Synthesis of Imidoyltrialkylphosphonium Salts through Photocatalytic Reactions between Isocyanides and Tri-*t*-butylphosphine

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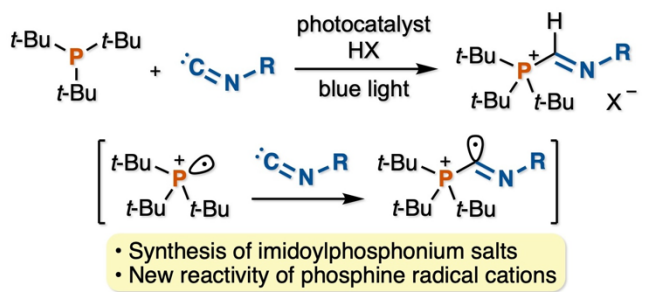
Abstract

Isocyanides and tri-*t*-butylphosphine undergo a C–P bond-forming reaction under photocatalytic conditions. The resulting imidoyltrialkylphosphonium salts represent a new class of organophosphorus compounds that can be isolated by silica gel chromatography under air. This transformation exhibits broad functional group tolerance and affords a range of imidoylphosphonium salts in good to moderate yields. Mechanistic studies suggest a reaction pathway involving addition of a phosphine radical cation to the isocyanide, followed by single-electron reduction to form a phosphorus ylide intermediate. Furthermore, the imidoylphosphonium salts exhibit unique reactivity under reductive conditions, enabling their conversion to imidoylphosphines through elimination of a *P*-substituent.

Keywords: isocyanides, phosphines, photoredox catalysis

Graphical abstract



Isocyanides are versatile organic building blocks widely utilized in synthetic chemistry due to their unique ability to exhibit both nucleophilic and electrophilic properties. This ambiphilic nature allows them to participate in multicomponent reactions,[1] cycloadditions,[2] and radical-mediated transformations.[3] Recent advancements in photoredox catalysis have further expanded the scope of isocyanide chemistry, providing access to structurally diverse nitrogen-containing compounds with high efficiency.[4] Among these, the addition of *P*-centered radicals to isocyanides represents a valuable strategy for synthesizing a unique class of compounds containing both nitrogen and phosphorus atoms.[5] However, the available radical precursor in these systems has largely been limited to diphenylphosphine oxide (Fig. 1a). On the other hand, we demonstrated that phosphine radical cations are generated by photocatalytic single-electron oxidation of tertiary phosphines, which react with unsaturated compounds such as alkenes and alkynes to form diverse organophosphorus compounds.[6] Based on these previous studies, we investigated the use of tertiary phosphines as *P*-centered radical precursors in photocatalytic reactions with isocyanides.

Herein reported is a photocatalytic synthesis of imidoylphosphonium salts, representing a new family of organophosphorus compounds (Fig. 1b). Upon photoirradiation of tri-*t*-butylphosphine with various isocyanides in the presence of a photocatalyst and a proton source, the corresponding imidoyltrialkylphosphonium salts were obtained.

These products are air-stable and amenable to purification by silica gel chromatography. Mechanistic studies suggest that the reaction proceeds via the addition of a phosphine radical cation to the isocyanide, followed by single-electron reduction of the resulting sp^2-carbon-centered radical to generate a phosphorus ylide intermediate. Furthermore, the imidoylphosphonium salts undergo photocatalytic reduction to afford imidoylphosphines through elimination of one of the phosphorus substituents.

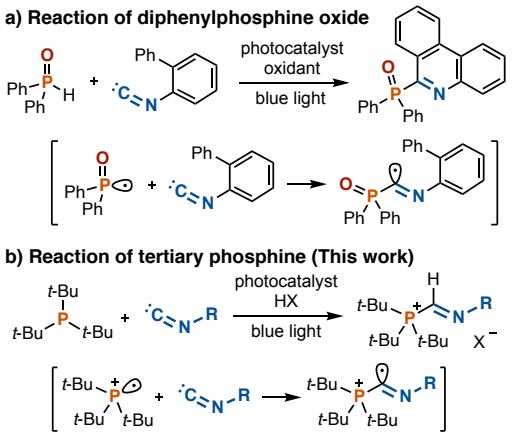
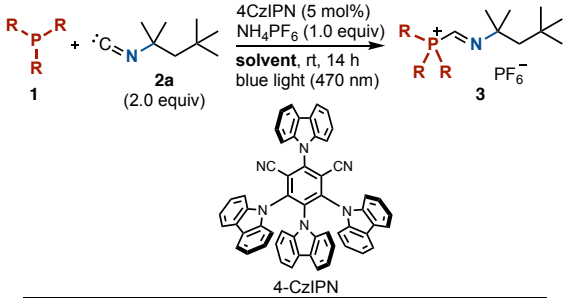


Fig. 1. Photocatalytic reactions with isocyanides. (a) Reaction of diphenylphosphine oxide (Previous works). (b) Reaction of tertiary phosphine (This work).

