Chemistry
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Chemistry Europe
European Chemical Societies Publishing

## Accepted Article

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**To be cited as:** *Chem. Eur. J.* 10.1002/chem.202004930

**Link to VoR:** https://doi.org/10.1002/chem.202004930

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10.1002/chem.202004930

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RESEARCH ARTICLE

# Stereo- and Enantioselective Synthesis of Propionate-Derived Trisubstituted Alkene Motifs

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**Abstract:** We report a new method for constructing propionate-derived trisubstituted alkene motifs in a stereoselective manner. 1-Substituted 1,1-di(pinacolatoboryl)-(*E*)-alk-2-enes are *in situ* generated from 1-substituted 1,1-di(pinacolatoboryl)alk-3-enes through ruthenium(II)-catalyzed double-bond transposition. These species undergo a chiral phosphoric acid-catalyzed allylation reaction of aldehydes to produce the *E* isomers of *anti*-homoallylic alcohols. On the other hand, the corresponding *Z* isomers of *anti*-homoallylic alcohols are obtained when a dimeric palladium(I) complex is employed as the catalyst for this double-bond transposition. Thus, both *E* and *Z* isomers can be synthesized from the same starting materials. A B–C($sp^2$) bond remaining with the allylation product undergoes the Suzuki-Miyaura cross-coupling reaction to furnish a propionate-derived trisubstituted alkene motif in a stereo-defined form. The present method to construct the motifs with (*E*)- and (*Z*)-alkenes are successfully applied to the syntheses of (+)-isotrichostatic acid, (–)-isotrichostatin RK, and (+)-trichostatic acid, respectively.

## Introduction

Propionate-derived substructures are prevalent in many naturally-occurring compounds.[1,2] For example, this structural motif, highlighted in blue line (Figure 1), is found in the secondary metabolites of bacteria, fungi, and marine organisms. The occurrence of its corresponding oxidized form, highlighted by dotted line (Figure 1), is also frequently observed in nature. The structural motif is represented by (i) a carbinol (or carbonyl) group juxtaposed by a chiral methyl-substituted α-carbon, and (ii) a trisubstituted alkene constituting β,γ-unsaturation to the oxygen functionality. Accordingly, there are two stereochemical issues to address in synthesis for constructing this structural motif, one is associated with the chiral centers and the other is associated with the *E*/*Z* stereochemistry of the double bond. With this in mind, one of conceivable disconnection approaches to the substructure(s) is shown Figure 2a. The homoallylic alcohol can be disconnected to an aldehyde and a crotylboron species with its α-carbon substituted by a methyl group and another substituent ($R^2$).[3,4] Typically an allylation reaction of an aldehyde with a crotylboron species proceeds through a six-membered chair-like transition state. Axial/equatorial arrangements of substituents in the chair-like transition state dictate the stereochemistries of the product.

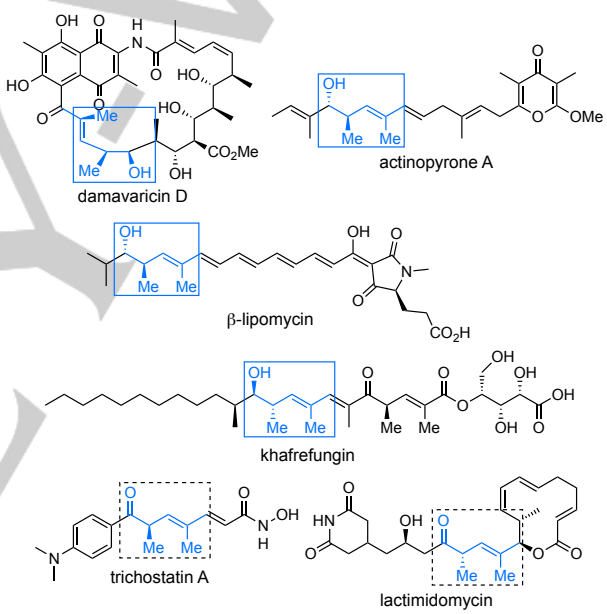


**Figure 1.** Selected polyketide natural products containing propionate-derived substructure.

The aldehyde orients in such a way that the hydrogen takes an axial position and the $R^1$ substituent takes an equatorial position. Enantioselectivity is attributed to which face of the aldehyde the crotylboron species attacks, and this facial selection is possibly dictated by a chiral phosphoric acid, so-called TRIP.[5,6] Thus, it would be feasible for an (*E*)-crotylboron species to stereoselectively forge the two adjacent chiral centers in an *anti* fashion during the carbon–carbon bond-forming step. On the other hand, it is considerably more difficult to differentiate any carbon substituent $R^2$ from a methyl group by sterics, and therefore, it is more challenging to control the stereochemistry of trisubstituted alkenes.[7]

