

Visible-Light-Promoted Transition-Metal-Free Phosphinylation of Heteroaryl Halides in the Presence of Potassium *tert*-Butoxide

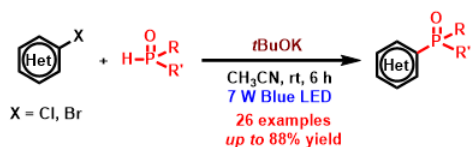
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Supporting Information Placeholder



- Visible-light-promoted C–P bond formation
- Without the use of transition metal
- Without the use of photoredox catalysts and oxidants
- Readily accessible substrates

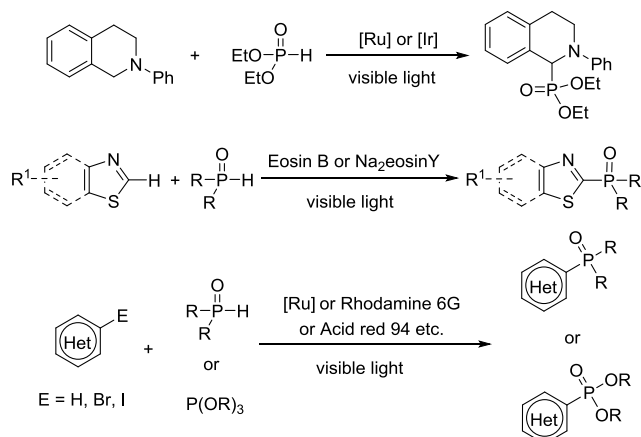
ABSTRACT: A novel visible-light-promoted C–P bond formation reaction in the absence of both transition metal and photoredox catalysts is disclosed. By employing easily available and inexpensive heteroaryl chlorides/bromides as substrates, a variety of heteroaryl phosphine oxides were obtained in moderate to good yields. This strategy provides a simple and efficient route to heteroaryl phosphine oxides.

Phosphorus-containing hetero-aromatic molecules are an important class of compounds that find useful applications in synthetic transformations, medicinal chemistry and photoelectric materials, and as useful ligands for transition metal catalysis.¹ Although great effort has been devoted to the development of new and efficient strategies for C–P bond formation in recent decades, the synthesis of heteroaryl phosphines still meets with challenge owing to the effect of coordination of heteroatom to metal ion, which can suppress catalytic processes.^{2–5} Traditionally, heteroaryl phosphines are prepared by nucleophilic substitution reaction of heteroaryl-metal unit and phosphine chlorides. At present, for the phosphonation of C(sp²)-H bonds, a number of catalytic systems based on palladium, copper, and silver have been developed by several groups.³ Along with the development of auto-oxidative C(sp²)-P formation, Wu and co-workers disclosed a direct phosphorylation of thiazole and quinoxaline derivatives induced by oxygen under metal-free and solvent-free conditions.⁴ Very recently, Yamaguchi and co-workers reported a Ni-catalyzed C–P bond formation reaction of heteroaromatic esters and organophosphorus at high temperature (150–170 °C).⁵

Visible-light photoredox catalysis has emerged as a powerful and useful strategy to construct C–P bond via

photoinduced electron transfer (PET) processes in recent years (Figure 1).^{2a, 2b, 6–11} In 2011, Rueping and co-workers described the first C(sp³)-P oxidative cross-coupling reaction of amines with phosphite esters using a visible light photoredox catalysis procedure.⁷ Since then, a number of visible-light absorbing catalysts have been developed to construct C–P bond via phosphonylation of C–H bonds.⁸ Meanwhile, Xiao and co-workers reported the coupling of diarylphosphine oxide with heteroaryl iodides by a photoredox/nickel dual-catalytic process.⁹ König and co-workers reported phosphonylation of heteroaryl bromides using Rhodamine 6G as a photocatalyst.¹⁰ Despite these advances, these reactions usually suffer from limited substrate scope. In addition, high catalyst loading and harsh reaction conditions as well as the usage of co-catalysts or excess of oxidant are required in usual circumstances. Therefore, the development of more environmentally friendly and efficient methods for the synthesis of various heteroaryl phosphines remains a challenge. Herein, we report an efficient C–P bond formation reaction between heteroaryl chlorides/bromides and diarylphosphine oxides in the presence of potassium *tert*-butoxide, and under oxidant-free and catalyst-free conditions.

