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4CzIPN-^{t}Bu-Catalyzed Proton-Coupled Electron Transfer for Photosynthesis of Phosphorylated *N*-Heteroaromatics

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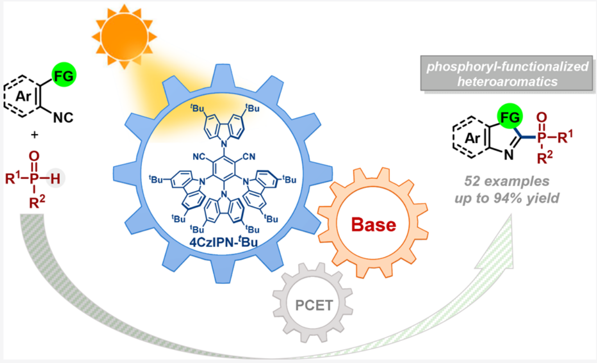
Cite This: *J. Am. Chem. Soc.* 2021, 143, 964−972

ABSTRACT: 2,4,5,6-Tetrakis(3,6-di-*tert*-butyl-9*H*-carbazol-9-yl)-isophthalonitrile (4CzIPN-^{t}Bu) was developed as a photocatalyst for the phosphorus-radical-initiated cascade cyclization reaction of isocyanides. By using 4CzIPN-^{t}Bu as catalyst, we developed a visible-light-induced proton-coupled electron transfer strategy for the generation of phosphorus-centered radicals, via which a wide range of phosphorylated phenanthridines, quinolines, and benzothiazoles were successfully constructed.



INTRODUCTION

Over the past decade, visible-light-driven photoredox catalysis has stimulated a resurgence of interest in the exploration of radical reactions.[1] These attractive synthetic manifolds are mainly spurred by the exploitation of exogenous photocatalysts to facilitate the primary photoinduced events, such as single-electron transfer (SET),[2] hydrogen-atom transfer (HAT),[3] energy transfer (EnT),[4] and proton-coupled electron transfer (PCET),[5] to generate open-shell reactive species that enable the molecular architectures upon photoexcitation.[6] Among them, ruthenium- and iridium-polypyridyl complexes stand at the forefront, due to their strong absorptions, long-lived excited states, and broad redox capabilities in the visible regime of the light spectrum.[7] Nevertheless, several intrinsic drawbacks regarding toxicity of metals, high cost, as well as restrictive conformational constraint hinder their large-scale application in photosynthetic chemistry.[8] In this context, organic dyes offer a metal-free alternative to their transition-metal counterparts, thus expending the accessibility to photoredox catalysis in a more environmentally benign and sustainable manner.[8b,9]

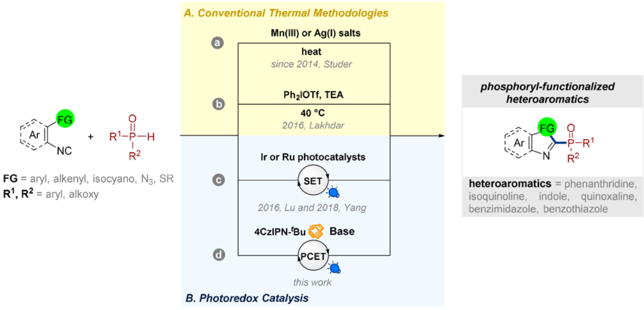
Currently, the structural design and development of organic dyes relies on the (hetero)anthracene-based fluorescent platform, from which a majority of classic photocatalysts (e.g., 9,10-dicyanoanthracene,[10] Eosin Y,[11] methylene blue,[12] Rhodamine B,[13] Mes-Acr^{+},[14] *N*-phenylphenothiazine,[15] etc.) were derived. This situation has been partially alleviated because carbazolyl dicyanobenzenes (CDCBs) emerged as a novel donor−acceptor (D−A) fluorophore with intriguing photoelectric performance, greatly expanding the photocatalyst toolbox of organic chemists.[16] In particular, the 1,2,3,5-tetrakis(carbazol-9-yl)4,6-dicyanobenzene (4CzIPN)[17] is ubiquitously applied in many photodriven transformations, including organic dye/metal dual catalytic coupling reactions,[18] photoredox-enabled alkylation of imines,[19] photocarboxylation with CO_2,[20] radical addition cyclization cascades,[21] etc. More importantly, by tailoring the number and alignment of carbazolyl and cyano units on the benzene ring, the HOMO−LUMO energy levels as well as photoredox potentials of the resulting CDCBs can be easily adjusted.[22]

