Title
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Journal
Organic Letters 27 (12)

Published
2025-03-17

URL (The Version of Record)
https://doi.org/10.1021/acs.orglett.5c00414

Flavin-Catalyzed Chemoselective Aerobic Oxygenation of Heteroarylmethanes to Ketones

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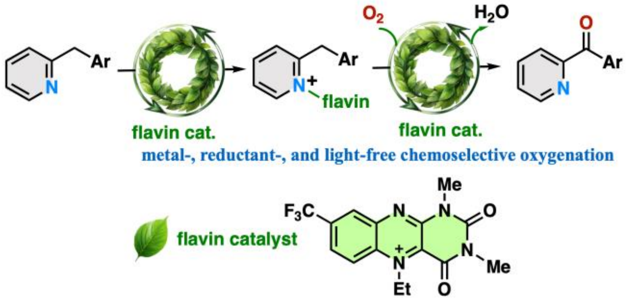
Supporting Information Placeholder



ABSTRACT: A novel flavin-catalyzed chemoselective aerobic oxygenation of arylheteroarylmethanes to ketones has been developed under metal-free and mild conditions. This catalytic system employs a cationic flavin to activate sp^3 C–H bonds through the formation of pyridinium-flavin adducts, enabling precise proton and electron transfer for oxygen-atom insertion. As a result, this method exhibits high chemoselectivity, effectively distinguishing between arylheteroarylmethanes and diarylmethanes.

The direct and selective oxygenation of sp^3 C–H bonds remains one of the most critical challenges in organic chemistry.[1] In particular, aerobic oxygenation using molecular oxygen (O_2) has gained significant attention because O_2 is the greenest, most cost-effective, readily available, and sustainable oxidant.[1b,2] Arylheteroarylmethanones, particularly 2- or 4-benzoylpyridines, are key intermediates in the synthesis of active pharmaceutical ingredients, including antihistamines (e.g., pheniramine, doxylamine, and arpromidine),[3] antiarrhythmic agents (e.g., disopyramide),[4] and anticancer therapeutics (Figure 1A).[5] The chemoselective aerobic oxygenation of heterobenzylic sp^3 C–H bonds represents a promising and atom-economical route to arylheteroarylmethanones. However, successful examples of the chemoselective oxygenation of arylheteroarylmethanes are limited because the bond dissociation energies (BDEs) and oxidation potentials (E_{ox}) of these compounds are extremely similar to those of diarylmethanes (Figure 1B).[6-9]

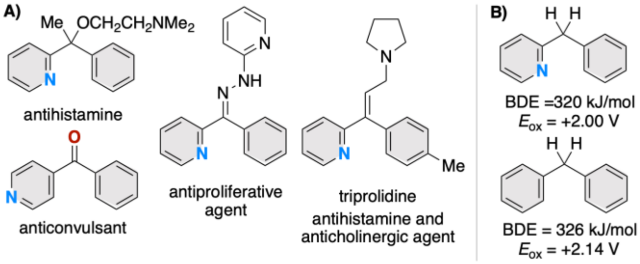
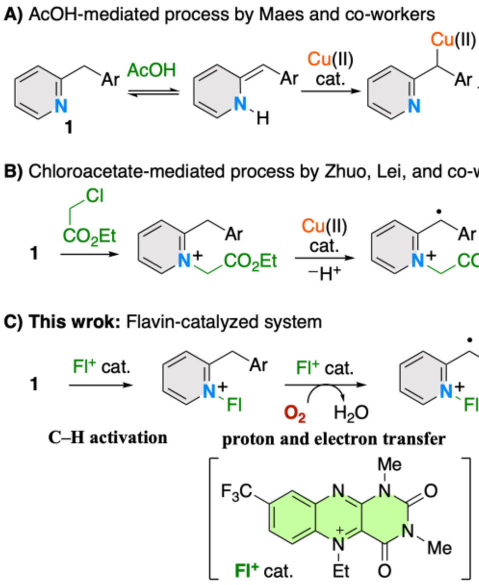


Figure 1. (A) Biologically and pharmaceutically important compounds derived from arylheteroarylmethanones and (B) comparison of BDEs and oxidation potentials (E_{ox} vs SCE).

In 2012, Maes *et al.* reported the chemoselective aerobic oxygenation of 2-benzylpyridines **1** to 2-benzoylpyridines **2**, catalyzed by copper and iron at 100 °C. Oxygenation of **1** occurs selectively rather than diphenylmethane and 3-benzylpyridines in the presence of acetic acid (1 equiv.), promoting the imine-enamine tautomerization to activate the heterobenzylic sp^3 C–H bond (Scheme 1A).[6-8] Zhuo, Lei, and coworkers demonstrated the selective copper-catalyzed aerobic oxygenation of **1**, in which a stoichiometric amount of chloroacetate was used at 130 °C to activate **1** (Scheme 1B).[9] The formation of pyridinium cations from **1** and chloroacetate activated the sp^3 C–H bond of **1** to promote the copper-catalyzed radical process for aerobic oxygenation. In this study, we report a novel method for the chemoselective aerobic oxygenation of arylheteroarylmethanes under metal-free and relatively mild conditions (Scheme 1C). This system utilizes a flavin-based organocatalyst that activates sp^3 C–H bonds through pyridinium-flavin adduct formation and facilitates catalytic proton/electron transfer processes, enabling efficient oxygen-atom insertion.

