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Synthesis of Adjacent Quaternary Stereocenters by Catalytic Asymmetric Allylboration

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Supporting Information

ABSTRACT: Allylboration of ketones with γ-disubstituted allylboronic acids is performed in the presence of chiral BINOL derivatives. The reaction is suitable for single-step creation of adjacent quaternary stereocenters with high selectivity. We show that, with an appropriate choice of the chiral catalyst and the stereoisomeric prenyl substrate, full control of the stereo- and enantioselectivity is possible in the reaction.

Asymmetric synthesis has been a remarkably successful research area for the preparation of small molecules with new elements of chirality.[1] Although many excellent, highly stereoselective techniques have been reported, a couple of challenging problems still remain to be solved. Synthesis of quaternary stereocenters, in particular so-called "all-carbon" stereocenters, is still a difficult problem.[2] Even more difficult is to create two adjacent quaternary stereocenters in a single reaction step.[3] Nevertheless, such stereocenters are abundant in biomolecules, and therefore it is highly desirable to develop new synthetic techniques for single-step synthesis of adjacent quaternary stereocenters.[4] The main problem for such a synthesis is that at least six bulky, non-hydrogen substituents need to be placed in a precise 3D order around two stereogenic quaternary centers. In addition, propagating the chiral information to quaternary centers is particularly difficult in acyclic molecules.[2b] The bulkiness of the six substituents leads to steric repulsion between the quaternary stereocenters, because the CC bond between the quaternary carbons is long (typical CC bond lengths are 1.58−1.65 Å) and weak.[5] Accordingly, CC bonds with adjacent quaternary carbons are difficult to form and easy to cleave.[6] Therefore, enantioselective single-step formation of adjacent stereocenters[5,6] in acyclic molecules still represents a formidable challenge in organic synthesis.[2,3,5,7] Use of organoboron reagents proved to be very successful for generating quaternary and adjacent stereocenters.[7e,8] In particular, allylboration of carbonyl compounds and imines can be used for stereoselective formation of adjacent stereocenters.[4,9] One of the reasons for the high selectivity is that the two stereocenters are created in a single-step process via a Zimmermann−Traxler transition state (TS).[4,10] In this TS the two stereofaces of the allylboron compound and the carbonyl or imine substrate come into very close proximity, ensuring a high stereoselectivity and stereochemical fidelity.[10,11] In the reported examples of asymmetric synthesis, usually esters of allylboronic acid were used as allyl sources. In those studies two basic techniques were applied. One solution is asymmetric catalysis, often by using BINOL- or diol-based catalyst.[7b,d,e,g,12] Another possibility is chirality transfer using chiral boronates.[7a,f,13] Aggarwal et al.[5,7a] recently demonstrated that the reaction of chiral allylboronic acid esters with ketones or imines is suitable for enantioselective synthesis of acyclic compounds with adjacent quaternary stereocenters. However, as far as we know, such reaction using asymmetric catalysis has never been reported.

As mentioned above, formation of quaternary stereocenters is thermodynamically unfavored because of the weak bonding between the adjacent stereocenters.[5,6] In addition, the boron−oxygen contact in the TS of the reaction should be very short, ensuring a high stereoselectivity.[10,11] Considering these factors, we hypothesized that the selective formation of adjacent chiral quaternary centers by catalytic allylboration is probably hampered by using allylboronic *esters* as precursors. Recently, we described a new method for synthesis and isolation of allylboronic acids (e.g., **1a**−**c**, Figure 1).[14] Functionalized allylboronic acids show a much higher reactivity toward carbonyl compounds[14,15] and imines[11,16] than the corresponding allylboronic esters. In these reactions the allylboration proceeds with a very high stereoselectivity, and we demonstrated that synthesis of adjacent (non-asymmetric) quaternary stereocenters can be

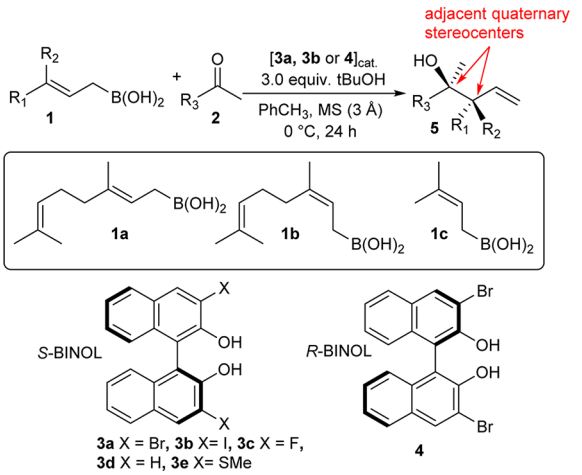

Figure 1. Adjacent quaternary stereocenters formed by allylboration of ketones with allylboronic acids in the presence of catalytic amounts of BINOL derivatives.

