

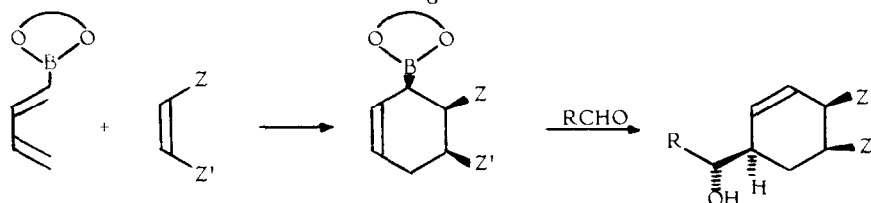
DIELS-ALDER REACTIONS OF 1,3-DIENYLBORONATES AS A NEW ROUTE TO FUNCTIONALIZED CARBOCYCLES.

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Abstract - Hydroboration of enynes with various hydroborating agents followed by refunctionalization at boron furnished 1,3-dienylboronates which undergo clean Diels-Alder addition to typical dienophiles. The resulting adducts contain an allylboronate functionality. Accordingly they add to aldehydes in a highly stereoselective fashion establishing the relative configuration at up to four stereogenic centers.

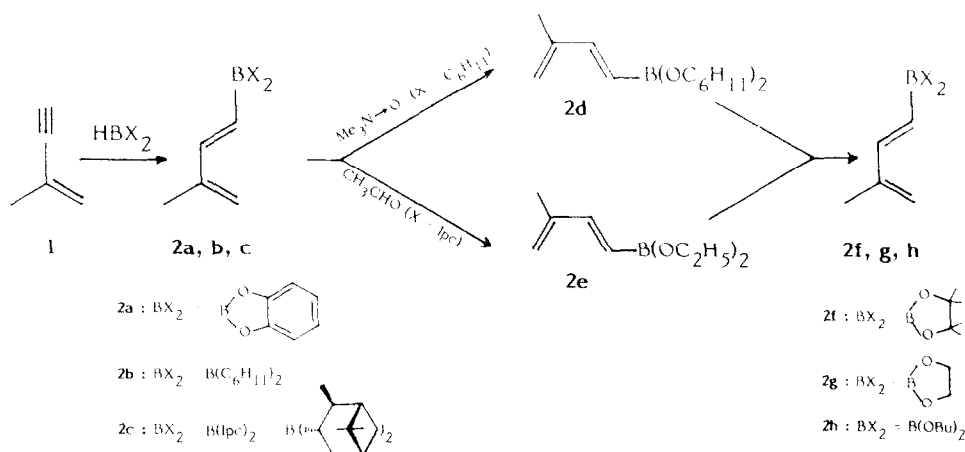
Six-membered carbocycles are frequently prepared by the Diels-Alder addition. The use of silicon ⁽¹⁾ or tin-substituted 1,3-dienes ⁽²⁾ leads to metal-substituted cyclohexenes, in which the reactivity of the metal-carbon bond opens the way to functionalized carbocycles with control of the relative configuration of the created stereogenic centers. Boron-substituted 1,3-dienes should bring some interesting features according to the numerous possibilities of functionalization of the boron-carbon bond. We envisioned that the Diels-Alder reactions of 1,3-dienylboronates would give allylboronates in a stereodefined way, which could be used for further elaboration of 6-membered rings (scheme 1) :



Scheme 1

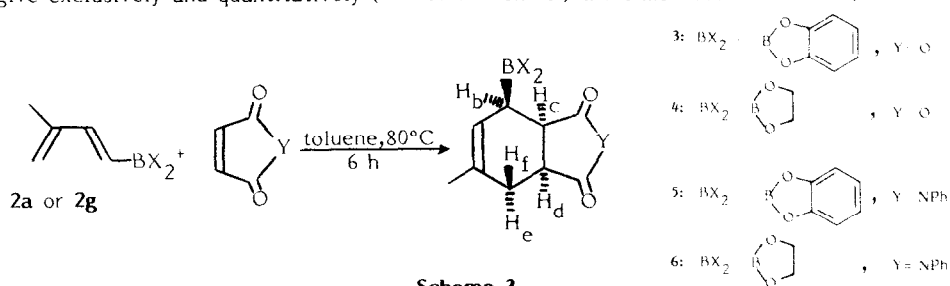
There is one example of a Diels-Alder addition of a 1,3-dienyl borinate to maleic anhydride ⁽³⁾, establishing the first step of the sequence envisioned in the scheme 1. A general application of this scheme requires a general access to 1,3-dienyl-boronates. The hydroboration of the enyne **1** with various hydroborating agents proceeded readily to give the expected dienes **2** (**2a**, b.p._{0.02} = 70°C, yield = 77 % ; **2b** and **2c** quantitative by NMR).

