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Mendeleev Commun., 2007, **17**, 139–141

Mendeleev Communications

Stereoselectivity of allylboron–acetylene condensation with crotylic boranes: synthesis of 4-methyl-1-boraadamantane derivatives

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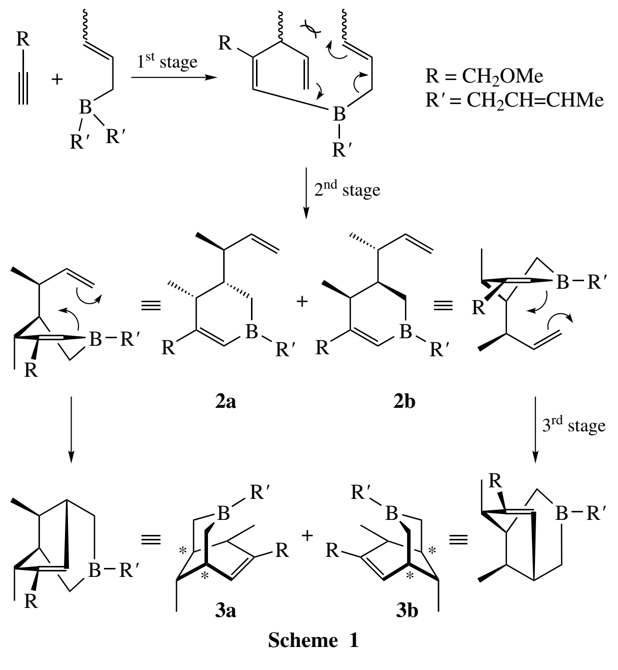
DOI: 10.1016/j.mencom.2007.05.002

The determining influence of the nature of a crotylborating reagent on the stereoresult of the allylboron–acetylene condensation with crotylic boranes has been revealed and applied to the synthesis of 4-methyl-1-boraadamantane derivatives.

The diastereo- and enantioselective crotylboration of compounds containing activated multiple bonds is successfully applied to the synthesis of natural and biologically active molecules due to the availability of configurationally stable esters of crotylboronic acid, as well as enantiopure B-[*E*]- and B-[*Z*]-crotylic boranes.[1]

On the other hand, there is the only example when tricrotylborane was used in allylboron–acetylene condensation (ABAC[2]): the thermal reaction of triallylboranes with terminal acetylenes. The formation of 3-crotyl-8-*syn*-9-*anti*-dimethyl-6-methoxymethyl-3-borabicyclo[3.3.1]non-6-ene[3] **3** as the only product implies the strong stereocontrol on the second stage of ABAC resulting in the formation of only two of eight possible isomeric 1-boracyclohex-2-enes **2a** and **2b**, which give rise to the racemate of only one of possible 8,9-dimethyl substituted bicycles **3a** and **3b** (Scheme 1).

This result is non-trivial because tricrotylborane was previously found[4] to exist as an equilibrated mixture of *Z*- and *E*-isomers in a 3:7 ratio due to the fast 1,3-migration of the boryl group (permanent allylic rearrangement).



Scheme 1

Here, we report the determining influence of the methyl group in the 3-position of (penta-1,4-dien-1-yl)borane (product of the first stage) on the stereoresult of intramolecular crotylboration at the second stage of ABAC.

The stereoselectivity observed in the reaction of 3-methoxyprop-1-yne with tricrotylborane[3] is a general regularity. As we have shown, the condensation of phenylacetylene with tricrotylborane (135–140 °C) followed by treatment of the reaction mixture with methanol (Scheme 2) gives rise to only product **4** with 8-*syn*, 9-*anti* methyl groups.[†] The stereochemistry of **4** was determined by a chemical method.

The reduction of the endocyclic double bond in **4** with hydrogen easily proceeds at ambient temperature on $Pd/SrCO_3$ and afforded 3-borabicyclo[3.3.1]nonane derivative **5**. Protolytic cleavage of the latter with butyric acid furnished 2,3,4,5-tetramethyl-1-phenylcyclohexane **6** (Scheme 2).

