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Stereo- and Regiospecific Synthesis of Trisubstituted Alkenes via the Palladium-catalyzed Cross-coupling Reaction of Diisopropyl (E)-(1-Alkyl-1-alkenyl)boronates with Organic Halides†

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The reaction of diisopropyl (Z)-(1-bromo-1-alkenyl)boronates readily obtainable, with organolithiums and bases takes place readily to give (E)-(1-organo-1-alkenyl)boronates, the cross-coupling of which with various organic halides proceeds smoothly in the presence of Pd-catalyst and base to afford stereodefined trisubstituted alkenes in good yields.

The transition metal-catalyzed reaction of organometallics with organic halides has been extensively studied to provide a new approach to the selective formation of carbon-carbon bonds. Recently, we have reported such reactions of 1-alkenylboranes with 1-alkenyl,$^{1)}$1-alkynyl,$^{1)}$aryl,$^{2)}$allylic,$^{3)}$ and benzylic halides$^{3)}$ in the presence of Pd catalysts and bases. It is well-known that stereodefined (E)-1-alkenylboronates$^{4)}$ **1** are readily prepared by hydroboration of 1-alkynes with catecholborane stereospecifically, more than 99% (Eq.1). An excellent method for the synthesis of highly pure (Z)-1-alenylboronates **3** was recently reported by Brown and Imai,$^{5)}$ via hydroboration of 1-bromo-1-alkynes with dibromoborane/dimethyl sulfide complex ($HBBr_2:SMe_2$), followed by treatment with potassium triisopropoxyborohydride (KIPBH) (Eq.2). The cross-coupling reaction of these (Z)-1-alkenylboronates **3** with (E)- or (Z)-1-alkenyl halides has been most recently become apparent to afford conjugated (E,Z)- or (Z,Z)-alkadienes in excellent yields, stereospecifically.$^{6)}$ Especially, the synthesis of conjugated (Z,Z)-dienes not readily obtainable by coventional methods should be noteworthy.

We now wish to report that the reaction of (Z)-(1-bomo-1-alkenyl)boronates **2**, intermediates formed by the Brown's method, with organolithiums takes place readily to give (E)-(1-alkyl-1-alkenyl)boronates **5**.$^{7)}$ The cross-coupling reaction of these boronates with various organic halides also proceeds smoothly under the similar conditions which are used in the previous reports,$^{1-3)}$ to give almost exclusively the corresponding trisubstituted alkenes **6** with high stereospecificity (Eqs. 3 and 4).

Initially, we considered that α-bromoalenylboronates **2**, on treatment with organolithiums, may give immediately the (E)-(1-alkyl-1-alkenyl)boronates **5**.

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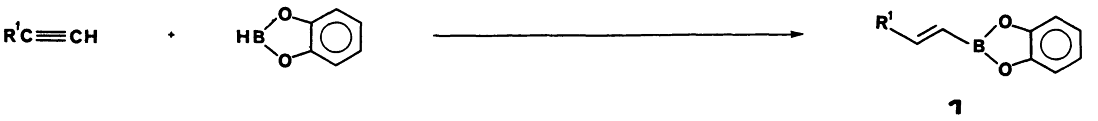
† Dedicated to Professor George Zweifel of the University of California, Davis on the occasion of his 60th birthday.



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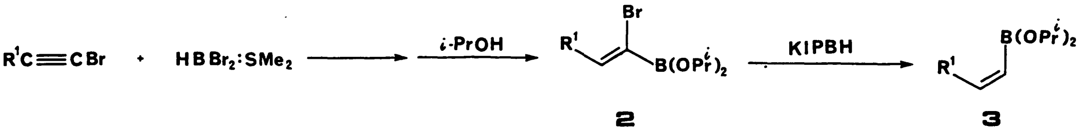

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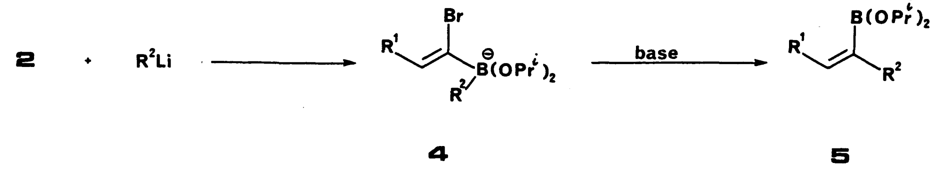
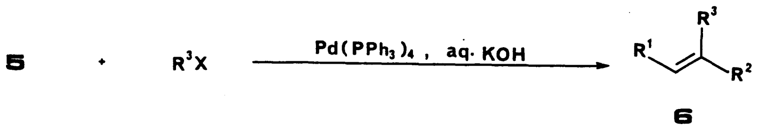


