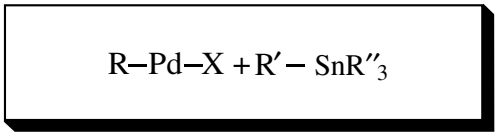

III.2.3 Overview of the Stille Protocol with Sn

MASANORI KOSUGI and KEIGO FUGAMI

A. INTRODUCTION

The Stille protocol is defined as the carbon–carbon bond formation by Pd-catalyzed coupling of organic electrophiles (usually halides or triflates) with organotin reagents (**Scheme 1**). Organotin reagents tolerate a variety of functional groups that many other reactive organometallics do not. Moreover, since most organotin reagents are sensitive to neither moisture nor oxygen, they can easily be isolated and stored. Many functionalities on the electrophiles can also survive the cross-coupling reaction. Thus, organic chemists can easily handle them but with special care because of their toxicity. In consequence, a number of preparation techniques for such reagents have been developed and this protocol has widely been applied to syntheses of a vast number of densely functionalized substances such as biologically intriguing compounds.

The present overview starts with early historical developments. The Pd-catalyzed reaction of organotin compounds was first published by Eaborn's group in 1976 (**Scheme 2**).[1] It was initially considered as a variation of the Kharasch-type reaction, namely, radical reaction.

In 1977, three reports appeared from Kosugi and Migita's group, which are concerned with transition metal-catalyzed carbon–carbon bond-forming reactions, that is, rhodium-catalyzed reaction of acid chlorides with allyl or benzyltributyltin,[2] Pd-catalyzed reaction of acid chlorides with other organotins,[3] and then Pd-catalyzed reaction of aryl halides with allyltributyltin.[4] The Milstein–Stille paper that appeared in 1978 was on a ketone synthesis utilizing acid chlorides and organotin compounds catalyzed by $BnPdCl(PPh_3)_2$ in HMPA.[5],[6] The reaction conditions became milder and the yields higher. Subsequently, the solvent was changed to chloroform to avoid the strongly carcinogenic HMPA (**Scheme 3**).[7]

In 1979 the reaction of benzyl and aryl halides as well as its mechanism were reported.[8],[9] The first Pd-catalyzed carbonylative coupling of organic halides with organotin compounds was reported by Tanaka in the same year (**Scheme 4**).[10]

Aldehyde synthesis by means of the Pd-catalyzed reduction of acid chloride using tributyltin hydride was published by Four and Guibe in 1980.[11],[12] The first report from Beletskaya's group also appeared in 1980.[13] She has developed a wide variety of

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$$RX + R'SnR''_3 \xrightarrow{[Pd]} R{-}R' + R''_3SnX$$

Scheme 1

$$ArBr + Bu_3SnSnBu_3 \xrightarrow[\text{in PhMe}]{Pd(PPh_3)_4} ArSnBu_3 + ArAr + Bu_3SnBr$$

Scheme 2

$$RCOCl + Bu_3SnR' \xrightarrow[\text{in } CHCl_3]{BnPdCl(PPh_3)_2} RCOR' + Bu_3SnCl$$

Scheme 3

$$R^1X + CO + R^2{}_4Sn \xrightarrow[\text{30 atm CO, in HMPA}]{PhPdI(PPh_3)_2} R^1COR^2$$

Scheme 4

reactions using mainly ligandless palladium catalysts and published her review in 1983.[14] The scope of the reaction was widened by employment of vinyl triflates instead of halides as organic electrophiles that was introduced by Stille and co-workers in 1984.[15]

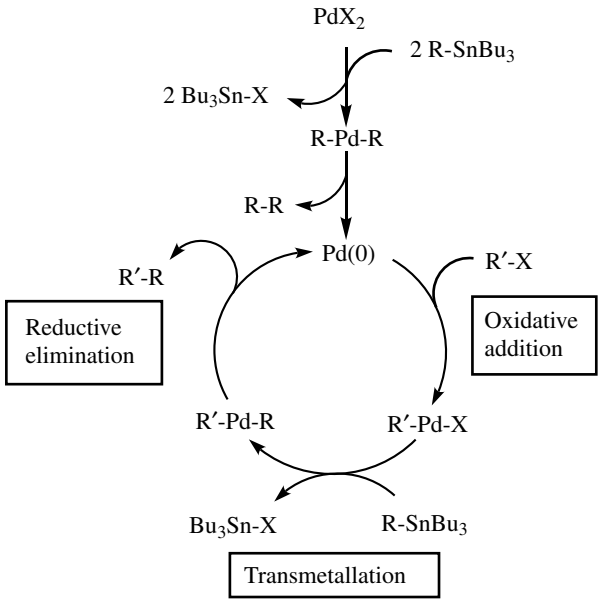
Stille's famous review was published in 1986.[16] Mitchell's review is also noteworthy.[17] Since then it has been recognized that the organotin protocol is useful for organic synthesis. The monograph *Tin in Organic Synthesis* was published in 1987.[18] Mitchell's next review covered the literature from 1985 to 1990.[19] A number of synthetic applications were introduced in it. In the 1990s striking advances were brought about by Farina, who developed new ligands on palladium such as tri(2-furyl)phosphine and triphenylarsine and introduced copper(I) salts as additives to make the reaction conditions milder and the yields higher.[20]–[23] Recent progress up to 1996 was surveyed by Mitchell in the monograph *Metal-Catalyzed Cross-Coupling Reactions* in 1998.[24] A comprehensive survey of this protocol was given by Farina, Krishnamurthy, and Scott in 1997.[25]

The present overview is not concerned with the comprehensive story, but with typical types of reactions in this protocol.

B. GUIDING MECHANISM

The first discussed mechanism was for the reaction with benzylic and aryl halides in 1979.[8],[9] As shown in other protocols, the three-step catalytic cycle is widely accepted, that is, oxidative addition, transmetallation, and reductive elimination (**Scheme 5**).

