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A Cascade Cross-Coupling Hydrogen Evolution Reaction by Visible Light Catalysis

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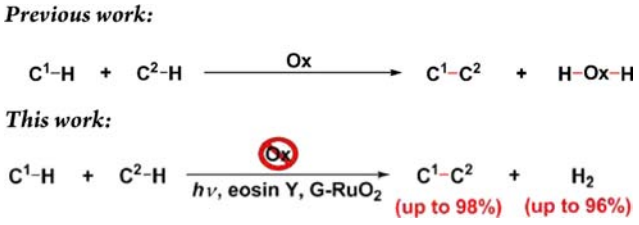
Supporting Information

ABSTRACT: Cross-dehydrogenative-coupling reaction has long been recognized as a powerful tool to form a C−C bond directly from two different C−H bonds. Most current processes are performed by making use of stoichiometric amounts of oxidizing agents. We describe here a new type of reaction, namely cross-coupling hydrogen evolution (CCHE), with no use of any sacrificial oxidants, and only hydrogen (H_2) is generated as a side product. By combining eosin Y and a graphene-supported RuO_2 nanocomposite (G-RuO_2) as a photosensitizer and a catalyst, the desired cross-coupling products and H_2 are achieved in quantitative yields under visible light irradiation at room temperature.

The design of mild, general, and efficient methods for C−C bond construction is an essential topic of synthetic chemistry.[1] Cross-dehydrogenative coupling (CDC) reaction is one of the most powerful tools to make a C−C bond directly from two different C−H bonds under oxidative conditions.[2,3] Such a coupling reaction avoids the prefunctionalization and defunctionalization that have been part of the traditional synthetic design, and thus reduces the number of steps to the target molecule. Over the past decade, this straightforward reaction has spurred tremendous research effort, and there have been numerous advances in the substrate scope, functional group tolerance, and a range of different catalysts for improving the transformation.[3] However, hydrogen (H_2) is not usually the byproduct because the thermodynamics of making a C−C bond with loss of H_2 is unfavorable. As a result, an appropriate sacrificial oxidant (Ox) is always required for the CDC reaction (Scheme 1, previous work).

Scheme 1



In this communication, we wish to report a new type of cross-coupling reaction for C−C bond construction, namely, cross-coupling hydrogen evolution (CCHE), which activates C−H bonds to afford a cross-coupling product and an equivalent amount of H_2 in good to excellent yields with no use of any sacrificial oxidants (Scheme 1, this work). Herein, an organic dye eosin Y is employed as a photosensitizer to initiate cross-coupling of amines with nucleophiles by visible light catalysis, and at the same time, a graphene-supported RuO_2 nanocomposite[3i] (G-RuO_2) is selected as a catalyst to capture the electron and proton eliminated from the C−H bonds of the substrates. As will be discussed later, this was found to be the case. With visible light irradiation for 20 h, the desired cross-coupling products are achieved smoothly at ambient condition, accompanying with H_2 formation in a quantitative yield (up to 96%). Spectroscopic study and product analysis provide direct evidence on the photoinduced electron transfer and H_2 evolution for this CCHE transformation.

Because of the prevalent skeleton of isoquinoline and indole in natural products,[4] our initial study focused on cross-coupling reaction of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) and indole (**2a**) that has been studied by using a photocatalyst and a sacrificial oxidant[6i] at room temperature. First, catalytic amounts of eosin Y (5 mol %) and G-RuO_2 (0.3 mol %) were added into the solution of **1a** and **2a**, and then the nitrogen-purged solution was irradiated by a high-pressure mercury lamp (500 W) with light wavelength longer than 450 nm for 10 h. To our delight, in the absence of a sacrificial oxidant the desired cross-coupling product was obtained in a moderate yield with 30% conversion of **1a**. More importantly, H_2 was generated in a 25% yield based on the consumption of **1a** (Table 1, entry 1). Increasing the concentration of eosin Y and irradiation time could significantly improve the performance. The cross-coupling product **3a** (89%) and H_2 (76%) were obtained with 90% conversion of **1a** after 20 h irradiation (Table 1, entries 2−3). Further increasing the amount of eosin Y from 20 to 50 mol %, however, resulted in lower conversion and yield of the transformation (Table 1, entries 4−6), probably due to light-filter effect at high concentration of eosin Y. In addition, the amount of indole was also found to

