

III.2.2 Overview of the Suzuki Protocol with B

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A. INTRODUCTION

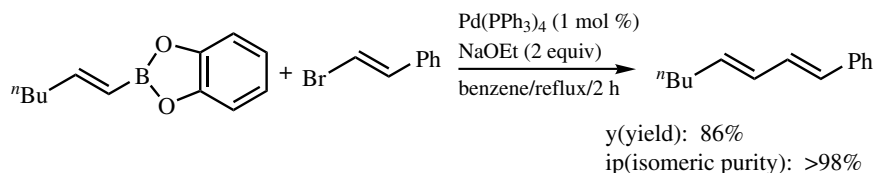
Carbon–carbon bond-formation reactions are the most important processes in organic chemistry. Until almost a half century ago, a number of the C—C bond-formation reactions were reported using organic molecules with $\text{sp}^3\text{-C}$ atoms, but there were no general direct methodologies for carbon–carbon bond formation between unsaturated species such as vinyl, aryl, and alkynyl moieties. The discovery of metal-catalyzed cross-coupling reactions, starting in the early 1970s, overcame the difficulties and such reactions were noted as the most powerful and useful synthetic tools.^[1]

Among metal-mediated cross-coupling reactions, the Pd-catalyzed cross-coupling reaction between different types of organoboron compounds and various organic electrophiles such as halides and triflates in the presence of base provides a powerful and general methodology for the formation of C—C bonds. The coupling reaction offers several advantages: ready availability of reagents, mild reaction conditions, water stability, toleration of a broad range of functional groups, good regio- and stereoselectivity, insignificant effect of steric hindrance, small amount of catalysts, application in one-pot synthesis, nontoxic reaction, and easy separation of inorganic boron compounds.^{[2]–[5]} The overview of the boron-coupling reactions is mentioned in this section.

B. COUPLING OF 1-ALKENYLBORON COMPOUNDS: SYNTHESIS OF CONJUGATED DIENES

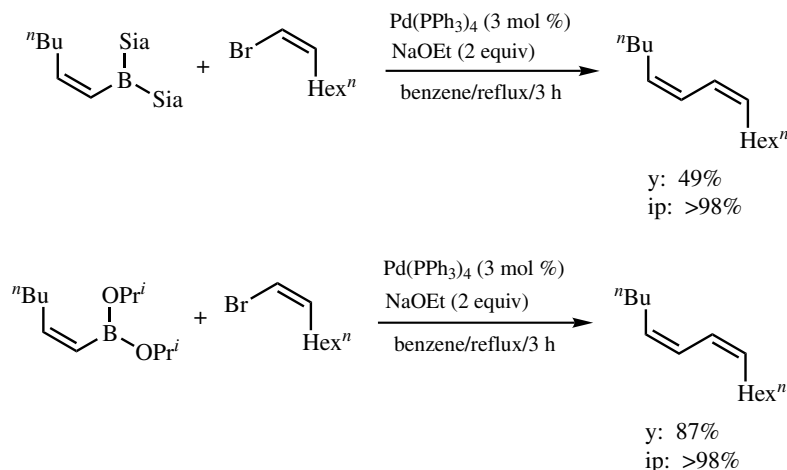
The stereo- and regioselective syntheses of conjugated alkadienes are of great importance in organic chemistry by themselves as well as their utilization in other reactions such as the Diels–Alder reaction. A number of new methods for the preparation of conjugated dienes and polyenes have been developed by utilizing various organometallic reagents. Among these procedures, the most promising ones are perhaps those based on the direct cross-coupling reaction of stereodefined alkenylmetals with stereodefined haloalkenes in the presence of a transition metal complex.^[2] However, there are several limitations when one wishes to obtain unsymmetrical dienes without homocoupling, highly functionalized dienes, or stoichiometric conditions relative to metal reagents and organic halides. Thus,

much attention has recently been focused on the use of 1-alkenylboron compounds, because a variety of 1-alkenylboron derivatives are now readily available. The first observation to prepare conjugated dienes is shown in **Scheme 1**.^{[6],[7]}



Scheme 1

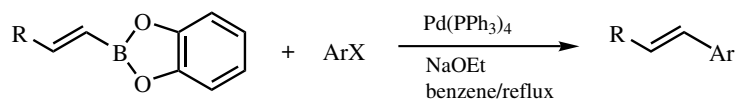
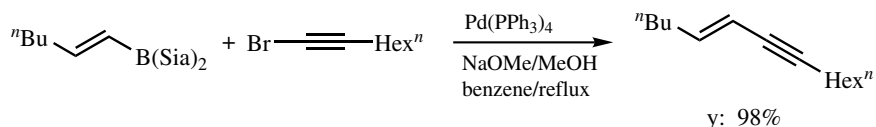
The high yield of the diene is obtained when relatively strong bases such as sodium ethoxide and hydroxide are used with a phosphine-based Pd complex, for example, $\text{Pd(PPh}_3)_4$ and $\text{PdCl}_2(\text{PPh}_3)_2$. As 1-alkenylboron compounds, disiamyl- and 9-BBN derivatives can be utilized in the coupling reactions. However, the coupling of such (*Z*)-1-alkenylboron reagents with 1-alkenyl halides gives insufficient results in yield and stereo-selectivity. One such result is shown in **Scheme 2**.^[8] The difficulty is surmounted by using diisopropoxyboron derivative instead of disiamyl- or dicyclohexylboron compounds. Consequently, all kinds of conjugated alkadienes are able to be synthesized by the cross-coupling reaction regio- and stereoselectively in high yields under suitable reaction conditions.



