J|A|C|S ARTICLES

Published on Web 05/18/2009

Investigation of the Scope and Regiochemistry of Alkynylboronate Cycloadditions with Sydnones

Duncan L. Browne,[‡] Jérôme F. Vivat,[‡] Andrew Plant,[§] Enrique Gomez-Bengoa,*[,†] and Joseph P. A. Harrity*[,‡]

Departamento de Química Orgánica I, Facultad de Química, Universidad del País Vasco, San Sebastián, Spain, Department of Chemistry, University of Sheffield, Sheffield S3 7HF, United Kingdom, and Research Chemistry, Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, United Kingdom, and Syngenta Crop Protection AG, Schaffhauserstrasse, 4332 Stein, Switzerland

Received February 20, 2009; E-mail: enrique.gomez@ehu.es; j.harrity@sheffield.ac.uk

Abstract: The cycloaddition of alkynylboronates and sydnones provides a convenient and highly regioselective method for the synthesis of a broad range of di-, tri-, and tetrasubstituted pyrazole boronic esters. The origins of an observed regiochemical divergence in the reactions of terminal alkynylboronates with their more substituted analogues have been studied by DFT methods.

Introduction

Pyrazoles represent a key motif in heterocyclic chemistry, and these diazoles are present in a large number of bioactive molecules within both pharmaceutical and agrochemical industries.[1] These compounds are commonly prepared by condensation of hydrazines with 1,3-dicarbonyl compounds (or equivalents); however, cycloaddition reactions of diazo-compounds and nitrile imines represent a useful alternative.[1a,2] While these ring construction strategies have the advantage of being quite general and employ simple and accessible starting materials, the ability to also incorporate useful functionality so that a range of subsequent chemistry can be carried out toward specific targets of interest is a desirable attribute. In this regard, the synthetic versatility of the carbon−boron bond[3] makes pyrazole boronic acid derivatives an especially attractive scaffold; such compounds are known and are generally accessed via the appropriate organolithium intermediate.[4] Given that pyrazole ring lithiation generally proceeds at C-5 and can be accompanied by competing ring-opening processes, traditionally routes generally rely on bromination followed by lithium−halogen exchange.[5]

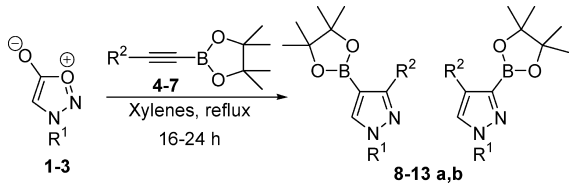
A potentially more direct route to these compounds that would avoid the need for heterocycle lithiation processes would be to carry out a cycloaddition reaction whereby the boronate moiety is incorporated into one of the reacting substrates.[6,7] This concept has been demonstrated by Matteson in the [3 + 2] cycloaddition of diazoalkane derivatives; however, the reaction is extremely slow and limited only to the terminal alkyne substrate.[8] Sydnones represent an unusual alternative cycloaddition substrate for pyrazole synthesis.[9] These mesoionic reagents are readily prepared in two steps from N-functionalized amino acids, are readily stored and handled, and can be further elaborated by metal-catalyzed cross-coupling processes.[10] We envisaged that these compounds could provide a powerful and flexible alternative to existing methods for the synthesis of pyrazoles, and preliminary studies confirmed that this strategy was viable.[11] We report herein a full account of the evolution of this idea, in particular with regard to reaction regioselectivity,

[†] Universidad del País Vasco.
[‡] University of Sheffield.
[§] Jealott's Hill International Research Centre and Syngenta Crop Protection AG.

(1) (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3, p 1. (b) Lamberth, C. *Heterocycles* **2007**, *71*, 1467. (c) Singh, P.; Paul, K.; Holzer, W. *Bioorg. Med. Chem.* **2006**, *14*, 5061, and references cited therein.
(2) (a) Makino, K.; Kim, H. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1998**, *35*, 489. (b) Elnagdi, M. H.; Elgemeie, G. E. H.; Abd-Elaal, P. A. E. *Hetereocycles* **1985**, *23*, 3121.
(3) *Boronic Acids*, Hall, D. G., Ed.; Wiley−VCH: Weinheim, 2005.
(4) (a) Li, H.; Wang, Y.; McMillen, W. T.; Chatterjee, A.; Toth, J. E.; Mundla, S. R.; Voss, M.; Boyer, R. D.; Sawyer, J. S. *Tetrahedron* **2007**, *63*, 11763. (b) McLaughlin, M.; Marcantonio, K.; Chen, C.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 4309.
(5) (a) Grimmett, M. R.; Iddon, B. *Heterocycles* **1994**, *37*, 2087. For a recent direct arylation approach, see: (b) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042.
(6) For recent examples of the synthesis of aromatic and heteroaromatic boronic esters by alkynylboronate cycloadditions, see: (a) Moore, J. E.; Goodenough, K. M.; Spinks, D.; Harrity, J. P. A. *Synlett* **2002**, 2071. (b) Hilt, G.; Smolko, K. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2795. (c) Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712. (d) Gandon, V.; Leca, D.; Aechtner, T.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *Org. Lett.* **2004**, *6*, 3405. (e) Gandon, V.; Leboeuf, D.; Amslinger, S.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7114. (f) Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860. (g) Sato, S.; Isobe, H.; Tanaka, T.; Ushijima, T.; Nakamura, E. *Tetrahedron* **2005**, *61*, 11449. (h) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6707. (i) Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3889. (j) Delaney, P. M.; Moore, J. E.; Harrity, J. P. A. *Chem. Commun.* **2006**, 3323.
(7) For reviews of alkynylboronate cycloadditions, see: (a) Hilt, G.; Bolze, P. *Synthesis* **2005**, 2091. (b) Gandon, V.; Aubert, C.; Malacria, M. *Curr. Org. Chem.* **2005**, *9*, 1699.
(8) Matteson, D. S. *J. Org. Chem.* **1962**, *27*, 4293.
(9) Gribble, G. W. In *Heterocyclic Compounds*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; Vol. 59, p 681.
(10) (a) Applegate, J.; Turnbull, K. *Synthesis* **1988**, 1011. (b) Browne, D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem.* **2009**, *74*, 396.

