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Aerobic Organocatalytic Oxidation of Aryl Aldehydes: Flavin Catalyst Turnover by Hantzsch's Ester

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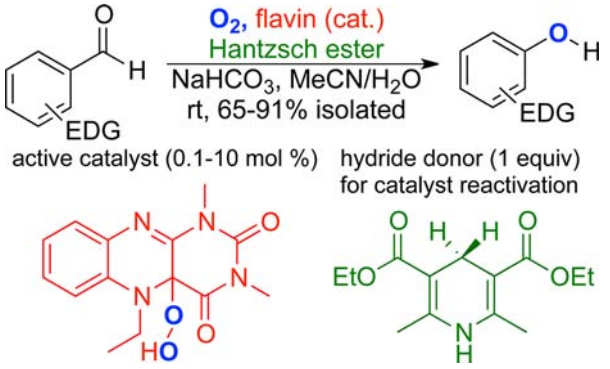
ABSTRACT



The first Dakin oxidation fueled by molecular oxygen as the terminal oxidant is reported. Flavin and NAD(P)H coenzymes, from natural enzymatic redox systems, inspired the use of flavin organocatalysts and a Hantzsch ester to perform transition-metal-free, aerobic oxidations. Catechols and electron-rich phenols are achieved with as low as a 0.1 mol % catalyst loading, 1 equiv of Hantzsch ester, and O_2 or air as the stoichiometric oxidant source.

Molecular oxygen is regarded as a green oxidant in many respects. Its abundance, high atom efficiency, and ease of byproduct (H_2O) disposal are unmatched by other oxidants.[1−3] Oxygen is predominantly activated by metal catalysts or stoichiometric cooxidants.[3,4] Unfortunately, aerobic oxidations by *organocatalysts* are surprisingly scarce. Nature, however, has employed flavin-dependent monooxygenases that activate triplet oxygen by organic cocatalysts, FAD or FMN, and gently oxidize diverse substrates at moderate temperature and pH, and in an aqueous environment.[5−8] In these enzymes, a reductive coenzyme such as NAD(P)H is needed to regenerate the reduced form of flavin cofactors, which interacts with O_2, completing the catalytic cycle. In this work, we evaluated a range of reducing agents to achieve an aerobic, catalytic, transition metal-free Dakin oxidation of benzaldehydes to phenols by flavin mimics, **1a**−**e** (Figure 1). The quintessential Hantzsch ester (**2**)[9] was found to be most compatible with both starting materials and products and is shown for the first time to effectively regenerate flavin catalysts for the nucleophilic oxidation of carbonyl containing substrates.

Biomimetic flavin organocatalysts have been designed to perform extensive electrophilic (amine and sulfur) oxidations and limited nucleophilic (Baeyer−Villiger) oxidations,

(1) Arends, I. W. C. E.; Sheldon, R. A. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Darmstadt, 2010; pp 147−180.
(2) Eissen, M.; Metzger, J. O.; Schmidt, E.; Schneidewind, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 414–436.
(3) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2012**, *105*, 2329–2364.
(4) Gelalcha, F. G. *Chem. Rev.* **2007**, *107*, 3338–3361.
(5) Fraaije, M. W.; Janssen, D. B. In *Modern Biooxidation*; Schmid, R. D., Urlacher, V., Eds.; Wiley-VCH: Darmstadt, 2007; pp 77−94.
(6) Kamerbeek, N.; Janssen, D.; van Berkel, W.; Fraaije, M. *Adv. Synth. Catal.* **2003**, *345*, 667–678.
(7) van Berkel, W. J. H.; Kamerbeek, N. M.; Fraaije, M. W. *J. Biotechnol.* **2006**, *124*, 670–689.
(8) Bruice, T. C. *Acc. Chem. Res.* **1980**, *13*, 256–262.
(9) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223–243.
(10) Imada, Y.; Iida, H.; Ono, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2003**, *125*, 2868–2869.

