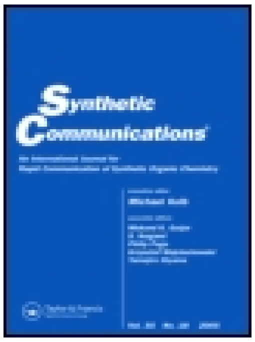

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Copper-catalyzed one-pot synthesis of alkynylphophonates

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ABSTRACT
Copper is found to be an effective catalyst for the preparation of alkynylphophonates. A novel copper-catalyzed one-pot synthesis of alkynylphophonates from terminal alkynes and dialkyl phosphites is developed which involves the haloalkynes intermediates. This method provides a unique and alternative approach to the well-documented oxidative coupling or arylpropiolic acid strategies.

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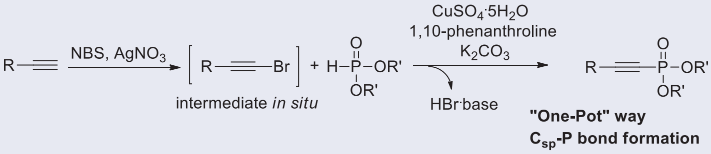
Alkynylphophonates; copper; haloalkynes; one-pot

GRAPHICAL ABSTRACT



Introduction

The phosphorus-containing compounds could be widely applied as ligands and organocatalysts or could be converted into diverse molecules by Wittig, Horner–Wadsworth–Emmons (HWE) reactions, cross-couplings, and cyclization in organic synthesis.[1] Alkynylphosphonates, as one of the most focused phosphorus reagents, are very useful building blocks for the synthesis of versatile phosphorus-containing compounds by conjugate-additions or cycloaddition reactions.[2] In addition, the alkynylphosphonates have attracted increasing attention due to their potential biological activities.[3] The traditional ways to access the alkynylphosphonates, including Michaelis–Arbuzov reaction, Michaelis–Becker reaction, and palladium-catalyzed reaction, usually suffer from a lack of functionality tolerance.[4]

In recent years, earth-abundant metal-catalyzed C$_{sp}$–P coupling reaction emerges to be the most straightforward and sustainable approach to prepare the alkynylphosphonates. In 2009, Han and Zhao group reported copper-catalyzed oxidative coupling of

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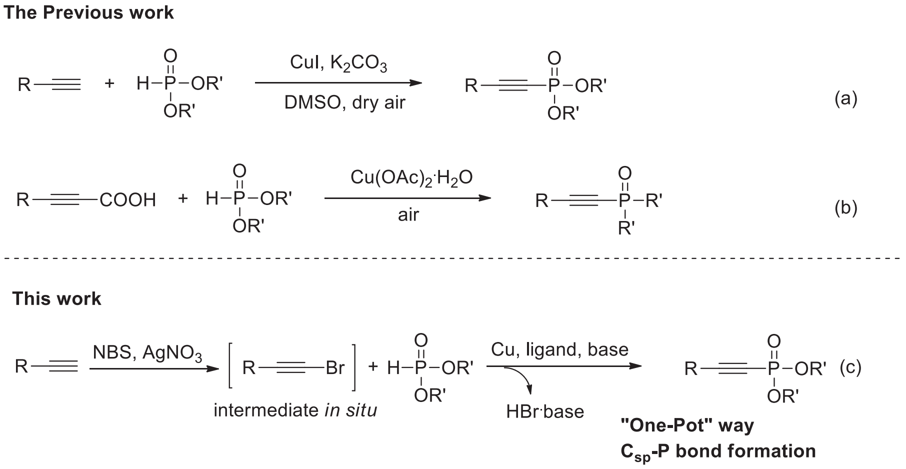


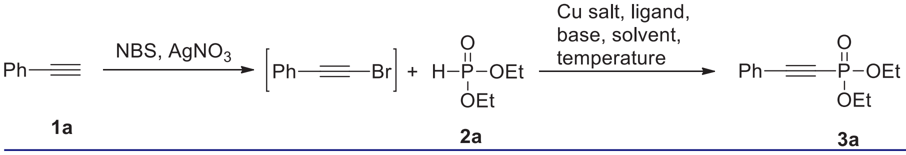
Scheme 1. Copper-catalyzed one-pot synthesis of alkynylphosphonates from terminal alkynes and dialkyl phosphite.

