

## A PRELIMINARY COMPUTATION STUDY OF COUNTER ION EFFECT ON TRANSITION STATE MODELS IN ETHYNYL SUBSTITUTION OF FLUORINE IN *F*-BODIPY.

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**ABSTRACT.** Substitution of the fluorine atoms bonded to the boron center in 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (*F*-BODIPY) compounds with ethynyl or aryl linkages can be achieved through either Grignard or lithium organometallic reagents. Use of Grignard reagents allows for the isolation of monosubstituted and disubstituted products, whereas use of organolithium reagents allows for the isolation of only the disubstituted product. Using SPARTAN modeling software and quantum chemical calculations, preliminary theoretical  $S_N2$  transition state energies were determined for both the mono- and disubstituted transition states using both Grignard and lithium trimethyl silyl protected ethynyl reagents. These models were used to calculate differences in theoretical activation energies between the mono- and disubstitution processes,  $\Delta\Delta E = -11.3$  kJ/mol for the lithium reagent and  $\Delta\Delta E = 35.9$  kJ/mol for the Grignard reagent. The lower second substitution activation energy for our lithium reagent (negative  $\Delta\Delta E$ ) and the higher second step for our Grignard reagent (positive  $\Delta\Delta E$ ) supports the experimental findings where organolithium reagents are only capable of producing the disubstituted product.

**Keywords:** BODIPY, quantum chemical calculations, semi-empirical, density functional theory, transition states

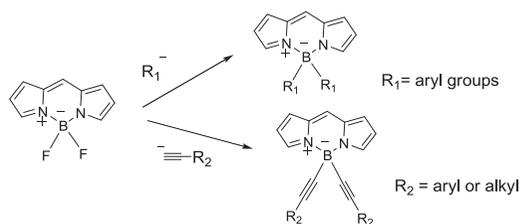
### INTRODUCTION

The ever accelerating growth of modern technology has created a profound demand for more efficient fluorophores which possess qualities such as a large Stokes' shift, high molar absorption coefficients, high fluorescence quantum yields, high photo stability, high emission peak intensities, and low intersystem crossing (Loudet & Burgess 2007; Ulrich et al. 2008). New fluorescent compounds are being developed for applications in fields such as sensors, light emitting devices, and biological labeling (Saki et al. 2006; Ziessel et al. 2009; Ju et al. 1995). The 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (*F*-BODIPY) dyes are a family of highly investigated dyes. *F*-BODIPY dyes possess many of the previously mentioned properties paramount to modern fluorophores, including extremely high quantum yields, high molar absorption coefficients, and high emission peak intensities. However, they have a very small Stokes shift (Goze et al. 2007). Fluorophores with small Stokes shifts are susceptible to self-quenching of fluorescence (Moerner, W. E., 2007). This problem has been addressed by substituting the two fluorines bonded to boron in *F*-BODIPY with chromophoric molecules, such as pyrene, anthracene,

phenanthracene, and biphenyl. These aromatic molecules absorb photons at a shorter wavelength than *F*-BODIPY and transfer their energy to the BODIPY core, which can then release the energy through fluorescent decay (Ulrich et al. 2005; Goze et al. 2006; Goze et al. 2007).

Substitution of fluorine with various chromophores can be done by using aryl nucleophiles or ethynyl nucleophiles (Scheme 1) to create a large, virtual Stokes shift, anywhere in the range of  $8,000\text{ cm}^{-1}$  to  $16,000\text{ cm}^{-1}$  (Ulrich et al. 2005; Goze et al. 2006; Goze et al. 2007; Nzeata & Hewavitharanage 2012).

It is important to note that substitution of fluorine has little effect on the  $\lambda_{\text{max}}$  of absorbance, which remains in the range of  $515\text{ cm}^{-1}$  to  $526\text{ cm}^{-1}$  because substituted chromophores are not in conjugation with the



Scheme 1.—Synthesis of BODIPY derivatives.

