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# Covalent Assembly of Heterosequenced Macrocycles and Molecular Cages through Orthogonal Dynamic Covalent Chemistry (ODCC)

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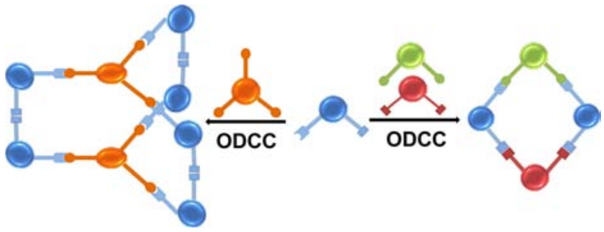
## ABSTRACT



**Shape-persistent heterosequenced 2-D macrocycles and 3-D molecular cages have been prepared in one pot from two or three different monomers, through orthogonal dynamic covalent chemistry using dynamic imine and olefin metathesis.**

Shape-persistent two-dimensional (2-D) macrocycles and three-dimensional (3-D) molecular cages have been the focus of a growing amount of research in the past 20 years. Two-dimensional shape-persistent macrocycles[1] have been explored for applications, such as conducting molecular wires,[2] sensors,[3] and liquid crystals.[2b,4] Three-dimensional organic molecular cages[5] have been studied for catalysis,[6] gas adsorption,[7] and small-molecule separation.[8] There have been many advances in the thermodynamically controlled synthesis of these molecules using dynamic covalent chemistry (DCvC). DCvC relies on reversible covalent bond-forming reactions, such as imine metathesis, olefin metathesis, and boronic acid condensation, to arrive at thermodynamically most favored species.[9] However, current molecular architectures constructed

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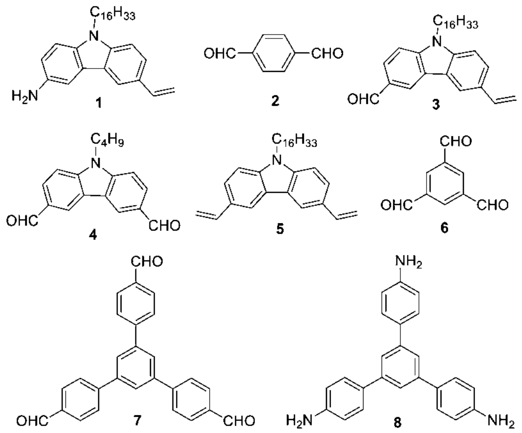
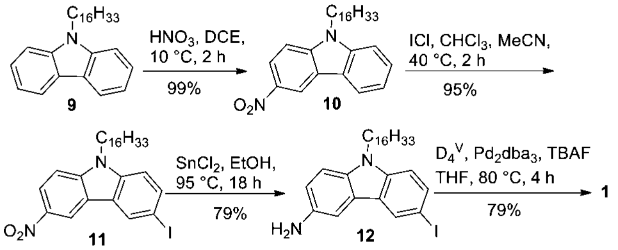
through DCvC are mainly limited to homosequenced, highly symmetric ones, usually bearing a single type of functionality.[1d,e,10] In order to realize more complex, multifunctional molecular architectures, heterosequenced targets with more than one type of functionality are highly desired.[11] Up to date, heterosequenced architectures typically have been constructed under kinetically controlled conditions that frequently employ lengthy stepwise syntheses resulting in low overall yields.[1a,c−f] In order to address this problem, we began exploring the concept of orthogonal dynamic covalent chemistry (ODCC), conducting two dynamic covalent reactions in a one-pot fashion.[12] Previously, we successfully prepared a series of heterosequenced benzene-based macrocycles through one-pot imine condensation/metathesis and olefin metathesis.[12] Herein, we demonstrate that heterosequenced rectangular-shape macrocycles containing up to three different building blocks can be successfully constructed via one-pot ODCC. The same strategy was also applied to the synthesis of a more challenging target, a shape-persistent 3-D molecular cage containing eight monomer units.

