

The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles

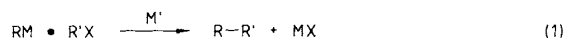
New Synthetic
Methods (58)

By John K. Stille*

The cross-coupling of organotin reagents with a variety of organic electrophiles, catalyzed by palladium, provides a novel method for generating a carbon-carbon bond. Because this mild, versatile reaction is tolerant of a wide variety of functional groups on either coupling partner, is stereospecific and regioselective, and gives high yields of product, it is ideal for use in the synthesis of elaborate organic molecules. When the coupling reaction is carried out in the presence of carbon monoxide, instead of a direct coupling, carbon monoxide insertion takes place, stitching the two coupling partners together and generating a ketone.

1. Introduction

There are relatively few basic reaction types that generate a new carbon-carbon bond, although this is one of the most critical operations in the synthesis of organic molecules. Group VIII transition metals, particularly nickel and palladium, are effective in catalyzing the cross-coupling of organometallic reagents with organic halides and related electrophiles [Eq. (1)].^[1,-10]



In order for the coupling reaction to be useful, it should be relatively straightforward and require only a small amount of catalyst. Moreover, the reaction conditions and reagents, particularly the organometallic partner, should tolerate a wide variety of functional groups so that tedious protection-deprotection reactions are not necessary. Of the organometallic reagents available, many will not tolerate sensitive functionality on the coupling partners, are difficult to prepare, or are air or moisture sensitive, and few can be purified and stored.

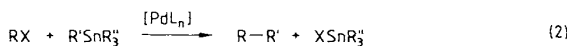
Various organometallic reagents, RM, have been used in coupling reactions with disparate success. High conversions often are not obtained with lithium or Grignard reagents, neither of which will tolerate a wide variety of functional groups on either coupling partner,^[2,3] and often homocoupling of the organic halide is observed. The copper-promoted coupling of alkenyl or aryl compounds is more successful, but it often results in extensive homocoupling.^[11] In addition, the methods of synthesis of copper reagents do not always allow the presence of the more reactive functional groups on the organocopper partner.

The use of organometallic reagents containing metals of intermediate electropositive character generally leads to higher yields of coupled product and fewer side reactions. Many of these organometallic compounds tolerate a wide range of functional groups in either or both of the coupling partners. Organozinc compounds are particularly good in

this regard, although the methods of synthesis limit the variety of structures that can be incorporated into the organic portion of the organozinc reagent. Organomercurials also tolerate functionality, but the methods for their synthesis are somewhat limiting; moreover, methods for the alkylation of organomercurials are unfortunately limited to a few examples with organic halides.^[12,13] Organometallic partners in which the metal is boron or aluminum often are not conveniently synthesized or the structure of the organic portion is limited by the methods of synthesis available, usually hydroboration or hydroalumination.^[4-7] Organozirconium reagents have the advantage that ether or acetal groups are tolerated in the hydrozirconation reaction and carbonyl and ester groups may be present in the alkenyl halide partner.^[14] In coupling reactions, low turnovers of catalyst are observed, however.

One of the most versatile organometallic reagents in palladium-catalyzed coupling reactions is the organotin reagent. Organotin compounds containing a variety of reactive functional groups can be prepared by a number of routes; moreover, these reagents are not particularly oxygen or moisture sensitive. Because of their value in coupling reactions, a brief survey of their syntheses, particularly some of the more recent ones, is presented.

In the palladium-catalyzed coupling of organic electrophiles with organotin reagents, essentially only one of the groups on tin enters into the coupling reaction [Eq. (2)].



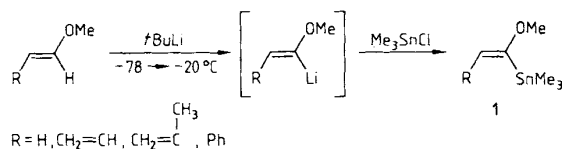
This is not a problem if a relatively simple organic group, for example, methyl, is to be transferred, since tetramethyltin can be used. If the group is more expensive or difficult to synthesize, however, then the utilization of only one of four identical groups would be a distinct disadvantage. Fortunately, different groups are transferred with different selectivities from tin, the simple alkyl group having the slowest transfer rate (see Section 3.1). Thus, an unsymmetrical organotin reagent containing three simple alkyl groups (such as methyl or butyl) is chosen; the fourth group, which undergoes transfer, is usually an alkenyl, alkenyl, aryl, benzyl, or allyl group.

