

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)- $\alpha$ -Boryl-crotylboron reagents via Z-selective alkene isomerization and application to stereoselective syntheses of (E)- $\delta$ -boryl-syn-homoallylic alcohols<sup>†</sup>

Shang Gao,<sup>‡</sup> Jichao Chen<sup>‡</sup> and Ming Chen<sup>\*</sup>

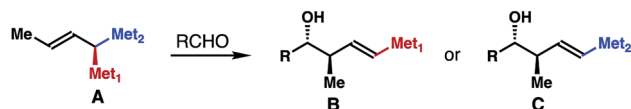
Stereoselective synthesis of (Z)- $\alpha$ -boryl-crotylboronate is developed. Ni-catalyzed Z-selective alkene isomerization of  $\alpha$ -boryl substituted homoallylboronate provided the targeted (Z)-crotylboronate with high selectivity. Stereoselective addition of the novel crotylboron reagent to aldehydes gave (E)- $\delta$ -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<sub>1–7</sub> fragment of the natural products nannocystin A and nannocystin Ax.

## Introduction

1,1-Bimetallic 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,<sup>1</sup> addition of these 1,1-bimetallic 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<sub>1</sub>  $\neq$  Met<sub>2</sub>, 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  $\delta$ -substituted homoallylic alcohol **B** or **C** can be produced selectively. Owing to their versatile reactivities, several types of 1,1-bimetallic crotylation reagents have been developed in the past three decades,

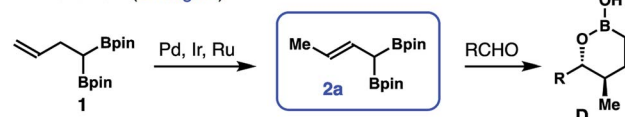
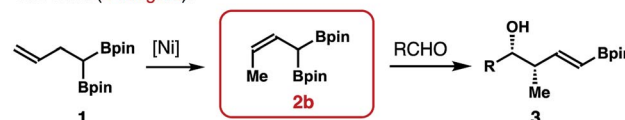
including B/Si,<sup>2</sup> B/Sn,<sup>3</sup> Si/Sn,<sup>4</sup> Si/Si,<sup>5</sup> and Sn/Sn-substituted crotylation reagents.<sup>6</sup> Importantly, many of these reagents have been successfully applied to the syntheses of bioactive natural products, which highlights the synthetic utilities of these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

One subset of 1,1-bimetallic crotylation reagents is  $\alpha$ -boryl substituted crotylboronates **2a** and **2b** (Scheme 2; Met<sub>1</sub>, Met<sub>2</sub> = 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<sup>8</sup> to give  $\delta$ -boryl-substituted homoallylic alcohols. In spite of their apparent synthetic potential, the synthesis of (*E*)-reagent **2a** has only been disclosed recently.<sup>9</sup> The Murakami<sup>9a,b</sup> and Cho<sup>9c</sup> 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  $\delta$ -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-Bimetallic crotylation reagents.

Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849, USA. E-mail: mzc0102@auburn.edu

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

(*Z*)-reagent **2b** with aldehydes should form  $\delta$ -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  $\delta$ -boryl-substituted (*E*)-*syn*-homoallylic alcohols **3** would be desirable. With our continuing efforts in developing novel allylboron reagents,<sup>10</sup> we have developed and reported herein stereoselective synthesis of (*Z*)- $\alpha$ -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*)- $\alpha$ -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.<sup>11</sup> Inspired by their studies, we decided to pursue a Ni-catalyzed isomerization of 1,1-di(boryl)but-3-ene **1**<sup>12</sup> to prepare (*Z*)-crotylboronate reagent **2b**. As shown in Table 1, in the presence of 10 mol% of NiCl<sub>2</sub> and dppp, 5 mol% Ph<sub>2</sub>PH, and 20 mol% of Zn and ZnI<sub>2</sub>, isomerization of homoallylboronate **1** did not form any product in CH<sub>2</sub>Cl<sub>2</sub> at -20 °C for 24 h (entry 1, Table 1). However, when NiCl<sub>2</sub> was replaced by NiBr<sub>2</sub>, 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)<sub>2</sub> 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)<sub>2</sub> was employed as the catalyst (entry 4). A similar *Z*/*E* ratio (7 : 1) was obtained with NiCl<sub>2</sub>·glyme as the catalyst, albeit in a low yield (entry 5). Intriguingly, reactions with preformed Ni catalysts, Ni(dppp)Cl<sub>2</sub> or Ni(dppe)Cl<sub>2</sub>, gave inferior results (entries 6 and 7). When NiBr<sub>2</sub>·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<sub>2</sub>·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*)- $\alpha$ -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*)- $\delta$ -boryl-*syn*-homoallylic alcohol **3a** in 90% yield. The olefin geometry in product **3a** was assigned as *E* based on <sup>1</sup>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.<sup>9a,b</sup>

