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Cross-Coupling for Cross-Conjugation: Practical Synthesis and Diels–Alder Reactions of [3]Dendralenes

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ABSTRACT

The parent [3]dendralene and 2-substituted [3]dendralenes are made easily through cross-coupling reactions. Contrary to some earlier reports, [3]dendralene is sufficiently stable to be handled using standard synthetic methods. These compounds allow the one-step stereoselective construction of polycyclic frameworks through reactions with dienophiles. Site selectivity and stereoselectivity in Diels–Alder reactions with dienophiles are generally *not* influenced by the nature of the [3]dendralene's 2-substituent; these features can, however, be influenced with Lewis acids.

Dendralenes are acyclic cross-conjugated oligoalkenes with great potential in synthesis.[1] The preparation of the simplest member of the family, [3]dendralene, **1**, was first reported in 1955.[2] Some groups contend that the hydrocarbon is too prone to polymerization to be synthetically useful.[3] Other groups have reported that [3]dendralene can be isolated, participates in [4 + 2] cycloadditions with electron-poor dienophiles at room temperature,[4] and undergoes relatively clean Diels−Alder dimerization at elevated temperatures.[5]

[3]Dendralene has eight sites for substitution and annelation (Figure 1). Synthetic methods for the preparation of [3]dendralenes *mono*substituted at the central methylene (i.e., **4**) have been reported,[6] and the synthetic potential of these trienes has been exploited in elegant investigations by Fallis[7] and others.[8] Reports have also recently appeared on the

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(1) (a) Hopf, H. In *Organic Synthesis Highlights V*; Schmalz, H.-G., Wirth, T., Eds.; Wiley-VCH: Weinheim, Germany, 2003; pp 419−427. (b) Hopf, H. *Classics in Hydrocarbon Chemistry: Syntheses, Concepts, Perspectives*; Wiley-VCH: Weinheim, Germany, 2000. (c) Hopf, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 705−707. (d) Hopf, H. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 948−960.

(2) (a) Blomquist, A. T.; Verdol, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 81−83. (b) Bailey, W. J.; Economy, J. *J. Am. Chem. Soc.* **1955**, *77*, 1133−1136.

(3) (a) Wada, E.; Nagasaki, N.; Kanemasa, S.; Tsuge, O. *Chem. Lett.* **1986**, 1491−1494. (b) Hosomi, A.; Masunari, T.; Tominaga, Y.; Yanagi, T.; Hojo, M. *Tetrahedron Lett.* **1990**, *31*, 6201−6204.

(4) Cadogan, J. I. G.; Cradock, S.; Gillam, S.; Gosney, I. *J. Chem Soc., Chem. Commun.* **1991**, 114−115.

(5) Trahanovsky, W. S.; Koeplinger, K. A. *J. Org. Chem*. **1992**, *57*, 4711−4716.

(6) (a) Woo, S.; Squires, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573−575. (b) Chin, C. S.; Lee, H.; Park, H.; Kim, M. *Organometallics* **2002**, *21*, 3889−3896. (c) Miller, N. A.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 937−940.

(7) (a) Woo, S.; Legoupy, S.; Parra, S.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 1013−1016. (b) Clay, M. D.; Riber, D.; Fallis, A. G. *Can. J. Chem.* **2005**, *83*, 559−568.

(8) (a) Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 13402−13404. (b) See ref 6c.

