

Chapter 2

Mechanisms and Fundamental Reactions

Masayuki Iwasaki and Yasushi Nishihara

Abstract It is widely accepted that the catalytic cycle of cross-coupling reactions of organometallic reagents with aryl halides catalyzed by transition metals consists of three fundamental processes: oxidative addition, transmetalation, and reductive elimination. Although the details of oxidative addition and reductive elimination have been extensively studied, little research on detailed mechanisms for transmetalation has been exploited until recently. In this chapter, recent examples of the transmetalation process (a transfer of organic groups to palladium) are generally outlined, vis-à-vis the intermediate complexes after transmetalation in Suzuki–Miyaura coupling and the effect of added copper salts in Migita–Kosugi–Stille coupling.

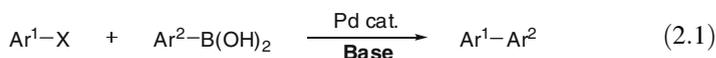
Keywords Reaction mechanism · Transmetalation · Suzuki–Miyaura coupling · Migita–Kosugi–Stille coupling · Copper effect

2.1 Transmetalation in Suzuki–Miyaura Coupling

The cross-coupling reactions of organometallic reagents with organic halides catalyzed by transition metals such as palladium and nickel are extremely useful and reliable methods for the construction of carbon–carbon bonds [1, 2]. The cross-coupling reactions can be applicable to a variety of organometallic compounds from Grignard reagents to organosilicon compounds. In particular, Suzuki–Miyaura coupling (as shown in Eq. 2.1) [3], using organoboron reagents

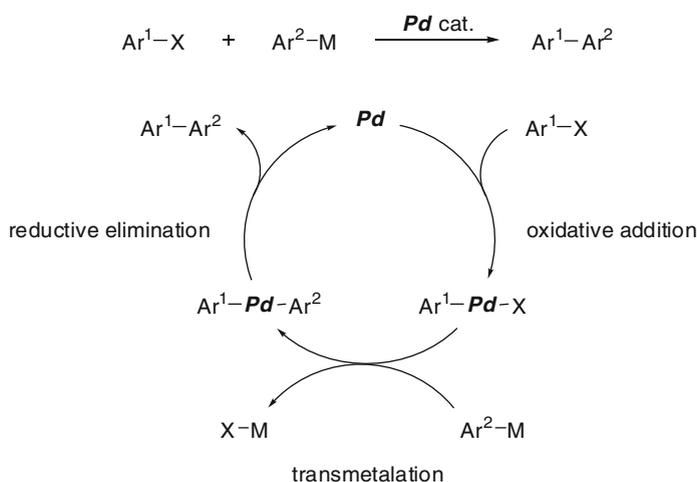
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(especially organoboronic acids) with the aid of a base as an activator, is extensively utilized for the synthesis of natural products and biologically active substances. Suzuki–Miyaura coupling is also widely used for the production of functional organic materials with biaryl motifs in a variety of research fields. This versatility is due to: (1) the stability of organoboronic acids to water, air, and heat; (2) the high functional group tolerance of organoboron compounds; and (3) a lower toxicity of the boron-containing by-products produced by the reactions.



However, unlike the more reactive Grignard and organozinc reagents, the transfer of the organic groups (transmetalation) from boron to the palladium center is limited by the poor nucleophilicity of organoboronic acids. In 1979, Suzuki and Miyaura disclosed that the addition of a base to the reaction system enhances transmetalation between organoboron reagents and palladium to undergo the reaction efficiently [4]. Since that time, Suzuki–Miyaura coupling has been significantly refined and has brought important technical improvements to the field of carbon–carbon bond formation.

Generally, the cross-coupling reactions are believed to occur through three fundamental steps: oxidative addition, transmetalation, and reductive elimination, in a catalytic cycle as shown in Scheme 2.1. In Suzuki–Miyaura coupling, as well as in other cross-coupling reactions, both the oxidative addition and reductive elimination stages have been well studied; on the other hand, the mechanisms of transmetalation involving an accelerating effect by the addition of bases have scarcely been examined until lately. Recently, many experimental and theoretical aspects of the transmetalation mechanisms in Suzuki–Miyaura coupling have been explored. Herein, the transmetalation step in Suzuki–Miyaura coupling is reviewed from the perspective of a series of cross-coupling reactions, examining the effects of the bases on transmetalation.

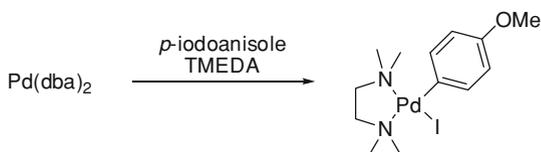


Scheme 2.1 A catalytic cycle of the palladium-catalyzed cross-coupling reactions

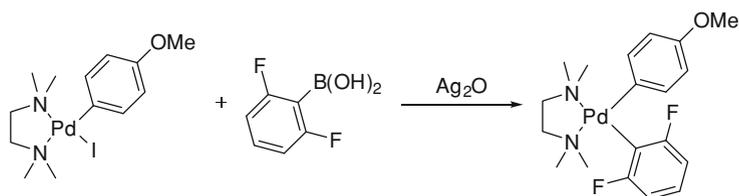
2.1.1 Stoichiometric Reactions of Suzuki–Miyaura Coupling

To provide mechanistic insight into the transmetalation, each stoichiometric reaction of Suzuki–Miyaura coupling is elucidated, as depicted in Scheme 2.2. Oxidative addition of organic halides to palladium is already known, and the formed halogeno(aryl)palladium(II) complexes can be isolated [5–9], whereas diarylpalladium(II) complexes as intermediates have not been isolated until recently due to spontaneous reductive elimination after transmetalation. Osakada has succeeded in the isolation and structural determination of the diarylpalladium(II) complexes after transmetalation by using arylboronic acids substituted with fluorine in the ortho position, leading to a retardation of the reductive elimination [10–12]. Upon heating of the isolated diarylpalladium(II) complexes, reductive elimination occurs smoothly to afford biaryls as cross-coupled products. These experimental results suggest that the rate-determining step in Suzuki–Miyaura coupling is transmetalation. Moreover, it is noteworthy that in this stoichiometric transmetalation reaction, the reaction does not occur at all when no Ag_2O additive is added.

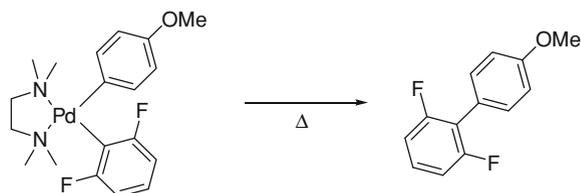
(oxidative addition)



(transmetalation)



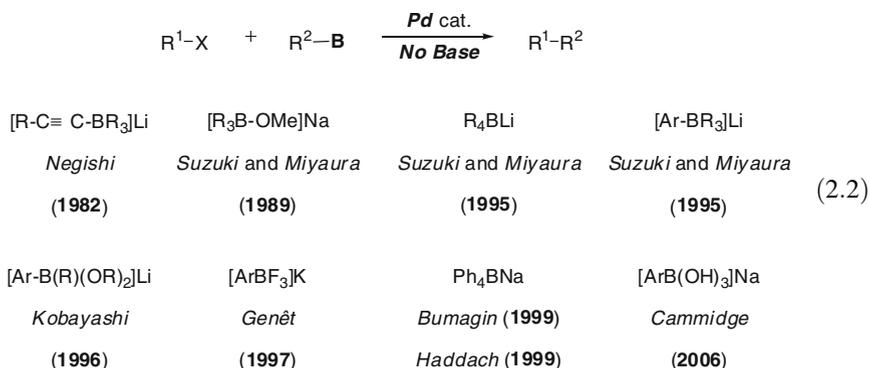
(reductive elimination)



Scheme 2.2 Three fundamental reactions

2.1.2 Base-Assisted Transmetalation

An accelerating effect on the transmetalation step of Suzuki–Miyaura coupling was observed when the bases were added to the reactions of halogeno(aryl)palladium(II) complexes with trialkylboranes or organoboronic acids. This is not seen in other types of cross-coupling reactions. Organoboronic acids are generally inert toward halogeno(aryl)palladium(II) complexes without any assistance of bases. However, highly nucleophilic organoborates can enhance transmetalation across halogeno(aryl)palladium(II) complexes without bases, and reductive elimination spontaneously follows to form the cross-coupled products, as shown in Eq. 2.2 [13–19].



On the other hand, Suzuki and Miyaura have reported that when the oxo complexes such as methoxo-, hydroxo-, and acetoxypalladium complexes (Fig. 2.1) were used as the starting compounds, the transmetalation with boronic acids occurred smoothly even under neutral conditions [20, 21].

