# External Oxidant-Free Oxidative Cross-Coupling: A Photoredox Cobalt-Catalyzed Aromatic C−H Thiolation for Constructing C−S Bonds

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**S** *Supporting Information*

**ABSTRACT:** An external oxidant-free oxidative coupling for aromatic C−H thiolation by visible-light photoredox cobalt-catalysis has been developed. Various substrates could afford benzothiazoles in good to excellent yields, and only $H_2$ is generated as a side product. When catalytic TBAOH was used as the base, not only 2-aryl but also 2-alkylbenzothiazoles could be obtained through this novel dehydrogenative coupling reaction. This method could be scaled up and applied to the synthesis of biologically active molecules bearing benzothiazole structural scaffolds (potent antitumor agents). Furthermore, the unexpected oxidation byproduct amides, which are often generated in oxidative cyclization of thiobenzanilides, can be completely avoided. Mechanistic studies showed that the $H_2$ originates from the substrates. The kinetic studies indicate that the interaction between the cobalt catalyst and proton might be involved in the rate-limiting process.
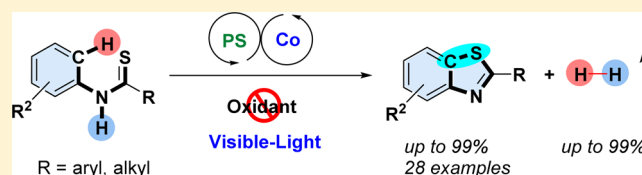
## INTRODUCTION

Construction of carbon−heteroatom bonds is a fundamental research area in chemical science, since the introduction of heteroatoms is important to the functional properties of organic compounds. Cross-coupling is perhaps the most powerful tool for constructing carbon−heteroatom bonds.[1] However, in the classic cross-coupling between a nucleophile and an electrophile, significant amounts of undesirable byproducts are usually produced.[2] The recent developed oxidative cross-coupling between C−H and heteroatom−H nucleophiles has advanced the construction of C−heteroatom bonds toward sustainable synthesis.[3] However, oxidants and proton acceptors have to be applied as the sacrificial reagents, which lead to some wasteful byproducts or oxidation side reactions.

Therefore, it would be appealing to develop oxidative cross-couplings between C−H and heteroatom−H nucleophiles for constructing C−heteroatom bonds under oxidant-free and proton-acceptor-free conditions.[4] However, there are only a few examples where this mechanistic paradigm has been applied to the construction of C−C,[5] S−S,[6] C−N,[7] and C−P[8] bond formations from their corresponding C−H and X−H (X = C, N, P, S) nucleophiles. As one of the most important carbon−heteroatom bonds in organic chemistry, C−S bonds are frequently found in important pharmaceuticals and biologically active natural compounds.[9] To the best of our knowledge, there is no report on C−S bond formation from C−H thiolation under oxidant-free condition with generation of $H_2$. Especially, up to now, no examples have been reported to realize intramolecular cross-coupling under oxidant-free conditions. Herein, we report our progress on aromatic C−H thiolation with liberation of $H_2$ by visible-light photocatalysis (Scheme 1).

**Scheme 1. Oxidant-Free Aromatic C−H Thiolation to Construct C−S Bonds**
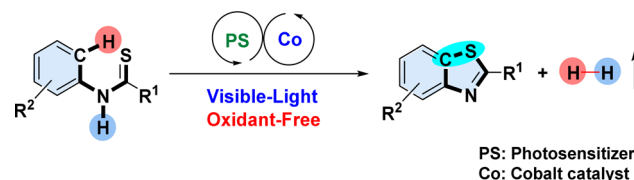


The products of this transformation are benzothiazoles, a class of structurally important scaffolds that have drawn much attention on developing synthetic methods for accessing such ubiquitous structural units.[10]

Among such synthetic methods, the intramolecular cyclization of thiobenzanilide derivatives is a significant approach to form benzothiazoles, such as transition-metal-catalyzed cyclization of o-halothiobenzanilides[10b,c] and direct oxidative C−H functionalization of thiobenzanilides.[10e−i] Despite these ad-

vances, it is sometimes difficult to keep away from tiring prefunctionalization and unexpected byproducts. For example, the conversion from thiobenzanilides to benzothiazoles might face the problem of oxidation byproducts, amides, resulting from the use of oxidants. In this article, we report the development of a novel external oxidant-free photoredox cobalt-catalyzed C−H functionalization reaction, in which the generation of benzamides was successfully avoided.

## ■ RESULTS AND DISCUSSION

**Initial Exploration and the Impact of the Proton-Reducing Catalyst.** We initially explored the intramolecular oxidative cyclization of N-phenylbenzothioamide **1a** under external oxidant-free conditions. The transformation could be achieved smoothly with the combination of a photosensitizer and a proton reducing catalyst under weak alkaline conditions, and $H_2$ was detected as the only byproduct (for details, see Supporting Information, Table S1). It is noteworthy that the chemo-selectivity of this transformation was excellent without the generation of benzamides. After the initial screening, the irradiation of 3 mol % $Ru(bpy)_3(PF_6)_2$, 8 mol % $Co^{III}(dmgH)_2PyCl$ (dmgH = dimethylglyoximate), and 1.2 equiv of base, sodium carbonate, in $CH_3CN$ could give 75% yield of **2a** (Table 1, entry 1). In the presence of photosensitizer and base, a range of cobaloximes as the proton-reducing catalysts (Table 1, Co catalyst A−D) were

