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**Cross-Coupling Reaction of Organoboron Compounds via Base-Assisted
Transmetalation to Palladium(II) Complexes**

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Abstract

Until recently, organoboronic acids have been of limited use in organic synthesis due to their low reactivity for ionic reactions. During the past two decades; however, it has become increasingly clear that they are valuable reagents capable of undergoing many carbon-carbon bond formations in organic syntheses. In 1979, catalytic carbon-carbon bond formation, via transmetalation between organoboron compounds and palladium(II) halides, was found to proceed in the presence of a base.

1 Historical Perspectives

Although organoboronic acids are highly advantageous as reagents in

laboratories and industries because they are largely unaffected by the presence of water, tolerate a broad range of functionalities, and yield nontoxic by-products, the boron-carbon bond is highly inert to ionic reactions. Transmetalation to other metals, especially to transition metals, is one promising process that enables the carbon-carbon bond formation by using organoboronic acids [1-3]. The interaction between 1-hexenylboronic acid and palladium(II) acetate was first demonstrated by Heck [4]. *In situ* preparation of (*E*)- or (*Z*)-1-alkenylpalladium(II) acetate *via* transmetalation was followed by its conjugate addition to ethyl acrylate (Scheme 1). Negishi found that boron-ate complexes such as lithium 1-alkynyltributylborate can participate in Pd-catalyzed cross-coupling [5, 6]. Heck-type addition-elimination mechanism was proposed because other types of lithium tetraalkylborates, such as alkyl-, alkenyl-, and aryl derivatives, were unreactive. In spite of these previous observations, it was very difficult to use organoboron compounds to the palladium-catalyzed cross-coupling reaction; thus, an alternative and two-step procedure involving transmetalation of trialkylboranes to alkylmagnesium halides was developed by Murahashi [7].

<<Scheme 1>>

In 1976, we attempted a stoichiometric reaction between trialkylboranes and π -allylpalladium(II) chloride [8]. However, our first attempt failed because the reaction resulted in the exclusive formation of β -hydride elimination products. It was interesting that trialkylboranes readily alkylate π -allylpalladium(II) chloride without the assistance of a base immediately precipitating palladium black; however, a major process was β -elimination even in the presence of triphenylphosphine or an aqueous base, which

was in sharp contrast to the selective cross-coupling of Grignard reagents previously reported by Kumada-Tamao [9] and Kochi [10]. Although it was later found that aryl- and 1-alkenylboron compounds smoothly undergo cross-coupling with allyl halides [1g, i], alkylmetals possessing β -hydrogens were the worst choice because of the much slower reductive elimination from the σ -alkyl- π -allylpalladium(II) complex than that of σ -aryl- or σ -alkenyl derivatives.

<<Scheme 2>>

In 1979, we first reported the direct cross-coupling reaction of 1-alkenylboronic esters and 1-bromo- or 1-iodo-1-alkenes in the presence of a base as well as a palladium catalyst (Scheme 3) [11].

<<Scheme 3>>

Various bases accelerated the reaction; however, relatively strong bases such as sodium alkoxides or aqueous alkaline metal hydroxides were found to be most efficient for the vinyl-vinyl coupling. Later, a remarkably high accelerating effect of TIOH was demonstrated by Kishi in the synthesis of Palytoxin [12]. On the other hand, relatively weak bases such as aqueous NaHCO_3 and Na_2CO_3 mediated the biaryl coupling reaction of arylboronic acids [2 and 13]. The choice of a suitable base has played a more important key role than that of a palladium catalyst, since smooth transmetalation was always critical for such metalloids with low nucleophilicity. The protocol has been proved to be a quite general technique for a wide range of selective carbon-carbon bond formations, including the coupling reactions of 1-alkenyl-, aryl-, alkyl-, allyl-, benzyl-, 1-alkynyl-, and diboron compounds (Scheme 4). Palladium- or

nickel-catalyzed cross-coupling reactions of organoboron compounds, their mechanisms, and their synthetic applications have been reviewed elsewhere [1-3].

