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(*Z*)-α-Boryl-crotylboron reagents *via Z*-selective alkene isomerization and application to stereoselective syntheses of (*E*)-δ-boryl-*syn*-homoallylic alcohols†

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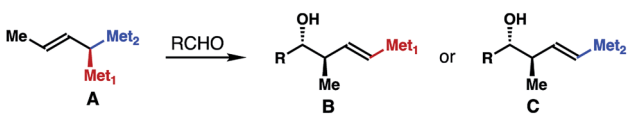
Stereoselective synthesis of (*Z*)-α-boryl-crotylboronate is developed. Ni-catalyzed *Z*-selective alkene isomerization of α-boryl substituted homoallylboronate provided the targeted (*Z*)-crotylboronate with high selectivity. Stereoselective addition of the novel crotylboron reagent to aldehydes gave (*E*)-δ-boryl-substituted *syn*-homoallylic alcohols with excellent diastereoselectivities. The vinyl boronate unit in the products can be directly used for a subsequent C–C bond-forming transformation as illustrated in the synthesis of the C_{1-7} fragment of the natural products nannocystin A and nannocystin Ax.

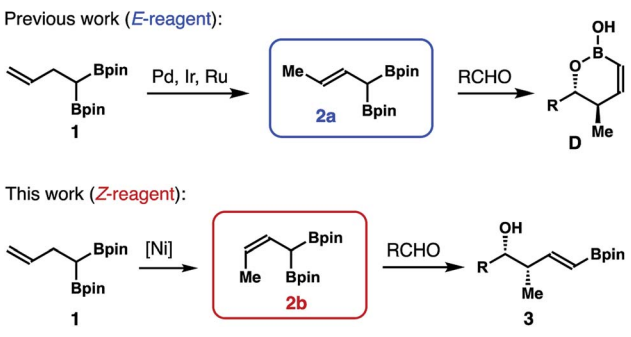
Introduction

1,1-Bismetallic crotylation reagents, such as **A** (Scheme 1), are an important class of molecules that have recently attracted considerable attention. In contrast to the traditional crotyl organometallics,[1] addition of these 1,1-bismetallic crotylation reagents to carbonyl compounds (*e.g.*, aldehydes) will produce homoallylic alcohol products (*i.e.*, **B** or **C**) with a functionalized alkene group that can directly engage in a C–C bond-formation event, for example, a cross-coupling reaction. In the case of $Met_1 \neq Met_2$, reagent **A** is chiral and reactions of carbonyl compounds with **A** typically proceed through chirality transfer. The enantiomeric excess of the alcohol products will largely depend on the optical purity of the starting agent **A**. Additionally, depending on the different electronic properties and reactivities of the metal substituents, either δ-substituted homoallylic alcohol **B** or **C** can be produced selectively. Owing to their versatile reactivities, several types of 1,1-bismetallic crotylation reagents have been developed in the past three decades, including B/Si,[2] B/Sn,[3] Si/Sn,[4] Si/Si,[5] and Sn/Sn-substituted crotylation reagents.[6] Importantly, many of these reagents have been successfully applied to the syntheses of bioactive natural products, which highlights the synthetic utilities of these reagents.[7]

One subset of 1,1-bismetallic crotylation reagents is α-boryl substituted crotylboronates **2a** and **2b** (Scheme 2; Met_1, Met_2 = Bpin). An attractive feature of boronates **2** is that they are achiral, and their reactions with carbonyl compounds should proceed by way of the well-established, six-membered transition state[8] to give δ-boryl-substituted homoallylic alcohols. In spite of their apparent synthetic potential, the synthesis of (*E*)-reagent **2a** has only been disclosed recently.[9] The Murakami[9a,b] and Cho[9c] groups independently showed that (*E*)-crotylboronate **2a** can be generated *via* transition-metal catalyzed alkene transposition from the homoallylic bisboronate precursor **1** (Scheme 2). Addition of **2a** to aldehydes provided δ-boryl-substituted (*Z*)-*anti*-homoallylic alcohols (*anti*-1,2-oxaborinan-3-enes **D** after intramolecular cyclization) with high selectivities. On the other hand, reactions of



Scheme 1 1,1-Bismetallic crotylation reagents.



