OL Organic Letters

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Visible-Light-Induced Nickel-Catalyzed $P(O)-C(sp^2)$ Coupling Using Thioxanthen-9-one as a Photoredox Catalysis

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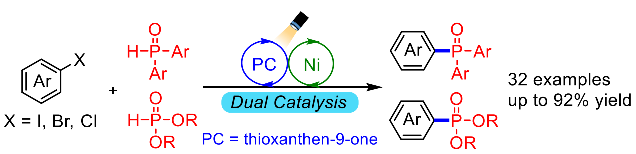
Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03892 Read Online

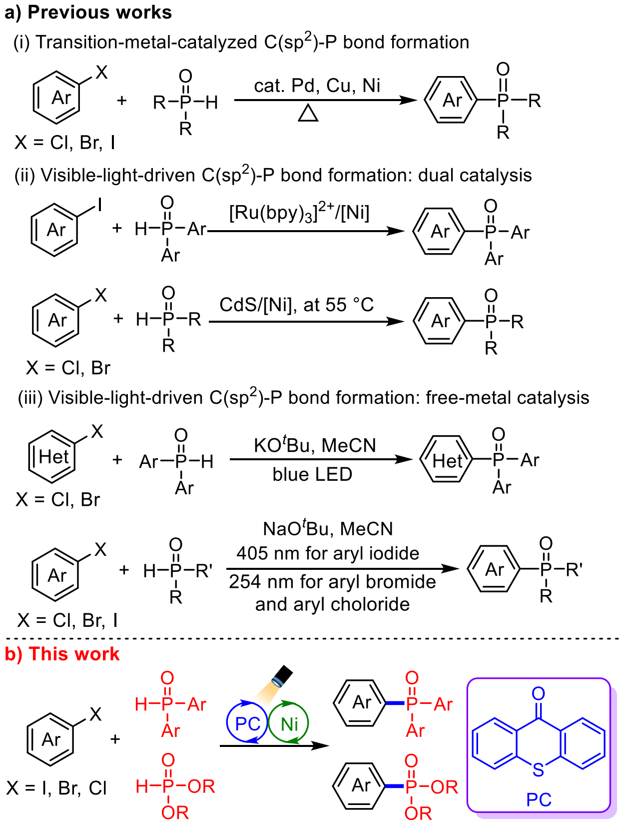
ABSTRACT: An efficient method has been developed for photocatalytic $P(O)-C(sp^2)$ coupling of (hetero)aryl halides with H-phosphine oxides or H-phosphites under the irradiation of visible light or sunlight. The thioxanthen-9-one/nickel dual catalysis mediates this phosphonylation to give arylphosphine oxides and arylphosphonates in moderate to excellent yields. This transformation is widely tolerant to a range of functional groups and proceeds efficiently on a gram scale.



Arylphosphine oxides and arylphosphonates have wide applications in organic synthesis, medicinal chemistry, and material sciences.[1] Numerous efforts have been made for the construction of these complexes.[2] The transition-metal-catalyzed arylations of H-phosphine oxides or H-phosphites with aryl halides, based on Pd,[3] Cu,[4] and Ni,[5] have been developed as an efficient method for $C(sp^2)-P(O)$ bond formation (Scheme 1a). However, those thermal conversions have some drawbacks such as the use of expensive catalysts and high temperatures.[2−5] Compared to the traditional reactions, photocatalysis is very well-suited to the requirement of sustainable and green synthesis. Recently, much attention has been focused on the visible-light-driven $P(O)-C(sp^2)$ bond formation.[6] The group of Xiao and Lu reported the visible-light-induced nickel-catalyzed phosphonylation of aryl halides using expensive and/or toxic $[Ru(bpy)_3]^{2+}$ or CdS as the photoredox catalyst.[7] Che, Yu, and co-workers established a photocatalyst-free visible-light-mediated $C(sp^2)-P(O)$ bond formation from diarylphosphine oxides with heteroaromatic chlorides or bromides in the presence of KO^tBu.[8] Zeng co-workers demonstrated an ultraviolet or visible-light-induced coupling of (hetero)aryl halides with dialkyl phosphonates or diarylphosphine oxides using NaO^tBu as the base.[9] The strong base and/or high-energy ultraviolet irradiation required for metal-free photoredox reactions limit functional-group tolerance. Therefore, there is a strong demand for an efficient and mild phosphorylation process, which shows various substrates under visible light.

