CROSS-COUPLING REACTIONS OF ORGANOBORANES: AN EASY WAY FOR C-C BONDING

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by

AKIRA SUZUKI

Hokkaido University, Sapporo, Hokkaido, Japan.

INTRODUCTION

Carbon-carbon bond formation reactions are important processes in chemistry, because they provide key steps in building complex, bio-active 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 bond-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 a base provides a powerful and general methodology for the formation of carbon-carbon bonds. The C(sp^2)-B compounds (such as aryl- and 1-alkenylboron derivatives) and C(sp^3)-B compounds (alkylboron compounds) readily cross-couple with organic electrophiles to give coupled products selectively in high yields. Recently, the C(sp)-B compounds (1-alkynylboron derivatives) have been also observed to react with organic electrophiles to produce expected cross-coupled products.

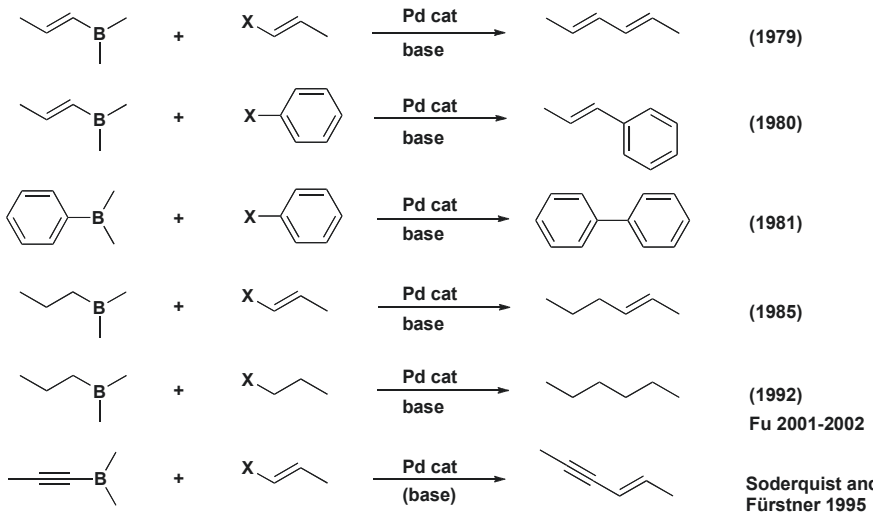


Figure 1. Some of representative reactions between various organoboranes and a number of organic electrophiles are shown here. Numbers in parentheses indicate the years first reported by our group.

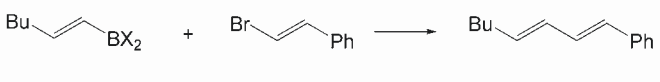
Such coupling reactions offer several advantages:

1. ready availability of reactants
2. mild reaction conditions and high product yields
3. water stability
4. easy use of the reaction both in aqueous and heterogeneous conditions
5. toleration of a broad range of functional groups
6. high regio- and stereoselectivity of the reaction
7. insignificant effect of steric hindrance
8. use of a small amount of catalysts
9. application in one-pot synthesis
10. nontoxic reaction
11. easy separation of inorganic boron compound
12. environmentally friendly process

As one of defects of the reaction, one would point out 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.

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 palladium catalysts only. During the initial stage of our exploration, we postulated that this might be due to 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 (Diederich and Stang, 1998). 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 a study by Gropen and Haaland (Gropen and Haaland, 1973), 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 a 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 I).



1 **2** **3**

1[a]	Catalyst[b] (mol%)	Base (Equiv / **2**)	Solvent	Reac. time(h)	Yield (%) of **3**
1b	PdL_4 (3)	None	THF	6	0
1b	PdL_4 (3)	None	Benzene	6	0
1a	PdL_4 (3)	2M NaOEt(2)-EtOH	THF	2	73
1b	PdL_4 (1)	2M NaOEt(2)-EtOH	Benzene	2	86

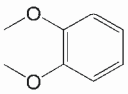
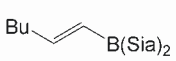
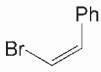
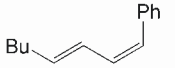
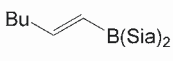
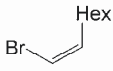
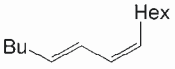
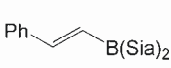
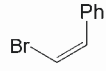
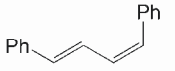
a) **1a**, $X_2 = (Sia)_2$; **1b**, X_2 =  b) L = PPh_3

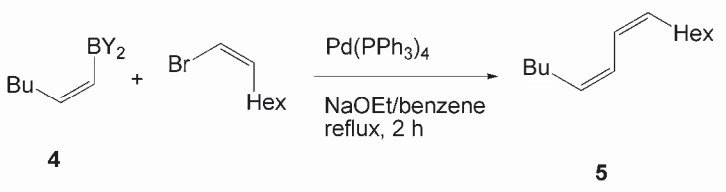
Table I. Cross-coupling reaction of 1 with 2.

Although the coupling reaction of (E)-1-alkenylboranes easily obtained via 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 II), (Z)-1-alkenylboranes, prepared by hydroboration of 1-haloalkynes followed by the reaction with *t*-butyllithium, gave low product yields, near 50% (Table III).

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

Reaction conditions: $Pd(PPh_3)_4$/NaOEt/benzene/reflux/2 h

Table II. Cross-coupling reaction of (E)-1-vinyldisiamylboranes.



4 **5**

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

Table III. Cross-coupling of (Z)-1-Hexenyldisiamyl- or (Z)-1-Hexenyldiisopropoxyborane.

Fortunately, it turned out that high yield and high stereoselectivity could be achieved by coupling (Z)-1-alkenyl halides with (Z)-1-alkenyldialkoxyboranes, instead of disiamyl- and dicyclohexylborane derivatives, as shown in Table III (Miyaura *et al.*, 1986). Consequently, the cross-coupling reaction of 1-alkenylboranes with 1-alkenyl halides can readily be achieved for syntheses of all kinds of conjugated alkadienes. The reaction has been applied to syntheses of many natural and unnatural compounds which have conjugated alkadiene structures (Miyaura and Suzuki, 1995; Suzuki, 1998; Suzuki, 1999; Suzuki, 2002). Among many synthetic applications of Suzuki coupling reaction for conjugated alkadienes, the total synthesis of palytoxin (Figure 2), a complex and toxic natural product is an epoch-making contribution (Kishi et al., 1989). As another example, the total synthesis of lucilactaene is shown in Figure 3 (Coleman *et al.,* 2005).

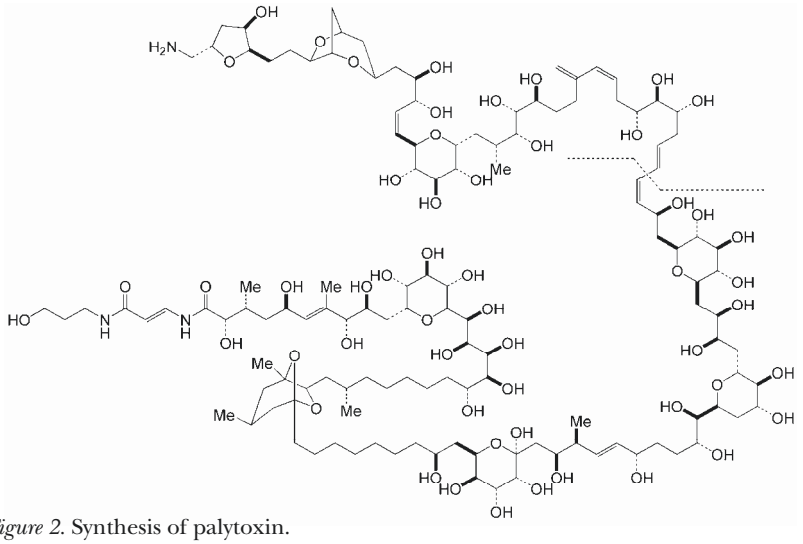


Figure 2. Synthesis of palytoxin.

