

# Pd-Catalyzed Regio- and Stereoselective Cyclization–Heck Reaction of Monoesters of 1,2-Allenyl Phosphonic Acids with Alkenes

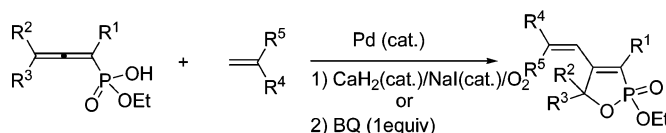
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## ABSTRACT



The cyclization–Heck reactions of monoesters of 1, 2-allenyl phosphonic acids with alkenes were studied. The reaction afforded 4-(1-Z-alkenyl)-2-ethoxy-2,5-dihydro[1,2]oxaphosphole 2-oxides regio- and stereoselectively. Pd(II) was regenerated from the in situ formed Pd(0) using  $\text{CaH}_2(\text{cat.})/\text{NaI}/\text{O}_2$  or benzoquinone to furnish the catalytic cycle.

In transition-metal-catalyzed organic transformations, palladium-catalyzed reactions have been emerging as the most powerful methods for the formation of carbon–carbon and carbon–heteroatom bonds.<sup>1</sup> Among these reactions, the Heck reaction has been intensively studied<sup>2,3</sup> and applied to the total synthesis of many natural products<sup>4</sup> because of its high versatility. Although the coupling–cyclization of functionalized allenes<sup>5,6</sup> with aryl/alkenyl halide,<sup>7,8</sup> allylic halide,<sup>9</sup> ( $\omega$ -1)-alkenyl halide,<sup>10</sup> propargylic carbonates,<sup>11</sup> or 2,3-allenols<sup>9d,12</sup> has been demonstrated, the coupling–cyclization of these allenes with alkenes, which may provide an efficient pathway to the alkenyl-substituted cyclic compounds, has

not been studied. A palladium-catalyzed mechanism may be envisioned for such a reaction: *endo*-mode cyclic nucleopalladation of allenes **I** would form cyclic palladium intermediates **II**. Then, the carbon–carbon double bond in the alkenes

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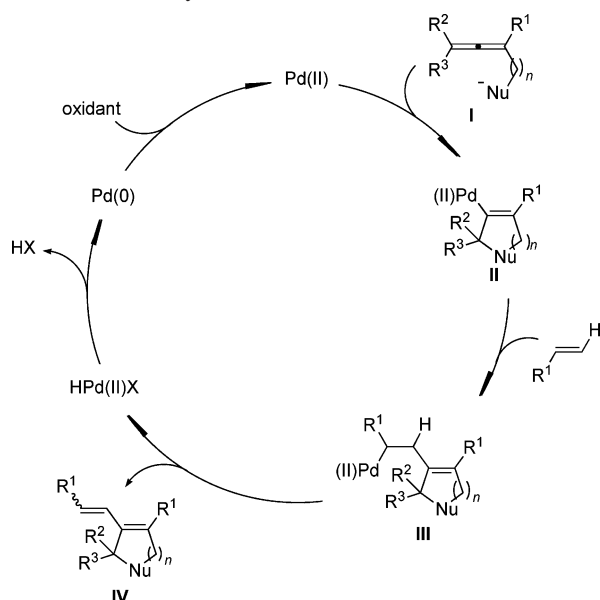
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inserts into the C–Pd bond in intermediates **II** to form intermediates **III**, which would afford the products **IV** via  $\beta$ -H elimination. The in situ generated palladium hydride species would form Pd(0) species.<sup>13</sup> To make the reaction catalytic in Pd, the Pd(0) species must be oxidized to the catalytically active Pd(II) species (Scheme 1). On the other

**Scheme 1.** Proposed Catalytic Cycle for Palladium-Mediated Cyclization–Heck Reaction

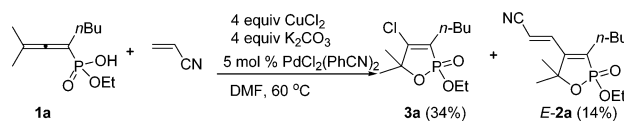


hand, many heterocycles that include a phosphorus atom and an oxygen atom usually have important biological activities.<sup>14</sup> Although some methods have been developed,<sup>15</sup> development of a highly efficient method for the synthesis of these molecules with diversity is still of high interest. In this paper, we disclose our recent observation on the cyclization–Heck

reaction of monoesters of 1,2-allenyl phosphonic acids with alkenes.