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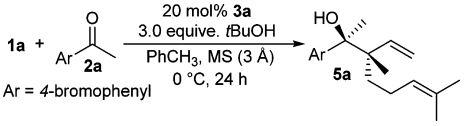
Table 1. Optimal Conditions for Catalytic Asymmetric Allylboration of Ketones with Geranylboronic Acid



entry	conditions	er	yield (%)[a]
1	without change	97:3	75
2	using ligand **4** instead of **3a**	93:7[b]	79
3	*t*AmOH instead of *t*BuOH	94:6	76
4	HFPP[c] instead of *t*BuOH	93:7	71
5	without *t*BuOH	86:14	80
6	MeOH instead of *t*BuOH		nr
7	*i*PrOH instead of *t*BuOH		nr
8	without MS	85:15	36
9	without alcohol and MS	90:10	70
10	using **3b** instead of **3a**	95:5	71
11	using **3c** instead of **3a**	67:33	27
12	using **3e** instead of **3a**	81:19	59
13	using **3d** instead of **3a**	54:46	34
14	without BINOL	50:50	34

[a]Isolated yields. nr = no reaction. [b]Opposite enantiomer of **5a**. [c]HFPP = 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanol.

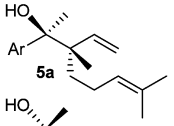
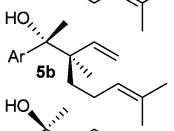
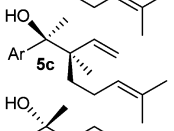
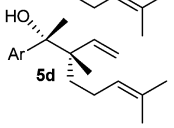
performed at room temperature without any additives.[14,15] We decided to develop a catalytic asymmetric version of this procedure, to widen the scope of synthetic methodologies for accessing acyclic compounds with adjacent quaternary stereocenters (Figure 1). Asymmetric allylboration using allylboronic esters and carbonyl compounds in the presence of Lewis and Brønsted acid catalysts is a useful methodology for synthesis of chiral homoallyl alcohols.[17] The groups of Chong,[18] Schaus,[7d,g] and Senanayake[12b] employed BINOL derivatives for enantioselective allylboration. Schaus et al.[7d] showed that the isopropoxy ester derivative of crotylboronic acid reacts with ketones in the presence of BINOL derivative **4** with high enantioselectivity.

We now find (Table 1) that γ-disubstituted boronic acid **1a** and ketone **2a** can be reacted in the presence of catalytic amounts of bromo-BINOL derivative **3a** and ^{t}BuOH. This allylboration reaction affords homoallylic alcohol **5a** with adjacent quaternary stereocenters with high enantioselectivity (enantiomer ratio (er) 97:3) and diastereoselectivity (diastereomer ratio (dr) >98:2). When **4**, the enantiomeric form of bromo-BINOL **3a**, was used (entry 2), the opposite enantiomer of **5a** was formed in excellent selectivity (er 93:7). All other deviations from the optimal conditions led to a decrease of the enantioselectivity and in some cases even the yield. Changing the tertiary alcohol to amyl alcohol[19] led to a slight decrease of the selectivity (entry 3), while hexafluoro alcohol HFPP (entry 4) led to a slight drop in the yield. Without any tertiary alcohol (entry 5) or molecular sieves (entry 8), the selectivity dropped (er 86:14 and 85:15 respectively). Interestingly, using MeOH or ^{i}PrOH instead of ^{t}BuOH led to complete inhibition of the reaction, and **5a** did not form at all (entries 6, 7).

When both ^{t}BuOH and the molecular sieves were excluded (entry 9), the selectivity was somewhat higher (er 90:10) than in the presence of one of these components. We have briefly studied the effect of the replacement of bromo-BINOL **3a** with other BINOL-based catalysts. Iodo-BINOL **3b** was almost as efficient as the bromo analogue (cf. entries 10 and 1). However, both the selectivity and the yield were substantially reduced when fluoro-BINOL **3c** was used (entry 11). The parent BINOL **3d** (entry 13) gave very poor selectivity (er 54:46), indicating the importance of the γ-substituent in BINOL for the enantioselectivity-determining step of the reaction. BINOL derivative **3e** with SMe substituent give a much higher enantioselectivity than BINOL **3d** but still a lower selectivity than **3a** (entry 13). Without BINOL derivatives (entry 12) the unselective background reaction is very slow, as the yield drops to 34%.

To demonstrate the generality of the above asymmetric catalysis, we synthesized all four possible enantiomers of isomeric prenyl alcohols **5a–d** (Table 2) with the above method. As

Table 2. Synthesis of All Four Enantiomeric Forms of Isomeric Terpenoid Alcohols with Adjacent Quaternary Stereocenters[a]

Entry	Boronic acid	Ketone	Catalyst	Product	Yield[b]
1	**1a**	**2a**[c]	**3a**[d]		75 % 97:3 e.r.
2	**1a**	**2a**	**4**		89 % 95:5 e.r.
3[e]	**1b**	**2a**	**3b**		80 % 97:3 e.r.
4	**1b**	**2a**	**4**		83 % 96:4 e.r.

