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Bioinspired Oxidative Aromatizations: One-Pot Syntheses of 2-Substituted Benzothiazoles and Pyridines by Aerobic Organocatalysis

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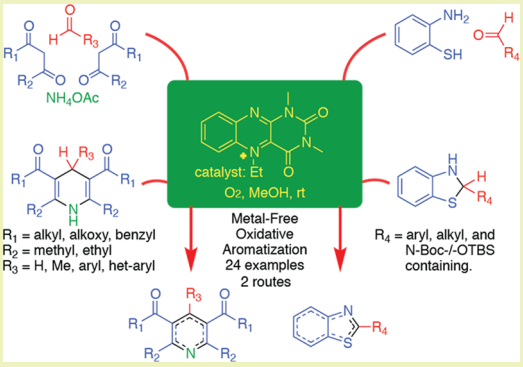
Supporting Information

ABSTRACT: Heteroaromatic structures are abundant in bioactive natural products, medicines, and other functional materials. Oxidative aromatization is a common method for preparing heteroaromatic species from simple building blocks. A bioinspired method was developed using robust flavin mimics as organocatalysts that perform O_2-fueled oxidations of 1,4-dihydropyridines to pyridines and benzothiazolines to benzothiazoles in high yields (>95%) and purity at ambient temperature in methanol. The efficient oxidative aromatizations facilitated one-pot multicomponent syntheses of pyridines (from various aldehydes, dicarbonyl compounds, and ammonium acetate, in yields ranging from 35 to 95%) and benzothiazoles (from 2-aminothiophenol and various aldehydes, in 78−95% yield) without metals or reactive stoichiometric oxidants. For most substrates, neutral conditions were effective. Hindered 4-substituted dihydropyridines that oxidized slowly were accelerated by selection of more electrophilic flavin catalysts and the addition of various acids in a manner inversely proportional to pK_a.



KEYWORDS: *Aerobic organocatalytic oxidation, Biomimetic synthesis, Flavin mimics, Aromatization*

INTRODUCTION

Economic, efficient, and sustainable methods for synthetic chemistry are necessary for the continued preparation of functional organic molecules, materials, and medicines.[1−4] Oxidation reactions, in particular, present serious challenges to the synthetic community when considering chemoselectivity, cost, and environmental, health, and safety concerns.[5] In recent decades, aerobic oxidation by transition-metal catalysts has enhanced the chemoselectivity and stereoselectivity of these reactions.[6−9] In comparison, aerobic organocatalytic methods that have the ability to address sustainability concerns are vastly underdeveloped.[10,11]

Nature provides numerous examples of aerobic organocatalytic oxidations. For example, flavin-dependent monooxygenases perform chemoselective oxidations leading to manifold structural diversifications of complex molecules.[12,13] Though enzymes are superior to synthetic methods of oxidation by most measures of efficiency, proteins often react capriciously to slight system changes and frequently require costly stoichiometric reagents.[14,15] Bioengineered proteins offer exciting advances to the paradigm of biosynthesis in organic synthesis,[16] but bioinspired organocatalysis provides an alternative approach to catalyst design guided by the investigation of desirable physical properties that control biosynthetic processes, while not restricted to either the building blocks or chemical transformations observed in nature.[17−20] This communication discloses the syntheses of heterocycles by oxidative aromatization of simple building blocks under mild conditions, which are inspired by ubiquitous flavin/nicotinamide coenzyme redox pairs.[21,22]

Synthetic flavin mimics (N1,N3,N5-trialkylated alloxazines **1** and N3,N5,N10-trisubstituted isoalloxazines, **2**, Figure 1) are robust redox active organocatalysts,[23,24] which achieve two electron reduction and oxidation transformations outside of

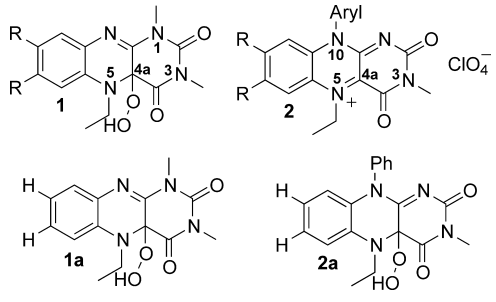


Figure 1. Alloxazine derived N1,N3,N5-trisubstituted 4a-hydroperoxyflavins (**1**) and isoalloxazine derived N3,N5,N10-trisubstituted 4a-hydroperoxyflavins (**2**).

