Unlocking Novel P-Containing Scaffolds by Exploration of a Photocatalyzed Halogen-Bonding-Assisted EDA-SET Reaction.

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ABSTRACT: The synthesis of new heterocyclic structures is a challenging endeavor in organic chemistry. It requires the development of innovative methods that can generate novel frameworks, thereby allowing exploration of uncharted chemical spaces for potential applications. In this context, Halogen-Bonding-Assisted EDA-SET strategy presents a promising and efficient approach. In our study, we propose employing this strategy to facilitate the exploration of diverse phosphorus-based scaffolds, which hold significant potential for future research endeavors. By leveraging the EDA strategy, we aim to unlock new opportunities and advance the field of phosphorus-based chemistry.

Synthesis of uncommon heterocycles in order to reach new promising scaffolds and potent drugs, OLEDs or agrochemicals remains a big challenge in organic synthesis. In addition, it is important to explore new chemical spaces using innovative synthetic methods. For instance, compounds **I**, **II** and **III** present some remarkable photophysical properties, thus attracting chemists to study their synthesis.[1,2] However, synthetic pathways remain scarce,[3–8] encouraging us to design a new and efficient synthetic strategy, particularly towards industrial development. Here, we propose the access to new phosphorous containing scaffolds which have interesting applications for OLEDs development (figure 1). For this purpose, we have developed a novel visible light EDA catalysis as a promising and unexplored strategy.

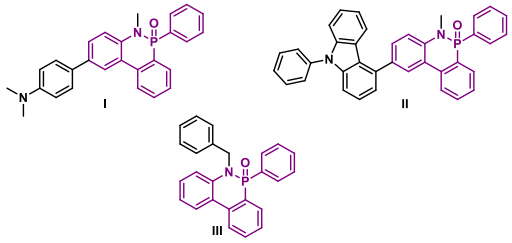
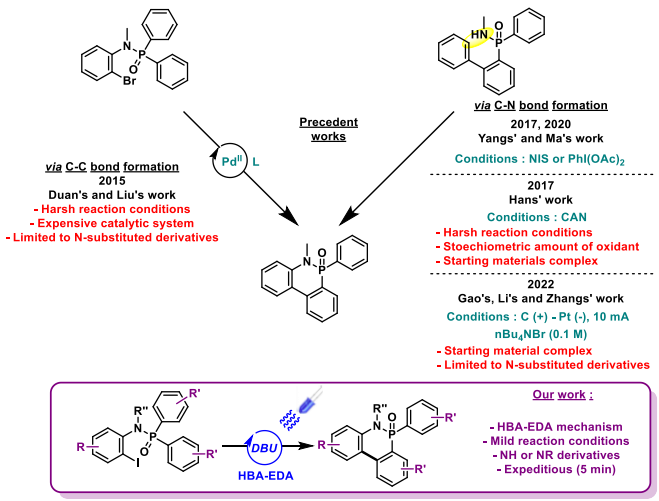


Figure 1. Examples of phosphinamides in OLEDs or in chiral atropoisomeric ligands

In order to access to these fascinating phophorous-based scaffolds, some methods have been reported in the literature describing, for example, to the use of transition metals (scheme 1). Duan, Liu and Ma reported a C-H activation strategy to build such scaffolds.[5,8] In these strategies, a C-C bond is formed between the aniline moiety and one phenyl bearing the P-containing function. Despite dissymmetrical possibilities, the use of harsh and expensive conditions may limit its field of application. In addition, several strategies, reported in the literature, consist in the formation of C-N bond thanks to the use of NIS, DBH, iodonium salts, iodine or CAN, however these methods remain limited to the use of stoichiometric amount of oxidant.[3,4,6] Moreover, synthesis of starting materials remains a major negative constraining point due to different substituants on phosphorous atom. Electrochemistry was also proposed for the C-N bond formation but remains limited for its versatility and moreover requires specific apparatus.[7]

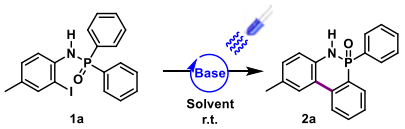


Scheme 1. Our proposed photoinduced strategy towards phosphinamide synthesis.

