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VIP *Very Important Paper*

Matteson Homologation of Arylboronic Esters

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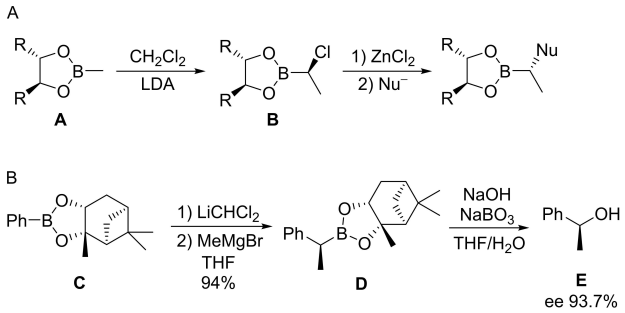
Commercially available arylboronic acids can easily be converted into chiral boronic esters which can be subjected to Matteson homologations using Grignard reagents. The best results are obtained in one pot protocols without isolation of the α-chloroboronic ester intermediates. Alkoxides can also be used as nucleophiles, but the corresponding homologated boronic esters are found to be not stable.

Introduction

The Matteson homologation, a highly stereoselective one-carbon prolongation of an alkyl boronic ester is an extremely valuable tool in organic synthesis.[1] Based upon the discovery of metallate rearrangements in the early 1960's[2] and development of this method by Donald Matteson in the 1980's,[3] this protocol found several applications in the synthesis of drugs[4] and natural products.[5] Typically, chiral alkyl boronic esters **A** are reacted with deprotonated dichloromethane giving rise to an α-chloroboronic ester **B** in a highly diastereoselective fashion (Scheme 1A). Subsequent addition of a nucleophile onto the boron atom generates a boronate complex undergoing a 1,2-shift of the nucleophile and a substitution of the chlorine atom under inversion.[2] A wide range of nucleophiles can be applied to obtain α-chiral substituted alkylboronic esters, which are suitable for further homologation reactions.[1] Not only lithium or magnesium reagents are well suited, but also other nucleophiles such as alkoxides, azides or enolates can be applied.[5b,6] Depending on the chiral auxiliary used in the boronic ester excellent diastereoselectivities are obtained, especially with C_2-symmetric 1,2-diols such as 1,2-diisopropylethanediol (DIPED)[7] or 1,2-dicyclohexylethanediol (DICHED)[8] (Scheme 1A). In contrast to the many applications of alkylboronic esters, almost nothing is known about comparable reactions of arylboronic esters. This is very surprising, especially because so many arylboronic acids are commercially available[8] since the ascension of the Suzuki-Miyaura coupling as standard tool in drug synthesis.[10]

The first example using chiral arylboronic ester **C** was reported by Matteson in 1980 (Scheme 1B).[3] Prolongation under the usual conditions using $LiCHCl_2$ and subsequent reaction with MeMgBr produced boronic ester **D** in high yield. Oxidation gave access to secondary alcohol **E** with an ee of 93.7%. Although this selectivity is synthetically useful, it is significantly lower compared to homologations of alkyl boronic esters. Similar results were reported by Brown et al.[11] and Kabalka et al.[12] also using chiral phenylboronic esters.



Scheme 1. Matteson homologations.

This forced Matteson et al. to investigate this phenomenon in greater detail.[13] Obviously, the LiCl liberated during the formation of the α-chloroboronic esters causes an epimerization which in case of arylboronic esters is around 20 times faster than with alkyl boronic esters.[13] $ZnCl_2$, which is generally added during the reaction also is able to cause isomerization. The lowest epimerization rate is observed if LiCl and $ZnCl_2$ are present in a 1:1 ratio, probably because a rather stable $LiZnCl_3$-complex is formed. With the higher epimerization rate of the resulting benzylic α-chloroboronic esters in mind, the only few examples of Matteson reactions with arylboronic esters in literature becomes understandable. Since many of these examples date back to the first years after the development of the reaction,[11] pinanediol was used as the chiral auxiliary. Further examples with this auxiliary were reported by Prati,[14] Lejon[15] and Jiang et al..[16] Nevertheless, to the best of our knowledge no further applications of other aromatic boronic esters are reported so far, especially with the C_2-symmetric diols DIPED or DICHED.

Results and Discussion

Since a couple of years our group is involved in the synthesis of natural products containing polyketide fragments.[17] The Matteson homologation is perfectly suited for this purpose and we

