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Cobalt-Catalyzed Cross-Dehydrogenative Coupling Reaction in Water by Visible Light

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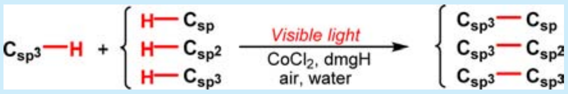
S *Supporting Information*



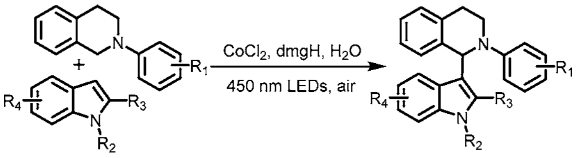
ABSTRACT: By using catalytic amount of $CoCl_2$ with dmgH (dimethylglyoxime) as ligand to form a photosensitizer in situ, a highly selective, efficient, and environmentally benign visible light mediated cross-dehydrogenative coupling (CDC) reaction has been developed in aqueous medium. The desired cross-coupling C−C bonds that involve C_{sp3} with C_{sp}, C_{sp2}, and C_{sp3}, respectively, were achieved exclusively in high yields without formation of any other byproduct.

Construction of C−C bonds has always been a research focus of organic chemists, and transition-metal-catalyzed activation of C−H bonds is well-known to provide atom-economic and efficient ways for such transformation.[1] As one of the most powerful C−H activation processes, cross-dehydrogenative-coupling (CDC) reaction[2] constructs C−C bonds directly from two different C−H bonds under oxidative conditions. The oxidation protocol involves metal catalysts together with oxygen or organic oxidants. This straightforward reaction avoids the prefunctionalization and defunctionalization of substrates, which has been part of traditional synthetic design, and has made considerable progress in the past decades.[3] In particular, the visible light[4] catalyzed CDC reaction[5] has appeared at the forefront owing to its mild, clean, and environmentally benign characteristics. Various noble metal complexes based on Ir(III),[5a] Ru(II),[5b] Pt(II),[5h] Au(III),[5f,i] and Pd(II)[5j] have been employed as photocatalysts to initiate the cross-coupling reactions efficiently. However, these catalysts were expensive and suffered complicated synthesis. Developing inexpensive and easily available metal complexes would be a superior choice and would meet the requirements of green chemistry.

On the other hand, it is noteworthy that most of the cross-coupling reactions have been performed in organic solvents. The use of water as a solvent for organic transformations has attracted considerable attention because it not only offers several "green chemistry" benefits but also accelerates the rate and increases the selectivity of the reaction. To realize this type of transformation in water featured with greenness, nontoxicity, and low cost has yet to be explored. To date, only limited examples utilizing water as the reaction medium have been reported.[6] Li et al. made use of copper bromide to catalyze a cross-coupling reaction between two sp^3 C−H bonds in water.[6b] Our group[31] realized an efficient aerobic CDC reaction in water catalyzed by recyclable graphene-supported RuO_2 nanoparticles. Despite advances, to the best of our knowledge, there are no reports about visible light catalyzed CDC reactions performed in water.

As an extension of our continuous research efforts to explore greener and milder CDC reactions, we developed a new system for the activation of C−H bonds mediated by visible light in water in ambient conditions. During this reaction, one cobaloxime complex generated in situ from earth-abundant and cost-effective transition metal cobalt salts[7] and dmgH (dimethylglyoxime) was used as a photocatalyst instead of traditional light-harnessing photocatalysts. Good to excellent yields of the desired cross-coupling products of *N*-phenyl-1,2,3,4-tetrahydroisoquinolines and indoles were obtained in aqueous solution under visible light irradiation (Scheme 1).

Scheme 1. Cobalt-Catalyzed Cross-Dehydrogenative Coupling Reaction in Water by Visible Light



Noticeably, the developed simple system herein could compete with photocatalyzed CDC reactions based on traditional noble metal complexes in yield as well as selectivity. On the other hand, compared with traditional thermal CDC reactions that were carried out in organic solvents, the established system still maintained the efficiency in water, which satisfied the need of modern organic chemistry.