10.1021/ol7021998 CCC: $37.00

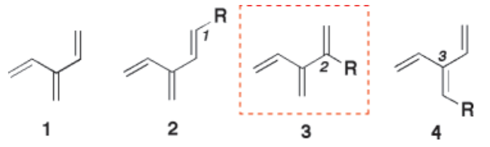
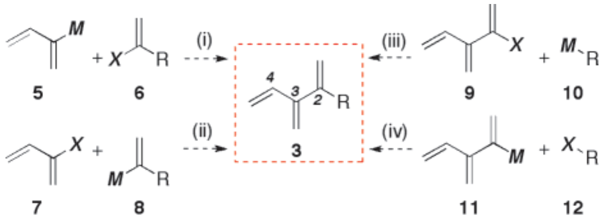


Figure 1. The parent [3]dendralene and its three monosubstituted analogues. The 2-substituted system (highlighted) is the subject of the present study.

synthesis and cycloaddition reactions of [3]dendralenes comprising endocyclic and semicyclic diene units.[9−14] In contrast, *mono*substituted [3]dendralenes **2** and **3** are very poorly represented in the literature.

In fact, none of the published reports of 2-substituted [3]dendralenes **3** describe either general or practical syntheses.[15−24] Herein we describe straightforward procedures for the multigram-scale synthesis of an extensive range of 2-substituted [3]dendralenes by way of Tamao−Kumada−Corriu[25,26] or Negishi[27,28] cross-couplings. The routes involve either the union of ethenyl- and 1,3-butadien-2-yl units [Table 1, paths (i) and (ii)] or the functionalization of a pre-formed [3]dendralene system [paths (iii) and (iv)].

Table 1. The Four Cross-Coupling Approaches to 2-Substituted [3]Dendralenes



a R = Cl **e** R = p-(NO$_2$)C$_6$H$_4$
b R = Ph **f** R = OEt
c R = Me **g** R = CO$_2$Me
d R = p-(MeO)C$_6$H$_4$ **h** R = H

entry	product	method[a]	M	X	yield (%)
1	**3a**	(i)	MgCl	Cl	65 (87[b])
2	**3b**	(i)	MgCl	Br	79
3	**3b**	(ii)	ZnBr	I	60
4	**3b**	(iii)	MgBr	Cl	76
5	**3b**	(iv)	ZnBr	I	67
6	**3c**	(ii)	MgBr	Cl	(31[b])
7	**3d**	(iii)	MgBr	Cl	68
8	**3e**	(iv)	ZnBr	I	40
9	**3f**	(i)	MgCl	Br	38
10	**3g**	(iv)	ZnBr	Cl	40
11	**1** (R = H)	(ii)	MgBr	Cl	(30[b])

[a] Reagents and conditions. (i) and (iii): Ni(dppp)Cl$_2$ (1−3 mol %), THF, −20 to 25 °C, 2−20 h; (ii) and (iv): Pd(PPh$_3$)$_4$ (1−3 mol %), THF, −78 to 25 °C, 20 h. [b] Triene obtained as a solution in THF/light petroleum. Yield estimated by ^{1}H NMR spectroscopy.

Thus, [3]dendralenes substituted at the 2-position with alkyl, halogen, aryl, alkoxy, and carboxy groups are readily prepared by the simple cross-coupling procedures listed in Table 1. Paths (iii) and (iv) require the key electrophile 2-chloro[3]dendralene **3a**, which was prepared in high yield by Tamao−Kumada−Corriu coupling between the chloroprene Grignard reagent **5** and excess 1,1-dichloroethylene **6** (X = R = Cl) (Table 1, entry 1). 2-Chloro[3]dendralene **3a** was readily converted into ca. 0.5 M THF solutions of its corresponding Grignard reagent **11** (M = MgCl) through reaction with activated Mg powder. Attempts to generate more concentrated solutions of this Grignard reagent were met with dimerization of the chloride precursor. The organozinc analogue **11** (M = ZnBr) was accessed simply by transmetalation of the Grignard reagent with zinc dibromide. Dienic and trienic nucleophiles and electrophiles **5**, **7**, **9**, and

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(9) (a) Bräse, S.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2545−2547. (b) Bräse, S.; Wertal, H.; Frank, D.; Vidović, D.; de Meijere, A. *Eur. J. Org. Chem.* **2005**, 4167−4178.

(10) (a) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186−15187. (b) Brummond, K. M.; You, L. *Tetrahedron* **2005**, *61*, 6180−6185.

