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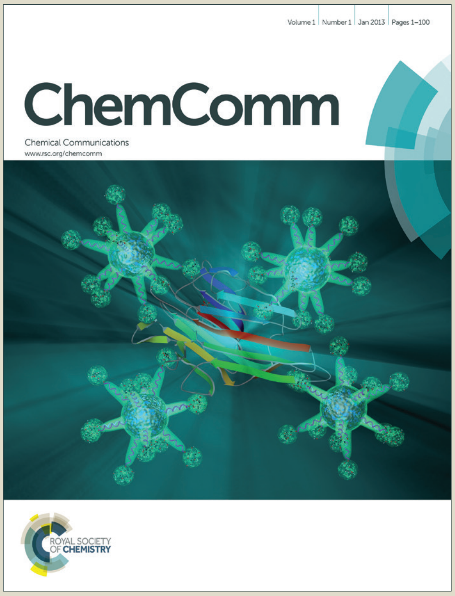

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ARTICLE TYPE

Directly Regioselective Phosphonation of Heteroaryl *N*-oxides with H-phosphonates under Metal and External Oxidant Free Conditions

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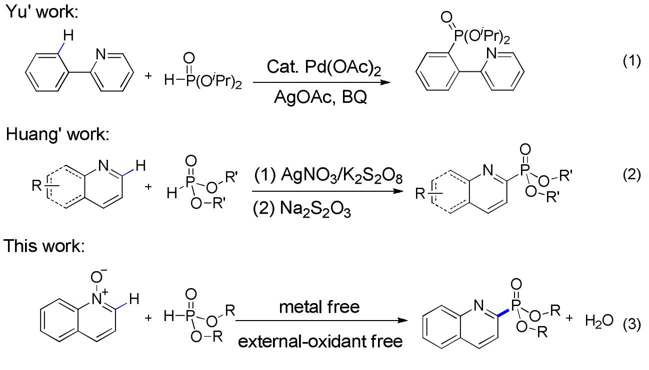
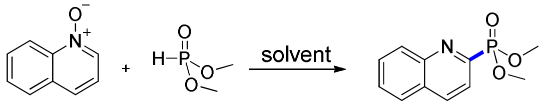
A direct C−H/P−H functionalization of heteroaryl *N*-oxides with H-phosphonates has been described. A wide variety of heteroaryl phosphonates were afforded up to 92% yield in chemo- and regioselective manners under oxidant and metal free conditions. This procedure features with practicality, high efficiency, environmental friendliness and atomic economy.

The heteroaryl phosphonates have wide application in many fields, such as material sciences[1], pharmaceuticals[2], pesticides[3] and organic synthesis[4]. However, the process of building such a structure has lagged behind. Only very recently, Yu[5] group reported a procedure to aryl phosphonates *via* palladium-catalyzed C−H phosphonation reaction from H-phosphonates (**Scheme 1**, eq 1). H-phosphonates were required to be added slowly with a syringe pump to avoid the existence of an excess amount of strong coordinative phosphorus over metal center, which would hamper a process to activate C-H bonds. Then, Murakami[6] have independently developed a palladium-catalyzed direct synthesis of phosphonate derivatives using α-hydroxyalkylphosphonates as the masked phosphonating reagent. Stoichiometric or excessive external oxidants and metal as catalyst[7] are necessary in both procedures. On the other hand, C−H bond phosphonation of arenes or heteroarenes using an oxidant as a radical initiator through radical process has recently emerged as an alternative practical procedure to construct C−P bond (**Scheme 1**, eq 2).[8] Yet, stoichiometric and environmentally unfriendly oxidants, such as manganese[8a-8j], silver salts[8k-8t] were often required, which would reduce the overall "greenness" of the process and limit their widespread usages. Therefore, the development of mild, efficient, and environmentally benign methods for the synthesis of aryl and heteroaryl phosphonates is highly desired. Herein, we disclose our preliminary results on the direct C−H bond phosphonation of heteroaryl *N*-oxides under oxidant, additives and metal free conditions (**Scheme 1**, eq 3).



Scheme 1. Different strategies to construct C-P bond *via* C-H activation.