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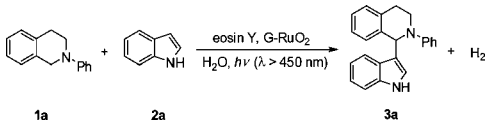
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

				yield	
entry	eosin Y (equiv %)	time (h)	conv (%)[b]	**3a** (%)[c]	H_2 (%)[d]
1	5	10	30	50	25
2	20	10	70	62	78
3	20	20	90	89	76
4	15	20	68	77	58
5	25	20	84	81	75
6	50	20	85	77	52
7[e]	20	20	90	92	83
8[f]	20	20	94	94	88
9[g]	20	20	98	95	90

[a]Conditions: 0.1 mmol **1a**, 0.2 mmol **2a**, 0.0003 mmol G-RuO_2, and corresponding amount of eosin Y in 5 mL of H_2O under N_2, irradiation of $\lambda > 450$ nm at room temperature. [b]Corresponding to **1a**. [c]Based on **1a** and determined by NMR using 4-nitroacetophenone as an internal standard. [d]Based on **1a**. [e]2.5 equiv of **2a**. [f]3.0 equiv of **2a**. [g]4.0 equiv of **2a**.

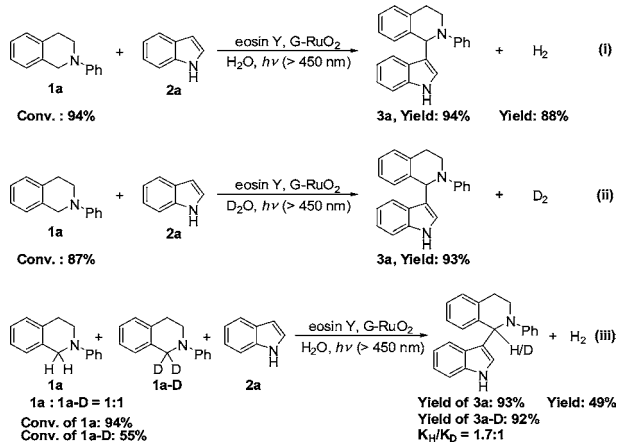
influence the CCHE process to some extent (Table 1, entries 7−9), and as the mixed solvents were used to replace water, the adverse effects occurred (Table S1, Supporting Information (SI)). It is of significance that under an optimal condition almost complete conversion of **1a** (98%) and excellent yields for **3a** (95%) and H_2 (90%), respectively, were achieved in the CCHE transformation (Table 1, entry 9). The absence of either eosin Y or G-RuO_2, however, led to a negligible conversion of **1a** under the same conditions (Table S1 (SI)). Moreover, no conversion could be detected when the reaction was conducted in the dark (Table S1 (SI)). These results suggest that light, eosin Y and G-RuO_2 are all essential for the reaction.

It has long been known that thermodynamics of making a C−C bond with the loss of H_2 is typically unfavorable and thus requires an external driving force, stoichiometric sacrificial oxidants,[3] such as peroxides, quinones and molecular oxygen. In particular, the use of visible light[5,6] has been recently demonstrated promising in aerobic CDC reactions, where molecular oxygen is necessary to accept the electron and proton eliminated from the substrates. In the current study, however, the whole reaction undergoes under an inert atmosphere. And the absence of oxygen led to negligible product formation when the aqueous solution of eosin Y, **1a**, and **2a** was irradiated by visible light ($\lambda > 450$ nm) (Table S1 (SI)). Nevertheless, a catalytic amount of G-RuO_2 (0.3 mol %) was able to produce **3a** and an equivalent amount of H_2 from the same reaction vessel with excellent yields (Table 1, entry 9). Obviously, G-RuO_2 plays a crucial role in operating this unique CCHE reaction.

