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Communication

Organocatalytic Synthesis of α-Trifluoromethyl Allylboronic Acids by Enantioselective 1,2-Borotropic Migration

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ABSTRACT: Chiral α-substituted allylboronic acids were synthesized by asymmetric homologation of alkenylboronic acids using CF_3/TMS-diazomethanes in the presence of BINOL catalyst and ethanol. The chiral α-substituted allylboronic acids were reacted with aldehydes or oxidized to alcohols in situ with a high degree of chirality transfer. The oxygen-sensitive allylboronic acids can be purified via their isolated diaminonaphthalene (DanH)-protected derivatives. The highly reactive purified allylboronic acids reacted in a self-catalyzed reaction at room temperature with ketones, imines, and indoles to give congested trifluoromethylated homoallylic alcohols/amines with up to three contiguous stereocenters.

Chiral allylboronic acids[1] are ideal reagents for asymmetric synthesis because of their high reactivity in self-catalyzed allylboration reactions that occur with high stereochemical fidelity. *However, the synthesis of chiral allylboronic acids has been an unmet challenge in organic synthesis.* Our experience with Pd-catalyzed synthesis of (achiral) allylboronic acids[2] (Figure 1a) and conclusions based on related mechanistic studies[3] suggested that a metal-free approach would be rewarding for effective control of the stereoselectivity. We hypothesized that the synthesis of *chiral* allylboronic acids may be devised by using an organocatalytic homologation strategy. The first methods for asymmetric homologation of organoboron compounds were reported by the Matteson group.[4,5] Aggarwal and co-workers[6] applied a useful lithiation−borylation method (Figure 1b) for the synthesis of chiral allyl-Bpin species,[7] including an example of an α-trifluoromethyl allylboronate derivative.[8] This method is based on stoichiometric formation of chiral lithium carbenoid intermediates, and therefore, it is not suitable for the direct synthesis of allylboronic acids. The Ley[9−11] and Wang[12] groups (Figure 1c) reported a homologation method based on diazo carbenoid reagents. This method was suitable for the synthesis of (achiral) allylboronic acids, which were used in one-pot allylborations[9,11] or converted to their Bpin derivatives.[12] A similar approach was employed by Molander and co-workers (Figure 1c) for the synthesis of benzylboronic acids from trifluoromethyl diazomethane.[13,14] Arnold and co-workers presented a method for the synthesis of chiral α-CF_3 alkyl- and benzylboron compounds by directed evolution of enzymes.[15,16] Fluorinated organoboronates are useful reagents for selective synthesis of organofluorines.[13−21] The CF_3 motif very often occurs[22−24] in pharmaceuticals and agrochemical products (Figure 1d).[25−29]

Here we present a new methodology for the synthesis of chiral α-CF_3 allylboronic acids (Figure 1e). Our concept (Figure 2) is based on reacting alkenylboroxine **2**, trifluor-