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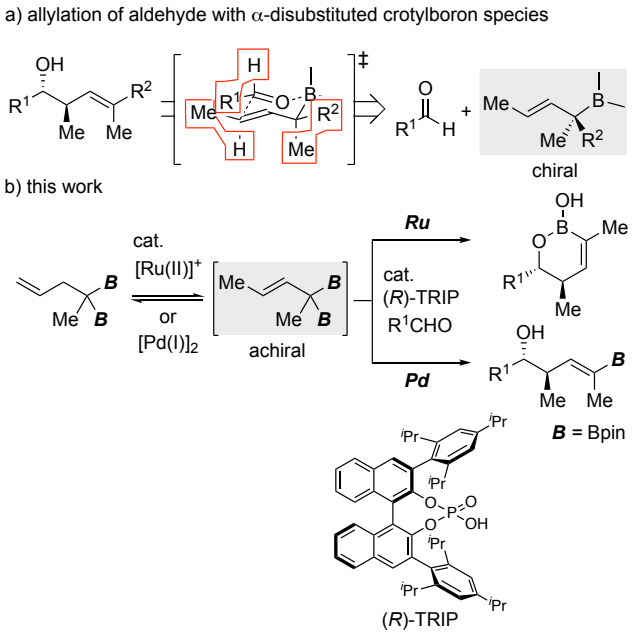
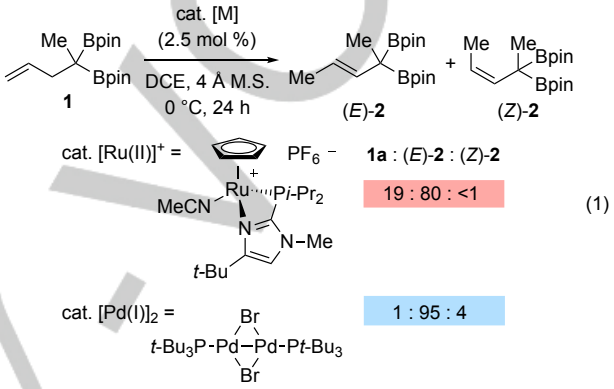



**Figure 2.** Stereo- and enantioselective synthesis of *anti*-homoallylic alcohols possessing trisubstituted alkenes.

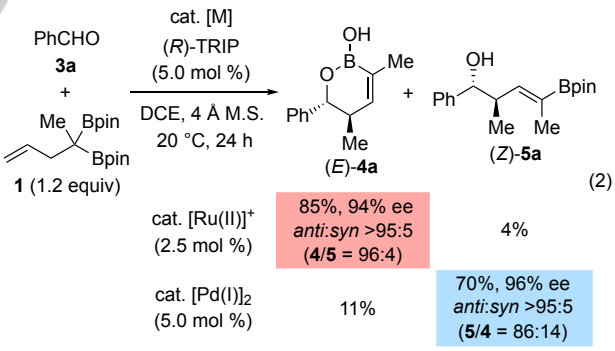
We[8] and others[9] have developed the enantioselective allylation reaction of aldehydes with 1,1-di(pinacolatoboryl)but-2-ene *in situ* generated from 4,4-di(pinacolatoboryl)but-1-ene through transition metal-catalyzed double-bond transposition.[10] We found the Grotjahn complex ([CpRu(2-P*i*-Pr$_2$-4-*t*-Bu-1-Me-imidazole)(MeCN)]PF$_6$, abbreviated as [Ru(II)]$^+$)[11] and the dimeric Pd(I) complex ([Pd(μ-Br)(P*t*-Bu$_3$)]$_2$, abbreviated as [Pd(I)]$_2$)[12] were the most effective catalysts for the double-bond transposition. In the chair-like transition state, the exocyclic boryl substituent exhibited a peculiar preference for its position. The pinacolatoboryl group was far bulkier than hydrogen,[13] nonetheless, it adopted an axial orientation. The contradictory preference was explained by assuming that severe gauche-type interactions developed between the two pinacolatoboryl groups[14] when the exocyclic one adopted an equatorial orientation. Thus, it was possible to stereoselectively install a pinacolatoboryl group on the disubstituted alkene.[15,16] Geometrical isomerization to a thermodynamically more stable form was also achieved.[8a] The installed boryl group acted as the surrogate of a carbon substituent when combined with the Suzuki-Miyaura cross-coupling reaction. Moreover, a well-established method was applicable to organize enantioselection on the allylation reaction.[5] TRIP catalyst could induce a high enantioselectivity. Next, we tried to establish a method to construct the propionate-derived trisubstituted alkene motif mentioned above in a stereo- and enantio-defined form on the basis of this protocol. Herein reported are the results of our study along this line.[17] Of note is that both (*E*)- and (*Z*)-stereochemistries are available for trisubstituted alkenes with this method (Figure 2b), which have found a successful application to the syntheses of (+)-isotrichostatic acid, (–)-isotrichostatin RK, and (+)-trichostatic acid, respectively.

## Results and Discussion

4,4-Di(pinacolatoboryl)pent-1-ene (**1**) was easily prepared by allylation of commercially available 1,1-bis(pinacolatoboryl)ethane with allyl bromide under basic conditions.[18] Its behavior toward the two catalysts previously used for the double-bond transposition was briefly examined (See Supporting Information for screening of other catalysts). Both [Ru(II)]$^+$ and [Pd(I)]$_2$ complexes were highly active, giving a mixture of parent **1** and crotylboron species (*E*/*Z*)-**2** with the **1**:(*E*)-**2**:(*Z*)-**2** ratios of 19:80:<1 and 1:95:4, respectively, after 24 hours at 0 °C (eq 1). The [Pd(I)]$_2$ complex was slightly more active than the [Ru(II)]$^+$ complex. The (*E*)-**2**, which was thermodynamically more stable than (*Z*)-**2** and the parent **1** by 2.3 and 3.9 kcal/mol, respectively,[19] was formed in preference to (*Z*)-**2** in both cases.




