

# Gold-Catalyzed Sequential Alkyne Activation for the Synthesis of 4,6-Disubstituted Phosphorus 2-Pyrones

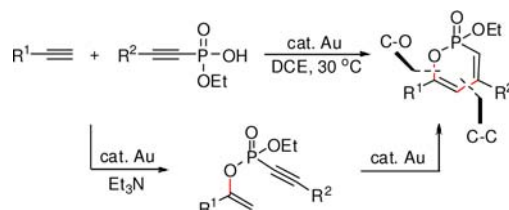
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## ABSTRACT



Tandem gold-catalyzed addition of alkynyl phosphonic acid monoethyl esters to terminal alkynes and cyclization were developed for the synthesis of 4,6-disubstituted phosphorus 2-pyrones in one reaction vessel based on the concept of sequential alkyne activation. Alkynyl enol phosphonates were selectively obtained through the gold-catalyzed addition reaction in the presence of a catalytic amount of triethylamine. Also, gold-catalyzed cyclization of alkynyl enol phosphonates was successful in giving a variety of 4,6-disubstituted phosphorus 2-pyrones.

2-Pyrones are an important structural motif found not only in valuable biologically active compounds<sup>1</sup> but also in diverse synthetic intermediates.<sup>2</sup> Recently, the activity of

2-pyrones as potent HIV protease inhibitors led to further investigations of 2-pyrone and its derivatives.<sup>3</sup>

Organophosphorus compounds continue to receive widespread attention due to their ubiquity in biological systems<sup>4</sup> and their potential to serve as novel pharmaceuticals.<sup>5</sup> Since there is a remarkable similarity in reactivity and bioactivity between the carbon species

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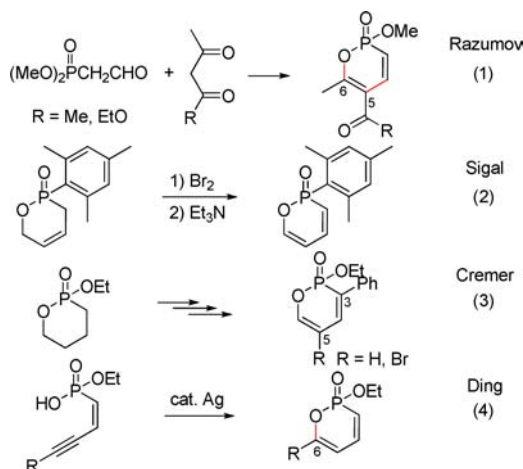
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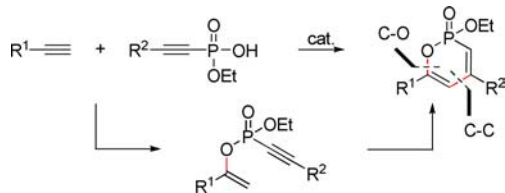
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and their phosphorus counterparts,<sup>6</sup> we imagined phosphorus 2-pyrones to have potential bioactivities similar to

those of the 2-pyrones reported. However, so far, only four synthetic methods of phosphorus 2-pyrones have been described in the literature. In 1978, Razumov et al. reported the synthesis of two phosphorus 2-pyrones through intermolecular aldol condensation and sequential thermal cyclization reactions (eq 3).<sup>7</sup> In the same year, Sigal et al. prepared phosphorus 2-pyrone by addition of bromine to mesityl-2-butenyl phosphinate and successive dehydrobromination (eq 2).<sup>8</sup> In 2002, Cremer et al. prepared two phosphorus 2-pyrones through a bromination–dehydrobromination sequence (4 steps) from the corresponding saturated phostone (eq 3).<sup>9</sup> These methods depend on the functionalization of a preformed cyclic phosphinate and phostone nucleus. Recently, Ding et al. reported an efficient procedure to synthesize 6-substituted phosphorus 2-pyrones through Ag-catalyzed cyclization of (*Z*)-2-alken-4-ynylphosphonic acid monoethylesters (eq 4).<sup>10</sup> However, to the best of our knowledge, a synthetic method for 4,6-disubstituted phosphorus 2-pyrones has never been reported thus far. Based on the concept of sequential alkyne activation,<sup>11</sup> we herein describe gold-catalyzed sequential intermolecular addition of 1-alkynylphosphonic acid monoethyl esters to alkynes followed by intramolecular cyclization of alkynyl enol phosphonates in one reaction vessel, leading to the formation of the 4,6-disubstituted phosphorus 2-pyrones (Scheme 1).

