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Aerobic Oxidative C−H Azolation of Indoles and One-Pot Synthesis of Azolyl Thioindoles by Flavin−Iodine-Coupled Organocatalysis

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Cite This: *Org. Lett.* 2021, 23, 2084−2088 Read Online

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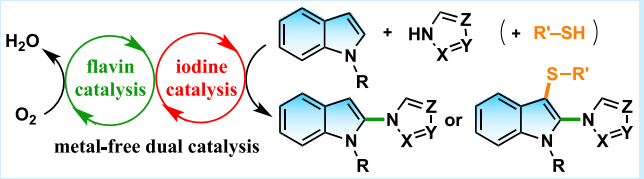
ABSTRACT: The aerobic oxidative cross-coupling of indoles with azoles driven by flavin-iodine-coupled organocatalysis has been developed for the green synthesis of 2-(azol-1-yl)indoles. The coupled organocatalytic system enabled the one-pot three-component synthesis of 2-azolyl-3-thioindoles from indoles, azoles, and thiols in an atom-economical manner by utilizing molecular oxygen as the only sacrificial reagent.



The indole ring system is the most ubiquitous heterocycle in nature and is also the most potent pharmacophore that is found in a range of natural products.[1] Thus, considerable efforts have been made toward the development of methodologies for the efficient preparation and functionalization of indole derivatives.[2] Among the indole derivatives, 2-(azol-1-yl)indoles are found in biologically and pharmaceutically active compounds such as celogentin C[3] and potent anticancer agents **I**,[4] **II**,[5] and **III**[6] (Figure 1). The direct C−N bond formation of

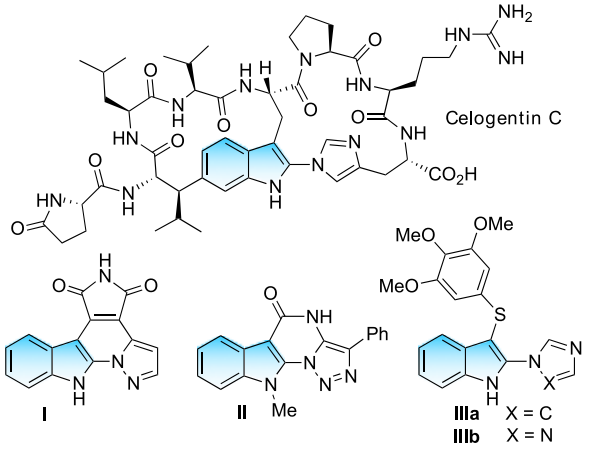
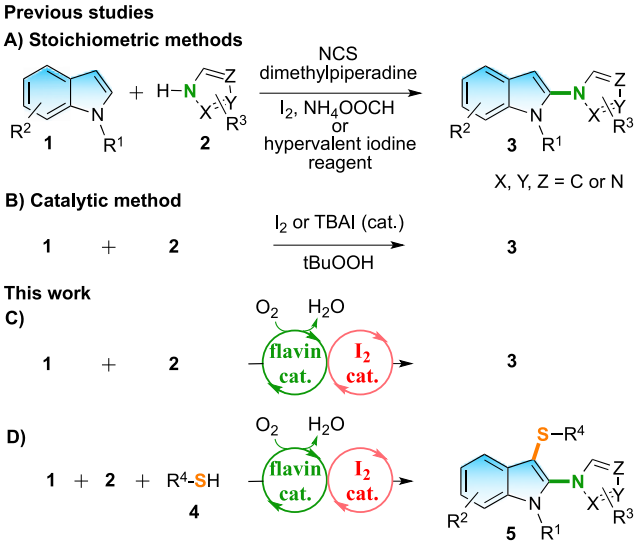


Figure 1. Structures of biologically active 2-(azol-1-yl)indoles.

nonactivated simple indoles and azoles is an atom-economical approach to access 2-(azol-1-yl)indoles; however, the oxidative cross-coupling of indoles and azoles to form 2-(azol-1-yl)indoles has been rarely reported. Although a number of the metal-catalyzed oxidative coupling of indoles and azoles has been developed, the C−C bond formation was performed rather than the C−N bond formation.[2a,c−e]

The stoichiometric cross-coupling reactions were performed using an excess amount of oxidant and base such as NCS/1,4-dimethylpiperazine[7,8] and I_2/NH_4OOCH (Scheme 1A).[9] Hypervalent iodine reagents efficiently promoted the oxidative C−N coupling reaction.[10] There is only one approach on the efficient catalytic azolation; in this reaction, the iodine-catalyzed system required a stoichiometric amount of *tert*-butylhydroperoxide (TBHP) as a terminal oxidant (Scheme 1B).[11] Nicewicz and co-workers demonstrated the photo-

