

New synthetic transformations via organoboron compounds

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Abstract: It was previously reported that the palladium-catalyzed cross-coupling reaction of 1-alkenylboron compounds with various vinylic or aryl halides in the presence of base provides the corresponding coupling products in high yields, stereo- and regioselectively. The recent progress of such reactions, including the reaction of sterically hindered arylboronic acids with sterically hindered haloarenes, the palladium-catalyzed carbonylative cross-coupling to provide a versatile ketone synthesis, the synthesis of functionalized organotin compounds, the stereoselective synthesis of exocyclic alkenes, and the syntheses of allylic and benzylic boronates, is described.

INTRODUCTION

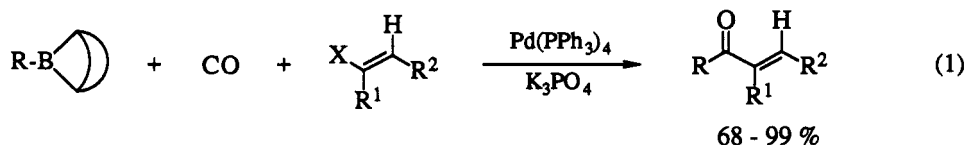
The cross-coupling reactions of various organoboranes with a number of organic halides in the presence of a catalytic amount of palladium complexes and bases were reported to give versatile and useful synthetic methods for conjugated alkadienes and alkenynes, arylated alkenes, 1,4-alkadienes, allylic benzenes, α,β -unsaturated carboxylic acids, and 2,4-alkadienoates (ref. 1). Thereafter, a modified method for the synthesis of conjugated alkadienes, syntheses of stereodefined trisubstituted alkenes, benzo-fused heteroaromatic compounds, and α,β -unsaturated ketones were presented (ref. 2). Although the palladium-catalyzed cross-coupling reactions of 1-alkenyl- and arylboranes with organic halides proceed readily and stereo- and regioselectively to give expected coupling products in high yields, organoboranes with alkyl groups on boron were not used successfully for the coupling under similar conditions. Recently, it was found that the reaction between 9-alkyl-9-BBN derivatives and 1-halo-1-alkenes or haloarenes in the presence of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) and base, such as sodium hydroxide, potassium carbonate, and phosphate gives the corresponding alkenes or arenes in excellent yields (ref. 2). By using the reaction, cycloalkenes, benzo-fused cycloalkenes, and exocyclic alkenes are readily synthesized (ref. 2). The palladium-catalyzed coupling reactions of 1-alkenyl-, aryl-, and alkylboron compounds with aryl or 1-alkenyl triflates, instead of organic halides, take place with ease to give expected coupling products in high yields under mild conditions (ref. 2).

Most recently, we have found new synthetic methods related to the palladium-catalyzed cross-coupling reactions of organoborane derivatives, which are described in this review.

CARBONYLATIVE CROSS-COUPLING OF 9-ALKYL-9-BBN DERIVATIVES WITH 1-HALO-1-ALKENES (ref. 3) AND IODOALKANES (ref. 4)

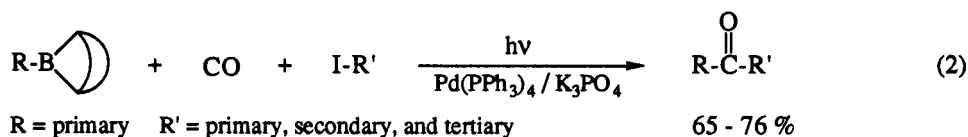
Carbonylative cross-coupling of organometallic compounds with organic halides are reported to give a method for the synthesis of ketones. Among a variety of organometallic reagents, a method using organoboron compounds was first examined by Kojima and his coworkers (ref. 5) for the synthesis of

alkyl aryl ketones. Due to the low nucleophilicity of alkyl group on boron, the transmetalation between organoboranes and acylpalladium(II) species generated in the catalytic cycle is anticipated to be a step of retarding in the coupling of organoboron compounds. They found that bis(acetylacetonato)zinc(II) accelerates the transmetalation step and the palladium-catalyzed carbonylative coupling of organoboranes with aryl and benzyl halides gives the corresponding ketones. However, when we applied the procedure in the reaction with 1-halo-1-alkenes, it was recognized that no expected α,β -unsaturated ketones are obtained. Thus, we have reinvestigated such a carbonylative cross-coupling reaction, and observed that the coupling of 9-alkyl-9-BBN derivatives (9-R-9-BBN) with carbon monoxide and 1-iodo-1-alkenes is effectively induced with K_3PO_4 at room temperature in the presence of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ (eq. 1).