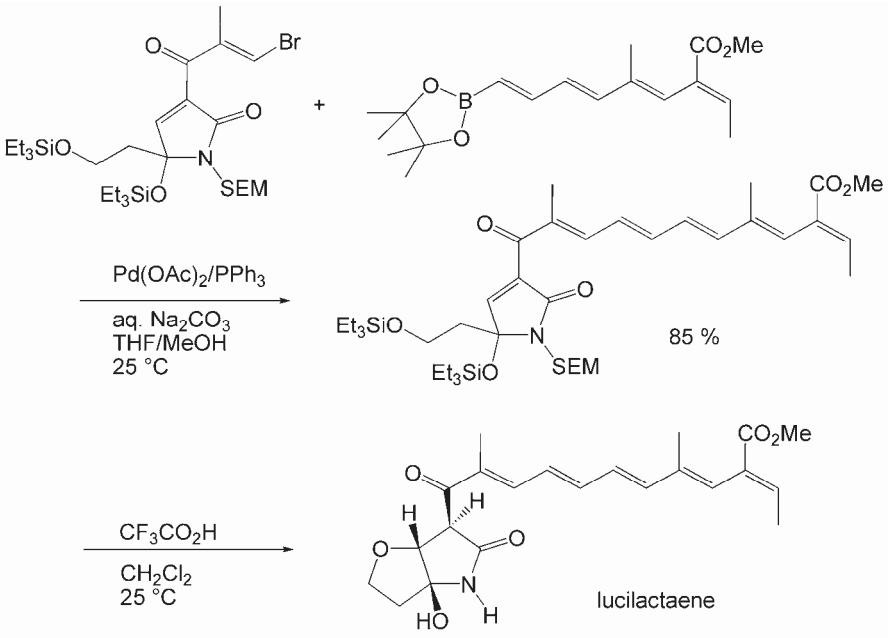


Figure 3. Synthesis of lucilactaene.

Mechanism of the Vinylic-Vinylic Cross-Coupling

The principal features of the cross-coupling reaction are as follows: (a) Small catalytic amounts of 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 Eq. 1. The coupled product, however, was obtained only in 9%. 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**, as depicted in Eq 2 and Eq 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 as shown in Figure 4 (Miyaura *et al.*, 1985).

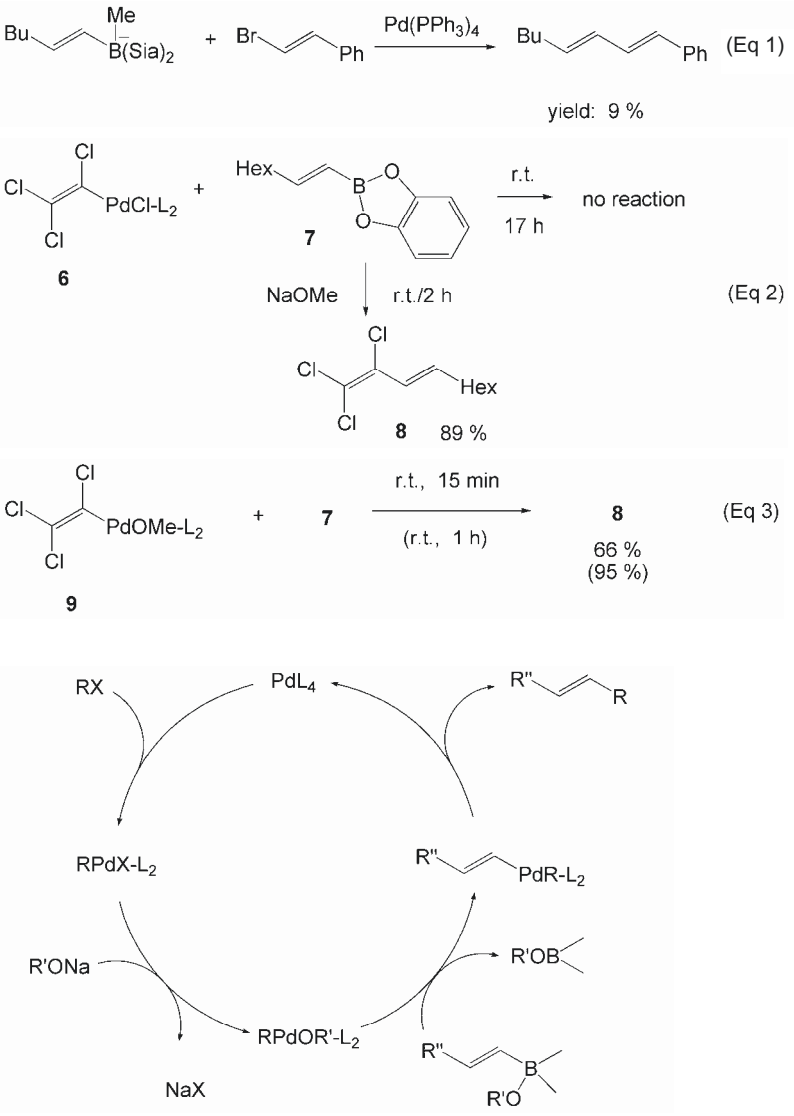
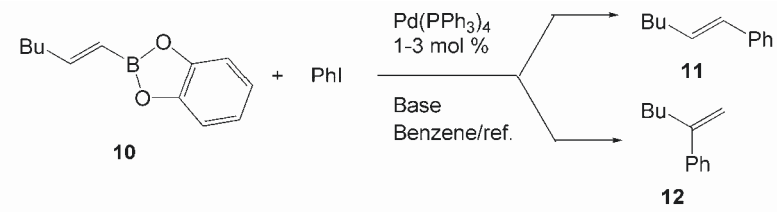


Figure 4. Catalytic cycle for the coupling reaction of alkenylboranes with haloalkenes.

Reaction with Aryl Halides

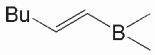
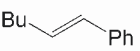
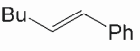
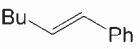
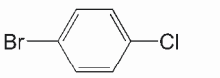
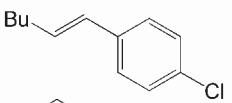
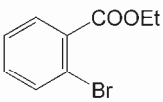
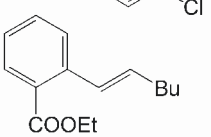
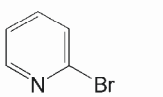
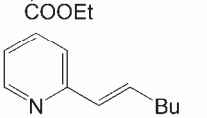
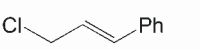
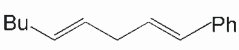
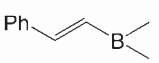
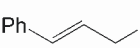
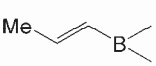
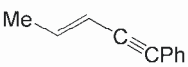
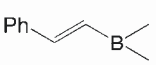
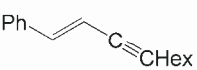
As described in the previous section, it was discovered that vinylic boron compounds readily react with vinylic halides to give coupled products, conjugated alkadienes. We next attempted to examine the reaction of 1-alkenylboranes with haloarenes which have also sp2 hybridized carbon-halogen bonds, and found that the reaction takes place smoothly. Representative results are exhibited in Table IV.