Scheme 2 Recent development of α-boryl substituted crotylboron reagents.

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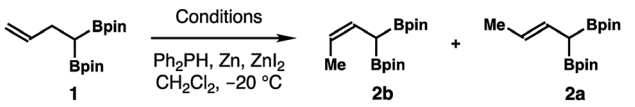
(*Z*)-reagent **2b** with aldehydes should form δ-boryl-substituted (*E*)-*syn*-homoallylic alcohols **3** (Scheme 2) that would be highly useful in the construction of polyketide natural products. However, methods that could efficiently produce reagent **2b** are still not available. Therefore, the development of methods that can allow access to such a reagent and δ-boryl-substituted (*E*)-*syn*-homoallylic alcohols **3** would be desirable. With our continuing efforts in developing novel allylboron reagents,[10] we have developed and reported herein stereoselective synthesis of (*Z*)-α-boryl crotylboronate **2b** and studies on crotylboration of aldehydes with reagent **2b**.

Results and discussion

We envisaged a *Z*-selective alkene isomerization approach to access (*Z*)-α-boryl crotylboronate **2b** from homoallylic bisboronate precursor **1** given its ready availability (Scheme 2). It has been shown by Hilt and co-workers that terminal alkenes can undergo transition metal-catalyzed olefin isomerization to give (*Z*)-2-alkene isomers with moderate to high selectivity.[11] Inspired by their studies, we decided to pursue a Ni-catalyzed isomerization of 1,1-di(boryl)but-3-ene **1**[12] to prepare (*Z*)-crotylboronate reagent **2b**. As shown in Table 1, in the presence of 10 mol% of $NiCl_2$ and dppp, 5 mol% Ph_2PH, and 20 mol% of Zn and ZnI_2, isomerization of homoallylboronate **1** did not form any product in CH_2Cl_2 at −20 °C for 24 h (entry 1, Table 1). However, when $NiCl_2$ was replaced by $NiBr_2$, the isomerization reaction occurred to give a 5 : 1 inseparable mixture of **2b** and **2a** in 70% yield, favouring the *Z*-isomer **2b** (entry 2). Encouraged by the initial success, reactions with several Ni catalysts were examined next. The reaction with $Ni(OAc)_2$ as the catalyst gave a 2 : 1 mixture of **2b** and **2a** in low yield (entry 3). An improved *Z*/*E* ratio (6 : 1) was achieved when $Ni(acac)_2$ was employed as the catalyst (entry 4). A similar *Z*/*E* ratio (7 : 1) was obtained with $NiCl_2 \cdot$glyme as the catalyst, albeit in a low yield (entry 5). Intriguingly, reactions with preformed Ni catalysts, Ni(dppp)Cl_2 or Ni(dppe)Cl_2, gave inferior results (entries 6 and 7). When $NiBr_2 \cdot$diglyme and dppp were used as the catalyst/ligand combination, a 7 : 1 mixture of **2b** and **2a** was obtained in 58% yield (entry 8). Gratifyingly, when 1,2-dichloroethane was used as the solvent, isomerization of homoallylic bisboronate **1** gave an excellent *Z*/*E* ratio (**2b** : **2a** > 20 : 1) in the presence of $NiBr_2 \cdot$diglyme and dppp. Reagent **2b** was isolated in 70% yield (entry 9). A 2 mmol-scale reaction produced (*Z*)-crotylboronate **2b** in 74% yield (entry 10).