It is important to note that, in all these reported methods, nitrogen atom has to be substituted to make these reactions possible. This issue could also be detrimental for a wide investigation of such type of derivatives. Based on these observations, we thus propose a hitherto unreported route to build the C-C bond using only visible-light and an inexpensive base (DBU). This proposal takes benefit from recent development in halogen bonding strategy to allow an electron transfer from DBU to halogen residue.[9–17] Visible light proved to be an interesting synthetic strategy[18–22] because of several advantages such as: mild approaches since the energy is only coming from a light bulb, new mechanisms and molecules resulting from non-conventional retrosynthetic pathways which can be illustrated by HAT[23], PCET[24] or EDA_S strategies[25–27], for example. In our continuing effort, we aimed to build exotic scaffolds bearing phosphoramidates or thiophosphoramidates functions, which remain undeveloped, through the formation of a possible EDA complex.

Developing chemical methods, that are able to use light and undertake chemical processes, without the need of photocatalysts, appears to be an attractive strategy to build important and several bonds in a one pot manner. Towards this goal, several strategies have been previously settled by numerous groups indicating each possibility.[28]

Table 1. Optimization of the reaction conditions[a]



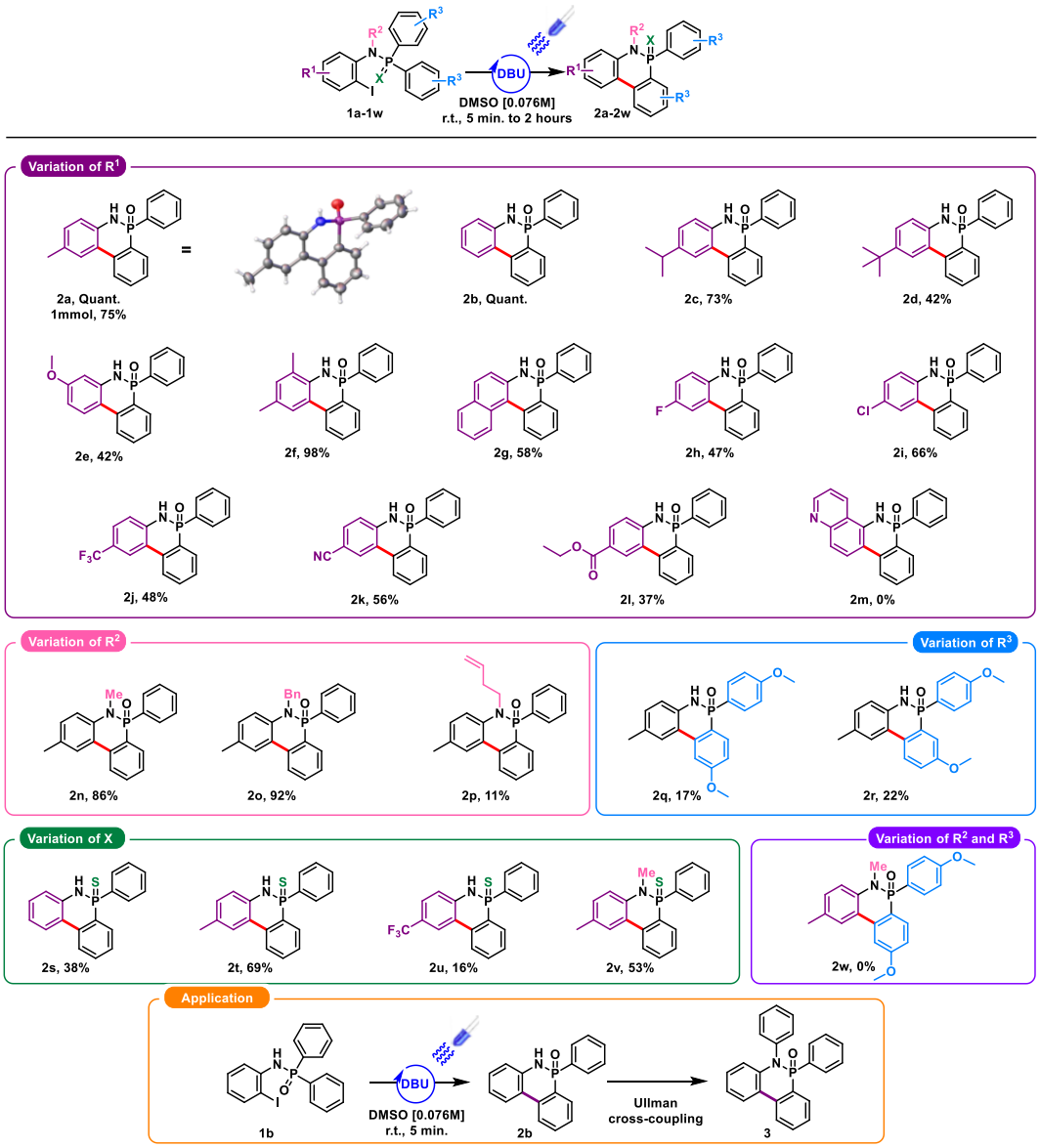
Entry	Conditions[a]	Yield (%)[b]
1	Et_3N, DMSO	46
2	DIPA, DMSO	0
3	DIPEA, DMSO	8
4	KOH, DMSO	37
5	NaH, DMSO	49
6	**DBU, DMSO**	**Quantitative**[c]
7	DBU, MeCN	70
8	DBU, Toluene	89
9	DBU, Acetone	52
10	DBU, EtOH	11
11	DBU, DMSO [0.038M]	70
12	DBU, DMSO, in dark	0
13	Without DBU, DMSO	0

