Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds

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I. Introduction

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

\[
\text{R-M} + \text{R'-X} \xrightarrow{\text{Pd-catalyst}} \text{R-R'}
\]

In 1972, Kumada and Tamao¹ and Corriu² reported independently that the reaction of organonitrogen reagents with alkynyl or aryl halides could be markedly catalyzed by Ni(II) complex. Kochi³ found the efficiency of Fe(III) catalyst for the cross-coupling of Grignard reagents with 1-halo-1-alkenes and Li₂CuCl₄ 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 Negishi⁵ 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 Migita⁷ and Stille,⁸ 1-alkenylcopper(I) by Normant,⁹ organosilicon compounds by Hiyama.¹⁰ These reac-

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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]). 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), magnesium(II), aluminum(II), tin(IV), copper(I), and mercury(II) halides have been extensively studied. In 1978, Negishi reported that iodobenzene selectively couples with the 1-alkynyl group on lithium 1-hexynyltributylborate through a palladium-catalyzed addition-elimination sequence (Heck-type process), 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. 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.

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 (eq 2 and 3). The first stereocontrolled synthesis of alkylboronic acids and esters involves the reaction of a (Z)- or (E)-2-buten-2-ylmagnesium bromide with trimethyl borate (eq 4).

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 boronic 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). Trisopropyl 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). 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. 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). The hydroboration with 2a can also be carried out under milder conditions by using palladium, rhodium, or nickel catalysts.

The hydroboration of alkynes with dihaloboranes (HBCl2,SMgBr or HBBR2,SMgBr), followed by hydrolysis to vinylboronic acids or alcoholysis to boronic esters (3b) have been used for the same purpose. However, a recent and more convenient variant is the in situ preparation of HBCl2 in a hydrocarbon solvent from BCl3 and HSiEt3. The reagent exhibits extremely high reactivity to alkene and alkyne allowing the hydroboration to proceed at -78°C. Disiamylborane (2c) is also one of the mildest and selective hydroboration reagents for...
Reactions of Organoboron Compounds

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 \( \text{g-[(E)-1-alkenyll-9-BBN derivatives (3d) in high yields with high trans selectivity.}^{30} \)

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.\(^{38,39} \)

C. Haloboration of Terminal Alkynes

Terminal 2,2-diorgano-1-alkenylboronates (9) are made by bromoboration of a terminal alkyne to \( \beta \)-bromo-1-alkenylboronic ester (8) (eq 14),\(^{37} \) followed by the palladium-catalyzed displacement of the \( \beta \)-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-alkenylboronates (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(borylmethanes. The (E)/(Z) isomeric ratio is
reported to be $\sim 20:1$ (eq 17). On the other hand, a trimethylsilyl analog gives a cis-rich isomer ($\sim 70:30$) on reaction with aldehydes (eq 18). The reaction of lithiotriborylmethane with aldehydes or ketones yields 1,1-alkenyldiborates (eq 19).

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

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

The addition of diboron compounds to alkynes is an excellent method for the synthesis of cis-diboryl alkenes (eq 23). 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$_4$ or Sn–B$_4$ 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.

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.

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. It is significant that the great majority of cross-coupling reactions catalyzed by Ni(0), Pd(0), and Fe(II) are rationalized in terms of this common catalytic cycle.

Oxidative addition of 1-alkenyl, 1-alkynyl, allyl, benzyl, and aryl halides to a palladium(0) complex affords a stable trans-$\alpha$-palladium(II) complex (11). The reaction proceeds with complete retention of configuration for alkyl 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 $\alpha$-organopalladium(II) species. However, it has been recently shown that iodoalkanes undergo the cross-coupling reaction with organoboron compounds (sections IV.F and VI).

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-chloroanone 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. Palladium complexes that contain fewer than four phosphine ligands or bulky phosphines such as tris(2,4,6-tri-
methoxyphenyl)phosphine are, in general, highly reactive for the oxidative addition because of the ready formation of coordinate unsaturated palladium species.

Reductive elimination of organic partners from 12 reproduces the palladium(0) complex. 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 π-orbital of aryl group during the bond formation (eq 24). Although the step of 1-alkenyl- or 1-alkenylpalladium(II) complexes is not studied, the similar effect is observed in the reductive elimination of related platinum(II) complexes.59

![Chemical Structure](image)

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).58b

The formation of normal coupling product 13 can be best understood by the mechanism of Heck reaction for vinyllic metal compounds, that often predominates on the cross-coupling reaction of weakly active aryl groups.