Scheme 1. (A and B) Previous and (C and D) Present Methods for the Cross-Coupling of 1 with 2



Received: January 21, 2021
Published: March 3, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00241
Org. Lett. 2021, 23, 2084−2088

catalytic aerobic C−H azolation of diverse aryl and heteroaryl compounds, including indoles. However, indoles hardly reacted, resulting in poor yields (up to 12%).[12]

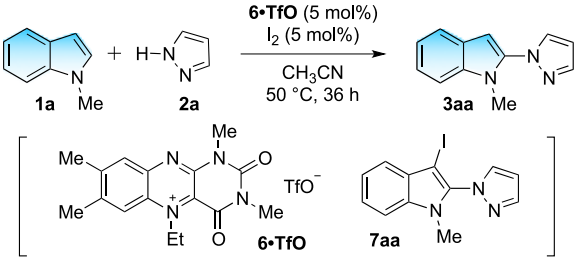
Green aerobic systems have drawn considerable attention because molecular oxygen (O_2) utilized in these systems is an ideal oxidant with many advantages such as sustainable abundance, safety, cost-effectiveness, atom-economy, and minimal pollution.[2e,13] Flavin catalysts, which are prepared by mimicking the function of flavin-dependent monooxygenase,[14] have attracted significant interest because of their biomimetic organocatalytic ability to activate O_2.[15,16] Inspired by the aerobic system of the flavoenzymes, we recently developed a novel strategy for green, oxidative transformations by combining the flavin catalyst and iodine catalyst.[17,18] The flavin−iodine-coupled organocatalytic system successfully promoted the aerobic oxidative sulfenylation of indole analogues[19] and imidazo[1,2-*a*]pyridine ring formation[20] under metal-free conditions. In these reactions, the flavin catalyst activated O_2 through electron transfer from the coupled iodine catalyst, thereby allowing a green oxidative coupling reaction with O_2 (1 atm or air). O_2 was the only sacrificial reagent, and no other oxidizing or reducing agents were required for these reactions. On the basis of this coupled organocatalysis, in this study we developed the first efficient method for the aerobic cross-coupling of indoles **1** and azoles **2** through the catalytic C−H activation of **1** (Scheme 1C). Moreover, the C−H azolation reaction was coupled with the previously developed sulfenylation reaction, allowing the one-pot three-component synthesis of 2-(azol-1-yl)-3-thioindoles **5** from **1**, **2**, and thiols **4** (Scheme 1D).

First, we examined the cross-coupling reaction of 1-methylindole (**1a**) with pyrazole (**2a**) in the presence of a range of flavin catalysts and iodine sources in diverse solvents under an O_2 atmosphere (Tables S1 and S2). The desired compound, 2-azolylindole **3aa**, was selectively obtained in 78% yield when riboflavin-derived alloxazinium salt **6·TfO**[21] (5 mol %) and I_2 (5 mol %) were used as the catalysts under an O_2 (1 atm, balloon) atmosphere in CH_3CN at 50 °C (entry 1, Table 1). In the absence of **6·TfO**, the yield of **3aa** decreased to 21%, suggesting that the flavin-catalyzed O_2 activation played an important role in the progress of this reaction (entry 2). I_2 and O_2 were necessary for the catalytic transformation to **3aa** (entries 3 and 4). When air (1 atm, balloon) was used as the oxidant, the yield was reasonably lower (56%) than that under O_2 (entry 5). When a stoichiometric amount of I_2 was used in the absence of **6·TfO** and O_2, the desired product **3aa** was hardly obtained; instead, the corresponding 3-iodo adduct **7aa** was formed in 12% yield (entry 6).

With the optimized reaction conditions in hand, we examined the substrate scope and limitations of this cross-coupling reaction (Scheme 2). A series of indoles bearing alkyl substituents at the N1 position (**1a**−**d**) successfully reacted with **2a** to give the corresponding products **3aa**−**3da** in 58−80% yields.