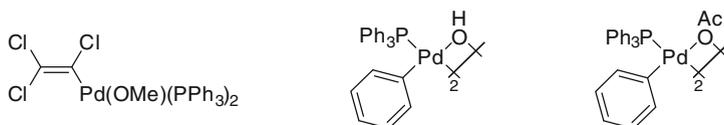


Fig. 2.1 Various oxopalladium complexes

Other examples of Suzuki–Miyaura coupling have been reported under neutral conditions by using the electrophiles shown in Fig. 2.2, because the oxopalladium complexes were immediately obtained by oxidative addition of these reagents [22–27]. In sharp contrast, oxidative addition of Ph_2IX , $PhI(OH)OTf$, or ArN_2BF_4 generates the cationic palladium species, which also rapidly undergo transmetalation without the addition of bases [28–31].

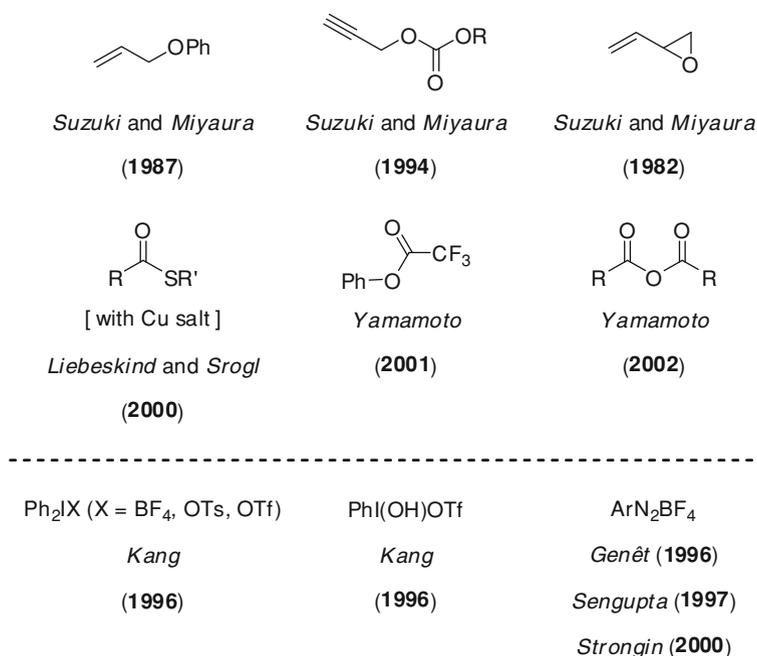
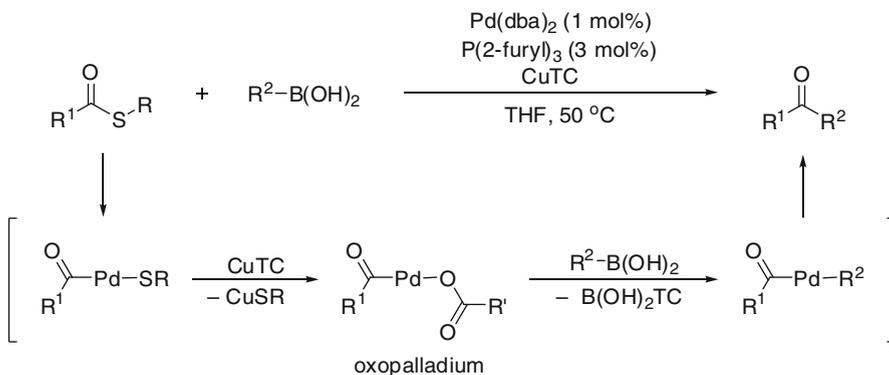


Fig. 2.2 Organic electrophiles directly yielding oxopalladium complexes via oxidative addition

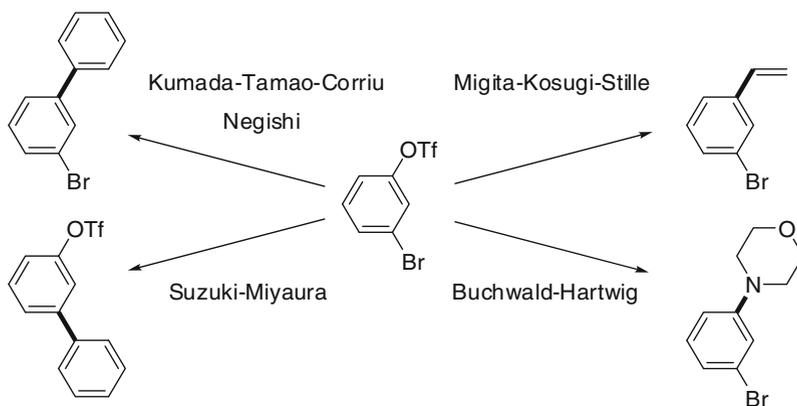
An example of the above-mentioned reactions, the Liebeskind–Srogl coupling, is shown in Scheme 2.3 [22]. The coupling reactions of the arylboronic acids with thioesters afforded the corresponding ketones under the palladium catalysis with the assistance of copper(I) 2-thiophenecarboxylate (CuTC) under neutral conditions. The reaction is thought to occur without the base because thiolatopalladium(II) complexes are converted into the carboxylatopalladium complexes by copper(I) carboxylates [32–42].



Scheme 2.3 Reaction of arylboronic acids with thioesters

2.1.3 The Turnover Limiting Step in Suzuki–Miyaura Coupling

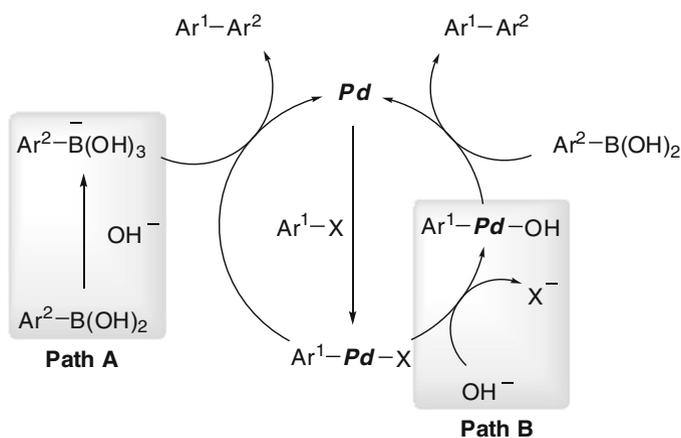
Transmetalation is believed to be the rate-determining step in most Suzuki–Miyaura couplings from the research on substituent effect of organic halides and organoboronic acids [43, 44]. This hypothesis is also supported from theoretical calculations; but, the presumption that transmetalation is the rate-determining step in all Suzuki–Miyaura couplings has become uncertain in recent years owing to the diversity of substrates and reaction conditions. For instance, Buchwald achieved cross-coupling reactions at room temperature by promoting transmetalation with sterically bulky phosphine ligands bearing biaryl backbones [45–47]. Furthermore, Fu reported that the less reactive alkyl chlorides can be used as electrophiles in Suzuki–Miyaura couplings [48]. Fu et al. proposed that the rate-determining step of these reactions is not transmetalation but oxidative addition. However, in most Suzuki–Miyaura couplings, under typical reaction conditions, transmetalation is the rate-controlling reaction in the catalytic cycle. Because a smooth transmetalation is essential for an efficient cross-coupling reaction, future investigation to improve this class of reactions should pay close attention to the transmetalation process. Brown compared the reaction rates by using arenes substituted with both triflates and bromides in a series of cross-coupling reactions. The results disclosed that the bromide chemoselectively reacted in Suzuki–Miyaura coupling, whereas the triflates preferentially reacted in Negishi, Kumada–Tamao–Corriu, and Migita–Kosugi–Stille couplings and Buchwald–Hartwig aminations (Scheme 2.4) [49]. It is clear that these very different results are ascribed to the transmetalation process in each coupling reaction, because the oxidative addition step is reversible [50].