Base	Reaction time (h)	Product yield (%)	Ratio of **11** : **12**
None	6	0	
NaOEt	2	100	100 : 0
NaOMe	2	100	100 : 0
NaOH	2	100	100 : 0

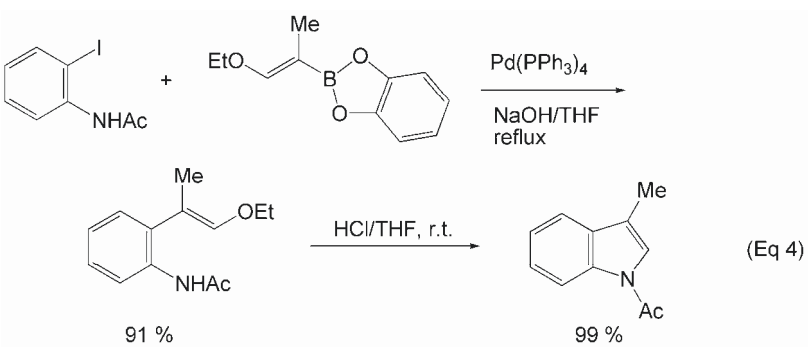
Table IV. Cross-coupling reaction of 10 with Iodobenzene.

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 V. 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 be also used as coupling partners. Ortho-substituents on the benzene ring do not cause difficulty. Thus, the cross-coupling reaction is used for the synthesis of benzo-fused heteroaromatic compounds (Eq 4) (Satoh *et al.*, 1987).

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 %

Table V. Coupling of 1-Alkenylboranes with Various Organic Halides.

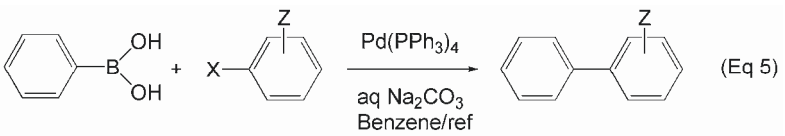


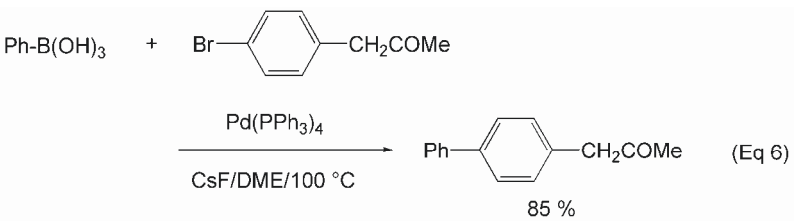
(Eq 4)

Reaction 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 arylboranes with haloarenes was reported in 1981 (Eq 5) (Miyaura *et al.*, 1981). The reaction proceeds even under heterogeneous conditions to give the corresponding coupled products selectively in high yields. After 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 usual bases (Eq. 6) (Wright *et al.*, 1994). Phosphine-based palladium catalysts are generally employed since they are stable under prolonged heating; however, extremely high coupling reaction rate can be sometimes achieved by using palladium catalysts without a phosphine ligand such as $Pd(OAc)_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$, and $Pd_2(dba)_3$.



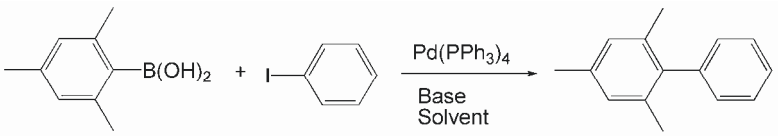


Carbon-carbon bond formation reactions employing organoboron compounds and organic electrophiles have recently been recognized as powerful tools for the construction of new organic compounds. Among such reactions, aromatic-aromatic (or heteroaromatic) couplings between aromatic boronic acids or esters and aromatic electrophiles providing 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 (Suzuki, 2003).

COUPLING OF ARYLBORONIC ACID DERIVATIVES HAVING HIGHLY STERIC HINDRANCE OR ELECTRON-WITHDRAWING FUNCTIONALITIES

Although steric hindrance of aryl halides is not a major factor for the formation of substituted biaryls, low yields are resulted when ortho-disubstituted arylboronic acids are used. For example, the reaction with mesitylboronic acid proceeds only slowly because of steric hindrance during the transmetalation to 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 (Watanabe *et al.,* 1992). The results are summarized in Table VI.



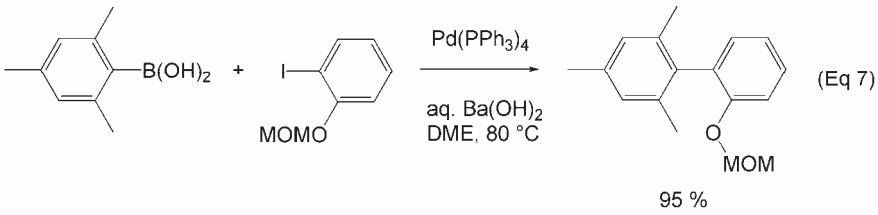
Base	Solvent	Temp/°C	Yield/%[a]		
		Time	8 h	24 h	48 h
Na_2CO_3	Benzene/H_2O	80	25(6)	77(12)	84(25)
Na_2CO_3	DME/H_2O	80	50(1)	66(2)	83(7)
K_3PO_4	DME/H_2O	80	70(0)		
NaOH	DME/H_2O	80	95(2)		
$Ba(OH)_2$	DME/H_2O	80	99(2)		

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

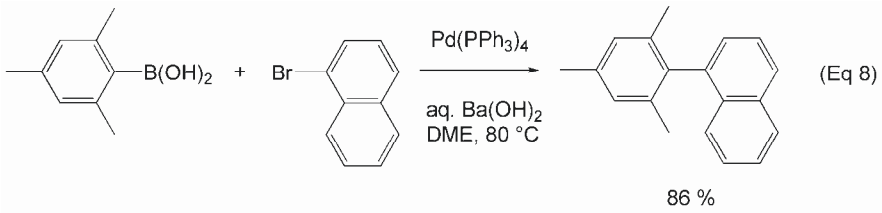
Table VI. Reaction of mesitylboronic acid with lodobenzene under different conditions.

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 2 days. Although the side reactions such as homocoupling are negligibly small, the formation of mesitylene was observed by hydrolytic deboronation increasing with the reaction time. It is noteworthy that such hydrolytic deboronation is faster in benzene/H_2O than the modified conditions using 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 acceleration of the rate of coupling. By using aqueous $Ba(OH)_2$ in DME at 80°C, mesitylboronic acid couples with iodobenzene within 4 hours to give the corresponding biaryl in a quantitative yield. Some of such coupling reactions are depicted in Eq.7 and Eq. 8..

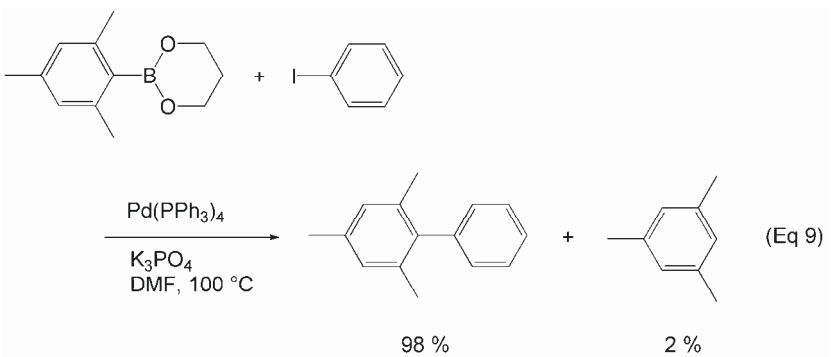


(Eq 7)



(Eq 8)

