New Enantiomerically Pure Allylboronic Esters in Allyl Additions: Synthesis and NMR Investigation of Intermediates

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Abstract: Enantiomerically pure allylboronic esters 1 + 2 with a stereogenic center α to the boron moiety can be obtained by a sigmatropic rearrangement of boron containing allyl alcohols. Allyl additions with the new reagents are highly selective, which was shown via the direct measurement of the diastereoisomeric ratio of the intermediates 5 + 6 by characteristic NMR chemical shifts. The observations are not limited to ester containing reagents, but holds also true for hydrocarbon side-chains (e.g. in 11 + 12) that were readily obtained by reducing the ester.

Key words: spectroscopy, allylations, boron, stereoselectivity

One of the key reactions in organic synthesis is the allyl addition, especially using allylboronic esters; regularly homoallylic alcohols are conveniently formed in high yield and enantioselective excess.1–6 Reagents having a stereogenic center in the position α to the boronic ester are less often used since they are more difficult to prepare in enantiomerically pure form.7–14 We have recently demonstrated that highly stable reagents of the general type 1 or 2 are readily available via a Johnson rearrangement of the corresponding boron-substituted allyl alcohols.15–17 The derivatives are easy to handle and store, and add highly selectively to a number of aldehydes giving either homoallylic alcohol 3 or 4 with the enantiomeric excess ranging from 92 to >99% (Scheme 1). The formation of the Z-double bond and the configuration of the newly formed stereogenic centers were unambiguously proven by means of chemical correlation. The results could also be rationalized by a transition state as shown in Scheme 1 – the substituent in position α to boron is preferentially axial – which is in full agreement with a previous report by Hofmann and Weidmann.7

A drawback of the procedure was the fact that the enantiomeric excess of homoallylic alcohols was regularly determined – as it is common practice – by forming diastereoisomeric Mosher esters8,19 (when direct methods fail) and thus only indirectly establishing the stereochemical outcome of the transformation. Obviously, there are two problems associated with the approach: A diastereomeric discrimination of the ester formation must be ruled out and, more importantly, the hydrolysis of the intermediate boric esters (in our case 5 and 6) must occur with similar rates. In many cases this might not be a problem; however, occasionally we observed a rate difference that would lead to incorrect results, even when direct methods to determine the enantiomeric excess were used. An obvious solution to the problem would be the utilization of the formed diastereoisomeric intermediates 5 and 6 that should show distinct differences in their NMR spectra. Hence we decided to start a NMR investigation of the reaction before work-up and especially chromatographic separation.

First, we investigated the most simple derivatives 5a and 6a (Figure 1) and found that almost all signals in the proton NMR (500 MHz) show distinct differences in the
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chemical shift. Generally, the most telling signals correspond to the proton of the newly formed stereogenic center (6-H) and also the adjacent protons (5-H). However, the 5-H protons can usually not be used to determine the diastereomeric ratio since the multiplicity of the signals make the integration imprecise. It is interesting to note that also signals of relatively remote groups show an impressive difference in chemical shifts for the two diastereoisomers. At this point it can be speculated whether the carbonyl group of the ester moiety is coordinated to the electrophilic boron. Nevertheless, the most important result can be observed when comparing the spectra in the region around 6-H: within the accuracy of the NMR method, neither of the diastereoisomers 5a or 6a is contaminated with the other!

We were pleased to find that the observation was not singular. As a matter of fact it was rather general, independent of the aldehyde (Figure 2; diastereoisomers 5b and 6b) or the kind of reagent (diastereoisomers 5c + d and 6c + d) used. It is interesting to note that the Δ ppm value is diagnostic and the relative shifts are generally showing the same trend. The only exceptions are the 5-H protons of compounds 5c and 6c with the phenyl group obviously inducing a different conformation and thus influencing the magnetic environment. Both 5,6-disubstituted derivatives 5c + d and 6c + d are most conveniently interpreted, because of the reduced multiplicity: The 6-H protons (e.g. in 5c and 6c) or even the 5-Me group in 5d and 6d give simple doublets that allow a reliable determination of the diastereoisomeric ratio. It should be noted that for convenience in all cases the arithmetic means of diastereotopic protons were used in the tables in Figures 1 and 2 since the configuration of the individual protons could not be established.

