

## Synthesis of Phototrappable Shape-Shifting Molecules for Adaptive Guest Binding

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**Abstract:** We have designed and synthesized oligosubstituted bullvalenes **1** and **2** as adaptive molecules that can change their shapes in order to bind tightly to a suitable guest. By incorporation of a photolabile *o*-nitroveratryloxycarbonate (NVOC) group into bullvalenes **1** and **2**, tightly binding species can be selectively isolated from a population of hundreds of interconverting structural isomers. Spontaneous strain-assisted Cope rearrangements allow these shape-shifting molecules to exist in a dynamic equilibrium of configurationally distinct valence isomers, as revealed by dynamic NMR and HPLC studies. When NVOC bullvalenes **1** and **2** were exposed to UV light, the cleavage of the NVOC group resulted in a mixture of static isomers of the corresponding bullvalone. Binding studies of NVOC bisporphyrin bullvalene **1** demonstrated that the dynamic isomeric equilibrium shifted in the presence of C<sub>60</sub>, favoring configurations with more favorable binding affinities. Irradiation of a mixture of **1** and C<sub>60</sub> with UV light and isolation of the major static isomer yielded an isomer of bisporphyrin bullvalone with a binding affinity for C<sub>60</sub> that was ~2 times larger than that of the nonadapted isomer bisporphyrin bullvalone **41**.

### Introduction

Chemical systems that can adapt in response to environmental cues represent an emerging paradigm in the discovery and implementation of new host–guest interactions.<sup>1</sup> Dynamic combinatorial libraries consist of sets of functional molecules that form reversible bonds with each other to generate a virtual library of transient species in thermodynamic equilibrium. In response to an appropriate stimulus, usually a molecular guest, this thermodynamic equilibrium shifts toward those species that have the most favorable interactions with the guest molecule. Such a system has the ability to dynamically respond to a species or stimulus of interest, an approach that has been used to discover novel receptors,<sup>2</sup> sensors,<sup>3</sup> catalysts,<sup>4</sup> and systems capable of self-assembly and self-replication.<sup>5</sup>

The successful design of an adaptive dynamic system requires careful consideration of its constituent components and the reversible reactions used to mediate the interconversion of the transient species that make up the library. Imine-like exchange,<sup>2f</sup> disulfide formation,<sup>2g</sup> and acyl exchange<sup>6</sup> reactions have successfully been utilized to generate structurally and functionally diverse dynamic libraries. The efficacy of these transformations results from their high reversibility under a given set of conditions and the ability to quench this reversibility upon

modification of these conditions. Even so, typical systems often suffer from long equilibration times and the need for additional reagents both to mediate the reversible reactions and to freeze the equilibrium once adaptation has occurred. Furthermore, many of these systems generate diversity through the formation of cyclic and linear oligomers from a set of component monomers. The multicomponent assembly of such structures faces statistical and entropic challenges in forming oligomeric macrocyclic structures from monomeric components.

In order to overcome these inherent challenges to the expanding field of dynamic combinatorial chemistry, we have sought to develop “self-contained dynamic combinatorial libraries”, in which the adaptive structures are limited to intramolecular rearrangements. This proposal requires the identification of discrete chemical entities that can spontaneously change their configuration or chemical properties without the need for added chemical reagents or catalysts that might interfere with the desired recognition events or favor selected members of the

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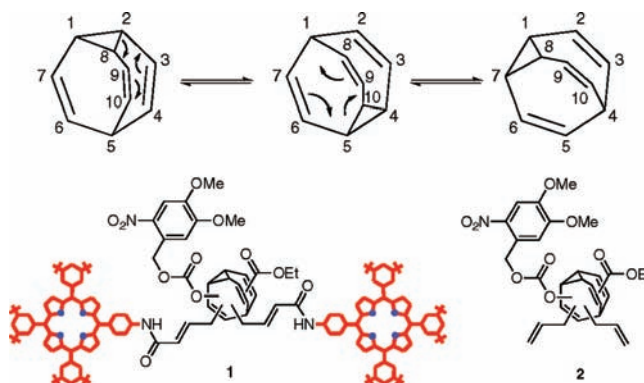
(1) (a) Ladame, S. *Org. Biomol. Chem.* **2008**, *6*, 219–226. (b) Lehn, J.-M. *Chem. Soc. Rev.* **2007**, *36*, 151–160. (c) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711. (d) Otto, S. *J. Mater. Chem.* **2005**, *15*, 3357–3361. (e) Rowan, S.; Cantrill, S.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952. (f) Lehn, J. M. *Chem.—Eur. J.* **1999**, *5*, 2455–2463.

(2) (a) Leclaire, J.; Husson, G.; Devaux, N.; Delorme, V.; Charles, L.; Ziarelli, F.; Desbois, P.; Chaumonnot, A.; Jacquin, M.; Fotiadu, F.; Buono, G. *J. Am. Chem. Soc.* **2010**, *132*, 3582–3593. (b) West, K. R.; Ludlow, R. F.; Corbett, P. T.; Besenius, P.; Mansfield, F. M.; Cormack, P. A. G.; Sherrington, D. C.; Goodman, J. M.; Stuart, M. C. A.; Otto, S. *J. Am. Chem. Soc.* **2008**, *130*, 10834–10835. (c) Corbett, P. T.; Sanders, J. K. M.; Otto, S. *Chem.—Eur. J.* **2008**, *14*, 2153–2166. (d) Kerckhoffs, J. M. C. A.; Mateos-Timoneda, M. A.; Reinhoudt, D. N.; Crego-Calama, M. *Chem.—Eur. J.* **2007**, *13*, 2377–2385. (e) Voshell, S.; Lee, S. J.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 12422–12423. (f) Lam, R. T. S.; Belenguer, A.; Roberts, S. L.; Naumann, C.; Jarosson, R.; Otto, S.; Sanders, J. K. M. *Science* **2005**, *208*, 667–669. (g) Otto, S.; Furlan, R. L.; Sanders, J. K. M. *Science* **2002**, *297*, 590–593. (h) Bunyapaboonsri, T.; Ramström, O.; Lohmann, S.; Lehn, J. M.; Peng, L.; Goeldner, M. *ChemBioChem* **2001**, *2*, 438–444. (i) Ramström, O.; Lehn, J. M. *ChemBioChem* **2000**, *1*, 41–48. (j) Huc, I.; Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2106–2110.

interconverting population. A considerable number of chemical systems that equilibrate between two or more different structural isomers are known, including epimerizable stereocenters,<sup>7</sup> metastable atropisomers,<sup>8</sup> ring–chain tautomers,<sup>9</sup> and dynamic foldamers.<sup>10</sup> The majority of these, however, would not make suitable platforms for dynamic combinatorial chemistry because of either the very small number of structurally distinct isomers or the presence of highly reactive chemical functionality.

Bullvalene<sup>11</sup> is a 10-carbon bridged tris(vinyl)cyclopropane whose unique bonding pattern endows it with the intriguing ability to alter the bonding pattern and spatial orientation of its atoms spontaneously through degenerate strain-assisted Cope rearrangements (Scheme 1). The dynamic properties of bullvalene were first conceived by Doering and Roth<sup>11a,b</sup> during their work on strain-assisted Cope rearrangements. They hypothesized that a structure such as bullvalene would give rise to a rapid fluxional tautomerism of ~1.2 million degenerate structures resulting in a single <sup>1</sup>H NMR resonance. Indeed, the subsequent photochemical synthesis of bullvalene by Schroeder<sup>11c</sup> as well as other syntheses of bullvalene<sup>11d,e,12</sup> and its fundamental derivatives<sup>13</sup> have validated this hypothesis and allowed for informative

**Scheme 1.** Degenerate Strain-Assisted Cope Rearrangements of Bullvalene and Oligosubstituted Bullvalenes Synthesized in This Work



studies of the nature of this spontaneous rearrangement.<sup>14</sup> While isomerization occurs rapidly at ambient temperature, this dynamic molecular skeleton is remarkably stable even at high temperatures. Although the rapidity and reagentless nature of this rearrangement could provide a powerful reaction to mediate the interconversion of configurationally distinct isomers of an appropriately functionalized bullvalene,<sup>1f</sup> the lack of a versatile synthesis to provide these intricately functionalized bullvalenes has precluded its successful application as a dynamic shape-shifting molecule.

