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Efficient AgOTf or $Ph_3PAuCl–AgSbF_6$ catalyzed cyclization of 1-hydroxy-2-alkynylallylphosphonates/2-alkynylallyl alcohols to 2-furylphosphonates/2,3,5-trisubstituted furans

Ramesh Kotikalapudi, K. C. Kumara Swamy *

School of Chemistry, University of Hyderabad, Hyderabad 500 046, AP, India

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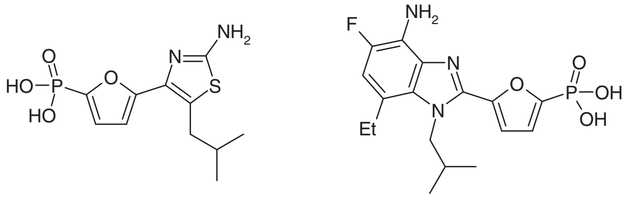
ABSTRACT

The reaction of 1-hydroxy-2-alkynylallylphosphonates, synthesized by the addition of the corresponding phosphites to 2-alkynylcinnamaldehydes, under AgOTf or $Ph_3PAuCl–AgSbF_6$ catalyzed cycloisomerization afforded 2-furylphosphonates in good to excellent yields. These cyclization reactions were compared with those of 2-alkynylallyl alcohols that led to multisubstituted furans.

Furan ring system is an important structural unit that appears in many natural products[1] and pharmaceuticals.[2] Functionalized furans are also useful intermediates in organic synthesis.[3] Many heteroarylphosphonates,[4,5] in particular furylphosphonates and their analogues, have found applications in drug discovery.[6] Two drugs involving furylphosphonic acid moiety which are useful as therapeutic agents in treating type 2 diabetes mellitus[7] are shown in Figure 1. Organophosphonates themselves have a diverse range of bio-related functions (e.g., glyphosate, fosfomycin).[8] Thus, there is a twofold interest in furylphosphonates. Despite the synthesis of the similar structural units reported previously by introducing a phosphonate group directly on furan,[7a,9] many of these methods are not amenable to synthesize poly-substituted furylphosphonates. Although there are reports on gold,[10] silver,[11] and palladium[12] catalyzed cyclization of 2-alkynylallylic alcohols leading to multisubstituted furans in addition to a *t*-BuOK[13] activated route, there is no precedence for the cycloisomerization of 1-hydroxy-2-alkynylallylphosphonates leading to polysubstituted furylphosphonates. Cyclization of phosphonoalkynols leading to phosphonylated isochromenes[14]/isobenzofurans[15] has been reported but the synthetic routes involve an entirely different reaction sequence. Because of the pivotal role of gold catalysts[10,16] in cycloisomerization of alkynyl compounds, our interest in cyclizing the phosphonoalkynols has been oriented toward gold catalysis which is reported in this Letter; we have discovered that simple AgOTf also catalyzes such reactions. 2-Alkynyl cinnamaldehydes **2** and their derivatives are functionalized molecules which have been proved as elegant precursors in synthesizing polysubstituted furans,[17] bicyclic furoazepines,[18] furooxazine,[19] allenes,[20] pyrans,[21] and isoxazoles.[22] Hence as an extension to our methodology, we have included these reactions.

Initially, various new 1-hydroxy-2-alkynylallylphosphonates **3**–**13** were synthesized from the corresponding H-phosphonates **1a**–**c** and 2-alkynylcinnamaldehydes **2a**–**i** via the Pudovik reaction (Scheme 1).[23] Yields in these reactions were in the range of 88–94%.

To accomplish the cyclization, we started with the alcohols depicted in Scheme 1. Initially, we performed AgOTf catalyzed cyclization of **3** (Scheme 2) in 1,2-dichloroethane and obtained 58% of



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[5-(4-Amino-7-ethyl-5-fluoro-1-isobutyl-1H-benzoimidazol-2-yl)-furan-2-yl]-phosphonic Acid

Figure 1. Drugs containing furylphosphonic acid moiety.

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* Corresponding author. Tel.: +91 40 2313 4856; fax: +91 40 2301 2460.
E-mail address: kckssc@uohyd.ernet.in (K.C. Kumara Swamy).

