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The Participation of Alkynylboronates in Inverse Electron Demand [4 + 2] Cycloadditions: A Mechanistic Study

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Abstract: The participation of alkynylboronates in [4 + 2] cycloadditions has been investigated using both kinetic and DFT studies. Kinetic studies of the cycloaddition of tetrazine **1** with alkynylboronate **2** strongly suggest that a concerted cycloaddition mechanism is in operation. This mechanism has been confirmed by DFT calculations; moreover, a highly synchronous transition state appears to operate in this process. The experimentally observed poor reactivity of electron-rich dienes with alkynylboronates has also been confirmed by theoretical studies by analyzing the transition states of the cycloadditions with bis-2,5-trimethylsilyloxyfuran. The surprising conclusion has been made that alkynylboronates are relatively electron rich and have a cycloaddition reactivity that resembles that of acetylene. In contrast, the related dichloroalkynylborane cycloaddition reactivity resembles that of dimethylacetylene dicarboxylate.

Introduction

Aromatic and heteroaromatic boronic acids and esters represent one of the most heavily utlilised classes of synthetic intermediates in recent times.[1] These compounds have traditionally been prepared from appropriate aryl organolithium or Grignard reagents;[2] however, a milder Pd-catalyzed variant[3] has also received significant attention. In addition, the employment of C−H activation processes toward this class of compounds has shown promise as it avoids the preparation of a precursor aromatic halide or triflate.[4] An alternative strategy to these intermediates that has gained widespread attention of late is the employment of cycloaddition processes of alkynylboronates.[5] Indeed, this approach has allowed a wide variety of benzenoid-based boronic ester intermediates[6,7] as well as heterocyclic variants[8] to become available from relatively simple starting materials.

Although our preliminary studies focused on a Cr-mediated benzannulation process for the synthesis of functionalized aromatic boronic ester intermediates,[6a,b] we ultimately sought to obviate the requirement for a stoichiometric organotransition metal intermediate and attempted to design routes that were "metal-free". Indeed, we have been able to realize this goal and, to-date, have reported three complementary reaction processes that fulfill the criteria of generating functionalized arylboronates from simple alkynes in the absence of a transition metal promoter. Specifically, as outlined in Figure 1, the use of cyclopentadienones,[7a] tetrazines,[8f] and 2-pyrones[7c] as diene components provides direct access to highly functionalized organoboron intermediates.

The reactions highlighted in Figure 1 show an interesting trend: the alkynylboronates appear to perform as inverse

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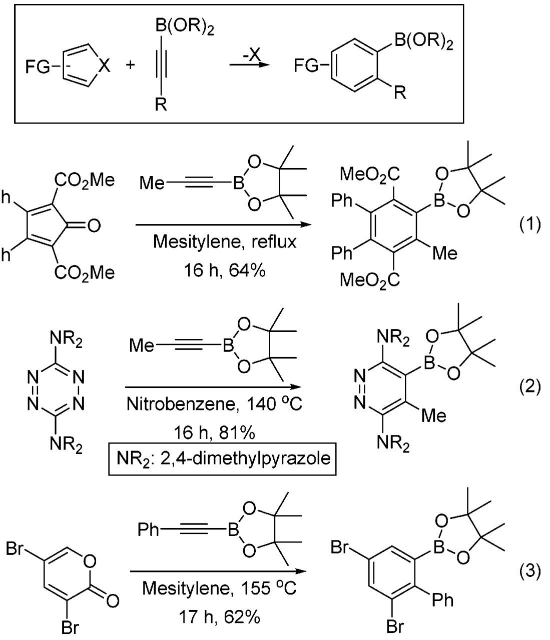

Figure 1.

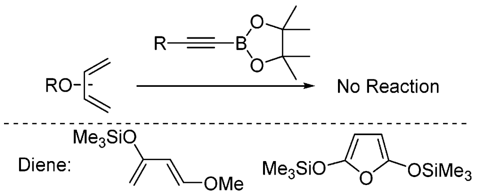

Figure 2.

electron demand dienophiles. This is surprising in view of the fact that alkynylboronates may be viewed as electrophilic reagents. For example, their ^{13}C signal for the β-carbon atom appear at lower field relative to alkylacetylenes (δ 85−95 ppm versus δ 70−80 ppm).[6c] Furthermore, attempts to perform Diels−Alder cycloadditions with electron-rich dienes such as those outlined in Figure 2 were unsuccessful and the corresponding cycloadducts could not be obtained (Figure 2).

This apparently counter-intuitive reactivity profile encountered in [4 + 2] cycloaddition reactions of alkynylboronates was intriguing and in contrast to the corresponding reactions of alkynylboranes and dichloroalkynylboranes. Specifically, experimental and theoretical studies by Singleton[9] and Goodman[10] have demonstrated that alkynylboranes undergo cycloaddition with electron-rich dienes to afford a mixture of Diels−Alder and 1,4-alkynylboration products. These investigations highlighted the potential of a nonclassical [4 + 3] transition state involving advanced bonding of the diene to the boron atom.[11]

In an effort to rationalize the observed reactivity profiles of alkynylboronates in diene cycloadditions, we decided to explore the mechanism of these processes further. Specifically, we outline herein the results of our kinetic investigations on the reaction of alkynylboronates with tetrazines (Figure 1, eq 2), and we also describe the results of theoretical DFT investigations into the cycloaddition reactions of electron-rich and electron-deficient dienes with alkynylboronates that provides a rationale for the observed reactivity trends highlighted in Figures 1 and 2 above.

Results and Discussion

Before embarking on theoretical studies, we decided to establish that alkynylboronates could reasonably react by a concerted cycloaddition mechanism. We decided to study the kinetics of the Carboni−Lindsey reaction of a representative alkynylboronate **2** with tetrazine **1** because this reaction was high yielding and could be easily followed by monitoring the disappearance of the strong $n \rightarrow \pi^*$ absorption of the tetrazine at $\lambda = 533$ nm by UV spectrometry. Experiments were run under pseudo-first-order conditions at 140 °C in nitrobenzene.

