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Development of Perfluoroarene−Arene Interactions for Macrocyclic En-yne Metathesis and the Total Synthesis of Macrocyclic Natural Products

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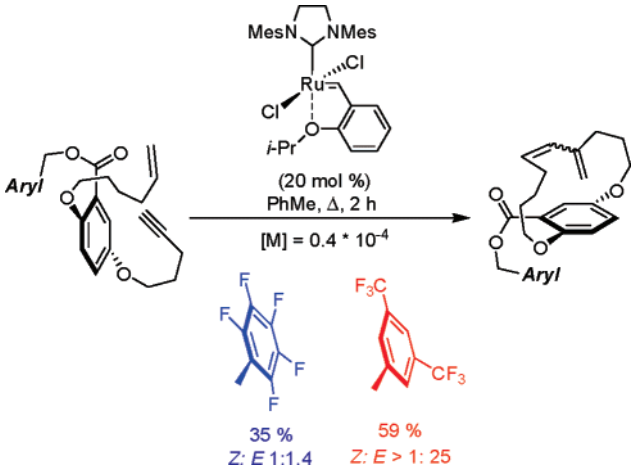

Efficient direct en-yne metathesis of strained macrocyclic systems is possible using highly active Grubbs−Hoveyda second-generation catalyst and when exploiting fluoroarene−arene gearing interactions. These interactions are effective even under high reaction temperatures and in the presence of a competitive π-rich solvent such as toluene. These results suggest that efficient $\pi-\pi$ stacking or $\pi-$lp interactions between auxiliaries containing pentafluorophenyl and 3,5-bis(trifluoromethyl)phenyl groups are responsible for the good yields of macrocyclization products. The 3,5-bis(trifluoromethyl)benzyl gearing elements provide higher yields and greater *E*-selectivity in the macrocyclic en-yne metathesis to form model paracyclophanes that could be applied toward the preparation of members of the longithorone family of natural products.

Introduction

A frequent challenge in the synthesis of complex natural products is efficient formation of macrocyclic structures.[1] Indeed, a variety of natural products that possess varying sizes of carbocyclic and heterocyclic rings systems with fascinating biological activities have been isolated.[2] Hence, macrocycles have come to play an important role in biology, medicine, and chemistry. Although the preparation of macrocyclic systems can be challenging because of entropic factors and/or ring strain, synthetic chemists have shown that many reactions can be altered to afford a macrocyclic variant. Most often in the total synthesis of macrocyclic natural products, a linear structure is constructed and fully elaborated, possessing most of its stereocenters and/or complex functionality already stereodefined. Typical retrosynthetic strategy has macrocyclization occurring near the end of the synthesis. The macrocyclization methods

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often employ two different functional groups that come together to form the cycle. Normally these reactions do not create stereocenters because the influence of the macrocyclic structure on their formation is difficult to predict.[3] The Yamaguchi macrolactonization is an excellent example of such a reaction that under optimized conditions favors macrocyclization to form a lactone.[4,5] While the synthetic strategy described above is both convergent and aesthetically pleasing, it can be improved. A more efficient approach would be to develop macrocyclization reactions that would not only form the macrocycle but also, in doing so, create new important functionality present in the natural product in a stereo-, regio-, and chemoselective fashion. In addition, it would be important to develop reactions that result in the formation of carbon−carbon (C−C) bonds. This would result in an increase in convergence and a more efficient synthesis as much more complexity would be possible per synthetic operation. Macrocyclizations to form C−C bonds that result in an increase in molecular complexity have become increasingly important. The macrocyclic Ni-catalyzed coupling of aldehydes and alkynes[6] and the Ru-catalyzed cycloisomerization[7] reaction are examples of reactions that can undergo macrocyclization and produce significant levels of new functionality in the process.

Olefin metathesis has emerged as one of the "go-to" methods for macrocycle formation, especially as it forms a new C−C bond.[8,9] Despite this advantage, it is still influenced by ring strain and entropic factors that can be difficult to overcome.[10] At times, this can force a reexamination of the synthetic route and a return to a more "traditional" retrosynthetic disconnection.[11] It is also possible that the intermediate preceding macrocyclization can also adopt conformations that are unfavorable toward macrocyclization.[12] This has stimulated the development of imaginative new routes to coercing ring closure by olefin metathesis employing relay ring closing metathesis.[13] The difficulty in controlling the isomeric distribution of products has also prompted the development of macrocyclic alkyne metathesis as an alternative.[14]

Although the use of olefin metathesis in natural product synthesis is well-established, the use of en-yne metathesis is relatively poorly explored. This is surprising for a number of reasons. There has been an increased amount of study dedicated to understanding the mechanism of en-yne metathesis and how it can be exploited to afford substituted cyclic molecules.[15,16] Most importantly, en-yne metathesis differs from olefin and alkyne metathesis in that it has the potential to form a multitude of different products using the same relatively simple functionalities of an alkene and alkyne. In macrocyclic en-yne metathesis, it is possible to afford both endo and exo products that possess different carbon connectivities.[17] The complexity of the resulting products is multiplied when considering that each cyclization mode could afford both *E*- and *Z*-isomers.[18] The exo mode of metathesis can also be rendered more complex if combined with a tandem cross-metathesis. Despite this flexibility, the ability to form a variety of products can also be problematic. Macrocyclic en-yne metathesis rarely affords a sole thermodynamic product with complete selectivity. This can lead to problems in purification of the desired product as the products often possess similar physical properties. Indeed, there is significant potential in macrocyclic en-yne metathesis; however, the challenge is to develop methods to control the products formed, via either substrate or catalyst control.[16b]

An additional level of complexity can be introduced into the macrocyclization process when strained systems are formed. In such cases, the restricted rotation of functional groups such as aromatic or heteroaromatic groups can result in the formation of an element of planar chirality. This is not uncommon as there are many classes of biologically active natural products that possess strained macrocycles, many of which exhibit elements of planar chirality.[19] In such cases, conformational controlling elements or "gearing elements" are employed to help promote successful cyclization.[20] In a strict sense, the term "geared molecule" makes reference to molecules where a level of strain is present because of unavoidable steric crowding, the result of which is a rigidified structure typically incorporating bonds exhibiting restricted rotation. Although the term "gearing effect" or "gearing element" has become increasingly used to describe

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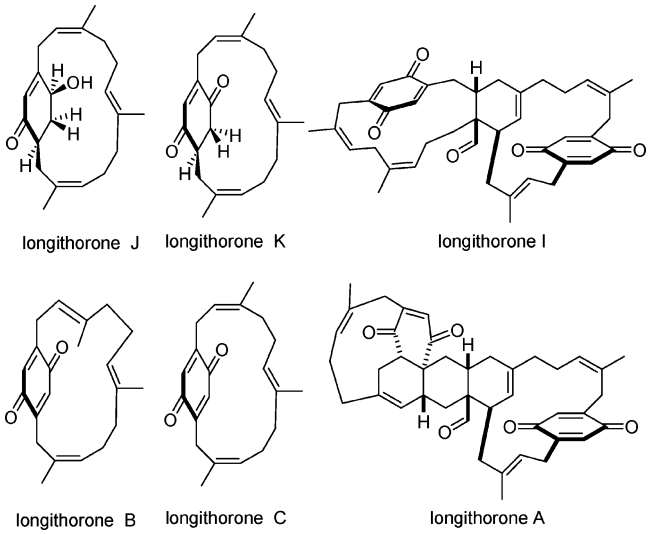

FIGURE 1. Members of the longithorone family of natural products.

functional groups that influence certain molecular conformations, regardless of the level of rigidity of the molecule, the term "conformational control element" will be used. If en-yne metathesis is to develop into a reliable technology for total synthesis, new methods are necessary that may control one or several characteristics of the resulting products (endo vs exo mode of cyclization, *E*:*Z* selectivity, stereochemistry). One possible solution to this problem is through the development of conformational control elements or auxiliaries that may control some of these factors.

