Stereoselective Synthesis of Conjugated 2,4-Alkadienoates via the Palladium-Catalyzed Cross-Coupling of 1-Alkenylboronates with 3-Bromo-2-alkenoates

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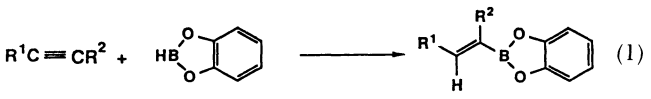
(2*E*,4*E*)-, (2*Z*,4*E*)-, and (2*E*,4*Z*)-2,4-Alkadienoates can be synthesized in high yields by the cross-coupling of ethyl (*E*)-3-bromoacrylate, methyl (*E*)-3-bromo-2-methylpropenoate, ethyl (*Z*)-3-bromocrotonate,1-bromo-2-(ethoxycarbonyl)cyclohexene, and 4-bromocoumarin with 2-[(*E*)-1-alkenyl]-1,3,2-benzodioxaboroles or diisopropyl (*Z*)-1-hexenylboronate in the presence of 3 mol% of $Pd(OAc)_2$, 6 mol% of PPh_3, and 2 equivalents of Na_2CO_3 or K_2CO_3 in alcoholic solvents while retaining the original configuration of the double bonds in β-bromo esters and 1-alkenylboronates. Although the coupling reaction with 1-hexenylboronate with (*Z*)-3-bromoacrylate gave a mixture of ethyl (2*Z*,4*E*)- and (2*E*,4*E*)-nonadienoates in a ratio of 63 : 37, it was found that the use of bis(diphenylphosphino)ferrocene as a ligand of palladium brought about the stereoselective coupling under mild conditions.

2,4-Alkadienoic acid esters are versatile intermediates for a variety of chemical reactions such as Diels-Alder, and are also frequently found in skeletons of natural products. The Wittig or Horner olefin synthesis[1a] provides the most general and flexible approach for the synthesis of stereoisomers of these esters. Conjugated addition of vinylcopper reagents to acetylenic esters also gives a particularly facile route to stereodefined 2,4-dienoates.[1b,c] Although such methods have their own excellence, the scope of these reactions has still been limited to the synthesis of one or two stereoisomers among four, or they have often suffered the disadvantage that an accurate estimate of the stereochemical course of reaction is difficult. Recently, we have reported[2] a stereoselective synthesis of alkadienes and trienes by the palladium-catalyzed cross-coupling reaction of 1-alkenylboronates with 1-halo-1-alkenes. Synthesis of conjugated dienones[3] by the reaction of 1-alkenylboronates with 3-halo-2-alken-1-ones was also demonstrated. In this paper, we describe the development of the reaction for the synthesis of stereodefined 2,4-alkadienoates (**5**, **8**, and **11**)[4] as shown in Eqs. 2—4.



(1)

1 2 3

(2)

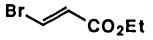
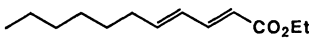
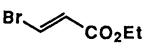
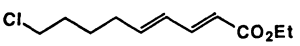
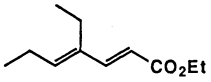
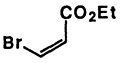
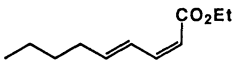
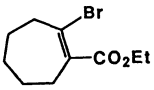
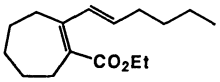
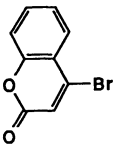
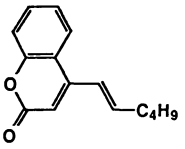
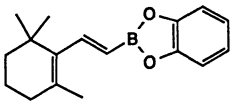
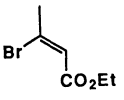
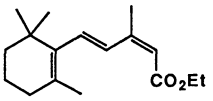
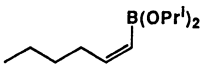
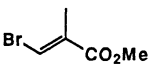
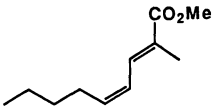
4 5