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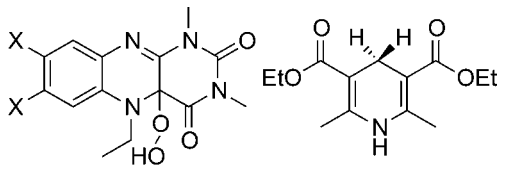


1a-e
X = **a** Cl, **b** F, **c** H
d Me, **e** OMe

2
Hantzsch ester

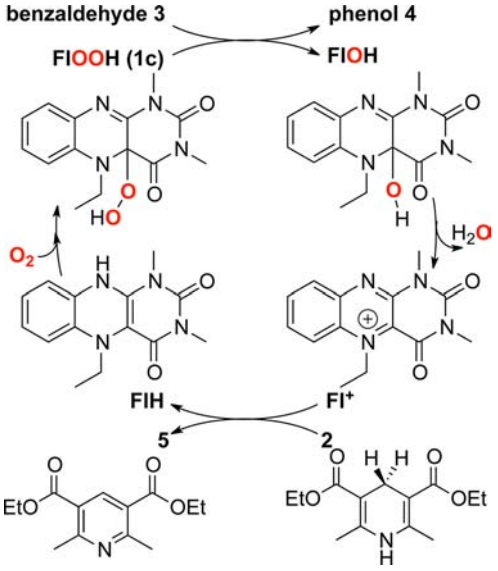
Figure 1. Flavin catalysts **1a**–**e** and Hantzsch ester **2**.

using molecular oxygen[10–12] or hydrogen peroxide[13–18] as terminal oxidants. In previous work, hydrazine and zinc dust effectively reduced flavin mimics to complete an aerobic catalytic cycle.[10,11,19–22] However, these reducing agents are not fully compatible with aldehyde substrates. In search of new nucleophilic flavin oxidations, we discovered that hydroperoxyflavins efficiently performed the Dakin oxidation of electron-rich benzaldehydes.[23] Pleasingly, the flavin-catalyzed oxidation of electron-poor benzaldehydes to benzoic acids was recently reported by a similar mechanism.[24] The Dakin oxidation (Scheme 1) is related to the Baeyer–Villiger oxidation.[25] Many methods have been investigated to perform this transformation. Most Dakin oxidation methods utilize hydrogen peroxide or peracids as an oxidant, often requiring activation by metal catalysts or elevated temperatures.[26–34]

To our knowledge, no example utilizing molecular oxygen as the terminal oxidant for Dakin oxidations exists. Here we achieve a catalytic system in which O_2 is activated by flavin catalysts, and the Hantzsch ester **2** is an effective reducing agent,[35,36] completing the catalytic cycle, to perform transition-metal-free, efficient, and mild Dakin oxidations.

Hydrogen peroxide based Dakin oxidations were previously investigated in our laboratory with five 1,3,5-trialkylated alloxazines (**1a**–**e**), a class of flavins documented to attain considerable stability[15] and a range of catalytic activity in comparison to related alloxazines and isoalloxazines.[15,18,37,38] The new 4*a*-hydroperoxyflavin catalyst **1a** proved most efficient in Dakin oxidations.[23] We initiated the aerobic Dakin oxidation of arylaldehydes by applying similar conditions using these alloxazine catalysts.

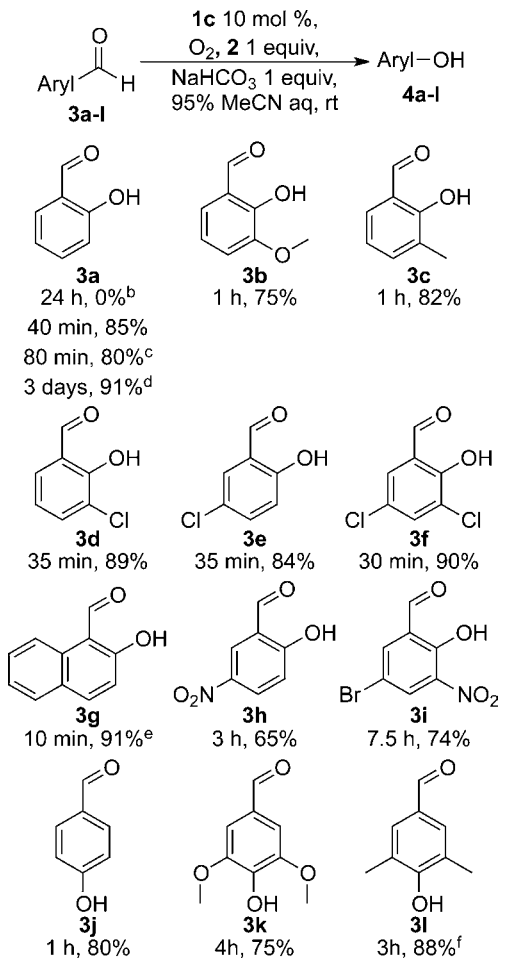
Scheme 1. General Mechanism for Organocatalytic Aerobic Oxidation of Substrate **3** to **4** by 4*a*-Hydroperoxyflavin **1c**



