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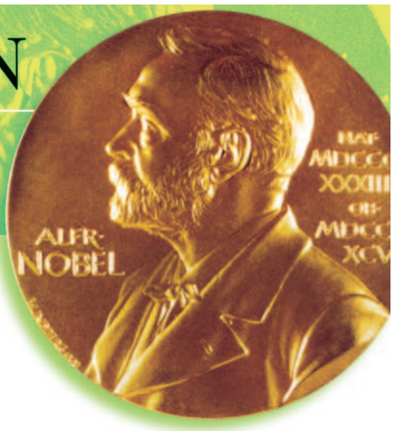

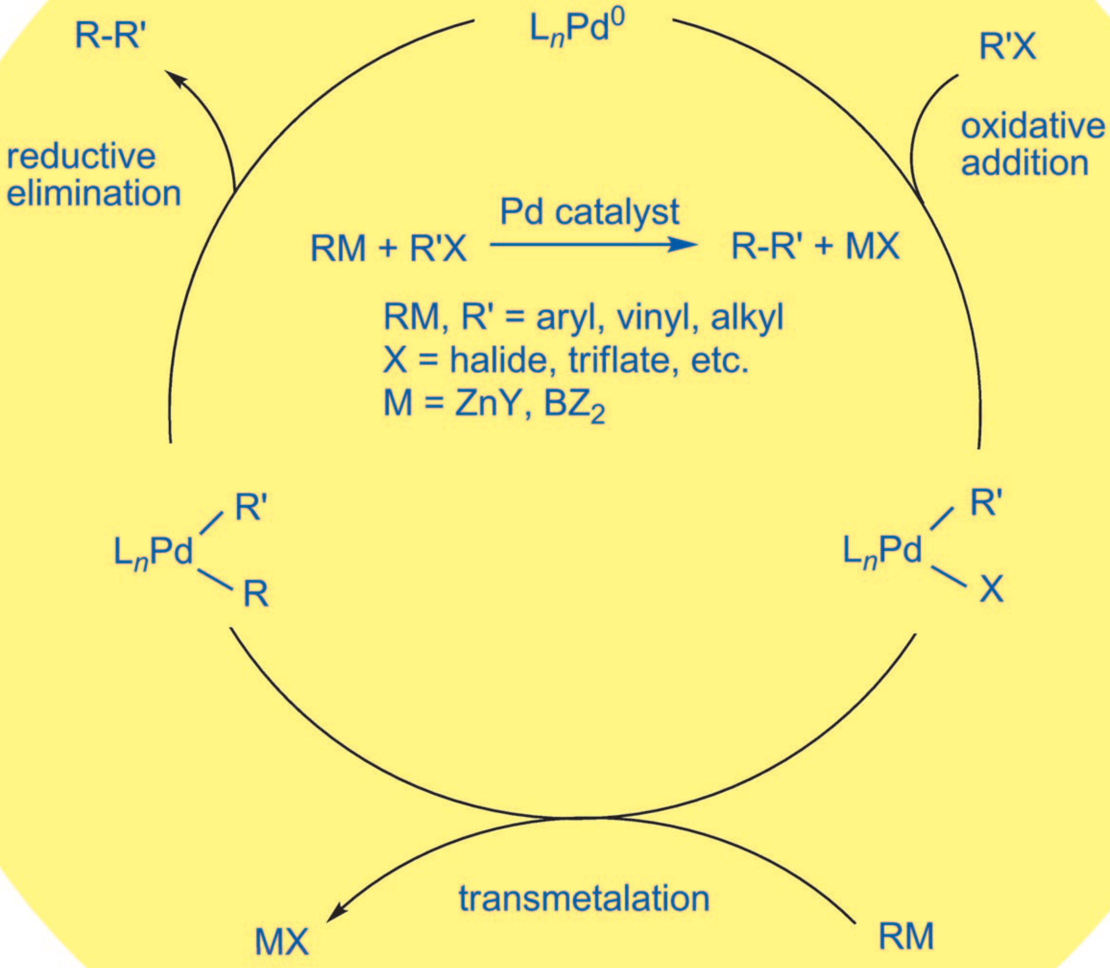


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Cross-Coupling Reactions Of Organoboranes: An Easy Way To Construct C–C Bonds (Nobel Lecture)**

*Akira Suzuki**

cross-coupling · organoboranes · palladium · Suzuki coupling

Biography

I was born on September 12, 1930 in Mukawa, a small town in Hokkaido, Japan. I attended the primary school there and entered secondary school at Tomakomai, where we had one of the biggest paper companies in Japan. During my high school, I was interested in mathematics. Consequently, when I entered Hokkaido University in Sapporo, I was thinking of studying it. In the junior course, I became interested in organic chemistry by reading the book "Textbook of Organic Chemistry," written by L. F. Fieser and M. Fieser. Finally, I decided to major in organic chemistry.

The title of my doctoral thesis was "Synthesis of the Model Compounds of Diterpene Alkaloids". In the study, I used organometallic compounds, Grignard reagents, and organozinc compounds as synthetic intermediates, and I perceived that such organometallic compounds are interesting and versatile intermediates for organic synthesis. After I completed the PhD program at the Graduate School of Science, Hokkaido University, in 1959, I was employed as a research assistant in the Chemistry Department. In October 1961, after two years and six months, I was invited to become an assistant professor of the Synthetic Organic Chemistry Laboratory at the newly founded Synthetic Chemical Engineering Department in the Faculty of Engineering. In April 1973, I succeeded Professor H. Otsuka at the Third Laboratory in the Applied Chemistry Department. In total, I have spent 35 years at Hokkaido University as a staff member—two and a half years in the Faculty of Science, and another thirty-two and a half years in the Faculty of Engineering. Other than about two years of study in America, and a few months at other places overseas, most of my life has been spent at the Faculty of Engineering. Including my nine years as a student, the majority of my life has been at Hokkaido University. After my retirement from Hokkaido University in 1994, I joined two private universities in Okayama prefecture—Okayama Science University and Kurashiki University of Science and Arts—and I retired from the universities in 2002. In the following I would like to describe a few memories of my life in chemistry.

Professor Herbert C. Brown and Purdue University

As I reflect on these long years, I see that there were many difficult periods as well as joyful ones. Memories of the tough, trying experiences tend to fade with time. I think now mainly about the fun things, and I will describe a few memories that I have from my work.

It was on a Saturday afternoon in 1962. I visited the Maruzen bookstore in Sapporo. As I browsed the chemistry books, I discovered a very unacademic looking volume, bound in red and black. This book was *Hydroboration* by H. C. Brown, the 1979 Nobel Laureate in Chemistry. I took the book in my hands, and began looking through its pages to find words written in Professor Brown's unique style. I purchased the book and returned home. I can still remember clearly how I picked it up after dinner that evening, and could not put it down. It is not very long, but it remains as one of the few scholarly books which I have stayed up all night to read. At the time, I had just transferred to the Faculty of Engineering from Science, and I wanted to begin research in a new area at my new workplace. This is perhaps one reason why this book had such an impact on me.

Inspired by this experience, I went to Purdue University in Indiana in the August of 1963 (Figure 1) and spent almost two years at Professor Brown's laboratory researching the newly discovered hydroboration reaction as a postdoctoral research associate (Figure 2). It was my first time in a foreign country, and one of the things that left an impression on me was the strength that America had at that time. For instance, one American dollar was worth 360 yen. My monthly salary as a doctoral researcher was four times what I received even as an assistant professor in Japan. There was little difference in the food between the rich and the poor. There were many such things that I found that were unimaginable in Japan. Purdue University has a strong relationship with Hokkaido University. In the past, the former president of the university, Professor S. Ito, had studied at Purdue. Professor S. Nomachi and Professor T. Sakuma were at Purdue at the same time as I was.

From Professor Brown I learned many things, including his philosophy towards research, but there is one thing he said that I can recall with clarity: "Do research that will be in the textbooks". It is not easy to do this kind of work, but this has remained my motto. Professor Brown was 51 years old, and he

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Figure 1. Leaving Tokyo/Haneda Airport for the US, August 1963.

Figure 2. Working at Professor H. C. Brown's Lab., Purdue Univ., August 1964.

was an extremely active researcher. He visited Hokkaido University three times. I had the opportunity to meet him and Mrs. Brown more than ten times (Figure 3), but we missed them in 2004 and 2005, unfortunately.