The most popular conformational control element is to position a substituted methylene group adjacent to an aromatic ring or planar heterocycle. This conformational control element was elegantly exploited by Shair and co-workers in their synthesis of longithorone A.[21] The longithorone family of natural products are farnesylated quinones, whereby the farnesyl unit is wrapped around the quinone core to produce a rigid cyclophane structure (Figure 1).[22] Higher members of this family are dimers of two cyclophanes and are thought to arrive biosynthetically via intramolecular Diels−Alder reactions between two appropriately functionalized [12]paracyclophanes. Shair and co-workers used an intramolecular macrocyclic en-yne metathesis in a biomimetic strategy to form the [12]-paracyclophane structures **2** and **4** (Scheme 1). The reaction was extremely difficult, requiring large catalyst loadings, extended reaction times, and the presence of an ethylene atmosphere, and most importantly, the presence of the *t*-butyldimethylsilyl-protected alcohol adjacent to the aromatic ring was essential for any productive cyclization to occur. The control of the *E*:*Z* ratios and atroposelectivities were dependent on the nature of the product and not the removable conformational control element. Because few conformational control elements have been investigated, the development of novel gearing auxiliaries that would promote efficient macrocyclization and control the various variables in the en-yne metathesis would be of value. Herein we report the development of fluoroarene−arene interactions and novel aromatic auxiliaries to promote intramolecular macrocyclic en-yne metathesis that influence the resulting geometry of the formed internal olefin.

Results and Discussion

As part of a research program targeted toward the total synthesis of members of the longithorone family of natural products, we focused on the development of new protocols for macrocyclization. The major synthetic challenge associated with the total synthesis of these macrocyclic quinones was likely the formation of the strained [12]paracyclophane cores. Our group has been investigating novel gearing elements that are based on noncovalent interactions. During studies directed toward the preparation of longithorone C,[23] we developed a novel conformational control element technology based upon perfluoroarene−arene interactions. We have recently reported that perfluoroarene−arene interactions in the solution state can be used to achieve difficult macrocyclizations using olefin metathesis (Scheme 2).[24]

For example, when the pentafluorobenzyl ester **5** is treated with Grubbs first-generation catalyst (**G1**), the macrocycle **6** is obtained in 41% yield. No cyclization is observed with any other ester group. We have studied the mechanism of the gearing effect via molecular modeling using both AM1 and MP2 levels of theory, suggesting the gearing effect is a result of an energetically more stable $\pi-\pi$ stacking conformer **5-S** that exhibits a significant degree of overlap with the aromatic core and aids in gearing the alkenyl sidechains for productive metathesis. It is surprising that this interaction has seen limited use in synthesis and catalysis. A sole example of such quadrupolar interactions in the *solution* state had been previously observed by Marsella and co-workers.[25] Noncovalent interactions such as $\pi-\pi$ interactions are known to contribute significantly to the conformational stability of biological systems.[26] Consequently, the study of the effects of the inclusion of pentafluorophenyl groups and the resulting quadrupolar interactions in peptides have attracted increased attention.[27] In addition, intramolecular $\pi-\pi$ interactions have long been known

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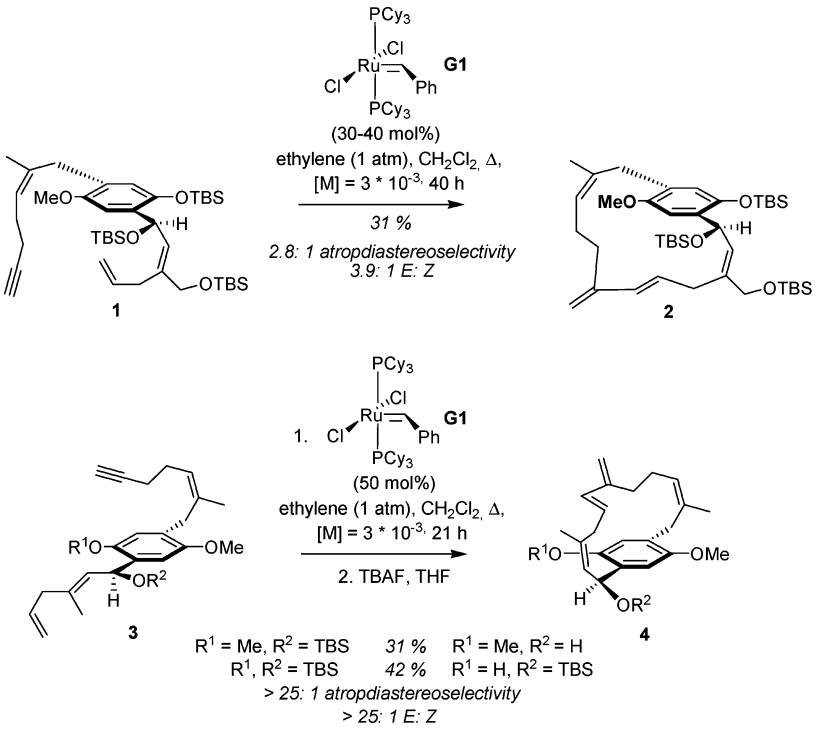
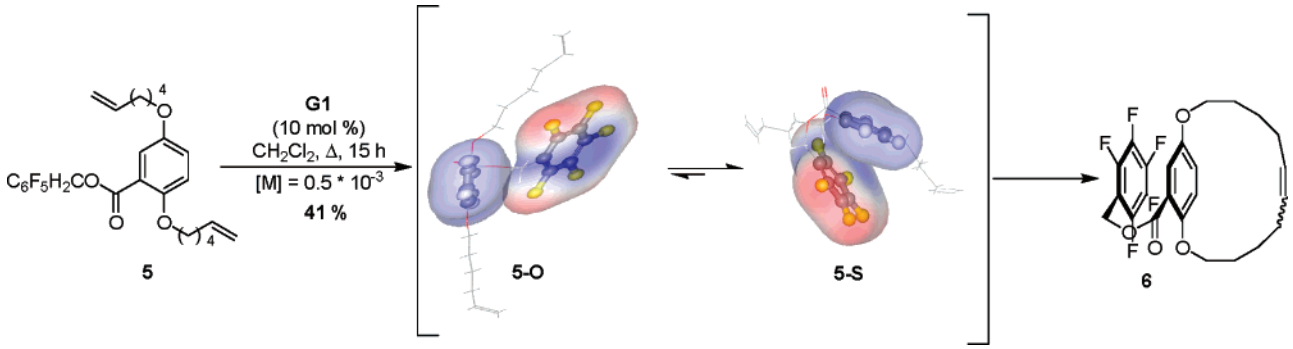
SCHEME 1. Preparation of Functionalized Macrocycles by En-yne Metathesis by Shair and Co-Workers[21]



