

III.2.9 Palladium-Catalyzed Cross-Coupling between Allyl, Benzyl, or Propargyl Groups and Unsaturated Groups

EI-ICHI NEGISHI and FANG LIU

A. INTRODUCTION

In 1977 Kosugi et al.^[1] reported the Pd-catalyzed allylation with allyltins, which most probably is the first Pd-catalyzed allylation reaction and the first Pd-catalyzed cross-coupling with organotins, while Negishi et al.^[2] reported what appears to be the first Pd-catalyzed benzylation with benzylzinc halides. So, Pd-catalyzed allylation and benzylation began in 1977 (**Scheme 1**). The related propargylation most probably was reported first in 1980.^[3] Prior to these developments, the stoichiometric reaction of arylmercuric halides with allyl halides and Pd complexes was reported by Heck.^[4] The catalytic version of this and related reactions was later developed as the Heck reaction, as discussed in **Part IV**.

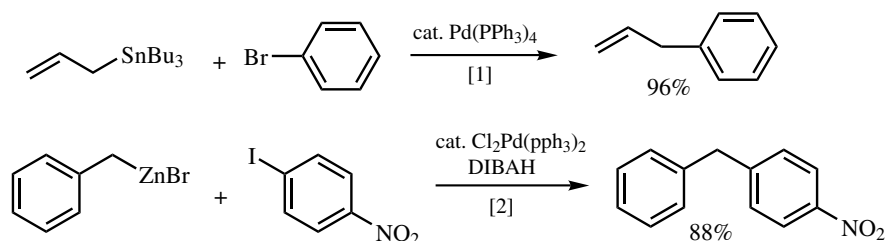
Curiously, both of the prototypical reactions shown in **Scheme 1** involve the use of allyl- or benzylmetals. Their charge affinity-inverted versions, which are currently much more commonly employed, were reported by Tamao et al.^[5] in 1978 on allylation and by Milstein and Stille^[6] in 1979 on benzylation (**Scheme 2**). Thus, the foundation of Pd-catalyzed allylation and benzylation was laid in the late 1970s. Of Pd-catalyzed allylation, benzylation, and propargylation, allylation has been most extensively investigated by far.

B. Pd-CATALYZED ALLYLATION

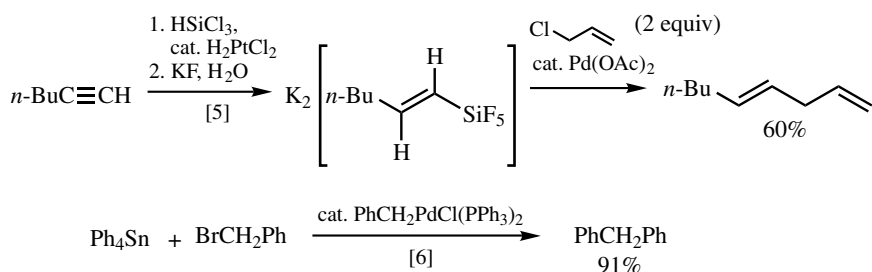
B.i. Background

Traditionally, allylation of organometals has been achieved mainly with organometals containing relatively electropositive metals, such as Mg. Catalysis with Cu compounds, such as Li_2CuCl_4 , along with the stoichiometric organocopper reactions has significantly expanded the synthetic scope of allylation. In many instances, these conventional reactions provide some of the most satisfactory procedures for allylation. So, the use of expensive Pd catalysts has to be amply justified and reserved for those cases that do require catalysis by Pd complexes. There are indeed many such cases and many different reasons for the use of Pd catalysts. Generation of alkenyl- and alkylmetals via

hydrometallation and carbometallation followed by direct cross-coupling has often required catalysis with Pd and other metals. Use of allylic acetates, carbonates, and other less reactive allylic electrophiles has also mandated the use of catalysts.



Scheme 1



Scheme 2

Pd-catalyzed allylation is closely related to the Tsuji–Trost reaction involving allylation of enolates. Interestingly, enolates and “harder” organometals have been shown to follow different reaction courses, as discussed later in this section. Mechanistically and historically, the Tsuji–Trost reaction has been viewed as a process involving nucleophilic attack on coordinated π -allyl ligands, and it is therefore discussed in **Part V**. However, it is not unreasonable to view it as a group of Pd-catalyzed cross-coupling reactions. Remember that the term “cross-coupling” does not imply any particular mechanism, as it only pertains to a certain starting material–product relationship.

It is striking that, despite the pioneering investigation of Pd-catalyzed allylation with allyltins,^[1] subsequent investigations have been almost totally dominated by Pd-catalyzed allylation with allylic electrophiles, as can be gleaned from the discussions presented below. In this connection, it should be clearly recognized that the Pd-catalyzed reaction of allylmetals can be and has, in some cases, been shown to be significantly different from that of allylic electrophiles, even though many of these reactions may be expected to converge at the intermediary stage of allyl(organyl)palladium(II) derivatives. Although mechanistic details have not yet been well clarified, it is entirely conceivable that allylmetals, especially those containing more electropositive metals, can strongly interfere with Pd-containing species generated in a catalytic cycle. Because of their tendency to serve as bidentate η^3 ligands, interaction of allylmetals with Pd species can be more intense than other organometals, such as those containing alkyl, aryl, and alkenyl groups. Since allyl electrophiles are not expected to readily react with Pd(II) intermediates, their catalyst

poisoning effects must be less serious. Also expected are much less intense effects exerted by benzylmetals. Indeed, benzylmetals resemble in many ways saturated alkylmetals more than allylmetals. Whatever the true reason for the general difficulties associated with the use of allylmetals in Pd-catalyzed allylation, it is to be generally avoided provided that allylation with allyl electrophiles is a viable option. In allyl–allyl cross-coupling, however, the use of allylmetals is unavoidable. In reality, only those allylmetals containing electronegative metals, mostly allyltins, have been used as discussed in **Sect. III.2.10**.

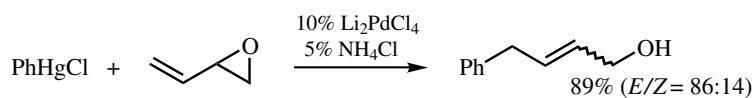
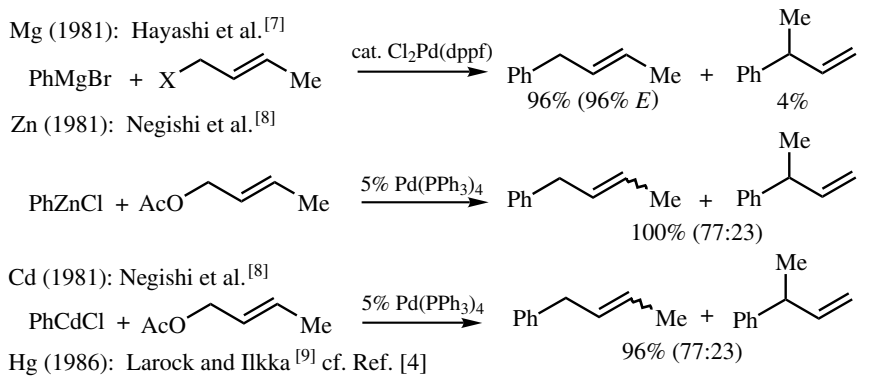
With the notable exceptions of allyl–allyl coupling (**Sect. III.2.10**) and enolate allylation (**Sect. V.2.1.4**), Pd-catalyzed allylation has been achieved mostly with alkenylmetals (alkenyl–allyl coupling) and arylmetals (aryl–allyl coupling). The use of alkylmetals and alkynylmetals has been rare perhaps because their allylation can be performed satisfactorily with appropriate Grignard reagents, whose reactivity can be modified favorably with either stoichiometric or catalytic amounts of Cu compounds, as needed.

B.ii. Scope

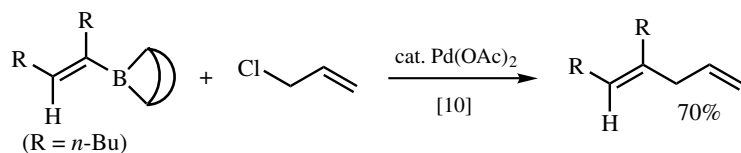
B.ii.a. Metal Counteractions. Although Pd-catalyzed allylation can be complicated by a number of side reactions and undesirable processes as detailed below, it is nonetheless a fundamentally favorable transformation that can be achieved with a wide variety of allyl derivatives containing a bewilderingly wide array of heteroatom groups in the allylic position, as discussed later. It has also been observed with a wide range of organometals, especially aryl- and alkenylmetals containing a number of main group metals, such as Mg, Zn, Cd, Hg, B, Al, Si, and Sn, as well as transition metals including Ti and Zr. Some prototypical examples of Pd-catalyzed allylation with various organometals mentioned above are shown in **Scheme 3**. With most of these metals, the earliest examples were reported in the early 1980s.

The general trends observed with various metals in Pd-catalyzed cross-coupling in general are also seen in allylation. Thus, the highest reactivity under catalytic conditions is observed with metals of intermediate electronegativity, that is, $\text{Zn} > \text{Al} > \text{Zr}$, the relative intrinsic reactivity order among them being as shown above. Even though objective comparative studies are relatively scarce, the superior intrinsic reactivity of Zn has been clearly indicated by the results shown in **Schemes 4**^[8] and **5**.^[17]

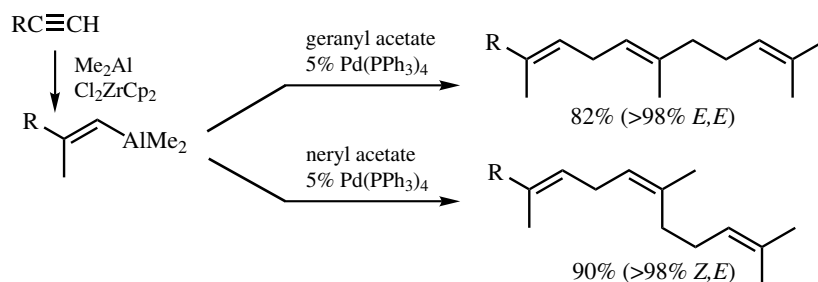
Those metals that readily participate in hydrometallation, that is, B, Al, and Zr, have provided particularly attractive synthetic procedures. Hydrostannylation and recently developed hydro- and carbozincation reactions have also been profitably combined with Pd-catalyzed allylation. Despite a concern about toxicity, Sn has been used extensively. The available literature information indicates that Al, B, Mg, Sn, Zn, and Zr are the six metals that have been most widely used, even though their relative merits and demerits are often not very clear (**Scheme 6**). The generally low chemoselectivity associated with Mg is a limiting factor. However, as organometals containing other metals, such as Zn and Sn, are often prepared from the corresponding Grignard reagents, it is advisable to test the usefulness of Grignard reagents before converting them into other organometals. Facile and undesirable redox processes that would interfere with the desired Pd-catalyzed reaction can take place with heavy metals, such as Cd and Hg. These metals as well as Sn are also associated with toxicity problems that can be a serious concern. The intrinsic reactivity of organosilanes, which must generally be activated by added reagents for Pd-catalyzed cross-coupling *vis-à-vis* the availability of several satisfactory metals, mandates justification of the use of Si with some unique advantages it might offer.