Scheme 2.4 Transformations of 3-bromophenyl triflate

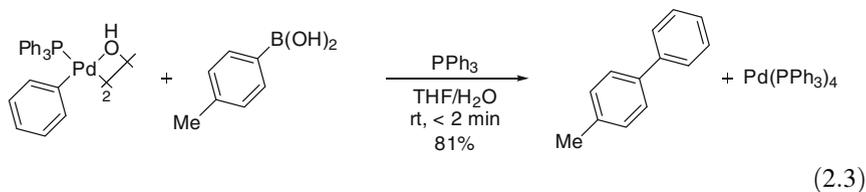
2.1.4 Pathways for Transmetalation

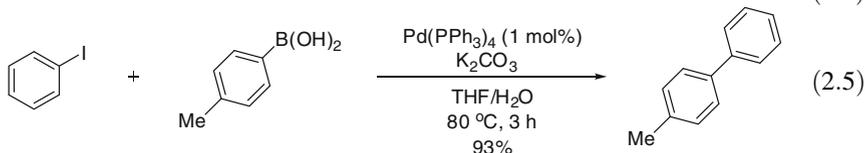
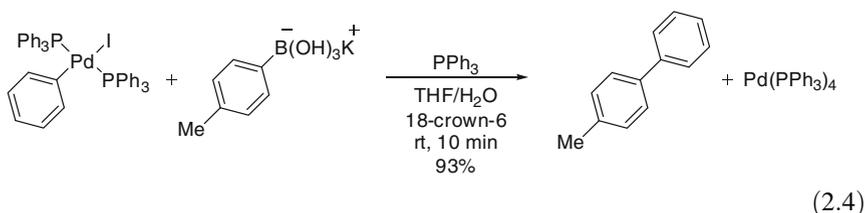
Two possible mechanisms of transmetalation in the base-accelerated Suzuki–Miyaura coupling can be considered. One involves the formation of the nucleophilic borates from the reactions of boronic acids with the added bases, which leads to a nucleophilic attack on the halogenopalladium(II) complexes (Scheme 2.5, Path A); the other contains a nucleophilic attack of the base (a hydroxyl ion) on halogenopalladium(II) complexes to generate the hydroxopalladium(II) intermediate, which further reacts with the neutral organoboron compounds to complete transmetalation (Scheme 2.5, Path B). Although to date there has been no definitive evidence to explain which transmetalation mechanism is correct, recently Hartwig et al. provided insight on the process [51].



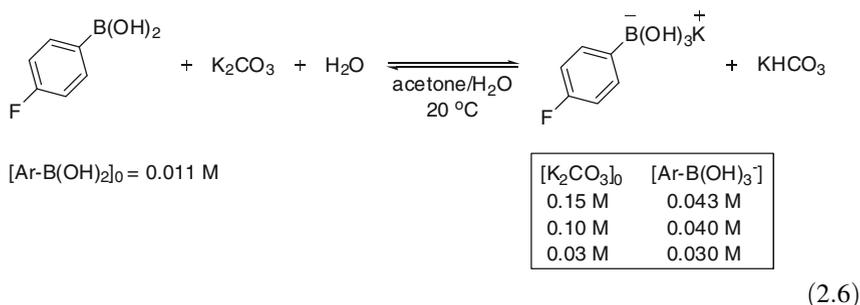
Scheme 2.5 Two possible pathways of transmetalation in Suzuki–Miyaura coupling

First of all, Hartwig examined a series of stoichiometric reactions of isolated arylpalladium(II) complexes with several organoboron reagents; the results indicated that the respective reactions of an arylboronic acid with a hydroxopalladium(II) complex (Eq. 2.3) and of an arylborate with an iodopalladium complex (Eq. 2.4) are much faster than the net catalytic reaction (Eq. 2.5). Therefore, both of the mechanisms (Paths A and B) may be involved in the catalytic cycle of Suzuki–Miyaura coupling.

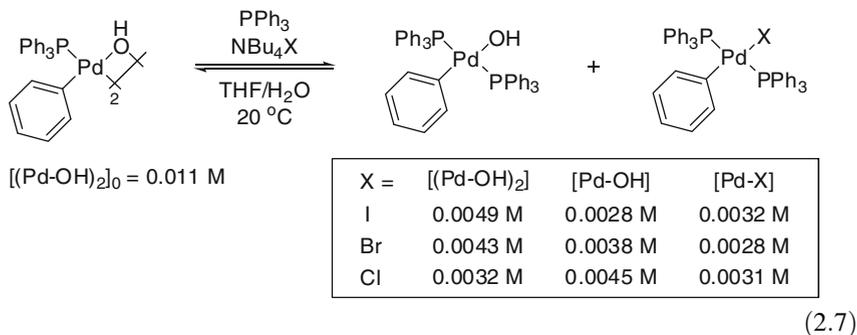




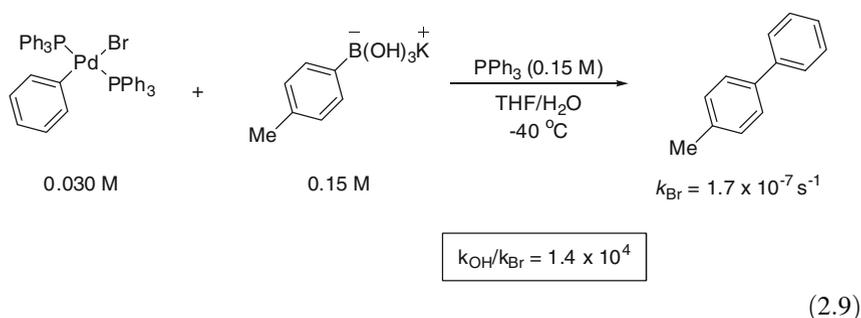
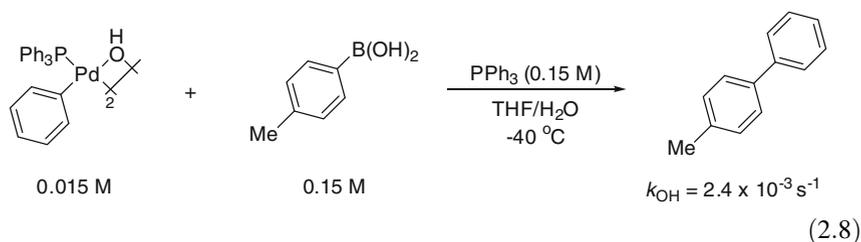
Next, the concentrations of the boronic acid, the borate, the halogenopalladium(II), and the hydroxopalladium complexes were measured by monitoring the ^{31}P and ^{11}B NMR spectra in the reactions. As a result, it was found that the ratio between boronic acid and borate is 1:1 to 1:3 under general conditions, i.e., a slightly basic condition in the organic solvent containing water (Eq. 2.6).



It was also clarified that there was no difference in the ratio between iodopalladium and hydroxopalladium complexes at equilibrium (shown in Eq. 2.7).



Finally, the reaction rates of a boronic acid with a hydroxopalladium complex and of a borate with a bromopalladium complex were compared. When each reaction was monitored by ^{31}P NMR, a rate constant for the reaction of a boronic acid and a hydroxopalladium complex was found to be $2.4 \times 10^{-3} \text{ s}^{-1}$ (Eq. 2.8); whereas that of a bromopalladium complex and a potassium borate was $1.7 \times 10^{-7} \text{ s}^{-1}$ (Eq. 2.9), giving rise to significantly different ratios by a factor of 1.4×10^4 .



These experimental results thus indicate that the transmetalation progresses via Path B in Scheme 2.5. However, it is noteworthy that: (1) this experimental data cannot be applied to all of Suzuki–Miyaura reactions; (2) although weak bases such as carbonates and phosphates are used in most cases of Suzuki–Miyaura reactions, Path B would compete with Path A when stronger bases are employed, leading to the prior generation of the borates; and (3) these data do not reflect any detailed mechanism for a transfer of the organic groups from boron to palladium.

2.1.5 Computational Studies of the Transmetalation Step in Suzuki–Miyaura Coupling

The theoretical calculations for the mechanism of the transmetalation process in Suzuki–Miyaura coupling support the experimental evidence provided by

Hartwig [51]. Maseras has performed the DFT calculations and the energy profiles corresponding to Paths A and B are shown in Figs. 2.3 and 2.4, respectively [52]. The energy profile of the reaction of a bromopalladium complex with vinylborate shown in Fig. 2.3, indicates that transmetalation proceeds exothermically, and the largest activation barrier in this route is rather small at 4.2 kcal/mol. Therefore, this calculation result supports that the bromo(vinyl)palladium complex can react with vinylborate in a catalytic cycle.

