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Organophotocatalytic Synthesis of Phosphoramidates

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Abstract: We describe the use of visible light in conjunction with an organic dye for the synthesis of phosphoramidates. Cross dehydrogenative coupling reactions between phosphites and amines are reported using organic dyes and light as catalysts for the first time. It is not only a novel application of organic dyes but also fulfils the requirement of sustainability and green chemistry avoiding the use of chromatographic purification techniques. The product was simply isolated from the reaction mixture *via* an acid-base work-up procedure, rendering the pure product in good yields.

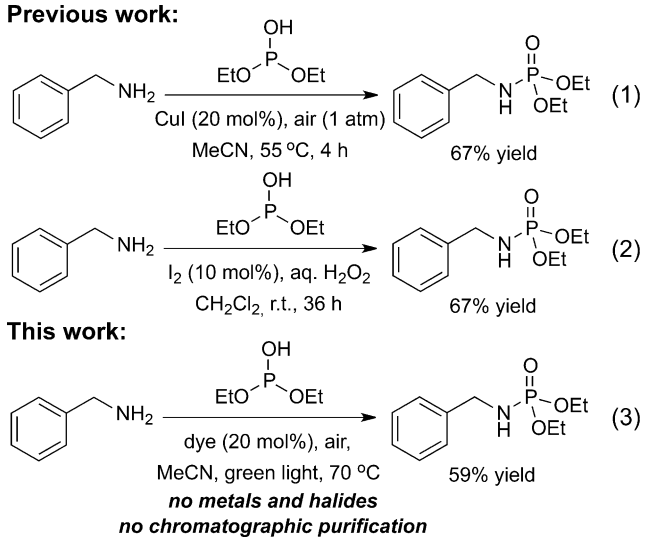
Keywords: cross dehydrogenative coupling (CDC) reactions; dyes; green chemistry; phosphoramidates; photocatalysis

The quest for green procedures has become of paramount importance for organic chemists in the last decade. Discovery of benign, green and atom economic processes is one of the corner stones for chemists nowadays.[1] One of the most promising eco-friendly processes is the use of light in combination with a photosensitizer to catalyze organic reactions. Advantages to use light as a source of energy are that it is a renewable source, clean, non-toxic and cheap. For these reasons, the use of photocatalysis has grown exponentially in recent years.[2]

For similar reasons, cross dehydrogenative couplings (CDCs) have become a hot topic of interest for chemists.[3] CDCs present some advantages such as no requirement of prefunctionalized starting materials and typically highly efficient, atom-economic processes, which should be an excellent way to shorten the common synthetic routes or to introduce late-stage functionalization for interesting scaffolds. In our research group, we are interested in the development of green organocatalytic reactions that allow us to build new atom-atom σ-bonds. To do this, photocatalytic reactions for CDC have attracted our attention. Inspired by previous works of Rueping,[4] among others, we envisioned that photocatalysis, using organic dyes, could be contributing to the development of new reactions for the synthesis of phosphoramidates.

Phosphoramidates are very important structural scaffolds in many biologically active molecules[5] and industrially important products.[6] Moreover, in recent years, phosphoramidates have become important chiral ligands for several metal-catalyzed reactions.[7] In medicinal chemistry, phosphoramidate ProTide technology has been used to bypass the rate-limiting step of the initial phosphorylation of nucleosides and to act as a better inhibitor.[8] Recently, Zhou and coworkers have used chiral phosphoramidates as organocatalysts for several reactions such as addition of oxindoles to nitrostyrenes[9] or the Michael addition of fluorinated silyl enol ethers[10] with excellent results, showing the importance of this type of functional molecule as catalyst scaffold.

Despite the importance of phosphoramidates, their synthesis requires harsh conditions and/or the use of halides or precious transition metals. Typical methodologies for the synthesis of phosphoramidates are described as follows: (i) they were conventionally synthesized by the reaction of amine with the appropriate phosphorus halide.[11] Generally, these kinds of phosphorus reagents are moisture sensitive and thermally unstable; (ii) Other methods require the use of potentially explosive and toxic reagents or need multi-step synthesis. For example, the Staudinger-phosphite reaction uses azides or phosphoryl azides.[12] In addition; highly toxic chlorinating agents were used as solvents, for example, CCl_4 in the



