

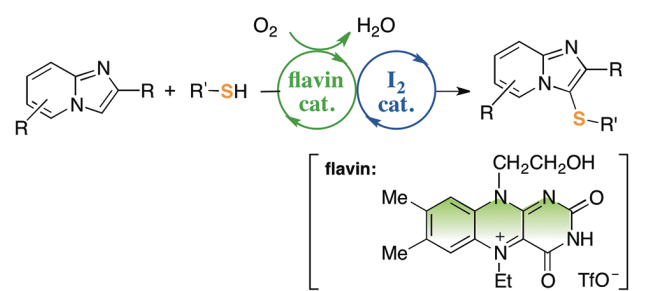
# Tandem Flavin-Iodine-Catalyzed Aerobic Oxidative Sulfenylation of Imidazo[1,2-*a*]Pyridines with Thiols

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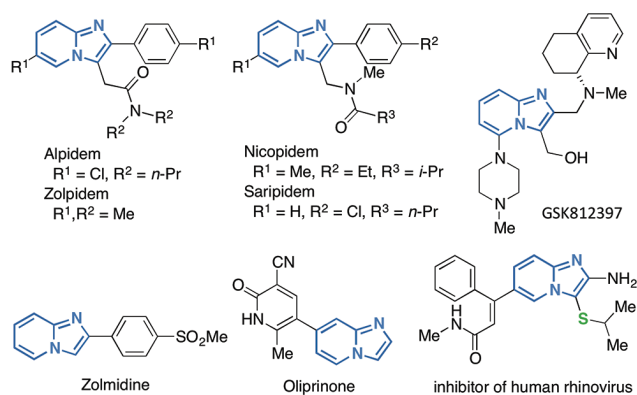
Supporting Information Placeholder

**ABSTRACT:** A green, aerobic sulfenylation of imidazo[1,2-*a*]pyridines was performed using thiols, a flavin-and-iodine dual catalytic system, and environmentally benign molecular oxygen as the only sacrificial reagent. The dual metal-free catalysts smoothly promote a unique step-wise tandem process, beginning with the aerobic oxidation of a thiol to afford a disulfide that is utilized in the oxidative sulfenylation of the imidazo[1,2-*a*]pyridine. This process has afforded diverse 3-sulfonylimidazo[1,2-*a*]pyridines of biological interest, and is environmentally friendly as benign H<sub>2</sub>O is the only by-product.



The construction of C-S bonds is a fundamental process in the synthesis of heteroaryl thioethers, and their derivatives. The sulfenylation of imidazo[1,2-*a*]pyridines has recently attracted increasing attention as imidazo[1,2-*a*]pyridines have been recognized as an important class of heterocyclic compounds that are found in a wide range of bioactive pharmaceuticals and natural products.<sup>1</sup> As shown in Figure 1, the imidazo[1,2-*a*]pyridine scaffold is found in various biologically active compounds and commercially available drugs like alpidem,<sup>2</sup> zolpidem,<sup>2</sup> nicopidem,<sup>3</sup> saripidem (anxiolytic agent),<sup>3</sup> zolimidine (gastroprotective agent),<sup>4</sup> olprinone (cardiotonic agent),<sup>5</sup> rifaximin (antibiotic),<sup>6</sup> and GSK812397 (treatment of HIV infection).<sup>7</sup> Furthermore, imidazo[1,2-*a*]pyridines possessing thio functionality have been recognized as promising candidates for use in medicinal compounds. Indeed, this moiety has been incorporated in medicinally

active compounds such as anthelmintic,<sup>8</sup> and an inhibitor of human rhinovirus (Figure 1).<sup>9</sup> Therefore, various processes have been developed for the sulfenylation of imidazo[1,2-*a*]pyridines at C3, using a variety of reagents as the source of sulfur, such as a thiol,<sup>10</sup> disulfide,<sup>11</sup> sulfonyl chloride,<sup>8</sup> sulfonylchloride,<sup>12</sup> sulfinate,<sup>13</sup> sulfonothioate,<sup>14</sup> sulfoxide,<sup>15</sup> sulfonylhydrazide,<sup>16</sup> and sulfur.<sup>17</sup> Thiols are the simplest, most atom-economical, and readily available of the sulfenylation reagents, as other reagents are often prepared from thiols and thus require additional synthetic manipulations. However, the oxidative sulfenylation with thiols has been limited to a few methods using hypervalent iodine reagents,<sup>10a</sup> NCS,<sup>10b</sup> iodine catalysts with stoichiometric oxidants,<sup>10d,e</sup> copper catalysts,<sup>10c,f</sup> and photocatalysts.<sup>10g</sup> Unfortunately, these reagents have several drawbacks such as the need for stoichiometric amounts of expensive sacrificial reagents, toxic metals, and photoirradiation. The development of a novel, facile approach that fulfils the strong demand for green and sustainable chemistry therefore remains an on-going challenge.



