Accepted Manuscript

Title: Silver-mediated aminophosphinoylation of propargyl alcohols with aromatic amines and H-phosphine oxides leading to α-aminophosphine oxides

Authors: Qiang Huang, Lei Zhu, Dong Yi, Xiaohui Zhao, Wei Wei

PII: S1001-8417(19)30453-X
DOI: https://doi.org/10.1016/j.cclet.2019.07.049
Reference: CCLET 5132

To appear in: *Chinese Chemical Letters*

Accepted date: 24 July 2019

Please cite this article as: Huang Q, Zhu L, Yi D, Zhao X, Wei W, Silver-mediated aminophosphinoylation of propargyl alcohols with aromatic amines and H-phosphine oxides leading to α-aminophosphine oxides, *Chinese Chemical Letters* (2019), https://doi.org/10.1016/j.cclet.2019.07.049

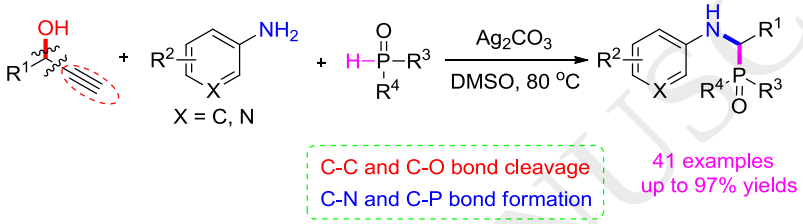
Communication

Silver-mediated aminophosphinoylation of propargyl alcohols with aromatic amines and H-phosphine oxides leading to α-aminophosphine oxides

Qiang Huang[a], Lei Zhu[a], Dong Yi[b,*], Xiaohui Zhao[c,*], Wei Wei[c,d,*]

[a] *Department of Clinical Pharmacy, School of Pharmacy, Zunyi Medical University, Zunyi 563099, China*
[b] *School of Pharmacy, Southwest Medical University, Luzhou 646000, China*
[c] *Qinghai Provincial Key Laboratory of Tibetan Medicine Research and Key Laboratory of Tibetan Medicine Research, Northwest Institute of Plateau Biology, Chinese Academy of Sciences, Qinghai 810008, China*
[d] School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, China
∗ Corresponding authors.
E-mail addresses: *yidong0751@163.com (D. Yi); xhzhao@nwipb.cas.cn (X. Zhao); weiweiqfnu@163.com (W. Wei)*

Graphical abstract



A new and convenient silver mediated aminophosphinoylation of propargyl alcohols with aromatic amines and H-phosphine oxides for the construction of α-aminophosphine oxides has been developed.

ABSTRACT

A new silver mediated aminophosphinoylation of propargyl alcohols with aromatic amines and H-phosphine oxides for the construction of α-aminophosphine oxides has been developed. The C-N and C-P bond could be efficiently formed in one pot operation *via* sequential C–C and C-O bond cleavage of propargylic alcohols. This present methodology, which not only provides a simple and alternative strategy for the synthesis of α-aminophosphine oxides, but also opens a new window for the cleavage reactions of propargyl alcohols *via* dealkynalation coupling.

Keywords: *Silver; Aminophosphinoylation; C−C bond cleavage; Propargylic alcohols; α-Aminophosphine oxides*

Transition-metal-mediated selective cleavage of C−C bond has been regarded as an intriguing and powerful protocol for the construction of various complex organic molecules [1]. In the past decades, many strategies involving C-C bond cleavage have been significantly developed, such as ring-opening of strained molecules with three-or four-membered rings [2], decarbonylation of ynones [3], C-C bond cleavage of ketones [4]. Despite the great progress that has been made in this field, the development of new C-C bond cleavage method to access important valuable organic compounds is still highly desirable.