capable of catalyzing the desired reaction, with $[Co^{III}(dmgH)_2(4\text{-}NMe_2\text{-}C_5H_4N)Cl]$ leading to the highest yield of $H_2$ generation and chemical yield (Table 1, entry 3).
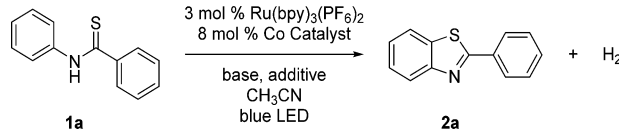
**Impact of the Base.** The key of this transformation was the careful selection of an appropriate base, which would meet three criteria: (a) a $pK_b$ low enough to abstract a proton from substrates; (b) a mild conjugate acid to act as a hydrogen atom donor, which could achieve the protonation process of the proton reducing catalysts; and (c) redox inertia (would not act as an electron donor). On reducing the amount of base to 1 equiv (entry 5), or even 0.6 equiv (see Supporting Information, Table S1), the yield of **2a** was still excellent with efficient evolution of $H_2$. Further examinations of base were conducted (Table 1, entries 5−11), which revealed a strong dependence on the reaction pH. A relatively weak base ($pK_a = 9-12$), such as carbonate or sodium glycinate, was effective, while a stronger base or weaker one was not suitable for this transformation. When the carbonates were chosen as the base, a high yield of benzothiazole product could be obtained, while a low yield of $H_2$ was detected (Table 1 entries 1−7). It might be due to that some $CO_2$ could be *in situ* generated, and the low yield of $H_2$ relative to benzothiazole might result from the reduction of $CO_2$.[11] Therefore, sodium glycinate was used instead of $Na_2CO_3$ (Table 1, entry 11). Further improvement in efficiency of $H_2$ evolution was achieved through the addition of 0.4 equiv of DMAP (entry 12, 99% yield and 99% $H_2$ generation). DMAP might act as a weak organic base, whose more acidic conjugate acid could promote the protonation of cobalt catalyst. In addition, when the light source was replaced by a white fluorescent lamp, the reaction still had a good efficiency (Table 1, entry 13).

Control experiments without the addition of either photosensitizer, proton-reducing catalyst, base, or the irradiation of visible light clearly demonstrated that visible-light and all components are essential in the catalytic system (for details, see Supporting Information, Table S2, entries 1−5). No $H_2$ evolution was observed when the substrate **1a** was absent in the mixture (Table S2, entry 6), which indicated that the substrate might act as the electron donor in the reaction.
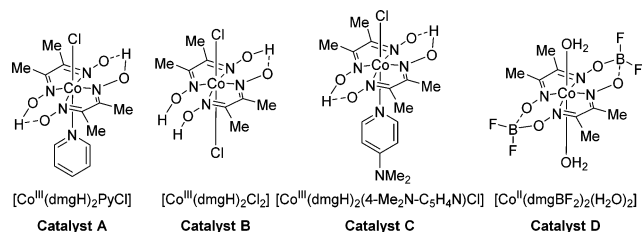
**Comparison with Photoredox-Catalyzed Oxidative Conditions.** In the comparison with the photoredox-catalyzed oxidative conditions, it was found that the presence of oxidants, such as $O_2$,[10g] $K_2S_2O_8$ and $H_2O_2$, would increase the generation of oxidation byproduct N-phenylbenzamide **1a** (Table 2, entries 2−4). By contrast, under the external oxidant-free conditions, the desired coupling product **2a** could be afforded with high selectivity.

**The Scope of Intramolecular External Oxidant-Free Oxidative Cyclization of Thiobenzanilides.** We next explored the scope and generality of this oxidant-free cyclization protocol using the optimized conditions (condition A, Table 1, entry 12). As shown in Scheme 2, a range of N-phenylbenzothioamides, with either electron-rich or electron-poor substituents on the *ortho* or *para* position of N-aryl ring, was viable in this transformation (Scheme 2, **2a−2j**). Notably, halogen substituents including Cl, Br, and I could be well tolerated under the standard reaction conditions (Scheme 2, **2c−2e**) and displayed high activity with an equivalent amount of $H_2$ generation, providing more chances for further functionalization or modification of these molecules. However, strong electron-donating group (−OMe) or strong electron-withdrawing groups (−CF$_3$) on N-aryl ring decreased the reactivity (Scheme 2, **2i** and **2j**). In addition, the *meta*

**Table 1. Optimization of the Reaction Conditions**[a]



| entry | Co catalyst | base | additive | yield (%)[b] | $H_2$ (%)[c] |
|---|---|---|---|---|---|
| 1[d] | A | $Na_2CO_3$ | − | 75 | 25 |
| 2[d] | B | $Na_2CO_3$ | − | 55 | 9 |
| 3[d] | C | $Na_2CO_3$ | − | 99 | 69 |
| 4[d] | D | $Na_2CO_3$ | − | 0 | 0 |
| 5 | C | $Na_2CO_3$ | − | 99 | 70 |
| 6 | C | $K_2CO_3$ | − | 94 | 38 |
| 7 | C | $Cs_2CO_3$ | − | 36 | 5 |
| 8 | C | NaOAc | − | 0 | 0 |
| 9 | C | DBU | − | 0 | 0 |
| 10 | C | DMAP | − | 0 | 0 |
| 11 | C | Na-Gly | − | 99 | 79 |
| 12[e] | C | Na-Gly | DMAP | 99 | 99 |
| 13[e,f] | C | Na-Gly | DMAP | 99 | 99 |



[Co$^{III}$(dmgH)$_2$PyCl]
**Catalyst A**

[Co$^{III}$(dmgH)$_2$Cl$_2$]
**Catalyst B**

[Co$^{III}$(dmgH)$_2$(4-Me$_2$N-C$_5$H$_4$N)Cl]
**Catalyst C**

[Co$^{II}$(dmgBF$_2$)$_2$(H$_2$O)$_2$]
**Catalyst D**

[a]Conditions: **1a** (0.20 mmol), $Ru(bpy)_3(PF_6)_2$ (3 mol %), Co catalyst (8 mol %) and base (1.0 equiv) were added in $CH_3CN$ (2 mL) under an argon atmosphere and irradiation of 3W blue LEDs for 12 h at rt. [b]Isolated yields were showed. [c]Determined by GC-TCD using pure methane as an internal standard. [d]1.2 equiv of base was used. [e]0.4 equiv of additive was added. [f]23W white fluorescent light was used; DMAP = 4-dimethylaminopyridine.