Scheme 1. (A) AcOH- and (B) chloroacetate-mediated processes for oxygenation of 1 and (C) present study on flavin-catalyzed system.

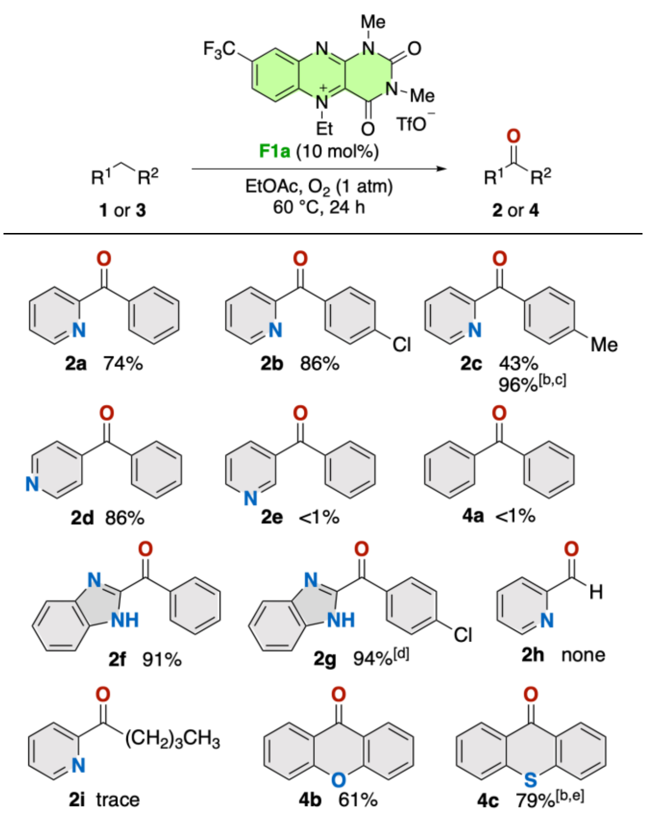


Cationic flavin catalysts have been developed to mimic the enzymatic function of flavin monooxygenase (FMO), which promotes oxygen-atom transfer to substrates in the presence of NAD(P)H.[10] Simplified flavin catalysts can promote the chemoselective aerobic oxygenation of various substrates, including heteroatoms,[11] carbonyl compounds,[12] and boronic acids.[13] However, these systems require chemical reductants to supply two electrons to the flavin catalyst, similar to how FMO requires two electrons from NAD(P)H. Alternatively, the photocatalysis of flavins has been applied to the aerobic photooxygenation of benzylic C–H bonds, such as those in toluene.[14] However, the high oxidation ability of excited flavins (1.67–2.67 V vs SCE),[14h,15] makes chemoselective oxygenation of heterobenzylic C–H bond via flavin photocatalysis difficult. The development of nonenzymatic aerobic oxygenation methods that do not rely on chemical reductants or light irradiation remains a long-standing challenge. Recently, we reported the flavin-iodine-catalyzed synthesis of imidazo[1,5-*a*]pyridines via tandem C–H imination and amination of pyridylacetates and aminomethanes.[16] In this transformation, the sp^3 C–H bond of ethyl-2-(pyridin-2-yl)acetate was oxygenated to a sp^2 C=O bond without light irradiation. However, the detailed mechanism remains unclear. Therefore, we present a novel application of flavin catalysis for chemoselective aerobic oxygenation of arylheteroarylmethanes without the use of reductants or light irradiation.

The effects of various flavin catalysts with different structures and redox potentials[17] on the oxygenation of 2-benzylpyridine (**1a**) were investigated in the presence (10 mol%) of the flavin catalysts in CH_3CN under O_2 (1 atm, balloon) at 40 °C for 24 h (Supporting Information, Table S1). As a result, we selected **F1a** as the most suitable catalyst for aerobic oxygenation. Following further optimization of the reaction conditions (Table S2), the yield of **2a** increased to 81% when EtOAc was used as the solvent at 60 °C.

The substrate scope of the proposed system for aerobic oxygenation is determined by considering the optimized conditions (Table 1). Various phenyl-2-pyridylmethanes, corresponding to the electron-donating and -withdrawing groups on the phenyl ring, underwent oxygenation, yielding the corresponding phenyl-2-pyridylketones **2a–c** in 74–96% yields. Phenyl-4-pyridylmethane (**1d**) was oxygenated successfully to give **2d** in 86% yield, consistent with the observed results for the reaction of 2-pyridyl substrate **1a**. In contrast, the oxygenation of 3-pyridyl substrate **1e** to **2e** and diphenylmethane (**3a**) to the corresponding ketone **4a** was hardly observed. This observed regioselectivity of the pyridine unit suggests that sp^3 C–H activation occurs via the formation of a pyridinium-flavin adduct, as illustrated in Scheme 1C. 2-Benzimidazolyl substrate **1f** and **1g** also gave **2f** and **2g** in excellent yield (91 and 94%). On the other hands, 2-methylpyridine (**1h**) and 2-pentylpyridine (**1i**) with aliphatic substituents were not converted to the corresponding products **2h** and **2i**, respectively, due to their low reactivity.

