Bull Soc Chim Fr (1996) 133, 1143-1148

What is the reason for the difference in Diels–Alder reactivity of isomeric substituted dienes? A case involving 1,3-dienylboronates

Gilles Ohanessian[1], Yvan Six[2], Jean-Yves Lallemand[2]*

[1] *DCMR, URA 1307 du CNRS, École polytechnique, 91128 Palaiseau cedex;*
[2] *DCSO, URA 1308 du CNRS, École polytechnique, 91128 Palaiseau cedex, France*

(Received 27 June 1996; accepted 24 October 1996)

Summary — Semi-empirical and ab initio calculations were run to account for the differences in reactivity of 1,3-dienylboronates **1**, (*E*)-**2** and (*Z*)-**2** in the Diels-Alder cycloaddition with methyl acrylate. The results show that the *s-cis* conformation is accessed from the most stable *s-trans*, as easily for the unreactive (*Z*)-**2** isomer as it is for the reactive (*E*)-**2** isomer and for **1**. Furthermore, the diene geometries and π molecular orbitals in the *s-cis* conformation are not sufficiently affected by (*Z*) versus (*E*) substitution to explain the experimental observations. These results lead to the conclusion that variations in diene reactivity are most probably governed by steric repulsions in the Diels–Alder transition state in the case of (*Z*)-**2**.

Diels–Alder / 1,3-dienylboronate / diene conformation / isoprene / steric constraint / ab initio calculation

Résumé — D'où vient la différence de réactivité de diènes substitués isomères vis-à-vis de la réaction de Diels–Alder? Cas de 1,3-diénylboronates. *Des calculs semi-empiriques et ab initio ont été effectués dans le but d'expliquer la différence de réactivité des 1,3-diénylboronates **1**, (E)-**2** et (Z)-**2** vis-à-vis de la cycloaddition de Diels–Alder sur l'acrylate de méthyle. Les résultats indiquent qu'à partir de la conformation la plus stable* s-trans, *l'isomère non-réactif (Z)-**2** peut tout aussi bien accéder à la conformation* s-cis *que les diènes réactifs (E)-**2** et **1**. De plus, dans la conformation* s-cis, *la géométrie et les orbitales moléculaires π ne sont pas suffisamment affectées par une différence de stéréochimie (Z) ou (E) pour rendre compte des observations expérimentales. Ces résultats conduisent à conclure que les variations de réactivité des diènes étudiés sont probablement induites par des répulsions stériques dans l'état de transition de la cycloaddition dans le cas de (Z)-**2**.*

Diels–Alder / 1,3-diénylboronate / conformation de diène / isoprène / contrainte stérique / calcul ab initio

Introduction

The use of the Diels–Alder reaction between a dienophile and a 1,3-dienylboronate [1] is a powerful method to obtain cyclohexenes containing an allylboronate moiety, offering a number of possibilities for further stereocontrolled functionalizations [2]. We have studied this method in an approach aimed at the synthesis of Clerodin [1d-f], a naturally occurring insect antifeedant (fig 1).

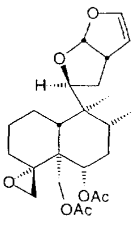


Fig 1. Clerodin.

Our strategy [1d,e] is based on the stereocontrolled aldehyde condensation on such a Diels–Alder adduct (fig 2). The use of diene (*Z*)-**2** instead of diene **1** would be valuable, as it would introduce the missing methyl group on ring B at the very beginning of the synthesis, with the right configuration. We thus prepared boronates (*E*)-**2** (fig 3) and (*Z*)-**2** (fig 4), and led further studies on the case of the Diels–Alder reaction involving methyl acrylate as the dienophile, and either **1**, (*Z*)-**2** or (*E*)-**2** as the diene.