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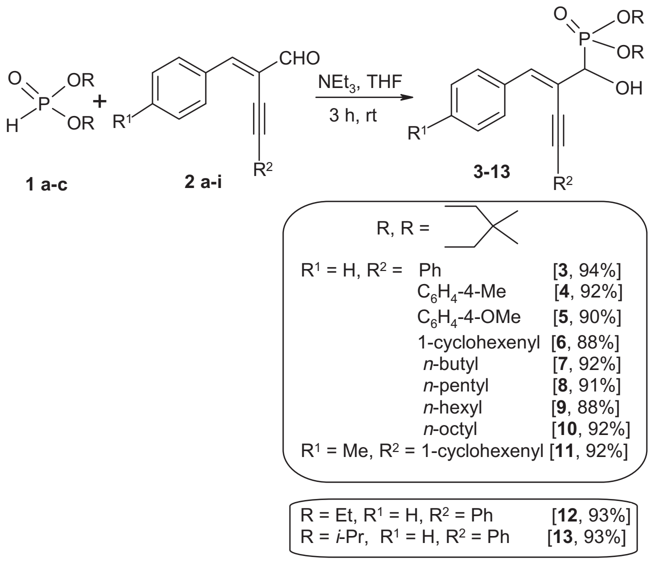
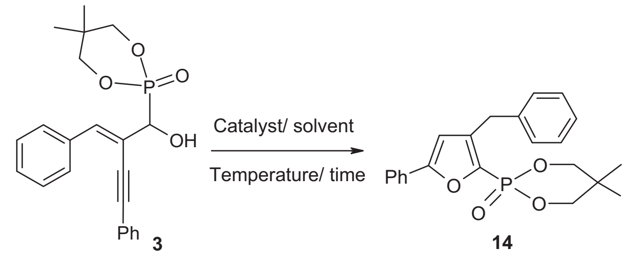


Scheme 1. Synthesis of 1-hydroxyphosphonates **3–13**.



Scheme 2. Reaction of 1-hydroxyphosphonate **3** leading to furylphosphonate **14**.

the product **14** when 5 mol % catalyst was used (Table 1, entry 1; Fig. 2); increasing the amount of catalyst increased the yield of the *isolated product* to 88% (entry 2). The ^{31}P NMR monitoring of the reaction mixture showed a single product with the entire phosphorus precursor being consumed. We were able to utilize this condition to isolate cyclized products **14**–**24** in 85–94% yield. Under the conditions employed, $Cu(OTf)_2$ (entry 3), $Zn(OTf)_2$, and $Sc(OTf)_3$ were ineffective. At the same time, we were allured by the prospect of using gold(I) complexes, since it is known that they can effect activation of C≡C bonds at low catalyst loading. Thus by using 3% $Ph_3PAuCl/AgOTf$, the furan **14** was obtained in 81% isolated yield (Table 1, entry 4). Gratifyingly, the use of 3% $Ph_3PAuCl/AgSbF_6$ led to 90% isolated yield (Table 2, entry 5). At a lower loading of the catalyst (1%), the yield decreased to 62% (Table 1, entry 6); $AgSbF_6$ alone could not effect the cyclization (Table 1, entry 7). Different solvents like THF, toluene, acetonitrile, and CH_2Cl_2 were examined in the presence of 3% $Ph_3PAuCl/AgSbF_6$, but these gave a poor yield of the furan (entries 8–11); there was no reaction in nitromethane (entry 12). Thus our studies indicated that either 10% AgOTf or 3% $Ph_3PAuCl/AgSbF_6$ was the most suitable catalytic system for this conversion.[24] The efficacy of the above catalytic conditions was verified with various phosphonoalkynols which were efficiently cycloisomerized to 2-furylphosphonates in excellent yields as summarized in Table 2.

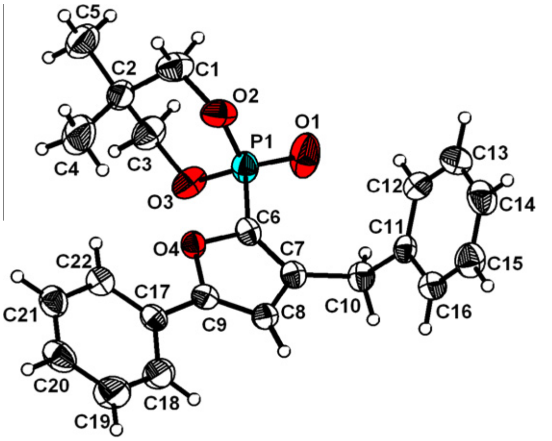


Figure 2. ORTEP diagram for compound **14**. Selected bond lengths [Å] with esd's in parentheses: O4–C9 1.358(3), C6–C7 1.357(3), C7–C10 1.497(3), C8–C9 1.349(3), and C8–H8 0.9300.

