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Biomimetic Flavin-Catalyzed Aldehyde Oxidation

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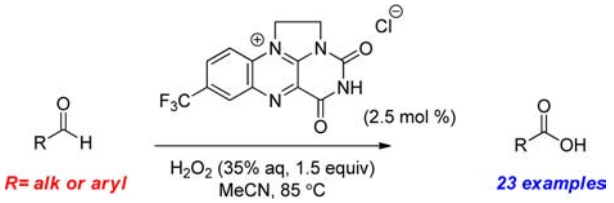
ABSTRACT

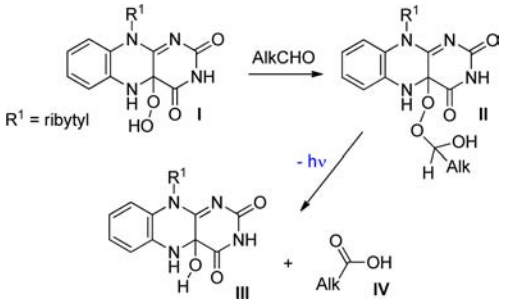


The oxidation of alkyl and aryl aldehydes to their corresponding carboxylic acids has been achieved through the action of a biomimetic bridged flavin catalyst. The reaction uses readily available 35% aqueous hydrogen peroxide and is operationally simple. The oxidation is a green and sustainable reaction, obviating chlorinated solvents with minimal byproducts.

Bacterial bioluminescence has attracted significant interest, with flavoenzyme monooxygenases now known to mediate light production.[1] Extensive mechanistic studies have identified that an enzyme-bound flavin hydroperoxide **I** undergoes nucleophilic addition to a fatty aldehyde electrophile, forming peroxyhemiacetal **II** (Scheme 1). It is the collapse of **II** to hydroxy flavin **III** and the fatty carboxylic acid that effects the ejection of a photon. Arguably, most studies have concentrated on the mechanism of luminescence as opposed to the synthetic potential of a "green" flavin-catalyzed aldehyde oxidation.[2]

The molecular understanding of flavin monooxygenase chemistry has, to a large extent, been elucidated through the study of simplified small-molecule flavin models. For instance, flavinium perchlorate salt **1** has been key in demonstrating that many oxygen transfer reactions mediated by flavin monooxygenases do so via flavin hydroperoxide intermediates, as modeled by hydroperoxide **2** (Figure 1). Indeed, Bruice has been successful in

Scheme 1. Flavoenzymatic Bacterial Bioluminescense Mediated by Aldehyde Oxidation



demonstrating chemoluminescence with **2** and benzaldehyde. However, this was only accomplished on an analytical scale, with benzoic acid only recovered in a 2% yield.[3]

Many oxidation reactions mediated by flavin–hydroperoxide intermediates do so with electrophilic behavior; i.e., oxygen is transferred to a nucleophile with representative examples being oxygen transfer to sulfides,

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(1) For a general overview of flavoenzyme biochemistry, see: *Flavins and Flavoproteins*; Bray, R. C., Engel, P. C., Mayhew, S. E., Eds.; DeGruyter: Berlin, 1984.

(2) Industrially relevant, clean oxidation protocols in nonchlorinated solvents have been identified as reactions desirable for further development; see: Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(3) (a) Kemal, C.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 7064. (b) Shepherd, P. T.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 7774. (c) Bruice, T. C.; Noar, J. B.; Ball, S. S.; Venkataram, U. V. *J. Am. Chem. Soc.* **1983**, *105*, 2452.

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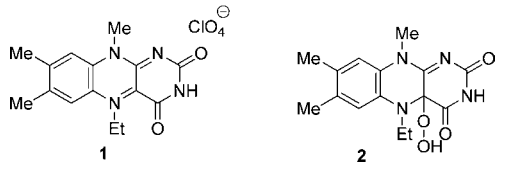
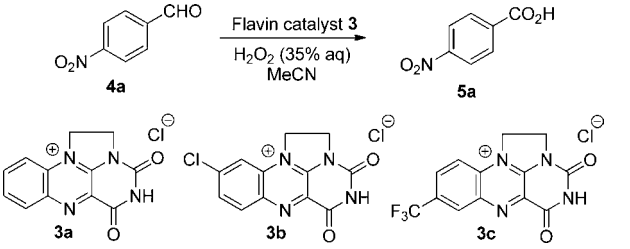


