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Flavin–Iodine Coupled Organocatalysis for Aerobic Oxidative Direct Sulfenylation of Indoles with Thiols under Mild Conditions

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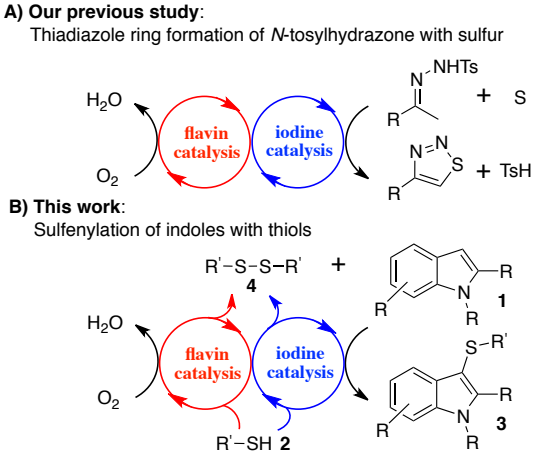
A unique coupled redox organocatalysis system using flavin and iodine catalysts efficiently promoted metal-free aerobic oxidative direct sulfenylation of indoles with thiols at ambient temperature without any sacrificial reagents, except environmentally benign molecular oxygen. Biomimetic flavin catalysis plays multiple roles in aerobic oxidative transformations, not only regenerating I_2 from in situ generated I^-, but also converting thiols into disulfides.

Recent demand for green and sustainable oxidative transformations has driven the use of ambient molecular oxygen, which is an atom-economical, easily available, and minimally polluting oxidant. However, direct oxidation with molecular oxygen is often kinetically unfavorable.[1] To achieve efficient aerobic oxidative transformations, construction of biomimetic multiple catalytic systems is recognised as one of the most promising, but challenging approaches.[2] Flavin and flavinium catalysts have been developed to mimic enzymatic aerobic oxygenations of flavin-dependent monooxygenases,[2,3] thus providing diverse organocatalytic oxidative transformations using molecular oxygen.[4,5] Although previously reported biomimetic aerobic oxygenations generally require sacrificial reductants, such as hydrazine,[4a,c,d,k] zinc,[4b,g] Hantzsch esters,[4f] ascorbic acid,[4h] and formic acid,[4j] we have recently reported a novel strategy using flavin and iodine catalysts without additional sacrificial reagents, except for molecular oxygen (Scheme 1A).[6] In the two-component redox organocatalysis system, the flavin catalyst activates molecular oxygen via electron transfer from the coupled iodine catalyst, thus achieving aerobic thiadiazole ring formation using *N*-tosylhydrazone and sulfur. In contrast, flavoenzymes are known to carry out dehydrogenation of various substrates, as demonstrated by flavin-dependent oxidases such as mitochondrial monoamine oxidase and D-amino acid oxidase.[7] By simulating the function of such oxidases, flavin-catalysed dehydrogenative oxidation of thiols to disulfides has been reported.[8]

By combining the flavin–iodine coupled system with oxidase-mimicking thiol oxidation, in this study, we demonstrated flavin–iodine catalysed direct sulfenylation of indoles with thiols using molecular oxygen (1 atm) as the only sacrificial reagent, generating environmentally benign H_2O (Scheme 1B). The coupled flavin catalysis played multiple roles in the present sulfenylation of indoles, realizing aerobic oxidation of both I^- and thiols to yield I_2 and disulfides, respectively. Owing to the great importance of indole derivatives as biologically active substances and building blocks for diverse pharmaceuticals,[9] methods for the formation of C–C and C–X (X = heteroatom) bonds in indoles via direct C–H bond functionalization with electrophiles have been developed to synthesize substituted indoles.[10] Among these methods, sulfenylation of indoles has attracted considerable attention for synthesizing sulfenylindoles.[11,12] Although various sulfenylation reagents are available for the sulfenylation of indoles,[11] thiols



Scheme 1 Flavin–iodine-catalysed aerobic oxidative transformations.

