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Palladium-Catalyzed Diastereoselective Synthesis of Homoaldol Equivalent Products

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ABSTRACT

A palladium-catalyzed reaction of easily accessible 3-(pinacolatoboryl)allyl acetates and aldehydes provides facile access to synthetically useful homoaldol equivalent products with high diastereoselectivity. The reaction presumably proceeds via allylation of aldehydes with α-acetoxy allylboronates that produced in situ by reductive elimination from allylic *gem*-palladium/boryl intermediates.

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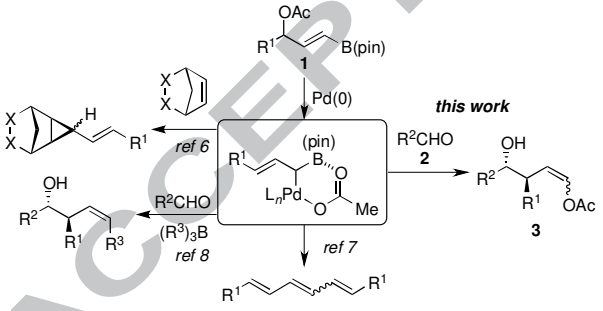
Introduction

Devising synthetic strategies for constructing molecular complexity and diversity from simple reagents is an important subject in organic synthesis. In particular, catalytic synthetic strategies can offer enormous advantages for such purposes because they can individually generate several intermediates that react in different manners from the same reagent. Allylpalladium species are one representative example. For example, π-allylpalladium species are generally recognized to serve as synthetically useful electrophilic allylating agents toward many nucleophiles.[1] In contrast, σ-allylpalladium species possessing ligands that donate electrons acts as nucleophilic allylating agents toward electrophiles.[2] Moreover, umpolung reaction of π-allylpalladium alters its reactivity pattern to nucleophilic.[3,4] Fillion and our recent studies on allylic *gem*-heterobimetallic species revealed individually that the distinct reactivities of allylic *gem*-palladium/metalloid species cannot be reached by hitherto reported allylpalladium species.[5-8] For example, the allylic *gem*-palladium/boryl species take part in the stereoselective cyclopropanation of strained alkenes,[6] carbene dimerization reaction,[7] and three-component coupling reaction with aldehydes and triorganoboranes (Scheme 1).[8] During the course of our study of three-component coupling reactions, a palladium-catalyzed methodology for diastereoselective synthesis of homoaldol equivalent products was discovered during a control reaction attempt in the absence of a triorganoborane; the palladium-catalyzed reaction of 3-(pinacolatoboryl)allyl acetates **1** and aldehydes **2** gave *anti*-(*Z*)-*δ*-hydroxy vinyl acetates **3** with high levels of diastereoselectivity and alkene stereocontrol.[8a]

Since the pioneer work of Nakamura and Kuwajima on the catalytic homoaldol reactions,[9,10] generation of homoenolates and homoenolate equivalents using transition-metal catalysts and organocatalysts have emerged as strategically different approaches.[11-13] In addition, catalytic asymmetric versions have also been developed.[14] Although significant progress has been made in this area, the diastereoselective synthesis of homoaldol equivalent products by catalytic processes still needs to be explored.[15] Herein, we report a palladium-catalyzed methodology for the diastereoselective synthesis of homoaldol equivalent products.

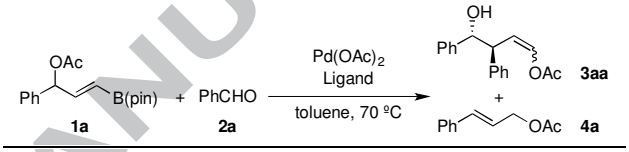


Scheme 1. Distinct reactivities of allylic *gem*-palladium/boryl species.

Results and discussion

We initially optimized the reaction conditions for the palladium-catalyzed reaction of (1-phenyl-3-pinacolatoboryl)allyl acetate (**1a**) as a model substrate with benzaldehyde (**2a**) by evaluating various ligands (Table 1). The $Pd(OAc)_2/PPh_3$ catalytic system provided a *anti*-homoaldol equivalent product **3aa** in 60% yield, accompanied by **4a** (entry 1). The relative stereochemistry of **3aa** was determined to be *anti* by derivatization to give a literature known material (see the Supplementary Material). It was found that both the electronic nature and the amount of the phosphine ligand play an important role in improving the yield of **3aa** (entries 2–4). However, a non-negligible amount of **4a** was also obtained. The enhancement of the Brønsted base character of the carbon atom between the palladium and the pinacolatoboryl group in allylic *gem*-palladium/pinacolatoboryl species presumably induces protodeboronation to form **4a**.[5,6] However, addition of MS 4A to prevent the formation of **4a** by residual H_2O failed (entry 6).[7] Although the catalyst loading could be reduced to 5 mol% without significant loss of catalytic activity, we were pleased to find that use of an excess amount of **2a** (3 equiv to **1a**) improved the yield of **3aa** (entry 7). Besides the monodentate phosphine ligand, use of bidentate phosphine ligands also efficiently promoted the present reaction (entries 8–12). Among them, Xantphos[16] exhibited the comparable results with $(p\text{-}CF_3C_6H_4)_3P$ (entries 7 and 12). In all cases, the relative configuration of the two newly formed stereogenic centers is *anti* (*anti*/*syn* >20/1), and the *Z*-isomer was the primary product.

