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o-Fluoranil: Stereochemistry and Mechanism of Its Diels−Alder Reactions

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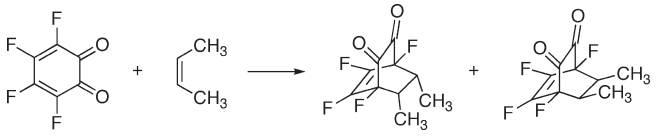
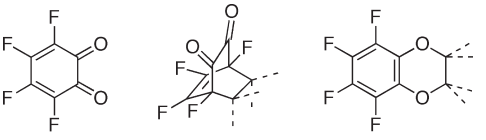


In the absence of significant steric effects, Diels−Alder reactions of the title quinone generally take place with preservation of configuration, and are therefore probably concerted. However, hybrid density functional calculations indicate that often these reactions are highly asynchronous. Steric hindrance can result in reaction at quinone oxygen instead of carbon. Preference for endo over exo cycloaddition is observed, and is reinforced by a repulsive secondary orbital interaction in exo transition states.

Introduction

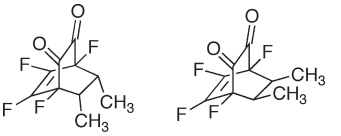
o-Fluoranil (tetrafluoro-*o*-benzoquinone, **1**) undergoes [4 + 2] cycloaddition with alkenes and acetylenes either by Diels−Alder reaction on the ring diene to give an α-diketone (**2**) or by hetero-Diels−Alder addition on the carbonyl oxygens to give a dioxene (**3**) (or dioxin).[1,2] Despite a strong thermodynamic bias favoring the latter mode of reaction, normal Diels−Alder addition occurs with many alkenes and acetylenes, both electron-rich and electron-deficient. This is illustrated in Figure 1 with calculated pathways for reaction of the quinone with the archetypal dienophile ethylene,[3] and the predicted formation of the normal Diels−Alder adduct **4** to the exclusion of its hetero counterpart **5** has now been verified experimentally. Likely reasons for the kinetic bias favoring normal Diels−Alder reaction were discussed in our earlier report.[2] Whether normal Diels−Alder reactions take place concertedly or stepwise, and the closely related question whether dienophile stereochemistry is preserved in the reaction, have not been addressed. In the present report these questions and that of endo vs. exo preference are explored both computationally and experimentally with selected examples.



1 **2** **3**

Results and Discussion

Symmetrical Dienophiles. The transition states for the observed and hypothetical [4 + 2] cycloadditions of ethylene are both predicted to be perfectly symmetrical; i.e., the reactions should not only be concerted, but also synchronous. The question of concert was addressed experimentally with stereochemically labeled alkenes. Cis isomers were employed because loss of configuration in a stepwise reaction should be faster and more extensive than with the corresponding trans isomers because of nonbonded repulsion. Again theory predicted nearly symmetrical transition states for endo and exo Diels−Alder addition to the quinone of *cis*-2-butene, as shown in Table 1 where the calculated lengths of the newly forming C−C σ bonds are recorded. In the event, *cis*-2-butene added to the quinone at 70 °C to give endo, cis (**6**) and exo, cis (**7**) Diels−Alder adducts



6 **7**

but no trans adduct, in harmony with theory. Since the carbonyls of *o*-fluoranil's Diels−Alder adducts generally

(1) Shteingarts, V. D.; Budnik, A. G. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1967**, 124.
(2) Lemal, D. M.; Ramanathan, S.; Shellito, J. *J. Org. Chem.* **2008**, *73*, 3392.
(3) *Jaguar*, version 7.0; Schrodinger, LLC: New York, 2007. Frequency calculations carried out on all transition states found a single negative frequency corresponding to motion along the reaction coordinate. Except where a larger basis set is indicated, calculations were performed at the B3LYP/6-31G** level of theory.

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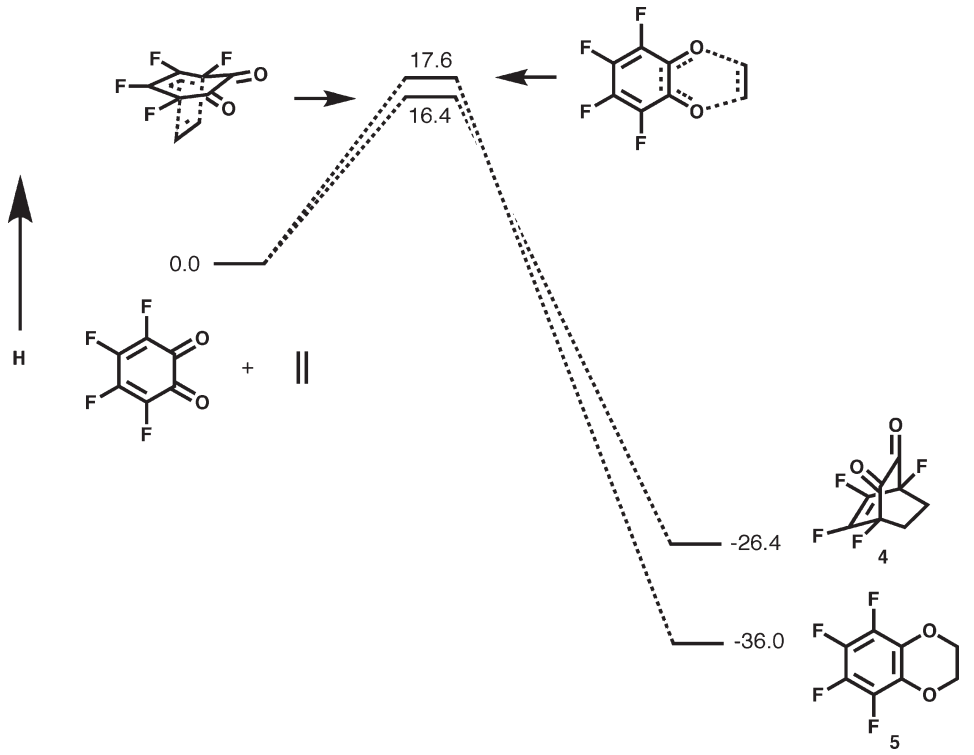


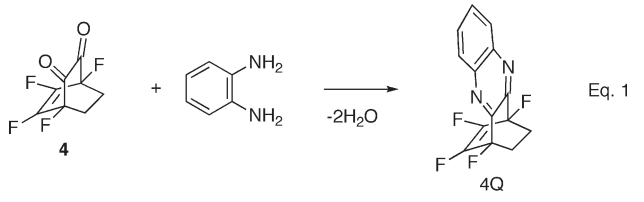
FIGURE 1. Enthalpy changes in the reactions of ethylene with *o*-fluoranil.

