

III.2.6 Palladium-Catalyzed Alkenyl–Aryl, Aryl–Alkenyl, and Alkenyl–Alkenyl Coupling Reactions

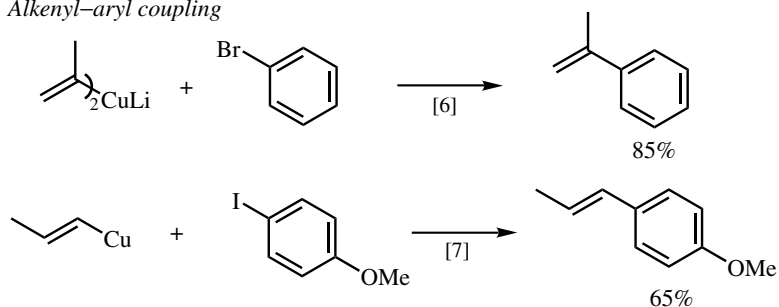
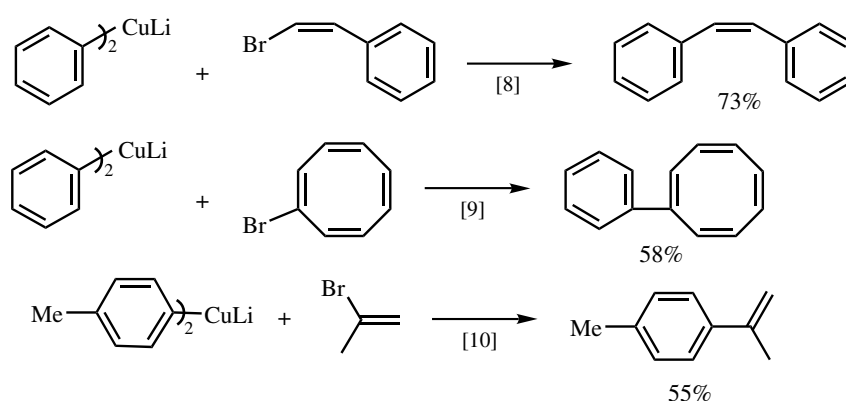
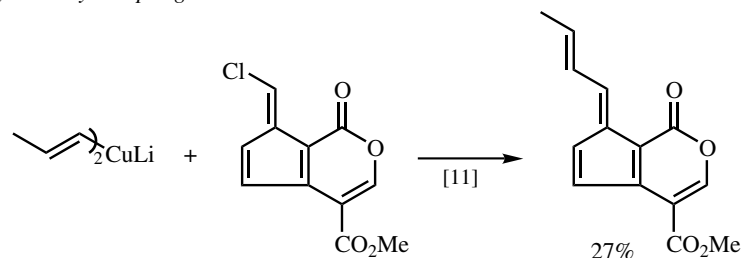
SHOUQUAN HUO and EI-ICHI NEGISHI

A. INTRODUCTION

The synthesis of alkene-substituted arenes by cross-coupling can, in principle, be achieved either by the reaction of alkenylmetals with aryl halides and related electrophiles or by that of arylmetals with alkenyl electrophiles. For the sake of simplicity, the former reaction is termed the *alkenyl–aryl coupling*, while the latter is termed the *aryl–alkenyl coupling* in this Handbook. Similar terms may be devised by linking the carbon groups of the organometal and organic electrophile with a dash in this order.

There are four classes of the C_{sp^2} – C_{sp^2} coupling reactions involving alkenyl and/or aryl derivatives. Of the four, the aryl–aryl coupling is discussed in **Sect. III.2.5**. In this section, the other three combinations of the C_{sp^2} – C_{sp^2} coupling reactions, that is, alkenyl–aryl, aryl–alkenyl, and alkenyl–alkenyl couplings, are discussed in the order indicated above.

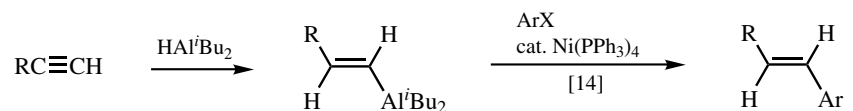
The development of general and satisfactory methods for the C_{sp^2} – C_{sp^2} coupling is of relatively recent origin. This may, in part, be attributable to the general inability of Grignard reagents and organolithiums to react with alkenyl and aryl electrophiles for Carbon–Carbon bond formation. Although the reaction of Grignard reagents with organic halides was shown to be catalyzed by various late transition metal compounds (the Kharasch reaction) in the 1950s,^[1] it was not until the early 1970s that the applicability of this catalytic method was extended to the cross-coupling involving alkenyl and aryl halides catalyzed by Ag ,^{[2],[3]} Fe ,^[4] and other late transition metal complexes. However, the feasibility of achieving the C_{sp^2} – C_{sp^2} coupling by the Kharasch reaction was virtually never demonstrated in these early investigations. In the meantime, the stoichiometric reaction of organocoppers with organic halides was extensively developed since the 1960s as a generally applicable cross-coupling method that is applicable to those cases involving alkenyl and aryl electrophiles. Even so, only several examples of the Cu-promoted C_{sp^2} – C_{sp^2} coupling summarized in **Scheme 1** can be found in an extensive and seemingly thorough review published in 1975.^[5] Thus, despite their synthetic potential, they did not lead to the widespread use of the C_{sp^2} – C_{sp^2} coupling.

Alkenyl–aryl coupling*Aryl–alkenyl coupling**Alkenyl–alkenyl coupling*

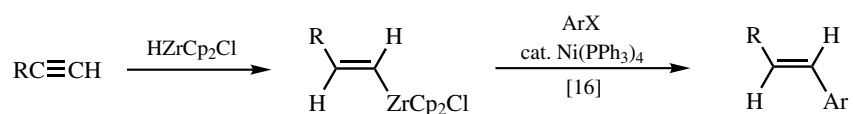
Scheme 1

A few critical findings reported in the 1970s laid the foundation for the current widespread use of the Ni- or Pd-catalyzed methods for the $\text{C}_{\text{sp}^2}\text{-C}_{\text{sp}^2}$ coupling. Following the discovery of the cross-coupling reaction of the Grignard reagents with alkenyl and aryl halides catalyzed by Ni–phosphine complexes in the early 1970s,^{[12],[13]} the feasibility of developing one-pot hydrometallation (or carbometallation)–cross-coupling tandem processes involving Al and Zr and a few notable advantages of Pd catalysts over Ni catalysts used in conjunction with Mg, Zn, Al, Zr, and others were demonstrated in the mid 1970s.^{[14]–[18]} In the meantime, Pd-catalyzed reaction of Grignard reagents was also reported.^{[19],[20]} The use of homogeneous Ni–phosphine and Pd–phosphine complexes appears to be the single most critical factor distinguishing this new methodology from the previous ones. Some prototypical examples of Ni- or Pd-catalyzed $\text{C}_{\text{sp}^2}\text{-C}_{\text{sp}^2}$ coupling reactions reported during this period are shown in **Schemes 2–4**.

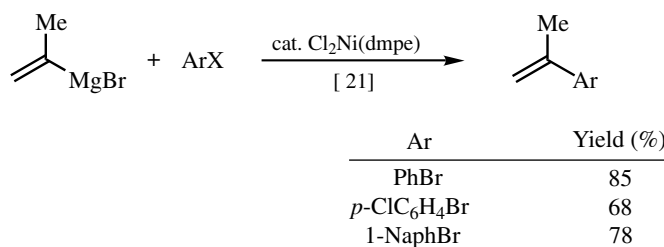
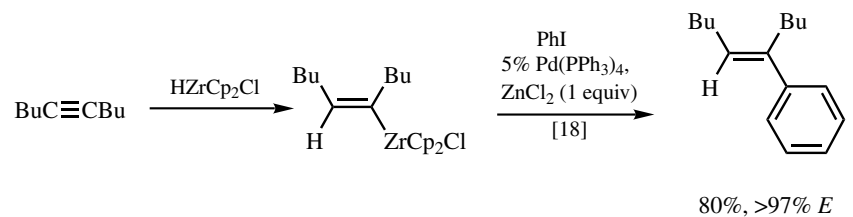
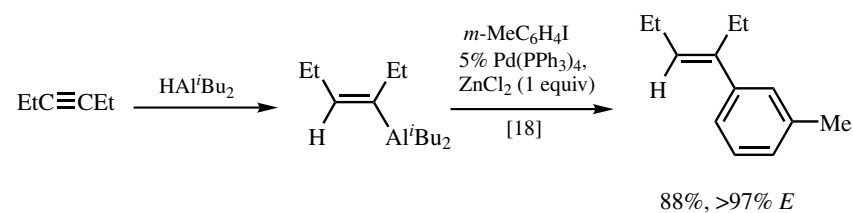
Alkenyl-aryl coupling



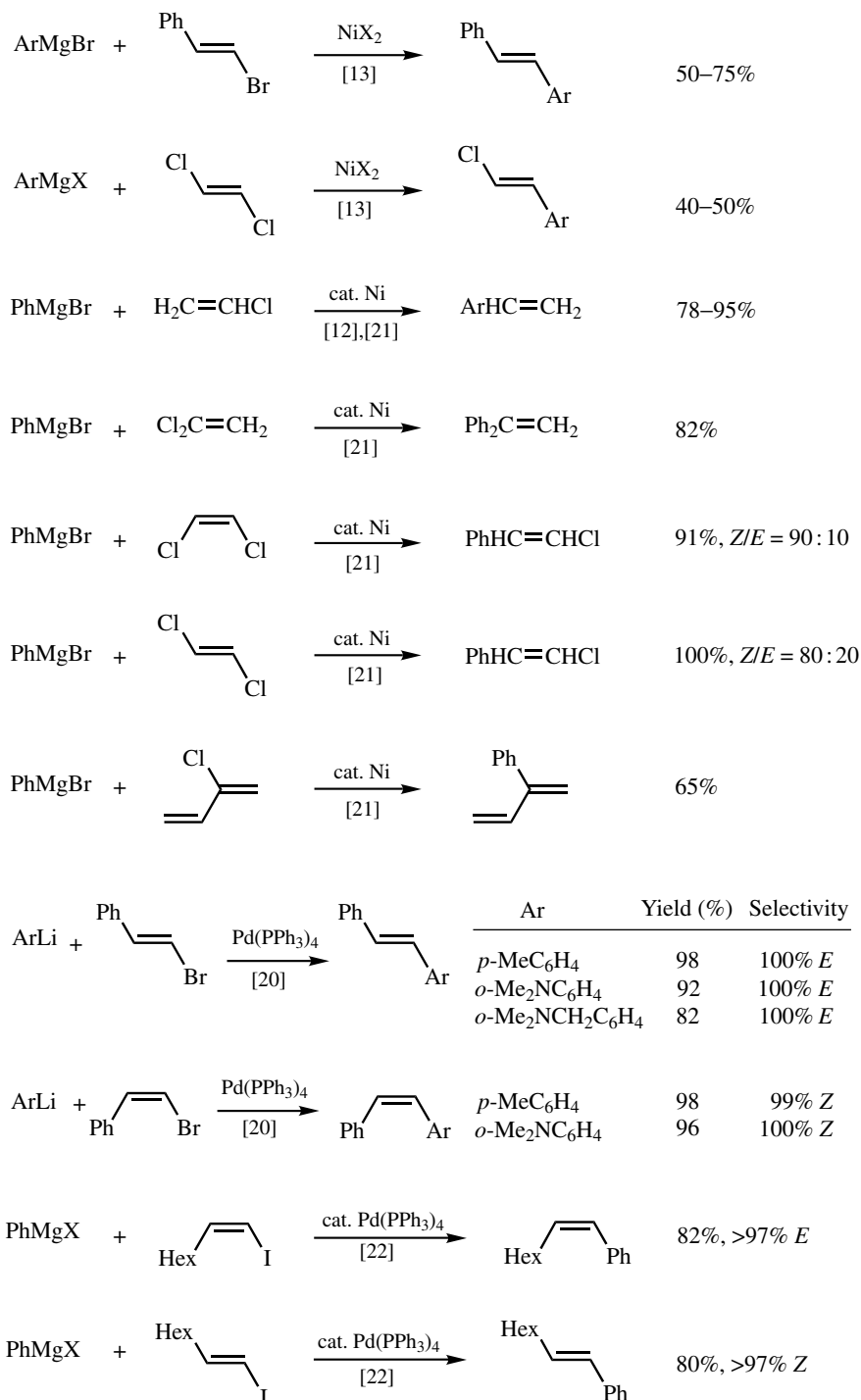
R	ArX	Yields (%)
<i>n</i> -Bu	PhBr	85
<i>n</i> -Bu	1-NaphBr	93
<i>c</i> -Hex	<i>p</i> -MeC ₆ H ₄ Br	75



R	ArX	Yields (%)
<i>n</i> -Pent	PhI	96
<i>n</i> -Pent	1-NaphBr	70
EtO	PhI	99
<i>n</i> -Bu	<i>p</i> -MeOC ₆ H ₄ I	80
<i>n</i> -Bu	<i>p</i> -MeO ₂ CC ₆ H ₄ Br	92



Scheme 2

Aryl-alkenyl coupling

Scheme 3

Reaction 15: $R^1C\equiv CH$ reacts with HAi^tBu_2 to form $R^1CH=CHAl^tBu_2$. This intermediate then reacts with $I-CH=CH-R^2$ (5% Cat., [15]) to yield $R^1CH=CH-CH=CH-R^2$. Catalysts: $Ni(PPh_3)_4$ (70% yield, 95% *E,E*), $Pd(PPh_3)_4$ (74% yield, >99% *E,E*). $R^1 = n-C_5H_{11}$, $R^2 = n-C_4H_9$.

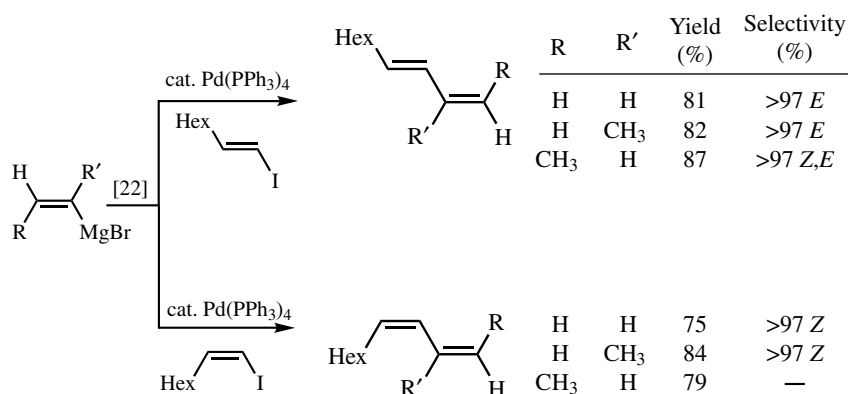
Reaction 16: $R^1C\equiv CH$ reacts with $HZrCp_2Cl$ to form $R^1CH=CHZrCp_2Cl$. This intermediate then reacts with $I-CH=CH-R^2$ (5% $Pd(PPh_3)_4$, [16]) to yield $R^1CH=CH-CH=CH-R^2$ (91%, >97% *E,E*). $R^1 = n-C_5H_{11}$, $R^2 = n-C_4H_9$.

Reaction 18: $R^1C\equiv CH$ reacts with Me_3Al and cat. Cp_2ZrCl_2 to form $R^1CH=CHAlMe_2$. This intermediate then reacts with $Br-CH=CH_2$ (5% $Pd(PPh_3)_4$, $ZnCl_2$ (1 equiv), [18]) to yield $R^1CH=CH-CH=CH_2$ (73%, >99% *E*). Alternatively, it reacts with $I-CH=CH-R^2$ (5% $Cl_2Pd(PPh_3)_2$ + DIBAH, $ZnCl_2$ (1 equiv), [18]) to yield $R^1CH=CH-CH=CH-R^2$ (65%, >97% *E,E*).

Reaction 19, 20: $CH_2=CH-MgBr$ + $Ph-CH=CH-Br$ $\xrightarrow{Pd(PPh_3)_4}$ $Ph-CH=CH-CH=CH_2$ (81%, 99% *E*, [19, 20]).

Reaction 21: $CH_3-CH=CH-MgBr$ + $CH_3-CH=CH-Br$ $\xrightarrow{cat. Ni}$ $CH_3-CH=CH-CH=CH_2$ (79%, [21]).

Scheme 4 (Continued)

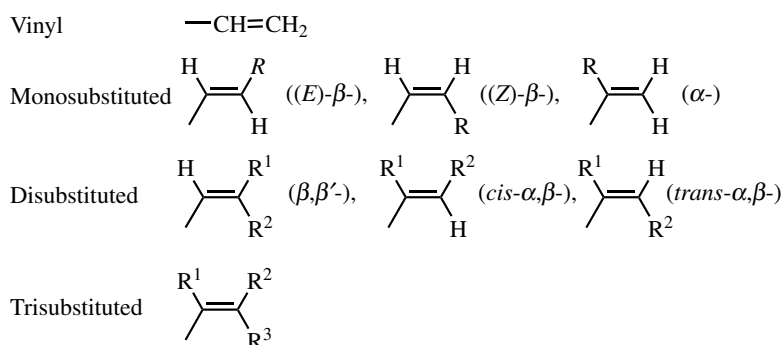


Scheme 4 (Continued)

Over the past two decades, Pd- or Ni-catalyzed cross-coupling, especially Pd-catalyzed version, has become one of the most common methods (possibly the most common method) for highly selective synthesis of arylated alkenes, conjugated dienes, conjugated enynes (**Sect. III.2.8**), and other related alkene derivatives. In addition to Mg, Zn, Al, and Zr used since the 1970s,^[23] several other metals including B,^[24] Si,^[25] Sn,^{[26],[27]} and Cu^{[28]–[33]} have been extensively employed since around 1980.

In the following three subsections, the alkenyl–aryl (**Sect. B**), aryl–alkenyl (**Sect. C**), and alkenyl–alkenyl (**Sect. D**) coupling reactions catalyzed by Pd complexes are discussed primarily in the forms of schemes and tables. Some related Ni-catalyzed reactions are also presented, as deemed appropriate.

Alkenylmetals and alkenyl electrophiles may be classified into eight structural types according to the number and positions of the substituents relative to the metal or the electrophilic leaving group in the alkenyl group (**Scheme 5**). The entries in the tables are arranged according to the alkenyl structural types in the order shown in **Scheme 5** except in **Tables 2** and **8**, which are arranged according to the aryl structural types, and their priority order is as detailed in **Sect. III.2.5**. Within the same structural type, the alkenyl groups are listed in the following order of the substituent type: alkyl, alkenyl, aryl, and alkynyl, and the carbon numbers are used as the tie breakers. Heteroatom



Scheme 5

group-containing alkenyl groups are listed in increasing order of priority determined by the Cahn–Ingold–Prelog rule. Alkenylmetals containing the same alkenyl group are finally arranged according to the group numbers of the metal counterions, that is, Li, Mg, Zn, B, Al, Si, Sn, Cu, Zr, and so on, while the alkenyl electrophiles containing the same alkenyl group are arranged according to decreasing number of the group numbers of alkenyl-bound atoms, that is, halogens (I, Br, Cl, F), O, S, N, P, and so on.

B. ALKENYL-ARYL COUPLING

B.i. Alkenyl-Aryl Coupling versus Aryl-Alkenyl Coupling

Alkenylated arenes or arylated alkenes by cross-coupling can, in principle, be prepared via either alkenyl-aryl or aryl-alkenyl coupling. Although Pd- or Ni-catalyzed cross-coupling is well-suited for either of these two categories, one may be more satisfactory than the other in a given case, and the relative merits and demerits depend on a number of factors, of which the substitution pattern and other structural parameters of the alkenyl group are especially significant.

More specifically, many of the alkenylmetals and alkenyl electrophiles can be prepared by appropriate addition reactions, such as hydrometallation, carbometallation, and heterometallation, of alkynes. In cases where such addition reactions generate the desired alkenylmetals, one-pot procedures for the alkenyl-aryl coupling can be devised, as indicated by **Protocol I** in **Scheme 6**, and such procedures are usually preferred to the others. On the other hand, the required alkenyl halides and related electrophiles, such as vinyl bromide and 2-iodo-1-alkenes, may be more readily accessible than the corresponding alkenylmetals. In such cases, the aryl-alkenyl coupling represented by **Protocol II** in **Scheme 6** may be a viable option. In yet other cases, the required alkenyl electrophiles and alkenylmetals may have to be generated from alkynes via addition-trapping by electrophiles and from alkenyl electrophiles via metallation (**Protocol III**) or metallation-transmetallation (**Protocol IV**), respectively, for observing the optimal results. It is, however, clear that, in cases where all four protocols, that is, **Protocols I–IV**, are at least reasonably satisfactory, the general order of preferences should be (i) **Protocol I**, (ii) **Protocol II**, (iii) **Protocol III**, and (iv) **Protocol IV**.

Although less critical, the accessibility of aryl electrophiles and arylmetals is also an important factor. The majority of arylmetals containing relatively electropositive metals, such as Li and Mg as well as Zn in some cases, are prepared by oxidative metallation of aryl halides, while those containing relatively electronegative metals, such as B, Al, Si, Cu, and Sn, as well as Zn, are most commonly prepared by transmetallation of aryllithiums and arylmagnesium halides. These facts indicate that aryl halides are generally more readily available than arylmetals, even though directed metallation^[34] of arenes and possibly some other methods would make arylmetals more readily available than aryl halides. Overall, the alkenyl-aryl coupling by the reaction of alkenylmetals generated *in situ* by suitable addition reactions with aryl halides and sulfonates accessible via phenols^[35] (**Protocol I**) would be the most efficient route to arylated alkenes in the absence of overriding difficulties. Indeed, the alkenyl-aryl coupling has been much more frequently employed than the aryl-alkenyl coupling for the synthesis of arylated alkenes.

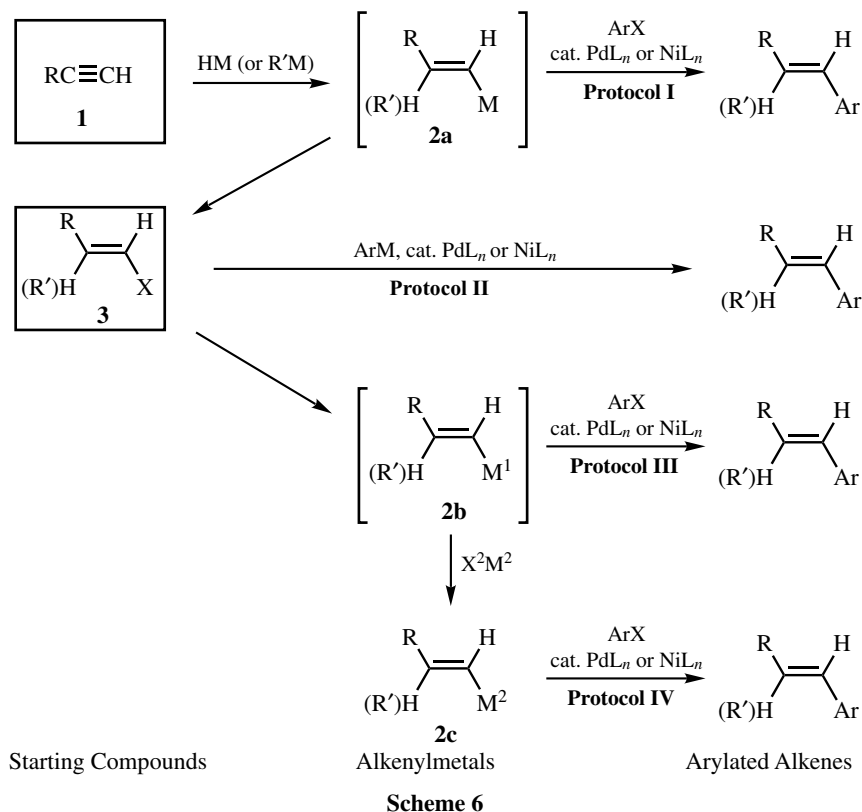


Table 1 summarizes some of the most satisfactory routes to the alkenyl reagents of various classes and the preferred cross-coupling protocols.

B.ii. Alkenyl–Aryl Coupling with Vinylmetals

Since both vinyl halides and various aryl electrophiles are commercially available, either of them may be metallated to generate organometallic partners for cross-coupling. Indeed, various types of vinylmetals containing Mg, B, Zn, Al, Si, and Sn have been employed for converting aryl electrophiles into styrene derivatives. **Table 2** summarizes some of the currently viable results of cross-coupling with vinylmetals. The results with different metals are comparably favorable. In cases where the required aryl electrophiles are readily available as aryl sulfonates from phenols, the alkenyl–aryl coupling is generally preferred over aryl–alkenyl coupling. Even sterically hindered aryl sulfonates can readily be vinylated as indicated by the results shown in **Scheme 7**.^{[61],[62]}

In general, critical comparisons among various metal counteractions is lacking. Since many of them are comparably effective, vinylmagnesium halides that can readily be obtained as the first-generation vinylmetals should be considered first. Only if it is unsatisfactory for one reason or another, should one then consider other metals such as Zn, Si, and Sn. For yet unclear reasons, vinylboron derivatives have rarely been used.

