Gold Catalysis

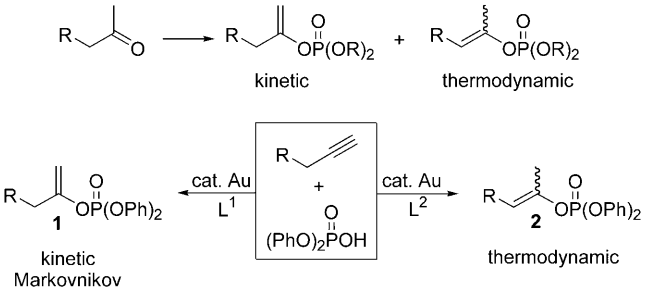
DOI: 10.1002/anie.201001799

Gold(I)-Catalyzed Addition of Diphenyl Phosphate to Alkynes: Isomerization of Kinetic Enol Phosphates to the Thermodynamically Favored Isomers**

Phil Ho Lee, Sundae Kim, Aeri Park, Bathoju Chandra Chary, and Sunggak Kim**

Dedicated to Professor Masakatsu Shibasaki

The conversion of carbonyl compounds into enol phosphates is of a great synthetic importance, since enol phosphates are versatile intermediates which undergo various synthetically useful transformations.[1] A general method for the preparation of enol phosphates involves the quenching of lithium enolates with dialkyl phosphorochloridates.[2] The major issue in this transformation is selectivity (kinetic versus thermodynamic). In particular, the more substituted thermodynamic enol derivatives from unsymmetrical ketones normally predominate under thermodynamic conditions but do not form exclusively, which is a serious problem in organic synthesis. Thus, the preparation of thermodynamic enol phosphates with high selectivity is of synthetic importance and still a very challenging problem.[2b,3] Herein, we report the gold-catalyzed addition of diphenyl phosphate to terminal alkynes as an unprecedented approach for the preparation of both kinetic and thermodynamic enol phosphates (Scheme 1).[4,5] We also disclose the gold-catalyzed isomerization of enol phosphates, produced under kinetic control, to the much less accessible thermodynamically favored enol phosphates.



Scheme 1. Formation of kinetic enol phosphates and the thermodynamically more stable isomers. L^1 and L^2 are ligands.

To examine the feasibility of the hydrophosphoryloxylation of alkynes, we began our study with the catalyst $[Ph_3PAuCl]/AgOTf$.[6] We found that the reaction was very sensitive to the solvent. Among the solvents tested, toluene gave the best result. When the reaction was carried out with 1-octyne and diphenyl phosphate in dichloromethane, nitromethane, acetonitrile, or ethanol at room temperature for 15 h, it did not proceed to give an observable amount of the product, whereas the reaction in toluene afforded the thermodynamic enol phosphate product **2** in 48% yield along with the Markovnikov addition product **1** (10%). Evidently, **2** was produced by the isomerization of **1**.

Encouraged by this preliminary result, we carried out several experiments to control selectivity by the fine-tuning of the ligands attached to gold. The reaction did not occur in the presence of a catalytic amount of $AuCl_3$, $AuCl_3/AgOTf$, or $AuCl_3/AgPF_6$ (Table 1, entries 1–3), and [(NHC)AuCl] complexes (NHC=N-heterocyclic carbene) were totally ineffective (entries 4 and 5).[7] Of various silver cocatalysts examined, $AgPF_6$ was the most effective. When it was used in combination with the catalyst $[Ph_3PAuCl]$, enol phosphate **1** was formed selectively in 88% yield (Table 1, entry 11). $AgBF_4$ was slightly less effective (Table 1, entry 8). Somewhat surprisingly, the selectivity was completely reversed with $[(C_6F_5)_3PAuCl]/AgOTf$,[8] which produced the thermodynamic product **2** in 88% yield without any of the anti-Markovnikov product (Table 1, entry 12). Apparently, the reaction proceeded through the addition of diphenyl phosphate to alkynes in a Markovnikov fashion, followed by isomerization. To check the possibility of catalysis by a protic acid, we attempted the reaction in the presence of triflic acid (5 mol%) in toluene at room temperature and at 110°C. Under these conditions, the reaction did not proceed (Table 1, entry 13).

