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Metal-Free Synthesis of 6-Phosphorylated Phenanthridines: Synthetic and Mechanistic Insights

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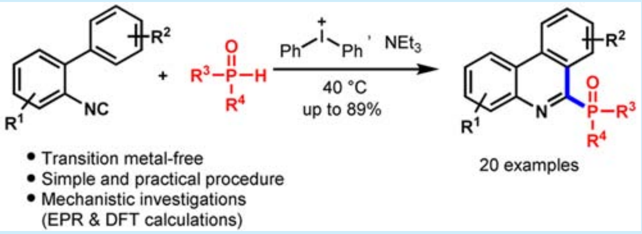
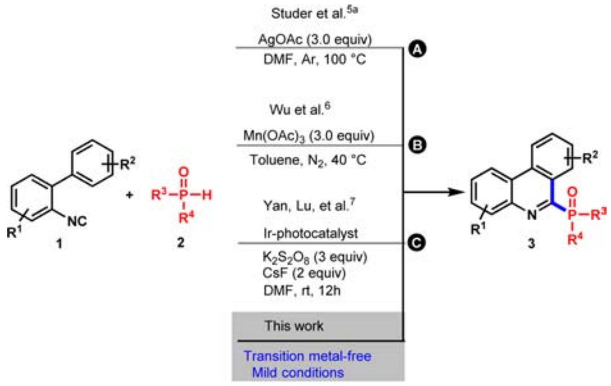
Ⓢ *Supporting Information*

ABSTRACT: A novel and efficient method for the generation of phosphinoyl radicals from the combination of diphenyliodonium salt ($Ph_2I^+, {}^-OTf$) with triethylamine (Et_3N) in the presence of secondary phosphine oxides is reported. By employing this practical and simple approach, a large variety of 6-phosphorylated phenanthridines have been synthesized through the addition of phosphinoyl radicals to isonitriles as radical acceptors. The reaction works smoothly in the absence of any transition metal or photocatalyst. On the basis of electron paramagnetic resonance (EPR) and density functional theory (DFT) calculations, the mechanism of this reaction is discussed.



Isonitriles **1** are radical acceptors "par excellence". Their synthetic potential has been triggered by Curran, who demonstrated that isonitriles can efficiently be employed for the synthesis of nitrogen based heterocycles.[1] While the development of this chemistry has grown slowly, recent years have witnessed remarkable interest in radical insertion reactions into isonitriles.[2] This has allowed construction of nitrogen heterocycles such as phenanthridines, indoles, quinolines, quinoxalines, and isoquinolines.[3] This impressive development in the field is obviously due to the discovery of efficient and mild methods for the generation of radical species such as visible-light photoredox catalysis.[2,4] Among those heterocycles, phenanthradines have recently emerged as an interesting scaffold with promising applications in medicinal chemistry and material sciences.[2] In this context, Studer et al. have reported an elegant method for the synthesis of 6-phosphorylated phenanthridines **3** from the reactions of aryl isonitriles **1** with secondary phosphine oxides **2** in the presence of stoichiometric amounts of AgOAc (3 equiv) at 100 °C (Scheme 1).[5a] The key step of this reaction involves the addition of phosphinoyl radical to isonitrile as a radical acceptor. Shortly thereafter, Wu et al. demonstrated that stoichiometric manganese(III) acetate (3 equiv) can also afford phosphorylated isonitriles **3** from the reaction of **1** and **2**.[6] During the preparation of this manuscript, Yan, Lu, et al. showed that the same reaction can proceed through visible light photoredox catalysis in the presence of $K_2S_2O_8$ (3 equiv) and CsF (2 equiv) at room temperature.[7] Despite the robustness of these methods, the use of stoichiometric or expensive transition metals still remains a disadvantage. Therefore, the development of a mild metal-free method for the synthesis of these phosphorylated molecules that is mechanistically distinct from the approaches mentioned above is highly appealing.

