

Cite this: *Chem. Sci.*, 2019, 10, 3637

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 15th January 2019
Accepted 3rd February 2019

DOI: 10.1039/c9sc00226j

rsc.li/chemical-science

(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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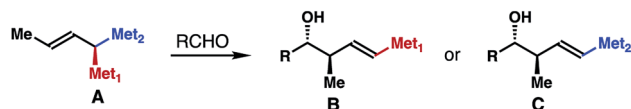
Stereoselective synthesis of (Z)- α -boryl-crotylboronate is developed. Ni-catalyzed Z-selective alkene isomerization of α -boryl substituted homoallylboronate provided the targeted (Z)-crotylboronate with high selectivity. Stereoselective addition of the novel crotylboron reagent to aldehydes gave (E)- 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-Bismetallc 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-bismetallc 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 Met₁ \neq Met₂, 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-bismetallc crotylation reagents have been developed in the past three decades,

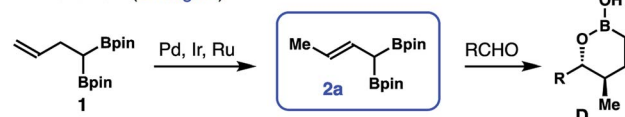
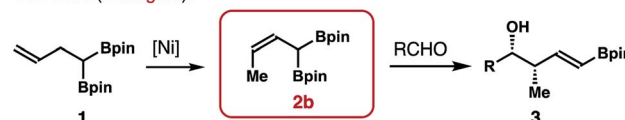
including B/Si,² B/Sn,³ Si/Sn,⁴ Si/Si,⁵ and Sn/Sn-substituted crotylation reagents.⁶ Importantly, many of these reagents have been successfully applied to the syntheses of bioactive natural products, which highlights the synthetic utilities of these reagents.⁷

One subset of 1,1-bismetallc crotylation reagents is α -boryl substituted crotylboronates **2a** and **2b** (Scheme 2; Met₁, Met₂ = 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 state⁸ 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-Bismetallc crotylation reagents.

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[†] Electronic supplementary information (ESI) available. See DOI: 10.1039/c9sc00226j[‡] These authors contributed equally.Previous work (*E*-reagent):This work (*Z*-reagent):Scheme 2 Recent development of α -boryl substituted crotylboron reagents.

(*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 NiCl₂ and dppp, 5 mol% Ph₂PH, and 20 mol% of Zn and ZnI₂, isomerization of homoallylboronate **1** did not form any product in CH₂Cl₂ at –20 °C for 24 h (entry 1, Table 1). However, when NiCl₂ was replaced by NiBr₂, 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 NiCl₂·glyme as the catalyst, albeit in a low yield (entry 5). Intriguingly, reactions with preformed Ni catalysts, Ni(dppp)Cl₂ or Ni(dppe)Cl₂, gave inferior results (entries 6 and 7). When NiBr₂·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 NiBr₂·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).

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 ¹H 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}

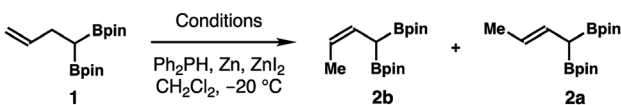
The scope of an aldehyde that participates in this reaction was explored, and the results are summarized in Scheme 3. In general, the reaction worked well with a broad spectrum of aldehydes, including aromatic, heteroaromatic and α,β -unsaturated aldehydes. Reactions of **2b** with aromatic aldehydes 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 strain¹³ 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

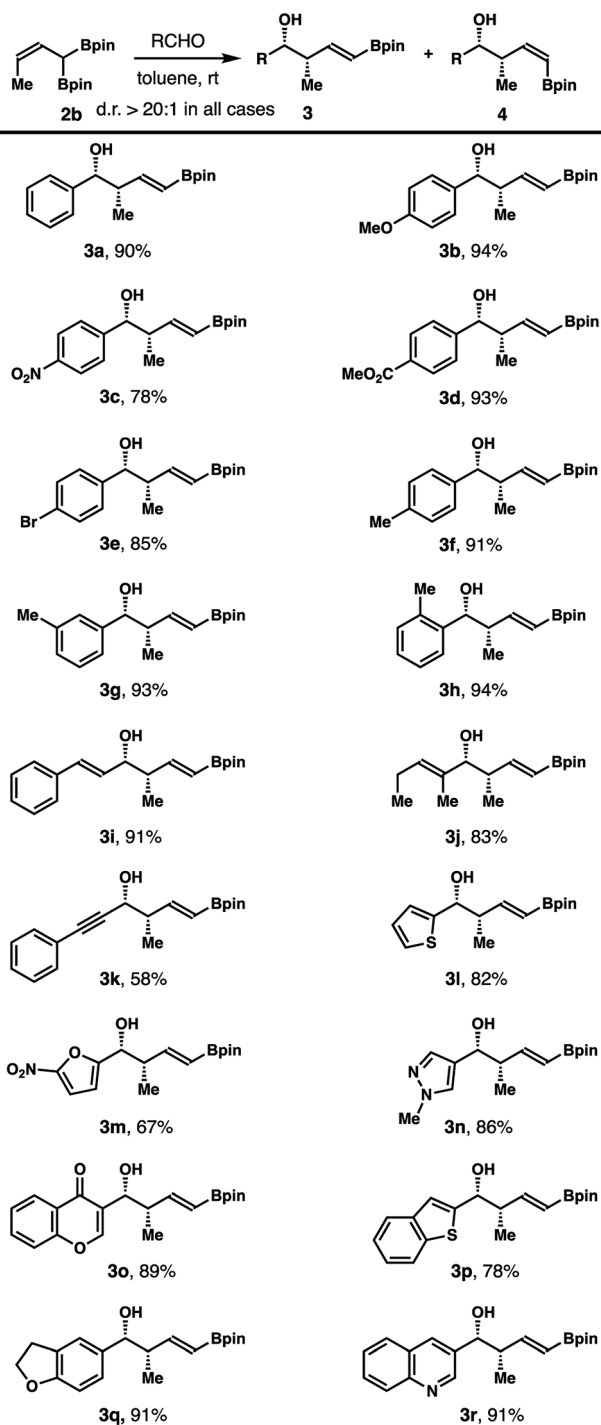
Table 1 Evaluation of reaction conditions for the synthesis of (*Z*)- α -boryl crotylboronate **2b**^a



