

# Assembly of Macrocycles by Zirconocene-Mediated, Reversible Carbon–Carbon Bond Formation

VIKTORIA H. GESSNER, JOHN F. TANNACI, ADAM D. MILLER,  
AND T. DON TILLEY\*

*Department of Chemistry, University of California, Berkeley, Berkeley,  
California 94720-1460, United States*

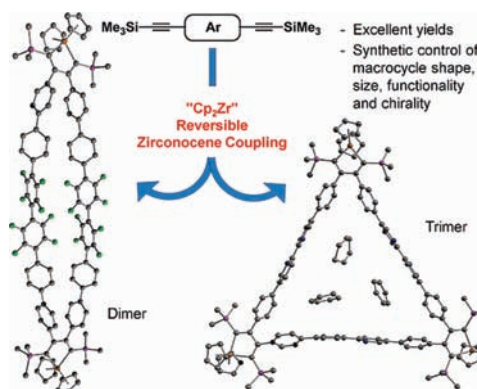
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## CONSPECTUS

Macrocyclic compounds have attracted considerable attention in numerous applications, including host–guest chemistry, chemical sensing, catalysis, and materials science. A major obstacle, however, is the limited number of convenient, versatile, and high-yielding synthetic routes to functionalized macrocycles. Macrocyclic compounds have been typically synthesized by ring-closing or condensation reactions, but many of these procedures produce mixtures of oligomers and cyclic compounds. As a result, macrocycle syntheses are often associated with difficult separations and low yields. Some successful approaches that circumvent these problems are based on “self-assembly” processes utilizing reversible bond-forming reactions, but for many applications, it is essential that the resulting macrocycle be built with a strong covalent bond network. In this Account, we describe how zirconocene-mediated reductive couplings of alkynes can provide reversible carbon–carbon bond-forming reactions well-suited for this purpose.

Zirconocene coupling of alkenes and alkynes has been used extensively as a source of novel, versatile pathways to functionalized organic compounds. Here, we describe the development of zirconocene-mediated reductive couplings as a highly efficient method for the preparation of macrocycles and cages with diverse compositions, sizes, and shapes. This methodology is based on the reversible, regioselective coupling of alkynes with bulky substituents. In particular, silyl substituents provide regioselective, reversible couplings that place them into the  $\alpha$ -positions of the resulting zirconacyclopentadiene rings. According to density functional theory (DFT) calculations and kinetic studies, the mechanism of this coupling involves a stepwise process, whereby an insertion of the second alkyne influences regiochemistry through both steric and electronic factors.

Zirconocene coupling of diynes that incorporate silyl substituents generates predictable macrocyclic products in very high yields. In the absence of significant steric repulsion, the macrocyclization appears to be entropically driven, thereby providing the smallest strain-free macrocyclic structure. The scope of the reaction has been explored by variation of the spacer group between the alkynyl substituents and by incorporation of functional and chiral groups into the macrocycle. The size and shape of the resulting macrocycles are largely determined by the length and geometry of the dialkyne spacer, especially in the case of terminal trimethylsilyl-substituted diynes. For example, linear, rigid diynes with four or fewer phenylene rings lead to trimeric macrocycles, whereas bent or flexible diynes produce dimers. Depending on the reaction conditions, functional groups (such as *N*-heterocycles and imines) are tolerated in zirconocene coupling reactions, and in selected cases, they can be used to influence the shape of the final macrocyclic product. More recently,  $\text{Cp}_2\text{Zr}(\text{pyr})(\text{Me}_3\text{SiC}\equiv\text{CSiMe}_3)$  has been employed as a more general zirconocene synthon; it affords higher yields and increased functional group tolerance. Functional groups can also be incorporated through transformation of the zirconacyclopentadiene products, with acid hydrolysis to the corresponding butadiene being the most efficient derivatization. Furthermore, construction of chiral macrocycles has been accomplished by stereoselective macrocyclizations, and triynes have been coupled into three-dimensional cage compounds. We also discuss various design factors, providing a perspective on the utility of zirconocene-mediated couplings in the assembly of macrocyclic and cage compounds.

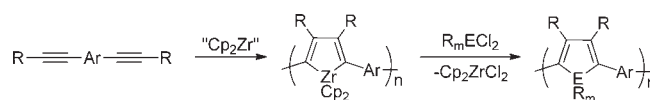


## 1. Introduction

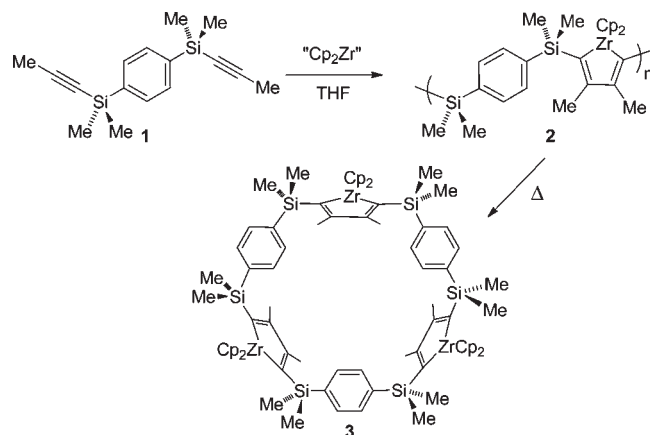
Numerous synthetic achievements of the recent past are based on the principles of supramolecular chemistry, which utilizes weak, noncovalent chemical interactions for the assembly of large, ordered structures including macrocycles, cages, helices, host–guest complexes, and open frameworks.<sup>1</sup> The “weak link” chemical interactions used to build these structures include hydrogen bonds, metal–ligand dative bonds, hydrophobic forces, van der Waals attractions, and  $\pi$ -stacking. The use of stronger, directional interactions (e.g., as in carbon–nitrogen or carbon–carbon covalent bonds) is potentially quite attractive since this could lead to more stable structures; however, this approach is rather limited given the inherently nonlabile character of such bonds. Nonetheless, the latter approach has been successfully employed in select cases, as in the construction of helical and macrocyclic structures via reversible condensations of amines and aldehydes to imines<sup>2</sup> and in macrocyclizations via reversible C=C bond formations in alkyne metathesis reactions.<sup>3</sup> A particularly attractive strategy involves use of labile bonds for assembly of the desired structure, followed by chemical conversions of these weak links into more stable, nonlabile bonds. As described in this Account, the latter approach is possible with use of zirconocene-mediated, reversible carbon–carbon bond formations from the coupling of alkynyl groups.