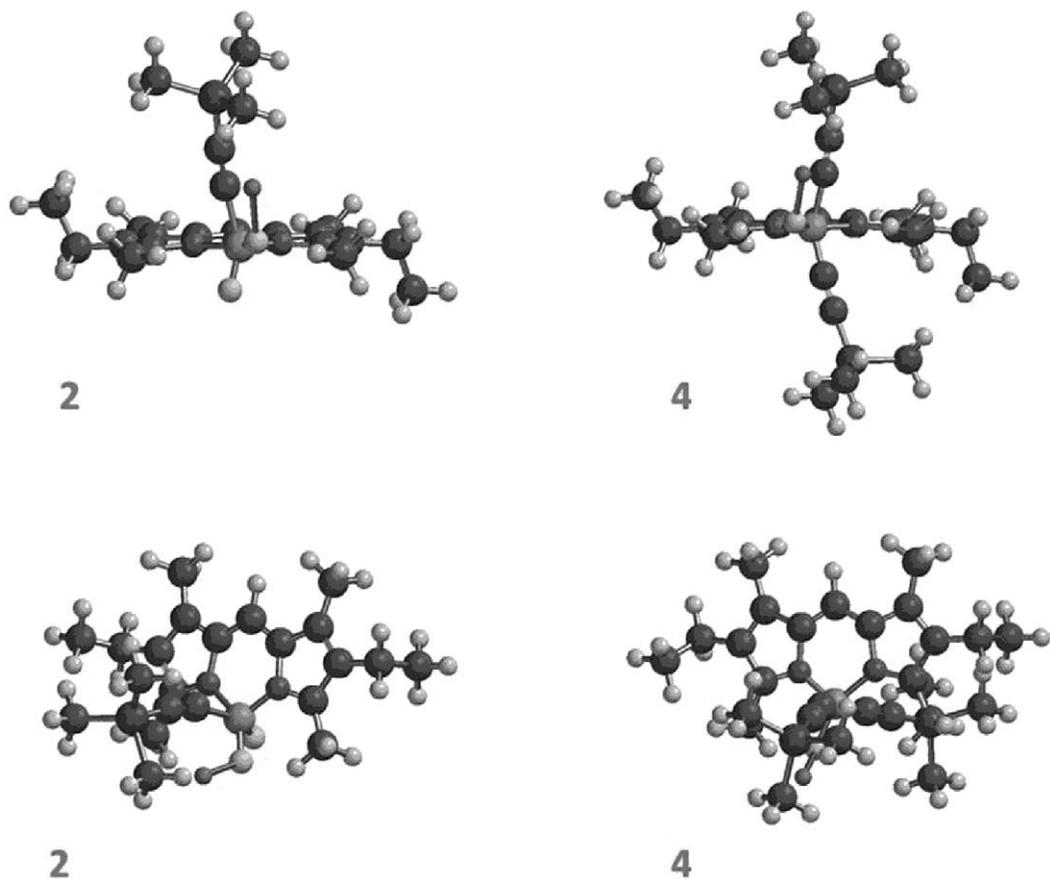
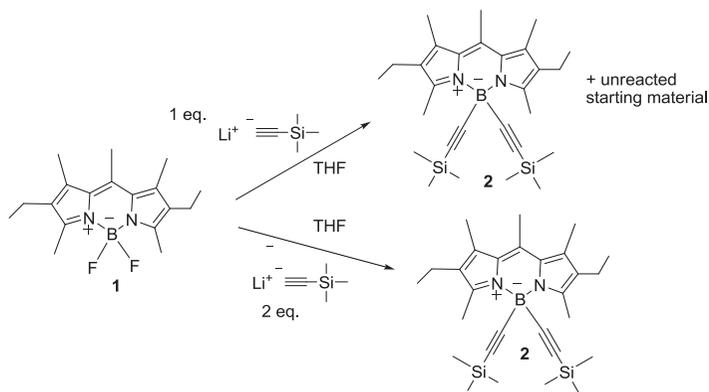


Figure 1.—Transition state models with lithium cation(2 for monosubstitution and 4 for disubstitution).