The reaction is supposed to start with oxidative addition of an electrophilic component to Pd(0) species. Pd(0) catalysts such as $Pd(PPh_3)_4$ and $Pd(dba)_2$ with or without an added ligand are often used. Although Pd(II) catalyst precursors such as $PdCl_2(PPh_3)_2$,



Scheme 5

$BnPdCl(PPh_3)_2$, $PdCl_2(MeCN)_2$, and $Pd(OAc)_2$ are favored in some cases, they are assumed to be reduced to Pd(0) species either by the stannane or an added phosphine ligand prior to the main catalytic process.

The reaction rates and or yields sometimes vary with the choice of Pd(0) or Pd(II). Although the reason is not simple, it seems that the stoichiometric ratio between palladium and ligand is important in most of such cases. It has been reported that an excess of triphenylphosphine retards the oxidative-addition step that is often the rate-determining step.[5] The transmetallation step is also sometimes the rate-determining step; however, the detailed mechanism is still not clear.[21],[26],[27] It is also important to select the proper solvent and ligand on palladium.

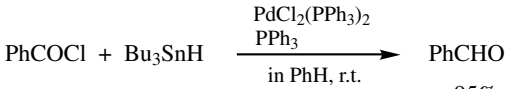
C. REACTIONS OF ACID CHLORIDES WITH ORGANOTINS

The synthesis of ketones from acid chlorides and organotin compounds is quite general with respect to both substrates and reagents tolerating a wide variety of functional groups, such as nitro, nitrile, methoxy, ester, and even formyl groups. Initially the catalyst used was $Pd(PPh_3)_4$ in benzene[3] and then $BnPdCl(PPh_3)_2$ in HMPA[5],[6] followed by $CHCl_3$.[7] For the reaction of ethynyltin compounds, 1,2-dichloroethane was used as solvent (**Scheme 8**).[28] On the other hand, Beletskaya used π-allylpalladium chloride without phosphine ligand in HMPA and called it ligandless palladium.[14] It was found that use of polar solvent such as HMPA, DMF, and $CHCl_3$ gives better results than that of aromatic solvent regardless of the catalyst used. Decarbonylation is a major side process and can be suppressed by carrying out the reaction under a CO atmosphere (**Scheme 9**).[29],[30] Relatively new reaction conditions by Farina are $Pd_2(dba)_3$ + 2 P(2-furyl)$_3$ in THF, which seem to be more general,[21] and the reaction proceeds at room temperature (**Scheme 10**).

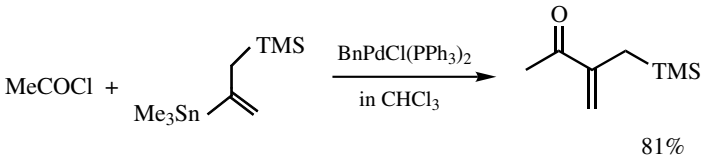
By using trimethyl- or tributyltin as anchoring groups, the order of group transfer from tin is as follows:

$$RC{\equiv}C > RCH{=}CH > \text{aryl} > \text{allyl, benzyl} > \text{alkyl}$$

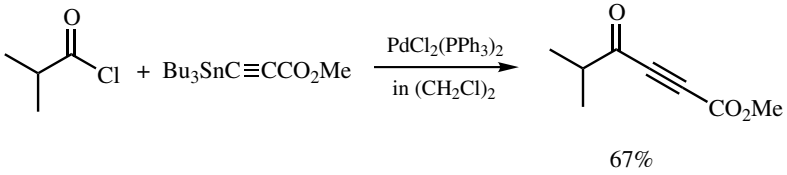
This order appears to be general to other electrophiles. Though oxalyl chloride is not a good substrate, chloroformates and carbamoyl chlorides are good substrates (**Schemes 11** and **12**).[31],[32] Some imidoyl chlorides are known to react with stannanes.[33],[34] Typical examples are shown in **Schemes 6–12**.



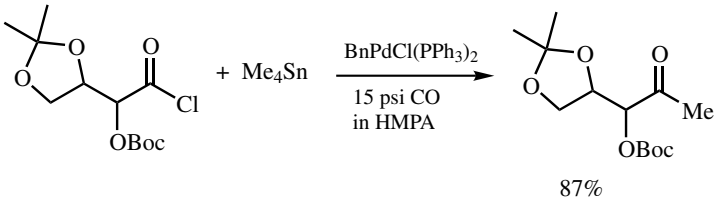
Scheme 6[12]



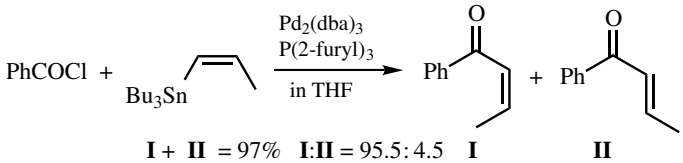
Scheme 7[31]



Scheme 8[28]

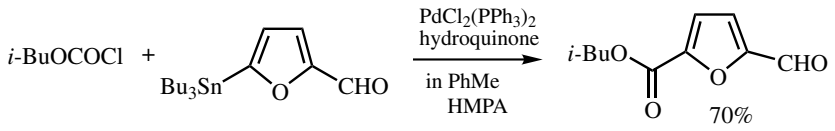


Scheme 9[29]

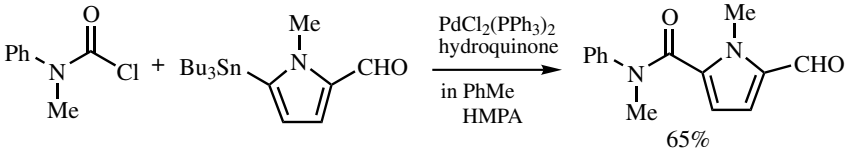


I + **II** = 97% **I**:**II** = 95.5 : 4.5 **I** **II**

Scheme 10[21]



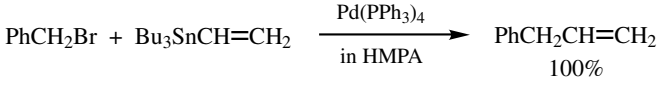
Scheme 11[32]