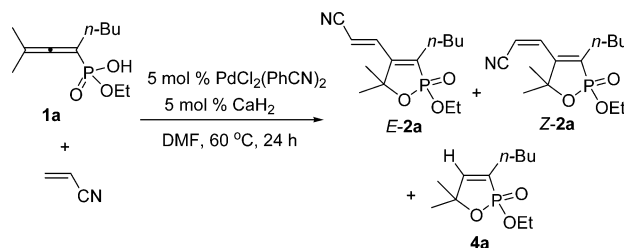
Under the catalysis of  $\text{PdCl}_2(\text{PhCN})_2$ , only 14% yield of cyclization product **2a** was formed together with a significant amount of chlorocyclization product **3a** when  $\text{CuCl}_2$  (4.0 equiv) and  $\text{K}_2\text{CO}_3$  (4.0 equiv) were used (Scheme 2).<sup>16</sup> When

**Scheme 2**



the reaction was conducted in air with a  $\text{CaCl}_2$  drying tube in the presence of 0.2 equiv of  $\text{NaI}$ ,<sup>17</sup> **E-2a** was formed stereoselectively (*E/Z* ratio = 7:1) in 49% yield (entry 1, Table 1). To our surprise, when a catalytic amount of  $\text{CaH}_2$

**Table 1.** Pd-Catalyzed Cyclization–Heck Reaction of Ethyl (2-Methylocta-2,3-dien-4-yl)phosphonic Acid **1a** with Acrylonitrile<sup>a</sup>



entry	oxidant (0.2 equiv)	yield of <b>E-2a</b> (%) <sup>b</sup>	yield of <b>Z-2a</b> (%) <sup>b</sup>
1 <sup>c</sup>	$\text{NaI}$	49	7
2	$\text{NaI}$	70	4
3 <sup>c</sup>	$\text{NaI}$	16	2
4 <sup>d</sup>	$\text{NaI}$	9	trace
5 <sup>e</sup>	$\text{NaI}$	70	7
6 <sup>d</sup>	$\text{NaI}$	41	10
7 <sup>f</sup>	$\text{NaI}$	9	1
8	—	27	7
9	$\text{BQ}^g$	35	6
10	$\text{CuCl}_2$	38	17
11	$\text{KI}$	34	4
12	<i>n</i> -BuI	46	4
13	$\text{NaBr}$	34	6
14	$\text{NaCl}$	9	2

<sup>a</sup> The reactions were conducted in air with a  $\text{CaCl}_2$  drying tube unless otherwise stated. <sup>b</sup> Determined by  $^1\text{H}$  NMR analysis with  $\text{CH}_2\text{Br}_2$  as the internal standard. <sup>c</sup> With 0.5 equiv of  $\text{CaH}_2$ . <sup>d</sup> With 1 equiv of  $\text{CaH}_2$ . <sup>e</sup> 0.05 equiv of  $\text{NaH}$  in air without a  $\text{CaCl}_2$  drying tube. <sup>f</sup> In an Ar atmosphere. <sup>g</sup> Benzoquinone.

was added, the yield of **2a** increased significantly (entry 2, Table 1). However, when we increased the amount of  $\text{CaH}_2$  further, lower yields and the formation of palladium black were observed (entries 3 and 4, Table 1). A catalytic amount of  $\text{NaH}$  gave a very similar result under comparable

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**Table 2.** Cyclization–Heck Reaction of Monoesters of 1,2-Allenyl Phosphonic Acids **1** with Alkenes<sup>a</sup>

entry	<b>1</b>			alkenes		conditions	yield of <i>E</i> - <b>2</b> (%) <sup>b</sup>	<i>E/Z</i> <sup>c</sup>	
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>				
1	<i>n</i> -Bu	Me	Me	( <b>1a</b> )	COOMe	H	A	88 ( <b>2b</b> )	>99:1
2	<i>n</i> -Bu	Me	Me	( <b>1a</b> )	COOEt	H	A	84 ( <b>2c</b> )	>99:1
3 <sup>d</sup>	<i>n</i> -Bu	Me	Me	( <b>1a</b> )	Ph	H	A	52 ( <b>2d</b> ) <sup>e</sup>	<i>f</i>
4	<i>n</i> -Bu	Me	Me	( <b>1a</b> )	Ph	H	B	85 ( <b>2d</b> )	<i>f</i>
5	<i>n</i> -Bu	–(CH <sub>2</sub> ) <sub>4</sub> –		( <b>1e</b> )	COOMe	H	A	69 ( <b>2e</b> )	>99:1
6	Me	–(CH <sub>2</sub> ) <sub>5</sub> –		( <b>1f</b> )	COOMe	H	A	79 ( <b>2f</b> )	>99:1
7	Bn	Me	Me	( <b>1g</b> )	COOMe	H	A	75 ( <b>2g</b> )	<i>f</i>
8	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	Et	Et	( <b>1h</b> )	COOMe	H	A	85 ( <b>2h</b> )	>99:1
9	<i>n</i> -Bu	Me	Me	( <b>1a</b> )	COOMe	Me	B	61 ( <b>2i</b> )	>99:1
10	<i>n</i> -Bu	Me	Me	( <b>1a</b> )	COONH <sub>2</sub>	H	B	86 ( <b>2j</b> )	>99:1
11	<i>n</i> -Hept	H	Me	( <b>1k</b> )	COOEt	H	B	63 ( <b>2k</b> )	55:1
12	<i>n</i> -Hept	H	Me	( <b>1k</b> )	Ph	H	B	63 ( <b>2l</b> )	<i>f</i>
13	<i>n</i> -Bu	H	H	( <b>1m</b> )	COOEt	H	B	46 ( <b>2m</b> )	>99:1
14	<i>n</i> -Bu	H	H	( <b>1m</b> )	COONH <sub>2</sub>	H	B	48 ( <b>2n</b> )	<i>f</i>
15	H	–(CH <sub>2</sub> ) <sub>5</sub> –		( <b>1o</b> )	COOEt	H	B	61 ( <b>2o</b> )	>99:1
16	H	–(CH <sub>2</sub> ) <sub>5</sub> –		( <b>1o</b> )	COONH <sub>2</sub>	H	B	34 ( <b>2p</b> )	<i>f</i>