**Scheme 1.** Synthesis of 4,6-Disubstituted Phosphorus 2-Pyrones



We initiated our investigation using phenylethynyl phosphonic acid monoethyl ester **2a** and 5-phenyl-1-pentyne

(**1a**) (Table 1). 1-Alkynyl phosphonic acid monoethyl esters were readily prepared from the basic hydrolysis of diethyl 1-alkynyl phosphonates, which were synthesized by the reaction of lithium alkynides with diethyl phosphoryl chloride.<sup>12</sup> AuCl and AuCl<sub>3</sub> in the presence of AgOTf or

**Table 1.** Optimization of Tandem Addition and Cyclization<sup>a</sup>

entry	cat. (mol %)	temp (°C)	time (h)	yield (%) <sup>b</sup>
1	AuCl (5)	80	12	0
2	AuCl (5)/AgOTf (5)	40	24	0
3	AuCl <sub>3</sub> (5)	80	12	0
4	AuCl <sub>3</sub> (5)/AgOTf (15)	40	24	0
5	Ph <sub>3</sub> PAuCl (5)/AgOTf (5)	40	24	51
6	Ph <sub>3</sub> PAuCl (5)/AgOTf (5)	60	24	50 (13) <sup>c</sup>
7	Ph <sub>3</sub> PAuCl (5)/AgNTf <sub>2</sub> (5)	40	9	62
8	Ph <sub>3</sub> PAuCl (5)/AgSbF <sub>6</sub> (5)	40	16	55
9	JohnPhos-Au <sup>d</sup> (5)	30	14	68
10	AgOTf (5)	80	12	0

<sup>a</sup> **1a** (0.4 mmol) and **2a** (0.2 mmol) were used in DCE (0.8 mL).

<sup>b</sup> Isolated yield of **3a**. <sup>c</sup> 2-Ethoxy-6-methyl-4-phenyl-5-phenethyl-1,2-oxaphosphorin 2-oxide (**4a**). <sup>d</sup> JohnPhos-Au: (acetonitrile)[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate.

not failed to catalyze the tandem reaction (entries 1–4). Treatment of **1a** and **2a** with Ph<sub>3</sub>PAuCl and AgOTf (5 mol % each) as a catalyst selectively gave the cyclized tandem product **3a** in 51% yield in DCE at 40 °C after 24 h (entry 5). The reaction was sensitive to the temperature. When this reaction was carried out in DCE at 60 °C for 24 h, **3a** was obtained in 50% yield and, in addition, 2-ethoxy-6-methyl-5-phenethyl-4-phenyl-1,2-oxaphosphorin 2-oxide (**4a**) was isolated in 13% yield (entry 6). The noncoordinating counterion of the cationic gold(I) catalyst had a little effect on the product distribution. When AgNTf<sub>2</sub> or AgSbF<sub>6</sub> was used, we selectively isolated **3a** in 62% and 55% yields, respectively (entries 7 and 8). The best result was obtained by using the catalyst (acetonitrile)[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (5 mol %) in dichloroethane at 30 °C after 14 h, which gave rise to **3a** in 68% yield through C–O and sequential C–C bond formation in one reaction vessel (entry 9). AgOTf alone failed to catalyze the tandem reaction (entry 10). To check the possibility of catalysis by a protic acid, we attempted the tandem reaction in the presence of trifluoromethanesulfonic acid (5 mol %) in dichloromethane at 30 °C. Under these conditions, the reaction did not proceed.

The scope of the tandem reaction was examined with a variety of alkynes **1** and 1-alkynyl phosphonic acid monoethyl esters **2** (Table 2). Treatment of **2a** with 1-hexyne (**1b**) and 3-phenyl-1-propyne (**1c**) with a gold catalyst gave the

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cyclized 4,6-disubstituted phosphorus 2-pyrones **3b** and **3c** in 71% and 70% yields, respectively, in DCE at 30 °C within 16 h (entries 1 and 2). Reaction of **2a** with enyne **1d** in the presence of the gold catalyst gave the desired **3d** in 62% yield albeit with an excess amount (5 equiv) of **1d** (entry 3). Under the optimized reaction conditions, ethynyl phosphonic acid monoethyl ester **2b** having an electron-donating 4-methylphenyl group was reacted with 1-hexyne (**1b**) and 3-cyclohexyl-1-propyne (**1e**) to afford **3e** and **3f** in good yields in one reaction vessel (entries 4 and 5). Certain labile functional groups commonly employed in organic synthesis such as chloro or ester moieties substituted on the alkyne were tolerated under these reaction conditions (entries 6 and 7). Phosphonic acid monoethyl ester **2c** having an electron-withdrawing 4-chlorophenyl group underwent the Au-catalyzed tandem reaction with **1a** and **1f**, producing the phosphorus 2-pyrones **3i** (56%) and **3j** (50%) in slightly lower yields, presumably because the capacity of the triple bond of **2c** to coordinate gold and the nucleophilicity of phosphonic acid monoethyl ester is diminished by the existing chloride group (entries 8 and 9). The chloride functionality provides a handle to introduce other groups at the *para* position of phenyl group at the C-4 position via transition-metal-catalyzed cross-coupling reactions. Subjecting 1-hexynylphosphonic acid monoethyl ester **2d** to **1b** and **1h** produced the phosphorus 2-pyrones **3k** and **3l** in moderate to good yields (entries 10 and 11). When 4-phenyl-1-butyne (**1i**) and 5-phenyl-1-pentyne (**1a**) were used, the corresponding desired phosphorus 2-pyrones **3m** and **3n** were obtained in 67% and 62% yields, respectively (entries 12 and 13). Exposure of 5-chloro-1-pentyne (**1f**) and **2d** to the gold catalyst afforded **3o** in 64% yield through intermolecular C–O followed by intramolecular C–C bond formation (entry 14).

