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Transient Protection of Organic Azides from Click Reactions with Alkynes by Phosphazide Formation

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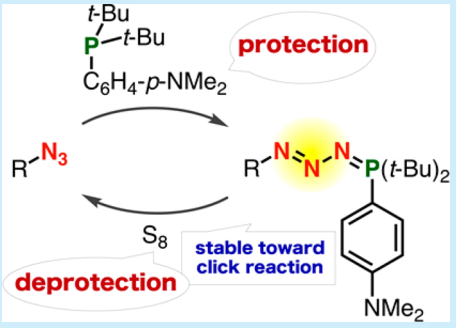
Supporting Information

ABSTRACT: A method for protecting organic azides from click reactions with alkynes is reported. Treatment of azides with Amphos affords phosphazides, which are stable under click reaction conditions and are easily converted back to azides by treatment with elemental sulfur. Thus, the method allows for facile modification of azide compounds via site-selective click reactions.



Organic azides are widely used as pharmaceutical drugs and versatile synthetic intermediates for nitrogen-containing compounds.[1] Moreover, the utility of azides has expanded enormously with the rise of click chemistry methodologies such as copper-catalyzed azide−alkyne cycloaddition (CuAAC)[2] and strain-promoted azide−alkyne cycloaddition (SPAAC).[3] These reactions present reliable and convenient methods for molecular conjugation and have been applied in a broad range of disciplines, including materials sciences and chemical biology.[4]

With the growing availability of these click reactions, the demand for functionalized azides and strained alkynes have also increased. However, these functionalized molecules are difficult to prepare straightforwardly by click reactions, because click conjugation in the presence of other clickable groups with higher reactivity is difficult to achieve selectively.[5−7] In this context, we recently developed a facile method for protecting strained alkynes from the SPAAC reaction with azides by complexation with a cationic copper salt (Figure 1A).[8] This method enabled selective CuAAC conjugation at the terminal alkyne moiety of diyne **1** to afford triazole **2**, leaving the strained alkyne moiety with higher azidophilicity untouched. To expand this concept, we have developed a protection method for azides.

Normally, an SPAAC reaction between a diazide compound and a cyclooctyne derivative affords a mixture of cycloadducts, particularly when the two azido groups in the diazide have similar ynophilicities (Figure 1B). Furthermore, although there are several reports on azido-type selective triazole formation using multiazides, the azido groups are consumed in the order of their reactivity, and leaving the most ynophilic azido group unchanged is difficult.[9] We reasoned that site-selective protection of an azido group would enable site-selective click

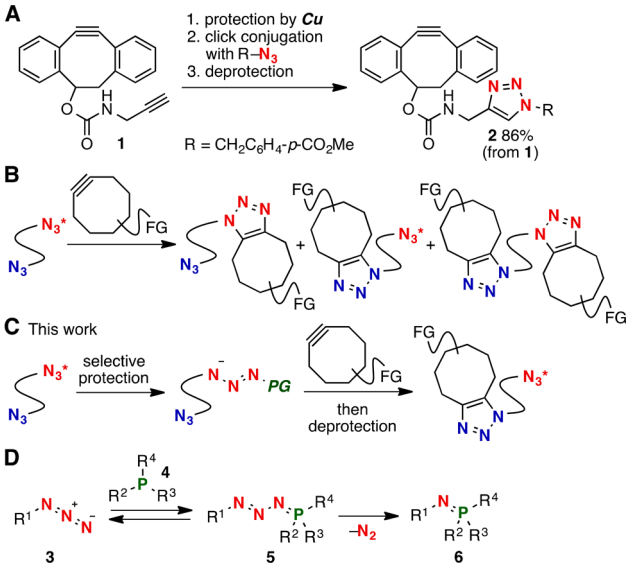


Figure 1. Backgrounds and basic concept of this work: (A) our previous work, (B) typical reaction of a diazide compound with a strained alkyne, (C) concept of this work, and (D) equilibrium generation of phosphazide **5** from azide **3** and phosphine **4** and the formation of aza-ylide **6**.