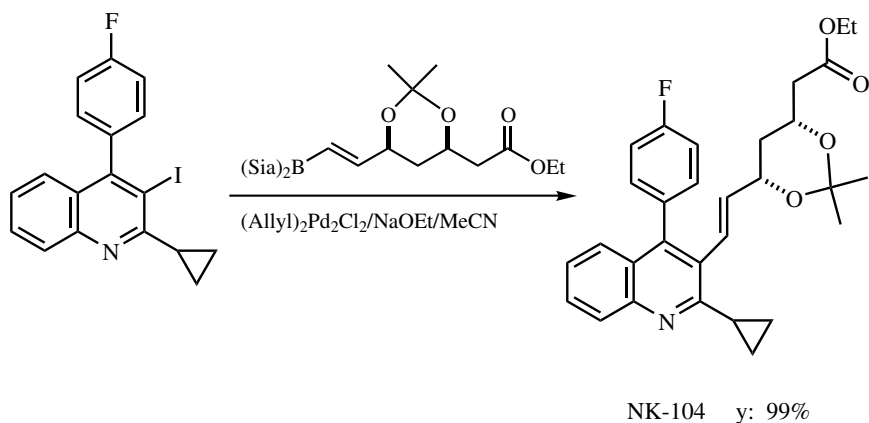
Scheme 2

This reaction was applied to the synthesis of many alkadiene structures including complex natural products such as palytoxin,^[9] chlorothricolide,^[10] and rutamycin B.^[11] A new synthesis of vitamin A with essentially complete control of regio- and stereochemistry has recently been reported.^[12]

The cross-coupling reaction of 1-alkenyl(disiamyl)boranes with 1-bromo-1-alkynes gives conjugated enynes in high yields (**Scheme 3**).^[7] The cross-coupling of 1-alkenyl-boronates is useful for alkenylation of haloarenes (**Scheme 3**).^[13] The relative reactivity appears to be $\text{PhI} > p\text{-ClC}_6\text{H}_4\text{Br} > \text{PhBr} > o\text{-MeC}_6\text{H}_4\text{Br} > o\text{-MeOC}_6\text{H}_4\text{Br}$.^[13] The order of reactivity is in good agreement with substituent effect in the oxidative addition of aryl halides to the $\text{Pd}(0)$ complex. The procedure gives new access to HGM-CoA reductase inhibitor NK-104 (**Scheme 4**).^[14]



Scheme 3

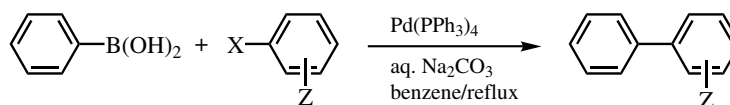


Scheme 4

C. COUPLING OF ARYLBORON COMPOUNDS

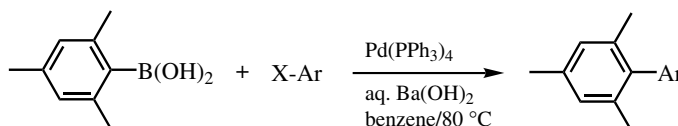
The first method to prepare biaryl by the cross-coupling reaction between arylboron compounds and aryl halides was reported in 1981 in the presence of $\text{Pd}(\text{PPh}_3)_4$ and aqueous Na_2CO_3 in benzene at reflux temperature (**Scheme 5**).^[15] After this discovery, various modifications were made for reaction conditions. A combination of $\text{Pd}(\text{PPh}_3)_4$ or $\text{PdCl}_2(\text{PPh}_3)_2$ and aqueous Na_2CO_3 in dimethoxyethane (DME) works satisfactorily in most cases.^{[16],[17]}

Phosphine-based palladium catalysts are generally used since they are stable on prolonged heating; however, extremely high coupling reaction rates can sometimes be achieved by using palladium catalysts without a phosphine ligand.^[18]



