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COMMUNICATION

Aerobic Oxidative Synthesis of Benzimidazoles by Flavin Photocatalysis

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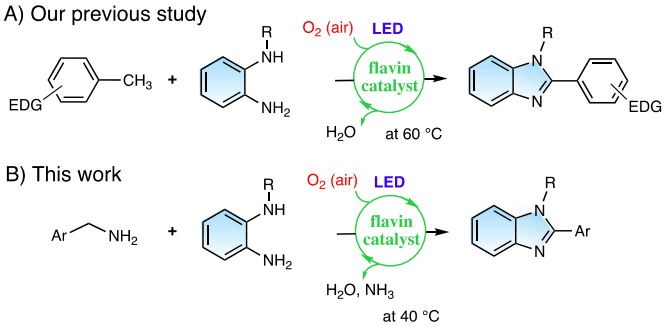
Flavin photocatalysis were utilised for an aerobic oxidative reaction between arylamines and *o*-phenylenediamine. This metal-free reaction proceeded in methanol under visible light irradiation and consumed only atmospheric molecular oxygen, providing a novel eco-friendly method for the synthesis of benzimidazoles.

Benzimidazole is one of the important heterocyclic structures present in pharmacologically active compounds, dyes, and natural products.[1] Among the various methods that have been developed for their synthesis, oxidative ring formation using benzylamines and *o*-phenylenediamines as readily accessible starting materials is a promising method to obtain benzimidazoles with diverse functionalities. In particular, its aerobic version using molecular oxygen as an oxidant is an attractive method because of the significant economic and environmental advantages, such as sustainable abundance, safety, cost-effectiveness, atom economy, and minimal pollution. In addition to metal-catalysed systems,[2] metal-free organocatalytic methods have attracted attention, which can employ carbon nitride photocatalysts,[3] graphene oxide,[4] salicylic acid derivatives,[5] or polydopamine,[6] although they require high-pressure oxygen and/or heating conditions. Quinone-based organocatalysts have succeeded in the aerobic oxidative synthesis of benzimidazoles under relatively mild conditions (45–60 °C);[7] however, the development of novel approaches is needed.

Riboflavin (vitamin B_2) and its derivatives function as photo-organocatalysts under visible light irradiation, promoting dehydrogenation of alcohols[8] and other reactions.[9,10] The dehydrogenation of amines was also reported, but this was limited to one example.[11] Recently, we demonstrated a riboflavin-based photocatalysis for the synthesis of benzimidazoles via aerobic cross-dehydrogenative coupling between toluenes and *o*-phenylenediamines (Scheme 1A).[12] This metal-free system afforded the facile and atom-economical synthesis of benzimidazoles, but it suffered from a narrow substrate range; only electron-rich toluenes with alkoxy substituents worked as the starting materials. As an alternative useful method with a broader substrate scope, we herein report the efficient synthesis of benzimidazoles under mild conditions via the aerobic oxidative reaction of various benzylamines and *o*-phenylenediamines using riboflavin-based photocatalysis (Scheme 1B).



Scheme 1 Flavin-catalysed synthesis of benzimidazoles via aerobic photooxidative reaction of *o*-phenylenediamines with (A) electron-rich toluenes and (B) benzylamines.

We began our study by examining the reaction of benzylamine (**1a**) and *N*-phenyl-*o*-phenylenediamine (**2a**) in the presence of various flavin catalysts under light-emitting diode (LED) lamp irradiation in MeOH under air (1 atm, balloon) at 60 °C (Table 1). Because simultaneous mixing of **1a** and **2a** afforded **3aa** in a modest yield of 28% (entry 1), we decided to conduct the reaction in a sequential manner. First, aerobic oxidation of **1a** was performed by stirring **1a** for 2 h, and then **2a** was added to the reaction mixture for oxidative imidazole-ring formation, which gave **3aa** in 98% yield. The neutral flavin catalysts, *i.e.* riboflavin tetraacetate (**4**) and electron-deficient alloxazine (**5**), afforded the high yield of **3aa** (entries 2 and 3). Meanwhile, the