 10.1021/ja902460n CCC: $40.75

Table 1. Exploring the Cycloaddition of N-Substituted Sydnones



entry	R^1	R^2	yield **(a:b)**
1[a]	Ph; **1**	H; **4**	**8**; 54% (1:7)
2[a]	Ph; **1**	^{n}Bu; **5**	**9**; 64% (5:2)
3	Ph; **1**	Me_3Si; **6**	**10**; 76% (2:1)
4	Ph; **1**	Ph; **7**	**11**; 58% (>98:2)
5[a,b]	Me; **2**	Ph; **7**	**12**; 53% (>98:2)
6	Bn; **3**	Ph; **7**	**13**; 62% (>98:2)

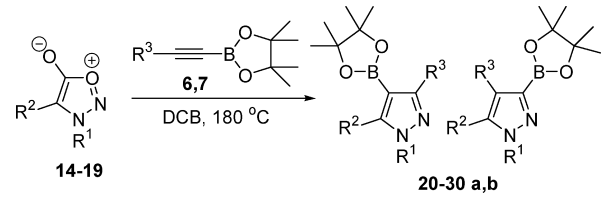
[a] Reaction conducted in refluxing mesitylenes. [b] Reaction run for 48 h.

and demonstrate how this process stands as an effective alternative strategy to the synthesis of functionalized pyrazole boronic ester intermediates.

Results and Discussion

We decided to explore the potential of a sydnone cycloaddition reaction with alkynylboronates to access functionalized pyrazole boronic esters. Borylated alkynes have found widespread use in cycloaddition reactions, and these processes have been studied experimentally[6] and theoretically.[12] Moreover, alkynylboronates participate in transition metal-catalyzed cross-coupling reactions[13] and have recently been identified as valuable precursors for the asymmetric synthesis of propargylamides and β-alkynyl ketones.[14] In an effort to establish the viability of the proposed alkynylboronate/sydnone cycloaddition, we explored the reaction of simple N-substituted sydnones with a range of alkynylboronates, and our results are highlighted in Table 1. Given the viability of pyrazole formation via terminal alkyne cycloadditions with α-diazocompounds,[8] we were pleased to find that sydnone **1** was also compatible and provided the corresponding pyrazole with good levels of regiocontrol for the 3-boronate **8b** (entry 1). Switching to the *n*-alkyl-substituted alkyne **5** provided an opportunity to generate more heavily substituted products; this reaction successfully generated the corresponding pyrazoles **9** with poor selectivity albeit favoring the other regioisomer (entry 2). Trimethylsilyl-substituted alkyne **6** performed similarly (entry 3); however, we were delighted to find that phenyl-substituted alkyne **7** provided pyrazole **11** as a single regioisomer (entry 4). Finally, we found that changing the N-substituent on the sydnone did not appear to significantly alter the reactivity, and the corresponding products were generated in similar yields with excellent regiocontrol (entries 5, 6).[15]

Table 2. Exploring the Cycloaddition of Disubstituted Sydnones[a]



entry	R^1	R^2	R^3	time	yield **(a:b)**
1	Ph	Ph; **14**	Ph; **7**	48 h	**20**; 59% (>98:2)
2	Ph	Ph; **14**	Me_3Si; **6**	48 h	**21**; 73% (>98:2)
3	Me	Ph; **15**	Me_3Si; **6**	48 h	**22**; 68% (>98:2)
4	Ph	Me; **16**	Ph; **7**	48 h	**23**; 53% (>98:2)
5	Ph	^{i}Pr; **17**	Ph; **7**	48 h	**24**; 38% (>98:2)
6	Ph	Me; **16**	Me_3Si; **6**	48 h	**25**; 56% (>98:2)
7	Ph	^{i}Pr; **17**	Me_3Si; **6**	48 h	**26**; 43% (>98:2)
8	PNP	Me; **18**	Ph; **7**	18 h	**27**; 67% (>98:2)
9	PNP	^{i}Pr; **19**	Ph; **7**	24 h	**28**; 45% (>98:2)
10	PNP	Me; **18**	Me_3Si; **6**	18 h	**29**; 80% (>98:2)
11	PNP	^{i}Pr; **19**	Me_3Si; **6**	24 h	**30**; 69% (>98:2)

[a] DCB: *o*-dichlorobenzene.

These preliminary studies suggested that the larger substituent on the alkyne had a tendency to be incorporated at C-3 in the pyrazole, and so we considered that the incorporation of a substituent at C-4 on the sydnone could provide an opportunity for greater steric differentiation and ultimately higher regioselectivities in general. To investigate this issue, we prepared a selection of disubstituted sydnones and examined their cycloaddition with alkyne **6** (found to be poorly regioselective in reactions outlined in Table 1) and the highly selective phenyl-substituted alkyne **7**; our results are shown in Table 2.

Cycloaddition of 4-phenyl sydnone **14** with alkyne **7** provided the corresponding pyrazole **20** in good yield as a single regioisomer (entry 1). Pleasingly, repeating this reaction with TMS-alkyne **6** also provided the corresponding cycloadducts **21** and **22** with excellent regiocontrol (entries 2, 3). In an effort to explore the scope of this selective process, we prepared sydnones with Me- and ^{i}Pr-substituents at C-4 and were delighted to find that these provided the corresponding cycloadducts **23**−**26** as single regioisomers (entries 4−7). We had noted a significant drop in the reaction yield when sydnones **16** and **17** were utilized and wondered if we could improve yields by employing a more reactive sydnone. Our preliminary studies had shown that incorporation of a *p*-nitrophenyl substituent (PNP) at nitrogen on the sydnone resulted in shorter reaction times.[11] We therefore prepared sydnones **18** and **19** and were pleased to find that these substrates underwent cycloaddition in higher yields to provide the corresponding products, again as single regioisomers (entries 8−11).[16] It is worth noting that a further advantage of the PNP group is that it can be removed by a two-step nitro reduction/oxidation.[11]

Having demonstrated that this methodology could be employed to prepare fully substituted pyrazoles with excellent regiocontrol, we opted to carry out the reaction of **18** and **19** with terminal alkyne **4** to establish if the same sense of regiocontrol as that highlighted in Table 1, entry 1 was maintained. As shown in Scheme 1, the cycloaddition gave the expected regioisomers **31** and **32** with excellent regiocontrol and in high yield.[16]

(11) Browne, D. L.; Helm, M. D.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8656.
(12) (a) Singleton, D. A.; Leung, S.-W. *J. Org. Chem.* **1992**, *57*, 4796. (b) Singleton, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 6563. (c) Leung, S.-W.; Singleton, D. A. *J. Org. Chem.* **1997**, *62*, 1955. (d) Silva, M. A.; Pellegrinet, S. C.; Goodman, J. M. *J. Org. Chem.* **2002**, *67*, 8203. (e) Silva, M. A.; Pellegrinet, S. C.; Goodman, J. M. *J. Org. Chem.* **2003**, *68*, 4059. (f) Sáez, J. A.; Arnó, M.; Domingo, L. R. *Tetrahedron* **2003**, *59*, 9167.
(13) Castanet, A.-S.; Colobert, F.; Schlama, T. *Org. Lett.* **2000**, *2*, 3559.
(14) (a) Wu, T. R.; Chong, J. M. *Org. Lett.* **2006**, *8*, 15. (b) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244.
(15) For the regioselectivity determination of trisubstituted pyrazoles, see the Supporting Information.
(16) Nuclear overhauser effects confirmed the regiochemistry of pyrazoles **21**−**23**, **25**, **27**, **29**, and **31a**,**b** (see the Supporting Information). The assignment of regiochemistry for the related pyrazoles is made by inference.