In recent years, commercially available, cheap carbonyl-photoredox and transition-metal synergetic catalysis has been found to construct $C(sp^3)-O$,[10] $C(sp^2)-O$,[11] $C(sp^2)-C(sp^2)$,[12] $C(sp^2)-C(sp^3)$,[13] $C(sp^2)-C(sp)$,[14] and $C(sp^3)-C(sp^3)$[15] bonds. Nevertheless, their application to C−P bond formation remains rather unexplored. We herein report the carbonyl/Ni dual catalysis for the construction of arylphosphine oxides and arylphosphonates through an efficient visible-

Scheme 1. Phosphonylation of Aryl Halides

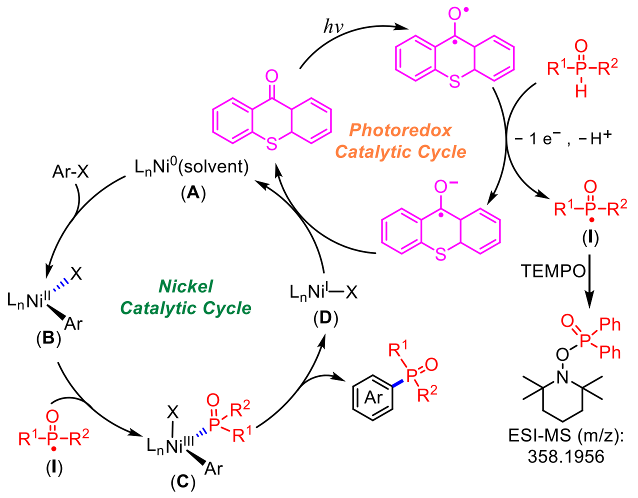


Received: November 24, 2020

light photoredox arylation of H-phosphine oxides and H-phosphites with aryl halides at room temperature (Scheme 1b).

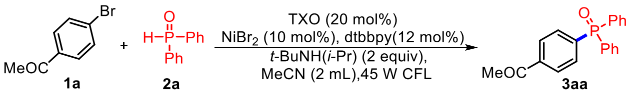
Photoexcited aryl ketones feature high reductive potentials (E^*_{red} = 1.28 V versus saturated calomel electrode (SCE) for thioxanthen-9-one (TXO)),[11] which are sufficient to oxidize H-phosphine oxide and H-phosphite with E_{ox} of about 1.0 V versus SCE.[16] Moreover, carboxyl complexes exhibit potent hydrogen-abstracting ability that makes them efficient photocatalysts for the X−H activation.[16,17] So $[R_2P(O)H]$ or $[(RO)_2P(O)H]$ is easily activated by the triplet state of carbonyl into $[R_2P(O)^\bullet]$ or $[(RO)_2P(O)^\bullet]$ via single electron transfer (SET) or hydrogen atom transfer (HAT) process. Based on the previous studies, we hypothesized that diradical TXO* could readily participate in SET or HAT with $R^1R^2P(O)H$ to generate $[R^1R^2P(O)^\bullet]$ (**I**) and $[TXO]^{\bullet-}$ (Scheme 2). The intermediate **I** then enters into the nickel-catalyzed cycle. The oxidative addition of the low-valent form L_nNi^0(solvent) (**A**) with ArX gives $L_nNi^{II}(Ar)X$ (**B**). P-centered radical **I** adds to **B** to produce a high-valent Ni(III) intermediate $L_nNi^{III}(Ar)(POR^1R^2)X$ (**C**). Subsequently, **C** undergoes reductive elimination to form the desired product along with generating L_nNi^IX species (**D**). Finally, reduction of **D** with $[TXO]^{\bullet-}$ [$E_{red}(TXO/TXO^{\bullet-})$ = −1.70 V in MeCN,[11] $E(Ni^{II}/Ni^0)$ = −1.20 V in DMF versus SCE[18]] concurrently completes both TXO-photoredox and nickel catalytic cycles.

