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# With DBU-activated *N*-bromophthalimide as potential N-sources to achieve P—N cross-coupling of P(O)—H compounds

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**ABSTRACT**

We have demonstrated that N-haloimides can be utilized as an aminating reagent, in addition to traditional brominating reagent. Herein, the P—N cross-coupling of P(O)—H compounds and *N*-bromophthalimide has been developed with the DBU activation strategy. The nitrogen source may arise from internal *N*-bromophthalimide itself (a self-immolating reagent) or external phthalimide derivatives (with NBS-DBU activation system). The reaction features broad phosphorous compounds scope, including *H*-phosphinates, *H*-phosphonates and *H*-phosphine oxides, and short reaction time (less than 10 min). This method provides a simple, convenient, efficient and green route towards phosphoramidates which are of biological importance under mild conditions.

*Keywords*: P—N cross-coupling; P(O)—H compounds; *N*-bromophthalimide; aminating reagent; DBU

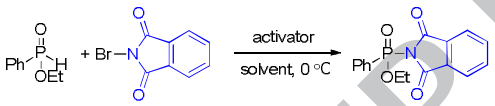
Phosphoramidates are key structural units in a number of biologically active natural products, which not only show antibacterial, antifungal, antitumor (such as Agrocin 84[1a], Phosmidosin[1b], Microcin C7[1c]) and anti-HIV biological activities,[1] but also are important chiral auxiliaries for asymmetric synthesis.[2] Phosphoramidates are also used as flame retardants.[3] One of the synthetic methods for phosphoramidates involves the utilization of phosphoryl halides or phosphoryl azide species, which need to prepare in advance and are potentially hazardous.[4] The development of novel and green synthetic procedures for phosphoramidates directly from P(O)—H substrates is highly desirable, because they are more readily available, easy-to-handle and no prefunctionalization step is required. Thus the overall synthetic efficiency is greatly improved. To date, there has been made significant progress in the development of P N bond forming reactions via direct activation of the P—H bond, for example, well-known Atherton–Todd reaction.[5] However, the reaction is limited by the use of toxic $CCl_4$, excess base and long reaction time. Metal-catalyzed P N cross-coupling reaction of P(O)—H compounds has been recently reported.[6] Mizuno and co-workers communicated a cross-coupling of phosphites and amides to form phosphoramidates by using Cu(II) acetate and a stoichiometric amount of base.[6a] Hayes et al. presented a Cu(I) iodide-catalyzed aerobic oxidative cross-coupling reaction of *H*-phosphonates and amines.[6b] Metal-free phosphorylation of amines is accomplished using molecular iodine as a catalyst and $H_2O_2$ or molecular oxygen in air as the sole oxidant under mild reaction conditions.[7a,b]

Our research group has demonstrated the N-haloimides like N-bromosuccinimide (NBS) and N-bromophthalimide (NBP) can be utilized as an aminating reagent, in addition to traditional brominating reagent. By DBU activation strategy, a variety of amination reaction of -dicarbonyl

compounds, aryl alkyl ketones, , -unsaturated enones, specific alkenes and indole derivatives, by employing *N*-haloimides as potential *N*-sources has been developed.[8] We hoped to expand the general utility of the *N*-haloimides-DBU combination system to a variety of fundamental substrates. In this work, we set out to explore the imidation reaction of trivalent phosphorus compounds to achieve phosphoramidate derivatives which are of great importance.[9] As a result, a metal-free P N cross-coupling of P(O) H compounds with *N*-bromophthalimides was developed, which provides a simple, convenient and efficient protocol towards phosphoramidates, directly from P(O)—H substrates.

Beginning with our previously reported reaction conditions, we tested the DBU (1.5 equiv) mediated coupling reaction between ethyl phenylphosphinate **1a** and *N*-bromophthalimide (NBP, 1.5 equiv) (Table 1). The reaction conducted either at room temperature or upon heating was messy. Thus, we decided to try the reaction by lowering the temperature. To our delight, the reaction conducted in DMF at 0 °C gave the desired ethyl (1,3-dioxoisoindolin-2-yl)(phenyl)phosphinate (**2a**) in 42% yield (entry 1). Other solvents like THF, toluene and DCM afforded improved yields (entries 2-4) and MeCN proved to be the most efficient, furnishing **2a** in 85% yield within 10 min (entry 5). Other than DBU, Lewis bases including MTBD, DBN, DABCO, $Et_3N$ and $PPh_3$ were selected as the activator. The results indicate that all of them were much less efficient than DBU (entries 6-10). Furthermore, inorganic bases like NaOH, *t*-BuOK and $K_2CO_3$ were proved to be inefficient, indicating that DBU works not only as a base, but also an effective activator. Catalytic amount of DBU (e.g. 0.5 equiv) was not enough to drive the reaction to completion (entry 11).[10]