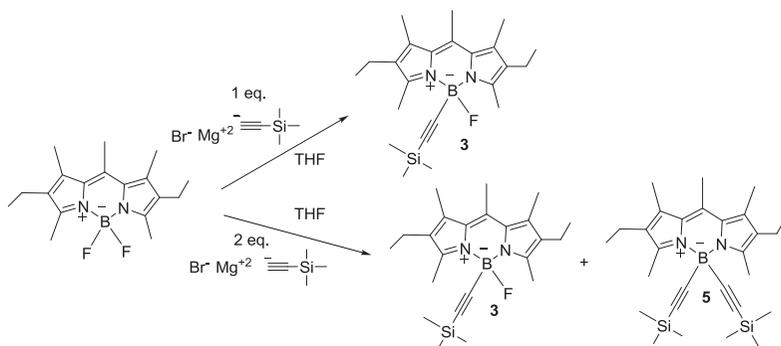
BODIPY core (Goze et al. 2006; Goze et al. 2007). *E*-BODIPY compounds offer the potential for further modification when the substituting nucleophile is an ethynyl group, including nucleophilic addition to and polymerization of the compound at the alkyne site (Goze et al.

2006; Nagi et al. 2008, Nzeata & Hewavitharanga 2012).

The substitution of fluorine with an ethynyl anion can be accomplished by using a lithium organometallic reagent, Scheme 2, or a Grignard reagent, Scheme 3.



Scheme 2.—Synthesis of *E*-BODIPY using ethynyl anion generated with *n*-butyllithium.



Scheme 3.—Synthesis of E-BODIPY using ethynyl anion generated with a Grignard reagent.

According to our results (Nzeata & Hewavitharanage 2012; Hewavitharanage et al 2013) and those of others (Goze et al. 2006; Goze & Ziessel 2007), ethynyl nucleophiles reveal that only the disubstituted product can be produced when using a lithium reagent (Scheme 2), while either the monosubstituted or disubstituted

product can be produced when using a Grignard reagent (Scheme 3).

In an attempt to understand why this would happen with such similar reagents and identical nucleophiles, preliminary semi-empirical and density functional quantum chemical calculations of theoretical  $S_N2$  transition state energies