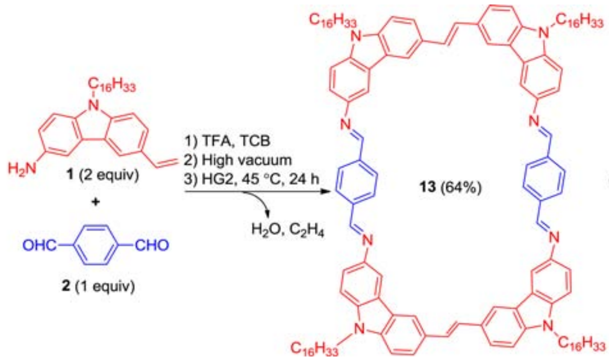
**Scheme 1.** Building Blocks for Macrocycles and Cages Through ODCC



**Scheme 2.** Synthesis of Monomer **1**



In our previous communication, we reported that macrocycles of different size and shape can be prepared from combinations of a small set of monomers, *ortho*-, *meta*-, or *para*-substituted phenylenes.[12] In this work, we examined readily available carbazole-containing monomers (**1**, **3**−**5**) which can serve as rigid 90° corner pieces in the syntheses of rectangular macrocycles (Scheme 1). The electron-rich characteristics of the carbazole building blocks makes these macrocycles interesting candidates for electronic device applications, particularly for those donor−acceptor systems. Carbazole monomer **1** was prepared from 9-hexadecyl-9H-carbazole (**9**) through mononitration using 70% nitric acid,[13] iodination, reduction of the nitro group, followed by vinylation (Scheme 2).[14] In our initial trial, we explored utilizing two-component ODCC to prepare rectangular-shape macrocycle **13**. The carbazole monomer **1** (2 equiv) was reacted with 1,4-phthalaldehyde **2** (1 equiv) in 1,2,4-trichlorobenzene (TCB) using trifluoroacetic acid (TFA) as the catalyst. After 30 min, the reaction mixture was exposed to vacuum to remove the acid and water byproduct. Hoveyda-Grubbs second-generation catalyst (HG2, 5 mol % per vinyl group) was then added, and the reaction mixture was heated at 45 °C under open argon atmosphere to remove ethylene byproduct. After stirring for 22 h, macrocycle **13** was obtained in good isolated yield (64%, eq 1).



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Given the successful synthesis of macrocycle **13** consisting of two different building blocks, we next explored the three-component macrocycle synthesis. Although dynamic covalent chemistry has shown numerous successes in the covalent assembly of sophisticated molecules, the incorporation of three or more building blocks is still challenging and largely unexplored. Simultaneous utilization of two dynamic covalent reactions that do not interfere with each other allows easy access to multicomponent assembly with increased complexity.[11a,c,15] In covalent self-assembly, the component structures, functionality, and the ratio of complementary functional groups determine the assembly process and outcome. We envisioned that three-component macrocycles could be obtained by manipulating

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the substitution pattern and ratio of the functional groups. We chose vinylaminocarbazole **1**, diformyl carbazole **4**, and divinyl carbazole **5** as the three monomers. Two possible macrocycles, **14** and **15**, with minimum angle strain and fewest building units, can be formed from the above three monomers. We installed *n*-butyl chain instead of *n*-hexadecyl in monomer **4** in order to differentiate macrocycles **14** and **15**, which otherwise have identical molecular weights in the MALDI-MS spectrum. Although macrocycles **14** and **15** have similar thermadynamic stability, with a 2:1:1 ratio of monomers **1**, **4**, and **5** used and all the end-groups reacted, macrocycle **14** is expected to be the predominant product instead of macrocycle **15** at the equilibrium. We followed the same procedure as previously described: addition of TFA to the mixed solution of three monomers in TCB, stirring for 30 min, application of the vacuum, then olefin metathesis. As expected, macrocycle **14** was indeed formed predominantly after 48 h, evidenced by the $^1$H NMR analysis (Figure 1a). We observed a small amount of homosequenced macrocycle **15**[10] as a side product. In the MALDI-MS spectrum, we also observed acyclic dimer and trimer of monomer **5**, whose molecular weights are 836 (M + Na$^+$) and 1282 (M + Li$^+$), respectively. The macrocycles **14** and **15** were inseperable through either flash column chromatography or recrystallization. It should be noted that the $^1$H NMR chemical shifts of macrocycles vary significantly with the change in their concentrations, and it was difficult to differenciate the peaks of macrocycle **15** from other oligomeric side products in the crude product $^1$H NMR. Therefore, the ratio of **14**:**15** (7:1, mol/mol) was determined after purification based on the $^1$H NMR integration (Figure 1a, IV). The formation of macrocycle **15** can be minimized with the use of 0.7 equiv of monomer **5**. The pure cyclic tetramer **14** was obtained after purification through column chromatography followed by recrystallization in benzene (Figure 1a, II). Although macrocycle **14** appears to be the predominant product in $^1$H NMR spectra and GPC trace of the crude product mixture (Figure 1a, I and III), the pure compound **14** was obtained in a low isolated yield (20%), presumably due to the weight loss during the purification process. Macrocycles **13** and **14** were fully characterized using $^1$H NMR, HSQC, HMBC, MALDI-MS, and GPC (SI).

