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Development of quadrupolar engaging auxiliaries as novel gearing elements for macrocyclization*

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Abstract: The formation of various macrocyclic cyclophanes via ring-closing olefin metathesis is possible through the use of a pendant pentafluorobenzyl ester group. A quadrupolar interaction between the cyclophane core and the auxiliary is proposed to act as a gearing element facilitating cyclization. The development of these noncovalent interactions as gearing elements as well as the investigation of the effect of the site of metathesis upon the macrocyclization process is described.

Keywords: macrocyclization; olefin metathesis; fluoroarenes; quadrupolar; cyclophanes.

Noncovalent interactions play an integral role in many areas of chemistry, biology, and materials science. These forces are responsible for formation of the DNA double helix and the tertiary structure of proteins. Experimental and theoretical evidence imply that these types of interactions are largely driven by electrostatic and dispersion forces, however, the interplay between the quadrupole moments arising from aromatic π-clouds is also significant. The magnitude and nature of the aromatic interaction can be altered by introduction of aromatic ring substituents that affect the quadrupole moment. A particularly striking example is the substitution of all six protons of benzene by six electronegative fluorine atoms. This results in a dramatic shift in the quadrupole moment of benzene ((Q) for C_6H_6 = -29.0×10^{-40} Cm^{-2}); hexafluorobenzene possesses a quadrupole moment which is similar in magnitude but of opposite sign ($Q_{C6F6} = 31.7 \times 10^{-40}$ Cm^{-2}) [1,2]. This interaction results in a crystalline complex exhibiting nearly parallel molecules, stacked alternately in infinite columns [3]. The strength of interaction in this complex has been estimated to be ~4–5 kcal mol^{-1} by ab initio and density functional theory (DFT) methods [3]; on the order of a moderate hydrogen-bonding interaction. Although the exact nature of the arene:perfluoroarene interaction in the C_6H_6:C_6F_6 complex remains a controversial subject [2], the phenyl–perfluorophenyl interaction is considered general and predictable and has been exploited in a variety of applications. Perfluoroarene:arene co-crystals have been actively studied [4], and the predictability of the packing conformations can be used to construct electro-luminescent materials for light-emitting diodes (LEDs) [5] and to stabilize liquid-crystal phases [6]. The increased hydrophobicity of perfluorinated hydrocarbons has been exploited by Kool and coworkers to investigate alternate modes of DNA base-pairing [7].

It is surprising that this interaction has seen limited use in synthesis and catalysis, particularly since intramolecular π–π interactions such as π-cation–arene interactions [8], are synthetically useful for face-selective transformations [9]. A sole example of such quadrupolar interactions in the *solution*

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state has been previously observed by Marsella et al. [10]. The Pd-catalyzed macrocyclization of acetylenic cyclophanes gave higher yields when one arene was substituted with four fluorine atoms. It was postulated that this led to a preorganization of the linear intermediate via perfluoroarene:arene interactions, thus aiding macrocyclization.

Although entropic factors are likely responsible for the inefficient ring-closing described by Marsella et al., ring strain is also a recurring roadblock to efficient macrocyclization. Typically, chemists resort to templation, when possible [11], and high dilution conditions to favor ring-closing. Recently, the addition of gearing elements to substrates has proved an effective route to aiding macrocyclization en route to various natural products [12]. In a strict sense, the term "geared molecule" makes reference to molecules where a level of strain is present due to unavoidable steric crowding, the result of which is a rigidified structure typically incorporating bonds exhibiting restricted rotation. However, the terms "gearing effect" or "gearing element" have become increasingly used to describe functional groups that influence certain molecular conformations, regardless of the level of rigidity. The most popular of which involves a gearing element taking the form of a substituted methylene adjacent to an aromatic ring. The minimization of resulting $A^{1,3}$ strain is responsible for orienting the reactive centers in a conformation conducive to ring-closing. Consequently, we developed a new gearing element based upon perfluoroarene:arene interactions for the synthesis of [12]paracyclophanes [13] (Fig. 1). 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 π–π stacking conformer in the case of the pentafluoro substrate **1e** in comparison to the benzyl ester **1a**. In addition, the pentafluoro (**1e**) conformer exhibits a significantly greater degree of overlap with the aromatic core and aids in gearing the alkenyl side chains for productive metathesis. Herein, we describe our investigation of other electron-poor aromatics as gearing elements, expand the scope of reaction to larger macrocycles, and investigate a peculiar dependence of the product yield on the site of metathesis along the *ansa*-bridge.

