# A C−F Bond Directed Diels−Alder Reaction

Mark D. Struble, Liangyu Guan, Maxime A. Siegler, and Thomas Lectka*

Department of Chemistry, New Chemistry Building, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218, United States

S *Supporting Information*

ABSTRACT: We demonstrate a C−F bond driven Diels−Alder reaction of a fluorinated dienophile and a borole that shows remarkable diastereoselectivity. The product's structure was confirmed by X-ray crystallography, revealing an unusual conformation featuring a hypercoordinate boron. Calculations suggest that a B···F interaction instigates the reaction chemistry, the magnitude of which is maximized in the transition state—in essence, the B···F distance "yo-yos" from long to short in the transition state and back again to long in the product.
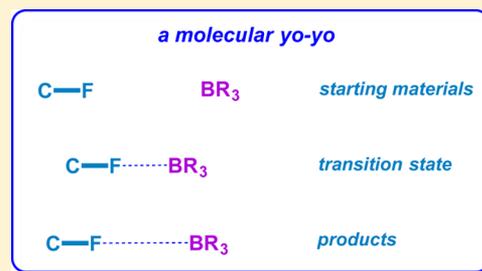
A tremendous amount of interest has been generated toward understanding the reactivity of fluorine-containing molecules. This is at least partly due to the prevalence of fluorinated pharmaceuticals[1] and perfluorinated polymers on the market.[2] The addition of fluorine atoms to these substances often results in a marked decrease in external reactivity, shown by a resistance to biological metabolism in some fluorinated drugs[3] and the low reactivity of perfluoropolymers like Teflon.[4] In some ways, these properties have led to the belief that the C−F bond is inert and cannot be utilized in reactive chemistry as the other halogens. It is likely that the strength of the C−F bond (∼110 kcal/mol) and the tight fashion in which it holds its lone pairs of electrons contribute to this misconception.[5] However, this is not always the case: C−F bond activations by transition metals,[6] silyl cations,[7] and even carbocations[8] are well-established processes; the nucleophilic displacement of benzylic, allylic, and tertiary C−F bonds is also commonplace.[9] On the other hand, situations in which the C−F bond itself serves as an activating or directing group (anchimeric assistor) are exceedingly rare. For our part, we have recently shown that a C−F bond positioned over the π-cloud of an arene ring can activate it toward electrophilic nitration.[10] In the search for other reactions with participating C−F bonds, we focused on signature processes in organic chemistry, such as the Diels−Alder (DA) reaction.

The DA reaction is an excellent way of forming C−C bonds, but it can result in several stereoisomers, depending on how the dienophile and diene approach each other (*endo*/*exo*), the reactants' symmetry, or some combination of both.[11] There have been attempts to increase the reaction's selectivity by relying on the anchimeric effect, and some success has been reported with alcohols, a commonly employed directing group.[12] Is it possible that a fluorine atom could act as a directing group, as well? Herein, we report a notably selective DA reaction between a fluorinated dienophile and a borole. Calculations show that the interaction between B and F is a prime instigator in the reaction chemistry, and that its
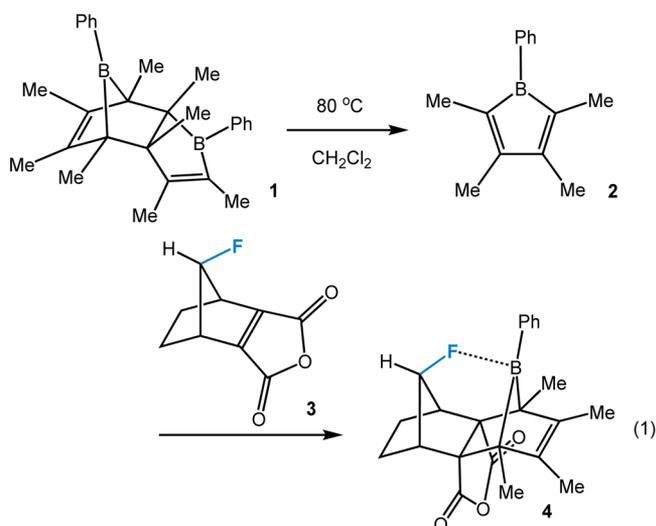
magnitude is maximized at (or very near) the transition state (TS).