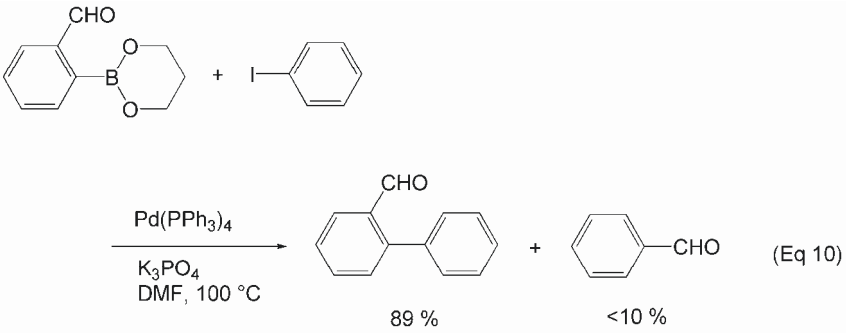
An alternative procedure, using the esters of boronic acids and an anhydrous base has been developed for sterically hindered arylboronic acids, providing high yields. The coupling can be readily achieved by using trimethylene glycol ester of mesitylboronic acid and Cs_2CO_3 or K_3PO_4 in DMF at 100°C to give a quantitative yield of the coupled products (Eq. 9) (Watanabe *et al.*, 1992).



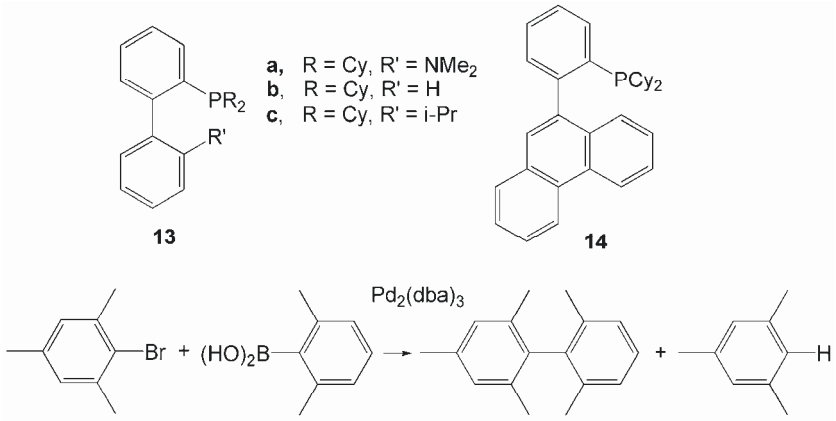
(Eq 9)

Even without sterically hindered substrates, the reaction under aqueous conditions is often undesirable because of competitive hydrolytic deboronation. Kinetic study (Abraham *et al.,* 1985) into the reaction of substituted arylboronic acids showed that electron-withdrawing substituents accelerate the deboronation. Although there is no large effect between *meta* and *para* substituted phenylboronic acids, substituents at the *ortho* position may greatly increase the rate of deboronation. For example, the 2-formyl group on arylboronic acids is known to accelerate the rate of hydrolytic deboronation (Abraham *et al.*, 1985). 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 sensitive to an 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% of benzaldehyde formation (Eq. 10) (Watanabe *et al.*, 1992).



Recently, Buchwald *et al.* have reported interesting catalysts and ligands to prepare tetra-*ortho*-substituted unsymmetrical biaryles (Yin and Buchwald, 2002). Among biphenyl-based ligands, **14** gave an excellent result, whereas significant amounts of aryl bromide reduction were observed when the ligands **13** were used (Table VII).



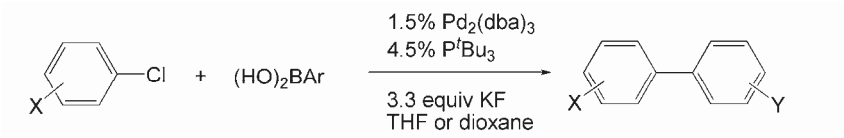
Ligand	Conv (%)	Biaryl (%)	Biaryl/Ar-H
13a	47	33	2.3
13b	20	10	0.9
13c	74	40	1.9
14	100	91	10

Table VII. Ligand effects in the coupling of hindered substrates.

COUPLING WITH AROMATIC CHLORIDES

In aromatic-aromatic cross-coupling reactions, cheap and readily accessible aryl chlorides are particularly important as starting materials from an industrial viewpoint. Recently, some research groups, especially Fu's group (Littke *et al.*, 2000) and Buchwald's group (Wolfe *et al.*, 1999) have reported very efficient methods for aryl chloride reaction. For example, Fu and his coworkers (Littke *et al.*, 2000) have observed that the use of $Pd_2(dba)_3$/$PtBu_3$ as a catalyst and ligand for a wide range of aryl and vinyl halides, including chlorides, undergo Suzuki cross-coupling with arylboronic acids in very good yield, typically at room temperature (Table VIII). Furthermore, these catalysts display novel reactivity patterns, such as the selective coupling by $Pd_2(dba)_3$/PCy_3/KF of a sterically hindered aromatic chloride (Eq 11).

Despite the good yields in many Suzuki reactions of chloroarenes, generally, 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 industrially acceptable conditions (Zapf *et al.*, 2000). For instance, as new efficient catalyst system, they used diadamantyl-*n*-butylphosphane ($BuPAd_2$) as a ligand and found that it proved to be extremely reactive. One typical example is shown in Eq. 12.



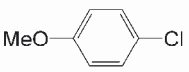
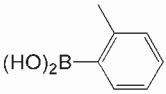
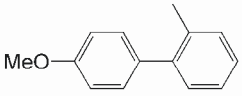
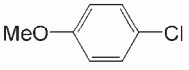
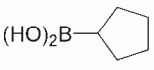
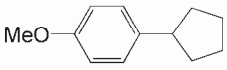
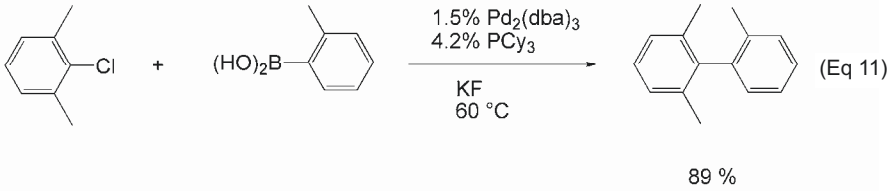
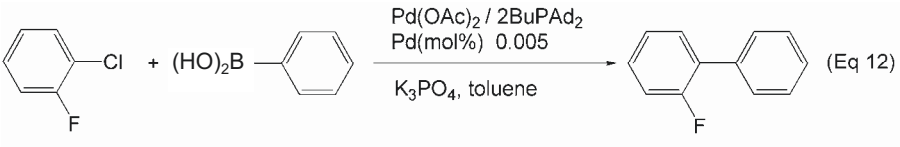
Aryl Chloride	Boronic Acid	Product	Temp(°C)	Yied (%)
			70	88
			100	75

Table VIII. Suzuki Couplings of Unactivated Aryl Chlorides.