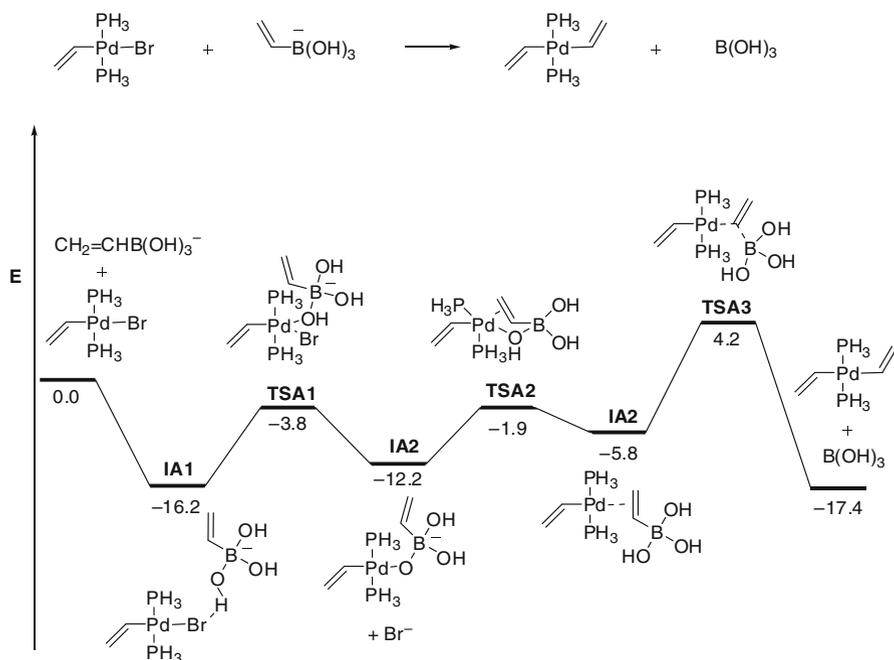


Fig. 2.3 An energy profile for Path A

On the other hand, Fig. 2.4 shows an energy profile for the reaction of vinylboronic acid with a hydroxo(vinyl)palladium(II) complex. This route is also exothermic, and the activation barrier was found to be only 0.6 kcal/mol. Comparison of the respective energy profiles for paths A and B, shown in Figs. 2.3 and 2.4, indicates that the energy of the transmetalation product **TSC3**, divinylpalladium(II) complex in Fig. 2.4, is much smaller. Therefore, path B is favored, which is consistent with the experimental outcomes by Hartwig.

In addition, Maseras calculated the direct reaction of a bromo(vinyl)palladium(II) complex with vinylboronic acid in the absence of the base. The most probable structures in this mechanism are shown in Fig. 2.5. This reaction pathway consists of the following processes: (1) a coordination of the double bond of the boronic acid to the palladium center; (2) a transfer of the bromide from palladium

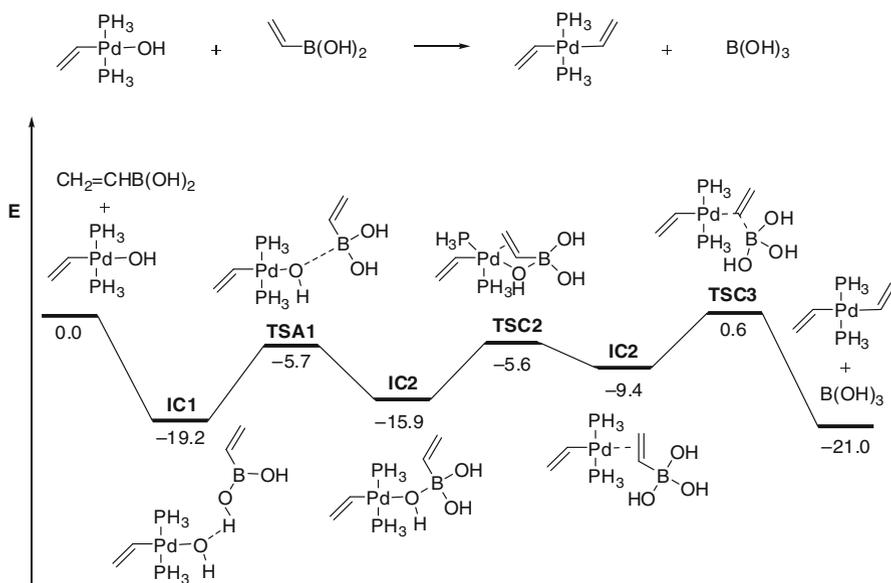


Fig. 2.4 An energy profile for Path B

to boron; and (3) a transfer of the vinyl group from boron to palladium to generate the divinylpalladium complex. Calculated results shown in Fig. 2.5 suggest that this path is endothermic (31.6 kcal) and that there is a large energy barrier (39.3 kcal) from the intermediate **I02** to the transition state **TS02**. This result signifies that the direct transmetalation between the bromopalladium complex and boronic acid in the absence of a base does not occur, which is also supported by experimental data.

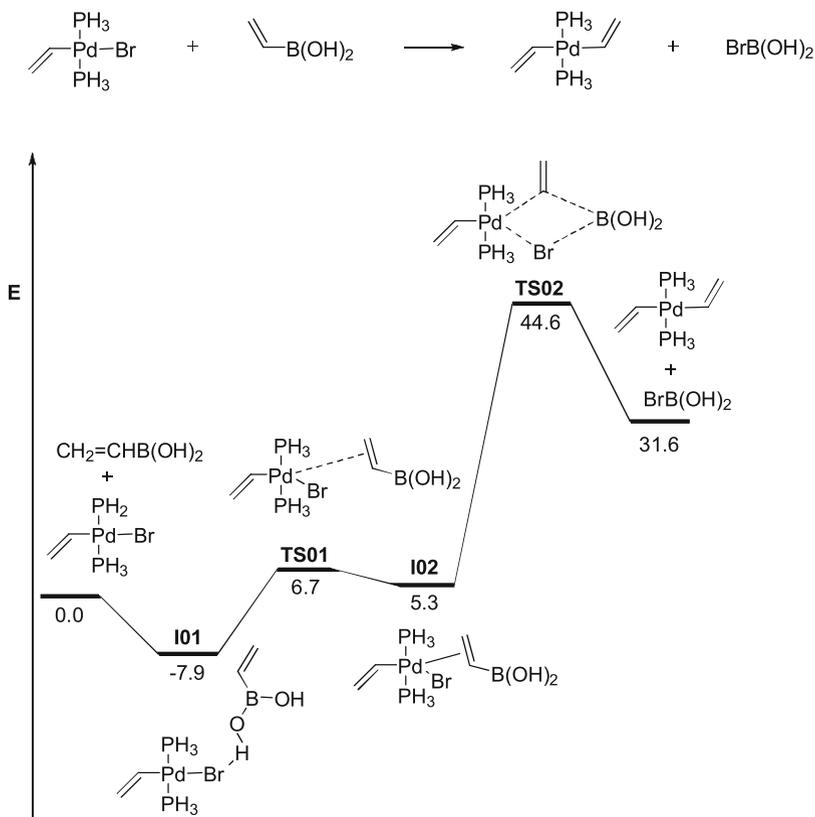
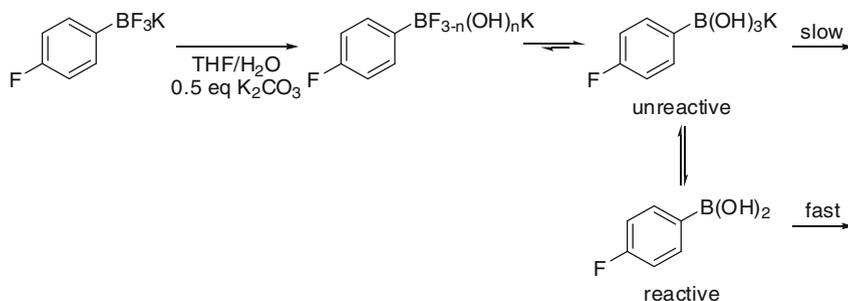


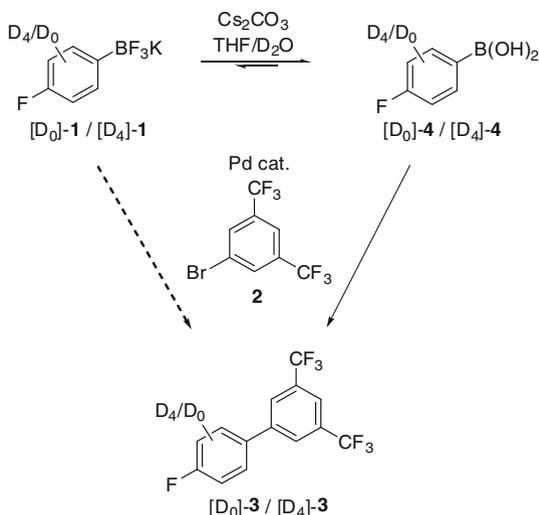
Fig. 2.5 An energy profile for the reaction of a bromo(vinyl)palladium(II) complex with vinylboronic acid

2.1.6 An Interconversion Between Trifluoroborate and Boronic Acid

Very recently, Lloyd-Jones experimentally clarified that in Suzuki–Miyaura coupling of potassium trifluoroborate, hydrolysis of the trifluoroborate takes place to generate the corresponding boronic acid, which further reacts with a hydroxopalladium(II) complex (Scheme 2.6) [53]. This evidence indicates that the transmetalation of potassium trifluoroborate proceeds through Path B shown in Fig. 2.4.