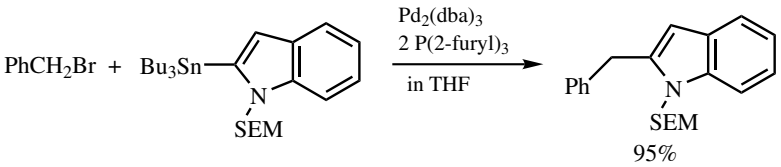
Scheme 12[32]

D. REACTIONS OF BENZYL HALIDES WITH ORGANOTINS

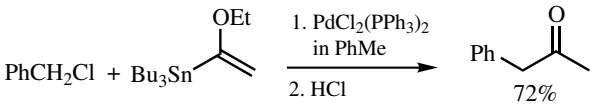
Relatively few reactions of this type have been performed. Benzyl bromide reacts with tetramethyltin, vinyltributyltin, and tetraphenyltin under catalysis by $BnPdCl(PPh_3)_2$ in HMPA to produce the corresponding methylated, vinylated, and phenylated products, respectively, in good yields. The reaction between Me_4Sn and optically active benzylic bromide proceeds with inversion of configuration at the stereogenic center.[8],[9] Some exmples are shown in **Schemes 13–17**. An unfamiliar example is the reaction using nitrogen ligand on palladium (**Scheme 16**).[37]



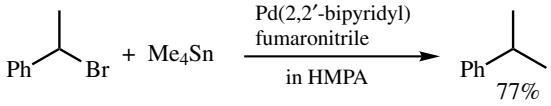
Scheme 13[9]



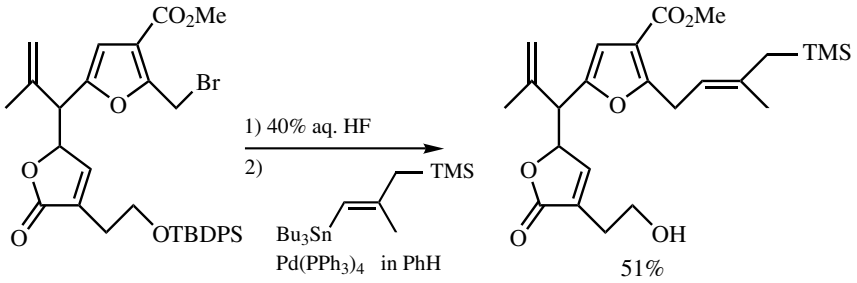
Scheme 14[35]



Scheme 15[36]



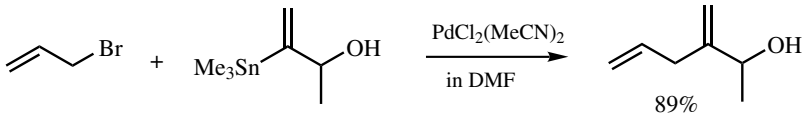
Scheme 16[37]



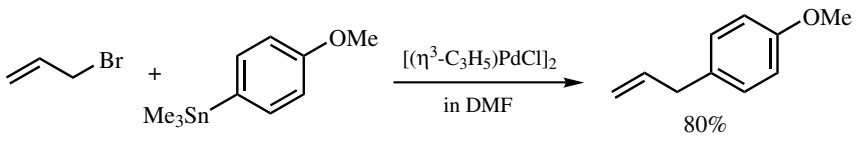
Scheme 17[38]

E. REACTIONS OF ALLYL HALIDES AND ACETATES WITH ORGANOTINS

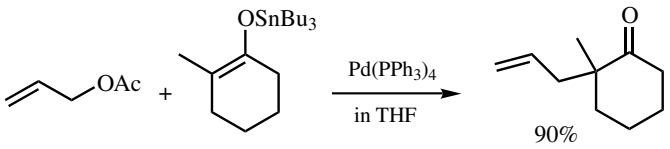
In 1980 Godschalx and Stille[39] and Trost and Keinan[40],[41] independently reported the coupling of allyl bromides and acetates with allyltin reagents, respectively. Since the reaction may proceed via π-allylpalladium intermediate initially formed, the coupling at either the α- or the γ-position seems to be possible. The reaction takes place in most cases at the less substituted terminus of the allylic moiety in the halide or acetate, but predominant allylic rearrangement is observed with that in the tin. More information is available from the literature.[25] In 1981 Beletskaya reported the formation of some amounts of homo-coupling product derived from the stannane along with the cross-coupling reaction of allyl acetates with aryl- or vinyltins.[42]–[45] The reaction with allyl bromide in HMPA readily occurs under ligandless palladium, but phosphine ligand on palladium was necessary for the reaction of less reactive acetates. The use of propargyl halide is rather rare. Their reaction with some stannanes gives allene derivatives predominantly.[46] Some examples are shown in **Schemes 18**–**21**.



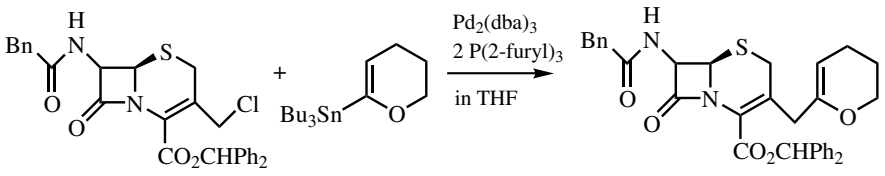
Scheme 18[47]



Scheme 19[48]



Scheme 20[40]



Scheme 21[49]

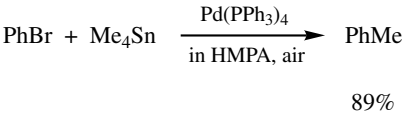
F. REACTIONS OF ARYL OR HETEROCYCLIC HALIDES AND TRIFLATES WITH ORGANOTINS

An initial report was on the reaction of aryl bromides with allyltins under $Pd(PPh_3)_4$ in benzene, indicating that aryl bromides are good substrates, but aryl iodides are poor.[4] A careful tuning of solvents and catalysts enabled the enrollment of both aryl bromides and iodides.[9],[13],[14] Use of chlorides is limited to those with electron-withdrawing substituents at the proper positions.