Initially, the [Ru(II)]$^+$ complex was examined for a sequence of double-bond transposition and asymmetric allylation in one pot. A mixture of benzaldehyde (**3a**, 0.3 mmol), **1** (1.2 equiv), and 4 Å molecular sieves (4 Å M.S.) in 1,2-dichloroethane (DCE) was stirred at 20 °C for 24 hours in the presence of [Ru(II)]$^+$ (2.5 mol %) and (*R*)-TRIP (5.0 mol %). The allylation products (*E*)-**4a** and (*Z*)-**5a** were obtained in 85% and 4% isolated yields, respectively (eq 2: upper) and the enantiomeric excess of (*E*)-**4a** was 94% ee.




No *syn* isomers of either (*E*)-**4a** or (*Z*)-**5a** were detected by $^1$H NMR (400 MHz). A larger scale experiment using 8.0 mmol of **3a** (849 mg) gave a comparable result [1.4 g of (*E*)-**4a**, 90% yield, 94% ee]. The preferential formation of (*E*)-**4a** over (*Z*)-**5a** can be explained by assuming the following sequence. The [Ru(II)]$^+$ complex catalyzes double-bond transposition of **1** to stereoselectively generate (*E*)-**2**. Following this process, (*E*)-**2** undergoes addition to the aldehyde **3a** through a six-membered chair-like transition state. Given the preferred axial/equatorial arrangement of the H/Ph pair, two transition states TS-**A** and TS-**B** are conceived to compete (Figure 3). In TS-**A**, the exocyclic pinacolatoboryl group adopts the axial orientation, leading to (*E*)-

**6a**, and in TS-**B**, the pinacolatoboryl group occupies the equatorial orientation, leading to (*Z*)-**6a**. TS-**B** suffers from significant gauche-type interactions between the two pinacolatoboryl groups[14] in addition to the Me/H 1,3-allylic strain. These destabilizing interactions favor TS-**A** over TS-**B**. Moreover, (*R*)-TRIP offers an enantioselectivity. During the procedure for work-up and/or purification, the major product (*E*)-**6a** is transformed to the cyclic boronic ester (*E*)-**4a** while the minor adduct (Z)-**6a** is simply hydrolyzed to form (*Z*)-**5a**. The spontaneous cyclization of (*E*)-**6a** to (*E*)-**4a** was beneficial for separation of the *E*/*Z* isomers, which would otherwise be problematic.

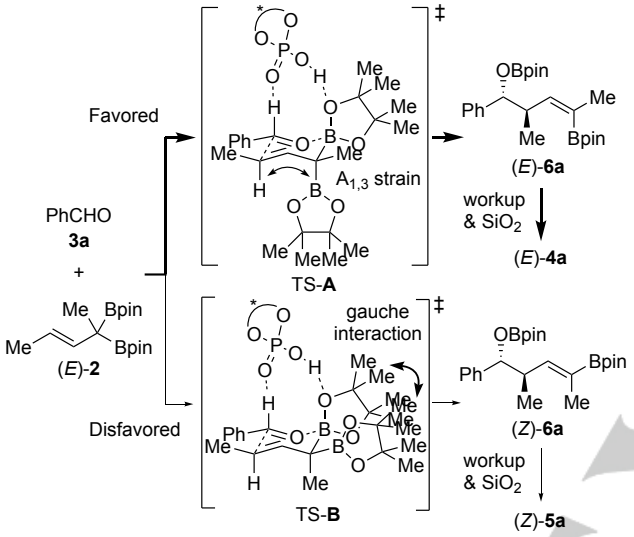
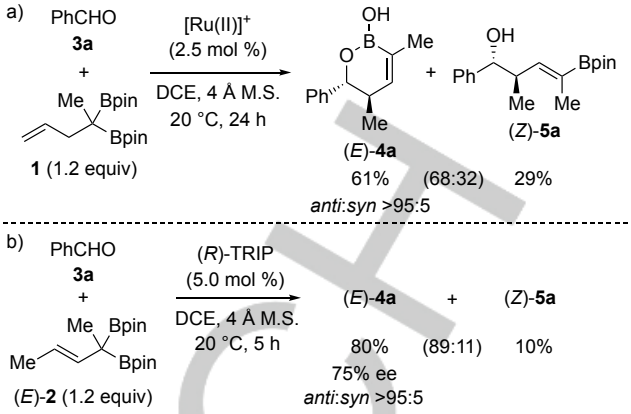



**Figure 3.** Proposed transition states for the allylation of benzaldehyde (**3a**) with (*E*)-4,4-di(pinacolatoboryl)pent-2-ene ((*E*)-**2**).

For comparison, when the same reaction was carried out in the absence of (*R*)-TRIP (Scheme 1a), the allylation products (*E*)-**4a** and (*Z*)-**5a** were obtained in a 68:32 ratio. This deviation in the *E*/*Z* ratio indicates that the (*R*)-TRIP catalyst has another influence on the *E*/*Z* selectivity, as observed in the previous cases.[8b,20] (*R*)-TRIP is a bidentate phosphoric acid having 2,4,6-triisopropylphenyl substituents on the binaphthyl backbone, and consequently, sterically very demanding. In the proposed chair-like transition state shown in Figure 3, it binds to the aldehydic hydrogen and the pinacolato oxygen, shielding the upper side. The repulsive force that the (*R*)-TRIP exerts from the top would destabilize TS-**B** with an upward-oriented pinacolatoboryl substituent more than TS-**A** with a downward-oriented pinacolatoboryl substituent, making the energy difference between TS-**A** and TS-**B** even larger than in its absence.