(3)

R^2= alkyl, 1-alkenyl, benzyl, and aryl



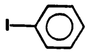
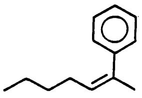
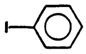
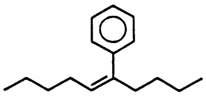
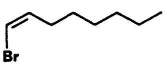
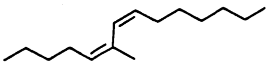
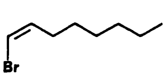
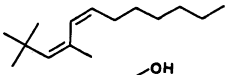
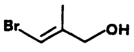
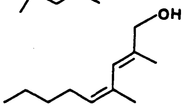
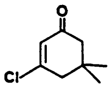
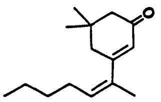
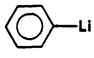
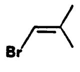
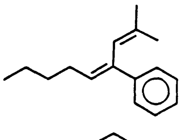
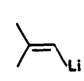
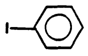
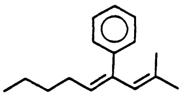
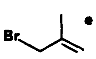
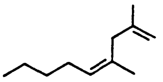
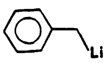
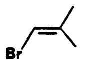
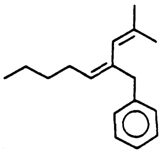
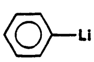
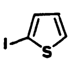
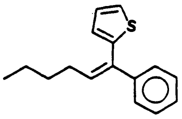
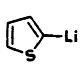
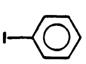
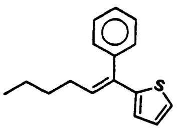
(4)

R^3= 1-alkenyl, allylic, and aryl

However,it was confirmed that such migration of organic groups (R^2) on boron to the vinylic carbon occurs by addition of bases such as sodium methoxide, ethoxide, and potassium hydroxide, as shown in the reaction of phenyl- or methyllithium with (Z)-(1-bromo-1-hexenyl)boronate 2 (R^1=Bu), followed by protonolysis with acetic acid or alkaline hydrogen peroxide oxidation, the result of which are summarized in Table 1. The cross-couplig reaction of alkenylboronates 5 thus obtained with a variety of organic halides such as 1-alkenyl, allylic, and aryl halides was achieved in the presence of Pd catalyst and base. The best results were obtained when the reaction was carried out in benzene using tetrakis(triphenylphosphine)-palladium as a catalyst and aqueous potassium hydroxide as a base. Table 2 shows the representative results available by this sequential alkylation procedure using (Z)-(1-bromo-1-hexenyl)boronate 2 (R^1=n-Bu) (Eqs. 3 and 4). From these results, it has become apparent that (E)-(1-organo-1-hexenyl)boronates 5 derived from alkyl-, 1-alkenyl-, benzyl-, and aryllithiums give excellent yields of the expected trisubstituted alkenes 6 stereospecifically, over 97%.

The following general procedure was used. To a solution of diisopropyl (Z)-(1-bromo-1-hexenyl)boronates (2, R^1=n-Bu, 1.0 mmol)[5)] in THF (2 ml) was added 1M solution of methyllithium in ether (1.1 mmol) at -78 °C with stirring under nitrogen. The resulting mixture was stirred for 30 min, then allowed to stand to room temperature, and stirred for 30 min further. The solvent was removed under reduced pressre, and then benzene (4 ml) and an aqueous 4M KOH solution (0.75 ml) were added. The reaction mixture was refluxed for 1 h to complete the migration of methyl group. $Pd(PPh_3)_4$ (0.03 mmol) and (E)-3-bromo-2-methyl-2-propenol (1.1 mmol) were added at room temperature, and finally the mixture was refluxed for 5 h. The product was extracted with benzene, washed with an aqueous NaOH solution and brine, and dried over $MgSO_4$. Analysis by GLPC (silica capillary column, OV-

Table 2. Synthesis of Trisubstituted Alkenes (Eqs. 3 and 4)[a]

Boronate **2** R¹=	R^2Li	R^3X	Product	Yield[b]	I.P.[c]
n-Bu	MeLi			85	>99
n-Bu	*n*-BuLi			89	>99
n-Bu	MeLi			70	>99
t-Bu	MeLi			66	>97
n-Bu	MeLi			70	>99
n-Bu	MeLi		 d)	76	>99
n-Bu				72	>99
n-Bu				61	>99
n-Bu	MeLi	 e)		71	>99
n-Bu				59	>99
n-Bu				94	>97
n-Bu				98	>97

a) All reactions were carried out under conditions described in the text, unless otherwise noted. b) GLPC yields based on boronates **2**. c) Isomeric purity, determined by GLPC. d) The cross-coupling reaction was carried out in EtOH and H_2O (4:1) containing Na_2CO_3(2 equiv.) and $Cl_2Pd(PPh_3)_2$(3 mol %) under reflux for 3 h. The detail of the reaction of 1-alkenylboronates with 3-halo-1-enones will be reported elsewhere. e) Three equivalents of 2-methyl-2-propenylbromide were used.