TABLE 1. Bond Lengths in Diels–Alder Transition States[a]

cycloaddend	r_{C-C} (Å)[b]
ethylene	2.211, 2.211
cis-2-butene	2.237, 2.275
cis-2-butene (exo)	2.202, 2.211
maleonitrile	2.178, 2.184
malealdehyde	1.943, 2.697
dimethyl maleate	2.014, 2.518
butadiene	1.951, 2.739
butadiene (exo)	2.056, 2.461
styrene	1.951, 2.804
styrene (exo)	1.948, 2.900
methyl acrylate	1.956, 2.624

[a]Endo unless otherwise noted; calculated at the B3LYP/6-311G**+ level of theory. [b]Newly forming carbon–carbon σ bonds.

hydrate readily and often voraciously, these and other adducts were not isolated as such, but were transformed with *o*-phenylenediamine into and characterized as quinoxalines (eq 1).[1,2] Because reduction of the adducts by the diamine competed with quinoxaline formation, water was added at the outset to protect them as hydrates from that side reaction. The basis for assignment of adduct configurations is discussed below.



Eq. 1

To learn whether electron-deficient alkenes would behave similarly to the electron-rich 2-butene, transition states were calculated for endo Diels–Alder addition to *o*-fluoranil of maleonitrile, malealdehyde, and dimethyl maleate. That of maleonitrile is nearly symmetrical (Table 1), and for malealdehyde a similar transition state was found with newly forming C–C σ bond lengths of 2.162 and 2.202 Å (Figure 2A). However, a second transition state (Figure 2B) was located for the aldehyde that was very unsymmetrical (Table 1), and it is both lower in enthalpy than A by 3.14 kcal/mol and higher in entropy by 5.37 cal/(mol K). Intrinsic reaction coordinate calculations confirmed that both transition structures connect with starting materials and product, and show that A arises from the s-trans, s-trans conformation of the aldehyde while B originates with the s-cis, s-trans conformation. In both A and B the carbonyl groups are aligned to overlap well with the developing C–C bonds.

Endo addition of dimethyl maleate is more complicated because the methoxycarbonyl groups are enough bulkier than formyl groups that only one carbonyl group is aligned with a developing C–C bond in a transition structure. There are four ways that one carbonyl group can be so aligned with the other carbonyl twisted roughly perpendicular to it. We found four transition structures, each corresponding to one of these orientations, the lowest energy of which appears in Table 1 and Figure 3. All four are comparably unsymmetrical, and lie within 3 kcal/mol of each other. As would be expected, in each case it is the longer, weaker developing C–C bond that is aligned with a carbonyl.

Whether the reaction of dimethyl maleate with *o*-fluoranil is concerted was thus an open question. Most commercial dimethyl maleate contains a few percent of the fumarate ester, so maleate free of its isomer was prepared from the acid with diazomethane. Because of its electron-deficiency, vigorous conditions (a day at ~100 °C) were required for the maleate–quinone reaction. ^{19}F NMR analysis of the reaction mixture revealed the endo, cis Diels–Alder adduct (**8**) as a major product, but there was no more than a trace of the

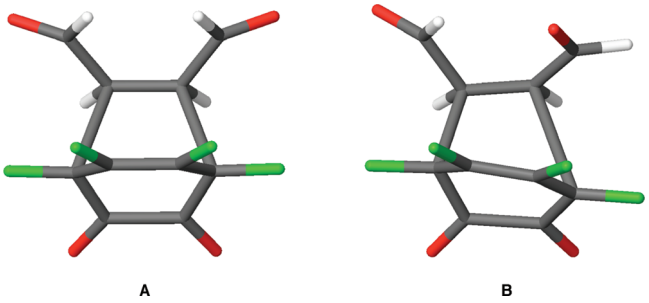


FIGURE 2. Calculated transition structures for endo addition of malealdehyde to *o*-fluoranil (B3LYP/6-311G**+).

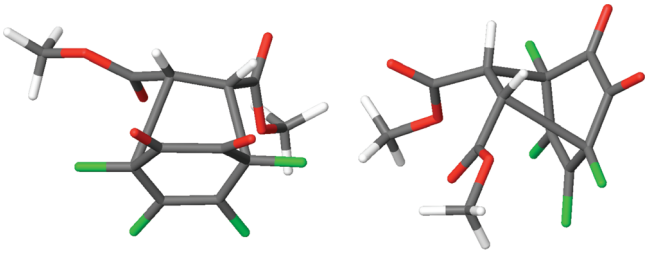
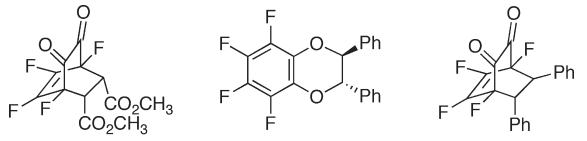


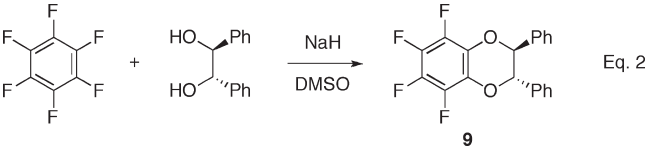
FIGURE 3. Two views of the lowest energy transition structure for endo addition of dimethyl maleate to *o*-fluoranil.

trans (fumarate) adduct. So this cycloaddition too was completely stereoselective, implying concerted reaction.



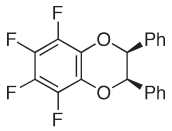
8 **9** **10**

cis-Stilbene reacted with *o*-fluoranil quite differently from the other symmetrical dienophiles. Unless the quinone was carefully purified, the products obtained were the dioxene **9** and the Diels–Alder adduct **10** in a 5:1 ratio, both with the trans configuration. It was found that the cis alkene isomerized to the trans form under the reaction conditions (even though calcium carbonate was present to destroy any adventitious HF), and that the products arose from the trans isomer. Starting with *trans*-stilbene, the same products were obtained in essentially the same ratio. That Diels–Alder adduct **10** has the trans configuration is obvious from the chemical shift inequivalence of the bridgehead fluorines and of the vinyl fluorines, but the dioxene would possess 2-fold symmetry whether it were cis or trans. Our finding that the reaction of *dl*-hydrobenzoin with hexafluorobenzene effected by sodium hydride in DMSO yielded the same compound provided further confirmation that the configuration of **9** is trans (eq 2).[4]



Eq. 2

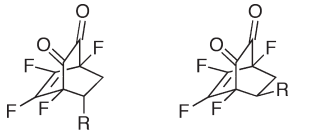
Stilbene isomerization occurred with quinone that appeared to be pure by ^{19}F and ^{1}H NMR, but truly pure *o*-fluoranil reacted with *cis*-stilbene to give *cis*-dioxene **11** with at most a far smaller amount of cis Diels–Alder product. With its phenyl rings twisted 43° out-of-plane,[5] *cis*-stilbene brings considerable steric hindrance to cycloaddition, so its strong preference for attack on the periphery of the quinone molecule is understandable.