Macrocyclic compounds have attracted considerable attention due to their uses in, for example, host–guest chemistry, catalysis, chemical sensing, and materials chemistry.<sup>1,4</sup> These applications often require well-defined macrocyclic structures and the tailored incorporation of functional groups, which represent significant synthetic challenges given the limited number of convenient, versatile, and high-yielding routes to macrocycles. Synthetic procedures for macrocycles, based on ring-closing or condensation reactions, are often associated with low yields, the formation of structurally similar byproducts, and difficult separations.<sup>5</sup> Research in these laboratories has addressed this synthetic issue with development of efficient, high-yielding routes to C–C bonded macrocyclic compounds with use of zirconocene couplings. The zirconocene coupling of alkenes and alkynes has been known for a number of years and has been utilized extensively in novel, versatile pathways to functionalized organic compounds.<sup>6</sup> In certain cases, such couplings are reversible, and this characteristic allows the efficient construction of macrocycles and cages. The fundamental characteristics of this synthetic approach and its current applicability to different types of macrocycles are discussed herein.

SCHEME 1



SCHEME 2



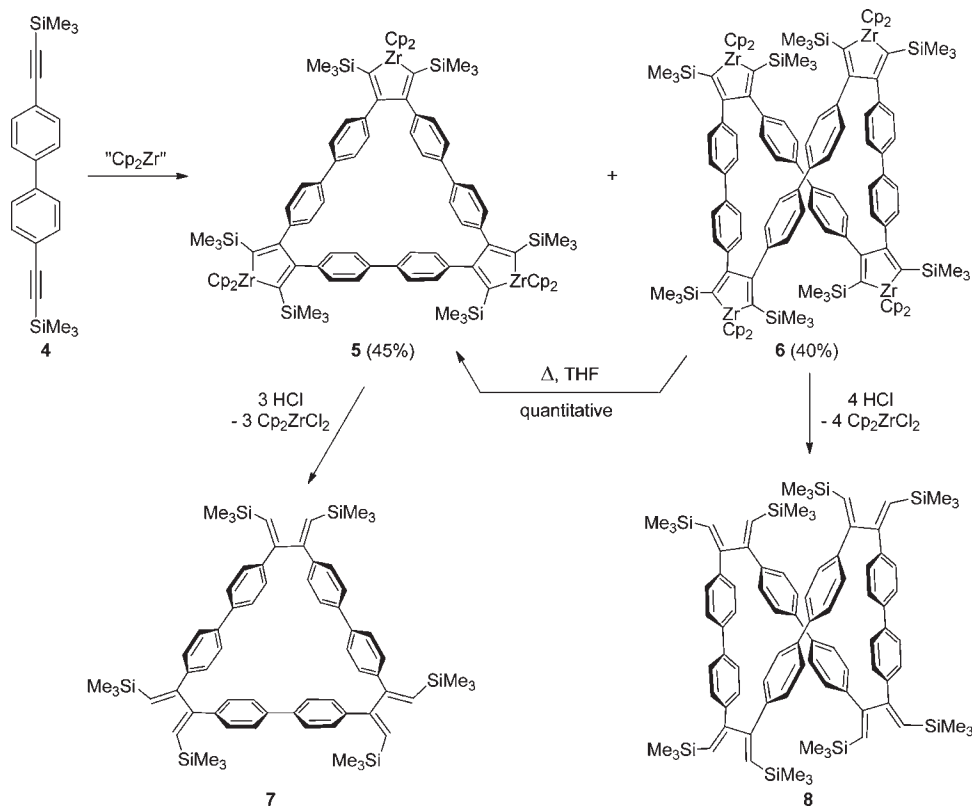
## 2. Discovery of Zirconocene-Mediated Macrocyclizations

The zirconocene coupling of rigid diynes was initially envisioned as a potential route to families of conjugated polymers via transformations of the type shown in Scheme 1. This general approach, which takes advantage of the versatility of zirconocene-transfer reactions in accessing various heterocycles,<sup>7</sup> has in fact been used to obtain conjugated polymers with new structures.<sup>8</sup> However, zirconocene couplings of diynes do not always occur in the regioregular manner indicated by Scheme 1, and various strategies have been employed to overcome this problem.<sup>9</sup>

An early, successful attempt to produce a regioregular organosilicon polymer with limited conjugation utilized the previously established,  $\alpha$ -directing ability of silyl groups<sup>10</sup> in the coupling of diyne **1** to polymer **2** ( $M_w/M_n = 13\,000/4600$ ; Scheme 2).<sup>11</sup> Surprisingly, gentle heating of this polymer in THF solution resulted in its quantitative depolymerization to a single molecular species, the trimeric macrocycle **3** in 93% yield (Scheme 2).