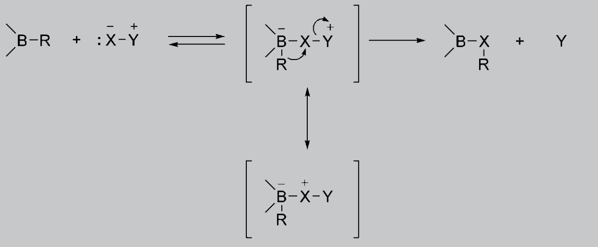
Hydroboration is the reaction of alkenes with borane to produce organic boron compounds. These boron compounds differ from other organometallic compounds: they are chemically inactive, particularly in ionic reactions. For example, organic boron compounds are stable in the presence of water and alcohol, and do not undergo Grignard-type reactions. Therefore, it was thought that such compounds would be unsuitable as synthetic intermediates. Between 1963 and 1965, when I was at Purdue, there were more than 30 doctoral researchers and graduate students from all over the world in the Brown Lab. Many of these friends shared the opinion that the boron compounds were inactive. In contrast, I thought that the stable character of organoboron compounds could be an advantage in some cases. For example, we could use these compounds in the presence of water without any special care. I decided that there might be some way to use these compounds in organic reactions, and I created a new research plan upon my return to Japan in April 1965 (Figure 4).

Figure 3. With Professor and Mrs. Brown at their home in IN (USA), June 1995.

Figure 4. My family, October 1969.

Discovery of Alkyl Radical Formation from R$_3$B

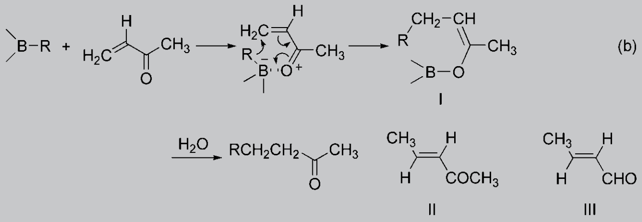
At the time, I focused on three characteristics of organoboron compounds. First, compared to other organometallic compounds, the difference in the electronegativity of the C–B bond is small, meaning that it is an almost perfect covalent bond. Second, the boron atom has an open π-electron structure, meaning that it might be susceptible to nucleophilic reagents. This suggested that the compounds might undergo reactions as shown in Equation (a). Third, studies of the C–B



(a)

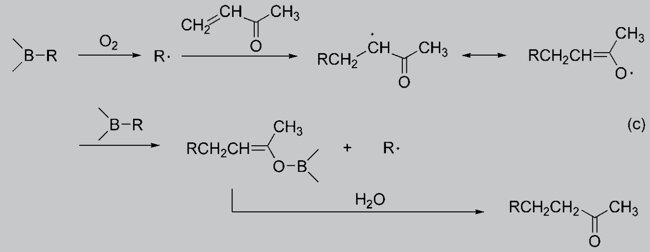
bonding distance showed that it was almost equal to the C–C bonding distance.

In consideration of these three points, I decided to study the reaction of organic boron compounds with α,β-unsaturated ketones. In other words, I hypothesized that intermediate (I) in Equation (b) would be obtained through a quasihexagonal transition state, which would be hydrolyzed to give a saturated ketone. When we examined methyl vinyl ketone in the reaction, we found that the predicted corresponding saturated ketone was produced in a quantitative yield [Eq. (b)]. We obtained these results in 1966, and I notified Professor Brown of our findings in a letter, and he was extremely interested. He told us that he wanted to explore the results at Purdue as well. I supported his proposal, and we continued to study α,β-unsaturated ketones at Hokkaido, while α,β-unsaturated aldehydes would be investigated at Purdue. We analyzed the scope of the reaction, and tried several types of α,β-unsaturated ketone reactions and found that each produced favorable amounts of the corresponding saturated ketones at room temperature. Although we discovered that compounds with a substituent in the β position, such as compounds II, would not react at room temperature, we found that the expected proportions of products could be formed in THF (tetrahydrofuran) solution at reflux temperature. I received a letter from G. Kabalka (now professor at the University of Tennessee), who was then a graduate student doing related research at Purdue. According to the letter, something similar was found for α,β-unsaturated aldehydes. None of the corresponding saturated aldehydes were produced by the reaction of compounds such as III, which had a substitution group in the β position, even though many similar compounds such as acrolein reacted easily at room temperature. I proposed that each laboratory confirm the results of the other, and we began experiments on III and found that the reaction proceeded in THF at reflux temperature. However, subsequent experiments at the Brown lab did not find that our reaction occurred. I remember a sentence in the letter I received from Professor Brown reporting their results. “Chemistry should be international. Why do we have such a big difference between two places, Sapporo, Japan, and West Lafayette, USA?”


(b)

When we looked more closely at these contradictory results, we discovered something quite unexpected. A trace amount of oxygen contaminating in the nitrogen gas we used in our reaction system was catalyzing the reaction. At the time, we knew that organoboron compounds reacted with oxygen, so both we and the Brown Lab conducted the reactions in nitrogen gas. In our laboratory, we used nitrogen purchased from Hokkai Sanso (now called Air Water Inc.), which we further purified. Nevertheless, trace amounts of oxygen were still present in our nitrogen gas. The oxygen acted as a catalyst and promoted the reaction. In the USA, extremely pure nitrogen could easily be purchased in those days, and the nitrogen gas did not contain sufficient amounts of oxygen to cause the reaction.

From such unexpected results, we found that with small amounts of oxygen catalyst, organoboron compounds would produce alkyl radicals. Furthermore, the reaction followed the radical chain mechanism as shown in Equation (c), rather than the coordination mechanism that we had inferred previously [Eq. (b)].


(c)

Serendipity

One often hears lately of the idea of “serendipity” in research. Serendipity refers to the capability to discover the crucial and essential components from unexpected phenomena. I believe that any researcher has the chance to exhibit serendipity. However, in order to make the most of such opportunities, a researcher must have the humility to see nature directly, an attentiveness that does not let even the dimmest spark escape, and an insatiable appetite for research. Some amount of luck also matters, but what can be said with certainty is that little will come of a half-hearted effort.

Quick Publication

In 1970, we were performing experiments to directly produce carboxylic acid from organoboron compounds. One possibility we explored was to use complexes derived from organoboron compounds and a cyanide ion which react with protonic acids. We were not able to obtain our intended result, but we discovered that these cyano complexes could produce symmetrical ketones in good yield when reacted with electrophilic reagents like benzoyl chloride. Nonetheless, I was busy preparing for a presentation at an international conference to be held in Moscow in 1971, and we left for the conference without finishing our paper on it. After I had successfully given my invited lecture, I left the lecture hall to quench my thirst with a glass of water. At that time, a tall foreign man introduced himself to me. That man was Professor A. Pelter of Manchester University in the UK. He later transferred to the University of Wales, Swansea, and served as the chair of the Department of Chemistry as well as the Vice-Chancellor of the university. At our first encounter in Moscow, I had no idea that he was studying organoborane chemistry. We spoke about many things that day and, to my surprise, I learned that he had also performed the very research that we had just done, and had already published his results the previous month in *Chemical Communications*. As a result, our work remains unpublished. Today, that reaction is sometimes called the Pelter reaction. Knowing about our situation, Professor Pelter sympathized with us and consoled us, but no one else knew anything about it. We learned from it. When doing research, we must keep three things in mind. First, we must study the existing literature carefully and comprehensively. Second, we need to be aware that other researchers, near and far, are thinking about the same things that we are. Third, we must quickly publish papers on our results (not just oral presentations).

Tragic Accident

Thinking back on that conference—the International Conference on Organo-Metallic Chemistry in Moscow 1971—I cannot help but think of the tragic accident, in which an ANA passenger jet collided with a Japan Self-Defense Force aircraft in the skies above Shizuku-ishi in Iwate prefecture. On that day, I had flown from Sapporo/Chitose to Tokyo/Haneda to stay for one night before boarding an Aeroflot plane to Moscow the next day. I flew on a Japan Airlines flight in the afternoon, with no idea that the plane that departed only thirty minutes earlier would be involved in such a terrible accident. Knowing nothing of the tragedy, I landed in Haneda, and headed to the Haneda Tokyu Hotel near the Airport, and then learned of the accident. All passengers and crew, 162 persons, were killed.

Haloboration Reaction

Thereafter, our group carried out research on the synthesis of organic compounds through haloboration. I had one memory from this that I will reflect upon. This research was based on the discovery that a certain type of haloborane derivative adds to terminal carbon–carbon triple bonds. This reaction was discovered in 1981, but we first disclosed part of this research in the United States in 1982. That fall, the American Chemical Society hosted a symposium in Midland, Michigan, on organic synthesis involving organoboron compounds. I was one of the special invited speakers, and was preparing to travel to the US when I received a letter from Professor Brown. It was an invitation to visit Purdue to give a lecture before the symposium. The topic of that lecture was haloboration. Professor Brown listened to my presentation intently, and raised his hand to comment the moment I finished speaking. He said that his group had studied the possibility and usefulness of the same reaction at almost the same time as we had. They had looked at haloboration reactions for acetylene compounds, but they had only looked at reactions of the internal acetylenes as substrates. Their work was unsuccessful, and they ended the research. The goddess of fortune is capricious, indeed.