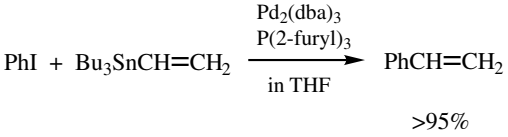
When ligandless palladium is generated from such palladium complexes as $LiPdCl_3$ or $PdCl_2(MeCN)_2$ in solvents, such as HMPA, DMF, or acetone, the coupling reactions with aryl iodides take place at ambient temperature.[14]

Not only allyl, vinylic, and aryltins, but also alkyl and some hetero-substituted tins can be utilized in this protocol. Cyanomethylation, acetonylation, ethoxycarbonylmethylation, and *N*,*N*-diethylamination required tri(*o*-tolyl)phosphine as ligand on palladium.[50]–[53] Quite recently, aromatic amination was developed without the use of stannylamines.[54]–[56]

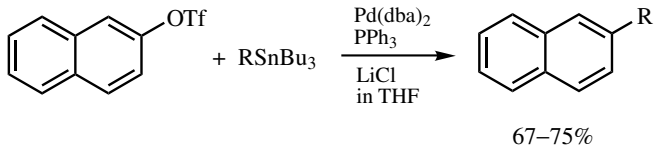
Aromatic diazonium salts instead of the aryl halides also undergo Pd-catalyzed coupling of organotins, but they are less used.[57] Aryl triflates are more popular.[58] The reaction of the triflate required LiCl as an additive. It was explained that triflate ligand of the oxidative adduct has to be replaced by chloride ligand before the transmetallation step. The system composed of $AsPh_3$ as ligand and NMP as solvent seems so far to be the most efficient for cross-coupling with aryl triflates.[22] It does not require LiCl as an additive. The tolerance of heteroaryl halides and triflates is also noteworthy. Some examples are shown in **Schemes 22–28**.



Scheme 22[9]

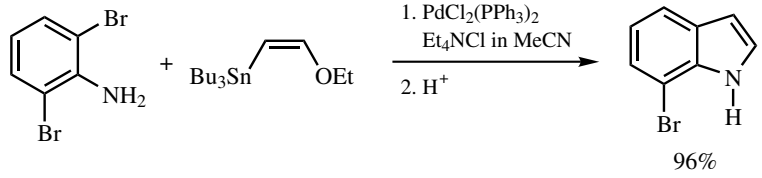


Scheme 23[23]

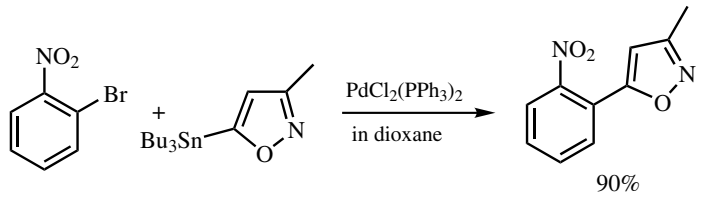


R = H, CH=CH$_2$, 2-thienyl, Ph, (*E*)-CH=CHPh, C≡CPh

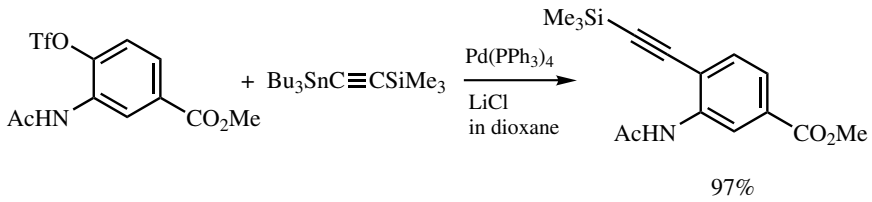
Scheme 24[59]



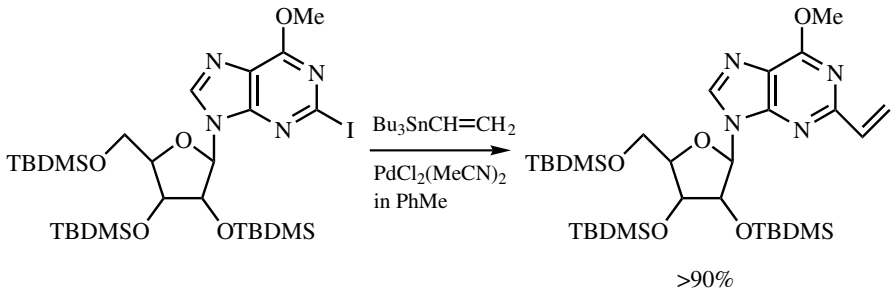
Scheme 25[48]



Scheme 26[60]



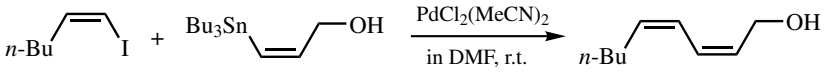
Scheme 27[61]



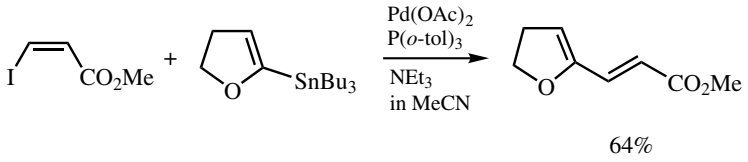
Scheme 28[62]–[64]

G. REACTIONS OF ALKENYL HALIDES AND TRIFLATES WITH ORGANOTINS

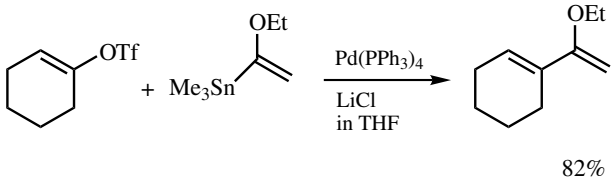
Although few examples of alkenyl chlorides are involved, the corresponding bromides and iodides are generally useful electrophiles. The cross-coupling of alkenyl iodides is often stereospecific, but that of the bromides sometimes involves *E/Z* isomerizations due to the required elevated reaction temperatures. The tolerance of alkenyl triflates has quite enhanced the potential of this protocol as a useful synthetic tool owing to the ready availability of isomerically pure alkenyl triflates. Their reactions usually require the addition of excess LiCl, while it is not necessary when $AsPh_3$ and NMP are used as a ligand and a solvent, respectively, as described in **Sect. F**.[22] Some reactions are shown in **Schemes 29–33**.



