Cyclophanes

DOI: 10.1002/ange.200503112

Exploitation of Perfluorophenyl–Phenyl Interactions for Achieving Difficult Macrocyclizations by Using Ring-Closing Metathesis**

*Yassir El-azizi, Andreea Schmitzer, and Shawn K. Collins**

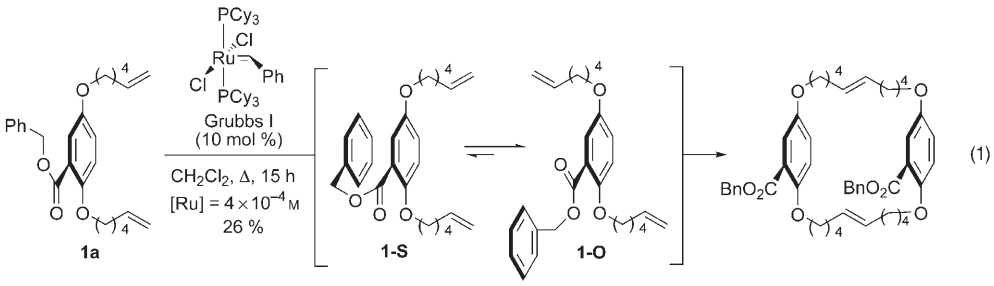
Macrocycles continue to attract interest in light of their unique properties and abundance in natural products. Over the past decade, ring-closing olefin metathesis (RCM) has not only emerged as a powerful method for macrocyclization[1] but has inspired the development of ring-closing alkyne metathesis (RCAM)[2] and macrocyclic ene-yne metathesis.[3] Despite the convenience of olefin metathesis, numerous examples have been documented in which ring strain and entropic factors have spawned new and imaginative routes to coercing ring closure. Among these, templates,[4] dilution, and gearing elements[5] have been employed in directing macrocyclization processes.

Our interest in the synthesis of the quinone natural product longithorone C[6] led us to investigate the preparation of 12-membered macrocyclic paracyclophanes by olefin metathesis. Numerous attempts to cyclize various substituted [12]paracyclophanes using the Grubbs first generation catalyst, such as benzyl ester **1a**, met with failure. Treatment with the Grubbs second generation catalyst also led to similarly low yields of dimeric products [Eq. (1)].[7] Furthermore, variation in the concentration and the nature of the aromatic substituents consistently led to preferential dimer and/or oligomer formation. Although **1a** likely exists in a variety of conformations in solution, we sought reaction conditions that would favor the conformation **1-S** (S = stacked) with π–π-stacking interactions versus the conformation **1-O** (O = open) [Eq. (1)]. The resulting shielding of one face in **1-S** would decrease the degrees of freedom for rotation in the olefin-bearing side chains and thus increase the probability of forming the desired macrocycle.

Consequently, we envisioned exploiting a perfluorophenyl–phenyl interaction as a novel gearing element to

[*] Y. El-azizi, Prof. Dr. A. Schmitzer, Prof. Dr. S. K. Collins
Department of Chemistry
Université de Montréal
C.P. 6128 Succursale Centre-ville,
Montréal, Québec, H3C3J7 (Canada)
Fax: (+1) 514–343–7586
E-mail: shawn.collins@umontreal.ca

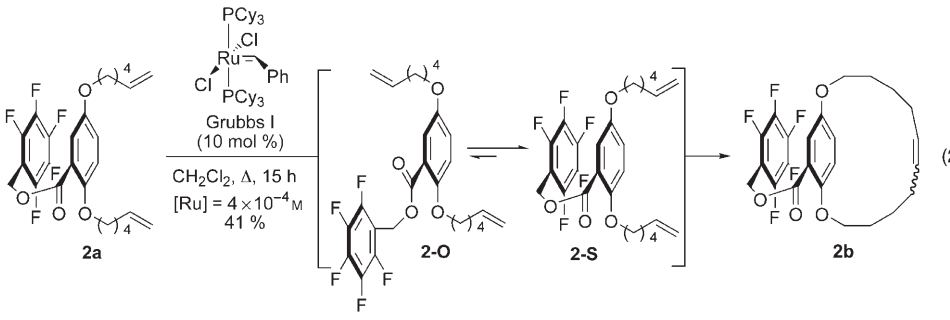
[**] We are grateful to the National Sciences and Engineering Research Council of Canada (NSERC), Fonds de Québec pour la Recherche en Nature et Technologie (FQRNT), the Canadian Foundation for Innovation, and the Université de Montréal for generous financial support of this research. We thank the laboratories of A. Charette and H. Lebel (University of Montréal) for sharing equipment, chemicals, and fruitful discussions.



