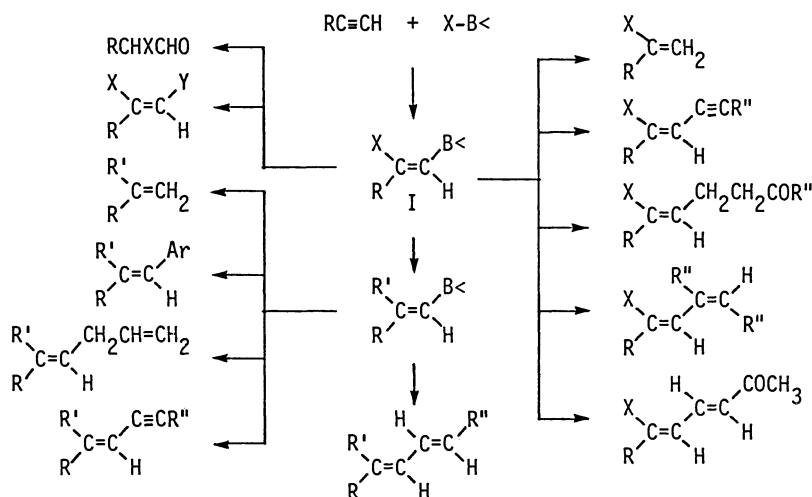


New application of organoboron compounds in organic synthesis

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Abstract - This paper describes the haloboration reaction of 1-alkynes and its application to organic synthesis. B-Bromo- or B-iodo-9-borabicyclo[3.3.1]nonane (B-X-9-BBN) and other haloboranes react readily with 1-alkynes through Markovnikov *cis*-addition of the X-B moiety to C≡C bonds. The haloboration occurs chemoselectively at terminal C≡C bonds, but not at internal C≡C, terminal and internal C=C bonds. The haloboration adducts (I) thus obtained are valuable intermediates to afford various organic compounds stereospecifically in good yields, some of which are shown below.

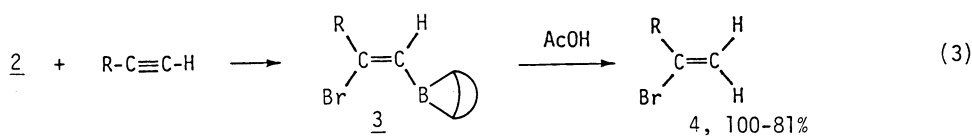
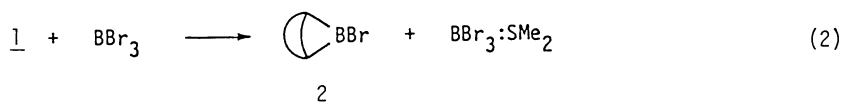
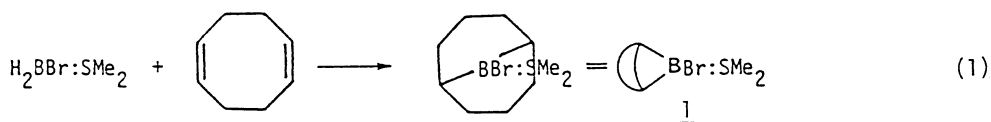


I. HALOBORATION OF 1-ALKYNES WITH B-X-9-BBN

Most recently we reported a general and convenient method for the stereo- and regioselective synthesis of conjugated alkadienes, alkenynes, arylated alkenes, and other olefinic compounds by the cross-coupling reaction of 1-alkenylboranes with a wide variety of unsaturated organic halides in the presence of a catalytic amount of palladium complexes, and bases (ref. 1). In connection with the development of such a cross-coupling, the importance of stereoselective synthesis of alkenyl halides has increased. As one of new types of those syntheses, one can anticipate the hydrometallation or carbometallation of 1-alkynes followed by metal-halogen exchange reaction (ref. 2). For instance, the synthesis of 1-halo-1-alkenes has been efficiently achieved by the reaction sequence, but it is not applicable to the preparation of 2-halo isomers. On the other hand, although the halometallation reaction is considered to be a powerful tool for a method of obtaining 2-halo-1-alkenes, the reaction has not adequately developed for such purposes (ref. 3).

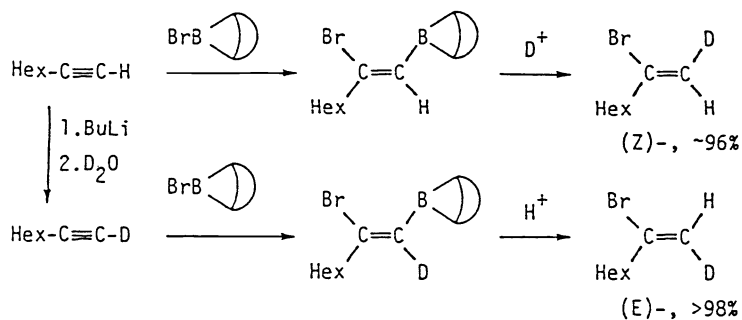
The systematic work of haloboration reaction of unsaturated hydrocarbons with BX_3 seemed to be reported for the first time by Lappert and his coworkers (ref. 4). Nevertheless, there were no reports to apply the haloboration to organic synthesis when we initiated this work. Recently we found that B-X-9-BBN (X=Br or I) reacts with 1-alkynes stereo-, regio-, and chemoselectively. The reasons why we chose the reagent as a haloborating agent are as follows. (1) When BX_3 is employed, there is a possibility to react with di- or triequivalents of alkynes. (2) Steric bulkiness of the borabicyclo[3.3.1]nonane moiety in B-X-9-BBN may increase the reaction selectivity. (3) The ready preparation of B-X-9-BBN was already reported by Brown and his group (ref. 5),