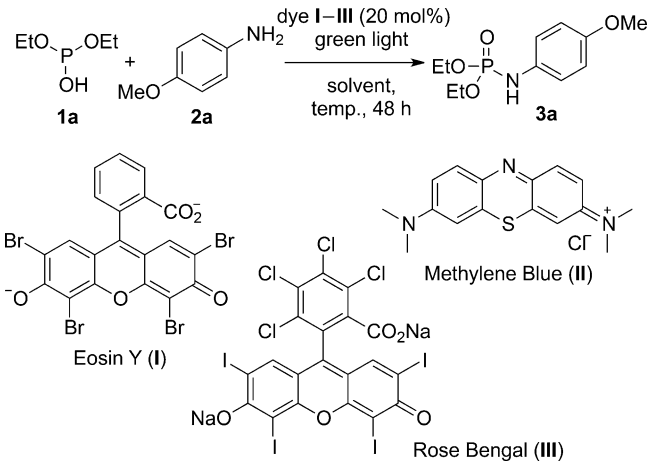
Scheme 1. Previous works and our work.

Atherton–Todd reaction, to generate the reactive phosphorus halide species. In order to overcome the above-mentioned limitations, some examples of direct catalytic approaches were recently reported based on the concept of CDCs process: (i) copper-catalyzed aerobic oxidative coupling between amines and phosphonates with excellent results were developed by the groups of Hayes and Mizuno independently in 2013 [Scheme 1, Eq. (1)];[13] (ii) Prabhu and co-workers reported the use of I_2 as catalyst with (over)stoichiometric amounts of H_2O_2 as oxidant to obtain phosphoramidates in good yields [Scheme 1, Eq. (2)].[14] From a practical and green chemistry point of view, however, general solutions such as the elimination of the use of precious transition metals or stoichiometric oxidants are still highly desirable.

Herein, we report a simple, non-toxic, and transition metal-free, P–N bond-forming CDC reactions between phosphites and amines for the synthesis of phosphoramidates in a one-pot manner using an organic dye as photocatalyst and air as oxidant under irradiation of green light-emitting diodes (LEDs) [Scheme 1, Eq. (3)]. Moreover, the large-scale production of the desired product is demonstrated without the need of chromatographic purification.

We initially commenced with the CDC reaction between diethyl phosphite **1a** and *p*-anisidine **2a** in acetonitrile under aerobic conditions, catalyzed by several organic dyes at room temperature (Table 1). The reaction furnished phosphoramidate **3a** with low conversion at room temperature. Among organic dyes, Rose Bengal (**III**) was proven to be the best dye in combination with green light for this study whereas other dyes such as Eosin Y (**I**) or Methylene Blue (**II**), surprisingly, did not render any product (Table 1, entries 1 and 2). After screening of several solvents, it was found that toluene gave comparable result to that

Table 1. Screening of parameters.[a]



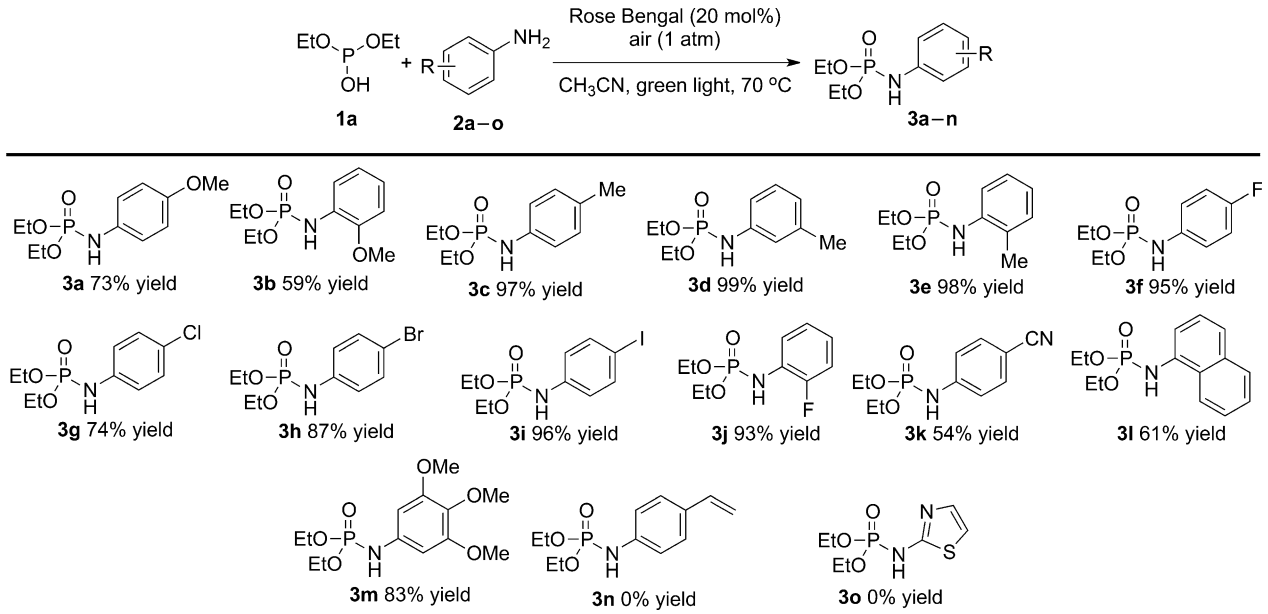
Entry	Dye	Green light	Solvent	Temp. [°C]	Yield [%][b]
1	**I**	yes	CH_3CN	r.t.	n.r.
2	**II**	yes	CH_3CN	r.t.	n.r.
3	**III**	yes	CH_3CN	r.t.	36
4	**III**	yes	toluene	r.t.	40
5	**III**	yes	$CHCl_3$	r.t.	26
6	**III**	yes	EtOAc	r.t.	13
7	**III**	yes	DMSO	r.t.	17
8	**III**	yes	toluene	70	54
9	**III**	yes	CH_3CN	70	95
10	–	yes	CH_3CN	r.t.	n.r.
11	**III**	no	CH_3CN	r.t.	n.r.