Propargyl alcohols as readily available building blocks have been widely used in organic synthesis [5]. Generally, the reactions using propargyl alcohols mainly focus on the propargylic substitutions [6] and rearrangements [7]. So far, only a few examples of C–C bond cleavage reactions of propargyl alcohols have been reported owing to the relative inertness and thermodynamic stability of C-C bond [8]. In this context, propargyl alcohols were usually utilized as alkynylation reagents to construct the alkynylation products *via* deacetonative coupling reactions catalyzed by Pd and Rh salts in high temperature [9]. For example, Wu and co-workers reported palladium-catalyzed oxidative deacetonative coupling of *tert*-propargyl alcohols with H-phosphonates leading to alkynylphosphonates through C-C cleavage process (Scheme 1a) [9c]. Multicomponent reactions as one of the most versatile and powerful synthetic protocols have attracted an increasing attention to assemble complex compounds from simple and readily available starting materials [10]. As our ongoing interest in the synthesis of organic phosphorus compounds [11] and multicomponent reactions [12], herein, we wish to report a new and efficient silver mediated aminophosphinoylation of propargyl alcohols with amines and H-phosphine oxides leading to α-aminophosphine oxides, which are an important class of organic phosphorus compounds that exhibit a wide range of biological and pharmacological activities [13]. The present methodology provides a convenient and alternative approach to access various α-aminophosphine oxides with moderate to good yields, in which the new dealkynylation coupling was achieved *via* C−C bond cleavage of propargyl alcohols (Scheme 1b).

Initially, 1-phenylprop-2-yn-1-ol (**1a**), aniline (**2a**) and diphenylphosphine oxide (**3a**) were chosen as model substrates to optmize the reaction parameters. When the model reaction was performed in DMSO at 70 °C under air in the presence of Ag_2O (2 equiv.), the product

4a was isolated in 19% yield (Table 1, entry 1). Next, various oxidants were investigated to improve the reaction efficiency (Table 1, entries 2–10). To our delight, the yield of product **4a** was increased to 68% when Ag_2CO_3 was employed as oxidant (Table 1, entry 3). When other oxidants such as $CuCl_2$, $FeCl_3$, $K_2S_2O_8$, TBHP, DTBP, and O_2 were examined, none of desired product **4a** was detected (Table 1, entries 5–10). The screening of solvents indicated that DMSO was still optimal than others such as DMF, CH_3CN, Toluene, THF, 1,4-dioxane and DCE (Table 1, entries 3, 11–16). Further investigation of the reaction temperature showed the highest yield of **4a** (78%) was obtained when the reaction was conducted at 80 °C (Table 1, entry 18). The decrease or increase of reaction temperature would lead to the lower reaction efficiency (Table 1, entries 17, 19 and 20).

With the optimal condtions in hand, the scope of propargyl alcohols was firstly examined and the results were shown in Scheme 2. In general, various aryl propargyl alcohols containing *para*-substituted electron-donating or electron-withdrawing groups were compatible for this transformation, giving corresponding products **4a-4i** in moderate to excellent yields. Aryl propargyl alcohols bearing electron-donating groups were converted to the corresponding compounds **4b-4d** in higher yields relative to the electron-withdrawing substituted analogs (**4e-4i**). *meta*- or *ortho*-substituted aryl propargyl alcohols were also well tolerated in the reaction, affording the desired products **4j-4n** in 76%-97% yields. Additionally, multi-substituted aryl propargyl alcohols reacted smoothly with aniline and diphenylphosphine oxide, giving the corresponding products **4o** and **4p** in 75% and 67% yields, respectively. 1-(Naphthalen-2-yl)prop-2-yn-1-ol could also afford **4q** in 65% yield. It should be noted that aliphatic propargylic alcohols were also suitable substrates leading to the products **4r** and **4s** in good yields. Nevertheless, when 2-phenylbut-3-yn-2-ol was used in the present reaction system, none of the desired prodcut **4t** was observed.

Next, the scope of various amines and H-phosphine oxides was explored. As shown in Scheme 3, both electron-donating and electron-withdrawing aryl amines were suitable for this reaction to give the corresponding products in moderate to good yields (**5a-5i)**. The steric hindrance of substituents on the aryl amines had a slightly effect on the yields of desired products **5j** and **5k**. Gratifyingly, the di-substituted aryl amines like 3,5-dimethylaniline, 3,5-dimethoxyaniline and 4-fluoro-2-methylaniline could afford the corresponding products **5l-5n** in good yields. Heterocyclic amines were suitable for this reaction, but leading to the corresponding products **5o** and **5p** in relatively lower yields. Finally, the compatibility of various H-phosphine oxides was tested. In addition to diphenylphosphine oxide **3a**, a series of aryl or alkyl substituted H-phosphine oxides were all compatible for the reaction to produce the corresponding **5q-5u** in moderate to good yields. H-Phosphonate such as diethyl phosphite could also be used in this reaction, affording the desired product **5v** in relatively lower yield.