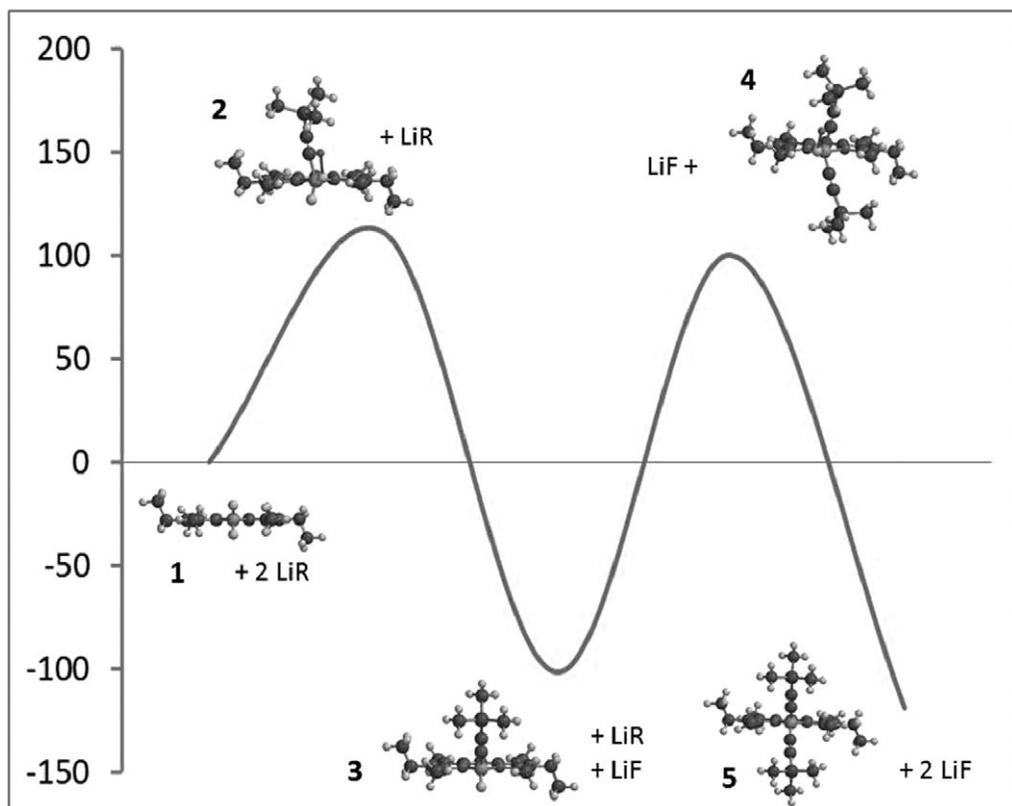


Figure 2.—Energy profile for the substitution of fluorine on F-BODIPY with lithium ethynyl anion. R = trimethylsilylacetylide anion.

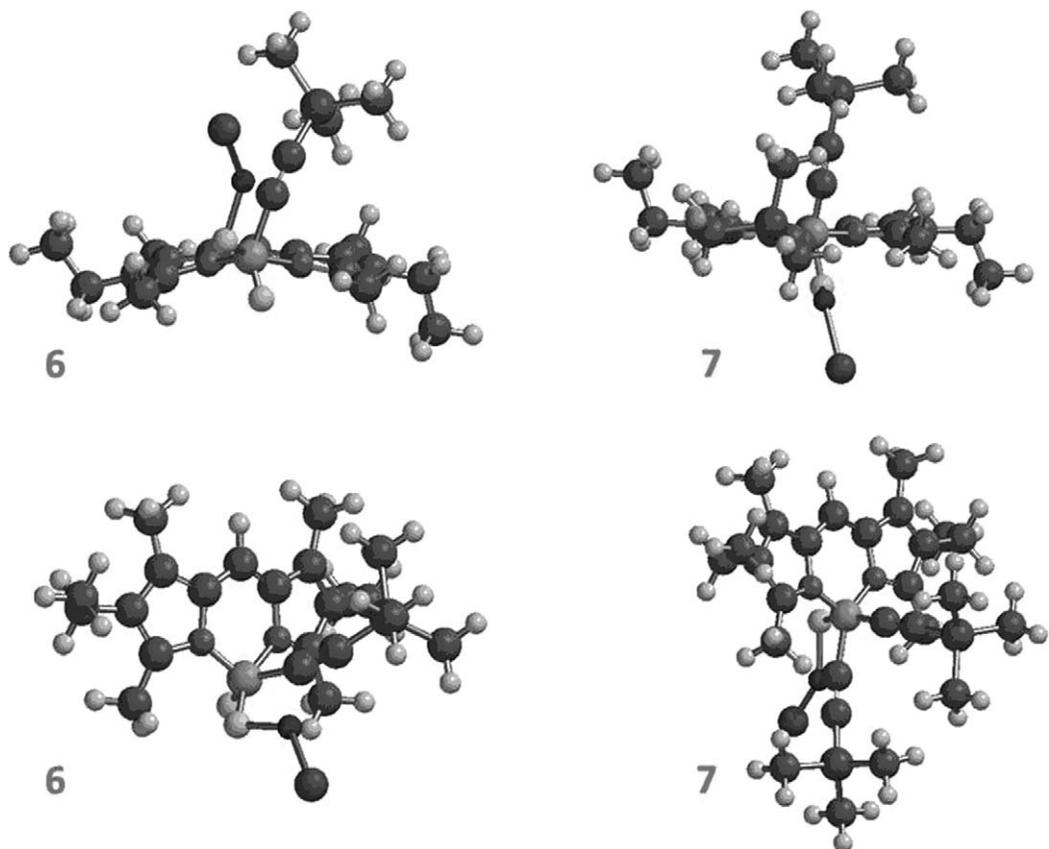


Figure 3.—Transition state models with Grignard reagent (6 for monosubstitution and 7 for disubstitution).

for the mono- and disubstituted BODIPY derivatives were performed. Models of the reagents, products, and reaction intermediates were also constructed in order to estimate the overall reaction energy profiles.