Dienes **1** and (*E*)-**2** react with methyl acrylate under thermal conditions (80 °C, 12 h, neat) to yield the expected Diels–Alder adduct. No reaction was observed with (*Z*)-**2**, under identical conditions, at temperatures up to 120 °C (sealed tube), or with either toluene or ethane-1,2-diol as solvent. The dienophile may be activated by coordination with a Lewis acid, in which case the reaction proceeds in dichloromethane at 0 °C for 50 h or more conveniently at room temperature for 6 h in the case of **1**. However, no reaction between (*Z*)-**2** and methyl acrylate was observed when this improved

---

* Correspondence and reprints

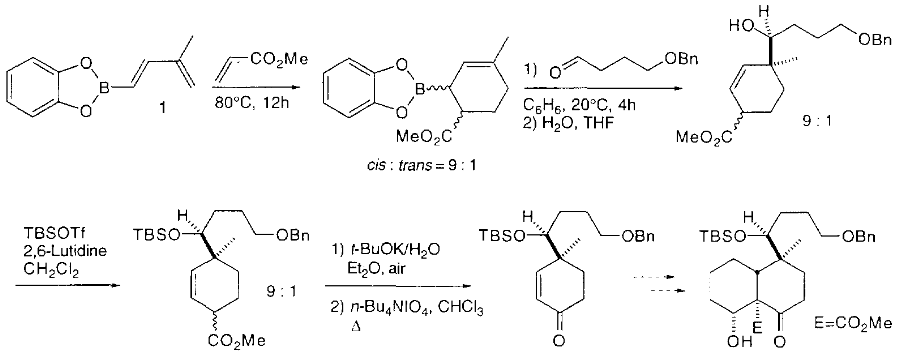


Fig 2

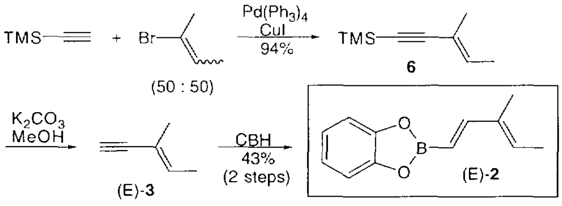


Fig 3

procedure was used [1f]. Diene (*Z*)-**2** thus appears to be far less reactive than **1**.

Similar examples of drastically different reactivities of isomers of polysubstituted dienes in reactions where an *s-cis* conformation is necessary are reported in the literature [3]. In such dienes, the most stable conformation is usually *s-trans*, while the most reactive is *s-cis*. The results are often explained by the high steric constraints of the *s-cis* conformation of the unreactive dienes, preventing them from reaching it. However, no quantitative data exist to support this idea. Furthermore, recent ab initio calculations on the energy profile of the rotation around the central C-C bond of 1,2-dimethylbutadienes [4] are in contradiction with this hypothesis, as the rotation barrier is higher for the (*E*) isomer than for the (*Z*) isomer.

In an attempt to clarify this point, conformational studies and molecular orbital (MO) calculations were run on dienes **1**, (*E*)-**2** and (*Z*)-**2**. In addition, it was hoped that the MO calculations could provide a better understanding of the effect of a boronate group on these dienes.

Since the π MOs of (*E*)-**2** and (*Z*)-**2** are expected to be essentially similar, the lack of reactivity of (*Z*)-**2** could be attributed to a number of other factors: (i) the energy of the *s-cis* conformation relative to that of the *s-trans* might be too high; (ii) there might be a prohibitively high barrier connecting these conformations; (iii) steric constraints in the *s-cis* might cause significant distortion in the dienyl fragment; and (iv) steric repulsion with the dienophile in the Diels–Alder step might be higher in this case (in the cyclohexene product, no significant steric difference is expected).

It has been reported [5] that Lewis acid catalysis lowers the activation energy to a value as low as 10.4 kcal/mol in the case of the $AlCl_3$-catalyzed addition of methyl acrylate to butadiene. Therefore, it cannot be a priori decided which step has the highest activation barrier, diene isomerization or Diels–Alder reaction.

