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Palladium catalyzed coupling of organotin reagents with organic electrophiles

J. K. Stille

Department of Chemistry, Colorado State University, Fort Collins,
Colorado 80523, U.S.A.

Abstract: A novel, synthetically useful palladium catalyzed cross-coupling reaction of organotin reagents with a variety of organic electrophiles that generates a new carbon-carbon bond has been discovered recently. Because this mild, versatile reaction is tolerant of a wide variety of organic functionality on either coupling partner, is stereospecific, and gives high yields, it is ideal for use in the synthesis of complicated organic molecules. In the presence of carbon monoxide, instead of a direct coupling reaction, carbon monoxide insertion takes place, stitching the coupling partners together and generating a ketone. The utility of this coupling reaction has been demonstrated by the synthesis of a macrodiolide antibiotic, marine sesquiterpenes, insect pheremones and a number of key synthetic intermediates.

INTRODUCTION

The cross-coupling of an organic electrophile with an organometallic reagent is catalyzed by a number of Group VIII transition metals, particularly nickel and palladium (ref. 1). In order for this reaction, which generates a new carbon-carbon bond, to be useful, it should be highly catalytic and take place under mild reaction conditions. In addition, a wide variety of other functionality on either coupling partner should be able to endure the reaction conditions such that tedious protection-deprotection sequences of these functional groups carried into the product are not required. Of the various organometallic reagents available, many will not tolerate sensitive functionality on the coupling partners, are difficult to prepare, are air or moisture sensitive, and few can be purified and stored.

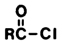
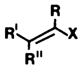
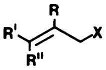
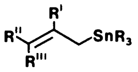
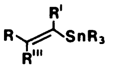
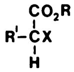
One of the most versatile organometallic reagents is the organotin reagent. Organotins containing a variety of reactive functional groups can be prepared by a number of different reaction types, and these reagents are not particularly oxygen or moisture sensitive (ref. 2-4). In fact, many organotin reagents can be purified by silica column chromatography or by distillation without decomposition.

The coupling reaction of organic electrophiles with organotin reagents catalyzed by palladium takes place under mild conditions in high yields. A wide variety of organic electrophiles and organotins can be utilized. The organic electrophiles and organotin partners that will enter into the coupling reaction, either directly or in the presence of carbon monoxide (to yield a ketone RCOR', vide supra) are numerous, leading to many possible coupling combinations (Table 1). Most importantly, the reaction will tolerate a wide variety of functionality on either partner, including ester, nitrile, alcohol and even aldehyde. In addition, the reaction is regioselective in coupling reactions of allyl partners. It is stereospecific with inversion of configuration at carbon occurring at the sp^3 carbon centers bound to tin and/or halogen; retention of geometry at the double bond is observed when either vinyl tin or vinyl halides are utilized.

$$RX + R'SnMe_3 \xrightarrow{PdL_n} R\text{-}R' + XSnMe_3$$

Two general types of catalytic coupling reactions of organic electrophiles with organotins have been carried out. In direct catalytic coupling reaction, acid chlorides, organic halides, and vinyl triflates have been utilized. The catalytic cycle (Fig. 1) serves to illustrate how this coupling reaction works; the mechanisms of many of the individual steps in this reaction have been documented (ref. 5-10). If, however, carbon monoxide is present in the reaction, CO insertion can take place subsequent to the oxidative addition step to yield an acylpalladium complex (Fig. 2). Thus, a ketone synthesis can be obtained by running the coupling reaction in the presence of CO (carbonylative coupling) and this reaction is treated separately from the direct coupling. The synthetic utility of certain of these coupling reactions will be illustrated in the following sections.

TABLE 1. Organotin and electrophilic coupling partners.

ORGANIC ELECTROPHILE	ORGANOTIN REAGENT	ORGANIC ELECTROPHILE	ORGANOTIN REAGENT
 $RC(O)-Cl$	$H-SnR_3$	 [X = I, OTf]	$ArSnR_3$
 [X = Cl, Br]	$R'C{\equiv}C-SnR_3$	ArX [X = Br, I]	
$ArCH_2X$ [X = Cl, Br]		 $R'-CH(CO_2R)X$ [X = Br, I]	$C_nH_{2n+1}SnR_3$

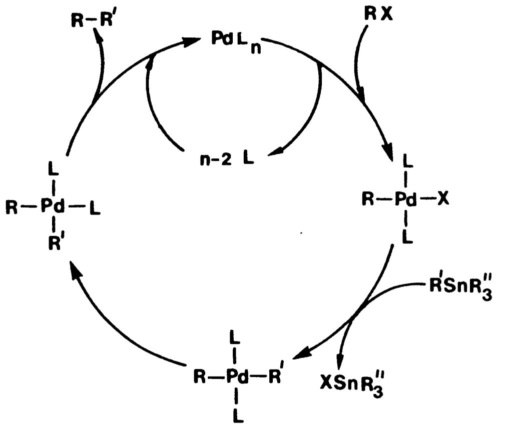


Fig. 1. Direct coupling.

