asymmetric oxidations.

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In summary, we have developed an efficient biomimetic alloxan-catalyzed oxidation method for a variety of sulfides and amines with H_2O_2 or O_2. This method successfully simulates the functions of **FMO** and requires no original complicated flavin skeleton but can afford the target products quickly and cleanly under mild conditions by using the simple alloxan. As the most efficient simple alloxan, **5a** has shown us its significant catalytic activity, better than the best-reported alloxazinium catalysts and pyrazinium salts in sulfoxidation with H_2O_2. After mechanism studies, the whole catalytic cycle has been proved to be a biomimetic way with a shared highly reactive intermediate alloxan hydroperoxide **8c** in both H_2O_2 and O_2 systems, which is slightly different from the reported catalytic mechanism of flavinium-like catalyst. Because of the simple nonionic structure, alloxan is easy to prepare and introduce chiral substituents to construct chiral catalysts for the investigations of biomimetic asymmetric oxidation. Because of the above obvious advantages, this alloxan-based catalytic system has great potential in the biomimetic oxidation. Further studies to expand the reaction scope of the novel catalyst and its application in asymmetric catalysis are currently underway in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.9b04508.

Experimental procedures and compound characterization (PDF)

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Piera, J.; Backvall, J. E. Catalytic oxidation of organic substrates by molecular oxygen and hydrogen peroxide by multistep electron transfer - A biomimetic approach. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506−3523.

(2) (a) Iida, H.; Imada, Y.; Murahashi, S. I. Biomimetic flavin-catalysed reactions for organic synthesis. *Org. Biomol. Chem.* **2015**, *13*, 7599−7613. (b) Murahashi, S. I. Synthetic Aspects of Metal-Catalyzed Oxidations of Amines and Related Reactions. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443−2465.

(3) (a) Bruice, T. C. Mechanisms of flavin catalysis. *Acc. Chem. Res.* **1980**, *13*, 256−262. (b) van Berkel, W. J. H.; Kamerbeek, N. M.; Fraaije, M. W. Flavoprotein monooxygenases, a diverse class of oxidative biocatalysts. *J. Biotechnol.* **2006**, *124*, 670−689. (c) Huijbers, M. M. E.; Montersino, S.; Westphal, A. H.; Tischler, D.; van Berkel, W. J. H. Flavin dependent monooxygenases. *Arch. Biochem. Biophys.* **2014**, *544*, 2−17.

(4) (a) Piano, V.; Palfey, B. A.; Mattevi, A. Flavins as Covalent Catalysts: New Mechanisms Emerge. *Trends Biochem. Sci.* **2017**, *42*, 457−469. (b) Entsch, B.; van Berkel, W. J. Structure and mechanism of para-hydroxybenzoate hydroxylase. *FASEB J.* **1995**, *9*, 476−483. (c) Kamerbeek, N. M.; Janssen, D. B.; van Berkel, W. J. H.; Fraaije, M. W. Baeyer-Villiger monooxygenases, an emerging family of flavin-dependent biocatalysts. *Adv. Synth. Catal.* **2003**, *345*, 667−678.

(5) Imada, Y.; Iida, H.; Ono, S.; Murahashi, S. I. Flavin catalyzed oxidations of sulfides and amines with molecular oxygen. *J. Am. Chem. Soc.* **2003**, *125*, 2868−2869.

(6) Murahashi, S. I.; Oda, T.; Masui, Y. Flavin-Catalyzed Oxidation of Amines and Sulfur-Compounds with Hydrogen-Peroxide. *J. Am. Chem. Soc.* **1989**, *111*, 5002−5003.

(7) Kotoučová, H.; Strnadová, I.; Kovandová, M.; Chudoba, J.; Dvořáková, H.; Cibulka, R. Biomimetic aerobic oxidative hydroxylation of arylboronic acids to phenols catalysed by a flavin derivative. *Org. Biomol. Chem.* **2014**, *12*, 2137−2142.

(8) Bryliakov, K. P. Catalytic Asymmetric Oxygenations with the Environmentally Benign Oxidants H2O2 and O-2. *Chem. Rev.* **2017**, *117*, 11406−11459.

(9) (a) Imada, Y.; Kitagawa, T.; Wang, H. K.; Komiya, N.; Naota, T. Flavin-catalyzed aerobic oxidation of sulfides in aqueous media. *Tetrahedron Lett.* **2013**, *54*, 621−624. (b) Murahashi, S.; Zhang, D.; Iida, H.; Miyawaki, T.; Uenaka, M.; Murano, K.; Meguro, K. Flavin-catalyzed aerobic oxidation of sulfides and thiols with formic acid/triethylamine. *Chem. Commun.* **2014**, *50*, 10295−10298. (c) Lindén, A. A.; Krüger, L.; Bäckvall, J.-E. Highly Selective Sulfoxidation of Allylic and Vinylic Sulfides by Hydrogen Peroxide Using a Flavin as Catalyst. *J. Org. Chem.* **2003**, *68*, 5890−5896.