Over many long years, I have had many different experiences. I have encountered many friends at the Faculty of Engineering, Hokkaido University, especially among many of the people who continue to work at the Third Laboratory of the Applied Chemistry Department, and the Organic Synthetic Chemistry Laboratory in the Synthetic Chemical Engineering Department. They have allowed me to enjoy a long career in research. I conclude by expressing my sincere gratitude to these students and colleagues in research.

I have won several awards for my work, listed below:

- The Chemical Society of Japan Award, 1989.
- The Society of Synthetic Organic Chemistry Japan, Special Award, 2004.
- Japan Academy Award, 2004.
- The Order of the Sacred Treasure, Gold Rays with Neck Ribbon, 2005.
- P. Karrer Gold Medal, 2009.
- Nobel Prize in Chemistry, 2010.
- The Order of Culture of Japan, 2010.
- H. C. Brown Award of the American Chemical Society, 2011.

Nobel Lecture

Introduction

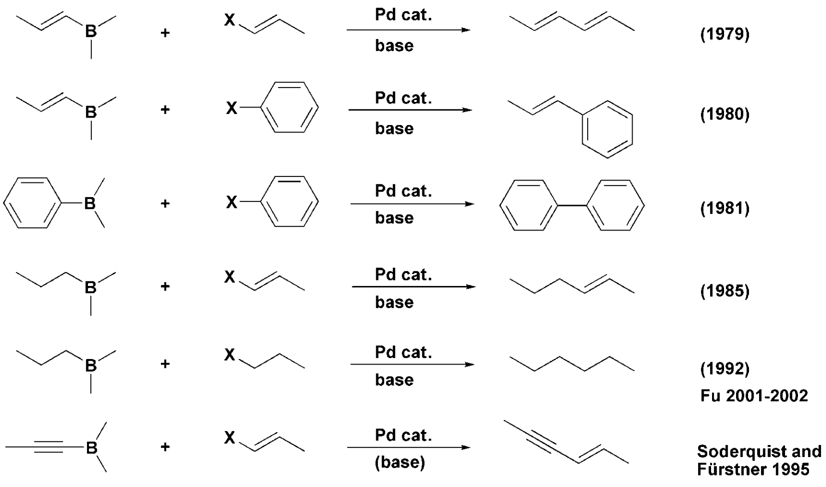
Carbon–carbon bond-formation reactions are important processes in chemistry, because they provide key steps in the building of complex, bioactive molecules developed as medicines and agrochemicals. They are also vital in developing the new generation of ingeniously designed organic materials with novel electronic, optical, or mechanical properties, likely to play a significant role in the burgeoning area of nanotechnology.

During the past 40 years, most important carbon–carbon bong-forming methodologies have involved using transition metals to mediate the reactions in a controlled and selective manner. The palladium-catalyzed cross-coupling reaction between different types of organoboron compounds and various organic electrophiles including halides or triflates in the presence of base provides a powerful and general methodology for the formation of carbon–carbon bonds. The $(sp^2)C{-}B$ compounds (such as aryl- and 1-alkenylboron derivatives) and $(sp^3)C{-}B$ compounds (alkylboron compounds) readily cross-couple with organic electrophiles to give coupled products selectively in high yields. Recently, the $(sp)C{-}B$ compounds (1-alkynylboron derivatives) have also been observed to react with organic electrophiles to produce the expected cross-coupled products.

Some of representative reactions between various organoboranes and a number of organic electrophiles are shown in Scheme 1. The numbers in parentheses indicate the year they were first reported by our group.

Such coupling reactions offer several advantages:

(1) ready availability of reactants;
(2) mild reaction conditions and high product yields;
(3) water stability;



Scheme 1.

(4) easy use of the reaction both under aqueous and heterogeneous conditions;
(5) toleration of a broad range of functional groups;
(6) high regio- and stereoselectivity;
(7) insignificant affect of steric hindrance
(8) use of a small amount of catalyst;
(9) application in one-pot synthesis;
(10) nontoxic reaction;
(11) easy separation of inorganic boron compound;
(12) environmentally friendly process.

As one of the defects of the reaction, one would point out the use of bases. However, the difficulty can be overcome by using suitable solvent systems and adequate bases. Consequently, these coupling reactions have been actively utilized not only in academic laboratories but also in industrial processes.

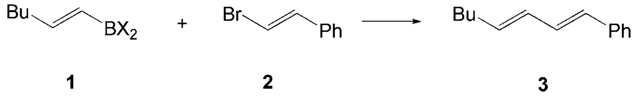
Coupling Reactions of (sp^2)C–B Compounds

Reactions of Vinylic Boron Compounds with Vinylic Halides

Synthesis of Conjugated Alkadienes

Cross-coupling reactions between vinylic boranes and vinylic halides were not reported to proceed smoothly in the presence of only palladium catalysts. During the initial stage of our exploration, we postulated that a drawback of the coupling is caused by the following aspects of the mechanism. The common mechanism of transition-metal-catalyzed coupling reactions of organometallic compounds with organic halides involves sequential a) oxidative addition, b) transmetalation, and c) reductive elimination.[1] It appeared that one of the major reasons that 1-alkenylboranes cannot react with 1-alkenyl halides is step (b). The transmetalation process between RMX (M = transition metal, X = halogen) and organoboranes does not occur readily because of the weak carbanion character of the organic groups in the organoboranes. To overcome this difficulty we anticipated the use of tetracoordinate organoboron compounds, instead of tricoordinate organoboron derivatives. According to the study by Gropen and Haaland,[2] the methyl group in tetramethylborate was observed to be 5.5 times more electronegative than the methyl group in trimethylborane. Such behavior was also expected for the reaction of triorganoboranes in the presence of base. Thus, we found that the 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 provide the expected conjugated alkadienes and alkenynes stereo- and regioselectively in excellent yields (Table 1).

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



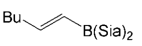
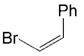
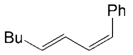
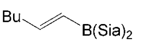
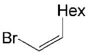
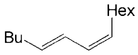
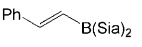
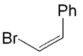
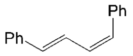
1[a]	Cat.[b] (mol %)	Base (equiv/**2**)	Solvent	t [h]	Yield [%] of **3**
1b	PdL_4 (3)	none	THF	6	0
1b	PdL_4 (3)	none	benzene	6	0
1a	PdL_4 (3)	2 M NaoEt(2)-EtOH	THF	2	73
1b	PdL_4 (1)	2 M NaOEt(2)-EtOH	benzene	2	86

[a] **1a**, X_2 = $(Sia)_2$ (Sia = 1,2-dimethylpropyl); **1b**, X_2 = catecholate. [b] L = PPh_3.

Although the coupling reaction of (E)-1-alkenylboranes, readily obtained by the hydroboration of appropriate alkynes with disiamylborane or dicyclohexylborane, proceeds readily with (E)- and (Z)-1-alkenyl bromides and iodides to give the corresponding dienes (Table 2), (Z)-1-alkenylboranes, prepared by hydroboration of 1-haloalkynes followed by reaction with *tert*-butyllithium, gave low product yields, near 50 % (Table 3).

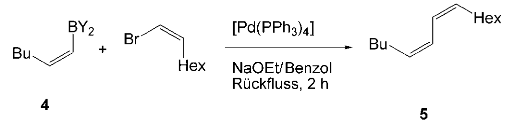
Fortunately, it was found that high yields and high stereoselectivity could be achieved by coupling (Z)-1-alkenyl halides with (Z)-1-alkenyldialkoxyboranes, instead of disiamyl- and dicyclohexylborane derivatives (Table 3).[3] Consequently, the cross-coupling reaction of 1-alkenylboranes with 1-alkenyl halides can be achieved readily for the

Table 2: Cross-coupling reaction of (E)-1-vinyldisiamylboranes.[a]

1-Alkenylborane	1-Alkenylbromide	Product	Yield [%] (purity [%])
 Bu B(Sia)2	 Ph Br	 Ph Bu	86 (98)
 Bu B(Sia)2	 Hex Br	 Hex Bu	88 (99)
 Ph B(Sia)2	 Ph Br	 Ph Ph	89 (98)

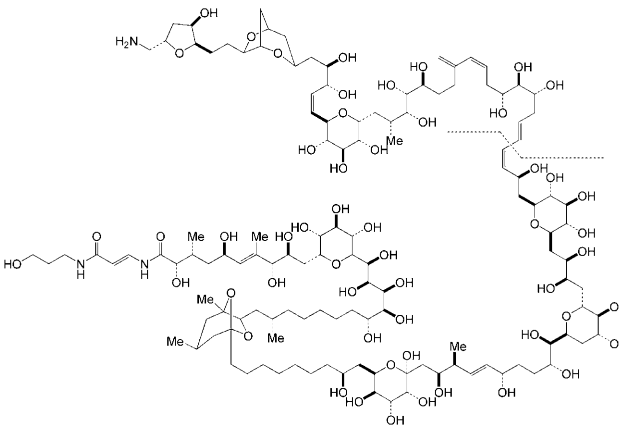
[a] Reaction conditions: $[Pd(PPh_3)_4]$, NaOEt, benzene, reflux, 2 h.