[a] To an oven-dried sealable glass vial were added diphenylphosphonic amide (1 equiv.) and Base (2 equiv.) in solvent (2.1 mL/0.16 mmol) under air atmosphere. The vials were sealed with 20 mm crimp caps and put under 450 nm irradiation at 20°C. After completion of the reaction, the mixture was purified by silica gel column chromatography. [b] Isolated yields. See the complete table in the ESI. [c] The same result was observed under argon atmosphere.

In this study, we report an unprecedented intermolecular HBA-EDA (Halogen Bonding Assisted – Electron Donor Acceptor) between a nitrogen and a halogen *via* a Charge Transfer interaction allowing access to dibenzoazaphosphininoxide. Such derivatives may give access to OLEDs and new pharmacophores for therapeutic

applications. We started our optimization study with the evaluation of the nature of the base, using *N*-(2-iodo-4-methylphenyl)-*P*,*P*-diphenylphosphinic amide as a model substrate. With the use of the base Et_3N, (Table 1, entry 1), we were delighted to observe the desired cyclized product was obtained in a 46% yield. Encouraged by this result supporting our hypothesized EDA we investigate several bases. Secondary amine base such as DIPA (Table 1, entry 2) or tertiary amine base such as DIPEA (Table 1, entry 3) decreased the yield. Among other bases (see ESI), KOH and NaH resulted in a lower yield with respectively 37% and 49% (Table 1, entries 4 and 5). As part of the ongoing optimization, we evaluated DBU and we were delighted to obtain a quantitative yield in DMSO. We switched then our optimization to the modification of the solvent, in order to study its impact on the reaction. Most of the used solvents led to a decrease in the final yield: for example, ACN, Toluene, Acetone and EtOH gave 70%, 89%, 52% and 11% respectively (Table 1, entries 7, 8, 9 and 10). In addition, the reduction of the reactant's concentration lowered the final yield to 70% (Table 1, entry 11). Finally, the reaction didn't occur without light and without base (Table 1, entries 12 and 13). Reaction time was also assessed (see S.I.), starting from overnight time, we finally found that only 5 minutes are required to reach a quantitative yield of **2a**. In consequence, we established the best reaction conditions using diphenylphosphonic amide (1 equiv.) and DBU (2 equiv.) in DMSO (0.076 mmol/mL), under 450 nm irradiation during 5 minutes at 20°C under air atmosphere.