Scheme 5

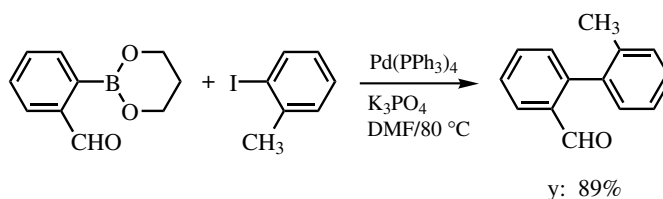
Although steric hindrance of aryl halides is not a major factor for the formation of substituted biaryls, low yields resulted when *ortho*-disubstituted arylboronic acids were used. For example, the reaction with mesitylboronic acid proceeds slowly because of steric hindrance during the transmetalation to Pd(II) halide. The addition of strong bases, for example, aqueous NaOH or Ba(OH)₂, both in benzene and DME exerts a remarkable effect on the acceleration of the coupling rate (**Scheme 6**).^[19]



ArX: 2-MeOC₆H₄I (80%), 2-ClC₆H₄I (94%),
2-bromonaphthalene (86%)

Scheme 6

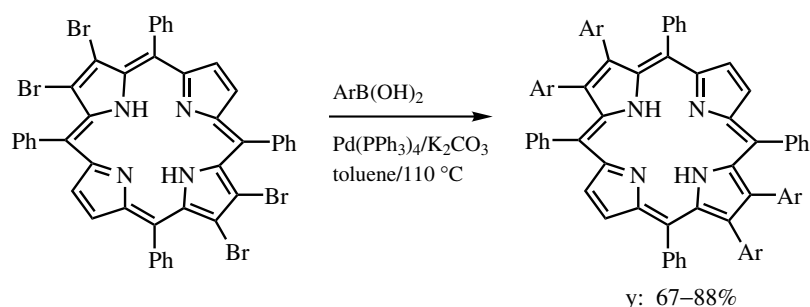
Even if there is no great steric hindrance, the reaction under aqueous conditions gives undesirable results due to competitive deboronation. For instance, coupling of 2-formylphenylboronic acid with 2-iodotoluene at 80 °C using an aqueous Na₂CO₃ in benzene gives only 54% of the expected biaryl with the formation of benzaldehyde (39%). The yield can be improved to 89% by using the corresponding ester of the boronic acid and anhydrous K₃PO₄ suspended in DMF (**Scheme 7**).^[19]



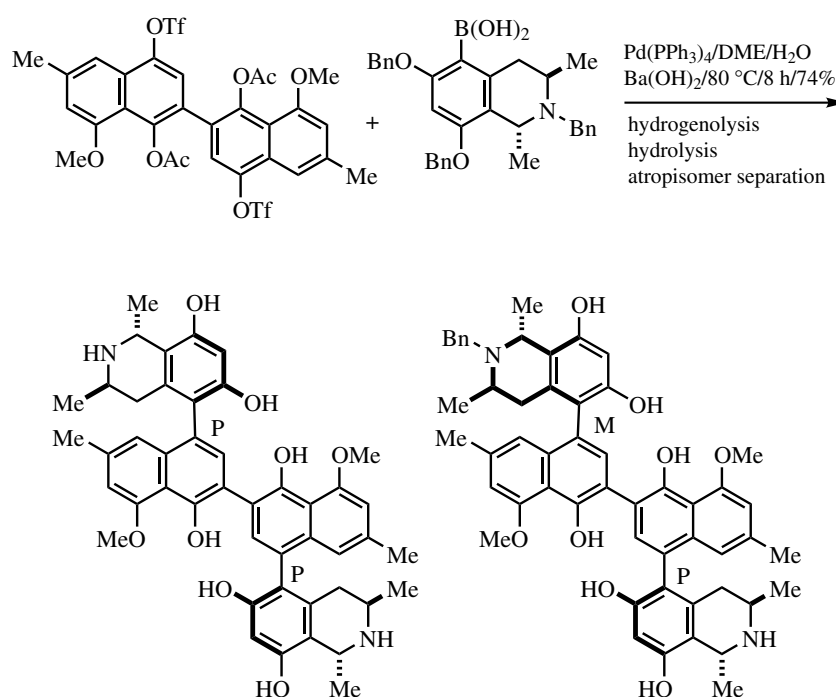
Scheme 7

The cross-coupling reaction of arylboronic acids is largely unaffected by the presence of water, tolerating a broad range of functionality and yielding nontoxic by-products. The reaction offers an additional great advantage of being insensitive to the presence of *ortho*-functional groups or heteroaromatic rings. An example is shown in **Scheme 8**.^[20]

Most recently, the anti-HIV alkaloids michellamines A and B have successfully been synthesized by a double Suzuki-type cross-coupling reaction between a binaphthalene ditriflate and an isoquinolineboronic acid (**Scheme 9**).^{[21],[22]}



