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Stereoselective Synthesis of (Z)-(1-Organo-1-alkenyl)boronic Esters by the Palladium-Catalyzed Cross-Coupling Reaction of (Z)-(1-Iodo-1-alkenyl)boronic Esters with Organozinc Reagents

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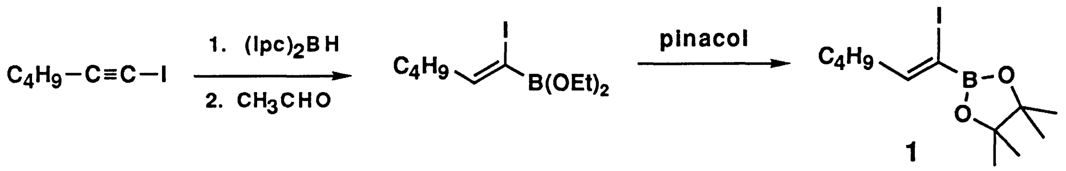
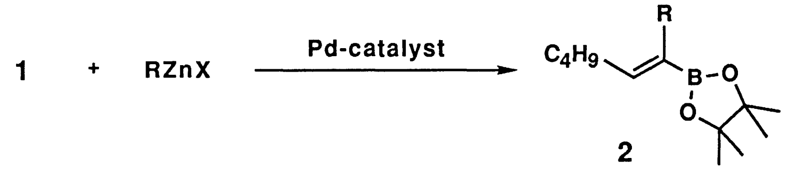
The cross-coupling reaction of organozinc reagents with a pinacol ester of (Z)-(1-iodo-1-hexenyl)boronic acid in the presence of $Pd(PPh_3)_4$ proceeded with complete retention of the configuration of the starting boronate. The reaction provided (E)-(1-organo-1-hexenyl)boronic esters which were not available by the conventional hydroboration technique. The utility of the reaction was demonstrated by stereoselective synthesis of an exocyclic alkene *via* the cross-coupling reaction with chloroenone.

1-Alkenylboronic esters are valuable intermediates in organic synthesis.$^{1)}$ Various types of substituted 1-alkenylboronates are now readily available. Preparation of (E)- $^{2)}$ and (Z)-1-alkenylboronic esters$^{3)}$ *via* hydroboration of terminal alkynes or 1-halo-1-alkynes has been reported previously. 2,2-Disubstituted-1-alkenylboronates were obtained by the haloboration of alkynes followed by cross-coupling with organozinc compounds.$^{4)}$ Alkylation of 1-halo-1-alkenylboronates with organolithiums also provided a new access to variously substituted 1-alkenylboronates. We and Brown's group reported a highly stereo- and regioselective synthesis of the (E)-(1-organo-1-alkenyl)boronic esters and utilized them for the synthesis of stereodefined alkenes and dienes.$^{5)}$ In this study, we have developed a new route to (Z)-(1-organo-1-alkenyl)boronic ester, for example **2**, by the cross-coupling reaction of **1** with organozinc reagents (Eqs. 1 and 2). The conventional hydroboration method may not provide such (Z)-alkenylboronates because the addition of boranes to internal alkynes is usually not regioselective.



(1)



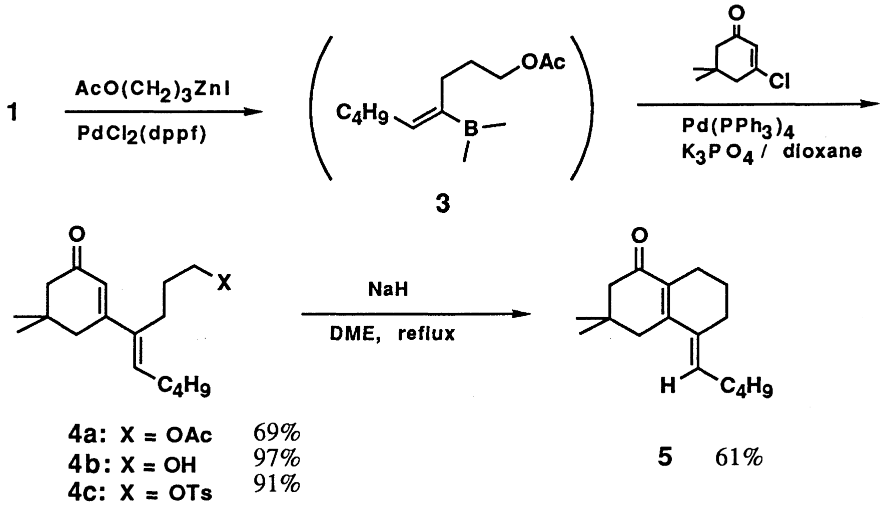
(2)