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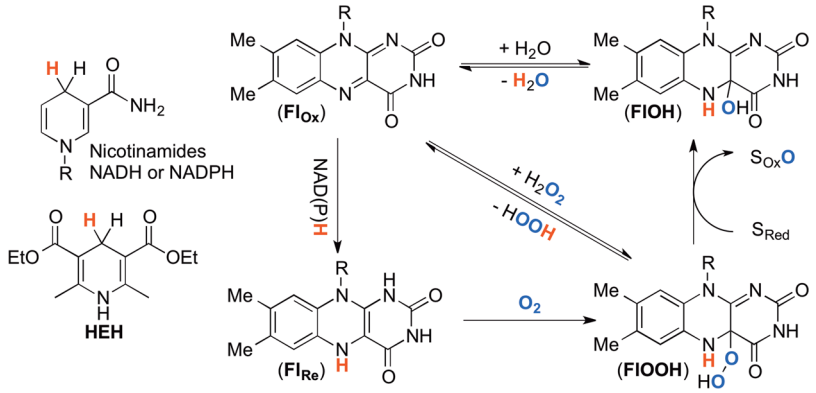


Figure 2. Riboflavin-mimic catalyzed oxidations fueled by H_2O_2 or O_2 with reductant.

enzyme active sites. Recent examples include the oxidation of sulfides or amines by 4a-hydroperoxyflavins (for example **1a**, **2a**) or 10a-hydroperoxyflavins (not shown);[25−28] the reduction of π-systems by catalytic flavin-diimide complexes;[29−31] and nucleophilic Baeyer−Villiger oxidations (BVOs) of cyclobutanones to γ-lactones,[32−34] BVOs of arylaldehydes to arylacids,[35] and the BVOs of arylaldehydes to phenols[36,37] (Dakin oxidation).[38] Mechanistically, flavin-mediated monooxidations are performed by active 4a-hydroperoxyflavin catalysts (**FlOOH**, **5**), which may be generated by one of two general methods (Figure 2): (1) H_2O_2 may add to oxidized flavin precatalysts ($\mathbf{Fl_{Ox}}$, **3**)[27] or (2) in aerobic systems,[39−41] formal addition of a hydride to $\mathbf{Fl_{Ox}}$ produces reduced flavins ($\mathbf{Fl_{Re}}$, **4**). $\mathbf{Fl_{Re}}$ reacts with triplet O_2 by single electron transfer and radical ion pair combination to form **FlOOH**. Potent oxidant **FlOOH** reacts with substrates ($\mathbf{S_{Red}}$) to yield 4a-hydroxyflavin (**FlOH**, **6**) and oxidized products ($\mathbf{S_{Ox}O}$). Subsequent elimination of H_2O from **FlOH** regenerates $\mathbf{Fl_{Ox}}$, completing the catalytic cycle. Additionally, **FlOOH** can dissociate to $\mathbf{Fl_{Ox}}$ and H_2O_2 through a dark reversible process that is regulated by the environment. In nature, aerobic systems often generate $\mathbf{Fl_{Re}}$ by nicotinamide cocatalyst reductions of $\mathbf{Fl_{Ox}}$ species through a hydride transfer reaction driven by an overall gain in aromatic stabilization.[21] To our knowledge, this is the first work that takes advantage of the reduction step of the flavin catalytic cycle from $\mathbf{Fl_{ox}}$ to $\mathbf{Fl_{Re}}$ to oxidize commonly available starting materials to value-added heteroaromatic molecules.