As a model, macrocyclization via ring-closing olefin metathesis [14] to form rigid, substituted [12]paracyclophanes that resemble the carbon skeleton of the natural product Longithorone C [15] was investigated. Various methylester-substituted cyclophane precursors were synthesized and subjected to Grubbs' 1st generation catalyst, each resulting solely in the formation of a dimeric product. Treatment with Grubbs' 2nd generation catalyst also led to a similar low yield of dimeric products [16]. Varying the concentration and the nature of additional aromatic substituents did not lead to the formation of monomeric products. Subsequently, the optimization of π–π stacking interactions and their ability to induce a gearing effect was investigated. Previous tuning of electronic properties of the pendant benzyl ester, in the form of a pentafluorobenzyl ester, resulted in a π–π stacking interaction that gears the alkene-bearing side chains closer to one another for reaction [13]. However, it was unclear as to how many fluorine atoms were necessary to induce the gearing effect and whether other electron-withdrawing substituents could act in a similar manner. As a control, benzyl ester **1a** was treated with Grubbs' 1st generation catalyst and yielded a 51 % yield of the corresponding dimer. To increase the probability of π–π stacking, the quadrupole moment of pendant benzyl ester was altered via the addition of one or two fluorine atoms in the *para*- or *ortho*-positions. However, the inclusion of the fluorine atoms in precursors **1b** and **1c** had little impact on the product outcome and the dimeric products were again isolated in 43 and 55 % yield, respectively, in both cases. Upon installation of a 2,3,4-trifluorobenzyl ester **1d**, small quantities of the desired monomeric cyclophane were observed (9 % yield), however, the undesired dimer was still the major product following chromatography (55 % yield). The pentafluorobenzyl ester **1e** remained the optimum auxiliary, as subjection to ring-closing conditions using Grubbs' 1st generation catalyst provided a 41 % yield of *only* the desired macrocycle following chromatography. The small size and significant electronegativity of fluorine make it an ideal substituent to modify the electronic properties of an aromatic ring. However, we also explored the usage of nitro groups to induce a dipole between the aromatic moieties. The mono-nitro benzyl ester **1f** produced a gearing effect sim-

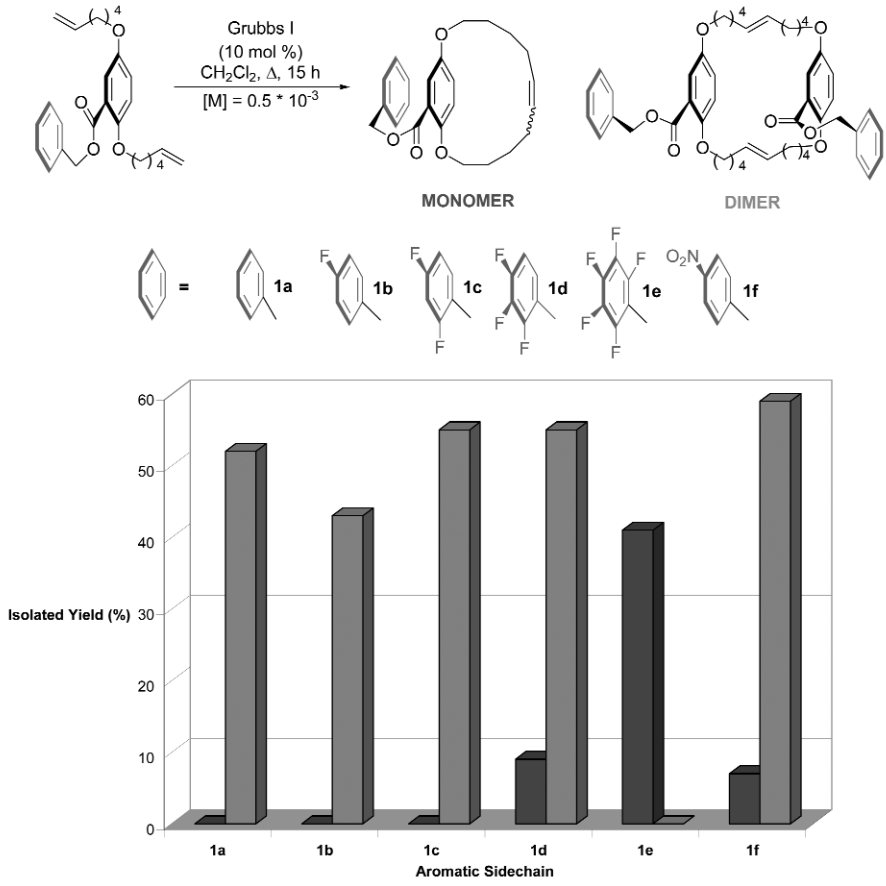
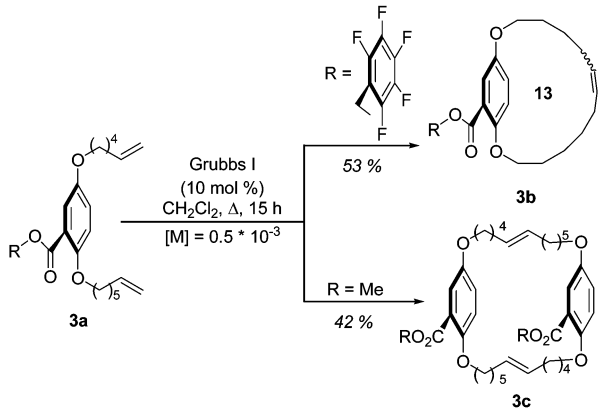