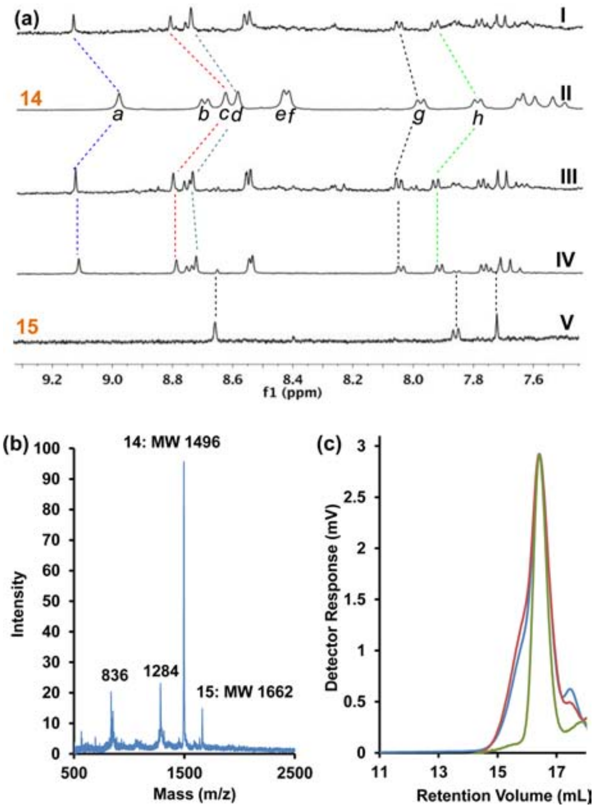
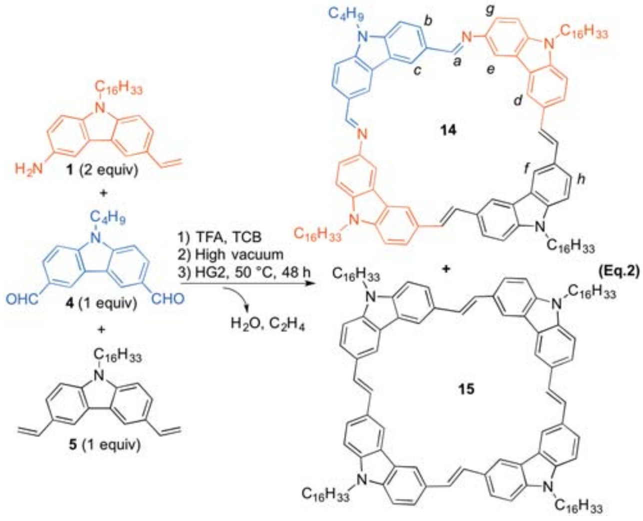
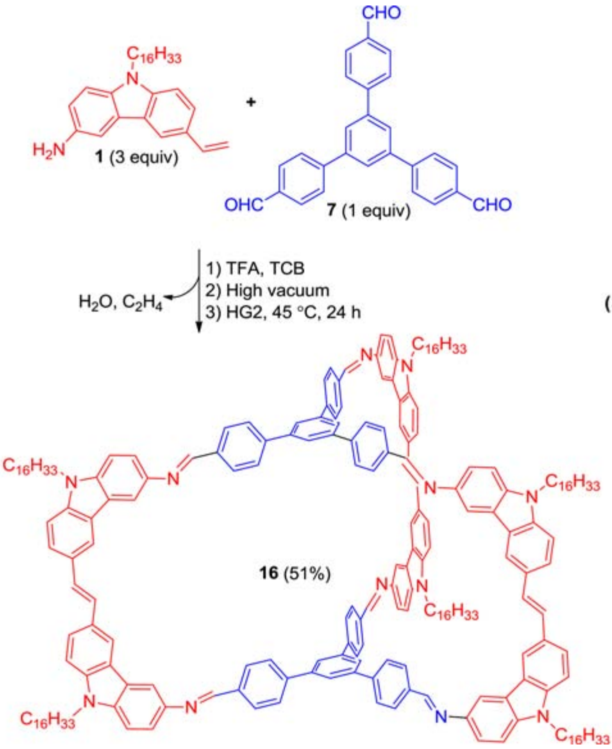


