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Facile assembly of three cycloalkyne-modules onto a platform compound bearing thiophene *S,S*-dioxide moiety and two azido groups†

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An efficient method to assemble three cycloalkyne-modules onto a platform compound bearing a thiophene *S,S*-dioxide moiety and two azido groups has been developed. The sequential reactions without catalysis or additives enabled the facile preparation of trifunctional molecules by a simple procedure. One-pot assembly was also achieved using the platform and three cycloalkynes.

Modular synthesis by consecutive reactions onto a platform molecule has gained attention as a facile method for preparing a wide variety of products from diverse modules.[1,2] On the basis of the remarkable achievements by recently emerging click chemistry[3] including copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC)[4] and strain-promoted azide–alkyne cycloaddition (SPAAC),[5,6] efficient assembly of modules by multi-click chemistry using well-designed platform molecules has been accomplished (Fig. 1). For example, Jiráček and coworkers achieved a triple-CuAAC reaction using platform **1** bearing terminal, triethylsilyl, and triisopropylsilyl alkynes through selective desilylprotonation (Fig. 1A).[7] Triple-conjugation by tetrazine–norbornene ligation, CuAAC, and thiol–maleimide reaction using platform **3** developed by Knall and coworkers allowed for assembling three-types of modules (Fig. 1B).[8] Recently, we also developed a tris(triazole) formation method by three sequential reactions using platform **5** having three-types of azido groups. This method enabled to assemble three types of azidophiles having functional groups, such as HaloTag ligand, fluorescent, and biotin moieties (Fig. 1C).[9] Despite these continuous efforts, an ideal method for assembling modules onto a platform molecule under catalysis-free conditions is not easy to develop due to the limited methods for reliable conjugation[10] and difficulties to synthesize a platform molecule bearing discriminatable reactive groups. Herein, we describe an efficient method for highly selective triple-conjugation of three cycloalkynes onto a newly designed platform bearing discriminatable thiophene *S,S*-dioxide moiety and two azido groups (Fig. 1D).

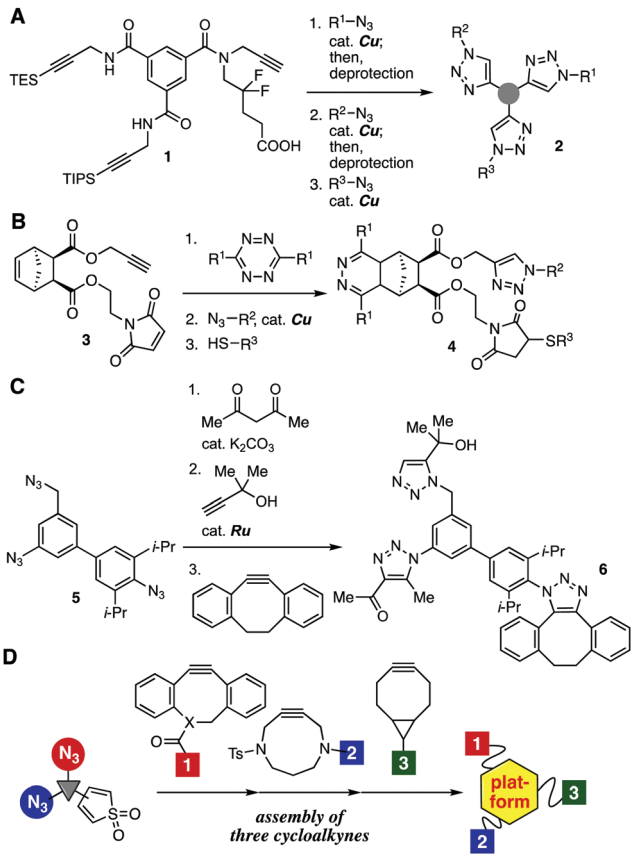

Fig. 1 Methods to assemble three modules onto a platform molecule. (A) Jiráček's work. (B) Knall's work. (C) Our previous work. (D) This work.