TABLE 1. Some Preferred Alkenyl Reagents for the Synthesis of Arylated Alkenes via Pd- or Ni-Catalyzed Cross-Coupling and Preferred Cross-Coupling Protocols















Structural Type of the Alkenyl Group	Generally Preferred Reagents	Generally Preferred Route	Generally Preferred Cross-Coupling Protocol
$\text{H}_2\text{C}=\text{CH}-$ (Vinyl)	$\text{H}_2\text{C}=\text{CHX}$ $\text{X} = \text{Br, I, or Cl}$	Commercially available	Aryl-alkenyl (Protocol II) and alkenyl-aryl (Protocol I)
 (<i>E</i> - β -mono)	 ($\text{M} = \text{Zn, B, Al, Si, Zr}$)	<i>syn</i> -Hydrometallation	Alkenyl-aryl (Protocol I)
 (<i>Z</i> - β -mono)	 ($\text{M} = \text{B, Cu}$)	Hydroboration–hydride migration ^{[36],[37]} Carbocupration ^[38]	Alkenyl-aryl (Protocol I)
 (α -mono)	 ($\text{X} = \text{Br, I, OTf, Cl}$)	Markovnikov addition of HX ³⁹ Sulfonation of enolates ^[38]	Aryl-alkenyl (Protocol II) and alkenyl-aryl (Protocol I)
 (<i>E</i> - or <i>Z</i> - α,β -di)		Hydrometallation	Alkenyl-aryl (Protocol I)
 (β,β -di)	 ($\text{M} = \text{Al, Zn, Cu}$)	Carbometallation ^{[38],[40]–[42]}	Alkenyl-aryl (Protocol I)
 (<i>trans</i> - α,β -di)	 ($\text{M} = \text{B}$)	Hydroboration–C-Migration ^{[43],[44]}	Alkenyl-aryl (Protocol I)
	 ($\text{M} = \text{Zn, Al}$)	Carbometallation ^{[38],[40]–[42]}	Alkenyl-aryl (Protocol I)

TABLE 2. Pd-Catalyzed Cross-Coupling of Vinylmetals with Aryl Electrophiles ^a


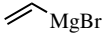

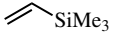

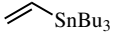

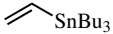
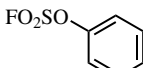
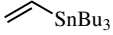
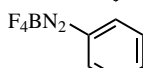
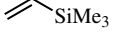
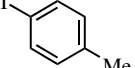

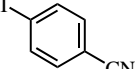
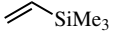
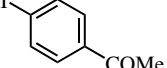
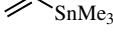
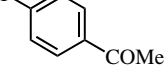
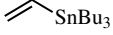
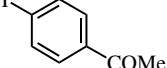
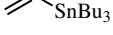
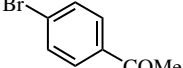
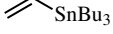
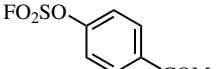
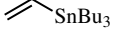
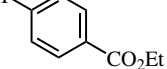
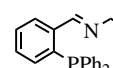
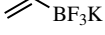
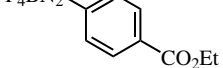
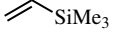
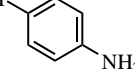

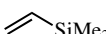
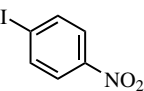
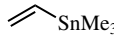
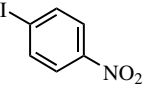
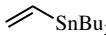
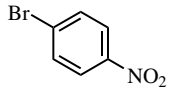
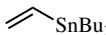
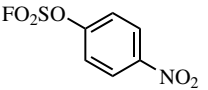

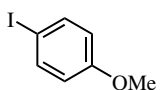

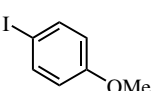
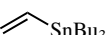
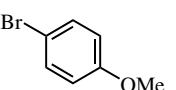
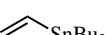
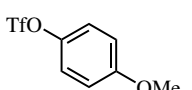
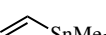
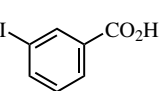
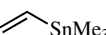
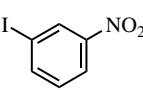
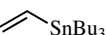
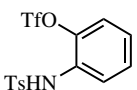
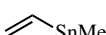
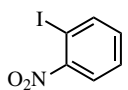

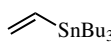
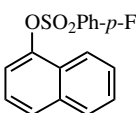
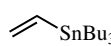
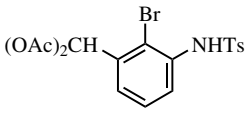
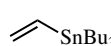
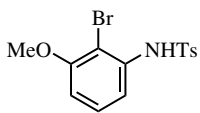
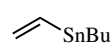
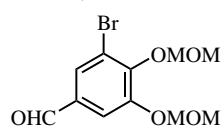
 M	Type of Aryl Electrophile	Ar-X	Conditions	Yield (Selectivity) %	Reference
	<i>Phenyl</i>				
 MgBr			Cl ₂ Pd(dppf), THF	95	[45]
 SiMe ₃			Pd ₂ dba ₃ , KF, ⁿ Bu ₄ NCl, toluene	94	[46]
 SnBu ₃			Pd ₂ dba ₃ , LiCl, NMP, TFP or AsPh ₃	>95	[47]
 SnBu ₃			Cl ₂ Pd(PPh ₃) ₂ , LiCl, DMF	80	[48]
 SnBu ₃			Pd(OAc) ₂ , 1,4-dioxane or Pd(dba) ₂	44 80	[49]
	<i>p-Mono</i>				
 SiMe ₃			[ClPd(π-C ₃ H ₅) ₂], TASF, HMPA	89	[50]
 ZnCl			Cl ₂ Pd(dppf), THF	98	[51]
 SiMe ₃			[ClPd(π-C ₃ H ₅) ₂], TASF, HMPA	86	[50]
 SnMe ₃			Cl ₂ Pd(MeCN) ₂ , DMF-THF	100	[51],[52]
 SnBu ₃			10%Pd/C, CuI, AsPh ₃	79	[53]
 SnBu ₃			Pd(PPh ₃) ₄ , toluene	82	[54]
 SnBu ₃			Cl ₂ Pd(PPh ₃) ₂ , LiCl, DMF	75	[48]
	<i>p-Mono-</i>				
 SnBu ₃			[ClPd(π-C ₃ H ₅) ₂], toluene 	90	[55]
 BF ₃ K			Pd(OAc) ₂ , 1,4-dioxane	65	[56]
 SiMe ₃			[ClPd(π-C ₃ H ₅) ₂], TASF, HMPA	85	[50]

TABLE 2. (Continued)

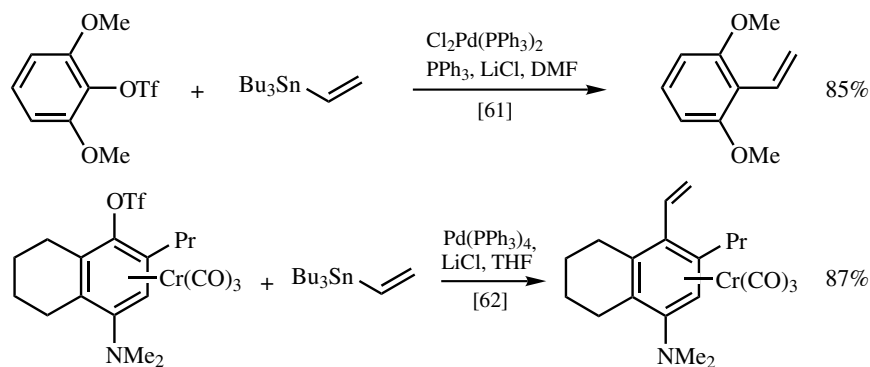
 M	Type of Aryl Electrophile	Ar-X	Conditions	Yield (Selectivity) %	Reference
			[ClPd(π -C ₃ H ₅)] ₂ , TASF, HMPA	83	[50]
			Cl ₂ Pd(MeCN) ₂ , DMF-THF	100	[51], [52]
			Pd(PPh ₃) ₄ , toluene	80	[54]
			Cl ₂ Pd(PPh ₃) ₂ , LiCl, DMF	85	[48]
			Cl ₂ Pd(dppf), THF	98	[45]
			Cl ₂ Pd(dppf), THF	100	[51]
			Pd(PPh ₃) ₄ , toluene	76	[54]
			Cl ₂ Pd(PPh ₃) ₂ , LiCl, dioxane	82	[57]
	<i>m</i> -Mono-		Cl ₂ Pd(MeCN) ₂ , DMF-THF	99	[51]
	<i>m</i> -Mono-		Cl ₂ Pd(MeCN) ₂ , DMF-THF	100	[51]
	<i>o</i> -Mono-		Pd(PPh ₃) ₄ , LiCl, dioxane/DMF	80	[57]
			Cl ₂ Pd(MeCN) ₂ , DMF-THF	95	[51]

(Continued)

TABLE 2. (Continued)

	Type of Aryl Electrophile	Ar-X	Conditions	Yield (Selectivity) %	Reference
	2,3-Di-		Pd(OAc) ₂ , LiCl, DMF, dppp	50	[58]
	2,6-Di-		Pd(PPh ₃) ₄ , toluene	86	[59]
			Pd(PPh ₃) ₄ , toluene	76	[59]
	2,3,5-Tri-		Pd(PPh ₃) ₄	87	[60]

^a The entries are arranged according to the substitution patterns in the Ar groups, that is, degree of substitution and their regiochemistry. Within the same category, the Cahn–Ingold–Prelog rule is applied in increasing order. Finally, the leaving groups and then the metal counterions are arranged as discussed in the text.



Scheme 7

B.iii. Alkenyl–Aryl Coupling with Disubstituted Alkenylmetals

There are three types of disubstituted alkenylmetals according to the classification discussed in Sect. A. Tables 3, 4, and 5 summarize some representative examples of their coupling reactions, arranged in the order of (*E*)- β -, (*Z*)- β -, and α -substituted alkenylmetals.

B.iii.a. (*E*)- β -Substituted Alkenylmetals. Some prototypical examples of this type of coupling are shown in Scheme 2. In these early studies, the reactions were mainly catalyzed by Ni–phosphine complexes,^{[14][16][21]} even though Pd–phosphine complexes

TABLE 3. Pd-Catalyzed Cross-Coupling of (*E*)- β -Substituted Alkenylmetals with Aryl Electrophiles^a

$R-\text{CH}=\text{CH}-M$	Ar-X	Conditions	Yield (Selectivity) %	Ref- erence
		Pd(PPh ₃) ₄ , NaOH	87	[70]
		Pd(PPh ₃) ₄ , NaOH, EtOH	100(99)	[66]
		Pd(PPh ₃) ₄ , NaOH, EtOH	98(99)	[66]
		Pd(PPh ₃) ₄	89	[14]
		Pd(OAc) ₂ , NaOH, THF	80	[88]
		Cl ₂ Pd(PEt ₃) ₂ , TBAF, DMF	83	[83]
		Pd(PPh ₃) ₄ , K ₃ PO ₄ , dioxane	95	[91]
		Pd(PPh ₃) ₄	84	[92]
		[ClPd(π -C ₃ H ₅)] ₂ , P(OEt) ₃ , TBAF, THF	91(>99)	[82]
		Pd(PPh ₃) ₄ , C ₆ H ₆	70–85	[93]
		Cl ₂ Pd(PPh ₃) ₂ , LiCl, DMF	82	[57]
		Pd(PPh ₃) ₄ , LiCl, DMF	51	[57]
		Pd(PPh ₃) ₄ , LiCl, DMF	88	[60]
		Pd(PPh ₃) ₄ , NaOH	48	[73]

(Continued)

TABLE 3. (Continued)

$R-\text{CH}=\text{CH}-M$	Ar-X	Conditions	Yield (Selectivity) %	Ref- erence
		$\text{Pd}(\text{PPh}_3)_4$, NaOH	81	[73]
		$\text{Pd}(\text{PPh}_3)_4$, NaOH, EtOH	98(99)	[66]
		$\text{Pd}(\text{OAc})_2$, LiCl, DMF, DPPP	69	[58]
		$\text{Pd}(\text{PPh}_3)_4$, NaOH	60	[70]
		10% Pd/C, CuI, AsPh ₃	82(~100)	[53]
		$\text{Pd}(\text{PPh}_3)_4$, NaOH	80	[70]

^a The alkenyl groups are arranged (i) according to the types of substitutions, *i.e.*, alkyl > alkenyl > aryl > alkynyl and (ii) in the increasing order of priority determined by the Cahn–Ingold–Prelog rule. For a given alkenyl group, the aryl electrophiles are arranged according to their substitution patterns, *i.e.*, the degree and regiochemistry of substitution. Finally, the leaving group and then the counterions are arranged as discussed in the text.

TABLE 4. Pd-Catalyzed Cross-Coupling of (Z)- β -Substituted Alkenylmetals with Aryl Electrophiles^a

$R-\text{CH}=\text{CH}-M$	Ar-X	Conditions	Yield (Selectivity) %	Ref- erence
		$\text{Pd}(\text{PPh}_3)_4$, LiCl, DMF	82	[48]
		$\text{Pd}(\text{PPh}_3)_4$, NaOEt, EtOH	89(>97)	[98]
		$\text{Cl}_2\text{Pd}(\text{PEt}_3)_2$, TBAF, THF	91	[83]
		$\text{Pd}(\text{PPh}_3)_4$, TBAF, THF	73	[104]

TABLE 4. (Continued)

	Ar-X	Conditions	Yield (Selectivity) %	Ref- erence
		Cl ₂ Pd(PEt ₃) ₂ , TBAF, THF	58	[86]
		Cl ₂ Pd(dcpe), C ₆ H ₆ , 80 °C	55	[88]
		Pd(OAc) ₂ , THF	70	[88]
		Pd(OAc) ₂ , THF	66	[88]
		Pd(PPh ₃) ₄ , NaOEt, EtOH	93(>90)	[98]
		Pd(PPh ₃) ₄ , THF	60	[99]
		Pd(PPh ₃) ₄ , NaOEt, EtOH	96(>84)	[98]

^aSee Table 3.TABLE 5. Pd-Catalyzed Cross-Coupling of α -Substituted Alkenylmetals with Aryl Electrophiles^a

	Ar-X	Conditions	Yield (Selectivity) %	Ref- erence
		Pd(PPh ₃) ₄ , NaOH,	96	[117]
		Pd(PPh ₃) ₄ , NaOH,	83	[117]
		Pd(PPh ₃) ₄ , NaOH,	76	[117]
		Pd(PPh ₃) ₄ , THF	96	[108]

(Continued)

TABLE 5. (Continued)

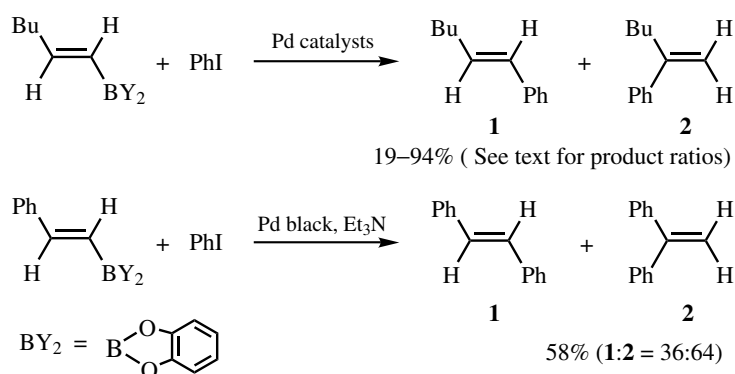
$R-\text{CH}=\text{CH}-M$	$Ar-X$	Conditions	Yield (Selectivity) %	Ref- erence
		$\text{Pd(PPh}_3)_4$, THF	90	[108]
		$\text{Pd(PPh}_3)_4$, THF	95	[108]
		$\text{Pd(PPh}_3)_4$, THF	85	[108]
		$\text{Pd(PPh}_3)_4$, THF	83	[108]

^aSee Table 3.

were also shown to be very satisfactory.^[14] These studies also introduced a one-pot hydrometallation–cross-coupling tandem process for the stereoselective conversion of alkynes into arylated (*E*)-alkenes^[14] (**Protocol 1**). Alkenylaluminums or alkenylzirconiums, generated *in situ* by hydroalumination^[63] or hydrozirconation^[64] of alkynes, respectively, were reacted with aryl halides in the presence of Pd or Ni catalysts to produce arylated *E*-alkenes in high yield with excellent stereoselectivity.

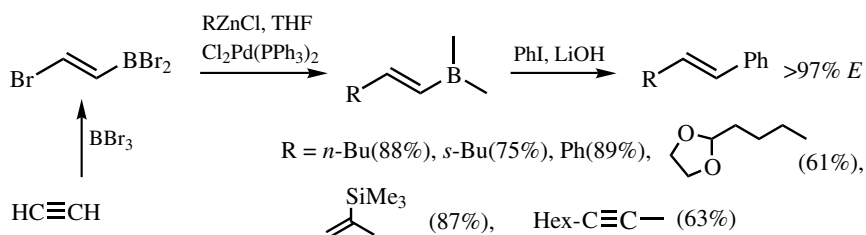
This tandem protocol has been investigated extensively in other cross-coupling reactions involving Sn, Si, and particularly B. Stereodefined (*E*)-alkenylborons are readily available by monohydroboration of alkynes^[65] and their cross-coupling with aryl halides was demonstrated in 1979.^[66] The reaction was effected by the use of a suitable base, such as sodium hydroxide and sodium ethoxide. The effect of bases is believed to promote the formation of four-coordinated borates, which had been shown to be reactive in Pd-catalyzed cross-coupling with carbon electrophiles.^[67] Various functional groups such as OMe, esters, and halogens can be tolerated in this reaction. Although the reaction proceeds with retention of stereochemistry in alkenylboranes, loss of regiochemistry is observed in some cases. In the presence of palladium black, alkenylborane was reacted with iodobenzene to give the desired cross-coupling products (**1**)^[68] only as the minor product, the major product being the “head-to-tail” isomer (**2**) (**Scheme 8**). The ratio of products **1** and **2** varies from 39 : 61 to 97 : 3 depending on the reaction conditions. However, even under optimal conditions, the coupling of (*E*)-phenylethenylborane with iodobenzene gives a mixture of (*E*)-stilbene and 1,1-diphenylethylene in the 36:46 ratio. An intramolecular version of this unusual “head-to-tail” coupling was reported in the synthesis of methylenecycloalkenes.^[69] The mechanism for the reaction was believed to consist of (i) addition of an organopalladium iodide to the alkenylborane, (ii) isomerization of the intermediate, and (iii) elimination of IPdBX_2 .

Dihydroboration–dehydroboration of terminal alkynes has been developed to prepare (*E*)-alkenyl-9-BBN derivatives, and they are successfully cross-coupled with aryl electrophiles to give arylated (*E*)-alkenes.^[70] Alternatively, (*E*)-alkenylboron compounds are generated from



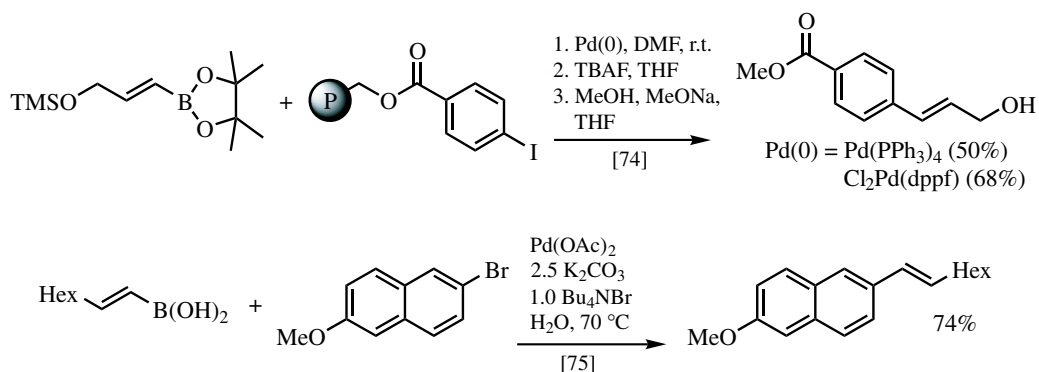
Scheme 8

a one-pot process associated with the heteroboration of acetylenes followed by chemoselective cross-coupling with organic zinc reagents.^{[71]–[73]} The observed chemoselectivity is in agreement with the earlier finding that organozinc compounds are much more reactive in Pd-catalyzed cross-coupling with organic electrophiles than organoboron compounds.^{[14],[15]} The stereodefined alkenylboron derivatives thus obtained can now be reacted with aryl halides in the presence of a Pd catalyst and a base to give arylated (*E*)-alkenes^[71] (**Scheme 9**).



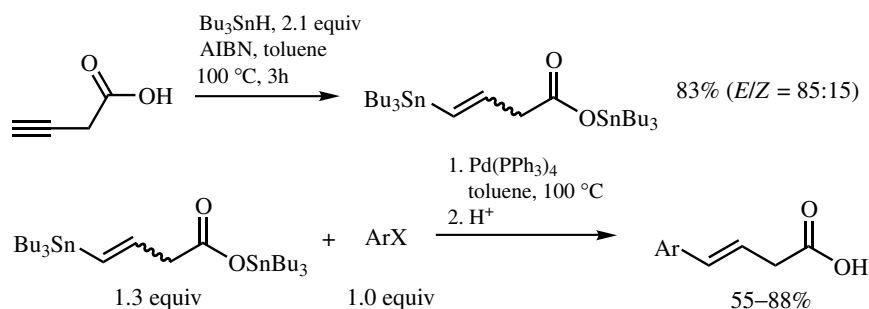
Scheme 9

The solid phase and aqueous Suzuki coupling reactions involving alkenylboron compounds and aryl electrophiles have also been demonstrated, as shown in **Scheme 10**.^{[74],[75]}



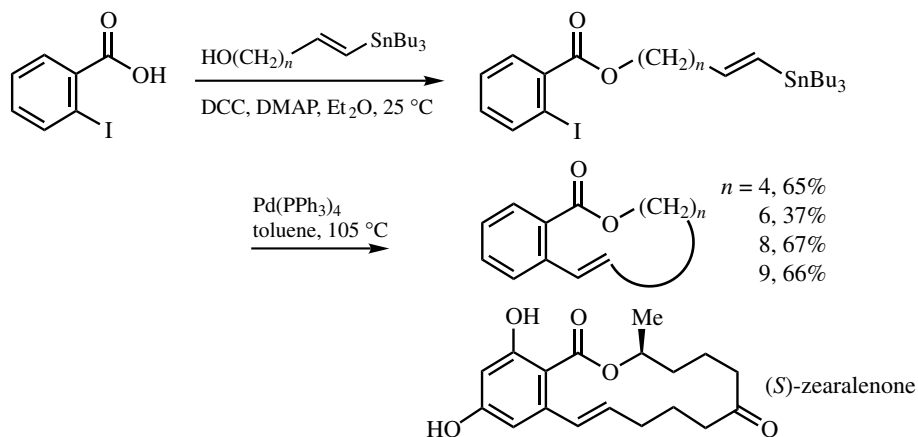
Scheme 10

Although hydrostannation of monosubstituted alkynes to give alkenylstannanes is mostly regiospecific, *E/Z* mixtures are often obtained.^[26] Therefore, the hydrostannation–cross-coupling tandem is not generally well suited for the synthesis of stereodefined arylated alkenes.^[76] However, this difficulty may be circumvented by the use of an excess amount of alkenyltin reagents in some cases. For example, when 1.3 equiv of an alkenyltin reagent generated as an *E/Z* (85 : 15) mixture by hydrostannation of but-3-ynoic acid was coupled with aryl halides, only the *E*-isomer of the desired product was produced under the reaction conditions^[77] (**Scheme 11**).



Scheme 11

E-Alkenyltin compounds may be prepared by transmetalation using triorganyltin halides. Several (*E*)-alkenylstannyl alcohols have been prepared from ω -alkynols via hydrozirconation chemistry^[42] and used in Pd-catalyzed intramolecular cross-coupling in the synthesis of zearalenone shown in **Scheme 12**.^[78]

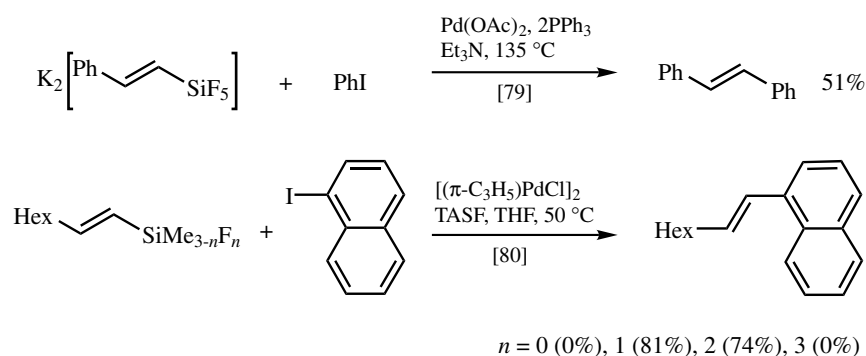


Scheme 12

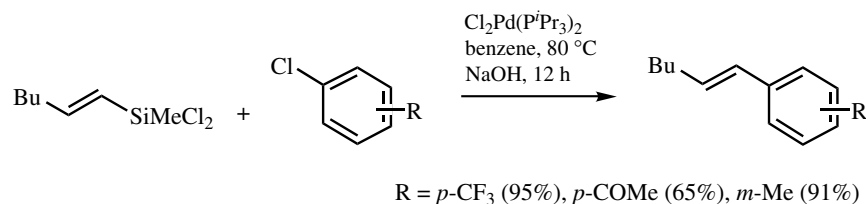
Alkenylsilicon compounds themselves are generally inert in Pd-catalyzed cross-coupling with aryl electrophiles. However, their reactivity could be remarkably enhanced by the addition of fluorides to generate pentacoordinate alkenylsilicon derivatives that can undergo the desired cross-coupling. Some typical examples are shown in

Scheme 13.^{[79],[80]} Earlier, the use of benzenediazonium salts as cross-coupling partners was demonstrated.^[81] However, it was not until 1988 that a more convenient and practically useful protocol for the cross-coupling of alkenylsilicon compounds was developed. Initially, at least one Si—F bond in the alkenylsilicon reagents requiring an excess of TBBF or TASF was shown to be necessary.^[80] However, further studies have indicated that the alkenylsilicon compounds containing Si—OR,^[82] Si—Cl,^[83] and Si—OH^{[84],[85]} are also effective substrates for cross-coupling. Most notably, the cross-coupling of alkenylchlorosilanes with aryl chlorides has recently been achieved.^[83] The favorable results may, in part, be ascribed to the exceptional thermal stability of organochlorosilanes, which show no sign of decomposition even under drastic conditions (90–150 °C, 24–48 h). However, the use of trialkylphosphine–Pd complexes as catalysts is also essential. Electron-rich trialkylphosphine ligands must significantly increase the nucleophilicity of the palladium complexes, thereby promoting their oxidative addition reaction with aryl chlorides. Indeed, bulky trialkylphosphine–palladium complexes are effective catalysts for various reactions of organic chlorides.^{[86],[87]} More recently, this reaction has been improved by using NaOH as a base instead of TBAF. With this modification the reaction could be completed under relatively mild conditions (80 °C),^[88] as shown in **Scheme 14**.

It should be noted that the required alkenylsilanes can readily be prepared by either hydrosilylation^[89] of alkynes or silylation of alkenyl halides.^[90]



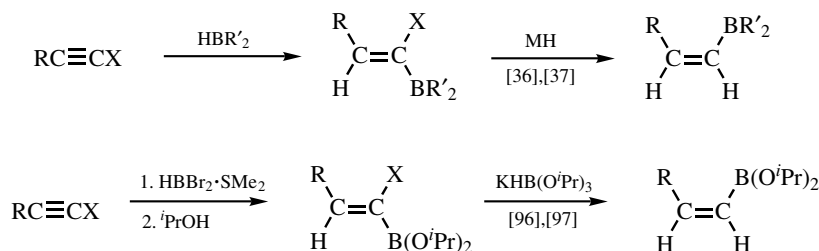
Scheme 13



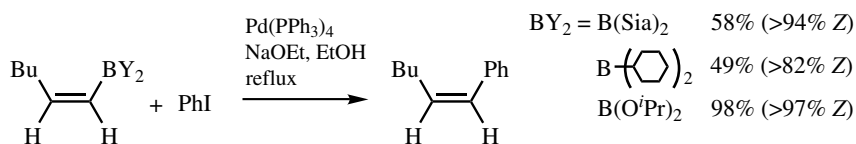
Scheme 14

B.iii.b. (Z)- β -Substituted Alkenylmetals. The stereodefined (Z)- β -substituted alkenylmetals can generally be prepared by either metallation or metallation–transmetallation of the corresponding (Z)-alkenyl electrophiles. However, several other methods are notable.^{[36]–[38],[94],[95]} A stereoselective synthesis of (Z)-alkenylboranes via hydroboration

of 1-haloalkynes followed by migratory insertion was developed by Negishi and co-workers in 1975^[36] (**Scheme 15**). Its variants involving the use of *t*-BuLi^[37] and KHB(OPr-*i*)₃^{[96],[97]} have also been reported (**Scheme 15**). The (*Z*)-alkenylboron derivatives thus obtained readily participate in Pd-catalyzed cross-coupling under the Suzuki conditions^[98] (**Scheme 16**).