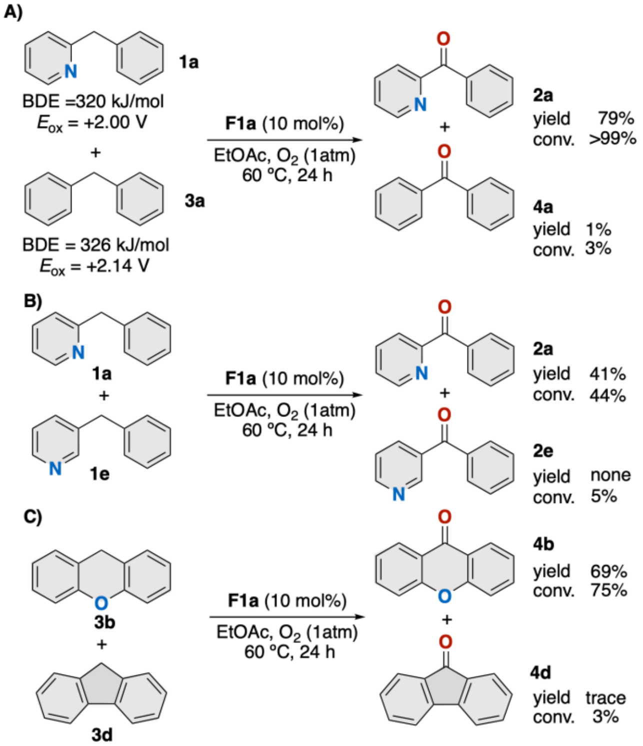
Table 1. Scope of aerobic oxygenation of diarylmethanes 1 or 3.[a]



[a] General conditions: **1a** (0.4 mmol, 1 M) and **F1a** (10 mol%) were stirred in EtOAc under O_2 (1 atm) at 60 °C for 24 h. Isolated yields. [b] **F1a** (15 mol%) was used for 30 h. [c] Yields were determined by ^1H NMR using 1,3,5-trioxane as internal standard. [d] 1 mmol scale reaction: **1g** (1 mmol, 244 mg) was used for 30 h. [e] CH_3CN was used as a solvent.

Next, the chemoselectivity of aerobic oxygenation of various diarylmethanes is investigated (Scheme 2). When **1a** and diphenylmethane (**3a**) are reacted simultaneously under standard conditions, the oxygenation of **1a** to **2a** occurs preferentially (Scheme 2A). Although the conversion of **1a** exceeded 99%, that of **3a** was very low (3%), indicating high chemoselectivity. The oxidation potentials of **1a** and **3a**, determined by differential pulse voltammetry in CH_3CN (1.0 mM), were similar (Figure S1): **1a** (E_{ox} = +2.00 V, vs SCE) and **3a** (E_{ox} = +2.14 V, vs SCE). Therefore, the chemoselectivity between **1a** and **3a** is unlikely to be explained by direct electron transfer from the substrate to the flavin catalyst. The lower the BDE and the more stable the generated radical, the easier the hydrogen atom transfer (HAT), enabling the homolytic cleavage of the C–H bonds.[18] However, the BDE of **1a** (320 kJ/mol) was close to that of **3a** (326 kJ/mol), [6b] suggesting that direct HAT of **1a** did not occur during oxygenation. Furthermore, 2-pyridyl **1a** is selectively oxygenated in the presence of 3-pyridyl **1e** (Scheme 2B).

Scheme 2. Chemoselectivity in flavin-catalyzed C(sp^3)–H oxygenation of diarylmethanes.



Additionally, we attempted the substrates with fused ring structures, such as xanthene (**3b**) and thioxanthene (**3c**), which are anticipated to undergo the oxidation more readily than **1a** and **3a** due to the presence of oxygen and sulfur atoms.[19] As a result, the oxygen-atom insertion into the C–H bond occurrs to afford the corresponding **4b** and **4c** in 61 and 79% yields, respectively (Table 1). In the mixture of **3b** and **3d**, the oxygenation of **3b** occurs chemoselectively under standard conditions, affording **4b** in 69% yield, despite the absence of a pyridyl unit (Scheme 2C). This revealed that the controlled "modest" oxidation activity of **F1a** plays a critical role in chemoselectivity of the aerobic oxygenation described in this study.

