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Metal-free phosphonation of heteroarene N-oxides with trialkyl phosphite at room temperature †

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A new protocol is described for the conversion of heteroarene *N*-oxides to heteroarylphosphonates through in situ activation with bromotrichloromethane. The *N*-oxides of isoquinoline, quinoline, quinoxaline and 1,10-phenanthroline were fast transformed into the corresponding heteroarylphosphonates in up to 92% yield under mild conditions in the absence of solvent and metal catalysts. The good functional group tolerance, the low cost, the feasibility of scale up, and the wide availability of reagents make the method a prominent complement to the Hirao coupling.

Phosphonic acid derivatives have various applications in many fields, such as organic synthesis, medicinal chemistry, and materials chemistry.[1, 2] Among them, arylphosphonates are widely used as passive coating agents to inhibit the corrosion of ferrous metals, as antistatic agents in the textile and polymer industry, as emulsifiers for insecticides and agricultural chemical mixtures, and as surface modification reagents in material sciences.[3] A reliable palladium-catalyzed method for the synthesis of arylphosphonates from haloarenes ArX (X = Br, I) was disclosed by Hirao and co-workers in the 1980s because of its high efficiency and good tolerance to functionalities.[4] However, the process of developing methods for preparing heteroarylphosphonates has lagged behind. The first general approach is based on the nucleophilic reactions of *N*-alkoxypyridinium salts with alkali metal derivatives of dialkyl hydrogenphosphonate (Scheme 1, A1). These reactions were conducted under water-free conditions below –15 °C due to decomposition of the unstable reactants, and formed dialkyl heteroarylphosphonates in only low to moderate yields.[5] A few reactions on the variants of *N*-alkoxypyridinium salts such as *N*-trifluoromethane sulphonyl pyridinium and *N*-(alkoxycarbonyl)oxy pyridinium, were then developed (Scheme 1, A2), in which toxic or moisture-sensitive regents were required.[6] Recently, the strategy of C-H bond functionalization successfully facilitated the synthesis of heteroarylphosphonates.[7, 8] Typically, Huang et al developed a dehydrogenative coupling reaction of heteroarenes with dialkyl hydrophosphonates by the use of a noble metal and excess of stoichiometric amount of oxidants (Scheme 1, B1).[7a] In addition, Wu and co-workers reported a method via C-H functionalization of heteroaryl *N*-oxides that worked at an elevated temperature for dozens of hours (Scheme 1, B2).[8]

Normally, heteroarene *N*-oxides are highly polar molecules, but they are not so active. It requires to be at an elevated temperature for the direct reactions between heteroarene *N*-oxides with P(III) nucleophiles, such as hydrophosphonates.[8] Accordingly, activation of the substrate is an alternative for allowing such reactions to work under mild conditions.

In situ activation highlights high step economy and the ease of operation. However, in situ activation of heteroarene *N*-oxides is theoretically challenging when a phosphorous nucleophile is present because the activating agents possibly prefer the nucleophile rather than the weakly nucleophilic *N*-oxide substrate. In continuation of our work on activating agents in situ formed from the reagent combination of phosphine derivatives with additives,[9] we found that $CBrCl_3$ is able to activate the reactions of heteroarene *N*-oxides with trialkyl phosphites, allowing the synthesis of heteroarylphosphonates under very mild conditions in the absence of solvents, metal catalysts and extra common activating agents (Scheme 1, C).

At the outset of the investigation, isoquinoline *N*-oxide (**1a**) was chosen as the substrate in the model reaction (Table 1). It was previously disclosed that the reaction of $P(OMe)_3$ with iodine quickly formed dimethoxyphosphoryl iodide, an active intermediate capable of activating the carboxyl group.[9a] On the other hand, it is well known that the deoxygenative chlorination of pyridine *N*-oxides can be achieved with $POCl_3$.[10] We hoped that in situ formed dimethoxyphosphoryl iodide could be used as an activator of *N*-oxides, similar to $POCl_3$. Therefore, we firstly tried the reagent combination of $P(OMe)_3$

