Stereoselective Synthesis of Conjugated Dienones via the Palladium-Catalyzed Cross-Coupling Reaction of 1-Alkenylboronates with 3-Halo-2-alken-1-ones

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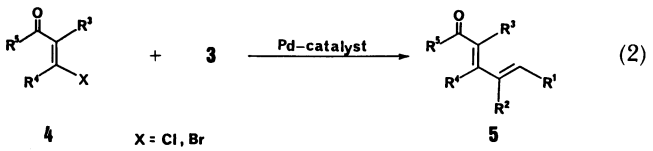
Synopsis. The synthesis of conjugated dienones by means of palladium-catalyzed cross-coupling reaction between (*E*)-1-alkenyl-1,3,2-benzodioxaboroles or diisopropyl (*Z*)-1-hexenylboronate with 3-halo-2-alken-1-ones is described.

In our recent papers,[1-3] we reported a stereoselective synthesis of (*E,E*)-, (*E,Z*)-, (*Z,E*)-, and (*Z,Z*)-alkadienes and trienes by the palladium-catalyzed cross-coupling reaction of (*E*)- or (*Z*)-1-alkenylboronates and (*E*)- or (*Z*)-1-halo-1-alkenes. In this paper, we describe the development of reaction for the synthesis of conjugated dienones **5** as shown in Eqs. 1 and 2.

Since 1-alkenylboronates are quite inert toward many functional groups including carbonyl, the coupling reaction can be carried out without any protection of these groups. On the other hand, the reaction proceeds in the presence of bases such as sodium alkoxides and hydroxide. Consequently, vinylic halides with functional groups sensitive to base, such as halo enones **4** may cause difficulties.



(*E*)-1-Hexenyl-1,3,2-benzodioxaborole (**3**, R^1=*n*-Bu, R^2=H) was initially chosen, and its reaction with 3-bromo-5,5-dimethyl-2-cyclohexen-1-one (**4**, R^3=H, R^4, R^5=CH_2–CMe_2–CH_2) was investigated under various different conditions as shown in Table 1.

Unlike our earlier palladium-catalyzed reactions,[1-3] relatively weak bases such as sodium acetate and triethylamine are effective in obtaining high yields of the coupling product **6**. The solvent also appears to play a critical role in determining the yield of **6**. Comparison of THF, DMF, and MeOH as solvents under various conditions demonstrates that the higher yields of dienone **6** are obtained in a methanol solution. When THF and DMF are employed as solvents, a substantial amount of the head-to-tail coupling product **7**[4] was prepared as a by-product. The solvent effect seems to be concerned with the mechanism of cross-coupling. We previously proposed a mechanism[1] which involves the intermediacy of alkoxopalladium(II) complexes for the cross-coupling reaction of 1-alkenylboronates with 1-halo-1-alkenes. The present reaction should also involve a methoxopalladium(II) **9**, prior to the transmetalation with 1-alkenylboronates. Such an exchange reaction of ligand in **8** can be accelerated by the trans effect[5] of electron-withdrowing carbonyl group, which may be a major reason to explain the difference between the present and former results.[1-3] All of the palladium complexes studied were proved to be used in catalytic amounts. Both palladium(II) acetate and dichlorobis(triphenylphosphine)palladium(II) appear to be more effective than tetrakis(triphenylphosphine)palladium(0). Thus, we used $PdCl_2(PPh_3)_2$ and sodium acetate in refluxing methanol as a general procedure for the reaction. Under these conditions, the coupling with 1-alkenylboronates is fortunately faster than the nucleophilic displacement of halogen in **4** with sodium acetate or other side reactions such as aldol condensation. The full scope of this cross-coupling reaction has been investigated by using a variety of 1-alkenylboronates **3** and halo enones **4**. The results are summarized in Table 2.

Table 1. Effects of Reaction Conditions for Cross-Coupling of (*E*)-1-Hexenyl-1,3,2-benzodioxaborole with 3-Bromo-5,5-dimethyl-2-cyclohexen-1-one[a]

Catalyst	Base	Solvent	Yield/%[b]	(**6**:**7**)
$Pd(OAc)_2$	NaOAc	MeOH	91	(100: 0)
$Pd(OAc)_2$	NaOAc	DMF	65	(41:59)
$Pd(OAc)_2$	Et_3N	DMF	37	(37:63)
$Pd(OAc)_2$	Et_3N	THF	23	(60:40)
$Pd(OAc)_2$	Et_3N	MeOH	97	(100: 0)
$Cl_2Pd(PPh_3)_2$	NaOAc	MeOH	98	(100: 0)
$Pd(PPh_3)_4$	NaOAc	MeOH	33	(100: 0)

a) Reactions were carried out under conditions described in the text. b) Yields are based on the haloenone used.

