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Metal-free Atom-economical Synthesis of Tetra-substituted Imidazoles via Flavin-Iodine Catalyzed Aerobic Cross-Dehydrogenative Coupling of Amidines and Chalcones

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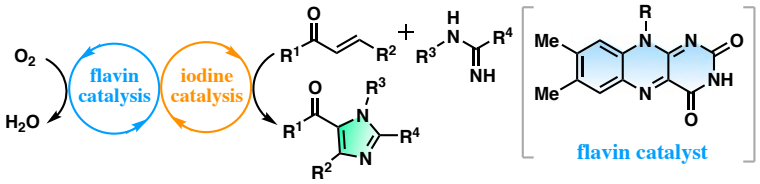
Supporting Information Placeholder

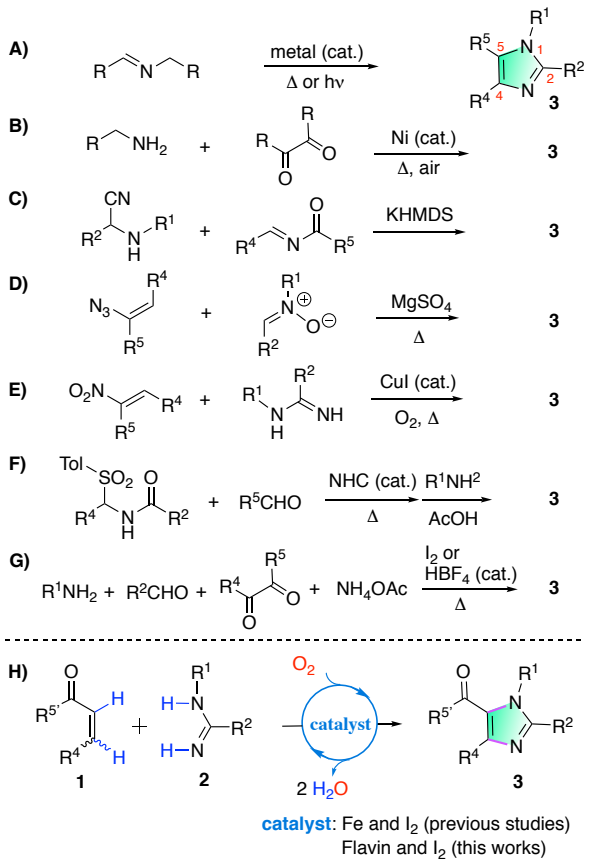


ABSTRACT: Herein, we demonstrated the oxidative cross-dehydrogenative coupling between amidines and chalcones catalyzed by flavin and iodine. The riboflavin-iodine catalytic system played multiple roles in substrate- and O_2-activation, enabling the facile and atom-economical synthesis of tetra-substituted imidazoles in good yields (60–87%). This metal-free reaction consumed only 1 equiv of molecular oxygen and generated 2 equiv of environmentally benign H_2O as the only by-product.

Cross-dehydrogenative coupling (CDC) to form new C-X (X=C, S, O, N) bonds using the C-H and X-H bonds of the substrates directly removes the necessity of redundant intermediate steps and the usage of stoichiometric reagents for the pre-activation of substrates. Therefore, it has become a powerful tool for step- and atom-economical syntheses in organic chemistry.[1] In oxidative transformations, molecular oxygen (O_2) is recognized as an ideal oxidant because of its economical and environmental advantages, such as sustainable abundance, safety, cost-effectiveness, atom economy, and minimal pollution.[2-4] Therefore, aerobic CDC that generates the environmentally benign H_2O as the only waste is an ideal atom-economical and green approach that combines the advantages of both the CDC and the O_2-mediated process.[3] Recently, we have developed a novel dual catalytic system for aerobic CDC using a coupled redox catalyst system consisting of a biomimetic flavin organocatalyst[5] and an iodine catalyst.[6] The coupled flavin-iodine catalyst promoted aerobic CDC through direct C-H bond functionalization when applied to the azolation of indoles, specifically the formation of imidazo[1,2-*a*]pyridine from acetophenones and 2-aminopyridines.[7] Although aerobic CDC generally requires transition metal catalysts, these flavin-iodine-catalyzed CDC reactions are unique metal-free systems, which facilitate non-metal redox catalysis for O_2- and substrate activation. In addition to its environmental advantages, the coupled flavin-iodine catalyst occasionally demonstrated excellent chemoselectivity and enabled further applications in multistep syntheses, which have not been achieved by the metal-catalyzed systems.[7,8]