Herein, we report a versatile stepwise synthesis of novel highly functionalized bullvalene derivatives, including photolabile *o*-nitroveratryloxycarbonate (NVOC) bullvalenes **1** and **2**. This synthetic challenge required not only an efficient method to access the fluxional tetracyclic bullvalene scaffold but also methods for the installation of recognition motifs such as porphyrin units, a means of inducing the dynamic behavior at a late stage in the synthetic sequence, and the design and incorporation of a mechanism to halt the dynamic isomerization of the bullvalene core. NVOC bisporphyrin bullvalene **1** constitutes a dynamic combinatorial library that rapidly equilibrates and can be immobilized without the need for additional chemical reagents. Using <sup>1</sup>H NMR and UV binding studies, we were able to demonstrate that this molecule can adapt its shape to form favorable binding interactions with C<sub>60</sub> (Figure 1). Furthermore, these structural conformations could be frozen and isolated, establishing the utility of **1** as a virtual library in which all of the components can be accessed by a single molecule. The self-contained nature of this system offers advantages over the more complex multicomponent assemblies and opens up new possibilities for the development of self-contained dynamic combinatorial libraries.

## Results and Discussion

**Synthetic Plan.** The successful implementation of functionalized bullvalenes in a dynamic combinatorial context required three key design considerations. The primary obstacle was the

- (3) (a) Gasparini, G.; Bettin, F.; Scrimin, P.; Prins, L. *J. Angew. Chem., Int. Ed.* **2009**, *48*, 4546–4550. (b) Otto, S.; Severin, K. *Top. Curr. Chem.* **2007**, *277*, 267–288. (c) Buryak, A.; Pozdnoukhov, A.; Severin, K. *Chem. Commun.* **2007**, 2366–2368. (d) Buryak, A.; Severin, K. *J. Comb. Chem.* **2006**, *8*, 540–543. (e) Giuseppone, N.; Fuks, G.; Lehn, J.-M. *Chem.—Eur. J.* **2006**, *12*, 1723–1735. (f) Buryak, A.; Severin, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7935–7938. (g) Giuseppone, N.; Lehn, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 11448–11449.
- (4) (a) Gasparini, G.; Prins, L. J.; Scrimin, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 2475–2479. (b) Vial, L.; Sanders, J. K. M.; Otto, S. *New J. Chem.* **2005**, *29*, 1001–1003. (c) Brisig, B.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1270–1273.
- (5) (a) Carnall, J. M. A.; Waudby, C. A.; Belenguer, A. M.; Stuart, M. C. A.; Peyralans, J. J.-P.; Otto, S. *Science* **2010**, *327*, 1502–1506. (b) Tauk, L.; Schröder, A. P.; Decher, G.; Giuseppone, N. *Nat. Chem.* **2009**, *1*, 649–656. (c) Nguyen, R.; Allouche, L.; Buhler, E.; Giuseppone, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 1093–1096. (d) Williams, R. J.; Smith, A. M.; Collins, R.; Hodson, N.; Das, A. K.; Ulijn, R. V. *Nat. Nanotechnol.* **2009**, *4*, 19–24. (e) Xu, S.; Giuseppone, N. *J. Am. Chem. Soc.* **2008**, *130*, 1826–1827. (f) Sadownik, J. W.; Philip, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 9965–9970.
- (6) Rowan, S.; Brady, P. A.; Sanders, J. K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2143–2145.
- (7) Chen, H.; Parkinson, J. A.; Novákova, O.; Bella, J.; Wang, F.; Dawson, A.; Gould, R.; Parsons, S.; Brabec, V.; Sadler, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 14623–14628.
- (8) (a) Takeuchi, M.; Ikeda, M.; Sugasaki, A.; Shinkai, A. *Acc. Chem. Res.* **2001**, *34*, 865–873. (b) Gawroński, J.; Kacprzak, K. *Chirality* **2002**, *14*, 689–702. (c) Kawai, H.; Katoono, R.; Fujiwara, K.; Tsuji, T.; Suzuki, T. *Chem.—Eur. J.* **2005**, *11*, 815–824. (d) Katoono, R.; Kawai, H.; Fujiwara, K.; Suzuki, T. *Tetrahedron Lett.* **2006**, *47*, 1513–1518. (e) Lavin, J. M.; Shimuzu, K. D. *Org. Lett.* **2006**, *8*, 2389–2392. (f) Lavin, J. M.; Shimuzu, K. D. *Chem. Commun.* **2007**, 228–230. (g) Clayden, J.; Vallverdú, L.; Clayton, J.; Halliwell, M. *Chem. Commun.* **2008**, 561–563. (h) Zhang, Y.; Lavin, J. M.; Shimuzu, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 12062–12063.
- (9) (a) Valters, R. E.; Fülöp, F.; Korbonits, D. *Adv. Heterocycl. Chem.* **1995**, *64*, 252–321. (b) Valters, R. E.; Fülöp, F.; Korbonits, D. *Adv. Heterocycl. Chem.* **1996**, *66*, 1–71. (c) Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* **2003**, 3025–3042.
- (10) (a) Tanatani, T.; Hughes, T. S.; Moore, J. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 325–328. (b) Chang, K.-J.; Kang, B.-N.; Lee, M.-H.; Jeong, K.-S. *J. Am. Chem. Soc.* **2005**, *127*, 12214–12215. (c) Kim, U.-I.; Suk, J.-m.; Naidu, V. R.; Jeong, K.-S. *Chem.—Eur. J.* **2008**, *14*, 11406–11414. (d) Lee, B.-C.; Chu, T. K.; Dill, K. A.; Zuckermann, R. N. *J. Am. Chem. Soc.* **2008**, *130*, 8847–8855.
- (11) (a) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1963**, *19*, 715–737. (b) Doering, W. v. E.; Roth, W. R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 115. (c) Schröder, G.; Oth, J. F. M.; Merényi, R. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 752. (d) Schröder, G.; Roth, J. F. M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 414–423. (e) Doering, W. v. E.; Ferrier, B. M.; Fosse, E. T.; Hartenstein, J. H.; Jones, M.; Klumpp, G.; Rubin, R. M.; Saunders, M. *Tetrahedron* **1967**, *23*, 3943–3963.

(12) Font, J.; Lopez, F.; Serratos, F. *Tetrahedron Lett.* **1972**, *13*, 2589–2590.

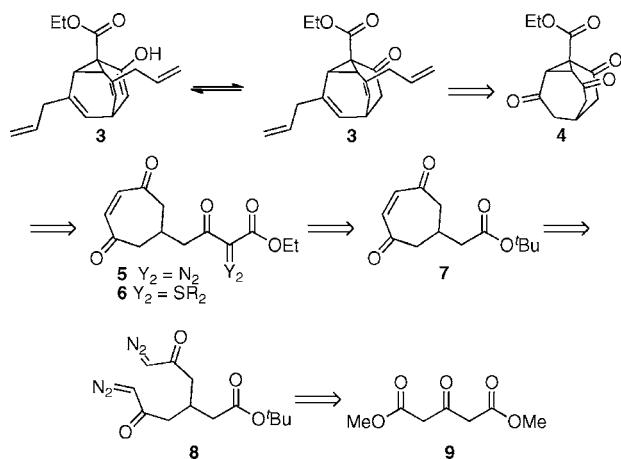
(13) (a) Rebsamen, K.; Schroder, G. *Chem. Ber.* **1993**, *126*, 1419–1423. (b) Rebsamen, K.; Schroder, G. *Chem. Ber.* **1993**, *126*, 1425–1427. (c) Sarma, K.; Witt, W.; Schroder, G. *Chem. Ber.* **1986**, *119*, 2339–2349. (d) Sarma, K.; Witt, W.; Schroder, G. *Chem. Ber.* **1983**, *116*, 3800–3812. (e) Schroder, G.; Witt, W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 311–312.

(14) Oth, J. F. M.; Mullen, K.; Gilles, J.; Schroder, G. *Helv. Chim. Acta* **1974**, *57*, 1415–1433.



**Figure 1.** NVOC bisporphyrin bullvalene **1** exists in a dynamic equilibrium of 840 possible isomers. After it is adaptively bound to a  $C_{60}$  guest, UV irradiation cleaves the NVOC group, resulting in static isomers of bisporphyrin bullvalone with optimized binding affinities.

### Scheme 2. Retrosynthetic Analysis of Bullvalone **3**

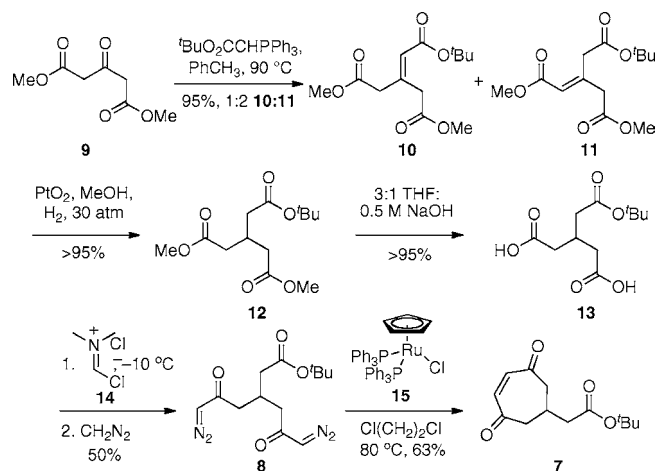


formation of the tetracyclic bullvalene core consisting of a bridged tris(vinyl)cyclopropane. Second was the requirement that this core contain functional handles by which desired recognition motifs could be appended in a highly convergent manner. It was also necessary to design a mechanism by which the exchange process between the valence isomers could be halted, allowing for the analysis and isolation of an adapted species. Our initial synthetic target, bisallyl bullvalone **3**<sup>15</sup> (Scheme 2), satisfied these criteria, as an intramolecular cyclopropanation could form the tetracyclic core, allylic arms provided handles for further elaboration, and a ketone to enol tautomerization could serve as a base-sensitive switch for toggling between the static bullvalone and a dynamic hydroxy-bullvalene.