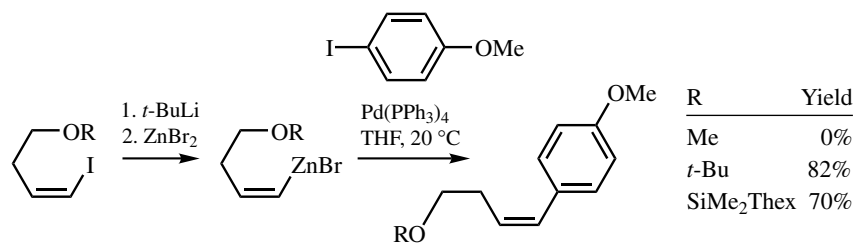


Scheme 15



Scheme 16

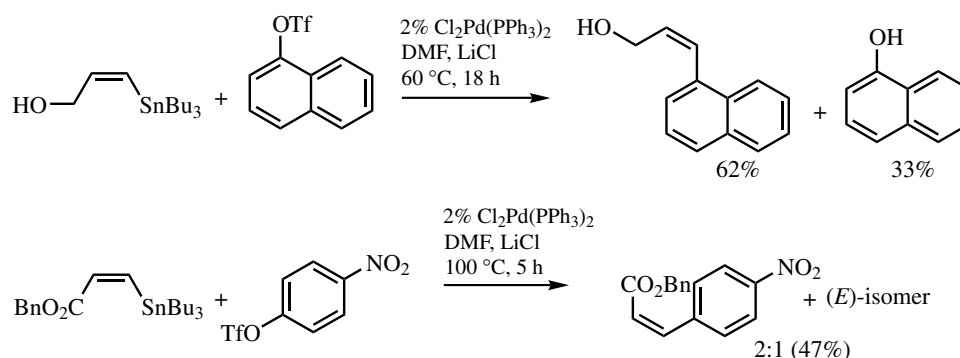
A chelation effect has been observed in Pd-catalyzed cross-coupling of (*Z*)-4-alkoxy-1-alkenylzinc bromides with *p*-iodoanisole. When R is a bulky alkoxy group, such as *t*-BuO and ThexMe₂SiO groups, the reaction proceeds very well to give the desired products as shown in **Scheme 17**.^[99] However, when R is sterically less hindered (e.g., Me), no cross-coupling is observed. The results point to a strong chelation between O and Zn. Similar (*Z*)-β-substituted alkenylzinc bromides bearing either a primary or a secondary allylic or homollylic O^{*i*}Bu group have been reacted with *p*-iodoanisole to give the corresponding arylated (*Z*)-alkenes^[99] (cf. **Table 4**).



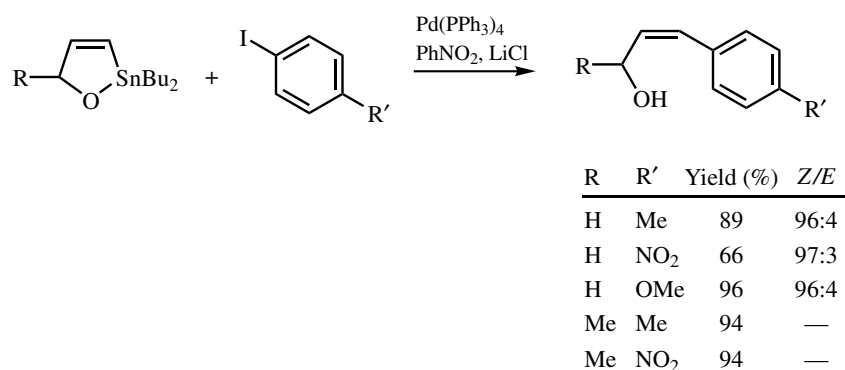
Scheme 17

(*Z*)-3-(tri-*n*-butylstannyl)-2-propen-1-ol, prepared from propargylic alcohol by metal hydride reduction and transmetalation,^[100] has been coupled with 1-naphthyl triflate to give (*Z*)-3-α-naphthyl-2-propen-1-ol with retention of the double bond

geometry.^[57] However, the reaction of benzyl (Z)-3-(tri-*n*-butylstannyl)propenoate^[101] with *p*-nitrophenyl triflate gives a 2 : 1 mixture of the *Z* and *E* isomers of the desired product (**Scheme 18**). On the other hand, the reaction of (Z)-1-propenyltributyltin and phenyl fluorosulfonate has been reported to produce exclusively (Z)- β -methylstyrene.^[48] Stannoxanes, prepared from propargyl alcohol and 3-butyne-2-ol,^[102] are utilized to synthesize arylated (Z)-allylic alcohols by Stille coupling.^[103] The use of nitrobenzene as solvent dramatically improves the yields in many cases (**Scheme 19**).



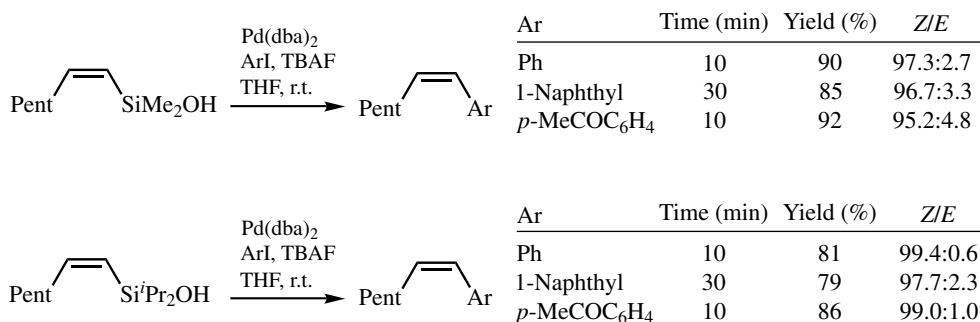
Scheme 18



Scheme 19

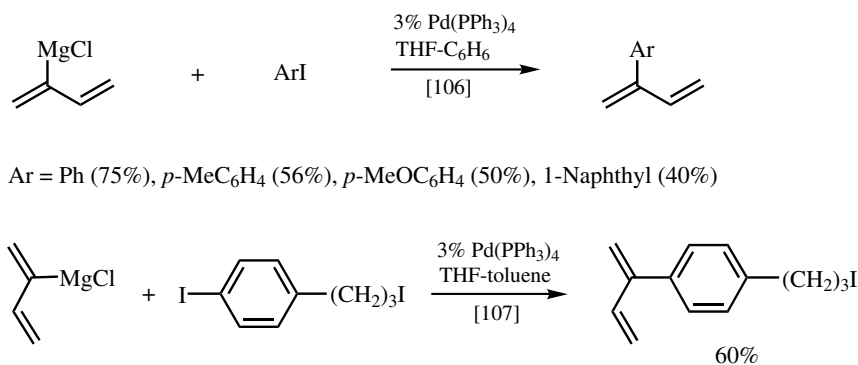
The Pd-catalyzed cross-coupling reactions of (Z)- β -substituted alkenylsilanes with aryl electrophiles, such as aryl bromide,^[88] aryl chloride,^{[83],[88]} and aryl triflate,^[104] have been demonstrated (**Table 4**). In these reactions, the presence of either two Si—F bonds or Si—Cl bonds appears to be required for successful coupling, and the addition of bases, such as TBAF and NaOH, is also necessary. In addition, when chloroarenes are used as electrophiles, trialkylphosphines, such as *t*Pr₃P, Et₃P, and dcpe, must be used as effective ligands. The reaction proceeds with retention of the stereochemistry of the alkenylsilicon derivatives. More recently, a highly stereospecific cross-coupling of alkenylsilanols has been demonstrated,^[84] as shown in **Scheme 20**. The product yields and stereoselectivities are generally high, and the (Z)-alkenyldiisopropylsilanols are superior to the

corresponding (*Z*)-alkenyldimethylsilanols with respect to the stereoselectivity. The major advantage over the previous methods is the mild reaction conditions (room temperature, 10–30 min).



Scheme 20

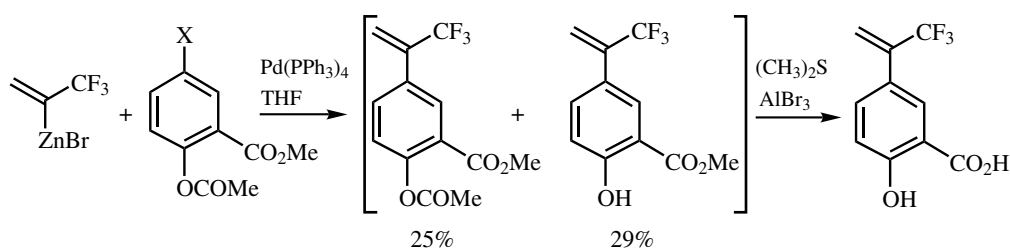
B.iii.c. α -Substituted Alkenylmetals. α -Substituted alkenylmetals containing Mg and Zn can be prepared by oxidative metallation of the corresponding alkenyl halides. 2-(1,3-Butadienyl)magnesium chloride, prepared from 2-chloro-1,3-butadiene and magnesium,^[105] was coupled with several aryl iodides in the presence of Pd(PPh₃)₄ to give 2-arylated 1,3-butadienes in fair to good yields.^[106] Neither Ni(acac)₂ nor Ni(pph₃)₄ was effective for this reaction, since either polymerization occurred or no reaction ensued. In cases where both an alkyl iodide and an aromatic iodide are present in an electrophile, the aromatic iodides preferentially reacted,^[107] as exemplified by the results shown in **Scheme 21**.



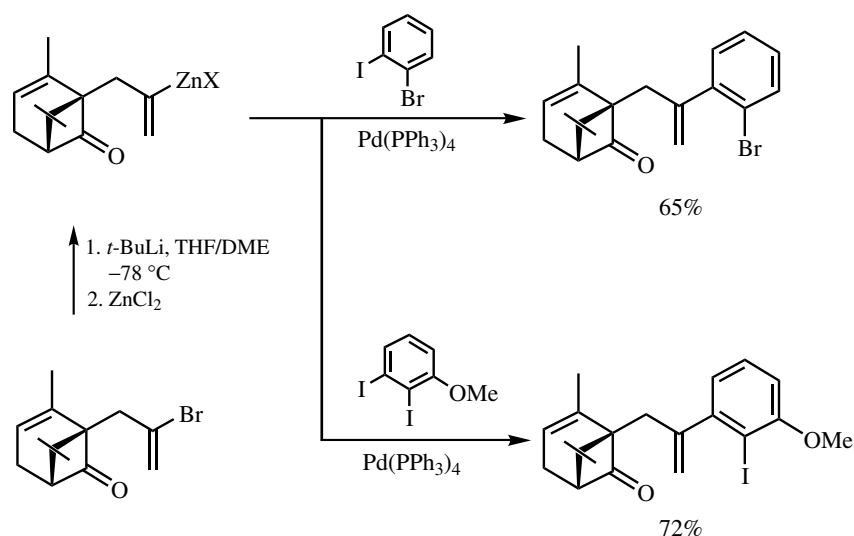
Scheme 21

Trifluoroisopropenylzinc reagent is prepared in nearly quantitative yield by the direct zincation of 2-bromo-3,3,3-trifluoropropene in the presence of TMEDA. This organozinc reagent readily undergoes Negishi coupling with a wide variety of aryl halides. Various functional groups, such as Br, Ac, OMe, NO₂, OAc, and CHO, are tolerated. Excellent yields are achieved in most cases. However, *o*-amino- and acetylamino-substituted

bromobenzenes fail to react with the reagent under the same conditions.^[108] This zincation–cross-coupling procedure (**Protocol III**) has been used in the synthesis of fluorovinylsalicylic acid derivatives^[109] (**Scheme 22**). The zinc reagents are often generated by lithiation of the alkenyl halides followed by transmetalation with zinc halides. Some chemoselective and regioselective coupling reactions of alkenylzinc reagents, generated by a lithiation–transmetalation procedure, with *o*-dihaloarenes have been demonstrated, as shown in **Scheme 23**.^[110]

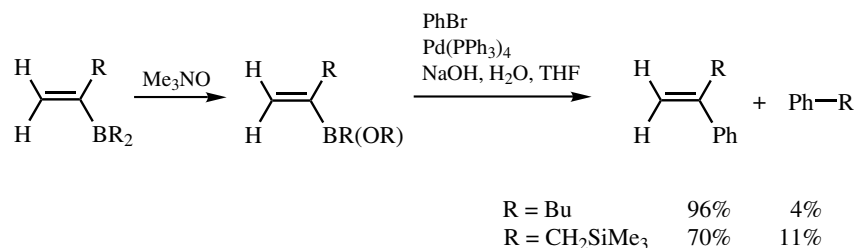


Scheme 22



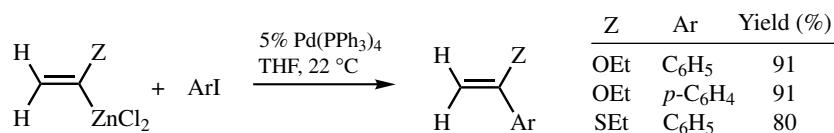
Scheme 23

Although Markovnikov alkenylboranes have been known since 1975,^{[111]–[114]} their Pd-catalyzed cross-coupling had not been reported until an improved procedure for the preparation of Markovnikov alkenylboranes in pure form was recently reported.^[115] In these reactions, however, the primary alkyl groups compete with the 2-alkenyl groups and produce alkylbenzenes, but *i*Pr, *s*Bu, and *t*Bu virtually do not. On the other hand, when the alkenylboranes are treated first with 1 equiv of trimethylamine *N*-oxide, which presumably gives alkenylalkoxyborane,^[116] the yields of the desired α -substituted styrenes increase dramatically^[117] (**Scheme 24**).



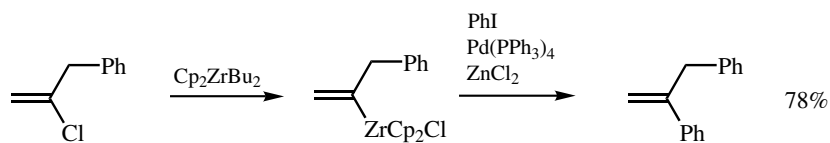
Scheme 24

It is noteworthy that α -alkoxy- and α -alkylthio-substituted vinylzinc reagents, generated by treating the corresponding organolithium reagents with zinc chloride, undergo Negishi coupling with aryl halides to produce the corresponding arylated α -heterosubstituted alkenes in high yields^[118] (**Scheme 25**). This approach has been demonstrated repeatedly in related Stille and Suzuki coupling reactions (**Sect. III.2.13.2**).



Scheme 25

α -Substituted alkenyltins or alkenylsilicones have not been used as often as their Zn and B counterparts. One problem associated with the use of α -phenyl-substituted vinylfluorosilane with aryl iodides is the formation of a mixture of regioisomers. Their ratio depends on the nature of the substituents in the aryl iodides.^[18] α -Substituted alkenylzirconiums can be prepared by oxidative addition of 2-haloalkenes to zirconocene, and their subsequent Negishi-type coupling with aryl halides has been demonstrated^[119] (**Scheme 26**).



Scheme 26

B.iv. Trisubstituted Alkenylmetals

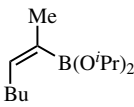
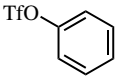
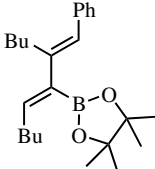

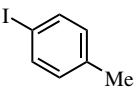
Some representative examples of the cross-coupling of three different types of trisubstituted alkenylmetals with aryl electrophiles are shown in **Table 6** and arranged in the order: β,β' -, *cis*- α,β -, and *trans*- α,β -substituted alkenylmetals.

TABLE 6. Pd-Catalyzed Cross-Coupling of Trisubstituted Alkenylmetals with Aryl Electrophiles^a

Alkenylmetals	Ar-X	Conditions	Yield (Selectivity) %	Ref- erence
β,β-Di-				
		$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$, MeOLi , MeOH	65(97)	[122]
		$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$, MeOLi , MeOH	73(99)	[122]
		$\text{Pd}(\text{PPh}_3)_4$, THF	80	[99]
		$[\text{ClPd}(\pi\text{-C}_3\text{H}_5)]_2$, TBAF, $\text{P}(\text{OEt})_3$, THF	79(95)	[82]
<i>cis</i>-α,β-Di-				
		$\text{Pd}(\text{PPh}_3)_4$, NaOEt , EtOH	87(99)	[66]
		$\text{Pd}(\text{PPh}_3)_4$, ZnCl_2	88(>97)	[18]
		$\text{Pd}(\text{PPh}_3)_4$, THF	85(99.5)	[131]
		$\text{Pd}(\text{PPh}_3)_4$, THF	72(>99)	[131]
		$\text{Pd}(\text{PPh}_3)_4$, THF	50(>99)	[131]
		$[\text{ClPd}(\pi\text{-C}_3\text{H}_5)]_2$, TBAF, $\text{P}(\text{OEt})_3$, THF	90(>99)	[82]
		$\text{Ni}(\text{PPh}_3)_4$, ZnCl_2	80(>97)	[18]
		$[\text{ClPd}(\pi\text{-C}_3\text{H}_5)]_2$, TBAF, $\text{P}(\text{OEt})_3$, THF	77(>99)	[82]
		$\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$, ZnCl_2 , LiCl , dioxane	43	[137]

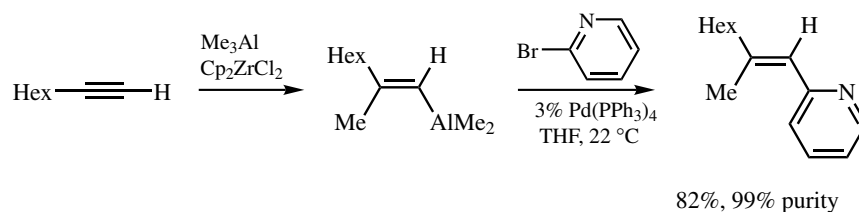
(Continued)

TABLE 6. (Continued)

Alkenylmetals	Ar-X	Conditions	Yield (Selectivity) %	Ref- erence
<i>trans</i> - α,β -Di				
		Pd(PPh ₃) ₄ , K ₃ PO ₄ , dioxane	68	[138]
		Pd(PPh ₃) ₄ , CsF, DMF	29	[124]
		Pd(PPh ₃) ₄ , CsF, DMF	34	[124]

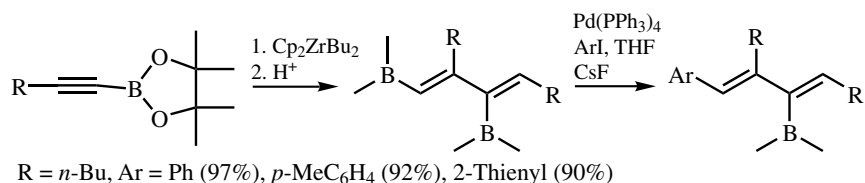
^aSee Table 3.

B.iv.a. β,β' -Substituted Alkenylmetals. Carbometallation reactions of 1-alkynes, most notably carboalumination^[40] and carbocupration,^[38] collectively provide a powerful route to the synthesis of β,β' -substituted alkenylmetals. The alkenylmetals generated *in situ* may be used directly for Pd- or Ni-catalyzed cross-coupling with aryl electrophiles (**Protocol 1**). One prototypical example of the carbometallation–cross-coupling tandem process is shown in **Scheme 27**.^[120]



Scheme 27

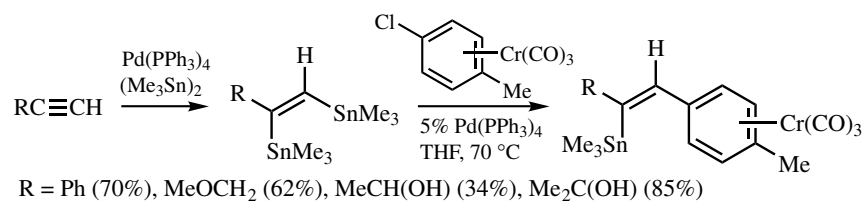
In addition to the carbometallation reactions mentioned above, there are various additional methods for the synthesis of trisubstituted alkenes, as discussed below. Various β,β' -substituted alkenylboron compounds can be prepared from 1-alkynes by a haloboration^[121]–chemoselective cross-coupling tandem process similar to that shown in **Scheme 9**. Their subsequent reaction with iodobenzene is effected by the addition of a base to give stereodefined arylated alkenes in fair to good yields.^[122] A series of 1,3-dibora-1,3-butadienes have been prepared by a zirconocene-mediated reductive cyclization of 1-alkynyl boronates using Negishi's reagent^[123] (Cp₂ZrCl₂ + 2*n*-BuLi). Their cross-coupling with aryl halides proceeds to selectively replace the terminal B group giving 2-bora-1,3-butadiene derivatives^{[124],[125]} (**Scheme 28**). The synthetic utility of this method is severely limited due to the restriction that the two R groups be the same.



Scheme 28

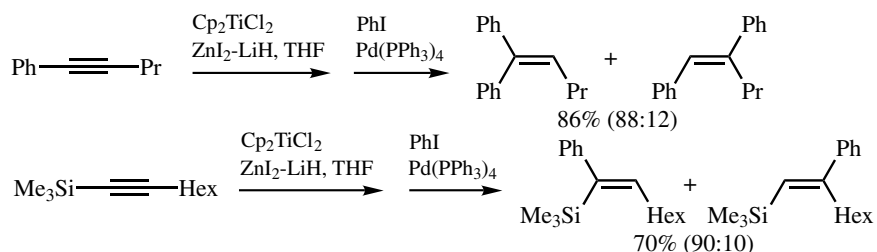
The reaction of 2-bis(trimethylstannyl)-1-alkenes, readily available by the addition of hexamethylditin to 1-alkynes using Pd(PPh₃)₄ as catalyst,^{[126],[127]} with π -chloroarene chromium complexes give regio- and stereospecifically the corresponding cross-coupling products in 34–85% yields^[128] (Scheme 29). On the other hand, uncomplexed haloarenes, such as chlorobenzene or even bromobenzene, fail to undergo the desired cross-coupling. The success with the chromium complexes may be attributable to the electron-withdrawing tricarbonylchromium group, which favors the oxidative addition of aryl chlorides to Pd(0) complexes.^[129]

The Pd-catalyzed reaction of (*Z*)-exocyclic silyldienes^[130] with aryl halides has been reported to proceed with some loss of stereochemistry (5–10%)^[82] (Table 6).



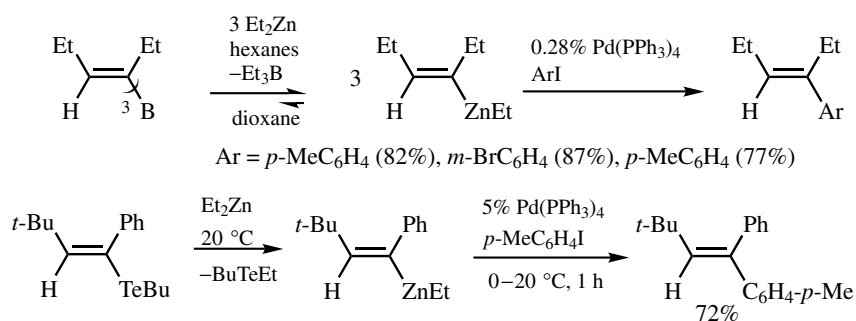
Scheme 29

B.iv.b. *cis*- α,β -Substituted Alkenylmetals. *cis*- α,β -Substituted alkenylmetals containing B, Al, Zr, Sn, and Si can conveniently be prepared via hydrometallation of internal alkynes, and their Pd-catalyzed cross-coupling with aryl electrophiles has been investigated extensively. Some representative results are shown in Table 6. The recently reported Ti-catalyzed hydrozincation that can directly provide stereodefined alkenylzinc reagents^[131] from alkynes permits a one-pot Negishi coupling with aryl halides to give arylated alkenes in good yields and in high stereoselectivity. Hydrozincation of unsymmetrically alkyl-substituted alkynes generally produces mixtures of two regioisomers in nearly 1:1 ratios, even though the presence of Ph or an Me₃Si group can result in ca. 90:10 regioselectivity. Their cross-coupling with iodobenzene gives mixtures of two regioisomers also in ca. 90:10 ratio^[131] (Scheme 30).



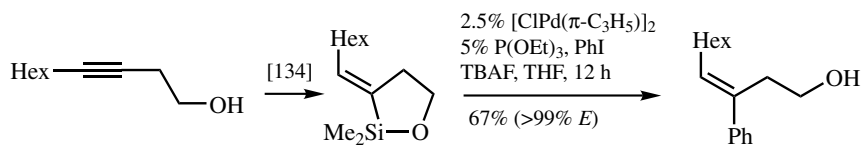
Scheme 30

An alternative preparation of stereodefined *cis*- α,β -substituted alkenylzinc reagents involves transmetalation of the corresponding trialkenylboranes or alkenyl tellurides with diethylzinc.^{[132],[133]} The alkenylzincs thus obtained undergo Negishi coupling with aryl iodides in good yields (**Scheme 31**).



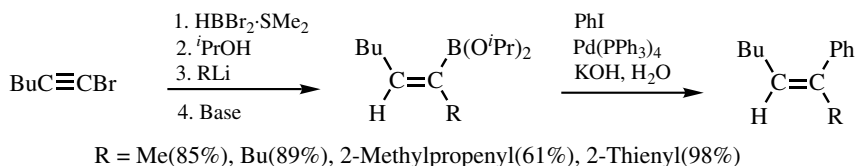
Scheme 31

The use of *cis*- α,β -substituted alkenylalkoxysilanes in Pd-catalyzed cross-coupling with aryl halides has been demonstrated.^[82] The synthetic utility of these coupling reactions has further been demonstrated by the one-pot transformation of a homopropargyl alcohol to regio- and stereodefined trisubstituted homoallyl alcohol (**Protocol 1**), as shown in **Scheme 32**.