To understand the primary process of the reaction, we examined the possibility of G-RuO_2 to function as a catalyst for H_2 evolution. It was noted that H_2 could evolve when nucleophile indole was absent from the reaction system, but in the absence of G-RuO_2 no H_2 was detected (Figure S1 and Table S1 (SI)). To confirm G-RuO_2 responsible for H_2 evolution, we used tertiary amine triethanolamine (TEOA), a typical sacrificial electron donor for photosynthesis of H_2,[7] to replace **1a**. The system, containing eosin Y, G-RuO_2, and TEOA, evolved H_2 immediately with turnover number (TON) of 832 for 8 h of irradiation (Figure S2 (SI)), which is greater than that of the best system achieved by RuO_2 for H_2 evolution so far (TON = 120).[8a] For systematic comparison, $RuO_2{\cdot}nH_2O$ and Al_2O_3-supported RuO_2 (Al_2O_3−RuO_2)[8b] were further prepared as the catalyst for CCHE reaction. And the results indicated that G-RuO_2 is much more efficient than $RuO_2{\cdot}nH_2O$ and Al_2O_3−RuO_2 under the same condition (Table S1 (SI), entries 7−8). Clearly, the electronic conductivity of the graphene[9] may accelerate the electron transfer between eosin Y and RuO_2 on the surface of graphene during the reaction.

Next, we carried out an experiment with a deuterated substrate to identify the source of H_2 in the reaction. When deuterated substrate **1a-D** was selected to react with indole **2a** under the same condition, the conversion and efficiency were significantly decreased, indicating that the dissociation of proton from amine **1a-D** is a rate-determining step for the CCHE process. When D_2O was used as the solvent, D_2 was generated instead of H_2 as the only byproduct with no alteration of the reaction efficiency, which suggests that the released protons from the substrates are quickly exchanged with D_2O (Scheme 2). From the above results, we could speculate that G-RuO_2 is able to accept the protons of the substrates.

Scheme 2. Deuterium Experiments for CCHE Reactions



The following question is whether G-RuO_2 could be an electron acceptor. To answer this question, a flash-photolysis study was carried out in a degassed aqueous solution at room temperature. Thanks to the rich spectroscopic property of eosin Y,[6e,10] we obtained valuable information on the intermediates during irradiation. Upon laser excitation by 532 nm light, a strong negative bleach of the ground-state absorption of eosin Y at ~530 nm and characteristic absorptions at ~560 nm with a lifetime of 115 μs were seen immediately (Figure S3-a (SI)), the latter of which is consistent with that of the triplet excited state of eosin Y, ^{3}[eosin Y]*.[10] When TEOA was added into the solution of eosin Y, new absorptions appeared with a maximum at ~400 nm in addition to the strong absorptions of ^{3}[eosin Y]* (Figure S3-b (SI)). With reference of spectroscopic character of eosin Y,[10] the new species at ~400 nm is ascribed to reduced eosin Y radical anion, [eosin Y]$^{\bullet-}$. From the kinetics probed at 400 nm, we inferred the lifetime of [eosin Y]$^{\bullet-}$ being 94.3 μs. In contrast, direct introduction of G-RuO_2 into the solution of eosin Y caused the absorptions of ^{3}[eosin Y]* unchanged (112 μs, Figure S3-c (SI)) indicative the oxidative quenching ^{3}[eosin Y]* by G-RuO_2 is negligible. Alternatively, with the addition of G-RuO_2 into a mixture of eosin Y and

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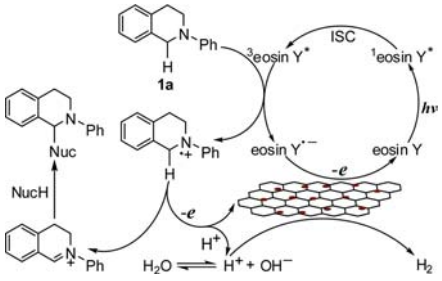
TEOA in aqueous solution, the system exhibited almost the same absorptions of $[\text{eosin Y}]^{\bullet-}$ (Figure S3-d (SI)), but the lifetime of absorption at 400 nm decreased to 54.6 μs. This finding provided direct evidence on the electron transfer from $[\text{eosin Y}]^{\bullet-}$ to G-RuO_2.