SCHEME 2. Development of a Perfluoroarene−Arene Conformational Control Element



to play important roles in stereoselective reactions.[28] Recently, π−pyridinium cation interactions[29] have emerged as synthetically useful tools for face selective transformations.[30] We chose to investigate whether we could expand the scope of the gearing elements that function via intramolecular $\pi-\pi$ interactions to other macrocyclization protocols. Our interest in the higher members of the longithorone family of natural products (such as longithorone A and longithorone I) persuaded us to investigate macrocyclic en-yne metathesis. We immediately set forth to develop a methodology that would be synthetically useful for the preparation of functionalized macrocycles useful in natural product synthesis. We initially chose to investigate the macrocyclization to form the strained [12]paracyclophane ester **8A**, for several reasons. We assumed that no products resulting from exo cyclization would be formed because prior investigations had demonstrated that it was not possible to form these types of [11]paracyclophanes via metathesis.[31] Second, **8A** represents a simplistic model of the [12]paracyclophanes **2** and **4** prepared by Shair and co-workers, possessing the same number of atoms in the macrocyclic ring and having the en-yne metathesis occur at exactly the same position along the ansa-bridge (Figure 2).[21]

Initial Screening/Optimization of Reaction Conditions. We decided to base our initial investigations into whether the perfluoroarene auxiliaries could be used for macrocyclic en-yne metathesis by applying the optimized conditions reported by Shair and co-workers during the synthesis of longithorone A. These reaction conditions included the use of an ethylene atmosphere. Although it is known that these conditions can lead to preferential cross-metathesis between ethylene and the alkyne moiety of the en-yne metathesis precursors, the resulting dienes have been shown to undergo subsequent olefin metathesis to yield 1,3-diene products. This strategy, termed "indirect en-yne metathesis" can result in yields and *E*:*Z* selectivities higher than those of the "direct en-yne metathesis" that occurs between alkyne and alkene.[17,32] Hence, the initial investigations of macrocyclization of **7A** with **G1** (10 or 20 mol %) in CH_2Cl_2

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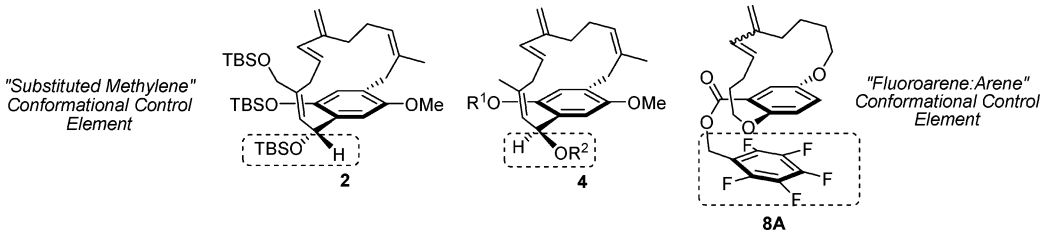
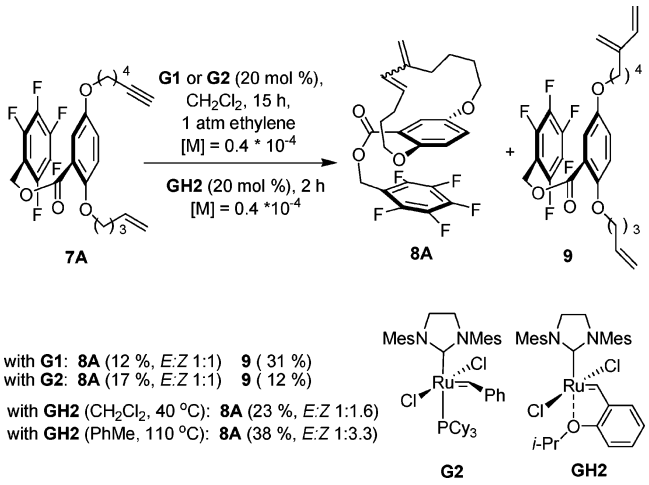


FIGURE 2. Target [12]paracyclophanes to be formed via en-yne metathesis.

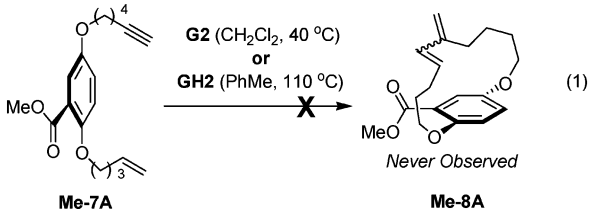
SCHEME 3. Catalyst Optimization



at reflux were performed under an atmosphere of ethylene (1 atm). Incomplete conversion of **7A** (56%) was observed after 15 h, and purification of the reaction mixture afforded only a 12% yield of macrocycle **8A** (Scheme 3). The macrocycle was formed with complete endo selectivity and an *E*:*Z* ratio of 1:1. The major product of the reaction was the 1,3-diene **9** isolated in 31% yield resulting from cross-metathesis of ethylene with the pendant alkyne. In an effort to improve conversion, we repeated the protocol with Grubbs' second-generation catalyst **G2** (Scheme 3). Although we succeeded in improving conversion (86%) and reducing the amount of **9** (isolated in 12% yield), the yield of the desired product **8A** was only marginally improved to 17% (*E*:*Z*, 1:1). The macrocycle **8A** is believed to be formed via a direct en-yne metathesis process, because subjecting **9** to similar reaction conditions does not promote ring closure and only oligomerization was observed. In an effort to evade the formation of **9**, we eliminated ethylene from the reaction conditions and investigated the use of more reactive Grubbs−Hoveyda-type catalysts (Scheme 3). Upon treatment of **7A** with Grubbs−Hoveyda second-generation catalyst (**GH2**) in CH_2Cl_2 at 40 °C, **9** was completely eliminated from the reaction profile and the starting material was completely consumed. In addition, the yield of **8A** had improved to 23% (*E*:*Z*, 1:1.6). Typically, macrocyclization can be improved by using higher temperatures; however, this has been shown to afford side products that are difficult to separate from the desired product.[33] Nonetheless, other RCM reactions have been shown to benefit from higher reaction temperatures.[34] However, when the macrocyclization was performed in toluene at 110 °C for 2 h, the macrocycle **8A** was obtained in an isolated yield of 38% with an *E*:*Z* ratio of 1:3.3.

These yields approach what we have observed for macrocyclizations via olefin metathesis, despite the fact that these cyclizations form macrocycles bearing 1,3-dienes that are considerably more strained than those bearing a simple olefin. This is evident from the preference for the formation of a cis olefin within the macrocycle. The ^{1}H NMR spectra also clearly show that the methylene protons of the auxiliary are diastereotopic, indicating the formation of atropisomers due to the ansa-bridge's restricted rotation.[35]

It is also important to note that only traces of the macrocycle are ever observed in the absence of the pentafluorophenyl auxiliary (eq 1). *The absence of the perfluorobenzyl conformational control element results in the formation of a linear dimer and oligomerization.* Modifying the reaction concentration, nature of the catalyst, or the method of substrate addition failed to afford any macrocyclization when using the corresponding methyl ester of **7A**. These results suggest that a combination of higher temperatures and reactive catalysts can be used to help affect macrocyclic en-yne metathesis. Perhaps what is most notable is that the auxiliary gearing element efficiently directs macrocyclization even in a solvent capable of competitive π-interactions. This may point to fluorinated aromatics as an attractive alternative for use in catalysis over pyridinium cations.[36]



(1)

Although the yields of the macrocyclic en-yne metathesis reactions were comparable to those obtained with traditional conformational control elements, we felt further improvements were possible. We also desired a conformational control element that might increase the preference for forming *E*-olefins in the product, as was necessary if a total synthesis of the longithorone family of natural products was to proceed.

