A Simple, Efficient Route to Cage Compounds via Zirconocene Coupling

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Macrobicyclic (cage) molecules possessing an intramolecular cavity are of interest due to their potential host/guest properties,[1] as well as their use as nanoscaled building blocks for supramolecular assemblies.[2] An attractive synthetic strategy for the construction of such cages involves the dimerization of trifunctional, concave molecular precursors. However, attempts to employ this approach via 3-fold C−C couplings have been associated with multistep procedures, low yields, high dilution conditions, and difficult separations since formation of the desired cage is statistically disfavored.[3]

We have recently described efficient synthetic routes to macrocycles[4] and polymers[5] based on the zirconocene coupling of diynes possessing rigid spacer groups. This process involves the formation of C−C bonds, and with silyl substituents in the alkynyl groups, the coupling is highly regioselective and reversible. It is the reversible nature of these couplings which provides efficient, high-yield routes to particular macrocyclic structures. The macrocycles thus formed contain zirconacyclopentadiene fragments, which allow further derivatizations. Here, we report that this efficient cyclization reaction may be extended to three dimensions, in the coupling of suitable triynes to cagelike structures with all-carbon or carbosilane frameworks.

The starting triynes **1** and **2** (Figure 1) were prepared by standard procedures.[6] The zirconium-containing macrobicycles **3** and **4** were isolated in 82 and 78% yields, respectively, via addition of ^{n}BuLi to a cold (−78 °C) THF solution containing Cp_2ZrCl_2[7] and the appropriate triyne. Yellow crystals of **3** and **4**, which are moderately air-sensitive, were obtained from THF/hexane. Crystals of **3** contain four molecules of THF per cage, none of which occupy the central cavity of the cage. Molecules of **3** (Figure 1) possess a crystallographic 2-fold axis which parallels the *b* axis and passes through a zirconium atom and the midpoint of the MeSi···SiMe vector. The phenylene groups on each Si atom adopt a propeller-like arrangement. Given the rather acute angle defined by the two C(phenylene)−C(metallacyle) bonds of each zirconacyclopentadiene unit (ca. 50°), the cage takes on a somewhat “collapsed” appearance with an intramolecular Si···Si separation of 6.27 Å.

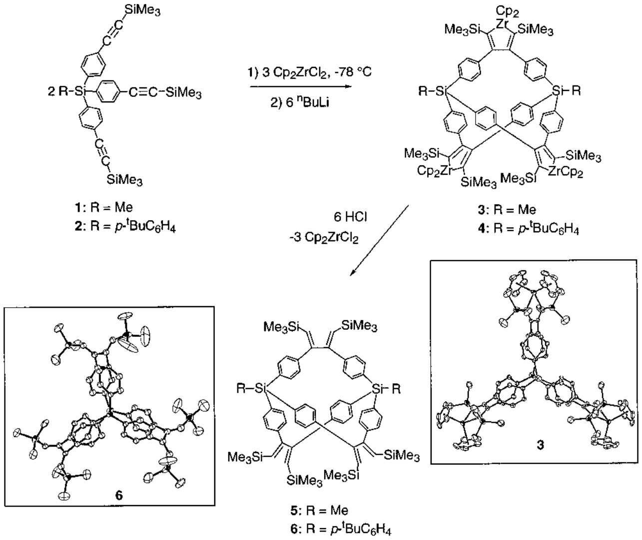

Figure 1. Synthesis of cage molecules **3**−**6**, and ORTEP diagrams for **3** and **6**. Note that the *p*-$^tBuC_6H_4$ groups of **6** have been omitted for clarity.

Compounds **3** and **4** are readily hydrolyzed in high yield (92 and 90%, respectively) to the corresponding cage molecules **5** and **6** (Figure 1). Colorless crystals of **6**, grown from a solvent mixture of toluene and acetonitrile, contain 3.5 equiv of toluene per molecule. The hydrolysis reaction results in a significant twisting of the diene units, such that their torsion angles adopt values of 36(1)°, 43(1)°, and 50(1)°. This conformational change allows for a slight “opening” of the cage, as indicated by a Si···Si distance of 6.78 Å. Variable-temperature NMR studies on **3**−**6** provide room-temperature spectra consistent with the solid-state structures, with inequivalent “inner” and “outer” phenylene hydrogens. The observed coalescence temperatures (77 °C for **3**, $\Delta G^{\ddagger} = 16.2(3)$ kcal mol^{-1}; 72 °C for **4**, $\Delta G^{\ddagger} = 16.0(3)$ kcal mol^{-1}; 77 °C for **5**, $\Delta G^{\ddagger} = 16.1(3)$ kcal mol^{-1}; 67 °C for **6** $\Delta G^{\ddagger} = 15.7(3)$ kcal mol^{-1}) for rotation of the phenylene groups are nearly identical, reflecting similar steric properties for all four cages.

For the coupling of 1,3,5-tris(3′-((trimethylsilyl)ethynyl)phenyl)benzene (**7**; Figure 2), the zirconium-containing product was not isolated and hydrolysis of the latter species in situ gave the 3-fold-coupled dimer **8** in 60% yield. For this synthesis, better results were obtained when the triyne was added dropwise to a preformed, cold (−78 °C) solution of the zirconocene reagent. Compound **8**, which was purified by crystallization from methanol/chloroform, was characterized by NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectrum of **8** revealed the presence of four spin systems for the four inequivalent aromatic protons, as well as one singlet for the olefinic and Me_3Si hydrogens, reflecting C_3-symmetry. Semiempirical calculations (PM3 model)[8] carried out to estimate the geometry of the cavity in **8** indicated an intracavity distance between the central benzene planes of 6 Å. For comparison, attempted coupling of 1,3,5-tris(4′-((trimethylsilyl)ethynyl)phenyl)benzene gave only a complex mixture of products which could not be separated or characterized.

