A C–F Bond Directed Diels–Alder Reaction

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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 pharmaceuticals1 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 drugs3 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 carbocations8 are well-established processes; the nucleophilic displacement of benzyl, 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 assistors) 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 nitrination.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 notable 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 pair 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 CH₂Cl₂ 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
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. For example, the reaction of 3 with 1,3-cyclopentadiene occurs at 180 °C to afford a mixture of two diastereomers (5 and 6) in roughly a 1:1.2 ratio (eq 2).13a

Crystals of product 4 suitable for X-ray structure determination were grown from a mixture of CH2Cl2 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 B···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-phenylboronyl cation and has been observed in a few other cases, such as in dimer 1.18,19

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**/ob97xd)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 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 thus seems to be 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 CH2Cl2 (3 mL), 0.2 equiv of borole dimer 1 was heated at 80 °C with 1 equiv of the dienophile 3 and a

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.

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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. 1H and 13C spectra were acquired on a 400 MHz NMR in CDCl3 at 25 °C; 19F spectra were obtained on a 300 MHz NMR.
NMR in CDCl3, at 25 °C. The 1H, 13C, and 19F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and/or CFCl3 (δ 0.00 ppm). NMR data are reported in the following format: chemical shifts (multiplicity = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants [Hz]). IR data were obtained using a FT-IR with a flat CaF2, 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 Spectral and analytical data for the synthetic route reported in literature.10 Spectral and analytical data for the synthetic route reported in literature.15 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. Spectral and analytical data were in agreement with previous reports.

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**REFERENCES**