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Phosphoryl Azides as Versatile New Reaction Partners in the Cu-Catalyzed Three-Component Couplings

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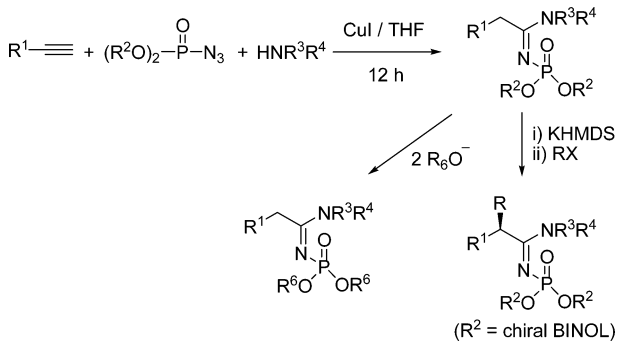

Phosphoryl azide was successfully employed as an efficient reacting partner in the Cu-catalyzed three-component reaction with 1-alkynes and amines to produce the corresponding phosphoryl amidines in high yields. A range of fruitful applicability of the produced amidines was also demonstrated such as an alkoxide exchange and asymmetric α-alkylation of optically active BINOL-derived amidines.

Since the introduction of organic azides by Griess,[1] extensive investigation on those compounds has been carried out to develop synthetically important transformations such as cycloaddition,[2] nitrene transfer,[3] Schmidt reactions,[4] etc.[5] In particular, the Cu-catalyzed cycloaddition of alkyl or aryl azides with 1-alkynes has dramatically broadened the scope and utility of azides.[6] We have, in more recent years, explored the synthetic utility of sulfonyl azides in the Cu-catalyzed three-component reactions of 1-alkynes with amines, alcohols, or water leading to *N*-sulfonyl amidines, imidates, and amides, respectively.[7,8]

The developed three-component coupling is believed to proceed via three stages: copper-catalyzed cycloaddition between sulfonyl azides and alkynes to afford triazole species, rearrangement of the cyclic compounds to form ketenimine intermediates upon release of nitrogen, and then subsequent addition of heteroatomic moieties leading to the *N*-sulfonimino products.[9]

During the course of investigating the scope of azide components, we were much interested in the utility of phosphoryl azides since the produced *N*-phosphorylated moiety is more labile than the *N*-sulfonylated moiety.[10] In addition, it was envisioned that the prospective products, phosphoryl amidines, were highly versatile because they were already known to have interesting bioactivities such as oncolytic activity.[11] In addition, a phosphoramidic acid has been used as a prodrug for inhibition of D-alanine.[12] Therefore, we envisaged that the *N*-phosphorylimino group would expand significantly the utility of amidine chemistry.

Herein, we disclose the results of utilizing phosphoryl azides in the Cu-catalyzed three-component reaction with terminal alkynes and amines. Subsequent synthetic applications of the obtained phosphoryl amidines also will be described.

We initially examined the feasibility of a range of phosphoryl azides[13] in the CuI-catalyzed reaction with phenylacetylene and diisopropylamine (Table 1). Reactions with phosphoryl azides derived from aliphatic alcohols were sluggish regardless of their structural variations, thus leading to poor yields under ambient conditions (entries 1 and 2). In sharp contrast, diphenylphosphoryl azide (DPPA) participated in the coupling reaction with excellent efficiency to afford the corresponding *N*-phophoryl amidine in 90% yield (entry 3). Electronic variation on the phenoxy substituent turned out to affect significantly the reaction efficiency as demonstrated in entry 4. Notably, an azide prepared from BINOL readily underwent the coupling reaction in high yield (entry 5). It should be mentioned that the low efficiency encountered in the reaction with *N*-alkylphosphoryl azides could be circumvented by an exchange reaction of *N*-arylphosphoryl amidines with alkoxides (vide infra).