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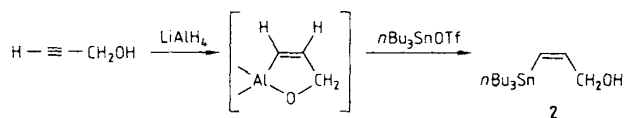
2. Synthesis of Organotin Reagents

2.1. Synthesis from Electrophilic and Nucleophilic Triorganotin Compounds

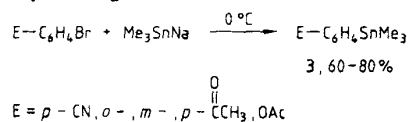
A variety of methods for the synthesis of unsymmetrical organostannanes are known.^[15-18] Although the reaction of a triorganotin halide with an organometallic compound is widely used, its scope of application is limited since the organometallic compound (usually M = Li, Al, Mg) does not allow a large variety of functional groups to be introduced into the organotin product. There are a number of valuable synthetic procedures involving organic anions, however. Lithiation of an enol ether followed by reaction with trimethyl- or tributyltin chloride gives a vinyltin reagent **1** that can serve as an acyl anion equivalent.^[19,20]



The reaction of propargyl alcohol with lithium aluminum hydride followed by tributyltin trifluoromethanesulfonate (triflate) yields the *Z*-vinyltin reagent **2**.^[21] Cuprates also undergo *cis* addition to acetylenes, generating a vinyl metal compound, which reacts with tributyltin triflate to yield the (*Z*)-vinyltin compound.^[22]

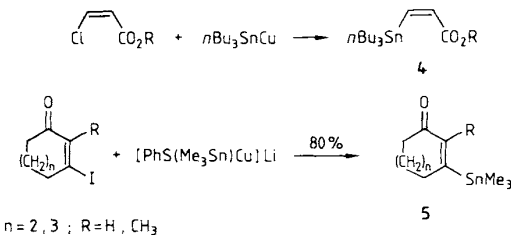


The inverse reaction of a trimethyl- or tributyltin anion with an organic electrophile is more versatile. The displacement of a halide or tosylate by a trimethyltin anion can be made to take place with inversion of configuration at an sp³ carbon. Reaction of sodium trimethylstannate with an aryl bromide takes place under mild conditions, without reaction at other electrophilic substituents, to yield aryltin reagents **3**.^[16,17]

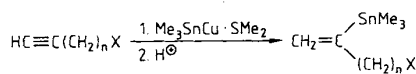
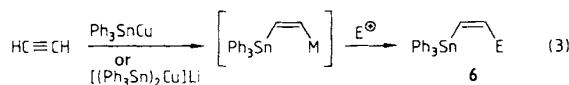


The reaction of lithium tributylstannate with (*Z*)-β-chlorostyrene occurs with retention of configuration of the double bond. This reaction provides a method of synthesis of either pure (*E*)- or (*Z*)-β-tributyltin acrylates **4** from the

corresponding (*E*)- and (*Z*)-β-chloroacrylates.^[23] The reaction of a tin cuprate with an α,β-unsaturated β-iodo ketone gives high yields of the corresponding tin reagent **5**.^[17,18]

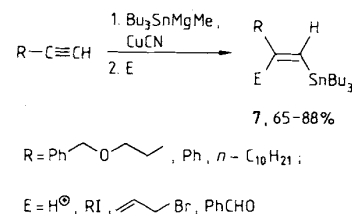


An especially useful reaction is the stereospecific addition of a complex containing a copper-tin bond across a triple bond. The stereochemistry of addition depends on the particular copper reagent and the reaction conditions. Acetylene undergoes a *cis* addition with the copper(I) reagents Ph₃SnCu and [(Ph₃Sn)₂Cu]Li [Eq. (3)].^[24] The initially