Given the strong interest in macrocycles, and the fact that they are typically synthesized by procedures involving multiple steps, difficult separations, and low to moderate yields, we began to examine additional couplings of silyl-substituted diynes to evaluate the generality and utility of this approach as an efficient route to macrocycles. The longer biphenylene spacer group of the diyne

SCHEME 3



MeC≡CSiMe<sub>2</sub>—C<sub>6</sub>H<sub>4</sub>—C<sub>6</sub>H<sub>4</sub>—SiMe<sub>2</sub>C≡CMe provides a larger trimeric macrocycle with an approximate cavity size of 17–18 Å (in 90% yield).<sup>12</sup> Interestingly, silyl groups in the terminal diene positions, as in Me<sub>3</sub>SiC≡C—C<sub>6</sub>H<sub>4</sub>—C<sub>6</sub>H<sub>4</sub>—C≡CSiMe<sub>3</sub> (**4**), lead more directly to macrocycles, and these possess an all-carbon backbone (polymers have not yet been observed in such cases). The coupling of **4** leads to trimeric **5** and tetrameric **6** at room temperature, but gentle heating of the reaction mixture drives all of the product to triangularly shaped **5** (Scheme 3).<sup>12</sup> The latter conversion of **6** to **5** illustrates a common theme in this chemistry, which is that the assembly of macrocycles occurs by a low-energy pathway provided by carbon–carbon bond formations that are reversible in the presence of zirconocene. Significantly, the zirconocene-containing products may be transformed into very stable, nonlabile cyclophanes (e.g., **7** and **8**) by simple treatment with acid to remove the zirconium (Scheme 3).

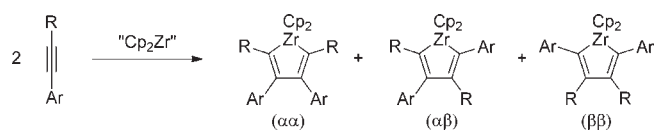
### 3. Regiochemistry and Reversibility

Once it became apparent that zirconocene couplings of diynes might provide general, efficient routes to macrocycles, it was of interest to evaluate the utility of this

synthetic approach. The examples depicted above demonstrate that reversibility of the zirconocene coupling is a basic requirement for the selective formation of macrocycles from oligomeric or polymeric analogues. Such ring–chain equilibria are well-known for certain polycondensation reactions, where cyclic oligomers are formed via “backbiting” reactions from active chain ends<sup>13</sup> or by ring-closing and ring-opening metathesis reactions, some of which have also been employed for macrocycle syntheses.<sup>3,14</sup> However, there are only a few examples of near-quantitative formation of metal-containing macrocycles via polymer degradation. Indeed, such transformations generally yield macrocycles with a distribution of sizes and therefore require tedious separations for purification.<sup>15</sup> One example, reported by U. H. F. Bunz and co-workers, is based on alkyne metathesis of the diyne <sup>i</sup>Pr<sub>2</sub>Si(OC<sub>6</sub>H<sub>4</sub>CCMe)<sub>2</sub> with a molybdenum catalyst, which results in elimination of 2-butyne and formation of a mixture of tetrameric (14%) and trimeric (18%) shape-persistent macrocycles.<sup>16</sup>

Erker and co-workers first reported that zirconocene-mediated couplings of alkynes may be reversible, and that cleavage of a metallacyclopentadiene ring is promoted by

SCHEME 4

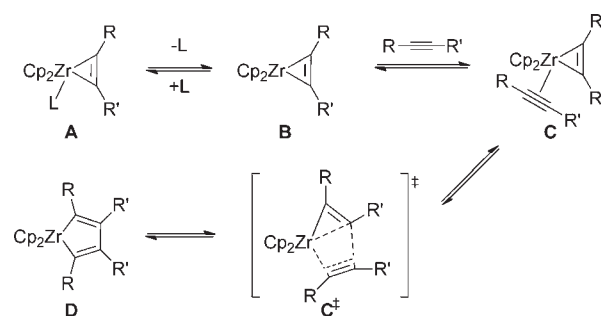


sterically demanding groups such as  $-\text{SiMe}_3$ .<sup>10</sup> Clearly, it is this reversibility that provides a low-energy pathway for formation of the most thermodynamically stable macrocycle. Apparently, the enthalpy change for equilibria involving small and large cyclic species is negligible in the absence of differential steric interactions and ring strain. Thus, entropy drives such equilibria to the smallest strain-free ring possible, which is often the only observed product.

In addition to the requirement for reversibility, a zirconocene-mediated macrocyclization must involve regioselective couplings.<sup>10</sup> For unsymmetrical alkynes, the substituents can adopt the  $\alpha$ - or  $\beta$ -position of the resultant zirconacyclopentadiene ring, potentially leading to three possible isomers as indicated in Scheme 4. While reversibility is required for polymer degradation, the regiochemistry determines the structure of the macrocycle. For example, a  $\beta$ -directing alkyne substituent, which forces the carbon that it is bound to into the  $\beta$ -position of the zirconacyclopentadiene ring, may favor the formation of noncyclic oligomeric structures by incorporation of the diyne spacer group (corresponding to Ar in Scheme 4) into the  $\alpha$  position.

Thus, macrocycle syntheses require the presence of substituents that promote both regioselectivity and reversibility for alkyne couplings. To date, alkyne substituents that best fulfill these roles are silyl groups, which couple exclusively into the 2,5 ( $\alpha\alpha$ ) positions of the zirconacyclopentadiene ring. Besides silyl groups, various substituents have been examined for their applicability in selective coupling reactions, and the regiochemistry has been found to be sensitive to both steric and electronic factors. The most effective  $\alpha$ -directing groups are generally sterically demanding (e.g., trialkylsilyl, *tert*-butyl,<sup>9,17</sup> and diphenylphosphino groups<sup>18</sup>). Such groups also promote reversibility for the alkyne coupling and are therefore quite useful in macrocycle syntheses. Electron-withdrawing substituents (e.g.,  $\text{C}_6\text{F}_5$ ) have been found to prefer the  $\beta$ -positions of a zirconacyclopentadiene ring, and this can be explained in terms of charge distribution in the transition state for alkyne coupling, and orbital interactions between the zirconocene-based orbital and the  $\pi^*$  LUMO of the alkyne.<sup>19</sup> Despite their ability to control regioselectivity, electron-withdrawing groups have not yet proven useful in macrocyclizations, because they have not

