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Palladium(II)-Catalyzed *ortho*-Olefination of Benzylic Phosphonic Monoesters

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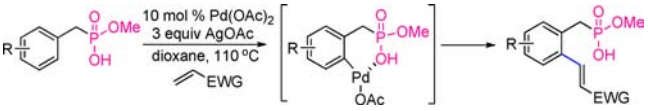
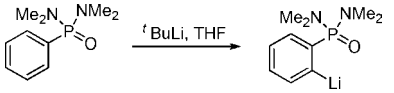
ABSTRACT



The new monophosphonic acid directing group is successfully utilized in the Pd(II)-catalyzed *ortho*-olefination of benzylic phosphonic monoesters and offers further development of other phosphoryl-related directing groups in the transition-metal-catalyzed C−H activations.

Transition-metal-catalyzed direct functionalization of C−H bonds has proven to be a highly efficient way to form C−C bonds and C-hetero bonds.[1] The *ortho* C−H activation can be enormously enhanced and controlled by the use of the directing groups through coordination. Among various directing groups for C−H activation,[2] carboxylic acid derivatives have been widely utilized.[3]

Scheme 1. *ortho*-Lithiation of Tetramethylphenylphosphonic Diamide



The phosphonic acid and its derivatives have served as important intermediates or reagents in organic chemistry.[4] Especially, benzylic phosphonates have already become a powerful tool for the preparation of alkenyl derivatives via the Horner−Wadsworth−Emmons reactions.[5] In addition, a wide range of biologically active phosphonate-containing compounds have been identified and the phosphonic acid derivatives have been recognized as attractive

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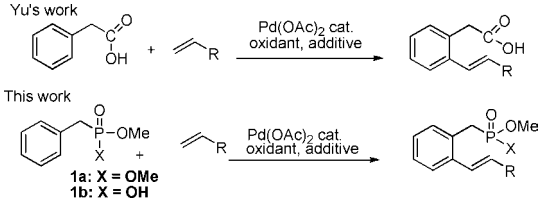
analogues for the biologically important phosphate moiety.[6]

Our interest in the transition-metal-catalyzed C−H activation has been focused on phosphoryl-related directing groups. Although the phosphonic acid derived-directing group was used in *ortho*-metalation as shown in Scheme 1,[7,8] as far as we are aware, its use in transition-metal-catalyzed C−H activation has not been reported. In addition, the structural modification of phosphonic acid derivatives would be more versatile than that of carboxylic derivatives by introducing two different groups such as an amino, an alkoxyl, and a hydroxyl group. Previously, Yu reported a carboxylate-directed Pd(II)-catalyzed C−H olefination reaction with phenylacetic acid derivatives.[9b] In our approach, we were interested in the possibility of insertion of Pd into C−H bond through chelation of P═O bond using benzylic phosphonic acid diesters and/or monoesters (Scheme 2).

Scheme 2. Olefination of Phenylacetic Acid and Benzylphosphonate **1a** and **1b**



We first began our studies with dimethyl benzyl phosphonate (**1a**) in the Pd-catalyzed *ortho*-olefination reaction as shown in Table 1. When **1a** was treated with ethyl acrylate (2 equiv) using $Pd(OAc)_2$ (10 mol %) and $Na_2S_2O_8$ oxidant (3 equiv) in 1,2-dichloroethane at 110 °C for 24 h, the reaction did not occur and the starting material was recovered unchanged (entry 1). Further attempts to effect the reaction by varying the oxidizing agent or changing the solvent were unsuccessful (entries 2 and 3). Inspired by recent reports on the hydroxyl-directed C−H activations using carboxy,[3f,g,9] hydroxyl,[10] and silanol groups[11] along with a weak coordination-driven concept,[3f] we next turned our attention to methyl hydrogen benzylphosphonate (**1b**). Reaction of **1b** with ethyl acrylate (2 equiv) using $Cu(OAc)_2$ (2 equiv) and Ag_2O (2 equiv) as oxidants in the presence of 10 mol % of $Pd(OAc)_2$ and Li_2CO_3 (1 equiv) in *tert*-amyl alcohol at 110 °C for 24 h proceeded to an observable extent, affording a small amount of mono-olefinated product (entry 4). AgOAc improved the reaction significantly, giving a mixture of mono- and bis-olefinated product and the starting material in a ratio of 38:27:35 (entry 5). The addition of an amino acid ligand (Boc-Val-OH and Boc-Leu-OH) improved the reaction to some extent, and the reaction was also sensitive to solvent (entries 6 − 9).[9b,10c,12] Dioxane gave slightly better results than *tert*-amyl alcohol using AgOAc (entry 10), and the oxidants Ag_2O and Ag_2CO_3 gave inferior results (entries11 and 12). Furthermore, it is noteworthy that the reaction was slightly improved in the absence of Li_2CO_3 (entry 13). To improve the mono-substitution, when the reaction was repeated using 1 equiv of ethyl acrylate, a 51:20 mixture of mono- and bis-olefinated product along with the starting material (entry 14). Thus, the remaining reactions were carried out with ethyl acrylate (2 equiv) and AgOAc (3 equiv) using $Pd(OAc)_2$ (10 mol %) in 1,4-dioxane at 110 °C for 24 h.