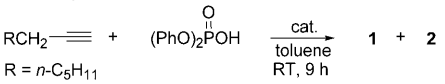
To explore the scope of the reaction with respect to the alkyne substrate, we carried out further reactions in toluene with $[Ph_3PAuCl]/AgPF_6$ (5 mol%; Table 2). The reaction of 3-phenyl-1-propyne proceeded well without the Friedel–Crafts cyclization (Table 2, entry 2). 3-Cyclohexyl-1-propyne

[*] Prof. Dr. P. H. Lee, Dr. S. Kim, A. Park
Department of Chemistry, Kangwon National University
Chuncheon 200-701 (Republic of Korea)
Fax: (+82) 33-253-7582
E-mail: phlee@kangwon.ac.kr
Homepage: http://indium.kangwon.ac.kr
B. C. Chary, Prof. Dr. S. Kim
Division of Chemistry and Biological Chemistry
School of Physical and Mathematical Sciences
Nanyang Technological University, Singapore 637371 (Singapore)
Fax: (+65) 6791-1961
E-mail: sgkim@ntu.edu.sg

[**] P.H.L. acknowledges financial support from the National Research Foundation of Korea (NRF) through the NRL Program, an NRF grant funded by the Korean government (MEST; 2009-0087013), and the 2nd phase BK 21 program. S.K. acknowledges financial support from Nanyang Technological University.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001799.

Table 1: Reaction optimization.[a]

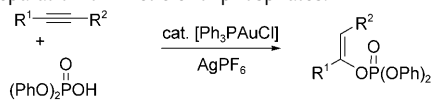


Entry	Catalyst	Yield [%] 1	2
1	$AuCl_3$	<1	0
2	$AuCl_3$/AgOTf[b]	<1	0
3	$AuCl_3$/$AgPF_6$[b]	<1	0
4	[(IPr)AuCl]/$AgPF_6$	0	0
5	[(IMes)AuCl]/$AgPF_6$	0	0
6	[Ph_3PAuCl]/AgOTf	10	48 (1:3.8)[c]
7	[Ph_3PAuCl]/$AgSbF_6$	<1	0
8	[Ph_3PAuCl]/$AgBF_4$	72	0
9	[Ph_3PAuCl]/$AgAsF_6$	12	14 (1:3.7)[c]
10	[Ph_3PAuCl]/$AgNTf_2$	<1	0
11	[Ph_3PAuCl]/$AgPF_6$	88	0
12	[$(C_6F_5)_3$PAuCl]/AgOTf	4	88 (1:3)[c]
13[d]	TfOH	0	0

[a] Reactions were carried out with 5 mol% of the Au catalyst and 5 mol% of the Ag cocatalyst. [b] The reaction was carried out with 15 mol% of the Ag cocatalyst. [c] *E*/*Z* ratio. [d] Reactions were carried out with TfOH (5 mol%) at RT for 24 h and at 110°C for 10 h. IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, IMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, Tf = trifluoromethanesulfonyl.

reacted smoothly with diphenyl phosphate in the presence of [Ph_3PAuCl]/$AgPF_6$ to provide the desired product in 80% yield (Table 2, entry 4). A chloro and a bromo group on the propargylic carbon atom were tolerated under these reaction conditions (Table 2, entries 5 and 6). The reaction of 5-chloro-1-pentyne gave the Markovnikov addition product selectively in 78% yield (Table 2, entry 7). Phenylacetylene and derivatives containing substituents with diverse electronic properties on the aromatic ring, such as a trifluoromethyl or *n*-pentyl group, all reacted smoothly with diphenyl phosphate to afford

Table 2: Preparation of kinetic enol phosphates.[a]



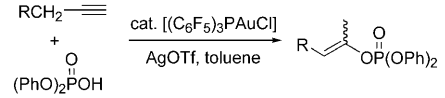
Entry	R^1	R^2	*T* [°C]	*t* [h]	Yield [%]
1	*n*-C_6H_{13}	H	RT	9	88
2	$PhCH_2$	H	RT	9	87
3	$Ph(CH_2)_3$	H	RT	9	81
4	*c*-$C_6H_{11}CH_2$	H	RT	17	80
5	$ClCH_2$	H	RT	15	70
6	$BrCH_2$	H	RT	16	92
7	$Cl(CH_2)_3$	H	RT	7	78
8	Ph	H	60	12	88
9	4-CF_3-C_6H_4	H	60	17	80
10	4-*n*Pent-C_6H_4	H	60	8	95
11	$PhCH_2S$	H	RT	2	98
12	H	CO_2Et	RT	10	84
13	Ph	CO_2Et	60	10	78
14	Et	Et	110	15	72
15	Me	Ph	110	10	69

[a] Reactions were carried out with 5 mol% of the Au catalyst and 5 mol% of the Ag cocatalyst.

the desired products in good yields; however, these reactions required heating at 60°C (Table 2, entries 8–10). Diphenyl phosphate underwent a clean regioselective addition to benzylthioacetylene (Table 2, entry 11). Similarly, the addition of diphenyl phosphate to activated alkynes, such as ethyl propiolate and ethyl phenylpropiolate, occurred by *trans* addition in a regio- and stereoselective manner (Table 2, entries 12 and 13). Dialkyl and alkyl, aryl-substituted alkynes were much less reactive than terminal and activated alkynes and required heating at reflux (110°C) for a long period of time (Table 2, entries 14 and 15).

