Organic LETTERS

Letter

pubs.acs.org/OrgLett

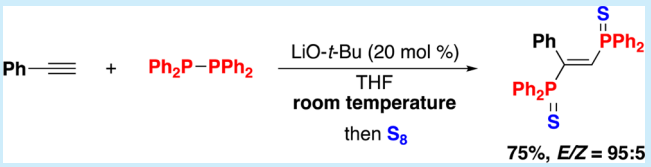
Brønsted Base Mediated Stereoselective Diphosphination of Terminal Alkynes with Diphosphanes

Yuto Okugawa, Koji Hirano,* and Masahiro Miura*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

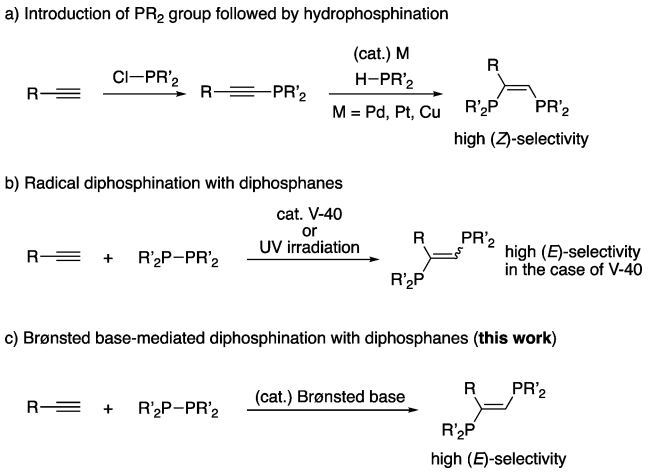
Supporting Information

ABSTRACT: A Brønsted base mediated stereoselective diphosphination of terminal alkynes with diphosphanes proceeds to deliver the corresponding (*E*)-1,2-diphosphinoethenes in good yields. The reaction of aromatic alkynes occurs efficiently in the presence of a catalytic amount of LiO-*t*-Bu while $MN(TMS)_2$ (M = Li or Na) gave better results in the case of aliphatic substrates. The Brønsted base mediated protocol can offer a good alternative to precedented transition-metal-catalyzed or radical-promoted approaches to the 1,2-diphosphinoethene framework of potent interest in catalysis and coordination chemistry.



Organophosphines now represent an important class of compounds in organic chemistry because of their ubiquity in synthetic reagents,[1] supported ligands for transition metal catalysts,[2] and organic functional materials.[3] Particularly, 1,2-diphosphinoethenes have received significant attention in the fields of catalysis[4] and coordination chemistry.[5] Among several protocols for their preparation,[6] *vicinal*-introduction of two phosphino moieties to alkyne platforms is the most straightforward approach to the above target structure (Scheme 1). The conversion of terminal alkynes to 1-alkynylphosphines is followed by *anti*-hydrophosphination to form the (*Z*)-1,2-bisphosphinoethenes in good overall yields (Scheme 1a). This strategy was originally reported by Carty,[7] with a stoichiometric amount of Pd or Pt, in 1979, and Yorimitsu and Oshima[8] subsequently developed the catalytic variant using a readily available Cu salt.[9] The direct *vicinal*-diphosphination of terminal alkynes was also achieved by a radical reaction with diphosphanes in the presence of a radical initiator V-40 or under UV irradiation (Scheme 1b).[10,11] Notably, high (*E*)-selectivity was observed in the former case.[10a] Herein, we report the third route to 1,2-bisphosphinoethenes from terminal alkynes: a Brønsted base-mediated *vicinal*-diphosphination of terminal alkynes with diphosphanes is described. The present reaction can offer an alternative approach to (*E*)-1,2-diphosphinoethene frameworks (Scheme 1c).