Our preliminary studies focused on the cross-coupling of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) with indole (**2a**) under the irradiation of blue LEDs (λ_{max} = 450 nm) at room temperature. To our delight, when the mixture containing

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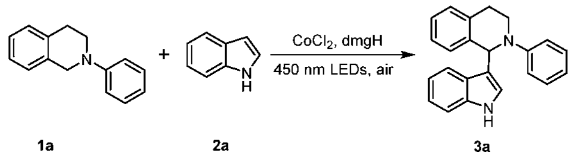
catlytic amount of $CoCl_2$ with dmgH (dimethylglyoxime) as ligand and the substrates in CH_3CN was irradiated under visible light, the formation of the desired cross-coupling product was observed in 40% yield (Table 1, entry 1). To enhance the reaction efficiency, we tried to optimize the reaction conditions. When the reaction was conducted in DMF or CH_2Cl_2, negligible amount of the desired cross-coupling product could be observed (Table 1, entries 2 and 3). Compared with the reaction in CH_3CN, a similar yield of 43% was obtained in CH_3OH (Table 1, entry 4). Furthermore, a different performance was shown when the reaction was performed in different volume ratio of H_2O/CH_3CN mixture. The increased ratio of H_2O/CH_3CN resulted in an improved yield of the cross-coupling product (Table 1, entries 5−6). This finding suggested the possibility of H_2O as the green solvent. Indeed, when the reaction was performed in H_2O, the yield achieved 83% (Table 1, entry 7). Afterward, we found that 8 mol % of $CoCl_2$ and 16 mol % of dmgH were the optimal amounts (Table 1, entries 8−10). Increasing the amount of nucleophilic indole to 4 equiv resulted in the best yield of 95% in the reaction (Table 1, entries 8 and 11−13). As a result, the visible light mediated CDC reaction was able to efficiently proceed in the optimized conditions, i.e., 8 mol % of $CoCl_2$ with 16 mol % of dmgH in H_2O, irradiated by blue LEDs for 24 h in aerobic conditions at room temperature. Control experiments indicated that each component of the reaction is critical to the reaction efficiency (Supporting Information, Table S1, entries 1−4). Significantly, during the process, only the desired cross-coupling product could be generated, and no byproduct was detected.

Table 1. Optimization of the Reaction Conditions[a]



entry	$CoCl_2$ (mol %)	dmgH (mol %)	solvent	yield[b] (%)
1	16	32	CH_3CN	40
2	16	32	DMF	none
3	16	32	CH_2Cl_2	trace
4	16	32	CH_3OH	43
5[c]	16	32	H_2O/CH_3CN	58
6[d]	16	32	H_2O/CH_3CN	66
7	16	32	H_2O	83
8	8	16	H_2O	84
9	8	8	H_2O	73
10	8	24	H_2O	75
11[e]	8	16	H_2O	76
12[f]	8	16	H_2O	95
13[g]	8	16	H_2O	96

[a] Reaction conditions: 0.1 mmol of **1a**, 0.3 mmol of **2a**, corresponding $CoCl_2$, and dmgH were added in 1 mL of solvent, the solution was irradiated under blue LEDs (λ = 450 nm) in air for 24 h. [b] Yields determined by ^1H NMR using diphenylacetonitrile as an internal standard. [c] Volume ratio of H_2O/CH_3CN was 1:1. [d] Volume ratio of H_2O/CH_3CN was 1:0.5. [e] 0.2 mmol of **2a** was used. [f] 0.4 mmol of **2a** was used. [g] 0.5 mmol of **2a** was used.

