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Preparation of α-substituted allylboronates by chemoselective iridium-catalyzed asymmetric allylic alkylation of 1-propenylboronates

Feng Peng and Dennis G. Hall*

Department of Chemistry, University of Alberta, Edmonton, AB, Canada T6G 2G2

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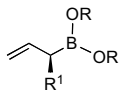
Abstract—Chiral α-substituted allylic boronates are attractive reagents that add to aldehydes with very high stereoselectivity. This study examined the feasibility of an improved method of preparation based on the catalytic asymmetric allylic alkylation of simple 3-hydroxy-1-propenylboronate derivatives with malonate anions. Whereas palladium catalysis failed in promoting the desired process, iridium catalysis led to a regioselective formation of the desired, branched allylboronates with up to 84% ee using a chiral monophosphoramidite ligand. This allylation reagent adds to aldehydes with high chirality transfer. A diastereoselective alkoxycyclization on the resulting homoallylic alcohols allows a separation of the epimeric *E*/*Z* isomers.

1. Introduction

Additions of allylic boron reagents to carbonyl compounds have long been a workhorse of organic synthesis for the stereoselective preparation of acetate and propionate units found in polyketide natural products.[1] Three strategies have been developed for controlling enantiofacial selectivity in additions of allylic boron reagents to achiral aldehydes: (1) The use of a chiral director like a diol, diamine, or terpene unit as boron's two non-allylic substituents;[2] (2) the use of chiral Lewis and Brønsted acid catalysis with achiral boronates;[3] and (3) the use of optically pure α-substituted reagents (also called 'α-chiral' allylboronates).[4] The dreaded borotropic shift of allylic dialkylboranes precludes the preparation of α-substituted borane derivatives[5] and makes the more stable boronate derivatives more suitable. The preparation of acyclic α-substituted allylboronates **1** and their additions to aldehydes were pioneered by Hoffmann.[4]



1 (R^1 = alkyl, halogen, alkoxy)

These reagents are generally prepared by a Matteson asymmetric homologation of alkenylboronates, which requires a stoichiometric chiral director (Fig. 1, Eq. 1).[6]

More recently, a preparation using the [3,3] rearrangement of chiral 3-hydroxy propenylboronates was reported (Eq. 2).[7] Improved methods of preparation that circumvent the use of stoichiometric chiral directors have been developed in the past few years. Examples include a catalytic enantioselective diboration of allenes (Eq. 3)[8] and a stereospecific copper-catalyzed allylic alkylation (Eq. 4).[9] The reagent-controlled additions of α-substituted allylboronates of type **1** to aldehydes proceed with near perfect transfer of chirality to give two diastereomeric products **4** and **5** (Fig. 2). These *Z* and *E* allylic alcohol products are epimeric, and their proportion is highly dependent on the nature of the α-substituent (R^1) and the structure of the boronic ester.[4] The selectivity between **4** and **5** can be explained in terms of steric and dipolar effects on the two competing transition structures **2** and **3**. With a non-polar alkyl substituent R^1, steric interactions play a dominant role. Transition structure **2** can be destabilized by steric interactions between a large boronic ester and the pseudo-equatorial α-substituent R^1. On the other hand, chairlike transition structure **3** features unfavorable allylic interactions due to the pseudo-axial position of the R^1 substituent. The use of a hindered ester, such

* Corresponding author. Tel.: +1 780 492 3141; fax: +1 780 492 8231; e-mail: dennis.hall@ualberta.ca