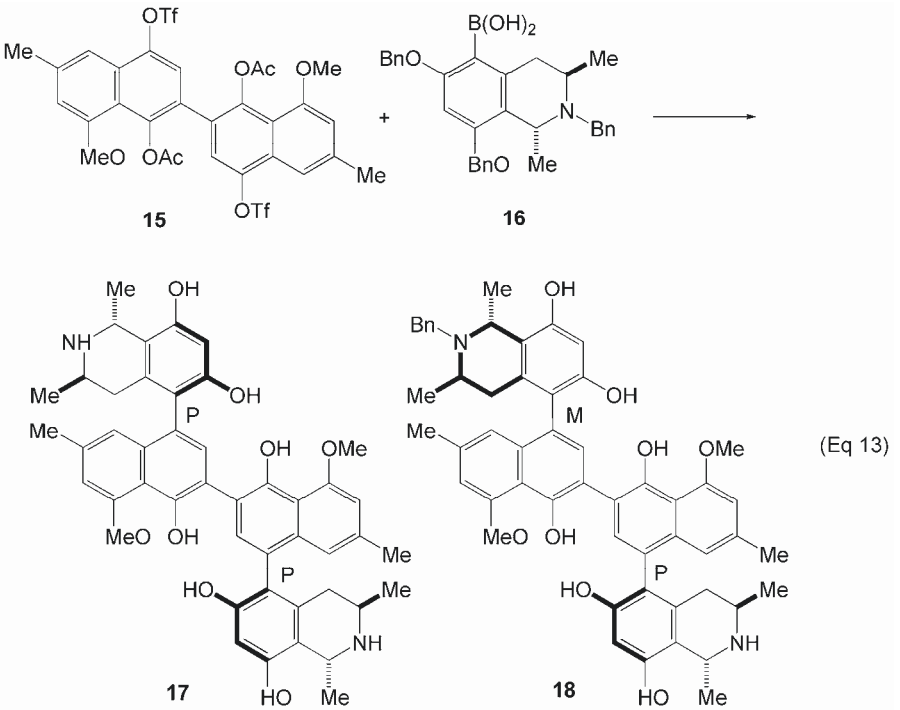
(Eq 11)



TON = 19,200

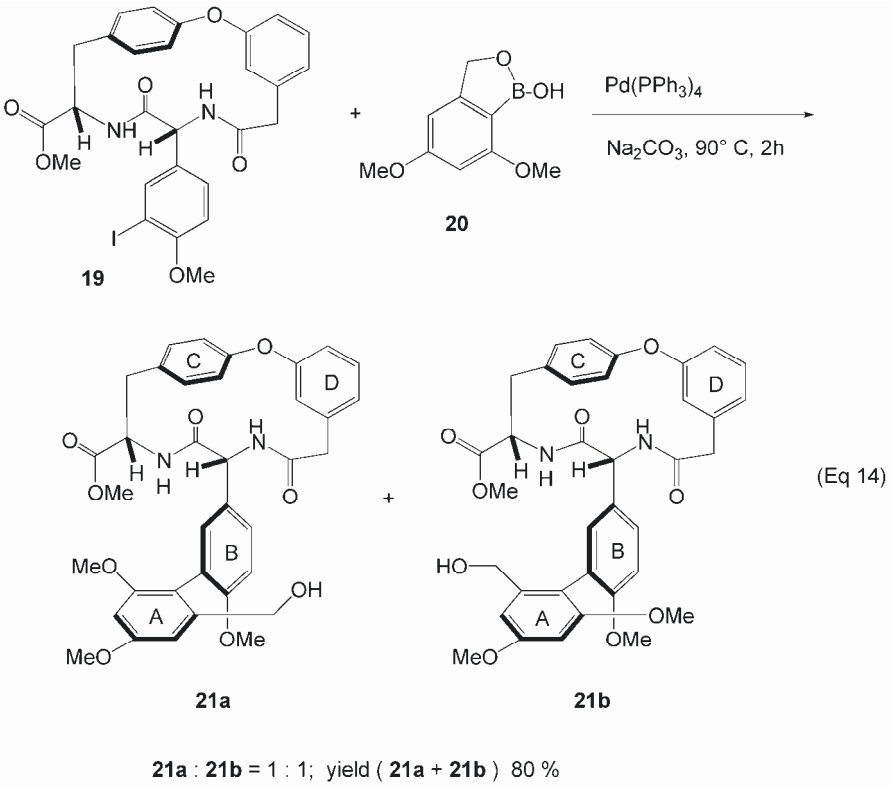
APPLICATIONS TO SYNTHESIS OF BIARYLS

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 dinaphtalene ditriflate **15** and isoquinolineboronic acid **16** (Eq. 13) (Bringmann *et al.*, 1998).



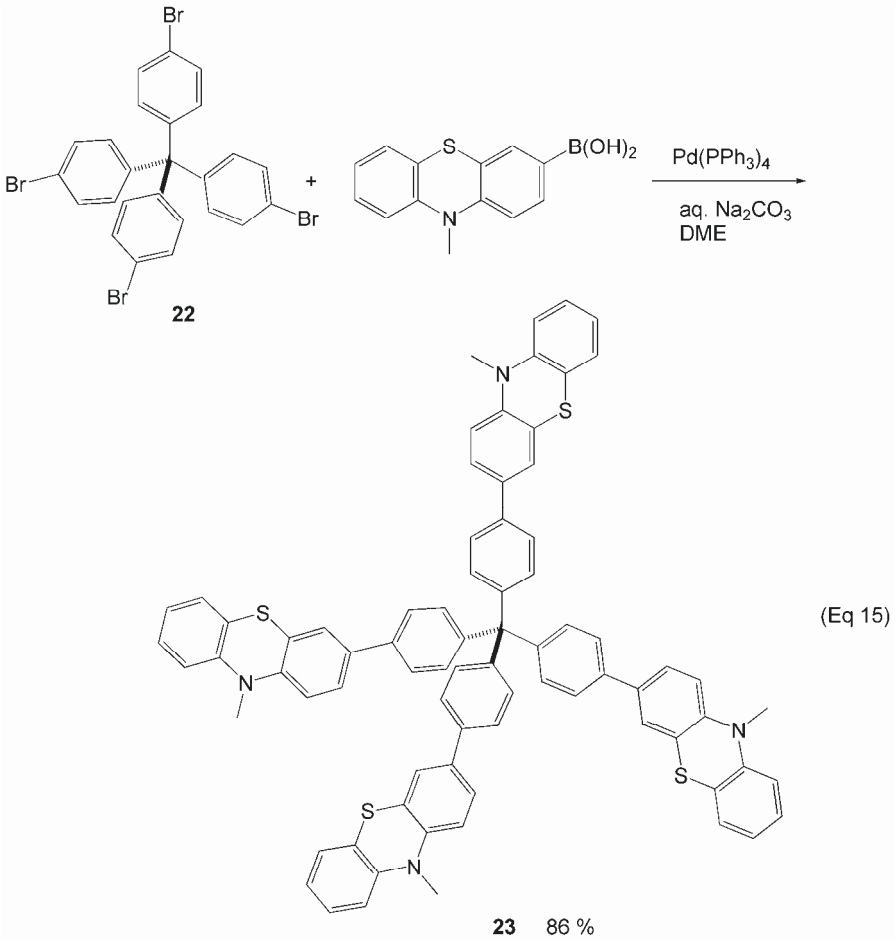
The discovery and development of penicillin and other antibacterial agents as drugs to fight infectious diseases were milestone victories of humankind over bacteria. While these agents saved millions of lives, they did not tame bacteria. On the contrary, this war led to the emergence of newer and more 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 struc-

ture 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). Nicolaou and his group reported a Suzuki coupling approach to the AB-COD bicyclic system of vancomycin (Nicolaou *et al.*, 1997). Suzuki coupling of the iodide **19** with **20** was facilitated by $Pd(PPh_3)_4$ 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 has been reported by the same workers (Nicolaou *et al.*, 1999).



