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Photoredox Mediated Acceptorless Dehydrogenative Coupling of Saturated *N*-Heterocycles

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ABSTRACT: We report herein a direct unsymmetric coupling and controllable aromatization reaction of saturated *N*-heterocycles enabled by synergistic photoredox and acid catalysis. The reaction furnishes C2-C3 connected bi-heterocycles in a highly chemo- and regioselective manner under rather mild conditions. Mechanistic studies indicated that the reaction proceeded *via* enamine-iminium coupling leading to exclusively C2-C3 connection.

KEYWORDS: *acceptorless photoredox dehydrogenation • enamine/iminium coupling • unsymmetric coupling • heterocycles • synergistic multiple catalysis.*

Catalytic dehydrogenation reaction is one of the most important strategies in organic transformations and manufacture of commodity chemicals.[1] Comparing to the traditional oxidative dehydrogenation and hydrogen-transfer strategies, catalytic acceptorless dehydrogenation avoids the use of any external oxidants with hydrogen gas as the sole by-products and hence has received great attention in recent years due to its sustainable features.[2] In particular, catalytic acceptorless dehydrogenation has been successfully applied in the dehydrogenation of *N*-heterocycles as a viable approach toward hydrogen storage materials (Scheme 1, I).[3,4] Pioneering contributions from groups of Fujita,[4a,d] Xiao,[4c] Jones[4e,g] and Crabtree[5f] et al. presented independently acceptorless dehydrogenation of 1,2,3,4-tetrahydroquinolines (THQs) catalyzed by iridium, iron and cobalt complex, respectively. Li,[5a] Kanai[5b] and Wang[5c] reported photoredox dehydrogenation of the same reaction at ambient temperature in the presence of photocatalyst (PC).[5] Very recently, Lei[5h] successfully developed the first electrochemical acceptorless dehydrogenation of *N*-heterocycles. Such dehydrogenation processes eliminate the use of chemical oxidants and hence are atom-economic and of high chemoselectivity. They also display potential applications in hydrogen-storage materials (Scheme 1, I, path A).[6] Mechanistically, all these processes proceed via dehydrogenation of amines into imine intermediate, which are readily tautomerized into enamine. These intermediates could be further manipulated to achieve selective α- or β-C-H functionalization of *N*-heterocycles but only in the presence of stoichiometric amount of oxidant (Scheme 1, I, path B).[7,8] The synthetic potentials of acceptorless dehydrogenation process remain to be further explored.

Herein, we report a distinctive enamine-iminium coupling in the photoredox dehydrogenation of tetrahydroquinolines. The reaction led to bi-*N*-heterocylces in a highly chemo- and regio-selective manners (Scheme 1, II). The resulted bi-heterocycle with C2-C3 connection turns out to be prevalent structural motif in a number of bioactive alkaloids[9] such as Lycodine,[9a] Complanadine A[9b] and Complanadine E (Figure 1).[9d] The existing

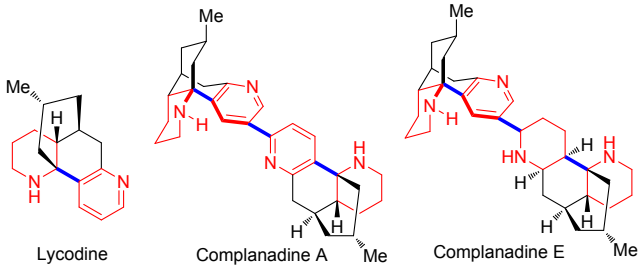
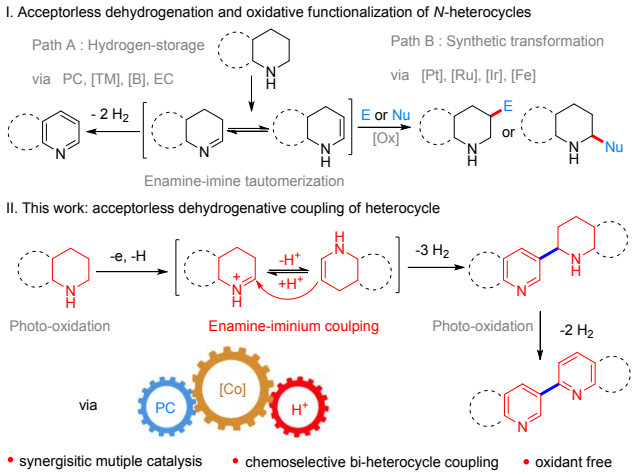


Figure 1. C2-C3 connected bi-heterocycles scaffold in natural compounds.