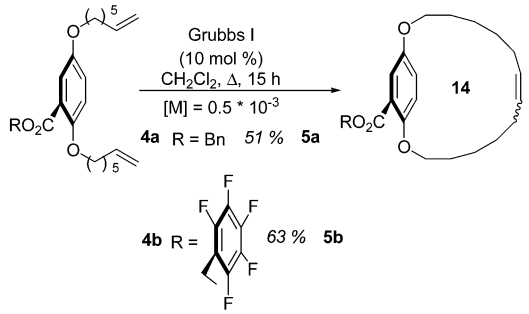
Fig. 1 Optimization of the gearing effect of pendant benzyl esters.

ilar to what was observed for the trifluoro-derivative **1d**. The desired cyclophane was isolated in only 7 % yield, and the dimeric product was isolated in 59 % yield.

We have expanded the reaction scope beyond the [12]paracyclophane skeleton to include both [13]- and [14]paracyclophanes. Larger ring sizes that produced solely dimeric products upon treatment with Grubbs' 1st generation catalyst gave good yields of macrocyclic products following attachment of the pendant pentafluorobenzyl moiety (Scheme 1). The [13]paracyclophane **3b** was produced in 57 % yield, while its corresponding methyl ester produced only dimeric products under identical conditions. Although the corresponding benzyl ester **4a** yields the monomeric [14]paracyclophane in 51 % yield, substitution for a pentafluorobenzyl ester provided an increased yield of 63 % (Scheme 2).

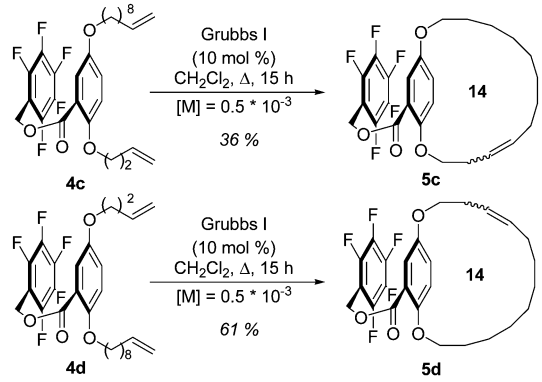


Scheme 1



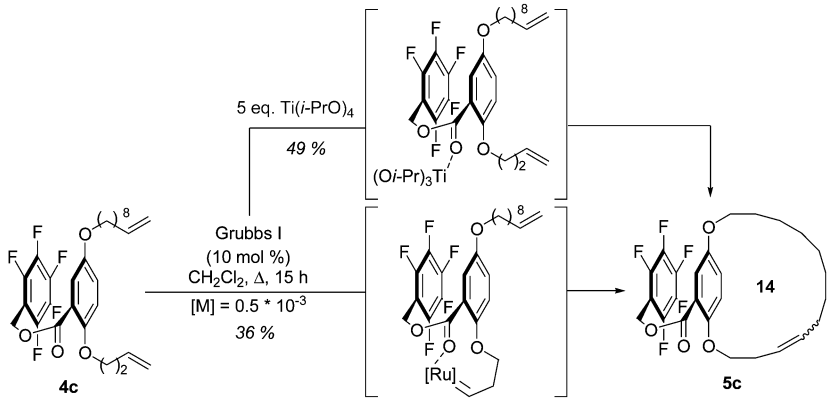
Scheme 2

When the site of metathesis was moved closer to the aromatic core, the yield of macrocyclization decreased providing **5c** in 36 % yield (Scheme 3). However, it is also noteworthy that the site of metathesis has moved closer the ester functionality as well. Interactions between the carbonyl of an ester group and olefin metathesis catalysts are well documented [17]. Subsequently, we performed the ring-closing closer to the aromatic core but away from the ester group. When diene **4d** was subjected to the identical reaction conditions, the macrocycle **5d** was isolated in 61 % yield. This suggests that the interaction between the catalyst and the carbonyl of the ester functionality may be inhibiting cyclization.