To investigate the underlying reason for the observed chemoselectivity, we recorded the ^1H NMR spectra of **F1a** before and after adding pyridine to CD_3CN (Figures 2 and S2). Upon the addition of pyridine, the aromatic protons of **F1a** (H_a–H_c, in the range of 8.4–8.8 ppm, spectrum i) were significantly shifted upfield to 7.1–7.6 ppm (spectrum iii). Conversely, the protons of pyridine (H_d–H_f) exhibited the downfield shift after mixing with **F1a** (spectra ii and iii). This remarkable peak shift was not observed when **F1a** and **3a** were mixed (spectrum iv).[22] The absorption spectral change of **F1a** upon the addition of **1a** and **3a** also revealed that the π-conjugated structure of **F1a** was significantly changed in the presence of **1a** (Supporting Information, Figure S4). These results suggest the formation of a 4a-adduct by **F1a** with pyridine (**F1a-py**, Figure 2) because cationic flavins are known to form 4a-adduct in the presence of amines.[20] Subsequently, we conducted the electrospray ionization (ESI) mass spectrometry measurement for the mixture of **F1a** and **1d** in CH_3CN. The observed 507.1864 m/z peak matches well with the theoretical value of 507.1877 ($C_{27}H_{24}F_3N_5O_2^+$) corresponding to the intermediate **X**, which forms after the proton/electron transfer of the **F1a–1d** adduct (Figures S5-S8). Despite its diminutive size, the peak attributed to the hydroperoxide intermediate **Y** (m/z = 540.1830), formed through the reaction with O_2, was also detected. We further conducted electron spin resonance (ESR) measurements on a solution of **F1a** (Figure S9). The ESR spectrum of **F1a** after the addition of **1a** exhibited the resonance characteristics of a stable flavin radical **F1a**$_{\textbf{rad}}$ with a g-value of 2.00135,[21] which was attributable to the electron transfer from the **F1a–1a** adduct to **F1a** (spectra i–ii). However, no signal was observed when **3a** was added to the solution of **F1a** (spectra iii).

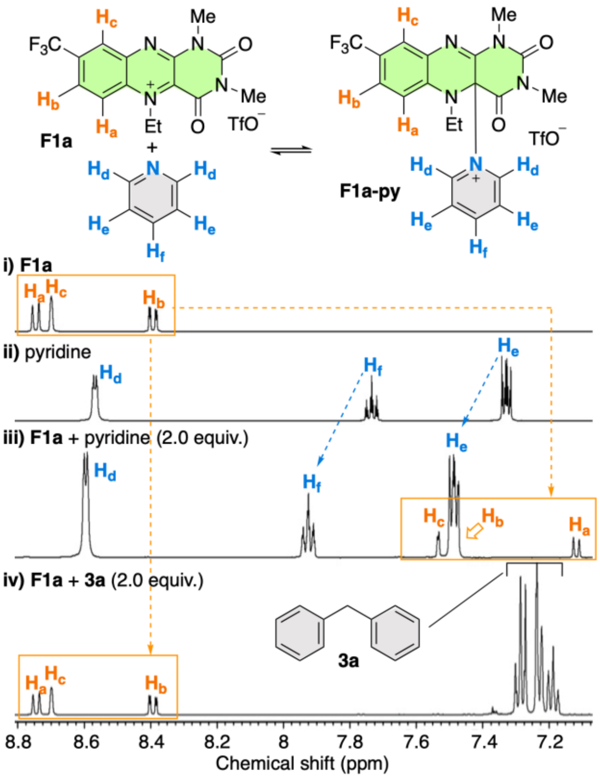
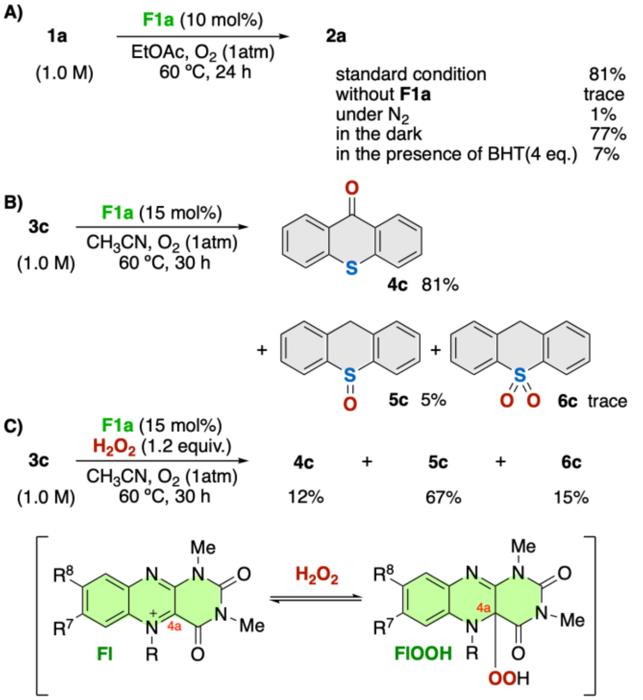


Figure 2. ^{1}H NMR spectra of (i) **F1a** (0.02 M), (ii) pyridine (0.02 M), and mixture of **F1a** (0.02 M) with (iii) pyridine (2.0 equiv.) and (iv) **3a** (2.0 equiv.) in CD_3CN at 25 °C.