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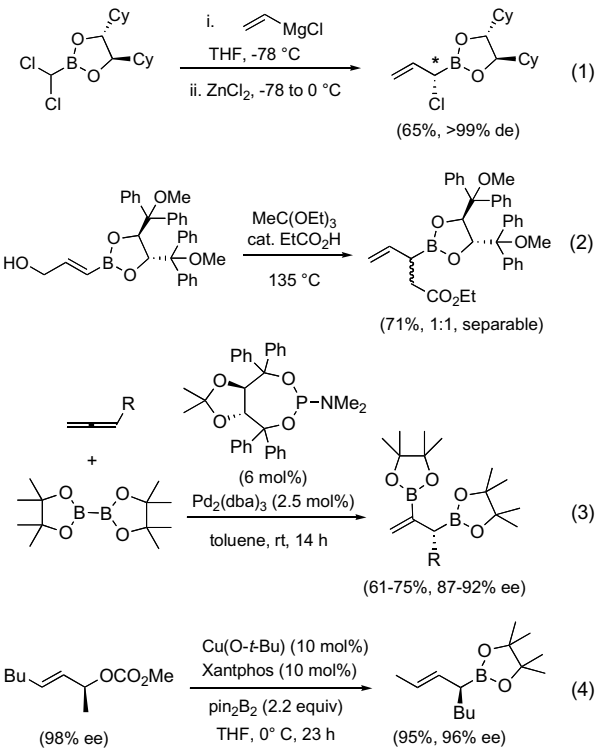


Figure 1. Selected literature methods for the preparation of optically active acyclic α-substituted allylic boronates.

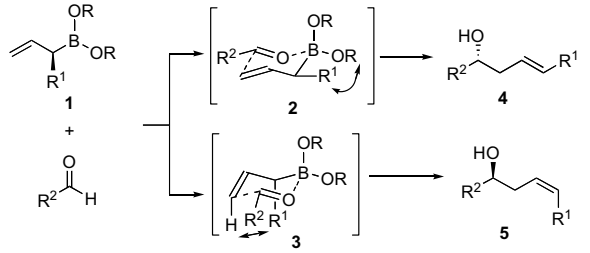


Figure 2. Competing transition structures in the allylation of aldehydes with α-substituted allylboronates (**1**).

as pinacolate, aggravates interactions between R^1 and the dioxaborolane unit in structure **2**, and tends to encourage transition structure **3** leading to mixtures of products **4** and **5** in modest selectivities.[10]

We believe that a simple, catalytic enantioselective method for the preparation of α-substituted allylboronates from achiral materials could render these reagents very attractive. Here, we describe our efforts using transition metal (TM) catalyzed asymmetric allylic alkylation of 3-hydroxypropenyl boronate derivatives **6** (Fig. 3).

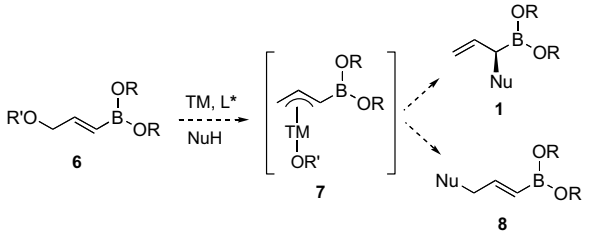
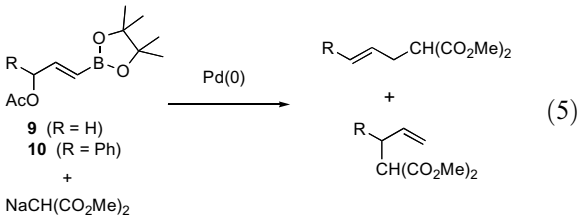


Figure 3. Catalytic allylic alkylation strategy for the regio- and enantioselective preparation of 'α-chiral' allylboronates (**1**).

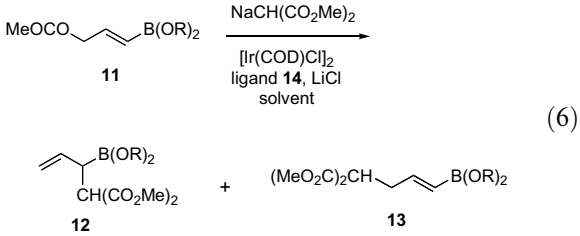
2. Results and discussion

Our first objective was the optimization of the regioselectivity using substrates and conditions that favor the formation of the desired branched product, allylboronate **1**, over the competing alkenylboronate product **8** (Fig. 3). This approach presents additional issues of chemoselectivity. Whereas insertion into an allylic ester or carbonate to give intermediate **7** should be facile, the desired product **1** may be susceptible to further insertion into the allylic C–B bond, with consequent undesired processes such as deboronation or allyl–allyl coupling (i.e., dimerization).