<<Scheme 4>>

2 Base-Assisted Transmetalation

A catalytic cycle for the cross-coupling reaction of organoboron compounds involves oxidative addition-transmetalation-reductive elimination sequences. 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. Although the mechanisms of oxidative addition and reductive elimination sequences are reasonably well understood and these are presumably common fundamental processes for all cross-coupling reactions of organometallics, little is known about the transmetalation process. The addition of sodium hydroxide or other bases exerts a remarkable accelerating effect on the transmetalation between R-Pd-X and trialkylboranes or organoboronic acids, which is quite different from the related reactions of other organometallics. Although organoboronic acids are highly inert to R-Pd-X (X=halogen), ate-complexes such as $[\text{RC}\equiv\text{CBR}_3]\text{Li}$ [6], R_4BLi [1g], $[\text{ArBR}_3]\text{Li}$ [1g], Ph_4BNa [14, 15], $[\text{R}_3\text{BOMe}]\text{Na}$ [16], $[\text{ArB}(\text{R})(\text{OR})_2]\text{Li}$ [17], and $[\text{ArBF}_3]\text{K}$ [18] readily couple with organic electrophiles in the presence of a palladium or nickel catalyst. Thus, quarternization of the boron atom with a negatively charged base enhances the nucleophilicity of the organic group on the boron atom for alkylation of R-Pd-X (6).

Although there is no direct evidence for analogous hydroxyboronate anions, RB(OH)_3^- (**7**), which exists in alkaline solution in equilibrium with a free organoboronic acid, could similarly alkylate R-Pd-X (**6**) (path A). The transmetalation to **1** decreasing in the order of $\text{Cl} > \text{Br} > \text{I}$ is the reverse of the oxidative addition of organic halides to palladium(0) complexes and is highly dependent on the counter cation of the added bases.

<<Scheme 5>>

An alternative process is transmetalation to an alkoxo-, hydroxo-, acetoxo-, or (acetylacetoxo)palladium(II) complex (**9**) *in situ* generated by the ligand exchange between R-Pd-X and a base ($\text{R}''\text{O}^-$) (path B). Such (oxo)palladium(II) complexes smoothly undergo transmetalation with organoboronic acids without the aid of a base. For example, methoxo- (**11**) [11c], hydroxo- (**12**) [19], and (acetoxo)palladium(II) complexes (**13**) [11c] give the corresponding coupling products upon treatment with an organoboron compound [Scheme 6]. The reaction of arylboronic acids with thiol esters assisted by $\text{R}''\text{CO}_2\text{Cu}$ as well as a palladium catalyst was recently found to occur under neutral conditions since the copper(I) carboxylate converts the $\text{RCO-Pd-SR}'$ intermediate to the corresponding $\text{RCO-Pd-O}_2\text{CR}''$ [20], as was demonstrated in carbonylative coupling in the presence of $\text{Zn}(\text{acac})_2$ [21]. Thus, the coupling reaction often proceeds under neutral conditions for organic electrophiles directly yielding such (oxo)palladium(II) species (**9**) *via* oxidative addition to a palladium(0) complex (path C). Cross-coupling reactions of allyl phenoxide [22], propargyl carbonates [23], 1,3-butadiene monoxide [24], and phenyl trifluoroacetate [25] were carried out in the

absence of a base. Such transmetalation may involve a rate-determining coordination of the R"O ligand to the boron atom [23]. As a result of complex formation (**5**), the transfer of an activated organic group from boron to palladium then takes place. High reactivity of the oxo-palladium complexes can be attributed to both the high basicity of the Pd-OR" species and the high oxophilicity of the boron center. The basicity of R-Pd-OH is not known, but related platinum complexes, such as PtH(OH)[P(*i*Pr)₂] or *trans*-Pt(OH)(Ph)(PPh₃)₂, have been reported to be more basic than NaOH [26]. On the other hand, the oxidative addition of Ph₂IX (X=BF₄, OTs, OTf) [27], PhI(OH)OTs [27], or ArN₂BF₄ [28] generating a cationic palladium species directly undergoes transmetalation with arylboronic acids, as was reported in a related reaction between [Pt(MeOH)₂(PPh₃)₂]²⁺ and PhB(OH)₂ [29].