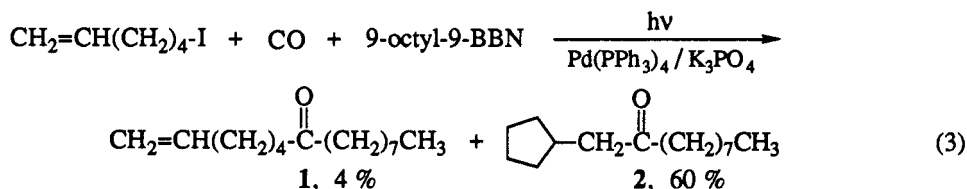


The reaction is considered to proceed via a pathway similar to that of the palladium-catalyzed carbonylative coupling reaction of other organometallics which involves (a) oxidative addition of haloalkenes to $Pd(0)$ complex, (b) insertion of carbon monoxide to give acylpalladium(II) halide, (c) transfer of alkyl group on boron to acylpalladium(II) halide with the aid of K_3PO_4 , and (d) reductive elimination to ketone. One of advantages of this ketone synthesis is to be able to use for the synthesis of ketones with various functional groups, because of the tolerant character of organoboranes.

In the course of the studies, we have discovered that 9-alkyl-9-BBN derivatives react with iodoalkanes under a carbon monoxide pressure in the presence of K_3PO_4 and a catalytic amount of $Pd(PPh_3)_4$ yielding unsymmetrical dialkyl ketones. Although the reaction takes place slowly under dark, the irradiation of light, especially visible, accelerates the rate of coupling to give products in high yields (eq. 2, ref. 4). The irradiation of UV or a high carbon monoxide pressure gives no satisfactory results. A



particularly interesting transformation is observed in the case of reaction with 1-iodo-5-hexene (eq. 3).



The reaction with 9-octyl-9-BBN under the standard carbonylative coupling conditions does not give the expected ketone (1) as the major product, instead, 1-cyclopentyl-2-decanone (2) is obtained in 60% yield. The transformation is considered to occur by prior isomerization of the hexenyl iodide to (iodomethyl)cyclopentane followed by cross-coupling of this latter iodide (ref. 6).

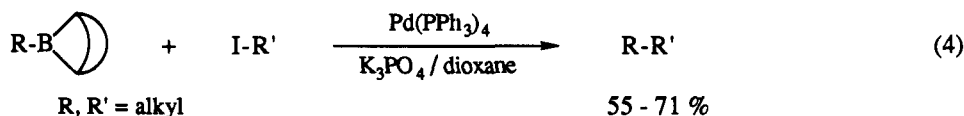
The use of alkyl halides for the palladium-catalyzed cross-coupling reaction was regarded to be difficult, because of the slow rate of oxidative addition step and the β -elimination from oxidative adducts. The

present study may open a window to utilize alkyl halides as organic electrophiles in the coupling reaction. Indeed, iodoalkanes have been revealed to couple with 9-alkyl-9-BBN derivatives to yield the corresponding alkanes, such a reaction of which will be discussed next.

ALKYL-ALKYL CROSS-COUPLING OF 9-ALKYL-9-BBN DERIVATIVES WITH IODOALKANES POSSESSING β -HYDROGENS (ref. 7)

Although a wide variety of organic electrophiles, such as aryl, 1-alkenyl, benzyl, allyl, and 1-alkynyl halides, have been efficiently utilized for the palladium-catalyzed cross-coupling reactions with various organometallic reagents, it has been considered that such reactions cannot be extended to alkyl halides with sp^3 -carbon having β -hydrogens due to the slow rate of oxidative addition of alkyl halides to palladium(0) complexes and the fast β -hydride elimination from σ -alkylpalladium intermediates in the catalytic cycle. Thus, the use of alkyl halides as coupling partners is a challenging problem in several recent publications. Castle and Widdowson (ref. 8) reported recently that Pd(dppf), formed *in situ* by the reduction of PdCl₂(dppf) with DIBAL, effectively catalyzes the cross-coupling of iodoalkanes with Grignard reagents. However, Yuan and Scott (ref. 9) published thereafter that the reaction reported by Castle and Widdowson provides exclusively reduction products of alkyl halides instead of coupling products.

In the case of organoboron compounds, we have found that such a reaction of usual iodoalkanes with 9-alkyl-9-BBN derivatives proceeds readily in the presence of Pd(PPh₃)₄ and K₃PO₄ in dioxane to give the corresponding coupling products in fairly good yields (eq. 4, ref. 7).