Scheme 1

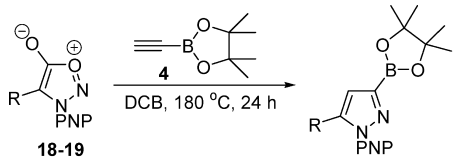
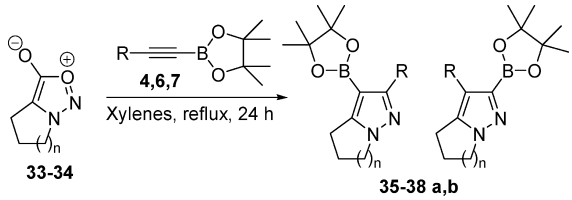


Table 3. Exploring the Cycloaddition of Bicyclic Sydnones



entry	*n*	R	yield **(a:b)**
1[a]	1; **33**	Me_3Si; **6**	**35**; 21% (>98:2)
2	2; **34**	Me_3Si; **6**	**36**; 79% (>98:2)
3	2; **34**	Ph; **7**	**37**; 70% (>98:2)
4	2; **34**	H; **4**	**38**; 78% (1:9)

[a] Reaction run for 72 h in refluxing mesitylenes.

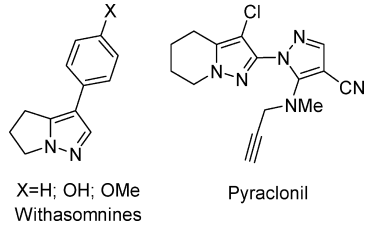


Figure 1. Examples of bioactive compounds containing bicyclic pyrazole motifs.

We were intrigued by the potential to exploit the high levels of regioselectivity observed in the cycloadditions of disubstituted sydnones in the synthesis of bicyclic pyrazoles, as such motifs constitute the core of the withasomnines[17] as well as a large number of fine chemicals sector relevant bioactive compounds; the pesticide pyraclonil[18] is an illustrative example (Figure 1). Accordingly, we carried out a study of the cycloaddition of bicyclic sydnones **33** and **34**, and our results are shown in Table 3.

Sydnone **33** derived from proline was first investigated in the cycloaddition reaction with silylalkyne **6**; disappointingly, however, the corresponding pyrazole **35** was furnished in poor yield, albeit with the expected high levels of regiocontrol (entry 1). We were aware that **33** had been shown to undergo decomposition at elevated temperatures[19] and decided to examine the homologous sydnone **34** in the hope that better yields would be obtained in this case. Pleasingly, this substrate underwent smooth cycloaddition with alkynes **6** and **7** to provide the corresponding pyrazoles in high yield and with good to excellent levels of regiocontrol (entries 2−4).[20] Once again, a turnover in regiochemistry was observed when terminal alkyne **4** was employed (entry 4).

Scheme 2

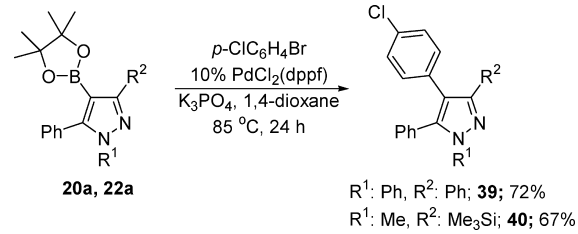
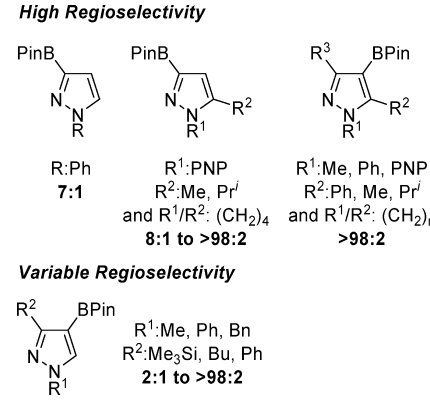


Chart 1



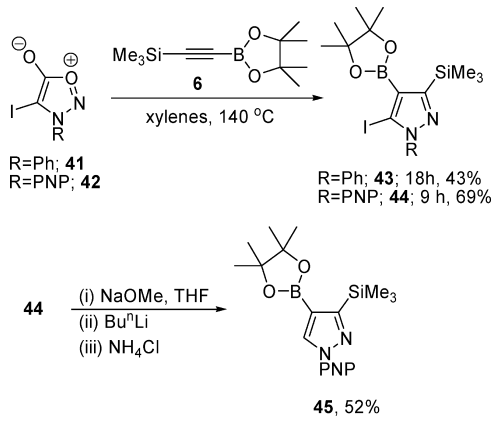
With regard to exploring the basic scope of this chemistry for the synthesis of pyrazoles, we were concerned that the sterically encumbered products generated by this methodology could compromise their participation in any subsequent cross-coupling reaction. We therefore decided to carry out the Suzuki coupling of representative pyrazoles **20a** and **22a**. Pleasingly, successful cross-couplings were achieved with *p*-bromochlorobenzene in good yields using readily available catalysts under nonoptimized conditions (Scheme 2).

Having carried out a general exploration of the scope of the cycloaddition chemistry with respect to the alkynes and the sydnones, the experimental data suggest that the majority of pyrazole scaffolds accessed by this methodology are generated with high levels of regiocontrol and that the selectivity is largely independent of the sydnone N-substituent. The exception to this generalization is the products of cycloaddition of substituted alkynes and monosubstituted sydnones, which proceed with variable regioselectivity. These conclusions are illustrated in Chart 1.