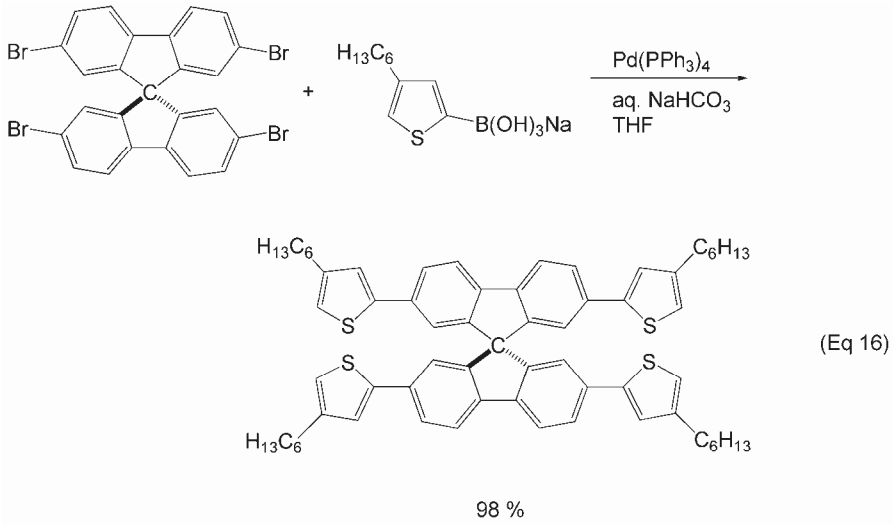
21a : **21b** = 1 : 1; yield (**21a** + **21b**) 80 %

The novel class of 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) (Krämer *et al.*, 2002).



(Eq 15)

Oligothiophene functionalized 9,9-spirobifluorene derivatives have been synthesized by Suzuki coupling in high yields. The Negishi coupling reaction between oligothienylzinc chloride and various 9,9'-spirobifluorene bromides with $Pd(PPh_3)_4$ as catalyst successfully produce the desired compounds. However, the Negishi coupling provided low yields, compared to Suzuki coupling (Eq 16) (Pei *et al.*, 2002).



(Eq 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 been largely developed mainly by the reaction of a resin-bound aryl halide with solution-phase boronic acids (Suzuki, 2003). Recently, the viability of solid-supported boronic acids as reagents for Suzuki couplings was successfully demonstrated (Carboni *et al.,* 1999).

APPLICATION 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 aryldiboronic acids and dihaloarenes for the synthesis of poly(*p*-phenylenes) was first reported by Schlüter (Rehahn *et al.,* 1989). SPC is a step-growth polymerization of bifunctional aromatic monomers to poly(arene)s and related polymers (Figure 5) (Schlüter, 2001). The required functional groups, boronic acids or esters on the 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).

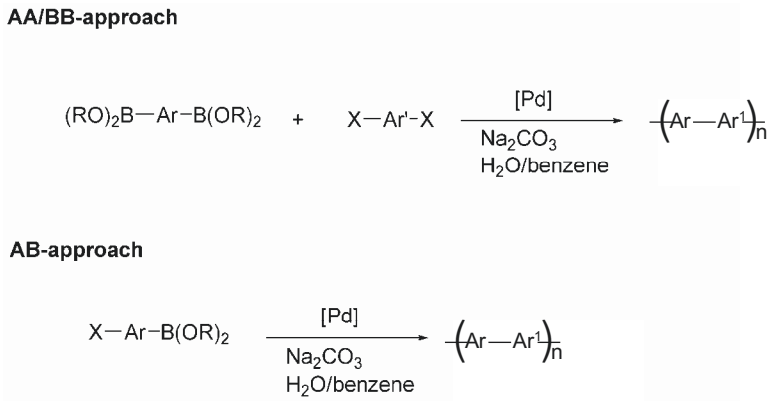
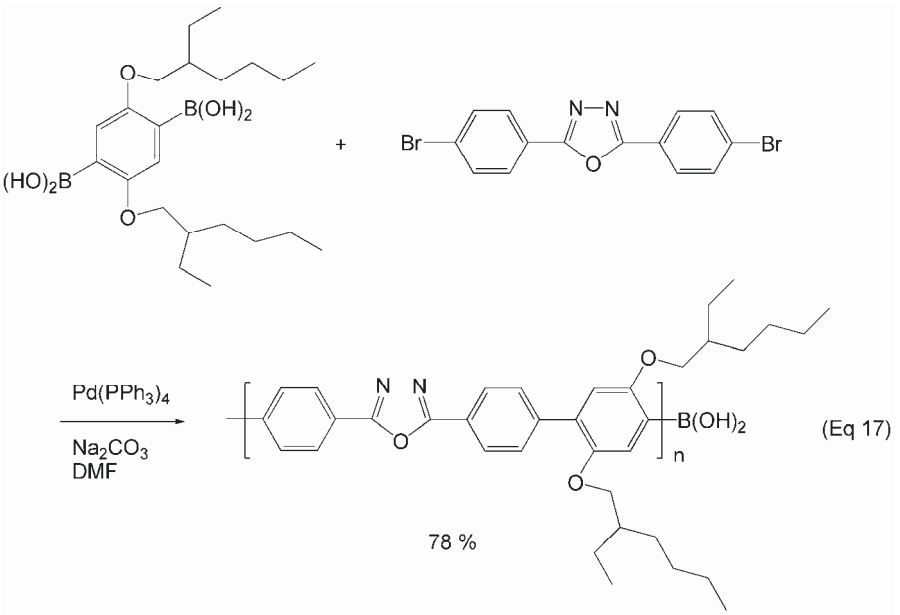


Figure 5. Graphical representation of Suzuki polycondensation.

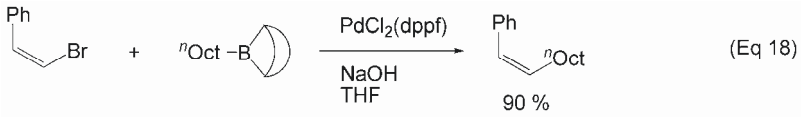
The method was extensively applied to mono-disperse aromatic dendrimers, water-soluble poly(*p*-phenylene), planar poly(*p*-phenylenes) fixed with the ketoimine bonds, poly(phenylenes) fused with polycyclic aromatics, and nonlinear optical materials (Suzuki, 2003). Here, one of such applications is shown (Eq. 17) (Wang *et al.*, 2001).



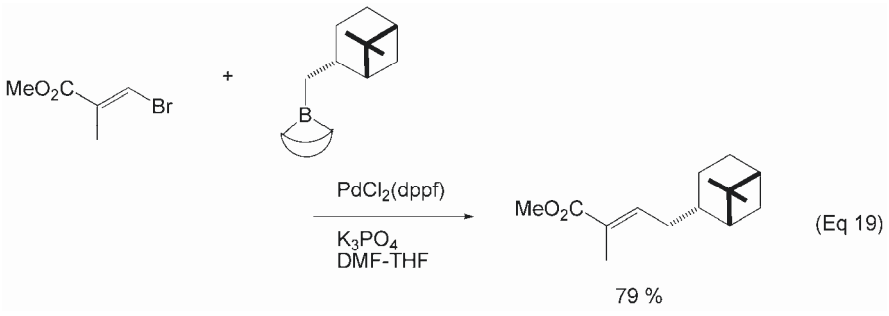
COUPLING REACTIONS OF C(sp^3)-B COMPOUNDS

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 containing β-hydrogens were severely limited due to

