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ARTICLE

Aerobic oxidative C–C bond formation through C–H bond activation catalysed by flavin and iodine

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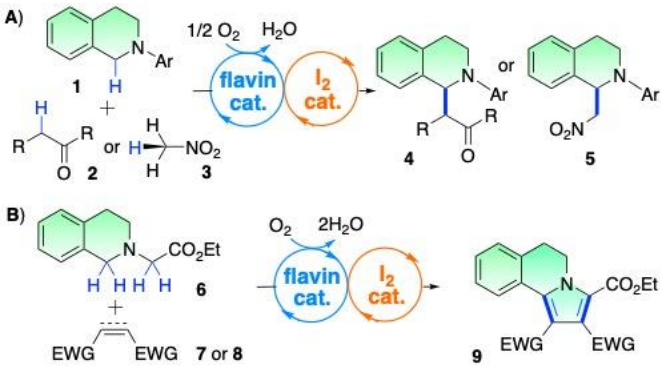
We report a metal/light-free aerobic oxidative C-C bond formations using a sp^3 C-H bond activation of tetrahydroisoquinolines catalyzed by flavin and iodine. The dual catalytic system enabled the oxidative Mannich and aza-Henry reactions by the cross-dehydrogenative coupling between two sp^3 C-H bonds. Furthermore, the flavin-iodine-couped catalysis was applied to the synthesis of pyrrolo[2,1-*a*]isoquinolines through the sequential oxidative 1,3-dipolar cycloaddition and dehydrogenative aromatization. The biomimetic flavin catalysis efficiently activates molecular oxygen, thus the non-metal dual catalytic system enables green oxidative transformation using molecular oxygen as an environmentally friendly terminal oxidant which generates benign water.

Introduction

Molecular iodine (I_2) has recently attracted considerable attention as a readily available and easy-to-handle redox catalyst, enabling diverse oxidative transformations under light/metal-free conditions.[1] In particular, iodine-catalysed oxidative C–H functionalization has been recognized as a rapidly growing area in synthetic organic chemistry because of its availability and applications in the synthesis of pharmacologically important molecules and natural products.[2] Generally, I_2-catalysed oxidative transformations require an excess amount of oxidants, such as *t*BuOOH, H_2O_2, oxone, and DMSO, to reoxidise in-situ generated I^- to I_2, which is a relatively expensive process and/or generates large amounts of waste. In the oxidation reactions, the use of molecular oxygen (O_2) as a terminal oxidant has been recognised as an ideal green approach owing to its sustainability, abundance, safety, cost-effectiveness, atom-economy, and environmental friendliness.[3] However, because the oxidising power of O_2 is not sufficient to promote the oxidation of I^- efficiently under mild conditions, the development of useful aerobic I_2-catalysed reactions remains challenging. Recently, we reported a novel O_2-mediated iodine-catalysed reaction system, in which a biomimetic flavin catalyst[4] was used for O_2 activation.[5] C–X bond formation (X = C, O, N, S, etc.) via catalytic cross-dehydrogenative coupling (CDC) between the C–H and X–H bonds of substrates is a powerful tool for step- and atom-economical syntheses, as the pre-activation of starting materials can be avoided in these processes.[6] Since the flavin–iodine-coupled catalyst enables the use of O_2 in I_2-catalysed processes, which conventionally require persulfates and peroxides, several C–S[5b-d] and C–N[5e-h] bond formation reactions using the flavin–iodine-catalysed aerobic CDC between C–H, N–H, and S–H bonds have been reported. However, this dual catalytic system has not been applied to C–C bond formation, although the construction of C–C bonds through C–H activation is of central importance in synthetic organic chemistry. Herein, we report the first example of a C–C bond formation reaction catalysed by flavin and iodine. The flavin–iodine-coupled catalyst enables the C–H activation of tetrahydroisoquinolines **1** and tetrahydroisoquinolinylacetate **6**. Therefore, it was successfully applied to the oxidative Mannich reactions of α-methylene carbonyl compounds **2**, the oxidative aza-Henry reaction of nitromethane (**3**), and the oxidative synthesis of pyrrolo[2,1-*a*]isoquinolines **9**, which was performed via tandem 1,3-dipolar cycloaddition and aromatisation with dipolarophiles **7** and **8** (Scheme 1).