**Table 2. Comparison with Photoredox Catalyzed Oxidative Conditions[a]**



| entry | oxidant | yield (%)[b] | |
|---|---|---|---|
| | | **2a** | **1a** |
| 1[c] | – | 99 | 0 |
| 2[d] | $O_2$ | 7 | 49 |
| 3 | $K_2S_2O_8$ | 26 | 38 |
| 4 | $H_2O_2$ | 16 | 17 |

[a]Reaction conditions: **1a** (0.35 mmol), $Ru(bpy)_3(PF_6)_2$ (3 mol %), oxidant (2 equiv), sodium-Gly (1.0 equiv) and DMAP (0.4 equiv) were added in $CH_3CN$ (2 mL) under irradiation of 23W white fluorescent lamp for 12 h at rt. [b]Yield was determined by GC analysis. [c]$Co(dmgH)_2(4\text{-}NMe_2Py)Cl$ (8 mol %) was used in place of oxidant. [d]1 atm $O_2$ was used.

**Scheme 2. Substrate Scope of the Synthesis of Substituted 2-Arylbenzothiazoles[a]**
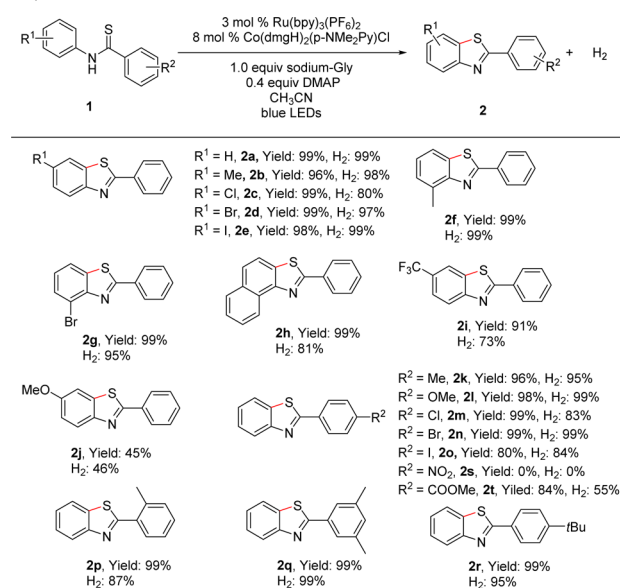


[a]Reaction condition A: **1** (0.20 mmol), $Ru(bpy)_3(PF_6)_2$ (3 mol %), $Co(dmgH)_2(4\text{-}NMe_2Py)Cl$ (8 mol %), sodium-Gly (1.0 equiv) and DMAP (0.4 equiv) were added in $CH_3CN$ (2 mL) under an argon atmosphere and irradiation of 3W blue LEDs for 12 h at rt; $H_2$ was detected by GC-TCD using pure methane as an internal standard; and isolated yields of benzothiazoles were shown.

substitution on *N*-aryl ring of thioanilides would afford a mixture of products with C−H functionalization on *ortho* and *para* position by using this method (for details, see Supporting Information, Figure S15). The reaction of *N*-naphthalene-substituted benzothioamide could also give an excellent yield for the cyclization product (Scheme 2, **2h**, 99%). Substituent diversity of 2-aryl group was also explored by using this photoredox catalytic system (Scheme 2, **2k**−**2r**). Both electron-rich and electron-poor substituents on 2-aryl group reacted smoothly to give the corresponding benzothiazoles in high yields (Scheme 2, **2l** and **2t**). From the reactions of various substrates with substituents at *ortho*, *meta*, or *para* position of aromatic ring, the corresponding 2-arylbenzothiazoles were obtained in generally excellent yields (Scheme 2, **2k**, **2p**, and

**2q**). In addition, halo substituents in 2-aryl group were also tolerated (Scheme 2, **2m**−**2o**). Then we further applied this optimized reaction conditions for the synthesis of 2-alkylbenzothiazoles. When 2-aryl groups were replaced by alkyl groups such as *tert*-butyl or methyl, however, low yields were obtained, presumably as a result of their higher $pK_a$, which makes them harder to deprotonate (Scheme 3).

**Scheme 3. Oxidative Cyclization for the Synthesis of 2-Alkylbenzothiazoles**
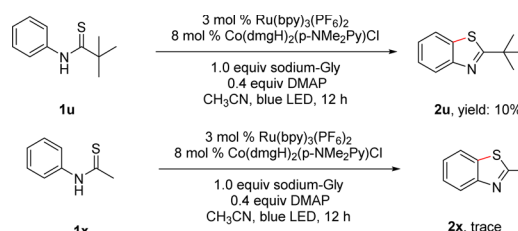


Therefore, a stronger base like tetrabutylammonium hydroxide was used instead of sodium glycinate. Interestingly, the concentration of proton seemed to have an important influence on the efficiency of reaction (Table 3). Due to the
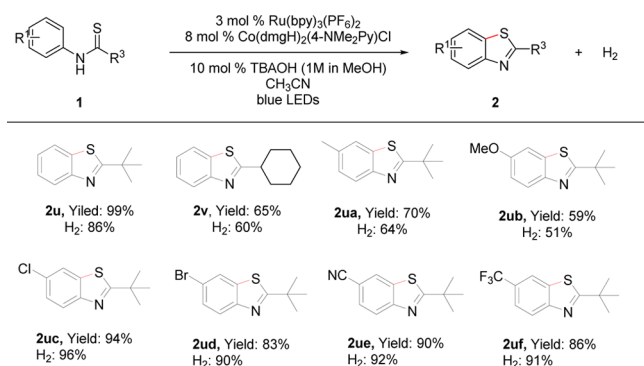
**Table 3. Influence of the Base Loading[a]**



| entry | $X$ | yield (%)[b] | $H_2$ (%)[c] |
|---|---|---|---|
| 1 | 100 | trace | trace |
| 2 | 30 | 38 | 21 |
| 3 | 10 | 99 | 86 |
| 4 | 5 | 0 | 0 |

[a]Conditions: **1u** (0.20 mmol), $Ru(bpy)_3(PF_6)_2$ (3 mol %), $Co(dmgH)_2(4\text{-}NMe_2Py)Cl$ (8 mol %) and TBAOH (1 M in MeOH) were added in $CH_3CN$ (2 mL) under an argon atmosphere and irradiation of 3W blue LEDs for 12 h at rt. [b]Isolated yields were showed. [c]Determined by GC-TCD by using pure methane as an internal standard.

low concentration of proton, the use of 1 equiv of TBAOH as the external base provided the corresponding benzothiazole **2u** from 2,2-dimethyl-*N*-phenylpropanethioamide **1u** in poor yield (Table 3, entry 1). However, employing the catalytic amount of TBAOH as the base, the yield of **2u** was significantly increased (Table 3, entries 2−3). Especially, when 10 mol % TBAOH was used, the corresponding 2-alkylbenzothiazole **2u** and generation of $H_2$ were achieved in yield 99% and 86%, respectively (Table 3, entry 3). But further decrease of the base loading would inhibit the efficiency of reaction (Table 3, entry 4).