Figure 1. Flavins and hydroperoxides relevant to this study.

tertiary amines and phosphines to form sulfoxides, *N*-oxides, and phosphine oxides, respectively.[4] However, there are examples of synthetically useful flavin-catalyzed reactions which operate through a nucleophilic flavin hydroperoxide.[5,6] Key among these oxidations are flavin-catalyzed Baeyer–Villiger reactions which use H_2O_2 as terminal oxidant. Accordingly, we believed there to be scope to examine a biomimetic oxidation of aldehydes. We and others have further examined the synthetic utility of Sayre's ethylene-bridged flavin catalysts (**3a**–**c**, Table 1)[7] in oxidative[8] and reductive transformations.[9] These catalysts are readily prepared in three steps, without recourse to intermediate purification, and therefore offer themselves as thermally stable and versatile organocatalysts.

We initially chose to examine the flavin-catalyzed oxidation of 4-nitrobenzaldehyde **4a** to 4-nitrobenzoic acid **5a** mediated by aqueous hydrogen peroxide. Reasonable oxidation with catalyst **3a** was only observed when heated to 85 °C in acetonitrile as solvent (entries 1–3).[10] There is some sensitivity to the exact structure of the catalyst with 7-CF_3-substituted catalyst **3c** offering improvement over **3a** and **3b** (entries 3–5). Increasing the reaction time also was beneficial (entry 6). Intriguingly, we have observed that the reaction offers an improved reaction as gauged by an improved final conversion after 3 h when catalyst loading was lowered to 2.5 and 1 mol % (entries 7 and 8). Full conversion can be achieved by conveniently raising the loading of oxidant and allowing the reaction to proceed to a longer duration (entry 11). Minimal background reaction is observed in the absence of the flavin catalyst, confirming the key role played by **3** (entry 12). In addition, no oxidation is observed in the absence of H_2O_2,

Table 1. Biomimetic Oxidation of 4-Nitrobenzaldehyde **4a**



entry	**3** (mol %)	H_2O_2 (equiv)	temp (°C)	time (h)	conv[a] (%)
1	**a** (5)	1.25	23	1	0
2	**a** (5)	1.25	50	1	0
3	**a** (5)	1.25	85	1	49
4	**b** (5)	1.25	85	1	54
5	**c** (5)	1.25	85	1	60
6	**c** (5)	1.25	85	3	66
7	**c** (2.5)	1.25	85	3	79
8	**c** (1)	1.25	85	3	76
9	**c** (1)	1.5	85	3	85
10	**c** (2.5)	1.5	85	3	96[b]
11	**c** (2.5)	5	85	17	100
12		1.25	85	3	6
13	**c** (2.5)	0	85	3	0

[a] NMR conversion; assayed by relevant ^{1}H NMR integrals. [b] Isolated yield = 89%.

supporting an activation of H_2O_2 rather than a redox-centered catalytic cycle that activates molecular oxygen (entry 13).

Having developed an effective oxidation protocol, as optimized on **4a**, we looked to examine the scope with other aromatic aldehydes (Scheme 2). This protocol works well with electron-deficient aryl aldehydes, as seen with regioisomeric nitro- and chlorobenzaldehydes **4a**–**f**. The heteroaromatic substrate picolinaldehyde **4n** also demonstrates this point. In contrast, the regioisomeric anisaldehydes **4j**–**l** result in lower isolated yields of carboxylic acid products (Scheme 2). The presence of the strong electron-donating groups in the *ortho*- and *para*-positions led to the formation of phenol byproducts, consistent with a competitive Dakin oxidation.

This flavin-catalyzed reaction is also generally excellent for the oxidation of alkyl aldehydes, with high yields observed in many instances. Interestingly, diminished yields were observed with aldehydes bearing nonconjugated aryl groups (**4v**,**w**). It is unclear exactly why this is the case; however, ^{1}H NMR analysis of the crude reaction mixture of **5w** appears to support the presence of a stable peroxy hemiacetal. This observation suggests a slow formation of carboxylic acid in this instance.