The bulky phenyl substituent in **6** plays a role of a conformational lock arranging a chair molecule of **6** in an equatorial conformation. In the ^{13}C NMR spectrum of **6**, there are signals

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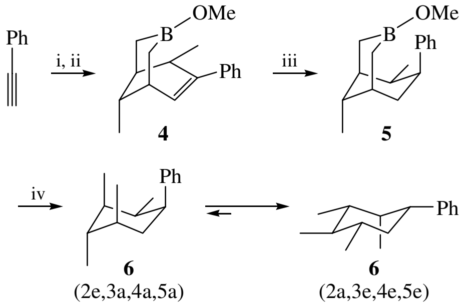
[†] For **4**: 63% yield; bp 142–143 °C (2 Torr). ^1H NMR (200.13 MHz, $CDCl_3$) δ: 0.72–1.61 [m, 4H, H(2), H(4)], 0.98 (d, 3H, 8-Me, ^3J 6.6 Hz), 1.26 (d, 3H, 9-Me, ^3J 7.3 Hz), 2.08–2.59 [m, 3H, H(5), H(8β), H(9*syn*)], 3.15 [m, 1H, H(1), *J* 6.3 Hz], 3.79 (s, 3H, OMe), 5.79 [d, 1H, H(6), $^3J_{H(6)-H(5)}$ 5.5 Hz], 7.24–7.56 (m, 5H, Ph). ^{13}C NMR (DEPT-135) (50.32 MHz, $CDCl_3$) δ: 17.5, 18.1 (8-Me, 9-Me), 20.3 [br., C(2)], 25.0 [br., C(4)], 30.4 [C(9)], 37.6 [C(1)], 37.9 [C(8)], 39.6 [C(5)], 53.0 (OMe), 125.9 (*p*-Ph), 126.3 (*o*-Ph), 127.5 (*m*-Ph), 134.0 [C(7)], 138.9 [C(6)], 143.0 (*ipso*-Ph). ^{11}B NMR (64.21 MHz, $CDCl_3$) δ: 54.3. Found (%): C, 80.68; H, 9.14; B, 3.93. Calc. for $C_{17}H_{23}BO$ (%): C, 80.33; H, 9.12; B, 4.25.

For **5**: 80% yield; bp 146–148 °C (2 Torr). ^1H NMR (200.13 MHz, $CDCl_3$) δ: 0.60–2.67 (m, 11H, 3-BBN core), 1.17 (d, 3H, Me, ^3J 1.7 Hz), 1.21 (d, 3H, Me, ^3J 1.0 Hz), 3.29 (s, 3H, OMe), 7.08–7.47 (m, 5H, Ph). ^{13}C NMR (DEPT-135) (50.32 MHz, $CDCl_3$) δ: 18.7, 19.3 (8-Me, 9-Me), 22.7 [br., C(2)], 27.4 [br., C(4)], 31.7, 32.8 [C(8), C(9)], 33.4 [C(6)], 39.1, 39.8, 40.7 [C(1), C(5), C(7)], 52.5 (OMe), 124.7 (*p*-Ph), 127.5 (*o*-Ph), 129.3 (*m*-Ph), 145.1 (*ipso*-Ph). ^{11}B NMR (64.21 MHz, $CDCl_3$) δ: 54.0. Found (%): C, 79.75; H, 9.62; B, 3.81. Calc. for $C_{17}H_{25}BO$ (%): C, 79.70; H, 9.84; B, 4.22.

For **6**: 56% yield. ^1H NMR (200.13 MHz, $CDCl_3$) δ: 0.53 (d, 3H, Me, ^3J 7.6 Hz), 0.59–3.02 (m, 10H, cyclohexane ring, Me), 0.95 (d, 3H, Me, ^3J 6.6 Hz), 1.03 (d, 3H, Me, ^3J 6.2 Hz), 7.12–7.53 (m, 5H, Ph). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 6.7 (2-Me), 16.7, 18.5, 20.7 (3-Me, 4-Me, 5-Me), 33.4 [C(6)], 38.3 [C(4)], 39.3 [C(5)], 41.8 [C(2)], 42.9 [C(3)], 47.3 [C(1)], 125.5 (*p*-Ph), 127.5 (*o*-Ph), 127.9 (*m*-Ph), 145.9 (*ipso*-Ph). Found (%): C, 88.66; H, 11.31. Calc. for $C_{16}H_{24}$ (%): C, 88.82; H, 11.18. MS, *m*/*z* (%): 216 $[M]^+$ (27.8).