Scheme 1. Dehydrogenative functionalization of *N*-heterocycles

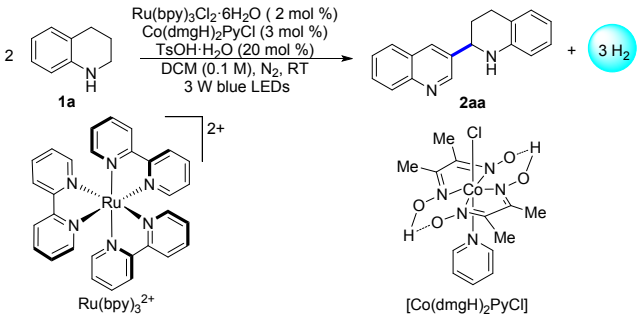


E = electrophiles; Nu = nucleophiles; Ox = oxidant; EC = electrochemical catalysis

strategies normally require tedious steps to achieve regioselective C2-C3 bi-heterocycle connection.[10] On the basis of intrinsic property of enamine and iminium, an enamine-iminium coupling would lead only to C2-C3 coupling of saturated *N*-heterocycles, thus bypassing the perplexing regioselective issue. Such a bis-heterocycle coupling was made possible by judicious combination of photoredox e/H transfer and acid promoted enamine/iminium tautomerization/coupling (Scheme 1, II).[11]

In our experiments, 1,2,3,4-tetrahydroquinoline **1a** was first selected as the model substrate with $Ru(bpy)_3Cl_2•6H_2O$ as the photosensitizer and $Co(dmgH)_2PyCl$ as the hydrogen transfer catalyst. To our delight, the reaction proceeded smoothly with TsOH as an additive. Under the conditions, conversion was complete within 8 h and the desired unsymmetric product **2aa** was obtained with 90% isolated yield and >99% H_2 yield (Table 1, entry 1). Variation of organic or inorganic acids led to reduced activity or inhibition of the transformation (Table 1, entries 2-5). The optimal loading of acid was determined to be 20 mol%. Further increasing the loading led to decreased production of both **2a** and H_2 (SI for details). It is known that acid could effectively promote enamine-iminium tautomerization in aminocatalysis.[11a] In this case, we speculated that TsOH, as an acid additive can promoted enamine-iminium tautomerization (*vide infra* for detailed discussion) and their subsequent coupling by supressing the aromatization to quinolone (entry 8 vs entry 1).[5a] Other photosensitizers such as $[Acr^+Mes]BF_4^-$ gave rather low yield (Table 1, entry 6) and the typical organic dye eosin Y couldn't promote the reaction (Table 1, entry 7). Control experiments revealed that acid, photocatalyst, cobalt catalyst and visible light were essential in the reaction (Table 1, entries 8-11), and no desired reaction or poor yield was observed in their absence.

Table 1. Screening and optimization.[a]



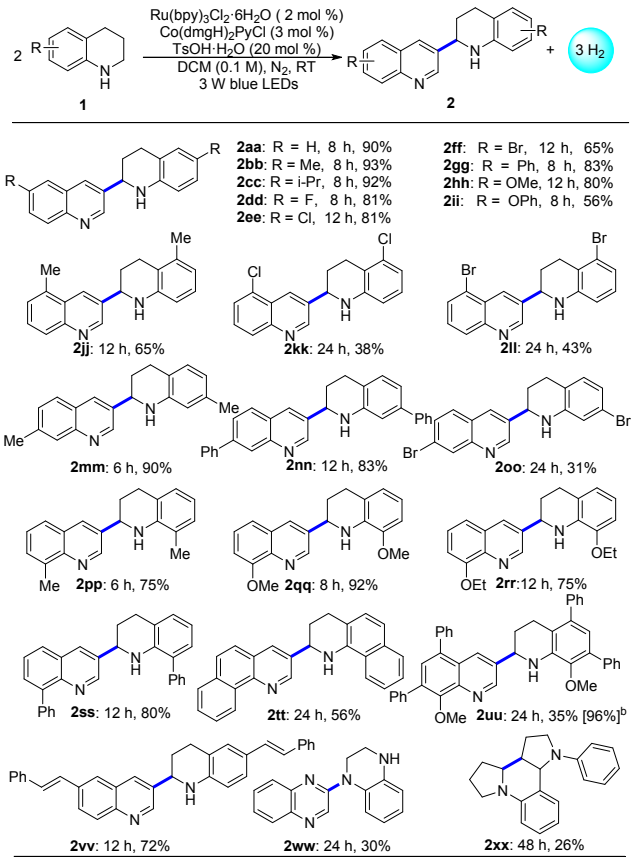
Entry	Variation from standard conditions	Yield **2aa** (%)[b]	H_2 Yield (%)[c]
1	None	92 (90)[d]	> 99
2	TfOH instead of TsOH	90	> 99
3	CF_3COOH	42	67
4	HBF_4 (48 wt. % in H_2O)	20	53
5	$HClO_4$	< 10	41
6	$[Acr^+Mes]BF_4^-$ (5 mol %)	trace	9
7	Eosin Y (5 mol %)	trace	0
8	No TsOH	0[e]	n.d.[g]
9	No $Co(dmgH)_2PyCl$	< 5	0
10	No $Ru(bpy)_3Cl_2•6H_2O$	n.r.[f]	n.d.[g]
11	In dark	n.r.[f]	n.d.[g]