(10) (a) Imada, Y.; Iida, H.; Ono, S.; Masui, Y.; Murahashi, S.-I. Flavin-Catalyzed Oxidation of Amines and Sulfides with Molecular Oxygen: Biomimetic Green Oxidation. *Chem. - Asian J.* **2006**, *1*, 136−147. (b) Bergstad, K.; Backvall, J. E. Mild and efficient flavin-catalyzed H2O2 oxidation of tertiary amines to amine N-oxides. *J. Org. Chem.* **1998**, *63*, 6650−6655.

(11) (a) Mazzini, C.; Lebreton, J.; Furstoss, R. Flavin-catalyzed Baeyer-Villiger reaction of ketones: Oxidation of cyclobutanones to gamma lactones using hydrogen peroxide. *J. Org. Chem.* **1996**, *61*, 8−9. (b) Imada, Y.; Iida, H.; Murahashi, S.; Naota, T. An aerobic, organocatalytic, and chemoselective method for Baeyer-Villiger oxidation. *Angew. Chem., Int. Ed.* **2005**, *44*, 1704−1706. (c) Pouy, M. J.; Milczek, E. M.; Figg, T. M.; Otten, B. M.; Prince, B. M.; Gunnoe, T. B.; Cundari, T. R.; Groves, J. T. Flavin-Catalyzed Insertion of Oxygen into Rhenium−Methyl Bonds. *J. Am. Chem. Soc.* **2012**, *134*, 12920−12923. (d) Murray, A. T.; Matton, P.; Fairhurst, N. W. G.; John, M. P.; Carbery, D. R. Biomimetic Flavin-Catalyzed Aldehyde Oxidation. *Org. Lett.* **2012**, *14*, 3656−3659. (e) Chen, S.; Hossain, M. S.; Foss, F. W. Organocatalytic Dakin Oxidation by Nucleophilic Flavin Catalysts. *Org. Lett.* **2012**, *14*, 2806−2809. (f) Ménová, P.; Dvořáková, H.; Eigner, V.; Ludvík, J.; Cibulka, R. Electron-Deficient Alloxazinium Salts: Efficient Organocatalysts of Mild and Chemoselective Sulfoxidations with Hydrogen Peroxide. *Adv. Synth. Catal.* **2013**, *355*, 3451−3462.

(12) Bergstad, K.; Bäckvall, J.-E. Mild and Efficient Flavin-Catalyzed H2O2 Oxidation of Tertiary Amines to Amine N-Oxides. *J. Org. Chem.* **1998**, *63*, 6650−6655.

(13) (a) Zurek, J.; Cibulka, R.; Dvorakova, H.; Svoboda, J. N-1,N-10-Ethylene-bridged flavinium salts derived from L-valinol: synthesis and catalytic activity in H2O2 oxidations. *Tetrahedron Lett.* **2010**, *51*, 1083−1086. (b) Dong, Z. Y.; Wang, Y. G.; Yin, Y. Z.; Liu, J. Q. Supramolecular enzyme mimics by self-assembly. *Curr. Opin. Colloid Interface Sci.* **2011**, *16*, 451−458. (c) Mojr, V.; Herzig, V.; Budesinsky, M.; Cibulka, R.; Kraus, T. Flavin-cyclodextrin conjugates as catalysts of enantioselective sulfoxidations with hydrogen peroxide in aqueous media. *Chem. Commun.* **2010**, *46*, 7599−7601. (d) Iida, H.; Iwahana, S.; Mizoguchi, T.; Yashima, E. Main-Chain Optically Active

