Organic LETTERS

Cross-Coupling Hydrogen Evolution Reaction in Homogeneous Solution without Noble Metals

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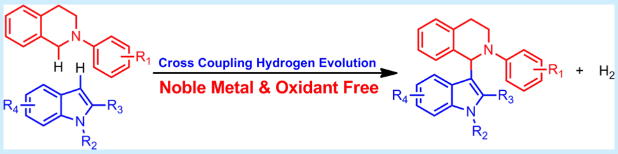
Ⓢ *Supporting Information*

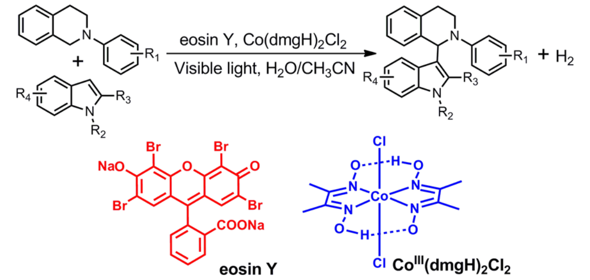
ABSTRACT: A highly efficient noble-metal-free homogeneous system for a cross-coupling hydrogen evolution (CCHE) reaction is developed. With cheap, earth-abundant eosin Y and molecular catalyst Co(dmgH)$_2$Cl$_2$, good to excellent yields for coupling reactions with a variety of isoquinolines and indole substrates and H$_2$ have been achieved without any sacrificial oxidants. Mechanistic insights provide rich information on the effective, clean, and economic CCHE reaction.



Developing efficient and atom-economic methods for C−C bond formation is always an important concern in synthetic chemistry.[1,2] The cross-dehydrogenative coupling reaction[3] is a desirable synthetic approach toward C−C bond formation, as it does not require additional functionalization of subcomponents. Reactions of this type often involve the use of stoichiometric sacrificial oxidants, which leads to low atom economy and possible generation of toxic wastes. A new type of reaction, cross-coupling hydrogen evolution (CCHE) reaction,[4] has recently appeared, which avoids the use of any sacrificial oxidants and yields hydrogen gas (H$_2$) as the sole byproduct. By combining eosin Y and a graphene-supported RuO$_2$ nanocomposite (G-RuO$_2$)[5] as a photosensitizer and a catalyst, the CCHE reaction proceeds smoothly to afford the desired cross-coupling products and H$_2$ in quantitative yields under visible light irradiation. This novel reaction offers a potential solution for highly efficient, clean, and economical C−C bond formation.

In an effort to expand our knowledge and to develop a new system of the CCHE reaction, we replaced the noble metal heterogeneous catalyst G-RuO$_2$ with inexpensive molecular catalysts. In this contribution, we report an elegant new catalytic system for the CCHE reaction in a homogeneous solution. Here, an earth-abundant Co(dmgH)$_2$Cl$_2$ (dmgH = dimethylglyoximate) complex is used as a catalyst to capture the electrons and protons eliminated from the C−H bonds of the substrates (Scheme 1). For a systematic comparison of the G-RuO$_2$ system, eosin Y is employed as a photosensitizer to initiate the cross-coupling of *N*-phenyl-tetrahydroisoquinolines and indoles, a typical cross-coupling reaction under visible-light catalysis.[6,7]

Scheme 1. Cross-Coupling Hydrogen Evolution in Homogeneous Solution without Noble Metals



Our initial study focused on the cross-coupling of *N*-phenyl-tetrahydroisoquinolines and indoles for their prevalent skeleton in natural products.[8] After 1 mol % of eosin Y and 5 mol % of Co(dmgH)$_2$Cl$_2$ were added into a mixture of CH$_3$CN and H$_2$O containing *N*-phenyl-tetrahydroisoquinoline **1a** and indole **2a**, the reaction mixture was deaerated by bubbling nitrogen and then irradiated by green LEDs (λ = 525 ± 10 nm) at room temperature. Significantly, 55% and 63% yields of the desired cross-coupling product and H$_2$, respectively, could be obtained with no use of any sacrificial oxidants (Table 1, entry 1). And the cross-coupling product and H$_2$ are the only products detected. Increasing the amount of Co(dmg)$_2$Cl$_2$ and eosin Y resulted in a large improvement in both conversion and yield of the reaction (Table 1, entries 2−5). When 3 mol % of eosin Y and 8 mol % of Co(dmgH)$_2$Cl$_2$ were used, the conversion approached 100% and the yields of the cross-coupling product and H$_2$ were achieved in yields of 94% and 98%, respectively. When the CCHE reaction proceeded in H$_2$O, however, only a 12% yield of the cross-coupling product and a 16% yield of H$_2$ were obtained (Table 1, entry 6). Addition of an organic solvent greatly enhanced the performance of the reaction (Table 1, entries 5, 7, 8). Among various organic solvents, CH$_3$CN was the best for the CCHE reaction. H$_2$O is also of significance in the reaction. When the CCHE reaction was carried out in CH$_3$CN, a negligible amount of desired cross-

