Carbon–carbon bonding made easy

Akira Suzuki

DOI: 10.1039/b507375h

The palladium-catalyzed cross-coupling reaction between organoboranes and organic electrophiles in the presence of base was first developed 30 years ago. It offers a powerful and general methodology for forming carbon–carbon bonds. The scope of the reaction has continued to evolve and broaden to meet modern synthetic requirements.

Introduction

Reactions in which new carbon–carbon bonds are formed are key steps in building the complex, bio-active molecules developed as drugs 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, the most important carbon–carbon bond-forming methodologies have involved using transition metals to mediate the reactions in a controlled and selective manner. Perhaps the most widely used of these chemistries is Suzuki coupling, which is the cross-coupling reaction of various organoboron compounds with organic electrophiles catalyzed by a palladium complex. It is now regarded as an integral part of any synthetic route used to build complex organic chemicals.

Suzuki coupling has many advantages. The reactants are readily available, non-toxic, and air- and water-stable. They react under mild conditions and are amenable to a variety of reaction conditions, including the use of aqueous solvents and substrate supports. The inorganic boron byproduct can be easily removed after the reaction. Most important of all, the coupling proceeds with high regio- and stereoselectivity, and is little affected by steric hindrance. It does not affect other functional groups in the molecule, and can be used in one-pot strategies.

The reaction has proved to be extremely versatile. It was first carried out between alkenyl reactants but over the years, we and others have extended its range to couple carbons in aryl, alkyl and alkynyl groups under a wide variety of conditions, as this review shows.

Division of Molecular Chemistry, School of Engineering, Hokkaido University, Sapporo, 060-8628, Japan

The author is in the Division of Molecular Chemistry, School of Engineering, Hokkaido University, Japan. Professor Suzuki received his PhD in 1959 from Hokkaido University, where he later became a professor in the Department of Applied Chemistry from 1973 to 1994. Between 1963 and 1965, he worked as a postdoctoral associate with Herbert C. Brown investigating the stereochemistry of the hydroboration reaction. It was as a result of working in Professor Brown's group on organoborane chemistry that Professor Suzuki saw the potential of organoboron compounds in cross-coupling reactions.

A route to conjugated alkadienes

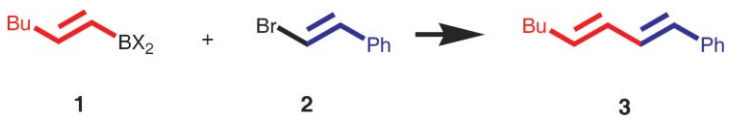
In the mid-1970s, our group at Hokkaido University was attempting to find a way of synthesizing conjugated alkadienes stereo- and regio-selectively. Many such compounds have interesting biological activity – antibacterial, antiviral and so on – and so are of great importance in medicinal and biological chemistry.

At that time, research into developing simple and general methods for creating the necessary carbon–carbon bonds between unsaturated species was still in its infancy. In the previous few years, several approaches had been developed utilizing metal-mediated cross-coupling reactions,[1] but although some were successful, their scope was limited by either the type of organometallic reagent or the procedure employed.

Like many chemists, we believed that organoboron compounds offered the best way forward. Hydroboration, discovered in 1956 by Herbert C. Brown (for which he was awarded the Chemistry Nobel Prize in 1979), had made a wide variety of highly stable organoboranes readily available, and their unique and promising reactivities were just beginning to be exploited. However, no-one had yet managed to develop a general cross-coupling reaction using the necessary alkenyl boranes and another alkenyl compound. The triphenylphosphine palladium complex, $Pd(PPh_3)_4$, looked to be a promising catalyst but the reaction did not proceed smoothly.

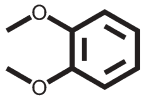
Fortunately, we discovered that what was needed was the addition of a base. An alkenylboron compound and an alkene halide would then couple in the presence of a small amount of palladium complex (1–3 mol%) to give a conjugated

Table 1



1 2 3

1[a]	Catalyst[b] (mol%)	Base (Equiv. **2**)	Solvent	Reaction 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)	2 M NaOEt (2)–EtOH	THF	2	73
1b	PdL_4 (1)	2 M NaOEt (2)–EtOH	Benzene	2	86

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

alkadiene in excellent yields. What is more, if the starting materials were stereo-defined, their three-dimensional configurations were also retained in the product (at greater than 98%). The Suzuki coupling reaction was born (Table 1).[2]

The mechanism

Why was a base necessary? We postulated that the answer lay in the following aspects of the mechanism.

