ORGANIC
LETTERS

2013
Vol. 15, No. 24
6266–6269

Regioselective Palladium-Catalyzed Phosphonation of Coumarins with Dialkyl *H*-Phosphonates via C−H Functionalization

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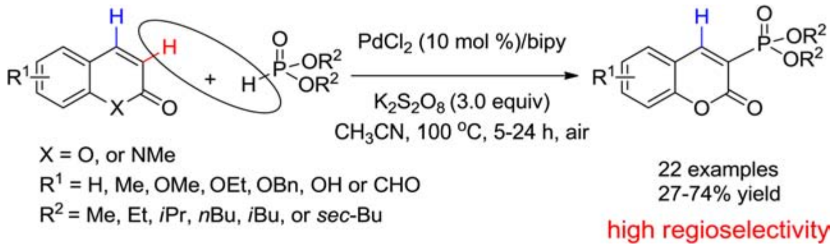
Received October 30, 2013

ABSTRACT



A novel Pd(II)-catalyzed dehydrogenative cross-coupling reaction between coumarins and *H*-phosphonates has been developed to give the corresponding 3-phosphonated products in moderate to good yields with high selectivity.

Coumarins, a common motif in a variety of natural occurring compounds, have been extensively investigated because of their pharmacological activity[1] and outstanding optical properties.[2] In particular, several 3-phosphorated coumarins have been shown to exhibit their cytotoxicity on some human leukemia cell lines as well as high alkylating activity.[3] In the past, 3-phosphonation of coumarins has typically involved the Knoevenagel reaction or Arbuzov reaction.[4] These protocols rely on multistep reaction sequences, do not match atom economy, and are therefore of low efficiency. To the best of our knowledge, only one report has described the phosphonation of coumarins through a radical process,[5] which required stoichiometric Mn(OAc)$_3$ (3 equiv) and aliphatic acid as solvent.

Recently, direct C−H functionalization has emerged as an atom-economical and environmentally friendly synthetic tool as it eliminates the need for prefunctionalization

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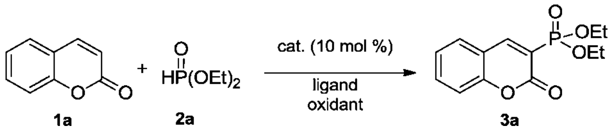
of coupling partners.[6] Significant progress has been made in the development of C–P bond forming reactions via direct C–H activation.[7] A pyridine-directed C–H phosphonation reaction with *H*-phosphonates via palladium catalyst was successfully realized by Yu and co-workers.[8] At the same time, Murakami et al.[9] described the analogous phosphonation reaction of 2-arylpyridines, in which an α-hydroxyalkylphosphonate served as the masked phosphonating reagent to save the catalyst from deactivation. Although Pd-catalyzed direct arylation[10] and olefination[11] of coumarins have been reported by the Shafiee, Duan, and Hong groups, so far no report has developed transition-metal-catalyzed direct phosphonation of coumarins. Thus, the discovery of a novel catalytic protocol for selective synthesis of phosphonated coumarin derivatives should be challenging and have great significance. Herein, we depict an efficient palladium-catalyzed C-3 selective dehydrogenative phosphonation of coumarin derivatives.

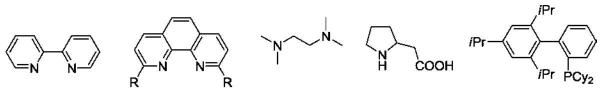
Initially, the optimization for the reaction between coumarin (2*H*-chromen-2-one, **1a**) and diethyl *H*-phosphonates (**2a**) started with 10 mol % of $Pd(OAc)_2$ and $K_2S_2O_8$ in CH_3CN at 100 °C for 24 h, and the phosphonation occurred at the C-3 position of the coumarin core with high regioselectivity giving relatively low but promising isolated yield of 21% (Table 1, entry 1). When 2,2′-bipyridine (**L1**) was introduced into the reaction system as a ligand, the yield was improved up to 46% (Table 1, entry 2). Then, some commercially available transition-metal sources ($Pd(OAc)_2$, CuBr, and CuI) were screened with 2,2′-bipyridine and did not display better catalytic activity except $PdCl_2$ showing the same activity as that of $Pd(OAc)_2$ (Table 1, entries 2 and 3; Table S1, entries 2–6, Supporting Information). Among the organic and inorganic oxidants examined, $K_2S_2O_8$ was the best choice (Table 1, entries 4–7; Table S2, Supporting Information). However, the reaction yield was reduced by decreasing the amount of $K_2S_2O_8$ (Table 1, entry 4). Organic oxidants such as BQ (*p*-benzoquinone) and TBHP (*tert*-butyl hydroperoxide) could impede this catalytic process (Table 1, entries 6 and 7). Some other amino acid **L5** and bidentate nitrogen ligands **L2**, **L3**, and **L4** were also evaluated, and no improvement was observed (Table 1, entries 8–12). Although X-phos (**L6**) gave a similar yield with 2,2′-bipyridine, considering environmentally friendly and cost-effective factors, 2,2′-bipyridine was chosen as the optimal ligand for this reaction (Table 1, entries 2 and 12). A solvent screen (DMF, THF, dioxane, and toluene) revealed a significant solvent dependence, where CH_3CN turned out to be optimal (Table S4, Supporting Information). No further increase in the yield of **3a** was observed upon increasing the loading of $PdCl_2$ up to 20 mol % (Table 1, entry 15). However, on adding a larger amount of diethyl *H*-phosphonate to this system, the dehydrogenative reaction afforded the desired product in a lower yield (Table 1, entry 16), presumably owing to the strong coordinating character of phosphorus reagents.[7]