Our first attempts involved the use of well-known palladium-catalyzed alkylation conditions with malonate anion as a mild nucleophile.[11] Unfortunately, under all conditions investigated with various catalysts, substrate **10** led to mixtures of regioisomeric deboronation products (Eq. 5) while the unsubstituted derivative **9**[12] led to other unidentified materials. These compounds may originate from further undesirable insertion into the desired product **1**. This process, and other side reactions like allyl–allyl coupling are possible and are precedented in palladium catalysis.[13]

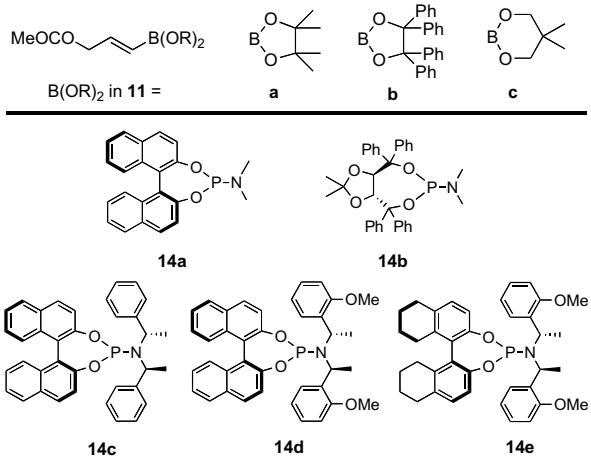


The iridium-catalyzed alkylation of the methyl carbonate derivative of 3-hydroxypropenyl boronates **11** showed more promise (Eq. 6).[14] This procedure makes use of chiral monophosphoramidite ligands.[15]



Pinacolate ester **11a** was examined first as a model substrate with dimethyl malonate as the nucleophile. As shown in Table 1, the regiochemistry was found to be strongly dependent on the structure of the phosphoramidite ligand (entries 1–5). Ligand **14d** led to the largest proportion of the desired allylboronate **12a** (entry 4). All other ligands favored the undesired regioisomer **13a**. Using chiral monophosphoramidite ligand **14d**, other solvents were examined. The use of ether, dichlorometh-

Table 1. Optimization of the regioselectivity with dimethyl malonate as the nucleophile (Eq. 6)[a]



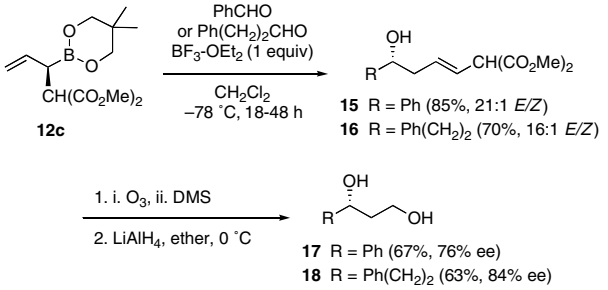
Entry	Boronate	Solvent	Ligand	Ratio **12**:**13**[b]
1	**11a**	THF	**14a**	1:2
2	**11a**	THF	**14b**	1:6
3	**11a**	THF	**14c**	1:1.8
4	**11a**	THF	**14d**	1.7:1
5	**11a**	THF	**14e**	1:3
6	**11a**	Et_2O	**14d**	s.m.
7	**11a**	CH_2Cl_2	**14d**	s.m.
8	**11a**	Toluene	**14d**	s.m.
9	**11a**	DMF	**14d**	1:>20
10	**11a**	DMSO	**14d**	1:>20
11	**11a**	Dioxane	**14d**	1:6
12	**11b**	THF	**14d**	1:>20
13	**11c**	THF	**14d**	4.2:1
14	**11c**	THF	**14e**	1:1

[a] Reaction conditions: boronate (1 equiv), $NaCH(CO_2Me)_2$ (2 equiv), LiCl (1 equiv), $[Ir(COD)Cl]_2$ (2.5 mol %), ligand (5.0 mol %), in the indicated solvent at room temperature for 15 h.

