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(Hexafluoroacetylacetonato)copper(I)–cycloalkyne complexes as protected cycloalkynes†

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A protection method for cycloalkynes by the formation of (hexafluoroacetylacetonato)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](hexafluoroacetylacetonato)copper(I) ((btmsa)Cu(hfacac)),[9] in which the cycloalkyne–copper complexes can be easily purified by silica-gel column chromatography (Fig. 1C).

In our recent studies of cycloalkyne–metal complexes,[8,10] we faced a limitation in the protection of dibenzo-fused azacyclooctyne (DIBAC)[4d] by cationic copper, silver, or gold (Table 1). Although we succeeded in the protection of DIBAC **1** with $(MeCN)_4CuBF_4$ in methanol,[8a,11] cyclization took place to afford tetracyclic compound **2** when treating DIBAC **1** with cationic copper, silver, or gold salt in $CDCl_3$ (entries 1–3). The ring formation providing **2** would proceed through π-activation of cycloalkyne **1** by cationic metal salts followed by intramolecular nucleophilic attack of the nitrogen and acyl migration (Fig. 2).[12] This mechanistically intriguing but undesired cyclization motivated us to develop an alternative protection method of cycloalkynes.

After screening of alternative methods for the protection using dibenzo-fused cyclooctyne (DIBO) **3**[4c] as a model cycloalkyne, we

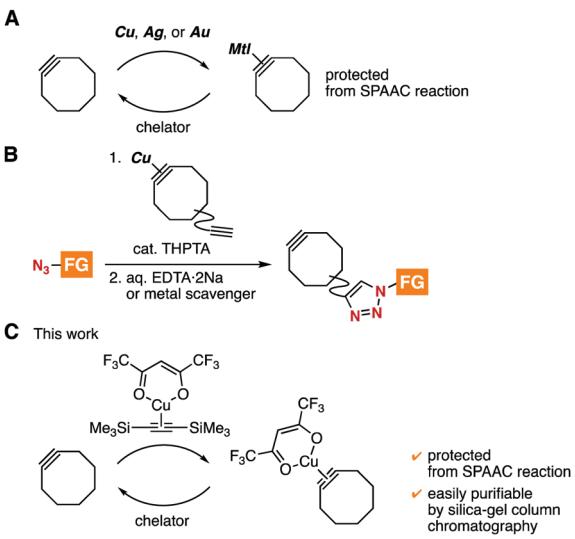

Fig. 1 Synthetic methods through cycloalkyne–metal complexes. (A) Transient protection of cycloalkynes by complexation with copper, silver, or gold. (B) Azide-to-cycloalkyne switching approach. (C) This work. FG = functional group.

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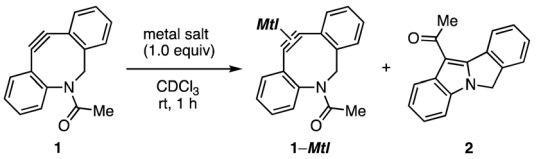
Table 1 Attempts of complexation between DIBAC **1** and metal salts



Entry	Metal salt	**1**-*MtI* (%)	**2** (%)
1	$(MeCN)_4CuBF_4$	Not detected	49
2	$AgBF_4$	Not detected	30
3[a]	$AuBF_4$	Not detected	46

[a] $AuBF_4$ was prepared from AuCl and $AgBF_4$.

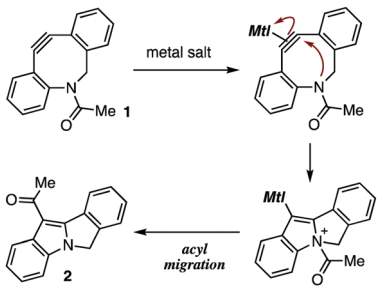


Fig. 2 Plausible reaction mechanism of undesired ring-closure.