<<Scheme 6>>

Available information suggests that there are two transmetalation processes (path A and path B) for the cross-coupling reaction of organoboron compounds in alkaline solution; however, it is not yet obvious in many reactions which process is predominant. We proposed path B for the cross-coupling reaction of bis(pinacolato)diboron with aryl, 1-alkenyl, and allyl halides or triflates in the presence of KOAc [30]. The treatment of *trans*-Pd(Ph)(Br)(PPh₃)₂ with KOAc gave *trans*-Pd(Ph)(OAc)(PPh₃)₂, which coupled with the diboron at room temperature yielding a phenylboronic ester. The presence of KOAc is critical for the coupling reaction of the diboron with allyl chlorides [31] (path B), whereas an analogous reaction of allyl acetates smoothly proceeded under neutral conditions since the oxidative

addition directly yields π -allylpalladium acetate [32] (path C). Recently, it has also been demonstrated by Soderquist that the reaction of 9-alkyl-9-BBN with iodobenzene in the presence of aqueous KOH proceeds through the former process (path A) and that the latter process (path B) is predominant in a less-acidic 9-oxa-10-borabicyclo[3.3.2]decane (**14**) [33]. The results indicate that there are three probable processes, but these are highly dependent on organoboron reagents, bases, and presumably also organic electrophiles and the functionality therein. A heterogeneous system consisting of an organic solvent and an aqueous base interferes with detailed mechanistic study.

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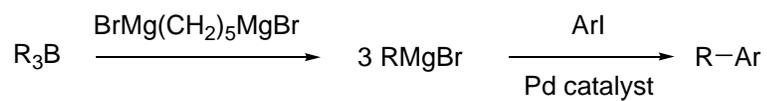
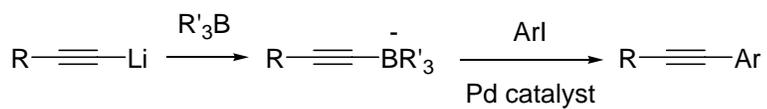
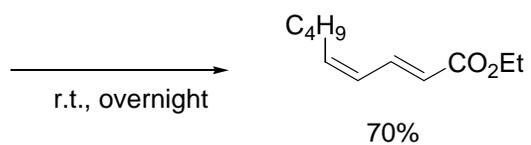
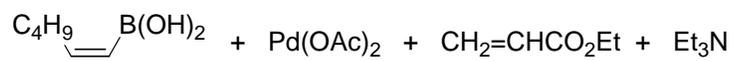
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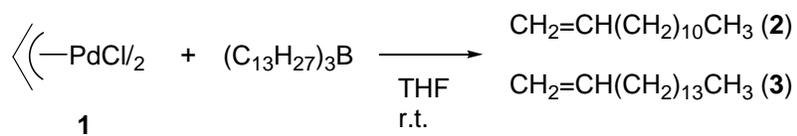
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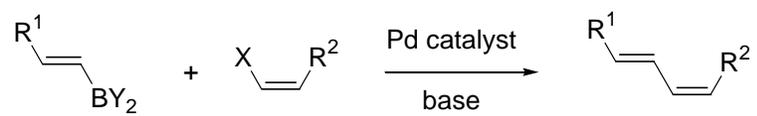


Scheme 1. Previous Observations



ligand	base	2 /%	3 /%
none	none	93	0
PPh ₃	none	80	11
PPh ₃	aq. NaOH	67	24

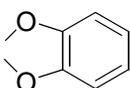
Scheme 2. Cross-Coupling with π -Allylpalladium Chloride