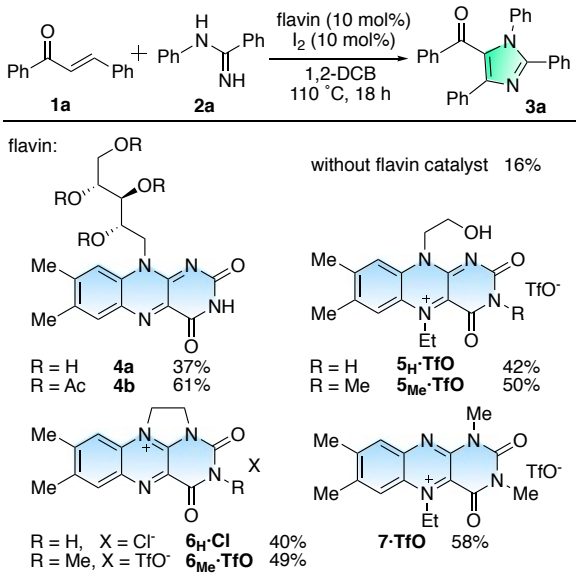
Imidazoles are one of the most prevalent heterocyclic skeletons, which are found in biologically active natural products, pharmaceuticals, and functional molecules, such as ionic liquids, precursors of N-heterocyclic carbene catalysts and ligands, organic semiconductors, and optoelectrical materials.[9] Over the years, numerous synthetic methods for imidazole derivatives have been developed. However, most of these are limited to mono-, di-, or tri-substituted imidazoles; facile and efficient synthetic methods for the bulky tetra-substituted imidazoles are relatively scarce. Some synthetic methods have been reported for tetra-substituted imidazoles, *e.g.* transition-metal-catalyzed dehydrogenation of amines and imines (Scheme 1A),[10a,b] Ni-catalyzed coupling of aldehydes with diketones (Scheme 1B),[10c] cross-coupling of aldimine (Scheme 1C),[10d] domino reaction of azidoacrylates and nitrones (Scheme 1D),[10e] Cu-catalyzed cycloaddition of amidines (Scheme 1E)[10f], multi-component reactions (Scheme 1 and G),[10g-m] and others.[10n-p] However, most of them have disadvantages such as the use of harmful and less-available substrates and metal reagents, harsh reaction conditions, high catalyst loading, and low regioselectivity. The catalytic aerobic CDC of chalcones **1** and amidines **2** may be the most promising method for regioselective and atom-economical synthesis of 1,2,4,5-substituted imidazoles **3**, in which, through the activation of two C(sp^2)-H bonds of **1**, two C-N bonds are formed along with H_2O as the by-product (Scheme 1H). However, this synthetic route is limited to only the coupled iron(III)-iodine catalyst system;[11] thus, other approaches to synthesize tetra-substituted imidazoles must be developed. In this study, we applied the flavin-iodine-catalyzed C-H bond functionalization[7] to the aerobic CDC between **1** and **2** and successfully synthesized **3** under atom-economical metal-free conditions.

Scheme 1. Synthetic Strategy of Tetrasubstituted-Imidazoles.



