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Organocatalytic Dakin Oxidation by Nucleophilic Flavin Catalysts

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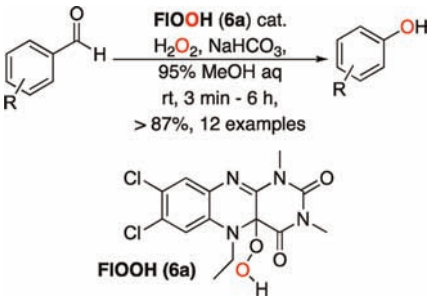
ABSTRACT



Flavin catalysts perform the first organocatalytic Dakin oxidation of electron-rich arylaldehydes to phenols under mild, basic conditions. Catechols are readily prepared, and the oxidation of 2-hydroxyacetophenone was achieved. Aerobic oxidation is displayed in the presence of Zn(0) as a reducing agent. This reactivity broadens the scope of biomimetic flavin catalysis in the realm of nucleophilic oxidations, providing a framework for mechanistic investigations for related oxidations, such as the Baeyer–Villiger oxidation and Weitz–Scheffer epoxidation.

Riboflavin-derived coenzymes perform an array of redox reactions at the active sites of flavin-dependent enzymes.[1−4] Outside of the enzyme, flavin mimics catalyze the activation of O_2 or H_2O_2 for electrophilic oxidation of N, P, S, and Se and have led to decades of investigations and advances.[5−16] Unfortunately, small molecule flavin mimics have shown diminished functionality in valuable nucleophilic oxidations of carbon-centered functional groups, such as the Baeyer–Villiger oxidation (BVO) and Weitz–Scheffer epoxidation (WSE).

Although Baeyer–Villiger monooxygenases (BVMOs) are flavoenzymes capable of converting wide ranges of cyclic and acyclic ketones to their synthetically valuable lactones,[1−4,17−22] only cyclobutanones and cyclopentanones containing electron-rich substituents alpha to the

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ketone underwent BVO by flavin mimics.[5,7−15,23] This disparity in reactivity not only displays the enzyme's role in tuning flavin reactivity but also suggests that a biomimetic system could be developed to modulate inate flavin reactivity in solution.

To broaden the synthetic capability of flavin catalysts to useful nucleophilic oxidations, the Dakin oxidation of electron-rich benzaldehydes (Figure 1) was investigated. The Dakin oxidation[24] is a privileged variation of the BVO that converts benzaldehydes (**1**) to phenols (**3**) by BVO and subsequent hydrolysis of the aryl formate intermediate (**2**), effectively oxidizing both aryl and acyl sp^2 carbons.[25−27] Dakin's original procedure utilized excess hydrogen peroxide and sodium hydroxide at elevated temperatures.[24] Common substrates contain electron-rich aromatic rings for rapid collapse and carbon migration of the tetrahedral Criegee intermediate (**CI**$^-$).

Because synthetically challenging aromatic hydroxylations can be formally achieved by aryl acylation followed by Dakin oxidation,[28−32] numerous stoichiometric alkylperoxides and catalytic transition metal complexes have been developed for mild Dakin oxidations.[33−41] No organocatalytic processes exist for the Dakin oxidation. Therefore, we saw the transformation as an attractive entry point to study nucleophilic flavin reactivity.

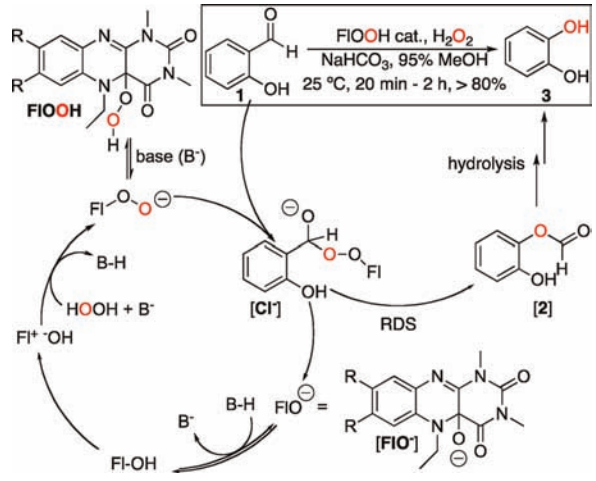

Figure 1. Potential flavin catalyzed dakin oxidation mechanism. Focus on energetic demanding steps similar to Baeyer−Villiger-like transformations: **1** + **FlOO**$^-$ → **CI**$^-$ and **CI**$^-$ → **2** + **FlO**$^-$.