The planar cisoid conformations of dienes **1** and (*Z*)-**2**, which are required for a concerted Diels–Alder reaction to take place, were calculated at the ab initio Hartree–Fock level using the 6-31G basis set [6], and their optimized geometries are shown in figure 5 [7]. From these geometries, the distances between the terminal dienyl carbons can be calculated, and are

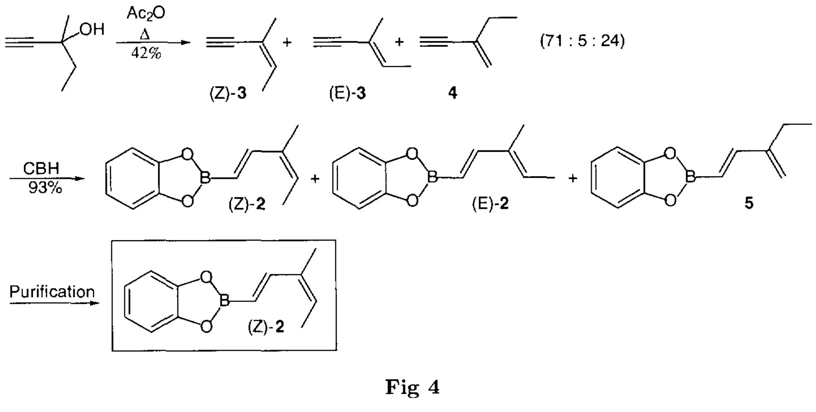


Fig 4

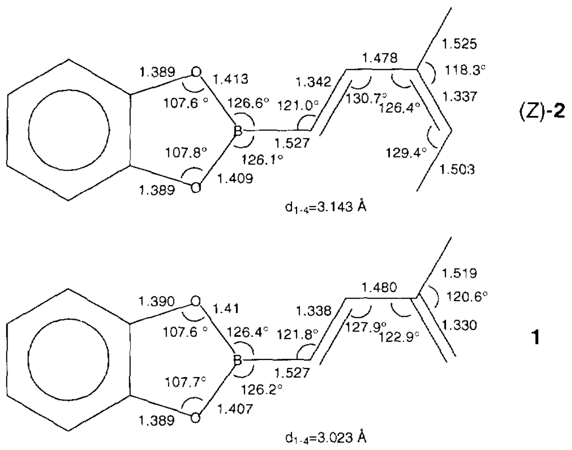


Fig 5

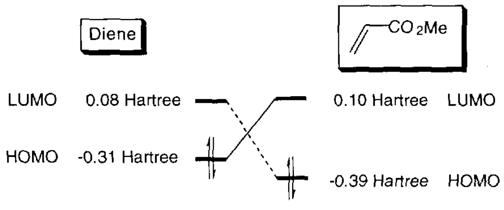


Fig 6

displayed in figure 5. The 0.12 Å difference should not be responsible for the observed difference in reactivity.

The LUMO and the HOMO energies of the dienes were found to be about +0.08 and −0.31 Hartree, respectively. For electron-deficient dienophiles like methyl acrylate, these values are about 0 and −0.4 Hartree. The main interactions are therefore expected to occur between the LUMO of methyl acrylate and the HOMO of the dienes (fig 6). In order to try and understand the effect of a terminal boronate substitution on a diene, we have compared the MOs of dienes **1** and (*Z*)-**2** with those of isoprene (see fig 7). The HOMO of isoprene has an energy of −0.315 Hartree, while the energy of the next occupied π orbital is −0.422 Hartree. Its LUMO has an energy of +0.124 Hartree. The largest coefficient of the HOMO is on carbon C4, the smallest on carbon C2.

The orbitals of diene **1** display important differences: the two HOMOs are close in energy (−0.311 and −0.339 Hartree) and they both have important coefficients on the dienyl system. The next π orbital (−0.344 Hartree) is centered on the catechol fragment, and the next, at −0.432 Hartree, is centered on the diene and is derived from the lowest π orbital of isoprene. The LUMO is lower than for isoprene, +0.077 Hartree [8]. The main interactions eventually occur between the LUMO of methyl acrylate and the two HOMOs of diene **1**. These two must both be considered because their energies are similar. No significant qualitative differences with the HOMO of isoprene are observable. The main coefficient is still located on carbon C4 for both orbitals, the lowest is still on C2, although it is quite lower on the second occupied MO. The coefficient on boron is virtually zero in the HOMO and small in the second orbital. Hence, the boronate group does not seem to induce any significant polarization of the diene. This was confirmed by calculating the π electronic charges. This was near zero on each carbon atom of the π dienic system of isoprene, and of diene **1** as well, except on carbon C2 which bears a small charge of +0.11. The π charge on boron is +0.65. When the orbitals of