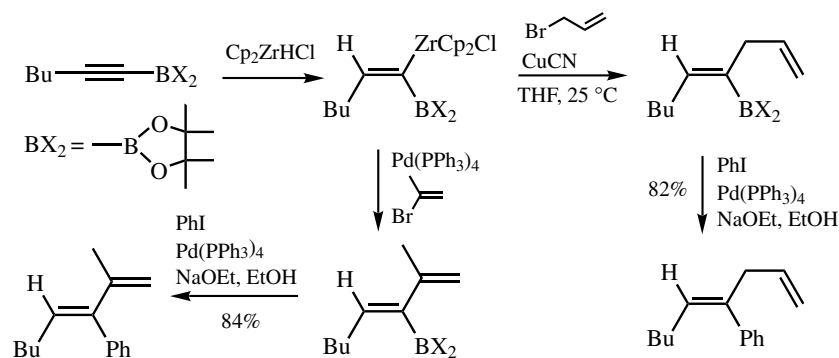
Scheme 32

B.iv.c. *trans*- α,β -Substituted Alkenylmetals. The accessibility of *trans*- α,β -substituted alkenylmetals is still rather limited, and only a few examples of this type of cross-coupling reactions have been reported (**Table 6**). Notably, *trans*- α,β -substituted alkenylboronates can be prepared by hydroboration of 1-bromo-1-alkynes followed by subsequent treatments with organolithiums and bases, a procedure similar to that for the preparation of (*Z*)- β -substituted alkenylboron compounds.^{[94]–[97]} The Pd-catalyzed cross-coupling reaction of the resultant organoboranes with aryl halides proceeds with complete retention of alkenyl stereochemistry to give trisubstituted alkenes^[135] (**Scheme 33**).



Scheme 33

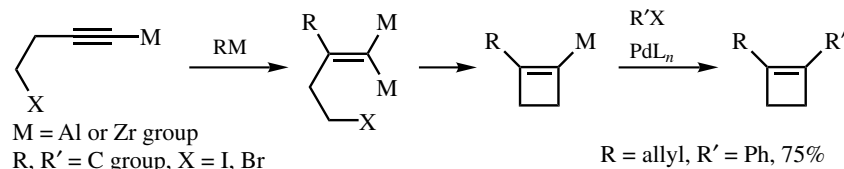
Alternatively, hydrozirconation of 1-alkynyldioxaborolanes with HZrCp_2Cl affords 1,1-dimetallalkenes containing both B and Zr, which can then be reacted with various electrophiles to give *trans*- α,β -substituted alkenylboronates via preferential reaction of the carbon–zirconium bond^[136] as shown in **Scheme 34**. The subsequent Suzuki coupling with iodobenzene gives trisubstituted alkenes in good yields.



Scheme 34

B.v. Tetrasubstituted Alkenylmetals

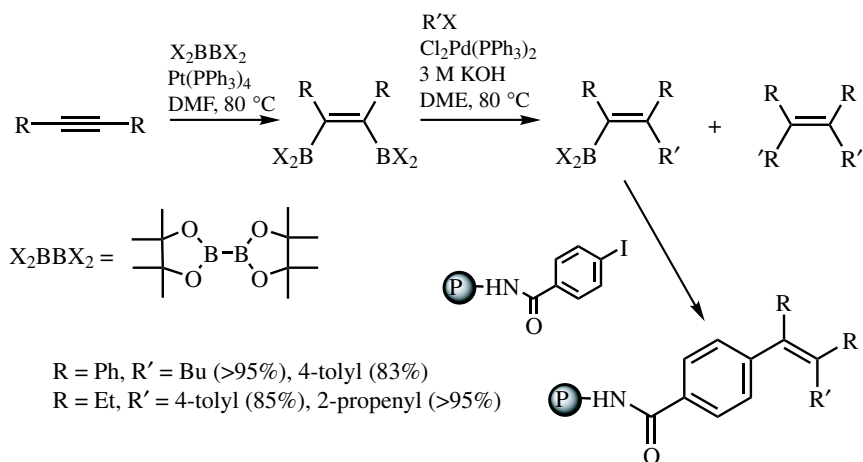
Several coupling reactions of 2-substituted cycloalkenylmetal reagents have been reported.^{[139]–[141]} For example, cyclobutenylmetals, generated *in situ* via carbometallation of 4-halo-1-metallo-1-alkynes, are reacted with iodobenzene to give 1,2-disubstituted cyclobutenes,^[139] as shown in **Scheme 35**.



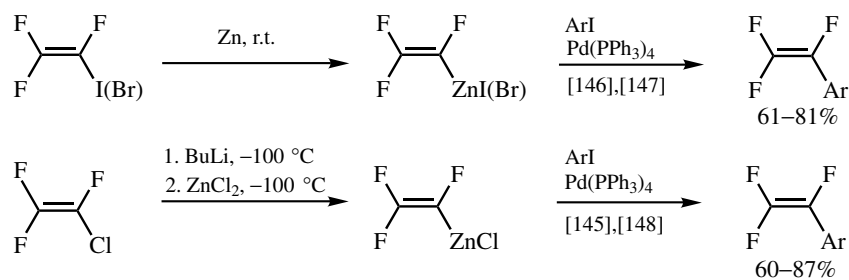
Scheme 35

1,2-Bis(boryl)alkenes can be prepared by the Pt-catalyzed stereoselective diboration of alkynes.^[142] Their two consecutive Suzuki coupling reactions have provided some polymer-bound tetrasubstituted alkenes (**Scheme 36**).^[143] The second coupling is carried out on a solid support permitting easy separation of the undesired tetrasubstituted alkenes formed in the first coupling reaction. This approach has been applied to the parallel synthesis of tamoxifen and related derivatives.^[144]

α,β -Trifluorosyrenes can be prepared in good yields by Negishi coupling of perfluorovinylzinc reagents with aryl halides. A wide variety of substituents in the aryl group can be tolerated.^{[145]–[148]} The perfluorovinylzinc reagents are prepared by either transmetalation of perfluorovinyl lithium with zinc halides^{[145], [149]} or direct zinc insertion into 1-iodo- and 1-bromo-trifluoroethylene^{[146], [147]} (**Scheme 37**).



Scheme 36



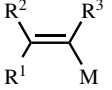
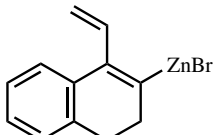
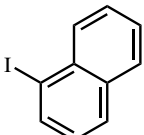
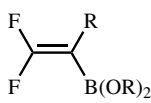
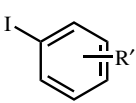
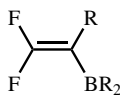
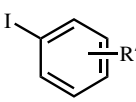
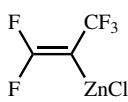
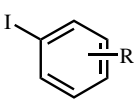
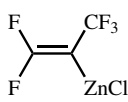
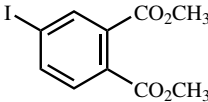
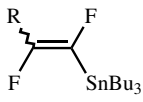
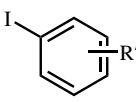
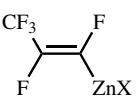
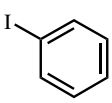
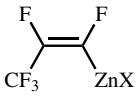
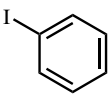
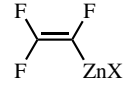
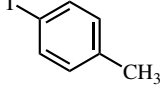
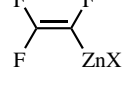
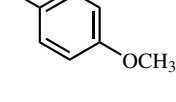
Scheme 37

Some other related synthesis of α - and/or β -fluorine-substituted styrenes by the reaction of the corresponding alkenylmetals containing Zn,^[150] B,^{[151],[152]} and Sn^{[153],[154]} with various aryl electrophiles are also summarized in **Table 7**.

TABLE 7. Pd-Catalyzed Cross-Coupling with Tetrasubstituted Alkenylmetals^a

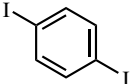
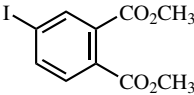
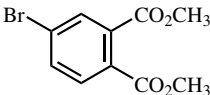
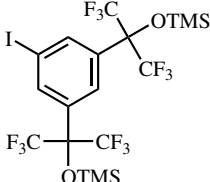
$\begin{matrix} R^2 & R^3 \\ \diagdown & / \\ C & =C \\ / & \diagdown \\ R^1 & M \end{matrix}$	Ar-X	Conditions	Yield (Selectivity) %	Reference
		Pd(PPh ₃) ₄ , CuI	66	[141]
		Pd(PPh ₃) ₄ , THF	47	[140]

TABLE 7. (Continued)

	Ar-X	Conditions	Yield (Selectivity) %	Ref- erence
		Pd(PPh ₃) ₄ , THF	69	[140]
		Cl ₂ Pd(PPh ₃) ₂ +BuLi, TBAF, K ₃ PO ₄	63–86	[151]
R = ⁿ Bu, ^s Bu				
		Pd ₂ dba ₃ , PPh ₃ , CuI, THF	91–94	[152]
R = ⁿ Bu, ^s Bu				
		Pd(PPh ₃) ₄ , THF/TG	45–75	[150]
		Pd(PPh ₃) ₄ , TG	48	[109]
		Pd(PPh ₃) ₄ , CuI, DMF	85–92	[154]
R = CH ₃ , ⁿ Bu, ^s Bu, ^t Bu, C ₆ H ₅ , ⁿ Hex				
		Pd(PPh ₃) ₄ , THF	80(100)	[146]
		Pd(PPh ₃) ₄ , THF	100(100)	[147]
		Pd(PPh ₃) ₄ , THF	75	[148]
		Pd(PPh ₃) ₄ , THF	85	[148]

(Continued)

TABLE 7. (Continued)

$\begin{array}{c} \text{R}^2 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{R}^1 \end{array} \begin{array}{c} \text{R}^3 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{M} \end{array}$	Ar-X	Conditions	Yield (Selectivity) %	Ref- erence
$\begin{array}{c} \text{F} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{F} \end{array} \begin{array}{c} \text{F} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{ZnX} \end{array}$		Pd(PPh ₃) ₄ , THF	60	[148]
$\begin{array}{c} \text{F} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{F} \end{array} \begin{array}{c} \text{F} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{ZnX} \end{array}$		Pd(PPh ₃) ₄ , THF	71	[109]
$\begin{array}{c} \text{F} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{F} \end{array} \begin{array}{c} \text{F} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{ZnX} \end{array}$		Pd(PPh ₃) ₄ , THF	41	[109]
$\begin{array}{c} \text{F} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{F} \end{array} \begin{array}{c} \text{F} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{ZnX} \end{array}$		Pd(PPh ₃) ₄ , THF	83	[155]

^a The alkenyl groups are arranged according to the increasing order of priority as determined by the Cahn–Ingold–Prelog rule. In cases where the same alkenyl group is used, the entries are arranged according to the degree of substitution and regiochemistry of the aryl groups. Finally, the leaving groups and then the counteranions are arranged as discussed in the text.

C. ARYL-ALKENYL COUPLING

An alternative approach to the synthesis of stereodefined arylated alkenes by the Pd-catalyzed cross-coupling involves the reaction of arylmetals with alkenyl electrophiles, *i.e.*, aryl-alkenyl coupling (Sect. A). Table 8 summarizes some representative examples of the Pd-catalyzed aryl-alkenyl coupling reactions.

TABLE 8. Pd-Catalyzed Aryl-Alkenyl Cross-Coupling^a

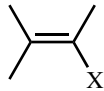
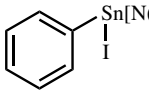
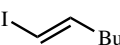
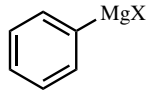
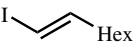
Type of Aryl Group	Ar-M		Conditions	Yield (Selectivity) %	Ref- erence
Phenyl			Pd(PPh ₃) ₄ , TBAF THF, dioxane	75	[176]
			Pd(PPh ₃) ₄ , C ₆ H ₆	82(>97)	[22]

TABLE 8. (Continued)

Type of Aryl Group	Ar-M		Conditions	Yield (Selectivity) %	Reference
			Pd(OAc) ₂ , TPPTS	53	[171]
			Pd(PPh ₃) ₄ , C ₆ H ₆	82(>97)	[22]
			Cl ₂ Pd(PPh ₃) ₂ , DMF	77	[177]
			Pd ₂ (dba) ₃	72	[174]
			Pd(PPh ₃) ₄ , DMF	65–73	[178]
			Pd(PPh ₃) ₄ , THF	83(50)	[179]
			Pd(PPh ₃) ₄	75(>97)	[139]
			Pd(PPh ₃) ₄	86(>97)	[139]
<i>para</i> -			Pd(PPh ₃) ₄ , C ₆ H ₆	85(99)	[19],[20]
<i>para</i> -			Cl ₂ Pd(PPh ₃) ₂ + BuLi DMF	93(>98)	[180]
			Pd ₂ (dba) ₃ AsPh ₃ , DMF	79	[181]
			Pd ₂ (dba) ₃ AsPh ₃ , DMF	85	[181]

(Continued)

TABLE 8. (Continued)


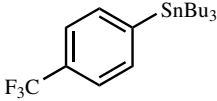

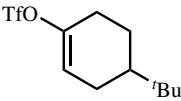
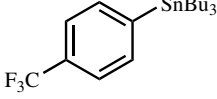

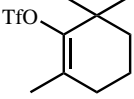
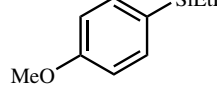

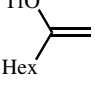
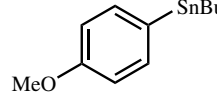

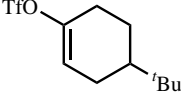
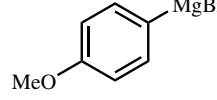

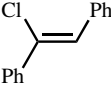
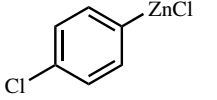

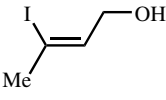
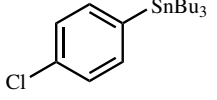

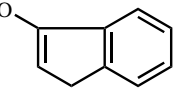
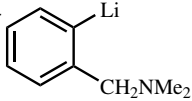

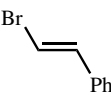
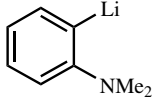

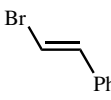
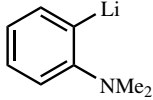

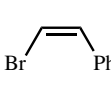
Type of Aryl Group	Ar-M		Conditions	Yield (Selectivity) %	Reference
			Pd(0)/AsPh ₃ /NMP/LiCl	87	[174]
			Pd(0)/AsPh ₃ /NMP/ZnCl ₂	89	[182]
			Pd(0)/AsPh ₃ /NMP	83	
			Pd ₂ (dba) ₃ , LiCl	60	[174], [182]
			Pd(PPh ₃) ₄ TBAF	62	[104]
			Pd ₂ (dba) ₃ , AsPh ₃	89	[174], [182]
			Cl ₂ Pd(PPh ₃) ₂ , Et ₂ O	75	[163]
			Pd(PPh ₃) ₄ DMF	97(>98)	[180]
			Pd ₂ (dba) ₃	68	[174]
<i>ortho</i> - 			Pd(PPh ₃) ₄ , C ₆ H ₆	60(99)	[20]
<i>ortho</i> - 			Pd(PPh ₃) ₄ , C ₆ H ₆	75(100)	[20]
			Pd(PPh ₃) ₄ , C ₆ H ₆	87(100)	[20]

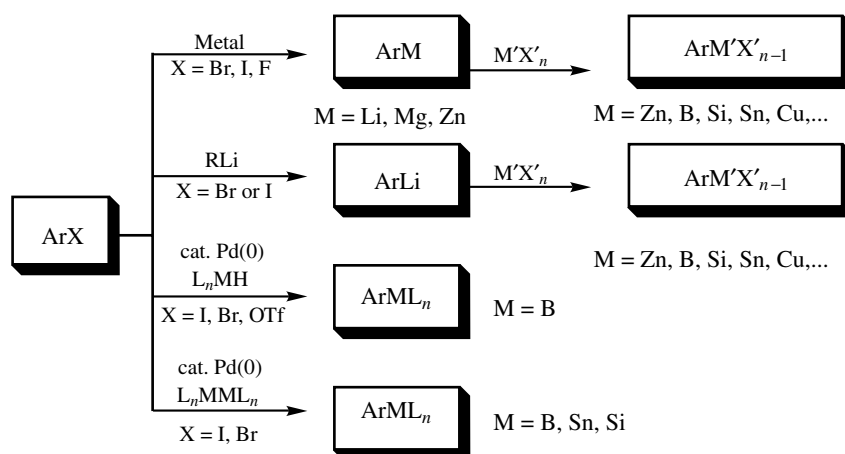
TABLE 8. (Continued)

Type of Aryl Group	Ar-M		Conditions	Yield (Selectivity) %	Reference
			Pd(PPh ₃) ₄ DMF	97(>98)	[180]
3,4-			Pd(PPh ₃) ₄ , THF	97	[183]

^aThe entries are arranged according to the degree of substitution and regiochemistry of the aryl groups. In cases where the same aryl group is used, they are arranged according to the type of the alkenyl groups. Finally, the leaving groups and then the counteranions are arranged as discussed in the text.

C.i. Accessibility of Arylmetals

Although arylmetals containing various metals, such as Li, Mg, Zn, B, Al, Sn, Si, and Cu, have been used in Pd-catalyzed aryl-alkenyl (Table 8), aryl-aryl (Sect. III.2.5), and other cross-coupling reactions, their accessibility varies widely depending on the metal counterions. Scheme 38 summarizes four representative methods for the preparation of various arylmetals. Aryl electrophiles including halides and triflates have been used as the starting materials in nearly all cases except in the directed metallation of arenes.^[34] Arylmetals containing relatively electropositive metals, such as Li and Mg, are readily prepared by oxidative metallation of aryl halides. Aryllithiums are also accessible via Li-halogen exchanges. On the other hand, those containing relatively electronegative metals, such as B, Al, Si, Cu, and Sn, are most commonly prepared via transmetalation of aryllithiums and arylmagnesium halides. Arylzincs represent an interesting class of arylmetals in that they can be prepared either by direct metallation of aryl bromides and

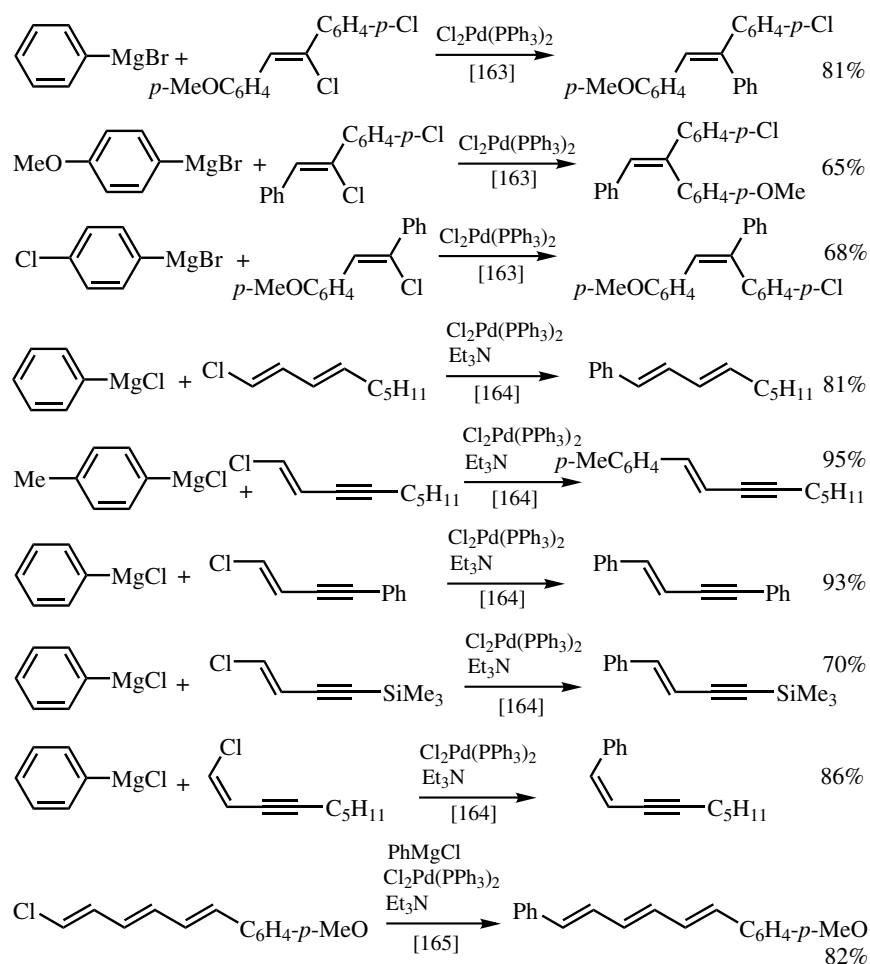


Scheme 38

iodides^[156] or via transmetalation. In addition to the methods discussed above, Pd-catalyzed stannation,^{[157]–[159]} borylation,^{[160],[161]} and silylation^[162] of aryl halides or triflates provide promising routes to arylmetals containing Sn, B, and Si, respectively. At present, however, the required dimetallic reagents are rather expensive, and this problem would have to be resolved before these reactions become truly useful.

C.ii. Scope of Pd-Catalyzed Aryl–Alkenyl Coupling

Aryllithiums are rarely used in Pd-catalyzed aryl–alkenyl coupling, although aryllithiums containing a chelating orthosubstituent (e.g., NMe₂ and CH₂NMe₂) have been reported to undergo Pd-catalyzed cross-coupling in good yields.^[20] On the other hand, Pd-catalyzed reaction of arylmagnesium derivatives with alkenyl electrophiles has been extensively investigated (**Table 8**). It is noteworthy that some even alkenyl chlorides, which are generally much less reactive than the corresponding bromides and iodides, have been successfully coupled with arylmagnesiums^{[163]–[165]} (**Scheme 39**). It should be clearly noted,

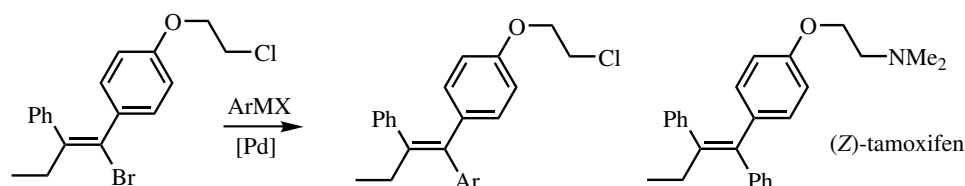


Scheme 39

however, that the alkenyl chlorides used in these reactions are limited to arylated alkenyl chlorides and conjugated chloroenynes and chlorodienes. Thus, the general applicability of alkenyl chlorides in Pd-catalyzed aryl-alkenyl coupling needs to be further delineated.

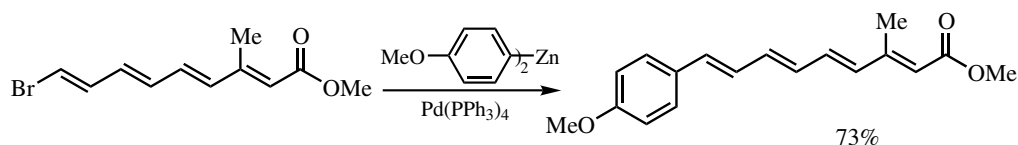
As in other cases of Pd- or Ni-catalyzed cross-coupling, Grignard reagents should probably be considered first in the aryl-alkenyl coupling because of their ready accessibility as the first-generation arylmetals. As needed, other metals should then be considered as potentially superior alternatives, and Zn, B, and Sn may have been the three most widely used metals, although some other metals including Al, Si, and Cu may also prove to be useful and even superior to the others mentioned above in some cases.

Rigorous comparisons of metal counteractions are still relatively rare. In the synthesis of (Z)-tamoxifen and related compounds,^{[166]–[168]} Mg and Zn appear to be superior to Sn in terms of stereospecificity and operational simplicity^[167] (**Scheme 40**). In cases where chemoselectivity is critically important, as in the synthesis shown in **Scheme 41**,^[169] Zn would have to be chosen over Mg.



ArMX	Conditions	Isolated Yield (%)	Z (%)
PhMgCl	Pd(PPh ₃) ₄ , PhMe, 110 °C, 1 h	99	95
PhZnCl	Pd(PPh ₃) ₄ , PhMe, 110 °C, 1 h	98	94
PhSnBu ₃	[ClPd(π-C ₃ H ₅)] ₂ , 25 °C, 24 h	94	72
	LiBr, Me ₂ NCOMe		
PhSnBu ₃	[ClPd(π-C ₃ H ₅)] ₂ , 25 °C, 24 h	96	91
	LiBr, HMPA		

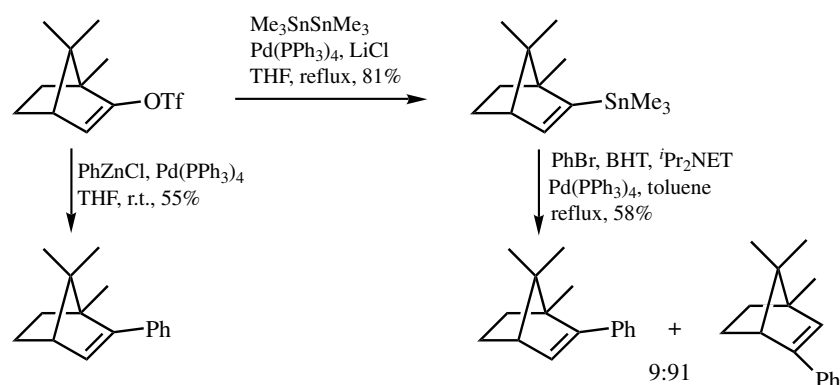
Scheme 40



Scheme 41

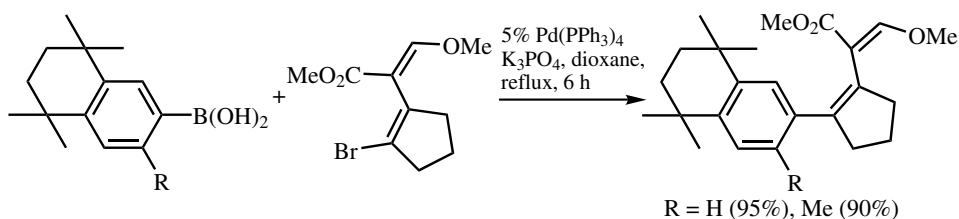
In some cases, more highly contrasting results may be obtained by using two or more different metals. In the reactions shown in **Scheme 42**, the aryl-alkenyl coupling using PhZnCl is regiospecific with retention. In sharp contrast, the alkenyl-aryl coupling using the corresponding alkenyltin derivative produces the unexpected regioisomer to the extent of 91%.^[170]

The reaction of arylboron compounds with alkenyl electrophiles has not been extensively investigated, and unfavorable results associated with fair yields in Pd-catalyzed



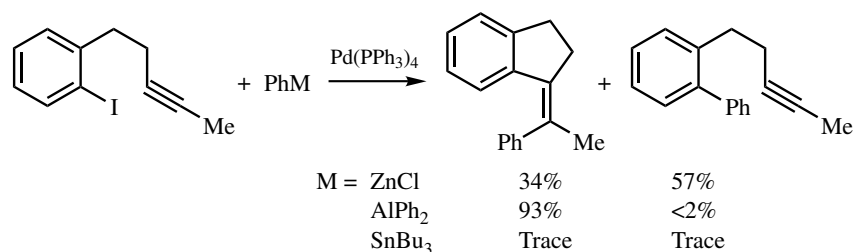
Scheme 42

aryl–alkenyl coupling have been observed.^[171] However, in the light of their extensive involvement in Pd-catalyzed aryl–aryl coupling (Sect. III.2.5), arylboron compounds are expected to participate in Pd-catalyzed aryl–alkenyl coupling much more extensively, as exemplified by a recent favorable result shown in **Scheme 43**.^[172]



Scheme 43

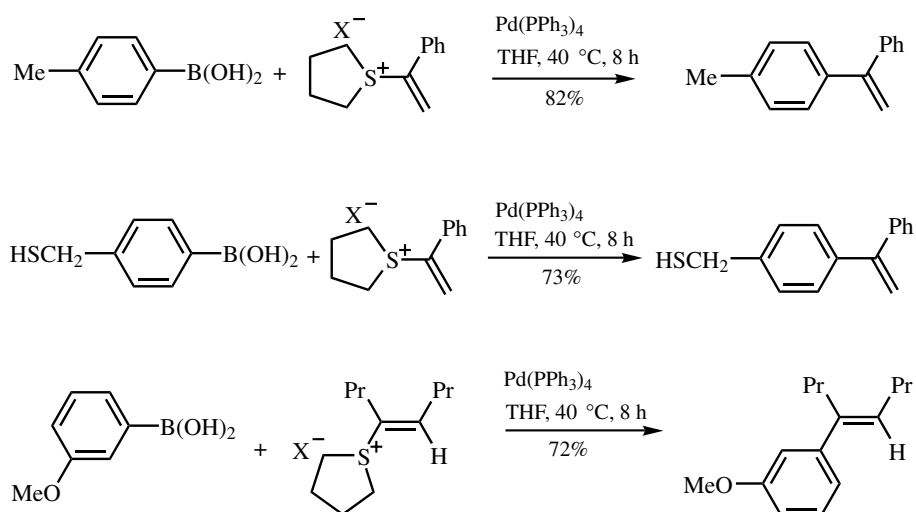
Arylaluminums have not been used as extensively as some other arylmetals in Pd-catalyzed cross-coupling. However, the intrinsic reactivity of arylaluminums appears to be somewhere between that of Zn and Sn. It is this relatively low intrinsic reactivity of arylaluminums that is critically required in the cyclic carbopalladation–cross-coupling tandem process shown in **Scheme 44**. The high intrinsic reactivity of Zn leads to the formation of the unwanted direct cross-coupling product in 57% yield, while the corresponding reaction of PhSnBu_3 does not produce either product under the conditions used.^[173]



Scheme 44

The low intrinsic reactivity of aryltins can be enhanced through optimization of the reaction conditions. In a comprehensive study of the effects of catalysts, ligands, solvents, and additives in Pd-catalyzed coupling of aryltins with organic sulfonates, the use of triphenylarsine as a ligand in conjunction with Pd_2dba_3 is recommended.^[174] In general, intrinsically less reactive B, Si, Sn, and so on appear to require more elaborate and extensively optimized reaction conditions for observing favorable results than Mg, Zn, and some other more reactive metals.