Scheme 1. Diphosphination Approaches to 1,2-Diphosphinoethenes from Terminal Alkynes

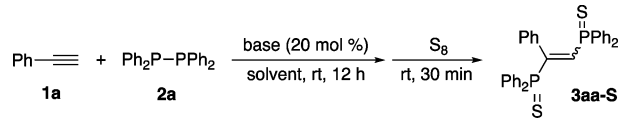


Due to our recent interest in the phosphination reaction of alkenes and alkynes,[12] we examined the reactivity of phenylacetylene (**1a**; 0.25 mmol) with tetraphenyldiphosphane (**2a**; 0.30 mmol) and serendipitously found that the *vicinal*-diphosphination of **1a** occurred in the presence of 20 mol % LiO-*t*-Bu (Table 1, entry 1). For ease of handling, the diphosphinated product **3aa** was analyzed and isolated as the corresponding sulfide **3aa-S** after treatment with S_8. Notably, the reaction proceeded even at room temperature in THF, and **3aa-S** was obtained in 85% $^{31}P\{^1H\}$ NMR yield with 95:5 *E*/*Z* selectivity (75% isolated yield of pure (*E*)-product). Inspired by the intriguing result, we subsequently screened various bases. Other alkali metal alkoxides and hydroxides including NaO-*t*-Bu, KO-*t*-Bu, LiOMe, LiOH, and NaOH also promoted the reaction, but LiO-*t*-Bu was somewhat superior in view of the yield and stereoselectivity probably because of its better solubility in THF (entries 2−6).[13] Neither more basic metal amide (entry 7) nor less basic fluoride and carbonate (entries 8 and 9) increased the reaction efficiency. Additional investigation of solvent revealed that THF was best from the viewpoint of yield of **3aa-S** (entries 10−17); in some more and less polar solvents such as DMF, MeOH, and hexane, the reaction stopped at an early stage, and unreacted diphosphane was largely recovered although the reason was unclear. The

Received: April 21, 2017

DOI: 10.1021/acs.orglett.7b01209
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization for Base-Mediated Stereoselective Diphosphination of Phenylacetylene (1a) with Tetraphenyldiphosphane (2a)[a]



entry	base	solvent	yield (%),[b] E/Z[c]
1	LiO-*t*-Bu	THF	85 (75), 95:5
2	NaO-*t*-Bu	THF	83, 95:5
3	KO-*t*-Bu	THF	30, 83:17
4	LiOMe	THF	84, 95:5
5	LiOH	THF	83, 95:5
6	NaOH	THF	73, 95:5
7	$NaN(TMS)_2$	THF	6, 97:3
8	CsF	THF	59, 96:4
9	Cs_2CO_3[d]	THF	33, 96:4
10	LiO-*t*-Bu	1,4-dioxane	68, 94:6
11	LiO-*t*-Bu	PhOMe	84, 95:5
12	LiO-*t*-Bu	toluene	84, 95:5
13	LiO-*t*-Bu	hexane	28, 90:10
14	LiO-*t*-Bu	DMF	44, 98:2
15	LiO-*t*-Bu	DMSO	14, 77:23
16	LiO-*t*-Bu	CH_2Cl_2	81, 97:3
17	LiO-*t*-Bu	MeOH	14, 100:0
18[e]	LiO-*t*-Bu	THF	71 (60), 95:5