To our delight, the coupling reactions of indoles that were not substituted at the N1 positions (**1e** and **1f**) with **2a** also proceeded smoothly to produce **3ea** and **3fa**. The presence of substituents at the C3 (**1e**), C5 (**1d, f**), and C7 (**1c**) positions of the indole ring did not prevent the azolation reaction. Electron-rich indole **1g** and electron-deficient indole **1h** gave the desired products (**3gb** and **3hb**) in 73% and 65% yields, respectively, although a relatively higher amount of **2** or I_2 was required. Indole bearing cyano group **1i** gave the correspond-

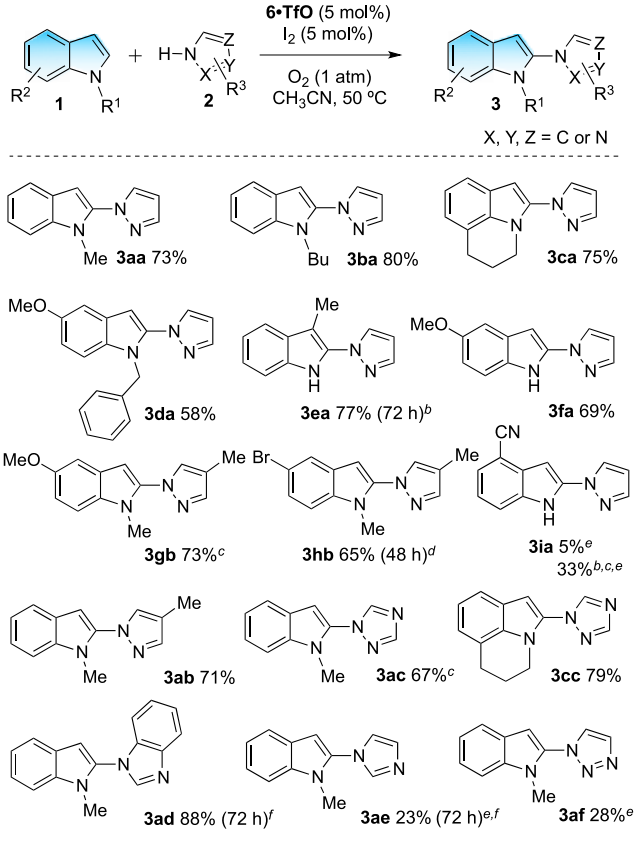
Table 1. Synthesis of 3aa via cross-coupling of 1a with 2a[a]



entry	flavin (mol %)	I_2 (mol %)	atmosphere	yield (%)
1	**6·TfO** (5)	I_2 (5)	O_2	78
2	none	I_2 (5)	O_2	21
3	**6·TfO** (5)	none	O_2	none
4	**6·TfO** (5)	I_2 (5)	N_2	4
5	**6·TfO** (5)	I_2 (5)	air	56
6	none	I_2 (120)	N_2	1 (12)[b]

[a]Conditions: **1a** (1.0 M), **2a** (2.0 M), **6·TfO**, I_2, and CH_3CN under O_2, N_2, or air (1 atm, balloon) at 50 °C. Yield was determined by ^1H NMR or GC measurements with 1,1,2,2-tetrachloroethane or triethylene glycol dimethyl ether as an internal standard. [b]3-Iodo adduct **7aa** was formed.

Scheme 2. Substrate Scope of Flavin−Iodine-Catalyzed Aerobic Oxidative Cross-Coupling of 1 with 2[a]



[a]Conditions: **1** (1 M), **2** (2 M), **6·TfO** (5 mol %), and I_2 (5 mol %) in CH_3CN under O_2 (1 atm, balloon) atmosphere at 50 °C for 36 h. [b]1,4-Dioxane was used as the solvent. [c]Four equiv of **2** was used. [d]Twenty-five mol % of I_2 was used. [e]Determined by ^1H NMR measurement. [f]**1** (4 M), **2** (1 M), **6·TfO** (5 mol %), and I_2 (5 mol %) in 1,4-dioxane under O_2 (1 atm) atmosphere at 80 °C for 72 h.

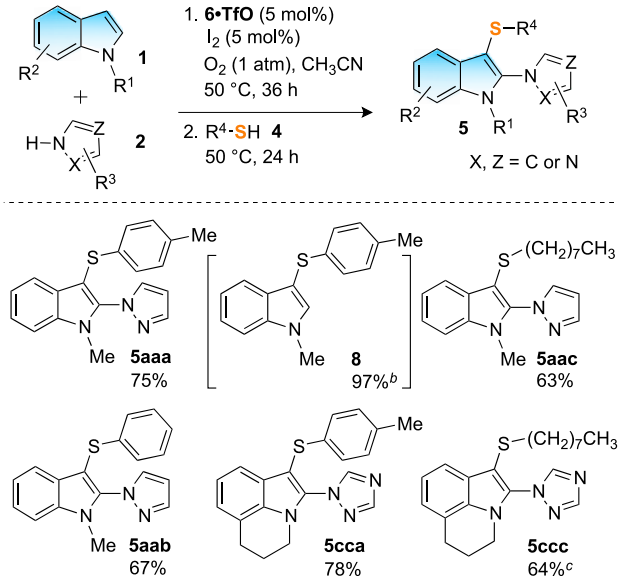
https://dx.doi.org/10.1021/acs.orglett.1c00241
Org. Lett. 2021, 23, 2084−2088