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therefore also became interested in the incorporation of aryl substituents. We decided to use the chiral DICHED-auxiliary, because it gave the best results in previous reactions.[17,18] The desired aryl boronic esters could easily be obtained in almost quantitative yield from commercial available boronic acids and enantiomerically pure (*S*,*S*)- or (*R*,*R*)-1,2-dicyclohexylethanediol[19] in the presence of $MgSO_4$. We started our investigations with phenylboronic ester **1a** which was subjected to a Matteson homologation under the same conditions we generally use in the reaction of alkyl boronic esters (Table 1, entry 1). The lithium carbenoid was generated by deprotonation of dichloromethane with LDA at −40 °C before ester **1a** was added.[5b] If the reaction mixture was allowed to warm to room temperature partial decomposition of the α-chloroboronic ester **2a** was observed and benzaldehyde was formed as side product. If the reaction was quenched at 0 °C, ester **2a** could be isolated. Because these esters are obviously very sensitive, they should directly be subjected to the next step, the nucleophilic replacement of the chlorine. Therefore, **2a** was dissolved again in THF, cooled to −78 °C before the Grignard reagent and $ZnCl_2$ was added. Warming the reaction mixture again to 0 °C provided the desired homologated ester **3a** in 50% yield. As a side product the formation of methylboronic ester **F** was observed (10%). Similar side product formations were observed previously, e.g. in reaction of vinyl Grignard reagents.[18b,20] These side products probably result from the addition of excess Grignard reagent to product **3a**. A boronate complex is formed which on hydrolysis either provides **3a** or the side product **F**. Reducing the amount of Grignard reagent does not result in better yields, because in this case no complete conversion is observed. To determine the stereoselectivity of the homologation step, **3a** was oxidized to the secondary alcohol **4a**, which could easily be analyzed by GC. Under the described reaction conditions an ee of only 30% was obtained. Obviously, isolation of the α-chloroboronic ester, which provides better results in many other cases, is not an option here.

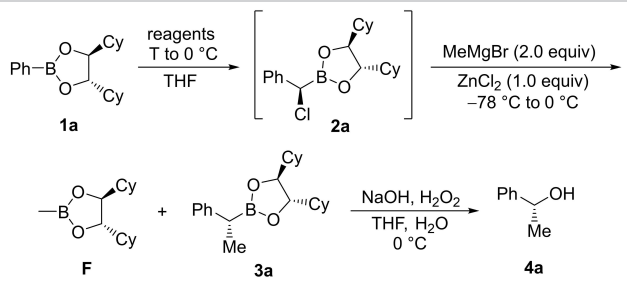
Therefore, we cooled the solution of **2a** after warming to 0 °C again to −78 °C and added the Grignard reagent. And indeed, in this case the yield could be increased significantly and almost no side product was formed, but the ee of the corresponding alcohol could only be increased to 43% (entry 2).

Since Matteson reported that the drop of the ee-value (d.r. value before oxidation to secondary alcohol) is caused by chloride ions in solution and that the formation of $LiZnCl_3$ by additional $ZnCl_2$ might help to suppress this undesired side reaction, we decided to change the deprotonation protocol.

While the LDA-method requires two equivalents $ZnCl_2$, because one equivalent is complexed by the diisopropylamine formed, deprotonation of dichloromethane with BuLi circumvents this problem and the base and $ZnCl_2$ can be used in a 1:1 ratio. In this case, deprotonation should be carried out at −100 °C, and under otherwise identical conditions the ee could indeed be increased to 95.3% (entry 3).

To proof the scope and limitations of the protocol we investigated a range of different substituted arylboronic esters (Scheme 2). Electron-donating groups and halogens are well accepted giving reproducible high yields in the range of 80 % or higher, with almost no side product formation. For analytical purposes the boronic esters **3** were oxidized, and the corresponding alcohols **4** were analyzed. High ee values (94.4–

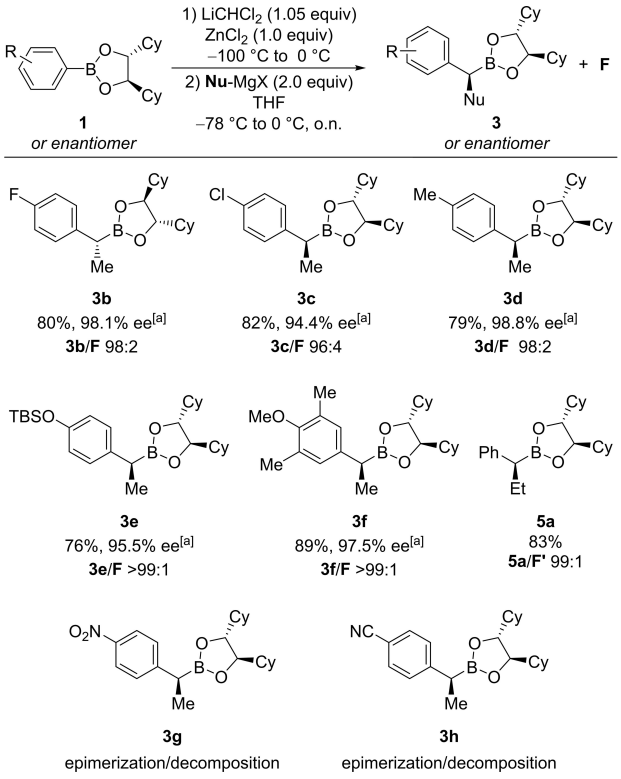
Table 1. Matteson homologation of phenylboronic ester **1a**.



1a 2a F 3a 4a

Entry	Reagents [equiv]	T [°C]	Ratio **3a**:**F**	Yield [%]	*ee* (**4a**) [%]
1	CH_2Cl_2 (3.0) LDA (1.25) $ZnCl_2$ (2.0)	−40	90:10	50	30[a]
2	CH_2Cl_2 (3.0) LDA (1.25) $ZnCl_2$ (2.0)	−40	98:2	80	43[b]
3	CH_2Cl_2 (1.7) BuLi (1.05) $ZnCl_2$ (1.0)	−100	93:7	74	95.3[b]

[a] **2a** isolated. [b] **2a** not isolated.



