ORGANIC
LETTERS

2013
Vol. 15, No. 13
3358–3361

Synthesis of Phosphaisocoumarins through Rhodium-Catalyzed Cyclization Using Alkynes and Arylphosphonic Acid Monoesters

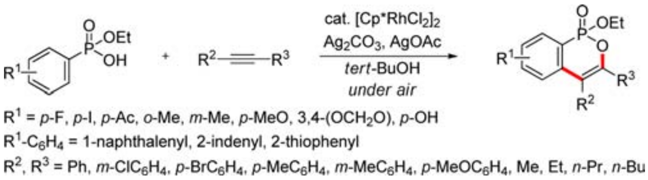
Jungmin Seo, Youngchul Park, Incheol Jeon, Taekyu Ryu, Sangjune Park, and Phil Ho Lee*

Department of Chemistry, Kangwon National University, Chuncheon 200-701, Republic of Korea

phlee@kangwon.ac.kr

Received May 18, 2013

ABSTRACT



A rhodium-catalyzed cyclization using alkynes and arylphosphonic acid monoesters for the synthesis of phosphaisocoumarins is reported. A number of arylphosphonic acid monoesters were selectively cyclized in high yields with functional group tolerance. In addition, unsymmetrical alkynes are applied in high regioselectivity.

C–H bond functionalizations catalyzed by transition metals are interesting since these procedures permit for a more clear-cut synthetic strategy to products devoid of demanding prefunctionalization of starting materials, thus avoiding byproducts in step-economical manner.[1] In order to have a broad synthetic strategy in a C–H functionalization, the desired C–H bond in the starting material should be selectively activated over all the C–H bonds existing in the substrate. In particular, since there is a trivial difference in the reactivity between the C–H bonds in aromatic compounds, a selective C–H bond functionalization is very crucial. Recently, a series of examples of C–C and C–heteroatom bond formation have been described by introducing directing groups.[2] As a consequcnce, a number of coordinating directing groups have been employed for atom- and step-economical C–H bond functionalization. Among those, imines,[3] amides[4] and heterocyclic compounds bearing nitrogen[5] are most frequently utilized as directing groups. In addition, C–H functionalization using hydroxyl[6] and carboxyl[7] as directing groups through

---

(1) (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (c) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.

(2) (a) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (d) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (e) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (f) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (h) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (i) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212.

(3) (a) Kuninobu, T.; Tokunage, T.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (b) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141.

(4) (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (b) Hyster, T. L.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (c) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (d) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250.

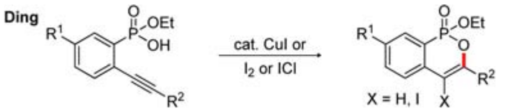
(5) (a) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2115. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (d) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898. (e) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952. (f) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (g) Kwak, J.; Ohk, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 17778.

(6) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *132*, 12203.

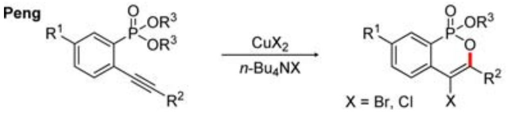
10.1021/ol401407v

weak coordination has been studied to a great extent.[1,2] However, there is still a need to develop useful functional groups for direct *ortho*-selective C–H bond cleavage, which will provide a significant effect in synthetic applications. Encouraged by a number of transition metal-catalyzed cyclizations using a carboxylic acid group,[8] we imagined that C–H bond functionalization with phosphonic acid monoesters would perform as an desirable platform for the preparation of phosphaisocoumarins, which may be phosphorus heterocycles exhibiting effective biological activity.[9]

Moreover, to date, phosphaisocoumarin scaffolds have been synthesized through intramolecular cyclization. Although alkynylarylphosphates[9k] or their monoesters[9g,h] have been used in the cyclization (eqs 1 and 2), as far as we know, a rhodium-catalyzed cyclization using alkynes and arylphosphonic acid monoesters has not been utilized for the synthesis of phosphaisocoumarins.



(1)



(2)

Furthermore, to the best of our knowledge, methods using phosphorus compound as a directing group is few.[10] Inspired by recent our interests[11] in organophosphorus compounds, we decided to examine C–H bond functionalization with phosphonic acid monoester. Herein, we have described Rh-catalyzed cyclization using alkynes and phosphonic acid monoester for the synthesis of phosphaisocoumarins (Scheme 1).