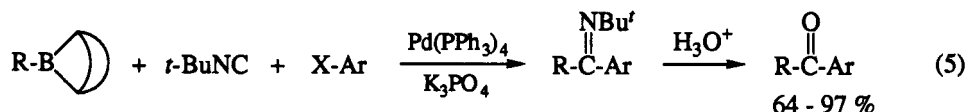


In order to examine the effect of organometallic reagents in the coupling reaction, a molar amount of 1-iododecane is allowed to react with various butylmetal reagents under the conditions which we used above, [Pd(PPh₃)₄-K₃PO₄/dioxane] and the Widdowson's conditions [PdCl₂(dppf)/THF]. Among the reagents we examined, the 9-alkyl-9-BBN derivatives are only effective for the coupling reaction. Neither tributylborane nor lithium tetrabutylborate as a boron reagent is suitable for the reaction. Other metal reagents, such as Mg, Zn, Al, Sn, Zr, and Hg, give no satisfactory results at all. In all of these experiments, decane and decene caused by β -hydride elimination are commonly obtained.

IMINOCARBONYLATIVE CROSS-COUPLING BETWEEN HALOARENES, *t*-BuNC, AND 9-ALKYL-9-BBN DERIVATIVES. SYNTHESIS OF ALKYL ARYL KETONES (ref. 10)

In the previous section, it was mentioned that the carbonylative cross-coupling reaction between organic halides, carbon monoxide, and organoboron compounds in the presence of Pd catalyst and base to give ketones. Although isocyanides are isoelectronic with carbon monoxide and, hence, might be expected to exhibit a similar feature for insertion reactions, only a few reports on the cross-coupling were published. The difficulty of use of isocyanides for the coupling reaction is mainly due to their tendency to cause multiple insertions to transition metal complexes which leads to polyisocyanides. In order to make clear this point, we have tried the reaction with *t*-butylisocyanide, and discovered that 9-alkyl-9-BBN derivatives react with *t*-butylisocyanide to form relatively stable complexes which readily participate in the cross-coupling reaction catalyzed by palladium complex and base. The results are successfully applied to the iminocarbonylative cross-coupling of 9-alkyl-9-BBN compounds with haloarenes under

mild conditions (eq. 5, ref. 10). The protonolysis of intermediates, ketimines, gives the corresponding

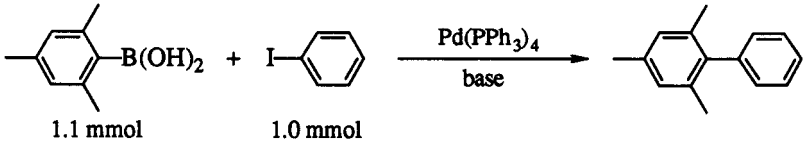


alkyl aryl ketones in good yields. The coupling is highly specific with 9-alkyl-9-BBN and iodoarenes. The reaction of trialkylboranes with iodobenzene and *t*-BuNC under similar conditions does not provide the expected ketone. Quite low yields are obtained by using bromobenzene in place of iodobenzene.

SYNTHESIS OF STERICALLY HINDERED BIARYLS VIA CROSS-COUPLING OF ARYLBORONIC ACIDS OR THEIR ESTERS WITH HALOARENES (ref. 11)

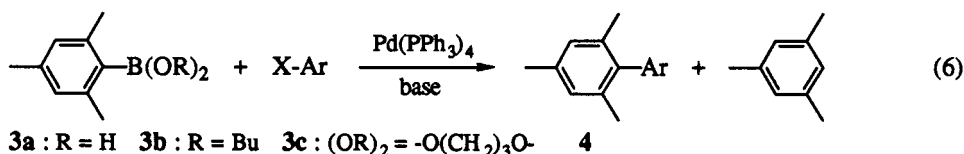
Previously, we reported a simple and versatile method for the synthesis of unsymmetrical biaryls via the cross-coupling of arylboronic acids with haloarenes (ref. 12) in the presence of palladium catalyst and base. Then, many articles with respect to the application of this reaction were published. Although our original procedure (ref. 12) using Pd(PPh₃)₄ and aqueous Na₂CO₃ in benzene at 80 °C was found to work effectively for the most of arylboronic acids, it was pointed out that sterically hindered (ref. 13) or electron-withdrawing group substituted (ref. 14) arylboronic acids never provide satisfactory results owing to steric hindrance or competitive hydrolytic deboration. Consequently, we have attempted to reinvestigate the coupling reaction of such sterically hindered arylboronic acids having *ortho*-substituents or functional groups which accelerate the hydrolytic deboration.

Table 1. Reaction of mesitylboronic acid with iodobenzene

		Yield (%) ^a		
Solvent	Base	8 h	24 h	48 h
		Benzene / H ₂ O	Na ₂ CO ₃	25 (6)
	Ba(OH) ₂	92 (13)		
	TlOH	91 (20)		
DME / H ₂ O	Na ₂ CO ₃	50 (1)	66 (2)	83 (7)
	K ₃ PO ₄	70 (0)	83 (3)	
	Ba(OH) ₂	99 (2)		

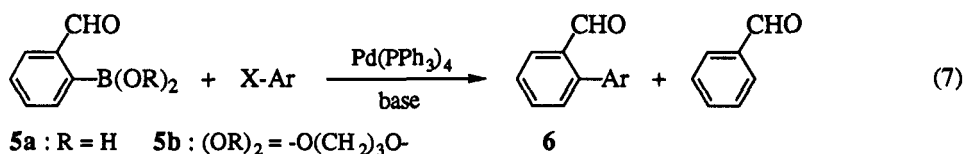
^a Mesitylene yields are shown in parentheses.

