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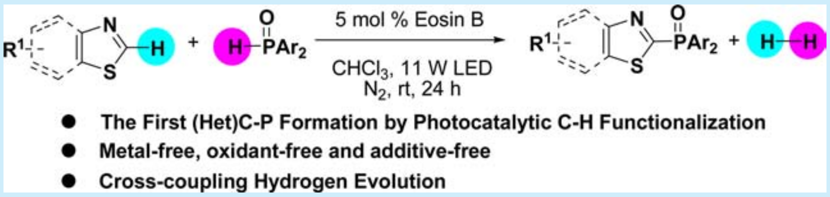
Cross-Coupling Hydrogen Evolution by Visible Light Photocatalysis Toward C(sp^2)−P Formation: Metal-Free C−H Functionalization of Thiazole Derivatives with Diarylphosphine Oxides

Kai Luo,[†,‡,§] Yao-Zhong Chen,[†,‡,§] Wen-Chao Yang,[†] Jie Zhu,[†] and Lei Wu*,[†]

[†]Jiangsu Key Laboratory of Pesticide Science and Department of Chemistry, College of Sciences, Nanjing Agricultural University, Nanjing 210095, China

[‡]College of Plant Protection, Nanjing Agricultural University, Nanjing 210095, China

S Supporting Information



ABSTRACT: Visible light along with 5 mol % eosin B catalyzed the first direct C−H phosphorylation of thiazole derivatives with diarylphosphine oxides by a photoredox process in the absence of an external oxidant. The scope of thiazoles and phosphine oxides was further investigated, as was functional group tolerance. The general and operational simplicity provides a novel metal and oxidant-free alternative for the formation of heteroaryl-P bonds, and only molecular hydrogen is generated as a byproduct.

In the past decades, organophosphorus compounds have emerged as a flourishing research area owing to their wide applications in biochemistry, material chemistry, organic synthesis, and catalysis.[1] Generally, phosphorus substituents regulate important biological, medicinal, and material functions; they perform as ligands or directing group for transition metal catalysis.[2] As such, the introduction of organophosphorus functionalities in convenient means continues to motivate the research for methods for their synthesis. Of these methods, coupling of phosphonate esters or phosphine oxides with electrophiles catalyzed by transition metals has been recognized as one of the most efficient and promising approaches for C(sp^2)−P bond formation. Palladium, nickel, copper, rhodium, silver, etc., were extensively applied to enable the phosphorylation of alkynes,[3] propargylic derivatives,[4] styrenes,[5] arylboronic acids,[6] aryl(pseudo) halides,[7] and (hetero)arenes.[8] However, these transformations are associated with one or more limitations such as expensive, toxic or stoichiometric transition metals, air-sensitive ligands, additives/oxidants, elevated temperatures, and so on.

Intriguingly, the practices in visible light photocatalysis have actively responded to the demands of reaction economics, operational simplicity, and environmental friendliness. Great efforts have been devoted to the development of visible-light-mediated C−C and C−X formations.[9] Notably, direct C−H functionalization has become an increasing significant subject.[10−12] Among which, organic dye-type photocatalysts exhibited superiority to their transition metal counterparts, such as ruthenium and iridium complexes, with regard to the aforementioned criteria. For representative examples, König reported a direct intermolecular C−H arylation of heteroarenes including furan, thiophene, and pyrrole with aryl diazonium salts through a photoredox process using eosin Y (Scheme 1a).[11a] In 2013, Wu et al. described the first C(sp^2)−C(sp^3) cross-coupling hydrogen evolution reaction from indoles with tetrahydroisoquinoline derivatives by combining eosin Y and graphene-supported RuO_2 nanocomposite as the photosensitizer.[12a] Furthermore, although significant progress has been made in C−X bond formation, examples for the C(sp^2)−P formation by photocatalysis are still scarce.[13] One was developed by Toste et al. through the *P*-arylation of aryldiazonium salts with *H*-phosphonates via dual gold and ruthenium photoredox catalysis (Scheme 1b).[13a] Recently, Xiao and co-workers demonstrated another dual-catalytic C(sp^2)−P formation reaction of diphenylphosphine oxide with aryl iodides by combining nickel catalyst and ruthenium complex (Scheme 1b).[13b] Inspired by these leading researches, we hypothesized that P-centered radical might be able to couple with heteroarenes via synergistic interactions of visible light stimulation and organic dye sensitization. As part of our continuing interest in synthesis and application of organophosphorus chemistry,[14] herein, we report a mild and efficient direct C−H functionalization of thiazole derivatives with diarylphosphine oxides by photoredox process (Scheme 1c). To the best of our knowledge, this is the first example of direct C−H phosphorylation of heteroarenes via cross-coupling hydrogen evolution by organic dye-sensitized photocatalysis without metal, oxidant, or additive.[15]