**Scheme 1.** Control experiments in the absence or presence of (*R*)-TRIP: (a) Using **1** and (b) Using pre-generated (*E*)-**2**.

For comparison, the TRIP-catalyzed allylation reaction was examined using the pre-generated (*E*)-**2**,[21] and the result verified the augmentative influence of (*R*)-TRIP upon the *E*/*Z* selectivity. When (*E*)-**2** was subjected to a reaction with benzaldehyde (**3a**) in the presence of (*R*)-TRIP (5 mol %) at 20 °C, a mixture of (*E*)-**4a** and (*Z*)-**5a** was obtained in 80% and 10% yields, respectively [(*E*)-**4a**:(*Z*)-**5a** = 89:11] (Scheme 1b). Of note was that the enantioselectivity of (*E*)-**4a** had decreased to 75% ee. The decreases in both *E*/*Z* ratio and enantioselectivity are explained by assuming that there are two pathways operating for allylation. One is the pathway promoted by the (*R*)-TRIP catalyst, shown in Figure 3, and the other is a non-catalyzed spontaneous pathway. The former is assumed to be faster than the latter pathway. When (*E*)-**2** is gradually generated from **1**, the catalyzed pathway is dominant, giving (*E*)-**4a**:(*Z*)-**5a** = 96:4 and 94% ee (eq 1: upper). When pre-generated (*E*)-**2** is used, it is far more abundant in the reaction media than the (*R*)-TRIP catalyst, and consequently, the non-catalyzed pathway competes to deteriorate the both *E*/*Z* ratio and enantioselectivity.[22] The inferior result obtained with the use of the pre-generated (*E*)-**2** demonstrates that the present protocol based on *in situ* generation of crotylboron species is uniquely able to allow the (*R*)-TRIP catalyst (5 mol %) to induce high enantioselectivities at ambient temperature.[17]

Next, the $[Pd(I)]_2$ catalyst was employed; **3a** was reacted with **1** in the presence of $[Pd(I)]_2$ (5.0 mol %) and (*R*)-TRIP (5.0 mol %) at 20 °C, and after 24 hours, the reaction mixture was subjected to an aqueous work-up. Contrary to the reaction using the $[Ru(II)]^+$ complex, the alcohol (*Z*)-**5a** was obtained as the major product in 70% isolated yield with 96% ee (eq 2: lower). The cyclic boronic ester (*E*)-**4a** was formed in 11% yield (NMR) in addition to (*Z*)-**5a**. When the reaction was quenched after 3 hours, however, (*E*)-**4a** was dominant over (*Z*)-**5a** (54% and 17% isolated yields, respectively). The time-dependent reversal of the *E*/*Z* selectivity is accounted for by assuming the following scenario involving both transposition and geometrical isomerization of the double bond. As is the case with the $[Ru(II)]^+$ catalyst, the crotylboron species (*E*)-**2** is stereoselectively generated from **1**, and it reacts with **3a** through TS-**A** shown in Figure 3 to initially produce (*E*)-**6a**. Since the pinacolatoboryl group is sterically bulkier than the methyl group, the (*Z*)-**6a** is thermodynamically more stable. The palladium catalyst is, after executing the allylation reaction, still active enough to induce isomerization of the initially produced *E* isomer to the more stable *Z* isomer through a mechanism of

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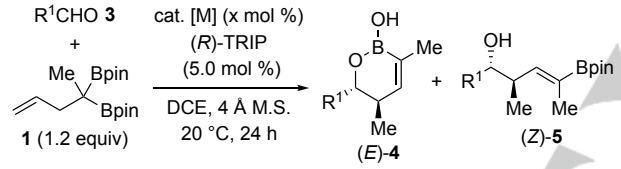
addition/elimination of a Pd-H species. Computations estimated the difference in the thermodynamic stabilities between (*E*)-**6a** and (*Z*)-**6a** to be 0.90 kcal/mol,[19] which accorded with the observed ratio of (*E*)-**4a**/(*Z*)-**5a**.

Thus, the present allylation reaction offers stereo- and enantioselective accesses to both *E* and *Z* isomers of the potential precursor of the propionate-derived substructure by making a choice between the $[Ru(II)]^+$ and $[Pd(I)]_2$ catalysts. We next examined the reaction scope with respect to aldehydes (Table 1). Firstly, the $[Ru(II)]^+$ complex was used as the catalyst in combination with an electronically and sterically diverse array of aromatic aldehydes **3b**–**3f** to provide the corresponding cyclic boronic esters (*E*)-**4b**–**4f** in yields ranging from 81% to 89% with the product ratios **4**/**5** over 95:5. No formation of the *syn* isomers was observed within the detection limit of $^1$H NMR (400 MHz). The enantioselectivities of **4** were over 90% ee in all cases (entries 1–5). α,β-Unsaturated aldehyde **3g** successfully participated in the reaction, affording (*E*)-**4g** in 81% yield with 96% ee (entry 6). Aliphatic aldehydes such as 3-phenylpropanal (**3h**) and cyclohexanecarboxaldehyde (**3i**) were eligible to the reaction, although the enantioselectivities were around 85% ee (entries 7 and 8).

