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Enantioselective Catalysts for the Synthesis of α-Substituted Allylboronates—An Accelerated Approach towards Isomerically Pure Homoallylic Alcohols

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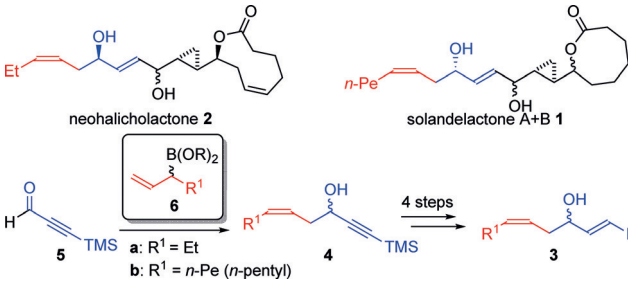
Dedicated to Professor Steven V. Ley on the occasion of his 70th birthday

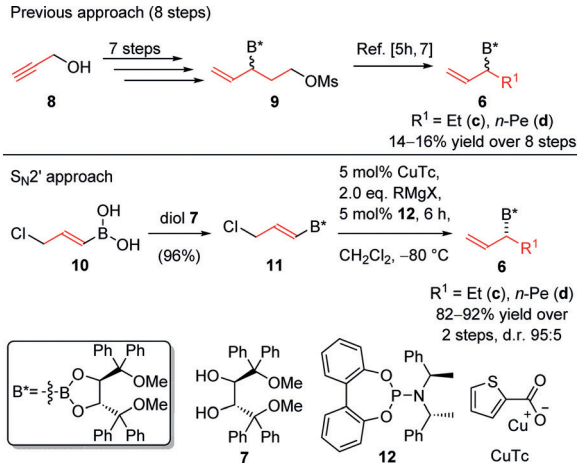
Abstract: *The use of a convenient protecting group for boronates allows a selective, catalyzed S_N2' reaction to generate allylboronates which are applied for the synthesis of enantiomerically pure homoallylic alcohols. Depending on the configuration of both catalyst and the protecting group any of the four possible stereoisomers can be formed. The rationale behind the selective addition is supported by density functional theory calculations.*

Z-configured homoallylic alcohols are often found as structural motifs in natural products, for example in oxylipines such as solandelactone A + B (**1**) and neohalicholactone (**2**) and related compounds of marine origin (Scheme 1).[1,2] Many syntheses rely on the same key reaction, the Nozaki–Hiyama–Kishi reaction[3] starting with vinyl iodides **3** (**3a**[4]/**3b**[5]). The present study led to a general approach towards intermediate **4**.[4b,5b] Central to the success was the fast and selective allylation of aldehyde **5** with a readily available allylboronate **6**.[6]

The starting point of the endeavor was the known eight-step synthesis of diol **7** based boronates **6c/6d** from propargylic alcohol (**8**) via mesylate **9** (Scheme 2).[4f,7] The stereogenic center in α-position to the boron moiety stems from a (3,3)-sigmatropic rearrangement.[8] While the route was applied in a number of syntheses, the overall yields are only moderate and a shorter alternative would be more attractive, especially if it would circumvent the sophisticated separation of diastereoisomers. Since boronic acid **10** is commercially available, boronate **11** is readily accessible in one step in high yield upon condensation (96%). It is an ideal substrate for S_N2' reactions directly leading to allylboronates **6c/6d**.



Scheme 1. Allylboronates in the synthesis of marine oxylipin side chains.



Scheme 2. Comparison of approaches towards boronates **6c/6d**.

Suitable parameters have been screened following various references (see the Supporting Information), but best results were obtained using the conditions promoted by Carosi and Hall:[9] The combination of copper thiophene carbonate (CuTc) and phosphoramidite ligand **12** led to high yields (82–92%) and good diastereo- (>95:5) and regioselectivities (>20:1); formation of α-product is negligible. The general

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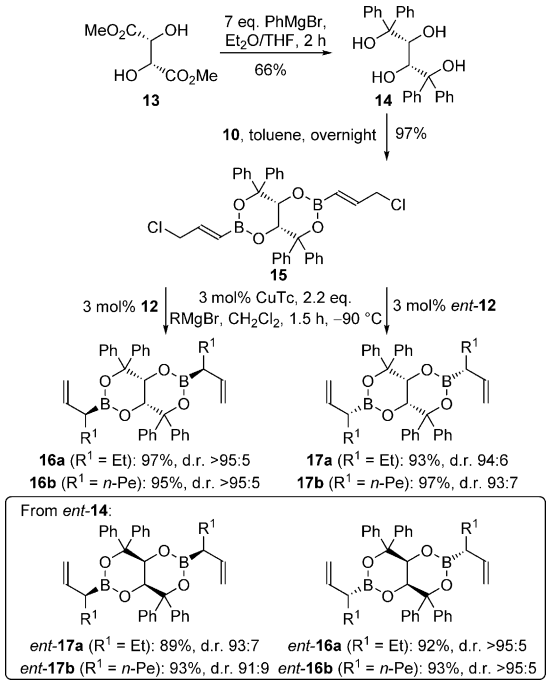
applicability of this short and efficient method has been demonstrated for various α-alkyl-substituted allylboronates with different chain lengths (albeit not $R^1 = Me$; see the Supporting Information).