Scheme 1. Flavin–iodine-catalysed C–C bond formation via α-C–H bond activation of tertiary amines applied to (A) oxidative Mannich and aza-Henry-type reactions and (B) oxidative synthesis of pyrrolo[2,1-*a*]isoquinolines promoted by tandem 1,3-dipolar cycloaddition and aromatisation.

Results and discussion

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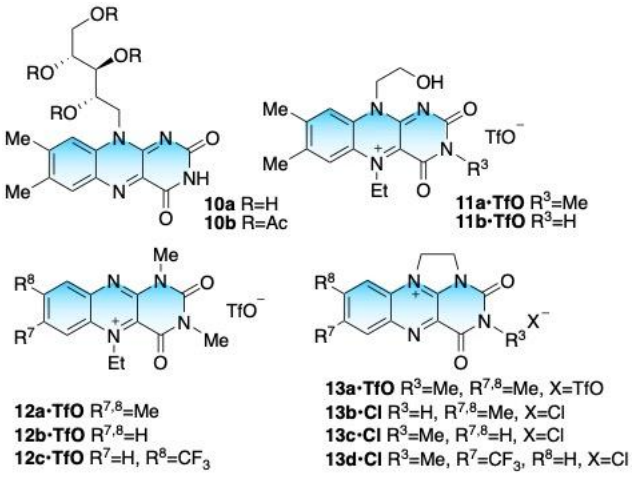
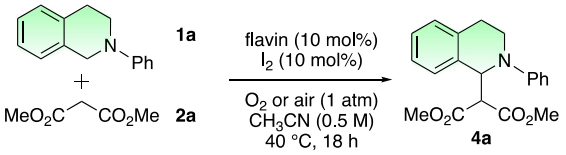
We first applied the flavin–iodine-catalyst system to the oxidative Mannich reaction of tertiary amines and α-methylene carbonyl compounds. This is because the oxidative Mannich reaction is an important C–C bond formation reaction to produce synthetically and biologically important β-aminocarbonyl products from simple starting materials.[7] I_2 is known to catalyse the oxidative Mannich reaction by activating the α-C–H bond of nitrogen in tertiary amines under light-free conditions. However, the I_2-catalysed reactions require relatively expensive stoichiometric oxidants such as H_2O_2[8] and *t*BuOOH.[9] Although the aerobic version proceeds under mild metal- and light-free conditions, no successful examples have been reported.

We investigated the effects of various flavin catalysts on the oxidative Mannich reaction involving CDC between 2-phenyl-tetrahydroisoquinoline (**1a**) and dimethyl malonate (**2a**). In the presence of flavin catalysts **10–13** (10 mol%, Scheme 2)[10] and I_2 (10 mol%), a mixture of **1a** and **2a** (3.0 equiv) was stirred in CH_3CN under O_2 (1 atm, balloon) at 40 °C for 18 h (Table 1). To clarify the redox activity of the flavin catalysts, the redox potentials of the first single-electron reduction (E_1) steps were determined by cyclic voltammetry (CV) in a solution of CH_3CN (1.0 mM); these values are listed in Table 1.[10] Although neutral riboflavin (**10a**) and riboflavin tetraacetate (**10b**) did not afford good results (entries 1 and 2), 7,8-dimethylflavinium salts **11a•TfO**, **12a•TfO**, and **13a•TfO**, which were readily prepared from inexpensive and commercially available **10a**,[10a] successfully promoted the CDC reaction, thereby affording the desired coupling product **4a** in 21% to 61% yields (entries 3, 5, and 10). The corresponding N^3-non-substituted isoalloxazinium **11b•TfO** afforded better yields than N^3-methylated **11a•TfO** (entry 4). However, the N^3-non-substituted 1,10-ethylene-bridged alloxazinium salt **13b•Cl** displayed lower activity compared to **13a•TfO** (entry 11). An N^3-alkyl substituent is often required to control the effect of acidic imide protons, although it decreases the oxidising power of the catalyst. To investigate the effects of substituents on the catalytic activity, we performed these reactions using electron-deficient alloxazinium salts, such as 7,8-non-substituted **12b•TfO** and **13c•Cl** and trifluoromethyl-substituted **12c•TfO** and **13d•Cl**. Among the 5-ethyl-alloxazinium salts (**12**), **12c•TfO**, which showed the most positive potentials of −0.168 V vs Fc/Fc^+, afforded **4a** in the highest yield, followed by **12b•TfO** and **12a•TfO** (entries 5–7). The same was observed for 1,10-ethylene-bridged alloxaziniums **13•Cl**. Thus, the most efficient catalyst was **13d•Cl** with relatively positive potentials of −0.426 V vs. Fc/Fc^+ rather than **13c•Cl** (entries 12 and 13). The large structural difference in the π-conjugated system makes it difficult to directly compare the catalytic activities of **12**s and **13**s. However, this apparent correlation between yield and redox potential for the same series of flavin catalysts reveals that flavin catalysis plays a crucial role in the aerobic CDC reaction. Among the 11 flavin catalysts tested, **12c•TfO** displayed the best yield (81%, entry 7). This CDC reaction was also performed under air (1 atm, balloon) instead of pure O_2, without significant decrease in efficiency; the desired product **4a** was obtained in 74% and 73% yields in the presence of **12c•TfO** and **13d•Cl**, respectively (entries 8 and 14). Recently, the aerobic oxidative Mannich reaction under pure O_2 (1 atm) was catalysed solely by the 1,10-ethylene-bridged alloxazinium salt **13d•Cl** without an iodine catalyst.[10c] Indeed, in the absence of I_2, **13d•Cl** afforded **4a** in 64% yield, whereas the combined use of **13d•Cl** and I_2 afforded a better yield of 73% (entries 14 and 15). In the absence of I_2, the aerobic oxidative Mannich reaction hardly proceeded in the presence of the best catalyst, **12c•TfO**. However, the combined use of **12c•TfO** and I_2 afforded **4a** in 74% yield (entries 8 and 9). The catalyst **12c•TfO** exhibits little catalytic activity by itself but plays a crucial role in promoting the iodine-catalysed process, as described below. Therefore, we chose **12c•TfO** as the optimal catalyst for the present iodine-catalysed process.



