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Chemoselective Layer-by-Layer Approach Utilizing Click Reactions with Ethynylcyclooctynes and Diazides

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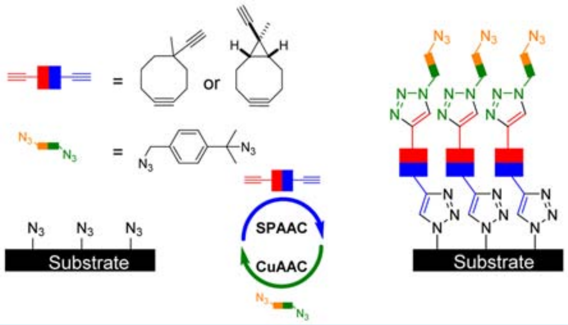
Ⓢ *Supporting Information*

ABSTRACT: Ethynylcyclooctynes and diazides were synthesized and applied for a chemoselective sequence of copper(I)-catalyzed azide–alkyne cycloadditions and strain-promoted azide–alkyne cycloadditions. Chemoselectivity within the reaction sequence was achieved by balancing three factors: Cu-catalysis/ring strain/steric shielding. A cholic acid derived triazide was subjected to the cycloaddition sequence as a model system for a layer-by-layer synthesis on surfaces.



The tailored modification of surface substrates is an important goal to regulate their physical, electronic, photophysical and chemical properties. For constructing well-defined thin films of controlled thickness and composition the layer-by-layer (LbL) assembly has turned out to be a versatile and efficient method. The original approach developed by Decher is based on the sequential deposition of polyelectrolytes (PE) on a charged substrate.[1] Because of the limited stability of this noncovalently bonded PE film, there are several approaches to assemble LbL films by covalent bonding.[2] Caruso was the first who combined the efficient copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) with LbL to prepare multilayer films of poly(acrylic acid).[3] Following this basic idea, the approach was extended to multilayers of small molecules,[4] dendrimers,[5] and polymer/small molecule combinations.[6] Although this method is very powerful and was used for applications, usually only symmetrical building blocks are utilized. This communication reports a molecular LbL approach using unsymmetrical small molecules in chemoselective "click" reactions.[7]

A previous reported concept of molecular LbL thin film fabrication utilizing CuAAC is shown in Figure 1A.[4] First, an azide-modified substrate is reacted with a symmetrical multiacetylene functionalized molecule in the presence of Cu(I) to create a surface which is now terminated with acetylene moieties. Next, a multiazide functionalized molecule is reacted with the substrate under similar conditions to regenerate an azide-terminated surface. These two CuAAC reactions can be repeated indefinitely until the desired film thickness is achieved.

Inspired by the work of Dinolfo, we thought about an extension of this concept using unsymmetrical molecules (Figure 1B). In order to get well-defined layers, the choice of an appropriate multialkyne as well as multiazide is crucial. For the alkyne building block, a cyclooctyne of type **1** and **2** was envisaged (Figure 2). Due to their strained structure, cyclooctynes react with azides without the need of a Cu catalyst (strain-promoted azide–alkyne cycloaddition, SPAAC).[8] Subsequent CuAAC with a bis-azide would provide the azide functionalized surface again. To achieve chemoselectivity in the CuAAC bisazide, **3** was

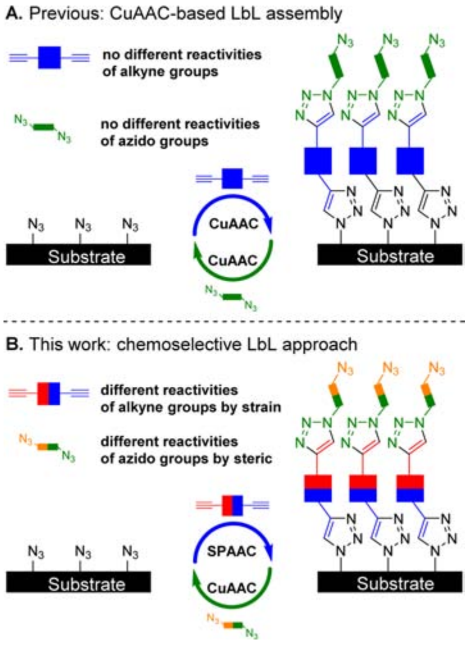


Figure 1. (A) Typical CuAAC-based LbL assembly using symmetrical small molecules. (B) Presented approach using sequentially chemoselective "click" reactions.