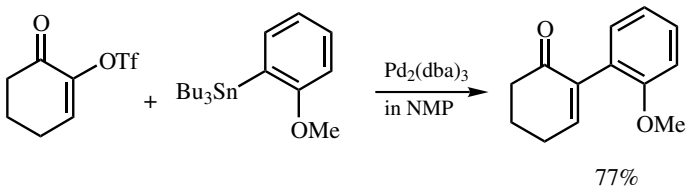
Scheme 29[65]



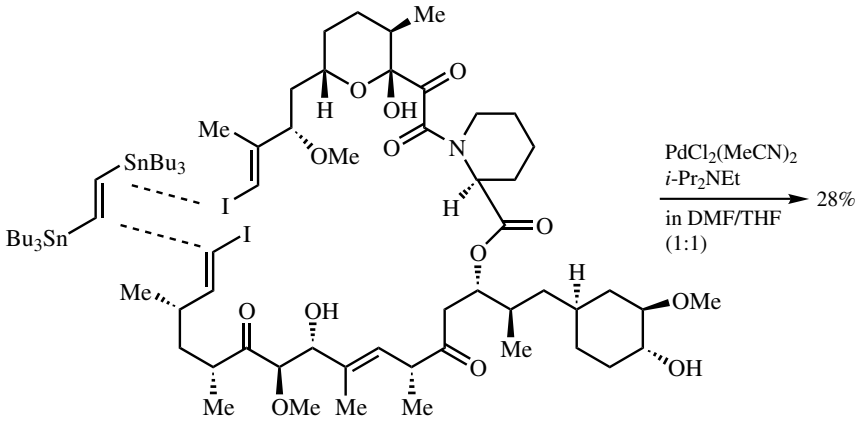
Scheme 30[66]



Scheme 31[67]



Scheme 32[22],[68]

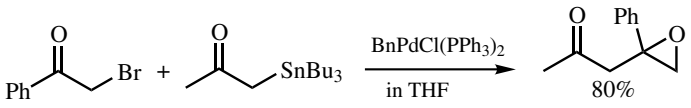


Scheme 33[69]

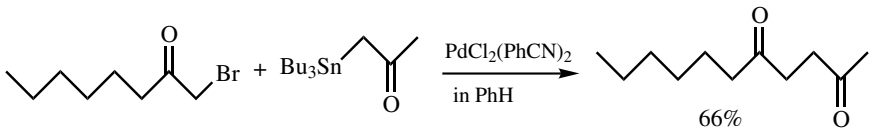
H. REACTIONS OF ALKYL AND ALKYNYL HALIDES WITH ORGANOTINS

Alkyl halides are less investigated in this protocol. α-Halo ethers, thioethers, and lactones can be used in this protocol.[70],[71] α-Halocarbonyl compounds react abnormally with allyl- and acetonyltins to give oxiranes via the attack at the carbonyl followed by the cyclization (**Scheme 34**).[70]–[73] The reaction appears to be a variation of a simple Lewis-acid-catalyzed aldol-type condensation. On the other hand, if a catalyst without phosphine ligand is used, 1,4-diketone is formed (**Scheme 35**).[74]

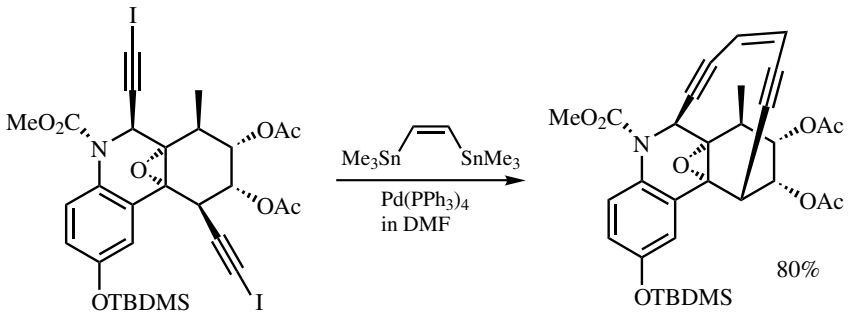
The use of alkynyl halides is rare, but a remarkable result is reported (**Scheme 36**).[75]



Scheme 34[70]–[73]



Scheme 35[74]



Scheme 36[75]

I. CARBONYLATIVE COUPLING

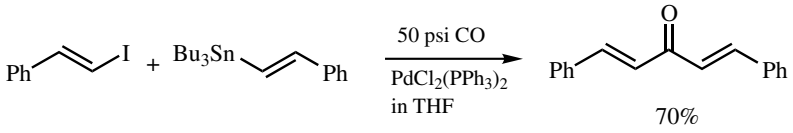
For the ketone synthesis via the present protocol, acid chlorides are useful precursors indeed. Nevertheless, carbonylative cross-coupling with organic halides is strategically the most simple and direct way to this purpose. The Pd-catalyzed carbonylative cross-coupling reaction with various organic halides has been investigated extensively, because of its merits from a synthetic as well as a phenomenal point of view (**Scheme 37**). Acid chlorides are not always readily available, and their preparation is not always compatible with many sensitive functionalities. Therefore, the development of this type of reaction widens the scope of the ketone synthesis in the present protocol because of the ready availability and storability of organic halides and pseudohalides.

$$R^1X + CO + R^2SnR^3{}_3 \xrightarrow{[Pd]} R^1COR^2 + R^3{}_3SnX$$

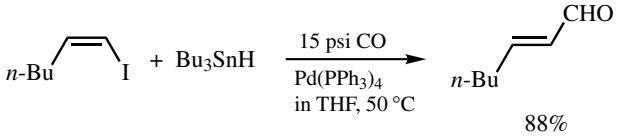
Scheme 37

A guiding mechanism is analogous to the direct coupling shown in **Scheme 1**, except CO insertion takes place after the oxidative-addition step and prior to the transmetallation step.

