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Flavin-Catalyzed Aerobic Oxidative C–C Bond Formation by Metal/light-Free Cross-Dehydrogenative Coupling

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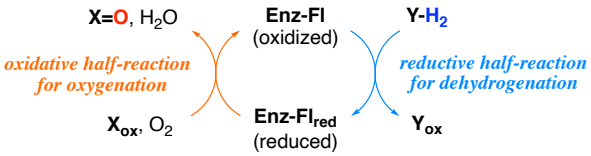
Abstract. Biomimetic flavin catalysts enable green and selective aerobic oxidative transformations. However, most previous studies tended to focus on reproducing the enzymatic function of flavin monooxygenase, thereby limiting the applications of flavin catalysts to oxygen-atom transfer reactions. We herein report a cross-dehydrogenative coupling (CDC) between the sp^3 C–H bond of tetrahydroisoquinolines and the sp^3 and sp^2 C–H bonds of carbon nucleophiles, such as α-methylene carbonyl compounds, nitromethane, and indoles, for C–C bond formation promoted by flavin catalysts. Flavin catalysis enables the oxidative C–H activation of tetrahydroisoquinolines and the efficient activation of molecular oxygen (1 atm) under mild and metal/light-free conditions, thus facilitating a green aerobic CDC that generates benign water as the sole by-product.

Keywords: C-C coupling; dehydrogenation; flavin; aerobic oxidation; organocatalyst

In living organisms, binding of naturally occurring flavins such as riboflavin (vitamin B_2), flavin mononucleotide (FMN), and flavin adenine dinucleotide (FAD) to proteins is necessary for many diverse and complex roles that sustain life.[1] Flavin monooxygenase (FMO), a flavoprotein, catalyzes the oxygenation of substrate $\mathbf{X_{ox}}$ to the oxidized product **X=O** (oxidative half-reaction of Scheme 1) by consuming an electron or a hydride source $\mathbf{Y\text{-}H_2}$ such as NAD(P)H (reductive half-reaction of Scheme 1). By mimicking the enzymatic functions of FMO, many simple cationic flavin compounds have been developed as unique organocatalysts for in vitro synthetic organic reactions.[1c,2] Under mild conditions, flavin catalysts efficiently activate molecular oxygen, which is an ideal oxidant with many advantages, such as sustainable abundance, safety, cost-effectiveness, atom economy, and minimal pollution. Therefore, flavin catalysts are used as a unique tool for green and selective aerobic oxidative transformations, a major

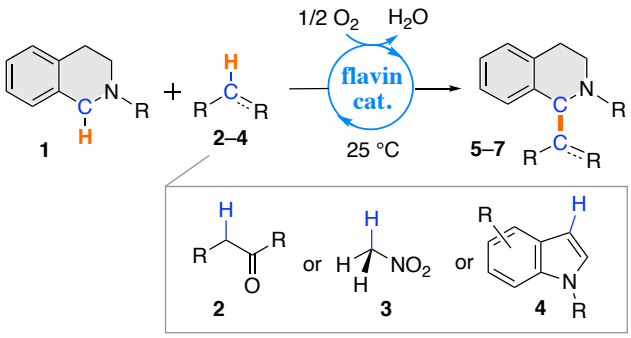


Scheme 1. Catalytic cycles of flavoenzymes comprising oxidative and reductive half-reactions.

but highly rewarding challenge in modern chemistry.[1c,3,4] However, previous studies on cationic flavin catalysts primarily focused on reproducing the enzymatic function of FMO. Consequently, their applications are mostly limited to oxygen-atom transfer reactions using the oxidative half-reaction for substrate conversion (Scheme 1).[3,5] A novel approach is required to explore the potential applications of flavin catalysis.