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envisaged in which the two azido groups have different steric hindrance. It would also be possible to take bis-azide **4**,[9] which reacts chemoselectively because of chelating effects. Following these basic considerations, we report here the synthesis of compounds **1**−**3**. Additionally, initial studies for LbL assembly were performed on molecular model systems in solution.

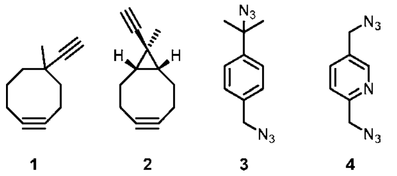
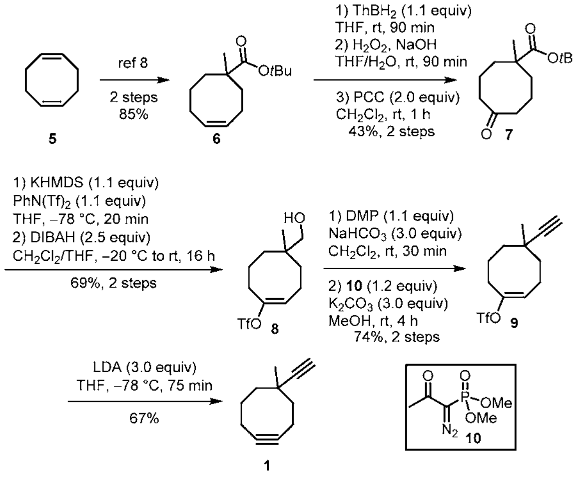


Figure 2. Appropriate molecules for chemoselective LbL approach.

The starting point for the synthesis of cyclooctyne **1** was the cyclooctene ester **6**, which is accessible from COD (**5**) in two steps (Scheme 1).[10] Subsequent hydroboration with thexylborane provided the desired alcohol as a mixture of regio- and diastereomers which were oxidized directly with PCC to the corresponding ketones (2:1 regioselectivity for the hydroboration). It was possible to separate the regioisomeric ketones by SiO_2 flash chromatography to give the desired product **7** in moderate yield.

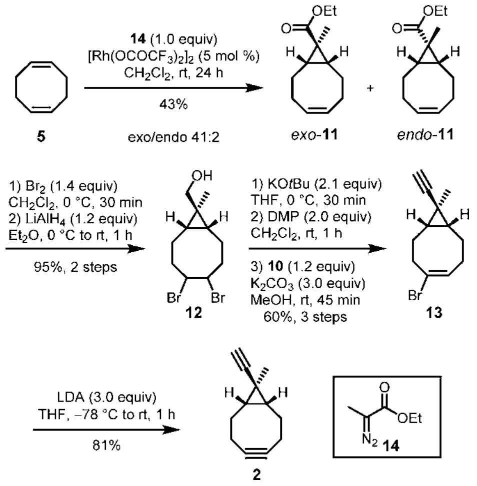
Scheme 1. Synthesis of Cyclooctyne 1



Treatment of **7** with KHMDS in the presence of phenyl triflimide led to the formation of the corresponding vinyl triflate. Subsequent reduction of the ester group was performed with DIBAH to obtain alcohol **8** in 69% yield over two steps. The terminal alkyne group was introduced via a two-step sequence. Oxidation of the primary alcohol in **8** to the corresponding aldehyde was afforded with Dess−Martin periodinane (DMP) under basic conditions. The sensitive aldehyde therefore was directly converted into alkyne **9** via an Ohira−Bestmann reaction. With cyclooctyne precursor in hand, we turned our attention to the final elimination step. Fortunately, the elimination to cyclooctyne **1** proceeded very smoothly with LDA at −78 °C. In contrast to previous results in the field of cyclooctyne synthesis,[11] no warming to ambient temperature was necessary to afford the elimination reaction. With the presented synthetic route, racemic ethynylcyclooctyne **1** was available in nine steps with an overall yield of 13%. Although the synthesis was reliable and could be performed in gram scale up to the alcohol **8**, the lack of high regioselectivity in the hydroboration reaction was unsatisfactory. Thus, an alternative, more regioselective synthesis to alcohol **8** was developed using a Weinreb amide as a directing group for the hydroboration step (regioselectivity 25:1). The details of this route are shown in the Supporting Information.

