

Minireview

Cross-coupling reactions via organoboranes

Akira Suzuki*

Department of Chemistry and Bioscience, Kurashiki University of Science and the Arts, Kurashiki-shi 712-8505, Japan

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Abstract

The palladium-catalyzed cross-coupling reaction between different types of organoboron compounds, sp^2 -, sp^3 -, and sp -hybridized carbon–boron compounds and various organic electrophiles in the presence of base provides a powerful and general methodology for the formation of carbon–carbon bonds. The coupling reaction offers several advantages. An overview of the coupling reaction will be presented. © 2002 Published by Elsevier Science B.V.

Keywords: Organoboranes; Organic halides; Organic triflates; Coupling reaction; Palladium catalysts; Ligands

1. Introduction

Carbon–carbon bond formation reactions are some of the most important processes in chemistry, that provide key steps in the building of more complex molecules from simple precursors. Over the last several decades, reactions for carbon–carbon bond formation between molecules with saturated sp^3 C-atoms have been developed. However, there were no simple and general methods for carbon–carbon formation between unsaturated groups such as vinyl, aryl, and alkynyl moieties, until the discovery and development of metal-mediated cross-coupling reactions in the 1970s.

In organoboron compounds the boron–carbon bonds are considered to be highly covalent, thus limiting the use of organoboron reagents for ionic reactions. However, such boron derivatives have many advantages; e.g. (1) ready availability of reagents by hydroboration and transmetalation, (2) stability in water and related solvents, (3) toleration toward various functional groups, etc. Consequently, if organoboron reagents are effective for cross-coupling reactions with various organic electrophiles, we can expect a wide range of applications as a new methodology for carbon–carbon bond formation in organic synthesis. The coordination

of negatively charged bases to the boron atom was recognized to be an efficient method for increasing its nucleophilicity and transfer of the organic group on boron to the adjacent positive center (1,2-migration reaction). However, intermolecular transfer reactions such as a Grignard-like reaction were rare, although Negishi described that *o*-iodotoluene selectively coupled with the 1-alkynyl group of lithium 1-heptynyl(tributyl)borate in the presence of a palladium complex [1].

In the mid-1970s we were attempting to find a stereo- and regioselective synthetic method of conjugated alkadienes that are of great importance in organic chemistry in themselves and in their utilization in other reactions such as the Diels–Alder reaction. Although a number of methods for the preparation of conjugated dienes and polyenes were developed utilizing organometallic compounds, one of the promising procedure for preparing conjugated dienes or enynes in a selective manner was considered to be the direct cross-coupling reaction of stereodefined haloalkenes or haloalkynes with stereodefined alkenylboron compounds readily preparable from alkynes by hydroboration in the presence of transition metal catalyst. In spite of efforts to find alkenylboron-based coupling reactions, there were no successful reports when we started this work.

At the initial stage of our exploration, we considered that the difficulty in such a coupling might stem from the following. One widely accepted mechanism of

* Tel.: +81-86-440-1081; fax: +81-86-440-1062.

E-mail address: suzuki@chem.kusa.ac.jp (A. Suzuki).

transition metal catalyzed cross-coupling reactions between organometallic compounds and organic halides involves a sequence consisting of (a) oxidative addition, (b) transmetalation, and (c) reductive elimination [2]. It appeared that 1-alkenylboranes could not readily react with 1-alkenyl- or 1-alkynyl halides, because the transmetalation process between RMX (M = transition metal, X = halogen) and organoboranes would not occur readily due to the weak carbanionic character of organic groups in the organoboranes. To overcome this difficulty, we anticipated to use tetracoordinated organoboron compounds instead of tricoordinated organoboron derivatives. It was observed that the methyl group in tetramethylborate was 5.5 times more electronegative than the methyl group of trimethylborane [3]. Such speculation is also expected in a case of the reaction of triorgano-boranes in the presence of base. Actually we have found that the cross-coupling reaction of vinylic boron compounds with vinylic halides proceeds smoothly in the presence of a base and a catalytic amount of a palladium complex to give stereo- and regioselectively the expected conjugated alkadienes and alkenynes in excellent yields. Not only such vinyl borane derivatives but also different types of organoboron compounds were revealed to react with electrophiles under such reaction conditions. Thus, it was proved that (sp³)C–B compounds (alkylboron compounds) and (sp²)C–B compounds such as aryl- and 1-alkenylboron derivatives readily cross-couple with a number of organic electrophiles to provide coupling products selectively in high yields. Although (sp)C–B compounds (1-alkynylboron derivatives) could not be coupled with organic electrophiles under our conditions, the coupling reaction of such organoboron compounds were reported by American and German chemists independently. These reactions offer several advantages:

- 1) Ready availability of reagents.
- 2) Mild reaction conditions.
- 3) Water stability.
- 4) Easy use of the reaction both in aqueous and heterogeneous conditions.
- 5) Toleration of a broad range of functional groups.
- 6) High regio- and stereoselectivity of the reaction.
- 7) Insignificant effect of steric hindrance.
- 8) Use of a small amount of catalysts.
- 9) Application in one-pot synthesis.
- 10) Nontoxic reaction.
- 11) Easy separation of inorganic boron compounds.

In this brief review, the cross-coupling reactions of organoboron compounds are described in the order of 1-alkenyl-, aryl-, 1-alkyl-, and 1-alkynylboron compounds, which is roughly the order of discovery of the reactions.

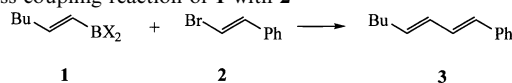
2. Cross-coupling of 1-alkenylboranes

2.1. With 1-alkenyl halides

Actually, we found that the palladium-catalyzed cross-coupling reaction of vinylic boron compounds with vinylic halides proceeds smoothly in the presence of base to give the expected conjugated alkadienes and alkenynes stereo- and regioselectively in high yields (Table 1) [4]. Although the coupling reaction of (*E*)-1-alkenylboranes, readily obtained via the hydroboration of appropriate alkynes with disiamylborane or dicyclohexylborane, proceeds smoothly with (*E*)- and (*Z*)-1-alkenyl bromides and iodides to give the corresponding dienes readily [4] (Table 2), (*Z*)-1-alkenylboranes, prepared by hydroboration of 1-haloalkynes followed by the reaction with *t*-butyllithium, gave product yields only around 50% (Table 3).

Fortunately, it became apparent that high yields and stereoselectivity could be achieved by coupling (*Z*)-1-alkenyl halides with (*Z*)-1-alkenyldialkoxyboranes, instead of disiamyl- and dicyclohexylborane derivatives, as shown in Table 3 [5]. Consequently, the cross-coupling reaction of 1-alkenylboranes with 1-alkenyl halides can be achieved for nearly all conjugated alkadienes. The reaction has been applied for syntheses of many natural and unnatural compounds which have conjugated alkadiene structures. For example, Burk et al. have most recently reported that the coupling of (*Z*)-methyl 2-acetamido-3-bromoacrylate having several functional groups, with a variety of vinylboronic acids furnishes corresponding coupling products in excellent yields (Eq. (1)) [6]. Lignarenone A in the *Cylichnidae* *Scaphander lignarius*, is synthesized by such a procedure (Eq. (2)) [7].

Table 1
Cross-coupling reaction of **1** with **2**



1	Catalyst ^b (mol%)	Base (Equiv / 2)	Solvent	Reac. time(h)	Yield (%) of 3
1b	PdL ₄ (3)	None	THF	6	0
1b	PdL ₄ (3)	None	Benzene	6	0
1a	PdL ₄ (3)	2M NaOEt(2)-EtOH	THF	2	73
1b	PdL ₄ (1)	2M NaOEt(2)-EtOH	Benzene	2	86

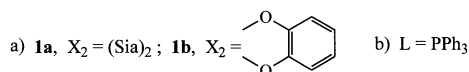
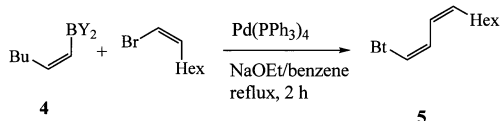