Molecular oxygen played an important role in this system. None of the desired cross-coupling product was observed when the reaction was carried out in N_2 atmosphere (Supporting Information, Table S1, entry 4). Moreover, the yield would achieve 95% if the reaction underwent under oxygen atmosphere (Table S1, entry 5). In order to determine the function of the molecular oxygen in the process, we studied the active species of oxygen in the system by electron-spin resonance (ESR)[8] spectroscopy as shown in Figure 1. 2,2,6,6-Tetramethylpiperidine (TEMP) was employed as a probe to trap $^1O_2$, and 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) was used to capture $O_2^{\bullet-}$. No any signal was detected when the mixture containing TEMP, $CoCl_2$, and dmgH was irradiated by blue LEDs, even if *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) was present. There was no signal when DMPO was added into the H_2O/CH_3CN solution containing $CoCl_2$ and dmgH. However, a characteristic signal of $O_2^{\bullet-}$ captured by DMPO was clearly observed after addition of **1a**. This finding indicated that the addition of **1a** resulted in photoinduced electron transfer to generate $O_2^{\bullet-}$, which was a crucial intermediate in the reaction.

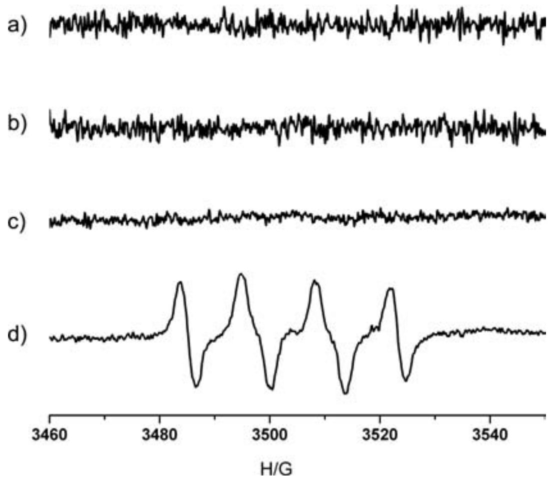


Figure 1. ESR measurements of (a) a solution in H_2O/CH_3CN of $CoCl_2$, dmgH without **1a** in the presence of TEMP under the irradiation of blue LEDs; (b) a solution in H_2O/CH_3CN of $CoCl_2$, dmgH with **1a** in the presence of TEMP under the irradiation of blue LEDs; (c) a solution in H_2O/CH_3CN of $CoCl_2$, dmgH without **1a** in the presence of DMPO under the irradiation of blue LEDs; (d) a solution in H_2O/CH_3CN of $CoCl_2$, dmgH with **1a** in the presence of DMPO under the irradiation of blue LEDs.

To understand the interaction, UV−vis absorption spectra of the subcomponents and their mixture were monitored (Figure 2). After the mixture was stirred for 2 h in air, the absorption spectra of the mixture of $CoCl_2$ and dmgH in H_2O/CH_3CN became similar to that of $Co^{III}(dmgH)_2Cl_2$, and the high-resolution mass spectra have also proved the generation of $Co^{III}(dmgH)_2Cl_2$ (Figure S1, Supporting Information). Based on above results, we speculated that $Co^{III}(dmgH)_2Cl_2$ generated in situ was the catalyst in essence. To verify the speculation, $Co^{III}(dmgH)_2Cl_2$ was used instead of $CoCl_2$ and dmgH in the reaction under the same condition and a yield of 98% could be achieved after 24 h (Supporting Information, Table S1, entry 6). In addition, $CoCl_2$ was found to be unable to interact with dmgH to form $Co^{III}(dmgH)_2Cl_2$ in CH_2Cl_2 and DMF (Figure S2, Supporting Information), leading to poor reaction performance (Table 1, entries 2 and 3).

On the basis of the above results, we proposed a plausible mechanism shown in Scheme 2. $CoCl_2$ together with dmgH in