We wanted to develop a more general cycloaddition protocol to prepare 1,3,4-trisubstituted pyrazole boronic esters with predictably high levels of regiocontrol and opted to explore the potential of employing a removable steric controlling group at C-4 of the sydnone. Accordingly, we prepared 4-iodosydnones **41** and **42** and were delighted to find that they both underwent cycloaddition with **6** to provide the corresponding pyrazoles as single regioisomers (Scheme 3).[21] Once again, we found the PNP-substituted sydnone to be more efficient in this cycload-

(17) Aladesanmi, A. J.; Nia, R.; Nahrstedt, A. *Planta Med.* **1998**, *64*, 90.
(18) Iijima, K.; Saka, M.; Odanaka, Y.; Kato, Y.; Takada, M.; Hosomi, M. *J. Pestic. Sci.* **2006**, *31*, 190.
(19) Nikitenko, A. A.; Winkley, M. W.; Zeldis, J.; Kremer, K.; Chan, A.W.-Y.; Strong, H.; Jennings, M.; Jirkovsky, I.; Blum, D.; Khafizova, G.; Grosu, G. T.; Venkatesan, A. M. *Org. Process Res. Dev.* **2006**, *10*, 712.
(20) Nuclear overhauser effects confirmed the regiochemistry of bicyclic pyrazoles **35** and **36** (see the Supporting Information). The assignment of regiochemistry for the other bicyclic pyrazoles is made by inference.
(21) Interestingly, the corresponding 5-bromosydnones failed to provide the corresponding pyrazoles and appear to be more prone to decomposition at elevated temperatures.

Scheme 3



dition process. We next endeavored to remove the iodide and were intrigued by a recent report by Jiang et al.[22] that showed that functionalization of arylbromides can be carried out in the presence of pinacol boronic esters by first generating the intermediate ate-complex. Notably, however, the authors did not demonstrate the employment of this method in the case of ortho-disubstituted bromoaryl boronic esters. Nonetheless, using a modification of this protocol, we were able to confirm the successful Li−halogen exchange at C-5 to generate regioisomer **45** in acceptable yield, while maintaining the potentially labile boronic ester moiety.

The regiochemistry of cycloaddition of C-4-unsubstituted sydnones is intriguing, in particular the high and contrasting selectivities observed with Ph-substituted and terminal alkynylboronates **7** and **4** when compared to butyl- and silyl-substituted dienophiles **5** and **6**. In an effort to better understand these observations, we decided to explore the mechanism of these processes using theoretical DFT methods. The transition states for the reactions of the experimentally studied alkynylboronates **4**, **6**, and **7** and sydnones **1**, **14**, **16**, and **18** were computed (Scheme 4). For each reaction, two regioisomeric channels were considered, leading to the two experimentally observed 3- and 4-regioisomers. The R^1, R^2, and R^3 labels in Scheme 4 will be used during the discussion and in Figures 3−6 to facilitate the identification of the corresponding substrates.

Computational Methods

All reported structures were optimized at the DFT level using the B3LYP[23] hybrid functional as implemented in Gaussian 03.[24] Optimizations were carried out using the standard 6-31G* basis set for all implied atoms H, B, C, N, O, and Si. Density functional theory has been shown to reliably predict the results of cycloaddition reactions.[25] All energy minima and transition structures were characterized by harmonic frequency analysis at the same level. The energies reported in this work, which are given in kcal/mol, include thermal and zero-point vibrational energy corrections (ZPVE) and are not scaled. The stationary points were characterized by frequency calculations to verify that they have the correct number of negative eigenvalues. The intrinsic reaction coordinates (IRC)[26] were followed to verify the energy profiles connecting each TS to the correct associated local minima. Atomic charges and charge transfer values were calculated within the natural bond orbital (NBO) analysis.[27] Electrophilicity index[28] (ω) was computed as $\omega = \mu^2/\eta$, where the electron chemical potential (μ) is the average of the energies of HOMO and LUMO orbitals, $\mu = (E_H + E_L)/2$, and the chemical hardness (η) is the difference between the energies of LUMO and HOMO orbitals, $\eta = E_L - E_H$.

Theoretical Results

The reaction mechanism involves a cycloaddition reaction between the alkynylboronate and the sydnone, and a subsequent retro-cycloaddition reaction with loss of CO_2 to form the pyrazole boronic esters (Figure 2). The first transition state corresponds to a concerted cycloaddition process[29] (**TS-step1**, Figure 2) that from the point of view of the sydnones can be viewed as a [3 + 2] dipolar cycloaddition with intervention of the C^--N-N^+ fragment as the dipole or, alternatively, as a [4 + 2] Diels−Alder-like process with intervention of the $C{=}C-O^+{=}N$ fragment as the diene. Both formal denominations correspond to the same mechanism. As previously described for alkynylboronates, the donating effect of the two oxygen atoms on the unoccupied orbital of the boron strongly reduces its Lewis acid character, avoiding any appreciable interaction between boron and different dienes or dipoles in related cycloaddition reactions.[12f,30] Accordingly, we did not find any transition structure containing substantial interaction of the empty p-orbital of boron with the polar groups of the sydnones. The cycloaddition step presents activation enthalpies ranging from 17 to 27 kcal/mol depending on the substitution pattern (vide infra). As expected for a concerted cycloaddition process, the Gibbs activation energies are ca. 14 kcal/mol higher than the activation enthalpies, ranging from 30 to 42 kcal/mol. The first cycloaddition leads to the formation of a bicyclic intermediate (e.g., **46**, Figure 2), which lies ca. 13 kcal/mol (ΔH) lower in energy than the sum of the starting reactants. The intermediate **46** further evolves to the final products by an almost barrierless loss of CO_2 (**TS-step2**, Figure 2). The overall process is highly exothermic, and the final products are >100 kcal/mol more stable than the sum of the starting materials. The concerted formation of the two σ-bonds (C−C and C−N) in the first step is rate determining and is therefore the only one described in detail in the present study.