(1)

favor the desired intramolecular macrocyclization. These nonbonding interactions are the result of the orthogonal electron densities of aromatic and perfluoro aromatic compounds.[8,9] As a consequence of their predictable preference for face-to-face stacking with other aromatic compounds in the solid state,[10] these interactions have attracted considerable interest in medicinal chemistry[11] and materials science.[12] Surprisingly, relatively little use of these interactions in catalysis has been demonstrated, despite the tremendous utility of intramolecular π–π interactions in synthetically useful face-selective transformations.[13] A sole example of such quadrupolar interactions in the solution state was previously observed by Marsella et al.,[14] which is in contrast to π-cation–arene interactions, whose applicability in the solution state was recently demonstrated by Yamada and Morita for the face-selective addition of nucleophiles to pyridines.[15] Herein, we report the development of a strategy that exploits quadrupolar perfluorophenyl–phenyl interactions, analogous to π-cation–arene interactions, for the construction of macrocycles.

Based on precedent,[10,11] fluorinated ester **2a** was expected to prefer the solution-state conformation **2-S** to a much greater degree than **1a** would prefer conformation **1-S** [Eq. (2)]. Consequently, fluorinated ester **2a** was treated with



(2)

the Grubbs first generation catalyst, and a dramatic change in product selectivity resulted, thus solely affording the cyclized cyclophane **2b** in 41% yield.[16]

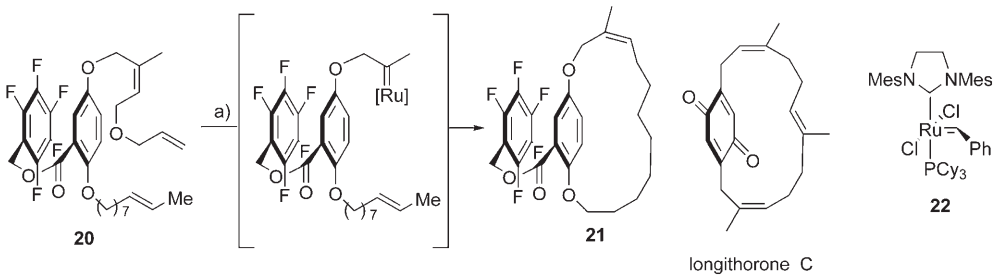
Higher yields of paracyclophane **2b** were observed using the Grubbs I versus Grubbs II catalyst; the second generation catalyst was shown to affect ring opening of **2b**, and the formation of oligomers was observed. Solvent studies revealed that the quadrupolar-interaction gearing element was effective in selectively forming the desired cyclophane in a variety of solvents. However, the rate of metathesis is significantly decreased relative to reaction in CH_2Cl_2.[17] Ring-closing metathesis in THF afforded negligible product after 48 h at 40 °C despite the addition of two additional aliquots of catalyst (5 mol%). Similar reaction times and catalyst loading were necessary for macrocyclization with hexanes as the solvent at 40 °C (20% yield of **2b**, 58% conversion). Interestingly, reaction in benzene at 40 °C gave **2b** in 29% yield (57% conversion), and no dimer products were observed, thus suggesting that the excess benzene does not interfere with the intramolecular perfluorophenyl–phenyl interaction.