We next turned our attention to the direct preparation of thermodynamic enol phosphates through hydrophosphoryloxylation and subsequent isomerization with the [$(C_6F_5)_3$PAuCl]/AgOTf catalyst. The present method was effective with both 3-phenyl-1-propyne and 5-phenyl-1-pentyne: the corresponding enol phosphates were formed selectively at room temperature (Table 3, entries 3 and 4).

Table 3: Preparation of thermodynamically favored enol phosphates.[a]



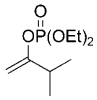
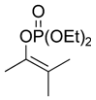
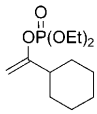
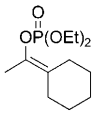
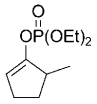
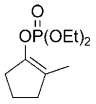
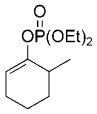
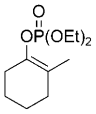
Entry	R	Yield [%]
1	*n*-C_5H_{11}	86 (1:35;[b] 1:2.6[c])
2[d]	*c*-C_6H_{11}	93 (1:17; 1:1.8)
3	Ph	87 (0:100; 1:3.6)
4	$Ph(CH_2)_2$	85 (1:25; 1:2)
5	$Cl(CH_2)_2$	86 (1:17; 1:2.6)

[a] Reactions were carried out with 5 mol% of the Au catalyst and 5 mol% of the Ag cocatalyst at room temperature for 24 h. [b] Ratio of kinetic and thermodynamic isomers. [c] *E*/*Z* ratio. [d] The reaction was carried out at 80°C for 24 h.

The treatment of 3-cyclohexyl-1-propyne with [$(C_6F_5)_3$PAuCl]/AgOTf in toluene at 80°C for 24 h provided the thermodynamic enol phosphate in 93% yield (Table 3, entry 2). When 5-chloro-1-pentyne was subjected to the reaction conditions, the thermodynamic enol phosphate was obtained in 86% yield (Table 3, entry 5). In all cases, the ratio of the thermodynamic to the kinetic isomer was at least 17:1.

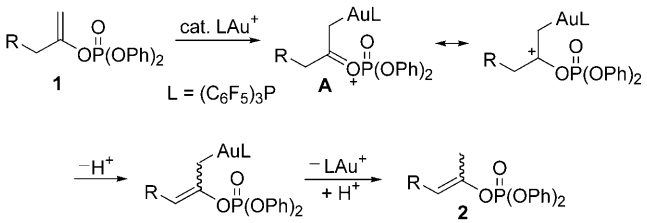
Finally, we examined the previously unknown conversion of kinetically formed enol phosphates into the thermodynamically favored enol phosphates. [$(C_6F_5)_3$PAuOTf] was found to be slightly more efficient than [$(C_6F_5)_3$PAuCl]/AgOTf for the isomerization (Table 4, entries 1 and 2). The kinetic enol phosphate derived from 2-butanone and diethyl chlorophosphate was completely isomerized in toluene at 70°C to the thermodynamic product in 87% yield within 2 h (Table 4, entry 1). Furthermore, the isomerization was also complete in 15 h at room temperature (Table 4, entry 3). To check whether a protic acid participates in the isomerization, we repeated the reaction in the presence of allyltrimethylsilane (10 mol%). We observed a similar result, indicative of the sole participation of [$(C_6F_5)_3$PAuOTf] (Table 4, entry 4).[9] Additional acyclic kinetic enol phosphates underwent smooth isomerization to afford the thermodynamically favored

Table 4: Isomerization of kinetic enol phosphates to the thermodynamically favored enol phosphates with $[(C_6F_5)_3PAuOTf]$.[a]

Entry	Reactant	T [°C]	t [h]	Product	Yield [%][b]
1		70	2		87 (0:100)[c]
2[d]		70	2		84 (1:25)
3		RT	15		87 (1:36)
4[e]		70	2		90 (1:29)
5		70	2		96 (0:100)
6		70	4		86 (1:26)
7		100	3		88 (1:34)
8		100	3		90 (1:21)

