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# Copper-catalyzed phosphorylation of sp$^2$ C–H bonds†

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Shan Wang, Rui Guo, Gao Wang, Shan-Yong Chen* and Xiao-Qi Yu*

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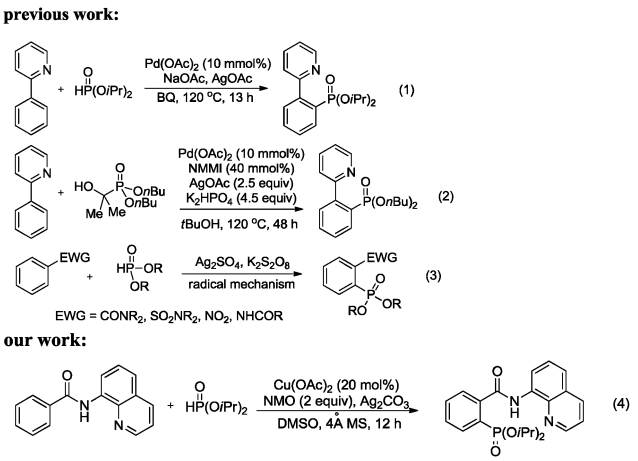
**The phosphorylation of the *ortho* C–H bonds in benzamides containing an 8-aminoquinoline moiety as a bidentate directing group with H-phosphonates using copper as a catalyst under mild temperature conditions is described. This method shows high functional group compatibility and selectively gives mono-substituted products.**

Aryl phosphonates and derivatives have found a wide range of applications in medicinal chemistry,[1] materials chemistry,[2] and catalysis.[3] Since the pioneering work developed by Hirao and co-workers in 1981,[4] the coupling of aryl halides or pseudohalides with dialkyl phosphates has become one of the most straightforward routes to construct C(sp$^2$)–P bonds.[5] Recently, the direct functionalization of carbon–hydrogen (C–H) bonds has emerged as an atom-economical and environmentally friendly synthetic method as it eliminates the need for prefunctionalization of coupling partners.[6] However, the direct formation of C–P bonds through C–H activation is problematic because of the strong coordinating character of phosphorus reagents.[7,8] Very recently, the Yu group and the Murakami group addressed this problem by using a non-removable pyridine as the directing group and a palladium reagent as the catalyst (Scheme 1, eqn (1) and (2)).[9,10] A silver-catalyzed phosphonation of arenes bearing electron-withdrawing groups through a radical mechanism has also been developed (Scheme 1, eqn (3)).[11] Herein, we present a method for direct C–H phosphorylation by using a removable amide as the directing group and copper(II) acetate as the catalyst (Scheme 1, eqn (4)).

The use of low cost and toxicity copper reagents as catalysts for C–H bond activation is particularly attractive. Many good examples of the copper-catalyzed C–H functionalization reactions have been reported.[12–16] However, as far as we know, no copper-catalyzed direct intermolecular arene C–H phosphorylation reaction has been reported. The use of a removable 8-aminoquinoline-based amide as a directing group,[17] originally developed by Daugulis in a direct arylation reaction,[17a] was reported to have the potential for stabilizing high-valent Cu intermediates.[18] As an outgrowth of these studies, we hypothesized that an 8-aminoquinoline auxiliary would also affect the *ortho*-phosphonation of C(sp$^2$)–H bonds.




Scheme 1 C–H phosphorylation reactions.

Initially, the optimization of the reaction between *N*-(quinolin-8-yl)benzamide (**1a**) and diisopropyl phosphonate (**2a**) started with 20 mol% of Cu(OAc)$_2$, NMO and $Ag_2CO_3$ in NMP at 120 °C for 12 h, giving a relatively low but promising isolated yield of 30% (Table 1, entry 1). When the temperature was increased to 140 °C, the yield of product **3a** was reduced to 23% (entry 2). We were strongly aware of the vital role the temperature played in the reaction (entries 2–4). The temperature effect was investigated in detail (Table S2, ESI†) and 55 °C was proved to be the optimal temperature for this reaction (entry 3). In view of the strong coordinating properties of phosphorus reagents, the reaction was stirred at 15 °C for 30 min before diisopropyl phosphonate was added, then the mixture was transferred and the reaction was carried out at

*Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu, 610064, P. R. China. E-mail: chensy@scu.edu.cn, xqyu@scu.edu.cn; Fax: +86-28-85415886; Tel: +86-28-85415886*

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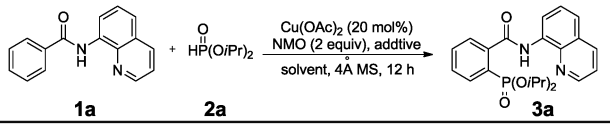
Table 1 Optimization of the reaction conditions[a]




1a 2a 3a

| Entry | $T$ (°C) | Solvent | Additive | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 120 | NMP | $Ag_2CO_3$ | 30 |
| 2 | 140 | NMP | $Ag_2CO_3$ | 23 |
| 3 | 55 | NMP | $Ag_2CO_3$ | 59 |
| 4 | 10 | NMP | $Ag_2CO_3$ | NR |
| 5[c] | 55 | NMP | $Ag_2CO_3$ | 70 |
| 6[c] | 55 | DMSO | $Ag_2CO_3$ | 78 |
| 7[c] | 55 | DMSO | — | 22 |
| 8[c,d] | 55 | DMSO | $Ag_2CO_3$ | NR |

[a] Reaction conditions: amide (0.2 mmol), $Cu(OAc)_2$ (20 mol%), NMO (2 equiv.), additive (2 equiv.), 4 Å MS (100 mg), solvent (0.8 mL) and diisopropyl phosphonate (2 equiv.). [b] Isolated yields. [c] The mixture was stirred at 15 °C for 30 min before diisopropyl phosphonate was added. Then the reaction mixture was transferred and the reaction was carried out at 55 °C immediately. [d] Without $Cu(OAc)_2$. NMO = *N*-methylmorpholine oxide. NMP = *N*-methyl pyrrolidone.

55 °C immediately, affording **3a** in 70% yield (entry 5). The yield was further improved to 78% when the solvent NMP was replaced with DMSO (entry 6). The reaction yield became quite low in the absence of $Ag_2CO_3$ (entry 7). No reaction could be realized without $Cu(OAc)_2$ (entry 8).

The effect of directing groups was next examined. The reaction of *N*-methylamide (Fig. 1, **A**) with diisopropyl phosphonate failed, implying that the relatively acidic NH in **1a** is also assumed to exhibit great significance in the coupling. When **1a** was replaced by some structurally similar but monodentate directing groups, no reaction took place, which suggested that the *N*,*N*-bidentate directing group is essentially crucial for the reaction to proceed (**B–D**). Furthermore, the utilization of the *N*-benzylpicolinamide (**E**) or 2-(methylthio)aniline (**F**) moiety as the bidentate directing group led to trace yields of the phosphorylation products. Accordingly, the reaction appears to be more efficient upon using the 8-aminoquinoline motif as the directing group.

With the optimized reaction conditions in hand, we next examined the scope of a variety of benzoic acid derivatives using the coupling partner **2a** and obtained the isolated yields with substrates **1a–1t** (Table 2). Both electron-rich (**1b**, **1c**, **1l**, **1m**) and electron-deficient (**1d–1k**, **1n–1p**) benzoic acid derivatives are suitable substrates for providing cross-coupling products in moderate to good yields. Only *ortho*-monophosphonylated products were achieved in these cases. In addition, the reaction displayed an outstanding functional group tolerance, including ethers (**3c**, **3m**), halides (**3d–3g**, **3n–3p**), esters (**3k**), nitriles (**3j**) and nitro groups (**3i**). When the *meta*-substituted benzamides were used, no matter what the electronic nature of the substituent is, most of the phosphorylation proceeded selectively at the less sterically hindered position (**3l–3p**). Furthermore, heterocyclic amides are compatible with the reaction conditions. Both five- and six-membered heterocyclic substrates remained reactive under these conditions. Pyridine (**1r**) and thiofuran (**1s**) derivatives were converted to monosubstituted products in synthetically useful yields. This copper-catalyzed direct phosphorylation is also applicable to vinylic C–H bonds (**3t**). To our delight, there was no significant loss of yield when the reaction was scaled up at least tenfold (Scheme 2).