B (1980): Yatagai^[10], Miyaura et al.^[11]

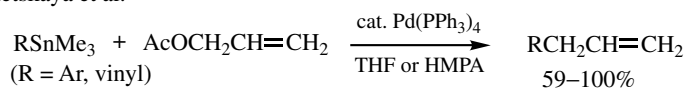


Al (1981): Negishi et al.^[8]

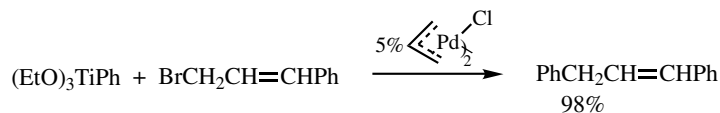


Si (1978): Tamao et al.^[5] cf. **Scheme 2**

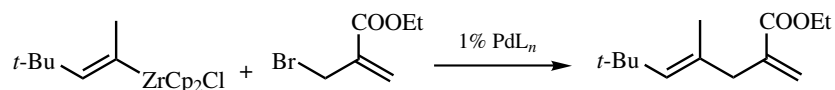
Sn (1981): Beletskaya et al.^[12]



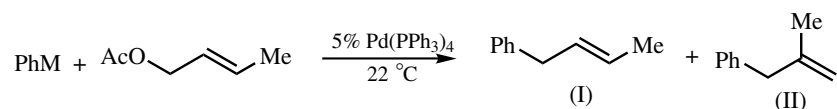
Ti (1984): Tolstikov and Kasatkin^[13]



Zr (1981): Schwartz et al.^[14] cf. Refs. [15] and [16] for the stoichiometric version

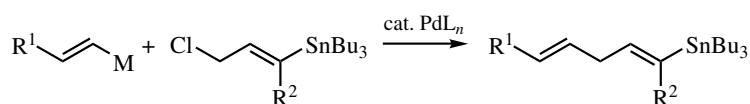


Scheme 3



M	Reaction Time (h)	Total Yield (%)	(I)/(II)
MgBr	3	15	48:52
ZnCl	3	100	77:23
CdCl	12	96	77:23
AlPh ₂	3	55	62:38
ZrPh ₃	24	25	46:54

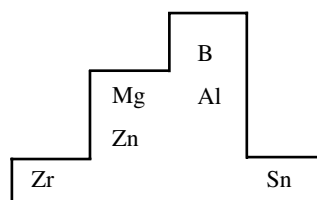
Scheme 4



M	React. Cond.	Yield (%)
Li[9-MeO-9-BBN]	60 °C, 3h	5
ZrCp ₂ Cl	60 °C, 3h	4
AlEt ₂	50 °C, 2h	42
ZnBr	r.t., 0.5 h	80

Scheme 5

Six most widely used metals
in Pd-catalyzed allylation



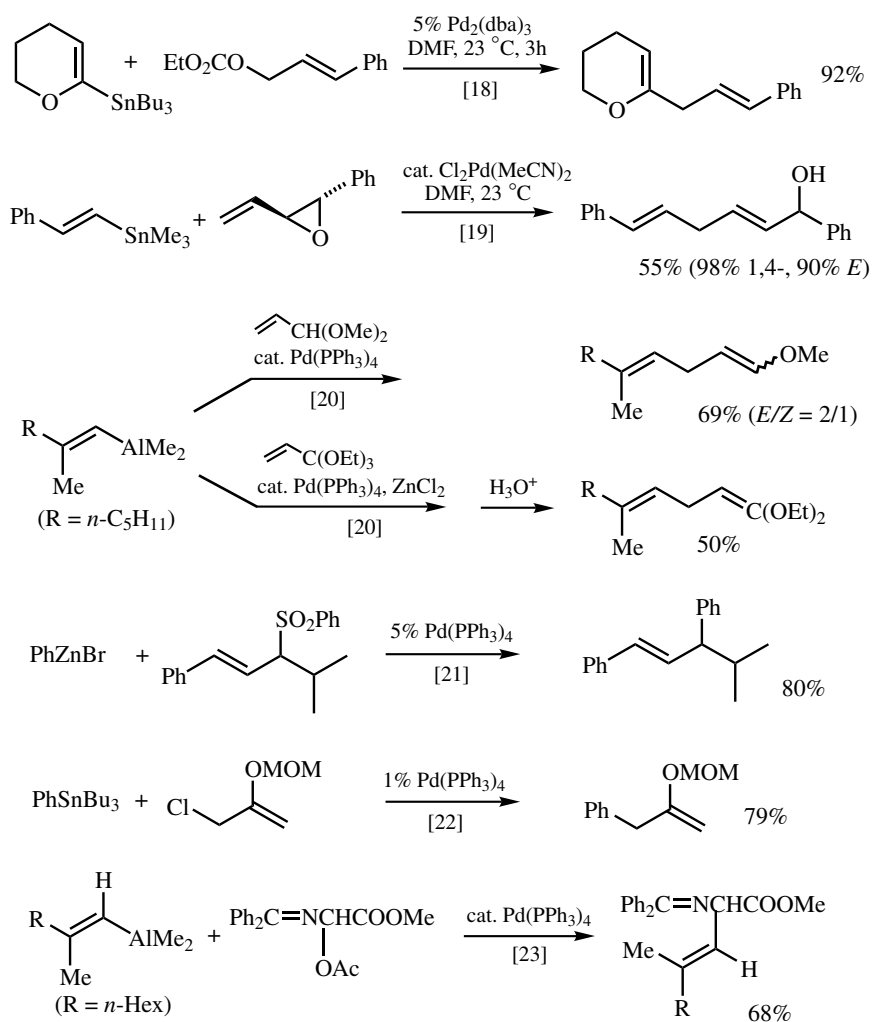
Scheme 6

B.ii.b. Allylic Electrophiles. Pd-catalyzed allylation can take place with a wide variety of allylic electrophiles. A systematic study of the scope with respect to the leaving group in the reaction of alkenylalanes with geranyl derivatives summarized in **Table 1** has indicated that not only Cl and OAc, but also other oxy groups such as OAlMe₂, OPO(OEt)₂, and even OSiR₃ including OSiMe₃ and OSiMe₂Bu-*t* participate in the reaction at room temperature.^[8]

Allylic iodides may be too reactive and, more significantly, too unstable to be useful. Even allylic bromides have rarely been used and are generally unnecessary. On the other hand, many other intrinsically less reactive allylic derivatives have been used satisfactorily. They include allylic carbonates,^[18] epoxides,^[19] acetals,^[20] sulfones,^[21] 2-alkoxyallyl derivatives,^[22] and even 2-azaallyl derivatives,^[23] and some representative examples are shown in **Scheme 7**.

TABLE 1. The Effect of Leaving Groups in the Pd-Catalyzed Reaction of Geranyl Derivatives with (*E*)-2-Methyl-1-hexenyl-dimethylalane (at 22 °C)

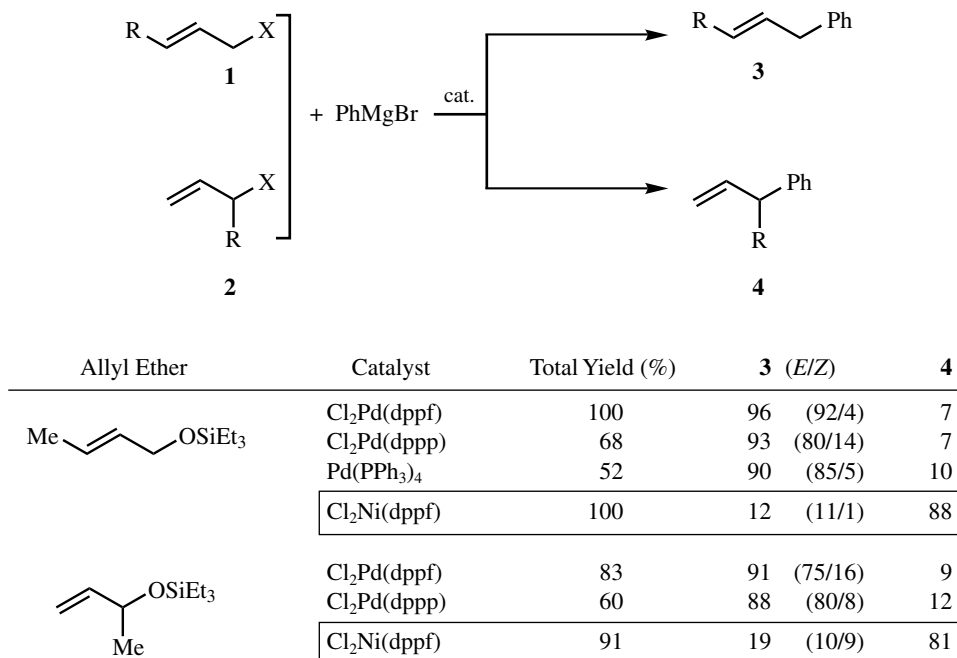
Leaving Group	Product Yield (%)		
	1 h	6 h	48 h
Cl	100	—	—
OAc	100	—	—
OAlMe ₂	43	—	—
OPO(OEt) ₂	33	93	100
OSiMe ₃	18	41	94
OSiMe ₂ Bu- <i>t</i>	Trace	37	46

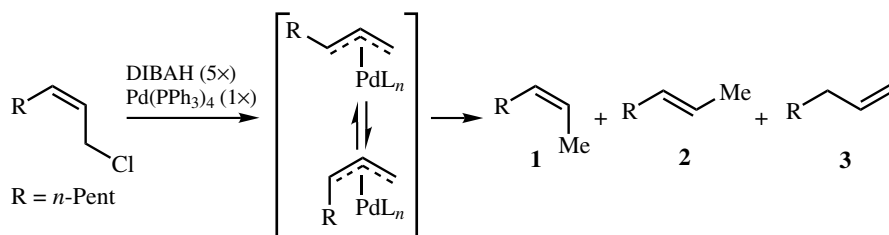
**Scheme 7**

B.iii. Regiochemistry, Stereochemistry, and Mechanism

B.iii.a. Regiochemistry. Pd-catalyzed allylation of organometals containing Zn, B, Sn, and other metal counterions can proceed with retention of regiochemistry of allylic electrophiles, as exemplified by the reaction of geranyl and neryl acetates shown in **Scheme 3** and the results summarized in **Scheme 5**. The extent of retention of the allyl regiochemistry depends on the relative rates of the α - and γ -allylation of organometals. In allylic electrophiles, either α - or γ -position of allylic electrophiles may be substituted with 0, 1, or 2 substituents. In cases where the α -position is unsubstituted and the γ -position is disubstituted, complete or nearly complete retention of regiochemistry may be observed and has indeed been observed in many cases. Conversely, if the α - and γ -positions are substituted with 2 and 0 substituents, respectively, an extensive allylic rearrangement may be observed. The other cases are expected to lie between these two extreme cases, and the currently available data indeed support this generalization. In general, allylic rearrangement occurring at least to minor extents should be anticipated in cases where the difference in the extents of substitution in the α - and γ -positions is 0 or 1, as exemplified by the first four entries in **Scheme 3**. It should also be noted that allylic rearrangement is usually accompanied by stereoisomerization to varying degrees. Any predictions beyond these useful but somewhat vague generalizations are difficult, and experiments are needed to find the extents of regioselectivity except in the favorable cases of γ,γ -disubstituted allylic derivatives.

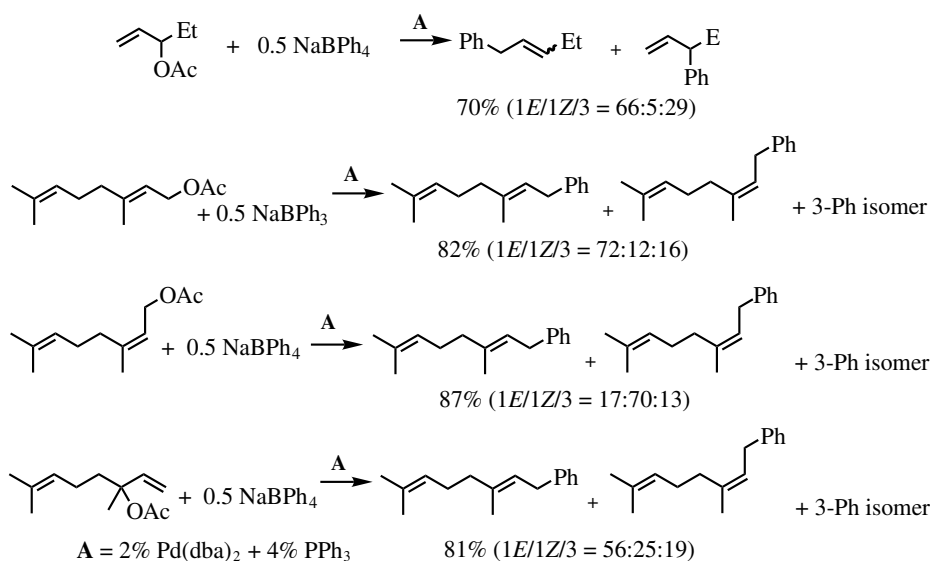
The capricious nature of the regiochemistry of Pd- or Ni-catalyzed allylation of organometals is amply demonstrated by the results summarized in **Schemes 8–10**.

**Scheme 8**



Temperature (°C)	Total Yield (%)	Composition (%)		
		1	2	3
-78	100	100	0	0
-45	87	70	6	24
0	76	26	18	56
r.t.	69	34	14	52

Scheme 9



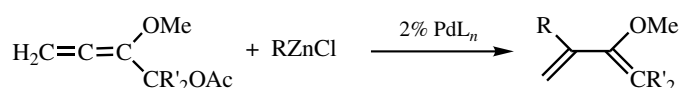
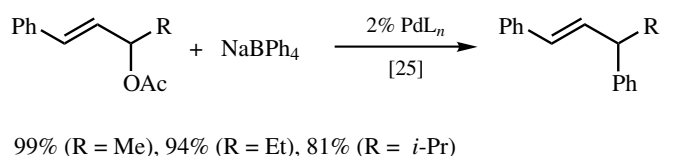
Scheme 10

The results summarized in **Scheme 8**^[7] indicate that, under the same conditions using the same catalysts and other reagents and solvents, these allylation reactions tend to be regioconvergent, leading to similar regioisomeric ratios whether the starting allylic electrophiles are α - or γ -substituted. It is interesting to note that the diametrically opposed regiochemical outcomes are observed with Pd and Ni catalysts.

The results of the reaction of (*Z*)-2-octenyl chloride with 5 equiv of DIBAH and 1 equiv of $\text{Pd}(\text{PPh}_3)_4$ summarized in **Scheme 9**^[24] indicate that the regio- and stereochemistry of allylation can significantly be influenced by the reaction temperature.

The results summarized in **Scheme 10**^[24a] provide further useful information about the regiochemistry of Pd-catalyzed allylation of organometals. Even in cases where the α - and γ -positions are maximally differentiated as in the cases of the second through fourth entries, regiochemical scrambling accompanied by stereoisomerization can occur to significant extents. The significantly lower levels of stereospecificity relative to those observed with organoaluminum compounds (**Scheme 3**) must be a consequence of lower rates of the desired allylation relative to stereoisomerization (and regioisomerization) in the reaction of NaBPh₄.