terminal alkynes and dialkyl phosphites under dry air (Scheme 1a).[5] Later, Zhao, Yang, and Wu group achieved the preparation of alkynylphosphonates from the arylpropiolic acids (Scheme 1b).[6] The advantages of those methodologies are using air (oxygen) as the oxidant to release water as the by-product. Beyond the well-documented copper-catalyzed reactions, new strategies are still highly desired. Haloalkynes, usually as the alternative substrates to the propiolic acids, could be easily converted to various internal alkynes by the transition metal-catalyzed reactions,[7] which would make the alkynylphosphonates formation safer and more approachable. It is also very convenient to generate haloalkynes *in situ* from the terminal alkynes. Herein, we report a copper-catalyzed one-pot synthesis of alkynylphophonates from terminal alkynes and dialkyl phosphite involving haloalkyne intermediate and C_{sp}–P bond formation (Scheme 1c).

Results and discussion

Initially, phenylethyne **1a** and diethyl phosphite **2a** were selected as model substrates for the optimal reaction conditions. Treating **1a** with NBS and silver nitrate in acetone afforded crude bromoalkyne intermediate, which was used directly in the next step without further purification. In the presence of Cu(I) or Cu(II), the coupling reaction could occur smoothly for the preparation of diethyl (phenylethynyl)phosphonate **3a** (Table 1, entries 1–3). Among the copper sources, $CuSO_4·5H_2O$ gave the best yield when using 1,10-phenanthroline and potassium carbonate as ligand and base. Without ligand, the yield decreased dramatically (Table 1, entry 4). Compared to other commercially available ligands (e.g. triethylamine and TMEDA), 1,10-phenanthroline was demonstrated to be the best ligand in this reaction (Table 1, entries 5 and 6). Besides potassium carbonate, other potassium salts were also screened (Table 1, entries 7 and 8). To our delight, tripotassium phosphate also worked in this transformation. But for the potassium tert-butoxide, no desired product was acquired. The reaction could be conducted in DMSO or DMF with lower yields (Table 1, entries 9 and 10). It failed to proceed in MeCN or $CHCl_3$ (Table 1, entries 11 and 12). We also briefly investigated

Table 1. Optimization of the reaction conditions[a].



Entry	Cu salt	Ligand	Base	Solvent	Yield(%)[b]
1	$CuSO_4·5H_2O$	1,10-Phen	K_2CO_3	toluene	86
2	CuI	1,10-Phen	K_2CO_3	toluene	81
3	CuCl	1,10-Phen	K_2CO_3	toluene	78
4	$CuSO_4·5H_2O$	–	K_2CO_3	toluene	46
5	$CuSO_4·5H_2O$	NEt_3	K_2CO_3	toluene	57
6	$CuSO_4·5H_2O$	TMEDA	K_2CO_3	toluene	48
7	$CuSO_4·5H_2O$	1,10-Phen	K_3PO_4	toluene	77
8	$CuSO_4·5H_2O$	1,10-Phen	KO*t*-Bu	toluene	trace
9	$CuSO_4·5H_2O$	1,10-Phen	K_2CO_3	DMSO	66
10	$CuSO_4·5H_2O$	1,10-Phen	K_2CO_3	DMF	67
11	$CuSO_4·5H_2O$	1,10-Phen	K_2CO_3	MeCN	trace
12	$CuSO_4·5H_2O$	1,10-Phen	K_2CO_3	$CHCl_3$	trace
13[c]	$CuSO_4·5H_2O$	1,10-Phen	K_2CO_3	toluene	trace
14[d]	$CuSO_4·5H_2O$	1,10-Phen	K_2CO_3	toluene	82

[a] The reaction conditions: under N_2 atmosphere, 1-phenylethyne (1 equiv.), NBS (1.2 equiv.), silver nitrate (0.1 equiv.) in acetone (1 M) at RT for 1 h, then removal of precipitation and solvent to afford crude bromoalkyne intermediate. Diethyl phosphite (1 equiv.), copper salt (0.1 equiv.), ligand (0.2 equiv.), base (2 equiv.) and solvent (0.5 M) were added to the crude bromoalkyne intermediate at 65 °C overnight.

[b] Isolated yield based on **1a**.