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

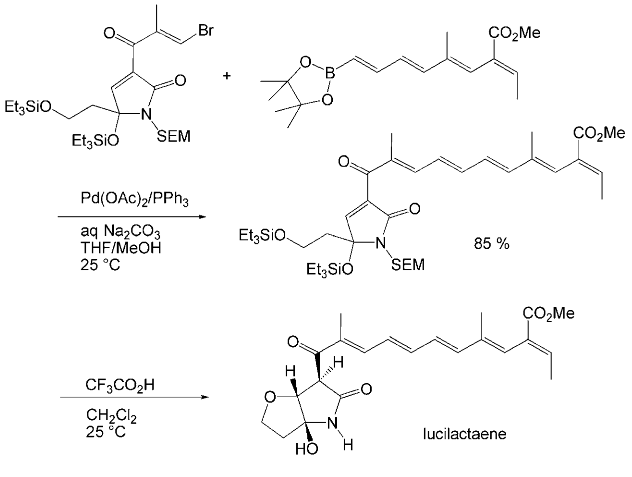


BY_2 in **4**	Yield [%] of **5**	Purity [%] of **5**
$B(Sia)_2$	49	> 98
$B(OiPr)_2$	87	> 99

synthesis of all kinds of conjugated alkadienes. The reaction has been applied to the synthesis of many natural and unnatural compounds which have conjugated alkadiene structures.[4–7] Among the many synthetic applications of the Suzuki coupling reaction for conjugated alkadienes, the total synthesis of palytoxin (Scheme 2), a complex and toxic natural product, is an epoch-making contribution.[8] As another example, the total synthesis of lucilactaene is shown in Scheme 3.[9]



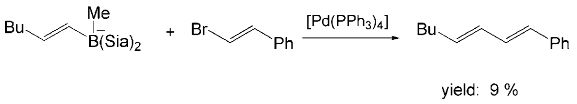
Scheme 2. Synthesis of palytoxin.



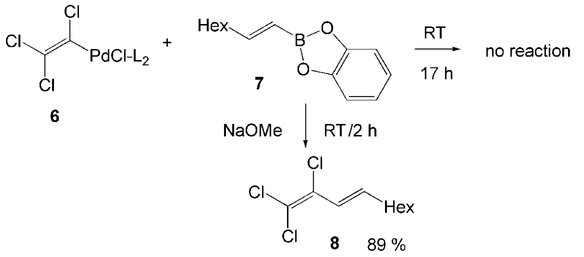
Scheme 3. Synthesis of lucilactaene.

Mechanism of the Vinylic-Vinylic Cross-Coupling

The principal features of the cross-coupling reaction are as follows: a) Small catalytic amounts of the palladium complexes (1–3 mol %) are required to obtain the coupled products. b) The coupling reactions are highly regio- and stereoselective and take place while retaining the original configurations of both the starting alkenylboranes and the haloalkenes. The isomeric purity of the products generally exceeds 98 %. c) A base is required to carry out a successful coupling. In the initial stage of the study, as mentioned previously, we considered that tetracoordinate organoboron compounds facilitate the transfer of organic groups from the boron to the palladium complex in the transmetalation step. In order to check this possibility, the reaction of lithium (1-hexenyl)methyldisiamylborate was examined, as shown in Equation (1). The coupled product, however, was obtained only in 9 % yield. On the other hand, it was found that (trichlorovinyl)palladium(II) complexes **6** and **9**, both prepared as pure solids, reacted with vinylborane **7** to give diene **8** [Eqs. (2) and (3)]. In the case of **6**, no reaction occurs without a base, whereas the coupling reaction proceeds smoothly in the presence of a base to give the coupled product in 89 % yield. The intermediate **9** readily reacts with **7** without a base to provide the same product **8** in almost quantitative yield after 1 h. Consequently, such evidence suggests that vinylic alkoxypalladium(II) compounds such as **9** were necessary intermediates in these cross-coupling reactions. Accordingly, it is considered that the reaction proceeds through the catalytic cycle shown in Scheme 4.[10]



(1)



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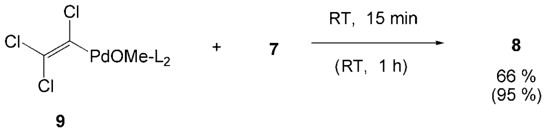
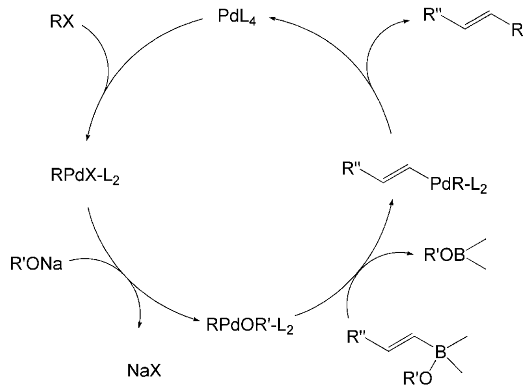


(3)

Reactions with Aryl Halides

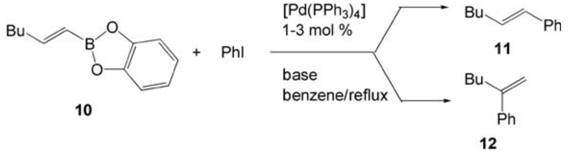
As described in the previous section, it was discovered that vinylic boron compounds readily react with vinylic halides to give coupled products—conjugated alkadienes.



Scheme 4. Catalytic cycle for the coupling reaction of alkenylboranes with haloalkenes.

We next attempted to examine the reaction of 1-alkenylboranes with haloarenes which also have sp^2-hybridized carbon–halogen bonds, and found that the reaction takes place smoothly. Representative results are shown in Table 4.

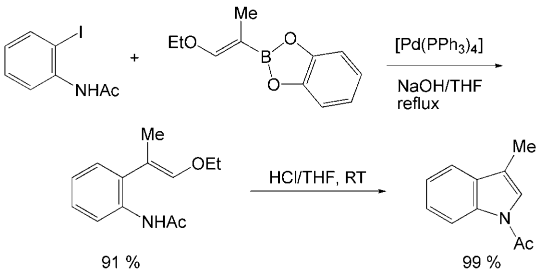
Table 4: Cross-coupling reaction of **10** with iodobenzene.



10, **11**, **12**

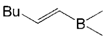
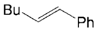
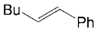
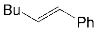
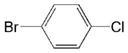
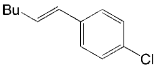
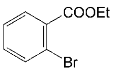
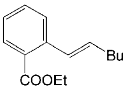
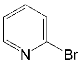
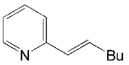
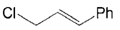
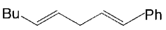
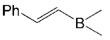
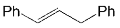
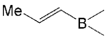
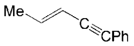
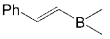
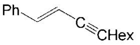
Base	*t* [h]	Yield [%]	Ratio of **11**/**12**
none	6	0	
NaOEt	2	100	100:0
NaOMe	2	100	100:0
NaOH	2	100	100:0

This reaction has one more advantage that only one product **11** (head-to-head coupled product) is formed. Additional coupling reactions of vinylic boranes are shown in Table 5. Aromatic bromides and iodides easily react with vinylic boron compounds, but aromatic chlorides do not participate in the coupling, except reactive chlorides, such as allylic and benzylic derivatives. Heteroaromatic halides can also be used as coupling partners. *Ortho* substituents on the benzene ring do not give difficulty. Thus, the cross-coupling reaction can be used for the synthesis of benzo-fused heteroaromatic compounds [Eq. (4)].[11]



(4)

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
	$PhCH_2Br$		97
	BrC≡CPh		93
	BrC≡CHex		95

[a] Isomeric purity >98 %.

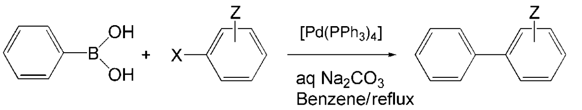
Aromatic Boron Compounds

Reactions with Aromatic Halides

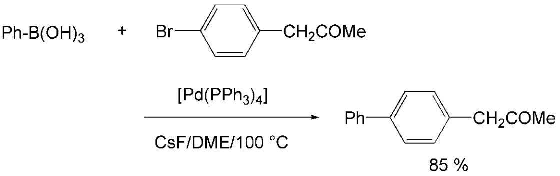
Synthesis of Biaryls

The coupling of aryl halides with copper at very high temperature is called the Ullmann reaction, which is of broad scope and has been used to prepare many symmetrical biaryls. However, when a mixture of two different aryl halides is used, there are three possible biaryl products. Consequently, the development of a selective and general synthesis of all kinds of biaryls has been desired.