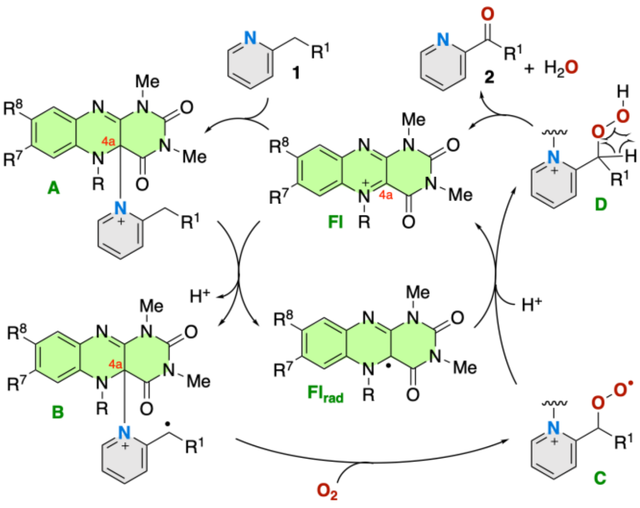
Control experiments are performed to gain additional insights into the reaction mechanism and catalytic cycle of flavin (Scheme 3). The aerobic oxygenation of **1a** did not exhibit good results in the absence of flavin catalyst **F1a** and under anaerobic N_2 conditions (Scheme 3A). In contrast to the standard conditions carried out under ambient light, the reaction was conducted under dark conditions using a reaction vessel wrapped in a light-shielding film in a dark room to elucidate the effect of light irradiation. The yield of **2a** (77%) did not change significantly in the dark conditions, suggesting that this reaction was not a photoreaction. However, in the presence of the radical inhibitor, 2,6-di-*tert*-butyl-4-methylphenol (4 equiv.), the yield of **2a** decreased to 7%, suggesting that the present reaction involved a radical process. In conventional FMO-mimicking flavin-catalyzed oxygenation using chemical reductants, 4a-hydroperoxyflavin **FlOOH** was the active oxidative species responsible for the oxygenation of substrates.[10c,d,11,23] However, when sulfur-containing **3c** is reacted in the present system, oxygenation of the sp^3 C–H bond occurs preferentially to give the corresponding ketone **4c** rather than sulfoxidation, yielding **5c** and **6c** (Scheme 3B). **FlOOH** is formed from the cationic flavin **Fl** through an equilibrium reaction with H_2O_2, as shown in Scheme 3C, and is known to promote the catalytic electrophilic oxidation of sulfides to sulfoxides and sulfones.[10a,24] When 1.2 equiv. of H_2O_2 is added in the reaction of **3c** with **F1a**, the sulfoxidation preferentially occurs rather than the oxygenation of sp^3 C–H, affording sulfoxide **5c** and sulfone **6c** in 67% and 15% yields, respectively (Scheme 3C). The products **5c** and **6c** were not generated during the reaction of **3c**, suggesting that 4a-hydroperoxyflavin **FlOOH** was not efficiently generated in the system.[25] These results were in contrast to those observed in conventional FMO-mimicking oxygenation.[10c,d,11,23]

Scheme 3. Control experiments.



Based on the experimental results and literature, a plausible mechanism is proposed in Scheme 4. The pyridinyl unit of **1** promotes a nucleophilic attack on the 4a position of **Fl** resulting in 4a-adduct **A**. Because the sp^3 C–H bond of **1** is activated by 4a-adduct formation, as observed for the formation of the pyridinium cation from **1** and chloroacetate (Scheme 1B),[9] proton and electron transfer from 4a-adduct **A** to the cationic flavin **Fl** takes place to form the stable flavin radical **Fl$_{\text{rad}}$** and radical intermediate **B**, which is detected by ESI-mass spectrometry (Figure S5). Benzyl radical **B** reacts with O_2 to produce the peroxy radical species **C**, which is reduced by **Fl$_{\text{rad}}$** to form hydroperoxide **D**. Elimination of water and dissociation from flavin afforded the desired product **2** and regenerated the initial **Fl** to complete the catalytic cycle. To gain further insights into the catalytic C–H oxygenation, we conducted a kinetic isotope effect (KIE) study using **1a** and its deuterated analog at the benzylic position (**1a**-d_2).[26] A primary KIE of $k_H/k_D = 3.9$ was observed in two separate competition reactions between **1a** and **1a**-d_2, suggesting that hydrogen atom abstraction is likely involved in the rate-limiting step (Supporting Information, Figure S12).

Scheme 4. Proposed flavin catalytic cycle for aerobic oxygenation of 1.



