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Stereoselective Syntheses of Conjugated 1-Phenylthio-1,3-alkadienes and 1,3,5-Alkatrienes through the Palladium-Catalyzed Cross-Coupling Reaction of (E)- or (Z)-1-Alkenylboronates with (E)- or (Z)-2-Bromo-1-phenylthio-1-alkenes†

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1-Phenylthio-1,3-alkadienes and 1,3,5-alkatrienes are obtained in excellent yields stereo- and regioselectively by the cross-coupling between 1-alkenyl or 1,3-alkadienyl-1,3,2-benzodioxaboroles and (E)- or (Z)-2-bromo-1-phenylthio-1-alkenes in the presence of a catalytic amount of $Pd(PPh_3)_4$. These sulfides are converted to the corresponding conjugated alkatrienes and tetraenes by the reaction with Grignard reagents in the presence of Ni-catalyst.

In our recent papers,[1,2] we reported a stereoselective synthesis of (E,E)-, (E,Z)- and (Z,Z)-alkadienes by the palladium-catalyzed cross-coupling reaction between (E)- or (Z)-1-alkenylboronates and (E)- or (Z)-1-halo-1-alkenes. The major advantage of this coupling in synthesis is the ready availability of a variety of (E)- and (Z)-1-alkenylboronates via hydroboration of alkynes or 1-halo-1-alkynes and the cross-coupling reaction takes place while retaining the original cofigurations of both the starting alkenylboranes and the halides.

We now wish to report that the reaction of 1-alkenylboronates with 2-bromo-1-phenylthio-1-alkenes (**2** and **4**)[3] proceeds smoothly under conditions similar to those of the usual 1-halo-1-alkenes to give almost exclusively the 1-phenylthio-1,3-alkadienes and 1,3,5-alkatrienes (**3** and **5**), stereoselectively (Eqs. 1 and 2). Alkylthioalkenes are known to undergo a cross-coupling with Grignard reagents in the presence of Ni- or Pd-catalysts (Eq. 3).[4,5] Although various methods for syntheses of alkenyl sulfides have been explored, the major methods lead to a mixture of stereoisomers which often difficult to separate. The present procedure should give a new and convenient route to stereodefined alkenyl sulfides and conjugated polyenes though the cross-coupling reactions.

When (Z)-2-bromo-1-phenylthio-1-propene (**4**, R^4=Me) reacted with (E)-1-hexenyl-1,3,2-bezodioxaborole (**1a**, R^1=n-Bu, R^2=R^3=H) in the presence of 3 mol% of $Pd(PPh_3)_4$ and aqueous KOH (3 equiv.) for 5 h in refluxing benzene, the substitution of the bromine was found to occur readily and gave (1Z,2E)-2-methyl-

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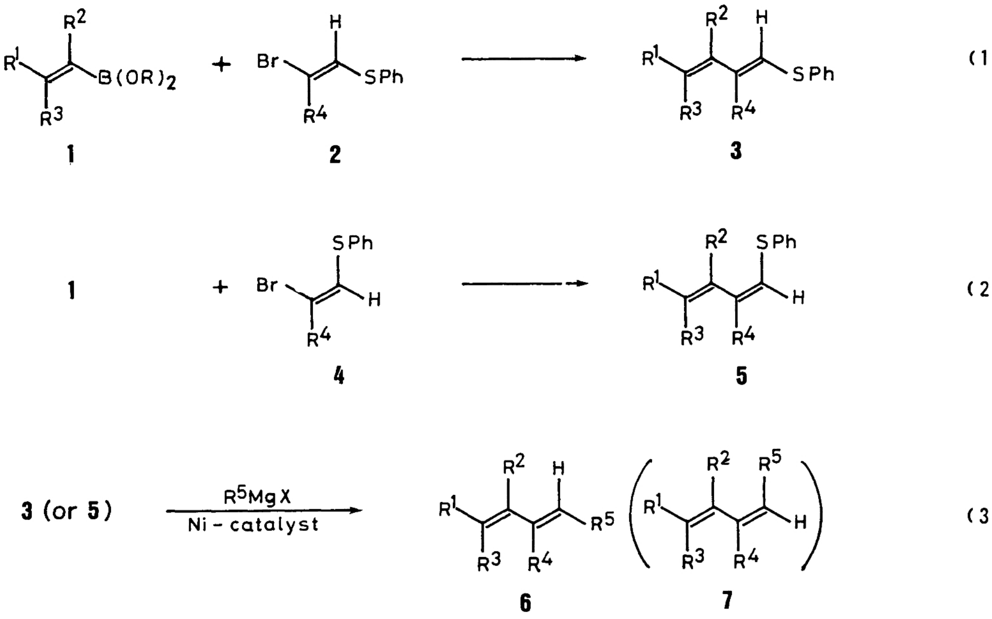
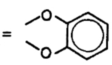
† Dedicated to Professor Teruaki Mukaiyama of the University of Tokyo on the occasion of his 60th birthday.