The dienes **2b** and **2c** were converted to the boronates by treatment with trimethylamine N-oxide ⁽⁴⁾ or an excess of acetaldehyde ⁽⁵⁾ respectively to give **2d** and **2e** which could be transesterified in benzene with e.g. pinacol, glycol or n-butanol to give **2f**, **2g** and **2h** (scheme 2) ⁽⁶⁾.



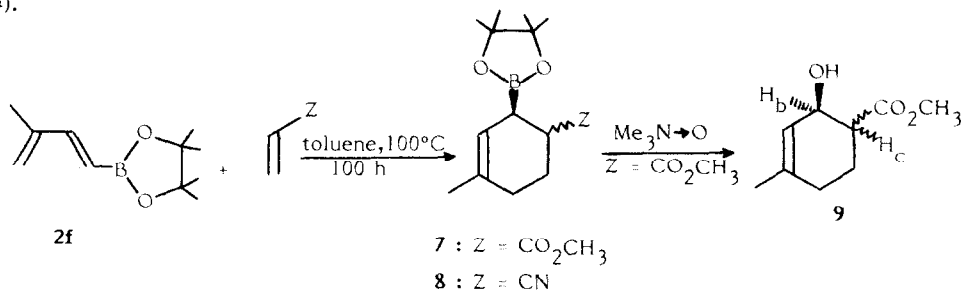
Scheme 2

The E stereochemistry of the 1,2 double bond manifested itself in a large $^3J_{\text{HH}}$ coupling constant (**2f**: 18.1 Hz, **2g**: 17.8 Hz; **2h**: 17.6 Hz). The 1,3-dienylboronates **2a** and **2g** reacted smoothly with maleic anhydride or N-phenyl maleimide chosen as typical dienophiles to give exclusively and quantitatively (^{13}C -NMR control) the *endo* adducts **3** to **6** (scheme 3).



Scheme 3

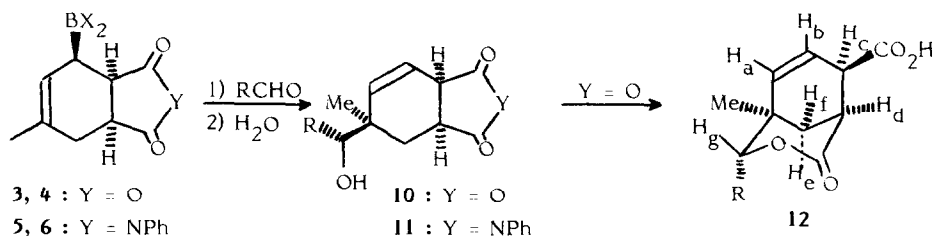
The stereochemistry of the adducts **3**, **4**, **5** and **6** was established as being *endo* on the basis of the ^1H NMR data (300 MHz). This is born out by the following coupling constants for **3**: $J_{\text{H}_\text{C}\text{H}_\text{d}} = 10.0$ Hz, $J_{\text{H}_\text{b}\text{H}_\text{C}} = 5.8$ Hz, $J_{\text{H}_\text{d}\text{H}_\text{f}} = 8.1$ Hz and $J_{\text{H}_\text{d}\text{H}_\text{e}} = 2.8$ Hz. The reaction of **2f** with a three fold excess of methyl acrylate or acrylonitrile led regioselectively to the adducts **7** or **8** as a mixture of *endo* and *exo* diastereomers (**7**: 1:1.8, 69 %; **8**: 1:1.6, 50 %) (scheme 4).



Scheme 4

The regiochemistry of **7** and **8** was established by oxidation of **7** with trimethylamine-N-oxide to the β -hydroxyester **9** displaying a characteristic coupling between H_b and H_c of 3.5 Hz in the cis-isomer and 8.0 Hz in the trans-isomer.

The cyclohexenyl derivatives **3** to **8** contain an allylboronate functionality and react accordingly with aldehydes in a highly diastereoselective fashion (scheme 5).