We developed the flavin-catalyzed aerobic oxygenation of arylheteroarylmethanes without chemical reductants by utilizing a novel approach that differs from the conventional flavin-catalyzed system mimicking the monooxygenase activity. The flavin catalyst served a dual role in the chemoselective activation of *N*-heteroarylbenzylic sp^3 C–H and precise proton/electron transfer, enabling the atom-economical aerobic oxygenation of arylheteroarylmethanes under metal-free conditions. While radical oxygenation with O_2 generally encounters challenges owing to undesired side reactions because of the high reactivity of radical intermediates, the aerobic oxygenation discussed in this study achieved high chemoselectivity attributable to the well-controlled redox activity and the unique C–H activation mechanism of the flavin catalyst. This finding provides an atom-economical green method for the aerobic oxygenation of various substrates. Moreover, flavin catalysis facilitates the formation of pyridinium-flavin adduct, holding potential for application in a wide range of novel chemoselective bond formation reactions involving aerobic oxidation processes.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge.
Experimental procedures, characterization of synthesized compounds, and spectroscopic data (PDF).

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Author Contributions

H. I. conceived and directed the study. T. F. and H. M. performed the experiments and characterization. T. F. and H. I. wrote the manuscript. All the authors discussed the results and commented on the manuscript.

ACKNOWLEDGMENT

This work was partially supported by JSPS/MEXT KAKENHI (Grant-in-Aid for Scientific Research (C), No. 24K08511), the Electric Technology Research Foundation of Chugoku and an SDGs Research Project of Shimane University. H. M. gratefully acknowledges support from JST SPRING (JPMJSP2155). The authors also appreciate the support from the Interdisciplinary Center for Science Research, Shimane University, for the spectroscopic measurements, and the Shimane Institute for Industrial Technology for the ESR measurement. The authors thank Prof. Takahisa Ikeue of Shimane University for his help with the electrochemical measurements.

REFERENCES

(1) (a) White, M. C.; Zhao, J. P. Aliphatic C–H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 13988–14009. (b) Sterckx, H.; Morel, B.; Maes, B. Catalytic Aerobic Oxidation of C(sp^3)–H Bonds. *Angew. Chem., Int. Ed.* **2019**, *58*, 7946–7970.
(2) (a) Hill, C. L. Homogeneous Catalysis - Controlled Green Oxidation. *Nature* **1999**, *401*, 436–437. (b) Bryliakov, K. P. Catalytic Asymmetric Oxygenations with the Environmentally Benign Oxidants H_2O_2 and O_2. *Chem. Rev.* **2017**, *117*, 11406–11459. (c) Grant, J. T.; Venegas, J. M.; McDermott, W. P.; Hermans, I. Aerobic Oxidations of Light Alkanes over Solid Metal Oxide Catalysts. *Chem. Rev.* **2018**, *118*, 2769–2815.
(3) Kleemann, A.; Engel, J.; Kutscher, B. Pharmaceutical Substances: Syntheses, Patents and Applications of the Most Relevant AIPs, Thieme, **2009**.
(4) Guyton, A. C.; Hall, J. E. *Textbook of Medical Physiology*, 11th Edition ed., Elsevier Saunders, Philadelphia.
(5) (a) Easmon, J.; Heinisch, G.; Pürstinger, G.; Langer, T.; Österreicher, J. K.; Grunicke, H. H.; Hofmann, J. Azinyl and Diazinyl Hydrazones Derived from Aryl *N*-Heteroaryl Ketones: Synthesis and Antiproliferative Activity. *J. Med. Chem.* **1997**, *40*, 4420–4425. (b) Reis, D. C.; Pinto, M. C.; Souza-Fagundes, E. M.; Wardell, S. M.; Wardell, J. L.; Beraldo, H. Antimony(III) Complexes with 2-Benzoylpyridine-Derived Thiosemicarbazones: Cytotoxicity Against Human Leukemia Cell Lines. *Eur. J. Med. Chem.* **2010**, *45*, 3904–3910.
(6) (a) De Houwer, J.; Tehrani, K. A.; Maes, B. U. Synthesis of Aryl(di)azinyl Ketones through Copper- and Iron-Catalyzed Oxidation of the Methylene Group of Aryl(di)azinylmethanes. *Angew. Chem., Int. Ed.* **2012**, *51*, 2745–2748. (b) Sterckx, H.; De Houwer, J.; Mensch, C.; Caretti, I.; Tehrani, K. A.; Herrebout, W. A.; Van Doorslaer, S.; Maes, B. Mechanism of the Cu^{II}-Catalyzed Benzylic Oxygenation of (Aryl)(heteroaryl)methanes with Oxygen. *Chem. Sci.* **2016**, *7*, 346–357.
(7) Similar selenium- and iodine-catalyzed aerobic oxygenation of **1** have been reported using acetic acid for activation of the sp^3 C–H bond. (a) Ren, L.; Wang, L.; Lv, Y.; Li, G.; Gao, S. Synergistic H_4NI-AcOH Catalyzed Oxidation of the C_{sp3}-H Bonds of Benzylpyridines with Molecular Oxygen. *Org. Lett.* **2015**, *17*, 2078–2081. (b) Jin, W.; Zheng, P.; Wong, W. T.; Law, G. L. Efficient Selenium-Catalyzed Selective C(sp^3)-H Oxidation of Benzylpyridines with Molecular Oxygen. *Adv. Synth. Catal.* **2017**, *359*, 1588–1593.