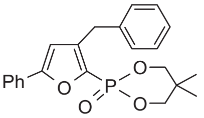
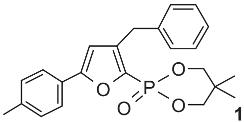
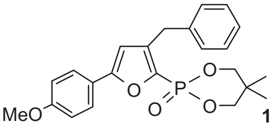
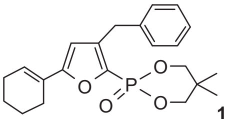
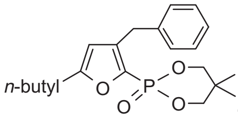
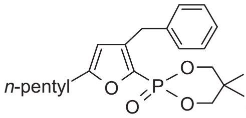
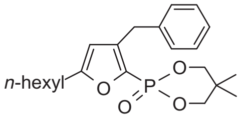
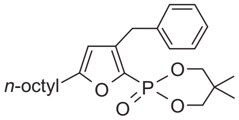
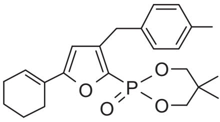
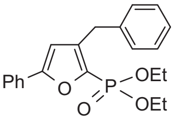
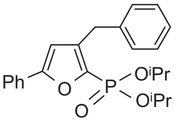
The role of gold(I) catalyst in the above cyclization was further explored by applying the catalyst in the cycloisomerization of 2-alkynylallyl alcohols (Scheme 3 see Supplementary data for the synthesis of precursors) also. Interestingly, alcohol **25** upon treatment with even 1% $Ph_3PAuCl/AgSbF_6$ in dichloromethane *at room temperature*, led to **31** in 91% yield. By varying the catalyst to 1% $Ph_3PAuCl/AgOTf$, the yield decreased to 72%. $AuCl_3$ in DCE[10a] at 70 °C afforded furan in only 10% yield. The compounds Ph_3PAuCl, AgOTf, and $AgSbF_6$ individually were not effective in the cyclization process. These alkynols when treated with DBU did not form the furan whereas *t*-BuOK led to furan in 85% yield; however, 1 mol equiv of the base was required. These data are presented in Table 3. Hence it was concluded that $Ph_3PAuCl/AgSbF_6$ was the most efficient catalyst for this cycloisomerization (cf. Table 4).

Table 1
Effect of catalyst/solvent in cycloisomerization of **3** (cf. Scheme 2)

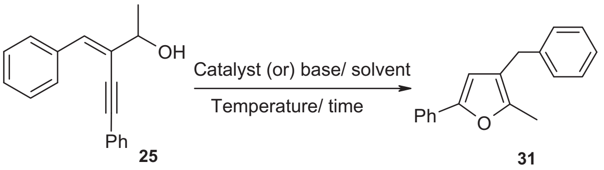
Entry	Catalyst (mol %)	Temp. (°C)/Time (h)	Solvent	Yield[a] (%)
1	5% AgOTf	70/12	DCE	58[b]
2	10% AgOTf	70/3	DCE	88[c]
3	5% $Cu(OTf)_2$	70/12	DCE	No reaction
4	3% $Ph_3PAuCl/AgOTf$	70/3	DCE	81
5	3% $Ph_3PAuCl/AgSbF_6$	70/3	DCE	90
6	1% $Ph_3PAuCl/AgSbF_6$	70/12	DCE	62[b]
7	5% $AgSbF_6$	70/12	DCE	Trace
8	3% $Ph_3PAuCl/AgSbF_6$	70/12	THF	20
9	3% $Ph_3PAuCl/AgSbF_6$	70/12	Toluene	42
10	3% $Ph_3PAuCl/AgSbF_6$	70/12	CH_3CN	32
11	3% $Ph_3PAuCl/AgSbF_6$	rt/12	DCM	15
12	3% $Ph_3PAuCl/AgSbF_6$	70/12	Nitro-methane	No reaction

[a] Isolated yield.
[b] Starting material remained.
[c] This condition could also be used to obtain furans **14**–**24** in excellent yields of 85–94%.