as revealed in eq. 1. It was found that although B-Br-9-BBN:dimethyl sulfide complex (1) itself does not react, the free B-Br-9-BBN (2) readily generated on treatment with tribromoborane reacts with 1-alkynes to afford the corresponding bromoboration products (3), which are converted to 2-bromo-1-alkenes (4) by the protonolysis with acetic acid (eqs. 2 and 3) (ref. 6).



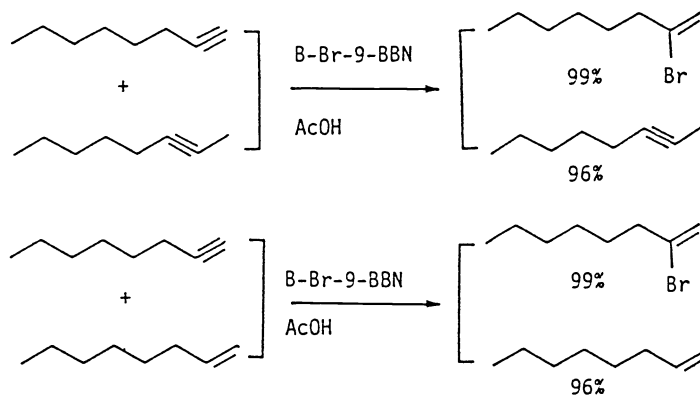
In order to establish the stereochemistry, the experiments depicted in Scheme 1 were carried out, and the results thus obtained definitely indicate that the haloboration proceeds via Markovnikov cis-addition of halogen-boron to the terminal triple bond. In addition, when the reaction of an

Scheme 1



equimolar mixture of 1-octyne and 2-octyne with B-Br-9-BBN followed by protonolysis with acetic acid was examined, it was ascertained that 1-octyne reacts completely to give 2-bromo-1-octene,

Scheme 2

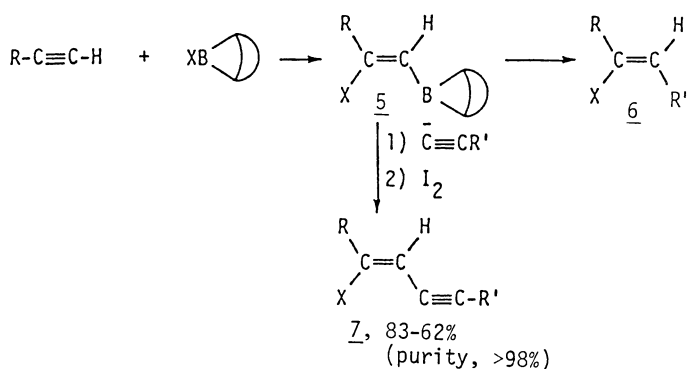


whereas 2-octyne remains unchanged, as shown in Scheme 2. Both 1- and 2-octenes also do not react with the haloborating agent under the same conditions. Consequently, it is concluded that the bromoboration using B-Br-9-BBN occurs only at terminal $C\equiv C$ bonds, not at internal $C\equiv C$, terminal and internal $C=C$ bonds (ref. 6). Further, since many functional groups such as ester and halogen groups can tolerate the reaction conditions, the haloboration is applicable to 1-alkynes with those functional groups. B-I-9-BBN can be also employed for the reaction, whereas B-Cl-9-BBN is very inert as a haloborating agent.

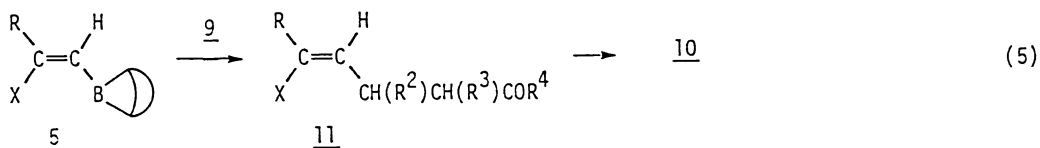
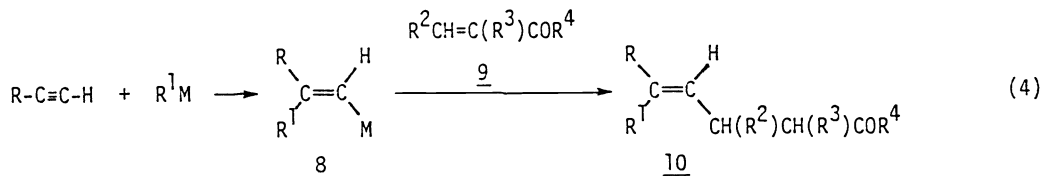
II. SYNTHESIS OF DIORGANO-SUBSTITUTED VINYLIC HALIDES VIA HALOBORATION ADDUCTS OBTAINED FROM B-X-9-BBN