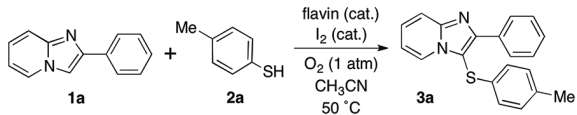
**Figure 1.** Structures of medicinally active imidazo[1,2-*a*]pyridines.

There has been a recent demand for oxidative transformations with molecular oxygen, which can be used as an atom-economical, easily available, and minimally polluting oxidant.<sup>18</sup> Flavin catalysts, which have been developed by mimicking the functions of flavin-dependent monooxygenases, have attracted particular interest as these biomimetic organocatalysts are able to activate molecular oxygen.<sup>19,20</sup> Taking inspiration from the enzymatic aerobic oxidation system, we recently developed a novel strategy for green, oxidative transformations by coupling flavin and iodine catalysis.<sup>21</sup> The dual catalytic system successfully promoted aerobic oxidative thiadiazole ring formation of *N*-tosylhydrazones with sulfur,<sup>21</sup> and then could be extended to the sulfenylation of indoles with thiols.<sup>22</sup>

Herein, we present the flavin-iodine-catalyzed, aerobic oxidative sulfenylation of imidazo[1,2-*a*]pyridines with thiols, proceeding in CH<sub>3</sub>CN at 25 or 50 °C. This method offers a unique green approach to the sulfenylation of this important class of compounds as, in addition to using the dual non-metal catalytic system, the sulfenylation was promoted by molecular oxygen as the only sacrificial reagent, yielding environmentally benign H<sub>2</sub>O.

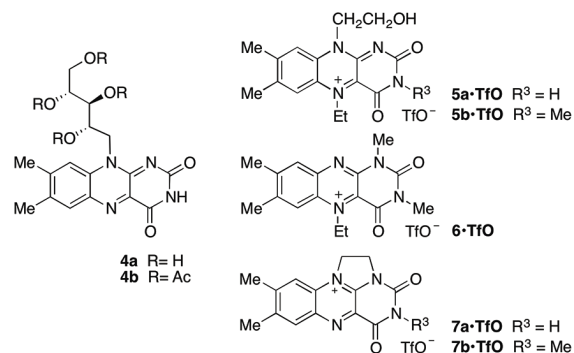
In the initial studies, the reaction conditions were optimized using 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and 4-methylbenzenethiol (**2a**, 1.2 equiv) in the presence of a range of flavin or cationic flavin (flavinium) catalysts (5 mol%) and I<sub>2</sub> (5 mol%) at 50 °C under O<sub>2</sub> atmosphere (Table 1, Figure 2). Commercially available riboflavin (**4a**) and its tetraacetate (**4b**) failed to promote the sulfenylation reaction (entries 1 and 2). The cationic flavin catalysts 5-ethylisoalloxazinium (**5a•TfO** and **5b•TfO**), 5-ethylalloxazinium (**6•TfO**), and 1,10-ethylene-bridged alloxazinium salts (**7a•TfO** and **7b•TfO**), which can be derived from **4a**, were also investigated as these are known to display different redox and catalytic properties which is dependent upon the  $\pi$ -conjugation of the ring structure.<sup>23</sup> The results showed that the success of the reaction was likely dependent upon the electrophilicity of the catalyst, as the most electrophilic of the cationic catalysts **5a•TfO** smoothly catalyzed the sulfenylation of **1a** to give the desired product **3a** in 95% yield within 1 h; however, the less electrophilic catalysts **5b•TfO**, **6•TfO**, **7a•TfO**, and **7b•TfO** showed poor to moderate catalytic activity (entries 3-7). Attempts using various iodine sources such as I<sub>2</sub>, TBAI, NH<sub>4</sub>I, and KI showed that I<sub>2</sub> gave the highest yield (Table S1, Supporting Information). Further optimization studies revealed that the sulfenylation proceeded in excellent yield with only 2 mol% of **5a•TfO** and 4 mol% of I<sub>2</sub> in CH<sub>3</sub>CN at 50 °C for 4 h (entry 8).<sup>24</sup>

