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A protection method for cycloalkynes by the formation of (hexafluoroacetylacetato)copper(I)-cycloalkyne complexes is disclosed. Various complexes having functional groups were efficiently prepared, which are easily purified by silica-gel column chromatography. Selective click reactions were realized through the complexation of cycloalkynes with copper.

Strain-promoted azide–alkyne cycloaddition (SPAAC) reactions have served as catalyst-free click reactions in broad disciplines including materials chemistry, pharmaceutical sciences, and chemical biology.^{1–5} To realize efficient molecular conjugations, a variety of cycloalkynes have been developed so far.⁴ However, controlled SPAAC reactions for preparing multifunctional molecules by assembling a number of functional molecules is still challenging due to the significantly reactive cycloalkynes and immature protecting group chemistry.^{5,6} In the course of our studies on click chemistry,⁷ we found transient protection methods of cycloalkynes from triazole formation with azides by complexation with cationic copper, silver, or gold (Fig. 1A).⁸ Furthermore, we developed an efficient synthetic method of functionalized cycloalkynes from functionalized azides by complexation of cycloalkynes having an ethynyl group with cationic copper followed by copper-catalyzed triazole formation at the ethynyl group and subsequent deprotection with chelators (Fig. 1B).^{8a,b} Herein, we disclose an alternative method for the protection of cycloalkynes by complexation with [bis(trimethylsilyl)acetylene][hexafluoroacetylacetato)copper(I) ((btmsa)Cu(hfacac)),⁹ in which the cycloalkyne–copper complexes can be easily purified by silica-gel column chromatography (Fig. 1C).

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(Hexafluoroacetylacetato)copper(I)-cycloalkyne complexes as protected cycloalkynes[†]

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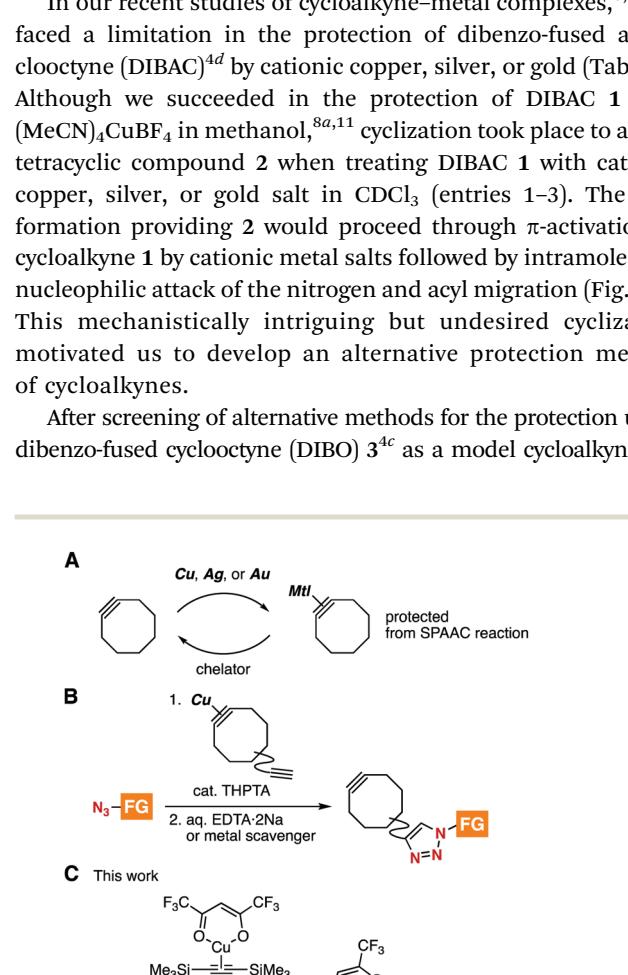


Table 1 Attempts of complexation between DIBAC 1 and metal salts

| Entry | Metal salt | 1-Mtl (%) | 2 (%) |
|----------------|---------------------------------------|--------------|-------|
| 1 | (MeCN) ₄ CuBF ₄ | Not detected | 49 |
| 2 | AgBF ₄ | Not detected | 30 |
| 3 ^a | AuBF ₄ | Not detected | 46 |

^a AuBF₄ was prepared from AuCl and AgBF₄.

