# Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds

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Norio Miyaura was born in Hokkaido, Japan in 1946. He received his B.Sc. and his Dr. from Hokkaido University. He became a research associate and an associate professor of A. Suzuki's research group and was promoted to the professor of the same group in 1994. In 1981, he joined J. K. Kochi research group at Indiana University and studied the catalytic and noncatalytic epoxidation of alkenes with oxo–metal reagents. His current interests are mainly in the field of transition-metal-catalyzed reactions of organoboron compounds, with emphasis on applications to organic synthesis. For examples, cross-coupling reaction, catalytic hydroboration, catalytic thioboration, and catalytic diboration of alkenes and alkynes.

Akira Suzuki was born in Hokkaido, Japan, in 1930. He received his undergraduate and graduate training at Hokkaido University and joined the faculty in 1961 as an assistant professor. He spent two years as a postdoctoral associate with Professor Herbert C. Brown at Purdue University and was promoted to the rank of professor in 1971. After retirement from Hokkaido University, Akira Suzuki moved to Okayama University of Science as a chemistry professor in 1994. His current interests are mainly in the field of organoboron chemistry, with emphasis on applications to organic synthesis, organometallic chemistry, and the study of reactive intermediates.

## I. Introduction

The cross-coupling reaction now accessible via a variety of organometallic reagents may provide a fundamentally common synthetic methodology (eq 1).

$$\text{R-M} + \text{R'-X} \xrightarrow{\text{Pd-catalyst}} \text{R-R'} \qquad (1)$$

In 1972, Kumada and Tamao[1] and Corriu[2] reported independently that the reaction of organomagnesium reagents with alkenyl or aryl halides could be markedly catalyzed by Ni(II) complex. Kochi[3] found the efficiency of Fe(III) catalyst for the cross-coupling of Grignard reagents with 1-halo-1-alkenes and $Li_2CuCl_4$ catalyst for haloalkanes. The palladium-catalyzed reaction of Grignard reagents was first reported by Murahashi,[4] the synthetic utility of which was then amply demonstrated by Negishi[5] on the reactions of organoaluminum, zinc, and zirconium reagents. After those discoveries, many other organometallic reagents have proven to be highly useful as nucleophiles for the cross-coupling reaction, e.g., organolithiums by Murahashi,[6] organostannans by Migita[7] and Stille,[8] 1-alkenylcopper(I) by Normant,[9] organosilicon compounds by Hiyama.[10] These reac-

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tions are mechanically and synthetically closely related to the present article; however, the reactions, mechanism, and their synthetic utility have been extensively reviewed elsewhere.[11]

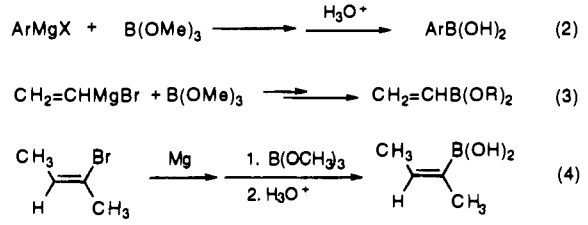
Organoboron compounds are highly electrophilic, but the organic groups on boron are weakly nucleophilic, thus limiting the use of organoboron reagents for the ionic reactions. The coordination of a negatively charged base to the boron atom has been recognized to be an efficient method of increasing its nucleophilicity to transfer the organic group on boron to the adjacent positive center (1,2-migration reaction).[12] However, intermolecular transfer reaction such as the Grignard-like reaction are relatively rare. Fortunately, organoboron compounds, even organoboronic acids and esters, have sufficiently enough reactivity for the transmetalation to other metals. Transmetalations to silver(I),[13] magnesium(II),[14] zinc(II),[15] aluminum(II),[16] tin(IV),[17] copper(I),[18] and mercury(II)[19] halides have been extensively studied. In 1978, Negishi reported that iodobenzene selectively couples with the 1-alkynyl group on lithium 1-hexynyl(tributyl)borate through a palladium-catalyzed addition–elimination sequence (Heck-type process);[5i] however, the cross-coupling reaction of organoboron compounds, which involves the transmetalation to palladium(II) halides as a key step, was found to proceed smoothly when these were activated with suitable bases and have proven to be a quite general technique for a wide range of selective carbon–carbon bond formation.[20] Many organometallic reagents undergo similar cross-coupling reactions, but much attention has recently been focused on the use of organoboronic acids in laboratories and industries since they are convenient reagents, which are generally thermally stable and inert to water and oxygen, thus allow their handling without special precautions. This review summarizes the palladium-catalyzed cross-coupling reaction of organoboron compounds with organic halides or triflates, the reaction mechanism, the scope of synthetic applications, and other related catalytic processes with transition-metal complexes are discussed.[20]

## II. Synthesis of Organoboron Reagents

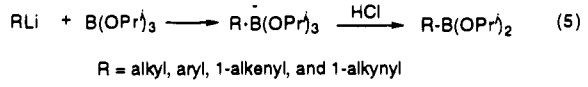
### A. Synthesis from Organolithium or Magnesium Reagents

The classical synthesis of aryl- and 1-alkenylboronic acids or their esters from Grignard reagents or lithium reagents and trialkyl borates is an efficient method for making relatively simple boron compounds in large quantities (eqs 2 and 3).[21] The first stereocontrolled synthesis of alkenylboronic acids and esters involves the reaction of a (*Z*)- or (*E*)-2-buten-2-ylmagnesium bromide with trimethyl borate (eq 4).[22]

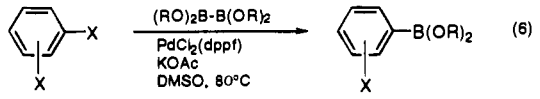
However, the application of these classical procedures for organoboronic acid or ester synthesis may suffer from the contamination of small mount of the opposite stereoisomers, or bis-alkylation leading to the borinic acid derivatives and the formation of trialkylboranes. A recent useful variant utilizes organolithium reagents and triisopropyl borate, followed by acidification with HCl to give directly alkyl-,




aryl-, 1-alkynyl-, and 1-alkenylboronic esters in high yields, often over 90% (eq 5).[23] Triisopropyl borate is shown to be the best of available alkyl borates to avoid such multiple alkylation of the borates.

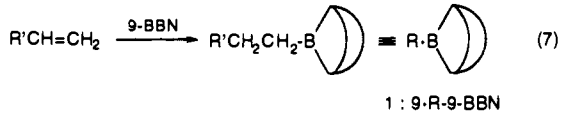



Very recently, arylboronic esters have been directly obtained from aryl halides via the cross-coupling reaction of (alkoxy)diboron (eq 6).[24] The reaction tolerates various functional groups such as ester, nitrile, nitro, and acyl groups.



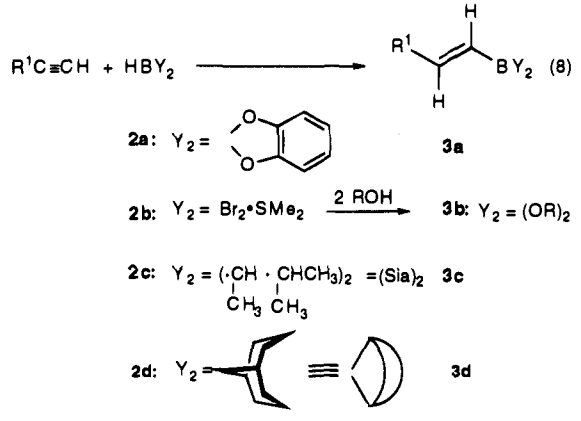

### B. Hydroboration of Alkenes and Alkynes

The addition of dialkylboranes such as 9-borabicyclo[3.3.1]nonane (9-BBN), disiamylborane, or dicyclohexylborane to 1-alkenes gives mixed alkylboron compounds.[25] The reaction is essentially quantitative, proceeds through *cis* anti-Markovnikov addition from the less hindered side of double bond, and can tolerate various functional groups. The 9-alkyl-9-BBN derivatives thus obtained are particularly useful for the transfer of primary alkyl groups by the palladium-catalyzed cross-coupling reaction since the 9-alkyl group exclusively participates in a catalytic reaction cycle (eq 7).

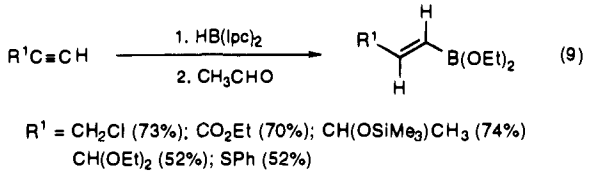



The use of the hydroboration reaction is especially valuable for the synthesis of stereodefined or functionalized alkenylboronic acids and their esters. The general and most convenient method is the hydroboration of a terminal alkyne with catecholborane (**2a**) to produce 1-alkenylboronic ester (eq 8).[25,26] The hydroboration with **2a** can also be carried out under milder conditions by using palladium, rhodium, or nickel catalysts.[27] The hydroboration of alkynes with dihaloboranes ($HBCl_2 \cdot SMe_2$ or $HBBr_2 \cdot SMe_2$), followed by hydrolysis to vinylboronic acids or alcoholysis to boronic esters (**3b**) have been used for the same purpose.[25,28] However, a recent and more convenient variant is the *in situ* preparation of $HBCl_2$ in a hydrocarbon solvent from $BCl_3$ and $HSiEt_3$.[29] The reagent exhibits extremely high reactivity to alkenes and alkynes allowing the hydroboration to proceed at −78 °C. Disiamylborane (**2c**) is also one of the mildest and selective hydroboration reagents for

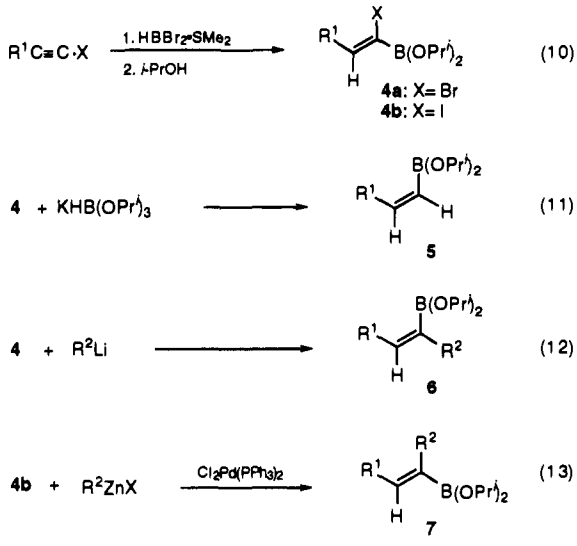
functionalized alkynes, but their use for the cross-coupling can be more difficult than that of boronic acids or their esters. Hydroboration of terminal alkynes with 9-BBN leads to the formation of significant quantities of dihydroboration products. However, dihydroboration of 1-alkynes, followed by deboration with benzaldehyde provides 9-[(*E*)-1-alkenyl]-9-BBN derivatives (**3d**) in high yields with high *trans* selectivity.[30]




These reactions work well with terminal and symmetrical internal alkynes, but the difficulties are often encountered by the lack of regiochemistry or chemoselectivity (e.g., reduction of functional groups) upon addition to general internal alkynes or functionalized alkynes. Diisopinocampheylborane has been used as a reagent for asymmetric hydroboration, and additionally it has attractive features as a hydroboration reagent for alkynes, e.g., the inertness to many functional groups except aldehyde and ketone carbonyls, the high regioselectivity resulting from its bulkiness, and ease of dealkylation to boronic esters under neutral conditions.[31] The hydroboration of propargyl chloride and ethyl propiolate provides terminal boron derivatives with excellent regiochemistry,[32] whereas the hydroboration with catecholborane or disiamylborane (**2c**) gives an inseparable mixture of internal and terminal boron adducts (eq 9).



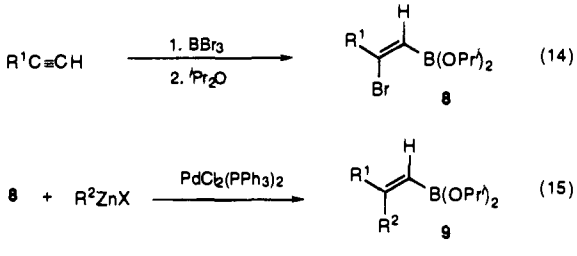

Terminal and internal (*Z*)-1-alkenylboronates are prepared from (*Z*)-(haloalkenyl)boronic esters (**4**) which can be readily obtained by hydroboration of 1-halo-1-alkyne (eq 10).[28,32,33] The internal $S_N2$ like displacement of the halogen with $KHB(OPr^i)_3$[33,34] or organolithiums[35] takes place with complete inversion of configuration at the $sp^2$ carbon (eqs 11 and 12). The reaction is almost quantitative and highly selective (inversion >99%). Thus, the boron derivatives prepared *in situ* can be directly used for the following cross-coupling reaction without further purification. On the other hand, alkylation of **4b** with organozinc reagents in the presence of a palladium catalyst stereospecifically provides (*E*)-1-alkenylboronates (**7**)



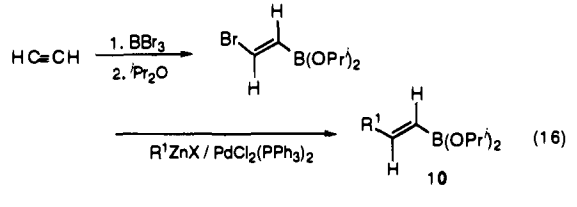

which are not available by conventional hydroboration of internal alkynes (eq 13).[36]

## C. Haloboration of Terminal Alkynes

Terminal 2,2-diorgano-1-alkenylboronates (**9**) are made by bromoboration of a terminal alkyne to β-bromo-1-alkenylboronic ester (**8**) (eq 14),[37] followed by the palladium-catalyzed displacement of the β-halogen with organozinc reagents which proceeds strictly with retention of configuration (eq 15).[38]




Haloboranes add to terminal alkynes *via* a *cis* anti-Markovnikov manner; however, the bromoboration of acetylene itself exceptionally provides a *trans*-adduct which gives the corresponding (*E*)-1-alkenylborates (**10**) by the reaction with organozinc halides (eq 16).[39] The addition of tribromoborane to acetylene first gives a *cis*-adduct, which then isomerizes to the *trans*-isomer during its isolation.[40]

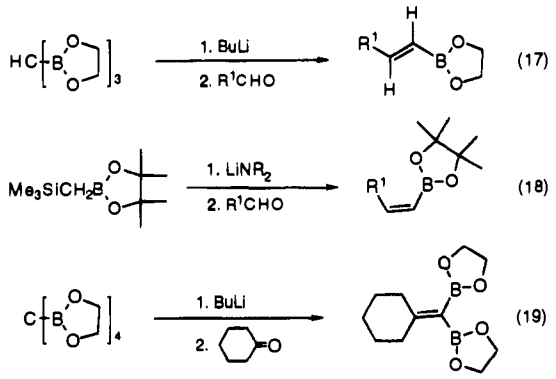



These two-step procedures are useful to achieve a formal carboboration of alkynes with a variety of organic groups.

## D. Miscellaneous Methods

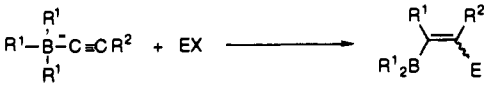
An efficient route to (*E*)-1-alkenylboronates from carbonyl compounds is achieved by the reaction with lithio(boryl)methanes. The (*E*)/(*Z*) isomeric ratio is

reported to be ~20:1 (eq 17).[41] On the other hand, a trimethylsilyl analog gives a *cis*-rich isomer (~70:30) on reaction with aldehydes (eq 18).[42] The reaction of lithiotriborylmethane with aldehydes or ketones yields 1,1-alkenyldiborates (eq 19).[43]




(17) (18) (19)

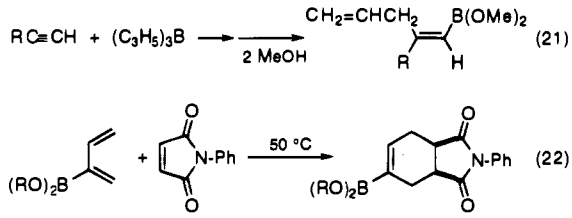
Alkynylboronates are attacked by many electrophiles at the position $\beta$ to the boron atom. The following rearrangement gives a variety of functionalized 1-alkenylboranes (eq 20).[12,44] The stereochemistry can be either *E* or *Z*, or a mixture of the two in most cases.



