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Triazole formation of phosphinyl alkynes with azides through transient protection of phosphine by copper †

Norikazu Terashima, Yuki Sakata, Tomohiro Meguro, Takamitsu Hosoya, and Suguru Yoshida*

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An efficient preparation method of functionalized phosphines by copper-catalyzed azide–alkyne cycloaddition (CuAAC) through the transient protection of phosphine from the Staudinger reaction is disclosed. Diverse phosphines were prepared from phosphinyl alkynes and azides by the click reaction at the ethynyl group without damaging the phosphinyl group. Double- and triple-click assemblies of azides were accomplished by triazole formations and robust azaylide formation.

Click chemistry has played significant roles to prepare functional molecules in a broad range of research fields such as materials chemistry, pharmaceutical chemistry, and chemical biology.[1–6] Various click reactions including copper-catalyzed azide–alkyne cycloaddition (CuAAC)[2] and strain-promoted azide–alkyne cycloaddition (SPAAC)[3] have been developed so far for efficient conjugations of molecules.[4,5] On the basis of emerging click reactions, a number of methods to assemble modules using trivalent platforms have been gained attention.[6] We herein disclose a method assembling azides onto a newly designed trivalent platform molecule through the CuAAC reaction of phosphinyl alkynes with azides via transient protection of phosphine from Staudinger reaction by the treatment with copper.

Recently, our group[7] and Ramström and Yan's group[8] independently reported rapid Staudinger reactions forming azaylides with good stability (Figures 1A and 1B).[9] For example, we found that 2,6-dichlorophenyl azides spontaneously react with triphenylphosphine derivatives to furnish robust azaylides (Figure 1A). Of note, this rapid Staudinger reaction realized efficient chemical modification inside cells, while SPAAC reactions inside cells are not always easy due to the instability of cyclooctynes inside cells.[10] Ramström, Yan, and coworkers also reported a Staudinger reaction between perfluoroaryl azides and phosphines affording stable azaylides (Figure 1B). Since these biocompatible reactions enable facile chemical modification of biomolecules, an efficient method to synthesize a wide variety of functionalized phosphines will serve in the modification of functionalized 2,6-dichlorophenyl or perfluorophenyl azide derivatives.

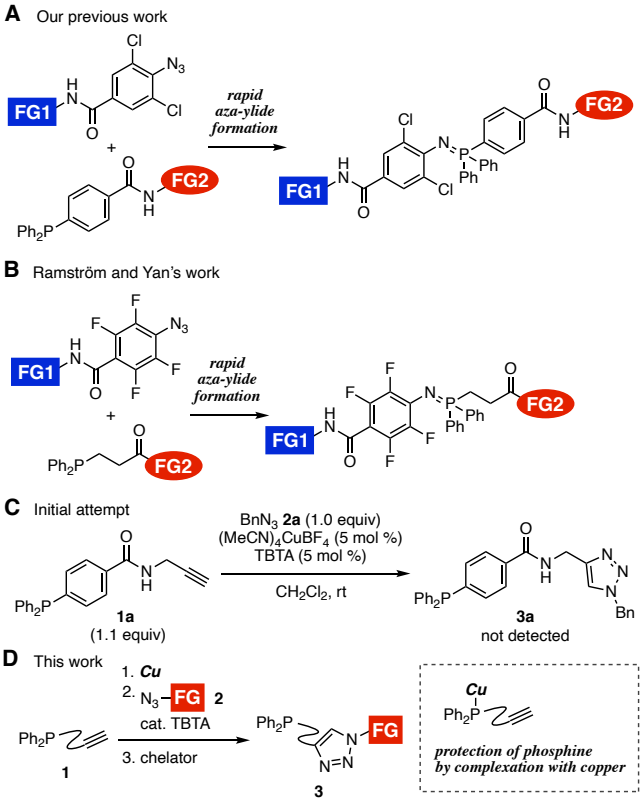

Fig. 1 Background of this study. (A) Our previous study. (B) Ramström and Yan's work. (C) Initial attempt. (D) This work. TBTA = tris(benzyltriazolylmethyl)amine.