Auxiliary Development. In an effort to develop even more efficient conformational control elements to aid in difficult

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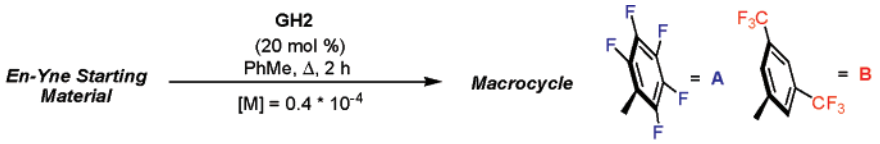
(33) At high temperatures or prolonged heating, migration of the alkene to form a more substituted olefin can occur. Subsequent metathesis would result in the loss of propene during the reaction. The products can be very difficult to separate; see ref 3a. For another example of the loss of propene during a macrocyclization, see: Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635−8638.

(34) Wojtkielewicz, A.; Morzycki, J. W. *Org. Lett.* **2006**, *8*, 839−842.

(35) The methylene signals of the ansa-bridge are also observed to be diastereotopic. In addition, several methylene signals can sometimes be observed resonating between 0.5−1 ppm. This shielding effect has been observed in other rigid macrocycles. See: Furstner, A.; Krause, H. *J. Org. Chem.* **1999**, *64*, 8281−8286.

(36) Yamada, S.; Morimoto, Y. *Tetrahedron Lett.* **2006**, *47*, 5557−5560.

TABLE 1. Evaluation of Different Fluoroarene Conformational Control Elements for the Formation of Strained [12]Paracyclophanes[a]



Entry	Precursor	Macrocycle	Aryl	Yield (%)	Z : E
1	7A 10B	8A 11B	A B	38 47	9.6:1 6: 1
2	12A 14B	13A 15B	A B	35 59	1:1.4 > 1: 25
3	16A 18B	17A 19B	A B	33- 36 49	3.3:1 2.5: 1
4	20A 22B	21A 23B	A B	34 54	1: 8.3 1: 8
5	24A 26B	25A 27B	A B	43 69	3.6:1 2: 1
6	28A 30B	29A 31B	A B	51 53	1.8:1 1: 10

[a] Reported yields are after isolation by silica gel flash chromatography. *Z*:*E* ratios are determined by ^{1}H NMR.

macrocyclic en-yne metathesis reactions, we investigated replacing the five fluorine atoms of the pentafluorobenzyl auxiliary for other electron-withdrawing substituents. We hoped that with proper optimization, even higher, more synthetically useful macrocyclization yields could be obtained. We also wondered whether these conformational control auxiliaries could be used to control the resulting *Z*:*E* ratios of the products. In modifying the auxiliary, we decided to avoid using other pentahalogen-substituted aromatics, because we feared that an increase in the steric bulk might result in repulsion between the auxiliary and aromatic core and a less efficient control over substrate conformation in solution. We had already observed that a nitro group could be used to affect the formation of trace quantities of [12]paracyclophane products in macrocyclic olefin metathesis.[24b] However, we did not want to construct auxiliaries with multiple NO_2 groups and considered a CF_3 group, another excellent electron-withdrawing group, as an alternative.[37] In addition, Tidwell and co-workers had reported that efficient π-stacking was observed in the solid state between a tolyl group and a bis-(3,5)-trifluoromethyl group.[38] We decided to investigate the use of a (3,5)-bistrifluoromethylbenzyl ester as a gearing element (Table 1).

When **8A** was formed, it was isolated in 38% yield and favored the formation of a predominately *Z*-isomer (*Z*:*E*, 9.6:1) (Table 1, entry 1). When the auxiliary was exchanged for the CF_3-bearing auxiliary, the yield increased further and **11B** was isolated in 47% while the isomeric ratio decreased to *Z*:*E*, 6:1. Although it looked as if the CF_3-bearing auxiliary was more *E*-selective, we decided to investigate moving the position of metathesis along the ansa-bridge to confirm this hypothesis. We have previously observed that this can have a significant effect on the yield of metathesis. When the site of metathesis was moved a single carbon further along the chain, we again

(37) For examples of the use of the CF_3 group in catalysis and biological chemistry, see: (a) Ooi, T.; Fukumoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3839−3842. (b) Yang, L.; Zhou, C.; Guo, L.; Morriello, G.; Butora, G.; Pasternak, A.; Parsons, W. H.; Mills, S. G.; MacCoss, M.; Vicario, P. P.; Zweerink, H.; Ayala, J. M.; Goyal, S.; Hanlon, W. A.; Cascieri, M. A.; Springer, M. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3735−3739. (c) Vargas, A.; Hoxha, F.; Bonalumi, N.; Mallat, T.; Baiker, A. *J. Catal.* **2006**, *240*, 203−212. (d) Diezi, S.; Ferri, D.; Vargas, A.; Mallat, T.; Baiker, A. *J. Am. Chem. Soc.* **2006**, *128*, 4048−4057. (e) Betageri, R.; Zhang, Y.; Zindell, R. M.; Kuzmich, D.; Kirrane, T. M.; Bentzien, J.; Cardozo, M.; Capolino, A. J.; Fadra, T. N.; Nelson, R. M.; Paw, Z.; Shih, D.-T.; Shih, C.-K.; Zuvela-Jelaska, L.; Nabozny, G.; Thomson, D. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4761−4769. (f) Guiu, E.; Caporali, M.; Munoz, B.; Muller, C.; Lutz, M.; Spek, A. L.; Claver, C.; van Leeuwen, P. W. N. M. *Organometallics* **2006**, *25*, 3102−3104. (g) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432−5446.

(38) Allen, A. D.; Kwong-Chip, J. M.; Mistry, J.; Sawyer, J. F.; Tidwell, T. T. *J. Org. Chem.* **1987**, *52*, 4164−4171.

observed the same trend (entry 2). Cyclophane **13A** was isolated in 35% yield with a nearly equal ratio of *Z*:*E* isomers present (*Z*:*E*, 1:1.4). However, switching to the CF_3-bearing auxiliary resulted in a jump in the isolated yield and **15B** was isolated in 59%. Furthermore, the ^{1}H NMR spectra showed a single conformational isomer (*Z*:*E* > 1:25). This particular example demonstrates that the auxiliary is having a dramatic effect on the isomeric ratio of the products. Next, we investigated the influence of switching the relative position of the side chains with respect to **7A** (i.e., the alkynyl side chain is ortho to the ester functionality). When **16A** was submitted to the optimized metathesis conditions, the pentafluorobenzyl ester cyclophane **17A** was isolated in 33−36% yield and exhibited a *Z*:*E* ratio of 3.3:1. Switching to the CF_3-bearing auxiliary did not have a dramatic effect on the *Z*:*E* ratio, giving a slightly higher quantity of the *E*-isomer (2.5:1). However, once again the yield of the cyclophane product **19B** increased to 49%. This trend of increasing yields was also observed in the formation of cyclophanes **21A** and **23B**, as the yield of **23B** is ∼20% higher than that observed for **21A**, but the isomeric ratio remains essentially the same (entry 4). The aromatic core could be modified as well while maintaining the same trends. The naphthyl en-yne **24A** (entry 5) cyclized to afford **25A** in 43% yield with a *Z*:*E* ratio of 3.6:1. However, **26B** did not provide **27B** with a significantly higher *E*-selectivity, although the product was once again observed in higher yield (69%). The addition of a second pentafluorobenzyl group (entry 6) also afforded the corresponding [12]paracyclophane product **29A** in 51% yield with an *Z*:*E* ratio of 1.8:1 (Figure 3). In contrast, **30B** afforded the cyclophane product **31B** in a yield similar to that of **29A** (53 vs 51%). However, the *E*-selectivity was high, and a 1:10 *Z*:*E* ratio was observed. These results reinforce the belief that subtle changes in the structure of the macrocycle can alter the resulting *E*:*Z* ratios significantly. However, it is clear that, while it is not possible to completely override the thermodynamic preference of the system, the auxiliary is being shown to be capable of influencing the resultant isomeric ratio of products. To date, there has not been a catalyst-controlled method devised to influence these ratios, although Grubbs−Hoveyda-type catalysts bearing unsymmetrical NHC ligands have been shown to affect *E*:*Z* ratios in cross-metathesis reactions and may have promise in en-yne metathesis as well.[39]