Working from a synthesis of unfunctionalized bullvalene performed by Serratos,<sup>12</sup> we imagined that trisubstituted bullvalone **3** could be attained from regioselective functionalization of the triketone **4** containing a desymmetrizing group that would allow for steric differentiation of the ketones (Scheme 2). A key intramolecular cyclopropanation of diazoketone **5** or sulfur ylide **6** derived from enedione intermediate **7** would provide the tetracyclic skeleton. Initially, we sought to synthesize enedione **7** through an intramolecular bisdiazoketone decomposition of meso intermediate **8**, which could be generated through parallel functionalization of commercially available dimethyl acetone-1,3-dicarboxylate (**9**).

**Synthesis of Enedione **7** via Diazoketone Decomposition.** The synthetic endeavor began with the Wittig olefination<sup>16</sup> of **9** with *tert*-butyl triphenyl phosphorane (Scheme 3). Good yields of a

### Scheme 3. Intramolecular Bisdiazoketone Decomposition Route To Form Enedione **7**



statistical mixture of the olefinic tautomers **10** and **11** were obtained. Hydrogenation of this mixture under high-pressure  $H_2$  in the presence of  $PtO_2$  followed by hydrolysis of the methyl esters provided bis(acid) **13** in excellent yield over the three-step sequence from **9**. In the conversion of bis(acid) **13** to the corresponding bis(acid chloride), we found it necessary to employ a stoichiometric amount of the Vilsmeier salt **14**<sup>17</sup> at  $-10\text{ }^\circ\text{C}$  in order to avoid cleavage of the *tert*-butyl ester as well as cyclic anhydride formation, as these side products plagued a large number of other conditions attempted for the preparation of the bis(acid chloride). Treatment of the bis(acid chloride) with freshly prepared diazomethane provided bisdiazoketone **8** in 50% overall yield from the diacid. With catalysis by chlorocyclopentadienylbis(triphenylphosphine)ruthenium-(II)<sup>18</sup> (**15**), **8** underwent intramolecular bisdiazoketone decomposition to produce enedione intermediate **7** in 63% yield.

**Revised Route to the Enedione Intermediate.** Although this route provided access to the desired enedione **7**, the modest yield of the diazoketone formation as well as the hazards associated with the large-scale preparation of diazomethane prompted us to seek a more practical route to this intermediate. We postulated that instead of the formation of a seven-membered ring through a sequence of steps that required multiple functional group transformations prior to the ultimate ring-closing event, this same intermediate could be more easily attained in a scalable fashion through the oxidative elaboration of cycloheptanone.

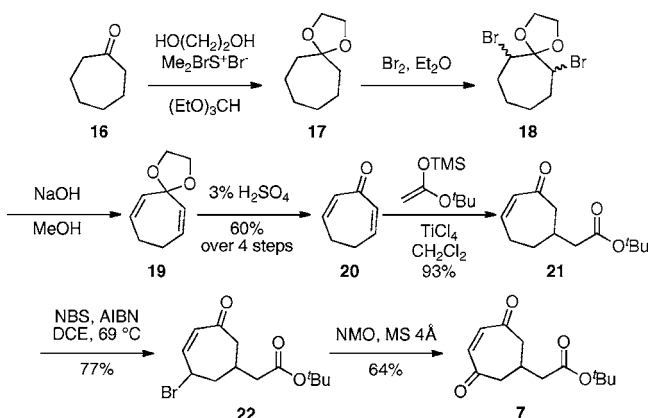
(15) Lippert, A. R.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 14738–14739.

(16) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.

(17) Fujisawa, T.; Sato, T. *Org. Synth.* **1988**, *66*, 121–126.

(18) Del Zotto, A.; Baratta, W.; Verardo, G.; Rigo, P. *Eur. J. Org. Chem.* **2000**, 2795–2801.

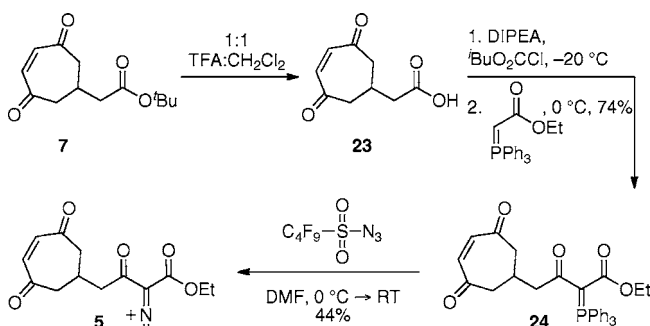
## Scheme 4. Revised Synthesis of Enedione 7



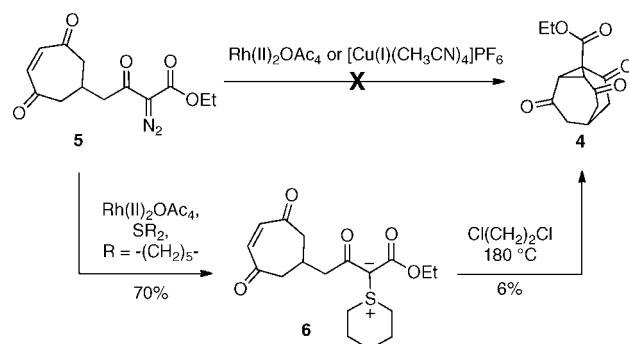
Cycloheptadienone **20** was readily prepared from cycloheptanone by a known procedure<sup>19</sup> (Scheme 4). Protection of the ketone as an acetal was followed by bisbromination with elemental bromine and biselimination with sodium hydroxide. Cleavage of the acetal with dilute sulfuric acid produced **20** in 60% yield over the four-step sequence. Carbon–carbon bond formation was accomplished with a titanium tetrachloride-catalyzed Mukaiyama Michael addition<sup>20</sup> using *tert*-butyl trimethylsilyl ketene acetal<sup>21</sup> to produce enone **21** in excellent yield. A direct *tert*-butyl peroxide-mediated, metal-catalyzed allylic oxidation of enedione **21** was attempted using a range of metal catalysts, including Pd(OH)<sub>2</sub>,<sup>22</sup> rhodium(II) caprolactam,<sup>23</sup> [Cu(I)(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub>, and Cu(I)(OTf). The best result was obtained using rhodium(II) caprolactam, which provided the oxidized product **7** in a modest 45% yield. Selenium dioxide followed by PCC oxidation<sup>24</sup> and chromium(III) oxide and dimethylpyrazole<sup>25</sup> also gave only low yields of the oxidized product. The best results were obtained in a two-step procedure starting with an AIBN-initiated radical bromination followed by an *N*-methylmorpholine-*N*-oxide-mediated Ganem<sup>26</sup> reaction to transform the secondary bromide into a ketone. This provided oxidized enedione **7** in good yield on a multigram scale; the only observed side product was the bisenone formed by elimination of the bromide.

**Intramolecular Cyclopropanation.** In the initial attempts to form the desired triketone **4** via an intramolecular cyclopropanation, it was necessary to advance the *tert*-butyl ester functionality into a stabilized diazoketone. Inspired by a report of the transformation of phosphorus ylides into diazoketones through the use of sulfonyl azide diazo-transfer reagents,<sup>27</sup> we began to study the possibility of installing the diazoketone in this manner. Treatment of enedione **7** with a 1:1 mixture of trifluoroacetic acid (TFA) and dichloromethane followed by aqueous workup yielded the deprotected acid **23** (Scheme 5).

