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# Metal-free synthesis of chlorinated and brominated phosphinoyl 1,3-butadiene derivatives and its synthetic applications

Teng Liu, Yun-Tao Xia, Jie Zhu, Ai-Min Lu, Lei Wu *

*Jiangsu Key Laboratory of Pesticide Science and Department of Chemistry, College of Sciences, Nanjing Agricultural University, Nanjing 210095, China*

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ABSTRACT

We report here an efficient and transition-metal free strategy for the synthesis of chlorinated and brominated phosphinoyl 1,3-butadienes and derivatives. Pre-prepared HCl/HBr solutions enabled the in situ rearrangement of phosphinoyl-α-allenic alcohols to conjugated vinyl cations, which afforded various novel polysubstituted phosphinoyl 1,3-butadienes in medium to excellent yields. The resulting products could be converted into multi-functionalized allylphosphine oxides; moreover, their couplings with electron-deficient arylboronic acid provided an efficient approach to synthesize electron-deficient phosphinoyl 1,3-butadienes.

## Introduction

Organophosphorus compounds, particularly those possessing reactive functionalities, are versatile building blocks for varieties of transformations in catalysis, biochemistry, materials chemistry and organic synthesis.[1] Primarily, from the synthetic point of view, α,β-unsaturated phosphorous compounds is so appealing to synthetic researchers because they can be useful synthons for the preparation of biologically active compounds. As representative functionalized organophosphorus compounds, phosphinoyl 1,3-butadienes are widely used intermediates in organic reactions, including Michael addition with nucleophiles to afford allylic phosphonates,[2] Diels–Alder reaction with dienophiles to form cycloadducts,[3] cycloaddition with enamines to give cyclohexadienylphosphonates,[4] addition with aldehydes to yield vinyl allenes,[5] polymerization to phosphine-functionalized copolymers etc.[6] However, the methods to generate phosphinoyl 1,3-butadienes are still underdeveloped comparing with the blooming of 1,3-dienes.[7]

The conventional methods for synthesizing phosphinoyl 1,3-dienes involve the reaction of $P(OEt)_3$ with 1,4-dichloro-2-butene, or a nucleophilic substitution with preformed 1,3-butadienylphosphonic dichloride.[8] These methods incur obnoxious odor and also suffer from complicated and trivial substrate preparations. Moreover, preparation of multisubstituted phosphinoyl 1,3-dienes is especially challengeable. Alternatively, transition-metal catalysis for the synthesis of phosphinoyl 1,3-dienes and their derivatives were commonly developed during the past decade, among which addition of $R_2P(O)H$ to alkynes through oxidative addition of transition metals to P-H bonds has been recognized as the most promising and atom-economical process. In 2005, Han et al. reported the nickel-catalyzed generation of phosphinoyl 1,3-butadienes, consisting of the metal catalyzed addition of diphenylphosphine oxide and related P(O)H compounds to propargyl alcohols followed by an acid-catalyzed dehydration.[9] Takaiki and co-workers prepared dipenylphosphinyl-dienes via a one-pot process containing dimerization, hydrophosphination and oxidative work-up. Enynes were first generated through Ytterbium-catalyzed dimerization of terminal alkynes, after which hydrophosphination with $Ph_2PH$ was carried out to give phosphinoyl-1,3-dienes as target compound after oxidative work-up.[10] Very recently, our group revealed the first palladium-catalyzed Suzuki–Miyaura couplings of aryl ether functionalized allenylphosphine oxides with arylboronic acids to generate phosphinoyl 1,3-butadienes and derivatives.[11] More interestingly, changing the substrates into allenic alcohols enabled the atom-economical preparation smoothly 'on water' without any additives.[12] However, those catalytic methods are associated with one or more limitations such as expensive,

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* Corresponding author. Tel./fax: +86 25 84396716.
*E-mail address:* rickywu@njau.edu.cn (L. Wu).