Larger rings bearing less strain, such as [13]paracyclophanes, could also be formed efficiently (Table 2). The [13]paracyclophane **33A** was obtained in 31% yield, and the loss in strain was apparent as the *E*-isomer was favored (*Z*:*E*, 1:9). Once again, using the CF_3-bearing auxiliary provided the cyclophane **35B** in increased yield (45%) and with high *E*-selectivity (*Z*:*E* > 1:25). As a matter of fact, regardless of the placement of the side chains relative to the ester (entry 2) or of substitution on the aromatic core (entry 3), the yields were typically ∼50% and the cyclophanes (**37B**, **39B**) were obtained in high *E*-selectivity (*Z*:*E* > 1:25).

We also sought to apply the fluoroarene−arene technology to the formation of more substituted 1,3-dienes (Scheme 4). We prepared the precursor **40A** bearing the appropriate extension to exploit a relay ring closing strategy.[13] When **40A** was subjected to the optimized reaction conditions, the cyclization afforded **41A** in 33% yield and an *E*:*Z* ratio of 1:2.[40] While the usage of the CF_3-bearing auxiliary did not improve the *Z*:*E* ratio of the product, we did observe higher yields of **43B** using this auxiliary (41%). To the best of our knowledge, this is the first use of the relay ring closing metathesis strategy in macrocyclic en-yne metathesis.

Molecular Modeling. The success of the 3,5-(trifluoromethyl)benzyl ester group as a conformational control auxiliary prompted us to conduct a series of molecular modeling experiments to help understand why the substitution of the five fluorine atoms by two CF_3 groups provided increased yields in macrocyclization. We decided to use a model system similar to that used in our previous studies (see **5**, Scheme 2).[41] Previous reports of the stacking interactions of perfluoroarenes and other arenes in the solid state point toward a preference for a face-to-face orientation (conformer **I**, Figure 4).[42,43] In addition, our previous molecular modeling studies using AM1 and MP2 levels of theory also suggested that $\pi-\pi$ interactions may be responsible for the gearing effect. However, we postulated two other possible noncovalent interactions that could influence the solution-state conformation of the macrocyclization substrates (Figure 4). Doyon and Jain have previously shown that $F-H_{aromatic}$ interactions provided increased binding affinities of inhibitors of carbonic anhydrase.[44] If a similar interaction was present, we would expect a conformation resembling **II** (Figure 4) to be favored. However, previous studies have identified that all five fluorine atoms are required for efficient conformational control, suggesting that one or two $F-H_{aromatic}$ interactions are unlikely to be responsible for the macrocyclization. We also theorized that a conformer exhibiting an oxygen lone pair−arene (lp$-\pi$ interaction) could be possible considering the relative electron deficiency of the gearing element and the proximity of the oxygen atoms in these model systems (conformer **III**, Figure 4). An elegant study by Gung and coworkers showed that lp$-\pi$ interactions can influence solution-state conformations.[45] In addition, electron-deficient π-systems have been shown by ad initio calculations to engage in favorable

(39) Vehlow, K.; Maechling, S.; Blechert, S. *Organometallics* **2006**, *25*, 25−28.

(40) We have not yet identified which is the major isomer. However, we tentatively assign the major isomer as being the *Z*-isomer, on the basis of the tendency to favor the *Z*-isomer in the formation of all other [12]-paracyclophanes reported herein. Interestingly, during ^{1}H NMR studies aimed at identifying the *Z*-isomer, **41A** was heated at 110 °C in DMF-d_7 overnight and no degradation was observed with only minor coalescence of the ^{1}H NMR signals.

(41) Although the model systems in our study contain two olefinic side chains instead of an alkyne and alkene side chain, this minor structural change is unlikely to alter the solution-state conformations in a significant manner.

(42) (a) Gung, B. W.; Amicangelo, J. C. *J. Org. Chem.* **2006**, *71*, 9261−9270. (b) Martin, C. B.; Mulla, H. R.; Willis, P. G.; Cammers-Goodwin, A. *J. Org. Chem.* **1999**, *64*, 7802−7806.

(43) (a) Watt, S. W.; Dai, C.; Scott, A. J.; Burke, J. M.; Thomas, R. L.; Collings, J. C.; Viney, C.; Clegg, W.; Marder, T. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3061−3063. (b) Collings, J. C.; Roscoe, K. P.; Robins, E. G.; Batsanov, A. S.; Stimson, L. M.; Howard, J. A. K.; Clark, S. J.; Marder, T. B. *New J. Chem.* **2002**, *26*, 1740−1746. (c) Collings, J. C.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Can. J. Chem.* **2006**, *84*, 238−242. (d) Collings, J. C.; Batsanov, A. S.; Howard, J. A. K.; Dickie, D. A.; Clyburne, J. A. C.; Jenkins, H. A.; Marder, T. B. *J. Fluorine Chem.* **2005**, *126*, 515−519. (e) Collings, J. C.; Burke, J. M.; Smith, P. S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Org. Biomol. Chem.* **2004**, *2*, 3172−3178.

(44) Doyon, J. B.; Jain, A. *Org. Lett.* **1999**, *1*, 183−186.

(45) (a) Gung, B. W.; Xue, X.; Reich, H. J. *J. Org. Chem.* **2005**, *70*, 7232−7237. (b) Gung, B. W.; Xue, X.; Reich, H. J. *J. Org. Chem.* **2005**, *70*, 3641−3644.

