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Efficient Diastereoselective Syntheses of Chiral Macrocycles via Zirconocene Coupling. Synthetic Control of Size and Geometry

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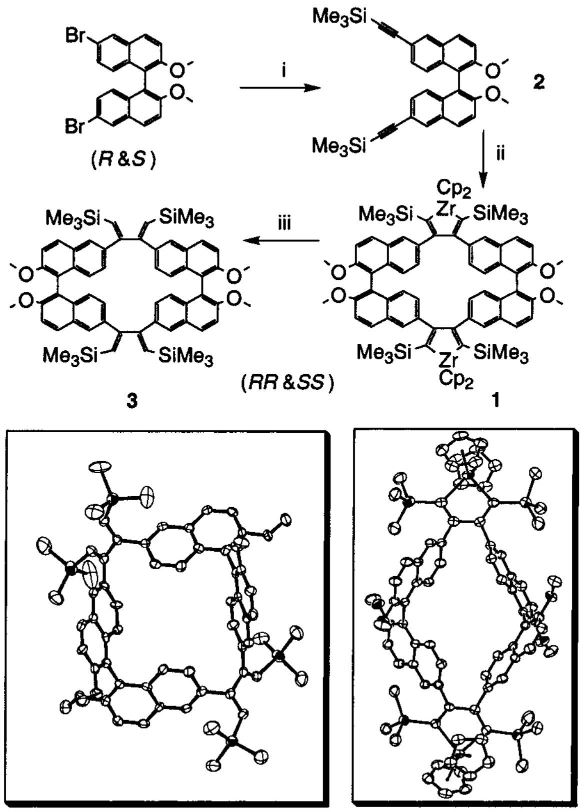
Previous reports from this laboratory have described convenient and high-yield preparations of carbon-based cyclophanes via the zirconocene coupling of silicon-substituted diynes.[1,2] Recently, we have shown that the geometry of rigid building blocks may be used to determine the stoichiometry of coupling to produce macrocycles with different shapes,[2] as well as cage compounds.[3] This methodology has been shown to tolerate various heteroatoms, such that functionalized macrocycles may also be prepared.[4] Herein we report the application of zirconocene coupling in the diastereoselective preparations of functionalized chiral macrocycles from racemic starting materials, via the controlled di- and tricyclizations of chiral diynes.

Chiral macrocycles are desirable synthetic targets due to their extensive use in chiral recognition,[5] and more recently as ligand systems in asymmetric catalysis.[6] However, the preparation of these molecules is often fraught with difficult procedures (e.g., high dilution), low yields, and laborious purifications. Furthermore, syntheses from racemic starting materials typically result in complex diastereomeric mixtures. Thus, the development of efficient, diastereoselective syntheses of these highly desirable compounds from racemic starting materials remains of key interest.

1,1′-Bi-2-naphthol (BINOL) has been used in the preparation of various chiral macrocycles in modest yields, such as those assembled via ether linkages,[7,10] ethynylene spacers,[8,10] and direct BINOL coupling.[9,10] Here we report efficient and high-yield synthetic routes to multigram quantities of chiral BINOL-containing macrocycles using zirconocene coupling. Macrocycles of different size have been accessed by controlling the building block geometry via a simple directing group strategy. Most importantly, we have observed that the zirconocene coupling routes described here proceed in a highly diastereoselective fashion to yield homochiral products.

Scheme 1[a]



[a] Reagents and conditions: (i) $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, HN(*i*Pr)$_2$, toluene, 80 °C, 14 h, 70%; (ii) Cp_2ZrCl_2, 2 equiv, *n*-BuLi, THF, −78 °C to room temperature, 16 h, 91%; (iii) $PhCO_2H$, toluene, room temperature, 14 h, 81%.

Dimeric macrocycle **1** was prepared from the known diyne **2**[11] as shown in Scheme 1, using Negishi-type zirconocene coupling conditions.[12] The combined crops of three recrystallizations from a toluene solution resulted in isolation of orange crystalline **1** in 91% yield. This represents an overall yield of 76% from the BINOL starting material (5.0 g of racemic BINOL gave 6.6 g of macrocycle **1**).

On the basis of the geometry of diyne **2**, we had expected to obtain the product of cyclodimerization. Use of racemic **2** could in principle yield four stereoisomers of macrocycle **1**; however, only one pair of enantiomers was formed in this reaction. Homochiral, enantiopure macrocycles were easily prepared from (*R*)-**2** and gave the same NMR spectra as the macrocycles obtained from racemic **2**. Thus, the diastereoselectivity of this reaction was established; racemic starting materials give homochiral **1**, as confirmed by X-ray crystallography (Scheme 1). Macrocycle **1** has D_2 molecular symmetry and crystallizes as a racemic mixture of chiral macrocycles, with four formula units per unit cell. The distance from one naphthyl plane across the macrocycle to the opposite naphthyl plane is 7 Å. Of particular interest is the large dihedral angle between the naphthyl planes of each BINOL unit (110°). This obtuse dihedral angle deviates substantially from that of the preferred *cisoid* conformation of methyl-protected BINOL, which is <90°.[13] In the case of **1**, the steric constraint of the planar zirconacyclopentadiene rings enforces a larger dihedral angle.