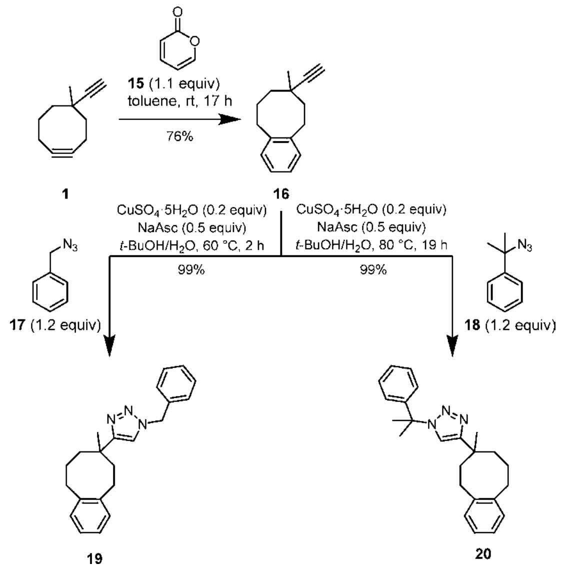
The use of chiral cyclooctynes such as **1** in cycloaddition reactions raises stereoselectivity issues. In order to circumvent such stereoselectivity challenges, synthesis of an achiral (ethynylcyclopropyl)cyclooctyne **2** was envisaged. One further advantage of the use of a C_s-symmetrical cyclooctyne is the formation of a single regioisomer upon cycloaddition with an organoazide. The *exo*-diastereomer was chosen in order to avoid intramolecular side reactions of both triple bonds. The synthesis of cyclooctyne **2** is described in Scheme 2 and began with a Rh-catalyzed cyclopropanation of COD (**5**) with diazo compound **14**,[12] which gave *exo*-**11** in moderate yield and excellent diastereoselectivity (dr 41:2). Following the reversed protocol of van Delft, *exo*-**11** was converted to **12** in quantitative yield after bromination and reduction. The subsequent treatment with KO-*t*-Bu gave the corresponding alkenyl bromide (not shown) in good yield. The terminal alkyne was installed via the Ohira-Bestmann reaction and afforded **13** in 60% yield. Finally, cyclooctyne **2** was formed after LDA-induced elimination to yield the product in a total of seven steps in 20% yield from COD (**5**). Notably, attempts to get the desired product directly from the corresponding dibromide by double elimination failed.

Scheme 2. Synthesis of Cyclooctyne 2



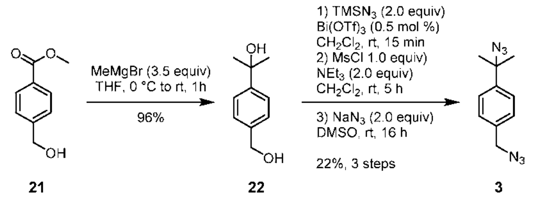
A necessary prerequisite for the defined construction of layers with a "double-click" approach is the use of a bis-azide with inherently different reactivities for the two azido groups in AAC. The utilization of steric effects is a reliable strategy to influence the reactivity of functional groups. Therefore, a comparison of the AAC reactivities of the primary azide **17** and the tertiary azide **18** was undertaken (Scheme 3). Treatment of the α-pyrone **15** with cyclooctyne **1** led, via Diels−Alder/retro-Diels−Alder reaction, to the benzocyclooctene **16**. With compound **16**, the impact of steric shielding of the azido group in CuAAC was examined. In the presence of $CuSO_4$ at 60 °C, alkyne **16** selectively reacted with benzyl azide **17** to afford the triazole **19** in high yield. Under the same conditions, no reaction of **16** with the sterically more hindered azide **18** was observed. To get the desired triazole **20**, higher temperatures (80 °C) and longer reaction times were needed. The differences in reactivity opened up an opportunity to introduce two azido groups with different steric demand into one substrate. This diazide allows for sequential "click" reactions to build up defined chains without a protection/deprotection procedure. Thus, unsymmetrical diazide **3** was identified as an appropriate candidate for the intended subsequent chemistry.