**Table 1.** Asymmetric allylation of various aldehydes **3b**–**3i** with **1** using Grotjahn's catalyst and $[Pd(\mu\text{-Br})(P\textit{t}\text{-Bu}_3)]_2$.[a]



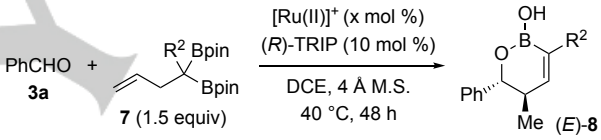

| Entry | $R^1$ (**3**) | cat. $[Ru(II)]^+$ (2.5 mol %) Yield of **4** (%)[b,c] | ee of **4** (%)[d] | **4**/**5**[e] | cat. $[Pd(I)]_2$ (5.0 mol %) Yield of **5** (%)[b,c] | ee of **5** (%)[d] | **5**/**4**[e] |
|---|---|---|---|---|---|---|---|
| 1 | 4-$ClC_6H_4$ (**3b**) | 84 | 97 | > 95:5 | 75 | 97 | 82:18 |
| 2 | 4-$BrC_6H_4$ (**3c**) | 84 | 93 | > 95:5 | 68 | 96 | 85:15 |
| 3 | 4-$MeOC_6H_4$ (**3d**) | 89 | 96 | > 95:5 | 70 | 94 | 84:16 |
| 4 | 4-$MeC_6H_4$ (**3e**) | 88 | 97 | > 95:5 | 66 | 94 | 85:15 |
| 5 | 2-$MeC_6H_4$ (**3f**) | 81[f] | 90 | 95:5 | 59[f] | 85 | 81:19 |
| 6 | PhCH=CH (**3g**) | 81[g] | 96 | > 95:5 | 69[g] | 97 | 90:10 |
| 7 | $PhCH_2CH_2$ (**3h**) | 73[h] | 85 | 90:10 | 66[h,j] | 77 | 85:15 |
| 8 | Cy (**3i**) | 64[h,i] | 85 | 90:10 | 68[h,j] | 67 | 91:9 |

[a] On a 0.30 mmol scale. [b] Isolated yield after chromatographic purification. [c] *Anti*/*syn* ratios of **4** and **5** were determined to be >95:5 by $^1$H NMR in all cases. [d] The ee values of **4** determined by chiral HPLC of phenylated products and **5** determined by chiral HPLC. [e] The product ratios determined by $^1$H NMR. [f] 10 mol % of (*R*)-TRIP was used. [g] 7.5 mol % of (*R*)-TRIP was used. [h] 1.5 equiv of **3** and 10 mol % of (*R*)-TRIP were used. The reaction time was 36 h. [i] The yield determined by $^1$H NMR. [j] 10 mol % of $[Pd(I)]_2$ was used.

Next, the $[Pd(I)]_2$ complex was used as the catalyst. The allylation reaction proceeded also smoothly with aromatic aldehydes **3b**–**3f** and α,β-unsaturated aldehyde **3g**, giving the *Z* isomers of **5b**–**5g** in preference to the corresponding *E* isomers (entries 1–6). The product ratios (**5**/**4**) were around 85:15 regardless of the aldehyde, because they were largely governed by the difference of the thermodynamic stabilities of the alkene moiety (*Z* versus *E*). The enantioselectivities of the *Z* isomers were similar to those observed with the ruthenium(II)-catalyzed reaction. On the other hand, the reaction of aliphatic aldehydes **3h** and **3i** exhibited only moderate enantioselectivities (entries 7 and 8). This was probably because the generation of (*E*)-**2** is faster with the $[Pd(I)]_2$ complex and the allylation is slower with aliphatic aldehydes. Consequently, the non-catalyzed pathway takes over to a certain degree (*vide supra*).

1,1-Di(pinacolatoboryl)alk-3-enes **7** possessing other substituents at the 1-position were examined in the reaction with benzaldehyde (**3a**) using $[Ru(II)]^+$ as the catalyst (Table 2). The ethyl- and benzyl-substituted 1,1-di(boryl)alk-3-enes **7a** and **7b** gave the cyclic boronic esters (*E*)-**8a** and (*E*)-**8b** in good yields (entries 1 and 2). However, their double-bond transposition required a higher temperature of 40 °C, probably because of the increased steric demand, leading to moderate enantioselectivities of 82% ee and 76% ee, respectively. The reaction of phenyl-substituted one **7c** yielded racemic (*E*)-**8c** and (*Z*)-**9c** with the product ratio **8**/**9** of 53:47 (entry 3). The phenyl substituent is bulkier than a methyl group diminishing the energy difference between two transition states that correspond to TS-**A** and TS-**B**. Repulsive interactions that the (*R*)-TRIP catalyst exerts over both transition states would considerably increase to favor a non-catalyzed pathway, leading to the formation of the racemic products.