11

The dominance of dioxene **9** over **10** in the product from *trans*-stilbene is probably also attributable to steric hindrance even though this stilbene isomer is planar.[6] See below for the contrasting behavior of styrene.

Unsymmetrical Dienophiles. As shown in Figure 4, butadiene was predicted to prefer Diels–Alder over hetero-Diels–Alder cycloaddition with *o*-fluoranil despite the very strong thermodynamic bias favoring the latter reaction course. The prediction was borne out when we found that butadiene reacted readily at room temperature to yield a mixture of endo (**12**) and exo (**13**) Diels–Alder adducts but almost no dioxene. Both Diels–Alder transition structures were predicted to be highly unsymmetrical (Figure 5 and Table 1). At room temperature styrene also gave endo (**14**) and a small amount of exo (**15**) Diels–Alder adduct but no dioxene, and again calculations generated very unsymmetrical transition structures (Table 1).[7] These results suggested that styrene might well react via a biradical intermediate.



12 R = vinyl **13** R = vinyl
14 R = phenyl **15** R = phenyl

The stepwise vs. concerted question was addressed with *trans*-β-deuteriostyrene. Endo adducts from both the unlabeled and labeled styrene were isolated and purified as their quinoxaline derivatives. The three aliphatic hydrogens of the unlabeled quinoxaline were well separated in the 500 MHz ^{1}H NMR spectrum, and the highest field of these signals corresponding to the exo methylene hydrogen was virtually absent in the labeled quinoxaline spectrum. Thus, within experimental error, the adduct obtained from

(4) An analogous reaction of hexafluorobenzene with ethylene glycol was carried out, see: Burdon, J.; Damodaran, V. A.; Tatlow, J. C. *J. Chem. Soc.* **1964**, 763.

(5) Traetteberg, M.; Frantsen, E. B. *J. Mol. Struct.* **1975**, *26*, 69. Molina, V.; Merchan, M.; Roos, B. O. *Spectrochem. Acta, Part A* **1999**, *55*, 433.

(6) The fact that the thermodynamic bias favoring dioxene formation over Diels–Alder addition is nearly the same for styrene and *trans*-stilbene ($\Delta\Delta H$ = 14.0 vs. 13.4 kcal/mol, respectively) supports the conclusion that steric effects are responsible for the dioxene from *trans*-stilbene. The thermodynamic bias is considerably greater for *cis*-stilbene (ΔH = 18.5 kcal/mol), a reflection of steric hindrance in the (endo) Diels–Alder adduct, not just in the transition structure leading to it.

(7) An irc calculation for the endo transition structure smoothly connected starting materials with the adduct.

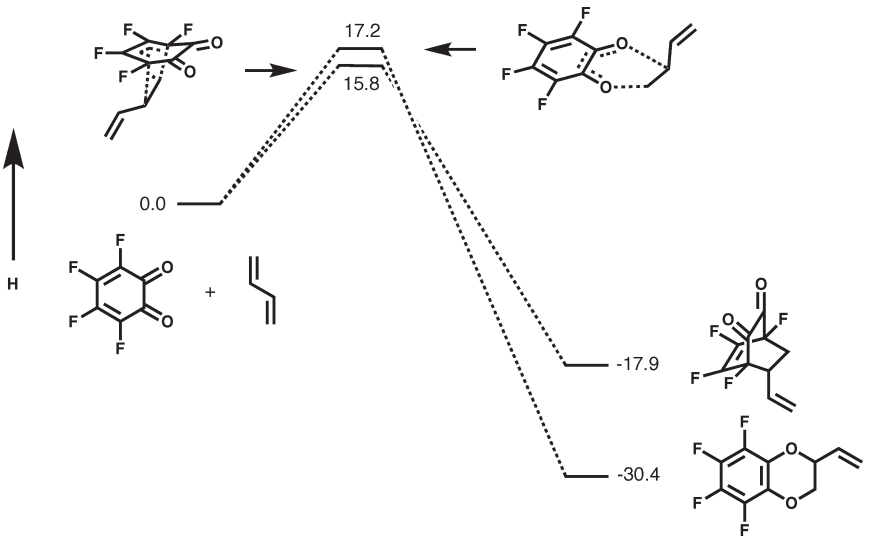


FIGURE 4. Enthalpy changes in reactions of butadiene with *o*-fluoranil.

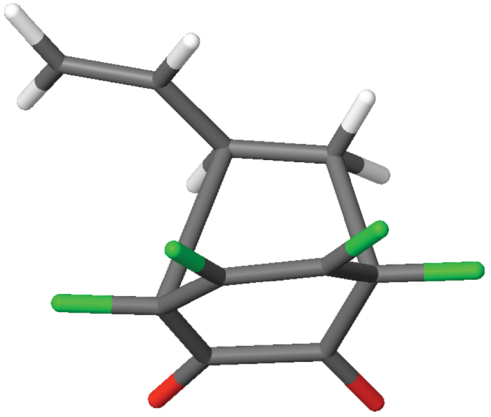
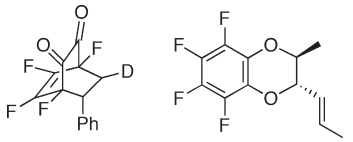


FIGURE 5. Calculated transition structure for endo addition of butadiene to *o*-fluoranil (B3LYP/6-311G**+).

trans-β-deuteriostyrene was exclusively trans (**16**), consistent with concerted cycloaddition.