A variety of structures were cyclized by using this protocol (Table 1).[18] The site of metathesis had little effect on the yields of macrocyclization for [12]paracyclophanes. Diene **4** gave a slightly higher yield of the corresponding monomeric cyclophane (**5**: 48%) than diene **1a** (**2**: 41%; Table 1, entries 1 and 2, respectively). Further substitution of the aromatic nucleus had little impact on the yields of the cyclizations. The cyclization was found to be tolerant of a free hydroxy group (entry 3) and the addition of an additional electron-withdrawing ester substituent (entry 4). The addition of a second pentafluorobenzyl ester group had no effect on the yield of the macrocyclization, whereas the corresponding dibenzyl ester provided the dimer in only 39% yield. Larger ring sizes that produced solely dimeric products upon treatment with the olefin-metathesis catalyst gave good yields for the macrocyclic products following attachment of the pendant pentafluorobenzyl moiety. The [13]paracyclophane **11** was produced in 57% yield, whereas substitution of the pentafluorobenzyl ester for a methyl ester produced only dimeric products under identical conditions (entry 5). Although the corresponding benzyl ester of diene **12** yields the monomeric [14]paracyclophane in 51% yield, substitution for a pentafluorobenzyl ester provided an increased yield of 63% (entry 6). When the site of metathesis was moved closer to the aromatic core, the yield of macrocyclization decreased to provide **15** in 36% yield (entry 7). Interestingly, diene **16**, which possesses an additional arene moiety fused to the aromatic group, also gave the corresponding naphthylenophane **17** in 42% yield (entry 8). Examination of the ^{1}H NMR spectrum of **17** revealed diastereotopic signals for the protons of the methylene groups adjacent to the naphthenolic oxygen atoms and the ester oxygen atom, thus indicating an element of planar chirality. The trisubstituted olefins found in the cyclophane natural product longithorone C (Scheme 1) prompted us to explore their formation by using the penta-

Table 1: Macrocyclizations by olefin metathesis exploiting perfluorophenyl–phenyl interactions.[a]

Entry	Metathesis precursor	Cyclophane	Yield [%]
1	**1a** ($n=4$, $m=4$, $R^1=H$)	**2**	41
2	**4** ($n=3$, $m=5$, $R^1=H$)	**5**	48
3	**6** ($n=4$, $m=4$, $R^1=CH_2OH$)	**7**	41
4	**8** ($n=4$, $m=4$, $R^1=CO_2CH_2C_6F_5$)	**9**	39
5	**10**	**11**	57
6	**12** ($n=5$, $m=5$)	**13**	63
7	**14** ($n=8$, $m=2$)	**15**	36
8	**16**	**17**	42
9	**18** ($n=8$, $R^1=H$)	**19**	10

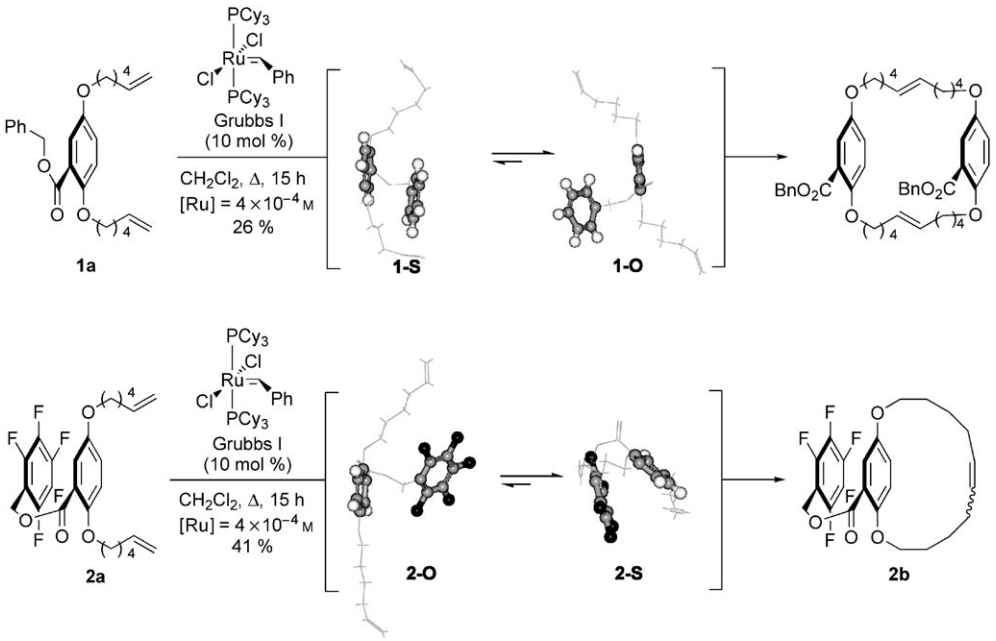
[a] Substrate was added dropwise over 2 h to a solution of Grubbs I catalyst (10 mol%) in CH_2Cl_2 at reflux for 15 h ($[Ru]=4\times10^{-4}$ M).