With these best conditions in hand, we investigated the substrate scope of the reaction. Gratefully, this reaction occurs with a variety of substituted compounds to obtain the desired final products with good yields (compounds **2a**–**2x**). The first modification has been made on the aniline entity of the substrate (Scheme 2, R^1). We were pleased to observe a quantitative yield with the non-substituted aniline substrate (compound **2b**). Alkyl groups have been selected and good yields were obtained; indeed, isopropyl and tert-butyl groups (compounds **2c**–**2d**) gave respectively 73% and 42% final yields. Meta substitution with a methoxy group was also possible to give **2e** in a 42% yield. In addition, the presence of an additional methyl in the ortho-position of the aniline substrate did not affect the yield of the reaction, giving rise to 98% of the desired compound **2f**. A final compound containing a naphthalene substrate was also efficiently synthesized to furnish **2g** with 58% yield. Then, we evaluated the efficacy of the reaction outcome with several electron-withdrawing groups such as halogens, trifluoromethyl cyano or ester groups. Indeed, fluoride and chloride in *para* position gave respectively 47% and 66% yields (compounds **2h** and **2i**). The presence of a trifluoromethyl, a nitrile and an ester group in *para* position conducted respectively to compound **2j** in 48%, to compound **2k** in 56% and compound **2l** in 37% yield. The presence of a heterocycle was also investigated for instance in compound **2m** bearing a quinoline, however the targeted product was not formed with no consumption of the starting material.



Scheme 2. Scope of the reaction

Secondly, we evaluated the scope's expansion while modifying the phosphinamide substitution (Scheme 2, R^2). In consequence, the nitrogen was functionalized by a methyl or a benzyl group conducting to compound **2n** in 86% yield and compound **2o** in 92% yield. A butene substitution was also proposed in this step, however we observed a low 11% yield of the desired product **2p** due to a plethora of side products certainly coming from radical trapping by this unsaturated moiety (see S.I.). Additionally, the presence of a methoxy in *para* position of the phenyl groups substituting the phosphorus atom was studied (Scheme 2, R^3). The desired compound **2q** was obtained with 17% yield. However, we were able to characterize a rearrangement product (compound **2r**) with 22% yield. This specific rearrangement will be explained in the mechanistic studies part. Finally, thiophosphinamide derivatives have been evaluated (compounds **2s**-**2v**). Compounds bearing non-functionalized aniline, methyl and trifluoromethyl groups gave 16 to 69 % yields (compounds **2s**-**2u**). The reaction on *N*-methylthiophosphinamidate conducted to 53% isolated yield of the desired product **2v**. Finally, compound **1w** with substitutions on R^2 and R^3 was inefficient in our reaction conditions.

In order to apply our method to attracting scaffolds, we performed the synthesis of compound **3** recognized as a promising OLED derivative. To do so, an Ullmann cross-coupling reaction[29–31] was achieved on **2b** affording **3** with a two-steps 25% yield.

MECHANISTIC STUDIES

To gain insight of implied mechanisms, we undertook several experiments. First of all, UV-Visible absorbance studies were conducted (Figure 2), showing that our starting material (SM compound **1a**, pink curve) and DBU (blue curve) absorb in the UV area. However, when both compounds are mixed (SM (**1a**) +DBU, green and purple curves), a bathochromic shift is observed. This red shift was also observed while using NaH as base (SM (**1a**) + NaH, yellow

curve) confirming that both purple and yellow curves correspond to the deprotonated substrate that can absorb at 455 nm, which is our working wavelength. It is worth to note that our substrate **1a** could also absorb at 390 nm. Thus, we have conducted the reaction on both N-H and N-Me substrates at this 390 nm wavelength in the absence of DBU (Scheme 4). Interestingly, the desired product was indeed formed with a 15% NMR yield. Consequently, we hypothesized that our substrate can undergo the reaction thanks to its excitation under irradiation at 390 nm and with DBU at 455 nm.

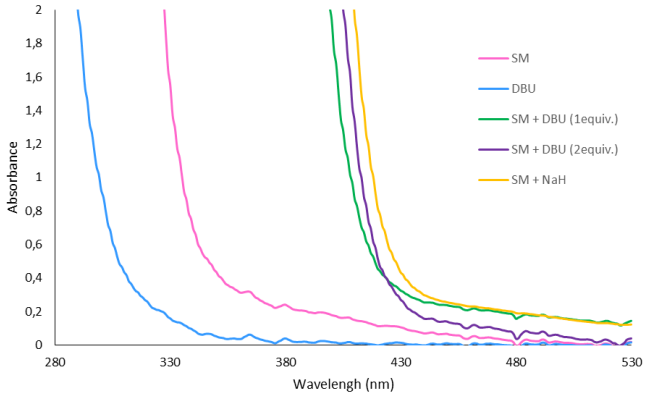
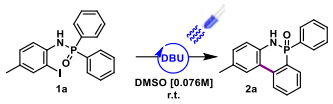


Figure 2. Absorption spectra of the solution of the starting material with and without base (DBU and NaH).

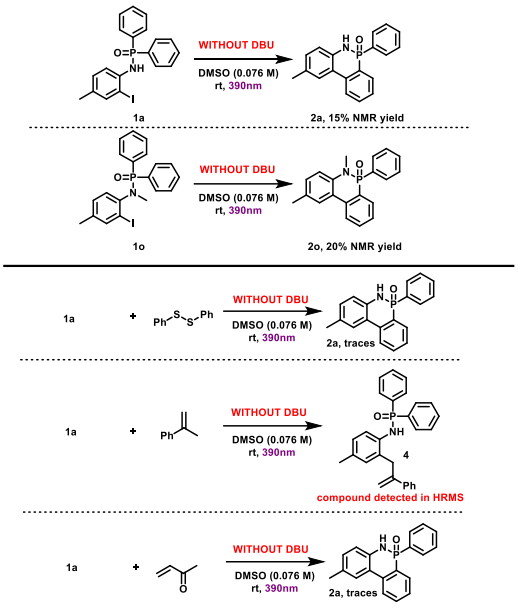
To confirm this hypothesis, we decided to launch reactions with an energy acceptor reagent, such as anthracene reagent, known to quench the energy involved in photoredox processes.[32] Several reactions with different equivalents of anthracene were evaluated (Table 2). The addition of 0.5 equiv. of anthracene lowered the reaction yield to 32% (Table 2, entry 2); when more equivalents were added, the final yield decreased drastically (Table 2, entry 3-5). Thus, we confirm the proposal of the excitation of our deprotonated substrate, which may certainly initiate the reaction.



Entry	Equivalent of Anthracene[a]	NMR Yield (%)
1	0	Quantitative
2	0.5	32
3	1	30
4	2.5	24
5	5	9

Table 2. Yields obtained with anthracene addition to the reaction media.

Mechanistic studies continued by radical trapping experiments in order to determine the implication of a radical in the mechanism. Several trapping reactions were launched with different partners such as TEMPO, diphenyl disulfide or *alpha*-methylstyrene (Scheme 3). These experiments were either ran with DBU under 455 nm irradiation or without DBU under 390 nm irradiation. These reactions showed only traces of our desired cyclized product. Moreover, when conducted with the *alpha*-methylstyrene in absence of DBU and under 390 nm irradiation, a radical adduct was detected by HMRS (compound **4**) thus, confirming the presence of a radical that would correspond to the carbon-iodide bond cleavage.



Scheme 3. Radical trapping reactions

To understand the mechanism, we proceeded DFT calculations on critical points. The results are summarized in Figure 3. Starting from the radical anion **A** obtained after proton abstraction from DBU and photoexcitation, a conformational reorganization was first found (**TS_AB**) which leads to an intermediate **B** where the radical is nicely positioned to attack the other phenyl ring. Two possible elementary steps are emerging from **B**: either an attack on one of the ortho carbon (**TS_BC**) or an attack on the ipso carbon of the phenyl ring (**TS_BD**). Both attacks are relatively low in energy, respectively 6.27 kcal.mol-1 and 5.43 kcal.mol-1 and are thus in competition at the considered temperature (298K). From product **D**, two other steps are necessary to reach the observed product: first, a bond breaking between the phosphorus and the ipso carbon (**TS_DE**), small barrier of 2.53 kcal.mol-1) followed by an attack of the radical localized on the phosphorus towards an ortho carbon with a barrier of 6.87 kcal.mol-1 (**TS_EF**). It means that both ways are viable in solution and leads to the same product after rearomatization. This proposed way is corroborated by our results observed on products **2r** and **2s**.

To go further and add experimental proof for a radical mechanism, EPR studies have been conducted. The 450 nm irradiation of an oxygen-free mixture of SM **1a** and DBU in the presence of a large excess of PBN led to the generation of a complex EPR signal with over five- to ten-fold higher intensity than that observed in controls without SM **1a** or DBU (Figure 4). The high PBN/SM **1a** ratio required to detect radicals is consistent with a competition of the spin trapping reaction with an intramolecular radical process. The simulation best fit was calculated as the superimposition of four individual signals. The most informative feature, a doublet of triplet of doublets, characterized by a_N = 1.419 mT, a_H = 0.243 mT, a_P = 2.285 mT; g = 2.0059, is compatible with the formation of a phosphorus-centered radical PBN-adduct [33], which confirms the proposed ipso attack mechanism (Scheme 4). The second signal (*i.e.*, a_N = 1.366 mT, a_H = 0.200 mT; g = 2.0061) is assigned to a carbon-centered radical PBN-adduct, derivated from SM **1a** and was present in the control without DBU (Figure 5A, Scheme 5).