[a] *Reaction conditions:* **1a** (0. 362 mmol), **2a** (0.724 mmol), dye **I–III** (20 mol%), air (1 atm), green light, solvent (1.5 mL).
[b] Isolated yields.

obtained in acetonitrile at room temperature (Table 1, entries 3 and 4). On the other hand, the use of chloroform, EtOAc, and DMSO as solvents gave lower yields (Table 1, entries 5–7). In order to improve the reaction rate and the yields, the reaction was carried out in either toluene or acetonitrile at 70 °C. Acetonitrile gave a striking difference in terms of the yield compared with toluene, giving the desired product in almost quantitative yield (95%) (Table 1, entry 9). Control reactions demonstrated that no reaction occurred in the absence of organic dye **III** or light source (Table 1, entries 10 and 11).

Having the optimal conditions in hand, we focused our attention on the reaction scope of a variety of aromatic and aliphatic amines with **1a**.

As shown in Scheme 2, the presence of electron-donating substituents, such as 4-OMe (**3a**), 3,4,5-OMe (**3m**), on the aromatic ring of the anilines produced the corresponding phosphoramidates in high yields, whilst that of a 2-OMe substituent gave slightly lower yields. When methyl-substituted anilines were employed, the final products were obtained in almost quantitative yields (*p*-methylaniline-derived product



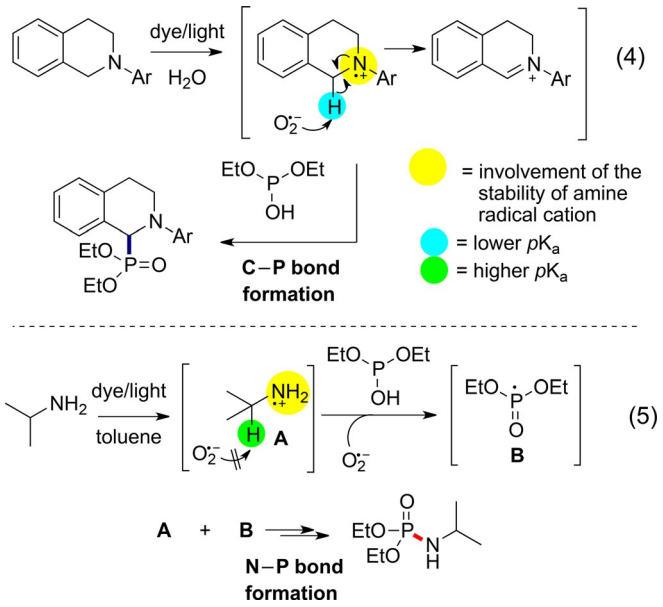
Scheme 2. Substrate scope of aromatic amines.

3c, 97%; *m*-methylaniline-derived product **3d**, 99%; *o*-methylaniline-derived product **3e**, 98%) regardless of the substituent position. When an electron-withdrawing substituted aniline (**3k**) and sterically congested 1-naphthylamine (**3l**) were used, moderate yields were achieved. We also examined the functional group tolerance with halogenated aromatics (**3f–j**). All of the halogenated anilines produced the desired products with extremely high yields under our reaction conditions: 4-F (**3f**) 73%; 4-Cl (**3g**) 74%; 4-Br (**3h**) 87%; 4-I (**3i**) 96%; 2-F (**3j**) 93%.