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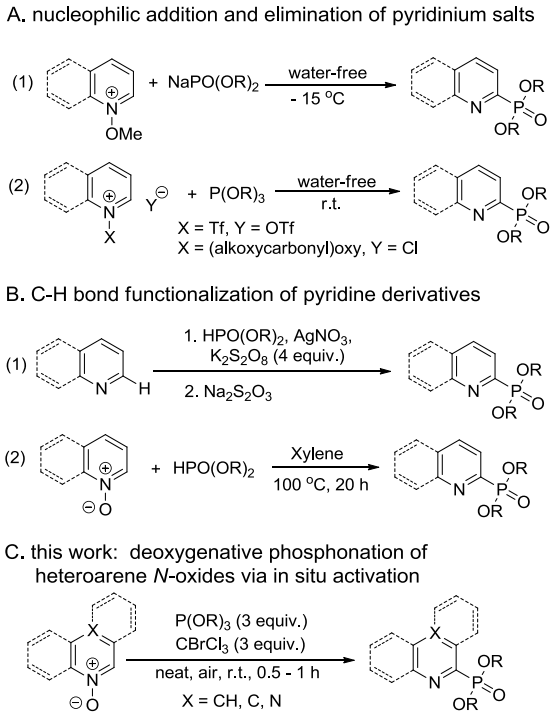
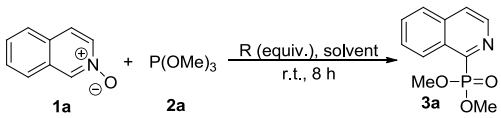
and I_2 for the deoxygenative phosphonation of **1a**. Unfortunately, no desired product formed despite the fact that **1a** was completely converted (entries 1 & 2). We then tried CCl_4 and CCl_3CN since the combinations of PPh_3/CCl_4 and PPh_3/CCl_3CN were capable of deoxygenative chlorination of alcohols and heteroarene *N*-oxides, respectively.[11] When CCl_3CN was employed as the additive in CCl_4, the deoxygenative phosphonation took place, but the yield was very low. A control experiment indicated that it was not CCl_4 but CCl_3CN promoted the reaction (entries 3–5).



Scheme 1 Different strategies for the synthesis of heteroarylphosphonate derivatives.

More recently, Thiemann and co-workers noted the use of $CBrCl_3$ as a surrogate of CCl_4 in Appel type transformations.[11a, 12] We then turned to $CBrCl_3$, a preferred reagent over CCl_4 because of environmental concern.[13] The transformations worked, but good results could not be obtained despite attempting several optimization experiments (entries 6–12). Fortunately, when $P(OMe)_3$ (**2a**) was used as solvent, the desired product was isolated in good yield (entry 13). Further screening the amounts of reagents relative to *N*-oxide **1a** suggested that the best result was achieved with 3 equivalents of **2a** and $CBrCl_3$ in the absence of solvent (entry 14). The reaction did not occur at the temperature as low as ice point (entry 18). When **2a** was replaced with dimethyl hydrogenphosphonate, the phosphonation did not work (entry 19). Therefore, we established optimized conditions for the deoxygenative phosphonation of heteroarene *N*-oxides via in situ activation for the preparation of heteroarylphosphonates. The reaction was complete within one hour using $P(OMe)_3$ (3 equiv.) and $CBrCl_3$ (3 equiv.) at room temperature under the ambient atmosphere in the absence of solvent.

Table 1 Optimization of the reaction conditions[a]



1a **2a** **3a**

Entry	R (equiv.)	Solvent	Yield
1[b]	I_2 (2)	DCM	0
2[b]	I_2 (2)	CCl_4	0
3	CCl_3CN (2)	DCM	trace
4	CCl_3CN (2)	CCl_4	19%
5[c]	-	CCl_4	N.R.
6	$CBrCl_3$ (2)	CCl_4	56%
7	$CBrCl_3$ (3)	CCl_4	60%
8	$CBrCl_3$ (3)	Toluene	29%
9	$CBrCl_3$ (3)	CH_3CN	trace
10	$CBrCl_3$ (3)	DCM	35%
11	$CBrCl_3$ (3)	Et_2O	40%
12	$CBrCl_3$ (3)	THF	41%
13[d]	$CBrCl_3$ (3)	**2a**	75%
14	$CBrCl_3$ (3)	-	81%
15[e]	$CBrCl_3$ (2)	-	44%
16	$CBrCl_3$ (2)	-	46%
17[e]	$CBrCl_3$ (3)	-	54%
18[f]	$CBrCl_3$ (3)	-	N.R.
19[g]	$CBrCl_3$ (3)	-	N.R.

