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Visible-light-mediated α -phosphorylation of *N*-aryl tertiary amines through the formation of electron-donor-acceptor Complexes: synthetic and mechanistic studies

Valentin Quint,^a Nourhène Chouchène,^b Moheddine Askri,^b Jacques Lalevée,^c Annie-Claude Gaumont,^a and Sami Lakhdar*^a

This work describes an efficient α -phosphorylation of a wide variety of *N*-aryl tertiary amines under mild conditions. It consists of a simple combination of amines (electron donors) with *N*-ethoxy-2-methylpyridinium tetrafluoroborate (electron acceptor) in the presence of P(V)-H compounds under visible light irradiation. Physical organic investigations support the formation of an electron-donor-acceptor complex (amine/pyridinium ion) as a key intermediate.

Introduction

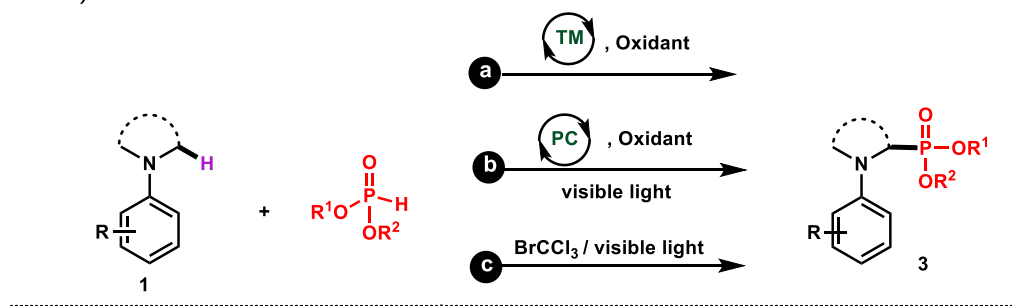
The direct and efficient α -C(sp³)-H functionalization of tertiary amines into carbon-phosphorus bonds is a challenging organic transformation that attracted much attention during the last few decades.¹ This is obviously due to the potential biological activities of α -aminophosphonates and α -aminophosphonic acids in numerous natural and pharmaceutical compounds.²

Based on the use of the well-known cross-dehydrogenative coupling (CDC) technology³ between an sp³C-H bond adjacent to a nitrogen atom of *N*-aryl amines **1** and an H-P bond, various approaches have been reported for the synthesis of α -phosphorylated amines **3**. As depicted in Scheme 1 (upper part), these methods rely on the use of transition metal catalysts (method a),^{1a-c,1i} organic- or organometallic-based photocatalysts (method b)^{1d-j} or the employment of polyhalomethanes under blue light irradiations.^{1k} It should be mentioned that Zeitler *et al.* have recently reported a visible light photocatalyst free approach for α -functionalization of tertiary amines, which has successfully been applied for carbon-carbon as well as carbon-phosphorus bonds (method c).^{1k} Detailed mechanistic studies of these different approaches revealed the intermediacy of an iminium ion, which can then be intercepted with the phosphorus nucleophiles to furnish the desired α -phosphonated amines.