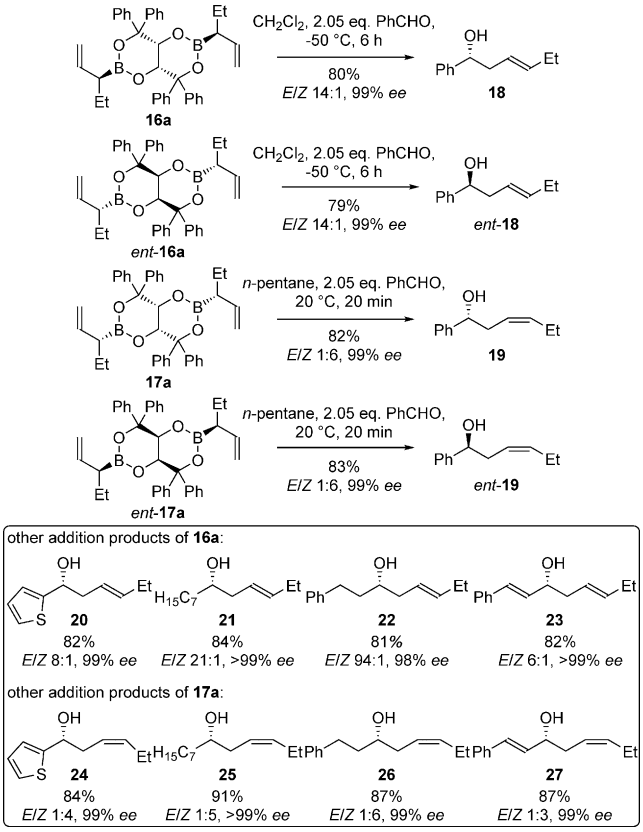
Despite the dramatic improvement of the sequence, there are still drawbacks that need addressing: a) The synthesis of diol **7** is step intensive;[6f] b) The reaction rates for allyl additions are relatively low and in some cases reaction times > 7 days are necessary; c) Both γ-products **6** and *dia*-**6** form predominantly the *Z*-homoallylic alcohols, while the corresponding *E* compounds cannot be obtained. Tartrate **13**/**14** based bisboronate **15** might be an alternative (Scheme 3).[10]



Scheme 3. Tetraol-based synthesis of allylboronates **16** and **17** in three steps.

Zhou and Shan[10a] reported on the selective condensation of tetraol **14** and phenylboronic acid and we demonstrated that the corresponding reaction of tetraol **14** with boronic acid **10** is feasible in high yield (97%), and in particular that the established substitution conditions are also applicable ($R^1 =$ Et, *n*-Pe): High yields (**16**/**17**: 89–93%) and selectivities were observed for all eight cases despite the fact that two boron moieties were present! Depending on the configuration of ligand **12** vs. *ent*-**12** and the tetraol **14** vs. *ent*-**14** any of the symmetric reagents are obtainable with diastereomeric ratios > 95:5 for **16** and *ent*-**16** and > 91:9 for **17** and *ent*-**17**. The stereochemical outcome of this three-step sequence from methyl tartrate was established by X-ray structure analyses of bisboronates **16a** and **17a**.[11]

Having all four stereoisomeric allylboronates **16a** and **17a** (and their enantiomers) in our hands, allyl additions were tested utilizing benzaldehyde as the electrophile (Scheme 4). While diol-based boronate **6c** requires long reaction times of several days, it was noted that even in dilute solution the new

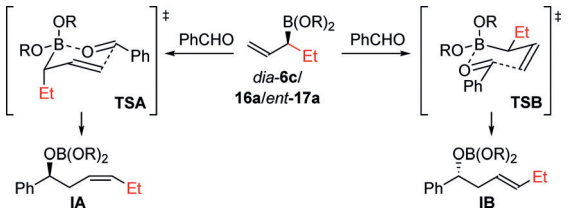


Scheme 4. Selective synthesis of all stereoisomeric homoallyl alcohols.