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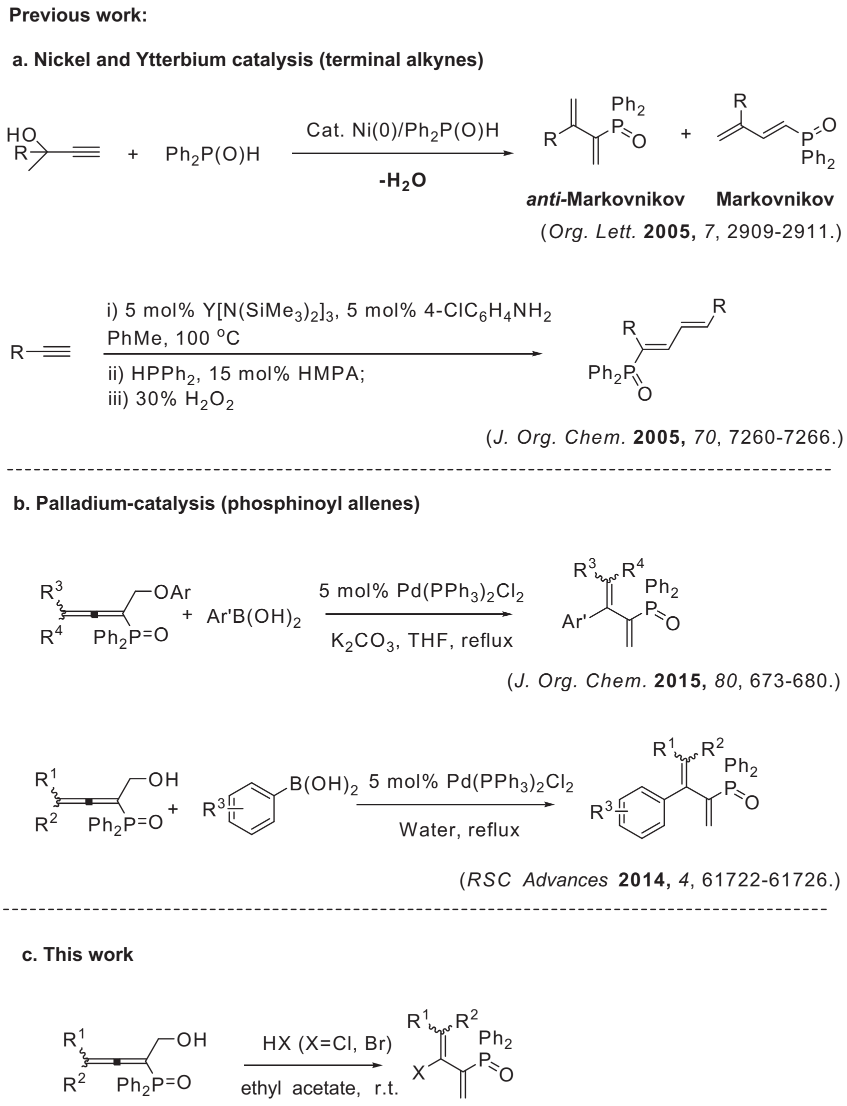
toxic or metallic catalysts, air-sensitive reagents, low regioselectivity, long reaction time, elevated temperatures, and so on. Thus, the potential development of such chemical synthesis in a metal-free manner with higher selectivity/efficiency and easier operations is in a great demand. In continuation of our work on the synthesis and application of organophosphorus chemistry,[13] we report herein an efficient and transition-metal free strategy for the synthesis of chlorinated and brominated phosphinoyl 1,3-butadienes and its applications (Scheme 1).[14]

## Results and discussion

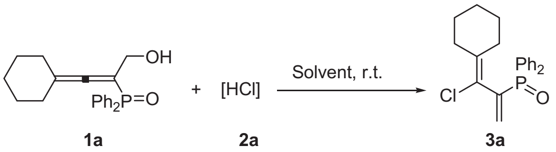
The phosphinoyl-α-allenic alcohols (**1a**–**1h**) were readily synthesized according to our reported procedures.[12] When 3-cyclohexylidene-2-(diphenylphosphine oxide) prop-2-en-1-ol (**1a**) was treated with in situ generated hydrogen chloride in acetyl chloride/dichloromethane (technical grade) solution for 5 h, (1-chloro-1-cyclo-hexylideneprop-2-en-2-yl)diphenylphosphine oxide (**3a**) was isolated in 37% yield (entry 1). No product was observed in acetyl chloride/methanol solution, although AcCl/MeOH has been widely accepted as ideal combinations to generate HCl, and in situ generation of HCl from NaCl/conc.$H_2SO_4$ gave negative results as well. Encouraged by these initial results, we were curious to investigate the solvent effects on this reaction. To improve the yield, varieties of pre-prepared hydrogen chloride solutions were applied, and the results are listed in Table 1. Hydrogen chloride in common aprotic solvents including dichloromethane, ethyl acetate, THF, ether and acetone facilitated the reactions with medium to good yields (entries 4–8), among which ethyl ether as solvent gave the best result of 80% isolated yield within 20 h. Interestingly, hydrogen chloride from 37% concentrated HCl solution worked as well (entry 12), albeit with a little lower yield, which provided a convenient procedure for scale-up preparations. In all the cases of protic solvents (entries 9–11), the substrates remained intact, even with higher concentration of hydrogen chloride or extended reaction time.