Scheme 3. Reactivity Studies of Alkyne 1 in CuAAC



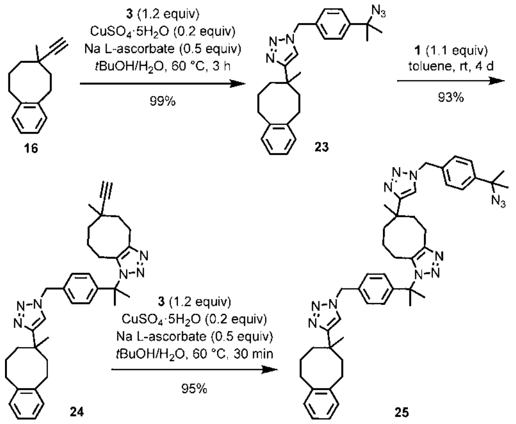
The selected diazide **3** was synthesized starting from commercially available benzoate **21** (Scheme 4). First, **21** was converted into diol **22** using methylmagnesium bromide. Next, the tertiary alcohol was substituted onto an azido group under S_N1 conditions.[13] The remaining alcohol was then transformed into the corresponding mesylate, which was treated with sodium azide in DMSO to give the desired diazide **3** in overall moderate yield.

Scheme 4. Synthesis of Diazide 3



With the building blocks **1**, **3**, and **16** in hand, the sequential chemoselective combination of CuAAC–SPAAC reactions was examined next (Scheme 5). The CuAAC of **16** with diazide **3** gave the triazole **23** chemoselectively; only the reaction of the primary azido group was observed. Subsequent SPAAC of **23** with cyclooctyne **1** led to the chemoselective formation of bis-triazole **24** as a mixture of regioisomers. Another CuAAC with diazide **3** led to the cycloadduct **25** as a mixture of regioisomers with respect to the central triazole ring. The reaction sequence (**16** → **25**) proves the envisaged chemoselectivity in the reaction of the bifunctional building blocks **1** and **3**. The regioselectivity problem with the SPAAC of **23** and **1** can be circumvented by use of the symmetrical bis-alkyne **2**.

Scheme 5. CuAAC–SPAAC Reaction Sequence



In order to develop the chemoselective CuAAC-SPAAC reaction toward a surface LBL sequence, a molecular surface was chosen as model system first. Due to its rigid subunit as well as its high level of functionality, literature known cholic acid derivative **26**[14] (Figure 3) was identified as an appropriate molecule to mimic surface chemistry. Put in simplified terms, compound **26** could be considered as a model system for an azide-terminated surface. Performing the LbL assembly with **26**, the bis-alkynes (**1**, **2**) and the diazide **3** should give a meaningful prediction about the expected chemoselectivity, particularly of the CuAAC, on a real surface (e.g., Si(001)).[15]