Scheme 2. Proposed Mechanism for P(O)−C(sp^2) Coupling



We began by examining the feasibility of the proposed P(O)−C(sp^2) bond formation by coupling reaction of 4-bromoacetophenone (**1a**) and diphenylphosphine oxide (**2a**). To our delight, the desired product 1-(4-(diphenylphosphoryl)phenyl)ethan-1-one (**3aa**) was obtained in 92% yield using TXO (20 mol %), $NiBr_2$ (10 mol %), 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy, 12 mol %), *t*-BuNH(*i*-Pr) (2.0 equiv) in MeCN under photoirradiation by a household 45 W compact fluorescent lamp (CFL) (Table 1, entry 1, Figure S1a,b). Decreasing the TXO loading to 10 mol % led to 82% yield of **3aa** (Table 1, entry 2). No P-arylation of **2a** was observed when TXO was excluded from this protocol (Table 1, entry 3), which makes clear the crucial role of photocatalyst in promoting this coupling. Lower yields were achieved using *N*,*N*-dimethylformamide (DMF, 83%) or dimethyl sulfoxide (DMSO, 62%) as a solvent (Table S1, entries 2 and 3). No product was formed when the reaction was carried out in CH_2Cl_2 (Table S1, entry 4). The use of other nickel catalysts ($NiBr_2{\cdot}3H_2O$, $Ni(acac)_2$ (acac = acetylacetonate), $NiCl_2{\cdot}$glyme, $Ni(OAc)_2{\cdot}4H_2O$, $NiSO_4{\cdot}6H_2O$) resulted in lower yields for **3aa** (Table S1, entries 5−9). No P-arylation took place in the absence of Ni catalyst (Table 1, entry 4). Other organic bases, like DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), Et_3N, $(i\text{-}Pr)_2NEt$, and Et_2NH also gave **3aa**, albeit in lower yields (Table S1, entries 10−13). Using Cs_2CO_3 or K_3PO_4 as the base (Table S1, entries 14 and 15), the reaction proceeded in 60% and 36% yields, respectively. The base is indispensable in this cross coupling because it neutralizes the in situ formed HBr during the catalytic reaction (Table 1, entry 5). Screening ligands identified dtbbpy as the most suitable choice (Table S1, entries 16−18). When $NiBr_2$ alone was used to catalyze this cross coupling, the light-initiated reaction was greatly inhibited, resulting in 10% yield of **3aa** in the absence of dtbbpy (Table 1, entry 6). No reaction occurred under the exclusion of light (Table 1, entry 7), indicating that this C(sp^2)−P coupling is a photoinduced reaction. Satisfactorily, the irradiation of the model reaction with natural sunlight for 8 h afforded **3aa** in 75% yield (Table 1, entry 8, Figure S1c). The photoreaction was carried out under the irradiation of a 300 W xenon lamp equipped with a 400 nm cutoff filter for 8 h, providing **3aa** in 90% yield (Table 1, entry 9). Visible light does effectively promote this P(O)−C(sp^2) coupling reaction.

Table 1. Parameters for P-Arylation of 2a with 1a[a]



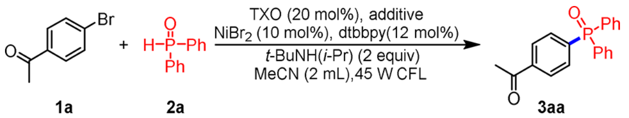
entry	variations from above conditions	conversion of **1a** (%)	yield (%)
1	none	>99	92
2	using 10 mol % TXO	>99	82
3	no TXO	0	0
4	no nickel	30	0
5	no *t*-BuNH(*i*-Pr)	5	0
6	no dtbbpy	25	10
7	no light	0	0
8[b]	sunlight instead of CFL	81	75
9[c]	λ > 400 nm instead of CFL	99	90
10	fluoren-9-one instead of TXO	26	23
11	$Ru(bpy)_3Cl_2$ instead of TXO	10	8
12	rose bengal instead of TXO	0	0

