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Visible-Light-Induced Metal-Free Synthesis of 2-Phosphorylated Thioflavones in Water

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Dedicated to the 100th anniversary of Nankai University

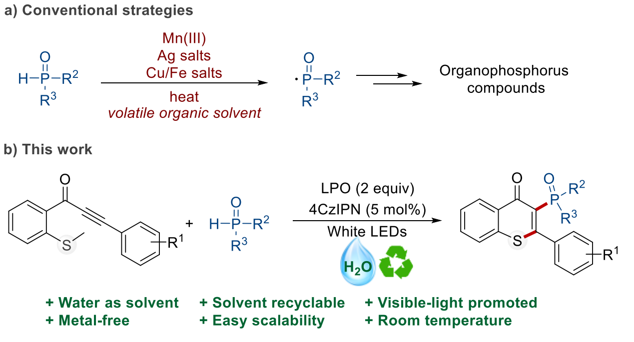
Abstract: Using water as a reaction medium, a large number of 2-phosphorylated thioflavones were prepared *via* the reaction of methylthiolated alkynones and phosphine oxides catalyzed by 4CzIPN under visible-light irradiation. These reactions can be carried out at ambient temperature, feature simple operation, wide reaction scope, and recyclability of aqueous media.

The increasing concern about minimizing the environmental impact of chemical synthesis has become an area of growing significance and has prompted the development of environmentally friendly and green procedures for organic transformations. One of the major impacts of classical organic synthesis on the environment is due to the utilization of toxic and volatile organic solvents. Additionally, the application of organic solvents in heat- or gas-releasing reactions may present potential safety issues, such as combustion and explosion. Since the definition of “green chemistry” was proposed by Anastas and Warner in 1991, organic transformation in green solvents, which were considered as well-accepted and effective solutions for these problems, has attracted widespread attention.[1] As a natural liquid with abundant reserves, water is uniquely advantageous as a reaction medium with obvious merits, such as non-toxicity, low cost, and easy acquisition.[2] In addition, the use of water instead of traditional organic solvents can effectively avoid toxicity and potential risks in chemical processes, as water is perfectly bio-compatible and is a non-flammable liquid with high heat capacity.[3] From economic, environmental points of view, organic reactions carried out in water are attractive and highly desired, which is in harmony with the philosophy of green chemistry.[4]

Visible-light represents a highly economical and eco-friendly energy source. Recently, visible-light-induced reactions have emerged as versatile tools for chemical transformations.[5] Although significant advances have been made in the past decade, visible-light catalysis is generally carried out in traditional organic solvents.[6] Obviously, running photocatalytic organic reactions in water is an attractive strategy but is less developed. Therefore, the development of photocatalytic systems using water as a green solvent is still highly desirable for green organic synthesis.[7]

Phosphorus-containing compounds have received increasing attention in the past few decades due to their wide range of applications in medicinal chemistry, materials science, and organic synthesis.[8] In recent years, P-centered radicals added to unsaturated double and triple bonds have been recognized as powerful and efficient approach for the construction of P-containing compounds.[9] The synthesis of structurally diverse phosphorus-containing compounds *via* P-centered radicals initiated reaction has been witnessed.[10] However, the generation of P-center radicals in these transformations generally requires the use of transition-metal salts and high reaction temperatures, limiting their practical applications (Scheme 1a).[11]

Thioflavones are meaningful functional motifs that occur in numerous nature products, drugs and functional materials.[12] The intrduction of phosphorus functional groups to the skeleton of thioflavones is an attractive task and of great significance. With our continuing interest in green chemistry and phosphorus chemistry,[13] we herein report a metal-free visible-light-induced radical cascade cyclization in water for the preparation of 2-phosphorylated thioflavones from methylthiolated alkynones and phosphine oxides (Scheme 1b). By using the organophotocatalyst 4CzIPN, a range of 2-phosphorylated thioflavones were prepared *via* the aqueous reaction with satisfactory yields at room temperature. To the best of our knowledge, this is the first example of the photocatalytic construction of C-P bonds by using 4CzIPN as a photocatalyst in water, in which the waste and toxicity issues of organic solvents could be avoided, and aqueous media could be recycled.



Scheme 1. Radical reaction for the construction of organophosphorus compounds

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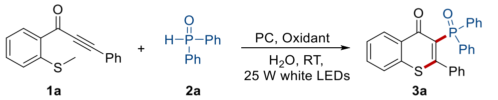
Supporting information for this article is given via a link at the end of the document.