Pyridines are privileged scaffolds for drug discovery.[42] The oxidation of dihydropyridines to pyridines is well studied due to the known metabolic interaction of dihydropyridine therapeutics with specific CYP450's.[43] Dihydropyridines target numerous ion channels and G-protein coupled receptors resulting in important cardiac and other beneficial effects.[44] Benzothiazoles occur naturally,[45] but more numerous synthetic species display broad biological activities and are found in functional materials.[46−50] The study of dihydropyridine and benzothiazoline oxidation is further driven by their ability to function as hydride sources.[51,52]

Numerous methods report oxidative aromatization as a route to heteroaromatic species. Often, these involve the use of metals, acids, excess of powerful oxidants, and/or high temperatures.[53] Recently, aerobic (O_2-fueled) oxidations of dihydropyridines were achieved by enzymatic systems,[54,55] and aerobic synthetic approaches in neat,[56] polar solvent,[43,57,58] microwave,[59,60] or metal-catalyzed systems exist.[61−66] Conventional methods for benzothiazole preparations involve metal-catalyzed[67,68] or radical-initiated[69] intramolecular cyclizations of *N*-(2-haloaryl)-thioamides, condensation reactions of *o*-aminothiophenol with carboxylic acids[70] under harsh conditions, and benzaldehydes[71,72] condensation with *o*-aminothiophenol followed by strong oxidation conditions. Recently, metal-free aerobic preparations of benzothiazoles were developed using radical,[73] high temperature,[74] and I_2-catalyzed[75] conditions. This work displays the first mild, room temperature, and aerobic organocatalytic synthesis of benzothiazoles and adds a convenient, mild, and efficient method to the few multicomponent pyridine syntheses utilizing O_2 as a terminal oxidant. Key advantages to flavin-catalyzed oxidative aromatizations include: O_2 as a terminal oxidant; metal-free catalysis; minimal catalyst loading of inexpensive organocatalysts; multicomponent single-pot reactions to reduce solvent consumption and purification steps;[76,77] a preferred[4] nonhalogenated solvent enhances catalyst turnover, and neutral and room temperature conditions are possible for a wide range of substrates facilitating broad functional group tolerance.

EXPERIMENTAL SECTION

Flavin-Catalyzed Oxidation of Dihydropyridines 7a−h to Pyridines 8a−h. Dihydropyridine **7a−h** (0.2 mmol), catalyst **1a** (3 mg, 0.01 mmol) and methanol (2 mL) were added to a 1 dram vial with a septum-containing screw cap. The vial was filled with oxygen gas by applying an O_2 balloon via needle above the solvent. The reaction was stirred at room temperature and followed by TLC and NMR. Upon completion of the reaction, the mixture was transferred to a small round-bottom flask and the solvent was evaporated under vacuum to give **8a−h** as products. The purity of each product was greater than 95% by NMR with DMSO as an internal standard (See Table 2 for specifics).

Flavin-Catalyzed Multicomponent Synthesis of Pyridines 8a−h. To a 2 dram vial was added formaldehyde (37 wt % in H_2O, 1 mmol), 1,3-dicarbonyl compound **9** (2 mmol), ammonium acetate (1 mmol), catalyst **1a** (6 mg, 0.02 mmol), and methanol (2 mL). The reaction was stirred with the vial open to atmosphere at room temperature for the time given (Table 2). After completion of the reaction, the mixture was dried under vacuum. Flash column chromatography (ethyl acetate/hexane) was used to purify the crude product to give products **8a−h** (see the Supporting Information (SI) for specifics).

Flavin-Catalyzed Oxidation of Dihydropyridines 7i−n to Pyridines 8i−n. Dihydropyridine **7i−o** (0.2 mmol), catalyst **2a** (4.3 mg, 0.01 mmol), perchloric acid (28.6 mg of 70 wt % $HClO_4$), and methanol (2 mL) were added to a 1 dram vial. The vial was filled with oxygen by applying an O_2-filled balloon via needle. The reaction was stirred at 50 °C for the time given within Table 3. After the disappearance of the starting material, the reaction mixture was neutralized with saturated aqueous Na_2CO_3 (0.2 mL). The solvent was

evaporated under vacuum and the resulting material was directly purified by flash column chromatography (ethyl acetate/hexane) to give **8i–o** as chromatographically and spectroscopically pure products (See Table 3 and the SI for specifics).