(11) Shibata, T.; Takesue, Y.; Kadowaki, S.; Takagi, K. *Synlett* **2003**, 268−270.

(12) Kang, B.; Kim, D.-h.; Do, Y.; Chang, S. *Org. Lett.* **2003**, *5*, 3041−3043.

(13) Ahmed, M.; Atkinson, C. E.; Barrett, A. G. M.; Malagu, K.; Procopiou, P. A. *Org. Lett.* **2003**, *5*, 669−672.

(14) Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 1346−1352.

(15) Gajewski, J. J.; Shih, C. N. *J. Org. Chem.* **1972**, *37*, 64−68.

(16) Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 378−380.

(17) Hopf, H.; Gottschild, D.; Lenk, W. *Isr. J. Chem.* **1985**, *26*, 79−87.

(18) Kanemasa, S.; Sakoh, H.; Wada, E.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3312−3319.

(19) Djahanbini, D.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 3441−3452.

(20) Zefirov, N. S.; Kuznetsova, T. S.; Gromov, A. V.; Kozhushkov, S. I.; Vatlina, L. P.; Kozlovskii, V. I. *Zh. Org. Khim.* **1990**, *26*, 1432−1437.

(21) Lukin, K. A.; Timofeeva, A. Y.; Zefirov, N. S. *Zh. Org. Khim.* **1990**, *26*, 1888−1891.

(22) Kimura, M.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1995**, *60*, 3764−3772.

(23) Liu, G.; Lu, X. *Org. Lett.* **2001**, *3*, 3879−3882.

(24) (a) Valentić, N. V.; Vitnik, Z.; Kozhushkov, S. I.; de Meijere, A.; Uščumlić, G. S.; Juranić, I. O. *J. Serb. Chem. Soc.* **2003**, *68*, 67−76. (b) Valentić, N. V.; Uščumlić, G. S. *J. Serb. Chem. Soc.* **2003**, *68*, 525−534. (c) Valentić, N. V.; Vitnik, Z.; Kozhushkov, S. I.; de Meijere, A.; Uščumlić, G. S.; Juranić, I. O. *J. Mol. Struct.* **2005**, *744−747*, 901−908.

(25) (a) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144−144. (b) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374−4376.

(26) Recent reviews: (a) Negishi, E.-i.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. Palladium- or Nickel-Catalyzed Cross-Coupling with Organometals Containing Zinc, Aluminum, and Zirconium: The Negishi Coupling. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 815−889. (b) Knochel, P.; Sapountzis, I.; Gommermann, N. Carbon−Carbon Bond-Forming Reactions Mediated by Organomagnesium Reagents. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 671−698. (c) Takahashi, T.; Kanno, K.-i. In *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 2, pp 41−55.

(27) King, A. O.; Okukado, N.; Negishi, E.-i. *J. Chem. Soc., Chem. Commun.* **1977**, 683−684.

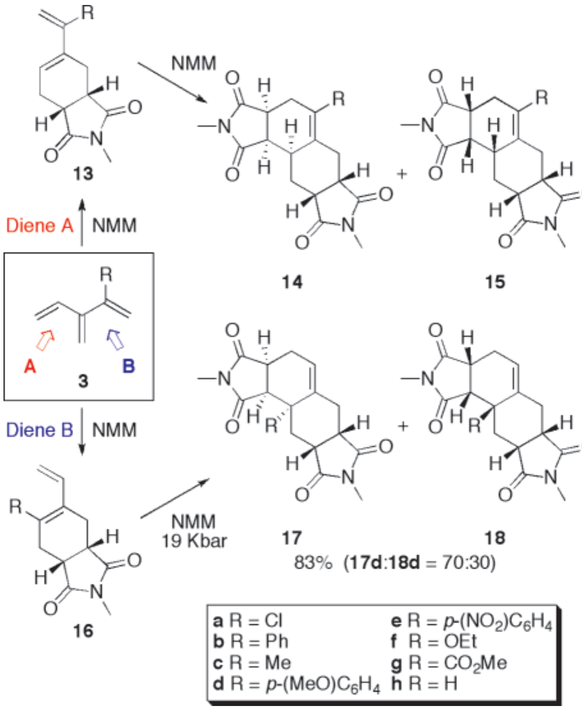
(28) Recent reviews: (a) Negishi, E.-i. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, Part III, pp 215−1119. (b) Knochel, P.; Calaza, M. I.; Hupe, E. Carbon−Carbon Bond-Forming Reactions Mediated by Organozinc Reagents. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 619−670. (c) See ref 26a. (d) Negishi, E.-i.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71−88.