R^1=alkyl,1-alkenyl R^2=alkyl R^3=alkyl

R^4=H,Me R^5=alkyl,1-alkenyl,aryl

1a $(OR)_2$=



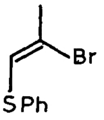
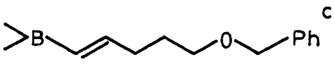
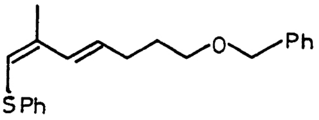
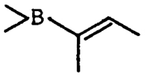
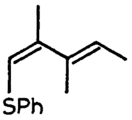
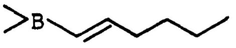
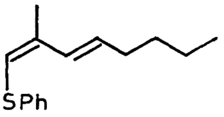
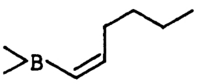
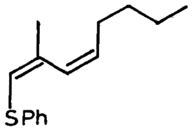
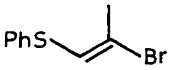
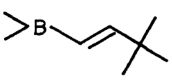
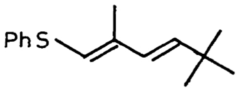
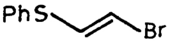
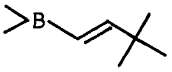
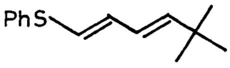
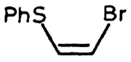
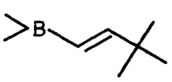
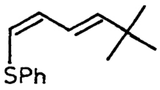
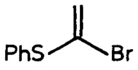
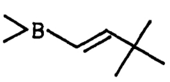
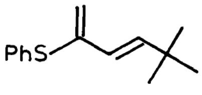
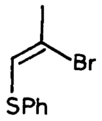
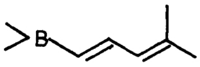
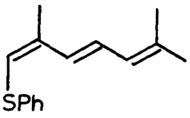
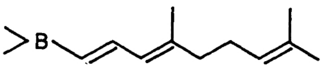
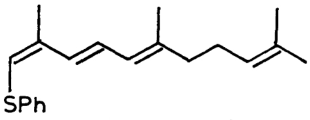
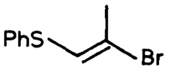
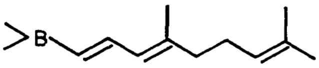
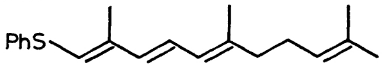
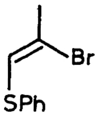
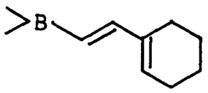
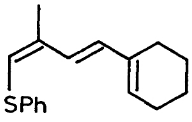
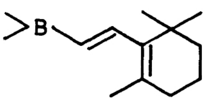
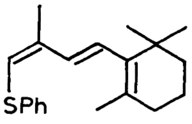
1b $(OR)_2=(OPr^i)_2$

1-phenylthio-1,3-octadiene in a yield of 91%, with isomeric purity of 98%. The reaction was highly selective to the C-Br bond, and the C-S bond was inert even for longer reaction time and in the presence of an excess of 1-hexenylboronate. It should be noted that a high yield of the coupling product can be obtained when a combination of benzene-KOH is used as solvent and base, whereas when the reaction is carried out in benzene-NaOEt which is generally used for the cross-coupling reaction of alkenylboronates, the product yield is only 5%.

In the Table 1, the representative results of the reaction of a variety of (E)- and (Z)-1-alkenylboronates (**1**) with 2-bromo-1-phenylthio-1-alkenes (**2** and **4**) are summarized. The Table clearly shows that this reaction is highly regioselective and gives the products which are prepared by the coupling at the C-Br bond, and the isomeric purity in each reaction is higher than 97%, which is determined by direct comparison with an authentic sample.

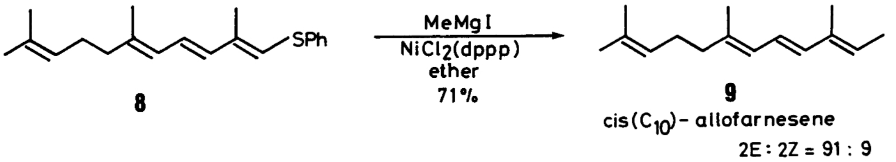
A typical procedure is as follows. A 25ml-flask equipped with a magnetic stirring bar, a septum inlet, and a reflux codenser was charged with $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) and flushed with nitrogen. Benzene (4 ml) and (Z)-1-bromo-2-phenylthioethene (0.215 g, 1 mmol)$^{3)}$ were added and the mixture was stirred for 15 min. Then, (E)-3,3-dimethyl-1-butenyl-1,3,2-benzodioxaborole (**1a**, R^1=t-Bu, R^2=R^3=H)$^{6)}$ and aqueous KOH (4M solution, 0.75 ml) were added. After refluxing for 5 h, the reaction mixture was cooled down to room temperature and diluted with 30 ml of hexane. The organic layer was separated, dried over $MgSO_4$, and then was treated with a few crystals of phenothiazine.$^{7)}$ An analytically pure sample was obtained by chromatography over silica gel with hexane/CH_2Cl_2 (5:1); 0.21 g (96%). Analysis by VPC (fused silica capillary column, OV-101, 25 m) indicated that a ratio of 1-phenylthio-5,5-dimethyl-(1Z,3E)-hexadiene to (1E,3E)-isomer is 97:3.