In order to gain insights into the reaction mechanism, several control experiments were carried out (Scheme 4). When radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added in the model reaction system, the desired product **4a** was still obtained in 72% yield, indicating that a radical process might not be involved in this transformation (Scheme 4a). Furthermore, benzaldehyde **6a** was isolated in 17% yield when 1-phenylprop-2-yn-1-ol **1a** was separately treated with Ag_2CO_3 under standard conditon for 3 h (Scheme 4b). This result showed that aldehyde would be formed in the C-C bond cleavage of propargyl alcohol. Moreover, the reaction of imine **7a** with diphenylphosphine oxide **3a** afforded the corresponding product **4a** in 96% yield, suggesting that imine intermediate might be involved in the present reaction system (Scheme 4c). When the reaction of 1-phenylprop-2-yn-1-one, aniline (**2a**) and diphenylphosphine oxide (**3a**) was carried out under standard conditions, the side-product (*Z*)-1-phenyl-3-(phenylamino)prop-2-en-1-one **8a** was isolated in 46% yield and product **4a** was not observed (Scheme 4d). Furthermore, the reaction did not occur when 1,3-diphenylprop-2-yn-1-ol or 1-phenylbut-2-yn-1-ol was used in the present reaction system (Scheme 4e). The above results indicated that terminal alkyne and hydroxy group of propargyl alcohols should play a key role in silver mediated C−C bond cleavage of propargylic alcohols.

Based on the experimental results and previous reports [14], a possible reaction pathway was proposed for the synthesis of α-aminophosphine oxides as shown in Scheme 5. Firstly, the reaction of 1-phenylprop-2-yn-1-ol **1a** with Ag_2CO_3 might lead to the formation of alkynyl silver, which further underwent C-C bond cleavage to generate benzaldehyde **6a** under heating conditions. Next, the condensation reaction of benzaldehyde **6a** with aniline **2a** generated imine intermediate **7a**. Finally, the addition of diphenylphosphine oxide **3a** to imine **7a** afforded the desired product **4a**.

In summary, we have developed a new and efficient silver-mediated three-component reaction of propargyl alcohols, aromatic amines, and H-phosphine oxides leading to α-aminophosphine oxides. The present aminophosphinoylation reaction could be achieved in one pot operation via sequential C–C and C-O bond cleavage of propargyl alcohols. This strategy provides an attractive and alternative approach to construct α-aminophosphine oxides from simple and readily available materials with wide substrate scope and good functional group tolerance. Further synthetic application and mechanistic investigation is ongoing in our group.

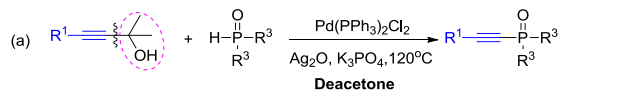
Acknowledgements

This work was supported by the Scientific Research Foundation of Zunyi Medical University, the Joint Funds of the Southwest Medical University & Luzhou Municipal Government of China (No. 2018LZXNYD-ZK39), and the Natural Science Foundation of Shandong Province (No. ZR2018MB009).