11 require coupling partners, and the availability of such compounds is a major factor in determining the synthetic pathway of choice [Table 1, reactions (i)−(iv)]. For example, some 2-substituted [3]dendralenes are most easily accessed through path (iii) (Table 1, entries 4 and 7). In cases where path (iii) would require a nucleophile with functionality incompatible with a Grignard reagent, path (iv) is the method of choice (Table 1, entries 8 and 10). A direct comparison of the four approaches (Table 1, entries 2−5) demonstrates that 2-phenyl[3]dendralene **3b** can be made with roughly the same ease.

Since it is evident that some cross-conjugated oligoalkenes are more stable than others,[29] the thermal stability of these [3]dendralenes was investigated. It was found that the parent [3]dendralene **1** and its 2-substituted congeners **3a**−**g** can be handled in the laboratory without special precautions. These compounds can be stored neat or in solution at −20 °C for several weeks. The degradation half-lives of these dendralenes at 120 °C were found to be in the range of 1−30 h.[30]

Thus far, the main synthetic interest in [3]dendralenes stems from their participation in diene-transmissive Diels−Alder (DTDA) sequences.[31] This involves the cycloaddition of a dienophile to one of the [3]dendralene's conjugated butadienes, which in turn generates a new semicyclic 1,3-diene capable of undergoing a second cycloaddition event to generate a decalin ring system. 2-Substituted [3]dendralenes are interesting since there is an issue of site selectivity in their cycloadditions with dienophiles (Table 2). In the only previous report of a 2-substituted [3]dendralene reacting with dienophiles, Tsuge observed a single product **14f**, when **3f** was treated with *N*-methylmaleimide (NMM).[18] Would the nature of the 2-substituent influence the site selectivity of dienophile addition to a [3]dendralene? In our hands, when exposed to excess NMM at room temperature, trienes **3** furnished a mixture of three products: diastereomeric bisadducts **14** and **15**, and monoadduct **16**.[32] The bisadducts result from an initial addition to the less substituted 1,3-butadiene moiety of **3** (i.e., diene **A**), and the monoadduct **16** is the product of addition to the more substituted diene of **3** (i.e., diene **B**). Bisadduct **14** was the major product from all these reactions, irrespective of the nature of the substituent. The π-diastereofacial selectivity seen during the conversion of **13** → **14** + **15** is in the range of 5:1 → 9:1. As is evident upon following these reactions by ^{1}H NMR, triene **3**, monoadduct **13**, and bisadducts **14** and **15** are all present in the reaction mixture, even after the consumption of relatively small amounts (ca. 10%) of **3**.