Scheme 2. Matteson homologations of different arylboronic esters. [a] ee-values were obtained after oxidation to the corresponding alcohols **4**.

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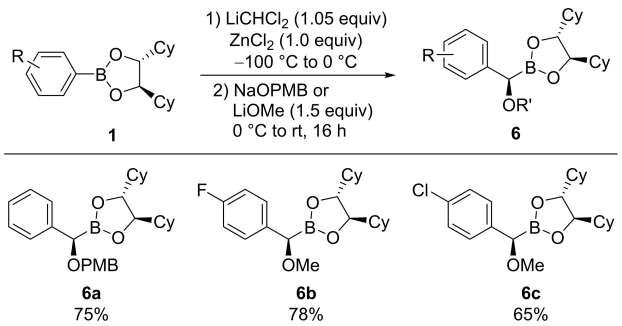
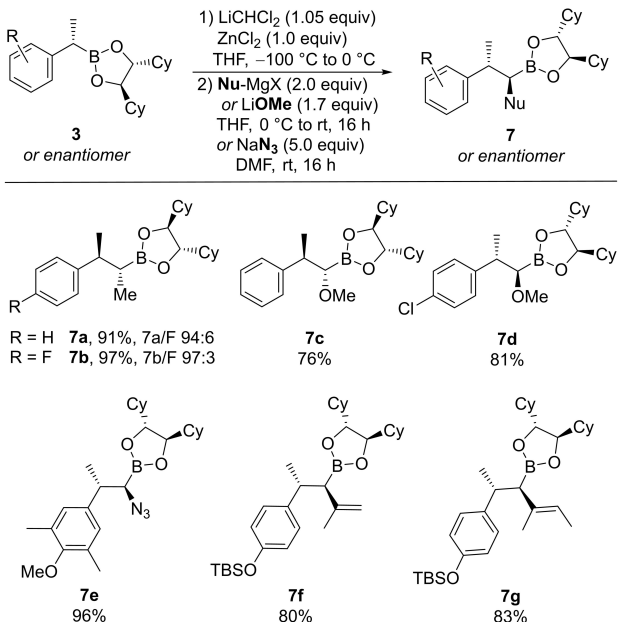
98.9% ee) were obtained in all cases. In contrast, aromatic boronic esters with electron-withdrawing groups such as NO_2 or CN are not suitable. Here complete epimerization of the α-chloroboronic ester and partial decomposition was observed. In previous investigations we observed that the formation of the undesired side product can be reduced by increasing the steric demand of either the substituent of the boronic ester or the nucleophile.[18b] Reacting **1a** with EtMgBr provided the desired product **5a** in high yield with only trace amounts of ethylboronic ester as side product.

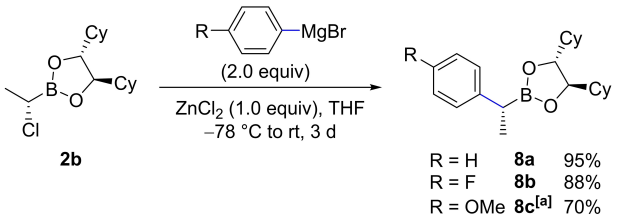
Next, we investigated reactions using alkoxides as nucleophiles (Scheme 3). Also here, acceptable yields of **6** were obtained, which were in the average around 10% lower compared to the Grignard reactions, an observation we also made with alkyl boronic esters previously.[17,18] But in comparison to the alkylated products the aryl substituted products **6** were rather unstable and decomposed on storage even at −20 °C under argon. Already during NMR-measurements a decomposition and formation of aromatic aldehydes was observed. Attempted homologations of **6a** even directly after isolation led



Scheme 3. Matteson homologations of arylboronic esters with alkoxides.



Scheme 4. Prolongation of aryl substituted boronic ester **3**.



Scheme 5. Matteson homologations with aryl nucleophiles.[a] The enantiomer *ent*-**8c** was prepared from *ent*-**2b**.

to mainly decomposed products and low yields. Probably these α-alkoxylated boronic esters are not suitable for further Matteson homologations.

But the other arylated α-alkyl boronic esters can be applied in further Matteson reactions. Subjecting boronic esters **3a** and **3b** to a second homologation with MeMgBr provided **7a** and **7b** in excellent yield with only trace amounts of the methylboronic ester side product **F** (Scheme 4). No side product formations were observed in reactions with MeOLi (**7c**,**d**) or NaN_3 (**7e**). Reactions with vinyl Grignard reagents give access to allyl boronic esters **7f** and **7g** which can be used in carbonyl additions[7] or for the synthesis of allylic alcohols

Finally, to show that also the other stereoisomers can also be obtained we subjected methylboronic ester to Matteson homologations with several aryl Grignard reagents (Scheme 5). In this case, the α-chloroboronic ester **2b** is stable and can be isolated.[18] Therefore, it has to be synthesized only once and can directly be reacted with the different Grignard reagents. The reactions required longer reaction times, due to the lower reactivity of the aryl Grignard reagents. Due to the formal exchange of introduced nucleophile the obtained products are diastereomers to the previously described compounds **3**. Compounds **8a**–**8c** were obtained in good yields and oxidizing compound **8c** to the corresponding alcohol **9c** with an ee value of 98.3% indicated a highly stereoselective reaction with aryl nucleophiles.