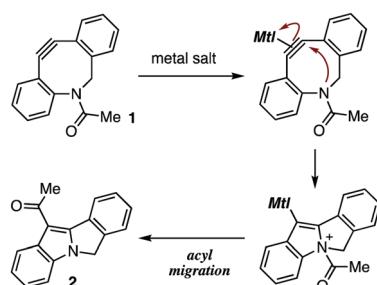


Fig. 2 Plausible reaction mechanism of undesired ring-closure.

found that ligand exchange of [bis(trimethylsilyl)acetylene] (hexafluoroacetylacetone)copper(i) ((btmsa)Cu(hfacac)) with 3 took place efficiently to provide cycloalkyne–copper complex 4a quantitatively (Fig. 3A). It is worthy to note that complex 4a was easily purified by silica-gel column chromatography owing to the high stability and low polarity.¹³ Treatment of DIBO–copper complex 4a with azide 5 in dichloromethane resulted in the recovery of azide 5 in excellent yield without triazole formation, clearly showing that cycloalkyne–copper complex 4a worked as a protected cycloalkyne (Fig. 3B, upper).¹⁴ Deprotection of 4a successfully proceeded by the treatment with chelators or nitrogen ligands such as aqueous ammonia (Fig. 3B, lower). Increasing the amounts of (btmsa)Cu(hfacac) from 0.1 to 1.0 equiv. in complexation with cyclooctyne 3 resulted in a gradual upfield shift of alkyne sp carbon signals in ¹³C NMR analyses (Fig. 3C). This result indicates the equilibrium formation of DIBO–copper complex 4a.

A wide range of cycloalkynes involving DIBAC 1 participated in the complexation with (btmsa)Cu(hfacac) (Fig. 4). For instance, the complexation of DIBOs with copper smoothly proceeded to furnish 4b and 4c in high yields without affecting by hydroxy and ethynyl groups. Of note, we succeeded in preparing DIBAC–copper complex 4d without undesired cyclization, clearly demonstrating an advantage of Cu(hfacac) complexes compared to cycloalkyne complexes with cationic metal salts. A variety of bicyclo[6.1.0]nonyne (BCN) complexes 4f–g were prepared without damaging not only hydroxy group but also active carbonate and terminal alkyne moieties.^{4f} We also accomplished the complexation of 4,8-diazacyclononynes (DACNs) with (btmsa)Cu(hfacac) to afford 4h and 4i leaving

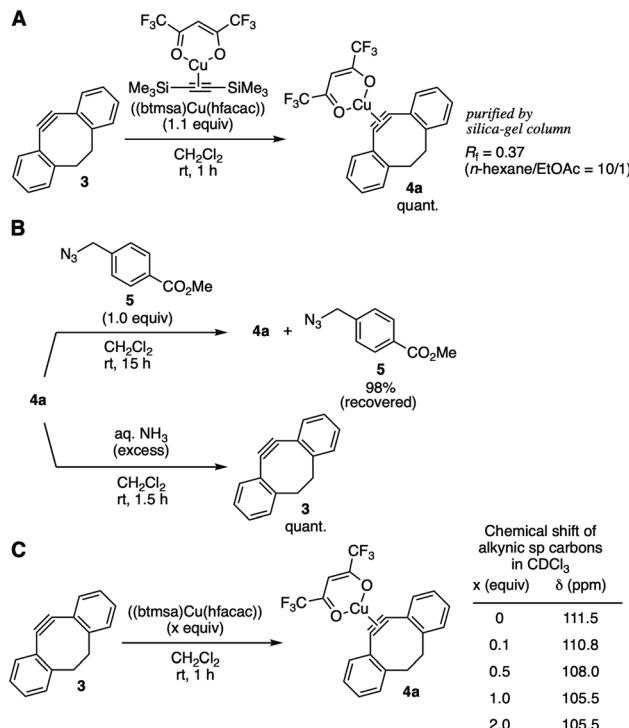


Fig. 3 DIBO–(btmsa)Cu(hfacac) complex 4a. (A) Complexation of 3 with (btmsa)Cu(hfacac). (B) Reactivity toward azide 5 and deprotection. (C) NMR study.

cycloalkyne, sulfonamide, amide, and terminal alkyne moieties untouched.^{4k}

A synthetic utility of cycloalkyne(hfacac)copper(i) complexes was showcased by preparing BCN–copper complex 4l having an azido group (Fig. 5A).⁶ Indeed, treatment of BCN 6 with (btmsa)Cu(hfacac) followed by acylation with 4-(azidomethyl)benzoyl chloride (7) in the presence of triethylamine and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) provided azide-containing BCN–Cu(hfacac) complex 4j. We succeeded in click conjugation of complex 4j with alkyne 8 catalyzed by copper at the azido group and subsequent removal of the copper salt with aqueous ammonia to furnish BCN 9 in good yield without reacting the cycloalkyne moiety. These results clearly showed that cycloalkyne(hfacac)copper(i) complexes can be transformed as protected cycloalkynes, which will expand the synthetic utility of cycloalkynes.