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 ·glyme, dppp	7 : 1	36
6	Ni(dppp)Cl ₂	3 : 1	56
7	Ni(dppe)Cl ₂	3 : 1	64
8	NiBr ₂ ·diglyme, dppp	7 : 1	58
9 ^d	NiBr ₂ ·diglyme, dppp	>20 : 1	70
10 ^e	NiBr ₂ ·diglyme, dppp	>20 : 1	74

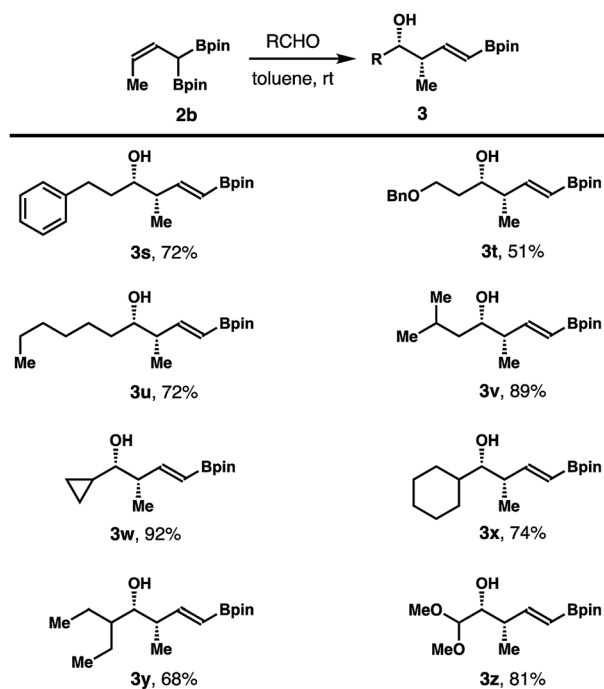
^a Reaction conditions: boronate **1** (0.2 mmol, 1.0 equiv.), catalyst (10 mol%), ligand (10 mol%), Ph₂PH (5 mol%), Zn (20 mol%), ZnI₂ (20 mol%), CH₂Cl₂ (0.5 mL), –20 °C. ^b The *Z*/*E* ratios were determined by ¹H NMR analysis of the crude reaction products. ^c Yields of isolated products are listed. ^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.



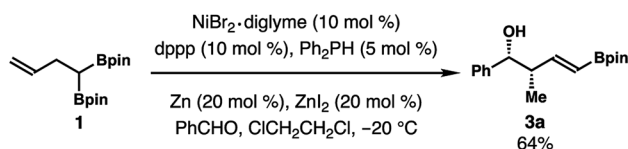


Scheme 3 Scope of aromatic, heteroaromatic and α,β -unsaturated aldehydes for the reactions with (*Z*)- α -boryl-crotylboronate **2b**. (a) Reaction conditions: crotylboronate **2b** (0.13 mmol, 1.3 equiv.), aldehyde (0.1 mmol, 1.0 equiv.), toluene (0.3 mL), rt. (b) The diastereoselectivities and *E/Z*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

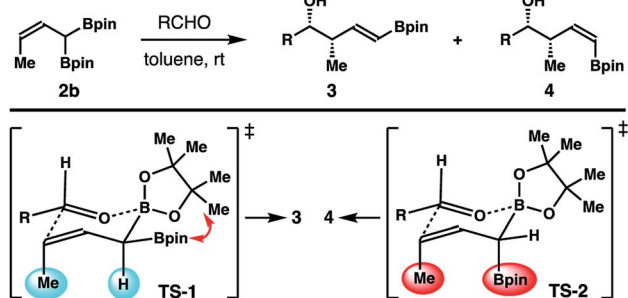
the $A^{1,3}$ allylic strain between the -Bpin and methyl groups is severe enough to overcome the *gauche* interactions. As a result, crotylboration of aldehydes with reagent **2b** proceeded through



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 ¹H NMR analysis of the crude reaction products. (c) Yields of isolated products are listed.