We at first assumed that a CuAAC reaction of phosphinyl alkynes with azides realizes the efficient preparation of functionalized phosphines, which can react rapidly with

Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan. E-mail: s-yoshida.cb@tmd.ac.jp

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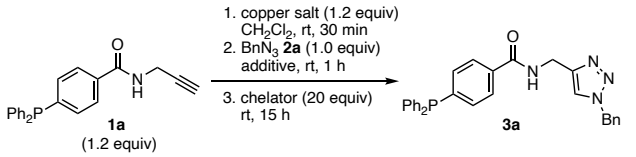
electron-deficient azides.[11,12] However, an attempt using phosphinyl alkyne **1a** with azide **2a** in the presence of copper catalysis resulted in failure due to the Staudinger reaction at the phosphinyl group (Figure 1C). Considering our recent success on the protection of cyclooctynes,[13] we then conceived an idea to achieve the facile synthesis of triazole **3a** from phosphinyl alkyne **1** under mild conditions (Figure 1D). The idea was that pretreatment of phosphinyl alkyne **1** with copper for the protection from the Staudinger reaction followed by CuAAC reaction with azides **2** and removal of copper salt will enable the selective triazole formation.

Table 1 Optimization of the reaction conditions



entry	copper salt	additive	chelator	yield/%
1	$(CH_3CN)_4CuBF_4$	TBTA (5 mol %)	aq. EDTA·2Na	12
2	$(CH_3CN)_4CuBF_4$	TBTA (5 mol %)	aq. NTA·2Na	23
3	$(CH_3CN)_4CuBF_4$	TBTA (5 mol %)	aq. DTPA·5Na	84
4	$(CH_3CN)_4CuBF_4$	TBTA (5 mol %)	PS-TPP	3
5	$(CH_3CN)_4CuBF_4$	TBTA (5 mol %)	SiliaMetS Thiourea	34
6	$(CH_3CN)_4CuBF_4$	TBTA (5 mol %)	SiliaMetS Triamine	91
7	$CuSO_4·5H_2O$	Na asocorbate	aq. DTPA·5Na	n.d.
8[b]	CuI	*i*-Pr_2NEt (3.0 equiv)	aq. DTPA·5Na	17

EDTA·2Na = ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid disodium salt. EDTA·2Na = ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid disodium salt. NTA·2Na = nitrilotriacetate disodium salt. DTPA·5Na = diethylene triamine pentaacetic acid pentasodium salt

Efficient synthesis of triazole **3a** from phosphinyl alkyne **1a** and azide **2a** was accomplished by the protection of the phosphinyl group and CuAAC reaction both using a cationic copper salt, and following deprotection with a suitable chelator (Table 1). Firstly, the treatment of phosphinyl alkyne **1a** with $(CH_3CN)_4CuBF_4$ followed by the addition of azide and a catalytic amount of TBTA[2c] realized the desired CuAAC reaction with avoiding the Staudinger reaction as expected, although triazole **3a** was obtained in low yields by the subsequent removal of the copper with aqueous EDTA·2Na or NTA·2Na (entries 1 and 2). The use of aqueous DTPA·5Na as a chelator remarkably improved the yield of triazole **3a** (entry 3). Triazole **3a** was also obtained in high yield using SiliaMetS Triamine (entry 6), while the deprotection with other metal scavengers such as polystyrene-supported triphenylphosphine and SiliaMetS Thiourea resulted in low efficiencies (entries 4 and 5). In sharp contrast, the efficient triazole formation was not easy under other conditions for the CuAAC reaction using $CuSO_4·5H_2O$[2b] or copper iodide[2a] (entries 7 and 8).