[a] Reactions were carried out with 5 mol% of the catalyst $[(C_6F_5)_3PAuOTf]$. [b] The ratio of the reactant to the product is given in parentheses. [c] The *E*/*Z* ratio for this reaction was 1:2. [d] The reaction was carried out with $[(C_6F_5)_3PAuCl]$ (5 mol%) and AgOTf (5 mol%). [e] The reaction was carried out in the presence of allyltrimethylsilane (10 mol%).

isomers (Table 4, entries 5 and 6). The isomerization of cyclic kinetic enol phosphates to the thermodynamically preferred isomers proceeded cleanly but required higher reaction temperatures for completion (Table 4, entries 7 and 8). Mechanistically, the isomerization reaction would proceed via the oxocarbenium intermediate **A**, the deprotonation of which could yield the more thermodynamically stable enol phosphate **2** (Scheme 2).[10]



Scheme 2. Proposed mechanism of the isomerization reaction.

In summary, we have developed a gold(I)-catalyzed hydrophosphoryloxylation of alkynes with diphenyl phosphate, whereby the catalyst $[Ph_3PAuCl]/AgPF_6$ affords the kinetic enol phosphates exclusively, whereas the catalyst $[(C_6F_5)_3PAuCl]/AgOTf$ gives the thermodynamically favored enol phosphates with high selectivity. Furthermore, kinetic enol phosphates were isomerized to the thermodynamically favored isomers with $[(C_6F_5)_3PAuOTf]$. Further studies on the isomerization of alkenyl derivatives with $[(C_6F_5)_3PAuCl]/AgOTf$ are underway.

Experimental Section

Typical procedure: 1-Octyne (66.0 mg, 0.6 mmol) was added to a suspension of $[Ph_3PAuCl]$ (12.4 mg, 0.025 mmol), $AgPF_6$ (6.3 mg, 0.025 mmol), and diphenyl phosphate (125.0 mg, 0.5 mmol) in toluene (2 mL) at room temperature by using a V Vial, and the resulting mixture was stirred at room temperature for 9 h. The solvent was then removed under reduced pressure, and the crude product was purified by silica-gel column chromatography (EtOAc/hexane 1:5) to give oct-1-en-2-yl diphenyl phosphate (159.0 mg, 88%) as a colorless liquid. IR (film): $\tilde{\nu}$ = 3071, 2931, 2859, 1940, 1864, 1783, 1726, 1659, 1560, 1591, 1490, 958, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 7.37–7.33 (m, 4H), 7.25–7.19 (m, 6H), 4.93 (t, J = 2.2 Hz, 1H), 4.59 (t, J = 2.0 Hz, 1H), 2.19 (t, J = 7.6 Hz, 2H), 1.44 (quint, J = 7.4 Hz, 2H), 1.31–1.19 (m, 6H), 0.87 ppm (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 155.9 (d, $J_{C,P}$ = 9.5 Hz), 150.5 (d, $J_{C,P}$ = 7 Hz), 129.8, 125.5, 120.1 (d, $J_{C,P}$ = 5 Hz), 98.0 (d, $J_{C,P}$ = 4 Hz), 34.3 (d, $J_{C,P}$ = 5.4 Hz), 31.5, 28.4, 26.1, 22.5, 14.1 ppm; HRMS (EI): *m*/*z* calcd for $C_{20}H_{25}O_4P$: 360.1490 $[M]^+$; found: 360.1488.

Received: March 26, 2010
Revised: June 16, 2010
Published online: August 4, 2010

Keywords: alkynes · gold · homogeneous catalysis · isomerization · phosphates

[1] See, for example: a) J. Wu, Z. Yang, *J. Org. Chem.* **2001**, *66*, 7875; b) J. A. Miller, *Tetrahedron Lett.* **2002**, *43*, 7111; c) F. L. Galbo, E. G. Occhiato, A. Guarna, C. Faggi, *J. Org. Chem.* **2003**, *68*, 6360; d) J. Y. Onishi, T. Takuwa, T. Mukaiyama, *Chem. Lett.* **2003**, *32*, 994; e) E. G. Occhiato, F. L. Galbo, A. Guarna, *J. Org. Chem.* **2005**, *70*, 7324; f) U. S. Larsen, L. Martiny, M. Begtrup, *Tetrahedron Lett.* **2005**, *46*, 4261; g) A. L. Hansen, J.-P. Ebran, T. M. Gogsig, T. Skrydstrup, *Chem. Commun.* **2006**, 4137; h) A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby, T. Skrydstrup, *Angew. Chem.* **2006**, *118*, 3427; *Angew. Chem. Int. Ed.* **2006**, *45*, 3349; i) A. L. Hansen, J.-P. Ebran, T. M. Gogsig, T. Skrydstrup, *J. Org. Chem.* **2007**, *72*, 6464; j) J.-P. Ebran, A. L. Hansen, T. M. Gogsig, T. Skrydstrup, *J. Am. Chem. Soc.* **2007**, *129*, 6931; k) P. Cheruku, S. Gohil, P. G. Andersson, *Org. Lett.* **2007**, *9*, 1659; l) G. Cahiez, O. Gager, V. Habiak, *Synthesis* **2008**, 2636; m) S. Protti, M. Fagnoni, *Chem. Commun.* **2008**, 3611; n) A. T. Lindhardt, T. M. Gogsig, T. Skrydstrup, *J. Org. Chem.* **2009**, *74*, 135; o) D. Gauthier, S. Beckendorf, T. M. Gogsig, A. T. Lindhardt, T. Skrydstrup, *J. Org. Chem.* **2009**, *74*, 3536; p) P. G. Steel, T. M. Wood, *Synthesis* **2009**, 3897.

