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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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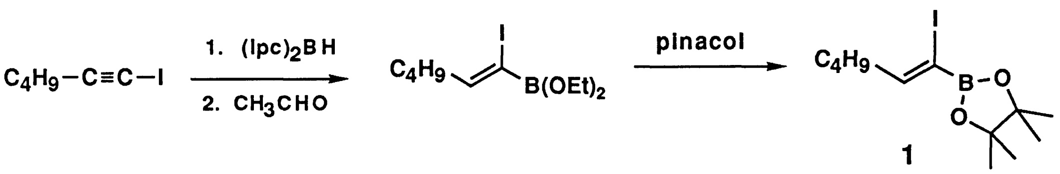
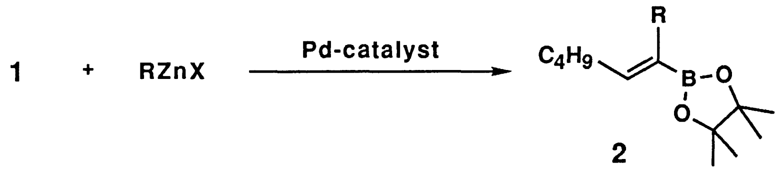
The cross-coupling reaction of organozinc reagents with a pinacol ester of (Z)-(1-iodo-1-hexenyl)boronic acid in the presence of $Pd(PPh_3)_4$ proceeded with complete retention of the configuration of the starting boronate. The reaction provided (E)-(1-organo-1-hexenyl)boronic esters which were not available 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 esters3) *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)



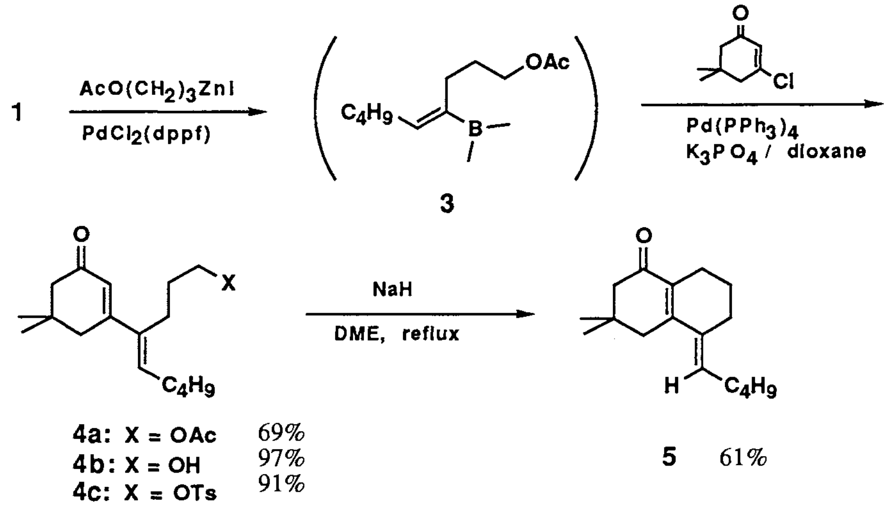
(2)

(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

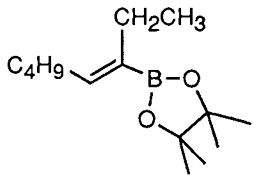
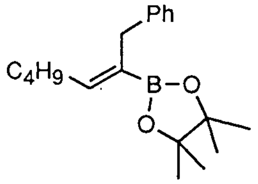
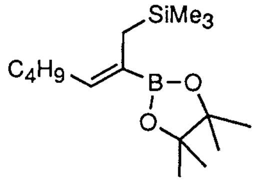
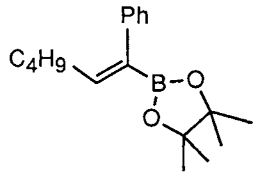
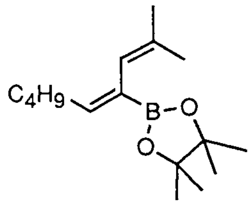
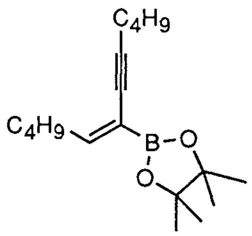
4a: X = OAc 69%
4b: X = OH 97%
4c: X = OTs 91%

5 61%

(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)]

References

1) H. C. Brown and J. B. Campbell, *Aldrichimica Acta*, **14**, 3 (1981); D. Matteson, *Tetrahedron*, **45**, 1859 (1989); A. Pelter, K. Smith, and H. C. Brown, "*Borane Reagents*," Academic Press, New York (1988).
2) H. C. Brown and V. Somayaji, *Synthesis*, **1984**, 919.
3) H. C. Brown, "Organic Synthesis via Boranes," John Wiley & Sons, New York (1975).
4) Y. Sato, H. Serizawa, N. Miyaura, S. Hara, and A. Suzuki, *Tetrahedron Lett.*, **29**, 1811 (1988); A. Suzuki, *Pure Appl. Chem.*, **58**, 629 (1986).
5) M. Sato, N. Miyaura, and A. Suzuki, *Chem. Lett.*, **1986**, 1329; H. C. Brown, T. Imai, and N. G. Bhat, *J. Org. Chem.*, **51**, 5277 (1986).
6) H. C. Brown and T. Imai, *Organometallics*, **3**, 1392 (1984).
7) P. Martinez-Fresneda, M. Vaultier, *Tetrahedron Lett.*, **30**, 2929 (1989); A. Kamabuchi, T. Moriya, N. Miyaura, and A. Suzuki, *Synth. Commun.*, in press (1993).
8) The precipitation of zinc metal was observed, presumably due to the formal reductive elimination of diene from divinylzinc generated by disproportionation of vinylzinc halide. G. A. Molander and P. W. Zinke, *Organometallics*, **5**, 2161 (1986).
9) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, and K. Hirotsu, *J. Am. Chem. Soc.*, **106**, 158 (1984).
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.
12) N, Sato, T. Ishiyama, N. Miyaura, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, **60**, 3471 (1987).
13) E. Piers and A. V. Gava, *J. Org. Chem.*, **55**, 2380 (1990).
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.
15) T. Oh-e, N. Miyaura, and A. Suzuki, *J. Org. Chem.* **58**, 2201 (1993).

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