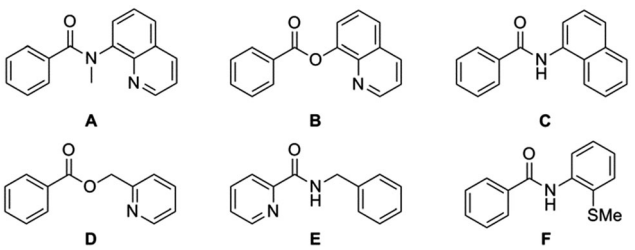
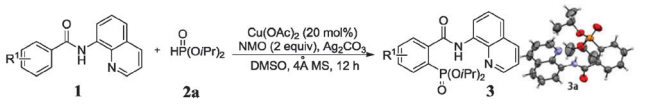
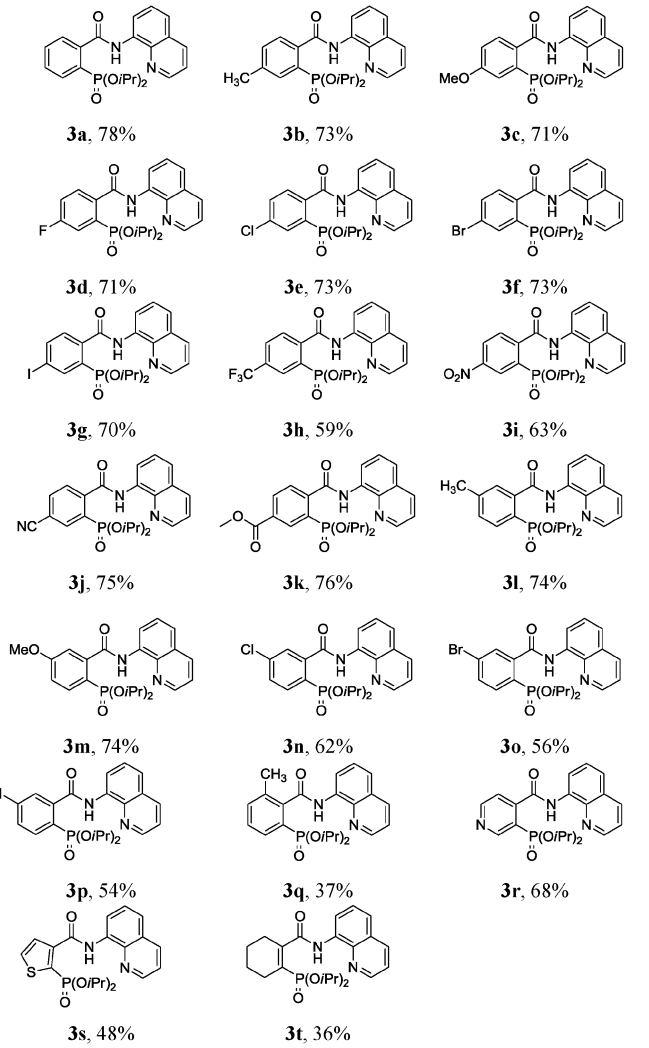



Fig. 1 Ineffective directing groups.

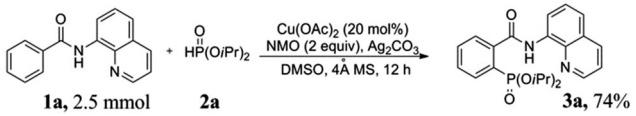
Table 2 Copper-catalyzed phosphorylation of carboxylic acid derivatives[a,b]



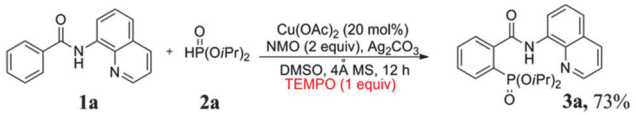

1 2a 3 3a




[a] Amide (0.2 mmol), $HPO(OiPr)_2$ (2 equiv.), $Cu(OAc)_2$ (20 mol%), NMO (2 equiv.), $Ag_2CO_3$ (1 equiv.), DMSO (0.8 mL), 55 °C, 12 h. [b] Isolated yields.




