Metal-Free Photoredox Phosphonation of C–N and C–X Bonds in Aqueous Solvent Mixtures

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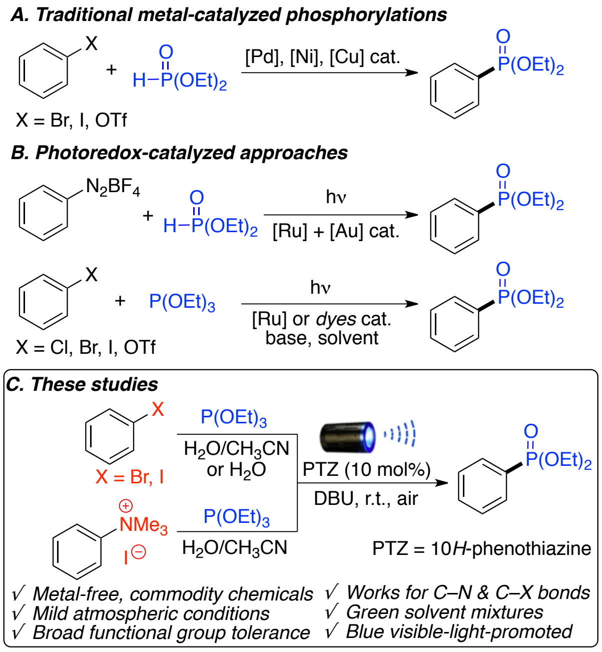
Abstract: Aryl phosphonate esters are valuable moieties for the pharmaceutical and agrochemical industries. Accessing such compounds from affordable and abundant phosphite reagents and a wide range of aromatic building blocks under metal-free, visible light-induced reaction conditions would represent a desirable technology. Herein, we present an efficient and mild methodology for the synthesis of aromatic phosphonate esters in good to excellent yields using DBU and phenothiazine as a photoredox catalyst. The reaction exhibits wide functional group compatibility enabling the transformation in presence of ketone, amide, ester, amine, and alcohol moieties. Importantly, the reaction proceeds using a green solvent mixture primarily composed of water, thus lowering the environmental footprint of this transformation compared to current methods.

The aromatic phosphonate ester motif is found in a wide variety of pharmaceutically active molecules, photoelectric materials, agrichemical compounds, and in ligands for metal catalysis.[1] For these reasons, the synthesis of C–P bonds has attracted significant interest in the past decade.[2] Traditional ways to access aryl phosphonates requires the activation of P–H bonds in reagents such as diethyl phosphite ($H(O)P(OEt)_2$) using transition-metal catalysis (Scheme 1A). Coupling partners for these reactions have been widely explored and include aryl halides, ary triflates, and aryl boronic acids.[3] However, the expensive and sometimes toxic nature of the catalysts and reagents required for these transformations, alongside substrate scope limitations due to harsh reaction conditions, have encouraged the development of milder methodologies. In the last decade, photoredox-catalyzed methods to generate aryl phosphonates has gained traction as an attractive alternative to traditional methods due to their milder conditions and broader functional group tolerance (Scheme 1B).[4] Pioneering work by Toste was the first to achieve phosphonation of aryldiazonium salts using $H(O)P(OEt)_2$ in presence of a gold(I) catalyst and a Ru photocatalyst.[4a] Later work by König achieved these transformations using a Ru photocatalyst and a rhodamine dye.[4b,4c] More recently, the combination of photoredox catalysis and electrochemistry enabled Wickens to achieve the phosphonation of aryl chlorides.[4d]

Despite all the progress achieved by these methods, their environmental footprint is far from desirable. The uses of rare metals, problematic solvents, highly toxic organic dyes,[5] or anhydrous and inert atmosphere remain challenges to the green synthesis of these valuable and industrially relevant compounds. Importantly, improving the sustainability of these transformations has to be achieved without compromising substrate scope and functional group compatibility.



Scheme 1. Current and proposed approaches to aryl C–P bond formation.

Our interest in the development of metal-free green synthetic methodologies,[6] recently led us to explore new approaches for the radical activation of aryl halides.[6b] Here, we report the first metal-free photoredox-catalyzed phosphonation of aryl trimethylammonium salts and aryl halides (iodides and bromides) using affordable phosphite reagents in green aqueous solvent mixtures. This reaction uses 10*H*-phenothiazine (PTZ), a common and inexpensive commodity chemical, as a photoredox catalyst. In addition to lowering the environmental footprint provided by the possible use of water as a solvent, this transformation proceeds unaffected under atmospheric conditions without the need for degassing or distilling the solvents, or placing the reaction under inert atmosphere. These mild reaction conditions also provide broad functional group tolerance in presence of reactive ketone, amide, ester, amine, and alcohol moieties.