Table 2
Cross-coupling reaction of (*E*)-1-vinyldisiamylboranes

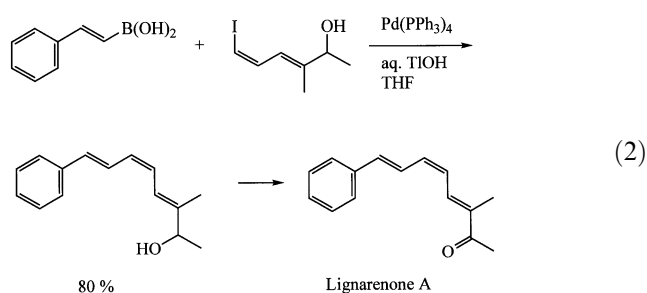
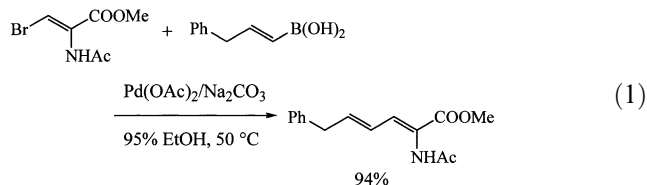
1-Alkenylborane	1-Alkenyl bromide	Product	Yield/% (Purity/%)
			86 (98)
			88 (99)
			89 (98)

Reaction conditions: Pd(PPh₃)₄–NaOEt–benzene–reflux–2 h.

Table 3
Cross-coupling reaction of (*Z*)-1-hexenyldisiamyl- or (*Z*)-1-hexenyldiisopropoxyborane



BY ₄ in 4	Yield (%) of 5	Purity (%) of 5
B(Sia) ₂	49	> 98
B(OPr ^{<i>i</i>}) ₂	87	> 99



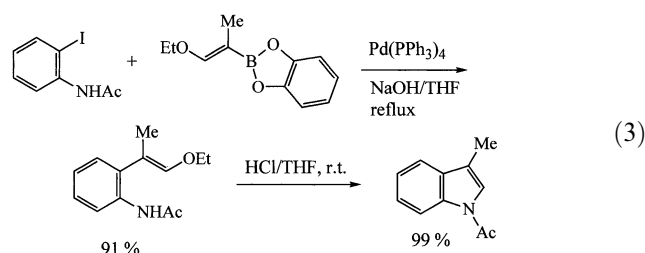
1-Alkenyl halides also react with a number of 1-alkenylboranes to provide conjugated (*E*)- and (*Z*)-alkenyne in high yields stereo- and regioselectively.

2.2. With aryl halides

As described in the previous section, it was discovered that vinylic boron compounds readily react with vinylic halides to give coupling products. Consequently, we next attempted to examine the reaction of 1-alkenylbor-

anes with haloarenes which have also sp² hybridized carbon–halogen bonds, and found that the reaction takes place smoothly. Some of representative results are exhibited in Table 4.

This reaction has the advantage that only one product (7) (head-to-head coupling product) is formed. Additional results are shown in Table 5. Aromatic bromides and iodides easily react with vinylic boron compounds, but chlorides do not participate, except the reactive allylic and benzylic derivatives. Heteroaromatic halides can be used as coupling partners. *Ortho*-substituents on benzene ring do not give difficulty. Thus, the cross-coupling reaction is used for the synthesis of benzo-fused heteroaromatic compounds (Eq. (3)) [8].



Höfle et al. have reported a synthesis of epothilone related compounds employing such a method between vinyl boronic acids and aryl halides (Eq. (4)) [9].

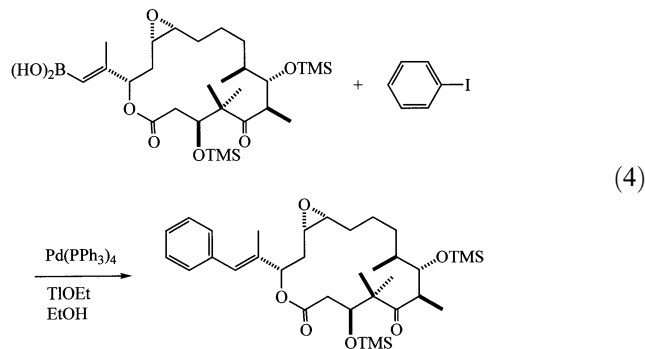
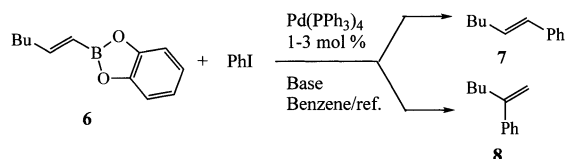