The selectivity of the SPAAC reaction between BCN 6 or DIBAC 1 and DACN 10 with azide 5 was switchable through complexation using (btmsa)Cu(hfacac) (Fig. 5B and C). For example, treatment of an equimolar mixture between BCN 6 and DACN 10 with 4-(methoxycarbonyl)benzyl azide (5) in dichloromethane without the addition of (btmsa)Cu(hfacac) afforded triazole 11 in high yield along with recovery of unreacted DACN 10 (Fig. 5B, upper). On the other hand, when azide 5 was added after the complexation of the mixture between 6 and 10 with (btmsa)Cu(hfacac), a selective SPAAC reaction took place efficiently to furnish triazole 12 in excellent yield by virtue of the selective formation of BCN–copper complex 4e similar to the case with AgBF₄ (Fig. 5B, lower).^{8c}



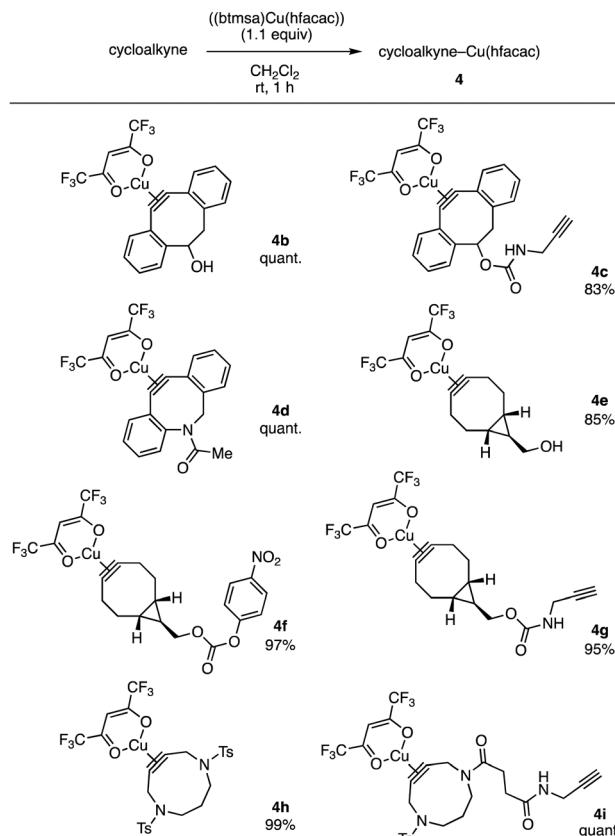


Fig. 4 Scope of cycloalkyne(hfacac)copper(I) complexes. See ESI† for structures of the cycloalkynes used.

Since the yield of triazole **12** was remarkably increased compared to the reaction using $(\text{MeCN})_4\text{CuBF}_4$,^{8c} the use of copper salt with lower Lewis acidity would improve the selective cycloalkyne–copper complexation. Furthermore, switchable click reactivity between DIBAC **1** and DACN **10** was also demonstrated by virtue of the complexation with (btmsa)Cu(hfacac). While a selective SPAAC reaction of DIBAC **1** with azide **5** proceeded without the protection, the pretreatment of the mixture between **1** and **10** with (btmsa)Cu(hfacac) followed by the addition of azide **5** provided triazole **12** along with the formation of DIBAC–Cu(hfacac) complex **4d**. This switchable click conjugation using DIBAC **1** and DACN **10** indicates a significant improvement from our previous study with silver and gold.

The DACN-selective triazole formation enabled click conjugation of diyne **14** with an azide keeping BCN moiety intact (Fig. 5D). After pretreatment of diyne **14** possessing BCN and DACN moieties with (btmsa)Cu(hfacac), SPAAC reaction with azide **5** proceeded efficiently at the DACN moiety. Following deprotection with an aqueous solution of EDTA-2Na afforded triazoles **15** leaving the BCN moiety intact. Since the Lewis acidity of Cu(hfacac) complexes was lower than that of cationic transition metal complexes, this method will expand available functional ynopophiles in the efficient sequential conjugations of functional molecules from recently reported methods using diynes.^{8c}

In summary, we have developed an alternative protection method of cycloalkynes with (btmsa)Cu(hfacac). A wide range

