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A highly selective synthesis of 1-substituted (*E*)-buta-1,3-dienes with 4,4,5,5-tetramethyl-2vinyl-1,3,2-dioxaborolane as building block

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Highly selective synthesis of 1-substituted (*E*)-buta-1,3-dienes via palladium-catalyzed Suzuki–Miyaura cross-coupling of (*E*)-alkenyl iodides with 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1) is reported. The vinylboronate pinacol ester (1) acts as a vinyl building block to show high chemoselectivity for the Suzuki–Miyaura pathway versus Heck coupling in the presence of biphasic conditions (Pd(PPh₃)₄, aqueous K₂CO₃, toluene and ethanol). Copyright © 2014 John Wiley & Sons, Ltd.

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Introduction

The palladium-catalyzed Suzuki–Miyaura reaction of aryl or alkenyl halides with organoboronic acids represents a straightforward and highly effective method for carbon–carbon bond formation.^[1] The Suzuki–Miyaura reaction also provides a versatile method for the vinylation of aryl and alkenyl halides; however, it is plagued by a number of drawbacks. Vinylboronic acids are readily polymerized and cannot be isolated.^[2] Furthermore, vinylboronic esters are not selective in cross-coupling reactions, yielding mixtures of Suzuki–Miyaura and Heck coupled products.^[3] Many of the recent development efforts on the cross-coupling reaction have been focused on the catalyst system and boronate coupling partners that facilitate Suzuki–Miyaura cross-coupling and expand its scope.

Pinacol vinylboronate ester – 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Fig. 1, compound **1**) – undergoes both Suzuki–Miyaura and Heck cross-coupling with aryl halides to give a mixture of styrenes and styryl boronates, depending upon the reaction conditions.^[4] Whiting and co-workers reported that 4,4,6trimethyl-2-vinyl-1,3,2,-dioxaborinane (Fig. 1, compound **2**) can act as an alternative two-carbon alkenyl building block, being able to react selectively via either Heck^[5] or Suzuki–Miyaura^[6] pathways.

On the other hand, there are only a few examples of the synthetic application of commercially available vinylboronate pinacol ester **1** in the selective synthesis of buta-1,3-diene derivatives. Whiting and co-workers reported selective coupling of (*Z*)-iodoacrylate with **1** in the presence of a Pd(OAc)₂/Ag₂CO₃ catalytic system.^[7] Selective vinylation of (*Z*)-alkenyl iodide by **1** has also been developed during studies on the synthesis of herbicide phthoxazolin A.^[3a] More recently, vinylboronate pinacol ester **1** has been used as building block to form a diene side chain in the synthesis of structural analogues of macrocyclic product (–)-exiguolide.^[8] The buta-1,3-diene unit was introduced stereoselectively via Suzuki–Miyaura coupling of macrocyclic (*E*)-alkenyl iodide with **1** in the presence of a [Pd₂(dba)₃]/Ph₃As/Ag₂O catalytic system.^[8]

Herein, we report an improved protocol for the highly chemoand stereoselective synthesis of 1-substituted (*E*)-buta-1,3-dienes based on catalytic coupling of (*E*)-alkenyl iodides with commercially available 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane **1** which applies classical biphasic Suzuki–Miyaura conditions without use of any silver additive.

Experimental

General Procedure for the Synthesis of (E)-Buta-1,3-dienes

A mixture consisting of the following components added in order – (*E*)-alkenyl iodide (1 mmol) $Pd(PPh_3)_4$ (0.05 mmol), vinylboronate pinacol ester **1** (1.1 mmol), 1 M aqueous K_2CO_3 (3.0 ml) and ethanol (0.88 ml) in toluene (10 ml) – was placed in a 50 ml Schlenk bomb flask fitted with a plug valve and heated at 55 °C for 24 h. After cooling the reaction mixture to room temperature, the organic layer was extracted with toluene. The organic layer was concentrated and the product was purified by column chromatography on silica gel, eluting with *n*-hexane–EtOAc (98:2).

(E)-2-(Buta-1,3-dien-1-yl)isoindoline-1,3-dione (2f)



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Figure 1. Vinylboronic esters: 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1) and 4,4,6-trimethyl-2-vinyl-1,3,2,-dioxaborinane (2) (Whiting ester).

¹H NMR (300 MHz, CDCl₃): δ = 5.18 (dd, 1H, *J* = 10.0, 1.6 Hz, =CH₂), 5.36 (dd, 1H, *J* = 16.9, 1.6 Hz, =CH₂), 6.32–6.44 (m, 1H, -CH=CH₂), 6.84–6.89 (m, 1H, >N-CH=CH-), 7.24 (d, 1H, *J* = 14.4 Hz, >N-CH=CH-), 7.73–7.78 (m, 2H, Ar), 7.85–7.89 (m, 2H, Ar). ¹³C NMR (CDCl₃, 75 MHz) δ = 120.4 (C9), 121.3 (C7), 123.6 (C4), 123.8 (C6), 131.7(C3), 134.5 (C5), 135.0 (C8), 166.2 (C2). MS *m*/*z* = 199 (M⁺, 100%), 198 (25), 170 (11), 133 (53), 115 (10), 105 (59), 104 (70), 77 (25), 76 (42), 50 (40). HRMS (*m*/*z*) = 199.0628, calcd for C₁₂H₉NO₂: 199.0633.