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Scheme 1. (a) Representative C(sp^2)−H Functionalization of Heteroarenes by Organic Dyes under Visible Light; (b) C(sp^2)−P Formation by Photoredox/Metal Dual Catalysis; (c) This Work

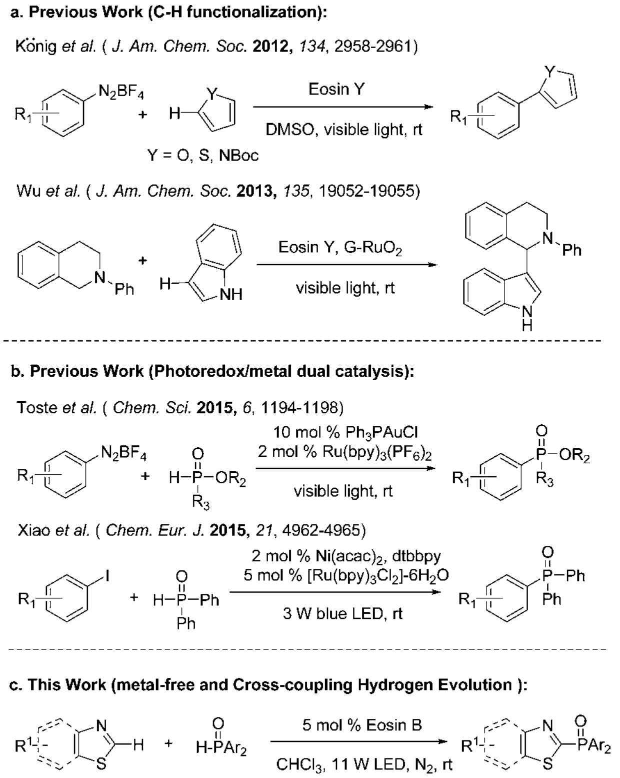
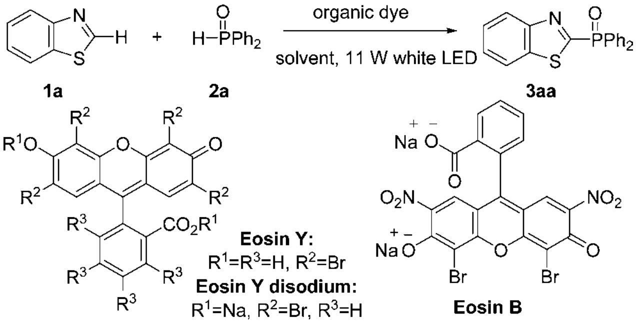


Table 1. Optimization of the Reaction Conditions[a]



entry	organic dye	solvent	yield (%)[b]
1	Eosin Y	THF	N.R.
2	Eosin Y	DMF	N.R.
3	Eosin Y	CH_3CN	N.R.
4	Eosin Y	toluene	69
5	Eosin Y	H_2O	67
6	Eosin Y	DMSO	83
7	Eosin Y	$CHCl_3$	86
8	Eosin Y disodium	$CHCl_3$	75
9	**Eosin B**	**$CHCl_3$**	**87**
10	Fluorecein	$CHCl_3$	33
11	Rhodamine B	$CHCl_3$	22
12	Alizarin Red S	$CHCl_3$	25
13	Rose Bengal	$CHCl_3$	trace
14	Ru(bpy)$_3$Cl$_2$, *i*-PrNEt$_2$	$CHCl_3$	9
15[c]	Eosin B	$CHCl_3$	77%
16[d]	Eosin B	$CHCl_3$	58%
17[e]	Eosin B	$CHCl_3$	N.R.
18[f]	Eosin B	$CHCl_3$	N.R.