Reducing agent selection was key to the success of catalytic aerobic Dakin oxidations (Scheme 1). Based on previous aerobic amine, sulfur, and Baeyer–Villiger oxidation methods, hydrazine and zinc were regarded as efficient reducing agents to reduce oxidized flavin mimics ($\mathbf{Fl}^+$).[10,11] Hydrazine predictably forms hydrazones with benzaldehyde substrates, yielding no desired product. Activated zinc showed good reactivity in the oxidation of salicylaldehyde to produce catechol. However, when the

(11) Imada, Y.; Iida, H.; Murahashi, S.-I.; Naota, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1704–1706.
(12) Imada, Y.; Iida, H.; Ono, S.; Masui, Y.; Murahashi, S.-I. *Chem.—Asian. J* **2006**, *1*, 136–147.
(13) Murahashi, S.-I.; ODA, T.; Masui, Y. *J. Am. Chem. Soc.* **1989**, *111*, 5002–5003.
(14) Mazzini, C.; Lebreton, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 8–9.
(15) Bergstad, K.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 6650–6655.
(16) Minidis, A. B.; Bäckvall, J. E. *Chem.—Eur. J.* **2001**, *7*, 297–302.
(17) Murahashi, S.-I.; Ono, S.; Imada, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 2366–2368.
(18) Lindén, A. A.; Johansson, M.; Hermanns, N.; Bäckvall, J.-E. *J. Org. Chem.* **2006**, *71*, 3849–3853.
(19) Imada, Y.; Iida, H.; Naota, T. *J. Am. Chem. Soc.* **2005**, *127*, 14544–14545.
(20) Imada, Y.; Iida, H.; Kitagawa, T.; Naota, T. *Chem.—Eur. J.* **2011**, *17*, 5908–5920.
(21) Imada, Y.; Kitagawa, T.; Ohno, T.; Iida, H.; Naota, T. *Org. Lett.* **2010**, *12*, 32–35.
(22) Smit, C.; Fraaije, M. W.; Minnaard, A. J. *J. Org. Chem.* **2008**, *73*, 9482–9485.
(23) Chen, S.; Hossain, M. S.; Foss, F. W., Jr. *Org. Lett.* **2012**, *14*, 2806–2809.
(24) Murray, A. T.; Matton, P.; Fairhurst, N. W. G.; John, M. P.; Carbery, D. R. *Org. Lett.* **2012**, *14*, 3656–3659.
(25) Dakin, H. D. *Am. Chem. J.* **1909**, *62*, 477–498.
(26) Kabalka, G. W.; Reddy, N. K.; Narayana, C. *Tetrahedron Lett.* **1992**, *33*, 865–866.
(27) Yamazaki, S. *Chem. Lett.* **1995**, 127–128.
(28) Roy, A.; Reddy, K. R.; Mohanta, P. K.; Ila, H.; Junjappat, H. *Synth. Commun.* **1999**, *29*, 3781–3791.
(29) Zambrano, J. L.; Dorta, R. *Synlett* **2003**, *2003*, 1546–1546.
(30) Brink, ten, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105–4124.
(31) Bernini, R.; Coratti, A.; Provenzano, G.; Fabrizi, G.; Tofani, D. *Tetrahedron* **2005**, *61*, 1821–1825.
(32) Hansen, T. V.; Skattebøl, L. *Tetrahedron Lett.* **2005**, *46*, 3357–3358.
(33) Bernini, R.; Mincione, E.; Barontini, M.; Crisante, F.; Fabrizi, G.; Gambacorta, A. *Tetrahedron* **2007**, *63*, 6895–6900.
(34) da Silva, E. T.; Câmara, C. A.; Antunes, O. A. C.; Barreiro, E. J.; Fraga, C. A. M. *Synth. Commun.* **2008**, *38*, 784–788.
(35) Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* **2011**, *13*, 1084–1105.
(36) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498–2518.
(37) Bergstad, K.; Jonsson, S. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 10424–10425.
(38) Closson, A.; Johansson, M.; Bäckvall, J.-E. *Chem. Commun.* **2004**, 1494–1495.

Scheme 2. Substrate Study for Aerobic Oxidation[a]



[a] Yields refer to isolated yields. [b] No catalyst added. [c] Air was used as an oxidant. [d] Air was used as an oxidant, with 0.1 mol % **1c**, and 10 mmol of substrate **3a**. [e] Naphthoquinone isolated. [f] 65% quinone and 23% dihydroquinone isolated.