Pleasingly, the kinetics indicated that the reaction was pseudo-first order with respect to the tetrazine under these conditions, and as outlined in Figure 3, measurement of the reaction rate at four different alkyne concentrations allowed us to establish a second-order rate constant of for this reaction at 140 °C in nitrobenzene; $k_2 = 2.227 \times 10^{-2}$ L mol^{-1} s^{-1}. Finally, an Eyring plot allowed us to establish that $\Delta S^{\ddagger} = -41$ cal mol^{-1} K^{-1}, in agreement with a highly ordered rate-determining transition state, as expected for a concerted cycloaddition. Having obtained experimental confirmation that a concerted cycloaddition reaction of alkynylboronates with electron deficient dienes was possible, we turned our attention to the use of ab initio methods to further probe the nature of cycloaddition processes of alkynylboronates and related compounds.

Computational Methods

All structures were optimized using the functional B3LYP[12] and the 6-31G* basis set as implemented in Gaussian 03.[13] Density Functional Theory has been shown to reliably predict the results of [4 + 2] Diels−Alder and other pericyclic reactions.[14] All energy minima and transition structures were characterized by frequency analysis. The energies reported in this work include the zero-point vibrational energy corrections (ZPVE) and are not scaled. The stationary points were characterized by frequency calculations in order to verify that they have the right number of negative eigenvalues. The intrinsic reaction coordinates (IRC)[15] were followed to verify the energy profiles connecting each TS to the correct local minima. Wiberg bond orders[16] and atomic charges were calculated within the natural bond orbital (NBO) analysis.[17]

Theoretical Results

The most striking aspect of the aforementioned reaction can be summarized as the inability of alkynylboronate **3** to react with electron-rich dienes such as bis-2,5-trimethylsilyloxyfuran

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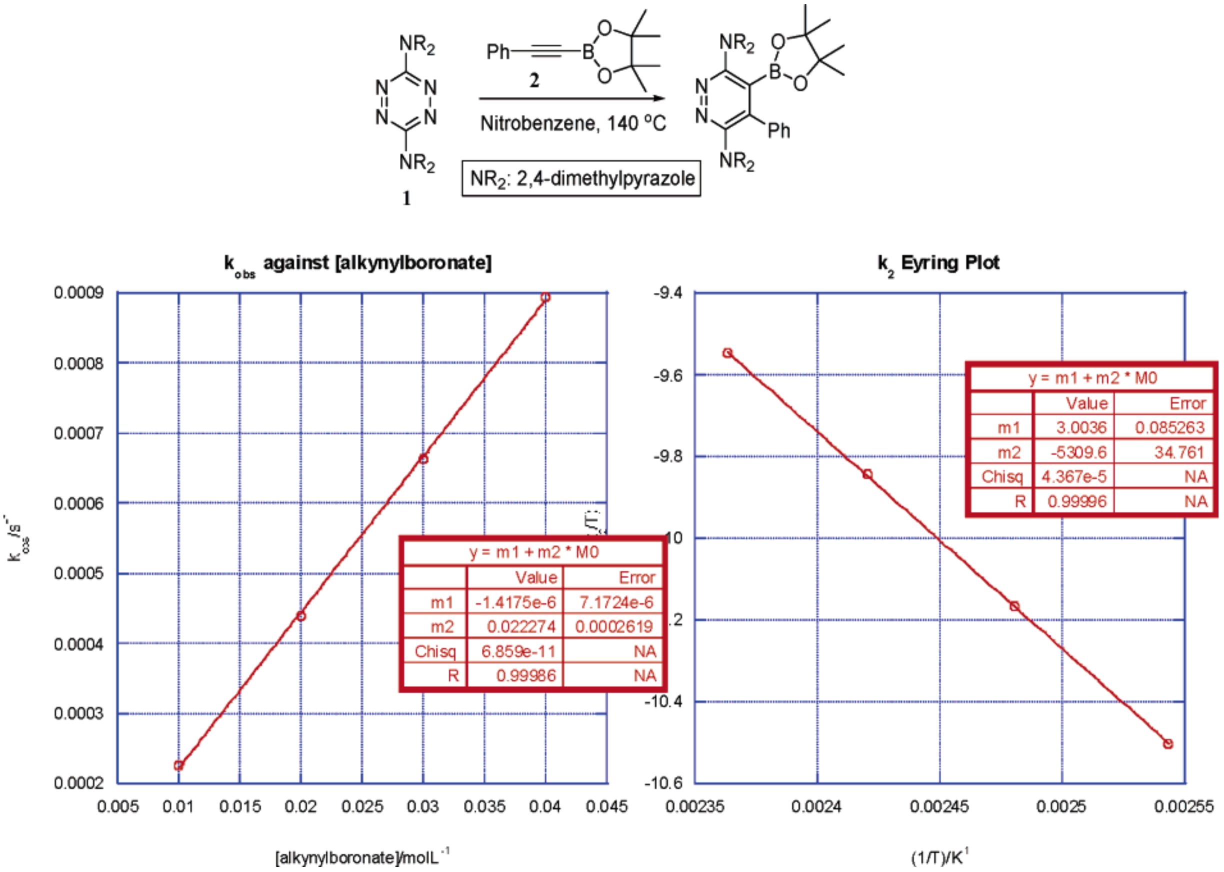

Figure 3. Kinetic measurements and Eyring plot for the cycloaddition between **1** and **2**.

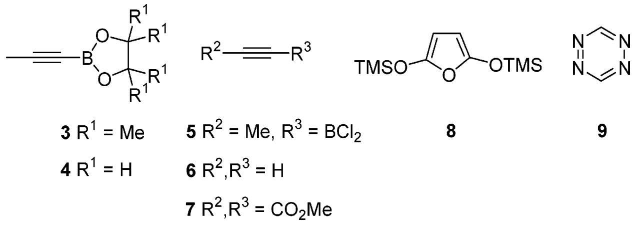

Figure 4. Alkynes **3**−**7** and dienes **8**−**9** used as models for the computational studies.

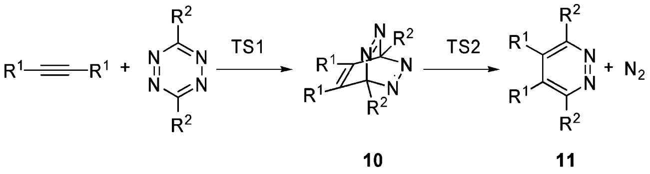

Figure 5. Mechanism for the Diels−Alder reaction of alkynes with tetrazines.

