

## III.2.14.2 Palladium-Catalyzed Cross-Coupling Involving $\beta$ -Hetero-Substituted Compounds Other than Enolates

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### A. Introduction

In addition to enolates that are viewed here as  $\beta$ -oxo-organometal equivalents (or  $\alpha$ -metallocarbonyl compounds) and discussed in **Sect. III.2.14.1**, there are many other types of  $\beta$ -hetero-substituted organometals and organic electrophiles. Due to the location of heteroatoms (i.e.,  $\beta$ ), there are, in principle, many more classes of these types of compounds than their  $\alpha$ -hetero-substituted counterparts, and their systematic and detailed classification is not very meaningful (**Sects. III.2.12** and **III.2.13**). Nonetheless, their classification into eight or so types shown in **Table 1** is useful, and this section is accordingly arranged. Efforts are made to emphasize those cases where  $\beta$ -heteroatoms are of some special synthetic significance rather than mere substituents without significant chemical consequences. Many classes of  $\beta$ -hetero-substituted compounds serve as enolate equivalents, and their Pd-catalyzed cross-coupling reactions have significantly complemented the classical enolate chemistry. Another topic of importance is the use of  $\beta$ -hetero-substituted compounds as *E* or *Z* C=C and C $\equiv$ C synthons for the synthesis of conjugated oligoenes and oligoynes. Their more specific applications are discussed further in **Sect. III.2.17**. The third topic of significance is the use of *o*-hetero-disubstituted arenes in the synthesis of arene-fused cyclic compounds. This topic is also discussed in various other sections in **Parts III–VI**. So, its discussion in this section is mainly to point out various available options for the synthesis of heterocyclic and carbocyclic compounds using *o*-hetero-disubstituted arenes.

### B. $\beta$ -HETERO-SUBSTITUTED ETHYNYLMETALS AND ETHYNYL ELECTROPHILES

Various different kinds of  $\beta$ -hetero-substituted ethynylmetals and ethynyl electrophiles are conceivable, and several kinds of such compounds have been used in Pd-catalyzed cross-coupling (**Sect. III.2.8**). The most widely used are  $\beta$ -silylethynylmetals. In these compounds, the silyl group primarily serves as the protecting group. The metals

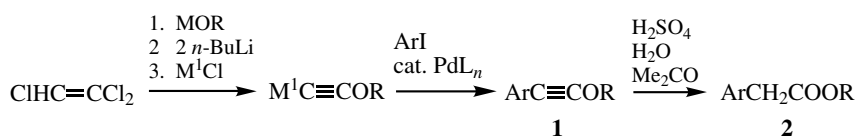
**TABLE 1. Various Types of  $\beta$ -Hetero-Substituted Organometals and Electrophiles of Synthetic Significance Used in Pd-Catalyzed Cross-Coupling<sup>a</sup>**

Hybridization of C Bonded to M or X	Type of $\beta$ -Hetero-Substituted Organometals or Electrophiles	
$C_{sp}$	$M-C\equiv C-Y$	$X-C\equiv C-Y$
$C_{sp^2}$	$M-\overset{ }{\underset{ }{C}}=\overset{ }{\underset{ }{C}}-Y$	$X-\overset{ }{\underset{ }{C}}=\overset{ }{\underset{ }{C}}-Y$
	$\begin{array}{c}   \\ -C=C-M \\   \\ C\equiv Y \end{array}$	$\begin{array}{c}   \\ -C=C-X \\   \\ C\equiv Y \end{array}$
	$\begin{array}{c}   \\ -C=C-M \\   \\ Z-C=Y \end{array}$	$\begin{array}{c}   \\ -C=C-X \\   \\ Z-C=Y \end{array}$
	(Y or Z may be C or H)	
$C_{sp^3}$	$\begin{array}{c}   \\ -C=C-M \\   \\ -C-Y \\   \end{array}$	$\begin{array}{c}   \\ -C=C-X \\   \\ -C-Y \\   \end{array}$
	$M-\overset{ }{\underset{ }{C}}-\overset{ }{\underset{ }{C}}\equiv Y$	$X-\overset{ }{\underset{ }{C}}-\overset{ }{\underset{ }{C}}\equiv Y$
	$M-\overset{ }{\underset{ }{C}}-\overset{ }{\underset{ }{C}}=Y$	$X-\overset{ }{\underset{ }{C}}-\overset{ }{\underset{ }{C}}=Y$
	(Y or Z may be C or H)	
	$M-\overset{ }{\underset{ }{C}}-\overset{ }{\underset{ }{C}}-Y$	$X-\overset{ }{\underset{ }{C}}-\overset{ }{\underset{ }{C}}-Y$

<sup>a</sup>M = Metal; X = electrophilic leaving group; Y and Z = heteroatoms and groups including metals and halogens.

in these compounds include  $Sn^{[1],[2]}$  and  $Zn^{[3],[4]}$ . After cross-coupling, the silyl protecting groups are usually removed to produce terminal alkynes. Since these terminal alkynes can be synthesized directly using unprotected ethynylmetals containing Zn, Mg, and  $Sn^{[5]-[9]}$  (**Sect. III.2.8.2**), the use of  $\beta$ -silylethynylmetals does not appear to be necessary in most cases.

$\beta$ -Alkoxyethynylmetals containing  $Zn^{[10]}$  and  $Sn^{[11]}$  have been used to prepare alkoxyalkynes containing various aromatic groups (**Scheme 1**). The required reagents can be generated from  $\beta$ -alkoxyethynyllithium, which, in turn, can be prepared from 1,1,2-trichloroethylene. Since the products can be hydrolyzed to give the corresponding



M <sup>1</sup>	R	Ar	<b>1</b> (%)	<b>2</b> (%)	Reference
ZnCl	Et or <i>i</i> -Pr	Ph, 4-MeC <sub>6</sub> H <sub>4</sub> 3- or 4-ClC <sub>6</sub> H <sub>4</sub>	53–85	—	[10]
SnBu <sub>3</sub>	Et	Ph	60	—	[11]
		4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	52	62	
		4-EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	59	59	
		4-MeOC <sub>6</sub> H <sub>4</sub>	60	—	
		3-Pyridyl	61	88	
		2-Thienyl	47	—	

Scheme 1

areneacetate esters,  $\beta$ -alkoxyethynylmetals serve as alkoxycarbonylmethyl synthons or Reformatsky reagent equivalents. Since direct synthesis of areneacetate esters via Pd- or Ni-catalyzed cross-coupling with the Reformatsky reagents<sup>[12]</sup> is known, the use of the indirect method would be justified only if it provides distinctly higher overall yields.

$\beta$ -Aminoethynylmetals containing Zn, Sn, and even Si undergo Pd-catalyzed reaction with (*E*)- $\beta$ -iodoacrolein to give the corresponding enynals.<sup>[13]</sup>

### C. $\beta$ -HETERO-SUBSTITUTED ETHENYLMETALS AND ETHENYL ELECTROPHILES

$\beta$ -Hetero-substituted ethenylmetals and ethenyl electrophiles have been shown to be useful as *E* or *Z* C=C and C $\equiv$ C synthons. They can be classified into the following three categories: (i) 1,2-dihaloethylenes (X<sup>1</sup>CH=CHX<sup>2</sup>), (ii) 1,2-dimetalloethylenes (M<sup>1</sup>CH=CHM<sup>2</sup>), and (iii) other 1,2-hetero-disubstituted ethylene derivatives.

#### C.i. 1,2-Dihaloethylenes

There are six 1,2-dihaloethylenes containing Cl, Br, and/or I, each of which can be either *E* or *Z*. (*E*)- or (*Z*)-1,2-Dichloroethylene and a mixture of (*E*)- and (*Z*)-1,2-dibromoethylene are commercially available, and they have been used extensively in Pd-catalyzed cross-coupling. Although the initial investigation of the stoichiometric reactions of both (*E*)- and (*Z*)-1,2-dichloroethylene and PhLi (2 equiv) and Pd(PPh<sub>3</sub>)<sub>4</sub> (1 equiv) led to low product yields and stereoisomerization,<sup>[14]</sup> subsequent investigations of their Pd-catalyzed cross-coupling have led to synthetically useful results, as discussed below. With the exception of 1-chloro-2-bromoethylene, the others—that is, 1-chloro-2-iodoethylene,<sup>[15]</sup> 1-bromo-2-iodoethylene,<sup>[16]</sup> and 1,2-diiodoethylene<sup>[17]</sup>—can readily be prepared by addition of ICl, IBr, and I<sub>2</sub> to acetylene, respectively, and have been used in Pd-catalyzed cross-coupling. Some basic facts about these dihaloethylenes are summarized in **Table 2**.

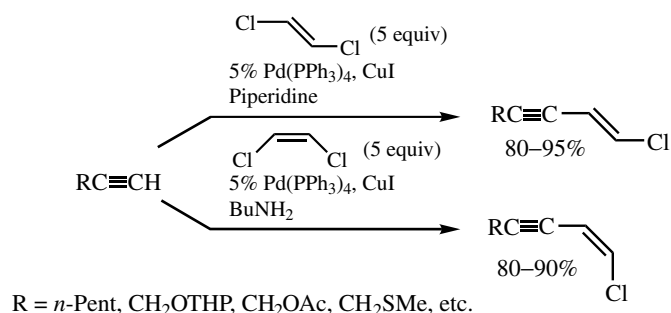
TABLE 2. 1,2-Dihaloethylenes

1,2-Dihaloethylene	MW	Commercial Availability	Method of Synthesis	Other	Reference
( <i>E</i> )-ClCH=CHCl	96.94	Yes	HC≡CH + NH <sub>4</sub> Cl + HCl + H <sub>2</sub> O		[18]
( <i>Z</i> )-ClCH=CHCl	96.94	Yes	<i>a</i>		<i>a</i>
( <i>E</i> ) and ( <i>Z</i> )-BrCH=CHCl	141.37	No	Br <sub>2</sub> C=CCl <sub>2</sub> + Zn		[19]
( <i>E</i> )-ICH=CHCl	188.40	No	HC≡CH + ICl	83% yield	[15] [20]
( <i>E</i> )- and ( <i>Z</i> )-BrCH=CHBr	185.86	Yes	Br <sub>2</sub> C=CBr <sub>2</sub> + Zn		[21] [22]
( <i>E</i> )-ICH=CHBr	232.82	No	HC≡CH + IBr + HBr	74% yield	[16]
( <i>E</i> )-ICH=CHI	279.82	No	HC≡CH + I <sub>2</sub> + Al <sub>2</sub> O <sub>3</sub>	33% yield	[17]
( <i>E</i> )- and ( <i>Z</i> )-ICH=CHI	279.82	No	( <i>E</i> )-ICH=CHI + cat. I <sub>2</sub> at 160 °C		[23]

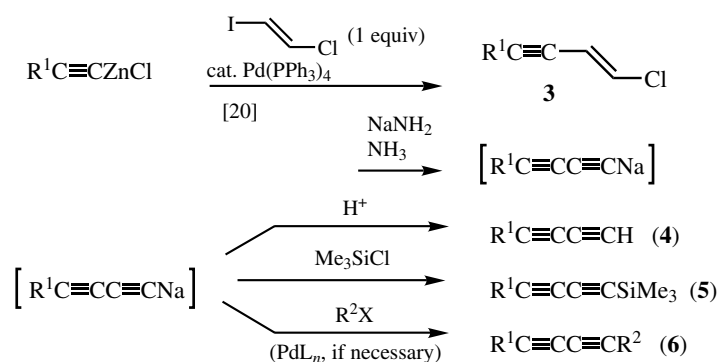
<sup>a</sup> The commercial method of preparation is not reported in the literature.

**C.i.a. Synthesis of Haloenynes and Conjugated Unsymmetrical Diynes.** (*E*)-1-Chloro-2-iodoethylene<sup>[15]</sup> and (*E*)-1-bromo-2-iodoethylene<sup>[17],[24]</sup> contain two different halogen atoms permitting facile Pd-catalyzed monosubstitution at the iodine substituted C atom. Although the two halogen atoms in 1,2-dichloroethylene are the same, the first substitution is significantly more facile than the second due to activation by the second Cl atom. All of these compounds readily undergo monoalkynylation either by Sonogashira coupling or Negishi coupling with alkynylzincs, as indicated by the results summarized in **Scheme 2**,<sup>[25],[26]</sup> **Scheme 3**,<sup>[20]</sup> and **Scheme 4**.<sup>[16]</sup> Since the chloroenynes and bromoenynes thus obtained can readily be converted to the corresponding terminal 1,3-diynes,<sup>[20]</sup> the two-step sequence provides a potentially most general, selective, and satisfactory procedure for the synthesis of unsymmetrical conjugated diynes of various kinds. Although not yet well recognized, this protocol should prove to be generally more selective and satisfactory than the classical Cadiot–Chodkiewicz reaction.<sup>[27]</sup> It should be pointed out that the new protocol requires procurement of a dihaloethylene and an electrophile for the introduction of the second substituent. On the other hand, the Cadiot–Chodkiewicz protocol requires the preparation of the second alkyne and its conversion to a haloalkyne. So, three steps are needed in either case (**Scheme 5**).

Monoalkynylation of an *E* and *Z* isomeric mixture of 1,2-dibromoethylene with alkynylzincs in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> can stereoselectively produce (*E*)-bromoenynes in moderate yields,<sup>[28]</sup> provided that the required amount of (*E*)-1,2-dibromoethylene is present in the *E* and *Z* isomeric mixture. Although it is interesting to note that the (*E*)- isomer is substantially more reactive than the (*Z*)-isomer, complications associated with the use of an isomeric mixture and the moderate cross-coupling yields seem to make this reagent generally less satisfactory than some of the others mentioned above. There has been no report of successful monosubstitution of 1,2-diiodoethylene.

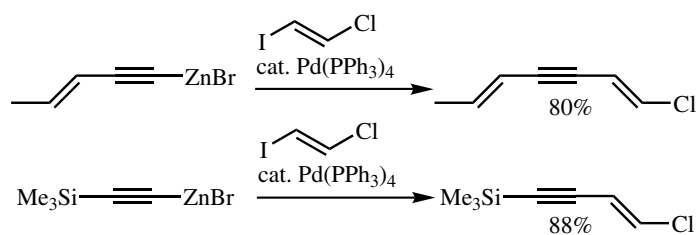


Scheme 2



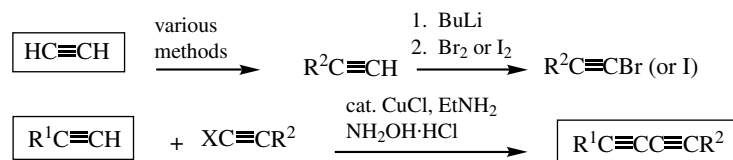
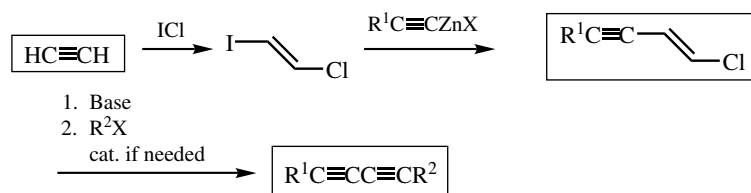
$\text{R}^1\text{C}\equiv\text{CH}$	Yield (%)			
	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
1-Octyne	73	68	70	67 ( $\text{R}^2 = \text{Me}$ )
2-Methyl-1-buten-3-yne	75			
Phenylethyne	91		71	89 ( $\text{R}^2 = \text{Me}$ )
1,3-Decadiyne	78			

Scheme 3



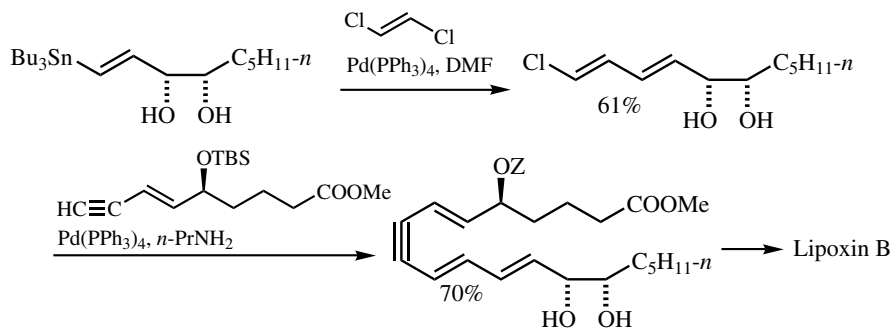
Scheme 4

Substitution with other groups, such as alkenyl, aryl, and alkyl, has been less well investigated. The currently available results summarized in **Table 3** indicate that (*E*)-ICH=CHCl is a satisfactory reagent for Pd-catalyzed monoalkenylation.<sup>[16]</sup> The reaction of (*E*)-ICH=CHBr with alkenylmetals containing Zn and Zr is also satisfactory, but the yields tend to be modest, the formation of homocoupled dienes being one

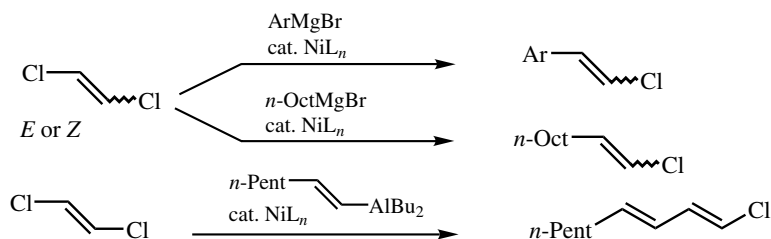
*Cadiot–Chodkiewicz protocol**Pd-catalyzed dihaloethylene cross-coupling*

Scheme 5

potentially serious side reaction. The use of the corresponding alkenylstannanes leads to nearly exclusive formation of homocoupled dienes without producing the desired bromodienes.<sup>[16]</sup> Arylation of (*E*)-ICH=CHBr appears to be generally more problematical. Although some examples of substitution of ClCH=CHCl with alkenyl, aryl, and alkyl groups by Pd-catalyzed cross-coupling are known<sup>[29]</sup> (Scheme 6), it is generally difficult. On the other hand, the Kumada–Tamao coupling with Grignard reagents<sup>[30]</sup> and the Negishi coupling with alkenylalanes<sup>[31]</sup> catalyzed by Ni–phosphine complexes have been satisfactorily employed,<sup>[25],[32]</sup> as shown in Scheme 7.