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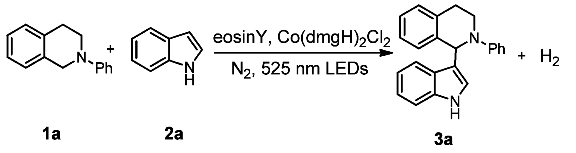
Table 1. Optimization of the Reaction Conditions[a]



entry	EY	cat.	solvent[b]	convn[c]	H_2 (%)[d]	3a (%)[e]
1	1%	5%	H_2O/CH_3CN	65	63	55
2	1%	8%	H_2O/CH_3CN	80	76	69
3	1%	10%	H_2O/CH_3CN	82	79	71
4	3%	8%	H_2O/CH_3CN	100	98	94
5	5%	8%	H_2O/CH_3CN	100	97	91
6	3%	8%	H_2O	18	16	12
7	3%	8%	H_2O/DMF	45	43	39
8	3%	8%	H_2O/CH_3OH	55	54	50
9[f]	3%	8%	CH_3CN	6	3	5

[a] Reaction conditions: 0.1 mmol of *N*-phenyl-tetrahydroisoquinoline **1a**, 0.2 mmol of indole **2a**, corresponding eosin Y, and cat. ($Co(dmgH)_2Cl_2$) were added, and the solution was strictly deaerated and irradiated for 16 h by 525 nm green LEDs, with methane as the internal standard. [b] H_2O/CH_3CN 4:1. [c] Corresponding to **1a**. [d] Yields detected by gas chromatography using pure methane as an internal standard based on **1a**. [e] Yields detected by NMR using 4-nitroacetophenone as an internal standard based on **1a**. [f] $Co(dmgH)_2pyCl$ instead of $Co(dmgH)_2Cl_2$.

coupling product and H_2 were detected (Table 1, entry 9). When D_2O instead of H_2O was used as the solvent, D_2 was obtained as the only byproduct with no alteration of the reaction efficiency (Scheme S1), possibly a result of a quick exchange of H_2O with the released proton from the substrate. And the best ratio of H_2O to CH_3CN was found to be 4:1 (Table S1). Further experiments indicated that the conversion of **1a** was negligible when eosin Y or $Co(dmgH)_2Cl_2$ was absent from the reaction mixture, and no conversion of **1a** could be detected if the reaction was conducted in darkness.

Given that noble-metal G-RuO_2[4] was replaced by the inexpensive $Co(dmgH)_2Cl_2$ molecular catalyst, we compared the two systems and found that the amount of eosin Y was decreased from 20 to 3 mol % for the CCHE reaction in the homogeneous solution, and simultaneously **1a** could be completely converted to the desired cross-coupling product and H_2 in a shorter reaction time but with higher yields (Table 1, entry 4). For the indole with an ester group that showed the lowest reactivity in the G-RuO_2 heterogeneous system,[4] the reactivity of this noble-metal-free homogeneous reaction system enhanced four times (Scheme 3). Moreover, the homogeneous reaction can be carried out in a mixture of organic solvent and water. Therefore, it is possible to expand the scope of water-insoluble substrates for the CCHE reaction.

