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Journal Name

ARTICLE

Direct C4-H Phosphonation of 8-Hydroxyquinoline Derivatives Employing Photoredox Catalysis and Silver Catalysis

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A simple and efficient protocol for the C4-H phosphonation of 8-hydroxyquinoline derivatives was developed under photoredox/silver(I) cocatalysis system, providing a new approach to phosphonated 8-hydroxyquinoline derivatives. Note that the reaction did not occur at the C5 site, but regioselectively at an unusual C4 site. Moreover, the reaction proceeded smoothly under mild reaction conditions (a catalytic amount of silver salt and room temperature) with good functional groups compatibility.

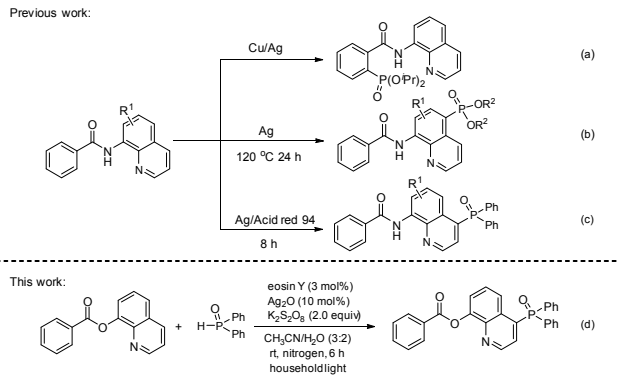
Introduction

Organophosphorus compounds have received increasing interest of many chemists owing to their wide existence in various functional materials, pharmaceuticals and natural products.[1] Usually, construction of C-P bond can be realized from the Pd-catalyzed classic cross-coupling of aryl halides with H-phosphonates, which was first discovered by the group of Hirao in 1981.[2] However, these protocols typically require prefunctionalized arenes such as aryl halides as starting materials.

During the past decades, the direct functionalization of C-H bonds has become a reliable and robust tool in organic synthesis, and afterwards, a series of transformations from C-H bond to C-C or C-heteroatom bond have been demonstrated.[3] Especially, various versions for C-H bond phosphonation of the quinoline ring[4] and other heterocycles[5] were developed under transition metal catalysis or even under transition metal-free conditions.

In 2014, Huang described a direct C2-H phosphonation of the quinoline ring with H-phosphonates without the help of any directing group;[4a] Yu and co-workers also developed a copper-catalyzed phosphonation of the 8-aminoquinoline amides at the C2 site in the aromatic ring (Scheme 1a).[4b] In recent years, the research interest in our group mainly focuses on the C–H functionalization of arene derivatives at an unusual site, especially the direct functionalization of 8-aminoquinoline derivatives[4c,4d,6] and 1-naphthylamine derivatives.[7] For example, our group has demonstrated silver-promoted C5-H or C4-H phosphonation of 8-aminoquinoline amides (Scheme 1b and c).[4c,4d] Although several versions of phosphonation of 8-aminoquinoline amides has been demonstrated, to the best of our knowledge, the reports for C4-H phosphonation of 8-hydroxyquinoline esters remain rare.

On the other hand, photoredox catalysis has become a hot topic and emerged as an environmentally friendly and powerful tool in green chemistry, making the reaction under lower energy consumption and milder conditions.[8] In comparison, organic dyes as photocatalysts exhibited superiority to transition metal counterparts due to their commercial availability and lower cost. And herein, we envisioned developing a mild and efficient catalyst version for C4-H phosphonation of 8-hydroxyquinoline esters under a dual catalysis of silver salt and organic dye-mediated photoredox (Scheme 1d).



Scheme 1. Direct phosphonation of quinoline derivatives.