Scheme 2 *Reagents and conditions*: i, tricrotylborane, 135–140°C, 3 h; ii, MeOH, reflux for 2 h; iii, H_2, 1 atm, Pd/$SrCO_3$, 20 °C; iv, Bu^nCOOH, reflux for 3 h.

Table 1 Calculated and experimental ^{13}C NMR chemical shifts of a cyclohexane ring in 2,3,4,5-tetramethyl-1 phenylcyclohexane **6**.

C atom	^{13}C NMR shift, δ/ppm		
	Calculated for **6a**	Calculated for **6b**	Experimental
C-1	47.0	51.2	47.3
C-2	41.2	40.8	41.8
C-3	42.0	42.0	42.9
C-4	38.9	39.3	38.3
C-5	39.4	34.9	39.3
C-6	35.6	35.6	33.4

of four methyl groups, three of which must be assigned as equatorial (16.7, 18.5, 20.7 ppm) and one, as axial (6.7 ppm),[5,6] which could correspond to two isomers of **6**, shown in Figure 1.

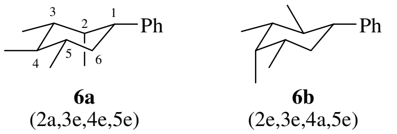
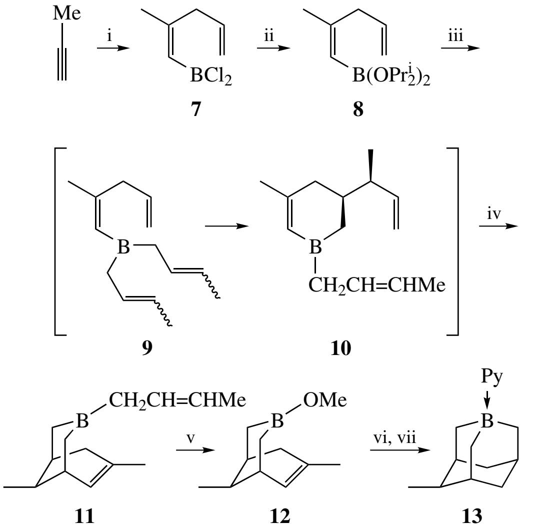


Figure 1

^{13}C NMR chemical shifts of a cyclohexane ring in isomeric **6a** and **6b** were calculated on the basis of an additive scheme of substituent effects[5,6] (starting from phenylcyclohexane[7]) and compared with experimental data (see Table 1). The values of δ corresponding to C-1 and C-5 uniquely argue for the structure of **6a** and the 8-*syn*, 9-*anti* arrangement of methyl groups in ABAC product **4**.

As shown in Scheme 1, the intramolecular crotylboration of the terminal double bond at the second stage of ABAC stereospecifically leads to 4-methyl-5-(but-1-en-3-yl)-1-boracyclohex-2-enes **2a** and **2b** with an *anti* arrangement of Me groups in a borinene ring and the but-1-en-3-yl fragment, that means that the crotyl group attacks the face opposite the methyl group in the 3-position of (penta-1,4-dien-1-yl)borane **1**.

The absence of 3-methyl in **1** should result in the loss of selectivity; however, as we have found, unexpectedly changes the stereoselectivity of crotylboration to opposite. The thermal bicyclization of (2-methylpenta-1,4-dien-1-yl)dicrotylborane **9** prepared from propyne, allyldichloroborane[‡] (generated *in situ* by the redistribution reaction of All_3B and BCl_3[8,9]) and crotylic Grignard's reagent (so-called step-by-step controlled ABAC[10]) gave 3-borabicyclo[3.3.1]non-6-ene derivative **11** with the 9-*syn* arrangement of the methyl group, the methanolysis of which afforded methoxy bicycle **12** (formation of *ca.* 5% of 9-*anti*-Me isomer was also observed). The hydroboration–isomerization of the latter with BH_3·THF in a THF solution after treatment of the reaction mixture with pyridine gives rise to air-stable pyridine-4-*syn*-methyl-1-boraadamantane **13** (Scheme 3).[§]



Scheme 3 *Reagents and conditions*: i, CH_2Cl_2, $AllBCl_2$, –78 °C, 15 min; ii, Et_3N/Pr^iOH, –78 °C → 20 °C, reflux for 2 h; iii, $MeCH{=}CHCH_2MgBr$, Et_2O/THF, reflux for 8 h; iv, 135–140 °C, 3 h; v, MeOH, reflux for 2 h; vi, BH_3·THF, THF, reflux for 4 h; vii, pyridine, THF.