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

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Base</th>
<th>Time, h</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd[PPh₃]₂</td>
<td>benzene</td>
<td>none</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Pd[PPh₃]₂</td>
<td>benzene</td>
<td>NaOEt (2)</td>
<td>2</td>
<td>99 (100/0)</td>
</tr>
<tr>
<td>Pd[PPh₃]₂</td>
<td>benzene</td>
<td>NaOH (2)</td>
<td>2</td>
<td>99 (100/0)</td>
</tr>
<tr>
<td>Pd[PPh₃]₂</td>
<td>DMF</td>
<td>Et₄N (5)</td>
<td>20</td>
<td>54 (10/90)</td>
</tr>
<tr>
<td>Pd[PPh₃]₂</td>
<td>DMF</td>
<td>Et₄N (5)</td>
<td>20</td>
<td>66 (8/92)</td>
</tr>
<tr>
<td>Pd black</td>
<td>DMF</td>
<td>Et₄N (5)</td>
<td>20</td>
<td>94 (4/96)</td>
</tr>
<tr>
<td>Pd black</td>
<td>DMF</td>
<td>NaOH (2)</td>
<td>6</td>
<td>88 (56/44)</td>
</tr>
</tbody>
</table>

All reactions were carried out at 80 °C by using Pd catalyst (3 mol %), PhI (1 equiv), base, and 3a (1.1 equiv).
nucleophilic organometallics, such as 1-alkenylmercury,\textsuperscript{67} -silanes,\textsuperscript{68} and -tin compounds.\textsuperscript{69}

Organopalladium(II) halides add mainly to the electron-deficient carbon of unsymmetrical alkene\textsuperscript{66} to give 15, which readily isomerizes to 16 via a sequence of elimination and readdition of the hydrido-palladium(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 P-hydrogen transfers to the terminal carbon (Figure 2).\textsuperscript{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 alkoxide.\textsuperscript{71} 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\textsuperscript{65b}, 1,3-butadiene monoxide\textsuperscript{71}, and propargyl carbonates\textsuperscript{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.

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.\textsuperscript{12} In fact, it is reported that such ate complexes undergo a clean coupling reaction with organic halides.\textsuperscript{51} 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.\textsuperscript{73}

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.\textsuperscript{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)\textsubscript{3}\textsuperscript{−}, 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 \( \approx 7-8.5 \) is retarded relative to the reaction at pH \( \approx 9.5-11.7 \).\textsuperscript{75} The \( pK_a \) of phenylboronic acid is 8.8, thus suggesting the formation of the hydroxyboronate anion \( [RB(OH)\textsubscript{3}\textsuperscript{−}] \) at pH \( > pK_a \) and its transmetalation to the palladium(II) halides. The formation of \( ArB(OH)\textsubscript{3}\textsuperscript{−} \) at pH \( \approx 11-12 \) has been recently reported.\textsuperscript{76}

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

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).

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).\textsuperscript{65b,78} Thus, the (\( \tau \)-allylphenoxo)– and (\( \tau \)-
allylacetoxo)palladium(II) intermediates generated by oxidative addition may undergo transmetalation without bases. The isolated complexes of (η⁶-C₃H₅)PdX react with 1-alkenylborates to give the coupling products when the ligand X is OAc or acetylacetonato (aca). 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 β-elimination occurs very quickly to give the hydridopalladium(I) species and carbonyls. 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. The (hydroxo)palladium complex recently reported by Alper also gives a cross-coupling product (70%) together with biphenyl (15%) (eq 35).

Tsuij and co-workers have shown that propargylic carbonate 22 oxidatively adds to the palladium(0) complex to provide an (alkoxo)palladium intermediate with elimination of carbon dioxide (eq 36). 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. 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 p value (+0.73), demonstrating that electron-withdrawing substituents accelerate the reaction (eq. 38 and Figure 3).