First, we elucidated the effects of various flavin catalysts on the aerobic CDC. In the presence of flavins **4**-**7**[12] (10 mol%) and I_2 (10 mol%), **1a** was reacted with **2a** (1.5 equiv) in 1,2-dichlorobenzene (1,2-DCB) under molecular oxygen (1 atm, balloon) at 110 °C (Scheme 2). As a result, the desired **3a** was obtained in 37–61% yields in the presence of riboflavin **4a**, riboflavin tetraacetate **4b**, isoalloxaziniums **5**, and alloxaziniums **6** and **7**, whereas a poor 16% yield was achieved in the absence of a flavin catalyst. This result revealed that the flavin-iodine catalysis was effectively applied to the aerobic CDC of **1a** and **2a**. Among the seven flavin catalysts tested, the cationic flavinium catalysts **5-7,** which generally work as efficient organocatalysts for aerobic oxygenations,[5c,5d,13] showed moderate catalytic activity. The best yield was obtained by neutral riboflavin tetraacetate **4b**, which can be readily prepared from the inexpensive and commercially available riboflavin **4a** (vitamin B_2). The superior catalytic activity of neutral **4b** is ascribed to its stability under basic conditions because cationic flavinium catalysts often show reduced catalytic activity under basic conditions owing to the formation of an adduct formation with various nucleophiles.[5d]

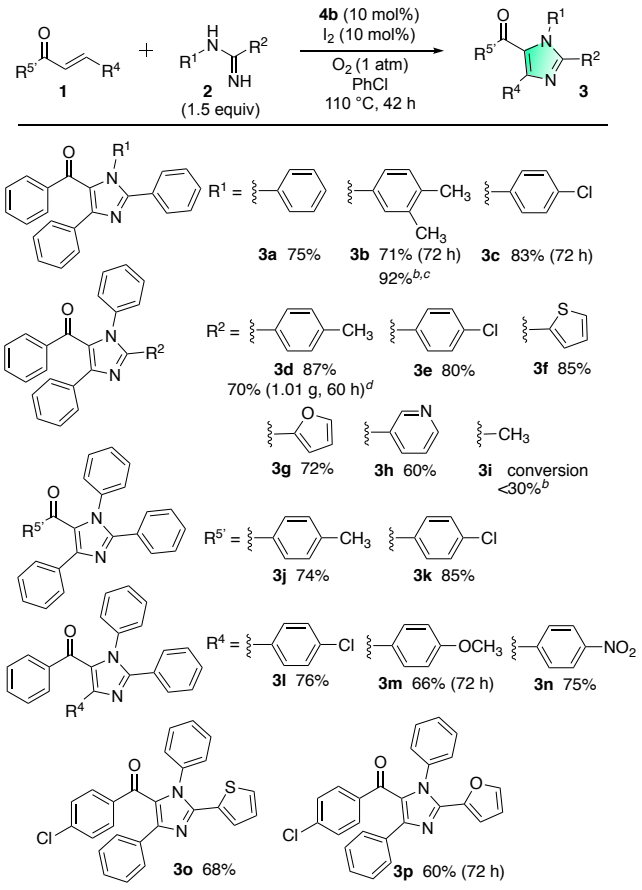
Scheme 2. Effects of flavin catalysts on the aerobic CDC of 1a and 2a to produce 3a.[a]



[a] Conditions: **1a** (0.25 M), **2a** (0.30 M), flavin, I_2, and 1,2-DCB under O_2 (1 atm, balloon) at 110 °C. Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.