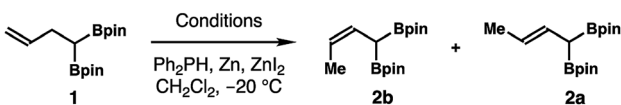
The scope of an aldehyde that participates in this reaction was explored, and the results are summarized in Scheme 3. In general, the reaction worked well with a broad spectrum of aldehydes, including aromatic, heteroaromatic and  $\alpha,\beta$ -unsaturated aldehydes. Reactions of **2b** with aromatic 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,  $\beta$ -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<sup>1,3</sup> allylic strain<sup>13</sup> between the pseudo-axially oriented -Bpin group and the methyl group (shown in red in **TS-2**). In contrast, the A<sup>1,3</sup> 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

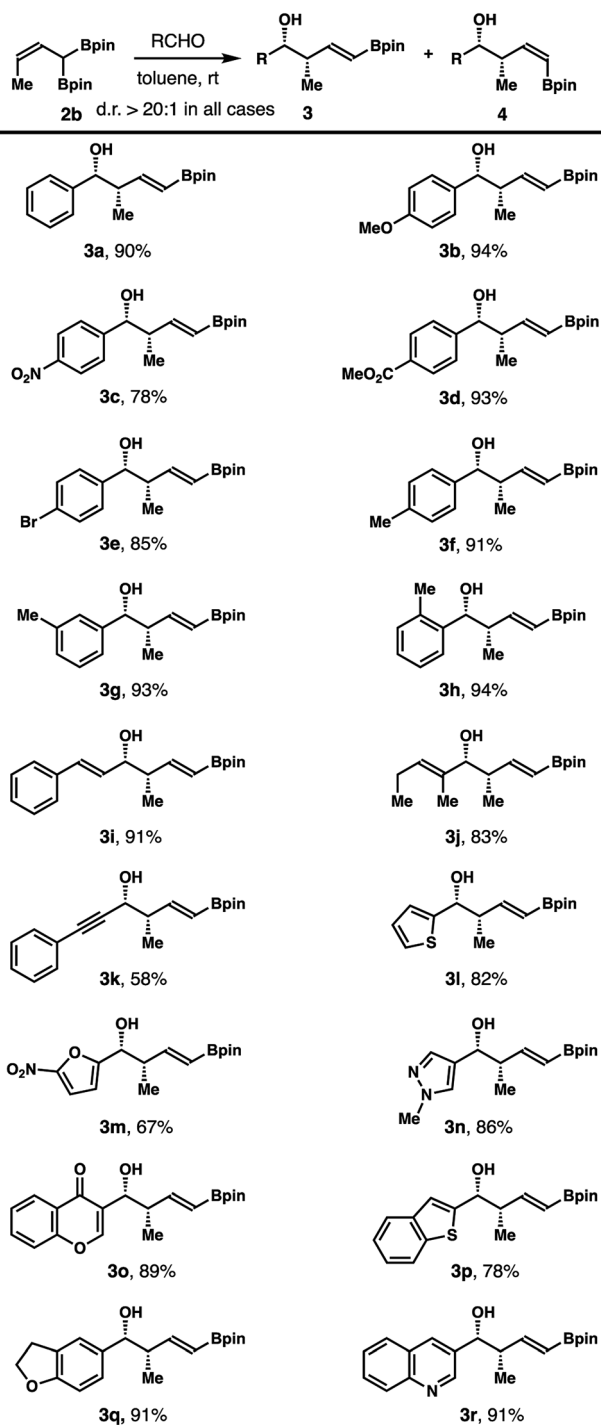
Table 1 Evaluation of reaction conditions for the synthesis of (*Z*)- $\alpha$ -boryl crotylboronate **2b**<sup>a</sup>