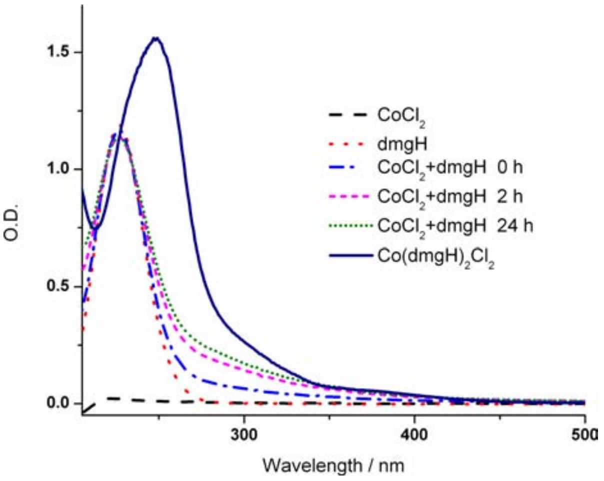
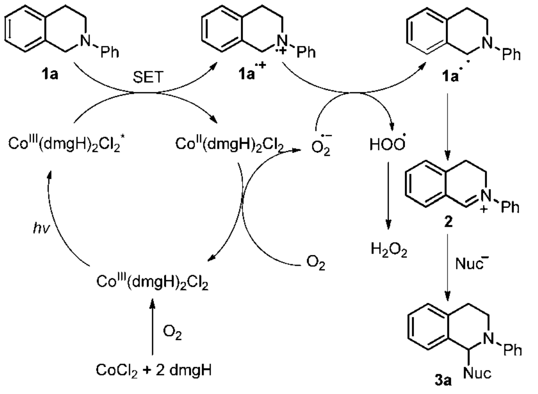
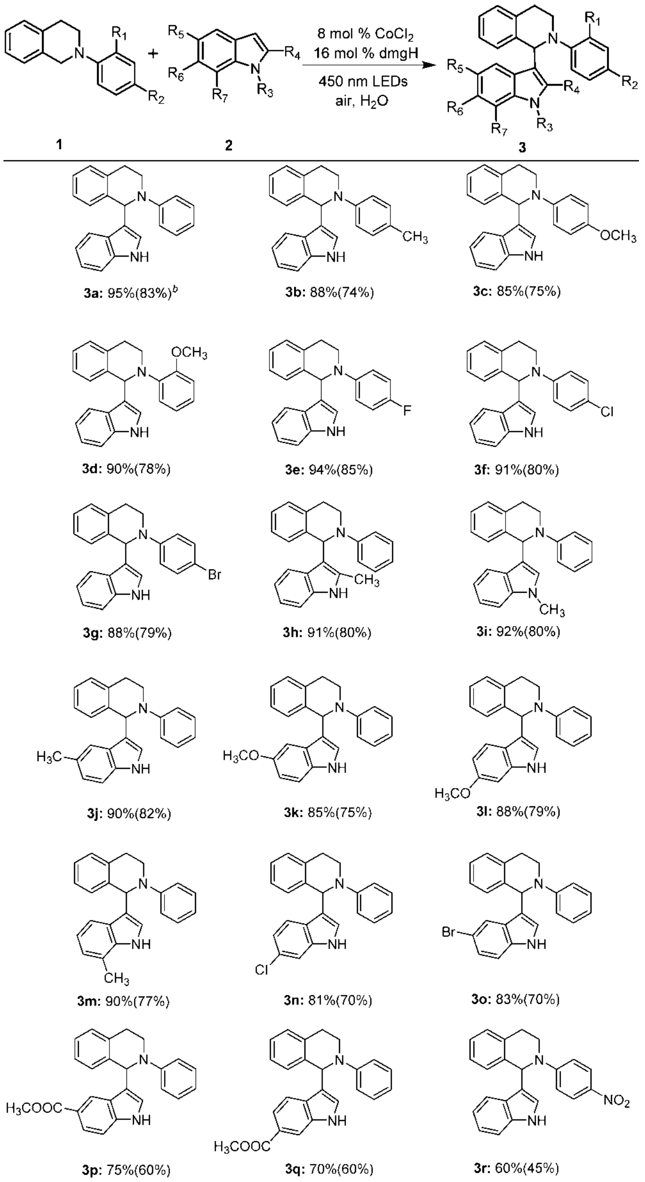


