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Pd-Catalyzed Three-Component Reaction of 3-(Pinacolatoboryl)allyl Acetates, Aldehydes, and Organoboranes: A New Entry to Stereoselective Synthesis of (*Z*)-*anti*-Homoallylic Alcohols

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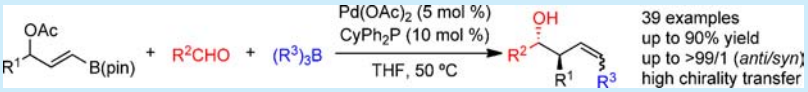
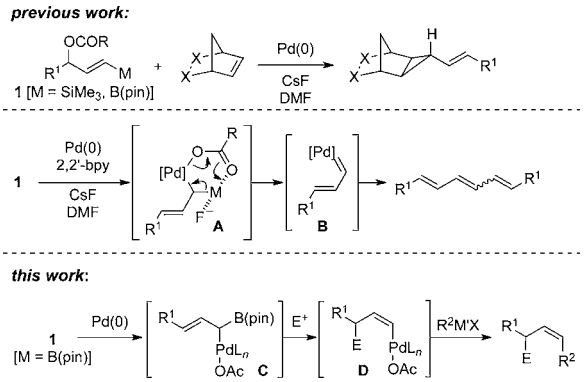
Supporting Information



ABSTRACT: The Pd-catalyzed three-component reaction of 3-(pinacolatoboryl)allyl acetates, aldehydes, and organoboranes is described. The reaction is initiated by the formation of an allylic *gem*-palladium/boryl intermediate, which then undergoes allylation of aldehydes by allylboronates followed by a coupling reaction of in situ generated (*Z*)-vinylpalladium acetates with organoboranes to provide the (*Z*)-*anti*-homoallylic alcohols with high levels of diastereoselectivity and alkene stereocontrol.

Organo-*gem*-sp^3-heterobimetallic reagents have appeared to enhance the synthetic application of C−C bond forming reactions and opened the facile synthetic route to many molecular constructions in single-step reactions.[1] In general, these methods require more than the stoichiometric amount of metal reagents and additional steps to install two different types of metal at geminal positions in advance. Moreover, most of the C−C bond-forming reactions are limited to nucleophilic reaction. Recently, Fillion et al. demonstrated the unique reactivities of organo-*gem*-sp^3-transition metal/main-group metal intermediates for the C−C bond-forming reactions.[2] They pioneered the cyclopropanation of strained alkenes and dimerization reactions starting from organostannatranes, and 1,2-alkyl migration from organoalanes. In addition to these advancements, however, synthetic applications of organo-*gem*-sp^3-transition metal/metalloid intermediates utilizing two different types of C−C bond forming reactions in a single synthetic-step operation have rarely been exploited. In our recent studies, we demonstrated the distinct reactivities of allylic *gem*-palladium/metalloid intermediates that could serve as C3 units in reactions other than allylation reactions. For example, we have reported the stereoselective cyclopropanation of strained alkenes by the Pd-catalyzed reaction of **1** (Scheme 1).[3] Furthermore, a Pd-stabilized vinylcarbene intermediate **B** was formed from **A**, and it can be used in the carbene dimerization.[4] We envisaged that an allylboronate generated during the formation of an allylic *gem*-palladium/boryl intermediate **C** would initially undergo nucleophilic allylation toward an electrophile if an appropriate electrophile is present,[5] possibly resulting in the formation of a (*Z*)-vinylpalladium acetate intermediate **D** that potentially undergoes further coupling reaction. Herein, we report the Pd-catalyzed three-component reaction of 3-(pinacolatoboryl)allyl acetates, aldehydes, and organoboranes; this reaction involves Suzuki−Miyaura-type vinyl−alkyl and vinyl−aryl coupling reactions under neutral conditions that make it even more tolerant of functional groups.[6] Moreover, this method provides (*Z*)-*anti*-homoallylic alcohols, with high stereoselectivity, that cannot be easily accessed by known catalytic conditions.[7,8]