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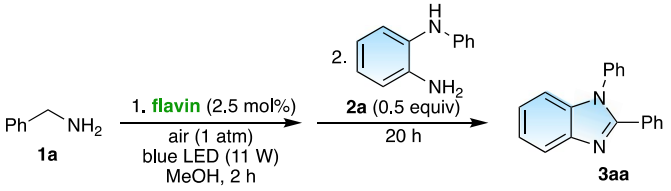
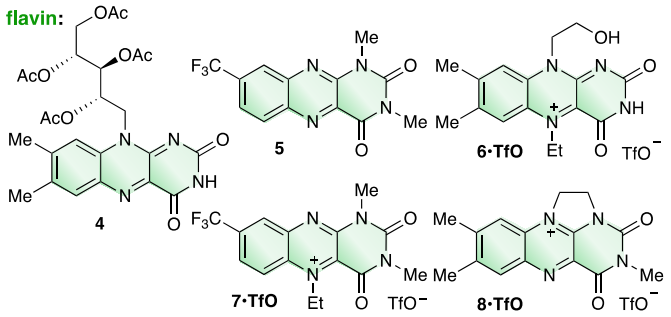
cationic flavinium salts (**6**–**8**), which are known to efficiently promote oxygenation in the dark,[13] hardly promoted the reaction, producing **3aa** in yields of 8%–14% (entries 4–6). The catalytic effect of **4** and **5** was also supported by the fact that the reaction did not occur smoothly in the absence of the flavin catalyst (entry 7). Although **4** and **5** gave almost equally good results, we selected **4** as the best catalyst because it is easily synthesised from commercially available riboflavin (vitamin B_2),[14] a sustainable and inexpensive organic compound produced industrially by microbial fermentation of glucose.[15] The analysis of the temperature effect indicated that the reaction proceeded efficiently under mild conditions. While the yield decreased slightly with a reduction in the temperature, it was sufficiently high (95% yield) even at 40 °C (entries 8–10).

Table 1 Optimisation of the aerobic oxidative benzimidazole ring formation of **1a** and **2a**[a].