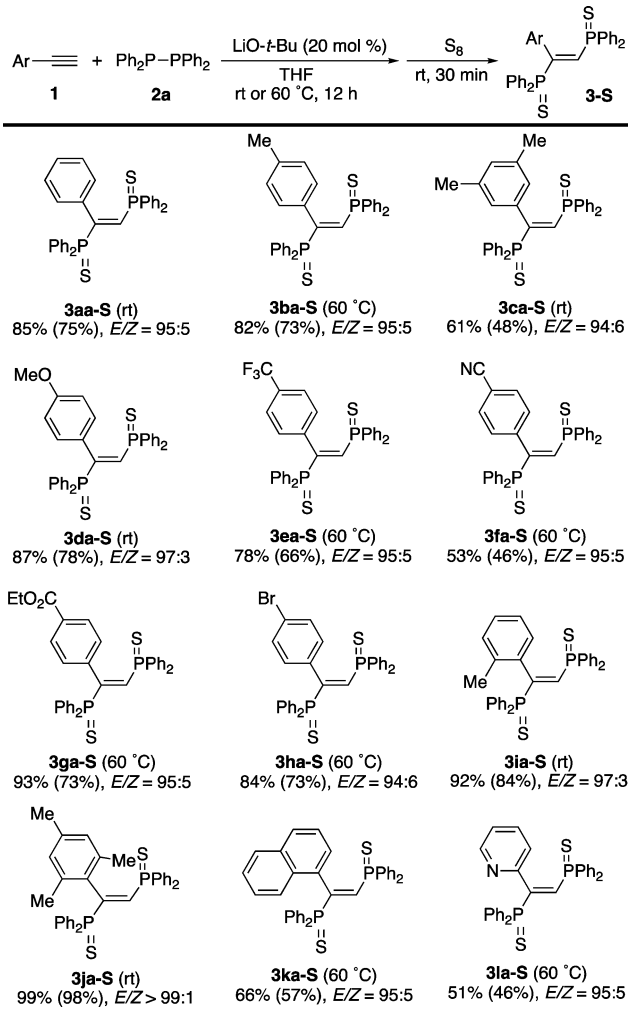
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), base (0.050 mmol), solvent (1.5 mL), rt, 12 h, N_2 then S_8 (0.75 mmol), rt, 30 min, N_2. [b]Determined by $^{31}P\{^1H\}$ NMR with $P(O)(OEt)_3$ as internal standard. Isolated yield of isomerically pure (*E*)-**3aa-S** is in parentheses. [c]Determined by $^{31}P\{^1H\}$ NMR of the crude mixture. [d]With 18-crown-6 (0.050 mmol). [e]1.0 mmol scale. At 60 °C.

diphosphination reaction could also be conducted on a 1.0 mmol scale under somewhat forceful conditions (60 °C; entry 18).

We next investigated the scope of terminal alkynes under conditions using LiO-*t*-Bu. The reaction was usually performed at room temperature, but in some cases the higher reaction temperature (60 °C) improved the reaction efficiency. The representative products are shown in Scheme 2. The reaction was compatible with arylalkynes that bear electronically diverse functional groups including methyl, methoxy, trifluoromethyl, cyano, and ester groups (**3ba-S**, **3ca-S**, **3da-S**, **3ea-S**, **3fa-S**, and **3ga-S**). The aryl-Br moiety also remained intact (**3ha-S**), which can be a good handle for further manipulations. Sterically demanding *ortho*-methylphenyl, mesityl, and 1-naphthyl substituents did not interfere with the reaction to form the corresponding diphosphinated products **3ia-S**, **3ja-S**, and **3ka-S** in good to excellent yields. Moreover, the heteroaromatic 2-pyridylacetylene was also concerted to **3la-S** in an acceptable yield. In all cases, the stereoselectivity was uniformly high (E/Z > 94:6).[14]

On the other hand, aliphatic 1-octyne did not react with **2a** under the standard conditions of entry 1 in Table 1. Thus, we carried out additional optimization studies. Pleasingly, the portionwise addition of $NaN(TMS)_2$ (0.050 mmol × 3, every 3 h) in heated 1,4-dioxane (90 °C) dramatically improved the yield of desired **3ma-S** to 63% $^{31}P\{^1H\}$ NMR yield with 95:5 E/Z selectivity (51% isolated yield of pure (*E*)-isomer) (Scheme 3). The addition of 0.15 mmol of $NaN(TMS)_2$ in one portion caused undesired olefin isomerization (see the

Scheme 2. LiO-*t*-Bu-Mediated Stereoselective Diphosphination of Terminal Aryl Alkynes 1 with Tetraphenyldiphosphane (2a)[a]