Transition-metal catalyzed coupling reactions of organometallic compounds with organic halides involve three steps: oxidative addition; followed by transmetallation; and then reductive elimination. One of the major reasons that 1-alkenylboranes did not react with 1-alkenyl (or 1-alkynyl) halides appeared to lie with the second step: the transmetallation process between the catalytic intermediate RMX (M = transition metal, X = halogen), formed by the initial addition, and the organoborane does not occur readily because of the weak carbanion character of the organic groups in organoboranes.

To overcome this difficulty, we decided to exploit tetracoordinate organoboron compounds instead of the tricoordinate versions. According to the study by Gropen and Haaland,[3] the methyl group in tetramethylborate is five and half times more electronegative than that in trimethylborane. Such behaviour would also be expected for the reaction of triorganoboranes in the presence of base. Indeed, this is what we found. The reaction is considered to proceed through the catalytic cycle shown in Fig. 1.[4]

We did find that the yield could be affected by the stereochemistry of the starting materials. (*E*)-1-alkenylboranes (obtained *via* the hydroboration of appropriate alkynes with disiamylborane or dicyclohexylborane), readily coupled with (*E*)- and (*Z*)-1-alkenyl bromides and iodides to give the corresponding (*E*,*E*)- and (*E*,*Z*)-conjugated dienes in high yield. However, (*Z*)-1-alkenylboranes (prepared by hydroboration of 1-haloalkynes followed by reaction with *t*-butyllithium) gave a product yield of only around 50%. Fortunately, we found that using a different class of borane derivatives, (*Z*)-1-alkenyldialkoxyboranes, resulted in a successful coupling with (*Z*)-1-alkenyl halides, with high yields and stereoselectivity, as shown in Table 2.[5]

Many natural and unnatural compounds have conjugated alkadiene and polyene structures, and Suzuki coupling of vinyl compounds was soon being applied to their syntheses. It was the key reaction in the enantioselective synthesis of the antibiotic vicenistatin in 2002,[6] as well as in the total synthesis in 1989 of palytoxin, one of the most formidably complex natural products ever created in the laboratory.[7]

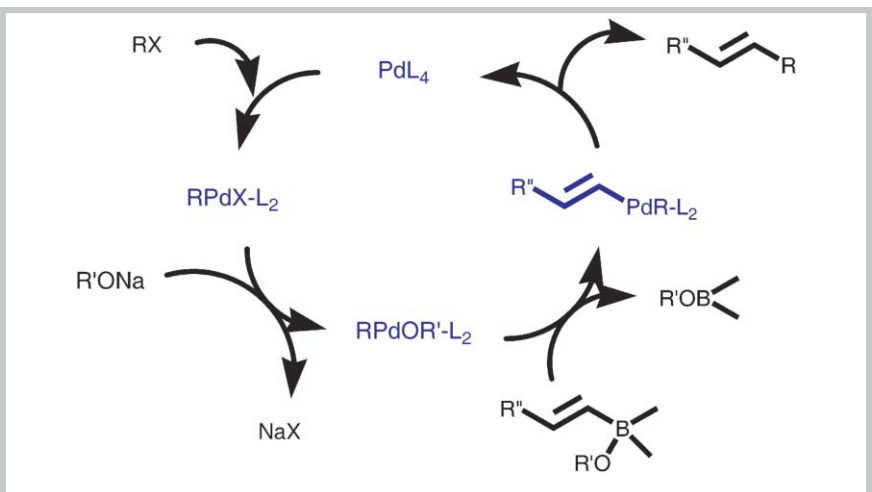
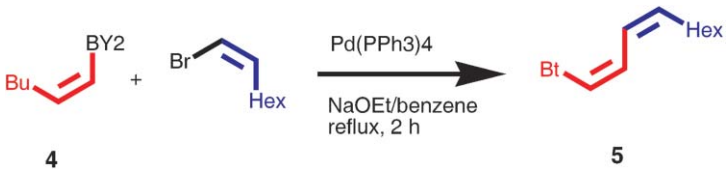


Fig. 1

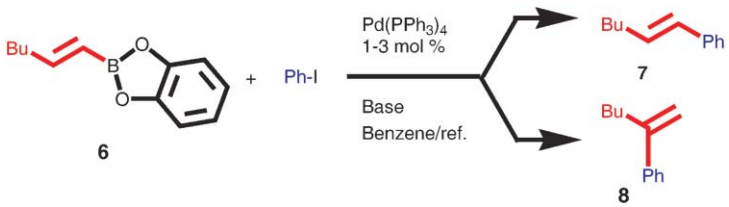
Table 2



4 5

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

Table 3



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

Coupling reactions with aromatic halides and boranes

Of course, many biological and technologically important materials contain aromatic units, so the next logical step was to explore the value of the coupling reaction involving aryl moieties. Not surprisingly, aryl halides, which like alkenyl halides also have bonds between sp^2 hybridized carbon and a halogen, coupled smoothly with 1-alkenylboranes as shown in Table 3.