a) Previous studies



b) Our work

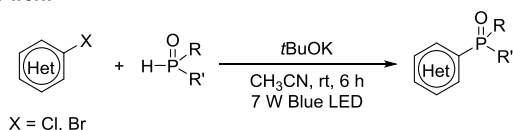


Figure 1. Synthesis of Heteroaryl Phosphines and Phosphonates by Visible-Light Photoredox Catalysis

Table 1. Optimization of the Reaction Conditions^a

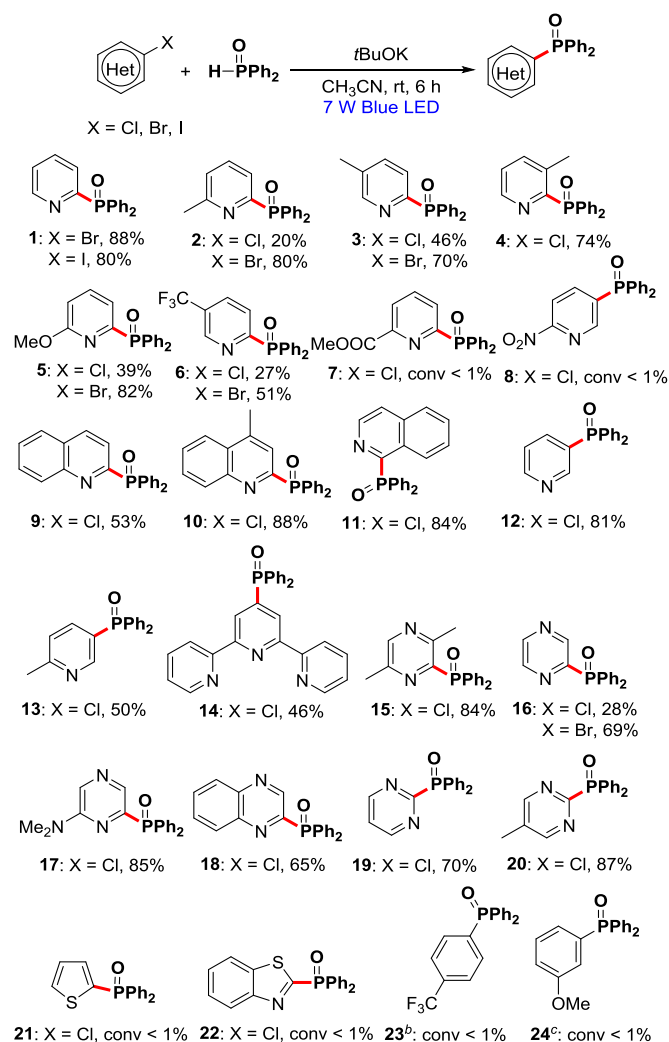
entry	solvent	base	time (h)	conv (%) ^b
1	DCM	<i>t</i> BuOK	17	19
2	DMSO	<i>t</i> BuOK	17	40
3	CH ₃ CN	<i>t</i> BuOK	17	88
4	DMF	<i>t</i> BuOK	17	76
5	Toluene	<i>t</i> BuOK	17	77
6	THF	<i>t</i> BuOK	17	86
7	CH ₃ CN	<i>t</i> BuONa	17	52
8	CH ₃ CN	<i>t</i> BuOLi	17	3
9	CH ₃ CN	KOH	17	47
10	CH ₃ CN	NaOH	17	56
11	CH ₃ CN	Na ₂ CO ₃	17	<1
12	CH ₃ CN	K ₂ CO ₃	17	<1
13	CH ₃ CN	Cs ₂ CO ₃	17	<1
14	CH ₃ CN	<i>t</i>BuOK	6	88 (85)^c
15	CH ₃ CN	<i>t</i> BuOK	4	81
16	CH ₃ CN	<i>t</i> BuOK	17	6 ^d

^a Reaction conditions: 2-chloropyridine (0.24 mmol), diphenylphosphine oxide (0.20 mmol) and base (0.3 mmol) in anhydrous solvent (1 mL) at room temperature under N₂ and 7 W blue LED. ^b Based on ³¹P NMR. ^c Isolated yield. ^d Reaction performed in the absence of light.