8 whereas it easily reacts with tetrazine **9** (Figure 4).[8f] In an effort to offer a rationale for this phenomenon, we performed a DFT analysis of a series of DA reactions between electron-rich and electron-poor dienes and different alkynylboron based dienophiles. Apart from the experimentally studied alkynylboronate **3**,[8f] we chose two other boron substituted alkynes with different steric and electronic properties at boron (**4** and **5**), as well as two other symmetrical alkynes (**6** and **7**), as examples of poor and good dienophiles respectively. To get some insight for the preference that alkynylboronates exhibit toward electron deficient dienes, we calculated all the possible transition structures for the Diels−Alder reactions employing substrates in Figure 4, and characterized their electronic features by analysis of the global electrophilicity indexes and the energies of the HOMO−LUMO orbitals.

Before discussing the computational results there are two considerations that deserve comment. First, the inverse electron demand Diels−Alder reactions between tetrazines and alkynes afford pyridazines (e.g., **11**, Figure 5).[18] The bicyclic intermediates (e.g., **10**) have never been observed and are instead further transformed into the final product **11** after nitrogen loss (Figure 5). Recent computational studies have shown that this reaction proceeds through two sequential transition states, with a very low or almost nonexistent barrier for the second step (TS2).[19] Therefore, for the present study of the reactivity of tetrazines with alkynes we only focused on the description of the first step (TS1), which determines the feasibility of the reaction.

Second, two different main mechanisms have been found for the Diels−Alder reactions of alkynyldichloroboranes ($RBCl_2$, e.g. **5**) and alkynylboranes (RBH_2) with all-carbon dienes; the classical [4 + 2] cycloaddition pathway, and a [4 + 3] mechanism that involves a strong carbon-boron interaction Diels−Alder.[9,10] However, we were unable to locate a similar [4 + 3] transition state for the reaction between furan **8** and **5**, and instead, only the corresponding classical [4 + 2] seems to

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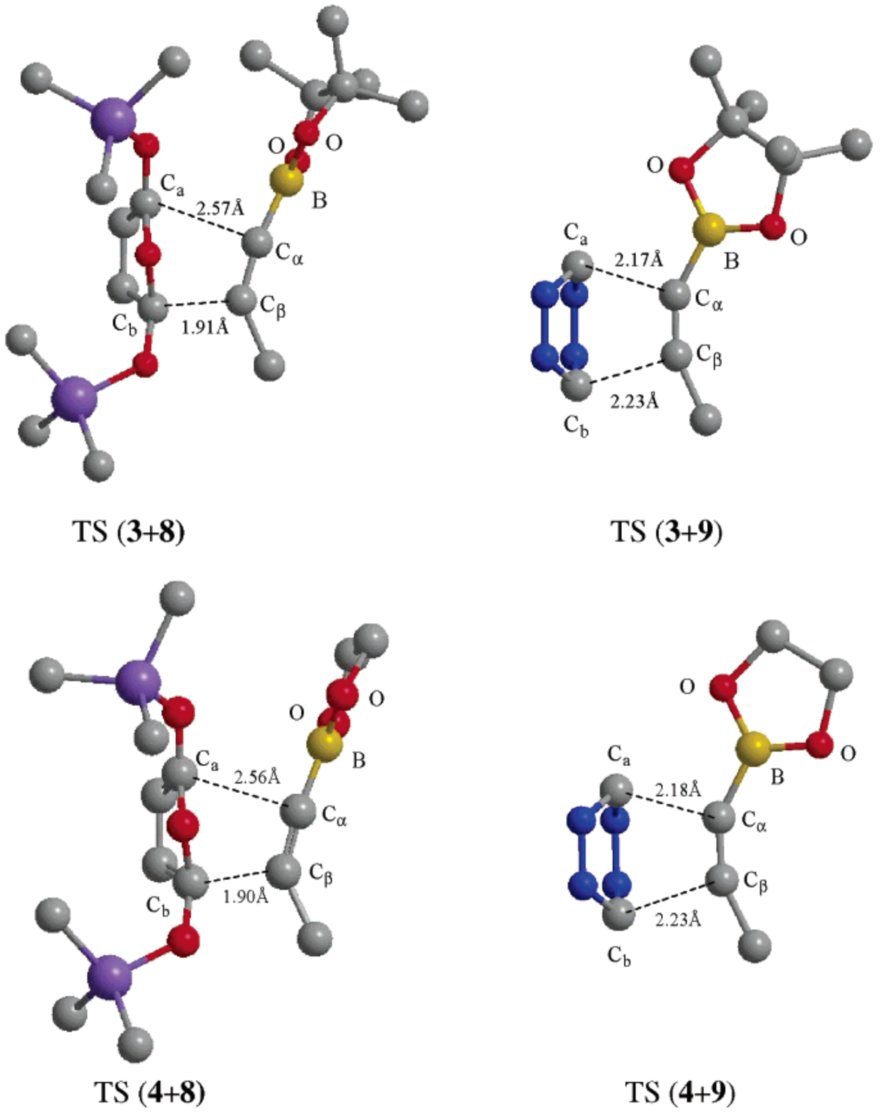

TS (**3**+**8**) TS (**3**+**9**)

TS (**4**+**8**) TS (**4**+**9**)

Figure 6. B3LYP/6-31G* optimized transition state geometries for reactions between dienes **8**/**9** and alkynylboronates **3**/**4**.

be operative.[20] Cossío et al. have found that [4 + 3] vs [4 + 2] character of transition state is strongly affected by the substituents on boron,[21] and that the [4 + 3] character of certain cycloadditions of boryldienes (RBH_2) gradually disappears as oxygen atoms are attached at boron (i.e., cyclic boronates), which show a larger [4 + 2] character. This behavior is due to the donating effect of the oxygen on the unoccupied pz orbital of the boron that reduces its Lewis acid character. Accordingly, we did not find any transition state associated with a [4 + 3] cycloaddition pathway for any reaction involving alkynylboronates **3** or **4** with dienes such as cyclopentadiene, Danishefsky's diene or furan **8**. Instead, we found a classical [4 + 2] transition state for the reaction between **3** and **8** (Figure 6). Therefore, we focused on the [4 + 2] transition states of the reactions between substrates in Figure 4.