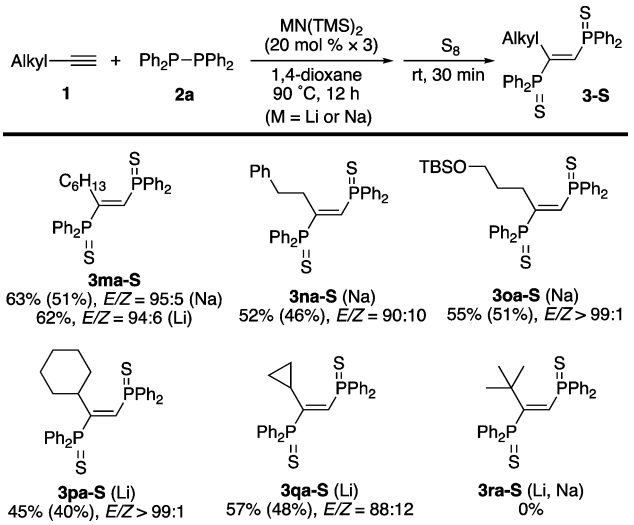
[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.30 mmol), LiO-*t*-Bu (0.050 mmol), THF (1.5 mL), rt or 60 °C, 12 h, N_2 then S_8 (0.75 mmol), rt, 30 min, N_2. The reaction temperature is in parentheses. Yields are determined by $^{31}P\{^1H\}$ NMR with $P(O)(OEt)_3$ as internal standard. Isolated yield of isomerically pure (*E*)-**3-S** is in parentheses. The E/Z ratios are determined by $^{31}P\{^1H\}$ NMR of the crude mixture.

Supporting Information for details). The use of $LiN(TMS)_2$ also gave a comparable result. Under $MN(TMS)_2$-meditaed modified conditions, the diphosphination of several aliphatic terminal alkynes **1** was performed. Primary alkyl alkynes that bear phenyl- and silyl-protected alcohol moieties underwent the diphosphination to furnish **3na-S** and **3oa-S** with synthetically useful levels of yield and stereoselectivity. In the cases of secondary alkyl substituents, $LiN(TMS)_2$ showed better activity: cyclohexylacetylene and cyclopropylacetylene participated in the reaction, and the corresponding **3pa-S** and **3qa-S** were formed in 45% and 57% yields, respectively. However, the latter resulted in somewhat lower stereoselectivity (E/Z = 88:12). On the other hand, more congested *tert*-butylacetylene gave no desired diphosphinated product (**3ra-S**).

The obtained diphosphinated product **3aa-S** could be easily desulfidated under radical conditions using $(TMS)_3SiH$ reductant and AIBN initiator to afford the corresponding trivalent P(III) compound **3aa** in 79% yield (Scheme 4).[15]

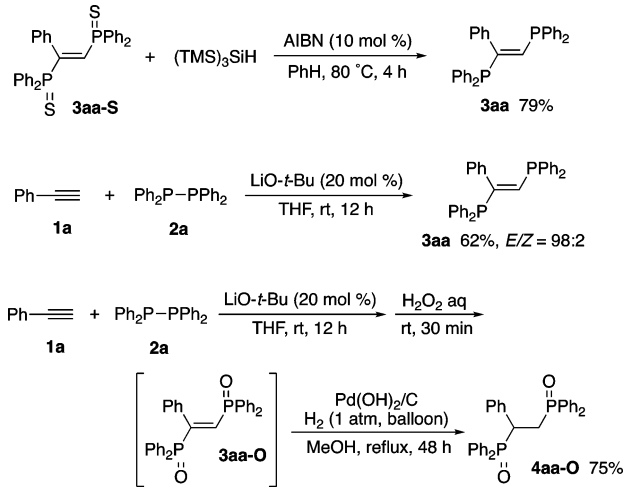
DOI: 10.1021/acs.orglett.7b01209
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. $MN(TMS)_2$-Mediated Stereoselective Diphosphination of Terminal Alkyl Alkynes 1 with Tetraphenyldiphosphane (2a)[a]