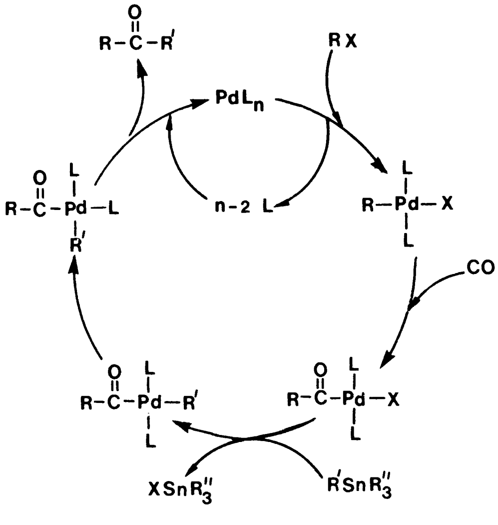
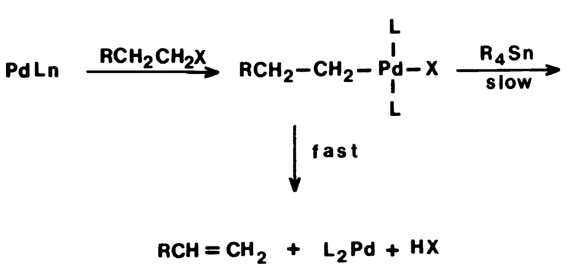
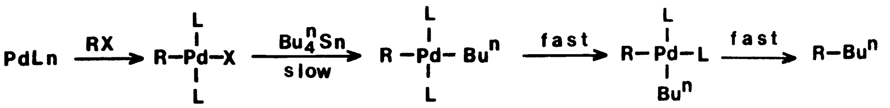


Fig. 2. Carbonylative coupling.

Notably absent from the list of electrophiles (Table 1) are those organic halides--and other organic compounds containing a leaving group--that have a hydrogen on an sp^3 carbon β- to the carbon bearing the leaving group. This limitation is imposed because the slow step in the catalytic cycle, the transmetallation step, is much slower than the β-elimination that takes place with the alkylpalladium halide complex (Eq. 1). This limitation is not imposed on the organotin partner, however, since the catalytic steps taking place after transmetallation--trans to cis isomerization and reductive elination--apparently are faster than β-elimination (Eq. 2).

 (1)

$$PdLn \xrightarrow{RCH_2CH_2X} RCH_2-CH_2-\underset{L}{\overset{L}{Pd}}-X \xrightarrow[slow]{R_4Sn}$$
$$\downarrow \text{fast}$$
$$RCH{=}CH_2 + L_2Pd + HX$$

 (2)

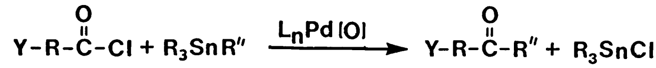
$$PdLn \xrightarrow{RX} R-\underset{L}{\overset{L}{Pd}}-X \xrightarrow[slow]{Bu^n_4Sn} R-\underset{L}{\overset{L}{Pd}}-Bu^n \xrightarrow{fast} R-\underset{Bu^n}{\overset{L}{Pd}}-L \xrightarrow{fast} R-Bu^n$$

DIRECT COUPLING

The direct palladium catalyzed coupling reactions of acid chlorides, benzyl halides, allyl halides, vinyl halides, vinyl triflates and aryl halides with various organotins have been reasonably well worked out. Our initial studies were directed at the reactions of acid chlorides to yield ketone .

Acid chlorides

The coupling has been applied to the synthesis of ketones from acid chlorides (ref. 11-15). We have shown (ref. 11,12) that the reaction is quite general with respect to the organotin reagent and the acid chloride. Aromatic, aliphatic and heterocyclic acid chlorides give high yields of product (75-100%) in 15 min - 1 h under very mild (25°C), neutral reaction conditions and catalytic turnovers of 1000 have been achieved. Sterically hindered acid chlorides react normally, α,β-unsaturated acid chlorides do not undergo conjugate addition, and diacid chlorides can be utilized. There is no further addition to the product ketone, and a wide variety of functional groups (Y) can be tolerated, including nitro, nitrile, haloaryl, methoxy, ester and <u>even aldehyde</u>.



