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Photoinduced Transition-Metal-Free Cross-Coupling of Aryl Halides with H-Phosphonates

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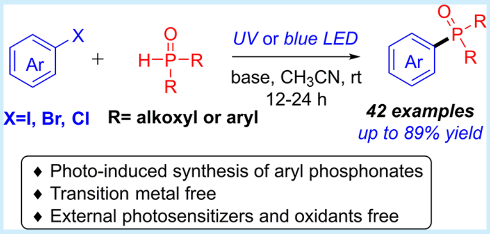
Supporting Information

ABSTRACT: Photoinduced transition-metal- and photosensitizer-free cross-coupling of aryl halides (including Ar−Cl, Ar−Br, and Ar−I) with H-phosphonates (including dialkyl phosphonates and diarylphosphine oxides) is reported. Various functional groups were tolerated, including ester, methoxy, dimethoxy, alkyl, phenyl, trifluoromethyl, and heterocyclic compounds. This simple and green strategy provides a practical pathway to synthesize arylphosphine oxides.



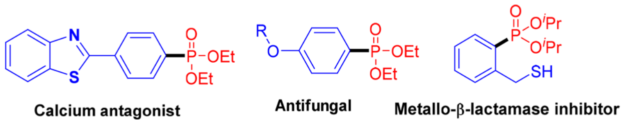
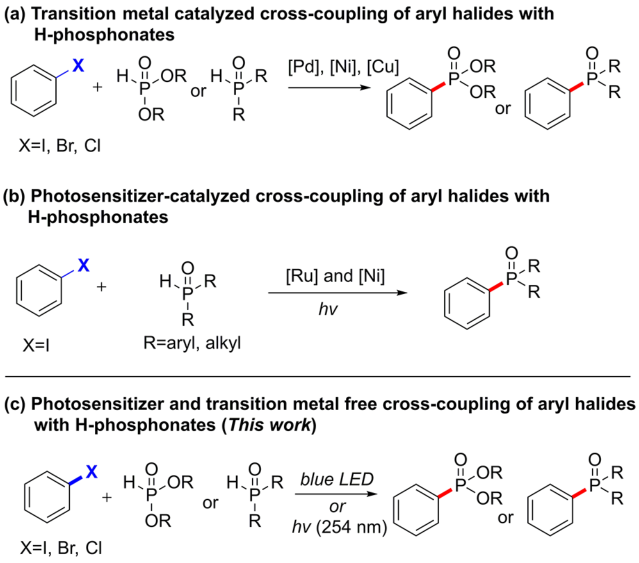


Figure 1. Representative biologically active phosphorus-containing compounds.

Phosphorus-containing compounds are important for pharmaceuticals (Figure 1), agrochemicals, and flame-resistant materials.[1] They are also important as ligands for various transition-metal-catalyzed reactions. Because of their functional and biological activities, C−P bond formation has attracted significant interest from organic chemists.[2] Traditionally, aryl phosphonates were synthesized from aryl halides and H-phosphonates catalyzed by palladium.[2a,3] Catalysts with cheaper transition metals, such as copper[4] and nickel,[5] for this transformation were developed subsequently (Scheme 1a). Recently, Xiao's group reported nickel and ruthenium dual-catalyzed cross-coupling of aryl iodides with H-phosphonates upon irradiation by visible light (Scheme 1b).[6] König's group reported the organic-photosensitizer-catalyzed Arbuzov reaction of aryl bromides and trialkyl phosphites.[7] Although great advances have been achieved, the more active aryl iodides and aryl bromides have been used as the substrates. For photoredox reactions, only a few examples of aryl chlorides were successful for the C−P bond formation.[7] Photoinduced and photosensitizer-free catalysis has been developed as a greener pathway for carbon−heteroatom bond formation.[8] It is thus highly desirable to develop alternative photoinduced methods for cross-coupling of aryl halides with H-phosphonates that do not use photosensitizers and transition metals.[9] Herein we report a photoinduced photosensitizer- and transition-metal-free cross-coupling of aryl halides (including Ar−Cl, Ar−Br, and Ar−I) or heteroaryl halides with H-phosphonates (including dialkyl phosphonates and diarylphosphine oxides) (Scheme 1c).

