Enantiomerically pure 1,3,2-dioxaborolanes: new reagents for the hydroboration of alkynes

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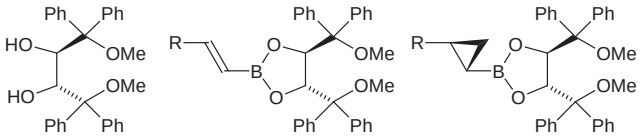
Received (in Liverpool, UK) 14th September 1998, Accepted 26th October 1998

Stable, enantiomerically pure alkenylboronic esters 2 are conveniently prepared by direct hydroboration employing the new 1,3,2-dioxaborolane 4; their highly diastereoselective cyclopropanation can be achieved.

Alkyl- and alkenyl-boronic esters are versatile intermediates in organic syntheses, readily available *via* several well established routes.[1] Arguably, the direct hydroborations of alkenes and alkynes using either catechol-[2] or pinacolborane[3] are the most straightforward method to accomplish their preparation. However, the products are frequently water-sensitive[2] or thermolabile[4] and as such they are not always easy to handle, purify and store. Recently, we reported on the high stability of boronates formed by the condensation of alkenylboronic acids with diol **1**,[5] which was conveniently synthesized from dimethyl tartrate.[6] The cyclopropanation of alkenylboronic ester **2** with CH_2N_2 (Pd^{II} catalyzed) was a high yielding process giving readily separable cyclopropylboronic esters **3**, albeit the diastereomeric ratio was low.[5]

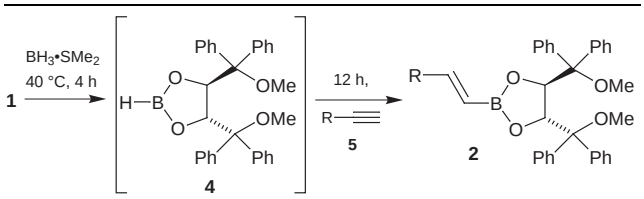


1 **2** **3**

In order to improve the overall efficiency of these reactions, we were not only interested in increasing the selectivity of the cyclopropanation, but especially in omitting the somewhat laborious sequence of alkyne hydroboration, hydrolysis and condensation to give **2**.[3,7] In addition, boroxine formation[5b,8] and their sluggish reaction with diol **1** made us look for alternatives. We envisaged a direct hydroboration with a chiral hydroborating reagent. Although several attempts to make use of, for example, pinanediol failed in the past,[3,9] we were encouraged by the findings of Knochel *et al*. who utilized pinacolborane under exceptionally mild conditions.[3]

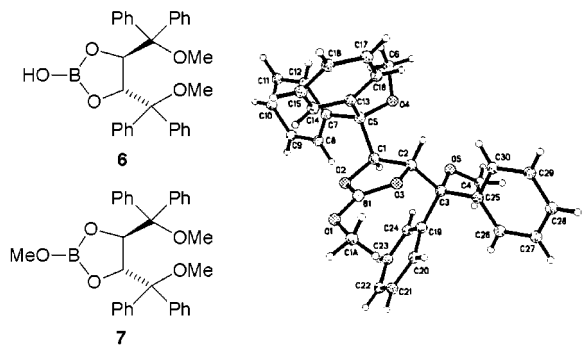
The preparation of the hydroborating reagent **4** was straightforward (Table 1). On the other hand, hydroboration of alkyne **5** with **4** did not occur either at room temperature, or in refluxing CH_2Cl_2. After hydrolysis, 1-hydroxy-1,3,2-dioxaborolane **6** was the only isolated product, whose structure was unequivocally determined by X-ray crystallography† after recrystallization from MeOH (formation of ester **7**; Fig. 1). It was established that the desired hydroboration could be achieved to give **2** by heating the alkyne **5** with **4** neat at higher temperature (120 °C).‡ The stable alkenylboronic ester **2a** was directly crystallized† from the reaction mixture (Fig. 2). Only traces of a regioisomer (< 1%) could be detected. It proved advantageous to use two equivalents of alkynes in cases where the starting materials, *e.g*. **5b**,**c**, have relatively low boiling points and consequently the reaction temperatures needed to be decreased (90 °C). This was probably also the reason for the failure of all attempts to hydroborate 3,3-dimethylbutyne **5d**. Protected propargyl alcohols are valuable starting materials that were also successfully employed in this sequence. Both, *tert*-butyldiphenylsilyl (TBDPS) and *tert*-butyldimethylsilyl (TBDMS) protected alcohols **5e**,**f** gave microanalytically pure esters **2e**,**f** in good yield (66–83%). Increasing the reaction temperature, which is compatible with high-boiling compounds like **5g**, not only decreased the reaction time, but also allowed for better yields.