Phosphorus-radical-mediated approaches are a powerful tool for the rapid and facile access to structurally diverse phosphorus-containing scaffolds.[23] Unfortunately, the direct additions of electrophilic P-centered radical to electron-deficient heteroarenes are less favored in contrast to alkenes and alkynes.[24] The radical cascade cyclization of isocyanides can circumvent the aforementioned limitations by introducing phosphoryl groups simultaneously with constructing *N*-heterocycles. Considering the great significance of both heteroarene[25] and organophosphorus motifs,[26] the P-radical-initiated radical cascade cyclization of isocyanides has been extensively studied.[27] Early methods for generating P-radicals required stoichiometric amounts of Ag(I) or Mn(III) salts as radical

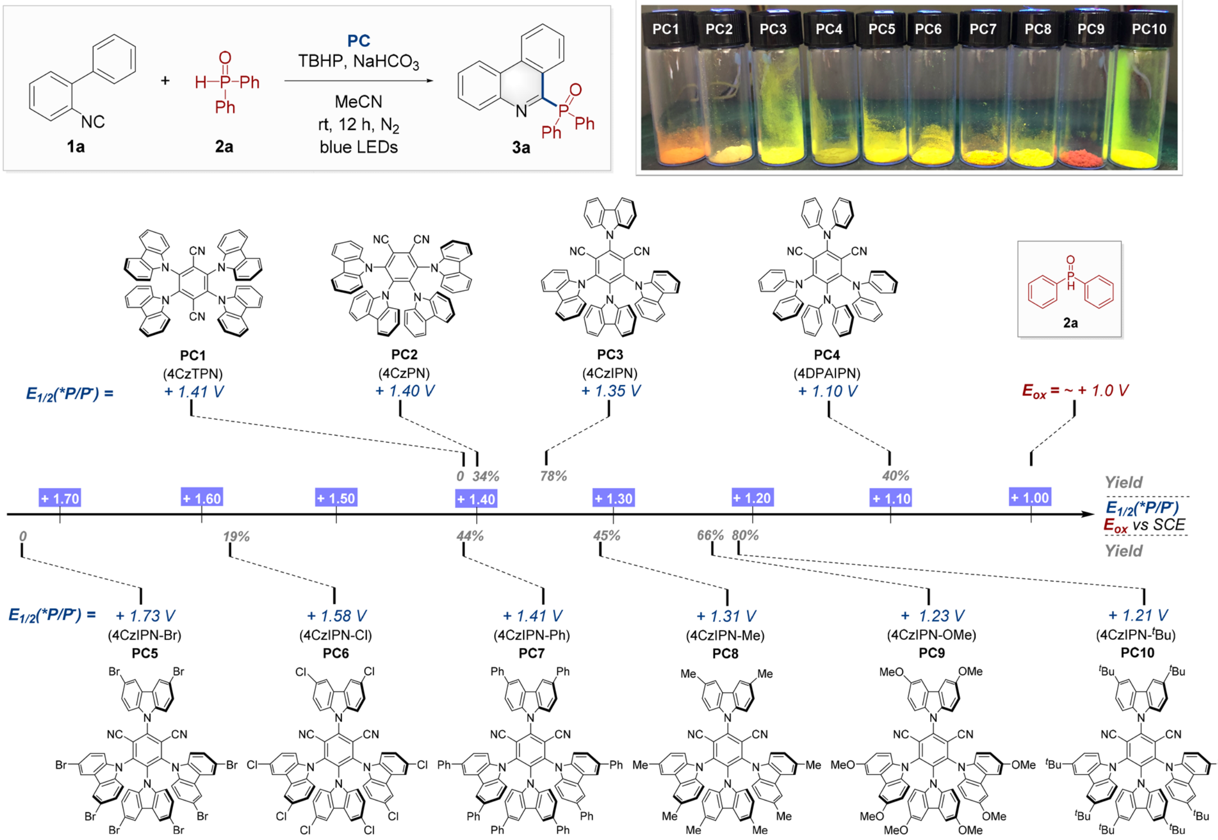
Received: October 22, 2020
Published: December 29, 2020

