RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

COMMUNICATION

Copper-Mediated Reaction of Oxazirconacyclopentenes with Dichlorophenylphosphine: A New Pathway for the Formation of 1,2-oxaphosphole Derivatives

Received 00th January 20xx,
Accepted 00th January 20xx

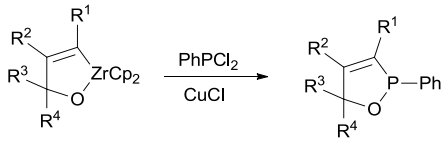
DOI: 10.1039/x0xx00000x

www.rsc.org/

Yiqing Zhou[a,b], Sheng Wang[a], Chao Chen[a] and Chanjuan Xi[a*]

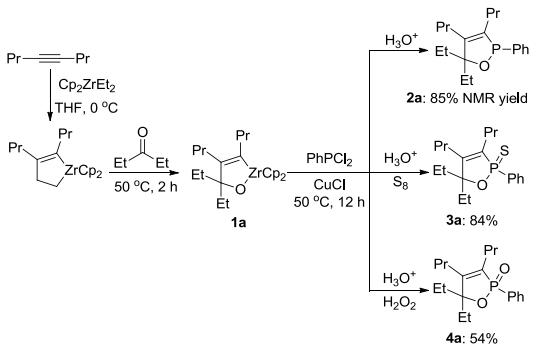
Copper-mediated reaction of oxazirconacyclopentenes with dichlorophenylphosphine afforded 2,5-dihydro-1,2-oxaphosphole in high yields, in which the reaction was performed conveniently in one-pot from an alkyne, carbonyl compound and dichlorophosphine.

Organophosphorus compounds are important intermediates in organic synthesis and have been widely used as pharmaceutical[1] and chemical agents.[2] Recently, phosphorus heterocycles[3] have received considerable interest because of their unique biological activities[4] and wide-ranging utilities as synthetic intermediates in organic synthesis.[5] Consequently, much attention has been directed to the synthesis of these compounds. Among them, particular interest was paid to the oxaphosphole derivatives. Although some progress has been achieved for synthesis of the oxaphospholes,[6] the most efficient one seems the direct transformation of oxametallacyclopentenes to oxaphospholes. In this regard especially attractive one is oxazirconacyclopentenes, which are easily prepared by the coupling reaction of alkynes and carbonyl compounds with zirconocene-ethylene species.[7] The oxazirconacyclopentenes are useful intermediates in a number of organic reactions,[7g,8] such as reaction of the oxazirconacyclopentenes with propynoates to afford 2,5-dihydrofurans,[8a] and reaction with but-2-ynedioates to afford α-methylene-δ-lactone.[8b] As part of our ongoing project on the chemistry of organozirconium and organophosphorus,[9] we herein describe a new pathway for the synthesis of 1,2-oxaphospholes based on the reaction of oxazirconacyclopentenes with dichlorophenylphosphine in the presence of CuCl (Eq. 1).



(Eq. 1)

Typical procedure is as follows. To a solution of oxazirconacylopentene **1a** in THF (3 mL), prepared from Cp_2ZrCl_2(292 mg, 0.6 mmol), EtMgCl (2.0 M THF solution, 0.6 mL, 1.2 mmol), 4-octyne (78 μL, 0.5 mmol), and 3-pentanone (60 μL, 0.5 mmol) according to the reported procedure,[7a] was added CuCl (100 mg, 1 mmol) and dichlorophenylphosphine (82 μL, 0.6 mmol). The reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was quenched with 3 M HCl and 1,2-oxaphosphole **2a** was obtained in 85% NMR yield. Direct purification of **2a** by column chromatography on Al_2O_3 led to the formation of complex inseparable mixture. Since **2a** was sensitive under air ambient for direct isolation, this reaction mixture with crude product was treated by addition of elemental sulfur to afford 1,2-oxaphosphole 2-sulfide **3a** in 84% isolated yield (Scheme 1). In addition, the reaction mixture was treated with hydrogen peroxide and 1,2-oxaphosphole oxide **4a** was isolated in 54% yield. It is notable that the reaction of oxazirconacylopentene with dichlorophosphine did not proceed in the absence of CuCl.



