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Selective strain-promoted azide–alkyne cycloadditions through transient protection of bicyclo[6.1.0]nonynes with silver or gold†

Keisuke Adachi,^a Tomohiro Meguro,^a Yuki Sakata,^a Kazunobu Igawa,^b Katsuhiko Tomooka,^b Takamitsu Hosoya^a and Suguru Yoshida^{*a}

Complexation of bicyclo[6.1.0]nonynes with a cationic silver or gold salt results in protection from a click reaction with azides. The cycloalkyne protection using the silver or gold salt enables selective strain-promoted azide–alkyne cycloadditions of diynes keeping the bicyclo[6.1.0]nonyne moiety unreacted.

Click reactions, such as strain-promoted azide–alkyne cycloaddition (SPAAC) using cycloalkynes, have been used for reliable molecular conjugation in a broad range of research fields including materials chemistry, pharmaceutical sciences, and chemical biology.^{1–7} In particular, remarkable reactivities of bicyclo[6.1.0]nonynes (BCNs) realized catalyst-free functionalizations by reaction with a number of ynophiles such as azides, nitrones, nitrile oxides, tetrazines, triazines, sydnone, thiophene *S,S*-dioxides, and so on.⁵ In the course of our studies on click chemistry,⁶ we recently developed a transient protection method for cycloalkynes involving BCNs from the SPAAC reaction by complexation with (MeCN)₄CuBF₄, which was easily deprotected by treatment with chelators (Fig. 1A).⁷ A wide variety of functionalized cycloalkynes were synthesized using an azide-to-cycloalkyne switching approach by the protection of a cycloalkyne having a terminal alkyne moiety with (MeCN)₄CuBF₄ followed by copper-catalyzed azide–alkyne cycloaddition (CuAAC) with functionalized azides and subsequent deprotection with an aqueous solution of disodium ethylenediaminetetraacetate (EDTA·2Na) (Fig. 1B).⁸ We herein disclose a selective protection method for BCNs from other cycloalkynes by silver or gold complexation, realizing facile synthesis of functionalized BCNs by selective SPAAC reactions using diyne platforms leaving the BCN moiety intact (Fig. 1C).

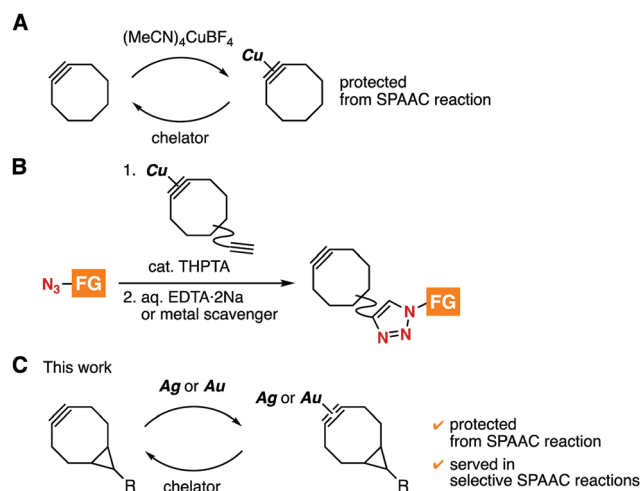


Fig. 1 Protection methods of cycloalkynes. (A) Protection with copper. (B) The azide-to-cycloalkyne switching approach. (C) This work. FG = functional group.

With previous reports of cyclooctyne–metal complexes in mind,^{9,10} we envisioned that silver and gold salts can protect cycloalkynes from the SPAAC reaction by complexation. Thus, we screened silver and gold salts in the complexation with BCN **1a** in CDCl₃ followed by the addition of azide **2a** (Table 1). As a result, a variety of silver salts decreased the yield of triazole **3a** along with the recovery of azide **2a** and precipitate formation of **1a**–metal complexes (entries 2–7), while azide **2a** was completely consumed when the reaction was performed without any metal salt (entry 1). In particular, the examination using AgBF₄ resulted in no triazole formation and almost complete recovery of azide **2a** (entry 7), clearly showing that the cationic silver salt completely prevented the SPAAC reaction. Furthermore, AuBF₄ prepared from AuCl and AgBF₄ also realized the protection of cycloalkyne **1a** from the SPAAC reaction (entry 8).