Scheme 2. Structures of flavin **10** and flavinium salts **11–13**.

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

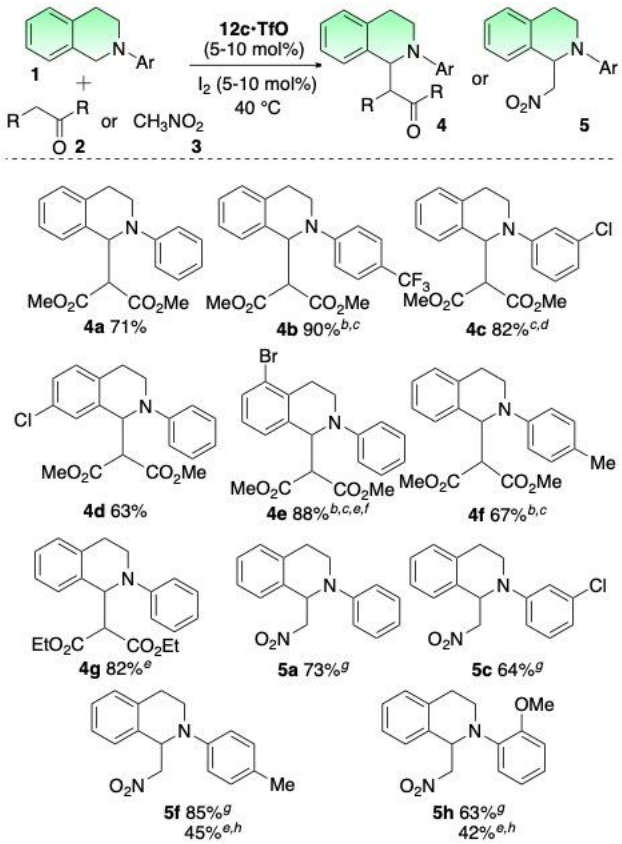


Entry	Flavin	E_1[b] (V vs Fc/Fc^+)	Yield (%)
1	**10a**	–	2
2	**10b**	−1.18	1
3	**11a•TfO**	−0.136	21
4	**11b•TfO**	−0.118	28
5	**12a•TfO**	−0.425	37
6	**12b•TfO**	−0.326	64
7	**12c•TfO**	−0.168	81
8	**12c•TfO**	− 0.168	74[d]
9	**12c•TfO**	−0.168	20[d,e]
10	**13a•TfO**	−0.650	61
11	**13b•Cl**	−0.608[c]	35
12	**13c•Cl**	−0.564[c]	39
13	**13d•Cl**	−0.426[c]	75
14	**13d•Cl**	−0.426[c]	73[d]
15	**13d•Cl**	−0.426[c]	64[d,e]

[a]Conditions: **1a** (1 M), **2a** (3.0 eq.), flavin (10 mol%), and I_2 (10 mol%) in CH_3CN under O_2 (1 atm) at 40 °C for 18 h. Yield was determined by ^1H NMR using 1,3,5-trioxane and 1,3,5-trimethoxybenzene as an internal standard. [b]From Refs 10. [c]The TfO salts were used for electrochemical measurements. [d]Under air (1 atm). [e]Without I_2.