Zn/O_2 protocol was applied to substituted salicylaldehydes (**3b**, **3c**, **3g,** Scheme 2), catechols were isolated in very low yields. Either robust bisphenolate zinc complexes, such as zinc bis(2-ethylzincoxyphenoxide) and zinc bis(2- ethylzincoxyphenylmethoxide), or polyphenols are believed to form, sequestering the desired product.[39] Methods (acid, base, EDTA treatment and extraction) to liberate product from the possible organometallic structures were unsuccessful. Other reducing agents, such as $Na_2S_2O_4$, $NaBH_3CN$, $NaBH(OAc)_3$, and trialkylsilanes, yielded no desired products. Other d-block species (Mg, Cu, and Fe) were expected to result in decomposition of the reactive hydroperoxyflavins by Fenton or Fenton-like chemistry. No catechol was detected by these metal reducing agents.

Hantzsch ester **2**, the hydrogen transfer reagent closely related to NAD(P)H's nicotinamide reactive core,[40] selectively reduces imines in the presence of aldehydes.[35,36] When zinc powder was replaced with 1 equiv of **2**, aerobic Dakin oxidations proceeded smoothly to form corresponding phenol products (Schemes 1 and 2). The production of undesired benzyl alcohols or benzoic acids[41−43] was not detected. Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate, **5**, could be isolated from reactions as the oxidized byproduct.

Control reactions without flavin catalysts ensured that no autoxidation of benzaldehydes occurred during oxidation of **3a**.[41−43] Reactions were also performed in the dark to eliminate possible photooxidation pathways. The aerobic Dakin oxidation conditions were then optimized in three aspects: catalyst substitution, solvent, and base.

Five alloxazines with different substituents at the 7- and 8-positions were compared. With a 5 mol % catalyst loading, the conversion of salicylaldehyde to catechol was calculated by NMR, utilizing DMSO as an internal standard. Flavin **1c** showed the greatest reactivity, followed by 7,8-dimethyl (**1d**) and 7,8-dimethoxy (**1e**) substituted alloxazines. Electron-poor 7,8-difluoro (**1b**) and 7,8-dichloro (**1a**) alloxazines, which provided the fastest reaction rates in H_2O_2-fueled Dakin oxidations, performed aerobic oxidation poorly (Figure SI-1).

The catalyst results suggest that competing rate-determining steps influence the observable reaction rate: (1) collapse of the Criegee intermediate via a 1,2-aryl shift (putative rate-determining step of the Dakin oxidation)[23,44] and (2) molecular oxygen activation by reduced flavins.[8,45] While we previously showed that electron-withdrawing groups facilitate the Dakin oxidation by stabilizing the 4*a*-oxaflavin anion (**FlO**$^-$) leaving group, the same substituents attenuate the single-electron transfer process from flavin to triplet oxygen by altering the oxidation potentials of the reduced flavins.[16,46] The hypothesis, in correlation with previous data,[45−47] is as follows: electron-poor hydroperoxyflavins (Scheme 1, **FlOOH**), in comparison to more electron-rich catalysts, are more efficient Dakin oxidation catalysts, but their respective reduced structures (**FlH**) react with O_2 more slowly.

Solvents were investigated (Figure SI-2). Water miscible solvents were investigated to solvate sodium bicarbonate by 5% water addition, which also promotes hydrolysis of the Dakin oxidation intermediate. Acetonitrile, 95% in water, achieved the fastest reaction rate and highest yields. In general, alcohols suppressed reaction rates. Anhydrous acetonitrile failed to conduct aerobic Dakin oxidation.

Base is essential in the flavin catalyzed Dakin oxidation system. However, only mild bases (sodium bicarbonate

(39) Kuran, W.; Mazanek, E. *J. Organomet. Chem.* **1990**, *384*, 13–17.
(40) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1 VL* **2002**, 1141–1156.
(41) Kaneda, K.; Haruna, S.; Imanaka, T.; Hamamoto, M.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1992**, *33*, 6827–6830.
(42) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Tetrahedron Lett.* **1993**, *34*, 3405–3408.
(43) Kaneda, K.; Ueno, S.; Imanaka, T.; Shimotsuma, E.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 2915–2917.
(44) Hocking, M. B.; Bhandari, K.; Shell, B.; Smyth, T. A. *J. Org. Chem.* **1982**, *47*, 4208–4215.
(45) Murthy, Y. V. S. N.; Massey, V. *J. Biol. Chem.* **1998**, *273*, 8975–8982.
(46) Li, X.-L.; Fu, Y. *THEOCHEM* **2008**, *856*, 112–118.
(47) Lindén, A. A.; Hermanns, N.; Ott, S.; Krüger, L.; Bäckvall, J.-E. *Chem.—Eur. J.* **2005**, *11*, 112–119.

or carbonate) were necessary. Hydroxides were not as effective in this system, presumably due to hydrolysis of the flavin catalyst (Figure SI-3).