The reaction shown has one more advantage in that only one compound, **7** (the head-to-head coupled product), is formed; compound **8** is not produced at all. We noted also that heteroaromatic halides also readily undergo Suzuki coupling, and that steric hindrance was not an issue for *ortho*-substituted benzene derivatives.

However there was one problem: while aromatic bromides and iodides reacted easily with vinylic boron compounds, aromatic chlorides did not (except for reactive chlorides such as allylic and benzylic derivatives). This was a distinct disadvantage, as aryl chlorides are readily available and therefore cheap. They are the precursors preferred by the chemical industry when stitching aryl groups together. Nevertheless, this obstacle was eventually overcome, as we shall see.

Application to biaryls

The synthesis of biaryls is of particular interest to industry. These motifs increasingly turn up in materials important to society such as pharmaceuticals and biocides. Nicolaou and his group famously used a Suzuki coupling in 1997 to create the challenging bicyclic structure of vancomycin – a vital weapon in the ongoing fight against antibiotic-resistant bacteria.[8]

Biaryls are also often the construction blocks of new generations of specialised engineering materials such as high-strength, rigid-rod polymers, molecular wires, liquid crystals and nonlinear optical materials, all attracting enormous interest both within the chemical community and outside.[9] Schlüter and colleagues have used the Suzuki polycondensation of aryldiboronic acids and dihaloarenes to synthesize electrically conducting poly(*p*-phenylene).[10]

When we first started looking at biaryls, the main industrial process employed was the Ullmann reaction – the coupling of aryl halides using a copper catalyst at drastically high temperatures. This reaction has a broad scope and has been used to prepare many symmetrical biaryls. However, it has the drawback that when applied to a mixture of two different aryl halides to obtain unsymmetrical biaryls, three possible products are obtained. Consequently, a better, selective and more general synthesis of biaryls was needed.

Suzuki coupling offered better selectivity. In 1981, we first made biaryls by cross-coupling arylboranes with haloarenes (Eq. 1).[11] The reaction proceeds even under heterogeneous conditions to give the required corresponding coupled products in high yields. We used the usual bases – Na_2CO_3, $NaHCO_3$, Tl_2CO_3, K_3PO_4 – although in some cases, CsF or Bu_4NF worked better.[12] We also employed the same phosphine-based palladium catalysts since they are stable on prolonged heating.

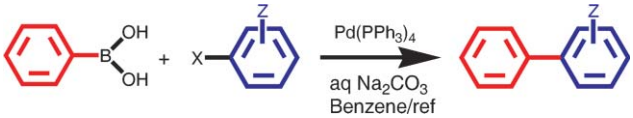
However, several research groups have since discovered new palladium catalysts that have both led to a higher coupling rate and have allowed the exploitation of the much-desired aryl chlorides as starting materials. In 2000, Fu and his group reported an efficient reaction using very small amounts of a mixture of $Pd_2(dba)_3$ and $PtBu_3$ as the respective catalyst and ligand.[13] This combination has proved to work well for a wide range of aryl and vinyl halides, including chlorides; it gives very good yields – and has the added bonus of working at room temperature. At the same time, Buchwald and his team achieved similar results under 'ligand-free' conditions using minute amounts of $Pd(OAc)_2$ as catalyst.[14]

Dealing with steric hindrance

Other significant aspects in extending the generality of Suzuki coupling to biaryl systems are the effects of steric hindrance and the presence of electron-withdrawing functions.

