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Controllable Stereoselective Synthesis of (*Z*)- and (*E*)-Homoallylic Alcohols Using a Palladium-Catalyzed Three-Component Reaction

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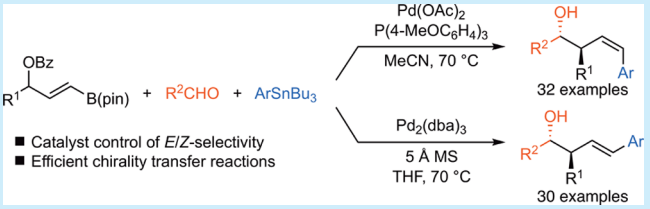
Supporting Information

ABSTRACT: Diastereoselective synthesis of (*Z*)- and (*E*)-homoallylic alcohols using a Pd-catalyzed three-component reaction of 3-(pinacolatoboryl)allyl benzoates, aldehydes, and aryl stannanes was developed, which provides an alternative method for the allylboration of aldehydes using α,γ-diaryl-substituted allylboronates. Both sets of reaction conditions enable access to either (*Z*)- or (*E*)-homoallylic alcohols with good to high alkene stereocontrol. The present method showed good functional group compatibility and generality. Efficient chirality transfer reactions to afford enantioenriched (*Z*)- and (*E*)-homoallylic alcohols were also achieved.

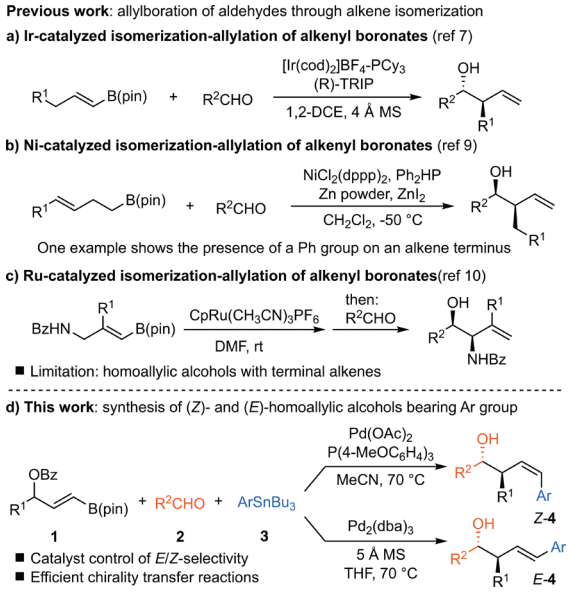


Allylboration of carbonyl compounds is well established as one of the most important and promising methods for the stereoselective synthesis of homoallylic alcohols.[1] Recent advances in the preparation of allylic boronates have contributed in making this reaction more reliable and useful.[2] For example, highly diastereo- and enantioselective allylborations of aldehydes using α,γ-disubstituted allylic boronates, without changing the substituents around the boron atom, were reported.[3] However, this elegant method still lacks alkene stereocontrol. In addition, the rather narrow functional group compatibility hampers its general and practical use due to the intrinsic difficulty in the elaboration of functional-group-tolerated α,γ-disubstituted allylic boronates.[4] Alternative methods, including catalytic variants, for the diastereoselective synthesis of functional-group-tolerated (*Z*)- and (*E*)-homoallylic alcohols is highly desired.

Transition-metal-catalyzed alkene isomerization of alkenyl boronates has emerged as a surrogate reaction to the stereoselective synthesis of allylic boronates[5] because alkenyl boronates are stable, easy-to-handle, and readily available.[6] Murakami and Miura reported the Ir-catalyzed alkene isomerization of alkenyl boronates into (*E*)-allylic boronates that gives anti-homoallylic alcohols enantio- and diastereoselectively (Scheme 1a).[7,8] The Ni-catalyzed alkene isomerization/allylation reaction affords complementary stereochemical results (Scheme 1b).[9] Notably, Ru-catalyzed isomerization of *N*-allyl amides produce thermodynamically less-stable (*Z*)-γ-aminoallylic boronates, which then react with aldehydes to provide *syn*-homoallylic alcohols (Scheme 1c).[10] Although these precedents offer more convenient stereoselective synthesis of homoallylic alcohols with terminal alkenes, catalytic methods for the synthesis of homoallylic alcohols bearing *E*- or *Z*-disubstituted alkenes,[11] especially aryl-substituted alkenes, have been less explored.[12]

