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COMMUNICATION

Aerobic Cross-Dehydrogenative Coupling of Toluenes and *o*-Phenylenediamines by Flavin Photocatalysis for Facile Synthesis of Benzimidazoles

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Herein, we demonstrate green atom-economical synthesis of benzimidazoles via the flavin-photocatalysed aerobic oxidative cross-dehydrogenative coupling of toluenes and *o*-phenylenediamines. The proposed metal-free reaction proceeds in methanol/H_2O under visible light irradiation by consuming only molecular oxygen from atmospheric air and produces only water as waste.

Benzimidazole and its derivatives exhibit a broad range of biological and pharmaceutical activities (Fig. 1).[1] Therefore, much research has been conducted to develop diverse synthetic methods for benzimidazoles. Typically, they are produced via the dehydrative condensation of benzoic acids with *o*-phenylenediamines; however, this requires strong acidic conditions and/or high reaction temperatures.[2] To eliminate the harsh operating conditions, benzaldehydes have been used as substrates under oxidative conditions.[3] However, aldehydes are generally unstable, necessitating the use of excess amounts of expensive chemical oxidants for the transformation of benzaldehydes, which decreases atom and economic efficiency. Therefore, as an alternative greener method that overcomes these challenges, the sequential aerobic oxidative reaction of benzyl alcohols with *o*-phenylenediamines has been demonstrated.[4] The most straightforward method of these involves aerobic cross-dehydrogenative coupling (CDC).

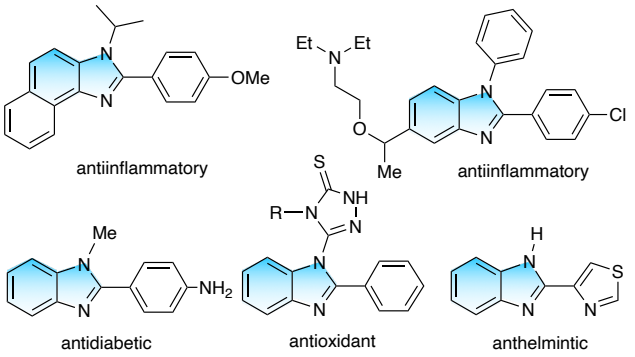

Fig. 1 Pharmaceutically important compounds containing benzimidazole core unit.

CDC is one of the most powerful tools for directly forming new C–X bonds (X = C, N, and O) from the C–H and X–H bonds of substrates under oxidative conditions.[5] CDC reactions do not require pre-functionalisation and de-functionalisation of substrates, thereby reducing the number of steps and stoichiometric reagents required. Furthermore, some CDC reaction can efficiently proceed with molecular oxygen (O_2) as the oxidant; O_2 is recognised as the ideal oxidant as it possesses economic and environmental advantages such as being sustainably abundant, inherently safe, cost-effective, atom-economical, and minimally polluting.[6] In addition, aerobic CDC generates only water, which is environmentally benign, as waste, making it an ideally atom-economical and green approach that combines the virtues of CDC and O_2-mediated processes.[7]

However, the CDC of toluenes and *o*-phenylenediamines without pre-functionalisation for benzimidazole production has been scarcely reported; furthermore, all the reported syntheses involved the use of metal-based catalysts such as Mn,[8] Bi/Mo,[9] Au/Mn,[10] Ag/Mn,[10] and Mn/Co/Fe catalysts.[11] Herein, as part of