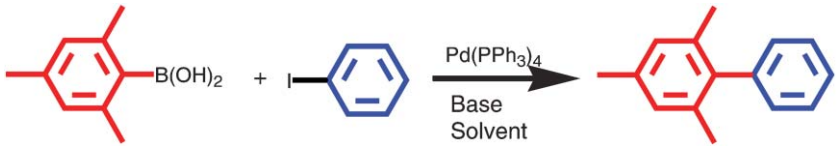
We had found that steric hindrance is not a major factor in aryl halides with one *ortho* group, however when *ortho*-disubstituted arylboronic acids are used, the yields drop drastically. For example, the reaction with mesitylboronic acid proceeds only slowly, presumably because of steric hindrance during the transmetallation to the palladium(II) complex (Table 4).[15]

Although the side-reactions such as homocoupling are negligibly small, mesitylene was formed by hydrolytic deboronation. It is worth noting that this reaction is faster in benzene/H_2O than in modified conditions using aqueous DME. On the other hand, adding stronger bases, for example, aqueous NaOH or $Ba(OH)_2$, both in benzene and DME, considerably accelerates the rate of coupling. We found that an alternative procedure employing the esters of boronic acids and anhydrous base does, in fact, give good yields.[15]



(1)

Table 4



Base	Solvent	Temperature/°C	Yield/%[a] Time 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.

Aromatic boronic acids with electron-attracting substituents such as formyl at the *o*-position may greatly increase the rate of deboronation in aqueous basic conditions. Consequently in such cases, we found that aprotic conditions are recommended, using the corresponding boronic esters and appropriate bases.[15]

So by using appropriately modified catalysts and ligands, problems of steric hindrance can be overcome. Remarkably, Buchwald and colleagues have recently even prepared tetra-*ortho*-substituted unsymmetrical biaryls in excellent yields, using versions of Suzuki coupling with interesting catalysts and ligands.[16]

Coupling with alkyl compounds

One area where Suzuki coupling has been successful more recently is in coupling with alkyl compounds. Although organometallic reagents have been used to couple 1-alkenyl, 1-alkynyl, and aryl groups for many years, their use with alkyl groups having (sp^3)carbons containing beta-hydrogens was severely limited due to competitive side-reactions. In 1971–1972, Kochi, Kumada, and Corriu independently reported that the reaction of alkyl Grignard reagents with alkenyl or aryl halides was markedly catalyzed by Fe(III) or Ni(II) complexes. Negishi then demonstrated the synthetic utility of alkylzinc compounds with a palladium catalyst. Thereafter, alkyllithium, -tin, and -aluminium reagents were also employed for such cross-coupling reactions.[1,17]

Since alkylborane derivatives can easily be prepared *via* hydroboration from readily available alkenes, we decided in the late 1980s to examine the coupling reactions between alkylboron compounds and various organic halides in the presence of the usual base and palladium phosphine complex. To our disappointment, we found that the reactions between *B*-alkyl-9-borabicyclo-[3.3.1]nonanes (B-R-9-BBN) and 1-halo-1-alkenes, or haloarenes did not proceed under the standard coupling conditions. However, by changing to a new catalyst, $PdCl_2$(dppf) and using bases, NaOH, K_2CO_3, and K_3PO_4, we found that the coupling proceeded smoothly to give the corresponding alkenes or arenes in excellent yields (Eq. 2).[18]

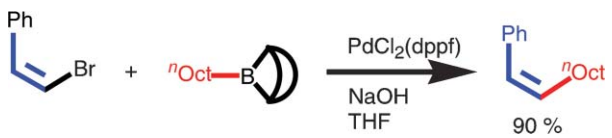
Many chemists have since applied this Suzuki coupling using *B*-saturated alkylboron compounds.[9] For example, in the 1990s Danishefsky and his team used it in the synthesis of the potential anticancer agent (−)-epothilone B and its sister compound epothilone A.[19]

Coupling with alkynylboranes

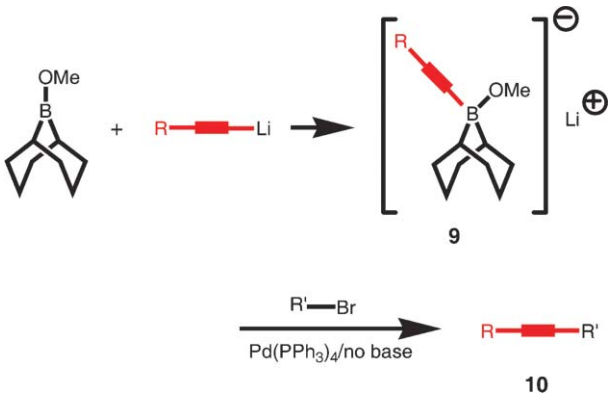
Coupled alkynyl compounds have represented the ultimate challenge for Suzuki coupling. Alkynylboranes have long been known to be useful synthetic intermediates, but, compared with other organoboranes, they are easily hydrolyzed under aqueous basic conditions. We therefore had not tried to use them in the Suzuki coupling reaction, which requires the presence of a base.