Figure 2. UV−vis absorption spectra of system: (a) $CoCl_2$ (1.0×10^{-4} M) in H_2O/CH_3CN 1:1; (b) dmgH (2.0×10^{-4} M) in H_2O/CH_3CN 1:1; (c) mixture of $CoCl_2$ (1.0×10^{-4} M) and dmgH (2.0×10^{-4} M) in H_2O/CH_3CN 1:1; (d) mixture of $CoCl_2$ (1.0×10^{-4} M) and dmgH (2.0×10^{-4} M) in H_2O/CH_3CN 1:1 after irradiation under blue LEDs in air for 2 h; (e) mixture of $CoCl_2$ (1.0×10^{-4} M) and dmgH (2.0×10^{-4} M) in H_2O/CH_3CN 1:1 after irradiation under blue LEDs in air for 24 h; (f) $Co^{III}(dmgH)_2Cl_2$ (1.0×10^{-4} M) in H_2O/CH_3CN 1:1.

Scheme 2. Proposed Reaction Mechanism



Scheme 3. Scope of Tetrahydroisoquinolines and Indoles[a]



[a]Reaction conditions: 0.1 mmol of **1**, 0.4 mmol of **2**, 0.008 mmol of $CoCl_2$, and 0.016 mmol of dmgH were added in 1 mL of water; the solution was irradiated under blue LEDs (λ = 450 nm) in air for 24 h. [b]Yields determined by ^1H NMR using diphenylacetonitrile as an internal standard; isolated yields are given in parentheses.

air conditions resulted in the formation of $Co^{III}(dmgH)_2Cl_2$. Upon irradiation by visible light, $Co^{III}(dmgH)_2Cl_2$ reached its exicited state and then abstracted one electron from **1a** to generate **1a**$^{\bullet+}$ and Co (II) intermediate.[9] Subsequently, Co(II) intermediate reacted with O_2 to produce the superoxide radical anion ($O_2^{\bullet-}$) and regenerate $Co^{III}(dmgH)_2Cl_2$. $O_2^{\bullet-}$ abstracted one proton from **1a**$^{\bullet+}$ to create the $HOO^{\bullet}$ radical, which continued to capture a hydrogen atom to form H_2O_2.[10] The generated **1a**$^{\bullet}$ further lose one electron to afford iminium ion **2**, followed by nucleophile addition to give rise to the desired product **3a**.

With the understanding of the reaction mechanism, we attempted to investigate the universality of the visible light mediated cobalt-catalyzed CDC reaction in water. First, the scope with respect to tetrahydroisoquinolines was examined (Scheme 3, **3a**−**g**,**r**). For both electron-withdrawing and electron-donating groups, the desired coupling products could be obtained in good to excellent yields. When tetrahydroisoquinoline was linked with electron-donating groups, the yield of the product decreased slightly which may be due to the electronic effect. The strong electron-withdrawing nitro group would reduce the yield greatly (Scheme 3, **3r**). Meanwhile, it can be seen that steric hindrance has no effect on the outcome of this transformation. Furthermore, good to excellent yields were also obtained by using a variety of substituted nucleophilic indoles (Scheme 3, **3h**−**q**). Note that indoles containing electron-donating groups proceeded better than those with electron-withdrawing groups which can be explained by the fact that the electron-donating substituents could enhance the nucleophilicity of the indoles. Significantly, the desired products with halogen substituent on the rings were potential intermediates for further functionalization. Other nucleophilic substrates such as sp^3 C−H of nitroalkane and dimethyl malonate even sp C−H of phenylacetylene are also effective for such transformation (Scheme S1, Supporting Information).

In summary, we have developed a highly selective, efficient, and environmentally benign method for the visible light mediated cobalt-catalyzed CDC reaction in aqueous medium. By using earth-abundant and simple cobalt salt with dmgH as a ligand to form a photosensitizer in situ, good to excellent yields of the desired cross-coupling products could be achieved in aerobic conditions at room temperature under visible light irradiation. The catalytic process has no other byproduct showing exclusive selectivity for the cross-coupling C−C bonds formation of sp^3 C−H with sp^3 C−H, sp^2 C−H, and sp C−H. Moreover, the reaction is performed in water which is environmentally benign. Such an approach enriches low cost metal catalysis and represents a lower cost, milder, and greener process for organic transformation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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