Scheme 5 One-pot alkene isomerization and aldehyde allylboration.

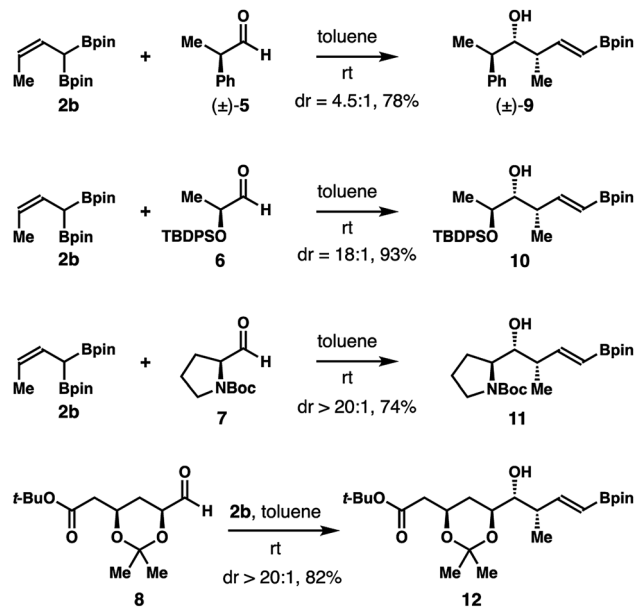


Scheme 6 Transition state analyses for selective formation of homoallylic alcohols **3** from crotylboronate **2b**.

the 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-

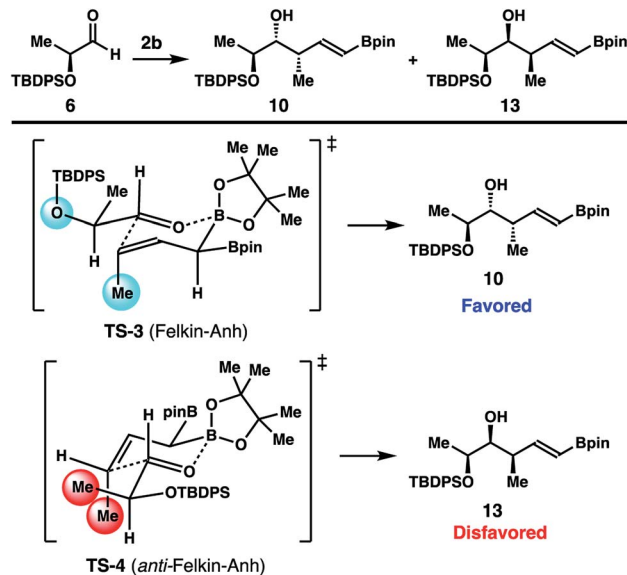




Scheme 7 Diastereoselective crotylboration of chiral aldehydes with (Z)-crotylboronate **2b**.

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*-proline (**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.

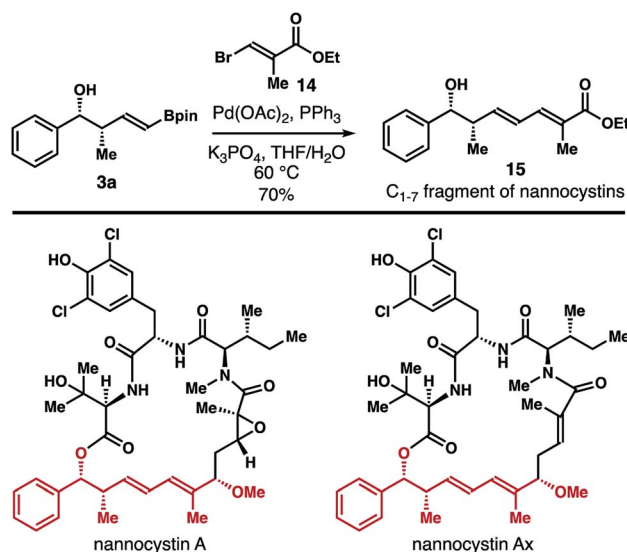
A stereochemical model for the high diastereoselectivities in the reactions with enantioenriched aldehydes **6–8** is delineated in Scheme 8. The reaction of aldehyde **6** with reagent **2b** could proceed through two potential transition states (**TS-3** and **TS-4**; Scheme 8) to produce two alcohol products, **10** and **13**. **TS-3** operates under Felkin–Anh¹⁶ 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 interaction¹⁷ 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,



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

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 C₁₋₇ fragment of the natural products nannocystin A and nannocystin Ax was carried out.^{19,20} As shown in Scheme 9, Pd-catalyzed Suzuki coupling²¹ of free alcohol **3a** with vinyl bromide **14**²² provided compound **15**, the C₁₋₇ 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 -borylcrotylboron 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 C₁₋₇ 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

Financial support provided by Auburn University is gratefully acknowledged.

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