Notably, and in line with the experimental results, the computed activation energies correctly predict the regioselectivity trend in all cases. Figures 3 and 4 illustrate the relevant transition states together with the energy differences, predicted

(22) Jiang, Q.; Ryan, M.; Zhichkin, P. *J. Org. Chem.* **2007**, *72*, 6618.
(23) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974.
(24) Frisch, M. J.; *Gaussian 03*, revision E.01; Gaussian, Inc.: Wallingford, CT, 2004.
(25) (a) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036. (b) Wiest, O.; Montiel, D. C.; Houk, K. N. *J. Phys. Chem. A* **1997**, *101*, 8378. (c) García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415. (d) Birney, D. M. *J. Am. Chem. Soc.* **2000**, *122*, 10917.
(26) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.
(27) (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.
(28) (a) Parr, R. G.; von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922. (b) Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417. (c) Domingo, L. R.; Pérez, P.; Contreras, R. *Tetrahedron* **2004**, *60*, 6585.
(29) Our assumption of the concerted nature of sydnone cycloaddition with alkynes is based on the kinetic studies of the cycloaddition of a series of sydnones with dimethylacetylene dicarboxylate that demonstrate large and negative entropies of activation with the enthalpy/entropy parameters unaffected by the solvent, see:Youn, B. H.; Lyu, H. S.; Han, J. H.; Hahn, S. J.; Kim, S. H. *Bull. Korean Chem. Soc.* **1987**, *8*, 233.
(30) (a) Carreaux, F.; Possémé, F.; Carboni, B.; Arrieta, A.; Lecea, B.; Cossío, F. P. *J. Org. Chem.* **2002**, *67*, 9153. (b) Gomez-Bengoa, E.; Helm, M. D.; Plant, A.; Harrity, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 2691.

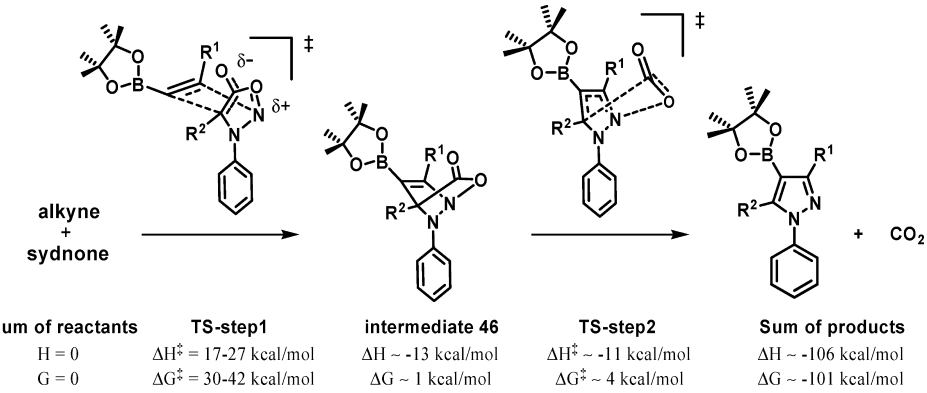
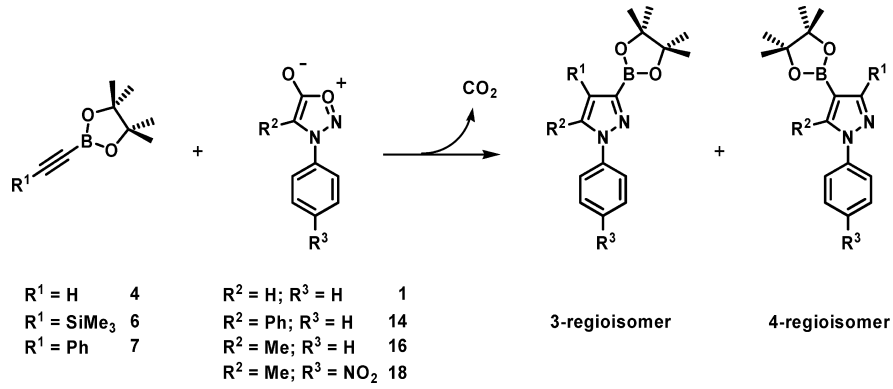


Figure 2. Cycloaddition and retro-cycloaddition transition states in the reaction of alkynylboronates and sydnones, with formation of intermediate **46**.

Scheme 4. Representation of the Reactions between Alkynylboronates and Sydnones Computationally Studied at the B3LYP/6-31G* Level



regioselectivities, and experimentally observed regioisomeric ratios. The reaction between the least substituted substrates (**4** + **1**, $R^1 = H$; $R^2 = H$, Scheme 4) is the only computed case in which the 3-regioisomeric channel (**TS1**, Figure 3) shows lower activation energies than its 4-isomeric transition state (**TS2**), in accordance with the experimental formation of **8b** as the major product of the reaction (**4** + **1**, entry 1, Table 1). Meanwhile, the incorporation of a bulky silyl substituent in the alkynylboronate (**6**, $R^1 = SiMe_3$, Scheme 4) induces a switch in regioselectivity, favoring the formation of the 4-isomer (**TS4**, **TS6**, and **TS8**, Figure 3). The smallest energy difference between both isomers corresponds to the reaction of **6** and **1** (**TS3** vs **TS4**, $\Delta\Delta H^{\ddagger} = 1.0$, $\Delta\Delta G^{\ddagger} = 1.3$ kcal/mol), while this difference increases in the presence of bulkier substituents on the sydnone, that is, **TS5** versus **TS6** ($\Delta\Delta H^{\ddagger} = 1.9$, $\Delta\Delta G^{\ddagger} = 2.1$ kcal/mol) and **TS7** versus **TS8** ($\Delta\Delta H^{\ddagger} = 2.1$, $\Delta\Delta G^{\ddagger} = 2.3$ kcal/mol). These results are in line with the low selectivity observed in the reaction of **6** + **1** (entry 3, Table 1), and the higher selectivities observed for **6** + **14** (entry 2, Table 2) and **6** + **16** (entry 6, Table 2).

On the other hand, the experimental level of regioselectivity for the phenyl-substituted alkynylboronate (**7**, $R^1 = Ph$, Scheme 4) is always higher than 98:2, favoring the 4-isomer (Tables 1 and 2). The theoretical results also agree with this observation, and the 4-isomer is computationally predicted to be favored in the three cases outlined in Figure 4, presenting activation barrier differences ($\Delta\Delta H^{\ddagger}$) of 1.7 kcal/mol (**TS9** vs **TS10**), 1.9 kcal/mol (**TS11** vs **TS12**), and 2.5 kcal/mol (**TS13** vs **TS14**), which correspond to computed selectivities of 18:1, 25:1, and 70:1, respectively. The computed selectivities slightly increase if $\Delta\Delta G^{\ddagger}$ is considered (Figure 4).