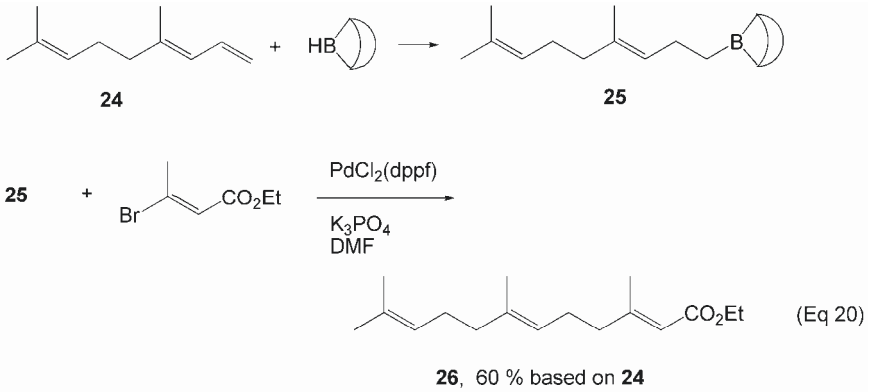
competitive side reactions. In 1971–1972 Kochi, Kumada, and Corriu reported independently that the reaction of alkyl Grignard reagents with alkenyl or aryl halides are markedly catalyzed by Fe(III) or Ni(II) complexes, and then Negishi demonstrated the synthetic utility of alkylzinc compounds by use of palladium catalyst. Thereafter, alkyllithium, tin, and aluminum reagents were also employed for such cross-coupling reactions. The reaction of alkylborane derivatives is particularly useful when one wish to start from alkenes via hydroboration. Consequently, we intended to examine the coupling reactions between alkylboron compounds and various organic halides in the presence of base and 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. However, the coupling proceeds smoothly by using a catalytic amount of $PdCl_2$(dppf) and bases such as NaOH, K_2CO_3, and K_3PO_4 to give the corresponding substituted alkenes or arenes in excellent yields (Eq 18). (Miyaura and Ishiyanma *et al.*, 1986; 1989). 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 a steroid **27** (Eq 21) (Miyaura and Ishiyanma *et al.*, 1986; 1989).

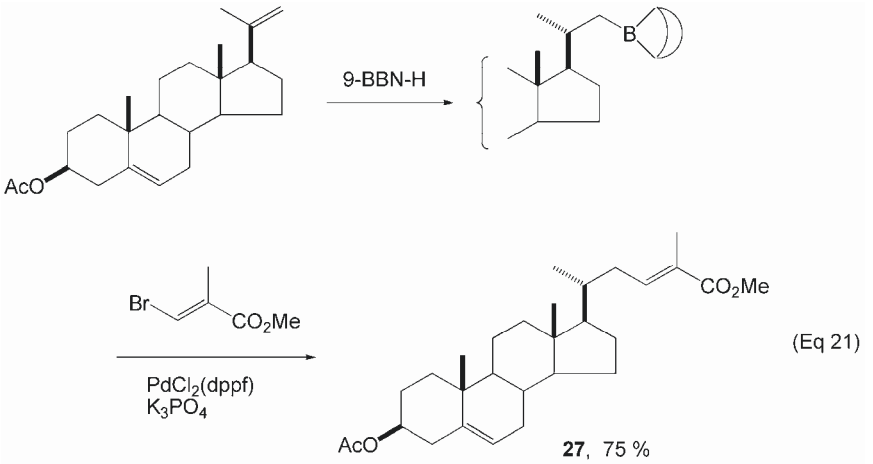


(Eq 18)

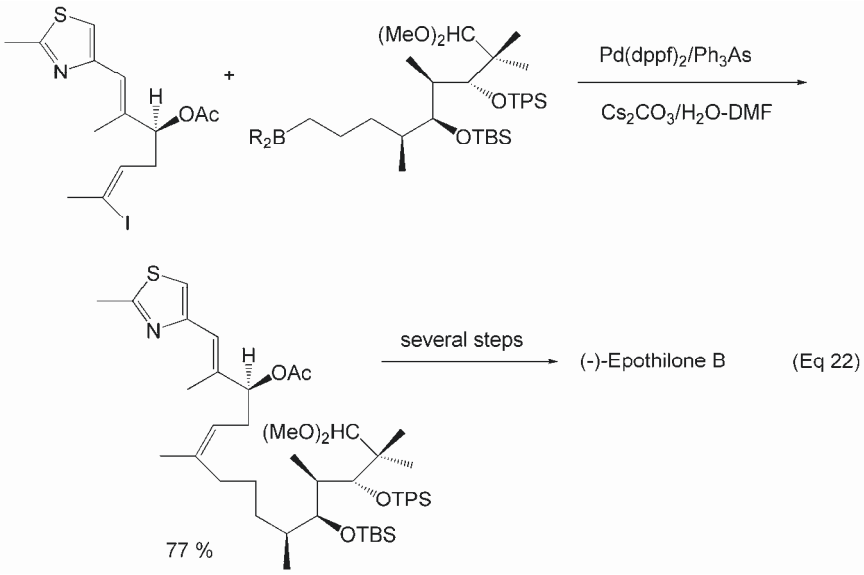


(Eq 19)

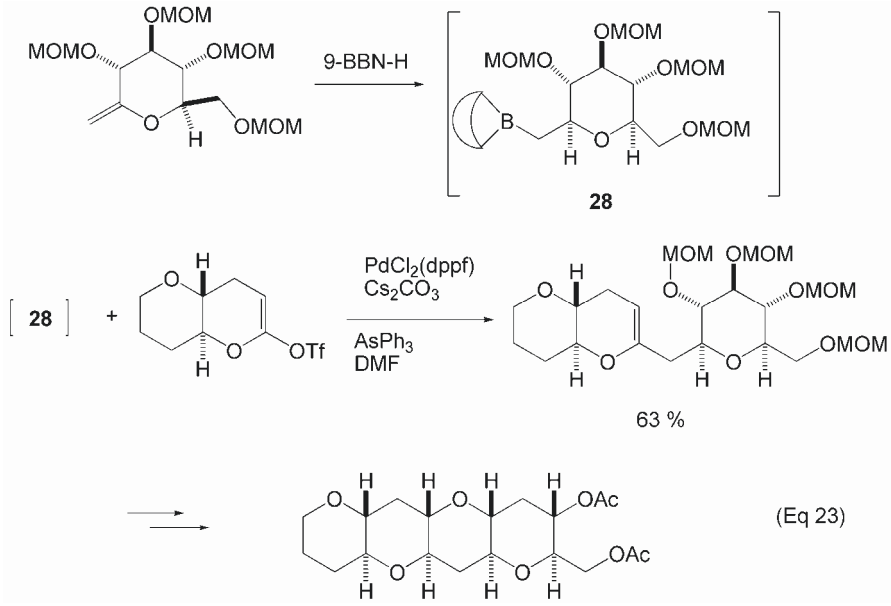




Many chemists have applied such a Suzuki coupling reaction using β-saturated alkylboron compounds. For instance, Danishefsky *et al.* reported a total synthesis of the promising anticancer agent (–)-epothilone B using the coupling method as shown below (Eq 22) (Su *et al.*, 1997; Balog *et al.*, 1998), and a sister compound, epothilone A was also synthesized by a similar procedure (Balog *et al.*, 1996). A full paper on the total synthesis of epothilones A and B has been appeared more recently (Meng *et al.*, 1997).

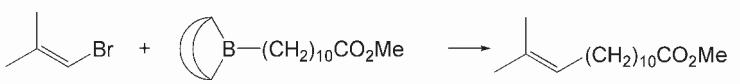


Marine polyether toxins present challenging synthetic targets due to their structural complexity and exceptionally potent biological activities. The most critical issue in the synthesis of these large polyether compounds is development of synthetic methods for convergent coupling of polyether fragments. In spite of recent advantages in the synthesis of medium-sized cyclic ethers, only a few methodologies for the convergent assembly of 6-membered polyether structures were reported. A new strategy for such synthesis of *trans*-fused polyethers based on the palladium(0)-catalyzed Suzuki coupling reaction of alkylboranes with cyclic enol triflates has been developed by Tachibana *et al.* (Sasaki *et al.*, 1998). As shown in Eq. 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.