Under the optimized conditions, the reaction scope was subsequently examined by using DPPA as a representative azide

(1) Griess, P. *Philos. Trans. R. Soc. London* **1864**, *154*, 667.
(2) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565.
(3) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889.
(4) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965.
(5) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
(6) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (c) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.
(7) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038. (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (c) Chang, S.; Lee, M.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366. (d) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347. (e) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1897.
(8) For some related reports from other groups, see: (a) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154. (b) Cui, S.-L.; Lin, X.-F.; Wang, Y.-G. *Org. Lett.* **2006**, *8*, 4517. (c) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585. (d) Jin, Y.; Fu, H.; Yin, Y.; Jiang, Y.; Zhao, Y. *Synlett* **2007**, 901.
(9) (a) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154. (b) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730.
(10) (a) Shioiri, T.; Kawai, N. *J. Org. Chem.* **1978**, *14*, 2936. (b) Gao, G.-Y.; Jones, J. E.; Vyas, R.; Harden, J. D.; Zhang, X. P. *J. Org. Chem.* **2006**, *71*, 6655.
(11) Souza, M. C.; Macedo, W. P.; Silva, M. C. M.; Ramos, G. C.; Alt, H. G. *Phosphorus, Sulfur Silicon* **2004**, *179*, 1047.
(12) Chakravarty, P. K.; Greenlee, W. J.; Parsons, W. H.; Patchett, A. A.; Combs, P.; Roth, A.; Brusch, R. D.; Mellin, T. N. *J. Med. Chem.* **1989**, *32*, 1886.
(13) For preparation: Lee, H. W.; Guha, A. K.; Kim, C. K.; Lee, I. C. *J. Org. Chem.* **2002**, *67*, 2215.

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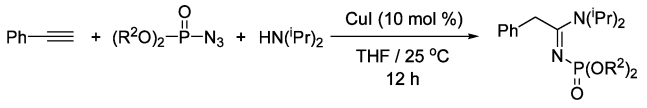
TABLE 1. Cu-Catalyzed Three-Component Coupling for the Formation of Amidines Testing Various Phosphoryl Azides[a]



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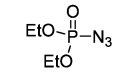
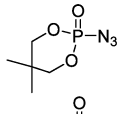
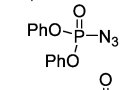
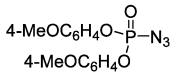
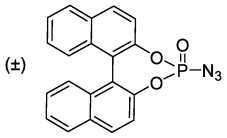
1		13
2		26
3		90
4		59
5		93[c]

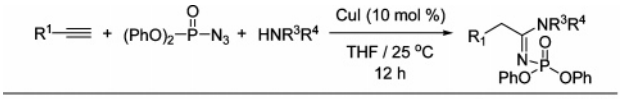
[a] A mixture of phenylacetylene (1.0 mmol), phosphoryl azide (0.5 mmol), diisopropylamine (0.75 mmol), and CuI (0.05 mmol) in THF (1 mL) was stirred at room temperature for 12 h. [b] Isolated yield. [c] CuI (0.15 mmol) was used.

(Table 2). A wide range of terminal alkynes were reacted all smoothly, and the corresponding *N*-phosphoryl amidines were obtained in good to excellent yields. Not only simple aliphatic alkynes but also substrates bearing certain functional groups readily participated in the reaction (entries 1−4). It should be noted that steric bulk around the triple bond of alkyne has little influence on the reaction efficiency as demonstrated in entry 4. Conjugated enynes turned out to be another viable substrate type for this transformation (entry 5). With aryl alkynes, electronic variation on the aromatic moiety did not affect the reaction efficacy (entries 6−8). Among heterocyclic alkynes examined, while the 3-thienyl group was tolerant under the conditions, the 2-pyridyl group displayed a deteriorating effect (entries 9 and 10, respectively).

Functionalized alkynes such as methyl propargylate or silylacetylene were smoothly reacted with DPPA and diisopropylamine to afford the corresponding substituted amidines in good yields (entries 11 and 12, respectively). In addition, bisphosphoryl amidines could be produced by the reaction of 1,*n*-dialkynyl substrates (entry 13). The scope of the amine counterpart also turned out to be broad, and various primary and secondary amines were readily employed with high efficiency (entries 14 and 15).

As mentioned above (Table 1), the scope of phosphoryl azides was relatively limited, and only aryl derivatives were effectively employed for satisfactory results. This limitation for the formation of *N*-alkylphosphoryl amidines was circumvented by an alkoxide exchange process (Table 3). With the use of stoichiometric amounts of alkali metal alkoxides, the facile exchange with the phosphoryl moiety could be easily achieved. Treatment of *N*-diphenyl phosphoryl amidine with sodium methoxide, lithium isopropoxide, or potassium *tert*-butoxide resulted in a clean substitution of phenoxy with alkoxides leading to *N*-dialkyl phosphoryl amidines in high yields (entries 1−3).