Entry	Conditions	<b>2b</b> : <b>2a</b> <sup>b</sup>	Yield <sup>c</sup> (%)
1	NiCl <sub>2</sub> , dppp	N.D.	N.R.
2	NiBr <sub>2</sub> , dppp	5 : 1	70
3	Ni(OAc) <sub>2</sub> , dppp	2 : 1	38
4	Ni(acac) <sub>2</sub> , dppp	6 : 1	76
5	NiCl <sub>2</sub> ·glyme, dppp	7 : 1	36
6	Ni(dppp)Cl <sub>2</sub>	3 : 1	56
7	Ni(dppe)Cl <sub>2</sub>	3 : 1	64
8	NiBr <sub>2</sub> ·diglyme, dppp	7 : 1	58
9 <sup>d</sup>	NiBr <sub>2</sub> ·diglyme, dppp	>20 : 1	70
10 <sup>e</sup>	NiBr <sub>2</sub> ·diglyme, dppp	>20 : 1	74

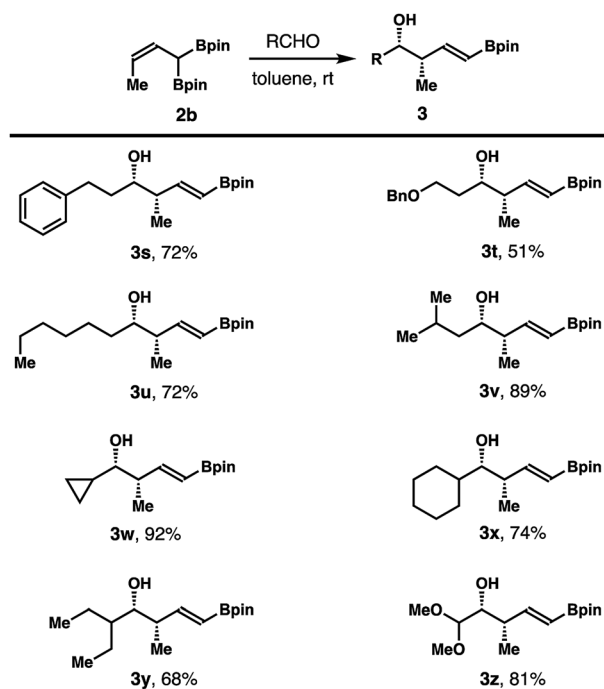
<sup>a</sup> Reaction conditions: boronate **1** (0.2 mmol, 1.0 equiv.), catalyst (10 mol%), ligand (10 mol%), Ph<sub>2</sub>PH (5 mol%), Zn (20 mol%), ZnI<sub>2</sub> (20 mol%), CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL), -20 °C. <sup>b</sup> The *Z*/*E* ratios were determined by <sup>1</sup>H NMR analysis of the crude reaction products. <sup>c</sup> Yields of isolated products are listed. <sup>d</sup> DCE was used as the solvent. <sup>e</sup> The reaction was conducted on a 2 mmol scale in DCE. dppp: 1,3-bis(diphenylphosphino)propane; dppe: 1,2-bis(diphenylphosphino)ethane.