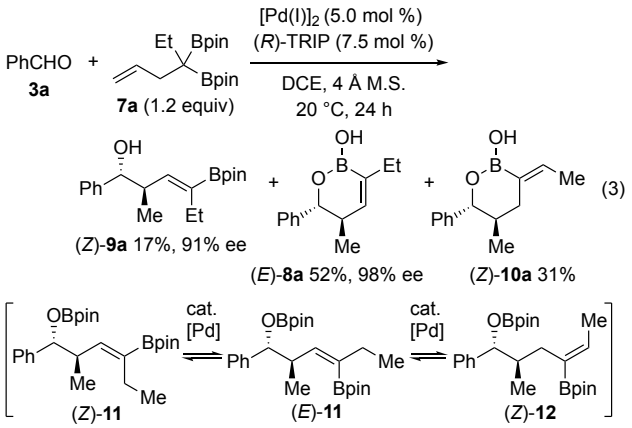
**Table 2.** Asymmetric allylation of benzaldehyde (**3a**) with various 1-substituted 1,1-di(pinacolatoboryl)alk-3-enes **7a**–**7c**.[a]



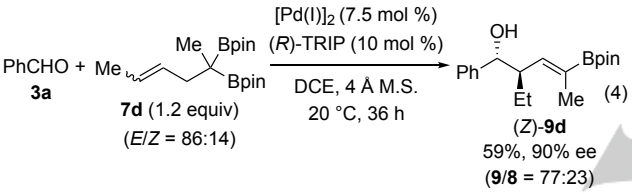

| Entry | $R^2$ | $[Ru(II)]^+$ (x mol %) | **8** | Yield (%)[b,c] | ee (%)[d] | **8**/**9**[e] |
|---|---|---|---|---|---|---|
| 1 | Et (**7a**) | 5.0 | **8a** | 68 | 82 | 95:5 |
| 2 | Bn (**7b**) | 10 | **8b** | 77 | 76 | > 95:5 |
| 3 | Ph (**7c**) | 7.5 | **8c** | 48[f] | 0 | 53:47 |

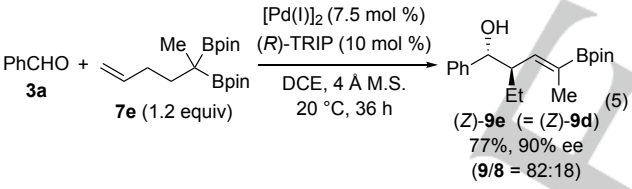
[a] On a 0.30 mmol scale. [b] Isolated yield after chromatographic purification. [c] *Anti*/*syn* ratios of **8** were determined to be >95:5 by $^1$H NMR in all cases. [d] The ee values of **8** determined by chiral HPLC of phenylated products. [e] The product ratios determined by $^1$H NMR. [f] The yield determined by $^1$H NMR.

Next, the reaction of ethyl-substituted 1,1-di(pinacolatoboryl)alk-3-ene **7a** was examined using $[Pd(I)]_2$ as the catalyst. Three allylation products (*Z*)-**9a**, (*E*)-**8a**, and (*Z*)-**10a** were formed in 17%, 52%, 31% yields, respectively (eq 3). The result was accounted for by assuming that the palladium catalyst induces subsequent isomerization of the initially produced isomer to other isomers through an addition/elimination mechanism, being steered by their thermodynamic stabilities.

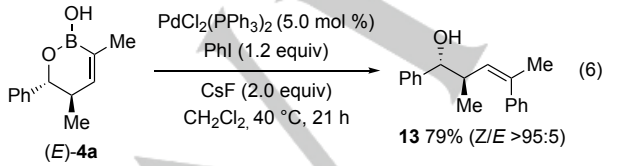



The reaction of 5,5-di(pinacolatoboryl)hex-2-ene (**7d**) with benzaldehyde (**3a**) using the $[Pd(I)]_2$ catalyst gave the *anti*-homoallylic alcohol (*Z*)-**9d** in 59% yield with 90% ee (eq 4). 5,5-Di(pinacolatoboryl)hex-1-ene (**7e**) possessing an alkene moiety at a more remote position by one carbon participated in the reaction with **3a**, affording *anti*-homoallylic alcohol (*Z*)-**9e** (= (*Z*)-**9d**) in 77% yield with 90% ee (eq 5).[23]

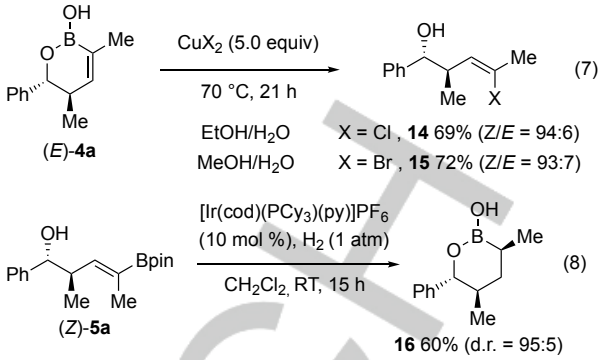


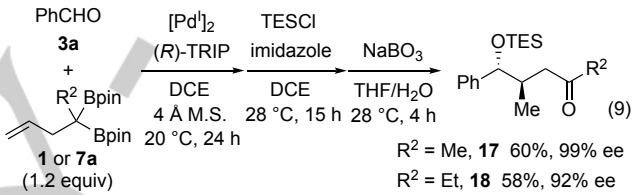

The allylation products equipped with the B–C($sp^2$) linkage are synthetically versatile, and we demonstrated their usefulness by carrying out their further synthetic transformations. The Suzuki-Miyaura cross-coupling reaction of the cyclic boronic ester (*E*)-**4a** with iodobenzene afforded the trisubstituted alkene **13** in 79% yield with its geometrical integrity maintained (*Z*/*E* >95:5), proving that (*E*)-**4a** served as a convenient precursor of a propionate-derived trisubstituted alkene motif (eq 6).