The cross-coupling reaction of 1-alkenylboron compounds with organic halides proceeds in the presence of a suitable base and palladium catalyst. The organic halides with electron-withdrawing groups such as 3-bromoacrylate are highly susceptible to SN2 displacement at the bromine position with base or saponification of the ester group. For example, the reaction of 2-(1-hexenyl)-1,3,2-benzodioxaborole with 3-bromoacrylate in the presence of 3 mol% of $Pd(PPh_3)_4$ and 2 equivalents of sodium ethoxide, such reaction conditions of which are employed in most cases of the coupling reaction[2] of 1-alkenylborates, lead to extremely fast formation of 3-ethoxyacrylate without any formation of the desired coupling product. Thus, the conditions used for usual haloalkenes can not be applicable for such substrates. Although relatively strong bases such as NaOH or NaOR were required for the coupling of 1-alkenylborates with unfunctionalized haloalkenes, we found that Na_2CO_3 or K_2CO_3 suspended in an alcoholic solvent was effective for the reaction with 3-bromoacrylate. A combination of palladium(II) acetate and two equivalents of triphenylphosphine was recognized to be more effective than $Pd(PPh_3)_4$ commonly used. Thus, we used the conditions using $Pd(OAc)_2$ (3 mol%), PPh_3 (6 mol%), and Na_2CO_3 or K_2CO_3 (2 equivalents) in refluxing methanol or ethanol as a general procedure for the present reaction. The representative results are summarized in Table 1.

(*E*)-1-Alkenylboronates can be most conveniently prepared by hydroboration[5] of alkynes with catecholborane (1,3,2-benzodioxaborole) (Eq. 1). 2-[(*E*)-1-Alkenyl]-1,3,2-benzodioxaboroles derived from terminal and internal alkynes gave 2,4-alkadienoates in good yields by the reaction with (*E*)-3-bromoacrylate, their methylated derivatives, or cyclic α,β- unsaturated β-bromo esters. The dienoates thus obtained were indicated to be (2*E*,4*E*)-isomers by ^1H NMR and GLC analysis, and their isomeric purity is 99% in each case.

We previously reported[2a] that (*Z*)-1-alkenylboronates couple with 1-halo-1-alkenes preserving their *Z*-configuration. (*Z*)-1-Alkenylboronates[6] are readily prepared by the hydroboration of 1-bromo-1-alkynes with dibromoborane-dimethyl sulfide, followed by the reaction with 2-propanol and then with

Table 1. Synthesis of 2,4-Alkadienoate

Run	1-Alkenylboronate (3)		Haloester	Conditions[a]	Product	Yield/%[b]
	R^1=	R^2=				
1	C_6H_{13}	H		A		89(>99)
2	$Cl(CH_2)_4$-	H		A		71(>99)
3	C_2H_5	C_2H_5		A		88(>99)
4	C_4H_9	H		B		73(>95)
5	C_4H_9	H		C		53(>99)
6	C_4H_9	H		C		88(>(99)
7				C		43(>98)
8				D		95(>98)

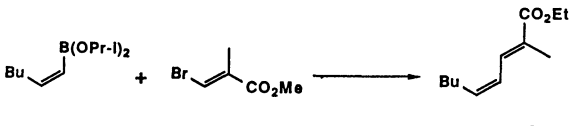
a) The coupling reactions are conducted under the following conditions. A: $Pd(OAc)_2$ (3 mol%), PPh_3 (6 mol%), and Na_2CO_3 (2 equiv) in 75% ethanol at refluxing temperature for 4 h. B: $Pd(OAc)_2$ (3 mol%), DPPF (3 mol%), and K_2CO_3 (2 equiv) in 75% ethanol for 24 h at room temperature. C: $Pd(OAc)_2$ (3 mol%), PPh_3 (6 mol%), and K_2CO_3 (2 equv) in dry ethanol at refluxing temperature for 3—5 h. D: The same conditions with C, except methanol is used in place of ethanol. b) GLC yields are based on the bromoesters employed, and the isomeric purity in each case is shown in the parenthesis.

Table 2. Effect of Catalysts for Cross-Coupling of (*Z*)-3-Bromoacrylate (Eq. 4)

Catalyst[a]	Temp/°C	Time/h	Yield/%	(2*E*,4*E*)/(2*Z*,4*E*)
$Pd(OAc)_2(PPh_3)_2$	Reflux	5	70	37/63
$Pd(OAc)_2$(dppe)	Reflux	5	86	80/20
$Pd(OAc)_2$(dppf)	Reflux	5	86	23/77
$Pd(OAc)_2$(dppf)	50	5	71	19/81
$Pd(OAc)_2$(dppf)	20	24	73	5/95

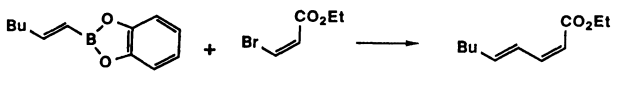
a) Dppe and dppf are bis(diphenylphosphino)ethane and bis(diphenylphosphino) ferrocene.

potassium hydrotriisopropoxyborate. The above conditions also gave a good result for the reaction of (*Z*)-1-hexenylborate (**6**) to give (2*E*,4*Z*)-isomer (**8**) in a yield of 95% with the isomeric purity of 98% (Eq. 3).