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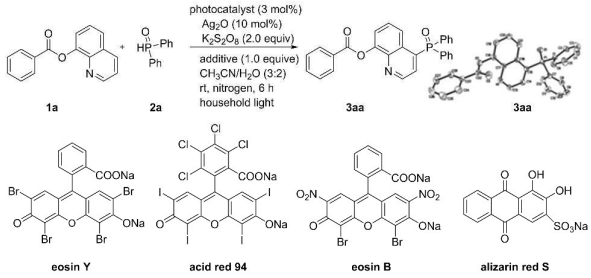
Results and discussion

Initially, the phosphonation of 8-hydroxyquinoline esters **1a** with diphenylphosphine oxide **2a** was explored as a model reaction, and the results are displayed in Table 1. The reaction was first performed using Ag_2O and acid red 94 as a catalyst system in the presence of $K_2S_2O_8$ as an oxidant, affording the desired product **3aa** in 50% isolated yield (Table 1, entry 1). When other silver salts were also checked in this reaction, only $AgNO_3$ and Ag_2CO_3 afforded the products in lower yields of 44% and 48%, respectively (Table 1, entries 2-6, and Supporting Information (SI)); among various photocatalysts, eosin Y exhibited a higher activity, leading to the product in 78% yield (Table 1, entries 7-11). Some oxidants were then evaluated such as $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$, the products were obtained in relatively lower yields of 57% and 45%, respectively (Table 1, entries 7 *vs* 12-14, and SI). Finally, some control experiments were explored. For example, reducing the reaction time to 4 h, performing the reaction in air or oxygen did not afford the better results (Table 1, entries 15-17*vs* entry 7). The molecular structure of **3aa** was unambiguously confirmed by single crystal X-ray diffraction study.[9]

Table 1. Screening of reaction conditions[a]

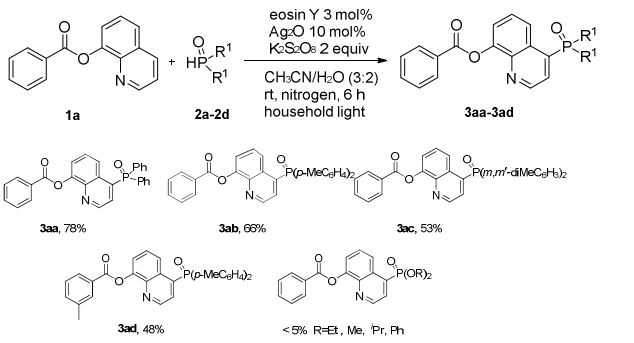


Entry	Photocatalyst	AgX	Oxidant	Yield (%)[b]
1	acid red 94	Ag_2O	$K_2S_2O_8$	50
2	acid red 94	AgOAc	$K_2S_2O_8$	<5
3	acid red 94	$AgNO_2$	$K_2S_2O_8$	37
4	acid red 94	Ag_3PO_4	$K_2S_2O_8$	<5
5	acid red 94	$AgNO_3$	$K_2S_2O_8$	44
6	acid red 94	Ag_2CO_3	$K_2S_2O_8$	48
7	**eosin Y**	**Ag_2O**	**$K_2S_2O_8$**	**78**
8	eosin B	Ag_2O	$K_2S_2O_8$	43
9	$[Ru(bpy)_3]Cl_2$	Ag_2O	$K_2S_2O_8$	42
10	Alizarin red S	Ag_2O	$K_2S_2O_8$	20
11	$Ir(bpy)_3$	Ag_2O	$K_2S_2O_8$	43
12	eosin Y	Ag_2O	TBHP	38
13	eosin Y	Ag_2O	$Na_2S_2O_8$	57
14	eosin Y	Ag_2O	$(NH_4)_2S_2O_8$	45
15[c)]	eosin Y	Ag_2O	$K_2S_2O_8$	57
16[d)]	eosin Y	Ag_2O	$K_2S_2O_8$	34
17[e)]	eosin Y	Ag_2O	$K_2S_2O_8$	<5

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), AgX (10 mol%), photocatalyst (3 mol%, 26 W household light), oxidant (0.2 mmol, 2 equiv) in CH_3CN/H_2O(3:2) (1.0 mL) under nitrogen for 6 h. [b] Isolated yield. [c]For 4 h. [d]Under air. [e]Under oxygen.