As the haloboration of 1-alkynes with B-X-9-BBN was proved to occur regio-, chemo-, and stereo-selectively, we attempted to displace the boron function with organic groups. Although the carbometallation of 1-alkynes is expected to provide a possible synthetic procedure of diorgano-substituted vinylic halides, the method is not applicable to the synthesis of a type of compounds (6) (ref. 2a). Fortunately, we found that the reaction of 5 with lithium acetylides followed by treatment with iodine gives 1-alkynyl-2-halo-1-alkenes (7) in relatively good yields. Since the stereochemistry of 5 is completely retained during the reaction, this reaction provides a convenient stereodefined synthesis of (Z)-1-alkynyl-2-halo-1-alkenes (7), as shown in Scheme 3 (ref. 7).

Scheme 3

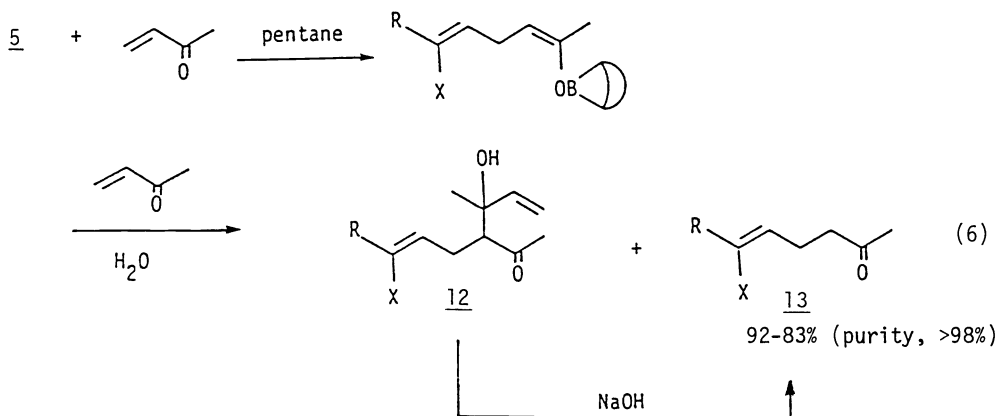


δ,δ -Disubstituted- γ,δ -unsaturated ketones (10) have been reported to be important intermediates in the synthesis of natural products such as terpenes. One of the methodologies for the straightforward synthesis of 10 is a sequence of reactions involving carbometallation of 1-alkynes and conjugate addition of the resultant alkenylmetallics to α,β -unsaturated ketones (9) (eq. 4). However, these Michael-type addition reactions have serious defects because of the inapplicability to readily-polymerizable acyclic α,β -unsaturated ketones (ref. 8). On the other hand, organoborane derivatives are well-known to give good results even for acyclic enones (9) (ref. 9), although there is no direct and general method to synthesize the intermediate β,β -disubstituted alkenylboranes (8, $M=B$) (eq. 4). If the conjugate addition of 5 to 9 occurs smoothly to give 11, it will serve as a useful and versatile intermediate for the synthesis of 10 (eq. 5). However, the expectation



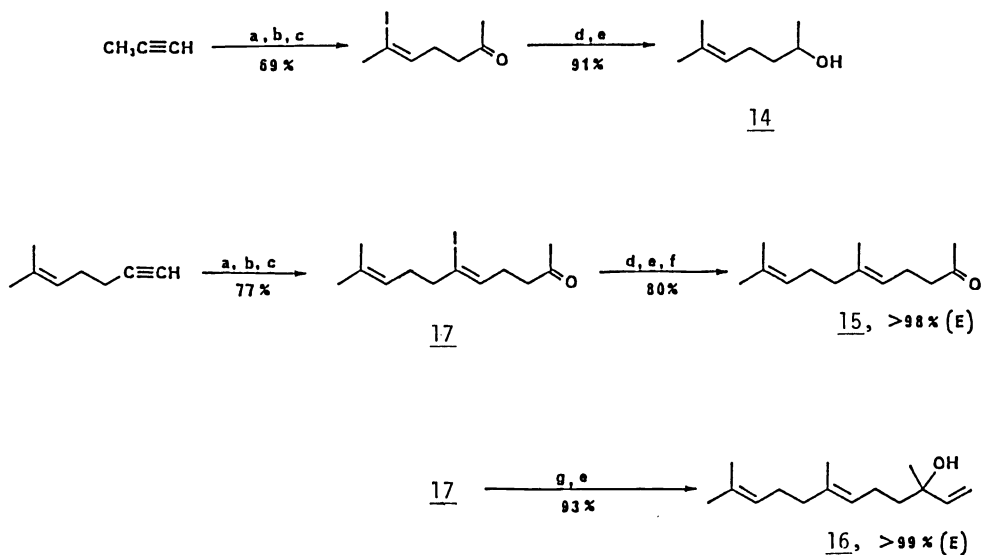
has not been realized, because the haloalkenylboranes (5) are far less reactive, compared with simple alkenylboranes obtained by hydroboration of 1-alkynes, presumably owing to the electro-negative halogen substituent. Thus, we found that the reaction of B-(Z)-2-bromo-1-heptenyl-9-BBN (5, $R=C_5H_{11}$, $X=Br$) with methyl vinyl ketone (MVK) gives 13 in a poor yield (ca. 10%) under the conditions Brown and Jacob employed for B-alkenyl-9-BBN's (reflux in THF) (ref. 10).