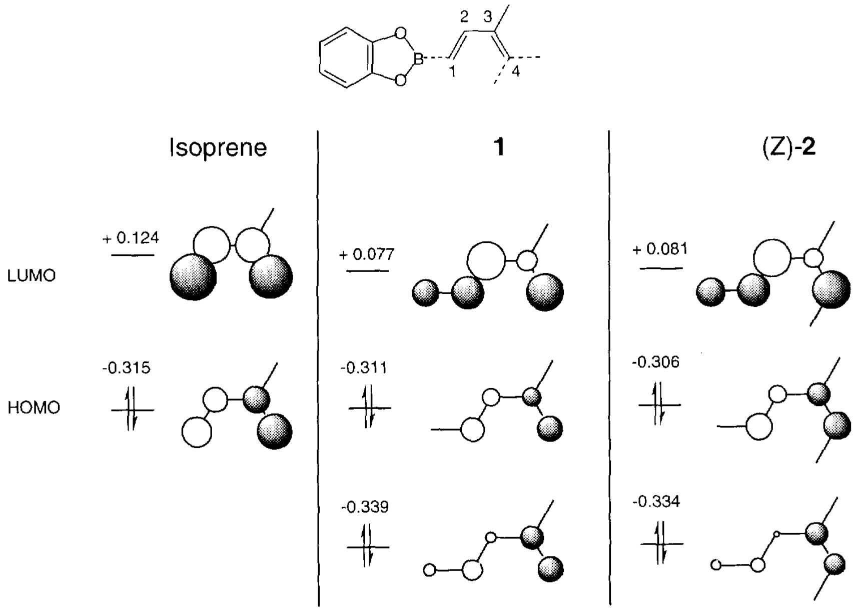


Fig 7. Molecular orbitals of isoprene, **1** and (*Z*)-**2**. For the sake of clarity, only the coefficients on the dienyl carbons and the boron atom are shown.

diene (*Z*)-**2** were calculated, we found that they can in no way account for its difference of reactivity in comparison to diene **1**. They are essentially very similar, in the repartition of the coefficients as well as in the π electronic charges. The two HOMOs lie only slightly higher in energy (−0.306 and −0.334 Hartree) because of the electron-donating effect of the additional methyl group, and hence closer to the LUMO of the dienophile, which should rather increase the reactivity, contrary to our observations. The explanation of the differences of reactivity between diene (*Z*)-**2** and both dienes (*E*)-**2** and **1** must therefore be found elsewhere, and so, of course, the role of steric interactions was investigated.

In order to get a deeper insight on the origin of the different reactivities of the dienes under study, it seemed necessary to look at their conformational energy profiles. We first ran AM1 calculations [6], optimizing the geometry for a series of dihedral angles corresponding to the rotation around the central C-C single bond. The profile obtained in this way for isoprene clearly disagrees with the 6-31G* ab initio profile [4] (fig 8). However, an acceptable curve with a close fit is obtained (fig 8) when energy calculations are done at the ab initio Hartree–Fock level using the 6-31G basis set [6], on the AM1 optimized geometries for each dihedral angle (denoted 6-31G//AM1).