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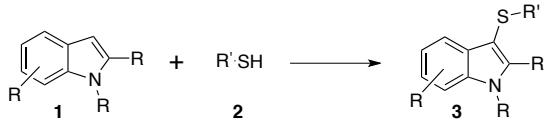


Previous works

shoichiometric reagents: PIFA; Selectfluor™; NCS; oxone; $FeCl_3$; NaOH[12b-f]

iodine catalysis: TBHP or DMSO, I_2 (cat.), 60 °C[12i,l]

O_2, $Vo(acac)_2$ (cat.), KI (cat.), BHT (cat.), 60 °C[12a]

O_2, serum albumin (biocat.), I_2 (cat.), 50 °C[12k]

air, I_2 (cat.), 80 °C[12j]

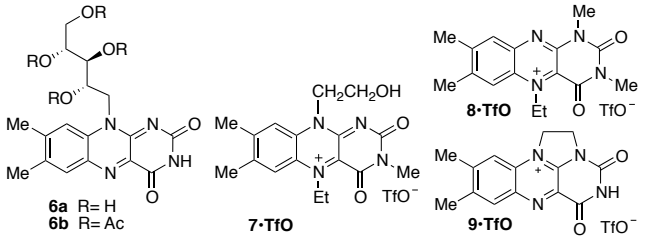
photocatalysis: air, rose bengal (photocat.), $h\nu$[12m]

This work

O_2 or air, flavin–I_2 (cat.), 25 °C

Scheme 2 Previous and present works for the direct sulfenylation of indoles with thiols.

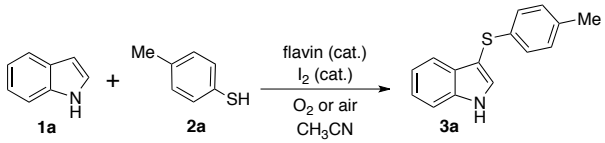
are used as simple, inexpensive and readily available reagents.[12] Direct sulfenylation with thiols has emerged as a promising strategy to produce sulfenylindoles, but previous examples generally have drawbacks, such as the need for toxic or expensive metal and biological catalysts, photoirradiation, heating conditions, or stoichiometric amounts of sacrificial reagents (Scheme 2).[12] The development of a green multiple catalytic approach to perform direct sulfenylation under mild ambient conditions without the use of polluting, less accessible reagents remains challenging.



6a R= H
6b R= Ac
7•TfO
8•TfO
9•TfO

Fig. 1 Structures of flavins and flavinium salts.

Table 1 Optimization of sulfenylation of **1a** with **2a**



1a **2a** **3a**

entry	flavin (mol%)	I_2 (mol%)	temperature (°C)	time (h)	yield (%)
1[a]	7•TfO (5)	10	40	4	6
2[a]	8•TfO (5)	10	40	4	57
3[a]	9•TfO (5)	10	40	4	29
4[a]	**6a** (5)	10	40	4	15
5[a]	**6b** (5)	10	40	4	44
6[b]	8•TfO (2)	2	25	20	92

[a] Conditions: **1a** (0.6 M), **2a** (0.5 M), flavin (5 mol%), I_2 (10 mol%), and CH_3CN under O_2 (1 atm) at 40 °C for 4 h. Yield was calculated on the basis of **2a**, as determined by GC. [b] Conditions: **1a** (1.5 M), **2a** (1.8 M), **8•TfO** (2 mol%), I_2 (2 mol%), and CH_3CN under O_2 (1 atm) at 25 °C for 20 h. Yield was calculated on the basis of **1a**, as determined by GC.

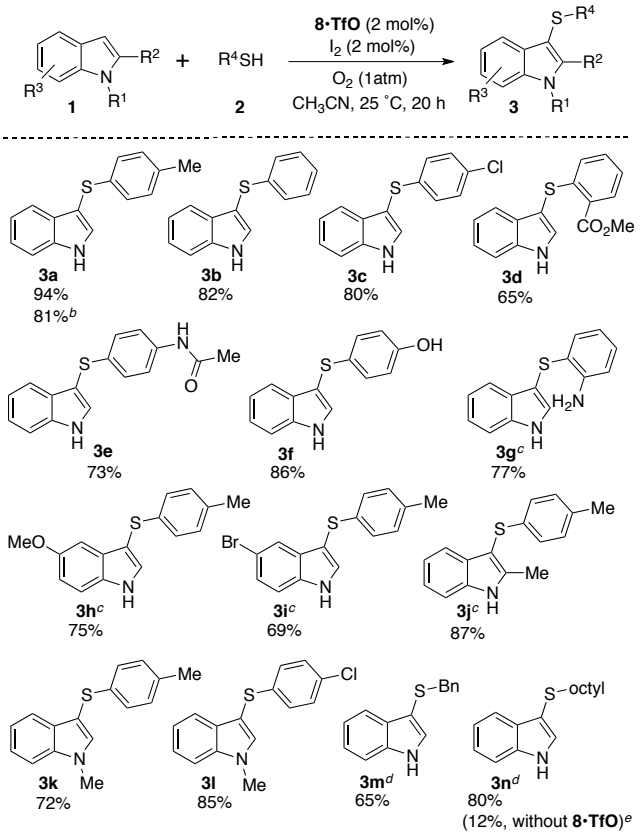
We first investigated the catalytic activities of diverse flavin compounds and iodine sources for the reaction between indole (**1a**) and 4-methylbenzenethiol (**2a**) under molecular oxygen (1 atm) in CH_3CN at 40 °C for 4 h (Table 1, Fig. 1). Among the five flavins and flavinium salts (**6**–**9**, 5 mol%) tested in the presence of I_2 (10 mol%), **8•TfO**, which could be synthesised from riboflavin (**6a**, Supplementary Information), successfully promoted the sulfenylation of **1a**, giving corresponding sulfenyl indole **3a** in 57% yield (entries 1–5). An examination of 11 solvents and 4 iodine sources (Table S1, Supplementary Information) revealed that the best efficiency was achieved in the presence of I_2 in CH_3CN. Further optimization of the reaction conditions showed that the present system proceeded successfully with only 2 mol% **8•TfO** and 2 mol% I_2 under O_2 at 25 °C (entry 6).