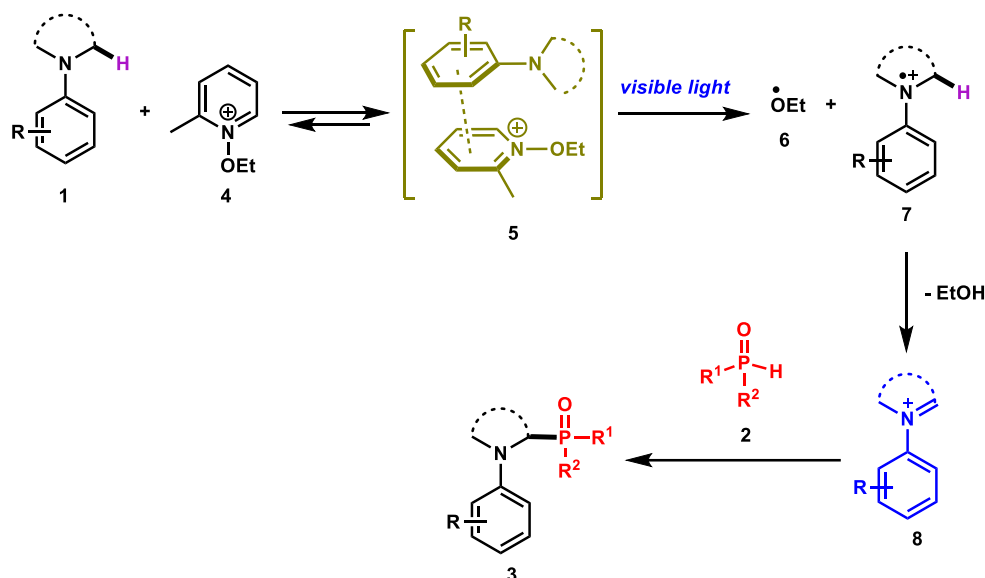
Although the efficiency of these methods, they have mainly been restricted to tetrahydroisoquinolines (THIQ) as tertiary amines and to *H*-phosphonates as phosphorus nucleophiles. For instance, secondary phosphine oxides **2** (R₁R₂P(O)H) are not compatible with many of the reaction conditions outlined above due to their low stability of in the presence of oxidants.⁴ In order to solve this synthetic issue and to provide an efficient approach for the formation of C-P bonds between *N*-aryl tertiary amines and secondary phosphine oxides, we hypothesized the working reaction mechanism depicted in Scheme 1. It consists of the association of an *N*-aryl amine **1**

with *N*-ethoxy-2-methylpyridinium tetrafluoroborate **4**,⁵ which is a well-known electron-acceptor cation, to form an electron-donor-acceptor (EDA) complex **5**.⁶

a) Previous work:



b) This work:



Scheme 1. a) Common approaches for the phosphonylation of tertiary amines. b) Our working hypothesis for the generation of iminium ions through the association of *N*-aryl tertiary amines with *N*-ethoxy-2-methylpyridinium tetrafluoroborate under visible light irradiation. TM: transition metal catalysts; PC: photocatalysts.

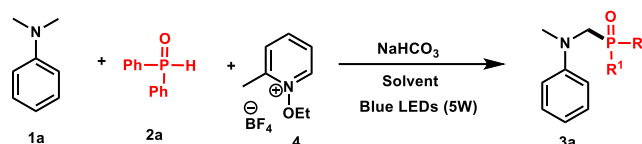
Upon visible light irradiation, a single electron transfer (SET) between both components should take place to give rise to the formation of the ethoxy radical (EtO^\bullet , **6**) along with the tertiary amine radical cation **7** (Scheme 1). Because of the very weak bond dissociation energy of the α C–H bond of the radical cation ($\text{BDE} \approx 42 \text{ kcal/mol}$),⁷ a fast hydrogen atom abstraction (HAT) occurs with EtO^\bullet to form the corresponding iminium ion **8**, which can be intercepted by secondary phosphine oxides (Scheme 1).

Results and discussion

To test this hypothesis, we started our investigation by combining *N,N*-dimethylaniline **1a** (1 equiv.) with diphenylphosphine oxide **2a** (1 equiv.) in the presence of *N*-ethoxy-2-methylpyridinium tetrafluoroborate **4** (1. equiv.) as an oxidant and NaHCO_3 (1.2 equiv.) as a base in DMF under blue light irradiation. Under these conditions, a good

conversion of **3a** has been attained by ^{31}P NMR after 24h (Table 1, entry 1, 78%). Using sodium acetate as a base (entry 2), or carrying out the reaction in the absence of a base (entry 3), gave modest 63% and 47% conversions, respectively, thus, showing the efficiency of NaHCO_3 as a base in the reaction.