Table 1. Reaction Conditions Optimization[a]



entry	catalyst	ligand	oxidant	yield[b] (%)
1	$Pd(OAc)_2$		$K_2S_2O_8$	21
2	$Pd(OAc)_2$	**L1**	$K_2S_2O_8$	46
3	$PdCl_2$	**L1**	$K_2S_2O_8$	46
4[c]	$PdCl_2$	**L1**	$K_2S_2O_8$	38
5[d]	$PdCl_2$	**L1**	$K_2S_2O_8$	48
6	$PdCl_2$	**L1**	BQ	NR
7	$PdCl_2$	**L1**	TBHP	NR
8	$PdCl_2$	**L2**	$K_2S_2O_8$	27
9	$PdCl_2$	**L3**	$K_2S_2O_8$	26
10	$PdCl_2$	**L4**	$K_2S_2O_8$	28
11	$PdCl_2$	**L5**	$K_2S_2O_8$	38
12	$PdCl_2$	**L6**	$K_2S_2O_8$	46
13[e]	$PdCl_2$	**L1**	$K_2S_2O_8$	46
14[f]	$PdCl_2$	**L1**	$K_2S_2O_8$	45
15[g]	$PdCl_2$	**L1**	$K_2S_2O_8$	33
16[h]	$PdCl_2$	**L1**	$K_2S_2O_8$	38

[a] Reaction conditions: coumarin (0.5 mmol), $HPO(OEt)_2$ (1.0 mmol), cat. (10 mol %), ligand (30 mol %), oxidant (1.5 mmol), CH_3CN (3.0 mL), 24 h. [b] Isolated yield. [c] $K_2S_2O_8$ (2.0 equiv) was used. [d] $K_2S_2O_8$ (4.0 equiv) was used. [e] 20% $PdCl_2$. [f] 60% **L1**. [g] 12 h. [h] 1.5 mmol $HPO(OEt)_2$.



L1 **L2**, R = H; **L3**, R = Me. **L4** **L5** **L6**

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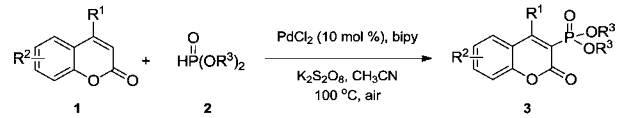
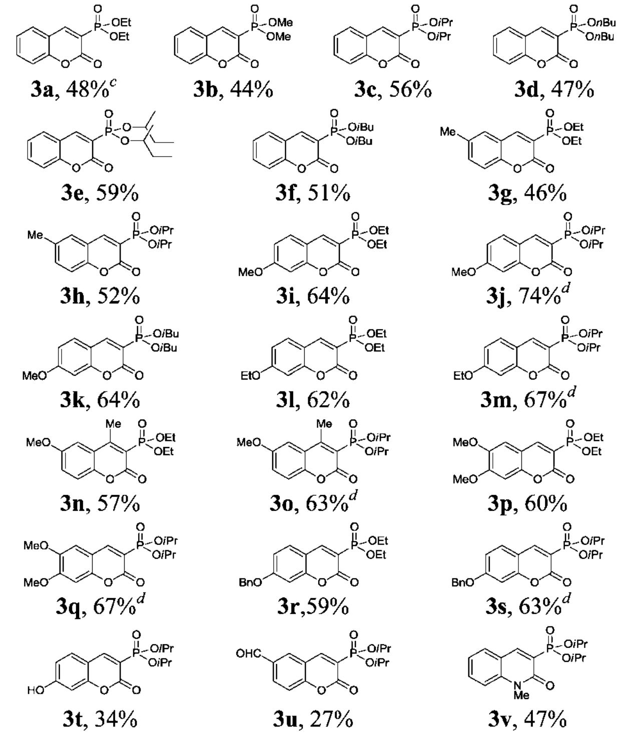
Table 2. Palladium Catalyzed C–H Phosphonation of Coumarin Derivates[a],[b]





3a, 48%[c]; **3b**, 44%; **3c**, 56%; **3d**, 47%

3e, 59%; **3f**, 51%; **3g**, 46%

3h, 52%; **3i**, 64%; **3j**, 74%[d]

3k, 64%; **3l**, 62%; **3m**, 67%[d]

3n, 57%; **3o**, 63%[d]; **3p**, 60%

3q, 67%[d]; **3r**,59%; **3s**, 63%[d]

3t, 34%; **3u**, 27%; **3v**, 47%

[a] Reaction conditions: coumarins **1** (0.5 mmol), HPO(OR^3)$_2$ **2** (1.0 mmol), PdCl$_2$ (10 mol %), bipyridine (30 mol %), K$_2$S$_2$O$_8$ (1.5 mmol), CH$_3$CN (3.0 mL), in 100 °C for 24 h under air. [b] Isolated yields. [c] 4 equiv of K$_2$S$_2$O$_8$. [d] 5 h.