Table 2. Diels−Alder Reactions of 2-Substituted [3]Dendralenes with *N*-Methylmaleimide[a]



entry	R	**14**:**15**:**16**	yield (%)
1	Cl	61:12:27	65
2	Ph	58:6:36	90
3	Me	56:8:36	64
4	*p*-(MeO)C_6H_4	65:7:28	67
5	*p*-(NO_2)C_6H_4	65:7:28	90
6[b]	OEt	81:10:9	41
7	CO_2Me	68:8:24	66
8[c]	H	90:10:0	66

[a] Triene **3** (1 molar equiv), NMM (5 molar equiv), $CHCl_3$, 25 °C, 18 h. [b] Triene **3** (1 molar equiv), NMM (5 molar equiv), CaH_2 (0.33 mol equiv), CH_2Cl_2, 25 °C, 72 h. Tsuge reports a single product **14f** for this reaction.[18] [c] Cadogan reports a single product **14h** for the reaction between [3]dendralene (**1**) and (*N*-H)-maleimide.[4]

Thus, NMM addition to diene **A** occurs with similar ease to the addition to its daughter adduct **13**. At ambient temperature and pressure, monoadduct **16**, with its *inside* diene substituent, resists further reaction. Compound **16d** can be coerced into cycloaddition with NMM at high pressure (19 kbar, 25 °C), however, to give the two diastereomeric bisadducts **17d** and **18d** (83%, **17d**:**18d** = 70:30).

It is clear from inspection of the data presented in Table 2 that the diene site selectivity of 2-substituted [3]dendralenes is not significantly influenced by the nature of the substituent. In their study with 2-ethoxy[3]dendralene, Tsuge et al.[18] suggest that the preference for dienophile addition to the less substituted diene is the result of a *ground state* destabilization of the *s-cis* conformation of the 2,3-disubstituted diene of dendralene **3f**. Computational modeling of the reaction of 2-chloro[3]dendralene (**3a**) with NMM at the B3LYP/6-31G(d) level of theory shows that the ground state interaction identified by Tsuge operates *in the transition state*. Four

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(29) (a) We recently demonstrated that [4]dendralene (i.e., 2-vinyl[3]-dendralene) is stable: Payne, A. D.; Willis, A. C.; Sherburn, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12188−12189. (b) Some other substituted [3]dendralenes readily polymerize: Nüske, H.; Bräse, S.; Kozhushkov, S. I.; Noltemeyer, M.; Es-Sayed, M.; de Meijere, A. *Chem.*−*Eur. J.* **2002**, *8*, 2350−2369.

(30) Solutions (0.2 M) of dendralenes in C_6D_6 containing an internal standard were held at 120 °C in sealed tubes. Consumption of the triene was measured by ^{1}H NMR analysis.

(31) For a review of sequences of Diels−Alder reactions, see: Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167−176.

(32) Where detectable, all cycloadditions involving NMM dienophiles were found to proceed exclusively through the *endo*-mode.

endo-transition structures (TSs) for each of the two possible diene sites were located, all of which differ in the conformation of the olefinic substituent about the 1,3-butadiene reaction site. The lowest free energy (298 K) TS for initial cycloaddition to (2-chlorovinyl)butadiene **A** and to (2-chloro-3-vinyl)butadiene **B** are depicted in Figure 2.

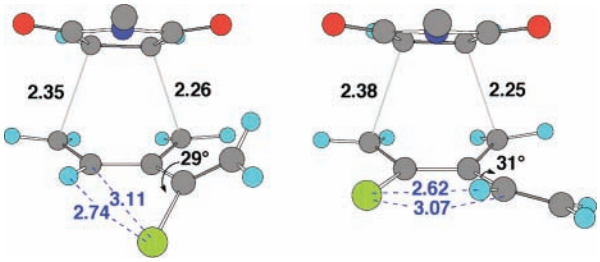
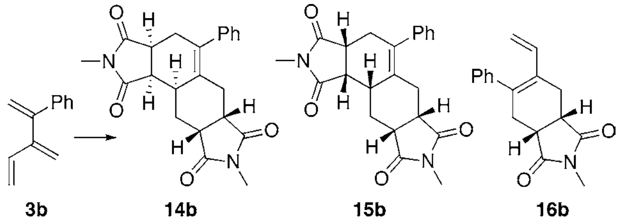


Figure 2. B3LYP/6-31G(d) optimized Diels−Alder *endo*-TSs for cycloadditions of NMM to diene **A** (left) and diene **B** (right) of 2-chloro[3]dendralene (**3a**). NMe H atoms have been omitted for clarity. All distances are in angstroms.

