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An Unprecedented Electronic Preference for the "Meta" Product in Diels–Alder Reactions of Ethynyldialkylboranes. [(Trimethylsilyl)ethynyl]-9-BBN as a Reactive and Versatile Dienophile

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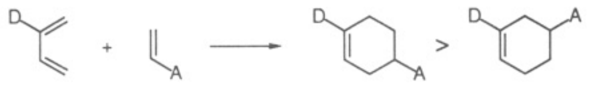
Summary: [(Trimethylsilyl)ethynyl]-9-BBN undergoes Diels–Alder reactions with acyclic dienes at 100 °C to afford 1,4-cyclohexadienes in high yields. The novel regiochemistry of these reactions is consistent with an ab initio prediction of advanced bonding to boron in a [4 atom + 3 atom] transition state.

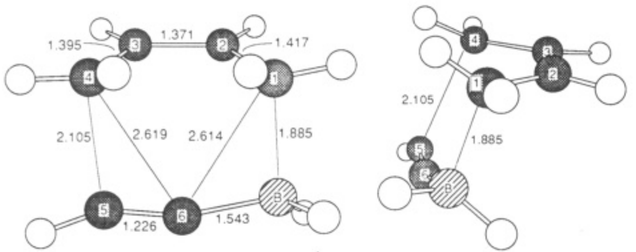
We have reported that vinyldialkylboranes are exceptional dienophiles.[1] Recently, the unique features of the Diels–Alder reactions of vinylboranes have been explained by ab initio calculations predicting a [4 atom + 3 atom] transition state.[2] We report here some promising first examples of Diels–Alder reactions of ethynyldialkylboranes[3] and theoretical and experimental results detailing the unprecedented and mechanistically significant regiochemistry of these reactions.

In Diels–Alder reactions of simple 2-alkyl- or 2-alkoxybutadienes with activated dienophiles, there is preferential formation of the 1,4-disubstituted ("para") product over the 1,3-disubstituted ("meta") product. Although the regiochemistry of more complex reactions is not always so predictable, the electronic preference for the para product in simple reactions has been invariable. Diels–Alder reactions with vinylboranes follow this rule; although steric factors are often important, normal regioisomeric products are preferred in the absence of steric effects.[1c]



D = R, OR
A = CHO, C(O)R, CO_2R, SO_2R, CN, BR_2, $P(O)(OEt)_2$, NO_2, etc.

We were therefore intrigued when ab initio calculations suggested a different regiochemical outcome for Diels–Alder reactions of ethynylboranes. The fully optimized transition state for the reaction of ethynylborane with butadiene at the RHF/3-21G level is shown in **1**.[4] The [4 atom + 3 atom] character of **1** is similar to that predicted by calculations with vinylboranes, but **1** is unique in that the bonding between C_1 and B is significantly more advanced than the bonding between C_4 and C_5. The asynchronicity of **1** is "reversed" from that predicted for vinylborane transition states. The advanced bonding of C_1 with B results in a relatively positive charge on C_2 compared to C_3 (0.17 e difference in 6-31G* Mulliken charges). Thus, the stabilizing effect of a donating substituent on C_2 should lead to a preference for the meta product.



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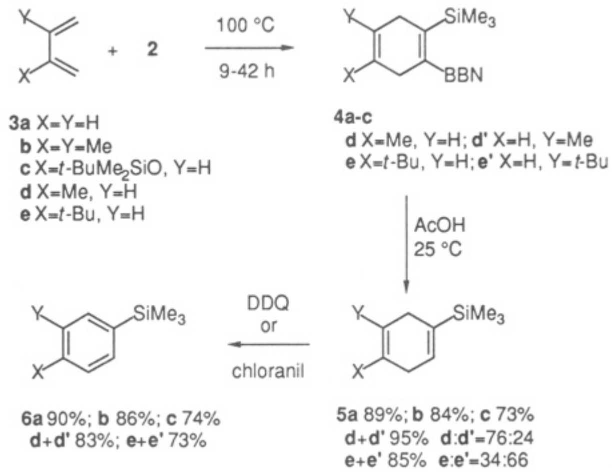
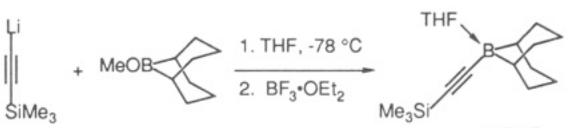
Scheme I