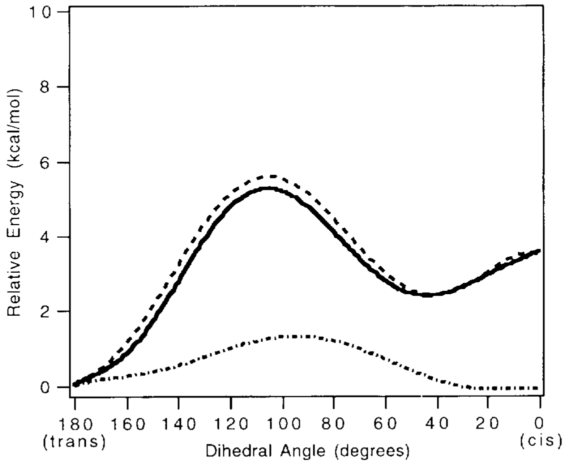
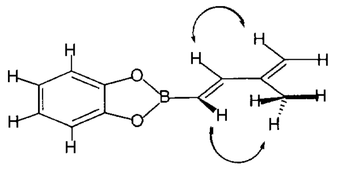


Fig 8. Energy curves for isoprene. --- 6-31G//AM1; — 6-31G*; ·-·- AM1.

Once this method was determined to be valid, we used it to calculate the energy profiles for dienes **1**, (*Z*)-**2** and (*E*)-**2**. The corresponding curves are displayed in figure 9. The most stable conformation in all cases was planar *s-trans*, which is in accord with a NOESY NMR experiment run on diene **1**, revealing the following NOE correlations on a Bruker AM 400 (400 MHz) spectrometer:



In the *s-cis* conformation, the MO energies and the geometries we obtained for **1** and (*Z*)-**2** were essentially the same as with full ab initio calculations (previous paragraph). The relative energy values for the planar *s-cis* conformer are the same for (*Z*)-**2** and (*E*)-**2**, and slightly higher (by 1 kcal/mol) than that of **1**. Yet, the rotational energy barrier (corresponding approximately to a dihedral angle of 100°) of (*Z*)-**2** is about 4 kcal/mol lower than that of (*E*)-**2** and 2 kcal/mol lower than that of **1**. If, as is conventionally admitted, we consider that the diene must initially adopt a planar cisoid conformation to react with methyl acrylate, the above results clearly indicate that the unreactive (*Z*)-**2** should be able to react at 80 °C, since **1** does so even at 0 °C.

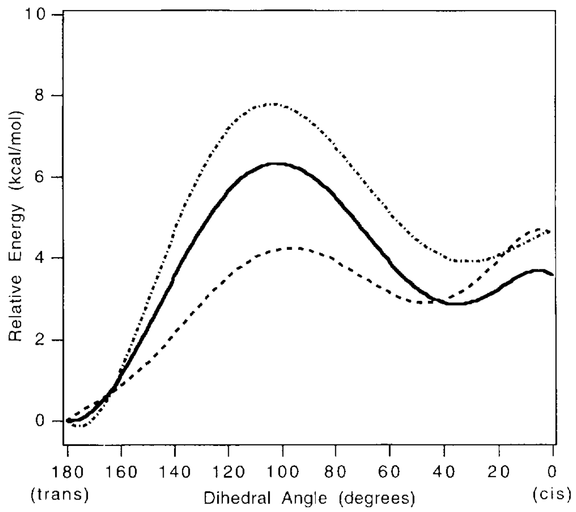


Fig 9. Energy curves for dienes **1** (—), (*E*)-**2** (·-·-) and (*Z*)-**2** (---).

Consequently, our results tend to show that the usual explanation is not acceptable and lead us to conclude that the steric constraints induced by the methyl group on diene (*Z*)-**2** are responsible for the difference in reactivity with dienes (*E*)-**2** and **1**. Since such constraints are not expected to be significantly different in the cyclohexene product, we are led to the conclusion that the difference arises in the Diels–Alder transition state. Since the methyl in (*Z*)-**2** does not induce a significant distortion of the diene skeleton (see fig 1), we propose that it induces a larger steric repulsion between the diene and the dienophile in the Diels–Alder transition state. This appears to be general for Diels–Alder reactions of dienes bearing a terminal methyl substituent, in agreement with the calculations of Guo and Karplus [4]. It should also be noted that the boronate group does not have a strong influence on the Diels–Alder reactivity of the dienes under study here, because of its negligible contribution to the HOMO. However it is found to lower the LUMO energy so that it might increase the reactivity toward electron-rich dienophiles. This is currently under experimental investigation.