Table 1
Optimization of reaction conditions[a]



Entry	$Pd(OAc)_2$ (mol%)	Ligand (mol%)	**3aa** (%)	**3aa** (*Z*/*E*)	**4a** (%)
1	10	Ph_3P (20)	60	7/1	2
2	10	$(p\text{-}MeOC_6H_4)_3P$ (20)	53	8.2/1	19
3	10	$(p\text{-}CF_3C_6H_4)_3P$ (20)	71	9/1	0
4	10	$(p\text{-}CF_3C_6H_4)_3P$ (30)	77	9.4/1	7
5	5	$(p\text{-}CF_3C_6H_4)_3P$ (15)	64	10/1	19
6[b]	5	$(p\text{-}CF_3C_6H_4)_3P$ (15)	38	8/1	38
7[c]	5	$(p\text{-}CF_3C_6H_4)_3P$ (15)	84	9/1	12
8	10	DPEphos (10)	33	10/1	4
9	10	DPPPent (10)	60	8.3/1	14
10	10	Xantphos (10)	62	10/1	13
11	5	Xantphos (5)	61	9.6/1	13
12[c]	5	Xantphos (5)	83	10/1	11

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$, and ligand [DPEphos = 2,2'-bis(diphenylphosphino)diphenyl ether, DPPPent = 1,5-bis(diphenylphosphino)pentane, Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene] in toluene (2 mL) at 70 °C for 1–6 h.
[b]MS 4A (500 mg) was used.
[c]PhCHO (3 equiv) was used.

Having determined the optimal conditions (Table 1, entry 12), the substrate scope with regard to aldehydes **2** was first explored by reactions with **1a** (Table 2). It was found that a broad range of aromatic aldehydes was tolerated. Indeed, the reaction proceeded without being influenced by the electronic nature of the substituent to afford **3ab–3ag**. Unfortunately, 4-bromobenzaldehyde and 4-hydroxybenzaldehyde did not take part in the reaction. Altough 2-thiophenecarboxaldehyde could be transformed effectively into its corresponding products **3ah** in

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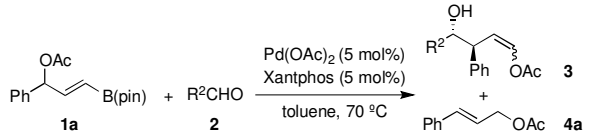
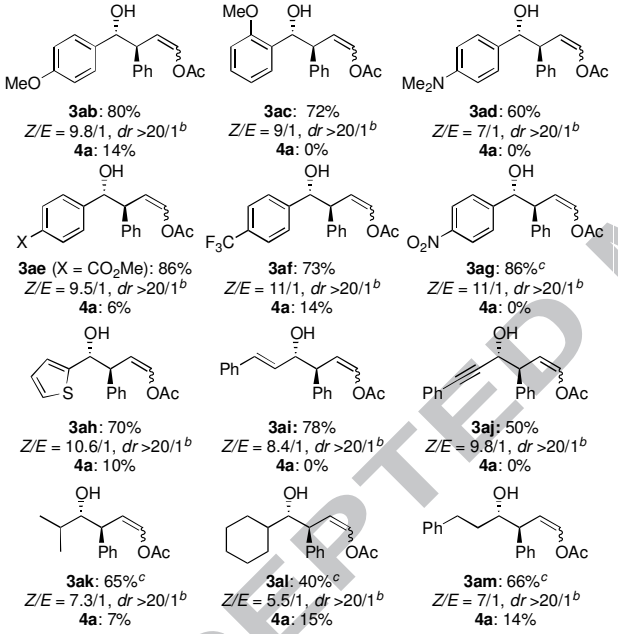
70% yield with excellent diastereoselective fashion, the use of 3- and 4-pyridinecarboxyaldehyde resulted in no reaction. Additionally, α,β-unsaturated aldehydes also underwent the current homoaldol equivalent reaction to give **3ai** and **3aj**, respectively. Although substantially less reactive aliphatic aldehydes also took part in the palladium-catalyzed homoaldol equivalent reaction, the desired products were isolated in lower yield. For example, **3ak** and **3am** were obtained in 55% and 56% yields, respectively. However, this problem was overcome when $(p\text{-}CF_3C_6H_4)_3P$ was employed as a ligand, giving **3ak** and **3am** in 65% and 66% yields, respectively. On the other hand, a moderate isolated yield of **3al** was still observed with cyclohexanecarboxaldehyde. In all cases, the excellent diastereoselectivities were observed for all aldehydes examined.