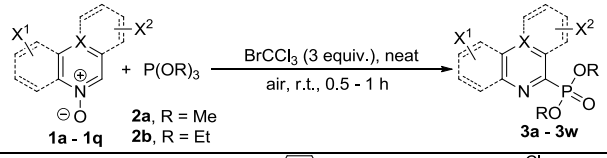
[a] Reaction conditions: **1a** (1 mmol), **2a** (350 μL, 3 mmol), solvent (1 mL) at room temperature (r.t.) for 8 h unless otherwise stated. For entries 13 – 17, the reaction time was 1 h. Yield of isolated product. N.R. = no reaction, which means **1a** was unchanging as monitored by thin-layer chromatography (TLC). [b] 2 mL of solvent was used. TLC indicated that **1a** was completely transformed into a complicated mixture, and no confirmed compound was identified. [c] The reaction was performed from r.t. to 75 °C. [d] 0.5 mL of **2a** (4.3 mmol) was used. [e] 230 μL of **2a** (2 mmol) was used. [f] The reaction was performed at 0 °C. [g] conditions as entry 14, but with dimethyl hydrogenphosphonate (275 μL, 3 mmol) rather than **2a**.

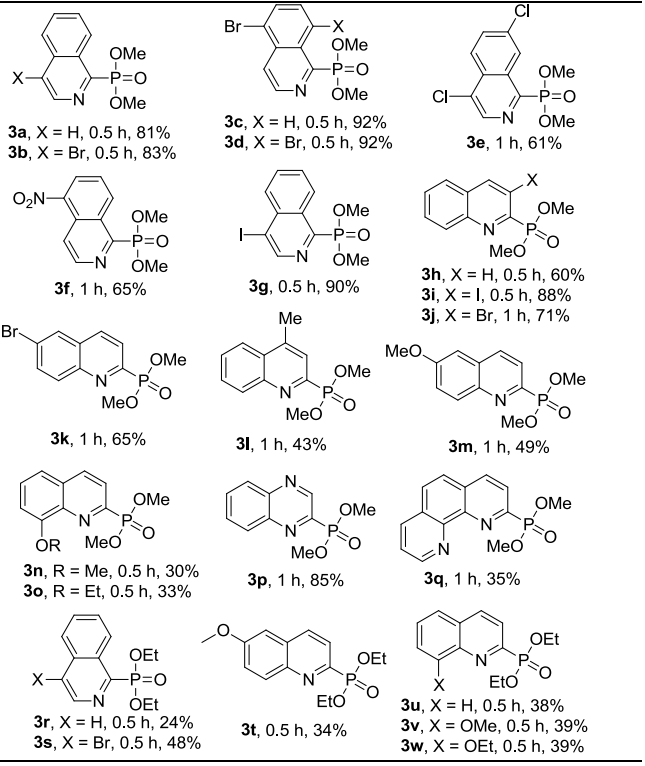
To assess the scope of the present protocol, various heteroarene substrates were examined. The results, summarized in Table 2, showed that the heteroarene *N*-oxides produced the expected phosphonation products very fast under mild conditions. For most of the tested substrates, dimethyl heteroarylphosphonates were isolated in acceptable yields (**3a**–**3q**), and many of them were isolated in good to excellent yields. Generally, isoquinoline *N*-oxides gave better results than quinoline *N*-oxides (**3a**–**3g** vs **3h**–**3o**), while quinoxaline *N*-oxides better than 1,10-phenanthroline *N*-oxides (**3p** vs **3q**). The comparison of the substrate structures reveales that the N-O bond in quinoline and 1,10-phenanthroline *N*-oxides suffers from more steric hindrances than that in isoquinoline and quinoxaline *N*-oxides, respectively. Thus, the results suggest that the steric hindrance around the N-O bond significantly impacted the deoxygenative phosphonation.

Remarkably, most halogenated substrates, whether bromo or iodo, gave the expected heteroarylphosphonates in good to excellent yields (**3b**–**3d**, **3g**, **3i**). The outcomes are important due to the fact that halo groups at aryl ring are desired in the

extensive applications of cross-couplings, but they are often incapable of tolerating the conditions of Hirao coupling.[4] Therefore, the present protocol, as a prominent complement to the Hirao coupling, is beneficial to the synthesis of halo-substituted heteroarylphosphonates for their post-transformations.