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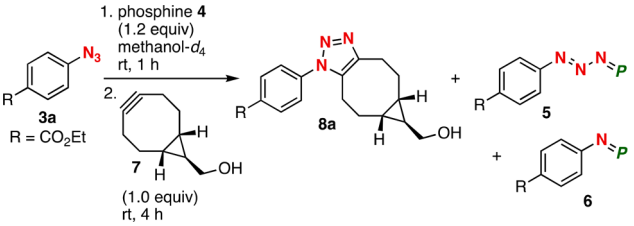
Table 1. Screening of Phosphines for Preventing the SPAAC Reaction between Azide 3a and Cyclooctyne 7



entry	phosphine	4	8a[a] (%)	5[a] (%)	6[a] (%)
1	none		98[b]		
2	PPh_3	**4a**	0	**5a**, 0	**6a**, 93
3	$P(n\text{-Bu})_3$	**4b**	0	**5b**, 0	**6b**, 0
4	$P(c\text{-Hex})_3$	**4c**[c]	14	**5c**, 86	**6c**, 0
5	$P(t\text{-Bu})_3$	**4d**[d]	8	**5d**, 91	**6d**, 0
6	$Ph_2P(t\text{-Bu})$	**4e**	33	**5e**, 16	**6e**, 51
7	$PhP(t\text{-Bu})_2$	**4f**	15	**5f**, 85	**6f**, 0
8	4-F_3C−$C_6H_4P(t\text{-Bu})_2$	**4g**	56	**5g**, 44	**6g**, 0
9	4-Me_2N−$C_6H_4P(t\text{-Bu})_2$ (Amphos)	**4h**	0	**5h**, quant	**6h**, 0
10	$P(NMe_2)_3$	**4i**	0	**5i**, quant	**6i**, 0

[a]Yields based on ^{1}H NMR analysis, unless otherwise noted. [b]Isolated yield. [c]Toluene solution (20 wt %) was used. [d]Hexanes solution (10 wt %) was used.

conjugation of diazide compounds (Figure 1C). To realize this simple, but challenging, idea, we focused on equilibrium generation of phosphazide **5** from azide **3** and phosphine **4** (Figure 1D).[10] In the course of our previous study on azido-type selective reduction by the Staudinger reaction, we found that aromatic azides react smoothly with various phosphines to afford aza-ylides or phosphazides, depending on the phosphine used.[10m,o] A literature survey also indicated the equilibrium generation of bulky phosphazides,[10h] prompting us to search for a suitable phosphine that forms stable, yet reversible, phosphazides upon the reaction with various azides.

An extensive screening revealed that bulky and electron-rich phosphines efficiently prevented the SPAAC reaction between aromatic azide **3a** and cyclooctyne **7** (see Table 1). Without phosphine, **3a** reacted quantitatively with **7** in methanol-d_4 to afford triazole **8a** (Table 1, entry 1). By pretreating **3a** with a phosphine for 1 h, the yield of **8a** decreased, depending on the type of phosphine employed (Table 1, entries 2−10). Although cycloadduct **8a** was not formed by the pretreatment of **3a** with triphenylphosphine or tri(*n*-butyl)phosphine, aza-ylide **6a** and a complex mixture of products, respectively, were obtained instead, indicating that these phosphines are unsuitable for our purposes (Table 1, entries 2 and 3). In contrast, the use of bulky phosphine **4c** or **4d** afforded phosphazide **5c** or **5d**, respectively, in high yields, while a small amount of **8a** was also obtained in these cases (Table 1, entries 4 and 5). To achieve efficient phosphazide formation without the formation of **8a**, several other bulky phosphines were examined (Table 1, entries 6−9). While a significant amount of aza-ylide **6e** was obtained when *tert*-butyl(diphenyl)phosphine (**4e**) was used (Table 1, entry 6), treatment of **3a** with di(*tert*-butyl)phenylphosphine (**4f**) afforded phosphazide **5f** in high yield (Table 1, entry 7). Although the corresponding aza-ylide **6f** was not formed in this case, a small amount of **8a** was obtained. Therefore, the effect of the substituent on the phenyl group of **4f** was examined. While the efficiency for phosphazide formation decreased upon using the more electron-deficient phosphine **4g**, bearing a 4-(trifluoromethyl)phenyl group (Table 1, entry 8), quantitative phosphazide formation was achieved using the more electron-rich phosphine, Amphos (**4h**), bearing a 4-(dimethylamino)phenyl group (Table 1, entry 9). In addition, the reaction between **3a** and hexamethylphosphorous triamide (**4i**) also afforded phosphazide **5i** quantitatively without formation of **8a** (Table 1, entry 10).