BASE PROBLEM

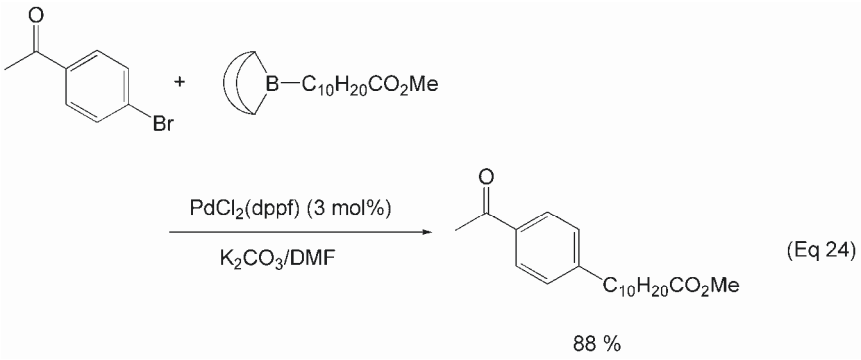
In cross-coupling reactions of organoboron compounds, the presence of bases is essential; no reaction occurs without a base. On the other hand, many organic compounds are sensitive to bases. Consequently, careful use of bases is required in such cases. For example, Table IX shows that the selection of a base and solvent system provides markedly different yields of coupled products. By careful selection of the reaction conditions (e.g., $PdCl_2$(dppf)/K_2CO_3/DMF), high yields of the desired coupled products can be achieved (Eq. 24 and Eq. 25).



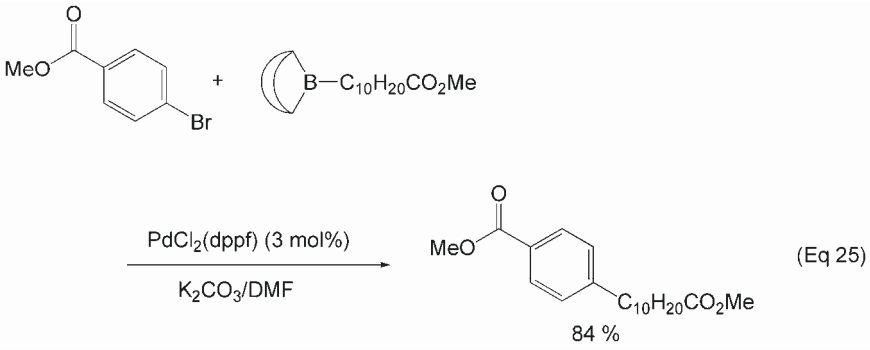
Solvent	Base (equiv)	Temp.(°C)	Time (h)	Yield (%)
DMF	KOAc (4)	50	18	18
DMF	K_2CO_3 (2)	50	18	64
CH_3CN	K_2CO_3 (4)	50	18	46
DMF	K_3PO_4 (4)	50	20	92

a) Catalyst: $PdCl_2$(dppf)

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



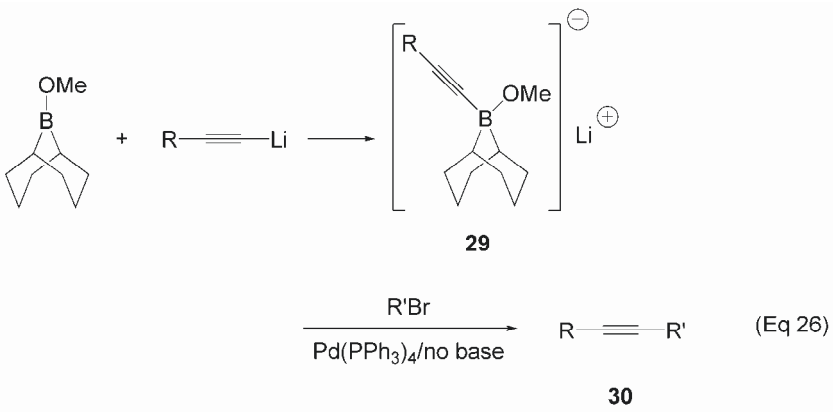
(Eq 24)



(Eq 25)

COUPLING REACTIONS OF C(sp)-B COMPOUNDS

Alkynylboranes have long been known to be useful synthetic intermediates. Compared to other organoboranes, they are easily hydrolyzed by bases. 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 9-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 X) (Soderquist *et al.*, 1995).



R	R'	Product 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) Isolated yields of analytically pure compounds (GC yields)

Table X. Coupled products from 29.

Almost at the same time, Fürstner and Seidel reported the same reaction (Fürstner and Seidel, 1995); 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-alkynyl sodium, potassium, and lithium compounds, and not as usually from boranes and bases. This approach allows cross-couplings of organic halides with e.g. alkynyl-, methyl-, or TMSCH2-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 XI. This reaction is used to prepare the compound **31** which is highly valuable for its chemoluminescence property.

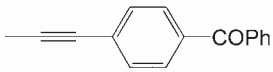
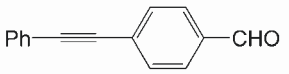
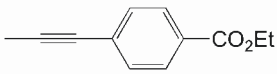
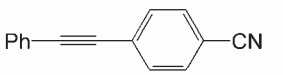
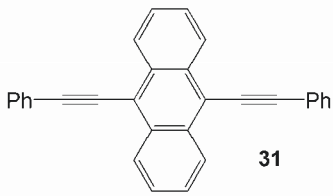
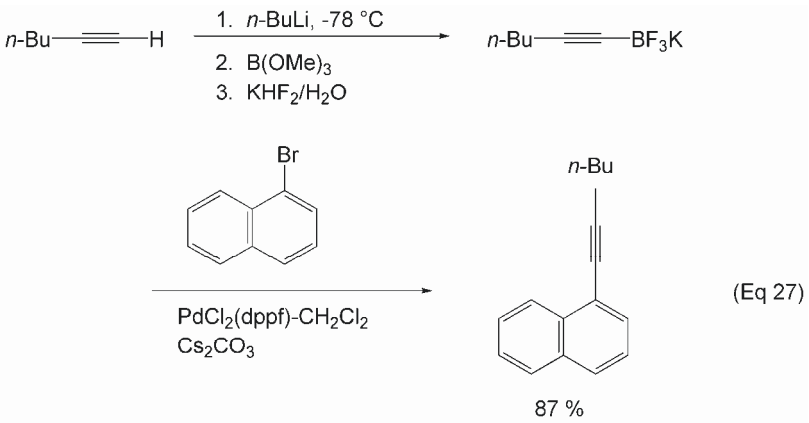
Substrate	RM	Product	Yield/%
4-bromobenzophenone	MeC≡CNa		89
4-bromobenzaldehyde	PhC≡CNa		77
ethyl 4-bromobezoate	MeC≡CNa		86
4-bromobenzonitrile	PhC≡CNa		93
9,10-dibromoanthracene	PhC≡CLi	 **31**	84

Table XI. Pd-catalyzed arylation of alknyl metal reagents mediated by 9-MeO-9-BBN derivatives.

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 application to combinatorial chemistry (Eq 27) (Molander, 2002).



(Eq 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 using either resin-bound aryl halides with solution-phase boronic acids (Suzuki, 2003) or *vice versa* (Carboni *et al.*, 1999). Such approaches, of course, play an important role in the combinatorial and parallel methodologies now used to explore chemical reactivity and are especially well-suited to medicinal chemistry.

Increasingly, industry is seeking to use more environmentally-friendly processes. These often require ingenious solutions to which the 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 concentration in water (Arvela *et al.*, 2005), 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 (Kabalka *et al.*, 1999). Ionic liquids, which are excellent solvents for transition-metal catalysts, are also being investigated (Mathewa *et al.*, 2000).

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

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