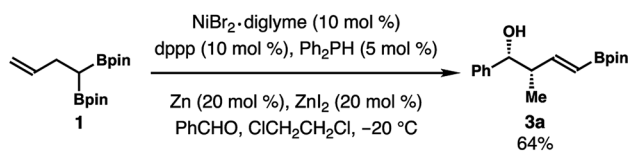


Scheme 3 Scope of aromatic, heteroaromatic and  $\alpha,\beta$ -unsaturated aldehydes for the reactions with (*Z*)- $\alpha$ -boryl-crotylboronate **2b**. (a) Reaction conditions: crotylboronate **2b** (0.13 mmol, 1.3 equiv.), aldehyde (0.1 mmol, 1.0 equiv.), toluene (0.3 mL), rt. (b) The diastereoselectivities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

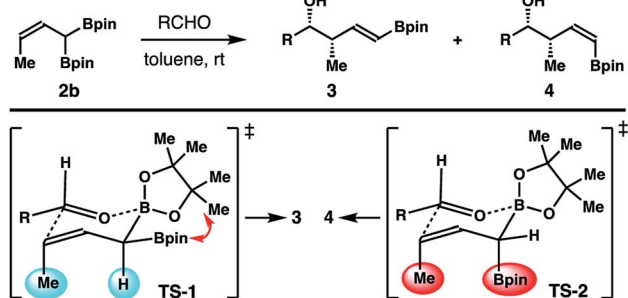
the  $A^{1,3}$  allylic strain between the -Bpin and methyl groups is severe enough to overcome the *gauche* interactions. As a result, crotylboration of aldehydes with reagent **2b** proceeded through



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  $^1\text{H}$  NMR analysis of the crude reaction products. (c) Yields of isolated products are listed.



Scheme 5 One-pot alkene isomerization and aldehyde allylboration.

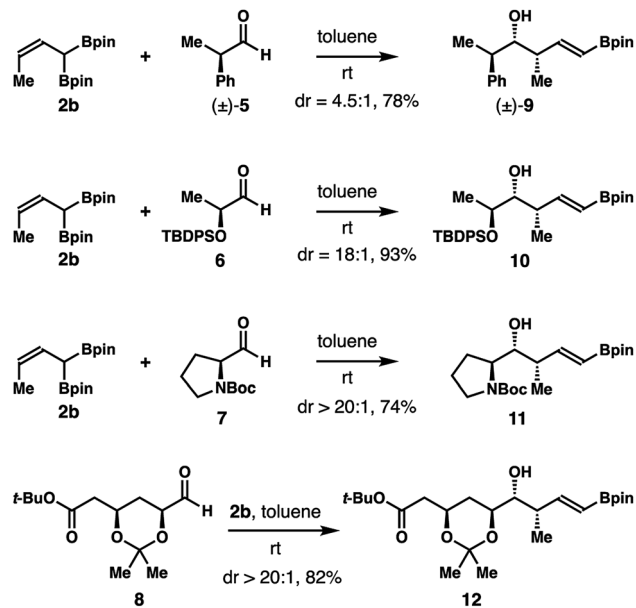


Scheme 6 Transition state analyses for selective formation of homoallylic alcohols **3** from crotylboronate **2b**.

the 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-

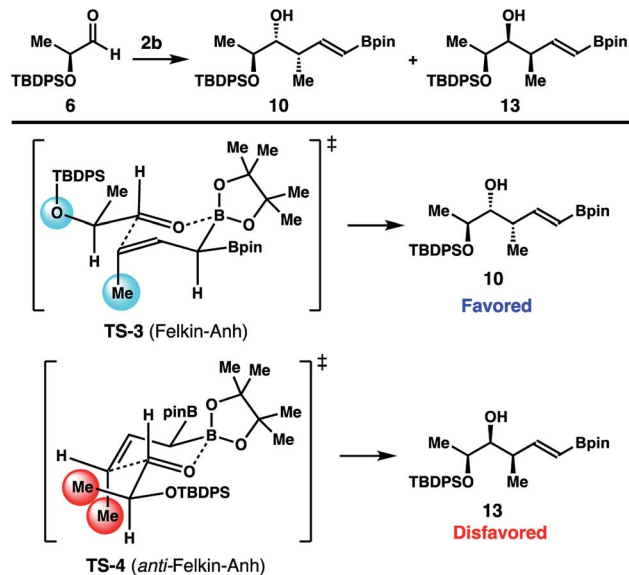




Scheme 7 Diastereoselective crotylboration of chiral aldehydes with (Z)-crotylboronate **2b**.

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.<sup>14</sup> The absolute configuration of the newly formed secondary hydroxyl groups of **10** and **12** was assigned by Mosher ester analysis.<sup>15</sup> 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.