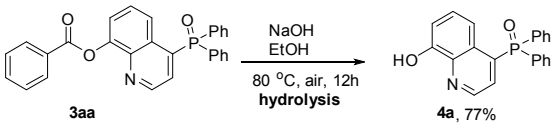
With these optimized reaction conditions in hand, the scope of different phosphonation reagents in the reaction was investigated (Table 2). The reaction of different diarylphosphine oxides lead to desired products in mostly moderate to good yields and diphenylphosphine oxide showed the best reactivity (**3aa**-**3ad**). However, the products could not be observed in the case of dialkyl H-phosphonates.

Table 2. Substrate scope of phosphonation reagents[a,b]



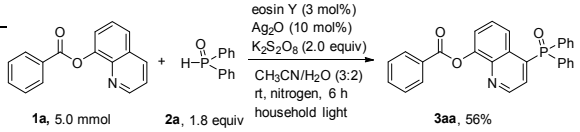
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Ag_2O (10 mol%), eosin Y (3 mol%), 26 W household light, $K_2S_2O_8$ (0.2 mmol, 2 equiv) in CH_3CN/H_2O (1.0 mL) under nitrogen for 6 h. [b] Isolated yield.

Subsequently, the substrate scope of 8-hydroxyquinoline esters was examined, and the results are summarized as Table 3. The results demonstrated that both electron-donating (Me and OMe) and electron-withdrawing (e.g., F, Cl, Br, I, CN and CF_3) groups on the benzene ring were all well tolerated (**3aa**-**3va**). Moreover, the substrates bearing the electron-donating group on the quinoline ring could also smoothly afford the desired products in moderate yields (**3ta**-**3va**). Nevertheless, aliphatic 8-hydroxyquinoline esters can also be tolerated in this phosphonation, albeit resulting in the target products in lower yields of 34% and 37%, respectively (**3wa** and **3xa**). Furthermore, the product **3aa** could be easily transformed into C4 phosphonated 8-hydroxyquinoline **4a** in 77% yield *via* hydrolysis process (Scheme 2)



Scheme 2. The hydrolysis of **3aa**

To further demonstrate the synthetic utility of this reaction, a gram-scale reaction was conducted to afford the desired product **3aa** in 56% yield (Scheme 3).



Scheme 3. A gram scale experiment.

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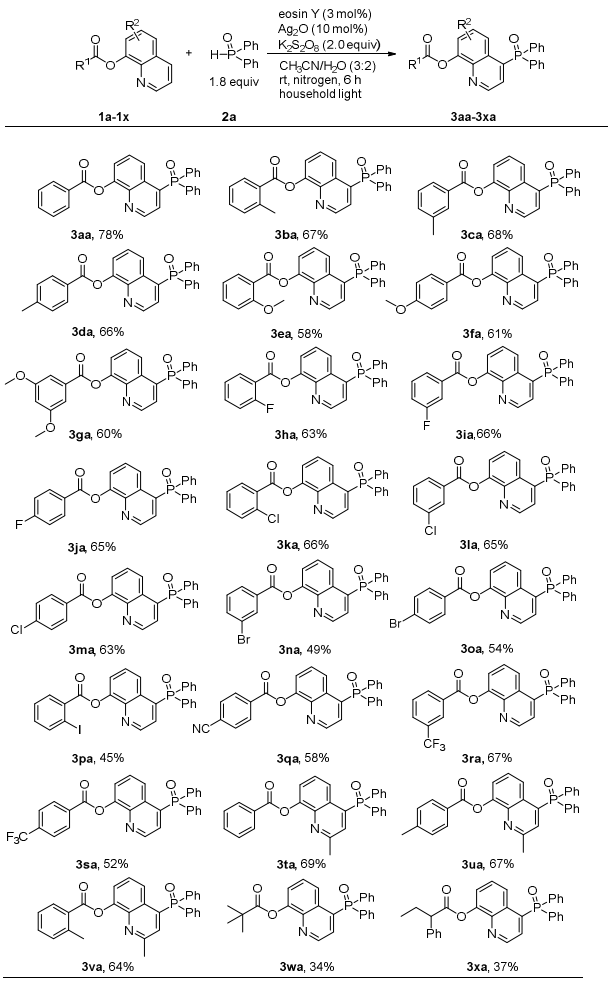
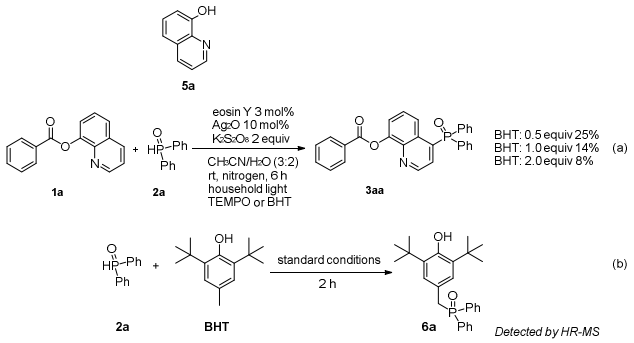
Table 3. Substrate scope of 8-hydroxyquinoline esters[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Ag_2O (10 mol%), eosin Y (3 mol%), 26 W household light, $K_2S_2O_8$ (0.2 mmol, 2 equiv), CH_3CN/H_2O (1.0 mL) under nitrogen for 6 h. [b]Isolated yield.