These electronic effects are consistent with the S₆₂ (coord) mechanism involving a coordination of the alkoxy ligand to the boron atom at the rate-determining step. As a result of complex formation, the transfer of an activated organic group from boron to palladium then takes place (eq 38) (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 or -tinate and palladium(II) halides, the S₆₂ (cyclic) or S₆₂ (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), which have been postulated as

\[
\begin{align*}
\text{RCH=CHCH₂OX} & \xrightarrow{3a (R' = 'Bu)} \text{BuCH=CHCH₂CH₃} \quad \text{(33)} \\
\text{Cl} \quad \text{Cl} & \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \\
\text{X=COMe; R=Ph (12%), X=Ph; R=H (75%)} \\
\text{Cl} \quad \text{Cl} & \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \\
\text{X=Cl (0%), X=OMe (79%)} \\
\text{Ph} \quad \text{Pd-Oh} & \xrightarrow{\text{p-MeOC₆H₄(B(OH))₂}} \text{THF, rt} \quad \text{70%} \\
\text{22 (R=Me)} & \xrightarrow{3a} \text{BuCH=CHCH₂CH₃} \quad \text{(34)} \\
\text{R'BrX} & \xrightarrow{\text{RCBX₂}} \text{R'BrX} \quad \text{(36)} \\
\text{22 + Ph-PdOH₂} & \xrightarrow{\text{p-MeOC₆H₄(B(OH))₂}} \text{THF, rt} \quad \text{70%} \\
\text{22: R=Me (78%), Et (76%), Bu (47%), Ph (12%)} \\
\text{22 (R=Me) + X} & \xrightarrow{\text{24 (R' = p-XC₆H₄)}} \text{(38)} \\
\text{Rel. rate: MeO (0.7), Me (0.9), H (1.0), F (1.7), MeCO (2.6)}
\end{align*}
\]

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

**Figure 4.** S₆₂ (coord) transition state.
reaction intermediates\textsuperscript{65} or isolated\textsuperscript{78,80} 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).\textsuperscript{66} The cross-coupling reaction with haloenones is accelerated by exceptionally weak bases such as NaOAc or even EtsN, 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 \textit{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).\textsuperscript{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(I) bromide with KOAc gives a trans-Ph\textsubscript{2}PdOAc(PPh\textsubscript{3})\textsubscript{2} (29)\textsuperscript{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 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).\textsuperscript{88}

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.\textsuperscript{90} Although the related reactions of boron compounds are not yet well developed, the Rh-, Pd-, or Ni-catalyzed hydroboration of alkenes\textsuperscript{27} and alkynes\textsuperscript{27b} (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).\textsuperscript{91m} Asymmetric hydroboration of styrene is achieved using a bidentate chiral ligand (eq 44).\textsuperscript{91l} Hydroboration of 1,3-butadiene stereoselectively affords a (Z)-crotylboronate with a palladium(0) complex (eq 45). The PdCl\textsubscript{2}(dppf) and NiCl\textsubscript{2}(dppe) or -(dppp) complexes afford good results for the hydroboration of alkynes (eq 46).\textsuperscript{91k}

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).\textsuperscript{92} The addition of (alkoxy)diboron to alkynes to give cis-bis(aryl)alkenes (diboration) is catalyzed by a platinum(0) catalyzt\textsuperscript{47} (eq 23). The additions proceed regioselectively in favor of terminal boron adducts to produce (Z)-1-alkenylboron compounds through a \textit{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, Y2B) to the transition-metal complex [M(0)] to form X-M-BY2 species (32), followed by the migratory \textit{cis} insertion of alkenes or alkynes into the X-M bond, and finally the reductive
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The oxidative adducts such as B–Rh–H and B–Ir–H intermediates in the catalytic hydroboration, and the B–Pt–B intermediate 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 carbynylation and the homo coupling of aryl- or vinylmercurials. Similar reaction type such as dimerization, protolysis of the C-B bonds (eq 48), and Heck-type addition (eq 49) of aryl- or alkylboronic 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.

IV. Cross-Coupling Reaction

A. Coupling of 1-Alkenylboron Derivatives: Synthesis of Conjugated Dienes

The first observation to prepare conjugated dienes is shown in eq 50. 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(PPh3)2 and PdCl2(PPh3)2. In general, a combination of Pd(PPh3)2 and sodium ethoxide works satisfactorily for the coupling with 1-bromo-1-alkenes, and PdCl2(PPh3)2 and aqueous sodium hydroxide for 1-iodo-1-alkenes. The use of palladium catalyst without phosphine ligand or weak bases (KOAc or Et3N) has a tendency to be contaminated by undesired head-to-tail coupling product.