In sharp contrast, we found that the reaction takes place smoothly under Lewis acidic conditions (in pentane, 100% excess of B-X-9-BBN). Unexpectedly, the major product isolated after the reaction with MVK under the aforementioned conditions was not the enone (13) but the aldol (12). No aldol adducts were formed in the cases of enones other than MVK. Although attempts to circumvent the unexpected aldol condensation were unsuccessful, the adduct (12) was found to undergo selective retro-aldol condensation when heated with a base (NaOH) (eq. 6). Consequently, this method provides a general route to the haloenones (13) inaccessible by conventional procedures (ref. 11).



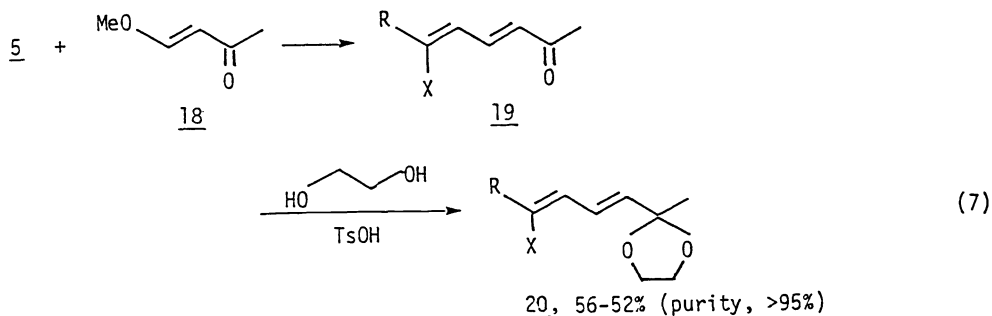
The haloboration-conjugate addition sequence was applied to the synthesis of several natural products, such as sulcatol (14), *trans*-geranyl acetone (15), and *trans*-nerolidol (16) (Scheme 4).

Scheme 4



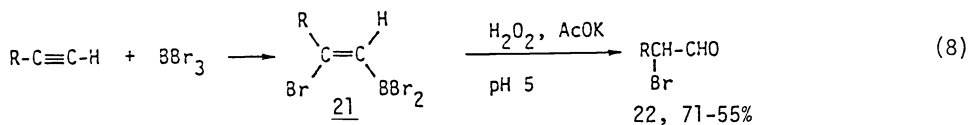
Reagents: ^aB-I-9-BBN, ^bMVK, ^caq. NaOH, heat, ^dNaBH₄, ^eLiCuMe₂,
^fPCC, ^gCH₂=CHMgBr.

Regarding this reaction, we also tried the reaction of 5 with (*E*)- β -substituted MVK (18), and found that the adducts (5) prepared by using an equimolar amount of B-I-9-BBN reacted with 18 to give in moderate yields the corresponding 19, which were isolated and analyzed as their ethylene acetal derivatives (20) (eq. 7) (ref. 12). This reaction was utilized for the synthesis of pseudoionone from 6-methyl-5-hepten-1-yne.

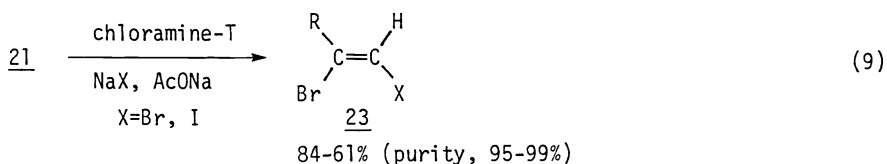


III. OTHER HALOBORATING AGENTS AND THEIR APPLICATION

As an extension of synthetic application of 5, we attempted the synthesis of 2-bromoalkenals by the oxidation of 5. The usual conditions for the hydrogen peroxide oxidation of alkenylboranes are not applied to 5, because they require the presence of relatively strong bases which promote β -elimination, and the complicated oxidation reactions appear to occur under such conditions. Thus, in spite of efforts to find preferable conditions for the oxidation, no successful results were obtained from haloboration adducts prepared from 1-alkynes by treatment with not only B-bromo- and B-iodo-9-BBN's but also hexyldibromoborane and phenyldibromoborane. Tribromoborane was known to be used as a selective haloborating agent if 1-alkyne is haloborated at low temperature (-78°C) (ref. 13). Though the bromoboration adducts (21) thus obtained never gave the corresponding bromoalkenals (22) satisfactorily under the usual oxidation conditions, the prior addition of a solution buffered at pH 5 and potassium acetate was observed to suppress the undesired side reaction (eq. 8) (ref. 14). This method is also applicable for the synthesis of 2-bromoalkenals possessing functional groups.