#### METHODS

All calculations were performed using SPARTAN '08 modeling software (Wavefunction, Inc). The transition state (TS) models were developed by full transition state geometry optimizations using semi-empirical PM3 calculations. Theoretical  $S_N2$  transition states were chosen for the models because both the reagents in question are strong nucleophiles and it aligns with the geometry of the reaction center. Additional IR frequency calculations were performed on each transition state, and each model showed only one imaginary frequency corresponding to ethynyl anion attack and fluoride departure. The reagents, products, and intermediates necessary to

develop reaction energy diagrams were obtained using full equilibrium geometry optimizations, also using semi-empirical PM3 calculations. Gas phase single point energy calculations were performed on all semi-empirical optimized transition states, reagents, products, and intermediates using density functional theory B3LYP 6-31G\* method (Laird et al., 1996; Salahub & Zerner, 1989; Elstner, 2007). These DFT values were used to determine activation energies and create reaction energy diagrams.

#### RESULTS AND DISCUSSION

Including the ethynyl anion's respective counter cation, either lithium or magnesium bromide, allowed for more realistic TS models with a coordination between the fluoride leaving group and the nucleophile's respective cation. Although inclusion of dimeric organometallic reagents and solvent molecules has been demonstrated both experimentally and

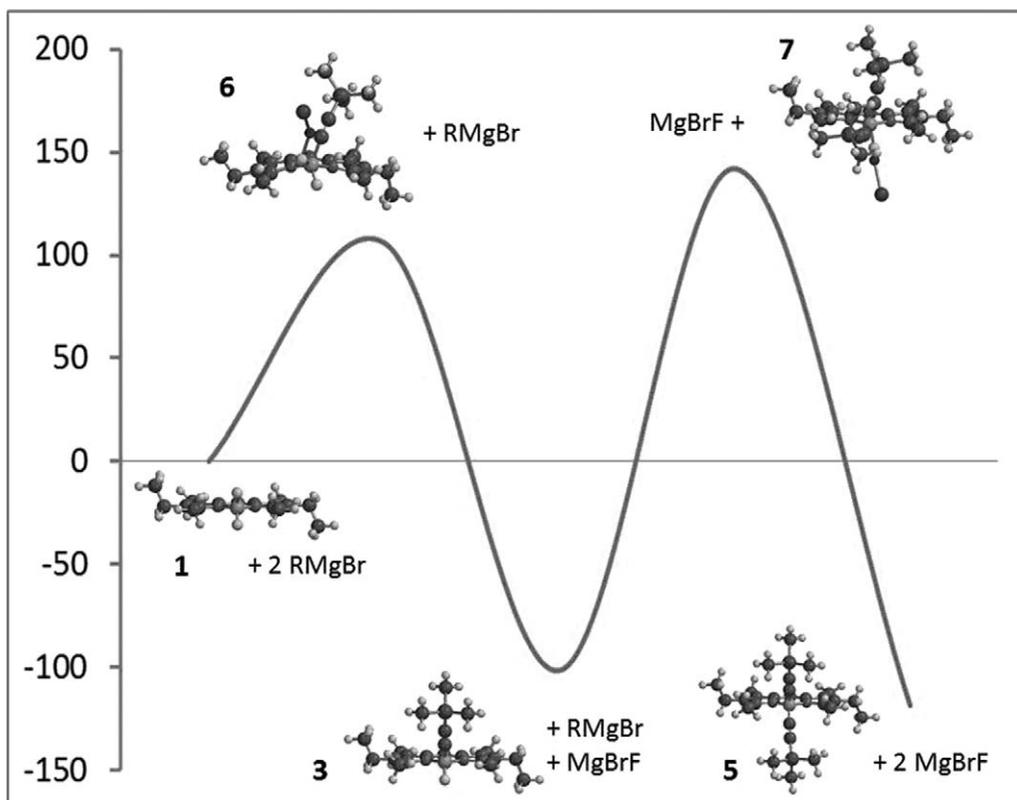


Figure 4.—Energy profile for the substitution of fluorine on F-BODIPY with magnesium bromide ethynyl anion. R = trimethylsilylacetylide anion.

computationally (Anders et al., 1996, Barbosa et al., 2011 and Mongin & Harrison-Marchand, 2013) to be important in reactions, we have opted for a more simplistic view in this preliminary study.