Having established the optimal conditions, we next examined the substrate scope of *H*-phosphonates and coumarins (Table 2). A range of coumarin derivatives were found to undergo dehydrogenative phosphonation in moderate to good yields with high regioselectivity. The reactions of tested dialkyl *H*-phosphonates and coumarins could proceed smoothly under the optimized conditions in moderate yields (**3a**–**f**). The diisopropyl and di-*sec*-butyl *H*-phosphonates were found to be better partners for phosphonation of coumarins. Generally, coumarins with electron-donating groups could give better yields than analogues with electron-withdrawing groups. A coumarin derivative with methyl group at the C-6 position gave lower yields of **3g** and **3h** (46% and 52%) in comparison with nonsubstituted coumarin **3a** and **3c** (48% and 56%). Gratifyingly, moderate to good reaction yields (57–74%) were obtained when courmarins were substituted by electron-donating groups such as –OMe, –OEt, –OBn at the C-7 position even in a shorter time (**3i**–**s**). In addition, –OH and –CHO groups were tolerated in the new system of phosphonation albeit in low yields (**3t** and **3u**). It was worth to note that the new protocol was effectively applied to 1-methyl-2-quinolinone, affording product **3v** in 47% yield, which was reported as an inhibitor of human immunodeficiency virus (HIV-1) and a novel antibacterial agent.[12]

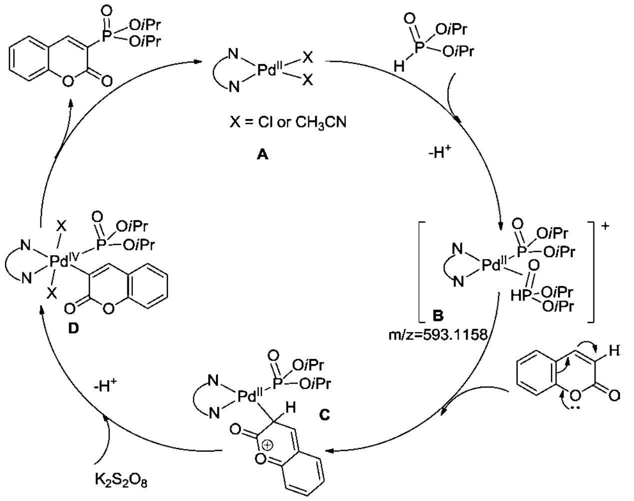


Figure 1. Proposed reaction mechanism.

In order to investigate the mechanism of this reaction, 1 equiv of tetramethylpiperidinyloxy (TEMPO), a radical scavenger, was added into the reaction system of coumarin and diethyl *H*-phosphonate. A 37% yield of **3a** was obtained which is similar to that of the model reaction without TEMPO. The result suggests that the reaction may not undergo a radical mechanism. Subsequently, the technology ESI-MS was used to monitor the reaction between coumarin and diisopropyl *H*-phosphonates. Expectedly, it was shown in the ESI-MS(+) spectrum that a cationic palladium complexes **B** (m/z = 593) was detected in the reaction mixture (Figure 1 Figures S1 and S2, Supporting Information). On the basis of the previous analysis and other related reports,[7j,10e,10f] a plausible mechanism of the dehydrogenative cross-coupling reaction was proposed shown in Figure 1. The reaction starts with the nucleophilic coordination of the phosphate and Pd^{II} to afford the monocationic palladium intermediate **B**. Due to the more nucleophilic character of the C-3 position of coumarin, electrophilic palladation of coumarin results in another palladium complex **C**. Subsequently, the process of oxidation/dehydrogenation takes place in the presence of K$_2$S$_2$O$_8$, thus generating Pd^{IV} species **D**. The following reductive elimination affords 3-phosphonated coumarin and Pd^{II} species which goes back into the catalytic cycle. However, alternative mechanistic pathways are equally likely and the further study of mechanism is ongoing in our laboratory.

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In conclusion, we have successfully achieved the Pd(II)-catalyzed C−H phosphonation of coumarins with dialkyl phosphites. A variety of C-3 phosphorated coumarins were afforded in moderate to good yields with a high regioselectivity. The methodology not only provides a new protocol for the efficient preparation of 3-phosphonated coumarins but also is a complement to the direct C−H phosphonation of heterocyclic compounds.

Acknowledgment. This work was supported by the National Natural Science Foundation (NSF) of China (21172200 and 21302172).

Supporting Information Available. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.