The catalyst changed from G-RuO_2 to $Co(dmgH)_2Cl_2$, which resulted in greatly improved catalytic performance, prompting us to shed light on the mechanism of the CCHE reaction. For consistency regarding reaction conditions, all subsequent mechanistic studies were performed under the optimal conditions. Although no obvious change could be detected in the UV−vis absorption spectrum of each component, eosin Y, **1a**, $Co(dmgH)_2Cl_2$, and indoles as well as their mixtures, these spectra suggested that only eosin Y in the reaction mixture could be excited by green LED light (SI, Figure S1). In this situation, two reaction pathways are possible. One is that the photoexcited eosin Y might be oxidatively quenched by $Co(dmgH)_2Cl_2$ to generate [eosin Y]$^{\bullet+}$ for the oxidation of **1a**. The other is that the photoexcited eosin Y could be reductively quenched by **1a** to produce [eosin Y]$^{\bullet-}$, which delivers an electron to the $Co(dmgH)_2Cl_2$ catalyst for proton reduction to H_2. To determine the dominant reaction pathway in the system, a flash photolysis investigation was undertaken in terms of the rich spectroscopic property of eosin Y.[9] As shown in Figure 1a, immediately after a laser excitation by 532 nm light, a strong negative bleach of the ground state absorption of eosin Y at approximately 520 nm and the characteristic absorption assigned to the triplet excited state (^{3}[eosin Y]*) at 560 nm were observed. When *N*-phenyl-tetrahydroisoquinoline **1a** was introduced into the solution of eosin Y, a new absorption band, which is in accordance with the eosin Y radical anion ([eosin Y]$^{\bullet-}$), appeared at 410 nm at the expense of the ^{3}[eosin Y]* absorption at 560 nm. The result suggested that the electron transfer from **1a** to ^{3}[eosin Y]* took place. In contrast, introduction of $Co(dmgH)_2Cl_2$ into the eosin Y solution with 532 nm laser irradiation resulted in no change of the ^{3}[eosin Y]* absorption (SI, Figure S2c). Clearly, the reductive quenching pathway of the photoexcited ^{3}[eosin Y]* dominates the homogeneous catalytic system.

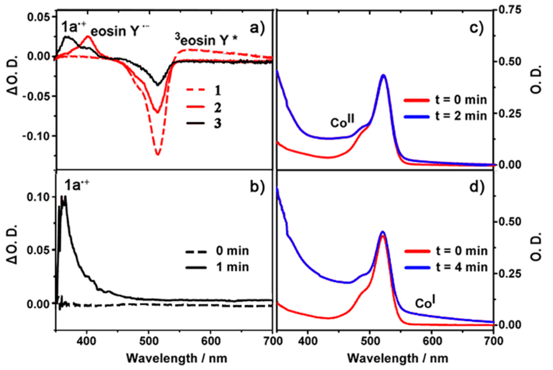
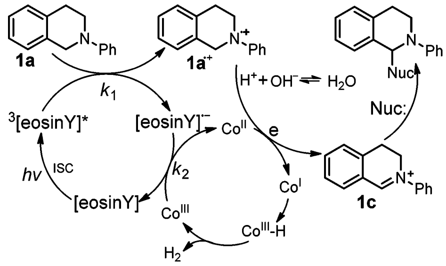


Figure 1. (a) Transient absorption spectra observed after laser excitation (λ_{ex} = 532 nm) of system containing (1) eosin Y (1.0×10^{-5} M); (2) eosin Y (1.0×10^{-5} M), **1a** (3.3×10^{-4} M); (3) eosin Y (1.0×10^{-5} M), **1a** (3.3×10^{-4} M), $Co(dmgH)_2Cl_2$ (2.7×10^{-5} M). The concentration ratio of the substrate is identical to that in the reaction. (b) Spectroelectrochemical absorption spectrum of $1a^{\bullet+}$ in CH_3CN/H_2O by oxidation of **1a** (1.0×10^{-5} M) at 0.90 V voltage relative to NHE. (c and d) UV−vis absorption spectra of system containing **1a** (4.0×10^{-4} M), **2a** (8.0×10^{-4} M), eosin Y (1.2×10^{-5} M), $Co(dmgH)_2Cl_2$ (3.2×10^{-5} M) in H_2O/CH_3CN 4:1 before and after irradiation by green LEDs (525 ± 10 nm).