Diisopropyl (*Z*)-1-hexenylboronate **10a**[13] prepared by the hydroboration of 1-bromo-1-hexyne with dibromoborane, followed by the reaction with 2-propanol and potassium hydrotriisopropoxyborate also gave the dienone **11a** preserving the stereochemistry of (Z)-double bond, Z>96% (Eq. 3). The reaction of diisopropyl (*E*)-(1-methyl-1-hexenyl)boronate (**10b**) with 3-chloro-5,5-dimethyl-2-cyclohexen-1-

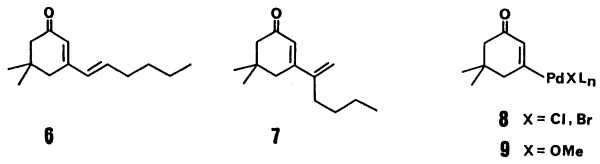
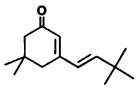
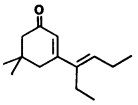
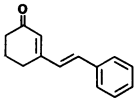
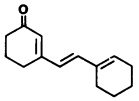
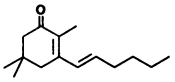
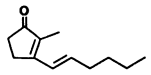
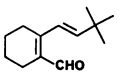
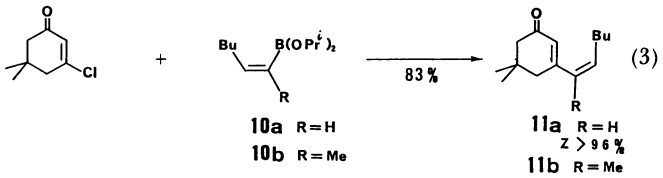


Table 2. Synthesis of Dienones and Trienones **5**

Run	1-Alkenylboronate		Haloenone				Product	No.	Yield/%[a]
	R^1=	R^2=	R^3=	R^4=	R^3=	X=			
1	*t*-Bu	H	H	$-CH_2CMe_2CH_2-$		Cl		**5a**	—(87)
2	Et	Et	H	$-CH_2CMe_2CH_2-$		Cl		**5b**	96
3		H	H	$-CH_2CH_2CH_2-$		Cl		**5c**	98
4		H	H	$-CH_2CH_2CH_2-$		Cl		**5d**	84
5	*n*-Bu	H	Me	$-CH_2CMe_2CH_2-$		Br		**5e**	98
6	*n*-Bu	H	Me	$-CH_2CH_2-$		Br		**5f**	97
7	*t*-Bu	H						**5g**	—(85)

a) GLC yields based on haloenones and the isolated yields are shown in parenthesis.

one was reported elsewhere.[3]



(3)

Conjugated dienones and polyenones are promising versatile intermediates for the synthesis of naturally occurring compounds. Most recently, we reported a stereoselective synthesis of a fungal prohormone (±)trisporol B[6] by means of such a crosscoupling reaction of 1-alkenylboronates. The present reaction affords an alternative and general procedure of obtaining stereodefined conjugated dienones and trienones.

Experimental

All reactions were carried out under nitrogen atmosphere. 1-Hexyne, 3,3-dimethyl-1-butyne, phenylethyne, and 3-hexyne are commercial products and purified by distillation before use. 1-Cyclohexenylethyne was prepared according to the method reported by Brandsma.[7] 3-Halo-2-cycloalkene-1-ones[8,9] were prepared from the corresponding 1,3-cycloalkadienones.

The IR spectra were recorded on a Hitachi-Perkin Elmer Model 125 spectrometer. The ^{1}H NMR spectra were taken on a Hitachi R-22 spectrometer (90 MHz, TMS as the internal reference). The measurement of mass spectra was carried out on a JEOL JMS-D 300 spectrometer (70 eV).

Palladium Complexes. Palladium(II) acetate was commercial. Dichlorobis(triphenyphosphine)palladium(II)[10] and tetrakis(triphenylphosphine)palladium(0)[11] were prepared according to the reported procedures.