Boroles (boracyclopentadienes) were first synthesized in 1969, but it is only recently that they have been seen as more than a novelty.[13] This is likely due to their antiaromatic nature, which results in a high degree of reactivity, especially toward DA reactions, as well as air and moisture sensitivity. Efforts to understand the chemistry of boroles and combat their poor stability through substitution of stabilizing groups are underway.[14] Borole-containing molecules also have the potential to activate certain chemical reactions and form unique materials.[15] This paper focuses on its reactivity toward DA chemistry. We synthesized the borole dimer **1** in two steps from dimethylacetylene following the zirconacycle transfer method of Fagan and co-workers.[16] When heated at 80 °C, **1** readily converts into monomeric borole **2** (eq 1). We imagined that the Lewis acidic boron atom on formally antiaromatic borole **2** could interact in solution with a suitable Lewis base, such as the lone pairs of fluorine in a C−F bond, in an appropriately configured dienophile. This interaction could help position the borole and thereby improve reaction selectivity. Boron has been shown to have a high affinity for fluoride and is often incorporated in fluoride sensors.[17] We hope to see similar affinity to the C−F bond in our system. It seemed that alkene **3** would be a good dienophile candidate, as an interaction between B and F in a hypothetical Diels−Alder TS is stereoelectronically feasible, whereas that between B and the O on the carbonyls is not.

The borole dimer and the dienophile were both dissolved in CH_2Cl_2 and heated at 80 °C to facilitate the retro-DA reaction of the dimer. We observed that borole **2** reacts rapidly and smoothly to produce a moderate yield (45%) of diastereomerically pure adduct **4**. The other observed compounds proved to

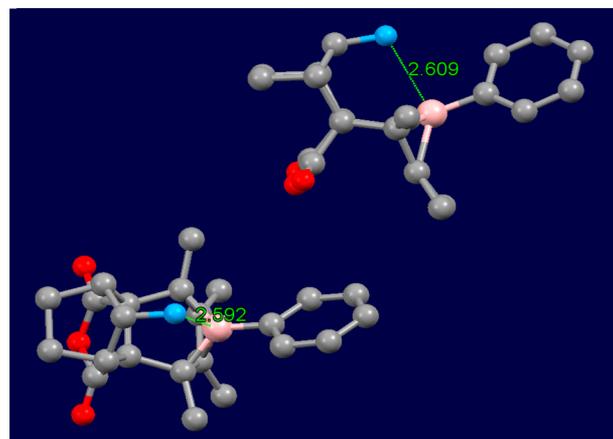**Figure 1.** Crystal structure of **4** (hydrogen atoms have been removed), showing the two crystallographically independent molecules. Fluorine in blue; oxygen in red; boron in salmon. Note that the crystal is twinned.

be starting material and decomposed borole; no other adducts were observed. In our experience, other Diels−Alder reactions of dienophile **3** afford mixtures of stereoisomers, a fact which suggested that the reaction could be directed by the boron's coordination to the fluorine.[18] For example, the reaction of **3** with 1,3-cyclopentandiene occurs at 180 °C to afford a mixture of two diastereomers (**5** and **6**) in roughly a 1:1.2 ratio (eq 2).[15a]
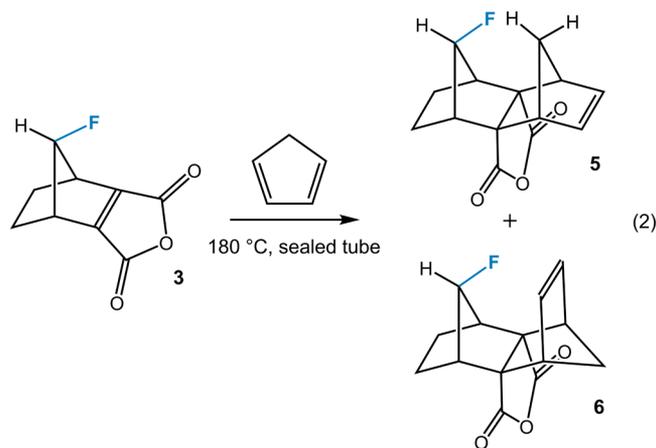
Crystals of product **4** suitable for X-ray structure determination were grown from a mixture of CH$_2$Cl$_2$ and diethyl ether. The asymmetric unit contains two crystallographically independent molecules of **4** for which the phenyl rings are rotated in a different conformation (Figure 1). In the crystal, the two B···F distances are 2.5919(18) and 2.6095(18) Å, depending on the conformation. Not surprisingly, a strong interaction between B and the vicinal C=C bond is noted. The boron is 1.896(2)/1.900(2) or 1.934(2)/1.936(2) Å away from the double bond, depending once again on which rotamer is observed. Although the crystal indicates bonding between the boron and the double bond, the carbon atoms still appear to be generally sp²-hybridized. In fact, the methyl groups seem to be tilted slightly upward toward the boron. This structure is isoelectronic to the 7-phenylnorbornenyl cation and has been observed in a few other cases, such as in dimer **1**.[14,19] Numerous attempts were made to functionalize the vicinal double bond of **4**, but it was found to be unreactive to various substitution reactions, such as halogenation and hydrogenation.