With this optimized condition in hand (condition B), we examined the scope of alkyl substituted thioamide derivatives for the synthesis of corresponding 2-alkylbenzothiazoles (Scheme 4). Alkyl group such as *tert*-butyl (**2u**) and cyclohexyl (**2v**) groups could be compatible with this external oxidant-free condition, and the desired products were isolated in good to excellent yields. Unfortunately, only a trace amount of 2-methylbenzothiazole (**2x**) could be observed in this catalytic system. Then, we also studied the influence of the substituents on the *N*-aromatic ring of substrates. Both electron-donating
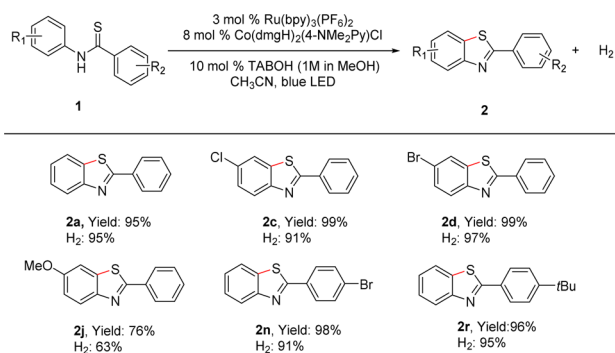
**Scheme 4. Substrate Scope of the Synthesis of Substituted 2-Alkylbenzothiazoles[a]**



**2u**, Yiled: 99%
H2: 86%

**2v**, Yield: 65%
H2: 60%

**2ua**, Yield: 70%
H2: 64%

**2ub**, Yield: 59%
H2: 51%

**2uc**, Yield: 94%
H2: 96%

**2ud**, Yield: 83%
H2: 90%

**2ue**, Yield: 90%
H2: 92%

**2uf**, Yield: 86%
H2: 91%

[a]Condition B: **1u**, **1ua−f** or **1v** (0.20 mmol), Ru(bpy)$_3$(PF$_6$)$_2$ (3 mol %), Co(dmgH)$_2$(4-NMe$_2$Py)Cl (8 mol %) and 10 mol % TBAOH (1 M in MeOH) were added in CH$_3$CN (2 mL) under an argon atmosphere and irradiation of 3W blue LEDs for 12h at rt; H$_2$ was detected by GC-TCD using pure methane as an internal standard; and isolated yields of benzothiazoles were shown.

and electron-withdrawing substituents, such as methyl (**2ua**), methoxyl (**2ub**), cyano (**2ue**), and trifluoromethyl (**2uf**) groups, gave good to excellent chemical yields with the H$_2$ evolution. The electron-withdrawing group on the benzene ring promotes this transformation by making deprotonation of the corresponding substrate more easily (**2uc−2uf**). In addition, this reaction can be applied to the substrates bearing halogen atoms such as Cl (**2uc**) and Br (**2ud**), which provided the possibility for further functionalization.

To further demonstrate the usefulness of this catalytic protocol (condition B), the application of this method in synthesis of 2-arylbenzothiazoles was also investigated (Scheme 5). Under condition B, 2-aryl substituted benzothiazole derivatives could also be afforded in good to excellent yields.
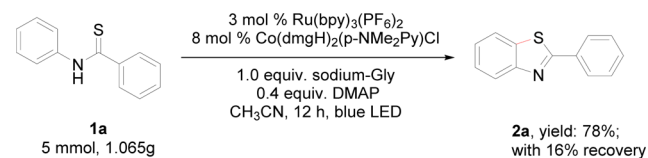
**Application of the Reaction to the Synthesis of Biologically Active Molecules.** It is worth noting that the reaction can be effectively scaled up with good efficiency. For example, the oxidative cyclization of N-phenylbenzothioamide **1a** is operationally simple and amenable to gram-scale synthesis

**Scheme 5. Substrate Scope of the Synthesis of Substituted 2-Arylbenzothiazoles Using Condition B[a]**



**2a**, Yield: 95%
H2: 95%

**2c**, Yield: 99%
H2: 91%

**2d**, Yield: 99%
H2: 97%

**2j**, Yield: 76%
H2: 63%

**2n**, Yield: 98%
H2: 91%

**2r**, Yield: 96%
H2: 95%

[a]Condition B: **1** (0.20 mmol), Ru(bpy)$_3$(PF$_6$)$_2$ (3 mol %), Co(dmgH)$_2$(4-NMe$_2$Py)Cl (8 mol %) and 10 mol % TBAOH (1 M in MeOH) were added in CH$_3$CN (2 mL) under an argon atmosphere and irradiation of 3W blue LEDs for 12 h at rt; H$_2$ was detected by GC-TCD using pure methane as an internal standard; and isolated yields of benzothiazoles were shown.

in 78% yield with 16% recovery of starting material (Scheme 6). Moreover, due to the high selectivity and efficiency, this visible-

**Scheme 6. Gram-Scale Reaction of the Synthesis of 2-Arylbenzothiazoles**



**1a**
5 mmol, 1.065g

3 mol % Ru(bpy)$_3$(PF$_6$)$_2$
8 mol % Co(dmgH)$_2$(p-NMe$_2$Py)Cl
1.0 equiv. sodium-Gly
0.4 equiv. DMAP
CH$_3$CN, 12 h, blue LED

**2a**, yield: 78%;
with 16% recovery

light-mediated cobalt-catalyzed coupling strategy offers promising synthetic routes for the construction of a library of medicinal compounds having benzothiazole structural scaffolds. For instance, the 4-fluoro-2-(3,4-dimethoxyphenyl)-benzothiazole (**2w**) is a potent antitumor agent and showed good inhibitory potency against the human cancer cells.[12] By using condition A, **2w** could be constructed with good chemoselectivity and efficiency (Scheme 7, condition A: 78%). However, a lower yield was observed under condition B (Scheme 7, condition B: 40%).