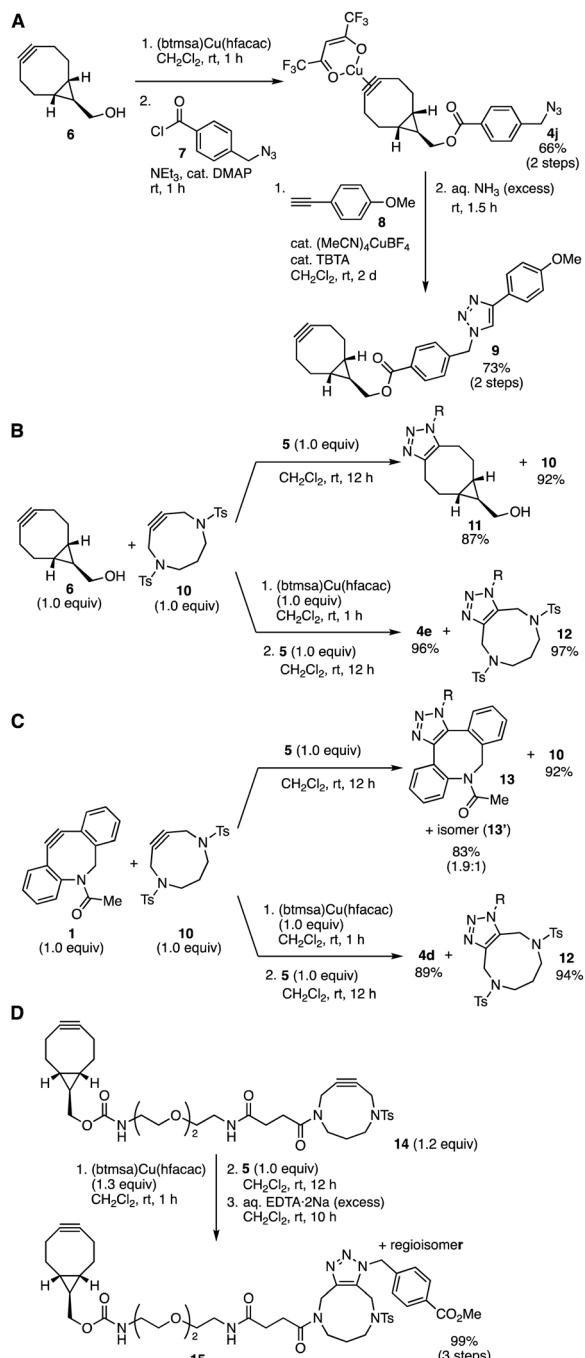


Fig. 5 Selective triazole formations. (A) Synthesis of **9**. (B) Switchable triazole formations between **6** and **10**. (C) Switchable triazole formations between **1** and **10**. (D) DACN-selective triazole formation using diyne **14**. R = $\text{CH}_2\text{C}_6\text{H}_4-p\text{-CO}_2\text{Me}$.

of cycloalkyne–copper complexes were efficiently obtained by treating cycloalkynes with (btmsa)Cu(hfacac) and silica-gel column chromatography. The modest Lewis acidity of the Cu(hfacac) complexes enabled efficient sequential click reactions. Further studies such as expansion of available ynopophiles, applications for bimolecular modification, and assembling functional molecules through the selective SPAAC reaction are now ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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- Treatment of cycloalkyne **1** with $(\text{MeCN})_4\text{CuBF}_4$ (1.1 equiv.) in methanol followed by the addition of azide **5** (1.0 equiv.) resulted in no triazole formation and the recovery of unreacted azide **5** in 91% yield. When aq. EDTA-2Na (90 equiv.) was added after the pretreatment of cycloalkyne **1** with $(\text{MeCN})_4\text{CuBF}_4$ (1.1 equiv.) in methanol, cycloalkyne **1** was recovered in 86% yield.
- Ring-closure of DIBAC without acyl migration by hydrogen bromide was reported in ref. 4d.
- Labile nature of a complex from **3** and $(\text{MeCN})_4\text{CuBF}_4$ rendered the purification by silica-gel column chromatography difficult.
- 14** DIBO-copper complex **4a** was stable in methanol, toluene, or *N,N*-dimethylformamide. In addition, a dichloromethane solution of **4a** was stable toward aqueous hydrochloric acid, aqueous ammonium chloride, aqueous sodium bicarbonate, and amino acids such as cysteine, tyrosine, and lysine.

