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

Juntae Mo,[†] Dongjin Kang,[†] Dahan Eom,[†] Sung Hong Kim,[‡] and Phil Ho Lee*,[†]

Department of Chemistry, Kangwon National University, Chuncheon 200-701, Republic of Korea and Analysis Research Division Daegu Center, Korea Basic Science Institute, Daegu 702-701, Republic of Korea

phlee@kangwon.ac.kr

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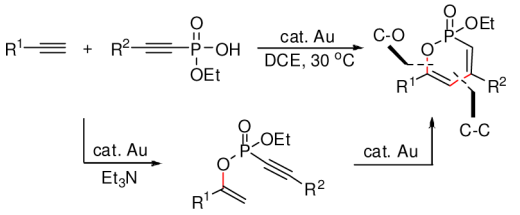
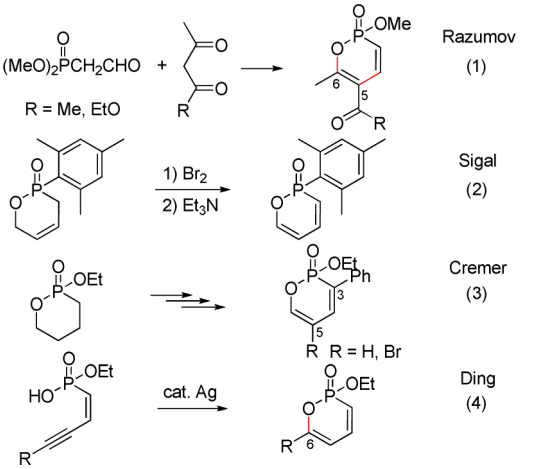
ABSTRACT



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[1] but also in diverse synthetic intermediates.[2] Recently, the activity of 2-pyrones as potent HIV protease inhibitors led to further investigations of 2-pyrone and its derivatives.[3]

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



and their phosphorus counterparts,[6] we imagined phosphorus 2-pyrones to have potential bioactivities similar to

[†] Kangwon National University.
[‡] Korea Basic Science Institute.

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(4) (a) Melzer, M.; Chen, J. C.-H.; Heidenreich, A.; Gäb, J.; Koller, M.; Kehe, K.; Blum, M.-M. *J. Am. Chem. Soc.* **2009**, *131*, 17226. (b) Chanda, A.; Khetan, S. K.; Banerjee, D.; Ghosh, A.; Collins, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 12059. (c) Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589.

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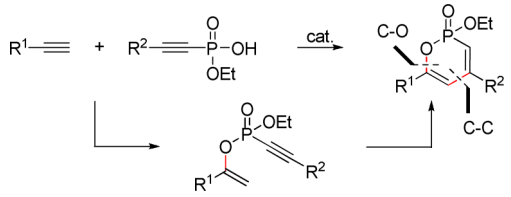
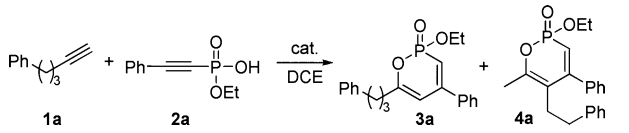
those of the 2-pyrones reported. However, so far, only four synthetic methods of phosphorus 2-pyrones have been described in the literature. In 1978, Razumov et al. reported the synthesis of two phosphorus 2-pyrones through intermolecular aldol condensation and sequential thermal cyclization reactions (eq 3).[7] In the same year, Sigal et al. prepared phosphorus 2-pyrone by addition of bromine to mesityl-2-butenyl phostinate and successive dehydrobromination (eq 2).[8] In 2002, Cremer et al. prepared two phosphorus 2-pyrones through a bromination−dehydrobromination sequence (4 steps) from the corresponding saturated phostone (eq 3).[9] These methods depend on the functionalization of a preformed cyclic phostinate 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).[10] 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,[11] 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.[12] AuCl and $AuCl_3$ in the presence of AgOTf or not failed to catalyze the tandem reaction (entries 1−4). Treatment of **1a** and **2a** with Ph_3PAuCl 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 $AgNTf_2$ or $AgSbF_6$ 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.