**Table 1. Optimization of the reaction conditions**[a-c]

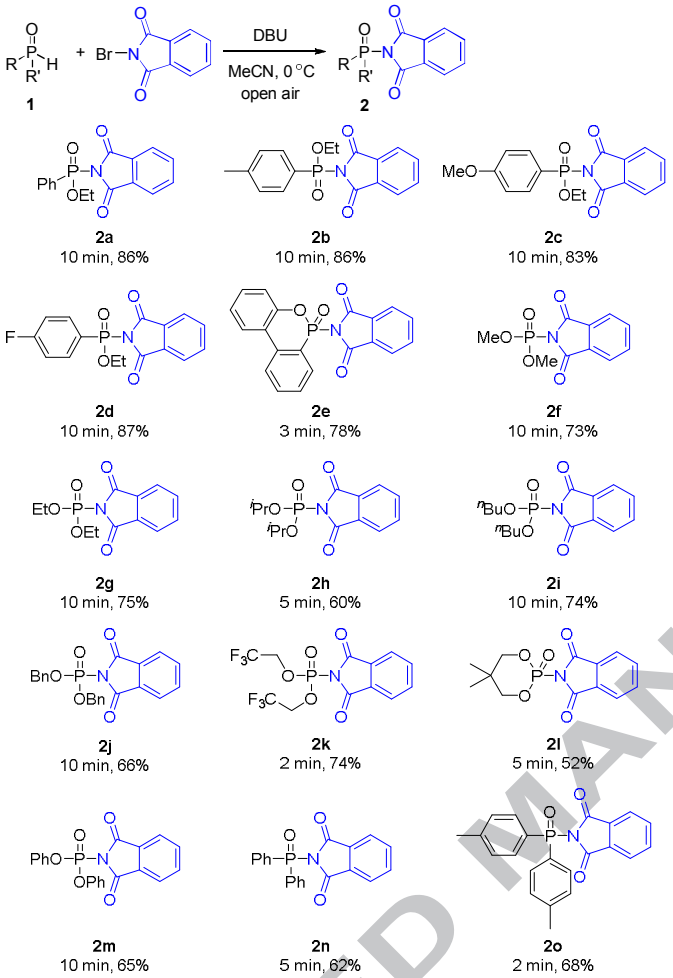



1a 2a

| Entry | Activator (equiv) | Solvent | Time (min) | Yield (%)[d] |
|---|---|---|---|---|
| 1 | DBU (1.5) | DMF | 10 | 42 |
| 2 | DBU (1.5) | THF | 10 | 58 |
| 3 | DBU (1.5) | toluene | 90 | 78 |
| 4 | DBU (1.5) | DCM | 10 | 82 |
| **5** | **DBU (1.5)** | **MeCN** | **10** | **85** |
| 6 | MTBD (1.5) | MeCN | 10 | trace |
| 7 | DBN (1.5) | MeCN | 30 | 48 |
| 8 | DABCO (1.5) | MeCN | 90 | 40 |
| 9 | $Et_3N$ (1.5) | MeCN | 90 | 0 |
| 10 | $PPh_3$ (1.5) | MeCN | 90 | 0 |
| 11 | DBU (0.5) | MeCN | 90 | 32 |

[a] Reactions were carried out with **1a** (1 mmol), NBP (1.5 equiv) and activator (1.5 equiv) in solvent (2.0 mL) at 0 °C. [b] Reactions were carried out in the open air. [c] In all cases, NBP mixed with DBU firstly, followed by the addition of the P(O)—H substrates. [d] Isolated yield. DBU = 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine; MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBN = 3,4,6,7,8,9-hexahydro-2H-pyrido[1,2-a]pyrimidine; DABCO = 1,4-diazabicyclo[2.2.2]octane.

**Table 2. P—N cross-coupling: Scope of P(O)—H substrates**[a-c]




[a] Reactions were carried out with **1** (1 mmol), NBP (1.5 equiv) and DBU (1.5 equiv) in MeCN (2.0 mL) at 0 °C. [b] In all the cases, NBP mixed with DBU firstly, followed by the addition of the P(O)—H substrates. [c] Isolated yield.