Focusing on the remarkable reactivities of cycloalkynes allowing for efficient conjugation under mild conditions without catalysis, we at first explored ynophiles with discriminatable

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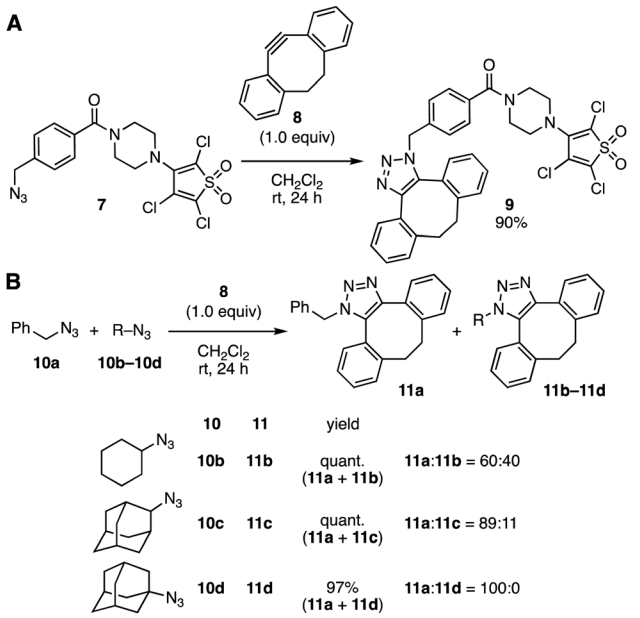

Fig. 2 SPAAC reactions between azides and dibenzo-fused cyclooctyne **8**. (A) Selective reaction of platform **7**. (B) Competition experiments using azides and cyclooctyne **8**.

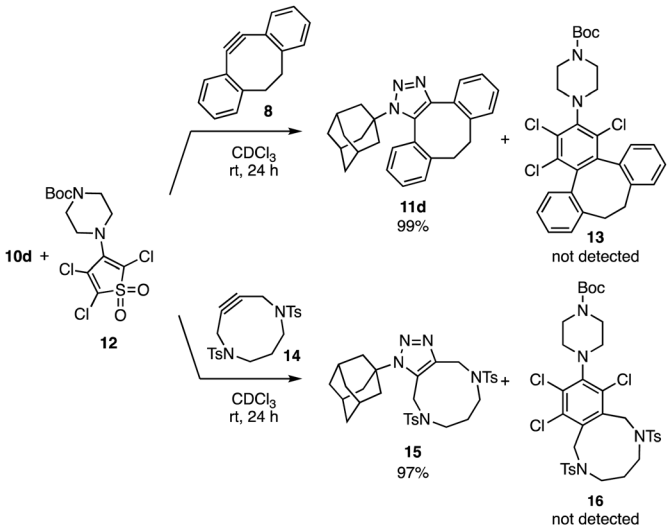

Fig. 3 Competition experiments treating a mixture of azide **10d** and thiophene dioxide **12** with cyclooctyne **8** or **14**.

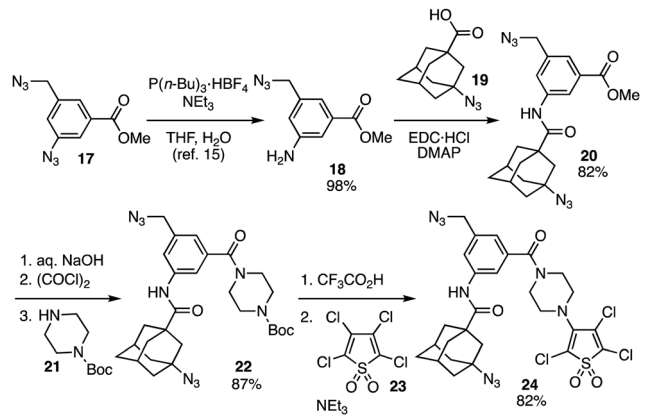

Fig. 4 Synthesis of platform **24**. EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. DMAP = 4-dimethylaminopyridine.