[c] The reaction was set at room temperature.

[d] The reaction was set at 110 °C.

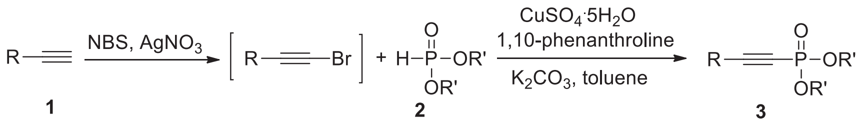
Note: 1,10-phen: 1,10-phenanthroline; TMEDA: tetramethylethylenediamine.

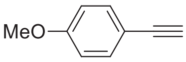
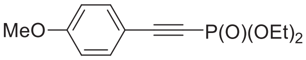
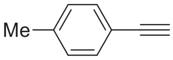
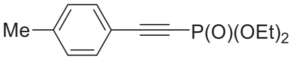
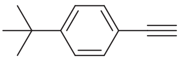
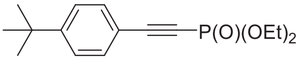
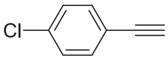
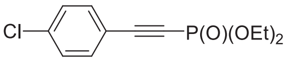
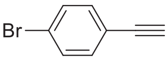
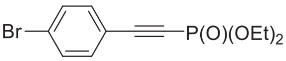
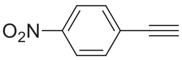
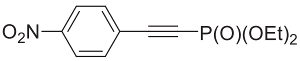
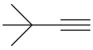
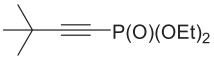
the temperature for this reaction. No reaction occurred at room temperature. Surprisingly, the yield slightly dropped to 82% in reflux condition (Table 1, entries 13 and 14).

With the optimized conditions in hand, we explored the scope of this one-pot synthesis of alkynylphophonates from terminal alkynes and dialkyl phosphite. Various dialkyl phosphites were used as substrates at 65 °C in inert gas protection to afford alkynylphophonates in good yields (up to 86%) (Table 2, entries 1–4). Besides diethyl phosphite, other dialkyl phosphites, such as methyl, isopropyl, and *n*-butyl phosphites, could also participate in this "one-pot" reaction smoothly (**3a**–**3d**). However, the yield for *n*-butyl phosphite was lower than other substrates. Subsequently, the electronic effect for the terminal alkynes was examined (Table 2, entries 5–10). No obvious electronic effect was observed in this transformation. The introduction of electron-donating groups could slightly decrease the yields comparing to electron-withdrawing groups. The methoxyl, methyl, tert-butyl, halogen, and nitro groups could be well tolerated in this process with good yields obtained (**3e**–**3j**). When the aliphatic alkyne **1k** was used instead of the aryl alkyne, the yield of **3k** was dramatically decreased to 61% (Table 2, entry 11).

Finally, the derivation of the alkynylphophonates was explored (Scheme 2). A tandem cycloaddition and deprotection process were employed to afford related fully substituted 1,2,3-triazolyl-4-phosphonic acid in 72% yield. The cycloaddition between the alkynylphophonate **3e** and benzyl azide **4** occurred firstly, followed

Table 2. One-pot synthesis of alkynylphosphonates from terminal alkynes and dialkyl phosphite[a].



Entry	Substrate **1**	Substrate **2**	Product **3**	Yield (%)[b]
1	$\mathrm{Ph{-}{\equiv}}$ **1a**	$\mathrm{HP(O)(OEt)_2}$ **2a**	$\mathrm{Ph{-}{\equiv}{-}P(O)(OEt)_2}$ **3a**	86
2	$\mathrm{Ph{-}{\equiv}}$ **1a**	$\mathrm{HP(O)(OMe)_2}$ **2b**	$\mathrm{Ph{-}{\equiv}{-}P(O)(OMe)_2}$ **3b**	83
3	$\mathrm{Ph{-}{\equiv}}$ **1a**	$\mathrm{HP(O)(O^{\mathit{i}}Pr)_2}$ **2c**	$\mathrm{Ph{-}{\equiv}{-}P(O)(O^{\mathit{i}}Pr)_2}$ **3c**	79
4	$\mathrm{Ph{-}{\equiv}}$ **1a**	$\mathrm{HP(O)(O^{\mathit{n}}Bu)_2}$ **2d**	$\mathrm{Ph{-}{\equiv}{-}P(O)(O^{\mathit{n}}Bu)_2}$ **3d**	75
5	 **1e**	$\mathrm{HP(O)(OEt)_2}$ **2a**	 **3e**	77
6	 **1f**	$\mathrm{HP(O)(OEt)_2}$ **2a**	 **3f**	79
7	 **1g**	$\mathrm{HP(O)(OEt)_2}$ **2a**	 **3g**	76
8	 **1h**	$\mathrm{HP(O)(OEt)_2}$ **2a**	 **3h**	81
9	 **1i**	$\mathrm{HP(O)(OEt)_2}$ **2a**	 **3i**	82
10	 **1j**	$\mathrm{HP(O)(OEt)_2}$ **2a**	 **3j**	84
11	 **1k**	$\mathrm{HP(O)(OEt)_2}$ **2a**	 **3k**	61