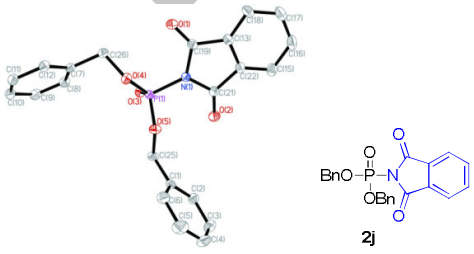


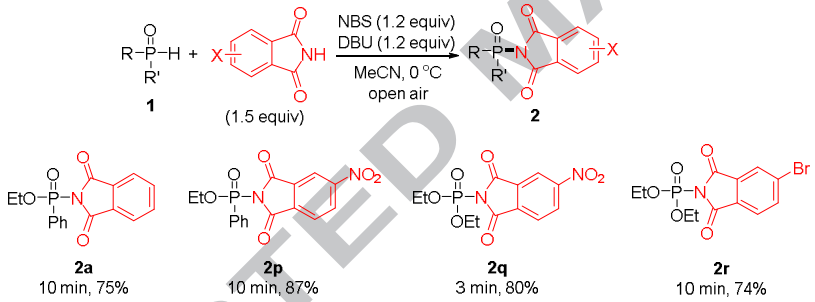

**Figure 1**. The X-ray structure of **2j**.

In the following work, we investigated the generality of the protocol for various trivalent phosphrous substrates (Table 2).[11] *H*-phosphinates (both cyclic and acyclic) afforded the corresponding phosphoramidates **2b-e** in 78-81% yields. A series of *H*-phosphonates were tested under otherwise identical conditions. The substituents on the P center include alkyloxy, $CF_3$-containing alkyloxy and aryloxy. The phosphoramidate products **2f-m** were obtained in moderate yields (52-75%). The structure of **2j** was confirmed by X-ray single-crystal diffraction (Fig. 1).[12] Diarylphosphine oxides can

also engage in the cross-coupling with NBP to produce the corresponding phosphoramidate derivatives **2n** and **2o** in moderate yields. From above one can see that the scope of the P(O)—H components in the P—N coupling reaction is broad and the reaction time is quite short (less than 10 min). It was noteworthy that all the reactions listed in Table 2 need to be carried out in the open air. No reaction took place under a $N_2$ atmosphere. This indicated that dioxygen in air might facilitate the reaction, however, the reason was still unclear.

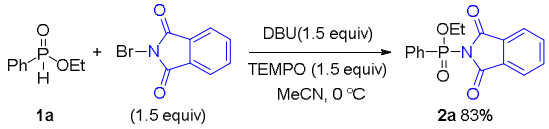
The scope of *N*-Haloimide components were investigated, but appears to be narrow. For *N*-halophthalimides (halogen = Br and Cl), although NBP is efficient (85% yield), NCP was less efficient (45%). *N*-halosuccinimides (halogen = Cl, Br and I), *N*-bromosaccharin and 1,3-dibromo-5,5-dimethyl hydantoin were inefficient for the coupling reaction.[13]

In view that the reaction of NBS/DBU with **1a** gave no phosphoramidate product, we decided to introduce external nitrogen nucleophiles to the reaction (Scheme 1). In this case, DBU-activated NBS is supposed to transform the P(O)—H substrates into phosphoryl bromides. With NBS/DBU system, the reaction of **1a** and phthalimide (1.5 equiv) may take place, giving compound **2a** in 75% yield. In the P N coupling reactions of ethyl phenylphosphinate and diethyl phosphonate with 4-nitrophthalimide (1.5 equiv) in the presence of NBS (1.2 equiv) and DBU (1.2 equiv), the imidated products **2p** and **2q** were achieved in 87% and 80% yields, respectively. Diethyl phosphonate reacts with 4-bromophthalimide to give diethyl (5-bromo-1,3-dioxoisoindolin-2-yl)phosphonate **2r** in 74% yield. We did not get a success for other type of external *N*-components presently.