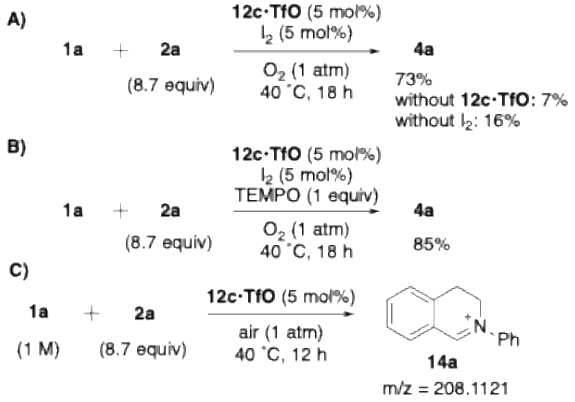
Further optimisation of the reaction conditions revealed that **4a** was obtained in 79% yield (71% as an isolated yield) when a mixture of **1a** and **2a** was stirred in the presence of **12c•TfO** (5 mol%) and I_2 (5 mol%) under air (1 atm, balloon) at 40 °C for 48 h (Table S1). Using these optimised conditions, we elucidated the substrate scope for this reaction and its limitations (Table 2). A series of *N*-phenyl isoquinolines bearing electron-withdrawing and -donating substituents on the phenyl ring successfully underwent CDC with **2a** to afford the corresponding products **4a–f** in 63% to 90% yields. Diethyl malonate was used as a nucleophile to afford the desired compound, **4g**, in 82% yield. Moreover, **3** was employed as a nucleophile in the present system, and the flavin–iodine-coupled system promoted the oxidative aza-Henry reaction between **1** and **3** via CDC. The aerobic oxidative aza-Henry reactions of **1**s bearing electron-withdrawing and -donating substituents successfully afforded the corresponding products **5a**, **c**, **f**, and **h** in 63% to 85% yields. In our previous study, the flavin catalyst **13d•Cl** was reported to catalyse the aerobic oxidative aza-Henry reaction of **1a** and **3**.[10c] However, the activity of the flavin catalyst was relatively lower when the reaction was carried out using tetrahydroisoquinolines **1f** and **1h** bearing electron-donating groups, which afforded the desired products **5f** and **5h** in low yields of 45% and 42%, respectively (Table 2). In the present dual catalytic system, it is the iodine catalyst that activates the C−H bond of **1**, rather than the flavin catalyst. This in turn improves the substrate scope.

Table 2. Substrate scope of flavin–iodine-catalysed aerobic CDC of **1** with **2** and **3**[a]