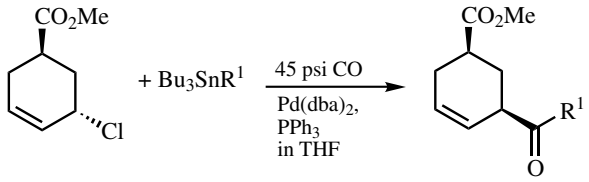
The reaction of alkenyl iodides with alkenyltins takes place under neutral and mild conditions (40–50°, under 1–3 atm CO pressure in THF) (**Scheme 38**).[76] The major side reaction is the direct coupling without CO insertion, which can be suppressed employing slightly higher CO pressures. A problem to be solved is *Z/E* isomerization of alkenyl groups from both of the reaction components, especially when *Z*-alkenyl derivatives are used (**Scheme 39**).[77] Aryl iodides and bromides also readily take part in this reaction, while chlorides usually do not. In this case, the side reaction mentioned above is also obvious, especially when the aromatic ring possesses an electron-withdrawing group. The reaction is also tolerant of allylic and benzylic chlorides, giving the corresponding ketones without any double-bond migration (**Scheme 40**).[79] A variety of heterostannanes such as alkoxy, thioalkoxy, and aminostannanes can be used in this type of reaction to yield the corresponding carboxylic acid derivatives (**Scheme 41**).[78] Alkenyl and aryl triflates widen availability of the electrophilic reaction components (**Schemes 42** and **43**).[80],[81] Some examples are as follows:



Scheme 38[76]

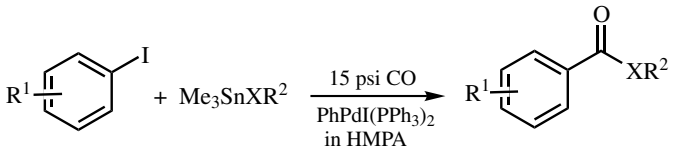


Scheme 39[77]



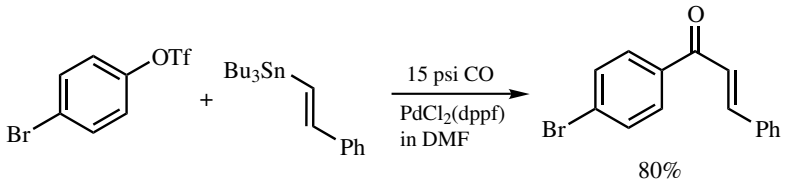
R^1 = Ph, alkenyl, allyl, H

Scheme 40[79]

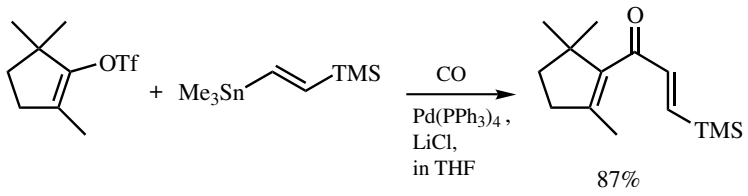


XR^2 = OMe, SPh, NEt_2

Scheme 41[78]



Scheme 42[80]

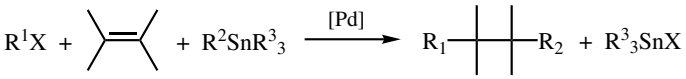


Scheme 43[81]

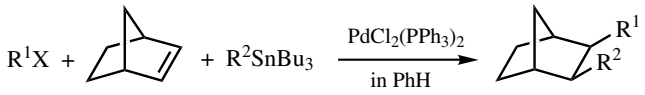
J. TANDEM HECK–STILLE COUPLING

The Stille protocol in the presence of alkenes or alkynes may result in three-component coupling, that is, the formation of two C—C bonds at once. A guiding mechanism appears to be similar to that of carbonylative couplings (**Scheme 44**).

Although this kind of multi bond formation looks efficient from the synthetic point of view, this strategy is rather limited. The reactions are successful only when the Heck adduct does not undergo β-palladium-hydride elimination. Norbornenes (**Scheme 45**)[82],[83] and 1,3-dioxoles (**Scheme 46**)[84] are good exmples of alkenes. Alkynes are also used in place of alkenes (**Schemes 47** and **48**).[85],[86] Besides the three-component connection, there are some examples of this category with the organotin reagents or the electrophiles bearing the alkenic or alkynic moiety (**Schemes 49** and **50**).[87],[88]

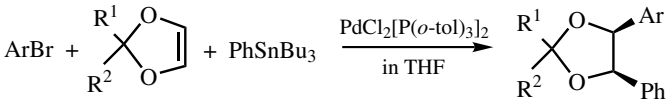


Scheme 44

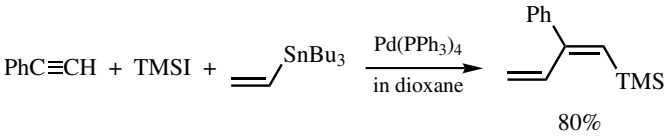


R^1 = aryl, alkenyl
R^2 = aryl, alkenyl

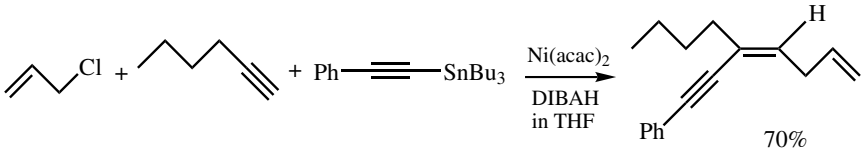
Scheme 45[82]