**Scheme 1.** P N cross-coupling between P(O) H compounds and phthalimide derivatives.

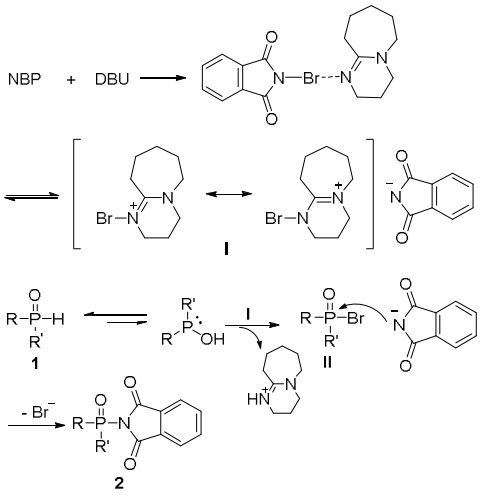
In a control experiment, TEMPO (1.5 equiv) was added immediately to a mixture of ethyl phenylphosphinate (1.0 mmol), NBP (1.5 equiv) and DBU (1.5 equiv) in MeCN at 0 °C (Scheme 2). Compared to the reaction without TEMPO, the yield has almost no change. The result may help one to exclude the possible radical pathway.




**Scheme 2.** Control experiment.

A possible mechanism for the coupling reaction was proposed in Scheme 3. NBP reacts with DBU to form 1-bromo-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepin-1-ium 1,3-dioxoisoindolin-2-ide (**I**)[8,14] followed by in situ electrophilic bromination of P(O)—H compounds to give phosphoryl bromide

**II**.[7a] Further addition/elimination affords the corresponding cross-coupled product **2**. The function of DBU is to deprotonate the phosphorus substrates (as base) and to activate NBP (as a promoter) to be more electrophilic bromine cation and potentially nucleophilic phthalimide anion.[15]




**Scheme 3.** Possible mechanism.

In summary, we have developed a DBU-mediated cross-coupling reaction of a variety of phosphorous compounds including *H*-phosphinates, *H*-phosphonates and *H*-phosphine oxides and *N*-bromophthalimide for the formation of phosphoramidate products under mild conditions. This process uses *N*-bromophthalimide as cationic halogen and anionic *N*-nucleophile sources. In situ formation of phosphoryl bromide and subsequent addition/elimination make the reaction to be environmentally benign and synthetically efficient. Further research on the utilization of *N*-haloimide as potential nitrogen source in organic transformations is ongoing in our laboratory.

**Acknowledgements**

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**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi .org/10.1016/j.tetlet.2016.??????.

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9 For an early work on the reaction of trialkyl phosphites with *N*-haloimides, see: Tsolis, A. K.; McEwen, W. E.; VanderWerf, C. A. *Tetrahedron Lett.* **1964**, *43*, 3217.

10 HBr side-product would consume 1.0 equiv of DBU.

11 General procedure for the preparation of **2** (**2a** as an example): To a solution of NBP (1.5 mmol, 0.339 g) and DBU (1.5 mmol, 0.218 mL) in MeCN (2.0 mL), ethyl phenylphosphinate **1a** (1.0 mmol, 0.154 mL) was added. The reaction mixture was stirred at 0 $^{o}$C for 10 min. After the starting material **1a** was consumed as indicated by TLC, the reaction mixture was poured into water and then extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, petroleum ether : ethyl acetate = 3 : 1) to give **2a** (268 mg, 85%) as a white solid.

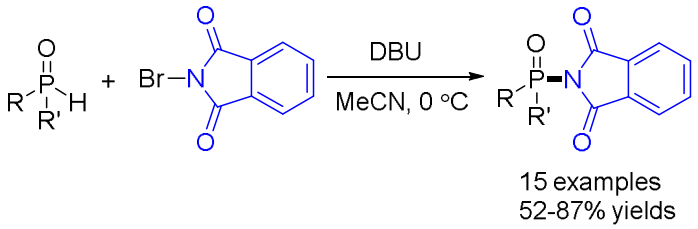
11 CCDC number 1407192 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

12 The reason for this is unclear at the moment.

13 The existence of strong interaction between NBP and DBU has been demonstrated by i) DFT calculation; ii) $^{1}$H NMR study; and iii) the ionic conductivity measurement. See ref. 8e.

14 Only in the case of NBP mixed with DBU firstly, followed by the addition of P(O)—H compounds, can the target compound be observed. That P-atom acting as a nucleophile to directly react with NBP in the first step was tentatively excluded. Please refer to: Mitova, V.; Koseva N.; Troev, K. *RSC Adv.*, **2014**, *4*, 64733.

**Graphical abstract**



- A metal-free P—N cross-coupling is developed.
- Halogen bonding activation by DBU is the driving force for the P—N cross-coupling.
- An ionic rather than a radical mechanism is proposed.
- N-haloimides can be utilized as an aminating reagent.