Table 1. Optimization of reaction conditions.^a



Entry	Solvent	Yield of 3a , % ^b
1	DMF	78
2	DMF	63 ^c
3	DMF	47 ^d
4	CH_3CN	66
5	DMSO	75
6	MeOH	57
7	DMF	74 ^e
8	DMF	93 ^f
9	DMF	82 ^g
10	DMF	0 ^h
11	DMF	0 ⁱ

^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **4** (0.5 mmol), NaHCO_3 (0.6 mmol), solvent (4 mL), 24h. ^b NMR yields are determined from ^{31}P NMR spectroscopy, using tri-*n*-octylphosphine oxide as an internal standard. ^c Base: NaOAc . ^d No base. ^e Irradiation with white LEDs. ^f **1a** (0.5 mmol), **2a** (1 mmol), **4** (0.6 mmol), NaHCO_3 (0.6 mmol), solvent (4 mL), 24h. ^g **1a** (1 mmol), **2a** (0.5 mmol), **4** (0.6 mmol), NaHCO_3 (0.6 mmol), solvent (4 mL), 24h. ^h The reaction is protected from external light with foil and heated at 40 °C to reproduce the heat caused by the LED lamp. ⁱ No oxidant.

Although good results have been observed with acetonitrile (entry 4, 66%) and DMSO (entry 5, 75%), the conversion dropped in polar and protic solvents such as MeOH (entry 6, 57%). We furthermore tested the stoichiometry of the reactants and observed that using two equivalents of **2a** with respect to **1a** furnished 93% of **3a** (entry 8), whereas 82% of conversion was observed when an excess of **1a** was used (entry 9). We

finally confirmed the necessity of light (entry 10) and oxidant (entry 11) as no reaction took place in their absence.

With the optimized reaction conditions in hand, we next explored the scope of the process by using different *N*-aryl amines and secondary phosphine oxides.

As shown in Figure 1, various ring-substituted *N,N*-dimethylanilines carrying electron donor substituents **1b,d** can be phosphorylated in excellent yields (81-87%). The reaction proceeds also well with *N,N*-dimethyl anilines having fluoro- or bromo- groups at the *para* position of the aromatic ring **1e** (71%) and **1f** (68%), respectively. Interestingly, apart from the *N,N*-dimethylanilines, the phosphorylation worked efficiently with *N,N*-diethylaniline **1g** (76%) and THIQ **1h** (91%).

Diarylphosphine oxides bearing different groups such as *t*-Bu (**2i**), OMe (**2j**), CF₃ (**2k**) at *para* position of aromatic rings were all applicable to the coupling with 72–93% yields. The reaction of the sterically hindered di(*o*-tolyl)phosphine (**2l**) with **1a** successfully afforded the desired adduct **3l** in 74% yield. Finally, the reaction of **1a** with *H*-diethylphosphite gave the corresponding phosphonated adduct **3m** in 77%.