initiators to trigger the following isocyanide annulations (Scheme 1a).[28] In 2014, Lakhdar's group reported a metal-free method in the presence of diphenyliodonium salt with triethylamine to access various 6-phosphorylated phenanthridines (Scheme 1b).[29] Afterward, Lu and co-workers developed a photoredox-mediated tandem cyclization of isocyanides with $[Ir(ppy)_2(dtbpy)]PF_6$ as photocatalyst leading to $P(O)Ph_2$-containing phenanthridines and isoquinolines.[30] A concurrent work by Yang et al. provided a photoinduced approach to the construction of 2-phosphinoylindoles by using a ruthenium photocatalyst (Scheme 1c).[31] Despite that significant progress has been achieved in this area, the dye-catalyzed P-radical-initiated cascade cyclization of isocyanides to access phosphoryl-functionalized *N*-heteroaromatics has not yet been established. Herein, we would like to disclose the application of 2,4,5,6-tetrakis(3,6-di-*tert*-butyl-9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN-^{t}Bu) as a metal-free photocatalyst for the visible-light-induced proton-coupled electron transfer reaction to generate phosphorus-centered radicals, by which a wide range of phosphorylated phenanthridines, quinolines, and benzothiazoles were successfully synthesized. To the best of our knowledge, this is the first example of applying 4CzIPN-^{t}Bu as a photocatalyst to trigger phosphorus-radicals via an unprecedented photoredox-catalyzed proton-coupled electron transfer process (Scheme 1d).

Scheme 1. P-Radical-Initiated Cascade Cyclization of Isocyanides



Scheme 2. Excited-State Oxidative Potentials of CDCB-Based Photocatalysts and Screening of PC1−10 for the Photosynthesis of 3a[a]



[a]The values of $E_{1/2}(^*P/P^-)$ and E_{ox} (vs SCE in MeCN) were obtained in the reported literature.[33a,c,34,35] Typical reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv), PC (5 mol %), $NaHCO_3$ (2.0 equiv), and TBHP (2.0 equiv) were mixed in 2 mL of MeCN under irradiation of blue LEDs with N_2 protection at rt for 12 h, and the corresponding ^{31}P NMR yields of **3a** were given with trioctylphosphine oxide as an internal standard. PC = photocatalyst, 4CzTPN = 2,3,5,6-tetra(9*H*-carbazol-9-yl)terephthalonitrile, 4CzIPN = 3,4,5,6-tetra(9*H*-carbazol-9-yl)phthalonitrile, 4CzIPN = 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile, 4DPAIPN = 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile, 4CzIPN-Br = 2,4,5,6-tetrakis(3,6-dibromo-9*H*-carbazol-9-yl)isophthalonitrile, 4CzIPN-Cl = 2,4,5,6-tetrakis(3,6-dichloro-9*H*-carbazol-9-yl)isophthalonitrile, 4CzIPN-Ph = 2,4,5,6-tetrakis(3,6-diphenyl-9*H*-carbazol-9-yl)isophthalonitrile, 4CzIPN-Me = 2,4,5,6-tetrakis(3,6-dimethyl-9*H*-carbazol-9-yl)isophthalonitrile, 4CzIPN-OMe = 2,4,5,6-tetrakis(3,6-dimethoxy-9*H*-carbazol-9-yl)isophthalonitrile, 4CzIPN-^{t}Bu = 2,4,5,6-tetrakis(3,6-di-*tert*-butyl-9*H*-carbazol-9-yl)-isophthalonitrile.

■ RESULTS AND DISCUSSION

To avoid the use of expensive and toxic transition-metal photocatalysts, we initiated our study by using CDCB-based organic dyes. Previous studies on CDCBs generally focus on the fine-tuned assembly of carbazolyl and cyano groups;[16a,b,22a,32] however, the exploration of substituted CDCBs remains scarce.[33] Accordingly, as illustrated in Scheme 2, four reported CDCB analogues (i.e., 4CzIPN, 4CzTPN, 4CzIPN, and 4DPAIPN) as well as six substituted 4CzIPNs bearing electron-withdrawing groups (i.e., 4CzIPN-Br and 4CzIPN-Cl) or electron-donating groups (i.e., 4CzIPN-Ph, 4CzIPN-Me, 4CzIPN-OMe, and 4CzIPN-^{t}Bu) at the *para*-position on the carbazoles were prepared through a reported one-step nucleophilic substitution reaction followed by simple filtration isolation (see the Supporting Information for details). An obvious trend that adding electron-donating groups leads to a lower oxidative potential of the excited state ($E_{1/2}$(*P/P$^-$) vs SCE in MeCN), while the electron-withdrawing ones can make it more oxidizing, was observed among our available substituted 4CzIPNs, and the order of $E_{1/2}$(*P/P$^-$) values follows the sequence as Br > Cl > Ph > Me > OMe > ^{t}Bu, exhibiting widely distributed oxidative capabilities ranging from +1.10 to +1.73 V (Scheme 2). Considering the essential parameter of oxidative potential for a photoexcited catalyst in the reductive quenching cycle to produce a radical by oxidation, it is rational to envisage that our CDCB-based photocatalysts could possibly oxidize P-radical precursors (e.g., diphenylphosphine oxide **2a** with E_{ox} = ~+1.00 V vs SCE in MeCN)[34] to generate the corresponding radicals upon visible light excitation.