## Scheme 5. Synthesis of Diazoketone 5 from Phosphorus Ylide 24



## Scheme 6. Intramolecular Cyclopropanation To Form Tetracyclic Cyclopropane 4



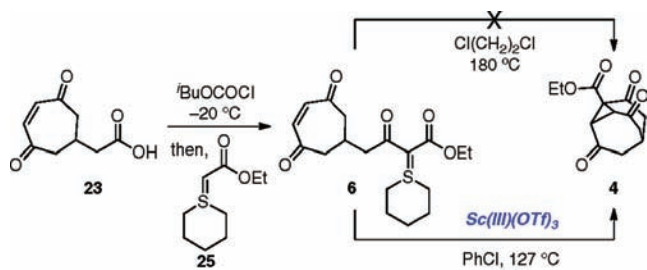
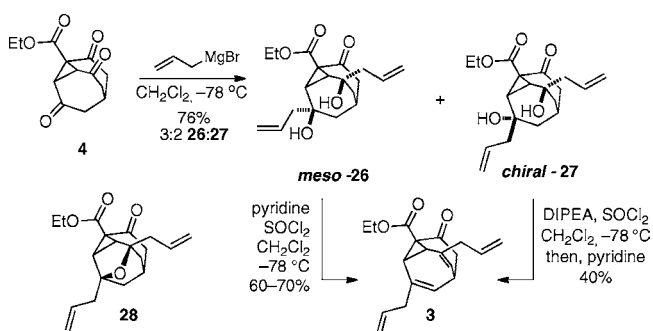
Activation of the acid with isobutyl chloroformate followed by coupling with ethyltriphenylphosphorane produced the doubly stabilized ylide **24** in 74% yield.<sup>28</sup> A screening of sulfonyl azides, including tosyl azide, mesyl azide, *o*-nitrophenylsulfonyl azide, and perfluorobutylsulfonyl azide (nofyl azide)<sup>29</sup> revealed that nofyl azide most effectively mediated this transformation, producing diazoketone **5** in 44% yield.

Reactions using [Cu(I)(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> and Rh(II)<sub>2</sub>(OAc)<sub>4</sub> as catalysts did not produce any of the desired cyclopropane product in the key intramolecular cyclopropanation (Scheme 6). We suspected that the olefin was too electron-deficient for the carbene-mediated cyclopropanation to occur. However, studies by Aggarwal<sup>30</sup> demonstrated that the addition of catalytic sulfides could promote cyclopropanation of diazoketones with electron-deficient olefins through the intermediacy of a catalytically generated sulfur ylide. Inspired by these studies, a sulfur ylide-mediated cyclopropanation was pursued. Stoichiometric amounts of pentamethylene sulfide and catalytic Rh(II)<sub>2</sub>(OAc)<sub>4</sub> were used to form doubly stabilized sulfur ylide **6**. Heating **6** in degassed dichloroethane at 180 °C did indeed afford triketone **4**, albeit in low yield.

In order to circumvent the low-yielding diazoketone formation, we investigated the direct coupling of a sulfur ylide with

(19) Krabbenhoft, H. O. *J. Org. Chem.* **1979**, *44*, 4285–4294.  
 (20) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817–826.  
 (21) Okabayashi, T.; Iida, A.; Takai, K.; Nawate, Y.; Tomonori, M.; Tanabe, Y. *J. Org. Chem.* **2007**, *72*, 8142–8145.  
 (22) Corey, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2005**, *125*, 3232–3233.  
 (23) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622–13623.  
 (24) Davies, H. M. L.; Loe, O.; Stafford, D. G. *Org. Lett.* **2005**, *7*, 5561–5563.  
 (25) Fleming, F. F.; Zhang, Z.; Wei, G. *Synthesis* **2005**, 3179–3180.  
 (26) (a) Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 4825–4826. (b) Griffith, W. P.; Jolliffe, J. M.; Ley, S. V.; Springhorn, K. F.; Tiffin, P. D. *Synth. Commun.* **1992**, *22*, 1967–1971.  
 (27) Harvey, G. R. *J. Org. Chem.* **1966**, *31*, 1587–1590.

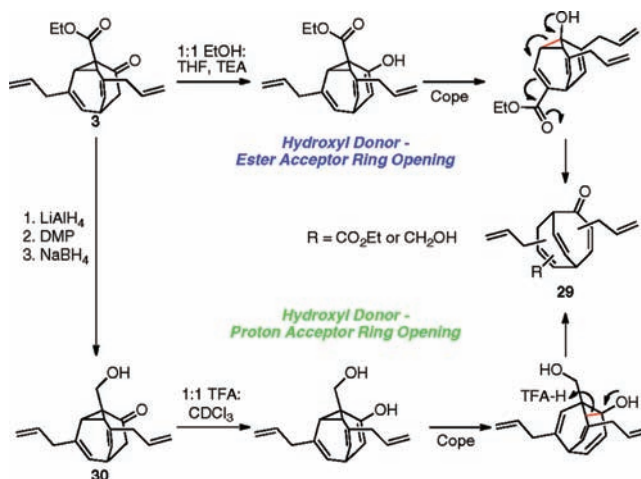
(28) (a) Cooke, M. P., Jr.; Burman, D. L. *J. Org. Chem.* **1982**, *47*, 4955–4963. (b) Wasserman, H. H.; Kuo, G. *Tetrahedron* **1992**, *48*, 7071–7082.  
 (29) Zhu, S.-Z.; He, P.; Zhao, J.-W.; Cai, X. *J. Fluorine Chem.* **2004**, *125*, 445–450.  
 (30) (a) Aggarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H.; Fieldhouse, R.; Spey, S. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3267–3276. (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433–1436. (c) Aggarwal, V. K.; Grange, E. *Chem.—Eur. J.* **2006**, *12*, 568–575.

**Scheme 7.** Ylide Coupling and Optimized Cyclopropanation**Scheme 8.** Synthesis of Bisallyl Bullvalone 3

an activated carboxylate.<sup>31</sup> We were delighted to discover that after activation of acid **23** with isobutyl chloroformate, coupling with the pentamethylenesulfide-derived ylide **25** produced the desired coupled ylide **6** (Scheme 7), nicely establishing a new carbon–carbon bond and setting up the requisite functionality in a single step. Surprisingly, however, the sulfur ylide synthesized in this way failed to produce any of the desired triketone **4**, even at elevated temperatures.

We postulated that residual  $\text{Rh(II)}_2(\text{OAc})_4$  from the conversion of **5** into sulfur ylide **6**, whose presence was evidenced by its green coloration and mass spectral analysis, may have catalyzed the cyclopropanation. Reasoning that the  $\text{Rh(II)}_2(\text{OAc})_4$  acted as a Lewis acid to promote the cyclopropanation, we investigated the effects of other Lewis acids to facilitate the desired transformation. We found that the ylide was smoothly converted to the desired triketone **4** (Scheme 7) using a variety of Lewis acids. Optimization revealed chlorobenzene to be the best solvent, and  $\text{Sc(III)(OTf)}_3$  performed better than  $\text{Yb(III)(OTf)}_3$ ,  $\text{Y(III)(OTf)}_3$ , or  $\text{Zn(II)Cl}_2$ , reproducibly forming triketone **4** in 70% yield.

**Synthesis of Oligosubstituted Bullvalone.** Having developed a scalable route to the advanced triketone intermediate, we turned our efforts toward its functionalization and conversion into an elaborately derivatized bullvalene. Selective functionalization of the two less hindered ketones by reaction with allylmagnesium bromide yielded a mixture of the meso diastereomer **26** and the chiral diastereomer **27** (**26/27**  $\approx$  3:2; Scheme 8). Exploration of a variety of biselimination conditions, including Burgess reagent,<sup>32</sup> xanthate formation,<sup>33</sup> triphenylphos-

**Scheme 9.** Elucidation of Degradation Pathways of Bullvalones **3** and **30**

phine/iodine,<sup>34</sup> catalytic acid, phosphorus pentachloride with various bases,<sup>35</sup> and thionyl chloride with various bases,<sup>36</sup> revealed that premixing of thionyl chloride and pyridine<sup>37</sup> followed by addition of the meso diol **26** gave the best results for the elimination of the meso diastereomer, yielding the desired bullvalone **3** in 60% yield. When the chiral diastereomer was subjected to the same conditions, however, tetrahydrofuran product **28** was the major product. Further experimentation revealed that upon treatment of the *chiral* diol **27** with a premixed solution of Hünig's base and thionyl chloride followed by addition of pyridine, the desired bullvalone **3** could be obtained in 40% yield.

**Elucidation of Degradation Pathways.** Previous deuterium incorporation studies<sup>15</sup> revealed that ketone to enol tautomerization of the carbonyl of bisallyl bullvalone **3** could be used as a chemical switch to toggle between a static bullvalone and a dynamic hydroxybullvalene. While these experiments demonstrated that base could indeed result in configurational isomerization via the mediation of a transient hydroxybullvalene, incomplete deuterium incorporation suggested that degradation pathways resulting in static constitutional isomers might be present. Isolation of the major components after treatment with base revealed that some of the isomers had structures that could not be assigned to a bullvalone and were most likely ring-opened structures such as **29** ( $\text{R} = \text{CO}_2\text{Et}$ ). It was theorized that Cope rearrangements of the hydroxybullvalene would produce some isomers in which the hydroxyl group was positioned on the cyclopropane ring. If in addition the ester were positioned appropriately, then a donor–acceptor ring opening of the cyclopropane could occur. Our initial approach to solve this problem was to remove the acceptor aspect of the donor–acceptor pair by converting the ester into the primary alcohol **30** using a three-step procedure (Scheme 9). Unfortunately, deuterium incorporation experiments suggested that a decomposition pathway still existed. It was also found that TFA could mediate the isomerization and ring opening. Isolation of ring-opened products such as **29** ( $\text{R} = \text{CH}_2\text{OH}$ ) indicated that a proton could

(31) (a) Ratts, K. W.; Yao, A. N. *J. Org. Chem.* **1966**, *31*, 1689–1693. (b) Ziegler, E.; Wittmann, H.; Sterk, H. *Monatsh. Chem.* **1987**, *118*, 115–125.