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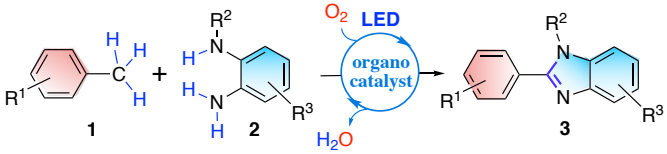
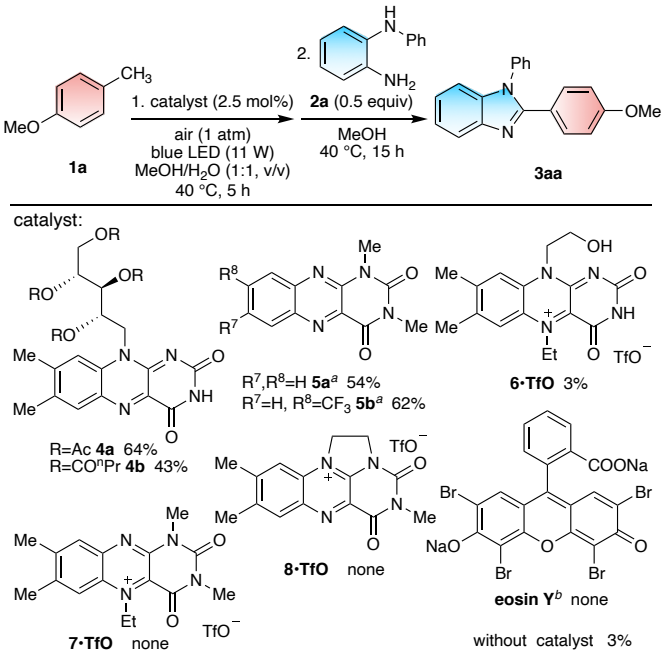
an ongoing investigation to develop an alternative metal-free synthetic method, we report the first aerobic CDC of toluenes **1** with *o*-phenylenediamines **2** to produce benzimidazoles **3** under metal-free conditions (Scheme 1). We chose for the reaction to be photo-organocatalysed by flavin, which promotes environmentally friendly oxidation under visible-light irradiation.[12–14] In particular, flavin compounds are known to catalyse the aerobic oxidation of benzylic C–H bonds under visible light irradiation.[12a,13c,15] We therefore hypothesised that the C–H activation of the benzylic C(*sp3*)–H group by flavin photocatalysis could be applied for the aerobic CDC of **1** with **2**.



Scheme 1 Atom-economical synthesis of **3** via catalytic aerobic CDC between **1** and **2**.

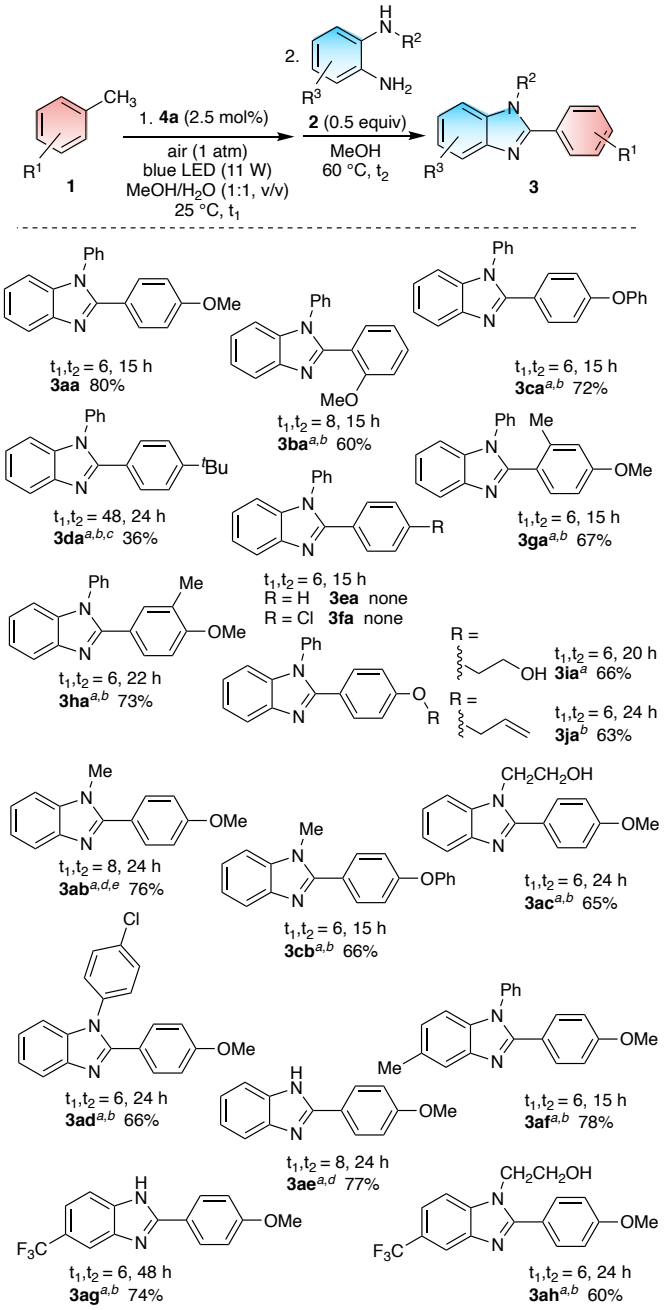
First, we investigated the catalytic activity of various flavin compounds (**4**–**8**) for the reaction of **1a** and **2a** under blue LED irradiation in MeOH/H_2O (1:1, v/v) under air (1 atm, balloon) at 40 °C (Scheme 2). Because **2a** is unstable under light irradiation, we carried out the reaction in a sequential manner: aerobic oxidation of **1a** was performed first by stirring for 5 h, followed by imidazole-ring formation by adding **2a** to the reaction mixture. The aerobic CDC of **1a** with **2a** was successfully achieved in the presence of the neutral flavin catalysts—the isoalloxazines **4** and alloxazines **5**—and the desired benzimidazole **3aa** was produced with yields in the range of 43–64%; to our delight, the simple **4a**, which can be readily derived by the acetylation of commercially available riboflavin (vitamin B_2),[16] exhibited the best result (64% yield) among the flavin catalysts tested. It is noteworthy that riboflavin is a sustainable organic compound that is industrially produced by microbial fermentation from glucose.[17] Without a catalyst, the reaction afforded only a 3% yield of **3aa**, confirming the catalytic activity of flavin. The cationic flavinium salts **6**-**8** and eosin Y did not work in this system.