Conclusions

In conclusion, we could show that aryl boronic esters can be used in Matteson homologations and under optimized conditions high yields and selectivities can be obtained. The most important parameters are the reaction with $LiCHCl_2$ at −100 °C, warming up to a maximum of 0 °C and conversion of the α-chloroboronic ester without prior isolation. Alkoxides can be used as nucleophiles as well, but the corresponding α-alkoxyboronic esters formed are found to be not stable and unsuitable for further homologations.

Experimental Section

General information: All air and moisture sensitive reactions were carried out in dried glassware (>100 °C) under nitrogen atmos-

phere. Anhydrous solvents were purchased from Acros Organics or dried before use (THF was distilled over sodium/benzophenone) and stored under nitrogen atmosphere. The products were purified by column chromatography on silica gel columns (Machery-Nagel 60, 0.063–0.2 mm). Mixtures of diethyl ether (Et_2O) and pentane (distilled prior to use) were generally used as eluents. For reverse-phase chromatography (indicated by C-18-silica), a Büchi *Reverleris PREP Chromatography* system was used with *Telos Flash C18* columns and MeCN/H_2O solvents. Analytical TLC was performed on pre-coated silica gel plates (Machery-Nagel, Polygram Sil G/UV_{254}). Detection was accomplished with UV light (254 nm), $KMnO_4$ solution or cerium(IV)/ ammonium molybdate solution. Melting points were determined with a MEL-TEMP II (Laboratory devices) apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance II 400 MHz spectrometer [^1H 400 MHz and ^{13}C 100 MHz], a Bruker Advance I 500 MHz spectrometer [^1H 500 MHz and ^{13}C 125 MHz] or a Bruker AV 500 Neo spectrometer [^1H 500 MHz and ^{13}C 125 MHz]. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS or internal solvent signal. Peaks were assigned using (^1H,^1H)-COSY, (^1H,^{13}C)-HSGC and (^1H,^{13}C)-HMBC spectra. Mass spectra were recorded with a Finnigan MAT 95 spectrometer (quadrupole) using the CI technique. Optical rotations were measured with a Jasco P-2000 polarimeter in a thermostated (20 °C ± 1 °C) cuvette, using a sodium vapor lamp (λ = 589 nm) as radiation source. $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm^2 g^{-1}.

General procedures (GP)

GP1: Preparation of the arylboronic esters 1: (*R*,*R*)- or (*S*,*S*)-DICHED[19b] (1.0 equiv) and the corresponding arylboronic acid (1.2 equiv) were suspended in Et_2O (5 mL/mmol), before $MgSO_4$ (3.0 equiv) was added and the mixture was stirred overnight. The mixture was filtrated, the solvent was evaporated in vacuo and the crude product was purified by column chromatography (silica, pentane/Et_2O).

GP2: Matteson homologation: In a flame-dried Schlenk flask, anhydrous CH_2Cl_2 (1.7 equiv) was dissolved in anhydrous THF (2.0 mL/mmol) and cooled to a temperature between −110 °C to −100 °C using an ethanol/liquid nitrogen bath. To the cooled solution, *n*-BuLi (1.05 equiv, 2.5 M in hexanes) was added dropwise. For larger quantities, the *n*-BuLi solution was diluted with 1–2 mL anhydrous THF, pre-cooled to −78 °C and added by cannulation. The mixture was stirred for 30 min at −100 °C before a solution of the boronate (1.0 equiv) in anhydrous THF (1.5 mL/mmol) was added. After another 30 min of stirring, a solution of $ZnCl_2$ (1.05–3.05 equiv, flame-dried *in vacuo*) in anhydrous THF (0.8 mL/mmol $ZnCl_2$) was added. The mixture was allowed to warm to room temperature and stirred for 6–24 h before the nucleophile solution was slowly added at a certain temperature. The reaction mixture was allowed to warm to 0 °C or room temperature and stirred for 16–72 h. Upon completion (checked by ^1H NMR or TLC analysis), the reaction mixture was added to a separating funnel with saturated NH_4Cl solution and pentane. The phases were separated, the aqueous phase was extracted with pentane and the combined organic phases were dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by column chromatography.

GP3: Oxidation of boronic esters: The boronic ester (1.0 equiv) was dissolved in THF (3 mL/mmol) and NaOH (5.0 equiv) in H_2O (3 mL/mmol boronic ester) and H_2O_2 (5.0 equiv, 33% in H_2O) were added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with sat. NaCl solution, extracted with Et_2O (2x) and the organic phase was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-phenyl-1,3,2-dioxaborolane (1 a): According to GP1 phenylboronic acid (1.90 g, 8.39 mmol) was reacted with (*S*,*S*)-DICHED (2.13 g, 9.24 mmol) and $MgSO_4$ (3.03 g, 25.2 mmol). After workup the crude product was purified by flash chromatography (silica, pentane/ether 9:1) to provide **1 a** as a colorless solid (2.60 g, 8.33 mmol, 99%).

(4*S*,5*S*)-4,5-Dicyclohexyl-2-(4-fluorophenyl)-1,3,2-dioxaborolane (1 b): According to GP1 4-fluorophenylboronic acid (680 mg, 4.86 mmol) was reacted with (*S*,*S*)-DICHED (1.00 g, 4.42 mmol) and $MgSO_4$ (1.60 g, 13.3 mmol). After workup the crude product was purified by flash chromatography (silica, pentane/ether 95:5) to provide **1 b** as a colorless solid (1.31 g, 3.95 mmol, 90%).