C–C bond formation using cross-dehydrogenative coupling (CDC) between the two C–H bonds of substrates has emerged as a useful strategy for step- and atom-economical synthetic methods, because it can bypass the pre-activation of substrates.[6] In particular, aerobic CDC, which uses molecular oxygen under mild conditions, is attracting significant interest as an ideal green approach because of its environmental and economic advantages. The CDC reaction involving the α-C–H bond of nitrogen in tertiary amines was pioneered by Murahashi[7] and Li.[8] Various nucleophiles have been used to intercept activated amines.[9] Among these, the oxidative Mannich reaction using α-methylene carbonyl compounds as carbon nucleophiles is recognized as a fundamental C–C bond-formation step in organic synthesis. The aerobic version of the oxidative Mannich reaction is being actively developed because it provides an easy and atom-economical access to synthetically and biologically important *β*-aminocarbonyl products from simple starting materials and molecular oxygen.[10] However, these

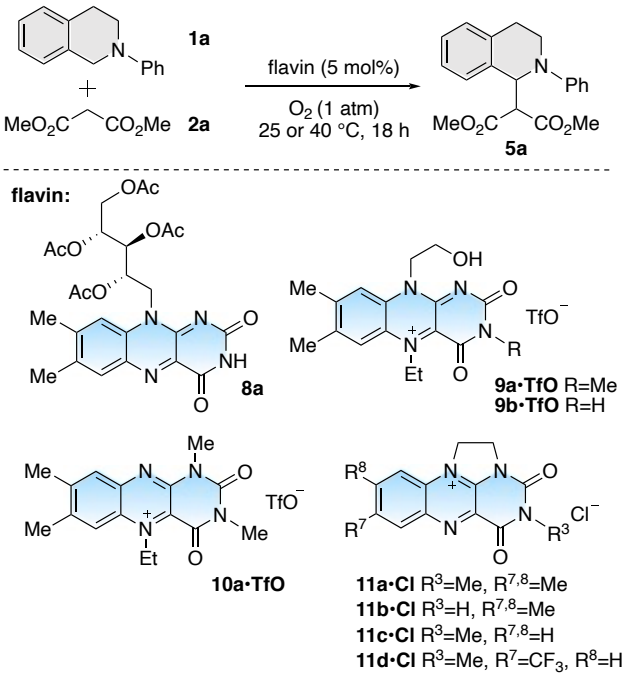
generally require transition metal-based catalysts,[10a,b,f,h-j,p,q] photo-irradiation,[10d,g,n,r] or radical processes such as autooxidation.[10c-e,i-p] An alternative organocatalytic approach, performed under metal/light-free and mild conditions without the formation of highly reactive radical intermediates, is needed for facile and atom-economical synthesis that fulfills the requirements of green and sustainable chemistry. This study discusses the application of the reductive half-reaction of the flavin redox cycle for the C–H activation of the sp^3 C–H bond of tetrahydroisoquinolines (Scheme 1). In contrast to the oxidative half-reaction for oxygenation, the reductive half-reaction for dehydrogenation is underutilized,[11] although various enzymatic dehydrogenations of flavoprotein oxidases in living organisms proceed through the reductive half-reactions.[12] Herein, we report the aerobic oxidative Mannich reaction of *N*-aryl tetrahydroisoquinolines **1** with α-methylene carbonyl compound **2** via flavin-catalyzed CDC at ambient temperature under metal/light-free conditions (Scheme 2). This flavin-catalyzed CDC can also be used for the C–C bond formation of **1** with other carbon nucleophiles bearing sp^3 and sp^2 C–H bonds, such as nitromethane (**3**) and indole **4**.



Scheme 2. Flavin-catalyzed C–H activation of tetrahydroisoquinolines **1** for aerobic oxidative C–C bond formation with carbon nucleophiles **2**–**4**.