A halogenation reaction of (*E*)-**4a** with an excess of $CuX_2$ (X = Cl, Br) furnished the corresponding chloride **14** and bromide **15**,[24] although their geometrical purities were not completely maintained (eq 7). Diastereoselective hydrogenation of the double bond of (*Z*)-**5a** using Crabtree's catalyst gave the cyclic boronic ester **16** stereoselectively (eq 8).

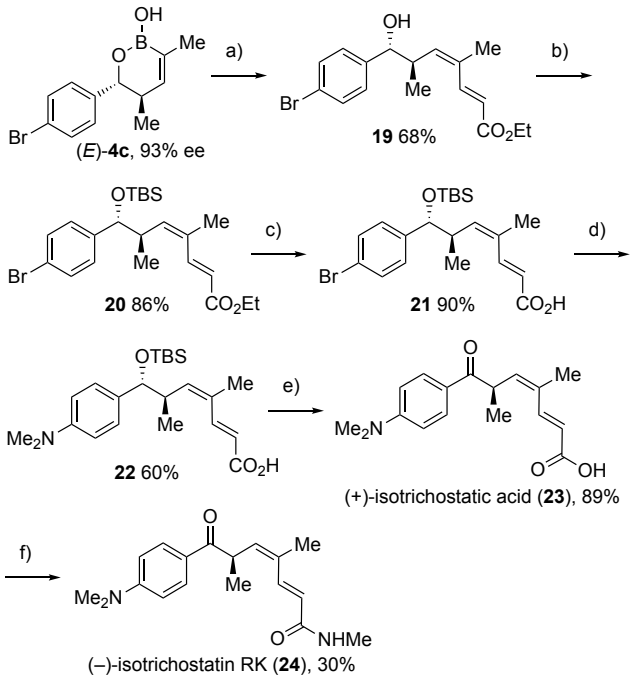



Oxidation of the B–C($sp^2$) bond with sodium perborate generated a carbonyl group (eq 9); *anti*-γ-hydroxy ketone **17** was obtained in 60% yield (based on **3a**) with 99% ee when the crude mixture of the allylation reaction of **3a** with 4,4-di(pinacolatoboryl)pent-1-ene (**1**) was sequentially treated with TES-Cl and sodium perborate. 4,4-Di(pinacolatoboryl)hex-1-ene (**7a**) was also applicable to this reaction sequence, affording the *anti*-γ-hydroxy ketone **18** in 58% yield (based on **3a**) with 92% ee.



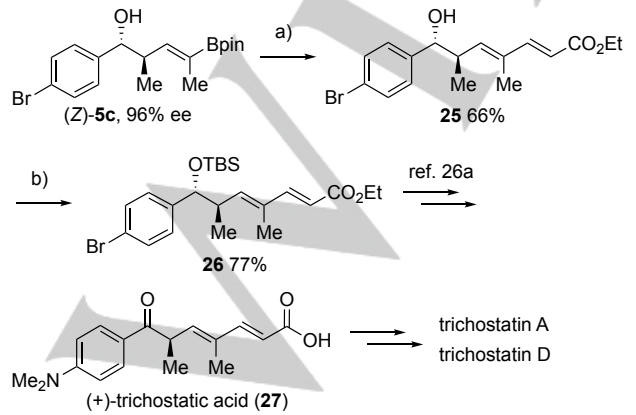

Trichostatin A is a potent histone deacetylase inhibitor, presenting a lead compound for the development of *anti*-cancer agents.[25] Therefore, a synthetic method which is applicable to a diverse range of trichostatin analogues has been sought.[26] For example, an effective method using a vinylogous Mukaiyama aldol reaction was developed and applied to the asymmetric synthesis of (+)-trichostatic acid and (+)-trichostatin D by Hosokawa and Tatsuta.[26a] As shown above, the combination of the present allylation reaction with the Suzuki-Miyaura cross-coupling reaction provides a powerful method for stereo- and enantioselective construction of the propionate-derived trisubstituted alkene motif. The feasibility of our method was next demonstrated by synthesizing (+)-isotrichostatic acid (**23**), which is a new member of the trichostatin family, isolated from the rice fermentation of the *Streptomyces* sp. CPCC 203909 in 2015 (Scheme 2).[27] Its structure is unique in that the stereochemistry of the double bond is opposite to those of other propionate-derived natural products. Initially, the Suzuki-Miyaura cross-coupling reaction of the cyclic boronic ester (*E*)-**4c**, which was obtained from **1** and **3c**, with ethyl (*E*)-3-iodoacrylate afforded the diene ester **19** in 68% yield with retention of stereochemistry. The hydroxy group was protected as the *tert*-butyldimethylsilyl ether. Then, the diene ester **20** was transformed to **23** through a three-step procedure reported for the synthesis of (+)-trichostatin acid;[26a] the ethoxycarbonyl group was hydrolyzed under basic conditions to provide the carboxylic acid **21**. A Buchwald-Hartwig amination reaction with dimethylamine gave the aniline derivative **22**. Finally, benzylic oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) afforded (+)-isotrichostatic acid (**23**). The spectroscopic ($^1H/^{13}C$ NMR, IR, MS) and optical rotation data matched with those in literature.[27] (+)-Isotrichostatic acid (**23**) is a promising precursor for the synthesis of a family of trichostatin

analogs. Thus, **23** was derivatized to (–)-isotrichostatin RK (**24**), which is isolated from marine-derived *Streptomyces* sp. SCSIO 40028 in 2020,[28] by introducing an amide linkage.