**Table 1. Optimization of the Sulfenylation of 1a with 2a<sup>a</sup>**



entry	flavin (mol%)	I <sub>2</sub> (mol%)	time (h)	yield (%)
1	<b>4a</b> (5)	5	1	<1
2	<b>4b</b> (5)	5	1	<1
3	<b>5a•TfO</b> (5)	5	1	94
4	<b>5b•TfO</b> (5)	5	1	84
5	<b>6•TfO</b> (5)	5	1	41
6	<b>7a•TfO</b> (5)	5	1	10
7	<b>7b•TfO</b> (5)	5	1	12
8 <sup>b</sup>	<b>5a•TfO</b> (2)	4	4	95
9	None	4	4	1
10	<b>5a•TfO</b> (2)	None	4	<1
11 <sup>c</sup>	<b>5a•TfO</b> (2)	4	4	<1

<sup>a</sup>Conditions: **1a** (0.5 M), **2a** (0.6 M), flavin, I<sub>2</sub>, and CH<sub>3</sub>CN under O<sub>2</sub> (1 atm) at 50 °C. Yield was determined by GC. <sup>b</sup>**1a** (1 M) and **2a** (1.2 M) were used. <sup>c</sup>Under N<sub>2</sub>.

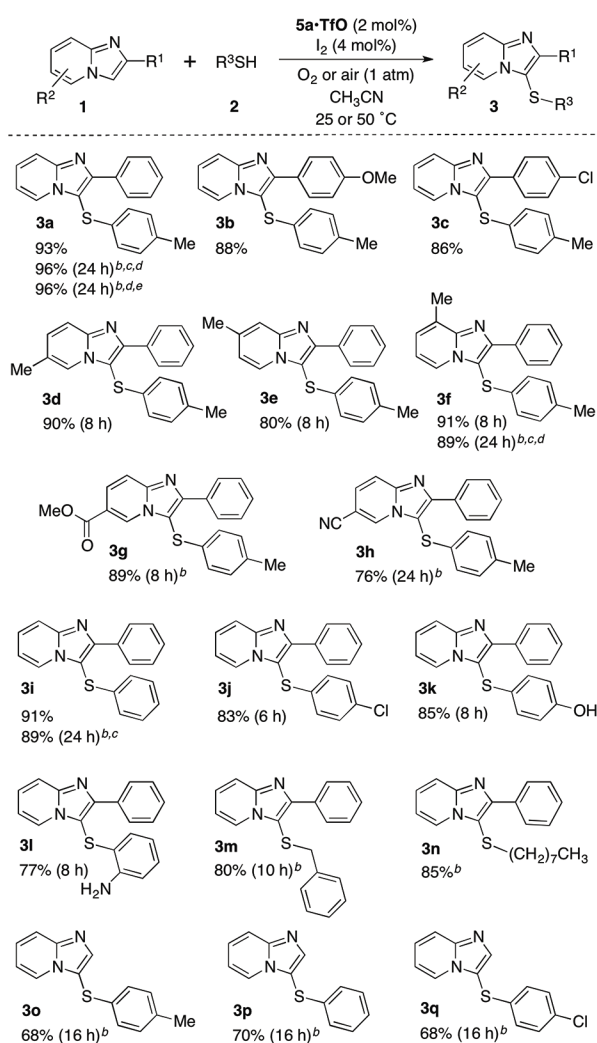


**Figure 2.** Structures of riboflavin and riboflavin-derived catalysts.

Having optimized the conditions on the model system, the substrate scope of the reaction was investigated using a diverse range of imidazo[1,2-*a*]pyridines **1** and thiols **2** (Table 2). Under these conditions, imidazo[1,2-*a*]pyridines bearing either electron-donating or electron-withdrawing groups on the phenyl ring (**3a–c**) successfully underwent sulfenylation. In addition, imidazo[1,2-*a*]pyridines with substituents at the 6, 7, and 8 positions successfully reacted to yield the corresponding 3-sulfonylated products (**3d–f**). The sulfenylation of electron-deficient imidazo[1,2-*a*]pyridines bearing ester and cyano groups was also performed (**3g,h**). A diverse range of thiols (**3i–l**) was then investigated and, to our delight, the hydroxy and amino functionalities were compatible with the optimized reaction conditions (**3k,l**). Thiols possessing

benzyl and alkyl substituents also proceeded in good yield, although 5 mol% of **5a**•TfO and 10 mol% of I<sub>2</sub> were required (**3m,n**). The sulfenylation of 2-unsubstituted imidazo[1,2-*a*]pyridines occurred chemoselectively to give the 3-sulfenylated products in 68-70% yields (**3o-q**). It is noteworthy that the reaction could be performed at 25 °C (**3a,f,i**), whereas the previous catalytic sulfenylations of imidazo[1,2-*a*]pyridines with thiols had required heating conditions or photoirradiation.<sup>10c-g</sup> Air could be utilized instead of pure O<sub>2</sub> as an oxidant although a higher catalyst loading and longer reaction time was required, as might be expected (**3a**).