Electrophiles other than commonly used alkenyl halides and sulfonates have also been shown to participate in Pd-catalyzed aryl-alkenyl coupling. A recent work demonstrated the use of alkenyl-sulfonium salts in Pd-catalyzed aryl-alkenyl coupling with arylboronic acids,^[175] as shown in **Scheme 45**.



Scheme 45

D. ALKENYL-ALKENYL COUPLING

Pd-catalyzed alkenyl-alkenyl coupling has provided a highly efficient and selective methodology for the construction of stereodefined conjugated dienes of almost any substitution patterns including a wide variety of complex natural products (**Sect. III.2.18**). The protocols outlined in **Sects. B** and **C** are, in principle, applicable to alkenyl-alkenyl coupling as well by replacing arylmetals or aryl electrophiles with appropriate alkenyl reagents. However, the stereochemistry associated with alkenyl-alkenyl coupling is distinctly more complicated, since four possible stereoisomers, that is, *E,E*-, *E,Z*-, *Z,E*-, and *Z,Z*-conjugated dienes, are possible for any given alkenyl-alkenyl coupling, and due attention should be paid to this potentially complex stereochemical aspect of alkenyl-alkenyl coupling. Furthermore, the eight different alkenyl structural types (**Scheme 5**) lead to 64 possible structural types of conjugated dienes. For the sake of simplicity, this section is divided into eight subsections according to the structural types of alkenylmetals, and all eight possible structural types of alkenyl electrophiles are considered in each subsection.

D.i. Vinylmetals

1,3-Dienes containing a terminal vinyl group can be synthesized by either vinyl–alkenyl or alkenyl–vinyl coupling. The merits and demerits of the use of vinyl metals relative to that of vinyl halides are discussed in **Sect. B.i**. Some representative examples of Pd-catalyzed vinyl–alkenyl coupling reactions are summarized in **Table 9**.

TABLE 9. Pd-Catalyzed Coupling of Vinylmetals with Alkenyl Electrophiles^a




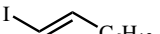
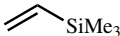
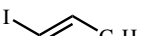
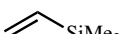

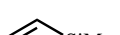

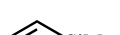
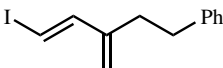
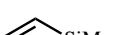
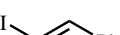
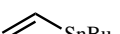
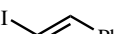
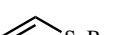
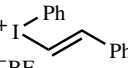
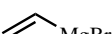

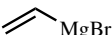
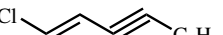

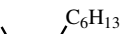
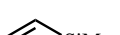

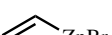
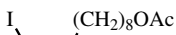


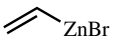
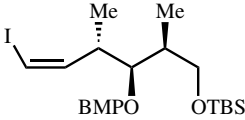
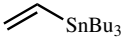
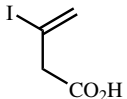
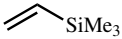
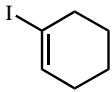
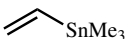
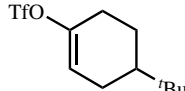
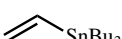
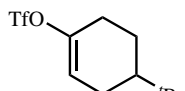
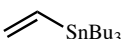
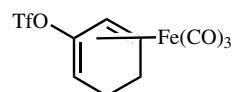
 M	Type of Alkenyl Electrophiles		Conditions	Yield (Selectivity) %	Reference
 MgX	(<i>E</i>)-β-		Pd(PPh ₃) ₄ , C ₆ H ₆	81(>97)	[22]
 SiMe ₃			[ClPd(π-C ₃ H ₅)] ₂ , TASF, P(OEt) ₃ , THF	100	[50]
 SiMe ₃			[ClPd(π-C ₃ H ₅)] ₂ , TASF, P(OEt) ₃ , THF	70	[50]
 SiMe ₃			[ClPd(π-C ₃ H ₅)] ₂ , TASF, P(OEt) ₃ , THF	52	[50]
 SiMe ₃			[ClPd(π-C ₃ H ₅)] ₂ , TASF, P(OEt) ₃ , THF	85	[50]
 SiMe ₃			[ClPd(π-C ₃ H ₅)] ₂ , TASF, P(OEt) ₃ , THF	93	[50]
 SnBu ₃			Cl ₂ Pd(MeCN) ₂ , DMF	85	[184]
 SnBu ₃			Cl ₂ Pd(MeCN) ₂ , DMF	79	[185]
 MgBr			Pd(PPh ₃) ₄ , C ₆ H ₆	91(99.5)	[19]
 MgBr			Cl ₂ Pd(PPh ₃) ₂ , Et ₃ N	71	[164]
 MgX	(<i>Z</i>)-β-		Pd(PPh ₃) ₄ , C ₆ H ₆	75(>97)	[22]
 SiMe ₃			[ClPd(π-C ₃ H ₅)] ₂ , TASF, P(OEt) ₃ , THF	76	[50]
 ZnBr			Pd(PPh ₃) ₄ , THF	67(99)	[186]

TABLE 9. (Continued)



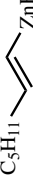
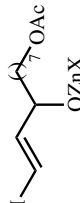
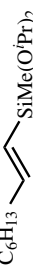



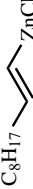
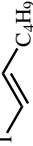



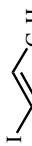




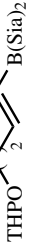
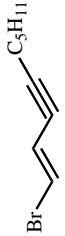
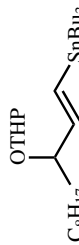
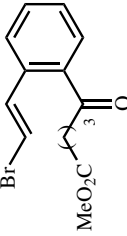
	Type of Alkenyl Electrophiles		Conditions	Yield (Selectivity) %	Reference
			Pd(PPh ₃) ₄ , THF	79	[187]
	α -		Cl ₂ Pd(MeCN) ₂ , DMF	60	[177]
	(<i>E</i>)- α,β -		[ClPd(π -C ₃ H ₅)] ₂ , TASF, P(OEt) ₃ , THF	100	[50]
			Cl ₂ Pd(MeCN) ₂ , DMF, 25 °C	80	[184]
			Pd(PPh ₃) ₄ , LiCl, THF	91	[188], [189]
			Cl ₂ Pd(PPh ₃) ₂ , LiCl, NMP	81	[190]

^a The entries are arranged according to the structural types of alkenyl electrophiles summarized in **Scheme 5**. With the same category, they are arranged (i) according to the types of substituents, *i.e.*, alkyl > alkenyl > aryl > alkynyl, and (ii) in the increasing order of priority determined by the Chan–Ingold–Prelog rule. Finally, the leaving groups and then the counteranions are arranged as discussed in the text.

D.ii. (*E*)- β -Substituted Alkenylmetals

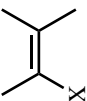
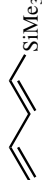

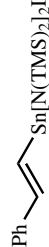
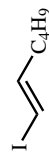
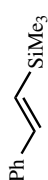
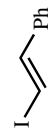
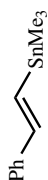
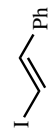
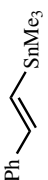
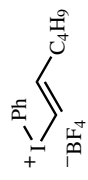
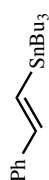
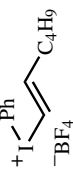
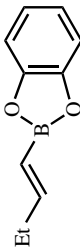

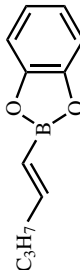

Alkenylmetals containing Mg, Zn, B, Al, Si, Sn, and Zr have been successfully coupled with alkenyl electrophiles, mainly halides and triflates. Alkenyl electrophiles of all eight possible structural types have been used in these coupling reactions as shown in **Table 10**.


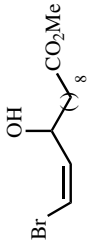
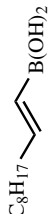
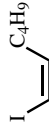
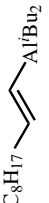
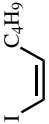
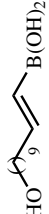
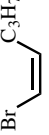
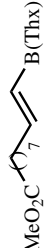
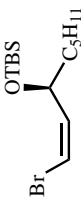
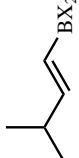
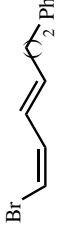
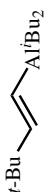
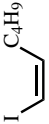
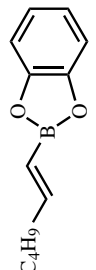


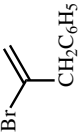
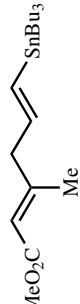
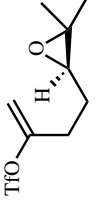
Earlier systematic investigations on the Pd- or Ni-catalyzed alkenyl–alkenyl cross-coupling addressed several fundamentally important issues^{[15][16][92]} that are still critically important, such as stereochemistry, comparison of different metal counteranions, comparison of Pd- and Ni-catalysts, and hydrometallation–cross-coupling tandem process for the conversion of alkynes to stereo- and regio-defined conjugated dienes. It should be recalled that palladium catalysts have been shown to be superior to nickel catalysts in terms of stereoselectivity in the alkenyl–alkenyl coupling, permitting nearly 100% retention of the stereochemistry of each alkenyl group. On the contrary, stereochemical scrambling has been observed to significant extents in the corresponding Ni-catalyzed reactions. Generally, alkenylmetals containing Zn and Mg display the highest intrinsic reactivity in a given

C_5H_{11} 	C_5H_{11} 	$Pd(PPh_3)_4$, THF	91(>97)	[17],[92]
C_5H_{11} 	C_5H_{11} 	$Pd(PPh_3)_4$, THF	94(99.9)	[197]
C_6H_{13} 	Br 	$[CIPd(\pi-C_3H_5)]_2$, TBAF, $P(OEt)_3$, THF	71(>99)	[82]
C_6H_{13} 	Cl 	$Ni(PPh_3)_4$, THF	80(>99)	[198]
C_8H_{17} 	I 	$Pd(PPh_3)_4$, THF	95	[92]
C_8H_{17} 	I 	$Pd(PPh_3)_4$, NaOH	74(99)	[199]
HO 	I 	$Pd(PPh_3)_4$, NaOEt, C_6H_6	66	[200]
MeO_2C 	I 	$Pd(PPh_3)_4$, NaOEt, C_6H_6	50	[201]
MeO_2C 	I 	$Cl_2Pd(PPh_3)_2$ + DIBAH	82(>98)	[92]
THPO 	Br 	$Pd(PPh_3)_4$, NaOH, H_2O	23(>98)	[202]
C_8H_{17} 		$Pd(PPh_3)_4$, toluene	54	[203]

(Continued)

TABLE 10. (Continued)

R	Type of Alkenyl Electrophile		Conditions	Yield (Selectivity) %	Reference
			[ClPd(π -C ₃ H ₅) ₂], TASF, P(OEt) ₃ , THF	78	[50]
			Pd(PPh ₃) ₄ , TBAF, THF, dioxane	77	[176]
			[ClPd(π -C ₃ H ₅) ₂], TASF, P(OEt) ₃ , THF	32	[50]
			Cl ₂ Pd(MeCN) ₂ , DMF	71 (86)	[184]
			Cl ₂ Pd(MeCN) ₂ , DMF	53	[185]
			Cl ₂ Pd(MeCN) ₂ , DMF	69	[185]
	(Z)- β -		Pd(PPh ₃) ₄ , BHA, NaOEt, EtOH	73–87	[193]
			Pd(PPh ₃) ₄ , NaOEt, C ₆ H ₆	91	[200]

C_5H_{11} 		$Pd(PPh_3)_4$, THF	88(99)	[197]
C_8H_{17} 		$Pd(PPh_3)_4$, NaOH, THF	74(99)	[199]
C_8H_{17} 		$Cl_2Pd(PPh_3)_2$ + DIBAH	55(>98)	[92]
HO 		$Pd(PPh_3)_4$, NaOEt, C_6H_6	82	[200]
MeO_2C 		$Cl_2Pd(PPh_3)_2$, NaOH, THF	54	[204]
		$Pd(PPh_3)_4$, NaOEt, C_6H_6	40–50	[205]
t -Bu 		$Cl_2Pd(PPh_3)_2$ + DIBAH	36(97)	[92]
C_4H_9 		$Pd(PPh_3)_4$, NaOEt, C_6H_6	80(~100)	[196]
C_6H_{13} 		$[CIPd(\pi-C_3H_5)]_2$, TBAF, $P(OEt)_3$, THF	31(>99)	[82]
MeO_2C 		$Pd(PPh_3)_4$, Cs, THF	58	[206]

(Continued)

TABLE 10. (Continued)

R	Type of Alkenyl Electrophile	Alkenyl Electrophile	Conditions	Yield (Selectivity) %	Reference
			Cl ₂ Pd(MeCN) ₂ , DMF	50	[177]
			Cl ₂ Pd(MeCN) ₂ , DMF	82	[177]
			Pd(PPh ₃) ₄ , THF	93	[192]
	β,β-		Pd(PPh ₃) ₄ , NaOEt, C ₆ H ₆	81(~100)	[194],[196]
	cis-α,β-		Pd(PPh ₃) ₄ , K ₃ PO ₄ , dioxane	76	[91],[138]
			10% Pd/C, CuI, AsPh ₃	80(100)	[53]
	trans-α,β-		Pd(PPh ₃) ₄ , DMF	81(>98)	[180]

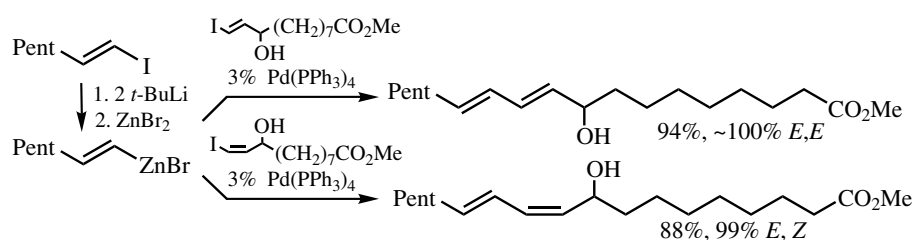
		$\text{Pd}(\text{PPh}_3)_4$, NaOEt	51	[207]
		$\text{Pd}(\text{PPh}_3)_4$, NaOEt , C_6H_6	45(>96)	[180]
		$\text{Pd}(\text{PPh}_3)_4$, NaOEt , C_6H_6	52	[208]
α, β, β - 		$\text{Pd}(\text{PPh}_3)_4$, K_3PO_4 , dioxane	97	[91],[138]
		$\text{Pd}(\text{PPh}_3)_4$, THF	78(>97)	[139]

^a The entries are arranged according to the structural types of the alkenyl electrophiles summarized in **Scheme 5**. With the same category, they are arranged according to the substituents in the alkenyl/metals as in the previous tables. For a given alkenyl group in the alkenyl/metal reagents, the entries are arranged according to the priority order of the substituents in the alkenyl electrophiles. Finally, the leaving groups and then the counterions are arranged as discussed in the text.

alkenyl–alkenyl coupling, but the reaction of alkenylmagnesium derivatives has been associated with various undesirable features including low chemoselectivity and low product yields. Although generally less reactive, alkenylmetals containing Al and Zr are attractive reagents, since they are often readily accessible via hydrometallation and carbometallation of alkynes and since highly satisfactory results have in fact been obtained in many cases. As is well known, various (*E*)- β -substituted alkenylmetals are most generally and reliably obtainable by hydroboration of alkynes. This advantage, however, is offset to considerable extents by the low intrinsic reactivity of alkenylboranes in Pd-catalyzed cross-coupling. Despite the development of the Suzuki protocol for alkenyl–alkenyl coupling, the overall synthetic scope of B-based methods appears to be more limited than that of Zn-based methods. Another widely used metal for Pd-catalyzed alkenyl–alkenyl coupling is Sn. Its intrinsically low reactivity and toxicity are two main limitations associated with Sn. In many favorable cases, its reactions are often as favorable as those of other favorable metals mentioned above. In more demanding cases, however, Sn has often been shown to be significantly inferior to Zn, B, and some other metals,^{[209]–[211]} as illustrated later. Another complication associated with Sn is the capricious and often difficult-to-predict courses of hydrostannation of alkynes.^[26] On the other hand, Sn as well as B has been very useful in achieving intramolecular alkenyl–alkenyl coupling, which often requires the generation of cyclization precursors containing both a nucleophilic alkenylmetal moiety and an electrophilic alkenyl moiety.^[212] Other less frequently used metals in Pd-catalyzed cross-coupling include Li, Cd, Si, and Cu; Si^[25] and Cu^[28] have provided some promising results. It is entirely possible that they may become widely used metal counteractions in the future.

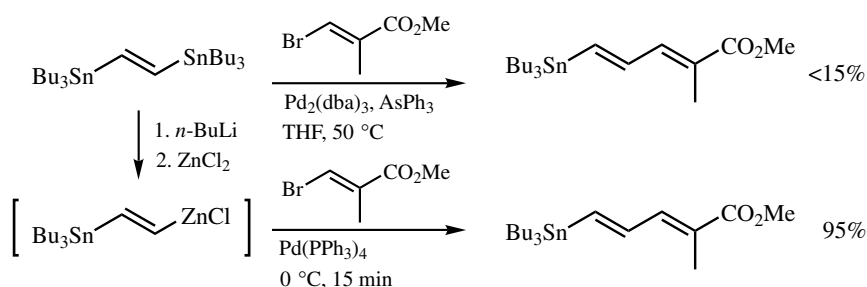
The following specific examples are presented to further support the above-mentioned generalizations.

The use of alkenylzincs as excellent organometallic partners in Pd-catalyzed alkenyl–alkenyl coupling has amply been demonstrated.^{[180],[192],[197],[213]} In most cases, reactions proceed smoothly to produce the desired products in excellent yields and high stereoselectivities, as exemplified by the synthesis of methyl dimorphecolates shown in **Scheme 46**.^[197]



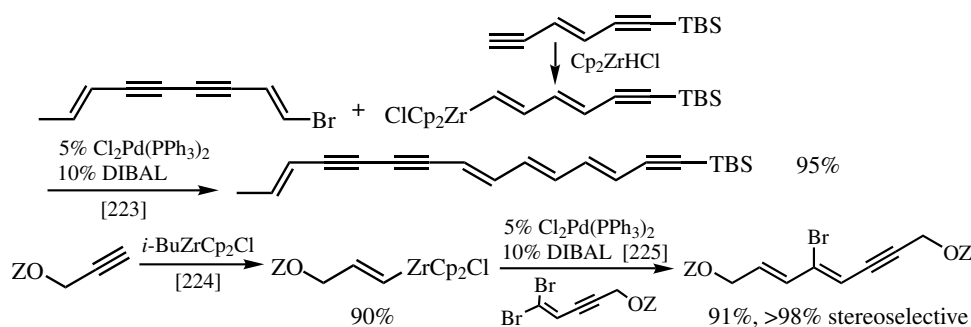
Scheme 46

Even though Sn and B may have been the two most frequently used metals in Pd-catalyzed alkenyl–alkenyl coupling over the past two decades, it has been demonstrated with increasing frequency that a few of the metals associated with Negishi coupling, especially Zn and Zr in some cases, are more advantageous, leading to decidedly more satisfactory results. For example, the Stille coupling between (*E*)- $\text{Bu}_3\text{SnCH=CHSnBu}_3$ and (*E*)- β -bromomethylacrylate gives no more than 15% of the desired product even with the use of triphenylarsine as ligand of the Pd catalyst.^[47] In sharp contrast, the corresponding coupling with (*E*)- $\text{Bu}_3\text{SnCH=CHZnCl}$, generated *in situ* by stepwise transmetalations, proceeds rapidly to produce the desired product in 95% yield (**Scheme 47**).^[209]



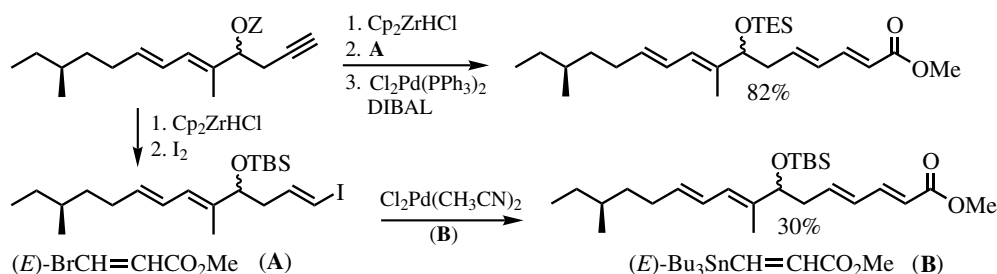
Scheme 47

The use of Zr in the hydrometallation–cross-coupling tandem process has been particularly attractive. Even in some highly demanding cases where polyconjugated enynes are used in cross-coupling reactions, the hydrozirconation–cross-coupling tandem reaction proceeds very smoothly to lead to satisfactory results as demonstrated in the synthesis of xerulin^[223] (**Scheme 48**). Alkenylzirconium reagent, generated *in situ* by hydrogen transfer hydrozirconation of TBS-protected propargyl alcohol, is reacted with 1,1-dibromo alkene to stereoselectively produce *trans*-cross-coupled product^[225] (**Scheme 48**).



Scheme 48

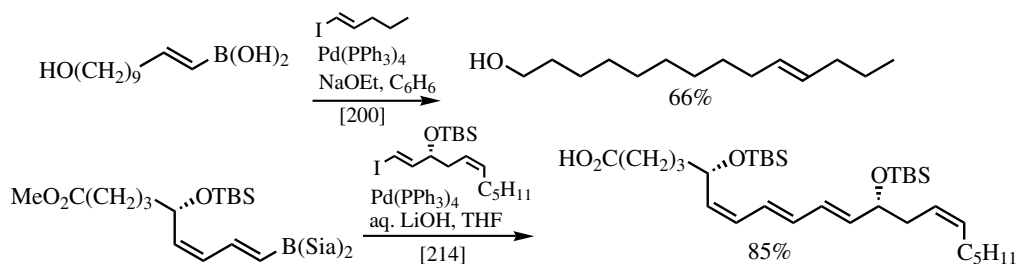
The superiority of alkenylzirconiums to other alkenylmetals has further been demonstrated in the synthesis of papulacandin D (**Sect. III.2.18**). The initial use of Stille coupling to synthesize the chain moiety resulted in less than 30% of desired product. However, the related coupling by using *in situ* generated alkenylzirconium gave the desired product in 82% yield^[211] (**Scheme 49**).



Scheme 49

Although further comparisons of alkenylzirconiums to other alkenylmetals in Pd-catalyzed cross-coupling are desirable, the results discussed above clearly indicate that alkenylzirconiums are among the best alkenylmetals in alkenyl–alkenyl coupling, and the hydrozirconation–cross-coupling tandem process provides a convenient and satisfactory route to conjugated dienes and polyenes.

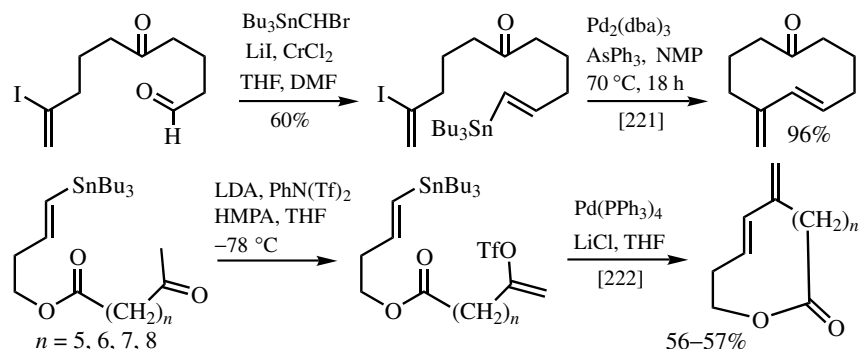
Although the intrinsic reactivity of alkenyl boranes in Pd-catalyzed cross-coupling is rather low, the use of a base remarkably enhances their reactivity as demonstrated by Suzuki and co-workers.^{[194]–[196],[200]} Compared with other organometals containing Li, Mg, Zn, Al, Cu, and Zr, alkenylborons are very stable, even to alcohols and H₂O. Thus, a wide variety of functional groups can be tolerated in their coupling reactions, as shown in **Scheme 50**.