In a further set of experiments, we examined the scope and generality of the present sulfenylation of indoles under the optimum reaction conditions (Table 2). Thiols bearing either electron-donating or electron-withdrawing groups on the phenyl ring (**3a**–**c**) underwent smooth sulfenylation. Remarkably, sulfenylation also proceeded under air (1 atm), although a slightly higher temperature (40 °C) was required to achieve sulfenylation within 24 h. The reaction tolerated a range of functional groups, such as ester, amide, hydroxy, and amino groups, to produce **3d**–**g** chemoselectively. Furthermore, 1-, 2-, and 5-substituted indoles reacted with thiols to give the desired sulfenylated products (**3h**–**l**) in 69%–87% yields. The sulfenylation of benzyl and alkyl thiols was also promoted, although a higher catalyst loading and a relatively higher temperature (60 °C) were required (**3m** and **n**). As observed in the previous flavin–iodine-catalysed thiadiazole formation,[6] the thiol functionality was not oxidised, even though sulfides are known to be easily converted to sulfoxides under flavin-catalysed oxidative conditions.[3]

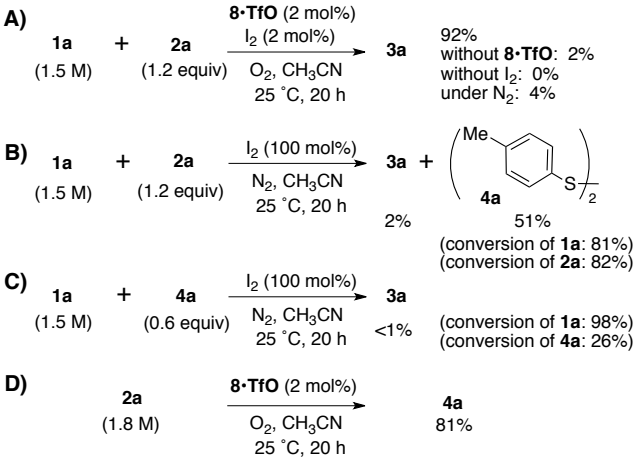
To gain insight into the reaction mechanism, control experiments were carried out, as shown in Scheme 3. In sharp contrast to the reaction under standard conditions, sulfenylation hardly occurred without **8•TfO**, I_2, or O_2 (Scheme 3A). Interestingly, when a stoichiometric amount of I_2 was used, **3a** was scarcely obtained, whereas disulfide **4a** was yielded by the I_2-meditated oxidation of **2a** along with the consumption of **1a** (Scheme 3B). In addition, no sulfenylation of **1a** with **4a** occurred in the presence of a stoichiometric amount of I_2 (Scheme 3C). These results reveal a distinct advantage of the present coupled catalytic system, which decreases the possibility of side reactions, e.g., oligomerization or polymerization of **1a**.[13]

The time-courses of the yields and conversions were determined for the catalytic sulfenylation of **1a** with **2a** (Fig. S1, Supplementary Information). It is noteworthy that thiol oxidation was observed in the initial stage of the present sulfenylation, with the oxidative conversion of **2a** to **4a** almost completed within the initial 2 h. Therefore, **1a** seems to mainly react with **4a** rather than **2a** in the present sulfenylation. We then monitored the time-course of the reaction with **4a** and compared it to that with **2a** (Fig. S1e and a). However, contrary to expectations, sulfenylation with **2a** was slightly faster than