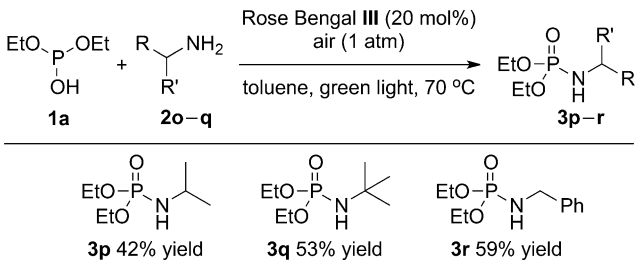
The only limitation of the present methodology is the use of terminal vinylaniline because of its sensitive radical nature which may give oligo- or polymerization by radical cations, or the use of heteroaromatic amines such as 2-aminothiazole that decomposes under the reaction conditions. It is noteworthy that the pure products were obtained in most cases after a simple acid-base work-up procedure without any need for additional purification techniques.

Next, we investigated the reaction scope with more challenging aliphatic amine substrates. Previously, aliphatic amines have been introduced in similar CDC reactions with diethyl phosphite under organic dye-catalyzed photoredox reactions by the group of Rueping. However, the Kabachnik–Fields (K-F) product (i.e., α-amino phosphonate) was observed *via* C–P bond formation during the course of the reaction [Scheme 3, Eq. (4)].

In contrast to the work of Rueping, phosphoramidate products (**3p** and **3q**) were selectively rendered in reasonable yields (42–59%) *via* N–P bond formation when the reaction was performed in toluene under our optimized reaction conditions [Scheme 3, Eq. (2) and Scheme 4]. These results are dependent on the stabilization of tertiary or primary amine radical cations, followed by the subsequent deprotonation efficiency of proton at the α-position of amine radical cations by base (e.g., superoxide anion), which is governed by the pK_a value of the relevant acidic protons. For example, when tetrahydroisoquinoline was used, a mixture of the K-F product and the phosphoramidate was found (14:1 ratio). Unfortunately, no product was observed when the reaction was tested with



Scheme 3. Competitive reactions between C–P and N–P bond formation.

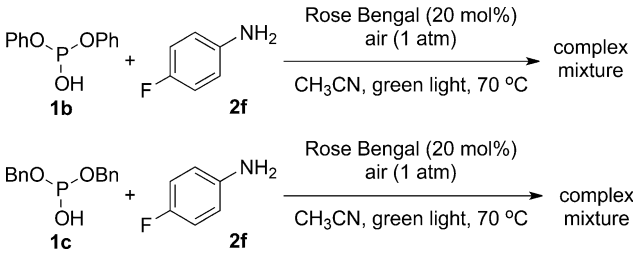


Scheme 4. Substrate scope of aliphatic amines.

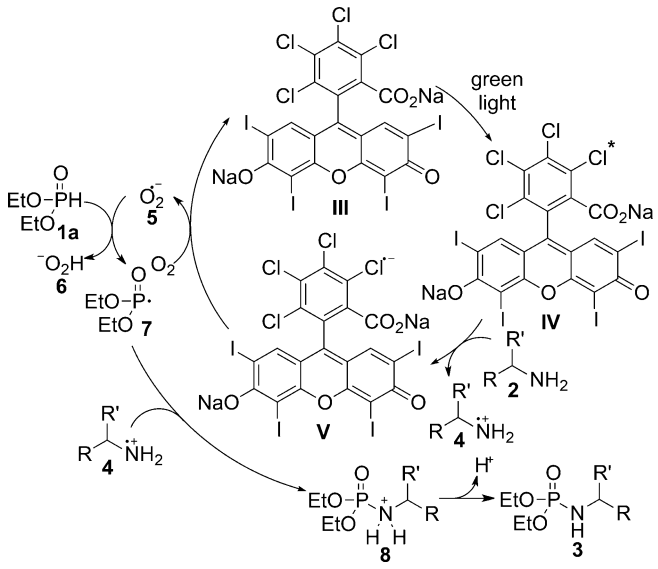
secondary amines such as morpholine, piperidine or pyrrolidine.

Next, we studied the reaction with different phosphorus sources. As it is shown in Scheme 5, the reactions with diphenyl phosphite (**1b**) or dibenzyl phosphite (**1c**) render a mixture of products.