Table 2
Screening of aldehydes[a]

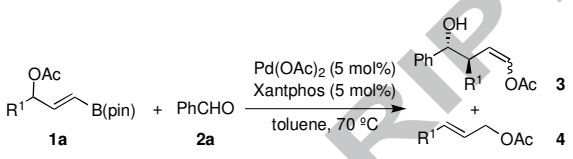


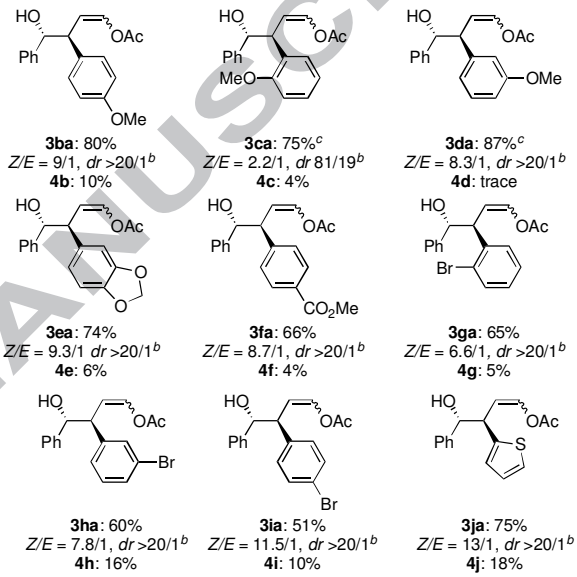


[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (5 mol%), and Xantphos (5 mol%) in toluene (2 mL) at 70 °C for 1–3 h.
[b]The relative stereoconfiguration was determined by analogy.
[c] $(p\text{-}CF_3C_6H_4)_3P$ (15 mol%) was used instead of Xantphos.

Next, we examined the substrate generality of the reaction. A variety of aryl-substituted substrates were subjected to the reaction conditions (Table 3). In general, both substrates with electron-withdrawing and electron-donating substituents on aromatic ring took part in the reaction to produce the corresponding products **3ba–3ia** in good to high yield. Although use of Xantphos as a ligand gave **3ca** and **3da** in 32% and 42 % yields, respectively, changing Xantphos to $(p\text{-}CF_3C_6H_4)_3P$ improved the chemical yield. The substrate bearing a methoxy-substituent at the *ortho* position on the aromatic ring gave **3ca** with moderate diastereoselectivity (*dr* = 81/19). Notably, *o*-bromo-, *m*-bromo-, and *p*-bromo-substituted-phenyl substrates were also compatible with the present reaction conditions, providing **3ga–3ia** in 65%, 60%, and 51% yields, respectively, and the C–Br bond remained intact. This protocol tolerated a heterocycle-substituted substrate such as 2-thienyl, and provided a corresponding homoaldol equivalent product **3ja** in 75% yield. Unfortunately, only trace amounts of desired product were obtained when alkyl-substituted substrates such as methyl- and cyclohexyl-substituted substrates were applied. Moreover, use of ketones such as acetophenone and 1,2-cyclohexanedione instead of aldehydes did not produce the desired homoaldol equivalent products.

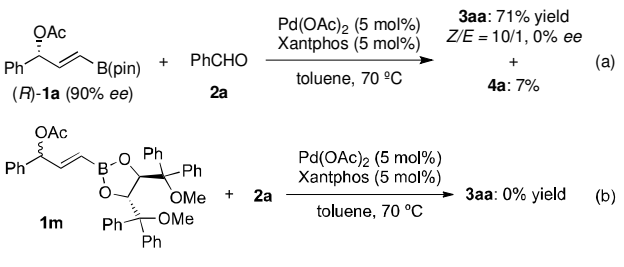
Table 3
Substrate Scope[a]





[a]Conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (5 mol%), and Xantphos (5 mol%) in toulene (2 mL) at 70 °C for 1-3 h.
[b]The relative stereoconfiguration was determined by analogy.
[c]$(p\text{-}CF_3C_6H_4)_3P$ (15 mol%) was used instead of Xantphos.