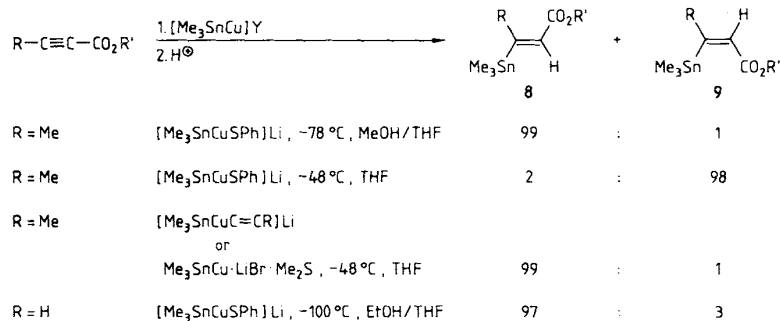


n = 1-4, 6; X = OH, OTHP, OSi^tBuMe₂, Cl

formed anion can be trapped with a variety of electrophiles to yield the substituted vinyltin reagents **6**. When Me₃SnCu·SMe₂ is used, the regiochemistry of addition to a monoalkyl-substituted acetylene is that expected for anionic addition; the alkyne can bear a variety of alkyl groups (THP = tetrahydropyranyl).^[25] Methylmagnesium tributylstannate in the presence of copper(I) cyanide, however, yields product **7** of opposite regiochemistry. A vari-

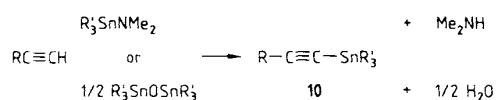


ety of electrophiles may be used to trap the vinyl anion.^[26] Either *cis* or *trans* addition of trimethylstannyl copper reagents to substituted and unsubstituted propiolate esters can be achieved to yield either (*E*)-**8** or (*Z*)-**9**, depending on the cuprate and the reaction conditions (THF = tetrahydrofuran).^[27,28]

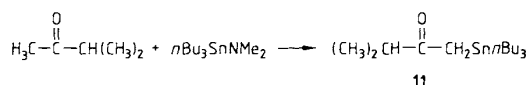


2.2. Synthesis from Tin Amides and Oxides

Weakly acidic hydrogen can be replaced by tin in a reaction with tin amides or oxides.^[15-17,29] This serves as a mild method for the synthesis of acetylenic tin reagents **10** and α -stannyl ketones **11**.

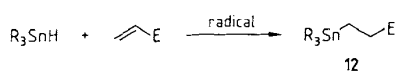


R = alkyl, aryl, CN, CH=CHOMe, OEt



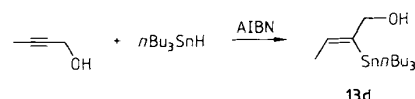
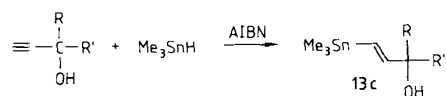
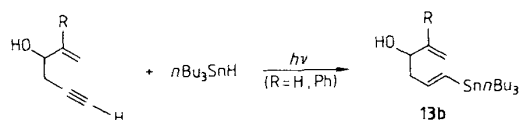
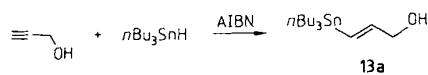
2.3. Tin Hydride Additions to Alkenes and Alkynes

The free radical addition of triorganotin hydrides to olefins takes place regioselectively.^[15] This reaction has limited use, however, since the product **12** is a mixed alkyltin reagent, which will not necessarily transfer the newly added group exclusively in a catalytic coupling reaction.

