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Letter

Synthesis of (Z)-Alkene-Containing Linear Conjugated Dienyl Homoallylic Alcohols by a Palladium-Catalyzed Three-Component Reaction

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Abstract A synthesis of (*Z*)-alkene-containing linear conjugated dienyl homoallylic alcohols by using a palladium-catalyzed three-component reaction has been developed. This method shows good functional-group compatibility and generality, with high diastereoselectivity. Additionally, in many cases, the present method controls the alkene stereo-chemistry of the newly formed C–C bond and overcomes the inherent preference for (*E*)-alkene formation, giving (*Z*,*E*)- and (*Z*,*Z*)-products.

Key words allylation, homoallylic alcohols, palladium catalysis, multicomponent reaction, vinyl stannanes

Homoallylic alcohols that incorporate a (*Z*)-alkene-containing linear conjugated diene are widespread structural motifs in natural products such as lactimidomycin,¹ (6E,10*Z*)-2'-O-methylmyxalamide D,² macrolactin A,³ and spirangien A⁴ (Figure 1). In addition, they are also valuable building blocks in organic synthesis.⁵



Figure 1 Representative structures incorporating (*Z*)-alkene-containing linear conjugated dienyl homoallylic alcohols

Various dienylmetals (Sn, Si, In, Zn, Cr, or Ti)⁶ and α -(1,3dioxenylallyl)boronate⁷ have been successfully used for the allylation of aldehydes to prepare dienyl homoallylic alcohols (Schemes 1a and 1b). However, these methods suffer from limitations in relation to the preparation of the requisite organometallic reagents, regioselectivity, and functional-group tolerance. In addition, the reaction generally gives a mixture of homoallylic alcohols containing linear conjugated (*E*,*E*)-diene (α -adduct) and skipped diene (γ -adduct) moieties, depending on the Lewis acid that is used.^{6b,8} Bisvinylogous Mukaiyama aldol reactions with the corresponding silvl ketene acetals furnish linear conjugated dienyl homoallylic alcohols with high selectivity at the remote γ -position.⁹ Although these methods are useful for the synthesis of linear conjugated (E,E)-dienyl homoallylic alcohols and their derivatives, formation of the corresponding (Z)alkenes remains a challenge.¹⁰ To overcome this problem, powerful catalytic methods have emerged, providing structurally diverse (Z)-alkene-containing linear conjugated dienyl homoallylic alcohols. For example, the Hiyama-Denmark cross-coupling reaction of 1-oxa-2-silacyclohex-3-enes with vinyl iodides permits facile access to the desired compounds (Scheme 1c).¹¹ However, its application to diastereoselective reactions has not yet been reported. To the best of our knowledge, there exists only one report on a stereoselective synthesis of (Z)-alkene-containing linear conjugated dienyl homoallylic alcohols by a Suzuki-Miyaura cross-coupling reaction of 1,2-oxaborinan-3-enes (Scheme 1d).¹² Although this is an elegant synthetic transformation, the development of synthetic methods to access this important structural motif from easily accessible reagents still remains a challenge.

We have previously developed the stereoselective synthesis of (*Z*)- and (*E*)-homoallylic alcohols by a palladiumcatalyzed three-component reaction of aldehydes, γ -borylated allylic benzoates, and aryl stannanes (Scheme 1e).¹³

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^a Reaction conditions: **1a** (1.2 mmol), **2a** (0.5 mmol), **3a** (0.75 mmol), Pd(OAc)₂ (5 mol%), ligand (10 mol% for monodentate, 5 mol% for bidentate), solvent (4 mL), 70 °C, under Ar.

^b Isolated yield.

^c Determined by ¹H NMR analysis of the crude reaction mixture.

^d CPME = cyclopentyl methyl ether.

e LiCl (1.5 mmol) was added.

We envisaged that the use of vinyl stannanes instead of aryl stannanes might lead to a related reaction. However, this would be particularly remarkable, given the large thermodynamic preference for the (*E*,*E*)-isomer over the (*Z*,*E*)product.¹⁰ With the notion that our method had the potential to provide (*Z*)-alkene-containing linear conjugated dienyl homoallylic alcohols, we examined the palladium-catalyzed three-component reaction of aldehydes, γ -borylated allylic acetates, and vinyl stannanes.