[a]Unless otherwise stated, ketone **2a** (0.12 mmol), **1a** or **1b** (0.1 mmol), catalyst **3b** or **4** (0.03 mmol), ^{t}BuOH (0.3 mmol), and MS (3 Å) were stirred at 0 °C for 24 h. [b]Isolated yield affording dr 98:2. [c]Ar = 4-bromophenyl. [d]0.02 mmol of catalyst **3a** was used. [e]The reaction was performed at room temperature.

mentioned above, **1a** and **2a** reacted with BINOL derivatives **3a** and **4** with high selectivity (entries 1, 2), giving the enantiomeric forms of the trans diastereomer **5a** and **5b**, respectively. When the reaction was performed with nerylboronic acid **1b** instead of geranylboronic acid **1a** in the presence of **3b**, the epimeric form of **5a**, compound **5c**, was formed (entry 3) with high enantioselectivity (er 97:3). We then reacted nerylboronic acid **1b** and **2a** in the presence of **4** (entry 4), affording the epimeric form of **5b** with a high selectivity (er 96:4).

Subsequently, we studied the synthetic scope of the reaction (Table 3). It was found that changing the position of the bromo substituent (**2b**) in the aromatic ring (entry 1) did not change the selectivity and slightly increased the yield. When the bromo substituent in **2a** was replaced with an acetoxy group, the enantioselectivity decreased very slightly (entry 2). The reaction (entry 3) with a methyl sulfonyl substituent in the ketone component (**2d**) proceeded with very high selectivity (er 97:3). The enantioselectivity did not change when the reaction was scaled up to 5 times. The product **5g** is a solid, and thus we were able to obtain its X-ray structure to determine the absolute configuration of the product. When we increased the steric bulk of the ketone (entry 4) by using naphthyl derivative **2e**, the enantioselectivity was slightly decreased (er 96:4). Heterocyclic ketone **2f** also performed well (entry 5), providing **5i** with high enantioselectivity and yield. Aliphatic ketone **2g** gave **5j** with an er of 95:5 (entry 6). Using **4** as catalyst, homoallylic alcohol **5k** was formed selectively, which is the enantiomer of **5j**. Switching

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Table 3. Synthetic Scope of the Asymmetric Prenylation[a]

Entry	Boronic Acid	Ketone	Catalyst	Product	Yield[b]
1[c]	1a	2b	3a	5e	89 % 97:3 e.r.
2	1a	2c	3a	5f	95 % 96:4 e.r.
3	1a	2d	3a	5g	60% /72%[d] 97:3 e.r.
4	1a	2e	3a	5h	65 % 96:4 e.r.
5	1a	2f	3a	5i	81 % 95:5 e.r.
6	1a	2g	3a	5j	62 % 95:5 e.r.
7	1a	2g	4	5k	54 % 95:5 e.r.
8	1b	2c	3b	5l	76 % 95:5 e.r.
9	1b	2h	3b	5m	81 % 96:4 e.r.
10	1c	2a	3a	5n	71 % 96:4 e.r.
11	1c	2a	4[e]	5o	78 % 94:6 e.r.
12	1c	2d	3a	5p	69 % 95:5 e.r.
13	1a	2i	3a[e]	5q	93 % 90:10 e.r.

[a]Unless otherwise stated, **2** (0.12 mmol), **1** (0.1 mmol), catalyst **3b** or **4** (0.02 mmol), ^{t}BuOH (0.3 mmol), and MS (3 Å) were stirred at 0 °C for 24 h. [b]Isolated yield affording dr >98:2. [c]The reaction was performed at room temperature. [d]Yield for 0.5 mmol scale reaction. [e]0.03 mmol of catalyst **3a** was used.

from geranyl- (**1a**) to nerylboronic acid (**1b**), the diastereomeric prenyl alcohol derivatives **5l** and **5m** could be synthesized (entries 8, 9).

The high enantioselectivity (er 96:4) was also preserved in the prenylation reactions (entries 10–12). One of the homoprenyl alcohol products (**5p**) could be crystallized, and thus its absolute configuration could be determined by X-ray diffraction. Finally, we studied the stereoselectivity of the reaction of geranylboronic acid **1a** and cyclic ketone **2i**. The reaction provided a single diastereomer in which the all-carbon quaternary center was created with good enantioselectivity (er 90:10).