1-Alkenylboronate 3. 1-Alkenyl-1,3,2-benzodioxaboroles were prepared by the Brown's method[1,12] from 1,3,2-benzodioxaborole (catecholborane) and 1-alkynes, and they were purified by distillation before use; **3a** (R^1=*n*-Bu, R^2=H): Bp 86—87 °C/ 0.3 mmHg (1 mmHg=133.322 Pa) (lit,[12] 82 °C/0.25 mmHg); **3b** (R^1=*t*-Bu, R^2=H): Bp 128 °C/ 12 mmHg; **3c** (R^1=Et, R^2=Et): Bp 63 °C/0.1 mmHg (lit,[12] 81 °C/0.2 mmHg); **3d** (R^1=phenyl, R^2=H): Mp 78 °C (lit,[12] 78—78.5 °C); **3e** (R^1=cyclohexenyl, R^2=H): Bp 135—149 °C/0.1 mmHg, Mp 76—79 °C. 1-Alkenylboronates except **3e** are stable toward air and can be handled by the usual method.

Reaction Conditions (Table 1). The best conditions for the formation of conjugated dienone **6** were determined by the following general procedure. The palladium complex (0.03 mmol), an appropriate solvent (3.5 ml of MeOH, DMF, or THF), base (1.5 mmol of NaOAc or Et_3N), and 3-bromo-5,5-dimethyl-2-cyclohexen-1-one (1.0 mmol) were placed in a 25 ml-flask, and flushed with nitrogen. (*E*)-1-Hexenyl-1,3,2-benzodioxaborole (1.1 mmol) was then added by means of a hypodermic syringe through the septum inlet, and the resultant mixture was heated under reflux for 3 h. In the case of DMF, the reaction temperature was controlled at 80 °C for 3 h. After the completion of reaction, the mixture was cooled to room temperature and the residual organoborane was oxidized with an aqueous solution (3 M (1 M=1 mol dm^{-3}), 0.2 ml) of NaOH-H_2O_2 (30% solution, 0.2 ml) for 1 h. The product was extracted with benzene, washed with brine, dried over $MgSO_4$, and analyzed directly by GLC (15% SE-30 on Uniport B, 2 m). The product was isolated by column chromatography over silica gel with hexane/ether. **6**: Bp 90—93 °C/0.1 mmHg; n^{22}=1.5149; IR

(film) 3040, 1670, 1635, 1595, and 975 cm^{-1}; ^1H NMR (CCl_4) δ=0.93 (t, 3H, J=6.5 Hz), 1.08 (s, 6H), 1.2—1.7 (m, 4H), 2.0—2.3 (m, 6H), 5.78 (broad s, 1H), 6.0 (dt, 1H, J=6.5 and 16 Hz) and 6.26 (d, 1H, J=16 Hz); Found:C 81.27; H, 10.55%. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75%.

Standard Procedure for the Synthesis of Dienone 5c (Table 2). In a dry 100 ml-flask equipped with a septum inlet and a magnetic stirring bar were placed $PdCl_2(PPh_3)_2$ (0.21 g, 0.3 mmol) and NaOAc (1.23g, 15 mmol). The flask was flushed with nitrogen and charged with 15 ml anhydrous methanol, 3-halo-2-alken-1-one (10 mmol), and 1-alkenyl-1,3,2-benzodioxaborole (11 mmol). The reaction mixture was then refluxed for 3 h. After completion of the reaction, aqueous NaOH (0.5 ml of a 3 M solution) and 30%-H_2O_2 (0.5 ml) were added at room temperature in order to oxidize the unreacted borane. The product was extracted with benzene, washed with brine and dried over $MgSO_4$. The extracts thus obtained were analyzed by GLC (15% SE-30 on Uniport B, 2 m, or fused silica capillary colum, 20 m). Analytically pure samples were obtained by chromatography over silica gel with hexane–ether or distillation under reduced pressure.

The dienones prepared by the above procedure are as follows.

5a: Mp 54 °C; IR (film) 3040, 1670, 1635, 1595, and 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.07 (s, 6H), 1.09 (s, 9H), 2.26 (s, 2H), 2.32 (broad s, 2H), 5.91 (t, 1H, J=1.3 Hz), 6.24 (d, 1H, J=16 Hz), and 6.26 (d, 1H, J=16 Hz); MS m/z (rel intensity) 107 (100), 191 (83) and 206 (47); Found: m/z 206.16711. Calcd for $C_{14}H_{22}O$: M, 206.16711.

5b: Bp 68—69 °C/0.05 mmHg; n^{21}=1.5217; IR (film) 3040, 1660, 1615, and 1580 cm^{-1}; ^1H NMR (CCl_4) δ=0.9—1.2 (m, 6H), 1.07 (s, 6H), 2.12 (s, 2H), 2.3 (s, 2H), 2.0—2.5 (m, 4H), 5.85 (t, 1H, J=7 Hz), and 5.96 (s, 1H); Found: C, 81.30; H, 10.55%. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75%.