(32) (a) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224–5225. (b) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26–31.

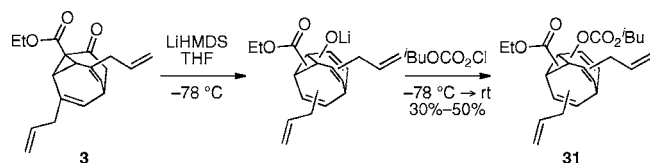
(33) Nace, H. R. *Org. React.* **1962**, *12*, 57–100.

(34) Alvarez-Manzaneda, E. J.; Chahboun, E.; Torres, C.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* **2004**, *45*, 4453–4455.

(35) Sauers, R. R. *J. Am. Chem. Soc.* **1959**, *81*, 4873–4876.

(36) Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613–627.

(37) Greene, A. E.; Edgar, M. T. *J. Org. Chem.* **1989**, *54*, 1468–1470.

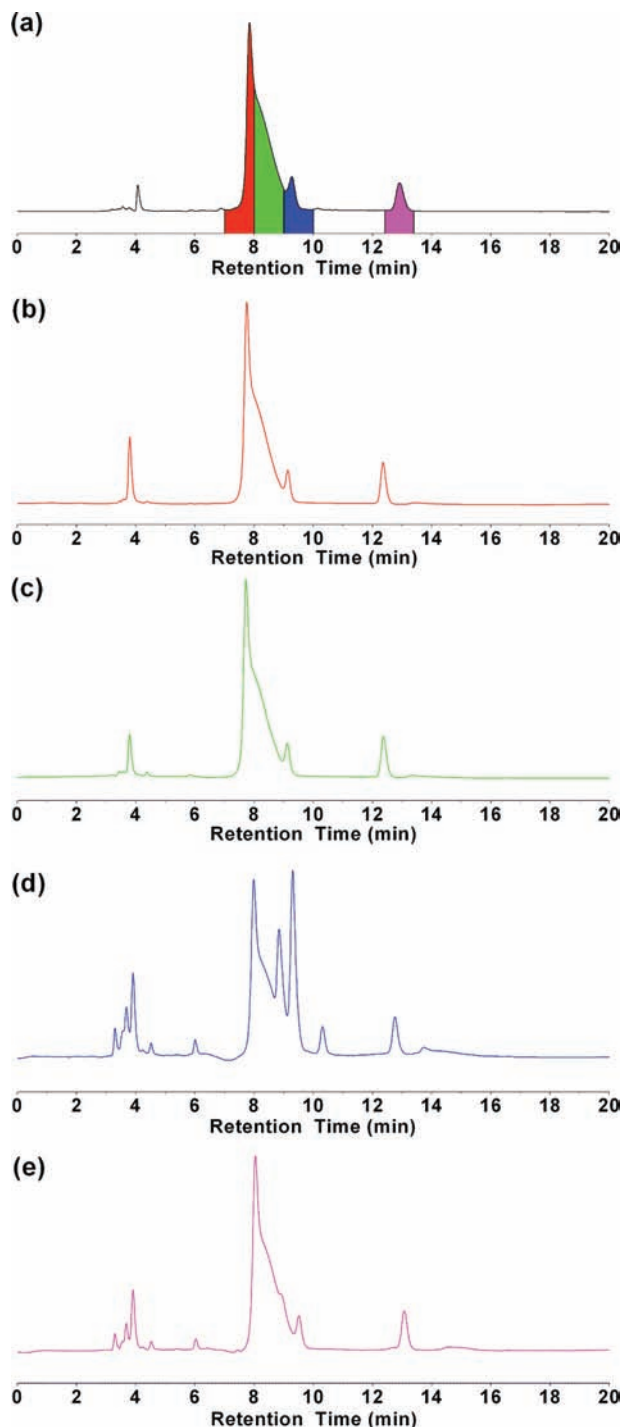
**Scheme 10.** Synthesis of Isobutyl Carbonate Bisallyl Bullvalene **31**

also act as an acceptor in the donor–acceptor ring opening of the bullvalone cyclopropane. On the basis of these experiments, it became clear that it would be necessary to remove the donor capability of the hydroxyl group in order for a robust and stable isomerization to occur.

**Synthesis of Isobutyl Carbonate Bisallyl Bullvalene **31**.** It was reasoned that trapping of the enolate of bisallyl bullvalone **3** might provide access to an isolable oligosubstituted bullvalene. After treatment with LiHMDS at  $-78\text{ }^{\circ}\text{C}$ , the lithium enolate was treated with isobutyl chloroformate and allowed to warm to room temperature (Scheme 10). Upon workup and purification, the stable isobutyl carbonate bisallyl bullvalene **31** was isolated and characterized.<sup>38</sup> Variable-temperature (VT) NMR spectroscopy demonstrated that the strain-assisted Cope rearrangement occurred spontaneously at room temperature with complete coalescence of the bullvalene core protons at  $120\text{ }^{\circ}\text{C}$  in  $(\text{CD}_3)_2\text{SO}$ . Additionally, two-dimensional exchange correlation spectroscopy (2D-EXSY) revealed chemical exchange among the olefin, cyclopropyl, and methine protons.<sup>38</sup>

**HPLC Demonstration of Interconversion.** Chromatographic purification of functionalized bullvalenes was complicated by the fact that the purified material appears as multiple bands by chromatographic analysis. For example, the HPLC trace of the purified isobutyl carbonate bisallyl bullvalene **31** displayed multiple peaks at different retention times (Figure 2a); the broadening and peak-shape distortion attest that significant isomerization occurred during elution of the bullvalene through the HPLC column. After isolating four fractions from the HPLC column and reinjecting each of these fractions into the chromatograph, we observed the reappearance of the peaks from the original bullvalene isomeric distribution (Figure 2b–e). This attests to the identity of these compounds as interconverting isomers. Most of the isolated bullvalene fractions resulted in nearly perfect reproductions of the original bullvalene chromatogram upon reinjection, indicating rapid equilibration. Reinjection of the fraction with a retention time of 9–10 min (Figure 2d), however, provided a chromatogram with an altered isomeric ratio, indicating the presence of slowly equilibrating or static compounds.

**NVOC Bisallyl Bullvalene **2**.** A crucial component of a dynamic combinatorial library is the mechanism to halt the reversibility of the equilibration reaction, allowing the isolation and analysis of an adapted product. We had originally proposed that the ketone of a bullvalone could serve as a chemical handle capable of mediating between the static bullvalone and the dynamic bullvalene. However, it was determined that the bullvalone was not stable under the conditions necessary to toggle between these two states. Trapping the hydroxybullvalene as a carbonate presented a solution in that the ring-opening pathways responsible for degradation of the bullvalone could be suppressed while still allowing for the diversity-generating Cope rearrangements to occur. In addition, selecting a carbonate



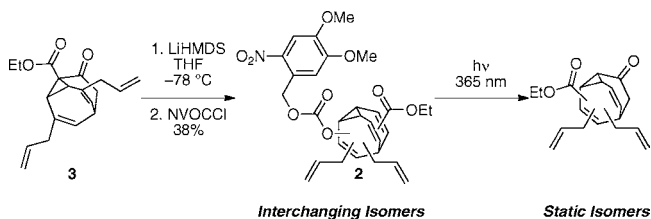
**Figure 2.** Isolation of bullvalene isomers followed by reinjection into the HPLC column. (a) HPLC trace of purified isobutyl carbonate bisallyl bullvalene **31**. (b–e) HPLC traces after isolation and reinjection of the fractions from (b)  $t_r = 7$  to 8 min, (c)  $t_r = 8$  to 9 min, (d)  $t_r = 9$  to 10 min, and (e)  $t_r = 12.5$  to 13.5 min.

protecting group that could be cleaved under the desired conditions would provide a way to halt the dynamic rearrangement of the bullvalene. In order to explore this possibility, we sought to prepare bullvalene derivatives with photolabile carbonate substituents. To this end, NVOC bisallyl bullvalene **2** was synthesized by trapping the lithium enolate of bullvalone **3** with NVOC chloroformate (Scheme 11).