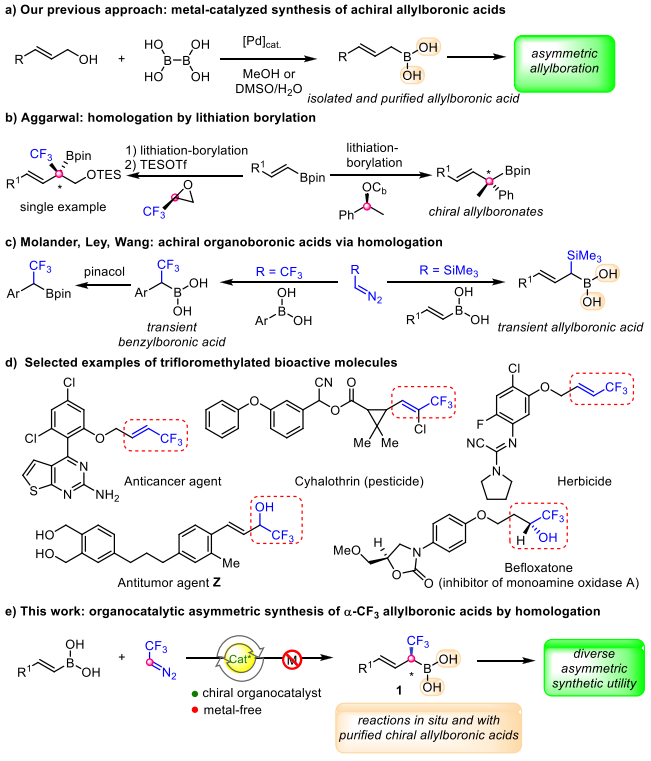

Figure 1. Synthesis of organoboronates and boronic acids as well as examples of bioactive molecules with a CF_3 group.

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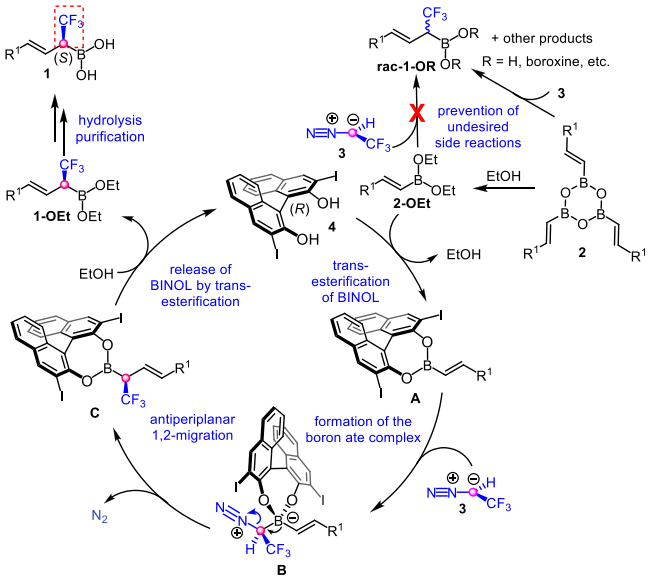
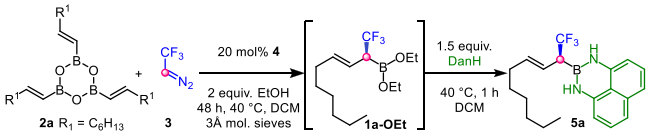


Figure 2. Concept of catalytic asymmetric homologation with 1,2-borotropic migration.

omethyl diazomethane **3**, catalytic amounts of BINOL (**4**),[30−36] and stoichiometric amounts of EtOH. Alkenylboroxine **2** readily reacts with diazo compound **3**.[9−11] However, this reaction results in racemic product, such as **rac-1-OR**. The racemic background reaction can be avoided by addition of EtOH to the reaction mixture, which forms unreactive alkylboronic esters **2-OEt**, which are weaker Lewis acids[37] than the corresponding boroxines **2**.[30,31] Because of the dynamic covalent bonding[38] ability of boron, BINOL **4** undergoes transesterification with **2-OEt** to form chiral alkenyl boronate **A**. Exchange of the alkyl group to an aromatic moiety leads to a substantial increase in the Lewis acidity of boron,[37] and therefore, **A** and **3** form ate complex **B** in the stereoinduction step of the process (see Figure S3). Then the alkenyl group undergoes stereoselective 1,2-migration[10,39] to afford **C**. Subsequently, ethanolysis of **C** gives product **1-OEt**.