reagents provided products within minutes. Surprisingly, even at low temperatures down to −50 °C complete conversion was observed within hours. All products **18**/**19** were obtained in essentially enantiomerically pure form; the configuration of the stereogenic center was dictated by the tetraol configuration. Furthermore, we were surprised to observe that reagents **16** and *ent*-**16** provided in high selectivity ($E/Z =$ 14:1) the *E*-configured homoallylic alcohols **18** and *ent*-**18**, and not the expected *Z* compounds, in analogy to boronates **17** and *ent*-**17** forming **19** and *ent*-**19**, respectively.[12] Apparently, the relative configuration—side chain to auxiliary—is the dominant factor for the double-bond configuration. The reaction is not limited to benzaldehyde, but could be extended also giving comparable yields (79–91%) and selectivity for *E*-(**20**–**23**) and *Z*-products (**24**–**27**).

Two questions arise based on these findings: a) How can the relative acceleration between the two related types of reagents (*dia*-**6c** vs. *ent*-**17a**) be explained, and b) what is the rationale behind the unexpected *E*-selectivity for **16a**? One aspect could be the relatively close distance (3.1 Å) between the boron atom and the secondary oxygen atom which might activate the allylboronate functionality. The hypothesis is supported by findings of Morken as well as Hall and coworkers, who demonstrated the possibility of enhancing reactivity by intra- and intermolecular Lewis acid activation.[13]

To answer these questions, we analyzed the reaction as depicted in Scheme 5 by using DFT calculations [M06-2X-

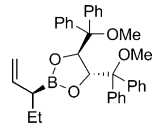
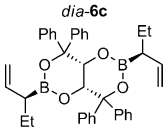
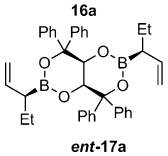


Scheme 5. Transition states and intermediates of allylations of benzaldehyde.

D3/def2-TZVPP/IEFPCM(CH_2Cl_2)//M06-L-D3/6-31+G-(d,p)].[14] As similar results were obtained for the reactions of *ent*-**17a** in CH_2Cl_2 and in *n*-pentane solutions, we will discuss only the values obtained in dichloromethane for the sake of clarity (see the Supporting Information for details). The free energies for the transformations are highly exergonic ($-31.3 < \Delta G < -26.9$ kcal mol^{-1}). Independent of the employed allylboronate, they all fall within a similar range, with the tetraol-based systems **16a** and *ent*-**17a** being slightly more exergonic. Based on the calculated high exergonicities and the low reaction temperatures we have to conclude that the selectivities arise from differences in activation energies (i.e., kinetic control) in line with previous investigations.[14] Consequently, we have calculated transition states—that are commonly depicted as **TSA** and **TSB**—for the formation of all intermediates **IA** and **IB** (and their enantiomers) obtained from benzaldehyde and allylboronates *dia*-**6c**, **16a**, and *ent*-**17a**. The calculated activation free energies are summarized in Table 1 and selected transition-state structures are depicted in Figure 1 (for others, see the Supporting Information). In all cases, chair-like transition states are significantly lower in energy than their corresponding boat-like structures, in line with the accepted mechanistic model.[6c,d,15]

For the diol-based boronate *dia*-**6c**, the lowest-energy transition state **TS1** leads (after hydrolysis of **IA**) to the product *ent*-**19**, while transition states for the other stereoisomers are significantly higher in energy (Table 1). In this transition-state structure, the ethyl substituent is located in an axial position (see the Supporting Information) to minimize the overall dipole moment and to avoid unfavorable steric interactions with the dioxaborolane system. The findings do correlate very well with the experimental results (*ent*-**19** was formed from *dia*-**6c** in 83% yield and >99% *ee*[7]).

Table 1: Calculated activation free energies (in kcal mol^{-1}) for the reactions of benzaldehyde and allylboronates *dia*-**6c**, **16a**, and *ent*-**17a**.

Boronate	$\Delta G^{\ddagger}(R,E)$	$\Delta G^{\ddagger}(S,E)$	$\Delta G^{\ddagger}(R,Z)$	$\Delta G^{\ddagger}(S,Z)$
 *dia*-**6c**	+22.8	+29.3	+26.1	+19.6 (**TS1**)
 **16a**	+13.8 (**TS2**)	+20.3	+23.2	+15.1
 *ent*-**17a**	+15.8	+19.7	+20.6	+15.3 (**TS3**)