The stereochemistry of **13** was determined from ^{13}C NMR data. Chemical shifts of the 1-boraadamantane core in isomers of **13** were calculated[3,11] starting from a parent compound[12] and are presented in Table 2.

[‡] Allyldichloroborane prepared *in situ* at –78 °C from 1 equiv. of All_3B and 2 equiv. of BCl_3. ^{11}B NMR (64.21 MHz, $CDCl_3/CH_2Cl_2$) δ: 61.2.

[§] For **7** (reaction mixture): ^1H NMR (200.13 MHz, $CH_2Cl_2/CDCl_3$) δ: 2.11 (s, 3H, Me), 3.49 [d, 2H, H(3), $^3J_{H(3)-H(4)}$ 6.6 Hz], 5.20 [d, 1H, H(5A), $^3J_{H(5A)-H(4)}$ 10.0 Hz], 5.24 [dd, 1H, H(5B), $^3J_{H(5B)-H(4)}$ 17.0 Hz, $^2J_{H(5B)-H(5A)}$ 1.4 Hz], 5.91 [ddt, 1H, H(4), $^3J_{H(4)-H(5B)}$ 17.0 Hz, $^3J_{H(4)-H(5A)}$ = = 10.0 Hz, $^3J_{H(4)-H(3)}$ 6.6 Hz], 6.07 [s, 1H, H(1)]. ^{13}C NMR (DEPT-135) (50.32 MHz, $CH_2Cl_2/CDCl_3$) δ: 28.2 (Me), 39.9 [C(3)], 117.0 [C(5)], 126.0 [br., C(1)], 131.6 [C(2)], 134.6 [C(4)]. ^{11}B NMR (64.21 MHz, CH_2Cl_2) δ: 50.9. IR (CH_2Cl_2, ν/cm^{-1}): 1608 ($\nu_{BC=C}$).

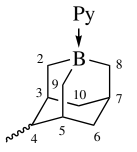
For **8**: 74% yield; bp 54–57 °C (2 Torr). ^1H NMR (200.13 MHz, $CDCl_3/CH_2Cl_2$) δ: 1.16 [d, 12H, Me (OPr^i), ^3J 6.2 Hz], 1.82 (s, 3H, Me), 3.03 [d, 2H, H(3), $^3J_{H(3)-H(4)}$ 6.9 Hz], 4.43 (m, 2H, OCH, ^3J 6.2 Hz), 4.99 [d, 1H, H(5A), $^3J_{H(5A)-H(4)}$ 10.0 Hz], 5.05 [dd, 1H, H(5B), $^3J_{H(5B)-H(4)}$ 17.0 Hz, $^2J_{H(5B)-H(5A)}$ 1.4 Hz], 5.25 [s, 1H, H(1)], 5.82 [ddt, 1H, H(4), $^3J_{H(4)-H(5B)}$ 17.0 Hz, $^3J_{H(4)-(5A)}$ 10.0 Hz, $^3J_{H(4)-H(3)}$ 6.9 Hz]. ^{13}C NMR (DEPT-135) (50.32 MHz, $CDCl_3/CH_2Cl_2$) δ: 24.4 [Me (OPr^i)], 26.0 (Me), 41.0 [C(3)], 65.2 (OCH), 115.2 [C(5)], 137.0 [C(4)], 154.0 [C(2)]. ^{11}B NMR (64.21 MHz, $CDCl_3/CH_2Cl_2$) δ: 26.6. IR (CH_2Cl_2, ν/cm^{-1}): 1628 ($\nu_{BC=C}$). Found (%): C, 68.75; H, 11.12; B, 4.95. Calc. for $C_{12}H_{23}BO_2$ (%): C, 68.59; H, 11.03; B, 5.14.