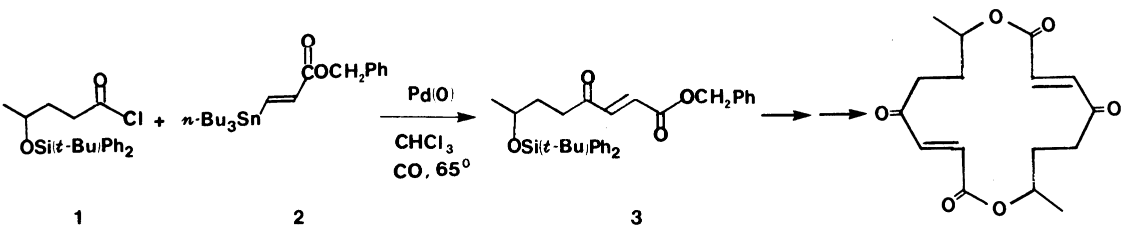
$$\text{Y-R-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-Cl} + \text{R}_3\text{SnR}'' \xrightarrow{\text{L}_n\text{Pd(O)}} \text{Y-R-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-R}'' + \text{R}_3\text{SnCl}$$

There are virtually no side reactions and the workup is simple. The end of the reaction is clearly visualized by the precipitation of palladium(0), and there is no need to run the reaction in an inert atmosphere.

The tetraorganotin reagent transfers the first group rapidly, but the second leaves about 100 times slower from R_3SnCl. Thus, with a stoichiometric amount of tetraorganotin, only one group is transferred. This simple transfer of an organic group from tin is not a problem if a relatively simple organic group, for example methyl, is to be transferred, since tetramethyltin can be used. This reaction has, in fact, been used for the synthesis of a key methyl ketone intermediate in the total synthesis of (±) quadrone (ref. 16). If the partner on tin to be transferred is more expensive or difficult to synthesize, however, then the utilization of only one of those four partners would be a distinct advantage. Fortunately, different types of groups transfer selectively from tin, the simple alkyl group having the slowest transfer rate (ref. 17). Thus, by using a trimethyl or tributylorganotin reagent, the group other than the methyls or butyls transfers <u>exclusively</u>. Allyl transfer takes place with allylic transposition, coupling at benzyl carbon takes place with complete inversion (ref. 18) and coupling at vinyl takes place with retention of geometry.

$$\text{RC}{\equiv}\text{C-} > \text{RCH=CH-} > \text{Ar-} > \text{RCH=CH-CH}_2\text{-} \sim \text{ArCH}_2\text{-} \gg \text{C}_n\text{H}_{2n+1}$$

With this knowledge of transfer order, a coupling reaction of an acid chloride (1) with a tributylvinyltin reagent (2) was carried out to obtain a vinyl ketone (3), which is a key intermediate in the synthesis of the antibiotic pyrenophorin (4) (ref. 19,20). Since the Mitsunobu coupling reaction to yield 4 proceeds with inversion of configuration at the chiral secondary alcohol center, and the (S)-enantiomer of the starting lactone is available, the synthesis of the naturally occurring (R,R)-pyrenophorin is accessible. The synthesis illustrates the utility of the coupling reaction, and indicates that the reaction can be utilized for the synthesis of even more complicated ketones.



1 2 3

4

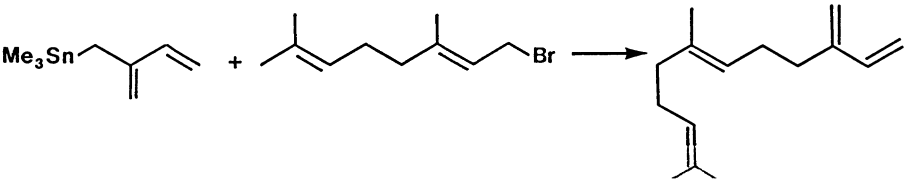
Benzyl halides

In the coupling reaction of benzyl bromide, with tetramethyltin, the reductive elimination reaction from the benzylmethylpalladium intermediate takes place with retention of configuration at the benzyl carbon (ref. 21). Overall, inversion of configuration takes place as a result of inversion in the oxidative addition step and retention in the reductive elimination. The reaction can be carried out catalytically and stereospecifically (ref. 22), to afford high yields of cross-coupled products (ref. 22,23). Also, the palladium catalyzed coupling reactions with aryl bromides and iodides have been observed with a variety of organotins, including allyl (ref. 23), methyl (ref. 21), phenyl (ref. 21,24,25), phenylethynyl (ref. 24), and acetonyl (ref. 26).