[2] For examples of enolate formation, see: a) H. B. Mekelburger, C. S. Wilcox in *Comprehensive Organic Synthesis*, *Vol. 2* (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, pp. 99–131; b) D. L. Boger in *Modern Organic Synthesis*, TSRI, La Jolla, **1999**, pp. 147–206; c) W. Carruthers, I. Coldham in *Modern Methods of Organic Synthesis*, Cambridge University Press, Cambridge, **2004**, pp. 9–19.

[3] M. E. Krafft, R. A. Holton, *Tetrahedron Lett.* **1983**, *24*, 1345.

[4] The ruthenium-catalyzed addition of diphenylphosphinic acid ($Ph_2P(O)OH$) to terminal alkynes was reported previously; however, the reaction was unsuccessful with diphenyl phosphate ($(PhO)_2P(O)OH$): R. Hua, M. Tananka, *Chem. Lett.* **1998**, 431.

[5] For reviews on metal-catalyzed reactions of alkynes, see: a) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675; b) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079; c) C. Bruneau, P. H. Dixneuf, *Angew. Chem.* **2006**, *118*, 2232; *Angew. Chem. Int. Ed.* **2006**, *45*, 2176; d) Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817.

[6] For reviews on gold catalysis, see: a) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896; b) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; c) A. S. K. Hashami, *Chem. Soc. Rev.* **2008**, *37*, 1766; d) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239; e) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266; f) N. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395; g) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885; h) J. Muzart, *Tetrahedron* **2008**, *64*, 5815; i) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917; j) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766.

[7] a) P. de Fremont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics* **2005**, *24*, 2411; b) R. Dorta, E. D. Stevens, N. M. Scott, C. Costabile, L. Cavallo, C. D. Hoff, S. P. Nolan, *J. Am. Chem. Soc.* **2005**, *127*, 2485.

[8] a) C. Nieto-Oberhuber, S. Lopez, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178; b) S. Shin, *Bull. Korean Chem. Soc.* **2005**, *26*, 1925; c) C. Nieto-Oberhuber, M. P. Munoz, S. Lopez, E. Jimenez-Nunez, C. Nevado, E. Herrero-Gomez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677; d) C. Lim, J.-E. Kang, J.-E. Lee, S. Shin, *Org. Lett.* **2007**, *9*, 3539; e) H. J. Bae, B. Baskar, S. E. An, J. Y. Cheong, D. T. Thangadurai, I.-C. Hwang, Y. H. Rhee, *Angew. Chem.* **2008**, *120*, 2295; *Angew. Chem. Int. Ed.* **2008**, *47*, 2263; f) M.-Z. Wang, M.-K. Wong, C.-M. Che, *Chem. Eur. J.* **2008**, *14*, 8353; g) S. S. Gunatilleke, A. M. Barrios, *J. Inorg. Chem.* **2008**, *102*, 555; h) B. Baskar, H. J. Bae. S. E. An, J. A. Cheong. Y. H. Rhee, A. Duschek, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 2605.

[9] We found that triflic acid was effective for the isomerization of kinetic enol phosphonates to the thermodynamically favored isomers. For example, the treatment of but-1-en-2-yl diethyl phosphate with triflic acid (5 mol%) in toluene at room temperature for 1 h afforded the thermodynamic enol phosphate. Studies on the triflic acid catalyzed isomerization of enol derivatives are under way and will be reported in due course.

[10] a) Y. Peng, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 5062; b) G. Li, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 3740; c) C. H. M. Amijs, V. Lepez-Carrillo, A. M. Echavarren, *Org. Lett.* **2007**, *9*, 4021; d) J. Zhao, C. O. Hughes, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 7436; e) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442; f) A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515.