Flavin-Catalyzed Oxidation of Benzothiazolines 10a–i to Benzothiazoles 11a–i. Benzothiazoline **10a–i** (0.2 mmol), catalyst **1a** (3 mg, 0.01 mmol), and methanol (2 mL) were added to a 1 dram vial. The vial was filled with oxygen gas by applying an O_2 balloon via a needle. The reaction was stirred at room temperature for a given time (Table 3). After the reaction was complete (followed by TLC and NMR), the reaction mixture was transferred to a small round-bottom flask and the solvent was evaporated under vacuum to give **11a–i** as products. The purity of the products was determined to be greater than 95% by ^{1}H NMR analysis with DMSO as an internal standard (see the SI for specifics).

Flavin-Catalyzed One-Pot Two-Step Synthesis of Benzothiazoles 11a–i. Both 2-aminothiophenol **12** (125 mg, 1 mmol) and aldehyde **13a–i** (1 mmol) were mixed in methanol (3 mL) in a 1.5 dram vial. The reaction was stirred at room temperature for 6 h to ensure complete formation of corresponding benzothiazolines **10**. Then, catalyst **1a** (15 mg, 0.05 mmol) was added into the reaction. An O_2 balloon was applied to the vial. The reaction was stirred under oxygen for an additional 1.5 h. After completion of the reaction, the solvent was evaporated under reduced vacuum, and the corresponding benzothiazoles **11a–i** were purified by flash column chromatography (See Table 4 and the SI for specifics).

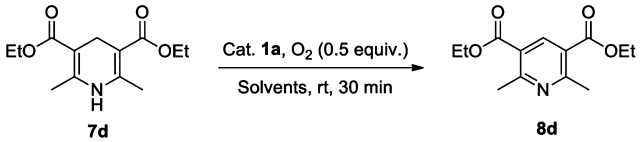
RESULTS AND DISCUSSION

In search of carbonyl-compatible reducing agents for aerobic flavin catalysis, we considered Hantzsch's prototypical dihydropyridine (**HEH**, **7d**) to reduce oxidized flavin mimics, $\mathbf{Fl_{Ox}}$. While successful,[37] we wondered if flavins' oxidative aromatization of NAD(P)H and **7d** could be generally extended to the synthesis of a range of important heterocycles. To our delight, flavin mimics were found to catalyze aerobic oxidations of dihydropyridines (**7**) to pyridines (**8**) and benzothiazolines (**10**) to benzothiazoles (**11**). Seeking systems that favor **FlOOH**'s dissociation (Figure 2, 5 → 3 + H_2O_2) enabled turnover of the catalytic cycle without the need for stoichiometric substrates as **FlOOH** reductants (Figure 2, 5 → 6).

An initial solvent investigation was performed for the aerobic oxidation of Hantzsch ester **7d** by 5 mol % flavin catalyst **1a**, an effective flavin catalyst for oxygen activation,[37] in the presence of O_2 for 30 min (SI Table SI-1). Polar solvents were most efficient at promoting FlOOH dissociation, as expected, based on the results mentioned in studies by Bruice and co-workers.[78] Methanol performed best among the polar protic solvents, while yields decreased for increasingly branched alcohols. Water resulted in low efficiency, likely due to the poor solubility of **7d**. Polar aprotic solvents such as dichloromethane, chloroform, and anhydrous acetonitrile performed the transformation efficiently. While 5% aqueous base addition to acetonitrile suppressed pyridine formation,[37] acid additives were well-tolerated (vida infra). In accord with Bruice's studies,[78] less polar systems (1,4-dioxane, toluene, tetrahydrofuran, ethyl acetate, and CCl_4) likely stabilize **FlOOH**, reducing dissociation, catalyst turnover, and therefore oxidative aromatization.

A quantitative study was performed for five promising solvents (Table 1) using 0.5 equiv of O_2 added to degassed reaction mixtures. Catalyst **1a** was necessary for oxidation (entry 1). With 5 mol % loading of catalyst, conversion (based on dihydropyridine) was too rapid (entry 2); therefore catalyst loadings were adjusted to 1 mol % to compare reactions at 30 min time points. Although CH_2Cl_2 and $CHCl_3$ characteristically solubilized **7d** best, methanol produced the highest yield after 30 min.