Allyl halides

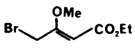
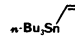
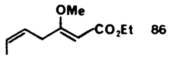
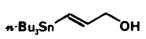
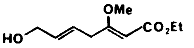
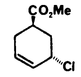
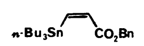
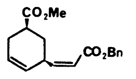
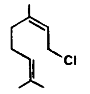
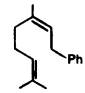
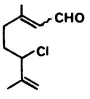
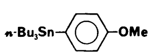
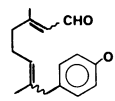
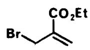
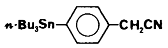
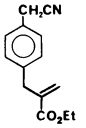
We have carried out the coupling reactions of allyl bromides with allyl tin reagents (ref. 27). The results were repeated later by others (ref. 28). The coupling reactions takes place without homocoupling, but some allylic rearrangement takes place in the allyl halide partner, while allylic transposition predominates in the tin partner (ref. 27,29).

Nevertheless, in allylic bromides and particularly allylic tin reagents in which allylic transposition is redundant, useful coupling reactions can be achieved (ref. 29), although in these examples, the coupling takes place more readily in the presence of zinc chloride.



The palladium catalyzed coupling reaction of allyl bromides or chlorides with vinyl or aryl tin reagent leads to 1,4-dienes in uniformly high (isolated) yields (Table 2, ref. 30,31). The reaction is quite mild and, unlike many other transition metal catalyzed cross-coupling reactions, is tolerant of a wide variety of reactive organic functionality, including ester (entries 1-3,6) nitrile (entry 6), hydroxyl (entry 2), and even aldehyde (entry 5). The reaction also proceeds with retention of double bond geometry in the vinyl partner (entries 1-3) and retention of the Z-olefin geometry in neryl chloride (entry 4). In the allyl partner, coupling shows regioselectivity for the primary allylic carbon rather than secondary (entry 5; compare also entries 1,2 and 4). Thus, this reaction exhibits stereospecific and regioselective carbon-carbon bond formation while having the ability to bring a wide variety of functionality into the framework of the coupled product.

TABLE 2. Palladium catalyzed coupling of allyl halides with organotins[a].

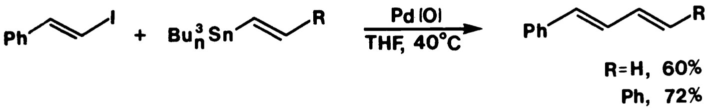
ENTRY	ALLYL HALIDE	ORGANOTIN	PRODUCT	% YIELD[b]
1				86
2				82
3				80
4		n-Bu$_3$SnPh		90
5				87
6				81

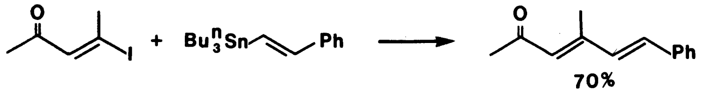
a. The reactions were carried out in dry THF at 50°C for 24-48 h, using equimolar amounts of the allyl halide and organotin in the presence of 3 mole % Pd(dba)$_2$ and 6 mole % PPh$_3$.

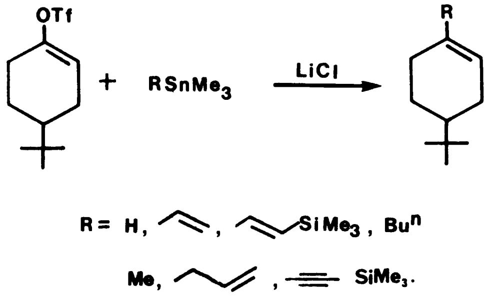
b. Isolated yields.

Vinyl halides and vinyl triflates

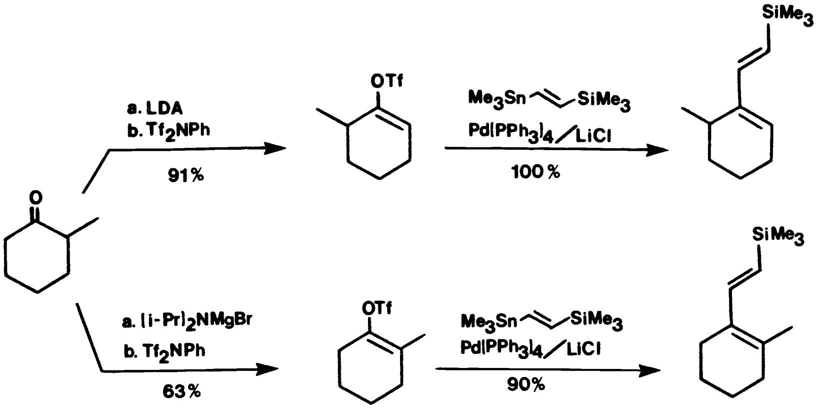
Vinyl iodides undergo direct, palladium catalyzed cross-coupling with vinyl tin reagents to give good yields of conjugated dienes. Although the scope of this reaction has not been probed, it appears that retention of geometry in the vinyl coupling partners is observed. Recently we have found that vinyl triflates undergo coupling provided lithium chloride is added to the reaction (ref. 32). Apparently the vinyl palladium chloride is required for the transmetallation reaction, as the palladium triflates will not undergo transmetallation with vinyltin readily.