This is likely a combination of the bond donating electron density to the boron as well as steric hindrance from the methyl groups and the partial coordination of fluorine.

Density functional theory (DFT) calculations (6-311++G**/ωb97xd)[20] of four possible TSs for the reaction are shown in Scheme 1. As expected, TS **7**, leading to the observed adduct **4**, is almost 4.5 kcal lower than the closest competitor **8**, presumably due in part to the interaction between B and F. Calculations also predict that the reaction proceeds in TS **7** through an unusual trajectory. Using DFT, the B···F distance was calculated at various lengths of the two C−C σ-bonds formed during the DA reaction. This allowed us to map the changes to the B···F interaction as the reaction proceeds (Figure 2). Initially, as the two reactants approach each other, the B and the F are also drawn closer together. The smallest B···F distance, 2.27 Å, is predicted to be reached very close to or at TS **7**. Once the transition state is passed and product **4** begins to form, the F···B distance is predicted to lengthen again. The B···F interaction is evidently being diminished by a strong, through-space donating effect from the newly formed vicinal C=C double bond in the product. This results in the B···F distance in **4** being almost 0.33 Å longer than in TS **7**. The F···B interaction thus seems to "yo-yo" from tight in the TS to loose in the product, wherein the donation from the C=C double bond takes precedence. An atoms-in-molecules (AIM) analysis of **4** shows a bond critical point (BCP) between B and F, which is indicative of a through-space interaction.[21] However, in TS **7**, the BCP shows the same B···F relationship, only stronger. The result is that the boron is unusually coordinated in product **4**—weakly to the C−F bond, strongly in a homoaromatic interaction to the C=C bond, and covalently to three carbon atoms—to attain hypervalency.

Having accumulated some evidence pointing to the B···F interaction providing a directing effect, we developed a competition experiment to quantify its *kinetic* consequences, that is, whether it actually accelerates the DA reaction. It is known that just about all other Diels−Alder reactions of dienophile **3** require forcing conditions, either high temperatures or high pressures; on the other hand, borole **2** is an unusually reactive diene, so a faster rate is expected.[10,15] In a minimal amount of CH$_2$Cl$_2$ (3 mL), 0.2 equiv of borole dimer **1** was heated at 80 °C with 1 equiv of the dienophile **3** and a