Scheme 1. Methods for Cross-Coupling of Aryl Halides with H-Phosphonates



Our investigation commenced with the reaction of bromobenzene (**1a**) and dimethyl phosphonate (**2a**) with TMEDA (2.0 equiv) and sodium iodide (0.5 equiv) in acetonitrile (1.0 mL) at room temperature under an argon atmosphere in a quartz tube with irradiation by 254 nm light. No desired product was detected (Table 1, entry 1). The same

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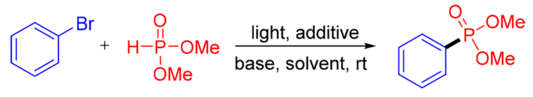
Table 1. Screening of the Conditions[a]



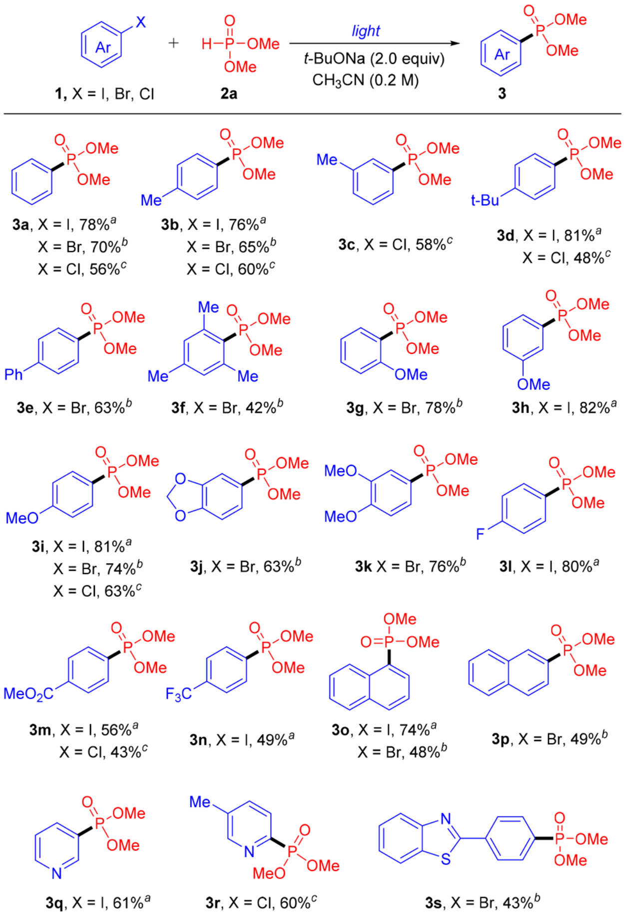
entry	base	solvent	additive	yield (%)[b]
1	TMEDA	CH_3CN	NaI	n.p.
2	DABCO	CH_3CN	NaI	n.p.
3	K_2CO_3	CH_3CN	NaI	n.p.
4	K_3PO_4	CH_3CN	NaI	n.p.
5	NaOH	CH_3CN	NaI	n.p.
6	Cs_2CO_3	CH_3CN	NaI	17
7	EtONa	CH_3CN	NaI	9
8	*t*-BuONa	CH_3CN	NaI	64
9	*t*-BuONa	CH_3CN	–	52
10	*t*-BuONa	CH_3CN	KI	68
11	*t*-BuONa	CH_3CN	LiI	31
12	*t*-BuONa	CH_3CN	I_2	n.p.
13	*t*-BuONa	CH_3CN	TBAI	80 (70)
14	*t*-BuONa	H_2O	TBAI	<5
15	*t*-BuONa	DMF	TBAI	23
16	*t*-BuONa	DMA	TBAI	41
17	*t*-BuONa	CH_3CN/H_2O	TBAI	<5
18[c]	*t*-BuONa	CH_3CN	TBAI	73
19[d]	*t*-BuONa	CH_3CN	TBAI	78
20[e]	*t*-BuONa	CH_3CN	TBAI	<5
21[f]	*t*-BuONa	CH_3CN	TBAI	n.p.
22[g]	*t*-BuONa	CH_3CN	TBAI	n.p.
23[h]	*t*-BuONa	CH_3CN	TBAI	n.p.