Scheme 1. Synthesis of 6-Phosphorylated Phenanthridines



Design Plan. Given the accessible bond dissociation energies (BDE ≈ 90 kcal mol^{-1}) of the P–H bond of secondary phosphine oxides and related structures,[8] the use of stoichiometric amounts of metal oxides (methods A and B,

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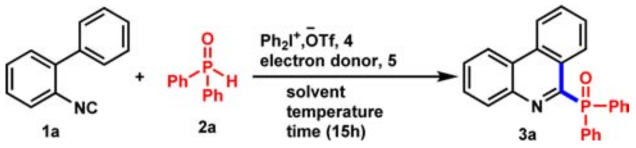
Scheme 1) or photocatalyst/$K_2S_2O_8$ (method C) to generate phosphinoyl radicals can be replaced by milder metal-free conditions. Indeed, because open-shell species can be formed when an electron donor−acceptor complex (EDA) undergeos a single-electron-transfer event (SET),[9] one can employ this technology for the generation of phosphorus-centered radicals. For instance, diaryliodonium ions ($Ph_2I^+,^-OTf$) are now recognized as suitable electron-acceptor substrates for the formation of EDA complexes when combined with electron donors.[10] When these complexes undergo SET events photochemically or thermally, they generate aryl radicals.[11] While this strategy has been used for arylating radical reaction in the past, one can envision taking advantage of the strong hydrogen abstraction ability of this radical to generate phosphinoyl radical from related phosphine oxides.[12]

On the basis of this hypothesis, we reacted isonitrile **1a** with diphenyl phosphine oxide **2a** in the presence of Et_3N, **5a**, and $Ph_2I^+,^-OTf$, **4**, under white light irradiation (26 W CF-lamp) at rt in DMF (Table 1). The reaction proceeds smoothly, furnishing **3a** in 45% yield (entry 1). Remarkably, a control experiment revealed that light is not required for the reaction, a comparable result being observed in the dark (entry 2). This suggests that the electron-transfer event within the EDA complex is thermodynamically viable in the absence of photochemical activation. The yield was further improved upon gentle heating of the reaction mixture to 50 °C (72%; entry 3). Interestingly enough, the reaction is compatible with a wide range of bases (entries 5−9), including KOH (**5c**), $NaHCO_3$ (**5d**), K_2CO_3 (**5e**), K_3PO_4 (**5f**), Cs_2CO_3 (**5g**), and Et_3N (**5a**). Although the two latter gave similar results, Et_3N, which is less expensive, has been selected to study the scope of the reaction. Among all tested solvents, dichloromethane has been identified as optimal for the reaction (entry 12). Lastly, optimization attempts showed that the temperature can be decreased to 40 °C without any loss in efficiency (entry 15). Varying the concentration of the mixture has almost no influence on the reaction efficiency. Finally, we found that 2 equiv of Et_3N allowed a further increase to a 74% conversion (entry 16). A control experiment revealed the essential role of the base as only trace amounts of **3a** have been detected without any base (entry 17).

Table 1. Optimization of the Radical Phosphorylation of Isonitrile 3a



entry[a]	**5**, electron donor (equiv)	solvent	temp (°C)	**3a**, yield[b] (%)
1	**5a**, Et_3N (1.3)	DMF[c]	20[e]	45
2	**5a**, Et_3N (1.3)	DMF[c]	20	41
3	**5a**, Et_3N (1.3)	DMF[c]	50	72
4	**5b**, NaOAc (1.3)	DMF[c]	50	31
5	**5c**, KOH (1.3)	DMF[c]	50	45
6	**5d**, $NaHCO_3$ (1.3)	DMF[c]	50	62
7	**5e**, K_2CO_3 (1.3)	DMF[c]	50	66
8	**5f**, K_3PO_4 (1.3)	DMF[c]	50	67
9	**5g**, Cs_2CO_3 (1.3)	DMF[c]	50	68
10	**5g**, Cs_2CO_3 (1.3)	THF[c]	50	28
11	**5g**, Cs_2CO_3 (1.3)	toluene[c]	50	62
12	**5g**, Cs_2CO_3 (1.3)	CH_2Cl_2[c]	40	61
13	**5g**, Cs_2CO_3 (1.3)	DMF[d]	50	70
14	**5g**, Cs_2CO_3 (2.0)	CH_2Cl_2[d]	40	64
15	**5a**, Et_3N (1.3)	CH_2Cl_2[d]	40	58
16	**5a, Et_3N (2.0)**	**CH_2Cl_2**[d]	**40**	**74**
17		CH_2Cl_2[d]	40	trace

[a] Reaction conditions: aryl isonitrile **1a** (0.25 mmol; 1 equiv), diphenylphosphine oxide **2a** (2.5 equiv), diphenyliodonium triflate **4** (1.3 equiv), base **2** (x equiv), solvent (4 or 1 mL), 15 h. [b] Determined by ^{31}P NMR using trioctylphosphine oxide as internal standard. [c] [**1a**] = 0.063 M. [d] [**1a**] = 0.25 M. [e] Irradiation with white LEDs.