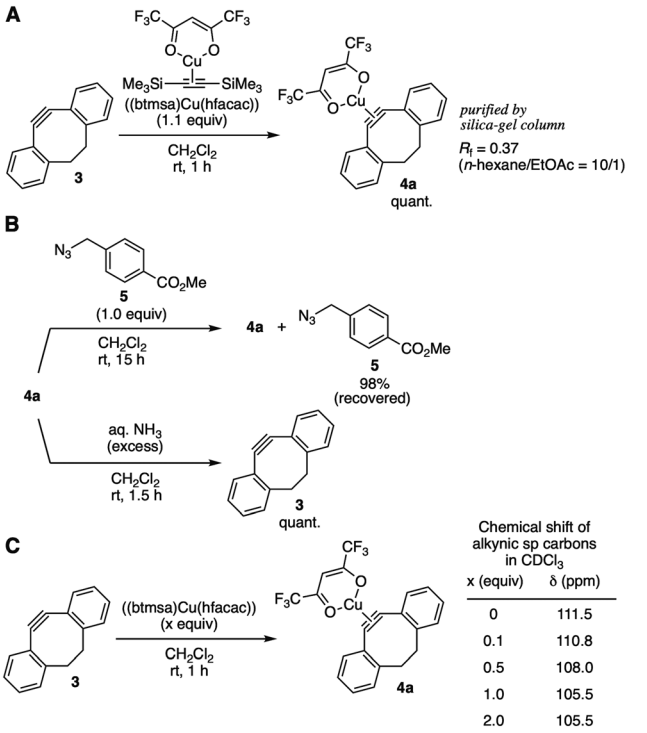


Fig. 3 DIBO–(btmsa)Cu(hfacac) complex **4a**. (A) Complexation of **3** with (btmsa)Cu(hfacac). (B) Reactivity toward azide **5** and deprotection. (C) NMR study.

found that ligand exchange of [bis(trimethylsilyl)acetylene] (hexafluoroacetylacetonato)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 alkynic sp carbon signals in ^{13}C 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 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 $AgBF_4$ (Fig. 5B, lower).[8c]

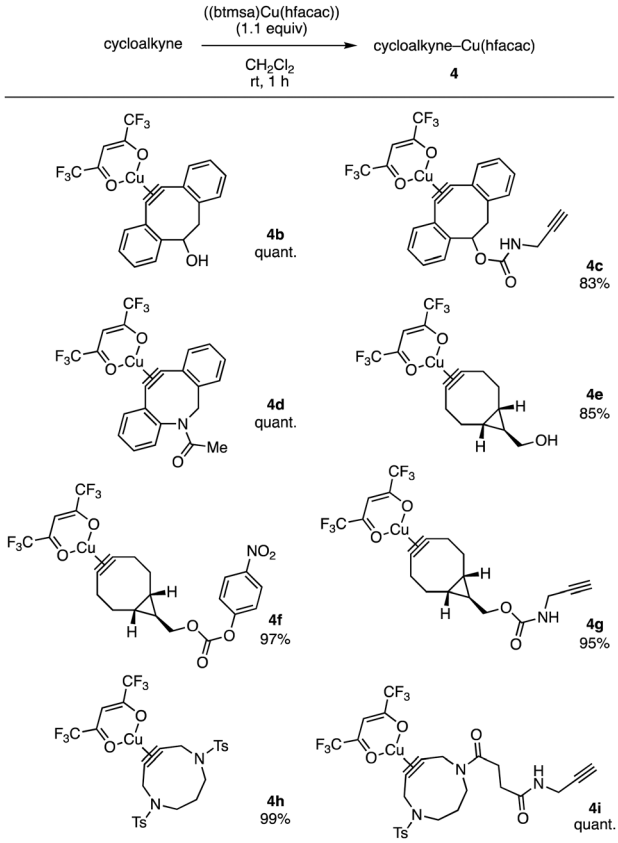


Fig. 4 Scope of cycloalkyne(hfacac)copper(I) complexes. See ESI† for structures of the cycloalkynes used.