Table 1 Synthesis of highly stable alkenylboronic esters **2** *via* direct hydroboration using the new reagent **4**



Compound	R	*T*/°C	Yield of **2** (%)
a	Ph	120	82
b	n-C_5H_{11}	90	68
c	Bu^n	90	70
d	Bu^t	40–90	—
e	$TBDPSOCH_2$	120	66
f	$TBDMSOCH_2$	120	70
g	$TBDPSO(CH_2)_3$	135	83

The following experiments proved that this method is rather general. (1*R*,2*R*,3*S*,5*R*)-Pinanediol[9] and (*R*)-1,1,2-triphenyl-



6

7

Fig. **1** Molecular structure of **7**, obtained after hydrolysis of reagent **4** (furnishing **6**) and recrystallization from MeOH.

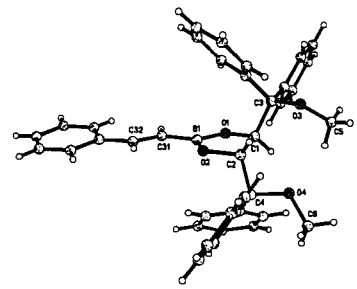
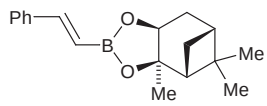
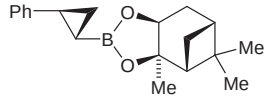


Fig. **2** Molecular structure of **2a**.

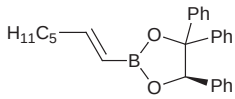
ethane-1,2-diol[10] furnished the corresponding alkenylboronic esters **8** and **9** in good yield (81 and 67%), respectively. Diastereoselective cyclopropanation using CH_2N_2 and $Pd(OAc)_2$ yielding cyclopropanes **10** and **11** was also possible (> 95%), however, the diastereomeric ratio was relatively low (Fig. 2; major diastereomers shown).§ Furthermore, we observed that ester **11** slowly hydrolyzes on silica. While cyclopropane **10** is perfectly stable under these conditions, separation of diastereomers cannot yet be achieved. Under the same, now optimized conditions (0 °C, slow addition and 5–10 mol% catalyst), we obtained cyclopropanes **3a** and **3b** in superior selectivity (86:14 and 93:7) as white solids that were easily separable from their diastereomers (> 95%).



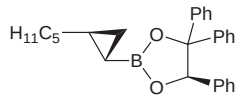
8
(120 °C, 81%)



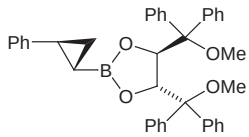
10
dr 63:37



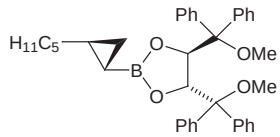
9
(120 °C, 67%)



11
dr 60:40



3a
dr 86:14



3b
dr 93:7

The reason for the good selectivity is not well understood. Examining the X-ray structures of compounds **2a** and **7** (Fig. 1 and 2), it is obvious that the conformation of the 1,3,2-dioxaborolane rings with the bulky substituents is in both cases very similar, efficiently blocking three quadrants. This should also be true for the reactive conformation and consequently one face of attack should be favoured.