reactivity (Fig. 2). Based on our previous report that 2,3,4,5-tetrachlorothiophene *S*,*S*-dioxide slowly reacted with dibenzo-fused cyclooctyne **8** at room temperature,[11,12] selective SPAAC reaction of cyclooctyne **8** with platform **7** proceeded smoothly at the benzyl azido group to provide triazole **9** leaving thiophene dioxide moiety untouched (Fig. 2A). We then envisioned that a bulky alkyl azide can remain intact in the SPAAC reaction of the benzyl azido group,[13,14] although the difference of the click-ability between benzyl azide and phenyl azide in the SPAAC reaction was not satisfied.[2c,6f] Thus, a competitive SPAAC reaction of cyclooctyne **8** with an equimolar mixture between benzyl azide (**10a**) and bulky alkyl azide **10b**, **10c**, or **10d** was examined (Fig. 2B). It was shown that the SPAAC of benzyl azide (**10a**) took place selectively when using 1-adamantyl azide (**10d**), while the selectivity was not satisfiable in the reaction of a mixture between secondary azide **10b** or **10c** and benzyl azide (**10a**). Furthermore, selective [2+3] cycloaddition between 1-adamantyl azide (**10d**) and thiophene dioxide **12** was accomplished by treatment with dibenzo-fused cyclooctyne **8**[6d] or 4,8-diazacyclononyne (DACN) derivative **14**[6g] at room temperature without providing undesired products by the reaction of thiophene dioxide (Fig. 3). These results clearly showed that selective reactions of cycloalkynes with a platform having benzyl azide, 1-adamantyl azide, and thiophene dioxide moieties would proceed efficiently to furnish conjugated products without any undesired side products.

Having three discriminatable ynophiles in hand, we designed platform molecule **24** possessing these ynophilic moieties (Fig. 4). The synthesis of platform **24** was achieved from simple building blocks **17**, **19**, **21**, and **23**. Indeed, selective reduction at the aromatic azido group[15] of diazide **17**[16] followed by amide formation using 3-azidoadamantane carboxylic acid (**19**) afforded diazide **20** in good yield. Then, transformations of methoxycarbonyl group to (4-(*tert*-butoxycarbonyl)piperazino)carbonyl group and subsequent removal of the *tert*-butoxycarbonyl group and substitution reaction with 2,3,4,5-tetrachlorothiophene *S*,*S*-dioxide (**23**) successfully provided platform **24** leaving two azido groups untouched.

Consecutive reactions using platform **24** with three cycloalkynes **8**, **14**, and **25** enabled efficient assembly to afford the desired conjugate **26** in a highly selective manner (Fig. 5). Indeed, SPAAC reaction of platform **24** with dibenzo-fused cyclooctyne **8** proceeded selectively as expected without reactions of 1-adamantyl azide or thiophene dioxide moieties (Fig. 5A). The remaining tertiary azide smoothly reacted with DACN derivative **14** with gentle heating and subsequent reaction between thiophene dioxide and bicyclo[6.1.0]non-4-yne (BCN) derivative **25**[6e] took place efficiently.[17] Thus, facile assembly by three consecutive catalysis-free reactions was achieved by the simple procedure without yielding any side products. Furthermore, one-pot assembly of the three components onto platform **24** successfully proceeded by sequential addition of cycloalkynes **8**, **14**, and **25** (Fig. 5B).[18]

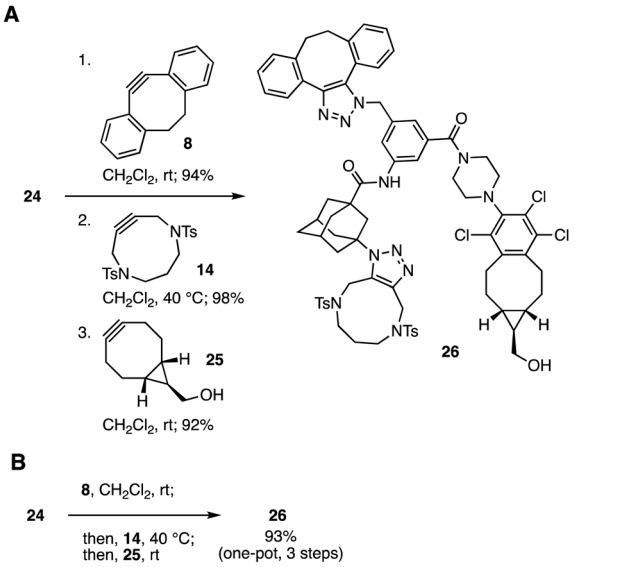

Fig. 5 Assembly of three cycloalkynes **8**, **14**, and **25** onto platform **24**.

