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Direct regioselective phosphonation of heteroaryl *N*-oxides with H-phosphonates under metal and external oxidant free conditions†
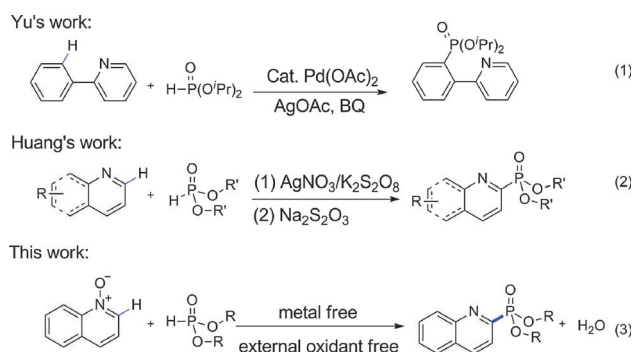
Hui Wang,[a] Xiuling Cui,*[ab] Yu Pei,[a] Qianqian Zhang,[a] Jie Bai,[a] Donghui Wei[a] and Yangjie Wu*[a]

A direct C–H/P–H functionalization of heteroaryl *N*-oxides with H-phosphonates is described. A wide variety of heteroaryl phosphonates were obtained in up to 92% yield in a chemo- and regioselective manner, under oxidant and metal free conditions. This procedure features practicality, high efficiency, environmental friendliness and atom economy.

Heteroaryl phosphonates have a wide application in many fields, such as material sciences,[1] pharmaceuticals,[2] pesticides[3] and organic synthesis.[4] However, the process of developing methods for building such a structure has lagged behind. Only very recently, Yu's group[5] reported a procedure for the synthesis of aryl phosphonates *via* a palladium-catalyzed C–H phosphonation reaction starting from H-phosphonates (Scheme 1, eqn (1)). The H-phosphonates were required to be added slowly

Scheme 1 Different strategies for the construction of C–P bonds *via* C–H activation.

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using a syringe pump to avoid the existence of an excess amount of strongly coordinating phosphorus over the metal center, which would hamper the activation process of C–H bonds. Then, Murakami *et. al.*[6] independently developed a palladium-catalyzed direct synthesis of phosphonate derivatives using α-hydroxyalkylphosphonates as a masked phosphonating reagent. Stoichiometric or excessive external oxidants and a metal catalyst[7] are necessary in both procedures. On the other hand, C–H bond phosphonation of arenes or heteroarenes through a radical process, using an oxidant as a radical initiator, has recently emerged as an alternative practical procedure for the construction of C–P bonds (Scheme 1, eqn (2)).[8] Yet, stoichiometric and environmentally unfriendly oxidants, such as manganese,[8a–j] or silver salts[8k–t] were often required, which would reduce the overall "greenness" of the process and limit its widespread usage. 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,[9] additive and metal free conditions (Scheme 1, eqn (3)).

The condensation of quinoline *N*-oxide (**1a**) with dimethyl H-phosphonate (**2a**) was initially chosen as a model reaction for screening of 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, an 86% yield could be achieved in the absence of both Pd(OAc)$_2$ and TFA (entry 2). TFA and 4 Å MS were not favorable for use in this reaction and caused the yield to decrease to 69% and 76%, respectively (entries 3 and 4). The use of Na$_2$CO$_3$, was not appropriate for this phosphonation reaction (entry 5). Further investigations showed that the transformation is highly solvent dependent (entries 2, 6–12). Xylene was the most suitable solvent and resulted in the desired product being obtained in 89% yield (entry 10). Decreasing the temperature or prolonging the reaction time brought about a significant decrease in the yield (entries 13–16). An 88% yield could be obtained when a new
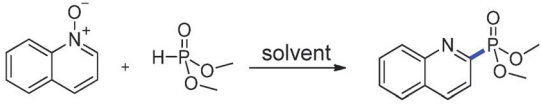
Table 1 Screening of the various reaction parameters for the phosphonation of quinoline N-oxide (**1a**) with dimethyl H-phosphonate (**2a**)[a]
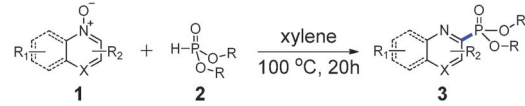