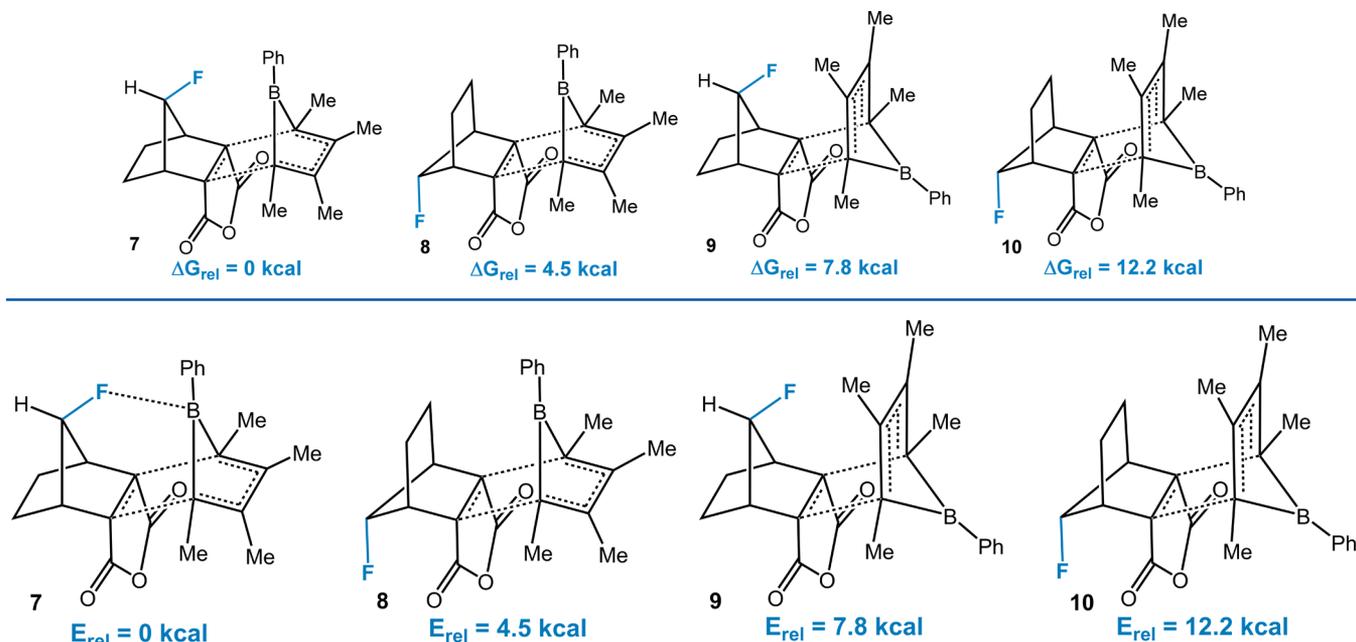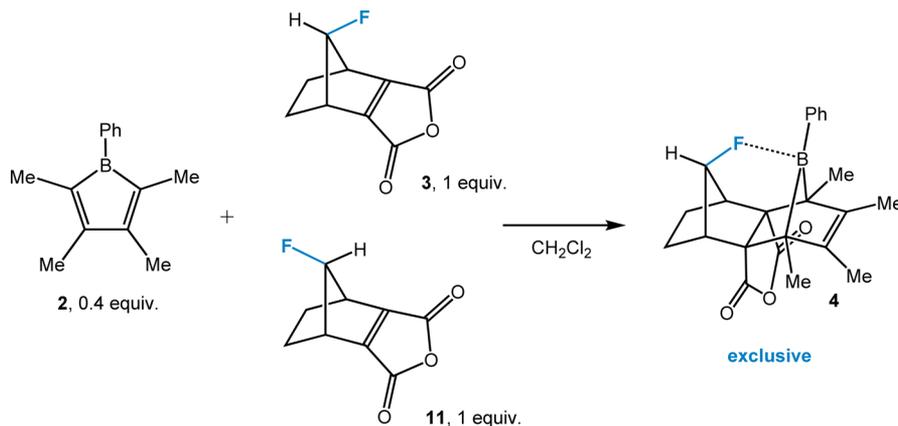**Scheme 1. Relative Energy and Activation Energy of Each TS Pathway**

Figure 2. Calculated B···F distance during the C−C bond formation in TS **7**; curve fitted to a fourth-order polynomial. The vertical dotted line corresponds to the C−C bond length predicted for TS **7**.

Scheme 2. In- versus Out-Fluorine Competition Reaction

second equiv of control dienophile **11** in a sealed tube (Scheme 2). In theory, the borole dimer should yield 0.4 equiv of **2**; however, it was in practice less due to its extreme air sensitivity. Dienophile **11** is similar to **3** but has its fluorine pointed away from the double bond, so any DA product derived therefrom must form through a transition state bereft of fluorine participation. An assay of reaction progress after 1 day showed adduct **4** to be the *sole observed* DA derived product to the limit of detection. The only other observed peaks were from starting materials **11** and **3** and their decomposition products. This result indicates that the B···F interaction has a substantial effect on the rate (and selectivity) of the reaction versus a closely configured control. In comparison to dienophile **11**, C−F···B coordination can only result in the formation of a non-productive precomplex and thus must play no role in reaction chemistry. This rules out steric interactions as the primary driving force for the reaction's selectivity as the two dienophiles have relatively similar structures, but dienophile **3** is overwhelmingly favored.

In conclusion, we have reported a highly selective DA reaction between a fluorinated dienophile and a borole. Interestingly, the source of the selectivity of this reaction appears to be a rare case of a fluorine on a C−F bond acting as a Lewis base and coordinating to the Lewis acidic p-orbital on the boron. In the TS, the fluorine is predicted to act as a templating element in the reaction by coordinating to the borole as it is suspended over the double bond. After the reaction is complete, the boron's empty p-orbital is drawn to the newly formed vicinal double bond. However, both DFT calculations and crystallography indicate that there still exists an interaction between fluorine and boron in the final product.