Previously, it has been reported that either (E)- or (Z)-1,2-dihalo-1-alkenes can be prepared by the haloboration of 1-halo-1-alkynes (ref. 15). However, the stereoselectivity of the reaction was not satisfactory, which led us to continue the effort to improve it. As the haloboration of 1-alkynes proceeds stereo- and regiospecifically to give (Z)-2-halo-1-alkenylboranes (21), the stereospecific displacement of the boron group to halogens may afford (Z)-1,2-dihalo-1-alkenes (23). In this approach, however, serious difficulty might interfere with the reaction, that is, the halogenolysis of alkenylboranes requires basic conditions, whereas 21 is unstable under the conditions. When B-X-9-BBN's were used as haloborating agents, all attempts for the subsequent halogenolysis were unsuccessful. Fortunately, we found that the expected (Z)-1,2-dihalo-1-alkenes (23) were obtained specifically in good yields by the bromoboration of 1-alkynes with tribromoborane and then by the halogenolysis of the resulting adducts with iodine chloride or bromine chloride, and sodium acetate (eq. 9) (ref. 16).



Other haloborane derivatives (ref. 17) are utilized as haloborating agents. Further, Brown and his coworkers have recently reported that dibromoborane-dimethyl sulfide ($\text{HBBr}_2\text{:SMe}_2$) undergoes direct hydroboration of both terminal and internal alkynes with remarkable facility to give alkenyl-

of excess amounts of *n*-butylzinc chloride to a solution of (*Z*)-2-bromo-1-octenyldibromoborane (21, R=*n*-hexyl) resulted in quantitative recovery of 1-octyne (Table I). Despite that, the cross-coupling between 21 and organometallics is effected by prior addition of a catalytic amount of transition metal complexes. The presumed intermediate (27, R=*n*-hexyl) reacts with acetic acid to give 2-butyl-1-octene (28, R=*n*-hexyl), the yields of which under various combinations of organometallics and reaction conditions are summarized in Table I (Scheme 5) (ref. 26). The reaction of 27 with iodine chloride in the presence of sodium acetate gives the corresponding vinylic iodides (29) (ref. 26). Retention of the stereochemistry at the coupling stage is confirmed by the direct comparison with authentic samples prepared by known procedures. The glpc analyses and NMR spectra of such alkenyl iodides show the isomeric purity of the iodides to be more than 98%. Moreover, this method has made it possible to introduce various types of organic groups (R' in Scheme 5) with *sp*- and *sp*²-carbons as well as *sp*³ carbons.

TABLE 1. Reaction of 21 with Organometallics (R'M) in the Presence of Transition-Metal Complexes Followed by Treatment with AcOH to Give 28 (Scheme 5: R=*n*-Hexyl, R'=*n*-Butyl)

<i>n</i> -Butyl-M, M= (equiv.)	Transition-metal complex ^a	Yield of <u>28</u> , % ^b
ZnCl (3.0)	none	0
ZnCl (3.0)	PdCl ₂ (PhCN) ₂	8
ZnCl (3.0)	Pd(PPh ₃) ₄	70
ZnCl (3.0)	PdCl ₂ (PPh ₃) ₂	70
ZnCl (1.0)	PdCl ₂ (PPh ₃) ₂	34
ZnCl (3.0)	NiBr ₂ (PPh ₃) ₂	32
ZnCl (3.0)	NiBr ₂ (diphos) ^c	14
ZnCl (3.0)	PdCl ₂ (PPh ₃) ₂ + 2dibal ^d	52
ZnCl (3.0)	Pd(diphos) ₂	34
ZnCl (3.0)	PdCl ₂ (dppf) ^e	42
ZnCl (3.0)	PdCl ₂ [P(<i>o</i> -tol) ₃] ₂	67
Li (3.0)	PdCl ₂ (PPh ₃) ₂	0
MgBr (3.0)	PdCl ₂ (PPh ₃) ₂	35
SnBu ₃ (3.0)	PdCl ₂ (PPh ₃) ₂	0
BBu ₃ (3.0)	PdCl ₂ (PPh ₃) ₂	0