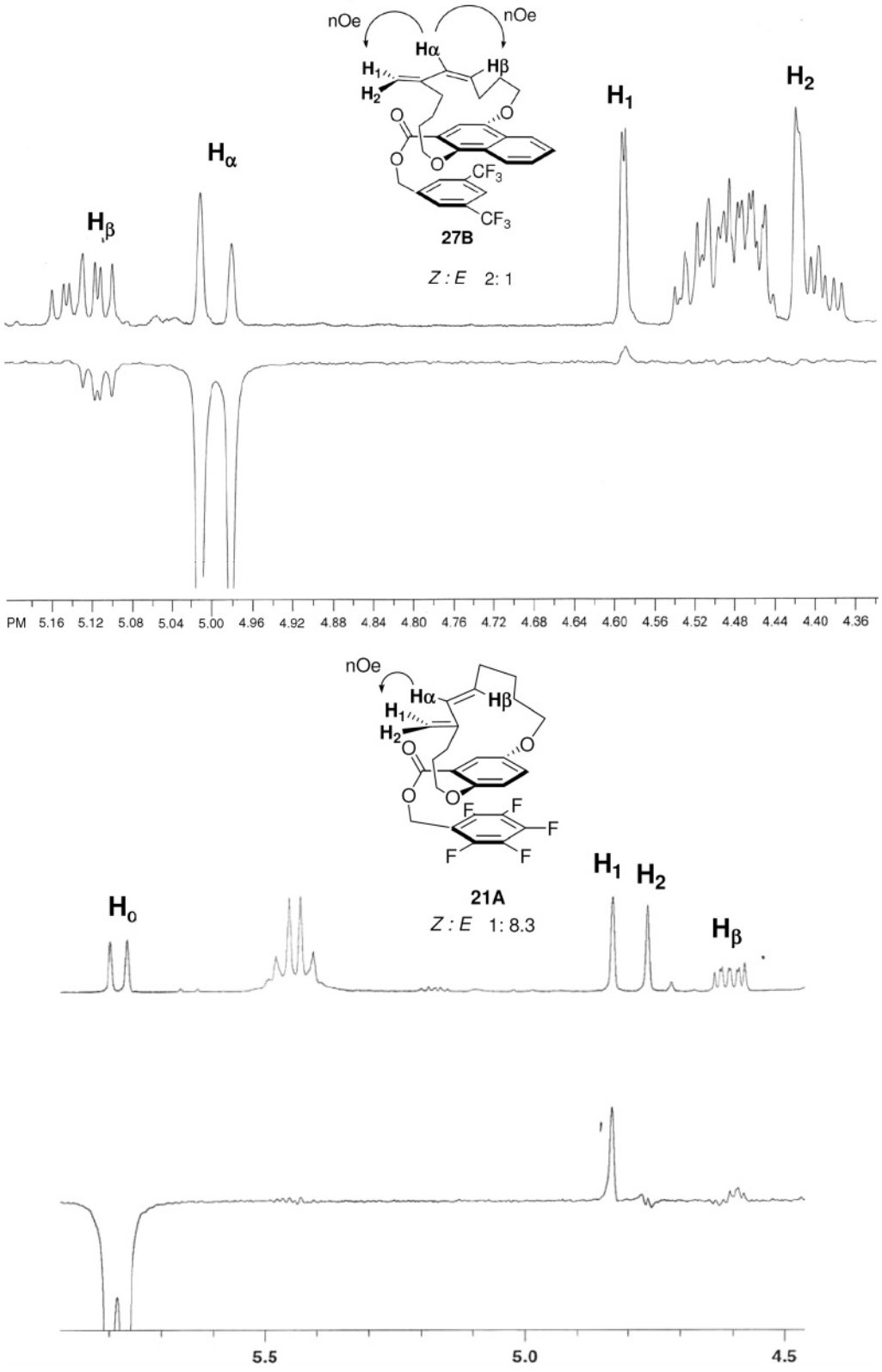
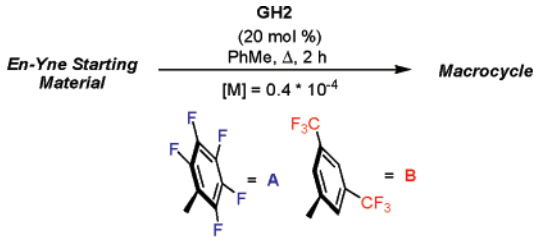


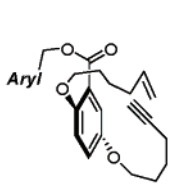
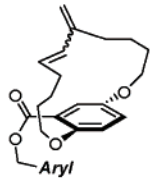
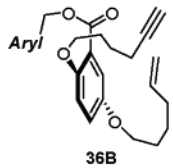
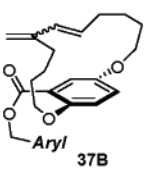
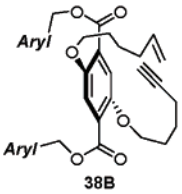
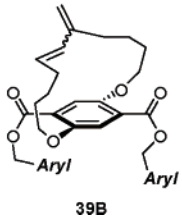
FIGURE 3. Determination of *Z*:*E* isomeric ratios in [12]paracyclophanes.

lp−π interactions.[46] Thus, we believe a conformation resembling **III** is also plausible, where the pendant arene would interact with the phenolic oxygen that is ortho with respect to the ester group. Consequently, we conducted a new series of molecular modeling studies using a DFT[47] level geometric and energy analysis. It was hoped that the use of this higher level of theory compared to our previous study would help to shed light on the various conformational possibilities of the arenes in these systems.

To further probe the mechanism of the conformational control effect, molecular modeling studies were performed in a series of steps.[48] First, the initial geometry optimizations for **5** were

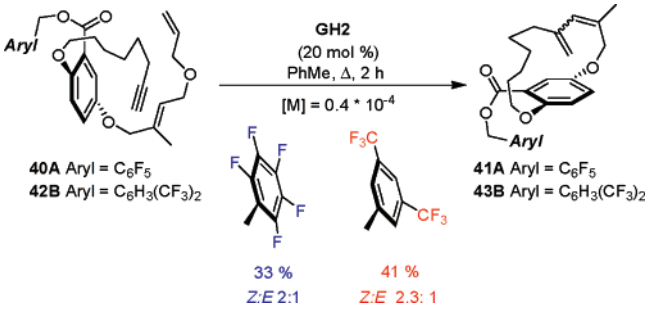
TABLE 2. Evaluation of Different Fluoroarene Conformational Control Elements for the Formation of [13]Paracyclophanes[a]



Entry	Precursor	Macrocycle	Aryl	Yield (%)	*Z* : *E*
1			A	31	1:9
	32A	**33A**	B	45	>1 :25
	34B	**35B**			
2			B	48	> 1: 25
	36B	**37B**			
3			B	51	> 1: 25
	38B	**39B**			

[a] Reported yields are after isolation by silica gel flash chromatography. *Z*:*E* ratios are determined by ^{1}H NMR.

SCHEME 4. Relay Ring Closing En-yne Metathesis



performed using semiempirical methods (AM1)[49] to afford both maximum and minimum energy conformers. These conformers displayed either an "open" conformation where the benzyl ester is elongated away from the aromatic core or a "closed" conformation in which the arene of the benzyl ester is positioned underneath the aromatic core in a slipped type arrangement. MP2[50] perturbation theory with a 6-31G* basis set was then used to provide more accurate energies for each conformer.

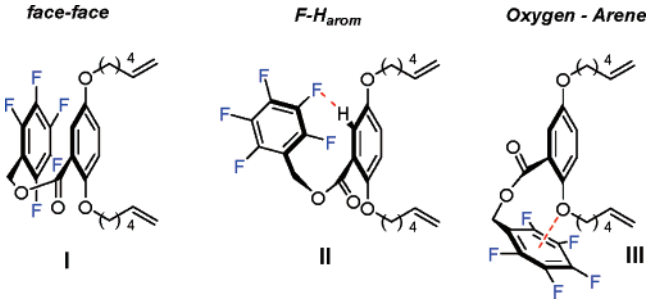


FIGURE 4. Potential noncovalent interactions that could influence the solution-state conformation of **5**.

Subsequently, we resubmitted the "closed" conformer to a DFT level geometric and energy analysis. We once again observed an "open" conformer **5-O*** and a stacked or "closed" conformer **5-S*** (Figure 5).[51] DFT calculations showed that the closed conformer was more favored by −0.20 kcal/mol than the closed conformer. Importantly, the nature of the closed conformer **5-S*** differs considerably from that of **5-S** previously obtained through calculation using AM1 and MP2 levels of theory. In fact, in **5-S*** the auxiliary does not overlap efficiently with the arene core, instead opting to sit over the pendant oxygen atoms in these systems (Figure 5). This sort of lp−π interaction has been previously studied using hexafluorobenzene and a molecule of H_2O using the MP2/6-31G** level of theory.[43] We then pursued a similar analysis of the analogous 3,5-(trifluoromethyl)benzyl ester **44** to discover if similar lp−π interactions were also responsible for controlling conformer distribution and perhaps productive macrocyclization.