Table 1 Evaluation of reaction conditions for the synthesis of (*Z*)-α-boryl crotylboronate **2b**[a]



Entry	Conditions	**2b** : **2a**[b]	Yield[c] (%)
1	$NiCl_2$, dppp	N.D.	N.R.
2	$NiBr_2$, dppp	5 : 1	70
3	$Ni(OAc)_2$, dppp	2 : 1	38
4	$Ni(acac)_2$, dppp	6 : 1	76
5	$NiCl_2 \cdot$glyme, dppp	7 : 1	36
6	Ni(dppp)Cl_2	3 : 1	56
7	Ni(dppe)Cl_2	3 : 1	64
8	$NiBr_2 \cdot$diglyme, dppp	7 : 1	58
9[d]	$NiBr_2 \cdot$diglyme, dppp	>20 : 1	70
10[e]	$NiBr_2 \cdot$diglyme, dppp	>20 : 1	74

[a] Reaction conditions: boronate **1** (0.2 mmol, 1.0 equiv.), catalyst (10 mol%), ligand (10 mol%), Ph_2PH (5 mol%), Zn (20 mol%), ZnI_2 (20 mol%), CH_2Cl_2 (0.5 mL), −20 °C. [b] The *Z*/*E* ratios were determined by ^{1}H NMR analysis of the crude reaction products. [c] Yields of isolated products are listed. [d] DCE was used as the solvent. [e] The reaction was conducted on a 2 mmol scale in DCE. dppp: 1,3-bis(diphenylphosphino)propane; dppe: 1,2 bis(diphenylphosphino) ethane.

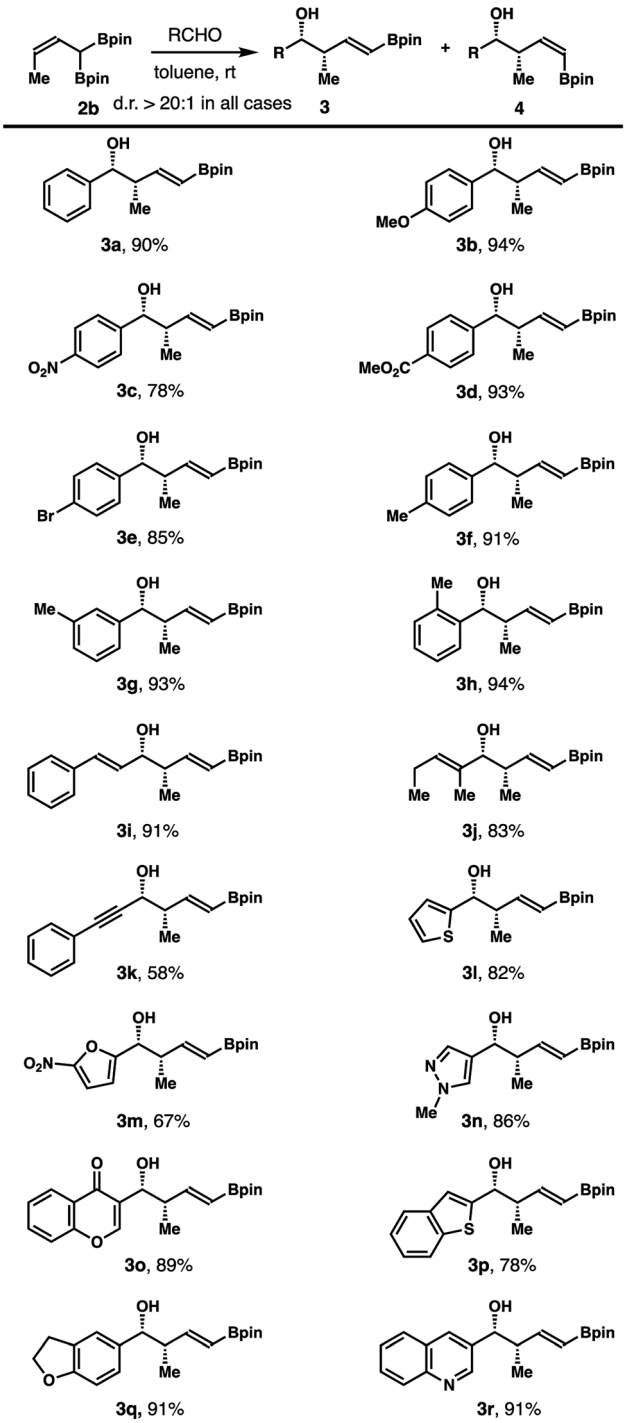
After obtaining (*Z*)-α-boryl-crotylboronate **2b**, we conducted subsequent studies on aldehyde crotylboration with reagent **2b**. In initial experiments, treatment of benzaldehyde with 1.3 equiv. of reagent **2b** in toluene for 12 h provided (*E*)-δ-boryl-*syn*-homoallylic alcohol **3a** in 90% yield. The olefin geometry in product **3a** was assigned as *E* based on ^{1}H NMR analysis of the coupling constant of olefinic protons. The stereochemical relationship of **3a** was assigned as *syn* after comparing to the literature data.[9a,b]