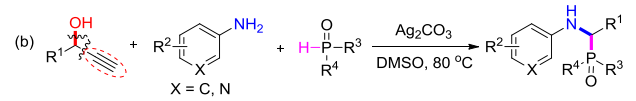
References

[1] (a) T. Wang, N. Jiao, Acc. Chem. Res. 47 (2014) 1137-1145.
(b) X. Yang, G. Cheng, J. Shen, et al., Org. Chem. Front. 2 (2015) 366-368.
(c) L.Y. Xie, S. Peng, L.L. Jiang, et al., Org. Chem. Front. 2 (2019) 167-171
(d) X.H. Ouyang, R.J. Song, J.H. Li, Chem. -Asian J. 13 (2018) 2316-2332.
(e) T. Yuan, C. Pi, C. You, et al., Chem. Commun. 55 (2019) 163-166.
(f) J.S. Li, Q. Yang, G.Q. Chen, et al., ChemistrySelect. 3 (2018) 10621-10623.
(g) Y. Yu, Y. Feng, R. Chauvin, et al., Org. Lett. 20 (2018) 4209-4212.
[2] (a) R. Ren, H. Zhao, L. Huan, et al., Angew. Chem. Int. Ed. 54 (2015) 12692-12696.
(b) H. Zhao, X. Fan, J. Yu, et al., J. Am. Chem. Soc. 137 (2015) 3490-3493.
(c) J-Y. Wang, P. Zhou, G. Li, et al., Org. Lett. 19 (2017) 6682-6685.
(d) X. Wu, C. Zhu, Chem. Rec.18 (2018) 587-598.
[3] (a) R.E. Whittaker, G. Dong, Org. Lett. 17 (2015) 5504-5507.
(b) K. Chen, S. Liu, D. Wang, et al., J. Org. Chem. 82 (2017) 11524-11530.
(c) J. Shen, X. Wang, X. Lin, et al., Org. Lett. 18 (2016) 1378-1381.
(d) C. Wu, H.J. Xiao, S.W. Wang, et al., ACS Sustainable Chem. Eng. 7 (2019) 2169-2175.
(e) C. Wu, L. Hong, H. Shu, et al., ACS Sustainable Chem. Eng. 7 (2019) 8798-8803.
(f) W.H. Bao, M. He, J.T. Wang, et al., J. Org. Chem. 84 (2019) 6065-6071.
(g) K.J. Liu, S. Jiang, L.H. Lu, et al., Green Chem. 20 (2018) 3038-3043.
[4] (a) W.H. Bao, Z. Wang, X. Tang, et al., Chin. Chem. Lett. (2019) 10.1016/j.cclet.2019.06.052.
(b) J.S. Li, D.M. Fu, Y. Xue, et al., Tetrahedron 71 (2015) 2748-2752.
(c) J.S. Li, F.F. Cai, Z.W. Li, et al., RSC Adv. 4 (2014) 54039-54042.
(d) X.M. Xu, D.M. Chen, Z.L. Wang, Chin. Chem. Lett. (2019) 10.1016/j.cclet.2019.05.048.
(e) J.S. Li, Q. Yang, F. Yang, et al., Org. Biomol. Chem. 16 (2016) 140-145.
(f) J.S. Li, Y.D. Da, G.Q. Chen, et al., ChemistrySelect 2 (2017) 1770-1773.
[5] (a) S. Muthusamy, A. Balasubramani, E. Suresh, Org. Biomol. Chem. 16 (2018) 756-764.
(b) Y. Li, X. Luo, Y. Shao, L. Chen, J. Org. Chem. 83 (2018) 8768-8774.
[6] (a) Y. Nishibayashi, Synthesis (2012) 489-503.
(b) J. Moran, M. Dryzhakov, E. Richmond, Synthesis 48 (2016) 935-959.
(c) R. Roy, S. Saha, RSC Adv. 8 (2018) 31129-31193.
[7] (a) Y. Zhu, L. Sun, P. Lu, Y. Wang, ACS Catal. 4 (2014) 1911-1925.
(b) D. Roy, P. Tharra, B. Baire, Asian J. Org. Chem. 7 (2018) 1015-1032.
(c) Y. Zhang, K. Sun, Q. Lv, et al., Chin. Chem. Lett. 30 (2019) 1361-1368.
[8] (a) Y.W. Kang, Y.J. Cho, K.Y. Ko, et al., Catal. Sci. Technol. 5 (2015) 3931-3934.
(b) T. Li, Z. Wang, M. Zhang, et al., Chem. Commun. 51 (2015) 6777-6780.
(c) Z. Liu, Y. Xia, S. Feng, et al., Org. Chem. Front. 3 (2016) 1691-1698.
[9] (a) H. Hu, F. Yang, Y. Wu, J. Org. Chem. 78 (2013) 10506-10511.
(b) X. Li, S. Sun, F. Yang, et al., Org. Biomol. Chem. 13 (2015) 2432-2436.
(c) F. Sun, M. Li, Z. Gu, Org. Chem. Front. 3 (2016) 309-313.