(Z)-1-Halo-1-alkenylboronates have been synthesized by the hydroboration of 1-halo-1-alkynes with dibromoborane-dimethyl sulfide complex followed by alcoholysis.$^{6)}$ However, we have recently found that the preparation could be easily carried out with improved yields (Eq. 1). Thus, the hydroboration of 1-iodo-1-hexyne with diisopinocampheylborane followed by dealkylation with acetaldehyde provided a stereochemically pure (Z)-(1-iodo-1-hexenyl)boronic acid pinacol ester **1** in 90% yield.7)

The cross-coupling reaction of **1** with organozinc reagents for the synthesis of (Z)-1-alkenylboronates was examined (Table 1). The $Pd(PPh_3)_4$ catalyst was effective in carrying out the coupling reaction in THF at room temperature. Under these conditions, phenyl, benzyl, and 1-alkynyl derivatives were synthesized without any difficulty. However, the coupling with vinylic zinc reagents was somewhat troublesome, presumably due to the thermal instability of the vinylzinc reagents.8) Although 2-methyl-1-propenylzinc chloride gave a moderate yield (entry 5), the coupling with ethenylzinc chloride failed. The $PdCl_2$(dppf) complex equally worked well, and this catalyst can be advantageous for the coupling with alkylzinc reagents having a β-hydrogen because the reaction with alkyl is known to provide by-products coupled with isomerized alkyls.9) All the reaction shown in Table 1 proceeded through complete retention of the configuration of **1**. For example, the protodeboronation of **2** (R=Ph) provided cis-1-phenyl-1-hexene (Z>99%).10) Alkaline hydrogen peroxide oxidation of this boronate gave phenyl pentyl ketone.

The following procedure is representative. To a solution of $ZnCl_2$ (30 mmol) in THF was added a solution of phenyllithium in ether (30 mmol) at 0 °C to prepare a phenylzinc chloride solution. $Pd(PPh_3)_4$ (0.15 mmol) and **1** (15 mmol) were added and the resulting solution was stirred for 2 h at room temperature. GC analysis of the reaction mixture indicated the complete disappearance of **1** and formation of a single new compound. The reaction mixture was diluted with hexane, washed with aqueous 1M HCl, aqueous $NaHCO_3$ (10%), brine, and finally dried over $MgSO_4$. The chromatography over silica gel with hexane/ethyl acetate=20/1 gave **2** (R=Ph) in 87% yield. ^1H NMR δ 0.76 (t, 3H, J=6.4 Hz), 1.03-1.57 (m, 4H), 1.19 (broad s, 12H), 1.95-2.19 (m, 2H), 6.54 (t, 1H, J=7.4 Hz), and 6.98-7.37 (m, 5H).

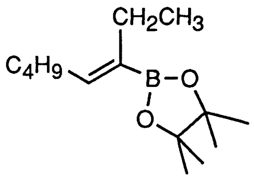
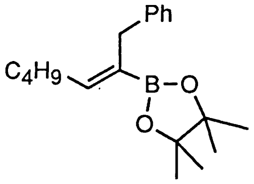
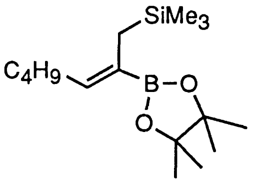
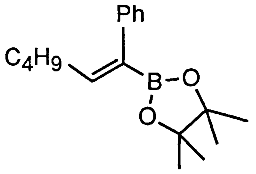
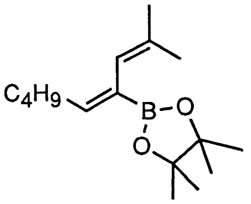
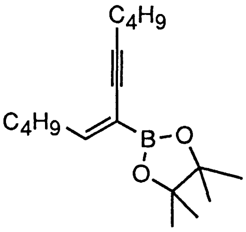
The utility of the present reaction was demonstrated by the synthesis of a stereodefined exocyclic alkene (Eq. 3). (3-Acetoxypropyl)zinc iodide (2 equivs)11) prepared by the method of Knochel was coupled