Table 1. Screening the various reaction parameters for the phosphonation of quinoline *N*-oxide **1a** with dimethyl H-phosphonate **2a**[a]



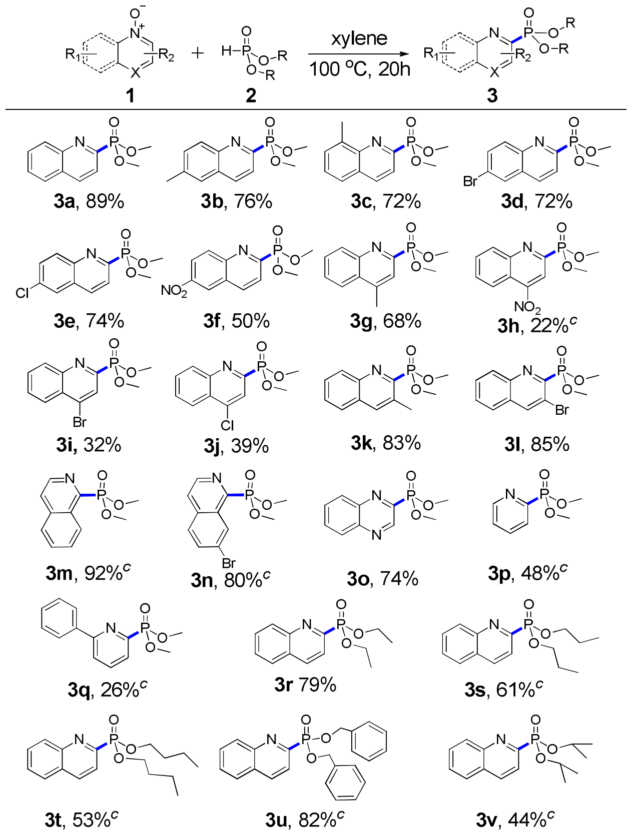
1a **2a** **3a**

Entry	Additions	solvent	T/°C	t/h	yields[b]
1[c]	TFA	toluene	100	20	75%
2	—	toluene	100	20	86%
3	TFA	toluene	100	20	69%
4	4Å MS	toluene	100	20	76%
5[d]	—	toluene	100	20	–
6	—	CH_3CN	100	20	19%
7	—	DCE	100	20	trace
8	—	THF	100	20	21%
9	—	1,4-dioxane	100	20	38%
10	**—**	**xylene**	**100**	**20**	**89%**
11	—	DMF	100	20	nd[e]
12	—	DMSO	100	20	trace
13	—	xylene	100	16	69%
14	—	xylene	100	12	49%
15	—	xylene	80	20	46%
16	—	xylene	30	20	trace
17[f]	—	xylene	100	20	88%

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol) solvent (2.0 mL). [b] Isolated yields based on **1a**. [c] 10% $Pd(OAc)_2$. [d] 3.0 equiv of Na_2CO_3. [e] nd is not detected. [f] The new tube and magneton were used.

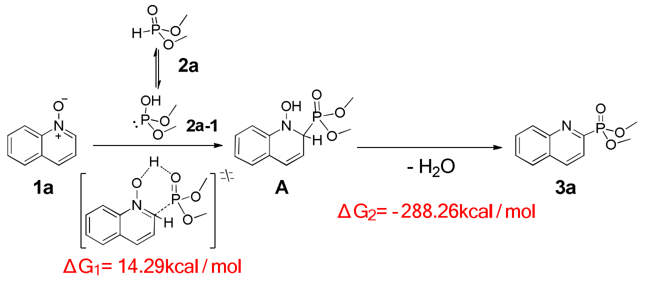
The condensation of quinoline *N*-oxide **1a** with dimethyl H-phosphonate **2a** was initially chosen as a model reaction to screen the various reaction parameters (**Table 1**). The phosphonated product **3a** was obtained in 75% yield with high regioselectivity in the presence of $Pd(OAc)_2$ (10 mol %) and TFA (0.2 equiv) (entry 1). Surprisingly, 86% yield could be achieved in the absence of $Pd(OAc)_2$ (entry 2). TFA and 4Å MS were not favorable for this reaction and made the yield decrease to 69% and 76%, respectively (entries 3, 4). The base, such as Na_2CO_3, was not suitable for this phosphonation reaction (entry 5). Further investigation showed that this transformation was highly solvent dependent (entries 2, 6−12). Xylene was the most suitable solvent and gave the desired product in 89% (entry 10). Decreasing the temperature or prolonging the reaction time brought a significant decrease in the yields (entries 13−16). 88% Yield could be obtained when the new tube and magneton were used. Finally, the optimal reaction conditions for the direct regioselective phosphonation of quinoline *N*-oxide were identified to be xylene as the solvent at 100 °C for 20 hours.