Although the mechanism of the present reaction has not been fully established at the present stage, a possible reaction pathway is shown in Scheme 2. Coordination of a gold catalyst to the triple bond in alkyne **1** results in the formation of the intermediate **A** which, upon nucleophilic attack of the oxygen on the 1-alkynyl phosphonic acid monoethyl ester **2**, is converted to a  $\sigma$ -gold complex **B**. Then, 1-alkynyl enol phosphonate **5** was produced after deprotonation followed by protodeauration of **B**. The triple bond in alkyne **1** rather than **2** was first activated by a gold catalyst, presumably because the capacity of the triple bond of **2** to coordinate gold is diminished by conjugation. Coordination of a gold catalyst to a triple bond in **5** results in the formation of the intermediate **C** which, upon nucleophilic attack of the carbon on the enol phosphonate, is cyclized leading to a  $\sigma$ -gold complex **D**. Subsequent deprotonation and protodeauration of **D** afforded the phosphorus 2-pyrone derivative **3** to release the gold catalyst back into the catalytic cycle. In addition, gold-catalyzed isomerization of **5** may occur at a higher temperature to produce the more substituted enol

**Table 2.** Au-Catalyzed Preparation of Phosphorus 2-Pyrones<sup>a</sup>

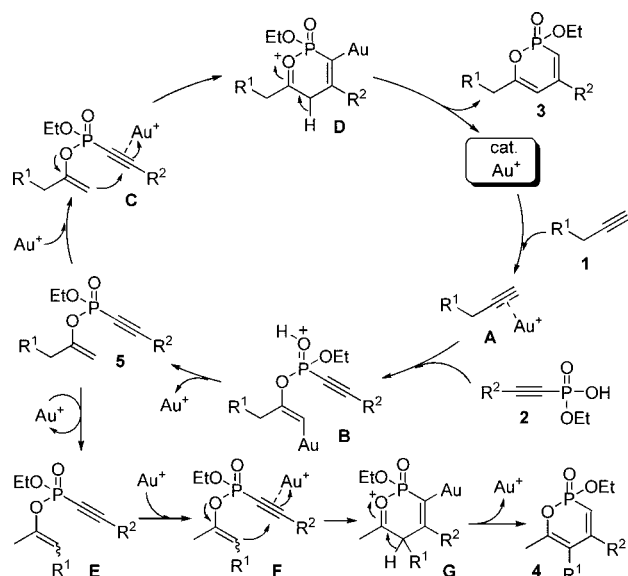
$\text{R}^1\text{—}\text{C}\equiv\text{C—H} + \text{R}^2\text{—}\text{C}\equiv\text{C—P(=O)(OH)OEt} \xrightarrow{\text{cat. Au}} \text{3}$					
entry	alkyne	R <sup>2</sup>	product	time (h)	yield (%) <sup>b</sup>
1		Ph ( <b>2a</b> )		14	71
2		Ph		16	70
3 <sup>c</sup>		Ph		18	62
4		C <sub>6</sub> H <sub>4</sub> -4-Me ( <b>2b</b> )		16	64
5		C <sub>6</sub> H <sub>4</sub> -4-Me		16	64
6		C <sub>6</sub> H <sub>4</sub> -4-Me		16	71
7 <sup>c</sup>		C <sub>6</sub> H <sub>4</sub> -4-Me		24	53
8		C <sub>6</sub> H <sub>4</sub> -4-Cl ( <b>2c</b> )		24	56
9		C <sub>6</sub> H <sub>4</sub> -4-Cl		24	50
10		n-Bu ( <b>2d</b> )		14	65
11		n-Bu		18	51
12		n-Bu		14	67
13		n-Bu		14	62
14		n-Bu		16	64

<sup>a</sup> Reactions were carried out with **1** (0.4 mmol), **2** (0.2 mmol), and (acetonitrile)[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (5 mol %) in DCE (0.8 mL) at 30 °C. <sup>b</sup> Isolated yield. <sup>c</sup> Alkyne (5 equiv) was used.