With optimized reaction conditions in hand (Table 1, entry 7), several substituted phosphinoyl-α-allenic alcohols were applied to investigate the substrate scopes, and the results are summarized in Table 2. To be noted, when we utilized various substituted phosphinoyl-α-allenic alcohols, most of the substrates except **1a** exhibited poor solubility in HCl/ethyl ether solution. The reactions



**Scheme 1.** (a) Synthesis of phosphinoyl 1,3-butadienes from terminal alkynes catalyzed by Nickel or Ytterbium; (b) synthesis of phosphinoyl 1,3-butadienes from phosphinoyl allenes catalyzed by palladium; (c) this work.

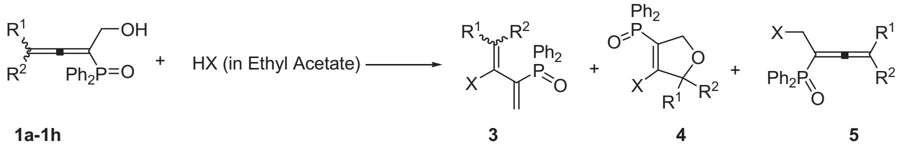
**Table 1**
Reaction condition optimizations: hydrogen chloride sources[a]



| Entry | HCl Source | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | AcCl | $CH_2Cl_2$ | 5 | 37 |
| 2 | AcCl | MeOH | 20 | 0 |
| 3 | NaCl/conc.$H_2SO_4$ | $CH_2Cl_2$ | 20 | 0 |
| 4 | HCl[c] | $CH_2Cl_2$ | 20 | 49 |
| 5 | HCl[c] | Ethyl acetate | 20 | 75 |
| 6 | HCl[c] | THF | 20 | 73 |
| 7 | HCl[c] | Ethyl ether | 20 | 80 |
| 8 | HCl[c] | Acetone | 20 | 50 |
| 9 | HCl[c] | MeOH | 20 | 0 |
| 10 | HCl[c] | EtOH | 20 | 0 |
| 11 | HCl[c] | *i*-PrOH | 20 | 0 |
| 12 | HCl[d] | Ethyl acetate | 20 | 71 |

[a] 1.5 mmol phosphinoyl-α-allenic alcohol, 3 mmol hydrogen chloride source, 20 h.
[b] Isolated yield based on allenes.
[c] Pre-prepared solution.
[d] 37% HCl solution.