The scope of an aldehyde that participates in this reaction was explored, and the results are summarized in Scheme 3. In general, the reaction worked well with a broad spectrum of aldehydes, including aromatic, heteroaromatic and α,β-unsaturated aldehydes. Reactions of **2b** with aromatic aldehydes at ambient temperature in toluene gave alcohol products **3a–h** in 78–94% yields. Alkenyl or alkynyl aldehydes reacted with **2b** to furnish homoallylic alcohols **3i–k** in 58–91% yields. Importantly, a variety of heteroaromatic aldehydes also participated in the reaction to provide alcohols **3l–r** in 67–91% yields. Formation of other isomeric products was not observed in any of these reactions.

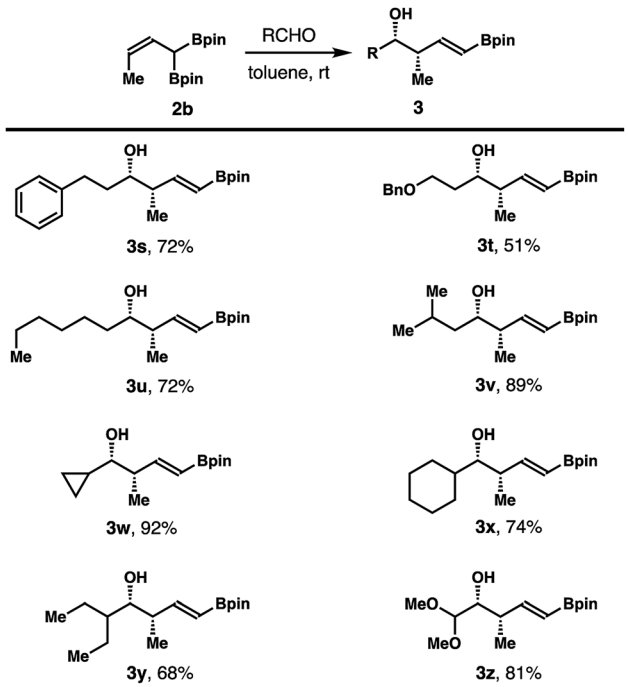
Reactions of aliphatic aldehydes with boronate **2b** were examined next. As shown in Scheme 4, aliphatic aldehydes including primary alkyl aldehydes, β-branched alkyl aldehydes, and secondary alkyl aldehydes all reacted with reagent **2b** in toluene at ambient temperature to give homoallylic alcohols **3s–z** in 51–92% yield with excellent diastereoselectivities and *E*/*Z* selectivities in all cases.

The alkene isomerization and crotylation reaction sequence can be conducted in one pot. As illustrated in Scheme 5, alkene isomerization in the presence of benzaldehyde at −20 °C for 24 h gave product **3a** in 64% yield as a single isomer. Detectable amounts of other isomers were not formed from this one-pot procedure.