TABLE 2. Scope of Amidine Reaction with DPPA[a]



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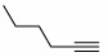
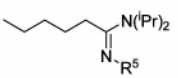
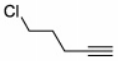
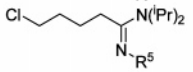
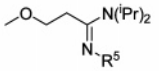
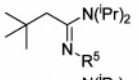
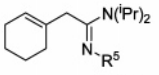
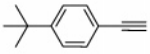
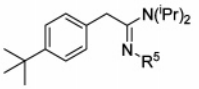
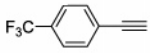
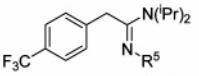
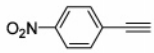
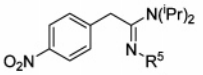
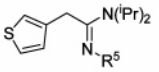
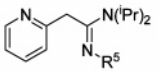
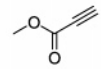
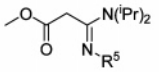
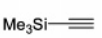
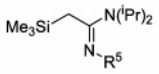
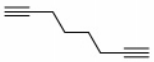
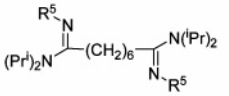
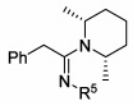
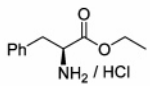
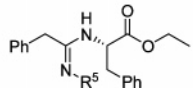
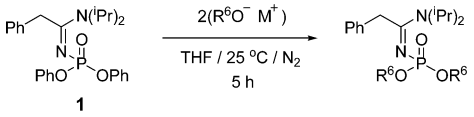
1				68
2				85
3				92
4				87
5				72
6				78
7				97
8				99
9				92
10				38[d]
11				80
12				80
13				53[e]
14				77
15				62[f]

[a] A mixture of alkyne (1.0 mmol), DPPA (0.5 mmol), amine (0.75 mmol), and CuI (0.05 mmol) in THF (1 mL) was stirred at 25 °C for 12 h. [b] R^5: $(PhO)_2P(O)-$. [c] Isolated yield. [d] CuI (0.15 mmol) was used. [e] Alkyne (0.5 mmol), DPPA (1.0 mmol), CuI (0.1 mmol), and amine (1.0 mmol) were used. [f] Alkyne (0.5 mmol), DPPA (0.6 mmol), and amine (0.53 mmol) were reacted under 60 °C with triethylamine (0.75 mmol).

We next turned our attention to optically active *N*-phosphoryl amidines and their synthetic utilities. Considering that binaphthol has been most widely used as an excellent chiral auxiliary,[14] a chiral phosphoryl azide bearing the diol was prepared by the reaction of (*S*)-1,1′-bi(2-naphthol) with phosphorus oxychloride

(14) For a recent review on the utility of BINOL, see: Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857.

TABLE 3. Exchange of Phenoxy Group with Aliphatic Alcohols[a]

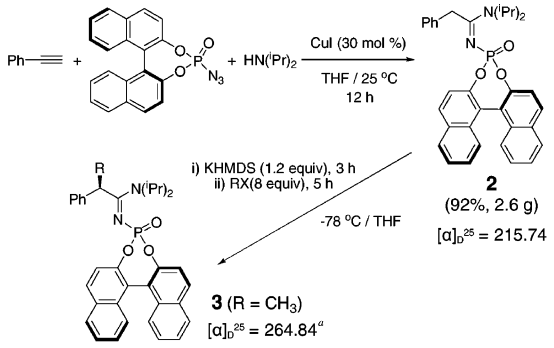


1

entry	alkoxide	yield (%)[b]
1	MeO^-Na^+	88
2	$^iPrO^-Li^+$	99[c]
3	$^tBuO^-K^+$	82

[a] Alkoxide (3.0 mmol) and **1** (0.5 mmol) in THF (3 mL). [b] Isolated yield. [c] Run at 60 °C.

SCHEME 1. Amidine Synthesis with Chiral Binaphthol Azide and Subsequent Alkylation at the α-Position of the Amidine



entry[b]	RX	yield (%)[c]	*dr*[d]
1	CH_3I	80	9:1
2	CH_2=$CHCH_2Br$	74[e]	6:1
3	$PhCH_2Br$	78[e]	4:1

[a] For the isolated major isomer **3**. [b] **2** (0.1 mmol), KHMDS (0.12 mmol), RX (0.8 mmol) in THF (1 mL). [c] Isolated yield. [d] Diastereomeric ratio was determined by both ^{1}H NMR and HPLC (see the Supporting Information). [e] Isolated yield of a mixture of two diastereomers.

and sodium azide.[15] We were pleased to observe that the chiral phosphoryl azide readily underwent the Cu-catalyzed three-component reaction even in a gram scale with high yield (Scheme 1). Optical purity of the produced BINOL moiety was observed to maintain completely without any racemization during the three-component reaction.