Various benzylic phosphonic acid monoesters were subjected to the standard conditions to determine the scope and limitations of the present method as summarized in Table 2. For facile purifications, the crude monobenzylic phosphonic acids were methylated using TMS-diazomethane to afford **4** and **5**. As we expected, *para*-substituted substrates worked well but gave a significant amount of bis-olefinated products (**5d**, **5j**). The *ortho*-substitution did not influence the reaction, and *meta*-substituted substrates underwent alkenylations regioselectively at the sterically less hindered position. Thus, the *o*- and *m*-methyl- and dimethyl-substituted substrates (**3a**, **3b**, **3c**) underwent clean olefinations to afford the corresponding olefinated products in high yields. Similarly, substrates (**3e**−**g**) containing electron-donating methoxy groups worked well. Although the electron-withdrawing fluoride and chloride substituents are completely compatible under the present conditions, the reaction was not influenced by the chloride substituent, yielding **4h** and **4i** in high yields. However, the fluoride substituent was sensitive to the position of aromatic moiety. The *m*-fluoro-substituted **3k**

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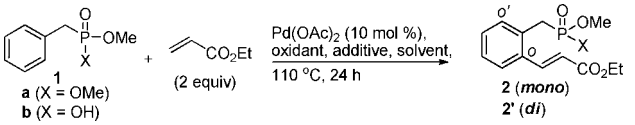
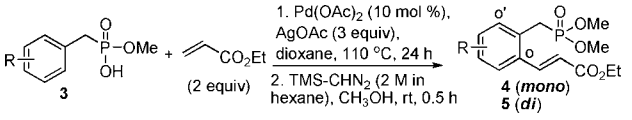
Table 1. Optimization of Reaction Conditions

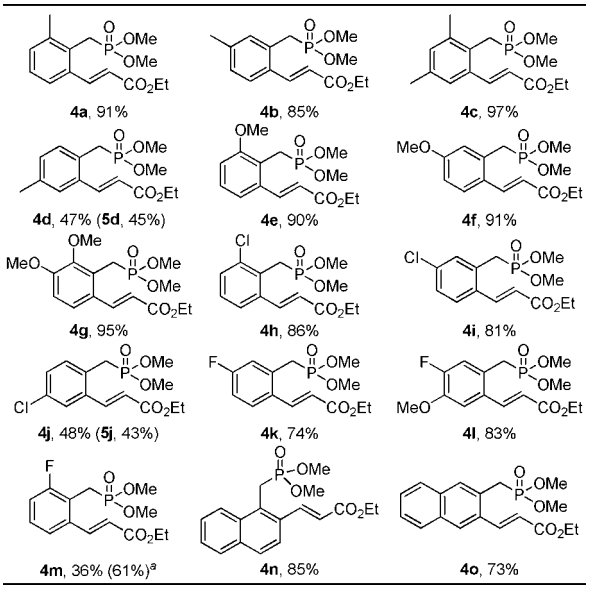


entry	substrate	ligand (20 mol %)	additive (1 equiv)	oxidant (equiv)	solvent	ratio (%)[a] **2**:**2′**:**1**
1	**1a**			$Na_2S_2O_8$ (2)	DCE	0:0:100
2	**1a**			AgOAc (3)	dioxane	0:0:100
3	**1a**			$Cu(OAc)_2$(2)	DCE	0:0:100
4	**1b**		Li_2CO_3	$Cu(OAc)_2$ (2) Ag_2O (2)	*tert*-amyl OH	10:5:85
5	**1b**		Li_2CO_3	AgOAc (3)	*tert*-amyl OH	38:27:35
6	**1b**	Boc-Val-OH	Li_2CO_3	AgOAc (3)	*tert*-amyl OH	55:22:27
7	**1b**	Boc-LeuOH	Li_2CO_3	AgOAc (3)	*tert*-amyl OH	54:35:11
8	**1b**	Boc-Val-OH	Li_2CO_3	AgOAc (3)	DMF	5:0:95
9	**1b**	Boc-Val-OH	Li_2CO_3	AgOAc (3)	toluene	39:26:35
10	**1b**		Li_2CO_3	AgOAc (3)	dioxane	52:35:13
11	**1b**		Li_2CO_3	Ag_2O (2)	dioxane	41:16:43
12	**1b**		Li_2CO_3	Ag_2CO_3 (2)	dioxane	25:7:68
13	**1b**			AgOAc (3)	dioxane	48:47:5
14[b]	**1b**			AgOAc (2)	dioxane	51:20:29

[a] The ratio of the products was determined by ^{1}HNMR analysis. [b] 1 equiv of ethyl acrylate was used.