Steric factors appear to contribute to a great extent to the reversal of regioselectivity between unsubstituted alkynylboronate **4** ($R^1 = H$) and the more hindered derivatives **6** ($R^1 = SiMe_3$) and **7** ($R^1 = Ph$).[31] Within the alkynylboronate counterpart, the bond-forming distances are in general shorter for C_β than for C_α. This effect is especially important in the 3-isomeric transition states highlighted in Figure 3, wherein the C_β(boronate)$-C_4$(sydnone) distances are always shorter than 2.1 Å, inducing steric hindrance between the substituents at those positions. Thus, the incorporation of bulky substituents in C_β strongly destabilizes the corresponding transition states, as can be seen in the increasing activation barriers of structures **TS1**, **TS3**, **TS5**, and **TS7** (Figure 3). The effect is also evident in the phenyl alkynylboronate (**7**), wherein steric hindrance raises the energy of the 3-isomeric transition states **TS9**, **TS11**, and **TS13** (Figure 4). In fact, the $NC_\beta C_iC_o$ dihedral angles (defining the approaching geometry of the phenyl ring in the reaction coordinate toward the sydnone) show computed values close to 0° in the 4-regioisomeric channel (Figure 4), indicating that the phenyl ring approaches perpendicular to the reaction trajectory in those transition states, and also that the reactive π bond of the alkyne (4-isomer) is that which is nonconjugated with the phenyl ring. In contrast, the $C_4C_\beta C_iC_o$ dihedral angles range from 42° to 56° in **TS9**, **TS11**, and **TS13** (Figure 4), indicating that the phenyl ring has to rotate in the 3-isomeric channels to avoid the contact with the substituent at C_4 in the sydnone, distorting the structure and inducing an increase in the activation energy. This steric hindrance is evident even in

(31) A similar regioselectivity reversal induced by steric hindrance was theoretically studied by Domingo et al. in the 1,3-dipolar cycloaddition between nitrile *N*-oxides and alkynylboronates; see ref 12f.

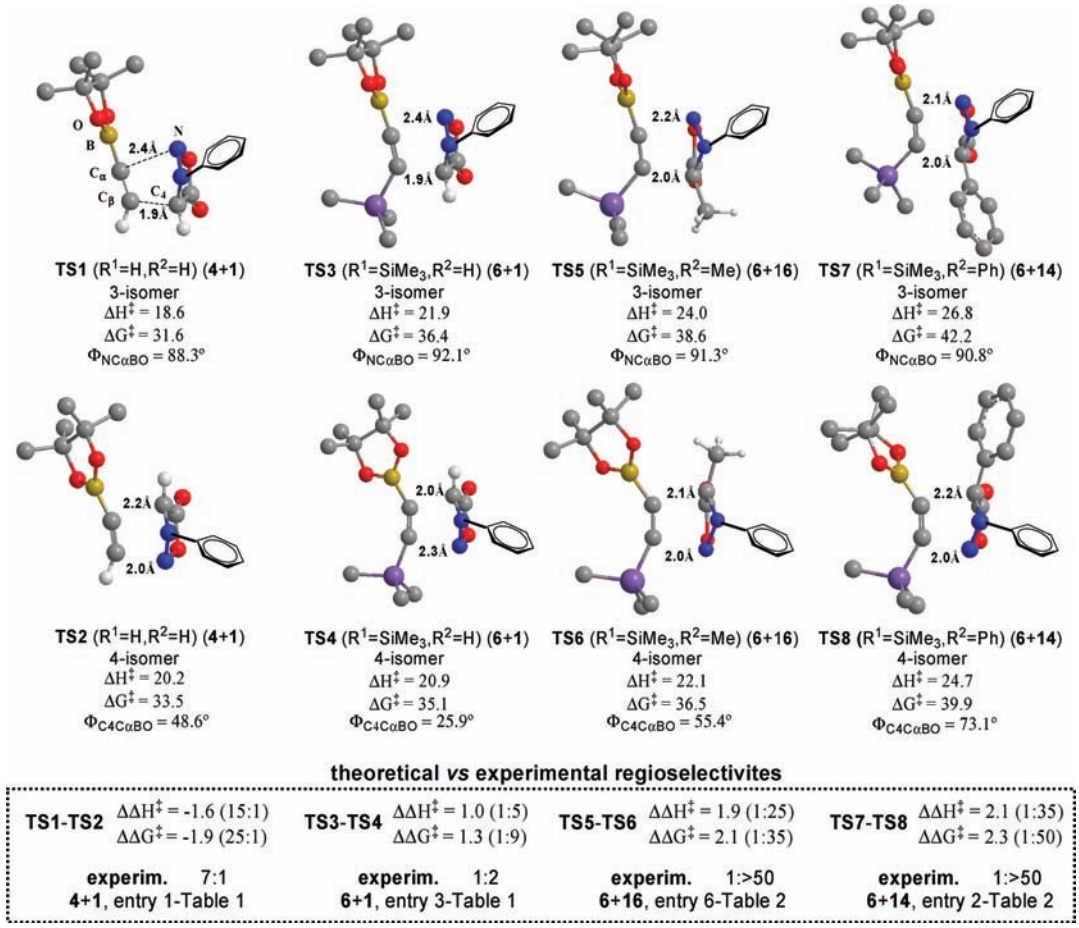


Figure 3. Transition structures for the reactions of alkynylboronates **4** and **6**. Most of the H atoms have been omitted for clarity. R^1 and R^2 refer to the labels outlined in Scheme 4.

the case of the nonsubstituted sydnone (**1**, R^2 = H). In fact, rotation of the dihedral angle $\Phi_{C4C\beta CiCo}$ of that specific structure (**TS9**) to 11° (like in **TS10**) brings the sydnone C_4H and *o*-CH hydrogen atoms to within only 1.5 Å (Chart 2). Obviously, the steric hindrance is higher in **TS11** and **TS13**.