Our initial studies aimed at the phosphonation of 4-iodoanisole (**1a**) using triethyl phosphite (**2a**) as our phosphorous containing reagent (Table 1). To achieve our objectives of performing this transformation under the most environmentally friendly and cost-effective conditions possible, we focused our attention to the screening of bases, solvents, and atmospheric conditions using PTZ as our photocatalyst (<$90/Kg).[7]

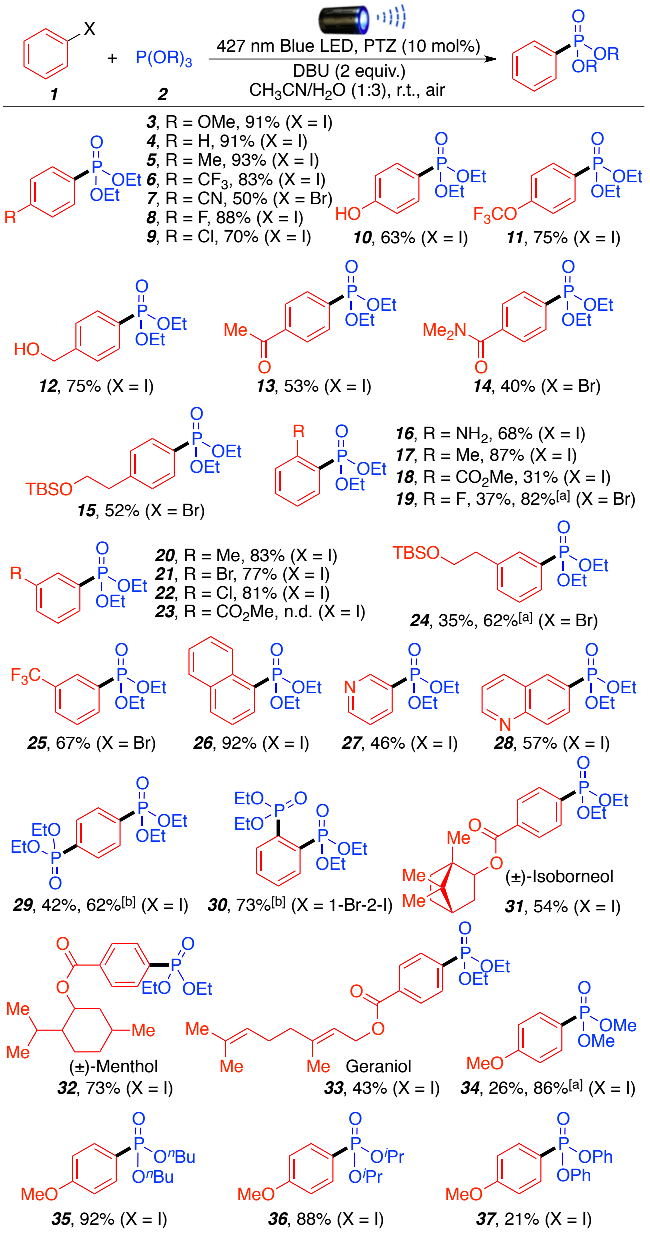
Table 1. Optimization of the reaction conditions.[a]

Entry	Base (equiv)	**2a** (equiv)	Solvent	Product **3** Yield (%)[b]	Recovered **1a** Yield (%)[b]
1	DBU (3.0)	3.0	CH_3CN	89 (**A**)	-
2	Et_3N (3.0)	3.0	CH_3CN	10 (**A**)	90
3	DIPEA (3.0)	3.0	CH_3CN	12 (**A**)	87
5	K_2CO_3 (3.0)	3.0	CH_3CN	34 (**B**)	60
6	LiO*t*Bu (3.0)	3.0	CH_3CN	58 (**B**)	39
7	–	3.0	CH_3CN	9 (**B**)	90
8[c]	DBU (3.0)	3.0	CH_3CN	6 (**B**)	83
9[d]	DBU (3.0)	3.0	CH_3CN	– (**B**)	97
10[e]	DBU (3.0)	3.0	CH_3CN	85 (**B**)	trace
11	DBU (2.0)	3.0	CH_3CN	92 (**B**)	trace
12	DBU (3.0)	2.0	CH_3CN	66 (**B**)	23
13[e]	DBU (2.0)	3.0	CH_3CN/H_2O (1:3)	90 (**B**)	4
14[e]	DBU (2.0)	3.0	CH_3CN/H_2O (1:9)	87 (**B**)	6
15[e]	DBU (2.0)	3.0	H_2O	72 (**B**)	15

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), DBU (0.6 mmol), solvent (1 mL), room temperature around the reaction flask is 35 °C (heating caused by the 456 nm (**A**) or 427 nm (**B**) LED lamp), under argon, 24 h. [b] Yields are based on **1a**, determined by ^{1}H-NMR using dibromomethane as an internal standard. [c] The reaction was performed in the absence of PTZ. [d] The reaction was performed in the dark, covered by aluminium foil. [e] The reaction was performed in air.

