Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.202000018

Link to VoR: http://dx.doi.org/10.1002/adsc.202000018

10.1002/adsc.202000018

Very Important Publication

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Phosphoramidates as Transient Precursors of Nitrogen-Centered Radical Under Visible-Light Irradiation: Application to the Synthesis of Phthalazine Derivatives.

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Phosphoramidates are for the first time presented as efficient N-Centered Radical (NCR) precursors under visible light irradiation. More precisely among this class of phosphorus-derived compounds, we studied the radical reactivity of phosphonohydrazones, under mild reaction conditions, which allowed the synthesis of a wide and diversified library of the scarcely reported phthalazine scaffold. Mechanistic investigations confirmed the formation of a NCR from these brand-new phosphonohydrazones (derivatived from phosphoramidates), which were further engaged in an intramolecular 6-*exo*-dig cyclization to provide phthalazines. Compared to other pre-activated moieties, the phosphoramidate group is self-immolative thus enhancing its attractiveness for the C-N bond formation.

Keywords: Nitrogen Centered Radical; Photocatalysis; Traceless Nitrogen Activator; Phthalazines

Introduction

Carbon-nitrogen bond is certainly one of the most important chemical link due to its prevalence in many useful compounds such as pharmaceuticals and agrochemicals for instance.[1] Chemists have thus deployed a wide variety of methods to efficiently build this bond. Nowadays, thanks to transition metals, a plethora of structures are accessible and easier to synthesize. We may cite as representative reactions: the Ullmann-Goldberg reaction, the Buchwald-Hartwig cross-coupling or the Chan-Evans-Lam reaction.[2–5] These reactions, particularly efficient, are widely applicable to a variety of substrates. Despites tremendous improvements brought by these methods and others to build the C-N bond some structures are still inaccessible, difficult to make or scarcely investigated, such as phthalazines and their derivatives.[6] Moreover, depletion of rare metals on earth and global warming effect led to find alternative strategies to transition metal catalysis.
To this end, the recent regain of interest in the literature for visible-light catalysis, although described a century ago,[7-8] appeared as an alternative strategy to build bonds and particularly the C-N bond.[9–16] Indeed, several reactivity pathways are possible: reductive or oxidative quenching mechanism but also the Proton Coupled Electron Transfer strategy (PCET).[17] Many improvements have been done using these ideas but still remain limited due to the youth of these approaches. The investigation of these strategies is thus highly needed. Hence, our laboratory is involved in the development of new precursors to generate Nitrogen Centered Radicals (NCR) since they could be the key step to create the CN bond.[18,19] In this perspective, the less investigated oxidative pathway is privileged in our research developments and has already been successfully applied on an interesting hydroamination/Smiles rearrangement cascade.[20]

Sulfonohydroxylamines,[21] sulfonohydrazones[22] or benzoylhydroxylamines[23] have recently been described as efficient precursors to generate NCRs via an oxidative quench of an *in situ* generated anion specie (N^-). Thanks to this approach, several cyclization modes (5-*endo*, 6-*exo*) and heterocyclic structures could be reached such as pyrazoles, phthalazines, tetrahydropyridazines or isoquinolones.[20-22] Despite these efforts, the search for new NCR precursors is still requested in order to improve the C-N bond formation *via* the oxidative quenching strategy. In all previous cases, the NCR is stabilized by an α-sulfonyl- or a benzoyl- group, which after cyclization imposes an additional step in order to remove what remains of the pre-activated moiety. This