The first method to prepare biaryls by the cross-coupling of aryl boranes with haloarenes was reported in 1981 [Eq. (5)].[12] The reaction proceeds even under heterogeneous conditions to give the corresponding coupled products selectively in high yields. Since this discovery, various modifications have been made to the reaction conditions. As the bases, Na_2CO_3, $NaHCO_3$, Tl_2CO_3, K_3PO_4, etc. are employed. In some cases, CsF or Bu_4NF can be used instead of the usual bases [Eq. (6)].[13] Phosphine-based palladium



(5)



(6)

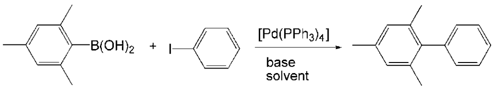
catalysts are generally employed since they are stable to prolonged heating; however, extremely high coupling reaction rates can sometimes be achieved by using palladium catalysts without a phosphine ligand, such as $Pd(OAc)_2$, $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$, and $[Pd_2(dba)_3]$.

Carbon–carbon bond-forming reactions employing organoboron compounds and organic electrophiles have been recently recognized as powerful tools for the construction of new organic compounds. Among such reactions, aromatic–aromatic (or heteroaromatic) couplings between aromatic boronic acids or esters and aromatic electrophiles to provide symmetrical and unsymmetrical biaryls selectively in high yields have been used most frequently. The importance of biaryl units as components in many kinds of compounds, pharmaceuticals, herbicides, and natural products, as well as engineering materials, such as conducting polymers, molecular wires, and liquid crystals, has attracted enormous interest from the chemical community. Such aromatic–aromatic, aromatic–heteroaromatic, and heteroaromatic–heteroaromatic coupling reaction have been recently reviewed in detail.[14]

Coupling of Aryl Boronic Acid Derivatives Having Highly Sterically Hindered or Electron-Withdrawing Functionalities

Although steric hindrance of aryl halides is not a major factor in the formation of substituted biaryls, low yields result when *ortho*-disubstituted aryl boronic acids are used. For example, the reaction with mesitylboronic acid proceeds only slowly because of steric hindrance during the transmetalation to the palladium(II) complex. The reaction of mesitylboronic acids with iodobenzene at 80 °C in the present of $[Pd(PPh_3)_4]$ and various bases has been reported.[15] The results are summarized in Table 6.

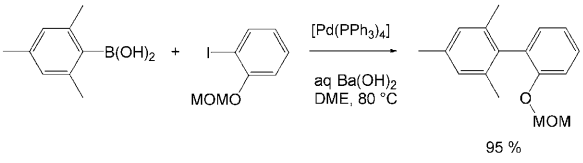
Table 6: Reaction of mesitylboronic acid with iodobenzene under different conditions.



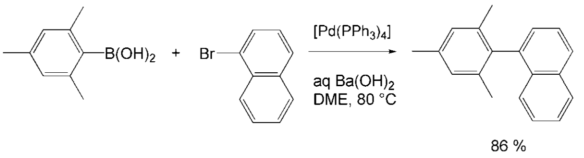
Base	Solvent	*T* [°C]	Yield [%][a] 8 h	24 h	48 h
Na_2CO_3	benzene/H_2O	80	25 (6)	77 (12)	84 (25)
Na_2CO_3	DME/H_2O	80	50 (1)	66 (2)	83 (7)
K_3PO_4	DME/H_2O	80	70 (0)		
NaOH	DME/H_2O	80	95 (2)		
$Ba(OH)_2$	DME/H_2O	80	99 (2)		

[a] GLC yields of the coupling product based on iodobenzene; the yields of mesitylene are shown in parentheses.

Aqueous Na_2CO_3 in benzene or DME (dimethoxyethane) is not effective as a base for the coupling of mesitylboronic acid and the reaction is not completed even after two days. Although the side reactions such as homocoupling are negligibly small, the formation of mesitylene by hydrolytic deboronation was observed, increasing with the reaction time. It is noteworthy that such hydrolytic deboronation is faster in benzene/H_2O than in the modified conditions of aqueous DME. On the other hand, the addition of stronger bases, e.g., aqueous NaOH or $Ba(OH)_2$, both in benzene and DME, exerts a remarkable effect on the acceleration rate of the coupling. By using aqueous $Ba(OH)_2$ in DME at 80 °C, mesitylboronic acid couples with iodobenzene within 4 h to give the corresponding biaryl in a quantitative yield. Some such coupling reactions are depicted in Equations (7) and (8).

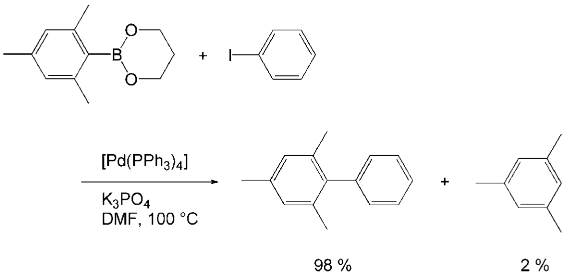


(7)



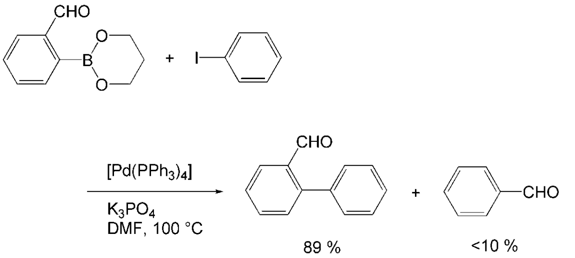
(8)

An alternative procedure, using the esters of boronic acids and anhydrous base, has been developed for sterically hindered aryl boronic acids and provide high yields. The coupling can be readily achieved by using the trimethylene glycol ester of mesitylboronic acid and Cs_2CO_3 or K_3PO_4 in DMF at 100 °C to give a quantitative yield of the coupled products [Eq. (9)].[15]



(9)

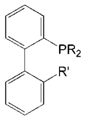
Even without sterically hindered substrates, the reaction under aqueous conditions is often undesirable because of competitive hydrolytic deboronation. A kinetic study[16] into the reaction of substituted aryl boronic acids showed that electron-withdrawing substituents accelerate the deboronation. Although there is no large difference between *meta*- and *para*-substituted phenylboronic acids, substituents at the *ortho* position may greatly increase the rate of deboronation. For example, a 2-formyl group on aryl boronic acids is known to accelerate the rate of hydrolytic deboronation.[16] Indeed, the coupling of 2-formylphenylboronic acid with 2-iodotoluene at 80 °C using Na_2CO_3 in DME/H_2O gives only a 54 % yield of the corresponding biaryl, with accompanying benzaldehyde (39 %). Aprotic conditions are desirable for such boronic acids that are sensitive to aqueous base. Thus, the trimethylene glycol ester of 2-formylphenylboronic acid readily couples with iodobenzene at 100 °C in DMF to give the coupled product in a yield of 89 %, with less than 10 % benzaldehyde formed [Eq. (10)].[15]



(10)

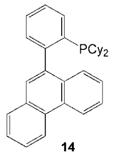
Recently, Buchwald et al. reported interesting catalysts and ligands for the preparation of tetra-*ortho*-substituted unsymmetrical biaryls.[17] Among the biphenyl-based ligands tested, **14** gave excellent results, whereas significant amounts of aryl bromide reduction were observed when the ligands **13** were used (Table 7).

Table 7: Ligand effects in the coupling of hindered substrates.