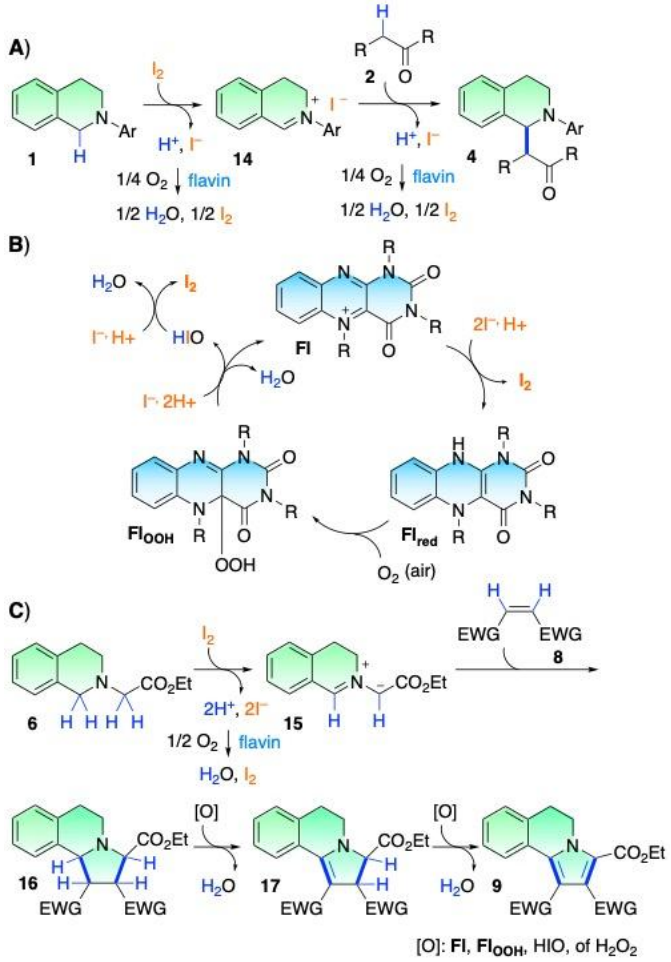
[a]Conditions: **1** (0.3 mmol), **2** (8.7 equiv), **12c•TfO** (5 mol%), and I_2 (5 mol%) under air (1 atm, balloon) at 40 °C for 48 h. Isolated yield. [b]**12c•TfO** (10 mol%) was used. [c]I_2 (10 mol%) was used. [d]Under O_2 (1 atm, balloon). [e]Yields were determined by ^{1}H NMR using 1,3,5-trioxane as the internal standard. [f]**1** (0.15 mmol) was used. [g]**3** (19 equiv) was used. [h]**1** (1 M), **3** (2 M, 2 equiv), and **13d•Cl** (5 mol%) in MeOH under O_2 (1 atm, balloon) at 40 °C for 24 h.

Control experiments were also performed to gain insight into the reaction mechanism. The catalytic oxidative Mannich reaction did not proceed well in the absence of **12c•TfO** and I_2 (Scheme 3A). This indicates that both catalysts are essential for promoting the present reaction. When 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1.0 equiv) was used as the radical inhibitor, **4a** was obtained in 85% yield, suggesting that the reaction mainly proceeded via the non-radical pathway (Scheme 3B).



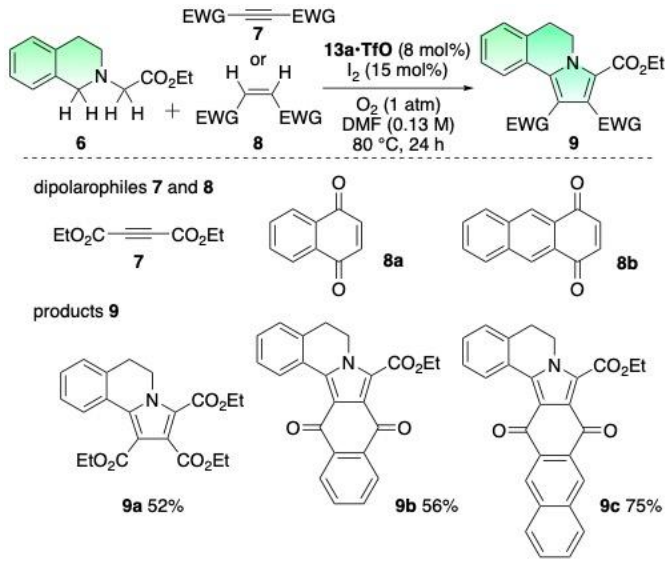
Scheme 3. Control Experiments.

Based on our experimental results and those reported in the literature, a plausible mechanism for the present flavin–iodine-coupled system is shown in Scheme 4. In this system, the oxidation of **1** with I_2 generates an iminium intermediate **14**, which is then attacked by carbon nucleophile **2**. Subsequently, C–C bond formation occurs, producing 1-alkylated isoquinoline **4**.[7a,8,11] Indeed, the generation of the iminium intermediate **14a** (m/z=208.1121) was confirmed using electrospray ionization (ESI) mass spectrometry of the reaction mixture obtained after stirring for 12 h under the standard conditions (Scheme 3C, Figure S1). During the CDC coupling between **1** and **2**, I_2 is converted to $2I^-$, accompanied with the generation of $2H^+$. The flavin catalysis promotes the aerobic oxidation of 2HI to I_2.[5a,5b] Cationic flavin **Fl** oxidizes $2I^-$ to I_2 and is reduced to $\mathbf{Fl_{red}}$, which reacts with molecular oxygen to produce $\mathbf{Fl_{OOH}}$. The oxidatively active hydroperoxy intermediate $\mathbf{Fl_{OOH}}$ promotes the oxygen-atom transfer to I^-, affording HIO. Subsequently, HIO generates I_2 by reacting with I^-.[12] Therefore, the present oxidative Mannich and aza-Henry reactions can be conducted under metal- and light-free conditions in a green, atom-economical way, where environmentally benign water is generated as the sole by-product by the consumption of air.