A control experiment clearly demonstrated that the electron-donating dimethylamino group of Amphos (**4h**) significantly facilitates the formation of phosphazide **5h** (see Figure 2).

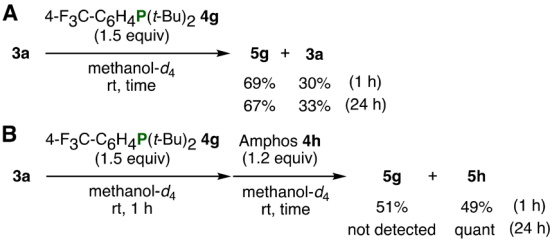


Figure 2. Control experiment: (A) preparation of an equilibrated mixture of azide **3a** and phosphazide **5g**; (B) time-dependent formation of phosphazide **5h** from a mixture of **5g** and **3a** by treatment with phosphine **4h**.

Treatment of an equilibrated mixture of azide **3a** and phosphazide **5g** in methanol-d_4 (Figure 2A) with **4h** resulted in the time-dependent conversion of phosphazide **5g** to **5h**, allowing complete conversion within 24 h (Figure 2B).

The inertness of phosphazide **5h** was demonstrated under various conditions. It was not only unreactive with a strained alkyne, but also stable toward air, moisture, basic conditions, and several amino acids. Furthermore, phosphazide **5h** could be purified by recrystallization, demonstrating that it is kinetically stable at room temperature. Thus, treatment of azide **3a** with Amphos (**4h**) (1.1 equiv) in methanol for 1 h, followed by the removal of methanol and recrystallization from *n*-hexane and ethyl acetate afforded phosphazide **5h** in an excellent yield. In addition, the s-*trans* structure of **5h** was confirmed by X-ray crystallographic analysis of a fine crystal obtained by recrystallization from methanol (see Figure 3).

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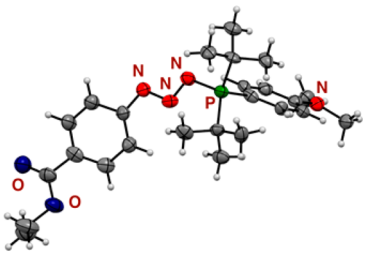


Figure 3. X-ray crystal structure of phosphazide **5h**.

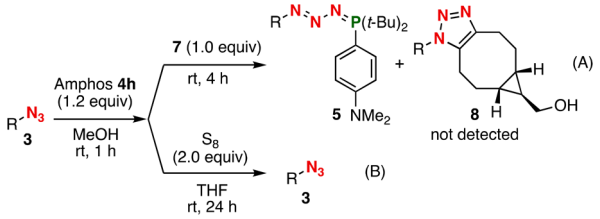
The regeneration of azide **3a** from phosphazide **5h** was efficiently and easily achieved using an oxidant, demonstrating the ability of this system to serve as a protection method. After extensive screening for an effective oxidant that reacts with phosphazide **5h** or regenerates phosphine **4h** at room temperature, we found that treatment of **5h** in THF with elemental sulfur (S_8) regenerates azide **3a** in an excellent yield (see Table 2, entry 6). Conversely, an attempt to regenerate **3a** from phosphazide **5i** under the same conditions was unsuccessful, indicating that hexamethylphosphorous triamide (**4i**) is unsuitable for protecting azides (Table 2, entry 7).