Scheme 50

However, the chemoselectivity in Pd-catalyzed cross-coupling of alkenylborons would suffer from the strongly basic condition and elevated reaction temperatures, when substrates with sensitive functional groups are employed. This limitation has been overcome, to some extent, by the use of aqueous solution of TIOH in place of NaOH or KOH as demonstrated by Kishi and co-workers in the synthesis of palytoxin.^[215] The dramatic rate enhancement of Suzuki coupling by TIOH allows the reaction to proceed smoothly even at 0 °C. The utility of this method has been demonstrated in other natural product syntheses as well^{[216]–[220]} (**Sect. III.2.18**).

As discussed earlier, the low intrinsic reactivity and high chemical stability of alkenyltins can be exploited in devising intramolecular alkenyl–alkenyl coupling^[212] particularly in the synthesis of cyclic natural products (**Sect III.2.18**). Macrocyclic ketones and macrolactones have been synthesized by this coupling reaction as shown in **Scheme 51**.

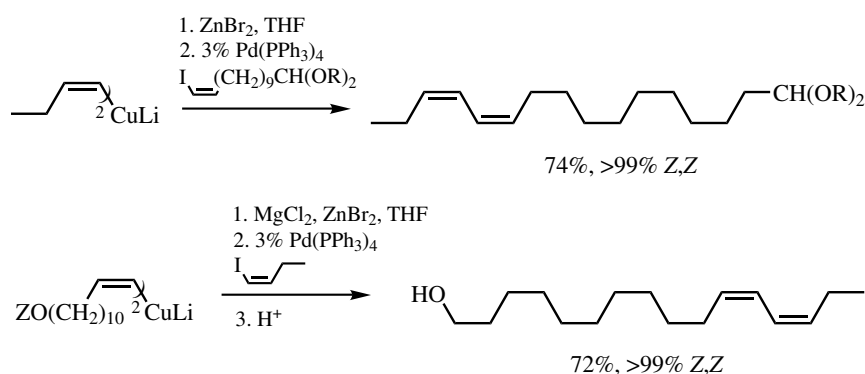


Scheme 51

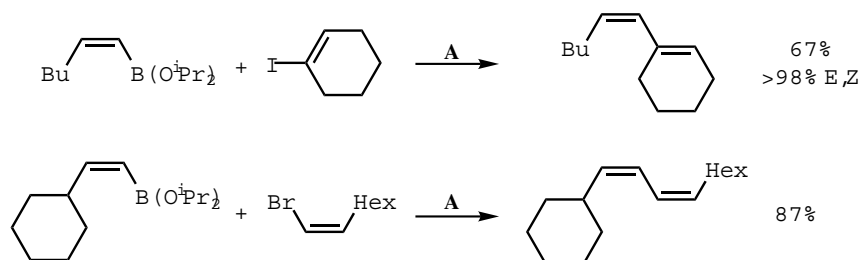
D.iii. (Z)- β -Substituted Alkenylmetals

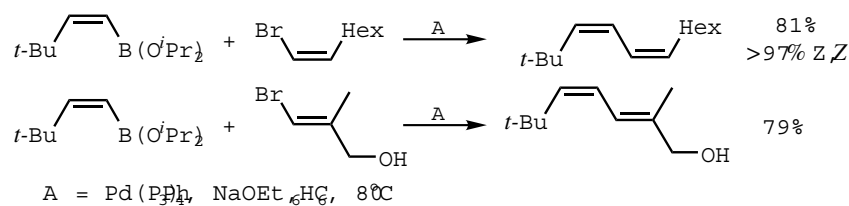
Although stereoselective *syn*-hydrogenation and its equivalents via *syn*-hydrometallation of conjugated diynes^[231] and enynes^[232] have provided some prototypical selective routes to (*Z,E*)- and/or (*Z,Z*)-conjugated dienes, Pd-catalyzed alkenyl-alkenyl coupling has proved to be the method of choice for their preparation because of its general applicability, stereoselectivity, and favorable overall results including generally high product yields.

(*Z,E*)-conjugated dienes can, in principle, be prepared by either the reaction of (*E*)-alkenylmetals with (*Z*)-alkenylelectrophiles, as discussed in **Sect. D.ii**, or that of (*Z*)-alkenylmetals with (*E*)-alkenyl electrophiles. Choice between these two options depends on a number of factors including the relative accessibility of the two required reagents. The ready accessibility of (*Z*)- β -substituted alkenylcoppers via carbocupration^[38] of ethyne makes Pd-catalyzed reaction of (*Z*)- β -substituted alkenylcoppers a very attractive route to (*Z,E*)- and (*Z,Z*)-conjugated dienes.^{[28],[226],[227]} Interestingly, the addition of ZnBr₂ as a cocatalyst^[18] has proved to have favorable effects on this reaction^{[226],[227]} (**Scheme 52**).

**Scheme 52**

As discussed in **Sect. B.iii.b**, (*Z*)- β -substituted alkenylboranes are obtainable via 1-haloalkynes hydroboration–1,2-hydride migration protocol.^{[36],[37],[96],[97]} Their Pd-catalyzed reactions with (*E*)- and (*Z*)-alkenyl electrophiles provide (*Z,E*)- and (*Z,Z*)-conjugated dienes, respectively (**Scheme 53**).^[48]

**Scheme 53 (Continued)**



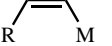


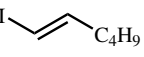
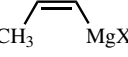
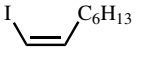
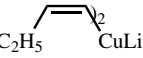
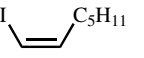
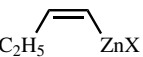
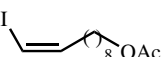
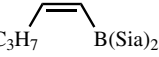
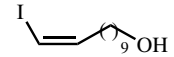
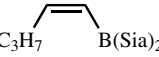
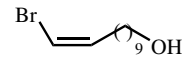
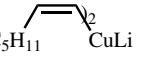
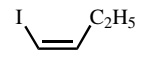
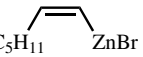
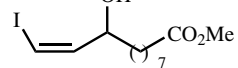
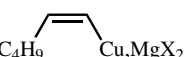
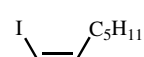

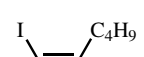
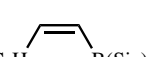
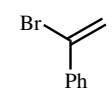
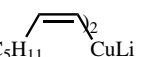
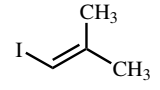
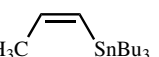
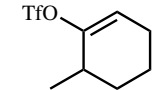
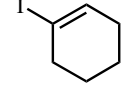
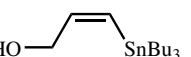
Scheme 53 (Continued)

At present, (*Z*)- β -substituted alkenylmetals containing other metals are less readily accessible than those mentioned above, even though the Zr-catalyzed carboalumination of ethyne has been shown to produce (*Z*)- β -substituted alkenylalanes.^[228] They are generally prepared via metallation–transmetalation of (*Z*)- β -substituted halides. Despite this drawback, (*Z*)- β -substituted alkenylzincs generated by this procedure have been shown to be superior reagents in the subsequent Pd-catalyzed cross-coupling reaction^{[186],[198],[229]} (Table 11).

TABLE 11. Pd-Catalyzed Coupling of (*Z*)- β -Substituted Alkenylmetals with Alkenyl Electrophiles^a

R	Type of Alkenyl Electrophile	X	Conditions	Yield (Selectivity) %	Reference
CH ₃ -CH=CH-MgX	(<i>E</i>)- β -	I-CH=CH-C ₆ H ₁₃	Pd(PPh ₃) ₄ , C ₆ H ₆	87(>99)	[22]
C ₂ H ₅ -CH=CH ₂ -CuLi		I-CH=CH-C ₅ H ₁₁	Pd(PPh ₃) ₄ , ZnX ₂ , THF	82(99)	[226]
C ₂ H ₅ -CH=CH ₂ -CuLi		Br-CH=CH-Ph	Pd(PPh ₃) ₄ , ZnX ₂ , THF	85(97.6)	[226]
C ₃ H ₇ -CH=CH ₂ -CuLi		I-CH=CH-CH ₂ -Cl	Pd(PPh ₃) ₄ , ZnX ₂ , THF	89(~100)	[186]
C ₃ H ₇ -CH=CH ₂ -CuLi		I-CH=CH-CH ₂ -I	Pd(PPh ₃) ₄ , ZnX ₂ , THF	76(~100)	[186]
C ₄ H ₉ -CH=CH-B(O ^{<i>i</i>} Pr) ₂		Br-CH=CH-C ₆ H ₁₃	Pd(PPh ₃) ₄ , NaOEt, C ₆ H ₆	70(>99)	[98]
C ₄ H ₉ -CH=CH-B(Sia) ₂		Br-CH=CH-Ph	Pd(PPh ₃) ₄ , NaOEt, C ₆ H ₆	49(99)	[196]
C ₅ H ₁₁ -CH=CH ₂ -CuLi		I-CH=CH-C ₂ H ₅	Pd(PPh ₃) ₄ , ZnX ₂ , THF	80(99)	[226]
C ₅ H ₁₁ -CH=CH-ZnBr		I-CH=CH-CH(OH)-CH ₂ -CO ₂ CH ₃	Pd(PPh ₃) ₄ , THF	92(~100)	[197]
^{<i>t</i>} Bu-CH=CH-Cu, MgX ₂		I-CH=CH-C ₅ H ₁₁	Pd(PPh ₃) ₄ , ZnX ₂ , THF	55(99)	[227]

TABLE 11. (Continued)

	Type of Alkenyl Electrophile		Conditions	Yield (Selectivity) %	Reference
			Cl ₂ Pd(CH ₃ CN) ₂ , DMF	74	[184]
	(Z)-β-		Pd(PPh ₃) ₄ , C ₆ H ₆	87(>97)	[22]
			Pd(PPh ₃) ₄ , ZnX ₂ , THF	86(99)	[226]
			Pd(PPh ₃) ₄ , THF	88(99.5)	[229]
			Pd(PPh ₃) ₄ , NaOEt, C ₆ H ₆	50	[200]
	(Z)-β-		Pd(PPh ₃) ₄ , NaOEt, C ₆ H ₆	69	[200]
			Pd(PPh ₃) ₄ , ZnBr ₂ , THF	86(>99)	[226]
			Pd(PPh ₃) ₄ , THF	95(99)	[197]
			Pd(PPh ₃) ₄ , ZnX ₂ , THF	53(99)	[227]
			Cl ₂ Pd(MeCN) ₂ , DMF	78	[184]
	α-		Pd(PPh ₃) ₄ , NaOEt	55(99)	[196]
	β,β-		Pd(PPh ₃) ₄ , THF	94(~100)	[226]
	cis-α,β-		Pd(OAc) ₂ , NMP	75	[230]
			Pd(OAc) ₂ , CH ₂ Cl ₂	>90	[230]
			Cl ₂ Pd(MeCN) ₂ , DMF	61	[184]

^aSee Table 10

D.iv. α -Substituted Alkenylmetals

The α -substituted alkenylmetals used in Pd-catalyzed cross-coupling have been mainly those containing Mg, Zn, B, and Sn, as shown in **Table 12** as well as **Schemes 54–57**. Of these, α -substituted alkenylmetals containing Mg and Zn can readily be prepared by direct oxidative metallation of 2-halo-1-alkenes^[192] that are easily accessible by Markovnikov addition of HX to 1-alkynes (**Scheme 54**). α -Substituted alkenyltin compounds have been prepared and used in the construction of bicyclic diene systems via intramolecular Stille coupling, as shown in **Scheme 55**.^[234]

TABLE 12. Pd-Catalyzed Coupling of α -Substituted Alkenylmetals with Alkenyl Electrophiles^a


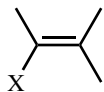
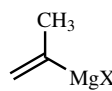
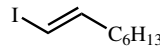
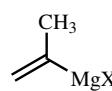
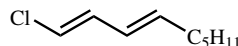
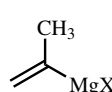
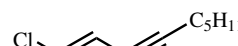
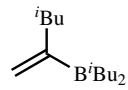
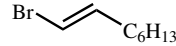
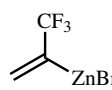
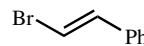
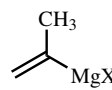
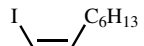
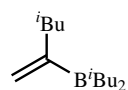
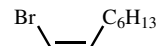
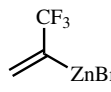

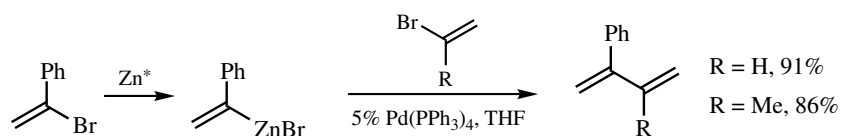
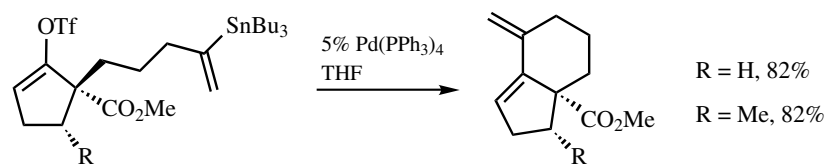
	Type of Alkenyl Electrophile		Conditions	Yield (Selectivity) %	Reference
<i>(E)</i> - β -					
			Pd(PPh ₃) ₄ , C ₆ H ₆	82(>97)	[22]
			Cl ₂ Pd(PPh ₃) ₂ , Et ₃ N (8 equiv)	55	[164]
			Cl ₂ Pd(PPh ₃) ₂ , Et ₃ N (8 equiv)	62	[164]
			Pd(PPh ₃) ₄ , NaOH, H ₂ O, THF	84(>99)	[117]
			Pd(PPh ₃) ₄ , THF	87–91	[233]
<i>(Z)</i> - β -					
			Pd(PPh ₃) ₄ , C ₆ H ₆	84(>97)	[22]
			Pd(PPh ₃) ₄ , NaOH, H ₂ O, THF	87(>99)	[117]
α -					
			Pd(PPh ₃) ₄ , THF	92	[233]

TABLE 12. (Continued)

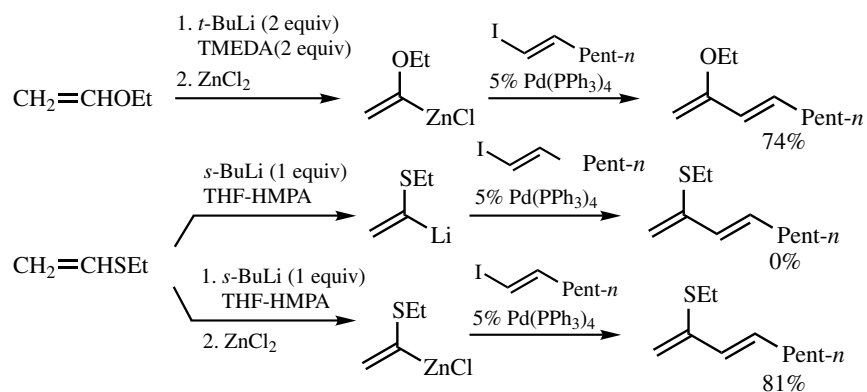
	Type of Alkenyl Electrophile		Conditions	Yield (Selectivity) %	Reference
	α, β -				
			Pd(PPh ₃) ₄ , THF	86	[233]
			Pd(PPh ₃) ₄ , THF	90	[233]

^aSee Table 10.

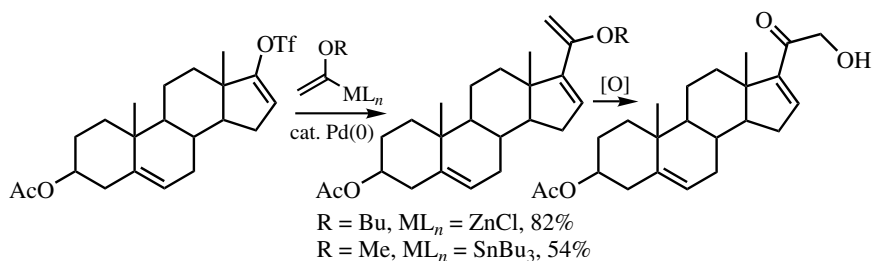
Scheme 54



Scheme 55



Scheme 56

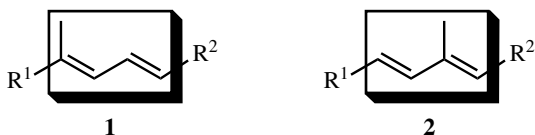


Scheme 57

The Pd-catalyzed reactions of α -heterosubstituted alkenylzincs containing alkoxy and thioalkoxy groups were developed with the goal of synthesizing heterosubstituted conjugated dienes for the Diels–Alder reaction^[118] (Scheme 56). The use of the parent alkenyllithiums did not produce the desired dienes in detectable amounts. This reaction has been applied to the synthesis of steroidal α -hydroxy enones^[235] (Scheme 57). It should be noted that Zn has been shown to be decidedly superior to Sn as the counteranion.

D.v. β, β -Substituted Alkenylmetals

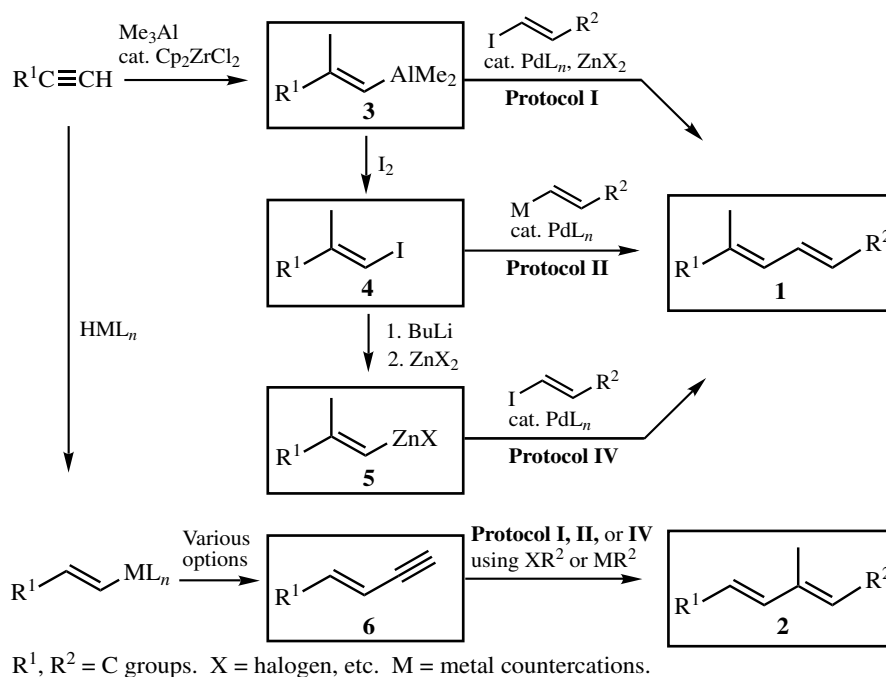
A large number of natural products, such as carotenoids, contain conjugated di- and oligo-ene moieties with at least one (*E*)-trisubstituted alkene unit, such as **1** and **2** shown in Scheme 58. Although all (*E*)-isomers are dominant, their stereoisomers are also known.



Scheme 58

Even today, carotenoids and other natural products represented by **1** and/or **2** are synthesized by using the Wittig and related carbonyl olefination reactions that are often not highly stereoselective, thus requiring delicate and tedious separations. Carbometallation reactions of alkynes,^{[38],[40]} especially the Zr-catalyzed carboalumination discovered in 1978,^{[236],[237]} used in conjunction with Pd-catalyzed cross-coupling^[18] have provided a totally different carbometallation–cross-coupling tandem protocol for the synthesis of **1** and **2** (Scheme 59).

Since the preparation of β, β -substituted alkenylmetals as the first-generation organometals has been achieved mostly by Zr-catalyzed carboalumination^[40] and carbocupration,^[38] the exploitation of Protocol I has largely resorted to these two carbometallation reactions, as indicated by the results summarized in Table 13. Moreover, since it is impractical to carry out methylcupration of alkynes requiring several days at $-25\text{ }^\circ\text{C}$,^[238] the synthesis of natural products represented by **1** and **2** by the use of Protocol I has mostly been limited to those cases where Zr-catalyzed carboalumination is



Scheme 59

TABLE 13. Pd-Catalyzed Coupling of β,β -Substituted Alkenylmetals with Alkenyl Electrophiles^a

$R^1-CH=CH-R^2-M$	Type of Alkenyl Electrophile	X	Conditions	Yield (Selectivity) %	Reference
<i>Vinyl</i>					
$C_5H_{11}-CH=CH-AlMe_2$		Br	$Pd(PPh_3)_4, ZnCl_2$	73(>97)	[18]
$CH_3-CH=CH-CH_2-CH_2-CH_2-CH=CH-AlMe_2$		Br	$Pd(PPh_3)_4, ZnCl_2$	70(>98)	[18]
$ZO-CH_2-CH_2-CH_2-CH=CH-AlMe_2$		Br	$Pd(PPh_3)_4, ZnCl_2$	43(94)	[251]
<i>(E)-β-</i>					
$H_3C-CH=CH-CuLi$ CH_3		I	$Pd(PPh_3)_4, THF$	96(>99)	[226]
$H_3C-CH=CH-Cu-MgX_2$ C_2H_5		I	$Pd(PPh_3)_4, ZnCl_2$	78(>99)	[227]
$H_3C-CH=CH-Cu-MgX_2$ C_2H_5		Br	$Pd(PPh_3)_4, THF$	74(99)	[227]

(Continued)

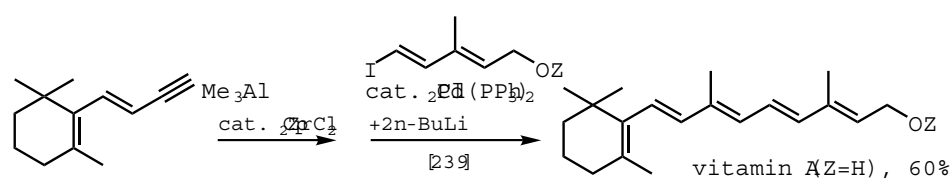
TABLE 13. (Continued)

$\begin{array}{c} R^1 \\ \\ R^2 - C = M \end{array}$	Type of Alkenyl Electrophile	$\begin{array}{c} \diagup \quad \diagdown \\ X - C = C \end{array}$	Conditions	Yield (Selectivity) %	Reference
$\begin{array}{c} C_5H_{11} \\ \\ C = AlMe_2 \\ \\ CH_3 \end{array}$		$\begin{array}{c} I - CH = CH - C_4H_9 \end{array}$	Pd(PPh ₃) ₄ , ZnCl ₂	65(>97)	[18]
$\begin{array}{c} H_3C \\ \\ C = Cu \cdot MgX_2 \\ \\ C_5H_{11} \end{array}$		$\begin{array}{c} I - CH = CH - C_5H_{11} \end{array}$	Pd(PPh ₃) ₄ , THF	70(>99)	[227]
$\begin{array}{c} C_6H_{13} \\ \\ C = BBr_2 \\ \\ C_4H_9 \end{array}$		$\begin{array}{c} I - CH = CH - C_6H_{13} \end{array}$	Pd(PPh ₃) ₄ , LiOH, H ₂ O	52(99)	[122]
$\begin{array}{c} TMS \\ \\ C = C - BBr_2 \\ \\ C_6H_{13} \end{array}$		$\begin{array}{c} I - CH = CH - C_6H_{13} \end{array}$	Pd(PPh ₃) ₄ , LiOH, H ₂ O	81(99)	[122]
$\begin{array}{c} H_3C \\ \\ C = CuLi \\ \\ CH_3 \end{array}$	(Z)-β-	$\begin{array}{c} I - CH = CH - C_5H_{11} \end{array}$	Pd(PPh ₃) ₄ , ZnX ₂	92(>99)	[226]
$\begin{array}{c} H_3C \\ \\ C = Cu \cdot MgX_2 \\ \\ C_2H_5 \end{array}$		$\begin{array}{c} I - CH = CH - C_5H_{11} \end{array}$	Pd(PPh ₃) ₄	64(>99)	[227]
$\begin{array}{c} H_3C \\ \\ C = Cu \cdot MgX_2 \\ \\ C_3H_7 \end{array}$		$\begin{array}{c} I - CH = CH - C_5H_{11} \end{array}$	Pd(PPh ₃) ₄	70(>99)	[227]
$\begin{array}{c} TMS \\ \\ C = C - BBr_2 \\ \\ C_6H_{13} \end{array}$	(Z)-β-	$\begin{array}{c} I - CH = CH - C_4H_9 \end{array}$	Pd(PPh ₃) ₄ , LiOH, H ₂ O	62	[122]
$\begin{array}{c} Ph \\ \\ C = Cu \cdot MgX_2 \\ \\ C_2H_5 \end{array}$		$\begin{array}{c} I - CH = CH - C_2H_5 \end{array}$	Pd(PPh ₃) ₄ , THF	70(>99)	[227]
$\begin{array}{c} H_3C \\ \\ C = CuLi \\ \\ CH_3 \end{array}$	β,β-	$\begin{array}{c} CH_3 \\ \\ I - CH = C - CH_3 \end{array}$	Pd(PPh ₃) ₄ , ZnX ₂	94(>99)	[226]
$\begin{array}{c} H_3C \\ \\ C = Cu \cdot MgX_2 \\ \\ C_2H_5 \end{array}$		$\begin{array}{c} C_4H_9 \\ \\ I - CH = C - CH_3 \end{array}$	Pd(PPh ₃) ₄ , THF	55(>99)	[227]
$\begin{array}{c} H_3C \\ \\ C = SnBu_3 \\ \\ CH_3 \end{array}$	cis-α,β-	$\begin{array}{c} \text{Tricyclic silyl enol ether} \end{array}$	Pd(PPh ₃) ₄ , LiCl, THF	80	[188], [189]

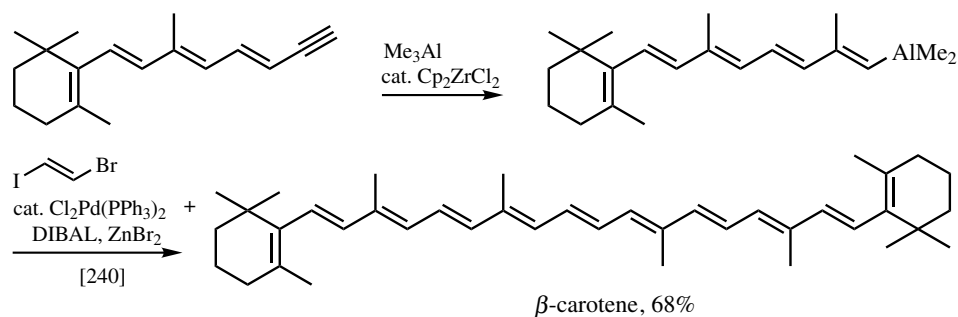
^aSee Table 10.