[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.30 mmol), $MN(TMS)_2$ (M = Li or Na, 0.050 mmol × 3, every 3 h), 1,4-dioxane (1.5 mL), 90 °C, 12 h, N_2 then S_8 (0.75 mmol), rt, 30 min, N_2. The countercation of $MN(TMS)_2$ used is in parentheses. Yields are determined by $^{31}P\{^1H\}$ NMR with $P(O)(OEt)_3$ as internal standard. Isolated yield of isomerically pure (*E*)-**3-S** is in parentheses. The *E*/*Z* ratios are determined by $^{31}P\{^1H\}$ NMR of the crude mixture.

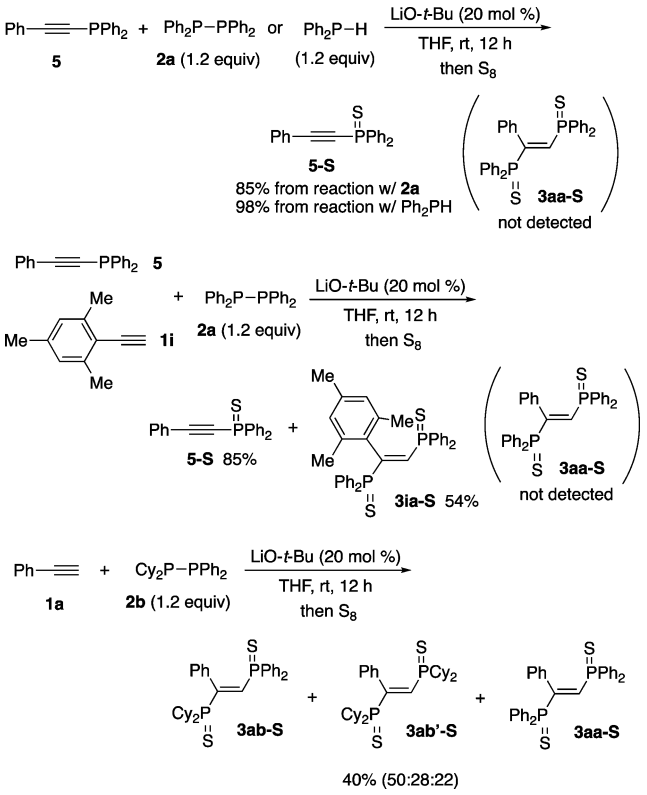
Scheme 4. Isolation of Trivalent P(III) Compounds and Reduction of Double Bond



Additionally, without S_8 quench, the same diphosphine **3aa** was obtained in 62% yield with a 98:2 *E*/*Z* ratio directly from the reaction of **1a** with **2a**. The corresponding diphosphine oxide **3aa-O** was selectively formed when 30% H_2O_2 aq instead of S_8 was used upon workup. Furthermore, the crude **3aa-O** underwent the hydrogenation under $Pd(OH)_2/C$ catalysis[16] to produce the diphosphine oxide **4aa-O** with the saturated ethylene linker in 75% overall yield.

To gain some mechanistic insight, we implemented the following experiments (Scheme 5). Although the independently prepared 1-alkynylphosphine **5** was subjected to the LiO-*t*-Bu-mediated standard reaction conditions, the diphosphinated **3aa-S** was not detected and alkynylphosphine sulfide **5-S** was