[a]Reaction conditions: **1a** (0.1 mmol), $Ru(bpy)_3Cl_2•6H_2O$ (2 mol %), $Co(dmgH)_2PyCl$ (3 mol %), TsOH (20 mol %) were added to 1.0 mL solvent, then deaerated and irradiated for 8 h with 3 W blue LEDs at room temperature. [b]Determined by ^1H NMR analysis using 1, 3, 5-trimethoxybenzene as an internal standard. [c]Determined by gas chromatography using methane as an internal standard. [d]Isolated yield. [e]40% yield of quinoline was obtained.[f]n.r. = no reaction. [g]n.d. = no detected.

Under the optimized conditions, the substrate scopes were then examined. As shown in Scheme 2, diverse 6-substituted THQs including alkyl, halogen, alkoxyl, aryl and phenoxyl could all furnish the corresponding 2,3-coupled products in good to excellent yields (Scheme 2, **2aa**-**2ii**). 5-Halogen or 7-halogen substituted substrates gave moderate yields (Scheme 2, **2kk**, **2ll**, **2oo**). These results indicated that the electronic property of substituents on the substrates affected the products yields significantly. In general, those substrates with electron-donating substituents afforded the products (Scheme 2, **2aa**-**2cc**, **2gg**, **2hh**) in relatively higher yields than those of electron-withdrawing substituents (Scheme 2, **2kk**, **2ll**, **2oo**). 8-Substituted THQs could react smoothly to give the coupling products with good to excellent yields (Scheme 2, **2pp**-**2ss**). Multi-substituted tetrahydroquinoline (Scheme 2, **2uu**) has also been examined to deliver the desired product with 35% yield (96% based on recovered starting material) and poor solubility as well as the bulkiness could be the reason for low conversion. Other *aza*-heterocycles such as pyrrolidine, morpholine or piperidine have also been examined, giving unfortunately no desired coupling products. 1,2,3,4-Tetrahydroquinoxaline gave the α-

amination product **2ww** with moderate yield. When *N*-phenyl pyrrolidine was applied, a dimerization adduct **2xx** was obtained as a result of cross coupling (a hetero-Diels-Alder type reaction) of the *in-situ* generated enamine and iminium ion.

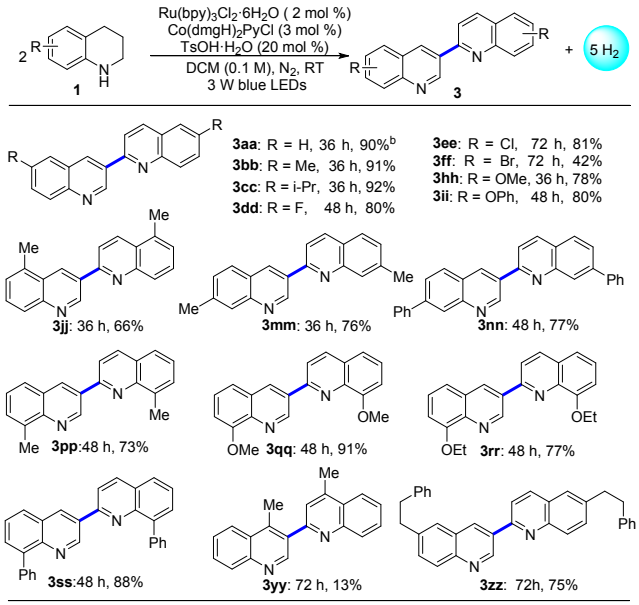
Scheme 2. Scopes of β-alkylation. [a]



[a]Isolated yield. [b]yield based on recovered starting material.