A wide range of click-conjugated phosphines **3** were synthesized from phosphinyl alkyne **1a** and various azides (Figure 2). Electron-donating and -deficient aromatic azides smoothly reacted with **1a** to afford triazoles **3b** and **3c** in high yields without the azaylide formation. Bulky but highly reactive 2,6-dichlorophenyl and 2,6-diisopropylphenyl azides also participated in the alkyne-selective click reaction to provide triazoles **3d** and **3e**.[7,14] Triazole **3f** was successfully synthesized using picolyl azide through efficient CuAAC reaction and removal of the copper with aqueous DTPA·5Na. The preparation of functional phosphines **3g**–**3i** was achieved by the click reaction of phosphinyl alkyne **1a** with a variety of azides having functions such as biotin, HaloTag ligand, and poly(ethyleneoxy) moieties.

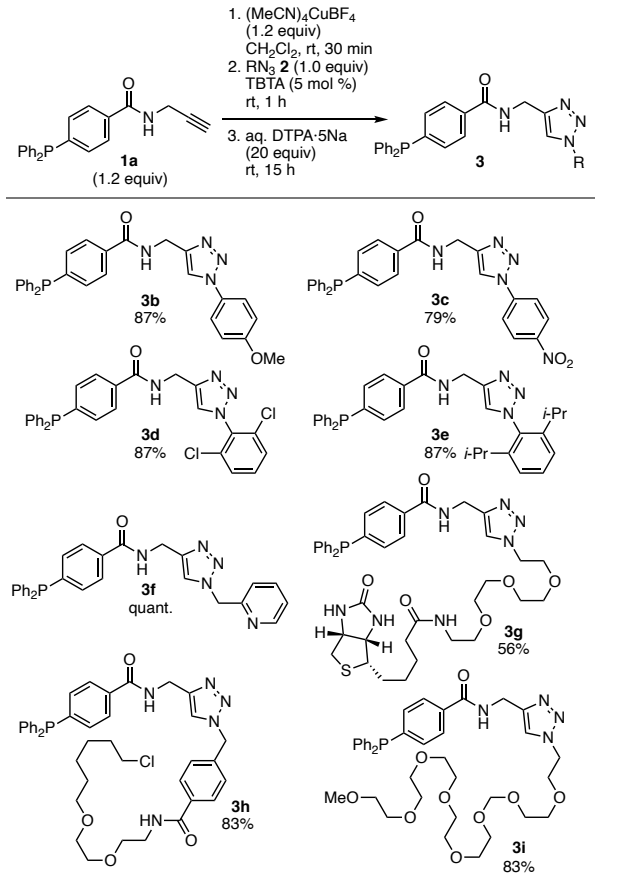


Fig. 2 Triazole formation using various azides.

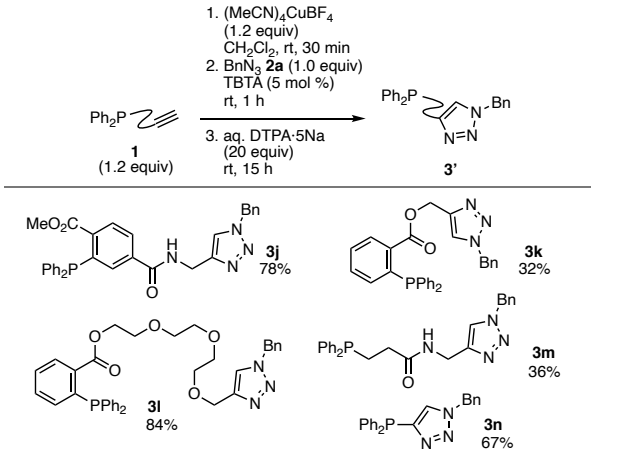


Fig. 3 Triazole formation using various alkynes.