Scheme 1. Utilization of Allylic *gem*-Palladium/Metalloid Intermediates



To demonstrate our hypothesis, we initially examined the reaction of 1-phenyl-3-(pinacolatoboryl)allyl acetate (**1a**) and benzaldehyde (**2a**) in the presence of catalytic amounts of $Pd(OAc)_2$ and Ph_3P (Scheme 2). As we expected, 4-acetoxy homoallylic alcohol **3** was obtained in 42% yield as a mixture of (*Z*)-*anti*-**3** and (*E*)-*anti*-**3** (*Z*/*E* = 11/1). Encouraged by this result, we selected triethylborane as a coupling partner and performed the reaction under similar reaction conditions.

The three-component reaction proceeded as designed, and the corresponding (*Z*)-*anti*-homoallylic alcohol **4aa** was obtained in good yield along with **5aa**. Notably, allylation of aldehydes with

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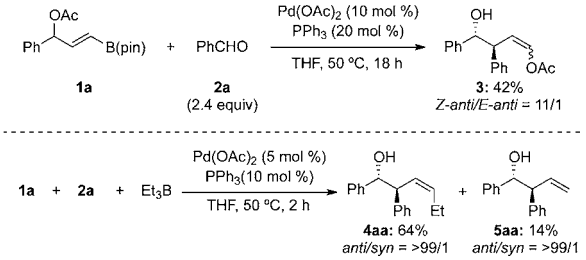
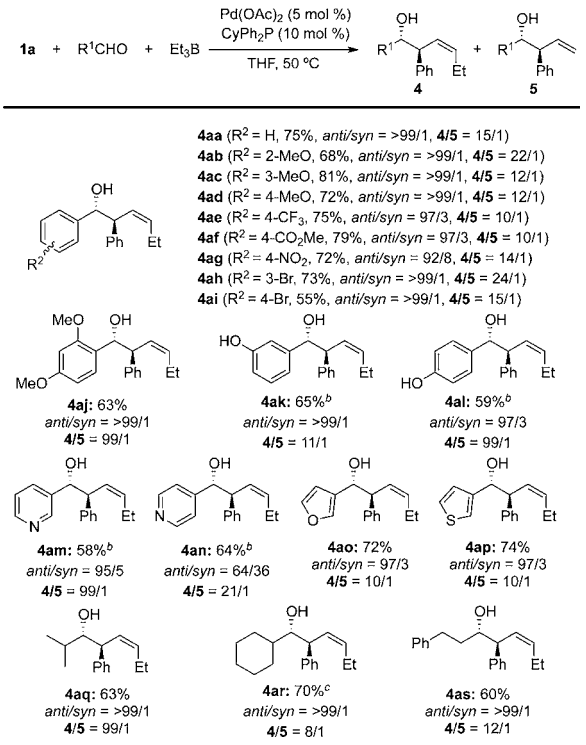
Scheme 2. Initial Studies for Palladium-Catalyzed Three-Component Reaction



Scheme 3. Reaction Scope of Aldehydes[a]

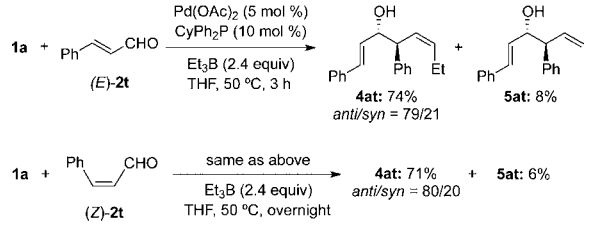


[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.2 mmol), $(R^3)_3B$ (1.2 mmol), $Pd(OAc)_2$ (5 mol %), and $CyPh_2P$ (10 mol %) in THF at 50 °C. The ratio of compounds **4** and **5** was determined by NMR analysis of the crude mixtures. [b]3.6 equiv of Et_3B were used. [c]$Pd_2(dba)_3CHCl_3$ (2.5 mol %), $(o\text{-tol})_3P$ (10 mol %), AcOK (2.4 equiv), and toluene as a solvent were used.