Scheme 1 Schematic showing the reaction of **1a** and $PhPCl_2$

[a] Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China.
[b] Beijing National Day School, Beijing 100039, China
Email: cjxi@tsinghua.edu.cn

Electronic Supplementary Information (ESI) available includes experimental procedures, NMR data and spectra of compounds for **3a-3h, 3j-3l**, **4a** and **5a-5c**. See DOI: 10.1039/x0xx00000x

Further study involving the using of various substituted oxazirconacylopentene bearing alkyl, aryl, and TMS groups resulted in all cases in the formation of 1,2-oxaphosphole 2-sulfide in good yields. Some representative examples of the results are summarized in Table 1. Reaction of oxazirconacyclopentenes tolerating four substituents (entries 1-8) with dichlorophenylphosphine gave the corresponding 1,2-oxaphosphole 2-sulfide derivatives in good to high yields. To our delight, the crystals of **3f** were suitable for the X-ray diffraction analysis, and its structure was confirmed as 1,2-oxaphosphole 2-sulfide (Fig. 1). When acetophenone was used, trace amount of expected product was observed in GC-MS (entry 9), the starting material remained. It is noteworthy that reaction of spirocyclic oxazirconacyclopentenes with dichlorophenylphosphine gave the corresponding spiro-oxaphospholene 2-sulfide derivatives in high yields (entries 10-12). The expected products, spirooxaphospholene, are popular targets for the development of new biologically active compounds.[10]

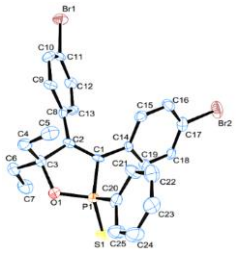
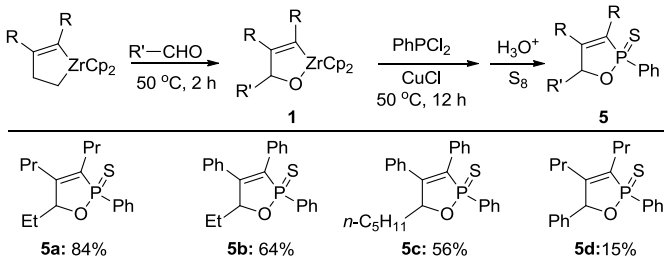


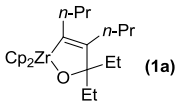
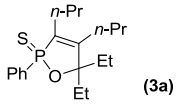
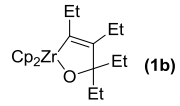
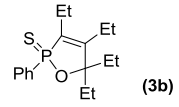
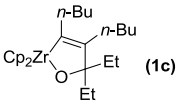
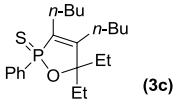
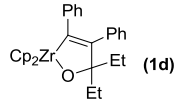
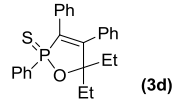
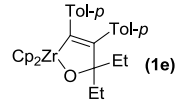
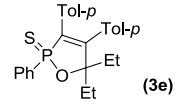
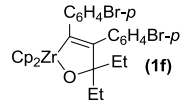
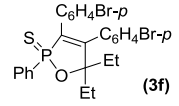
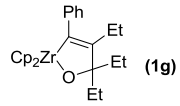
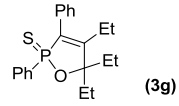
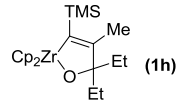
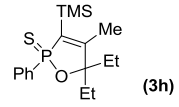
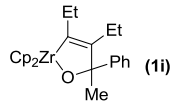
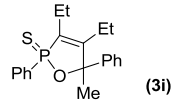
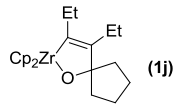
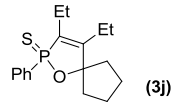
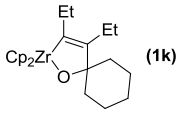
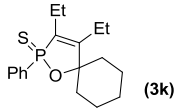
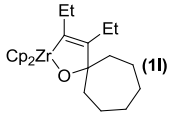
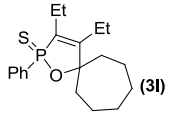
Figure 1 Perspective view of **3f** (CCDC 1412383)

Recently, Liu and co-workers developed an improved procedure for zirconium-mediated alkyne–aldehyde coupling reactions to afford three substituents oxazirconacyclopentenes.[7g] Reaction of the oxazirconacyclopentenes with dichlorophenylphosphine gave the corresponding 1,2-oxaphosphole 2-sulfide derivatives (Scheme 2). When alkyl aldehyde such as propionaldehyde and hexanal were employed and compound **5a**, **5b**, and **5c** were formed in 84%, 64%, and 56% yield, respectively. It is noteworthy that in the reaction to obtain **5b** and **5c**, two diastereomers of product **5b** and **5c** were observed in 6:1 and 2:1 ratio, respectively. When benzaldehyde was used and the product **5d** was formed in 15% yield, which could not be fully separated from unidentified by product. Together with result in entry 9 of Table 1, the aryl group on the carbon connected with oxygen in oxazirconacyclopentene gave the poor yield of desired products. That maybe attributed to bulky group.