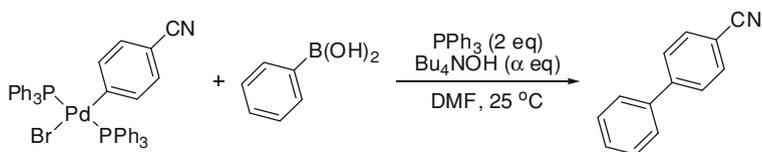
Scheme 2.6 Hydrolysis of potassium trifluoroborate



Scheme 2.7 Competitive reaction between an arylborate and an arylboronic acid

In addition, the mechanism of Suzuki–Miyaura coupling was investigated by using different molar ratios of an arylborate $[D_0]$ -1 and a deuterated arylboronic acid $[D_4]$ -4 (Scheme 2.7). When the mixture of a 1:1 ratio of $[D_0]$ -1 and $[D_4]$ -4 was used, the formation of the deuterated cross-coupled product $[D_4]$ -3 had a priority over $[D_0]$ -3. Surprisingly, even when a 9:1 mixture of $[D_0]$ -1 and $[D_4]$ -4 was used, the deuterated product $[D_4]$ -3 was obtained preferentially over $[D_0]$ -3. These results indicate that trifluoroborates can be a precursor of the corresponding boronic acids in the presence of a base in water.

Amatore and Jutand experimentally proved that the reaction becomes slower as the concentration of the hydroxide ion increases in the reaction of phenylboronic acid with a bromopalladium complex, as shown in Scheme 2.8 [54]. This observation is consistent with the experimental results from Hartwig and Lloyd-Jones, considering that Path B becomes inferior as the concentration of borates increases over boronic acids (under stronger basic conditions).

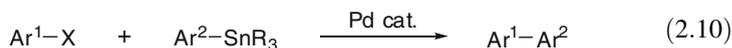


Scheme 2.8 The reaction of phenylboronic acid with a bromopalladium complex in the presence of the hydroxide ion

Herein the effect of the added bases and possible reaction paths in the Suzuki–Miyaura coupling have been discussed. However, the results of experiments by Hartwig and calculations by Maseras must be interpreted carefully. First, the data shown herein are not applicable to all reaction systems using various transition metals/ligands. Second, under the reaction conditions that use a stronger base, Path A competes with Path B because the concentration of the existing borates increases in the reaction mixture. Overall, these results have greatly contributed to the understanding of the transmetalation process because in most cases Suzuki–Miyaura coupling employs relatively weak bases such as carbonates and phosphates.

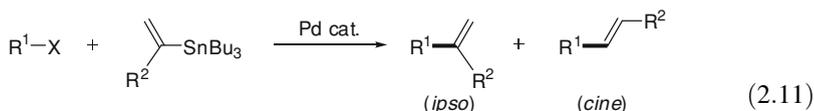
2.2 The “Copper Effect” in Migita–Kosugi–Stille Coupling

The Migita–Kosugi–Stille coupling, the palladium-catalyzed coupling reactions of organotin reagents with organic halides, as well as Suzuki–Miyaura coupling, are very useful carbon–carbon bond-forming reactions (Eq. 2.10) [55–57].



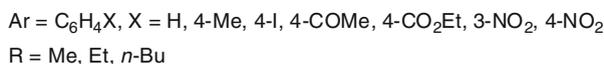
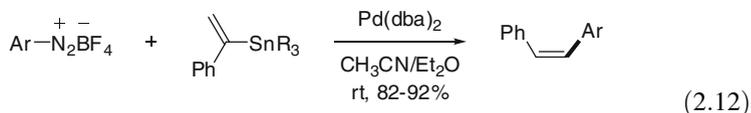
2.2.1 A *Cine* Substitution Reaction

Mechanistic investigation of the Migita–Kosugi–Stille coupling has persisted since its discovery. The traditional cycle of oxidative addition, transmetalation, and reductive elimination, prevalent in transition metal catalyzed carbon–carbon bond-forming reactions, has been widely accepted. When the bulky alkenyltin reagents are employed, a side reaction, the *cine* substitution reaction, is observed due to slow transmetalation (Eq. 2.11) [58].

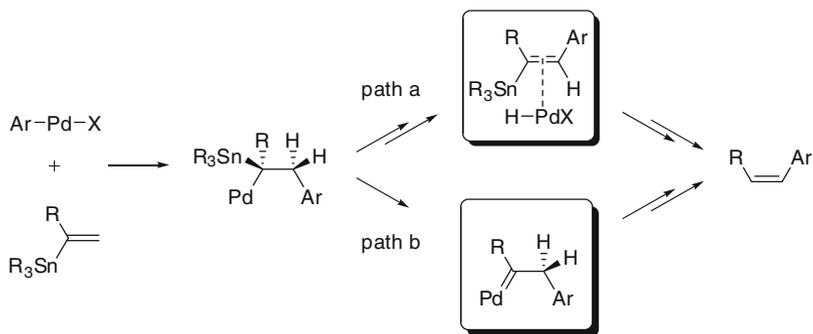


R^1 = aryl, vinyl; X = Cl, Br, I, OTf, OTs
 R^2 = phenyl, alkyl, ester

Kikukawa et al. found in 1986 that the reaction of ArN_2BF_4 with trialkyl(α -styryl)stannanes selectively produces the desired stereodefined (*Z*)-stilbene derivatives in high yields, not the α -arylated styrenes (Eq. 2.12) [59]. Due to slow transmetalation, this unexpected *cine* substitution reaction is observed in Migita–Kosugi–Stille coupling by using the bulky organotin reagents. In addition, it is reported that when an excess of diazonium salts are added, isomerization to the *Z*-stereoisomer becomes more substantial. The hydridopalladium complex plays an important role in this isomerization, which does not occur at all in the absence of the palladium catalyst.

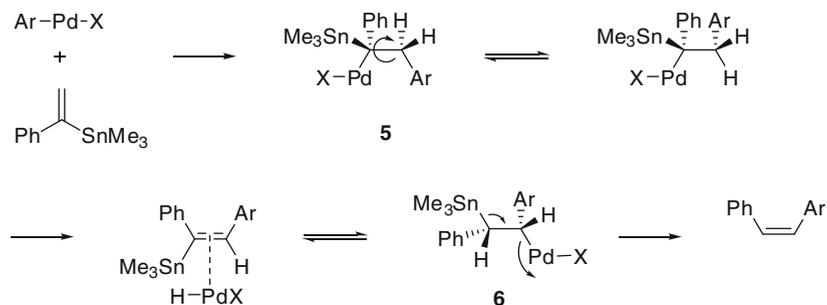


At present, two different reaction mechanisms giving rise to the *cine* substitution products are postulated, as shown in Scheme 2.9. One is the addition–elimination mechanism (path a) and the other is via the palladium carbene complex (path b). In both mechanisms, the reaction starts from a regioselective addition of the arylpalladium complex to the double bond of the α -substituted alkenylstannane.



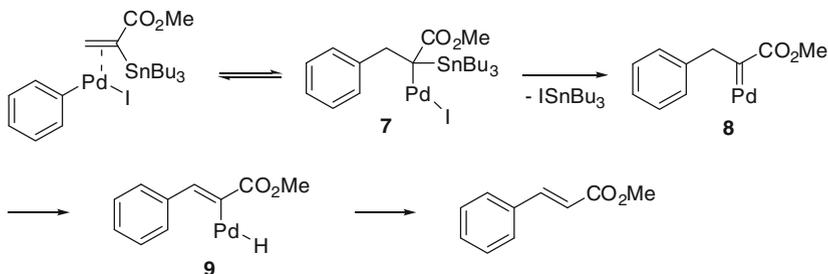
Scheme 2.9 Two reaction pathways of the *cine* substitution reaction

In the addition–elimination mechanism shown in Scheme 2.10, first carbopalladation occurs to the alkenylstannane regioselectively to generate intermediate **5**. The carbon–carbon bond in **5** rotates to give the *syn* configuration, from which β -hydrogen elimination takes place. The hydridopalladium complex adds to the generated alkenylstannane at the opposite position to give intermediate **6**. Finally, the *Z*-alkene is formed by the *anti*-elimination of a trialkylstannyl group and palladium, regenerating the catalyst [59]. However, definitive evidence to support this hypothesis has not been found to date, although many attempts to detect and identify the in situ formed alkenylstannanes have been made.