For the optimization of reaction conditions, methylthiolated phenylpropynone (**1a**) and diphenylphosphine oxide (**2a**) were utilized as model substrates, and the results were summarized in Table 1. When the model reaction was firstly performed in water by employing eosin Y as photocatalyst in the presence of TBHP/$NaHCO_3$ under the irradiation of white LEDs for 24 h, it is pleased to see that the desired product **3a** was obtained in 24% yield (entry 1). Inspired by this intriguing result, other frequently used photocatalysts, including eosin B, Na_2Eosin Y, Na_2Eosin B, rhodamine B, rose bengal, 4CzIPN, and fluorescein, were evaluated (entries 2-8). Among the above photocatalysts examined, 4CzIPN demonstrated the highest catalytic activity, affording the desired product **3a** in moderate yield (45%, entry 7). To further improve the reaction efficiency, various inorganic and organic bases were tested (entries 9-12). However, no better results were obtained. Surprisingly, this visible-light-induced transformation also proceeded smoothly under the base-free conditions, delivering the product of **3a** with 47% yield (entry 13). Furthermore, various oxidants, such as DTBP, BPO, $K_2S_2O_8$, LPO and O_2 were investigated (entries 14-18). To our delight, by employing LPO as oxidant, a satisfactory yield of **3a** was obtained (entry 17). It is especially worth mentioning here that 53% yield of **3a** can be obtained when O_2 was employed as green oxidant in this photooxidation processes (entry 18). Due to the higher efficiency, LPO was employed as oxidant for further investigation. Subsequent study on the investigation for the dosages of oxidant indicated that 2 equiv of LPO was the best choice for this transformation (entries 19-21). When the reaction was performed under air, a slight decrease in yield was observed (entry 22). Notably, no desired product was observed in the absence of either 4CzIPN or visible light (entries 23-24). Therefore, the optimized reaction conditions are illustrated as follows: **1a** (0.2 mmol), **2a** (0.4 mmol), 4CzIPN (5 mol%) and LPO (2 equiv) were mixed in H_2O with the irradiation of white LEDs under N_2 for 24 h.

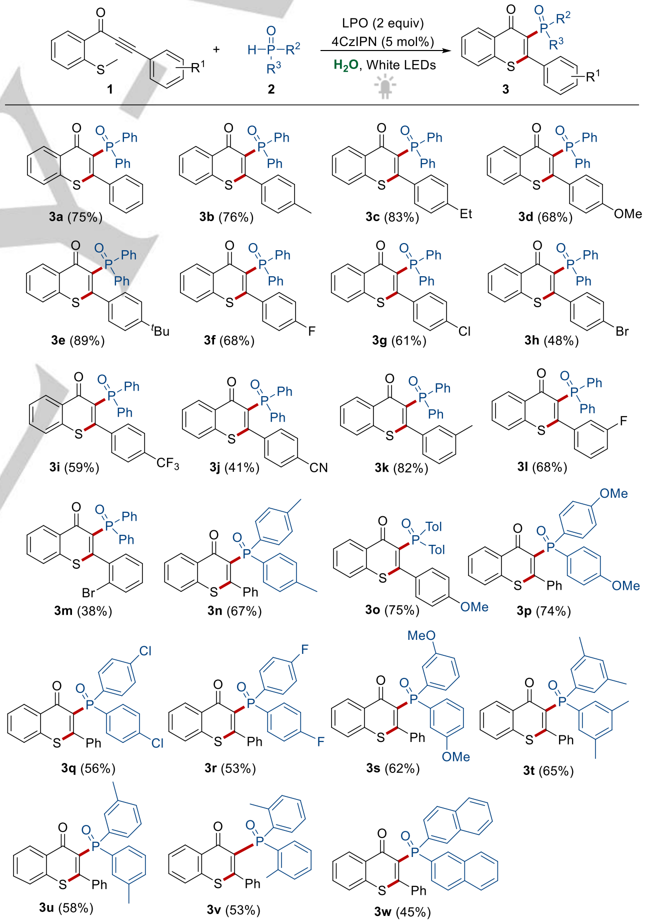
Table 1. Optimization of the reaction conditions



