

Supramolecular Chemistry | Hot Paper |

A Giant [8 + 12] Boronic Ester Cage with 48 Terminal Alkene Units in the Periphery for Postsynthetic Alkene Metathesis

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Abstract: Dynamic covalent chemistry (DCC) is a powerful synthetic tool to construct large defined molecules in one step from rather simple precursors. The advantage of the intrinsic dynamics of the applied reversible reaction steps is a self-correction under the chosen conditions, to achieve high yields of the target compound. To date, only a few examples are known, in which DCC was used to build up a molecular defined but larger product that was chemically transferred to a more stable congener in a second (irreversible) step. Here, we present a nanometer-sized [8 + 12] boronic ester cage containing 48 peripheral terminal alkene units which allows to put a hydrocarbon exoskeleton around the cage via alkene metathesis.

The concept of dynamic covalent chemistry (DCC)^[1] has pushed supramolecular and materials chemistry tremendously forward, because it allows the access to compounds that are otherwise difficult to achieve by “classical” synthetic approaches. The reversible nature of DCC provides a self-correction mechanism, generally resulting in high yields of thermodynamically driven products. Impressive examples are interwoven structures such as borromean rings,^[2] knots,^[3] giant organic cages and their catenanes,^[4] or orthoester cryptates,^[5] which are formed in a single step from readily available precursors. The advantage of DCC, the reversibility of formed covalent bonds, is at the same time a disadvantage due to the lack of thermal and chemical stability of the cage compound: When conditions are significantly changed, the thermodynamic equilibrium may shift towards a cleavage of the DCC product. Therefore, a second chemical transformation step is desirable to capture the initial DCC product. This is most trivial for imine-based compounds, which for instance can be transferred to corresponding amine groups by a simple reduction of the imine-bonds with complex hydrides. Recently, our group has

demonstrated that imine-based cages can also be stabilized by postsynthetic chemical reactions or complexation of cationic guest molecules.^[6] Although less common, disulfide-based macrocycles and cages can be transformed to the corresponding thioethers.^[7] For boronic esters, no direct transformation to a more stable functional group exists. Therefore, a remote functional group needs to be attached to the precursor, which can undergo an orthogonal reaction after the DCC product by generation of boronic ester units was formed. A few years ago, Lüning et al. described the covalent capture of a small DCC-compound consisting two boronic ester units by a twofold alkene metathesis reaction.^[8] Later on the method has been expanded to a triboronic ester, giving a macrocycle in 72% yield after threefold metathesis and subsequent hydrogenation of the alkene bonds.^[9] To the best of our knowledge no approach has been described to post-react a substantially larger discrete molecule achieved by DCC to capture the product by a second orthogonal covalent bond formation.

However, it is worth mentioning that a very few examples have been published, where a similar concept has been established for systems where the molecular subunits self-assembled by other reversible interactions such as metal coordination, π - π -stacking or hydrogen bonding before linking those covalently in a subsequent reaction. Already in 2003 Inomata and Konishi described that six porphyrin units are preorganized by thiol-gold interactions on a Au₅₅ nanoparticle before performing a twelvefold alkene metathesis reaction.^[10] Shionoya et al. made use of the formation of a Pd-based octahedron containing peripheral allyl ether units for the subsequent metathesis. After successful twelvefold alkene metathesis, the palladium ions were removed and the alkene units hydrogenated, giving a flexible purely organic cage.^[11] Leigh et al. obtained a star-like structure of fivefold symmetry by coordination of iron(III) with a tris(bipyridine) ligand containing peripheral alkene units, which was then stabilized by a fivefold alkene metathesis reaction.^[12] Recently the same concept was applied to generate new types of knots by the same group.^[13] Otto et al. exploited a dithiol building block creating a dynamic combinatorial library (DCL) with macrocycles of different sizes. The six-membered macrocycles self-assembled through π - π -stacking to supramolecular polymers of different lengths, which were then modified by orthogonal formation of disulfide bridges.^[14] Some time ago, the Böhmer group demonstrated that two calix[4]arenes forming a hydrogen-bonding dimer can be transformed into a multi-catenane via eightfold ring-closing metathesis.^[15] All those approaches have in common that the two types of bonding have to be orthogonal.^[16]