5a: $\text{Y}_2 = (\text{Sia})_2$ $\text{X} = \text{I}, \text{Br}, \text{OTf}$

5b: $\text{Y}_2 = (\text{OH})_2$

5c: $\text{Y}_2 = (\text{O}^i\text{Pr})_2$

5d: $\text{Y}_2 =$


Scheme 3. Cross-Coupling of Alkenylboron Compounds

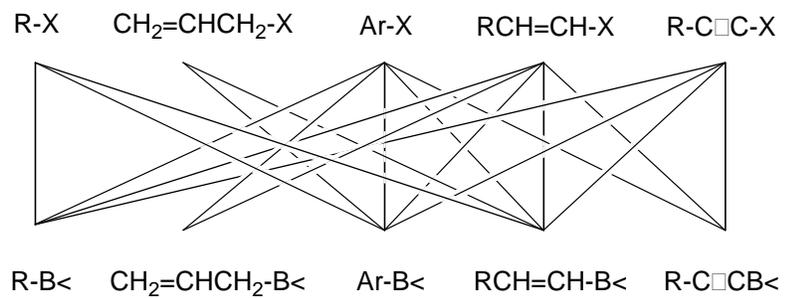
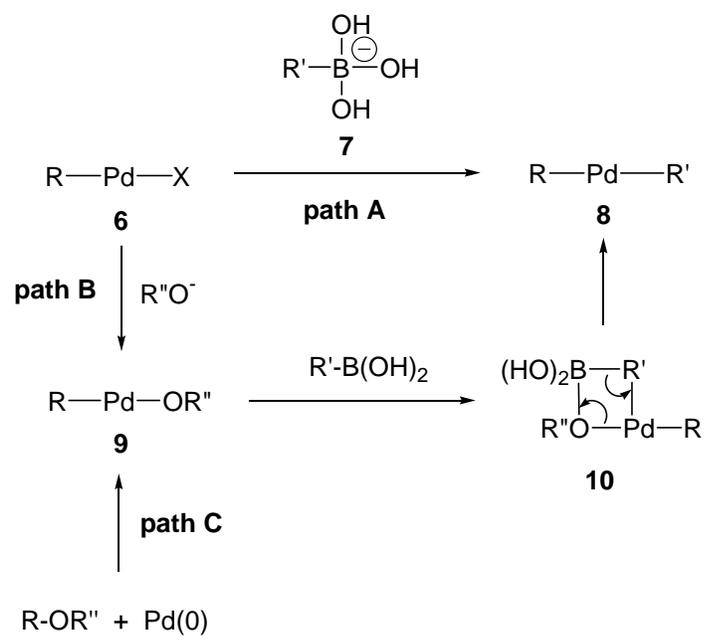
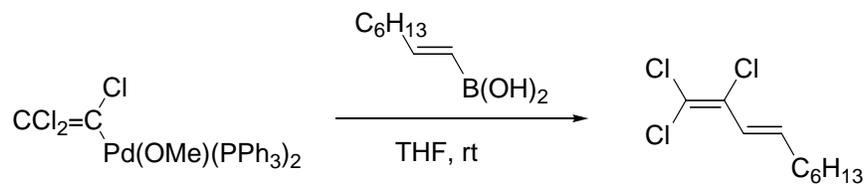


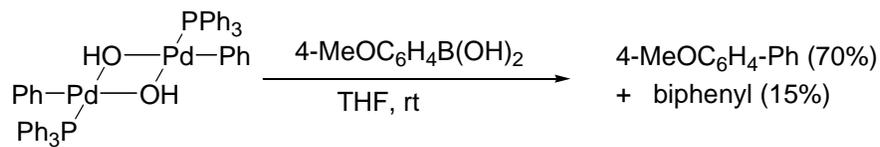
Figure 4. Scope of Reaction



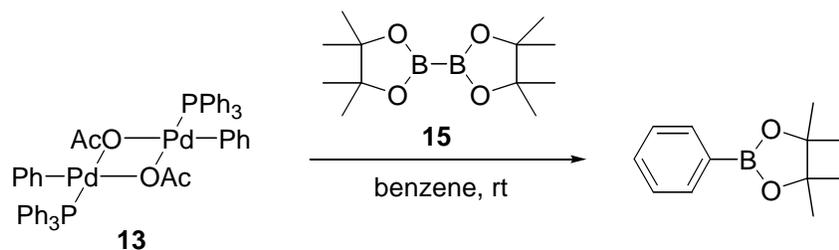
Scheme 5. Base-Assisted Transmetalation



11



12



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Scheme 6. Transmetalation to (Oxo)palladium(II) Complexes