Scheme 2 Effect of photocatalysts on the synthesis of **3aa** via the aerobic CDC of **1a** and **2a**. Reaction conditions: a mixture of **1a** (0.05 M) and catalyst (2.5 mol%) in MeOH/H_2O (1:1, v/v) was irradiated using blue LED lamps (11 W) while stirring under air (1 atm, balloon) at 40 ˚C for 5 h. A solution of **2a** in MeOH (0.025 M) was then added into the reaction mixture, and the mixture was stirred under irradiation at 40 ˚C for 15 h. Yield was determined by gas chromatography(GC) using biphenyl as an internal standard. [a] Purple LED was used. [b] Green LED was used.

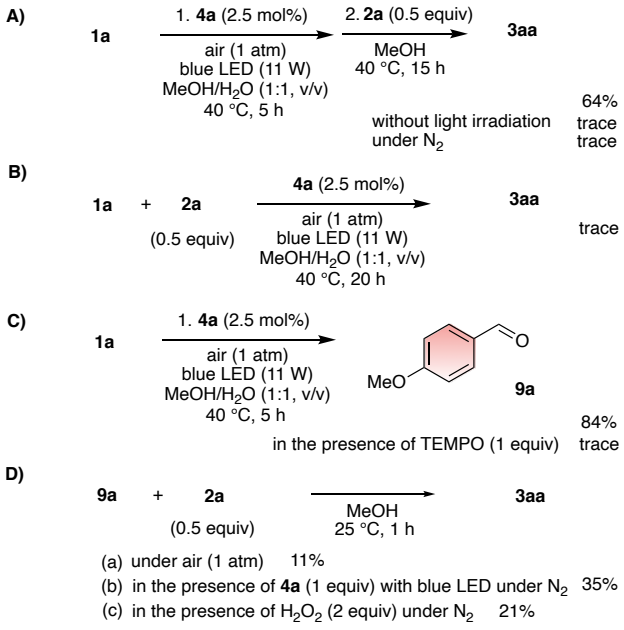
Further optimisation of the reaction conditions resulted in an 80% yield of the desired product **3aa** when the first step was carried out at 25 °C for 6 h and the second at 60 °C for 15 h (Scheme 3). Under these optimal conditions, we investigated the substrate scope for the aerobic CDC of **1** and **2**. The electron-rich methoxytoluenes **1a** and **1b** and phenoxytoluene **1c** successfully underwent aerobic CDC with **2a**, achieving 60–80% yields of the corresponding benzimidazoles **3aa**, **3ba**, and **3ca**. In contrast, the reaction of **2a** with 4-*tert*-butyltoluene (**1d**) yielded only 36% of **3da**. Meanwhile, the relatively electron-deficient non-substituted toluene (**1e**) and 4-chlorotoluene (**1f**) did not afford the corresponding products **3ea** and **3fa** under the chosen optimal conditions. This result displayed the limitations of this system, but it also suggested unique regio- and chemo-selectivity. Indeed, when 1-methoxy-3,4-dimethylbenzene (**1g**) and 1-methoxy-2,4-dimethylbenzene (**1h**) were used, the C–H bond of the methyl group located in the para position relative to the methoxy group was selectively functionalised to give **3ga** and **3ha** with 67 and 73% yields, respectively. Hydroxy and alkene moieties, which are often unstable under oxidative conditions, were tolerated, producing **3ia** and **3ja** with 66% and 63% yields, respectively. To our delight, the present benzimidazole synthesis is amenable to a variety of *o*-phenylenediamines. When reacted with **1a**, the relatively electron-rich *N*-alkyl phenylenediamines **2b** and **2c**, relatively