Further addition of $Co(dmgH)_2Cl_2$ into a mixture of eosin Y and **1a** in a 4:1 H_2O/CH_3CN solution led to a distinct quenching of [eosin Y]$^{\bullet-}$ upon laser excitation at 532 nm. The lifetime of [eosin Y]$^{\bullet-}$ changed from 39.8 to 4.3 μs indicating the electron transfer from [eosin Y]$^{\bullet-}$ to $Co(dmgH)_2Cl_2$. Simultaneously, a new absorption with a maximum appeared at 370 nm in the transient absorption spectra. The emerged absorption band is similar to that of **1a** under oxidation potential at 0.90 V versus NHE in CH_3CN/H_2O (Figure 1b). The result indicated that the $1a^{\bullet+}$ at 370 nm is generated by electron transfer from **1a** to the excited eosin Y. This is, to the best of knowledge, the first time the *N*-phenyl-tetrahydroisoquinoline radical cation was observed directly in the cross-coupling reactions. Importantly, monitoring the absorption spectral change before and after irradiation provided evidence of the formation of the reduced intermediates of Co-

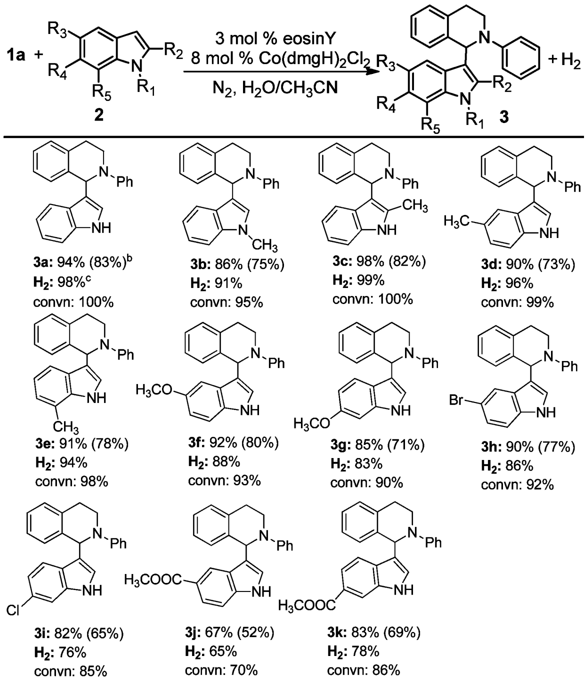
$(dmgH)_2Cl_2$. Before irradiation, the absorption spectrum was simply the sum of the individual components and eosin Y showed the absorption in the visible light region. Upon irradiation by green LEDs for 2 min, a characteristic absorption appeared at 450 nm consistent with the formation of Co^{II} species as reported in the literature (Figure 1c). Prolonged irradiation within 4 min led to new lower energy absorptions at 550–650 nm, in addition to the one at 450 nm (Figure 1d). The new lower energy bands are identical to Co^{I} species reported in the literature, which is a crucial intermediate for H_2 evolution.[10]

Scheme 2. Proposed Mechanism



On the basis of the above observations, we proposed a plausible mechanism for the CCHE reaction (Scheme 2). Upon visible light irradiation, eosin Y is immediately excited to its singlet excited state ^{1}[eosin Y]* followed by a quick intersystem crossing (ISC) to its triplet excited state ^{3}[eosin Y]* with a lifetime of 98.8 μs (SI, Figure S3a). Subsequent electron transfer from **1a** to ^{3}[eosin Y]* results in the formation of the eosin Y radical anion, [eosin Y]$^{\bullet-}$, and amine radical cation **1a**$^{\bullet+}$; the electron transfer rate constant (k_1) from **1a** to the excited ^{3}[eosin Y]* was estimated to be 3.76×10^9 M^{-1} s^{-1} according to the lifetime of ^{3}[eosin Y]* with (0.8 μs) and without (98.8 μs) **1a** (SI, Figure S3b). The generated amine radical cation **1a**$^{\bullet+}$ releases a proton and is further oxidized to generate an iminium intermediate, which can effectively react with nucleophiles to afford the desired cross-coupling product. The formed eosin Y radical anion ([eosin Y]$^{\bullet-}$), on the other hand, delivers an electron to $Co(dmgH)_2Cl_2$ to regenerate eosin Y to its ground state. Based on the lifetime alternation of [eosin Y]$^{\bullet-}$ from 39.8 to 4.3 μs (SI, Figure S3c, d), the rate of electron transfer (k_2) from [eosin Y]$^{\bullet-}$ to $Co(dmgH)_2Cl_2$ was determined to be 7.78×10^9 M^{-1} s^{-1}. The cascade electron transfer from substrate **1a** to the excited ^{3}[eosin Y]* to produce [eosin Y]$^{\bullet-}$, and then from the reduced radical anion [eosin Y]$^{\bullet-}$ to $Co(dmgH)_2Cl_2$, is believed to be responsible for the efficient CCHE reaction in the homogeneous solution. It is suggested that the formation of H_2 is protonation of Co^{I} to form a Co^{III}–H hydrid.[10] H_2 is generated by either protonation of the Co^{III}–H hydrid, H_2 elimination and reduction of Co^{III} to Co^{II}, or reduction of the Co^{III}–H hydrid to the Co^{II}–H hydrid followed by protonation to give H_2 and Co^{II}. The alternative involves a reaction between two Co^{III}–H hydrids to form H_2 and 2 molecules of Co^{II}.