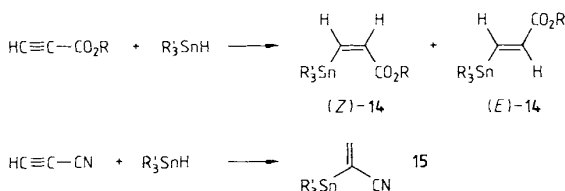


E = CONH₂, CH(OEt)₂, CH₂OH, CN

The radical addition of triorganotin hydrides to mono-substituted acetylenes to give substituted vinylstannanes **13** is mostly regioselective, the (*E*)-isomer being favored, although an (*E*)/(*Z*) mixture is often obtained (AIBN = azobisisobutyronitrile).^[30-34]



Radical addition to propiolate esters generally yields one regioisomer **14** as an (*E*)/(*Z*) mixture.^[15,35] In the absence of catalyst, especially in polar solvents, cyanoacetylene yields the vinyltin reagents **15**.

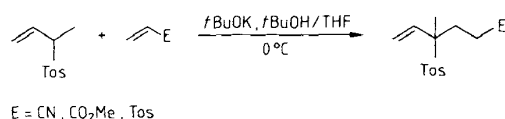


Triorganotin hydrides also react with diazoalkanes, giving the tin reagents **16** containing various functional groups.^[15] However, these tin reagents will be useful in coupling reactions only if selective transfer of the added alkyl group is realized.

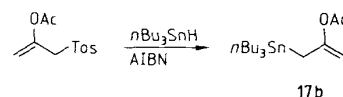
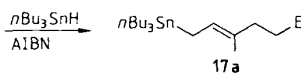


R' = CO₂Et, COCH₃, COC₆H₅, CN

The radical addition of tributyltin hydride to an olefin containing an allylic tosylate leaving group leads to the allyl tin reagents **17a**, bearing a nitrile, ester, or tosyl group, or **17b**, bearing an enolacetate group.^[36]

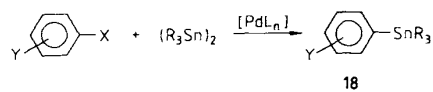


E = CN, CO₂Me, Tos



2.4. Reactions of Hexaalkyldistannanes with Organic Halides

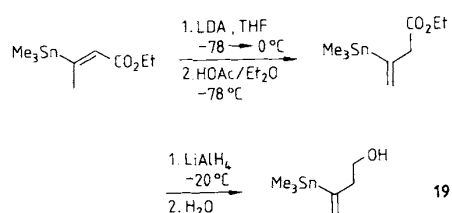
The mild, palladium-catalyzed coupling of hexaalkyldistannanes with aryl, benzyl, or allyl halides provides a unique method of synthesis of organotin reagents in which the organic group derived from the organic halide can have reactive substituents.^[37-39] This synthetic procedure is especially valuable for the synthesis of trialkylaryltin reagents **18**.



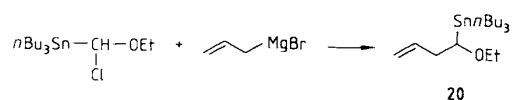
X = Br, I; Y = C(=O)CH₃, CN, NO₂; R = Me, nBu

2.5. Elaboration of Organotin Reagents

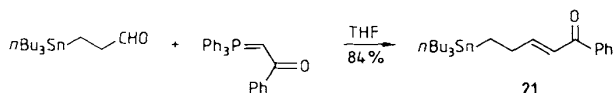
Tin-carbon bonds in organotin reagents are relatively stable, the bond energy being about 50 kcal/mol.^[15] Thus, it is not surprising that a wide variety of reactions can be performed at other functional groups in the molecule without breaking the Sn-C bond. For example, the permanganate oxidation of primary alcohols to carboxylic acids^[15] and the chromium trioxide oxidation of secondary alcohols to ketones,^[16, 17] as well as the lithium aluminum hydride reduction of esters, nitriles, and ketones to alcohols and amines,^[15-17, 40] can be carried out without cleavage of the carbon-tin bonds. Thus, the substituted vinyltin reagent **19**, containing a primary OH group, was obtained by an isomerization-reduction sequence (LDA = lithiumdiisopropylamide).^[41]