Scheme 1. Rh-Catalyzed Cyclization Using Alkynes and Phosphonic Acid Monoester

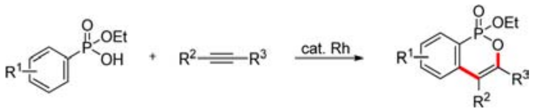
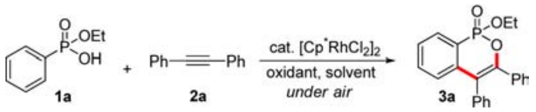


Table 1. Reaction Optimization[a]



entry	oxidant (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	$Cu(OAc)_2 \cdot H_2O$ (0.1)	DMF	120	18	0
2	Ag_2CO_3 (0.5)	DMF	120	18	0
3	Ag_2CO_3 (0.5)	1,4-dioxane	110	18	30
4	Ag_2CO_3 (0.5)	xylene	120	18	10
5	Ag_2CO_3 (0.5)	mesitylene	170	18	15
6	Ag_2CO_3 (0.5)	CF_3CH_2OH	90	18	0
7	Ag_2CO_3 (0.5)	C_6F_5OH	150	18	0
8	Ag_2CO_3 (0.5)	*t*-AmOH	110	18	55
9	Ag_2CO_3 (0.5)	*t*-BuOH	90	16	57
10	$AgSbF_6$ (0.5)	*t*-BuOH	90	16	0
11	AgOTf (0.5)	*t*-BuOH	90	16	0
12	AgOAc (0.5)	*t*-BuOH	90	16	45
13	Ag_2O (0.5)	*t*-BuOH	90	16	0
14	$Cu(OAc)_2 \cdot H_2O$ (0.5)	*t*-BuOH	90	16	23
15	Ag_2CO_3 (0.5)/$Cu(OAc)_2 \cdot H_2O$ (0.5)	*t*-BuOH	90	16	49
16	Ag_2CO_3 (0.5)/AgOAc (0.5)	*t*-BuOH	90	16	81
17	Ag_2CO_3 (1)/AgOAc (1)	*t*-BuOH	90	16	90

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.23 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), solvent (1 mL). [b] Isolated yields.

We started our studies with phenylphosphonic acid monoester **1a** (Table 1), which can be easily prepared from hydrolysis of diethyl phenylphosphonate. Miura reported that the oxidative coupling of benzoic acids with internal alkynes effectively proceeds in the presence of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2 \cdot H_2O$ as catalyst and oxidant, respectively, to produce the corresponding isocoumarin derivatives.[8a] However, when $[Cp^*RhCl_2]_2$ (2 mol %) and $Cu(OAc)_2 \cdot H_2O$ (0.1 equiv) in DMF at 120 °C for 18 h under air[8a] were applied to cyclization of phenylphosphonic acid monoester, the reaction did not proceed unfortunately (entry 1). Also, Ag_2CO_3 (0.5 equiv) as an oxidant was not effective in DMF (entry 2). Although trifluoroethanol and pentafluorophenol were not successful solvents (entries 6 and 7) with Ag_2CO_3 (0.5 equiv), 1,4-dioxane, xylene, and mesitylene gave the desired phosphaisocoumarin **3a** in 10–30% yields (entries 3–5). *tert*-Butyl alcohol was found to be the solvent of choice (entry 9). Next, a number of oxidants were tested and thus, the reaction was relatively sensitive to the choice of oxidants, with which $AgSbF_6$, AgOTf and Ag_2O were entirely ineffective

---

(7) (a) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (b) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169.

(8) (a) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362. (b) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930. (c) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 2030.

(9) (a) Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589. (b) 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. (c) Dillon, K. B.; Mathey, F.; Nixon, J. F. *Phosphorus: The Carbon Copy*; John Wiley & Sons: Chichester, 1998. (d) Li, X. S.; Zhang, D. W.; Pang, H.; Shen, F.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Org. Lett.* **2005**, *7*, 4919. (e) Li, B.; Zhou, B.; Lu, H.; Ma, L.; Peng, A.-Y. *Eur. J. Med. Chem.* **2010**, *45*, 1955. (f) Wei, T.; Ding, Y.-X. *J. Org. Chem.* **2006**, *71*, 8489. (g) Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2004**, *6*, 1119. (h) Peng, A.-Y.; Ding, Y.-X. *J. Am. Chem. Soc.* **2003**, *125*, 15006. (i) Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2005**, *7*, 3299. (j) Sigal, I.; Loew, L. *J. Am. Chem. Soc.* **1978**, *100*, 6394. (k) Peng, A.-Y.; Hao, F.; Li, B.; Wang, Z.; Du, Y. *J. Org. Chem.* **2008**, *73*, 9012.