Initially, we examined the reaction of 2-chloropyridine and diphenylphosphine oxide with *t*BuOK as a base and with a 7 W blue LED at room temperature for 17 h in different solvents

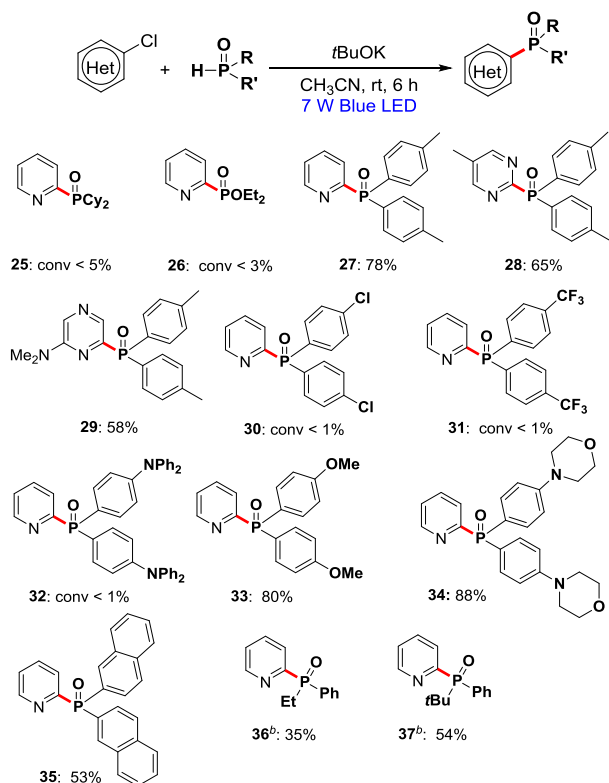
(Table 1, entries 1-6). In dimethyl sulfoxide and dichloromethane, the expected product **1** was obtained in 19% and 40% yields, respectively (Table 1, entries 1 and 2). Upon switching the solvent to acetonitrile, the yield significantly increased to 88% (Table 1, entry 3). Other solvents, such as *N,N*-Dimethylformamide, toluene, and THF, resulted in 76%, 77%, and 86% yields, respectively (Table 1, entries 4-6). Using *t*BuONa, *t*BuOLi, KOH, NaOH, Na₂CO₃, K₂CO₃ or Cs₂CO₃ as base, the conversion dramatically decreased (Table 1, entries 7-13) revealing the critical role of the base. Moreover, the reaction time could be reduced to 6 h (Table 1, entries 14 and 15). The expected product was scarcely observed in the absence of light (Table 1, entry 16). Meanwhile, the phosphinylation of 2-bromopyridine and 2-iodopyridine were also examined under the same conditions to afford compound **1** in 88% and 80% yields, respectively (Scheme 1).

Scheme 1. Visible-Light-Promoted Phosphinylation of Heteroaryl Chlorides/Bromides with diphenylphosphine oxide^a



^a Reaction conditions: heteroaryl chloride/bromide (0.6 mmol), diphenylphosphine oxide (0.5 mmol) and *t*BuOK (0.75 mmol) in anhydrous CH₃CN (2.5 mL) at room temperature for 6 h under N₂ and 7 W blue LED. ^b The substrate is 1-bromo-4-(trifluoromethyl)benzene. ^c The substrate is 1-bromo-3-methoxybenzene.

Scheme 2. Scope of Visible-Light-Promoted Phosphinylation of Heteroaryl Chlorides^a



^a Reaction conditions: heteroaryl chloride (0.6 mmol), HP(O)RR' (0.5 mmol) and *t*BuOK (0.75 mmol) in anhydrous CH₃CN (2.5 mL) at room temperature for 6 h under N₂ and 7 W blue LED. ^b 12 h

With these optimized conditions, we further evaluated the scope of this visible-light induced C–P formation process. As shown in Scheme 1, most heteroaryl chlorides reacted readily with diphenylphosphine oxide furnishing the corresponding products in moderate to good yields (20–88%). Electron-donating groups (Me and OMe) at the *ortho*-, *meta*-, and *para*-position of 2-chloropyridine are well tolerated, and the corresponding coupling products **2**–**5** were afforded in moderate to good yields (20–82%). The expected products were not found in the reactions of substrates bearing electron-withdrawing groups (COOMe and NO₂), but 2-chloro-5-(trifluoromethyl)pyridine gave product **6** in 27% yield. These results reveal that this reaction favors substrates bearing electron-donating groups. Failure to obtain products with electron-withdrawing group may be due to the high stability of the reduced intermediates, which hinders the formation of other species for the reaction to occur. Additionally, 2-chloroquinoline, 2-chloro-4-methylquinoline and 1-chloroisoquinoline gave the corresponding products in 53% (**9**), 88% (**10**) and 84% (**11**) yields, respectively. 3-Chloropyridine, 5-chloro-2-methylpyridine and 4'-chloro-2,2':6',2''-terpyridine also reacted with diphenylphosphine oxide to give the corresponding products in 81% (**12**), 50% (**13**) and 46% (**14**) yields, respectively. Other heteroaryl chlorides, such as 3-chloro-2,5-dimethylpyrazine, 2-chloropyrazine, 6-chloro-*N,N*-dimethylpyrazin-2-amine, 2-chloroquinoxaline, 2-chloropyrimidine and 2-chloro-5-methylpyrimidine, were also effective and gave the respective products with yields of 84% (**15**), 28% (**16**), 85% (**17**), 65% (**18**), 70% (**19**), and 87% (**20**). On the other hand, the corre-