Gratifyingly, the reaction proceeded in excellent yield (89%) in acetonitrile using DBU (1,8-Diazabicyclo(5.4.0)undec-7-ene) as a base (entry 1). Four other organic and inorganic bases were screened providing moderate yields for the desired product and poor conversions of the starting material **1a** (Table 1, entries 2-6). The main byproduct of these reactions is the proto-dehalogenation of the aryl halide **1a**. In the absence of base (entry 7) or photocatalyst (entry 8), the yields decreased dramatically (<10%), with an almost complete recovery of the starting material. Similarly, no desired product was obtained when the reaction was performed in the dark (entry 9). Importantly, the transformation did not seem to be negatively affected by the use of atmospheric conditions (entry 10). While reducing the amount of DBU to 2.0 equivalents improved the yield (entry 11), reducing the amount of phosphite **2a** had a deleterious effect on yield (entry 12). The reaction was also minimally affected by the addition of water (entries 13–14). Still, the use of water as the sole solvent (entry 15) afforded the desired product in good yield with minimal decomposition of **1a** (72% product yield and 15% recovered starting material). However, the used of other solvents and bases resulted in lower yields (see supporting information for full table of optimization).

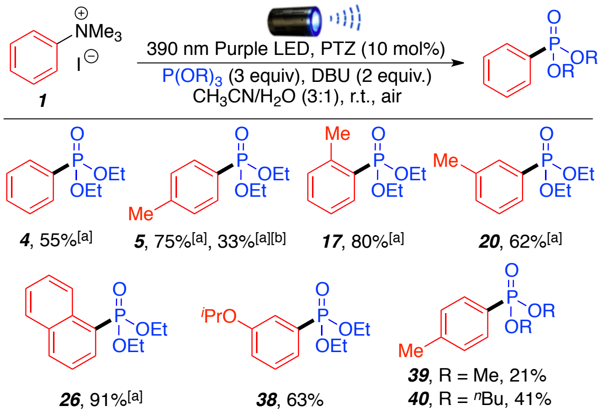
With a wide range of possible reaction conditions available, we chose to explore the substrate scope using the aqueous mixture of CH_3CN/H_2O (1:3) as it provides a good overview on how efficient the transformation can be in acetonitrile or water as sole solvents. A variety of aryl iodides and bromides (**1**), as well as different phosphite reagents (**2**) were investigated (Scheme 2).



Scheme 2. Aryl halides substrate scope and functional group compatibility. Reaction conditions: aryl halides **1** (0.2 mmol, 1 equiv), trialkyl phosphites **2** (0.6 mmol, 3 equiv), DBU (0.4 mmol, 2 equiv), PTZ (0.02 mmol, 10 mol%), CH_3CN/H_2O (0.25/0.75 mL), room temperature around reaction flask is 35 °C (heating caused by the 427 nm LED lamp), air, 24h. All yields are isolated. [a] CH_3CN/H_2O (0.9/0.1 mL). [b] Trialkyl phosphites **2** (1.2 mmol, 6 equiv).