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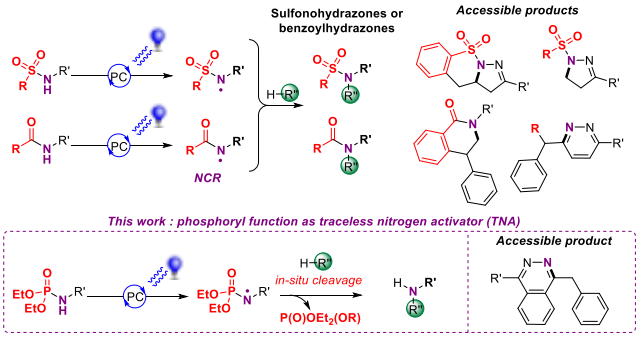
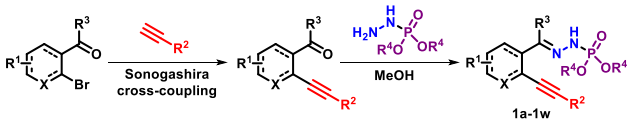
final step is thus time-consuming or sometimes difficult to operate. It appears particularly important to find new precursors which can be easily accessible, that can readily furnish the reactive NCR and which can be easily cleavable at the end of the reaction. Therefore, we focused our attention on the development of a new kind of NCR precursor based on the phosphoramidate scaffold. We ambitioned that this function would be able to stabilize a radical on the nitrogen next to the phosphorus atom and could be further engaged in a radical reaction. In addition, we postulated that this group could be cleaved *in situ* at the end of the reaction.[24] Our phosphorous derivative (phosphonohydrazone) could be thus envisaged as a traceless nitrogen activator (TNA) which is a new concept, in order to generate the NCR and further yield the carbon-nitrogen bond. Moreover, in this work, we were interested in reporting NCR cyclization on alkynyls groups which remains scarce in the literature.[9] Thus, we proposed to study the intramolecular cyclization of phosphonohydrazones on alkynes *via* a 6-*exo*-dig cyclization mode.



Scheme 1. N-centered radical synthesis via an oxidative quenching of the N-based anion.

Results and Discussion

To experiment our hypothesis, we proposed to evaluate the intramolecular cyclisation of a NCR, generated on a phosphonohydrazone unit, on an alkynyl group. This reaction will give us a straightforward method to build the phthalazine scaffold. Starting from this idea, we synthesized compound **1a** using a Sonogashira cross-coupling to obtain the 2-(arylethynyl)benzaldehyde substrates (see SI, and Scheme 2). Then, the previous aldehyde-containing derivatives are combined with phosphonohydrazine substrates (see SI), leading to the formation of phosphonohydrazones **1a-1x**. Interestingly, phosphonohydrazines are easily formed from the corresponding phosphite and hydrazine[25] or from the diarylphosphinic chloride reacted with hydrazine.[26]

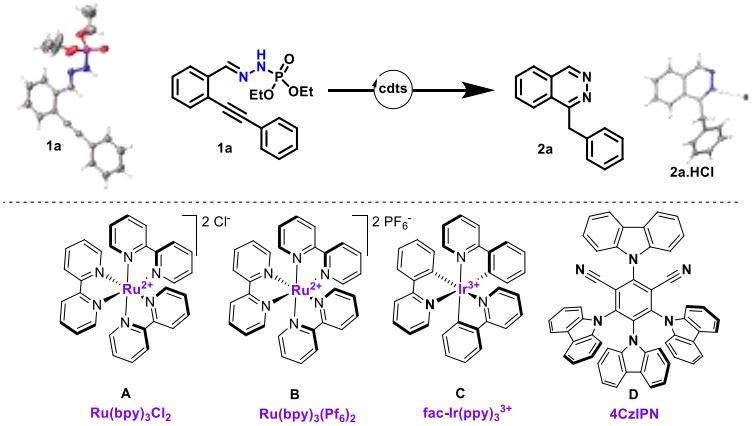


Scheme 2. Synthesis of the starting material.