electron-deficient *N*-chlorophenyl **2d**, and non-substituted **2e** produced the corresponding **3ab**, **3cb**, **3ac**, **3ad**, and **3ae** with yields in the range of 65–77%. The electron-donating and electron-withdrawing substituents on the aromatic ring of *o*-phenylenediamines did not significantly influence reactivity, and the corresponding products **3af**, **3ag**, and **3ah** were obtained with 60–78% yields.



Scheme 3 Scope of the photocatalysed synthesis of **3** through the aerobic CDC of **1** and **2**. Reaction conditions: a mixture of **1** (1.0 mmol, 0.04 M) and **4a** (2.5 mol%) in MeOH/H_2O (1:1, v/v) was irradiated using blue LED lamps (11 W) while stirring under air (1 atm, balloon) at 25 °C for an appropriate time (t_1). A solution of **2** (0.5 equiv, 0.02 M) in MeOH was then added into the reaction mixture, and the mixture was stirred under irradiation at 60 °C for an appropriate time (t_2). [a] **2** (0.33 equiv). [b] *t*-BuOH/H_2O (1:1, v/v) was used as the solvent. [c] **4a** (10 mol%). [d] **4a** (1 mol%). [e] **1** (1.5 mmol, 0.04 M).

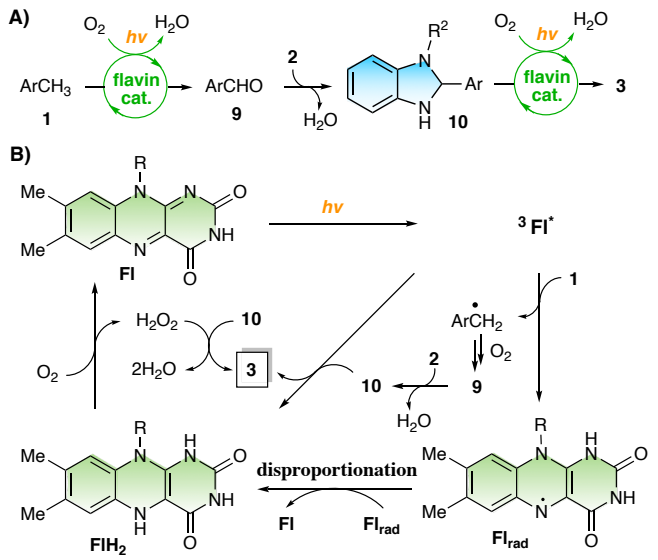
To gain insight into the reaction mechanism, control experiments were conducted. The reaction did not occur in the absence of light irradiation or under a molecular nitrogen atmosphere, whereas the reaction with light irradiation under air afforded **3aa** with 64% yield (Scheme 4A), revealing the essential role of visible light and molecular oxygen in this benzimidazole synthesis. When **1a** and **2a** were simultaneously reacted, the **3aa** yield was negligible; furthermore, the reaction mixture turned black, probably because of the decomposition of **2a** (Scheme 4B). Therefore, **2a** should be added after **1** is almost completely converted in the first step. When the second step, that is, the addition of **2a**, was omitted, benzaldehyde **9a** was obtained with an 84% yield (Scheme 4C). In sharp contrast, aerobic oxidation of **1a** hardly occurred in the presence of the radical inhibitor 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), indicating that the aerobic oxidation of **1a** proceeded through a radical process. The desired product **3aa** could be produced when **9a** reacted with **2a** under air (1 atm), but the yield was only 11% (Scheme 4Da); however, in the presence of 1 equiv. of **4a** under light irradiation, **3aa** was obtained with 35% yield even when the reaction was conducted under a molecular nitrogen atmosphere (Scheme 4Db). This suggests that catalysis by **4a** enhances not only the aerobic oxidation of **1a**, but also the subsequent oxidative imidazole ring formation of **3aa**.