The cross-coupling reaction of mesitylboronic acid with aryl halides was known to take place only slowly due to the steric hindrance of two *ortho*-methyl groups (ref. 13). Thus, we examined the reaction of mesitylboronic acid and its esters with iodobenzene at 80 °C in the presence of 2 mol% of Pd(PPh₃)₄ and 1.5 equivalents of various bases (eq. 6). The results are summarized in Table 1.

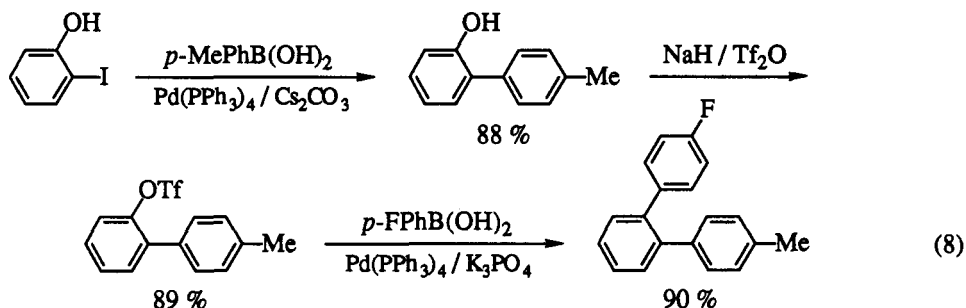


Our previous conditions [Pd(PPh₃)₄/Na₂CO₃/benzene-H₂O, ref. 12] and the modified conditions by Gronowitz [Pd(PPh₃)₄/Na₂CO₃/DME-H₂O, ref. 14] are not satisfactory for the coupling of mesitylboronic acid, and the reaction is not completed even after 2 days. Although the side reactions such as homocoupling are negligibly small, the formation of mesitylene obtained by hydrolytic deboronation increases slowly with the reaction time. On the other hand, the addition of stronger bases, e.g., aqueous NaOH or Ba(OH)₂, both in benzene and DME exerts remarkable effect on acceleration of the rate of coupling. By using such conditions, mesitylboronic acid couples with iodobenzene within 4 h to give the corresponding biaryl in a quantitative yield. For such hindered arylboronic acids, an alternative procedure employing the boronic esters and anhydrous bases is developed.

2-Formyl group on arylboronic acids is known to accelerate the rate of hydrolytic deboronation (ref. 14). Indeed, the coupling of 2-formylphenylboronic acid (**5a**) with 2-iodo-toluene at 80 °C using Na₂CO₃ in DME/H₂O gives only a 54% yield of the corresponding biaryl (**6**) accompanying benzaldehyde (39%), as shown in eq. 7. The aprotic conditions are desirable for such boronic acids sensitive to aqueous base.



Thus, the trimethylene glycol ester of 2-formylphenylboronic acid (**5b**) readily couples with 2-iodotoluene at 100 °C in the presence of K₃PO₄ in DMF in a yield of 89%, although less than 10% of benzaldehyde is still accompanied. In Table 2 the representative results are summarized. The combination of the present reaction and the cross-coupling with triflates (ref. 2) which is demonstrated in eq. 8, gives the unsymmetrically substituted diarylbenzene in a high yield.



CROSS-COUPLING OF ENOL ACETATES OF α -BROMOKETONES WITH 1-ALKENYL-, ARYL-, OR ALKYLBORON COMPOUNDS (ref. 15)

The cross-coupling reaction of alkyl enol ethers or enol acetates of α -bromo carbonyl compounds with representative organoboranes occurs smoothly to give enol ethers or acetates in good yields, which are readily converted into carbonyl compounds by protonolysis (eq. 9, ref. 15).