In our initial investigation, we chose the reaction of benzaldehyde (1a), boronate 2a, and vinylstannane 3a as a model reaction to optimize the reaction conditions (Table 1).¹⁴ As observed in our previous work (Scheme 1e),¹³ the use of $(4-\text{MeOC}_6H_4)_3P$ as a ligand was effective in promoting the formation of (*Z*,*E*)-**4aaa** in 43% isolated yield with high levels of alkene stereocontrol and high diastereoselectivity (Table 1, entry 1). Among the phosphine ligands tested, PPh₃ showed the best result and afforded (Z,E)-4aaa in 60% yield with high stereocontrol (entries 1-5). In this context, a prolonged reaction time did not lead to isomerization of (Z,E)-4aaa to (E,E)-4aaa. 1,5-Bis(diphenylphosphino)pentane (DPPPent) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), which showed good catalytic activities in our previous studies,13 were ineffective (entries 6 and 7). Among the solvents tested, the use of THF gave the best results (entries 3 and 8-11). Moreover, addition of LiCl, which often has a positive effect in Migita–Kosugi–Stille coupling reactions,¹⁵ had a profoundly detrimental effect, causing a large reduction in both chemical yield and alkene stereocontrol (entry 12). Although efforts were also made to vary the other reaction parameters, such as the reaction temperature, the ratio of reagents, the ratio of ligands, and the leaving group, no further improvement in the yield of **4aaa** was observed. Product **4aaa** was carefully confirmed as having an *anti*-configuration by its derivatization to a known compound.¹⁶

With the optimal reaction conditions in hand, we next assessed the reaction scope by using various aldehydes 1 with 2a and 3a (Scheme 2a).¹⁴ The reaction appeared to be sensitive to the electronic properties of the aromatic aldehydes. For example, although the reaction with *p*-anisaldehyde gave 4baa in 51% yield with good alkene stereocontrol, the reaction with aromatic aldehydes possessing an electron-withdrawing (trifluoromethyl, nitro, or methoxycarbonyl) group in the para-position proceeded to afford 4caa-eaa in 53-69% yields with high levels of alkene stereocontrol. Nevertheless, high diastereoselectivities were observed for all of the aromatic aldehydes examined.¹⁶ In the case of aliphatic aldehydes, the present threecomponent reaction could be successfully applied to hydrocinnamaldehyde and isobutyraldehyde to give 4faa and 4gaa in yields of 58 and 38%, respectively, with moderate to good alkene stereoselectivity.

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Next, we examined the generality of the reaction toward various boronates 2 (Scheme 2b), and we found that the electronic properties and the position of the substituent group on the aryl ring of 2 influenced the reactivity and the stereocontrol of the alkene product. For example, the presence of an electron-donating substituent, such as a methoxy group, at either the ortho- or para-position of the aromatic ring decreased the alkene stereocontrol in the homoallylic alcohols products 4aba and 4aca, which were obtained in yields of 66 and 48%, respectively. In contrast, 4ada and 4aea were obtained with high levels of alkene stereocontrol when *m*-chloro or *p*-trifluoromethyl groups were present on the aromatic ring. In addition, the 4-bromo- and 2-thienyl-substituted substrates 2f and 2g, respectively, were compatible with the reaction conditions, and produced the corresponding products 4afa and 4aga in moderate yields but with high levels of alkene stereocontrol. Attempts to use substrates substituted with an alkyl group, such as a hydrocinnamyl group, resulted in complex mixtures containing the β -hydride elimination product.

Finally, the generality of the reaction toward the vinylstannane was studied (Scheme 2c) and it was found that the alkene stereochemistry of the newly formed C-C bond depended on the substituents on vinylstannane. For example, (E)-vinylstannanes 3b and 3c afforded the corresponding products 4aab and 4aac with good to high levels of Letter

(Z|F)



Scheme 2 Scope of the palladium-catalyzed three-component reaction. Reagents and conditions: 1 (1.2 mmol), 2 (0.5 mmol), 3 (0.75 mmol), Pd(OAc)₂ (5 mol%), PPh₃ (10 mol%), THF (4 mL), 70 °C, 2-3 h. ^aThe Z/E ratios were determined by ¹H NMR analysis of the crude reaction mixture.

alkene stereocontrol. In contrast, moderate levels of alkene stereocontrol were observed in the formation of 4aad and **4aae** when β -(tributylstannyl)styrene (**3d**) and trimethyl[2-(tributylstannyl)vinyl]silane (3e), respectively, were used. Unfortunately, an attempt to use (E)-vinylstannanes

reoselectivity. Additionally, in many cases, the present method provides control of the alkene stereochemistry of the newly formed C-C bond and overcomes the inherent preference for (*E*)-alkene formation, giving (Z,E)- and (Z,Z)-

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products.