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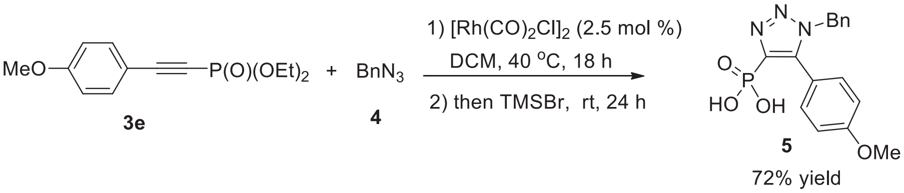
[a] The reaction conditions: under N_2 atmosphere, alkyne (1 equiv.), NBS (1.2 equiv.), silver nitrate (0.1 equiv.) in acetone (1 M) at RT for 1 h, then removal of precipitation and solvent to afford crude bromoalkyne intermediate. Dialkyl phosphite (1 equiv.), $CuSO_4{\cdot}5H_2O$ (0.1 equiv.), 1,10-phenanthroline (0.2 equiv.), K_2CO_3 (2 equiv.) and toluene (0.5 M) were added to the crude bromoalkyne intermediate at 65 °C overnight.

[b] Isolated yield based on **1**.



Scheme 2. The tandem cycloadditon and deprotection from the alkynylphosphonates.

by adding trimethylsilyl bromide (TMSBr) to deprotect the phophonates in "one-pot" way.

Conclusion

In summary, we have developed a novel copper-catalyzed one-pot synthesis of alkynylphophonates from terminal alkynes and dialkyl phosphite. Haloalkynes, as the alternative substrates to the well-defined propiolic acids, could be easily generated *in situ* from the terminal alkynes, which further reacted with dialkyl phosphites to form C_{sp}–P bond efficiently.

Experimental section

General procedure for the preparation of alkynylphosphonates 3

To the solution of alkyne (1 equiv.) and NBS (1.2 equiv.) in acetone (1 M) silver nitrate (0.1 equiv.) was added under N_2 atmosphere. The mixture was stirred at RT for 1 h, then removal of precipitation and solvent to afford crude bromoalkyne intermediate. Dialkyl phosphite (1 equiv.), $CuSO_4 \cdot 5H_2O$ (0.1 equiv.), 1,10-phenanthroline (0.2 equiv.), K_2CO_3 (2 equiv.) and toluene (0.5 M) were added to the crude bromoalkyne intermediate. The mixture was stirred at 65 °C overnight. The mixture was filtered through a short pad of silica gel using CH_2Cl_2 as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/hexane) gave the alkynylphosphonates 3.

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References

[1] (a) Fiorito, D.; Folliet, S.; Liu, Y.; Mazet, C.; A General Nickel-Catalyzed Kumada Vinylation for the Preparation of 2-Substituted 1,3-Dienes. *ACS Catal.* **2018**, *8*, 1392. DOI: 10.1021/acscatal.7b04030 (b) Chen, P.; Sun, Y.; Wu, Y.; Liu, L.; Zhu, J.; Zhao, Y.; A Theoretical Study on the Mechanism of Ruthenium(ii)-Catalyzed Phosphoryl-directed