The mechanism we propose for this flavin-catalyzed oxidation is outlined in Scheme 3. Flavin catalyst **3c** reacts with H_2O_2 to form hydroperoxide **6**. The C10[a] regioselectivity of peroxide addition is that proposed by Sayre as a

(4) For a review of the synthetic chemistry of flavin hydroperoxides, see: Gelalcha, F. G. *Chem. Rev.* **2007**, *107*, 3338.

(5) For examples of flavin-catalyzed Baeyer–Villiger reactions, see: (a) Mazzini, C.; Lebreton, J.; Furstoss, R. *Heterocycles* **1997**, *45*, 1161. (b) Mazzini, C.; Lebreton, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 8. (c) Imada, Y.; Iida, H.; Murahashi, S.-I.; Naota, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1704. (d) Murahashi, S.-I.; Ono; Imada, S., Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 2366.

(6) For a recent example of a flavin-catalyzed Dakin oxidation, see: Chen, S.; Hossain, M. S.; Foss, F. W., Jr. *Org. Lett.* **2012**, *14*, 2806.

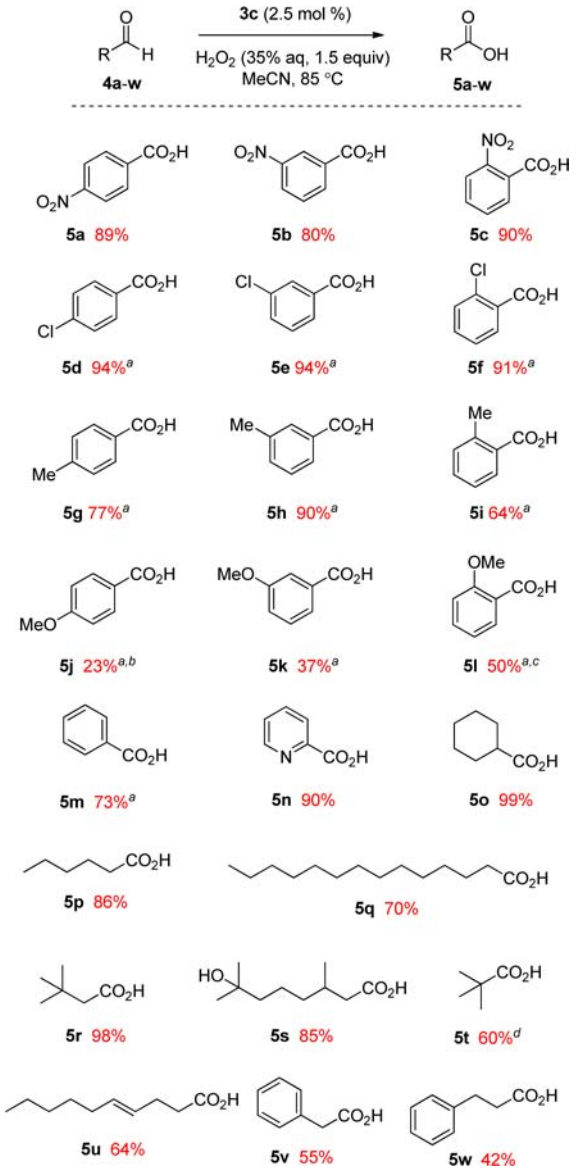
(7) (a) Li, W.-S.; Zhang, N.; Sayre, L. M. *Tetrahedron* **2001**, 4507. (b) Li, W.-S.; Sayre, L. M. *Tetrahedron* **2001**, *57*, 4523.

(8) (a) Marsh, B. J.; Carbery, D. R. *Tetrahedron Lett.* **2010**, *51*, 2362. (b) Zurek, J.; Cibulka, R.; Dvořáková, H.; Svoboda, J. *Tetrahedron Lett.* **2010**, *51*, 1083. (c) Jurok, R.; Cibulka, R.; Dvořáková, H.; Hampl, F.; Hodačová, J. *Eur. J. Org. Chem.* **2010**, 5217.

(9) Marsh, B. J.; Heath, E. L.; Carbery, D. R. *Chem. Commun.* **2011**, 280.

(10) See the Supporting Information for full reaction optimization.

