Asymmetric Synthesis

Enantioselective Synthesis of (E)-δ-Boryl-Substituted anti-Homoallylic Alcohols Using Palladium and a Chiral Phosphoric Acid
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Abstract: (E)-δ-Boryl-substituted anti-homoallylic alcohols are synthesized in a highly diastereomer- and enantioselective manner from 1,1-di(boryl)alk-3-enes and aldehydes. Mechanistically, the reaction consists of 1) palladium-catalyzed double-bond transposition of the 1,1-di(boryl)alk-3-enes to 1,1-di(boryl)alk-2-enes, 2) chiral phosphoric acid catalyzed allylation of aldehydes, and 3) palladium-catalyzed geometrical isomerization from the Z to E isomer. As a result, the configurations of two chiral centers and one double bond are all controlled with high selectivity in a single reaction vessel.

Steroselective construction of acyclic systems with contiguous chiral centers has been a central issue in organic synthesis. The allylation of carbonyl compounds with allylic boron reagents is one of the most reliable methods to build such systems through C–C bond formation with control of relative and absolute configurations.[1] The availability of stereochemically defined γ-substituted allylic boron reagents is a prime requisite for the syn/anti stereocore of the resulting homoallylic alcohols. We have developed a convenient preparative method for (E)-γ-substituted allylic boron reagents based on double-bond transposition.[2,3] For example, (E)-γ-substituted allylic boronates [1-(boryl)alk-2-enes] are generated in situ from 1-(boryl)alk-1-enes by iridium(I)-catalyzed double-bond transposition, and immediately undergo chiral phosphoric acid catalyzed allylation of aldehydes to produce anti-homoallylic alcohols with high enantioselectivity.[2b,4] Recently, an asymmetric allylation using chiral allylic boron reagents[5,6] functionalized with another semi-metal element, like tin, silicon, and boron,[7–9] has attracted much attention because the semi-metal elements remaining in the products allow a variety of additional transformations. For example, Roush and co-workers generated enantioenriched (S)-(E)-γ-substituted α-stannyl allylic boranes from allylstannanes, and synthesized (E)-β-stannyl-substituted anti-homoallylic alcohols with high enantioselectivity (Figure 1a).[5] This strategy was successfully applied to the asymmetric total syntheses of (−)-irradiamycin C[6a] and (−)-croacac C.[6c] Enantioenriched (S)-(E)-γ-substituted α-silyl allylic boranes are also feasible starting from allenylsilane.[10] When they engage in a reaction with aldehydes, (E)-δ-silyl-substituted anti-homoallylic alcohols are formed stereoselectively. In contrast, there has been no report on the generation of 1,1-di(boryl)alk-2-enes (α-boryl allylic boron reagents), probably because of the difficulty of their preparation.[11] We were interested in the use of 1,1-di(boryl)alk-3-enes as the precursor of 1,1-di(boryl)alk-2-enes based on the strategy of double-bond transposition. We now report the enantioselective synthesis of (E)-δ-boryl-substituted anti-homoallylic alcohols (Figure 1b). Of note is that the configurations of two chiral centers and one double bond are all controlled with high selectivity in a single reaction vessel.

1,1-Di(boryl)but-3-ene (2a) was easily prepared by allylation of commercially available bis(pinacolatoboryl)methane with allyl chloride.[5] We initially tried a reaction of the isolated 2a with benzaldehyde (1a) in the presence of [Ir(cod)BF₃(PCy₃)]₂ and (R)-TRIP (TRIP = 3,3’-bis(2,4,6-trisopropylphenyl)-1,1’-binaphthyl-2,2’-diyl hydrogen phosphinate).[12] Although an allylation reaction took place as a result of double-bond transposition, the products obtained were a mixture of the E/Z isomers of homoallylic alcohols and unidentified products (see the Supporting Information). Then, we turned our attention to the palladium(I) complex [Pd(µ-Br)(PrBu₃)]₂, which was originally reported by Gooßen and co-workers as the catalyst for double-bond transposition.[13] Thus, a mixture of 1a (0.20 mmol), 2a (2.0 equiv), and 4 Å molecular sieves (4 Å M.S.) in 1,2-dichloroethane (DCE)/toluene (1:1, 1.0 M) was stirred at 20°C for 17 hours in the presence of [Pd(µ-Br)(PrBu₃)]₂ (2.5 mol%) and (R)-TRIP (5.0 mol %) [Eq. (1)]. Chromatographic purification of the reaction mixture afforded a 98:2 mixture (anti and syn isomers) of the δ-boryl-substituted homoallylic alcohols 3aa and 4aa in 82% total yield. With...
regard to the double-bond geometry of the major anti-configured isomer (3aa), the E/Z ratio was 98:2. A high level of enantioselectivity (98% ee) was observed for (E)-3aa. Since the allylation products contain two chiral centers and one double bond, there are eight stereoisomers possibly generated from the achiral boron reagents and aldehydes. Of note is that the palladium(I) complex and the chiral phosphoric acid work in relay to form the one stereoisomer with high selectivity. A larger scale experiment using 638 mg (6.0 mmol) of 1a also gave a comparable result [3aa: 1.35 g (78% total yield, antisy=E=95:5, 98% ee)].