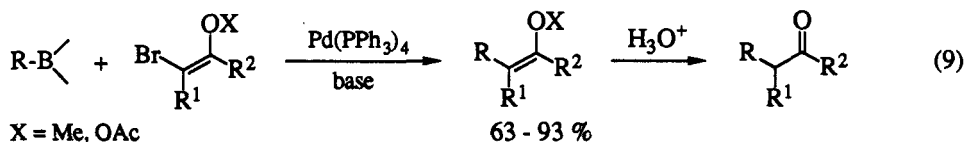
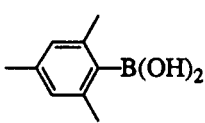
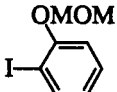
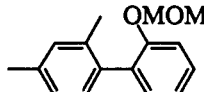
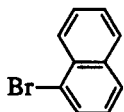
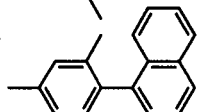
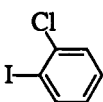
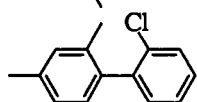
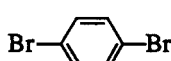
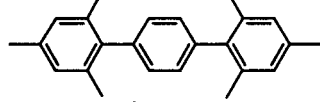
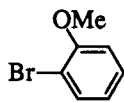
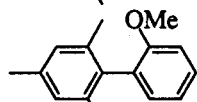
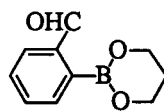
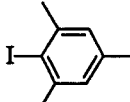
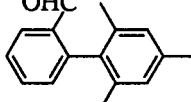
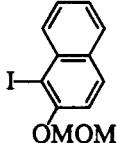
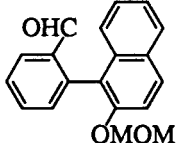
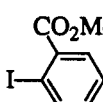
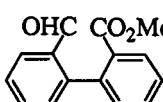
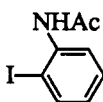
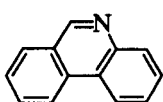
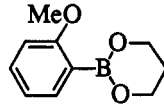
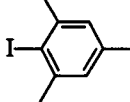
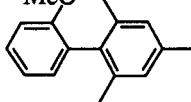
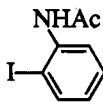
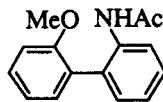


Table 2. Synthesis of hindered biaryls

Boronic acid	Halide	Method	Product	Yield (%) ^a
		A		95
		A		(86)
		A		94
		A ^b		(75)
		A		80
		B		(73)
		B		(85)
		B		63
		B ^c		79
		B		99
		B		95

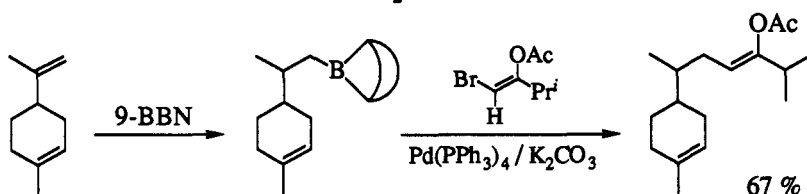
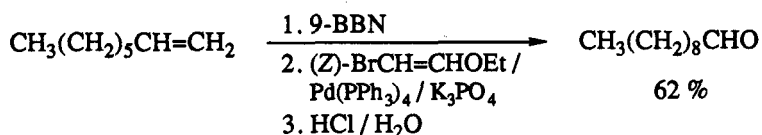
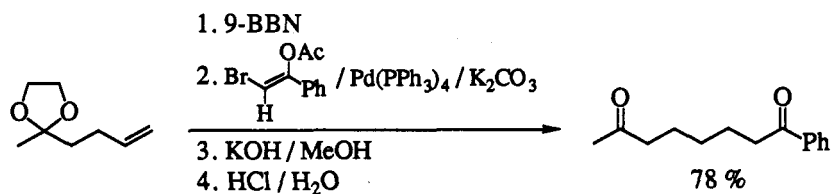
^a GLC yields are based on the aryl halides employed, and isolated yields are in parentheses.

^b Mesitylboronic acid of 2.2 equiv. was used. ^c K₃PO₄ of 2.5 equiv. was used.

Method A : Pd(PPh₃)₄ (2 mol%) and Ba(OH)₂ (1.5 equiv.) in DME-H₂O at 80 °C.

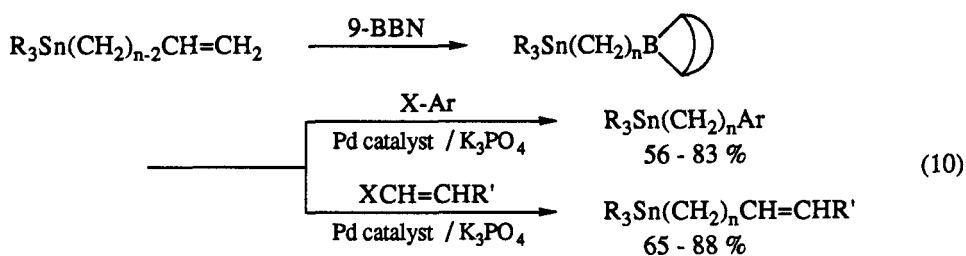
Method B : Pd(PPh₃)₄ (2 mol%) and K₃PO₄ (1.5 equiv.) in DMF at 100 °C.

Some of synthetic applications of the reaction will be shown below (ref. 15).