SCHEME 5

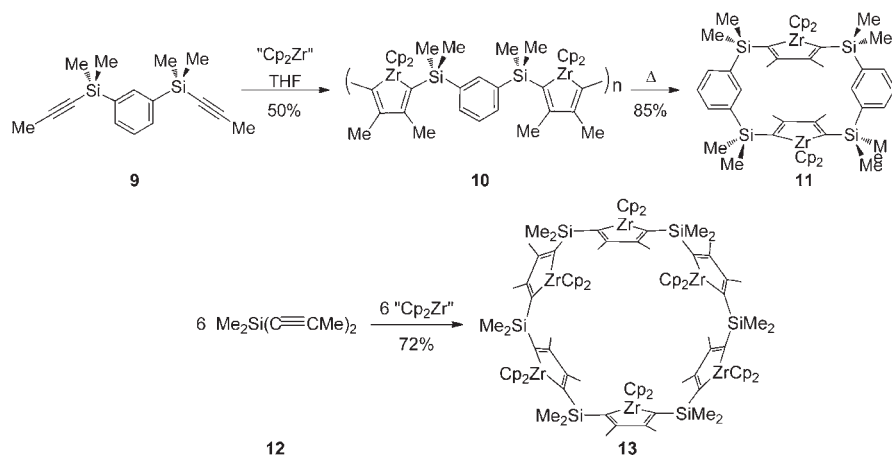


been found to promote reversibility. Interestingly, however, recent investigations have revealed that the mesityl group preferentially couples into the  $\beta$ -position of a zirconacyclopentadiene, and the steric bulk of this group also enhances the reversibility of alkyne couplings.<sup>20</sup>

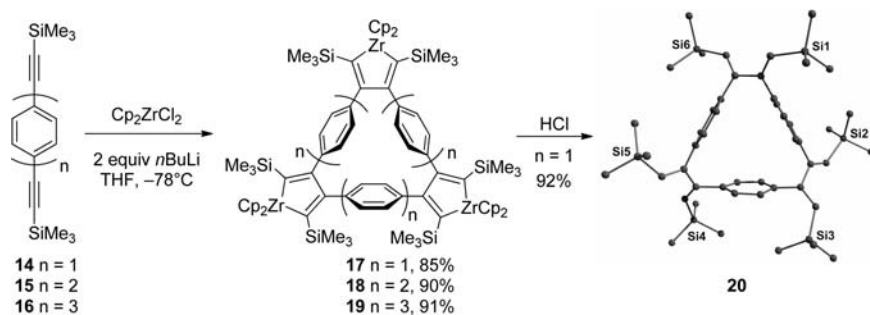
#### 4. Mechanistic Considerations

The mechanism of alkyne coupling by zirconocene has been examined by both kinetic investigations and DFT calculations. It appears that the zirconocene-promoted alkyne coupling reaction proceeds via a stepwise mechanism, rather than by a concerted process passing through a symmetrical zirconocene bisalkyne complex. In an initial stage of the reaction, the zirconocene fragment binds the first alkyne to give a monoalkyne complex that is often stabilized by additional ligands or solvent molecules (**A**, Scheme 5).<sup>19,21</sup> Such donor-stabilized zirconacyclopentadienes have been isolated and structurally characterized.<sup>22,18</sup> This complex is presumed to lose L to form the reactive zirconacyclopentadiene intermediate **B**, which then reacts with a second equivalent of alkyne to give an alkyne adduct of the zirconacyclopentadiene (**C**). DFT studies have shown that the transition state for alkyne coupling (**C<sup>‡</sup>**) is highly unsymmetrical, and involves a strongly activated alkyne (in a metallocyclopropene-type structure) and a nearly unperturbed alkyne weakly interacting with the zirconium center.<sup>19,21b</sup> In **C<sup>‡</sup>**, the first alkyne ligand has moved further into the "zirconocene wedge" to accommodate the C–C bond formation.<sup>23</sup> Thus, the coupling looks much like an insertion of alkyne into a Zr–C bond, as depicted by **C<sup>‡</sup>**.<sup>9,24,25</sup> The charge distribution in such transition states may explain some aspects of the observed regiochemistry, in that electron-withdrawing groups would be expected to prefer a position leading to  $\beta$ -substitution in the final product. In general, the steric and electronic properties of the alkyne substituents R and R' influence the structure of the transition state and therefore the substitution pattern in the final product.

SCHEME 6



SCHEME 7



The mechanism of zirconocene coupling has also been probed by kinetic studies on the reverse process, zirconacyclopentadiene fragmentation (the microscopic reverse of alkyne coupling).<sup>23</sup> The zirconacyclopentadienes examined in these studies possess trimethylsilyl substituents in the  $\alpha$ -positions. Kinetic studies of alkyne decouplings involved zirconacycles with the ancillary ligand sets  $\text{Cp}_2$ ,  $\text{Me}_2\text{C}(\eta^5\text{-C}_5\text{H}_4)_2$ , and  $\text{CpCp}^*$  ( $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$ ) and an excess of  $\text{PMe}_3$  and, in each case, led to quantitative formation of  $\text{PMe}_3$ -stabilized zirconacycloprenes. For these transformations, the rate of reaction is first-order in zirconacycle concentration and has no observed dependence on the concentration of  $\text{PMe}_3$ , implying the rate-determining dissociative loss of alkyne. The observed first-order rate constants depend very much on the nature of the ancillary bis(cyclopentadienyl) ligand sets, with the ratio of relative rates being 0.046:1:100 ( $\text{CpCp}^*/\text{Cp}_2/\text{Me}_2\text{C}(\eta^5\text{-C}_5\text{H}_4)_2$ ).<sup>23</sup> Contrary to what might be expected, the most sterically crowded metal center gives rise to the slowest elimination of alkyne. This trend may be explained, with the aid of DFT studies, by the required motion for C–C bond cleavage, which involves considerable movement

of the alkyne fragments away from one another, and further into the bis(cyclopentadienyl) wedge of the complex.