Further optimization of the reaction conditions revealed that I_2 worked efficiently in comparison with other iodine sources such as KI, NH_4I, and HI (Table S1). The desired **3a** was obtained in 87% yield (75% isolated yield) when a solution of **1a** and **2a** (1.5 equiv) in chlorobenzene was stirred in the presence of **4b** (10 mol%) and I_2 (10 mol%) under molecular oxygen (1 atm, balloon) at 110 °C for 42 h (Tables S1 and Scheme 3). In contrast, the yield decreased to 25% for the reaction without **4b**, evidently supporting the catalytic efficiency of **4b**. Using this optimized condition as the standard, we then investigated the substrate scope of the aerobic oxidative imidazole synthesis. A series of **2** bearing the electron-donating and -withdrawing substituents (such as methyl and chloro groups, respectively) at the phenyl rings reacted efficiently with **1a**, producing the corresponding **3b**-**e** in 71–87% yields. The yield of **3b** increased to 92% in a short reaction time of 42 h when 20 mol% of **4b** and I_2 were used. The reaction of thiophene and furan carboxamidines **2f** and **2g** also proceeded smoothly to produce the corresponding **3f** and **3g** in 85 and 72% yields, respectively. A carboxamidine bearing a basic pyridine unit, **2h**, successfully reacted to afford **3h** in 60% yield. In contrast, the reaction of methane carboxamidine **2i** hardly occurred. A series of chalcone bearing electron-donating and -withdrawing substituents reacted with **2a**, producing the corresponding **3j**-**p** good yields (60–85%). To demonstrate the synthetic utility of this method, a gram-scale reaction was conducted, producing **3d** in 70% yield (1.01 g) with an extended reaction time of 60 h.

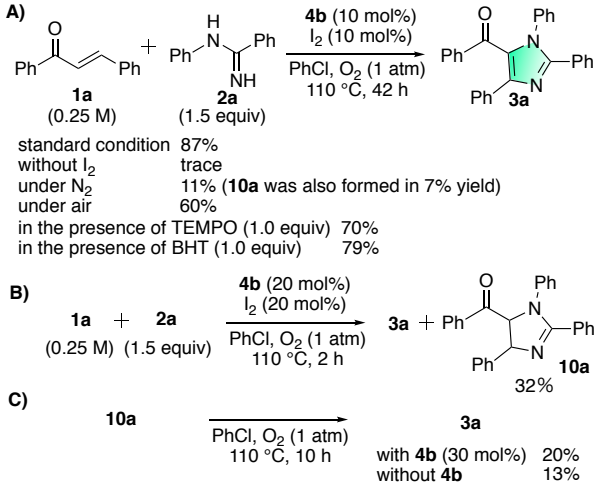
Scheme 3. Scope of flavin-iodine-catalyzed oxidative imidazole synthesis via aerobic CDC of 1 and 2.[a]



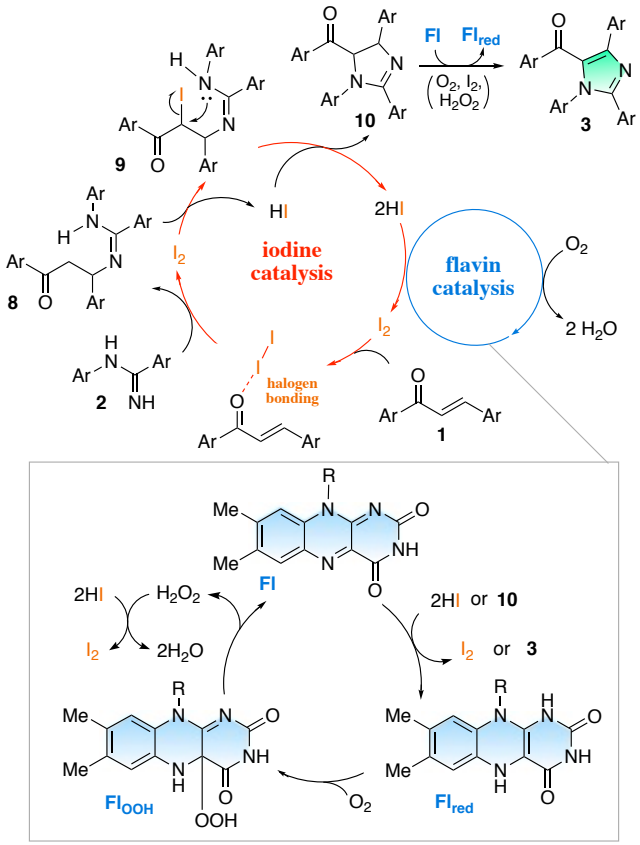
[a] Conditions: **1** (0.25 M), **2** (0.38 M), **4b** (10 mol%), I_2 (10 mol%), and PhCl under O_2 (1 atm, balloon) at 110 °C for 42 h. [b] **4b** (20 mol%) and I_2 (20 mol%) were used. [c] Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [d] **1a** (3.5 mmol) was used.