(3)

6 **7** **8**



(4)

9 **10** **11**

On the other hand, the reaction between (*E*)-1-hexenylboronate (**9**) and (*Z*)-3-bromoacrylate (**10**) also took place readily. However, 2,4-nonadienoate thus obtained under such conditions was a mixture of (2*Z*,4*E*)- and (2*E*,4*E*)-isomers in a ratio of 63 : 37. Pre-

sumably, isomerization[7] may occur while the boron compound and Pd complex are bound or before the reductive elimination proceeds in the mechanism[2a] of cross-coupling reaction. Bis(diphenylphosphino)-ferrocene (DPPF)[8] is known as a ligand to accelerate the reductive elimination from diorganopalladium complexes, and to minimize the isomerization around the double bond. By using DPPF as a ligand of palladium, the yield in Eq.4 was improved to give 73% yield of ethyl (2*Z*,4*E*)-2,4-nonadienoate and the isomeric ratio of (2*Z*,4*E*):(2*E*,4*E*) to be 95:5 (Table 2). However, such isomerization appears to be highly dependent on the structure of 3-bromo-2-alkenoates since no remarkable isomerization was observed in the reaction of 3-bromocrotonate (Run 7 in Table 1).

There have been some published procedures for the synthesis of α,β-unsaturated esters including conjugated 2,4-alkadienoates from alkynes via hydrometallation, for example, the palladium-catalyzed cross-coupling reaction of ethyl (*E*)- or (*Z*)-3-(tributylstannyl)propenoate[9] with 1-iodo-1-alkenes, and (*E*)-1-alkenylaluminum[10] or zirconium compounds with 3-bromoacrylates. We previously reported that the methoxycarbonylation[11] of 1-alkenylboronates with carbon monoxide and methanol in the presence of palladium catalyst provides a convenient procedure for synthesis of α,β-unsaturated ester, stereoselectively. The present method affords a convenient alternative procedure for the synthesis of the titled compounds.

Experimental

All reactions were carried out under nitrogen atmosphere. 1-Hexyne, 1-octyne, and 2-butyne were commercial products and purified by distillation before use. 6-Chloro-1-hexyne,[12] 1-ethynyl-2,6,6-trimethylcyclohexene,[13] ethyl (*E*)- and (*Z*)-3-bromoacrylates,[14] methyl (*E*)-3-bromo-2-methylpropenoate,[15] and ethyl (*Z*)-3-bromocrotonate[16] were prepared according to the literature procedures. 1,3,2-Benzodioxaborole (cathecolborane) from Aldrich Chemical Co. was used after distillation. 1-Bromo-(2-ethoxycarbonyl)-cycloheptene was prepared by the oxidation[17] of 2-bromo-1-formylcycloheptene[2d] with manganese(IV) oxide in the presence of sodium cyanide, followed by esterification with *N*,*N*-dimethylformamide diethyl acetal.

The ^{1}H NMR spectra were measured with a Hitachi R-90H (90MHz) spectrometer (solvent, $CDCl_3$; TMS as an internal reference). Mass spectra were recorded on a JEOL JMS-D 300 for high resolution analysis and Finnigan ITD 800. GLC analyses were performed with a Hitachi 023 gas chromatograph using a fused silica capillary column (OV-101, 25m).

1-Alkenylboronate (3). Preparations of (*E*)-1-hexenyl-, (*E*)-1-octenyl-, [(*E*)-6-chloro-1-hexenyl]-, and [(*E*)-1-methyl-1-propenyl]-1,3,2-benzodioxaboroles were reported[2a] previously. Hydroboration of 1-ethynyl-2,6,6-trimethylcyclohexene was carried out as follows. A dry 10 ml flask equipped with a septum inlet and a magnetic stirring bar was flushed with nitrogen, and was charged with the enyne (1.48 g, 10 mmol) and dry benzene (2 ml). 1,3,2-Benzodioxaborole (1.2 ml, 10.8 mmol) was added dropwise by a hypodermic syringe. The reaction mixture was stirred for 20 h at 70 °C, and then 0.1 ml of methanol was added at room temperature to destroy the residual hydride. The flask was quickly attached to Kugelrohr and flushed with nitrogen. Distillation under reduced pressure gave the dienylboronate (2.2 g 76%), bp 170 °C/0.55mmHg (1 mmHg= 133.322Pa); ^{1}H NMR ($CDCl_3$) δ=1.10 (s, 6H), 1.4—1.7 (m, 4H), 1.79 (s, 3H), 1.95—2.20 (m, 2H), 5.79 (d, 1H, J=18.6 Hz), 6.95—7.25 (m, 4H), and 7.45 (d, 1H, J=18.6 Hz).