Scheme 8



Scheme 9

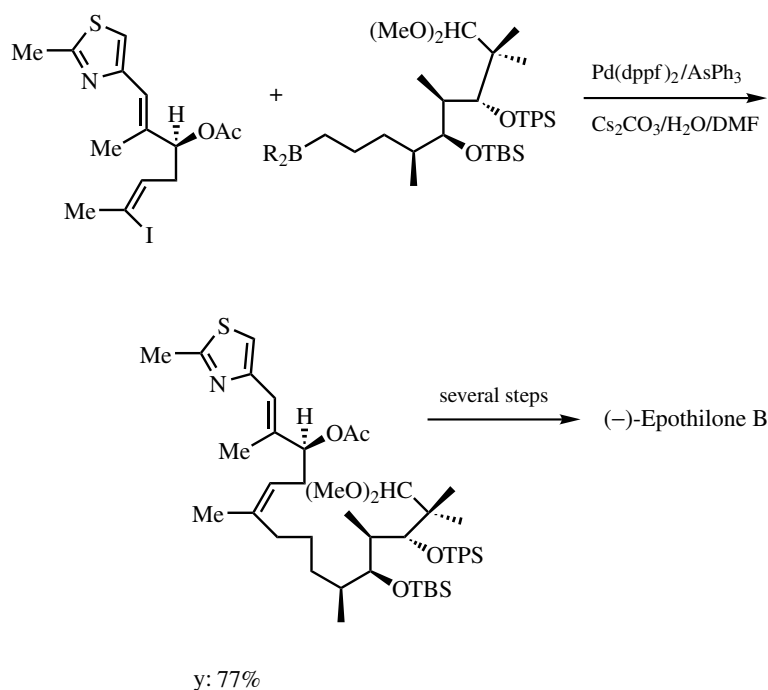
D. COUPLING OF ALKYLBORON COMPOUNDS

Although alkylmagnesium, -zinc, -tin, and -aluminum reagents have successfully been used for the cross-coupling reaction with organic halides, the reaction of alkylborane derivatives is particularly useful when one wishes to start from alkenes via hydroboration. Bases as well as palladium catalysts are essential for the success of the coupling reaction.^{[23],[24]} A combination of $\text{PdCl}_2(\text{dppf})$ and aqueous NaOH in THF works smoothly for most cases. Although strong bases accelerate the coupling reaction, weaker bases and aprotic conditions are desirable for functionalized alkylboron compounds or organic halides.

Meng et al.^[25] have recently reported a total synthesis of the promising anticancer agents epothilones A and B using alkylboranes coupling reaction as shown in **Scheme 10**.

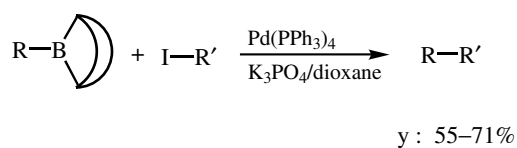
Such a coupling reaction has been employed for the synthesis of many complex natural products and related compounds, for example, roflamycoin,^[26] agelasimine A,^[27] and azasugars.^[28]

In contrast to stereochemical investigations of the related cross-couplings involving silanes and stannanes, the stereochemistry of the transmetalation of alkylboranes to palladium (either retention or inversion of configuration) has received little attention, although it was suggested to proceed with retention of configuration.^{[2]-[5]} Recently, it has been confirmed that primary alkylboranes undergo transmetalation to palladium with retention of configuration.^[29]



Scheme 10

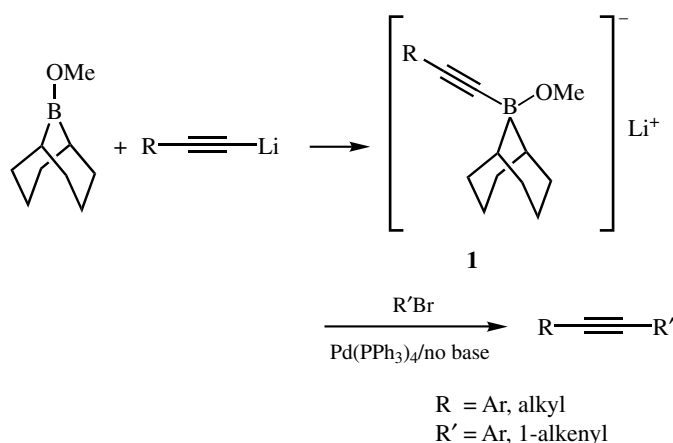
B-Alkylboron compounds react readily with various 1-alkenyl and aryl halides to give corresponding coupling products in high yields. However, it has been considered that such coupling reactions cannot be extended to alkyl halides with sp^3 -carbon having *b*-hydrogens due to the slow rate of oxidative addition of alkyl halides to Pd(0) complexes and the fast *b*-hydride elimination from *s*-alkylpalladium intermediates in the catalytic cycle. Thus, the use of alkyl halides as coupling partners was a challenging problem in several recent publications. Recently, it has been determined that the coupling reaction of usual iodoalkanes with 9-alkyl-9-BBN derivatives proceeds readily in the presence of Pd(PPh₃)₄ and K₃PO₄ in dioxane to provide the corresponding coupling products in reasonable yields (**Scheme 11**).^[30]