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Supporting Information

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bearing a triisopropylsilyl group in a vicinal position, for (E)-triisopropyl[2-(tributylstannyl)vinyl]silane example, (3f), failed in this three-component reaction, presumably as a result of steric hindrance caused by the triisopropylsilyl group. In addition, (E)-3-(tributylstannyl)prop-2-en-1-ol (**3g**) and methyl (*E*)-3-(tributylstannyl)prop-2-enoate (**3h**) did not engage in the present reaction; instead, a trace amount of the palladium-catalyzed coupling product of boronate **2a** with the vinylstannane **3** was observed.¹⁷

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In an attempt to expand the scope of the vinylstannane, the reaction was performed with the sterically encumbered vinvlstannane (Z)-**3a** (Scheme 3). However, a decreased alkene stereoselectivity was observed for the newly formed bond (Z/E = 8:1), and (Z,Z)-4aaa was obtained in 38% yield. In this context, unreacted (Z)-**3a** was recovered without any isomerization after the reaction.



nvlstannane

The scalability of this three-component reaction was demonstrated by an experiment scaled up to a gram scale of 2a, in which 4aaa was produced in 50% yield (Scheme 4).



Furthermore, to evaluate the usefulness of the hydroxy and conjugated dienyl groups, a manipulation of the homoallylic alcohol 4aaa obtained in this study was performed (Scheme 5). A vanadium-catalyzed hydroxy-directed epoxidation reaction¹⁸ [VO(acac)₂ (2 mol%), t-BuOOH] afforded epoxide syn-7 in 55% isolated yield (dr > 20:1).



In conclusion, we have developed a diastereoselective synthesis of (Z)-alkene-containing linear conjugated dienyl homoallylic alcohols by using a palladium-catalyzed threecomponent reaction of aldehydes, γ -borylated allylic acetates, and vinylstannanes. This method shows good functional-group compatibility and generality, with high diasteY. Horino et al.

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A 10 mL, two-neck, round-bottomed flask was charged with $Pd(OAc)_2$ (11.2 mg, 0.1 mmol), Ph_3P (26.4 mg, 0.2 mmol), and THF (1 mL), and the mixture was stirred at 70 °C for 0.5 h. A solution of **1a** (151.1 mg, 0.5 mmol), PhCHO (**2a**; 123 µL, 1.2 mmol), and vinylstannane **3a** (346.1 mg, 0.75 mmol) in THF (3

mL) was then added, and the mixture was then stirred at 70 °C for 2 h until the reaction was complete. The resulting mixture was diluted with EtOAc (10 mL) and washed with sat. aq NH₄Cl (2 × 10 mL), sat. aq NaHCO₃ (2 × 10 mL), and brine (2 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated, and the residue was purified by chromatography [silica gel, EtOAc-hexane (1:4)] to give a yellow oil; yield: 118.4 mg (60%); R_f = 0.41 (EtOAc-hexane, 1:4).

- ¹H NMR (400 MHz, CDCl₃): δ = 7.23–7.12 (m, 8 H), 7.07 (dm, *J* = 7.6 Hz, 2 H), 6.58 (dd, *J* = 11.2, 14.8 Hz, 1 H), 6.27 (t, *J* = 11.2 Hz, 1 H), 5.87 (t, *J* = 10.4 Hz, 1 H), 5.79 (td, *J* = 4.4, 14.8 Hz, 1 H), 4.84 (d, *J* = 7.6 Hz, 1 H), 4.22 (d, *J* = 4.4 Hz, 2 H), 4.04 (dd, *J* = 7.6, 10.4 Hz, 1 H), 2.22 (s, 1 H), 0.94 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 142.0, 141.2, 134.9, 131.4, 129.5, 128.5, 128.4, 128.0, 127.5, 126.72, 126.66, 124.4, 78.1, 63.4, 53.0, 26.1, 18.5, -5.1. HRMS (EI): *m/z* [M OH]⁺ calcd for C₂₅H₃₃OSi: 377.2295; found: 377.2260.
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