(20)

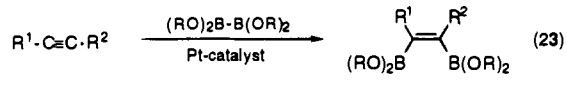
EX= ClSnMe$_3$, NCCH$_2$I, EtO$_2$CCH$_2$Br, oxirane

Allylboration of 1-alkynes proceeds at room temperature to give *cis* addition products in high yields (eq 21).[45] The Diels–Alder reaction between 2-(dialkoxyboryl)-1,3-butadiene and dienophiles at 50 °C provides cyclic 1-alkenylboronates (eq 22).[46]




(21) (22)

The addition of diboron compounds to alkynes is an excellent method for the synthesis of *cis*-diboryl alkenes (eq 23).[47] The reaction is catalyzed by Pt(PPh$_3$)$_4$ at 80 °C and works well with terminal and internal alkynes. The addition of the Si–B[48] or Sn–B[49] bonds to alkynes gives mixed-metal alkenylboron reagents which have potential ability for use in the stepwise double cross-coupling reaction at the both metalated carbons.




(23)

Organoboronic acids or their esters are generally stable to air and thermal treatment. Thus, the boronic esters can be isolated by distillation, and acids, by crystallization. Alternatively, the pinacol esters of boronic acids are reported to be isolated by flash chromatography on silica gel.[50]

## III. Palladium-Catalyzed Reactions of Organoboron Compounds and Their Mechanism

### A. Cross-Coupling Reaction

A general catalytic cycle for the cross-coupling reaction of organometallics, which involves oxidative addition–transmetalation–reductive elimination sequences, is depicted in Figure 1. Although each steps involves further knotty processes including ligand exchanges, there is no doubt about the presence of those intermediates (**11** and **12**) which have been characterized by isolation or spectroscopic analyses.[11,51] It is significant that the great majority of cross-coupling reactions catalyzed by Ni(0), Pd(0), and Fe(I) are rationalized in terms of this common catalytic cycle.

Oxidative addition[11,52] of 1-alkenyl, 1-alkynyl, allyl, benzyl, and aryl halides to a palladium(0) complex affords a stable *trans*-$\sigma$-palladium(II) complex (**11**). The reaction proceeds with complete retention of configuration for alkenyl halides and with inversion for allylic and benzylic halides. Alkyl halides having $\beta$-hydrogen are rarely useful because the oxidative addition step is very slow and may compete with $\beta$-hydride elimination from the $\sigma$-organopalladium(II) species. However, it has been recently shown that iodoalkanes undergo the cross-coupling reaction with organoboron compounds (sections IV.F and VI).[53]

Oxidative addition is often the rate-determining step in a catalytic cycle. The relative reactivity decreases in the order of I > OTf > Br ≫ Cl. Aryl and 1-alkenyl halides activated by the proximity of electron-withdrawing groups are more reactive to the oxidative addition than those with donating groups, thus allowing the use of chlorides such as 3-chloroenone for the cross-coupling reaction. A very wide range of palladium(0) catalysts or precursors can be used for cross-coupling reaction. Pd(PPh$_3$)$_4$ is most commonly used, but PdCl$_2$(PPh$_3$)$_2$ and Pd(OAc)$_2$ plus PPh$_3$ or other phosphine ligands are also efficient since they are stable to air and readily reduced to the active Pd(0) complexes with organometallics or phosphines used for the cross-coupling.[54] Palladium complexes that contain fewer than four phosphine ligands or bulky phosphines such as tris(2,4,6-tri-

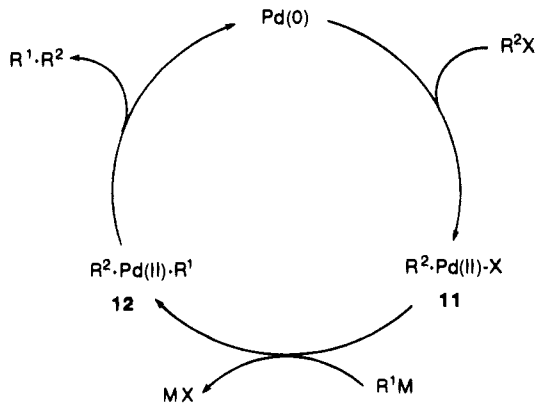
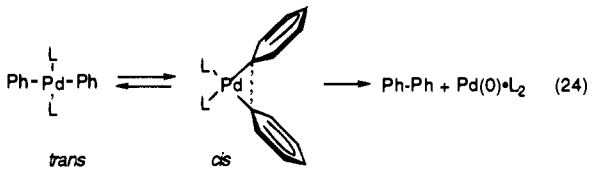


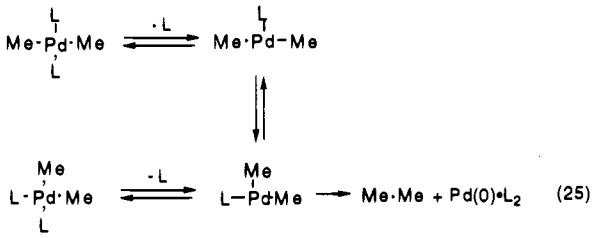

**Figure 1.** A general catalytic cycle for cross-coupling.

methoxyphenyl)phosphine are, in general, highly reactive for the oxidative addition because of the ready formation of coordinate unsaturated palladium species.[55]

Reductive elimination of organic partners from **12** reproduces the palladium(0) complex.[56-58] The reaction takes place directly from *cis*-**12**, and the *trans*-**12** reacts after its isomerization to the corresponding *cis*-complex (eqs 24 and 25). The order of reactivity is diaryl- > (alkyl)aryl- > dipropyl- > diethyl- > dimethylpalladium(II), suggesting participation by the $\pi$-orbital of aryl group during the bond formation (eq 24).[58b] Although the step of 1-alkenyl- or 1-alkynylpalladium(II) complexes is not studied, the similar effect is observed in the reductive elimination of related platinum(II) complexes.[59]



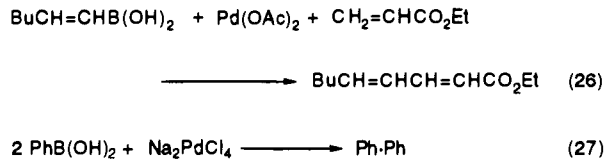

The thermolysis of *cis*-(dialkyl)palladium(II)•$L_2$, which is an intermediate on the alkyl–alkyl coupling, is inhibited by excess phosphine (L), hence it is considered to be initiated by the rate-determining dissociation of phosphine ligand (L) producing a three-coordinated *cis*-(dialkyl)palladium(II)•L complex (dissociative mechanism, eq 25).[57] Thus, the effect of phosphine ligands is comparable to the order of ease of their dissociation: dppe $\ll$ $PEt_3$ < $PEt_2Ph$ < $PMePh_2$ < $PEtPh_2$ < $PPh_3$.




On the other hand, *cis*-alkenyl- and *cis*-arylpalladium(II) complexes, which are intermediates in most of cross-coupling reactions discussed here, directly eliminate organic partners from the four-coordinated complex (nondissociative–nonassociative mechanism, eq 24).[58]

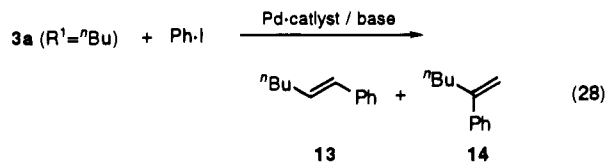
Although the mechanism of oxidative addition and reductive elimination sequences are reasonably well understood and are presumably fundamentally common processes for all cross-coupling reactions of organometallics, less is known about the transmetalation step because the mechanism is highly dependent on organometallics or reaction conditions used for the couplings.

The transmetalation between 1-hexenylboronic acid and palladium(II) acetate was first reported by Heck.[60] The *in situ* preparation of (*E*)- or (*Z*)-1-alkenylpalladium(II) species and its addition to ethyl acrylate readily proceeds at room temperature while retaining their original configurations (eq 26).[38] Before this observation, Davidson and Triggs reported the dimerization of phenylboronic acid with $Na_2PdCl_4$ catalyst (eq 27),[61] although it still remains obscure whether the reaction indeed proceeds through the transmetalation or other processes.




In spite of these previous reports, organoboron compounds are quite unlikely to participate in the catalytic cycle of cross-coupling reaction since they are inert to the organopalladium(II) halides (**11**) such as $PdCl_2$, $PdCl_2(PPh_3)_2$, or $PhPdI(PPh_3)_2$.[62] There is some experimental evidence for the transmetalation to the transition metals. The reaction of organoboranes with organomercurials proceeds under neutral conditions when $Hg(OAc)_2$, $Hg(OR)_2$, or HgO is used.[63] It has also been reported that the addition of sodium hydroxide or other bases exerts a remarkable effect on the transmetalation rate of organoboron reagents with metallic halides, such as mercuric,[19,63] silver,[13] auric,[64] and platinic halides.[64] Thus, the transmetalation with transition-metal complexes appears to proceed well indeed, but the choice of suitable bases and ligands on transition-metal complexes is essential.

Preliminary successful results have reported that (*E*)-1-hexenyl-1,3,2-benzodioxaborole couples with iodobenzene in the presence of $Pd(PPh_3)_4$ and bases to produce a mixture of desired and undesired coupling products depending on the base and the catalyst used (eq 28).[65]




The formation of normal coupling product **13** predominates when sodium hydroxide or alkoxides are used, whereas a combination of triethylamine and a palladium catalyst without phosphine ligands leads almost exclusively to an abnormal head-to-tail coupling product **14** (Table 1).[65b]

The formation of the abnormal coupling product **14** can be best understood by the mechanism of Heck reaction[66] for vinylic metal compounds, that often predominates on the cross-coupling reaction of weakly

**Table 1. Reaction Conditions for Head-to-Head and Head-to-Tail Cross-Coupling (Eq 28)**[a]

| catalyst | solvent | base (equiv) | time, h | yield, % (**13**/**14**) |
|---|---|---|---|---|
| $Pd(PPh_3)_4$ | benzene | none | 6 | 0 |
| $Pd(PPh_3)_4$ | benzene | NaOEt (2) | 2 | 99 (100/0) |
| $Pd(PPh_3)_4$ | benzene | NaOH (2) | 2 | 99 (100/0) |
| $Pd(PPh_3)_4$ | DMF | $Et_3N$ (5) | 20 | 54 (10/90) |
| $PdCl_2(PPh_3)_2$ | DMF | $Et_3N$ (5) | 20 | 66 (8/92) |
| Pd black | DMF | $Et_3N$ (5) | 20 | 94 (4/96) |
| Pd black | DMF | NaOH (2) | 6 | 86 (56/44) |

[a] All reactions were carried out at 80 °C by using Pd catalyst (3 mol %), PhI (1 equiv), base, and **3a** (1.1 equiv).

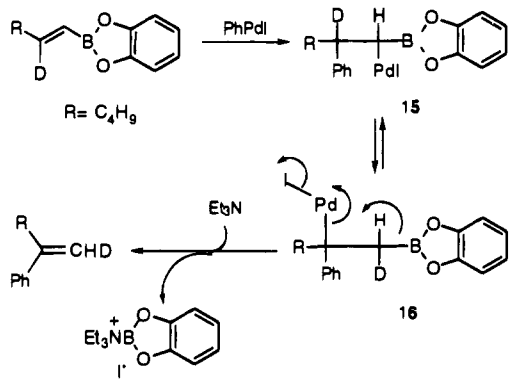
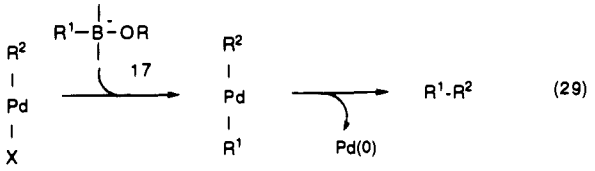



**Figure 2.** Addition–elimination mechanism for head-to-tail coupling.

nucleophilic organometallics, such as 1-alkenylmercurials,[67] -silanes,[68] and -tin compounds.[69]

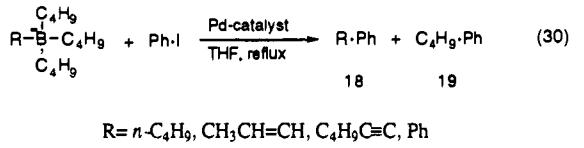
Organopalladium(II) halides add mainly to the electron-deficient carbon of unsymmetrical alkene[66] to give **15**, which readily isomerizes to **16** *via* a sequence of elimination and readdition of the hydridopalladium(II) iodide. Finally, the elimination of iodoborane with the aid of triethylamine gives the head-to-tail cross-coupling product. A deuterium-labeling study proves the addition–elimination mechanism where a $\beta$-hydrogen transfers to the terminal carbon (Figure 2).[70]

The cross-coupling reaction of organoboron compounds with organic halides or triflates selectively reacts in the presence of a negatively charged base, such as sodium or potassium carbonate, phosphate, hydroxide, and alkoxides.[20,65] The bases can be used as aqueous solution, or as suspension in dioxane or DMF. In contrast, the cross-coupling reaction with certain electrophiles, such as allylic acetates,[65b] 1,3-butadiene monoxide,[71] and propargyl carbonates,[72] occurs under neutral conditions without any assistance of base. The transmetalation of organoboron compounds with palladium halides under basic or neutral conditions can be considered to involve the following three processes: eqs 29, 32, and 39.




(29)

It is apparent that the transmetalation between organopalladium(II) halides and organoboron compounds does not occur readily due to the low nucleophilicity of organic group on boron atom. However, the nucleophilicity of organic group on boron atom can be enhanced by quaternization of the boron with negatively charged bases giving the corresponding "ate" complexes.[12] In fact, it is reported that such ate complexes undergo a clean coupling reaction with organic halides.[5i] The reaction of iodobenzene with representative ate complexes prepared from tributylborane and butyl-, 1-propenyl-, 1-hexynyl-, or phenyllithium is summarized in eq 30 and Table 2.[73]




(30)

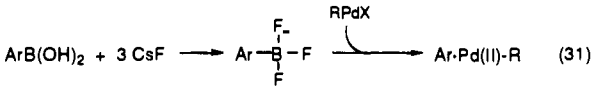
**Table 2. Cross-Coupling Reaction of "Ate" Complexes (Eq 30)**

| R | yield, % (**18**/**19**) Pd(PPh$_3$)$_4$ | PdCl$_2$(dppf) |
|---|---|---|
| $C_4H_9$ | 81 | 82 |
| $CH_3CH{=}CH$ | 85 (45/55) | 95 (53/47) |
| $C_4H_9C{\equiv}C$ | 98 (71/29) | 81 (95/5) |
| Ph | 79 (38/62) | 92 (53/47) |

During such a transmetalation, it is conceivable that the coordination of palladium(II) species to the carbon–carbon multiple bond constitutes the initial step for the interaction of both species and probably this $\pi$-interaction serves to accelerate the ligand exchanges.[74] Thus, the 1-hexynyl group exclusively couples with iodobenzene, but it is surprising that the transfer of primary alkyl group occurs quite smoothly compared with 1-alkenyl or phenyl groups.

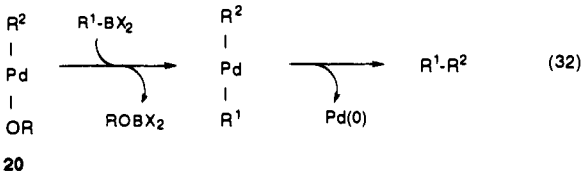
Thus, the quaternization of trialkylboranes accelerates indeed the transmetalation to the palladium(II) halides. Although there is no direct evidence that the boronate anions, such as $RB(OH)_3^-$, are capable of effecting the transmetalation, it is quite reasonable to assume the similar effect of base for the transmetalation of organoboronic acids. The cross-coupling reaction of arylboronic acids with aryl halides at pH = 7–8.5 is retarded relative to the reaction at pH = 9.5–11.[75] The p$K_A$ of phenylboronic acid is 8.8, thus suggesting the formation of the hydroxyboronate anion [$RB(OH)_3^-$] at pH > p$K_A$ and its transmetalation to the palladium(II) halides. The formation of $ArB(OH)_3^-$ at pH = 11–12 has been recently reported.[76]

Recently, fluoride salts have been found to effect to the cross-coupling reactions of 1-alkenyl- and arylboronic acids (eq 31).[77] The species that undergoes transmetalation is assumed to be organo(trifluoro)borate ion.




(31)

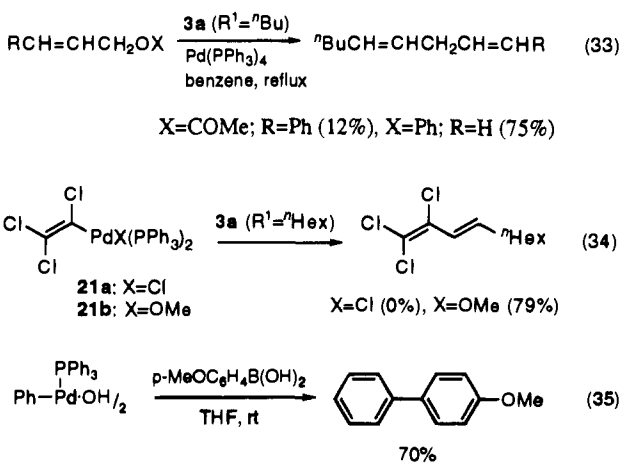
An alternative transmetalation process found during our investigations is that organoboron compounds readily transfer their organic groups to (alkoxo)-palladium(II) complexes under neutral conditions (eq 32).