involved. Some prototypical examples are shown in **Schemes 60–62**. Particularly noteworthy is the development of a highly efficient and stereoselective iterative and convergent method for the synthesis of carotenoids and retinoids shown in **Schemes 61** and **62**.^[240] It should be noted that the reactivity of β,β -substituted alkenylalanes can be significantly enhanced by the addition of ZnBr_2 or ZnCl_2 .^[18]

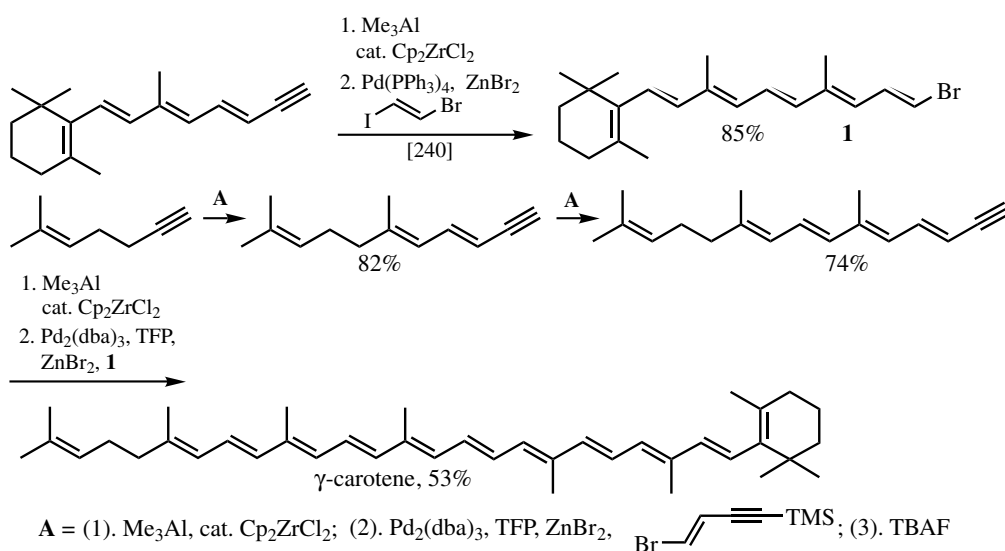
Despite the high efficiency and stereoselectivity associated with **Protocol I** shown in **Scheme 59**, its full development as a method for the synthesis of carotenoids, retinoids, and



Scheme 60

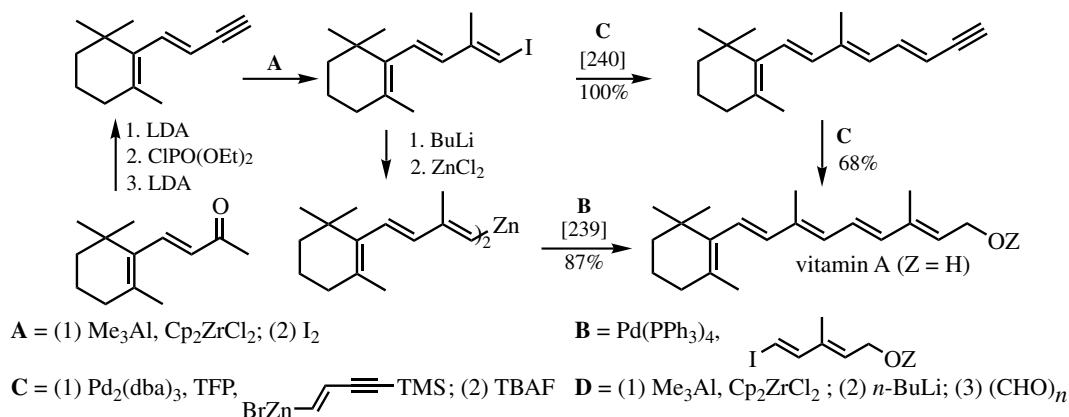


Scheme 61

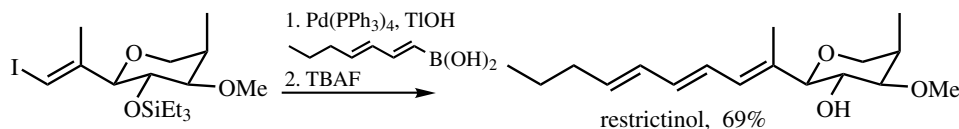


Scheme 62

other natural products has been made only within the past few years. Consequently, it has not yet been widely utilized. Although more circuitous, **Protocols II** and **IV** have been more widely exploited in the synthesis of a variety of natural products, such as rapamycin,^{[241],[242]} calciculin A,^{[243]–[245]} indanomycin,^[246] sanglifehrin A,^[247] vitamin A,^{[239],[248]} restrictinol,^[249] and β - and γ -carotenes,^[240] as exemplified by the results shown in **Schemes 63** and **64**. The structures of these natural products are shown in **Table 3** in **Sect. III. 2.18**.

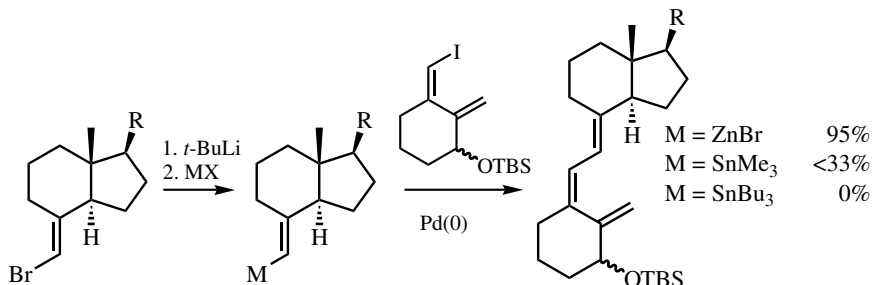


Scheme 63



Scheme 64

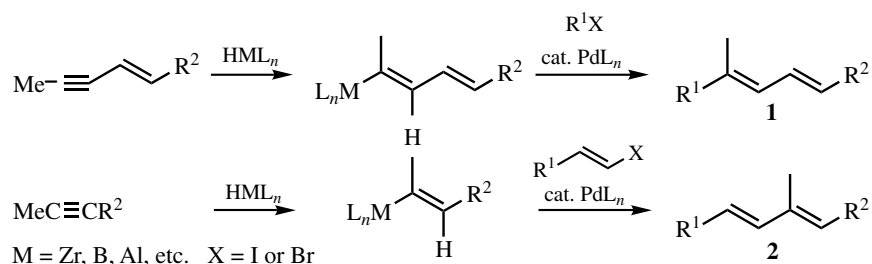
Haloboration of 1-alkynes followed by chemoselective cross-coupling can provide β,β -substituted alkenylborons that undergo Pd-catalyzed coupling with alkenyl halides to give stereodefined trisubstituted alkenes.^[122] The use of other β,β -substituted alkenylmetals has also been demonstrated. For example, exocyclic alkenylmetals containing Zn and Sn have been used in Pd-catalyzed cross-coupling approach to the vitamin D skeleton^[250] as shown in **Scheme 65**. It should be noted that the alkenylzinc appeared to be distinctly superior to the corresponding alkenyltins.



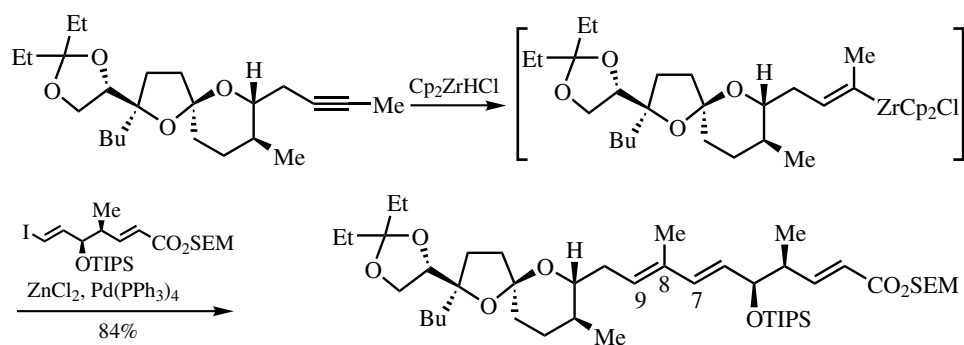
Scheme 65

D.vi. *cis*- α,β -Substituted Alkenylmetals

Conjugated dienes, such as those represented by **1** and **2** in the previous subsection, can, in principle, be synthesized also by hydrometallation–cross-coupling tandem processes shown in **Scheme 66**. This is indeed one of the most significant cases of the use of *cis*- α,β -substituted alkenylmetals in Pd-catalyzed alkenyl–alkenyl coupling.

**Scheme 66**

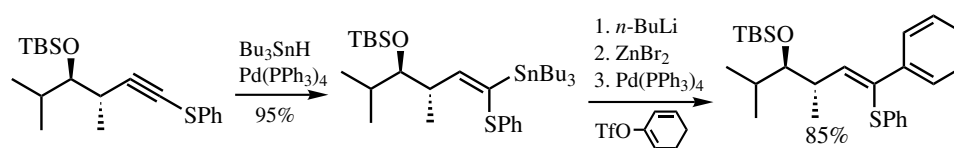
The crucial issue in the processes shown in **Scheme 66** is the regioselectivity of the hydrometallation, which tends to be generally less than satisfactory (<90–95%). Fortunately, HZrCp₂Cl displays a $\geq 95\%$ regioselectivity in the hydrozirconation of internal alkynes with Me as one of the two substituents.^{[252],[253]} This has been exploited in the regioselective syntheses of complex natural products represented by **1** and **2**, such as reveromycin B^[254] (**Scheme 67**) and β -amino acid Adda.^[255] It should be mentioned that attempts to exploit Stille coupling for the construction of C₇–C₈ bond in the synthesis of reveromycin B proved to be unsuccessful.^[254]



Intermediate for the synthesis of reveromycin (**Sect. III.2.18**)

Scheme 67

The reluctance to undergo Pd-catalyzed coupling has repeatedly been observed for alkenyltins. For example, although *cis*- α -hetero- β -alkylsubstituted alkenyltins were readily prepared by Pd-catalyzed hydrostannation of the corresponding alkynes, their further cross-coupling with alkenyl electrophiles was shown to be unfavorable. However, by stepwise transmetalations into the corresponding alkenylzincs, similar coupling with various electrophiles proceeded smoothly to give the desired products,^[256] as exemplified in **Scheme 68**.



Scheme 68

Another class of *cis*- α,β -substituted alkenylmetals used frequently in Pd-catalyzed alkenyl–alkenyl coupling are various cycloalkenylmetals (**Table 14**), but no additional comments are presented here.

TABLE 14. Pd-Catalyzed Coupling of *cis*- α,β -Substituted alkenylmetals with Alkenyl Electrophiles^a

	Type of Alkenyl Electrophile		Conditions	Yield (Selectivity) %	Reference
	<i>Vinyl</i>		Pd(PPh ₃) ₄ , ZnCl ₂	79(≥97)	[18]
	(<i>E</i>)- β -		Pd(PPh ₃) ₄ , ZnCl ₂	86(≥97)	[18]
			[ClPd(π -C ₃ H ₅)] ₂ , TBAF, P(OEt) ₃ , THF	45(>99)	[82]
			[ClPd(π -C ₃ H ₅)] ₂ , TBAF, P(OEt) ₃ , THF	73(≥99)	[82]
			[ClPd(π -C ₃ H ₅)] ₂ , TBAF, P(OEt) ₃ , THF	63(>99)	[82]
			[ClPd(π -C ₃ H ₅)] ₂ , TBAF, P(OEt) ₃ , THF	>42(>99)	[82]
	α -		Pd(PPh ₃) ₄ , NaOH	40	[257]
	β,β -		Pd(PPh ₃) ₄ , ZnCl ₂	65(≥97)	[18]
			Pd(PPh ₃) ₄ , ZnCl ₂	85(≥97)	[18]

TABLE 14. (Continued)

	Type of Alkenyl Electrophile		Conditions	Yield (Selectivity) %	Reference
			Pd(PPh ₃) ₄ , NaOH	60	[257]
	<i>cis</i> - α,β -		Pd(PPh ₃) ₄ , THF	80	[258]

^aSee Table 10.**D.vii. *trans*- α,β -Substituted Alkenylmetals**

Since most of the facile and general hydro- and carbometallation reactions involve *syn*-addition, the preparation of *trans*- α,β -substituted alkenylmetals via *syn*-addition of alkynes would require carbometallation of terminal alkynes placing the metal in the internal position. Although such reactions exemplified by carbopalladation^[259] are known, they are still more exceptional than normal. From the perspective of the current discussion, more commonly used are (i) some *anti*-hydrometallation reactions of proximally heterofunctional internal alkynes^{[260]–[263]} and (ii) the hydroboration–migratory insertion tandem process of 1-haloalkynes.^[135] Whereas the H migration produces (*Z*)- β -substituted alkenylboranes (Sect. D.iii), the corresponding C migration provides *trans*- α,β -substituted alkenylmetals.^[135] (See Table 15.)

TABLE 15. Pd-Catalyzed Coupling of *trans*- α,β -Substituted alkenylmetals with Alkenyl Electrophiles^a

	Type of Alkenyl Electrophile		Conditions	Yield (Selectivity) %	Reference
	(<i>Z</i>)- β -		Pd(PPh ₃) ₄ , NaOH, H ₂ O	70(>99)	[135]
			Pd(PPh ₃) ₄ , NaOH, H ₂ O	66(\geq 97)	[135]
	β,β -		Pd(PPh ₃) ₄ , NaOH, H ₂ O	70(>99)	[135]
			Pd(PPh ₃) ₄ , NaOH, H ₂ O	59(>99)	[135]

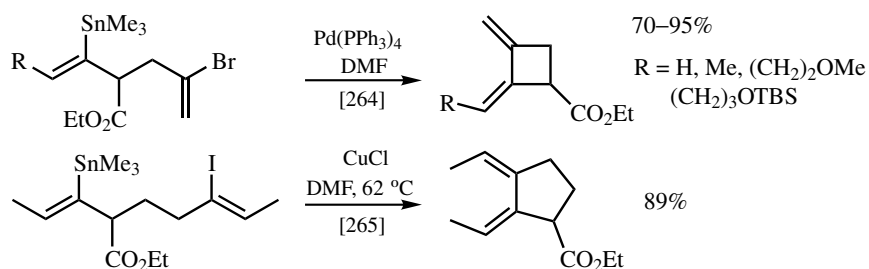
(Continued)

TABLE 15. (Continued)

	Type of Alkenyl Electrophile		Conditions	Yield (Selectivity) %	Reference
	<i>cis</i> - α,β -		Pd(PPh ₃) ₄ , NaOH, H ₂ O	72(>99)	[135]
			Pd(PPh ₃) ₄ , THF	90	[267]
			Pd(PPh ₃) ₄ , THF	86	[267]

^aSee Table 10.

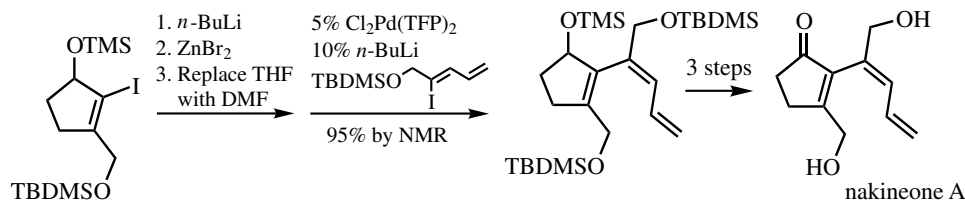
Some *trans*- α,β -, along with *cis*- α,β -substituted alkenyltin compounds have been prepared and used in intramolecular coupling reactions to synthesize cyclic compounds,^{[264],[265]} as shown in **Scheme 69**. The reaction could be mediated by stoichiometric CuCl instead of catalytic Pd complexes,^[265] while the use of Cu(I) as a cocatalyst in Stille coupling has been demonstrated.^{[30]–[33],[266]}



Scheme 69

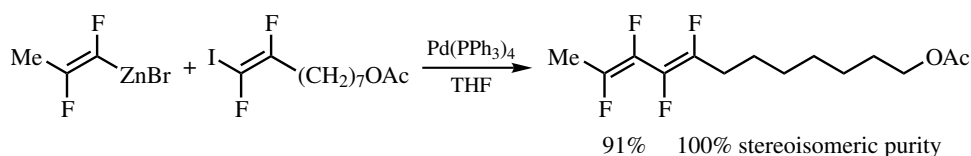
D.viii. Tetrasubstituted Alkenylmetals

In a synthesis of nakienone A, tetrasubstituted alkenylzinc, *in situ* generated from the corresponding alkenyliodide, was successfully coupled with the dienyl iodide to give the desired coupling product in 95% NMR yield, which was further converted into nakienone A in three steps^[268] (**Scheme 70**).



Scheme 70

A number of fluorine-substituted alkenylzincs have been coupled successfully with alkenyl halides,^{[269],[270]} and this reaction has been applied to the synthesis of fluorinated analogs of codlenone as shown in **Scheme 71**. The use of other tetrasubstituted alkenylmetals containing Zn, B, and Zr is shown in **Table 16**.



Scheme 71

TABLE 16. Pd-Catalyzed Coupling of Tetrasubstituted alkenylmetals with Alkenyl Electrophiles^a

	Type of Alkenyl Electrophile		Conditions	Yield (Selectivity) %	Reference
	(<i>E</i>)-β-				
			Pd(PPh ₃) ₄ , THF	95(>97)	[139]
			Pd ₂ dba ₃ -PPh ₃ , CuI, THF-HMPA	83–84	[271]
			Pd ₂ dba ₃ -PPh ₃ , CuI, THF-HMPA	82–86	[271]
			Pd(PPh ₃) ₄ , THF	78	[269]
			Pd(PPh ₃) ₄ , THF	83	[269]
			Cl ₂ Pd(PPh ₃) ₂ + DIBAH, CuI, THF, DMF	79	[99]
	(<i>Z</i>)-β-				
			Pd(PPh ₃) ₄ , THF	75	[269]
			Cl ₂ Pd(PPh ₃) ₂ + DIBAH, CuI, THF, DMF	81	[99]
	α,β,β-				
			Pd(PPh ₃) ₄ , CuCl, THF	64	[272]

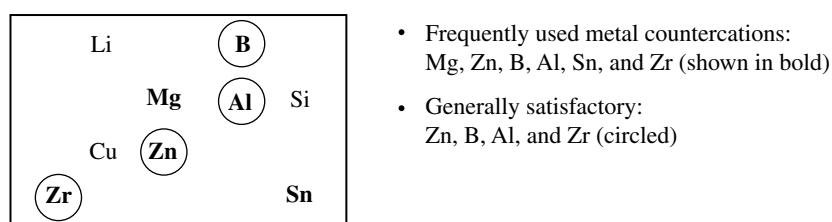
(Continued)

TABLE 16. (Continued)

$\begin{array}{c} \text{R}^2 \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{R}^1 \end{array}$ $\begin{array}{c} \text{R}^3 \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{M} \end{array}$	Type of Alkenyl Electrophile	$\begin{array}{c} \text{X} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \end{array}$	Conditions	Yield (Selectivity) %	Reference
$\begin{array}{c} \text{Et} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{Et} \end{array}$ $\begin{array}{c} \text{ZrCp}_2\text{Cl} \end{array}$		$\begin{array}{c} \text{I} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{Pr} \end{array}$	Pd(PPh ₃) ₄ , CuCl, THF	90	[272]
$\begin{array}{c} \text{F} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{C}_4\text{H}_9 \end{array}$ $\begin{array}{c} \text{F} \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{ZnCl} \end{array}$		$\begin{array}{c} \text{I} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{F} \end{array}$ $\begin{array}{c} \text{C}_4\text{H}_9 \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{F} \end{array}$	Pd(PPh ₃) ₄ , THF	78	[269]
$\begin{array}{c} \text{F} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{F} \end{array}$ $\begin{array}{c} \text{F} \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{ZnCl} \end{array}$		$\begin{array}{c} \text{I} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{Cl} \end{array}$ $\begin{array}{c} \text{F} \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{C}_5\text{H}_{11} \end{array}$	Pd(PPh ₃) ₄ , THF	80	[269]

^aSee Table 10.**D.ix. Summary**

Since its discovery in the 1970s (**Sect. A**), Pd- and Ni-catalyzed alkenyl–alkenyl coupling, particularly the Pd version, has been developed into one of the most important modern methodologies for carbon–carbon bond formation. Alkenylmetals containing Li, Mg, Zn, B, Al, Si, Sn, Cu, Zr, and other metal counterions have been used in the coupling, and their merits and demerits depend on a number of factors, such as stereochemistry, regiochemistry, chemoselectivity, product yield, reagent accessibility, efficiency, operational simplicity, toxicity, and other environmental concerns. Consequently, it is difficult to compare them and rank their overall merits and demerits. Nonetheless, several of them highlighted in bold letter (i.e., Mg, Zn, B, Al, Sn, and Zr) in **Scheme 72** have been more frequently used than the others.

**Scheme 72**

The currently available data, especially those pertaining to comparison of metal counterions, suggest that the metal of choice in a given case may generally be found among Zn, B, Al, and Zr. In many cases, Pd-catalyzed reactions of alkenyl- and arylzincs have been shown to be more favorable than those of the corresponding organomagnesiums. Similarly, it has become increasingly clear that organozincs and organoborons are generally superior to organotin in many of the more demanding Pd-catalyzed cross-coupling reactions.

Although less frequently used than Zn, B, and Sn, the ability of Al and Zr to participate in stereo- and regioselective hydrometallation and carbometallation of alkynes coupled with their generally favorable Pd-catalyzed cross-coupling, especially in cases when Zn salts are used as cocatalysts, make them two generally favorable metals, and their use may be expected to increase in the future. Despite these comparisons, some merits of Sn, such as its generally high chemoselectivity and its ability to undergo Pd-catalyzed cross-coupling in tandem cyclization and other multistage cascade processes, are noteworthy.

Alkenylcoppers have not been frequently used. However, generation of (*Z*)- β -substituted alkenylcoppers via carbocupration followed by their Pd-catalyzed cross-coupling appears to be the method of choice in the synthesis of 1,4-disubstituted (*Z,Z*)-conjugated dienes. It also nicely complements the synthesis of 1,4-disubstituted (*E,Z*)-conjugated dienes by the hydrometallation–cross-coupling tandem process involving B, Al, and Zr.

The use of alkenylsilicons in Pd-catalyzed cross-coupling still largely remains as a scientific novelty. Its current main drawback is the low intrinsic reactivity of the C—Si bond, which must be activated with fluoride and other bases. Furthermore, there do not appear to be many persuasive examples where the superiority of Si is clearly demonstrated. Further investigation, especially critical comparison of Si with other widely used metals, would be necessary for an objective evaluation of Si relative to the others.

REFERENCES

- [1] M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, **1954**, Chap. 16, p.1046–1132.
- [2] M. Tamura and J. K. Kochi, *J. Am. Chem. Soc.*, **1971**, 93, 1483.
- [3] J. K. Kochi, *Acc. Chem. Res.*, **1974**, 7, 351–360.
- [4] M. Tamura and J. K. Kochi, *J. Am. Chem. Soc.*, **1971**, 93, 1487.
- [5] G. H. Posner, *Org. React.*, **1975**, 22, 253–400.
- [6] O. P. Vig, J. C. Kapur, and S. D. Sharma, *J. Indian Chem. Soc.*, **1968**, 45, 734.
- [7] M. Nilsson and R. Wahren, *J. Organomet. Chem.*, **1969**, 16, 515.
- [8a] G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Am. Chem. Soc.*, **1969**, 91, 4871.
- [8b] A. T. Worm and J. H. Brewster, *J. Org. Chem.*, **1970**, 35, 1715.
- [9] J. Gasteiger, G. E. Gream, R. Huisgen, W. E. Konz, and U. Schnegg, *Chem. Ber.*, **1971**, 104, 2412.
- [10] O. P. Vig, S. D. Sharma, and J. C. Kapur, *J. Indian Chem. Soc.*, **1969**, 46, 167.
- [11] G. Büchi and J. A. Carlson, *J. Am. Chem. Soc.*, **1969**, 91, 6470.
- [12] K. Tamao, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.*, **1972**, 94, 4374.
- [13] R. J. P. Corriu and J. P. Masse, *J. Chem. Soc. Chem. Commun.*, **1972**, 144.
- [14] E. Negishi and S. Baba, *J. Chem. Soc. Chem. Commun.*, **1976**, 596.
- [15] S. Baba and E. Negishi, *J. Am. Chem. Soc.*, **1976**, 98, 6729.
- [16] E. Negishi and D. E. Van Horn, *J. Am. Chem. Soc.*, **1977**, 99, 3168.
- [17] N. Okukado, D. E. Van Horn, W. L. Klima, and E. Negishi, *Tetrahedron Lett.*, **1978**, 1027.
- [18] E. Negishi, N. Okukado, A. O. King, D. E. Van Horn, and B. I. Spiegel, *J. Am. Chem. Soc.*, **1978**, 100, 2254.
- [19] M. Yamamura, I. Moritani, and S. I. Murahashi, *J. Organomet. Chem.*, **1975**, 91, C39.