16 **17**

In contrast to butadiene, *trans*,*trans*-2,4-hexadiene surprisingly reacted with the quinone to give dioxene **17** instead of Diels−Alder adducts, in agreement with theoretical prediction (Figure 6). Since the thermodynamic bias in favor of dioxene formation is similar for butadiene and hexadiene ($\Delta\Delta H$ = 12.5 vs. 14.5 kcal/mol, respectively), nonbonded repulsions involving the methyl group on the reacting double bond may play a role in determining a different course of reaction for the hexadiene. Again, cycloaddition at the oxygens entails less nonbonded interaction in the transition state than attack at carbon. A further example of the difference a methyl group can make is provided by *cis*-β-methylstyrene. In sharp contrast to styrene, it reacts with *o*-fluoranil to yield *cis*-dioxene with much less, if any, Diels−Alder adduct.

Cycloaddition Preference: Endo vs. Exo. In light of the quinone's planarity, there can be little steric influence on the endo/exo preference. For Diels−Alder reactions in general, stabilizing secondary orbital interactions involving the frontier orbitals are present in endo, but not exo, transition states.[8] This is true as well for Diels−Alder reactions of *o*-fluoranil, the HOMO and LUMO of which are depicted in Figure 7.

Both the quinone LUMO−dienophile HOMO and quinone HOMO−dienophile LUMO interactions have a secondary component that is bonding, as represented in Figure 8. Because the carbonyl groups are part of the quinone's conjugated system, secondary orbital interaction can play a role in exo transition states as well, also illustrated in Figure 8. The node at the carbonyl carbons in the quinone HOMO precludes a secondary interaction with that orbital, but there is one involving the quinone LUMO and dienophile HOMO. This interaction is antibonding, and it therefore reinforces the endo preference in *o*-fluoranil's Diels−Alder reactions.

In Table 2 are presented calculated endo/exo transition state enhalpy differences, together with experimental endo/exo ratios. For *cis*-2-butene and butadiene the calculated values are misleading, but the deviations from experiment are < 1 kcal/mol. Endo stereochemistry dominates in all cases except *cis*-2-butene. Why exo is slightly preferred here is not clear, but this is the one dienophile for which secondary orbital interactions should be unimportant.[9]

We finally address the question of how configurations are assigned to the Diels−Alder adducts. Which isomer is which sometimes becomes apparent when an adduct mixture is treated with water. Owing to steric hindrance, hydration of a carbonyl group is often slower in the exo than in the endo

(8) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

(9) For a discussion of other factors that may control endo/exo selectivity, see: Lahiri, S.; Yadav, S.; Banerjee, S.; Patil, M. P.; Sunoj, R. B. *J. Org. Chem.* **2008**, *73*, 435.

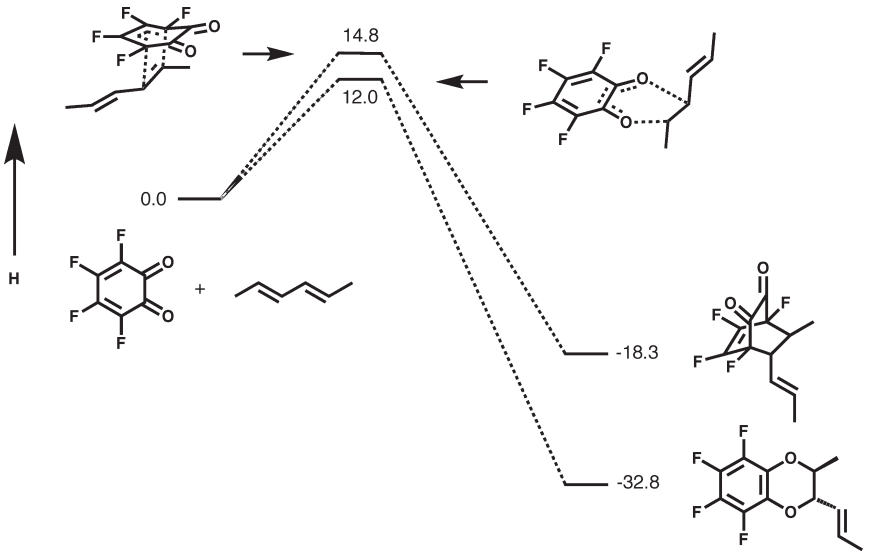


FIGURE 6. Enthalpy changes in reactions of *trans,trans*-2,4-hexadiene with *o*-fluoranil.

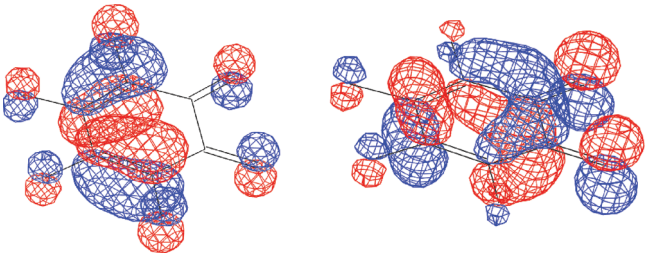


FIGURE 7. HOMO (left) and LUMO (right) of *o*-fluoranil (B3LYP/6-311G**+).

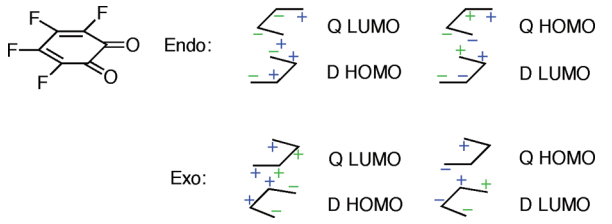


FIGURE 8. Frontier orbital interactions in Diels−Alder reactions of *o*-fluoranil: primary indicated in blue, secondary in green. Q = quinone, D = dienophile.

form. The same is true for reaction of the adducts with *o*-phenylenediamine to form quinoxalines. NMR chemical shifts of the vinyl CF groups of the quinoxalines are useful for configurational assignment (Table 2). In the quinoxaline from ethylene, the endo groups are unequivocally hydrogens, so this molecule serves as a reference for ^{19}F and ^{13}C chemical shifts. In the quinoxalines we have studied, an endo hydrogen gives rise to a fluorine δ value less than −152 ppm, but an endo substituent results in a value greater than −152 ppm. Similarly, an endo hydrogen gives rise to a vinyl carbon δ value greater than 137 ppm, but for an endo substituent it is less than 137 ppm. Table 2 also shows that when both endo groups are hydrogens, the vinyl fluorine chemical shifts are closer together than when one group is a substituent.