Entry	PC	Oxidant	Base [equiv]	Yield [%]
1	eosin Y	TBHP	$NaHCO_3$ (2)	24
2	eosin B	TBHP	$NaHCO_3$ (2)	23
3	Na_2Eosin Y	TBHP	$NaHCO_3$ (2)	31
4	Na_2Eosin B	TBHP	$NaHCO_3$ (2)	30
5	rhodamine B	TBHP	$NaHCO_3$ (2)	13
6	rose bengal	TBHP	$NaHCO_3$ (2)	19
7	4CzIPN	TBHP	$NaHCO_3$ (2)	45
8	fluorescein	TBHP	$NaHCO_3$ (2)	trace
9	4CzIPN	TBHP	Cs_2CO_3 (2)	trace
10	4CzIPN	TBHP	K_2CO_3 (2)	11
11	4CzIPN	TBHP	DABCO (2)	17
12	4CzIPN	TBHP	Et_3N (2)	18
13	4CzIPN	TBHP	---	47
14	4CzIPN	DTBP	---	22
15	4CzIPN	BPO	---	27
16	4CzIPN	$K_2S_2O_8$	---	58
17	4CzIPN	LPO	---	78 (75)[b]
18[c]	4CzIPN	O_2	---	53
19[d]	4CzIPN	LPO	---	67
20[e]	4CzIPN	LPO	---	77
21	4CzIPN	---	---	N.D.
22[f]	4CzIPN	LPO	---	66
23	---	LPO	---	N.D.
24[g]	4CzIPN	LPO	---	N.D.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), PC (5 mol%), oxidant (2 equiv), H_2O (2.5 mL) for 24 h under N_2. PC = photocatalyst, 4CzIPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene, TBHP = *tert*-butyl hydroperoxide, DTBP = di-*tert*-butyl peroxide, BPO = benzoyl peroxide, LPO = dilauroyl peroxide, N.D. = not detected. Yield were determined by ^{31}P NMR using trioctylphosphine oxide as an internal standard. [b] Isolated yield. [c] Under O_2 balloon. [d] LPO (1 equiv). [e] LPO (3 equiv). [f] Under Air. [g] In dark

Table 2. Substrate scope for 2-phosphorylated thioflavones



[a] Reaction conditions: **1** (0.2mmol), **2** (0.4 mmol), 4CzIPN (5 mol%), LPO (2 equiv), H_2O (2.5 mL), white LEDs, under N_2 for 24 h, RT. Isolated yields were given.

With optimized reaction conditions identified, a systematic study of substrate scope was carried out to evaluate the applicability of this visible-light-induced transformation by

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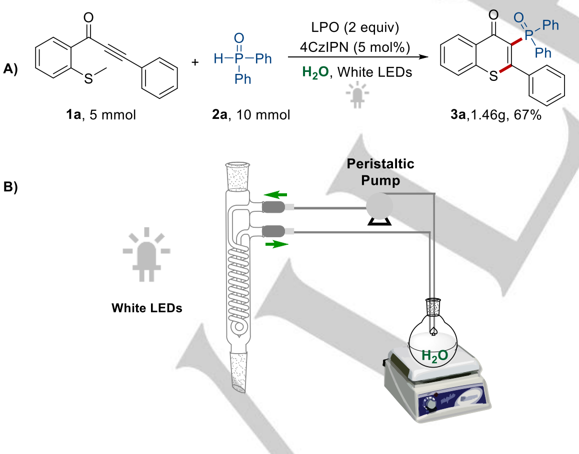
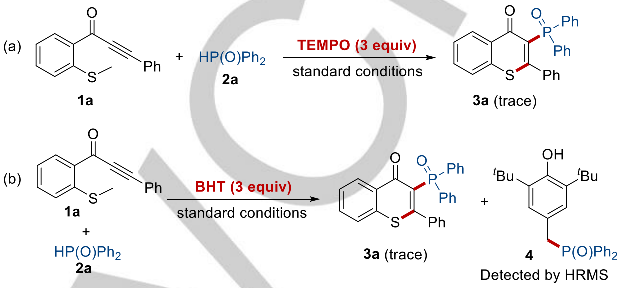
examining different methylthiolated alkynones **1** and phosphine oxides **2**, and the results are illustrated in Table 2. A variety of methylthiolated alkynones with diverse functionalities at the phenyl ring (R^1) worked well in the optimal condition reacting with diphenylphosphine oxide (**2a**), affording the corresponding products **3a**–**m** in moderate to excellent yields (up to 89%). In these cases, substrates bearing electron-donating groups (–Me, –OMe, –Et, and –*t*Bu) generally showed better reactivities than those attached with electron-withdrawing substituents (–F, –Cl, –Br, –CN, and –CF$_3$). Furthermore, the trifluoromethyl group, widespread in drugs and agrochemicals, was also well accommodated, leading to the corresponding CF$_3$-containing compound **3i** in moderate yields (59%). In addition, the reactivities of various phosphine oxides were also investigated. We were delighted to find that phosphine oxides with electron-donating and electron-withdrawing substituents were compatible under the optimized reaction conditions (**3n**-**3w**). The electron-withdrawing and electron-donating groups have no significant effect on the efficiency of this visible-light-induced transformation. In addition, reactant **2** containing naphthalene rings (R^2) was also suitable for this transformation, resulting in product **3w** in satisfactory yield. Additionally, products were not detected when dibutyl phosphine oxide, diethyl *H*-phosphonate, dimethyl *H*-phosphonate as well as diphenylphosphine sulfide were employed as phosphorus reaction partners, indicating that dialkyl phosphine oxides, dialkyl *H*-phosphinates and diarylphosphine sulfides were not suitable for this transformation.