Scheme 1. Macrocyclic olefin metathesis exploiting perfluorophenyl–phenyl interactions and relay ring-closing metathesis to form tertiary olefins. Reagents and conditions: a) **22** (10 mol%), CH_2Cl_2, Δ, 15 h, (68% yield based on recovered starting material). Mes = mesityl, Cy = cyclohexyl.

fluorophenyl–phenyl interactions to influence macrocyclization. Standard conditions all favored the formation of dimeric or oligomeric products.[19] As we were enticed by the possibility of a relay ring-closing metathesis protocol[20] in tandem with the gearing effect of the pentafluorophenyl–phenyl interaction, diene **18** was prepared and subjected to ring closure. Unfortunately, a very low yield of cyclized product **19** was observed and a linear dimer was isolated as the major product (entry 9).[21] Subsequently, diene **20** was synthesized to preferentially favor initial metathesis of the relay segment versus intermolecular dimerization (Scheme 1). Although the addition of a Me group to the terminal olefin may result in a slower rate of macrocyclization, the nonproductive intermolecular processes are slowed to a much greater extent and cyclophane **21** was isolated in 68% yield. Cyclophane **21** was isolated as a single isomer with the tertiary olefin in the *Z* configuration. Furthermore, the methylene groups adjacent to the phenolic oxygen atoms and the ester oxygen atom all displayed diastereotopic signals in the ^{1}H NMR spectrum, thus revealing a possible element of planar chirality. Preliminary experiments (heating in C_6D_6) have revealed that cyclophane **21** is configurationally stable at 50 °C in [D_6]benzene.

The exact nature of the observed gearing effect in solution is still debatable,[22] despite the well-documented preference of perfluoroarenes and phenyl groups for face-to-face stacking. To probe the mechanism of the gearing effect further, molecular modeling studies were performed to explore whether a face–face or "slipped"[8] arrangement of both arenes were possible in the solution-state conformations. 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. High-level treatment of electron correlation or the use of large basis sets was precluded because of the large size of the molecules in question. The initial geometric optimizations for benzyl ester **1a** was performed by using semiempirical methods (AM1)[23] and afforded conformers **1-S** and **1-O** (Scheme 2). Conformer **1-O** displayed the "open" conformation, in which the benzyl ester is elongated away from the aromatic

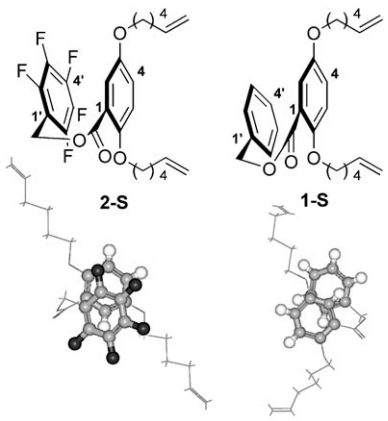


Scheme 2. Modeling studies of possible conformations that lead to productive metathesis.

core of **1a**. A conformation was observed that resembles **1-S**, in which the arene unit of the benzyl ester moiety is orientated underneath the aromatic core in a slipped-type arrangement.

The Moller–Plesset (MP2)[24] perturbation theory with a 6-31G* basis set was then used to provide more accurate energies for each conformer. Conformer **1-S** is estimated to be more stable than **1-O** by approximately -3.9 kcal mol^{-1} based on the difference of their relative heats of formation. Conformational analysis of the perfluorinated ester **2a** by using semiempirical methods (AM1) also revealed an open-type conformer **2-O**, in which the pentafluoroarene is elongated and oriented away from the aromatic core (Scheme 2). The minimum energy conformer was identified as **2-S**, in which the π–π overlap is predicted to a much greater extent than that observed for benzyl-substituted **1-S** (Scheme 3). Conformers **2-O** and **2-S** were further refined (MP2), and conformer **2-S** is estimated to be more stable than **2-O** by approximately -24.0 kcal mol^{-1}.