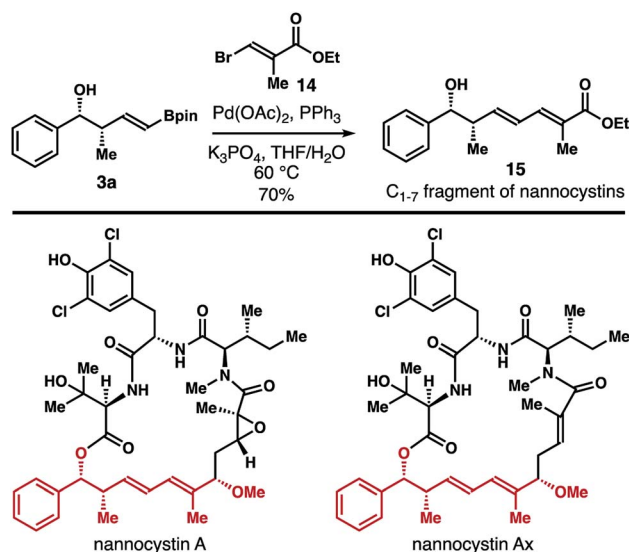
A stereochemical model for the high diastereoselectivities in the reactions with enantioenriched aldehydes **6–8** is delineated in Scheme 8. The reaction of aldehyde **6** with reagent **2b** could proceed through two potential transition states (**TS-3** and **TS-4**; Scheme 8) to produce two alcohol products, **10** and **13**. **TS-3** operates under Felkin–Anh<sup>16</sup> 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<sup>17</sup> 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<sub>1–7</sub> fragment of nannocystin A and nannocystin Ax.



used directly for a variety of subsequent transformations.<sup>18</sup> To further demonstrate the synthetic utility of this method, synthesis of the C<sub>1-7</sub> fragment of the natural products nannocystin A and nannocystin Ax was carried out.<sup>19,20</sup> As shown in Scheme 9, Pd-catalyzed Suzuki coupling<sup>21</sup> of free alcohol **3a** with vinyl bromide **14**<sup>22</sup> provided compound **15**, the C<sub>1-7</sub> 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*)- $\alpha$ -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*)- $\delta$ -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<sub>1-7</sub> 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.