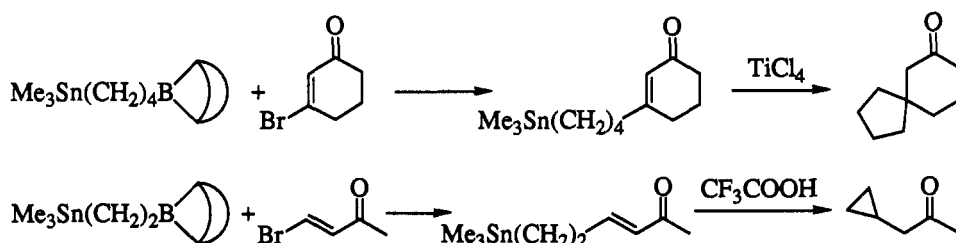


**SYNTHESIS OF FUNCTIONALIZED ORGANOTIN COMPOUNDS VIA
 CROSS-COUPLING OF ARYL OR 1-ALKENYL HALIDES WITH
 9-(ω -STANNYLALKYL)-9-BBN DERIVATIVES (ref. 16)**

Organotin compounds have been attracting currently chemists' attention because of their importance as synthetic intermediates. In connection with our interest in the palladium-catalyzed transformation of organoboron compounds, we have attempted to develop a new route to such organotin reagents based on the coupling of 9-(ω -stannylalkyl)-9-BBN with organic halides (eq. 10, ref. 16). As the catalyst,



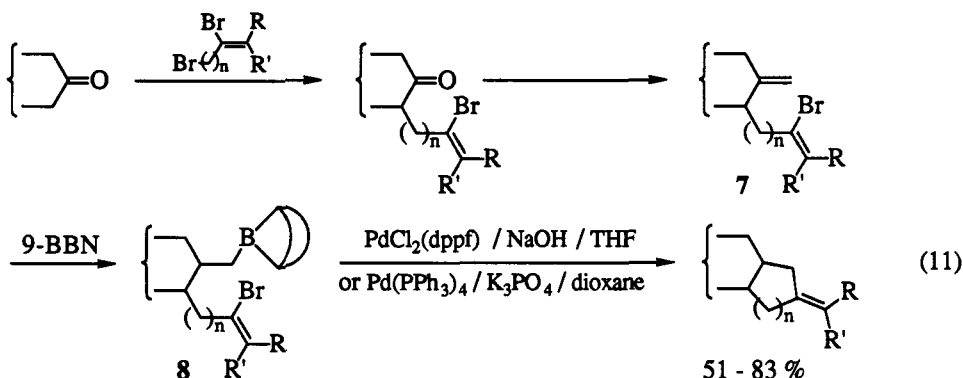
PdCl₂(dppf) in DMF or Pd(PPh₃)₄ in dioxane in the presence of K₃PO₄ gives good results. It is known that enones with ω -stannyl groups are readily destannylated in the presence of acid catalyst to afford carbocyclization products, as shown below.



**STEREOSELECTIVE SYNTHESIS OF EXOCYCLIC ALKENES VIA
HYDROBORATION-COUPLING SEQUENCE (ref. 17)**

The synthesis of exocyclic alkenes (ref. 18) is of great importance in natural product synthesis, because there are many biologically and medicinally interesting compounds with such structures, e.g., carbacyclin.

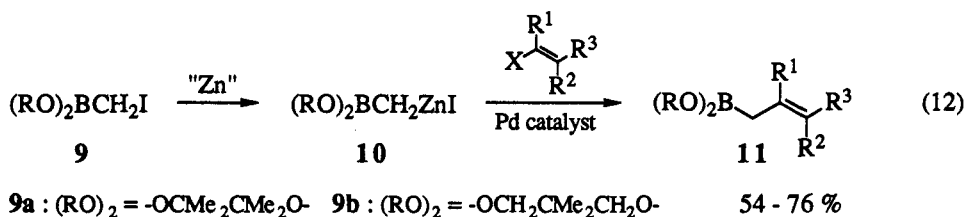
Bromoalkadienes (**7**), the key precursors for the synthesis, were prepared by the procedure as indicated in eq. 11. The palladium-catalyzed intramolecular cross-coupling of **8** gives exocyclic alkenes (eq. 11,



ref. 17). Five- and six-membered exocyclic derivatives can be easily obtained by such hydroboration-coupling sequence. The rate of hydroboration of alkenes is known to be sterically and electronically affected with substituents on alkenes. Especially, halogen groups give remarkable effect on reducing the rate of hydroboration. Consequently, the reaction of 9-BBN occurs chemoselectively at the unhalogenated C=C bond to give the borane intermediate (**8**).