Scheme 3. Scope of Indoles[a]

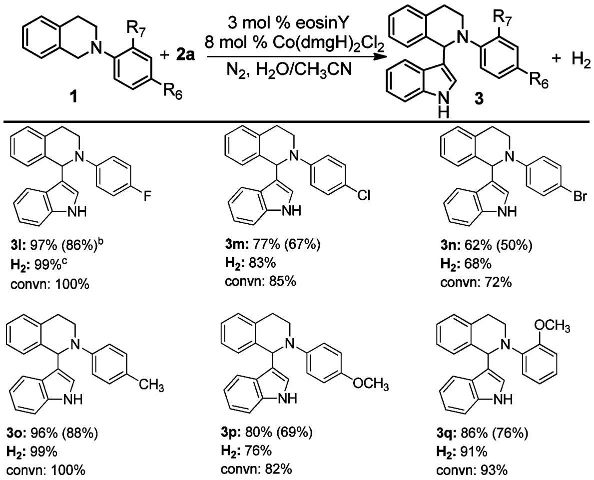


[a] Reaction conditions: 0.1 mmol of **1a**, 0.2 mmol of **2**, 4 mL of H_2O, 1 mL of CH_3CN, 2.04 mg of eosinY, 2.9 mg of $Co(dmgH)_2Cl_2$; the solution is strictly deaerated, with pure methane as the internal standard, and irradiated for 16–22 h by 525 nm green LEDs. [b] Yields detected by ^{1}H NMR using 4-nitroacetophenone as an internal standard based on **1a**; isolated yields are given in parentheses. [c] Corresponding to **1a**.

Under the optimized conditions, various indole derivatives were examined to show the generality of the CCHE reaction in a homogeneous solution (Scheme 3). When the electron-withdrawing or -donating groups were introduced at different positions of indoles, the desired cross-coupling product with concomitant emission of H_2 could also be obtained in good to excellent yields. In contrast to the reported heterogeneous system, the yield of the cross-coupling product and H_2 is greatly enhanced in the homogeneous solution when the substituted group is Br or ester in the indole skeleton. When *N*-phenyl-tetrahydroisoquinolines with various substituted groups were examined, good to excellent yields were also obtained (Scheme 4). As tabulated in Scheme 4, the steric hindrance seems not to have a big impact on the final results, while the yield of the cross-coupling product and H_2 decreased when R_6 was F, Cl, or Br, respectively.

In summary, we have developed a noble-metal-free homogeneous strategy for the CCHE reaction with no use of any sacrificial oxidants under visible light irradiation. Using low-cost, earth-abundant eosin Y and $Co(dmgH)_2Cl_2$ as a photosensitizer and a catalyst, good to excellent yields of cross-coupling products and virtual equivalents of H_2 evolution have been achieved without any sacrificial oxidants. The homogeneous CCHE reaction is attractive because it can be performed in a mixture of organic solvent and water, which greatly expands the scope of substrates not soluble in water. Mechanistic insights revealed that the efficient CCHE reaction relies on the cascade electron transfer from substrate **1a** to the excited ^{3}[eosin Y]* to generate the [eosin Y]$^{\bullet-}$ radical anion, which delivers an electron to $Co(dmgH)_2Cl_2$ for proton reduction to H_2. Importantly, direct evidence of the formation of cation radical **1a**$^{\bullet+}$ was obtained for the first time in the cross-coupling reaction by visible light catalysis and reduced Co^{II} and Co^{I} species as intermediates, which greatly enriches our knowledge for the development of cleaner, safer, and more atom-economic CCHE reactions.