sponding heteroaryl and aryl phosphine oxides (**21**–**24**) were not found in the reactions of five-membered heteroaryl chlorides and aryl bromides. Because the C–Br bond is weaker than C–Cl bond,¹² the reactions of 2-bromo-6-methylpyridine, 2-bromo-5-methylpyridine, 2-bromo-6-methoxypyridine, 2-bromo-5-(trifluoromethyl)pyridine and 2-bromopyrazine were found to be more efficient and gave the corresponding products in 80% (**2**), 70% (**3**), 82% (**5**), 51% (**6**) and 69% (**16**) yields, respectively.

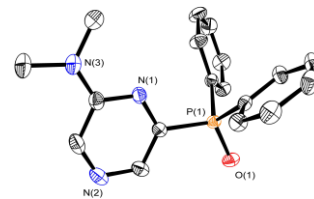
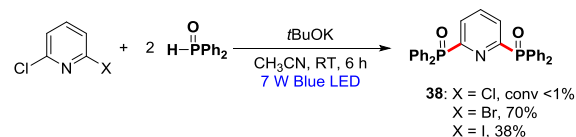


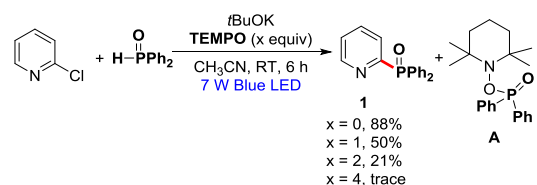
Figure 2. Ortep drawings of compound **17** with 30% ellipsoid probability. Hydrogen atoms and solvent molecule are omitted for clarity.

Further efforts were devoted to apply this C–P coupling reaction to other phosphine oxides and diethyl phosphonate (Scheme 2). The expected C–P bond formation products (**25**, **26**, **30**, **31** and **32**) were scarcely observed when dicyclohexylphosphine oxide, diethyl phosphonate, bis(4-chlorophenyl)phosphine oxide, bis(4-(trifluoromethyl)phenyl)phosphine oxide and bis(4-(diphenylamino)phenyl)phosphine oxide were used under the optimized conditions. Meanwhile, 2-chloropyridine, 2-chloro-5-methylpyrimidine and 6-chloro-*N,N*-dimethylpyrazin-2-amine reacted readily with di-*p*-tolylphosphine oxide to give the corresponding heteroaryl phosphine oxides in 78% (**27**), 65% (**28**) and 58% (**29**) yields, respectively. Bis(4-methoxyphenyl)phosphine oxide, bis(4-morpholinophenyl)phosphine oxide and di(naphthalen-2-yl)phosphine oxide reacted with 2-chloropyridine to give the respective products in 80% (**33**), 88% (**34**) and 53% (**35**). It is noted that unsymmetric phosphine oxides, such as ethyl(phenyl)phosphine oxide and *tert*-butyl(phenyl)phosphine oxide, are also effective in the phosphinylation of 2-chloropyridine to give the products in 35% (**36**) and 54% (**37**), respectively. Furthermore, the reaction of 2,6-dichloropyridine with 2 equivalents of diphenylphosphine oxide did not afford diphosphinylation product **38**, but the reactions with 2-bromo-6-chloropyridine and 2-chloro-6-iodopyridine gave the product **38** in 70% and 38% yields, respectively (Scheme 3).

Scheme 3. Visible-Light-Promoted Phosphinylation of 2,6-Dichloropyridine with Diphenylphosphine Oxide



Scheme 4. The Phosphinylation of Heteroaryl Chlorides in the Presence of TEMPO



In order to gain insight into the reaction mechanism, the reaction with 2,2,6,6-tetramethylpiperding-1-oxyl (TEMPO) as an additional reagent has been examined. When 4 equivalents of 2,2,6,6-tetramethylpiperding-1-oxyl were added under the optimized conditions, only a trace amount of desired product **1** and radical coupling product **A** were observed (Scheme 4, also see Figure S1 in the Supporting Information(SI)). Upon visible light irradiation, monitoring the reaction of 2-chloropyridine and *t*BuOK in CH₃CN by EPR spectroscopy revealed the presence of an EPR signal at *g* = 2.006, presumably this came from radical intermediate species generated by one electron transfer from electron-donor *t*BuOK to electron-deficient 2-chloropyridine. Moreover, after adding diphenylphosphine oxide, the shape of EPR signal is changed and its intensity decreased indicating that diphenylphosphine oxide could react with the *in situ* formed radicals (see Figure S2 in the Supporting Information(SI)).