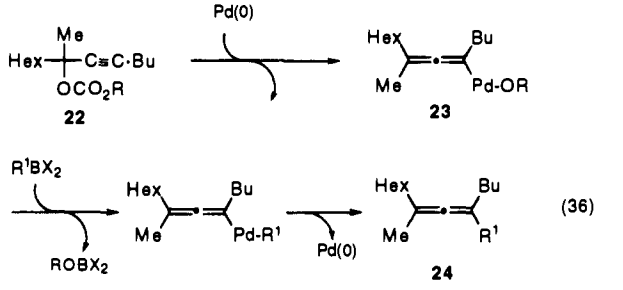

(32)

Although the cross-coupling reaction with organic halides generally requires the assistance of bases, allylic phenoxides and cinnamyl acetate react with 1-alkenylborates under neutral conditions to yield the corresponding 1,4-dienes, 75% and 12%, respectively (eq 33).[65b,78] Thus, the ($\pi$-allylphenoxo)- and ($\pi$-

allylacetoxo)palladium(II) intermediates generated by oxidative addition may undergo transmetalation without bases. The isolated complexes of ($\eta^3$-$C_3H_5$)-PdX react with 1-alkenylborates to give the coupling products when the ligand X is OAc or acetylacetonato (acac).[65b] The another piece of evidence for this unique ligand effect of the Pd–O bond is also observed on the alkenyl–alkenyl coupling reaction (eq 34). The (alkoxo)palladium(II) complexes are stable enough to be isolated if substituted with electron-withdrawing groups (**21b**), otherwise $\beta$-elimination occurs very quickly to give the hydridopalladium(II) species and carbonyls.[79] The isolated **21b** easily reacts with 1-alkenylborates precipitating palladium black, whereas the corresponding chloro complex (**21a**) is quite inert even at the refluxing temperature of THF.[65b] The (hydroxo)palladium complex recently reported by Alper[80] also gives a cross-coupling product (70%) together with biphenyl (15%) (eq 35).

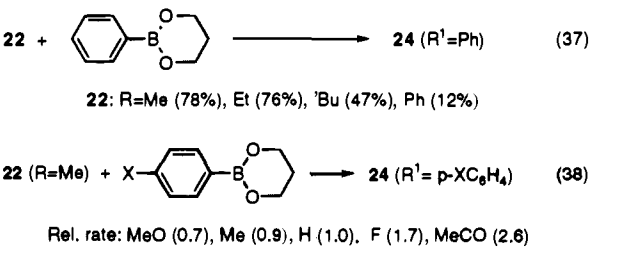



Tsuji and co-workers have shown that propargylic carbonate **22** oxidatively adds to the palladium(0) complex to provide an (alkoxo)palladium intermediate **23** with elimination of carbon dioxide (eq 36).[81] Thus, the reaction of **22** with alkylboranes, 1-alkenyl-, 1-alkynyl and arylboronic acids or their esters gives **24** in high yields under neutral conditions.[72]




The reaction offers other direct evidence for such a boron–palladium transmetalation process through an (alkoxo)palladium(II) species. The reaction of the phenylboronate with various carbonates indicates that less hindered and more nucleophilic alkoxy groups accelerate the cross-coupling (eq 37).

A series of the competitive reaction rate between *para*-substituted phenylboronates and **22** (R = Me) gives a slightly positive $\rho$ value (+ 0.73), demonstrating that electron-withdrawing substituents accelerate the reaction (eq. 38 and Figure 3).




These electronic effects are consistent with the $S_E2$ (coord) mechanism involving a coordination of the alkoxy ligand to the boron atom at the the rate-determining step. As a result of complex formation, the transfer of an activated organic group from boron to palladium then takes place[82] (Figure 4). Such complexation prior to migration is one of the crucial steps essential in all ionic reactions of organoboron compounds; namely, the well-known intramolecular 1,2-migration from the organoborane/electrophile complex.

For the transmetalation between optically active (1-phenylethyl)silicate[10d,e] or -tin[83] and palladium(II) halides, the $S_E2$ (cyclic) or $S_E2$ (open) mechanism which takes place with retention or inversion of the configuration at benzylic carbon atom is proposed. Unfortunately, these stereochemical features have not yet been established for organoboron compounds because their coupling reactions are still limited to primary alkylboranes.

Finally, it is of interest to note the possibility of involvement of the (alkoxo)palladium intermediate **20** in the palladium/base-induced cross-coupling reaction (eq 39).

It is known that the halogen ligand on organopalladium(II) halide is readily displaced by alkoxy, hydroxy, or acetoxy anion to provide the reactive Pd–OR complexes (**20**),[84] which have been postulated as

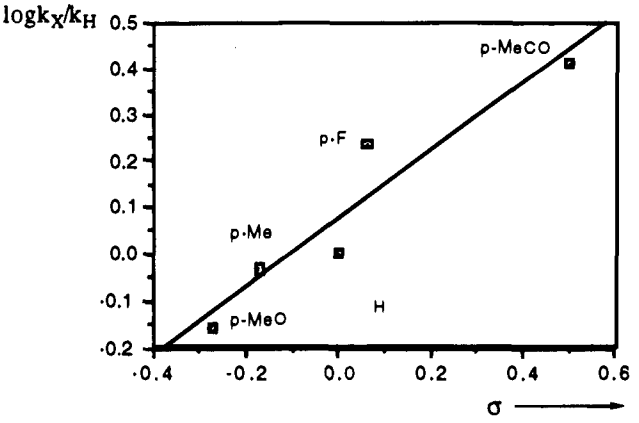



**Figure 3.** Linear free energy relationship for the cross-coupling reaction of *para*-substituted phenylboronate with **22** (R = Me).

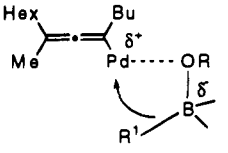
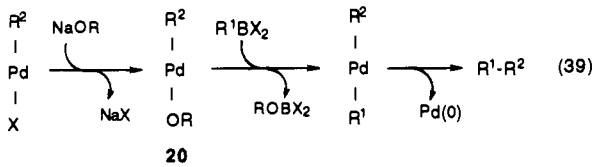
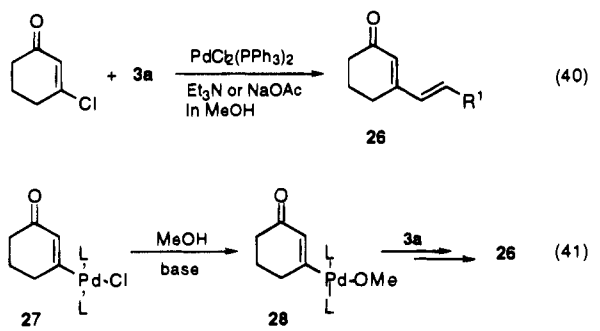



**Figure 4.** $S_E2$ (coord) transition state.




reaction intermediates[85] or isolated[79,80] from the reaction of organopalladium(II) halides with sodium hydroxide or methoxide. It is not yet obvious in many reactions which process shown in eq 29 or 39 is predominant; however, the formation of alkoxo-, hydroxo-, or acetatopalladium(II) intermediate should be considered to be one of the crucial transmetalation processes in the base/palladium-induced cross-coupling reactions.

The reaction of 1-alkenylboronates with haloenones shows a characteristic feature for the (alkoxo)palladium mechanism (eq 40).[86] The cross-coupling reaction with haloenones is accelerated by exceptionally weak bases such as NaOAc or even $Et_3N$, when methanol is used as a solvent. The results cannot be explained by the ate-complex mechanism shown in eq 27, and can be best understood by the formation of (alkoxo)palladium(II) intermediate (**28**) since **27** readily exchanges the halogen ligand with methanol due to its strong *trans* effect of the electron-poor alkenyl group (eq 41).




The palladium-catalyzed cross-coupling reaction of (alkoxy)diboron derivatives provides the first one-step procedure for arylboronic esters from aryl halides (eq 6).[87] Potassium acetate is one of the best bases to achieve a selective cross-coupling, and stronger bases such as potassium carbonate or phosphate give biaryl byproducts arising from further coupling of the product with aryl halides.

The treatment of the phenylpalladium(II) bromide with KOAc gives a *trans*-$PhPdOAc(PPh_3)_2$ (**29**)[87,88] which exhibits high reactivity toward (alkoxy)diboron derivatives selectively giving the phenylboronate at room temperature (Figure 5). Thus, the transmetalation involving formation of **29** and its reaction with

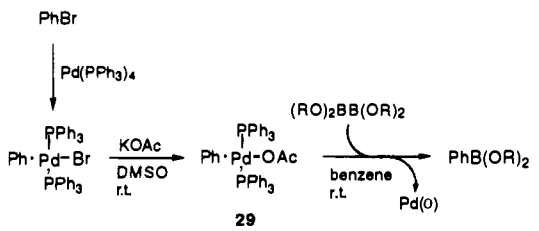



**Figure 5.** Formation of palladium(II) acetate and its transmetalation.

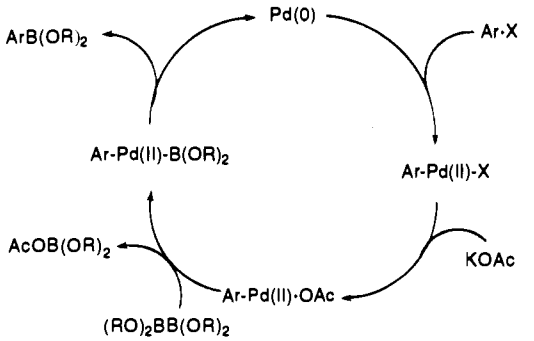
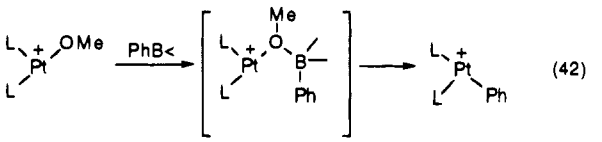



**Figure 6.** Cross-coupling with (alkoxy)diboron (eq 6).

the diboron is proposed as a key step. The acetoxy anions do not act as a base to coordinate with boron atom under the given reaction conditions. The catalytic cycle is shown in the Figure 6.

A similar (methoxo)platinum intermediate has been recently reported for the transmetalation between a cationic platinum(II) complex and potassium teraphenylborate (eq 42).[89]

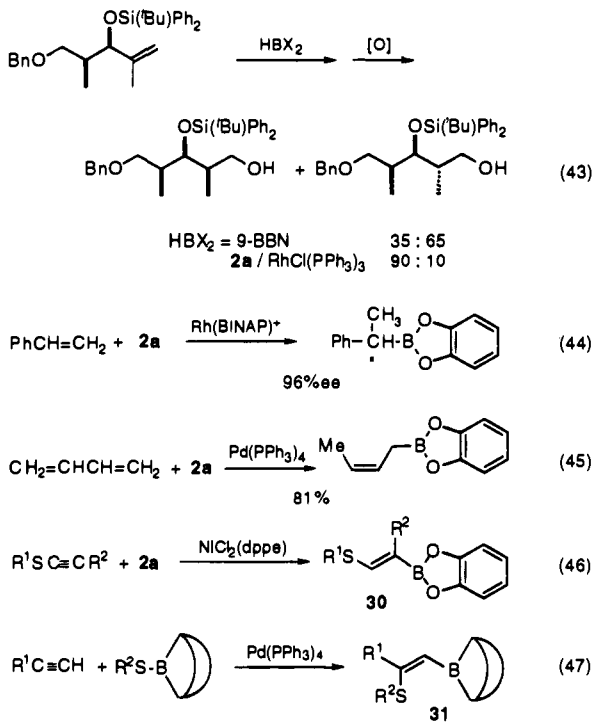



## B. Other Catalytic Process by Transition-Metal Complexes

Recently, transition-metal complexes have been reported as efficient catalysts for the addition of metal reagents, including magnesium, aluminum, silicone, zinc, germanium, and tin compounds to alkenes and alkynes.[90] Although the related reactions of boron compounds are not yet well developed, the Rh-, Pd-, or Ni-catalyzed hydroboration of alkenes[91] and alkynes[27] (eqs 43–46) has been extensively studied since the catalyst allows the reaction under very mild conditions and often can direct the course of the addition of borane to a different selectivity than the uncatalyzed reaction (eq 43).[91m] Asymmetric hydroboration of styrene is achieved using a bidentate chiral ligand (eq 44).[91l] Hydroboration of 1,3-butadiene stereoselectively affords a (*Z*)-crotylboronate with a palladium(0) complex (eq 45).[91k] The $PdCl_2$(dppf) and $NiCl_2$(dppe) or -(dppp) complexes afford good results for the hydroboration of alkynes (eq 46).[27b]

The Pd(0)-catalyzed addition of the B–S bond to terminal alkynes regio- and stereoselectively produces (*Z*)-2-(organothio)-1-alkenylboron reagents (eq 47).[92] The addition of (alkoxy)diboron to alkynes to give *cis*-bis(boryl)alkenes (diboration) is catalyzed by a platinum(0) catalyst[47] (eq 23).

The additions proceed regioselectively in favor of terminal boron adducts to produce (*Z*)-1-alkenylboron compounds through a *syn* addition of the X–B bond to 1-alkynes. The mechanism is fundamentally different from the uncatalyzed process and is postulated to proceed through the oxidative addition of the X–B bonds (X= H, RS, $Y_2B$) to the transition-metal complex [M(0)] to form X–M–$BY_2$ species (**32**), followed by the migratory *cis* insertion of alkenes or alkynes into the X–M bond, and finally the reductive




elimination of alkenylboron compounds from **33** regenerates the M(0) complex, as shown in Figure 7.[27d,47,92]

The oxidative adducts such as B–Rh–H and B–Ir–H intermediates[27d] in the catalytic hydroboration, and the B–Pt–B intermediate[93] in the diboration have been isolated and fully characterized by X-ray analyses, and by observing its insertion reaction to alkynes. Since the catalytic cycle is a very powerful and fundamentally common process with a group 10 transition metal, the further uses of this type of reaction will certainly be exploited in the future.

The oxidative addition of the C–Hg bond to Pd(0) complex is involved in the catalytic carbonylation and the homo coupling of aryl- or vinylmercurials.[94] Similar reaction type such as dimerization,[95] protonolysis of the C–B bonds (eq 48),[96] and Heck-type addition (eq 49)[97] of aryl- or alkenylboronic acids take place in moderate yields. The reactions can be catalyzed by palladium(0) catalysts without phosphine ligands. The mechanism has not yet been elucidated in detail, but it is reasonable to speculate the oxidative addition of the C–B bond to palladium(0) complex.

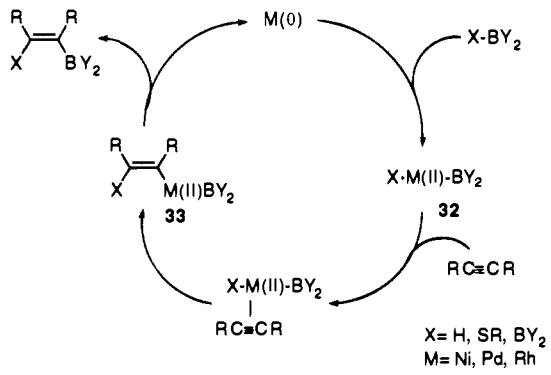
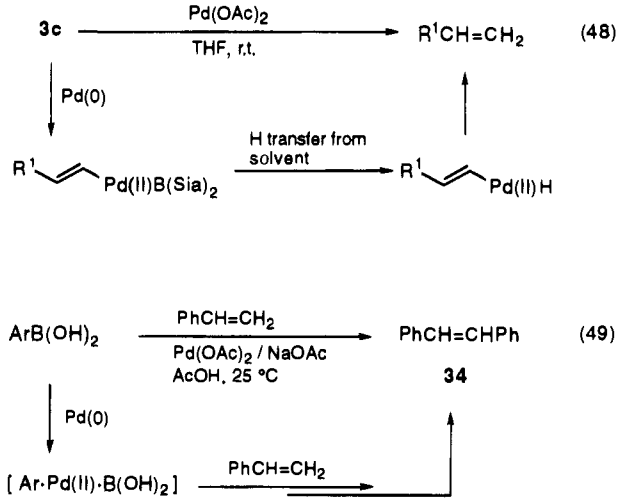



**Figure 7.** A general catalytic cycle for additions.



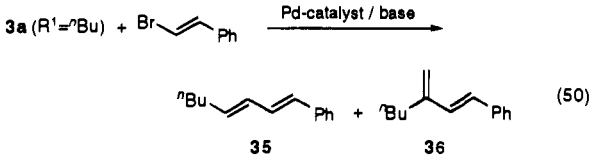

The mechanism for the carbonylative cross-coupling reaction for synthesis of ketones is discussed in section VI. The mechanisms for alkoxycarbonylation and dimerization of organoboron compounds, which require a reoxidant of palladium similar to the Wacker process, is discussed in section VII.