On the basis of the above results, we suggest a general mechanism of this CCHE reaction (Scheme 3). Upon visible

Scheme 3. Proposed Mechanism

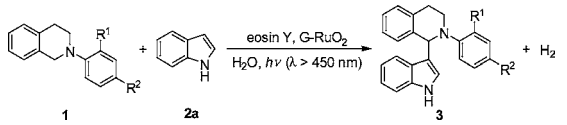


light irradiation, eosin Y is pumped to its singlet excited state $^1[\text{eosin Y}]^*$ that quickly transfers to its triplet state $^3[\text{eosin Y}]^*$ with the lifetime of 115 μs. With the addition of tertiary amine **1a** into the solution, an electron transfer from **1a** to $^3[\text{eosin Y}]^*$ state results in the formation of cation radical $[\mathbf{1a}]^{\bullet+}$ and eosin Y radical anion $[\text{eosin Y}]^{\bullet-}$, as evidenced by transient absorption spectra (Figure S3 (SI)). The generated $[\mathbf{1a}]^{\bullet+}$ further releases a proton into water and then is oxidized to afford an iminium ion intermediate. Subsequently, the nucleophilic addition to the iminium gives rise to the cross-coupling product **3a**. On the other hand, the formed radical anion $[\text{eosin Y}]^{\bullet-}$ is restored to its ground state by G-RuO_2 in water. The shortened lifetime of $[\text{eosin Y}]^{\bullet-}$ from 94.3 to 54.6 μs suggests an effective electron transfer from the $[\text{eosin Y}]^{\bullet-}$ to G-RuO_2, which can react with the protons delivered by $[\mathbf{1a}]^{\bullet+}$ to produce H_2 in water. Because the deuterium experiments indicate that the dissociation of proton from **1a** is a rate-determining step and D_2 was produced when D_2O was used as a solvent, together with the fact that the reaction efficiency is significantly decreased when water was replaced by mixed organic solvents, we believe that water is of significance in mediating the proton exchange in the cross-coupling process.

With understanding the reaction mechanism, we further explored the generality of the CCHE reaction on the scope of *N*-phenyl-1,2,3,4-tetrahydroisoquinolines (**1**). As shown in Table 2, most of the desired crossing-coupling products **3** and H_2 are obtained in good to excellent yields. In particular, the products containing chloro- or bromo- functionalities can serve as potential intermediates for further organic transformations (Table 2, entries 6−7). However, the strong electronic effect of the substituent retards the reaction dramatically (Table 2, entries 3−4), probably due to the reduction of the electrophilicity of imine cation generated during reaction. Meanwhile, a stronger electron-withdrawing group at the 4-position of *N*-phenyl tetrahydroisoquinoline makes the photoinduced electron transfer from *N*-phenyl tetrahydroisoquinoline to eosin Y thermodynamically unfavorable, thereby leading to no reaction at all (Table 2, entry 8).

Good to excellent yields were also obtained by using a variety of substituted nucleophilic indoles. Note that the CCHE reaction always occurs at the 3-position of indoles no matter which position is substituted by different electronic groups (Table 3). A good result was achieved when 7-methyl indole

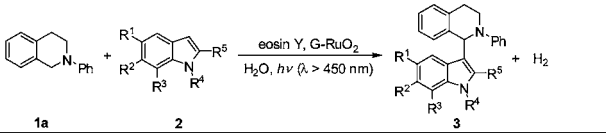
Table 2. Scope of 1,2,3,4-Tetraisoquinolines[a]