Here we show that flavin mimics catalyze the Dakin oxidation. Due to the lower pK_a and O−O heterolytic bond lability of hydroperoxyflavins in comparison to H_2O_2 and other alkyl peroxides,[42−45] the reactions are effective under relatively milder conditions. The time scale of the transformations allows for an initial mechanistic investigation of this nucleophilic flavin oxidation by NMR and HPLC techniques, experimentally illuminating the challenges that have faced flavin catalyzed BVOs of unstrained substrates and related oxidations.[23] It should be noted that our initial mechanistic findings for flavins correspond with recent investigations of BVMO mechanisms.[46−48]

Catalysts **6a**−**e** were synthesized as shown in Scheme 1 from **4a**−**e** (Scheme SI-1), which were prepared according to conventional methods.[8,49,50] Significant improvements were made to the general synthesis of 7,8-disubstituted-1,3-dimethyl-5-ethylflavins by modifications to the final reductive amination transformation. Catalysts **6a** and **6d** were not previously reported. Dichloromethane was required as a solvent to suppress hydrodechlorination of **4a**,[51−53] which yields undesired **6c** under standard hydrogenation conditions, to complete the most active catalyst **6a**. Compound **6b** required elevated H_2 pressure.

Catalysts **6a** and **6b** converted a range of electron-rich arylaldehydes to phenols (Table 1). While **6c**−**e** react at reduced rates, **6c** tends to reach comparable yields as **6a** and **6b** with prolonged reaction times. Entries 1−6 exemplify the utility of the flavin-catalyzed oxidation for the

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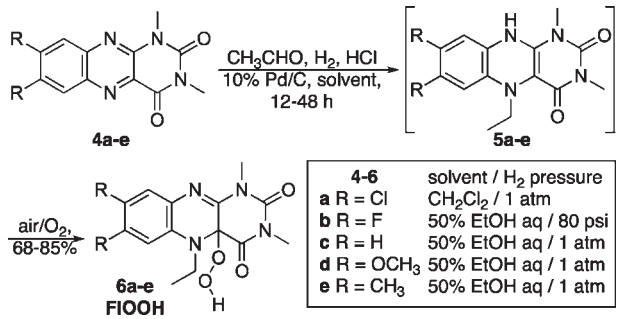
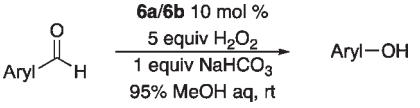
Scheme 1. Synthesis of Hydroperoxyflavin Catalysts **6a**–**e**

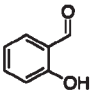
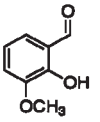
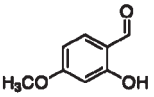
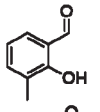
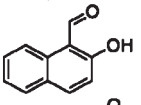
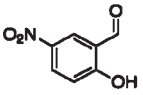
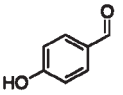
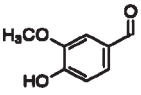
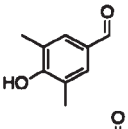
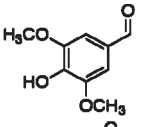
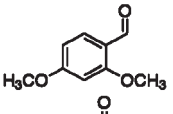
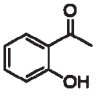


synthesis of catechols from salicylaldehyde (**1**) derivatives. Entries 7–10 show *para*-hydroxybenzaldehydes to react with equal or slightly reduced rates. Other electron-rich aldehydes also undergo the Dakin oxidation (11) under mild conditions, but further investigations are needed to understand the limits of nonhydroxylated substrates. When employing DMSO as an internal standard, we serendipitously found that this reactiviy was extended to 2-hydroxyacetophenone. Entry 12 shows the unoptimized oxidation of the acetophenone to catechol with 90:10 MeOH/DMSO. All transformations also were successful with only 1 equiv of H_2O_2. For example, **6a** (5 mol %) catalyzes >95% conversion of salicylaldehyde to catechol within 2 h in the presence of 1 equiv of H_2O_2 (Figure SI-2).