DOI: 10.1021/acscatal.9b04508
ACS Catal. 2020, 10, 245−252

Riboflavin Polymer for Asymmetric Catalysis and Its Vapochromic Behavior. *J. Am. Chem. Soc.* **2012**, *134*, 15103−15113.
(14) Murahashi, S. I.; Ono, S.; Imada, Y. Asymmetric Baeyer-Villiger reaction with hydrogen peroxide catalyzed by a novel planar-chiral bisflavin. *Angew. Chem., Int. Ed.* **2002**, *41*, 2366−2368.
(15) (a) Ménová, P.; Kafka, F.; Dvořáková, H.; Gunnoo, S.; Šanda, M.; Cibulka, R. Pyrazinium Salts as Efficient Organocatalysts of Mild Oxidations with Hydrogen Peroxide. *Adv. Synth. Catal.* **2011**, *353*, 865−870. (b) Sturala, J.; Bohacova, S.; Chudoba, J.; Metelkova, R.; Cibulka, R. Electron-Deficient Heteroarenium Salts: An Organocatalytic Tool for Activation of Hydrogen Peroxide in Oxidations. *J. Org. Chem.* **2015**, *80*, 2676−2699.
(16) (a) Chattopadhyay, P.; Rai, R.; Pandey, P. S. Two-Step Synthetic Route to 10-Substituted Isoalloxazines. *Synth. Commun.* **2006**, *36*, 1857−1861. (b) Panekjanc, D.; Koziol, J. Simple Synthesis of 6-Methylalloxazine, 3,9-Dimethylalloxazine, 3-Methylalloxazine, and 3,7,8-Trimethylalloxazine. *Tetrahedron Lett.* **1979**, *20*, 4117−4118. (c) Zhu, C. J.; Li, Q.; Pu, L. L.; Tan, Z. T.; Guo, K.; Ying, H. J.; Ouyang, P. K. Nonenzymatic and Metal-Free Organocatalysis for in Situ Regeneration of Oxidized Cofactors by Activation and Reduction of Molecular Oxygen. *ACS Catal.* **2016**, *6*, 4989−4994. (d) Minidis, A. B. E.; Backvall, J. E. Mild and efficient flavin-catalyzed H2O2 oxidations. *Chem. - Eur. J.* **2001**, *7*, 297−302.
(17) Rubin, M. B.; Gleiter, R. The Chemistry of Vicinal Polycarbonyl Compounds. *Chem. Rev.* **2000**, *100*, 1121−1164.
(18) Liao, S.; Čorić, I.; Wang, Q.; List, B. Activation of H_2O_2 by Chiral Confined Brønsted Acids: A Highly Enantioselective Catalytic Sulfoxidation. *J. Am. Chem. Soc.* **2012**, *134*, 10765−10768.
(19) Otsuji, Y.; Wake, S.; Imoto, E. Photochemistry of heterocyclic compounds—II: The photochemical decomposition of water catalyzed by alloxan monohydrate and its derivatives. *Tetrahedron* **1970**, *26*, 4139−4152.
(20) Lindén, A. A.; Hermanns, N.; Ott, S.; Krüger, L.; Bäckvall, J.-E. Preparation and Redox Properties of N,N,N-1,3,5-Trialkylated Flavin Derivatives and Their Activity as Redox Catalysts. *Chem. - Eur. J.* **2005**, *11*, 112−119.
(21) Carnell, A. J.; Johnstone, R. A. W.; Parsy, C. C.; Sanderson, W. R. N,N-dialkylalloxans - a new class of catalyst for dioxirane epoxidations. *Tetrahedron Lett.* **1999**, *40*, 8029−8032.
(22) (a) Murray, A. T.; Dowley, M. J. H.; Pradaux-Caggiano, F.; Baldansuren, A.; Fielding, A. J.; Tuna, F.; Hendon, C. H.; Walsh, A.; Lloyd-Jones, G. C.; John, M. P.; Carbery, D. R. Catalytic Amine Oxidation under Ambient Aerobic Conditions: Mimicry of Monoamine Oxidase B. *Angew. Chem., Int. Ed.* **2015**, *54*, 8997−9000. (b) Sakai, T.; Kumoi, T.; Ishikawa, T.; Nitta, T.; Iida, H. Comparison of riboflavin-derived flavinium salts applied to catalytic H2O2 oxidations. *Org. Biomol. Chem.* **2018**, *16*, 3999−4007. (c) Gelalcha, F. G. Heterocyclic Hydroperoxides in Selective Oxidations. *Chem. Rev.* **2007**, *107*, 3338−3361. (d) Cibulka, R. Artificial Flavin Systems for Chemoselective and Stereoselective Oxidations. *Eur. J. Org. Chem.* **2015**, *2015*, 915−932.
(23) Zmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. The effect of iodine on the peroxidation of carbonyl compounds. *J. Org. Chem.* **2007**, *72*, 6534−6540.
(24) (a) Zhang, W.; Shi, M. Reduction of activated carbonyl groups by alkyl phosphines: formation of alpha-hydroxy esters and ketones. *Chem. Commun.* **2006**, 1218−1220. (b) Zhu, J.; Yuan, Y.; Wang, S. Z.; Yao, Z. J. Synthesis of 2,3-Dialkylated Tartaric Acid Esters via Visible Light Photoredox-Catalyzed Reductive Dimerization of alpha-Ketoesters. *ACS Omega* **2017**, *2*, 4665−4677.
(25) (a) Ma, L. J.; Chen, S. S.; Li, G. X.; Zhu, J.; Wang, Q. W.; Tang, Z. Chiral Bronsted-Acid-Catalyzed Asymmetric Oxidation of Sulfenamide by Using H_2O_2: A Versatile Access to Sulfinamide and Sulfoxide with High Enantioselectivity. *ACS Catal.* **2019**, *9*, 1525−1530. (b) Liu, Z. M.; Zhao, H.; Li, M. Q.; Lan, Y. B.; Yao, Q. B.; Tao, J. C.; Wang, X. W. Chiral Phosphoric Acid-Catalyzed Asymmetric Oxidation of Aryl Alkyl Sulfides and Aldehyde-Derived 1,3-Dithianes: Using Aqueous Hydrogen Peroxide as the Terminal Oxidant. *Adv. Synth. Catal.* **2012**, *354*, 1012−1022.

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ACS Catal. 2020, 10, 245−252