(10) (a) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. (b) Lewis, J. C.; Wu, J.; Bergman, R. G.; Ellman, J. A. *Organometallics* **2005**, *24*, 5737. (c) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (d) Meng, X.; Kim, S. *Org. Lett.* **2013**, *15*, 1910. (f) Jeon, W. H.; Lee, T. S.; Kim, E. J.; Moon, B.; Kang, J. *Tetrahedron* **2013**, *69*, 5152. (h) Chan, L. Y.; Cheong, L.; Kim, S. *Org. Lett.* **2013**, *15*, 2186.

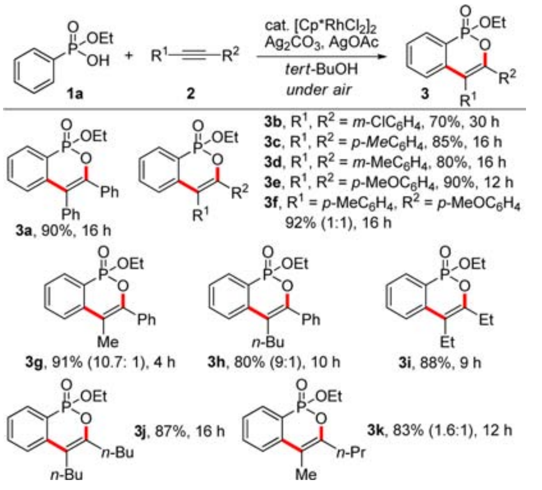
(11) (a) Mo, J.; Kang, D.; Eom, D.; Kim, S. H.; Lee, P. H. *Org. Lett.* **2013**, *15*, 26. (b) Chan, L. Y.; Kim, S.; Ryu, T.; Lee, P. H. *Chem. Commun.* **2013**, *49*, 4682. (c) Chary, B. C.; Kim, S.; Park, Y.; Kim, J.; Lee, P. H. *Org. Lett.* **2013**, *15*, 2692.

(entries 10, 11, and 13). However, AgOAc (0.5 equiv) and $Ag_2CO_3/Cu(OAc)_2 \cdot H_2O$ (0.5 equiv each) gave moderate transformation of the starting **1a** (entries 12 and 15). Gratifyingly, Ag_2CO_3/AgOAc (1 equiv each) turned out to be the most effective oxidant, resulting in the complete use of **1a** to furnish **3a** in 90% yield in DMF at 120 °C for 16 h (entry 17). No amount of **3a** were produced in the case using $[RuCl_2(p\text{-cymene})]_2$ and $(PCy_3)_2HRu(CO)Cl$ (see the Supporting Information). Treatment of equimolar mixture of **1a** and benzoic acid with standard conditions gave **3a** (69%) and isocoumarin (70%). As anticipated, this mixture was subjected to Miura conditions to afford only isocoumarin in 89% yield.

To determine the scope and limitations of the present method, various alkynes were applied to the standard conditions (Scheme 2). With respect to the alkyne substituent, the cyclization shows broad substrate tolerance among internal alkynes. Reaction of **1a** with various symmetrical diarylacetylenes **2** proceeded smoothly, as that with diphenylacetylene, to provide 3,4-diarylphosphaisocoumarins **3b**, **3c**, **3d**, and **3e** in good to excellent yields. However, electron-deficient bis(3-chlorophenyl)acetylene required longer reaction time (30 h) for completion of cyclization. Unsymmetrical diarylacetylene gave the desired phosphaisocoumarin **3f** in 92% yield. Electron-rich diarylacetylene is more reactive than electron-deficient one. When unsymmetrical alkylarylacetylenes are used, the phosphaisocoumarin having the phenyl group proximal to the oxygen was selectively produced due to the extended conjugation. 4-Alkyl-3-phenylphosphaisocoumarins **3g** and **3h** were predominantly obtained in 91% and 80% yields, respectively, together with minor amounts of their regioisomers. The rhodium catalysts were also found to be effective to dialkylalkynes, in which 3-hexyne and 5-decyne were subjected to **1a** to afford **3i** and **3j** in 88% and 87% yields, respectively. In the case of 2-hexyne, 4-methyl-3-propylphosphaisocoumarin **3k** was produced in 51% yield in major along with 3-methyl-4-propylphosphaisocoumarin (32%). However, terminal acetylenes, such as phenylacetylene, 4-phenyl-1-butyne, propargyl bromide, and 3-butyn-1-ol, were not cyclized with **1a**.