Standard Procedure for the Synthesis of 2,4-Alkadienoate (Eq. 2). A 200 ml flask equipped with a septum inlet, a reflux condenser and a magnetic stirring bar was flushed with nitrogen. The flask was charged with $Pd(OAc)_2$ (0.067 g, 0.3 mmol), PPh_3 (0.15 g, 0.6 mmol), Na_2CO_3 (2.12g, 20 mmol), and 40 ml of 75% ethanol (Conditions A in Table 1) or K_2CO_3 (2.76 g, 20 mmol) and 40 ml of dry ethanol (Conditions C). Ethyl (*E*)-3-bromoacrylate (1.79 g, 10 mmol) and 2-(1-alkenyl)-1,3,2-benzodioxaborole (11 mmol) were then added by a hypodermic syringe through septum inlet. The reaction mixture was heated gradually to reflux and then to keep reflux for 4 h. The product was extracted with 60 ml of 1:1 benzene-hexane, washed with water, and dried over $MgSO_4$. Analytically pure ester was obtained by chromatography over silica gel or distillation by Kugelrohr. GLC yields using hydrocarbons as internal standards are shown in Table 1.

The dienoates prepared by employing the above procedure are as follows.

Ethyl (2*E*,4*E*)-2,4-Undecadienoate: IR (neat) 1720, 1645, and 1620 cm^{-1}; ^{1}H NMR δ=0.90 (t, 3H, J=6.5 Hz), 1.30 (t, 3H, J=7.5 Hz), 1.25—1.70 (m, 8H), 2.05—2.30 (m, 2H), 4.13 (q, 2H, J=7 Hz), 5.71 (d, 1H, J=15 Hz), 6.0—6.4 (m, 2H), and 7.16 (ddd, 1H, J=3, 7, and 15 Hz); MS m/z 210, 165, 153, 125; Found: C, 74.07; H, 10.49%. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54%.

Ethyl (2*E*,4*E*)-9-Chloro-2,4-nonadienoate: IR (neat) 1710, 1645, and 1620 cm^{-1}; ^{1}H NMR δ=1.28 (t, 3H, J=7.5 Hz), 1.5—2.0 (m, 4H), 2.1—2.4 (m, 2H), 3.51 (t, 2H, J=6 Hz), 4.16 (q, 2H, J=7 Hz), 5.73 (d, 1H, 16Hz), 6.0—6.4 (m, 2H), and 7.19 (dd, 1H, J=10 and 16 Hz); MS m/z 216, 171, 143, and 125; Found: C, 61.29; H, 7.91%. Calcd for $C_{11}H_{17}O_2Cl$: C, 61.97; H, 7.91%.

Ethyl (2*E*,4*E*)-4-Ethyl-2,4-heptadienoate: IR (neat) 1715 and 1625 cm^{-1}; ^{1}H NMR δ=0.99 (t, 3H, J=7 Hz), 1.0 (t, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 2.0—2.4 (m, 4H), 4.11 (q, 2H, J=7 Hz), 5.71 (d, 1H, J=15.5 Hz), 5.77 (t, 1H, J=7 Hz), and 7.1 (d, 1H, J=15.5 Hz); Found: C, 72.28; H, 9.93%. Calcd for $C_{11}H_{18}O_2$: C, 72.49, H, 9.95%.

1-[(*E*)-1-Hexenyl]-2-(ethoxycarbonyl)cycloheptene: IR (neat) 1715, 1640, and 1595 cm^{-1}; ^{1}H NMR δ=0.895 (t, 3H, J=7 Hz), 1.31 (t, 3H, J=7 Hz), 1.1—1.9 (m, 10H), 1.9—2.3 (m, 2H), 2.3—2.6 (m, 4H), 4.21 (q, 2H, J=7.3 Hz), 5.85 (dt, 1H, J=7 and 16 Hz), and 6.75 (d, 1H, J=16 Hz); MS m/z 250, 205, 193, and 165; Found: m/z 250.1934. Calcd for $C_{16}H_{26}O_2$: M, 250.1933.