Table 2 Substrate scope of deoxygenative phosphonation of heteroarene *N*-oxides [a]

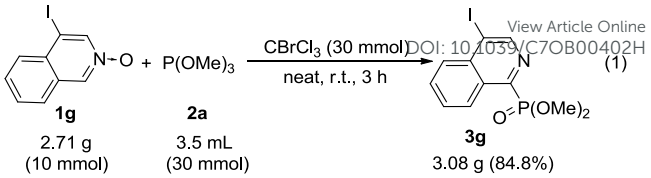




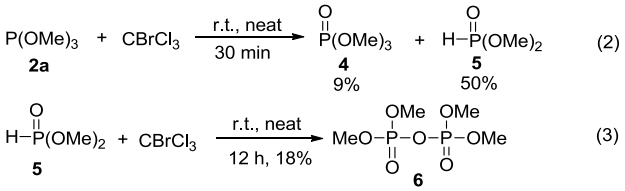
[a] *Reaction conditions*: *N*-oxide (**1a–1q**, 1 mmol), **2** (3 mmol) and $CBrCl_3$ (3 mmol) under the ambient atmosphere at room temperature. Yield of isolated product.

The substrates containing electron-donating substituents gave the products in much lower yields than others (**3l–3o** vs **3a–3k**) due to their low activities. Better results of these substrates were unsuccessful despite several attempts via extension of reaction time and change of reaction temperature. Moreover, the phosphite reagents bearing larger alkyls than methyl decreased the yields sharply (**3r**, **3s** & **3u** vs **3a**, **3b** & **3h**). No products were identified when $P(OBu)_3$ was employed (results not shown). In addition, pyridine *N*-oxide failed to realize the transformation under the current conditions.

Notably, the gram-scale preparation of deoxygenative phosphonation was feasible. The reaction efficiency affected little when **1g** was employed on a 10 mmol scale (Equation 1).



To establish the mechanism of the deoxygenative phosphonation, NMR spectroscopy was used to monitor the progress of the reaction. As shown in Figure 1, the main byproducts in the final mixture of the neat reactions were trimethyl phosphate (**4**), dimethyl hydrogenphosphonate (**5**), and tetramethyl diphosphate (**6**). We then used ^{31}P NMR spectroscopy to monitor the progress of the reaction that was conducted in a deuterated solvent. It was observed that the phosphorus-containing compounds were formed in the following sequence: firstly **4** and **5**, then the desired product and dimethyl (trichloromethyl)phosphonate (**7**),[14, 15] and finally **6** (Figures S1 and S2).[16] To elucidate the formation of these compounds in the neat reactions, two control experiments were conducted (Equations 2 and 3).



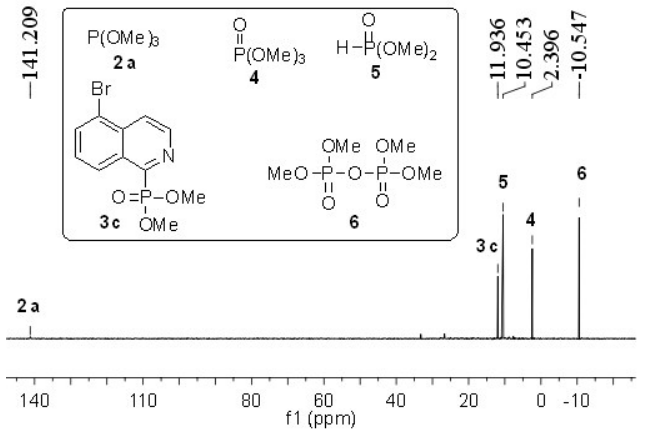
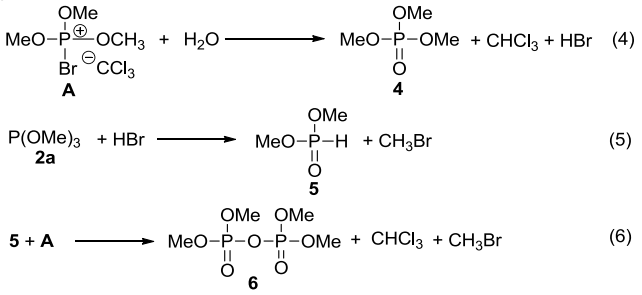