Table 1. Quantitative Solvent Analysis for Aerobic Oxidative Aromatizations



7d 8d

entry	solvent	catalyst loading (mol %)	conversion[a] (%)
1	$CHCl_3$	0	0
2	$CHCl_3$	5	50
3	$CHCl_3$	1	22
4	CH_2Cl_2	1	16
5	CH_3OH	1	26
6	CH_3CH_2OH	1	8
7	CH_3CN	1	9

[a]Average of three experiments, ^{1}H NMR analysis with DMSO as an internal standard.

Considering MeOH's superiority in initial studies and as a preferred solvent in regards to sustainable methods,[4] the oxidation of 1,4-dihydropyridines **7** was explored in MeOH, with O_2 as the terminal oxidant. C4-unsubstituted dihydropyridines **7a–h** oxidized at room temperature within 30–90 min (Table 2). Air is sufficient for all reactions, but rates appeared to be relative to the concentration of molecular oxygen. When the oxidation of **7d** to **8d** was performed under different conditions, (1) open to the air, (2) under a blanket of O_2, equilibrated to atmospheric pressure, and (3) under the slightly elevated pressure of an O_2 balloon, the respective conversions were 64%, 83%, and >95% after 30 min at room temperature. For convenience, reactions were mainly performed under the atmosphere of O_2 supplied by a standard balloon. No overoxidation was detected. Solvent removal led to products **8a–h** with greater than 95% purity (^{1}H NMR analysis). Encouraged by these positive results, this protocol was extended to the multicomponent synthesis of pyridines starting from formaldehyde (37 $^w/_w$% in H_2O), ammonium acetate, and corresponding acetoacetates in an open vessel with air as the oxygen source. Indeed, 1 mmol scale syntheses of pyridines were achieved in good to excellent yields with 2 mol % of flavin catalyst in methanol within 22 h. Again, no deleterious oxidation events were detected in the byproducts. The only exception was entry 8, in which intermediate dihydropyridine (**7h**) was nearly insoluble in small volumes of methanol and could be isolated by filtration. Reduced catalyst loading (0.1 mol %, entry 6) provided similar isolated yields as with 2 mol % flavin catalyst. Dihydropyridine formations were clearly slower than rates of oxidative aromatization.

C4-substituted dihydropyridines (Table 3: **7i–7o**) were not oxidized with alloxane catalyst (**1a**) after long reaction times and at elevated temperatures. Ménová and Cibulka recently described isoalloxane catalysts **2** as ~10^6 times more electrophilic than similar alloxazine species **1**.[27] This information, combined with the redox potentials for **2a** (E^0 = 0.388 V, −0.389 V) and **1a** (E^0 = 0.109 V, −0.695 V),[79] suggest that catalyst **2a** would accept a hydride from unreactive C4-substituted dihydropyridines more readily than **1a**. With 5 mol % of catalyst **2a**, the oxidation of **7i** occurred at 50 °C but with insufficient yields (48 h, 20%). The increased electrophilicity of

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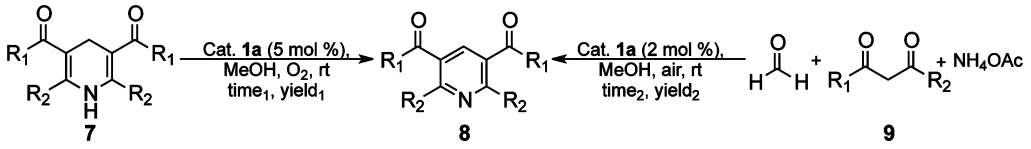
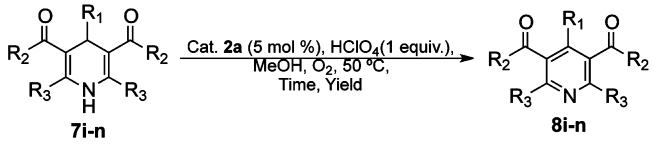
Table 2. Flavin Catalyzed Synthesis of Hantzsch Pyridines



entry	7	R_1	R_2	8	$time_1$ (h)	$yield_1$[a] (%)	$time_2$ (h)	$yield_2$[a] (%)
1	a	CH_3	CH_3	a	1.5	>95	12	93
2	b	OCH_3	CH_3	b	1.5	>95	22	76
3	c	OCH_3	CH_2CH_3	c	1	>95	22	72
4	d	OCH_2CH_3	CH_3	d	0.5	>95	22	85
5	e	$OCH(CH_3)_2$	CH_3	e	0.5	>95	22	73
6	f	$OC(CH_3)_3$	CH_3	f	0.5	>95	22	81(76[b])
7	g	$OCH_2CH{=}CH_2$	CH_3	g	0.5	>95	22	80
8	h	$CH_2C_6H_5$	CH_3	h	0.5	>95	48	>35(40[c])

[a]Isolated yield of **8**. [b]Isolated yield of **8** with 0.1 mol % catalyst loading. [c]Isolated yield of **7h**.