The optimal conditions for the homologation involved using **2a** with an excess of **3**, 20 mol % **4** and 2 equiv of EtOH (Table 1, entry 1). The oxygen-sensitive allylboronic ester **1a-OEt** was protected with diaminonaphthalene (DanH)[40] to give **5a** with 98% ee in 69% yield. When the reaction was repeated with 10 mol % catalyst **4**, the yield was substantially lowered (12%), but the enantioselectivity was practically unchanged (96% ee) (entry 2). Replacement of iodo-BINOL **4** with bromo-BINOL (entry 3) led to decreases in the yield (9%) and the enantioselectivity (88% ee). Interestingly, increasing the loading of bromo-BINOL (entry 4) to 30 mol % led to a high yield (73%) and selectivity (94% ee). When bulky γ-substituents were employed in the BINOL catalyst (entry 5), both the yield and selectivity strongly declined. Application of the parent BINOL as the catalyst gave a low yield (4%) and relatively low selectivity (72% ee). When a commercially available alkenylboronic acid was used as the substrate (entry 7), the reaction proceeded in poor yield (18%) but with excellent selectivity (97% ee). When EtOH was replaced by ^{i}PrOH (entry 8), the yield dropped (44%) but the selectivity was still high (96% ee). In the absence of EtOH (entry 9), a complex reaction mixture was obtained, from which **5a** was isolated in 4% yield with 47% ee. The poor enantioselectivity

Table 1. Optimal Conditions for Synthesis of α-CF_3 Allylboronic Acids[a]



Entry	Change	NMR yield[b] (%)	Yield[c] (%)	ee (%)
1	No change	>95	69	98
2	10 mol% of catalyst **4**	22	12	96
3	20 mol% (R)-3,3'-Dibromo-1,1'-bi-2-naphthol instead of **4**	34	9	88
4	30 mol% (R)-3,3'-Dibromo-1,1'-bi-2-naphthol instead of **4**	>95	73	94
5	20 mol% (R)-3,3'-Bis(3,5-bis(trifluoromethyl)phenyl)-1,1'-bi-2-naphthol instead of **4**	8	trace	43
6	20 mol% (R)-1,1'-Bi(2-naphthol) instead of **4**	8	4	72
7	Boronic acid **2** was used as received	54	18	97
8	2 equiv. ^{i}PrOH instead of EtOH	81	44	96
9	No alcohol added	14[d]	4	47
10	No alcohol added and no catalyst	18[d]	trace	0
11	No molecular sieves added	7	trace	84
12	Reaction at room temperature instead of 40 °C	9	3	96
13	Solvent is toluene instead of DCM	33	14	92

[a]Boroxine **2a** (0.033 mmol, equivalent to 0.1 mmol of the boronic acid), **3** (0.3 mmol), **4** (0.02 mmol, 20 mol %), and ethanol (0.2 mmol) were reacted in DCM (0.8 mL) for 48 h at 40 °C, and then DanH (0.15 mmol) was added. [b]Yields of **5a** determined by ^{19}F NMR spectroscopy. [c]Isolated yields. [d]A complex reaction mixture was obtained.

can be rationalized by the racemic background reaction (**2** + **3** → **rac-1-OR** in Figure 2). The complex reaction mixture is a consequence of the poor stability of **1** and its boroxine in the absence of EtOH. Simple aliphatic alcohols esterify the boronic acids/boroxines and thus protect them from decomposition under the reaction conditions of the borylation (Figure 1a).[2,32,41] When both EtOH and the BINOL catalyst were omitted (entry 10), a complex reaction mixture was obtained again. Without molecular sieves (entry 11), the yield was poor, probably because the slow formation of chiral alkenyl-BINOL-type intermediate **A** (Figure 2). At room temperature, changing dichloromethane (DCM) to toluene leads to lowering the yield and a slight decrease of the ee (entries 12−13).

Under the optimal conditions, alkyl-substituted alkenylboronic acids **2a−c** reacted readily to give the corresponding α-CF_3 allylboronic acid esters **1(a-c)-OEt** and Bdan derivatives **5a−c** (Figure 3a). Aryl-substituted alkenylboronic acids (**2d−g**) reacted somewhat slower than the aliphatic ones. Cinnamyl derivative **5d** was formed in 54% yield (93% ee) when 20 mol % catalyst was used. However, with 20 mol % catalyst, **5e** formed only in 26% yield (89% ee). Therefore, the catalyst loading was increased to 30 mol % to obtain acceptable yields of **5e−g** (50−70%). The absolute configuration of crystalline **5e** was determined to be *S* by X-ray diffraction. On the basis of the structural similarities of the substrates and the reaction conditions, we assumed that the absolute configuration of the other species (**5a−d**, **5f**, and **5g**) was the same. The reactions can be easily scaled up. For example, the synthesis of **5a** on 1 and 2 mmol scales occurred with 98 and 96% ee in 78 and 68% yield, respectively.