[a] General conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), base (2.0 equiv), additive (0.5 equiv), and solvent (1.0 mL) for 18 h under an argon atmosphere at room temperature with UV light (254 nm). Abbreviations: n.p., no product; DMF, *N*,*N*-dimethylformamide; DMA, *N*,*N*-dimethylacetamide; TBAI, tetrabutylammonium iodide. [b] Determined by ^{31}P NMR analysis using triethyl phosphate as an internal standard; an isolated yield is shown in parentheses. [c] TBAI (0.2 equiv). [d] TBAI (1.0 equiv). [e] 405 nm. [f] Blue LED. [g] White light. [h] In the dark.

results were obtained with other organic and inorganic bases (Table 1, entries 2–5). Fortunately, a small amount of the desired product was obtained when cesium carbonate or sodium ethoxide was used as the base (Table 1, entries 6 and 7). The best yield was obtained using the strong base potassium *tert*-butoxide (Table 1, entry 8). In the absence of sodium iodide additive, the yield was lowered to 52% (Table 1, entry 9). With other iodide sources (Table 1, entries 10–13),[10] the highest yield was detected when TBAI was used (Table 1, entry 13). With other solvents, such as water, DMF, DMA, and an MeCN/H_2O mixture, no improvement was observed (Table 1, entries 14–17). When the amount of additive was increased or reduced, the yield was slightly lowered (Table 1, entries 18 and 19). Different light sources were examined, such as 405 nm light, a blue LED, and white light, and all showed lower efficiency than 254 nm light (Table 1, entries 20–22). These results indicate that the light source is very important to this reaction. Since metal *tert*-butoxide can promote the reaction of bromobenzene to form benzene free radical without light,[11] a control experiment was also carried out under dark conditions, and no product was detected (Table 1, entry 23).

With the optimized reaction conditions in hand, the scope of aryl halides was explored with 2.0 equiv of dimethyl phosphonate at room temperature under an argon atmosphere using 2.0 equiv of *t*-BuONa as the base in acetonitrile (1.0 mL) under irradiation. As shown in Scheme 2, more reactive iodobenzene derivatives were irradiated with 405 nm light (method A), while the less reactive bromobenzene derivatives also worked very well upon addition of TBAI under irradiation at 254 nm together with a prolonged reaction time of 18 h (method B). Importantly, although chlorobenzene derivatives are usually more inert for metal-catalyzed cross-coupling reactions, they can also react smoothly upon irradiation at 254 nm with 0.2 equiv of TBAI (method C). A broad range of aryl halides containing different functional groups proved to be competent substrates. Aryl halides (including Ar–I, Ar–Br, and Ar–Cl) substituted with a weak electron-withdrawing