As in the case of isobutyl carbonate bisallyl bullvalene **31**, the HPLC trace of NVOC bisallyl bullvalene **2** also appeared

(38) Lippert, A. R.; Keleshian, V. L.; Bode, J. W. *Org. Biomol. Chem.* **2009**, *7*, 1529–1532.

**Scheme 11.** Synthesis and Photolysis of NVOC Bisallyl Bullvalene **2**



as multiple peaks (Figure 3). Irradiation of the purified bullvalene **2** at 365 nm for 20 h resulted in a complete disappearance of the peaks due to the starting material as well as the appearance of peaks corresponding to isomers of bisallyl bullvalone **3**.

**Synthesis of Bisporphyrin Bullvalenes.** With a versatile route to bisallyl bullvalenes in hand, we investigated appending suitable recognition motifs to the bullvalene core in order to demonstrate that an appropriately functionalized bullvalene is capable of responding to a guest molecule. The strong  $\pi$ - $\pi$  interactions between porphyrins and  $C_{60}$ <sup>39</sup> provided an ideal host-guest interaction to interrogate the possibility of utilizing functionalized bullvalenes as dynamic combinatorial libraries. A necessary prerequisite for this goal was the development of an efficient and versatile strategy to effect the functionalization of a dynamic bisallyl bullvalene. We envisaged that cross-metathesis would provide a convergent and chemoselective conjugation reaction to append complex molecular fragments such as porphyrins to the terminal olefins of the bisallyl bullvalene core.

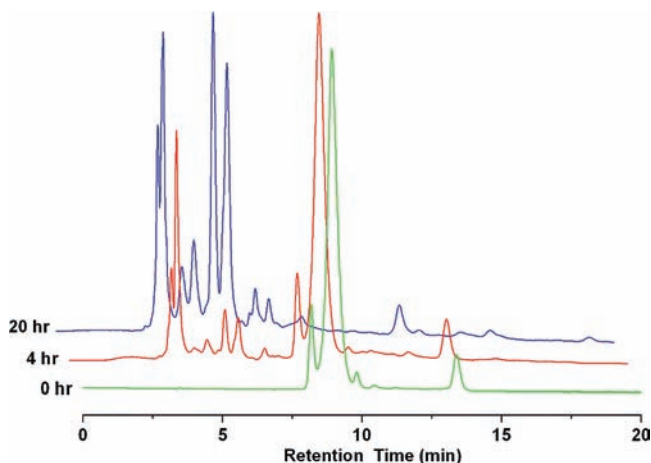
Initial studies of the cross-metathesis reaction were performed using bisallyl bullvalone **3**. Attempts at metathesis with allylamide porphyrin **33** (synthesized from methyl ester-functionalized porphyrin **31**<sup>40</sup> as outlined in Scheme 12) using either Grubbs second-generation catalyst **34**<sup>41</sup> or Hoveyda second-generation catalyst<sup>42</sup> (not shown) failed to produce the corresponding bisporphyrin bullvalone **35** (not shown), probably as a result of ruthenium-catalyzed isomerization of the olefin followed by decomposition of the resulting enamide.<sup>43</sup> A second stepwise strategy consisting of a successful metathesis with the known *tert*-butyloxycarbonyl-protected bisamine *cis*-olefin **36**<sup>44</sup> produced the protected bisamine bullvalone **37** (Scheme 13). Deprotection of the amine groups and coupling to the activated carboxylate of porphyrin **32** yielded a single product with the

correct mass in 38% yield. Although initial studies utilizing supercritical-fluid  $CO_2$  chromatography revealed that this bisporphyrin molecule does indeed bind  $C_{60}$ , it was eventually found that the TFA deprotection step caused a ketone-to-enol tautomerization (as in Scheme 9) followed by a Cope rearrangement and donor-acceptor ring opening of the resulting hydroxycyclopropane to yield the static isomer **38**.

A successful strategy was finally found using acrylamide porphyrin **40**<sup>38</sup> as a cross-metathesis coupling partner (Scheme 13). It is known that acrylamides are excellent substrates for cross-metathesis with terminal olefins,<sup>45</sup> and we were pleased to find that cross-metathesis with **40** (formed from the known aminoporphyrin **39**<sup>46</sup>) using Grubbs second-generation catalyst in  $CH_2Cl_2$  at 40 °C yielded bisporphyrin bullvalone **41**<sup>38</sup> in 20% yield. Furthermore, similar conditions were used to form isobutyl bisporphyrin bullvalene **42**<sup>38</sup> in 19% yield and NVOC bisporphyrin bullvalene **1** in 13% yield (Scheme 14).

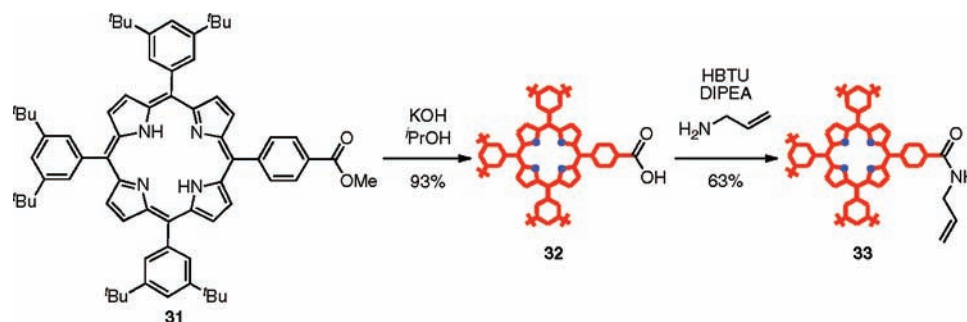
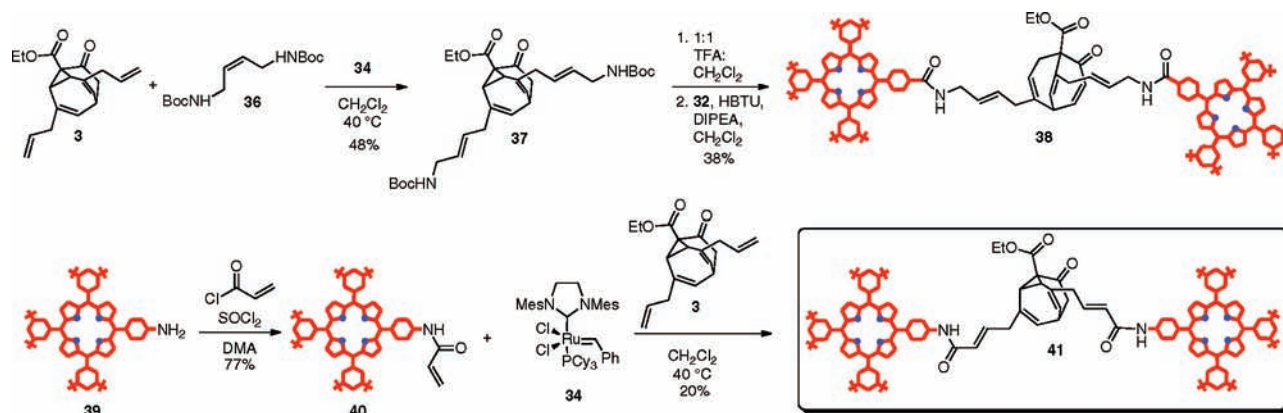
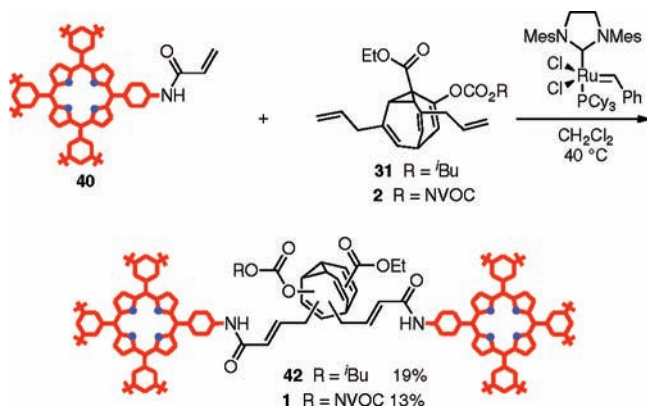
**Dynamic Combinatorial Chemistry.** NVOC bisporphyrin bullvalene **1** contains all of the elements needed for dynamic combinatorial chemistry: the bullvalene core provides a spontaneous and rapid process by which configurationally distinct isomers can interconvert with each other, the  $\pi$ - $\pi$  interactions between the bisporphyrin units and  $C_{60}$  provide a template for adaptation, and the photocleavable carbonate allows the system to be frozen after it has responded to the desired stimuli. Using <sup>1</sup>H NMR and UV studies, we previously explored the complexation of isobutyl carbonate bisporphyrin bullvalene **42** and compared its binding properties with those of bisporphyrin bullvalone **41** as a static control.<sup>38</sup> During the course of these studies, we established NMR methods to measure the binding constants of the major binding isomers of **42**. Comparison of these values with that of the static bisporphyrin bullvalone revealed that the bullvalene could adapt its shape in the presence of  $C_{60}$  to form isomers with more favorable binding properties.