Given these assumptions, we first computed the reactions of alkynylboronate **3** with furan derivative **8** and tetrazine **9**. In accordance with the experimental results, the computed activation energy of the DA reaction between alkynylboronate **3** and furan derivative **8** (26.26 kcal/mol) is much higher than that of the corresponding reaction with tetrazine **9** (20.42 kcal/mol). The comparatively high barrier found for the former reaction is in agreement with a very slow or inappreciable reaction.

It is evident that the transition states (**3**+**8**) and (**3**+**9**) shown in Figure 6 correspond to slightly different reaction mechanisms. The reaction with the electron-deficient tetrazine (**3**+**9**) is concerted and highly synchronous and the new C−C bonds are formed symmetrically. The computed bond orders of the two forming C−C bonds in the transition state are very similar 0.32 ($C_\alpha-C_a$) and 0.29 ($C_\beta-C_b$), and so are the distances, 2.17 Å ($C_\alpha-C_a$) and 2.23 Å ($C_\beta-C_b$). In contrast, the reaction between the alkynylboronate and furan derivative (**3**+**8**) is very asynchronous. The Wiberg bond orders are 0.201 for $C_\alpha-C_a$ and 0.523 for $C_\beta-C_b$, and the distances are 2.57 Å ($C_\alpha-C_a$) and 1.91 Å ($C_\beta-C_b$). The latter bond is half formed but, in spite of the asynchronicity, the reaction is still concerted as demonstrated by intrinsic reaction coordinate (IRC) calculations.

The mechanistic differences between dienes **8** and **9** are applicable for their DA reactions with all dienophiles (**3**−**7**) studied. Tetrazine **9** shows very symmetrical and synchronous

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[20] In preliminary studies we could actually locate related [4 + 2] and [4 + 3] transition states for the reaction between **5** and cyclopentadiene.

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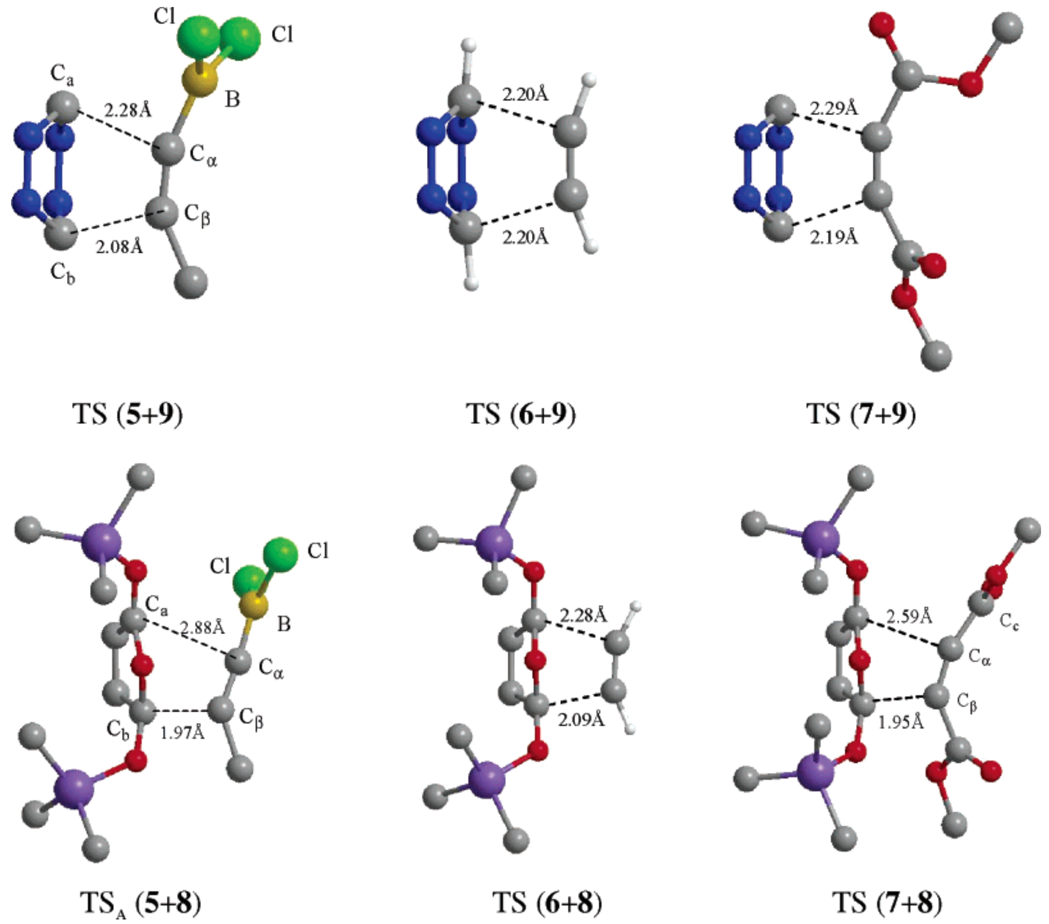

TS (**5**+**9**) TS (**6**+**9**) TS (**7**+**9**)

TS_A (**5**+**8**) TS (**6**+**8**) TS (**7**+**8**)

Figure 7. B3LYP/6-31G* optimized transition state geometries for reactions between dienes **8**/**9** and alkynes **5**/**6**/**7**.

Table 1. Activation Energies, Wiberg Bond Order Indexes, and Bond Distances (Å) in the Transition States

	activation energies[a]	Wiberg bond orders				bond distances (Å)	
		$B–C_\alpha$	$C_\alpha–C_a$	$C_\beta–C_b$	C_a-B	$C_\alpha–C_a$	$C_\beta–C_b$
8+**3**	26.26	1.021	0.201	0.523	0.026	2.57	1.91
8+**4**	26.02	1.025	0.199	0.526	0.029	2.56	1.90
8+**5**	17.97	1.195	0.083	0.469	0.043	2.88	1.97
8+**6**	25.88		0.301	0.380		2.28	2.09
8+**7**	16.18		0.176	0.472		2.59	1.95
9+**3**	20.42	0.899	0.324	0.291	0.006	2.17	2.23
9+**4**	21.01	0.902	0.324	0.291	0.005	2.18	2.23
9+**5**	24.78	0.957	0.281	0.373	0.034	2.28	2.08
9+**6**	19.38		0.305	0.305		2.20	2.20
9+**7**	21.05		0.259	0.297		2.29	2.19

[a] Activation energy in kcal/mol.

transition states in all cases (Figure 7). The distances of all forming bonds are in the range of 2.1−2.3 Å and bond orders are between 0.28 and 0.37 (Table 1). In contrast, furan **8** shows asynchronous transition states for all alkynes, with larger Wiberg bond index values for the forming $C_\beta−C_b$ bond and smaller values for $C_\alpha−C_a$. Consequently, the $C_\beta−C_b$ bond distances are in all cases shorter than $C_\alpha−C_a$ distances. The degree of asynchronicity with respect to the dienophiles increases in the order **6** < **3** ≈ **4** < **7** < **5**, (Table 1). The highest asynchronicity is observed in the reaction between **5** and **8**, with bond order values of 0.469 and distance of 1.97 Å for the more advanced $C_\beta−C_b$ bond and 0.083 for the less formed $C_\alpha−C_a$ bond (2.88 Å) (Figure 7). Even the transition state of acetylene dicarboxylate and furan derivative (**7**+**8**) is very asynchronous,[22] in spite of the fact that both reaction partners are completely symmetrical.