The nonparticipating olefinic substituents in both TSs are twisted out-of-plane with respect to the attached double bond component of the reacting diene. It is noteworthy that the nonreacting 1,3-butadiene moieties adopt skewed *s-cis* conformations.[33] The free energy (298 K) of the TS involving diene **A** is 4.9 kJ mol^{-1} lower than that of diene **B**, which equates to a predicted product ratio of 88:12 (coincidentally, inclusion of all eight TSs gives the same product ratio). This value is in fair agreement with the experimentally determined ratio of 73:27 (Table 2, entry 1). Inspection of the nonbonding Cl···H/C distances between C2 and C3 butadiene substituents (depicted in blue in Figure 2) suggests that the TS involving diene **B** (on the right) suffers greater steric congestion compared to diene **A**.[34] Evidently, the electronic influences of the substituents examined in the present study do not overcome this steric effect.

While the nature of the substituent does not significantly influence the site selectivity or stereoselectivity of the DTDA reactions of 2-substituted [3]dendralenes, these features can be manipulated by altering the reaction conditions (Scheme 1). Thus, whereas the treatment of **3b** with NMM gave **14b**, **15b**, and **16b** in a 58:6:36 ratio (Table 2, entry 2), exposure to NMM•2EtAlCl$_2$ results in two products, **14b** and **15b**, in a ratio of 33:66. Hence, complete site selectivity for the less substituted diene of the cross-conjugated triene is achieved by promoting the cycloaddition with EtAlCl$_2$. Furthermore, the Lewis acid brings about a reversal of the inherent π-diastereofacial selectivity of the second cycloaddition. Investigations into both the origins and applications of these intriguing findings are underway.

Scheme 1. Effect of Lewis Acids on Selectivity of the Diels−Alder Reaction of 2-Phenyl[3]dendralene (**3b**) with NMM



NMM, rt, 90% 58 : 6 : 36

NMM•2EtAlCl$_2$ −78 °C to rt, 67% 33 : 66 : 0

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Supporting Information Available: Full experimental procedures; computational details; atomic displacement ellipsoid plots for compounds **14a** and **14d** (CCDC numbers 654085 and 654086, respectively); ^{1}H and/or ^{13}C NMR spectra of compounds **1**, **3a−g**, **13a**,**b**,**d**, **14a−h**, **15a−h**, **16a−g**, **17d**, and **18d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[33] Tsuge and co-workers propose a skewed *s-trans* conformation of the nonreacting 1,3-butadiene moiety.[18] Gas phase electron diffraction measurements indicate that [3]dendralene adopts a conformation consisting of a planar *s-trans*-1,3-butadiene with the 2-vinyl group skewed 40° out of plane: Almenningen, A.; Gatail, A.; Grace, D. S. B.; Hopf, H.; Klaeboe, P.; Lehrich, F.; Nielsen, C. J.; Powell, D. L.; Tratteberg, M. *Acta Chem. Scand*. **1988**, *A42*, 634−650. [4]Dendralene behaves similarly, adopting an *s-trans*, *s-trans*, skew conformation according to calculations: Palmer, M. H.; Blair-Fish, J. A.; Sherwood, P. *J. Mol. Struct*. **1997**, *412*, 1−18.

[34] Although the Cl···H and Cl···C distances in the two TSs depicted in Figure 2 are not strikingly different, significantly stronger steric compression energy will develop in the TS involving addition to diene **B** (right) compared to diene **A** (left). This is because the interatomic distances lie within the sum of the van der Waals radii: Cl + C = 3.8 Å and Cl + H = 3.0 Å. Thus, the distances lie on the steep side of the van der Waals curve, and only a small change in distance can lead to a large change in energy.