Experimental section

NMR spectra were recorded in $\mathrm{CDCl_3}$ solutions using Bruker WP 200 (^{1}H at 200 MHz, ^{13}C at 50.1 MHz) or AM 400 (^{1}H at 400 MHz, ^{13}C at 100.3 MHz) spectrometers. ^{1}H NMR spectra were referenced to residual $\mathrm{CHCl_3}$ ($\delta = 7.26$ ppm) and ^{13}C NMR spectra to $\mathrm{CDCl_3}$ ($\delta = 77.0$ ppm). Flash column chromatography was performed with silica gel 60 (230–400 mesh, Merck). All reactions were performed under a nitrogen atmosphere. Anhydrous pentane was distilled from sodium/benzophenone; DMF was distilled under reduced pressure (15 mmHg) from $\mathrm{CaH_2}$. Diene **1** was prepared as previously described [1e].

*2-(3-Methylpenta-1,3-(E)-dienyl)-1,3,2-benzodioxaborole (E)-***2**

Catecholborane (1.07 mL, 10 mmol) was added at 0 °C to a solution of (*E*)-**3** in pentane (obtained from 10 mmol of **6**). The mixture was stirred 15 min at 0 °C, and then heated to reflux for 2 h 30 min, cooled and stirred overnight at room temperature. The solution was washed with water (3 x 10 mL), dried over magnesium sulfate and concentrated to afford 0.86 g (4.3 mmol, 43% in two steps) of diene (*E*)-**2**.

IR (ν, cm^{-1}): 1 603, 1 473, 1 401, 1 386, 1 366, 1 342, 1 326, 1 264, 1 236, 1 191, 992, 909.

^{1}H NMR δ (ppm): 7.41 (1H, d, $J = 18$ Hz), 7.25–7.18 (2H, m), 7.11–7.05 (2H, m), 5.94 (1H, q, $J = 6.5$ Hz), 5.75 (1H, d, $J = 18$ Hz), 1.84 (3H, s), 1.83 (3H, d, $J = 6.5$ Hz).

^{13}C NMR δ (ppm): 156.8, 148.2, 136.0, 133.7, 122.3, 112.0, 20.8, 13.9.

MS (GC, CI, $\mathrm{NH_3}$): 80, 185, 199, *200*, 201 (MH$^+$, ^{11}B), 229 (M...$\mathrm{C_2H_5^+}$, ^{11}B).

*2-(3-Methylpenta-1,3-(Z)-dienyl)-1,3,2-benzodioxaborole (Z)-***2**

Catecholborane (2.65 mL, 25 mmol) was added at 0 °C to a 71:5:24 mixture of enynes (*Z*)-**3**, (*E*)-**3** and **4** (2 g, 25 mmol) in a 25 mL three-necked flask fitted with a condenser. The mixture was heated to 70 °C for 1 h (the reaction was monitored using ^{1}H NMR), then cooled to room temperature. Dry pentane (10 mL) was added. The resulting solution was removed through a canula, filtered and concentrated to yield 4.65 g (23.2 mmol, 93%) of a mixture of dienes (*Z*)-**2**, (*E*)-**2** and **5**, in the same ratio as the starting enynes. (*Z*)-**2** could be purified: the mixture of dienes underwent a Diels–Alder reaction with methyl acrylate. Dienes (*E*)-**2** and **5** disappeared, while their Diels–Alder adducts were observed; (*Z*)-**2** remained unchanged. Flash column chromatography, followed by a pentane trituration (to remove residual catechol) yielded pure (*Z*)-**2**, which was then used in the Diels–Alder studies.

IR (ν, cm^{-1}): 1 600, 1 473, 1 394, 1 371, 1 342, 1 323, 1 309, 1 265, 1 236, 1 189, 991.