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Here we present the formation of a [12+8]-boronic ester cage, containing 48 terminal alkene units that can undergo alkene metathesis to generate a second (hydrocarbon) exoskeleton around the boronic ester cage core. The precursor was thoroughly constructed on the basis of a crystal structure of a [12+8] boronic ester cage (Figure 1).^[4a] Molecular modelling revealed that the ethyl chains should be replaced by rigid phenylacetylene units. In order to bridge those via two adjacent

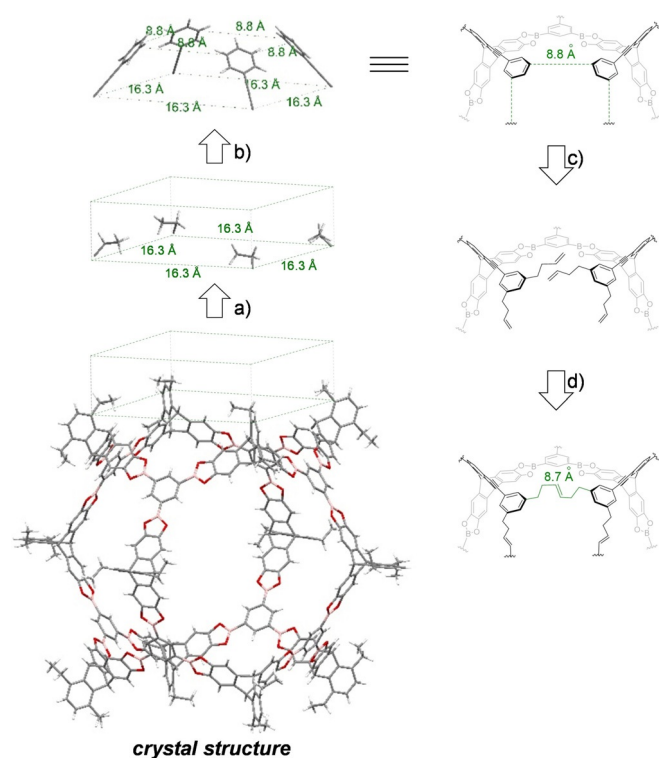


Figure 1. Evolution of the precursor design for boronic ester cage **9**. Bottom, left: Representation of the structure of ethyl [8+12] boronic ester cage as determined by X-ray crystal structure analysis.^[4a] Middle, left: Section of the cage showing a longitudinal distance of 16.3(±0.4) Å between the closest aryl carbons. Top, left: Exchange of the ethyl units by phenylacetylene substituents; the distance between two *meta*-positions of the phenyl rings is 8.8(±0.5) Å. Top, right: Top view of the same representation. Middle, right: Introduction of butenyl chains into the skeleton. Bottom, right: Cross-linking of the butylene chain after a ring-closing metathesis would lead to a linking hex-3-enylene unit with a length of 8.7 Å.

3,5-positions (distance of 8.8 Å), these should ideally be equipped with two 4-butenyl chains that could participate in a proximal oriented ring-closing metathesis. The resulting chain would cover a distance of 8.7 Å to generate a C–C-bonded outer exoskeleton around the boronic ester cage. Shorter olefinic substituents are considered to prefer undesired intermolecular alkene metathesis and longer ones could undergo unfavoured intramolecular distal crosslinking; both need to be avoided. As a result of these considerations, triptycene tetraol **7** was targeted as ideal precursor (see Scheme 1).

Tetraol **7** was synthesized in five consecutive steps (Scheme 1), beginning with a nucleophilic substitution of the two benzylic bromides of **1** with allyl magnesiumbromide, giving **2** in 90% yield. Sonogashira–Hagihara reaction with TMS-acetylene (TMS=trimethylsilyl), and subsequent desilylation gave **3** in 55% yield. The phenylacetylene was selectively deprotonated with *n*BuLi at the alkyne moiety and added to the carbonyl groups of quinone **4**, followed by in situ reduction with SnCl₂ to give triptycene **5**. Attempts to obtain tetraol **7** directly from triptycene **5** turned out to be a challenging task due to its high sensitivity to oxidation of the catechol subunits. Although a de-etherification of the methoxy groups with trimethylsilyliodide was successful, we were not able to highly purify the resulting TMS-ether by common means (column chromatography, recrystallization, etc.), which is important to avoid mismatches during cage-formation.^[17] In order to tackle this issue, triptycene **5** was directly converted to acetate **6** by addition of Ac₂O to the in situ formed TMS-ether. Acetate **6** was stable enough to be purified by column chromatography. Finally, tetraol **7**, the precursor for the boronic ester cage, could be generated by deprotection under mild basic conditions. As mentioned above, tetraol **7** was very sensitive to oxidation by air, so that even careful working with Schlenk-techniques could not totally prevent the compound from partly oxidizing to *o*-quinone derivatives. Therefore, ascorbic acid was added to generate pure **7** in a yield of 92%, which was directly used for the next step.^[18] Twelve molecules of tetraol **7** and eight molecules of boronic acid **8** reacted in a 48-fold condensation to give cage compound **9** in 70% yield after purification by size exclusion chromatography. The ¹H NMR spectrum of cage **9** showed all expected signals (Figure 2), and all of them could be assigned by 2D NMR experiments. The protons of the