## 5. Size and Shape Control of Macrocycles

For reversible zirconocene couplings of diynes, the resulting macrocycle size and shape is determined largely by the length and geometry of the dialkyne spacer. This was initially demonstrated for a series of diynes with silyl substituents as part of the spacer group (Scheme 6).<sup>26</sup> Zirconocene coupling of *meta*-substituted **9** affords dimeric **11** in excellent yield, while the single-atom spacer of diyne **12** generates a hexameric macrocycle **13** as the thermodynamic product. Unfortunately, extension of this methodology to longer spacer groups has proven difficult for  $\text{SiMe}_2$ -containing spacers, presumably because the macrocycles remain in equilibrium with energetically similar oligomers (*vide supra*). Thus, most efforts have centered on terminal trimethylsilyl-substituted diynes, which more readily form macrocycles with a wide array of shapes and sizes.

Rigid, linear spacer groups generally lead to triangular, trimeric macrocycles, as illustrated by the coupling of diynes

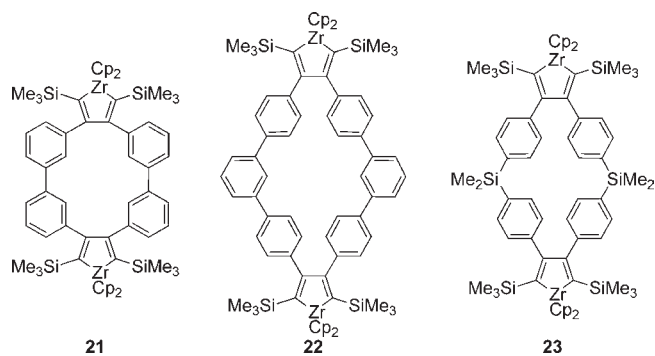


FIGURE 1

**14–16** with one to three 1,4-phenylene units (Scheme 7).<sup>27</sup> On the other hand, nonlinear spacer groups in Me<sub>3</sub>Si-terminated diynes consistently give rise to dimeric macrocycles. For example, *m*-substituted diyne spacers led to the dimeric products **21–23** (Figure 1). Interestingly, 1,3-bis(trimethylsilyl)ethynyl)benzene does not dimerize under zirconocene coupling conditions, presumably because the resultant macrocycle would possess too much strain or unfavorable steric interactions.

Given the established efficiency of zirconium-mediated macrocyclizations of Me<sub>3</sub>Si-terminated diynes, it was of interest to investigate this method as a potential route to large, nanoscopic macrocycles. Macrocycles of the latter type have attracted considerable interest due to their unique properties as rigid nanocontainers.<sup>28</sup> Early efforts to construct large macrocycles via the coupling of alkynyl-terminated oligo(*p*-phenylene)s, Me<sub>3</sub>SiCC(*p*-C<sub>6</sub>H<sub>4</sub>)<sub>*n*</sub>CCSiMe<sub>3</sub> (*n* ≥ 6), were severely hampered by the inherently low solubilities of linear oligophenylenes. The latter problem was eventually overcome with discovery of an efficient convergent synthetic route to soluble, partially fluorinated oligophenylenes. This route, based on nucleophilic aromatic substitution onto fluorinated aromatics, provided alkynyl-terminated oligophenylenes containing up to 12 phenylene units. Interestingly, the hexa- and nonaphenylene diynes gave dimeric, rather than trimeric, structures in 81–91% yields (Figure 2).<sup>29</sup> Presumably, the energetic cost of bending the perfluorinated oligophenylene chains into a dimer is compensated by entropic factors such as reduced solvent inclusion. Additionally, the utilization of Cp<sub>2</sub>Zr(pyr)(Me<sub>3</sub>SiC≡CSiMe<sub>3</sub>) as a zirconocene synthon proved to be advantageous.<sup>30</sup> This reagent allows for zirconocene coupling in nonethereal solvents and avoids the formation of stoichiometric lithium chloride, which can be difficult to remove from macrocycle products with limited solubility. In addition, the zirconocene synthon Cp<sub>2</sub>Zr(pyr)(Me<sub>3</sub>SiC≡CSiMe<sub>3</sub>) is a stable solid that can be

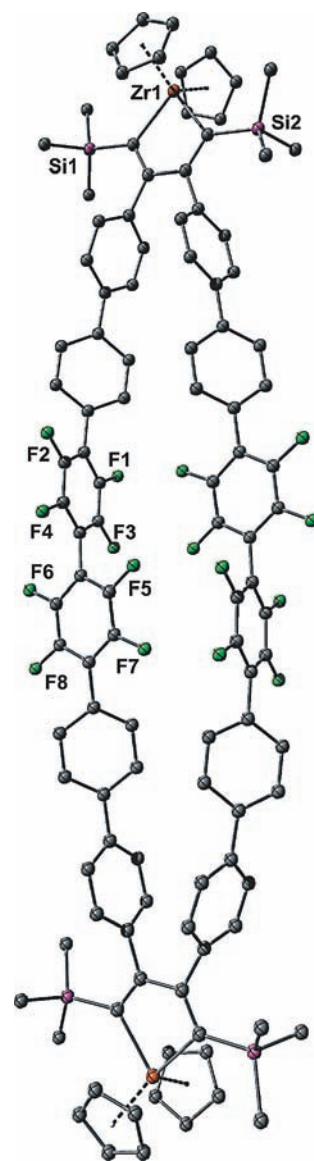


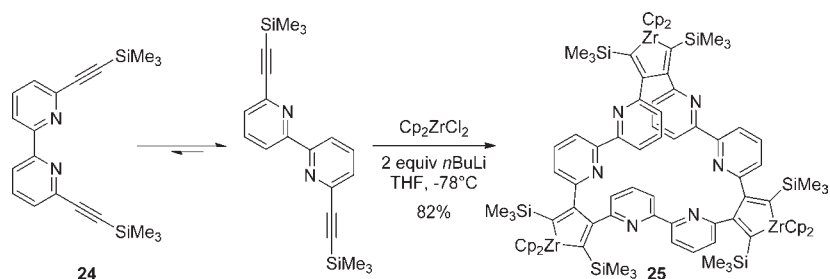
FIGURE 2

accurately weighed in a glovebox and, in circumventing the use of <sup>*n*</sup>BuLi during the cyclization, is more tolerant of functional groups.