Scheme 6



Scheme 7

TABLE 3. Pd-Catalyzed Monoalkenylation of (*E*)-1,2-Dihaloethylenes

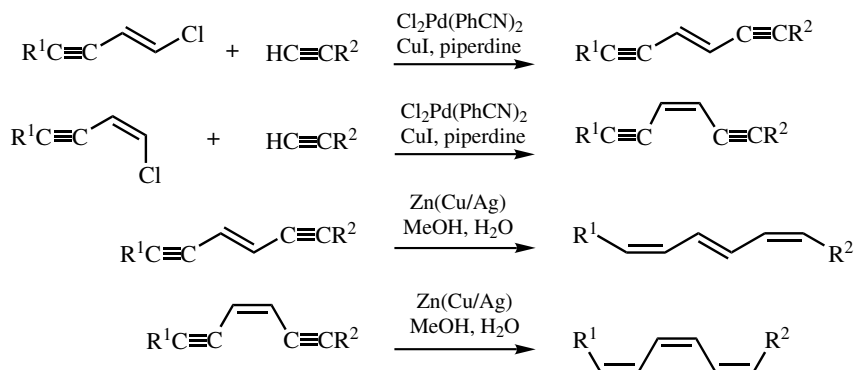
R <sup>1</sup>	R <sup>2</sup>	M	X	Y	Pd Catalyst	Solvent	Product (%)	Dimer (%)
H	<i>n</i> -Oct	ZrCp <sub>2</sub> Cl	I	Cl	A <sup>a</sup>	DMF	80	<i>b</i>
H	Ph	ZnBr <sup>c</sup>	I	Cl	A <sup>a</sup>	DMF		7
H	Ph	ZnBr <sup>c</sup>	I	Br	Pd(PPh <sub>3</sub> ) <sub>4</sub>	THF	38	16
H	Ph	ZnBr <sup>c</sup>	I	Br	Cl <sub>2</sub> Pd(PPh <sub>3</sub> ) <sub>2</sub> + DIBAH	THF	55	23
H	Ph	ZnBr <sup>c</sup>	I	Br	A <sup>a</sup>	THF-DMF	75	32
H	Ph	ZnBr <sup>c</sup>	Cl <sup>d</sup>	Cl <sup>d</sup>	A <sup>a</sup>	THF-DMF	17	28
H	Ph	ZnBr <sup>c</sup>	Br <sup>d</sup>	Br <sup>d</sup>	A <sup>a</sup>	THF-DMF	43	<i>b</i>
Me	<i>n</i> -Hex	AlMe <sub>2</sub>	I	Cl	Pd(PPh <sub>3</sub> ) <sub>4</sub>	THF	13	12
Me	<i>n</i> -Hex	AlMe <sub>2</sub>	I	Cl	Cl <sub>2</sub> Pd(PPh <sub>3</sub> ) <sub>2</sub> + DIBAH	THF	50	4
Me	<i>n</i> -Hex	AlMe <sub>2</sub>	I	Cl	A <sup>a</sup> , ZnBr <sub>2</sub>	THF-DMF	90	<i>b</i>

<sup>a</sup>A = Pd<sub>2</sub>(dba)<sub>3</sub> + TFP.<sup>b</sup>Not determined.<sup>c</sup>Generated *via* lithiation and zincation of (*E*)- $\beta$ -bromostyrene.<sup>d</sup>An excess of the reagent was used.

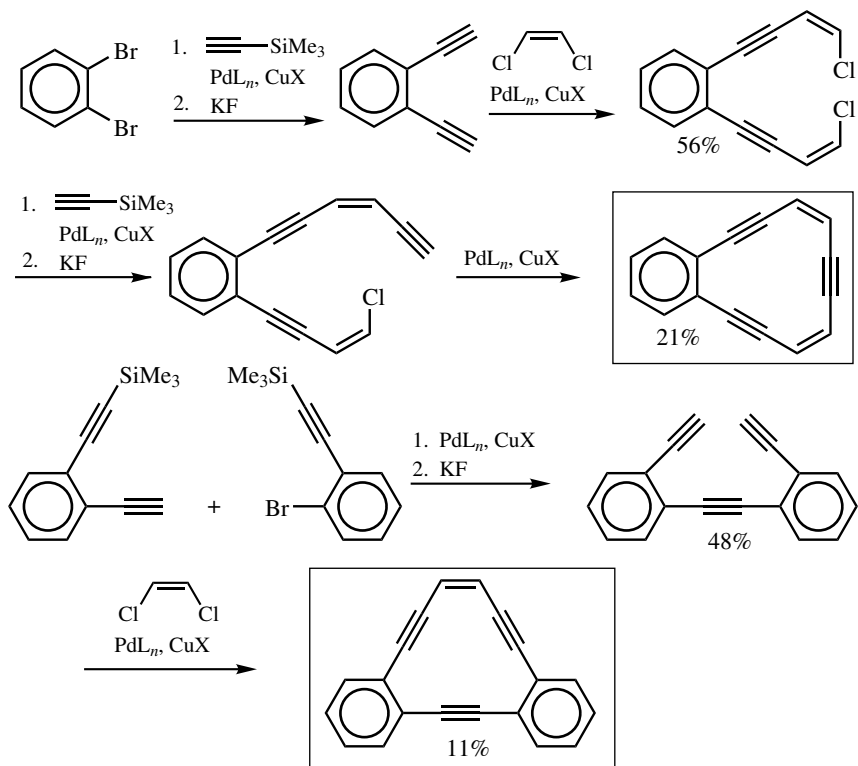
**C.i.b. Synthesis of 3-Ene-1,5-diynes.** The use of 1,2-dihaloethylenes as *E* or *Z* C=C synthons requires substitution of the second halogen atom. The second substitution does not have the benefit of activation by the presence of the second halogen atom. However, it does appear that the presence of an additional unsaturation in the haloenynes and halodienes has, in some cases, rate-accelerating effects, although this point needs to be further clarified. As in the first substitution, introduction of alkynyl groups using the Sonogashira protocol<sup>[33]</sup> is generally most satisfactory even in cases where alkenyl chlorides are used as electrophiles.<sup>[32],[34]</sup> Even so, the reaction is very much dependent on various reaction parameters, especially catalysts and promoters. The use of Cl<sub>2</sub>Pd(PhCN)<sub>2</sub> rather than Pd(PPh<sub>3</sub>)<sub>4</sub> has been claimed to be necessary or desirable either in the second substitution or in one-pot double substitution.<sup>[34],[35]</sup> In some cases, yield differentials can be more than 50%. Similarly, piperidine has been reported to be a superior base, especially in the second substitution. However, Linstrumelle's conditions for coupling with alkenyl chlorides mentioned above appear to be incompatible with the use of conjugated diynes, which presumably undergo competitive side reactions, such as alkyne addition involving piperidine and other amines and Cu.<sup>[36]</sup> Some of the representative results of two-stage double cross-coupling producing enynes in the second stage are summarized in **Scheme 8**.<sup>[34],[35]</sup> Since conjugated ethynyl groups can readily be reduced to the *Z* ethenyl group by Zn (Cu/Ag) in MeOH-H<sub>2</sub>O,<sup>[37]</sup> the overall sequence can provide

efficient and selective routes to certain classes of conjugated oligoenes containing strategically placed *Z* and *E* alkene units. This topic is further discussed mainly within the context of naturally occurring polyene syntheses in **Sect. III.2.17.1**.

Another important application of this protocol for the synthesis of enediynes is its use in the synthesis of natural products containing enediyne macrocycles, such as esperamicin/calicheamicin<sup>[38]–[42]</sup> and dynemicin A,<sup>[43]</sup> as discussed in **Sect. III.2.18**. Some applications to the synthesis of unnatural macrocycles have also been reported (**Scheme 9**).<sup>[44]</sup>



Scheme 8

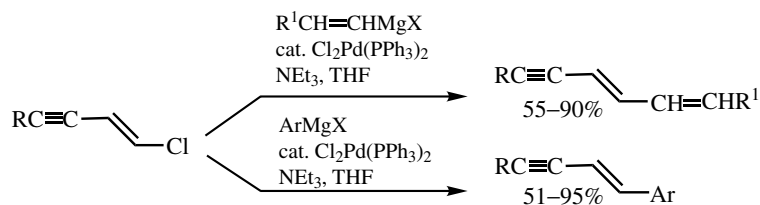


Scheme 9

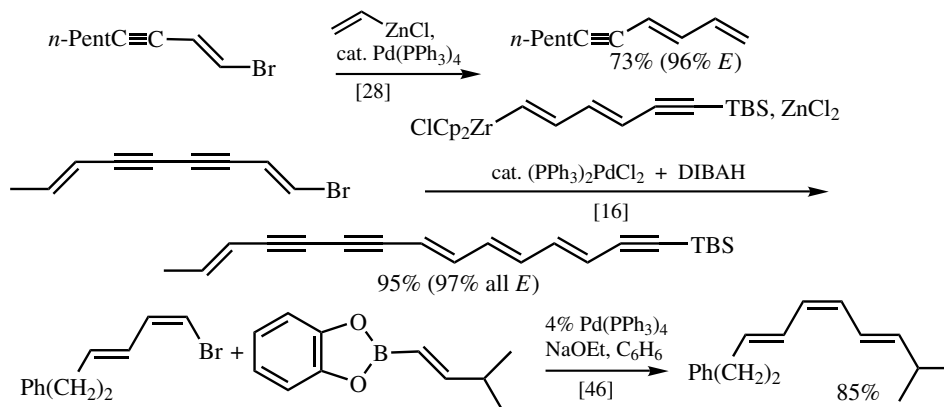


**C.i.c. Use of 1,2-Dihaloethylenes in Pd-Catalyzed Alkenyl-Alkenyl, Alkenyl-Aryl, and Other Cross-Coupling Reactions.** Substitution of the alkenyl chlorides, obtainable by the cross-coupling of  $\text{ClCH}=\text{CHCl}$  or  $\text{ICH}=\text{CHCl}$ , with alkenylmetals and arylmetals is generally more difficult than alkynylation. In this sense, the reaction of (*Z*)-1-butenylmagnesium bromide with THP-protected (*E*)-8-chloro-7-octen-1-ol using  $\text{Pd}(\text{PPh}_3)_4$  to produce the corresponding conjugated (*E,Z*)-diene, a precursor to the sex pheromone of *Lobesia botrana* in 96% yield,<sup>[25]</sup> is quite unexpected. Additional examples of this reaction appear to be very desirable. More recent studies indicate that (*E*)-chloroenynes satisfactorily cross-couple with alkenyl and aryl Grignard reagents in the presence of  $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$  and  $\text{NEt}_3$  in THF (**Scheme 10**).<sup>[45]</sup>

Alkenyl bromides obtainable via Pd-catalyzed cross-coupling with (*E*)- $\text{ICH}=\text{CHBr}$  are much more reactive than the corresponding chlorides. Here again, the presence of conjugated  $\pi$ -bonds appears to promote Pd-catalyzed cross-coupling in some cases. Alkenylmetals containing Zn,<sup>[28]</sup> Al,<sup>[28]</sup> Zr,<sup>[16]</sup> and B<sup>[46]</sup> have successfully been employed for this purpose, and double metal catalysis using  $\text{ZnCl}_2$  or  $\text{ZnBr}_2$ <sup>[47]</sup> in conjunction with Zr has also been effective.<sup>[16]</sup> Some representative examples are shown in **Scheme 11**.



Scheme 10



Scheme 11

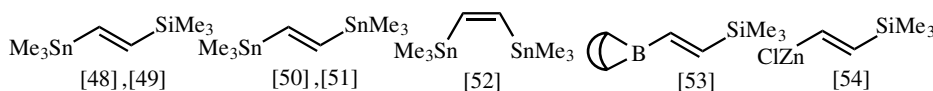
In summary,  $\text{ICH}=\text{CHCl}$  is the most favorable reagent for the first substitution, while  $\text{ICH}=\text{CHBr}$  is acceptable in many cases in both the first and the second substitution. These two reagents appear to be the two most satisfactory reagents in an overall sense. The range of applicability of  $\text{ClCH}=\text{CHCl}$  in Pd-catalyzed procedures is much more limited relative to  $\text{ICH}=\text{CHCl}$  due, in particular, to the greater difficulty associated with the first substitution, while the use of  $\text{BrCH}=\text{CHBr}$  is associated with different kinds of complications in the first substitution and therefore inferior to  $\text{ICH}=\text{CHBr}$ . The others,

that is,  $\text{ClCH}=\text{CHBr}$  and  $\text{ICH}=\text{CHI}$ , do not appear to offer significant advantages over those mentioned above except in a limited number of cases.

### C.ii. 1,2-Dimetalloethylenes

Although a wide variety of 1,2-dimetalloethylenes containing Mg, Zn, B, Al, Si, Sn, Cu, and Zr are conceivable as ethylene synthons in Pd-catalyzed cross-coupling, a relatively small number of them have been prepared and used in this context. Most of them contain Si and/or Sn, as indicated in **Scheme 12**. However, other related derivatives containing more electropositive metals, such as Mg, Zn, and Al, might also work similarly.

Since the general order of reactivity of the metals shown in **Scheme 12** in Pd-catalyzed cross-coupling is  $\text{Sn}$  or  $\text{B} > \text{Si}$ ,  $\text{Me}_3\text{SnCH}=\text{CHSiMe}_3$ <sup>[48],[49]</sup> and  $\text{C}_8\text{H}_{14}\text{BCH}=\text{CHSiMe}_3$ <sup>[53]</sup> can be used as trimethylsilyl ethenyl synthons (**Scheme 13**).



Scheme 12

<div style="display: flex; align-items: center; gap: 10px;"> <div style="border: 1px solid black; padding: 5px; text-align: center;"> <math>\text{Me}_3\text{Sn}-\text{CH}=\text{CH}-\text{SiMe}_3</math> </div> <div style="text-align: center;"> <math>\xrightarrow{\text{RX cat. PdL}_n}</math> </div> <div style="text-align: center;"> <math>\text{R}-\text{CH}=\text{CH}-\text{SiMe}_3</math> </div> </div>			
<div style="display: flex; align-items: center; gap: 10px;"> <div style="border: 1px solid black; padding: 5px; text-align: center;"> <math>\text{C}_8\text{H}_{14}\text{B}-\text{CH}=\text{CH}-\text{SiMe}_3</math> </div> <div style="text-align: center;"> <math>\xrightarrow{\text{RX cat. PdL}_n}</math> </div> <div style="text-align: center;"> <math>\text{R}-\text{CH}=\text{CH}-\text{SiMe}_3</math> </div> </div>			
M of $\text{MCH}=\text{CHSiMe}_3$	RX	Yield (%) of $\text{RCH}=\text{CHSiMe}_3$	Reference
Sn		90	[48]
Sn		100	[48]
Sn		100	[48]
Sn		90	[48]
Sn		56	[49]
Sn		68	[49]
Sn		26	[49]
B	PhBr	89	[53]
B		82	[53]
B		85	[53]
B	$n\text{-HexC}\equiv\text{CBr}$	88	[53]

Scheme 13

Although symmetrically structured, (*E*)-1,2-bis(stannyl)ethylene<sup>[50]</sup> can be either selectively monosubstituted or exhaustively disubstituted. The available results indicate that, like halogens, the second Sn group accelerates the Pd-catalyzed cross-coupling. Some very attractive applications of both (*E*)- and (*Z*)-1,2-bis(stannyl)ethylenes include their Pd-catalyzed double cross-coupling reactions with  $\alpha,\omega$ -diiodo compounds to produce macrocycles in the syntheses of rapamycin<sup>[51]</sup> and dynemicin A,<sup>[52]</sup> discussed in Sect. III.2.18.

### C.iii. Other 1,2-Hetero-Disubstituted Alkene Derivatives

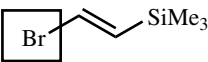
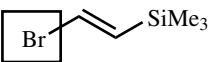
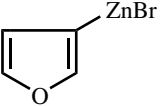
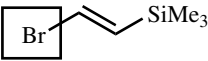
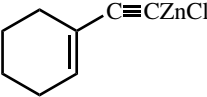
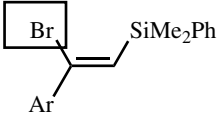
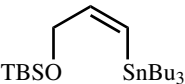
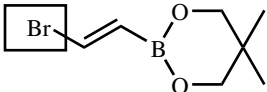
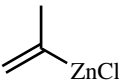
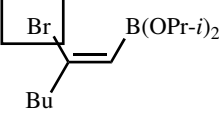
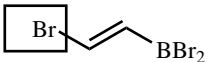
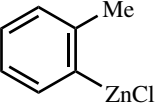
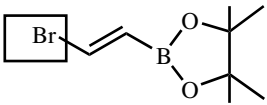
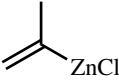
Various other types of 1,2-hetero-disubstituted alkene derivatives have been employed in Pd-catalyzed cross-coupling. Some act primarily as electrophiles, and representative examples are shown in Table 4. The others serve as nucleophiles and are summarized in Table 5.