TABLE 2. Comparison of Endo and Exo Cycloadditions and Derived Quinoxalines

				quinoxaline[b]	
cycloaddend	adduct configuration	calcd [a] $\Delta\Delta H^{\ddagger}_{\text{exo-endo}}$	exptl endo	vinyl F δ	vinyl C δ
ethylene				−153.2	137.2
cis-2-butene	endo	0.40	0.6:1	−151.4	136.1
	exo			−154.2	137.7
butadiene	endo	−0.18	2:1	−150.5, −154.1	137.3, 135.9
	exo			−152.8, −153.4	137.9, 137.6
styrene	endo	1.13	7:1	−149.0, −154.0	135.7, 137.5
	exo			−152.4, −153.4	
methyl acrylate[2]	endo	2.77[c]		−149.4, −152.6	137.0, 135.3
	exo				
dimethyl maleate	endo	3.81[c]		−149.2	135.9

[a]Transition state enthalpy difference in kcal/mol, calculated at the B3LYP/6-311G**+ level of theory. [b]Chemical shifts relative to internal $CC1_3F$ (for F) and TMS (for C). [c]Exo isomer not unambiguously identified.

Conclusions

In the absence of substantial steric hindrance, *o*-fluoranil normally undergoes Diels−Alder reactions with both electron-rich and electron-poor dienophiles with preservation of stereochemistry, and thus probably in concert. Hybrid density functional calculations indicate that some, though not all, symmetrically substituted dienophiles react not only concertedly, but also synchronously or nearly so. According to the theory, unsymmetrical substitution on the dienophile generally results in highly asynchronous reactions, but we have found that this need not cause loss of stereochemical control. Steric effects can greatly alter the course of events, however, resulting in reaction at oxygen instead of carbon. There is a preference for endo addition in the Diels−Alder chemistry of *o*-fluoranil, reinforced by a repulsive secondary orbital interaction in exo transition states.

Experimental Section

In some of the following experiments, *o*-fluoranil was introduced as a readily synthesized mixture with its much less reactive para isomer (ratio 59:41),[2,10] which was removed in the workup. Other experiments employed the ortho isomer alone, synthesized by a variation to be published on the tetrafluorocatechol preparation of Barthel and Bustrich[11] followed by the catechol oxidation of Shteingarts et al.[1] Quinoxalines are designated by the number of the corresponding Diels−Alder adduct followed by a Q.

1,4-Dihydro-1,2,3,4-tetrafluoro-1,4-ethanophenazine (4Q). A heavy-walled Pyrex tube (12 mm × 200 mm) was charged with a solution of 1.20 g of *o*,*p*-fluoranil mixture (3.9 mmol of ortho) in benzene (11 mL). It was briefly evacuated and cooled in liquid N_2. Ethylene (ca. 200 mL) contained in a balloon was vacuum transferred to the reaction tube, which was sealed with a flame. Placed in a pipe heater, the tube was maintained at 80−85 °C for 21 h. A small sample of the reaction mixture was evaporated, and the ^{19}F NMR spectrum ($CDCl_3$) of the residue showed signals for the unreacted *p*-quinone at δ −142.0 and the ethylene Diels−Alder adduct at δ −146.8 (s, 2F, vinyl) and −193.0 (s, 2F, bridgehead). ^{1}H NMR: δ 2.40 (m, 4H). The reaction solution was concentrated to ca. 5 mL, a few drops of water was added, and the mixture was shaken vigorously for several minutes. A solution of *o*-phenylenediamine (0.75 g, 6.9 mmol) in 5 mL of hot benzene was added. The resulting black mixture of liquid and solid was boiled for several minutes, then the hot liquid was transferred to a 25 g column of silica gel and followed with a benzene wash of the residual solid. The column was eluted with 20% ethyl acetate/hexanes, and crystalline fractions rich in the quinoxaline were combined in 30 mL of benzene. This solution was extracted with 10% aqueous Na_2CO_3 (10 mL) to remove tetrafluorohydroquinone formed by reduction of the *p*-quinone. After a wash with 5 mL of water, the benzene solution was dried over $MgSO_4$ with decolorizing charcoal present. Filtration through filter-cel and evaporation of the filtrate left a pale yellow solid (704 mg, 2.51 mmol, 64% yield). Treatment of the product with a few milliliters of hot benzene left, after cooling, a white solid that was recrystallized from benzene/hexanes to give pure quinoxaline, mp 189.5−190.5 °C. ^{19}F NMR ($CDCl_3$) δ −153.2 (s, 2F), −198.2 (s, 2F); ^{1}H NMR ($CDCl_3$) δ 8.20 (m, 2H), 7.85 (m, 2H), 2.58 (m, 2H), 2.26 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 148.9, 140.1, 137.2 ($^1J_{CF}$ = 294 Hz), 130.9, 129.3, 89.0 ($^1J_{CF}$ = 219 Hz), 29.6. Anal. Calcd for $C_{14}H_8F_4N_2$: C, 60.00; H, 2.88; N, 10.00. Found: C, 60.06; H, 2.84; N, 10.04.

***endo*,*cis*- and *exo*,*cis*-1,4-Dihydro-1,2,3,4-tetrafluoro-11,12-dimethyl-1,4-ethanophenazine (6Q and 7Q).** In a heavy-walled Pyrex tube (12 mm × 200 mm) was placed a solution of *o*-fluoranil (1.00 g, 5.56 mmol) in 8 mL of CH_2Cl_2. The tube was attached by way of a stopcock to a transfer bridge with a cylinder of *cis*-2-butene connected via a graduated Y-tube to the other end. After brief evacuation, the reaction vessel was cooled in liquid nitrogen. The whole system was evacuated and filled with nitrogen, then the Y-tube was cooled in a dry ice−isopropanol bath. *cis*-2-Butene (1.1 mL, ca. 100% excess) was condensed into the Y-tube, then allowed to transfer to the reaction vessel. Sealed with a flame, the vessel was mounted in a pipe heater and maintained at 70 °C for 22 h. The ^{19}F spectrum (CH_2Cl_2) of the product showed singlets at δ −146.5 and −198.6 for the endo Diels−Alder adduct and at δ −147.9 and −198.3 for the exo adduct, in the ratio 0.6:1. Water (400 μL, 300% excess) was added to the reaction mixture, which was shaken for a few minutes. Some hydrate crystallized out, but the solution, which showed a number of new ^{19}F signals, contained much unreacted exo adduct and a very small amount of the endo.