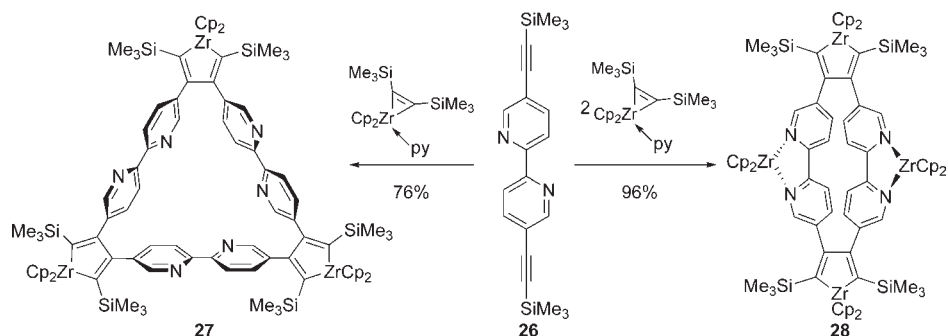
## 6. Synthesis of Functionalized and Chiral Macrocycles

Applications of macrocycles usually require the presence of specific functional groups. For zirconocene-mediated macrocyclizations, the incorporation of such functionalities is somewhat limited, given the reactive nature of zirconocene reagents toward many functional groups. Nonetheless, there are two promising approaches for achieving this goal. The first is to incorporate zirconocene-tolerant functional groups into the diynes used for macrocyclization. These

SCHEME 8



SCHEME 9



functional groups may have a dramatic influence on the shape of the resultant macrocycle, as illustrated by the cyclotrimerization of Scheme 8. While the *m*-substituted biphenyl diyne is cyclized to dimer **21**, the analogous bipyridine derivative **24** selectively undergoes cyclotrimerization.<sup>31</sup> This difference can be attributed to the preference of the bipyridyl diene for adopting an *anti*-geometry. Thus, the alkyne units are arranged in a parallel fashion, which results in the observed formation of the trimeric macrocycle **25**. In this example, the entropic driving force for formation of the smallest macrocyclic ring is not sufficient to overcome the preferred *anti*-conformation of the diyne precursor.

Bipyridines have often been employed as ligands in coordination and supramolecular chemistry. Thus, it is of interest to introduce bipyridyl groups into the framework of macrocycles. For macrocyclizations via zirconocene coupling, bipyridine-containing monomer units present a challenge, in that the zirconocene reagent may be decommissioned by complexation to the bipyridine. Fortunately, it was found that careful control over the stoichiometry gave a good yield of the expected trimeric macrocycle **27** (Scheme 9).<sup>32</sup> Interestingly, however, addition of 2 equiv of the zirconocene reagent resulted in binding of the bipyridine units to zirconocene to form a new type of diyne monomer

unit with significant bending of the spacer. Thus, in addition to diyne coupling, the zirconocene reagent exerts a templating effect in orienting the diyne toward a different type of cyclization, resulting in dimer **28**.

The same dependency on the amount of zirconocene reagent has been observed for the elongated, bipy-containing diyne  $\text{Me}_3\text{SiCC}-\text{C}_6\text{H}_4-(2,2'\text{-bipy})-\text{C}_6\text{H}_4-\text{CCSiMe}_3$ .<sup>32b</sup> In this case, the resultant dimeric macrocycle contains a benzene guest molecule (Figure 3). For the coupling of bipyridine-containing diynes, it was found that Rosenthal's zirconocene synthon  $\text{Cp}_2\text{Zr}(\text{py})(\text{Me}_3\text{SiC}\equiv\text{CSiMe}_3)$  provided the best results.<sup>30</sup> This reagent also allowed coupling of an imine-containing diyne **29**, as illustrated in Scheme 10.<sup>32a</sup>

A second strategy for incorporation of functional groups relies on postcyclization transformations involving the zirconacyclopentadiene groups of the macrocycle. In principle, this represents a versatile methodology, since zirconacyclopentadienes may be converted to various organic structures, including dienes,<sup>33</sup> arenes,<sup>34</sup> cyclopentadienes<sup>35,36</sup> and heterocycles<sup>37</sup> such as thiophenes,<sup>38</sup> siloles,<sup>39,40</sup> phospholes,<sup>41</sup> germales,<sup>8e</sup> pyrroles,<sup>42</sup> and thiophene oxides.<sup>43</sup> Treatment with iodine may also produce 1,4-diiododienes,<sup>8c</sup> which may then be transformed to additional functionalities. In practice, such transformations have exhibited

limited utility, since “zirconocene-transfer” reactions of these types are often low-yielding for zirconacycles with  $\alpha$ -SiMe<sub>3</sub> groups. As mentioned earlier, hydrolyses are often useful for removal of zirconocene and formation of stable diene-containing cyclophanes. In certain cases, it has proven possible to transform the zirconacycle units of a macrocycle into thiophene and germole<sup>44</sup> groups.

The incorporation of chirality into macrocycles is a highly desirable synthetic goal, due to the potential use of chiral macrocycles in recognition<sup>45</sup> or asymmetric catalysis.<sup>46</sup> Two synthetic approaches have been employed for the construction of chiral zirconocene macrocycles. The first involves use of a diyne that already possesses stereoinformation, and the second approach is based on the stereoselective macrocyclization of an achiral alkyne. Both strategies have successfully been employed with use of the BINOL-based diyne **31** (Scheme 11), which selectively couples to the corresponding dimeric macrocycle **32**.<sup>47</sup> The cyclization of (*R*)-**31** resulted in the expected homochiral, enantiopure macrocycle (*R,R*)-**32**. However, zirconocene coupling of the racemic mixture of the

BINOL diyne gave a stereoselective macrocyclization. Instead of three possible stereoisomers only one pair of enantiomers, the homochiral (*R,R*)-**32** and (*S,S*)-**32**, were obtained.