Entry	Additive	Solvent	$T/°C$	t/h	Yields[b]/%
1[c]	TFA	Toluene	100	20	75
2	—	Toluene	100	20	86
3	TFA	Toluene	100	20	69
4	4 Å MS	Toluene	100	20	76
5[d]	—	Toluene	100	20	—
6	—	CH$_3$CN	100	20	19
7	—	DCE	100	20	Trace
8	—	THF	100	20	21
9	—	1,4-Dioxane	100	20	38
10	**—**	**Xylene**	**100**	**20**	**89**
11	—	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)$_2$ was used. [d] 3.0 equiv. of Na$_2$CO$_3$ was used. [e] nd: not detected. [f] A new tube and magnetic stirring element were used.

tube and magnetic stirring element were used. Finally, the optimal reaction conditions for the direct regioselective phosphonation of quinoline N-oxide were identified to be the use of xylene as the solvent at 100 °C for 20 hours.

With the optimal reaction conditions in hand, we embarked on a study of the reaction generality and the scope of the substrates for this transformation. A wide range of heteroaryl N-oxides (**1**) were firstly evaluated in reaction 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 desired products in 22–89% yields (**3a**–**3l**). Notably, the effect of the substituents on the phenyl ring of the quinoline N-oxides was not apparent. The use of 6-methyl, 8-methyl, 6-bromo, 6-chloro or 6-nitro quinoline N-oxides provided the desired products in moderate to good yields (**3a**–**3f**). 4-Methyl quinoline N-oxide underwent the reaction smoothly and the phosphonated product was obtained in 68% yield with high regioselectivity (**3g**). Whereas electron-withdrawing groups, such as NO$_2$, Br and Cl, at the C$_4$-position disfavored the transformation and the corresponding products were obtained in only 22%, 32% and 39% yields, respectively (**3h**–**3j**). It should be noted that 3-methyl quinoline N-oxide and 3-bromo quinoline N-oxide, with steric hindrance, underwent an 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 the desired products **3m**, **3n** and **3o** were obtained in 92%, 80% and 74% yields, respectively. Pyridine N-oxide and 2-phenyl pyridine N-oxide were also

Table 2 Examination of the substrate scope for the direct C–H phosphonation reaction[a,b]

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

shown to be possible substrates and the corresponding products were obtained in 48% and 26% yields, respectively (**3p**, **3q**). No products were obtained when 2-bromo, 2-chloro or 2-nitrile pyridine N-oxides were utilized as the substrate. Next, we examined the generality of the reaction with respect to H-phosphonates. Dimethyl, diethyl, di-n-propyl, di-n-butyl and dibenzyl H-phosphonates could couple well with quinoline N-oxide and the corresponding products were obtained in 89%, 79%, 61%, 53% and 82% yields, respectively (**3a**, **3r**–**3u**). The use of di-iso-propyl H-phosphonate, with a large steric bulk, also provided the desired product in 44% yield (**3v**).

A plausible reaction mechanism for the direct C–H phosphonation was proposed according to density functional theory (DFT) calculations[10] and the experimental results obtained, and is shown in Scheme 2. Initially, intermediate **A** could be easily generated through a six-membered ring transition state by nucleophilic addition of the tautomeric dimethyl H-phosphonate to quinoline N-oxide, for which the activation energy was only 14.29 kcal mol^{-1}. Then intermediate **A** can undergo an elimination to produce the product **3a** and a molecule of H$_2$O, with an activation energy of −288 kcal mol^{-1}.[11] It is proposed that there are two possible reasons for the large ΔG: (1) the dissociation of water would lead to an increase in entropy; (2) the large conjugated system present in the product **3a** would lower the energy of **3a**.
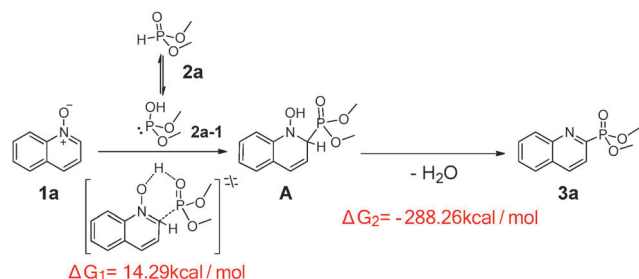
Scheme 2 Proposed reaction mechanism.

We have presented the first example of a C–H phosphonation of heteroaryl compounds under oxidant, additive and metal free conditions. The various heteroaryl phosphonate products were obtained in up to 92% yield in a chemo- and regioselective manner. Further investigations into the detailed reaction pathway and extension of the scope of the reaction are in process.

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