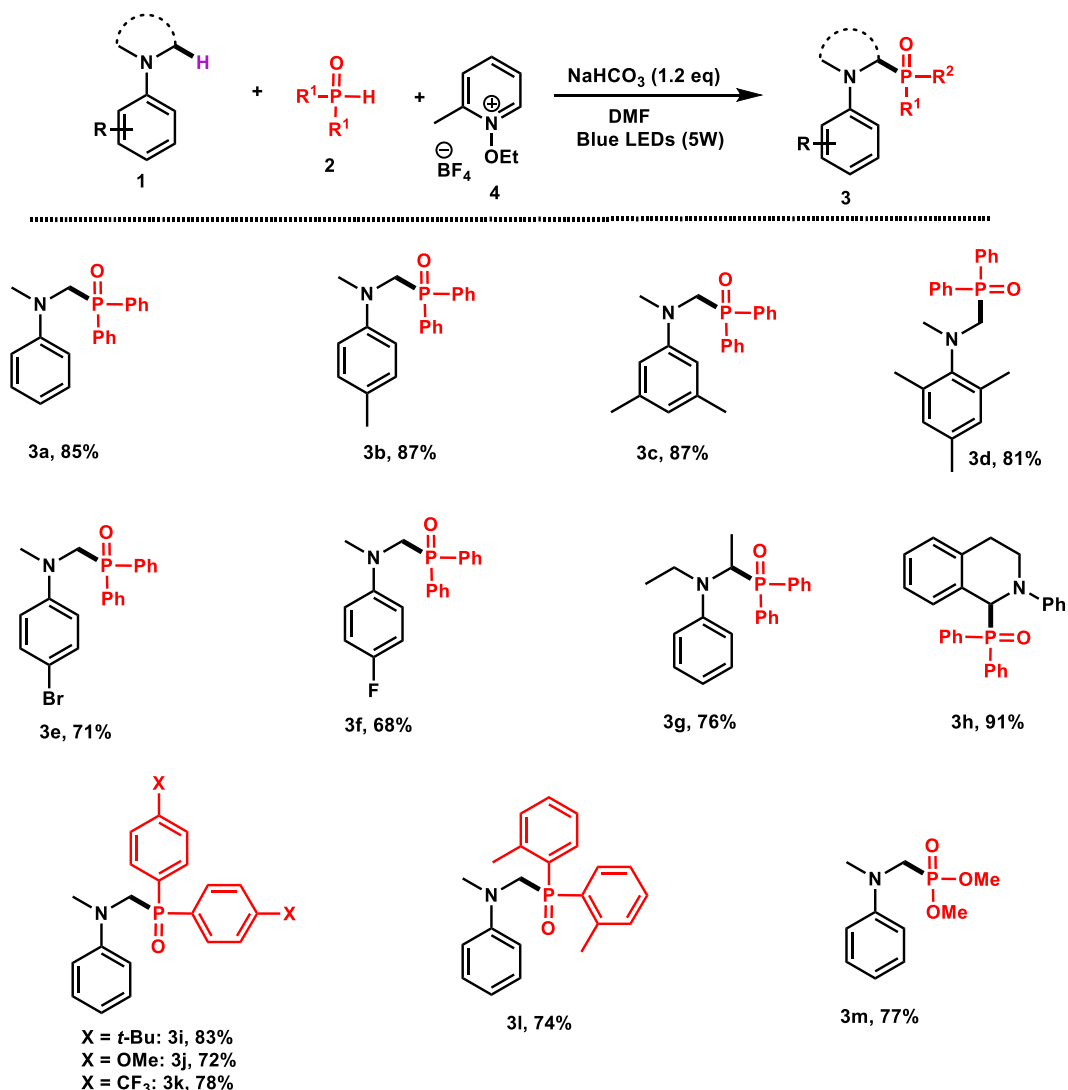


Figure 1. Scope of the reaction.

Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), **4** (0.6 mmol), NaHCO_3 (0.6 mmol), DMF (4 mL) were irradiated with blue LEDs (5W) for 24h.

Having investigated the scope of the photoreaction with different *N*-aryl amines and secondary phosphine oxides, we next turned our attention to study the mechanism of this phosphorylation reaction. As shown in Figure 2, while UV-Vis spectra of **1a** (blue) and **4** (red) in DMF are silent in the visible region, the spectrum of a mixture of both components (green) shows a bathochromic displacement above 400 nm. This new intermediate has been assigned to the formation of an EDA complex **5**.⁶ We next employed Job's method of continuous variations to determine the molar donor/acceptor ratio, which has been found to be 1:1 in DMF at 20 °C (Figure 3). Furthermore, an association constant K_{EDA} of 2.7 M^{-1} has been determined photometrically in DMF by using the Benesi-Hildebrand method (See ESI). This constant is in good agreement with those reported by Melchiorre for the EDA

complexes formed upon association of substituted 1 *H*-indoles with electron accepting benzyl and phenacyl bromides.^{6f}

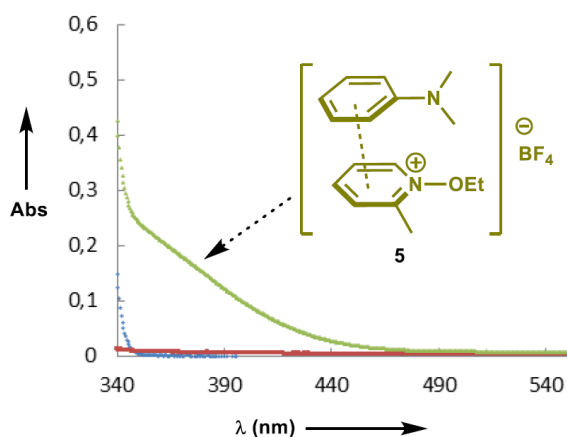


Figure 2: UV-Vis spectra of *N*-ethoxy-2-methylpyridinium tetrafluoroborate **4** ($[4] = 5 \times 10^{-2}$ M) (red); (b) *N,N*-dimethylaniline **1a** ($[1a] = 5 \times 10^{-2}$ M) (blue); a mixture of **1a** and **4** (green) in DMF at 20°C.