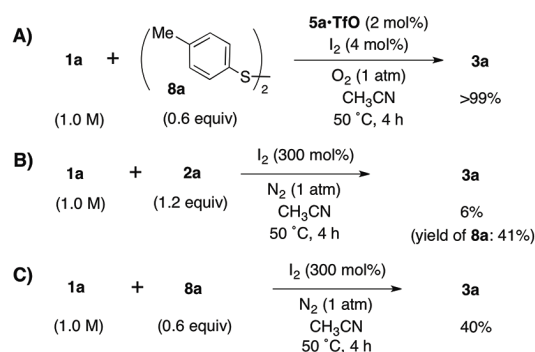
**Table 2. Scope of Imidazo[1,2-*a*]pyridines **1** and Thiols **2**<sup>a</sup>**



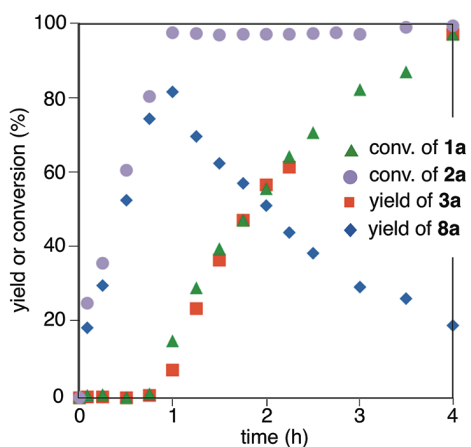
<sup>a</sup>Conditions: **1** (1 M), **2** (1.2 M), **5a**•TfO (2 mol%), I<sub>2</sub> (4 mol%), and CH<sub>3</sub>CN under O<sub>2</sub> (1 atm) at 50 °C for 4 h. <sup>b</sup>**5a**•TfO (5 mol%) and I<sub>2</sub> (10 mol%) were used. <sup>c</sup>At 25 °C. <sup>d</sup>Yield was determined by <sup>1</sup>H NMR using an internal standard. <sup>e</sup>Under air (1 atm).

To establish the mechanism of the reaction, control experiments were conducted. In stark contrast to the reaction under the optimized conditions, the sulfenylation did not proceed in the absence of **5a**•TfO, I<sub>2</sub>, or molecular oxygen (Table 1, entries 9-11). The disulfide **8a** could be used instead of the thiol **2a**, as indicated by the flavin-iodine-catalysed sulfenylation of **1a** with **8a** which proceeded smoothly (Scheme 1A). To gain further insight into the mechanism, the sulfenylation of **1a** with **2a** was studied by GC monitoring the time-course of the yield and conversion (Figure 3). During the sulfenylation with **2a**, **2a** was almost completely converted to **8a** within the first hour. Interestingly, the conversion of **1a** to **3a** only commenced once the thiol **2a** had been completely oxidized to **8a**, indicating that the sulfenylation proceeds via the disulfide. Based on these results, the following tandem process that progresses in a stepwise manner was proposed: (i) the aerobic oxidative transformation of the thiol **2a** to the disulfide **8a** followed by (ii) the aerobic oxidative sulfenylation of **1a** with **8a** (Scheme 2A). In scheme 1B and C, two control experiments are shown in which the flavin catalyst was omitted from the sulfenylation reaction of **2a** or **8a**. Even in the presence of a large excess of I<sub>2</sub> (300 mol%), the direct sulfenylation of **1a** with **2a** hardly progressed; however, I<sub>2</sub> promoted the oxidation of **2a** to **8a** (Scheme 1B). The reaction of **1a** with **8a** in the presence of 300 mol% of I<sub>2</sub> gave the sulfenylated product **3a** although in a modest yield (Scheme 1C). These results clearly revealed the need for both the flavin and I<sub>2</sub> catalysts, i.e. the dual catalytic system presented herein.

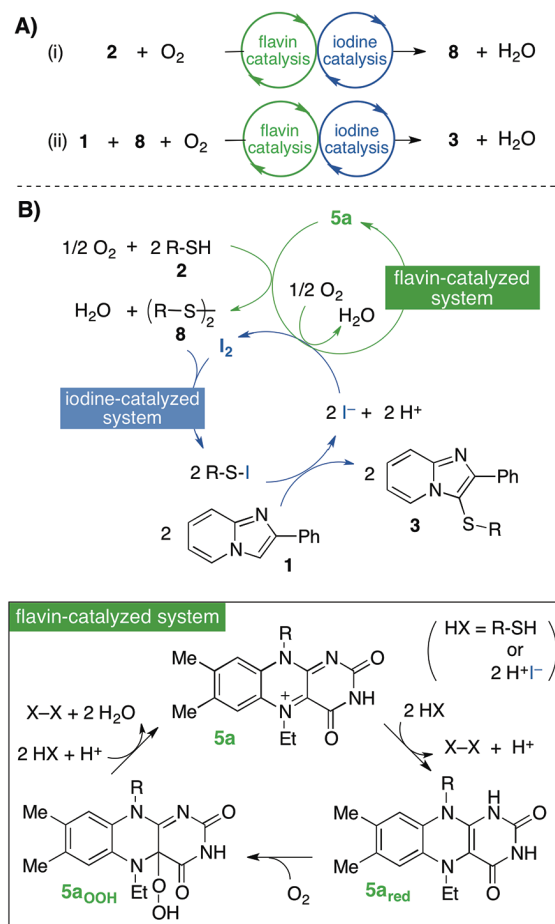
### Scheme 1. Control Experiments



The most plausible reaction mechanism for the flavin-iodine-catalyzed aerobic sulfenylation of imidazo[1,2-*a*]pyridines **1** with thiols **2** has been proposed, on the basis of the experimental results and previous reports (Scheme 2B). The thiol **2** is converted to the disulfide **8**, by the flavin-catalyzed aerobic oxidation reaction and the oxidation with I<sub>2</sub>.<sup>22,25</sup> The disulfide **8** then reacts with I<sub>2</sub> to provide R-SI, which undergoes nucleophilic attack by **1** to yield the desired product **3** along with I<sup>-</sup> and H<sup>+</sup>.<sup>10d,e</sup> The flavin organocatalyst **5a** efficiently promotes the catalytic oxidation of I<sup>-</sup> and H<sup>+</sup> to regenerate I<sub>2</sub> and the by-product



**Figure 3.** Time-course of the sulfenylation of **1a** (0.2 M) with **2a** (1.2 equiv) carried out in CH<sub>3</sub>CN in the presence of **5a•TfO** (2 mol%) and I<sub>2</sub> (4 mol%) under molecular oxygen (1 atm) at 50 °C.



**Scheme 2.** (A) Scheme for the Stepwise Tandem Process of the Present Oxidative Sulfenylation. (B) Proposed Mechanism for the Coupled Flavin-Iodine Organocatalysis

H<sub>2</sub>O, respectively, via the formation of the reduced flavin (**5a<sub>red</sub>**) and 4a-hydroperoxyflavin (**5a<sub>OOH</sub>**).<sup>21</sup> Although the oxidative generation of disulfides and the sulfenylation of substrates occurs simultaneously in the previously reported aerobic sulfenylation of indoles,<sup>22</sup> the present process progresses the tandem process in a stepwise manner (Scheme 2A). Through the oxidative generation of H<sub>2</sub>O, the present dual catalytic system can remove *in situ*-generated H<sup>+</sup> which would otherwise cause side-reactions that inhibit the sulfenylation and thus, presumably results in the efficient sulfenylation with thiols. Indeed, this would explain the poor results obtained when only I<sub>2</sub> was utilized, even if in large excess (Scheme 1B).

In conclusion, we have developed an efficient strategy for the regioselective C-3 sulfenylation of imidazo[1,2-*a*]pyridines with thiols, using a metal-free dual catalytic system consisting of a riboflavin-derived organocatalyst and an iodine catalyst. This methodology enables O<sub>2</sub>-driven sulfenylation in the absence of stoichiometric amounts of expensive sacrificial reagents, toxic metals, and photoirradiation, and thus provides attractive green sulfenylation chemistry to access biologically important 3-sulfenylimidazo[1,2-*a*]pyridines.

## Experimental Section

**General Information.** The NMR spectra were measured using JEOL JNM-L400 and JNM ECX-500 spectrometers (JEOL, Akishima, Japan) operating at 400 and 500 MHz, respectively, for <sup>1</sup>H and 100 and 126 MHz, respectively, for <sup>13</sup>C using tetramethylsilane (TMS) or a solvent residual peak as the internal standard. The electrospray ionization mass (ESI-MS) spectra were recorded using a Bruker microTOFII-SHIY3 mass spectrometer (Bruker, Billerica, MA). The GC measurements were performed on a Shimadzu GC-2014 gas chromatograph (Shimadzu, Kyoto, Japan) equipped with a flame ionization detector (FID) using Supelco Equity-5 (30 m x 0.25 mm) column.