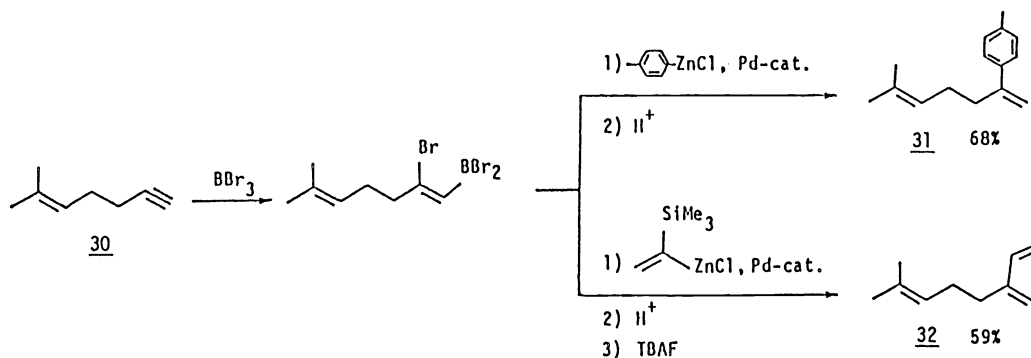
^aIn each case 5 mol% of the catalyst was used. ^bGlpc yield based on 1-octyne.

^cdiphos=1,2-bis(diphenylphosphino)ethane. ^ddibal=diisobutylaluminum hydride.

^edppf=1,1'-bis(diphenylphosphino)ferrocene.

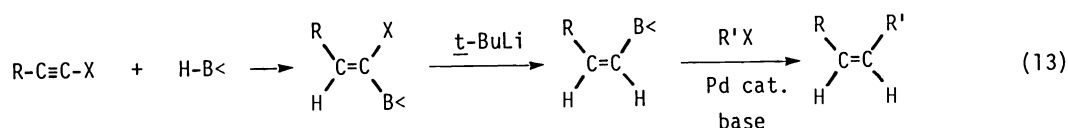
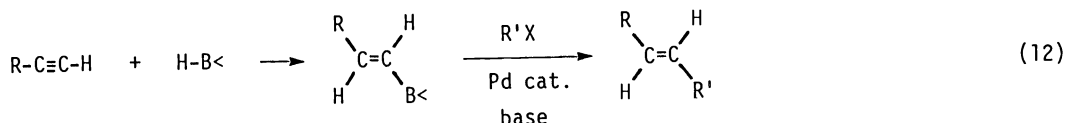
This reaction was applied for the synthesis of dehydro- α -curcumene (31) and myrcene (32) from 30 in yields of 68% and 59%, respectively, based on 30, as illustrated in Scheme 6 (ref. 26).

Scheme 6



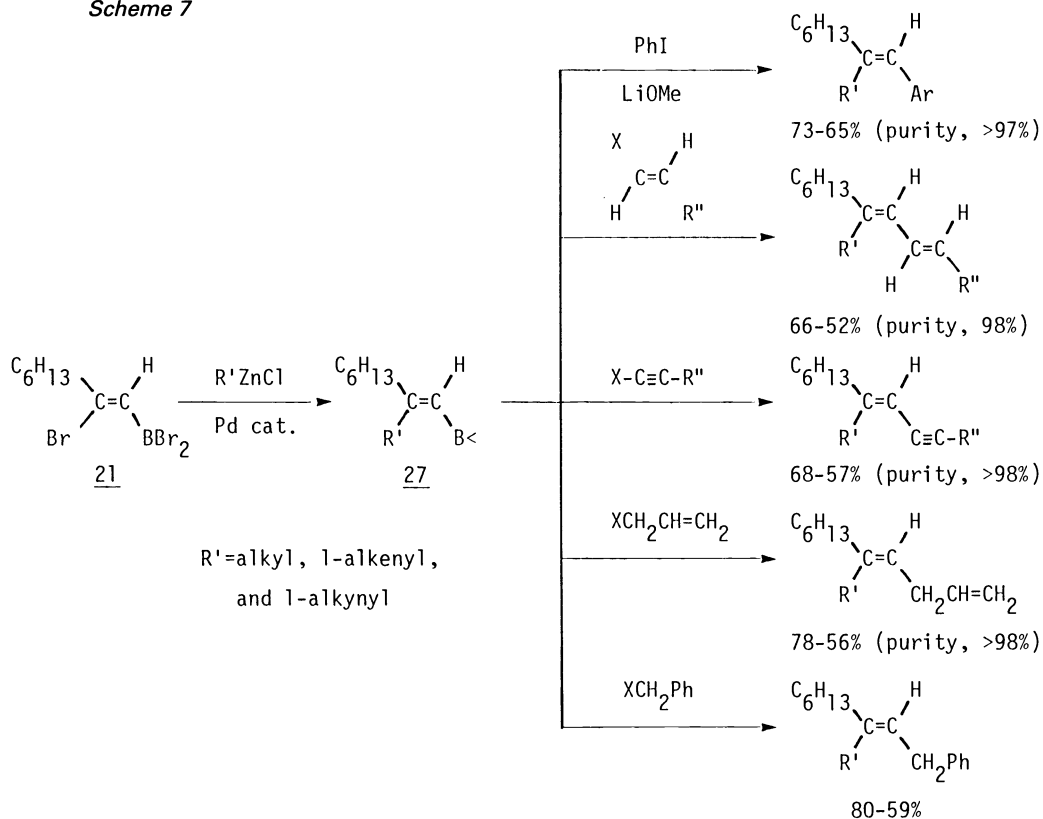
V. DIRECT AND STEREOCONTROLLED SYNTHESIS OF TRIORGANO-SUBSTITUTED OLEFINS BY THE STEPWISE CROSS-COUPLING REACTION OF (Z)-2-BROMO-1-ALKENYLDIBROMOBORANES (21)