Table 2
Synthesis of 2-furylphosphonates[a] (cf. Scheme 2)

Entry	Alcohol	Product	Yield[b] (%)
1	**3**	 **14**	90
2	**4**	 **15**	90
3	**5**	 **16**	93
4	**6**	 **17**	86
5	**7**	 **18**	88
6	**8**	 **19**	92
7	**9**	 **20**	85
8	**10**	 **21**	91
9	**11**	 **22**	88
10	**12**	 **23**	92
11	**13**	 **24**	93

[a] Conditions: Phosphonoalkynol (0.4 mmol), $Ph_3PAuCl/AgSbF_6$ (3 mol %), DCE (2 mL), 70 °C, 3 h.
[b] Yield of the isolated product.



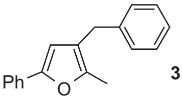
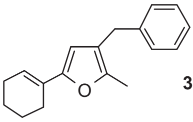
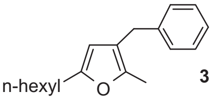
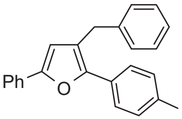
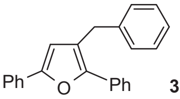
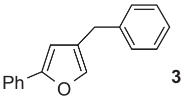
Scheme 3. Reaction of compound **25** leading to furan **31**.

Table 3
Effect of catalyst/solvent in cycloisomerization of **25** (cf. Scheme 3)

Entry	Catalyst (mol %)	Temp. (°C)/Time (h)	Solvent	Yield[a] (%)
1	1% $Ph_3PAuCl/AgSbF_6$	rt/1	DCM	91
2	1% $Ph_3PAuCl/AgOTf$	rt/1	DCM	72
3	1% $AuCl_3$	70/12	DCE	10
4	1% Ph_3PAuCl	70/12	DCE	No product
5	5% AgOTf	70/12	DCE	No product
6	5% $AgSbF_6$	70/12	DCE	No product
7	DBU[b]	70/12	DMSO	No reaction
8	*t*-BuOK[b]	70/3	DMSO	85

[a] Isolated yield.
[b] 1 Equiv of base was used.

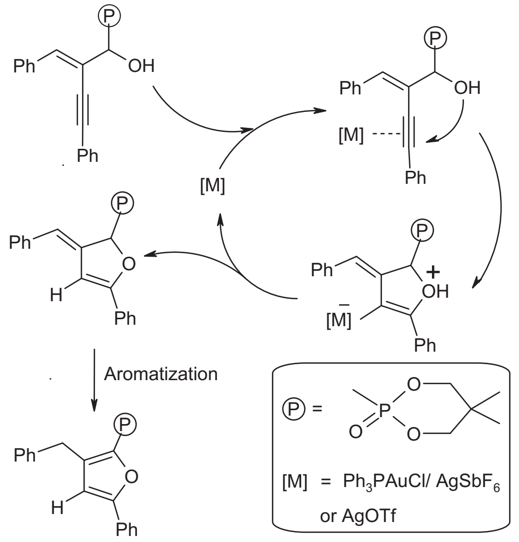
Table 4
Gold(I) catalyzed synthesis of various furans[a] (cf. Scheme 3)

Entry	Alcohol	Product	Yield[b] (%)
1	**25**	 **31**	91
2	**26**	 **32**	52
3	**27**	 **33**	92
4	**28**	 **34**	84
5	**29**	 **35**	88
6	**30**	 **36**	90

[a] Conditions: Alkynol (0.4 mmol), $Ph_3PAuCl/AgSbF_6$ (1 mol %), DCM (2 mL), rt, 1 h.
[b] Yield of the isolated product.

A possible pathway for the formation of phosphonofurans based on the available literature[10a] is presented in Scheme 4. Since we found that AgOTf also works well, it is likely that silver(I) also coordinates in a manner analogous to gold(I) in these reactions.[25] In the case of non-phosphorylated alkynols **25**–**30** leading to the cyclized products **31**–**36**, the pathway is analogous, but the reaction is more facile using the gold(I) catalytic system. Why AgOTf alone did not work in this case is still to be answered. The likely role of phosphoryl P═O in these reactions needs further investigation since simple AgOTf worked well in the cyclization reactions leading to phosphonofurans **14**–**24**.

To summarize, a new route to phosphonofurans using AgOTf or $Ph_3PAuCl/AgSbF_6$ as the catalytic system has been demonstrated. The latter system can also efficiently catalyze the cyclization of nonphosphorylated 2-alkynylallyl alcohols. Phosphonoalkynols required an elevated temperature for cyclization (hence the solvent DCE was used) when compared to other alkynols.



Scheme 4. A possible pathway for the formation of phosphonofurans **14–24**.