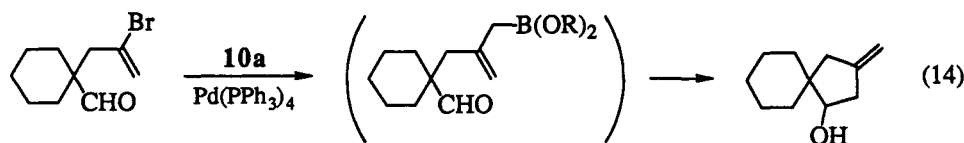
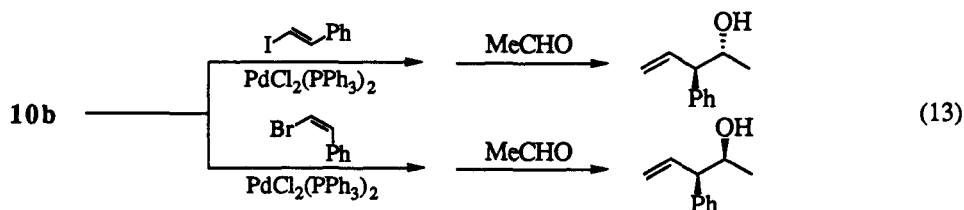
**STEREOSELECTIVE SYNTHESIS OF ALLYLIC AND BENZYLIC
BORONATES VIA CROSS-COUPLING OF (DIALKOXYBORYL)METHYLZINC
REAGENTS (refs. 19 and 22)**

From the viewpoint of synthetic methodology, the synthesis of allylic boronates has been desired (ref. 20). A variety of allylic boronates were made by the reaction of allylic lithium or magnesium compounds with halo- or alkoxyboron derivatives, or by the alkylation of (halomethyl)boronates with stereodefined 1-alkenyllithium reagents. Most recently, we have been interested in developing a synthetic method of such stereodefined allylic boronates (**11**) via the coupling reaction between (dialkoxyboryl)methylzinc compounds (**10**) and 1-halo-1-alkenes (eq. 12, ref. 19). Literature survey revealed a few reports on the

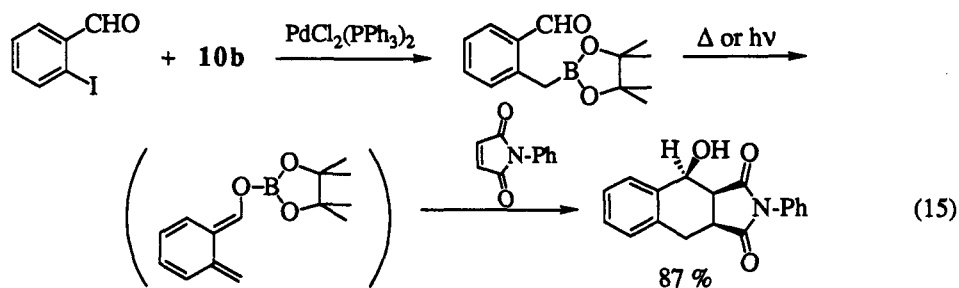


formation of stable borylmethylmetal reagents which can be utilized for the synthesis of allylic boronates through the cross-coupling reaction. However, the recent success of a direct preparation of borylmethylzinc compounds (**10**) from (iodomethyl)boronates (**9**) and activated zinc (ref. 21) prompted us to use them for the coupling reaction. We have found that not only the pinacol derivative (**9a**) reported by Knochel (ref. 21) but also the 2,2-dimethyl-1,3-propanediol derivative (**9b**) can be synthesized readily in almost quantitative yields. The solution of zinc reagents (**9a** and **9b**) is sufficiently stable to be stored in a cold room.

The cross-coupling reaction of **10** with 1-halo-1-alkenes in the presence of palladium catalyst proceeds through complete retention of configuration of haloalkenes to give stereodefined allylic boronates in good to moderate yields. The potential versatility of such coupling reactions is demonstrated in eqs. 13 and 14.

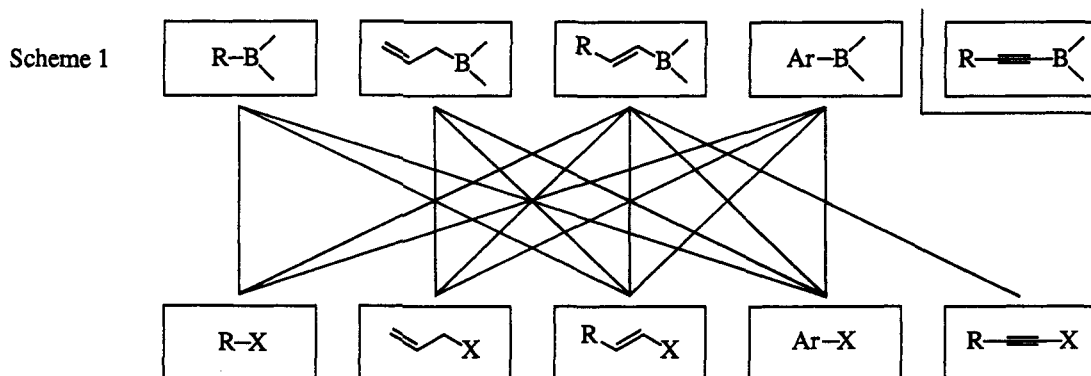


The coupling of **10b** with iodoarenes produces the corresponding benzylic boronates in high yields. Benzylic boronates with acyl groups at the *ortho* position readily undergo the 1,5-rearrangement to the carbonyl oxygen giving the *o*-quinodimethane derivatives under thermal or photochemical conditions. The reaction provides benzo-fused cycloalkanes by trapping with dienophiles, one of such examples of which is illustrated in eq. 15 (ref. 22).