To overcome such limitations, we reported that catalytically generated allylic heterobimetallic species[13] such as allylic Pd/boryl and Pd/stannyl species are useful intermediates for the umpolung allylation of aldehydes[14] to provide (*Z*)- and (*E*)-homoallylic alcohols, respectively, with good to high stereoselectivity.[15] However, such methods require the independent preparation of different starting materials. Although alkyl groups can be installed at the alkene terminus with high *Z*-stereoselectivity, poor *Z*-stereoselectivity was observed when the

Scheme 1. Transition-Metal-Catalyzed Isomerization/Allylation Reactions



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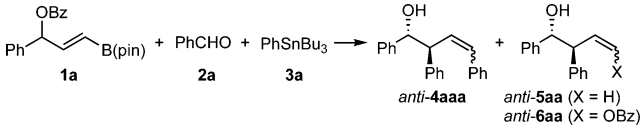
triphenylborane was used as a coupling partner. Stereocontrolled synthesis of (*Z*)- and (*E*)-homoallylic alcohols from the same starting materials is a highly appealing prospect. Herein, we report the controllable stereoselective synthesis of (*Z*)- and (*E*)-homoallylic alcohols using a Pd-catalyzed three-component reaction of 3-(pinacolatoboryl)allyl benzoates, aldehydes, and aryl stannanes. This method shows good functional group compatibility and generality and allows for the preparation of enantioenriched (*Z*)- and (*E*)-homoallylic alcohols **4** using chirality transfer reactions.

Our initial investigation focused on the three-component reaction of **1a**, **2a**, and **3a** (Table 1). Optimization of ligands,

Table 1. Optimization of Reaction Conditions[a]

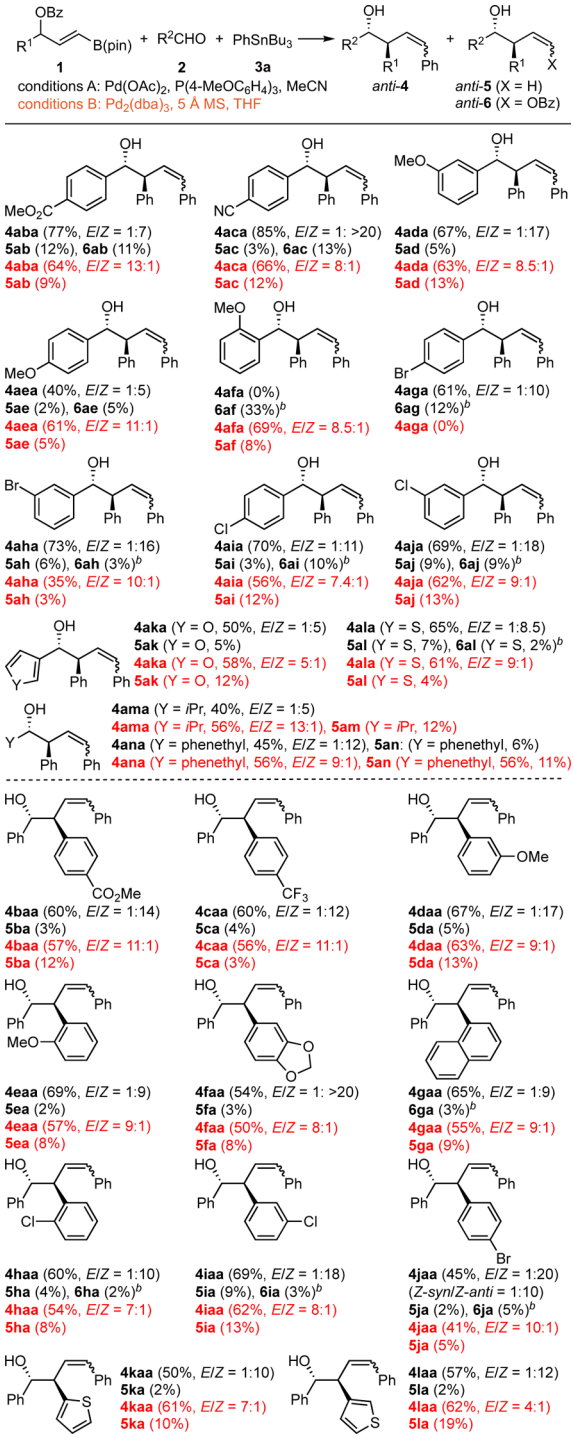


entry	Pd/ligand	solvent	**4aaa** (%)[b]	*E*/*Z*[c]	**5aa** (%)[b]
1	$Pd_2(dba)_3$/PPh_3	THF	69	1:3	2
2[d]	$Pd_2(dba)_3$/PPh_3	DMF	45	1:4.5	0
3	$Pd_2(dba)_3$/PPh_3	MeCN	69	1:6	3
4[d]	$Pd(OAc)_2$/PPh_3	MeCN	62	1:10	5
5[e]	$Pd(OAc)_2$/ P(4-$MeOC_6H_4)_3$	MeCN	73	1:13	4
6[d]	$Pd(OAc)_2$/ P(4-$CF_3C_6H_4)_3$	MeCN	55	1:1	5
7	$Pd_2(dba)_3$	THF	56	13:1	10
8	$Pd_2(dba)_3$	toluene	66	8:1	13
9[f]	$Pd_2(dba)_3$	THF	62	11:1	13
10[f,g]	$Pd_2(dba)_3$	THF	65	13:1	13