With the starting material **1a** in hand (XRD obtained, see SI and Table 1), we performed an extensive optimization of photoredox conditions. We started first with our previously reported conditions to generate a NCR from tosylhydrazones ($Ru(bpy)_3Cl_2.6H_2O$, 1.5 equiv. of NaOH in EtOH).[20] We were pleased to find that the expected product **2a** was formed in an encouraging isolated yield of 28% (Table 1, entry 1). This last compound (**2a)** has been successfully crystallized as its hydrochloride salt and its structure was definitely confirmed by XRD (Table 1 and SI). Interestingly, the final phthalazine product **2a** had no longer the phosphoramidate function incorporated which was confirming our hypothesis for the TNA strategy. We further improved the reaction conditions by modifying at first the nature of the photocatalyst. We focused our attention on catalysts prone to perform a reductive quenching as proposed in the reaction mechanism (i.e. with a compatible oxidation potential, see C.V.). Therefore, $Ir(ppy)_3$, 4-CzIPN or $Ru(bpy)_3(PF_6)_2$ were tested and led to **2a** in 35%, 24% and 43% yield respectively (Table 1, entry 2, 3 and 4). $Ru(bpy)_3(PF_6)_2$ was thus found to be the best catalyst tested and was selected to evaluate then the influence of the base (3 equivalents). We found that alkoxide or hydroxide bases such as NaOH, $Me_3(Bn)NOH$ (Triton B) or tBuONa gave the best results with an isolated yield of 43%, 23% and 51% respectively for **2a** (Table 1, entry 4, 5 and 6). Several organic bases (pyridine), carbonate bases (K_2CO_3) or phosphate base (K_3PO_4) have been tested but gave lower yields (See SI). The concentration of the reaction mixture appears to be an important factor. Indeed, by diminishing the concentration from 0.075 M to 0.0375 M, we observed no formation of the desired product **2a** with a slight degradation of the starting material (Table 1, entry 7). *A contrario*, increasing the concentration to 0.300 M provided an isolated yield of **2a** of 52% (Table 1, entry 8). The influence of the solvent of the reaction was also investigated and we concluded that protic solvents were the most efficient for this reaction. Indeed, PEG300 or MeOH gave respectively 49 % and 58 % yields of **2a**. Several other solvents such as DMSO, THF, toluene or acetonitrile gave trace of products (See SI). Any other modifications did not improve the yield of the reaction despite extensive effort (see SI for all details). Finally, control experiments without light, base and catalyst lead to no conversion of the starting material confirming the photoinduced nature of this reaction (Table 1, entry 11 and 12). We selected as the best reaction conditions: $Ru(bpy)_3(PF_6)_2$ (2.5 mol %, 7.5 µmol), *t*BuONa (3 equiv) in MeOH (0.3 M) irradiated with blue LED for 16 h. With these best

conditions in hand, we then investigated the scope of the reaction. We first investigated several substitutions on the pendant alkynyl group (Table 2, red modifications). In order to perform this study, several starting materials with aromatic patterns were synthesized. Electron-donating substitutions were investigated and we were pleased to see that with our conditions we were able to furnish the desired products with good yields (47-70%).

Table 1. Optimization table.



Entry	Catalyst	Base (3 equiv)	Solvent (M)	Yield[b]
1	**A** (2,5 mol%)	NaOH	EtOH (0.075 M)	28 %
2	**C** (2,5 mol%)	NaOH	EtOH (0.075 M)	35 %
3	**D** (5 mol%)	NaOH	EtOH (0.075 M)	24 %
4	**B (2,5 mol%)**	NaOH	EtOH (0.075 M)	43 %
5	B (2,5 mol%)	Triton B	EtOH (0.075 M)	23 %
6	B (2,5 mol%)	**tBuONa**	EtOH (0.075 M)	51 %
7	B (2,5 mol%)	tBuONa	EtOH (0.037 M)	0 %
8	B (2,5 mol%)	tBuONa	EtOH (0.300 M)	52 %
9	B (2,5 mol%)	tBuONa	PEG300 (0.300 M)	49 %
10	**B (2,5 mol%)**	**tBuONa**	**MeOH (0.300 M)**	**58 %**[a]
11	B (2,5 mol%)	tBuONa	MeOH (0.300 M)	0 %[c]
12	B (2,5 mol%)	-	MeOH (0.300 M)	0 %[d]

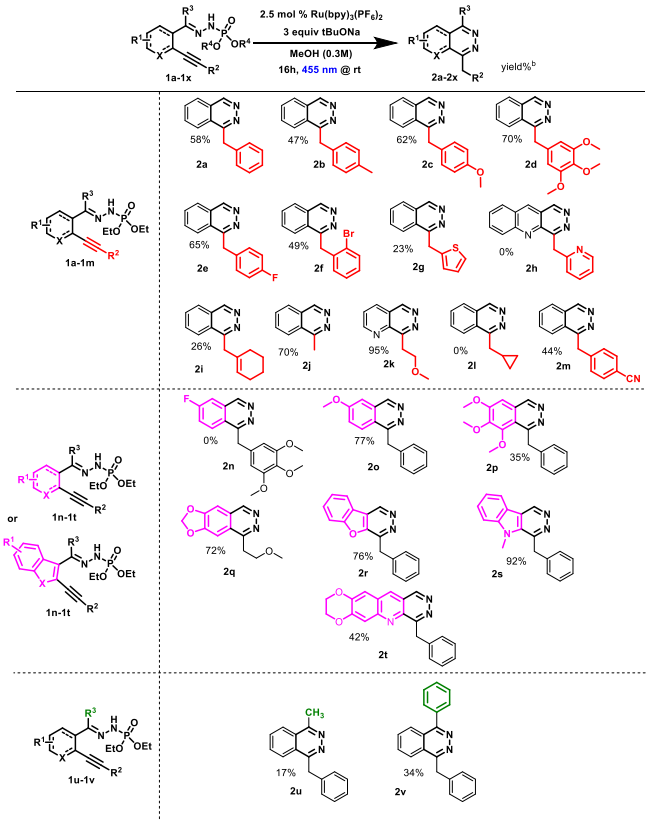
[a)] Standard condition: reactions were performed with **1a** (0.30 mmol), photocatalyst (2.5 mol %), and base (3 equiv,) in 1 mL of solvent and was irradiated with blue LED for 16 h. [b)] Isolated yields. [c)] Reaction performed without light. [d)] Reaction performed without base.