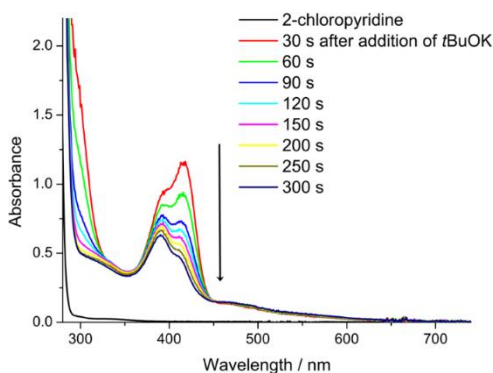
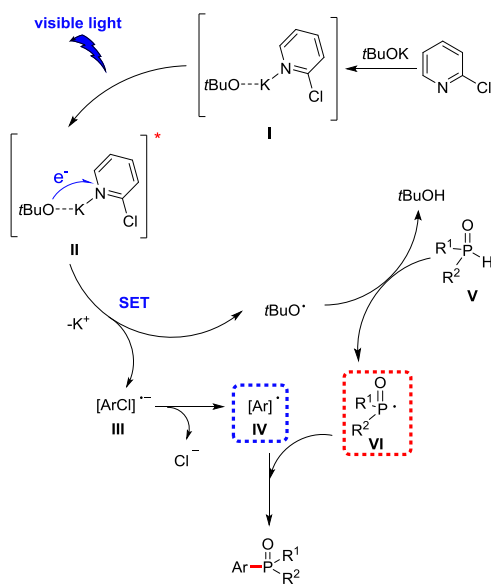


Figure 3. UV-vis absorption of the addition of *t*BuOK (1 equiv) into an CH₃CN solution of 2-chloropyridine (0.05 M). The arrow indicates the change in absorbance.

Scheme 5. Proposed Mechanism of the Phosphinylation of Heteroaryl Chlorides in the Presence of *t*BuOK



The pyridine substrates, diphenylphosphine oxide and *t*BuOK do not absorb in the visible spectral region. However, UV-visible absorption spectroscopic measurements showed that addition of *t*BuOK (1 equiv) into an CH₃CN solution of 2-chloropyridine (0.05 M) generated absorption bands with

peaks at ~390 and ~420 nm and a relatively weak absorption tail spanning from 450 to 620 nm (Figure 3). The absorption band at 420 nm decayed faster than that at ~390nm while that beyond 450 nm remained almost unchanged. It is possible that charge-transfer complex(es) was formed between the pyridine substrate and *t*BuOK with K⁺ serving as a bridge between the pyridine and *tert*-butoxide anion, which is similar to that proposed in related studies on the role of *t*BuOK as an electron donor.¹³⁻¹⁵ The photochemical reaction quantum yield was also measured in order to help understand whether radical chain processes were involved in the catalysis. By using potassium ferrioxalate as a chemical actinometer, the quantum yield of the reaction was calculated to be 0.30. Since the photochemical reaction quantum yield is much smaller than unity, it is possible that a closed radical mechanism is the dominating reaction pathway, though the possibility of a radical chain propagation mechanism cannot be excluded.^{13h}

On the basis of these experimental results, a tentative mechanism is given in Scheme 5. Initially, complex **I** undergoes a light-induced single electron transfer to give radical anion **III** and *tert*-butoxy radicals. Then, phosphine oxide **V** would react with *tert*-butoxy radicals via hydrogen atom abstraction to form the key phosphorus-centered radical **VI**.¹⁶ Meanwhile, dissociation of radical anion **III** gives heteroaryl radical **IV** which can combine with radical **VI** to give the desired product.

In conclusion, we have developed a mild, efficient, visible-light-promoted protocol for the synthesis of heteroaryl phosphine oxides by the phosphinylation of unactivated heteroaryl chlorides and bromides with symmetric and unsymmetric phosphine oxides. The C–P bond is constructed under visible-light irradiation condition at room temperature without the use of transition metal and photoredox catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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

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Notes

The authors declare no competing financial interest.

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