Scheme 5. Experiments for Mechanistic Investigation



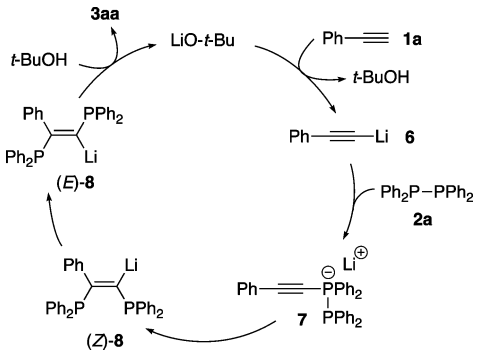
instead recovered. The same result was obtained under modified conditions using $Ph_2P–H$ instead of **2a**. The competitive reaction of **5** and mesitylacetylene (**1i**) in the same reaction vessel also gave only **3ia-S** arising from terminal alkyne **1i** with the alkynylphosphine sulfide **5-S** left intact. These results suggest no intermediacy of alkynylphosphine in the diphosphination reaction.[17] On the other hand, the reaction of **1a** with unsymmetrical diphosphane Cy_2P-PPh_2 **2b** (93% purity, contaminated with 2% $Ph_2P–PPh_2$ and 5% $Cy_2P–PCy_2$) formed a mixture of expected **3ab-S** and crossover products **3ab′-S** and **3aa-S**. The structure of **3ab-S** was unambiguously confirmed by X-ray crystallographic analysis,[18] and its regioisomer was not obtained.[19]

On the basis of the above outcomes, the reaction mechanism of **1a** with **2a** can involve (1) deprotonation of acidic C–H at the alkyne terminus of **1a** by LiO-*t*-Bu, (2) attack of the formed lithium acetylide **6** to diphosphane **2a**, (3) rearrangement of an initially formed tetracoordinated phosphonium species **7** into a *vicinal*-diphosphinated vinyllithium (*Z*)-**8**, (4) isomerization into more thermodynamically favored (*E*)-**8**, and (5) protonation with *t*-BuOH to produce **3aa** with regeneration of the starting LiO-*t*-Bu (Scheme 6). Given the above phosphorus scrambling with $Cy_2P–PPh_2$ **2b**, the rearrangement process from **7** to (*Z*)-**8** may proceed via a bimolecular mechanism.[20,21] However, further efforts are essential for uncovering the detailed mechanism.[22]

In conclusion, we have developed a Brønsted base mediated *vicinal*-diphosphination of terminal alkynes with diphosphanes. The reaction proceeds stereoselectively to form the corresponding (*E*)-1,2-diphosphinoethenes of potent interest in catalysis and coordination chemistry. This reaction can complement precedented transition-metal-mediated and radical-promoted diphosphination approaches to the 1,2-diphos-

DOI: 10.1021/acs.orglett.7b01209
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 6. Plausible Mechanism



phinoethene framework from terminal alkynes. Further development of related phosphination reactions of unsaturated molecules is ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01209.

^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H}, and ^{31}P{^{1}H} NMR spectra and ORTEP drawing (PDF)

Crystallographic data for **3ab-S** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: k_hirano@chem.eng.osaka-u.ac.jp.

*E-mail: miura@chem.eng.osaka-u.ac.jp.

ORCID

Koji Hirano: 0000-0001-9752-1985

Masahiro Miura: 0000-0001-8288-6439

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Nos. JP 15K13696 (Grant-in-Aid for Exploratory Research) and JP 15H05485 (Grant-in-Aid for Young Scientists (A)) to K.H. and JP 24225002 (Grant-in-Aid for Scientific Research (S)) to M.M. We thank Dr. Yuji Nishii (Osaka University) for his assistance of X-ray analysis.

■ REFERENCES

(1) (a) Cadogan, J. I. G. *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979. (b) Johnson, A. W. *Ylides and Imines of Phosphorus*; Wiley-Interscience: New York, 1993.

(2) (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: 2004. (b) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998. (c) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

(3) For selected examples, see: (a) Baumgartner, T.; Réau, R. *Chem. Rev.* **2006**, *106*, 4681. (b) Baumgartner, T. *Acc. Chem. Res.* **2014**, *47*, 1613.

(4) For recent applications of (*Z*)-1,2-diphosphinoethenes in catalysis, see: (a) Sun, Z.-M.; Zhang, J.; Manan, R. S.; Zhao, P. *J. Am. Chem. Soc.* **2010**, *132*, 6935. (b) Ghosh, A. K.; Kass, J.; Nicponski, D. R.; Keyes, C. *Synthesis* **2012**, *44*, 3579. (c) Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755. (d) Santhoshkumar, R.; Mannathan, S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2015**, *137*, 16116.