## IV. Cross-Coupling Reaction

### A. Coupling of 1-Alkenylboron Derivatives: 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 catalytic amount of a transition-metal complex.[5,8,10] Although the representative 1-alkenylmetal reagents undergo a similar type of coupling reactions with haloalkenes, there are several limitations when one wishes to obtain unsymmetrical dienes without homocoupling, highly functionalized dienes, or stoichiometric conditions relative to metal reagents and halides. Thus, much attention has been recently been focused on the use of 1-alkenylboronic acids or their esters,[20] because a variety of 1-alkenylboron derivatives are now readily available, as discussed in the section II.

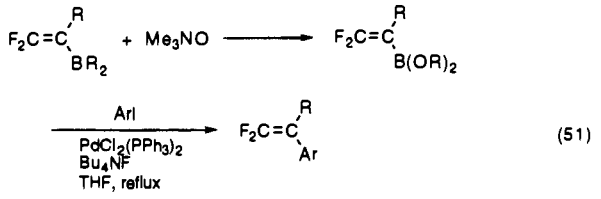
The first observation to prepare conjugated dienes is shown in eq 50.[65,98–100] The high yield of diene is obtained when relatively strong bases such as sodium ethoxide and hydroxide are used together with a phosphine-based Pd complex, e.g., $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$. In general, a combination of $Pd(PPh_3)_4$ and sodium ethoxide works satisfactorily for the coupling with 1-bromo-1-alkenes, and $PdCl_2(PPh_3)_2$ and aqueous sodium hydroxide for 1-iodo-1-alkenes. The use of palladium catalyst without phosphine ligand or weak bases (KOAc or $Et_3N$) has a tendency to be contaminated by undesired head-to-tail coupling product (**36**).[70] The reaction can be carried out in aqueous media by using water-soluble phosphine palladium catalyst.[101]



(50)

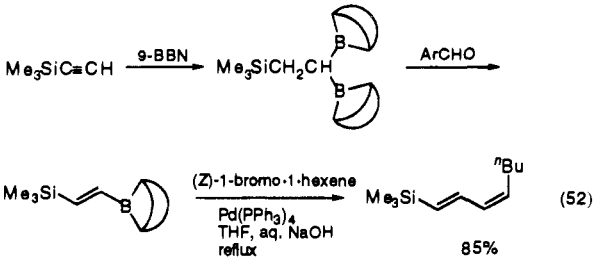
Although disiamyl- or dicyclohexylborane is a selective and efficient hydroboration reagent of alkynes, 1-alkenyldialkylboranes thus obtained give relatively poor yields of coupling products (~50%) with low stereoselectivity.[102] The difficulty appears to be due to side reactions arising from the protodeboronation with water or alcohols and the transfer of secondary alkyl group to the palladium(II) halide. Some loss of the reagent decreases the yields of coupling products and the transfer of secondary alkyl group forms an undesirable palladium(II) hydride species which induces isomerization of the double bond. The protodeboronation of 1-alkenylboron compounds with alcohols is faster than with water, and it decreases in the following order: 9-BBN > B(cyclohexyl)$_2$ > B(Sia)$_2$ ≫ B(OR)$_2$.[103] Thus, the high yields and high isomeric purity exceeding 99% can be achieved by using 1-alkenylboronic acids or their esters. Yields and stereoselectivity on the cross-coupling of (*Z*)-1-hexenylboron reagents with iodobenzene are shown in Table 3.[99]

Thus, the oxidation of the two boron−sp$^3$ carbon bonds with triethylamine *N*-oxide prior to the coupling solves the difficulty arising from the B−C bond protonolysis and the contamination of the coupling product with alkyl group (eq 51).[104,105]



(51)

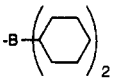
The absence of a convenient route to 9-vinyl-9-BBN has severely limited the use of 9-BBN derivatives in this coupling. However, the reagents are now available under very mild conditions by a sequence of dihydroboration of terminal alkynes and dehydroborylation with an aromatic aldehyde. The cross-coupling with organic halides readily undergoes in the refluxing THF in the presence of Pd(PPh$_3$)$_4$ and an aqueous NaOH (eq 52).[30,106]



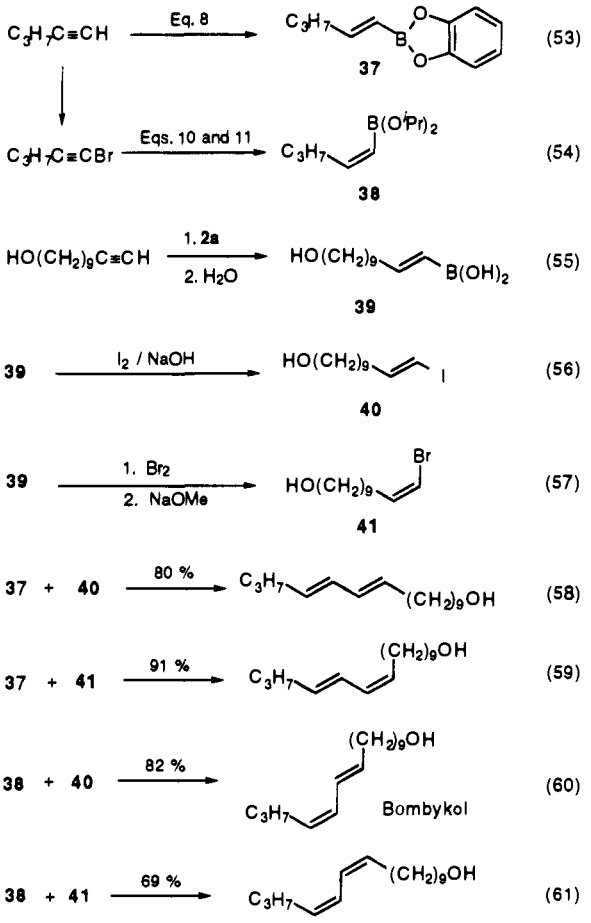
(52)

Bombykol is a well-known pheromone, first isolated from *Bombyx mori* L. Bombykol and the related three isomers were synthesized by the cross-coupling reaction. Three alkenylboronates or boronic acids (**37**−**39**) and two vinylic halides (**40** and **41**) required for the coupling are prepared by starting from two alkynes. The stereoselective syntheses of (*E*)- and (*Z*)-1-alkenylboronic acids or esters are discussed in the previous section (eqs 8 and 11). Halogenation of the corresponding alkenylboronic acids with iodine or bromine provides (*E*)- and (*Z*)-haloalkenes from the same starting material (eqs 56 and 57).[107] The palladium and base-assisted coupling of each five and 11 units stereoselectively provides bombykol and its three geometrical isomers (eqs 58−61).[108]

**Table 3. Reaction of (*Z*)-BuCH=CHBX$_2$ with PhI[a]**

| -BX$_2$ | yield, %[b] | isomeric purity, % |
|---|---|---|
| -B(Sia)$_2$ | 58 | >94 |
|  | 49 | >83 |
| -B(OPr$^i$)$_2$ | 98 | >97 |

[a] A mixture of Pd(PPh$_3$)$_4$ (3 mol %), 2 M NaOEt in EtOH (2 equiv), PhI (1 equiv), and (*Z*)-BuCH=CHBX$_2$ (1.1 equiv) in benzene was refluxed for 3 h. [b] Yields of (*Z*)-BuCH=CHPh.

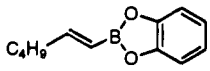
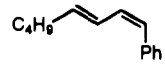
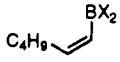
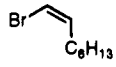
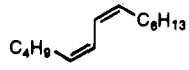
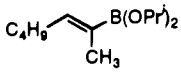
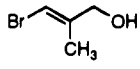
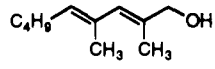
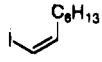
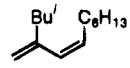
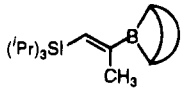
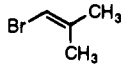
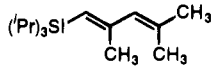
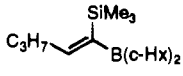
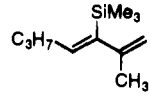
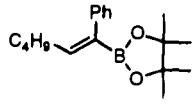
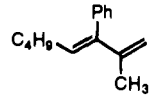
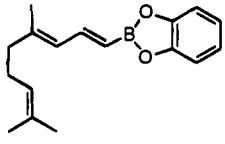
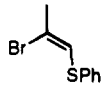
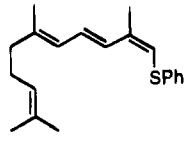
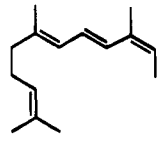
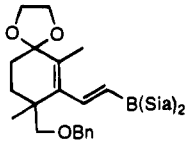
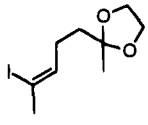
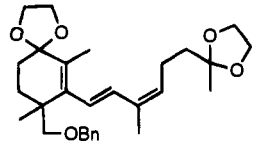


(53) (54) (55) (56) (57) (58) (59) (60) (61)

(*Z*,*E*)- or (*E*,*Z*)-dienic structures are rather common in the sex pheromones of insects. The procedure has been successfully applied to the syntheses of European grape wine moth,[109,110] red bollworm moth,[109] and Egyptian cotton leafworm[109,111] sex pheromones.

Since a variety of 1-alkenylboron reagents including (*E*)- and (*Z*)-isomers are now available, their cross-coupling with 1-halo-1-alkenes affords various stereodefined alkadienes and trienes.[98−100] Many syntheses of alkadienes and trienes such as unsaturated fatty acid amides,[112] alkenylsilanes,[106,113] *gem*-

**Table 4. Synthesis of Dienes and Trienes**

| Entry | Alkenylboron Reagent | Alkenyl Halide | Reaction Conditions, catalyst/base/solvent/temp. | Product | | Yield/% | Ref |
|---|---|---|---|---|---|---|---|
| 1 |  | | $Pd(PPh_3)_4$/NaOEt /benzene/reflux |  | | 86 (>98) | 98 |
| 2 |  |  | $Pd(PPh_3)_4$/NaOEt /benzene/reflux |  | X = Sia | 49 (>98) | 102 |
| 3 | | | | | X = $OPr^i$ | 97 (>99) | 99 |
| 4 |  |  | $Pd(PPh_3)_4$/aq. KOH /benzene/reflux |  | | 70 (>99) | 100 |
| 5 | |  | $Pd(PPh_3)_4$/aq.NaOH /THF/reflux |  | | 87 (>99) | 105 |
| 6 |  |  | $Pd(PPh_3)_4$/aq.NaOH /THF/reflux |  | | 85 ( - ) | 106a |
| 7 |  | | $Pd(PPh_3)_4$/aq.NaOH /THF/reflux |  | | 40 ( - ) | 113a,b |
| 8 |  | | $Pd(PPh_3)_4$/NaOEt /benzene/reflux |  | | 87 ( - ) | 117 |
| 9 |  |  | $Pd(PPh_3)_4$/aq. NaOH benzene, reflux |  | | 91 (>98) | 118 |
| 10 | | | $Pd(PPh_3)_4$/NaOEt /benzene/reflux |  | | 89 (>94) | 115 |
| 11 |  |  | $Pd(PPh_3)_4$/NaOEt /benzene/reflux |  | | 52 ( - ) | 116 |

difluoroalkenes,[104,113] cyclic alkenes,[114] (C10)-allofarnesene,[115] trisporol B,[116] and vinylsulfides[118] are reported by application of Pd-catalyzed cross-coupling. The representative syntheses and reaction conditions are summarized in Table 4.

The coupling rate enhancement was realized by Kishi by using an aqueous TlOH in place of sodium or potassium alkoxide or hydroxide. The cross-coupling between (*E*)-1-alkenylboronic acid and (*Z*)-iodoalkene stereoselectively furnished the C75–C76 bond formation of palytoxin at room temperature (Figure 8).[119]

Roush, Nicolaou, and Evans have also demonstrated the efficiency of thallium hydroxide on the synthesis of an aglycone of antibiotic kijanimicin,[120] chlorothricolide,[121] (5*Z*,8*Z*,10*E*,12*R*,14*Z*)-12-hydroxy-5,8,10,14-icosatetraenoic acid [(12*R*)-HETE],[122] and a macrolide antibiotic rutamycin B[123] (Figure 9). This modification of base has been realized on the assumption that the transmetalation involves a palladium(II) alkoxide or hydroxide intermediate (**20** in eq 39); namely, thallium base may accelerate the formation of **20** by forming water-insoluble thallium salts instead of NaX. However, another process, i.e., the transmetalation of alkenylboronic acids to thallium salts giving an alkenylthallium(I) or -(III) species, has not yet been investigated.[124]

Hydroboration of enynes provides 1,3-alkadienylboron derivatives. The coupling of dienylboron compounds with haloalkenes allows a short-step synthesis of conjugated trienes; for example, the synthesis of leukotriene $B_4$ shown in eq 62.[125,126] Due to the

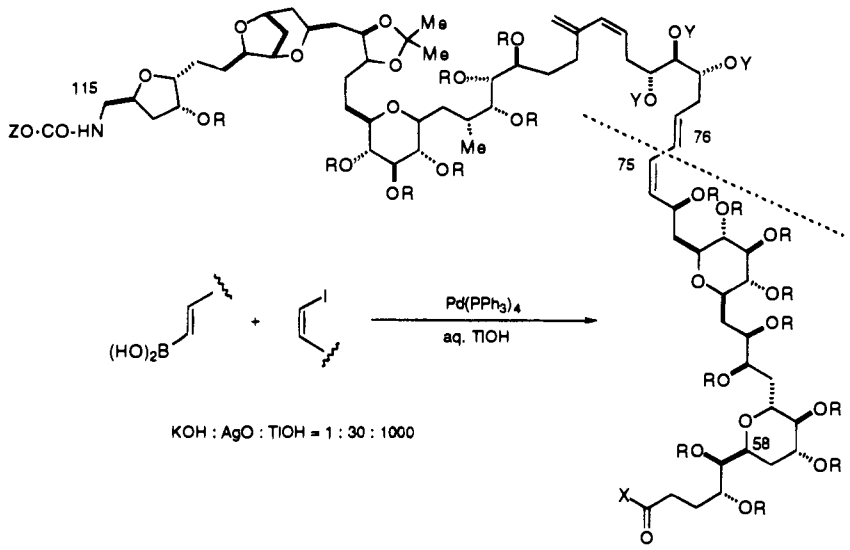



**Figure 8.** Synthesis of palytoxin precursor.

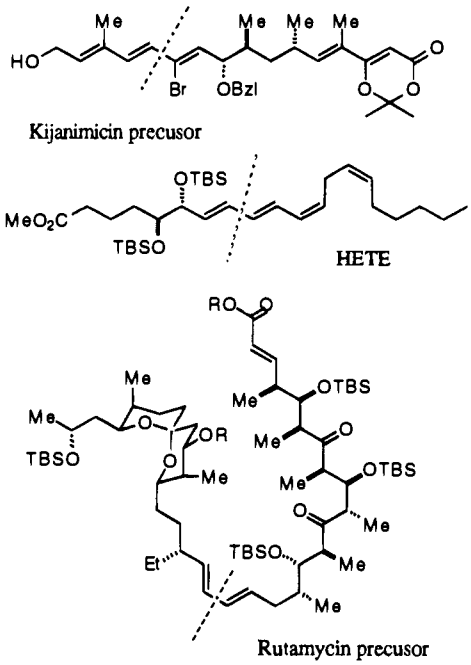
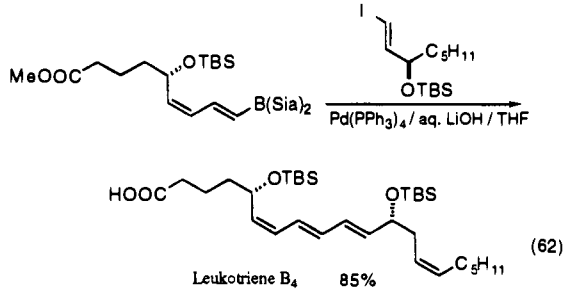
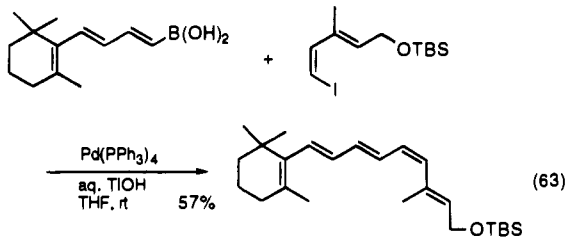