The double-bond transposition process was confirmed by the following experiment (Scheme 1). Treatment of 2a with a catalytic amount of [{Pd(μ-Br)(PhBu3)}]2 (2.5 mol%) at 20°C for 30 minutes gave a mixture of 2a/E-5a/Z-5a = 85:13:2. After 2 hours, it became a mixture of 2a/E-5a/Z-5a = 42:51:7. The E/Z ratio of 5a was almost constant (ca. 88:12).

It is assumed that [{Pd(μ-Br)(PhBu3)}]2 generates [Pd-(PhBu3)(H)Br], which catalyzes double-bond transposition by an addition/elimination pathway (Scheme 2). The Pd–H bond undergoes 1,2-addition across the double bond of 2a. Then, palladium eliminates along with a hydrogen atom located on the other neighboring carbon center, thus relocating a double bond. The transition-states (TSs) B and C, in which palladium and the neighboring hydrogen atom are nearly eclipsing, are assumed. The TS B is sterically favored over the TS C, thus generating the E isomer of 5a preferentially.

The E/Z ratio of 5a (88:12) was lower than the antisy ratio observed with the homoallylic alcohols (3aa/4aa = 98:2) [Eq. (1)]. The higher selectivity given by the allylation reaction is accounted for by assuming that (E)-5a reacts with 1a faster than (Z)-5a. Thus, the reactivities of (E)-5a and (Z)-5a toward aldehydes were compared by treating a 1:1 mixture of (E)-5a (1.0 equiv) and (Z)-5a (1.0 equiv) with 1a (2.0 equiv) at 20°C in the presence of (R)-TRIP (5.0 mol%) (Scheme 3). After 5 minutes, (E)-5a was completely consumed with 45% of (Z)-5a remaining, and corroborated the higher reactivity of (E)-5a than (Z)-5a.

Finally, the reaction of 1a with 2a (2.0 equiv) in the presence of [{Pd(μ-Br)(PhBu3)}]2 (5.0 mol%) and (R)-TRIP (5.0 mol%) was followed by 1H NMR spectroscopy (Scheme 4). After 30 minutes, the Z/E ratio with regard to the double bond of the resulting homoallylic alcohol 3aa (34% NMR yield) was greater than 95:5. The ratio changed to Z/E = 6:94 after 24 hours (81% NMR yield).

This time-dependent change of the double-bond geometry is explained by assuming that (Z)-3aa is initially formed from (E)-5a for kinetic reasons and that it gradually isomerizes to the thermodynamically more stable E isomer under the catalysis of palladium (Scheme 5). The TS structures shown account for the kinetic preference of (Z)-3aa over (E)-3aa'.
The six-membered chairlike TS E is more stable than the other TS D because the TS D suffers from gauche interactions between the pinacolato group on the chelated boron atom and the equatorial pinacolato boryl group.\[15\]

The most likely scenario to explain the stereoselective production of enantiomerically pure \((E)-3\text{aa}^\text{a}\) from \(2\text{a}\) is as follows: 1) Palladium-catalyzed double-bond transposition of \(2\text{a}\) generates \((E)-5\text{a}\) and \((Z)-5\text{a}\) with the former predominating. 2) The \((E)-5\text{a}\) reacts with benzaldehyde \((1\text{a})\) in preference to the \((Z)-5\text{a}\) under the catalysis of a chiral phosphoric acid, thus forming the \(Z\) isomer of the anti-homoallylic alcohol \((Z)-3\text{aa}^\text{a}\) via the TS E. 3) The palladium catalyst isomerizes \((Z)-3\text{aa}^\text{a}\) to the \(E\) isomer.\[16\]

The scope with respect to aldehydes was examined in the allylation reaction with \(2\text{a}\) (Table 1). An electronically and sterically diverse array of aromatic aldehydes \(1\text{a} - e\) gave the corresponding homoallylic alcohols \(3\text{aa} - \text{ea}\) in yields ranging from 78 to 90% (entries 1–5). In addition, 2-furaldehyde \((1\text{f})\), cinnamaldehyde \((1\text{g})\), as well as aliphatic aldehydes such as 2-phenylacetaldehyde \((1\text{h})\) and cyclohexanecarboxaldehyde \((1\text{i})\) successfully participated in the allylation reaction (entries 6–9). Of note was that good to high anti/syn ratios, E/Z ratios, and enantioselectivities were observed in all cases. The anti/syn ratios \((3\text{a} - \text{d})\) as well as the E/Z ratios with regard to the double-bond geometry of the \(E\)-configured anti-isomers of \(3\) ranging from 91 to 99% ee.

1,1-Di(boryl)alk-3-enes having a variety of \(R^1\) and \(R^3\) substituents were also prepared by allylation of bis(pinacolato)boryl methane with the corresponding allylic halides. They were subjected to the allylation reaction with benzaldehyde \((1\text{a}; \text{Table 2})\). As with the case of \(2\text{a}\) \((R^1, R^3 = \text{H}, \text{H})\), disubstituted olefinic boronates \((2\text{b} - \text{e})\) having methyl, isopropyl, phenyl, and trifluoromethyl groups all exhibited high stereoselectivities to give the products in 77–85% yields (entries 1–4). The trisubstituted olefinic boronates \(2\text{f} \) and \(2\text{g} \) were also amenable to the reaction (entries 5 and 6).