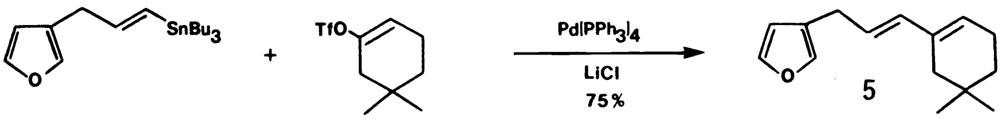




The discovery that vinyl triflates will undergo coupling with a variety of tin reagents has proven to be very valuable. Since the triflates can be obtained from ketones, enolate chemistry is available and triflates are formed selectively from an unsymmetrical ketone by generating either the kinetic or thermodynamic enolate (ref. 32).



This methodology has been utilized in a short synthesis of pleraplysillin-1 (5, ref. 32).



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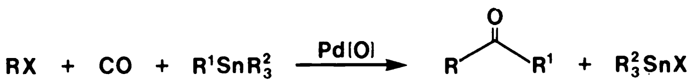
CARBONYLATIVE COUPLING

The palladium catalyzed carbonylative coupling reaction of organic halides with organotins in the presence of carbon monoxide is an especially valuable synthetic procedure for a number of reasons. First, if the acid is not readily available for a ketone synthesis by a direct coupling, then the organic halide of one less carbon can be utilized, since the same acyl palladium intermediate can be generated. Second, since an acid chloride is not involved in the synthesis, presumably other functional groups such as alcohol and amine suitably placed can be present in the organic halide partner. Although our original efforts to achieve this transformation were not particularly successful (ref. 11,12) recently this

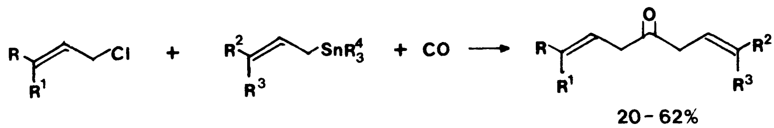


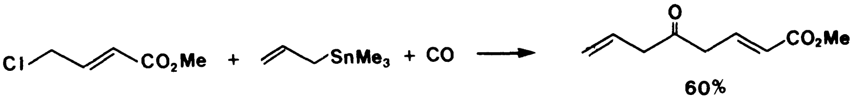
$$RX + CO + R^1SnR^2_3 \xrightarrow{Pd(0)} RC(O)R^1 + R^2_3SnX$$

type of reaction has been reported to proceed using symmetrical tetraalkyl tin reagents under more severe conditions (120°C, HMPA, 20 atm CO, ref. 33-35).

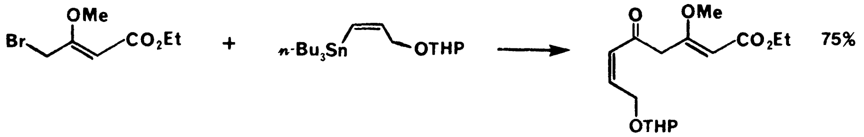
Allyl halides

Bis-allylic ketones were synthesized by the reaction of allyl chlorides and allyltin reagents in the presence of 3 atm of CO at 25°C (ref. 36). Higher temperatures resulted in the further addition of the allyltin reagent to the ketone to yield a tertiary alcohol (after hydrolysis). Rearrangement of the double bonds into conjugation with the carbonyl can be avoided. Coupling occurs without allylic rearrangement from the allyl tin and CO insertion takes place exclusively at the least hindered site of the allyl halide partner. This reaction also tolerates other functionality, including ester, alcohol and even aldehyde, at least on the allyl halide partner.