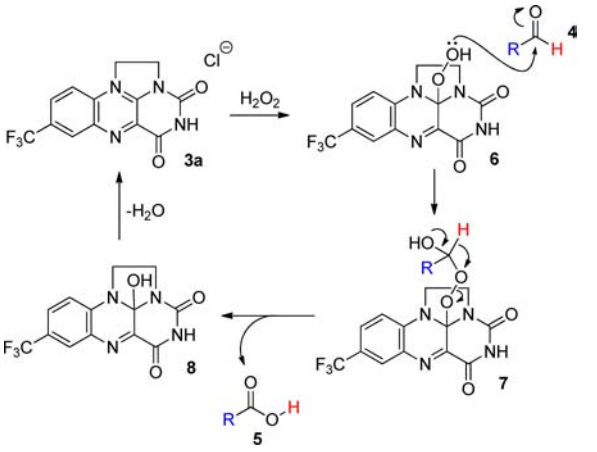
Scheme 2. Substrate Scope



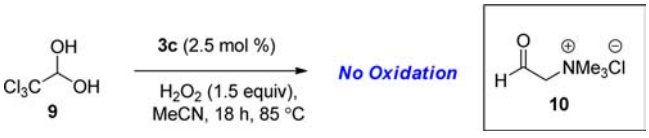
[a] Performed with 5 equiv of H_2O_2. [b] Dakin oxidation phenol observed in ^{1}H NMR of crude product (38%). [c] Dakin oxidation phenol observed in ^{1}H NMR of crude product (31%). [d] *tert*-Butyl alcohol observed in ^{1}H NMR of crude product (40%).

result of extensive ^{13}C NMR studies in the reaction of these bridged flavins and benzylamine. This hydroperoxide now acts as a nucleophile, reacting with an aldehyde substrate to form peroxyhemiacetal **7**.[11] This adduct now undergoes thermal collapse via 1,2-hydride migration with resultant O−O bond cleavage to form carboxylic acid **5** and hydrated flavin **8**. This flavin undergoes dehydration to regenerate catalyst **3**.

Scheme 3. Proposed Mechanism



Scheme 4. Attempted Oxidation of Chloral Hydrate



The nature of the aldehyde group is important. When this group is an electron-rich aryl or a tertiary alkyl group, migration of these groups becomes competitive resulting in the formation of a formate ester which hydrolyses under the reaction conditions. Such a flavin-catalyzed Dakin oxidation has very recently been reported.[6]

It is noteworthy that chloral hydrate **9** does not undergo oxidation using this protocol (Scheme 4). This is supportive of the aldehyde acting as as an electrophile for a nucleophilic hydroperoxide. In this context, flavoenzyme choline oxidase has been extensively studied with respect to the oxidation of betaine aldehyde (**10** Scheme 4) to glycine betaine.[12,13] This oxidation proceeds through the flavin cofactor acting as a hydride acceptor from an aldehyde hydrate, with this assertion also supported by the lack of enzymatic activity on the isosteric analogue **4r**. As noted already, **4r** acts as particularly good substrate in this reaction under our conditions, again suggesting the absence of an aldehyde hydrate mechanism.

In conclusion, ethylene-bridged flavin organocatalysts are competent catalysts for the activation of hydrogen peroxide in the oxidation of aldehydes to carboxylic acids. Complex reactivity trends have been noted in this paper that are not fully understood and are the subject of ongoing

(11) Preliminary efforts have been made to observe **7** by ESI-MS and ^{13}C NMR analysis of a reaction with stoichiometric loading of **3c**. This species has so far not been observed using these techniques in these initial mechanistic studies.

(12) (a) Fan, F.; Germann, M. W.; Gadda, G. *Biochemistry* **2006**, *45*, 1979. (b) Fan, F.; Gadda, G. *J. Am. Chem. Soc.* **2005**, *127*, 2067.

(13) For a general discussion of oxygen activation in flaviprotein oxidases, see: Gadda, G. *Biochemistry* **2012**, *51*, 2662.

mechanistic studies. The oxidation does not require chlorinated solvents and, with low loadings of H_2O_2, represents a clean oxidation protocol.

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Supporting Information Available. Full experimental details, full optimization, and copies of ^{1}H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.