Experimental studies paralleled these calculations. Due to the low stability of unsubstituted ethynylboranes[5,6] and our prior observation that a trimethylsilyl substituent had little effect on the reactivity of vinylboranes,[7] [(trimethylsilyl)ethynyl]-9-BBN (**2**) was chosen for initial studies. Using the general method of Brown,[5] **2**·THF was readily available in 97% yield by reaction of the adduct of (trimethylsilyl)ethynyllithium and *B*-methoxy-9-BBN with boron trifluoride etherate (eq 1). The crystalline **2**·THF is air-sensitive but appears to be indefinitely stable when kept in a freezer under an inert atmosphere.



2·THF (1)

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(1) (a) Singleton, D. A.; Martinez, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 7423. (b) Singleton, D. A.; Martinez, J. P.; Watson, J. V. *Tetrahedron Lett.* **1992**, *33*, 1017. (c) Singleton, D. A.; Martinez, J. P.; Watson, J. V.; Ndip, G. M. *Tetrahedron*, in press.

(2) Singleton, D. A. *J. Am. Chem. Soc.*, in press.

(3) Acetylenic boronic esters are poor dienophiles: Matteson, D. S.; Peacock, K. *J. Am. Chem. Soc.* **1962**, *82*, 5759. Woods, W. G.; Strong, P. L. *J. Organomet. Chem.* **1967**, *7*, 371.

(4) (a) Calculations were carried out using the GAMESS program. A frequency calculation on **1** found only one imaginary frequency. When structure **1** was displaced slightly along the transition vector toward product and then minimized, 1,4-cyclohexadienylborane was formed. No intermediate was found after the transition state, but a more systematic search would be necessary to ensure that none is present. (b) In ref 2, the qualitative features of the CASSCF transition structure were reproduced at the RHF/3-21G level.

(5) Brown, H. C.; Sinclair, J. A. *J. Organomet. Chem.* **1977**, *131*, 163.

(6) Köster, R.; Horstschäfer, H. J.; Binger, P. *Liebigs Ann. Chem.* **1968**, *717*, 1.

(7) Singleton, D. A.; Martinez, J. P. *Tetrahedron Lett.* **1991**, *32*, 7365.

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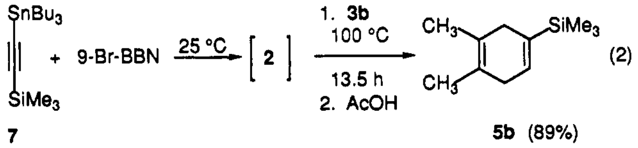
A variety of dienes (**3a–e**) reacted smoothly with **2** at 100 °C (Scheme I). As is normal for acetylenic dienophiles, **2** was less reactive than the corresponding vinylborane, but the formation of Diels–Alder adducts (**4a–e**) was clean and quantitative by NMR. Workup of **4** with acetic acid afforded cyclohexadienes **5** (contaminated by 2–10% of aromatized **6**) in excellent yield. The regiochemistry of these reactions was readily determined after the DDQ- or chloranil-mediated conversion of **5** to **6**. The difficulties associated with the isolation and manipulation of the air-sensitive **2**·THF may be avoided by forming **2** in situ (eq 2).[8] The formation of **2** from 9-bromo-9-BBN and [(trimethylsilyl)ethynyl]tributyltin[9] (**7**) appeared by NMR to be instantaneous and quantitative at 25 °C. The absence of the weakly complexing THF made little difference in the reactivity of **2**; the reaction of **3b** with **2** formed in situ proceeded at 100 °C, as with **2**·THF, to afford **5b** in 89% yield after an acetic acid workup.