We thereby turn to investigate the performance of our CDCB-based organic dyes (**PC1−PC10**) in the visible-light-driven radical cascade cyclization of isocyanides with phosphorylation reagents. The model reaction conditions were established as follows: **1a** (0.2 mmol), **2a** (2.0 equiv), PC (5 mol %), $NaHCO_3$ (2.0 equiv), and TBHP (2.0 equiv) were mixed in 2 mL of MeCN under irradiation of blue LEDs with N_2 protection at rt for 12 h (see Tables S1−S3), and the corresponding ^{31}P NMR yields of the desired product **3a** were displayed in Scheme 2. Among the four reported CDCB analogues (**PC1−PC4**), 4CzIPN, 4CzTPN, 4CzIPN, and 4DPAIPN, the 4CzIPN (**PC3**) with an appropriate oxidative potential of the excited state (+1.35 V) led to **3a** in a superior yield of 78%. Intriguingly, as for the six substituted 4CzIPNs (**PC5−PC10**), the yields of **3a** increased constantly from 0 to 80% with the decline of $E_{1/2}$(*P/P$^-$) values from +1.73 to +1.21 V, and 4CzIPN-^{t}Bu (**PC10**) outperformed the others to produce **3a** in 80%. Notably, the relatively poor reactivities of 4CzIPN-Br (**PC5**) and 4CzIPN-Cl (**PC6**) might be attributed to their inferior solubility.[33c] After extensive experimentation, 4CzIPN-^{t}Bu was selected as the optimal photocatalyst to continue our follow-up study.

DFT and TD-DFT computations of **PC10** (4CzIPN-^{t}Bu) revealed that the absorption band (λ_{abs} = 391 nm) is assigned to the HOMO−LUMO transition (95%) with the largest oscillator strength (f) of 0.1369. The carbazolyl moieties are markedly distorted from the dicyanobenzene plane by steric hindrance, resulting in the spatially separated highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMOs) of **PC10**. The HOMOs are mainly localized in the carbazolyl moieties, while the LUMOs are distributed over the dicyanobenzene moieties, respectively (Figure 1). These features of the orbital distribution are similar to those of **PC3** (4CzIPN), leading to the characteristic extension of the absorption band to the visible region and efficient intramolecular charge transfer (CT).[22b,36]

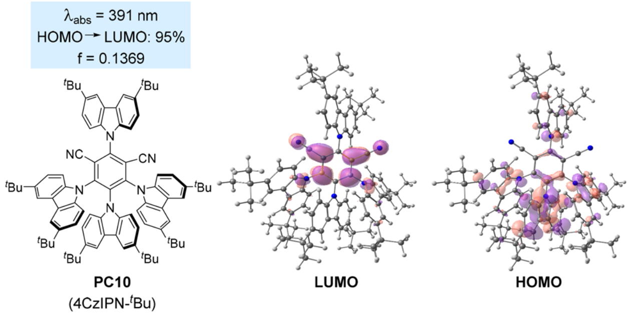
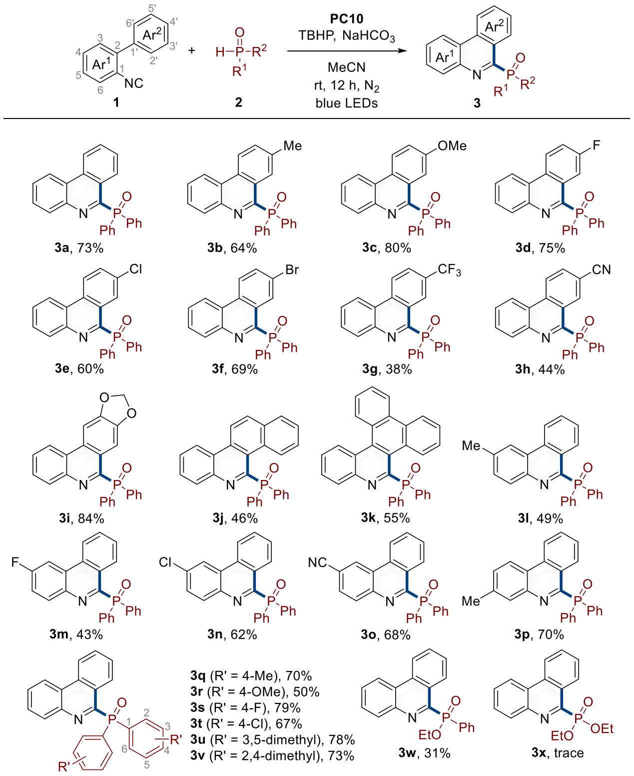