The reaction was not limited to β-alkylation of quinolines. When the reaction time was prolonged to 36 h, further dehydrogenation proceeded to an aromatized product **3aa**. The reaction time could be shortened to 12 h under 10 W blue LEDs irradiation. We believed that the product **3aa** was generated from further acceptorless dehydrogenation of the intermediate **2aa** via [Ru]/[Co] catalysis. Promoted by such an easily manageable unsymmetric coupling and aromatization transformation, THQs with a variety of substitutes on the phenyl moiety were tested in this reaction (Scheme 3). Those substituted THQs could transform smoothly to the desired β-arylation adducts with good to excellent yields. 4-Methyl THQ gave only 13% yield of coupled adduct **3yy** probably due to steric effect.

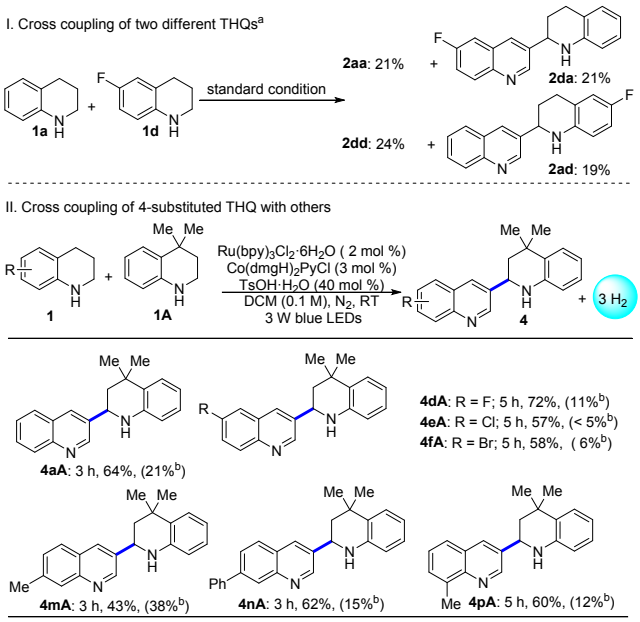
Scheme 3. Scopes of β-aromatization.[a]



[a]Isolated yield. [b] > 99 % H_2 yield (see SI Figure S4).

The cross coupling of two different THQs were next explored. Initial experiments revealed that homo-coupling was unavoidable (Scheme 4, I). In searching THQ derivatives with balanced redox property and enamine-iminium coupling reactivity, it was noted 4-substituted THQ was readily oxidized but reluctant to undergo homo-coupling likely due to steric effect (Scheme 3, **3yy**). In this regard, 4,4-dimethyl tetrahydroquinoline **1A** was identified to undergo cross-coupling with other THQs effectively with little competitive homo-coupling of **1**(Scheme 4, II).

Scheme 4. Scopes of cross-dehydrogenative coupling.



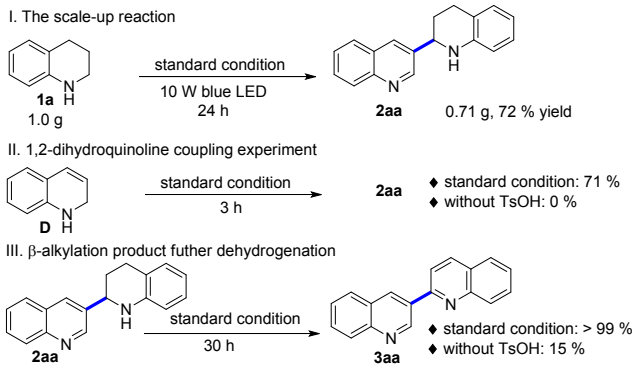
[a] Isolated yield. The ratio was determined by ^1H NMR and ^{19}F NMR analysis. [b]Homo-coupling yield of ***1****.*

To probe the utility of our method in preparative synthesis, a scale-up reaction of **1a** was performed. Under the standard conditions, conversion was complete within

24 h with 72% isolated yield (Scheme 5, I), highlighting the practical potential for large-scale applications.