Subsequently, we performed control experiments to gain insight into the reaction mechanism. Although the imidazole **3a** was obtained in 87% yield at the optimized reaction conditions, the reaction hardly occurred in the absence of I_2 or under N_2 atmosphere, indicating that the iodine catalyst and molecular oxygen are essential for the CDC (Scheme 4A). Air (1 atm) could be used instead of molecular oxygen, although the yield slightly decreased. The addition of radical inhibitors such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) did not significantly affect the reaction and afforded **3a** in 70 and 79% yields, respectively. This negligible effect of the radical inhibitors suggested a non-radical catalytic mechanism.

Scheme 4. Control experiments.



Scheme 5. Proposed mechanism for aerobic oxidative imidazole synthesis.



Based on these experimental results and previous reports, we propose a plausible mechanism for flavin-iodine-catalyzed imidazole synthesis (Scheme 5). Molecular iodine is a good halogen bond catalyst as evidenced by the iodine-catalyzed Michael addition on the carbonyl oxygen of chalcone.[14] We propose that a Michael adduct **8** is initially formed when **2** is reacted with **1** in the iodine-catalyzed reaction.[11] By the reaction of **8** with I_2, the α-iodination of the carbonyl group occurs to yield HI and the iodo intermediate **9**,[11] which subsequently undergoes intramolecular cyclization affording dihydroimidazole **10**.[11] The

intermediate **10a** was detected by HRMS analysis of the reaction mixture obtained after the 2 h stirring, and **10a** was isolated in 32% yield (Scheme 4B and Figure S1).[11a] The formation of **10a** (7% yield) in the reaction under an N_2 atmosphere was also confirmed by ^{1}H NMR (Scheme 4A). The subsequent dehydrogenative oxidation of **10** yielded the desired product **3** and by-product HI. In this system, flavin is responsible for the regeneration of I_2 (Scheme 5).[6a,15] The *in situ* generated HI is converted to I_2 by the oxidation of the neutral flavin **Fl**. The reduced flavin $\mathbf{Fl_{red}}$ reacts with molecular oxygen to form the hydroperoxyl intermediate $\mathbf{Fl_{OOH}}$, which then reverts to **Fl** through the elimination of H_2O_2.[16] Interestingly, the oxidatively active H_2O_2 oxidizes HI to generate I_2 and H_2O. Flavin catalysts are known to catalyze the aerobic dehydrogenative aromatization of heterocyclic compounds such as dihydropyridine,[17] benzothiazoline,[17] and indoline.[18] Therefore, in the present transformation, **Fl** not only oxidizes HI to I_2 but also catalyzes the dehydrogenative aromatization of **10** to **3**. Indeed, comparing the reaction of **10a** in the presence and absence of **4b** revealed that **4b** accelerated the dehydrogenative oxidation of **10a**, although the dehydrogenative oxidation is also performed by O_2, I_2 and *in situ* generated H_2O_2 (Scheme 4C).

In conclusion, the organocatalytic aerobic CDC of amidines and chalcones to synthesize tetra-substituted imidazoles has been successfully demonstrated for the first time in literature. In the flavin-iodine dual catalytic system, iodine exhibited not only redox catalysis for C-H activation but also halogen bond catalysis for the activation of chalcone. In addition, because of the presence of flavin, these multistep transformations consume only 1 equiv of molecular oxygen and generate 2 equiv of the environmentally benign water as the solo by-product, thus proving the atom economy of this synthetic method. We expect that the findings of this study would provide a novel non-metal-catalyzed methodology for the facile multistep synthesis of complex heterocyclic molecules, including other aerobic CDC reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for known and new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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