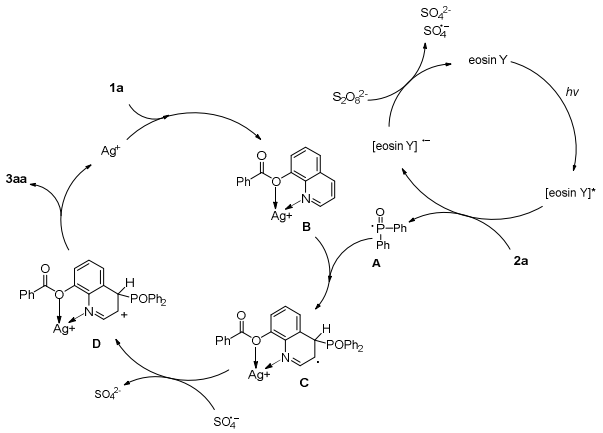
To gain insight into the reaction mechanism, some control experiments were performed (Scheme 4). Taking structurally similar substrates (**5a**) instead of the 8-hydroxyquinoline esters in the phosphonation with diphenylphosphine oxide **2a** did not lead to any product. The reaction of 1-naphthol ester also did not afford any product, indicating that the N,O dichelated 8-hydroxyquinoline skeleton is essential for the successful conversion. The reactive site might be determined by the stronger coordination bond of X→Ag. For example, phosphonation product is not detected for 1-naphthol ester due to no coordination effect of naphthalene ring to Ag atom; N_{pyr}→M is stronger than the O→Ag in 8-hydroxyquinoline, so the reaction of 8-hydroxyquinoline esters would regioselectively occur at the C4 position. The phosphonation was then performed in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT), and the reaction was successfully inhibited (Scheme 5a). Furthermore, an adduct **6a** of phosphine oxide and BHT was detected by HR-MS under



Scheme 4. Control experiment

standard conditions, indicating that the oxidative phosphonation might proceed *via* a radical process (Scheme 5b).

Based on above experimental results and previous reports[4b,4c,4d], a plausible mechanism is illustrated in Scheme 5. In the first case, the coordination of 8-hydroxyquinoline ester **1a** with Ag(I) affords a chelated intermediate **B**. Meanwhile, a phosphonyl radical **A** and an sulfate radical can be generated from the oxidation of diphenylphosphine oxide **2a** in the presence of $K_2S_2O_8$ *via* a photoredox catalytic cycle. The radical addition of the phosphonyl radical **A** to the intermediate **B** then occurs at the C4 position to form an intermediate radical **C**. Subsequently, the intermediate **D** is generated through oxidation of the intermediate **C** by the sulfate radical *via* a single electron transfer (SET) process. Finally, decomposition of intermediate **D** occurs, releasing a proton and successfully affording the desired product **3aa**, along with the regeneration of the active Ag(I) species to fulfil the catalytic cycle.