[b] Measured by ^1H NMR analysis of crude reaction product.

ane, and toluene led only to starting material probably due to the heterogeneous reaction conditions (entries 6–8). Consequently, more polar solvents were investigated. Whereas DMF, DMSO, and dioxane led predominantly to the undesired alkenylboronate **13a** (entries 9–11), the use of THF still provided the best ratio of 1.7:1 favoring regioisomer **12a** (entry 4). Considering this moderate ratio of regioisomers, product **12a** was isolated free of **13a** in the acceptable yield of 47%.[16]

The effect of the boronic ester was examined next, and the size of this group was also found to have a determinant influence on the regioselectivity of the alkylation (entry 4 vs entries 12–13). From these results, it is clear that large boronate groups disfavor the formation of the branched product **12**. Although the smaller boronate **11c** led to an improved ratio favoring the desired allylboronate **12c** over **13c** (entry 13), it was later found that **12c** is unstable to silica gel purification.[16] It may be more prone to hydrolytic pathways due to the less hindered nature of this boronic ester as compared to the corresponding pinacolates **12a** and **12b**. Consequently, we developed an aldehyde allylation procedure that would circumvent the need for purifying this reagent, by directly employing the crude extracted material from the

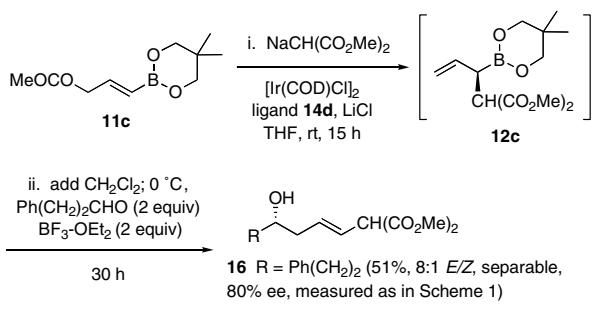


Scheme 1.

alkylation. As demonstrated with both benzaldehyde and hydrocinnamaldehyde, the low-temperature Lewis acid-catalyzed allylboration[17] with BF_3–OEt_2 provided homoallylic alcohols **15** and **16** with excellent *E*/*Z* ratio up to 21:1 (Scheme 1).[18] Interestingly, the uncatalyzed reaction at room temperature afforded a reverse *E*/*Z* ratio of 1:4.5. Unfortunately, reagent **12c** was too sensitive to be derivatized and allow a direct ee measurement. However, oxidative cleavage of alkene products **15**/**16** and reduction of the resulting aldehydes gave diols **17** and **18**. The latter were amenable to an evaluation of the optical purity, giving respectively 76% and 84% ee according to chiral HPLC analysis. A similar value can be inferred to reagent **12c** as it is well established that additions of α-substituted allylboronates occur with near-perfect stereochemical transfer.[4,19] The assessment of the absolute stereochemistry of **15** and **12c**, originating from ligand **14d**, was made by comparison with literature values of optical rotation for diol (*R*)-**17**.

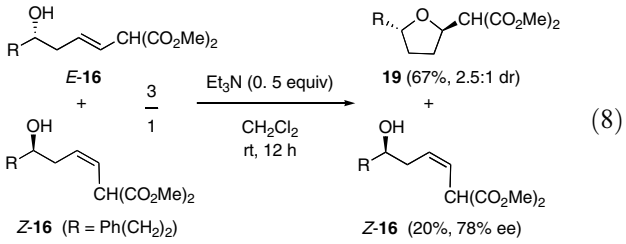
The excellent diastereoselectivity favoring the *E* isomer in the catalyzed additions of **12c** can be explained by the relatively small non-bonding interactions between the pseudo-equatorial α-substituent and the dioxaborinane unit in transition structure **2** (Fig. 2).[20] This situation is more favorable compared to the destabilizing interactions caused by a pseudo-axial α-substituent in transition structure **3**, which would lead to the *Z* isomer.