Figure 1. Electronic transition calculated by DFT and TD-DFT calculations and frontier orbitals of **PC10**.

We next investigated the substrate scope of biphenyl isocyanides and diphenylphosphine oxides by using **PC10** as a photocatalyst to access various 6-phosphorylated phenanthridines. As shown in Scheme 3, initially, the biphenyl isocyanides bearing different groups at the 4′-position of Ar^2 rings, such as H−, Me−, MeO−, F−, Cl−, Br−, CF_3−, and CN−, were tested to react with diphenylphosphines oxide **2a** itself, affording the corresponding products **3a−h** in yields up

Scheme 3. Synthesis of 6-Phosphorylated Phenanthridines by Reacting Biphenyl Isocyanides with Diphenylphosphine Oxides[a]

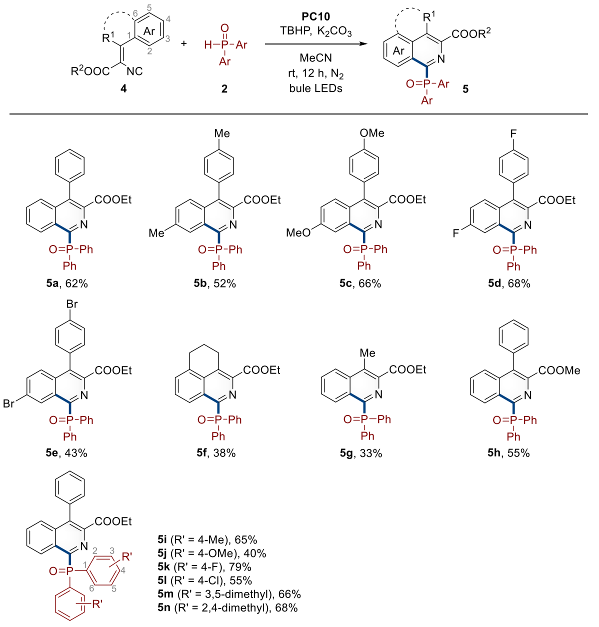


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **PC10** (5 mol %), TBHP (70% solution in water, 2.0 equiv), and $NaHCO_3$ (2.0 equiv) in 2 mL of MeCN under irradiation of blue LEDs with N_2 protection at rt for 12 h. Isolated yields were given on the basis of substrate **1**.

to 80%. Additionally, cyclization of polycyclic substituted isocyanobenzenes occurred successfully to give phosphorylated polyheteroarenes **3i−k** in good to moderate yields. It was observed that the biphenyl isocyanides with substituents of Me−, F−, Cl−, and CN− on the Ar^1 moiety also proceeded smoothly in this reaction (**3l−p**). Furthermore, a variety of phosphorus reagents, including 4-Me, 4-MeO, 4-F, 4-Cl, 3,5-dimethyl, and 2,4-dimethyl-substituted diarylphosphine oxides, were well tolerated to give their corresponding products **3q−v** with comparable yields. However, as for ethyl phenylphosphinate (**2w**) and diethyl *H*-phosphonadtes (**2x**), the corresponding products **3w** and **3x** were obtained in 31% and trace yields, respectively, which might be attributed to the higher theoretical bond dissociation energies (BDE) of the P−H bonds (357 and 375 kJ/mol) and oxidative potentials (E_{ox}, 1.62 and 1.65 V) (see Table S6).