Table 1. Syntheses of 1-Phenylthio-1,3-alkadienes and 1,3,5-alkatrienes(3 and 5)a)

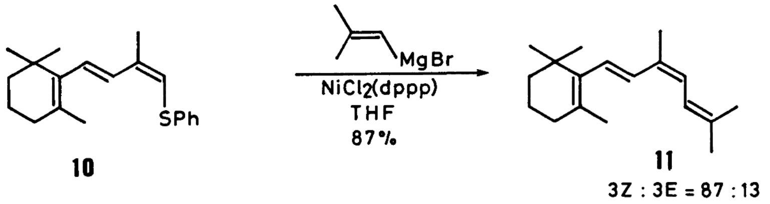
Entry	**2** or **4**	**1**	Product	Yield/%b)
1		 c)		95
2		 c)		87
3		 c)		76
4		 d)		90
5		 c)		97
6		 c)		86
7		 c)		96
8		 c)		71
9		 c)		89
10		 c)		91
11		 c)		88
12		 c)		90
13		 c)		93

a) All reactions were carried out in benzene at 80 °C for 3-5 h, using 5 mol% of $Pd(PPh_3)_4$ and 3 equiv. of aqueous 4M-KOH. b) Isolated yields.
c) 1,3,2-benzodioxaborole (**1a**).6) d) diisopropyl (**1b**).2)

The usefulness of the present method is demonstrated by the syntheses of (2E,4E,6E)-3,7,11-trimethyl-(2,4,6,10)-dodecateraene [cis(C_{10})-allofarnesene] (**9**),[8] and 1-(2,6,6-trimethylcyclohexenyl)-3,6-dimethyl-(1E,3Z,5E)-heptatriene (**11**). Thus, the treatment of the sulfide (**8**) obtained by the reaction of entry 11 in Table 1 with a solution of methylmagnesium iodide in ether (2 equiv.) in the presence of $NiCl_2$(dppp) (5 mol%) at room temperature for 24 h, gave **9** in 71% yield (Eq. 4). The synthesis of **11** by the coupling of sulfide (**10**) (entry 13) with 2-methyl-1-propenylmagnesium bromide (2 equiv.) in THF at room temperature is an example which shows that extention of an additional double bond can be readily achieved (Eq. 5).



(4)



(5)

Use of 1-bromo-2-phenylthioethene as a building block to the synthesis of stereodefined double bonds by sequential cross-coupling reactions with Grignard reagents has been originally reported by Naso and coworkers.[4] The present reaction affords a simple and new route to the generally more difficultly synthesized stereodefined 1,3-alkadienyl and 1,3,5-alkatrienyl phenyl sulfides which are valuable intermediates in the synthesis of conjugated polyenes.

References

1) N. Miyaura, K. Yamada, H. Suginome, and A. Suzuki, J. Am. Chem. Soc., 107, 972 (1985).
2) The synthesis of (Z)-1-alkenylboronates and its cross-coupling reaction with organic halides was reported; N. Miyaura, M. Satoh, and A. Suzuki, Tetrahedron Lett., 27, 3745 (1986).
3) E. Angeletti, F. Montanari, and A. Negrini, Gazz. Chim. Ital., 87, 1086 (1957). (E)- and (Z)-2-Bromo-1-phenylthio-1-alkenes can be readily separated by chromatography over silica gel with hexane. We appreciate Professor F. Naso for sending us a detailed manuscript for synthesis of **2** and **4**.
4) V. Fiandanese, G. Marchese, F. Naso, and L. Ronzini, J. Chem. Soc., Chem. Commun., 1982, 647; J. Chem. Soc., Perkin Trans. 1, 1985, 1115.
5) H. Okamura, M. Miura, and H. Takei, Tetrahedron Lett., 1979, 43 ; E. Wenkert, T. W. Ferreira, and E. L. Michelott, J. Chem. Soc., Chem. Commun., 1979, 637 ; S. Murahashi, M. Yamamoto, K.-i. Yanagisawa, N. Mita, and K. Kondo, J. Org. Chem., 44, 2408 (1979).
6) For the synthesis of 1-alkenyl-1,3,2-benzodioxaboroles, see; H. C. Brown " Organic Synthesis via Boranes", John Wiley & Sons, N.Y. (1975) and references 1 and 8.
7) The products, sulfides suffer deterioration in air. It is advisable therfore to store these sulfides under nitrogen in refrigerator in the presence of phenothiazine.
8) We reported previously the synthesis of trans(C_{10})-allofarnesene; N. Miyaura, H. Suginome, and A. Suzuki, Bull. Chem. Soc. Jpn., 55, 2221 (1982).

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