4-[(*E*)-1-Hexenyl]coumarin: Mp 67 °C; IR (Nujol) 1720, 1650, and 1610 cm^{-1}; ^{1}H NMR δ=0.96 (t, 3H, J=7 Hz), 1.2—1.6 (m, 4H), 2.2—2.5 (m, 2H), 6.41 (s, 1H), 6.43 (dt, 1H, J=6 and 21 Hz), 6.73 (d, 1H, J=21 Hz), and 7.1—7.9 (m, 4H); MS Found: m/z 228.1138. Calcd for $C_{15}H_{16}O_2$: M, 228.1151.

Ethyl (2*Z*,4*E*)-5-(2,6,6-Trimethylcyclohexenyl)-3-methylpentadienoate: IR (neat) 1715, 1615, 1230, and 955 cm^{-1};

^{1}H NMR δ=1.07 (s, 6H), 1.27 (t, 3H, J=7.2 Hz), 1.5—2.2 (m, 6H), 1.77 (s, 3H), 2.04 (s, 3H), 4.16 (q, 2H, J=6.8 Hz), 5.64 (s, 1H), 6.58 (d, 1H, J=16.3 Hz), and 7.63 (d, 1H, J=16.3 Hz); MS m/z 262, 246, 217, 189, and 119; Found: m/z 262.1915. Calcd for $C_{17}H_{26}O_2$: M, 262.1933.

Cross-Coupling of (*E*)-1-Hexenyl-1,3,2-benzodioxaborole (9) with Ethyl (*Z*)-3-Bromoacrylate (10) (Eq. 4). A mixture of the catalyst (0.03 mmol), K_2CO_3 (2 mmol), ethyl (*Z*)-3-bromoacrylate (1 mmol), and 2-[(*E*)-1-hexenyl]-1,3,2-benzodioxaborole (1.1 mmol) in 3 ml of 75% ethanol was stirred under the conditions indicated in Table 2. After the reaction was over, the product was extracted with benzene, washed with water and dried over $MgSO_4$. Chromatography over silica gel with hexane-ether gave **11**: IR (neat) 1713, 1640, and 1600 cm^{-1}; ^{1}H NMR δ=0.93 (t, 3H, J=7 Hz), 1.28 (t, 3H, J=7 Hz), 1.2—1.7 (m, 4H), 2.1—2.4 (m, 2H), 4.16 (q, 2H, J=7 Hz), 5.52 (d, 1H, J=11 Hz), 5.99 (dt, 1H, J=7 and 15 Hz), 6.47 (dd, 1H, J=11 and 11 Hz), 7.41 (dd, 1H, J=11 and 15 Hz); MS m/z 182, 153, 137, 125, and 109; Found: C, 71.63; H, 9.69%, Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%. The results are summarized in Table 2.

Synthesis of (Z)-1-Hexenylboronate (6) and Its Reaction with 7 (Eq. 3). To a solution of diisopropyl (*Z*)-(1-bromo-1-hexenyl)boronate (2.2 mmol) in ether (4 ml) was added 4 ml of a solution of potassium hydrotriisopropoxyborate in THF (0.6M solution, 2.4 mmol) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, and then for 30 min at room temperature. After evaporation of the solvent under reduced pressure, the residue **6** was dissolved in 8 ml of methanol. $Pd(OAc)_2$ (0.06 mmol), PPh_3 (0.12 mmol), K_2CO_3 (4 mmol), and methyl (*E*)-3-bromo-2-methylpropenoate (2 mmol) were added, and the mixture was refluxed for 5 h. The reaction mixture was diluted with benzene (30 ml), washed with water, and dried over $MgSO_4$. The product was isolated by chromatography over silica gel with benzene/ethyl acetate (20:1). Analysis by GLC revealed the formation of **8** (1.9 mmol, 95%): IR (neat) 1710, 1635, 1605, 1115, and 735 cm^{-1}; ^{1}H NMR δ=0.91 (t, 3H, J=7 Hz), 1.2—1.5 (m, 4H), 1.93 (s, 3H), 2.1—2.4 (m, 2H), 3.76 (s, 3H), 5.75 (dt, 1H, J=7.6 and 11.2 Hz), 6.27 (dd, 1H, J=11.2 and 11.6 Hz), and 7.49 (d, 1H, J=11.6 Hz); MS m/z 182, 151, and 125; Found: m/z 182.1289. Calcd for $C_{11}H_{18}O_2$: M, 182.1297.

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