Acknowledgments

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Supplementary data

Supplementary data (experimental data for all the new compounds reported and crystal data (CIF file) for compound **14**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.060.

References and notes

1. (a) Reid, S. T. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1983; Vol. 33, pp 1–95; (b) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 657–712; (c) Rodriguez, A. D. *Tetrahedron* **1995**, *51*, 4571; (d) Muhammad, I.; Li, X.-C.; Jacob, M. R.; Tekwani, B. L.; Dunbar, D. C.; Ferreira, D. *J. Nat. Prod.* **2003**, *66*, 804; (e) Majumdar, K. C.; Chattopadhyay, S. K. *Heterocycles in Natural Product Synthesis*; John Wiley & Sons, 2011.
2. (a) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; John Wiley & Sons: Weinheim, 1997; (b) Kafarski, P.; LeJczak, B. *Curr. Med. Chem. Anticancer Agents* **2001**, *1*, 301.
3. (a) Martin, S. F.; Guinn, D. E. *Tetrahedron Lett.* **1984**, *25*, 5607; (b)*Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; (c) Heaney, H.; Ahn, J. S. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 2, pp 297–357; (d) Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 2, pp 395–436; (e) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179; (f) Montagon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001.
4. (a) Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589; (b) Robbins, B. L.; Srinivas, R. V.; Kim, C.; Bischofberger, N.; Fridland, A. *Antimicrob. Agents Chemother.* **1998**, *42*, 612; (c) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177; (d) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868; (e) Dang, Q.; Kasibhatla, S. R.; Jiang, T.; Fan, K.; Liu, Y.; Taplin, F.; Schulz, W.; Cashion, D. K.; Reddy, K. R.; Poelje, P. D. V.; Fujitaki, J. M.; Potter, S. C.; Erion, M. D. *J. Med. Chem.* **2008**, *51*, 4331.
5. (a) Chakravarty, M.; Kumara Swamy, K. C. *J. Org. Chem.* **2006**, *71*, 9128; (b) Chakravarty, M.; Bhuvan Kumar, N. N.; Sajna, K. V.; Kumara Swamy, K. C. *Eur. J. Org. Chem.* **2008**, 4500; (c) Phani Pavan, M.; Chakravarty, M.; Kumara Swamy, K. C. *Eur. J. Org. Chem.* **2009**, 5927; (d) Bhuvan Kumar, N. N.; Nagarjuna Reddy, M.; Kumara Swamy, K. C. *J. Org. Chem.* **2009**, *74*, 5395; (e) Sajna, K. V.; Kotikalapudi, R.; Chakravarty, M.; Bhuvan Kumar, N. N.; Kumara Swamy, K. C. *J. Org. Chem.* **2011**, *76*, 920; (f) Srinivas, V.; Sajna, K. V.; Kumara Swamy, K. C. *Chem. Commun.* **2011**, *47*, 5629; (g) Phani Pavan, M.; Kumara Swamy, K. C. *Synlett* **2011**, 1288; (h) Srinivas, V.; Sajna, K. V.; Kumara Swamy, K. C. *Tetrahedron Lett.* **2011**, *52*, 5323.
6. (a) Colvin, O. M. *Curr. Pharm. Des.* **1999**, *5*, 555; (b) Mader, M. M.; Bartlett, P. A. *Chem. Res.* **1997**, *97*, 1281.
7. (a) Erion, M. D.; Dang, Q.; Reddy, M. R.; Kasibhatla, S. R.; Huang, J.; Lipscomb, W. N.; Poelje, P. D. V. *J. Am. Chem. Soc.* **2007**, *129*, 15480; (b) Dang, Q.; Kasibhatla, S. R.; Xiao, W.; Liu, Y.; Re, J. D.; Taplin, F.; Reddy, K. R.; Scarlato, G. R.; Gibson, T.; Poelje, P. D. V.; Potter, S. C.; Erion, M. D. *J. Med. Chem.* **2010**, *53*, 441; (c) Demmer, C. S.; Larsen, N. K.; Bunch, L. *Chem. Rev.* **2011**, *111*, 7981.
8. (a) Sikorski, J. A.; Gruys, K. J. *Acc. Chem. Res.* **1997**, *30*, 2; (b) Allenberger, F.; Klare, Y. *J. Antimicrob. Chemother.* **1999**, *43*, 211.
9. (a) Gooben, L. J.; Dezfuli, M. K. *Synlett* **2005**, 445; (b) Mu, X. J.; Zou, J. P.; Qian, Q. F.; Zhang, W. *Org. Lett.* **2006**, *8*, 5291.