We began our investigation by evaluating the reactivity of various tertiary phosphines in the photocatalytic reaction with isocyanide **2a**. A mixture of phosphine (0.10 mmol) and **2a** (0.20 mmol) in acetonitrile (CH_3CN, 1.0 mL) was irradiated with blue light (470 nm) at ambient temperature for 14 hours in the presence of the photocatalyst, 2,4,5,6-tetrakis(9*H*-carbazol-9-yl) isophthalonitrile (4-CzIPN, 5 mol%), and ammonium hexafluorophosphate (NH_4PF_6, 1.0 equiv) as a proton source. Triarylphosphines such as triphenylphosphine (**1a**) and tri-*o*-tolylphosphine (**1b**) failed to react with isocyanide, and **2a** was recovered. In contrast, trialkylphosphines were found to be suitable substrates. Tri-*n*-butylphosphine (**1c**) and tricyclohexylphosphine (**1d**) afforded the corresponding imidoyltrialkylphosphonium salts **3ca** and **3da** in 6% and 17% yields, respectively. Notably, tri-*t*-butylphosphine (**1e**) gave **3ea** in 27% yield under the same conditions.

To improve the yield of **3ea**, a range of solvents was examined. The use of less polar solvents such as toluene, dichloromethane (CH_2Cl_2), and tetrahydrofuran (THF) resulted in diminished yields, while methanol (CH_3OH) significantly improved the yield to 80%. Further enhancement to 87% was achieved by replacing NH_4PF_6 with ammonium chloride (NH_4Cl) as a proton source. The resulting imidoylphosphonium salt **3ea** was stable in air and could be purified by silica gel chromatography to afford analytically pure material in 71% isolated yield.

Table 1. Optimization of the photocatalytic reaction of phosphines with isocyanides.[a]



Entry	PR_3	Solvent	Yield of **3**
1	PPh_3 (**1a**)	CH_3CN	0%
2	P(*o*-tolyl)$_3$ (**1b**)	CH_3CN	0%
3	P(*n*-Bu)$_3$ (**1c**)	CH_3CN	6%
4	PCy_3 (**1d**)	CH_3CN	17%
5	P(*t*-Bu)$_3$ (**1e**)	CH_3CN	27%
6	P(*t*-Bu)$_3$ (**1e**)	toluene	0%
7	P(*t*-Bu)$_3$ (**1e**)	CH_2Cl_2	3%
8	P(*t*-Bu)$_3$ (**1e**)	THF	0%
9	P(*t*-Bu)$_3$ (**1e**)	CH_3OH	80%
10[b]	P(*t*-Bu)$_3$ (**1e**)	CH_3OH	87%

[a] **1** (0.10 mmol), **2a** (0.20 mmol, 2.0 equiv), NH_4PF_6 (0.10 mmol, 1.0 equiv), 4-CzIPN (0.005 mmol, 5.0 mol%), solvent (1 mL), ambient temperature, 14 h, blue light (470 nm). Yields were determined by ^1H NMR analysis. [b] NH_4Cl was used instead of NH_4PF_6.

With the optimal conditions in hand, a scope of isocyanides was examined (Fig. 2). The reaction of phosphine **1e** with 1-adamantyl isocyanide (**2b**) proceeded to form imidoylphosphonium salt **3eb** in 70% yield. However, sterically less hindered alkyl isocyanides such as benzyl isocyanide failed to give the desired products probably due to the lability of the produced imidoylphosphonium salt. Aryl isocyanides also participated in the present photocatalytic reaction. 2,6-Xylyl isocyanide (**2c**) afforded *N*-arylated product **3ec** in a good yield. Bromo-substituted aryl isocyanide **2d** participated in the reaction without compromising the integrity of the C(sp^2)–Br bond, affording **3ed** in 58% yield. Unlike previous reports where cyclization of the imidoyl radical intermediate led to phenanthridine products, biphenyl isocyanide **2e** selectively afforded imidoylphosphonium salt **3ee**. Although product **3ee** was obtained in 31% yield as determined by NMR analysis, the isolated yield was significantly lower at 9% due to the difficulty in separating the product. Next, isocyanides derived from benzoxazoles were examined.[7] Ester functionalities of these isocyanides did not affect the reaction efficiency, and the corresponding imidoylphosphonium salts (**3ef–3eh**) were obtained in yields ranging from 35% to 66%.