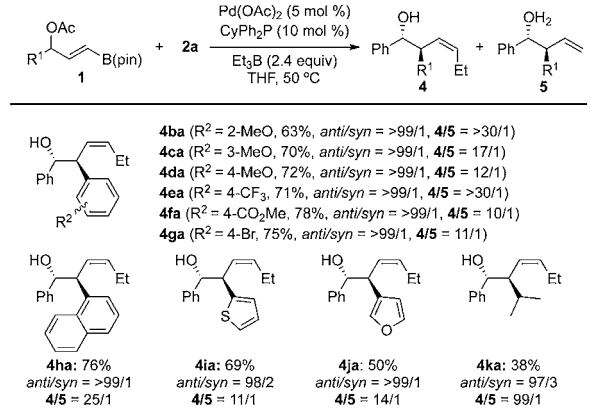
α-substituted allyl/crotylboronates often gives low E/Z selectivity.[8,9]

Under optimized reaction conditions,[10] the scope of various aldehydes was examined (Scheme 3). The reaction of **1a** and triethylborane with electron-rich and -deficient aromatic aldehydes gave **4ab**−**4ag** and **4aj**, respectively, in good to high yields with high levels of diastereoselectivity and complete alkene stereocontrol. In addition, bromo-substituted benzaldehydes were also suitable electrophiles for the reaction, affording **4ah** and **4ai** in good yields. Notably, 3- and 4-hydroxybenzaldehydes were utilized without prior protection of the hydroxyl group, although 3.6 equiv of Et_3B were required to achieve satisfactory reaction progress. Furthermore, the present reaction was also effective for the heterocyclic aldehydes, such as pyridyl-, furyl-, and thienyl-substituted heterocyclic aldehydes, giving **4am**−**4ap** in good yields. In this case, poor diastereoselectivity was observed when the 4-pyridinecarboxaldehyde was employed.

Scheme 4. Palladium-Catalyzed Three-Component Reaction of 1a, Cinnamaldehydes, and Triethylborane



Scheme 5. Substrate Screening[a]



[a]The ratio of compounds **4** and **5** was determined by NMR analysis of the crude mixtures.

Furthermore, not only aromatic aldehydes but also aliphatic aldehydes participated in the present reaction to afford the corresponding products **4aq**−**4as** in good yields. A beneficial effect on the chemical yield of **4ar** was observed when AcOK was added. However, this effect was limited to product **4ar**.[10] Moreover, the reaction of (*E*)-**2t** also proceeded smoothly to provide **4at** in good yield with modest diastereoselectivity (Scheme 4). On the other hand, when (*Z*)-**2t** was subjected to the reaction, the reaction time required to achieve full conversion was longer than that required by (*E*)-**2t** and provided **4at** in good yield. This reaction probably proceeded after isomerization of (*Z*)-**2t** to (*E*)-**2t** because (*Z*)-**2t** was recovered as (*E*)-**2t** after the reaction.

To demonstrate the scope of the present reactions, substituents at the C1 position of **1** were surveyed under optimized reaction conditions (Scheme 5). It was found that the reaction proceeded smoothly irrespective of the electronic nature of the substituent on the aromatic ring to give **4ba**−**4ja** in good yields with high diastereoselectivity and complete alkene stereocontrol. With respect to the isopropyl-substituted substrate **1k**, the reaction proceeded smoothly to provide **4ka** in moderate yield; a mixture of a stereoisomer of alkene geometry and the β-hydride elimination product of **1k** was obtained in 25% yield. We subsequently reacted **1** with benzaldehyde (**2a**) and various organoboranes to demonstrate the generality of the coupling reaction (Scheme 6). The scope with respect to the tri-*n*-alkylboranes was demonstrated to be fairly broad. For example, tri-*n*-alkylboranes prepared from styrene, 4-methoxystyrene, allylbenzene, and 1-hexene with the $BH_3{\cdot}SMe_2$ complex nicely participated in the coupling reaction to give **6a**−**6d**, respectively, in good yields with excellent stereoselectivity. In addition, a commercially available tri-*n*-butylborane also underwent a cross-coupling reaction to afford **6e** in 55% yield. Although trace