Ortho-selective C–H Bond Activations: The Phosphoryl Hydroxy Group Triggered Ru(ii)/Ru(0) catalytic Cycle. *Org. Chem. Front.* **2017**, *4*, 1482. DOI: 10.1039/c7qo00240h (c) Hu, G.; Shan, C.; Chen, W.; Xu, P.; Gao, Y.; Zhao, Y. Copper-Catalyzed Direct Coupling of Unprotected Propargylic Alcohols with P(O)H Compounds: Access to Allenylphosphoryl Compounds under Ligand- and Base-Free Conditions. *Org. Lett.* **2016**, *18*, 6066. DOI: 10.1021/acs.orglett.6b03028 (d) Montchamp, J. L.; Phosphinate Chemistry in the 21st Century: A Viable Alternative to the Use of Phosphorus Trichloride in Organophosphorus Synthesis. *Acc. Chem. Res.* **2014**, 47, 77. DOI: 10.1021/ar400071v (e) Demmer, C. S.; Krogsgaard-Larsen, N.; Bunch, L. Review on Modern Advances of Chemical Methods for the Introduction of a Phosphonic Acid Group. *Chem. Rev.* **2011**, *111*, 7981. DOI: 10.1021/cr2002646.

[2] (a) Zhu, S.; Zhang, Y.; Li, P.; Bi, W.; Chen, X.; Zhao, Y.; Synthesis of Novel Phosphorylated Chrysin Derivatives by 1, 3-dipolar Cycloaddition Reaction. *Phosphorus, Sulfur, and Silicon* **2017**, *192*, 1. DOI: 10.1080/10426507.2016.1223076 (b) Gupta, A.; Flynn, B.; Electrophilic Activation of P-Alkynes in the Synthesis of P-Substituted and P-Centered Heterocycles. *J. Org. Chem.* **2016**, *81*, 4012. DOI: 10.1021/acs.joc.6b00262 (c) Ashburn, B. O.; Carter, R. G.; Zakharov, L. N.; Synthesis of Tetra-Ortho-Substituted, Phosphorus-Containing and Carbonyl-Containing Biaryls Utilizing a Diels – Alder Approach. *J. Am. Chem. Soc.* **2007**, *129*, 9109. DOI: 10.1021/ja071163r (d) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. Asymmetric Assembly of Aromatic Rings to Produce Tetra-Ortho-Substituted Axially Chiral Biaryl Phosphorus Compounds. *K. Angew. Chem., Int. Ed.* **2007**, *46*, 3951. DOI: 10.1002/anie.200700064 (e) Seyferth, D.; Paetsch, J. D. H. Diels–Alder Reaction in Organometallic Chemistry. V. Tetramethyl Acetylenediphosphonate and Dimethyl Chloroacetylenephosphonate and Their Reactions with Cyclopentadiene, 1,3-cyclohexadiene, and Diazomethane. *J. Org. Chem.* **1969**, *34*, 1483. DOI: 10.1021/jo01257a070.

[3] (a) Van Derpoorten, K.; Migaud, M. E. Isopolar Phosphonate Analogue of Adenosine Diphosphate Ribose. *Org. Lett.* **2004**, *6*, 3461. DOI: 10.1021/ol0488993 (b) Mahajina, M.; Quistad, G. B.; Casida, J. E. Retro-Diels—Alder Reaction: Possible Involvement in the Metabolic Activation of 7-Oxabicyclo[2.2.1]hepta-2(3),5(6)-diene-2,3-dicarboxylates and a Phosphonate Analog. *Chem. Res. Toxicol.* **1996**, *9*, 241. DOI: 10.1021/tx950127f.

[4] (a) Lera, M.; Hayes, C.; A New One-Pot Synthesis of Alkynylphosphonates. *Org. Lett.* **2000**, *2*, 3873. DOI: 10.1021/010066173 (b) Iorga, B.; Eymery, F.; Carmichael, D.; Savignac, P. Dialkyl 1-Alkynylphosphonates: A Range of Promising Reagents. *Eur. J. Org. Chem.* **2000**, *2000*, 3103. DOI: 10.1002/1099-0690(200009)2000:18<3103::AID-EJOC3103>3.0.CO;2-V (c) Gil, J. M.; Sung, J. W.; Park, C. P.; Oh, D. Y. One-Pot Synthesis of 1-Alkynylphosphonates. *Synth. Commun.* **1997**, *27*, 3171. DOI: 10.1080/00397919708004175 (d) Lodaya, J. S.; Koser, G. F. Alkynyliodonium Salts as Alkynylating Reagents: Direct Conversion of Alkynylphenyliodonium Tosylates to Dialkyl Alkynylphosphonates with Trialkyl Phosphites. *J. Org. Chem.* **1990**, *55*, 1513. DOI: 10.1021/jo00292a026 (e) Chattha, M. S.; Aguiar, A. M. Convenient synthesis of 1-alkynylphosphonates. *J. Org. Chem.* **1971**, *36*, 2719. DOI: 10.1021/jo00817a034.