However, in 1995, Soderquist and colleagues discovered a new version of the coupling mechanism using alkynyllithium reagents. When added to *B*-methoxy-9-borabicyclo[3.3.1]nonane, it gives the stable complex **9** which undergoes efficient Suzuki coupling to produce a variety of alkynyl derivatives **10** (Eq. 3).[20]

Almost at the same time, Fürstner and Seidel independently reported the same reaction.[21] Namely, the necessary alkynyl borates are prepared from 9-methoxy-9-BBN and a polar organometallic reagent RM, such as 1-alkynyl sodium, potassium and lithium compounds. This approach allows cross-couplings of organic halides with, for example, alkynyl, methyl, or $TMSCH_2$ groups. The method is highly chemoselective, and turns out to be compatible with



(2)



(3)

aldehyde, amide, ketone, ester and cyano functions as well as with basic nitrogen atoms in the substrates.

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 using either resin-bound aryl halides with solution-phase boronic acids[9] or *vice versa*.[22] Such approaches, of course, play an important role in the combinatorial and parallel methodologies now used to explore chemical reactivity, especially in 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 ultra-low (ppb) palladium concentrations in water,[23] 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.[24] Ionic liquids, which are excellent solvents for transition-metal catalysts, are also being investigated.[25]

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

Acknowledgements

I wish to thank my many co-workers who helped me explore the riches of the New Boron Continent described in this article. Finally I would like to thank Ms. Nina Hall for her help in editing this manuscript.

Notes and references

1 F. Diederich and P. J. Stang (Eds.), *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 1998.
2 N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.*, 1979, **36**, 3437.
3 O. Gropen and A. Haaland, *Acta Chem. Scand.*, 1973, **27**, 521.
4 K. Yamada, N. Miyaura, H. Suginome and A. Suzuki, *J. Am. Chem. Soc.*, 1985, **107**, 972.
5 N. Miyaura, M. Satoh and A. Suzuki, *Tetrahedron Lett.*, 1986, **27**, 3745.
6 Y. Matsushima, H. Itoh, T. Nakayama, S. Horiuchi, T. Eguchi and K. Kakinuma, *J. Chem. Soc., Perkin Trans. 1*, 2002, 949.
7 R. W. Armstrong, J.-M. Beau, S.-H. Cheom., W. J. Christ, H. Fujiyoka, W.-H. Ham, L. D. Hawkins, H. Jin, S.-H. Kang and Y. Kishi, *J. Am. Chem. Soc.*, 1989, **111**, 7525.
8 K. C. Nicolaou, J. M. Ramanjulu, S. Natarajan, S. Bräse, H. Li, C. N. C. Boddy and F. Rübsam, *Chem. Commun.*, 1997, 1899.
9 A. Suzuki, *Suzuki Coupling*, Organic Syntheses via Boranes, Vol. 3, Aldrich, Milwaukee, 2003.
10 M. Rehahn, A. D. Schlüter, G. Wegner and W. Feast, *Polymer*, 1989, **30**, 1054.
11 T. Yanagi, N. Miyaura and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513.
12 S. W. Wright, D. L. Hageman and L. D. McClure, *J. Org. Chem.*, 1994, **59**, 6095.
13 A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020.
14 J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 9550.
15 T. Watanabe, N. Miyaura and A. Suzuki, *Synlett*, 1992, 207.
16 J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 1162.
17 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
18 N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh and A. Suzuki, *J. Am. Chem. Soc.*, 1989, **111**, 314.
19 D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorenson, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He and S. B. Horwitz, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 757.
20 J. A. Soderquist, K. Matos, A. Rane and J. Ramos, *Tetrahedron Lett.*, 1995, **36**, 2401.
21 A. Fürstner and G. Seidel, *Tetrahedron*, 1995, **51**, 11165.
22 B. Carboni, C. Pourbaix, F. Carreaux, H. Deleuze and B. Maillard, *Tetrahedron Lett.*, 1999, **40**, 7979.
23 R. K. Arvela, N. E. Leadbeater, M. S. Sangi, V. A. Williams, P. Granados and R. D. Singer, *J. Org. Chem.*, 2005, **70**, 1, 161.
24 G. W. Kabalka, R. M. Pagni and C. M. Hair, *Org. Lett.*, 1999, **1**, 1423.
25 C. J. Mathews, P. J. Smith and T. Welton, *Chem. Commun.*, 2000, 1249.