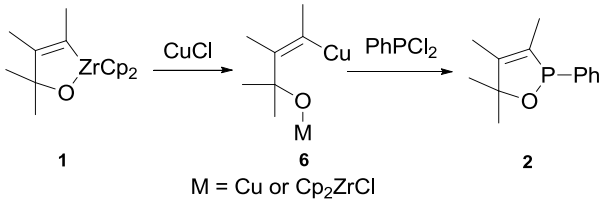
Scheme 2 Reaction of **1** derived from aldehyde to form oxaphosphole 2-sulfide

Table 1. Reaction of oxazirconacycles in the presence of CuCl

Entry	Oxazirconacycles	Product	Yield (%)[a]
1	 (1a)	 (3a)	84
2	 (1b)	 (3b)	75
3	 (1c)	 (3c)	79
4	 (1d)	 (3d)	64
5	 (1e)	 (3e)	58
6	 (1f)	 (3f)	55
7	 (1g)	 (3g)	63
8	 (1h)	 (3h)	72
9	 (1i)	 (3i)	trace
10	 (1j)	 (3j)	71
11	 (1k)	 (3k)	63
12	 (1l)	 (3l)	54

[a] Isolated yield.

Based on the results obtained here, the following reaction pathway can be proposed for the formation of 2,5-dihydro-1,2-oxaphospholes (Scheme 3). In the first step the Zr-C bond of oxazirconacyclopene **1** is transmetalated to the Cu-C bond to give **6**.[11,12] It is not clear whether only the Zr-C bond is transmetalated, or also the Zr-O bond. The intermediate **6** then reacts with dichlorophosphine to give 2,5-dihydro-1,2-oxaphosphole **2**.



Scheme 3 Possible reaction mechanism

We conclude that the reaction of oxazirconacyclopentenes with dichlorophenylphosphine in the presence of CuCl gives oxaphosphole derivatives. This reaction represents a convenient pathway to substituted 2,5-dihydro-1,2-oxaphosphole in one-pot from an alkyne, carboxyl compound and dichlorophosphine with zirconocene compound.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (21272132, 21472106 and 21032004) and national basic research program of China (2012CB933402).

Notes and references

1 (a) J. Collard and C. Benezra, *Tetrahedron Lett.,* **1982**, *23*, 3725; (b) I. Morita, K. Kunimoto, M. Tsuda, S. I. Tada, M. Kise and K. Kimura, *Chem. Pharm. Bull.,* **1987**, *35*, 4144; (c) Y. Segall, R. L. Grendell, R. F. Toia, J. Casida and *E. J. Agric. Food Chem.,* **1991**, *39*, 380; (d) J. D. Stewart, L. J. Liotta and S. J. Benkovic, *Acc. Chem. Res.,* **1993**, *26*, 396; (e) J. W. Darrow and D. G. Drueckhammer, *J. Org. Chem.,* **1994**, *59*, 2976; (f) M. M. Mader, P. A. Bartlett, *Chem. Rev.,* **1997**, *97*, 1281; (g) H. Seto, T. Kuzuyama, *Nat. Prod. Rep.,* **1999**, *16*, 589.

2 (a) A.K. Bhattacharya and G.Thyagarajan, *Chem. Rev.,* **1981**, 81, 415; (b) B. E. Marianoff and A. B. Reitz, *Chem. Rev.,* **1989**, 89, 863; (c) J. Motoyoshiya, *Trends Org. Chem.,* **1998**, 7, 63; (d) N. Kann and T. Rein, *Synthesis,* **2003**, 579.

3 (a) N.Bricklebank, *Organophosphorus Chem.*, **2003**, *33,* 289; (b) L. D. Quin, *The heterocyclic chemistry of phosphorus: systems based on the phosphorus-carbon bond*. Wiley, New York, **1981**; (c) J. W. Darrow and D.G. Drueckenhammer, *J. Org. Chem*., **1994**, *59*, 2976.