It was mentioned above that the ester group might influence the conformation of the intermediates. Furthermore, one could speculate whether the group is actually essential for the high selectivity of the allyl addition. To prove the generality of the concept, it would be essential to remove any group that would be able to coordinate to the boron moiety. Consequently, the esters 1a and 2a were used as starting materials for the realization of the task (Scheme 2). Reduction with diisobutylaluminum hydride (DIBAL-H) gave the corresponding alcohols 7 and 8 in high yield (92 and 94%, respectively), without touching the boron moiety. Activation of the alcohols as methylsulfonates 9 and 10 (95 and 93%, respectively) allowed the consecutive reduction with super hydride furnishing the allylboronic esters 11 and 12 (68% and 74%, respectively) with an ethyl side-chain. All boron derivatives were sta-

Figure 1 Characteristic NMR data of diastereoisomeric boric esters 5a and 6a.

Figure 2 Characteristic NMR data of diastereoisomeric boric esters 5b–d and 6b–d; explanations for symbols used, see Figure 1.
ble, could easily be purified and were hence isolated in microanalytically pure form. Again, the configuration of the two diastereoisomeric series could be confirmed by the NMR data that show the same characteristic chemical shift differences as previously observed, e.g. for 1a and 2a. Furthermore, the stereochemical integrity was unambiguously verified by an X-ray crystallographic analysis of boronic ester 11.20

The new reagents 11 and 12 were tested by using benzaldehyde, thus leading to the known homoallylic alcohols 13 (83%) and 14 (69%) (Scheme 3).21,22 The NMR analysis of the intermediate boronic esters 15 and 16 was in full agreement with the previous observations: Various protons proved to be diagnostic and showed a distinct difference in both diastereoisomers. Especially useful were protons 1-H (Δ ppm: +0.13) and 6-H (Δ ppm: –0.09); again the respective other diastereoisomer could not be detected (ee >95%). The results were independently validated by an HPLC and GC investigation of the alcohols 13 and 14 on chiral stationary phases and the more precise values could be determined (>99% and >99% ee, respectively). The observation underlines a) that characteristic NMR traces are a valuable general tool to follow this type of diastereoselective allylation and b) that there is no limitation to reagents bearing a carboxylic ester side-chain:

Finally, it was shown that the approach can potentially be extended to generally determine the enantiomeric excess of secondary alcohols. In a preliminary experiment, the commercially available enantiomers of substituted propargylic alcohols 17 and 18 were esterified to boronic esters 19 and 20, respectively, by stirring the alcohols in CDCl3 at room temperature with an excess of boric acid (Figure 3). Again, the diastereoisomeric derivatives show different NMR chemical shifts, especially for the protons attached to the stereogenic center (Δ ppm: –0.10 for 19a/20a and +0.04 for 19b/20b), but also – and this will sometimes prove more practical for analytical purposes – for more remote groups (e.g. the CH3 group – 1-H – in 19b/20b; Δ ppm: +0.11). Obviously, direct methods will al-

Scheme 2  Transformation of esters 1 and 2; X-ray crystallographic analysis of 11.20

Scheme 3  Allyl addition of 11 and 12 to benzaldehyde and representative NMR data of the intermediates 15 and 16.
ways be superior to the approach presented; however, should these fail, diastereoisomeric boric esters might be a valuable alternative.

In summary, we did describe the synthesis of a new pair of allylation reagents 11 and 12 by a convenient sequence starting from the known, diastereoisomerically pure boron derivatives 1 and 2. The high yields and selectivities observed for the consecutive allylation were thus not limited to reagents bearing a carboxylic ester group. Furthermore, in view of potential problems occurring during the investigation of the stereochimical course of the addition using indirect methods, a reliable direct NMR approach was presented. By analyzing the intermediate boric esters, erroneous data for a transformation can be omitted. While it is especially practical for allyl additions, it might also be extended for indirectly measuring the enantiomeric excess of secondary alcohols in general.