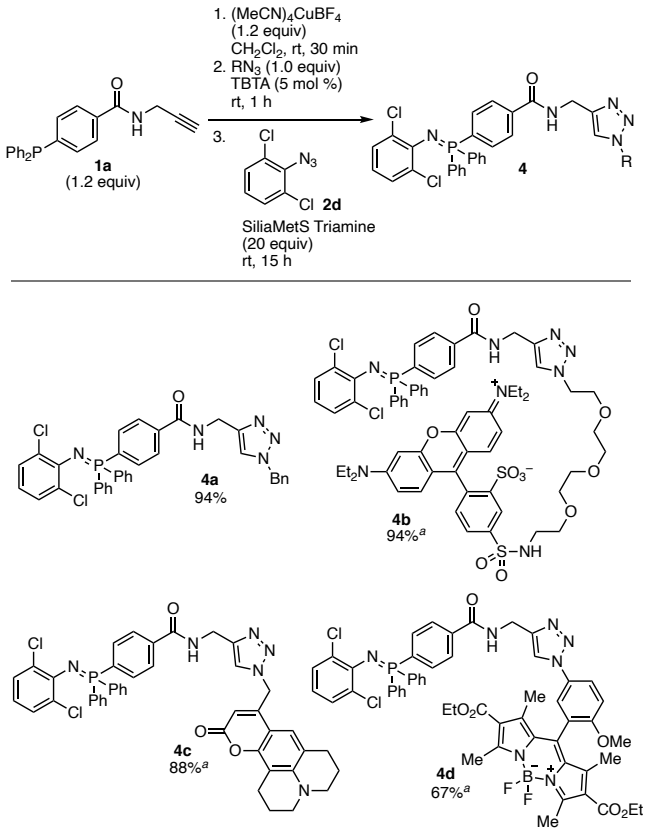


Fig. 4 Double-click conjugation using phosphinyl alkyne **1a**. [a]Azaylide formation with **2d** was performed after the removal of copper with aq. DTPA·5Na instead of SiliaMetS Triamine.

We succeeded in the facile preparation of click-conjugated phosphines **3** from a variety of alkynyl phosphines **1** (Figure 3). For example, the click conjugation enabled us to synthesize *ortho*-ester-substituted triarylphosphine **3j** in good yield, which will contribute to the Staudinger–Bertozzi ligation with alkyl azides.[15] Triazoles **3k** and **3l** were also prepared in moderate to high yields from the corresponding alkyne-substituted esters. It is worthy to note that the alkoxy group can be released by the Staudinger–Bertozzi ligation.[16] Alkyl(diaryl)phosphine **3m** was successfully synthesized by the click reaction at the ethynyl group without the formation of azaylide by virtue of the protection with copper. Ethynyl(diphenyl)phosphine participated in the CuAAC reaction to afford triazole **3n** leaving the phosphine moiety untouched through the complexation with copper.

Efficient double-click conjugation was realized by the CuAAC reaction of **1a** with diverse azides followed by the Staudinger reaction with 2,6-dichlorophenyl azide (**2d**) forming robust azaylides (Figure 4). For instance, after transient protection of phosphinyl alkyne **1a** with copper and following triazole formation with benzyl azide (**2a**), the addition of SiliaMetS triamine and azide **2d** resulted in the double-click conjugation to afford azaylide **4a** in high yield. Fluorescent azides bearing sulforhodamine, julolidine-fused coumarin, and BODIPY moieties smoothly reacted with phosphinyl alkyne **1a** to furnish fluorescent azaylides **4b**–**d** through the protection of diphenylphosphinyl group. Thus, the double-click conjugation through the CuAAC reaction and azaylide formation will serve in the fluorescent modification of azide-incorporated biomolecules with fluorescent azides and phosphinyl alkynes.