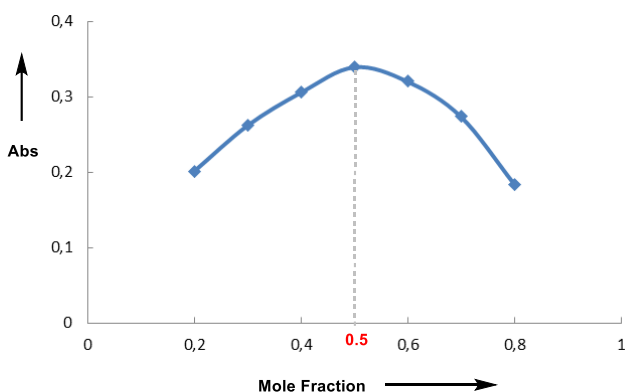


Figure 3. Job's plot for the association of **1a** and **4** in DMF at 20 °C.

Light on/off experiments of the reaction of **1a** with **2a** under the optimized reaction conditions have been conducted and revealed an interruption of the reaction progress in the absence of light, and recuperation of reactivity upon further illumination (See Figure S5, ESI). Furthermore, a quantum yield (ϕ) of 0.28 was determined, indicating that a radical chain process is presumably not operative.⁸

To characterize the nature of the radical species involved in this reaction, a spin trap EPR experiment was undertaken in the presence of *N*-tert-Butyl- α -phenylnitron (PBN) **9** as a spin trap. Interestingly the ethoxy-PBN adduct **10** was detected and the determined hyperfine coupling constants ($a_N = 13.7$ G and $a_H = 1.9$ G) was found to be in good agreement with those previously reported in the literature (Figure 4).⁵