4 (a) I. Morita, K. Kunimoto, M. Tsuda, S.I. Tada, M. Kise and Kimura, K. *Chem. Pharm. Bull.*, **1987**, *35*, 4144; (b) Racha, S, Vargeese, C, Vemishetti, P, El-Subbagh, H, E. Abushanab, R. P. Paniza, *J. Med. Chem.*, **1996**, *39*, 1130.

5 (a) G. Keglevich, H. Forintos, G. M. Keserü, L. Hegedüs and L. Tőke, *Tetrahedron,* **2000**, *56*, 4823; (b) V. K. Reddy, J. I. Onogawa, L. N. Rao, T. Oshikawa, M. Takahashi and M. *J.* Yamashita, *Heterocyclic Chem*., **2002**, *39*, 69; (c) M. Yamashita, V. K. Reddy, L. N. Rao, B. Haritha, M. Maeda, K. Suzuki, H. Totsuka, M. Takahashi and Oshikawa, T. *Tetrahedron Lett.,* **2003**, *44*, 2339; (d) J. Kovács, N. B. Szabó, Z. Nagy, K. Ludányi and G. Keglevich, *Heteroatom Chem.,* **2005**, *16*, 320; (e) T. Novák, J. Deme, K. Ludányi,and G. Keglevich, *Heteroatom Chem.,* **2008**, *19*, 28; (f) M. Yamada, M. Yamashita, T. Suyama, J. Yamashita, K. Asai, T. Niimi, N. Ozaki, M. Fujie, K. Maddali, S. Nakamura and K. Ohnishi, *Bioorganic & Medicinal Chem. Lett.,* **2010**, *20*, 5943.

6 (a) M. D. McReinolds, J. M. Dougherty and P. R. Hanson, *Chem. Rev.*, **2004**, *104*, 2239; (b) A. Y. Peng and Y. X. Ding, *Org. Lett*., **2005**, *7*, 3299; (c) F. Yu, X. Lian and S. Ma, *Org. Lett.*, **2007**, *9,* 1703; (d) F. Yu, X. Lian, J. Zhao, Y. Yu and S. Ma, *J. Org. Chem.*, **2009**, *74*, 1130; (e) P. Fourgeaud, C. Midrier, J. P. Vors, J.-N. Volle, J.-L. Pirat and D. Virieux, *Tetrahedron,* **2010**, *66*, 758; (f) P. Li, Z.-J. Liu and J.-T. Liu, *Tetrahedron,* **2010**, *66*, 9729; (g) N. Xin and S. Ma, *Eur. J. Org. Chem.,* **2012**, 3806; (h) J. H. Hah, B. S. Lee, S. Y. Lee and H.-Y. Lee, *Tetrahedron Lett.*, **2003**, *44*, 5811; (i) M. Moura, S. Josse, and D. Postel, *J. Org. Chem.,* **2013**, *78*, 8994. (j) A. I. Arkhypchuk, A. Orthaber, V. A. Mihali, A. Ehlers, K. Lammertsma and A. Ott, *Chem. Eur. J.* **2013**, *19*, 13692; (k) A. I. Arkhypchuk, M.-P. Santoni and S. Ott, *Angew. Chem. Int. Ed.*, **2012**, *51*, 7776; (l) I. Yavari, A. Alizadeh and M. Anary-Abbasinejad, *Tetrahedron Lett.*, **2003**, *44*,2877.

7 (a) T. Takahashi, M. Kageyama, V. Denisov, R. Hara and E. Negishi, *Tetrahedron Lett.,* **1993**, *34*, 687; (b) C. Coperet, E. Negishi, Z. Xi and T. Takahashi, *Tetrahedron Lett.,* **1994**, *35*, 695; (c) T. Takahashi, C. Xi, Z. Xi, M. Kageyma, R. Fischer, K. Nakajima and E. Negishi, *J. Org. Chem.,* **1998**, *63*, 6802; (d) T. Takahashi, C. Xi, U. Ura and K. Nakajima, *J. Am. Chem. Soc.,* **2000**, *122*, 3228; (e) C. Zhao, T. Yu and Z. Xi, *Chem. Commun.,* **2002**, 142; (f) C. Zhao, J. Yan, Z. Xi, *J. Org. Chem.,* **2003**, *68*, 4355; (g) S. Guo, H. Zhang, F. Song and Y. Liu, *Tetrahedron,* **2007**, *63* 2009.