The transient allylboron compounds **1-OEt** reacted with aldehyde **6a** in situ (Figure 1b). The enantioselectivity for the formation of **7a−d** varied between 90 and 98% ee. In addition, only one of the four possible diastereomers was formed in each case. We did not detect any *Z* isomer of **7a−e** in the crude product of the reaction. Usually, α-substituted allylboron

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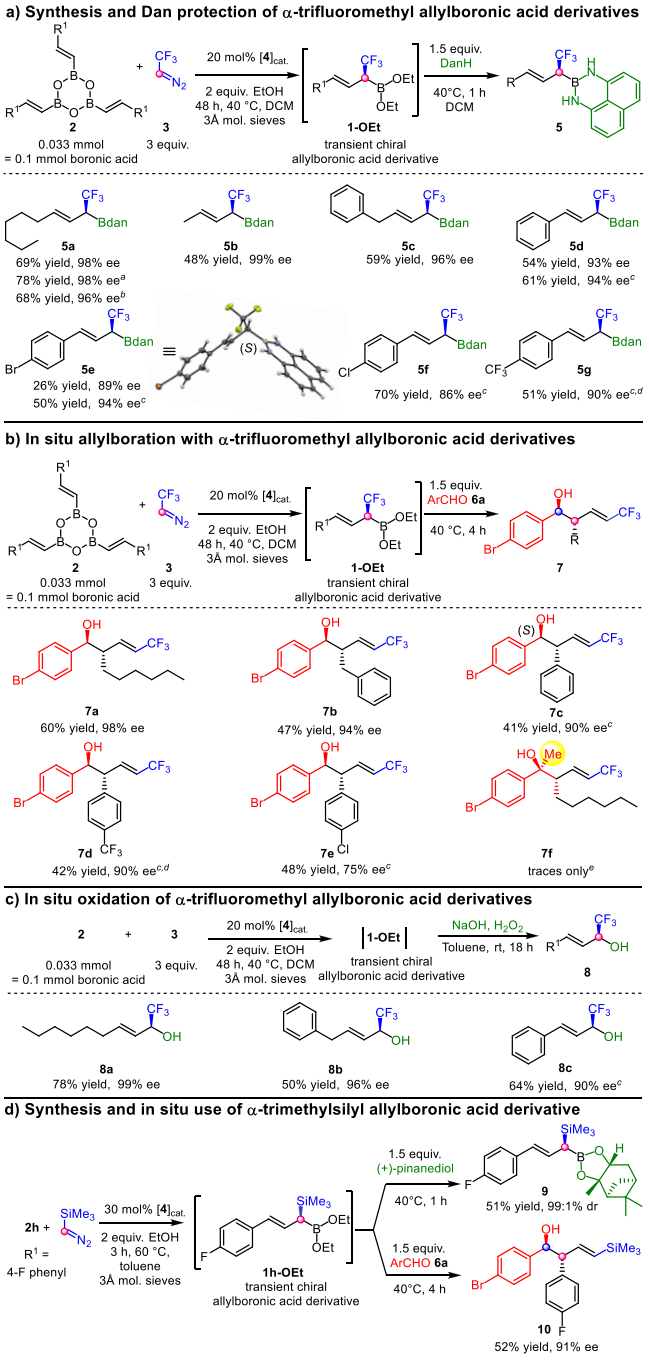

Figure 3. Synthesis and applications of chiral α-substituted allylboronic acids. [a]1 mmol scale. [b]2 mmol scale. [c]30 mol % **4** was used. [d]At 30 °C. [e]**6b** (0.15 mmol) was used.