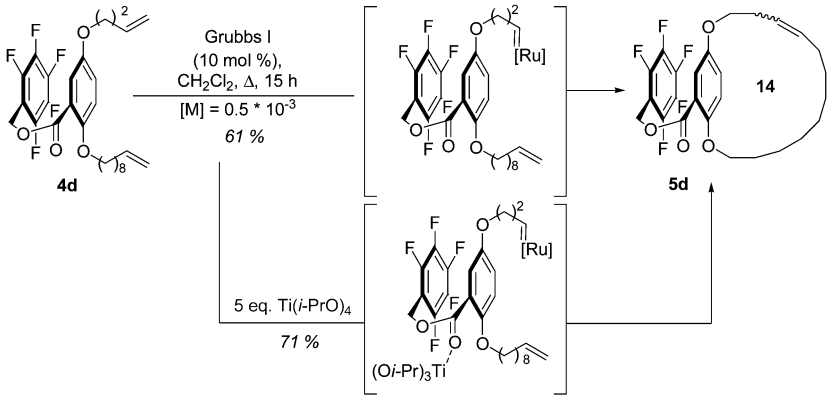
Scheme 3

Bunz and coworkers [18] have reported that the addition of a Lewis acid such as Ti(O*i*-Pr)$_4$ to a reaction mixture prior to metathesis can prevent catalyst coordination to the ester group. Based on available precedent, the pentafluoro ester **4c** was resubjected to the ring-closing metathesis protocol as a pretreated solution with 5 equiv of Ti(O*i*-Pr)$_4$ (Scheme 4). It was believed that the coordination of the ester with the Lewis acid would result in an increase in the product yield, similar to what was obtained in the macrocyclization of substrates **4b** and **4d**. Following purification, the [14]paracyclophane **5c** was isolated in 49 % yield (compared to 36 % yield without added Lewis acid). This suggests that the coordination of the carbonyl by the catalyst may indeed be hampering the cyclization.



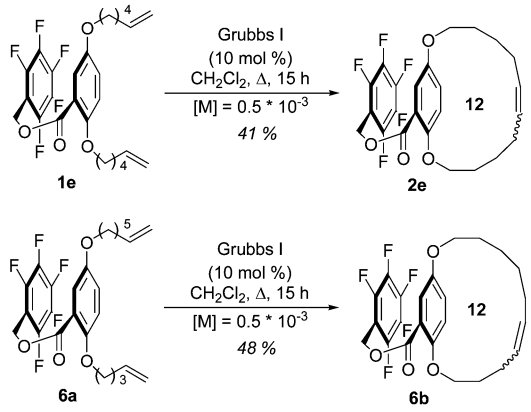
Scheme 4

To confirm this hypothesis, diene **4d** was also resubjected to reaction conditions as a solution in the presence of 5 equiv of Ti(O*i*-Pr)$_4$ (Scheme 5). Once again, the macrocyclization pathway was favored and an increase in the isolated yield was observed (71 % yield with added Lewis acid, Scheme 5) [19].



Scheme 5

Although it is reasonable to assume that some interaction with the carbonyl functionality may be occurring, its effect on the metathesis may still be unclear. Surprisingly, the trend is reversed with respect to [12]paracyclophanes (Scheme 6). Preliminary results show that moving the site of metathesis one methylene closer to both the aromatic ring and ester functionality results in a *slight increase* in the



Scheme 6

product yield. Further study, including trials with added Ti(*i*-PrO)$_4$, are warranted before any final conclusions can be drawn.

In summary, we have developed a novel gearing element to affect difficult macrocyclizations using ring-closing olefin metathesis. Data obtained suggests that a pentafluorobenzyl auxiliary is necessary to establish efficient π–π stacking in solution and induce a favorable conformation for macrocyclization. In addition, we have established that the gearing element functions for larger ring systems and identified the importance of the site of metathesis with respect to product yield. This effect is still under study, but suggests some interaction with the ester functionality and catalyst may be responsible and that the coordination between catalyst and substrate may be controlled with a Lewis acid as an additive. To date, conditions continue to be optimized for application towards ring-closing ene-yne and alkyne metathesis. Pentafluorophenyl–phenyl interactions represent a novel and complimentary π-shielding element to π-cation–arene interactions. Although we have demonstrated the use of pentafluorophenyl–phenyl interactions in macrocyclization, there are numerous instances of π–π interactions acting as powerful conformation controlling elements in organic synthesis. Therefore, these interactions have considerable potential and applications in various face-selective addition/cycloaddition reactions [9], and in the development of novel chiral auxiliaries based upon solution-phase quadrupolar interactions.

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