(4*R*,5*R*)-2-(4-Chlorophenyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (1 c): According to GP1 4-chlorophenylboronic acid (1.09 g, 6.97 mmol) was reacted with (*R*,*R*)-DICHED (1.43 g, 6.34 mmol) and $MgSO_4$ (2.28 g, 19.0 mmol). After workup the crude product was purified by flash chromatography (silica, pentane/ether 9:1) to provide **1 c** as a colorless solid (2.11 g, 6.08 mmol, 96%).

(4*R*,5*R*)-4,5-Dicyclohexyl-2-(*p*–tolyl)-1,3,2-dioxaborolane (1 d): According to GP1 4-methylphenylboronic acid (293 mg, 2.16 mmol) was reacted with (*R*,*R*)-DICHED (443 mg, 1.96 mmol) and $MgSO_4$ (707 mg, 5.88 mmol). After workup the crude product was purified by flash chromatography (silica, pentane/ether 95:5) to provide **1 d** as a colorless solid (622 mg, 1.91 mmol, 97%).

***tert*-Butyl(4-((4*R*,5*R*)-4,5-dicyclohexyl-1,3,2-dioxaborolan-2-yl)phenoxy)dimethylsilane (1 e)**: According to GP1 4-*tert*-butyldimethylsilyloxyphenylboronic acid (2.47 g, 9.83 mmol) was reacted with (*R*,*R*)-DICHED (1.85 g, 8.19 mmol) and $MgSO_4$ (2.96 g, 24.6 mmol). After workup the crude product was purified by flash chromatography (silica, pentane/ether 95:5) to provide **1 e** as a colorless oil (3.57 g, 8.07 mmol, 99%).

(4*R*,5*R*)-4,5-Dicyclohexyl-2-(4-methoxy-3,5-dimethylphenyl)-1,3,2-dioxaborolane (1 f): According to GP1 (4-methoxy-3,5-dimethyl)phenylboronic acid (2.50 g, 13.9 mmol) was reacted with (*R*,*R*)-DICHED (2.86 g, 12.6 mmol) and $MgSO_4$ (4.56 g, 37.9 mmol). After workup the crude product was purified by flash chromatography (silica, pentane/ether 95:5) to provide **1 b** as a colorless oil (4.56 g, 12.3 mmol, 98%).

(4*S*,5*S*)-4,5-Dicyclohexyl-2-((*R*)-1-phenylethyl)-1,3,2-dioxaborolane (3 a): According to GP2 boronate **1 a** (665 mg, 2.13 mmol) was reacted with abs. CH_2Cl_2 (0.23 mL, 3.62 mmol), *n*-BuLi (0.89 mL, 2.5 M in hexane, 2.24 mmol) and $ZnCl_2$ (305 mg, 2.24 mmol). MeMgBr (1.42 mL, 3.0 M in THF, 4.26 mmol) was added at −78 °C. After 24 h at 0 °C workup and purification by flash chromatography (silica, pentane/ether 9:1) provided **3 a** as a colorless oil (574 mg, 1.57 mmol, 74%). Purity: 93%, 7% methylboronic ester **F** was formed as side product.

For analytical purposes **3 a** was oxidized according to GP3 to the secondary alcohol **4 a**, which was analyzed by GC (95.3% ee).

(4*S*,5*S*)-4,5-Dicyclohexyl-2-((*R*)-1-(4-fluorophenyl)ethyl)-1,3,2-dioxaborolane (3 b): According to GP2 boronate **1 b** (400 mg, 1.21 mmol) was reacted with abs. CH_2Cl_2 (0.13 mL, 2.06 mmol), *n*-BuLi (0.51 mL, 2.5 M in hexane, 1.27 mmol) and $ZnCl_2$ (173 mg, 1.27 mmol). MeMgBr (0.81 mL, 3.0 M in THF, 2.42 mmol) was added at −78 °C. After 24 h at 0 °C workup and purification by flash chromatography (silica, pentane/ether 9:1) provided **3 b** as a colorless oil (355 mg, 971 μmol, 80%). Purity: 98%, 2% methylboronic ester **F** was formed as side product.

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For analytical purposes **3b** was oxidized according to GP3 to the secondary alcohol **4b**, which was analyzed by GC (98.1% ee).

(4*R*,5*R*)-2-((*S*)-1-(4-Chlorophenyl)ethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (3c): According to GP2 boronate **1c** (300 mg, 865 μmol) was reacted with abs. CH_2Cl_2 (0.10 mL, 1.47 mmol), *n*-BuLi (0.36 mL, 2.5 M in hexane, 909 μmol) and $ZnCl_2$ (124 mg, 909 μmol). MeMgBr (0.58 mL, 3.0 M in THF, 1.73 mmol) was added at −78 °C. After 24 h at 0 °C workup and purification by flash chromatography (silica, pentane/ether 9:1) provided **3c** as a colorless oil (276 mg, 707 μmol, 82%). Purity: 96%, 4% methylboronic ester **F** was formed as side product.

For analytical purposes **3c** was oxidized according to GP3 to the secondary alcohol **4c**, which was analyzed by GC (94.4% ee).