TABLE 4. Some  $\beta$ -Hetero-Substituted Electrophiles

Electrophile	Example of Nucleophile	Product Yield (%)	Reference
		85	[55]
	PhZnCl	79	[55]
		87	[56]
	HC≡CCH <sub>2</sub> OH (CuI, DBU)	84	[57]
		68	[58]
		80	[59]
	Me <sub>3</sub> Al	80	[60]

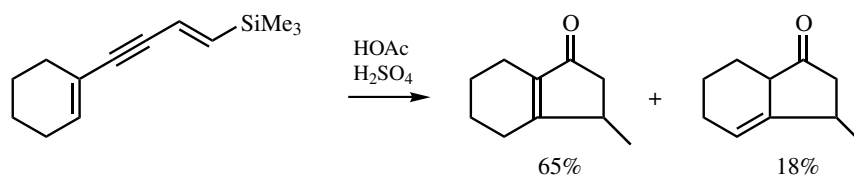
(Continued)

TABLE 4. (Continued)

Electrophile	Example of Nucleophile	Product Yield (%)	Reference
	<i>n</i> -OctMgBr	75	[61]
		86	[62]
		81	[63]
		94	[64]
		79	[54]
	PhC≡CZnCl	64	[65]
		74	[66]
		78	[67]

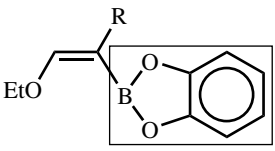
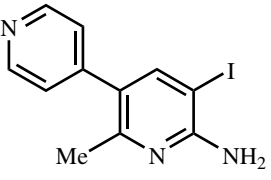
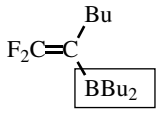
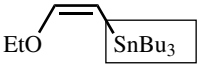
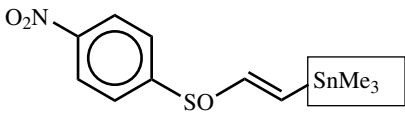
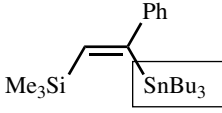
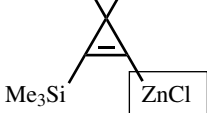
The presence of  $\beta$ -heteroatom substituents offers various synthetically attractive possibilities. For example, silyl-substituted dienynes<sup>[63]</sup> can undergo Si-assisted Nazarov-type cyclization, as exemplified in **Scheme 14**.

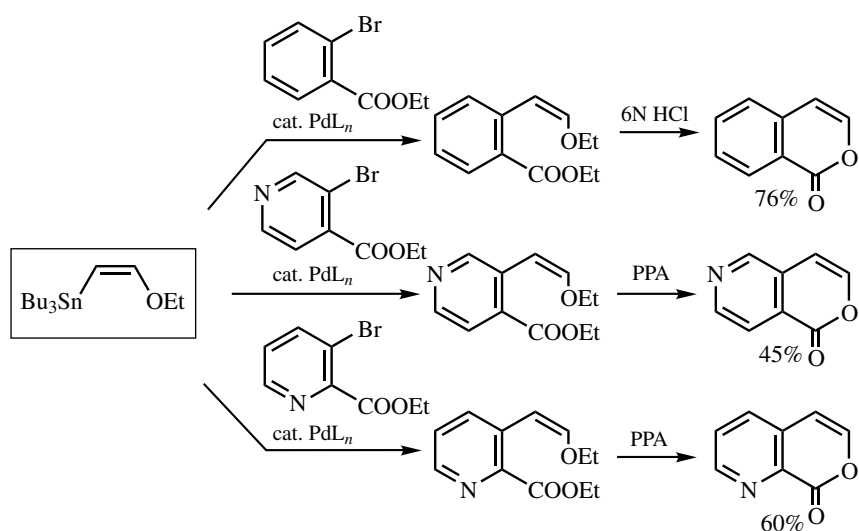
$\beta$ -Alkoxyethenyl derivatives are useful two-carbon synthons for the synthesis of heterocycles,<sup>[74]</sup> as indicated by the synthesis of arene-fused pyrones shown in **Scheme 15**.



Scheme 14

TABLE 5. Some  $\beta$ -Hetero-Substituted Nucleophiles

Nucleophile	An Example of Electrophile	Product Yield (%)	Reference
		78	[68]
	PhCH=CHBr	82	[69]
	PhBr	78	[70]
	Ph-OTf	78	[71]
	CH <sub>2</sub> =CHCH <sub>2</sub> Br	75	[72]
	BrCH=CHBr	58	[73]



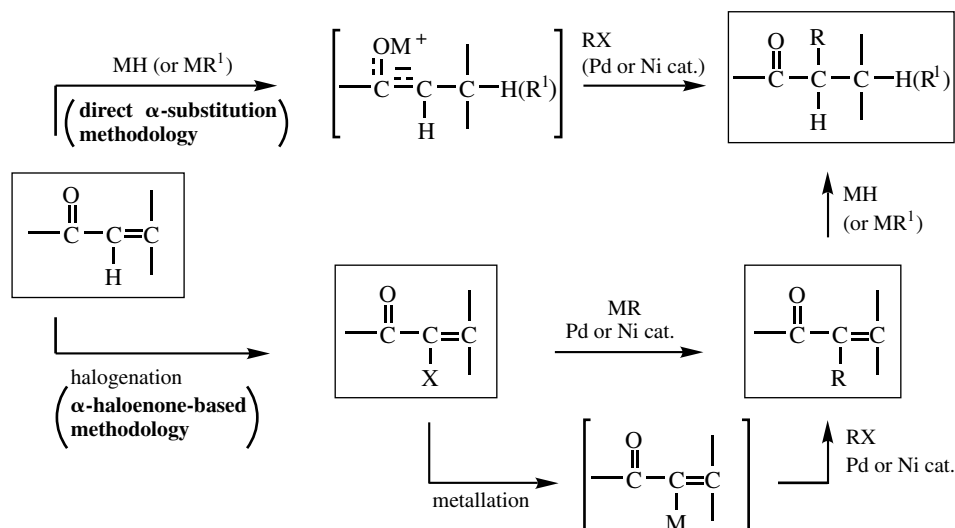
Scheme 15

### D. Pd-CATALYZED CROSS-COUPLING OF $\alpha,\beta$ -UNSATURATED CARBONYL DERIVATIVES CONTAINING $\alpha$ -HALOGEN OR $\alpha$ -METAL GROUPS

#### D.i. Background

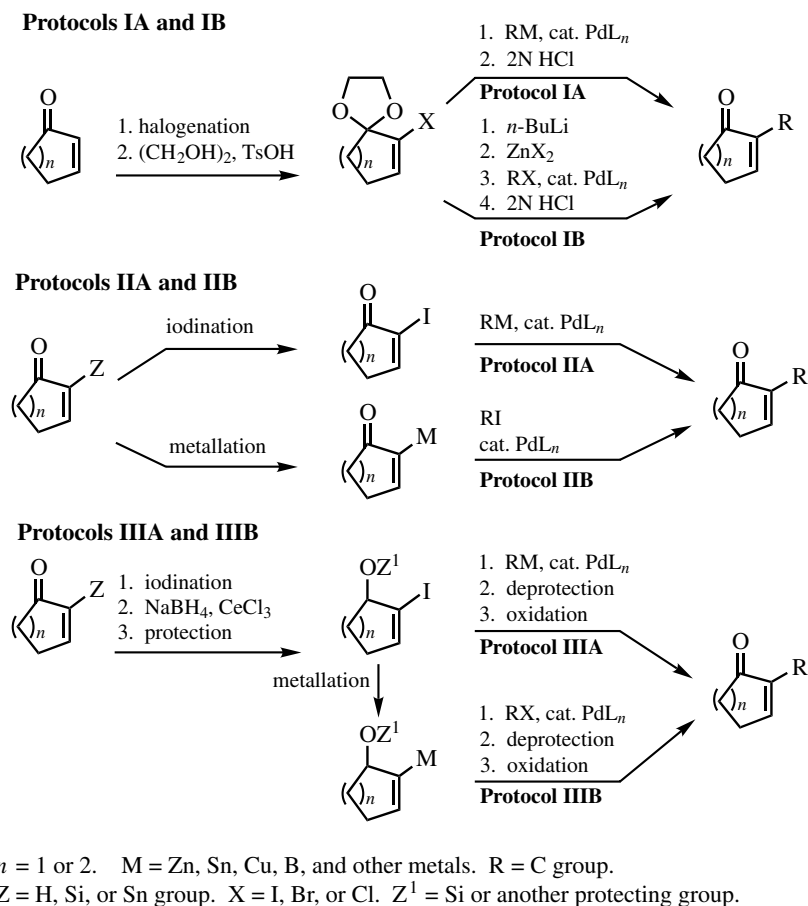
Introduction of simple hydrocarbon groups in the  $\alpha$ -position of ketones and other carbonyl compounds is most typically achieved by alkylation of enolates and related compounds.<sup>[75]</sup> As basic and important as it is, it has been associated with some limitations and undesirable features. First, the alkali and alkaline earth metal-based methodology is limited to the introduction of  $sp^3$  carbon groups of relatively low steric requirements, such as Me, primary alkyl, allyl, benzyl, and propargyl groups. Introduction of sterically hindered groups, such as tertiary alkyl and many secondary alkyl groups, is not practical, and  $sp^2$  and  $sp$  carbon groups, such as aryl, alkenyl, and alkynyl groups, cannot be introduced. Second, the reaction is prone to multiple substitution, and it is often difficult to achieve clean monosubstitution. Third, although so called “kinetic” and “thermodynamic” enolates can selectively be generated in a number of cases, strict regiochemical control requires special procedures, such as generation of enolates via conjugate reduction of  $\alpha,\beta$ -unsaturated enones, which must then be followed by regiospecific alkylation. Despite all these difficulties and limitations,  $\alpha$ -substitution of carbonyl compounds is a highly desirable synthetic operation. Critically needed is a methodology permitting introduction of all types of carbon groups, especially aryl, alkenyl, and alkynyl groups with strict control of the degree of substitution and regiochemistry. Pd- or Ni-catalyzed cross-coupling of either  $\alpha$ -halo- $\alpha,\beta$ -unsaturated carbonyl compounds or the corresponding  $\alpha$ -metallo derivatives has proved to be a very attractive alternative to the classical enolate alkylation. A few representative enone-based  $\alpha$ -substitution methodologies are shown in **Scheme 16**.

It has also been shown that further modifications of the  $\alpha$ -haloenone-based methodology shown in **Scheme 16** are desirable in some cases. Various strategies and protocols



Scheme 16

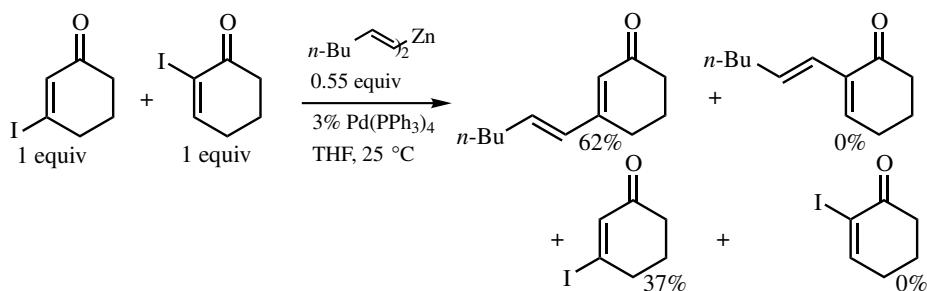
developed since the mid-1980s are summarized in **Scheme 17** and discussed below. For the sake of simplicity,  $\alpha$ -substitution of 2-cyclopentenones, 2-cyclohexenones, and their derivatives are shown in **Scheme 17** as representative cases.



**Scheme 17**

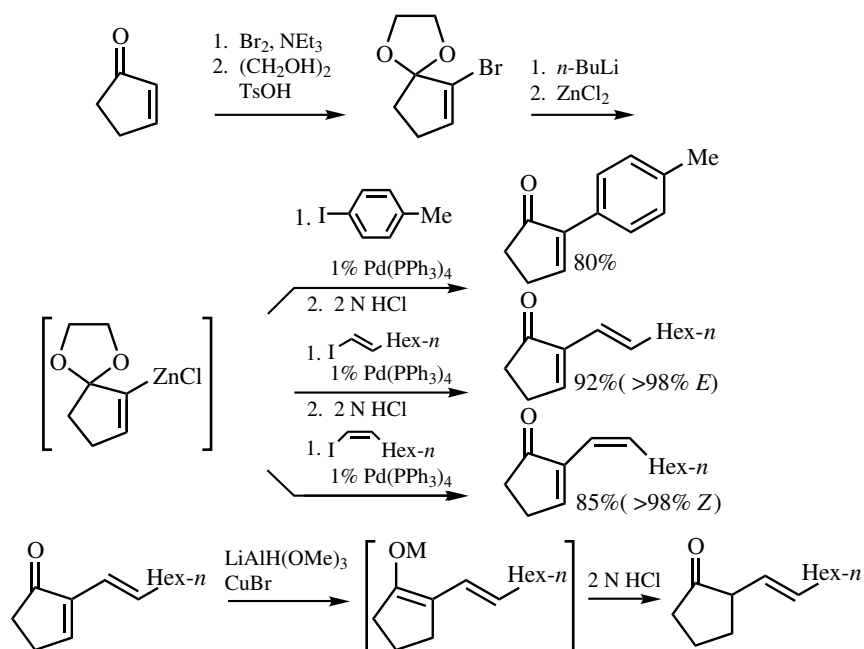
## D.ii. Pd-Catalyzed $\alpha$ -Substitution of $\alpha$ -Haloenones, $\alpha$ -Metalloenones, and Their Derivatives

**D.ii.a. Pd-Catalyzed  $\alpha$ -Arylation and  $\alpha$ -Alkenylation of Acetal-Protected Enone Derivatives (Protocol I).** The reaction of 2-bromo-2-cyclohexenone and 2-iodo-2-cyclohexenone with bis[(*E*)-1-hexenyl]zinc in the presence of 5 mol % of a  $\text{Pd-PPh}_3$  complex in THF at 25 °C gives 2-[(*E*)-1-hexenyl]-2-cyclohexenone in 0% and 31% yield, respectively.<sup>[76]</sup> In sharp contrast, the corresponding reaction of 3-bromo-2-cyclohexenone provides 3-[(*E*)-1-hexenyl]-2-cyclohexenone in 75% yield, with the balance of the starting bromoenone still remaining unreacted. The sluggish nature of  $\alpha$ -substitution and the greater instability of  $\alpha$ -haloenones are clearly indicated in the competitive experiment summarized in **Scheme 18**.<sup>[76]</sup>



Scheme 18

In view of the low intrinsic reactivity and high instability of  $\alpha$ -haloenones in Pd-catalyzed cross-coupling, acetal-protected  $\alpha$ -bromoenones were employed as key intermediates in an early study.<sup>[77]</sup> The Pd-catalyzed cross-coupling reaction of acetal-protected  $\alpha$ -bromoenones with organozincs and other organometals has turned out to be sluggish. On the other hand, their conversion to the corresponding zinc derivatives via lithiation with butyllithium permits clean and high-yield cross-coupling not only with aryl halides but, more significantly, with both *E* and *Z* alkenyl iodides using 1 mol % of  $\text{Pd(PPh}_3)_4$  (Scheme 19).<sup>[77]</sup> The corresponding alkenyllithiums are totally ineffective under comparable conditions. Conjugate reduction of 2-[(*E*)-1-octenyl]-2-cyclopentenone with  $\text{LiAlH(OMe)}_3$  and  $\text{CuI}^{[78]}$  followed by protonolysis with 2 N HCl at 0 °C cleanly provides 2-[(*E*)-1-octenyl]cyclopentanone in excellent yield. Thus, the putative dienolate intermediate must undergo exclusive  $\alpha$  protonation. Full retention of the regiochemistry is clearly indicated in the exclusive formation of 2-[(*E*)-1-octenyl]-6-



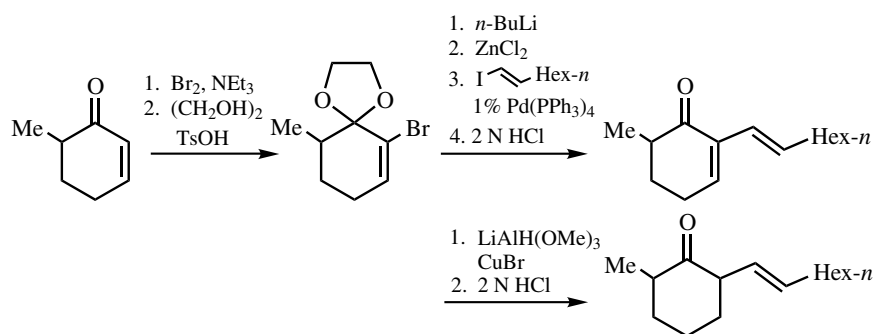
Scheme 19



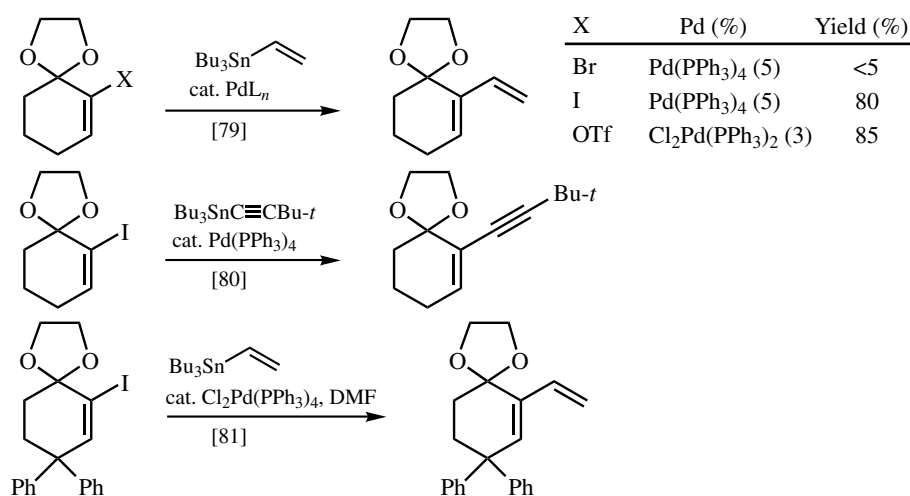
methylcyclohexanone from 6-methyl-2-cyclohexenone in 55% overall yield (**Scheme 20**).<sup>[77]</sup> Thus, the feasibility, dependability, and highly selective nature of Protocol IB have been firmly established by the results shown in **Schemes 19** and **20**.

Later studies have further demonstrated that alkenyl- and alkynylstannanes also react analogously (**Scheme 21**).<sup>[79]–[81]</sup>

Despite its dependability and high selectivity, Protocol I is indirect and cumbersome, and a more direct method—Protocol II—is clearly desirable.