In the case of the BINOL dialkyne, the chiral geometry of the spacer groups directs formation of homochiral products from racemic mixtures of the dialkyne. However, stereoselective macrocyclization can also be dictated by unsymmetrical, achiral diynes. This has been shown with use of 1,4-bis-[trimethylsilyl(ethynyl)]acenes as precursor.<sup>48</sup> Because the acene rings extend perpendicular to the macrocycle plane, two diastereomeric products (“all up” and “2 up, 1 down”) are possible as shown for trimer **33** in Figure 4. The geometry of the naphthalene and anthracene spacers dictates stereoselective trimerization under zirconocene coupling conditions, forming exclusively the “2 up, 1 down” diastereomer **33b** as the energetically favored product in 62% isolated yield.

## 7. Cage Structures via Zirconocene Coupling

In principle, it should be possible to extend the methods described above to the synthesis of more elaborate and larger molecular species with three-dimensional framework structures. This possibility has received limited attention, but a few cage compounds have been constructed via reductive zirconocene coupling and careful control of the three-dimensional geometry of the polyalkynyl precursors. For example, triynes **34** and **35** form dimeric cages in high yields using the Negishi protocol (Scheme 12).<sup>49</sup> Subsequent hydrolysis of the macrobicyclic products leads to large torsion angles in the resulting diene units, causing a slight “opening” of the cage, as measured by an increased Si–Si distance of 6.78 Å. Additional phenylene spacers can be inserted to extend the cavity size, but the precursor triyne **40** must be *meta*-substituted in order to have the correct geometry for dimerization (Scheme 13). Zirconocene coupling of the related *para*-substituted isomer gave an intractable mixture of products. Likewise, attempts to construct cages by the dimerization a tetraalkyne-substituted calixarene

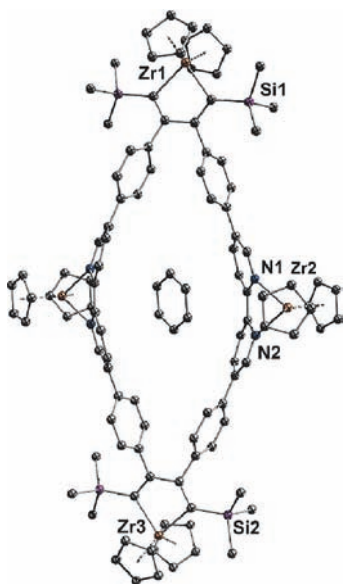
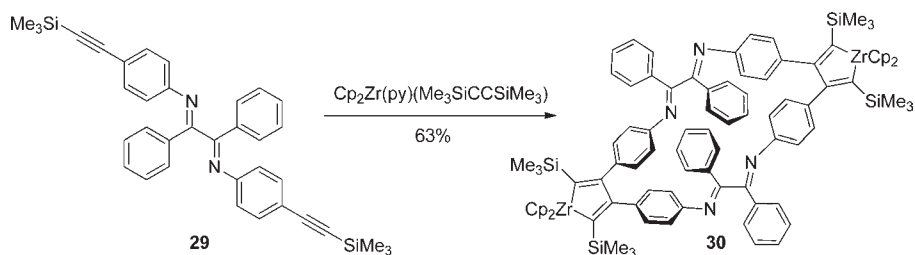


FIGURE 3

SCHEME 10





SCHEME 11

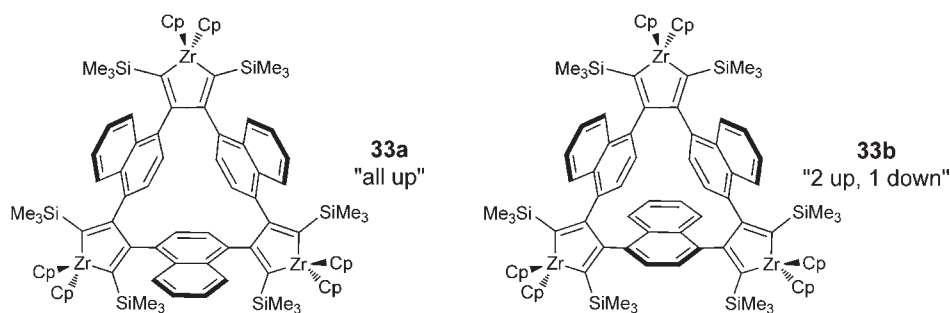
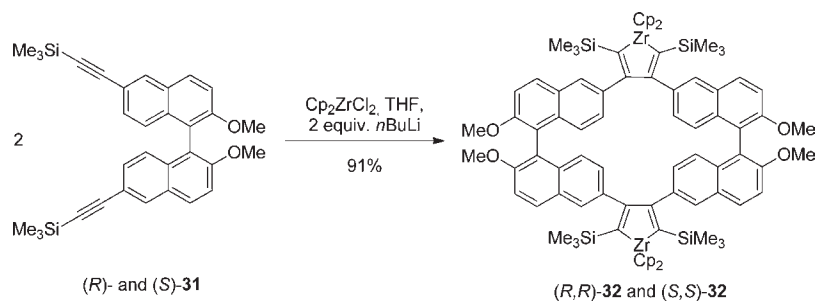
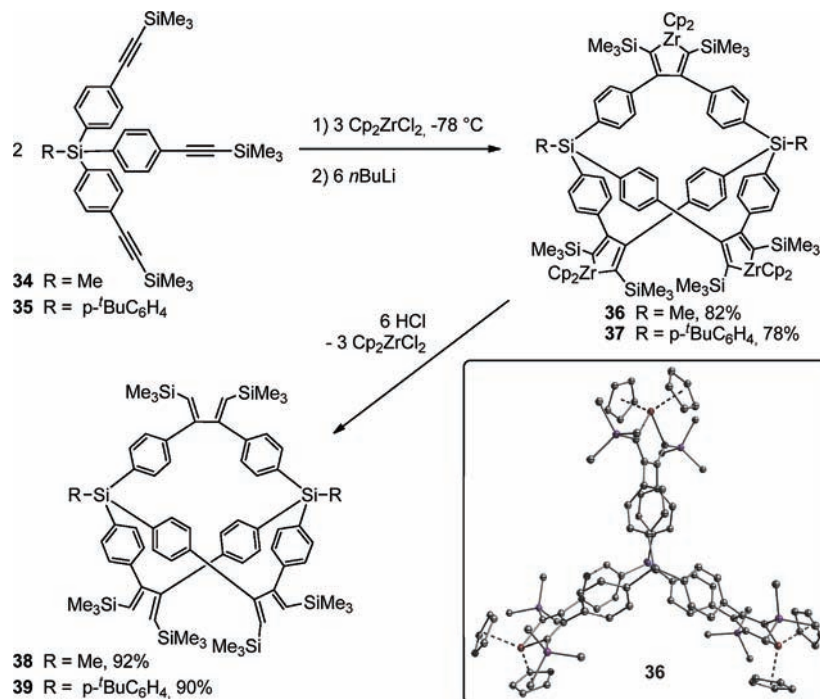