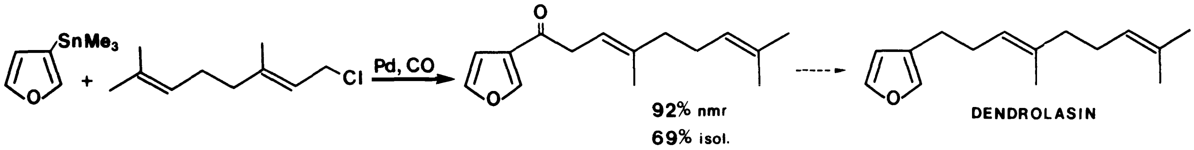




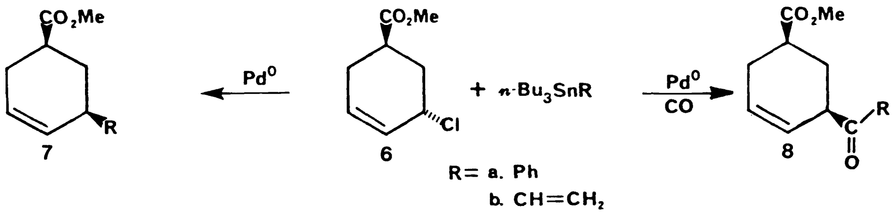
The use of vinyl tin reagents in the presence of 3 atm of carbon monoxide gives high yields of the carbonylated product (ref. 30,31).



Aryl tins yield carbonylative coupling products. This reaction type was the basis for the high yield synthesis of egomaketone and a precursor to dendrolasin by the carbonylative coupling between 3-furanyltin and prenyl chloride or geranyl chloride, respectively (ref. 31). This represents a simple straightforward route to the synthesis of these natural products.



The cross-coupling of 6 with either phenyltributyltin or vinyltributyltin proceeded with inversion at the allylic carbon center to yield 7 (see also entry 3, Table 2). In the presence of carbon monoxide, the carbonylated cis-cross-coupled product (8) was obtained (ref. 30,31).



Thus, the coupling of this allyl halide either in the absence of presence of carbon monoxide takes place with 100% net inversion of configuration at the allylic center.

Vinyl iodides and vinyl triflates

The palladium catalyzed reaction of vinyl iodides with vinyltins in the presence of carbon monoxide (3 atm) proceeds under mild reaction conditions to yield divinyl ketones (ref. 37). Selected examples of this reaction are listed in Table 3. Carbon monoxide acts to stitch the two vinyl groups together. Phenyl and acetylenic tins also undergo this cross-coupling reaction to yield vinyl phenyl and vinyl acetylenic ketones, respectively.

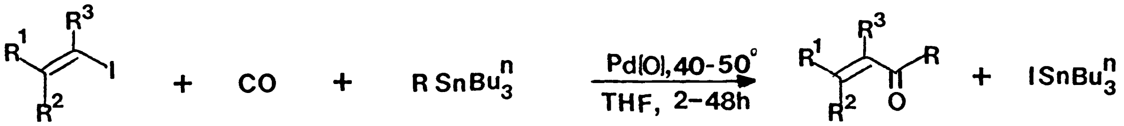
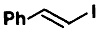
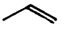
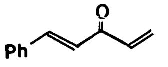
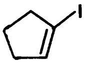
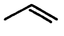
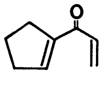
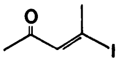
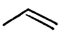
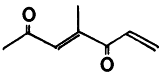
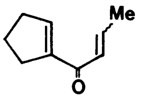
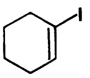
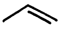
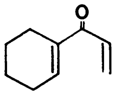
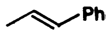
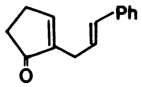
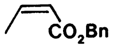
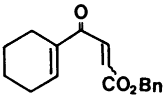
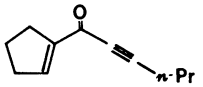
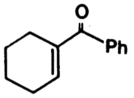
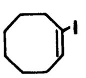
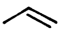
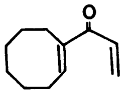
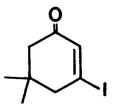
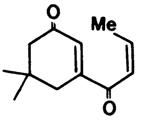


TABLE 3. Carbonylative coupling of vinyl iodides with organotins.