The catalytic system for aerobic Dakin oxidation is broadly described as shown in Scheme 1. Flavinium ($\mathbf{Fl}^+$) is reduced by **2** to form reduced flavin (**FlH**). Meanwhile, **2** is oxidized to pyridine **5**. **FlH** undergoes autoxidation to form an active catalyst (**FlOOH)**, which performs the Dakin oxidation. After protonation and water elimination, $\mathbf{Fl}^+$ is regenerated. A shunt process for the generation of H_2O_2 (made possible by disproportionation of **1** to $\mathbf{Fl}^+$ and HOO^- with consumption of **2** and O_2) is known in mutatated monooxygenases and some hydrophilic solvent systems. We were unable to detect turnover of this shunt process (by monitoring conversion of **2** to **5** in the absence of aldehyde) after long reaction times in either the presence or absence of substrate using the basic MeCN/H_2O reaction system.

A range of substituted benzaldehydes were screened to investigate the scope of this protocol (Scheme 2). In general, salicylaldehydes underwent aerobic Dakin oxidation faster than the 4-hydroxybenzaldehydes, likely due to neighboring group participation of the *ortho*-hydroxyl group involved in proton transfer events and hydrogen bond activation of the carbonyl.[48] Salicylaldehydes were smoothly converted into catechols at room temperature. Electron-withdrawing groups slowed the oxidation rate (**3i**). No reaction was detected at elevated temperatures for 3,5-dinitrosalicylaldehyde.

The reaction system functioned with air as an oxygen source, although longer reaction times were required. A 10 mmol scale reaction, with 0.1 mol % of catalyst and air as the oxygen source, was performed to challenge our catalytic system. A high yield of the product was achieved after 3 days at rt, and the byproduct **5**, which represents 99 w/w % of the reducing agent, was recovered in 95% yield. For products prone to autoxidation, the aerobic Dakin oxidation protocol yielded the expected oxidized products (**3g**, **3l**).

Electron-poor benzaldehydes, without a hydroxyl group on the *othro*- or *para*-position, failed to undergo Dakin oxidation in these conditions, even with the addition of a Lewis or Brønsted acid. Acetophenone remained unoxidized, even at elevated temperature (50 °C) using catalyst **1c**. Though unproductive, these substrates remained intact under the reaction conditions.

(48) Chung, G.; Kwon, O.; Kwon, Y. *J. Phys. Chem. A* **2012**, *102*, 2381–2387.

The reaction is selective for the nucleophilic Dakin oxidation in 95% MeCN aq.; thioanisole and triethylamine are not oxidized to a great extent. However, when MeCN was exchanged for trifluoroethanol (TFE), which convincingly assists in electrophilic addition by providing a useful hydrogen bond network during O−O bond cleavage,[12] thioanisole, salicylaldehyde, and triethylamine were oxidized in 80%, 18%, and 11% yield, respectively, over 1 h (see Supporting Information). Interestingly, **2** was fully converted to **5** in these TFE reactions. This revealed an underlying, flavin dependent, aerobic oxidation of dihydropyridines in certain solvents. Investigating the redox properties of the reductant in these systems may allow relatively slow Dakin oxidations to proceed without background dihydropyridine oxidation, which may be interesting, considering the abundance of oxidative aromatization reactions.[49−53]

In conclusion, we have developed an aerobic and mild catalytic system for the Dakin oxidation. A range of electron-rich benzaldehydes react in the presence of two biomimetic redox partners: flavin catalysts and Hantzsch ester **2**. The selection of **2** was crucial to the success of this reaction and provides an alternative reductant for flavin-catalyzed aerobic oxidations, especially those with ketones and aldehydes. The catalyst loading was effective at 0.1 mol %. Further experiments are underway to broaden the reaction scope to other important nucleophilic, flavin-catalyzed oxidations of carbon centers.

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Supporting Information Available. Synthetic methods, analytical methods, and full characterization of materials. This material is available free of charge via the Internet at http://pubs.acs.org.

(49) Gamapwar, S. V.; Tale, N. P.; Karade, N. N. *Synth. Commun.* **2012**, *42*, 2617–2623.

(50) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955–3957.

(51) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.

(52) Hirao, T.; Mori, M.; Ohshiro, Y. *J. Org. Chem.* **1990**, *55*, 358–360.

(53) Kawashita, Y.; Hayashi, M. *Molecules* **2009**, *14*, 3073–3093.

The authors declare no competing financial interest.