Scheme 2. Cross-Coupling of Different Aryl Halides with Dimethyl Phosphonate

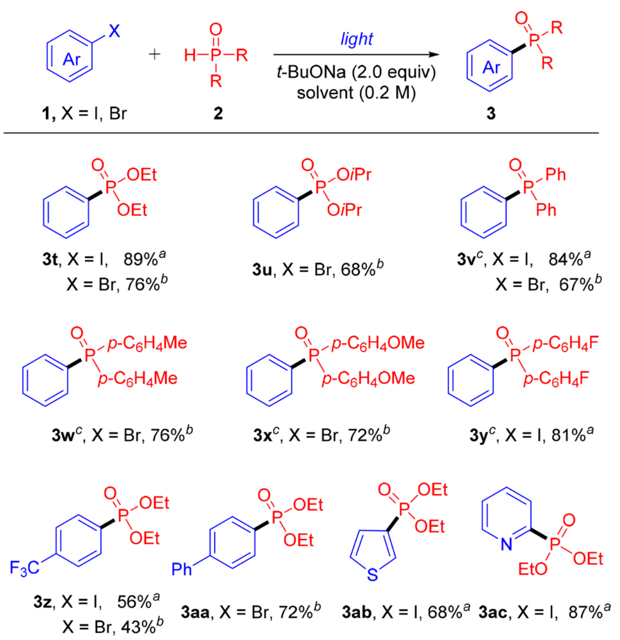


[a] Method A for ArI: aryl iodide **1** (0.2 mmol), **2a** (0.4 mmol), and *t*-BuONa (0.4 mmol) in CH_3CN (1.0 mL) irradiated by 405 nm light at room temperature in a sealed quartz tube under an argon atmosphere for 12 h. Isolated yields are shown. [b] Method B for ArBr: aryl bromide **1** (0.2 mmol), **2a** (0.4 mmol), TBAI (0.5 equiv), and *t*-BuONa (0.4 mmol) in CH_3CN (1.0 mL) irradiated by UV light (254 nm) at room temperature in a sealed quartz tube under an argon atmosphere for 18 h. Isolated yields are shown. [c] Method C for ArCl: aryl chloride **1** (0.2 mmol), **2a** (2.0 equiv), TBAI (0.2 equiv), and *t*-BuONa (0.4 mmol) in CH_3CN (1.0 mL) irradiated by UV light (254 nm) at room temperature in a sealed quartz tube under an argon atmosphere for 24 h. Isolated yields are shown.

group (e.g., methyl, *tert*-butyl, or phenyl) at different positions reacted very well, generating the corresponding products **3a**−**e** in moderate to high yields. Even 2,4,6-trimethylbromobenzene, with high steric hindrance, generated the cross-coupled product **3f** in moderate yield. Various aryl halides bearing a strong electron-donating group at different positions were all effective, forming the corresponding products **3g**−**k** in good to high yields. Substrates bearing different halides could be selectively cross-coupled with dimethyl phosphonate, as shown by the generation of fluorine-containing product **3l**. Substrates bearing strong electron-withdrawing groups also reacted smoothly to afford products **3m** and **3n**. The reaction of iodo- or bromonaphthalene generated the corresponding products **3o** and **3p**. Heterocyclic products **3q**−**s** were also obtained by this method.

To further investigate the scope of this reaction system, different phosphonate esters were also tested (Scheme 3).

Scheme 3. Cross-Coupling of Aryl Halides with Different H-Phosphonates

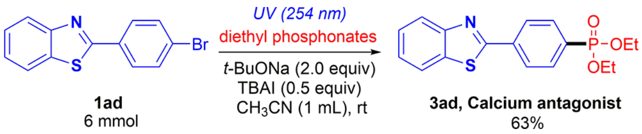


[a] Method A for ArI: aryl iodide **1** (0.2 mmol), **2** (0.4 mmol), and *t*-BuONa (0.4 mmol) in CH_3CN (1.0 mL) irradiated by 405 nm light at room temperature in a sealed quartz tube under an argon atmosphere for 12 h. Isolated yields are shown. [b] Method B for ArBr: aryl bromide **1** (0.2 mmol), **2** (0.4 mmol), TBAI (0.5 equiv), and *t*-BuONa (0.4 mmol) in CH_3CN (1.0 mL) irradiated by UV light (254 nm) at room temperature in a sealed quartz tube under an argon atmosphere for 18 h. Isolated yields are shown. [c] DMF was used as the solvent instead of CH_3CN.

Diethyl and diisopropyl phosphonates and various substituted diaryl phosphonates were successfully cross-coupled with aryl halides. Diethyl phenylphosphonate (**3t**), diisopropyl phenylphosphonate (**3u**), triphenylphosphine oxide (**3v**), phenyldi-*p*-tolylphosphine oxide (**3w**), bis(4-methoxyphenyl)(phenyl)phosphine oxide (**3x**), and bis(4-fluorophenyl)(phenyl)phosphine oxide (**3y**) were obtained in good to high yields. The method could also be applied to other substituted aryl halides and heterocyclic halides to give the corresponding products **3z**−**ac**.