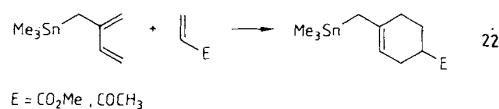
The Sn-C bond survives reactions of Grignard reagents, either when the Grignard reagent is allowed to react with an organotin compound containing an appropriate functional group or when a halogen-containing organotin compound is converted into a Grignard reagent.^[15, 17] Cyano and carbonyl groups on one of the organic groups of an unsymmetrical organotin reagent undergo Grignard reactions in the usual manner. An unsymmetrical organotin compound containing an α -chloroether function reacts with allylmagnesium bromide, for example, to yield the allylic tin reagent **20**.^[42]



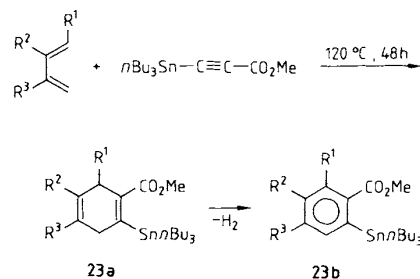
The NH₂ group undergoes typical reactions with various electrophiles;^[43] for example, amines may be converted into isocyanates with phosgene.^[16] Unsymmetrical organostannanes undergo the Wittig reaction, either by reaction of an aldehyde function on the organotin compound with methylenetriphenylphosphorane^[15, 16] or by reaction of an organotin-containing Wittig reagent with an aldehyde.^[17] This reaction has been used in the synthesis of the organotin reagent **21** containing an α,β -unsaturated ketone.^[44]



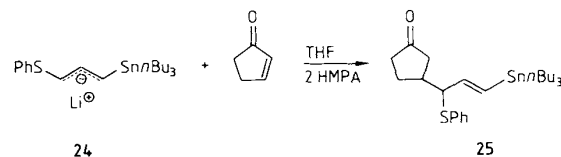
Olefinic groups on an organotin reagent can be hydroborated^[17] and acetylenic groups add alkylboranes.^[16] Cyclopropanation of an acetylenic group can be achieved with diazoalkanes.^[16] A 1,3-diene containing a trimethylstannylmethyl group in the 2-position will undergo the Diels-Alder reaction with an electron-poor dienophile,^[45] thereby providing a new allylic tin reagent **22**.



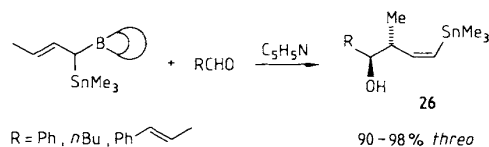
A Diels-Alder reaction between methyl tributylstannylpropionate and substituted butadienes at 120 °C gives good yields of the 1,4-cyclohexadiene adduct **23a**, which can be dehydrogenated to the aryltin reagent **23b**.^[46]



The ability to generate relatively stable anions on an organic group attached to tin, without carbon-tin bond cleavage, provides a versatile method of elaboration of organostannanes. The stabilized allyl anion **24**, for example, undergoes 1,4-addition to cyclopentenone to yield the vinyltin reagent **25** (HMPA = hexamethylphosphoramide).^[47]

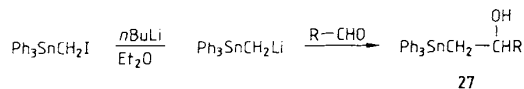


In a related reaction, aldehydes react with 9-borabicyclononane(9-BBN)-substituted organotin compounds with allylic rearrangement to yield the vinyltin reagents **26**.^[48]

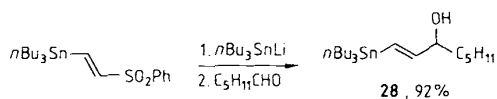


An anionic center in the α -position to tin reacts with a variety of electrophiles (such as aldehydes, ketones, and

allyl bromides) to give the organostannanes **27**.^[49] In the example shown, however, the alkyl group could not necessarily be expected to undergo selective transfer in transition-metal-catalyzed coupling reactions. A tributyltin-substituted vinyl anion also adds to aldehydes to give an al-