**Scheme 7. Application of the Reaction in the Synthesis of Antitumor Agent**



**1w** → **2w**, yield: 78%

**1w** → **2w**, yield: 40%
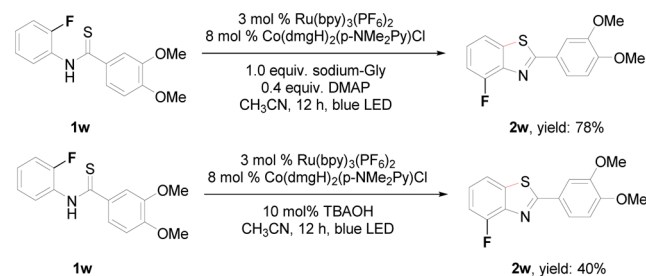
***In Situ* Hydrogenation of Nitroarenes.** In order to further utilize the generated H$_2$, we tried to combine this external oxidant-free oxidative coupling reaction to hydrogenation directly in one pot. Under condition A, the *in situ* hydrogenation of nitroarenes could be achieved in excellent yields without use of any sacrificial oxidant and reductant (Table 4, entry 1). Meanwhile, the control experiments were

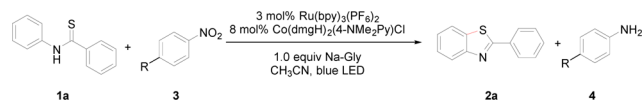**Table 4. *In Situ* Hydrogenation of Nitroarenes[a]**



| entry | PS | catalyst C | base | additive | yield (%)[b] | |
|---|---|---|---|---|---|---|
| | | | | | **2a** | **4a** |
| 1 | + | + | + | + | >99 | 87 |
| 2 | − | + | + | + | 11 | 10 |
| 3 | + | − | + | + | 36 | 34 |
| 4 | + | + | − | + | 0 | 0 |
| 5 | + | + | + | − | >99 | >99 |

[a]Reaction conditions: **1a** (0.35 mmol), **3a** (0.1 mmol), Ru(bpy)$_3$(PF$_6$)$_2$ (3 mol %), Co(dmgH)$_2$(4-NMe$_2$Py)Cl (8 mol %), sodium-Gly (1.0 equiv) and DMAP (0.4 equiv) were added in CH$_3$CN (2 mL) under an argon atmosphere and irradiation of 3W blue LEDs 24 h at rt. [b]Yield was determined by GC-FID analysis. PS: photosensitizer.

conducted. Both the conversion of **1a** and the yield of hydrogenation product would decrease in the absence of photosensitizer or cobalt catalyst (Table 4, entries 2−3), which showed that the generated Co−H intermediate might be crucial.[13] In addition, the reaction can proceed smoothly without adding DMAP (Table 4, entry 5).

Then, the generality of nitroarenes of this *in situ* hydrogenation reaction was explored under this condition (Table 5).

**Table 5. Generality of *in Situ* Hydrogenation of Nitroarenes**[a]



| | | yield (%)[b] | |
|---|---|---|---|
| entry | R | 2a | 4 |
| 1 | H(**3a**) | >99 | 99 |
| 2 | Me(**3b**) | >99 | 95 |
| 3 | OMe(**3c**) | >99 | >99 |
| 4 | COMe(**3d**) | 99 | 92 |
| 5 | Br(**3e**) | 40 | 12 |

[a]Reaction conditions: **1a** (0.35 mmol), **3** (0.1 mmol), $Ru(bpy)_3(PF_6)_2$ (3 mol %), $Co(dmgH)_2(4\text{-}NMe_2Py)Cl$ (8 mol %) and sodium-Gly (1.0 equiv) were added in $CH_3CN$ (2 mL) under an argon atmosphere and irradiation of 3W blue LEDs for 24 h at rt. [b]Yield was determined by GC-FID analysis.

Various substituted nitrobenzenes could be reduced to the corresponding anilines by the *in situ* generated reductants. Only the nitro group was reduced, while other easily reducible groups like bromo or carbonyl substituents in the nitrobenzenes would not change.

**Elucidation of the Mechanism.** From the profile of the reaction with the light off/on over time, it was observed that the transformation progressed smoothly under irradiation with visible-light, but no further conversion was observed when the light source was removed (Figure 1). This result showed that the continuous irradiation of visible light is indispensable and also indicated that the reaction proceeds through a photoredox catalytic pathway rather than radical chain propagation.
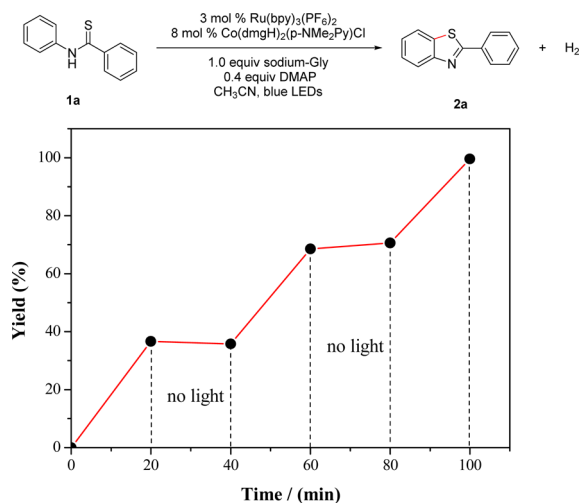


**Figure 1.** Profile of the reaction with the light off/on over time; yields were determined by GC analysis.

Furthermore, a series of emission quenching experiments were performed to acquire further insight into the photoredox catalytic cycle (Figure 2). As shown, the experiments revealed
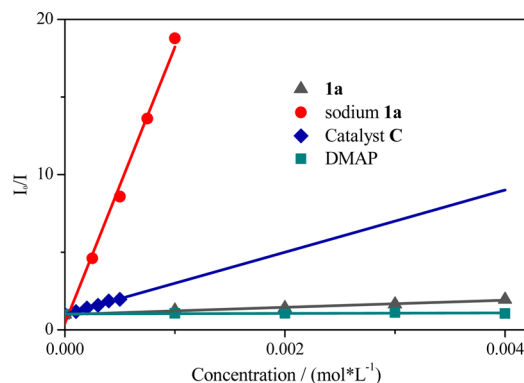


**Figure 2.** $Ru(bpy)_3(PF_6)_2$ emission quenching with *N*-phenylbenzothioamide, sodium *N*-phenylbenzimidothioate, $Co(dmgH)_2(4\text{-}NMe_2Py)Cl$ and DMAP; $I_0$ and $I$ represent the intensities of the emission in the absence and presence of the quencher.

that both sodium *N*-phenylbenzimidothioate and $Co^{III}(dmgH)_2(4\text{-}NMe_2Py)Cl$ could quench the excited state of $Ru(bpy)_3(PF_6)_2$ (Figure 2). However, the quenching rate constant of sodium *N*-phenylbenzimidothioate is much bigger than the cobalt complex. In addition, DMAP or substrate **1a** could not be an emission quencher of $Ru(bpy)_3^{2+}$. These results suggest that the reaction might undergo an efficiently reductive quenching mechanism, in which **1a** might deprotonate first and then be oxidized by the excited state of photosensitizer.

In order to find out the source of $H_2$, experiments with deuterated substrate were carried out. As shown in Scheme 8,
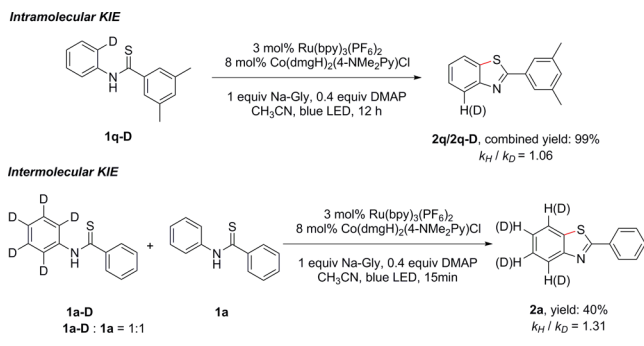
**Scheme 8. Deuterium Experiments for Reactions**
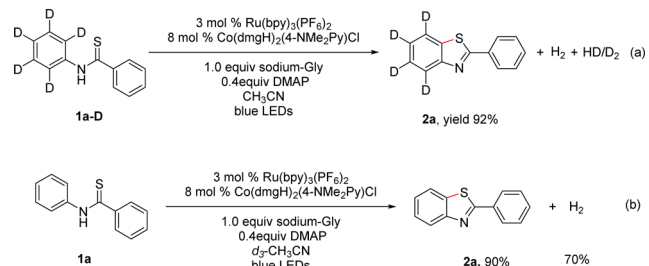


$D_2$ or HD would be formed as the byproducts, when *N*-phenylbenzothioamide **1a** was replaced by a deuterated substrate **1a-D** (Scheme 8a). However, when $d_3$-$CH_3CN$ was used as solvent, only $H_2$ would be found (Scheme 8b). In previous reports, water was frequently used as cosolvent, and it was believed to be important in mediating the proton exchange processes.[5c] However, in this reaction, we realized the cross-coupling with hydrogen evolution reactions in organic solvent. And these results indicated that the released $H_2$ directly originates from the substrates.

Intra- and intermolecular kinetic isotope effects (KIE, $k_H/k_D$) were obtained by using deuterated substrates (Scheme 9). No significant intramolecular KIE was observed (KIE value was 1.06, for details, see Supporting Information). Then parallel reactions were further performed with **1a** and **1a-D** to determine if cleavage of the aromatic C−H bond is the

**Scheme 9. Kinetic Isotope Effects of the Reaction**



**Figure 4.** Kinetic studies of the external oxidant-free oxidative coupling for aromatic C−H thiolation.

turnover-limiting step of the reaction. The reaction of the same amount of substrate **1a** and deuterated substrate **1a-D** under the standard conditions for 15 min provided a mixture of the products deuterium-**2a** (**2a-D**) and **2a** in 40% combined yields, in which the ratio of **2a**:**2a-D** was 1.31 (Scheme 9). Both of the observed intra- and intermolecular KIE values revealed that the C−H bond cleavage might not be the rate-determining step.

Subsequently, to further investigate the mechanism in detail, the kinetic experiments were conducted using *in situ* IR under condition B. Through *in situ* IR (Figure 3), 2-phenyl-
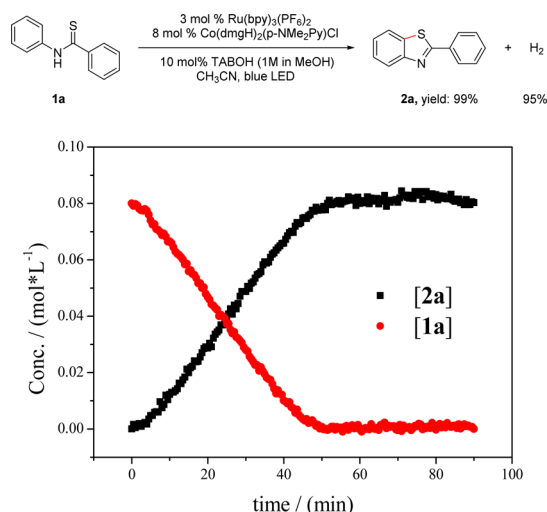


**Figure 3.** Kinetic profile of the reaction by *in situ* IR.

benzothiazole **2a** was detected and accumulated at the same rate as the consumption of *N*-phenylbenzothioamide **1a**. Under the irradiation of blue LEDs, **1a** was converted completely only in 1 h.