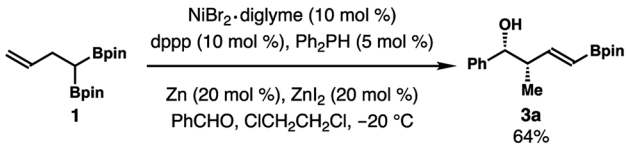
The high *E*-selectivity of this reaction can be rationalized by the following transition state analysis. Among the two competing transition states (**TS-1** and **TS-2**; Scheme 6) that lead to the formation of products **3** and **4**, **TS-2** suffers from a severe $A^{1,3}$ allylic strain[13] between the pseudo-axially oriented –Bpin group and the methyl group (shown in red in **TS-2**). In contrast, the $A^{1,3}$ allylic strain in **TS-1** is only between the methyl group and the H atom (shown in light blue in **TS-1**). Although a *gauche* interaction may also be involved in **TS-1**, it is apparent that



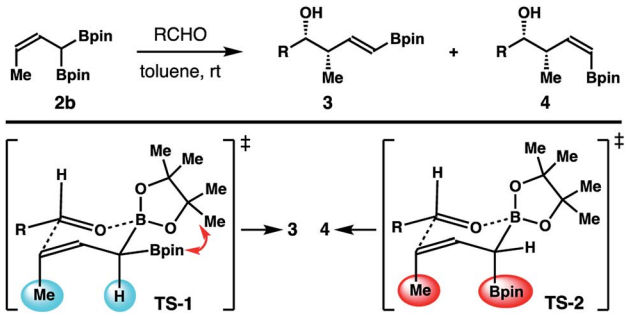
Scheme 3 Scope of aromatic, heteroaromatic and α,β-unsaturated aldehydes for the reactions with (*Z*)-α-boryl-crotylboronate **2b**. (a) Reaction conditions: crotylboronate **2b** (0.13 mmol, 1.3 equiv.), aldehyde (0.1 mmol, 1.0 equiv.), toluene (0.3 mL), rt. (b) The diastereoselectivities and *E*/*Z* selectivities were determined by ^{1}H NMR analysis of the crude reaction products. (c) Yields of isolated products are listed.



Scheme 4 Scope of aliphatic aldehydes for the reactions with (*Z*)-crotylboronate **2b**. (a) Reaction conditions: allyl boronate **2b** (0.13 mmol, 1.3 equiv.), aldehyde (0.1 mmol, 1.0 equiv.), toluene (0.3 mL), rt. (b) The diastereoselectivities and *E*/*Z* selectivities were determined by ^{1}H NMR analysis of the crude reaction products. (c) Yields of isolated products are listed.



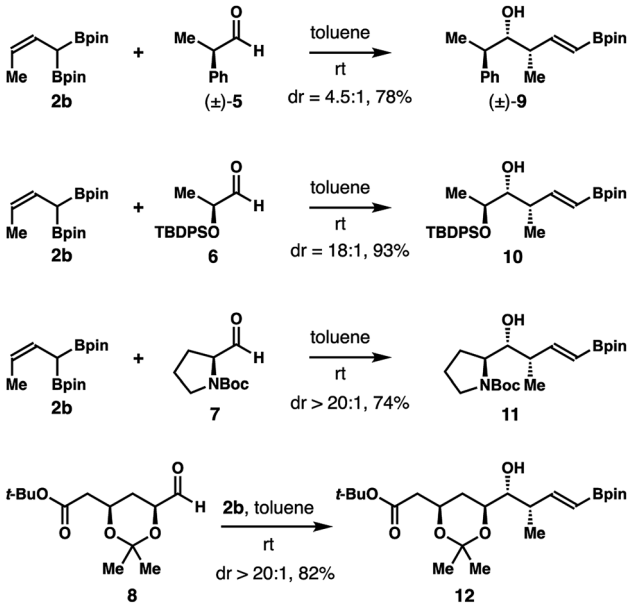
Scheme 5 One-pot alkene isomerization and aldehyde allylboration.