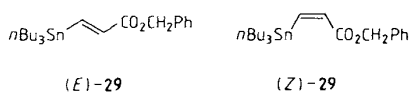
lylic alcohol **28** in which the Sn-C(sp²) bond could be expected to undergo preferential cleavage in coupling reactions.^[50]



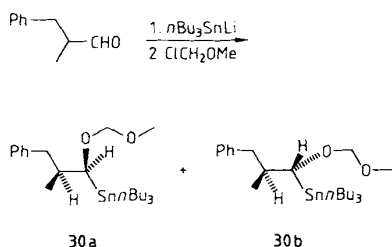
2.6. Separation and Purification of Organotin Compounds

Since organotin reagents are relatively stable, it should not be surprising that some can be purified by distillation. Higher-molecular-weight compounds can sometimes be crystallized. Most importantly, many of the reagents withstand chromatography on silica gel.

The separation of an (*E*)/(*Z*) mixture of benzyl tributylstannylacrylate **29**, obtained from the addition of tributyltin hydride to benzyl propiolate, can be achieved on a preparative scale by medium pressure liquid chromatography (MPLC) on silica gel. The (*Z*)-isomer elutes first and can be reisolated to an (*E*)/(*Z*) mixture, thereby providing a means of converting nearly all of the product into the (*E*)-isomer.



The reaction of 2-methyl-3-phenylpropanal with lithium tributylstannate followed by chloromethyl methyl ether yields two stereoisomers, **30a, b**, which also have been separated on an MPLC column.^[51]



3. Reactions with Organotin Compounds

The coupling reaction of organotin reagents with organic electrophiles catalyzed by palladium takes place under mild conditions in high yields. A wide variety of organic halides and organotin compounds can be coupled, either directly or in the presence of carbon monoxide (to yield a ketone, RCOR', see Section 3.2) (Table 1). Moreover, a wide variety of functional groups (e.g., CO₂R, CN, OH, and even CHO) are tolerated on either partner. In addition, the reaction is regioselective in coupling reactions of allyl partners and occurs stereospecifically with inversion of configuration at sp³ carbon centers bound to tin and/or halogen. Usually retention of configuration of the double bond is observed regardless of which reactant contains the double bond.

Table 1. Organotin reagents and electrophilic compounds suitable for coupling reactions.

Electrophile	Organotin reagent
R-C(=O)-Cl	H-SnR_3
$\text{R}'\text{-C(R)C(R'')=CH-X} \quad [\text{X}=\text{Cl, Br}]$	$\text{R}'\text{C}\equiv\text{C-SnR}_3$
$\text{Aryl-CH}_2\text{-X} \quad [\text{X}=\text{Cl, Br}]$	$\text{R}''\text{-C(R''')=C-SnR}_3$
$\text{R}'\text{-C(R)C(R'')=CH-X} \quad [\text{X}=\text{I, OTf}]$	Aryl-SnR_3
$\text{Aryl-X} \quad [\text{X}=\text{Br, I}]$	$\text{R}''\text{-C(R''')=C-CH}_2\text{-SnR}_3$
$\text{R}'\text{-C}\begin{array}{l} \text{CO}_2\text{R} \\ \\ \text{C-X} \\ \\ \text{H} \end{array} \quad [\text{X}=\text{Br, I}]$	$\text{Aryl-CH}_2\text{-SnR}_3$
	$\text{H}_{2n+1}\text{C}_n\text{SnR}_3$

In the following discussion, the direct coupling reaction of organotin compounds with acid chlorides, organic halides, and vinyl triflates will be treated separately from the carbonylative coupling (Section 3.2).

3.1. Direct Coupling

The catalytic cycle in Scheme 1 serves as a working model for the direct coupling reaction. Although this cycle has yet to be established for the coupling, many of the individual steps in the cycle have been documented;^[52-57] a more detailed mechanistic discussion of certain of the coupling reactions is given in Section 4.

Notably absent from the list of electrophiles in Table 1 are those organic compounds with a hydrogen on an sp³ carbon in the β-position to the carbon bearing the leaving group. This limitation is imposed because the slowest step

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