Table 4
Cross-coupling reaction of 6 with iodobenzene



Base	Reaction time (h)	Product yield (%)	Ration of 7:8
None	6	0	
NaOEt	2	100	100:0
NaOMe	2	100	100:0
NaOH	2	100	100:0

Table 5
Coupling of 1-alkenylboranes with various organic halides

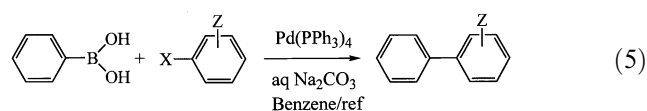
1-Alkenylborane	Halide	Product ^a	Yield (%)
	PhI		100
	PhBr		98
	PhCl		3
			100
			87
			83
			89
	PhCH ₂ Br		97
	BrC≡CPh		93
	BrC≡CHex		95

^aIsomeric purity, >98%.

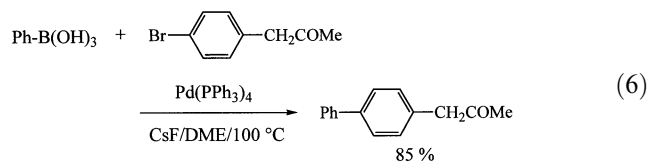
3. Cross-coupling of arylboranes

3.1. With aromatic halides. Synthesis of biaryls

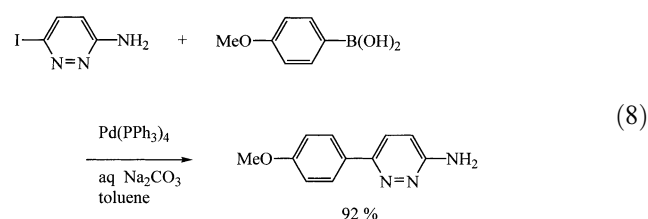
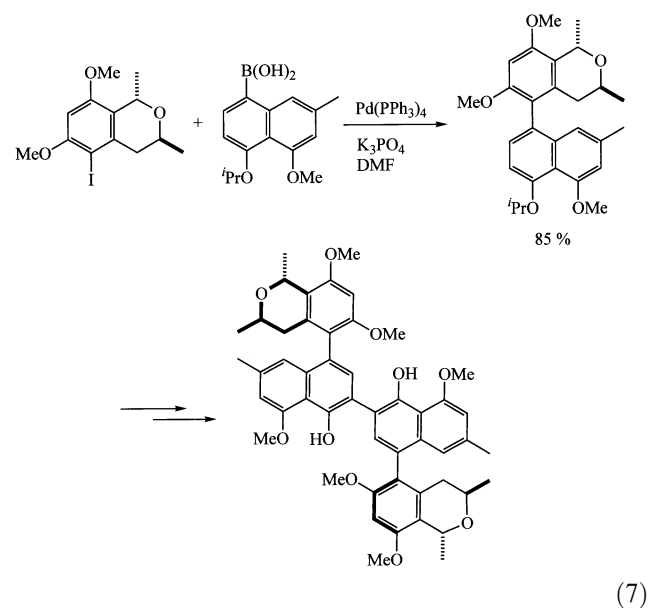
The first method to prepare biaryls by the cross-coupling of arylboranes with haloarenes was reported in 1981 (Eq. (5)) [10]. The reaction proceeds even under heterogeneous conditions to give the corresponding coupling products selectively in high yields. After this discovery, various modifications have been made for the reaction conditions. As the bases, Na₂CO₃, NaHCO₃, Ti₂CO₃, K₃PO, etc. are employed. In some cases, CsF or Bu₄NF can be used instead of usual bases (Eq. (6)) [11]. Phosphine-based palladium catalysts are generally used since they are stable on prolonged heating; however, extremely high coupling reaction rate can be sometimes achieved by using palladium catalysts without a phosphine ligand such as Pd(OAc)₂, [(h³-C₃H₅)PdCl]₂, and dPd₂(dba)₃.