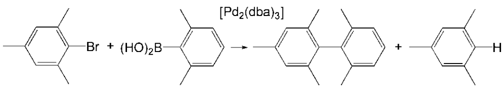


a, R = Cy, R' = NMe_2
b, R = Cy, R' = H
c, R = Cy, R' = *i*Pr

13



14

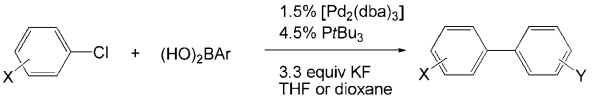


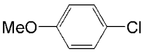
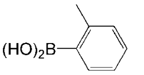
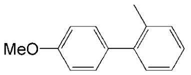
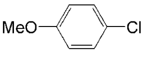
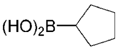
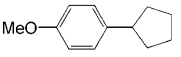
Ligand	Conv [%]	Biaryl [%]	Biaryl/ArH
13a	47	33	2.3
13b	20	10	0.9
13c	74	40	1.9
14	100	91	10

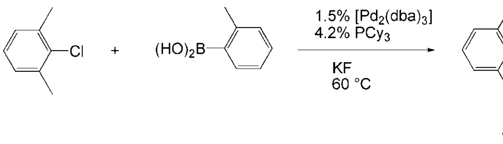
Coupling with Aromatic Chlorides

In aromatic–aromatic cross-coupling reactions, cheap and readily accessible aryl chlorides are particularly important from an industrial viewpoint as starting materials. Recently some research groups, especially Fu's group[18] and Buchwald's group[19] have reported very efficient methods for the reaction of aryl chlorides. For example, Fu and co-workers[18] have observed that the use of $[Pd_2(dba)_3]/PtBu_3$ as the catalyst and ligand result in a wide range of aryl and vinyl halides, including chlorides, undergoing Suzuki cross-coupling with aryl boronic acids in very good yield, typically at room temperature (Table 8). Furthermore, these catalysts display novel reactivity patterns, such as the selective coupling in the presence of $[Pd_2(dba)_3]/PCy_3/KF$ of a sterically hindered aromatic chloride [Eq. (11)].

Table 8: Suzuki couplings of unactivated acryl chlorides.

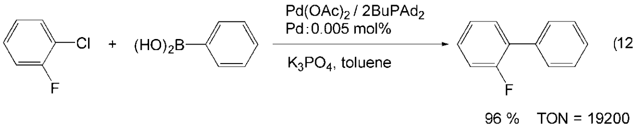


Aryl chloride	Boronic acid	Product	*T* [°C]	Yield [%]
			70	88
			100	75



(11)

Despite the generally good yields in many Suzuki reactions of chloroarenes, comparatively large amounts of catalyst are required. Beller et al. reported a new catalyst system, with which they achieved the coupling of non-activated and deactivated aryl chlorides highly efficiently in good yields with generally only 0.005 mol % palladium, and thus under the industrially allowed level.[20] For instance, as a new efficient catalyst system, they used diadamantyl-*n*-butylphosphane ($BuPAd_2$) as a ligand and found that it proved to be extremely reactive. A typical example is shown in Equation (12).

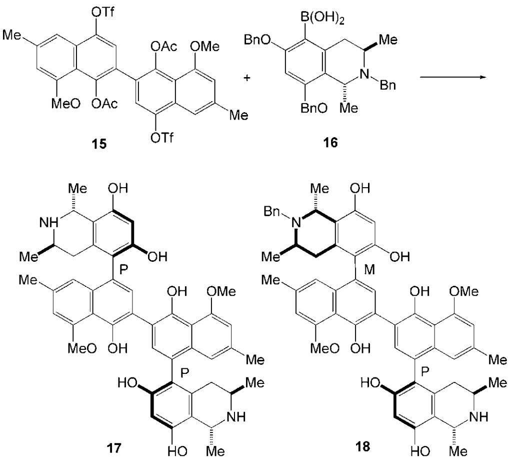


(12)

Applications in the Synthesis of Biaryls

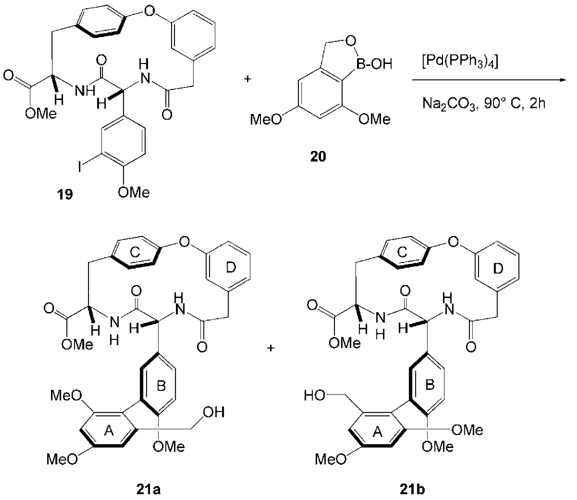
The anti-HIV alkaloids michellamine A (**17**) and B (**18**) have been synthesized. The tetraaryl skeleton of the michellamines was constructed by formation, first, of the inner (nonstereogenic) biaryl axis and subsequently of the two other (stereogenic) axes by using a double Suzuki-type cross-coupling reaction between the dinaphthalene ditriflate **15** and isoquinolineboronic acid **16** [Eq. (13)].[21]

The discovery and development of penicillin and other antibacterial agents as drugs to fight infectious diseases were milestone victories of humankind over bacteria. While these agents saved millions of lives, they did not tame bacteria. On the contrary, this war led to the emergence of newer and more-dangerous bacterial strains that responded defiantly against known antibacterial agents. Vancomycin is a member of the polycyclic glycopeptide class of antibiotics and has proved to be the last line of defense against drug-resistant bacteria. The daunting synthetic challenge posed by its structure is largely due to the strained nature of the 12-membered biaryl framework (AB ring system) and the two 16-membered biaryl ethers (COD and COE ring systems).



(13)

Nicolaou and his group reported a Suzuki coupling approach to the AB-COD bicyclic system of vancomycin.[22] Suzuki coupling of iodide **19** with **20** was facilitated by a $[Pd(Ph_3)_4]$ catalyst and Na_2CO_3 to give a 1:1 mixture of the two atropisomers **21a** and **21b** in 80% combined yield [Eq. (14)]. The coupling of the parent boronic acid corresponding to **20** (without methyl groups) with iodide **19** led to a single compound. Thereafter, the total synthesis of the vancomycin aglycon was reported by the same workers.[23]

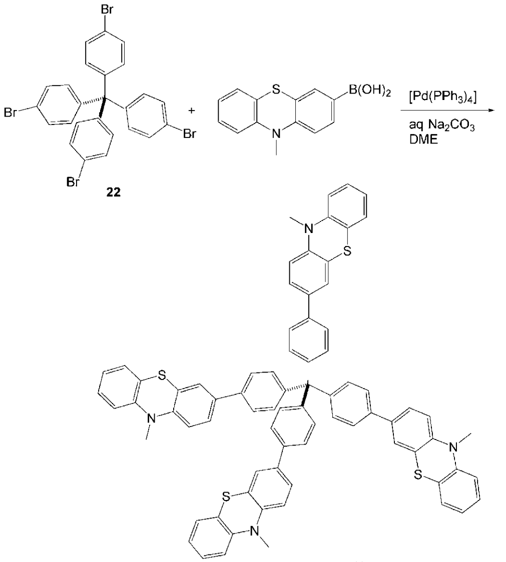


(14)

21a : **21b** = 1 : 1; yield (**21a** + **21b**) 80 %

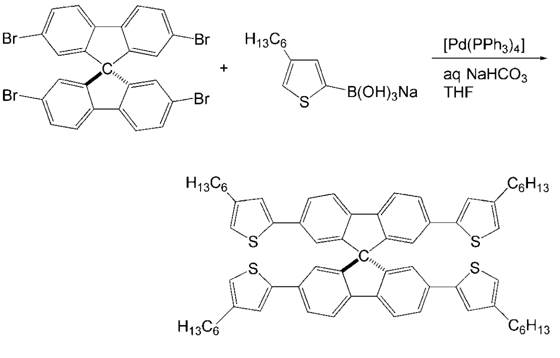
The novel compound tetrakis(phenothiazinylphenyl)methane (**23**), showing remarkably large Stokes shift and a reversible low oxidation potential, can be prepared in a good yield by Suzuki coupling of tetrakis(*p*-bromophenyl)methane [**22**; Eq. (15)].[24]

Oligothiophene-functionalized 9,9-spirobifluorene derivatives have been synthesized in high yields by Suzuki coupling. The Negishi coupling reaction between oligothienylzinc chloride and various 9,9′-spirobifluorene bromides with $[Pd(PPh_3)_4]$ as the catalyst successfully produce the desired compounds. However, the Negishi coupling provided low yields, compared to the Suzuki coupling [Eq. (16)].[25]



23 86 %

(15)



98 %

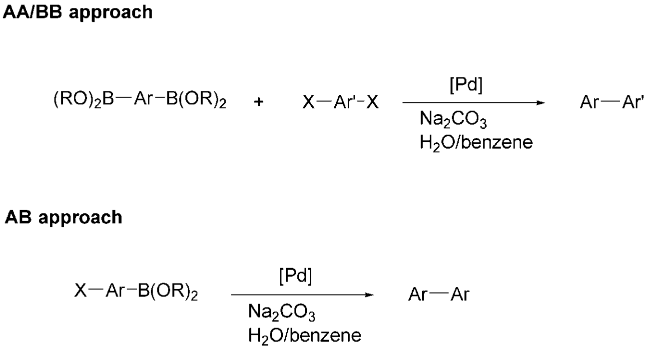
(16)