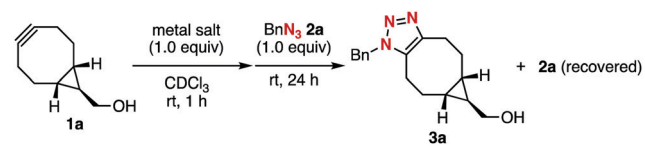
Deprotection of BCN–metal complexes **1a**–AgBF₄ and **1a**–AuBF₄ was achieved by proper choice of the silver and gold salts, and chelators (Table 2). For example, the treatment of **1a**–AgBF₄ with

^a 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

^b Institute for Materials Chemistry and Engineering, Kyushu University, 6-1 Kasuga-koen, Kasuga, Fukuoka 816-8580, Japan

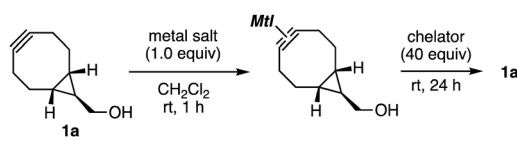
† Electronic supplementary information (ESI) available: Experimental procedures and characterization for the new compounds including NMR spectra. See DOI: 10.1039/d0cc04606j



Table 1 Screening of metal salts for the protection of cycloalkyne **1a** from the formation of **3a**


Entry	Metal salt	3a ^a (%)	2a ^a (%)
1	None	97	0
2	AgCl	92	7
3	AgF	80	16
4	AgOAc	91	9
5	AgSCN	72	28
6	AgNO ₃	36	57
7	AgBF ₄	0	97
8 ^b	AuBF ₄	0	94

^a Yields were determined using ¹H NMR analysis. ^b AuBF₄ was prepared from AuCl and AgBF₄.


Table 2 Screening of chelators for the deprotection of BCN-metal salts


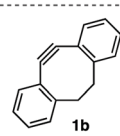
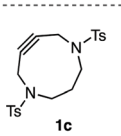
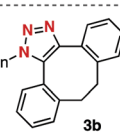

Entry	Metal salt	Chelator	1a ^a (%)
1	AgBF ₄	15 M aq. NH ₃	55
2	AgBF ₄	0.1 M aq. EDTA-2Na	15
3	AgBF ₄	SiliaMetS Thiourea	69
4 ^b	AgBF ₄	SiliaMetS Thiourea	93
5 ^b	AgBF ₄	Resin(polystyrene)-PPh ₂ (PS-TTP)	82
6 ^c	AuBF ₄	15 M aq. NH ₃	0
7 ^c	AuBF ₄	0.1 M aq. EDTA-2Na	24
8 ^{b,c}	AuBF ₄	SiliaMetS Thiourea	58
9 ^{b,c,d}	AuBF ₄	SiliaMetS Thiourea	83
10 ^{b,c}	AuBF ₄	Resin(polystyrene)-PPh ₂ (PS-TTP)	0

^a Yields were determined using ¹H NMR analysis. ^b Chelators (80 equiv.) were used. ^c AuBF₄ was prepared from AuCl and AgBF₄. ^d THF was used instead of CH₂Cl₂.

an aqueous solution of ammonia or EDTA-2Na resulted in the recovery of **1a** in low to moderate yields along with the decomposition of cycloalkyne **1a** (entries 1 and 2). In sharp contrast, the deprotection of **1a**-AgBF₄ with a solid-phase metal scavenger SiliaMetS Thiourea proceeded efficiently (entry 3). In particular, increasing the amount of SiliaMetS Thiourea improved the recovery yield (entry 4). The deprotection of **1a**-AgBF₄ with a polystyrene-conjugated phosphine also took place smoothly (entry 5). Among a variety of conditions screened for the deprotection of **1a**-AuBF₄ (entries 6–10), we succeeded in the efficient deprotection with SiliaMetS Thiourea in THF (entry 9).