For instance, *p*-tolyl or *p*-methoxyl derivatives gave corresponding phthalazines **2b** and **2c** in a good 47% and 62% yields respectively (Table 2). More electron rich compound such as the 3,4,5-trimethoxybenzene derivative gave the phthalazine **2d** in a good 70% yield. Then, we examined electron-withdrawing functions. Interestingly, our reaction conditions were still efficient with these substitutions (Table 2, compounds **2e** – **2g**). Starting materials bearing a *p*-fluoro or an *o*-bromo substitutions were tolerated giving anticipated products with, respectively, interesting yield of 65% for compounds **2e** and an average yield of 49% for the brominated derivative **2f**. It is interesting to note that the bromo group is maintained through the photocatalyzed reaction and could thus be further functionalized by metal-catalyzed cross-coupling reactions. This also indicates that ortho substituted derivatives are tolerated in this cyclization reaction. Heterocycles are also possible partners as substituents on the alkynyl moiety, but with poor yields. For instance, compound **2g** bearing a thiophene was obtained in 23% yield. Unfortunately, pyrido derivative **2h** was unreactive in our reaction conditions which may come from a possible chelation and inactivation of the catalyst by nitrogen in the starting material. Finally, alkynes bearing alkene or alkyl derivatives were also investigated. The cyclohexenyl substitution was compatible although giving the desired product with a low yield of 26% (Table 2, compound **2i**). Trimethylsilyl acetylene or methyl propargylether were efficient substrates giving expected products **2j** and **2k** in respectively 70% and 95% yields. It is important to note that the TMS group is lost during the reaction, and that in the case of **2k** the starting material bears a pyridine unit instead of the benzene. Sadly, the cyclopropyl substitution **2l** was not compatible under our optimized conditions giving only a slow degradation of the starting material. Interestingly, electron-withdrawing derivative such as nitrile is also well-tolerated in these conditions giving the desired product **2m** in 44% yield.

In a second time we explored the influence of the aromatic part (Table 2, pink) of the starting material. Interestingly, substitution on the position 5 by an electron-withdrawing group like a fluorine atom on the compound **2n** was detrimental for the reaction. On the contrary, a substitution on the same position by an electron-donating group such as a methoxy provided compounds **2o** in a good 77% yield. In addition, trimethoxy-substituted compound **2p** is also accessible but in a low 35% yield. On the opposite, methylenedioxy derivative **2q** was obtained with a good yield of 72%. Finally, fused-heterocycles were also targeted and we were pleased to see that benzofuran- **2r** or indolo- **2s** pyridazines were produced in very attractive yields of 76% and 92 % respectively. Moreover, it is important to note that such exotic fused-heterocycles are, to the best of our knowledge, never been reported. Finally, a fused quinoline-pyridazine derivative **2t** is also obtained in an average yield of 42%

In a third time, substitution on the α-position of the hydrazone was also explored. Methyl- **2u** or phenyl- **2v** substitutions were possible but gave low yield from 17% to 34% certainly due to steric hindrance around the NCR which is a limiting factor during the cyclization step.