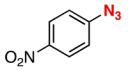
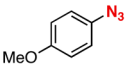
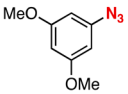
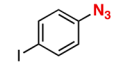
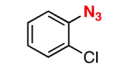
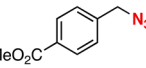
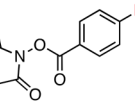
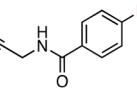
A wide range of azides could be protected completely from the SPAAC reaction with cyclooctyne **7** by the phosphazide formation with Amphos (**4h**) (Table 3, column A) and regenerated efficiently by the treatment with S_8 (Table 3, column B). These include electron-deficient and electron-rich aromatic azides **3b**–**f** bearing nitro, methoxy, iodo, or chloro groups at the *para*-, *meta*-, or *ortho*-positions (Table 3, entries 1–5). Aliphatic azide **3g** was also protectable, expanding the scope of this method (Table 3, entry 6). Notably, the azido groups in *N*-succinimidyl ester **3h** and propargyl amide **3i** were also rendered unclickable by treating with **4h** and could be regenerated leaving the reactive functional groups untouched (Table 3, entries 7 and 8).

Using the protection method developed in this study, formal aliphatic azido-selective click reactions of diazide **9**[11] were achieved (Scheme 1). Thus, treatment of **9** with an equimolar amount of **4h** resulted in a selective phosphazide formation at the aromatic azido group to afford monoazide **10**. The phosphazide formation at the aromatic azido group of diazide **9** was favored more than that at the aliphatic azido group, because the former phosphazide is more stabilized through the direct resonance with the benzene ring. A similar aromatic azido selectivity was observed in the Staudinger reduction.[10m] Subsequent SPAAC reaction of **10** with cyclooctyne **7** and removal of Amphos using S_8 efficiently afforded aromatic azide **11** in a one-pot manner.[12] Similarly, the aromatic azido group of diazide **9** was also protected from the CuAAC reaction with a terminal alkyne. Thus, phosphazide formation with **4h**, CuAAC reaction with **12**, removal of the copper salt by aqueous ammonia solution, and treatment with S_8 afforded aromatic azide **13** in a high overall yield.[12]

The preferential phosphazide formation at the aromatic azido group allowed for facile synthesis of a branched

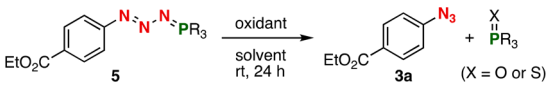
Table 3. Protection and Regeneration of Various Azides



entry	azide	3	(A) yield of **5** (%)[a]	(B) yield of recovered **3** (%)[b]
1		**3b**	**5j**, 96	92
2		**3c**	**5k**, quant	85
3		**3d**	**5l**, quant	80
4		**3e**	**5m**, quant	81
5		**3f**	**5n**, 99	84
6		**3g**	**5o**, quant	92
7[c]		**3h**	**5p**, quant	99
8		**3i**	**5q**, quant	quant

[a]Yields based on ^{1}H NMR analysis. [b]Isolated yield. [c]CH_2Cl_2 was used instead of MeOH as a solvent.

Table 2. Oxidative Regeneration of Azide 3a from Phosphazides 5



entry	PR_3	5	oxidant, solvent	yield of **3a**[a] (%)
1	Amphos	**5h**	$NaIO_4$ (2.0 equiv), THF/H_2O	42
2	Amphos	**5h**	*m*CPBA (2.0 equiv), CH_2Cl_2	10
3	Amphos	**5h**	$(PhCO_2)_2$ (2.0 equiv), CH_2Cl_2	58
4	Amphos	**5h**	DDQ (2.0 equiv), CH_2Cl_2/H_2O	0
5	Amphos	**5h**	NBS (2.0 equiv), CH_2Cl_2	90
6	Amphos	**5h**	S_8 (2.0 equiv), THF	99 (91)[b]
7	$P(NMe_2)_3$	**5i**	S_8 (10 equiv), THF	0

[a]Yields based on ^{1}H NMR analysis, unless otherwise noted. [b]Isolated yield in parentheses.