(d) F. Chang, Y. Liu, Syn. Commun. 47 (2017) 961-967.
(e) Z. Mi, J. Tang, Z. Guan, et al., Eur. J. Org. Chem. 2018 (2018) 4479-4482.
[10] (a) L.-H. Lu, Z. Wang, W. Xia, et al., Chin. Chem. Lett. 30 (2019) 1237-1240.
(b) C. Wu, J. Wang, X.Y. Zhang, et al., Org. Biomol. Chem. 16 (2018) 5050-5054.
(c) P. Bao, L. Wang, Q. Liu, et al., Tetrahedron Lett. 60 (2019) 214–218.
(d) C. Wu, L.H. Lu, A.Z. Peng, et al., Green Chem. 20 (2018) 3683-3688.
(e) L. Wang, M. Zhang, Y. Zhang, et al., Chin. Chem. Lett. (2019) DOI: 10.1016/j.cclet.2019.05.041.
(f) J. Chen, C.H. Ouyang, T. Xiao, H. Jiang, J.S. Li, ChemistrySelect. 4 (2019) 7327-7330.
(g) F.L. Zeng, X.L. Chen, S.Q. He, et al., Org. Chem. Front. 6 (2019) 1476-1480.
(h) L. Wang, Y. Zhang, M. Zhang, et al., Tetrahedron Lett. 60 (2019) 1845–1848.
(i) T.Y. Shang, L.H. Lu, Z. Cao, et al., Chem. Commun. 55 (2019) 5408-5419.
[11] (a) Q. Fu, D. Yi, Z. Zhang, et al., Org. Chem. Front. 4 (2017) 1385-1389.
(b) M.S. Li, Q. Zhang, D.Y. Hu, et al., Tetrahedron Lett. 57 (2016) 2642-2646.
(c) D. Yi, Q. Fu, S.Y. Chen, et al., Tetrahedron Lett. 58 (2017) 2058-2061.
(d) Z.J. Zhang, D. Yi, Q. Fu, et al., Tetrahedron Lett. 58 (2017) 2417-2420.
(e) W. Liang, Z. Zhang, D. Yi, et al., Chin. J. Chem. 35 (2017) 1378-1382.
(f) D.Y. Hu, M.S. Li, W.W. Zhong, et al., Chin. Chem. Lett. 27 (2016) 1691-1695.
(g) C. Liu, W. Wei, D. Yang, et al., Tetrahedron 71 (2015) 6901-6906.
(h) C. Liu, M. Zhu, W. Wei, et al., Org. Chem. Front. 2 (2015) 1356-1360.
(i) W.W. Zhong, Q. Zhang, M.S. Li, et al., Synth. Commun. 46 (2016) 1377-1385.
(j) Q. Huang, K. Dong, W. Bai, et al., Org. Lett. 21 (2019) 3332-3336.
[12] (a) W. Wei, P. Bao, H. Yue, et al., Org. Lett. 20 (2018) 5291-5295.
(b) H. Cui, W. Wei, D. Yang, et al., Green Chem. 19 (2017) 3520-3524.
(c) W. Wei, X. Liu, D. Yang, et al., Tetrahedron Lett. 56 (2015) 1808–1811.
(d) W. Wei, J. Wen, D. Yang, et al., RSC Adv. 5 (2015) 4416–4419.
(e) W. Wei, J. Li, D. Yang, et al., Org. Biomol. Chem. 12 (2014) 1861–1864.
(f) H. Cui, W. Wei, D. Yang, et al., Green Chem. 19 (2017) 3520–3524.
(g) W. Wei, H. Cui, H. Yue, et al., Green Chem. 20 (2018) 3197–3202.
(h) Q. Liu, L. Wang, H. Yue, et al., Green Chem. 21 (2019) 1609-1603.
[13] (a) Y. C. Guo, J. Li, J. L. Ma, et al., Chin. Chem. Lett. 26 (2015) 755-758.
(b) X.F. Zhu, J. Zhang, S. Sun, et al., Chin. Chem. Lett. 28 (2017) 1514-1518.
(c) M.K. Awad, M.F. Abdel-Aal, F.M. Atlam, et al., J. Mol. Struct. 1173 (2018) 128-141.
(d) C. Zhu, D. Wei, Y. Wu, et al., J. Alloys Compd. 778 (2019) 731-740.
(e) Y. You, K. Zhou, B. Guo, et al., ACS Sens. 4 (2019) 774-779.
(f) Y. Sheng, Y. You, Z. Cao, et al., Analyst 143 (2018) 2411-2415.
[14] (a) G. Keglevich, E. Balint, Molecules 17 (2012) 12821-12835.
(b) X.A. Li, J.Y. Li, B. Yang, et al., RSC Adv. 4 (2014) 39920-39923.
(c) S.A.R. Mulla, M.Y. Pathan, S.S. Chavan, et al., RSC Adv. 4 (2014) 7666-7672.