Scheme 2.10 The addition-elimination mechanism of the *cine* substitution reaction

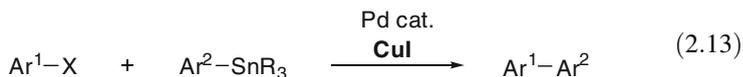
Another considered mechanism is via a palladium carbene complex. The regioselective insertion of an alkenylstannane into a carbon–palladium bond of the arylpalladium complex gives intermediate **7**. Iodostannane is released by α -elimination from the four-centered transitional state to generate the palladium carbene complex **8**. A 1,3-hydrogen shift from complex **8** forming the hydridopalladium complex **9** and the subsequent reductive elimination can afford the *cine* product (Scheme 2.11) [60]. The occurrence of the 1,3-hydrogen shift was confirmed by experiments with deuterated alkenyltin reagents.



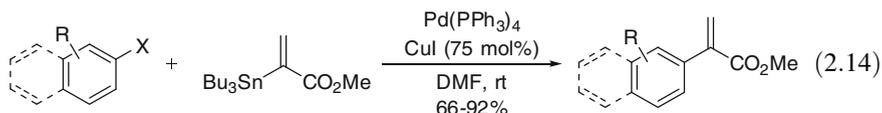
Scheme 2.11 Mechanism of the *cine* substitution reaction via a palladium carbene complex

2.2.2 The Copper Effect

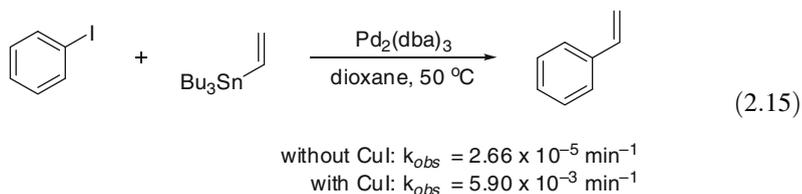
Although many reaction condition variables (including electrophiles, solvents, ligands, additives, etc.) were evaluated to avoid the *cine* substitution reaction as a side reaction in Migita–Kosugi–Stille coupling, the improvements of the product yields were not attained. The use of the bulky alkenyltin compounds and the slow transmetalation contribute to the *cine* substitution reactions. Only acceleration of transmetalation, the rate-determining step, can enable the desired reaction. The unambiguous improvement of the *ipso* selectivity and an accelerating effect for transmetalation have been observed by adding copper iodide and other copper(I) salts (Eq. 2.13) [61–73].



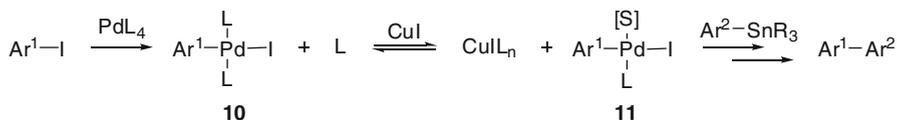
In 1993, for example, Levin reported that the reaction takes place in the *ipso* selective manner in Migita–Kosugi–Stille coupling when the sterically bulky alkenyltin reagents are employed with the copper iodide as a co-catalyst; no formation of the *cine* substitution product was observed (Eq. 2.14) [74].



This so-called “copper effect” was researched first by Farina and Liebeskind [75]. They compared the reaction rates of the cross-coupling of vinyltributyltin with iodobenzene in the presence and in the absence of copper iodide. As a result, it has been disclosed that the reaction with the addition of copper iodide ($k_{\text{obs}} = 5.90 \times 10^{-3} \text{ min}^{-1}$) is about 100 times faster than that without any copper additive ($k_{\text{obs}} = 2.66 \times 10^{-5} \text{ min}^{-1}$) (Eq. 2.15).

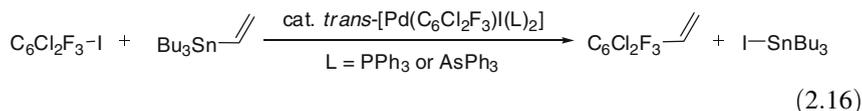


The rate-determining step in Migita–Kosugi–Stille coupling is believed to be the transmetalation process based on recent research [76, 77]. Farina and Liebeskind explained the “copper effect” as follows. The added copper(I) salt traps the triphenylphosphine dissociated from the metal center in oxidative adduct **10** to generate the unsaturated palladium complex **11**, and promotes the transmetalation process (Scheme 2.12). It is noteworthy that the added copper iodide does not promote the dissociation of the ligand from the oxidative adduct **10**, but it traps the ligand dissociated after oxidative addition. Also, the addition of copper salts was reported to prevent the progress of the reverse reaction from **11** to **10**.

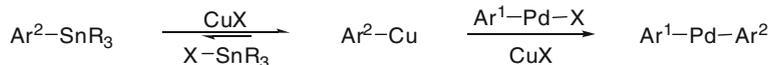


Scheme 2.12 “Copper effect” in Migita–Kosugi–Stille coupling

The soft arsine ligands did not show any accelerating effect, compared with the harder phosphine ligands, as shown in Eq. 2.16. This is because copper iodide has a stronger interaction with phosphine ligands than with arsine ligands [78, 79]. Moreover, when Pd(AsPh₃)₄ is used as a catalyst, the association rate of free ligands to the metal center becomes slower than that observed in the case of Pd(PPh₃)₄.



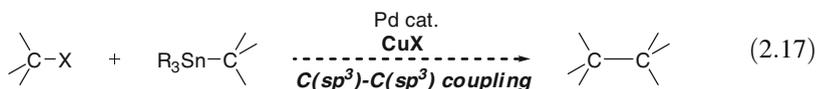
It is known that the organic groups transmetalate from tin to copper in polar solvents (Scheme 2.13) [80]. The generation of tin halides was confirmed by measuring the ¹¹⁹Sn NMR in NMP as the solvent. The newly formed organo-copper(I) species showed a higher activity of transmetalation to palladium than the corresponding organotin reagents. Therefore, the generated organocopper reagents take part in transmetalation in Migita–Kosugi–Stille coupling.



Scheme 2.13 Transmetalation from tin to copper

2.2.3 Perspectives

Clearly, there is an accelerating effect in Migita–Kosugi–Stille coupling when copper(I) salts are added. In the future, considering the effect of copper(I) salts, expanded use of Migita–Kosugi–Stille-type carbon(sp³)–carbon(sp³) bond-forming reactions is expected. These types of reactions are very challenging because alkyl electrophiles are undesirable for oxidative addition and the synchroal β-hydrogen elimination competitively takes place. However, unprecedented carbon(sp³)–carbon(sp³) couplings in the Migita–Kosugi–Stille reaction can be achieved by accelerating transmetalation, the rate-determining step, with the addition of copper(I) salts (Eq. 2.17).



2.3 Summary

This chapter focuses on the transmetalation of Suzuki–Miyaura and Migita–Kosugi–Stille coupling reactions, the various pathways and the mechanisms involved, and the effect of the bases and of copper(I) salts. It has been concluded that the reactions of the arylboronic acids with a hydroxopalladium complex are much faster than that of arylborates with a halogenopalladium(II) complex from experimental and theoretical findings. However, it cannot be asserted that the mechanism in *all* Suzuki–Miyaura reactions has been proven because only the general reaction conditions have been examined at this present stage. In the future, it can be expected that further research on the mechanisms will develop from the studies clarified to date. This will lead to the development of more efficient cross-coupling reactions.

References

1. de Meijere A, Diedrich F (2004) Metal-catalyzed cross-coupling reactions, 2nd edn. Wiley-VCH, Weinheim
2. Li JJ (2009) Name reactions for homologations. Wiley, Hoboken
3. Miyaura N, Suzuki A (1995) Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem Rev* 95:2457–2483
4. Miyaura N, Yamada K, Suzuki A (1979) A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Lett* 20:3437–3440
5. de Graaf W, Boersma J, Smeets WJJ, Spek AL, van Koten G (1989) Dimethyl(N, N, N', N'-tetramethylethanediamine)palladium(II) and dimethyl[1,2-bis(dimethylphosphino)ethane]palladium(II): syntheses, x-ray crystal structures, and thermolysis, oxidative-addition and ligand-exchange reactions. *Organometallics* 8:2907–2917
6. de Graaf W, Boersma J, van Koten G (1990) Cross-coupling versus homocoupling in the reactions of dimethyl(N, N, N', N'-tetramethylethanediamine)palladium with organic halides. *Organometallics* 9:1479–1484
7. Alsters PL, Engel PF, Hogerheide MP, Copijn M, Spek AL, van Koten G (1993) Rigid five- and six-membered C, N, N'-bound aryl-, benzyl-, and alkylorganopalladium complexes: sp² vs. sp³ carbon-hydrogen activation during cyclopalladation and palladium(IV) intermediates in oxidative addition reactions with dihalogens and alkyl halides. *Organometallics* 12:1831–1844
8. Markies BA, Canty AJ, de Graaf W, Boersma J, Janssen MD, Hogerheide MP, Smeets WJJ, Spek AL, van Koten G (1994) Synthesis and structural studies of phenyl(iodo)- and methyl(phenyl)palladium(II) complexes of bidentate nitrogen donor ligands. *J Organomet Chem* 482:191–199
9. Yagyu T, Hamada M, Osakada K, Yamamoto T (2001) Cationic arylpalladium complexes with chelating diamine ligands, [PdAr(N–N)(solvent)]BF₄ (N–N=N, N, N', N'-tetramethylethylenediamine, 2,2'-bipyridine, 4,4'-dimethyl-2,2'-bipyridine). Preparation, intermolecular coupling of the aryl ligands, and insertion of alkyne and allene into the Pd–C bond. *Organometallics* 20:1087–1101
10. Nishihara Y, Onodera H, Osakada K (2004) Synthesis and structural characterization of the first unsymmetrical diarylpalladium complex trans-Pd(C₆F₅)(2,4,6-C₆F₃H₂)(PEt₃)₂, derived from transmetalation between 2,4,6-trifluorophenylboronic acid and trans-Pd(C₆F₅)I(PEt₃)₂. *Chem Commun*, 192–193