The coupling reaction is applied for synthesis of various biaryls. For instance, a racemic isochroman



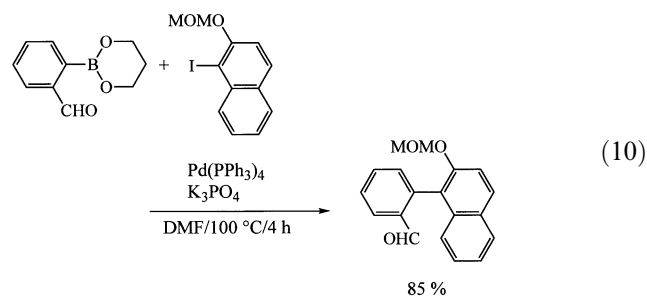
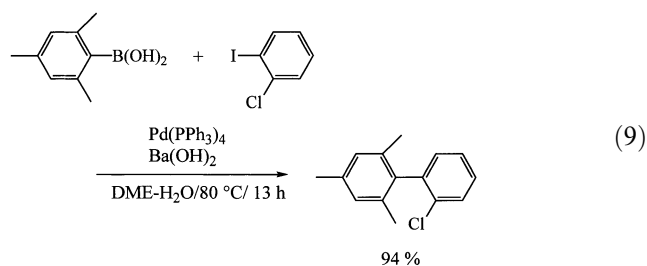
analogue of michellamines has been reported (Eq. (7)) [12]. Similarly, the reactions have been applied in aromatic–heteroaromatic and heteroaromatic–heteroaromatic couplings, because of synthetic usefulness in pharmaceutical industry. One of the examples is shown in Eq. (8) [13].



3.2. Reaction of arylboronic acids and their esters possessing highly steric hindrance or electron-withdrawing functionalities

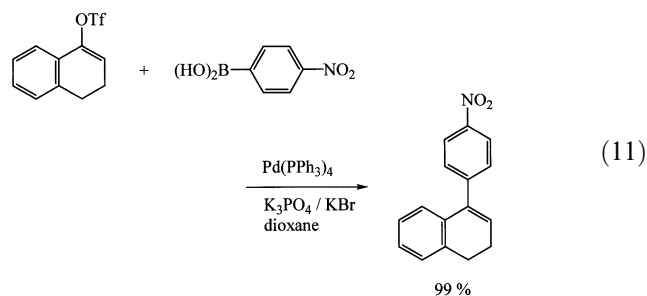
Sterically hindered *ortho*-disubstituted arylboronic acids such as mesitylboronic acid or arylboronic acids having electron-withdrawing substituents do not provide satisfactory results due to the steric hindrance and competitive hydrolytic deboronation. Consequently, we reinvestigated such coupling reactions. It was discovered that this difficulty could be overcome by using suitable

bases and solvent systems; examples are shown in Eqs. (9) and (10) [14].



3.3. With 1-alkenyl halides

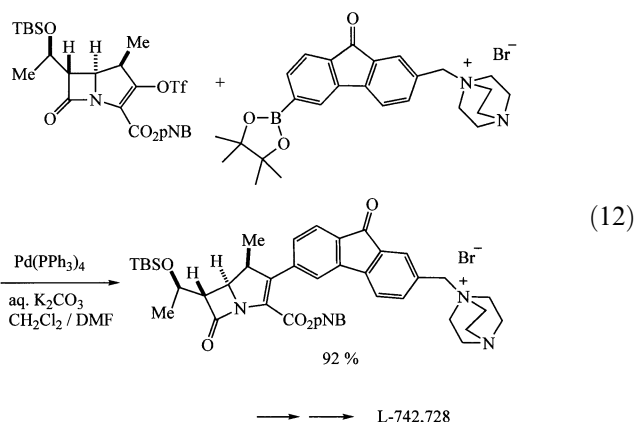
Arylboronic acids are also efficient reagents for arylation of 1-alkenyl halides and triflates. We reported the cross-coupling reactions between arylboronic acids



or esters and 1-alkenyl electrophiles such as halides and triflates in the presence of palladium catalyst and base (Eq. (11)) [15].