5c: Bp 139—140 °C/0.15 mmHg; Mp 49 °C; IR (film) 3030, 1665, 1615, and 1580 cm^{-1}; ^1H NMR (CCl_4) δ=2.0—2.25 (m, 2H), 2.25—2.50 (m, 2H), 2.60 (t, 2H, J=6 Hz), 5.99 (s, 1H), 6.90 (s, 2H), and 7.2—7.6 (m, 5H); Found: C, 84.97; H, 7.07%. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12%.

5d: Bp 123—125 °C/1.5 mmHg; Mp 55 °C; IR (film) 3040, 1725, 1670, 1605, 965, and 865 cm^{-1}; ^1H NMR (CCl_4) δ=1.5—1.8 (m, 4H), 1.9—2.6 (m, 10H), 5.87 (s, 1H), 5.96 (broad s, 1H), 6.18 (d, 1H, J=16 Hz), and 6.58 (d, 1H, J=16 Hz); Found: C, 82.90; H, 9.12%. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97%.

5e: Bp 93—94 °C/0.3 mmHg; n^{21}=1.5192; IR (film) 3040, 1660, 1630, 1585, and 965 cm^{-1}; ^1H NMR (CCl_4) δ=0.905 (t, 3H, J=6.5 Hz), 1.02 (s, 6H), 1.2—1.6 (m, 4H), 1.34 (s, 3H), 2.19 (s, 2H), 2.29 (s, 2H), 2.0—2.4 (m, 4H), 6.06 (dt, 1H, J=6 and 16 Hz), and 6.60 (d, 1H, J=16 Hz); Found: C, 81.52; H, 10.73%. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98%.

5f: Bp 84—86 °C/0.3 mmHg; n^{20}=1.5350; IR (film) 3025, 1690, 1640, 1600, and 965 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (t, 3H, J=6.5 Hz), 1.1—1.6 (m, 4H), 1.67 (s, 3H), 2.1—2.4 (m, 2H), 2.4—2.7 (m, 2H), 6.14 (dt, 1H, J=6 and 16 Hz), and 6.57 (d, 1H, J=16 Hz); Found: C, 80.60; H, 10.13%. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18%.

5g: n^{20}=1.5272; IR (film) 1700, 1670, 1630, 1595, 1145, and 963 cm^{-1}; ^1H NMR (CCl_4) δ=1.09 (s, 9H), 1.45—1.90 (m, 4H), 2.15—2.6 (m, 4H), 6.0 (d, 1H, J=16 Hz), 6.83 (d, 1H, J=16 Hz), and 10.27 (s, 1H); MS m/z (rel intensity) 135 (100), 136 (14), 149 (4), 177 (0.6), and 192 (0.2); Found: m/z 192.15097; Calcd for $C_{13}H_{20}O$: M, 192.15093.

Synthesis of (Z)-1-Hexenylboronate 10a and Its Reaction with Halo Enone (Eq. 3). To a solution of diisopropyl (Z)-(1-bromo-1-hexenyl)boronate[12,13] (1.1 mmol) in ether (2 ml) was added a solution of potassium hydrotriisopropoxyborate in THF (1 M solution, 1.2 mmol) at 0 °C. The mixture was stirred for 15 min at 0 °C. The cooling bath was removed, and stirring was continued for 30 min at room temperature. The solvent was evaporated under reduced pressure (0.01 mmHg) and then diisopropyl (Z)-1-hexenylboronate **10a** thus obtained was dissolved in methanol (4 ml). Sodium acetate (1.5 mmol), $PdCl_2(PPh_3)_2$ (0.03 mmol), and 3-chloro-5,5-dimethyl-2-cyclohexen-1-one (1.0 mmol) were added, and the mixture was refluxed for 5 h. The reaction mixture was diluted with benzene–hexane(1/1) (30 ml), washed with water, and dried over $MgSO_4$. Chromatography over silica gel with hexane–ether gave **11a** (0.17 g, 83%). Analysis by GLC (fused silica capillary column, OV-101, 20 m) indicated that E/Z is 4/96. **11a:** IR (film) 3020, 1670, and 1630 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (t, 3H, J=6.5 Hz), 1.07 (s, 6H), 1.2—1.5 (m, 4H), 2.1—2.4 (m, 6H), 5.7 (dt, 1H, J=6.5 and 12 Hz), 5.9 (d, 1H, J=12 Hz), and 5.93 (broad s, 1H); MS m/z (rel intensity) 206 (76), 191 (10), 177 (15), 163 (15), 149 (30), 121 (39), and 108 (100); Found: C, 81.27; H, 10.55%. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75%.

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