## Notes and references

- (a) Y. Yamamoto and N. Asao, *Chem. Rev.*, 1993, **93**, 2207; (b) S. E. Denmark and N. G. Almstead, *Modern Carbonyl Chemistry*, ed. J. Otera, Wiley-VCH, Weinheim, 2000, p. 299; (c) S. R. Chemler and W. R. Roush, *Modern Carbonyl Chemistry*, ed. J. Otera, Wiley-VCH, Weinheim, 2000, p. 403; (d) S. E. Denmark and J. Fu, *Chem. Rev.*, 2003, **103**, 2763; (e) H. Lachance and D. G. Hall, *Org. React.*, 2008, **73**, 1; (f) M. Yus, J. C. González-Gómez and F. Foubelo, *Chem. Rev.*, 2011, **111**, 7774; (g) M. Yus, J. C. González-Gómez and F. Foubelo, *Chem. Rev.*, 2013, **113**, 5595; (h) C. Diner and K. J. Szabó, *J. Am. Chem. Soc.*, 2017, **139**, 2.
- (a) Y. Yamamoto, H. Yatagai and K. Maruyama, *J. Am. Chem. Soc.*, 1981, **103**, 3229; (b) D. J. S. Tsai and D. S. Matteson, *Organometallics*, 1983, **2**, 236; (c) Y. Yamamoto, K. Maruyama, T. Komatsu and W. Ito, *J. Org. Chem.*, 1986, **51**, 886; (d) M. Shimizu, H. Kitagawa, T. Kurahashi and T. Hiyama, *Angew. Chem., Int. Ed.*, 2001, **40**, 4283; (e) L. Carosi, H. Lachance and D. G. Hall, *Tetrahedron Lett.*, 2005, **46**, 8981; (f) M. Chen and W. R. Roush, *Org. Lett.*, 2013, **15**, 1662; (g) M. Chen and W. R. Roush, *Tetrahedron*, 2013, **69**, 5468.
- (a) M. Chen, D. H. Ess and W. R. Roush, *J. Am. Chem. Soc.*, 2010, **132**, 7881; (b) M. Chen and W. R. Roush, *J. Am. Chem. Soc.*, 2011, **133**, 5744; (c) P. S. Stewart, M. Chen, W. R. Roush and D. H. Ess, *Org. Lett.*, 2011, **13**, 1478; (d) M. Chen and W. R. Roush, *J. Am. Chem. Soc.*, 2012, **134**, 3925.
- (a) M. Lautens, A. H. Huboux, B. Chin and J. Downer, *Tetrahedron Lett.*, 1990, **131**, 5829; (b) M. Lautens and P. H. M. Delanghe, *Angew. Chem., Int. Ed.*, 1994, **33**, 2448; (c) M. Lautens, R. N. Ben and P. H. M. Delanghe, *Tetrahedron*, 1996, **52**, 7221.
- (a) B. Princet, G. Anselme and J. Pomet, *Synth. Commun.*, 1999, **29**, 3329; (b) B. Princet, G. Anselme and J. Pomet, *J. Organomet. Chem.*, 1999, **5921**, 34; (c) B. Princet, H. Gardes-Gariglio and J. Pomet, *J. Organomet. Chem.*, 2000, **604**, 186; (d) D. M. Hodgson, S. F. Barker, L. H. Mace and J. R. Moran, *Chem. Commun.*, 2001, 153; (e) D. R. Williams, Á. I. Morales-Ramos and C. M. Williams, *Org. Lett.*, 2006, **8**, 4393; (f) L. Li, X. Ye, Y. Wu, Z. Song, Z. Yin and Y. Xu, *Org. Lett.*, 2013, **15**, 1068; (g) Y. Chu, Q. Pu, Z. Tang, L. Gao and Z. Song, *Tetrahedron*, 2017, **73**, 3707; (h) Z. Chu, K. Wang, L. Gao and Z. Song, *Chem. Commun.*, 2017, **53**, 3078.
- (a) H. Wakamatsu, M. Nishida, N. Adachi and M. Mori, *J. Org. Chem.*, 2000, **65**, 3966; (b) H. J. Reich and J. W. Ringer, *J. Org. Chem.*, 1988, **53**, 455.
- (a) H. Sun, J. R. Abbott and W. R. Roush, *Org. Lett.*, 2011, **13**, 2734; (b) M. Chen and W. R. Roush, *Org. Lett.*, 2012, **14**, 426; (c) M. Chen and W. R. Roush, *Org. Lett.*, 2012, **14**, 1880; (d) M. Chen and W. R. Roush, *J. Org. Chem.*, 2013, **78**, 3; (e) A. Grisin and P. A. Evans, *Chem. Sci.*, 2015, **6**, 6407; (f) Y.-H. Zhang, R. Liu and B. Liu, *Chem. Commun.*, 2017, **53**, 5549; (g) L. Kämmler and M. E. Maier, *J. Org. Chem.*, 2018, **83**, 4554.
- H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, 1957, **79**, 1920.
- (a) T. Miura, J. Nakahashi and M. Murakami, *Angew. Chem., Int. Ed.*, 2017, **56**, 6989; (b) T. Miura, J. Nakahashi, W. Zhou, Y. Shiratori, S. G. Stewart and M. Murakami, *J. Am. Chem. Soc.*, 2017, **139**, 10903; (c) J. Park, S. Choi, Y. Lee and S. H. Cho, *Org. Lett.*, 2017, **19**, 4054.
- (a) M. Wang, S. Khan, E. Miliordos and M. Chen, *Org. Lett.*, 2018, **20**, 3810; (b) S. Gao and M. Chen, *Org. Lett.*, 2018, **20**, 6174; (c) M. Wang, S. Khan, E. Miliordos and M. Chen, *Adv. Synth. Catal.*, 2018, **360**, 4634; (d) S. Gao, M. Wang and M. Chen, *Org. Lett.*, 2018, **20**, 7921.
- F. Weber, A. Schmidt, P. Röse, M. Fischer, O. Burghaus and G. Hilt, *Org. Lett.*, 2015, **17**, 2952.
- S. A. Murray, J. C. Green, S. B. Tailor and S. J. Meek, *Angew. Chem., Int. Ed.*, 2016, **55**, 9065.
- (a) R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841. For recent examples: (b) M. Althaus, A. Mahmood, J. R. Suárez, S. P. Thomas and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2010, **132**, 4025; (c) L. T. Kliman, S. N. Mlynarski, G. E. Ferris and J. P. Morken, *Angew. Chem., Int. Ed.*, 2012, **51**, 521; (d) B. Potter, A. A. Szymaniak, E. K. Edelstein and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 17918.