compounds with bulky protecting groups (e.g., pinacol or 9-BBN) react with poor E/Z selectivity in allylboration reactions.[42,43]

These selectivity issues can often be solved by application of additives, but in the presented processes, poor E/Z selectivity was avoided by the small size of the $B(OEt)_2$ group. Notably, small molecules with alkenyl-CF_3 motifs[44−48] are very important drugs, such as in anticancer agents,[25] pesticides,[26] and herbicides[27] (Figure 1d). Formation of **7e** from **1f** proceeded with 75% ee. The relatively low enantioselectivity is a consequence of the fact that **1f-OEt** is formed with lower selectivity (86% ee, **5f**) than other allylboronic acids. The yields are in the range of 41−60% based on alkenylboronic acid monomers after a two-step process. Another useful reaction is the stereoselective in situ oxidation of the chiral allylboron compounds to the corresponding α-CF_3 allylic alcohols **8a−c** (Figure 3c), which were obtained in 50−78% yield with 90−99% ee. The corresponding trifluoroethanol motif[49,50] occurs for example in antitumor agent Z[28] and the monoamine oxidase inhibitor befloxatone (Figure 1d).[29]

The asymmetric homologation concept can also be extended to the synthesis of chiral α-silyl allylboronic acids, such as **1h-OEt** (Figure 3d). In this reaction, **3** was replaced with TMS-diazomethane. Dan protection of **1h-OEt** failed, and therefore, we isolated pinane derivative **9**. The homologation affording **9** proceeded with high selectivity (99:1 d.r., corresponding to 98% ee for **1h-OEt**) in 51% yield. In situ allylboration of **6a** gave homoallylic alcohol **10** with high selectivity.

We were able to obtain purified oxygen-sensitive allylboronic acids such as **1a** and **1d** by hydrolysis of the corresponding isolated Dan-protected products (**5a** and **5d**) (Table 2). The increased reactivity of the purified products unleashed the outstanding synthetic potential of chiral allylboronic acids. As we reported previously, in the presence of molecular sieves (or other drying agents), pure allylboronic acids form very reactive allylboroxines.[2,30,31,37] Purified **1a** in the presence of molecular sieves reacted with **6a** in just 10 min to afford **7a** (Table 2, entry 1). Notably, the enantioselectivities with purified and in situ-formed **1a** were identical. This was also confirmed by the reaction of cinnamyl analogue **1d** with **6a** (entry 2). Allylboration of **6b** with in situ-generated **1a-OEt** failed to give **7f** (Figure 3b). However, purified **1a** in the presence of molecular sieves gave **1a-boroxine** (see the Supporting Information), which reacted with **6b** to afford **7f** (entry 3) with excellent selectivity (98% ee) in 67% yield. The purification (**1a-OEt** → **5a** → **1a** sequence) is essential to obtain **7f**, as demonstrated by a control experiment (entry 4). When 2 equiv of EtOH was added to **1a** prior to addition of **6b**, formation of **7f** was not observed. Likewise, **1a-Bpin** did not react with **6b** under the reaction conditions applied for **1a** (entry 5). Aliphatic ketones (**6c−e**) also reacted smoothly with allylboronic acids. Cyclohexanones **6c** and **6d** gave the corresponding products **7g** and **7h** with 91−97% ee in 50−72% yield (entries 6 and 7). The reaction of racemic methyl cyclohexanone **6d** with **1d** is spectacular, as in this reaction the major enantiomer (97% ee) **7h** was formed with three contiguous stereocenters in a single reaction step. Acyclic aliphatic ketone **6e** reacted in high yield (72%) but with only 82% ee, affording densely functionalized tertiary homoallyl alcohol **7i**. The synthetic utility of purified chiral allylboronic acids was further demonstrated by allylboration of indoles[11,31,51,52] **6f** and **6g** with **1d** to afford **7j** and **7k** with high selectivities (entries 9 and 10). From skatole **6g**, the E-alkenyl-CF_3 product **7k** with three adjacent stereocenters was formed with 89% ee. Isoquinoline derivative[31,53] **6h** reacted with purified **1d** to afford **7m** with 93% ee in 54% yield. Allylboration of **6i**[54,55] with **1a** gave α-amino acid derivative **7n** with 98% ee in 72% yield.