FIGURE 4

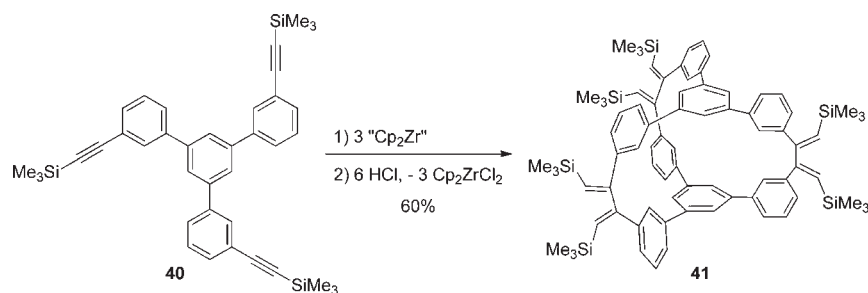
SCHEME 12



framework led instead to intramolecular coupling.<sup>49</sup> Further understanding of the design criteria for coupling these three-dimensional precursor polyalkynes could enable the synthesis

of complex macrobicyclic compounds for various applications, including functionalized cage molecules for host–guest chemistry.

## SCHEME 13



## 8. Concluding Remarks

Zirconocene-mediated alkyne couplings offer a unique approach for the assembly of macrocycles, cages, and related dynamic nanostructures. A particularly useful feature of this method is its utilization of labile carbon–carbon bonds, which may be readily converted to nonlabile bonds after assembly of the desired structure. Given the paucity of transformations of this kind, and the limited set of labile carbon–carbon bonds that are known, this synthetic methodology should find many uses in chemical synthesis. For wider applications of this chemistry, it will help to identify a broader range of substituents that promote reversibility in various couplings of unsaturated substrates, while controlling regiochemistry in a predetermined manner. The identification of new, efficient organometallic coupling reagents that might be used in this context should also broaden the scope of this method.

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### BIOGRAPHICAL INFORMATION

**Viktorija H. Gessner** studied chemistry at the Universities of Marburg and Würzburg, Germany, where she received her diploma in 2007. In 2009, she obtained her Ph.D. at TU Dortmund under the direction of Prof. Carsten Strohmam working in organolithium chemistry and afterwards joined the Tilley group (UC Berkeley) as a postdoctoral fellow working on zirconocene-mediated macrocyclizations. She is currently an independent researcher at the University of Würzburg, where her research involves the organometallic chemistry of geminal dianions and carbenoid compounds.

**John F. Tannaci** received his B.S. degree in chemical engineering, with distinction, from Stanford University in 2002. In 2008, he completed his Ph.D. thesis in the Tilley Group at UC Berkeley, studying both zirconocene coupling and the synthesis of novel

n-type organic semiconductors. He is currently an assistant professor at California Lutheran University in Thousand Oaks, where his research group focuses on developing palladium-catalyzed cross-coupling methodologies for organic electronic materials and biochemical applications.

**Adam D. Miller** received his B.S. degree in 2003 from the University of Wisconsin—Madison in chemical engineering and chemistry. Afterwards, he pursued a graduate degree at UC Berkeley under the direction of Prof. T. Don Tilley. His graduate studies focused on new chemical methodologies for the synthesis of conjugated polymers and macrocycles, and he was awarded a Ph.D. in fall 2008. His current research, in the lab of Dr. John B. Kerr at LBNL, is development of polymer electrolytes for lithium ion batteries and fuel cells.

**T. Don Tilley** received his B.S. degree from the University of Texas, Austin, in 1977. In 1982, he completed his Ph.D. thesis at UC Berkeley in the group of R. A. Andersen, studying organometallic lanthanide chemistry. In 1982–1983, he participated in a NSF-sponsored exchange program, working with Professors Robert Grubbs and John Bercaw at Caltech and with Professors Luigi Venanzi and Piero Pino at the ETH in Zürich, Switzerland. He started his independent career at UC San Diego in 1983 and rose to the rank of Professor of Chemistry before moving to his current positions as Professor of Chemistry at UC Berkeley, and Senior Scientist at Lawrence Berkeley National Laboratory. His research interests include synthetic, structural, catalytic, and mechanistic investigations in inorganic and organometallic chemistry.

### FOOTNOTES

\*To whom correspondence should be addressed. E-mail address: tdtalley@berkeley.edu.

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