Crystal data (**2f**). $C_{12}H_9NO_2$, $M_r = 199.20$, orthorhombic, Pca2₁, a = 25.620(4) Å, b = 4.3552(9) Å, c = 18.247(3) Å, V = 2036.0(6) Å³, Z = 8, $d_x = 1.30$ g cm⁻³, Mo- K_α radiation ($\lambda = 0.71069$ Å), $\mu = 0.090$ cm⁻¹, T = 295(2) K, 24 598 reflections measured, 3534 symmetry independent ($R_{int} = 0.083$), 1421 with $I > 2\sigma(I)$), final R = 18.9%, wR2 = 37.7%, max/min $\Delta \rho = 1.25/-0.44$ e Å⁻³.

(E)-9-(Buta-1,3-dien-1-yl)-9H-carbazole (2g)



¹H NMR (300 MHz, C_6D_6): $\delta = 5.04$ (dd, 1H, J = 10.1, 1.8 Hz, =CH₂), 5.15 (dd, 1H, J = 16.4, 1.8 Hz, =CH₂), 6.36 (ddd, 1H, J = 16.4, 10.3, 10.1 Hz, -CH=CH₂), 6.53 (dd, 1H, J = 13.9, 10.3 Hz, >N-CH=CH-), 6.85 (d, 1H, J = 13.9 Hz, >N-CH=CH-) 7.19–7.39 (m, 6H, Cbz), 7.90–7.93 (m, 2H, Cbz). ¹³C NMR (75 MHz, C_6D_6): $\delta = 110.9$ (C11), 115.5 (C3), 120.2 (C5), 120.6 (C6), 121.1 (C9), 124.7 (C4), 126.5 (C10), 126.7 (C7), 135.3 (C8), 139.8 (C2). MS (EI) m/z (rel. int.): 219 (M⁺ 100%), 204 (10), 192 (5), 53 (5). Anal. calcd for C₁₆H₁₃N: C 87.64; H 5.98; N 6.39; found: C 87.88; H 6.18; N 5.94.

Results and Discussion

Classical Suzuki-Miyaura conditions have been employed for coupling tests, i.e. using tetrakis(triphenylphosphine)palladium(0) with nucleophilic oxygen bases. After several attempts we found that vinylation of (E)-styryl iodides by 1 occurs efficiently when K₂CO₃ is employed, whereas the use of t-BuOK or KOH led to formation of significant amounts of by-products such as 1,4-diarylbut-1-en-3-yne^[6] and Heck coupling products. (Scheme 1) thus the cross-coupling reactions of (E)-alkenyl iodides with 1 were carried out under biphasic reaction conditions (toluene (0.1 м), aqueous K₂CO₃ (3 equiv., 1 м) and ethanol (15 equiv.)).^[9] We believe that the role of ethanol is to activate the vinylborane for transmetalation with palladium.^[10] Suzuki-Miyaura coupling of 1 with selected (E)-styryl iodides (Table 1, entries 1-5) and (E)-N-(2-iodovinyl)phthalimide,^[11] as well as (E)-9-(2-iodovinyl)-9H-carbazole^[12] (Table 1, entries 6 and7), proceeded smoothly at 55 °C in the presence of Pd(PPh₃)₄ catalyst (5 mol%) to give





Scheme 1. Cross-coupling of (*E*)-alkenyl iodides with 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (**1**).



Figure 2. A perspective view of one of the molecules of **2f** with labeling scheme. Relevant geometrical parameters (in square brackets, values for molecule B): C10–C11 1.282(15) [1.336(17)], C11–C12 1.497(16) [1.493 (17)], C12–C13 1.214917) [1.299(19)], C10–C11–C12–C13 176.2(16)° [–178.8(15)°]. CCDC-957172.

the corresponding (*E*)-buta-1,3-dienes **2a–g** within 24 h. Under these conditions, (*E*)-alkenyl iodides bearing functional groups such as –Me, –Br, –Cl, –MeO, *N*-phthalimide and *N*-carbazole reacted successfully with **1** to give the corresponding (*E*)-buta-1,3-dienes in moderate to high yields (55–83%), irrespective of the substituent electronic character. All the reactions were highly stereospecific and the *E*-double bond geometry was strongly favored, with approximately 92:8–99:1 *E/Z* ratio as measured by ¹H NMR. As the vinylboronic pinacol ester **1** was used in slight excess (1.1 equiv.), the formation of homo-coupling by-products – symmetrical 1,4-diarylbuta-1,3-diene derivatives – was not observed.

The most significant point to report from the results shown in Table 1 is high chemoselectivity for the Suzuki–Miyaura pathway under the conditions applied. In most examples only small amounts of Heck coupling products were observed (<10%). The results obtained are complementary with previously reported studies on reactivity of **1** with alkenyl iodides via the Heck coupling pathway^[3a] and show that the reaction conditions significantly affect the selectivity of the process towards either Suzuki–Miyaura or Heck coupling. Unfortunately, (*E*)-4-bromostyryl iodide as well as (*E*)-3-methoxystyryl iodide (Table 1, entries 2 and 5) reacted with lower chemoselectivity to form also Heck-arylated products in 16–20% yield; however, they can be separated by column chromatography.

The *E*-configuration of the carbon–carbon double bond in the buta-1,3-dienes isolated was determined on the basis of the ¹H and ¹³C NMR spectra. Moreover, compound **2f** proved to be a solid and yielded a crystal amenable to X-ray structure determination (Fig. 2). More details of the crystallographic data are given in the X-ray crystallographic files in CIF format (supporting information).

Conclusions

We have developed an improved protocol for highly stereoselective preparation of (*E*)-1-arylbuta-1,3-dienes via palladium-catalyzed Suzuki–Miyaura coupling of (*E*)-styryl iodides with vinylboronic pinacol ester as a two-carbon building block. As the method under the conditions established shows high chemoselectivity for Suzuki–Miyaura coupling versus Heck coupling, it can be applied to the synthesis of functionalized nitrogen-containing buta-1.3-dienes, which are versatile building blocks in organic synthesis.

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