Furthermore, the reaction is concerted for alkynes **3**, **4**, **6**, and **7** but stepwise for alkynylborondichloride **5**, as demonstrated by intrinsic reaction coordinate (IRC). In this case, the transition state TS_A(**5**+**8**) actually corresponds to the first step, formation of the $C_\beta−C_b$ bond, which appears half-formed in the transition state (bond order of 0.469). We could locate the corresponding zwitterionic intermediate (Figure 8), where a negative charge develops at C_α, and the three atoms C_α, C_β, and B are found in an almost linear arrangement (dihedral angle $C_\alpha−C_\beta−B$ of 175.0°) to maximize the overlap between the occupied pz orbital in C_α and the unoccupied pz orbital in boron that are now parallel to each other. The intermediate **10** lies 15.7 kcal/mol higher in energy than the starting reactants. The second step involves the formation of the $C_\alpha−C_a$ bond, but as can be seen from the energy data, the very low activation energy between the intermediate and TS_B (0.2 kcal/mol) suggests the presence of a flat region connecting the first transition state and the final product (Figure 8). We can therefore conclude that the reaction between **5** and **8** proceeds through two sequential transition states. The final Diels−Alder adduct **11** is 4.1 kcal/mol more stable than the starting materials. It is noteworthy that this finding is not relevant for an overall view of the differences in reactivity between the different alkynes, because it does not have

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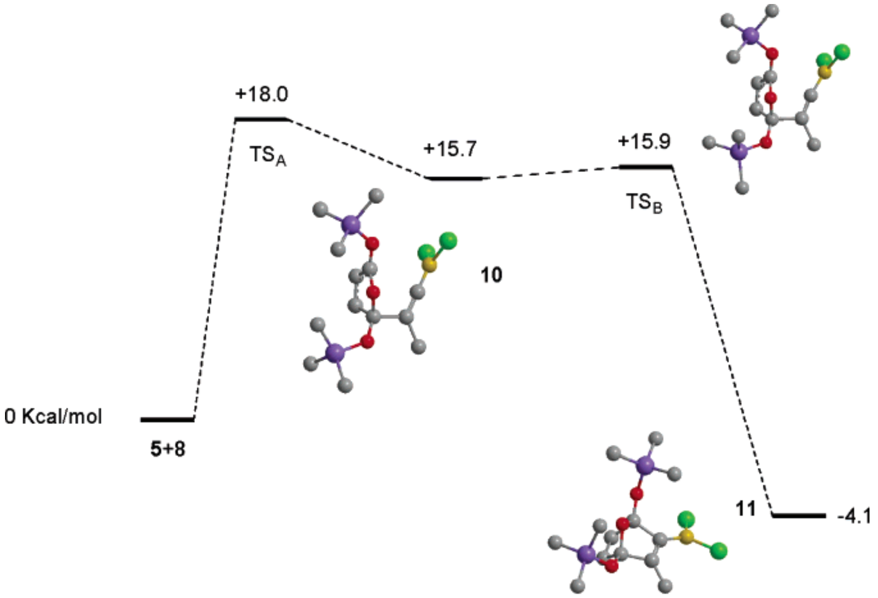

Figure 8. Stepwise Diels−Alder reaction between furan **8** and alkyne **5**. Energies are given in kcal/mol and refer to the ground state of reactants **5** and **8** as 0 kcal/mol.

Table 2. Charge[a] at Boron and the C−C Triple Bond (C_α and C_β) at the Transition State

transition state	B	C_α	C_β	heteroatom
8+**3**	1.043	−0.396	−0.026	−0.742 (O)
8+**4**	1.033	−0.398	−0.024	−0.725 (O)
8+**5**	0.391	−0.414	0.009	−0.196 (Cl)
8+**6**		−0.298	−0.281	
8+**7**		−0.156	−0.111	
9+**3**	1.102	−0.363	0.089	−0.730 (O)
9+**4**	1.100	−0.368	0.093	−0.712 (O)
9+**5**	0.464	−0.352	0.064	−0.105 (Cl)
9+**6**		−0.218	−0.218	
9+**7**		−0.076	−0.033	

[a] Charge in e.

any influence in the rate determining step noted as TS_A. Therefore, we will focus on the first transition state TS_A in Figure 7, to compare it with the transition states in the concerted processes.

On the other hand, the C_α−B bond in the alkynes show bond orders lower than 1 (bond weakening) along the transition state for the reactions with tetrazine, and larger than 1 (bond strengthening) in the reactions with furan, showing that the triple bond donates some charge to the unoccupied pz orbital of the boron during the reaction with furan, acting as an electron-deficient alkyne, and in contrast withdraws some of the charge from the C_α−B σ bond in the reaction with tetrazine, where it acts as an electron-rich dienophile.

As mentioned before, the very low bond orders between boron and C_a indicate that there are not any appreciable covalent interactions between the boron and the diene, excluding the [4 + 3] process. Bond orders between B and C_a are 0.006 for **3**+**9**, 0.034 for **5**+**9**, 0.026 for **3**+**8**, and 0.043 for **5**+**8** (Figures 6 and 7). As expected, the bond order slightly increases for furan as the diene, and for borondichloride as the alkyne. Consequently, in the reaction between tetrazine and boronate **3**, the interaction between C and boron is almost negligible.