ing product **3ia** in poor yields, suggesting that the electron-deficient indoles were relatively less active for the present azolation. The use of substituted pyrazole **2b**, 1,2,4-triazole (**2c**), and benzimidazole (**2d**) as the azole reagent for this cross-coupling reaction afforded **3ab**, **3ac**, **3cc**, and **3ad**, respectively. However, the reactivity of **2d** was relatively low, because of which 4 equiv of **1a** and a higher temperature (80 °C) were needed for the coupling reaction to reach completion. In contrast to **2a**, **2c**, and **2d**, the pK_a values of which are 2.5,[22a] 2.2,[22a] and 5.3,[22b] respectively, relatively basic and acidic azoles such as imidazole (**2e**, pK_a = 7.0)[22a] and 1,2,3-triazole (**2f**, pK_a = 1.2)[22a] were not effective for the coupling with **1a**, as apparent from the poor yields of the corresponding products **3ae** and **3af**.

On the basis of the results of the aerobic C−N bond formation, we explored the one-pot three-component synthesis of 2-(azol-1-yl)-3-thioindoles **5**. The aerobic one-pot, multistep, and multicomponent reaction will be an atom- and step-economical strategy to meet the acute demands of green and sustainable chemistry. Development of the O_2-mediated multistep reactions is one of the most rewarding challenges in synthetic organic chemistry. However, this often suffers from the low selectivity of the aerobic process. Previously, we demonstrated a green and efficient method for the direct aerobic oxidative sulfenylation of **1** with **4**, in which the aerobic oxidation of **4** and the following aerobic oxidative sulfenylation of **1** were selectively promoted under mild conditions via flavin-iodine coupled catalysis.[19a] Consequently, we expected that the present aerobic oxidative azolation of **1** with **2** would proceed in the same time as the previous aerobic sulfenylation with **4**, thus the target biofunctionalized indole **5** would be produced via the three-component coupling reaction of **1**, **2**, and **4** (Scheme 1D).[23] We first attempted the reaction of **1a**, **2a**, and **4a** in the presence of **6·TfO** and I_2; only 3-sulfenylated indole **8** was obtained in 97% yield, without the generation of bifunctionalized indole **5aaa** (Scheme 3). This suggested that the 2-azolation reaction was relatively slower than the 3-sulfenylation reaction, and there was no azolation after sulfenylation. Therefore, we carried out the one-pot bifunctionalization reaction in a sequential manner—the azolation of **1** with **2** was performed first, following which sulfenylation was performed by adding **4** into the reaction mixture. Consequently, a series of compound **5** was obtained in 63−78% yield via the three-component reaction of **1**, **2**, and **4**. To the best of our knowledge, this is the first example of the direct one-pot synthesis of **5** from simple compounds **1**, **2**, and **4**. This would provide a novel green way to readily access diverse compound **5**, which is of biological and pharmacological importance. For example, the potent anticancer agent **IIIb** has been prepared by the inefficient multistep reaction through the chemoselective iodination and azolation of **1i** with **2c**, followed by the microwave-assisted sulfenylation with **9d**, which was prepared by the stoichiometric oxidation of **4d**, thus generating copious amounts of wastes (Scheme 4A).[6,24] In sharp contrast, the present flavin-iodine-catalyzed three-component reaction of **1i**, **2c**, and **4d** afforded the desired compound **IIIb** in 78% yield through a one-pot reaction, generating only water as the sole waste (Scheme 4B). This clearly established the merit of the present green method.

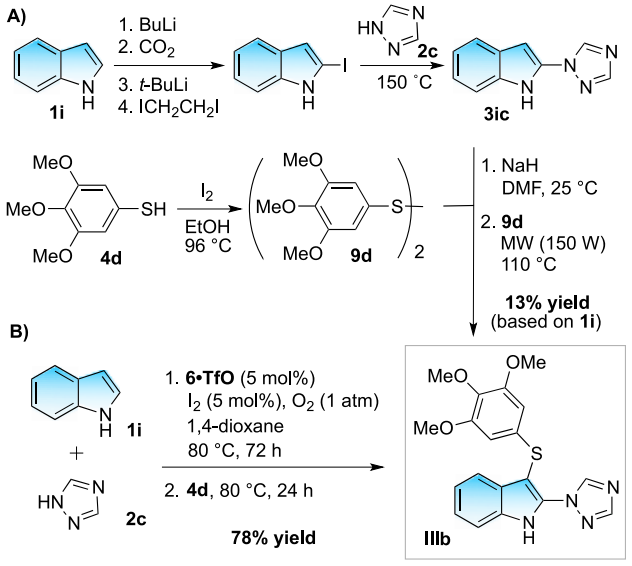
On the basis of the experimental results and relevant literature, a plausible mechanism of the present dual catalytic system is proposed in Scheme 5. Initially, the reaction of nucleophilic **1** with I_2 affords corresponding iodonium **10** and