Moreover, to evaluate the practicability of this photocatalytic phosphorylation reaction, a gram-scale synthesis of **3a** was conducted in a specially designed flow reactor under optimal conditions (Scheme 2). It is pleasing to see that the desired product **3a** was obtained in good yield (67%) when the reaction was performed on the 5-mmol scale, implying a promising industrial application in preparative synthesis.



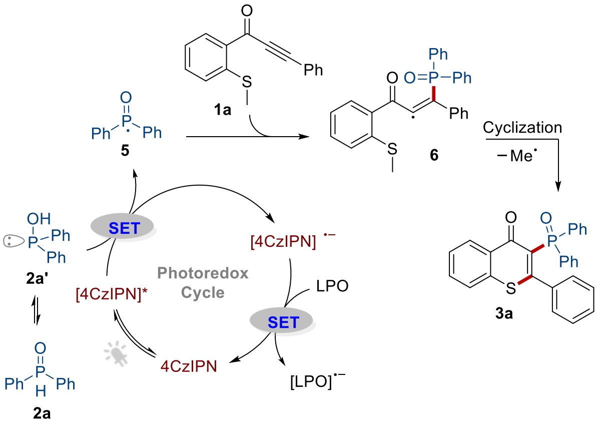
Scheme 2. Gram scale synthesis of **3a**

To obtain more potential mechanistic insights into this transformation, several control experiments were performed. As can be seen in Scheme 3, the purposeful addition of a radical scavenger, (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT), to the model reaction severely inhibited the reaction. These results suggested that a radical pathway should be involved in this visible-light-promoted reaction. Moreover, a BHT-P(O)Ph$_2$ adduct **4** was detected in the reaction mixture by high-resolution mass spectrometry (HRMS), indicating that phosphoryl radical was generated in the reaction process (Scheme 3b). Additionally, quantum yield for the model reaction was measured.[14] The low value (0.24) determined indicated that a radical chains process should not account for the full reaction productivity in this photochemical transformation (for details see the Supporting Information).



Scheme 3. Control experiments

Based on the experimental results as well as the previous literature,[15] a plausible reaction mechanism for this transformation is thereby proposed as shown in Scheme 4. Initially, the ground state of 4CzIPN was converted into the excited-state species, i.e., 4CzIPN*, under the irradiation of visible-light. Diphenylphosphine oxide **2a** is usually in equilibrium between tri-coordinated and tetra-coordinated forms. The tri-coordinated isomer **2a’** could react with the excited 4CzIPN* *via* a single-electron transfer (SET) process, leading to the formation of phosphoryl radical **5** and radical anion 4CzIPN$^{\bullet-}$. Importantly, the high redox potential of the photoexcited state of 4CzIPN ($E_{1/2}(P^*/P^-)$ = +1.35 V *vs* SCE) make this process credible and reasonable.[16] Next, the addition of phosphoryl radical **5** to the triple bond of **1a,** followed by an intramolecular cyclization, generated the final product **7**, releasing methyl radical. Moreover, LPO can oxidize the radical anion 4CzIPN$^{\bullet-}$ regenerating the ground state of 4CzIPN to complete the photoredox cycle.



Scheme 4. Proposed mechanism

Additionally, recycling study of aqueous media was carried out (see the Supporting Information). The experimental results show that water could be recycled and applied as solvent for this reaction at least five times without significant loss of reactivities (Figure 1).