The reaction can be carried out in aqueous media by using water-soluble phosphine palladium catalyst.
Although disiamyl- or dicyclohexylborane is a selective and efficient hydroboration reagent of alkenes, 1-alkenyldialkylboranes thus obtained give relatively poor yields of coupling products (~50%) with low stereoselectivity. 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. 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 iodo- benzene are shown in Table 3.

Thus, the oxidation of the two boron-sp³ 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). 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(PPh₃)₄ and an aqueous NaOH (eq 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). The palladium and base-assisted coupling of each five and 11 units stereoselectively provides bombykol and its three geometrical isomers (eqs 58-61).

\[
\text{Table 3. Reaction of (Z)-BuCH=CHBX_2 with PhI}\]

<table>
<thead>
<tr>
<th>BX₂</th>
<th>yield, %</th>
<th>isomeric purity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>-B(Sia)₂</td>
<td>58</td>
<td>&gt;94</td>
</tr>
<tr>
<td>-B(OPr)₂</td>
<td>98</td>
<td>&gt;97</td>
</tr>
</tbody>
</table>

* A mixture of Pd(PPh₃)₄ (3 mol %), 2 M NaOEt in EtOH (2 equiv), PhI (1 equiv), and (Z)-BuCH=CHBX₂ (1.1 equiv) in benzene was refluxed for 3 h. Yields of (Z)-BuCH=CHPh.
Reactions of Organoboron Compounds

Table 4. Synthesis of Dienes and Trienes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkenylboron Reagent</th>
<th>Alkenyl Halide</th>
<th>Reaction Conditions, catalyst/base/solvent/temp.</th>
<th>Product</th>
<th>Yield/%</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅=v-B</td>
<td>Br =Ph</td>
<td>Pd(PPh₃)₄/NaOEt/benzene/reflux</td>
<td>C₆H₅-CH=CH-Ph</td>
<td>86 (&gt;98)</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅=v-B</td>
<td>Br =C₆H₆</td>
<td>Pd(PPh₃)₄/NaOEt/benzene/reflux</td>
<td>C₆H₅-CH=CH-C₆H₆</td>
<td>X = Sia 49 (&gt;98)</td>
<td>102</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅=v-B</td>
<td>Br =C₆H₄</td>
<td>Pd(PPh₃)₄/aq. KOH/benzene/reflux</td>
<td>C₆H₅-CH=CH-C₆H₄</td>
<td>X = OPd</td>
<td>97 (&gt;99)</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₅=v-B</td>
<td>Br =CH₃</td>
<td>Pd(PPh₃)₄/aq. NaOH/THF/reflux</td>
<td>C₆H₅-CH=CH-CH₃</td>
<td>70 (&gt;99)</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Bu =Bu</td>
<td>CH₃</td>
<td>Pd(PPh₃)₄/aq. NaOH/THF/reflux</td>
<td>Bu =Bu</td>
<td>87 (&gt;99)</td>
<td>105</td>
</tr>
<tr>
<td>6</td>
<td>(Pr)₂Si=v-B</td>
<td>CH₃</td>
<td>Pd(PPh₃)₄/aq. NaOH/THF/reflux</td>
<td>(Pr)₂Si=v-B</td>
<td>85 (-)</td>
<td>106a</td>
</tr>
<tr>
<td>7</td>
<td>C₆H₅=v-B</td>
<td>Br =CH₃</td>
<td>Pd(PPh₃)₄/aq. NaOH/THF/reflux</td>
<td>C₆H₅-CH=CH-CH₃</td>
<td>40 (-)</td>
<td>113a,b</td>
</tr>
<tr>
<td>8</td>
<td>C₆H₅=v-B</td>
<td>Br =Ph</td>
<td>Pd(PPh₃)₄/NaOEt/benzene/reflux</td>
<td>C₆H₅-CH=CH-Ph</td>
<td>87 (-)</td>
<td>117</td>
</tr>
<tr>
<td>9</td>
<td>C₆H₅=v-B</td>
<td>Br =SPh</td>
<td>Pd(PPh₃)₄/aq. NaOH/benzene, reflux</td>
<td>C₆H₅-CH=CH-SPh</td>
<td>91 (&gt;98)</td>
<td>118</td>
</tr>
<tr>
<td>10</td>
<td>C₆H₅=v-B</td>
<td>Br =C₆H₄</td>
<td>Pd(PPh₃)₄/NaOEt/benzene/reflux</td>
<td>C₆H₅-CH=CH-C₆H₄</td>
<td>89 (&gt;94)</td>
<td>115</td>
</tr>
<tr>
<td>11</td>
<td>C₆H₅=v-B</td>
<td>Br =B(SiMe₃)₂</td>
<td>Pd(PPh₃)₄/NaOEt/benzene/reflux</td>
<td>C₆H₅-CH=CH-B(SiMe₃)₂</td>
<td>52 (-)</td>
<td>116</td>
</tr>
</tbody>
</table>