CONCLUSION

In summarizing, we wish to emphasize the usefulness of the coupling reaction in organic synthesis. Although we explored many reactions between organoboranes and organic halides, the problems which should be investigated still remain. The outline of the successful cross-coupling reactions is shown in Scheme 1.



1-Alkynylboron derivatives have never been used in the reaction, because they are unstable under basic conditions. However, as we have perceived most recently a hopeful sign that such compounds react with organic halides under mild basic conditions, the successful result might be reported in the near future.

Acknowledgements

The author wishes to thank the many coworkers whose skill and contribution have made this work possible. This research was supported by the Ministry of Education of Japan (Grant-in-Aid for Scientific Research on Priority Areas #01649008, #02231107, #03215107, and Grant-in-Aid for Scientific Research (B) #04453091) and the Akiyama Foundation.

REFERENCES

1. A. Suzuki, *Pure & Appl. Chem.*, **57**, 1749 (1985).
2. A. Suzuki, *Pure & Appl. Chem.*, **63**, 419 (1991); T. Oh-e, N. Miyaura, and A. Suzuki, *J. Org. Chem.*, **58**, 2201 (1993).
3. T. Ishiyama, N. Miyaura, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, **64**, 1999 (1991).
4. T. Ishiyama, N. Miyaura, and A. Suzuki, *Tetrahedron Lett.*, **32**, 6923 (1991).
5. Y. Wakita, T. Yasunaga, M. Akita, and M. Kojima, *J. Organomet. Chem.*, **301**, C17 (1986).
6. D. P. Curran and D. Kim, *Tetrahedron Lett.*, **27**, 5821 (1986); M. Newcomb and D. P. Curran, *Acc. Chem. Res.*, **21**, 206 (1988).
7. T. Ishiyama, S. Abe, N. Miyaura, and A. Suzuki, *Chem. Lett.*, 691 (1992).
8. P. L. Castle and D. A. Widdowson, *Tetrahedron Lett.*, **27**, 6013 (1986).
9. K. Yuan and W. J. Scott, *Tetrahedron Lett.*, **30**, 4779 (1989).
10. T. Ishiyama, T. Oh-e, N. Miyaura, and A. Suzuki, *Tetrahedron Lett.*, **33**, 4465 (1992).
11. T. Watanabe, N. Miyaura, and A. Suzuki, *Synlett.*, 207 (1992).
12. N. Miyaura, T. Yanagi, and A. Suzuki, *Synth. Commun.*, **11**, 513 (1981).
13. W. J. Thompson and J. Gaudino, *J. Org. Chem.*, **49**, 5237 (1984).
14. S. Gronowitz, A-B. Honfeldt, and Y. Yang, *Chem. Scripta*, **28**, 281 (1988).
15. S. Abe, N. Miyaura, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, **65**, 2863 (1992).
16. T. Ishiyama, N. Miyaura, and A. Suzuki, *Synlett.*, 687 (1991).
17. N. Miyaura, M. Ishikawa, and A. Suzuki, *Tetrahedron Lett.*, **33**, 2571 (1992).
18. D. K. Hutchinson and P. L. Fuchs, *J. Am. Chem. Soc.*, **109**, 4755 (1987); M. Sodeoka, S. Satoh, and M. Shibasaki, *ibid.*, **110**, 4823 (1988).
19. T. Watanabe, N. Miyaura, and A. Suzuki, *J. Organomet. Chem.*, **444**, C1 (1993).
20. R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **21**, 555 (1982); W. R. Roush and R. L. Halterman, *J. Am. Chem. Soc.*, **108**, 294 (1986); H. C. Brown and K. S. Bhat, *ibid.*, **108**, 293 (1986); H. C. Brown and M. V. Rangaishenvi, *Tetrahedron Lett.*, **31**, 7113 (1990).
21. P. Knochel, *J. Am. Chem. Soc.*, **112**, 7431 (1990); M. J. Rozema, A. R. Sidduri, and P. Knochel, *J. Org. Chem.*, **57**, 1956 (1992).
22. G. Kanai, N. Miyaura, and A. Suzuki, *Chem. Lett.*, 845 (1993).