Merck scientists have reported anti-MRSA activity in carbapenems bearing aromatic substituents at the 3-position. The most recent candidate to emerge from this program is L-742,728. This compound was prepared in

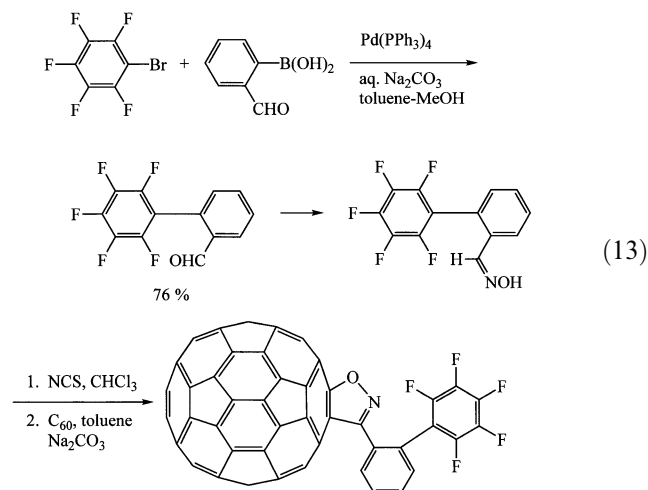
large quantity using the cross-coupling as the key reaction by Yasuda et al. (Eq. (12)) [16].



3.4. Applications in polymer chemistry

Aromatic, rigid-rod polymers play an important role in a number of diverse technologies including high-performance engineering materials, conducting polymers, and nonlinear optical materials. The cross-coupling reaction of arylboronic acids and dihaloarenes for the synthesis of poly(*p*-phenylenes) was first reported by Schlüter [17]. Recently, the synthesis of poly(*o*-phenylenes) has been reported [18].

Investigations on the synthesis and electrochemical behavior for a new class of acceptor substituted isoxazolofullerenes have been reported. In this case, such fullerene derivatives were synthesized by the borane coupling (Eq. (13)) [19].



3.5. Coupling with aromatic chlorides

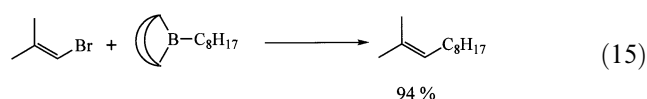
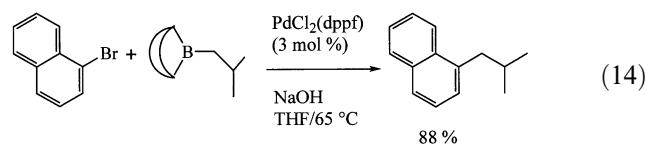
The palladium-catalyzed cross-coupling reaction of aryl bromides, iodides, and triflates is a general method

employed for the formation of C–C bonds. The use of aryl chlorides as chemical feedstock in coupling was reported difficult but would economically benefit a number of industrial processes. Most recently, Buchwald [20] and Fu [21] have reported independently phosphine-modified palladium-mediated coupling reactions which employ inexpensive aryl chlorides as substrates in excellent yields.