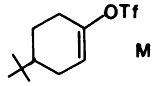
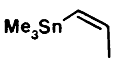
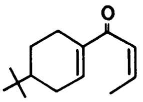
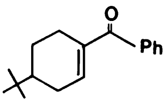
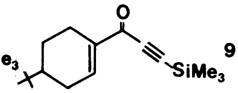
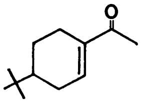
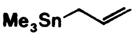
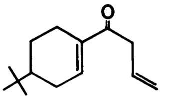
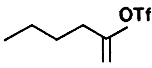
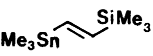
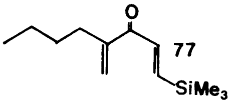
VINYL IODIDE	Bu^n_3SnR R	KETONE	YIELD [%]	VINYL IODIDE	Bu^n_3SnR R	KETONE	YIELD [%]
			65				90
			50				63
			93				60
			45				54
	Ph		40				74
			71				

The reaction tolerates carbonyl functionality in both partners, as well as acetylenic group in the tin partner. Under these mild reaction conditions, no further addition of the tin reagent to the product ketone takes place. Generally, the preparation of unsymmetrical ketones by transition metal catalyzed cross-coupling reaction is severely limited, since the organometallic partners often react with the product ketone.

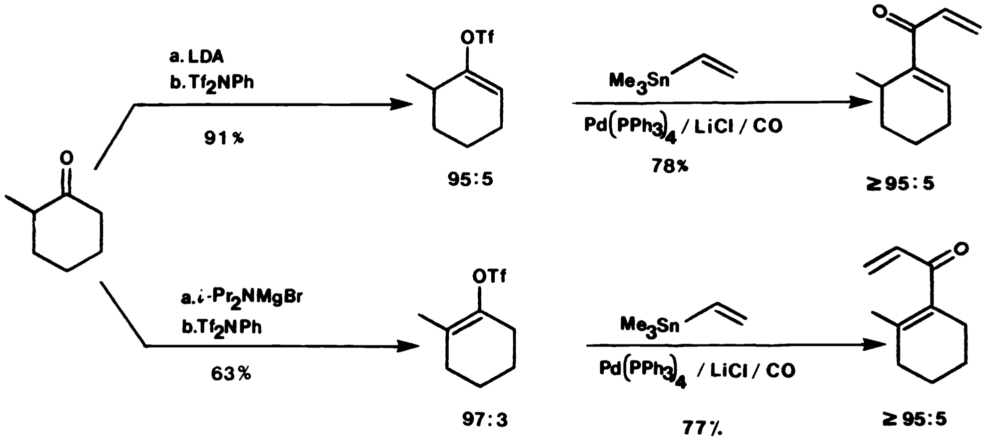
The E-geometry of the double bond both in the vinyl iodide and tin partners was retained in the product. Although the Z-geometry of the double bond in the vinyl tin partner was maintained in the coupling reaction, it was lost under the usual reaction conditions and the E-isomer in the product predominated. E,Z-Isomerization of vinyl ketones is very facile, however.

More recently, we have discovered that vinyl triflates also will undergo the palladium catalyzed carbonylative coupling reaction with various tin reagents provided lithium chloride is added to the reaction mixture (ref. 38). In coupling reactions with vinyltin reagents, the geometry of the double bond is maintained, and is not isomerized in the product under the reaction conditions (Table 4).

TABLE 4. Carbonylative coupling of vinyl triflates with organostannanes.

ENTRY	TRIFLATE	ORGANOSTANNANE	PRODUCT	ISOLATED YIELD [%]	ENTRY	TRIFLATE	ORGANOSTANNANE	PRODUCT	ISOLATED YIELD [%]
1				70	4		Me_3SnPh		93
2		$Me_3Sn{-}{\equiv}{-}SiMe_3$		95	5		Me_4Sn		73
3				95	6				77

An important aspect of this work is the ability to generate a vinyl triflate regioselectively utilizing well known enolate chemistry, and couple the triflate with an organostannane under a carbon monoxide atmosphere to give only one regioisomeric product.



The carbonylative coupling reaction followed by a Nazarov cyclization was utilized for a sequential annelation to assemble the fused 5-membered ring structure of $(\pm)\Delta^{9(12)}$-capnellene (Fig. 3, ref. 38).