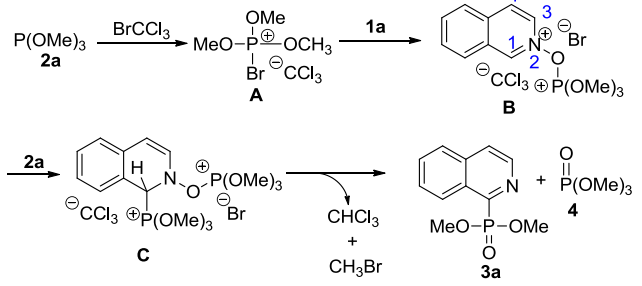
Figure 1. ^{31}P {^1H} NMR spectrum recorded for the final mixture of deoxygenative phosphonation in the absence of solvent. The bold codes above the peaks denote the assignment of each peak to the related molecule in the inserted box.

In principle, the Arbuzov reaction will possibly take place when an alkyl halide mixes with a trialkyl phosphite.[17] The reaction of CCl_4 with $P(OMe)_3$ (**2a**) produced **7**.[14] Unexpectedly, the neat reaction between $CBrCl_3$ and **2a** at room temperature gave **4** and **5** prior to **7** (Figure S3),[16] as shown in Equation 2. Meanwhile, the reaction of **5** with $CBrCl_3$ slowly generated **6** (Equation 3, Figure S4).[16] These results indicated that the reaction of $CBrCl_3$ with $P(OMe)_3$ (**2a**) was much faster than that with dimethyl hydrogenphosphonate (**5**). The intermediate of **2a** with $CBrCl_3$ was inferred to be phosphonium **A** (Equation 4).[9a, 11, 17] The reaction of **A** with trace of water from the

reagents and ambient atmosphere possibly releases **4** and HBr. Hydrogen halides are capable of decomposing trialkyl phosphites.[18] Accordingly, **2a** could be transformed into **5** (Equation 5). Similar to water, **5** is able to accelerate the inactivation of **A**, and gives tetramethyl diphosphate (Equation 6).



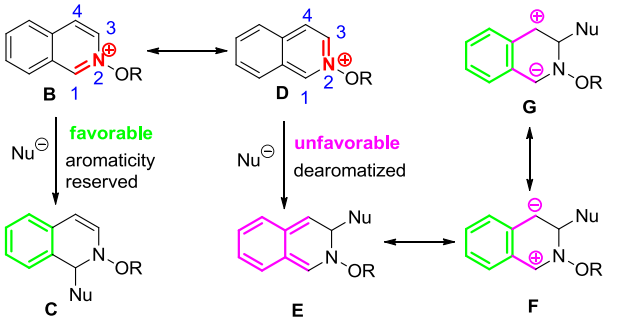
Based on the experimental observations, a mechanism is proposed for the deoxygenative phosphonation (Scheme 2). The reaction is initiated as the formation of phosphonium intermediate **A**. An *N*-oxide (**1a**) is activated by **A**, and forms biscation ion pair **B**. The nucleophilic attack of **2a** on **B** gives biscation ion pair **C**. **C** is fragmentized into the desired product (**3a**), accompanying with the byproducts that include trimethyl phosphate (**4**), chloroform and bromomethane.



Scheme 2 Proposed mechanism for the deoxygenative phosphonation.

The proposed mechanism features the in situ activation by phosphonium intermediate **A**, and the formation of biscation ion pairs **B** and **C**. **A** is active, [9a, 11] and could be inactivated by a nucleophile with little steric hindrance (e.g., H_2O). **A** will partially convert to **7** via the Arbuzov rearrangement in a relatively dilute solution where **A** is separated away from the nucleophilic *N*-oxide by solvent molecules (Figures S1 and S2).[16] Comparatively, the reaction system of high concentration facilitates the deoxygenative phosphonation. Consequently, the neat reactions become efficient due to the fact that the number of collision between **A** and the *N*-oxide (e.g., **1a**) increases. The formation of biscation ion pairs **B** and **C** was supported in some extent by a few examples of similar biscation ion pairs reported in literatures.[19] The S_NAr reactions of pyridine *N*-oxides that were efficiently promoted by phosphonium salt PyBroP rationalized the present mechanism.[20]