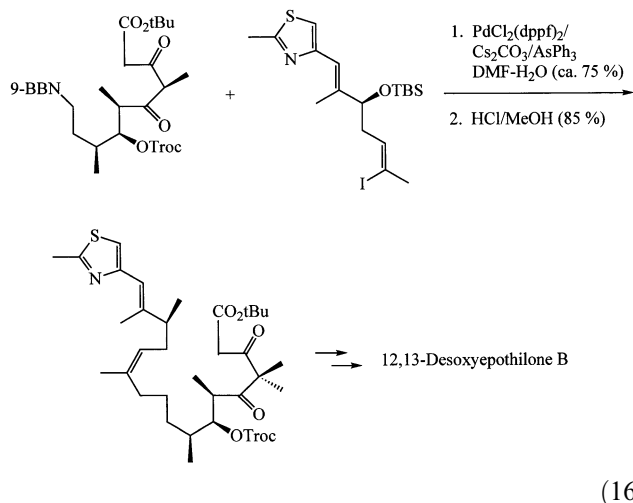
4. Cross-coupling of alkylboranes

4.1. With 1-alkenyl or aryl halides

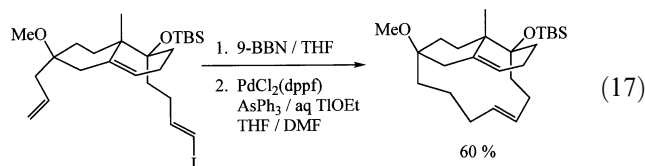
Although alkylmagnesium, -zinc, -tin, and -aluminum reagents were successfully used for some of cross-coupling reactions with organic halides, the reaction of alkylboranes is particularly useful when one wishes to start from alkenes via hydroboration. Alkylboranes are readily prepared by hydroboration of alkenes, which is essentially quantitative and proceeds through a *cis*-Markovnikov addition from the less hindered side of double bond. Since alkylboranes thus obtained are also quite inert toward many functional groups, the coupling can be carried out without protecting these groups. To confirm the advantages, we examined the cross-coupling of alkylboranes with organic halides using Pd(PPh₃)₄ and base. Unfortunately, we were unable to obtain coupling products. Initially, the difficulty was considered to be the reductive elimination step. Hayashi et al. [22] reported an effective catalyst at the reductive elimination step for the cross-coupling of Grignard and alkylzinc reagents with organic halides, which is dichloro[1,1'-bis(diphenylphosphino)ferrocene]-palladium(II) [PdCl₂(dppf)]. Therefore, we used this catalyst for the reaction of alkylboranes with organic halides, and discovered that the reaction occurs readily to give coupling products selectively in excellent yields. Examples of such reactions are depicted in Eqs. (14) and (15).



Most recently Danishefsky and his coworkers have reported the synthesis of the promising cancer chemotherapeutic agent 12,13-desoxyepothilone B using the coupling reaction (Eq. (16)) [23].



Transannular macrocyclizations via intramolecular B-alkyl reactions are also reported by Danishefsky's group. Regioselective terminal olefin hydroboration with 9-BBN-H followed by Pd(0)-catalyzed reaction in the presence of a base such as TIOEt at high dilution generates macrocycles with a high degree of control over geometry with isomerically pure *E* or *Z* vinyl iodide substrates (Eq. (17)) [24].



4.2. Base problem

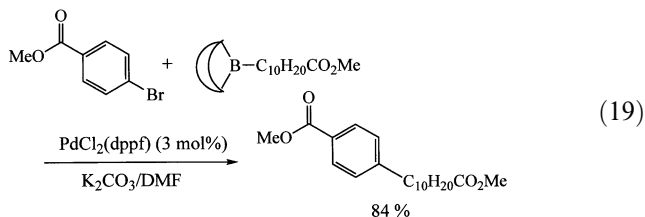
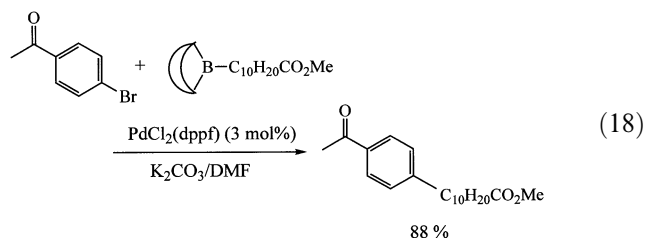
In cross-coupling reactions of organoboron compounds, the presence of bases is essential; no reaction occurs without bases. On the other hand, there are many organic compounds, sensitive towards bases. Consequently, careful uses of bases are required in such cases. For example, Table 6 shows that the selection of base and solvent provides markedly different yields of coupling products. By carefully selecting the reaction

Table 6
Solvent and base effects on the cross-coupling reaction^a

Solvent	Base (equiv)	Temperature (°C)	Time (h)	Yield (%)
DMF	KOAc (4)	50	18	18
DMF	K ₂ CO ₃ (2)	50	18	64
CH ₃ CN	K ₂ CO ₃ (4)	50	18	46
DMF	K ₂ CO ₃ (4)	50	20	92

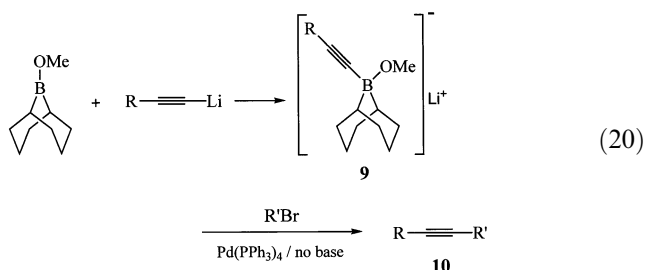
^a Catalyst: PdCl₂(dppf).

conditions, high yields of the desired coupling products can be achieved (Eqs. (18) and (19)).