- 14 (a) H. Brinkmann and R. W. Hoffmann, *Chem. Ber.*, 1990, **123**, 2395; (b) G. Niel, F. Roux, Y. Maisonnasse, I. Maugras, J. Poncet and P. Jouin, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1275; (c) F. Roux, I. Maugras, J. Poncet, G. Niel and P. Jouin, *Tetrahedron*, 1994, **50**, 5345.
- 15 (a) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512; (b) I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092; (c) T. R. Hoye, C. S. Jeffrey and F. Shao, *Nat. Protoc.*, 2007, **2**, 2451.
- 16 (a) M. Cherest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 1968, **18**, 2199; (b) N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, 1977, **1**, 61.
- 17 (a) W. R. Roush, *J. Org. Chem.*, 1991, **56**, 4151; (b) M. Chen and W. R. Roush, *J. Am. Chem. Soc.*, 2012, **134**, 3925.
- 18 (a) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (b) J. M. Murphy, X. Liao and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 15434; (c) C. Wang, T. Tobrman, Z. Xu and E.-i. Negishi, *Org. Lett.*, 2009, **11**, 4092; (d) R. E. Shade, A. M. Hyde, J.-C. Olsen and C. A. Merlic, *J. Am. Chem. Soc.*, 2010, **132**, 1202; (e) C. Körner, P. Starkov and T. D. Sheppard, *J. Am. Chem. Soc.*, 2010, **132**, 5968.
- 19 Isolation of nannocystins: (a) H. Hoffmann, H. Kogler, W. Heyse, H. Matter, M. Caspers, D. Schummer, C. Klemke-Jahn, A. Penarier, G. Bauer, L. Debussche and M. Brönstrup, *Angew. Chem., Int. Ed.*, 2015, **54**, 10145; (b) P. Krastel, S. Roggo, M. Schirle, N. T. Ross, F. Perruccio, P. Aspesi, T. Aust, K. Buntin, D. Estoppey, B. Liechty, F. Mapa, K. Memmert, H. Miller, X. Pan, R. Riedl, C. Thibaut, J. Thomas, T. Wagner, E. Weber, X. Xie, E. K. Schmitt and D. Hoepfner, *Angew. Chem., Int. Ed.*, 2015, **54**, 10149.
- 20 Syntheses of nannocystins: (a) L. Liao, J. Zhou, Z. Xu and T. Ye, *Angew. Chem., Int. Ed.*, 2016, **55**, 13263; (b) J. Huang and Z. Wang, *Org. Lett.*, 2016, **18**, 4702; (c) Z. Yang, X. Xu, C.-H. Yang, Y. Tian, X. Chen, L. Lian, W. Pan, X. Su, W. Zhang and Y. Chen, *Org. Lett.*, 2016, **18**, 5768; (d) Q. Liu, P. Hu and Y. He, *J. Org. Chem.*, 2017, **82**, 9217; (e) Y.-H. Zhang, R. Liu and B. Liu, *Chem. Commun.*, 2017, **53**, 5549; (f) C. Pooock and M. Kalesse, *Org. Lett.*, 2017, **19**, 4536; (g) Z. Meng, L. Souillart, B. Monks, N. Huwyler, J. Herrmann, R. Müller and A. Fürstner, *J. Org. Chem.*, 2018, **83**, 6977.
- 21 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
- 22 Y. Wang and W.-M. Dai, *Eur. J. Org. Chem.*, 2014, **2014**, 323.