10. (a) Praveen, C.; Kiruthiga, P.; Perumal, P. T. *Synlett* **2009**, 1990; (b) Hashmi, A. S. K.; Häffner, T.; Rudolph, M.; Rominger, F. *Eur. J. Org. Chem.* **2011**, 667; (c) Hashmi, A. S. K.; Haffner, T.; Rudolph, M.; Rominger, F. *Chem. Eur. J.* **2011**, *17*, 8195.
11. Zhang, D.; Yuan, C. *Eur. J. Org. Chem.* **2007**, 3916.
12. (a) Qing, F.-L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* **2000**, *65*, 2003; (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.
13. Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3435.
14. (a) Yu, X.; Ding, Q.; Wang, W.; Wu, J. *Tetrahedron Lett.* **2008**, *49*, 4390; (b) Wang, F.; Miao, Z.; Chen, R. *Org. Biomol. Chem.* **2009**, *7*, 2848.
15. Wang, F.; Wang, Y.; Cai, L.; Miao, Z.; Chen, R. *Adv. Synth. Catal.* **2008**, *350*, 2733.
16. (a) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976; (b) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409; (c) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489; (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180; (e) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395; (f) Corma, A.; Perez, A. L.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657.
17. (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164; (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679; (c) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609; (d) Oh, C. H.; Reddy, V. R.; Kim, A.; Rhim, C. Y. *Tetrahedron Lett.* **2006**, *47*, 5307; (e) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903; (f) Li, W.; Zhang, J. *Chem. Commun.* **2010**, *46*, 8839; (g) Cho, C. H.; Larock, R. C. *Tetrahedron Lett.* **2010**, *51*, 3417.
18. (a) Gao, H.; Zhao, X.; Yu, Y.; Zhang, J. *Chem. Eur. J.* **2010**, *16*, 456; (b) Gao, H.; Wu, X.; Zhang, J. *Chem. Commun.* **2010**, *46*, 8764.
19. (a) Liu, F.; Yu, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5505; (b) Liu, F.; Qian, D.; Li, L.; Zhao, X.; Zhang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 6669.
20. (a) Yu, X.; Ren, H.; Xiao, Y.; Zhang, J. *Chem. Eur. J.* **2008**, *14*, 8481; (b) Xiao, Y.; Zhang, J. *Chem. Commun.* **2010**, *46*, 752.
21. Yu, X.; Cao, Z.; Zhang, J. *Org. Biomol. Chem.* **2010**, *8*, 5059.
22. Yu, X.; Du, B.; Wang, K.; Zhang, J. *Org. Lett.* **1876**, *2010*, 12.
23. Muthiah, C.; Praveen Kumar, K.; Aruna Mani, C.; Kumara Swamy, K. C. *J. Org. Chem.* **2000**, *65*, 3733.
24. *General procedure for the synthesis of 2-furylphosphonates:* To a solution of phosphonoalkynol **3** (153 mg, 0.4 mmol) in dry DCE (2 mL) were added a solution of Ph_3PAuCl (0.03 equiv) and $AgSbF_6$ (0.03 equiv) in dichloroethane (DCE). The contents were stirred for 3 h at 70 °C. The solvent was removed under vacuum and the crude product was purified by column chromatography using silica gel with acetone/hexane (1:3) mixture as the eluent. X-ray data for **14** were collected on a Bruker AXS SMART diffractometer using Mo-K_α ($\lambda = 0.71073$ Å) radiation. The structures were solved and refined by standard methods. *Crystal data:* $C_{22}H_{23}O_4P$, $M = 382.37$, Monoclinic, Space group *P2(1)/c*, $a = 10.342(1)$, $b = 11.184(1)$, $c = 19.725(1)$ Å, $\beta = 121.16(1)^o$, $V = 1952.5(3)$ Å^3, $Z = 4$, $\mu = 0.165$ mm^{-1}, data/restraints/parameters: 3431/0/246, R indices ($I > 2\sigma(I)$): R1 = 0.0596, $wR2$ (all data) = 0.1385. CCDC no. 867562.
25. Gold(I) is soft and readily coordinates with the C≡C (triple) bonds. The presence of $AgSbF_6$ or AgOTf with the Ph_3PAuCl perhaps enhances the softness of the metal and allows for better activation of the triple bond. See: Lipshutz, B. H.; Yamamoto, Y. *Chem. Rev*. **2008**, *108*, 2793.