**Scheme 20**



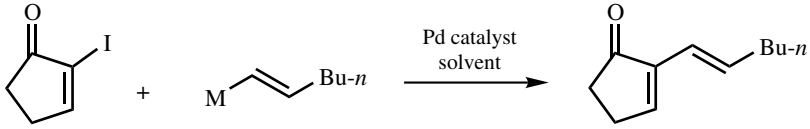
**Scheme 21**

#### D.ii.b. Pd-Catalyzed $\alpha$ -Arylation and $\alpha$ -Alkenylation of $\alpha$ -Iodoenones (Protocol IIA).

Although the reaction of 2-iodo-2-cyclohexenone with bis[(*E*)-1-hexenyl]zinc in the presence of a Pd catalyst (5 mol %) generated by the treatment of Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub> with 2 equiv of *n*-BuLi in THF was sluggish, it was soon found that the use of polar aprotic solvents would significantly improve the product yield. Thus, the use of DMF, DMSO, and NMP (*N*-methylpyrrolidone) improved the cross-coupling yields to  $\geq 88\%$ , 80%, and 74%, respectively.<sup>[76]</sup> (*E*)-1-Hexenyldialkylaluminums prepared by treating (*E*)-1-hexenyllithium with ClAlMe<sub>2</sub> and ClAl(*Bu-i*)<sub>2</sub> were also satisfactory, producing the

desired product in 71% and 89% yields, respectively, whereas alkenylaluminums generated by hydroalumination were less effective. Also unsatisfactory was the corresponding zirconocene derivative, which led only to a 27% yield of the desired product. The *n*-Bu<sub>3</sub>Sn-containing reagent was practically unreactive at room temperature, but it gave the desired product in 64% yield in 13 h at 60–65 °C. These results of reaction condition optimization are summarized in **Table 6**.<sup>[76]</sup> In summary, the use of organozinc reagents and DMF as a solvent appears to be optimal. In most cases, Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub> and

**TABLE 6.** Effects of Reaction Parameters in the Pd-Catalyzed Reaction of 2-Iodo-2-cyclopentenone with (*E*)-1-Hexenylmetals<sup>a</sup>

					
M-CH=CH-Bu- <i>n</i>	Pd Catalyst <sup>b</sup>	Solvent	Temperature (°C)	Time (h)	Product Yield (%) <sup>c</sup>
Zn(CH=CH-Bu- <i>n</i> ) <sub>2</sub>	I	THF	25	1	31
Zn(CH=CH-Bu- <i>n</i> ) <sub>2</sub>	I	THF-DMF	25	1	87
Zn(CH=CH-Bu- <i>n</i> ) <sub>2</sub>	I	DMF	25	1	100(86 <sup>d</sup> )
Zn(CH=CH-Bu- <i>n</i> ) <sub>2</sub>	II	DMF	25	1	88
Zn(CH=CH-Bu- <i>n</i> ) <sub>2</sub>	I	DMSO	25	1	80
Zn(CH=CH-Bu- <i>n</i> ) <sub>2</sub>	I	NMP	25	1	74
Me <sub>2</sub> Al-CH=CH-Bu- <i>n</i>	I	DMF	25	1	71
<i>i</i> -Bu <sub>2</sub> Al-CH=CH-Bu- <i>n</i>	I	DMF	25	1	89
<i>i</i> -Bu <sub>2</sub> Al-CH=CH-Bu- <i>n</i> <sup>e</sup>	I	DMF	25	1	44
ClCp <sub>2</sub> Zr-CH=CH-Bu- <i>n</i> <sup>e</sup>	I	DMF	25	1	27
Bu <sub>3</sub> Sn-CH=CH-Bu- <i>n</i>	I	DMF	25	1	Trace
Bu <sub>3</sub> Sn-CH=CH-Bu- <i>n</i>	I	DMF	60–65	13	64 <sup>f</sup>

<sup>a</sup> The alkenylmetals were prepared by treatment of (*E*)-1-hexenyllithium with appropriate metal halides, unless otherwise mentioned.

<sup>b</sup> I = Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub> + 2*n*-BuLi. II = Pd(PPh<sub>3</sub>)<sub>4</sub>.

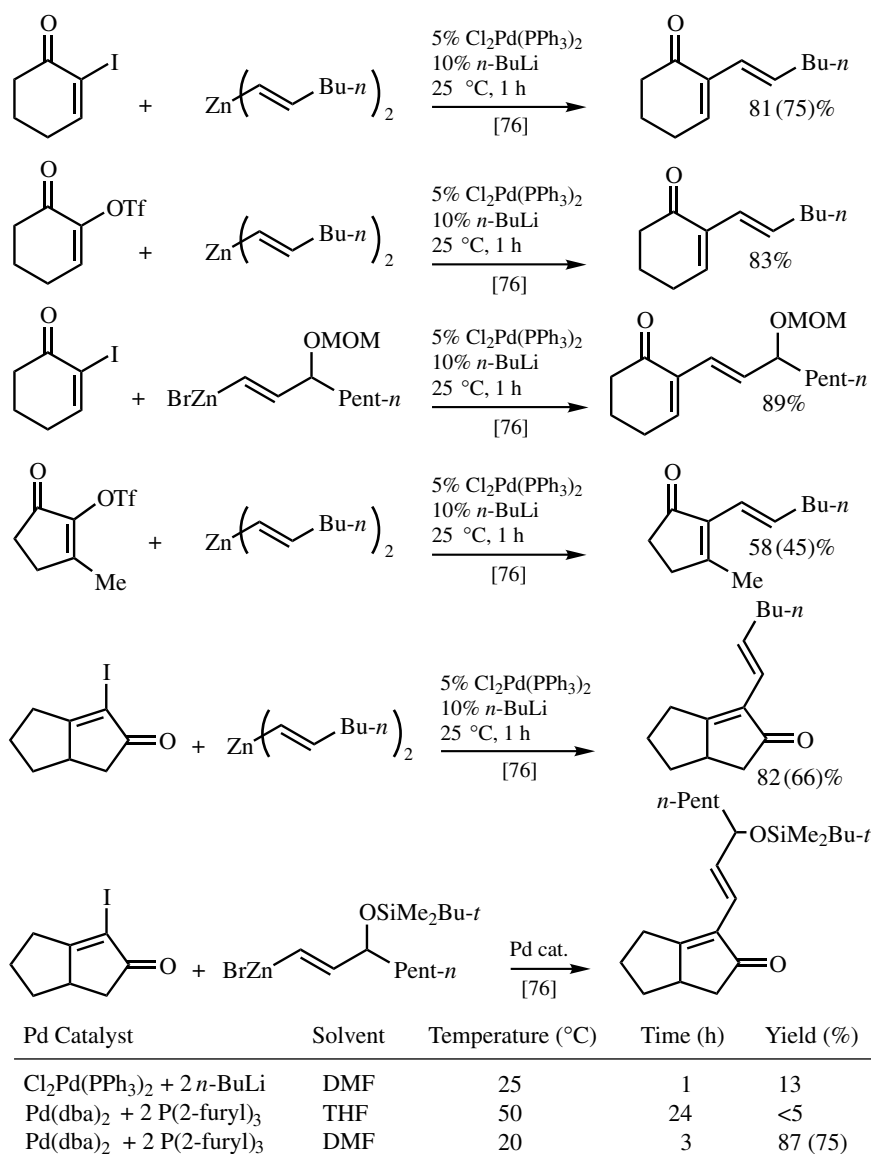
<sup>c</sup> By <sup>1</sup>H NMR and/or GLC.

<sup>d</sup> Isolated yield.

<sup>e</sup> Prepared by appropriate hydrometallation of 1-hexyne.

<sup>f</sup> 2-Iodo-2-cyclopentenone remained unreacted to the extent of 18%.

$\text{Pd}(\text{PPh}_3)_4$  are satisfactory catalysts. In some more demanding cases, however, the use of more effective catalysts, for example,  $\text{Cl}_2\text{Pd}[\text{P}(2\text{-furyl})_3]_2$ ,<sup>[82]–[84]</sup>  $\text{Pd}_2(\text{dba})_3 + \text{AsPh}_3$ ,<sup>[85]</sup> and  $\text{Pd}(\text{OAc})_2 + \text{AsPh}_3$ ,<sup>[86]</sup> has been shown to be desirable (**Scheme 22**).

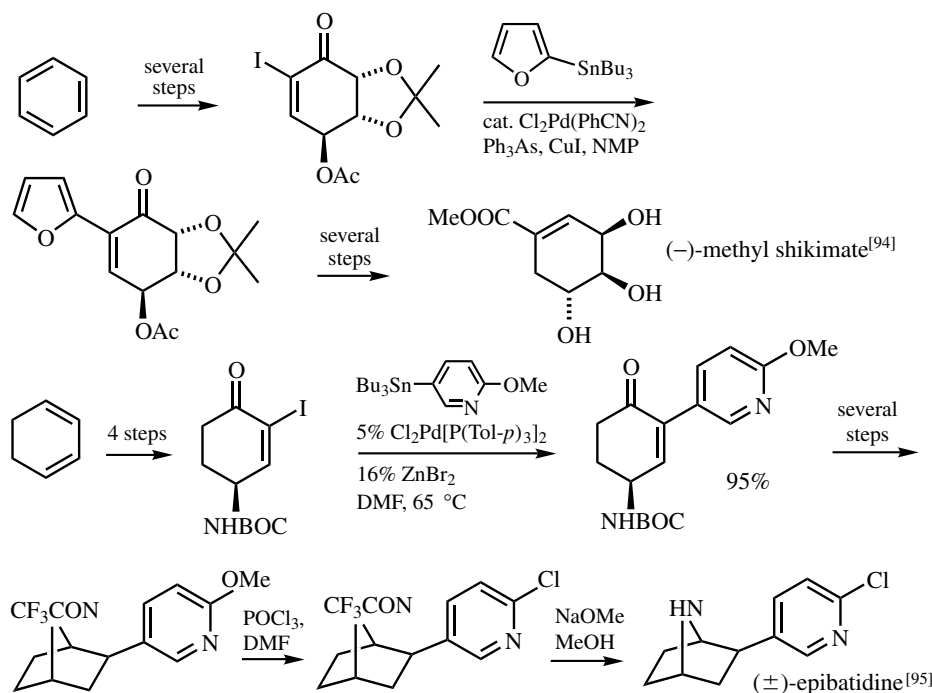


**Note:** The yields are determined by NMR and/or GLC. The numbers in parentheses are isolated yields.

**Scheme 22**

As indicated in **Table 6**, organotin compounds are considerably less reactive than organozinc compounds, but their reactions proceed satisfactorily in many cases at elevated temperatures, typically around 100 °C.<sup>[87]</sup> An exception to the above generalization is  $\alpha$ -arylation of  $\alpha$ -triflyloxy-substituted enones with arylstannanes in the presence of  $\text{Pd}_2(\text{dba})_3$  and either  $\text{AsPh}_3$  or  $\text{LiCl}$ ,

which proceeds well even at room temperature.<sup>[88],[89]</sup> Under those conditions that are satisfactory for organozincs, the corresponding organoboron compounds show little reactivity.<sup>[76]</sup> However, the use of  $\text{Ph}_3\text{As}$  as a ligand together with an excess of  $\text{Ag}_2\text{O}$  (1.5–6.0 equiv relative to the substrates) permits facile  $\alpha$ -arylation in THF even at 25 °C.<sup>[90]</sup> Some representative results observed with organotin<sup>[87]–[93]</sup> and organoborons<sup>[90]</sup> are summarized in **Table 7**. The organotin-based method has been applied to the synthesis of (–)-methyl shikimate<sup>[94]</sup> and (±)-epibatidine<sup>[95]</sup> (**Scheme 23**).



Scheme 23

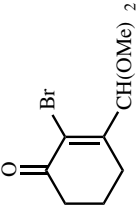
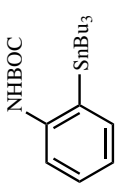
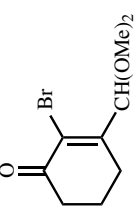
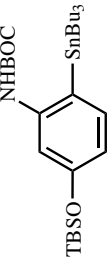
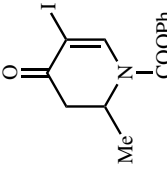
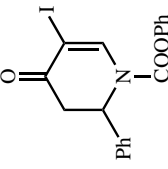
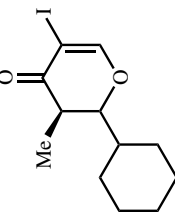
**D.ii.c. Pd-Catalyzed  $\alpha$ -Alkynylation of  $\alpha$ -Iodoenones (Protocol IIA).** Discovery of natural products of various potentially significant biological activities featuring  $\alpha$ -alkynylenones within the last decade prompted the development of procedures for  $\alpha$ -alkynylation of enones that might be more direct and more satisfactory than those discussed earlier.<sup>[98]–[101]</sup> Several independent studies have shown that applications of the methods for  $\alpha$ -arylation and  $\alpha$ -alkenylation discussed above involving  $\text{Sn}$ <sup>[102]</sup> and  $\text{Zn}$ <sup>[103]</sup> permit the desired  $\alpha$ -alkynylation in good yields. The Cu-based Sonogashira alkynylation was reported in one study to be unsatisfactory for the synthesis of tricholomenyn A,<sup>[104]</sup> but some other studies have shown that satisfactory results may be obtained using this reaction.<sup>[93],[105]</sup> These procedures have been applied to very efficient synthesis of harveynone and tricholomenyn A (**Scheme 24**).<sup>[103]–[105]</sup> Since their synthesis does not require subsequent conjugate reduction, these recently reported syntheses appear to represent some ultimately satisfactory constructions of this class of compounds. Some other results of  $\alpha$ -alkynylation are shown in **Schemes 25–27**.

**TABLE 7. Pd-Catalyzed Reaction of  $\alpha$ -Arylation and  $\alpha$ -Alkenylation of  $\alpha$ -Iodoenones with Organotin and Organoborane**

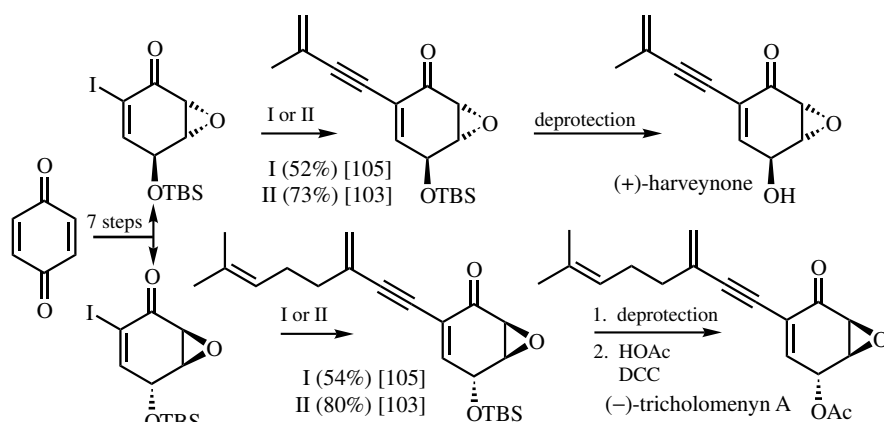
$\alpha$ -Iodoenone	Organometal	Catalyst <sup>a</sup>	Solvent	Temperature (°C)	Product Yield (%)	Reference
	CH <sub>2</sub> =CHSnBu <sub>3</sub>	I	NMP	25	80	[88]
	Me <sub>2</sub> C=CHSnBu <sub>3</sub>	I	NMP	80	76	[88]
	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> SnBu <sub>3</sub>	I	NMP	50	66	[88]
		II	THF	25	97	[90]
	Me <sub>2</sub> C=CHSnBu <sub>3</sub>	I	NMP	110	83	[88]
	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	II	THF	25	78	[90]
	<i>m</i> -TBSOC <sub>6</sub> H <sub>4</sub> SnBu <sub>3</sub>	III	NMP	70	81	[96]
	Me <sub>2</sub> C=CHSnBu <sub>3</sub>	I	NMP	80	80	[88]
	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> SnBu <sub>3</sub>	I	NMP	60	95	[88]
	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	II	THF	25	100	[90]
	CH <sub>2</sub> =CHSnBu <sub>3</sub>	I	NMP	35–50	47–65	[88],[91]
	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> SnBu <sub>3</sub>	I	NMP	85	87	[88]
	<i>p</i> -TBSOCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SnBu <sub>3</sub>	IV	NMP	24	83	[88],[89]
	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> SnBu <sub>3</sub>	V	NMP	24	77	[88],[89]

(Continued)

TABLE 7. (Continued)

$\alpha$ -Iodoenone	Organometal	Catalyst <sup>a</sup>	Solvent	Temperature (°C)	Product Yield (%)	Reference
		VI	NMP	60–70	78	[92]
		VI	Toluene	80	70	[92]
	$\text{CH}_2=\text{CHSnMe}_3$	VII	Toluene	90	79	[93]
	$\text{PhSnBu}_3$	VII	Toluene	90	61	[93]
	$\text{CH}_2=\text{CHSnBu}_3$ $\text{PhSnMe}_3$	VII VII	Toluene —	85 50	76 66	[97] [97]

<sup>a</sup> I = 5 mol %  $\text{Cl}_2\text{Pd}(\text{PhCN})_2$ , 10 mol %  $\text{Ph}_3\text{As}$ , 10 mol %  $\text{CuI}$ . II = 3 mol %  $\text{Cl}_2\text{Pd}(\text{PhCN})_2$ , 6 mol %  $\text{Ph}_3\text{As}$ , 1.6 equiv  $\text{Ag}_2\text{O}$ . III =  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ ,  $\text{Ph}_3\text{As}$ ,  $\text{CuI}$ . IV =  $\text{Pd}_2(\text{dba})_3 \cdot \text{LiCl}$ . V =  $\text{Pd}_2(\text{dba})_3$ ,  $\text{CHCl}_3$ . VI =  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ ,  $\text{P}(\text{Tol-}o)_3$ . VII =  $\text{Pd}(\text{PPh}_3)_4$ .