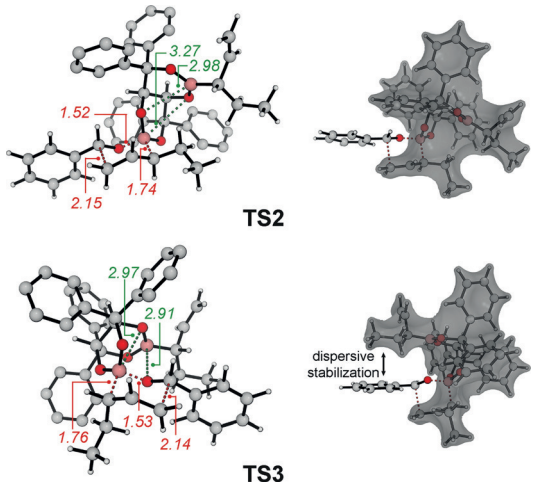


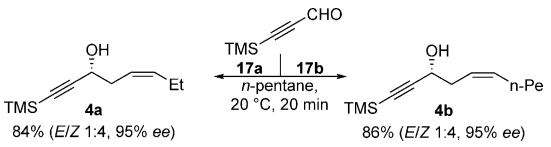
Figure 1. Calculated transition-state structures **TS2** and **TS3** with selected bond lengths (in Å) and side views highlighting the dispersive stabilization of **TS3**. For clarity, the hydrogens on the phenyl rings of the boronates are not shown.

A similar orientation (phenyl equatorial, ethyl axial) was also found in the lowest-energy transition state **TS3** for boronate *ent*-**17a** (Figure 1) resulting also in the formation of *ent*-**19**. In contrast, the lowest-energy transition state **TS2** for the reaction of the diastereomeric boronate **16a** with benzaldehyde features both the phenyl and the ethyl substituent in an equatorial position (Figure 1) yielding **18** as the kinetically preferred product. For both cases **16a** and *ent*-**17a**, the computed *E*/*Z* selectivity is in very good qualitative agreement with the experimental observations (Scheme 4). Furthermore, the calculations also correctly predict the tetraol-based systems to be significantly more reactive than the diol-based analogue (20 min at room temperature in dilute solution for *ent*-**17a** versus 2 days in concentrated solution for *dia*-**6c**[7]).

To rationalize the observed reactivities and stereoselectivities, we initially focused on putative boron–oxygen stabilization in the bisboronate series as outlined above. In fact, the transannular B–O bond lengths (green dashes in Figure 1) are significantly shorter than the sum of the van der Waals radii (3.41 Å)[16] in both **TS2** and **TS3**, indicating an attractive interaction between these atoms. Based on natural bond orbital analyses,[17] we found a binding interaction (ca. 2 kcal mol^{-1}) between the "uninvolved" boron and the oxygen atom next to the reaction center for **TS2**. However, this interaction was not observed for **TS3**. Instead, an interaction (ca. 5 kcal mol^{-1}) between the carbonyl oxygen of benzaldehyde and the "uninvolved" boron atom was found, which is also reflected in an even shorter B–O bond. While these additional B–O interactions rationalize the higher reactivities of **16a**/*ent*-**17a** over *dia*-**6c**, they are not responsible for the change in selectivity observed for the bisboronates, as these interactions are present in most transition state conformers of

TS2 and **TS3**. A closer examination of both structures (Figure 1, right) suggests that the different selectivity of *ent*-**17a** is rather caused by a different orientation of the bisboronate. While there are no significant additional interactions between the boronate **16a** and the aldehyde in **TS2**, the nonreacting pentenyl substituent of *ent*-**17a** interacts with the aldehyde in **TS3** by additional dispersive effects (e.g., C–H–π interactions).[18] These stabilizing effects are also verified by an NCIPLOT analysis (see the Supporting Information for details).[19]

In summary, computational investigations confirm the experimentally observed stereoselectivities for the reactions of the allyl boronates *dia*-**6c**, **16a**, and *ent*-**17a** with benzaldehyde. The higher reactivities of the bisboronates can be attributed to favorable B–O interactions. The high selectivities of these systems primarily arise from steric interactions with the phenyl groups of the adjacent dioxaborinane (see the Supporting Information), while the change in selectivity (**16a** vs. *ent*-**17a**) is caused by additional dispersive interactions in a tweezer-like geometry in the case of the latter. Finally, after having a) established a short and convenient approach towards the new reagents **16** and **17** and b) provided a rational for the unexpected high reactivity, we applied the method in the syntheses of the side chains of the marine oxylipins **1** and **2**. Again, the homoallylic alcohols (here **4a** from **17a** and **4b** from **17b**) were obtained in good yield and selectivity, thus considerable shortening the sequence towards the natural products (Scheme 6). The flexibility of the approach should



Scheme 6. Synthesis of key intermediates **4a**/**4b** for marine oxylipins.

render it versatile for a considerable number of further applications. A general method providing access to all four possible isomeric homoallylic alcohols has been presented. It is worth noting that the allylation reagents were synthesized in only three steps from dimethyl tartrate.

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