Scheme 4 Control experiments.

Based on the experimental results and relevant literature, a plausible three-step reaction mechanism was proposed (Scheme 5): the flavin-catalysed aerobic oxidation of **1** to **9**, the dehydrative condensation of **9** and **2** to the benzimidazoline **10**,

and the flavin-catalysed dehydrogenative (oxidative) aromatisation of **10** to **3** (Scheme 5A). With two of the three steps involving oxidation, the redox catalysis by flavin plays multiple roles (Scheme 5B). Upon photo-irradiation, the flavin catalyst **Fl** is known to generate excited ^{3}**Fl*** via the intermediary ^{1}**Fl***, which possesses a positively shifted redox potential,[15b] resulting in diverse catalysis.[12a,18] By generating $ArCH_2^•$ through electron transfer to ^{3}**Fl***, the benzylic C–H bonds of **1** are oxidatively activated to form the corresponding aldehyde **9**,[13c,15] which then undergoes nucleophilic attack by **2**, forming **10** through dehydrative condensation. As suggested by the control experiments in Scheme 4Db, the flavin catalyst enhanced the dehydrogenative aromatisation of **10** to **3**.[16,19] Indeed, the generation of **10aa** (m/z = 303.1492) was confirmed by electrospray ionisation mass measurement of the reaction mixture (Figure S1) when **9a** and **2a** were reacted in the absence of the flavin catalyst (Scheme 4Da). In contrast, the intermediate **10aa** disappeared when the same reaction was conducted in the presence of **4a** under light irradiation, confirming that flavin catalysis enhanced the conversion of **10** (Figure S2). The radical flavin $\mathbf{Fl_{rad}}$ generated via single-electron transfer from **1** undergoes disproportionation with another $\mathbf{Fl_{rad}}$ to form **Fl** and the reduced flavin $\mathbf{FlH_2}$ that received two electrons.[20] The reduced $\mathbf{FlH_2}$ is also generated by the dehydrogenative aromatisation of **10** to **3**, as mentioned above. Reduced flavins such as $\mathbf{FlH_2}$ possess unique O_2-activation ability, and thus react with air (O_2) to give the initial **Fl** and hydrogen peroxide.[12] Hydrogen peroxide generated in situ by flavin catalysis likely decompose to water and O_2 in the present photo-irradiation condition,[21] but some hydrogen peroxide supports the conversion of **10** to **3** (Scheme 5B), as revealed by the fact that hydrogen peroxide accelerates the reaction of **9a** and **2a** to form **3aa** (Scheme 4Da and c). Therefore, flavin photocatalysis enables the atom-economical and green synthesis of **3** via simple aerobic CDC between **1** and **2**, in which only oxygen in atmospheric air is consumed as the oxidant and only water is generated as waste.



Scheme 5 Possible mechanism of the flavin-photocatalysed aerobic CDC of **1** and **2**.

Conclusions

We achieved the first successful metal-free aerobic CDC between toluenes and *o*-phenylenediamines for the facile and atom-economical synthesis of benzimidazoles. The process involved aerobic oxidative transformation under visible light irradiation, in which organo- and photocatalysis by flavin played multiple roles in the C–H activation of toluenes, dehydrogenative aromatisation of benzimidazoline, and O_2-activation. The catalyst is readily prepared from the sustainable riboflavin that is commercially produced by microbial fermentation from glucose. The substrate scope is limited at this stage, however, this finding opens up new possibility of the riboflavin-based catalysis and provides a novel approach for metal-free aerobic CDC reactions, enabling green multistep and multicomponent syntheses.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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21. Hydrogen peroxide existed in the reaction mixture after the completion of the reaction was roughly estimated to be less than 0.01 equiv by potassium iodide-starch paper test.