These calculations highlight the fact that both stacked conformers **2-S** and **1-S** are preferred relative to their respective open conformers **2-O** and **1-O**. Conformer **2-S** is preferred to **2-O** to a much greater extent than the benzyl analogues (**1-S**–**1-O** ≈ -4 kcal mol^{-1} vs. **2-S**–**2-O** ≈ -24 kcal mol^{-1}). Importantly, the nature of the π stacking in **2-S** differs considerably from **1-S** (Scheme 3). The arene units are offset in **1-S**, and minimal overlap is observed. In contrast, conformer **2-S** exhibits a face-to-face-type interaction with considerable overlap of the aromatic core and pentafluoroarene. For example, the distance between C1 and C1′ in conformers **1-S** and **2-S** are almost identical (3.27 and 3.22 Å, respectively). However, C4′ is much closer to C4 in **2-S** than **1-S** (4.08 and 5.61 Å, respectively). It is possible that the energetic preference for conformer **2-S** in conjunction with its superior π overlap is what leads to the inclination towards macrocyclization.



Scheme 3. π–π Overlap in benzyl and pentafluorobenzyl conformers **1-S** and **2-S**, respectively.

It is important not to infer that the difference in energy between conformers is due solely to the aromatic interactions. There is no quantitative comparison of the molecular-strain energy with the relative energy gained through the perfluorophenyl–phenyl interactions. Although the strain energy can be estimated by using empirical potential functions,[25] the evaluation of strain energy by semiempirical or ab initio calculations is tenuous. In comparing the relative differences in the MP2-optimized energies of the various conformers, the strain energy is dominant in all cases, thus the energy difference includes not only the aromatic–aromatic interactions but also a preferred conformation for the alkyl chains.

In summary, we have developed a novel gearing element to affect difficult macrocyclizations by using ring-closing olefin metathesis. Data obtained from molecular-modeling studies suggest a possible quadrupolar interaction between the pentafluorobenzyl appendage and the cyclophane core which orients the substrate in a conformation that favors macrocyclization. We have also developed a protocol for the preparation of stereodefined tertiary olefins in conjunction with a relay ring-closing-metathesis strategy. The presence of the tertiary olefin produces a configurationally stable cyclophane in select cases, thus inhibiting rotation of the macrocycle at temperatures that exceed 50 °C. Currently, we are optimizing conditions for ring-closing ene-yne and alkyne

metathesis and pursuing a total synthesis of longithorone C by using the methods described herein. Although π-cation–arene interactions continue to be exploited in organic synthesis, pentafluorophenyl–phenyl interactions represent a novel and complimentary π-shielding element. Considering that intramolecular π–π interactions can be powerful conformation-controlling elements in various face-selective addition/cycloaddition reactions,[13] the development of chiral auxiliaries based upon solution-phase quadrupolar interactions have significant potential for a variety of chemical reactions.

Experimental Section

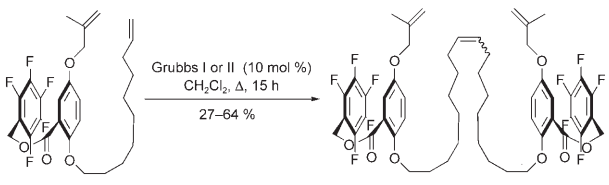
General procedure: A solution of **20** (25 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise over approximately 2 h to an anhydrous solution of Grubbs II catalyst (3.5 mg, 0.004 mmol) in CH_2Cl_2 (60 mL) at reflux. The solution was cooled to room temperature after 13 h at reflux. Silica gel was added, and the reaction mixture was concentrated and purified by chromatography on silica gel (hexanes/EtOAc = 7:1) to afford 16 mg of **21** (68%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$ (d, $J = 2.7$ Hz, 1H), 7.06 (dd, $J = 9.0$, 3.2 Hz, 1H), 6.92 (d, $J = 9.0$ Hz, 1H), 5.43 (dd, $J = 22.9$, 8.6 Hz, 2H), 5.07 (m, 1H), 4.56 (d, $J = 11.4$ Hz, 1H), 4.47 (d, $J = 11.4$ Hz, 2H), 4.02 (m, 1H), 3.95 (m, 1H), 1.97 (m, 2H), 1.64 (m, 2H), 1.57 (s, 3H), 1.40–1.13 ppm (m, 10H); ^{13}C NMR (75 MHz, C_6D_6): $\delta =$ 165.3, 152.6, 151.4, 133.5, 130.2, 124.0, 122.9, 122.5, 120.0, 78.8, 67.6, 53.4, 30.0, 29.4, 27.6, 27.4, 27.3, 25.9, 24.0, 14.0 ppm; HRMS (ESI): *m/z* calcd for $C_{25}H_{25}O_4F_5$ ($[M+H]^+$): 485.1746; found: 485.1734 .