**Kinetic Studies by *in Situ* IR.** Using *in situ* IR, some kinetic studies were performed to determine the order of reaction components in this external oxidant-free coupling reaction. In the presence of 10 mol % TBAOH as the catalytic base, initial rates were monitored upon changing the concentration of substrate (**1a**), photosensitizer and cobalt catalyst, respectively (Figure 4). The initial reaction rate was almost invariant when using different concentrations of the substrate (**1a**) or photosensitizer (Figure 4A,B). These results revealed that the reaction rate is independent of the concentration of substrate and photosensitizer, and consumption of substrate or photo-redox catalytic cycle might not be involved in the rate-limiting step. Then, further kinetic investigation for the relationship between reaction rate and the concentration of Co(dmgH)₂(4-

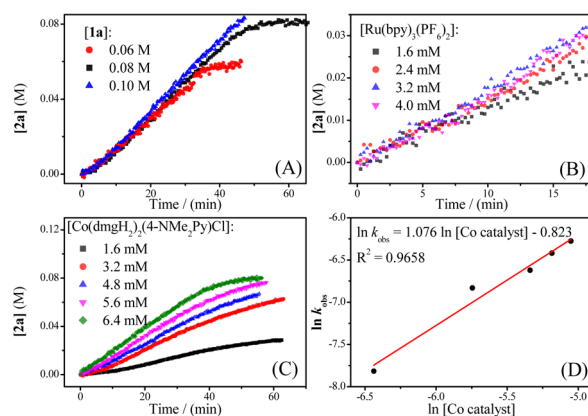NMe₂py)Cl was conducted (Figure 4C). It was found that the initial reaction rate changed under different concentrations of cobalt catalyst. Shown in the Figure 4D, the double-log plot of reaction rate against the concentration of cobalt catalyst exhibited approximately a linear relationship, and the slope is about 1.076, which suggested a first-order dependence on catalyst concentration in this range of concentration of Co catalyst. All of above-mentioned results suggested that the interaction between the proton-reducing catalyst and dissociated proton might be a slow step throughout the reaction, but consumption of substrate and photoredox catalytic cycle might be relative fast steps.

Base on the above experimental mechanistic data and the mechanistic insights of the previous cases, a plausible pathway for this oxidant-free aromatic C−H thiolation process is proposed. Specifically, both electron transfer and proton transfer were postulated through the synergistic combination of photoredox catalysis and cobalt catalysis. The specific mechanistic details are outlined in Scheme 10.

**Scheme 10. Proposed Mechanism**
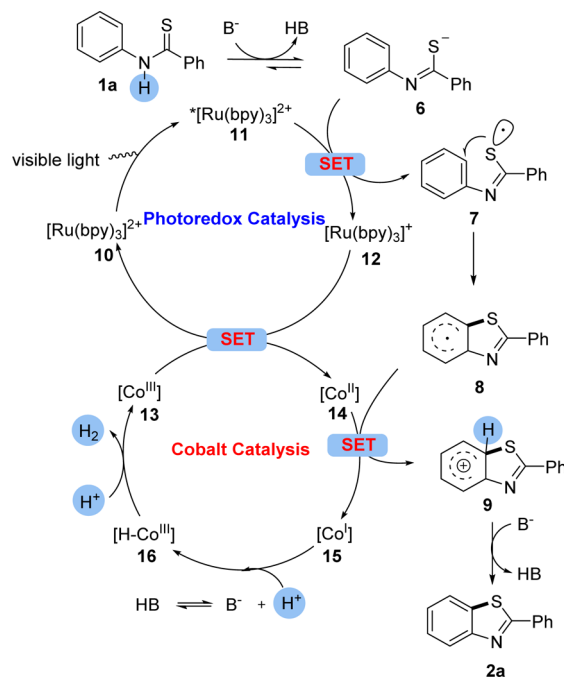
Initially, $Ru(bpy)_3^{2+}$ (**10**) is excited by visible light to provide a long-lived excited state (1100 ns),[14] $*Ru(bpy)_3^{2+}$ (**11**), which can be readily reduced or oxidized by substrate quenchers. While $*Ru(bpy)_3^{2+}$ is a strong oxidant ($E_{1/2\ red}$ [$*Ru(bpy)_3^{2+}$/ $Ru(bpy)_3^{3+}$] = +0.77 V vs SCE),[15] its capacity for single electron transfer (SET) with $N$-phenylbenzothioamide **1a** would be unfavorable (cyclic voltammetry experiments were carried out, see Supporting Information). However, an anion intermediate resulting from the acid–base equilibrium emerged with a dramatically decreased oxidation peak potential under alkaline conditions. Therefore, the SET from an anion intermediate of thioamide **6** to excited state of photosensitizer would be feasible to produce $Ru(bpy)_3^+$ and a sulfur centered radical **7**. Given that $Ru(bpy)_3^+$ has been shown to be a potent reductant ($E_{1/2\ red}$ [$Ru(bpy)_3^+$/$Ru(bpy)_3^{2+}$] = −1.33 V vs SCE),[15d] SET to the catalyst [$Co^{III}$] **13** would rapidly give [$Co^{II}$] **14** while itself being regenerated to $Ru(bpy)_3^{2+}$ to complete the photoredox cycle ($E_{1/2\ red}$ $Co^{III}/Co^{II}$ = −0.83 V vs SCE).[16] On the other hand, the addition of the sulfur radical **7** to the benzene ring produces the reactive aryl radical **8**. Thereafter, radical **8** release an electron to [$Co^{II}$] **14** ($E_{1/2\ red}$ $Co^{II}/Co^I$ = −1.08 V vs SCE)[16] to generate a cation **9**, which would release a proton and rearomatize to provide benzothiazole (**2a**). The [$Co^I$] species (**15**) can be protonated to form [$Co^{III}$−H] species (**16**) by the conjugate acid of base. Then this hydride could react with another proton to release $H_2$ and regenerate [$Co^{III}$] species (**13**).[17]

## CONCLUSIONS

We have developed an external oxidant-free C−H functionalization/C−S bond formation reaction to form the benzothiazoles. Stoichiometric oxidation reagents can be avoided, and dihydrogen is the only byproduct of the reaction. Notably, this reaction exhibits a wide range of functional groups tolerance with high activity. The base might act as a vital role of proton mediator. Especially, 2-alkylbenzothioazoles could be afforded in good to excellent yields when catalytic TBAOH was used as the base. These catalytic systems can be scaled up in gram scale and applied in the pharmaceutical synthesis. Meanwhile, the combination of the oxidant-free coupling reaction and hydrogenation of nitro-benzenes could be achieved in one-pot. A detailed mechanistic survey, including deuterium experiments, KIE, and *in situ* IR kinetic studies have been presented, which indicated that $H_2$ is generated directly from the substrates and the interaction between the cobalt catalyst and proton is the rate-limiting process. The transformation holds significant potential for the applications to a series of organic reactions.