(8) Sekar et al. reported that *N*-bromosuccinimide could also be used to activate the heterobenzylic sp^3 C–H bond, although DMSO and O_2 were required as oxidants for oxygenation. Guha, S.; Sekar, G. Metal-Free Halogen(I) Catalysts for the Oxidation of Aryl(heteroaryl)methanes to Ketones or Esters: Selectivity Control by Halogen Bonding. *Chem. -Eur. J.* **2018**, *24*, 14171–14182.

(9) Liu, J.; Zhang, X.; Yi, H.; Liu, C.; Liu, R.; Zhang, H.; Zhuo, K.; Lei, A. Chloroacetate-Promoted Selective Oxidation of Heterobenzylic Methylenes under Copper Catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1261–1265.

(10) (a) 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. (b) Murahashi, S.-I. Synthetic Aspects of Metal-Catalyzed Oxidations of Amines and Related Reactions. *Angew. Chem., Int. Ed.* **1995**, *34*, 2443–2465. (c) Iida, H.; Imada, Y.; Murahashi, S.-I. Biomimetic Flavin-Catalysed Reactions for Organic Synthesis. *Org. Biomol. Chem.* **2015**, *13*, 7599–7613.

(11) 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.

(12) (a) Imada, Y.; Iida, H.; Murahashi, S.-I.; Naota, T. An Aerobic, Organocatalytic, and Chemoselective Method for Baeyer-Villiger Oxidation. *Angew. Chem., Int. Ed.* **2005**, *44*, 1704–1706. (b) Chen, S.; Foss, F. W. Aerobic Organocatalytic Oxidation of Aryl Aldehydes: Flavin Catalyst Turnover by Hantzsch's Ester. *Org. Lett.* **2012**, *14*, 5150–5153.

(13) Kotoucová, H.; Strnadová, I.; Kovandová, M.; Chudoba, J.; Dvorakova, H.; Cibulka, R. Biomimetic Aerobic Oxidative Hydroxylation of Arylboronic Acids to Phenols Catalysed by a Flavin Derivative. *Org. Biomol. Chem.* **2014**, *12*, 2137–2142.

(14) (a) König, B.; Kümmel, S.; Svobodová, E.; Cibulka, R. Flavin Photocatalysis. *Phys. Sci. Rev.* **2018**, *3*, DOI: 10.1515/psr-2017-0168. (b) Svobodová, E.; Cibulka, R. in *Flavin-Based Catalysis* (Eds.: Cibulka, R.; Fraaije M. W.), Wiley-VCH, Weinheim, **2021**, pp. 265–291; (c) Lechner, R.; Kümmel, S.; König, B. Visible Light Flavin Photo-Oxidation of Methylbenzenes, Styrenes and Phenylacetic Acids. *Photochem. Photobiol. Sci.* **2010**, *9*, 1367–1377. (d) Mühldorf, B.; Wolf, R. Photocatalytic Benzylic C-H Bond Oxidation with a Flavin Scandium Complex. *Chem. Commun.* **2015**, *51*, 8425–8428. (e) Mühldorf, B.; Wolf, R. C-H Photooxygenation of Alkyl Benzenes Catalyzed by Riboflavin Tetraacetate and a Non-Heme Iron Catalyst. *Angew. Chem., Int. Ed.* **2016**, *55*, 427–430. (f) Tang, G.; Gong, Z.; Han, W.; Sun, X. Visible Light Mediated Aerobic Photocatalytic Activation of C-H Bond by Riboflavin Tetraacetate and *N*-Hydroxysuccinimide. *Tetrahedron Lett.* **2018**, *59*, 658–662. (g) Lesieur, M.; Genicot, C.; Pasau, P. Development of a Flow Photochemical Aerobic Oxidation of Benzylic C-H Bonds. *Org. Lett.* **2018**, *20*, 1987–1990. (h) Zelenka, J.; Svobodová, E.; Tarábek, J.; Hoskovcová, I.; Boguschová, V.; Bailly, S.; Sikorski, M.; Roithová, J.; Cibulka, R. Combining Flavin Photocatalysis and Organocatalysis: Metal-Free Aerobic Oxidation of Unactivated Benzylic Substrates. *Org. Lett.* **2019**, *21*, 114–119. (i) Shiogai, Y.; Oka, M.; Iida, H. Aerobic Cross-Dehydrogenative Coupling of Toluenes and *o*-Phenylenediamines by Flavin Photocatalysis for the Facile Synthesis of Benzimidazoles. *Org. Biomol. Chem.* **2023**, *21*, 2081–2085.