Solid-Phase Synthesis (Combinatorial Methodology)

Solid-phase reactions play an important role in parallel synthesis and combinatorial chemistry, particularly in the area of medicinal chemistry, where their potential has emerged as a result of the possibility of automation. A considerable amount of attention has been focused on adapting and exploiting the advantage of solid-phase synthesis (SPS) for the production of libraries of such organic compounds. In this context, transition-metal-promoted reactions serve as efficient methods because they proceed under mild conditions and are compatible with many functional groups. For instance, solid-phase Suzuki coupling has largely been developed by the reaction of a resin-bound aryl halide with solution-phase boronic acids.[14] Recently, the viability of solid-supported boronic acids as reagents for Suzuki couplings was successfully demonstrated.[26]

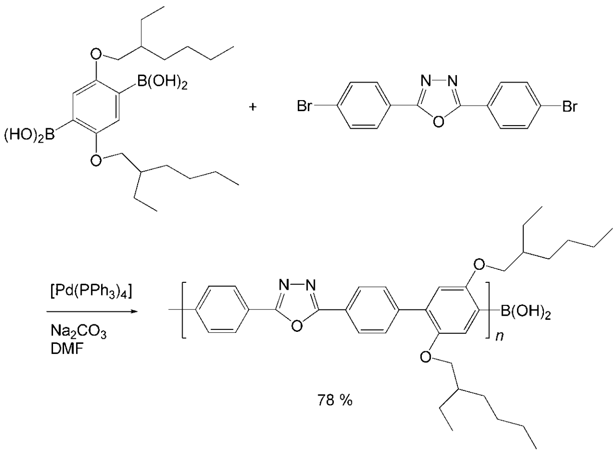
Applications in Polymer Chemistry

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 Suzuki polycondensation (SPC) reaction of aryl diboronic acids and dihaloarenes for the synthesis of poly(*p*-phenylenes) was first reported by Schlüter et al.[27] SPC is a step-growth polymerization of bifunctional aromatic monomers to poly(arene)s and related polymers (Scheme 5).[28] The required functional groups—boronic acids or esters on one side, and bromide, iodide, and so forth on the other—may be present in different monomers (AA/BB approach) or combined in the same monomer (AB approach).



Scheme 5. Graphical representation of the Suzuki polycondensation

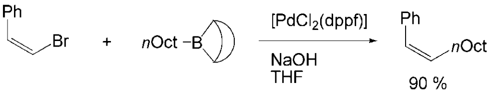
The method was extensively applied to monodisperse aromatic dendrimers, water-soluble poly(*p*-phenylene), planar poly(*p*-phenylenes) with fixed ketoimine bonds, poly-(phenylenes) fused with polycyclic aromatics, and nonlinear optical materials.[14] One such application is shown in Equation (17).[29]



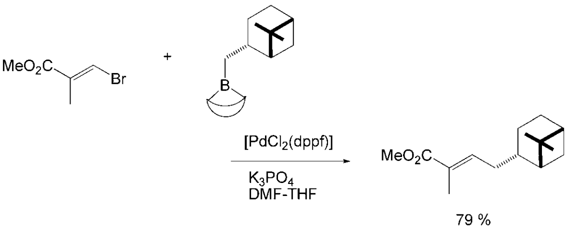
(17)

Coupling Reactions of (sp³)C–B Compounds

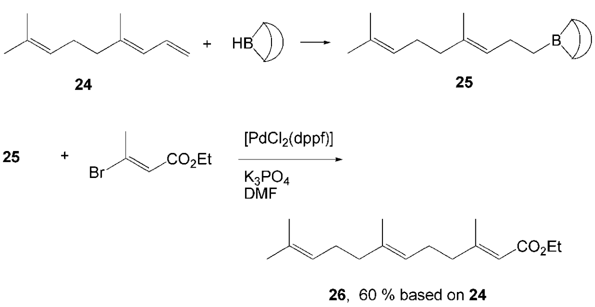
Although organometallic reagents with 1-alkenyl, 1-alkynyl, and aryl groups were successfully used for the coupling reactions, those with alkyl groups having sp^3 carbons with β hydrogens were severely limited due to the competitive side reactions. In 1971–1972 Kochi, Kumada, and Corriu reported independently that the reaction of alkyl Grignard reagents with alkenyl or aryl halides are markedly catalyzed by Fe^{III} or Ni^{II} complexes, and then Negishi demonstrated the synthetic utility of alkyl zinc compounds by the use of a palladium catalyst. Thereafter, alkyl lithium, tin, and aluminum reagents were also employed for such cross-coupling reactions. The reaction of alkyl borane derivatives is particularly useful when one wishes to start from alkenes via hydroboration. Consequently, we intended to examine the coupling reactions between alkyl boron compounds and various organic halides in the presence of a base and a palladium complex, and found that no cross-coupling reactions of B-alkyl-9-borabicyclo[3.3.1]nonanes (B-R-9-BBN), readily obtainable from alkenes by hydroboration, with 1-halo-1-alkenes or haroarenes occurred under the standard coupling conditions using [Pd(PPh$_3$)$_4$] as a catalyst, but the coupling proceeds smoothly by using a catalytic amount of [PdCl$_2$(dppf)] and bases, such as NaOH, K$_2$CO$_3$, and K$_3$PO$_4$ to give the corresponding substituted alkenes or arenes in excellent yields [Eq. (18)].[30,31] Because the reaction is tolerant of a variety of functionalities on either coupling partner, stereochemically pure functionalized alkenes and arenes can be obtained under mild conditions [Eq. (19)]. The utility of the reaction was demonstrated by the stereoselective synthesis of 1,5-alkadienes (**26**) [Eq. (20)] and the extension of a side chain in steroid **27** [Eq. (21)].[30,31]



(18)

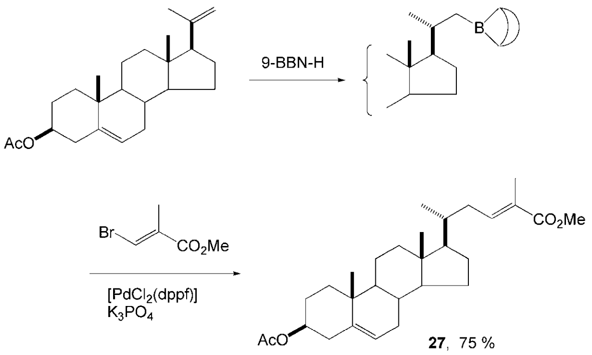


(19)



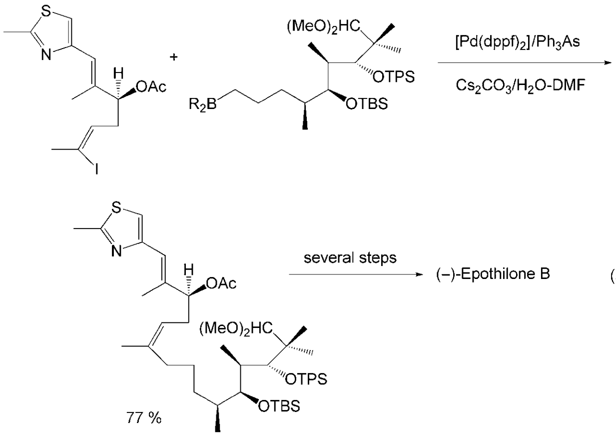
(20)

Many chemists applied such a Suzuki coupling reaction by using B-saturated alkylboron compounds. For instance, Danishefsky et al. reported a total synthesis of the promising anticancer agent (−)-epothilone B by using the coupling method [Eq. (22)],[32,33] and a sister compound, epothilone A, was also synthesized by a similar procedure.[34] A full paper



27, 75 %

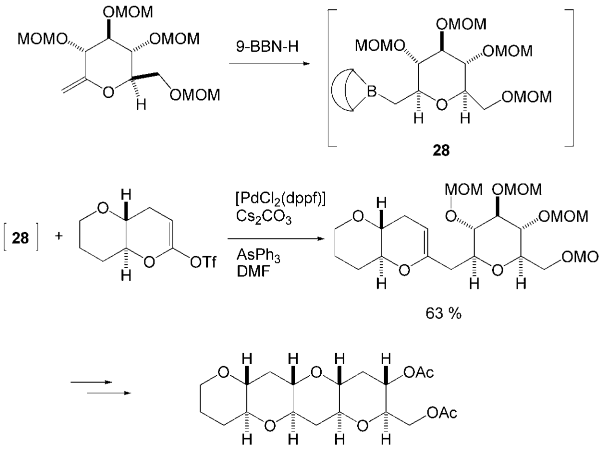
(21)



(22)

describing the total synthesis of epothilones A and B has appeared more recently.[35]

Marine polyether toxins present challenging synthetic targets because of their structural complexity and exceptionally potent biological activities. The most critical issue in the synthesis of these large polyether compounds is the development of synthetic methods for the convergent coupling of polyether fragments. Despite recent advantages in the synthesis of medium-sized cyclic ethers, only a few methodologies for the convergent assembly of six-membered polyether structures were reported. A new strategy for the synthesis of *trans*-fused polyethers based on the palladium(0)-catalyzed Suzuki coupling reaction of alkyl boranes with cyclic enol triflates has been developed by Tachibana et al.[36] As shown in Equation (23), the cross-coupling reaction is carried out in the presence of cesium carbonate as a base and triphenylarsine as a co-ligand in DMF at room temperature. Further reactions give the expected *trans*-fused polyether.