Roush, Nicolaou, and Evans have also demonstrated the efficiency of thallium hydroxide on the synthesis of an aglycone of antibiotic kijanimicin, chlorothricolide, (5Z,8Z,10E,12R,14Z)-12-hydroxy-5,8,10,14-icosatetraenoic acid [(12R)-HETE], and a macrolide antibiotic rutamycin B. 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.

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 B₄ shown in eq 62. Due to the
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).\textsuperscript{126}

A reverse combination of 1-alkenylboronates and l-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 this combination for synthesis of the conjugated pentaene (eq 63).\textsuperscript{127}

\[ \beta\text{-Halo-}\alpha,\beta\text{-unsaturated ketones and esters are highly susceptible to S_N2 displacement at the carbon attached to halogen, thus strong bases are undesirable for such substrates.} \textsuperscript{86,128\textendash}131 \text{ However, relatively weak bases, such as sodium acetate and even triethylamine, are effective when the reaction is conducted in alcohol solvents (eqs 40 and 64).} \textsuperscript{86} \text{ Sodium acetate suspended in methanol, and aqueous or solid carbonate in ethanol give best results for haloenones}\textsuperscript{86} \text{ and haloesters,}\textsuperscript{129} \text{ respectively. PdCl}_2\textsuperscript{(PPh}_3)_2 \text{ or a combination of Pd(OAc)\textsubscript{2} plus PPh}_3\text{ (4 equiv) is desirable to achieve high yields. The cis/ trans isomerization is rarely observed in the palladium-catalyzed cross-coupling, but the reaction with (Z)-}\beta\text{-bromoacrylate gives a mixture of stereoisomers. PdCl}_2\textsuperscript{(dppf)} \text{ is effective for carrying out the reaction at room temperature in order to depress the isomerization during the coupling (eq 65).} \textsuperscript{129} \]

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

\[
\text{3e} + \text{BrCCl}_2 \xrightarrow{\text{Pd(OAc)}_2\cdot 2\text{PPh}_3} \text{NaOMe-MeOH benzene, reflux} \rightarrow \frac{1}{R^1} + \frac{1}{R^2} \text{yield % (66)}
\]

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

\[
\text{3ab} + \text{ArX} \xrightarrow{\text{Pd(OAc)}_2\cdot 2\text{PPh}_3} \text{NaOMe-MeOH benzene, reflux} \rightarrow \frac{1}{R} + \frac{1}{Ar} \text{yield % (67)}
\]

The relative reactivity appears to be \( \text{PhI} > \text{p-ClC}_6\text{H}_4\text{Br} > \text{PhBr} > \text{o-MeC}_6\text{H}_4\text{Br} > \text{o-MeOC}_6\text{H}_4\text{Br} \).133 The order of reactivity is in good agreement with substituent effect in the oxidative addition of aryl halides to the palladium(0) complex,22 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

Cyclodehydration of 2-hydroxy- or 2-aminobenzenoethanal 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 areneethanal.

\[
\text{3} \xrightarrow{\text{EtOCH}=\text{CH}} \text{BH}_3 \rightarrow \text{EtOCH}=\text{CH}_2\text{B} (69)
\]

\[
\text{EtOCCr} + 2\text{a} \xrightarrow{\text{Pd(PPh)}_3} \text{NaOH THF, reflux} \rightarrow \text{EtOCCr} (70)
\]

\[
\text{43} (\text{R}=\text{Me}) \xrightarrow{\text{1-iodonaphthalene} \text{Pd(PPh)}_3} \text{NaOH THF, reflux} \rightarrow \text{OEt} \text{OMOM} (71)
\]

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 styrly ethers in high yields in the presence of Pd(PPh)_3 and powdered NaOH suspended in THF. 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 dealkoxylolation with polyphosphoric acid (PPA) at 100 °C (eq 71).138