Attempts to protect dibenzo-fused cyclooctyne (DIBO) **1b**¹¹ and 4,8-diazacyclononyne (DACN) **1c**¹² with silver or gold revealed their decreasing coordination strength compared to the complex between BCN **1a** and silver or gold (Table 3). When (MeCN)₄CuBF₄ was used, cycloalkynes **1b** and **1c** were successfully protected resulting in the recovery of azide **2a** in excellent yields (entries 1 and 4). On the other hand, the treatment of

Table 3 Screening of metal salts for the protection of cycloalkynes **1b** and **1c**


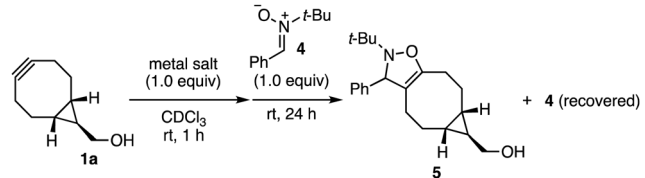





Entry	1	Metal salt	3 ^a (%)	2a ^a (%)
1	1b	(MeCN) ₄ CuBF ₄	3b , 0	98
2	1b	AgBF ₄	3b , 66	33
3 ^b	1b	AuBF ₄	3b , 22	54
4	1c	(MeCN) ₄ CuBF ₄	3c , 0	96
5	1c	AgBF ₄	3c , 85	15
6 ^b	1c	AuBF ₄	3c , 67	19

^a Yields were determined using ¹H NMR analysis. ^b AuBF₄ was prepared from AuCl and AgBF₄.

cycloalkynes **1b** and **1c** with AgBF₄ or AuBF₄ in CDCl₃ followed by the addition of azide **2a** furnished triazoles **3b** and **3c** in low to high yields (entries 2, 3, 5, and 6). Of note, the coordination strength between DACN **1c** and silver or gold was significantly weak, leading to the recovery of azide **2a** in low yields. These results clearly show the contrasting differences in the complexation of cycloalkynes with copper, silver, and gold depending on the electronic nature and ring strain of cycloalkynes.

Complexation of BCN **1a** with AgBF₄ served as protection from [2+3] cycloaddition with nitron **4** (Table 4). While BCN **1a** smoothly reacted with nitron **4** without the protection providing dihydroisoxazole **5** in high yield (entry 1), complexation of BCN **1a** with transition metals prevented the cycloalkyne-nitron cycloaddition (entries 2–4).¹³ However, nitron **4** was consumed completely by decomposition when using (MeCN)₄CuBF₄ or AuBF₄ (entries 2 and 4). On the other hand, the complexation of **1a** with AgBF₄ realized the protection of BCN **1a** along with the recovery of nitron **4** in good yield (entry 3).

Table 4 Screening of metal salts for the protection of cycloalkyne **1a** from formation of **5**


Entry	Metal salt	5 ^a (%)	4 ^a (%)
1	None	93	0
2	(MeCN) ₄ CuBF ₄	0	Decomposed
3	AgBF ₄	0	93
4 ^b	AuBF ₄	0	Decomposed

^a Yields were determined using ¹H NMR analysis. ^b AuBF₄ was prepared from AuCl and AgBF₄.



Table 5 Screening of metal salts for the selective protection of cycloalkynes

$1\mathbf{a} + 1\mathbf{b} \text{ or } 1\mathbf{c} \xrightarrow[\text{CDCl}_3, \text{rt, 1 h}]{\text{metal salt (1.0 equiv)}} \xrightarrow[\text{rt, 24 h}]{\text{BnN}_3 \text{ 2a (1.0 equiv)}} 3\mathbf{a} + 3\mathbf{b} \text{ or } 3\mathbf{c} + 2\mathbf{a} \text{ (recovered)}$					
Entry	1b or 1c	Metal salt	3a ^a (%)	3b or 3c ^a (%)	2a ^a (%)
1	1b	None	43	3b, 53	0
2	1b	(MeCN) ₄ CuBF ₄	5	3b, 58	36
3	1b	AgBF ₄	17	3b, 74	0
4 ^b	1b	AuBF ₄	0	3b, 92	1
5	1c	None	60	3c, 37	0
6	1c	(MeCN) ₄ CuBF ₄	0	3c, 68	28
7	1c	AgBF ₄	0	3c, 99	0
8 ^b	1c	AuBF ₄	0	3c, 74	18

^a Yields were determined using ¹H NMR analysis. ^b AuBF₄ was prepared from AuCl and AgBF₄.