^{1}H NMR δ (ppm): 7.88 (1H, d, $J = 18$ Hz), 7.26–7.23 (2H, m), 7.11–7.08 (2H, m), 5.89 (1H, d, $J = 18$ Hz), 5.78 (1H, q, $J = 6$ Hz), 1.92 (3H, s), 1.91 (3H, d, $J = 6$ Hz).

^{13}C NMR δ (ppm): 148.3, 148.2, 133.9, 130.9, 122.6, 112.3, 19.7, 13.5.

MS (GC, CI, $\mathrm{NH_3}$): 80, 144, 185, 199, *200* (MH$^+$, ^{10}B), 201 (MH$^+$, ^{11}B), 217, 218 (MH$^+$...$\mathrm{NH_3}$, ^{10}B), 219 (MH$^+$...$\mathrm{NH_3}$, ^{11}B).

*(E)-3-Methylpent-3-en-1-yne (E)-***3**

Potassium carbonate (21 mg, 0.15 mmol) was added to a solution of trimethylsilyl enyne **6** (1.52 g, 10 mmol) in dry methanol (4 mL), which was then stirred overnight at 40 °C. The mixture was then cooled to 0 °C, and pentane (10 mL) added. The solution was washed with chilled water (7 x 8 mL), dried over magnesium sulfate and filtered to afford a solution of (*E*)-**3** in pentane containing a minimal amount of methanol and directly used in the preparation of (*E*)-**2**.

^{1}H NMR δ (ppm): 6.01 (1H, qq, $J = 7.5$ Hz, $J = 1$ Hz), 2.74 (1H, s), 1.79 (3H, d, $J = 1$ Hz), 1.69 (3H, dd, $J = 7.5$ Hz, $J = 1$ Hz).

^{13}C NMR δ (ppm): 134.0, 117.8, 87.0, 73.2, 16.6, 14.0.

*(Z)-3-Methylpent-3-en-1-yne (Z)-***3**

Acetic anhydride (7.4 mL, 78 mmol) and *p*-toluenesulfonic acid monohydrate (0.46 g, 2.4 mmol) were charged in a 50 mL three-necked flask fitted with a dropping funnel and a distillation column (the reception flask was cooled to −78 °C). 3-Methylpent-1-yn-3-ol (6.8 mL, 60 mmol) was slowly added at 0 °C over 10 min. The mixture was then heated to the distillation of the product, and became very dark. The distillate was washed with a chilled 1 N NaOH solution (2 x 5 mL), dried over magnesium sulfate and filtered, to yield 2 g (25 mmol, 42%) of a 71:5:24 mixture of enynes (*Z*)-**3**, (*E*)-**3** and **4**.

^{1}H NMR δ (ppm): 5.77 (1H, q, $J = 5$ Hz), 3.13 (1H, s), 1.81 (3H, s), 1.81 (3H, d, $J = 5$ Hz).

^{13}C NMR δ (ppm): 134.3, 118.1, 83.3, 81.0, 23.0, 16.3.

2-Ethylbut-1-en-3-yne **4**

See the preparation of (*Z*)-**3**.

^{1}H NMR δ (ppm): 5.35 (1H, s), 5.26 (1H, s), 2.85 (1H, s), 2.15 (2H, q, $J = 7.5$ Hz), 1.08 (3H, t, $J = 7.5$ Hz).

2-(3-Ethylbuta-1,3-dienyl)-1,3,2-benzodioxaborole **5**

See the preparation of (*Z*)-**2**.

^{1}H NMR δ (ppm): 7.45 (1H, d, $J = 18.5$ Hz), 7.25–7.18 (2H, m), 7.11–7.05 (2H, m), 5.94 (1H, d, $J = 18.5$ Hz), 5.33 (1H, s), 5.31 (1H, s), 2.35 (2H, q, $J = 7.5$ Hz), 1.16 (3H, t, $J = 7.5$ Hz).

^{13}C NMR δ (ppm): 154.4, 148.3, 143.5, 122.5, 119.8, 112.3, 23.8, 12.5.