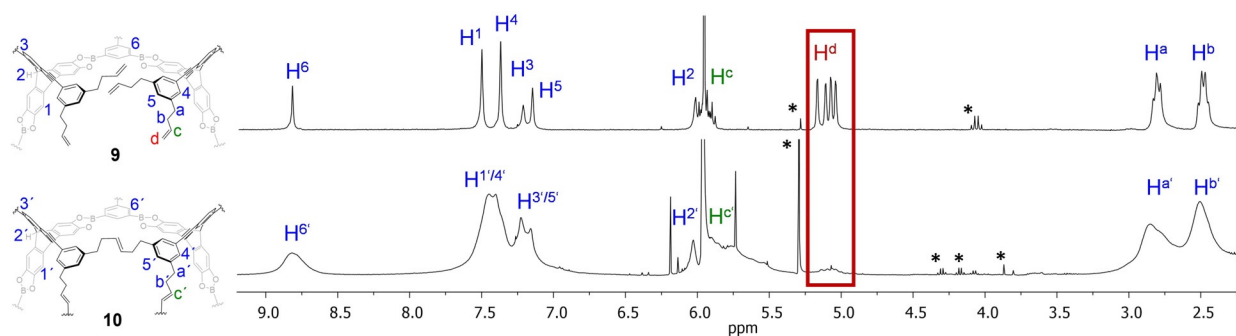
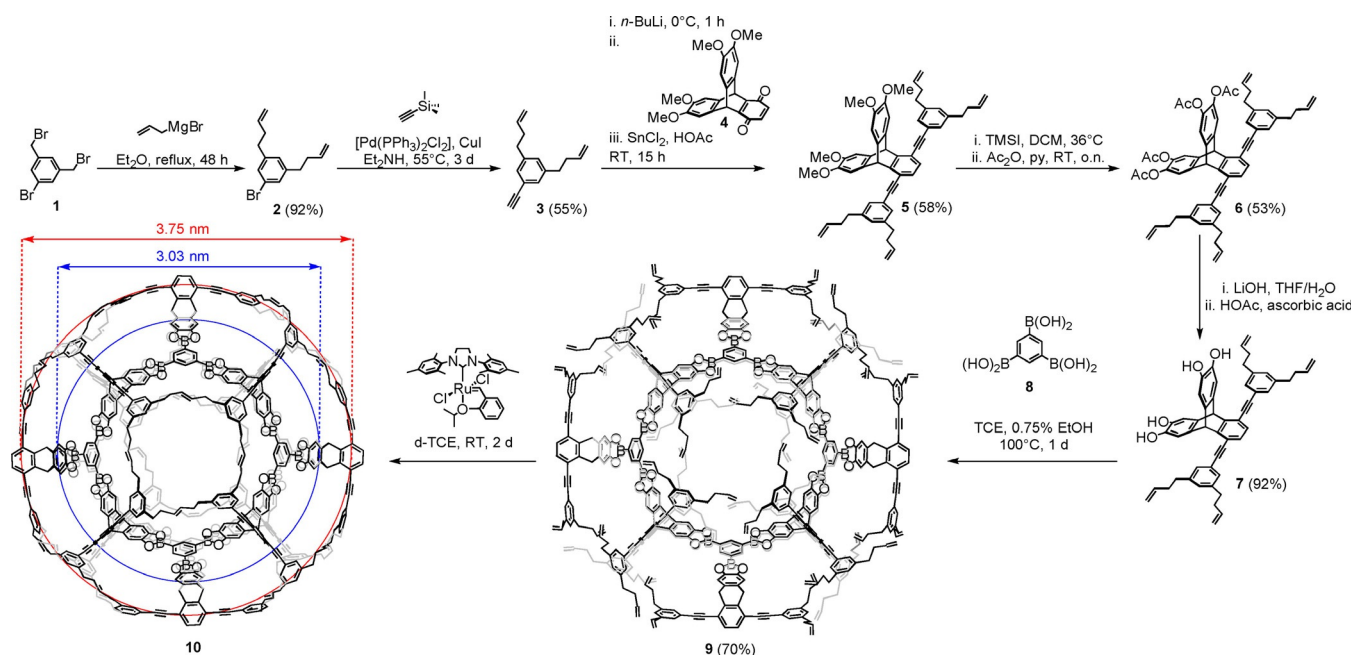