Strong effects on regiochemistry exerted by the Ph group shown in **Scheme 11** are also noteworthy, and they must be attributable to electronic effects. In such cases, nearly 100% regioselectivity may be observed, even when regiochemical scrambling might otherwise be expected.^[25] Strong electronic effects are also evident in the reaction of allylic acetates containing an allenyl group.^[26]



R	R'	Yield (%)
H ₂ C=CH—	H	50
Me ₃ SiC≡C—	H	85
Ph—	Me	95
<i>t</i> -BuCH=C=CH—	Me	90
H ₂ C=C(Me)C≡C—	Me	80

Scheme 11

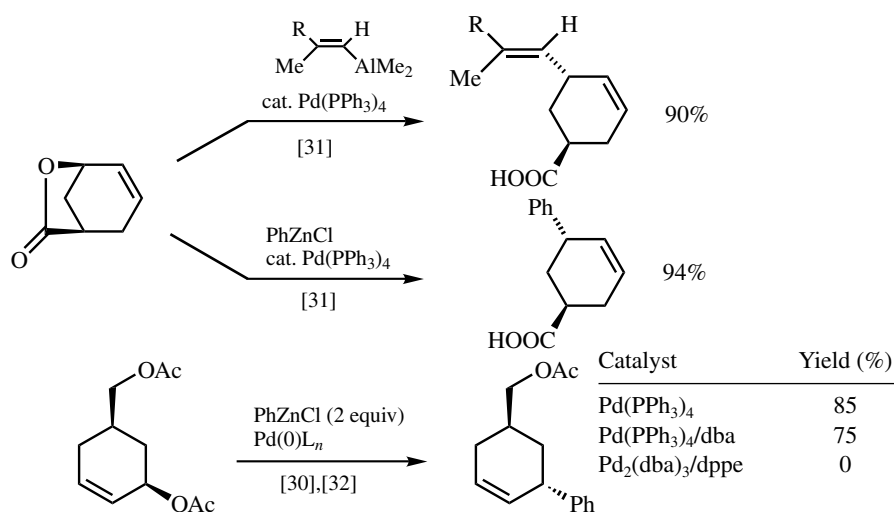
B.iii.b. Stereochemistry. The stereochemistry of Pd-catalyzed allylation of organometals is considerably more complicated than the regiochemistry discussed above, since it involves both *E,Z* stereochemistry of the C=C bond and *R,S*-configuration of the allylic C_{sp}³ center.

The extents of *E,Z* stereochemical retention or scrambling are intimately coupled with the retention or scrambling of the regiochemistry of the allylic electrophiles, as amply indicated in the previous subsections. Specifically, those reactions that proceed with retention of regiochemistry, such as the alkenylalane reaction in **Scheme 3**, the reaction in **Scheme 5**, the reaction run at -78°C in **Scheme 9**, and the first reaction in **Scheme 11**, also retain the *E* or *Z* stereochemistry, suggesting that these two phenomena must be mechanistically linked to each other, as discussed below.

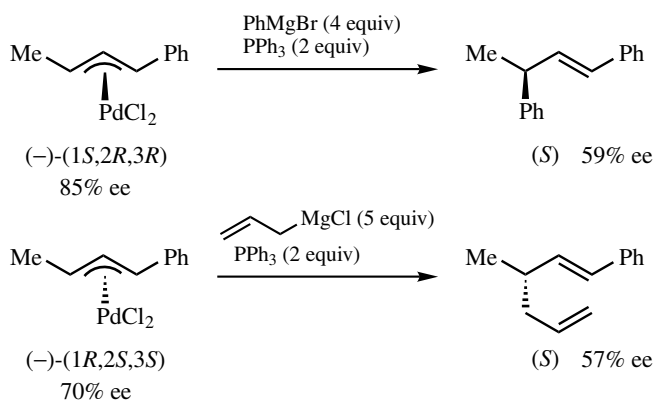
The stereochemistry at the allylic C_{sp}³ center is also a very intricate issue. In the 1970s it was demonstrated that Pd-catalyzed allylation of doubly stabilized enolates, that is, the Tsuji–Trost reaction, proceeded with retention at that C_{sp}³ center, resulting from double

inversions, first in oxidative addition and then in C—C bond formation via attack of π -allylpalladium intermediates by nucleophiles on the side opposite to Pd.^{[27],[28]} The same stereochemistry was also observed later even with “ordinary” enolates.^[29]

In the early 1980s the opposite stereochemistry, that is, overall inversion, was demonstrated first in the stoichiometric reaction of allylpalladium derivatives with organozirconiums by Schwartz and co-workers^{[15],[16]} and then in the catalytic reactions of an alkenylalane and a phenylzinc derivative by Matsushita and Negishi^[31] (**Scheme 12**). The same stereochemistry has since been repeatedly observed with organozinc.^{[30],[32]} Similar experiments with organotin compounds pointing to the same conclusion were also reported later by Stille and co-workers.^{[33],[34]} All of these investigations relied on diastereochemical relationships. The retention of configuration in the C—C bond-forming step was also confirmed subsequently by the determination of absolute configurations, as shown in **Scheme 13**.^[35]



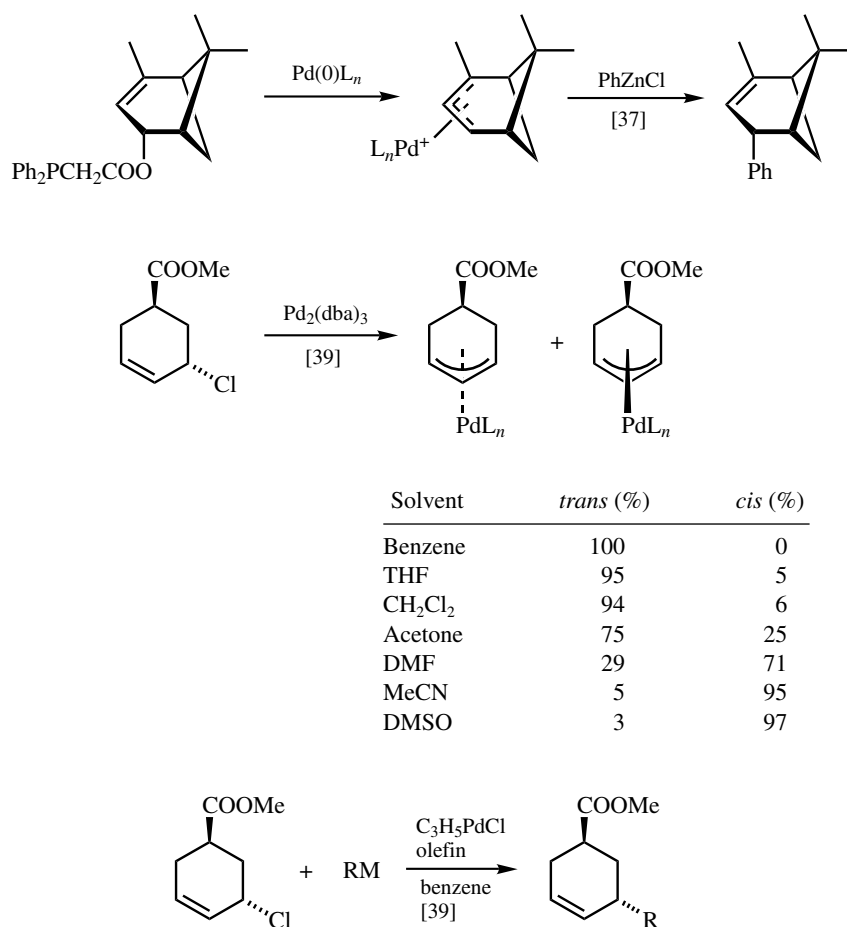
Scheme 12



Scheme 13

All of the conclusions in the investigations discussed above are predicated on an earlier conclusion that the oxidative addition reaction of allylic electrophiles with Pd complexes proceeds with inversion at the allylic C_{sp}³ center,^[36] and these conclusions appear to be still valid in many of the synthetically important Pd-catalyzed allylation reactions.

However, more recent studies spearheaded by Kočovský^{[37],[38]} and Kurosawa^{[39],[40]} have indicated that the stereochemistry of the oxidative addition of allylic electrophiles to Pd complexes can be much more complicated and dependent on solvents and other factors, covering the entire stereoselectivity range, that is, from 100% *R* to 100% *S*. Some noteworthy results are shown in **Scheme 14**.

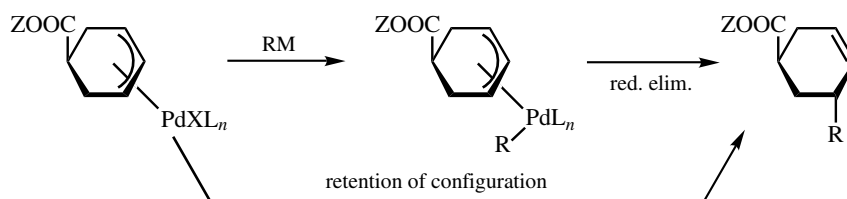


R = Ph (80%, *trans/cis* = 98:2), R = vinyl (92%, *trans/cis* = 92:8)

Scheme 14

B.iii.c. Mechanism. The currently available data indicate that both oxidative addition of allylic electrophiles with Pd complexes and the subsequent C—C bond formation can proceed with either inversion or retention of configuration at the allylic C_{sp}³ center, pointing

to the diverse nature of the mechanism of Pd-catalyzed allylation of organometals. It is nonetheless reasonable to state that the predominant course of the C—C bond formation reaction of allylpalladium intermediates with organometals appears to proceed with retention, strongly suggesting that organometals most likely attack Pd to produce diorganypalladium intermediates, which would then reductively eliminate to produce the observed products (**Scheme 15**). This then is in sharp contrast with the corresponding reactions of “softer” nucleophiles, such as enolates (the Tsuji–Trost reaction) and amines.

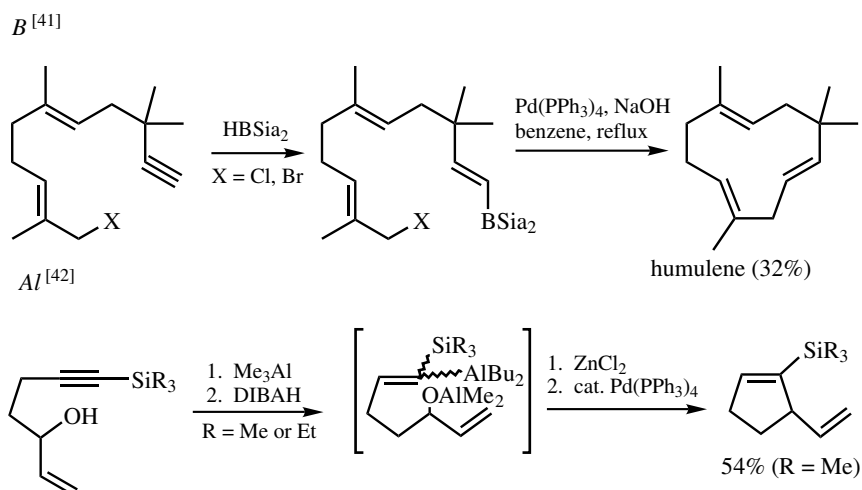


Scheme 15

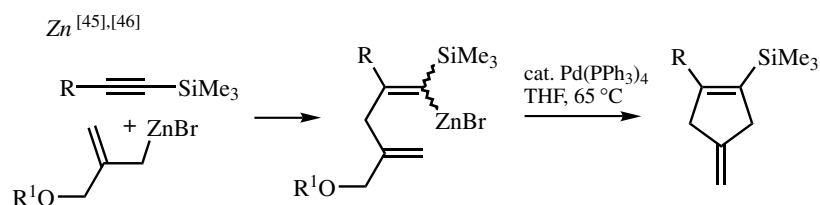
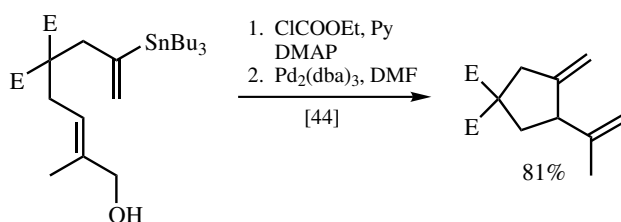
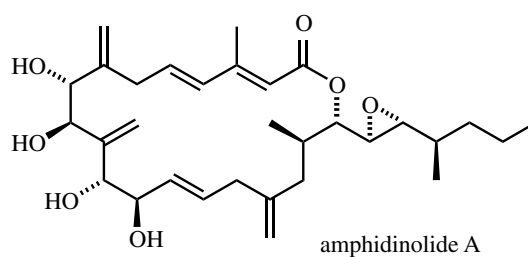
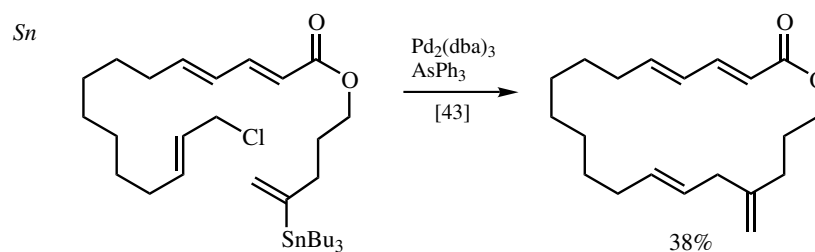
B.iv. Other Noteworthy Aspects of Pd-Catalyzed Allylation

B.iv.a. Pd-Catalyzed Cyclic Allylation. The fact that a wide range of allylic electrophiles including not only halides and sulfonates but also phosphates and even silyl ethers that are normally poor and unreactive electrophiles can be used as electrophiles in Pd-catalyzed allylation^[8] can be exploited in generating organometals containing relatively inert allylic electrophiles for the preparation of cyclic compounds via Pd-triggered cyclic allylation. As might be expected, it is advantageous to use organometals of relatively low intrinsic reactivity, such as B,^[41] Al,^[42] and Sn.^{[43],[44]} However, even Zn^{[45],[46]} has been shown to satisfactorily participate in Pd-catalyzed cyclic allylation.