The reactions were carried out by using standard Schlenk techniques under dry N2 with magnetic stirring. Glassware was oven-dried at 120 °C overnight. Solvents were dried and purified by conventional methods prior to use; THF was freshly distilled from sodium/benzophenone. Common solvents for chromatography (PE, EtOAc) were distilled prior to use; PE refers to a fraction with a PE content of 90%. EtOAc was distilled prior to use; PE refers to a fraction with a PE content of 10%. The high yields and selectivities observed for the consecutive allylation were thus not limited to reagents bearing a carboxylic ester group. Furthermore, in view of potential problems occurring during the investigation of the stereochimical course of the addition using indirect methods, a reliable direct NMR approach was presented. By analyzing the intermediate boric esters, erroneous data for a transformation can be omitted. While it is especially practical for allyl additions, it might also be extended for indirectly measuring the enantiomeric excess of secondary alcohols in general.

X-ray Crystallographic Analysis

The crystal data for compound 11 was determined with a Siemens P4 diffractometer with graphite monochromator in the o-scan mode with Cu-Ka (λ = 1.54178 Å) radiation. C35H37BO4, Mf = 632.48, colorless, F = 293 K, crystal size 0.50 × 0.25 × 0.02 mm, monochlinic, P2(1), a = 10.3707(6), b = 16.2076(19), c = 18.5250(14) Å, V = 3105.25(5) Å3, Z = 4, Dcalcd = 1.139 g·cm–3, μ = 0.570 mm–1, F(000) = 1136, θ range = 3.63–59.99°, 4963 measured/independent reflections, 1691 reflections with I > 2σ(I), the structure was solved by direct methods and refined by full-matrix least squares on F2 for all data weights to wF2 = 0.1718, wR = 0.2130, S = 0.981, H atoms were treated as riding atoms, max. shift/error < 0.002, residual ρmax. = 0.186 Å–3.

(i-Bu)2AlH-Reduction of 1a and 2a; General Procedure A

A solution of ester 1a or 2a (1.00 equiv) in THF (10 mL/mmol 1a/2a) was cooled to –78 °C and DIBAL-H (1 M solution in heptane, 3.00 equiv) was added. The reaction mixture was warmed to 4 °C over 2 h. Dilution with Et2O (10 mL/mmol 1a/2a) and careful addition of H2O (70 µL/mmol DIBAL-H), 2 M aq NaOH solution (1.40 µL/mmol DIBAL-H) and H2O (70[µL/mmol DIBAL-H] led to a precipitate after 20 min. The mixture was filtered, the solvent of the filtrate was evaporated and the crude product was purified by flash column chromatography.

(3S,4R,5'S)-3-[4,5'-Bis(methoxydiphenylmethyl)-1',3',2'-dioxaborol-2'-yl]pent-4-ene-1-ol (7)

Prepared according to the general procedure A. Ester 1a (3.00 g, 5.08 mmol) and DIBAL-H (1 M solution in heptane, 15.2 mL, 15.2 mmol) in THF (51 mL) were used. Purification by flash column chromatography on silica gel (51 g, PE–EtOAc, 85:15) yielded 2.57 g (92%) of 7 as spectroscopically pure colorless solid foam. MPLC of a small sample (PE–EtOAc, 80:20) gave the analytically pure colorless solid foam; recrystallization from pentane–CH2Cl2 yielded colorless crystals; mp 130 °C; [α]D = 0.10 (PE–EtOAc, 85:15); [α]D19 = –129 (c = 0.08, CHCl3).


1H NMR (500 MHz, CDCl3): δ = 1.30–1.41 (m, 3 H, OH, 2-H), 1.43–1.50 (m, 1 H, 3-H), 3.01 (s, 6 H, OCH3, 3.51 (s, 6 H, OCH3), 3.35 (m, 2 H, 1-H), 4.73 (ddd, J = 17.2 Hz, J = 1.7 Hz, J = 1.3 Hz, 1-H, 5-H), 4.77 (ddd, J = 10.3 Hz, J = 1.7 Hz, J = 1.3 Hz, 1-H, 5-H), 5.32 (s, 2 H, 2'-H, 5'-H), 5.50 (ddd, J = 17.2 Hz, J = 10.3 Hz, J = 8.3 Hz, 1-H, 4-H), 7.25–7.35 (m, 20 Haryl).