Conversion of haloarenes to areneethenal 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 biaryl is shown in eq 72.140 After this discovery, various modifications have been made for the reaction conditions. A combination of Pd(PPh)_3 or PdCl(2)(PPh)_2 and aqueous Na_2CO_3 in dimethoxyethane (DME) works satisfactorily in most cases.141,142

\[
\text{B(OCH}_2)_2 + X \rightarrow \text{Z} \rightarrow \text{NK 104 (68)}
\]

The combination with other bases such as Et,N, NaHCO_3, NaH, Na_2CO_3, THF, and K_2PO_4 with or without Bu_4NCl and 18-crown-6 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 readily 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. The coupling is also carried out in an aqueous medium by using water-soluble phosphine ligand ($m$-Na$_3$SC$_6$H$_4$PPh$_2$). 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$_4$NF (eq 31) allow the synthesis of various functionalized biaryls (eq 73).\footnote{Miyaura and Suzuki}

\[
\text{PhB(OH)$_2$ + PhBr} \xrightarrow{\text{Pd(PPh$_3$)$_4$}} \text{PhCH$_2$COCH$_3$}
\] (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)$_2$, [(t$_2$-C$_3$H$_5$)PdCl$_2$, and Pd$_2$(dba)$_3$. Phosphine-free palladiums are approximately 1 order of magnitude more active than ArPd$_3$PPh$_6$, both of which are in turn markedly more active than Pd(PPh$_3$)$_4$ (eq 74).

\[
\text{PhB(OH)$_2$ + PhNO$_2$} \xrightarrow{\text{catalyst: Pd(PPh$_3$)$_4$}} \text{PhCH$_2$COOH}
\] (74)

Although steric hindrance of aryl halides not a major factor for the formation of substituted 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).\footnote{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$_2$PO$_4$ > Na$_2$CO$_3$ > NaHCO$_3$.}

\[
\text{pd(PAr)$_3$, aq. Na$_2$C$_3$O$_3$ DME} \xrightarrow{\text{MeO-}} \text{Ar-X}
\] (75)

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 substituted bithienyls and thienylpyridines can be regioselectively synthesized by the cross-coupling reaction of thienylboronic acids (eq 78). Arylation of 5-bromonicotinates is demonstrated by Thompson (eq 79). Diethyl(3-pyridy1)borane synthesized by Terashima is a unique air-stable reagent for the heteroarylation (eq 80).
The ready availability of ortho-functionalized arylboronic acids by directed ortho-metallation-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. The utility of the sequence has recently shown by the industrial-scale synthesis of a nonpeptide angiotensin II receptor antagonist (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, ferrocene derivatives, bis-cyclolementating N-C-N hexadentated ligands, helically chiral ligands, michellamine, biphenomycin A, vancomycin, receptor molecules for oxo-leukotriene B4 receptor antagonist, hemispherand, l,l'-bi-2-naphthol, fascaplysin and streptonigrin alkaloids, ungerimine and hippadine alkaloids, and other biaryls. Some of examples are summarized in Figure 10.

Aromatic, rigid-rod polymers play an important role in a number of diverse technologies including high-performance engineering materials, conducting polymers, and nonlinear optical materials. The cross-coupling reaction of arylboronic acids and dihaloarenes for the synthesis of poly(p-phenylenes) was first reported by Schütter. The method has been extensively applied to monodisperse aromatic dendrimers, water-soluble poly(p-phenylene), planar poly(p-phenylenes) fixed with the ketoimine bonds, poly(phenylenes) fused with polycyclic aromatics, and nonlinear optical materials (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, 6-(alkoxy carbonyl)aminol-1-bromocyclohexene, 1-iodo-3,4,6-tri-O-(triisopropylsilyl)-D-glucal, and the bromoalkene precursor for (Z)-tamoxifen synthesis are achieved by the cross-coupling reaction of arylboronic acids. Arylcycloalkenes are prepared by the cross-coupling with corresponding triflates (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, 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. A combination of PdCl₂(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 K₂CO₃ or Cs₂CO₃ suspended in DMF at 50 °C in the presence of PdCl₂(dppf) catalyst. Pd(PPh₃)₄ catalyst works well when aqueous NaOH in benzene or Cs₂CO₃ in dioxane are used. The characteristic features of both catalysts are that PdCl₂(dppf) is used well in polar solvents (e.g., THF and DMF), but Pd(PPh₃)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. Thus, representative hydroboration reagents, such as 9-BBN, disiamylborane, bicyclohexylborane, 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. 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, for example, in the synthesis of dihydroxyserrulatic acid (Figure 12), the aggregation pheromone of Cathartus quadricollis (quadrilure), and aza-C-disaccharides.