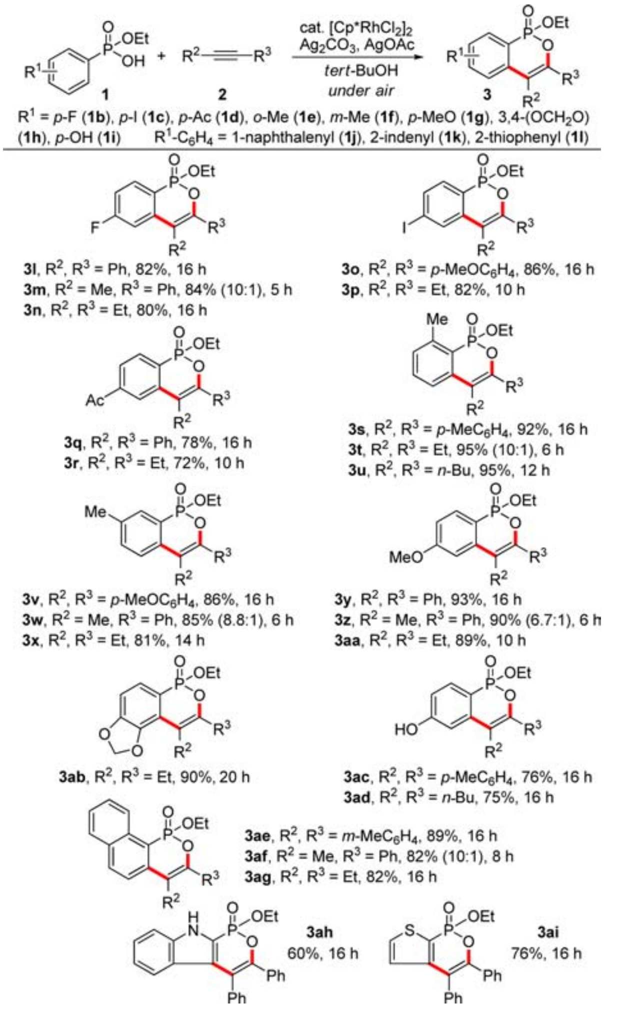
Next, the scope of the arylphosphonic acid monoesters **1** and alkynes **2** was investigated (Scheme 3). Electron-deficient phosphonic acid monoester **1b** having fluoro group on the phenyl ring underwent efficiently cyclization with a variety of alkynes, affording the desired phosphaisocoumarins **3l**, **3m** and **3n** in excellent yields. Functional groups commonly used in organic synthesis were tolerated. For example, substrates possessing iodo (**1c**) and ketone (**1d**) group were all smoothly cyclized to afford **3o-3r** in high yields. The tolerance of iodo group is especially important, as following catalytic cross-couplings are promising. In addition, electron-rich phosphonic acid monoester **1e**, **1f** and **1g** having *o*-methyl, *m*-methyl and *p*-methoxy on phenyl ring work equally well with

Scheme 2. Alkyne Scope[a]



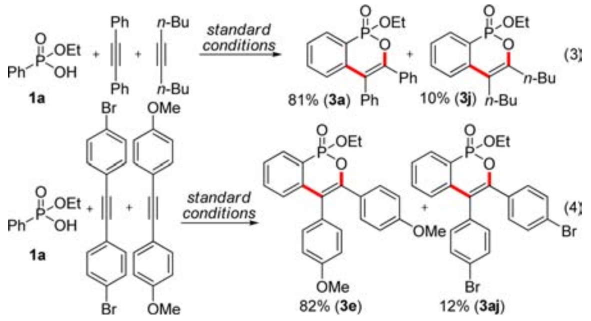
[a] Reaction conditions: **1** (0.15 mmol), **2** (0.23 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), Ag_2CO_3 (0.15 mmol), AgOAc (0.15 mmol), *t*-BuOH (1 mL) at 90 °C. [b] Numbers in parentheses indicate isomeric ratio.