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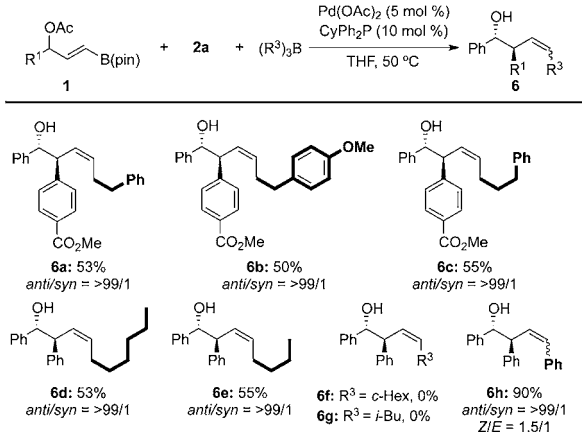
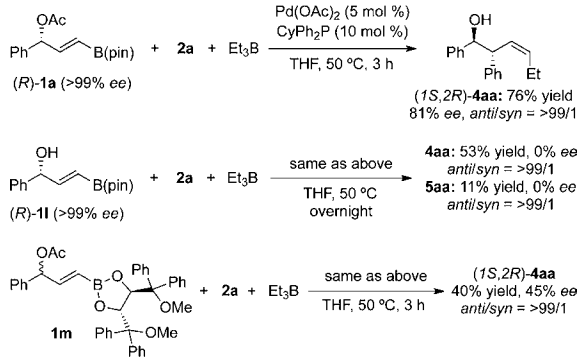
Scheme 6. Reaction Scope of Organoboranes[a]



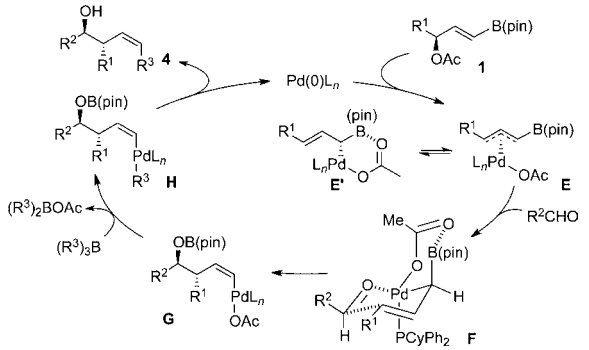
[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.2 mmol), $(R^3)_3B$ (1.5 mmol), $Pd(OAc)_2$ (5 mol %), and $CyPh_2P$ (10 mol %) in THF at 50 °C.