phosphonate **E**.<sup>13</sup> The repeated activation of the triple bond in **E** by the gold catalyst followed by cyclization,

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**Scheme 2.** Plausible Mechanism of Gold-Catalyzed Tandem Reaction



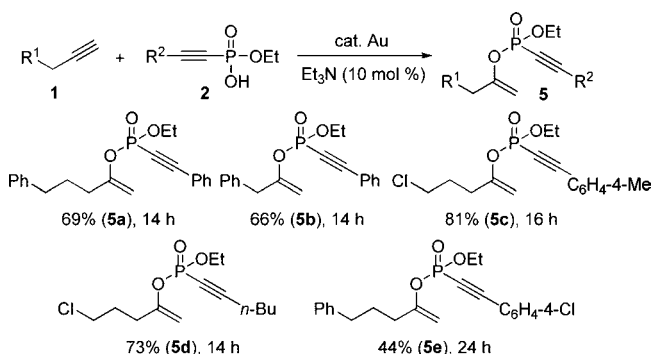
deprotonation, and protodeauration would give 4,5,6-trisubstituted phosphorus 2-pyrone **4**, which is supported by the formation of a side product (**4a**) in entry 6 (Table 1).

Next, we attempted to isolate the intermediate **5** to prove the plausible mechanism of the present tandem reaction. Gratifyingly, 1-alkynyl enol phosphonates were selectively obtained with the gold catalyst in the presence of triethylamine (Scheme 3).<sup>14</sup> For example, treatment of **1a** and **2a** with JohnPhos-Au (5 mol %) in the presence of triethylamine (10 mol %) selectively gave phenylethynyl enol phosphonate **5a** in 69% yield in DCE at 30 °C after 14 h without formation of the tandem product (**3a**). The addition of **2b** to **1f** proceeded smoothly to provide the desired enol phosphonate **5c** in 81% yield. Likewise, hexynyl enol phosphonate **5d** was synthesized in 73% yield from 5-chloro-1-pentyne (**1f**) and **2d**.

Based on the above mechanistic considerations, gold-catalyzed cyclization of **5** was examined (Table 3). We were pleased to observe that treatment of **5c** with John-Phos-Au (5 mol %) selectively provided **3g** in 83% yield in DCE at 30 °C after 3 h without formation of 4,5,6-trisubstituted phosphorus 2-pyrone (entry 3). Similarly, **5b** and **5d** were smoothly converted to the corresponding 4,6-disubstituted phosphorus 2-pyrones (**3c** and **3o**) in excellent yields under the mild reaction conditions (DCE, 30 °C, 1–2 h) catalyzed by gold (entries 2 and 5). Isolation of alkynyl enol phosphonates (Scheme 3) and their cyclization to phosphorus 2-pyrones (Table 3) indicate that the gold-catalyzed sequential alkyne activation process is operated as shown in Scheme 2.

(14) Additional studies of the role of Et<sub>3</sub>N in selectively giving 1-alkynyl enol phosphonates are currently underway. (a) Peng, A.; Ding, Y. *Synthesis* **2003**, 205. (b) Hua, R.; Tanaka, M. *Chem. Lett.* **1998**, 431.

**Scheme 3.** Au-Catalyzed Addition of 1-Alkynyl Phosphonic Acid Monoethyl Esters to Alkynes<sup>a</sup>



<sup>a</sup> Conditions: **1** (0.4 mmol) and **2** (0.2 mmol) in the presence of (acetonitrile)[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (5 mol %) and Et<sub>3</sub>N (10 mol %) were used in DCE (0.8 mL) at 30 °C.

**Table 3.** Au-Catalyzed Cyclization of 1-Alkynyl Enol Phosphonate<sup>a</sup>

entry	product	time (h)	yield (%)
1	<b>3a</b>	2	84
2	<b>3c</b>	2	86
3	<b>3g</b>	3	83
4	<b>3i</b>	6	72
5	<b>3o</b>	1	94

<sup>a</sup> **5** (0.2 mmol) and (acetonitrile)[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (5 mol %) in DCE (0.8 mL) at 30 °C.

In conclusion, we have developed the tandem gold-catalyzed addition of 1-alkynyl phosphonic acid monoethyl esters to terminal alkynes and cyclization for the synthesis of 4,6-disubstituted phosphorus 2-pyrones in one reaction vessel based on the concept of sequential alkyne activation. 1-Alkynyl enol phosphonates were selectively obtained through the gold-catalyzed addition reaction in the presence of a catalytic amount of triethylamine. Also, gold-catalyzed cyclization of alkynyl enol phosphonates was successful in giving phosphorus 2-pyrones.

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**Supporting Information Available.** Experimental procedure and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.