13C NMR (125 MHz, CDCl3): δ = 26.1 (br, C-3), 31.5 (C-2), 51.7 (OCH3), 62.1 (C-1), 77.6 (C-4', C-5'), 85.3 (Ph3O,Me), 113.3 (C-5), 127.3, 127.3, 127.6, 128.4, 129.7 (Caryl), 138.7 (C-4'), 141.1, 141.1 (Caryl).


(3R,4R,5S)-3-[4',5'-Bis(methoxydiphenylmethyl)-1',3',2'-dioxaborolan-2'-y]pent-4-en-1-yl Methanesulfonate (10)
Prepared according to the general procedure B. Alcohol 7 (2.61 g, 4.75 mmol), Et3N (988 µL, 7.13 mmol) and MeSO2Cl (554 µL, 8.17 mmol) in CH2Cl2 (9.51 mL) were used. Purification by flash chromatography on silica gel (100 g, PE–EtOAc, 86:14) yielded 2.77 g (93%) of 10 as analytically pure colorless solid foam. Softening range: 53–66 °C; Rf 0.25 (PE–EtOAc, 85:15); [α]20°−140 (c = 0.92, CHCl3).

IR (KBr): 3540, 3070, 3040, 3000, 2950, 2920, 2880, 2850, 2810, 1625, 1590, 1575, 1485, 1435, 1356, 740, 680 cm−1.

C NMR (126 MHz, CDCl3): δ = 25.3 (br, -C-3), 38.2 (C-C-4), 137.1 (C-5), 127.4, 127.6, 128.6, 128.9, 129.2 (CHarom), 138.5 (C-4), 141.0, 141.0 (Cparom).

MS (EI, 70 eV): m/z (%) = 652 (84, [M+Na]+), 197 (100, [MeOPh2C]+), 167 (9, [Ph2HC]+), 105 (12, [PhCO]+).


Reduction of Methanesulfonic Esters 9 and 10 with LiEt3BH; General Procedure C
To a vigorously stirred solution of the methanesulfonic ester 9 or 10 (1.00 equiv) in THF (1.00 mL/mmol 9/10) at r.t. was added LiEt3BH (1 M solution in THF, 2.00 equiv) in one batch. A colorless solid precipitated from the solution. After 1 h, a 3 M aq solution of NaOH (0.80 mL/mmol 9/10) and a 30% aq solution of H2O2 (0.8 mL/mmol 9/10) was added to the mixture. Stirring was continued for 1 h and then the mixture was diluted with Et2O (5 mL/mmol 9/10) and H2O (5 mL/mmol 9/10). The aqueous phase was extracted with Et2O (3 × 5 mL/mmol 9/10) and the combined organic layers were dried (MgSO4). After filtration and evaporation of the solvent, the crude product was purified by flash column chromatography.

(3S,4R,5S)-3-[4',5'-Bis(methoxydiphenylmethyl)-1',3',2'-dioxaborolan-2'-y]pent-4-en-1-ene (11)
Prepared according to the general procedure C. Methanesulfonic ester 9 (2.73 g, 4.36 mmol) and LiEt3BH (1 M solution in THF, 8.71 mL, 8.71 mmol) in THF (4.36 mL) were used. Purification by flash column chromatography on silica gel (85 g, PE–EtOAc, 95:5 to 85:15) yielded 1.57 g (68%) of 11 as colorless solid foam. Softening range: 50–62 °C; Rf 0.38 (PE–EtOAc, 95:5); [α]20°−140 (c = 1.30, CHCl3). Recrystallization from pentane–EtOH yielded crystals suitable for X-ray crystallographic analysis; mp 116–119 °C.
IR (KBr): 3070, 3040, 3015, 3005, 2940, 2920, 2890, 2850, 2810, 1620, 1590, 1570, 1480, 1435, 1060, 740, 680 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 0.64 (t, J = 7.2 Hz, 3H, 5-H), 1.06 (dd, J = 14.7 Hz, J = 7.2 Hz, J = 3.1 Hz, 1H, 4-H), 1.17–1.25 (m, 2H, 3-H, 4-H), 3.00 (s, 6H, OCH₃), 4.68 (ddd, J = 17.1 Hz, J = 2.2 Hz, J = 1.1 Hz, 1H, 1-H), 4.75 (dd, J = 10.3 Hz, J = 2.2 Hz, 1H, 1-H), 5.29 (2H, 4’-H, 5’-H), 5.43 (ddd, J = 17.1 Hz, J = 10.3 Hz, J = 8.3 Hz, 1H, 2-H), 7.22–7.35 (m, 20 H arom).