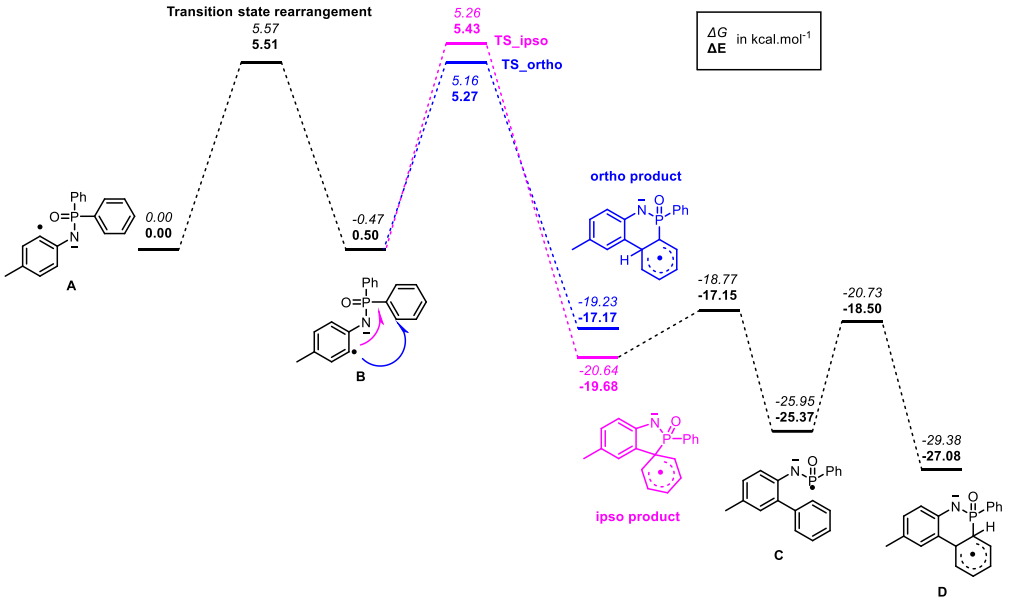


Figure 3. DFT energetic profile, calculated at the B3LYP-D3/def2-SV(P) level.

The third component is attributed to a carbon-centered radical PBN-adduct derived from DBU and was present in the control without SM **1a** (*i.e.*, a_N = 1.354 mT, a_H = 0.170 mT; g = 2.0061) (Figure 5B, scheme 5). The last component is likely an artefact caused by the dispropotionation of PBN adducts leading to a nitrone and a hydroxylamine. The nitrone product can in turn trap another radical leading to a triplet EPR signal (*i.e.*, a_N = 1.659 mT; g = 2.0059) (Figure 4, scheme5).

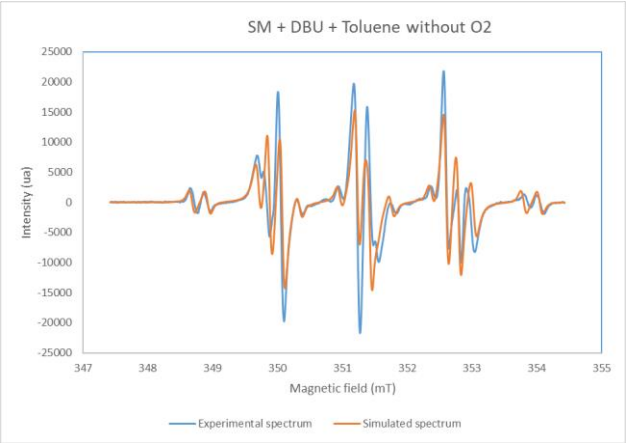
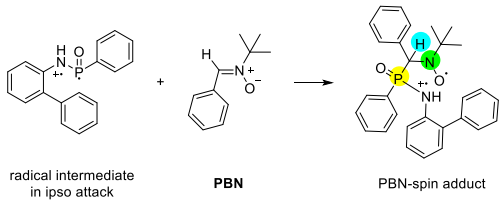
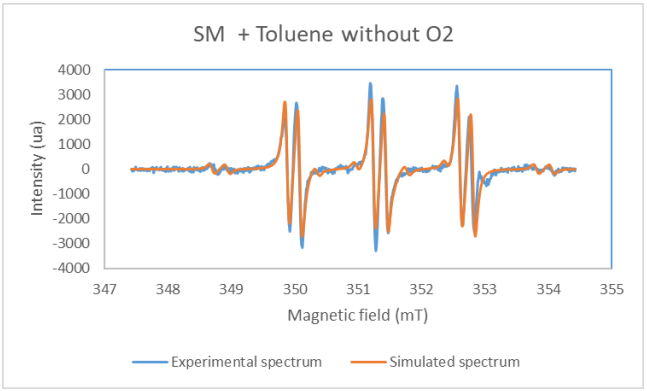