The lithium transition states (Figure 1) and energy profile (Figure 2) are considered first followed by the Grignard transition states (Figure 3) and energy profile (Figure 4).

**Lithium organometallic reagent.**—Both the monosubstituted and disubstituted transition states, **2** and **4** respectively, for the ethynyl substitution of fluorine with a lithium counter cation displayed unconventional geometry at the trigonal bipyramidal boron center. The ethynyl anion was found to attack in the axial position while the leaving fluoride ion, coordinated with a lithium cation, was in the equatorial position. All attempts to construct a conventional  $S_N2$  transition state were unsuccessful.

The reaction energy profile, along with transition state, reactant, and product models

can be viewed in Figure 2. All reported activation energies are based on single point DFT values and are relative to the starting materials, which were considered 0 kJ/mol. Transition states **2** and **4** have relative activation energies of 111.3 kJ/mol and 100.0 kJ/mol, respectively. Since the activation energy of the second substitution is lower than that of the first,  $\Delta\Delta E = -11.3$  kJ/mol, then there is necessarily enough energy in the system to support the second substitution. Also, the disubstituted product, **5**, has a lower relative energy than the F-BODIPY starting compound, **1**, and the monosubstituted product, **3**, implying that it is the most thermodynamically stable of the three compounds. This theoretical evidence supports the finding that only the disubstituted product is formed when using lithium organometallic reagents.

**Grignard reagent.**—Unlike the substitution of fluorine by an ethynyl anion with a lithium counter ion, the use of an ethynyl anion with a

magnesium bromide counter ion displays “text-book” transition state geometry. The mono-substituted and disubstituted transition states, **6** and **7** respectively (Figure 3 and Figure 4), had the ethynyl anion attacking the trigonal bipyramidal boron center in the axial position and the leaving group fluorine, coordinated with magnesium bromide, in the second axial position. All attempts to construct an unconventional S<sub>N</sub>2 transition state model were unsuccessful.

Figure 4 depicts the reaction energy profile, along with the transition state, reactant, and product models. The relative activation energies of **6** and **7** are 106.0 kJ/mol and 141.9 kJ/mol, respectively. Since the activation energy of the second substitution is considerably higher than that of the first substitution,  $\Delta\Delta E = 35.9$  kJ/mol, then there must be extra energy added to the system in order to encourage the formation of the disubstituted product. The formation of **3** requires significantly less energy than the formation of **5**. The relative energy of **3** is much lower than that of **1**, and the relative energy of **5** is only slightly lower than **3**. This means that the products are indeed more stable than the starting compound, but the activation energy required to form the transition state **7** is greater than that of **4**. Thus, the formation of the monosubstituted product prevails when using a Grignard reagent at 0°C. Goze et al. (2006) have shown that the addition of energy by raising the reaction temperature will allow the formation of the disubstituted product; this is supported by the data we have gathered.

In summary, the density functional theory single point energy calculations we performed on the semi-empirical PM3 optimized S<sub>N</sub>2 transition state models provided data that is consistent with our experimental results and those of others. That is, use of a lithium reagent to substitute for fluorine at the boron center in *F*-BODIPY will yield only the disubstituted product and use of a Grignard is capable of yielding both the mono- and disubstituted products. In the case of the lithium reagent, this is due to lower activation energy for the second substitution. This means that if the first substitution can occur, then there is necessarily enough energy in the system to support the second substitution. In the case of the Grignard reagent, the monosubstituted product is achievable at 0 °C because the activation energy for the second substitution is higher than that

of the first. However, when the reaction is performed at room temperature the increased amount of energy present in the system due to thermal excitation the disubstituted compound is the major product. From these calculations, it appears that the nucleophile dependent counter cation has an impact on the transition state energies and course of the ethynyl substitution of *F*-BODIPY. This is an indication that full DFT geometry optimizations and perhaps inclusion of solvent molecules, are worth pursuing using theoretical S<sub>N</sub>2 transition states in order to get more realistic values for the reaction energy profiles.

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