[a] Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.4 mmol, 2 equiv), $NiBr_2$ (0.02 mmol, 10 mol %), dtbbpy (0.024 mmol, 12 mol %), *t*-BuNH(*i*-Pr) (0.4 mmol, 2.0 equiv), TXO (20 mol %), 2 mL of MeCN, N_2, irradiation under a 45 W CFL for 24 h with cooling by a fan, HPLC conversion and yield. [b] Under sunlight (the maximum power density is about 7.80 mW cm^{-2}) for 8 h. [c] Irradiation under 300 W xenon lamp with a 400 nm cutoff filter for 8 h.

The reactivity was correlated with the excited-state redox potentials of photocatalyst (Table 1, entries 1, 10−12). TXO with highest excited-state redox potentials worked most efficiently. The utilization of fluoren-9-one (E^* = 0.95 V versus SCE)[11] and $Ru(bpy)_3^{2+}$ [$E(Ru^{II*}/Ru^I)$ = 0.77 V versus SCE][7a] with lower excited-state reduction potentials resulted in lower yields under the optimum reaction conditions. These findings support that this cross-coupling possibly proceeded via SET between the excited state of photocatalyst and H-phosphine oxides or H-phosphites. By utilizing Rose Bengal (RB), no product was obtained. Its excited-state (E^* = 0.99 V versus SCE)[19] might oxidize P-substrate. But the single-electron-reduced species $RB^{\bullet -}$ is a relatively weak reductant [$E(RB/RB^{\bullet -}) = -0.78$ V versus SCE],[19] which cannot reduce Ni(II) into Ni(0).[18] This result is in agreement with our proposed mechanism (Scheme 2).

To further probe the mechanism, we conducted the following control experiments. The reaction is highly sensitive to O_2 and the inhibition of the reactivity observed in air implied a radical mechanism (Scheme 3). When 2.0 equiv of 1,1-diphenylethylene was added to the standard reaction system, **3aa** was obtained in 10% yield. The presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 2 equiv) as a radical trap shut down the reaction completely. Substrates **1a** and **2a** were treated with TEMPO (2 equiv) or 1,1-diphenylethylene (2 equiv) under our optimized reaction conditions for 1 h, and the resulting mixture was characterized by electrospray ionization mass spectrometry (ESI-MS). The positive-ion ESI-MS analyses reveal the peaks at m/z = 358.1956 (Figure S2), 381.1439 (Figure S3), and 383.1554 (Figure S4) are assigned to be [2,2,6,6-tetramethylpiperidin-1-yl diphenylphosphinate + H]$^+$ (calculated m/z = 358.1930), [(2,2-diphenylvinyl)diphenylphosphine oxide + H]$^+$ (calculated m/z = 381.1403) and [(2,2-diphenylethyl)diphenylphosphine oxide + H]$^+$ (calculated m/z = 383.1559) ions, respectively. The above observations clearly indicate the generation of phosphorus-centered radical involved in this metallaphotoredox manifold.