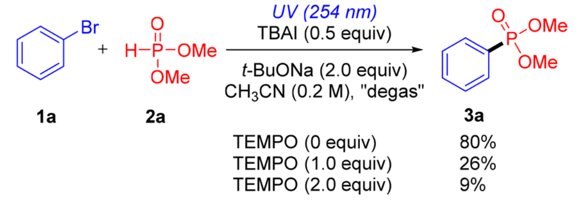
It is well-recognized that trace amounts of transition-metal residue are highly undesirable in the pharmaceutical industry. To demonstrate the advantage of this method, the calcium antagonist **3ad** was synthesized on a gram scale without the use of any transition metal (Scheme 4).

Scheme 4. Application to the Synthesis of a Calcium Antagonist on a Gram Scale



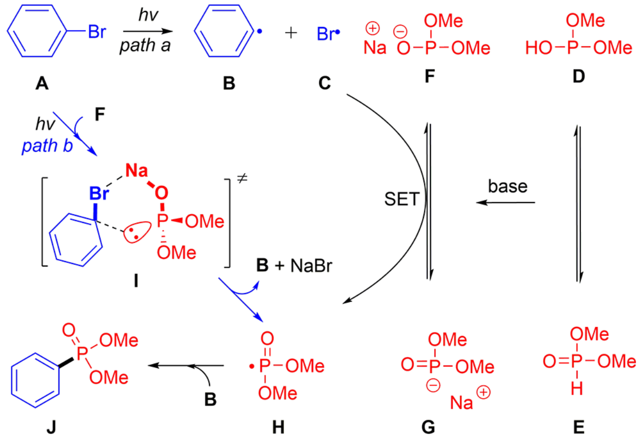
To investigate the reaction mechanism, radical trap experiments were carried out (Scheme 5). Different amounts of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) were added to the cross-coupling of bromobenzene with dimethyl phosphonate under the standard reaction conditions. With increasing amounts of TEMPO, the yield decreased accordingly. When 2.0 equiv of TEMPO was added to the reaction system, the cross-coupled product **3a** was obtained in only 9% yield. These experiments suggested that radicals may exist in this reaction.

Scheme 5. Radical Trap Experiments



On the basis of those experimental results, a tentative mechanism is proposed in Scheme 6. Aryl halide **A** is irradiated by light to form aryl free radical **B** and bromine free radical **C** via homolytic cleavage of the C−X bond (path a). Phosphite **D** tautomerizes with phosphonate **E**, which reacts with strong base to form another tautomerization pair between anions **F** and **G**. Then anion **F** or **G** is oxidized by bromine free radical **C** via a single electron transfer (SET) process to generate phosphonate free radical **H**, which cross-couples with aryl free radical **B** to generate the product **J**. Alternatively, the aryl

Scheme 6. Tentative Mechanism



halide can be irradiated by light to generate the excited state, which can form five-membered-ring transition state **I**, similar to that in our previous work,[8o] via weak halogen−metal bonding[12] between the halogen and sodium of intermediate **F** (path b). Subsequent "intramolecular" electron transfer from the lone pair of phosphorus to the C−X bond generates aryl radical **B** and sodium bromide, while phosphite **F** is concurrently oxidized to form phosphonate radical **H**. Then intermediate **H** is cross-coupled with aryl radical **B** to generate product **J**.

In conclusion, we have reported a novel cross-coupling of aryl halides with H-phosphonates under irradiation by light without using any transition metal or external photosensitizer reagents. Various aryl and heteroaryl halides were successfully cross-coupled with diarylphosphine oxides, dialkyl phosphonates, or arylphosphonates. Various functional groups were tolerated, including ester, methoxy, dimethoxy, alkyl, phenyl, trifluoromethyl, and heterocyclic compounds. This method provides a potentially greener pathway to synthesize phosphorus-containing pharmaceuticals, agrochemicals, and flame-resistant materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04081.

Experimental procedures, additional experimental data, and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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