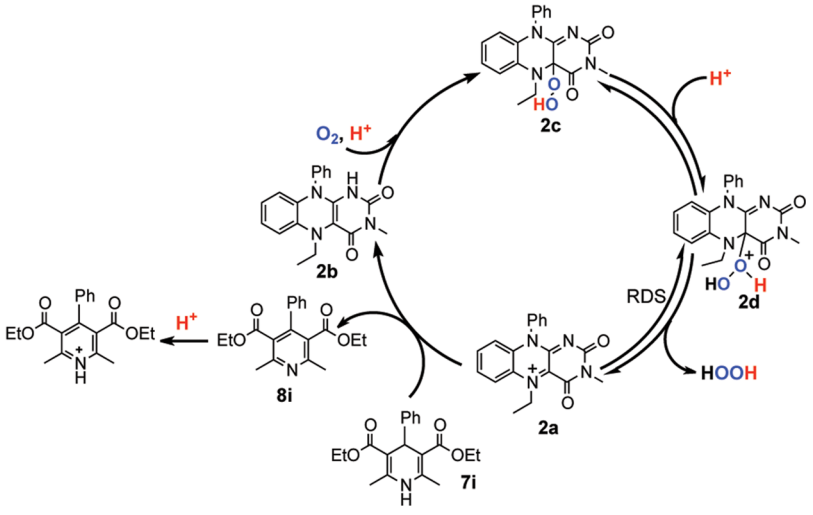
Table 3. Flavin Catalyzed Synthesis of C-4 Hantzsch Pyridines



entry	7	R_1	R_2	R_3	8	time (h)	yield[a](%)
1	i	phenyl	OCH_2CH_3	CH_3	i	10	92
2	j	4-methylphenyl	OCH_2CH_3	CH_3	g	12	91
3	k	4-chlorophenyl	OCH_2CH_3	CH_3	k	12	95
4	l	2-furanyl	OCH_2CH_3	CH_3	l	12	93
6	m	methyl	OCH_3	CH_3	m	48	89
7	n	methyl	OCH_3	CH_2CH_3	n	48	90

[a]Isolated yields.

Scheme 1. Catalytic Cycle for Aerobic Oxidative Aromatization with Acid Promotion



2a is paired with slowed O_2 reduction as well as dissociation of H_2O_2, likely inhibiting catalyst turnover. As hoped, acid addition accelerated turnover (Scheme 1). Acidic conditions could (a) accelerate the rate of H_2O_2 elimination from 4a-hydroperoxyflavin (**2d**) to regenerate the isoalloxazinium cation (**2a**),[27] (b) enhance the redox couple with O_2,[40,41] and/or (c) drive the reaction forward by protonation of the product. Oxidation of **7i** was greatly enhanced by $HClO_4$ addition, requiring only short reaction times. Oxidation was not observed in control $HClO_4$ reactions without flavin catalysts. After substrate consumption, aqueous Na_2CO_3 was added to isolate pyridine products. A range of acids was screened with a clear preference for lower pK_a's (SI Figure SI-2). Redox active sulfuric acid was the only acid to perform a significant background oxidation without flavin **2a**. Using $HClO_4$, C4-substituted dihydropyridines were oxidized in good to excellent yields (Table 3). It is important to note that environmental $HClO_4$ is linked to developmental defects and competitively

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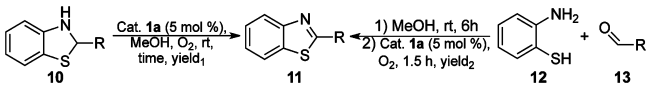
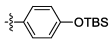
inhibits iodide transport in humans.[80−84] Strong (HCl or H_3PO_4) or weak (formic or acetic) acids were successful as substitutes for $HClO_4$, although with much longer reaction times compared to $HClO_4$.