To gain insights into the reaction mechanism, a chirality transfer experiment using (*R*)-**1a** was first performed under optimum reaction conditions (Scheme 2a). Unlike in the case of our previous work, **3aa** was produced as a racemic form.[8a] In addition, the use of **1m** possessing stereogenic centers onto the boronic ester moiety resulted in no conversion, and **1m** was recovered (Scheme 2b).[17]



Scheme 2. Chirality transfer reactions.

A preliminary reaction mechanism is depicted in Scheme 3. First, oxidative addition of **1** to a palladium complex forms an η^3-allylpalladium intermediate **A**. Then, reductive elimination from allylic *gem*-palladium/boryl intermediate **A′** (for simplicity,

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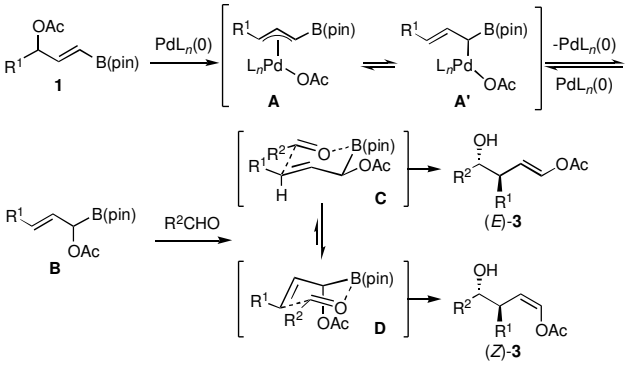
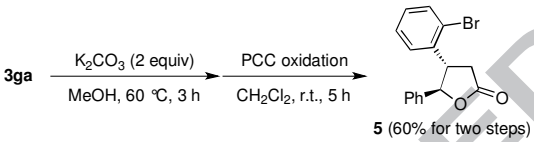
another η^1-allyl form is not depicted) would produce α-acetoxy allylboronate **B**. This step presumably involves isomerization through η^3-allylpalladium complex, which may account for the observed no chirality transfer as shown in Scheme 2a. Finally, allylboration of aldehyde via two competing chair-type transition states **C** and **D** takes place. Since the acetoxy substituent is a polar group, allylboration proceeds predominately via transition state **D** to give (*Z*)-*anti*-**3**.[15c, 18, 19]



Scheme 3. A plausible reaction path.

To evaluate the utility of the homoaldol equivalent products obtained in this study, **3ga** was hydrolyzed under mildly basic conditions to provide the corresponding formal homoaldol product, which was subsequently converted into synthetically useful *trans*-β,γ-diaryl-substituted-γ-butyrolactone **5** in 60% yield followed by PCC oxidation (Scheme 4).[20]



Scheme 4. Hydrolysis and oxidation of a homoaldol equivalent product.

In summary, we have developed a palladium-catalyzed methodology for the diastereoselective synthesis of *anti*-homoaldol equivalent products, which provides access to a variety of synthetically useful compounds. Furthermore, the present methodology enhances the utility of allylic *gem*-palladium/boryl species, making it attractive alternative to various synthetic strategies.

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19. To figure out the process of isomerization of **1** to the corresponding allylboronate by palladium catalysis, (1-phenyl-3-pinacolatoboryl)allyl benzoate (**6**) was treated with a catalytic amount of $Pd(OAc)_2$ (5 mol%) and Xantphos (5 mol%) in toluene at 70 °C for 3 h. However, (3-phenyl-1-pinacolatoboryl)allyl benzoate (**7**) was not observed by NMR analysis of the crude mixtures. When the reaction was conducted for prolonged reaction time, it led to competitive protodeboronation to produce cinnamyl benzoate. Although Pd-catalyzed isomerization of **7** to **6** was also examined, decomposition of **7** was observed. Allylboronates are known to participate in allyl–allyl cross-coupling with allyl electrophiles, see: (a) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778–16781; (b) Amanda, H. L.; Morken, J. *Org. Lett.* **2014**, *16*, 2096–2099.
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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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Homoaldol equivalent products can be synthesized with high diastereoselectivity.

Pd complex promotes isomerization of 1-alkenylboronates to generate allylboronates.

Reaction involves allylboration of aldehydes with α-acetoxy allylboronates.

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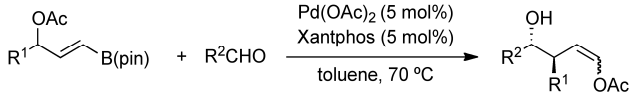

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