Scheme 4. A) Plausible mechanism for the flavin–iodine-catalysed oxidative Mannich reaction. B) Catalytic cycle for the present dual catalytic system. C) Proposed mechanism for the flavin–iodine-catalysed synthesis of **9**.

Table 3. Flavin–iodine-catalysed synthesis of **9** via tandem 1,3-dipolar cycloaddition and aromatisation of **6** with **7** and **8**.[a]



[a]Conditions: **7** or **8** (0.3 mmol), **6** (1.5 equiv), **13a•TfO** (8 mol%), and I_2 (15 mol%) under O_2 (1 atm) at 80 °C for 24 h. Isolated yield.

Finally, we applied the flavin–iodine-coupled catalyst to an oxidative cascade reaction. The pyrrolo[2,1-*a*]isoquinoline skeleton is found in lamellarins, which are marine alkaloids exhibiting a wide spectrum of biological and pharmacological activities.[13] For example, lamellarin D and lamellarin α-20-sulfate have the ability to inhibit human topoisomerase I and HIV integrase, respectively.[14] The potential utility of pyrrolo[2,1-*a*]isoquinolines has given rise to a variety of practical synthetic methods.[15] In 2011, Wang and co-workers reported the Cu-catalysed oxidation-dipolar cycloaddition–aromatisation cascade reaction of tetrahydroisoquinolines and dipolarophiles, such as quinones and alkynes.[16] This is a promising one-pot approach to access pyrrolo[2,1-*a*]isoquinolines from readily available starting materials. Transition metals such as Cu,[16-17] Rh,[18] Fe,[19] and Co[20] have been used for cascade synthesis; however, these methods require an over-stoichiometric amount of *t*-BuOOH to complete the oxidative aromatisation, except for aerobic reactions using the Cu-NHPI-coupled system.[17] While photocatalysed methods have also been developed,[21] metal- and light-free catalytic reactions are limited to iodine-catalysed systems requiring H_2O_2 and t-BuOOH as oxidants.[22] To the best of our knowledge, aerobic iodine-catalysed cascade reactions have not yet been reported, despite their advantages.

This flavin–iodine-coupled catalyst was successfully applied to the oxidation-dipolar cycloaddition–aromatisation cascade reaction of a tetrahydroisoquinoline derivative **6** with dipolarophiles **7** and **8** (Scheme 1 B). After the optimisation of the reaction conditions (Table S2), the reaction of ethyl 2-(3,4-dihydroisoquinolin-2(1H)-yl)acetate (**6**) and diethyl acetylenedicarboxylate (**7**) was carried out in the presence of **13a•TfO** and I_2 to afford the desired product **9a** in 52% yield (Table 3). When quinones, 1,4-naphthoquinone (**8a**) and anthraquinone (**8b**), were used as dipolarophiles, the sequential oxidative [3+2] cycloaddition and oxidative aromatisation occurred smoothly, and the corresponding products, **9b** and **9c**, were obtained in 56% and 75% yields, respectively.

Based on these results and those of previous studies, we propose the following mechanism for the flavin–iodine-catalysed synthesis of **9** (Scheme 4C). First, the dehydrogenative oxidation of **6** with I_2 forms an unstable azomethine intermediate **15**, which undergoes 1,3-dioploar cycloaddition with dipolarophile **8** to produce the corresponding hexahydropyrrolo[2,1-*a*] isoquinoline **16**. Under the present oxidative conditions, the sequential dehydrogenative oxidation of **16** and **17** occurs to afford pyrrolo[2,1-*a*]isoquinoline **9**. Flavin catalysts are known to promote the dehydrogenative aromatisation of heterocyclic compounds, such as dihydropyridines,[23] benzothiazolines,[23] dihydroimidazoles,[5g] and indolines.[24] In addition, the oxidatively active compounds generated in the present dual catalytic system, *i.e.* $\mathbf{FI_{OOH}}$, HIO, and H_2O_2 which can be generated from $\mathbf{FI_{OOH}}$,[4] would promote this aromatization step. Therefore, the desired product **9** can be efficiently obtained from **16** via oxidative aromatisation.