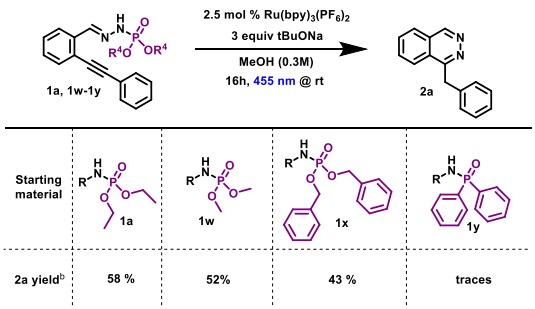
Table 2. Scope of the reaction.



a) Standard condition: reactions were performed with **1a-1v** (0.30 mmol), $Ru(bpy)_3(PF_6)$ (2.5 mol %, 7.5 µmol), and tBuONa (3 equiv, 0.9 mmol) in 1 mL of MeOH and was irradiated with blue LED for 16 h. b) Isolated yields.

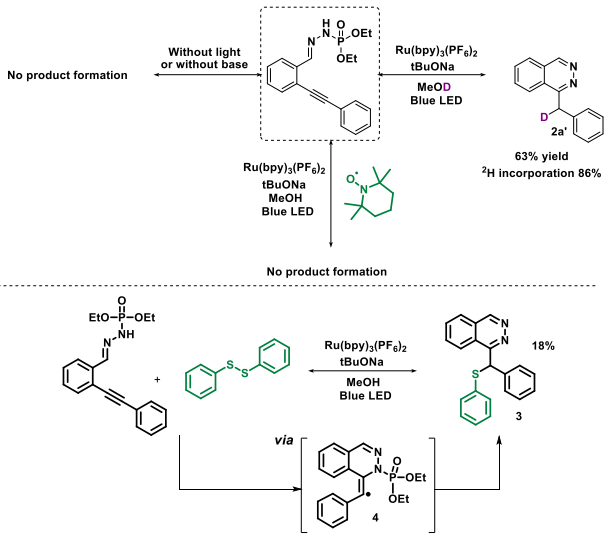
Thereafter, we supposed that changing the substitutions on the phosphorous atom may also play an important role in the reaction progress. Thus, several substitutions were investigated such as diethyl- **1a**, dimethyl- **1w**, or dibenzyl- **1x** phosphites but also diphenylphosphine **1y**. Dimethyl- substitution **1w** is slightly less efficient than diethyl- **1a** with a product yield of 52% compared to 58%. A bigger group on the phosphorous atom such as dibenzyl was less favorable for this reaction giving product **2a** in 43% yield. Finally, diphenyl phosphine is not efficient at all under our reaction conditions indicating that the phosphoramidate function is really important to form compound **2a**.

Table 3. Influence of the P-containing function.



a) Standard condition: reactions were performed with **1a**, **1w-1y** (0.30 mmol), $Ru(bpy)_3(PF_6)_2$ (2.5 mol %, 7.5 µmol), and tBuONa (3 equiv, 0.9 mmol) in 1 mL of MeOH and was irradiated with blue LED for 16 h. b) Isolated yields.

Some mechanistic investigations were then performed in order to better understand the reactivity of this new kind of precursor towards visible-light catalysis. As previously mentioned, experiments without light, base or photocatalyst gave no desired product indicating that we certainly have a photoinduced reaction and also the presence of the base is crucial to obtain the final product. The reaction was then performed in deuterated methanol which furnished the deuterated product **2a'** in a good 63% yield (86% deuterium incorporation, Scheme 3).



Scheme 3. Mechanistic investigations.

This allow us to confirm that the solvent is certainly the proton source for the final protonation step. Radical trapping experiments were then undertaken, first by using TEMPO as a trapping agent. In this case, we did not form any traces of product, or trapped any intermediates, but we observed only a slight degradation of the starting material (Scheme 3). This result may indicate that this reaction is certainly involving radical intermediates which have been in this case trapped by TEMPO. Moreover, since TEMPO is also known to easily react with photocatalyst under photoredox conditions,[27] this may explain the absence of final product due to the consumption of the reducing power of the ruthenium complex by TEMPO. To circumvent this phenomenon, diphenyl disulfide had been added to the reaction mixture and we were pleased to isolate the trapped radical intermediate **3** in 18% yield. This allow us to clearly identify the compound **4** as a radical intermediate in this mechanism (Scheme 3).