**Figure 9.** The coupling reactions induced by TlOH.




this combination for synthesis of the conjugated pentaene (eq 63).[127]

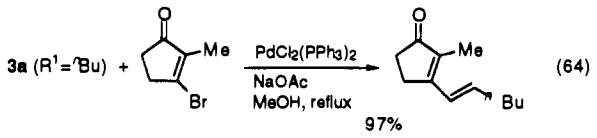



difficulty of purification of a geometrical mixture, the stereodefined syntheses might be essential for such trienes. As discussed previously, the coupling reaction is carried out more efficiently by 1-alkenylboronic acids or esters; however, 1-alkenyl(disiamyl)boranes have been often used as a coupling reagent since hydroboration of alkynes having allylic or propargylic hydroxy functional groups does not afford good results with catecholborane. Aqueous lithium hydroxide is shown to be one of the best bases that avoids the C–B bond breaking during the cross-coupling (eq 62).[126]

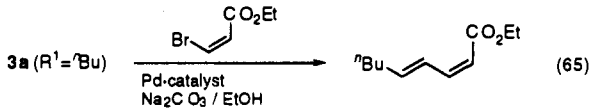
A reverse combination of 1-alkenylboronates and 1-halo-1,3-alkadienes is expected to lead to the same trienes, but this combination is generally not recommended because of the synthetic problems of unstable dienyl halides and the side reaction eliminating hydrogen halides with bases to produce the corresponding enyne. However, the thallium base allows

$\beta$-Halo-$\alpha,\beta$-unsaturated ketones and esters are highly susceptible to $S_N2$ displacement at the carbon attached to halogen, thus strong bases are undesirable for such substrates.[86,128–131] However, relatively weak bases, such as sodium acetate and even triethylamine, are effective when the reaction is conducted in alcohol solvents (eqs 40 and 64).[86] Sodium acetate suspended in methanol, and aqueous or solid carbonate in ethanol give best results for haloenones[86] and haloesters,[129] respectively. $PdCl_2(PPh_3)_2$ or a combination of $Pd(OAc)_2$ plus $PPh_3$ (4 equiv) is desirable to achieve high yields. The *cis/trans* isomerization is rarely observed in the palladium-catalyzed cross-coupling, but the reaction with (*Z*)-$\beta$-bromoacrylate gives a mixture of stereoisomers. $PdCl_2$(dppf) is effective for carrying out the reaction at room temperature in order to depress the isomerization during the coupling (eq 65).[129]

Conjugated enynes are of importance in themselves, as well as in their utilization for synthesis of conjugated dienes. The cross-coupling reaction of 1-alkenyl(disiamyl)boranes (**3c**) with 1-bromo-1-



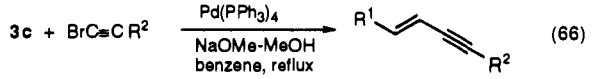
(64)



(65)

| catalyst | temp/°C | time/h | yield/% (2E/2Z) |
|---|---|---|---|
| $Pd(OAc)_2 \cdot 2PPh_3$ | reflux | 5 | 70 (37/63) |
| $Pd(OAc)_2 \cdot dppe$ | reflux | 5 | 80 (80/20) |
| $Pd(OAc)_2 \cdot dppf$ | reflux | 5 | 86 (23/77) |
| $Pd(OAc)_2 \cdot dppf$ | 20 | 24 | 73 ( 5/95) |

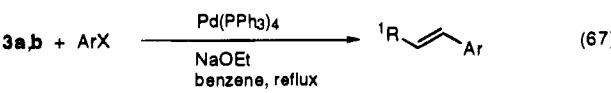
alkynes provides conjugated enynes in high yields (eq 66).[65] The enynes thus obtained can be readily converted into the corresponding dienes by hydroboration–protonolysis sequence.[132]



(66)

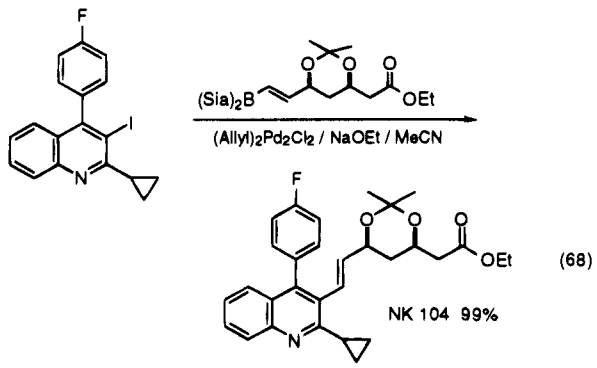
| $R^1$ | $R^2$ | yield/% |
|---|---|---|
| $C_4H_9$ | $C_6H_{13}$ | 98 |
| $C_4H_9$ | Ph | 74 |
| Ph | $C_6H_{13}$ | 95 |
| $CH_3$ | Ph | 93 |

The cross-coupling reaction of 1-alkenylboronates is useful for alkenylation of haloarenes (eq 67).[133,134]



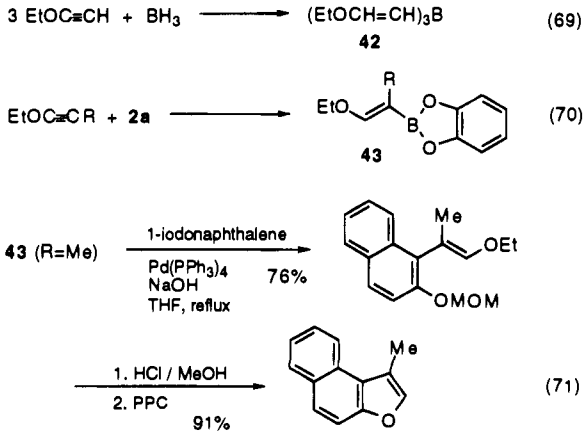
(67)

The relative reactivity appears to be PhI > $p$-$ClC_6H_4Br$ > PhBr > $o$-$MeC_6H_4Br$ > $o$-$MeOC_6H_4$-Br.[133] The order of reactivity is in good agreement with substituent effect in the oxidative addition of aryl halides to the palladium(0) complex,[52] and presumably the substituents accelerate the transmetalation rate in the same order. The procedure, involving a hydroboration-coupling sequence, gives a new access to HGM-CoA reductase inhibitor NK-104 (eq 68).[135]



(68)

Cyclodehydration of 2-hydroxy- or 2-aminobenzeneethanal derivatives is known as a general procedure for the synthesis of benzo-fused heteroaromatic compounds.[136] Although numerous modifications of this general method have been studied, the major difficulty seems to be the lack of a general method for the required *ortho*-functionalized areneethanals.



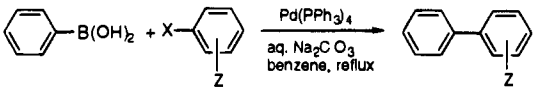
(69) (70) (71)

The cross-coupling reaction of tris(2-ethoxyethenyl)borane (**42**)[137] or 2-(2-ethoxy-1-alkenyl)-1,3,2-benzodioxaboroles (**43**) with iodoarenes produces styryl ethers in high yields in the presence of $Pd(PPh_3)_4$ and powdered NaOH suspended in THF.[138,139] Since **42** and **43** have a tendency to undergo base-induced decomposition on prolonged heating, it is desirable to use iodoarene derivatives as a substrate or an excess boron reagent for relatively unreactive haloarenes. Removal of the MOM protecting group, followed by cyclization gives benzo[*b*]furans in high yields by treatment with HCl in methanol (presumably to give cyclic acetals first), followed by dealkoxylation with polyphosphoric acid (PPA) at 100 °C (eq 71).[138]

Conversion of haloarenes to areneethanal precursors also can be carried out by the cross-coupling reaction of (2-organothio-1-alkenyl)boron derivatives which will be discussed in the section IV.E.

## B. Coupling of Arylboron Derivatives: Synthesis of Biaryls

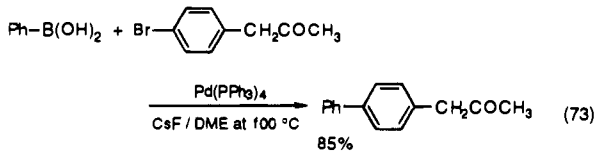
The first observed method to prepare biaryls is shown in eq 72.[140] After this discovery, various modifications have been made for the reaction conditions. A combination of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ and aqueous $Na_2CO_3$ in dimethoxyethane (DME) works satisfactorily in most cases.[141,142]



(72)

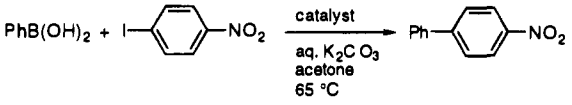
The combination with other bases such as $Et_3N$,[143] $NaHCO_3$,[141] $Cs_2CO_3$,[144] $Tl_2CO_3$,[145] and $K_3PO_4$[146] with or without $Bu_4NCl$[147] and 18-crown-6[144] also have been used. The reaction is successful for aryl triflates and iodo- and bromoarenes. Chlorobenzene derivatives are generally quite inert to oxidative addition, but some of $\pi$-difficient heteroaryl chlorides gives coupling products.[148] The reaction proceeds more rapidly in homogeneous conditions (aqueous base in DME), but the reasonable yields are also obtained under heterogeneous conditions. For example, $K_2$-

$CO_3$ suspended in toluene works well for base-sensitive reactants.[149] The coupling is also carried out in an aqueous medium by using water-soluble phosphine ligand ($m$-$NaO_3SC_6H_4PPh_2$).[101] Although the conditions using such bases are not entirely compatible with the functional groups present in the desired reactants, the extremely mild conditions using CsF or $Bu_4NF$ (eq 31) allow the synthesis of various functionalized biaryls (eq 73).[77]



(73)

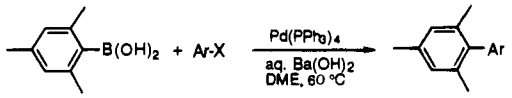
Phosphine-based palladium catalysts are generally used since they are stable on prolonged heating; however, extremely high coupling reaction rate can be sometimes achieved by using palladium catalysts without a phosphine ligand such as $Pd(OAc)_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$, and $Pd_2(dba)_3{\cdot}C_6H_6$.[75,150] Phosphine-free palladiums are approximately 1 order of magnitude more active than $ArPd^{II}I{\cdot}PPh_3)_2$, both of which are in turn markedly more active than $Pd(PPh_3)_4$ (eq 74).



(74)

catalyst:
$Pd(PPh_3)_4$ (8 h, 23%); $PhPdI(PPh_3)_2$ (0.33 h, 53%); $Pd(OAc)_2$ (0.75 h, 98%)

Although steric hindrance of aryl halides not a major factor for the formation of subsituted biaryls, low yields are resulted in when using *ortho*-disubstituted arylboronic acids. For example, the reaction with mesitylboronic acid proceeds only slowly because of steric hindrance during the transmetalation to palladium(II) halide. The addition of strong bases, e.g., aqueous NaOH or $Ba(OH)_2$, both in benzene and DME exerts a remarkable effect on the acceleration of the coupling rate (eq 75).[151-153] Although weak bases give better results for less hindered arylboronic acids, the order of reactivity for mesitylboronic acids corresponds to the basic strength: $Ba(OH)_2$ > NaOH > $K_3PO_4$ > $Na_2CO_3$ > $NaHCO_3$.[151]



(75)

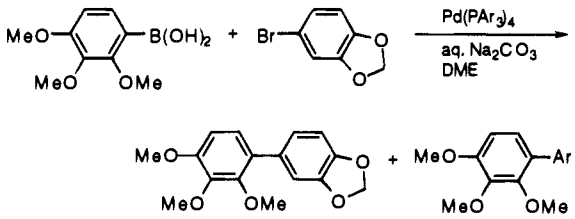
ArX: 2-$MeOC_6H_4I$ (80%), 2-$ClC_6H_4I$ (94%), 2-bromonaphthalene (86%)

(76)

ArX: iodomesitylene (73%), 2-$MOMOC_6H_4I$ (85%), 2-$MeO_2C\ C_6H_4Br$ (63%)

Even if there is no great steric hindrance, the reaction under aqueous conditions gives undesirable results due to competitive hydrolytic deboronation.[154] The rate for the cleavage of $XC_6H_4B(OH)_2$ with water at pH 6.7 is shown as follows: (relative to phenylboronic acid) 2,6-dimethoxy (125), 2-F (77), 2-Cl (59), 2-MeO (11), 4-MeO (4.2), 2-Me (2.5), 3-F (2.3), 3-Me (2), 4-F (1.7).[155] For example, the coupling of 2-formylphenylboronic acid with 2-iodotoluene at 80 °C using an aqueous $Na_2CO_3$ in DME gives only 54% of biaryl with benzaldehyde (39%). The yield can be improved to 89% by using the corresponding ester of boronic acid and anhydrous $K_3PO_4$ suspended in DMF (eq 76).[151] However, Negishi's coupling using corresponding arylzincs[5] or Stille's coupling using arylstannanes[8e] is perhaps a more general alternative in such cases.

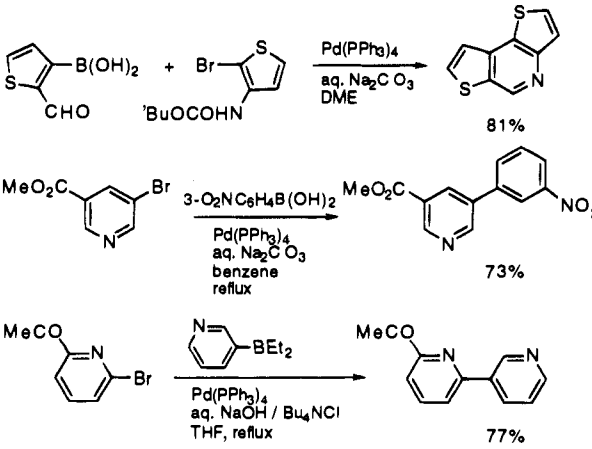
An aryl–aryl exchange between the palladium center and phosphine ligands in palladium(II) complexes is enhanced by electron-donating substituents.[156] The synthesis of biaryls substituted with electron-donating groups results in contamination of the coupling product with the aryl group on phosphine ligand. Tris(2-methoxyphenyl)phosphine is effective in reducing the formation of such by-product while maintaining a high yield of the desired product (eq 77).[157]



(77)

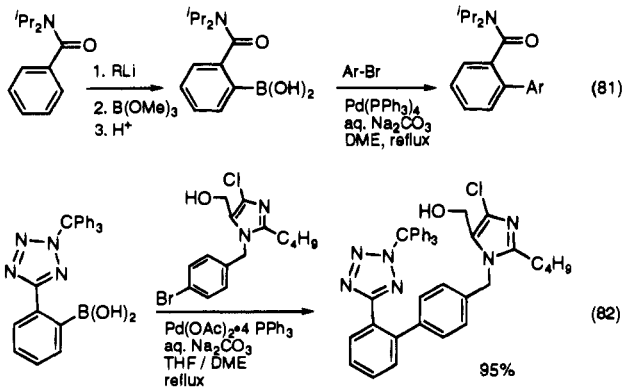
| | | |
|---|---|---|
| Ar = Ph | 54% | 27% |
| Ar = $o$-$MeOC_6H_5$ | 79% | 3% |

The cross-coupling reaction of arylboronic acids is largely unaffected by the presence of water, tolerating a broad range of functionality, and yielding nontoxic byproducts. The reaction offers an additional great advantage of being insensitive to the presence of *ortho*-functional groups or heteroaromatic rings. Gronowitz has shown that unsymmetrically subsitituted bithienyls[141,158] and thienylpyridines[159] can be regioselectively synthesized by the cross-coupling reaction of thienylboronic acids (eq 78). Arylation of 5-bromonicotinates is demonstrated by Thompson[160] (eq 79). Diethyl(3-pyridyl)borane synthesized by Terashima[147] is a unique air-stable reagent for the heteroarylation (eq 80).



(78) (79) (80)

The ready availability of *ortho*-functionalized arylboronic acids by directed *ortho*-metalation–boronation sequence provides a synthetic link to the cross-coupling protocol. Snieckus has amply demonstrated that the sequence has considerable scope for the synthesis of unsymmetrical biaryls, heterobiaryls, and terphenyls[161] (eq 81). The utility of the sequence has recently shown by the industrial-scale synthesis of a nonpeptide angiotensin II receptor antagonist[162] (eq 82).