Our next efforts focused on the development of a one-pot sequential allylic alkylation/allylboration. This procedure was achieved by simply diluting the solution with CH_2Cl_2 after the allylic alkylation, and lowering the temperature to 0 °C, and adding 2 equiv each of the aldehyde and $BF_3{\cdot}OEt_2$ (Eq. 7). We were glad to obtain the desired homoallylic alcohol *E*-**16** in good overall yield and with an ee similar to that of the stepwise approach.



(7)

The allylic malonate unit of the products can be of great use for designing further transformations of the allylation products of reagent **12c**. For example, basic treatment of a 3:1 *E*/*Z* mixture of **16** provides a 3:1 mixture of furan **19** along with unreacted *Z*-**16** (Eq. 8). Although the diastereoselectivity of this tandem isomerization/conjugate addition is modest, this result shows that the epimeric homoallylic alcohol products such as **16** can be separated based on this *E*/*Z*-selective alkoxycyclization process. Indeed, the recovered *Z*-**16** had an optical purity of 78% ee, with an absolute configuration opposite to that of *E*-**16**.



(8)

3. Conclusion

This preliminary Letter demonstrates the feasibility of an iridium-catalyzed asymmetric allylic alkylation approach to the preparation of useful α-substituted allylboronates from simple 3-hydroxy-1-alkenylboronate precursors. These conditions are fully compatible with the boronic ester functionality. The desired branched allylic boronates were obtained in moderate regioselectivity and enantioselectivity up to 84% ee using a chiral monophosphoramidite ligand. It is noteworthy that the Lewis acid-catalyzed manifold for aldehyde allylboration is operational even in the presence of the coordinating carboxyesters in the malonate substituent of reagents **12**. Future work to further improve this novel preparation of α-substituted allylboronates will focus on investigating new types of phosphoramidite ligands.

Acknowledgments

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16. *General procedure for the preparation of allylboronate* **12c**: In a 5 mL flame-dried round-bottom flask, $[Ir(COD)Cl]_2$ (2.5 mol %), ligand **14d** (5 mol %), and LiCl (1 equiv) were dissolved in 1 mL of THF under argon. The solution was stirred for 30 min at room temperature. Boronic ester **11c** (1 equiv) was added and 5 min later freshly prepared sodium malonate solution (2 equiv) was added. The reaction mixture was stirred for 15 h at room temperature, then quenched with saturated aqueous ammonium chloride solution, extracted with diethyl ether, dried over anhydrous magnesium sulfate, filtered and concentrated. Compound **12c**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.76 (ddd, $J = 17.1$, 10.2, 9.3 Hz, 1H), 5.06 (d, $J = 17.1$ Hz, 1H), 4.99 (d, $J = 10.2$ Hz, 1H), 3.77–3.75 (br s, 11H), 2.40 (dd, $J = 10.0$, 10.0 Hz, 1H), 0.95 (s, 6H). Allylboronate **12c** is not stable to silica gel purification but it can be used efficiently as a crude reagent. Compound **12a** is more robust and can be purified by silica gel chromatography. Compound **12a**: According to the procedure above, **12a** was obtained as a yellow oil. (142 mg, 47%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.75 (ddd, $J = 17.1$, 10.2, 9.1 Hz, 1H), 5.08 (d, $J = 17.1$ Hz, 1H), 5.01 (d, $J = 10.2$ Hz, 1H), 3.71–3.68 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 2.50 (dd, $J = 9.9$, 9.9 Hz, 1H), 1.23 (s, 6H), 1.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 169.6, 134.5, 116.7, 83.7, 53.1,

52.6, 52.3, 24.7, 24.6; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 31.89; IR (neat): 2979, 2955, 1738, 1634, 1436, 1366, 1330 cm^{-1}; HRMS (EI, m/z) calcd for $C_{14}H_{23}O_6B$: 298.1588; found 298.1586 [M^+].

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20. It was postulated that a late transition state featuring electrophilic activation by Lewis acid coordination to a boronate oxygen is operative.[17b] For a similar analysis with a pinacol allylic boronate, see: Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981–8985.