The initial **1a** catalyst system was applied to benzothiazolines, which are relatively mild prearomatic hydride donors.[85,86] Electron rich benzothiazolines were reported to undergo autoxidation in chloroform without additional catalyst.[87] We found that acid contaminants from solvent or aldehyde oxidation enhanced the rate of benzothiazoline oxidation for electron rich substrates but also led to benzothiazoline fragmentation to amino-thiophenol and aryl aldehydes. Purification of chloroform eliminated benzothiazoline oxidation for nearly all substrates investigated in this work. In our acid-free and metal-free catalytic system, control experiments without flavin catalysts were explored for all benzothiazolines in Table 4. After 1.5 h, most compounds showed no detectable

Table 4. Flavin Catalyzed Synthesis of Benzothiazole



10 11 12 13

Entry	10	R	11	time (h)	yield$_1$[a](%)	yield$_2$[a](%)
1	a	Phenyl	a	0.5	>95	94
2	b	2,6-dimethylphenyl	b	1	>95	78
3	d	4-nitrophenyl	d	1.5	>95	93
4	d	4-chlorophenyl	d	1	>95	82
5	e	4-trifluoromethylphenyl	e	1	>95	89
6	f	1-naphthyl	f	1	>95	84
7	g	2-naphthyl	g	1	>95	89
8	h[b]		h	0.5	>95	95
9	i		i	1.5	>95	90

[a]Isolated yield. [b]Reagent **10h** was isolated as a 3:1 mixture of **10h**:**11h**.

(<5%) benzothiazole formation, except for electron rich entries 4 and 8, which generated 20% and 25% benzothiazole conversion as background oxidation product. The flavin catalyzed oxidation of benzothiazolines yielded products within 1.5 h in methanol. Solvent evaporation gave products with purity greater than 95%.

On the basis of the high yields obtained by this method, a one-pot preparation of 2-substituted benzothiazoles from 2-amino-thiophenol and a range of aldehydes was sought. A simple two-stage, one-pot operation yielded the best results. Following preparations of benzothiazolines from amino-thiophenols and aldehydes in MeOH, within 6 h, flavin catalyst was added directly to the reaction without purification of the intermediate or solvent exchange. The mixture was stirred for 1.5 h under O_2 (balloon). Yields are given in Table 4. Entries 8 and 9 display the ability to tolerate acid labile functional groups by this mild method.

A concern at the outset of this work was overoxidation of desired heteroaromatic molecules. Though low concentrations of H_2O_2 are generated, unwanted oxidations were only detected with initial attempts for one-pot, single step benzothiazole synthesis. When **1a** was added to a mixture of 2-amino-thiophenol, unwanted byproducts were detected, likely from S-oxidation. (In support of H_2O_2 production, thioanisole added to a completed preparation of **8d** provided methylphenylsulfoxide in 67%.) A two-stage approach allowed for clean transformation when flavin catalysts were added after benzothiazoline intermediates were formed.

In conclusion, green and bioinspired oxidative aromatizations were developed by robust flavin organocatalysts. Flavin mimics catalyze the oxidation of dihydropyridines and benzothiazolines using oxygen as a terminal oxidant in methanol. The simple and high-yielding one-pot multicomponent synthesis of pyridines was described using 2 mol % of catalyst. Related two-stage one-pot syntheses of benzothiazoles were achieved. This catalytic process is consistent with observations in the literature of flavoenzyme and flavin mimic reactivity involving the dissociation of 4a-hydroperoxyflavins in polar protic environments, as mentioned above. Though not previously indicated in the metabolism of dihydropyridine-derived drugs, it seems chemically possible that flavoenzymes may perform the direct oxidation of various dihydropyridines drugs. Small molecule flavin mimics continue to unlock new areas of opportunity in synthesis, especially in the realm of aerobic organocatalysis. These advances are emblematic of the dynamic nature of flavin mimic catalysts and their ability to perform selective oxidations based on bioinspired method development, providing an attractive platform for efficient and sustainable oxidation research.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental methods, detailed analytical methods, supporting tables, and characterization of new molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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