More importantly, a close look to the activation energies in Table 1 allows us to make some intriguing conclusions: (1) Alkynylboronate **3** and acetylene **6** behave similarly and react much faster with tetrazine **9** than with furan **8**, acting as good nucleophilic alkynes. (2) Alkynylboron dichloride **5** and acetylenedicarboxylate **7** also behave similarly and react faster with furan **8** than with tetrazine **9**, acting as good electrophilic alkynes. (3) The fastest reaction takes place between electron-rich furan derivative **8** and electron deficient alkyne **7**, 16.18 kcal/mol. The slowest reaction happens to be that of furan **8** and boronate **3**, 26.26 kcal/mol.

The difference between alkynylborondichloride **5** and boronate **3** cannot be understood in terms of the steric hindrance introduced by the four methyl groups in **3**, because boronate **4** (lacking methyl groups) shows almost identical activation energies and geometries in its transition states. As a consequence, we can conclude that the heteroatom linked to the boron, oxygen, or chlorine plays a critical role in the nucleophilic−electrophilic character of the alkyne.

Related to these findings, the charge of boron in alkynylboron dichloride **5** is +0.470 e, whereas in boronate **3** is +1.063 e. Given that the alkynyl substituent of the boron is the same in both cases, the two oxygens are able to withdraw more charge form the boron than the two chlorines, in accordance to the larger electronegativity of oxygen than chlorine. Seemingly, we found a similar effect on the boron charge in the transition states of the reactions with both dienes. In all cases, the positive charge on boron is higher for boronate **3** or **4** than for dichloride derivative **5**.

During the transition states, the positive charge on boron is higher for reactions with tetrazine (tetrazine **9** + boronate **3**; 1.102 e) than for furan (furan **8** + boronate **3**; 1.043 e). Moreover, the carbon atom in the α-position to the boron is always more negatively charged than C_β, and both carbon atoms are more negatively charged in the reactions with furan than with tetrazine, suggesting that the charge is flowing from alkyne to tetrazine, and from furan to alkyne (Table 2).

Natural population analysis allows for the evaluation of the charge transfer during the transition state. It has been suggested that the feasibility of the DA reaction can be related to the charge transfer along the bond forming process, which corresponds to

Table 3. Charge Transfer[a] between Diene and Alkyne in the Transition State

dienophile/diene	furan **8**	tetrazine **9**
3	0.189	−0.123
4	0.196	−0.118
5	0.345	−0.056
6	0.093	−0.110
7	0.335	−0.015

[a] Charge transfer in e. A negative value means charge flowing from alkyne toward the diene, and a positive value indicates from diene to alkyne.

Table 4. Electrophilicity[a], Chemical Hardness[b], and Electron Chemical Potential[b] for Dienes and Dienophiles

diene/dienophile	electrophilicity ω	chemical hardness η	electron chemical potential μ
9	3.39	0.1349	−0.1833
5	2.08	0.2043	−0.1768
7	1.72	0.2343	−0.1720
4	0.87	0.2566	−0.1283
3	0.83	0.2553	−0.1251
6	0.54	0.3344	−0.1147
8	0.26	0.2244	−0.0655

[a] Electrophilicity in eV. [b] Chemical hardness and electronic chemical potential in au.

Table 5. HOMO−LUMO Energies[a] for the Different Dienes and Dienophiles

diene	HOMO	LUMO	alkyne	HOMO	LUMO
furan **8**	−4.84	1.27	**3**	−6.88	0.07
tetrazine **9**	−6.82	−3.15	**4**	−6.98	0.00
			5	−7.59	−2.03
			6	−7.67	1.43
			7	−7.87	−1.49

[a] Energies are given in eV.

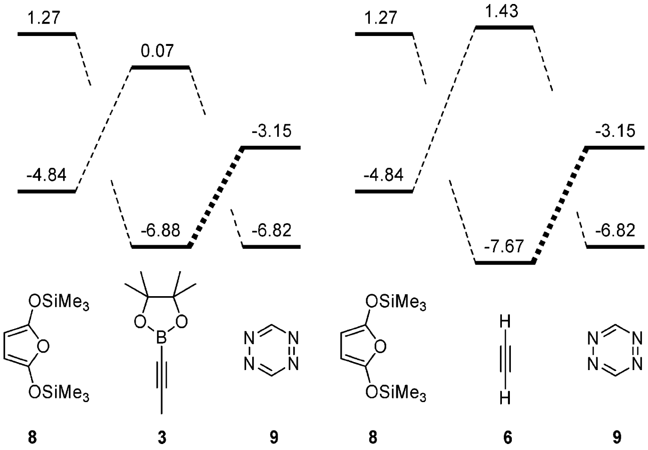

Figure 9. HOMO and LUMO energies (in eV) for reactions between **3**+**8**, **3**+**9**, **6**+**8** and **6**+**9** calculated at B3LYP/6-31G* level. Optimal HOMO−LUMO interactions for each alkyne are shown as bold dotted lines.

the polar character of the reaction.[23] For polar DA reactions, the dienophile must possess efficient electron withdrawing groups and the sole presence of electron releasing groups in the diene is not enough to favor the cycloaddition process.[23]

In our case, the study of the charge transfer between diene and alkyne confirms these aspects. The data in Table 3 reveal that tetrazine **9** is acting as an electron acceptor and furan **8** as an electron donor. Both alkynylboronates **3** and **4** and acetylene **6** are able to transfer a significant amount of charge, higher than 0.1 e, to tetrazine **9**, but at the same time they are bad acceptors with furan **8**, i.e. they behave as good nucleophiles. In contrast, dichloride **5** and acetylenedicarboxylate **7** are bad donors to tetrazine **9** and better acceptors from furan **8**, behaving as good electrophilic dienophiles. Due to the high charge transfer computed for reactions of **5**+**8** and **7**+**8**, these reactions can be considered as polar.[23]

Recently, the global electrophilicity index[24] was used to classify dienes and dienophiles on a unique scale of electrophilicity. The more or less polar character of the cycloaddition can be measured as the difference in electrophilicity of diene/dienophile.[25]

Electrophilicity can be described as $\omega = \mu^2/\eta$, where the electronic chemical potential μ is the average of the energies of HOMO and LUMO, $\mu = (E_H + E_L)/2$, and the chemical hardness is the difference between the energies of HOMO and LUMO $\eta = E_H - E_L$.[26] Considering the electrophilicity of the different reagents, those with a ω higher than 1 eV can be considered as electrophiles, and below that mark as nucleophiles (Table 4). In this regard, tetrazine **9** will behave as a very good electrophile. Alkynes with electron withdrawing groups such as acetylenedicarboxylate **7** or alkynylborondichloride **5** will act also as electrophiles. The most striking data is the large electrophilicity difference exerted by different types of substitution at boron (0.83 and 0.87 eV for boronates **3** and **4** and 2.08 eV for borondichloride **5**) and the fact that boronates have nucleophilic character with a similar index to that of acetylene **6** or electron-rich dienes, like Danishefsky's diene (0.62 eV) or cyclopentadiene (0.83 eV).