We first investigated the effects of flavin catalysts **8**–**11**[13] on the CDC reaction between tetrahydroisoquinoline (**1a**) and dimethyl malonate (**2a**), which is classified as an oxidative Mannich reaction (Table 1). In the presence of **8**–**11** (5 mol%), a mixture of **1a** and **2a** (8.7 equiv) was stirred under molecular oxygen (1 atm, balloon) at 40 °C for 18 h without any solvent. The redox potentials of the first single-electron reduction (E_1), determined by cyclic voltammetry (CV) in a solution of CH_3CN (1.0 mM), are shown in Table 1, which can be used to compare the redox activities of different flavin catalysts.[13a] Although neutral riboflavin tetraacetate (**8a**) and riboflavin-derived cationic flavins, 5-ethyl isoalloxazinium salts **9•TfO** and 5-ethyl alloxazinium salt **10•TfO**, hardly promoted the CDC reaction (entries 1-4), a riboflavin-derived 1,10-ethylene-bridged alloxazinium salt **11a•Cl** successfully afforded the desired product **3a** in 49% yield by the CDC between two sp^3 C–H bonds of **1a** and **2a** (entry 5). The poor result for **11b•Cl** without an N^3-methyl substituent indicates the importance of protecting the acidic N^3–H proton of the flavin catalyst (entry 6). The substituents at the 7,8-position of the flavin ring system are known to affect the redox potential and catalytic activity; hence, we attempted to use 1,10-ethylene-bridged alloxazinium salts without substituent **11c•Cl** and with an electron-withdrawing CF_3 substituent **11d•Cl** to investigate the effect of the redox potential on the catalytic activity (entries 7 and 8). Although no linear correlation between the catalytic activity and redox potential was observed, electron-poor **11d•Cl** with a relatively positive

Table 1. Effect of flavin catalysts on aerobic CDC between **1a** and **2a**.[a]



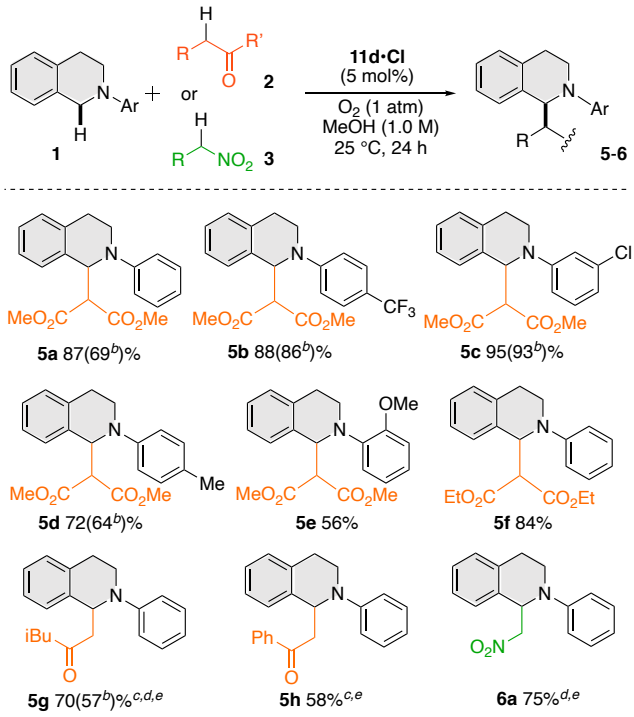
Entry	Flavin	E_1[b] (V vs Fc/Fc^+)	Yield (%)
1	**8a**	-1.18	10
2	**9a•TfO**	-0.136[c]	3
3	**9b•TfO**	-0.118	3
4	**10a•TfO**	-0.425[c]	9
5	**11a•Cl**	-0.650[d]	49
6	**11b•Cl**	-0.608[d]	12
7	**11c•Cl**	-0.564[d]	32
8	**11d•Cl**	-0.426[d]	72
9[e]	**11d•Cl**		86

[a] Conditions: **1a** (0.3 mmol), **2a** (8.7 eq.), and flavin (5 mol%) under O_2 (1 atm, balloon) at 40 °C. The yield was determined by ^1H NMR spectroscopy using 1,3,5-trioxane as an internal standard. [b] The electrochemical potential (E_1) of each flavin was determined using the relationship $E = (E^p_c+E^p_a)/2$ relative to Fc/Fc^+. [c] From Ref. 13a. [d] Measured using the triflate salts of flavins, **11•TfO**. [e] **2a** (2.0 eq.) in MeOH (0.3 mL) at 25 °C.