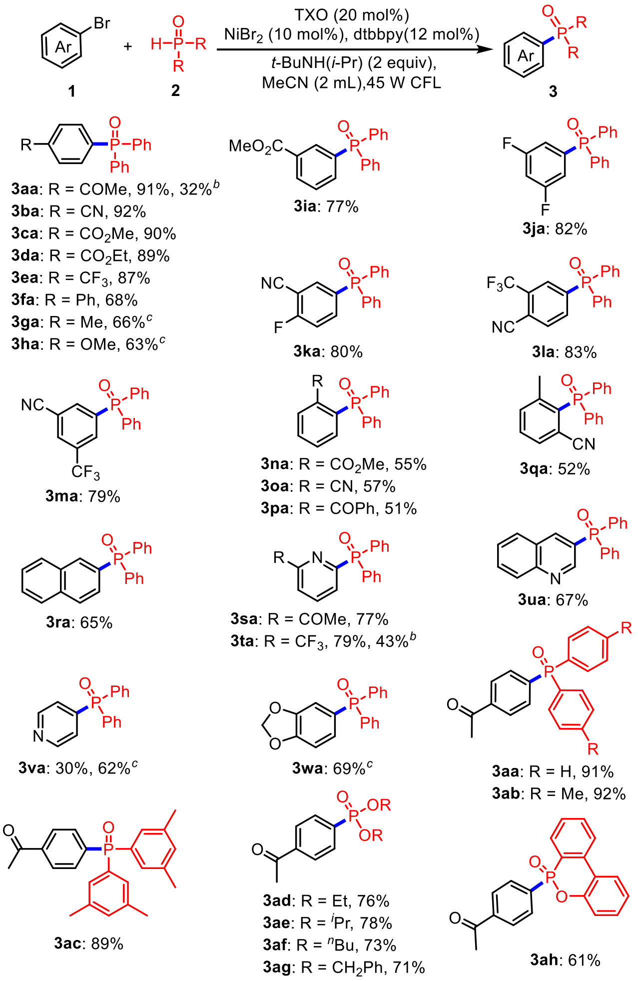
Scheme 3. Mechanistic Investigations



Optimized conditions	92%
Optimized conditions, in air	11%
Optimized conditions, with 2 equiv 1,1-diphenylethylene	10%
Optimized conditions, with 2 equiv TEMPO	trace

The generality of this dual photocatalysis for the construction of the C(sp^2)−P(O) bond was investigated using the optimized reaction conditions (Scheme 4). Various aryl bromides bearing electron-withdrawing acetyl, carboxylic ester, trifluoromethyl, and cyano groups at the *para*-position reacted with diphenylphosphine oxide **2a** to deliver the coupled triarylphosphine oxides **3aa**−**3ea** in 87−92% yields. 4-Bromo-1,1′-biphenyl (**1f**) is also suitable for this transformation, providing **3fa** in good yield. As for aryl bromides with electron-donating substituents such as 1-bromo-4-methylbenzene and 1-bromo-4-methoxybenzene, the expected C−P bond formation products were scarcely observed. However, 1-iodo-4-methylbenzene or 1-iodo-4-methoxybenzene reacted readily with **2a** to give arylphosphine oxides in 66% (**3ga**) and 63% (**3ha**) yields, respectively. Aryl bromides bearing substituents at the 3-, or 3,5-, 3,4-positions of phenyl rings afforded **3ia**−**3ma** in 77−83% yields. The reaction is sensitive to steric hindrance as *ortho*-substituted aryl bromides resulted in a consistent decrease in yields of 51−57% (**3na**-**3qa**). 2-Bromonaphthalene could also deliver the expected product **3ra** with a good yield of 65%. Heteroaryl bromides including 1-(6-bromopyridin-2-yl)ethan-1-one (**2s**), 2-bromo-6-(trifluoromethyl)pyridine (**2t**), 3-bromoquinoline (**2u**), and 4-bromopyridine (**2v**) were also well tolerated, affording **3sa**−**3va** in 30−79% yields. Notably, aryl chlorides, such as 4-chloroacetophenone and 2-chloro-6-(trifluoromethyl)pyridine, did also participate successfully in this dual catalytic system, giving **3aa** and **3ta** in moderate yields. 5-Bromobenzo[*d*][1,3]-dioxole was unsuitable substrates for this conversion. Aryl iodides couple with higher levels of efficiency than the corresponding aryl bromides. The P-arylation using 4-iodopyridine and 5-iodobenzo[*d*][1,3]dioxole proceeded efficiently, giving **3va** (62%) and **3wa** (69%), respectively.