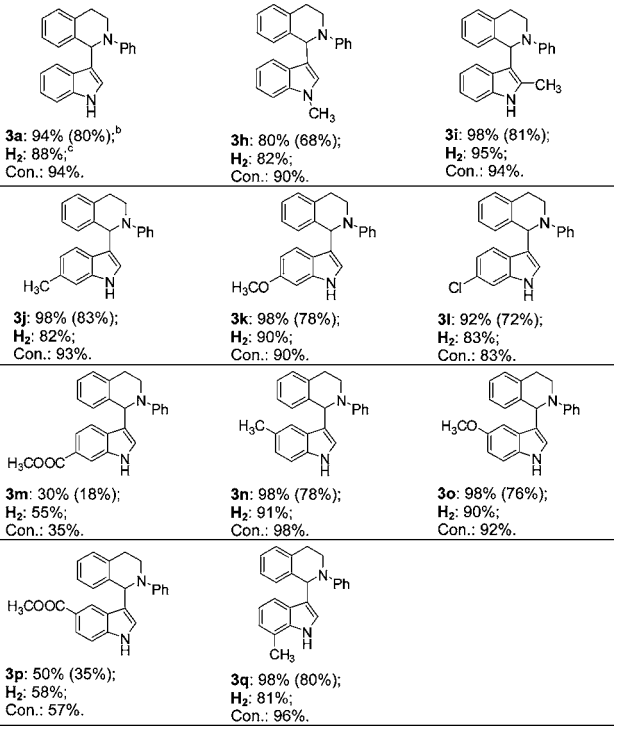


				yield	
entry	R^1	R^2	conv (%)[b]	**3** (%)[c]	H_2 (%)[d]
1	H	H	94	**3a**, 94(80)	88
2	H	CH_3	85	**3b**, 96(78)	96
3	H	OCH_3	35	**3c**, 83(58)	43
4	OCH_3	H	21	**3d**, 89(56)	80
5	H	F	91	**3e**, 96(82)	96
6	H	Cl	83	**3f**, 91(74)	76
7	H	Br	80	**3g**, 89(70)	73
8	H	CN	trace	0	trace

[a]Conditions: 0.1 mmol **1**, 0.3 mmol **2a**, 0.0003 mmol G-RuO_2, and 0.02 mmol eosin Y in 5 mL of water under N_2, irradiation of $\lambda > 450$ nm at room temperature. [b]Corresponding to **1**. [c]Based on **1** and determined by NMR using 4-nitroacetophenone as an internal standard, isolated yields are given in parentheses. [d]Based on **1**.

Table 3. Scope of Indoles[a]





[a]Conditions: 0.1 mmol **1a**, 0.3 mmol **2**, 0.0003 mmol G-RuO_2, and 0.02 mmol eosin Y in 5 mL of water under N_2, irradiation of $\lambda > 450$ nm at room temperature. [b]Based on **1a** and determined by NMR using 4-nitroacetophenone as an internal standard, isolated yields are given in parentheses. [c]Corresponding to **1a**.

was used (Table 3, **3q**). Because of the lower electron density for the nucleophilie addition, a strong electron-withdrawing substituent at indole displays a relatively lower reactivity (Table 3, **3m** and **3p**). More nucleophilic substrates, such as malonate

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esters and phosphite ester, were also used to replace indoles for the CCHE reaction. Satisfactorily, the reaction proceeds well resulting in the formation of the crossing-coupling products and H_2 in moderate to excellent yields (Scheme S1 (SI)).

In summary, we have succeeded in developing a new type of reaction, cross-coupling hydrogen evolution CCHE, by visible light catalysis. The cascade reaction is accomplished under an inert atmosphere by activation of C−H bonds via dehydrogenation that does not require any sacrificial oxidants, and an equivalent amount of H_2 is generated as an only side product. Combining eosin Y and G-RuO_2 as the photosensitizer and the catalyst, the CCHE reaction undergoes smoothly to afford the cross-coupling products and H_2 in good to excellent yields. Spectroscopic study and product analysis demonstrate the photoinduced electron transfer from tertiary amine to eosin Y to generate $[\text{eosin Y}]^{\bullet-}$, which further delivers an electron to G-RuO_2 for reduction of protons to H_2 and regeneration of eosin Y. This work constitutes the first example of photocatalytic dehydrogenative cross-coupling reaction to form a C−C bond by two different C−H bonds with concomitant emission of H_2. The operationally simple and general mode of activation is suitable for a broad range of reactants. We hope this CCHE reaction will become a useful method to construct C−C bonds for cleaner, safer, and more atom-economic organic transformation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, methods, and product characterization. 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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