**Table 2**
Substrate scopes of substituted phosphinoyl-α-allenic alcohols[a]

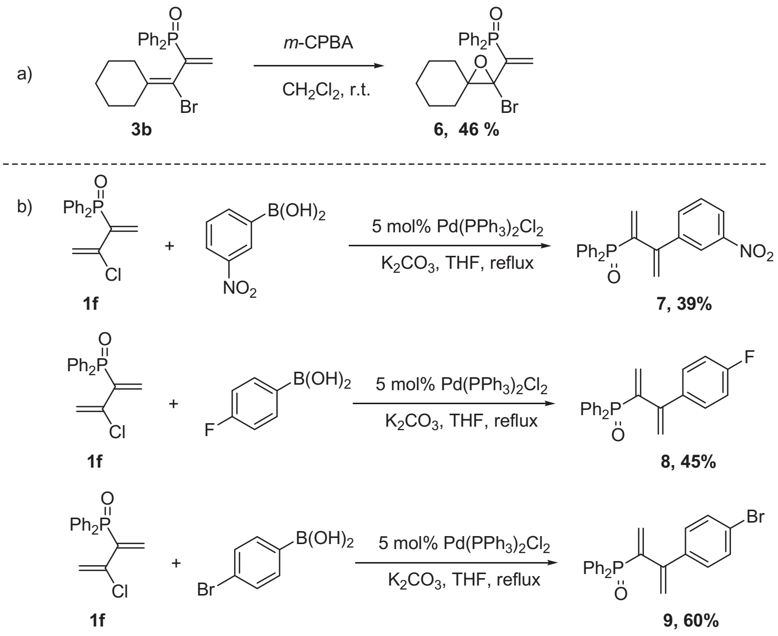


| Entry | $R^1$ | $R^2$ | HX | Yield of **3**, **4**, **5**[b] |
|---|---|---|---|---|
| 1 | $-C_5H_{10}-$ (**1a**) | | HCl | 75(**3a**,80[c]):0:0 |
| 2 | $-C_5H_{10}-$ (**1a**) | | HBr | 92(**3b**):0:0 |
| 3 | $CH_3$ | $CH_3$ (**1b**) | HCl | 23(**3c**):0:0 |
| 4 | $CH_3$ | $CH_3$ (**1b**) | HBr | 39(**3d**):0:0 |
| 5 | *p*-$CF_3C_6H_4$ | $CH_3$ (**1c**) | HCl | 84(**3e**):0:0 |
| 6 | *p*-$CF_3C_6H_4$ | $CH_3$ (**1c**) | HBr | 34(**3f**):0:0 |
| 7 | $CH_3CH_2$ | H (**1d**) | HCl | 83(**3g**):0:0 |
| 8 | $CH_3CH_2$ | H (**1d**) | HBr | 55(**3h**):0:0 |
| 9 | $CH_3CH_2$ | *p*-$ClC_6H_4$ (**1e**) | HCl | 70(**3i**):0:0 |
| 10 | $CH_3CH_2$ | *p*-$ClC_6H_4$ (**1e**) | HBr | 48(**3j**):0:0 |
| 11 | H | H (**1f**) | HCl | 55(**3k**):0:0 |
| 12 | *p*-$MeOC_6H_4$ | H (**1g**) | HCl | 0:75(**4a**):0 |
| 13 | *p*-$MeOC_6H_4$ | H (**1g**) | HBr | 0:42(**4b**):0 |
| 14 | Ph | Ph (**1h**) | HCl | 0:0:58(**5a**) |
| 15 | Ph | Ph (**1h**) | HBr | 0:0:51(**5b**) |

[a] 1.5 mmol phosphinoyl-α-allenic alcohol, 3 mmol pre-prepared HCl or HBr solution, 20 h.
[b] Isolated yield based on allenes.
[c] Isolated yield in ether based on allenes.

ceased under such heterogeneous manner, thus, ethyl acetate was used as solvent for substrates **1b**–**1h** instead of ethyl ether. The addition of $Cl^-$ or $Br^-$ smoothly proceeded with good to excellent yields to produce a variety of chlorinated and brominated phosphinoyl 1,3-butadienes.[15] Both alkyl substitutions and electron-deficient groups in the allenic alcohols have efficiently worked in this synthesis. In particular, even sterically hindered substrates afforded good to excellent yields (entries 5, 6, 9 and 10). To the best of our knowledge, this is the first synthesis of multi-substituted chlorinated and brominated phosphinoyl 1,3-butadienes. Notably, for substrates with strong electron-donation or high conjugation groups (entries 12–15), the products changed via different intermediates to give compounds **4** or **5**, respectively.[16]

To confirm the significance of this methodology, the application of resulting product phosphinoyl 1,3-butadiene derivatives was further studied. Take (1-bromo-1-cyclohexylideneprop-2-en-2-yl)



**Scheme 2.** Transformation of products.

diphenylphosphine oxide (**3b**) as an example, multi-functionalized allylphosphine oxides (**6**) could be easily obtained in 46% yield (Scheme 2a) through the oxidation of **3b**. With *m*-CPBA as oxidant, the epoxidation process proceeded exclusively on internal double bond and the region-selectivity remained even with excess oxidation reagent or higher reaction temperature. In addition, the couplings of chlorinated phosphinoyl 1,3-butadienes with nucleophiles were also investigated. In the presence of 5 mol % $Pd(PPh_3)_2Cl_2$, arylboronic acids bearing electron-deficient groups attacked **1f** to give corresponding *arylated* phosphinoyl 1,3-butadienes (**7**, **8**, **9**) with 39%, 45%, and 60% yields, respectively (Scheme 2b). It is worthy to mention that our previous couplings of arylboronic acids bearing electron-deficient groups with phosphinoyl-$\alpha$-allenic alcohols didn't work well,[12] where the yields as low as 25%. Interestingly, in this method, chlorinated phosphinoyl 1,3-butadienes reacted smoothly with higher yields to afford *arylated* phosphinoyl 1,3-butadienes, which provide a more efficient approach to synthesis of electron-deficient phosphinoyl 1,3-butadienes.

## Conclusion

We have revealed an efficient and transition-metal free strategy for the synthesis of chlorinated and brominated phosphinoyl 1,3-butadienes and their derivatives. The pre-prepared HCl/HBr solutions in ether or ethyl acetate enabled the in situ formation of vinyl cation, which afforded various novel polysubstituted phosphinoyl 1,3-butadienes in medium to excellent yields. The resulting products could be easily transformed into multi-functionalized allylphosphine oxides; moreover, their smooth couplings with electron-deficient arylboronic acids provided an alternative approach to synthesize electron-deficient phosphinoyl 1,3-butadienes. Designing and exploring the new applications of chlorinated and brominated phosphinoyl 1,3-butadienes are underway in our laboratory.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.029.