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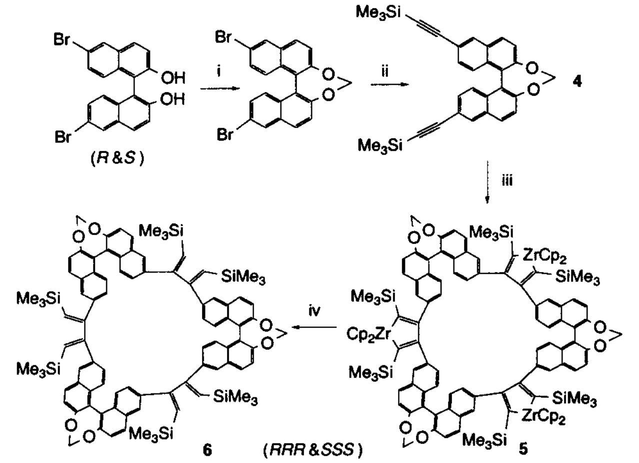
Scheme 2[a]



[a] Reagents and conditions: (i) CH_2I_2, K_2CO_3, DMF, 80 °C, 16 h, 88%; (ii) $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, $HN(iPr)_2$, toluene, 85 °C, 14 h, 91%; (iii) Cp_2ZrCl_2, 2 equiv, *n*-BuLi, THF, −78 °C to room temperature, 4 h, 60 °C, 8 h, 80%; (iv) $PhCO_2H$, toluene, room temperature, 16 h, 87%.

Upon reaction of **1** with benzoic acid, the metal-free macrocycle **3** was obtained in 81% yield. The crystal structure of **3** (Scheme 1) revealed a different macrocycle geometry, in which the twisted diene groups (torsion angle ≈ 66°) result in a smaller dihedral angle for the BINOL units of 101°.

Due to the fact that dimeric macrocycles **1** and **3** require a large dihedral angle between the naphthyl planes, it was anticipated that larger macrocycles could be accessed by restricting the accessible dihedral angles of the BINOL moiety. This was demonstrated with the use of a simple directing group strategy, in which a methylene tether was used to fix the dihedral angle between the naphthalene planes at approximately 60°.[14] Thus, the methylene tether severely limits the accessible dihedral angles, thereby making it very unlikely for cyclodimerization to take place.

The tethered diyne **4** was prepared as shown in Scheme 2, and subjected to standard zirconocene coupling conditions. Heating the reaction mixture to 60 °C for 8 h facilitated the conversion to macrocycle **5** in 80% yield. X-ray quality crystals were grown from a pentane solution at −80 °C (Figure 1). Here, the enforced smaller dihedral angle (an average of 60° in the solid state) had the anticipated effect, in which a larger macrocycle was formed due to zirconocene-mediated cyclotrimerization. Once again, the diastereoselective synthesis of homochiral macrocycles was achieved. In the solid state it is clear that the macrocycle adopts a highly folded geometry, with pseudo-C_2 molecular symmetry. The ^{1}H NMR spectrum of **5** is complex with three equal intensity peaks for both the Cp and $SiMe_3$ groups, indicating that the C_2 symmetric structure is maintained in solution. The rigid structure of macrocycle **5** was demonstrated in a variable-temperature NMR spectroscopic study, which showed that the ^{1}H NMR spectrum remained unchanged up to 70 °C. Thus, the D_3 symmetric representation depicted in Scheme **2** is apparently not accessible due to significant conformational constraints in the molecule.

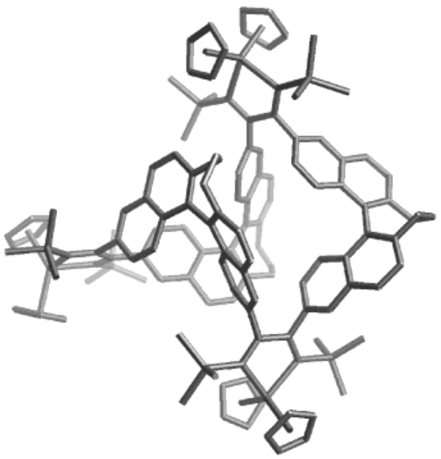


Figure 1. Crystal structure of homochiral (*SSS*), trimeric, zirconium containing macrocycle **5**.

Macrocycle **5** was treated with benzoic acid in toluene to give crude **6** as a yellow solid, which was further purified by precipitation from a benzene solution. In this case, NMR spectroscopy (in $CDCl_3$ solvent) indicated a C_3 symmetric structure. The ^{1}H NMR spectrum of **6** displays signals at 6.22, 5.64, and −0.15 ppm, consistent with vinyl, methylene, and trimethylsilyl groups, respectively. Retention of the trimeric nature of **6** was confirmed by FAB mass spectrometry in which the molecular ion at 1478 *m*/*z* clearly identified the macrocycle, with no observable signals corresponding to decomposed dimeric or monomeric BINOL-containing materials. Therefore, the conversion of **5** to **6** yields a more conformationally flexible macrocycle, resulting in a simplified spectrum that is consistent with a molecular C_3 axis of symmetry.

In conclusion, we have demonstrated the remarkable diastereoselectivity of zirconocene coupling of chiral diynes to give only homochiral macrocyclic products. The influence of building block geometry (as varied by a simple directing group strategy) provides a synthetic route for the selective preparation of either di- or trimeric chiral, functionalized macrocycles. These BINOL-containing macrocycles are of interest as new multiple-site ligands suitable for asymmetric catalysis. Finally, this efficient synthetic route is amenable to large-scale preparations of chiral macrocycles, from racemic starting materials, affording easily isolable crystalline products.

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Supporting Information Available: Text describing the experimental procedure and characterization data, including X-ray crystal structure data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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