(15) König, B.; Pelka, M.; Reichenbach-Klinke, R.; Schelter, J.; Daub, J. A Model System for Flavoenzyme Activity − Binding of Flavin and Modulation of Its Redox Potentials through Coordination to a Lewis-Acidic Azamacrocyclic Zinc(II) Complex. *Eur. J. Org. Chem.* **2001**, *2001*, 2297–2303.

(16) Fukuda, T.; Miyake, H.; Abe, S.; Yagishita, F.; Iida, H. Flavin–Iodine-Catalyzed Aerobic Oxidative Tandem C(sp^3)-H Imination and Amination: Synthesis of Fluorescent Imidazo[1,5-*a*]pyridines from Pyridylmethanes and Aminomethanes. *Adv. Synth. Catal.* **2024**, *366*, DOI: 10.1002/adsc.202400854.

(17) (a) Mizushima, T.; Oka, M.; Imada, Y.; Iida, H. Low-Voltage-Driven Electrochemical Aerobic Oxygenation with Flavin Catalysis: Chemoselective Synthesis of Sulfoxides from Sulfides. *Adv. Synth. Catal.* **2022**, *364*, 2443–2448. (b) Miyake, H.; Iida, H. Flavin-Catalyzed Aerobic Oxidative C-C Bond Formation by Metal/Light-Free Cross-Dehydrogenative Coupling. *Adv. Synth. Catal.* **2024**, *366*, 402–407.

(18) Capaldo, L.; Ravelli, D.; Fagnoni, M. Direct Photocatalyzed Hydrogen Atom Transfer (HAT) for Aliphatic C-H Bonds Elaboration. *Chem. Rev.* **2022**, *122*, 1875–1924.

(19) A comparison of BDE using the method of Stein et al. revealed that the BDE of **3b** (309.6 kJ/mol) is considerably lower than that of **3a** (351.5 kJ/mol). Stein, S. E.; Brown, R. L. Prediction of carbon-hydrogen bond dissociation energies for polycyclic aromatic hydrocarbons of arbitrary size. *J. Am. Chem. Soc.* **1991**, *113*, 787–793.

(20) (a) Kim, J. M.; Bogdan, M. A.; Mariano, P. S. Mechanistic Analysis of the 3-Methyllumiflavin-Promoted Oxidative Deamination of Benzylamine. A Potential Model for Monoamine Oxidase Catalysis. *J. Am. Chem. Soc.* **1993**, *115*, 10591–10595. (b) Iida, H.; Iwahana, S.; Mizoguchi, T.; Yashima, E. Main-Chain Optically Active Riboflavin Polymer for Asymmetric Catalysis and Its Vapochromic Behavior. *J. Am. Chem. Soc.* **2012**, *134*, 15103–15113.

(21) (a) Guzzo, A. V.; Tollin, G. Electron Paramagnetic Resonance Studies of Riboflavin and Its Derivatives. Electron Paramagnetic Resonance Studies of Riboflavin and Its Derivatives. I. The Isoalloxazine Semiquinones in Acid. *Arch. Biochem. Biophys.* **1963**, *103*, 244–248. (b) Heilmann, O.; Hornung, F. M.; Fiedler, J.; Kaim, W. Organometallic Iridium(III) and Rhenium(I) Complexes with Lumazine, Alloxazine and Pterin Derivatives. *J. Organomet. Chem.* **1999**, *589*, 2–10. (c) Casas, J.; Pianca, D.; Le Breton, N.; Jouaiti, A.; Gourlaouen, C.; Desage-El Murr, M.; Le Vot, S.; Choua, S.; Ferlay, S. Alloxazine-Based Ligands Appended with Coordinating Groups: Synthesis, Electrochemical Studies, and Formation of Coordination Polymers. *Inorg. Chem.* **2024**, *63*, 4802–4806.

(22) **3b** also did not exhibit the significant peak shift associated with adduct formation (Figure S3).

(23) Flavin-Based Catalysis, Wiley-VCH, Weinheim, 2021.

(24) Ménová, P.; Cibulka, R. Insight into the Catalytic Activity of Alloxazinium and Isoalloxazinium Salts in the Oxidations of Sulfides and Amines with Hydrogen Peroxide. *J. Mol. Catal. A:Chem.* **2012**, *363–364*, 362–370.

(25) Recently, Gan, Wu, and coworker reported the flavin-catalyzed oxygenation of (hetero)arylalkanes using an excess amount of *tert*-BuOOH as the oxidant, in which **FlOOH** was served as the oxidatively active specie. The reaction was mainly promoted anaerobically, and the substrates **3a** and **1e** were oxidized to the corresponding ketones without the chemoselectivity observed in the present system. Gan, H.; Ma, P.; Wu, H., Flavin-Catalyzed, TBHP-Promoted Oxidation of (Het)aryl Alkane to Ketone. *Mol. Catal.* **2024**, *567*, DOI: 10.1016/j.mcat.2024.114419.

(26) Simmons, E. M.; Hartwig, J. F., On the Interpretation of Deuterium Kinetic Isotope Effects in C–H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066–3072.