The mechanism provides a reasonable explanation for the regioselectivity of the phosphonation in case of isoquinoline *N*-oxides.[21] The reaction could occur at the 1- or 3-position of isoquinoline *N*-oxides (e.g., **3a**), and the steric hindrance at the 3-position is less than that of the 1-position (Scheme 2). However, the phosphonations exclusively took place at the 1-position.[8] In the activated form of substrates (**B**), both positions 1 and 3 are theoretically electrophilic due to the fact that the resonance structures **B** and **D** are relatively stable (Scheme 3). In the resonance contributor **B**, the 1-position that represents the carbon center of the iminium moiety is more electrophilic than the 3-position where the carbon atom adjacent to the nitrogen atom in an enamine moiety is located. When a nucleophile attacks on the 1-position, the aromaticity of the benzene ring in **B** is reserved. By contrast, the attack on the 3-position in **D** would give the dearomatized structure (**E**). If the aromaticity of the benzene ring in **E** is reserved via resonance, the resonance contributors would be present as the forms **F** and **G** that are predicted to be relatively unstable due to the separated charges.[22] Therefore, the 1-position in **B** is more favorable than the 3- position.



Scheme 3 The regioselectivity of the deoxygenative phosphonation.

In conclusion, a facile synthesis of heteroarylphosphonates from heteroarene N-oxides is described. It represents the first example of deoxygenative phosphonation of heteroarene *N*-oxides via the strategy of in situ activation. The reactions were employed under very mild conditions in the absence of solvents, metal catalysts and extra common activating agents. The *N*-oxides of isoquinoline, quinoline, quinoxaline and 1,10-phenanthroline were successfully transformed into the corresponding heteroarylphosphonates in a short time. The reaction can be scaled up to produce grams of heteroarylphosphonates under mild conditions. The control experiments demonstrated that the reaction of trimethyl phosphite with bromotrichloromethane did not pass through the classic Arbuzov rearrangement under the present conditions. The broad generality, the good functional group tolerance, the low cost, the wide availability of reagents, and the ease of use make the method a prominent complement to the Hirao coupling.

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15 The main byproducts included **4**–**7**, $CHCl_3$ and MeBr. They were identified by NMR spectroscopy. Dimethyl (trichloromethyl)phosphonate (**7**) was parallelly prepared according to the literature.[14a]

16 See the Supplementary Information (ESI).

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21 The ^{31}P NMR spectra indicated that the transformations of $P(OBu)_3$ with $CBrCl_3$ were similar to that of $P(OMe)_3$, but no desired products were identified when $P(OBu)_3$ was employed in the deoxygenative phosphonation. These results implied that the steric hindrance of a phosphite had a significant impact on the nucleophilic attack of the phosphite on the active intermediate, possibly in the step from **B** to **C** in Scheme 2.

22 Pyridine *N*-oxide failed to realize the deoxygenative phosphonation. The NMR spectra demonstrated that the *N*-oxide had been fully converted into a complicated mixture, but the desired compound did not yield (Figure S5).[16] The result is probably attributed to the instability of the pyridinium salt intermediate, a species corresponding to **B**. Similarly, pyridine *N*-oxide was not workable in the deoxygenative amination of heteroarene *N*-oxides. See: X. Chen, X. Li, Z. Qu, D. Ke, L. Qu, L. Duan, W. Mai, J. Yuan, J. Chen and Y. Zhao, *Adv. Synth. Catal.*, 2014, **356**, 1979.

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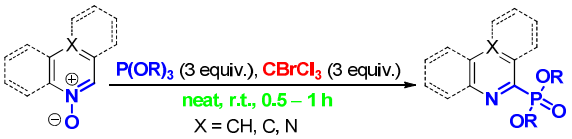

- through in situ activation
- metal-free and soventless
- without extra common activating agent
- capable of scale up
- 23 examples, up to 92% yield

Heteroarene *N*-oxides successfully converted to heteroarylphosphonates in a very short time under mild conditions through in situ activation with $CBrCl_3$.