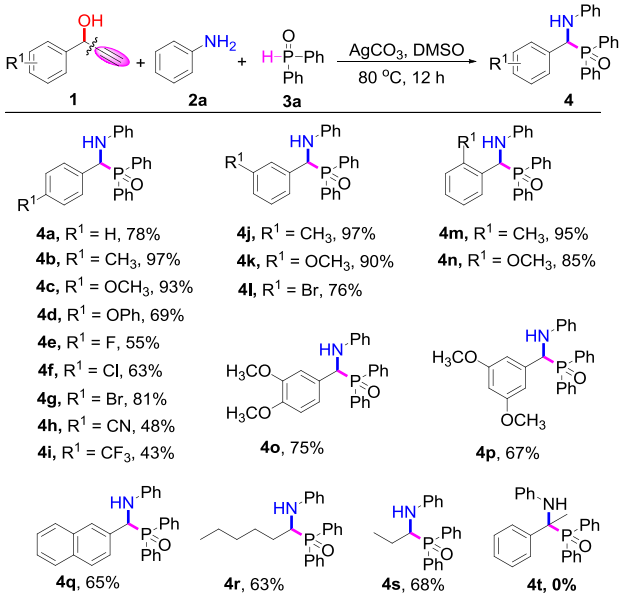
Previous work: *phosphorylation of propargyl alcohols via deacetonative coupling*



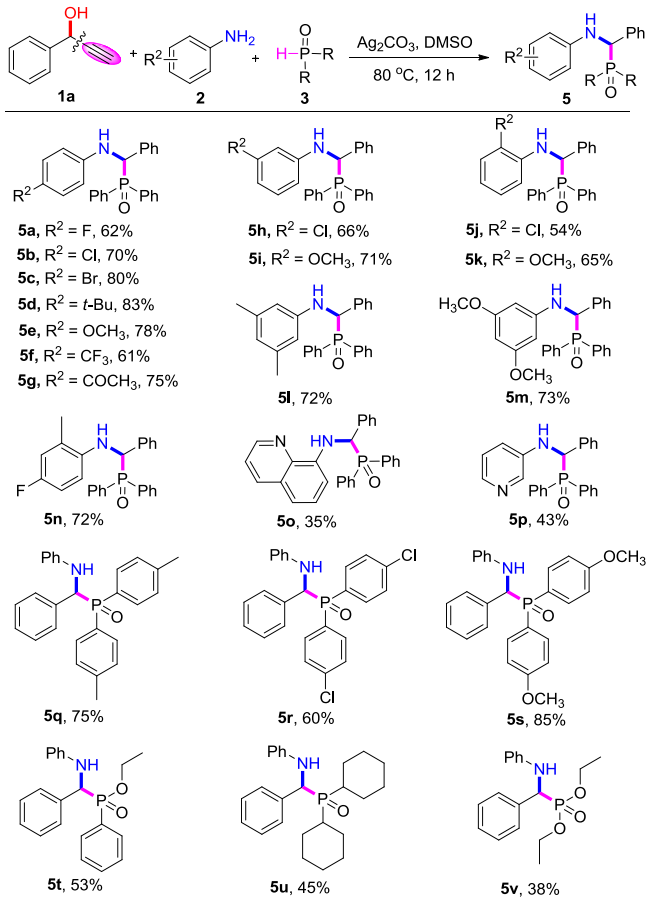
This work: *aminophosphinoylation of propargyl alcohols via dealkynylation coupling*