The analysis of the analogous 3,5-(trifluoromethyl)benzyl ester **44** was performed in the following manner. Starting with the **5-S**, the five fluorine substituents were exchanged for two CF_3 groups to give **44**. Subsequently, **44** was refined using the MP2 level of theory in which only the torsion angles about the ester functionality were allowed to vary. The resulting conformer was then further refined via a DFT level geometric and energy analysis. We again observed two distinct conformations, in which the stacked or "closed" conformer **44-S** was preferred over the "open" conformer **44-O** by −1.28 kcal/mol (Figure 6). These calculations suggest that both stacked conformers **5-S*** and **44-S** are preferred compared to their respective open conformers **5-O*** and **44-O**. The conformer **44-S**, however, is preferred to **44-O** to a much greater extent than the **5-S*** to **5-O***. This suggests that conformer **44-S** is highly likely to predominate in solution. It should be noted that the rates of reaction of both the "stacked" and "open" conformer, and hence the distribution of their respective macrocyclization products,

(46) (a) Gallivan, J. P.; Dougherty, D. A. *Org. Lett.* **1999**, *1*, 103−105. (b) Scheiner, S.; Kar, T.; Pattanayak, J. *J. Am. Chem. Soc.* **2002**, *124*, 13257−13264.

(47) (a) Koch, W.; Holthausen, M. C. In *A Chemist's Guide to Density Functional Theory;* Wiley-VCH: Weinheim, 2002. (b) Burke, K.; Werschnik, J.; Gross, E. K. U. *J. Chem. Phys.* **2005**, *123*, 062206.

(48) Accurate ab initio studies of aromatic clusters must include electron correlation to obtain good representations of dispersion and electrostatic forces that are responsible for conformation stability. Because of the large size of the molecules in question, high-level treatment of electron correlation or the use of large basis sets was precluded.

(49) Calculations were performed using *Hyperchem*, version 7.5; Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

(50) Moeller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618−622.

(51) We have assigned the compound numbers **5-S*** and **5-O*** to these conformers obtained from DFT analysis to distinguish them from those of an earlier study obtained from MP2 analysis that were assigned the compound numbers **5-S** and **5-O**.

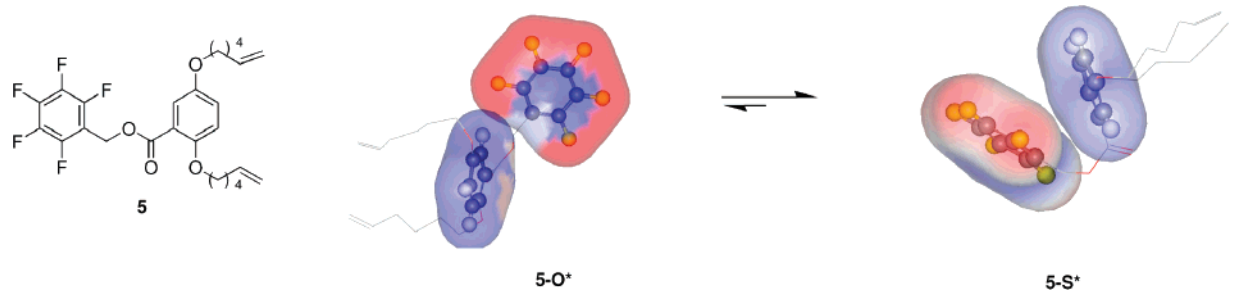


FIGURE 5. Conformational analysis of **5**.

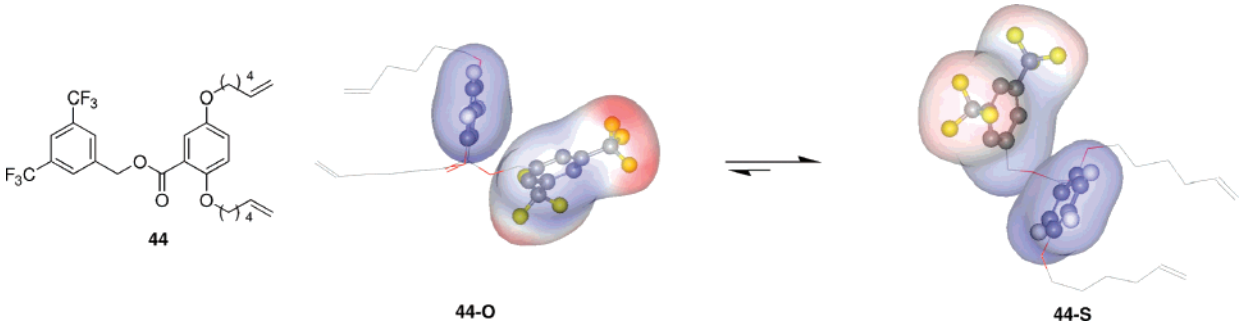


FIGURE 6. Conformational analysis of **44**.

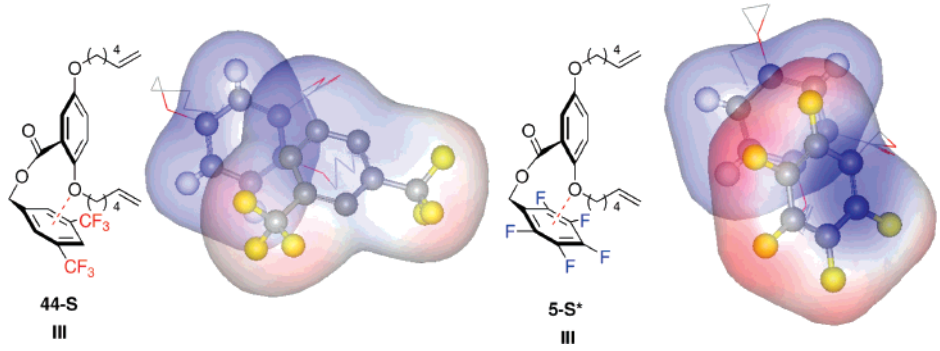


FIGURE 7. Conformations of **44-S** and **5-S*** exhibiting lp−π interactions.

depend on the relative energies of the transition states leading to those products. If the activation barrier from each ground-state conformer were equal, the difference in energy between those ground states would be reflected in the transition-state energies and would be responsible for the observed product distribution. However, the barrier for reaction of the stacked conformers **44-S** or **5-S*** may be even lower than that of their open conformers, since the "stacked" conformations are believed to orient the alkyl side chains closer together, thereby decreasing the entropic barrier for their reaction. In the case of the open conformer, the activation barrier of the dimerization reaction is apparently lower than that of the macrocyclization.

The origin for the highly favored **44-S** may be due to the electronic nature of the CF_3 substituents. Although **5** bears five aromatic fluorine atoms, they can act simultaneously as both σ-withdrawing and π-electron-donating groups.[52] In contrast, the two CF_3 groups are σ-withdrawing, but are devoid of any π-donating capability. This may allow for the existence of a less electron-rich aromatic auxiliary, thereby increasing the possibility for stabilizing π-interactions. Gung and co-workers have demonstrated that a CF_3 group is better at inducing arene−arene interactions than a single F atom.[40]

Once again, in conformer **44-S**, the auxiliary prefers to sit over the pendant oxygen atoms of the aromatic core (Figure 7). Gung and co-workers observed similar lp−π interactions for arenes bearing a single CF_3 group even in solvents capable of forming weak CH−O hydrogen bonds.[42] Their study did not include strongly electron-deficient arenes such as the pentafluorobenzyl and 3,5-bis(trifluoromethyl)benzyl ester groups in **5** and **44**, respectively. However, it is clear that effective macrocyclization observed with substrates bearing the CF_3 auxiliary may be explained by the superior energetic stability of the lp−π interaction of **44-S** versus **5-S***.