Since the yield of triazole **12** was remarkably increased compared to the reaction using $(MeCN)_4CuBF_4$,[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 ynophiles 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

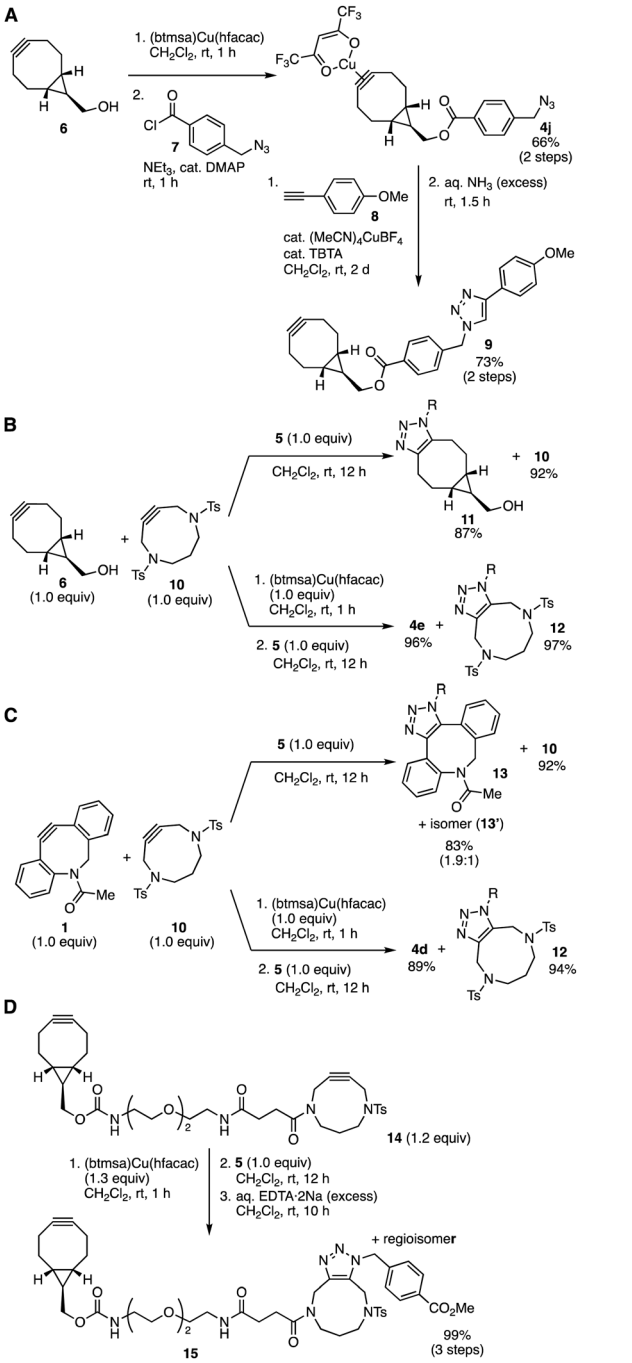


Fig. 5 Selective triazole formations. (A) Synthesis of **9**. (B) Switchable triazole formations between **6** and **10**. (C) Switchable triazole formations between **1** and **10**. (D) DACN-selective triazole formation using diyne **14**. R = $CH_2C_6H_4$-*p*-CO_2Me.

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 ynophiles, 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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11 Treatment of cycloalkyne **1** with $(MeCN)_4CuBF_4$ (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 $(MeCN)_4CuBF_4$ (1.1 equiv.) in methanol, cycloalkyne **1** was recovered in 86% yield.

12 Ring-closure of DIBAC without acyl migration by hydrogen bromide was reported in ref. 4*d*.

13 Labile nature of a complex from **3** and $(MeCN)_4CuBF_4$ 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.