**Scheme 2.** Total synthesis of (+)-isotrichostatic acid and (–)-isotrichostatin RK. (a) ethyl (*E*)-3-iodoacrylate, $PdCl_2(PPh_3)_2$, CsF, $CH_2Cl_2$, 40 °C, 24 h. (b) TBS-Cl, imidazole, DMF, 50 °C, 24 h. (c) LiOH aq., EtOH, 50 °C, 31 h. (d) $NHMe_2$, $Pd_2(dba)_3$, JohnPhos, NaO*t*-Bu, toluene, 70 °C, 21 h. (e) DDQ, $CH_2Cl_2/H_2O$, 0 °C, 10 min. (f) $NH_2Me$, EDC·HCl, THF, 50 °C, 7 h.

The diene ester **26**, the geometrical isomer of **20**, presents an intermediate for the synthesis of (+)-trichostatic acid (**27**) and other trichostatin analogues (Scheme 3).[26a] Thus, **26** was targeted starting from the *anti*-homoallylic alcohol (*Z*)-**5c**, which was also obtained from **1** and **3c**. The Suzuki-Miyaura cross-coupling reaction of (*Z*)-**5c** with ethyl (*E*)-3-iodoacrylate furnished **25** in 66% yield with retention of stereochemistry. Protection of the hydroxy group with TBS-Cl produced the diene ester **26**. A three-step procedure from the diene ester **26** leading to **27** has been already established in literature.[26a]




**Scheme 3.** Formal synthesis of (+)-trichostatic acid. (a) ethyl (*E*)-3-iodoacrylate, $PdCl_2(dppf)$, $Ba(OH)_2$, DMF, 40 °C, 3 h. (b) TBS-Cl, imidazole, DMF, 28 °C, 18 h.

## Conclusion

We have developed a stereo- and enantioselective allylation reaction of aldehydes with 1-substituted 1,1-di(pinacolatoboryl)alk-3-enes. It offers accesses to both *E* and *Z* isomers of propionate-derived trisubstituted alkene motif in an enantioenriched form from the same starting materials by selecting the appropriate transition metal catalyst for the double-bond transposition.

The supporting information contains experimental procedures, characterization of the new compounds, computational details, and spectroscopic data.

## Acknowledgements

We thank Mr. F. Kobayashi (Kyoto Univ.) and Dr. S. G. Stewart (The University of Western Australia) for the experimental assistance, and Dr. S. Hosokawa (Waseda University) for the kind advice to the trichostatin synthesis. This work was supported by ISHIZUE 2019 of Kyoto University Research Development Program (T.M.), JSPS KAKENHI Grant Number 20H04816 [Scientific Research on Innovative Areas (Hybrid Catalysis)] (T.M.), JST-ERATO Grant Number JPMJER1903 (Y.N.), and JSPS-WPI (Y.N.).

**Keywords:** allylation • asymmetric synthesis • palladium • propionate-derived substructure • ruthenium

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[22] When the reaction of **3a** with (*E*)-**2** was carried out in the presence of 20 mol % of (*R*)-TRIP at 20 °C, a mixture of (*E*)-**4a** and (*Z*)-**5a** was obtained in 82% and 3% yields, respectively [(*E*)-**4a**:(*Z*)-**5a** = 96:4]. The enantioselectivity of (*E*)-**4a** is 96% ee. The increase in the (*E*)-**4a**:(*Z*)-**5a** ratio and the enantioselectivity of (*E*)-**4a** is accounted for by assuming that the use of 20 % of (*R*)-TRIP accelerates the (*R*)-TRIP-catalyzed pathway to suppress the non-catalyzed spontaneous pathway.

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10.1002/chem.202004930

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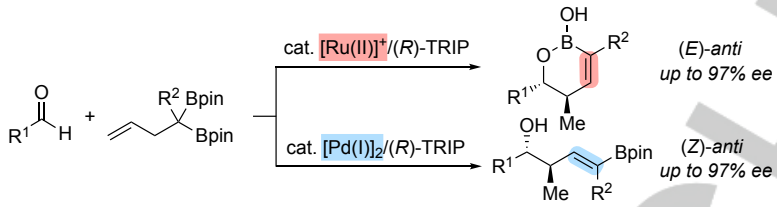


A stereo- and enantioselective allylation reaction of aldehydes with 1-substituted 1,1-di(pinacolatoboryl)alk-3-enes is developed. It offers accesses to both *E* and *Z* isomers of propionate-derived trisubstituted alkene motif from the same starting materials by selecting the appropriate transition metal catalyst. The present method are applied to the syntheses of (+)-isotrichostatic acid, (–)-isotrichostatin RK, and (+)-trichostatic acid.