Scheme 5. Proposed mechanism of the phosphonation reactions

Conclusions

In conclusion, we have successfully developed a convenient and environmentally friendly method for C4-H phosphonation

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of 8-hydroxyquinoline esters with diarylphosphine oxides under dual catalysis of eosin Y and silver salt under external base- or acid-free conditions, thereby providing a simple approach to the C4 phosphonated quinoline scaffolds. The reaction features high regioselectivity at the unusual C4 site, good functional group tolerance and mild conditions.

Experimental

Typical Procedure

A 20 mL Schlenk tube was equipped with a magnetic stir bar and charged with 8-hydroxyquinoline derivative **1** (0.1 mmol), diarylphosphine oxide **2** (0.2 mmol), eosin Y (2.1 mg, 0.003 mmol, 3 mol%), $K_2S_2O_8$ (0.2 mmol, 2 equiv), Ag_2O (2.3 mg, 0.01 mmol, 10 mol%) in CH_3CN/H_2O(3:2) (1.0 mL). The resulting mixture was stirred under the irradiation of 26 W household light under nitrogen at room temperature for 6 h. Upon completion, the mixture was added into H_2O (20 mL) and extracted with CH_2Cl_2 (20 mL) three times. The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100–200 mesh) using CH_2Cl_2/ethyl acetate as an eluent (2:1, V/V) to afford the pure product **3**.

Acknowledgements

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Notes and references

1 (a) Q. A. Khan, J. Lu and S. M. Hecht, *J. Nat. Prod*. 2009, **72**, 438-442; (b) Z. F. Duan, X. Li, H. X. Huang, W. Yuan, S. L. Zheng, X. Z. Liu, Z. Zhang, E. Choy, D. Harmon, H. Mankin and F. Hornicek, *J. Med. Chem*. 2012, **55**, 3113-3121.

2 T. Hirao, T. Masunaga, Y. Ohshiro and T. Agawa, *Synthesis* 1981, 56-57.

3 For selected reviews of transition metal-catalyzed C-H functionalization, see: (a) L. Yang and H. M. Huang, *Chem. Rev*. 2015, **115**, 3468-3517; (b) L. Souillart and N. Cramer, *Chem. Rev.* 2015, **115**, 9410-9464; (c) C. Shen, P. F. Zhang, Q. Sun, S. Q. Bai, T. S. A. Hor and X. G. Liu, *Chem. Soc. Rev*. 2015, **44**, 291-314; (d) C. Liu, J. W. Yuan, M. Gao, S. Tang, W. Li, R. Y. Shi and A. W. Lei, *Chem. Rev*. 2015, **115**, 12138-12204.

4 For reports of the phosphonation of the quinoline ring, see: (a) C.-B. Xiang, Y.-J. Bian, X.-R. Mao and Z.-Z. Huang, *J. Org. Chem.* 2012, **77**, 7706-7710; (b) S. Wang, R. Guo, G. Wang, S.-Y. Chen and X.-Q. Yu, *Chem. Commun*. 2014, **50**, 12718-12721; (c) M. Sun, S. Sun, H. Qiao, F. Yang, Y. Zhu, J. Kang, Y. Wu and Y. Wu, *Org. Chem. Front*. 2016, **3**, 1646-1650; (d) H. Qiao, S. Sun, Y. Zhang, H. Zhu, X. Yu, F. Yang, Y. Wu, Z. Li and Y. Wu, *Org. Chem. Front*. 2017, **4,** 1981-1986.