[a]Pd (5 mol % as Pd), ligand (10 mol %), **1a** (0.5 mmol), **2a** (1.2 mmol), **3a** (1.2 mmol), and solvent (3 mL) at 70 °C for 1−3 h. [b]Isolated yield. [c]Determined by NMR analysis. [d]Yields of **6aa** vary from 13 to 14% (*E*/*Z* = 1:>20). [e]**6aa** was obtained in 6% (*E*/*Z* = 1:>20). [f]**2a** (1.8 mmol) was used. [g]5 Å MS (500 mg) was used.

solvents, and coupling partners was proven to be crucial in obtaining high (*Z*)-stereoselectivity.[16] It was also found that the leaving group plays an important role on the yield of the reaction.[16] The use of MeCN as a solvent increased the (*Z*)-stereoselectivity (entries 1−3). During ligand screening, the $Pd(OAc)_2$/P(4-$MeOC_6H_4)_3$ catalyst system afforded **4aaa** in 73% yield with high (*Z*)-stereoselectivity (entries 4−6). The homoaldol equivalent product **6aa**[17] did not react with **3a** to provide **4aaa** under the $Pd(OAc)_2$/P(4-$MeOC_6H_4)_3$ catalyst system. In addition, isomerization of (*Z*)-**4aaa** to (*E*)-**4aaa** was not observed under the reaction conditions. Conversely, stereochemical changes to give (*E*)-isomer were observed when $Pd_2(dba)_3$ was employed in the absence of ligands (entries 7−8). Further optimization of the reaction conditions revealed that the use of 3.6 equiv of **2a** along with addition of molecular sieves (5 Å MS) provided some increase in (*E*)-selectivity (entries 9 and 10). The relative stereochemistry of **4aaa** was determined to be anti by derivatization to give a literature-known material.[16] With the optimized reaction conditions in hand, we subsequently explored the reaction scope using various aldehydes **2** with **1a** and **3a** under both sets of conditions (Scheme 2). A broad range of aromatic aldehydes was tolerated to provide (*Z*)- and (*E*)-homoallylic alcohols **4** with good to high levels of alkene stereocontrol. Indeed, the reactions proceeded without being influenced by the

Scheme 2. Scope and Limitations[a]



[a]Conditions A: $Pd(OAc)_2$ (5 mol %), P(4-$MeOC_6H_4)_3$ (10 mol %), **1** (0.5 mmol), **2** (1.8 mmol), **3a** (1.2 mmol), and MeCN (3 mL) at 70 °C for 1−3 h. Conditions B: $Pd_2(dba)_3$ (2.5 mol %), **1** (0.5 mmol), **2** (1.8 mmol), **3a** (1.2 mmol), 5 Å MS (500 mg), and THF (3 mL) at 70 °C for 1−3 h. [b]*E*/*Z* ratio of **6** varies from 1:10 to 1: >20.

electronic nature of the substituents (methoxycarbonyl, cyano, and methoxy) to afford **4aba**−**4aea** under both sets of conditions. Although a sterically hindered *o*-anisaldehyde did not participate in the reaction under (*Z*)-selective conditions, the reaction proceeded to give **4afa** under the (*E*)-selective conditions. Aromatic aldehydes bearing halide substituents also furnished

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good yields and alkene stereocontrol for products **4aga**–**4aja**, which can be used for further manipulation and diversification. Moreover, the reaction of heterocyclic aldehydes, such as 3-furaldehyde and 3-thiophenecarboxaldehyde, proceeded smoothly to produce **4aka** and **4ala**, respectively, in good to high yields and moderate to good levels of alkene stereocontrol. Aliphatic aldehydes were also applicable to the three-component reaction to afford the corresponding products **4ama** and **4ana** in 40%–56% yield and good to high *E*/*Z* ratios under both sets of conditions. Excellent diastereoselectivities were observed for all of the aldehydes examined.