Although these calculations provided better insight into the noncovalent interactions responsible for macrocyclization and why the CF_3 auxiliary was superior to the pentafluorobenzyl auxiliary, we were intrigued whether these conformational control elements could be used for all-carbon systems, such as those that would be explored in the context of a total synthesis of members of the longithorone natural products. Consequently, we performed an identical conformational search on **45** and **46**, in which the phenolic oxygen atoms have been replaced with

(52) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

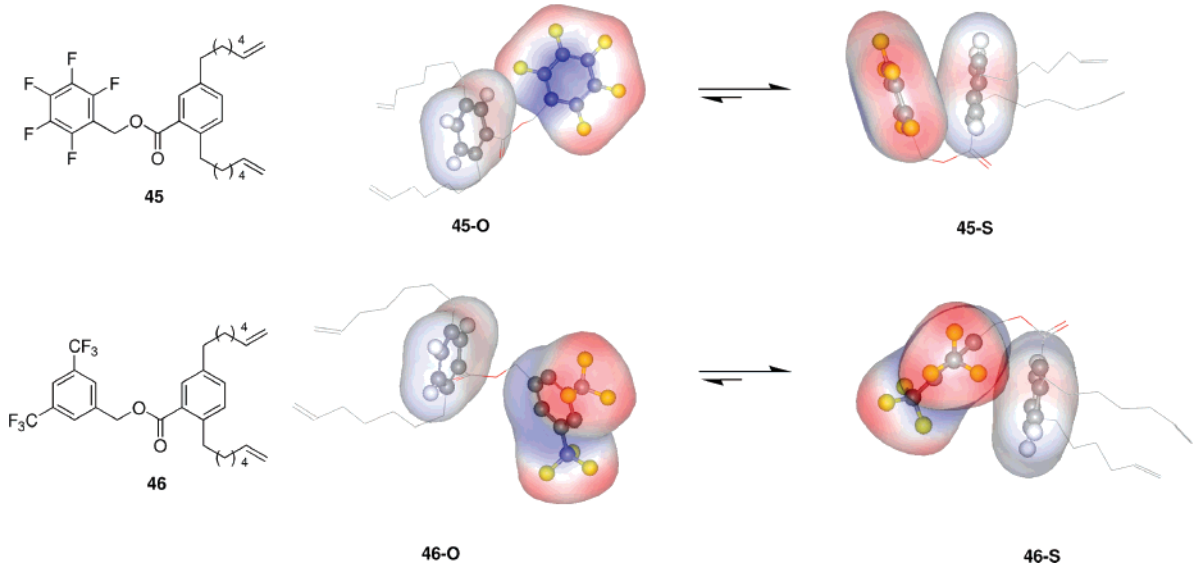


FIGURE 8. Conformational analysis of **45** and **46** models systems.

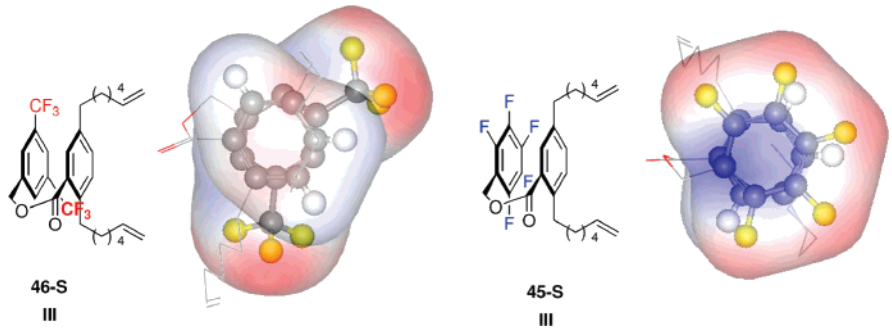


FIGURE 9. Conformers **46-S** and **45-S** exhibiting efficient π-overlap of the pendant auxiliary and arene core.

methylene groups (Figure 8). Once again, the DFT conformational and energetic analysis identified two major conformers corresponding to the "open" and "stacked" conformations previously observed. In the pentafluorobenzyl ester containing **45**, the "stacked" conformer **45-S** is preferred to the "open" conformer **45-O** by −0.55 kcal/mol. Satisfyingly, in this case the arenes are slightly offset and a great degree of π-overlap is observed (Figure 9). Interestingly, the "stacked" conformer **45-S**, exhibiting arene−arene interactions, is preferred energetically to a greater extent than the "stacked" conformer **5-S*** exhibiting lp−π interactions. This suggests that these auxiliaries should be equally as effective in the macrocyclization of all-carbon cyclophanes. Similarly, the "stacked" conformer **46-S** of the CF_3-bearing substrate also showed a face-to-face type arene−arene interaction with considerable overlap of the aromatic core and pendant arene. The **46-S** conformer was preferred by −0.41 kcal/mol over **46-O**, representing a decrease in energetic preference for a "stacked" conformation relative to **44-S** in which lp−π interactions were present. This suggests that the 3,5-bis(trifluoromethyl)phenyl group is more sensitive to lp−π interactions than the pentafluorophenyl group. These results predict that the superior π-overlap observed in the all-carbon series, combined with the energetic preference for the corresponding "stacked" conformations, will lead toward efficient macrocyclization.

In summary, we have demonstrated that efficient direct en-yne metathesis of strained macrocyclic systems is possible using highly active Grubbs−Hoveyda catalysts and when exploiting fluoroarene−arene interactions. This interaction is effective even under high reaction temperatures and in the presence of a competitive π-rich solvent such as toluene. These results suggest that efficient $\pi-\pi$ stacking displayed in a variety of solvents for both the pentafluorophenyl[24b] and 3,5-bis(trifluoromethyl)-phenyl groups could prove valuable in the design of new catalysts and ligands in asymmetric catalysis. In macrocyclization reactions, the yields of cyclophane products are comparable or better than those previously obtained via macrocyclic olefin metathesis, despite the fact that the 1,3-diene functionality resulting from en-yne metathesis creates a rigidified ansa-bridge with restricted rotation. The 3,5-bis(trifluoromethyl)benzyl conformational control elements provide higher yields and greater *E*-selectivity in the macrocyclic en-yne metathesis. Although "indirect" en-yne metathesis has been shown to afford higher yields of metathesis products with high *E*-selectivities, the 3,5-bis(trifluoromethyl)benzyl gearing elements are a rare display of an auxiliary capable of effecting "direct" en-yne metathesis macrocyclization with similarly high yields and *Z*:*E* selectivities. The efficient gearing of the macrocyclization substrates has been investigated through molecular modeling and suggests that both lp−π and $\pi-\pi$ interactions can be responsible for productive macrocyclization. Although study of the nature of lp−π interactions has attracted interest, the macrocyclizations described here demonstrate a practical application of these noncovalent interactions. Energetic differences

of ~1 kcal between conformations believed to be responsible for macrocyclization can result in significant increases in product yields. It is expected that chiral auxiliaries based upon the pendant pentafluorobenzyl ester moiety could be devised to construct enantio-enriched paracyclophanes that could be applied toward the asymmetric preparation of members of the longithorone family of natural products. Given the importance of $\pi-\pi$ interactions in catalysis and asymmetric synthesis, the fluoroarene−arene conformational control strategy should find application in other macrocyclization reactions and synthetic applications.

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Supporting Information Available: General procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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