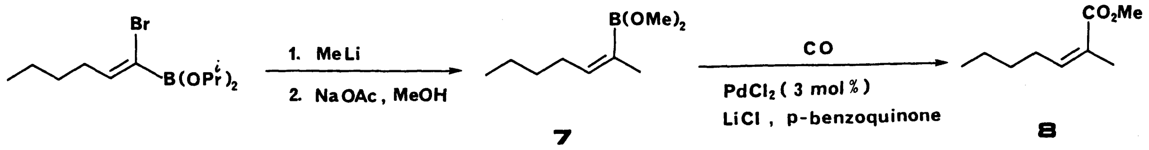
Table 1. Effects of Bases on the Reaction of (Z)-(1-Bromo-1-hexenyl)boronate **2** (R^1=n-Bu) with Organolithium Reagents (Eq.3)[a]

R^2Li	Base (equiv.)	Solvent	Yield/%[b),c)] of (E)-BuCH=CHR^2	Yield/%[d)] of BuCH_2COR^2
PhLi	none	THF-ether	3	-
PhLi	none	MeOH	51	-
MeLi	none	MeOH	-	80
PhLi	NaOMe(3)	MeOH	85	-
PhLi	NaOEt(3)	Benzene-EtOH	84	-
PhLi	KOH (3)	Benzene-H_2O	90	-
MeLi	KOH (3)	Benzene-H_2O	-	99

a) To a solution of **2** (R^1=n-Bu) in THF was added a solution of organolithium (1.1 equiv.) in ether at -78 °C. The mixture was allowed to stand to room temperature, and then stirred for 30 min. After evaporation of the solvent, a base and new solvent were added, and refluxed for 1 h. b) Protonolysis was achieved in acetic acid for 3 h under reflux. c) (E)-1-Phenyl-1-hexene, the isomeric purity was over 98% in each case. d) By the usual manner with alkaline hydrogen peroxide.4)

101) indicated that 0.70 mmol (70%) of (2E,4Z)-2,4-dimethyl-2,4-nonadienol had been formed. An analytically pure sample was obtained by chromatography on silica gel with benzene/ethyl acetate (10/1).

Previously we reported the palladium-catalyzed methoxycarbonylation8) of alkenylboranes to give α,β-unsaturated carboxylic esters. In Eq.5 it is exemplified that the boronate **7** obtained by the present method can be readily converted into the corresponding ester (yield, 79%; isomeric purity, >99%) with retention of configuration.9)



(5)

In conclusion, the present methodology opens up a promising new route to the generally more difficultly synthesized stereodefined trisubstituted alkenes. We are actively exploring full potentialities of this new route.

References

1) N. Miyaura, K. Yamada, H. Suginome, and A. Suzuki, J. Am. Chem. Soc., 107, 972 (1985). 2) N. Miyaura and A. Suzuki, J. Chem. Soc., Chem. Commun., 1979, 866. 3) N. Miyaura, T. Yano, and A. Suzuki, Tetrahedron Lett., 21, 2865 (1980). 4) H. C. Brown, "Organic Synthesis via Boranes," J. Wiely & Sons, New York (1975). 5) H. C. Brown and T. Imai, Organometallics, 3, 1392 (1984). 6) N. Miyaura, M. Satoh, and A. Suzuki, Tetrahedron Lett., in press. 7) During the course of our study on the present reaction, we knew that the reaction of **2** with alkyllithium is in progress by the Professor Brown's group; private communication. 8) N. Miyaura and A. Suzuki, Chem. Lett., 1981, 879. 9) A solution of methyllithium in ether was added into a solution of (Z)-(1-bromo-1-hexenyl)boronate in THF at -78 °C. After being allowed to warm up to room temperature, the solvent was evaporated in vacuo, and methanol and sodium acetate (2 equiv.) was added. The mixture was heated at reflux for 1 h. The methoxycarbonylation of the boronate in methanol was conducted in the presence of LiCl (10 equiv.), $PdCl_2$ (3 mol%), and p-benzoquinone (2 equiv.) under atmospheric pressure of carbon monoxide for 2 h at room temperature and then for additional 2 h at 50 °C. The usual work up afforded 79% of the expected ester stereospecifically (>99%).

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