A three-step, three-component synthesis of PGE₁ 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).

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 of haloalkenes or syntheses of allylic and propargylic silanes (eq 88).

The intramolecular cross-coupling proceeds especially smoothly when the cyclization results in the formation of either five- or six-membered rings. 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); (2)-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 organoboranes 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 Tl₂CO₃ and PdCl₂(dppf), although the reaction is limitedly used for activated halides having an electron-withdrawing group. A sequence of the Rh(I)-catalyzed hydroboration of allyl acetone and the cross-coupling with haloenones produces diketones in 62–69% yields (eq 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 with aluminum and zinc 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. The cross-coupling reaction of organic triflates is previously reviewed.

Although relatively strong bases such as aqueous NaOH and NaOEt in ethanol have been used for the reaction with halides, powdered K3PO4 suspended in THF or dioxane is sufficient enough to accelerate the coupling of 9-alkyl-9-BBN, 1-alkenyl-, and aryloborates with the triflates. PdCl2(PPh3)4 in dioxane at 65 °C is less effective than PdCl2(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 boronate esters (eq 92), and 9-alkyl-9-BBN derivatives are recommended as the best reagents for alkylation. The catechol esters of 1-alkenylboronates usually work more effectively than the corresponding boronic acids and disiamyl or dicyclohexyl derivatives (eq 91).

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). 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. Presumably, triphenylphosphine used as a ligand of palladium reacts with triflates to give phosphonium salts (eq 94). 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. Lithium chloride or potassium chloride is less effective, though LiCl has been used in most cases.

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).

The ready availability of cycloalkenyl triflates from ketone precursors is superior to the synthesis of corresponding halides. The syntheses of arylated cycloalkenenes and 2-substituted carbapenem (eq 96) have been achieved in excellent yields by the reaction with triflates.

E. Synthesis of Vinylic Sulfides

1-Alkenyl sulfides are valuable intermediates for the synthesis of ketones or aldehydes by hydrolysis with mercury(II) chloride, the synthesis of 1-alkenyl sulfoxides 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 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. Another route to vinylic sulfides involves cross-coupling reactions between (β-alkylthio)alkenyl halides and alkyl, aryl, and 1-alkenylmagnesium halides. Wittig and related methods unfortunately provide a mixture of stereoisomers.

The cross-coupling reaction of 9-(organothio)-9-BBN derivatives (46) with 1-alkenyl and aryl halides proceeds in excellent yields (eq 98).117 The reaction can be carried out under milder conditions than those of analogous reactions using lithium or tin thioalkoxides.

\[
RSH + 9-BBN \rightarrow RS-B
\]  
(97)

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

\[
RSC=CR' + 2e^{-} + \text{NiCl}_{2}(dpp) \rightarrow RS-B + \text{R'COCH}_{3}
\]  
(100)

\[R = \text{Me, Et, Ph; R'} = \text{H, alkyl, aryl, vinyl, SR}
\]

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\(_{2}\)(dpp) or Pd(PPh\(_{3}\))\(_{4}\) allows a complete reversal of the regiochemical preference providing 48, the regioselectivity of which is over 98% (eq 100). The reaction is synthetically complementary to the catalytic hydrostannylation of thioalkynes providing 1-(organothio)-1-alkenylstannanes. A vinylic sulfide is synthetically equivalent to a carbonyl compound. Thus, the cross-coupling products obtained from o-iodoacetanilide 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). Although the adduct 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

\[
\text{PhS} + \text{RCH} = \text{CH}_2 + \text{HgCl}_2 \rightarrow \text{RCH} = \text{CH}_2 \text{CH} = \text{CH}_2 \text{PhS} \quad \text{85%}
\]  
(105)
provide the thiol adducts regioselectively\(^\text{(eq 103)}\). Although ketones are quite inert to \(^\text{49}\), the addition to aldehydes at 50 °C, followed by the mercury(II)-induced hydrolysis gives an enone (eq 105),\(^\text{220}\)

### 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 \(\alpha\)-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\(^\text{221}\) had recently reported that Pd(dpp0, formed \textit{in situ} by the reduction of PdCl\(_2(dpp0\) with DIBm, effectively catalyzes the cross-coupling reaction of iodoalkanes with Grignard reagents, this unique reaction has been denied most recently by Yuan and Scott.\(^\text{222}\)