■ **EXPERIMENTAL SECTION**

General Methods. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and reagents were dried and distilled by standard methods. ^{1}H and ^{13}C spectra were acquired on a 400 MHz NMR in CDCl$_3$ at 25 °C; ^{19}F spectra were obtained on a 300 MHz

NMR in CDCl$_3$ at 25 °C. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and/or CFCl$_3$ (δ 0.00 ppm). NMR data are reported in the following format: chemical shifts {multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants [Hz]}. IR data were obtained using an FT-IR with a flat CaF$_2$ cell. All measurements were recorded at 25 °C unless otherwise stated. Melting points are uncorrected. HRMS calculations were performed on an ESI-ion trap mass spectrometer. Compounds **1**, **3**, and **11** were prepared according to literature procedures.[14,15,10] Spectral data were processed with ACD/NMR Processor Academic Edition.[22]

Computational Methods. The Gaussian 09 package was used for all geometry optimizations.[23] Geometry optimizations were likewise determined using the ωb97xd/6-311++G** level. AIM calculations were performed using the program AIMAll on structures optimized to ωb97xd/6-311++G**.[24]

Compound Characterization. *1-Phenyl-3,4,5-tetramethylborole dimer (1):* Tan solid, 0.971 g (92% yield); synthesized by following the synthetic route reported in literature.[14] Spectral and analytical data were in agreement with previous reports.

syn-8-Fluoro-4,5,6,7-tetrahydro-4,7-methanoisobenzofuran-1,3-dione (3): Tan solid, 0.971 g (23% yield); synthesized by following the synthetic route reported in literature.[15] Spectral and analytical data were in agreement with previous reports.

12-Fluoro-1,2,3,4-tetramethyl-13-phenyl-1,4,5,6,7,8-hexahydro-1,4-borano-5,8-methano-4a,8a-(methanooxymethano)-naphthalene-9,11-dione (4): To a sealed tube was added freshly made dimer **1** (0.971 g, 2.48 mmol) dissolved in 3 mL of dry degassed DCM and dienophile **3** (0.903, 4.96 mmol). The tube was sealed and heated at 80 °C for 6 h. The solvent was removed in vacuo, and the crude product was purified by flash column chromatography on Florisil with a 5% ethyl acetate and hexanes solution to yield **4** as white crystals (0.8426 g, 45% yield): mp = 162−168 °C; ^{1}H NMR (CDCl$_3$) δ 7.26−7.20 (m, 3H), 7.18−7.09 (m, 2H), 5.11 (d, 1H, J_{F-H} = 56.7 Hz), 2.96 (m, 2H), 1.88 (m, 6H), 1.82 (d, 2H, J = 8.8 Hz), 1.48 (s, 6H), 1.42 (m, 2 H); ^{13}C NMR (CDCl$_3$) δ 173.0 (J = 0.7 Hz), 133.58, 133.55, 131.0 (J = 2.6 Hz), 128.0, 127.7, 103.5 (J = 206.0 Hz), 73.0 (J = 4.8 Hz), 42.1 (J = 15.5 Hz), 21.6, 21.4, 12.1, 11.5; ^{19}F NMR (CDCl$_3$) δ −189.1 (d, 1F, J = 56.8 Hz); IR 3055, 2963, 2932, 1856, 1772, (cm^{-1}, CaF$_2$, CH$_2$Cl$_2$); HRMS (ESI+) calcd for NaC$_{23}$H$_{24}$BFO$_3$ 401.1695, found 401.1693.

anti-8-Fluoro-4,5,6,7-tetrahydro-4,7-methanoisobenzofuran-1,3-dione (11): Tan solid, 0.158 g (86% yield); synthesized by following the synthetic route reported in literature.[10] Spectral and analytical data were in agreement with previous reports.

ASSOCIATED CONTENT

ⓈSupporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01489.

> X-ray crystallography data, NMR spectra, and molecular modeling parameters/atom coordinates (PDF)
> X-ray data for compound **4** (CIF)

AUTHOR INFORMATION

Corresponding Author
*E-mail: lectka@jhu.edu.

Notes

The authors declare no competing financial interest.

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Mass spectral data were obtained at Old Dominion University's mass spectrometry center.

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