As mentioned above, we determined the absolute configuration of products **5g** and **5p**. Based on this information, we provide a plausible mechanism for the enantioselection process (Figure 2). Probably the initial stage of the reaction is

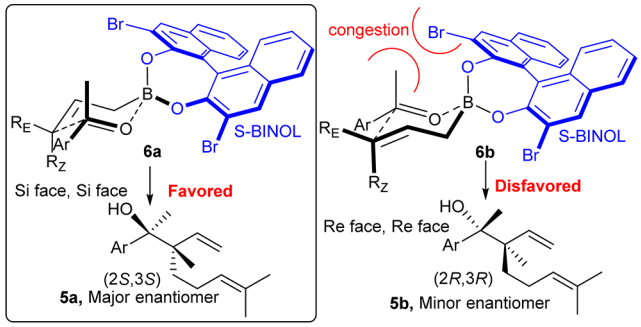

Figure 2. Plausible mechanism of the enantioselection.

esterification of **1a–c** by BINOL derivatives **3a,b** or **4**.[7g,18,20] Chiral diols may form mono-[7g,21] or diesters[7l,18] of allylboronic acids or their anhydrides (such as triallylboranes). DFT modeling by Pellegrinet et al.[20] demonstrated that boronic acid diesters of BINOL are more reactive than the corresponding monoesters. Monitoring the reaction of **1a** and **3c** by ^{19}F NMR also suggested that diesterification of the boronic acid functionality occurred (Supporting Information (SI)). Adding molecular sieves probably accelerates the formation of diesters of allylboronic acids. Considering the high reactivity of BINOL diesters[20] in allylboration and the expected easy esterification of allylboronic acids and their anhydrides,[7l,18] it is reasonable to assume that BINOL diesters of allylboronic acids are the active reaction intermediates in the above processes. The allylboration is supposed to proceed via Zimmermann–Traxler TSs **6a,b**.[4,10] The face selectivity for a certain BINOL derivative is probably determined by the steric interaction of the bromo substituent of the BINOL and the methyl group of the ketone. For example, in TS **6a**, *S*-BINOL **3a** is bound to the boronic acid group. In the case of *Si* face arrangement (ketone in the front side, boronic acid in the background), there is no steric congestion between the bromine atom and the methyl group of the ketone. This TS provides the major enantiomer, such as **5a**. In TS **6b**, with *Re* face arrangement (i.e., the boronic acid in the front and the ketone is in the background) steric repulsion between the bromine atom and the methyl group of the ketone raises a high activation barrier. Since this TS is disfavored, formation of **5b** is suppressed. When the configuration of the BINOL is switched from *S* (such as **3a**) to *R* (such as **4**), formation of **5b** is favored and **5a** is disfavored. As can be seen from Table 1, small amounts of ^{t}BuOH (entry 1) or other tertiary alcohols (entries 3, 4) were beneficial for high enantioselectivity. When ^{t}BuOH was used, the er increased to 97:3 (entry 1) from 86:14 (entry 5). We believe that ^{t}BuOH may help to regenerate the BINOL catalyst (such as **3a**), which is borylated after the allylation process.[7g] A borylated BINOL is not able to form boronic ester with allylboronic acid, which is necessary for the enantioselection (Figure 2). If free regenerated BINOL (such as **3a**) is not available, unselective (non-catalyzed) coupling may lead to a decrease of the enantioselectivity.

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As seen in Table 1, entries 6 and 7, when MeOH or ^{i}PrOH was added as an additive, the allylboration was inhibited. A possible explanation is that these primary and secondary alcohols esterify allylboronic acids, and thus inhibit the reaction of prenylboronic acids (such as **1a**) and ketones. Based on ^{1}H NMR monotoring studies, esterification of the $B(OH)_2$ group of **1a** can be suggested in the presence of ^{i}PrOH (see SI).

In conclusion, we have shown that adjacent quaternary stereocenters can be created from γ-disubstituted (prenyl) boronic acids and ketones in the presence of catalytic amounts of BINOL derivatives (such as **3a**). By altering the chirality of the BINOL derivative and choosing the stereoisomer of the allylboronic acid, full control of the diastereo- and enantioselectivity can be achieved. Both aromatic and aliphatic ketones undergo selective formation of chiral homoallyl alcohols by the above methodology. The control of the selectivity can be explained by in situ formation of BINOL esters of allylboronic acids. The selectivity is probably determined by the steric interactions in the Zimmermann−Traxler-type TSs. The described method gives new insights into the synthesis of quaternary stereocenters and control of the stereoselectivity. The above results will hopefully inspire new synthesis of natural products and bioactive molecules, including prenyl derivatives with adjacent quaternary stereocenters.[2b,4,15b,22] For example, in a very recent study, Li et al.[15b] used allylboronic acid **1a** in the synthesis of a key intermediate of terpenoid natural product hapalindole Q.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07498.

CIF files for 5g and 5p

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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