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((*S*)-1-(*p*–tolyl)ethyl)-1,3,2-dioxaborolane (3d): According to GP2 boronate **1d** (200 mg, 613 μmol) was reacted with abs. CH_2Cl_2 (0.07 mL, 1.04 mmol), *n*-BuLi (0.26 mL, 2.5 M in hexane, 644 μmol) and $ZnCl_2$ (88.0 mg, 644 μmol). MeMgBr (0.41 mL, 3.0 M in THF, 1.23 mmol) was added at −78 °C. After 24 h at 0 °C workup and purification by flash chromatography (silica, pentane/ether 9:1) provided **3a** as a colorless oil (176 mg, 487 μmol, 79%). Purity: 98%, 2% methylboronic ester **F** was formed as side product.

For analytical purposes **3d** was oxidized according to GP3 to the secondary alcohol **4d**, which was analyzed by GC (98.8% ee).

***tert*-Butyl(4-((*S*)-1-((4*R*,5*R*)-4,5-dicyclohexyl-1,3,2-dioxaborolan-2-yl)ethyl)phenoxy)dimethylsilane (3e)**: According to GP2 boronate **1e** (2.00 g, 4.52 mmol) was reacted with abs. CH_2Cl_2 (0.49 mL, 7.68 mmol), *n*-BuLi (1.90 mL, 2.5 M in hexane, 4.75 mmol) and $ZnCl_2$ (647 mg, 4.75 mmol). MeMgBr (3.62 mL, 3.0 M in THF, 9.07 mmol) was added at −78 °C. After 24 h at 0 °C workup and purification by flash chromatography (silica, pentane/ether 95:5) provided **3a** as a colorless oil (1.61 g, 3.42 mmol, 76%).

For analytical purposes **3e** was oxidized according to GP3 to the secondary alcohol **4e**, which was analyzed by GC (95.5% ee).

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((*S*)-1-(4-methoxy-3,5-dimethylphenyl)ethyl)-1,3,2-dioxaborolane (3f): According to GP2 boronate **1f** (2.45 g, 6.62 mmol) was reacted with abs. CH_2Cl_2 (0.72 mL, 11.3 mmol), *n*-BuLi (2.78 mL, 2.5 M in hexane, 6.95 mmol) and $ZnCl_2$ (947 mg, 6.95 mmol). MeMgBr (5.29 mL, 3.0 M in THF, 13.2 mmol) was added at −78 °C. After 24 h at 0 °C workup and purification by flash chromatography (silica, pentane/ether 92:8) provided **3a** as a colorless oil (2.34 g, 5.87 mmol, 89%).

For analytical purposes **3f** was oxidized according to GP3 to the secondary alcohol **4f**, which was analyzed by GC (97.5% ee).

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((*S*)-1-phenylpropyl)-1,3,2-dioxaborolane (5a): According to GP2 boronate *ent*-**1a** (300 mg, 961 μmol) was reacted with abs. CH_2Cl_2 (0.11 mL, 1.63 mmol), *n*-BuLi (0.40 mL, 2.5 M in hexane, 1.01 mmol) and $ZnCl_2$ (137 mg, 1.01 mmol). EtMgBr (0.80 mL, 3.0 M in THF, 2.40 mmol) was added at −78 °C. After 24 h at 0 °C workup and purification by flash chromatography (silica, pentane/ether 9:1) provided **3a** as a colorless oil (287 mg, 802 μmol, 83%). Purity: 99%, 1% ethylboronic ester **F'** was formed as side product.

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((*R*)-((4-methoxybenzyl)oxy)(phenyl)methyl)-1,3,2-dioxaborolan (6a): According to GP2 boronate *ent*-**1a** (2.80 g, 8.97 mmol) was reacted with abs. CH_2Cl_2 (0.98 mL, 15.2 mmol), *n*-BuLi (3.77 mL, 2.5 M in hexane, 9.42 mmol) and $ZnCl_2$ (1.28 g, 9.42 mmol) to α-chloroboronic ester *ent*-**2a**. In parallel, for the preparation of the nucleophile solution NaH (538 mg, 13.5 mmol, 60% suspension in oil) was suspended in DMSO (14 mL) and THF (7 mL) before *p*-methoxybenzylalcohol (1.78 mL, 14.4 mmol) was added and the mixture was stirred overnight at room temperature. The nucleophile solution was added to the solution of *ent*-**2a** at 0 °C. After stirring and warming overnight to room temperature, workup and purification by flash chromatography (silica, pentane/ether 75:25) provided **6a** as a colorless oil (3.12 g, 6.75 mmol, 75%).

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((*R*)-(4-fluorophenyl)(methoxy)methyl)-1,3,2-dioxaborolane (6b): According to GP2 boronate **1b** (196 mg, 593 μmol) was reacted with abs. CH_2Cl_2 (0.07 mL, 1.09 mmol), *n*-BuLi (0.25 mL, 2.5 M in hexane, 623 μmol) and $ZnCl_2$ (85 mg, 623 μmol) to α-chloroboronic ester **2b**. For the preparation of the nucleophile solution *n*-BuLi (0.40 mL, 2.5 M in hexane, 1.00 mmol) was added to MeOH (43.2 μL, 1.07 mmol) in THF (1 mL) at −20 °C. The cooling bath was removed and after stirring at room temperature for 30 min, the nucleophile solution was added to the solution of **2b** at 0 °C. After stirring and warming overnight to room temperature, workup and purification by flash chromatography (silica, pentane/ether 9:1) provided **6b** as a colorless oil (175 mg, 468 μmol, 79%).