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).\(^\text{223}\) The best yield is obtained when the reaction is conducted at 60 °C for 24 h by using 3 mol % of Pd(PPh\(_3\))\(_4\) and K\(_{3}PO\(_4\) (3 equiv) in dioxane. Although PdCl\(_2(dpp0\) 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(I) 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).\(^\text{57}\)

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 transmetallation and reductive elimination is a minor process. The formation of reduction products (decane in eq 106) can be mainly due to the involvement of radical oxidative addition process (see section VI).\(^\text{53}\)

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).\(^\text{223}\)

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

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.\(^\text{33,56}\)

### 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 allylbzenes in high yields.\(^\text{96,225}\) 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.\(^\text{225}\) The reaction has been applied in a short step synthesis of humulene (eq 110).\(^\text{226}\) The cross-coupling reaction of 1,3-disubstituted allylic carbonates with aryl- and alkenylborates are catalyzed by NiCl\(_2(dpp0\), and the reaction proceeds with inversion for the cyclic carbonate (eq 111).\(^\text{227}\) The stereochemistry indicates the process involving the oxidative addition with inversion and the arylation from the same face of the palladium.

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).\(^\text{71}\) 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).

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). 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). The coupling may occur through an (alkoxo)palladium(II) intermediate formed via oxidative addition by S2,2 type displacement with Pd(0), thus allowing the reaction under neutral conditions.

 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(PPh₃)₄-catalyzed reaction of tri(croty1)borane with iodobenzene in refluxing THF gives two coupling products in a 87% total yield (eq 114). The cross-coupling reaction of propargyborates, prepared in situ from alkyl-1,3,2-benzodioxaboroles and (a-lithiomethoxy)-1,2,3-butatriene, produces the allene product through the 1,3-rearrangement, presumably at the step of transmetallation (eq 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).

V. Head-to-Tail Coupling

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

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).

VI. Carbynylatve Coupling

Carbynylatve cross-coupling reactions of organic halides with organometallic compounds, such as organotin, boron, aluminum, and zinc 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 carbynylatve coupling reaction is analogous to the direct coupling except that carbon monoxide insertion takes place after the oxidative addition step and prior to the transmetallation step (Figure 13).

Figure 13. Mechanism for carbynylatve cross-coupling.
Among a variety of organometallics, organoboron compounds were first used by Kojima for the synthesis of alkyl aryl ketones (eq 120). The action of Zn(acac)₂ in this reaction is ascribed to the formation of RCOPd(acac) species (eq 121) which undergoes transmetalation without assistance of bases (eq 32).

A general carbonylative cross-coupling can be readily carried out using K₂CO₃ or KH₂PO₄ 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(PPh₃)₄ and K₂PO₄ (eq 122). 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 PdCl₂(PPh₃)₂ and K₂CO₃ (eq 123). The hydroboration-carbonylative coupling sequence is extended to intramolecular reaction to afford cyclic ketones (eq 124). The ate complexes obtained from α-lithioindoles and triethylborane are carbonylated and coupled with aryl iodides, alkyl iodides, or cycloalkenyl triflates to provide a simple route to 2-indolyl ketones (eq 125).

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. 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). 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.

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 sp³ 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 K₂PO₄ and a catalytic amount of Pd(PPh₃)₄ yielding unsymmetrical ketones in good yields (eq 127). The reaction is extremely accelerated by irradiation of sunlight.

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'X = Br). Thus, the iodoalkanes provides cyclized ketones via a sequence of radical cyclization, carbon monoxide insertion, and the coupling with 9-R-9-BBN (eqs 128 and 129). 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 shown in eq 129. 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-
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).246

**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-Benzoinone 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 PdCl2, 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.

![Diagram](attachment:diagram.png)

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

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). 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 allyl- and alkyloboron reagents fail to give the corresponding coupling products; presumably because the reductive elimination from α-alkyl-α-allyl- or di-α-allylpalladium(II) complexes is very slow to develop the catalytic
cycle. 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 (Sonogashira reaction) is more convenient in most cases.

References


A mixture of alkyne and 2a (1.1 equiv) in benzene was heated for 5 h at 60 °C. After the solvent was evaporated, the residue was dissolved in DMF and then treated with Pd(OAc)$_2$ (5 mol %) and Et$_3$N (2.5 equiv) for 14 h at 80 °C: Miyaura, N.; Suzuki, A.; unpublished results.