As a consequence, the reaction has been used extensively in the synthesis of natural and unnatural products and pharmaceuticals such as saddle-shaped host compounds,[163] ferrocene derivatives,[164] bis-cyclometalating N–C–N hexadentated ligands,[165] helically chiral ligands,[166] michellamine,[153] biphenomycine A,[167] vancomycin,[168] receptor molecules for oxo acids,[169] leukotriene B4 receptor antagonist,[170] hemispherand,[171] 1,1′-bi-2-naphthols,[161r] fascaplysin and streptonigrin alkaloids,[172] ungerimine and hippadine alkaloids,[161i] and other biaryls.[173] Some of examples are summarized in Figure 10.

Aromatic, rigid-rod polymers play an important role in a number of diverse technologies including

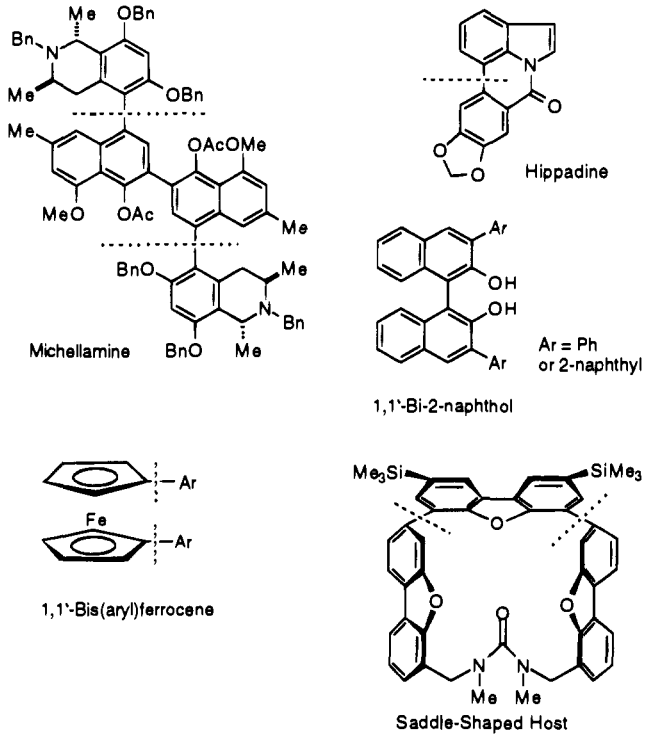



**Figure 10.** Synthesis of biaryls.

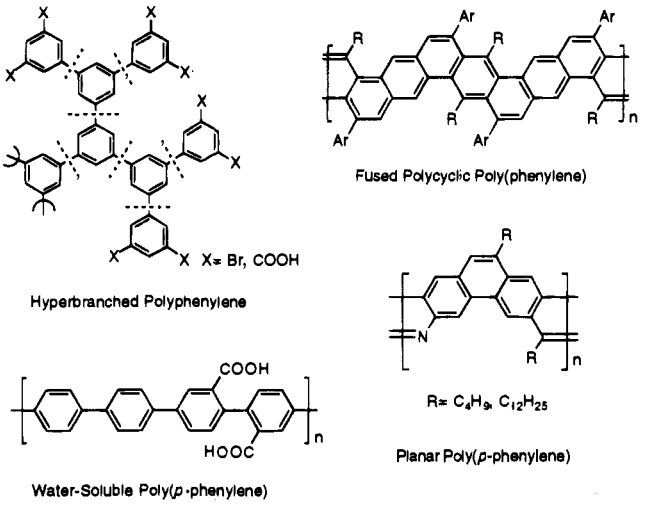
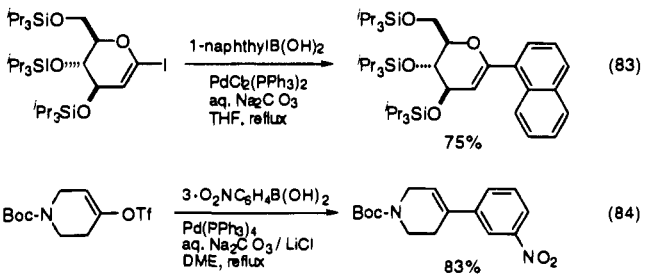



**Figure 11.** Aromatic rigid-rod polymers.

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 Schlüter.[174] The method has been extensively applied to monodisperse aromatic dendrimers,[175] water-soluble poly(*p*-phenylene),[176] planar poly(p-phenylenes) fixed with the ketoimine bonds,[177] poly(phenylenes) fused with polycyclic aromatics,[178] and nonlinear optical materials[179] (Figure 11).

Arylboronic acids are also efficient reagents for arylation of 1-alkenyl halides and triflates. Arylation of various haloalkenes such as α-iodo-α,β-unsaturated lactams,[180] 6-[(alkoxycarbonyl)amino]-1-bromocyclohexene,[181] 1-iodo-3,4,6-tri-*O*-(triisopropylsilyl)-D-glucal[182] (eq 83), and the bromoalkene precursor for (Z)-tamoxifen synthesis[183] are achieved by the cross-coupling reaction of arylboronic acids. Arylcycloalkenes are prepared by the cross-coupling with corresponding triflates[184] (eq 84). For the arylation of triflates, higher yields can be obtained in the presence of LiCl or LiBr (see: section IV.D).




## C. Coupling of Alkylboron Derivatives

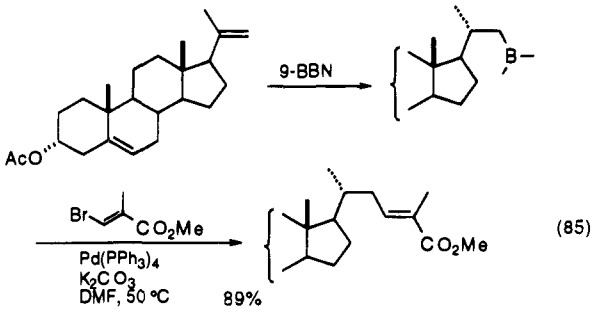
Although alkylmagnesium, -zinc, -tin, and -aluminum reagents have been successfully used for the cross-coupling reaction with organic halides,[1-11] the reaction of alkylborane derivatives is particularly useful when one wishes to start from alkenes *via* hydroboration.

Also, the base as well as palladium catalyst is essential for the success of the coupling reaction.[185-188] A combination of $PdCl_2$(dppf) and aqueous NaOH in THF works nicely for most cases. Although strong bases accelerate the coupling reaction, more weak bases and aprotic conditions are desirable for func-

tionalized alkylboranes or organic halides. The reaction can be carried out by powdered $K_2CO_3$ or $K_3PO_4$ suspended in DMF at 50 °C in the presence of $PdCl_2$-(dppf) catalyst.[185,186] $Pd(PPh_3)_4$ catalyst works well when aqueous NaOH in benzene or $K_3PO_4$ in dioxane are used.[185] The characteristic features of both catalysts are that $PdCl_2$(dppf) is used well in polar solvents (e.g., THF and DMF), but $Pd(PPh_3)_4$ gives good results in nonpolar solvents, such as benzene and dioxane.

One of primary alkyl groups in trialkylboranes participates in the coupling, and the reaction with secondary alkyl is very slow.[185] Thus, representative hydroboration reagents, such as 9-BBN, disiamylborane, dicyclohexylborane, and borane, can be used as hydroboration reagents for terminal alkenes. However, 9-BBN is most accessible due to its ease of use, high selectivity on hydroboration, and high reactivity on the cross-coupling reaction.

The hydroboration coupling approach for the construction of carbon skeletons affords several advantages (eq 85).[185] The high stereoselectivity of hydroboration provides a stereodefined alkyl center on boron. The hydroboration occurs chemoselectively at the less hindered C19–C20 double bond. In addition, the alkyl group thus constructed can be readily cross-coupled with alkenyl or aryl halides under mild conditions.




The procedure has been used in a variety of syntheses of natural products;[189,190] for example, in the synthesis of dihydroxyserrulatic acid (Figure 12),[191] the aggregation pheromone of *Cathartus quadricollis* (quadrilure),[192] and aza-C-disaccharides.[193]

A three-step, three-component synthesis of $PGE_1$ is achieved by utilization of the cross-coupling reaction of 9-alkyl-9-BBN with α-iodoenones. It is recognized that cesium carbonate in the presence of water extremely accelerates the coupling reaction carried out at room temperature (eq 86).[194]

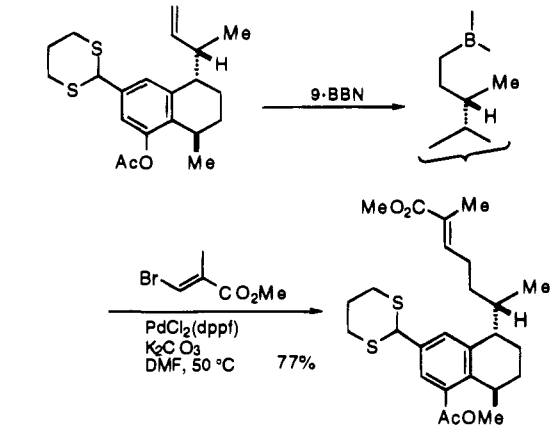
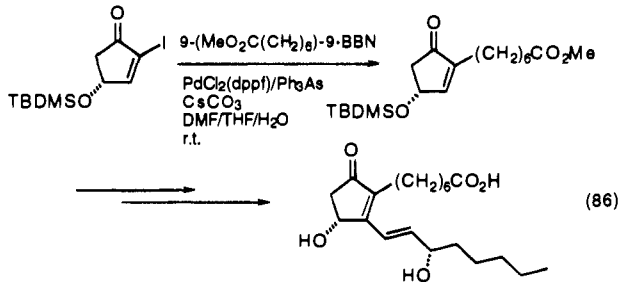
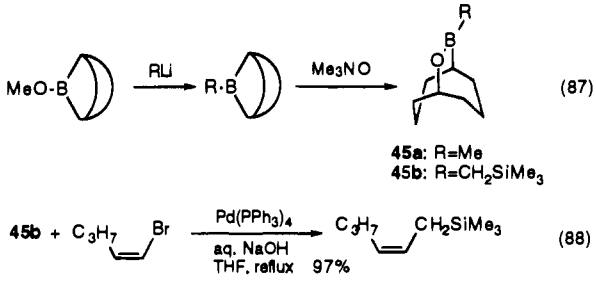


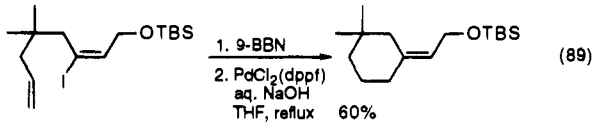

**Figure 12.** Synthesis of dihydroxyserrulatic acid.



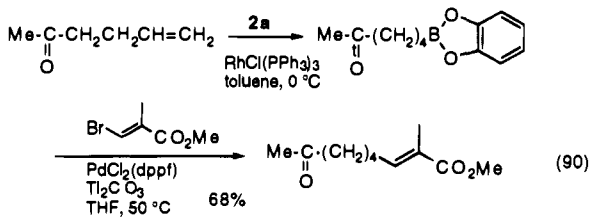

9-Methyl and 9-[(trimethylsilyl)methyl]-9-BBN are easily synthesized by the reaction of the corresponding lithium reagents with 9-methoxy-9-BBN. Unfortunately, such derivatives are spontaneously flammable in air, making them particularly hazardous to handle for isolation. However, selective oxidation with anhydrous trimethylamine *N*-oxide converts them to air stable borinate esters (eq 87) which are efficient reagents for methylation[195,196] of haloalkenes or syntheses of allylic and propargylic silanes[197] (eq 88).




The intramolecular cross-coupling proceeds especially smoothly when the cyclization results in the formation of either five- or six-membered rings.[185,198,199] The hydroboration of the terminal double bond with 9-BBN is faster than that of the halogenated double bond, e.g., (the relative rate), 2-methyl-1-pentene (196); 1-hexene (100); (*Z*)-1-bromo-1-butene (0.011). Thus, hydroboration coupling approach provides a new route for stereodefined exocyclic alkenes (eq 89).




Although alkylboronic acids or their esters are quite inert under above conditions, the organoboronates are more convenient to use, since they are stable in air and are handled easily for isolation. The cross-coupling of alkylboronates with 1-alkenyl or aryl halides proceeds in moderate yields in the presence of $Tl_2CO_3$ and $PdCl_2$(dppf), although the reaction is limitedly used for activated halides having an electron-withdrawing group. A sequence of the Rh(I)-catalyzed hydroboration[27a] of allyl acetone and the cross-coupling with haloenones produces diketones in 62–69% yields (eq 90).[200]

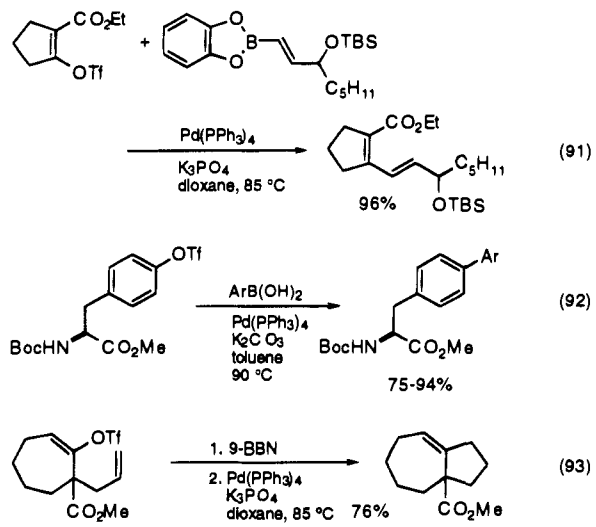



(90)

## D. Coupling with Triflates

Although the cross-coupling reaction with organic halides have been studied predominantly, it has been most recently discovered that trifluoromethanesulfonates (triflates) undergo a clean coupling with organoboron compounds, similar to organostannanes[8,201] aluminum[202] and zinc[203] compounds. The 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 and 1-alkenyl electrophiles.[204] The cross-coupling reaction of organic triflates is previously reviewed.[205]

Although relatively strong bases such as aqueous NaOH and NaOEt in ethanol have been used for the reaction with halides, powdered $K_3PO_4$ suspended in THF or dioxane is sufficient enough to accelerate the coupling of 9-alkyl-9-BBN, 1-alkenyl-, and arylboronates or boronic acids with the triflates.[206] $Pd(PPh_3)_4$ in dioxane at 65 °C is less effective than $PdCl_2$(dppf) in refluxing THF, but it may give a comparable yield by carrying out the reaction at 80 °C (eqs 91 and 92). The choice of suitable boron reagents effects high yields of products. For arylation of triflates, boronic acids afford better results than the corresponding boronic esters (eq 92), and 9-alkyl-9-BBN derivatives are recommended as the best reagents for alkylation. The catechol esters of 1-alkenylboronic acids usually work more effectively than the corresponding boronic acids and disiamyl or dicyclohexyl derivatives (eq 91).[206]



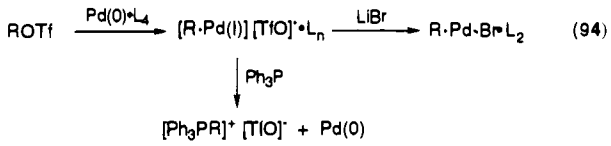

(91)

(92)

(93)

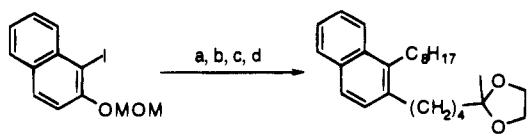
Although good yields are achieved for five- and six-membered cyclization by the intramolecular cross-coupling reaction of haloalkenes (eq 89), the scope of the reaction is still limited by the availability of haloalkenes, particularly due to the lack of a simple method for preparing cyclic haloalkenes from ketone precursors. The ready availability of triflates from carbonyl compounds now offers a valuable tool for annulation of ketones (eq 93).[206] Since the synthesis of the compounds having a metal and a leaving group in the same molecule is rather difficult by other methods, the hydroboration-coupling approach provides an efficient way for such cyclization *via* the intramolecular coupling.