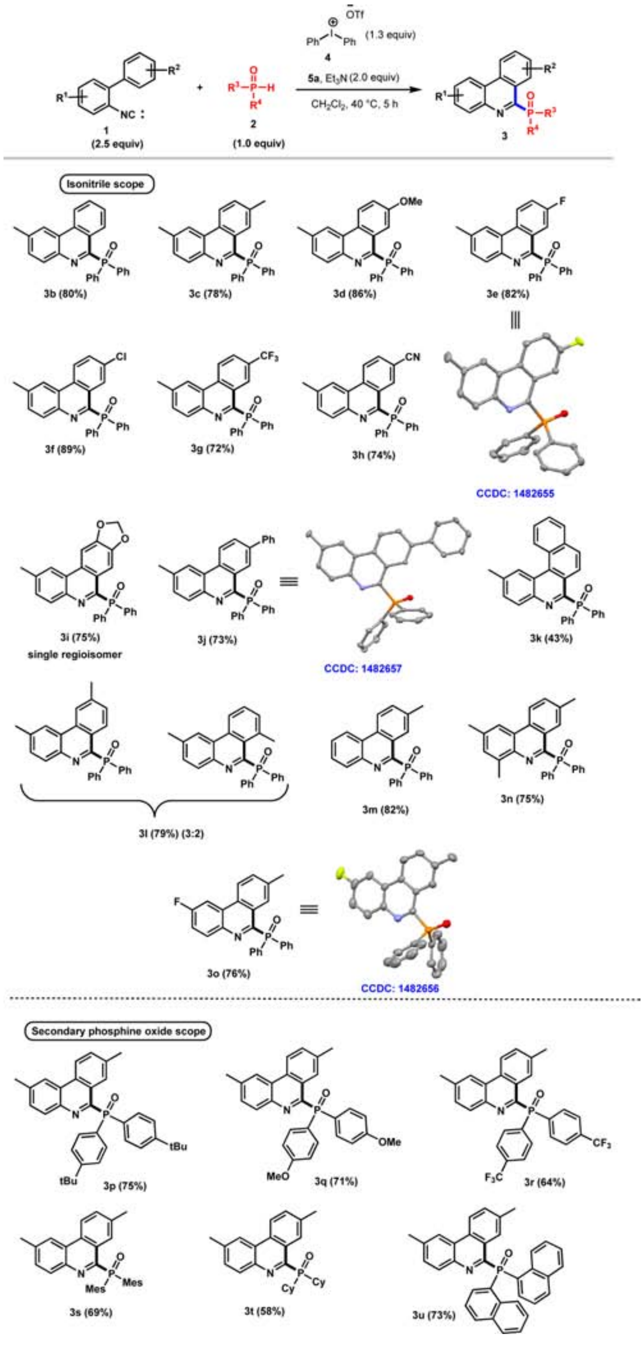


Figure 1. Scope of EDA-mediated 6-phosphorylation of isonitriles **1**. Reaction conditions: Reactions were run on 0.5 mmol scale in 2 mL of dichloromethane. Yields are obtained after isolation and purification. See the Supporting Information.