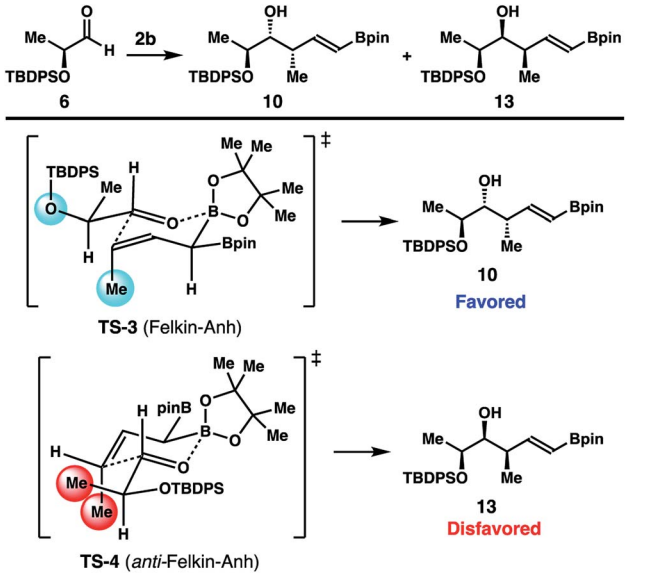
Scheme 6 Transition state analyses for selective formation of homoallylic alcohols **3** from crotylboronate **2b**.

the $\mathbf{A}^{1,3}$ allylic strain between the –Bpin and methyl groups is severe enough to overcome the *gauche* interactions. As a result, crotylboration of aldehydes with reagent **2b** proceeded through the lower energy transition state **TS-1** to give product **3** with high selectivity.

Studies on reactions of crotylboron reagent **2b** with several chiral aldehydes (**5**–**8**) were also conducted. As illustrated in Scheme 7, the reaction of crotylboronate **2b** with racemic 2-



Scheme 7 Diastereoselective crotylboration of chiral aldehydes with (*Z*)-crotylboronate **2b**.

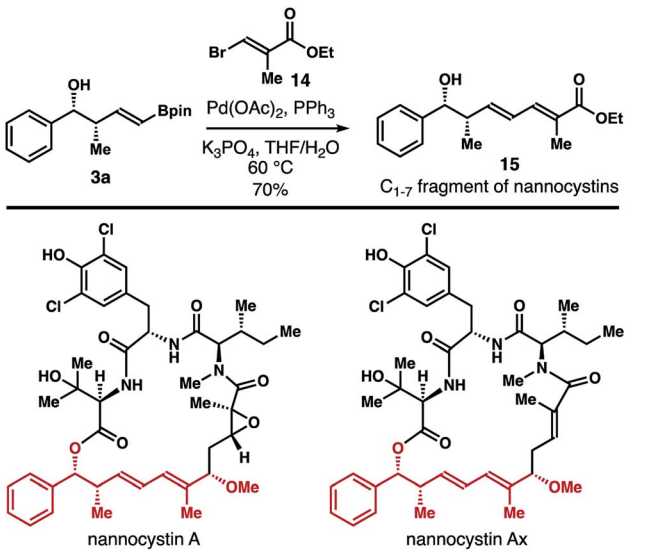


Scheme 8 Transition state analyses for the reaction of chiral aldehyde **6** with crotylboronate **2b**.