Scheme 4. Substrate Scope for Coupling of Aryl Halides with H-Phosphine Oxides or H-Phosphites[a]



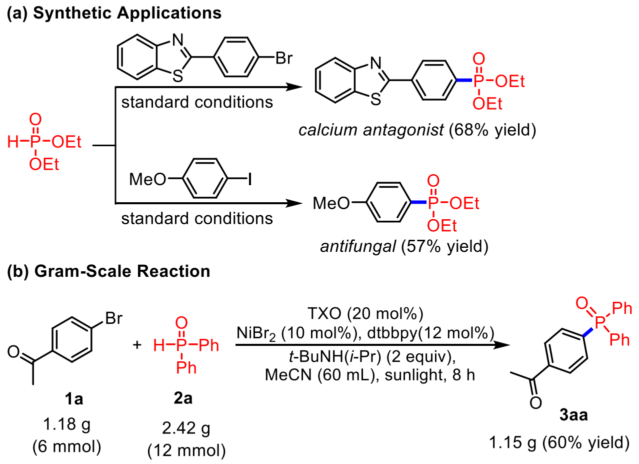
[a]**1** (0.2 mmol, 1 equiv), **2** (0.4 mmol, 2 equiv), $NiBr_2$ (0.02 mmol, 10 mol %), dtbbpy (0.024 mmol, 12 mol %), *t*-BuNH(*i*-Pr) (0.4 mmol, 2.0 equiv), TXO (20 mol %), 2 mL MeCN, N_2, irradiation under a 45 W CFL for 24 h, isolated yields. [b]Using aryl chloride as the substrate. [c]Using aryl iodide as the substrate.

We further examined the scope of H-phosphine oxide and H-phosphite substrates for the photoinduced phosphonylation of **1a** under the optimized reaction conditions (Scheme 4). Di-*p*-tolylphosphine oxide **2b** and bis(3,5-dimethylphenyl)-phosphine oxide **2c** reacted with **1a** to provide triarylphosphine oxides **3ab** (92%) and **3ac** (89%) in excellent yields. As we expected, commercially available dialkyl phosphites reacted smoothly with **1a** to afford the corresponding products **3ad**−**3ag** in good isolated yields. Dibenzo[*c*,*e*][1,2]oxaphosphinine 6-oxide underwent C(sp^2)-P cross coupling reaction with **1a** to deliver the arylphosphinate product of **3ah** in 61% yield. When the P(O)−C(sp^2) coupling reactions were performed in dimethylacetamide under blue LEDs at higher temperature

(55 °C), the dual catalysis of $NiCl_2/CdS$[7b] displayed activity comparable to that of $NiBr_2$/TXO.

After the substrate scope evaluation, we applied this current dual catalysis to the synthesis of biomolecules. The cross-coupling of diethyl phosphonate with 2-(4-bromophenyl)-benzo[*d*]thiazole or 1-iodo-4-methoxybenzene yielded calcium antagonist diethyl (4-(benzo[*d*]thiazol-2-yl)phenyl)-phosphonate and antifungal diethyl (4-methoxyphenyl)-phosphonate with good yields (Scheme 5a). In addition, a large-scale reaction (see the Supporting Information) of **1a** (1.18 g, 6 mmol) and **2a** (2.42 g, 12 mmol) was also performed to deliver the desired product **3aa** in 60% yield (1.15 g) under natural sunlight for 8 h (Scheme 5b, Figure S1d).

Scheme 5. Synthetic Applications and Gram-Scale Reaction



In summary, we have demonstrated an efficient photocatalytic protocol for the P-arylation of H-phosphites and H-phosphine oxides with (hetero)aryl halides through the merging of commercially available, inexpensive TXO and $NiBr_2$ as dual catalysis. This coupling reaction proceeds under visible light or natural sunlight at room temperature, displays broad scope and functional group tolerance, and delivers arylphosphine oxides and arylphosphonates in moderate to high yields. The cheap carbonyl/metal dual catalysis may provide a highly economical platform to construct C−C and C−heteroatom bonds under visible-light irradiation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03892.

Experimental procedures, ^1H, ^{13}C, ^{19}F, ^{31}P NMR spectra, and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support provided by the National Natural Science Foundation of China (21971182 and 21771131) and the “Priority Academic Program Development” of Jiangsu Higher Education Institutions. D.-L.Z. thanks Postgraduate Research & Practice Innovation Program of Jiangsu Province (KYCX20_2652).

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https://dx.doi.org/10.1021/acs.orglett.0c03892