Table 2 Scope of aerobic sulfenylation [a]



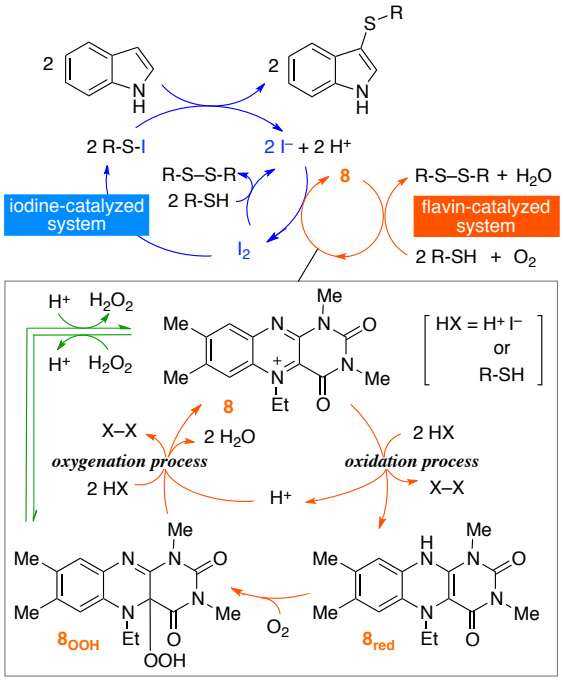
[a] Conditions: **1a** (1.5 M), **2a** (1.8 M), **8•TfO** (2 mol%), I_2 (2 mol%), and CH_3CN under O_2 (1 atm) at 25 °C for 20 h. [b] Under air (1 atm) at 40 °C for 24 h. Yield was determined by GC. [c] **8•TfO** (5 mol%) was used. [d] The reaction was carried out at 60 °C using **8•TfO** (10 mol%) and I_2 (4 mol%). [e] Determined by ^1H NMR.



Scheme 3 Control experiments.

that with **4a**. Thus, the use of thiols in the present system likely enhanced the reaction rate of sulfenylation, although an additional oxidative transformation to disulfide was required with thiols.

A plausible mechanism for the flavin–iodine-catalysed aerobic sulfenylation of indole is proposed in Scheme 4. In the iodine-catalysed system, in situ generated disulfide reacts with I_2 to produce R–SI,[11f,j] which electrophilically attacks the C-3 position of indole to give the desired sulfenyl indole and I^-. Efficient oxidative transformation of the generated I^- into I_2 occurs through both oxidation and oxygenation processes with molecular oxygen in the flavin-catalysed system.[6] Flavin catalyst **8** oxidizes I^- to give I_2 and reduced flavin $\mathbf{8}_{red}$, which activates molecular oxygen to yield hydroperoxyflavin $\mathbf{8}_{OOH}$. Oxidatively active $\mathbf{8}_{OOH}$ promotes the oxygenation of I^- to give I_2, **8**, and environmentally benign H_2O via the generation of IO^-.[14] Similarly, thiol can be converted to disulfide by the flavin-catalysed aerobic oxidation (Scheme 3D),[8] with disulfide also generated by oxidation with a catalytic amount of I_2 (Scheme 4). As hydroperoxyflavins, such as $\mathbf{8}_{OOH}$, are known to release H_2O_2 through a dynamic equilibrium (green arrows, Scheme 4),[3,15] a certain amount of H_2O_2 should be generated in the present system. Therefore, the flavin-catalysed oxidation of thiol, which is completed in the initial stage of the reaction (Fig. S1), would not only generate disulfide, but also result in the storage of H_2O_2,[8] which can participate in the flavinium-catalysed H_2O_2 oxygenation[2,3] of I^- to regenerate I_2. This phenomenon may explain why the sulfenylation with thiol was faster than that with disulfide in the present flavin–iodine-coupled system.



Scheme 4 Proposed mechanism for aerobic flavin–iodine-catalysed sulfenylation of indoles with thiols.

Conclusions

In summary, we successfully developed a two-component organocatalyst system realizing the novel direct aerobic sulfenylation of indoles with thiols under mild conditions by combining biomimetic flavin catalysis with iodine catalysis. The flavin–iodine-catalysed reaction can be driven by molecular oxygen as the only sacrificial reagent, thus generating

environmentally benign H_2O as the lone byproduct. Because of the unique multiple catalytic roles of flavin, the reaction rate of sulfenylation with thiol was enhanced in comparison to that with disulfide. The present coupled organocatalysis system will provide new paradigms for novel green aerobic transformations using multiple catalytic systems.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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