Next, we examined the substrate generality of the reaction. A variety of readily accessible aryl-substituted substrates were subjected to the both sets of conditions. Substrates bearing electron-withdrawing and -donating groups could be utilized to give **4baa**–**4faa**. A substrate bearing a 2-naphthyl group also underwent this reaction to give **4gaa**. Note that *o*-chloro-, *m*-chloro-, and *p*-bromo-substituted phenyl substrates were compatible with both sets of reaction conditions, providing **4haa**–**4jaa** in 41–69% yield with good to high *E*/*Z* ratios.

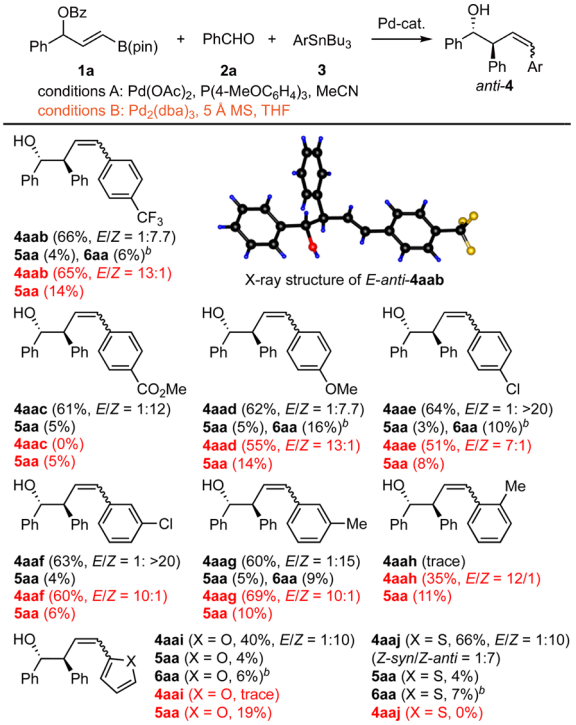
Among them, (*E*)-**4jaa** was obtained with a decreased *syn*/*anti* ratio. Heteroaryl-group-substituted substrates were also amenable to the reaction, giving **4kaa**–**4laa** in 50–62% yield with good *E*/*Z* ratios. Unfortunately, only trace amounts of the desired product were obtained when alkyl-substituted substrates, such as methyl- and isopropyl-substituted substrates, were applied.

The scope of the Pd-catalyzed three-component reaction with respect to aryl stannanes was also evaluated (Scheme 3). It was found that the reactions showed wide generality for various aryl stannanes containing trifluoromethyl, methoxycarbonyl, methoxy, chloro, and methyl groups on the aromatic ring, furnishing the desired (*Z*)- and (*E*)-**4aab**–**4aag** in good yields with good to high levels of alkene stereocontrol. Stereochemistry of **4aab** was assigned after X-ray analysis.[18] Among them, an aryl stannane bearing an ester group did not take part in the reaction to afford (*E*)-**4aac**. In addition, tributyl(*o*-tolyl)stannane was not compatible with the *Z*-selective conditions. Use of heteroaryl-substituted aryl stannanes was imposed on the *Z*-selective conditions, giving (*Z*)-**4aai** and (*Z*)-**4aaj** in 40 and 66% yields, respectively, having *E*/*Z* ratio of 1/10. (*Z*)-**4aaj** was obtained with a decreased diastereoselectivity.

To gain further mechanistic insights, we carried out chirality transfer experiments using (*R*)-**1a** (97% ee) under both sets of conditions (Scheme 4). Consistent with our previous report, a similarly efficient chirality transfer was observed under *Z*-selective conditions (Scheme 4a).[15a] Absolute stereochemistry of (*Z*)- and (*E*)-**4aaa** was determined to be (1*S*,2*R*) by transformation into known diols.[15a] When (*R*)-**1a** was subjected to *E*-selective conditions, (*E*)-**4aaa** was produced with a high degree of chirality transfer, from 97% ee of the starting material to 95% ee in the final product (98% es) (Scheme 4b). These products are only accessible via enantioenriched *α*,*γ*-diphenyl-substituted allylboronates.[19] Absolute stereochemistry of (*E*)-**4aaa** was opposite from that of the former case. These results indicate that two different reaction pathways need to be invoked to account for these transformations. In addition, both diastereomers of alkenyl boronate (*S*)-**1m** and (*R*)-**1m**[20] also enabled the chirality transfer reaction (Scheme 4c,d). Notably, stereochemical match/mismatch effects were observed. On the other hand, no reactions were observed under the *E*-selective conditions (Scheme 4e).