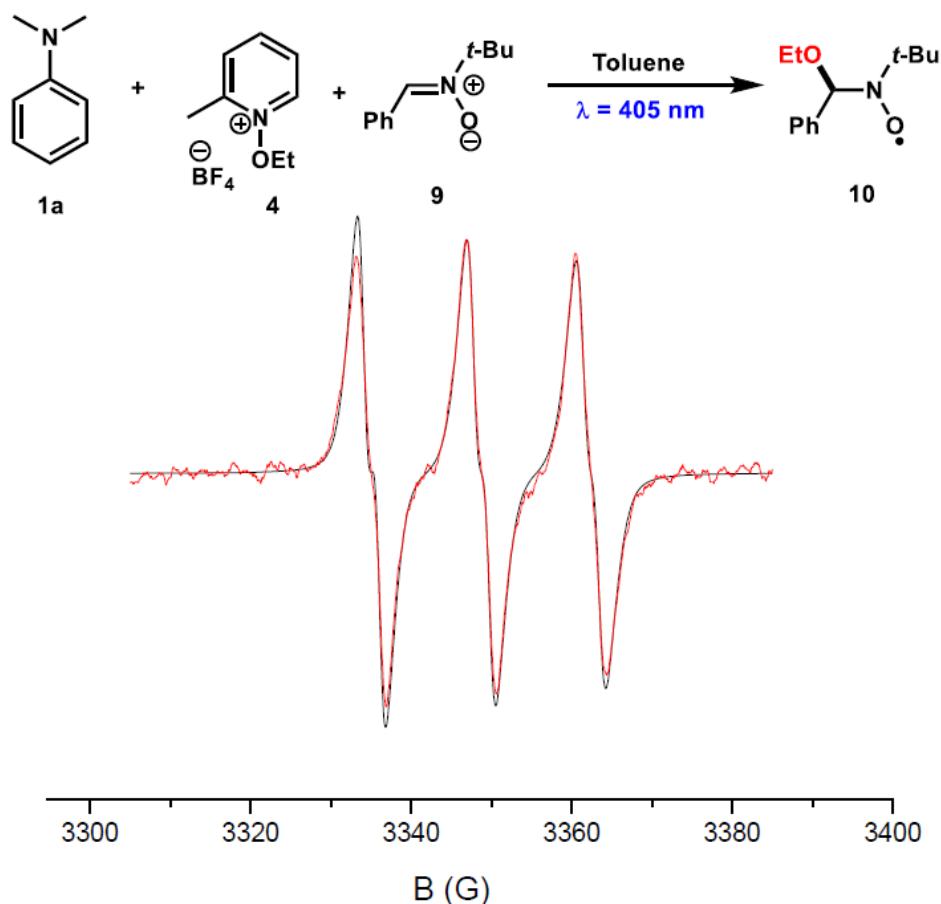
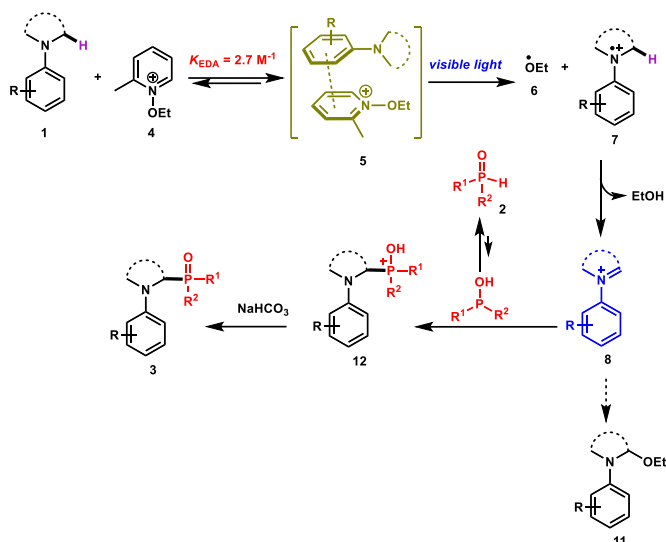


Figure 4. EPR spectra of spin adduct **10** generated in toluene from the reaction of *N,N*-dimethylaniline **1a** (1×10^{-2} M) with *N*-ethoxy-2-methylpyridinium tetrafluoroborate **4** (1×10^{-2} M) in the presence of PBN **9** (1×10^{-2} M) at 20°C.

Finally, in order to elucidate the intermediacy of the iminium ion **8** derived from *N,N*-dimethylaniline **1a**, we recorded ^1H NMR spectrum of the reaction of **1a** with **4** in CD_3CN . However, because of its high electrophilicity,⁹ it reacted with the generated ethanol to form the adduct **11** (Scheme 2). Interestingly, when THIQ (**1h**) was used instead of **1a**, the corresponding iminium ion was detected by NMR spectroscopy. Based on these physical organic investigations, a reaction mechanism is proposed (Scheme 2). The reaction starts with the association of the amine (electron donor) **1** with the pyridinium salt **4** to form an EDA complex **5**. After visible light irradiation, a single electron transfer takes place to generate the ethoxy radical (**6**) and the aminium radical cation **7**. A fast hydrogen atom abstraction takes place to generate the iminium ion **8** that reacts with the diarylphosphine oxide (P(III) tautomer) to form the phosphonium ion **12**. The deprotonation of the latter with a base yields the desired product **3**.



Scheme 2. Proposed reaction mechanism.

Conclusion

In conclusion, we have developed a metal-free, visible-light-induced method for the phosphorylation of *N*-aryl amines **1** with secondary phosphine oxides **2**. The reaction proceeds under mild, catalyst-free conditions. Key to the success of the reaction was the formation of EDA complexes between the amines **1** and the electron-deficient pyridinium **4**. The proposed reaction mechanism was supported by detailed mechanistic investigations, including spectrophotometry, NMR spectroscopy and EPR spectroscopy. We anticipate that this operationally simple approach should be amenable with other nucleophiles to synthesize various α -functionalized amines.

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