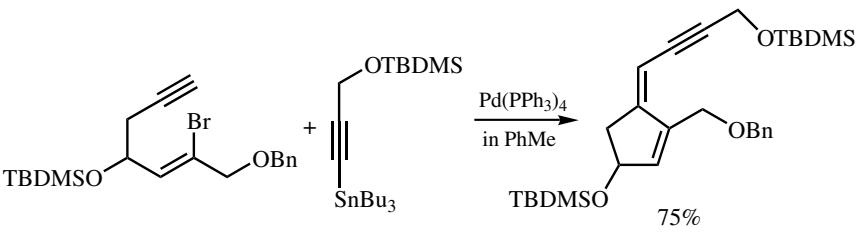
Scheme 46[84]



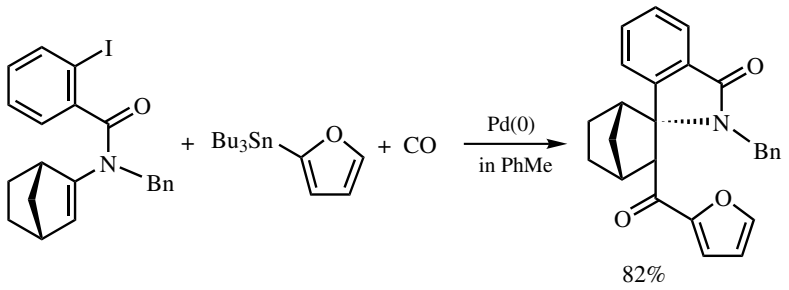
Scheme 47[85]



Scheme 48[86]

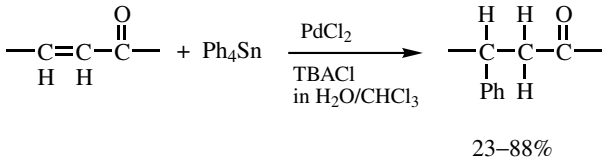


Scheme 49[87]

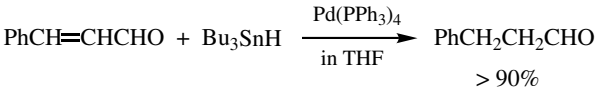


Scheme 50[88]

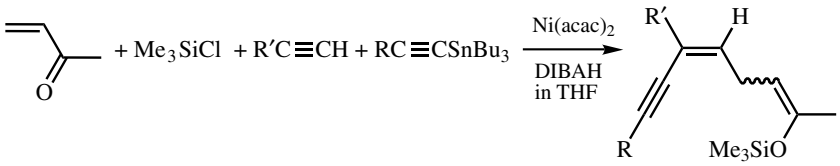
In 1979 Cacchi et al.[89] reported a Pd-catalyzed conjugate addition of tetraphenyltin to α,β-unsaturated ketones under a dual-phase system (**Scheme 51**), and the reaction in **Scheme 52** also seems to be in a similar category.[90] A more complex reaction was reported by Ikeda and Sato[91] using Ni-complex catalyst (**Scheme 53**).



Scheme 51[89]



Scheme 52[90]

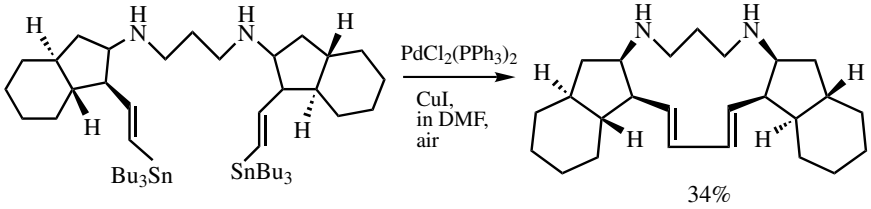


Scheme 53[91]

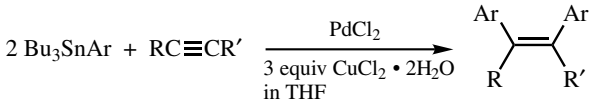
K. MISCELLANEOUS REACTIONS

A few examples of the oxidative homo-coupling of two alkenyltin moieties were reported recently. It is essential to use CuI (**Scheme 54**).[92] As other oxidizing agents, oxygen or air,[93],[94] ethyl 2,3-dibromo-3-phenylpropanoate,[95] and (*E*)-1,2-diiodoethene[96] have been used.

The combination of the homo-coupling and alkyne or alkene insertion may take place under similar conditions (**Scheme 55**).[97],[98] In these cases, copper(II) chloride, chloroacetone, or chloroacetonitrile was used as the oxidizing agent.

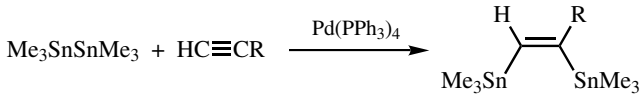


Scheme 54[92]



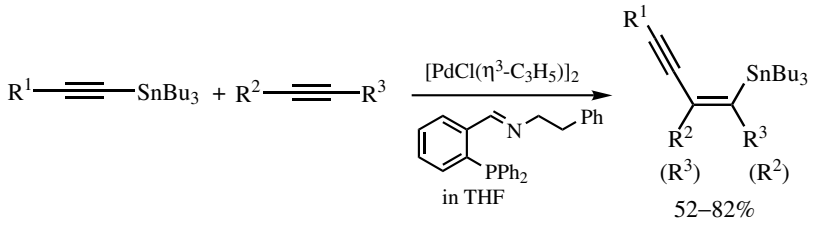
Scheme 55[97]

A reaction related to that mentioned above is distannylation of alkynes, which was reported for the first time in 1983 by Mitchell and co-workers.[99] The reaction is stereoselective, giving *syn*-adduct exclusively (**Scheme 56**). Silylstannanes and borylstannanes react similarly.[100],[101]



Scheme 56[99]

Quite recently, Pd-catalyzed carbostannylation of alkynes was reported by Shirakawa et al.[102]–[104] using rather special ligand (**Scheme 57**). Allyl- and arylstannylation of norbornene catalyzed by an ordinary palladium complex was also developed using an *in situ* generated allyltin trichloride.[105]–[107]



Scheme 57[102]

L. SCOPE OF THE TIN REAGENTS

Alkyltins. The transfer of alkyl groups from tin is much slower than that of other groups. The use of tetraalkyltins is essential in order to transfer an alkyl group from tin. Choice of ligand and solvent is quite important to obtain cross-coupling products in good yield.