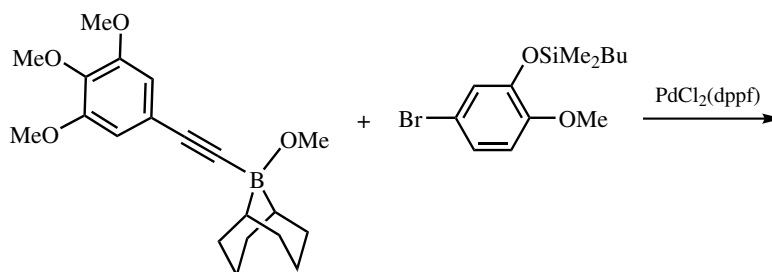
Scheme 11

E. COUPLING OF 1-ALKYNYLBORON COMPOUNDS

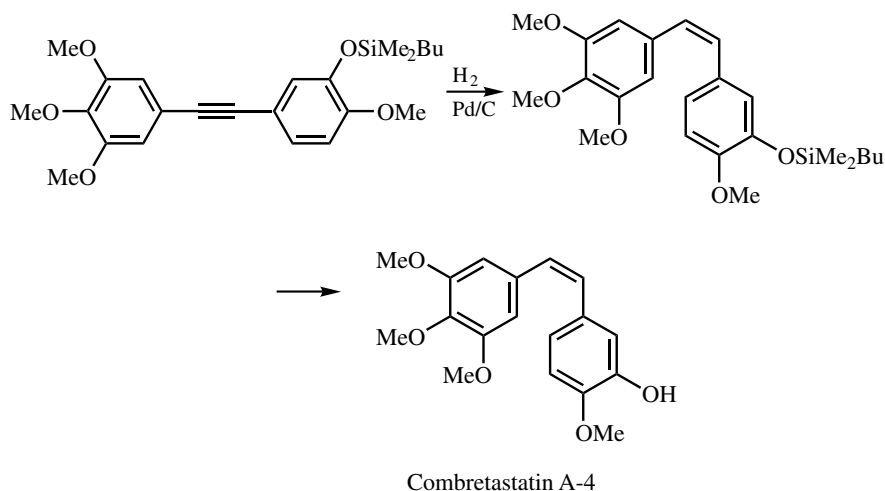
Alkynylboranes have long been known to be useful synthetic intermediates. Compared to other organoboranes, because they are stronger Lewis acids and are easily hydrolyzed, they have not been employed for the cross-coupling reaction, in which the presence of bases is essential. Most recently, Soderquist et al.^[31] and Früstner and Seidel^[32] have found independently that the addition of 9-methoxy-9-BBN to alkynylmetal reagents gives stable complexes (**1**) that undergo efficient Suzuki-coupling reactions to produce a variety of alkynyl derivatives (**Scheme 12**). 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. This method was employed for the synthesis of combretastatin A-4 (**Scheme 13**).^[33]