Scheme 2 Preparative scale experiment.

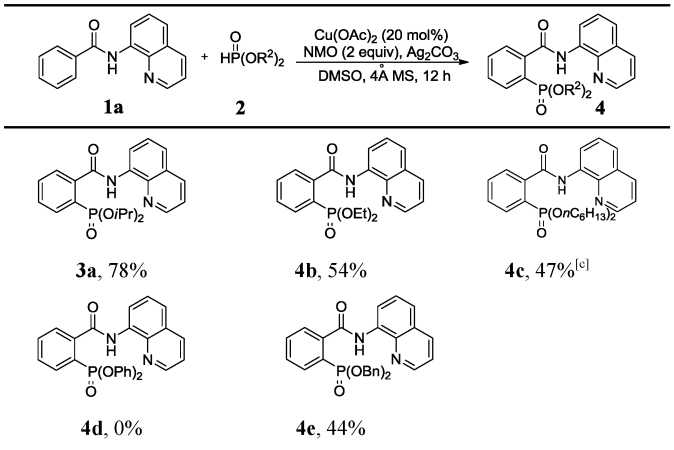



Scheme 3 A control experiment in the presence of TEMPO.

Different dialkyl H-phosphonates and diaryl H-phosphonates were also examined and most of the corresponding products were obtained in moderate yields (**3a**, **4b**, **4c**, **4e**). It seems that the steric and electronic effect of the phosphonates profoundly affected the rate and efficiency of the transformation. When the phosphonate coupling partner was changed to the long aliphatic chain dihexyl phosphonate, the equivalent of the phosphonate, the reaction time had to be increased to afford the desired product (**4c**) in the process. If diphenyl phosphonate as a phosphate reagent participated in the reaction, the transformation was completely blocked because of the bulky benzene rings. Thus, the diisopropyl phosphate was found to be the best partner for the phosphorylation of *N*-(quinolin-8-yl)benzamide derivatives.

Taking into account the previous observation that Ag(I)-mediated phosphorylation of indoles[19] or *N*,*N*-diethylbenzamide[11] with H-phosphonates proceeds *via* a radical pathway, a control experiment was carried out in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO). The addition of TEMPO did not decrease the yield of the model reaction (Scheme 3). Furthermore, this reaction did not proceed in the absence of copper catalyst (Table 1, entry 8). These results indicate that no radical was involved in the catalytic cycle of the phosphorylation (Table 3). Although the mechanism of the reaction is unclear at this moment, it is likely that this Cu-catalyzed phosphorylation reaction proceeds *via* Cu(III) intermediates (Scheme S1, ESI†).[20,21]

Table 3 Evaluation of different phosphorylation reagents[a,b]




[a] Amide (0.2 mmol), $HPO(OR^2)_2$ (2 equiv.), $Cu(OAc)_2$ (20 mol%), NMO (2 equiv.), $Ag_2CO_3$ (1 equiv.), DMSO (0.8 mL), 55 °C, 12 h. [b] Isolated yields. [c] $HPO(OC_6H_{13})_2$ (5 equiv.), 24 h.

In conclusion, we have developed a method for the direct, auxiliary-assisted intermolecular C–H phosphorylation of non-acidic benzamide *β*-C–H bonds. The reaction employs inexpensive copper acetate under mild conditions. Moreover, the process selectively gives only the mono-substituted products and demonstrates excellent functional group tolerance. This method offers a new and straightforward way for the preparation of *ortho*-phosphonated benzoic acid derivatives. Further investigation of the mechanism of the phosphorylation is in progress in our laboratory.

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