(4*R*,5*R*)-2-((*R*)-(4-Chlorophenyl)(methoxy)methyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (6c): According to GP2 boronate **1c** (240 mg, 692 μmol) was reacted with abs. CH_2Cl_2 (0.08 mL, 1.18 mmol), *n*-BuLi (0.29 mL, 2.5 M in hexane, 727 μmol) and $ZnCl_2$ (99 mg, 727 μmol) to α-chloroboronic ester **2c**. For the preparation of the nucleophile solution *n*-BuLi (0.47 mL, 2.5 M in hexane, 1.18 mmol) was added to MeOH (50.4 μL, 1.25 mmol) in THF (1 mL) at −20 °C. The cooling bath was removed and after stirring at room temperature for 30 min, the nucleophile solution was added to the solution of **2c** at 0 °C. After stirring and warming overnight to room temperature, workup and purification by flash chromatography (silica, pentane/ether 9:1) provided **6c** as a colorless oil (176 mg, 450 μmol, 65%).

(4*S*,5*S*)-4,5-Dicyclohexyl-2-((2*R*,3*S*)-3-phenylbutan-2-yl)-1,3,2-dioxaborolane (7a): According to GP2 boronate **3a** (105 mg, 309 μmol) was reacted with abs. CH_2Cl_2 (0.04 mL, 525 μmol), *n*-BuLi (0.13 mL, 2.5 M in hexane, 324 μmol) and $ZnCl_2$ (88.0 mg, 648 μmol). MeMgBr (0.21 mL, 3.0 M in THF, (617 μmol) was added at −78 °C. After 3 d at room temperature workup and purification by flash chromatography (silica, pentane/ether 92:8) provided **7a** as a colorless oil (110 mg, 281 μmol, 91%). Purity: 94%, 6% methylboronic ester **F** was formed as side product.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-((2*R*,3*S*)-3-(4-fluorophenyl)butan-2-yl)-1,3,2-dioxaborolane (7b): According to GP2 boronate **3b** (131 mg, 366 μmol) was reacted with abs. CH_2Cl_2 (0.05 mL, 625 μmol), *n*-BuLi (0.15 mL, 2.5 M in hexane, 384 μmol) and $ZnCl_2$ (105 mg, (768 μmol). MeMgBr (0.24 mL, 3.0 M in THF, (731 μmol) was added at −78 °C. After 3 d at room temperature, corresponding workup provided **7b** as a colorless oil (142 mg, 355 μmol, 97%). Purity: 97%, 3% methylboronic ester **F** was formed as side product.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-((1*S*,2*R*)-1-methoxy-2-phenylpropyl)-1,3,2-dioxaborolane (7c): According to GP2 boronate **3a** (110 mg, 323 μmol) was reacted with abs. CH_2Cl_2 (0.04 mL, 622 μmol), *n*-BuLi (0.14 mL, 2.5 M in hexane, 400 μmol) and $ZnCl_2$ (93 mg, 661 μmol) to the corresponding α-chloroboronic ester. For the preparation of the nucleophile solution *n*-BuLi (0.22 mL, 2.5 M in hexane, 550 μmol) was added to MeOH (23.6 μL, 582 μmol) in THF (1 mL) at −20 °C. The cooling bath was removed and after stirring at room temperature for 30 min, the nucleophile solution was added to the solution of the α-chloroboronic ester at 0 °C. After stirring and warming overnight to room temperature, workup and purification by flash chromatography (silica, pentane/ether 8:2) provided **7c** as a colorless oil (96.0 mg, 247 μmol, 76%).

(4*R*,5*R*)-2-((1*R*,2*S*)-2-(4-Chlorphenyl)-1-methoxypropyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (7 d): According to GP2 boronate **3 c** (118 mg, 315 μmol) was reacted with abs. CH_2Cl_2 (0.04 mL, 622 μmol), *n*-BuLi (0.13 mL, 2.5 M in hexane, 331 μmol) and $ZnCl_2$ (90 mg, 661 μmol) to the corresponding α-chloroboronic ester. For the preparation of the nucleophile solution *n*-BuLi (0.21 mL, 2.5 M in hexane, 535 μmol) was added to MeOH (23.0 μL, 567 μmol) in THF (1 mL) at −20 °C. The cooling bath was removed and after stirring at room temperature for 30 min the nucleophile solution was added to the solution of the α-chloroboronic ester at 0 °C. After stirring and warming overnight to room temperature, workup and purification by flash chromatography (silica, pentane/ether 9:1) provided **7 d** as a colorless oil (107 mg, 255 μmol, 81 %).