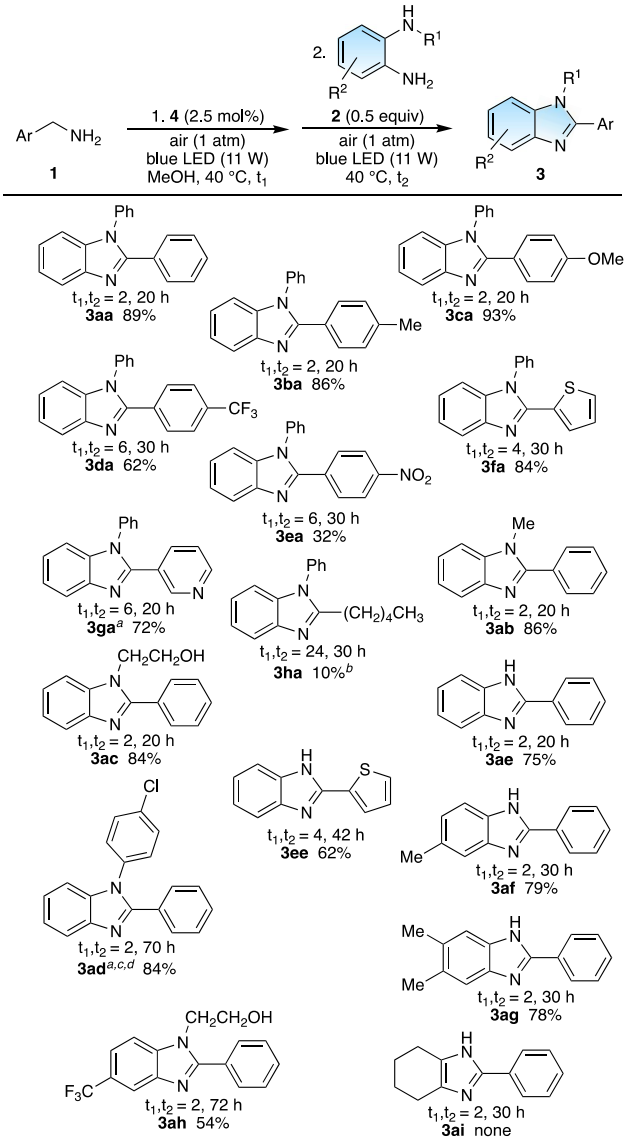


entry	flavin	temp. (°C)	yield (%)	entry	flavin	temp. (°C)	yield (%)
1[b]	**4**	60	28	6	**8·TfO**	60	14
2	**4**	60	98	7	–	60	4
3[c]	**5**	60	99	8	**4**	40	95
4	**6·TfO**	60	16	9	**4**	30	87
5[c]	**7·TfO**	60	8	10	**4**	25	71



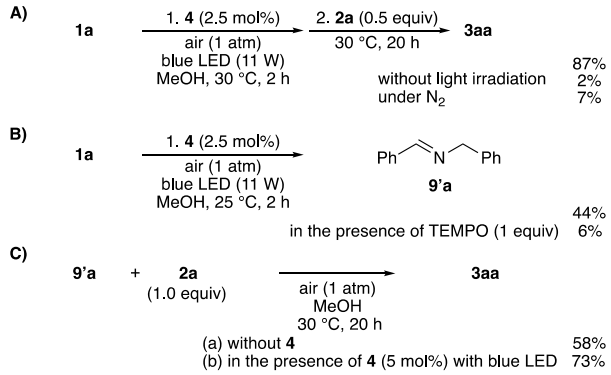
[a]A mixture of **1a** (0.3 mmol, 0.1 M) and flavin (2.5 mol%) in MeOH was irradiated using blue LED lamps (11 W, λ_{max} = 466 nm) while stirring under air (1 atm, balloon) at 60 °C for 2 h. **2a** (0.5 equiv) was then added to the reaction mixture, and the mixture was stirred under irradiation at 60 °C for 20 h. The yield was determined via gas chromatography (GC) using biphenyl as an internal standard, and calculated based on **2a**. [b]**1a** and **2a** were reacted simultaneously. [c]A purple LED was used.

With the optimised conditions, we investigated the substrate scope of **1** and **2** (Scheme 2). Non-substituted benzylamine (**1a**), relatively electron-rich 4-methylbenzylamine (**1b**), 4-methoxybenzylamine (**1c**), electron-deficient 4-(trifluoromethyl)benzylamine (**1d**), and 4-nitrobenzylamine (**1e**) successfully underwent the aerobic oxidation with **2a**, achieving modest to good yields of the corresponding benzimidazoles **3aa**, **3ba**, **3ca**, **3da**, and **3ea** respectively, although electron-poor **1d** and **1e** exhibited the relatively low yields in comparison with the electron-rich ones. In our previously reported benzimidazole synthesis using a flavin-catalysed reaction of toluenes and *o*-phenylenediamines (Scheme 1A), the desired benzimidazoles, such as **3aa** and **3da**, without electron-donating groups were not formed, because the oxidation potential of **4** (E*=+1.67 V vs SCE)[16] is insufficient to oxidise toluene (E_{ox}=+2.20 vs SCE).[8g,17] In contrast, benzylamines have relatively low oxidation potentials (E_{ox}=+1.08 vs SCE),[18] allowing the oxidative transformations. The reaction of **2a** with methylamines bearing heterocycles such as thiophenyl (**1e**) and the pyridyl group (**1f**) afforded the corresponding products **3fa** and **3ga** in yields of 84% and 72%, respectively. On the other hand, an aliphatic hexylamine (**1h**) did not work efficiently, resulting in the corresponding product **3ha** only in 10% yield. The present benzimidazole synthesis method was adaptable to various *o*-phenylenediamines. When **1a** was reacted with relatively electron-rich *N*-alkyl phenylenediamines **2b** and **2c** and electron-defficient *N*-chlorophenyl **2d**, the corresponding **3ab**, **3ac**, and **3ad** were produced in yields of 84%–86%. Despite the relatively low reactivity of the electron-deficient **2d**, the use of molecular oxygen (1 atm) and a higher temperature (60 °C) proved to be an effective for the efficient synthesis of **3ad**. Interestingly, *N*-unsubstituted phenylenediamine **2e** afforded the corresponding benzimidazoles **3ae** and **3ee** in yields of 75% and 62%. The use of *o*-phenylenediamines **2f** and **2g** with electron-donating substituents on the aromatic ring did not significantly affect the reaction, giving the corresponding products **3af** and **3ag** in yields of 79% and 78%, respectively, while *o*-phenylenediamines with an electron-withdrawing group **2h** required a longer reaction time to give **3ah** in 54% yield. When *cis*-1,2-diaminocyclohexane (**2i**) was used instead of *o*-phenylenediamines, the desired product **3ai** was not obtained.



Scheme 2 Scope of the photocatalysed synthesis of **3** through the aerobic oxidative benzimidazole formation of **1** and **2**. Reaction conditions: A mixture of **1** (1.0 mmol, 0.1 M) and **4** (2.5 mol%) in MeOH was irradiated using blue LED lamps (11 W, λ_{max} = 466 nm) while stirring under air (1 atm, balloon) at 40 °C for an appropriate time (t_1). **2** (0.5 equiv) was then added to the reaction mixture, and the mixture was stirred under irradiation at 40 °C for an appropriate time (t_2). The yield was calculated based on **2**. [a]**2** (0.33 equiv) was used. [b] The yield was determined by ^{1}H NMR measurement. [c]Under O_2 (1 atm, balloon). [d]At 60 °C.

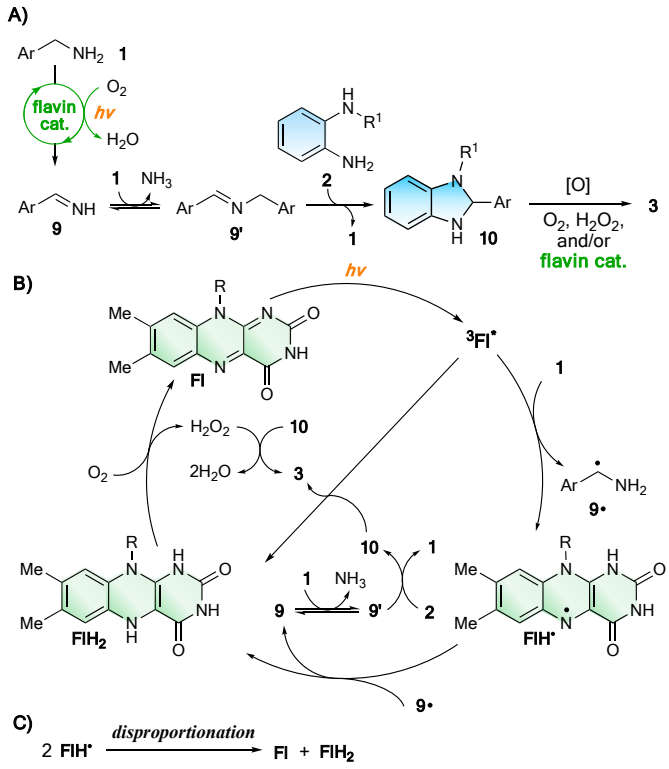
We next performed control experiments to investigate the reaction mechanism. Because the reaction of **1a** with **2a** to **3aa** proceeded efficiently at 25–30 °C (entries 9 and 10 of Table 1), the control experiments were conducted at this temperature range. The reaction proceeded with blue LED irradiation under air to give **3aa** in 87% yield, whereas **3aa** was hardly obtained without light irradiation or under molecular nitrogen (Scheme 3A). Thus, visible light irradiation and molecular oxygen are essential for this benzimidazole synthesis method. When the second step, *i.e.* the addition of **2a**, was omitted, the aerobic oxidation of **1a** gave *N*-benzylidenbenzylamine (**9'a**) in 44% yield (Scheme 3B). In contrast, the formation of **9'a** was inhibited in the presence of the radical inhibitor 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 1 equiv), suggesting that the aerobic oxidation of **1a** to **9'a** proceeds through a radical process. The reaction of **9'a** with **2a** in the absence of **4** gave **3aa** in 58% yield, and the yield of **3aa** increased to 73% in the presence of **4** (5 mol%) under blue LED irradiation (Scheme 3C). This suggested that **9'a** is an intermediate for the formation of **3aa** and that catalysis of **4** promotes not only the aerobic oxidation of **1a** but also the subsequent oxidative benzimidazole formation of **3aa**.



Scheme 3 Control experiments.

On the basis of the experimental results and the literature, a proposed reaction mechanism is shown in Scheme 4. The formation of benzimidazoles is proposed to proceed in three steps: i) flavin photocatalysed aerobic oxidation of **1** to **9**, which forms **9'** via condensation with **1**;[19,20] ii) dehydrative condensation of **9'** and **2** to form benzimidazoline (**10**); and iii) flavin-catalysed dehydrogenative aromatisation of **10** to form the desired product **3** (Scheme 4A). In the present system, flavin photocatalysis appear to play multiple roles in steps i and iii (Scheme 4B). The flavin catalyst **Fl** is excited by visible light irradiation to the triplet state ^{3}**Fl*** via the singlet state ^{1}**Fl***, resulting in a positive redox potential shift[8f] and catalysis of various reactions.[10a,21] Electron transfer and the subsequent proton transfer to ^{3}**Fl*** converts benzylamine (**1**) into benzylamine radical (**9**•).[8e] The electron transfer from **1** is supported by the Stern-Volmer plot for **1a** that showed a linear decrease in the emission intensity of **4** as the amount of **1a** increases (Figure S2). The radical **9**• further reacts with the formed radical flavin **FlH**• by hydrogen-atom transfer (HAT) to afford the reduced flavin **FlH$_2$** and benzylimine (**9**),[9] which undergoes condensation with **1** to form **9'**. Then, the nucleophilic attack of **2** towards **9'** occurs, forming **10** through intermolecular condensation and cyclisation. The radical flavin **FlH**• may also undergo a disproportionation reaction with another **FlH**• to form **Fl** and **FlH$_2$** (Scheme 4C).[22] As suggested by the control experiment in Scheme 3C, the subsequent dehydrogenative aromatisation from **10** to **3** occurs under O_2,

while the flavin catalyst slightly enhanced the process.[23] **FlH$_2$** is also produced by the dehydrogenative aromatisation of **10** into **3**. It is known that the reduced flavins such as **FlH$_2$** have a unique O_2-activating capacity and thus react with air (O_2) to produce the initial **Fl** and hydrogen peroxide.[10] The *in situ*-generated hydrogen peroxide is likely to decompose into water and oxygen under the present reaction conditions, but some hydrogen peroxide may promote the oxidation of **10** into **3**.[12,24] Therefore, the flavin photocatalytic reaction allows metal-free synthesis of benzimidazoles **3** via an aerobic oxidative multistep reaction of **1** and **2**, consuming only molecular oxygen, which is a sustainable oxidant produced by plants.



Scheme 4 (A) Possible mechanism underlying the flavin-photocatalysed aerobic oxidative benzimidazole formation of **1** and **2**, (B) plausible catalytic cycle of flavin, and (C) disproportionation of **FlH•**.

Conclusions

We successfully conducted an air-mediated metal-free oxidative multistep reaction of benzylamines with *o*-phenylenediamines, which allows facile synthesis of benzimidazoles. In this process, flavin organophotocatalysis played multiple roles in the dehydrogenative oxidation of benzyl amines, dehydrogenative aromatisation of benzimidazolines, and O_2 activation under visible light irradiation. Because the oxidation potential of the flavin catalyst is slightly higher than that of the amines, a series of benzylamines bearing electron-donating and withdrawing groups can be adapted to benzimidazole formation. This finding can be applied to the green and efficient formation of five-membered rings, such as benzoxazoles and benzothiazoles, and multistep oxidative reactions involving these rings.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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24. At this stage, the generation of water and H_2O_2 has not been experimentally confirmed. Proof of the exact mechanism remains a challenge.