Figure 2. ¹H NMR spectra (400 MHz, Cl₂CDCl₂, 298 K) of the reversible formed template **9** and irreversible locked cage **10**. The impurities marked with * corresponds to residual solvents. For full NMR spectra see Supporting Information.



Scheme 1. Synthesis of [12+8] boronic ester cage **9**. A 24-fold metathesis leads to a hydrocarbon exoskeleton and cage **10**, respectively. The dimensions of the inner and outer cage are highlighted in blue and red. Note, the size of the inner cage of **10** is assumed to be the same as for precursor. TMS = trimethylsilyl-; d-TCE: deuterion-tetrachloroethane.

terminal alkenes (H^d) resonate as a characteristic multiplet between 5.08 and 5.20 ppm. Moreover, integration of the diagnostic signal showed the expected 2:3-ratio of protons deriving from the two reactant molecules needed for a [12+8] condensation. In addition, the m/z ratio of 9629.4 measured by MALDI-TOF mass spectrometry corresponds to the $[M+H]^+$ signal of **9** (see Supporting Information). Furthermore, the formation of boronic ester units can be confirmed by the appearance of typical bands at 1306 cm^{-1} and 1343 cm^{-1} in the IR spectrum,^[19] while the band at 1641 cm^{-1} corresponds to the C=C bond stretching of terminal alkenes (Figure 3).^[10]

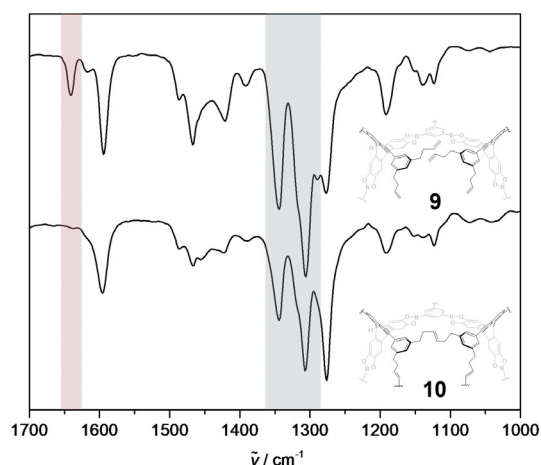


Figure 3. IR spectra of cage **9** and cage **10**. Signal at 1307 cm^{-1} and 1344 cm^{-1} appear after boronic ester formation and can be found in both compounds. The signal at 1641 cm^{-1} of cage **9** disappeared after ring-closing metathesis.

To construct the covalent exoskeleton, cage compound **9** was treated with the Hoveyda–Grubbs 2nd generation catalyst in [D₂]-tetrachloroethane in a sealed vessel for two days. After workup and separation by size-exclusion chromatography, the IR spectrum of **10** confirmed that the boronic ester units are still present (signals at 1307 cm^{-1} and 1344 cm^{-1})^[19] and secondly, the signal at 1641 cm^{-1} corresponding to terminal alkenes disappeared (Figure 3). In addition, the ^1H NMR spectrum of cage **10** shows all expected signals although these are rather broad. Nevertheless, the integrals of the signals in the ^1H NMR spectrum of cage **10** correspond to the expected values. The signal corresponding to the terminal alkenes (H^d) in cage **9** has significantly decreased, proposing that $>95\%$ of all alkene units underwent the alkene metathesis reaction. The broadness of the signals is expected because typically the alkene metathesis is not of high *E/Z*-selectivity^[9] and each of the 24 formed internal olefinic bonds is probably present in two isomeric forms resulting a vast set of overall 2^{24} (16,777,216) possible stereoisomers!^[20] Unfortunately, for cage **10**, no clear reliable mass spectrometric information to underpin the successful metathesis was achieved. However, it is worth mentioning that for some boronic ester cages these were also not detectable by MS, although clearly have been identified by single crystal X-ray diffraction.^[4f,21]