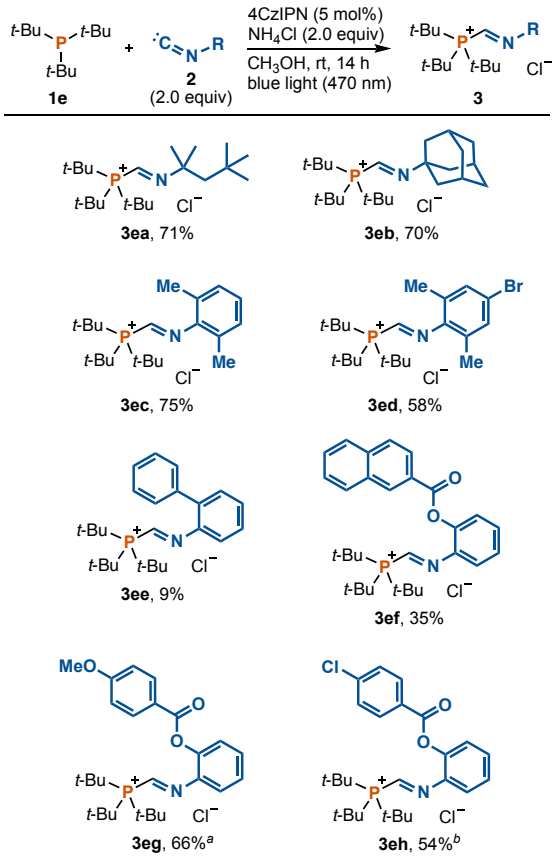


Fig. 2. Substrate scope. Reaction conditions: **1e** (0.10 mmol), **2** (0.20 mmol, 2.0 equiv), NH_4Cl (0.20 mmol, 2.0 equiv), 4-CzIPN (0.005 mmol, 5.0 mol%), CH_3OH (1 mL), ambient temperature, 14 h, blue light (470 nm). Isolated yields were shown. [a] 0.10 mmol (1.0 equiv) of NH_4Cl was used. [b] Products were obtained as a mixture of **3eh** (54% yield) and *N*-2-hydroxyphenyl-imidoylphosphonium salt (12% yield).

The synthetic applications were summarized in Fig. 3. The reaction could be scaled up, and imidoylphosphonium salt **3eb** was obtained in 81% yield from a 1 mmol quantity of phosphine **1e** with 2 equiv of isocyanide **2b** (Fig. 3a). After anion exchange from chloride (**3eb**) to tetraphenylborate (**4**), single crystals suitable for X-ray diffraction analysis were obtained by recrystallization from chloroform and diethyl ether (Fig. 3b). The crystal structure of **4** reveals a P–C–N bond angle of 120.2°, indicating sp^2 hybridization at the imine carbon. The observed C=N bond length of 1.24 Å is consistent with typical values for imine compounds.[8] The three bulky *t*-butyl groups on the phosphorus atom protect the imine carbon, which make the imidoylphosphonium kinetically inert toward nucleophiles such as water.

To investigate the reactivity of imidoylphosphonium salts, cyclic voltammetry analysis of **3eb** was performed. The reduction potential of **3eb** ($E_{1/2}$) was determined to be –1.26 V vs SCE in CH_3CN, indicating that **3eb** can be reduced by the excited state of the photocatalyst Ir(ppy)$_3$ ($E_{1/2}$ = –1.73 V vs SCE in CH_3CN).[9] Based on this result, photocatalytic reduction of **3eb** was attempted. When a mixture of **3eb** and triethylamine was irradiated with blue light (470 nm) in the presence of photocatalyst Ir(ppy)$_3$, imidoylphosphine **5** was obtained. The product could be isolated in a form of the borane-complex **6** in 27% yield after treatment with BH_3·THF (Fig. 3c). Although photocatalytic reductive C–P bond cleavage of α-functionalized alkylphosphonium salts has been reported,[10] this represents a unique example of the photocatalytic cleavage of a *t*-butylphosphonium salt.[11] Imidoylphosphines are known to serve as effective ligands in ethylene polymerization and oligomerization catalysts,[12] and therefore, phosphine **5** is a promising new ligand candidate for these transformations.