reduction potential (-0.426 V vs. Fc/Fc^+) displayed the best result compared with the relatively electron-rich flavins **11a•Cl** and **11c•Cl** showing negative reduction potentials (–0.650 and -0.564 V vs. Fc/Fc^+; entries 5, 7, and 8). Therefore, we chose **11d•Cl** as the appropriate catalyst for the subsequent reactions. Further optimization of the reaction condition using 2 equiv of **2a** in MeOH at 25 °C showed that the CDC reaction smoothly proceeded, affording the desired **3a** in 86% yield (entry 9 of Table 1 and Table S1).

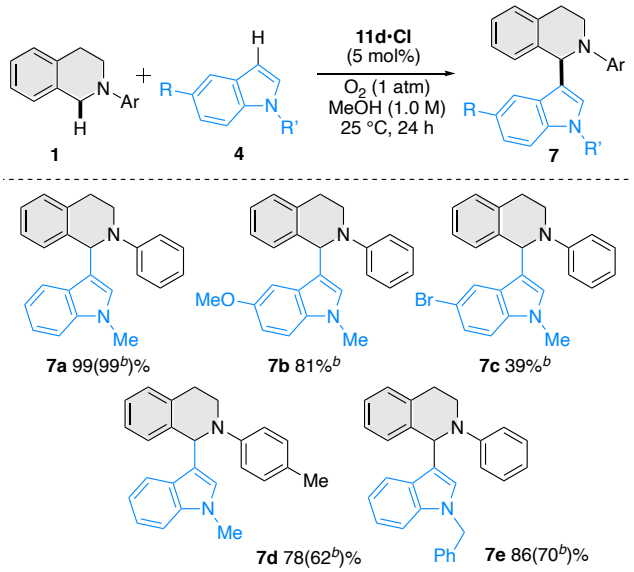
Using the optimized conditions as the standard, we elucidated the substrate scope (Table 2). A series of *N*-phenyl isoquinolines bearing electron-withdrawing and electron-donating substituents on the phenyl group successfully underwent CDC coupling with **2a** to afford the corresponding products **5a**–**5e** in 56–93% yields.[14] In addition to the dimethyl and diethyl malonate esters giving **5a** and **5f**, non-activated ketones, such as isobutyl methyl and phenyl methyl ketones, could be employed as nucleophiles to obtain **5g** and **5h** although their yields (70% and 58%, respectively) were slightly lower than those obtained using malonate esters. The present flavin-catalyzed aerobic C–H activation of **1** can be applied not only to the oxidative Mannich reaction using carbonyl

Table 2. Flavin-catalyzed aerobic CDC reaction of **1** with **2** and **3**.[a]



[a] Conditions: **1** (1 M), **2** (2 M, 2 equiv), and **11d•Cl** (5 mol%) in MeOH under O_2 (1 atm, balloon) at 25 °C for 24 h. Yield was determined by ^1H NMR using 1,3,5-trioxane or 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield. [c] A mixture of **1** (1 M) and **11d•Cl** (5 mol %) in MeOH was stirred for 24 h, following which **2** (2 equiv) and AcOH (3.0 equiv) were added, and the mixture was stirred for 24 h. [d] **2** or **3** (5.0 equiv) was used. [e] At 40 °C.

Table 3. Flavin-catalyzed aerobic CDC reaction of **1** with **4**.[a]