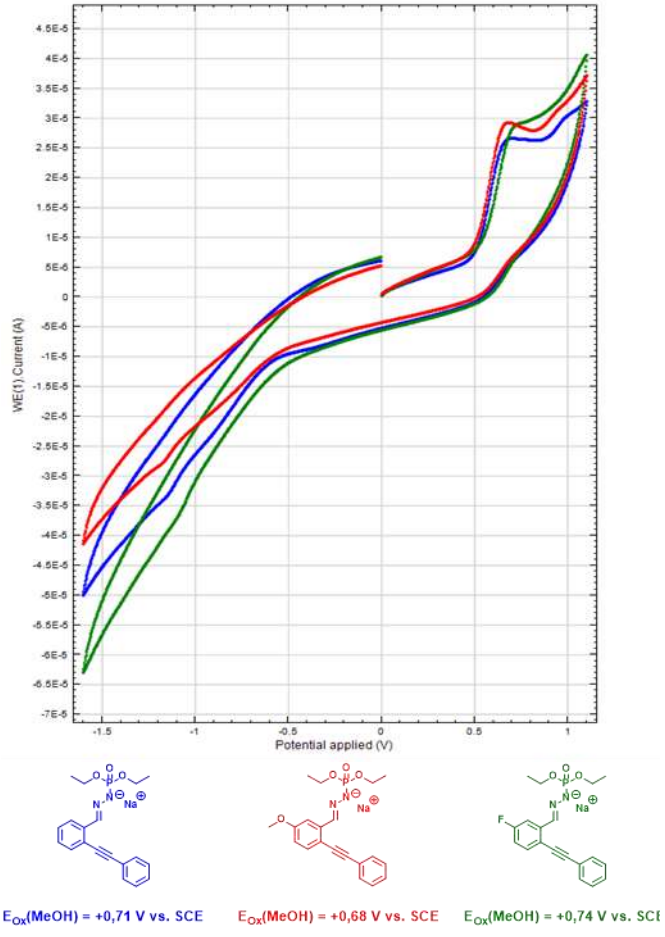
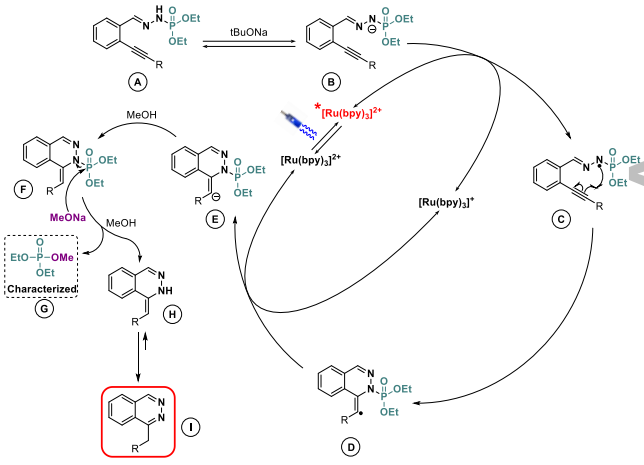


Figure 1. Cyclic voltammetry

Furthermore, on-off and cyclic voltammetry experiments have been performed (see SI). Thanks to these experiments, we found that oxidation potentials of anionic starting materials are between +0.68 V and +0.74 V vs. SCE in MeOH, in the presence of sodium *tert*-butoxide. Interestingly, oxidation potential can be tuned depending on the substitution on the left aromatic part of the molecule. Indeed, the more electron-poor substitutions are present, the stronger the oxidation potential is (see the fluoro derivative). On the contrary, an electron-donating group decreases the oxidation potential as shown by the methoxy substitution. The on-off experiment confirmed that the consumption of the starting material is correlated to the irradiation. Indeed, without light no conversion of the starting material occurs compared to the light irradiation conditions, indicating clearly the need of irradiation for the conversion of the starting material into the desired product (see SI).