5 For selected reports of the phosphonation of heterocycles except the quinoline ring, see: (a) W.-J. Yoo and S. Kobayashi, *Green Chem*. 2014, **16**, 2438-2442; (b) C. Li, T. Yano, N. Ishida and M. Murakami, *Angew. Chem. Int. Ed*. 2013, **52**, 9801-9804; (c) X. Mi, M. Huang, J. Zhang, C. Wang and Y. Wu, *Org. Lett*. 2013, **15**, 6266-6269; (d) C.-G. Feng, M. Ye, K.-J. Xiao, S. Li and J.-Q. Yu, *J. Am. Chem. Soc*. 2013, **135,** 9322-9325; (e) Y. Gao, X. Li, J. Xu, Y. Wu, W. Chen, G. Tang and Y. Zhao, *Chem. Commun*. 2015, **51**, 1605-1607; (f) M. Min, D. Kang, S. Jung and S. Hong, *Adv. Synth. Catal.* 2016, **358,** 1296-301; (g) H. Wang, X. Cui, Y. Pei, Q. Zhang, J. Bai, D. Wei and Y. Wu, *Chem. Commun*. 2014, **50,** 14409-14411; (h) M. Gao, Y. Li, L. Xie, R. Chauvin and X. Cui, *Chem. Commun*. 2016, **52**, 2846-2849; (i) K. Luo, Y.-Z. Chen, W.-C. Yang, J. Zhu and L. Wu, *Org. Lett*. 2016, **18,** 452-455.

6 (a) H. Qiao, S. Sun, F. Yang, Y. Zhu, W. Zhu, Y. Dong, Y. Wu, X. Kong, L. Jiang and Y. Wu, *Org. Lett*. 2015, **17**, 6086-6089; (b) H. Qiao, S. Sun, F. Yang, Y. Zhu, J. Kang, Y. Wu and Y. Wu, *Adv. Synth. Catal*. 2017, **359**, 1976-1980.

7 (a) Z. Li, S. Sun, H. Qiao, F. Yang, Y. Zhu, J. Kang, Y. Wu and Y. Wu, *Org. Lett*. 2016, **18**, 4594-4597; (b) P. Bai, S. Sun, Z. Li, H. Qiao, X. Su, F. Yang, Y. Wu and Y. Wu, *J. Org. Chem.* 2017, **82**, 12119-12127.

8 For selected reports for C–H functionalization under photoredox catalysis: (a) X. Li, X. Gu and P. Li, *ACS Catal*. 2014, **4**, 1897-1900; (b) W. Yang, S. Yang, P. Li and L. Wang, *Chem. Commun*. 2015, **51**, 7520-7523; (c) K. Luo, Y. Z. Chen, W. C. Yang, J. Zhu and L. Wu, *Org. Lett*. 2016, **18**, 452-455; (d) E. Meggers, *Chem. Commun.* 2015, **51**, 3290-3301; (e) G. Zhang, C. Bian and A. Lei, *Chinese J. Catal.* 2015, **36**, 1428-1439; (f) J. W. Beatty and C. R. J. Stephenson, *Acc. Chem. Res.* 2015, **48**, 1474-1484; (g) H. Huang, K. Jia and Y. Chen, *ACS Catal*. 2016, **6**, 4983-4988.

9 CCDC1580532 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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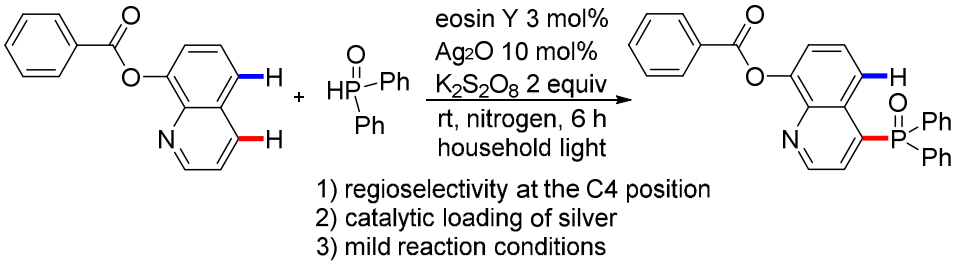
Direct C4-H Phosphonation of 8-Hydroxyquinoline Derivatives Employing Photoredox Catalysis and Silver Catalysis



A simple and efficient protocol for the C4-H phosphonation of 8-hydroxyquinoline derivatives was developed under photoredox/silver(I) cocatalysis system