Scheme 4. Scope of Tetrahydroisoquinolines[a]



[a]Reaction conditions: 0.1 mmol of **1a**, 0.2 mmol of **2**, 4 mL of H_2O, 1 mL of CH_3CN, 2.04 mg of eosinY, 2.9 mg of $Co(dmgH)_2Cl_2$. The solution is strictly deaerated, with pure methane as the internal standard, and irradiated for 16–22 h by 525 nm green LEDs. [b]Yields detected by ^1H NMR using 4-nitroacetophenone as an internal standard based on **1a**; isolated yields are given in parentheses. [c]Corresponding to **1a**.

■ 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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■ REFERENCES

(1) (a) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (b) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824. (c) Wang, D.-H.; Engle, K.-M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (f) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780.

(2) (a) Trost, B. *Science* **1991**, *254*, 1471. (b) Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437. (c) Li, C.-J.; Trost, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 13197. (d) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998. (e) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

(3) (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) Komiya, N.; Terai, H.; Nakae, T.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (c) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (d) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (e) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14044. (f) Li, C.-J. *Acc. Chem. Res.* **2008**, *42*, 335. (g) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (h) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74.

(4) Meng, Q.-Y.; Zhong, J.-J.; Liu, Q.; Gao, X.-W.; Zhang, H.-H.; Lei, T.; Li, Z.-J.; Feng, K.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 19052.

(5) Meng, Q.-Y.; Liu, Q.; Zhong, J.-J.; Zhang, H.-H.; Li, Z.-J.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Org. Lett.* **2012**, *14*, 5992.

(6) (a) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785. (b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (c) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (d) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (e) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(7) (a) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (b) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852. (c) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360. (d) Su, F.; Mathew, S. C.; Möhlmann, L.; Antonietti, M.; Wang, X.; Blechert, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 657. (e) To, W.-P.; Tong, G. S.-M.; Lu, W.; Ma, C.; Liu, J.; Chow, A. L.-F.; Che, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2654. (f) Liu, Q.; Li, Y.-N.; Zhang, H.-H.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Chem.—Eur. J.* **2012**, *18*, 620. (g) Zhong, J.-J.; Meng, Q.-Y.; Wang, G.-X.; Liu, Q.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z. *Chem.—Eur. J.* **2013**, *19*, 6443. (h) Gao, X.-W.; Meng, Q.-Y.; Xiang, M.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z. *Adv. Synth. Catal.* **2013**, *355*, 2158. (i) Kreis, L. M.; Krautwald, S.; Pfeiffer, N.; Martin, R. E.; Carreira, E. M. *Org. Lett.* **2013**, *15*, 1634. (j) Weiss, M. E.; Kreis, L. M.; Lauber, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11125.

(8) (a) Li, Z. P.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (b) Liu, P.; Zhou, C.-Y.; Xiang, S.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 2739. (c) Klussmann, M.; Boess, E.; Schmitz, C. *J. Am. Chem. Soc.* **2012**, *134*, 5317.

(9) (a) Joselevich, E.; Willner, I. *J. Phys. Chem.* **1995**, *99*, 6903. (b) Islam, S. D. M.; Konishi, T.; Fujitsuka, M.; Ito, O.; Nakamura, Y.; Usui, Y. *Photochem. Photobiol.* **2000**, *71*, 675.

(10) (a) Dempsey, J. L.; Brunschwig, B. S.; Winkler, J. R.; Gray, H. B. *Acc. Chem. Res.* **2009**, *42*, 1995. (b) Artero, V.; Chavarot-Kerlidou, M.; Fontecave, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7238. (c) Eisenberg, R.; Lazarides, T.; McCormick, T.; Du, P.; Luo, G.; Lindley, B. *J. Am. Chem. Soc.* **2009**, *131*, 9192.