An initial attempt to couple a tetrayne into a cage structure was based on coupling of a cone-shaped calixarene, functionalized

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(1) (a) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; *Monographs in Supramolecular Chemistry*; Royal Society of Chemistry: Cambridge, 1994. (b) Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1994**, *116*, 2301. (c) Dietrich, B.; Viout, P.; Lehn, J.-M. *Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry*; VCH: New York, 1992. (d) Pieters, R. J.; Diederich, F. *J. Chem. Soc. Chem. Commun.* **1996**, 2255.

(2) (a) Moore, J. S.; Zhang, J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 922. (b) Wu, Z.; Lee, S.; Moore, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 8730. (c) Diederich, F. *Nature* **1994**, *369*, 199. (d) Diederich, F.; Rubin. Y. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1101. (e) Saalfrank, R. W. *Nature* **1996**, *383*, 124.

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(5) (a) Mao, S. S. H.; Tilley, T. D. *Macromolecules* **1996**, *29*, 6362. (b) Mao, S. S. H.; Tilley, T. D. *J. Organomet. Chem.* **1996**, *521*, 425.

(6) The triynes **1** and **2** were obtained in 88 and 85% yields, respectively, by reaction of the corresponding alkyltrichlorosilanes with $LiC_6H_4C{\equiv}CSiMe_3$.

(7) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.

(8) Spartan version 4.1; Wavefunction, Inc., 18401 Von Karman Ave., #370, Irvine, CA 92715.

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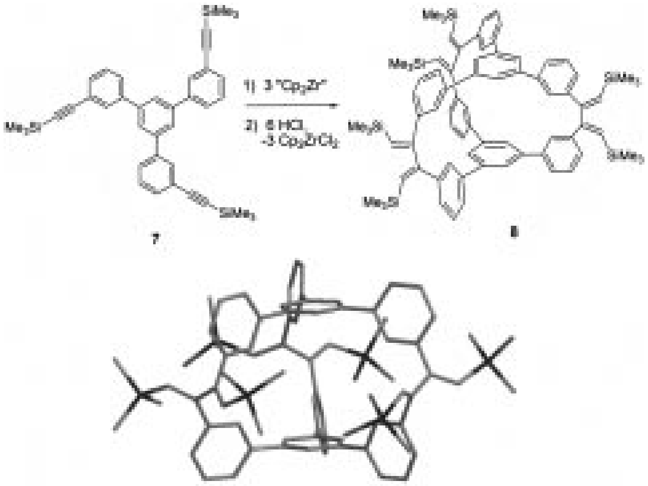
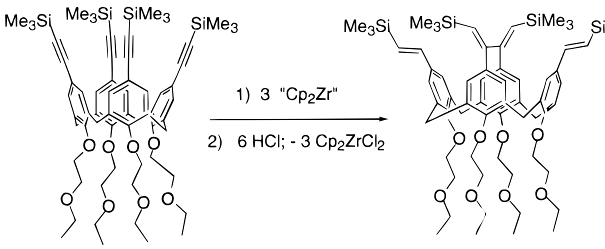


Figure 2. Synthesis and calculated (PM3) structure of **8**.

with four alkynyl groups. However, the coupling of **9** (synthesized by coupling of $Me_3SiC{\equiv}CH$ with the tetraiodo calixarene derivative[9]) did not afford a 4-fold-coupled dimer, but instead resulted in intramolecular coupling of two alkynyl groups to give the bridged calixarene **10** (eq 1). Note that related attempts to dimerize calix[4]arenes have also led to preferred intramolecular coupling.[10] The monomeric nature of the product was determined by mass spectrometry, and the structural assignment is based on NMR spectroscopy. The ^1H NMR spectrum contains two sets of signals for the ethoxyethyl chains and the Me_3Si groups, which integrate in a 1:1 ratio. The facts that the CH_2 bridges appear as a doublet of doublets and that there are only two different singlets for the aromatic protons further indicate that the product must be functionalized diagonally. The aromatic protons of the ethano-bridged aromatic rings are shifted to high field (5.44 ppm) compared to the other aromatic protons (7.04 ppm). The two remaining triple bonds were hydrogenated by excess zirconocene and subsequent hydrolysis. The coupling constant between the olefinic protons of the hydrogenated triple bonds is 15 Hz, indicating the *E*-configuration. Note that similar reactions of triple bonds have yielded the Z-configuration.[11]



(1)

9

10

Application of this coupling method is undoubtedly limited to use of rather rigid poly(yne) starting materials, which may convert to nearly strain-free systems, and by steric demands imposed by the bis(trimethylsilyl)zirconacyclopentadiene fragments. Future work will focus on construction of functionalized cage structures designed to selectively bind small molecules or to serve as building blocks for extended structures.

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Supporting Information Available: Characterization data for compounds **1**−**10**, tables of crystal, data collection, and refinement parameters, bond distances and angles, and anisotropic displacement parameters for **3** and **6** (39 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(10) (a) Siepen, A.; Zett, A.; Vögtle, F. *Liebigs Ann.* **1996**, 757. (b) Blanda, M. T.; Griswold, K. E. *J. Org. Chem.* **1994**, *59*, 4313. (c) Araki, K.; Sisido, K.; Hisaichi, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34*, 8297.

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