As a consequence, during the cycloaddition, the charge transfer must occur from the compounds with higher electronic chemical potential to the compounds with lower potential.[27] In other words, any compound will behave as a nucleophile to any other compound above it in the electrophilicity list and as an electrophile to any other compound below it, which is in accordance to the data shown in Table 3. It is noteworthy that the high $\Delta\omega$ values computed for these cycloadditions ($\omega_{\mathbf{9}} - \omega_{\mathbf{3}} = 2.56$ eV or $\omega_{\mathbf{5}} - \omega_{\mathbf{8}} = 1.82$ eV) explain the origin of the polar character of these processes and are in agreement with the large charge transfer computed for these reactions.

As seen before, the reactivity of the alkynylboron derivatives cannot be explained in terms of electrostatic properties of the boron moiety and the triple bond. In fact, important aspects of electrocyclic reactions can be better understood in terms of a HOMO−LUMO interaction diagram of reactants.[28] The best HOMO−LUMO interaction in the reaction of boronate **3** with tetrazine **9** takes place between the HOMO in boronate (−6.88 eV) and the LUMO in tetrazine (−3.15 eV) (Table 5 and Figure 9), and this corresponds to an inverse electron demand Diels−Alder reaction. The energy difference between the two reacting

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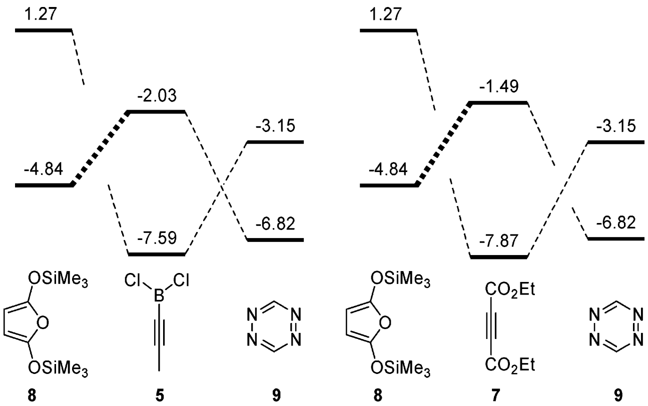

Figure 10. HOMO and LUMO energies (in eV) for reactions between **5**+**8**, **5**+**9**, **7**+**8**, and **7**+**9** calculated at B3LYP/6-31G* level. Optimal HOMO−LUMO interactions for each alkyne are shown as bold dotted lines.

molecular orbitals is 3.73 eV. In contrast, the reaction between furan **8** and boronate **3** should occur through the HOMO of the furan and LUMO of the alkynylboronate, as in a normal Diels−Alder cycloaddition, but due to the much higher energy of boronate's LUMO (0.07 eV) the energy difference between the two orbitals is now 4.91 eV, higher than in the former case, resulting in a poorer orbital overlap and a higher activation energy, consistent with the energies of the transition states shown before. *It appears therefore that the high energy of the boronate's LUMO (0.07 eV for **1**) and the consequent big energy difference between HOMO and LUMO are responsible for the low electrophilicity of **3** and for its tendency to react much faster with tetrazine **9** than with furan **8***. Acetylene shows a similar behavior and also reacts faster with tetrazine than with furan due again to the high energy of its LUMO (1.43 eV).

Acetylenedicarboxylate **7** and dichloride **5**, acting as good electrophiles, show the opposite chemoselectivity, and the best interactions now happen between the HOMO of furan **8** and the LUMO of the alkynes (Figure 10), which are much lower in energy (−1.49 eV and −2.03 eV) than those of alkynes **3** and **6**.

These observations are in full agreement with the arrangements of substituents on the diene and alkyne moieties found at the transition states (Figures 6 and 7). Specifically, in reactions with furan as the diene, the two C atoms in the triple bond and boron are almost lined up, with a dihedral angle ($B-C_\alpha-C_\beta$) of 169.0° for **3** and 174.5° for **5**. The empty pz orbital in boron is parallel to the π-system in the alkyne to maximize the charge withdrawal from the alkyne, as reaction takes place through the LUMO of the alkyne. Seemingly, the triple bond and the carbon of one of the ester groups of **7** are in-line during the reaction with furan, and the ester adopts a pseudo-coplanar conformation with the triple bond to maximize the overlap between the π-bond in triple bond and the π* C=O bond of the ester with an angle ($C_c-C_\alpha-C_\beta$) of 160.6°, allowing for optimal delocalization of the charge that is transferred from the diene (**7**+**8**, Figure 7). On the other hand, the inverse electron demand cycloadditions with tetrazine take place along concerted and synchronous processes where the triple bond of the alkyne maximizes its nucleophilicity by placing the empty pz-orbital on boron perpendicular to the reacting π-system in the alkyne. Moreover, the alkyne adopts a geometry typically found in [4 + 2] cycloadditions, with a $B-C_\alpha-C_\beta$ dihedral angle of 149.9° (**3**+**9**, Figure 6). This is in accordance with a reaction through the HOMO in alkyne.