The synthetic utility of the chiral *N*-phosphoryl amidine **2** was subsequently investigated in the stereoselective α-alkylation reactions.[16] As anticipated, the alkylation proceeded in a diastereoselective manner, the extent of which turned out to be varied depending on the type of electrophiles employed. For example, α-methylation took place by the reaction of **2** with iodomethane using KHMDS at −78 °C in good yield, and the diastereoselectivity of the crude product mixture was determined to be 9:1 by HPLC and ^{1}H NMR.[17]

The structure of α-methylated amidine **3** was determined unambiguously by an X-ray diffraction analysis of a single crystal. The diastereoselectivity was not further increased even when the reaction was carried out at lower temperature (e.g., −100 °C). On the other hand, allylation and benzylation of **2** was less stereoselective compared to that of methylation under otherwise identical conditions, resulting in the diastereomeric ratio of 6:1 and 4:1, respectively (entries 2 and 3).

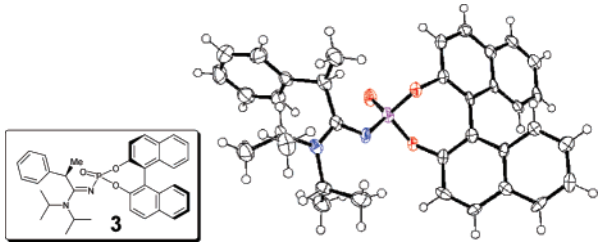


FIGURE 1. ORTEP of an α-methylated amidine **3**.

From the structural analysis of the obtained isomeric products, we postulate that 6-membered transition states inducing steric differentiation between the BINOL and diisopropyl amino group are one of the possible reasons for the stereoselectivity shown above.

In conclusion, phosphoryl azides have now been listed as new and efficient reacting partners in the Cu-catalyzed three-component coupling reactions with 1-alkynes and amines. The fruitful utilization of phosphoryl azides has allowed us to demonstrate the synthetic usefulness of those compounds, thus expanding the scope of multicomponent chemistry, even including an asymmetric version.

Experimental Section

General Procedure of Amidine Synthesis. To a stirred mixture of azide (0.5 mmol), alkyne (1 mmol), and CuI (0.05 mmol) in THF (1 mL) was slowly added an amine reactant (0.75 mmol) at room temperature under N_2 atmosphere. After the conversion was completed, which was monitored with TLC, the reaction mixture was diluted by adding CH_2Cl_2 (3 mL) and aqueous NH_4Cl solution (3 mL). The mixture was stirred for an additional 30 min and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatograph with an appropriate eluting solvent system.

***N*^{1},*N*^{1}-Diisopropyl-*N*^{2}-(diphenylphosphoryl)-2-enylacetamidine (Table 1, entry 3):** White solid; mp 95−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.16 (m, 13H), 7.05 (t, J = 6.9 Hz, 2H), 4.27 (s, 2H), 3.97−3.91 (m, 1H), 3.34 (br, 1H), 1.20 (d, J = 6.8 Hz, 6H), 0.84 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 166.0, 151.9, 151.8, 135.3, 129.2, 128.7, 127.8, 126.6, 123.9, 120.5, 120.4, 50.7, 47.6, 41.6, 41.5, 19.8, 19.4; IR (NaCl) ν 2969, 2933, 1566, 1488, 1380, 1224, 1130, 1066, 916 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{26}H_{31}N_2O_3P$ $[M]^+$ 451.2072, found 451.2079.

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Supporting Information Available: Experimental details plus spectral data and copies of ^{1}H and ^{13}C NMR spectra for new compounds and crystallographic data of **3** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) An, J.; Wilson, J. M.; An, Y. Z.; Wiemer, D. F. *J. Org. Chem.* **1996**, *12*, 4040.

(16) Asymmetric alkylation on *N*′-*tert*-butanesulfinyl amidines: Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652.

(17) See the Supporting Information for details.