In general, only one group among four can be transferred from the tins, because halogen-substituted tin is less reactive.[6],[14] Activation of alkyl groups on tin is one subject receving much attention. There are a number of reports that insist that highly coordinated alkyltin reagents more readily liberate the alkyl group. For example, owing to the intramolecular coordination of nitrogen to tin atom, the alkyl group R instead of the naphthyl group is transferred from compound **III** exclusively.[108] Compound **IV** is also excellent in providing a reactive R group by similar coordination (**Figure 1**).[109]

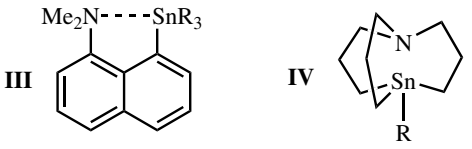


Figure 1

Other hypercoordinated alkyltin reagents are also generated by the addition of such a fluoride ion source as Bu_4NF to appropriate alkyltins.[110],[111]

Allyl, Benzyl, and Related Tins. Simple allyltrialkyltins may couple with acid chlorides, aryl halides, or aryl triflates to give the allylation product in good yield. Subsequent works revealed, however, that the reaction takes place at either the α or γ position, depending on the structure of the tins and the conditions used. At present, the regiochemistry of the coupling is still unpredictable. Moreover, allylic double bonds tend to move into conjugation, when acyl halides and aryl triflates are used as electrophiles. This can sometimes be suppressed by lowering the reaction temperatures.[21]

From the structural analogies of the allyl group and in view of the α-substituent bearing π- or unshared electrons, benzyl, hydroxymethyl, methoxymethyl, cyanomethyl, ethoxycarbonylmethyl, and acetonyl groups can be selectively transferred from the corresponding trialkyltins.[16]

Aryl or Heterocyclic Tins. Aryltrialkyltins with both electron-releasing and electron-withdrawing substituents on the aryl ring can be used in this protocol. Steric effects can be important, however. Presence of the alkyl group ortho to tin often retards the coupling, and alkyl group transfer may compete.[22] This problem can sometimes be overcome successfully by adding Cu(I) salts.[22] There are a number of examples using heteroaryltrialkyltins such as pyridyl-, furyl-, thienyl-, pyrrolyl-, and thiazolyl tins.[16]

There are examples using aryltrichlorotins in aqueous media, in which the reaction is facilitated probably by base-assisted generation of active hypervalent aryltin species.[112],[113] The reaction seems to be limited to water-soluble electrophiles. Quite recently, Bu_4NF was found to enable utilization of all four aryl moieties of tetraarylstannanes toward arylation of aryl halides.[114]

Alkenyltins. The coupling of alkenyltrialkyltins is a general and synthetically useful reaction. Most studies are on easily available 1,2-disubstituted substrates, which couple efficiently with good stereospecificity except for *Z* substrates. Again, steric hindrance makes the reaction with electrophiles slower or difficult. In this case, the addition of Cu(I) salts is effective.[23],[25] In the reactions with 1-substituted

1-stannylethene, cine-substitution was sometimes observed especially in the reaction of tins with electron-rich olefinic moieties.[115] This might be attributed to a participation of a Pd(0)–carbene species generated via α-elimination of regioisomeric Heck intermediate.[116]

Alkynyltins. These tins are the most reactive and couple with a variety of electrophiles smoothly, although there is no need to use these reagents if the Sonogashira reaction can substitute.[117]

Acyltins. Acyltins, which are sensitive toward oxygen giving stannyl carboxylate, can be coupled with acid chlorides to yield α-diketones.[118] A CO atmosphere suppresses decarbonylation which is the major side process.

Hexamethyl- and Hexabutylditin. These ditins undergo cross-coupling with a variety of organohalides and pseudohalides (such as aryl halides, vinyl triflates, acyl chlorides, and allyl halides) in this protocol to give the correponding tin compounds. The reaction is particularly useful for preparation of organotins with labile functionalities that are not compatible with other procedures.[16],[17],[19],[24]

Tributyltin Hydride. This reagent can be used for reduction of halides, hydrostannylation of alkynes, and preparation of hexabutylditin.

Aminostannanes. Aminostannanes react with aryl and alkenyl bromides to give the corresponding amino compounds.[53] But recently, tin-free systems have been developed.[54]–[56]

Alkoxystannanes. Only few examples are known of the coupling reactions with allylic and alkenyl electrophiles.[119]–[121]

Stannyl Sulfides and Stannylphosphine. These compounds can be used to prepare the sulfides[122],[123] and the phosphine[124] from the corresponding organohalides, respectively.

Polymer-Supported Stannanes and Fluorous Stannane. Some interesting procedures are being developed to make the present protocol more useful as a synthetic tool. Directed toward combinatorial synthesis, solid-phase syntheses have currently been under development using polymer-supported stannanes.[125],[126] In these cases trialkyltin halide is released during the course of the reactions. More recently, a new version was developed with inversed strategy. In this process, the stannyl group remains on the polystyrene support and could be recovered for reuse.[127]

The reaction of fluorous tin such as $ArSn(CH_2CH_2C_6F_{13})_3$ makes product isolation easier, because the organotin by-product formed after the reaction is easily separable by a three-phase extraction method.[128]–[130]

M. CONCLUSION

The Stille protocol is now well established and finds many uses in preparative chemistry. Especially noteworthy is application to the synthesis of bioactive substances. The choice

of catalyst and solvent, however, still remains veiled. If the reaction to be attempted is not well documented, one should first try to find the most suitable reaction conditions. Organotin compounds can be extremely toxic, and tributyltin compounds are recently suspected of being endocrine disrupters. The presence of even traces of organotin compounds in organic products must be avoided, if possible. In spite of these problems, the Stille protocol will continue to be a favorite method for carbon–carbon bond formation, owing to the mildness of the reaction conditions and the functional tolerability of both substrates and reagents.

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