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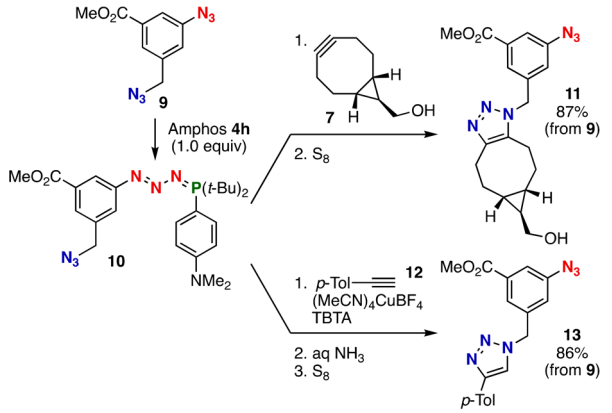
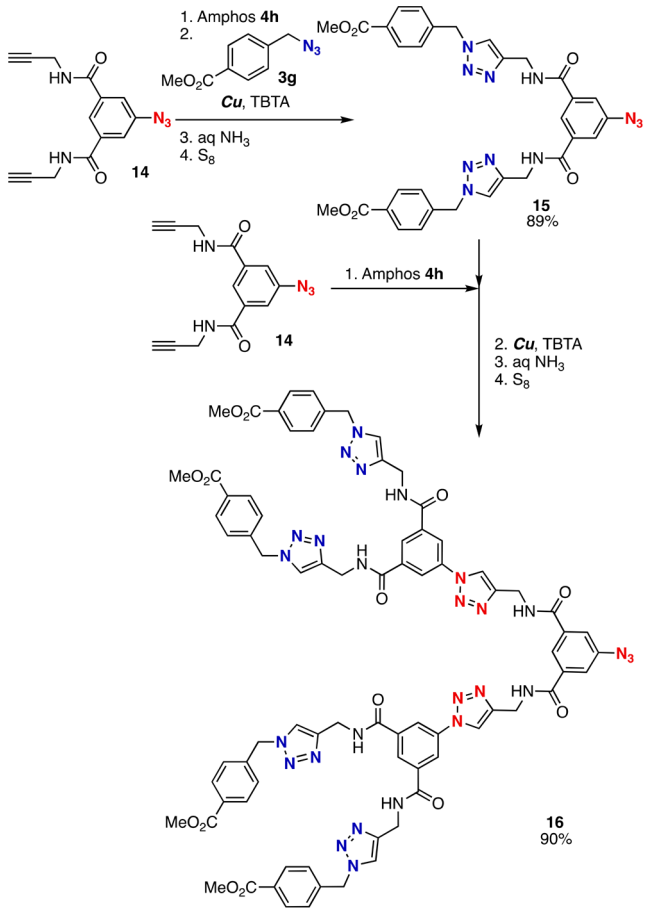
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 1. Aliphatic Azido-selective Click Reactions of Diazide 9 via Transient Protection of the Aromatic Azido Group



multitriazole oligomer[13] via an iterative site-selective CuAAC reaction using aromatic azide **14** bearing two propargyl groups (see Scheme 2). Thus, pretreatment of **14** with **4h** and subsequent CuAAC reaction with benzyl azide **3g**, followed by removal of the transient protective group afforded bistriazole **15** with the regenerated azido group in high yield. The second-generation CuAAC reaction of azide **15** with the same phosphazide prepared from **14** and **4h** also proceeded efficiently to afford hexakis(triazole) **16** without formation of undesired products.

Scheme 2. Sequential Site-selective CuAAC Reactions via Transient Protection of Azides



In summary, we have developed a convenient method to protect organic azides from click reactions with alkynes by phosphazide formation. A wide range of azides can be transiently protected by this method. The phophazides formed tolerated CuAAC and SPAAC reactions and are easily converted back to azides, enabling facile modification of azide compounds by click reactions leaving the azido group untouched. Further studies on the scope of protectable azides and application of the method to the preparation of functional azides are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01692.

Experimental procedures and characterization for new compounds, including copies of NMR spectra (PDF)

Accession Codes

CCDC 1844604 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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