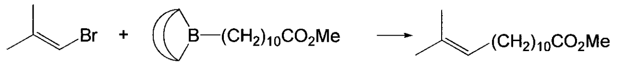


(23)

Base Problems

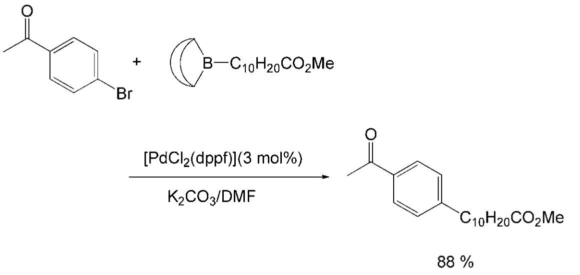
In cross-coupling reactions of organoboron compounds, the presence of a base is essential; no reaction occurs without base. On the other hand, there are many organic compounds that are sensitive to bases. Consequently, the careful use of bases is required in such cases. For example, Table 9 shows that the selection of a base and solvent system provides markedly different yields of the coupled products. By careful selection of the reaction conditions (e.g., [PdCl$_2$(dppf)]/K$_2$CO$_3$/DMF), high yields of the desired coupled products can be achieved [Eq. (24) and (25)].

Table 9: Solvent and base effects on the cross-coupling reaction.[a]

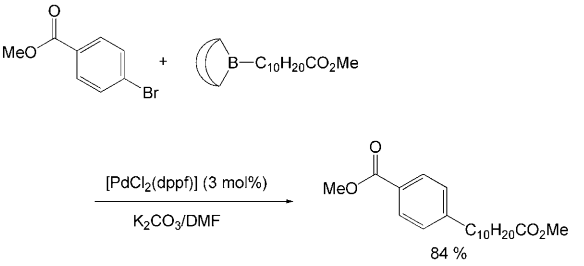


Solvent	Base (equiv)	*T* [°C]	*t* [h]	Yield [%]
DMF	KOAc (4)	50	18	18
DMF	K$_2$CO$_3$ (2)	50	18	64
CH$_3$CN	K$_2$CO$_3$ (4)	50	18	46
DMF	K$_3$PO$_4$ (4)	50	20	92

[a] Catalyst: [PdCl$_2$(dppf)].



(24)



(25)

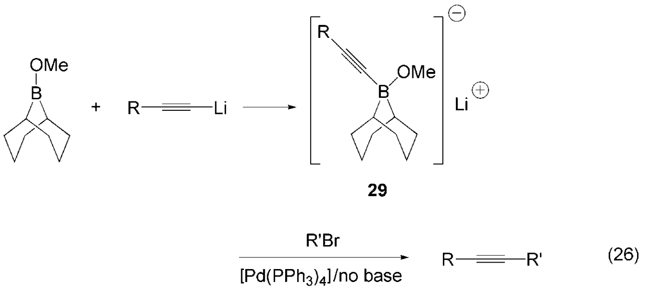
Coupling Reactions of (sp)C–B Compounds

Alkynylboranes have long been known to be useful synthetic intermediates. Compared to other organoboranes, they are easily hydrolyzed by base. Because of this property, alkynylboron compounds have not been employed in the Suzuki coupling reaction, in which the presence of bases is essential. Recently, Soderquist et al. have found that the addition of B-methoxy-9-borabicyclo[3.3.1]nonane to alkynyllithium reagents gives stable complexes **29**, which undergo efficient Suzuki coupling to produce a variety of alkynyl derivatives **30** [Eq. (26), Table 10].[37]

Table 10: Coupled products from **29** [see Eq. (26)].

R	R′	Yield [%][a]
*n*Bu	C_6H_5	60 (92)
$SiMe_3$	C_6H_5	64
Ph	C_6H_5	94
*n*Bu	*p*-$MeOC_6H_4$	62 (68)
$SiMe_3$	$CH_2{=}CC_6H_5$	88
*t*Bu	*cis*-CH=CH-*t*Bu	56
$SiMe_3$	*trans*-CH=CH-*n*Bu	55

[a] Yields of isolated analytically pure compounds (GC yields).



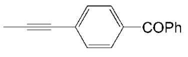
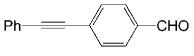
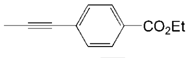
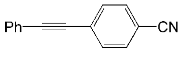
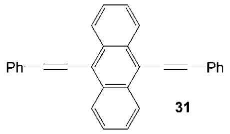
29

30

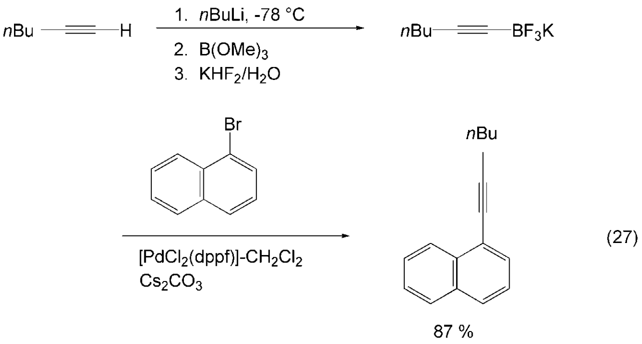
(26)

Almost at the same time, Fürstner and Seidel reported the same reaction.[38] The necessary alkynyl borates in the palladium-catalyzed C–C bond formation are prepared from 9-methoxy-9-BBN and a polar organometallic reagent RM, such as 1-alkynylsodium, -potassium, and -lithium compounds, and not as usual from boranes and bases. This approach allows cross-couplings of organic halides with, for example, alkynyl, methyl, or $TMSCH_2$ groups. The method is highly chemoselective and turned out to be compatible with aldehyde, amide, ketone, ester, and cyano functions as well as with basic nitrogen atoms in the substrates. Some of the results are shown in Table 11. This reaction has been used to prepare compound **31**, which is highly valuable for its chemoluminescence properties.

Table 11: Pd-catalyzed arylation of alkynylmetal reagents mediated by 9-MeO-9-BBN derivatives.

Substrate	RM	Product	Yield [%]
4-bromobenzophenone	$MeC{\equiv}CNa$		89
4-bromobenzaldehyde	$PhC{\equiv}CNa$		77
ethyl 4-bromobenzoate	$MeC{\equiv}CNa$		86
4-bromobenzonitrile	$PhC{\equiv}CNa$		93
9,10-dibromoanthracene	$PhC{\equiv}CLi$	 31	84

Most recently the palladium-catalyzed cross-coupling reaction of potassium alkynyltrifluoroborates with aryl halides or triflates has been reported to give readily coupled products. The potassium alkynyltrifluoroborates are air- and moisture-stable crystalline solids that can be stored indefinitely, which will provide an advantage in their application to combinatorial chemistry [Eq. (27)].[39]



(27)

The Future

Today, the Suzuki reaction continues to evolve, with many new possibilities reported during the past decade. For example, solid-phase Suzuki coupling has been developed by using either resin-bound aryl halides with solution-phase boronic acids[14] or vice versa.[26] Such approaches, of course, play an important role in the combinatorial and parallel methodologies now used to explore chemical reactivity, and is especially well-suited to medicinal chemistry.

Increasingly, industry is seeking to use more environmentally friendly processes. These often require ingenious solutions to which Suzuki coupling is well-suited. Research groups around the world are investigating modifications of the reaction that work in aqueous media or with trace amounts of catalysts. For example, Leadbeater and his team carry out Suzuki coupling using an ultralow (ppb) palladium concentration in water,[40] while Kabalka and colleagues have combined a solvent-free, solid-state approach with the application of microwave radiation to achieve coupling in just a few minutes.[41] Ionic liquids, which are excellent solvents for transition-metal catalysts, are also being investigated.[42]

We can expect to see many more interesting versions of the Suzuki coupling in the future.

I would like to acknowledge the late Professor Herbert C. Brown for his cordial encouragement and warm guidance to me, not only in chemistry but also my life. Thanks are also due to many former co-workers, including graduate and undergraduate students at Hokkaido University.

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