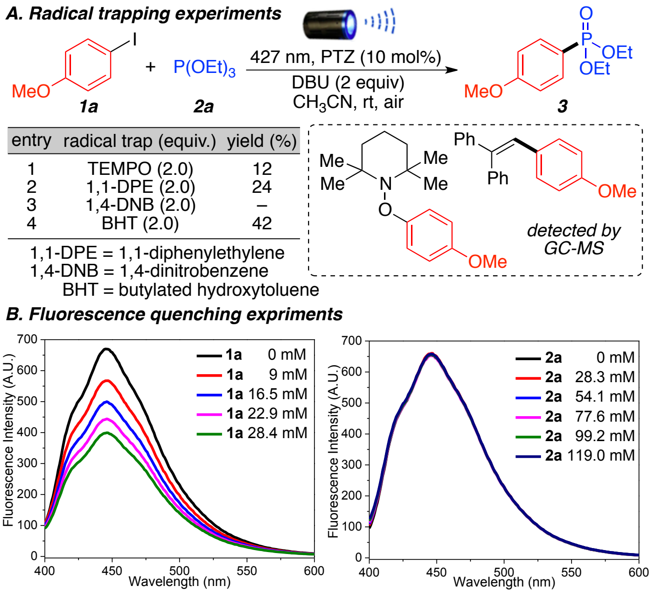
Various aryl iodides and bromides were first reacted with triethyl phosphite (**2a**) as the coupling partner. The reaction proceeds smoothly in the presence of electron-donating groups (**3**–**5**, 91–93%) and electron-withdrawing groups (**6**–**9**, 50–88%). Acidic and protic functional groups such as phenol and alcohol (**10**, **12**) were well tolerated (63–75%). Ketone (**13**) and amide (**14**) moieties afforded the product in moderate yield (40–53%). Of interest to synthetic chemist, silyl protected alcohols (**15**, **24**) afforded the desired phosphonated products in good yields (52-62%). It is important to highlight that all the yields can be further enhanced by improving the solubility of the starting substrates through the use of acetonitrile as main solvent. Sterics at both *ortho* (**16**-**19**) and *meta* (**20**–**25**) positions were well tolerated (31–87%) even in the presence of aniline group; the only exception being substrate **23**. 2-Iodonaphthalene afforded the desired product is excellent yield (**26**, 92%), and the method tolerated heteroaromatic pyridine (**27**) and quinoline (**28**) moieties often found in bioactive compounds (46–57%). The reaction of 1,4-diiodobenzene and 1-bromo-2-iodobenzene afforded the disubstituted products **29** and **30** in moderate to good yield (62–73%). Moreover, various medicinal and natural product frameworks containing esters were investigated (**31**–**33**) and generated the desired phosphonated products in in moderate to good yield (43–73%), further showing functional group compatibility and the possibility for late-stage functionalization of complex molecules. Finally, different trialkyl and triaryl phosphite reagents were tested (**34**–**37**) affording the desired products in low to excellent yields (21–92%).

Subsequently, we decided to apply this procedure to the phosphonation of aryl trimethylammonium salts. To this day, there are no examples of photoredox-catalyzed phosphonations of aryl ammonium salts. Current C–N phosphonation examples are limited to the use of aryl diazonium salts and hydrazine derivatives using metal catalyzed approaches.[4a,8] To our delight, the reaction successfully proceeds in comparable yields as with aryl halides, although a change in solvent mixture and light source was required. Indeed, quaternary arylammonium salts requires the use of CH_3CN as the major solvent and 390 nm Purple light source (Scheme 3).



Scheme 3. Aryl trimethylammonium salt substrate scope. Reaction conditions: aryl ammonium salt **1** (0.2 mmol, 1 equiv), trialkyl phosphites **2** (0.6 mmol, 3 equiv), DBU (0.4 mmol, 2 equiv), PTZ (0.02 mmol, 10 mol%), CH_3CN/H_2O (0.75/0.25 mL), room temperature around flask is 35 °C (heating caused by the 390 nm LED lamp), air, 24h. All yields are isolated unless noted otherwise. [a] Yields are based on **1**, determined by ^{1}H-NMR using dibromomethane as internal standard. [b] CH_3CN/H_2O (0.25/0.75 mL) with 427 nm LED lamp.

To explore the mechanism for this transformation, we carried out a series of radical trapping and fluorescence quenching experiments (Scheme 4). The addition of four different radical trapping reagents (TEMPO, 1,1-DPE, 1,4-DNB, and BHT) hampered the reactions and aryl radical intermediates were successfully trapped and observed via GC-MS (Scheme 4A). Also, the complete quenching of the reaction by 1,4-DNB strongly suggests the formation of a radical anion intermediate. Then, fluorescence quenching experiments (Scheme 4B, see supporting information for full experiments and Stern-Volmer plots; S18) show that the addition of aryl halide **1a** quenches fluorescence of the excited state of the photocatalyst (Scheme 4B-1), while addition of phosphite **2a** does not (Scheme 4B-2). It is important to highlight that, under our reaction conditions, we did not observe a significant difference in quenching by **1a** of a solution of PTZ alone and a solution of PTZ that contained DBU (see supporting information). These results differs from previous observations by the Larionov group,[9] which observed enhanced quenching when a mixture of PTZ + Cs_2CO_3 was used. These results suggest that, under our reaction conditions, PTZ alone is capable of reducing aryl iodides and that DBU only marginally increases PTZ's reactivity. DBU is however an essential base in the final steps of the reaction mechanism.