Having demonstrated that a bisporphyrin bullvalene could adapt its shape in response to  $C_{60}$ , we next wished to ascertain whether these constitutional isomers could be frozen and isolated. UV irradiation of NVOC bisporphyrin bullvalene **1**, which possesses a photolabile carbonate, should produce a mixture of static isomers of bisporphyrin bullvalone. We performed titration experiments on **1** before and after UV irradiation. Bullvalene **1** was loaded into NMR tubes with increasing amounts of  $C_{60}$ . Spectra were recorded for these samples before and after UV irradiation (Figure 4). Before irradiation, spectra similar to those observed for isobutyl



**Figure 3.** HPLC traces for the photolysis of NVOC bisallyl bullvalene **2** upon exposure to UV irradiation after (green) 0, (red) 4, and (blue) 20 h.

- (39) (a) Marois, J.-S.; Cantin, K.; Desmarais, A.; Morin, J.-F. *Org. Lett.* **2008**, *10*, 33–36. (b) Hosseini, A.; Taylor, S.; Accorsi, G.; Armaroli, N.; Reed, C. A.; Boyd, P. D. W. *J. Am. Chem. Soc.* **2006**, *128*, 15903–15913. (c) Haino, T.; Fugii, T.; Fukazawa, Y. *J. Org. Chem.* **2006**, *71*, 2572–2580. (d) Boyd, P. D. W.; Reed, C. A. *Acc. Chem. Res.* **2005**, *38*, 235–242. (e) Sun, D.; Tham, S. F.; Reed, C. A.; Chaker, L.; Boyd, P. D. W. *J. Am. Chem. Soc.* **2002**, *124*, 6604–6612.
- (40) Li, X.; Tanasova, M.; Vasileiou, C.; Borhan, B. *J. Am. Chem. Soc.* **2008**, *130*, 1885–1893.
- (41) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
- (42) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoyveda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
- (43) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem.—Eur. J.* **2003**, *9*, 5793–5799.
- (44) Morita, T.; Maughon, B. R.; Bielawski, C. W.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 6621–6623.
- (45) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277–1279.
- (46) Imahori, H.; Hagiwara, K.; Aoki, M.; Akiyama, T.; Taniguchi, S.; Okada, T.; Shirakawa, M.; Sakata, Y. *J. Am. Chem. Soc.* **1996**, *118*, 11771–11782.

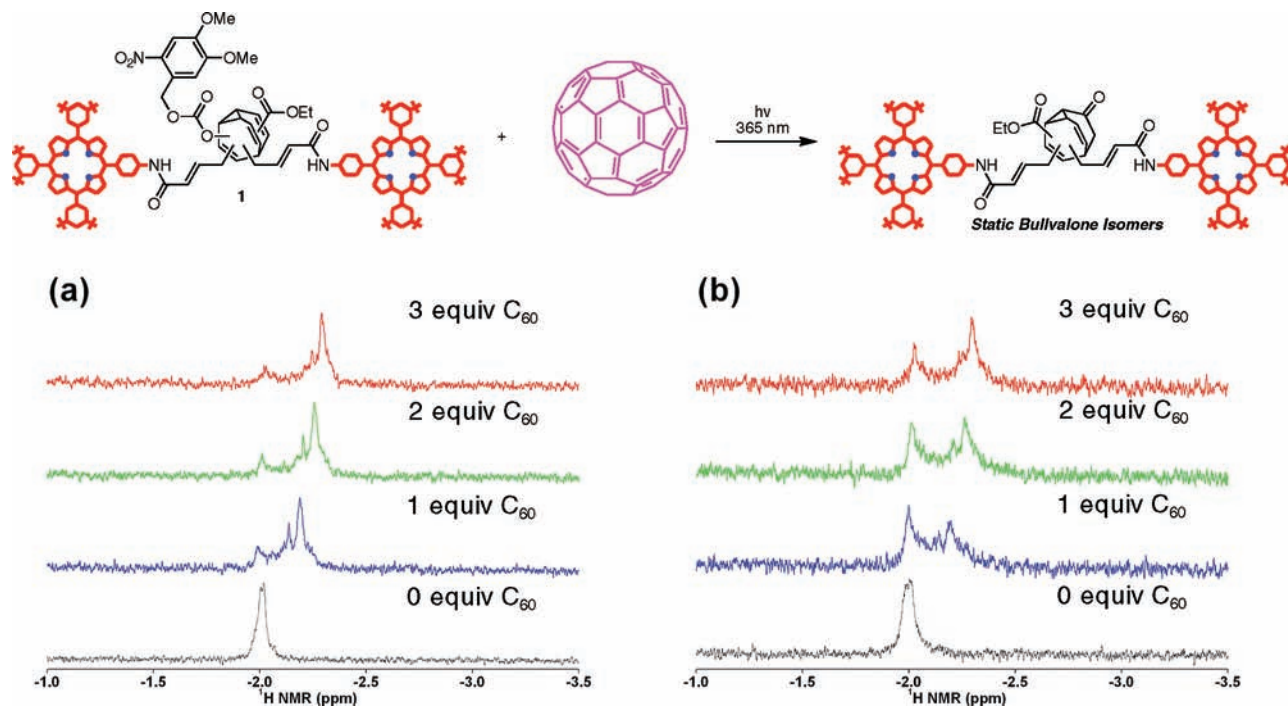
Scheme 12. Synthesis of Allylamide Porphyrin **33**Scheme 13. Synthesis of Bisporphyrin Bullvalone **41**Scheme 14. Synthesis of Bisporphyrin Bullvalenes **1** and **42**

carbonate bisporphyrin bullvalene **42** were observed. Two peaks appeared in the region of the porphyrin N–H resonance, each corresponding to a binding isomer in fast exchange between the bound and unbound species. Calculation of the binding constants yielded values similar to those calculated for **42**.<sup>38</sup> An unshifted peak at  $-2$  ppm was assigned to those isomers that do not bind well to  $C_{60}$ . Interestingly, the relative ratio of the more tightly binding isomer increased as more  $C_{60}$  was added, demonstrating the ability of this system to adapt to an appropriate guest. On the basis of the change in the chemical shift of these two peaks, binding constants of  $2550 \pm 240 \text{ M}^{-1}$  (Table 1, entry 5) and  $5790 \pm 1200 \text{ M}^{-1}$  (entry 6) were calculated for the less-upfield and more-upfield peaks, respectively. The average high-temperature binding constant of  $830 \pm 90 \text{ M}^{-1}$  (entry 12), which was determined by performing the titration on the coalesced peak at  $90^\circ\text{C}$ , was similar to the value of  $920 \pm 100 \text{ M}^{-1}$  found for **42** (entry 11).

Next, these NMR tubes were irradiated with UV light for 17 h, and spectra were again recorded. The peaks that were observed after irradiation arose from static isomers of bisporphyrin bullvalone **41**. As expected, we found an increasing amount of the more tightly binding isomers in the experiments that had greater amounts of  $C_{60}$ . Calculation of the binding constants of these major peaks gave values of  $3270 \pm 670 \text{ M}^{-1}$  (entry 7) and  $7580 \pm 1930 \text{ M}^{-1}$  (entry 8) for the less-upfield and more-upfield peaks, respectively. Finally, we isolated the major bullvalone product from the photolysis of **1** in the presence of  $C_{60}$ . Analysis by MALDI mass spectrometry (MALDI-MS) indicated this product had the mass of an isomer of **41**. Calculation of its binding affinity for  $C_{60}$  by spectrophotometric titration yielded a binding constant of  $7490 \pm 440 \text{ M}^{-1}$  (entry 9), which is remarkably close to the value calculated for the more tightly bound isomer in the NMR titration of NVOC bisporphyrin bullvalene **1** after photocleavage.

Table 1 summarizes the binding constants measured for bisporphyrin bullvalone **41** (entries 1, 2, and 10), isobutyl carbonate bisporphyrin bullvalene **42** (entries 3, 4, and 11), NVOC bisporphyrin bullvalene **1** before (entries 5, 6, and 12) and after (entries 7 and 8) photocleavage, and the major bisporphyrin bullvalone isomer isolated after photocleavage (entry 9). Similar values were obtained from  $^1\text{H}$  NMR measurements on isobutyl carbonate bisporphyrin bullvalene **42** and NVOC bisporphyrin bullvalene **1** for both the higher binding complex ( $\Delta\delta = 0.27$ ) and the lower binding complex ( $\Delta\delta = 0.24$ ) at  $25^\circ\text{C}$  as well as the coalesced peak at  $90^\circ\text{C}$ . Importantly, the values of the binding constants of NVOC bisporphyrin bullvalene **1** before and after photocleavage are comparable, demonstrating that the relatively slow exchange between the dynamic binding isomers introduces minimal error into the values obtained. The close agreement between value





**Figure 4.**  $^1\text{H}$  NMR titrations of NVOC bisporphyrin bullvalene **1** with  $\text{C}_{60}$  (a) before and (b) after UV irradiation.