The occurrence of intermolecular reaction of two or more unlinked cage species is unlikely, because the compound **10** was purified by size-exclusion chromatography as single fraction with a comparable retention time as found for cage **9**. Furthermore, by DOSY NMR spectroscopy a hydrodynamic radius is found that is too small for dimeric or oligomeric alkene metathesis products (see discussion below). Defects by distal crosslinking is mainly excluded because the alkenyl teth-

ers should be too short to allow this. The ring-closing metathesis reaction may simply suffer from incompleteness.^[9,22] Thus, the most reasonable explanation are unreacted moieties. In this respect it is worth to mention that Lünig et al. have found ratios between 79:21 and 99:1, respectively, for threefold and twofold (incomplete) metathesis reactions of a precursor containing six terminal alkenes.^[9] In this respect a conversion of > 95% is most likely at the edge of possibilities. Note that neither the addition of more catalyst nor the change in conditions led to significantly different results.

¹H DOSY experiments of compounds **9** and **10** were carried out to estimate the sizes of the cages (Figure 4). The spectra clearly revealed that no larger (polymeric) species were present in the samples of **9** and **10**, respectively, since only one trace of signals each has been found with the same diffusion coefficients and no signal corresponding to a lower diffusion coefficient was detected. Consequently, the intramolecular ring-closing metathesis is preferred under the investigated conditions. The hydrodynamic radii (r_{H}) were estimated by exploiting a semi-empirical modification of the Stokes–Einstein equation proposed by Chen et al. (see Supporting Information).^[23] The hydrodynamic radius of cage compound **9** was estimated to be $r'_{\text{(H)}} = 1.42$ nm. This value is in good agreement with the anticipated value of 1.51 nm derived from the boronic ester scaffold (Scheme 1) and comparable to values found before for other boronic ester cages.^[4a,b,e] The ring-closing metathesis led to an additional outer shell around the boronic ester cage **10**. The calculated hydrodynamic radius of $r'_{\text{(H)}} = 1.94$ nm is in good agreement with the expected radius of the outer exoskeleton (1.88 nm; Scheme 1). To the best of our knowledge, there is not much known about the effect of open and closed shell 3-dimensional sphere-like molecules of comparable size on diffusion coefficient studied by NMR spectroscopy. But it seems reasonable that the diffusion behaviour of cage **9** and **10** is affected by the periphery as observed. This assumption is supported by a similar observation recently made by Li et al.

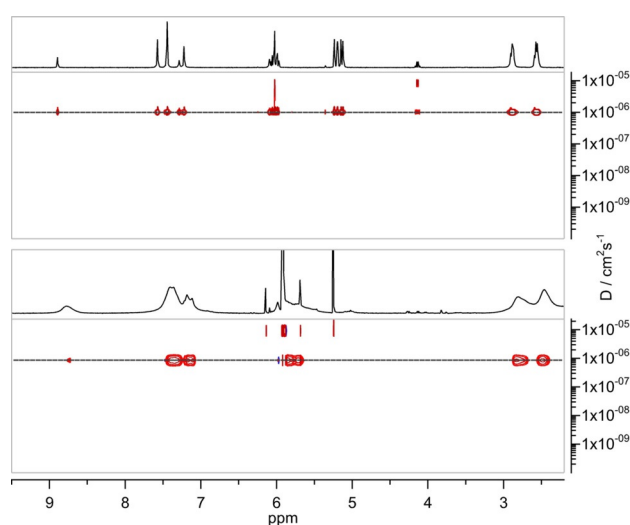


Figure 4. Comparison of ¹H DOSY spectra of cage **9** and cage-in-cage compound **10**, respectively (400 MHz, Cl₂CDCl₂, 298 K): $D_{(9)} = 1.00 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ and $D_{(10)} = 7.08 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$.

for large coordination macrocycles of the same outer shape but different size of the inner pore by ¹H DOSY experiments, which at least shows the same trend as we observed.^[24]

In summary, we showed that by rational design of a large discrete cage molecules derived by dynamic formation of 24 boronic ester bonds consisting 48 terminal alkene bonds can undergo an orthogonal 24-fold alkene metathesis reaction to create an exoskeleton around nanosized shape-persistent cage. It has to be mentioned that > 95% of all 48 alkene units have been transformed in an intramolecular fashion; to the best of our knowledge, the far largest number of alkene bonds formed in a discrete monodisperse molecule.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: boronic esters · covalent capture · organic cage · ring-closing metathesis · self-assembly

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