(4*R*,5*R*)-2-((1*R*,2*S*)-1-Azido-2-(4-methoxy-3,5-dimethylphenyl)propyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (7 e): According to GP2 boronate **3 f** (2.01 g, 5.05 mmol,) was reacted with abs. CH_2Cl_2 (0.55 mL, 8.58 mmol), *n*-BuLi (2.12 mL, 2.5 M in hexane, 5.30 mmol) and $ZnCl_2$ (1.44 g, 10.6 mmol) to the corresponding α-chloroboronic ester (2.26 g, 5.05 mmol, 100 %), which was isolated in this case and used directly in the second step. After dissolving in DMF (15 mL) and cooling to 0 °C, NaN_3 (735 mg, 11.3 mmol) was added and the solution was stirred overnight at room temperature. Sat. NH_4Cl-solution was added (Caution: more acidic conditions should be avoided to prevent the formation of potentially explosive hydrazoic acid!) and the product was extracted twice with pentane, dried (Na_2SO_4) and the solvent was removed in vacuo. Purification by flash chromatography (silica, pentane/ether 9:1) provided **7 e** as a colorless oil (984 mg, 2.17 mmol, 96 %).

tert-Butyl(4-((2*R*,3*R*)-3-((4*R*,5*R*)-4,5-dicyclohexyl-1,3,2-dioxaborolan-2-yl)-4-methylpent-4-en-2-yl)phenoxy)dimethylsilane (7 f): According to GP2 boronate 3e (1.35 g, 2.86 mmol,) was reacted with abs. CH_2Cl_2 (0.31 mL, 4.86 mmol), *n*-BuLi (1.20 mL, 2.5 M in hexane, 3.00 mmol) and $ZnCl_2$ (819 mg, 6.00 mmol) to the corresponding α-chloroboronic ester (1.49 g, 2.86 mmol, 100 %), which was isolated in this case and used directly in the second step. A certain amount thereof (680 mg, 1.31 mmol) was dissolved in THF (6.5 mL) together with $ZnCl_2$ (179 mg, 1.31 mmol) before isopropenylmagnesium bromide (6.55 mL, 0.50 M in THF, 3.28 mmol) was added at −78 °C. Stirring was continued for 3 d at room temperature before workup (according to GP2) and purification by flash chromatography (silica, pentane/ether 95:5) providing 7 f as a colorless oil (550 mg, 1.05 mmol, 80 %).

tert-Butyl(4-((2*R*,3*R*,*E*)-3-((4*R*,5*R*)-4,5-dicyclohexyl-1,3,2-dioxaborolan-2-yl)-4-methylhex-4-en-2-yl)phenoxy)dimethylsilane (7 g): Boronic ester 7 g was prepared from the α-chloroboronic ester (690 mg, 1.33 mmol), obtained during preparation of 7 f, $ZnCl_2$ (181 mg, 1.33 mmol) and 1-methyl-1-propenylmagnesium bromide (13.3 mL, 0.30 M in THF, 4.00 mmol) at −78 °C. Stirring for 24 h at room temperature, workup (according to GP2) and purification by flash chromatography (C-18-silica, MeCN/H_2O) provided 7 g as a colorless oil (596 mg, 1.11 mmol, 83 %).

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((*R*)-1-phenylethyl)-1,3,2-dioxaborolane (8 a): α-chloroboronate **2 b**[18] (870 mg, 2.83 mmol) was dissolved in anhydrous THF (10 mL/mmol) and $ZnCl_2$ (385 mg, 2.83 mmol, flame-dried *in vacuo*) was added. The mixture was cooled to −78 °C, PhMgBr (1.88 mL, 3.0 M in THF, 5.65 mmol) was added and the mixture was stirred for 24 h at 0 °C. The reaction mixture was added to a separating funnel with saturated NH_4Cl solution and pentane, the phases were separated and the aqueous phase was extracted with pentane again. The combined organic phases were dried over Na_2SO_4, the solvent was removed in vacuo and the crude product was purified by column chromatography (silica, pentane/ether 97:3). The product **8 a** was obtained as a colorless oil (914 mg, 2.68 mmol, 95 %).

(4*R*,5*R*)-4,5-Dicyclohexyl-2-((*R*)-1-(4-fluorophenyl)ethyl)-1,3,2-dioxaborolane (8 b): According to **8 a**, **2 b**[18] (200 mg, 670 μmol) was reacted with $ZnCl_2$ (183 mg, 1.34 mmol) and 4-fluorophenylmagnesium bromide (1.00 mL, 2.0 M in THF, 2.00 mmol) at 0 °C. After 3 d at room temperature workup and purification by flash chromatography (C-18-silica, MeCN/H_2O) provided **8 b** as a colorless oil (229 mg, 588 μmol, 88 %). Purity: 92 %, 8 % 4-fluorophenyl boronic ester **F''** was formed as side product.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-((*S*)-1-(4-methoxyphenyl)ethyl)-1,3,2-dioxaborolane (*ent*-**8 c**): According to **8 a**, *ent*-**2 b**[18] (475 mg, 1.59 mmol) was reacted with $ZnCl_2$ (433 mg, 3.18 mmol) and 4-methoxyphenylmagnesium bromide (3.98 mL, 1.0 M in THF, 3.98 mmol) at 0 °C. After 3 d at room temperature workup and purification by flash chromatography (silica, pentane/ether 95:5) provided *ent*-**8 c** as a colorless oil (413 mg, 1.12 mmol, 70 %).

For analytical purposes *ent*-**8 c** was oxidized according to GP3 to the secondary alcohol *ent*-**9 c**, which was analyzed by GC [(98.3 % ee).

Copies of NMR spectra of all compounds are reported in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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