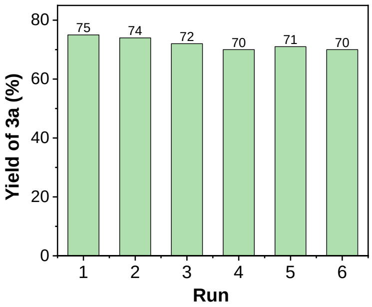
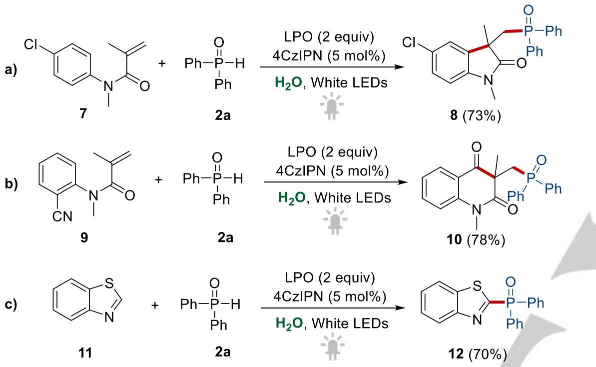


Figure 1. Recyclability of water.



Scheme 5. Preparation of phosphorylated *N*-heterocycles

Encouraged by these exciting results, we attempted to extend this green and sustainable strategy to different radical partners for the preparation of significant phosphorus-containing compounds. Gratifyingly, the conditions were suitable for the synthesis of phosphorylated *N*-heterocycles, including phosphorylated oxindole (**8**), phosphorylated quinoline-2,4(1*H*,3*H*)-dione (**10**) as well as phosphorylated benzothiazole (**12**) in water, as shown in Scheme 5, implying the broad applicability of our approach.

In conclusion, a metal-free photocatalytic system for C-P bond formation at room temperature was successfully developed under visible-light irradiation in water. With this green and sustainable strategy, a wide range of 2-phosphorylated thioflavones were prepared with satisfactory yields *via* the reaction of methylthiolated alkynones and phosphine oxides. Moreover, some phosphorylated *N*-heterocycles, including phosphorylated oxindole, phosphorylated quinoline-2,4(1*H*,3*H*)-dione as well as phosphorylated benzothiazole could be smoothly synthesized in good isolated yields by using this green and sustainable strategy. This is the first example of the photocatalytic construction of C-P bond using 4CzIPN as a photocatalyst in water, in which the waste and toxicity issues of organic solvents could be avoided, and aqueous media could be recycled. Further application of this photocatalytic strategy for the construction of more structurally diverse phosphorus-containing compounds is currently ongoing in our laboratory.

Experimental Section

A mixture of methylthiolated phenylpropynones (0.2 mmol, 1 equiv), phosphine oxides (0.4 mmol, 2 equiv), LPO (2 equiv), 4CzIPN (5 mol%) were sequentially added in a 10-mL reaction vial. Then, H_2O (2.5 mL) was added into this reaction system. The reaction vial was sealed under N_2 and stirred under the irradiation of white LEDs at room temperature until TLC (petroleum ether/ethyl acetate= 2/1) revealed that conversion of the starting material was completed. Next, the solvent was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate = 2/1) to give the desired products.

Acknowledgements

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Keywords: Photocatalysis • Metal-free • Aqueous reaction• Phosphorylation • Thioflavones

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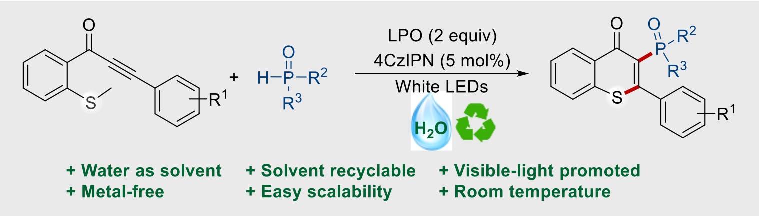

Using water as a reaction medium, a large number of 2-phosphorylated thioflavones were prepared via the reaction of methylthiolated alkynones and phosphine oxides catalyzed by 4CzIPN under visible-light irradiation. These reactions can be carried out at ambient temperature, feature simple operation, wide reaction scope, and recyclability of aqueous media.

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Visible-Light-Induced Metal-Free Synthesis of 2-Phosphorylated Thioflavones in Water