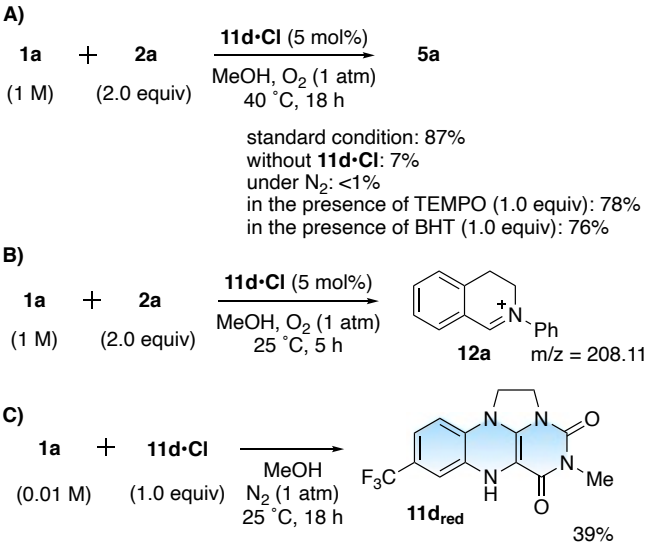


[a] Conditions: **1** (1 M), **4** (2 M, 2 equiv), and **11d•Cl** (5 mol%) in MeOH under O_2 (1 atm, balloon) at 25 °C for 24 h. Yield was determined by ^1H NMR using 1,3,5-trioxane or 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield.

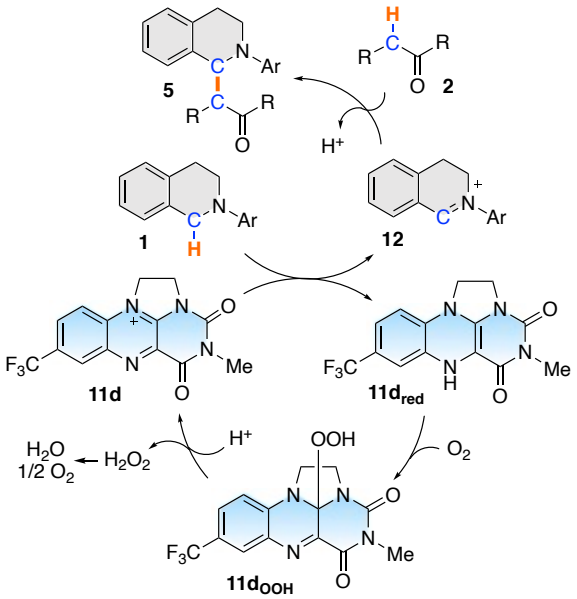
compound **2** as the carbon nucleophile, but also to the oxidative aza-Henry-type reaction using nitromethane (**3a**) as the nucleophile. Aerobic oxidative CDC coupling between **1a** and **3a** successfully produced the corresponding product **6a** in 75% yield.

In addition to carbon nucleophiles with sp^3 C–H bonds, indoles **4** bearing sp^2 C–H bonds underwent CDC with **1** (Table 3). The corresponding indolyl isoquinolines **7a** and **7b** were obtained in 99% and 81% yields, respectively. In contrast, the relatively electron-deficient indole afforded the corresponding product **7c** in a modest yield (39%). Isoquinolines **7d** and **7e** were also produced in 62 and 70% yields, respectively, by the reaction using *N*-tolyl isoquinoline and N-benzylindole.

Control experiments were performed to gain insights into the reaction mechanism. Aerobic CDC between **1a** and **2a** did not work well in the absence of flavin catalyst **11d•Cl** and under anaerobic N_2 condition (Scheme 3A). Hence, the flavin catalyst and molecular oxygen are essential for promoting the present system. Interestingly, when 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 3,5-dibutyl-4-hydroxytoluene (BHT) were used as radical inhibitors, **5a** was obtained in 78% and 76% yields, respectively, without a significant loss of the yield. This finding suggests that the present flavin-catalyzed system mainly proceeds through the non-radical hydride-transfer pathway,[15] in contrast to the previously reported systems that usually undergo the formation of highly reactive radical intermediates.[10c,e,k-m,o,16]



Scheme 3. Control experiments.



Scheme 4. Plausible mechanism of flavin-catalyzed aerobic CDC between **1** and **2**.