## References and notes

1. (a) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: New York, 2000; (b) Crepy, K. V. L.; Imamoto, T. *Top. Curr. Chem.* **2003**, *229*, 1–40; (c) Demmer, C. S.; Krogsgaard-Larsen, N.; Bunch, L. *Chem. Rev.* **2011**, *111*, 7981–8006.
2. Darling, S. D.; Muralidharan, F. N.; Muralidharan, V. B. *Tetrahedron Lett.* **1979**, 2761–2762.
3. (a) Griffin, C. E.; Daniewski, W. M. *J. Org. Chem.* **1970**, *35*, 1691–1693; (b) Palacios, F.; Aparicio, D.; Löpez, Y.; de los Santos, J. M.; Alonso, C. *Eur. J. Org. Chem.* **2005**, *0*, 1142–1147; (c) Villemin, E.; Robeyns, K.; Robiette, R.; Herent, M.-F.; Marchand-Brynaert, J. *Tetrahedron* **2013**, *69*, 1138–1147.
4. Darling, S. D.; Subramanian, N. *J. Org. Chem.* **1975**, *40*, 2851–2852.
5. Xi, Z.-F.; Zhang, W.-X.; Song, Z.-Y.; Zheng, W.-X.; Kong, F.-Z.; Takahashi, T. *J. Org. Chem.* **2005**, *70*, 8785–8789.
6. Ajellal, N.; Thomas, C. M.; Carpentier, J.-F. *Polymer* **2008**, *49*, 4344–4349.
7. (a) Paolis, M. D.; Chataigner, I.; Maddaluno, J. *Top. Curr. Chem.* **2012**, *327*, 87–146; (b) Zhang, Y.; Wang, J.-B. *Top. Curr. Chem.* **2012**, *327*, 239–269.
8. For the preparation of phosphinoyl 1,3-dienes: (a) Ojea, V.; Fernández, M. C.; Ruiz, M.; Quintela, J. M. *Tetrahedron Lett.* **1996**, *37*, 5801–5804; (b) Akermark, B.; Nyström, J.-E.; Rein, T.; Bäckvall, J.-E.; Helquist, P.; Aslanian, R. *Tetrahedron Lett.* **1984**, *50*, 5719–5722; (c) Darcel, C.; Bruneau, C.; Dixneaf, P. H. *Synthesis* **1996**, 711.
9. Han, L.-B.; Ono, Y.; Yazawa, H. *Org. Lett.* **2005**, *7*, 2909–2911.
10. (a) Komeyama, K.; Kawabata, T.; Takehira, K.; Takaki, K. *J. Org. Chem.* **2005**, *70*, 7260–7266; (b) Komeyama, K.; Kobayashi, D.; Yamamoto, Y.; Takehira, K.; Takaki, K. *Tetrahedron* **2006**, *62*, 2511–2519.
11. Chen, Y.-Z.; Zhang, L.; Lu, A.-M.; Yang, F.; Wu, L. *J. Org. Chem.* **2015**, *80*, 673–680.

12. Liu, T.; Dong, J.; Cao, S.-J.; Guo, L.-C.; Wu, L. *RSC Adv.* **2014**, *4*, 61722–61726.
13. (a) Wu, L.; Ling, J.; Wu, Z.-Q. *Adv. Synth. Catal.* **2011**, *353*, 1452–1456; (b) Wu, L.; Zhang, X.; Tao, Z.-M. *Catal. Sci. Technol.* **2012**, *2*, 707–710; (c) Wu, L.; Zhang, X.; Chen, Q.-Q.; Zhou, A.-K. *Org. Biomol. Chem.* **2012**, *10*, 7859–7862.
14. Copper(I) chloride-mediated synthesis of chlorinated phosphinoyl 1,3-butadiene, see: (a) Brel, V. K.; Ionin, B. I.; Petrov, A. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1982**, *52*, 816–825. 709-716; Synthesis of 1-aryl-3-halo-1,3-dienes from reactions of 1-aryl-2,3-allenols with LiX, see: (b) Ma, S.-M.; Wang, G.-W. *Tetrahedron Lett.* **2002**, *43*, 5723–5726.
15. Fluorination of substrates with pyridine-HF or KF was found to be sluggish.
16. From the point of reaction mechanism, substrates **1d** and **1g** might undergo the following pathways to afford different products (compounds **4** or **5**):