Figure 11 shows HOMO and LUMO orbitals for alkynes **4** and **5**.[29] It appears that HOMOs are all centered in the triple bond, basically formed by the π orbital of the triple bond that is perpendicular to the empty pz orbital of the boron. HOMOs show similar coefficients at both C_α and C_β, indicating that the triple bond is not much polarized, and a coefficient near 0 at boron. It might be expected that reactions through the HOMO should be highly synchronous, and this has been found to be the case (**4**+**9**, Table 1 and Figure 6). Boron does not participate at all in the transition state and the reactivity of alkynes through the HOMO resembles that of acetylene. On the other hand, LUMOs of boron substituted alkynes are strongly polarized, with the largest coefficients on the boron and terminal carbon atom C_β. The LUMO of the alkynylboronate **4** is formed by the antibonding π^* parallel (overlapping) to the pz-empty orbital of the boron, so the expansion coefficients are negative for C_β, positive for both C_α and B, and again negative for the oxygens. From this data, cycloadditions through the LUMO are expected to be very asynchronous, as computationally found (**4**+**8**, Table 1 and Figure 6). A comparison with the LUMO of alkynylborondichloride **5** reveals a similar topology, but the polarization of $LUMO_{(5)}$ is much higher than that of $LUMO_{(4)}$. Consequently, the LUMO expansion coefficients of boron are higher in **5** than in **4**, whereas the coefficient in C_α term is lower in **5** than in **4**. NBO analysis shows that the strongest interaction occurs between the oxygen-lone pairs and the boron-empty orbital in **4**, amounting to 55.6 kcal/mol for each oxygen, whereas the chlorines in **5** are not able to donate as much charge, stabilizing the molecule by 38.5 kcal/mol for each chlorine. As a consequence, $LUMO_{(5)}$ lies lower in energy than the LUMO of the boronate, making compounds such as **5** more electrophilic than boronates **3** or **4**.

Interestingly, it is not clear whether **5** is actually reacting with tetrazine through its HOMO or LUMO. From the electrophilicity and charge-transfer data we could conclude that **5** is acting as a weak nucleophile toward tetrazine **9** and the reaction seems to be very apolar.[30] But looking at the transition state geometry, it seems that **5** is exposing its LUMO to the reaction side (Figure 7). Besides, the reaction between **5** and **9** is slightly more asynchronous (Figure 7) than it should be for a clear $HOMO_{alkyne}/LUMO_{diene}$ reaction, like **3**+**9** or **6**+**9**. Actually, Figure 10 does not show a clear energy gap preference between $HOMO_{(9)}/LUMO_{(5)}$ and $HOMO_{(5)}/LUMO_{(9)}$. In this regard, it has been proposed for these borderline cases that the $HOMO_{diene}/LUMO_{dienophile}$ interaction exerts a larger influence on the energetics of a Diels−Alder reaction than the $HOMO_{dienophile}/LUMO_{diene}$ interaction, and therefore the normal Diels−Alder is favored over the inverse electron demand Diels−Alder reaction.[31] This preference could be applied for the reaction between **5** and **9**, although it does not interfere with the rest of the conclusions drawn for the other substrates.

Conclusions

DFT calculations have shown that the electronic character of the alkynylboron depends largely on the type of heteroatom

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(29) Gandon, V.; Aubert, C.; Malacria, M. *Current Org. Chem.* **2005**, *9*, 1699.
(30) The weak nucleophilicity of **9** along with the symmetry of tetraazine are responsible for the low polar character of this cycloaddition: Domingo, L. R.; Aurell, M. J.; Perez, P.; Contreras, R. *J. Org. Chem.* **2003**, *68*, 3884.
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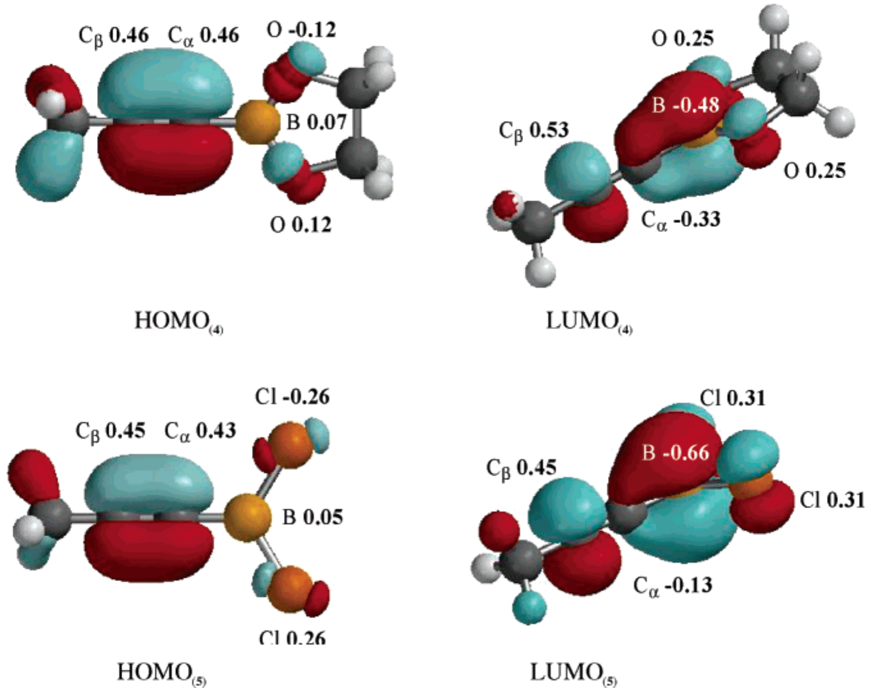

Figure 11. HOMO and LUMO representations for compounds **4** and **5**, as well as expansion coefficient values for representative atoms.

attached to the boron. Despite the larger electronegativity of oxygen than chlorine, alkynylboronates appear to show a reactivity more akin to acetylene whereas dichloroalkynylboranes react more like dimethylacetylene dicarboxylate. This counterintuitive effect can be understood in terms of the frontier molecular orbital theory. Strongly donating oxygen substituents result in a higher LUMO, reducing the electrophilic character of the alkynylboronates, whereas less donating chlorine atoms provide electrophilic dichloroalkynylboranes. Highly synchronous reactions of alkynylboronates with tetrazines via a HOMO that is centered on the triple bond and that lies perpendicular to the boron pz-orbital were found. In contrast, these alkynes participate in a much higher energy asynchronous cycloaddition with electron-rich furans via a LUMO that is aligned with the boron pz resulting in an almost linear arrangement of the alkyne moiety in the transition state. We believe that these studies will greatly assist in identifying compatible diene/dienophile substrates for efficient cycloaddition toward functionalized organoboron reagents, and our efforts in this area will be described in due course.

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Supporting Information Available: Experimental procedures of the kinetic measurements and calculation of the kinetic parameters, Cartesian coordinates of all computed stationary points, relative and absolute activation energies for all reactions, and complete reference 13. This material is available free of charge via the Internet at http://pubs.acs.org.

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