(5) For applications of (*E*)-1,2-diphosphinoethenes in coordination chemistry, see: (a) Lozano, E.; Nieuwenhuyzen, M.; James, S. L. *Chem. - Eur. J.* **2001**, *7*, 2644. (b) Brandys, M.-C.; Puddephatt, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 4839. (c) Brandys, M.-C.; Puddephatt, R. J. *J. Am. Chem. Soc.* **2002**, *124*, 3946.

(6) (a) Aguiar, A. M.; Daigle, D. *J. Am. Chem. Soc.* **1964**, *86*, 2299. (b) Banert, K.; Fendel, W.; Schlott, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 3289.

(7) Carty, A. J.; Johnson, D. K.; Jacobson, S. E. *J. Am. Chem. Soc.* **1979**, *101*, 5612.

(8) Kondoh, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4099.

(9) Only native ethynyldiphenylphosphine underwent noncatalyzed addition reaction with a lithium phosphide to form the corresponding (*E*)-1,2-bis(diphenylphosphino)ethene: King, R. B.; Kapoor, P. N. *J. Am. Chem. Soc.* **1971**, *93*, 4158.

(10) (a) Sato, A.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1694. (b) Kawaguchi, S.-i.; Nagata, S.; Shirai, T.; Tsuchii, K.; Nomoto, A.; Ogawa, A. *Tetrahedron Lett.* **2006**, *47*, 3919.

(11) For noncatalyzed diphosphination of specially activated alkynes including dimethyl acetylenedicarboxylate and methyl propiolate, see: Dodds, D. L.; Haddow, M. F.; Orpen, A. G.; Pringle, P. G.; Woodward, G. *Organometallics* **2006**, *25*, 5937.

(12) (a) Okugawa, Y.; Hirano, K.; Miura, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 13558. (b) Unoh, Y.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2017**, *139*, 6106.

(13) (a) Rathman, T. L.; Schwindeman, J. A. *Org. Process Res. Dev.* **2014**, *18*, 1192. (b) Okano, K. *Yuki Gosei Kagaku Kyokaishi* **2017**, *75*, 364.

(14) No reaction occurred when diphenylacetylene was applied under the standard conditions.

(15) (a) Romeo, R.; Wozniak, L. A.; Chatgilialoglu, C. *Tetrahedron Lett.* **2000**, *41*, 9899. (b) Kondoh, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 6996.

(16) The hydrogenation of the corresponding sulfide **3aa-S** did not occur under identical conditions using $Pd(OH)_2/C$.

(17) Actually, we could not detect the alkynylphosphine during the reaction of **1a** with **2a** in THF-d_8 by ^{31}P{^{1}H} NMR analysis.

(18) Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1544372). See the Supporting Information for details.

(19) Even under more forceful conditions (THF, 60 °C), the LiO-*t*-Bu-mediated reaction of phenylacetylene (**1a**) with tetracyclohexyldiphosphane $Cy_2P–PCy_2$ formed the desired diphosphinated product in only 15% ^{31}P{^{1}H} NMR yield.

(20) We observed no remarkable change of ^{31}P{^{1}H} NMR signals of diphosphanes (**2a** and **2b**) even upon treatment with LiO-*t*-Bu in THF-d_8. Thus, base-promoted phosphorus scrambling is unlikely. See the Supporting Information for details.

(21) See the Supporting Information for the detailed mechanistic scheme.

(22) Unfortunately, we could not observe the intermediate **7** in ^{31}P NMR analysis. Additionally, the addition of TEMPO and galvinoxyl completely shut down the reaction. Thus, we cannot exclude the possibility of the radical pathway.

DOI: 10.1021/acs.orglett.7b01209
Org. Lett. XXXX, XXX, XXX–XXX