In summary, we have presented a new methodology for the catalytic synthesis of chiral α-CF_3 or α-$SiMe_3$ allylboronic acids using stabilized diazomethane derivatives. The basic concept of stereoselective 1,2-borotropic migration can certainly be extended to nonstabilized diazoalkanes as well by solving the issues of electrophilic side reactions (e.g., protonation of the diazoalkanes) competing with the formation of the ate complex

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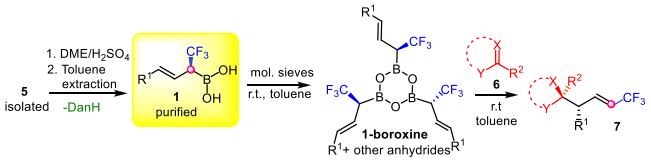
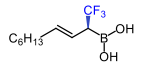
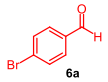
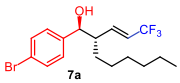
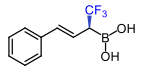
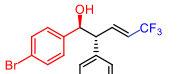
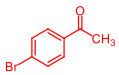
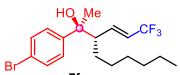
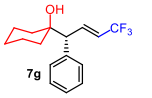
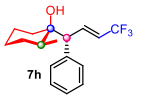
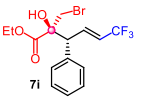
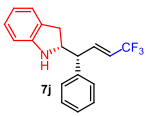
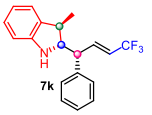
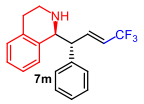
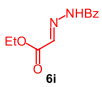
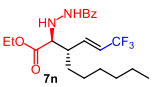
Table 2. Showcase for Application of Purified α-CF_3 Allylboronic Acids in Stereoselective Synthesis[a]



Entry	Boronic acid	Electrophile	Product	Time (h)	Yield[b] (%)	ee (%)
1	 **1a**[c]	 **6a**	 **7a**	0.13	43	98
2	 **1d**[c]	**6a**	 **7c**	4	53	93
3	**1a**	 **6b**	 **7f**	18	67	98
4	**1a** + EtOH[d]	**6b**	**7f**	18	no reaction	
5	**1a-Bpin**[e]	**6b**	**7f**	18	no reaction	
6	**1d**	 **6c**	 **7g**	18	72	91
7	**1d**	 **6d** (racemic)	 **7h**	18	50	97
8	**1d**	 **6e**	 **7i**	18	72	82
9	**1d**	 **6f**	 **7j**	18	62	93
10	**1d**	 **6g**	 **7k**	18	48	89
11	**1d**	 **6h**	 **7m**	18	54	93
12	**1a**	 **6i**	 **7n**	18	72	98

[a]Unless otherwise stated, **5** (0.1 mmol) was hydrolyzed with 3 N H_2SO_4 in DME, and then **1** was extracted with toluene under Ar. [b]Isolated yields. [c]^{1}H NMR spectra of **1a** and **1d** are given in the Supporting Information. [d]Using 2 equiv of EtOH without molecular sieves. [e]**1a-Bpin** and **6b** were stirred at 40 °C without molecular sieves.

(**B**). The enantioenriched α-CF_3 and α-$SiMe_3$ allylboronic acids readily undergo in situ allylboration with aldehydes or can be converted to the corresponding allylic alcohols with high levels of chirality transfer. The purified chiral allylboronic acids are very reactive and highly stereoselective reagents in the allylation of aldehydes, ketones, imines, and indoles. Very promising application areas for these types of allylboronic acids are in drug design (Figure 1d) and natural product synthesis.[56−60]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09923.

Materials and methods, characterization data, and NMR spectra (PDF)

Crystallographic data for **5e** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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