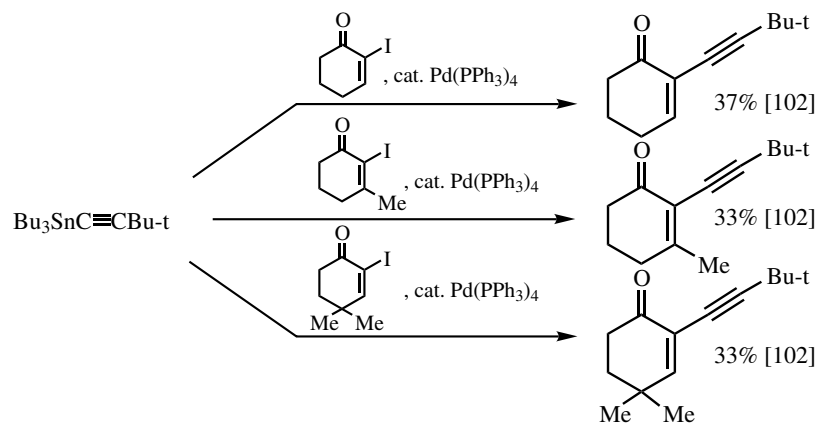


I = cat.  $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ ,  $\text{CuI}$ ,  $i\text{-Pr}_2\text{NH}$ ,  $\text{CH}_2=\text{C}(\text{R})\text{C}\equiv\text{CH}$ .

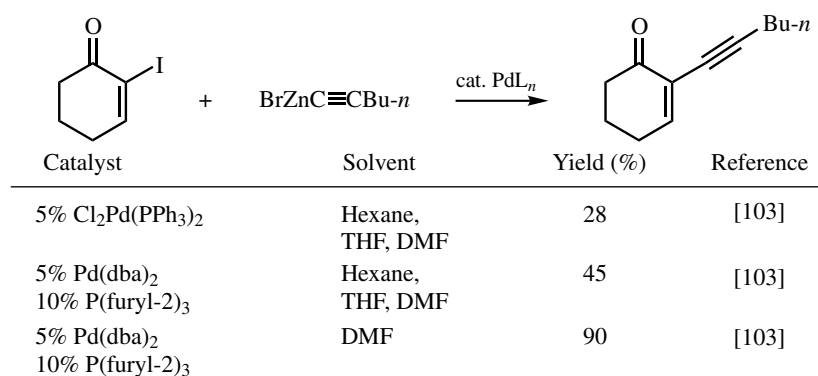
II = 5 mol %  $\text{Pd}(\text{dba})_2$ , 10 mol %  $\text{P}(\text{furyl-2})_3$ ,  $\text{CH}_2=\text{C}(\text{R})\text{C}\equiv\text{CZnBr}$ , DMF, 25 °C. The products in these cases were racemic mixtures.

R = Me and  $\text{Me}_2\text{C}=\text{CH}(\text{CH}_2)_2$

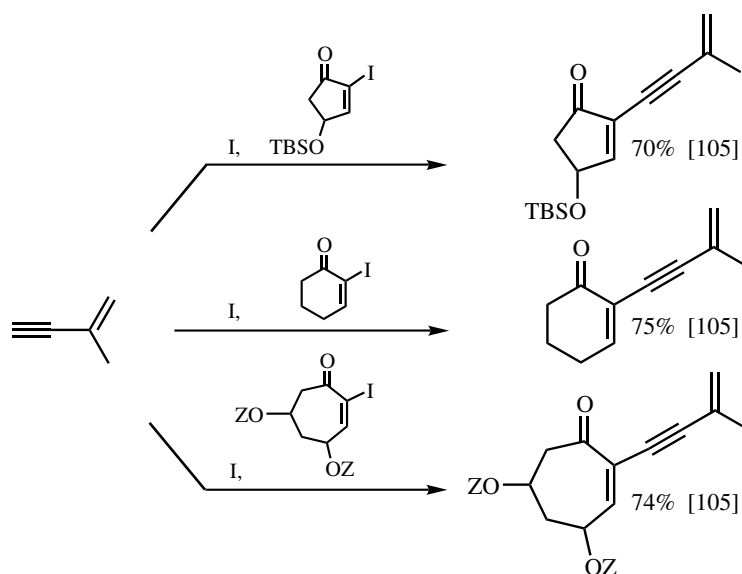
Scheme 24



Scheme 25

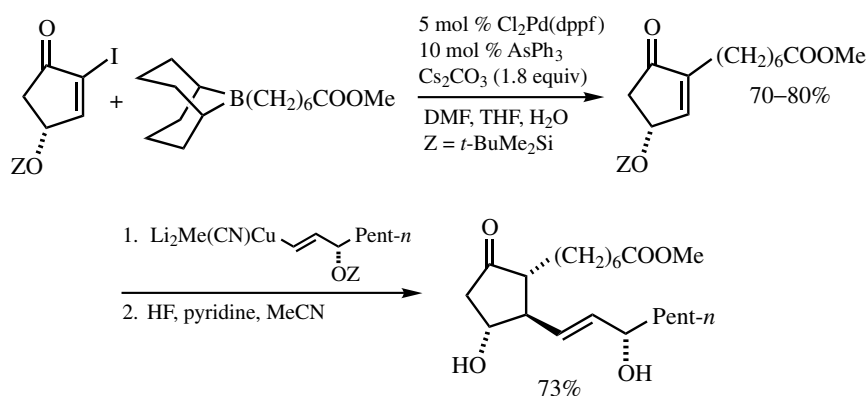


Scheme 26



Scheme 27

**D.ii.d. Pd-Catalyzed  $\alpha$ -Alkylation of  $\alpha$ -Iodoenones (Protocol IIA).** Although  $\alpha$ -alkylation of alkali metal enolates and related derivatives, such as enamines, proceeds satisfactorily in many cases, it is still desirable to develop a complementary  $\alpha$ -haloenone-based  $\alpha$ -alkylation methodology for the following reasons. First, it would provide an efficient route to  $\alpha$ -alkyl-substituted enones. Second, it might provide a satisfactory route to  $\alpha$ -alkyl-substituted ketones even in cases where the conventional alkylation methodology is unsatisfactory. An efficient synthesis of prostaglandin  $\text{E}_1$  involving Pd-catalyzed  $\alpha$ -alkylation of 2-iodo-4-(*t*-butyldimethylsiloxy)-2-cyclopentenone with *B*-(6-methoxycarbonyl)hexyl-9-BBN, where 9-BBN is 9-borabicyclo[3.3.1]nonane, is a representative example (Scheme 28).<sup>[106]</sup>



Scheme 28



A systematic investigation of the Pd-catalyzed cross-coupling reaction of  $\alpha$ -iodoenones with alkylzinc derivatives<sup>[107]</sup> indicates that both alkylzinc halides and dialkylzincs containing Me, primary alkyl, benzyl, homobenzyl, and homopropargyl groups react satisfactorily (Table 8). Benzylzinc derivatives prepared by treating benzylmagnesium bromide with

TABLE 8. Pd-Catalyzed  $\alpha$ -Alkylation of  $\alpha$ -Iodoenones<sup>a</sup>

$\alpha$ -Iodoenone	Alkylzinc Derivative	Method of Generation <sup>b</sup>	Catalyst <sup>b</sup>	Product Yield (%) <sup>b</sup>
	Me <sub>2</sub> Zn	A	I	85
	( <i>n</i> -Hex) <sub>2</sub> Zn	B	I	85 (81)
	( <i>i</i> -Bu) <sub>2</sub> Zn	B	I	85 (73)
	( <i>s</i> -Bu) <sub>2</sub> Zn	B	I	72 (61) <sup>e</sup>
	(PhCH <sub>2</sub> ) <sub>2</sub> Zn	B	I	Trace
	PhCH <sub>2</sub> ZnBr	C	I	82 (74)
	( <i>n</i> -Bu) <sub>2</sub> Zn	B	I	76 (66)
	( <i>n</i> -Bu) <sub>2</sub> Zn	B	I	67 (59)
	<i>n</i> -HexZnBr	B	I	96
	PhCH <sub>2</sub> ZnBr	C	I	94
	Me <sub>3</sub> SiC $\equiv$ C(CH <sub>2</sub> ) <sub>2</sub> ZnI	C	II	80 (61)
	H <sub>2</sub> C=CH(CH <sub>2</sub> ) <sub>2</sub> ZnBr	D	II	36
	PhCH <sub>2</sub> ZnBr	C	I	72
	<i>n</i> -BuZnBr	B	I	84
	PhCH <sub>2</sub> ZnBr	C	I	71
	Ph(CH <sub>2</sub> ) <sub>2</sub> ZnBr	D	I	83

<sup>a</sup> Unless otherwise mentioned, the reactions were carried out at 23 °C in DMF or DMF-THF using either 0.65 molar equiv of a dialkylzinc or 1.3 molar equiv of an alkylzinc bromide or iodide.

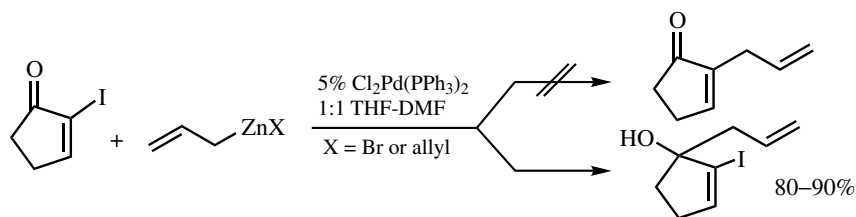
<sup>b</sup> A = Commercially available. B = RMgX +  $\frac{1}{2}$  ZnBr<sub>2</sub> (X = Br or I). C = RX + Zn.  
D = RX + Mg + ZnBr<sub>2</sub>.

<sup>c</sup> I = 5 mol % Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub>. II = 5 mol % Cl<sub>2</sub> Pd(TFP)<sub>2</sub>.

<sup>d</sup> By NMR and/or GLC. The numbers in parentheses are isolated yields.

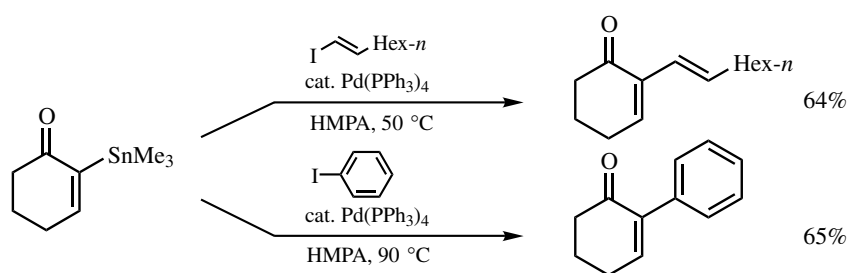
<sup>e</sup> Completely isomerized to *n*-butyl. Additionally, 3-(*s*-butyl)cyclopentanone was also obtained in 12% yield.

ZnBr<sub>2</sub> are ineffective, but benzylzinc bromide prepared by treating PhCH<sub>2</sub>Br with Zn is satisfactory. Secondary alkylzinc derivatives give cross-coupling products in high yields, but it is difficult to avoid extensive secondary-to-primary isomerization observed with Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub> or conjugate addition with concomitant deiodination observed with Cl<sub>2</sub>Pd(dppp) and Cl<sub>2</sub>Pd(dppf).<sup>[108]</sup> The results appear to indicate that substitution of  $\alpha$ -iodoenones is significantly more demanding than that of other ordinary alkenyl halides. Somewhat surprisingly, all attempts to allylate  $\alpha$ -iodocyclopentenone led to 1,2-addition of either allylzinc bromide or diallylzinc to the carbonyl group without the involvement of the C—I bond (**Scheme 29**).<sup>[107]</sup> The corresponding reaction of propargylzinc derivatives proceeds similarly via 1,2-addition.

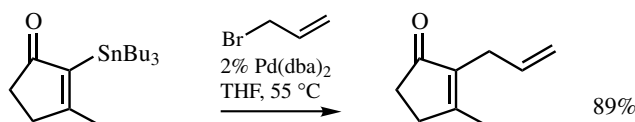


Scheme 29

**D.ii.e. Pd-Catalyzed  $\alpha$ -Substitution of  $\alpha$ -Metalloenones (Protocol IIB).** 2-Trimethylstannyl-2-cyclopentenone prepared via lithiation–stannylation of cyclic acetal-protected 2-bromo-2-cyclopentenone reacted with (*E*)-1-octenyl iodide in the presence of 5 mol % of Pd(PPh<sub>3</sub>)<sub>4</sub> to give the desired cross-coupling product in 80% yield.<sup>[76]</sup> Under comparable conditions, 2-trimethylstannyl-2-cyclohexenone reacted with (*E*)-1-octenyl iodide and phenyl iodide to give the corresponding cross-coupling products in about 65% yields (**Scheme 30**).<sup>[107]</sup> These may well represent the first set of examples of Pd-catalyzed cross-coupling of  $\alpha$ -stannyleneones. Unfortunately, attempts to alkenylate 2-trimethylstannylbicyclo[3.3.0]oct-1-en-3-one by the same reaction were unsuccessful, the yield of the desired product being <10%. A related  $\alpha$ -allylation of  $\alpha$ -stannyleneones is also known, as shown in **Scheme 31**.<sup>[109]</sup>



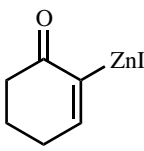
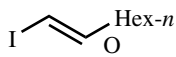
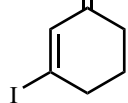
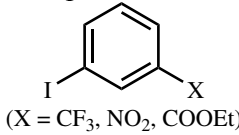
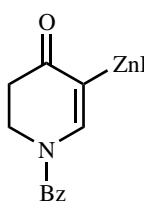
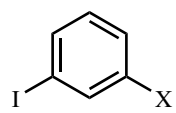
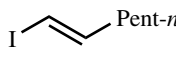
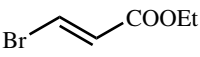
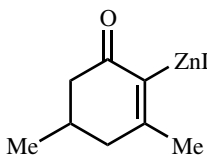
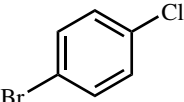
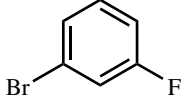
Scheme 30




Scheme 31

More recently, direct conversion of  $\alpha$ -iodoenones into the corresponding  $\alpha$ -zinc derivatives has been achieved using either an excess of Zn dust<sup>[110]</sup> or Zn–Ag couple (4 equiv) in the presence of TMEDA (1 equiv).<sup>[111]</sup> The Zn reagents thus generated are less reactive than the more usual alkenylzinc derivatives. Nonetheless, some satisfactory results have been obtained with aryl halides. On the other hand, variable results were obtained with alkenyl halides (**Table 9**).<sup>[110],[111]</sup> In summary, the  $\alpha$ -zincoenone-based procedures appear to be somewhat more involved than the corresponding  $\alpha$ -iodoenone-based procedures, and the cross-coupling yields tend to be lower. On the other hand, they do not require strongly basic organolithiums or Grignard reagents. Thus, they can tolerate a wider range of heteroatom functionalities.

**TABLE 9. Pd-Catalyzed  $\alpha$ -Arylation and  $\alpha$ -Alkenylation of  $\alpha$ -Zincoenones<sup>a</sup>**

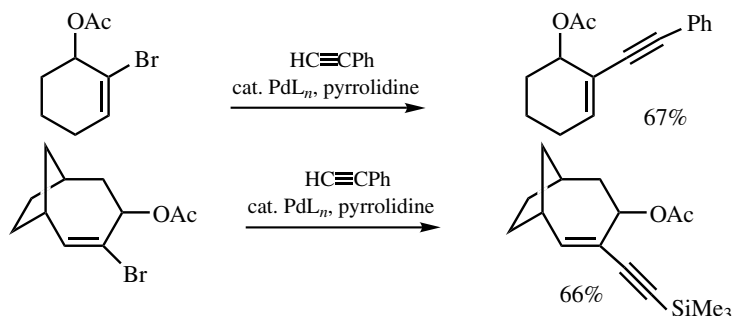
Enone	Aryl or Alkenyl Halide	Catalyst <sup>b</sup>	Product Yield (%)	Reference
		I	80	[110]
		I	71	[110]
	 (X = CF <sub>3</sub> , NO <sub>2</sub> , COOEt)	I	78–88	[110]
	 (X = CF <sub>3</sub> , NO <sub>2</sub> , COOEt)	I	70–81	[110]
		II	48	[111]
		III	32	[111]
		III	89	[111]
		III	70	[111]

<sup>a</sup> 1.3 to 2 equiv of organozinc reagents were used.

<sup>b</sup> I = 1 mol % Pd(dba)<sub>2</sub> and 4 mol % P()<sub>3</sub>. II = 5 mol % Pd(dba)<sub>2</sub> and 15 mol % AsPh<sub>3</sub>.