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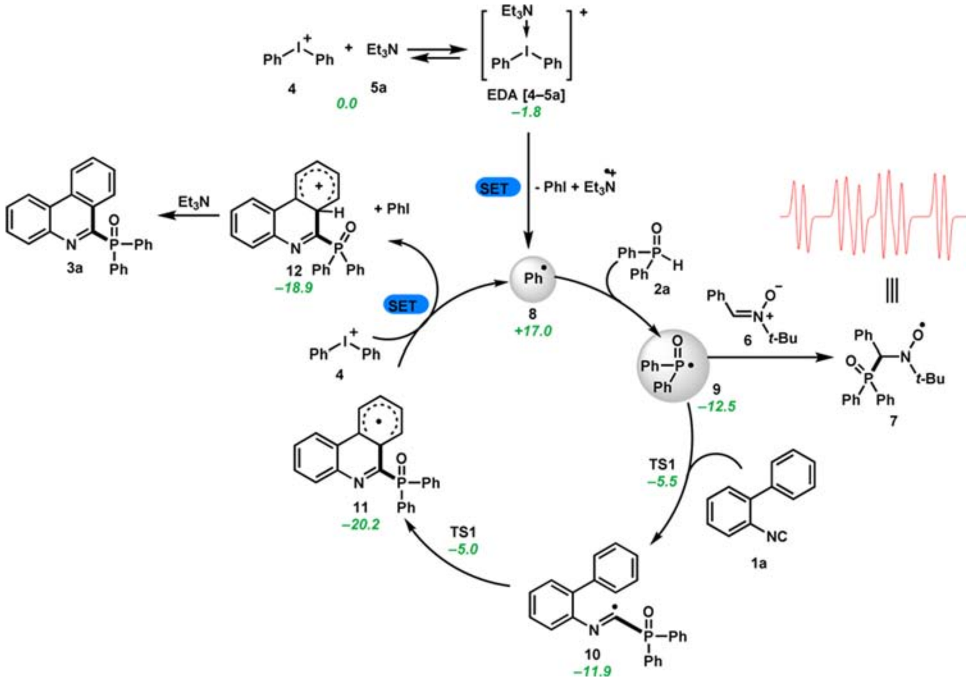
Scheme 2. Proposed Mechanism Including Calculated Free Energies for the Synthesis of 6-Phosphorylated Phenanthridine 3a



With optimal conditions established, the scope of the reaction was first explored with respect to the isocyanide component. As shown in Figure 1, aryl isonitriles bearing electron-donating or electron-withdrawing substituents at the *para* position of the arene ring that does not carry the isonitrile functionality furnished the desired heterocycles **3c–h,j** in good yields ranging from 72% to 89%. However, a moderate 43% yield was obtained with isonitrile **1k** bearing a naphthyl moiety. This result remains comparable to that reported by Studer under Ag-mediated conditions.[5] Interestingly, while the reaction of diphenylphosphine oxide **2a** with 3-methyl-substituted isocyanide **1l** gave two regioisomers **3l** and **3l′** (3:2) with 73% total yield, product **3i** was obtained with complete regiocontrol and in good yield (75%).

We have furthermore investigated the reaction with aryl isonitriles bearing substituents at the arene carrying the isonitrile functionality. As shown in Figure 1, the reaction proceeds well, and the phenanthridines **3m–o** were obtained in good yields (76 to 82%). Remarkably, in contrast to the conditions of Yan, Lu, et al.,[7] where the reaction did not occur when a strong electron-withdrawing group (F or CF_3) is located at the *para* position of isonitrile, the reaction proceeded well under our conditions, leading to the formation of **3o** in 76%. We finally extended the scope of our approach by investigating the reactions of isocyanides with other pentavalent phosphorus derivatives P(V). Interestingly, diarylphosphine oxides bearing *tert*-butyl, trifluoromethyl, or methoxy at the *para* positions of the aryl rings gave the desired P-substituted phenanthridines **3p–r** in decent yields (64 to 75%). The reaction works smoothly with dicyclohexylphosphine oxide **3t**, dinaphthylphosphine oxide **3u**, and dimesitylphosphine oxide **3s**, furnishing the desired adducts in 58–73% yields (Figure 1).

To gain insights into the reaction mechanism, preliminary mechanistic investigations have been undertaken. We first conducted electron paramagnetic resonance EPR spin-trapping experiments for the reaction of $Ph_2I^+,^-OTf$ **4** (1 equiv) with Et_3N **5a** (1 equiv) in *tert*-butylbenzene in the presence of α-phenyl-*N*-*tert*-butylnitrone (PBN) **6** at room temperature.