11. Osakada K, Onodera H, Nishihara Y (2005) Diarylpalladium complexes with a cis structure. Formation via transmetalation of arylboronic acids with an aryliodopalladium complex and intramolecular coupling of the aryl ligands, affording unsymmetrical biaryls. *Organometallics* 24:190–192
12. Suzaki Y, Osakada K (2006) Chemical properties of mononuclear and dinuclear phenylplatinum(II) hydroxo complexes with cod ligands. Transmetalation of arylboronic acids, coupling of the phenyl ligands, and carbonylation. *Organometallics* 25:3251–3258
13. Negishi E (1982) Palladium- or nickel-catalyzed cross coupling. A new selective method for carbon–carbon bond formation. *Acc Chem Res* 15:340–348
14. Miyaura N, Ishiyama T, Sasaki H, Ishikawa M, Satoh M, Suzuki A (1989) Palladium-catalyzed inter- and intramolecular cross-coupling reactions of B-alkyl-9-borabicyclo[3.3.1]nonane derivatives with 1-halo-1-alkenes or haloarenes. Syntheses of functionalized alkenes, arenes, and cycloalkenes via a hydroboration-coupling sequence. *J Am Chem Soc* 111:314–321
15. Kobayashi Y, Mizijiri R (1996) Nickel-catalyzed coupling reaction of lithium organoborates and aryl mesylates possessing an electron withdrawing group. *Tetrahedron Lett* 37:8531–8534
16. Darses S, Genêt J-P, Brayer J-L, Demoute J-P (1997) Cross-coupling reactions of arenediazonium tetrafluoroborates with potassium aryl- or alkenyltrifluoroborates catalyzed by palladium. *Tetrahedron Lett* 38:4393–4396
17. Haddach M, McCarthy JR (1999) A new method for the synthesis of ketones: the palladium-catalyzed cross-coupling of acid chlorides with arylboronic acids. *Tetrahedron Lett* 40:3109–3112
18. Bumagin NA, Korolev DN (1999) Synthesis of unsymmetric ketones via ligandless Pd-catalyzed reaction of acyl chlorides with organoboranes. *Tetrahedron Lett* 40:3057–3060
19. Andrew N, Cammidge AN, Goddard VHM, Gopee H, Harrison NL, Hughes DL, Schubert CJ, Sutton BM, Watts GL, Whitehead AJ (2006) Aryl trihydroxyborates: easily isolated discrete species convenient for direct application in coupling reactions. *Org Lett* 8:4071–4074
20. Miyaura N, Yamada Y, Suginome H, Suzuki A (1985) Novel and convenient method for the stereo- and regiospecific synthesis of conjugated alkadienes and alkenynes via the palladium-catalyzed cross-coupling reaction of 1-alkenylboranes with bromoalkenes and bromoalkynes. *J Am Chem Soc* 107:972–980
21. Miyaura N (2002) Cross-coupling reaction of organoboron compounds via base-assisted transmetalation to palladium(II) complexes. *J Organomet Chem* 653:54–57
22. Miyaura N, Tanabe Y, Suginome H, Suzuki A (1982) Cross-coupling reactions of 1-alkenylboranes with 3,4-epoxy-1-butene catalyzed by palladium or nickel complexes. *J Organomet Chem* 233:C13–C16
23. Sasaya F, Miyaura N, Suzuki A (1987) Palladium-catalyzed cross-coupling reaction of (E)-1-alkenyl-1,3,2-benzo-dioxaboroles with allylic phenoxides. A simple route 1,4-alkadienes from alkynes via hydroboration. *Bull Korean Chem Soc* 8:329–332
24. Moriya T, Miyaura N, Suzuki A (1994) Synthesis of allenes by palladium-catalyzed cross-coupling reaction of organoboron compounds with propargylic carbonates: transmetalation of organoboron compounds with (alkoxy)palladium complexes under neutral conditions. *Synlett*, 149–151
25. Liebeskind LS, Srogl J (2000) Thiol ester-boronic acid coupling. A mechanistically unprecedented and general ketone synthesis. *J Am Chem Soc* 122:11260–11261
26. Kakino R, Shimizu A, Yamamoto A (2001) Synthesis of trifluoromethyl ketones by palladium-catalyzed cross-coupling reaction of phenyl trifluoroacetate with organoboron compounds. *Bull Chem Soc Jpn* 74:371–376
27. Kakino R, Narahashi H, Shimizu I, Yamamoto A (2002) Palladium-catalyzed direct conversion of carboxylic acids into ketones with organoboronic acids promoted by anhydride activators. *Bull Chem Soc Jpn* 75:1333–1345
28. Kang S-K, Lee H-W, Jang S-B, Ho P-S (1996) Palladium-catalyzed cross-coupling of organoboron compounds with iodonium salts and iodanes. *J Org Chem* 61:4720–4724

29. Dares S, Jeffery T, Genêt J-P, Brayer J-L, Demoute J-P (1996) Cross-coupling of arenediazonium tetrafluoroborates with arylboronic acids catalysed by palladium. *Tetrahedron Lett* 37:3857–3860
30. Sengupta S, Bhattacharyya S (1997) Palladium-catalyzed cross-coupling of arenediazonium salts with arylboronic acids. *J Org Chem* 62:3405–3406
31. Willis DM, Strongin RM (2000) Palladium-catalyzed cross-coupling of aryl diazonium tetrafluoroborate salts with arylboronic esters. *Tetrahedron Lett* 41:6271–6274
32. Savarin C, Srogl J, Liebeskind LS (2001) Substituted alkyne synthesis under nonbasic conditions: copper carboxylate-mediated, palladium-catalyzed thioalkyne-boronic acid cross-coupling. *Org Lett* 3:91–93
33. Savarin C, Liebeskind LS (2001) Nonbasic, room temperature, palladium-catalyzed coupling of aryl and alkenyl iodides with boronic acids mediated by copper(I) thiophene-2-carboxylate (CuTC). *Org Lett* 3:2149–2152
34. Liebeskind LS, Srogl J (2002) Heteroaromatic thioether-boronic acid cross-coupling under neutral reaction conditions. *Org Lett* 4:979–981
35. Kusturin CL, Liebeskind LS, Neumann WL (2002) A new catalytic cross-coupling approach for the synthesis of protected aryl and heteroaryl amidines. *Org Lett* 4:983–985
36. Alphonse F-A, Suzenet F, Keromnes A, Lebreton B, Guillaumeta G (2002) Palladium-catalyzed 3-thiomethyltriazine-boronic acid cross coupling: easy access to 3-substituted-1,2,4-triazines. *Synlett*, 447–450
37. Lengar A, Kappe CO (2004) Tunable carbon–carbon and carbon-sulfur cross-coupling of boronic acids with 3,4-dihydropyrimidine-2-thiones. *Org Lett* 6:771–774
38. Nishihara Y, Inoue Y, Fujisawa M, Takagi K (2005) Room-temperature palladium-catalyzed and copper(I)-mediated coupling reactions of acid chlorides with boronic acids under neutral conditions. *Synlett*, 2309–2312
39. Arshad N, Hashim J, Kappe CO (2009) Palladium(0)-catalyzed, copper(I)-mediated coupling of cyclic thioamides with alkenylboronic acids, organostannanes, and siloxanes. *J Org Chem* 74:5118–5121
40. Kmentova I, Sutherland HS, Palmer BD, Blaser A, Franzblau SG, Wan B, Wang Y, Ma Z, Denny WA, Thompson AM (2010) Synthesis and structure-activity relationships of aza- and diazabiphenyl analogues of the antitubercular drug (6S)-2-nitro-6-[[4-(trifluoromethoxy)benzyl]oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (PA-824). *J Med Chem* 53:8421–8439
41. Modha SG, Trivedi JC, Mehta VP, Ermolat'ev DS, Van der Eycken EV (2011) An expeditious route toward pyrazine-containing nucleoside analogues. *J Org Chem* 76:846–856
42. Calter MA, Korotkov A (2011) Catalytic, asymmetric, interrupted Feist-Bénary reactions of α -tosyloxyacetophenones. *Org Lett* 13:6328–6330
43. Zim S, Lando VR, Dupont J, Monterio AL (2001) $\text{NiCl}_2(\text{PCy}_3)_2$: a simple and efficient catalyst precursor for the Suzuki cross-coupling of aryl tosylates and arylboronic acids. *Org Lett* 3:3049–3051
44. Moreno-Mañas M, Pérez M, Pleixats R (1996) Palladium-catalyzed Suzuki-type self-coupling of arylboronic acids, a mechanistic study. *J Org Chem* 61:2346–2351
45. Wolfe JP, Singer RA, Yang BH, Buchwald SL (1999) Highly active palladium catalysts for Suzuki coupling reactions. *J Am Chem Soc* 121:9550–9561
46. Ngyuen HN, Huang X, Buchwald SL (2003) The first palladium catalyst for Suzuki-Miyaura and carbonyl enolate coupling of aryl arenosulfonates. *J Am Chem Soc* 125:11818–11819
47. Martin R, Buchwald SL (2008) Palladium-catalyzed Suzuki-Miyaura cross-coupling reactions employing dialkylbiaryl phosphite ligands. *Acc Chem Res* 41:1461–1473
48. Lu Z, Fu GC (2010) Alkyl-alkyl Suzuki cross-coupling of unactivated secondary alkyl chlorides. *Angew Chem Int Ed* 49:6676–6678
49. Espino G, Kurbangalieva A, Brown JM (2007) Aryl bromide/triflate selectivities reveal mechanistic divergence in palladium-catalysed couplings; the Suzuki-Miyaura anomaly. *Chem Commun*, 1742–1744