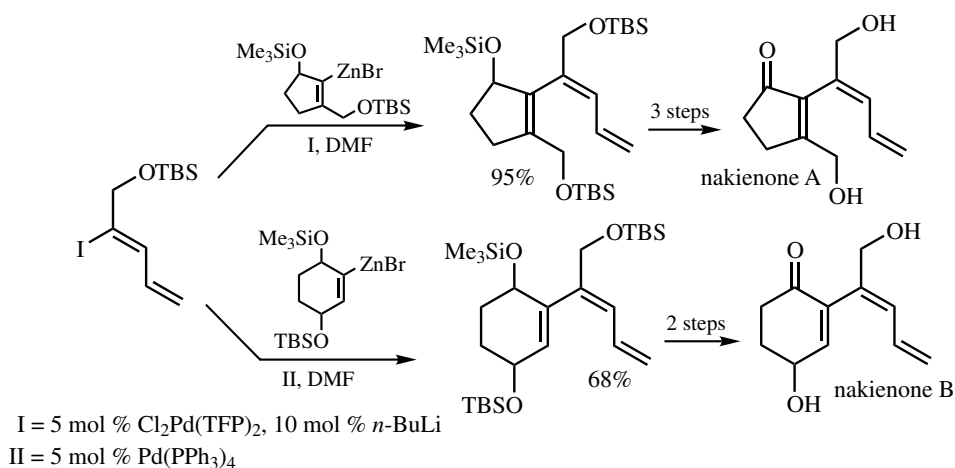
III = 5 mol % Pd(PPh<sub>3</sub>)<sub>4</sub>

**D.ii.f. Pd-Catalyzed  $\alpha$ -Substitution of  $\alpha$ -Haloenols and  $\alpha$ -Metalloenols (Protocols IIIA and IIIB).** Protocols I and II discussed in Sects. D.ii.a–D.ii.e collectively provide satisfactory procedures for  $\alpha$ -substitution of enones in a wide variety of cases. Nonetheless, development of additional alternative procedures has proved to be desirable in some very demanding and delicate situations. In certain cases where the products and/or intermediates are highly acid-sensitive and the desired cross-coupling is very demanding, Protocol III (Scheme 17) has been shown to be the most dependable, although it is more cumbersome than Protocols I and II. The earliest study of Protocol III, however, employed 2-bromoallylic acetates of relatively modest reactivity. Despite some favorable results reported for alkynylation shown in Scheme 32,<sup>[112]</sup> their Pd-catalyzed cross-coupling with other nucleophiles, such as alkenyl- and arylmetals, is complicated by a few side reactions including (i) elimination of allylic acetates to give conjugated bromodienes, (ii) deacetylation, and (iii) allylic substitution with pyrrolidine and other amines used as bases.<sup>[112]</sup>



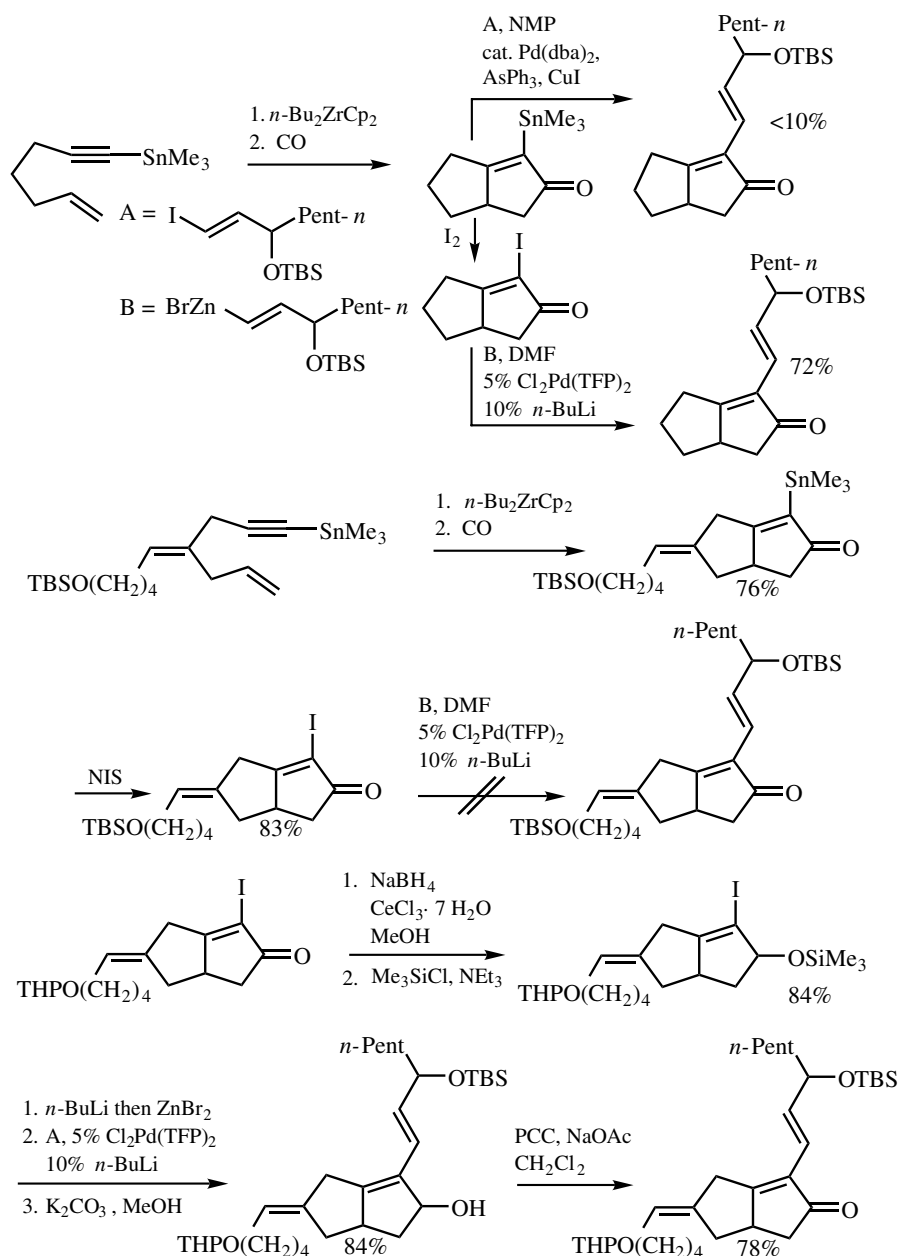
Scheme 32

Much more favorable results can be obtained with 2-iodoallyl alcohol derivatives. In the syntheses of highly acid-sensitive nakienones A<sup>[113]</sup> and B,<sup>[114]</sup> it was not readily feasible to zincate (Z)-2-iodo-2,4-pentadien-1-ol derivatives due to competitive  $\beta$ -elimination. It was therefore desirable to incorporate the cyclic enone moiety as nucleophiles, as summarized in Scheme 33.



Scheme 33

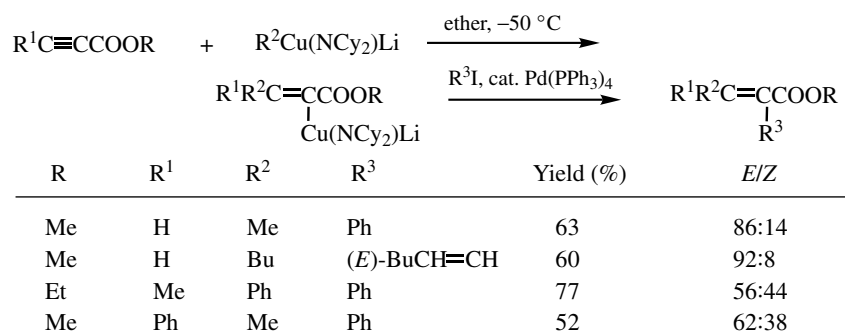
In a recent synthesis of carbacyclin,<sup>[115]</sup> a need for Protocol IIIA was encountered, when neither Protocol IIA nor Protocol IIB was shown to be satisfactory (**Scheme 34**). It is clear that Protocol II is the most desirable of all options discussed here. However, the need for Protocol III as discussed above indicates that there still is room for improvement of Protocol II. In the meantime, Protocol III may be employed as a reliable, if somewhat cumbersome, alternative for selective  $\alpha$ -substitution of enones.



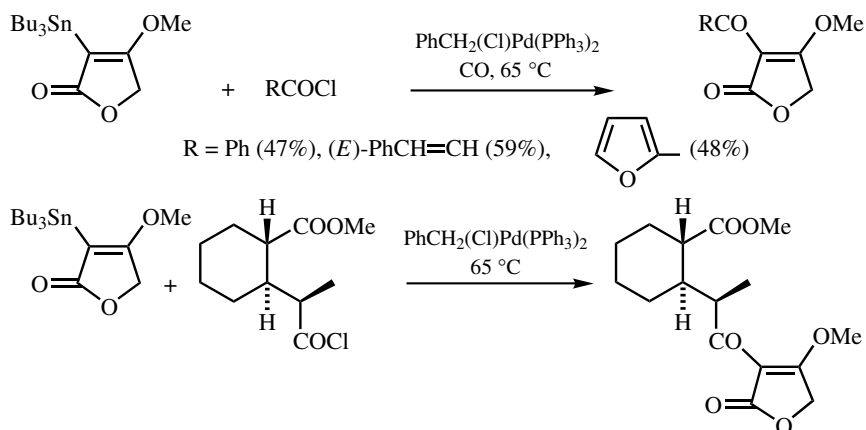
Scheme 34

### D. iii. Pd-Catalyzed $\alpha$ -Substitution of $\alpha,\beta$ -Unsaturated Esters and Amides

**D.iii.a. Pd-Catalyzed  $\alpha$ -Substitution of  $\alpha$ -Metalloesters and Amides.**  $\alpha$ -Substitution of  $\alpha,\beta$ -unsaturated esters, amides, and related compounds is closely related to that of  $\alpha,\beta$ -unsaturated enones. The synthesis of  $\alpha$ -aryl- and  $\alpha$ -alkenyl-substituted  $\alpha,\beta$ -unsaturated esters via conjugate carbocupration of  $\alpha,\beta$ -acetylenic esters followed by Pd-catalyzed cross-coupling reported in 1988<sup>[116]</sup> may represent the earliest example of reactions of this type. Unfortunately, the stereoselectivity was at best modest (**Scheme 35**).  $\alpha$ -Acylation of  $\alpha$ -stannylbutenolides is another prototypical example<sup>[117]</sup> (**Scheme 36**).

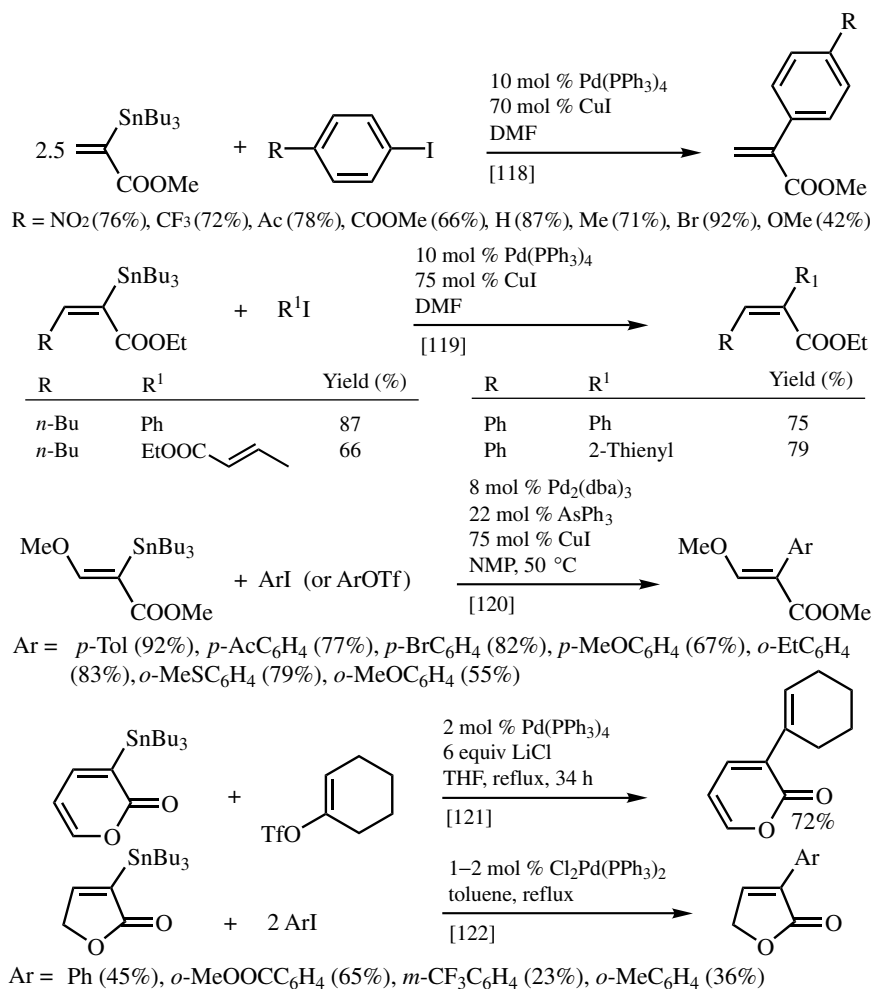


### Scheme 35

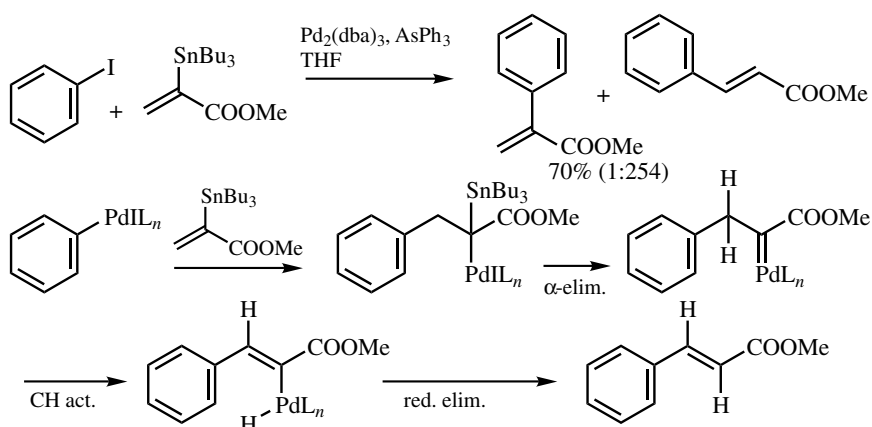


### Scheme 36

The Pd-catalyzed cross-coupling reactions of  $\alpha$ -stannyl- $\alpha,\beta$ -unsaturated esters and lactones have since been extensively developed, as indicated by the results shown in **Scheme 37**.<sup>[118]–[122]</sup> Despite many favorable results, these reactions are often associated with some undesirable features, such as the use of a significant excess of a stannane<sup>[118]</sup> or an organic halide,<sup>[122]</sup> relatively high catalyst loading (8–10 mol %),<sup>[118]–[120]</sup> and the use of toxic arsines.<sup>[120]</sup> In addition, an undesirable, if interesting,  $\alpha$ -to- $\beta$  regioisomerization has also been observed with a  $\beta$ -unsubstituted  $\alpha$ -stannylacrylic ester, which has been interpreted in terms of a carbopalladation–Pd-carbene formation via  $\beta$ -elimination– $\beta$ -CH activation–reductive elimination sequence (**Scheme 38**).<sup>[123]</sup> Clearly, further investigations and developments are desirable.

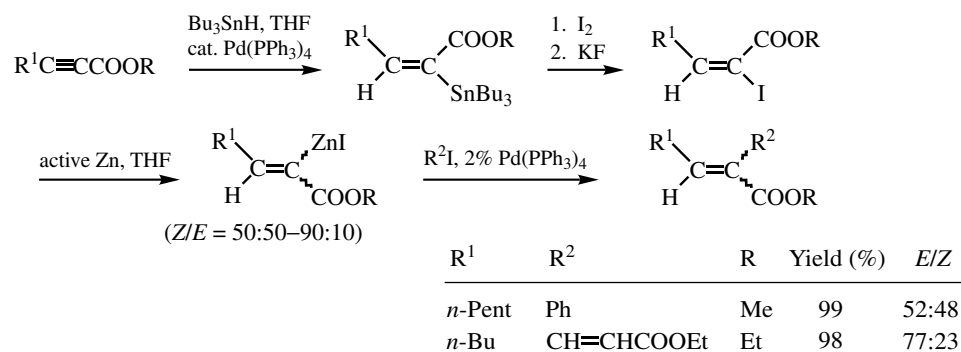


Scheme 37



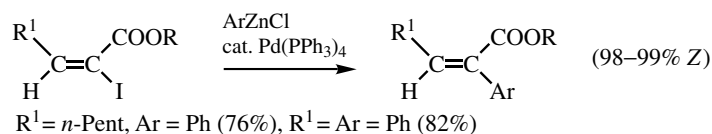
Scheme 38

Zinc is another metal that is compatible with esters.  $\alpha$ -Zinco- $\alpha,\beta$ -unsaturated esters readily undergo  $\alpha$ -alkenylation and  $\alpha$ -arylation typically in >90% yields in the presence of 2 mol % of  $\text{Pd}(\text{PPh}_3)_4$ , indicating the superior reactivity of organozincs.<sup>[124]</sup> Unfortunately, the reported synthesis of the organozinc derivatives is not only circuitous but also lacking stereoselectivity with the *Z/E* ratios ranging from 90:10 to essentially 50:50. The stereospecificity of cross-coupling appears to be >95%, however (**Scheme 39**). Development of a stereoselective and satisfactory route to  $\alpha$ -zinco esters is highly desirable.

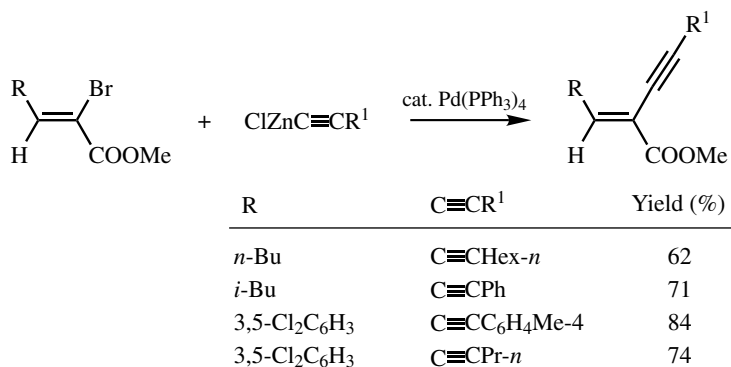


Scheme 39

**D.iii.b. Pd-Catalyzed  $\alpha$ -Substitution of  $\alpha$ -Haloesters and Amides.** Application of Protocol IIA to  $\alpha$ -substitution of esters and amides has also been investigated. The Pd-catalyzed reaction of arylzinc derivatives with  $\alpha$ -iodo- $\alpha,\beta$ -unsaturated esters appears to be generally satisfactory<sup>[125]</sup> (**Scheme 40**). The reaction of alkynylzinc chlorides is also satisfactory<sup>[126]</sup> (**Scheme 41**).