Table 1. Optimization of Tandem Addition and Cyclization[a]



1a 2a 3a 4a

entry	cat. (mol %)	temp (°C)	time (h)	yield (%)[b]
1	AuCl (5)	80	12	0
2	AuCl (5)/AgOTf (5)	40	24	0
3	$AuCl_3$ (5)	80	12	0
4	$AuCl_3$ (5)/AgOTf (15)	40	24	0
5	Ph_3PAuCl (5)/AgOTf (5)	40	24	51
6	Ph_3PAuCl (5)/AgOTf (5)	60	24	50 (13)[c]
7	Ph_3PAuCl(5)/$AgNTf_2$ (5)	40	9	62
8	Ph_3PAuCl (5)/$AgSbF_6$ (5)	40	16	55
9	JohnPhos-Au[d] (5)	30	14	68
10	AgOTf (5)	80	12	0

[a] **1a** (0.4 mmol) and **2a** (0.2 mmol) were used in DCE (0.8 mL). [b] Isolated yield of **3a**. [c] 2-Ethoxy-6-methyl-4-phenyl-5-phenethyl-1,2-oxaphosphorin 2-oxide (**4a**). [d] JohnPhos-Au: (acetonitrile)[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate.

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

(5) (a) Ruda, G. F.; Wong, P. E.; Alibu, V. P.; Norval, S.; Read, K. D.; Barrett, M. P.; Gilbert, I. H. *J. Med. Chem.* **2010**, *53*, 6071. (b) Congiatu, C.; Brancale, A.; Mason, M. D.; Jiang, W. G.; McGuigan, C. *J. Med. Chem.* **2006**, *49*, 452. (c) Kafarski, P.; LeJczak, B. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 301. (d) Colvin, O. M. *Curr. Pharm. Des.* **1999**, *5*, 555. (e) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281. (f) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193.

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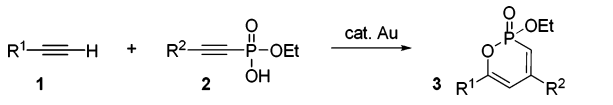
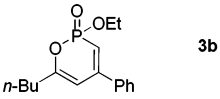
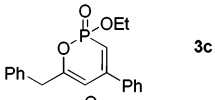
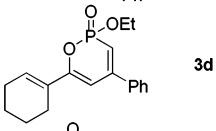
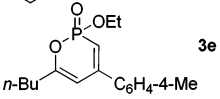
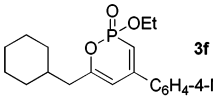
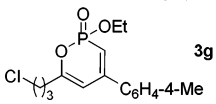
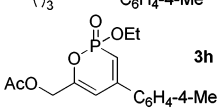
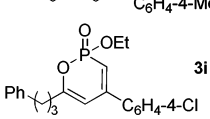
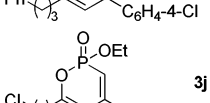
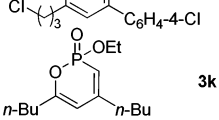
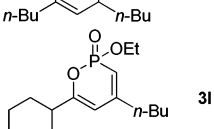
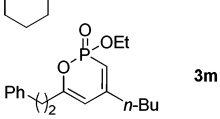
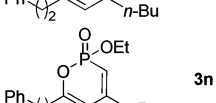
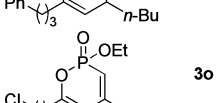
(12) Lahrache, H.; Robin, S.; Rousseau, G. *Tetrahedron Lett.* **2005**, *46*, 1635.

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 σ-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 σ-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 phosphonate **E**.[13] The repeated activation of the triple bond in **E** by the gold catalyst followed by cyclization,

Table 2. Au-Catalyzed Preparation of Phosphorus 2-Pyrones[a]