The coupling with triflates often fails to proceed due to the decomposition of catalysts, precipitating palladium black at the early stage of reaction.[206,207] Presumably, triphenylphosphine used as a ligand of palladium reacts with triflates to give phosphonium salts (eq 94).[208] Addition of 1 equiv of lithium or potassium bromide is effective in preventing such a decomposition of the catalyst, which is known to convert the labile cationic palladium(II) species to organopalladium(II) bromide.[209] Lithium chloride or potassium chloride is less effective, though LiCl has been used in most cases.[184,207]




(94)

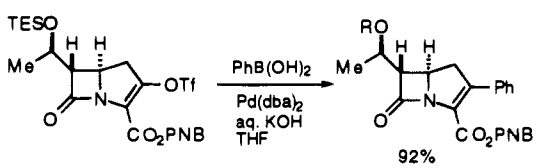
The order of reactivity of halides and triflates for the cross-coupling reaction of boron reagents is I > Br > OTf ≫ Cl. Thus, the sequential cross-coupling reaction of 4-bromophenyl triflate with two 9-alkyl-9-BBN derivatives, obtained from two different alkenes, furnishes the unsymmetrically disubstituted benzenes. However, an alternative and presumably reliable method to introduce two different organic groups to benzene rings is a stepwise double cross-couplings with iodophenol derivatives (eq 95).[151,206]




(95)

[a]9-Octyl-9-BBN/$PdCl_2$(dppf)/$K_3PO_4$ in THF, reflux. [b]HCl/MeOH, [c]NaH/$Tf_2O$. [d]9-[$MeC(O_2C_2H_4)(CH_2)_4$]-9-BBN/$PdCl_2$(dppf)/$K_3PO_4$ in THF, reflux

Ready availability of cycloalkenyl triflates from ketone precursors is superior to the synthesis of corresponding halides. The syntheses of arylated cycloalkenes[184,210] and 2-substituted carbapenem (eq 96)[211] have been achieved in excellent yields by the reaction with triflates.



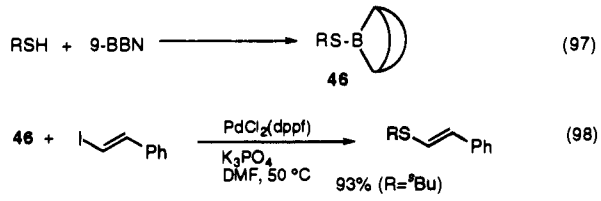

(96)

## E. Synthesis of Vinylic Sulfides

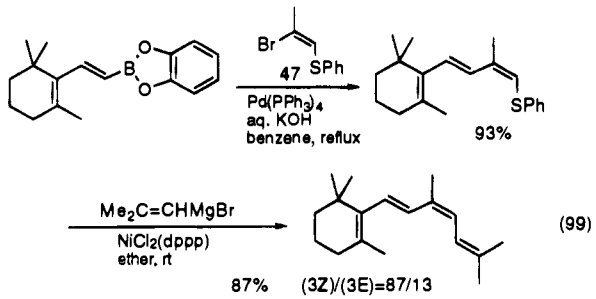
1-Alkenyl sulfides are valuable intermediates for the synthesis of ketones or aldehydes by hydrolysis with mercury(II) chloride,[212] the synthesis of 1-alkenyl sulfoxides[213] which can serve as dienophiles in the Diels–Alder reaction or as Michael acceptors, and

the synthesis of a variety of alkenes and dienes *via* the nickel-catalyzed cross-coupling reaction[214] of the C–S bond with Grignard reagents. However, there are only a few stereoselective syntheses of 1-alkenyl sulfides. The coupling reactions of 1-alkenyl halides with thioalkoxides in the presence of a transition-metal catalyst provide vinylic sulfides in excellent yields with high stereoselectivity.[6,215] Another route to vinylic sulfides involves cross-coupling reactions between (β-alkylthio)alkenyl halides and alkyl, aryl, and 1-alkenylmagnesium halides.[214] Wittig and related methods unfortunately provide a mixture of stereoisomers.[216]

The cross-coupling reaction of 9-(organothio)-9-BBN derivatives (**46**) with 1-alkenyl and aryl halides proceeds in excellent yields (eq 98).[217] The reaction can be carried out under milder conditions than those of analogous reactions using lithium or tin thioalkoxides.

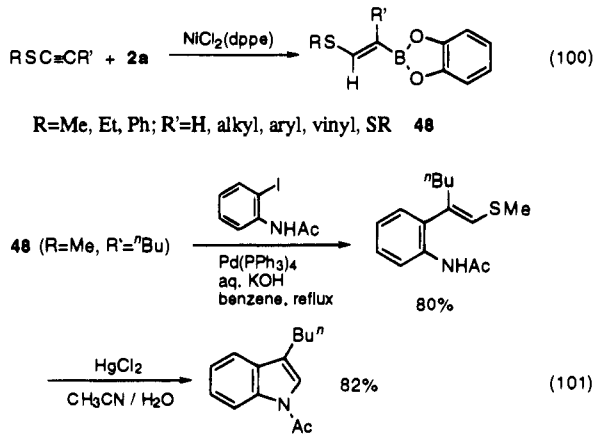



(*E*)- and (*Z*)-1-bromo-2-(phenylthio)alkenes (**47**) are efficient building blocks for the synthesis of stereodefined 1-alkenyl sulfides by the cross-coupling reaction with organoboron compounds (eq 99).[118,218] The sulfides **47** have several advantages in terms of their practical use for cross-coupling reaction. (*E*)- and (*Z*)-**47** are readily available and most importantly, both stereoisomers are readily separable by chromatography. The rate of coupling with the carbon–bromine bond is reasonably faster than that with the carbon–sulfur bond, which completely avoids the formation of the symmetrical coupling product.



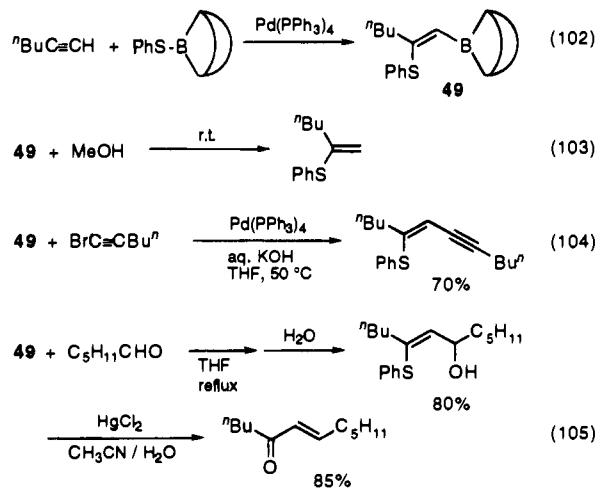

The sequential double cross-coupling of vinylboronates and vinylmagnesium reagents provides an alternative method for synthesis of conjugated polyenes (eq 99).[118] Unfortunately, a mixture of stereoisomers is given on the latter nickel-catalyzed reaction.[214] The possibility of improving catalytic conditions has not yet been explored.

The ready availability of 2-(organothio)-1-alkenylboron compounds obtained by catalytic hydroboration of 1-(organothio)-1-alkynes (eq 100)[27b] or thioboration[92] of 1-alkynes (eq 102) now offers more flexible and reliable routes to such stereodefined alkenyl sulfides in combination with the cross-coupling reaction with organic halides.




The hydroboration of thioalkynes with diorganoboranes predominantly gives vinylborane intermediates by the addition of boron atom at the carbon adjacent to the organothio group. However, the catalytic hydroboration of thioalkynes with catecholborane in the presence of $NiCl_2$(dppe) or $Pd(PPh_3)_4$ allows a complete reversal of the regiochemical preference providing **48**, the regioselectivity of which is over 98% (eq 100).[27b] The reaction is synthetically complementary to the catalytic hydrostannylation of thioalkynes providing 1-(organothio)-1-alkenylstannanes.[219] A vinylic sulfide is synthetically equivalent to a carbonyl compound. Thus, the cross-coupling products obtained from *o*-iodoacetoanilide derivatives are readily converted into indoles by treatment with aqueous mercury(II) chloride (eq 101).[27c]

When a solution of terminal alkyne and 9-RS-9-BBN in THF is heated at 50 °C for 3 h in the presence of $Pd(PPh_3)_4$ (3 mol %), the *cis* addition of the B–S bond to alkyne proceeds regio- and stereoselectively (eq 102).[92] Although the adduct **49** is too susceptible to C–B bond breaking or stereochemical isomerization during isolation, its *in situ* preparation and subsequent cross-coupling reaction with organic halides gives a variety of alkenyl sulfides retaining their original configuration of alkenylboron reagents (eq 104).[92]



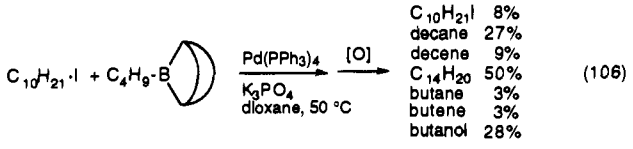

The vinylborane **49** has unusually high nucleophilicity due to the activation by an electron-donating β-organothio group. Consequently, protodeboronation proceeds instantaneously with methanol to

provide the thiol adducts regioselectively[92] (eq 103). Although ketones are quite inert to **49**, the addition to aldehydes at 50 °C, followed by the mercury(II)-induced hydrolysis gives an enone (eq 105).[220]

## F. Coupling with Iodoalkanes: Alkyl–Alkyl Coupling

Although a wide variety of organic electrophiles, such as aryl, 1-alkenyl, benzyl, allyl, and 1-alkynyl halides, have been utilized for the palladium-catalyzed cross-coupling reactions, it has been considered that such reactions cannot be extended to alkyl halides with $sp^3$ carbon having $\beta$-hydrogens due to the slow rate of oxidative addition of alkyl halides to palladium(0) complexes and the fast $\beta$-hydride elimination from $\sigma$-alkylpalladium intermediates in the catalytic cycle. Thus, the use of alkyl halides as coupling partners is a challenging problem in several recent publications. Although Castle and Widdowson[221] had recently reported that Pd(dppf), formed *in situ* by the reduction of $PdCl_2$(dppf) with DIBAL, effectively catalyzes the cross-coupling reaction of iodoalkanes with Grignard reagents, this unique reaction has been denied most recently by Yuan and Scott.[222]

Among the catalysts we examined for the cross-coupling reaction between 9-alkyl-9-BBN with primary iodoalkanes, the palladium complex with triphenylphosphine as ligand is recognized to be most effective (eq 106).[223] The best yield is obtained when

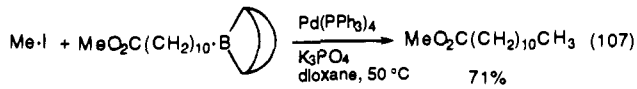


(106)

the reaction is conducted at 60 °C for 24 h by using 3 mol % of $Pd(PPh_3)_4$ and $K_3PO_4$ (3 equiv) in dioxane. Although $PdCl_2$(dppf) is reported as a selective catalyst to avoid $\beta$-hydride elimination for alkyl couplings, the complex does not act as an efficient catalyst in the present reaction. Other bidentate ligands such as dppe, dppp, and dppb also give low yields of coupling products. Such bidentate ligands may retard the step of reductive elimination because the reductive elimination from dialkylpalladium(II) proceeds from an unsaturated, three-coordinated species (eq 25), in contrast to the coupling with aryl or vinyl derivatives which can proceed through a four-coordinated saturated complex (eq 24).[57]

The difficulty of alkyl–alkyl coupling reaction is mainly due to the formation of alkane at the step of oxidative addition of iodoalkane to Pd(0) complex. The $\beta$-elimination during the steps of transmetalation and reductive elimination is a minor process. The formation of reduction products (decane in eq 106) can be mainly due to the involving radical oxidative addition process (see section VI).[53]

The available results indicate that the cross-coupling reaction of 9-alkyl-, 9-phenyl-, or 9-(1-alkenyl)-9-BBN gives 50–60% yields of products when using 50% excess of primary iodoalkanes and higher yields around 80% when using iodomethane (eqs 107 and 108).[223]



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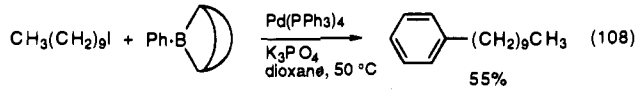
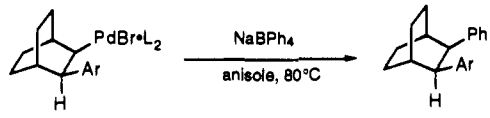


(108)

It is reported that the cycloalkylpalladium(II) bromide intermediate, which is produced by Heck reaction of norbornene with bromoarenes, couples with tetraphenylborate (eq 109).[224] However, the reaction with secondary iodoalkanes does not provide coupling products, presumably due to a very rapid $\beta$-hydride elimination.

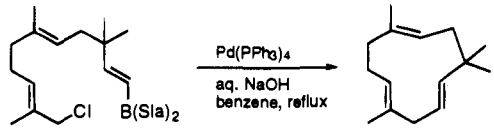


(109)

The cross-coupling with inactivated alkyl halides is still difficult to achieve in high yields with palladium-catalyst, but the potentiality and synthetic utility thus suggested should be explored in the future. The coupling reaction with alkyl halides by a $LiCuCl_4$ catalyst is perhaps a more general alternative, although the reaction is still limited to Grignard reagents.[3b,e]

## G. Coupling with Other Organic Halides and Boron Reagents

Hydroboration of alkynes with disiamylborane, followed by cross-coupling with allylic or benzylic halides in the presence of $Pd(PPh_3)_4$ and aqueous NaOH produces 1,4-alkadienes or allylbenzenes in high yields.[96,225] In the reaction with 1-bromo-2-butene, the bond formation occurs at two positions (the ratio of straight to branched is 72:28) in accordance with a mechanism involving $\pi$-allyl palladium intermediate.[225] The reaction has been applied in a short step synthesis of humulene (eq 110).[226] The cross-couplig reaction of 1,3-disubstituted allyllic carbonates with aryl- and alkenylborates are catalyzed by $NiCl_2$(dppf), and the reaction proceeds with inversion for the cyclic carbonate (eq 111).[227] The stereochemistry indicates the process involving the oxidative addition with inversion and the arylation from the same face of the palladium.



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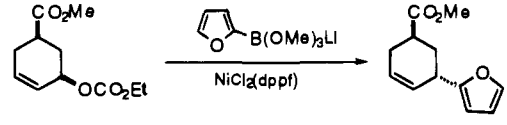
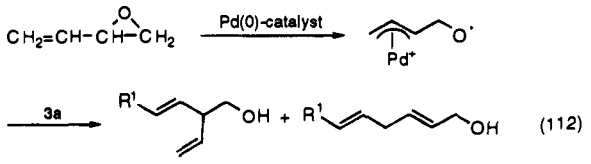


(111)

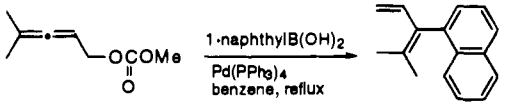
1-Alkenylboranes react with 3,4-epoxy-1-butene in the presence of palladium or nickel complexes to form internal and terminal coupling products with high regioselectivity in same cases (eq 112).[71] The ratio of two dienols can be reversed by changing the metal

complexes. The reaction proceeds under neutral conditions in good agreement with the mechanism through an (alkoxo)palladium(II) complex (**20** in eq 32).



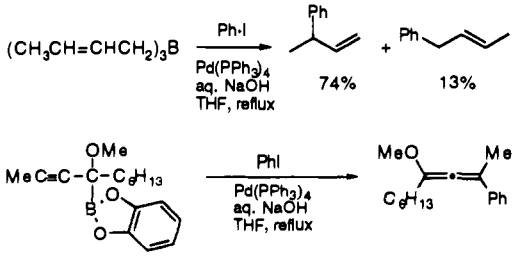

(112)

As discussed in the previous section, propargylic carbonates couple with aryl, 1-alkenyl-, 1-alkynyl-, or alkylboron compounds under neutral conditions using palladium catalyst to provide allenes in high yields (eq 36).[72] A similar coupling reaction of organoboron compounds with 2,3-alkadienyl carbonates produces 2-substituted 1,3-butadiene derivatives in the absence of base (eq 113).[228] The coupling may occur through an (alkoxo)palladium(II) intermediate formed *via* oxidative addition by $S_N2'$ type displacement with Pd(0), thus allowing the reaction under neutral conditions.