For **11** (as a mixture of 3:1 *E*- and *Z*-crotyl isomers) not isolated, formation of **11** on heating of the mixture of **9** and **10** was monitored by NMR spectroscopy. ^{13}C NMR (50.32 MHz) δ: 12.3 (Me, *Z*-crotyl), 17.8 (Me, *E*-crotyl), 18.3 (9-Me), 23.2 (7-Me), 32.6 (br., CB crotyl), 33.5 [C(9)], 34.3 [C(1)], 35.6, 35.9 [C(8), C(5)], 36.4 [br., C(2), C(4)]. ^{11}B NMR (64.21 MHz) δ: 84.6.

For **12**: 43% yield; bp 86–88 °C (2 Torr). ^1H NMR (200.13 MHz, $CDCl_3$) δ: 0.75–2.32 (br. m, 9H, 3-BBN core), 0.92 (d, 3H, 9-Me, ^3J 6.9 Hz), 1.53 (s, 3H, 7-Me), 3.59 (s, 3H, OMe), 5.27 [d, 1H, H(6), $^3J_{H(6)-H(5)}$ 3.5 Hz]. ^{13}C NMR (DEPT-135) (50.32 MHz, $CDCl_3$) δ: 18.7 (9-Me), 23.9 (7-Me), 25.1 [br., C(2)], 27.5 [br., C(4)], 33.3 [C(9)], 34.9 [C(1)], 36.2 [C(5), C(8)], 53.4 (OMe), 126.5 [C(6)], 129.1 [C(7)]. ^{11}B NMR (64.21 MHz, $CDCl_3$) δ: 54.8. Found (%): C, 73.71; H, 10.86; B, 6.22. Calc. for $C_{11}H_{19}BO$ (%): C, 74.09; H, 10.75; B, 6.18.

For **13**: 61% yield; mp 84–86 °C. ^1H NMR (200.13 MHz, $CDCl_3$) δ: 0.54–2.34 (m, 14H, intricate multiplet of 1-boraadamantane core protons), 1.03 (d, 3H, Me, ^3J 7.1 Hz), 7.45 (t, 2H, *m*-Py, *J* 6.6 Hz), 7.88 (t, 1H, *p*-Py, *J* 7.6 Hz), 8.47 (d, 2H, *o*-Py, *J* 5.2 Hz). ^{13}C NMR (DEPT-135) (50.32 MHz, [$^2H_6$]DMSO) δ: 19.5 (Me), 25.8 [br., C(2), C(9)], 32.1 [C(7)], 33.3 [C(6), C(10)], 33.8 [br., C(8)], 37.5 [C(3), C(5)], 40.2 [C(4)], 126.1 (*m*-Py), 140.2 (*p*-Py), 144.4 (*o*-Py). ^{11}B NMR (64.21 MHz, $CDCl_3$) δ: –3.8. Found (%): C, 79.45; H, 9.73; B, 4.79; N, 6.05. Calc. for $C_{15}H_{22}BN$ (%): C, 79.31; H, 9.76; B, 4.76; N, 6.17. MS, *m*/*z* (%): 227 [M]$^+$ (7.0).

Table 2 Calculated and experimental ^{13}C NMR chemical shifts of the 1-boraadamantane core in isomeric 4-methyl-1-boraadamantane pyridine adducts.



C atom	Chemical shift, δ/ppm		
	Calculated for 4-*syn*-Me **13**	Calculated for 4-*anti*-Me **13**	Experimental
C-2,9	26.6	34.7	25.8
C-8	33.9	33.9	33.8
C-3,5	38.5	38.5	37.5
C-7	32.8	33.1	32.1
C-6,10	33.9	42.0	33.3
C-4	41.5	41.5	40.2

In summary, we have demonstrated that ABAC with tricrotylborane proceeds stereoselectively giving rise to 7-substituted 3-crotyl-8-*syn*-9-*anti*-dimethyl-3-borabicyclo[3.3.1]non-6-enes. On the other hand, the step-by-step ABAC, when a crotylic fragment is introduced at the second stage leads to 9-*syn*-methyl-3-borabicyclo[3.3.1]non-6-ene derivative. These results show clearly that the stereochemistry of ABAC products is determined at the second stage.

This work was supported by the President of the Russian Federation (grant no. 2878.2006.3), the Russian Foundation for Basic Research (grant nos. 05-03-32953 and 05-03-33268) and the Division of Chemistry and Material Sciences of the Russian Academy of Sciences (Programme no. 1).

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Received: 12th January 2007; Com. 07/2859