50. Roy AH, Hartwig JF (2003) Directly observed reductive elimination of aryl halides from monomeric arylpalladium(II) halide complexes. *J Am Chem Soc* 125:13944–13945
51. Carrow BP, Hartwig JF (2011) Distinguishing between pathways for transmetalation in Suzuki-Miyaura reactions. *J Am Chem Soc* 133:2116–2119
52. Braga AAC, Morgan NH, Ujaque G, Maseras F (2005) Computational characterization of the role of the base in the Suzuki-Miyaura cross-coupling reaction. *J Am Chem Soc* 127:9298–9307
53. Butters M, Harvey J, Jover J, Lloyd-Jones G (2010) Aryl trifluoroborates in Suzuki-Miyaura coupling: the roles of endogenous aryl boronic acid and fluoride. *Angew Chem Int Ed* 49:5156–5160
54. Amatore C, Jutand A, Le Duc G (2011) Kinetic data for the transmetalation/reductive elimination in palladium-catalyzed Suzuki-Miyaura reactions: unexpected triple role of hydroxide ions used as base. *Chem Eur J* 17:2492–2503
55. Kosugi M, Sasazawa K, Shimizu Y, Migita T (1977) Reactions of allyltin compounds III. Allylation of aromatic halides with allyltributyltin in the presence of tetrakis(triphenylphosphine)-palladium(0). *Chem Lett*, 301–302
56. Milstein D, Stille JK (1978) A general, selective, and facile method for ketone synthesis from acid chlorides and organotin compounds catalyzed by palladium. *J Am Chem Soc* 100:3636–3638
57. Stille JK (1986) The palladium-catalyzed cross-coupling reactions of organotin reagents with organic electrophiles. *Angew Chem Int Ed Engl* 25:508–524
58. Suwinski Swierczek K (2001) *cine*- and *tele*-Substitution reactions. *Tetrahedron* 57:1639–1662
59. Kikukawa K, Umekawa H, Matsuda T (1986) Reaction of diazonium salts with transition metals: XII. Palladium-catalyzed aryldestannylation of α -styrylstannanes by arenediazonium salts. *J Organomet Chem* 311:C44–C46
60. Busacca CA, Swestock J, Johnson RE, Bailey TR, Musza L, Roger CA (1994) The anomalous Stille reactions of methyl α -(tributylstannyl)acrylate: evidence for a palladium carbene intermediate. *J Org Chem* 59:7553–7556
61. Liebeskind LS, Fengl RW (1990) 3-Stannylcyclobutenediones as nucleophilic cyclobutenedione equivalents. Synthesis of substituted cyclobutenediones and cyclobutenedione monoacetals and the beneficial effect of catalytic copper iodide on the Stille reaction. *J Org Chem* 55:5359–5364
62. Farina V, Krishnan B (1991) Large rate accelerations in the Stille reaction with tri-2-furylphosphine and triphenylarsine as palladium ligands: mechanistic and synthetic implications. *J Am Chem Soc* 113:9585–9595
63. Gómez-Bengoa E, Echavarren AM (1991) Synthesis of isoascididemin, a regioisomer of the marine alkaloid ascididemin. *J Org Chem* 56:3497–3501
64. Ye J, Bhatt RK, Falck JR (1993) Stereospecific α -alkoxystannane couplings with acyl chlorides: total synthesis of (+)-goniofufurone. *Tetrahedron Lett* 34:8007–8010
65. Liebeskind LS, Riesinger SW (1993) Substituted quinone synthesis by palladium-copper cocatalyzed cross-coupling of stannylquinones with aryl and heteroaryl iodides. *J Org Chem* 58:408–413
66. Saá JM, Martorell G (1993) Palladium-catalyzed cross-coupling synthesis of hindered biaryls and terphenyls. Cocatalysis by copper(I) salts. *J Org Chem* 58:1963–1966
67. Ye J, Bhatt RK, Falck JR (1994) Stereospecific palladium/copper cocatalyzed cross-coupling of α -alkoxy- and α -aminostannanes with acyl chlorides. *J Am Chem Soc* 116:1–5
68. Farina V (1996) New perspectives in the cross-coupling reactions of organostannanes. *Pure Appl Chem* 68:73–78
69. Farina V, Roth GP (1996) Recent advances in the Stille reaction. *Adv Met-Org Chem* 5:1–53
70. Soheil A, Albaneze-Walker J, Murry JA, Dormer PG, Hughes DL (2003) Efficient and general protocol for the copper-free Sonogashira coupling of aryl bromides at room temperature. *Org Lett* 5:4191–4194

71. Gelman D, Buchwald SL (2003) Efficient palladium-catalyzed coupling of aryl chlorides and tosylates with terminal alkynes: use of a copper cocatalyst inhibits the reaction. *Angew Chem Int Ed* 42:5993–5996
72. Mozzola RD, Giese S, Benson CL, West FG (2004) Improved yields with added copper(I) salts in carbonylative Stille couplings of sterically hindered vinylstannanes. *J Org Chem* 69:220–223
73. Wang Y, Burton J (2006) Copper(I)-only catalyzed reactions of (*E*)-2,3-difluoro-3-stannylacrylic ester with acid chlorides and mechanistic studies of the “copper effect” in Stille coupling reactions. *Org Lett* 8:1109–1111
74. Levin JI (1993) Palladium-catalyzed coupling of an α -stannyl acrylate to aryl iodides and triflates. A one-step synthesis of aryl propenoic esters. *Tetrahedron Lett* 34:6211–6214
75. Farina V, Kapadia S, Krishnan B, Wang C, Liebeskind LS (1994) On the nature of the “copper effect” in the Stille cross-coupling. *J Org Chem* 59:5905–5911
76. Wang M, Lin Z (2010) Stille cross-coupling reactions of alkenylstannanes with alkenyl iodides mediated by copper(I) thiophene-2-carboxylate: a density functional study. *Organometallics* 29:3077–3084
77. Peng Y, Li W-DZ (2010) *cis* Substitution and the Cu effect in Stille cross-coupling reactions: mechanistic perspectives and synthetic utility. *Eur J Org Chem*, 6703–6718
78. Casadro AL, Espinet P (2003) Quantitative evaluation of the factors contributing to the “copper effect” in the Stille reaction. *Organometallics* 22:1305–1309
79. Espinet P, Echavarren AM (2004) The mechanism of the Stille reaction. *Angew Chem Int Ed* 43:4704–4734
80. Mee SPH, Lee V, Baldwin JE (2004) Stille coupling made easier—the synergic effect of copper(I) salts and the fluoride ion. *Angew Chem Int Ed* 43:1132–1136



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