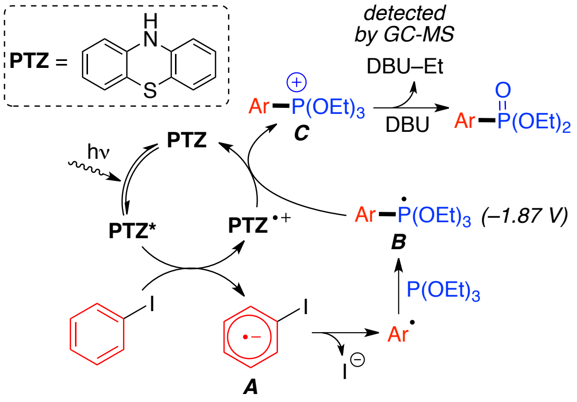


entry	radical trap (equiv.)	yield (%)
1	TEMPO (2.0)	12
2	1,1-DPE (2.0)	24
3	1,4-DNB (2.0)	–
4	BHT (2.0)	42

1,1-DPE = 1,1-diphenylethylene
1,4-DNB = 1,4-dinitrobenzene
BHT = butylated hydroxytoluene

Scheme 4. Mechanistic experiments. **A.** Radical trapping experiments were performed aryl halides **1** (0.2 mmol, 1 equiv), trialkyl phosphites **2** (0.6 mmol, 3 equiv), DBU (0.4 mmol, 2 equiv), PTZ (0.02 mmol, 10 mol%), and radical trapping agents ((0.4 mmol, 2 equiv), in CH_3CN (1mL) using 427 nm LED. **B-1.** Addition of aryl halide **1a** to a mixture of PTZ+DBU. **B-2.** Addition of phosphite **2a** to a mixture of PTZ+DBU.

On the basis of the above obtained mechanistic results and previous literature,[9] a plausible reaction mechanism is proposed (Scheme 5). First, photo-excited PTZ reduces aryl halide via a single electron transfer to generate aryl radical anion **A**. Loss of halogen produces aryl radical that then couples with triethyl phosphite and forms phosphoranyl radical **B**. Facile oxidation of **B** (E^0_{ox} = –1.87 V)[10] by $PTZ^{\bullet+}$ radical cation (E^0_{ox} = 0.71 V) produces phosphonium species **C** and regenerates the active photocatalyst. Further reaction of phosphonium intermediate **C** with DBU affords the desired final product. While other groups have proposed that the base behaves as a terminal oxidant to close the catalytic cycle,[11] we do not believe that to be the case in this reaction. Indeed, DBU has an oxidation potential of E^0_{ox} = 1.21 V, which makes the redox reaction with $\mathrm{PTZ}^{\bullet+}$ (E^0_{ox} = 0.71 V) not spontaneous.[10]



Scheme 5. Proposed reaction mechanism.

In summary, we have developed a simple and efficient photoredox cross-coupling reaction between aryl halides or aryl ammonium salts with trialkyl phosphites to form aromatic phosphonates. This transformation is the first to achieve the photoredox phosphonation of aryl ammonium salts. The reaction can be performed under atmospheric conditions in a wide range of aqueous solvent mixtures in the absence of transition-metals. The method exhibits broad tolerance of functional groups enabling the late stage phosphonation of complex compounds in the presence of ester, ketone, amide, amine, alcohol, and silyl functional groups.

Acknowledgements

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Keywords: Phosphonation • Photoredox-catalyzed • Green chemsitry • C–N bond • C–X bond

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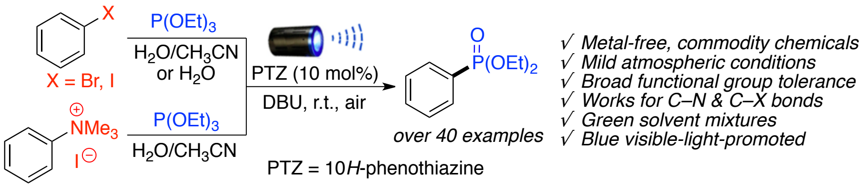

A metal-free photoredox-catalyzed phosphonation is achieved in green aqueous solvent mixture using affordable reagents and 10*H*-phenothiazine, a common and inexpensive commodity chemical, as a photoredox catalyst. This reaction is the first to achieve this transformation using aryl ammonium salts and also works with aryl halides. The reaction is tolerant to a wide range of functional groups and proceeds unaffected under atmospheric conditions.