[5] (a) Moglie, Y.; Mascaró, E.; Gutierrez, V.; Alonso, F.; Radivoy, G.; Base-Free Direct Synthesis of Alkynylphosphonates from Alkynes and H -Phosphonates Catalyzed by Cu 2 O. *J. Org. Chem.* **2016**, *81*, 1813. DOI: 10.1021/acs.joc.5b02528 (b) Liu, L.; Wu, Y.; Wang, Z.; Zhu, J.; Zhao, Y.; Mechanistic Insight into the Copper-Catalyzed Phosphorylation of Terminal Alkynes: A Combined Theoretical and Experimental Study. *J. Org. Chem.* **2014**, *79*, 6816. DOI: 10.1021/jo5007174 (c) Qu, Z.; Chen, X.; Yuan, J.; Qu, L.; Li, X.; Wang, F.; Ding, X.; Zhao, Y. CuSO 4 ·5H 2 O-Catalyzed Alkynylphosphonates Formation — An Efficient Coupling Reaction of Terminal Alkynes with H -Phosphonates. *Can. J. Chem.* **2012**, *90*, 747. DOI: 10.1139/v2012-029 (d) Gao, Y.; Wang, G.; Chen, L.; Xu, P.; Zhao, Y.; Zhou, Y.; Han, L.-B. Copper-Catalyzed Aerobic Oxidative Coupling of Terminal Alkynes with H -Phosphonates Leading to Alkynylphosphonates. *J. Am. Chem. Soc.* **2009**, *131*, 7956. DOI: 10.1021/ja9023397 (e) Niu, M.; Fu, H.; Jiang, Y.; Zhao, Y. Copper-catalyzed Addition of H-

phosphine Oxides to Alkynes Forming Alkenylphosphine Oxides. *Chem. Commun* **2007**, *0*, 272. DOI: 10.1039/b613416e.

[6] (a) Chen, W.; Ma, D.; Hu, G.; Hong, Z.; Gao, Y.; Zhao, Y.; Copper-Catalyzed Decarboxylative C – P Cross Coupling of Arylpropiolic Acids with Dialkyl Hydrazinylphosphonates Leading to Alkynylphosphonates. *Synth. Commun.* **2016**, *46*, 1175. DOI: 10.1080/00397911.2016.1192648 (b) Li, X.; Yang, F.; Wu, Y.; Wu, Y. Copper-Mediated Oxidative Decarboxylative Coupling of Arylpropiolic Acids with Dialkyl H-Phosphonates in Water. *Org. Lett.* **2014**, *16*, 992. DOI: 10.1021/ol4037242 (c) Hu, J.; Zhao, N.; Yang, B.; Wang, G.; Guo, L.-N.; Liang, Y.-M.; Yang, S.-D. Copper-Catalyzed C-P Coupling through Decarboxylation. *Chem. Eur. J.* **2011**, *17*, 5516. DOI:10.1002/chem.201003561

[7] (a) Wu, W.; Jiang, H.; Haloalkynes: A Powerful and Versatile Building Block in Organic Synthesis. *Acc. Chem. Res.* **2014**, *47*, 2483. DOI: 10.1021/ar5001499 (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Shi, Z.; Zhang, Y.; Hsung, R. P. Ynamides: A Modern Functional Group for the New Millennium. *Chem. Rev.* **2010**, *110*, 5064. DOI: 10.1021/cr100003s (c) Chen, Z.; Jiang, H.; Wang, A.; Yang, S. Transition-Metal-Free Homocoupling of 1-Haloalkynes: A Facile Synthesis of Symmetrical 1,3-Diynes. *J. Org. Chem.* **2010**, *75*, 6700. DOI: 10.1021/jo101216m.