Recently, it has been published that the reaction of (*E*)- or (*Z*)-1-alkenyldisiamylboranes or 2-(*E*)-1-alkenyl-1,3,2-benzodioxaboroles readily obtainable by hydroboration, with either (*E*)- or (*Z*)-1-alkenyl halides in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium, and bases such as sodium alkoxides gives the corresponding (*E,E*)-, (*E,Z*)-, (*Z,E*)- or (*Z,Z*)-conjugated alkenes stereo- and regiospecifically, while retaining the configurations of both the starting alkenylboranes and haloalkenes, e.g., as revealed in eqs. 12 and 13 (ref. 27). In this cross-coupling reactions, we can use not only 1-alkenyl halides but also aryl, 1-alkynyl, allylic, and benzylic halides (ref. 1).



However, such conditions are not applicable for the 2-halo-1-alkenylboranes prepared from halo-boration of 1-alkynes. For instance, the cross-coupling reaction of (*Z*)-2-bromo-2-phenyl-1-ethenylcatecholborane with iodobenzene in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium and aqueous sodium hydroxide led to the formation of a complex mixture, in which phenylacetylene formed by elimination of the B-X moiety and toluene are the major products, along with a small quantity of the cross-coupling product.

Scheme 7



Since the displacement reaction of halogen in 21 with organic groups are found to occur with no difficulty, as mentioned in the previous section, we next attempted the reaction of disubstituted alkenylboranes (27) with organic halides in order to synthesize triorgano-substituted olefins. This method may have two major advantages, one of which is that these intermediates (27) by no means suffer from the undesirable β -elimination of X-B, and another one is to make it possible to introduce organic groups with sp -, sp^2 -, and sp^3 -carbons as a group R' in 27. This reaction to obtain trisubstituted olefins seems to be achieved only by the addition of bases into the reaction mixture of the first cross-coupling (21 \rightarrow 27), because in the mixture there is the palladium catalyst which is also effective for the second cross-coupling (Scheme 7).

As supposed, the simple addition of iodobenzene to a solution of an alkenylborane (27) prepared by the method described in Section IV gave no cross-coupling product even after prolonged heating. However, the addition of a basic solution promotes the reaction to give the expected product. Among the bases examined, lithium methoxide and hydroxide gave good results, the reason of which may be due to their high solubilities to organic solvents. Judging from the ^1H NMR and capillary glpc examinations, the phenylated products were obtained in isomerically pure forms, more than 97%. Similarly, 1-alkenyl, 1-alkynyl, allylic, and benzylic halides react readily with 27 to afford the corresponding products under such reaction conditions (Scheme 7) (ref. 28). Although the mechanistic investigation of the double cross-coupling reaction has not explored thoroughly, the reaction is considered to proceed through the route which involves two catalytic wheels of palladium complex, as illustrated in Fig. 1.

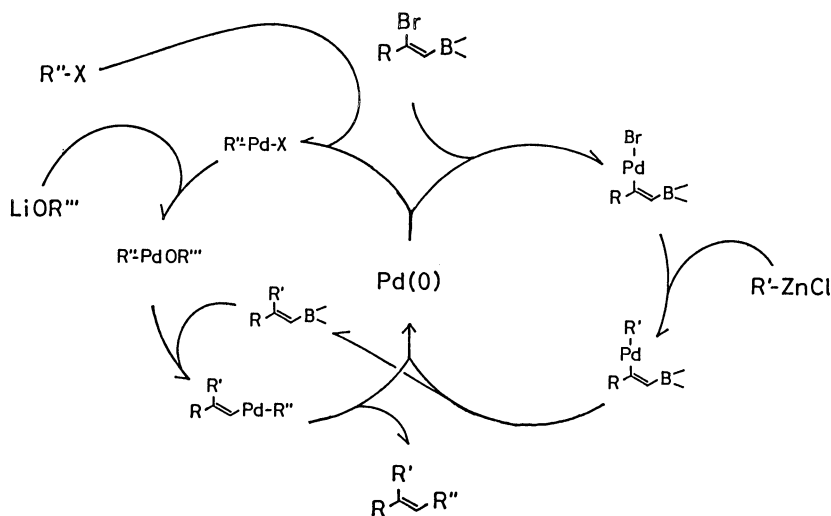


Figure 1. Catalytic cycle for the double cross-coupling reaction.