Scheme 3. Arylphosphonic Acid Monoester and Alkyne Scope[a]



[a] Reaction conditions: **1** (0.15 mmol), **2** (0.23 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), Ag_2CO_3 (0.15 mmol), AgOAc (0.15 mmol), *t*-BuOH (1 mL) at 90 °C. [b] Numbers in parentheses indicate isomeric ratio.

Scheme 4. Competition Experiments between Alkynes

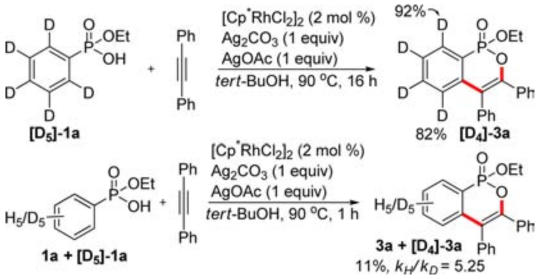


symmetrical and unsymmetrical diarylacetylenes as well as dialkylacetylenes. As anticipated, *m*-methyl substrates underwent Rh-catalyzed cyclization with alkynes regioselectively at the sterically less hindered position to afford phosphaisocoumarins **3v**, **3w**, and **3x** having methyl group on 7-position in high yields. In contrast, in the case of 3,4-(methylenedioxy)phenylphosphonic acid monoester **1h**, C−H bond activation occurred at C2 instead of C6 to give rise to **3ab** in 90% yield because coordination of both the 3-oxy and the phosphonic acid monoester group probably brings about functionalization at the C2 site. An unprotected hydroxyl group **1i** was compatible with the present conditions. Exposure of 1-naphthalenylphosphonic acid monoester **1j** with alkynes in the presence of $[Cp^*RhCl_2]_2$ catalyst led to the formation of phosphaisocoumarins **3ae**, **3af**, and **3ag** in high yields. Substrates containing heterocyclic moieties, such as indol and thiophene, underwent the cyclization, providing **3ah** and **3ai** in good yield.

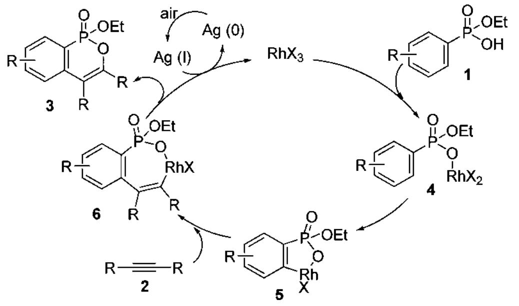
Competition experiments between alkynes were explored (Scheme 4). Phenylphosphonic acid monoester **1a** was treated with diphenylacetylene and 5-decyne (1.5 equiv each) to produce phosphaisocoumarin **3a** in major (Scheme 4, eq 3). A competition experiment between electron-rich (*p*-methoxy) and electron-deficient (*p*-bromo) diarylacetylenes affords mainly the phosphaisocoumarin **3e** obtained from the electron-rich alkyne (Scheme 4, eq 4).

To obtain insight into the reaction mechanism, we carried out kinetic isotope effect (KIE) studies (Scheme 5). A significant KIE was detected ($k_H/k_D = 5.3$),[12] indicating that the C−H bond cleavage at the C2 site of **1a** is most likely involved in the rate-limiting step.

Scheme 5. Studies with Isotopically Labeled Compounds



Scheme 6. Plausible Mechanism



A plausible mechanism for the reaction of phosphonic acid monoesters **1** with alkynes **2** is illustrated in Scheme 6. A proposed catalytic cycle was started by coordination of **1** to Cp^*RhX_2(III) to provide a rhodium(III) phosphonate **4**. Successive *o*-rhodation to afford a rhodacycle intermediate **5**, alkyne insertion and reductive elimination took place to give phosphaisocoumarins **3**.

In summary, we have developed an efficient rhodium-catalyzed cyclization using alkynes and arylphosphonic acid monoesters for the synthesis of phosphaisocoumarins. A range of substrates were selectively cyclized in high yield with functional group tolerance. Additionally, unsymmetrical alkynes are applied in high efficiency and regioselectivity. Further studies to examine differences or similarities between the reaction of aromatic acids and phosphonic acids and expand the synthetic scope of this reaction are currently underway.

Acknowledgment. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2011-0018355).

Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

[12] (a) Jones, W. D. *Acc. Chem. Res.* **2003**, *36*, 140. (b) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936.

The authors declare no competing financial interest.