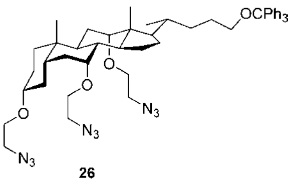
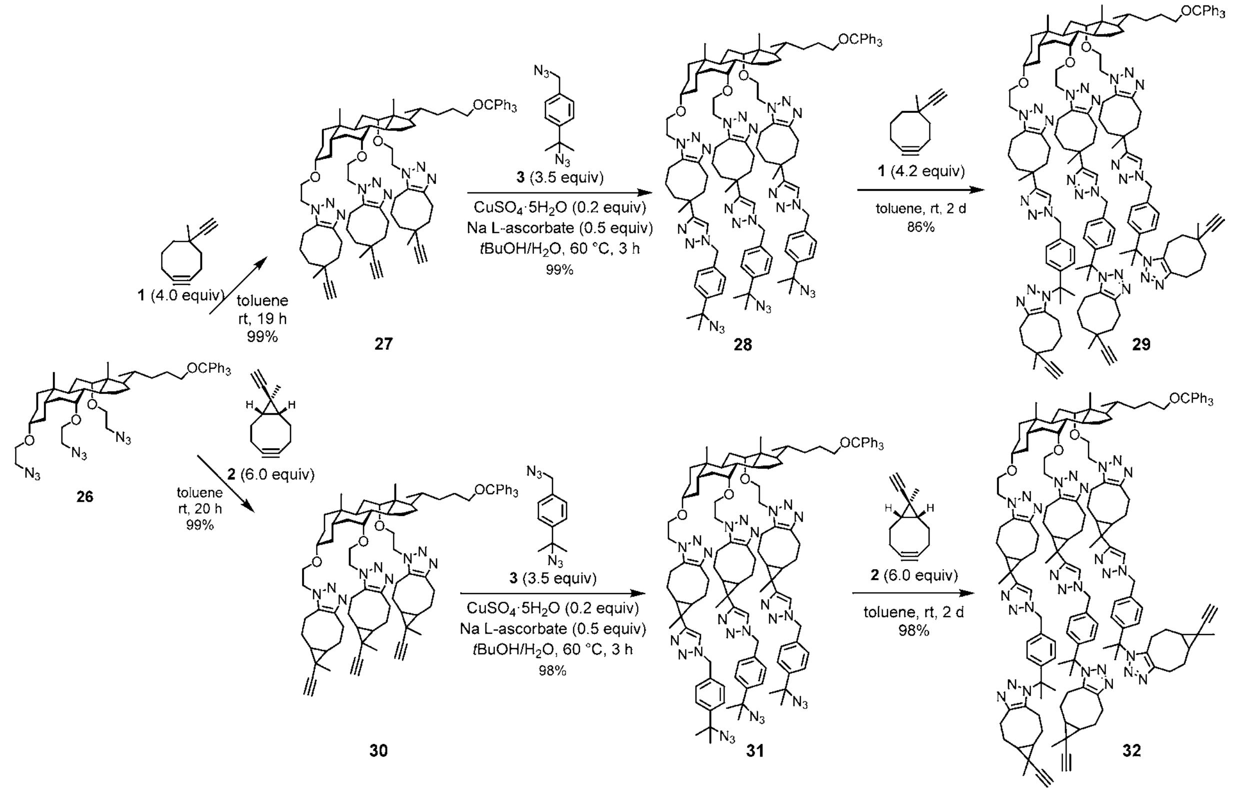


Figure 3. Structure of the cholic acid derived triazide **26**.

SPAAC of the bis-alkyne **1** and the triazide **26** provided the tris-triazole **27** in quantitative yield as a mixture of regio- and diastereomers (Scheme 6). The subsequent 3-fold CuAAC with the diazide **3** led to a second triazole layer. The third triazole layer was prepared by another SPAAC with the bis-alkyne **1** to deliver the nonatriazole **29**. Inspection of the ^1H NMR data and the ESI MS spectra revealed that no intramolecular side reactions took place during the cycloaddition sequence (**26** → **29**). The formation of regioisomers in the SPAAC could be avoided using the symmetrical bis-alkyne **2**. SPAAC of **26** with **2** gave the tris-triazole **30** as only product. Subsequent 3-fold CuAAC with the diazide **3** installed chemoselectively the second triazole layer in **31**. SPAAC of the latter with **2** resulted in formation of the nonatriazole **32** with three triazole layers.

In conclusion, a LBL approach for an "azide surface" has been developed by combining bis-alkynes and diazides with different reactivities in SPAAC/CuAAc reaction sequences. The strategy

Scheme 6. CuAAC−SPAAC LbL Synthesis Using the Triazide 26



developed in solution here should be adaptable to solid surfaces with potential applications in for semiconductors.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02048.

Experimental details; spectroscopic and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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