Based on literature data[9,11,12,15] and previous experiments[20] we may propose the following mechanism (Scheme 4). As shown before, the base is crucial in this mechanism and plays an important role since the beginning with the deprotonation of the starting material A to give the anion B. This anion can then be oxidized by the photoexcited ruthenium catalyst thanks to a compatible redox potential indicated by our cyclic voltammetry studies. This step gives the corresponding nitrogen-centered radical intermediate C. This intermediate can then undertake an intramolecular cyclization on the pendant alkynyl group in a 6-*exo*-dig mode to provide the vinyl radical D (this radical intermediate was trapped with diphenyl disulfide as shown before, compound **3**, Scheme 3). Then, reduction of this radical intermediate by the strongly reductive $Ru(bpy)_3^+$ is most likely involved at this step to close the catalytic cycle and furnish the corresponding anion E. This anion intermediate can then easily be protonated by the solvent (based on our deuteration experiments, Scheme 3). Moreover, the base played a second crucial role in this mechanism; indeed, we were able to isolate and characterize the diethyl methyl phosphate G as a byproduct generated during this reaction (see SI). We thus proposed that sodium methylate generated in the reaction medium can attack the phosphoramidate intermediate F to release the diethyl methyl phosphate G and the phthalazine H.[28] This last intermediate is in a very balanced equilibrium with the final product I.



Scheme 4. Mechanistic proposal[29]

Conclusion

A new *N*-centered radical precursor is thus proposed here. Compared to all previous methods utilizing an oxidative pathway, this method is the only one reporting an *in-situ* cleavage of the activating part. Moreover, phosphoramidate function has been for the first time investigated towards NCR formation *via* visible-light catalysis. Thanks to this approach, a library of heterocyclic structures based on phthalazines are thus accessible. Many of these structures were until now inaccessible or difficult to make. Thanks to mechanistic investigations (deuteriation, cyclic voltammetry, radical trapping), some intermediates have been isolated to prove the cyclization mode of the NCR intermediate and a mechanistic pathway has been proposed. This TNA strategy will thus be interesting to further obtain useful compounds without any final deprotection or limitations.

Experimental Section

General experimental methods

^{1}H NMR, ^{13}C NMR, ^{31}P NMR and ^{19}F NMR spectra were recorded on Bruker Avance 300, 400 or 600 MHz spectrometers in $CDCl_3$, DMSO-d_6 or acetone-d_6 solution with internal solvent signal as reference. NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), and coupling constants (Hz) and number of protons (for ^{1}H NMR). All reactions were monitored by thin-layer chromatography using Merck silica gel plates 60 F254. Visualization was accomplished with short wavelength UV light (254 and 365 nm) and/or staining with appropriate stains (anisaldehyde, orthophosphomolybdic acid). Standard flash chromatography was performed using silica gel of particle size 40−63 µm. Photocatalysts were purchased from Aldrich, TCI, and used without any further purification or synthesized as reported in litterature. All other commercially available reagents and solvents were used without further purification.

General experimental procedures

General procedure for the synthesis of phosphonohydrazones (1a-1x):

To an oven dried sealable glass vial were added aldehyde or ketone derivative (1 eq.), phosphonohydrazine (1.1 eq) and MeOH (0.8 M). The vials were sealed with 20mm crimp caps with silicone/PTFE septum and stirred overnight at 20°C. After completion of the reaction checked by TLC, the reaction medium was filtered using a Büchner funnel if precipitation of the phosphonohydrazone occurred. The product was dried under vacuum, characterized and used without any further purification. If precipitation did not occur, the crude mixture was concentrated and purification of the residue by silica gel column chromatography eluting with a cyclohexane/ethyl acetate mixture gave the desired product.

General procedure for the synthesis of phthalazines (2a-2u):

To an oven dried sealable glass vial were added phosphonohydrazone (0.3 mmol, 1 eq.), sodium tert-butoxide (0.9 mmol, 3 eq.), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.0075 mmol, 2.5 mol%) and MeOH (1 mL, 0.3 M). The vials were sealed with 20mm crimp caps with silicone/PTFE septum and stirred for 16 hours under visible-light irradiation. After completion of the reaction checked by TLC, the resulting suspension was filtered through a pad of celite eluting with ethyl acetate. The crude filtrate was concentrated and purification of the residue by silica gel col-umn chromatography eluting with a cyclohexane/ethyl acetate mixture gave the desired product.

CCDC-1944463 and 1944464 contain the supplementary crystallographic data for compounds **1a** and **2a'** of this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

This work was supported by a joint CNRS and INCa fellowship (ATIP) to PB. M. De Abreu thanks the MESR for funding. Dr. Florence Souquet is acknowledged for C.V. measurements.

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[29] We cannot totally exclude another plausible pathway, see SI.

10.1002/adsc.202000018

FULL PAPER

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