**Table 1.** Binding Constants Calculated for Bisporphyrin Bullvalone **41**, Isobutyl Carbonate Bisporphyrin Bullvalene **41**, and NVOC Bisporphyrin Bullvalene **1** before and after Photocleavage

entry	compd	$\Delta\delta$ (ppm) <sup>a</sup>	$T$ ( $^{\circ}\text{C}$ )	$K_b$ ( $\text{M}^{-1}$ )	method
1	<b>41</b>	—	25	$2700 \pm 120^d$	UV
2	<b>41</b>	0.23	25	$2800 \pm 210^d$	NMR
3	<b>42</b>	0.24	25	$3030 \pm 430^d$	NMR
4	<b>42</b>	0.27	25	$6770 \pm 1800^d$	NMR
5	<b>1</b>	0.24	25	$2550 \pm 240$	NMR
6	<b>1</b>	0.27	25	$5790 \pm 1200$	NMR
7	<b>1</b> + $h\nu^b$	0.24	25	$3270 \pm 670$	NMR
8	<b>1</b> + $h\nu^b$	0.27	25	$7580 \pm 1930$	NMR
9	<b>1</b> + $h\nu^c$	—	25	$7490 \pm 440$	UV
10	<b>41</b>	0.10	90	$570 \pm 650^d$	NMR
11	<b>42</b>	0.13	90	$920 \pm 100^d$	NMR
12	<b>1</b>	0.13	90	$830 \pm 90$	NMR

<sup>a</sup> Change in the chemical shift of the peak used to calculate  $K_b$  upon the addition of 3 equiv of  $\text{C}_{60}$ . <sup>b</sup> After photolysis. <sup>c</sup> Major bullvalone fraction isolated after photolysis. <sup>d</sup> Data from ref 38.

obtained by spectrophotometric titration of the isolated fraction (entry 9) and the value obtained by  $^1\text{H}$  NMR titration for the higher-binding isomer of **1** after the photocleavage (entry 8) provide a compelling demonstration of the ability of appropriately functionalized bullvalenes to rapidly discover optimized host–guest complexes.

## Conclusions and Future Prospects

In summary, we have developed a versatile 10-step synthesis of elaborately functionalized bullvalenes, including NVOC bisporphyrin bullvalene **1** and NVOC bisallyl bullvalene **2**, from readily available cycloheptadienone. A late-stage cross-metathesis strategy was used to append porphyrin units to the bullvalene scaffold and could allow for the production of a wide variety of other bullvalene derivatives with elaborate functionalities and recognition motifs. Furthermore, the formation of the bullvalene as an enol carbonate of the static bullvalone presents an ideal platform to which a number of chemical mechanisms could be introduced to modulate the dynamic nature

of the system.  $^1\text{H}$  NMR binding studies have clearly demonstrated that **1** adapts its structure in response to increasing concentrations of  $\text{C}_{60}$  to form those isomers with more favorable binding properties. Photolysis of the NVOC carbonate halts the facile Cope rearrangements, allowing for the isolation of these adapted structures. UV and  $^1\text{H}$  NMR binding experiments have provided compelling evidence of the ability of appropriately functionalized bullvalenes to serve as dynamic combinatorial libraries. These studies introduce the unique and far-reaching potential enabled by a versatile synthetic platform of highly functionalized bullvalene derivatives.

## Experimental Procedures

**Titration and Photocleavage of NVOC Bisporphyrin Bullvalene 1.** A  $1.8 \times 10^{-3}$  M stock solution of NVOC bisporphyrin bullvalene **1** in  $\text{C}_6\text{D}_5\text{CD}_3$  was prepared, and  $100 \mu\text{L}$  aliquots ( $1.8 \times 10^{-7}$  mol) were added to seven NMR tubes (10 mm). An appropriate aliquot of a stock solution of  $\text{C}_{60}$  ( $2.3 \times 10^{-3}$  M) in  $\text{C}_6\text{D}_5\text{CD}_3$  was added to each NMR tube, giving mixtures with 0, 0.5, 1, 1.5, 2, 2.5, and 3 equiv of  $\text{C}_{60}$ . All of the NMR tubes were diluted with additional  $\text{C}_6\text{D}_5\text{CD}_3$  to a final volume of  $400 \mu\text{L}$ . The chemical shift of the upfield N–H proton of the porphyrin was monitored. Plots of  $\Delta\delta$  versus  $[\text{C}_{60}]_t/[\text{BP}]_t$  were plotted (Figure S2 in the Supporting Information), and the binding constant ( $K_b$ ) and the chemical shift at saturation of binding sites ( $\Delta\delta_{\text{max}}$ ) were evaluated by a nonlinear least-squares fitting approach using the following equation:<sup>47</sup>

$$\Delta\delta = \frac{\Delta\delta_{\text{max}}}{2} \left\{ \frac{[\text{C}_{60}]}{[\text{BP}]} + 1 + \frac{1}{K_b[\text{BP}]} \pm \left[ \left( \frac{[\text{C}_{60}]}{[\text{BP}]} + 1 + \frac{1}{K_b[\text{BP}]} \right)^2 - 4 \frac{[\text{C}_{60}]}{[\text{BP}]} \right]^{1/2} \right\}$$

where  $\Delta\delta = \delta_{\text{obs}} - \delta_0$ ,  $[\text{C}_{60}]$  is the total concentration of  $\text{C}_{60}$  in solution, and  $[\text{BP}]$  is the total concentration of the bisporphyrin in solution. The appearance of multiple peaks upon the addition of

(47) Cao, Y.; Xiao, X.; Lu, R.; Guo, Q. *J. Mol. Struct.* **2003**, *660*, 73–80.

C<sub>60</sub> indicates the presence of several complexes that are in fast exchange with their respective unbound isomer (Figure S1). The binding constants at 25 °C were calculated by monitoring the shifts of two separate complexes that appeared as separated, distinct peaks. The titration was also performed at 90 °C, where coalescence of the peaks was observed (Figure S1). The seven NMR tubes were exposed to UV irradiation at 365 nm for 17 h. Upon completion of the photolysis, NMR spectra were recorded from the seven samples at 25 and 90 °C (Figure S3), and binding constants were determined as above (Figure S4).

**Isolation and Spectrophotometric Titration of an Adapted Isomer.** The major band from each of the tubes containing 2.0, 2.5, and 3.0 equiv of C<sub>60</sub> was isolated by PTLC after photolysis. A solution of this isolated fraction<sup>48</sup> (1650 μL, 1.89 × 10<sup>-6</sup> M) in spectral-grade toluene was added to a quartz cuvette, and the absorbance was measured upon the addition of 1.2–120 μL aliquots (1200 μL total) of a stock solution of C<sub>60</sub> (2.63 × 10<sup>-3</sup> M in toluene) to both the sample and the reference cuvette (Figure S5). Plots of ΔA at 422 nm versus [C<sub>60</sub>] were analyzed after dilution corrections, and the binding constant (K<sub>b</sub>) and absorbance at maximum saturation of binding sites (ΔA<sub>max</sub>) were evaluated by a nonlinear least-squares fitting approach using the following equation:<sup>39a</sup>

$$\Delta A = \Delta A_{\max} \left\{ (1 + K_b [C_{60}] + [BP] K_b) - \left[ (1 + K_b [C_{60}] + [BP] K_b)^2 - 4 K_b^2 [C_{60}] [BP] \right]^{1/2} \right\} / 2 K_b [BP]$$

where ΔA = A<sub>obs</sub> - A<sub>0</sub>, [C<sub>60</sub>] is the total concentration of C<sub>60</sub> in solution, and [BP] is the total concentration of the bisporphyrin in solution.

**Acknowledgment.** Financial support for this work was provided by the Camille and Henry Dreyfus Foundation (New Faculty Award to J.W.B.). J.W.B. is a Fellow of the Packard Foundation, the Beckman Foundation, and the Sloan Foundation and a Cottrell Scholar of the Research Corporation. A.N. was supported by the Ono Corporation. Unrestricted support from Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, and Roche is gratefully acknowledged. We thank Juthanat Kaeobamrung for the synthesis of intermediates and Yuko Iwamoto for synthetic protocols for the porphyrin.

**Supporting Information Available:** Detailed experimental procedures, spectral characterization, and binding data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA107314P

(48) MALDI MS (*m/z*): calcd for a bisporphyrin bullvalone isomer (C<sub>157</sub>H<sub>177</sub>N<sub>10</sub>O<sub>5</sub>)<sup>+</sup>, 2282.39; found, 2282.22.