5. Cross-coupling of 1-alkynylboranes

Alkynylboranes were known to be useful synthetic intermediates. Compared with other organoboranes, they are stronger Lewis acids and are easily hydrolyzed. Because of this property, alkynylboron compounds were not employed in the cross-coupling reaction, in which the presence of bases is essential. Negishi reported for the first time the cross-coupling of 1-heptynyl(tributyl)borate with *o*-iodotoluene in the presence of palladium catalyst [1]. Recently, Soderquist et al. have found that the addition of B-methoxy-9-borabicyclo[3.3.1]nonane to alkynyllithium reagents gives stable complexes **9** which undergo efficient coupling with organic halides to produce a variety of alkynyl derivatives **10** (Eq. (20), Table 7) [25]. Almost at the same time, Fürstner and Seidel reported the same reaction independently [26].

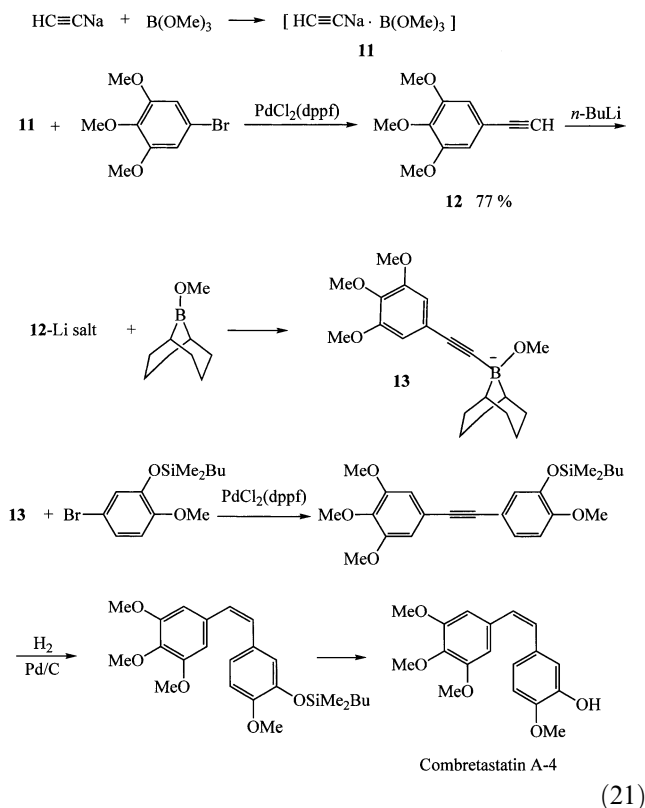


This method was applied for a synthesis of combretastatin A-4, which is an exceptionally strong inhibitor of tubulin polymerization and belongs to the most cytotoxic agents tested so far against murine lymphocytic leukemia, human ovarian and human colon cancer cell lines (Eq. (21)) [27].

Table 7
Coupling products from **9**

R	R'	Yield (%) ^a of 10
<i>n</i> -Bu	Ph	60 (92)
SiMe	Ph	64
Ph	Ph	94
<i>n</i> -Bu	<i>p</i> -MeOPh	62 (68)
SiMe ₃	CH ₂ =CPh	88
<i>t</i> -Bu	<i>cis</i> -CH=CH- <i>t</i> -Bu	56

^a Isolated yields (GC yields).



Recently a number of synthetic applications employing such cross-coupling reactions between various organoboron compounds and organic electrophiles have evolved into a powerful synthetic tool for the construction of new organic compounds both in academic and industrial fields. From the number of literatures reported most recently, the percentage of the applications for carbon–carbon bond formation reactions are as follows:

- Vinylborane coupling, 21%.
- Arylborane coupling, 64%.
- Alkylborane coupling, 14%.
- Alkynylborane coupling, 1%.

Although the utilization of aromatic–aromatic (or heteroaromatic) couplings occupies the top position because of importance in pharmaceutical processes,

other reactions also provide useful methodologies for carbon–carbon bonds.

Acknowledgements

The author is grateful to the coworkers who contributed to this study and whose names are described in the references listed below.

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