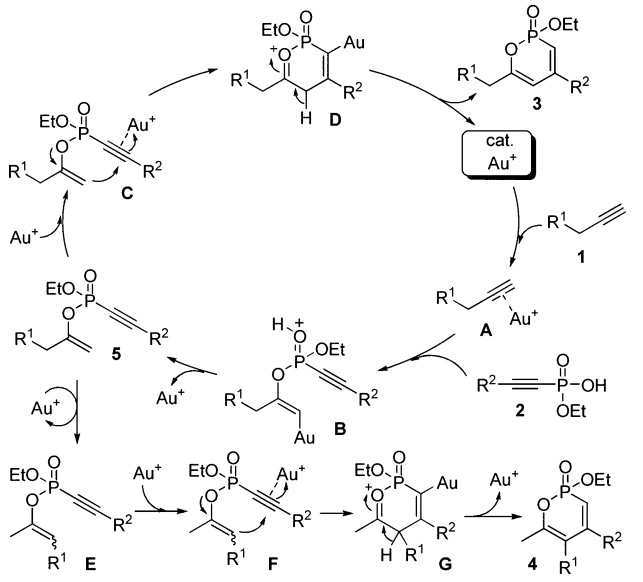


entry	alkyne	R^2	product		time (h)	yield (%)[b]
1	*n*-Bu—≡ **1b**	Ph (**2a**)		**3b**	14	71
2	Ph— **1c**	Ph		**3c**	16	70
3[c]	**1d**	Ph		**3d**	18	62
4	*n*-Bu—≡ **1b**	C_6H_4-4-Me (**2b**)		**3e**	16	64
5	**1e**	C_6H_4-4-Me		**3f**	16	64
6	Cl—(CH2)3— **1f**	C_6H_4-4-Me		**3g**	16	71
7[c]	AcO— **1g**	C_6H_4-4-Me		**3h**	24	53
8	Ph—(CH2)3— **1a**	C_6H_4-4-Cl (**2c**)		**3i**	24	56
9	Cl—(CH2)3— **1f**	C_6H_4-4-Cl		**3j**	24	50
10	*n*-Bu—≡ **1b**	*n*-Bu (**2d**)		**3k**	14	65
11	**1h**	*n*-Bu		**3l**	18	51
12	Ph—(CH2)2— **1i**	*n*-Bu		**3m**	14	67
13	Ph—(CH2)3— **1a**	*n*-Bu		**3n**	14	62
14	Cl—(CH2)3— **1f**	*n*-Bu		**3o**	16	64

[a] 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. [b] Isolated yield. [c] Alkyne (5 equiv) was used.

(13) (a) Lee, P. H.; Kang, D.; Choi, S.; Kim, S. *Org. Lett.* **2011**, *13*, 3470. (b) Lee, P. H.; Kim, S.; Park, A.; Chary, B. C.; Kim, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 6806. (c) Chary, B. C.; Low, W. S.; Kim, S.; Kim, H.; Lee, P. H. *Chem.—Asian J.* **2011**, *6*, 1970.

Scheme 2. Plausible Mechanism of Gold-Catalyzed Tandem Reaction



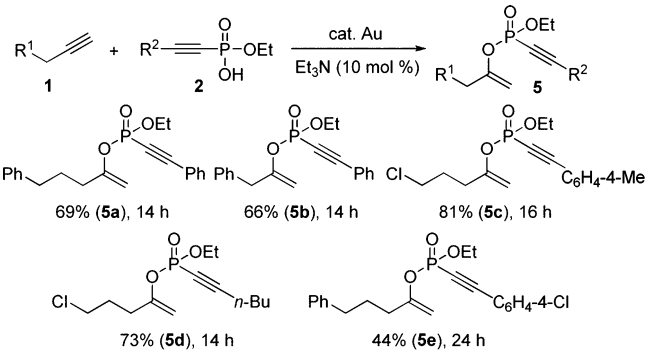
deprotonation, and protodeauration would give 4,5,6-trisubstituted phosphorus 2-pyrone **4**, which is supported by the formation of a side product (**4a**) in entry 6 (Table 1).

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).[14] 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.

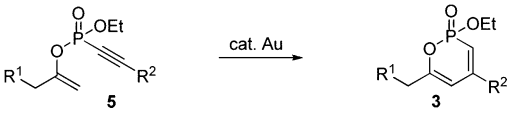
(14) Additional studies of the role of Et_3N in selectively giving 1-alkynyl enol phosphonates are currently underway. (a) Peng, A.; Ding, Y. *Synthesis* **2003**, 205. (b) Hua, R.; Tanaka, M. *Chem. Lett.* **1998**, 431.

Scheme 3. Au-Catalyzed Addition of 1-Alkynyl Phosphonic Acid Monoethyl Esters to Alkynes[a]



[a] 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_3N (10 mol %) were used in DCE (0.8 mL) at 30 °C.

Table 3. Au-Catalyzed Cyclization of 1-Alkynyl Enol Phosphonate[a]



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

[a] **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.