Scheme 12



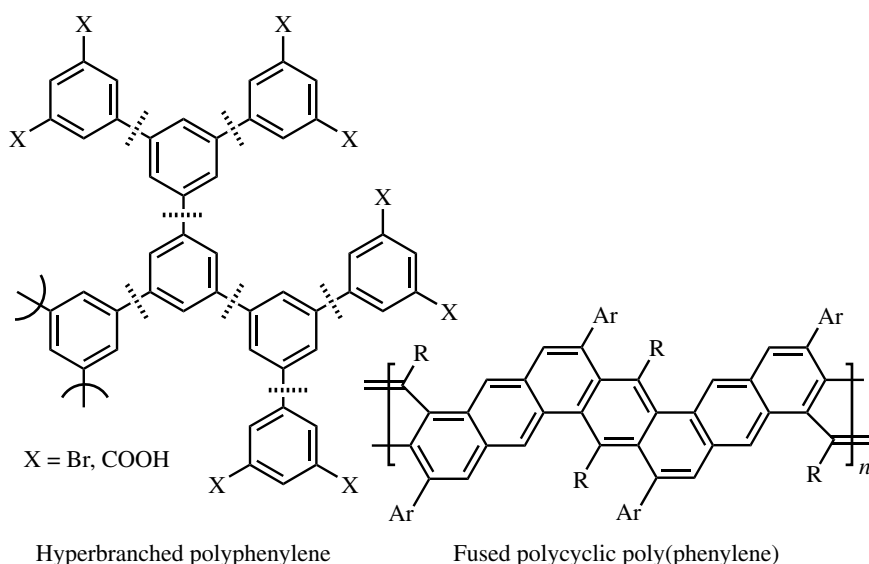
Scheme 13



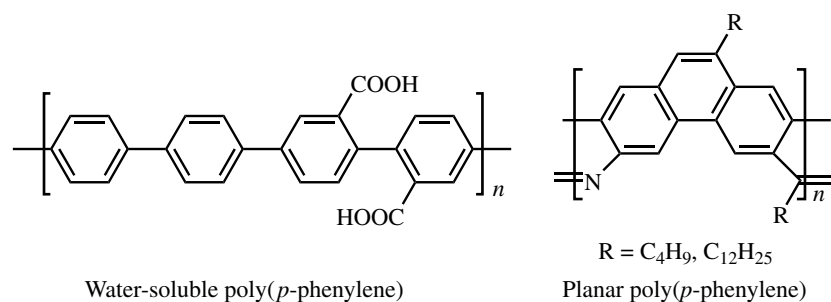
Scheme 13 (Continued)

F. APPLICATIONS TO 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 aryldiboronic acids and dihaloarenes for the synthesis of poly(*p*-phenylenes) was first reported by Rehahn et al.^[34] The method has been extensively applied to water-soluble poly(*p*-phenylene),^[35] planar poly(*p*-phenylenes) fixed with the ketoimine bonds,^[36] poly(phenylenes) fused with polycyclic aromatics,^[37] and nonlinear optical materials^[38] (Scheme 14).

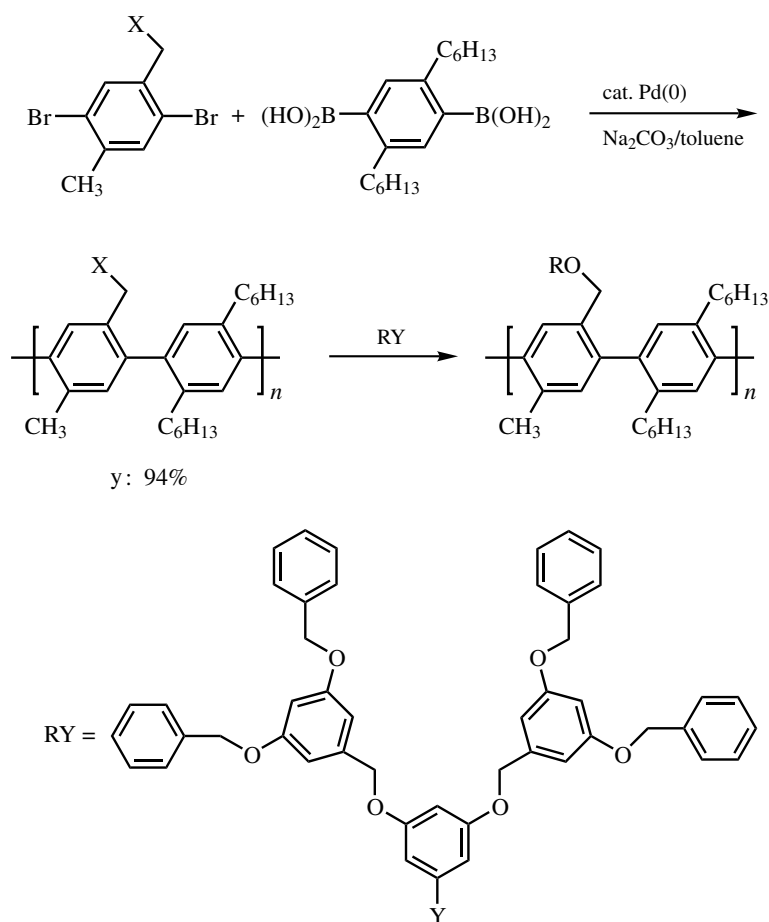


Scheme 14



Scheme 14 (Continued)

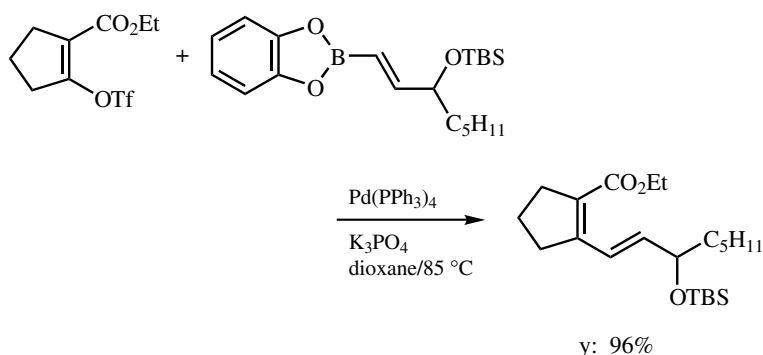
Most recently, the preparation of *ortho*-polyphenylene oligomers, having three to nine rings, using a rational Suzuki-coupling strategy, has been achieved.^[39] Useful synthetic procedures for dendrimers are being investigated. Many such syntheses have been reported using Suzuki polycondensation. An example is shown in Scheme 15.^[40]