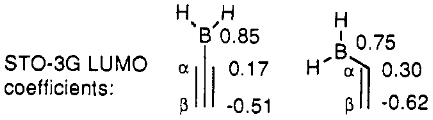
(2)

7

5b (89%)

The unusual regiochemistry of these reactions is apparent. 2-(*tert*-Butyldimethylsiloxy)butadiene (**3c**) afforded the adduct **4c**, with a meta orientation of siloxy and BBN groups,[10] as the only observable regioisomer. With isoprene, the meta adduct **4d** was preferentially formed over the para adduct **4d′**. If this preference for the meta products (**4c** and **4d**) was due to some unknown steric factor, enhanced formation of the meta product would be expected with 2-*tert*-butylbutadiene. Instead, a majority of the para product (**4e′**) was formed with 2-*tert*-butylbutadiene, indicating that sterics favor the para product while electronic effects favor the meta product. Thus, the regiochemistry of the reactions of **2** is consistent with the ab initio prediction.

This regiochemistry is difficult to explain in any other way. The "normal" regiochemistry of Diels–Alder reactions has most popularly been rationalized either by FMO[11] theory or by postulating a *biradicaloid*[12] transition state. Because boranes are powerful radical-stabilizing groups,[13] the observed regiochemistry with **2** would not be expected of a biradicaloid transition state. If only the LUMO coefficients in the reacting π bond of ethynylborane are considered, FMO theory also predicts the regiochemistry incorrectly. However, the regiochemistry is predictable from FMO theory based on the large LUMO coefficient on boron, once it is recognized that the boron is not an "innocent bystander" in these reactions. The advanced bonding of C_1 and B in **1** may be understood as the normal preferential bonding with the atom of the dienophile having the largest LUMO coefficient. In contrast, the LUMO of vinylborane is more evenly distributed between B and C_β, and low regioselectivity is observed in the absence of steric effects.



From a synthetic standpoint, products such as **4c** should be extremely versatile building blocks for further synthetic elaboration. Diels–Alder reactions of ethynylboranes should find broad use in organic synthesis, and we are continuing to explore both their synthetic utility and their intriguing physical organic properties.

Acknowledgment. We thank the Institute of General Medical Sciences of the National Institutes of Health and The Robert A. Welch Foundation for support of this research.

Supplementary Material Available: Experimental procedures and spectral data for all reactions, and the final geometry and energy of **1** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(8) For a similar procedure for vinylboranes, see: Singleton, D. A.; Martinez, J. P.; Ndip, G. M. *J. Org. Chem.* In press.

(9) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.

(10) A trimethylsilyl group has little effect on the regiochemistry of Diels–Alder reactions. For examples, see: Hayama, T.; Tomoda, S.; Takeuchi, Y.; Nomura, Y. *J. Org. Chem.* **1984**, *49*, 3235. Kloek, J. A. *J. Org. Chem.* **1981**, *46*, 1951. Hermeling, D.; Schäfer, H. J. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 233.

(11) For a leading reference to the application of FMO theory to the regioselectivity of Diels–Alder reactions, and a discussion of its limitations, see: Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, L. E. *J. Am. Chem. Soc.* **1986**, *108*, 7381.

(12) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771.

(13) Pasto, D. J.; Krasnansky, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062. Coolidge, M. B.; Borden, W. T. *J. Am. Chem. Soc.* **1988**, *110*, 2298.

Generation and Use of a Zinc Derivative of a Functionalized 1,3-Oxazole. Solution of the Virginiamycin/Madumycin Oxazole Problem

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Summary: 2-(Bromomethyl)-4-carbethoxy-1,3-oxazole reacts with Zn dust to give a new heteroaromatic "benzylic" organozinc derivative which undergoes nucleophilic addition to a variety of aldehydes and ketones; application to the synthesis of virginiamycin and other streptogramin antibiotics is envisioned.

Efforts in our laboratory have been aimed at the synthesis of members of the type A family of streptogramin

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