All starting materials were purchased from Aldrich (Milwaukee, WI), Wako Pure Chemical Industries (Osaka, Japan), and Tokyo Kasei (TCI, Tokyo, Japan) and were used as received. Riboflavin tetraacetate (**4b**),<sup>26</sup> 5-ethyl-10-(2-hydroxyethyl)-7,8-dimethylisoalloxazinium triflate (**5a•TfO**),<sup>23</sup> 5-ethyl-10-(2-hydroxyethyl)-3,7,8-trimethylisoalloxazinium triflate (**5b•TfO**),<sup>23</sup> 5-ethyl-1,3,7,8-tetramethylalloxazinium triflate (**6•TfO**),<sup>23</sup> 1,10-ethylene-7,8-dimethylalloxazinium triflate (**7a•TfO**),<sup>23</sup> and 1,10-ethylene-3,7,8-trimethylalloxazinium triflate (**7b•TfO**)<sup>23</sup> were synthesized according to the previously reported methods.

**Typical Procedure for Catalytic Sulfenylation of **1a** with **2a** in the Presence of **5a•TfO** and I<sub>2</sub>.** A mixture of **1a** (194 mg, 1.0 mmol), **2a** (149 mg, 1.2 mmol), I<sub>2</sub> (10.2 mg, 0.040 mmol), **5a•TfO** (9.28 mg, 0.020 mmol), and CH<sub>3</sub>CN (1.0 mL) was stirred at 50 °C for 4 h under O<sub>2</sub>. After an addition of water (30 mL), the mixture was

extracted with CHCl<sub>3</sub> (30 mL x 3), and the organic layer was washed with water (30 mL), dried over anhydrous MgSO<sub>4</sub>, and filtered. After the solvent was removed by evaporation, the residue was purified by column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) to give **3a** (294 mg, 93%) as a white solid. These results are summarized in Table 2.

Spectroscopic data of **3a**<sup>10e</sup>: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.27 (d, *J* = 6.9 Hz, 1H), 8.22 (d, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 9.1, 6.7 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.85 (t, *J* = 6.4 Hz, 1H), 2.25 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 151.4, 147.2, 136.2, 133.6, 131.6, 130.3, 128.7, 128.5, 128.5, 126.7, 125.9, 124.7, 117.8, 113.1, 107.0, 21.0.

Spectroscopic data of **3b**<sup>10e</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 100/0 to 4/1, v/v) afforded the desired product (122 mg, 88%) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.26 (d, *J* = 6.8 Hz, 1H), 8.18 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.33-7.27 (m, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.83 (t, *J* = 6.8 Hz, 1H), 3.83 (s, 3H), 2.25 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 160.1, 151.3, 147.1, 136.1, 131.8, 130.3, 129.8, 126.5, 126.2, 125.9, 124.6, 117.5, 114.0, 112.9, 106.0, 55.4, 21.0.

Spectroscopic data of **3c**<sup>10e</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 100/0 to 4/1, v/v) afforded the desired product (121 mg, 86%) as a beige solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.28 (d, *J* = 6.9 Hz, 1H), 8.19 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.33 (dd, *J* = 9.1, 6.8 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.90-6.85 (m, 3H), 2.26 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 150.1, 147.2, 136.4, 134.7, 132.1, 131.3, 130.4, 129.7, 128.8, 126.9, 126.0, 124.7, 117.8, 113.3, 107.2, 21.0.

Spectroscopic data of **3d**<sup>13c</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (119 mg, 90%) as a pale yellow solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.20 (d, *J* = 7.2 Hz, 2H), 8.06 (s, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.13 (dd, *J* = 9.5, 1.7 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 2.27 (s, 3H), 2.24 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 151.1, 146.1, 135.9, 133.7, 132.0, 130.2, 129.7, 128.44, 128.41, 128.3, 125.7, 122.9, 122.3, 117.0, 106.3, 20.9, 18.4.

Spectroscopic data of **3e**<sup>13c</sup>: This compound was purified by column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (105 mg, 80%) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.20 (d, *J* = 7.3 Hz, 2H), 8.11 (d, *J* = 7.0 Hz, 1H), 7.46 (s, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.64 (d, *J* = 7.0 Hz, 1H), 2.40 (s, 3H), 2.23 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 151.2, 147.5, 137.8,

136.0, 133.7, 131.9, 130.2, 128.5, 128.42, 128.37, 125.8, 123.7, 116.2, 115.6, 106.0, 21.5, 20.9.