Scheme 40

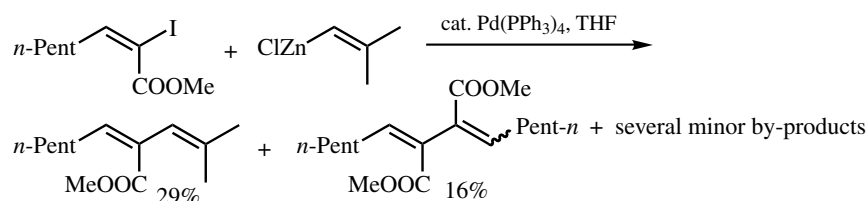


Scheme 41

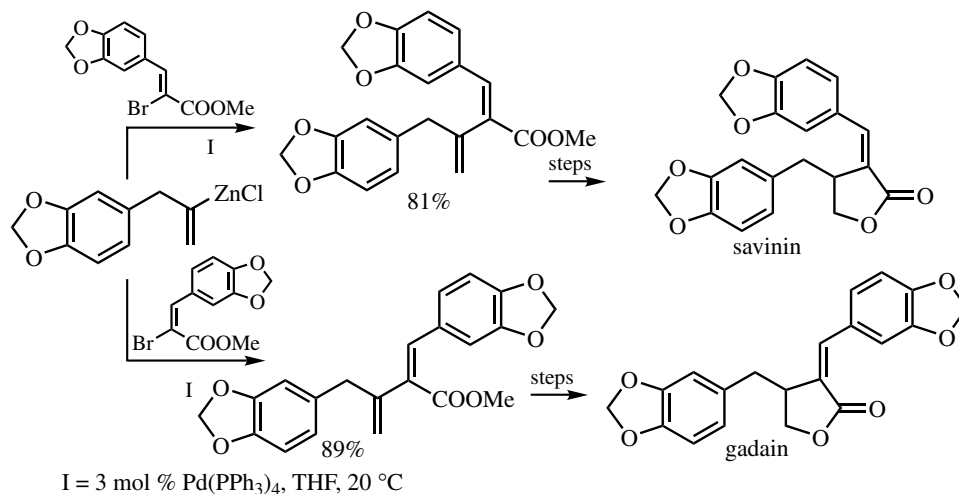


Alkylation is much less satisfactory and generally inferior to the corresponding reaction of alkylcoppers.<sup>[125]</sup> The use of  $\beta,\beta$ -disubstituted alkenylzinc derivatives can also be problematical, as indicated by the results shown in **Scheme 42**.<sup>[127]</sup> However, more recent results with  $\alpha$ -substituted vinylzinc chlorides are very satisfactory<sup>[128]</sup> (**Scheme 43**). A further systematic investigation of the scope and limitations is desirable.

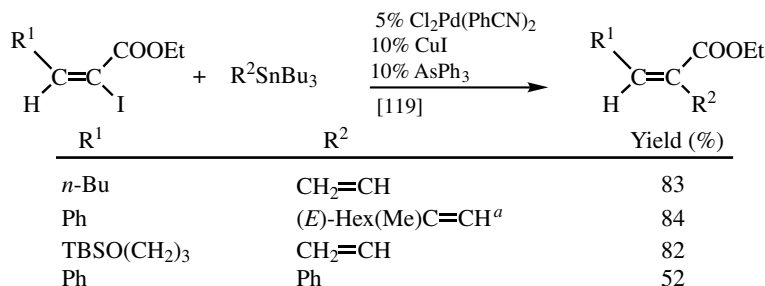
In addition to organozinc, organostannanes<sup>[119],[129],[130]</sup> and boranes<sup>[131],[132]</sup> have also been used, as indicated by the results shown in **Table 10** and **Schemes 44–46**. As in the other cases, their relative merits and demerits are not very clear, because comparative studies have rarely been performed.



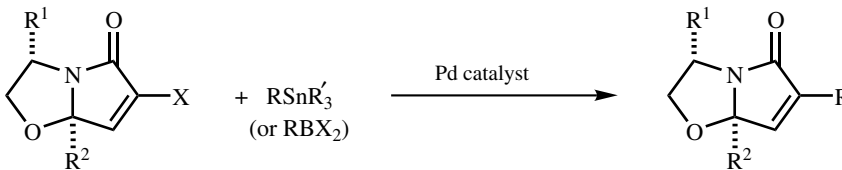
Scheme 42



Scheme 43

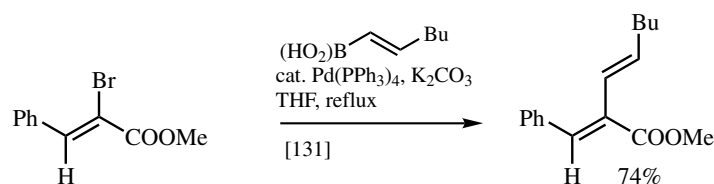


Scheme 44

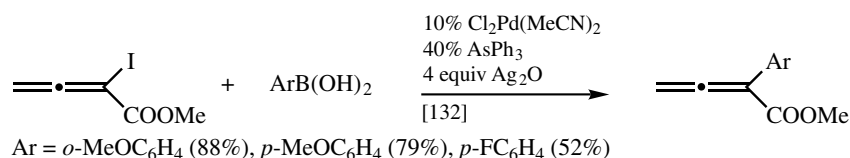
TABLE 10. Pd-Catalyzed  $\alpha$ -Substitution of  $\alpha$ -Halo- $\alpha, \beta$ -Unsaturated Bicyclic Lactams


R <sup>1</sup>	R <sup>2</sup>	X	R	Metal	Catalyst <sup>a</sup>	Product Yield (%)
Ph	Me or H	I or Br	Ph	Sn	I	57–75
Ph	Me or H	I or Br	CH <sub>2</sub> =CH	Sn	I	55–100
Ph	Me or H	I or Br	2-Furyl	Sn	I	42–70
Ph	Me	I	<i>n</i> -Hex	B	II	64
<i>i</i> -Pr	Me	I	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	B	III	76
Ph	Me	I	2-Furyl	B	IV	86

<sup>a</sup> I = 5 mol % Pd(OAc)<sub>2</sub>, 10 mol % CuI, 10 mol % PPh<sub>3</sub>, NMP, 100 °C. II = 5 mol % Cl<sub>2</sub>Pd(dppf), 14 mol % AsPh<sub>3</sub>, *n*-Hexyl-9-BBN (1.6 equiv), Ba(OH)<sub>2</sub>·8 H<sub>2</sub>O (1.5 equiv), DMF, room temperature. III = 9 mol % Cl<sub>2</sub>Pd(PhCN)<sub>2</sub>, 15 mol % AsPh<sub>3</sub>, aq. Na<sub>2</sub>CO<sub>3</sub> (1.5 equiv), benzene, 74 °C. IV = 9 mol % Cl<sub>2</sub>Pd(PhCN)<sub>2</sub>, 15 mol % AsPh<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub> (1.2 equiv), DME, 74 °C

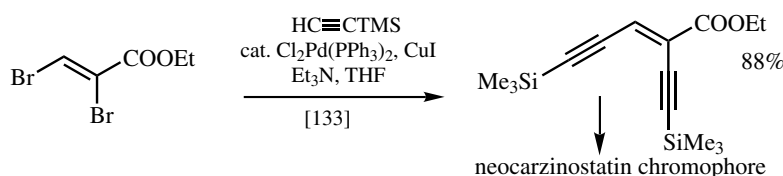


Scheme 45

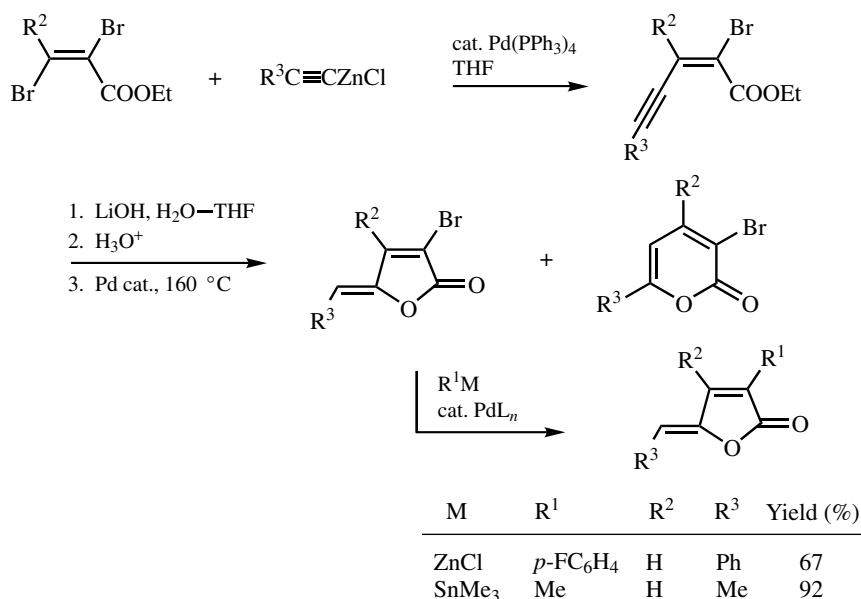


Scheme 46

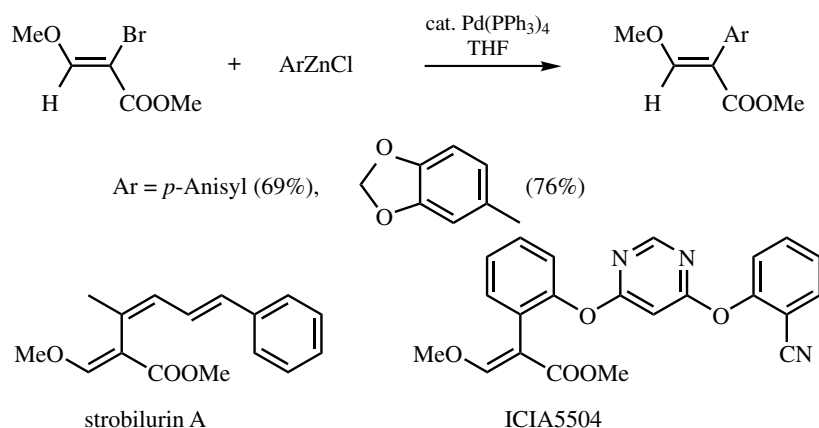
Bisalkynylation of (*Z*)- $\alpha, \beta$ -dibromoacrylic esters<sup>[133]</sup> (Scheme 47),  $\beta$ -alkynylation followed by lactonization and  $\alpha$ -substitution<sup>[134]</sup> (Scheme 48), and  $\alpha$ -arylation of (*Z*)-2-bromo-3-methoxyacrylic esters for the synthesis of strobilurin A and ICIA5504 exhibiting fungicidal activities<sup>[135]</sup> (Scheme 49) are interesting additional examples of  $\alpha$ -substitution of  $\alpha, \beta$ -unsaturated esters.



Scheme 47



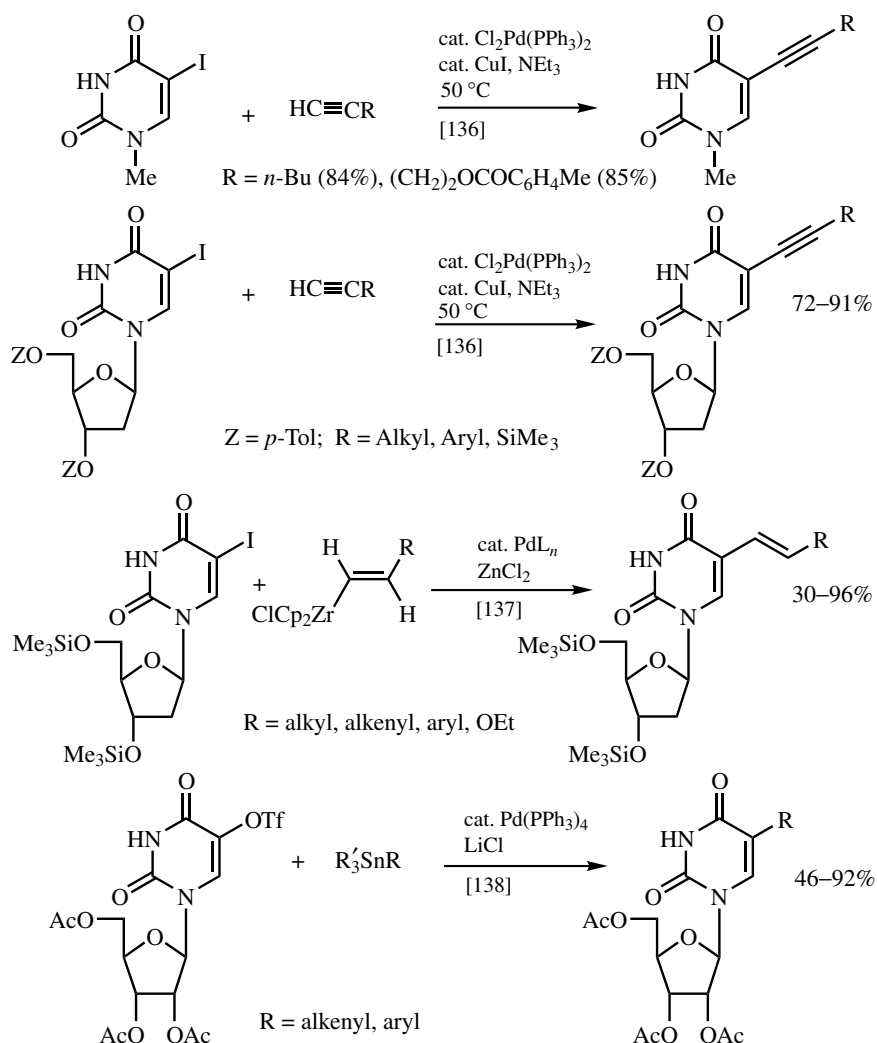
Scheme 48



Scheme 49

#### D.iv. Pd-Catalyzed $\alpha$ -Substitution of Heteroaromatic $\alpha,\beta$ -Unsaturated Carbonyl Derivatives, Quinones, and Related Compounds

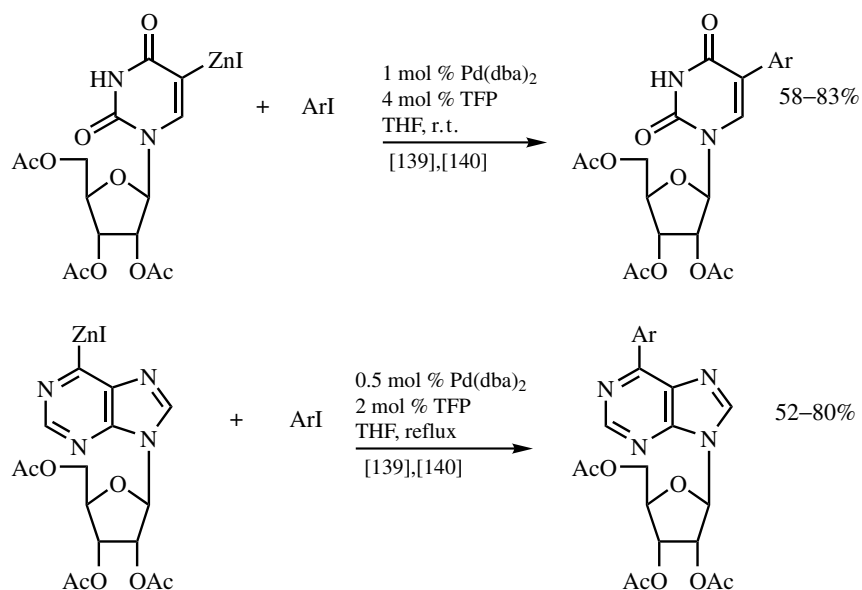
Application of Pd-catalyzed cross-coupling to  $\alpha$ -alkynylation,<sup>[136]</sup>  $\alpha$ -alkenylation,<sup>[137]</sup> and  $\alpha$ -arylation<sup>[137]</sup> of heteroaromatic  $\alpha,\beta$ -unsaturated carbonyl derivatives, such as 5-iodouracil derivatives, has been known since the early 1980s (Scheme 50). Although these reactions are formally related to the Pd-catalyzed  $\alpha$ -substitution discussed herein, the robust aromatic nature of the heteroaromatic substrates makes the requirements for their  $\alpha$ -substitution less demanding. These reactions should therefore be viewed as a class of cross-coupling reactions involving aryl halides rather than  $\alpha$ -halo- $\alpha,\beta$ -unsaturated carbonyl compounds. In most



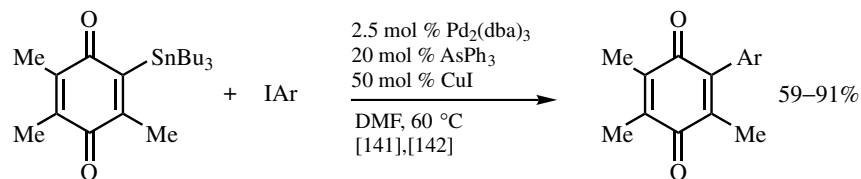
Scheme 50

cases, heteroaryl iodides<sup>[136],[137]</sup> and triflates<sup>[138]</sup> rather than heteroarylmetals have been used. However, heteroarylzinc derivatives have also been employed (**Scheme 51**).<sup>[139],[140]</sup> As in the cases of  $\alpha$ -substitution of enones, the required organozinc reagents are generated by treating the corresponding iodides with Zn. This added requirement must be offset by some merits associated with the charge-affinity inverted protocol.

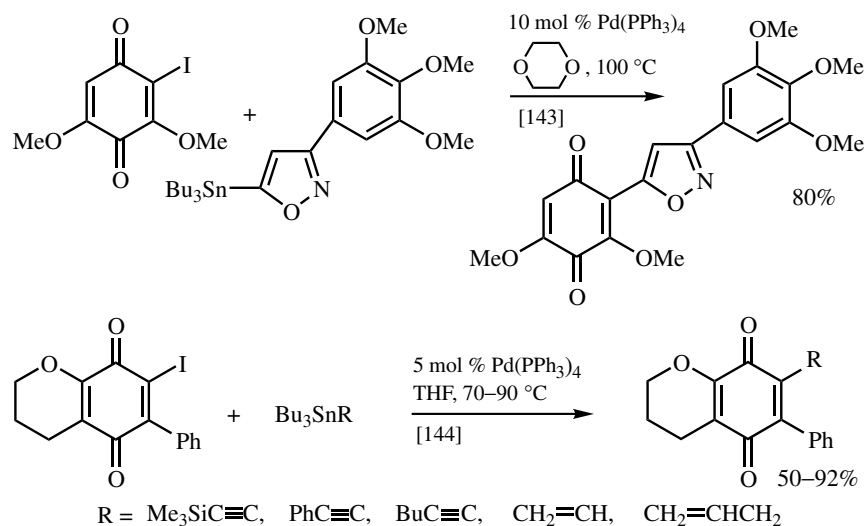
$\alpha$ -Substitution of haloquinones catalyzed by Pd complexes<sup>[141],[142]</sup> may also be formally viewed as Pd-catalyzed  $\alpha$ -substitution of enones. At the same time, however, these reactions also represent  $\beta$ -substitution of enones, which has been known to proceed much more readily than the corresponding  $\alpha$ -substitution.<sup>[143]</sup> They must therefore be classified and viewed differently from those discussed in **Sects. D.ii** and **D.iii**. Both iodoquinones<sup>[143]</sup> and metalloquinones<sup>[141],[142],[144]</sup> have been employed (**Scheme 52**).