Inspired by the primary results of the photosynthesis of 6-phosphorylated phenanthridines, we decided to expand the implementation of this strategy to other isocyanide systems. Whereas vinyl isocyanides have recently demonstrated the synthetic versatility in radical chemistry and garnered particular recognition in the preparation of isoquinoline derivatives, we hence commence exploring their scalable application in the synthesis of 1-phosphorylated isoquinoline derivatives. The studies were ongoing to use **PC10** as a photocatalyst for screening the experimental parameters of the model reaction, and the optimized conditions were established (see Table S4). As can be seen in Scheme 4, a large range of vinyl isocyanides **4** were reacted successfully with diphenylphosphine oxides **2** to provide diverse 1-phosphorylated isoquinolines **5a−n** in satisfactory yields ranging from 33% to 79%.

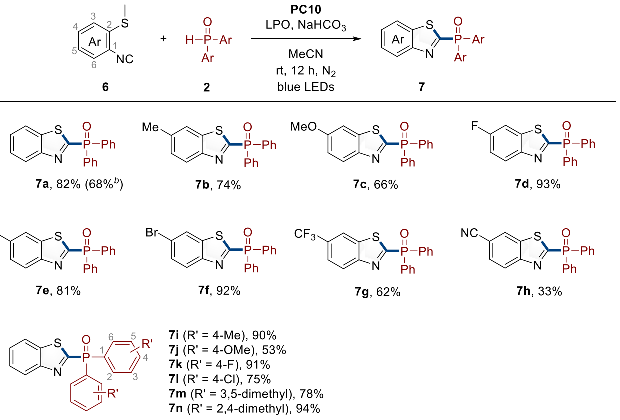
Scheme 4. Synthesis of 1-Phosphorylated Isoquinolines by Reacting Vinyl Isocyanides with Diphenylphosphine Oxides[a]



[a]Reaction conditions: **4** (0.2 mmol), **2** (0.4 mmol), **PC10** (5 mol %), TBHP (70% solution in water, 2.0 equiv), and K_2CO_3 (2.0 equiv) in 2 mL of MeCN under irradiation of blue LEDs with N_2 protection at rt for 12 h. Isolated yields were given on the basis of substrate **4**.

Because of our continuous interest in the radical cascade cyclization involving 2-isocyanoaryl thioethers,[37] we proceeded to probe the feasibility of this protocol for photosynthesis of benzothiazoles. Much to our delight, the practicality of **PC10** could be well extended to synthesize 2-phosphorylated benzothiazoles **7** by treating 2-isocyanoaryl thioethers **6** with diphenylphosphine oxides **2** in the presence of LPO and $NaHCO_3$ under irradiation of blue LEDs with N_2 protection at rt for 12 h (see Table S5). As shown in Scheme 5, it was found that 2-isocyanoaryl thioethers **6** bearing different substituents, such as H−, Me−, MeO−, F−, Cl−, Br−, CF_3−, and CN− at the 4-positions of the benzene rings, underwent cycloaddition smoothly to give the corresponding products **7a−h** from moderate to excellent yields. A range of *H*-phosphorus oxides were also evaluated to react with **6a** under standard conditions leading to the desired products (**7i−n**). Notably, the gram-scale synthesis of benzo[*d*]thiazol-2-yldiphenylphosphine oxide (**7a**) was performed via our specially designed reactor (Figure S2) with an isolated yield of 68%.

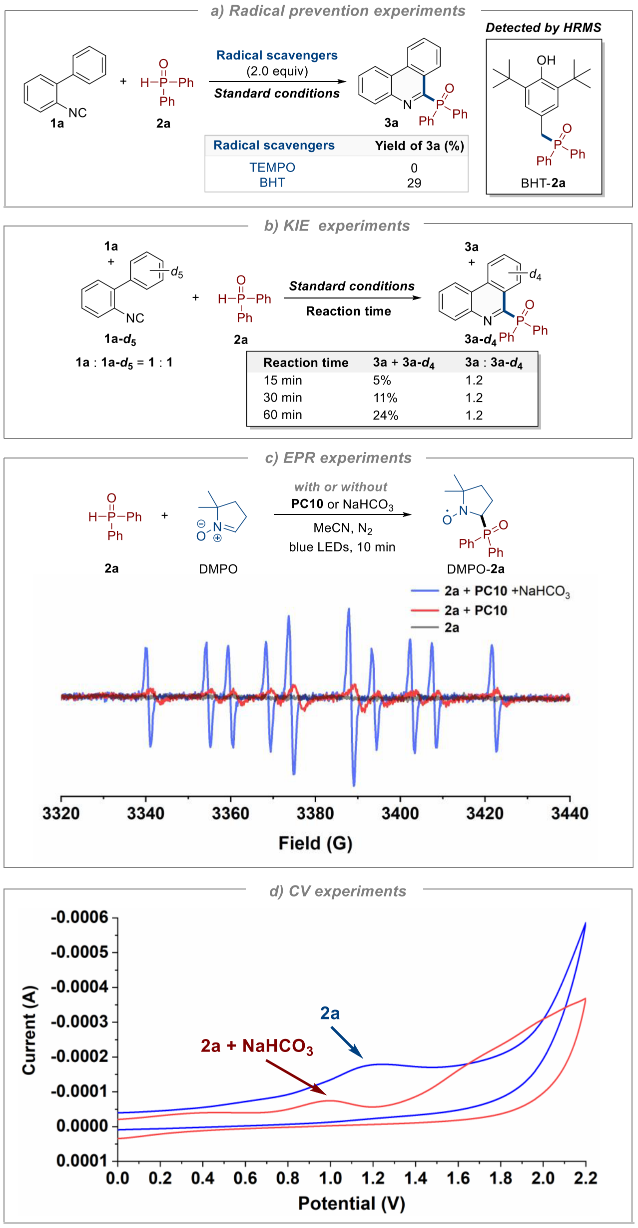
Scheme 5. Synthesis of 2-Phosphorylated Benzothiazoles by Reacting 2-Isocyanoaryl Thioethers with Diphenylphosphine Oxides[a]