In summary, we have demonstrated that direct hydroboration with chiral hydroborating reagents leads to enantiomerically pure, highly stable alkenylboronic esters. These building blocks should prove versatile for a plethora of further transformations, *e.g*. cycloaddition reactions. We have shown that cyclopropanation can easily be achieved in excellent yield and good diastereomeric ratio. This short sequence furnishing enantiomerically pure cyclopropylboronic esters should allow access to a variety of different stereochemically homogeneous 1,2-disubstituted cyclopropanes utilizing the vast synthetic potential of boronic esters.[1,5]

Financial support by the Fonds der Chemischen Industrie (doctoral fellowship for J. E. A. L. and Liebig fellowship for J. P.) and the Deutschen Forschungsgemeinschaft (fellowship for J. P.) is gratefully acknowledged. We also thank the Institut für Organische Chemie der Universität Stuttgart (Professor Dr F. Effenberger and Professor Dr V. Jäger), Dr W. Frey for performing the X-ray crystal structure analyses, and Degussa AG (Hanau) and Boehringer Ingelheim KG (Biberach) for their ongoing support.

Notes and references

† *Crystal data* for **2a**: $C_{38}H_{35}BO_4$, M_r = 566.5, colourless, crystal size 0.7 × 0.4 × 0.2 mm, a = 10.031(2), b = 16.714(3), c = 18.736(2) Å, U = 3142.0(6) Å^3, T = 293 K, orthorhombic, space group $P2_12_12_1$, Z = 4, D_c = 1.197 mg m^{-3}, μ = 0.076 mm^{-1}. 2807 measured reflections, 2807 independent reflections. Refined by full-matrix least-squares on F^2 for all data weights to R = 0.057, wR = 0.094, S = 1.067, H atoms riding, max. shift/error 0.001, residual ρ_{max} = 0.117 e Å^{-3}.

For **7**: $C_{31}H_{31}BO_5$, M_r = 494.4, colourless, crystal size 0.5 × 0.5 × 0.35 mm, a = 11.839(2), b = 8.6176(9), c = 13.7172(11) Å, β = 110.526(8)°, U = 1310.7(3) Å^3, T = 293 K, monoclinic, space group $P2_1$, Z = 2, D_c = 1.253 mg m^{-3}, μ = 0.083 mm^{-1}. 3197 measured reflections, 3054 independent reflections. Refined by full-matrix least-squares on F^2 for all data weights to R = 0.050, wR = 0.095, S = 1.043, H atoms riding, max. shift/error 0.001, residual ρ_{max} = 0.216 e Å^{-3}. CCDC 182/1066.

‡ Procedure for alkenylboronic ester **2a** is representative: Diol **2** (4.55 g, 10.0 mmol) was carefully dried at 50 °C under reduced pressure for 1 h. Under an atmosphere of nitrogen, CH_2Cl_2 (5 cm^3) was added and the solution cooled to 0 °C. $BH_3{\cdot}SMe_2$ (1.2 cm^3, 12 mmol, 10 M in SMe_2) was added dropwise with vigorous stirring, followed by refluxing the mixture for 4 h. The solvent was removed, the reagent cooled to 0 °C and alkyne **5a** (2.2 cm^3, 20 mmol) slowly added. The flask was closed with a septum, slowly heated to 120 °C and kept at this temperature for 12 h. After cooling to room temperature usual work-up and purification under standard conditions followed [ref. 5(*a*)]. Alternatively, the product **2a** could be directly crystallized (MeOH–light petroleum) from the resulting oil, furnishing a colourless solid (1.90 g, 3.40 mmol, 34%). From the remaining mother liquor additional product **2a** (2.70 g, 4.80 mmol, 48%) was obtained after chromatography (silica, eluent: Et_2O–pentane, 1:6). All spectra were in agreement with published data [ref. 5(*a*)].

§ Diastereomeric ratios of cyclopropylboronic esters were determined by ^{1}H NMR analysis using a Bruker ARX-500 spectrometer. Conversion to cyclopropanols with known configuration allowed the unambiguous stereochemical assignment of the cyclopropanes [ref. 5(*a*)].

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8 NMR experiments and mass spectrometric investigations established the trimeric nature. These compounds do not react directly with diol **1**, but must first be stirred with 1 equiv. of water in Et_2O before refluxing in the presence of molecular sieves to yield the alkenylboronic ester **2**.

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Communication 8/07163B