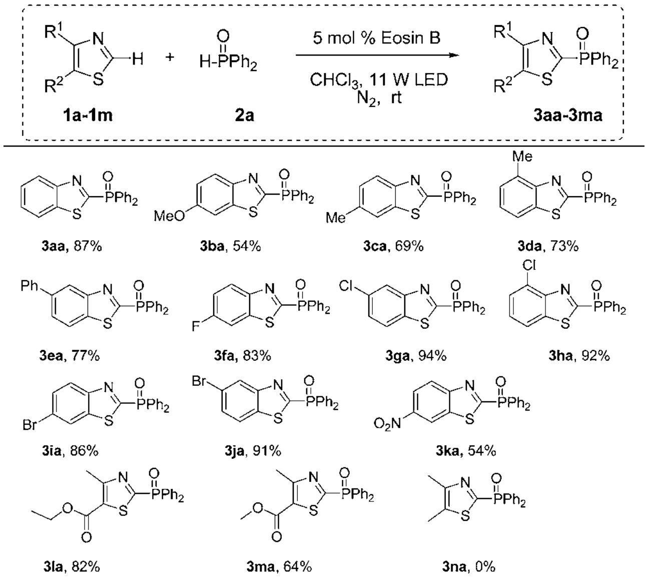
[a] Reagents and conditions: 0.2 mmol benzothiazole, 0.6 mmol diphenylphosphine oxide, 5 mol % organic dye, 1.5 mL of solvent, 11 W white LED, N_2, 24 h. [b] Isolated yields. [c] 3 mol % catalyst. [d] Under air. [e] In oxygen atmosphere. [f] Reaction in the dark.

With benzothiazole (**1a**), diphenylphosphine oxide (**2a**) as the model substrates, and a 11 W white LED bulb as the visible light source, we discovered that the desired phosphorylation product (**3aa**) was produced in 69% isolated yield in toluene at room temperature with organic dye eosin Y under a nitrogen atmosphere for 24 h. Reactions in THF, DMF, and acetonitrile left the reactants intact; in sharp contrast, DMSO as solvent enabled the C−H phosphorylation to a good yield of 83%. Interestingly, heterogeneous reaction in water performed smoothly with medium yield of 67%. When chloroform was further applied as the solvent, the substrate consumed completely, yielding of the product with 86% (Table 1, entry 7). Subsequently, other organic dyes including eosin Y disodium, eosin B, Fluorescein, Rhodamine B, Alizarin Red S, and Rose Bengal were evaluated. To our delight, investigations revealed that the yield of **3aa** could be improved to 87% when eosin B was employed as the photocatalyst (entry 9). As a comparison, the classical ruthenium-pyridyl complex afforded merely 9% under standard conditions (entry 14), which evidenced the superiority of organic dyes over the transition metal-derived counterpart in this type of C−H functionalization. Quite interestingly, sacrificial oxidants, such as air or molecular oxygen, which are recognized to accelerate the dehydrogenation process, led to significant reduction or complete inhibition of reactivity in the present conditions (entry 16 and 17). Moreover, no conversion could be observed when the reactions were conducted in the dark (entry 18). These results indicate that light, eosin B, and protecting atmosphere are all essential to achieve the reaction.

On the basis of this success, we evaluated the nature of thiazole derivatives that could participate in the photoredox cross-coupling with diphenylphosphine oxide. In general, the reactions were remarkably sensitive to the electron density of substitutions on phenyl moiety. Arylthiazoles bearing electron-donating groups, such as methoxy, methyl, and phenyl, were coupled with **2a** affording the corresponding adducts in medium to good yields (Scheme 2, compounds **3ba**−**3ea**). However, the reactivity was dramatically increased when arylthiazole containing electron-withdrawing groups such as -F, -Cl, -Br were used (Scheme 2, compounds **3fa**−**3ja**). Notably, strong withdrawing group (nitro) impaired the reactivity to afford medium yield of **3ka**. Interestingly, ethyl 4-methyl thiazole-5-carboxylate and methyl 4-methyl thiazole-5-carboxylate could also react under the standard conditions affording the products **3la** and **3ma** in yields of 82% and 64%, respectively. Unfortunately, 4,5-dimethylthiazole (**3na**) was inapplicable even after systematic screening, which might be attributed to the necessity of conjugation on substrates. Meanwhile, benzoxazole derivatives and dialkylphosphites were left intact under standard conditions.

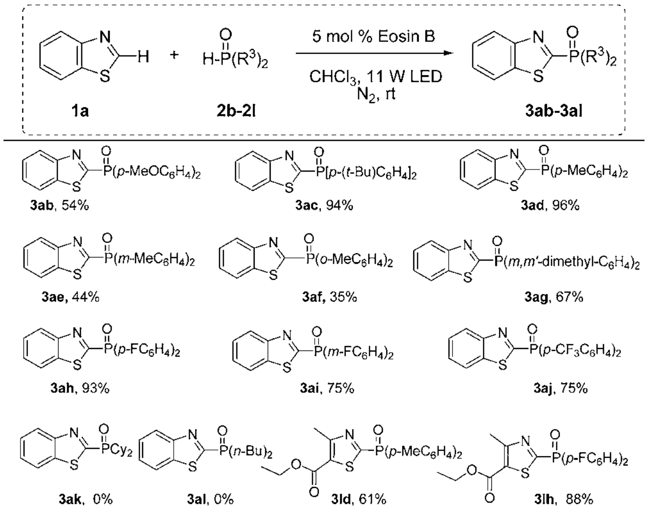
Next, the scope of diarylphosphine oxides was examined. As shown in Scheme 3, diarylphosphine oxides bearing electron-donating or withdrawing groups at their para-positions, including methoxy, *t*-butyl, methyl, fluoro, and trimethylfluoro, were applicable to the coupling with medium to excellent yields (compounds **3ab**−**3ad**, **3ah**, **3aj**, **3ld**, and **3lh**). It is worthy to mention that substitutions on meta-positions also proceeded efficiently with yields ranged from 44% to 75% (compounds **3ae**, **3ag**, and **3ai**). However, ortho-methyl substitution led to less

Scheme 2. Substrates Scope on Thiazole Derivatives[a]



[a]Reagents and conditions: 0.2 mmol benzothiazole, 0.6 mmol diphenylphosphine oxide, 5 mol % Eosin B, 1.5 mL of solvent, 11 W white LED, N_2, 24 h.

Scheme 3. Substrates Scope on Diarylphosphine Oxides[a]

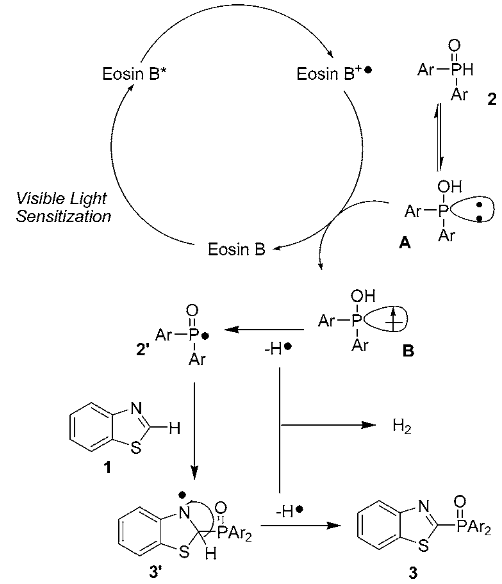


[a]Reagents and conditions: 0.2 mmol benzothiazole, 0.6 mmol diphenylphosphine oxide, 5 mol % Eosin B, 1.5 mL of solvent, 11 W white LED, N_2, 24 h.

reactivity, with only 35% yield of **3af** isolated. The steric hindrance effect of di(2,4,6-trimethylphenyl)phosphine oxide was found to be extremely detrimental, and no product was detected at all. In addition, dialkylphosphine oxides exhibited no reactivity toward the standard conditions.

More experiments were subsequently designed and conducted for understanding the related mechanisms. Initially, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a well-known radical scavenger, was found to inhibit the reaction process, which indicated that the reaction may occur through a radical mechanism. Since that no sacrificial oxidant was employed in our work, molecular hydrogen could be the only byproduct. Thus, we carried out experiments with deuterated substrates and solvents to identify the release and source of H_2 in the reaction (detected by gas chromatography, see details in Supporting Information). When deuterated **1a** and **2a** were employed under the standard conditions, D_2 was observed instead of H_2, which suggested that the protons were released from the substrates. The above results coupled with previous reports[11,13] collectively point to a plausible mechanism shown in Scheme 4. The photocatalytic cycle starts with reductive quenching of excited state Eosin $B^{+\bullet}$ with phosphinous acid **A** to yield the P-centered radical **2′** after deprotonation of radical-cation intermediate **B**. Then the nucleophilic addition of the radical diphenylphosphine oxide to thiazole **1** leads to intermediate **3′**. Finally, the deprotonation of this species furnish the desired product **3**. Meanwhile, the dissociated hydrogen radicals combine to produce H_2.

Scheme 4. Plausible Mechanism



In summary, we have reported the first example of direct C−H phosphorylation of heteroarenes via cross-coupling hydrogen evolution by organic dye-sensitized photocatalysis without metal, oxidant, or additive. The reaction tolerates various functional groups including bromides, ethers, and esters and furnishes the coupling products in medium to excellent yields. Further investigations of utilizing light-generated hydrogen are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03497.

Experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rickywu@njau.edu.cn.

Author Contributions

§These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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