The cycloaddition reaction is predicted to be very apolar. In the 3-isomeric transition states, a negligible charge transfer (0.02 to 0.06 e) flowing from the sydnone to the alkyne was observed, whereas almost no charge (0 to 0.02 e) transfers from sydnone to alkyne in the 4-isomeric transition states. The sydnones are slightly more electrophilic than the boronates (Figure 5), but this potentially misleading data might be a consequence of the higher energy gap between HOMO and LUMO orbitals within the boronates, which induces a greater hardness and a lower reactivity. In fact, the significant electron chemical potential (μ) index, which is the average of the energies of both orbitals, presents almost equal values for all substrates (slight variation from −0.13 to −0.15 au), confirming that indeed a very low charge transfer must occur during the transition state.[32] Also, the $HOMO_{boronate}-LUMO_{sydnone}$ and the opposite $HOMO_{sydnone}-LUMO_{boronate}$ energy gaps in Figure 5 are very similar in most cases. In this regard, the $NC_\alpha BO$ dihedral angles (defining the approaching geometry of the dioxaborolane ring in the reaction coordinate toward the sydnone) show computed values of ca. 90° in the 3-isomeric transition structures, indicating that the boron-containing ring approaches perpendicular to the reaction trajectory in those transition states, facing the empty p-orbital of boron toward the incoming sydnone. The angle values suggest that $LUMO_{boronate}$ (which involves the p-orbital of boron) might be acting to some extent as the reactive molecular orbital for the 3-isomeric channel. The geometries of the 4-isomeric transition states are more heterogeneous with respect to the boronate orientation and less conclusive. Thus, the charge transfer, electrophilicity, and HOMO−LUMO gap data suggest that in this apolar reaction, simultaneous HOMO−LUMO interactions in both directions are probably contributing to the overall reduction of the activation barriers, with a slight preference for $HOMO_{sydnone}-LUMO_{boronate}$ in the case of the 3-isomeric transition states.

Another important experimental finding is the higher reactivity of sydnones that bear a *p*-nitrophenyl substituent (Table 2 and Scheme 1). The theoretical results confirm this effect. In fact, **TS15** shows an activation enthalpy of only 17.0 kcal/mol ($\Delta G^{\ddagger}$ = 30.1 kcal/mol, Figure 6), which is the lowest value among all of the computed transition states. Also, the activation parameters of the reaction between **7** and **18** (**TS17**−**TS18**, Figure 6) are ca. 1.5−2.0 kcal/mol lower than those of the related reaction between **7** and **16** (**TS11** and **TS12**, Figure 3). Meanwhile, the incorporation of the nitro group does not significantly affect the regioselectivity. The 3-isomer is the experimentally observed major product of the reaction between **4** and **18** (8:1, Scheme 1), and, accordingly, **TS15** is 0.9 kcal/mol lower in enthalpy than **TS16** (∼5:1 computed selectivity).

(32) The charge transfer must occur from the compounds with higher electron chemical potential to the compounds with lower potential, see: Domingo, L. R. *Eur. J. Org. Chem.* **2004**, 4788.

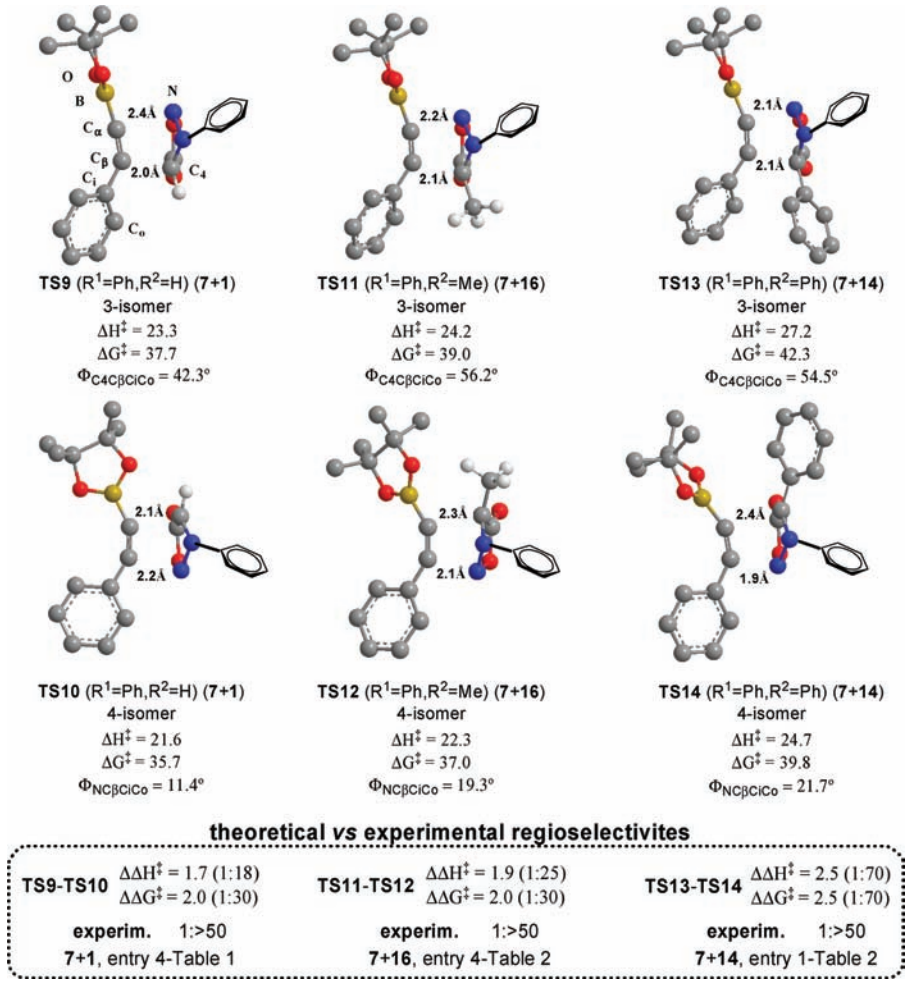


Figure 4. Transition structures for the reactions of alkynylboronate **7**. Most of the H atoms have been omitted for clarity. R^1 and R^2 refer to the labels outlined in Scheme 4.

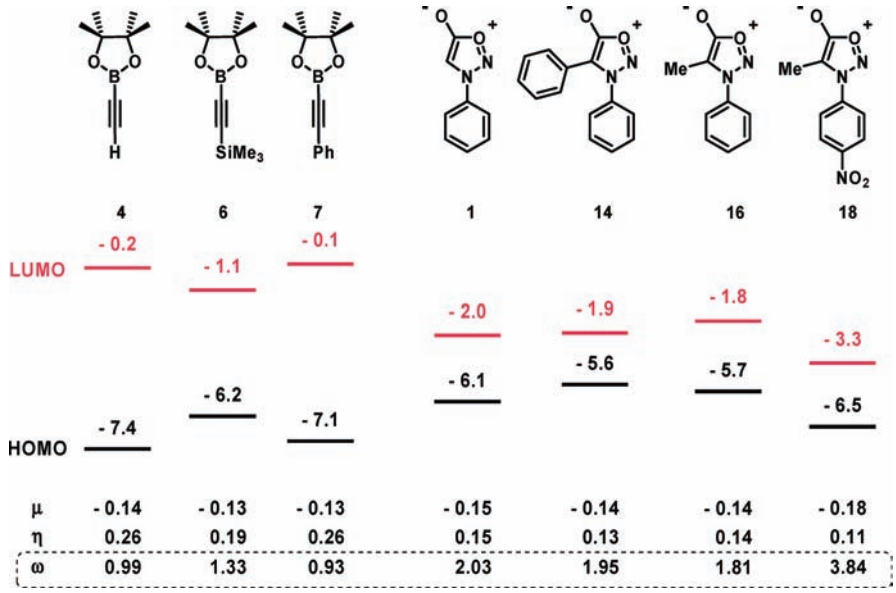


Figure 5. HOMO−LUMO energies, electron chemical potential (μ), chemical hardness (η), and electrophilicity (ω) indexes of the alkynes and sydnones. μ, η, and ω indexes are given in au; HOMO−LUMO energy values are given in eV.