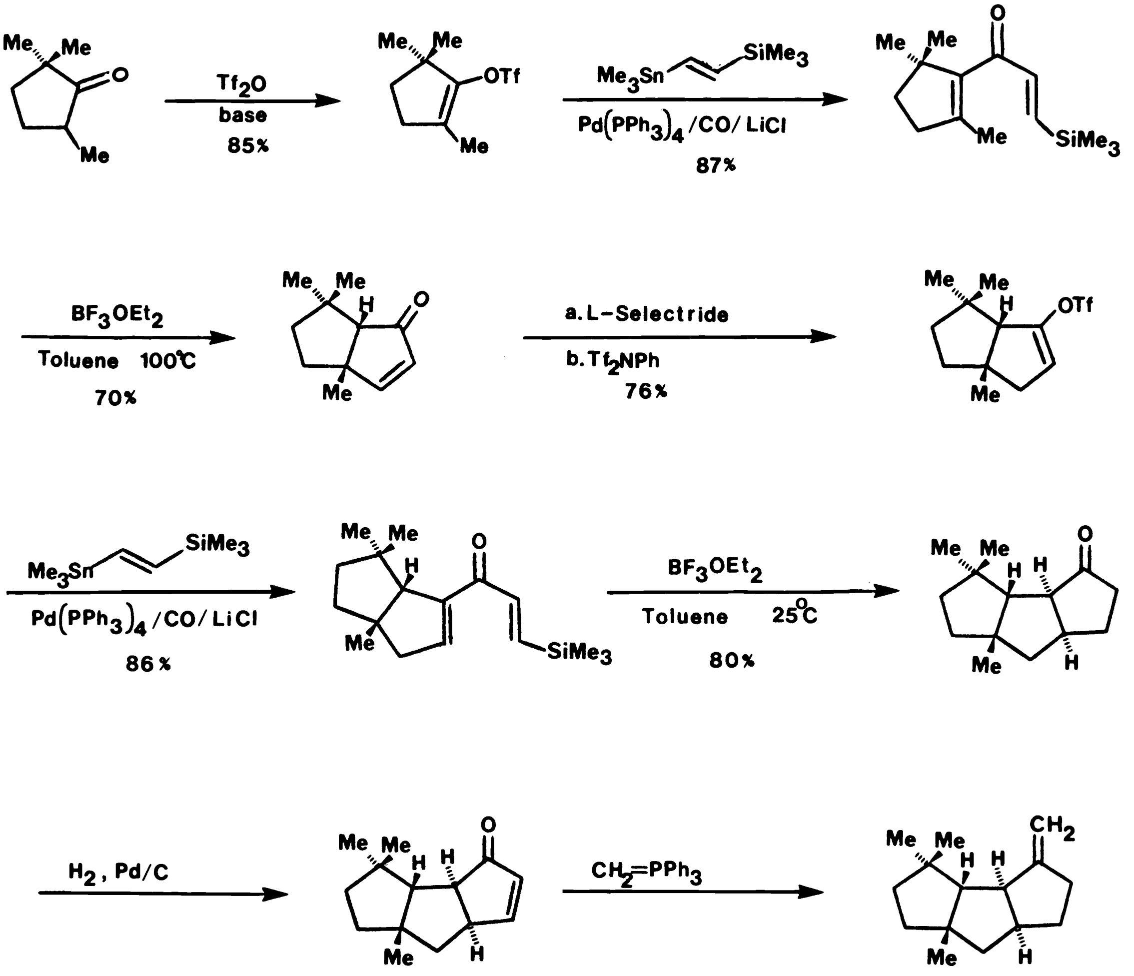


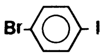
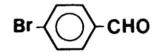
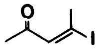
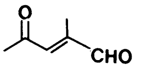
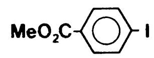
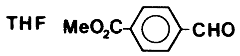
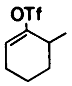
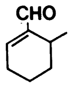
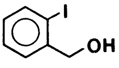
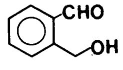
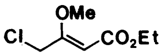
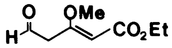
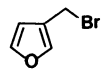
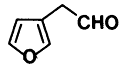
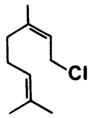
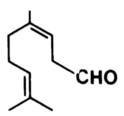
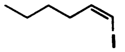
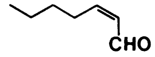
Fig. 3. Capnellene synthesis.

Aldehyde synthesis

The conversion of a variety of organic halides to aldehydes takes place in the presence of a palladium catalyst, carbon monoxide and tributyltin hydride under mild reaction conditions (ref. 39). Aryl, benzyl, vinyl and allyl halides can be converted to aldehydes, and other functional groups in the molecule remain unaffected under these reaction conditions (Table 5).

$$RX + CO + Bu^n_3SnH \xrightarrow[50^\circ C]{Pd(0)} RCHO + Bu^n_3SnX$$

TABLE 5. Formylation of organic halides[a].

ELECTROPHILE	SOLVENT	ALDEHYDE	% YIELD	ELECTROPHILE	SOLVENT	ALDEHYDE	% YIELD
	THF		87		THF		95
	THF		91		THF[b]		96
	$PhCH_3$		55		THF		86
	THF		67		THF		59
	THF		88				

a. Reactions were run at 50°C with $(Ph_3P)_4Pd$.
b. Lithium chloride added.

ACKNOWLEDGMENT

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