(113)

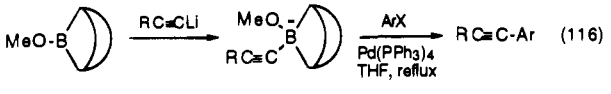
Allylic, benzylic, and propargylic boron derivatives are considered to be not useful for the cross-coupling reaction because these reagents are highly sensitive to protodeboronation with water or alcohols. However, it is interesting to note that these boron reagents provide the coupling products in high yields even in an aqueous medium. The $Pd(PPh_3)_4$-catalyzed reaction of tri(crotyl)borane with iodobenzene in the presence of aqueous NaOH in refluxing THF gives two coupling products in a 87% total yield (eq 114).[229] The cross-coupling reaction of propargylborates, prepared *in situ* from alkyl-1,3,2-benzodioxaboroles and (α-lithiomethoxy)-1,2,3-butatriene, produces the allene product through the 1,3-rearrangement, presumably at the step of transmetalation (eq 115).[230]




(114)

(115)

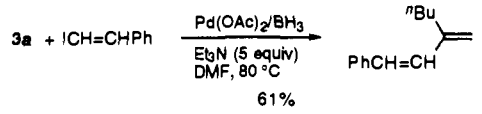
Only one example is reported for the cross-coupling reaction of 1-alkynylboron compounds. Methoxy(alkynyl)borates *in situ* prepared by addition of 9-methoxy-9-BBN to alkynyllithiums undergo efficient cross-coupling with aryl or 1-alkenyl halides to produce various alkynes (eq 116).[231]




(116)

## V. Head-to-Tail Coupling

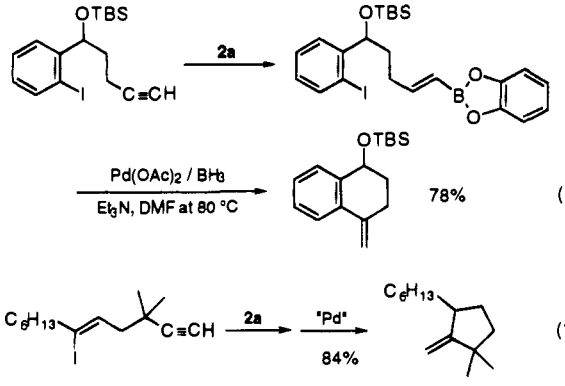
The reaction of phenyl or 1-alkenyl iodides with 1-alkenylboronic esters produces the unusual "head-to-tail" cross-coupling products in good yields (eqs 28 and 117)[70,232] through the mechanism shown in Figure 2.




(117)

The reaction is catalyzed by palladium black prepared *in situ* by the reduction of $Pd(OAc)_2$ in the presence of an excess of triethylamine in DMF. The use of phosphine-based palladium complexes and strong bases such as NaOEt, NaOH, and NaOAc may improve the formation of "head-to-head" coupling product (Table 1).

The intramolecular reaction affords a convenient method for the synthesis of (exomethylene)cycloalkenes (eqs 118 and 119).[233]




(118)

(119)

## VI. Carbonylative Coupling

Carbonylative cross-coupling reactions of organic halides with organometallic compounds, such as organotin,[234] boron,[235,236] aluminum,[237] and zinc[238] reagents have been extensively studied and reported to provide excellent methods for the synthesis of unsymmetrical ketones or aldehydes. The general catalytic cycle for this carbonylative coupling reaction is analogous to the direct coupling except that carbon monoxide insertion takes place after the oxidative addition step and prior to the transmetalation step (Figure 13).

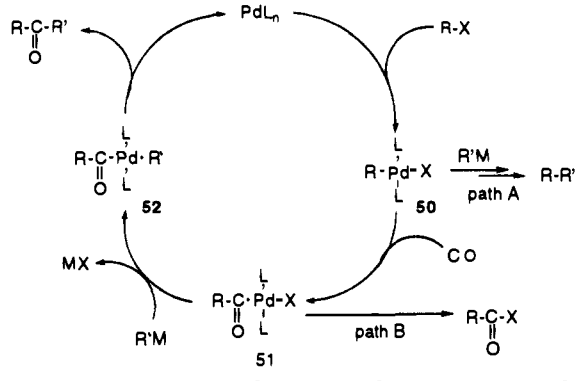
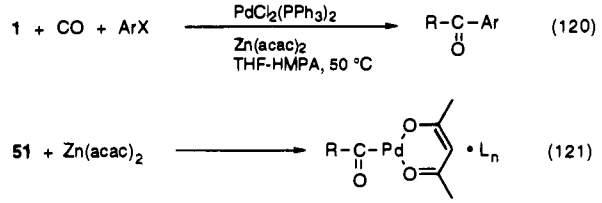
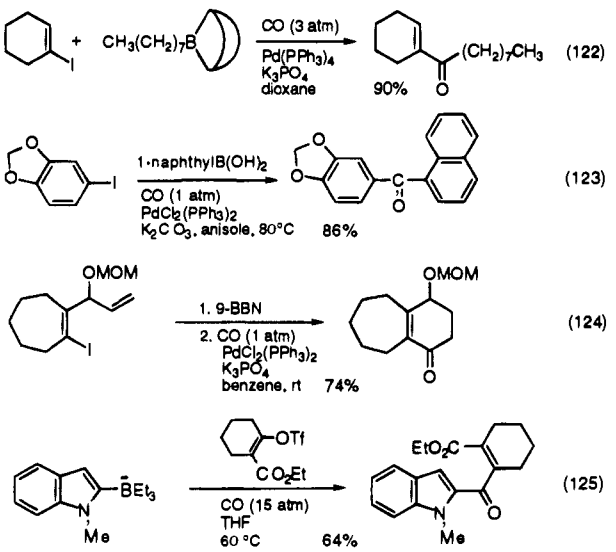



**Figure 13.** Mechanism for carbonylative cross-coupling.

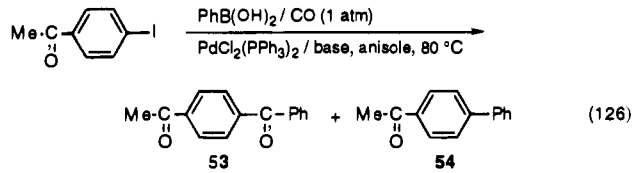
Among a variety of organometallics, organoboron compounds were first used by Kojima for the synthesis of alkyl aryl ketones (eq 120).[235] The action of $Zn(acac)_2$ in this reaction is ascribed to the formation of $RCOPd^{II}(acac)$ species (eq 121) which undergoes transmetalation without assistance of bases (eq 32).




A general carbonylative cross-coupling can be readily carried out using $K_2CO_3$ or $K_3PO_4$ as a base. Alkyl 1-alkenyl and alkyl aryl ketones are synthesized by the reaction of 9-alkyl-9-BBN with 1-alkenyl or aryl iodides in the presence of $Pd(PPh_3)_4$ and $K_3PO_4$ (eq 122).[239] For the synthesis of biaryl ketones, the cross-coupling reaction between arylboronic acids, carbon monoxide, and iodoarenes in anisole takes place at 80 °C in the presence of $PdCl_2(PPh_3)_2$ and $K_2CO_3$ (eq 123).[240] The hydroboration–carbonylative coupling sequence is extended to intramolecular reaction to afford cyclic ketones (eq 124).[239] The ate complexes obtained from α-lithioindoles and triethylborane are carbonylated and coupled with aryl iodides, alkenyl iodides, or cycloalkenyl triflates to provide a simple route to 2-indolyl ketones (eq 125).[241]



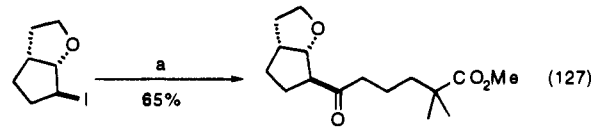

Although the reaction works well for iodoarenes and 1-iodo-1-alkenes having electron-donating groups, the application to the electron-deficient iodides is severely limited due to the side reaction forming direct coupling products without carbon monoxide insertion (Figure 13, path A). Namely, the presence of an electron-withdrawing group retards the insertion of carbon monoxide into the RPd(II)X intermediates, and it reversely accelerates the rate of transmetalation to generate the $R-Pd^{II}-R'$ species. The use of carbon monoxide under high pressure is a general method for suppressing such a side reaction.[234] Another efficient procedure involves the control of the rate of transmetalation to be sufficiently slower than that of carbon monoxide insertion by changing the organometallic reagents. The reaction of organoboron reagents can be controlled by choosing an appropriate base and a solvent to permit the selective coupling even under an atmospheric pressure of carbon monoxide (eq 126).[240]




Base (53/54)= $K_2CO_3$ (88/12), $Cs_2CO_3$ (75/25), $K_3PO_4$ (65/35)

The use of organic iodides is essential to achieving high yields. Organic bromides provide appreciable amounts of direct coupling products since the transmetalation of **50** (X = Br) with organoboron reagents is faster than the corresponding iodides (path A in Figure 13). In all of these reactions, some of the carboxylic acid derivatives formed from path B can be commonly observed.[239,240]

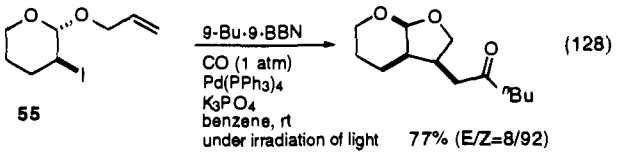
The cross-coupling reaction has been currently developed; however, such reactions are limitedly applicable to 1-alkenyl, 1-alkynyl, aryl, allyl, and benzyl halides and not being extended to alkyl halides with $sp^3$ carbon containing β-hydrogen, as discussed in the previous section. The problem of β-hydride elimination is not serious in the carbonylation reaction because the insertion of carbon monoxide converts them to the acylpalladium(II) halides. Thus, various iodoalkanes including primary, secondary, and tertiary iodides are carbonylated and coupled with 9-R-9-BBN in the presence of $K_3PO_4$ and a catalytic amount of $Pd(PPh_3)_4$ yielding unsymmetrical ketones in good yields (eq 127).[242] The reaction is extremely accelerated by irradiation of sunlight.




[a] 9-[$MeO_2CCMe_2(CH_2)_3$]-9-BBN / CO (1 atm) / $Pd(PPh_3)_4$ / $K_3PO_4$ / benzene, rt under irradiation of light

A particularly interesting feature in this transformation is that oxidative addition proceeds through the radical process; presumably, it is initiated by an electron transfer from palladium(0) complex to iodoalkanes to form a radical pair ($Pd^IX + R^•$).[53] Thus, the iodoalkenes provides cyclized ketones *via* a sequence of radical cyclization, carbon monoxide insertion, and the coupling with 9-R-9-BBN (eqs 128 and 129).[243] The cyclization is generally not stereoselective, but the reaction of **55** proceeds with high *endo* selectivity due to the anomeric effect which prefers the transition state (**56**) shown in eq 129.[244]

As isocyanides are isoelectronic with carbon monoxide, they might be expected to exhibit a similar insertion reaction. However, they have not been used for the cross-coupling reaction. The difficulty is mainly due to its tendency to cause multiple insertions to transition metal complexes leading to poly-

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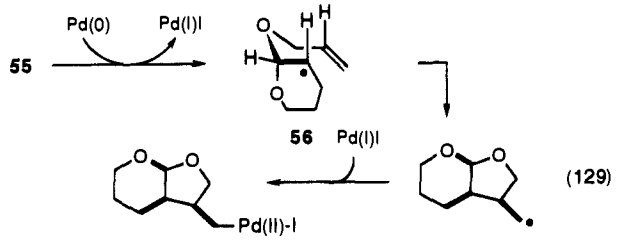
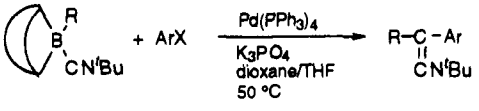



(129)

isocyanides. The 9-alkyl-9-BBN reacts with isocyanide to form a relatively stable 1:1 complexes which readily participates in the cross-coupling reaction catalyzed by palladium. The complexes are successfully used for the iminocarbonylative cross-coupling reaction of 9-alkyl-9-BBN derivatives with haloarenes (eq 130).[245]




(130)

## VII. Alkoxycarbonylation and Dimerization

Unlike the cross-coupling reaction discussed above, the palladium-catalyzed alkoxycarbonylation of organoboron compounds proceeds through the transmetalation of organic group on boron to palladium(II) atom, CO insertion into the C–Pd bond, and finally the reductive elimination to the products and Pd(0). Thus, suitable reoxidants of palladium(0) to palladium (II) are required to recycle the palladium catalyst (Figure 14). *p*-Benzoquinone in the presence of LiCl selectively oxidizes the palladium(0) complex in the presence of aryl- or 1-alkenylboronic esters.[246]

Under atmospheric pressure of carbon monoxide, 1-alkenylboronates are carbonylated at 50 °C in the presence of $PdCl_2$, NaOAc, *p*-benzoquinone, and LiCl in methanol (eqs 131 and 132).[247] The stereochemistry of 1-alkenylboronates can be retained over 99%. The hydroboration–carbonylation sequence cleanly provides terminal esters in contrast to the direct alkoxycarbonylation of terminal alkynes with carbon monoxide and alcohol in the presence of transition-metal catalyst.

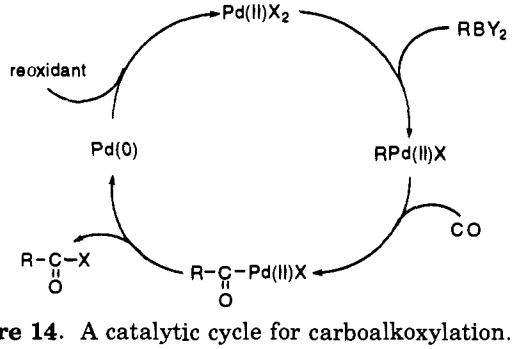
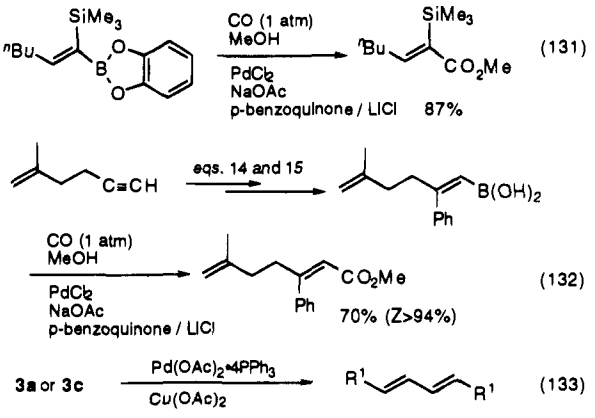



**Figure 14.** A catalytic cycle for carboalkoxylation.




(131)

(132)




(133)

In the presence of a catalytic amount of $Pd(OAc)_2$ and $Cu(OAc)_2$ as a reoxidant, 1-alkenylboronates readily dimerize in methanol to give symmetrical dienes (eq 133).[95] Although the blank test indicates that the dimerization proceeds to some extent in the absence of palladium catalyst, a few mole percent of $Pd(OAc)_2$ may greatly improve the yield of diene. Symmetrical biaryls can also be obtained from arylboronic acids.

## VIII. Conclusion

The cross-coupling reaction of organoboron reagents with organic halides or related electrophiles represents one of the most straightforward methods for carbon–carbon bond formation. The reaction proceeds under mild conditions, being largely unaffected by the presence of water, tolerating a broad range of functionality, and yielding nontoxic byproducts. Consequently, the cross-coupling reaction of organoboron reagents has been realized in significant and diverse applications not only in academic laboratories but also in industries. In view of retrosynthetic analysis, the reaction is conceptually basic and important for construction of carbon framework of target molecules. The scope of the palladium-catalyzed cross-coupling reaction of the representative organoboron compounds with organic halides are summarized in Figure 15.

A very wide range of aryl- and 1-alkenylboron reagents undergo the palladium(0)-catalyzed reactions with alkyl, allylic, 1-alkenyl, aryl, and 1-alkynyl substrates. Allylic halides react with aryl- and 1-alkenylboron reagents, but alkyl- and allylboron reagents fail to give the corresponding coupling products; presumably because the reductive elimination from $\sigma$-alkyl-$\pi$-allyl- or di-$\pi$-allylpalladium(II) complexes is very slow to develop the catalytic

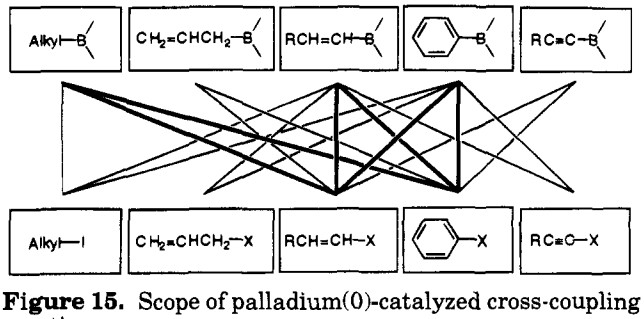



**Figure 15.** Scope of palladium(0)-catalyzed cross-coupling reaction.

cycle.[248] Since the palladium-catalyzed cross-coupling reaction of allylic metals or halides often suffers from poor regioselectivity, the corresponding cross-coupling reaction of organocopper reagents can be a more general alternative. Primary iodoalkanes couple with alkyl-, 1-alkenyl-, and arylboron reagents, but secondary and tertiary iodoalkanes are limitedly used for the carbonylative cross-coupling. The cross-coupling of 1-alkynylboron compounds has been used much less frequently as the direct cross-coupling reaction of terminal alkynes with aryl and alkenyl halides in the presence of a palladium catalyst, copper(II) iodide, and a secondary or tertiary amine (Sonogashira reaction)[249] is more convenient in most cases.

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