Some representative examples are shown in **Scheme 16**.



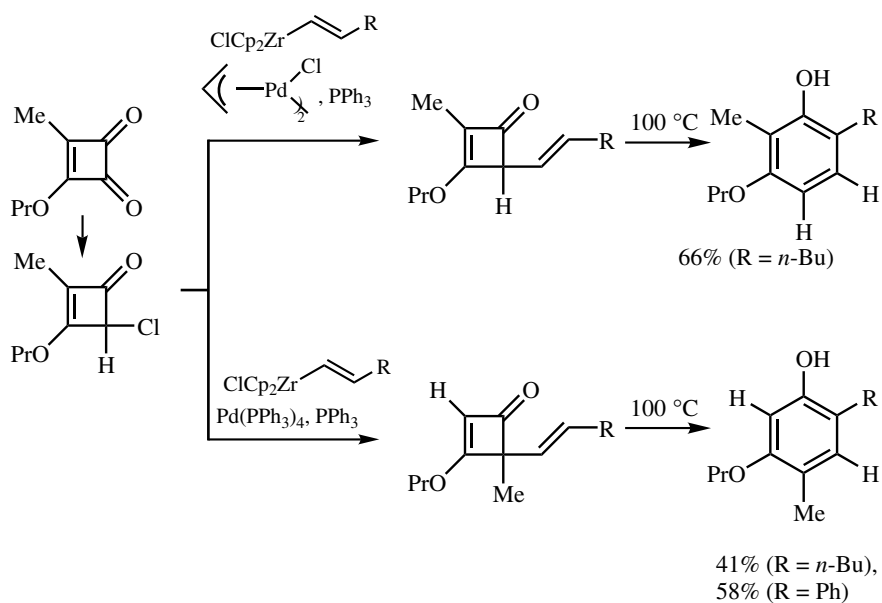
Scheme 16



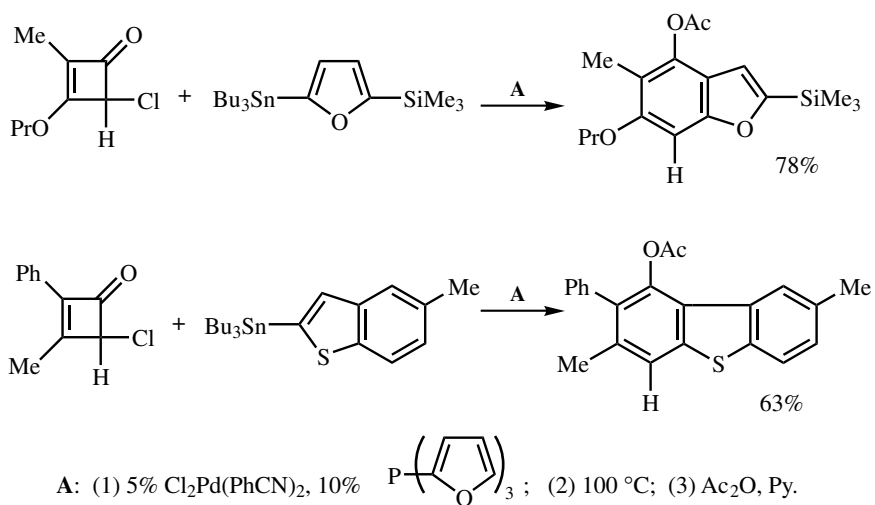
R	R ¹	Yield (%)
MeOCH ₂ —	Ph	51
Me ₃ SiOCH ₂ CH ₂ —	Ph	78
HOCH ₂ CH ₂ —	PhCH ₂	67
Cl(CH ₂) ₄ —	PhCH ₂	75

Scheme 16 (Continued)

B.iv.b. Regioselective Synthesis of Benzene Derivatives via Pd-Catalyzed Cross-Coupling of 4-Halo-2-cyclobuten-1-ones. The Pd-catalyzed reaction of 4-chloro-2-cyclobuten-1-ones with alkenylzirconium derivatives or alkenyltins and heteroaryl tins followed by thermolysis at 100 °C has regioselectively (~95%) produced multiply substituted benzene^[47] (Scheme 17) and heteroarene-fused benzene derivatives^[48] (Scheme 18), respectively.

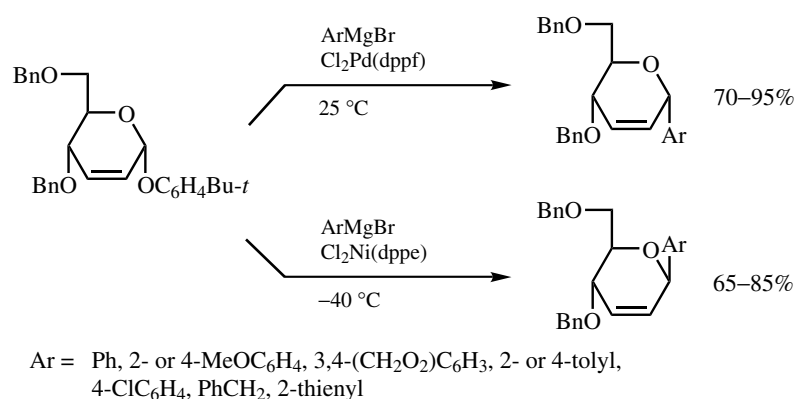


Scheme 17



Scheme 18

B.iv.c. Stereospecific Synthesis of C-Arylglycosides. The Pd- or Ni-catalyzed reaction of α -O- Δ^2 -glycopyranoside (1) with arylmagnesium bromides has provided α - or β -C-aryl- Δ^2 -glycopyranosides, respectively, exhibiting 100% stereospecificity in each case^{[49]–[51]} (Scheme 19). A related study with aryltins and arylsilicates has also been published.^[52]

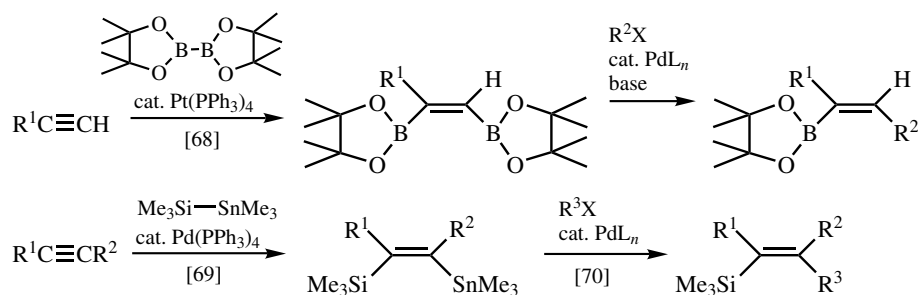


Scheme 19

B.v. Survey of Other Pd-Catalyzed Allylation

In this subsection, additional results of Pd-catalyzed allylation that are not discussed in the preceding subsections are summarized in the following order: aryl–allyl coupling (**Table 2**), allyl–aryl coupling (**Table 3**), alkenyl–allyl coupling with monometallated alkenes (**Table 4**) and alkenyl–allyl coupling with dimetallated alkenes (**Table 5**). The entries in each table are arranged according to the metal counterions in the order: Li, Mg, Zn, B, Al, Si, Sn, Cu, Ti, and Zr.

The Pt- or Pd-catalyzed metallometallation (**Sect. VII.4**) of alkynes with metal–metal bond-containing reagents shown in **Scheme 20** provides a novel, if rather expensive, route to *cis*-1,2-dimetalloalkenes. Their Pd-catalyzed cross-coupling produces regioselectively trisubstituted alkenes containing one metal group (**Table 5**).



Scheme 20

B.vi. Synthesis of Natural Products via Pd-Catalyzed Allylation

Although still small in number, Pd-catalyzed allylation has successfully been employed in more than a dozen natural product syntheses, and the number of its applications is expected to grow in the future. In this section, some noteworthy and prototypical examples not discussed earlier are highlighted. The structures of the natural products and cross-coupling partners are also listed in **Table 7** of **Sect. III.2.18**.

TABLE 2. Pd-Catalyzed Aryl-Allyl Coupling

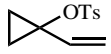
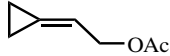
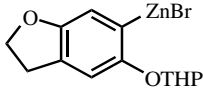
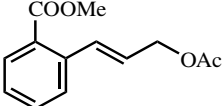
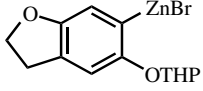
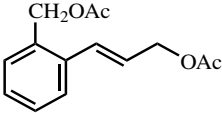
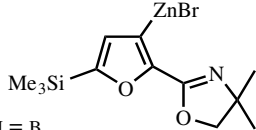
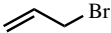
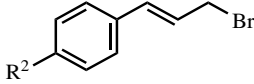
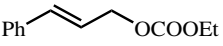
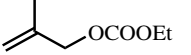
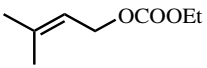
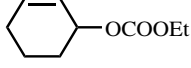
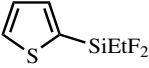

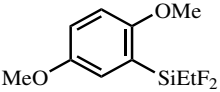
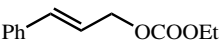
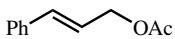
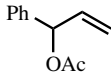
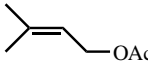
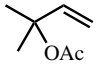
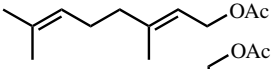
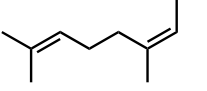
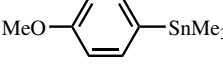



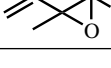
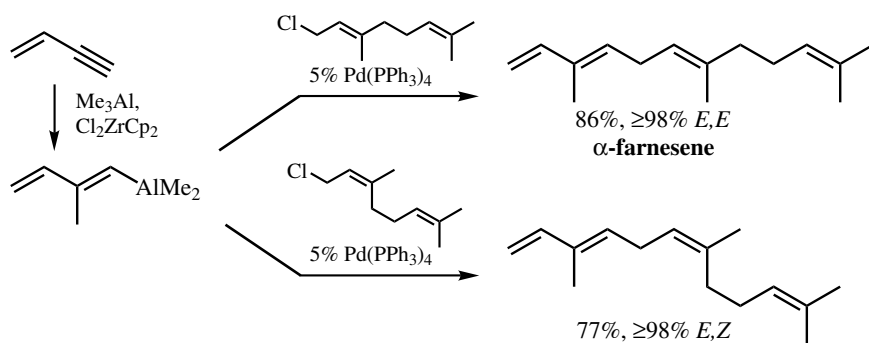
ArM	Allyl Electrophile	Catalyst	Other Conditions	Product Yield (%)	References
M = Zn PhZnCl		Pd(dba) ₂	dppe	66	[53]
PhZnCl		Pd(dba) ₂	dppe	75	[54]
		Pd(OAc) ₂	P(<i>o</i> -Tol) ₃	68	[55]
		Pd(OAc) ₂	P(<i>o</i> -Tol) ₃	75	[55]
		Pd(PPh ₃) ₄		79	[56]
M = B R ¹ -C ₆ H ₄ -B(OH) ₂		Pd(dba) ₂	K ₂ CO ₃		[57]
	R ¹	R ²	Yield (%)		
	H	H	72		
	MeO	H	58		
	Cl	H	78		
	H	Cl	77		
	Br	H	87		
	H	Br	91		
	Cl	Cl	78		
	Br	Cl	73		
	MeO	Cl	83		
M = Si PhSiEtF ₂		Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	84	[58]
PhSiEtF ₂		Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	52	[58]
PhSiEtF ₂		Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	33	[58]
PhSiEtF ₂		Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	40	[58]
		Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	97	[58]
		Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	97	[58]

TABLE 2. (Continued)

ArM	Allyl Electrophile	Catalyst	Other Conditions	Product Yield (%)	References
M = Sn					
PhSnMe ₃		Pd(dba) ₂	PPh ₃	57	[59]
PhSnMe ₃		Pd(dba) ₂	PPh ₃	32	[59]
PhSnMe ₃		Pd(dba) ₂	PPh ₃	65	[59]
PhSnMe ₃		Pd(dba) ₂	PPh ₃	69	[59]
PhSnMe ₃		Pd(dba) ₂	PPh ₃	81	[59]
PhSnMe ₃		Pd(dba) ₂	PPh ₃	76	[59]
		Pd(dba) ₂	PPh ₃	50	[59]
PhSnMe ₃		Cl ₂ Pd(MeCN) ₂	DMF	83 (88% 1,4-, E/Z = 18)	[60]
PhSnMe ₃		Cl ₂ Pd(MeCN) ₂	DMF	85 (88% 1,4-)	[60]
PhSnMe ₃		Cl ₂ Pd(MeCN) ₂	DMF	75	[60]

Aside from the stoichiometric construction of steroidal side chains by the reaction of alkenylzirconium derivatives with steroidal π -allylpalladiums,^[15] a one-pot synthesis of α -farnesene and its 6Z-isomer from geranyl and neryl chlorides, respectively, reported in 1981^[73] appears to be the first example of natural product syntheses via Pd-catalyzed allylation (**Scheme 21**).



Scheme 21

TABLE 3. Pd-Catalyzed Allyl–Aryl Coupling with Allyltributylstannane

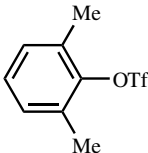
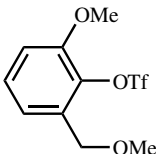
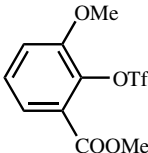
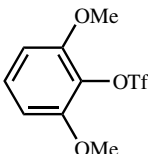
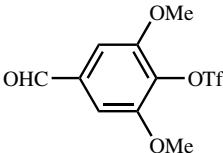
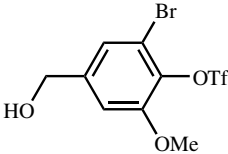
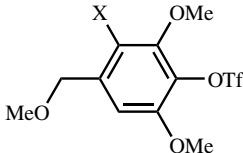
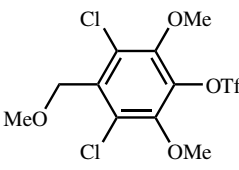
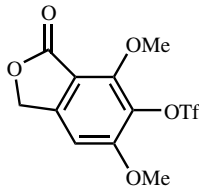
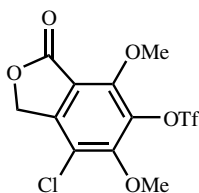
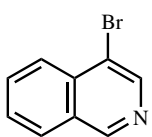
Ar	Catalyst	Other Conditions	Product Yield (%)	References
	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	62	[61]
	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	98	[61]
	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	97	[61]
	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	84	[61]
	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	78	[61]
	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	41	[61]
 (X = Cl or Br)	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	63 (Cl) 67 (Br)	[61]

TABLE 3. (Continued)

Ar	Catalyst	Other Conditions	Product Yield (%)	References
	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	28	[61]
	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	34	[61]
	$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$	PPh_3 , LiCl, DMF	0	[61]
	$\text{Pd}(\text{PPh}_3)_4$	toluene, 100°	85	[62]

Another noteworthy earlier example is the synthesis of humulene, albeit in 32% yield, via Pd-catalyzed intramolecular alkenyl–allyl coupling shown in **Scheme 16**.^[41]

In the earlier examples discussed above, those metals that readily participate in selective hydro- and carbometallation reactions of alkynes, that is, B, Al, and Zr, were used to develop efficient synthetic protocols. Puzzlingly, more recent examples reported mostly in the 1990s have heavily relied on the use of organotin, the use of which in the natural product synthesis was probably reported, for the first time, in 1983 in the synthesis of vitamin K.^[74] Pd-catalyzed intramolecular alkenyl–allyl coupling with alkenyltins to produce a large ring in the synthesis of amphidinolide A^[43] shown in **Scheme 16** is another example along with the synthesis of humulene, pointing to the advantage of the use of relatively electronegative metals, such as B and Sn. Despite the heavy use of Sn in recent years, its choice appears to have been made without rigorous metal counteraction screening in most cases. In the synthesis of α -bisabolene shown in **Scheme 22**,^[75] for example, the required alkenylstannane was prepared by Zr-catalyzed carboalumination–ate complexation–transmetalation procedure. Comparison of **Schemes 21** and **22** strongly suggests that the direct allylation of the alkenylalane intermediate would have provided a much simpler route.

TABLE 4. Pd-Catalyzed Alkenyl-Allyl Coupling with Monometallated Alkenes

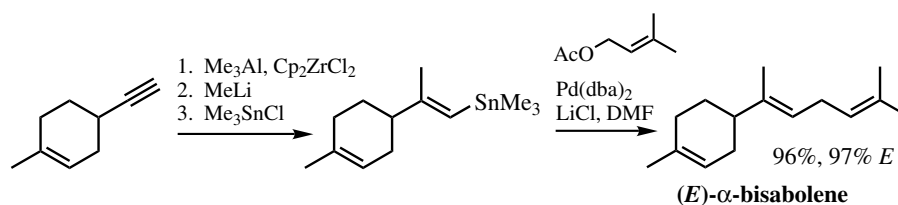
Alkenylmetal	Allyl Electrophile	Catalyst	Other Conditions	Product Yield (%)	References
M = Zn					
		Pd(OAc) ₂	TFP	81	[63]
		Pd(OAc) ₂	TFP	73	[63]
		Pd(OAc) ₂	TFP	67	[63]
		Pd(OAc) ₂	TFP	88	[63]
M = Al					
		Pd(PPh ₃) ₄	TFP-Hexane	75	[64]
		Pd(PPh ₃) ₄	TFP-ClCH ₂ CH ₂ Cl	86	[64]
M = Si					
		Pd(OAc) ₂	PPh ₃ , DMF	73	[58],[65]
		Pd(OAc) ₂	PPh ₃ , DMF	76 (α/γ = 62:14)	[58],[65]
		Pd(OAc) ₂	PPh ₃ , DMF	90 (α/γ = 70:20)	[58],[65]
M = Sn					
		Pd(dba) ₂	LiCl DMF	68	[59]
		Pd(dba) ₂	LiCl DMF	40	[59]
		Pd(dba) ₂	LiCl DMF	80	[59]

TABLE 4. (Continued)

Alkenylmetal	Allyl Electrophile	Catalyst	Other Conditions	Product Yield (%)	References
M = Sn					
		Pd(dba) ₂	LiCl DMF	69	[59]
		Pd(dba) ₂	LiCl DMF	64	[59]
		Pd(dba) ₂	LiCl DMF	88	[59]
		Cl ₂ Pd(MeCN) ₂	PPh ₃	70	[66]
		Cl ₂ Pd(MeCN) ₂	PPh ₃	30	[66]
		Cl ₂ Pd(MeCN) ₂	PPh ₃	60	[66]
		Cl ₂ Pd(MeCN) ₂	DMF	77 (87% 1,4, E/Z = 10)	[60]
		Cl ₂ Pd(MeCN) ₂	DMF	65 (82% 1,4, E/Z = 13)	[60]
		Cl ₂ Pd(MeCN) ₂	DMF	63	[60]
		Cl ₂ Pd(MeCN) ₂	DMF	72	[60]
		Cl ₂ Pd(MeCN) ₂	DMF	55	[60]
M = Ti					
				70	[67]

TABLE 5. Pd-Catalyzed Alkenyl–Allyl Coupling with 1,2-Dimetallated Alkenes

Alkenyl/metal	Allyl Electrophile	Catalyst	Other Conditions	Product Yield (%)	References
M = B					
$ \begin{array}{c} \text{H} \\ \diagup \\ \text{C} = \text{C} \\ \diagdown \quad \diagup \\ n\text{-Bu} \quad \text{B}(\text{O}_2\text{C}_2\text{Me}_4) \\ (\text{Me}_4\text{C}_2\text{O}_2)\text{B} \end{array} $	$ \left[\begin{array}{c} \text{Cl} \text{---} \text{CH}_2\text{CH}=\text{CH}\text{---} \text{Ph} \\ \text{Br} \text{---} \text{CH}_2\text{CH}=\text{CH}\text{---} \text{Ph} \\ \text{AcO} \text{---} \text{CH}_2\text{CH}=\text{CH}\text{---} \text{Ph} \end{array} \right] $	Cl ₂ Pd(dppf)	K ₃ PO ₄	67 56 62	[68]
$ \begin{array}{c} \text{R} \\ \diagup \\ \text{C} = \text{C} \\ \diagdown \quad \diagup \\ \text{R} \quad \text{B}(\text{O}_2\text{C}_2\text{Me}_4) \\ (\text{Me}_4\text{C}_2\text{O}_2)\text{B} \end{array} $ <p>R = Ph, Et</p>	X—CH ₂ CH=CH ₂	Cl ₂ Pd(PPh ₃) ₂	KOH	>95	[71]
M = Sn (Si)					
$ \begin{array}{c} \text{H} \\ \diagup \\ \text{C} = \text{C} \\ \diagdown \quad \diagup \\ \text{Ph} \quad \text{SiMe}_3 \\ \text{R}_3\text{Sn} \end{array} $ <p>$\left[\begin{array}{l} \text{R} = \text{Me} \\ \text{R} = \text{Bu} \end{array} \right]$</p>	Br—CH ₂ CH=CH ₂	PhCH ₂ Pd(PPh ₃) ₂ Cl		51 75	[70]
$ \begin{array}{c} \text{H} \\ \diagup \\ \text{C} = \text{C} \\ \diagdown \quad \diagup \\ \text{Ph} \quad \text{SiMe}_3 \\ \text{Me}_3\text{Sn} \end{array} $	Br—CH ₂ CH=CH—Ph	PhCH ₂ Pd(PPh ₃) ₂ Cl		49	[70]
$ \begin{array}{c} \text{H} \\ \diagup \\ \text{C} = \text{C} \\ \diagdown \quad \diagup \\ \text{H} \quad \text{SiMe}_2\text{Bu-}t \\ \text{Me}_3\text{Sn} \end{array} $	Br—CH ₂ CH=CH ₂	PhCH ₂ Pd(PPh ₃) ₂ Cl		95	[72]
$ \begin{array}{c} \text{Me} \\ \diagup \\ \text{C} = \text{C} \\ \diagdown \quad \diagup \\ \text{Me} \quad \text{SiMe}_2\text{Bu-}t \\ \text{Me}_3\text{Sn} \end{array} $	Br—CH ₂ CH=CH ₂	PhCH ₂ Pd(PPh ₃) ₂ Cl		97	[72]



Scheme 22

In addition to the several examples mentioned above, the syntheses of the following natural products and related compounds via Pd-catalyzed allylation have been reported, and they are summarized in **Sect. III.2.18**: (*E*)-neomanoalide,^[76] vineomycinone B2 methyl ester,^[77] cephalosporin analogs,^[78] hennoxazole A,^[79] stypoldione,^[80] 6-keto-prostanoids,^[81] constanolactones A and B,^[82] lurlene,^[83] lurlenic acid,^[84] and lurlenol.^[84]

C. Pd-CATALYZED BENZYLATION

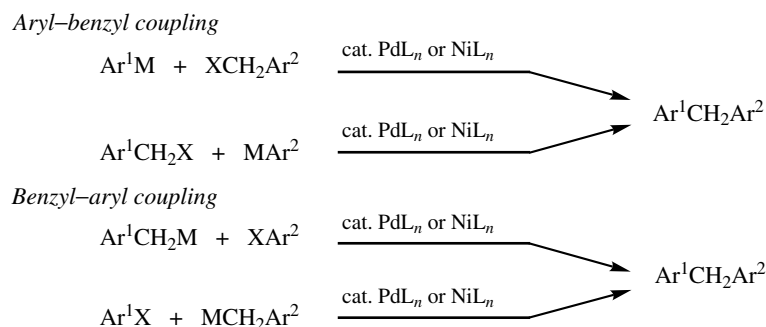
C.i. Background

Pd-catalyzed benzylation shares some fundamental features with Pd-catalyzed allylation. However, it is less complicated and generally more favorable than allylation, even though oxidative addition of benzylic electrophiles with Pd is kinetically less favorable than that of allylic electrophiles.^[85] Much of these differences between benzyl and allyl may be attributable to the fact that the β,γ π -bond in benzyl is part of an aromatic ring system and is hence less reactive toward Pd than that in allyl. Some fundamental features of the benzylic reagents in Pd-catalyzed cross-coupling are summarized in **Table 6**.

TABLE 6. Some Fundamental Features of the Benzylic Reagents in Pd-Catalyzed Cross-Coupling

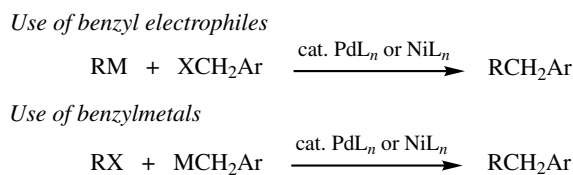
Feature	Benzylic Reagents (Versus Allylic Reagents)
Oxidative addition with Pd	<ul style="list-style-type: none"> • Generally favorable but kinetically less facile than that of allylic reagents
Stereochemistry	<ul style="list-style-type: none"> • Generally react with inversion of the α-C_{sp³} center (similar to the cases of allylic reagents) • No complication due to <i>E-Z</i> isomerization
Regiochemistry	<ul style="list-style-type: none"> • No complication due to allylic rearrangement
Dehydrometallation	<ul style="list-style-type: none"> • No complication due to β-dehydrometallation observable with ordinary alkyl reagents
Use of benzylic electrophiles	<ul style="list-style-type: none"> • Generally favorable and free of serious complications
Use of benzylic organometals	<ul style="list-style-type: none"> • Generation of benzylzinc derivatives by direct metallation is often facile, high-yielding, free of serious complications, and generally more favorable than that with other metals, including Li, Mg, B, Al, Si, and Sn • Use of benzylic organometals is generally much more favorable than that of allylic organometals

The synthesis of any given diarylmethanes ($\text{Ar}^1\text{CH}_2\text{Ar}^2$) via Pd-catalyzed cross-coupling can, in principle, be achieved by any of the four transformations shown in **Scheme 23**. It should also be noted that the corresponding Ni-catalyzed reactions have been highly competitive in many cases and that they should be considered and compared with the Pd-catalyzed counterparts. Although Ni-catalyzed benzylation is not systematically surveyed and discussed here, some of the results are included for comparison.



Scheme 23

In the other Pd- or Ni-catalyzed benzylation reactions, the number of synthetic options is reduced to the two processes shown in **Scheme 24**. Moreover, one of the two options shown in **Scheme 24** is often not available. Thus, for example, cross-coupling between benzyl and alkyl groups should be achieved primarily by alkyl-benzyl coupling using benzyl electrophiles rather than benzyl-alkyl coupling. On the other hand, benzylation of acyl derivatives should generally be achieved by benzyl-acyl coupling using benzylmetals. Since the Pd-catalyzed benzylation of alkyl (**Sect. III.2.11**), acyl (**Sect. III.2.12.1**), and other proximally heterosubstituted organic groups (**Sects. III.2.12–III.2.15**) is to be discussed later in the sections indicated in parentheses, attention in this subsection is focused on the Pd-catalyzed benzylation of aryl and alkenyl derivatives.

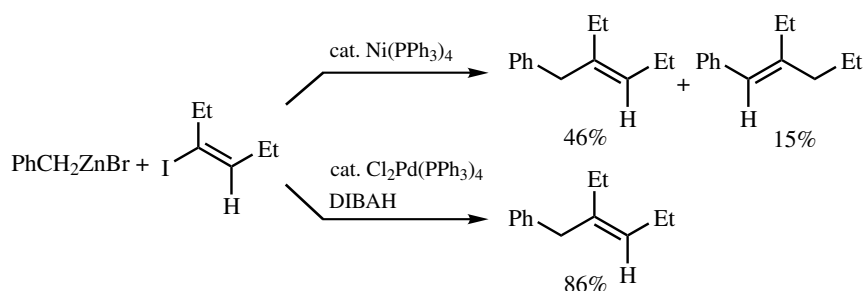


Scheme 24

Benzylic Electrophiles. Benzylic chlorides and bromides are widely and readily available. They are therefore the reagents of choice in most cases. Less readily available benzylic iodides and fluorides have hardly been used. More recently, the use of benzylsulfonium salts in Pd- or Ni-catalyzed cross-coupling has been reported.^{[86],[87]} These results are interesting in view of the fact that metal-mediated cleavage of the C—S bond has been shown to be an important biological process. It is not clear, however, in what cases this reaction would turn out to be the synthetic method of choice in preference to the corresponding reactions of benzyl chlorides and bromides.

Benzylmetals. As indicated in **Table 6**, benzylic organometals are readily, generally, and cleanly preparable by the treatment of benzylic bromides with Zn metal.^[88] This reaction is distinctly cleaner than the corresponding reaction with Mg, which tends to produce bibenzyls to varying extents, typically 5–15%, as by-products. Coupled with the superior reactivity of benzylzinc bromides in Pd- or Ni-catalyzed cross-coupling,^[2] Zn has proved to be by far the most favorable metal counteraction in cases where the use of benzylmetals is called for. Although Mg has also been used as part of the benzylmetal reagents since the original investigation of Pd- or Ni-catalyzed benzylation with benzylmetals,^[2] its reaction with benzyl halides is plagued with (i) competitive formation of bibenzyls, (ii) cross-homo scrambling most probably due to Mg–halogen exchange, (iii) lower reactivity in Pd- or Ni-catalyzed cross-coupling, and (iv) lower chemoselectivity in the conventional sense. As is well known, these difficulties are substantially magnified with Li and other alkali metals. On the other side of the spectrum, benzylmetals containing more electronegative metals including B, Al, Si, and Sn are less readily available than benzylzinc derivatives. They have, in fact, been rarely used. In a rare example of the use of a benzytin derivative, 3,4-dichlorobenzyltributylstannane was generated via the corresponding benzylzinc derivative only in 19% yield and used in the reaction with 2-methyl-3,4-dichlorophenyl triflate in the presence of Pd(PPh₃)₄, LiCl, and DMF to give the desired diarylmethane in 22% yield.^[89] Although no comparative data for this particular case were reported, it would be difficult to consider this procedure as a viable alternative. All in all, benzylzinc derivatives appear to be by far the most favorable benzylmetals in essentially all respects.

Catalysts. In the original study of benzylation, both Pd and Ni complexes were shown to be satisfactory catalysts.^{[2],[90]} In the synthesis of benzylated alkenes, however, the Ni-catalyzed reaction shown in **Scheme 25** provided the desired product in 46% yield along with a double bond isomer formed in 15% yield, while the corresponding Pd-catalyzed reaction cleanly produced the desired product in 86% yield.^[90]



Scheme 25

In contrast, the reaction of alkenylalanes with benzylic chlorides was reported to proceed faster and in higher yields in the presence of a Ni catalyst than in the presence of a Pd catalyst,^[91] as detailed later in the discussion of natural products synthesis. However, a more recent investigation has indicated that, aside from the rate of cross-coupling, the Pd-catalyzed reaction can proceed very satisfactorily in >90% yields in the same and closely related cases.^[92] It is therefore advisable to consider and compare Pd and Ni catalysts for a given case of benzylation.

C.ii. Scope of Pd-Catalyzed Benzylation

Some representative examples of Pd-catalyzed benzylation along with those of Ni-catalyzed benzylation are presented according to the following order mainly in the form of tables. In some cases, they are highlighted in schemes:

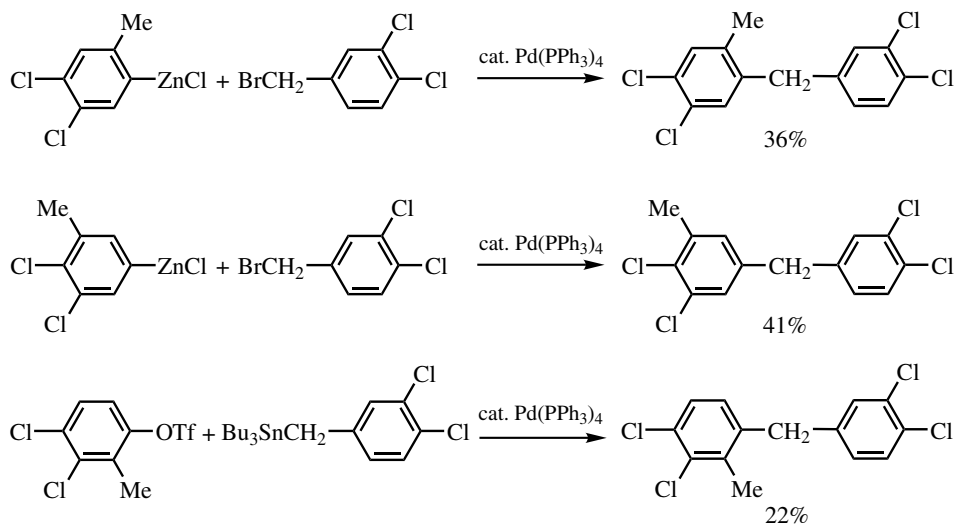
- (a) Benzyl–aryl coupling (**Table 7**)
- (b) Aryl–benzyl coupling (**Schemes 26 and 27**)
- (c) Benzyl–alkenyl coupling (**Table 8**)
- (d) Alkenyl–benzyl coupling (**Table 9**)

For the other types of Pd-catalyzed benzylation reactions, readers are referred to those sections mentioned in **Sect. C.i**.

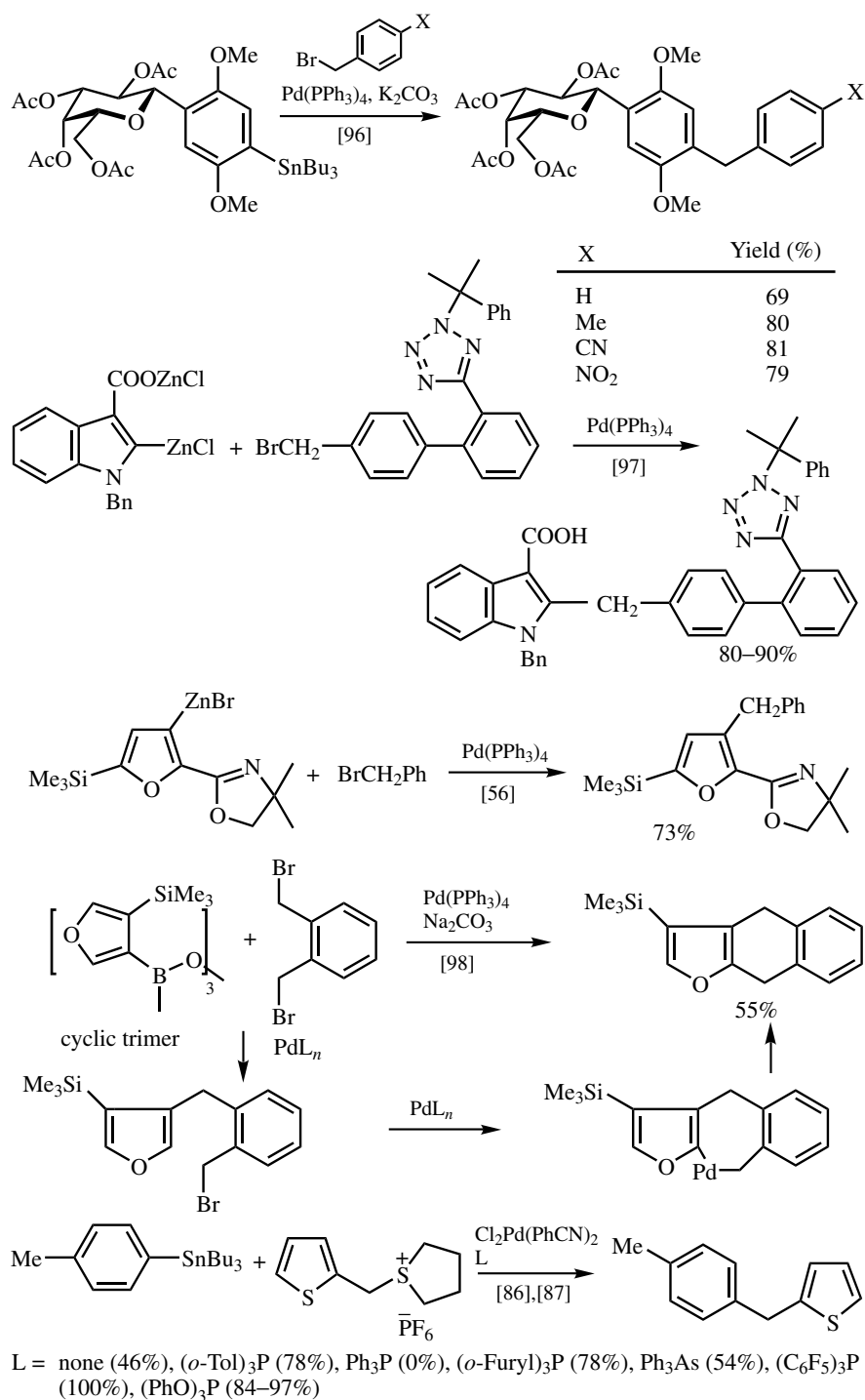
C.ii.a. Benzyl–Aryl Coupling. As indicated by the results shown in **Table 7**, Pd- or Ni-catalyzed benzyl–aryl coupling has been carried out by using benzylmetals containing Mg, Zn, and Sn. In those cases where these metals were compared (as in the highlighted examples), however, Zn was shown to be superior to either Mg or Sn. The level of chemoselectivity displayed by benzylzincs is noteworthy.

C.ii.b. Aryl–Benzyl Coupling. In contrast with the corresponding Pd- or Ni-catalyzed benzyl–aryl coupling, the range of satisfactory metals in the arylmetals is broader, and Zn, Sn, and B have been successfully used. The absence of comparative data does not permit their objective comparisons.

Specifically, diphenylmethane was prepared in >90% yield by the reaction of either Ph_4Sn or Ph_3SnMe with BrCH_2Ph in the presence of $\text{PhCH}_2\text{Pd}(\text{PPh}_3)_2\text{Cl}$.^[6] The synthesis of polychlorinated diarylmethanes shown in **Scheme 26** is noteworthy despite the modest product yields.^[89] Most of the other currently known examples of Pd-catalyzed aryl–benzyl coupling pertain to the synthesis of heteroarenes (**Scheme 27**).



Scheme 26



Scheme 27

TABLE 7. Pd-Catalyzed Benzyl–Aryl Coupling

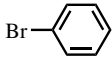
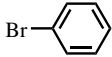
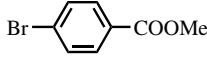
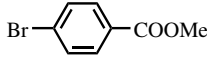
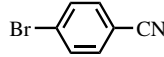
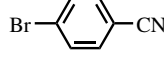
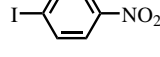
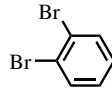
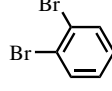
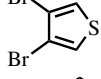
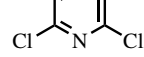
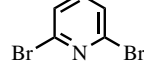
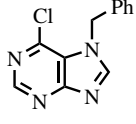
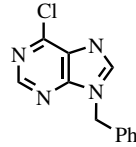
Benzylmetal	ArX	Catalyst	Other Conditions	Yield (%)	Reference
PhCH ₂ MgCl		Ni(acac) ₂	DIBAH	80	[2]
PhCH ₂ MgCl		Cl ₂ Pd(PPh ₃) ₂	DIBAH	86	[2]
PhCH ₂ MgCl		Ni(acac) ₂	PPh ₃ , DIBAH	12	[2]
PhCH ₂ ZnCl		Ni(acac) ₂	PPh ₃ , DIBAH	85	[2]
PhCH ₂ MgCl		Ni(acac) ₂	PPh ₃ , DIBAH	50	[2]
PhCH ₂ ZnCl		Ni(acac) ₂	PPh ₃ , DIBAH	92	[2]
PhCH ₂ ZnCl		Cl ₂ Pd(PPh ₃) ₂	DIBAH	88	[2]
				Recovered Starting Material	
				Mono	Di
PhCH ₂ MgCl		Pd(PPh ₃) ₄	79	20	0 [93]
PhCH ₂ ZnCl		Pd(PPh ₃) ₄	9	68	12 [93]
PhCH ₂ ZnCl		Pd(PPh ₃) ₄	20	52	6 [93]
PhCH ₂ ZnCl		Pd(PPh ₃) ₄	15	56	13 [93]
PhCH ₂ ZnCl		Pd(PPh ₃) ₄	13	60	15 [93]
PhCH ₂ ZnBr		Pd(PPh ₃) ₄	THF	82	[94]
PhCH ₂ SnBu ₃		Cl ₂ Pd(PPh ₃) ₂	DMF	62	[94]
PhCH ₂ ZnBr		Pd(PPh ₃) ₄	THF	91	[94]
PhCH ₂ SnBu ₃		Cl ₂ Pd(PPh ₃) ₂	DMF	48	[94]

TABLE 7. (Continued)

Benzylmetal	ArX	Catalyst	Other Conditions	Yield (%)	Reference
		Pd(dba) ₂	TFP	82–93	[95]
	X = COOEt, NO ₂ , OAc, Cl				
		Pd(dba) ₂	TFP	74–85	[95]
	X = COOEt, NO ₂ , OTf, Cl				
		Pd(dba) ₂	TFP	90–92	[95]
	X = COOEt, NO ₂				
		Pd(dba) ₂	TFP	84	[95]
		Pd(dba) ₂	TFP	79–82	[95]
	X = OMe, Cl				

C.ii.c. Benzyl–Alkenyl Coupling. As in the cases of benzyl–aryl coupling, benzylzincs appear to be the reagents of choice, although comparative data are virtually absent. Some representative results are shown in **Table 8**.

C.ii.d. Alkenyl–Benzyl Coupling. Alkenylmetals containing B, Al, and Sn have been employed in Pd- or Ni-catalyzed alkenyl–benzyl coupling. Somewhat surprisingly, Zn does not appear to have been used in this reaction. Puzzlingly, even an inhibitory effect of ZnCl₂ in the reaction of alkenylalanes with benzyl halides has been observed^[90] (**Table 9**). The overall usefulness of Zn in alkenyl–benzyl coupling is therefore yet to be clarified. An unsettled issue of Pd versus Ni in alkenyl–benzyl coupling was discussed in **Sect. C.i**.

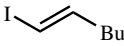
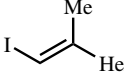
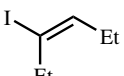
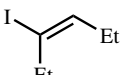
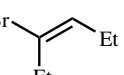
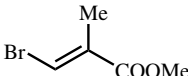
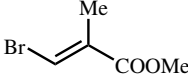
An interesting, if rather expensive, protocol for stereoselective syntheses of alkenylmetals containing two substituents is to achieve *syn*-metallometallation of alkynes involving B, Si, and Sn (**Scheme 28**).

C.ii.e. Pd-Catalyzed Asymmetric Benzylation. This topic has been investigated extensively by Hayashi et al.^{[99]–[101]} and Cross et al.^[102] For this topic, however, readers are referred to **Sect. III.2.16**.

C.iii. Applications to Natural Products Synthesis

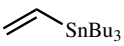
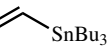
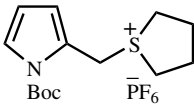
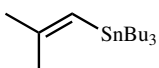
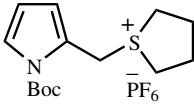
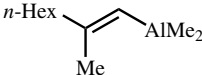
Only a small number of examples of the application of Pd- or Ni-catalyzed benzylation to the synthesis of natural products are known. Nonetheless, the examples shown in **Scheme 29** clearly point to the potentially high synthetic utility of Pd- or Ni-catalyzed benzylation.

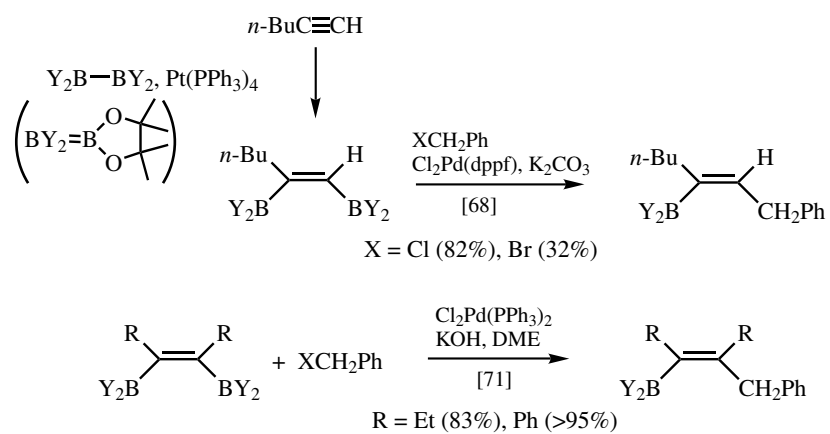
TABLE 8. Pd- or Ni-Catalyzed Benzyl-Alkenyl Coupling

Benzylmetal	Alkenyl Halides	Catalyst	Other Conditions	Yield (%)	References
PhCH ₂ ZnBr		Ni(PPh ₃) ₄		73	[90]
PhCH ₂ ZnBr		Pd(PPh ₃) ₄		78	[90]
PhCH ₂ ZnBr		Ni(PPh ₃) ₄		46 ^a	[90]
PhCH ₂ ZnBr		Cl ₂ Pd(PPh ₃) ₂	DIBAH	86	[90]
PhCH ₂ ZnBr		Cl ₂ Pd(PPh ₃) ₂	DIBAH	76	[90]
PhCH ₂ ZnBr		Ni(PPh ₃) ₄		65	[90]
PhCH ₂ ZnBr		Cl ₂ Pd(PPh ₃) ₂	DIBAH	75	[90]

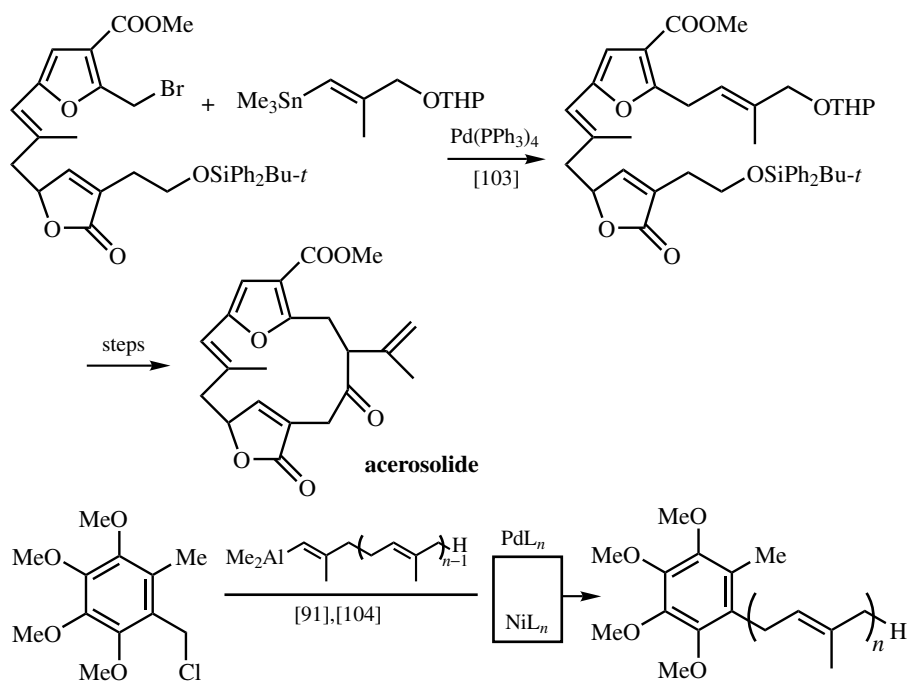
^a A styrene derivative was formed as a by-product in 15% yield (cf. **Scheme 25**).

TABLE 9. Pd- or Ni-Catalyzed Alkenyl-Benzyl Coupling

Alkenylmetal	Benzyl Halide	Catalyst	Other Conditions	Yield (%)	References
	BrCH ₂ Ph	PhCH ₂ Pd(PPh ₃) ₂ Cl		100	[6]
Ph- 		Pd ₂ (dba) ₃ ·CHCl ₃	P(OPh) ₃ CuI	97	[87]
		Pd ₂ (dba) ₃ ·CHCl ₃	P(OPh) ₃ CuI	78	[87]
	ClCH ₂ Ph	Pd(PPh ₃) ₄		92	[90]
	BrCH ₂ Ph	Pd(PPh ₃) ₄		93	[90]
	BrCH ₂ Ph	Pd(PPh ₃) ₄	10% ZnCl ₂	70	[90]
	BrCH ₂ Ph	Pd(PPh ₃) ₄	100% ZnCl ₂	45	[90]



Scheme 28

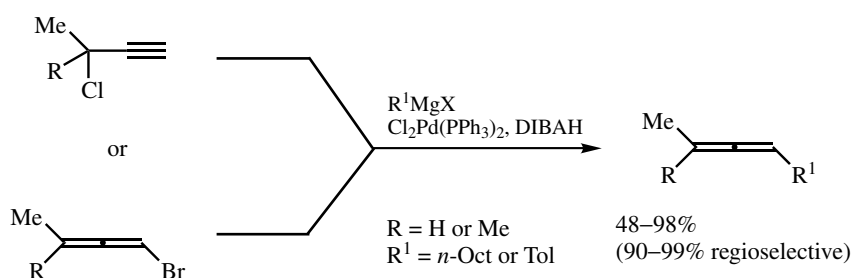


n	Catalyst	Temperature (°C)	Time (h)	Yield (%)
5	Pd(PPh ₃) ₄	r.t.	4	<3
5	Pd(PPh ₃) ₄	THF reflux	12	68
5	Cl ₂ Ni(PPh ₃) ₂	r.t.	0.25	87
	DIBAH	—		
3	Cl ₂ Ni(PPh ₃) ₂	r.t.	0.25	89
	DIBAH			

Scheme 29

D. Pd-CATALYZED ALLENYLATION AND PROPARGYLATION

Pd-catalyzed allenylation and propargylation of organometals has been much less extensively investigated than the corresponding allylation. The first report on the Pd-catalyzed reaction of organometals with propargylic electrophiles is most probably a paper reported in 1980 by Jeffery-Luong and Linstumelle on the reaction of *n*-octylmagnesium chloride and tolylmagnesium bromide with propargyl and allenyl halides in the presence of a Pd catalyst generated *in situ* from PdCl₂, PPh₃ (2 equiv), and DIBAH^[3] (Scheme 30). Regardless of whether propargylic chlorides or allenyl bromides were used, allenes were produced to the extent of 99% except in a couple of cases where the regioselectivity was 90–93%.



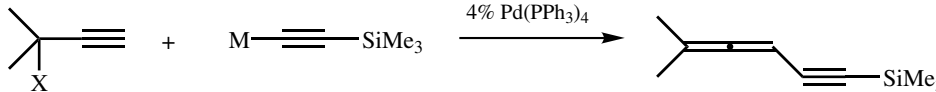
Scheme 30

This was soon followed by a series of detailed studies by Vermeer and co-workers on similar reactions of organometals containing Li, Mg, Zn, Cu, and Ag.^{[26],[105]–[108]} A systematic screening of metal counteranions summarized in **Tables 10** and **11**^[106] indicate the following. (i) Both allenyl and propargyl electrophiles selectively produce allenes rather than alkynes. (ii) In the reaction of allenyl electrophiles, only the bromide, but not the acetate, gives satisfactory results. In sharp contrast, a variety of propargylic electrophiles, such as those containing Br, OAc, OSOMe, and OPO(OEt)₂, can provide the desired allenyne in excellent yields. (iii) Alkynylmetals containing Mg, Zn, Cu, and Ag, but not Li, can produce the desired allenyne in excellent yields. However, Zn along with (CuLi)_{1/2} has consistently led to the highest product yields except with the allenyl acetate. Although somewhat inferior, Mg and Ag can lead to very satisfactory results in some cases. However, the results obtained with the Li reagents are uniformly poor.

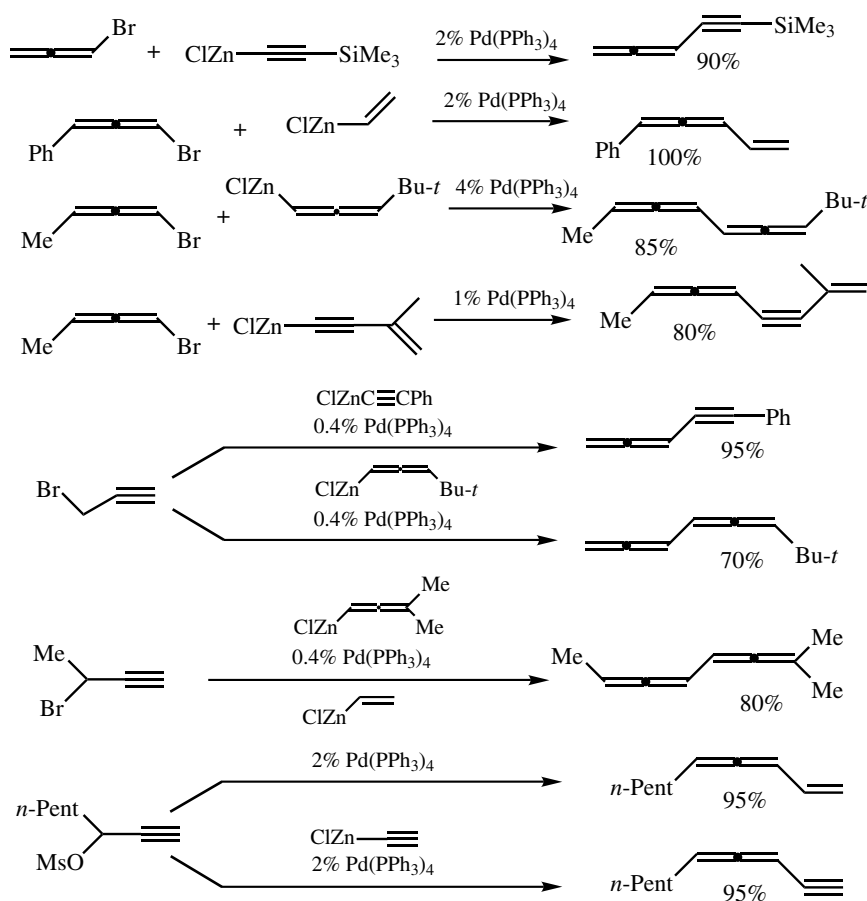
TABLE 10. Pd-Catalyzed Reaction of 3-Methyl-1,2-butadienyl Electrophiles with Trimethylsilylalkynylmetals

Product Yield (%)						
X	M = Li	M = MgCl	M = ZnCl	M = Cu	M = (CuLi) _{1/2}	M = Ag
Br	3	80	100	33	100	23
OAc	0	34	7	4	—	—

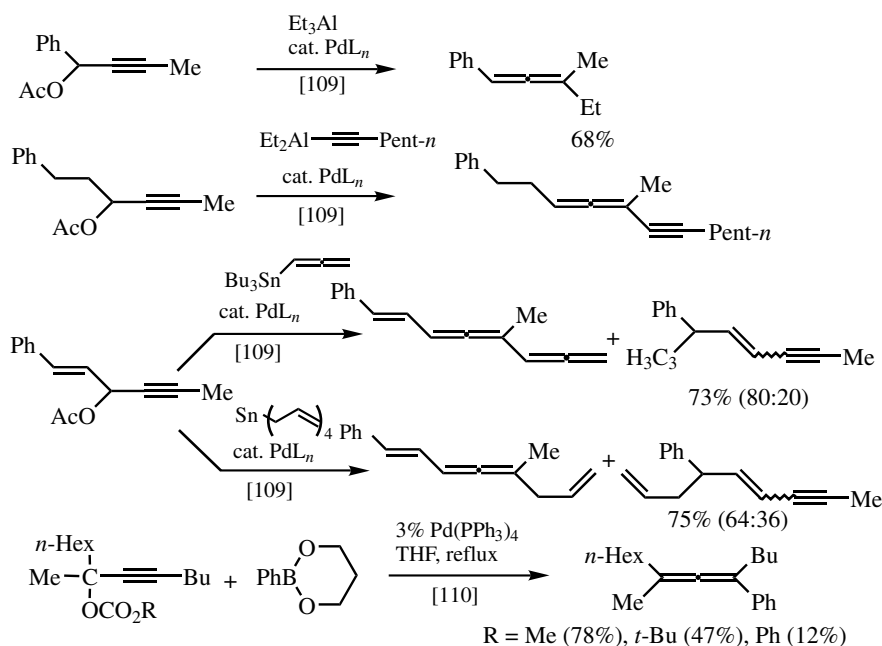
TABLE 11. Pd-Catalyzed Reaction of 2-Methyl-3-butyn-2-yl Electrophiles with Trimethylsilylethyne

					
Product Yield (%)					
X	M = Li	M = MgCl	M = ZnCl	M = Cu	M = Ag
Br	0	70	98	—	98
OAc	0	75	98	98	86
OSOMe	—	90	98	98	<5
OPO(OEt) ₂	20	98	98	—	80

The scope of these reactions has been further probed with various organozincs, and some representative results are shown in **Scheme 31**.^[106]

**Scheme 31**

Later studies have indicated that, in addition to Zn along with Cu, Mg, and Ag discussed above, Al,^[109] Sn,^[109] and B^[110] are effective in some Pd-catalyzed allenylation–propargylation reactions (**Scheme 32**). So, essentially all of the nine or ten metals used in Pd-catalyzed cross-coupling with the exception of Si and Zr may be used in this reaction. Among them, organozincs have been most extensively and successfully used, and they appear to be the reagents of choice in a general sense. As in many other Pd-catalyzed cross-coupling reactions, however, the selection of the optimal metal counteranion must take into consideration various other factors and parameters as well in each given case.

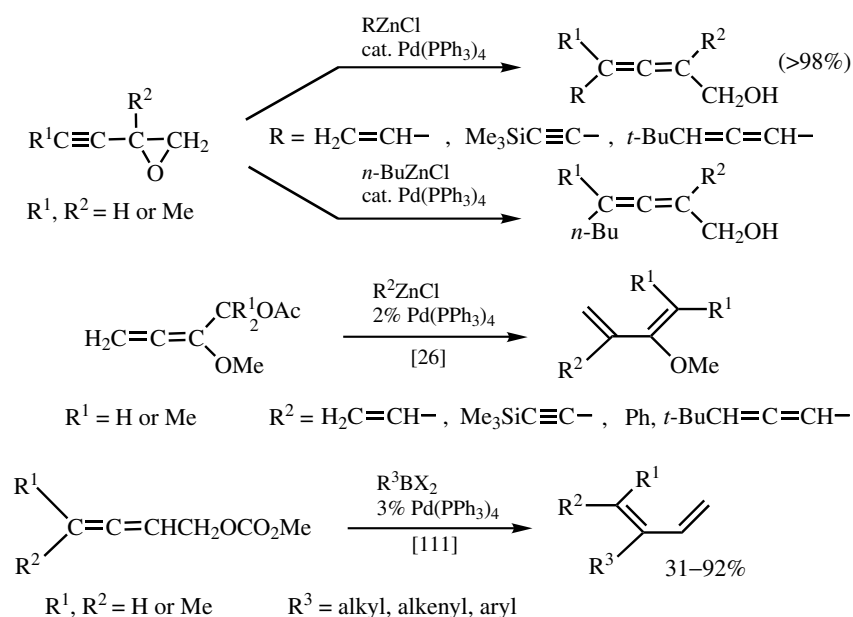


Scheme 32

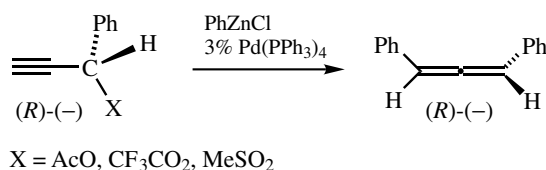
Interesting variations of potential synthetic utility include the use of α -acetylenic epoxides^[106] and α -allenic alcohol derivatives.^{[26],[111]} The latter, which can be obtained from the former, have been converted to conjugated dienes for use in the Diels–Alder and other reactions (**Scheme 33**).

As might be expected in analogy with Pd-catalyzed allylation, the overall inversion of configuration at the propargylic carbon center has been shown to be predominant^{[108],[112]} (**Scheme 34**). This is in accordance with a sequence consisting of oxidative addition with inversion, transmetalation, and reductive elimination with retention.

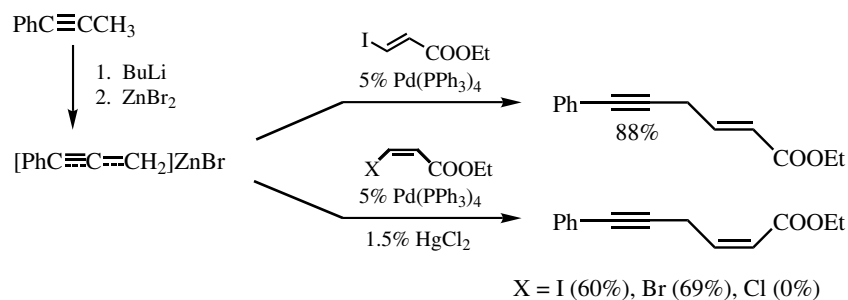
As indicated by the results shown in **Schemes 31–34** and **Tables 10** and **11**, Pd-catalyzed allenylation has been achieved mostly by using allenyl and propargyl electrophiles. Because of the predominant or even exclusive formation of allenes in these reactions, incorporation of a propargyl group has rarely been observed in these reactions. Only within the past few years has the use of allenyl- or propargylmetals been investigated, and a propargyl moiety has been incorporated in the products of Pd-catalyzed allenyl(propargyl)–alkenyl coupling (**Scheme 35**).^[113] This reaction clearly deserves further investigation.



Scheme 33



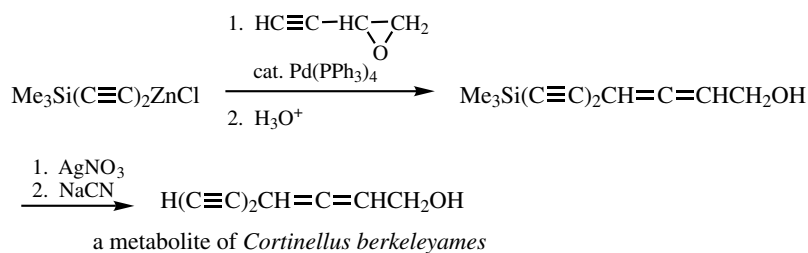
Scheme 34



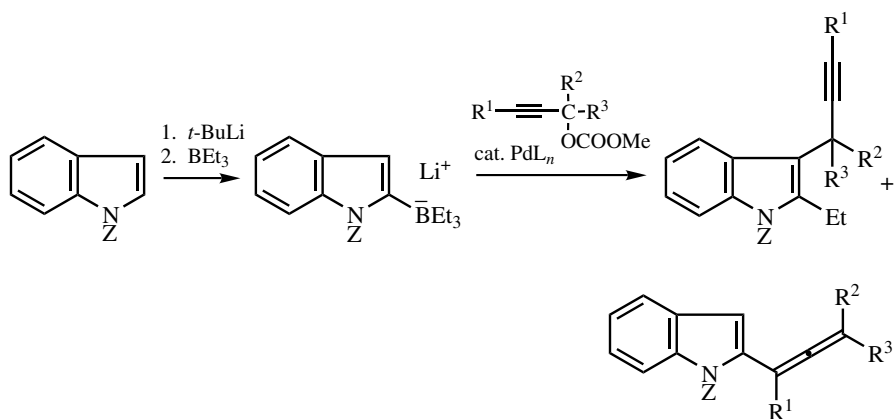
Scheme 35

Pd-catalyzed allenylation–propargylation has hardly been applied to natural products synthesis. To date, the synthesis of (\pm)-2,3-octadiene-5,7-diyn-1-ol, a metabolite from fungus *Cortinellus berkeleyanus* shown in **Scheme 36**,^[106] may well be the only example.

Although the products are not natural, the synthesis of indole derivatives shown in **Scheme 37** is noteworthy.^{[114]–[116]} Interestingly, α -allenylation and β -propargylation with concomitant α -ethylation have been observed. The ethyl group is derived from Et₃B used as a boron reagent.



Scheme 36



Scheme 37

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