Figure 4: Experimental (orange line) and calculated (blue line) EPR spectra obtained at 21°C in toluene under argon with a mixture of SM **1a** (80 mM), DBU (160 mM, 2 equivalents), and PBN (200 mM, 2.5 equivalents) after 1 h irradiation at 450 nm. Three components were taken into account in the simulation: A) a phosphorus-centred radical spin adduct, B) a carbon-centred radical spin adduct, and C) a spin adduct corresponding to double addition of a radical on PBN.



Scheme 4: Formation of phosphorus-centred radical spin adduct of PBN. The spin of the unpaired electron of the nitroxide spin adduct couples to nearby non-zero nuclear spins, i.e. nitrogen nucleus (I = 1), proton (I = 1/2) and phosphorus (I = ½), which leads to the splitting of the EPR line.

A



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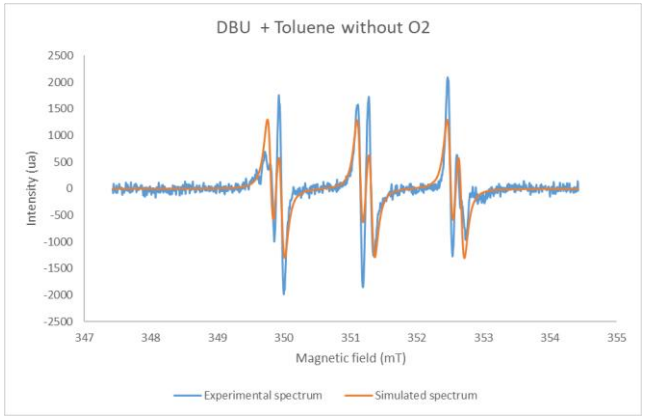
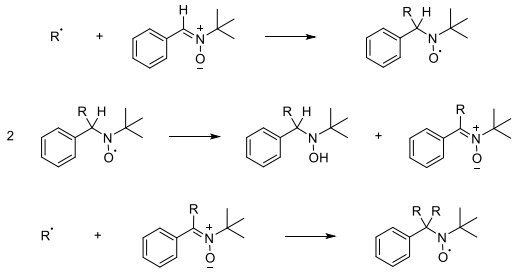


Figure 5: Experimental (orange line) and calculated (blue line) EPR spectra obtained after 1 h irradiation at 450 nm at 21°C in toluene under argon with a mixture of **(A)** SM **1a** (80 mM) and PBN (200 mM, 2.5 equivalents) or **(B)** DBU (160 mM, 2 equivalents) and PBN (200 mM, 2.5 equivalents).



Scheme 5: Artefactual formation of nitroxide spin adducts characterized by a triplet spectrum.