Scheme 15

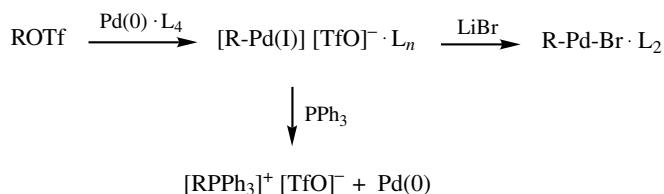
G. REACTION WITH OTHER ELECTROPHILES

Although the cross-coupling reaction with organic halides has been studied predominantly, it has recently been discovered that trifluoromethanesulfonates (triflates) undergo a clean coupling with organoboron compounds, similar to organostannanes, aluminum, and zinc compounds. Triflates are valuable as partners for the cross-coupling reaction, in part due to the easy access from phenols or carbonyl enolates, which allow the selective formation of aryl or 1-alkenyl electrophiles. Although relatively strong bases such as aqueous NaOH and NaOEt in ethanol have been used for the reaction with organic halides, powdered K_3PO_4 suspended in THF or dioxane is sufficient enough to accelerate the coupling of 9-alkyl-9-BBN derivatives and 1-alkenyl- and arylboronates or boronic acids with triflates (**Scheme 16**).^[41]



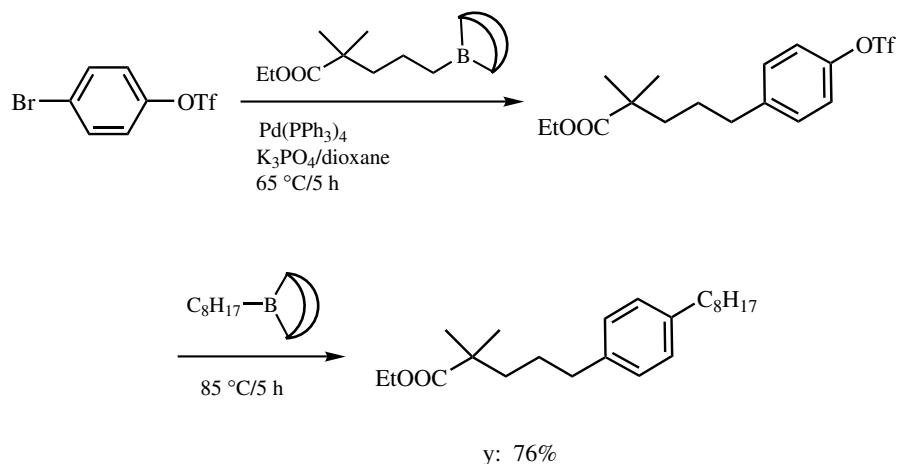
Scheme 16

The coupling with triflates often fails to proceed because of the decomposition of catalysts, precipitating palladium black at an early stage of the reaction. Presumably, triphenylphosphine used as a ligand of palladium reacts with triflates to give phosphonium salts (**Scheme 17**). Addition of 1 equiv of lithium or potassium bromide is effective in preventing such decomposition of the catalyst, which is known to convert the labile cationic palladium species to organopalladium(II) bromide.^[42]



Scheme 17

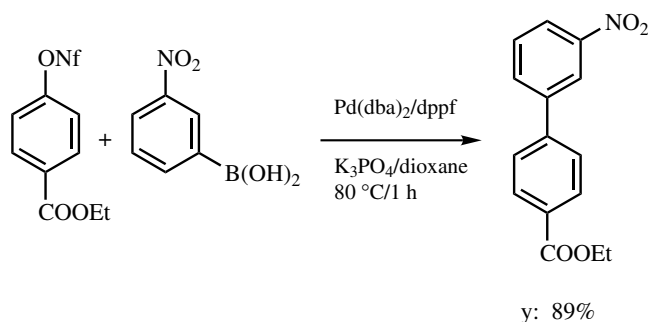
The order of reactivity of halides and triflates for the cross-coupling reaction of boron reagents is $\text{I} > \text{Br} > \text{OTf} \gg \text{Cl}$. Thus, the sequential cross-coupling reactions of 4-bromophenyl triflate with two 9-alkyl-9-BBN derivatives obtained from two different alkenes furnishes the unsymmetrically disubstituted benzene derivative (**Scheme 18**).^[41]



Scheme 18

One of the challenges in Suzuki-type cross-coupling is to extend this reaction from electron-rich aryl iodides, bromides, and triflates to less reactive aryl sulfonates and aryl chlorides, which show poor reactivity toward oxidative addition in the catalytic cycle. Aryl mesylates, benzenesulfonates, and tosylates are much less expensive than triflates and are unreactive toward palladium catalysts. The Ni(0)-catalyzed Suzuki-type cross-coupling reaction of arylsulfonates including mesylates with arylboronic acids in the presence of K_3PO_4 was reported.^[43]