Scheme 7. Chirality Transfer Reactions



amounts of protodepalladation products **5** were observed by NMR analysis of the crude mixtures in all cases, **5** could not be isolated. On the other hand, the present reaction did not proceed with tri-*sec*-alkylboranes such as tricyclohexylborane and tri-*sec*-butylborane; however, the use of Ph_3B provided the desired product **6h** in high yield as a mixture of (*E*)- and (*Z*)-isomers.[11] Another attempt to use *B*-alkyl-9-BBN and alkyl boronate esters did not result in any conversion. To further expand the scope of the reaction from a synthetic viewpoint, we conducted a chirality transfer experiment using (*R*)-**1a** under optimized reaction conditions (Scheme 7). Intriguingly, to our delight, an efficient chirality transfer was observed, and the inversion product **4aa** was obtained in 76% yield. The absolute stereochemistry of **4aa** was determined to be (1*S*, 2*R*) by transformation into known diols.[10] To address the racemization process, (*R*)-**1a** was treated with a catalytic amount of $Pd(OAc)_2$ (5 mol %) and $CyPh_2P$ (10 mol %) in THF at 50 °C for 3 h. In fact, (*R*)-**1a** was recovered in 56% yield without significant loss in optical purity (97% *ee*).[10] To gain additional insights into the reaction mechanism, (*R*)-**1l** was also applied to a chirality transfer experiment under the same reaction conditions since allylic alcohols can be used directly for the generation of η^3-allylpalladium intermediates in the presence of organoboranes.[14] As a consequence, unexpectedly, a chirality transfer was not observed (0% *ee*, 52% yield). A similar efficient chirality transfer experiment was reported in a Tsuji–Trost allylic alkylation.[12,13] However, these results show that leaving groups affect the chirality transfer in boryl-substituted η^3-allylpalladium-

Scheme 8. A Plausible Reaction Mechanism



mediated transformations. In addition, alkenylboronate **1m** that introduced stereogenic centers onto the boronic ester moiety also enables a chirality transfer reaction.[15] Consequently, chirality transfer into the product was observed in 45% *ee*.

Based on the results described above, a preliminary reaction mechanism is described in Scheme 5. First, oxidative addition of **1** to a palladium complex should lead to an η^3-allylpalladium intermediate **E**. To rationalize the stereochemical outcome of the reaction as shown in Scheme 8, the palladium atom in η^1-allylpalladium intermediate **E′** (depicted in another η^1-allyl form for simplicity) instead of the boron atom in an allylboronate moiety would coordinate to an aldehyde to form a putative *cis*-decalin-like transition state **F**.[16] Accordingly, the transition state is cyclic for an η^1-allylpalladium moiety and is open-chain for an allylboronate moiety. Because the oxygen atom of an acetoxy group can coordinate intramolecularly to the boron atom, this would mask the Lewis acidity of the boron atom and instead consequently enhance the ability of that of the palladium atom in **E′**. Furthermore, due to the formation of **E′**, racemization of the substrate would be restrained. Thus, the nucleophilic allylation of an aldehyde by an allylboronate takes place to form a (*Z*)-vinylpalladium acetate intermediate **G**. This reasonably can explain the observed chirality transfer. Finally, the transmetalation of **G** with an organoborane followed by reductive elimination from a vinylpalladium intermediate **H** gives the desired product **4**.

Yet, β-hydride elimination from **H** followed by reductive elimination of the resulting palladium hydride intermediate leads to product **5**. The present reaction mechanism via a formation of **F** is not a common path, however, other plausible reaction paths involving a closed transition state controlled by allylboronates do not match the observed chirality transfer.[17] For example, if **E′** reacts with an aldehyde in a fashion similar to Hoffman's reaction of aldehydes with α,γ-substituted crotylborane reagents, the overall transformation would lead to an opposite stereoisomer.[8a,b] Another interesting mechanistic feature of this reaction is that the C–Pd bond is maintained during the two processes because Pd-catalyzed tandem reactions usually proceed with breaking of the initially formed C–Pd bond to form the next C–Pd bond.[18]

In summary, we have developed a Pd-catalyzed three-component coupling reaction that provides access to a wide variety of (*Z*)-*anti*-homoallylic alcohols from easily accessible and stable 3-(pinacolatoboryl)allyl acetates, aldehydes, and organoboranes. Interestingly, the palladium complex and allylboronates function cooperatively in this process. This outstanding reactivity of allylic *gem*-palladium/boryl intermediates promises to serve as a powerful strategy for the development

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of η^3-allylpalladium-mediated transformations. Further investigations along these lines are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, and HRMS for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01244.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 8 has been updated. The revised version was posted on June 5, 2015.

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