Scheme 51



Ar = *o*-, *m*-, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, *o*-, *m*-, *p*-MeOC<sub>6</sub>H<sub>4</sub>, Ph, 2-thienyl, 5-pyrimidinyl, *p*-NH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 2-pyridyl



Scheme 52

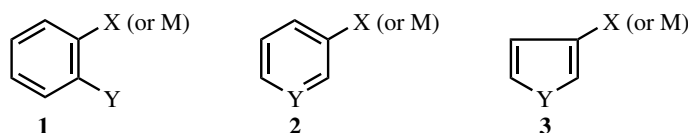
**D.v. Summary**

In sharp contrast with Pd-catalyzed cross-coupling of  $\beta$ -haloenones, which is generally more facile than that of the corresponding alkenyl halides without the carbonyl functionality, Pd-catalyzed cross-coupling of  $\alpha$ -haloenones is intrinsically more difficult not only because the rate of the desired reaction is lower, but also because  $\alpha$ -haloenones decompose more readily under the conditions used for cross-coupling. Despite these difficulties, satisfactory protocols have been developed for cross-coupling with organometals containing Zn, Sn, B, and Cu to give  $\alpha$ -organyleneones in high yields. As in the other cases of Pd-catalyzed cross-coupling, organozincs display generally the highest reactivity. Thus, their reactions are complete generally in a few to several hours at room temperature using Pd-PPh<sub>3</sub> complexes, whereas the other procedures tend to require more effective but potentially undesirable catalysts, such as those containing AsPh<sub>3</sub>, and higher temperatures, typically  $100 \pm 30$  °C. The use of polar aprotic solvents, such as DMF, appears to be generally more favorable than less polar solvents, such as THF, ether, benzene, and toluene. Essentially all types of organic groups, including aryl, alkenyl, alkynyl, methyl, primary alkyl, benzyl, homoallyl, homopropargyl, and homobenzyl, can be introduced in the  $\alpha$ -position of enones. Secondary and tertiary alkyl groups tend to undergo isomerization and other side reactions, while allyl- and propargylzinc derivatives undergo selective 1,2-addition with  $\alpha$ -iodoenones. Further developments are needed to accommodate these groups in the  $\alpha$ -position of enones. In highly demanding and/or delicate situations, some indirect protocols, that is, Protocols I and III, involving protection of carbonyl groups or their temporary reduction, help overcome difficulties encountered in direct  $\alpha$ -substitution (Protocols IIA and IIB). Collectively, these protocols represent novel and previously unavailable routes to  $\alpha$ -substituted enones including various natural products that are attractive, efficient, and regioselective.

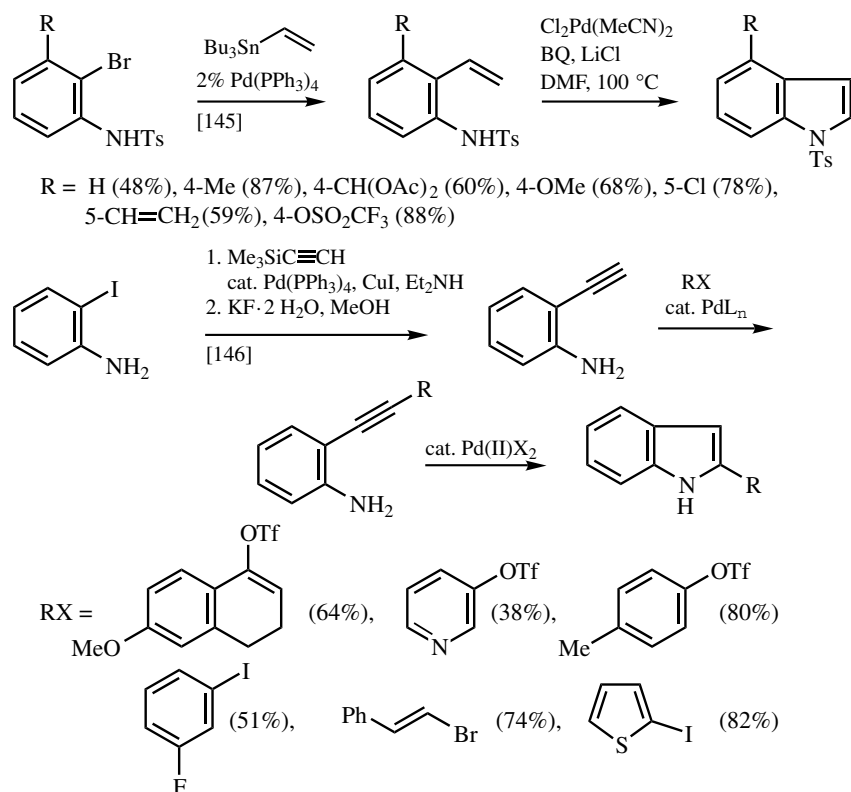
Equally important is that, in conjunction with conjugate reduction or conjugate addition, the enone-based Pd-catalyzed  $\alpha$ -substitution methodology significantly supplements the conventional methodology for  $\alpha$ -substitution of enolates. Particularly noteworthy features include (i) facile and reliable incorporation of unsaturated groups, such as aryl and alkenyl, in the  $\alpha$ -position of carbonyl compounds and (ii) strict control of regiochemistry.

**E.  $\beta$ -HETERO-SUBSTITUTED ARYL DERIVATIVES**

All *o*-hetero-substituted arylmetals and aryl electrophiles (**1**) as well as heteroaromatic compounds represented by **2** and **3** are  $\beta$ -hetero-substituted aryl derivatives. In most cases,  $\beta$ -heteroatoms merely exert some rate-enhancing or -retarding influences on the Pd-catalyzed cross-coupling process. In some cases, however, their presence offers additional synthetic opportunities of potential significance. Synthesis of arene-fused heterocyclic compounds is particularly noteworthy, as indicated by the results presented below. However, most of the known examples involve cross-coupling–heteropalladation tandem processes, which are also discussed in **Sect. V.3**. So, they are very briefly mentioned in this section.



*o*-Iodo- and *o*-bromoanilines as well as the corresponding carboxamides and sulfonamides can undergo Pd-catalyzed *o*-alkenylation and *o*-alkynylation. The cross-coupling products thus formed can then undergo catalytic aminopalladation to give indole derivatives. A few representative procedures for the synthesis of indoles are shown in **Scheme 53**.<sup>[145],[146]</sup>



**Scheme 53**

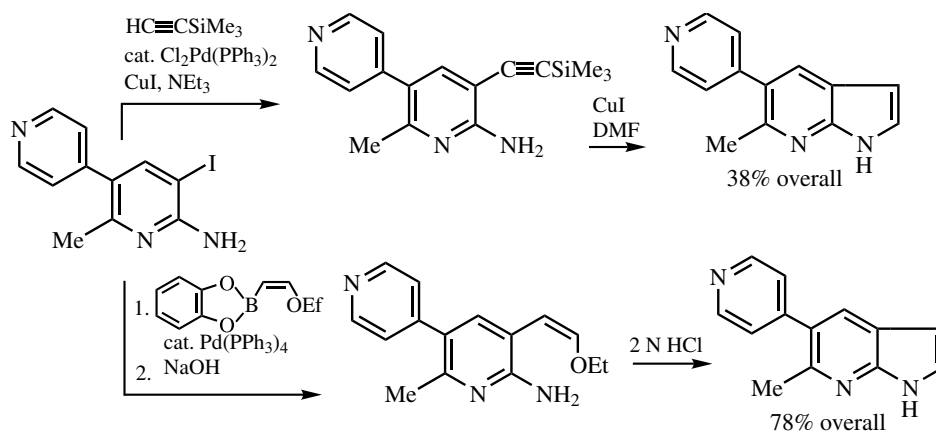
(*Z*)- $\beta$ -Ethoxyethenyl(tributyl)stannane<sup>[74]</sup> and (*Z*)-*B*- $\beta$ -ethoxyethenyl-catecolborane<sup>[68]</sup> have been used to introduce a (*Z*)- $\beta$ -ethoxyethenyl group in the *ortho* position in aniline and other aminoarenes. Although indole itself was obtained only in 29% overall yield from *o*-bromoaniline,<sup>[74]</sup> its application to the synthesis of 1*H*-pyrrolo[2,3-*b*]pyridine was reported to exhibit significantly higher product yields than the corresponding ethynyl derivatives<sup>[68]</sup> (**Scheme 54**).

*o*-Iodophenols can readily be converted to benzofuran derivatives via Pd-catalyzed alkynylation and oxypalladation (**Scheme 55**).<sup>[147]</sup>

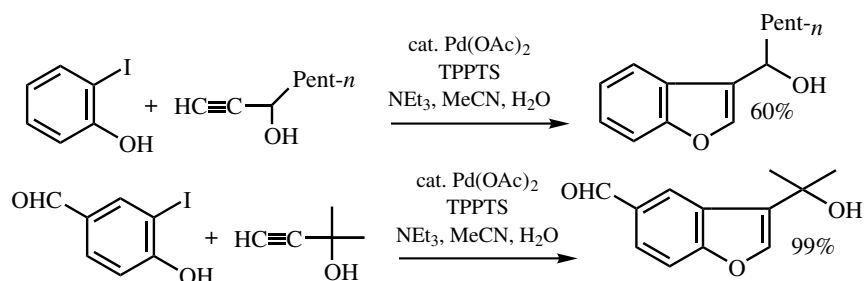
(*Z*)- $\beta$ -Ethoxyethenyltributylstannane has also been used to give benzofurans, but it is not clear if this procedure provides any advantage over the *o*-alkynylation protocol.

The reaction of *o*-iodoaniline with  $\text{HOOCCH}_2\text{CH}_2\text{SnCl}_3$  catalyzed by  $\text{PdCl}_2$  has been shown to give 3,4-dihydro-2(1*H*)-quinolone in modest yield<sup>[148]</sup> (**Scheme 56**).

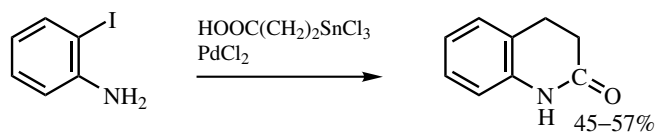
Arylic electrophiles containing two electrophilic groups that are *ortho* to each other can be used for the synthesis of cyclic compounds in a manner similar to the use of (*Z*)-dihaloethylenes. 2,3-Bis(triflyloxy)naphthalene is a prototypical example, as indicated by the results shown in **Scheme 57**.<sup>[149]</sup>



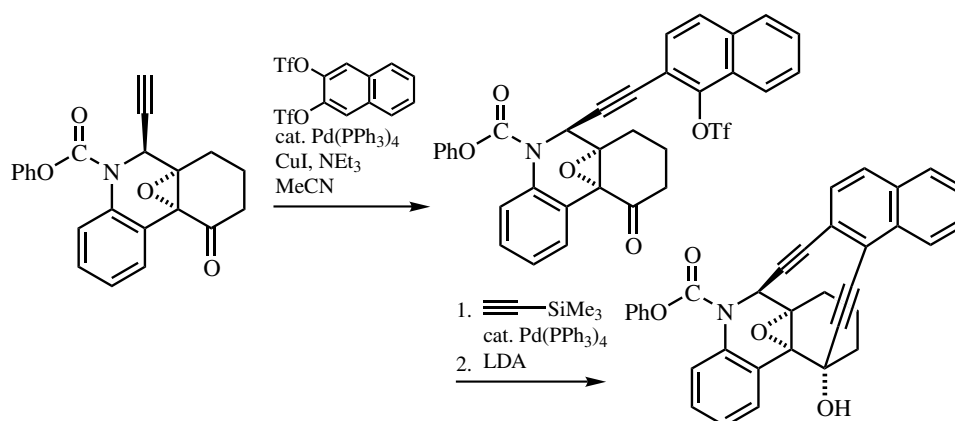
Scheme 54



Scheme 55



Scheme 56



Scheme 57

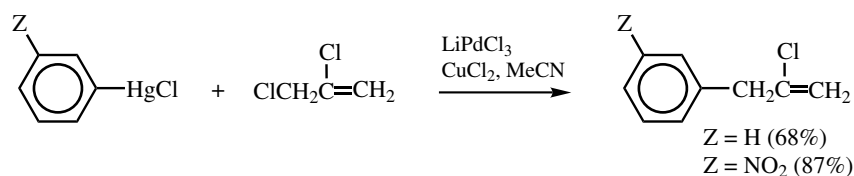


## F. $\beta$ -HETERO-SUBSTITUTED ALKYL METALS AND ALKYL ELECTROPHILES

By far the most important groups of compounds of this class are metal enolates and  $\alpha$ -halocarbonyl compounds discussed in **Sect. III.2.14.1**. Although there are many other types of compounds of this class, most of them have not yet shown their usefulness in Pd-catalyzed cross-coupling. However, the following are worth noting.

### F.i $\beta$ -Hetero-Substituted Allylic Electrophiles as $\alpha$ -Carbonylalkyl (i.e., $\beta$ -Oxoalkyl) Equivalents

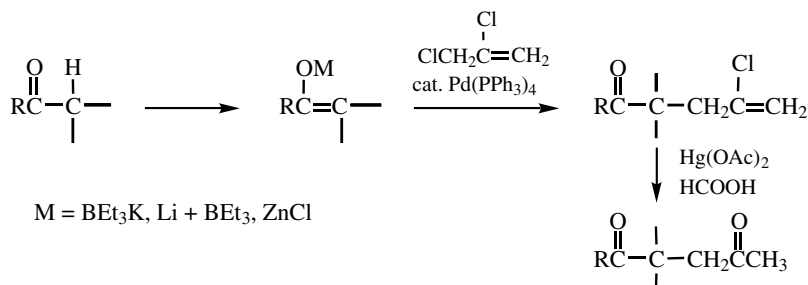
2,3-Dichloropropene appears to be the first example of this class of compounds used in Pd-catalyzed cross-coupling. The reaction of arylmercuric chlorides with 2,3-dichloropropene under the influence of  $\text{LiPdCl}_3\text{-CuCl}_2$  gave the cross-coupling products in good yields (**Scheme 58**).<sup>[150]</sup>



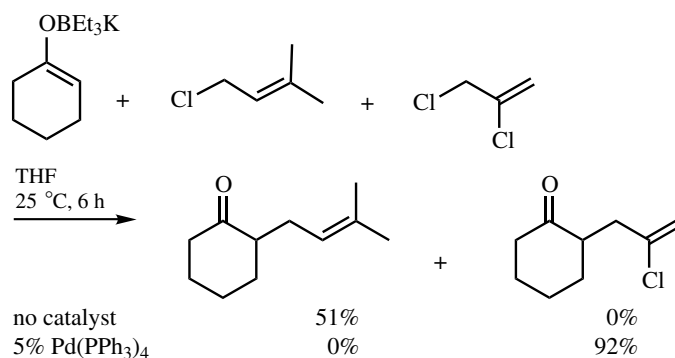
Scheme 58

The Pd-catalyzed reaction of 2,3-dichloropropene with enolates is especially useful as a route to 1,4-dicarbonyl compounds (**Scheme 59**).<sup>[151]–[153]</sup> This reaction is discussed in detail in **Sect. V.2.1.4**. One noteworthy feature associated with 2,3-dichloropropene is the relative reactivities of 2,3-dichloropropene and more usual allylic chlorides in the presence and absence of Pd catalysts, as indicated in **Scheme 60**.<sup>[151]</sup>

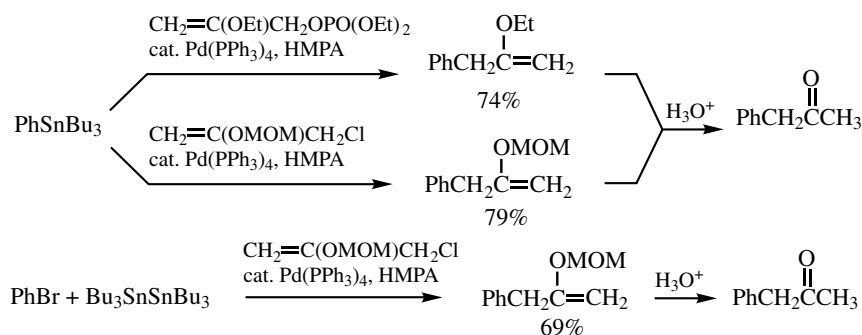
The use of 2,3-dichloropropene as an acetyl equivalent is essentially limited to those cases where enolates are used as nucleophiles, since clean chlorovinyl-to-acetyl conversion with  $\text{Hg}(\text{OAc})_2$  and  $\text{HCOOH}$  requires anchimeric assistance by a  $\gamma$ - or  $\delta$ -carbonyl group. To circumvent this difficulty, 2-alkoxyallyl electrophiles have been used in Pd-catalyzed aryl-allyl coupling.<sup>[154]</sup> The products can then be readily hydrolyzed to give  $\alpha$ -aryl-substituted acetones (**Scheme 61**). Further details of this reaction are presented in **Sect. III.2.9**.



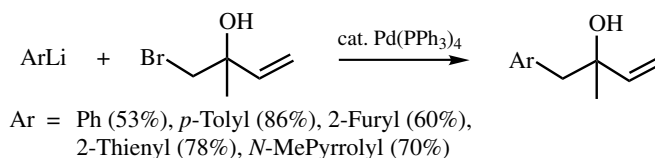
Scheme 59



Scheme 60



Scheme 61



Scheme 62

### F.ii Other $\beta$ -Hetero-Substituted Alkyl Derivatives

The reaction of aryllithiums with 1-bromo-2-methyl-3-buten-2-ol in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub><sup>[155]</sup> is a rare example of the use of alkyl halides in Pd-catalyzed cross-coupling (Scheme 62). The required oxidative addition step must be assisted by the homoallylic double bond and/or  $\beta$ -OH group. The absence of a  $\beta$ -H atom in the allylic position must also be critically responsible for the observed success.

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