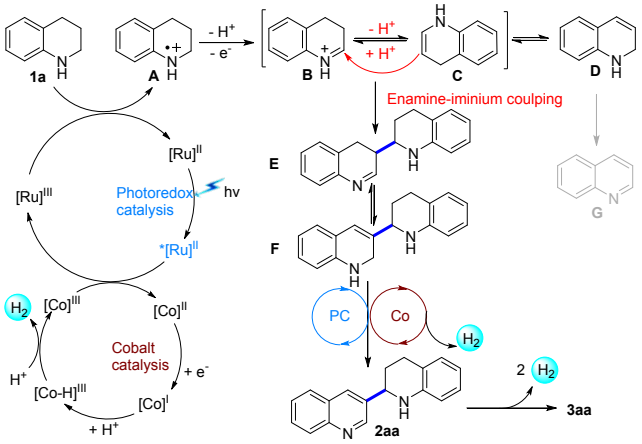
We have tried to synthesize enamine/iminium intermediate **B**/**C** (Scheme 6) and in all the attempts a conjugated 1,2-dihydroquinoline **D** was obtained. When **D** was subjected to the standard reaction conditions, the desired coupling product was isolated in 71% yield (Scheme 5, II), indicating a fast equilibrium between **B**/**C** and **D**. Control experiment also verified the dehydrogenation conversion of **2aa** to **3aa** under the catalytic conditions (Scheme 6, III). The oxidation potential of **2aa** was determined to be 1.233 V (*vs* Ag/AgCl), much higher than that of **1a** (1.080 V *vs* Ag/AgCl) (Fingure S11), and this may explain the controllable unsymmetric coupling (formation of **2aa**) and aromatization (formation of **3aa**) in our reaction system as **1a** would be preferentially photo-oxidized in the presence of **2aa**. The critical role of acid in facilitating both enamine-iminium coupling and aromatization could aslo be verified in the control experiments and sluggish reaction or no conversion was observed in its absence (Scheme 5).

Scheme 5. The scale-up reaction and control experiments



On the basis of previous reports and our own studies,[5a,11] a proposed mechanism was drawn in Scheme 6. Upon visible light irradiation, the excited state $*[Ru(bpy)_3]^{2+}$ is oxidized to $[Ru(bpy)_3]^{3+}$ by $[Co^{III}]$ through single-electron transfer (SET). Subsequently, another SET process between **1a** and $[Ru(bpy)_3]^{3+}$ produces a radical cation **A** and completes the [Ru] catalytic cycle.[12] The intermediate **A** undergoes further *e*/H transfer to give iminium **B** which readily tautomerizes to enamine **C** in the present of TsOH. $[Co^{II}]$ can capture the *e*/H in the process and form $[Co^{III}$-H], which is readily protonated by H^+ to release H_2. As known, the addition of acid could promote hydrogen production in this step,[13c, 13d] thus facilitating the aromatization as experimentally observed (Schem 5).[14] Acid promoted coupling of **B** and **C** and subsequent photo-oxidative electron/H transfer then affords the coupling product **2aa**, which undergoes further dehydrogenation to **3aa** under the standard conditions after **1a** was completely consumed.

Scheme 6. Proposed catalytic cycle.



In summary, we have developed a visible light promoted unsymmetric coupling and controllable aromatization of *N*-heterocycles enabled by combining Ru/Co mediated photoredox dehydrogenation and acid promoted enamine/iminium tautomerization. The current protocol provides a straight-forward approach to accessing bi-heterocycles bearing C2-C3 connection in a highly chemo- and regio-selective manner under rather mild conditions. The facile and regioselective nature of the current enamine-iminium coupling may also suggest a possible biosynthetic pathway for this type of natural alkaloids endowed with C2-C3 connected bi-heterocycles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.
NMR data, extended data about experimental procedures and scale-up reaction (PDF)

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Notes

The authors declare no competing financial interest.

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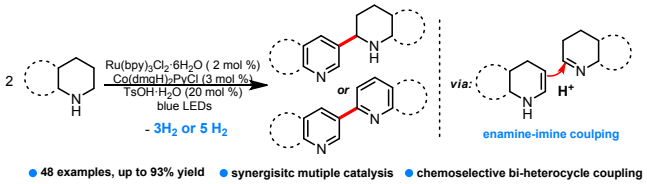
2
Ru(bpy)3Cl2·6H2O (2 mol %)
Co(dmgH)2PyCl (3 mol %)
TsOH·H2O (20 mol %)
blue LEDs
- 3H2 or 5 H2
or
via:
H+
enamine-imine coulping
48 examples, up to 93% yield
synergisitc mutiple catalysis
chemoselective bi-heterocycle coupling