Most recently, aryl fluoroalkanesulfonates $[ArOSO_2(CF_2)_nCF_3]$ have been proposed as an alternative to triflates, because they are easily prepared using commercially available fluoroalkanesulfonic anhydrides or halides. Aryl nonaflates are especially useful, being readily prepared and stable to flush column chromatography (Scheme 19).^[44]

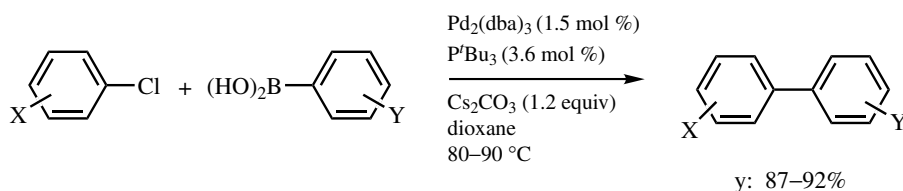


Scheme 19

As alternatives to the use of organic electrophiles, hypervalent iodonium compounds^[45] and organolead compounds^[46] have been employed in cross-coupling with organoboron compounds.

One limitation in the scope of the Suzuki reaction is its inefficiency when aryl chlorides are employed as substrates, although there have been several accounts on the

coupling of electron-poor aryl chlorides. Most recently, Littke and Fu^[47] has reported that the $[\text{Pd}_2(\text{dba})_3]/\text{P}^t\text{Bu}_3/\text{Cs}_2\text{CO}_3$ -catalyzed cross-coupling of aryl chlorides with benzenboronic acids proceeds smoothly to give the expected products in excellent yields, even in electron-rich aryl chlorides (**Scheme 20**). Old et al.^[48] and Lohse et al.^[49] have also independently reported the coupling reactions using aryl chlorides.

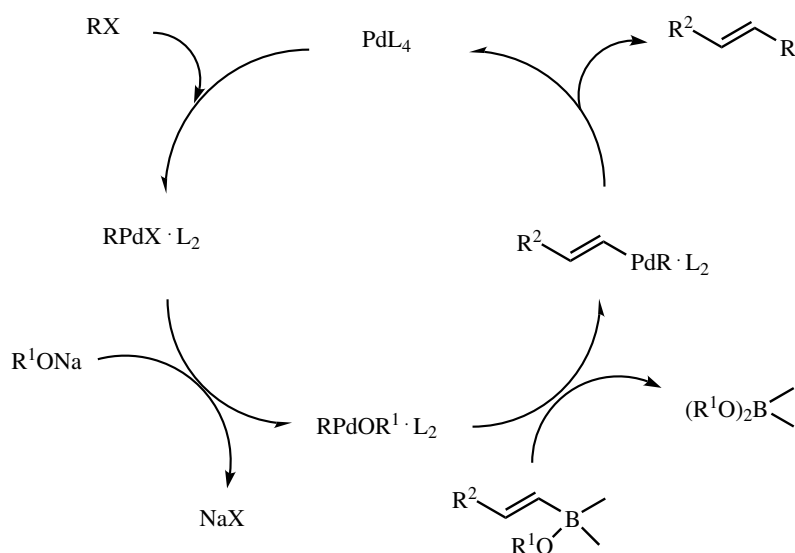


Scheme 20

H. REACTION MECHANISM

A mechanism of the cross-coupling reaction of 1-alkenylboranes with 1-haloalkenes was first reported to involve four steps: (i) the oxidative addition of a organic halide to palladium complex, (ii) the metathetical displacement of a halogen atom from RPd(II)X with a base to give an organo-organoxo-palladium intermediate, (iii) the transmetalation to such an intermediate to provide diorgano-palladium compound, and (iv) the final reductive elimination to give the coupling product (**Scheme 21**).^[7]

Although most recently, Matos and Soderquist^[50] have reported a precise investigation on the mechanism of the cross-coupling reaction between alkylboranes and bromobenzene, much more effort is needed on the mechanistic study of different kinds of coupling reactions.



Scheme 21

I. CONCLUSION

The Pd-catalyzed cross-coupling reactions between different types of organoboron compounds and various organic halides or related electrophiles in the presence of base provide one of the most straightforward methodologies for various carbon–carbon bond formations. The $\text{sp}^3\text{-C-B}$ compounds (alkylboron compounds) and $\text{sp}^2\text{-C-B}$ compounds such as aryl- and 1-alkenylboron derivatives readily cross-couple with organic electrophiles to give coupling products selectively in high yields. Most recently, the sp-C-B compounds (1-alkynylboron derivatives) have been also observed to react with organic electrophiles to produce cross-coupling products.

Such coupling reactions offer several advantages. One defect of the reaction is the use of bases. However, the difficulty could 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.

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