The EPR spectrum of this mixture reveals the clean formation of the phenyl-PBN radical adduct, characterized by typical hyperfine coupling constants (a_N = 14.4 G and a_H = 2.2 G) (Figure S1). These values perfectly match those reported previously.[12] The double integration of the EPR spectrum (DIEPR) of the EDA complex **4–5a** has been found to be proportional to the free-radical concentration (Figure S2). Importantly, in accordance with our observations gathered in Table 1 (entry 2), the DIEPR experiment shows that the phenyl radical is formed slowly and appeared for at least 72 h at room temperature before reaching a plateau. This suggests that the reduction of the iodonium salt **4** at room temperature goes through a slow and irreversible process. Addition of diphenylphosphine oxide **2a** into this mixture resulted in the formation of a new radical species **7** where the hyperfine coupling constants (a_N = 14.0 G, a_H = 3.0 G, and a_P = 18.4 G) are in good agreement with those previously determined for the PBN-diphenylphosphinoyl radical adduct **7** (Scheme 2).[11]

Furthermore, we employed density functional theory [B3LYP-D3BJ/aug-cc-pVTZ/IEFPCM(CH_2Cl_2)//B3LYP-D3BJ/6-31+G(d,p)] to investigate this transformation in more detail. Based on the experimental and computational findings, we now propose the reaction mechanism depicted in Scheme 2.[13] The reaction begins with the association of NEt_3 **5a** with $Ph_2I^+,^-OTf$ **4** to form the corresponding EDA complex **4–5a**. Although all attempts to characterize this ground-state complex failed, ROESY ^1H NMR experiments in acetone-d_6 at −40 °C showed that both components are in close proximity in solution (see the Supporting Information). It should be noted that Yu et al. have recently demonstrated the formation of EDA complex between hypervalent iodines such as Togni's reagent and tertiary amines, which has been employed for hydrotrifluoromethylation of unactivated alkenes and alkynes.[14] Furthermore, our DFT calculations showed that the association of **4** and **5a** is almost thermoneutral (Figure 2), which may explain

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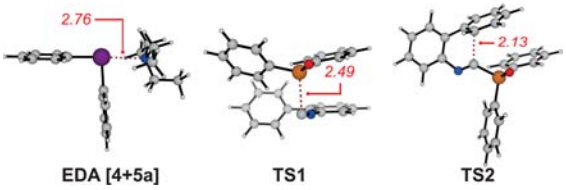

Figure 2. Computed structures of selected intermediates (selected bond lengths in angstroms).

the difficulty in characterizing the resulting complex. The EDA **4**−**5a** subsequently undergoes an endergonic SET to generate the phenyl radical **8** as confirmed by EPR. This radical then abstracts a hydrogen from the secondary phosphine oxide **2a** to form the corresponding phosphorus-centered radical **9**. No transition states could be located for this process, indicating the high reactivity of the phenyl radical **8**.[15] Next, the phosphinoyl radical adds to the isonitrile **1a** via **TS1**, giving rise to the imidoyl radical **10**. Rapid cyclization through **TS2** yields the cyclohexadienyl radical **11**. The latter is then oxidized with the diphenylidonium triflate **4** to form the arenium ion **12**, which is rapidly deprotonated with Et_3N, **5a**, to afford the final product **3a**. Based on the calculated free energies for the catalytic cycle of Scheme 2, all steps are thermodynamically feasible and proceed rapidly under the reaction conditions.

In summary, we have shown the high efficiency of diphenyliodonium ion **4** and Et_3N **5a** in forming an EDA complex, which in turn is able to generate a phenyl radical under very mild conditions. Although recent efforts have mainly been focused on the use of such a radical for arylation reactions, we capitalize here on its unique reactivity to act as a strong hydrogen atom abstractor to form phosphorus-centered radicals. This has been applied to describe the first metal-free approach for the synthesis of 6-phosphorylated phenanthridines, starting from easily accessible starting materials. The reaction mechanism of this process has been elucidated on the basis of EPR spectroscopy, which allowed the characterization of $Ph^\bullet$ and phosphinoyl radicals, thus providing evidence for their intermediacy in the reaction mechanism. Given the mildness of the process, this research should open doors for not only the generation of phosphorus-centered radicals but also many other radical types of potential applications in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02983.

> Full experimental procedures, spectroscopic characterizations, computational data, and NMR spectra; crystallographic data for compound **3j**, **3h**, and **3o** (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to memory of Dr. Alain-Pierre Chatrousse.

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