[a](a) Reaction conditions: **6** (0.2 mmol), **2** (0.4 mmol), **PC10** (5 mol %), LPO (2.0 equiv), and $NaHCO_3$ (2.0 equiv) in 2 mL of MeCN under irradiation of blue LEDs with N_2 protection at rt for 12 h. Isolated yields were given on the basis of substrate **6**. (b) Gram-scale synthesis of **7a** with the assistance of a specially designed reactor (see the Supporting Information for details).

To gain a deeper insight into the reaction mechanism, a series of mechanistic studies were carried out (Scheme 6). Initially, two well-known radical scavengers, (2,2,6,6-tetramethylpiperidin-1-yl)-oxidanyl) TEMPO and 2,6-di-*tert*-butyl-4-methylphenol (BHT), were employed in the prevention experiments, resulting in a significant loss in yield of **3a** in each case. A BHT-**2a** adduct was detected by high-resolution mass spectrometry (HRMS), reminding us that phosphoryl radical might be generated photochemically (Scheme 6a; see Figure S3 for details). The intermolecular kinetic isotope effect (KIE) experiments were carried out with a 1:1 mixture of substrates **1a** and deuterium-labeled substrates **1a**-d_5 to verify the rate-determining step, and the k_H/k_D for deuterium-labeled product was found to be 1.2, implying that the cleavage of the C(sp^2)−H bond might not be the rate-determining step and radical aromatic substitution might be involved in the cyclization step[38] (Scheme 6b; see Figures S4−S6 for details). The radical species were further confirmed by electron

Scheme 6. Mechanistic Studies



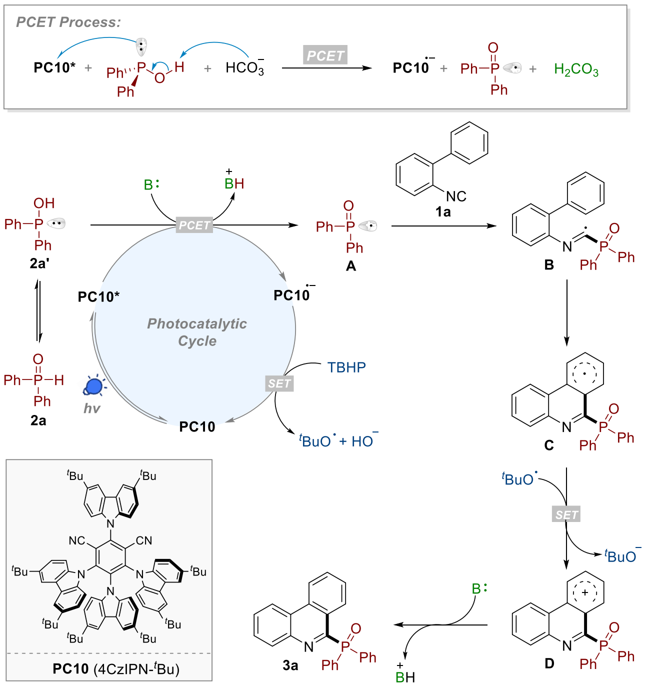
Radical scavengers	Yield of 3a (%)
TEMPO	0
BHT	29