Table 2. Olefination of Benzylic Phosphates with Ethyl Acrylate

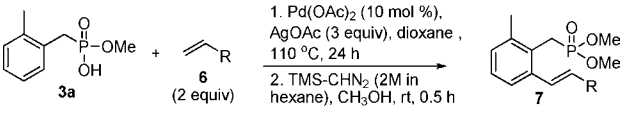


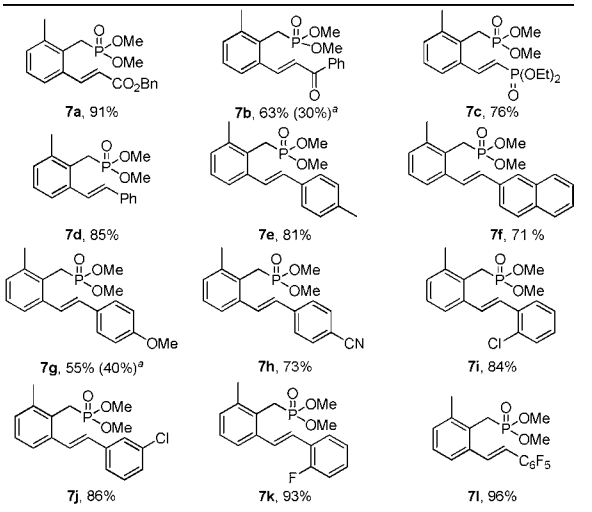


[a] The numbers in the parentheses indicate the isolated yield of the recovered starting material.

and **3l** worked well, but *o*-fluoro-substituted **3m** was much less reactive, yielding **4m** in less than 40% yield.

Table 3. Olefination of **3a** with Alkene Derivatives



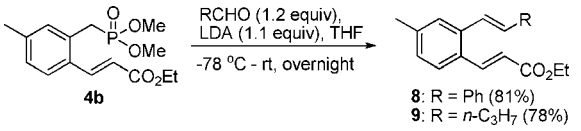


[a] The numbers in the parentheses indicate the isolated yield of the recovered starting material.

Furthermore, naphthyl derivatives **3n** and **3o** also underwent clean olefination.

We next studied the olefination of **3a** with various alkenes. As shown in Table 3, activated olefins such as benzyl acrylate and vinyl phosphate worked well to yield

Scheme 3. Horner–Wadsworth–Emmons Reactions of **4b**



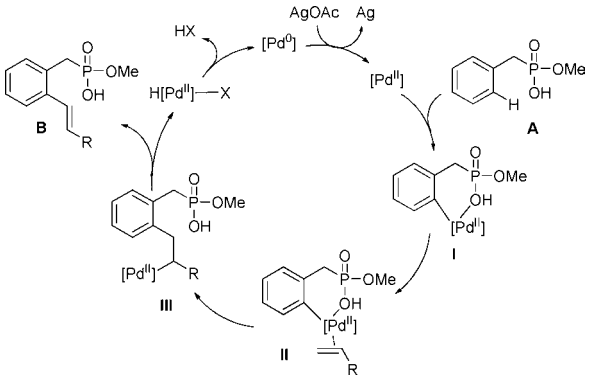
ortho-olefinated products **7a** and **7c**. In the case of phenyl vinyl ketone, the reaction was incomplete, yielding **7b** in 63% yield along with recovery of **3a** (30%). When various styrene derivatives were subjected to the standard conditions, the olefination occurred cleanly, indicating that the electron-withdrawing substituents gave the good to excellent yields, while the reaction was incomplete for an electron-donating methoxy substituent. Furthermore, the reaction with ethyl crotonate and allylbenzene failed to give the products.

Finally, when the olefination product **4b** was subjected to the Horner–Wadsworth–Emmons reaction (Scheme 3), the desired alkenes were obtained with good yields.

We envisioned the reaction would be initiated by hydroxyl-assisted insertion of [Pd^{II}] to the *o*-C–H bond to generate complex **I**, from which coordination with olefins would afford intermediate **II** (Scheme 4). Subsequent 1,2-migratory insertion and β-hydride elimination would provide the product **B** along with H[Pd^{II}]–X species followed by liberation of HX to regenerate the active Pd(0) and subsequent oxidation to Pd(II) species by AgOAc.

In summary, we have developed a new and highly efficient method for direct *ortho*-olefination of benzylic phosphonates based on Pd(II)-catalyzed C–H activation reactions using the phosphoryloxy directing group. The present approach would be further applied to *ortho*-C–H functionalizations of benzyl and aryl phosphonic acid derivatives.

Scheme 4. Plausible Reaction Mechanism



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Supporting Information Available. Experimental procedures and full spectroscopic 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.