A solution of *o*-phenylenediamine (617 mg, 5.71 mmol) in 10 mL of CH_2Cl_2 was added, and much dark solid formed immediately. The rapid formation of dark oxidation products from the diamine indicated that much reduction of adducts occurred in competition with the desired condensation reaction. The mixture was refluxed and progress was monitored by ^{19}F NMR. Because completion of quinoxaline formation from the exo adduct was very slow, refluxing was continued for 3.5 h. The mixture was dried over $MgSO_4$, filtered, and evaporated to leave dark brown syrup plus solid, which was dissolved as much as possible in hot benzene and placed on a column of silica gel (25 g). Elution with 30% ethyl acetate in hexanes yielded 653 mg (38%) of crude quinoxalines. The exo adduct eluted somewhat faster than the endo, but separation was far from complete. Recrystallization from methanol of a later fraction gave pure endo quinoxaline, mp 191−192 °C. ^{19}F NMR ($CDCl_3$) δ −151.4 (s, 2F), −203.9 (s, 2F); ^{1}H NMR ($CDCl_3$) δ 8.20 (m, 2H), 7.84 (m, 2H), 2.54 (2H), 1.29 (6H); ^{13}C NMR ($CDCl_3$) δ 149.2, 140.2, 136.1 ($^1J_{CF}$ = 294 Hz), 130.7, 129.3, 91.5 ($^1J_{CF}$ = 219 Hz), 39.0, 10.5. Anal. Calcd for $C_{16}H_{12}F_4N_2$: C, 62.33; H, 3.93; N, 9.09. Found: C, 62.40; H, 3.99; N, 9.11.

An early fraction from the chromatogram was recrystallized from methanol with decolorizing charcoal treatment and sublimed to give the exo quinoxaline, mp 172−173 °C. ^{19}F NMR ($CDCl_3$) δ −154.2 (s, 2F), −203.8 (s, 2F); ^{1}H NMR ($CDCl_3$) δ 8.22 (m, 2H), 7.85 (m, 2H), 2.95 (2H), 0.83 (6H); ^{13}C NMR ($CDCl_3$) δ 147.9, 140.2, 137.7 ($^1J_{CF}$ = 299 Hz), 130.7, 129.4, 91.1 ($^1J_{CF}$ = 213 Hz), 39.0, 10.1; HRMS calcd for $C_{16}H_{12}F_4N_2$ 308.0937, found 308.0935.

Dimethyl *endo*,*cis*-1,4-Dihydro-1,2,3,4-tetrafluoro-1,4-ethanophenazine-11,12-dicarboxylate (8Q). In a 25 mL round-bottomed flask were placed commercial dimethyl maleate (2.5 g, 17 mmol), 2.1 g of *o*,*p*-fluoranil mixture (6.9 mmol ortho), some $CaCO_3$, and 5 mL of toluene. The mixture was heated from 95 °C to the reflux temperature for 23 h. After cooling, the mixture was treated with water (200 μL, 11 mmol) and thoroughly shaken. A hot solution of *o*-phenylenediamine (1.3 g, 12 mmol) in 10 mL of benzene was added, and the resulting black mixture was boiled for several minutes. Residue from evaporation of the toluene was transferred to a column of silica gel (30 g), which was eluted with 20% ethyl acetate/hexanes. Fractions containing the Diels−Alder adduct were combined in CH_2Cl_2 and treated with decolorizing charcoal. The mixture was filtered and evaporated, then the residue was recrystallized from methanol to give pure endo quinoxaline, mp 222.5−223.5 °C. ^{19}F NMR ($CDCl_3$) δ −149.2 (s, 2F), −201.1 (s, 2F); ^{1}H NMR ($CDCl_3$) δ 8.21 (m, 2H), 7.89 (m, 2H), 3.83 (s, 6H), 3.63 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 167.3, 147.5, 140.3, 135.9 ($^1J_{CF}$ = 293 Hz), 131.5, 129.5, 89.1 ($^1J_{CF}$ = 225 Hz), 533.3, 49.9. Anal. Calcd for $C_{18}H_{12}F_4N_2O_4$: C, 54.55; H, 3.05; N, 7.07. Found: C, 54.56; H, 2.96; N, 7.08.

Dimethyl maleate free from the fumarate was prepared by treatment of a methanol solution of maleic acid with ethereal diazomethane. In a 5 mL round-bottomed flask were placed this ester (164 mg, 1.14 mmol), sublimed *o*-fluoranil (60 mg, 0.33 mmol, mp 66.5−67.5 °C), some $CaCO_3$, and toluene (ca. 0.8 mL). When the mixture had been refluxed under nitrogen for 10 h, its ^{19}F NMR spectrum showed the endo, cis adduct, unreacted quinone, and at best a trace of the fumarate adduct. Refluxing was continued for another 22 h to complete the reaction, and again the amount of fumarate adduct was negligible. ^{19}F NMR (toluene) for the maleate adduct: δ −145.8 (s, 2F), −196.5 (s, 2F). The ^{19}F NMR (toluene) signals of an authentic sample of the fumarate adduct appeared at δ −143.3 (s, 1F), −149.9 (s, 1F), −195.0 (s, 1F), and −195.9 (s, 1F).

(10) Shteingarts, V. D.; Budnik, A. G.; Yakobson, G. G.; Vorozhtsov, N. N., Jr. *Zh. Obsh. Khim.* **1967**, *37*, 1537.

(11) Barthel, J.; Bustrich, R. German patent DE 19633027, 1988.

***trans*-5,6,7,8-Tetrafluoro-2,3-diphenyl-2,3-dihydrobenzo[1,4]-dioxin (9).** In a 25 mL round-bottomed flask were placed *cis*-stilbene (1.01 g, 5.6 mmol), 0.86 g *o*,*p*-fluoranil mixture (2.8 mmol ortho), and 4 mL of toluene. The black mixture was refluxed under nitrogen for 23 h. The *trans*-dioxene and *trans*-Diels−Alder adduct were present in the ratio 5:1, together with unreacted *p*-quinone. ^{19}F NMR (toluene) for the dioxene: δ −164.2 (m, 2F), −170.1 (m, 2F). ^{19}F NMR (toluene) for the Diels−Alder adduct: δ −144.4 (s, 1F), −149.0 (s, 1F), −194.6 (s, 1F), −195.2 (s, 1F). The mixture was diluted with 15 mL of CH_2Cl_2 and extracted with 10 mL of 10% aqueous $NaHSO_3$ to remove the *p*-quinone. Phase separation was poor, so the aqueous phase was washed with another 5 mL of CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ with decolorizing charcoal added. After filtration through filter-cel, the solution was evaporated to leave a dark brown oil that was chromatographed on 20 g of silica gel with 20% ethyl acetate/hexanes as eluent. Fractions containing *trans*-stilbene and the slightly slower moving dioxene were combined and rechromatographed, again on 20 g of silica gel, but with 1% ethyl acetate/hexanes as eluent. This time the stilbene and dioxene were cleanly separated, and fractions bearing the latter were combined and evaporated to give yellow crystals. These were recrystallized from hexanes to yield a crop of thin, colorless plates (208 mg, 21%). Mp 152.5−153 °C; ^{19}F NMR ($CDCl_3$) δ −163.8 (m, 2F), −169.2 (m, 2F); ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 6H), 7.05 (m, 4H), 4.98 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 137.4 ($^1J_{CF}$ = 248 Hz), 135.9 ($^1J_{CF}$ = 247 Hz), 134.4, 129.2 128.4, 127.6, 81.1. Anal. Calcd for $C_{20}H_{12}F_4O_2$: C, 66.67; H, 3.36; F, 21.09. Found: C, 66.72; H, 3.19; F, 21.23.