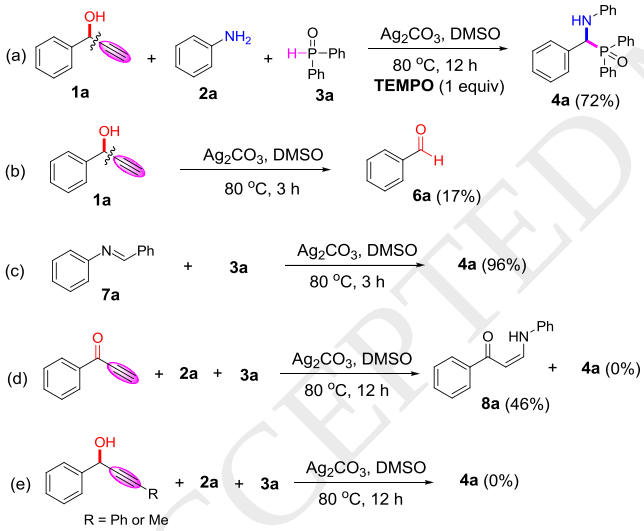
Scheme 1. Synthetic methods for synthesis of organic phosphorus compounds *via* C−C bond cleavage of propargyl alcohols.



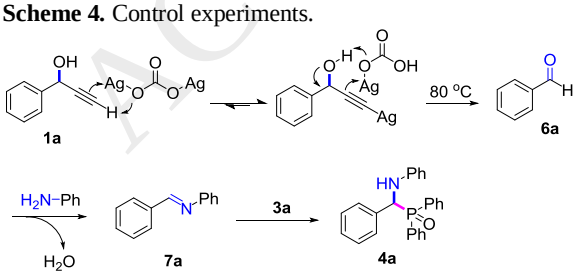
Scheme 2. Substrate scope of propargylic alcohols. Reaction conditions: **1** (0.6 mmol), **2a** (0.5 mmol), **3a** (1.0 mmol), Ag_2CO_3 (1.0 mmol), DMSO (4 mL), 80 °C, 12h. Isolated yields based on **2a**.



Scheme 3. Substrate scope of amines and H-phosphine oxides. Reaction conditions: **1a** (0.6 mmol), **2** (0.5 mmol), **3** (1.0 mmol), Ag_2CO_3 (1.0 mmol), DMSO (4 mL), 80 °C, 12 h. Isolated yields based on **2**.

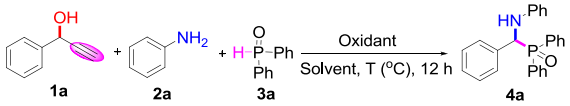


Scheme 4. Control experiments.



Scheme 5. Possible reaction pathway.

Table 1 Screening of the reaction conditions.[a]



Entry	Oxidant	Solvent	T (°C)	Yield(%)[b]
1	Ag_2O	DMSO	70	19
2	AgOAc	DMSO	70	41
3	Ag_2CO_3	DMSO	70	68
4	$AgNO_3$	DMSO	70	9
5	$CuCl_2$	DMSO	70	0
6	$FeCl_3$	DMSO	70	0
7	$K_2S_2O_8$	DMSO	70	0
8	TBHP	DMSO	70	0
9	DTBP	DMSO	70	0
10	O_2	DMSO	70	0
11	Ag_2CO_3	DMF	70	47
12	Ag_2CO_3	CH_3CN	70	19
13	Ag_2CO_3	Toluene	70	10
14	Ag_2CO_3	THF	70	26
15	Ag_2CO_3	1,4-Dioxane	70	18
16	Ag_2CO_3	DCE	70	59
17	Ag_2CO_3	DMSO	60	36
18	**Ag_2CO_3**	**DMSO**	**80**	**78**
19	Ag_2CO_3	DMSO	90	63
20	Ag_2CO_3	DMSO	100	52

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), **3a** (1.0 mmol), Oxidant (1.0 mmol), 60-100 °C, Solvent (4 mL), 12 h.
[b] Isolated yield based on **2a**.