The presence of the phenyl substitution in **7** leads to the formation of the 4-isomer as the experimental major product (>98:2, entry 8, Table 2), and **TS18** is predicted to lie 1.7 kcal/mol lower in energy than **TS17** (~20:1 computed selectivity). The presence of the *p*-nitro substituent induces a significant increase in the electrophilicity index of the sydnone (Figure 5),

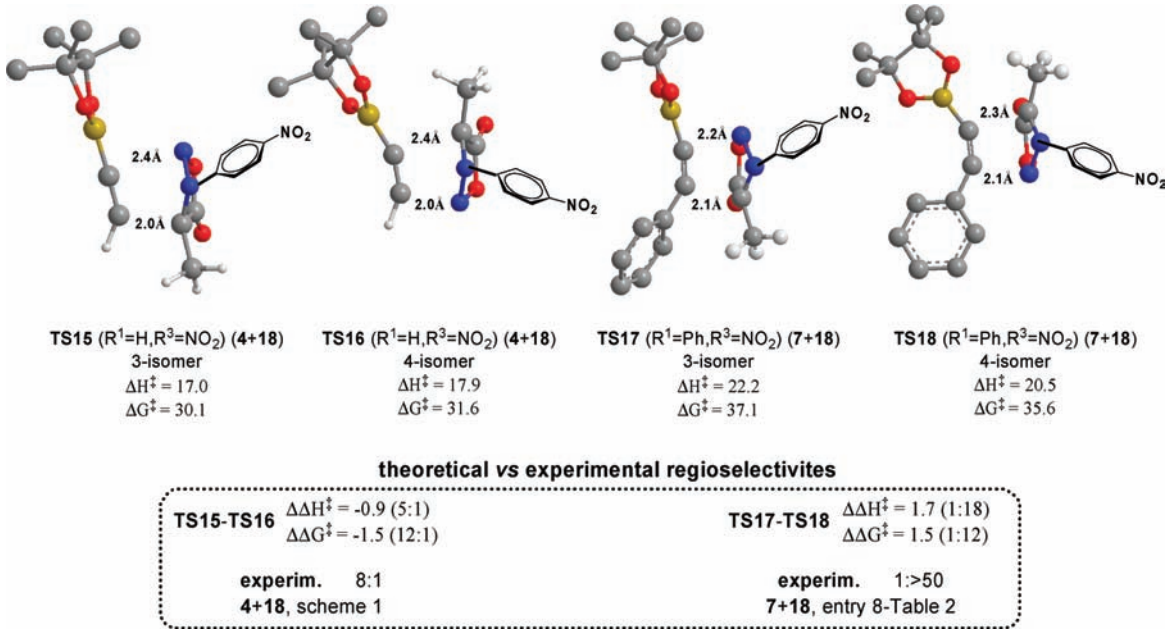
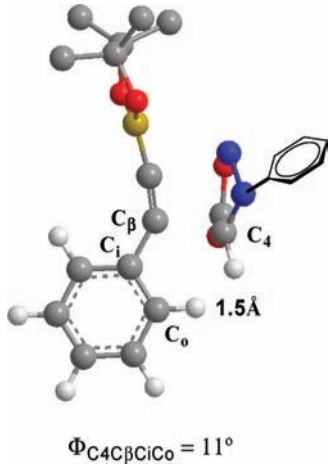


Figure 6. Transition structures for the reactions of syndone **18**. Most of the H atoms have been omitted for clarity. R^1 and R^3 refer to the labels outlined in Scheme 4.

Chart 2



which might be responsible for the higher reactivity of this substrate. Nonetheless, the charge transfer values between alkyne and sydnones in these two examples remain very low, below 0.05e.[33]

In conclusion, we report a flexible and highly regioselective method for the synthesis of pyrazole boronic esters. This strategy allows access to a broad range of di-, tri-, and tetrasubstituted analogues from simple and readily available starting materials. Furthermore, cycloaddition regiochemistry has been studied by DFT methods. Overall, the computed activation energies correctly predict the regiochemical outcomes in all cases examined. Moreover, it was found that the transition states for the formation of pyrazole 3-boronates show a trend whereby relatively short bond-forming distances are observed between the sydnone C-4 atom and the alkyne C_β atom. Therefore, the incorporation of subtituents at these positions results in unfavorable steric interactions and a consequential preference for the formation of the 4-boronate isomer. This regiochemical preference is switched for terminal alkynylboronates where the boronic ester is the sterically demanding group. Phenyl alkynylboronate **7** is an interesting case in that its favored mode of addition sees the Ph-ring lying perpendicular to the plane of the approaching sydnone ring. Consequently, high regioselectivities are observed in the reactions of this substrate, even in sydnones where only a hydrogen atom is present at C-4. Finally, PNP-substituted sydnones showed the lowest energies of all computed transition states. This observation is in line with the experimentally observed high reactivity of these substrates.

Acknowledgment. We are grateful for financial support from the EPSRC and Syngenta (D.L.B. and J.F.V.), and we also thank SGI/IZO-SGIker UPV/EHU for allocation of computational resources.

Supporting Information Available: Experimental procedures, regiochemical assignment by NOE experiments, Cartesian coordinates and absolute energies of all computed stationary points, and the full citation for ref 24. This material is available free of charge via the Internet at http://pubs.acs.org.

JA902460N

(33) The observation that the strongly electron-withdrawing *p*-nitrophenyl group does not affect the reaction regioselectivity is intriguing and may reflect its symmetrical positioning with respect to the C- and N-reacting centers of the sydnone. In addition, the fact that this group is not directly involved in the cycloaddition process may explain its negligible effect on charge transfer values. We thank one of the referees for these suggestions.