Complexation with silver or gold realized the selective protection of BCN in the presence of other cycloalkynes (Table 5). An equimolar mixture between BCN **1a** and DIBO **1b** (1.0 equiv. each) smoothly reacted with benzyl azide (**2a**) (1.0 equiv.) without protection to furnish a *ca.* 1:1.2 mixture of triazoles **3a** and **3b** (entry 1). The pretreatment of cycloalkynes **1a** and **1b** (1.0 equiv. each) with 1.0 equiv. of metal salts drastically changed the ratio of **3a** to **3b** (entries 2–4). In particular, we succeeded in the selective SPAAC reaction of DIBO **1b** affording triazole **3b** in high yield when using AuBF₄ by virtue of the BCN-selective protection (entry 4). The SPAAC reaction of an equimolar mixture of BCN **1a** and DACN **1c** with azide **2a** also proceeded efficiently to provide a *ca.* 1.6:1 mixture of triazoles **3a** and **3c** (entry 5). The pretreatment of cycloalkynes **1a** and **1c** with metal salts prevented the formation of triazole **3a** (entries 6–8). In particular, treatment of cycloalkynes **1a** and **1c** (1.0 equiv. each) with AgBF₄ (1.0 equiv.) followed by the addition of azide **2a** exclusively furnished triazole **3c** in excellent yield (entry 7).

The synthetic utility of the DIBO- and DACN-selective SPAAC reactions in the presence of a BCN moiety through the complexation was showcased by the selective triazole formation of diynes **6** and **8** keeping the BCN moiety unreacted (Fig. 2). Indeed, the pretreatment of diyne **6** with AuBF₄ followed by the addition of azide **2b** and subsequent removal of the gold salt with SiliaMetS Thiourea provided triazole **7** in good yield by the SPAAC reaction at the DIBO moiety without reacting the BCN moiety (Fig. 2A). Furthermore, we also achieved the DACN-selective triazole formation of diyne **8** by complexation with AgBF₄, addition of azide **2b**, and the removal of the silver salt with SiliaMetS Thiourea (Fig. 2B). Since the remaining BCN moiety contributes significantly to the catalyst-free click conjugation with various ynophiles in materials chemistry and chemical biology, the DIBO- and DACN-selective triazole formation of diynes allowed for sequential conjugations of a broad range of functional molecules.⁵

In conclusion, we have developed an efficient method for the transient protection of BCNs by complexation with silver or gold, enabling DIBO- or DACN-selective triazole formation.¹⁴ The selective SPAAC reactions realized the preparation of functionalized BCNs by the selective click conjugation of diynes. Further studies of cycloalkyne–metal complexes involving detailed solvent effects,

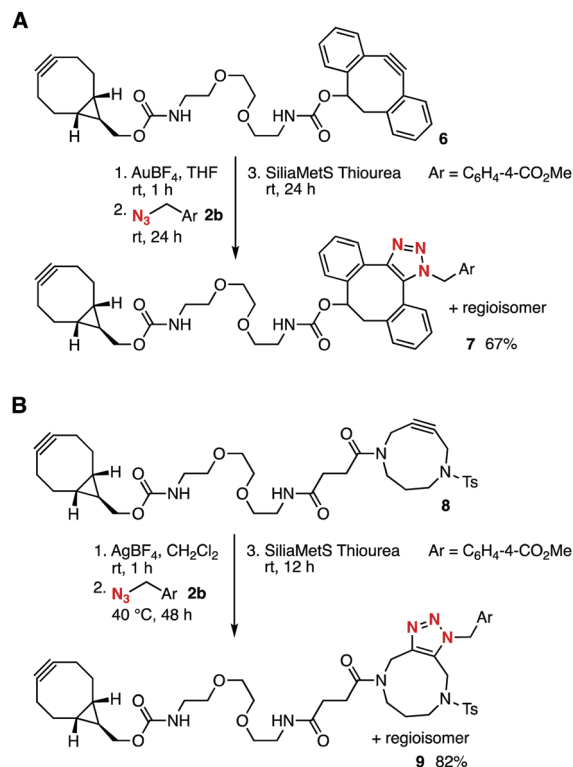


Fig. 2 Selective SPAAC reactions of diynes **6** and **8**. (A) Selective reaction of **6**. (B) Selective reaction of **8**.

protection from various ynophiles, and applications of sequential triazole formations of diynes are now in progress.

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Conflicts of interest

There are no conflicts to declare.

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