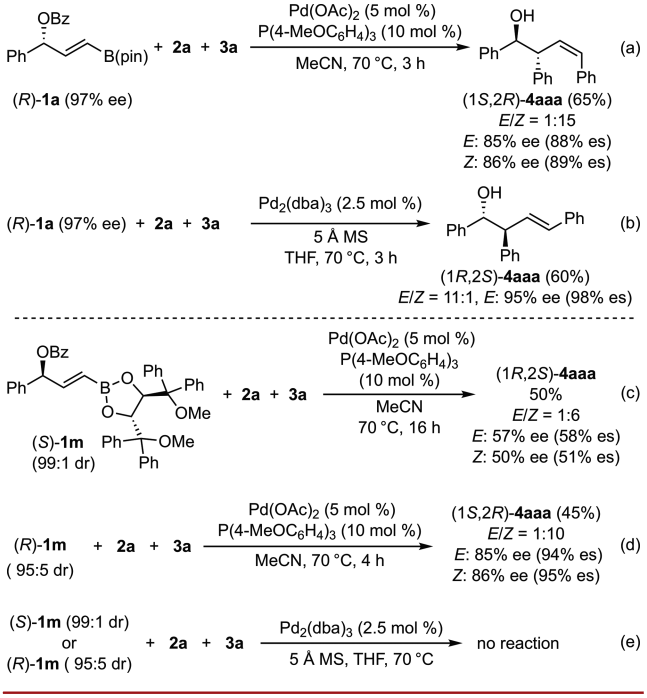
On the basis of the results of these chirality transfer reactions, the stereochemical outcome under *Z*-selective conditions might be rationalized in a manner similar to the previously reported mechanism (Scheme 5).[15a] First, oxidative addition occurs with an inversion of configuration, leading to η^3-allylpalladium intermediate **A**. The Pd atom in the η^1-allylpalladium intermediate would coordinate to a benzaldehyde to preferen-

Scheme 3. Reactions with Various Organostannanes[a]



[a]Reaction conditions identical to those in Scheme 2. [b]*E*/*Z* ratio of **6** varies from 1:10 to 1:>20.

Scheme 4. Chirality Transfer Reactions



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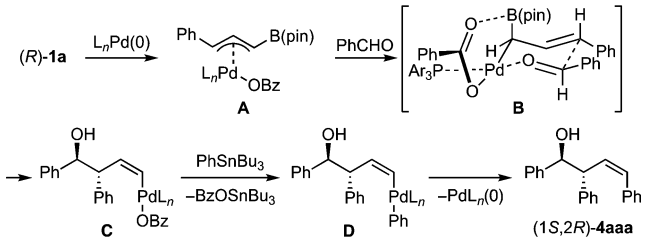
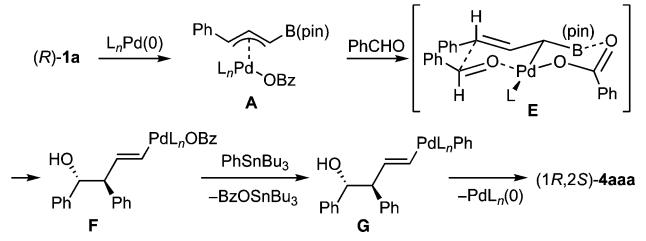
Scheme 5. Plausible Reaction Pathway under *Z*-Selective Conditions



tially form transition state **B**. Accordingly, the transition state is cyclic for an η^1-allylpalladium moiety and is open-chain for an allylic boronate moiety. Allylboration of the benzaldehyde forms a (*Z*)-vinylpalladium intermediate **C**. Finally, transmetalation of **C** with tributylphenylstannane, followed by reductive elimination from a vinylpalladium intermediate **D**, gives desired product (1*S*,2*R*)-**4aaa**. This reasonably accounts for the observed stereochemical outcome. If the phosphine ligand is absent, such as the *E*-selective conditions, an η^1-allylpalladium intermediate would coordinate to the benzaldehyde in a different manner to form the thermodynamically stable *trans*-decaline-like transition state **E** (Scheme 6). This leads to desired product (1*R*,2*S*)-**4aaa**.

Scheme 6. Plausible Reaction Pathway under *E*-Selective Conditions



In summary, we developed complementary reaction conditions to provide both (*Z*)- and (*E*)-homoallylic alcohols possessing aryl groups at the alkene terminus using a catalyst-controlled strategy. The reaction showed good scope and functional group tolerance, many of which could pose difficulties for other transition-metal-catalyzed alkene isomerizations of alkenyl boronates. Thus, the catalytically generated allylic Pd/boryl species promise to serve as synthetically useful intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02979.

Experimental procedure, characterization data, and NMR spectra (PDF)

X-ray crystallography data for (*E*)-*anti*-**4aab** (CIF)

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Notes

The authors declare no competing financial interest.

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