Scheme 5

Table - Synthesis of the cyclohexenes **11** and **12**

N°	Y	R	m.p. (°C)	yield % (a)
11A	NPh	Ph	80-81	69
11B	NPh	iPr	103-104	67
11C	NPh	Et	119-120	66
12A	O	Ph	242-243	80 (68) ^(b)
12B	O	iPr	213-214	75 (70)
12C	O	Et	227-228	70

(a) Overall yields for isolated pure products starting from **2a**.

(b) Yields in brackets are overall yields starting from the diene **2g**.

The compounds **3** and **4** reacted smoothly with an aldehyde at room temperature and the compounds **5** and **6** at 80°C. After hydrolysis the bicyclic derivatives **11** were isolated in good yields, whereas the corresponding adducts **10** cyclized spontaneously to the bicyclic lactones **12**. The ^{13}C NMR analysis of the crude reaction mixture indicated the formation of only one diastereomer. The results are summarized in the table.

The configuration of the newly formed stereogenic centers was established on the basis of the ^1H NMR data of the bicyclic lactone **12** : it relies on the diagnostic $^4J_{\text{H}_a\text{H}_f}$ coupling of 1.6, 1.4 and 1.6 Hz respectively for **12A**, **12B** and **12C**. This stereochemical assignment was corroborated by an X-ray analysis⁽⁷⁾ of the methyl ester obtained by treating **12A** with diazomethane.

The stereochemistry of the adducts **11** was assigned in analogy to **12**. Similarly the allylboronates **7** and **8** (diastereomeric mixture) reacted with benzaldehyde to give the expected homoallyl alcohols as mixtures of diastereomers. The relative configuration of the newly formed stereogenic centers is homogenous and assigned in analogy to the results given above. This is in line with the stereochemistry of the addition of a Z-crotylboronate to an aldehyde⁽⁸⁾.

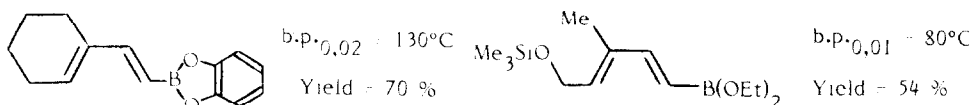
The results presented in this paper demonstrate a new generally applicable method for the construction of functionalized cyclohexenes with the control of up to four stereogenic centers, one being exocyclic.

R.W. H. and I.D. thank the Fonds der Chemischen Industrie for financial support of this work.

Typical procedure : A toluene solution (4 ml) of equimolar amounts of the diene **2a** (0.65g, 3.48 mmol) and maleic anhydride (0.34 g, 3.48 mmol) was maintained at 80°C for 3 h. After cooling to 0°C, 3.48 mmol of freshly distilled benzaldehyde (0.37 g) were added and the reaction mixture was allowed to reach room temperature. After one hour at 20°C, 0.5 ml of water was added and the reaction mixture was heated to 60°C for 0.5 h. The solvents were removed under vacuo and the crystalline residue washed with ether and recrystallized from hot acetonitrile giving 1.85 g of **12A**, m.p. 242-243°C. ^1H NMR (300 MHz), $\text{CDCl}_3 + \text{D}_2\text{O}$, δ : 0.86 (s, 3H) ; 1.48 (dm, H_f) ; 2.30 (ddd, H_e , $J_{\text{H}_e\text{H}_f} = 13.5$, $J_{\text{H}_e\text{H}_d} = 4.5$, $J_{\text{H}_e\text{H}_b} = 1.9$) ; 3.53 - 3.62 (m, 2H) ; 5.17 (d, H_g , $J_{\text{H}_f\text{H}_g} = 1.6$) ; 5.83 (ddm, H_b , $J_{\text{H}_a\text{H}_b} = 10.0$, $J_{\text{H}_b\text{H}_c} = 2.3$) ; 6.12 (dt, H_a , $J_{\text{H}_a\text{H}_c} = 1.4$, $J_{\text{H}_a\text{H}_d} = 1.4$) ; 7.15 - 7.20 (m, 2H) ; 7.32 - 7.45 (m, 3H). ^{13}C NMR (20.1 MHz), CDCl_3 , δ : 24.4 ; 30.2 ; 34.9 ; 40.4 ; 46.9 ; 88.2 ; 126.7 ; 128.5 ; 128.9 ; 129.3 ; 136.5 ; 138.4 ; 170.6 ; 172.7.

References and Notes

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- 7 - Full details concerning the X-ray analysis will appear in the full paper.
- 8 - R.W. HOFFMANN, Angew. Chem. Int. Ed. Engl., 1982, 21, 555.

(Received in France 2 July 1987)