<sup>a</sup> Conditions A: 1.0 equiv of **1**, 5.0 equiv of alkene, 0.2 equiv of NaI, 5 mol % of PdCl<sub>2</sub>(PhCN)<sub>2</sub>, and 5 mol % of CaH<sub>2</sub> in DMF in air with a drying tube at 60 °C for 24 h. Conditions B: 1.0 equiv of **1**, 5.0 equiv of alkene, 5 mol % of PdCl<sub>2</sub>(PhCN)<sub>2</sub>, and 1.0 equiv of BQ in DMF at 60 °C overnight. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by <sup>1</sup>H NMR spectra of the crude products. <sup>d</sup> The reaction was conducted at 100 °C. <sup>e</sup> The cycloisomerization product **4a** (25%) was isolated. <sup>f</sup> Only the signal of the *E*-isomers can be identified in the <sup>1</sup>H NMR spectra.

conditions (entry 5, Table 1). It is reasoned that a catalytic amount of CaH<sub>2</sub> or NaH may help the oxypalladation step in the beginning. However, in the presence of 0.5 or 1 equiv of CaH<sub>2</sub>, the generation of Pd(0) from HPd(II)X may be so fast that the NaI–O<sub>2</sub> system<sup>17</sup> may not be able to oxidize it back to the catalytically active species Pd(II) efficiently enough, thus forming Pd black. When the reaction was conducted in air without a drying tube in Ar or N<sub>2</sub> atmosphere, or in the absence of NaI, the yields of **2a** decreased significantly (entries 6–8, Table 1). The yields of **2a** also dropped with a catalytic amount of benzoquinone (BQ) and some other organic or inorganic halides (entries 9–14, Table 1). In all these reactions, the formation of **4a** was less than 2%, if any.

With the established standard conditions in hand, we studied the scope of the reaction (Table 2). The cyclization–

Heck reaction products were highly regio- and stereoselectively formed in high yields as a single isomer when acrylic acid esters were used (entries 1 and 2, Table 2). Some other fully substituted monoesters of 1,2-allenyl phosphonic acids with methyl acrylate also smoothly afforded the expected products in high yields and high *E/Z* ratios (entries 5–8, Table 2). However, this procedure is limited for some less reactive alkenes such as styrene, acrylamide or 2-methylpropenoic acid methyl ester, and 3-monosubstituted or 3-unsubstituted allenes. For example, we observed that when 1,2-allenyl phosphonic acid **1a** was reacted with styrene the desired product **2d** was obtained initially in 52% yield together with byproduct **4a** in 25% yield (entry 3, Table 2). However, this complication could be easily overcome by using BQ as the oxidant to produce the product **2d** in 85% yield as the only product (entry 4, Table 2). With this new procedure, 2-methylpropenoic acid methyl ester and acrylamide can also react with **1a** to afford **2i** and **2j** in 64% and 66% yields, respectively (entries 9 and 10, Table 2). This procedure can also be extended to the 3-monosubstituted or 3-unsubstituted allenes **1k**, **1n**, and **1o**: their reaction with ethyl acrylate, styrene, or acrylamide afforded the corresponding products **2k–p**, respectively (entries 11–16, Table 2).

In conclusion, we have established the cyclization–Heck reaction of 1,2-allenyl phosphonic acids with alkenes under oxidation conditions: CaH<sub>2</sub>(cat.)/NaI/O<sub>2</sub> or benzoquinone. Under the standard conditions, the cyclization–Heck reaction

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products were formed highly regio- and stereoselectively. Further studies in this area including the scope of substrates and the determination of the role of  $\text{CaH}_2$  are being conducted in our laboratory.

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**Supporting Information Available:** Synthesis and characterization for **2** and **3a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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