Experimental

Typical procedure for the catalytic synthesis of 4a.[25] A mixture of **1a** (62.8 mg, 0.30 mmol), **2a** (347 mg, 2.6 mmol, 8.7 equiv), I_2 (3.75 mg, 0.015 mmol, 0.05 equiv), and **12c•TfO** (7.22 mg, 0.015 mmol, 0.05 equiv) was stirred at 40 °C (oil bath) for 48 h under air (1 atm, balloon). The yield was determined to be 79% by ^{1}H NMR spectroscopy of the reaction mixture using 1,3,5-trioxane as the internal standard. After the solvent was removed by evaporation, the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate = 30/1 to 10/1, v/v), affording **4a** (71.9 mg, 71%) as a colourless oil. The results are summarised in Table 2. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, *δ*): 7.23–7.16 (m, 4H), 7.13–7.09 (m, 2H), 6.98 (d, J = 8.1 Hz, 2H), 6.76 (t, J = 7.2 Hz, 1H), 5.70 (d, J = 9.4 Hz, 1H), 3.95 (d, J = 9.3 Hz, 1H), 3.72–3.61 (m, 5H), 3.55 (s, 3H), 3.10–3.04 (m, 1H), 2.87 (dt, J = 16.5, 5.1 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C, *δ*): 168.4, 167.5, 148.9, 135.8, 134.9, 129.2, 129.1, 127.8, 127.2, 126.2, 118.7, 115.3, 59.2, 58.3, 52.7, 42.3, 26.1.

Typical procedure for catalytic synthesis of 9c.[26] A mixture of **6** (98.8 mg, 0.45 mmol, 1.5 equiv.), **8b** (62.5 mg, 0.30 mmol), **13a•TfO** (10.4 mg, 0.024 mmol, 0.08 equiv.), I_2 (11.4 mg, 0.045 mmol, 0.15 equiv.), and DMF (2.3 mL, 0.1 M) was stirred at 80 °C (oil bath) for 24 h under O_2 (1 atm, balloon). The yield was determined to be 87% by ^{1}H NMR spectroscopy of the reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard. After the solvent was removed by evaporation, the residue was purified by column chromatography (SiO_2, CH_2Cl_2), affording **9c** (94.9 mg, 75%) as an orange solid. The results of similar reactions are summarised in Table 3. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, *δ*): 8.97 (dd, J = 7.9, 0.8 Hz, 1H), 8.67 (s, 1H), 8.59 (s, 1H), 7.93–7.90 (m, 2H), 7.53–7.50 (m, 2H), 7.39 (td, J = 7.6, 1.1 Hz, 1H), 7.29 (td, J = 7.5, 1.2 Hz, 1H), 7.18 (d, J = 7.1 Hz, 1H), 4.55 (q, J = 7.2 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.03 (t, J = 6.6 Hz, 2H) , 1.53 (t, J = 7.2 Hz, 3H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C, *δ*): 179.4, 179.2, 161.6, 135.5, 134.8, 134.5, 133.5, 132.0, 131.2, 129.90, 129.86, 129.8, 129.2, 129.0, 128.8, 128.5, 127.3, 126.4, 126.0, 123.9, 118.2, 62.5, 43.1, 29.0, 14.1.

Conclusions

In conclusion, we successfully developed the first aerobic flavin–iodine-catalysed method for C–C bond formation under metal- and light-free conditions. Aerobic oxidative Mannich and aza-Henry reactions were efficiently promoted by the CDC of tetrahydroisoquinolines with carbonyl compounds and nitromethane. In these oxidative transformations, the atmospheric air can be used as an eco-friendly terminal oxidant by the coupled flavin-iodine catalysis, thus afforded desired products accompanied with the generation of the environmentally benign water as the solo by-product. Furthermore, this flavin–iodine-catalysed aerobic C–C bond formation was successfully applied to the oxidative cascade synthesis of pyrrolo[2,1-*a*]isoquinolines. This reaction was promoted by the sequential oxidative 1,3-dipolar cycloaddition–aromatisation of a tetrahydroisoquinoline derivative and dipolarophiles, such as quinones and an activated alkyne. This study may lead to the development a series of metal- and light-free C–C bond formation reactions, which involve the aerobic CDC of various substrates, enabling facile and eco-friendly multi-step and multi-component organic syntheses.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary Information.

Acknowledgements

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