13C NMR (126 MHz, CDCl₃): δ = 13.2 (C-5), 21.8 (C-4), 31.4 (C-3), 51.7 (OCH₃), 77.8 (C-4’, C-5’), 83.4 (CH₂OMe), 113.0 (C-1), 127.2, 127.3, 127.4, 127.8, 128.5, 129.7 (CH arom), 139.1 (C-2), 141.3, 141.5 (C arom).

IR: 3530, 3070, 3040, 3010, 2940, 2920, 2890, 2850, 2810, 1590, 1570, 1480, 1435, 1060, 740, 680 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 0.91 (t, J = 7.5 Hz, 3H, 6-H), 2.01 (ddq, J = 14.6 Hz, J = 7.5 Hz, J = 7.3 Hz, J = 1.6 Hz, 1H, 5-H), 2.03 (ddq, J = 14.6 Hz, J = 7.5 Hz, J = 7.3 Hz, J = 1.6 Hz, 1H, 5-H), 2.12 (d, J = 2.6 Hz, 1H, OH), 2.45 (ddd, J = 14.3 Hz, J = 6.9 Hz, J = 5.4 Hz, J = 1.6 Hz, 1H, 2-H), 2.55 (ddd, J = 14.3 Hz, J = 6.9 Hz, J = 7.8 Hz, J = 1.6 Hz, 1H, 2-H), 4.67 (ddd, J = 7.8 Hz, J = 5.4 Hz, J = 2.6 Hz, 1H, 1-H), 5.34 (dt, J = 10.8 Hz, J = 6.9 Hz, J = 1.6 Hz, 1H, 3-H), 5.54 (dtt, J = 10.8 Hz, J = 7.3 Hz, J = 1.6 Hz, 1H, 4-H), 7.23–7.27, 7.31–7.36 (m, 5 H arom).

13C NMR (126 MHz, CDCl₃): δ = 14.1 (C-6), 20.6 (C-5), 37.1 (C-2), 73.9 (C-1), 124.0 (C-3), 125.8, 127.4, 128.3 (CH arom), 135.2 (C aram), 141.3, 141.5 (C aram).

MS [DCI (CH₃)]: m/z (%): 532 (0.14, [M⁺]), 500 (8, [M⁺ – H2O]+), 478 (3), 317 (9), 194 (26, [M⁺ + Na]+), 176 (100, [M⁺]), 159 (45, [M + H – H2O]+).

HRMS (EI, 70 eV): m/z calculated for C₁₂H₁₆O: 176.1202; found: 176.1201.

(3R,4R,5R)-3-[4′,5′-Bis(methoxydiphenylmethyl)-1′,2′-dioxaborolan-2′-yl]pent-1-ene (12)

Prepared according to the general procedure D. Allylboronic ester 11 (193 mg, 0.36 mmol) and benzaldehyde (44 μL, 46 mg, 0.44 mmol) in CH₂Cl₂ (181 μL) were used. Purification by column chromatography on silica gel (31 g, PE–EtOAc, 95:5 to 85:15) yielded 44 mg (69%) of 14 as colorless solid foam. Softening range: 47–62 °C; Rf = 0.38 (PE–EtOAc, 95:5); [α]D²⁰ = -146 (c = 1.14, CHCl₃).

IR (KBr): 3070, 3040, 3010, 2940, 2920, 2890, 2850, 2810, 1590, 1570, 1480, 1405, 740, 680 cm⁻¹.

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References

(20) CCDC-273337 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk].