

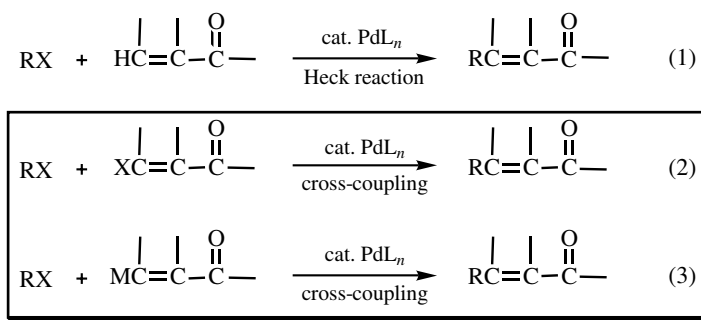
## III.2.15 Palladium-Catalyzed Conjugate Substitution

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### A. INTRODUCTION

In **Sects. III.2.12–III.2.14**, various Pd-catalyzed cross-coupling reactions involving  $\alpha$ - and  $\beta$ -heterosubstituted organometals and organic electrophiles are discussed. Many of these reactions have provided attractive routes to various proximally hetero-substituted organic compounds of synthetic significance. It is also noteworthy that proximal heteroatoms tend to exert strong influences on the course of Pd-catalyzed cross-coupling. Consequently, they often demand special attention. On the other hand, remote hetero-functional groups may be expected to act largely as “innocent” bystanders not requiring special consideration. Furthermore, the number of possible structural types of hetero-substituted organometals and organic electrophiles exponentially increases as the heteroatoms move away from the cross-coupling reaction centers. For these reasons, no systematic discussions of those containing heteroatoms in the  $\gamma$  and more remote positions are intended. Nonetheless, it is worthwhile to discuss the Pd-catalyzed  $\beta$ -substitution reactions of  $\alpha,\beta$ -unsaturated carbonyl compounds represented by Eqs. 1–3 shown in **Scheme 1**, which may be collectively termed as *conjugate substitution à la conjugate addition*. The reaction shown in Eq. 1 represents examples of the Heck reaction, which is discussed in **Part IV**, while those shown in Eqs. 2 and 3 represent various cases of Pd-catalyzed cross-coupling involving  $\gamma$ -oxo-alkenyl electrophiles and  $\gamma$ -oxo-alkenylmetals. In this section, these latter two reactions are discussed.

As in many other cases, the Heck reaction shown in Eq. 1 and the cross-coupling reactions shown in Eqs. 2 and 3 achieve similar synthetic transformations. Since the cross-coupling version is somewhat more involved than the corresponding Heck reaction, it must offer some clearcut advantages over the latter to justify more elaborate synthetic operations. In this connection, the following distinct difference between the Heck reaction shown in Eq. 1 and the cross-coupling shown in Eq. 2 should clearly be noticed. In the former, a Pd(0) complex is to undergo oxidative addition with RX to produce RPd(II)X, which then is to react with an  $\alpha,\beta$ -unsaturated carbonyl derivative. The latter process involving the interaction of an intrinsically electrophilic RPd(II)X with the electron-deficient C=C bond of the  $\alpha,\beta$ -unsaturated carbonyl compound is less favorable than that with normal and electron-rich alkenes. On the other hand, electron-deficient  $\beta$ -halo- $\alpha,\beta$ -unsaturated carbonyl compounds generally undergo oxidative addition with Pd(0) complexes with ease even in

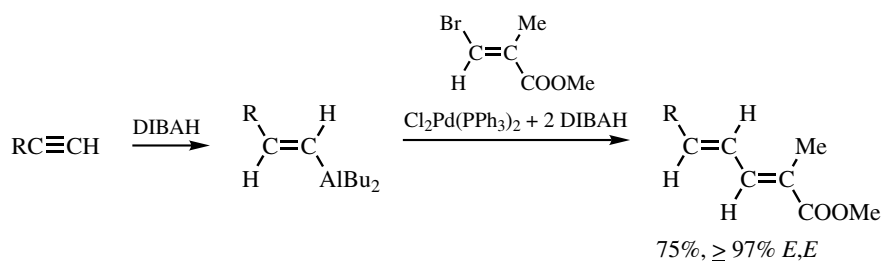


Scheme 1

cases where the halogen atom is Br or Cl.  $\beta$ -Oxy- $\alpha,\beta$ -unsaturated carbonyl compounds containing TfO, MsO, and other oxy groups are also attractive, since they are not only sufficiently reactive but also readily accessible via  $\beta$ -oxo-substituted carbonyl compounds. The reaction of the resultant  $\gamma$ -oxo-alkenylpalladium derivatives with a variety of organometals is also generally very facile. Consequently, the overall process represented by Eq. 2 is generally favorable, making it a synthetically useful transformation. The analysis above also suggests the reaction shown in Eq. 3 might, at least in some cases, be comparatively less favorable than that shown in Eq. 2.

Another significant difference between the two reactions shown in Eqs. 1 and 2 lies in the difference in accessibility of  $\text{RPdX}$  to be generated *in situ* via oxidative addition in Eq. 1 on the one hand and  $\text{RM}$  in Eq. 2 on the other. In the cases of alkenyl and aryl derivatives, the required reagents in the two reactions are comparably accessible. On the other hand, organopalladium intermediates containing alkynyl and alkyl groups are more readily available in Eq. 2 than in Eq. 1, since generation of alkynylpalladium derivatives via oxidative addition of 1-haloalkynes is more involved than that via transmetalation with alkynylmetals and since alkyl halides are generally very sluggish to undergo oxidative addition with Pd. Yet another difference between Eq. 1 and Eq. 2 lies in the extents of selectivity and specificity in terms of regio- and stereochemistry. As discussed in **Part IV**, the Heck reaction proceeding via addition and elimination is prone to regio- and/or stereoisomerization, which can often be avoided or minimized by resorting to Pd-catalyzed cross-coupling.

The reaction of alkenylalanes with methyl (*E*)- $\beta$ -bromomethacrylate catalyzed by  $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2 + 2 \text{ DIBAH}$  (**Scheme 2**) appears to represent the first example of conjugate substitution, which was reported in 1976.<sup>[1]</sup> Since then, essentially all possible classes of

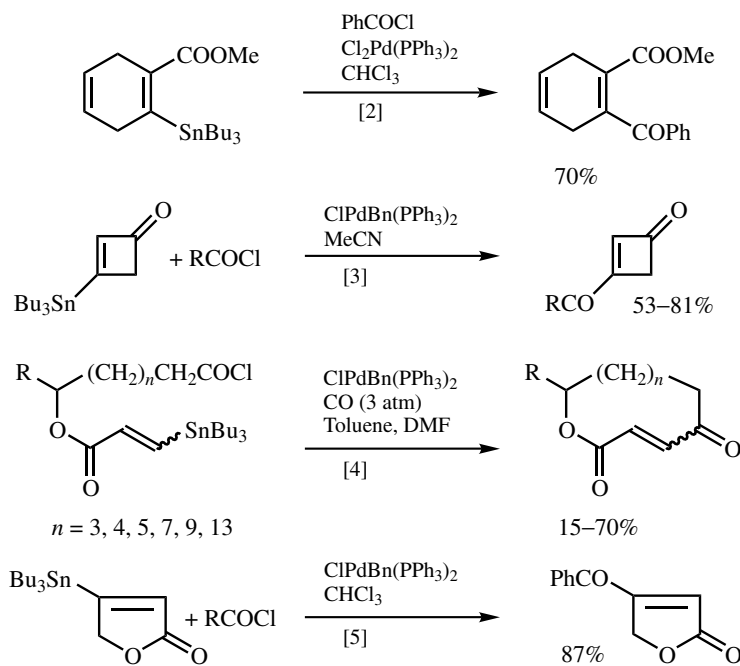


Scheme 2

organometals have been employed in this reaction mainly using Zn, Al, Zr (Negishi protocol), Sn (Stille protocol), and B (Suzuki protocol). In addition, alkynes have also been used by following the Sonogashira protocol. As in many other cases, the relative merits and demerits among various protocols are not very clear, since critical comparative data are largely lacking.

Specific examples of Eq. 2 are presented in **Sect. B**.

Although the charge-affinity inverted version of Eq. 2, that is, Eq. 3, might be intrinsically less favorable than Eq. 2, many such reactions can still proceed satisfactorily. In the great majority of cases,  $\beta$ -stannyl- $\alpha,\beta$ -unsaturated carbonyl compounds have been used as the organometallic reagents, although some examples of  $\beta$ -zinco- $\alpha,\beta$ -unsaturated carbonyl compounds have also been reported recently. In cases where both Eq. 2 and Eq. 3 are satisfactory, the comparative accessibility of the required reagents can be the critical factor, which generally favors the protocol represented by Eq. 2. The opposite, however, is true in some cases. For example, acylmetals containing main group metals are not as readily accessible as acyl halides. This clearly favors Eq. 3, as exemplified by the results shown in **Scheme 3**.



**Scheme 3**

Additional specific examples of Eq. 3 are presented in **Sect. C**.

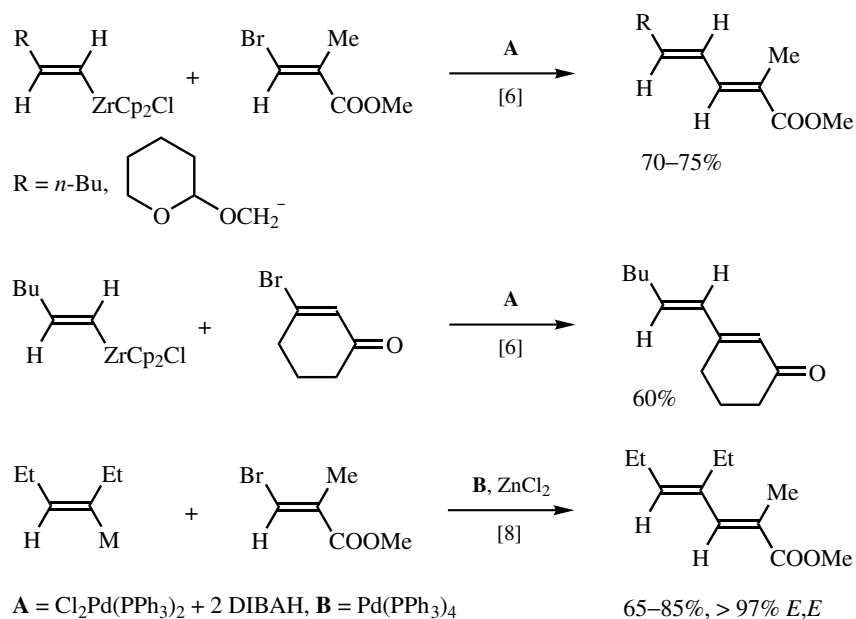
A number of aryl halides and arylmetals, especially those containing heteroatoms, are formally represented as  $\alpha,\beta$ -unsaturated carbonyl derivatives. Although their cross-coupling reactions may be formally classified as conjugate substitution processes, various requirements for these cases may be significantly different than in those cases discussed in **Sects. B** and **C** because of their aromatic nature. For this reason, specific examples of these reactions together with those of the reactions of quinone derivatives are discussed separately in **Sect. D**.

Finally, there are many variations of conjugate substitution including those of  $\alpha,\beta$ -unsaturated nitriles, acetals, sulfones, and sulfoxides. These miscellaneous variants are discussed in **Sect. E**.

## B. CONJUGATE SUBSTITUTION OF $\beta$ -HALO- $\alpha,\beta$ -UNSATURATED CARBONYL AND RELATED DERIVATIVES

### B.i. Conjugate Substitution with Alkenylmetals


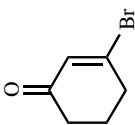

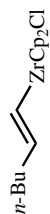
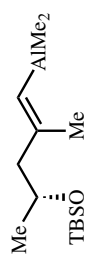
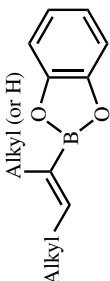

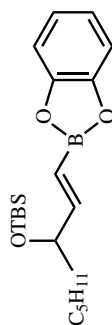
As shown in **Scheme 2**, Pd-catalyzed conjugate substitution with alkenylmetals was achieved first with alkenylalanes generated *in situ* by hydroalumination of alkynes.<sup>[1]</sup> This synthetically attractive hydrometallation–cross-coupling tandem process was soon extended so as to include hydrozirconation,<sup>[6]</sup> carboalumination,<sup>[7]</sup> and so on. It was also found that, in more demanding cases, addition of Zn salts (e.g.,  $\text{ZnCl}_2$  and  $\text{ZnBr}_2$ ) significantly accelerates Pd-catalyzed cross-coupling<sup>[8]</sup> (**Scheme 4**). In most cases, these reactions are essentially 100% stereospecific. In some demanding cases, however, extensive stereochemical isomerization, especially *Z*-to-*E* isomerization, has been observed.<sup>[9]</sup>



**Scheme 4**

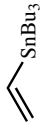

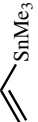
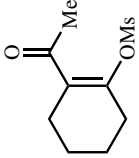

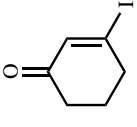
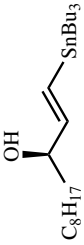
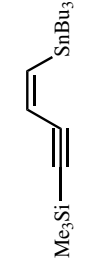
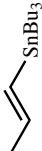
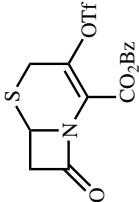
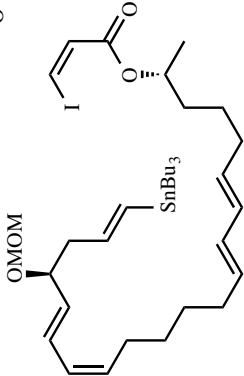
Subsequent studies have established that conjugate substitution of  $\beta$ -halo- $\alpha,\beta$ -unsaturated carbonyl compounds with alkenylmetals is a generally favorable reaction, which can be achieved by using B, Sn, and Zn in addition to Al and Zr mentioned above. Although  $\beta$ -iodo derivatives appear to be the most reactive,  $\beta$ -bromo,  $\beta$ -sulfonyloxy (e.g., TfO, MsO, FSO<sub>3</sub>), and even  $\beta$ -chloro derivatives in some cases are satisfactory. Some representative examples of conjugate substitution with alkenylmetals are presented in **Table 1**.

TABLE 1. Conjugate Substitution with Alkenylmetals

Alkenyl/metal	$\begin{array}{c} \text{O}=\text{C}-\text{C}=\text{C}-\text{X} \\   \quad   \quad   \\ \text{Y} \quad \text{R}^\alpha \quad \text{R}^\beta \end{array}$				<i>E</i> or <i>Z</i>	Conditions	Yield (%)	Reference	
	Y	R <sup>α</sup>	R <sup>β</sup>	X					
						Pd(PPh <sub>3</sub> ) <sub>4</sub> THF, 25 °C	94	[10]	
		OMe	Me	H	Br	<i>E</i>	Pd(PPh <sub>3</sub> ) <sub>4</sub> 1 equiv. ZnCl <sub>2</sub>	65	[8]
		OMe	Me	H	Br	<i>E</i>	Pd(PPh <sub>3</sub> ) <sub>4</sub> 1 equiv. ZnCl <sub>2</sub>	85	[8]
		OMe	H	H	Br	<i>Z</i> ( <i>Z</i> isomerized into <i>E</i> )	Pd(PPh <sub>3</sub> ) <sub>4</sub> 1 equiv. ZnCl <sub>2</sub>	40	[9]
		OEt	H	H	Br	<i>E</i>	Pd(OAc) <sub>2</sub> /2 PPh <sub>3</sub> Na <sub>2</sub> CO <sub>3</sub> 75% EtOH reflux	88	[11]
		OEt	H	H	I	<i>Z</i>	Pd(OAc) <sub>2</sub> /TPPS CH <sub>3</sub> CN Et <sub>3</sub> N or <i>i</i> Pr <sub>2</sub> NH	70–80	[12]
							Pd(PPh <sub>3</sub> ) <sub>4</sub> K <sub>3</sub> PO <sub>4</sub> , 85 °C, dioxane	96	[13]
<i>(Continued)</i>									

(Continued)

Alkenyl/metal	$\begin{array}{c} \text{O}=\text{C}-\text{C}=\text{C}-\text{X} \\   \quad   \quad   \\ \text{Y} \quad \text{R}^\alpha \quad \text{R}^\beta \end{array}$				<i>E</i> or <i>Z</i>	Conditions	Yield (%)	Reference
	Y	R <sup>α</sup>	R <sup>β</sup>	X				
						Pd(OAc) <sub>2</sub> /TPPS CH <sub>3</sub> CN·H <sub>2</sub> O Et <sub>3</sub> N or <i>i</i> Pr <sub>2</sub> NH	95	[12]
						PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> MeOH reflux NaOAc	84–98	[14]
						PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> MeOH reflux NaOAc	97	[13]
						PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> MeOH reflux NaOAc	98	[14]
						PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> MeOH reflux NaOAc	85	[14]
						PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub> P(2-furyl) <sub>3</sub> , NMP, 80 °C	99	[15]
						Pd <sub>2</sub> (dba) <sub>3</sub> /2 AsPh <sub>3</sub> NMP 35–40 °C	94	[16]

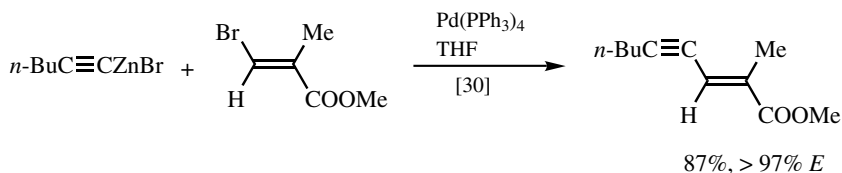
		BnPdCl(PPh <sub>3</sub> ) <sub>2</sub> HMPA, 55 °C	95	[17]
		Pd(PPh <sub>3</sub> ) <sub>4</sub> THF, reflux LiBr	73	[18]
		Pd(dba) <sub>2</sub> /2 P(2-furyl) <sub>3</sub> THF, 25 °C	84	[19]
		Pd <sub>2</sub> (dba) <sub>3</sub> /2 AsPh <sub>3</sub> NMP 35–40 °C	91	[16]
		Pd <sub>2</sub> (dba) <sub>3</sub> "ligandless" NMP or CH <sub>2</sub> Cl <sub>2</sub> , r.t.	95	[20]
		Pd <sub>2</sub> (dba) <sub>3</sub> , AsPh <sub>3</sub> DMF	58	[21]

**B.ii. Conjugate Substitution with Arylmetals**

As might be expected from the foregoing discussions, Pd-catalyzed conjugate substitution of  $\beta$ -halo- $\alpha,\beta$ -unsaturated carbonyl derivatives with arylmetals is also generally favorable. As metal counteranions, Zn, B, and Sn, but not Al or Zr, have been employed. Under specifically optimized conditions, Zn, B, and Sn seem to provide the desired products in comparable yields. The ready *in situ* generation is a distinct advantage associated with Zn, while higher chemoselectivity and reagent storability are some of the advantages associated with B and Sn. Some representative examples are summarized in Table 2.

**B.iii. Conjugate Substitution with Alkynylmetals**

The Pd-catalyzed reaction of 1-hexynylzinc bromide with methyl (*E*)- $\beta$ -bromomethacrylate<sup>[30]</sup> shown in Scheme 5 appears to be the prototypical example of this class of reactions.



Scheme 5

In addition to Zn, B, and Sn—three metal counteranions that were found to be highly satisfactory for alkynylation<sup>[31]</sup>—the Sonogashira alkynylation protocol (Sect. III.2.8.1) has also proved to be generally applicable to this case. Some representative examples of Pd-catalyzed conjugate substitution with alkynylmetals and terminal alkynes are summarized in Table 3.

**B.iv. Conjugate Substitution with Alkylmetals**

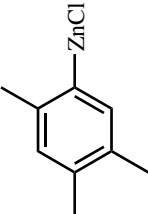
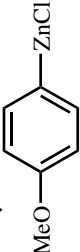
**B.iv.a. Synthesis of 1,5-Dienes Via Conjugate Substitution with Homoallyl- and Homopropargylmetals.** Pd-catalyzed conjugate substitution with alkylmetals was first investigated with the goal of developing a convenient and selective route to 1,5-dienes of terpenoid origin.<sup>[36],[37]</sup> The reaction of homoallylzincs with  $\beta$ -halo- $\alpha,\beta$ -unsaturated carbonyl compounds in the presence of a Pd catalyst or Ni catalyst in some cases has been shown to be generally satisfactory.<sup>[37]</sup> Although not specifically demonstrated, conjugate substitution with homopropargylmetals, for example, homopropargylzincs, is also expected to proceed similarly.<sup>[36]</sup> Some representative examples, especially those applied to the synthesis of natural products, are summarized in Scheme 6.

For a more general discussion of Pd-catalyzed cross-coupling with homoallylic and homopropargylic organometals, readers are referred to Sect. III.2.11.2.

**B.iv.b. Conjugate Substitution with Allyl-, Propargyl-, and Benzylmetals.** As discussed in Sects. III.2.9 and III.2.10, Pd-catalyzed cross-coupling involving alkylmetals of relatively electropositive metals, such as Zn and Mg, has not been generally satisfactory. Propargylmetals most probably resemble alkylmetals in this respect, although the same difficulty is not shared by benzylmetals. For Pd-catalyzed allylation with alkylmetals,



TABLE 2. Conjugate Substitution with Arylmetals

ArM	$\begin{array}{c} \text{O}=\text{C}-\text{C}=\text{C}-\text{X} \\   \quad   \quad   \\ \text{Y} \quad \text{R}^\alpha \quad \text{R}^\beta \end{array}$				E or Z	Conditions	Yield (%)	Reference
	Y	R <sup>α</sup>	R <sup>β</sup>	X				
PhZnBr	OH	H	Me	I	Z	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	83	[22]
ArZnCl	OEt	Br	H	Br	Z	10% Pd/C/4 AsPh <sub>3</sub> THF, r.t.	89	[23]
	OEt	Br	H	Br	E	10% Pd/C/4 AsPh <sub>3</sub> THF, r.t.	96	[23]
	OEt	Br	H	Br	E	10% Pd/C/4 AsPh <sub>3</sub> THF, r.t.	69	[23]
FG-ArZnX	OEt	Br	H	Br	Z	Pd(PPh <sub>3</sub> ) <sub>4</sub> THF, 20 °C	77–85	[24]
FG-ArZnX	OEt	Br	H	Br	E	Pd(PPh <sub>3</sub> ) <sub>4</sub> THF, 20 °C	52–79	[24]
PhB(OH) <sub>2</sub>	OEt	H	R <sup>β</sup>	OTf	Z	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub> /4 AsPh <sub>3</sub> THF, 20 °C, Ag <sub>2</sub> O	86	[25]

R<sup>β</sup> = homoallyl

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TABLE 2. (Continued)

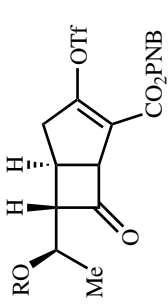
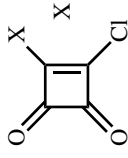
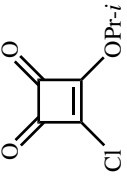
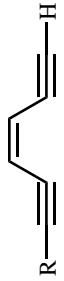
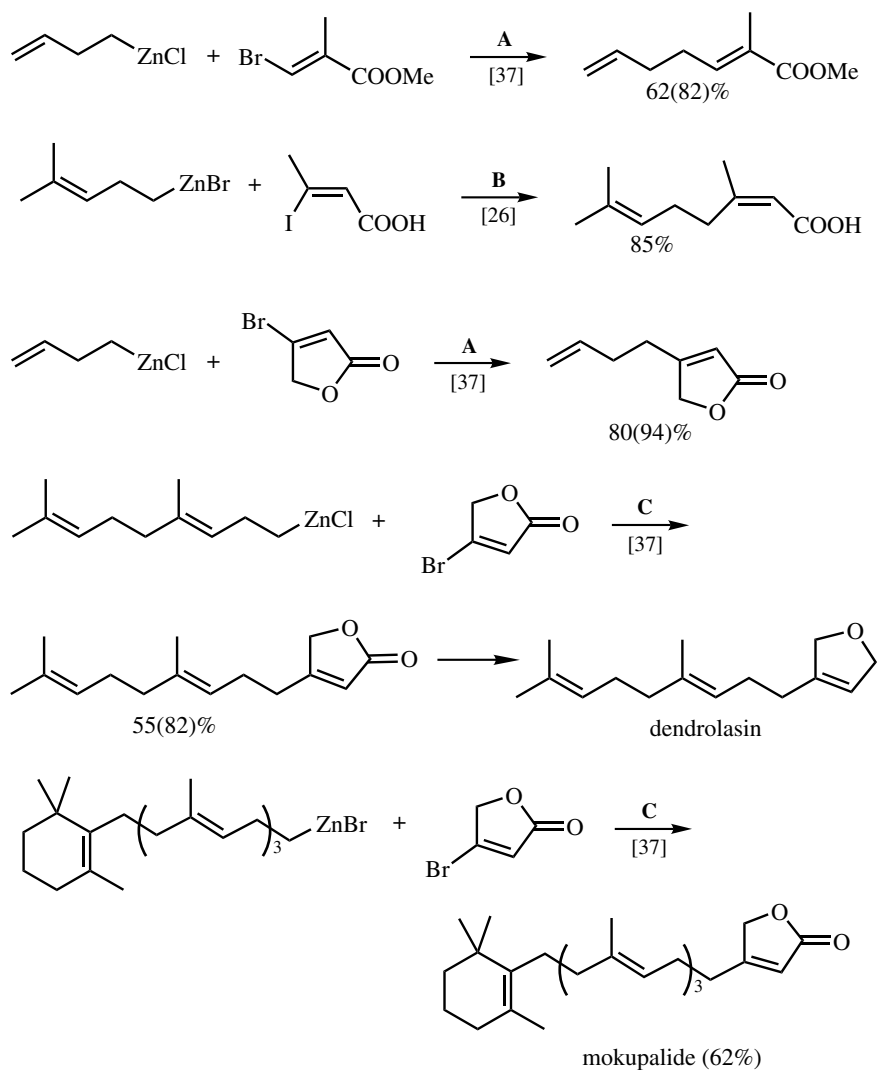
ArM	$  \begin{array}{c}  \text{O}=\text{C}-\text{C}=\text{C}-\text{X} \\    \quad   \quad   \\  \text{Y} \quad \text{R}^\alpha \quad \text{R}^\beta  \end{array}  $					Reference
	Y	R <sup>α</sup>	R <sup>β</sup>	X	E or Z	
ArB(OH) <sub>2</sub>						[26]
PhSnBu <sub>3</sub>	OEt	Br	H	Br	Z	[27]
PhSnMe <sub>3</sub>	Me	Ph	Br	I	Z	[28]
	(Br unreacted)					
PhSnMe <sub>3</sub>						[29]

TABLE 3. Conjugate Substitution with Alkynylmetals and Terminal Alkynes

RC≡CM (or H)	$\begin{array}{c} \text{O}=\text{C}-\text{C}=\text{C}-\text{X} \\   \quad   \quad   \\ \text{Y} \quad \text{R}^\alpha \quad \text{R}^\beta \end{array}$					Yield (%)	Reference
	Y	R <sup>α</sup>	R <sup>β</sup>	X	E or Z	Conditions	
Me <sub>3</sub> SiC≡CZnCl	OEt	Br	H	Br	Z	Pd(PPh <sub>3</sub> ) <sub>4</sub> THF, r.t.	91 [24]
Me <sub>3</sub> SiC≡CZnCl	OEt	Br	H	Br	E	Pd(PPh <sub>3</sub> ) <sub>4</sub> THF, 0 °C	62 [24]
RC≡CZnBr R = alkyl or SiMe <sub>3</sub>	OH	H	H	I	Z or E	PdCl <sub>2</sub> (MeCN) <sub>2</sub> DMF, ether, r.t.	69–96 [32]
n-BuC≡C SnBu <sub>3</sub>						BnPdCl(PPh <sub>3</sub> ) <sub>2</sub> /CuI CH <sub>3</sub> CN, 70 °C	58 [29]
Me <sub>3</sub> SiC≡CH	OEt	Br	H	Br	Z	Pd(PPh <sub>3</sub> ) <sub>4</sub> /4 CuI DMF, 0 °C, <i>i</i> -Pr <sub>2</sub> NEt	90 [33]
	OMe	Br	H	I	E	Pd(PPh <sub>3</sub> ) <sub>4</sub> /4 CuI Et <sub>3</sub> N	87 [34]
RC≡CH R = Ph, CH <sub>2</sub> OH, SiMe <sub>3</sub>	OEt	R <sup>α</sup>	H	Br	Z	Pd(PPh <sub>3</sub> ) <sub>4</sub> /4 CuI Et <sub>3</sub> N, r.t.	60–90 [35]
R <sup>α</sup> = NHCO <sub>2</sub> Me							

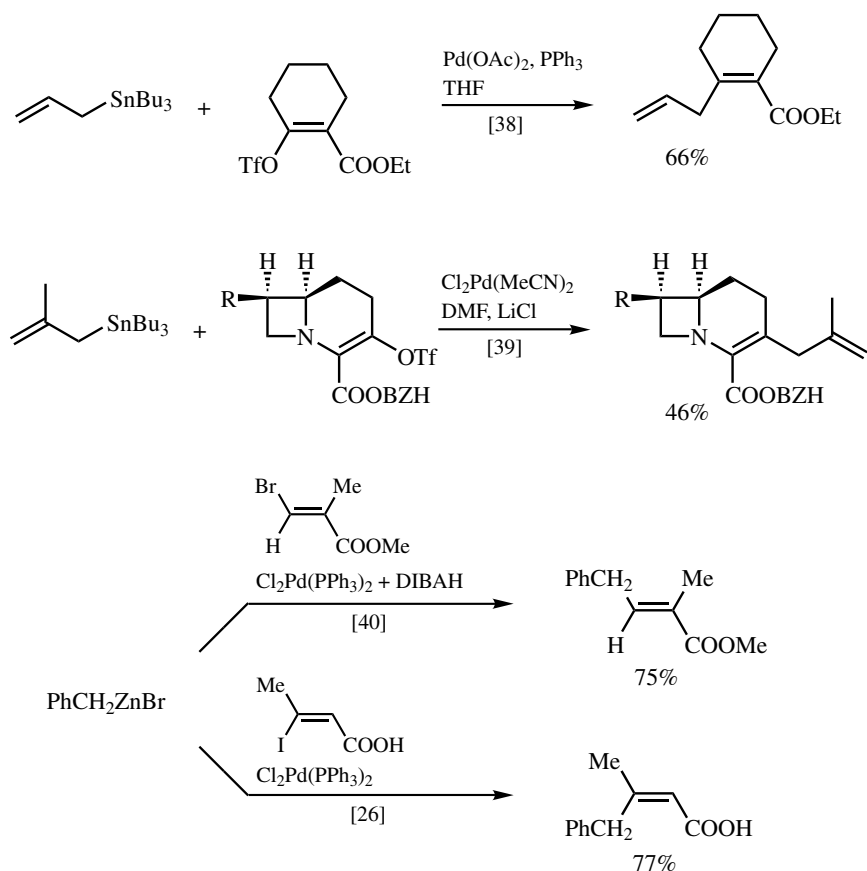


**A** =  $\text{Pd}(\text{PPh}_3)_4$ , **B** =  $\text{Cl}_2\text{Pd}(\text{Ph}_3)_2$ , **C** =  $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2 + 2 \text{ DIBAH}$   
 The numbers in parentheses are GLC or NMR yields.

Scheme 6

those containing Sn have been shown to be moderately satisfactory. A few such examples of conjugate allylation are shown in **Scheme 7**. In view of the relatively modest results observed in these cases, some other options not involving Pd catalysts, such as Cu-catalyzed or -promoted allylation, should also be considered. As mentioned above, benzylmetals react more as ordinary alkylmetals than as  $\beta,\gamma$ -unsaturated alkylmetals. A few such examples are also shown in **Scheme 7**.

**B.iv.c. Conjugate Substitution with Ordinary Alkylmetals.** Those conjugate substitution reactions involving ordinary alkylmetals resemble the cases of conjugate substitution with



Scheme 7

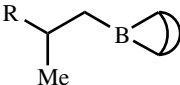
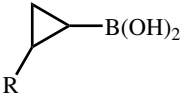
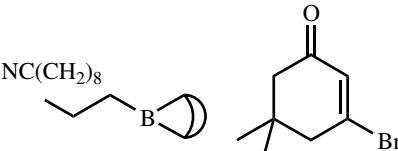
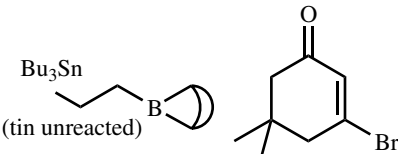
homoallylmethyls discussed above and most likely are generally even more facile, as no retardation due to chelation of Pd by the  $\gamma,\delta$ -unsaturated carbon–carbon bonds is involved. Although the number of examples involving the use of alkylzincs is still small, the available results suggest that it is generally very satisfactory. The yields of conjugate substitution with alkylboranes have been moderate to excellent. One distinct feature associated with alkylboranes is that they are often readily available by hydroboration of alkenes. Alkyltins are less reactive than alkylzincs or alkylboranes. With the exception of  $\text{Me}_4\text{Sn}$ , essentially no examples of Pd-catalyzed conjugate substitution with higher alkylstannanes appears to have been reported.

Some representative examples of Pd-catalyzed conjugate alkylation reactions are summarized in **Table 4**.

### C. CONJUGATE SUBSTITUTION OF $\beta$ -METALLO- $\alpha,\beta$ -UNSATURATED CARBONYL COMPOUNDS

As indicated in **Scheme 1**, Pd-catalyzed conjugate substitution can be achieved by the reaction of  $\beta$ -metallo- $\alpha,\beta$ -unsaturated carbonyl compounds with organic electrophiles,

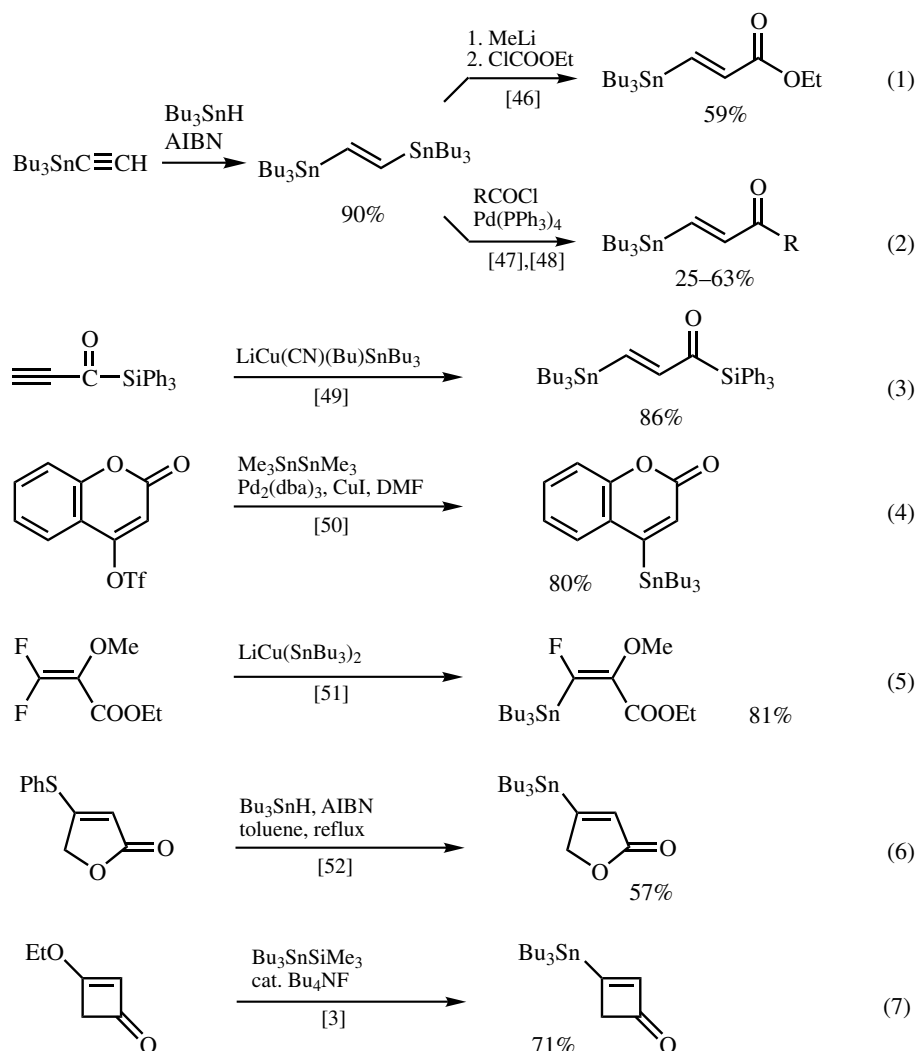
TABLE 4. Conjugate Substitution with Alkylmetals

Alkylmetals	$\begin{array}{c} \text{O}=\text{C}-\text{C}=\text{C}-\text{X} \\   \quad   \quad   \\ \text{Y} \quad \text{R}^\alpha \quad \text{R}^\beta \end{array}$				<i>E</i> or <i>Z</i>	Conditions	Yield (%)	Reference
	Y	R <sup>α</sup>	R <sup>β</sup>	X				
RZnBr R = Me, Et, <i>i</i> -Bu	OH	H	Me	I	<i>E</i>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> Et <sub>2</sub> O-THF, r.t.	80–95	[26]
MeB(OH) <sub>2</sub>	OEt	H	R <sup>β</sup>	OTf	<i>Z</i>	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub> /4 AsPh <sub>3</sub> dioxane, 20 °C K <sub>3</sub> PO <sub>4</sub> , Ag <sub>2</sub> O	82	[23]
	OEt	Me	H	Br	<i>E</i>	Pd(PPh <sub>3</sub> ) <sub>4</sub> K <sub>2</sub> CO <sub>3</sub> , DMF, 50 °C	89	[11]
	OEt	Me	H	Br	<i>E</i>	Pd(PPh <sub>3</sub> ) <sub>4</sub> K <sub>3</sub> PO <sub>4</sub> , toluene, 100 °C	81–94	[41]
						PdCl <sub>2</sub> (dppf) K <sub>2</sub> CO <sub>3</sub> , DMF- THF, 50 °C	81	[42]
						PdCl <sub>2</sub> (dppf) K <sub>2</sub> PO <sub>4</sub> , DMF, 50–60 °C	88	[43]
Me <sub>4</sub> Sn						BnPdCl(PPh <sub>3</sub> ) <sub>2</sub> HMPA, 55 °C	95	[21]
Me <sub>4</sub> Sn						Pd(MeCN) <sub>2</sub> Cl <sub>2</sub> DMF, LiCl, r.t.	70	[39]

provided that the former reagents are accessible. The majority of the  $\beta$ -metallo- $\alpha,\beta$ -unsaturated carbonyl compounds prepared and used in this reaction are those containing Sn in the  $\beta$ -position. Related Zn derivatives have also been recently prepared and used for the same purpose. Although related B derivatives are known,<sup>[44],[45]</sup> none of them appears to have been used in this reaction.

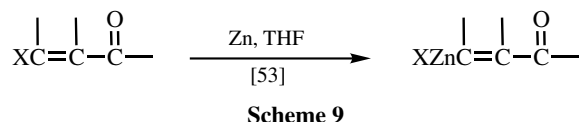
### C.i. Preparation of $\beta$ -Stannyl- and $\beta$ -Zinco- $\alpha,\beta$ -Unsaturated Carbonyl Compounds

**C.i.a.  $\beta$ -Stannyl- $\alpha,\beta$ -Unsaturated Carbonyl Compounds.** A wide variety of methods for the synthesis of this class of compounds are available, and several representative examples are shown in **Scheme 8**.



Scheme 8

**C.i.b.  $\beta$ -Zinco- $\alpha,\beta$ -Unsaturated Carbonyl Compounds.** These compounds have been prepared generally by treating  $\beta$ -halo- $\alpha,\beta$ -unsaturated carbonyl compounds with Zn in THF<sup>[53]</sup> (**Scheme 9**). As it is somewhat more involved than the direct use of the  $\beta$ -halo derivatives, the use of  $\beta$ -zinco derivatives must be well justified by some advantages associated with it.



#### C.ii. Examples of Conjugate Substitution with $\beta$ -Metallo- $\alpha,\beta$ -Unsaturated Carbonyl Compounds

Some representative examples of Pd-catalyzed conjugate substitution reactions of  $\beta$ -stannyl and  $\beta$ -zinco derivatives are shown in **Tables 5** and **6**, respectively.

### D. Pd-CATALYZED CONJUGATE SUBSTITUTION OF HETEROARENE AND QUINONE DERIVATIVES

The ease of reaction and various requirements for Pd-catalyzed conjugate substitution involving heteroarene and quinone derivatives are expected to be significantly different from many other cases. Some of the representative examples of heteroarene and quinone derivatives are shown in **Tables 7** and **8**, respectively.

### E. MISCELLANEOUS VARIATIONS

Some variations of Pd-catalyzed conjugate substitution of  $\alpha,\beta$ -unsaturated carbonyl derivatives are known. They involve the use of acetals, nitriles, sulfones, sulfoxides, and so on in place of carbonyl compounds. The current scope of these variations is still very limited. Some representative examples are shown in **Scheme 10**.

### F. SUMMARY

Pd-catalyzed conjugate substitution is an essentially new synthetic operation of considerable synthetic scope. Evidently, it is intrinsically more facile and favorable than Pd-catalyzed  $\alpha$ -substitution of  $\alpha,\beta$ -unsaturated carbonyl compounds discussed in **Sect. III.2.14.2**. All four main protocols—Negishi, Stille, Suzuki, and Sonogashira—for Pd-catalyzed cross-coupling are applicable and have been extensively applied to conjugate substitution. It should also be noted that Pd-catalyzed conjugate substitution followed by conjugate reduction would amount to conjugate addition.



TABLE 5. Conjugate Substitution of  $\beta$ -Stannyl- $\alpha,\beta$ -Unsaturated Carbonyl Compounds

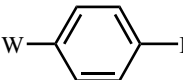
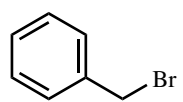
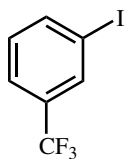
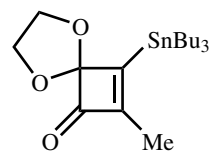
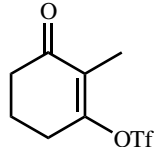
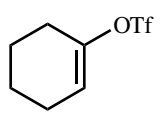
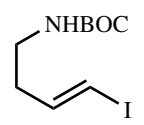
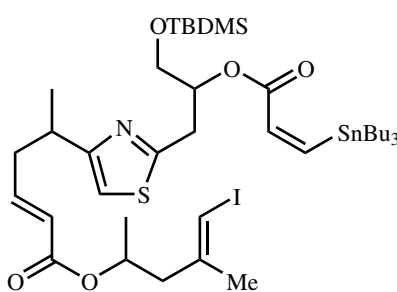
	$\begin{array}{c} \text{O}=\text{C}-\text{C}=\text{C}-\text{SnR}'_3 \\   \quad   \quad   \\ \text{Y} \quad \text{R}^\alpha \quad \text{R}^\beta \end{array}$												
RX	Y	R <sup>α</sup>	R <sup>β</sup>	SnR' <sub>3</sub>	E or Z	Conditions	Yield (%)	Reference					
 W = H or Br (unreacted)	OEt	OMe	F	SnBu <sub>3</sub>	E	Pd(PPh <sub>3</sub> ) <sub>4</sub> /CuI DMF	92–95	[51]					
PhI	Et	Me	R <sup>β</sup>	SnBu <sub>3</sub>	Z	Pd(PPh <sub>3</sub> ) <sub>4</sub> CuI, Et <sub>3</sub> N	89	[54]					
	Et	Me	R <sup>β</sup>	SnBu <sub>3</sub>	Z	Pd(PPh <sub>3</sub> ) <sub>4</sub> CuI, DMF, r.t.	92	[54]					
						Pd-C/CuI/AsPh <sub>3</sub> NMP, 80 °C	67	[55]					
	OMe	H	H	SnBu <sub>3</sub>	E	Pd(OAc) <sub>2</sub> /2 PPh <sub>3</sub> THF, 65 °C	68	[56]					
	OEt	OMe	F	SnBu <sub>3</sub>	E	Pd(PPh <sub>3</sub> ) <sub>4</sub> /CuI DMF	80	[51]					
	SiPh <sub>3</sub>	H	H	SnBu <sub>3</sub>	E	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub> DMF, r.t.	86	[49]					
						Pd <sup>(0)</sup> /AsPh <sub>3</sub> DMF	72	[57]					

TABLE 6. Conjugate Substitution with  $\beta$ -Zinco- $\alpha,\beta$ -Unsaturated Carbonyl Compounds

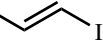
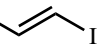
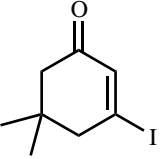
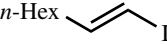
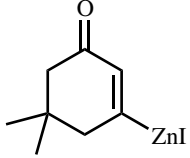
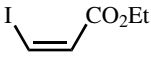
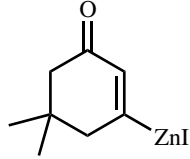
RX	$\begin{array}{c} \text{O}=\text{C}-\text{C}=\text{C}-\text{ZnX} \\   \quad   \quad   \\ \text{Y} \quad \text{R}^\alpha \quad \text{R}^\beta \end{array}$				<i>E</i> or <i>Z</i>	Conditions	Yield (%)	Reference
	Y	R <sup>α</sup>	R <sup>β</sup>	ZnX				
<i>n</i> -Hex 	OEt	H	H	ZnI	<i>E/Z</i> (11:89)	Pd(dba) <sub>2</sub> /4 PPh <sub>3</sub> THF	81	[58]
<i>n</i> -Hex 	Pent	H	H	ZnCl	<i>E/Z</i> (1:1)	Pd(dba) <sub>2</sub> /4 PPh <sub>3</sub> THF	55	[58]
	OEt	H	H	ZnI	<i>E/Z</i> (11:89)	Pd(dba) <sub>2</sub> /4 PPh <sub>3</sub> THF	88	[58]
<i>n</i> -Hex 						Pd(dba) <sub>2</sub> /4 PPh <sub>3</sub> THF, r.t.	82	[53]
								
 (in final product: <i>E/Z</i> = 5:95)						Pd(dba) <sub>2</sub> /4 PPh <sub>3</sub> THF, r.t.	93	[53]
								
PhI						Pd(dba) <sub>2</sub> /4 PPh <sub>3</sub> THF, r.t.	71	[53]

TABLE 7. Conjugate Substitution with Heteroarenes

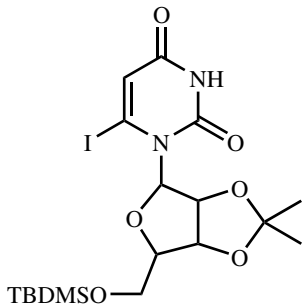
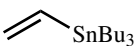
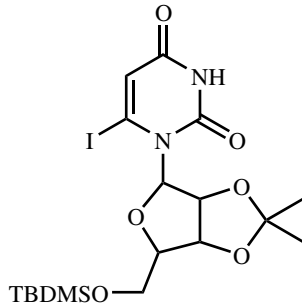
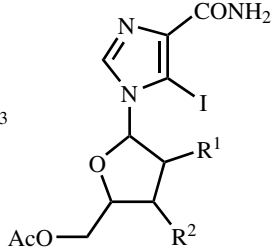
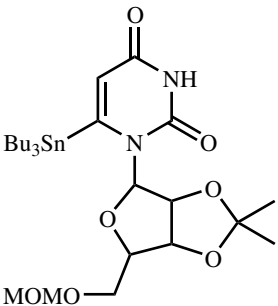
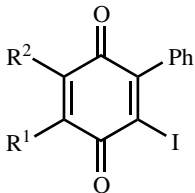
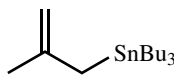
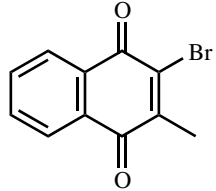
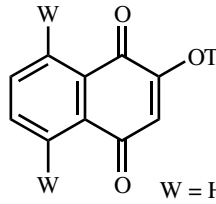
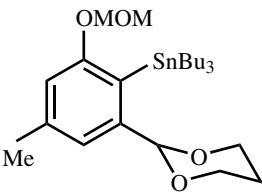
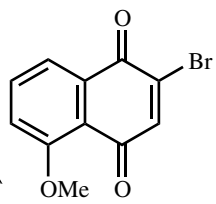
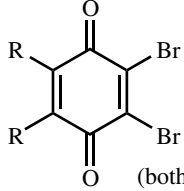
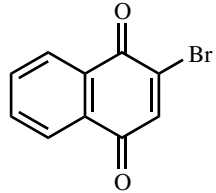
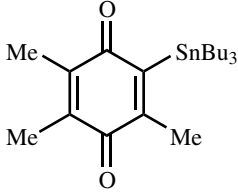
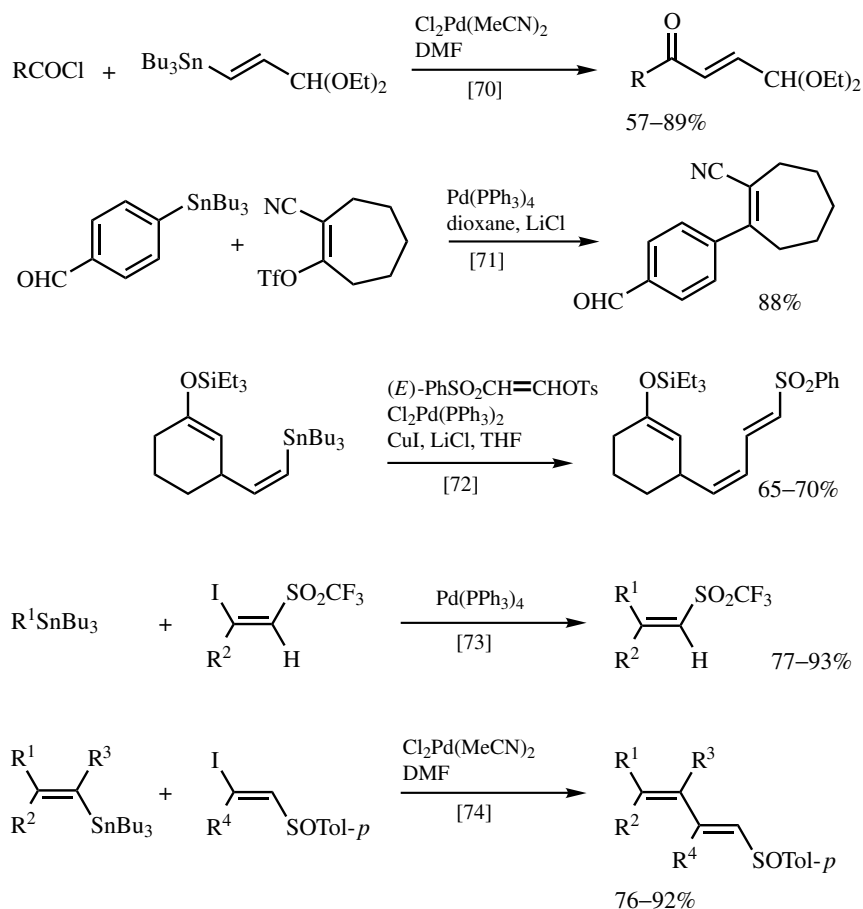
RM(X)	$\begin{array}{c} \text{(M)X}-\text{C}=\text{C}-\text{C}=\text{O} \\   \quad   \quad   \\ \text{R}^\beta \quad \text{R}^\alpha \quad \text{Y} \end{array}$	Conditions	Yield (%)	Reference
Me <sub>4</sub> Sn		PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> dioxane	100	[59]
		Pd(PPh <sub>3</sub> ) <sub>4</sub> DMF	100	[60]
TMSC≡CSnBu <sub>3</sub>		PdCl <sub>2</sub> (PhCN) <sub>2</sub> MeCN	69–79	[61]
RX		Pd(tfp) <sub>4</sub> /CuI DMF	47–88	[62]

TABLE 8. Conjugate Substitution with Quinones

RM(X)	$  \begin{array}{c}  \text{(M)X}-\text{C}=\text{C}-\text{C}=\text{O} \\    \quad   \quad   \\  \text{R}^\beta \text{ R}^\alpha \text{ Y}  \end{array}  $	Conditions	Yield (%)	Reference
R <sub>3</sub> SnBu R = ethynyl, vinyl, alkyl		Pd(PPh <sub>3</sub> ) <sub>4</sub> THF	19–92	[63]
		Pd(PPh <sub>3</sub> ) <sub>4</sub> /CuBr dioxane	93	[64]
PhSnBu <sub>3</sub>	 W = H or OH	Pd <sub>2</sub> (dba) <sub>3</sub> NMP	45–73	[65]
		Pd(PPh <sub>3</sub> ) <sub>4</sub> /CuI THF	85	[66]
2 ArSnBu <sub>3</sub>	 (both Br react)	Pd(PPh <sub>3</sub> ) <sub>4</sub> PhMe	37–90	[67]
R <sub>4</sub> Sn R = Me or <i>n</i> -Bu		Pd(PPh <sub>3</sub> ) <sub>4</sub> /CuBr dioxane, reflux	98–100	[68]
ArI		Pd <sub>2</sub> (dba) <sub>3</sub> /AsPh <sub>3</sub> CuI DMF	67–91	[69]



Scheme 10

## REFERENCES

- [1] S. Baba, and E. Negishi, *J. Am. Chem. Soc.*, **1976**, 98, 6729.
- [2] B. Jonsseume and P. Villeneuve, *Tetrahedron*, **1989**, 45, 1145.
- [3] L. S. Liebeskind, G. B. Stone, and S. Zhang, *J. Org. Chem.*, **1994**, 59, 7917.
- [4] J. E. Baldwin, R. M. Adlington, and S. H. Racharitar, *Tetrahedron*, **1992**, 48, 2957.
- [5] G. Reginato, A. Capperucci, A. Degl'Innocenti, A. Mordini, and S. Pecchi, *Tetrahedron*, **1995**, 51, 2129.
- [6] N. Okukado, D. E. Van Horn, W. L. Klima, and E. Negishi, *Tetrahedron Lett.*, **1978**, 1027.
- [7] E. Negishi, unpublished results.
- [8] E. Negishi, N. Okukado, A. O. King, D. E. Van Horn, and B. I. Spiegel, *J. Am. Chem. Soc.*, **1978**, 100, 2254.
- [9] R. M. Rzasz and D. Romo, *Tetrahedron Lett.*, **1995**, 36, 5307.
- [10] B. Jiang, and Y. Xu, *Tetrahedron Lett.*, **1992**, 33, 511.
- [11] T. Yanagi, T. Oh-e, N. Miayaura, and A. Suzuki, *Bull. Chem. Soc. Jpn.* **1989**, 62, 3892.

- [12] J. P. Genêt, A. Linquist, E. Blart, V. Mouriés, and M. Savignac, *Tetrahedron Lett.*, **1995**, 36, 1443.
- [13] N. Miyaura and A. Suzuki, *Chem. Rev.*, **1995**, 95, 2457.
- [14] N. Satoh, T. Ishiyama, N. Miyaura, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, **1987**, 60, 3471.
- [15] M. Kosugi, T. Sakay, S. Ogawa, and T. Migita, *Bull. Chem. Soc. Jpn.*, **1993**, 66, 3058.
- [16] B. H. Lipshutz and M. Alami, *Tetrahedron Lett.*, **1993**, 34, 1433.
- [17] J. K. Stille and M. P. Sweet, *Tetrahedron Lett.*, **1989**, 30, 3645.
- [18] C. M. Hettrick, J. K. Kling, and W. J. Scott, *J. Org. Chem.*, **1991**, 56, 1489.
- [19] R. Ostwald, P.-Y. Chavant, H. Stadtmüller, and P. Knochel, *J. Org. Chem.*, **1994**, 59, 4143.
- [20] S. R. Baker, G. P. Roth, and C. Sapino, *Synth. Commun.*, **1990**, 20, 2185.
- [21] R. J. Boyce and G. Pattenden, *Tetrahedron Lett.*, **1996**, 37, 3501.
- [22] M. Abarbri, J.-L. Parrain, and A. Duchêne, *Tetrahedron Lett.*, **1995**, 36, 2469.
- [23] R. Rossi, F. Bellina, A. Carpita, and R. Gori, *Synlett*, **1995**, 344.
- [24] F. Bellina, A. Carpita, M. De Santis, and R. Rossi, *Tetrahedron Lett.*, **1994**, 35, 6913.
- [25] Y. Mu and R. A. Gibbs, *Tetrahedron Lett.*, **1995**, 36, 5669.
- [26] N. Yasuda, L. Xavier, D. L. Rieger, Y. Li, A. E. DeCamp, and U.-H. Dolling, *Tetrahedron Lett.*, **1993**, 34, 3211.
- [27] R. Rossi and F. Bellina, *Org. Prep. Proc. Int.*, **1997**, 137, 162.
- [28] S. Fujiwara and A. B. Smith III, *Tetrahedron Lett.*, **1992**, 33, 1185.
- [29] L. S. Liebeskind and J. Wang, *Tetrahedron Lett.*, **1990**, 31, 4293.
- [30] A. O. King, N. Okukado, and E. Negishi, *J. Chem. Soc. Chem. Commun.*, **1977**, 683.
- [31] E. Negishi, in *Aspects of Mechanism and Organometallic Chemistry*, J. H. Brewster, Ed., Plenum Press, New York, **1978**, 285–317.
- [32] M. Abarbri, J.-L. Parain, J.-C. Cintrat, and A. Duchêne, *Synthesis*, **1996**, 82.
- [33] A. G. Myers, M. M. Alauddin, M. A. M. Fuhry, P. S. Dragovich, N. S. Finney, and P. M. Harrington, *Tetrahedron Lett.*, **1989**, 30, 6997.
- [34] S. L. Schreiber and L. L. Kiessling, *J. Am. Chem. Soc.*, **1988**, 110, 631–633.
- [35] B. Miossec, R. Danion-Bougot, and D. Danion, *Synthesis*, **1994**, 1171.
- [36] E. Negishi, L. F. Valente, and M. Kobayashi, *J. Am. Chem. Soc.*, **1980**, 102, 3298.
- [37] M. Kobayashi and E. Negishi, *J. Org. Chem.*, **1980**, 45, 5223.
- [38] I. N. Houpis, *Tetrahedron Lett.*, **1991**, 32, 6675.
- [39] G. K. Cook, W. J. Hornback, C. L. Jordan, J. H. McDonald III, and J. E. Munroe, *J. Org. Chem.*, **1989**, 54, 5828.
- [40] E. Negishi, H. Matsushita, and N. Okukado, *Tetrahedron Lett.*, **1981**, 22, 2715.
- [41] S.-M. Zhou, Y.-L. Yan, and M.-Z. Deng, *Synlett*, **1998**, 198.
- [42] N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, and A. Suzuki, *J. Am. Chem. Soc.*, **1989**, 111, 314.
- [43] V. Farina, V. Krishnamurthy, and W. J. Scott, *Org. React.*, **1997**, 50, 1–652.
- [44] E. Negishi, and T. Yoshida, *J. Am. Chem. Soc.*, **1973**, 95, 6837.
- [45] T. Ishikawa, S. Nonaka, A. Ogawa, and T. Hirao, *Chem. Commun.*, **1998**, 1209.
- [46] A. F. Renaldo, J. W. Labadie, and J. K. Stille, *Org. Synth.*, **1989**, 86.
- [47] M. Pérez, A. M. Castaño, and A. M. Echavarren, *J. Org. Chem.*, **1992**, 57, 5047.
- [48] A. M. Echavarren, M. Pérez, A. M. Castaño, and J. M. Cuerva, *J. Org. Chem.*, **1994**, 59, 4179.
- [49] A. Degl’Innocenti, E. Stucchi, A. Capperucci, A. Mordini, G. Reginato, and A. Ricci, *Synlett*, **1992**, 332.

- [50] P. G. Ciattini, E. Morera, and G. Ortar, *Synth. Commun.*, **1995**, 25, 2883.
- [51] G. Shi, Z. Cao, and X. Zhang, *J. Org. Chem.*, **1995**, 60, 6608.
- [52] G. J. Hollingworth and J. B. Sweeney, *Tetrahedron Lett.*, **1992**, 46, 7079.
- [53] P. Knochel and C. J. Rao, *Tetrahedron*, **1993**, 49, 29.
- [54] T. Takeda, Y. Kabasawa, and T. Fujiwara, *Tetrahedron*, **1995**, 51, 2515.
- [55] G. P. Roth, V. Farina, L. S. Liebeskind, and E. Peña-Cabrera, *Tetrahedron Lett.*, **1995**, 36, 2191.
- [56] I. N. Houpis, L. DiMichele, and A. Molina, *Synlett*, **1993**, 365.
- [57] D. J. Critcher and G. Pattenden, *Tetrahedron Lett.*, **1996**, 37, 9107.
- [58] C. J. Rao and P. Knochel, *J. Org. Chem.*, **1991**, 56, 4593.
- [59] H. Tanaka, H. Hayakawa, S. Shibata, K. Haraguchi, and T. Miyasaka, *Nucleosides Nucleotides*, **1992**, 11, 319.
- [60] S. Manfredini, P. G. Baraldi, R. Bazzanini, M. Marangoni, D. Simoni, J. Balzarini, and E. De Clercq, *J. Med. Chem.*, **1995**, 38, 199.
- [61] T. Hanawa, A. Watanabe, T. Tsuchiya, R. Ikoma, M. Hidaka, and M. Sugihara, *Chem. Pharm. Bull.*, **1995**, 284.
- [62] G. Palmisano and M. Santagostino, *Tetrahedron*, **1993**, 49, 2533.
- [63] K. S. Chan and C. C. Mak, *Tetrahedron*, **1994**, 50, 2003.
- [64] K. Krohn and N. Böker, *J. Prakt. Chem./Chem.-Ztg.* **1997**, 339, 114.
- [65] A. M. Echavarren, Ó. de Frutos, N. Tamayo, P. Noheda, and P. Calle, *J. Org. Chem.*, **1997**, 62, 4524.
- [66] Ó. de Frutos and A. M. Echavarren, *Tetrahedron Lett.*, **1996**, 37, 8953.
- [67] S. Yoshida, H. Kubo, T. Saika, and S. Katsumura, *Chem. Lett.*, **1996**, 139.
- [68] N. Tamayo, A. M. Echavarren, and M. C. Paredes, *J. Org. Chem.*, **1991**, 56, 6488.
- [69] L. S. Liebeskind and S. W. Riesinger, *J. Org. Chem.*, **1993**, 58, 408.
- [70] J.-L. Parrain, I. Beaudet, A. Duchêne, S. Watrelot, and J.-P. Quintard, *Tetrahedron Lett.*, **1993**, 34, 5445.
- [71] H.-S. Lin, A. A. Rampersaud, K. Zimmerman, M. I. Steinberg, and D. B. Boyd, *J. Med. Chem.*, **1992**, 35, 2658.
- [72] J. P. Marino and J. K. Long, *J. Am. Chem. Soc.*, **1988**, 110, 7916.
- [73] J. S. Xiang, A. Mahadevan, and P. L. Fuchs, *J. Am. Chem. Soc.*, **1996**, 118, 4284.
- [74] R. S. Paley, A. de Dios, and R. F. de la Pradilla, *Tetrahedron Lett.*, **1993**, 34, 2429.