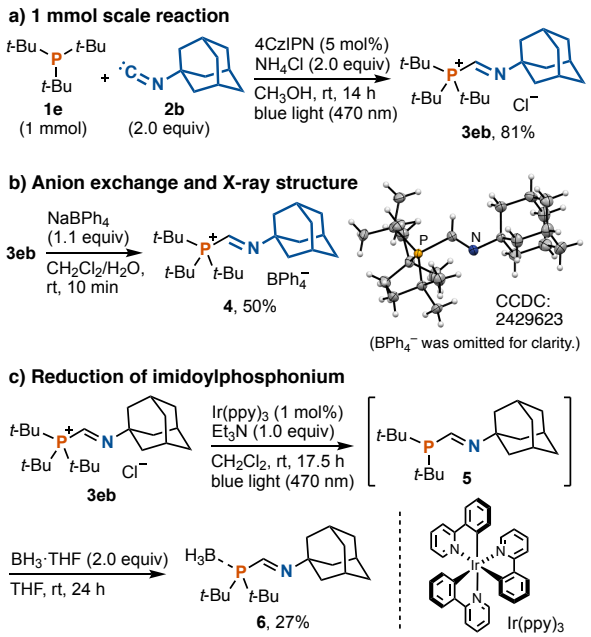


Fig. 3. Synthetic applications.

To gain mechanistic insights into the present photocatalytic reaction, an additional experiment was carried out. When the reaction was conducted in deuterated methanol (CD_3OD), a deuterium atom was introduced at the position α to the phosphorus atom of an imidoylphosphonium product (**3ea-*d***) (Fig. 4). This result indicates the involvement of a phosphonium ylide intermediate in the reaction pathway, which was rapidly deuterated by ND_4Cl, generated in situ through proton exchange between NH_4Cl and CD_3OD.

Fig. 4. Mechanistic experiment.

Based on the experimental results, we proposed the mechanistic scenario depicted in Fig. 5. Initially, an excited photocatalyst (**PC***) oxidizes tri-*t*-butylphosphine (**1e**) to generate phosphine radical cation **A** and a reduced state of the photocatalyst (**PC**$^{\bullet-}$). [13] The radical cation (**A**) then adds to the carbon atom of isocyanide **2** to form imidoyl radical species **B**. The resulting sp^2-carbon radical receives an electron from **PC**$^{\bullet-}$ to generate phosphonium ylide **C** with regeneration of the ground state photocatalyst (**PC**). Finally, protonation of ylide **C** with NH_4Cl produces imidoylphosphonium salt **3** along with NH_3 as a byproduct. Alternative to the stepwise pathway, concerted single-electron reduction and protonation, namely proton-coupled electron transfer,[14] of **B** may be operative in the formation of **3**.

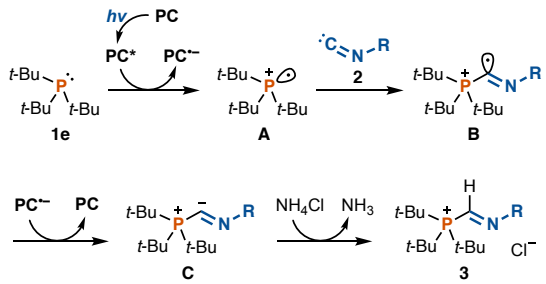


Fig. 5. Proposed reaction mechanism.

In summary, we developed a photocatalytic synthesis of imidoyltrialkylphosphonium salts. Under mild conditions employing a photoredox catalyst and a proton source, tri-*t*-butylphosphine and various isocyanides undergo efficient coupling to afford a new class of air-stable imidoylphosphonium salts. Mechanistic investigations suggest that the reaction proceeds through initial photocatalytic oxidation of the phosphine to generate a phosphine radical cation, followed by addition to the isocyanide and single-electron reduction of the resulting radical intermediate. Furthermore, the obtained imidoylphosphonium salts could be converted into imidoylphosphines via photocatalytic elimination of a phosphine substituent. This work not only provides a practical method for accessing structurally novel organophosphorus compounds but also unveils new reactivity of phosphine radical cations under photoredox conditions.

Supplementary data

Supplementary material is available at *Chemistry Letters*

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