Based on the experimental results and reported literature, a plausible mechanism for flavin-catalyzed CDC is shown in Scheme 4. Flavin catalyst **11d** promotes the C–H activation of **1** through dehydrogenative oxidation to produce the corresponding iminium intermediate **12** and reduced flavin **11d**$_{red}$. The formation of **12a** (*m/z* = 208.1121) was confirmed using electrospray ionization (ESI) mass spectrometry of the reaction mixture obtained after stirring for 5 h under standard conditions (Scheme 3B, Figure S1). We also performed the stoichiometric reaction of **11d** with **1a** under anaerobic N_2 atmosphere in the dark for 18 h (Scheme 3C and Figure S2). The generation of **12a** was confirmed by the ESI mass spectrometry of the reaction mixture, and the intermediate **11d**$_{red}$ could be isolated in 39% yield. This result supported the non-photoinduced hydride transfer process between **11d** and **1**, as shown in Scheme 4.[17] The electrophilically activated intermediate **12** undergoes nucleophilic attack of carbon nucleophile **2**. Thus, C–C bond formation affords 1-alkylated isoquinoline **5** (Scheme 4).[7a,18] Reduced flavin **11d**$_{red}$ reacts with molecular oxygen to give **11d**$_{OOH}$, which is converted to the initial **11d** with the formation of hydrogen peroxide.[19] The hydrogen peroxide present in the reaction mixture of **5a** after the reaction completion was approximately estimated to be <0.01 equiv by a potassium iodide starch paper test. Most of the hydrogen peroxide generated in situ is likely to decompose to water and O_2 after reaction completion under the present conditions. Therefore, the present oxidative C–C bond formation via aerobic CDC is conducted under metal/light-free conditions through a green, atom-economical manner in which only environmentally friendly molecular oxygen is consumed.

In conclusion, we successfully developed a novel flavin-catalyzed aerobic CDC system for C–C bond formation under metal- and light-free conditions at ambient temperature. The oxidative C–H functionalization of isoquinolines was conducted by the non-radical dehydrogenative oxidation of the biomimetic flavin catalyst, in which 1 atm of molecular oxygen was used as an eco-friendly terminal oxidant. Thus, the aerobic oxidative Mannich-type reaction with α-methylene carbonyl compounds, aza-Henry-type reaction with nitromethane, and indolylation were successfully preformed. This approach would facilitate the design of a novel methodology establishing C–C bond formations and multi-step reactions without the need for metal, light, or toxic and expensive reagents through aerobic CDC of various substrates, enabling atom-economical and green organic synthesis.

Experimental Section

Typical Procedure for Catalytic Synthesis of 5a. A mixture of **1a** (209 mg, 1.0 mmol), **2a** (264 mg, 2.0 mmol, 2.0 equiv), **11d•Cl** (17.9 mg, 0.050 mmol, 0.05 equiv), and methanol (1 mL, 1.0 M) was stirred at 25 °C (water bath) for 24 h under O_2 (1 atm, balloon). The yield was determined to be 87% by the ^{1}H NMR measurement of the reaction mixture using 1,3,5-trioxane as an internal standard. After the solvent was removed by evaporation, the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate/ *t*-butyl alcohol = 1500/50/3, v/v) afforded **5a** (234 mg, 69%) as a colorless oil. The results of similar reactions are summarized in Table 2.

Typical Procedure for Catalytic Synthesis of 7a. A mixture of **1a** (62.7 mg, 0.30 mmol), N-methylindole (**4a**, 79.1 mg, 0.60 mmol, 2.0 equiv), **11d•Cl** (5.39 mg, 0.015 mmol, 0.05 equiv), and methanol (0.3 mL, 1.0 M) was stirred at 25 °C (water bath) for 24 h under O_2 (1 atm, balloon). The yield was determined to be 99% by the ^{1}H NMR measurement of the reaction mixture using 1,3,5-

trioxane as an internal standard. After the solvent was removed by evaporation, the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate/ *t*-butyl alcohol = 500/25/1, v/v) afforded **7a** (96.2 mg, 99%) as a pale yellow solid. The results of similar reactions are summarized in Table 3.

Acknowledgements

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[14] Because some products were easily adsorbed on silica gel during column chromatography, the isolated yield was often lower than the yield determined by ^{1}H NMR measurements of the crude product.

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