In this article, a description has been given of the recent development of the haloboration reaction of 1-alkynes and the synthetic application of the haloboration adducts thus obtained. The syntheses of the various classes of organic compounds from such intermediates appears to provide useful, and in some cases, superior alternatives to those using previously established methods.

The major advantages of these reactions are as follows:

- (1) The haloboration of 1-alkynes with B-X-9-BBN and BBr_3 occurs through the Markovnikov *cis*-addition of X-B to terminal $\text{C}\equiv\text{C}$ bonds stereo-, chemo- and regio-selectively, therefore, providing the addition products with predictable structures.
- (2) The haloboration is tolerant of almost every functional group.
- (3) Haloboration adducts are stable toward water.
- (4) The synthetic reactions using haloboration adducts are usually carried out in "one-pot" preparation.
- (5) Such reactions occur under mild conditions.

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REFERENCES

1. A. Suzuki, Pure Appl. Chem., in press (1985).
2. (a) J. F. Normant, A. Alexakis, Synthesis, 841 (1981). (b) J. R. Zietz, Jr., G. C. Robinson, K. L. Lindsay, Comprehensive Organometallic Chemistry (ed. G. Wilkinson), Vol. 7, p. 385, Pergamon, Oxford (1982).
3. E. Negishi, Organometallics in Organic Synthesis, Vol. 1, Wiley, New York (1980).
4. (a) M. F. Lappert, Angew. Chem., 72, 36 (1960). (b) F. Joy, M. F. Lappert, Proc. Chem. Soc., 353 (1960). (c) F. Joy, M. F. Lappert, B. Prokai, J. Organometal. Chem., 5, 506 (1966). (d) M. F. Lappert, B. Prokai, J. Organometal. Chem., 1, 384 (1964).
5. H. C. Brown, S. U. Kulkarni, J. Org. Chem., 44, 2422 (1979). Thereafter, B-X-9-BBN used in this work was prepared by an alternative procedure involving the reaction between 9-borabicyclo[3.3.1]nonane (9-BBN) and bromine or HI [H. C. Brown, S. U. Kulkarni, J. Organometal. Chem., 168, 281 (1979)].
6. S. Hara, H. Dojo, S. Takinami, A. Suzuki, Tetrahedron Lett., 24, 731 (1983).
7. S. Hara, Y. Satoh, H. Ishiguro, A. Suzuki, Tetrahedron Lett., 24, 735 (1983).
8. A. Marfat, P. R. McGuirk, P. Helquist, J. Org. Chem., 44, 3888 (1979). See also ref. 2a.
9. For example, see: E. Negishi, Comprehensive Organometallic Chemistry (ed. G. Wilkinson), Vol. 7, p. 291, Pergamon, Oxford (1982).
10. P. Jacob, H. C. Brown, J. Am. Chem. Soc., 98, 7832 (1976).
11. Y. Satoh, H. Serizawa, S. Hara, A. Suzuki, J. Am. Chem. Soc., 107, in press (1985).
12. T. Tayano, Y. Satoh, S. Hara, A. Suzuki, unpublished work.
13. J. R. Blackborow, J. Organometal. Chem., 128, 161 (1977).
14. Y. Satoh, T. Tayano, H. Koshino, S. Hara, A. Suzuki, Synthesis, in press (1985).
15. S. Hara, T. Kato, A. Suzuki, Synthesis, 1005 (1983).
16. S. Hara, T. Kato, H. Shimizu, A. Suzuki, Tetrahedron Lett., 26, 1065 (1985).
17. (a) J. J. Eisch, F. Shen, K. Tamao, Heterocycles, 18, 245 (1982). (b) J. J. Eisch, H. P. Becker, J. Organometal. Chem., 171, 14 (1979). (c) R. Einnewirtz, H. Klingenberger, R. Welter, P. Paetzold, Chem. Ber., 116, 1271 (1983).
18. H. C. Brown, J. E. Campbell, Jr., J. Org. Chem., 45, 389 (1980).
19. S. Hyuga, S. Takinami, S. Hara, A. Suzuki, unpublished work.
20. S. Hyuga, S. Hara, A. Suzuki, unpublished work.
21. E. Negishi, Pure Appl. Chem., 53, 2333 (1981).
22. E. Negishi, D. E. Van Horn, T. Yoshida, C. L. Rand, Organometallics, 2, 563 (1983).
23. E. Negishi, J. A. Miller, J. Am. Chem. Soc., 105, 6761 (1983).
24. E. M. Mikhailov, Yu. N. Bubnov, Organoboron Compounds in Organic Synthesis, p. 609, Harwood, Chur, Switzerland (1984).
25. J. V. N. Prasad, C. N. Pillai, J. Organometal. Chem., 259, 1 (1983). See also ref. 2a.
26. Y. Satoh, H. Serizawa, S. Hara, A. Suzuki, unpublished work.
27. N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, J. Am. Chem. Soc., 107, 972 (1985).
28. Y. Satoh, H. Serizawa, N. Miyaura, S. Hara, A. Suzuki, unpublished work.