Spectroscopic data of **3f**<sup>13c</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (121 mg, 91%) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.20 (d, *J* = 7.3 Hz, 2H), 8.11 (d, *J* = 6.7 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 6.9 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.72 (t, *J* = 6.8 Hz, 1H), 2.69 (s, 3H), 2.23 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 150.9, 147.4, 135.9, 133.8, 131.9, 130.2, 129.9, 128.6, 128.5, 127.7, 125.9, 125.4, 122.4, 113.0, 107.1, 21.0, 16.9.

Spectroscopic data of **3g**<sup>10e</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (134 mg, 89%) as a beige solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 9.05 (s, 1H), 8.24 (d, *J* = 7.2 Hz, 2H), 7.87 (dd, *J* = 9.4, 1.7 Hz, 1H), 7.70 (d, *J* = 9.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 3.92 (s, 3H), 2.26 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 165.3, 152.8, 147.7, 136.6, 133.0, 131.2, 130.4, 129.1, 128.6, 128.5, 126.4, 126.3, 117.2, 117.1, 108.8, 52.6, 21.0.

Spectroscopic data of **3h**<sup>17b</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 100/1 to 4/1, v/v) afforded the desired product (99.4 mg, 76%) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.66 (s, 1H), 8.23 (d, *J* = 7.0 Hz, 2H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.53-7.36 (m, 4H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 153.3, 146.3, 133.6, 132.3, 130.5, 129.9, 129.5, 128.7, 128.5, 126.9, 126.6, 126.0, 118.6, 116.5, 108.7, 99.3.

Spectroscopic data of **3i**<sup>13c</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (109 mg, 91%) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.25 (d, *J* = 6.9 Hz, 1H), 8.21 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.34-7.28 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 2H), 6.84 (t, *J* = 6.8 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 151.4, 147.1, 135.2, 133.4, 129.5, 128.6, 128.4, 128.4, 126.7, 126.1, 125.6, 124.5, 117.7, 113.1, 106.3.

Spectroscopic data of **3j**<sup>13c</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 1/1, v/v) afforded the desired product (112 mg, 83%) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C): δ 8.21 (d, *J* = 6.8 Hz, 1H), 8.18 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.34-7.29 (m, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.86 (t, *J* = 6.8 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, 25 °C): δ 151.7, 147.3, 133.8, 133.3, 132.1, 129.6, 128.8, 128.5, 128.4, 126.9, 124.4, 117.8, 113.3, 105.8.

Spectroscopic data of **3k**<sup>17b</sup>: Column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>/MeOH = 100/0 to 40/1, v/v) afforded the desired product (108 mg, 85%) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>, 25 °C): δ 9.58 (s, 1H), 8.47 (d, *J* =

6.8 Hz, 1H), 8.26-8.20 (m, 2H), 7.73 (d,  $J = 9.0$  Hz, 1H), 7.54-7.33 (m, 4H), 7.06 (t,  $J = 6.8$  Hz, 1H), 6.93 (d,  $J = 8.7$  Hz, 2H), 6.69 (d,  $J = 8.8$  Hz, 2H);  $^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ , 25 °C):  $\delta$  156.8, 149.1, 146.1, 133.4, 128.6, 128.5, 128.4, 127.9, 127.1, 124.6, 122.4, 117.2, 116.8, 113.6, 107.8.

Spectroscopic data of **3l**: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (98.2 mg, 77%) as a pale green solid. MP: 185.7-186.9 °C. IR (KBr, cm<sup>-1</sup>): 3408, 3067, 3017, 1631, 1478, 1344, 736.  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  8.33 (d,  $J = 6.9$  Hz, 1H), 8.21 (d,  $J = 7.3$  Hz, 2H), 7.68 (d,  $J = 9.0$  Hz, 1H), 7.48 (t,  $J = 7.5$  Hz, 2H), 7.40 (t,  $J = 7.4$  Hz, 1H), 7.31-7.25 (m, 1H), 6.99 (t,  $J = 7.6$  Hz, 1H), 6.94 (d,  $J = 7.8$  Hz, 1H), 6.86 (t,  $J = 6.8$  Hz, 1H), 6.63 (d,  $J = 8.0$  Hz, 1H), 6.55 (t,  $J = 7.6$  Hz, 1H), 4.00 (s, 2H);  $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  151.0, 147.0, 145.9, 133.7, 130.6, 128.8, 128.8, 128.7, 128.6, 126.5, 124.8, 119.2, 117.8, 116.7, 116.1, 113.1, 106.9. HRMS (ESI+):  $m/z$  calculated for C<sub>19</sub>H<sub>16</sub>N<sub>3</sub>S (M + H<sup>+</sup>), 318.1059; found, 318.1062.