The allylation with the exo-olefinic boronate \(2\text{h} \) proceeded cleanly to give \(3\text{ah}\) in 98% yield, although the enantioselectivity was 20% ee [Eq. (2)].

In the case of 1,1-di(boryl)pent-4-ene \((2\text{i})\), having a double bond at a more remote position, double-bond transposition took place twice, and \(3\text{ah}\) was formed in 82% yield with high stereoselectivities [enantioselectivities > 95.5, E/Z > 95.5, 97% ee; Eq. (3)].

Table 1: Asymmetric allylation reactions of various aldehydes \((1\text{a} - \text{i})\) with \(2\text{a}\).[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1) ((1))</th>
<th>3</th>
<th>Yield [%]</th>
<th>anti/syn</th>
<th>E/Z (3/4)</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph ((1\text{a}))</td>
<td>anti (3\text{aa}^\text{a})</td>
<td>80</td>
<td>95.5</td>
<td>&gt;95.5</td>
<td>98([7])</td>
</tr>
<tr>
<td>2</td>
<td>4-ClC(6\text{H}_4) ((1\text{b}))</td>
<td>(3\text{ba})</td>
<td>90</td>
<td>95.5</td>
<td>95.5</td>
<td>99([7])</td>
</tr>
<tr>
<td>3</td>
<td>4-MeOC(6\text{H}_4) ((1\text{c}))</td>
<td>(3\text{ca})</td>
<td>80</td>
<td>95.5</td>
<td>&gt;95.5</td>
<td>98([7])</td>
</tr>
<tr>
<td>4</td>
<td>4-Me(2\text{C(6\text{H}_4})) ((1\text{d}))</td>
<td>(3\text{da})</td>
<td>82</td>
<td>95.5</td>
<td>95.5</td>
<td>98([7])</td>
</tr>
<tr>
<td>5</td>
<td>5-(2\text{Me(2\text{C(6\text{H}_4})})) ((1\text{e}))</td>
<td>(3\text{ea})</td>
<td>78</td>
<td>&gt;95.5</td>
<td>95.5</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>2-furyl ((1\text{f}))</td>
<td>(3\text{fa})</td>
<td>67</td>
<td>95.5</td>
<td>95.5</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>Ph(=\text{CH-CH}) ((1\text{g}))</td>
<td>(3\text{ga})</td>
<td>68</td>
<td>95.5</td>
<td>95.5</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>Ph(=\text{CH}) ((1\text{h}))</td>
<td>(3\text{ha})</td>
<td>72</td>
<td>95.5</td>
<td>&gt;95.5</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>Cy ((1\text{i}))</td>
<td>(3\text{ia})</td>
<td>71</td>
<td>95.5</td>
<td>&gt;95.5</td>
<td>96</td>
</tr>
</tbody>
</table>

[a] On a 0.20–0.40 mmol scale. Reaction conditions: see Equation (1).
[b] Total yield of 3 and 4 after chromatographic purification.
[c] Product ratio determined by \(\text{H}^1\) NMR analysis.
[d] The ee value of \(E\)-3 was determined by chiral-phase HPLC. [e] E/Z = 79:21. [f] The reaction mixture was stirred at 25°C for 23 h, then at 30°C for 15 h. [g] The reaction mixture was stirred at 25°C for 11 h, then at 30°C for 24 h.
The resulting δ-boryl-substituted anti-homoallylic alcohols were useful synthetic intermediates for a further transformation, for example, in a Suzuki–Miyaura cross-coupling. Thus, without intervention of any workup procedure after the allylation reaction, bromobenzene, KOH, and H₂O were directly added to the reaction mixture containing 3aa [Eq. (4)]. The (E)-alkenylboronate moiety underwent cross-coupling with bromobenzene with retention of the double-bond geometry to afford the corresponding product 7 in 95% yield (based on 1a).

In summary, we have developed a facile method for the synthesis of enantioenriched (E)-δ-boryl-substituted anti-homoallylic alcohols from 1,1-di(boryl)alk-3-enes and aldehydes. The two catalysts work in relay, thus forming one stereoisomer, out of eight possible stereoisomers, with high selectivity.

Acknowledgments

This work was supported by Grants-in-Aid for Scientific Research (S) (15H05756) and (C) (16K05694) from MEXT.

Conflict of interest

The authors declare no conflict of interest.

Keywords: allylation · asymmetric synthesis · homoallylic compounds · organocatalysis · palladium

How to cite: Angew. Chem. Int. Ed. 2017, 56, 6989–6993
Angew. Chem. 2017, 129, 7093–7097


[14] During aqueous workup, the Z isomer of 3aa was converted into the cyclized boronic ester 6aa. Therefore, what we isolated was a 98:2 mixture of (E)-3aa/6aa, not (E)-3aa/(Z)-3aa (see the Supporting Information). Other E/Z ratios were determined likewise.