(3)

with **1** (1 equiv) in DMF for 4 h at 90 °C in the presence of $PdCl_2$(dppf) (1 mol%). A sequence of extraction with hexane, washing with brine, drying over $MgSO_4$, and finally concentration provided the crude boronate

Table 1. Synthesis of (Z)-(1-Organo-1-hexenyl)boronic Acid Pinacol Esters[a)]

Entry	RZnX	Conditions	Product	Yield / %[b)]
1	C_2H_5ZnI	$PdCl_2(dppf)$ [c)] 25 °C/2 h		67
2	$PhCH_2ZnBr$	$Pd(PPh_3)_4$ 25 °C/15 h		62
3	Me_3SiCH_2ZnI	$Pd(PPh_3)_4$ 40 °C/17 h		85
4	PhZnCl [d)]	$Pd(PPh_3)_4$ 25 °C/2 h		87
5	$Me_2C{=}CHZnCl$ [d)]	$Pd(PPh_3)_4$ 25 °C/15 h		40
6	$C_4H_9C{\equiv}C\text{-}ZnCl$ [d)]	$Pd(PPh_3)_4$ 25 °C/2 h		67

a) See the experimental procedure in the text.
b) Isolated yields purified by distillation with Kugelrohr or chromatography over silica gel.
c) dppf is 1,1'-bis(diphenyphosphino)ferocene.
d) The reagents were prepared from the corresponding organolithiums and $ZnCl_2$ in THF.

3 which could be used directly for the next coupling reaction. Heating the mixture of **3**, 3-chloro-5,5-dimethyl-2-cyclohexenone (1.5 equiv), K_3PO_4 (2 equivs), and $Pd(PPh_3)_4$ (3 mol%) in dioxane at 80 °C for 20 h produced **4a** in 69% yield.[12)] Deprotection with K_2CO_3 in aqueous MeOH[13)] followed by tosylation with p-TsCl and pyridine gave **4c** in 88% yield. Cyclization was furnished with a 61% yield by treating **4c** with NaH (1 equiv) in dimethoxyethane at 20 °C overnight and then for 3 h at refluxing temperature. The stereochemistry of the exo-double bond was unambiguously established by the chemical shift of the vinylic proton at 5.92 ppm and NOE (12%) between the vinylic proton and allylic hydrogens at 2.36 ppm.[14)]

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10) The direct protonolysis of pinacol ester failed. The boronate in THF was sequentially treated with n-BuLi (1 equiv) at -78 °C for 1 h, acetyl chloride (1 equiv) at -78-20 °C, and then an excess of acetic acid at refluxing temperature for 5 h.
11) A solution of 3-acetoxypropyl iodide in DMF and excess zinc powder was heated at 40 °C for 3 h. The upper supernatant layer was used for the next coupling reaction; M. C. P. Yeh, P. Knochel and L. E. Santa, *Tetrahedron Lett.*, **29**, 3887 (1988) and references cited therein.
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14) ^1H NMR (400MHz) δ 0.93(t, 3H), 1.03 (s, 6H), 1.35-1.45 (m, 4H), 1.66 (tt, 2H, J=6.84 and 6.84), 2.18 (dt, 2H, J=6.84 and 6.84), 2.27 (s, 2H), 2.34 (t, 4H, J=5.86), 2.36 (s, 2H), and 5.92 (t, 1H, J=6.84). The (Z)-isomer prepared by a similar process from the corresponding (Z)-alcohol[15)] showed a vinylic proton signal at 5.43 ppm.
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