**Figure 1.** (a) $^1$H NMR spectra of crude product of eq 2 using 2:1:0.7 ratio of **1**:**4**:**5** (I), 2:1:1 ratio of **1**:**4**:**5** (III), the purified product of eq 2 using 2:1:0.7 ratio of **1**:**4**:**5** (II), 2:1:1 ratio of **1**:**4**:**5** (IV), pure macrocycle **15** (V). (b) MALDI-MS spectrum of the crude product of eq 2 using 2:1:1 ratio of **1**:**4**:**5**; (c) GPC trace of the crude product of eq 2 using 2:1:0.7 ratio of **1**:**4**:**5** (blue), 2:1:1 ratio of **1**:**4**:**5** (red), and the purified product (green).



With the successful synthesis of the heterosequenced macrocycles, we next investigated whether this ODCC approach could also be applied to the synthesis of more challenging 3-D cage-like structures. Providing 90° angle, 3,6-disubstituted carbazole moieties can serve as cornor pieces of trigonal prismatic cages assembled with six carbazole building blocks and two flat top and bottom panels. We initially tested the ODCC reaction between trialdehyde **6** and vinylaminocarbazole **1** in a 1:3 ratio. The imine condensation was successful, providing the imine intermediate. However, the olefin metathesis step was sluggish with the appearance of a shoulder in the higher molecular weight region in GPC trace even after extended reaction times (72 h), at higher temperatures (55 °C), and with addition of more catalyst (30 mol %). We failed to obtain the pure cage product through commonly used purification methods. In great contrast, when we reacted larger size trialdehyde **7** with carbazole **1** in a 1:3 ratio, both the imine and olefin metathesis proceeded smoothly (eq 3). The progress of the reaction was monitored by GPC. The GPC traces at



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different reaction time showed the gradual conversion of the monomers into the cage compound **16** along the reaction pathway (Figure S3). We obtained the purified product in decent yield (51%) by passing the crude product through a short plug of silica gel using chloroform as the eluent. We observed lower recovery yield when longer columns were used. The synthesis of cage **16** was also examined in a true one-pot, orthogonal fashion, by adding both acid and olefin metathesis catalysts at the same time with no preformed intermediate and high-vacuum condition. While the cage product was formed as indicated by GPC and MALDI-MS (Figures S4 and S5), we observed a broader peak in GPC compared to the sharp single peak that we observed under the stepwise reaction conditions. Nevertheless, this result indicates the feasibility of operating dynamic imine and olefin metathesis simultaneously to achive complex molecular architectures.

In conclusion, we have demonstrated that the ODCC methodology can be successfully applied to the synthesis of heterosequenced carbazole-containing macrocycles consisting of up to three different building blocks as well as the construction of a 3-D shape-persistent molecular cage. This proctocol would be a nice addition to the current tool box of dynamic covalent chemistry, easily accessing more complex macrocycles and cages with tunable shapes, sizes, and symmetries.

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**Supporting Information Available.** Materials and general synthetic methods, experimental procedures, GPC graphs, MALDI and NMR spectra of the selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.