8 (a) C. Xi, M. Kotora and T. Takahashi, *Tetrahedron Lett.*, **1999**, *40*, 2375; (b) Y. Zhou, X. Yan, C. Chen and C. Xi, *Organometallics,* **2013**, *32*, 6182.

9 (a) C. Xi, M. Ma and X. Li, *Chem. Commun.,* **2001**, 2554 ; (b) C. lai, C. Xi, C. Chen, M. Ma and X. Hong, *Chem. Commun.*, **2003**, 2736; (c) C. Lai, C. Xi, W. Chen and R. Hua, *Tetrahedron,* **2006**, *62*, 6295; (d) C. Xi, X. Yan and C. Lai, *Organometallics,* **2007**, *26*, 1084; (e) C. Xi, X. Yan, C. Lai, K.-I. Kanno and T. Takahashi, *Organometallics,* **2008**, *27,* 3834; (f) X. Yan, C. Xi, *Organometallics*, **2008**, *27*, 152; (g) X. Yan, B. Yu, L. Wang, N. Tang and C. Xi, *Organometallics*, **2009**, *28*, 6827; (h) X. Yan, C. Lai and C. Xi, *Chem. Commun.,* **2009**, 6026; (i) Y. Zhou, X. Yan and C. Xi *Tetrahedron Lett.*, **2010**, *51*, 6136; (j) X. Yan and C. Xi, *Acc. Chem. Res*., **2015**, *48*, 935.

10 (a) M. J. Camarasa, A. San-Felix, M. J. Perez-Perez, S. Velazquez, R. Alvarez, C. Chamorro, M. L. Jimeno, C. Perez, F. Gago, E. De Clercq and J. J. Balzarini, *Carbohydr. Chem.* **2000**, *19*, 451; (b) M.-J. Camarasa, A. San-Felix, S. Velazquez, M.-J. Perez-Perez, F. Gago, J. Balzarini, *Curr. Top. Med. Chem.* **2004**, *4*, 945.

11 (a) T. Takahashi, M. Kotora, K. Kasai, N. Suzuki and K. Nakajima, *Organometallics,* **1994**, *13*, 4184; (b) T. Takahashi, R. Hara, Y. Nishihara and M. Kotora, *J. Am. Chem. Soc.,* **1996**, *118*, 5154; (c) T. Takahashi, Z. Xi, A. Yamazaki, Y. Liu, K. Nakajima and M. Kotora, *J. Am. Chem. Soc*., **1998**, *120*, 1672; (d) T. Takahashi, W.-H. Sun, Y. Liu, K. Nakajima and M. Kotora, *Organometallics,* **1998**, *17,* 3841; (e) M. Kotora, C. Xi and T. Takahashi, *Tetrahedron Lett.,* **1998**, *39*, 4321; (f) C. Xi, M. Kotora, K. Nakajima and T. Takahashi, *J. Org. Chem.,* **2000**, *65*, 945; (g) C. Chen, C. Xi, Y. Jiang and X. Hong, *J. Am. Chem. Soc.,* **2005**, *127*, 8024; (h) Y. Nishihara, M. Miyasaka, M. Okamoto, H. Takahashi, E. Inoue, K. Tanemura and K. Takagi, *J. Am. Chem. Soc.,* **2007**, *129*, 12634; (i) Y. Nishihara, Y. Okada, J. Jiao, M. Suetsugu, M. Lan, M. Kinoshita, M. Iwasaki and K. Takagi, *Angew. Chem. Int. Ed.,* **2011**, *50*, 8660.

12 (a) M. Ogasawara, S. Arae, S. Watanabe, V. Subbarayan, T. Sato and T. Takahashi, *Organometallics*, **2013**, *32*, 4997; (b) T. Miyaji, Z. Xi, M. Ogasawara, K. Nakajima and T. Takahashi, *J. Org. Chem.*, **2007**, *72*, 8737; (c) S. Doherty, E. G. Robins, M. Nieuwenhuyzen, J. G. Knight, P. A. Champkin and W. Clegg, *Organometallics*, **2002**, *21*, 1383; (d) T. Miyaji, Z. Xi, K. Nakajima and T. Takahashi, *Organometallics*, **2001**, *20*, 2859; (e) S. Doherty, J. G. Knight, E. G. Robins, T. H. Scanlan, P. A. Champkin and W. Clegg, *J. Am. Chem. Soc.,* **2001**, *123*, 5110.