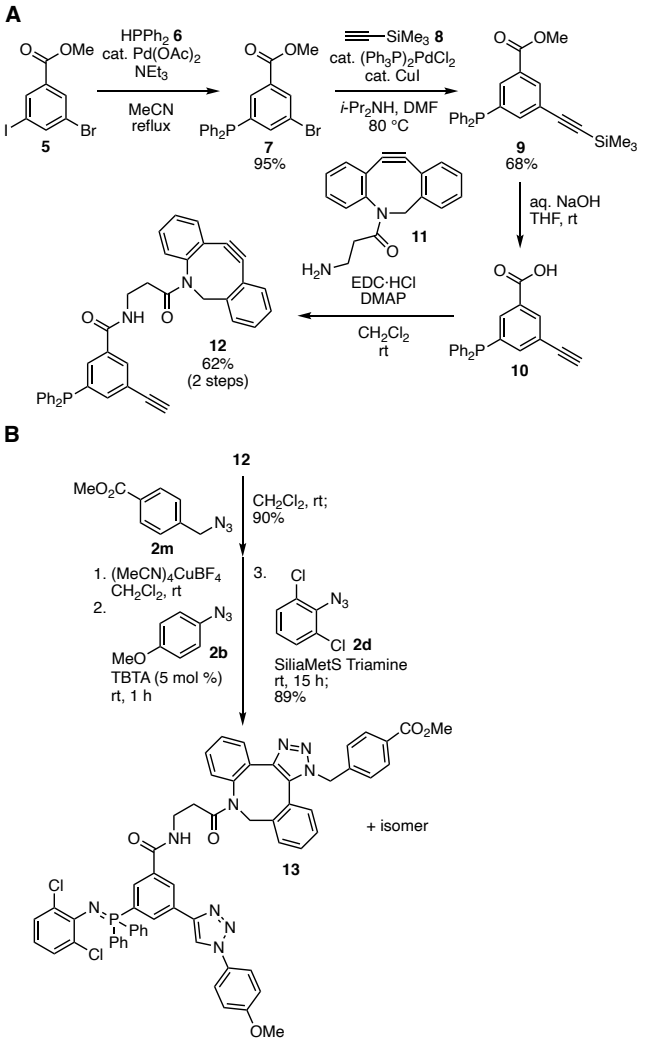


Fig. 5 Triple-click conjugation using **12**. (A) Synthesis of platform molecule **12**. (B) Assembly of azides **2b**, **2d**, and **2m** onto platform **12**.

We then turned attention to develop a trivalent platform **12** having a phosphine, terminal alkyne, and cycloalkyne moieties for triple-click conjugation by SPAAC, CuAAC, and robust azaylide formation (Figure 5). The trivalent platform **12** was designed with consideration that the SPAAC reaction predominantly took place when an equimolar mixture of a dibenzo-fused cyclooctyne and triphenylphosphine was treated with aliphatic azide.[7] A 4-step synthesis of platform **12** was realized from methyl 3-bromo-5-iodobenzoate (**5**) with diphenylphosphine (**6**), alkyne **8**, and cycloalkyne **11** (Figure 5A). Indeed, iodo-selective phosphinylation[15] of **5** and subsequent Sonogashira coupling[17] at the remaining bromo group with alkyne **8** provided **9** in good yields. Hydrolysis of the ester moiety and desilylprotonation was accomplished by treating **9** with aqueous sodium hydroxide. Condensation of the resulting carboxylic acid **10** with DIBAC **11** proceeded smoothly to afford trivalent platform **12** efficiently.[18]

Assembly of azides **2b**, **2d**, and **2m** onto trivalent platform **12** was achieved in good efficiency (Figure 5B). Firstly, SPAAC reaction of platform **12** with azide **2m** at the DIBAC moiety selectively proceeded without damaging the phosphine and terminal alkyne moieties. Then, CuAAC reaction of azide **2b** at the remaining terminal alkyne moiety was realized through the protection of the phosphinyl group with copper. Finally, we succeeded in the deprotection and azaylide formation with azide **2d** in the presence of SiliaMetS triamine. Thus, this efficient triple-click assembly onto trivalent platform **12** will allow us to synthesize multi-functionalized molecules from simple azide modules.

In summary, we have developed an efficient synthetic method of click-conjugated phosphines from phosphinyl alkynes via the protection of phosphines with copper. Double- and triple-click reactions assembling azides were achieved using platform molecules having phosphinyl and alkyne moieties. Further studies including other metals for the protection and applications to the preparation of molecular probes are ongoing.

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Conflicts of interest

There are no conflicts to declare.

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An efficient preparation of functionalized phosphines by triazole formation through the transient protection of phosphine from the Staudinger reaction is disclosed. Double- and triple-click assemblies of azides were accomplished.