## ASSOCIATED CONTENT

### Ⓢ Supporting Information

The experimental procedure, characterization data, and copies of $^1H$ and $^{13}C$ NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05665.

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### Notes
The authors declare no competing financial interest.

## REFERENCES

(1) (a) Lee, C.-F.; Liu, Y.-C.; Badsara, S. S. *Chem. - Asian J.* **2014**, *9*, 706. (b) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (f) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205.

(2) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Hiyama, T.; Obayashi, M.; Mori, I.; Nozaki, H. *J. Org. Chem.* **1983**, *48*, 912. (c) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (d) King, A. O.; Okukado, N.; Negishi, E.-i. *J. Chem. Soc., Chem. Commun.* **1977**, 683.

(3) (a) Liu, C.; Liu, D.; Lei, A. *Acc. Chem. Res.* **2014**, *47*, 3459. (b) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (c) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2256. (d) Liu, Q.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 13871. (e) Liu, D.; Liu, C.; Li, H.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 4453. (f) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (g) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (h) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (i) Chen, M.; Zheng, X.; Li, W.; He, J.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 4101. (j) Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709. (k) Zhao, Y.; Wang, H.; Hou, X.; Hu, Y.; Lei, A.; Zhang, H.; Zhu, L. *J. Am. Chem. Soc.* **2006**, *128*, 15048. (l) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810.

(4) He, K.-H.; Li, Y. *ChemSusChem* **2014**, *7*, 2788.

(5) (a) Zeug, N.; Buecheler, J.; Kisch, H. *J. Am. Chem. Soc.* **1985**, *107*, 1459. (b) Mitkina, T.; Stanglmair, C.; Setzer, W.; Gruber, M.; Kisch, H.; Konig, B. *Org. Biomol. Chem.* **2012**, *10*, 3556. (c) 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. (d) Zhong, J. J.; Meng, Q. Y.; Liu, Q.; Li, X. B.; Gao, X. W.; Lei, T.; Wu, C. J.; Li, Z. J.; Tung, C. H.; Wu, L. Z. *Org. Lett.* **2014**, *16*, 1988. (e) Gao, X.-W.; Meng, Q.-Y.; Li, J.-X.; Zhong, J.-J.; Lei, T.; Li, X.-B.; Tung, C.-H.; Wu, L.-Z. *ACS Catal.* **2015**, *5*, 2391.

(6) Li, X. B.; Li, Z. J.; Gao, Y. J.; Meng, Q. Y.; Yu, S.; Weiss, R. G.; Tung, C. H.; Wu, L. Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 2085.

(7) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950.

(8) Zhou, A.-X.; Mao, L.-L.; Wang, G.-W.; Yang, S.-D. *Chem. Commun.* **2014**, *50*, 8529.

(9) (a) Sun, Q.; Wu, R.; Cai, S.; Lin, Y.; Sellers, L.; Sakamoto, K.; He, B.; Peterson, B. R. *J. Med. Chem.* **2011**, *54*, 1126. (b) Mathis, C. A.; Wang, Y.; Holt, D. P.; Huang, G.-F.; Debnath, M. L.; Klunk, W. E. *J. Med. Chem.* **2003**, *46*, 2740. (c) Yoshida, H.; Nakao, R.; Nohta, H.; Yamaguchi, M. *Dyes Pigm.* **2000**, *47*, 239. (d) Yamamoto, K.; Fujita, M.; Tabashi, K.; Kawashima, Y.; Kato, E.; Oya, M.; Iso, T.; Iwao, J. *J. Med. Chem.* **1988**, *31*, 919.

(10) (a) Cheng, Y.; Peng, Q.; Fan, W.; Li, P. *J. Org. Chem.* **2014**, *79*, 5812. (b) Feng, E.; Huang, H.; Zhou, Y.; Ye, D.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2010**, *12*, 422. (c) Jaseer, E. A.; Prasad, D. J. C.; Dandapat, A.; Sekar, G. *Tetrahedron Lett.* **2010**, *51*, 5009. (d) Saha, D.; Adak, L.; Ranu, B. C. *Tetrahedron Lett.* **2010**, *51*, 5624. (e) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261. (f) Bose, D. S.; Idrees, M.

*Tetrahedron Lett.* **2007**, *48*, 669. (g) Cheng, Y.; Yang, J.; Qu, Y.; Li, P. *Org. Lett.* **2012**, *14*, 98. (h) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147. (i) Wang, H.; Wang, L.; Shang, J.; Li, X.; Wang, H.; Gui, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 76.

(11) Jeletic, M. S.; Mock, M. T.; Appel, A. M.; Linehan, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 11533.

(12) Mortimer, C. G.; Wells, G.; Crochard, J.-P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2006**, *49*, 179.

(13) Zhong, J.-J.; Wu, C.-J.; Meng, Q.-Y.; Gao, X.-W.; Lei, T.; Tung, C.-H.; Wu, L.-Z. *Adv. Synth. Catal.* **2014**, *356*, 2846.

(14) Juris, A.; Balzani, V.; Belser, P.; von Zelewsky, A. *Helv. Chim. Acta* **1981**, *64*, 2175.

(15) (a) Bock, C. R.; Connor, J. A.; Gutierrez, A. R.; Meyer, T. J.; Whitten, D. G.; Sullivan, B. P.; Nagle, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4815. (b) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159. (c) Pavlishchuk, V. V.; Addison, A. W. *Inorg. Chim. Acta* **2000**, *298*, 97. (d) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. *Chem. Rev.* **2013**, *113*, 5322.

(16) Du, P.; Schneider, J.; Luo, G.; Brennessel, W. W.; Eisenberg, R. *Inorg. Chem.* **2009**, *48*, 4952.

(17) (a) Artero, V.; Chavarot-Kerlidou, M.; Fontecave, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7238. (b) Dempsey, J. L.; Brunschwig, B. S.; Winkler, J. R.; Gray, H. B. *Acc. Chem. Res.* **2009**, *42*, 1995. (c) Du, P.; Knowles, K.; Eisenberg, R. *J. Am. Chem. Soc.* **2008**, *130*, 12576.