phenylpropionaldehyde (**5**) gave product **9** in 78% yield with 4.5 : 1 diastereoselectivity. The enantioenriched, lactate-derived aldehyde **6** reacted with reagent **2b** to provide an 18 : 1 mixture, with isomer **10** as the major product in 93% yield. Addition of reagent **2b** to *N*-Boc-L-prolinal (**7**) generated alcohol **11** in 74% yield with excellent diastereoselectivity (dr > 20 : 1). Finally, the reaction of reagent **2b** with a more advanced chiral, nonracemic aldehyde **8** delivered isomer **12** as the only product (dr > 20 : 1). Homoallylic alcohol **12** was obtained in 82% yield after purification. The stereochemistry of **9** and **11** was assigned by comparing to the literature data after protodeboronation.[14] The absolute configuration of the newly formed secondary hydroxyl groups of **10** and **12** was assigned by Mosher ester analysis.[15] Importantly, the mild reaction conditions and high diastereoselectivities of these reactions with chiral aldehydes augur well for further application of reagent **2b** in the syntheses of complex natural products and medicinally relevant agents.

A stereochemical model for the high diastereoselectivities in the reactions with enantioenriched aldehydes **6–8** is delineated in Scheme 8. The reaction of aldehyde **6** with reagent **2b** could proceed through two potential transition states (**TS-3** and **TS-4**; Scheme 8) to produce two alcohol products, **10** and **13**. **TS-3** operates under Felkin–Anh[16] control to give homoallylic alcohol **10**, while the competing transition state **TS-4** is under *anti*-Felkin–Anh control to furnish the diastereomeric alcohol product **13**. Upon close examination of the two transition states, it is apparent that **TS-4** suffers from an unfavourable *gauche*-pentane interaction[17] between the methyl group of aldehyde **6** and the methyl group of reagent **2b** (shown in red in **TS-4**). In contrast, **TS-3** operates under favourable Felkin–Anh control and only with minimal *gauche*-pentane interactions (shown in light blue in **TS-3**) between the methyl group of reagent **2b** and the oxygen atom of aldehyde **6** (with the large TBDPS group pointing away from the methyl group of reagent **2b**). Therefore, the reaction with aldehyde **6** proceeded through the favourable transition state, **TS-3**, to give product **10** with high diastereoselectivity. Based on this analysis, when the substituent of the aldehyde substrate is sterically much more demanding than a methyl group (*e.g.*, aldehydes **7** and **8**), **TS-4** is more destabilized relative to **TS-3** because of more severe *gauche*-pentane interactions. Consequently, reactions with these aldehydes should generate Felkin–Anh controlled products with higher selectivities. This prediction is fully consistent with the results obtained from the reactions of aldehydes **7** and **8**.

The products (*e.g.*, **3**) generated from the reaction of reagent **2b** with aldehydes contain a vinyl boronate group, which can be



Scheme 9 Synthesis of the C_{1-7} fragment of nannocystin A and nannocystin Ax.

used directly for a variety of subsequent transformations.[18] To further demonstrate the synthetic utility of this method, synthesis of the C_{1-7} fragment of the natural products nannocystin A and nannocystin Ax was carried out.[19,20] As shown in Scheme 9, Pd-catalyzed Suzuki coupling[21] of free alcohol **3a** with vinyl bromide **14**[22] provided compound **15**, the C_{1-7} fragment of nannocystin A and nannocystin Ax, in 70% yield (prepared in two steps from commercially available benzaldehyde).

Conclusions

In summary, we developed a Ni-catalyzed, (*Z*)-selective olefin isomerization approach to synthesize a novel (*Z*)-α-boryl-crotylboron reagent **2b**. Under optimized conditions, boronate **2b** was obtained in good yield with exclusive (*Z*)-selectivity. Subsequent allylboration of aldehydes with reagent **2b** gave (*E*)-δ-boryl-*syn*-homoallylic alcohols **3** in high yields with excellent diastereoselectivities. Reactions with several enantioenriched aldehydes proceeded under Felkin–Anh control to give homoallylic alcohol products with high diastereoselectivities. The vinyl boronate in products **3** can be directly used for subsequent C–C bond-forming transformations as illustrated in the synthesis of the C_{1-7} fragment of the natural products nannocystins A and Ax. Studies on asymmetric crotylation using reagent **2b** are currently on-going.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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