Scheme 3. One-Pot Three-Component Synthesis of 5[a]



[a]Conditions: A mixture of **1** (1 M), **2** (2 M), **6·TfO** (5 mol %), and I_2 (5 mol %) in CH_3CN was stirred under O_2 (1 atm, balloon) atmosphere at 50 °C for 36 h, following which **4** (1.2 M) was added, and the mixture was stirred at 50 °C for 24 h. [b]Condition: A mixture of **1** (1 M), **2** (2 M), **4** (1.2 M), **6·TfO** (5 mol %), and I_2 (5 mol %) in CH_3CN was stirred under O_2 (1 atm, balloon) atmosphere at 50 °C for 36 h. The yield was determined by ^{1}H NMR measurement. [c]Stirred for 48 h before the addition of **4**.

Scheme 4. (A) Conventional Multistep Synthesis and (B) Present One-Pot Three-Component Synthesis of IIIb



3-iodo iminium **11**, which are electrophilically activated (step i).[9,11a] Then, the nucleophilic attack of **2** at the C2 positions of **10** and **11** and the following elimination of H^+ and I^- afford the 2-azolated product **3** (step ii). The generated H^+ and I^- are efficiently converted to I_2 and water by the flavin **6**-catalyzed-aerobic oxidation.[17] Furthermore, in the presence of **4**, flavin catalysis promotes the aerobic oxidation of **4** to **9** (step iii), which readily reacts with I_2 to give sulfenyl iodide **12** (step iv).[19] Reactive intermediate **12** undergoes nucleophilic attack by **3**, producing the 3-sulfenylated product **5** along with H^+

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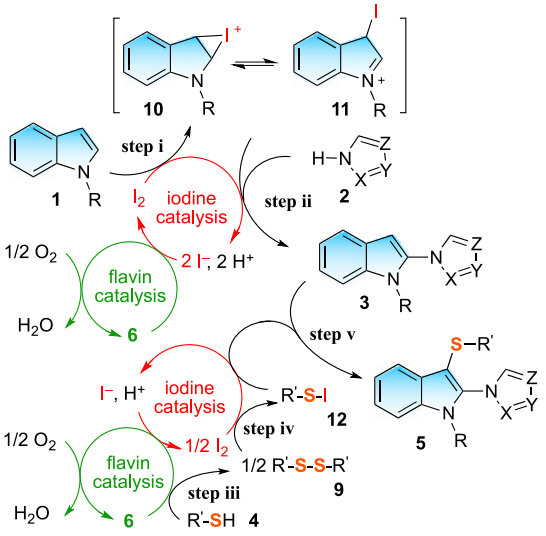
Scheme 5. Plausible Mechanism for the Catalytic Synthesis of 3 and 5



and I^- (step v), which are converted to I_2 and water by the aerobic flavin catalysis. Therefore, the bifunctionalization of **1** with **2** and **4** gives **5** through the aerobic oxidative C−N, S−S, and C−S bond formations, and the entire reaction proceeds in a highly atom-economical manner by the consumption of only O_2.

In conclusion, we performed the first efficient aerobic synthesis of **3** from simple compounds **1** and **2** via a metal-free, flavin−iodine-catalyzed reaction. Moreover, combination of the flavin−iodine-catalyzed aerobic oxidative azolation with sulfenylation readily afforded bifunctionalized compound **5** from the corresponding simple components **1**, **2**, and **4** via the one pot multistep reaction that involved oxidative C−N, S−S, and C−S bond formations. Owing to the coupled flavin−iodine catalysis, the present reaction required only O_2, which does not pose any risk of pollution, and generated environmentally benign water as the sole waste, thus establishing this reaction to be an atom-economical strategy. The present findings will provide a novel paradigm for green transformations and one-pot multistep synthesis using O_2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00241.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by JSPS/MEXT KAKENHI (Grant-in-Aid for Scientific Research (C), 19K05617) and the Electric Technology Research Foundation of Chugoku.

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https://dx.doi.org/10.1021/acs.orglett.1c00241
Org. Lett. 2021, 23, 2084−2088