o,*p*-Fluoranil mixture (75 mg, 0.25 mmol ortho) that had been recrystallized from hexanes was combined in a 5 mL round-bottomed flask with *cis*-stilbene, $CaCO_3$, and ca. 1 mL of toluene. The mixture was stirred and refluxed for 16 h. Again the ^{19}F spectrum (toluene) showed peaks for the *trans*-dioxene and Diels−Alder product, but in addition prominent signals at δ −164.1 (m, 2F) and −169.1 (m, 2F) corresponding to the *cis*-dioxene. A very small singlet at δ −194.0 may represent the bridgehead fluorines of a cis Diels−Alder adduct.

***endo*- and *exo*-1,4-Dihydro-1,2,3,4-tetrafluoro-11-vinyl-1,4-ethanophenazine (12Q and 13Q).** Into a heavy-walled glass tube with a sealable gas inlet connection was placed a solution of 2.50 g of *o*,*p*-fluoranil mixture (8.19 mmol ortho) in 15 mL of CH_2Cl_2. The vessel was cooled in liquid nitrogen, and butadiene (0.70 g, 13 mmol) was introduced by vacuum transfer. The tube was sealed and the reaction mixture was allowed to stand at room temperature for 23 h. A sample was taken for NMR analysis, and the solvent was replaced with $CDCl_3$. The principal products were the endo and exo Diels−Alder adducts in the ratio 2:1, respectively. ^{19}F NMR for the endo adduct: δ −144.8 (s, 1F), −148.1 (s, 1F), −193.7 (s, 1F), −195.7 (s, 1F). ^{19}F NMR for the exo adduct: δ −146.4 (s, 1F), −147.0 (s, 1F), −193.9 (s, 1F), −195.9 (s, 1F). The reaction mixture was transferred to a 100 mL round-bottomed flask and water (300 μL, 16.7 mmol) was added. After the mixture had been vigorously shaken for a few minutes, a hot solution of *o*-phenylenediamine (1.57 g, 14.5 mmol) in 10 mL of benzene was added followed by a benzene rinse. When the black mixture had been boiled for several minutes, ^{19}F NMR indicated that reaction had gone to completion. The mixture was concentrated to eliminate CH_2Cl_2, then diluted with benzene to ca. 60 mL. It was filtered hot and the filtrate was washed with 15 mL of 10% Na_2CO_3 solution to remove tetrafluorohydroquinone formed by reduction of the *p*-fluoranil. The organic layer was washed with water (5 mL) and dried over $MgSO_4$ with decolorizing charcoal added. Filtration through filter-cel followed by evaporation left a concentrated benzene solution that was placed on a column of silica gel (30 g). Elution was done with 20% ethyl acetate/hexanes. The main quinoxaline-containing fractions consisted of yellow crystals totaling 1.172 g (3.83 mmol, 47% crude yield).

Recrystallizations from hexanes and from methanol of an endo-rich fraction (487 mg) failed to free it of the less-soluble exo isomer (ratio 8.5:1), but it was pure otherwise. Mp 114−120 °C; ^{19}F NMR ($CDCl_3$) endo δ −150.5 (s, 1F), −154.1 (s, 1F), −199.0 (s, 1F), −201.5 (s, 1F); ^{1}H NMR ($CDCl_3$) endo δ 8.21 (m, 2H), 7.86 (m, 2H), 5.90 (m, 1H), 5.43 (m, 2H), 3.05 (m, 1H), 2.52 (m, 1H), 2.39 (m, 1H); ^{13}C NMR ($CDCl_3$) endo δ 149.1, 148.8, 140.2, 140.1, 137.3 ($^1J_{CF}$ = 294 Hz), 135.9 ($^1J_{CF}$ = 294 Hz), 132.9, 130.9, 130.8, 129.4, 129.3, 121.5, 90.6 ($^1J_{CF}$ = 220 Hz), 88.5 ($^1J_{CF}$ = 220 Hz), 44.6, 37.0. Anal. Calcd for $C_{16}H_{10}F_4N_2$: C, 62.74; H, 3.29; N, 9.15. Found: C, 62.88; H, 3.20; N, 9.18.

A fraction from the chromatogram containing slightly more exo than endo quinoxaline (466 mg) was enriched in the exo form by recrystallization from hexanes and from methanol/water, but the endo isomer could not be completely eliminated. Thus, the isomer mixture was recombined and chromatographed on 30 g of silica gel with CH_2Cl_2 as eluent. A fraction rich in the exo form was recrystallized from hexanes and then from methanol/water to yield exo quinoxaline containing just 2.6% of the endo isomer by ^{19}F NMR. Mp 154−156 °C; ^{19}F NMR ($CDCl_3$) exo δ −152.8 (s, 1F), −153.4 (s, 1F), −199.1 (s, 1F), −201.4 (s, 1F); ^{1}H NMR ($CDCl_3$) exo δ 8.21 (m, 2H), 7.86 (m, 2H), 5.21 (m, 3H), 3.44 (m, 1H), 2.88 (m, 1H), 2.04 (m, 1H); ^{13}C NMR ($CDCl_3$) exo δ 148.9, 147.4, 140.3, 140.2, 137.9 ($^1J_{CF}$ = 291 Hz), 137.6 ($^1J_{CF}$ = 291 Hz), 132.1, 131.0, 130.9, 129.5, 129.4, 121.5, 90.5 ($^1J_{CF}$ = 219 Hz), 88.4, ($^1J_{CF}$ = 219 Hz), 45.3, 36.9.