A proposed mechanism for the reaction is outlined in Scheme 6. The organic dye (Rose Bengal, **III**) accepts a photon from the visible-light source to populate the excited-state dye (**IV**), which removes one electron from the nitrogen atom of **2** to generate amine radical cation **4** by a single-electron transfer



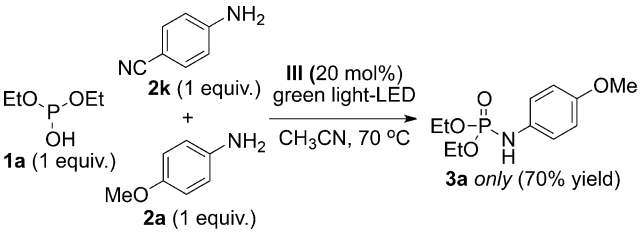
Scheme 5. Substrate scope of phosphites.



Scheme 6. Plausible mechanism for the synthesis of phosphoramidates.

(SET) process. The radical anion dye **V** is re-oxidized to the ground-state dye by molecular oxygen, forming the superoxide anion **5**. Next, the superoxide anion **5** reacts with the phosphite **1a** to liberate the phosphoryl radical **7** and hydrogen peroxide anion **6**. The final target molecule **3** is produced by the reaction of phosphoryl radical **7** and amine radical cation **4**, followed by the deprotonation of the protonated phosphoramidate **8** by hydrogen peroxide anion **6**.

To verify the stabilization of amine radical cation species, we decided to perform the reaction with an equal molar ratio of *p*-anisidine and *p*-cyanoaniline in a single flask under the optimal reaction conditions. Gratifyingly, the phosphoramidate **3a** derived from *p*-anisidine was exclusively formed, indicating that a better ability of electron-donating group such as -OMe to stabilize amine radical cation preferentially (Scheme 7). In order to prove the radical nature of



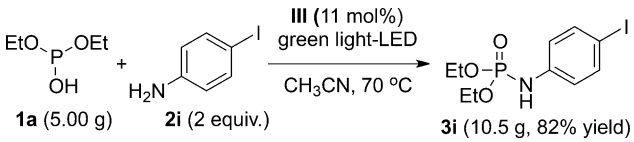
Scheme 7. Selective formation of phosphoramidate product **3a** *via* stabilization of the amine radical cation species by controlling the electronic properties of the substituents on the aromatic ring of anilines.

the intermediates, the reaction was conducted with 1 equiv. of TEMPO. Under these conditions no product was obtained, showing clearly that an intermediate radical is formed. Another fact that validates our mechanistic proposal of the formation of intermediate **4** is the mixture of phosphoramidation and K-F products when tetrahydroisoquinoline was used.

The recyclability of Rose Bengal was also examined. The organic dye catalyst was recovered and reused after completion of the reaction by simple acid-base extraction. The recovered catalyst exhibited similar results to those obtained in the first cycle: first cycle (74% yield) and second cycle (67% yield).

Finally, we applied this protocol to the large-scale production of the phosphoramidate **3i** derived from *p*-iodoaniline (Scheme 8). The reaction was repeated on a 5.00 g scale of diethyl phosphite **1a** with 2 equiv. of *p*-iodoaniline **2i**. The product **3i** was isolated in 82% yield without any assistance by chromatographic purification.

In summary, we have developed a new methodology for the synthesis of phosphoramidates catalyzed by organic dyes and light (a renewable energy) with excellent results. This methodology complements and



Scheme 8. Large-scale production of **3i**.

improves the existing technologies eliminating the use of metals or halide reagents and, importantly, the requirement of tedious purification steps. For these reasons, we believe that this new process fulfills all the requirements of green chemistry and opens a new gate to the development of more sustainable methodologies based on these observations. Further studies towards the use of more reactive dyes and expanding the scope of the reaction to other interesting compounds (alcohols, amides, thiols, etc.) are ongoing in our laboratory.

Experimental Section

General Procedure

In a closed vial were added in this sequence: the organic dye Rose Bengal (73 mg, 0.072 mmol, 20 mol%), the amine (0.724 mmol, 2 equiv.), the solvent (1.5 mL) and diethyl phosphite (47 μL, 0.362 mmol, 1 equiv.). The reaction mixture was stirred at 70 °C in the photoreactor under green light (see Table 1 for reaction times). $CHCl_3$ was added to the crude mixture and the organic phase was washed with 0.5 M HCl (3×20 mL), then with saturated aqueous $NaHCO_3$ solution (3×20 mL). The organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum to afford the desired phosphoramidate.

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