20 (clear oil): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33$ (d, $J = 3.6$ Hz, 1H), 7.04 (dd, $J = 9.1$, 3.6 Hz, 1H), 6.89 (d, $J = 9.1$ Hz, 1H), 5.94 (m, 1H), 5.75 (m, 1H), 5.44 (m, 2H), 5.42 (s, 2H), 5.31 (ddd, $J = 18.0$, 3.2, 0.2 Hz, 1H), 5.21 (m, 1H), 4.40 (s, 2H), 4.09 (d, $J = 6.6$ Hz, 2H), 4.00–3.93 (m, 4H), 2.78–2.60 (m, 2H), 2.11 (m, 2H), 1.77 (s, 3H), 1.74 (m, 2H), 1.63 (d, $J = 6.45$ Hz, 3H) 1.34 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.9$, 153.8, 152.4, 135.2, 135.1, 131.2, 125.0, 124.1, 121.4, 120.0, 117.8, 117.6, 115.4, 74.1, 71.7, 70.1, 66.6, 54.0, 29.9, 29.7, 29.62, 29.61, 27.2, 26.3, 14.5, 13.2 ppm; HRMS (ESI): *m/z* calcd for $C_{32}H_{38}O_5F_5$ ($[M+H]^+$): 597.2643; found: 597.2634.

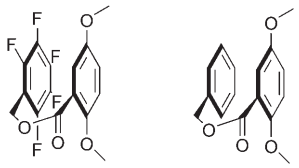
Received: September 1, 2005
Published online: December 28, 2005

Keywords: alkene metathesis · cyclophanes · macrocyclization · perfluoroarenes · quadrupolar interactions