Reaction time	3a + 3a-d_4	3a : 3a-d_4
15 min	5%	1.2
30 min	11%	1.2
60 min	24%	1.2

paramagnetic resonance (EPR) experiments using *tert*-butyl-*α*-phenylnitrone (DMPO) as a spin trap.[39] No signals were observed in the control group of **2a** and DMPO in MeCN under the irradiation of blue LEDs (gray line). When **PC10** and NaHCO$_3$ were added, a strong spectrum signal assigned to the spin adduct P(O)Ph$_2$−DMPO appeared as a multiplet of peaks (blue line). In the absence of NaHCO$_3$, the signal was significantly weakened (red line), and this suggested that the phosphoryl radical is a key intermediate and its generation relies on the presence of **PC10** and base (Scheme 6c; see Figure S7 for details). In 2019, Yu's group[20e] reported that the excited state of 4CzIPN can be quenched by **2a** and K$_2$CO$_3$; our luminescence quenching experiments also verified that the excited state of **PC10** was only quenched in the presence of **2a** and NaHCO$_3$ (see Figure S9 for details). Finally, cyclic voltammetry (CV) experiments indicate that, with the addition of NaHCO$_3$, the oxidation potential of **2a** can be effectively reduced from 1.2 to 1.0 V (Scheme 6d; see Figure S10 for details).

On the basis of our experimental results, a tentative mechanism for this protocol was proposed as shown in Scheme 7. Initially, ground-state **PC10** is photoactivated to its excited state (**PC10***), which leaves a vacancy in a ground-state orbital that can be filled by an electron donor. Diphenylphosphine oxide (**2a**) often exists in rapid equilibrium with its minor tautomer hydroxydiphenylphophine (**2a′**).[40] A proton-coupled electron transfer (PCET) process is followed, proceeding through an electron transfer from **2a′** to **PC10*** accompanying proton transfer from **2a′** to base (HCO$_3^-$), giving phosphoryl radical **A** as well as photocatalyst radical anion **PC10**$^{\bullet-}$, which subsequently reacts with TBHP, via SET from **PC10**$^{\bullet-}$ to TBHP, giving rise to hydroxide ion (OH$^-$) and *tert*-butoxyl radical together with regenerated **PC10**. Thereafter, **A** undergoes a radical addition to the isocyano group of substrate **1a** to afford the corresponding imidoyl intermediate **B**. Intramolecular cyclization of **B** subsequently occurs to render the radical intermediate **C**, which then immediately loses an electron to ^{t}BuO$^\bullet$ to form *tert*-butoxide anion and cation intermediate **D**. Because cation intermediate **D** is extremely inclined to donate a proton to base, to give structurally stable *N*-heteropolyaromatic product **3a**, the whole reaction is thus quickly driven to completion. Besides, a quantum yield (Φ = 0.3) was calculated, which was well consistent with our proposed mechanism shown in Scheme 7, excluding the radical chain process (see the Supporting Information for details).

Scheme 7. Proposed Mechanism



Proton-coupled electron transfer (PCET) is a chemical process that involves the concerted shift of a single electron and a single proton. PCET contrasts sharply with stepwise mechanisms in which the electron and proton are transferred sequentially.[41] To explore the possible pathways for the generation of phosphoryl radical in our case, the density functional theory (DFT) calculations have been performed at the M06-2X/DZVP level. The calculation results indicate that the individual electron transfer (ET) and proton transfer (PT) pathways operate at higher activation energies than does the concerted pathway, and the PCET pathway should be the most energetically favorable one among the three possible pathways (see Figure S13 for details).

■ CONCLUSION

2,4,5,6-Tetrakis(3,6-di-*tert*-butyl-9*H*-carbazol-9-yl)-isophthalonitrile (4CzIPN-^{t}Bu) was synthesized and demonstrated to be an efficient photocatalyst for the phosphorus-radical-initiated cascade cyclization reaction of isocyanides. With the catalysis of 4CzIPN-^{t}Bu, a wide range of phosphorylated aromatics including phenanthridines, quinolines, and benzothiazoles were successfully synthesized via a visible-light-induced proton-coupled electron transfer strategy. Such findings should be of great interest for the development of novel transition-metal-free photocatalysts for efficient organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11138.

Synthetic procedures, compound characterization, and additional data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the financial support from the National Natural Science Foundation of China (21971224, 22071222), the 111 Project (D20003), and the Key Research Projects of Universities in Henan Province (20A150006, 20B350001, 21A150053).

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