Spectroscopic data of **3m**<sup>17c</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 1/1, v/v) afforded the desired product (101 mg, 80%) as a pale yellow oil.  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  8.24 (d,  $J = 7.8$  Hz, 2H), 8.06 (d,  $J = 6.9$  Hz, 1H), 7.57 (d,  $J = 9.0$  Hz, 1H), 7.44 (t,  $J = 7.3$  Hz, 2H), 7.37 (t,  $J = 7.3$  Hz, 1H), 7.20-7.14 (m, 1H), 7.10-6.99 (m, 3H), 6.91 (d,  $J = 7.5$  Hz, 2H), 6.64 (t,  $J = 6.8$  Hz, 1H), 3.80 (s, 2H);  $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  150.3, 146.5, 137.2, 133.9, 128.8, 128.5, 128.4, 128.3, 127.4, 126.0, 124.3, 117.4, 112.3, 109.4, 40.7.

Spectroscopic data of **3n**: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (114 mg, 85%) as a white solid. MP: 43.2-44.5 °C. IR (KBr, cm<sup>-1</sup>): 3032, 2953, 2926, 2854, 1465, 1346, 758, 698.  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  8.49 (d,  $J = 6.9$  Hz, 1H), 8.31 (d,  $J = 7.3$  Hz, 2H), 7.65 (d,  $J = 9.0$  Hz, 1H), 7.47 (t,  $J = 7.7$  Hz, 2H), 7.37 (t,  $J = 7.4$  Hz, 1H), 7.29-7.23 (m, 1H), 6.89 (t,  $J = 6.7$  Hz, 1H), 2.63 (t,  $J = 7.2$  Hz, 2H), 1.41 (quin,  $J = 7.4$  Hz, 2H), 1.31-1.04 (m, 10H), 0.85 (t,  $J = 7.2$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  149.7, 146.5, 134.1, 128.5, 128.4, 128.2, 125.8, 124.5, 117.7, 112.6, 110.5, 35.8, 31.8, 29.5, 29.15, 29.12, 28.6, 22.7, 14.2. HRMS (ESI+):  $m/z$  calculated for C<sub>21</sub>H<sub>27</sub>N<sub>2</sub>S (M + H<sup>+</sup>), 339.1889; found, 339.1889.

Spectroscopic data of **3o**<sup>13c</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (65.3 mg, 68%) as a white solid.  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  8.20 (d,  $J = 6.8$  Hz, 1H), 7.97 (s, 1H), 7.69 (d,  $J = 9.0$  Hz, 1H), 7.28 (dd,  $J = 8.9, 7.0$  Hz, 1H), 7.01 (d,  $J = 8.1$  Hz, 2H), 6.93 (d,  $J = 8.2$  Hz, 2H), 6.84 (t,  $J = 6.4$  Hz, 1H), 2.45 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  148.0, 142.2, 136.4, 131.5, 130.1, 126.7, 125.9, 124.4, 118.2, 113.1, 111.5, 21.0.

Spectroscopic data of **3p**<sup>17b</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (64.8 mg, 70%) as a pale yellow solid.  $^1\text{H}$

NMR (500 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  8.21 (d,  $J = 6.8$  Hz, 1H), 7.99 (s, 1H), 7.70 (d,  $J = 9.0$  Hz, 1H), 7.30 (dd,  $J = 9.2, 6.8$  Hz, 1H), 7.20 (t,  $J = 7.5$  Hz, 2H), 7.13 (t,  $J = 7.4$  Hz, 1H), 7.00 (d,  $J = 7.3$  Hz, 2H), 6.87 (t,  $J = 6.5$  Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  148.2, 142.5, 135.3, 129.4, 126.30, 126.27, 126.1, 124.4, 118.2, 113.3, 110.8.

Spectroscopic data of **3q**<sup>13c</sup>: Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate = 5/1 to 2/1, v/v) afforded the desired product (72.0 mg, 68%) as a pale yellow solid.  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  8.17 (d,  $J = 6.9$  Hz, 1H), 7.99 (s, 1H), 7.71 (d,  $J = 9.0$  Hz, 1H), 7.32 (dd,  $J = 9.2, 6.8$  Hz, 1H), 7.17 (d,  $J = 8.6$  Hz, 2H), 6.96-6.85 (m, 3H);  $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  148.3, 142.7, 133.8, 132.3, 129.5, 127.5, 126.3, 124.2, 118.3, 113.4, 110.2.

## ASSOCIATED CONTENT

### Supporting Information

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

Data for the optimization of reaction condition and NMR spectra of products (PDF)

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