[1] a) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117–7140; b) C. W. Lee, R. H. Grubbs, *J. Org. Chem.* **2001**, *66*, 7155–7158.
[2] U. H. F. Bunz, L. Kloppenburg, *Angew. Chem.* **1999**, *111*, 503–505; *Angew. Chem. Int. Ed.* **1999**, *38*, 478–481.
[3] a) E. C. Hansen, D. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 15074–15080; b) E. C Hansen, D. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 15074–15080.
[4] a) A. V. Chuchuryukin, H. P. Dijkstra, B. M. J. Suijkerbuijk, R. J. M. Klein Gebbink, G. P. M. van Klink, A. M. Mills, A. L. Spek, G. van Koten, *Angew. Chem.* **2003**, *115*, 238–240; *Angew. Chem. Int. Ed.* **2003**, *42*, 228–230; b) A. F. M. Kilbinger, S. J. Cantrill, A. W. Waltman, M. W. Day, R. H. Grubbs, *Angew. Chem.* **2003**, *115*, 3403–3407; *Angew. Chem. Int. Ed.* **2003**, *42*, 3281–3285.
[5] a) M. E. Layton, C. A. Morales, M. D. Shair, *J. Am. Chem. Soc.* **2002**, *124*, 773–775; b) A. G. J. Commeureuc, J. A. Murphy, M. L. Dewis, *Org. Lett.* **2003**, *5*, 2785–2788.
[6] a) X. Fu, M. B. Hossain, F. J. Schmitz, D. van der Helm, *J. Org. Chem.* **1997**, *62*, 3810–3819; b) For a synthesis of the closely related longithorone B, see: T. Kato, K. Nagae, M. Hoshikawa, *Tetrahedron Lett.* **1999**, *40*, 1941–1944.
[7] Interestingly, cyclophanes bearing unsubstituted aromatic compounds can be cyclized: J. Tae, Y.-K. Yang, *Org. Lett.* **2003**, *5*, 741–744.
[8] M. R. Battaglia, A. D. Buckingham, J. H. Williams, *Chem. Phys. Lett.* **1981**, *78*, 421–423.
[9] Although the exact nature of the perfluoroarene–arene interaction in the C_6H_6–C_6F_6 complex remains a controversial subject, this face-to-face stacking arrangement likely acts to minimize quadrupole–quadrupole interaction energies. The hypothesis of a charge-transfer (CT) interaction was discarded based on the absence of a characteristic CT band in the UV/Vis absorption spectrum; see T. G. Beaumont, K. M. C. Davis, *J. Chem. Soc. B* **1967**, 1131–1134.
[10] a) J. S. W. Overell, G. S. Pawley, *Acta Crystallograph. B* **1982**, *38*, 1966–1972; b) J. H. Williams, J. K. Cockcroft, A. N. Fitch, *Angew. Chem.* **1992**, *104*, 1666–1667; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1655–1657.
[11] E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* **2003**, *115*, 1244–1287; *Angew. Chem. Int. Ed.* **2003**, *42*, 1210–1250.
[12] a) K. Reichenbaecher, H. I. Suess, J. Hulliger, *Chem. Soc. Rev.* **2005**, *34*, 22–30; b) Grubbs and co-workers have formed polymers by using olefin metathesis that incorporates pentafluorophenyl moieties: M. Weck, A. R. Dunn, K. Matsumoto, G. W. Coates, E. B. Lobkovsky, R. H. Grubbs, *Angew. Chem.* **1999**, *111*, 2909–2912; *Angew. Chem. Int. Ed.* **1999**, *38*, 2741–2745; c) F. Ponzini, R. Zagha, K. Hardcastle, J. S. Siegel, *Angew. Chem.* **2000**, *112*, 2413–2415; *Angew. Chem. Int. Ed.* **2000**, *39*, 2323–2325.
[13] a) G. B. Jones, *Tetrahedron* **2001**, *57*, 7999–8016; b) G. B. Jones, B. J. Chapman, *Synthesis* **1995**, 475–497.
[14] M. J. Marsella, Z.-Q. Wang, R. J. Reid, K. Yoon, *Org. Lett.* **2001**, *3*, 885–887.
[15] Y. S. Yamada, C. Morita, *J. Am. Chem. Soc.* **2002**, *124*, 8184–8185.
[16] In general, the corresponding acids are pentafluorobenzylated by the Mistunobu reaction with pentafluorobenzyl alcohol or alkylated selectively using CsF on celite: a) S. Hayat, R. Atta, M. Iqbal-Choudhary, K. M. Khan, W. Schumann, E. Bayer, *Tetrahedron* **2001**, *57*, 9951–9957; b) J. C. Lee, Y. Choi, *Synth. Commun.* **1998**, *28*, 2021–2026; the alkyl chains were subsequently installed by sequential Mitsunobu alkylations.
[17] M. S. Sanford, J. A. Love, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
[18] The ^{1}H NMR signals for the alkene protons overlap and appear in the form of a complex multiplet for all compounds in Table 1; hence, the calculation of *E*/*Z* ratios was not possible.
[19] For a solution that exploits catalyst reactivity, see: A. Furstner, O. R. Thiel, L. Ackermann, *Org. Lett.* **2001**, *3*, 449–451.
[20] T. R. Hoye, C. S. Jeffrey, M. A. Tennakoon, J. Wang, H. Zhao, *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211.
[21] The linear dimer below was commonly isolated in yields of up to 64%.



[22] Attempted X-ray analysis of simple models shown below have failed as both are isolated as oils at room temperature; low-temperature crystallization techniques were not successful.



[23] Calculations performed using Hyperchem v.7.5; M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902 – 3909.
[24] C. Moeller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618 – 622.
[25] N. L. Allinger, *J. Am. Chem. Soc.* **1977**, *99*, 8127 – 8134.