The mechanism and rate of FlOOH formation from trialkylated flavin precatalysts (Fl^+ and reduced flavins) were previously described, and it is generally believed that either creation or collapse of the **CI**$^-$ is rate-limiting for Dakin oxidations.[3,42,54–57] To experimentally investigate the rate-limiting step, HPLC analysis (Figures SI-3 and SI-4) was used to determine initial rates of Dakin oxidations by catalysts **6a**–**e**, which contain substituents yielding various inductive effects. A Hammett linear free-energy relationship (Figure 2) was completed with these data to indicate that conversion of **CI**$^-$ to **FlO**$^-$ and **2** is rate limiting. Linear agreements occurred between the individual and summed[58] σ_i values and $\log(k_R/k_H)$ yielding a positive slope (Figure 2, $\rho > 0$). This indicates an increase of electron density on the catalyst structure during the rate-limiting step. These initial data are consistent with formation of a 4a-oxaflavin anion (**FlO**$^-$) during the collapse of **CI**$^-$ (Figure 1). In many oxidations by alkylperoxides, heterolytic O–O bond breaking is endergonic with a late transition state,[42] which may explain the sensitivity to inductive effects, even though the substitutions are distal ($7/\sigma_{imeta}$ and $8/\sigma_{ipara}$ positions) to the forming anion. Regardless, the reverse outcome ($\rho < 0$) would have suggested that the initial nucleophilic addition to the carbonyl was rate-limiting, as is the case for some Dakin oxidations and BVOs.[27,48] Additional studies will further describe this mechanism.

Table 1. Conversion of Arylaldehydes to Phenols



	substrate	product yield (%)		
entry	structure	6a[a]	6b[a]	%[b]
1[c]		>95%, 20 min 63% (5 mol %) 32% (1 mol %) 5% (0 mol %)	>95%, 60 min	92
2		>95%, 3 min	>95%, 10 min	88
3		>95%, 5 min	>95%, 10 min	95
4		>95%, 25 min	>95%, 3 h	98
5		>95%, 10 min	>95%, 10 min	90[d]
6		>95%, 10 min	>95%, 15 min	75[e]
7		>95%, 20 min	>95%, 60 min	90
8		>95%, 5 min	>95%, 10 min	92
9		>95%, 3 min	>95%, 20 min	91
10		>95%, 15 min	>95%, 3 h	88
11		N/A	>95%, 16 h	89
12		87%, 6 h	58%, 6 h	79[e,f]

[a] NMR yields. [b] Isolated yield from **6b**-catalyzed reaction, post column. [c] **6a** yields represent a catalyst loading comparison after 30 min reaction (Figure SI-2). [d] Naphthoquinone isolated. [e] Isolated yield from **6a**-catalyzed reaction, post column. [f] Solvent was 90:10 MeOH/DMSO.

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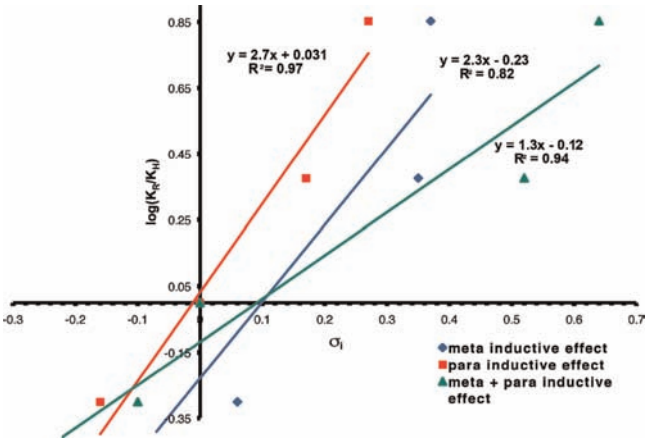
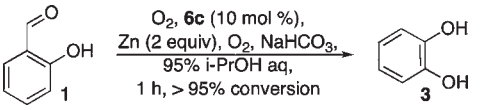


Figure 2. Hammett plot of relative initial rates (Figure SI-4) of reaction by catalysts **6a**–**e** versus *meta* (7-substituent), *para* (8-substitution), and *meta* + *para* inductive effects.

In at least one example (Scheme 2) we show that Murahashi's established O_2/Zn system[10] for regenerating the reduced flavin precatalyst is capable of carrying out Dakin Oxidations aerobically, eliminating any background reaction by H_2O_2 or HOO^- and need for careful pH control.[9] We believe these specific data provide a new reaction manifold for flavin mimics and will be a crucial aid in the development and monitoring of related nucleophilic flavin systems. Further work is ongoing to develop a biomimetic organocatalytic flavoprotein system for Dakin oxidations, BVO, and WSE with H_2O_2 or O_2 as a terminal oxidant. If successful, flavin mimics are poised to provide an organocatalytic companion to current peroxyacid, organometallic, and enzymatic efforts to provide efficient and safe oxidants to the synthetic community.

Scheme 2. Aerobic Oxidation of Salicylaldehyde to Catechol Displays H_2O_2-Free Dakin Oxidation



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Supporting Information Available. Full experimental and kinetic details. Structural characterization: ^1H, ^{13}C, and ^{19}F NMR, MS, HRMS, IR, melting points, and copies of spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.