***endo*-1,4-Dihydro-1,2,3,4-tetrafluoro-11-phenyl-1,4-ethanophenazine (14Q).** A small sample of *o*,*p*-fluoranil mixture and excess styrene were dissolved in $CDCl_3$ in an NMR tube, and the solution was allowed to stand for 23 h at room temperature. The ^{19}F spectrum revealed the presence of endo and exo Diels−Alder adducts in the ratio 7:1, respectively. ^{19}F NMR ($CDCl_3$) endo δ −144.0 (s, 1F), −148.0 (s, 1F), −193.6 (s, 1F), −193.7 (s, 1F); ^{19}F NMR ($CDCl_3$) exo δ −145.8 (s, 1F), −146.8 (s, 1F), −193.3 (s, 1F), −194.0 (s, 1F). The endo quinoxaline was prepared,[1] and because no spectral information had been reported, the following data appear here. ^{19}F NMR ($CDCl_3$) δ −149.0 (m, 1F), −154.0 (s, 1F), −199.3 (d, J = 4.5 Hz, 1F), −199.6 (s, 1F); ^{1}H NMR ($CDCl_3$) δ 8.24 (m, 2H), 7.88 (m, 2H), 7.44 (m, 5H), 3.60 (m, 1H), 2.83 (m, 2H); ^{1}H NMR (C_6D_6) δ 8.09 (m, 2H), 7.28 (m, 2H), 7.05 (m, 5H), 2.86 (m, 1H), 2.27 (m, 1H), 1.96 (m, 1H).

1,4-Dihydro-1,2,3,4-tetrafluoro-11-*exo*-deuterio-12-*endo*-phenyl-1,4-ethanophenazine (16Q). *trans*-β-Deuteriostyrene was synthesized by the method of Casey and Strotman.[12] By ^{1}H NMR, 2.5% of the styrene contained hydrogen at the trans, β position. The small signal at that position (δ 5.15, $CDCl_3$) comprised a doublet (J = 10.8 Hz) superimposed upon a broad singlet, corresponding to a mixture of undeuterated and α-deuterated styrene. In a 25 mL round-bottomed flask were placed 1.526 g of *o*,*p*-fluoranil mixture (5.00 mmol ortho), deuterated styrene (ca. 30% excess), $CaCO_3$, and 5 mL of CH_2Cl_2. The mixture was stirred and refluxed for 10 h. Another 5 mL of CH_2Cl_2 and water (200 μL, 11 mmol) were added, and the flask was shaken well for several minutes. Much hydrate came out of soluton as a fine precipitate. A hot solution of *o*-phenylenediamine (0.97 g, 9.0 mmol) in 8 mL of benzene was added, quickly enough that foaming resulted in some mechanical loss. After the mixture was boiled for several minutes, ^{19}F NMR indicated that reaction was complete. Evaporation left a dark, viscous syrup that was chromatographed on 20 g of silica gel with 20% ethyl acetate/hexanes as eluent. The exo quinoxaline eluted slightly faster than the endo, but the two were not well

(12) Casey, C. P.; Strotman, N. A. *J. Am. Chem. Soc.* **2004**, *126*, 1699.

separated (total weight 880 mg, 57% crude yield). Major fractions were combined in $CHCl_3$ and treated with decolorizing charcoal. The mixture was filtered hot through filter-cel, then concentrated to ca. 8 mL on a hot plate. Hexanes (12 mL) were added, and the solution was cooled in a refrigerator to obtain pure crystals of the endo quinoxaline, mp 184.5−185.5 °C. ^{19}F NMR ($CDCl_3$) δ −149.0 (s, 1F), −154.0 (s, 1F), −199.4 (s, 1F), −199.6 (s, 1F); ^{1}H NMR ($CDCl_3$) δ 8.23 (m, 2H), 7.88 (s, 2H), 7.44 (m, 5H), 3.60 (d, J = 4.5 Hz, 1H), 2.85 (s, 1H); ^{1}H NMR (C_6D_6) δ 8.09 (m, 2H), 7.28 (m, 2H), 7.05 (m, 5H), 2.86 (d, J = 4.2 Hz, 1H), 2.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 149.2, 140.2, 137.5 ($^1J_{CF}$ = 294 Hz), 135.9, 135.7 ($^1J_{CF}$ = 294 Hz), 131.0, 129.4, 129.1, 128.9, 128.7, 91.5 ($^1J_{CF}$ = 221 Hz), 88.7 ($^1J_{CF}$ = 219 Hz), 45.9, 38.6. Anal. Calcd for $C_{20}H_{11}DF_4N_2$: C, 67.22; H + D, 3.66; N, 7.84. Found: C, 66.90; H + D, 3.22; N, 7.81.

To have sufficient resolution in the aliphatic hydrogen region to answer the question of cycloaddition stereochemistry, it was necessary to run the ^{1}H spectrum in C_6D_6 at 500 MHz. The peak at δ 1.96 representing the exo methylene proton was very small. Its area was consistent with the composition of the styrene starting material, thereby indicating that the addition had occurred without loss of stereochemistry.

***trans*-5,6,7,8-Tetrafluoro-2-methyl-3-(*trans*-1-propenyl)-2,3-dihydrobenzo[1,4]dioxin (17).** To a saturated solution of *o*-fluoranil (1.0 g, 5.6 mmol) in benzene was added a solution of *trans*,*trans*-hexadiene (0.545 g, 6.0 mmol) in 10 mL of benzene, and the resulting solution was stirred at room temperature for 4−5 h. Evaporation of the solvent under reduced pressure left a gum that was transferred with a minimal amount of hexane to a column of silica gel. Elution was carried out with CH_2Cl_2/hexanes, and the dioxene was obtained as a white crystalline solid (0.80 g, 55% yield). It was then recrystallized from hexanes and sublimed, mp 74.5−75 °C. ^{19}F NMR ($CDCl_3$) δ −165.0 (m, 1F), −165.2 (m, 1F), −170.3 (m, 2F); ^{1}H NMR ($CDCl_3$) δ 6.05 (m, 1H), 5.50 (m, 1H), 4.18 (t, J = 8 Hz, 1H), 3.96 (m, 1H), 1.83 (d, J = 6.5 Hz, 3H), 1.40 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.2 ($^1J_{CF}$ = 246 Hz), 135.6 ($^1J_{CF}$ = 246 Hz), 134.6, 130.0, 124.4, 79.9, 73.8, 18.0, 16.9. Anal. Calcd for $C_{12}H_{10}F_4O_2$: C, 54.97; H, 3.84; F, 28.99. Found: C, 55.07; H, 3.64; F, 29.15.

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Supporting Information Available: Total energies at the B3LYP/6-311G**+ level of theory, ^{1}H and ^{13}C NMR spectra, and general experimental information. This material is available free of charge via the Internet at http://pubs.acs.org.