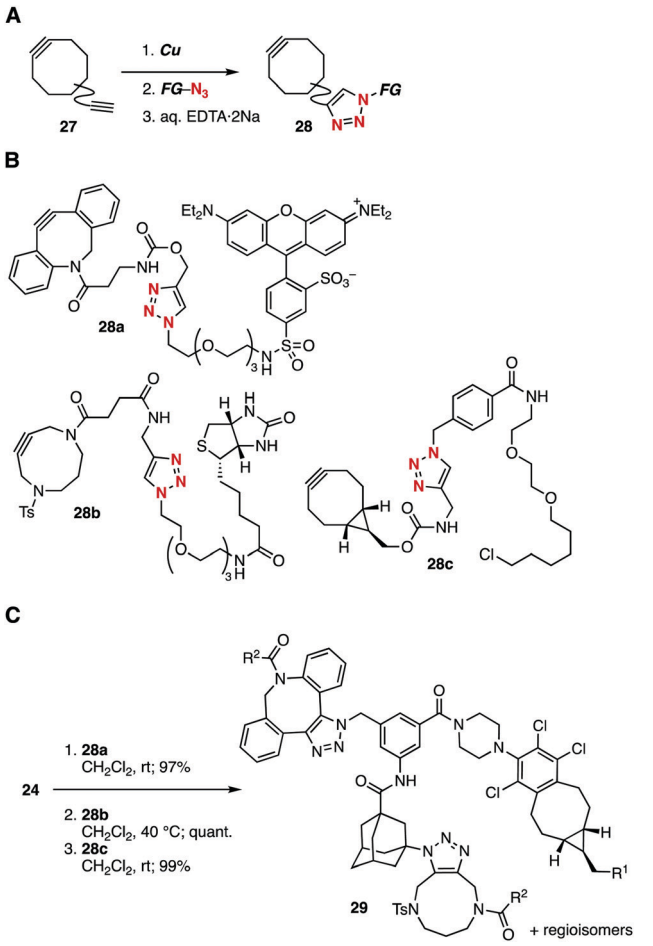

Fig. 6 Assembly of three cycloalkyne-modules. (A) Synthesis of cycloalkyne-modules **28**. (B) Structures of cycloalkyne-modules **28**. (C) Assembly of functional cycloalkynes **28** onto platform **24**. See the ESI† for the detailed structure of product **29**. EDTA·2Na = ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid disodium salt.

To showcase the simplicity and efficiency of the method for preparing conjugates from cycloalkyne-modules, synthesis of trifunctional molecule **29** was demonstrated by assembling three functional cycloalkynes **28a–c** onto platform **24** (Fig. 6). Three types of functional cycloalkynes **28a–c** having a fluorescent rhodamine, biotinyl group, and ligand moiety for HaloTag, were successfully synthesized by CuAAC reactions on the basis of azide-to-cycloalkyne switching approach using the corresponding diynes **27** through transient protection of cycloalkyne moieties with copper (Fig. 6A and B).[19] Then, these cycloalkyne-modules, azadibenzocyclooctyne (DIBAC) derivative **28a**, DACN derivative **28b**, and BCN derivative **28c**, were efficiently assembled to platform **24** in excellent yields as a mixture of regioisomers without damaging three functional moieties (Fig. 6C). Monitoring each step by HPLC analysis clearly showed the significant efficiency of this assembling method.[17]

In summary, we have developed an efficient method to assemble three cycloalkyne-modules using a platform compound having thiophene *S*,*S*-dioxide moiety and two azido groups. Since a broad range of functional cycloalkyne-modules are easily prepared by azide-to-cycloalkyne switching approach from easily available functional azides, this simple assembly method would serve in the preparation of various trifunctional molecules from easily available azide-modules. Further studies involving development of a thiophene dioxide-selective reaction of platform molecule **24** and application of this method are underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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