Table 2. The scope of the substrates for the direct C−H phosphonation reaction [a,b]



[a] Reaction conditions: heteroaryl *N*-oxides **1** (0.5 mmol), dimethyl phosphonate **2a** (1.5 mmol), 2.0 mL xylene, 20 hours, 100 °C. [b] Isolated yields. [c] Toluene was chosen as the solvent.

With the optimal reaction conditions in hand, we embarked on the generality and scope of the substrates for this transformation. A wide range of heteroaryl *N*-oxides **1** were firstly evaluated to react with dimethyl H-phosphonate **2a** (**Table 2**, **3a-3q**). Quinoline *N*-oxides containing electron-donating, neutral and electron-withdrawing groups underwent the reaction cleanly, affording the products in 22−89% yields (**3a**−**3l**). Notably, the effect of the substituents in the phenyl ring of quinoline *N*-oxides was not apparent. 6-Methyl, 8-methyl, 6-bromo, 6-chloro and 6-nitro quinoline *N*-oxides could give the desired products in moderate to good yields (**3a**−**3f**). 4-Methyl quinoline *N*-oxide worked smoothly and provided the phosphonated product in 68% yield with high regioselectivity (**3g**). While the electron-withdrawing groups, such as NO_2, Br and Cl, at the C_4-position disfavored this transformation and only gave the corresponding products in 22%, 32% and 39% yields, respectively (**3h**−**3j**). It was noting that 3-methyl quinoline *N*-oxide and 3-bromo quinoline *N*-oxide with steric hindrance underwent efficient reaction with dimethyl H-phosphonate to furnish the coupled products in 83% and 85% yields, respectively (**3k**, **3l**). In addition, this reaction system was also applied to isoquinoline *N*-oxide, 7-bromo-isoquinoline *N*-oxide and quinoxaline *N*-oxide and afforded the desired products **3m**, **3n** and **3o** in 92%, 80% and 74% yields, respectively. Pyridine *N*-oxide and 2-phenyl pyridine *N*-oxide were also shown to be possible substrates and gave the corresponding products in 48% and 26% yields, respectively (**3p**, **3q**). No products were afforded when 2-bromo, 2-chloro and 2-nitrile pyridine *N*-oxides were utilized as the substrates. Next, we examined the generality of H-phosphonates. Dimethyl, diethyl, di-*n*-propyl, di-*n*-butyl and dibenzyl H-phosphonates could couple well with quinoline *N*-oxide and obtain the corresponding products in 89%, 79%, 61%, 53% and 82% yields, respectively (**3a**, **3r**−**3u**). Di-*iso*-propyl H-phosphonates with large bulk could also give the desired products in 44% yield (**3v**).



Scheme 2. Proposed reaction mechanism.

A plausible reaction mechanism for the direct C−H phosphonation was proposed and shown in **Scheme 2** according to the density functional theory (DFT) calculations[10] and results obtained. Initially, intermediate **A** could be easily generated through a six-membered ring transition state by nucleophilic addition of the tautomeric dimethyl H-phosphonate with quinoline *N*-oxide, which activation energy was only 14.29 kcal/mol. Then the intermediate **A** underwent an elimination to produce the product **3a** and a molecule of H_2O with -288 kcal/mol.[11] It is proposed that there are two reasons for the large ΔG: 1) the dissociation of water would lead to the increase of entropy; 2) The large conjugated system in product **3a** would lower the energy of **3a**.

Conclusions

We have presented the first example of the C−H phosphonation of heteroaryl compounds under oxidant, additives and metal free conditions. The various heteroaryl phosphonates were obtained in up to 92% yield in chemo- and regioselective manners. Further investigations on the reaction pathway in detail and extending the scope of the reaction are in process.

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Notes and references

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