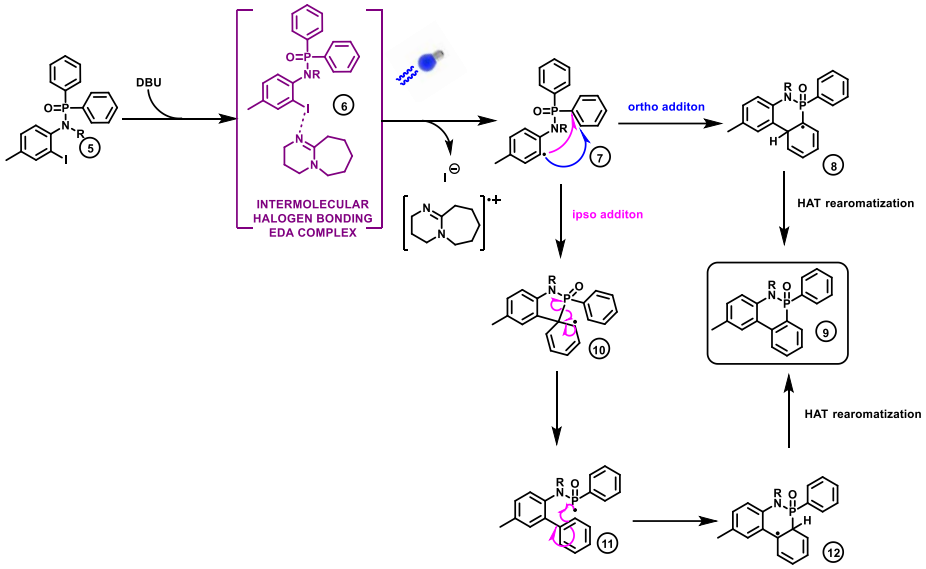
The irradiation at 450 nm of the argon-purged mixture of SM **1a** and PBN alone produced a five-to-six-fold lower intensity EPR signal (Figure 4A), compatible with the formation a carbon-centered radical PBN adduct together with very weak traces of phosphorus-centered radical PBN-adduct, which confirmed that the reaction proceeds much more slowly in the absence of DBU.

After all of these mechanistic studies, we were able to propose a plausible mechanism for the proposed reaction (Scheme 7). The substrate **5** is able to be associated to the DBU through a halogen bond, to obtain an EDA complex able to absorb visible light. Once the reaction mixture is placed under blue light at 455 nm, the substrate **6** is self-excited by light, allowing thus the carbon-iodide bond cleavage and a carbon radical formation through a single electron transfer event (substrate **7**). Then, two intramolecular cyclization can occur. On one hand, thanks to a pseudo-Michael radical addition on one aromatic of the phosphinamide. This cyclization allows the C-C bond formation to form a 6-membered ring cycle (compound **8**). The rearomatization of compound **8** thanks to a HAT process can then allow the release of the final product **9**. On the other hand, intermediate **7** may evolve through an *ipso*-addition on the carbon bearing the phosphorous function to generate the intermediate **10**. Rearomatization of the benzene ring would drive the formation of the P-centered radical intermediate **11**. Then a favorable radical addition on the introduced benzene ring can occur to form the radical on 6-membered heterocycle **12**. Final step of HAT event would release the obtained product **9**.

CONCLUSIONS

To summarize, we have developed a novel, gentle, efficient and expeditious method for synthesizing phosphinamides with various substitutions. This undeveloped strategy proceeds through a specific Single Electron Transfer induced by an Electron Donating Accepting complex formed though a Halogen Bond-Assisted interaction. Mechanistic experiments

suggest an intermolecular interaction allowing an effective C-C bond formation without the need of any additional photocatalyst, metallic catalysis or thermal activation. Of importance, empowering EPR experiments supported by DFT calculations proved the presence of carbon and phosphorous radicals allowing us to clearly elucidate the mechanistic pathways of the reaction. Interestingly, we have been able to clarify two reaction pathways, based on *ortho* or *ipso* attack on an intermediate, invisible in most cases but leading to two regioisomers upon the presence of specific substitution patterns. In addition, mild conditions developed allow the use of protected and unprotected phosphinamides, uncovering the easy access of new cyclic phosphinamides. This protocol has been successfully applied to the synthesis of a known OLED as an attractive application of our strategy for future development in a such highly important domain.



Scheme 7. Proposed mechanism

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

HBA: Halogen Bond Assisted
XAT: Halogen-Atom Transfer
EDA: Electron Donating Acceptor
SET: Single Electron Transfer
DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

REFERENCES

(Word Style "TF_References_Section"). References are placed at the end of the manuscript. Authors are responsible for the accuracy and completeness of all references. Examples of the recommended formats for the various reference types can be found at http://pubs.acs.org/page/4authors/index.html. Detailed information on reference style can be found in The ACS Style Guide, available from Oxford Press.

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