(E)-3-Methyl-1-(trimethylsilyl)pent-3-en-1-yne **6**

Tetrakis(triphenylphosphine)palladium(0) (0.34 g, 0.3 mmol) was added to a solution of *cis/trans*-2-bromobut-2-ene (4.3 mL, 42 mmol) in DMF (17 mL), protected from light. The mixture was cooled to 0 °C, and pyrrolidine (3.75 mL, 45 mmol), (trimethylsilyl)acetylene (4.24 mL, 30 mmol) and copper(I) iodide (0.11 g, 0.6 mmol) were added. The solution was heated to 50 °C for 3 h in the light and the color became dark. When cooled to room temperature, a saturated solution of ammonium chloride was added (30 mL). The organic layer was removed, while the aquous layer was extracted with pentane (3 x 30 mL). The combined organic layers were washed with a saturated solution of copper sulfate, then with water, and finally dried over magnesium sulfate, filtered and concentrated to afford 4.33 g (28.4 mmol, 94%) of almost pure enyne **6**, directly used without further purification. However, this compound may be distilled (bp = 56 °C/20 mbar).

IR (ν, cm^{-1}): 2 961, 2 921, 2 141, 1 250, 1 219, 858, 642.

^{1}H NMR δ (ppm): 6.00 (1H, qq, $J = 7$ Hz, $J = 1$ Hz), 1.77 (3H, d, $J = 1$ Hz), 1.67 (3H, dd, $J = 7$ Hz, $J = 1$ Hz), 0.17 (9H, s).

^{13}C NMR δ (ppm): 133.9, 118.6, 108.6, 89.6, 16.7, 14.0, 0.1.

MS (GC, CI, NH_3): *90*, 92, 153 (MH^+), 155, 170 ($MH^+...NH_3$).

References and notes

1 a) Mikhailov BM, Cherkasova KL, *Zh Obshch Khim* (1972) 42, 138 and 1744
b) Vaultier M, Truchet F, Carboni B, *Tetrahedron Lett* (1987) 28, 4169
c) Wang X, *J Chem Soc, Chem Commun* (1991) 1515
d) Renard PY, Thèse de l'université de Paris Sud, Orsay (1993)
e) Renard PY, Lallemand JY, *Bull Soc Chim Fr* (1996) 133, 143
f) Six Y, Lallemand JY, unpublished results
g) Garnier L, Plunian B, Mortier J, Vaultier M, *Tetrahedron Lett* (1996) 37, 6699

2 Recent general reviews:
a) Pelter A, Smith K, Brown HC, *Borane Reagents (Best Synthetic Methods)*, Academic Press, London, 1988
b) Yamamoto Y, Asao N, *Chem Rev* (1993) 93, 2207, and references therein
c) Brown HC, Ramachandran PV, *Pure Appl Chem* (1994) 66, 201, and references therein

3 See, for instance:
a) Rücker C, Lang D, Sauer J, Friege H, Sustmann R, *Chem Ber* (1980) 113, 1663
b) Dauben WG, Baker WR, *Tetrahedron Lett* (1982) 23, 2611
c) Reeve W, Reichel DM, *J Org Chem* (1972) 37, 68
d) Roth WR, Lennartz HW, Doering WVE, Dolbier WR Jr, Schmidhauser JC, *J Am Chem Soc* (1988) 110, 1883

4 Guo H, Karplus M, *J Mol Struct* (1992) 260, 347

5 Inukai T, Kojima T, *J Org Chem* (1967) 32, 872

6 Ab initio calculations were run using the HONDO 8.1 program, from MOTECC-90, Dupuis M et al, IBM Corp, Yorktown Heights, NY 12401 (1990); AM1 calculations were performed with the MOPAC 6.00 program:
a) Stewart JJP, *QCPE Bull* (1983) 3, 101
b) Olivella S, ibid (1986) 4, 109

7 Optimizations were carried out under the constraint of C_s symmetry. Full details about the optimized geometries are available upon request

8 The LUMO coefficient on the boron atom is fairly high, which is consistent with results involving vinylboranes: Singleton A, *J Am Chem Soc* (1992) 114, 6563