- [20] S. I. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita, and K. Kondo, *J. Org. Chem.*, **1979**, *44*, 2408.
- [21] K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, and M. Kumada, *Bull. Chem. Soc. Jpn.*, **1976**, *49*, 1958.
- [22] H. P. Dang and G. Linstrumelle, *Tetrahedron Lett.*, **1978**, 191.
- [23] E. Negishi and F. Liu, in *Metal-Catalyzed Cross-Coupling Reactions*, F. Diederich and P. J. Stang, Eds., VCH, Weinheim, **1998**, 1–47.
- [24] N. Miyaura and A. Suzuki, *Chem. Rev.*, **1995**, *95*, 2457–2483.
- [25] T. Hiyama and Y. Hatanaka, *Pure Appl. Chem.*, **1994**, *66*, 471–1478.
- [26] J. K. Stille, *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 508–524.
- [27] V. Farina, V. Krishnamurthy, and W. J. Scott, *Org. React.*, **1997**, *50*, 1–652.
- [28] J. F. Normant and A. Alexakis, in *Current Trend in Organic Synthesis*, H. Nozaki, Ed., Pergamon Press, New York, **1982**, 291–302.
- [29] A. Alexakis, C. Chuit, M. Commercon-Bourgain, J. P. Foulon, N. Jabri, P. Mangeney, and J. F. Normant, *Pure Appl. Chem.*, **1984**, *56*, 91–98.
- [30] J. P. Marino and J. K. Long, *J. Am. Chem. Soc.*, **1988**, *110*, 7916.
- [31] L. S. Liebeskind and R. W. Fengl, *J. Org. Chem.*, **1990**, *55*, 5359.
- [32] L. S. Liebeskind and J. Wang, *Tetrahedron Lett.*, **1990**, *31*, 4293.
- [33] L. S. Liebeskind and S. W. Riesinger, *J. Org. Chem.*, **1993**, *58*, 408.
- [34] V. Snieckus, *Chem. Rev.*, **1990**, *90*, 879–933.
- [35] K. Ritter, *Synthesis*, **1993**, 735–762.
- [36] E. Negishi, R. M. Williams, G. Lew, and T. Yoshida, *J. Organomet. Chem.*, **1975**, *92*, C4.
- [37] J. B. Campbell and Jr. G. A. Molander, *J. Organomet. Chem.*, **1978**, *156*, 71.
- [38] J. F. Normant and A. Alexakis, *Synthesis*, **1981**, 841–870.
- [39] J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1992**, 734.
- [40] E. Negishi, *Pure Appl. Chem.*, **1981**, *53*, 2333–2356.
- [41] E. Negishi, *Acc. Chem. Res.*, **1987**, *20*, 65–72.
- [42] E. Negishi and T. Takahashi, *Aldrichimica Acta*, **1985**, *18*, 31–48.
- [43] H. C. Brown, D. Basavaiah, and S. U. Kulkarni, *J. Org. Chem.*, **1982**, *47*, 3808.
- [44] H. C. Brown, T. Imai, and N. G. Bhat, *J. Org. Chem.*, **1986**, *51*, 5277.
- [45] N. A. Bumagin, N. L. Andryukhova, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, **1987**, *297*, 1126.
- [46] T. Jeffery, *Tetrahedron Lett.*, **1999**, *40*, 1673.
- [47] V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, **1991**, *113*, 9585.
- [48] G. P. Roth and C. E. Fuller, *J. Org. Chem.*, **1991**, *56*, 3493.
- [49] K. Kikukawa, K. Kono, F. Wada, and T. Matsuda, *J. Org. Chem.*, **1983**, *48*, 1333.
- [50] Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, **1988**, *53*, 918.
- [51] N. A. Bumagin, N. P. Andryukhova, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, **1989**, *307*, 375.
- [52] N. A. Bumagin, I. G. Bumagina, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, **1984**, *274*, 818.
- [53] G. P. Roth, V. Farina, L. S. Liebeskind, and E. Peña-Cabrera, *Tetrahedron Lett.*, **1995**, *36*, 2191.
- [54] D. R. Mckean, G. Parrinello, A. F. Renaldo, and J. K. Stille, *J. Org. Chem.*, **1987**, *52*, 422.
- [55] E. Shirakawa, H. Yoshida, and H. Takaya, *Tetrahedron Lett.*, **1997**, *38*, 3759.
- [56] S. Darses, J.-P. Genêt, J.-L. Brayer, and J.-P. Demoute, *Tetrahedron Lett.*, **1997**, *38*, 4393.

- [57] A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **1987**, *109*, 5478.
- [58] D. Badone, R. Cecchi, and U. Guzzi, *J. Org. Chem.*, **1992**, *57*, 6321.
- [59] M. E. Krolski, A. F. Renaldo, D. E. Rudisill, and J. K. Stille, *J. Org. Chem.*, **1988**, *53*, 1170.
- [60] J. A. Stafford and N. L. Valvano, *J. Org. Chem.*, **1994**, *59*, 4346.
- [61] G. Martorell, A. García-Raso, and J. M. Saá, *Tetrahedron Lett.*, **1990**, *31*, 2357.
- [62] A. M. Gilbert and W. D. Wulff, *J. Am. Chem. Soc.*, **1994**, *116*, 7449.
- [63] G. Zweifel and J. A. Miller, *Org. React.*, **1984**, *32*, 375–517.
- [64] J. Schwartz and J. A. Labinger, *Angew. Chem. Int. Ed. Engl.*, **1976**, *15*, 333–340.
- [65] H. C. Brown, *Organic Synthesis via Boranes*, Wiley, New York, **1975**, 283p.
- [66] N. Miyaura and A. Suzuki, *J. Chem. Soc. Chem. Commun.*, **1979**, 866.
- [67] E. Negishi, in *Aspects of Mechanism and Organometallic Chemistry*, J. H. Brewster, Ed., Plenum Press, New York, **1978**, 285–317.
- [68] N. Miyaura and A. Suzuki, *J. Organomet. Chem.*, **1981**, *213*, C53.
- [69] A. Suzuki, *Pure Appl. Chem.*, **1985**, *57*, 1749–1758.
- [70] J. C. Colberg, A. Rane, J. Vaquer, and J. A. Soderquist, *J. Am. Chem. Soc.*, **1993**, *115*, 6065.
- [71] S. Hyuga, Y. Chiba, N. Yamashina, S. Hara, and A. Suzuki, *Chem. Lett.*, **1987**, 1757.
- [72] S. Hyuga, N. Yamashina, S. Hara, and A. Suzuki, *Chem. Lett.*, **1988**, 809.
- [73] F. Yin, Y. Xu, and B. Jiang, *J. Fluorine Chem.*, **1993**, *65*, 111.
- [74] J. W. Guiles, S. G. Johnson, and W. V. Murray, *J. Org. Chem.*, **1996**, *61*, 5169.
- [75] D. Badone, M. Baroni, R. Cardamone, A. Ielmini, and U. Guzzi, *J. Org. Chem.*, **1997**, *62*, 7170.
- [76] J.-L. Parrain, A. Duchêne, and J.-P. Quintard, *Tetrahedron Lett.*, **1990**, *31*, 1857.
- [77] J. Thibonnet, M. Abarbri, J.-L. Parrain, and A. Duchêne, *Tetrahedron Lett.*, **1996**, *37*, 7507.
- [78] A. Kalivretenos, J. K. Stille, and L. S. Hegedus, *J. Org. Chem.*, **1991**, *56*, 2883.
- [79] J. Yoshida, K. Tamao, H. Yamamoto, T. Kakui, T. Uchida, and M. Kumada, *Organometallics*, **1982**, *1*, 542.
- [80] Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, **1989**, *54*, 268.
- [81] K. Kikukawa, K. Ikenaga, F. Wada, and T. Matsuda, *Chem. Lett.*, **1983**, 1337.
- [82] K. Tamao, K. Kobayashi, and Y. Ito, *Tetrahedron Lett.*, **1989**, *30*, 6051.
- [83] K. Gouda, E. Hagiwara, Y. Hatanaka, and T. Hiyama, *J. Org. Chem.*, **1996**, *61*, 7232.
- [84] S. E. Denmark and D. Wehrli, *Org. Lett.*, **2000**, *2*, 565.
- [85] K. Hirabayashi, J. Kawashima, Y. Nishihara, A. Mori, and T. Hiyama, *Org. Lett.*, **1999**, *1*, 299.
- [86] M. Portnoy and D. Milstein, *Organometallics*, **1993**, *12*, 1665.
- [87] M. Huser, M. T. Youinou, and J. A. Osborn, *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 1386.
- [88] E. Hagiwara, K. Gouda, Y. Hatanaka, and T. Hiyama, *Tetrahedron Lett.*, **1997**, *38*, 439.
- [89] K. Tamao, J. Yoshida, H. Yamamoto, T. Kakui, H. Matsumoto, M. Takahashi, A. Kurita, M. Murata, and M. Kumada, *Organometallics*, **1982**, *1*, 355.
- [90] H. Matsumoto, S. Nagashima, T. Kato, and Y. Nagai, *Angew. Chem. Int. Ed. Engl.*, **1978**, *17*, 279.
- [91] T. Oh-e, N. Miyaura, and A. Suzuki, *Synlett*, **1990**, 221.
- [92] E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn, and N. Okukado, *J. Am. Chem. Soc.*, **1987**, *109*, 2393.
- [93] J.-B. Verlhac, J.-P. Quintard, and M. Pereyre, *J. Chem. Soc. Chem. Commun.*, **1988**, 503.
- [94] B. H. Lipshutz and R. Keil, *Inorg. Chim. Acta*, **1994**, *220*, 41.
- [95] A. B. Smith and G. R. Ott, *J. Am. Chem. Soc.*, **1996**, *118*, 13095.
- [96] H. C. Brown and T. Imai, *Organometallics*, **1984**, *3*, 1392.

- [97] H. C. Brown and V. Somayaji, *Synthesis*, **1984**, 919.
- [98] N. Miyaura, M. Satoh, and A. Suzuki, *Tetrahedron Lett.*, **1986**, 27, 3745.
- [99] L. Labaudiniere and J. F. Normant, *Tetrahedron Lett.*, **1992**, 33, 6139.
- [100] E. J. Corey and T. M. Eckrich, *Tetrahedron Lett.*, **1984**, 25, 2419.
- [101] J. W. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, **1983**, 105, 6129.
- [102] M. Massol, J. Satge, and B. Bouyssieres, *Synth. Inorg. Met.-Org. Chem.*, **1973**, 3, 1.
- [103] G. A. Kraus and B. M. Watson, *Tetrahedron Lett.*, **1996**, 37, 5287.
- [104] Y. Hatanaka and T. Hiyama, *Tetrahedron Lett.*, **1990**, 31, 2719.
- [105] S. Nunomoto and Y. Yamashita, *J. Org. Chem.*, **1979**, 44, 4788.
- [106] S. Nunomoto, Y. Kawakami, and Y. Yamashita, *Bull. Chem. Soc. Jpn.*, **1981**, 54, 2831.
- [107] S. Nunomoto, Y. Kawakami, and Y. Yamashita, *J. Org. Chem.*, **1983**, 48, 1912.
- [108] B. Jiang and Y. Xu, *J. Org. Chem.*, **1991**, 56, 7336.
- [109] R. Filler, S. Lin, and Z. Zhang, *J. Fluorine Chem.*, **1995**, 74, 69.
- [110] P. A. Wender and T. E. Glass, *Synlett*, **1995**, 516.
- [111] H. C. Brown, A. B. Levy, and M. M. Midland, *J. Am. Chem. Soc.*, **1975**, 97, 5017.
- [112] H. C. Brown and M. M. Midland, *J. Org. Chem.*, **1975**, 40, 2845.
- [113] R. Koster and L. A. Hagelee, *Synthesis*, **1976**, 118.
- [114] A. B. Levy, S. J. Schwartz, N. Wilson, and B. Christie, *J. Organomet. Chem.*, **1978**, 156, 123.
- [115] J. A. Soderquist and I. Rivera, *Tetrahedron Lett.*, **1989**, 30, 3919.
- [116] J. A. Soderquist and M. R. Najafi, *J. Org. Chem.*, **1986**, 51, 1330.
- [117] I. Rivera and J. A. Soderquist, *Tetrahedron Lett.*, **1991**, 32, 2311.
- [118] E. Negishi and F. T. Luo, *J. Org. Chem.*, **1983**, 48, 1560.
- [119] T. Takahashi, M. Kotori, R. Fischer, Y. Nishihara, and K. Nakajima, *J. Am. Chem. Soc.*, **1995**, 117, 11039.
- [120] E. Negishi, F. T. Luo, R. Frisbee, and H. Matsushita, *Heterocycles*, **1982**, 18, 117.
- [121] Y. Satoh, H. Serizawa, S. Hara, and A. Suzuki, *Synth. Commun.*, **1984**, 14, 313.
- [122] Y. Satoh, H. Serizawa, N. Miyaura, S. Hara, and A. Suzuki, *Tetrahedron Lett.*, **1988**, 29, 1811.
- [123] E. Negishi, F. E. Cederbaum, and T. Takahashi, *Tetrahedron Lett.*, **1986**, 27, 2829.
- [124] G. Desormont, S. Dalton, D. M. Giolando, and M. Srebnik, *J. Org. Chem.*, **1996**, 61, 7943.
- [125] G. Desormont, R. Klein, S. Uhlenbrock, E. Laloë, L. Deloux, D. M. Giolando, Y. W. Kim, S. Pereira, and M. Srebnik, *Organometallics*, **1996**, 15, 3323.
- [126] T. N. Mitchell and H. Killing, *Organometallics*, **1984**, 3, 1318.
- [127] T. N. Mitchell, H. Killing, and D. Rutschow, *J. Organomet. Chem.*, **1986**, 304, 257.
- [128] T. N. Mitchell, K. Kwetkat, D. Rutschow, and U. Schneider, *Tetrahedron*, **1989**, 45, 969.
- [129] W. J. Scott, *J. Chem. Soc. Chem. Commun.*, **1987**, 1755.
- [130] K. Tamao, K. Kobayashi, and Y. Ito, *J. Am. Chem. Soc.*, **1989**, 111, 6478.
- [131] Y. Gao, K. Harada, T. Hata, H. Urabe, and F. Sato, *J. Org. Chem.*, **1995**, 60, 290.
- [132] K. A. Agrios and M. Srebnik, *J. Organomet. Chem.*, **1993**, 444, 15.
- [133] J. Terao, N. Kambe, and N. Sonoda, *Tetrahedron Lett.*, **1996**, 37, 4741.
- [134] K. Tamao, K. Maeda, T. Tanaka, and Y. Ito, *Tetrahedron Lett.*, **1988**, 29, 6955.
- [135] M. Satoh, N. Miyaura, and A. Suzuki, *Chem. Lett.*, **1986**, 1329.
- [136] L. Deloux, E. Skrzypczak-Jankun, B. V. Cheesman, and M. Srebnik, *J. Am. Chem. Soc.*, **1994**, 116, 10302.

- [137] A. Table and P. Kocienski, *Tetrahedron Lett.*, **1989**, 30, 1675.
- [138] T. Oh-e, N. Miyaura, and A. Suzuki, *J. Org. Chem.*, **1993**, 58, 2201.
- [139] E. Negishi, F. Liu, D. Choueiry, M. M. Mohamud, A. Silveira, Jr., and M. Reeves, *J. Org. Chem.*, **1996**, 61, 8325.
- [140] T. L. Gilchrist and R. J. Summersell, *J. Chem. Soc. Perkin Trans. 1*, **1988**, 2595.
- [141] K. Kasai, Y. Liu, R. Hara, and T. Takahashi, *Chem. Commun.*, **1998**, 1989.
- [142] T. Ishiyama, N. Matsuda, N. Miyaura, and A. Suzuki, *J. Am. Chem. Soc.*, **1993**, 115, 11018.
- [143] S. D. Brown and R. W. Armstrong, *J. Am. Chem. Soc.*, **1996**, 118, 6331.
- [144] S. D. Brown and R. W. Armstrong, *J. Org. Chem.*, **1997**, 62, 7076.
- [145] R. S. Sorokina, L. F. Rybakova, I. O. Kalinovskii, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR Ser. Khim.*, **1985**, 1647.
- [146] P. L. Heinze and D. J. Burton, *J. Fluorine Chem.*, **1986**, 31, 115.
- [147] P. L. Heinze and D. J. Burton, *J. Org. Chem.*, **1988**, 53, 2714.
- [148] F. Tellier, R. Sauvêtre, J. F. Normant, Y. Dromzee, and Y. Jeannin, *J. Organomet. Chem.*, **1987**, 331, 281.
- [149] F. Tellier, R. Sauvêtre, and J. F. Normant, *J. Organomet. Chem.*, **1985**, 292, 19.
- [150] P. A. Morken and D. J. Burton, *J. Org. Chem.*, **1993**, 58, 1167.
- [151] J. Ichikawa, T. Moriya, T. Sonoda, and H. Kobayashi, *Chem. Lett.*, **1991**, 961.
- [152] J. Ichikawa, T. Minami, T. Sonoda, and H. Kobayashi, *Tetrahedron Lett.*, **1992**, 33, 3779.
- [153] R. S. Sorokina, L. F. Rybakova, I. O. Kalinovskii, V. A. Chernoplekova, and I. P. Beletskaya, *Zh. Org. Khim.*, **1982**, 18, 2458.
- [154] L. Lu and D. J. Burton, *Tetrahedron Lett.*, **1997**, 38, 7671.
- [155] L. G. Sprague, A. W. Snow, and J. R. Griffith, *J. Fluorine Chem.*, **1991**, 52, 301.
- [156] E. Erdik, *Organozinc Reagents in Organic Synthesis*, CRC Press, Boca Raton, FL, **1996**, 411pp.
- [157] H. Azizian, C. E. Eaborn, and A. Pidcock, *J. Organomet. Chem.*, **1981**, 215, 49.
- [158] A. N. Kashkin, I. G. Bumagina, N. A. Bumagin, V. N. Bakunin, and I. P. Beletskaya, *J. Org. Chem. USSR*, **1981**, 17, 789.
- [159] N. A. Bumagin, I. G. Bumagina, and I. P. Beletskaya, *Dokl. Akad. Nauk SSSR*, **1984**, 274, 1103.
- [160] T. Ishiyama, M. Murata, and N. Miyaura, *J. Org. Chem.*, **1995**, 60, 7508.
- [161] M. Murata, T. Oyama, S. Watanabe, and Y. Masuda, *J. Org. Chem.*, **2000**, 65, 164.
- [162] H. Matsumoto, M. Kasahara, M. Takahashi, T. Arai, T. Nakano, and Y. Nagai, *J. Organomet. Chem.*, **1983**, 250, 99.
- [163] A. Minato, K. Suzuki, and K. Tamao, *J. Am. Chem. Soc.*, **1987**, 109, 1257.
- [164] P. Ramiandrasoa, B. Bréhon, A. Thivet, M. Alami, and G. Cahiez, *Tetrahedron Lett.*, **1997**, 38, 2447.
- [165] B. Crousse, M. Alami, and G. Linstrumelle, *Tetrahedron Lett.*, **1997**, 38, 5297.
- [166] R. B. Miller and M. I. Al-Hassan, *J. Org. Chem.*, **1985**, 50, 2121.
- [167] G. A. Potter and R. McCague, *J. Org. Chem.*, **1990**, 55, 6184.
- [168] T. Studemann and P. Knochel, *Angew. Chem. Int. Ed. Engl.*, **1997**, 36, 93.
- [169] B. H. Lipshutz, B. Ullman, C. Lindsley, S. Pecchi, D. J. Buzard, and D. Dickson, *J. Org. Chem.*, **1998**, 63, 6092.
- [170] G. Stork and R. C. A. Isaacs, *J. Am. Chem. Soc.*, **1990**, 112, 7399.
- [171] J. P. Genêt, E. Blart, and M. Savignac, *Synlett*, **1992**, 715.

- [172] X. Yue, F.-L. Qing, H. Sun, and J. Fan, *Tetrahedron Lett.*, **1996**, 37, 8213.
- [173] E. Negishi, Y. Noda, F. Lamaty, and E. J. Vawter, *Tetrahedron Lett.*, **1990**, 31, 4393.
- [174] V. Farina, B. Krishnan, D. R. Marshall, and G. P. Roth, *J. Org. Chem.*, **1993**, 58, 5434.
- [175] J. Srogl, G. D. Allred, and L. S. Liebeskind, *J. Am. Chem. Soc.*, **1997**, 119, 12376.
- [176] E. Fouquet, M. Pereyre, and A. L. Rodriguez, *J. Org. Chem.*, **1997**, 62, 5242.
- [177] A. Duchêne, M. Abarbri, J.-L. Parrain, M. Kitamura, and R. Noyori, *Synlett*, **1994**, 524.
- [178] P. G. Ciattini, E. Morera, and G. Ortar, *Tetrahedron Lett.*, **1992**, 33, 4815.
- [179] F.-T. Luo and L.-C. Hsieh, *J. Org. Chem.*, **1996**, 61, 9060.
- [180] E. Negishi, M. Ay, Yu. V. Gulevich, and Y. Noda, *Tetrahedron Lett.*, **1993**, 34, 1437.
- [181] E. Morera and G. Ortar, *Synlett*, **1997**, 1403.
- [182] V. Farina and G. P. Roth, *Tetrahedron Lett.*, **1991**, 32, 4243.
- [183] D. L. Comins and L. A. Morgan, *Tetrahedron Lett.*, **1991**, 32, 5919.
- [184] J. K. Stille and B. L. Groh, *J. Am. Chem. Soc.*, **1987**, 109, 813.
- [185] R. M. Moriarty and W. R. Epa, *Tetrahedron Lett.*, **1992**, 33, 4095.
- [186] M. Gardette, N. Jabri, A. Alexakis, and J. F. Normant, *Tetrahedron*, **1984**, 40, 2741.
- [187] D. T. Hung, J. B. Nerenberg, and S. L. Schreiber, *J. Am. Chem. Soc.*, **1996**, 118, 11054.
- [188] W. J. Scott, G. T. Crisp, and J. K. Stille, *J. Am. Chem. Soc.*, **1984**, 106, 4630.
- [189] W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, **1986**, 108, 3033.
- [190] M. R. Attwood, T. M. Raynham, D. G. Smyth, and G. R. Stephenson, *Tetrahedron Lett.*, **1996**, 37, 2731.
- [191] R. Rossi, A. Carpita, and M. G. Quirici, *Tetrahedron*, **1981**, 37, 2617.
- [192] L. Zhu, R. M. Wehmeyer, and R. D. Rieke, *J. Org. Chem.*, **1991**, 56, 1445.
- [193] F. Bjorkling, T. Norin, C. R. Unelius, and R. B. Miller, *J. Org. Chem.*, **1987**, 52, 292.
- [194] N. Miyaura, K. Yamada, and A. Suzuki, *Tetrahedron Lett.*, **1979**, 20, 3437.
- [195] N. Miyaura, H. Suginome, and A. Suzuki, *Tetrahedron Lett.*, **1981**, 22, 127.
- [196] N. Miyaura, K. Yamada, H. Suginome, and A. Suzuki, *J. Am. Chem. Soc.*, **1985**, 107, 972.
- [197] J.-M. Duffault, J. Einhorn, and A. Alexakis, *Tetrahedron Lett.*, **1991**, 32, 3701.
- [198] V. Ratovelomanana and G. Linstrumelle, *Tetrahedron Lett.*, **1984**, 25, 6001.
- [199] G. Cassani, P. Massardo, and P. Piccardi, *Tetrahedron Lett.*, **1983**, 24, 2513.
- [200] N. Miyaura, H. Suginome, and A. Suzuki, *Tetrahedron Lett.*, **1983**, 24, 1527.
- [201] W. R. Roush, J. S. Warmus, and A. B. Works, *Tetrahedron Lett.*, **1993**, 34, 4427.
- [202] A. Carpita, D. Neri, and R. Rossi, *Gazz. Chim. Ital.*, **1987**, 117, 503.
- [203] S. W. Djuric, R. A. Haack, and S. S. Yu, *J. Chem. Soc. Perkin Trans. 1*, **1989**, 2133.
- [204] Y. Kobayashi, S. Okamoto, T. Shimazaki, Y. Ochiai, and F. Sato, *Tetrahedron Lett.*, **1987**, 28, 3959.
- [205] J. Uenishi, R. Kawahama, O. Yonemitsu, and J. Tsuji, *J. Org. Chem.*, **1996**, 61, 5716.
- [206] Y. Naruse, T. Esaki, and H. Yamamoto, *Tetrahedron*, **1988**, 44, 4747.
- [207] N. Miyaura, H. Suginome, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, **1982**, 55, 2221.
- [208] N. Miyaura, Y. Satoh, S. Hara, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, **1986**, 59, 2029.
- [209] P. M. Pihko and A. M. P. Koskinen, *Synlett*, **1999**, 1966.
- [210] R. J. Boyce and G. Pattenden, *Tetrahedron Lett.*, **1996**, 37, 3501.
- [211] A. G. M. Barrett, M. Peña, and J. A. Willardsen, *J. Org. Chem.*, **1996**, 61, 1082.
- [212] M. A. J. Duncton and G. Pattenden, *J. Chem. Soc. Perkin Trans. 1*, **1999**, 1235–1246.
- [213] B. H. Lipshutz and C. Lindsley, *J. Am. Chem. Soc.*, **1997**, 119, 4555.

- [214] Y. Kobayashi, T. Shimazaki, H. Taguchi, and F. Sato, *J. Org. Chem.*, **1990**, 55, 5324.
- [215] J. Uenishi, J.-M. Beau, R. W. Armstrong, and Y. Kishi, *J. Am. Chem. Soc.*, **1987**, 109, 4756.
- [216] W. R. Roush and R. Riva, *J. Org. Chem.*, **1988**, 53, 710.
- [217] M. Avignon-Tropis, M. Treilhou, J. Lebreton, J. R. Pougny, I. Frécharde-Ortuno, C. Huynh, and G. Linstrumelle, *Tetrahedron Lett.*, **1989**, 30, 6335.
- [218] K. C. Nicolaou, J. Y. Ramphal, J. M. Palazon, and R. A. Spanevello, *Angew. Chem. Int. Ed. Engl.*, **1989**, 28, 587.
- [219] K. C. Nicolaou, J. Y. Ramphal, and Y. Abe, *Synthesis*, **1989**, 898.
- [220] W. R. Roush and R. J. Sciotti, *J. Am. Chem. Soc.*, **1994**, 116, 6457.
- [221] D. M. Hodgson, L. T. Boulton, and G. N. Maw, *Synlett*, **1995**, 267.
- [222] J. K. Stille and M. Tanaka, *J. Am. Chem. Soc.*, **1987**, 109, 3785.
- [223] E. Negishi, A. Alimardanov, and C. Xu, *Org. Lett.*, **2000**, 2, 65.
- [224] D. R. Swanson, T. Nguyen, Y. Noda, and E. Negishi, *J. Org. Chem.*, **1991**, 56, 2590.
- [225] C. Xu and E. Negishi, *Tetrahedron Lett.*, **1999**, 40, 431.
- [226] N. Jabri, A. Alexakis, and J. F. Normant, *Tetrahedron Lett.*, **1981**, 22, 959.
- [227] N. Jabri, A. Alexakis, and J. F. Normant, *Tetrahedron Lett.*, **1982**, 23, 1589.
- [228] E. Negishi unpublished results
- [229] F. Ramiandrasoa and F. Tellier, *Synth. Commun.*, **1990**, 20, 333.
- [230] S. R. Baker, G. P. Roth, and C. Sapino, *Synth. Commun.*, **1990**, 20, 2185.
- [231] P. I. Svirskaya, C. C. Leznoff, and W. L. Roelofs, *Synth. Commun.*, **1980**, 10, 391.
- [232] A. Commercon, J. F. Normant, and J. Villieras, *Tetrahedron*, **1980**, 36, 1215.
- [233] B. Jiang and Y. Xu, *Tetrahedron Lett.*, **1992**, 33, 511.
- [234] E. Piers, R. W. Friesen, and B. A. Keay, *Tetrahedron*, **1991**, 47, 4555.
- [235] P. G. Ciattini, E. Morera, and G. Ortar, *Tetrahedron Lett.*, **1990**, 31, 1889.
- [236] D. E. Van Horn and E. Negishi, *J. Am. Chem. Soc.*, **1978**, 100, 2252.
- [237] E. Negishi, D. E. Van Horn, and T. Yoshida, *J. Am. Chem. Soc.*, **1985**, 107, 6639.
- [238] A. Marfat, P. R. McQuirk, and P. Helquist, *Tetrahedron Lett.*, **1978**, 19, 1363.
- [239] E. Negishi and Z. Owczarczyk, *Tetrahedron Lett.*, **1991**, 32, 6683.
- [240] F. Zeng and E. Negishi, *Org. Lett.*, **2001**, 3, 719.
- [241] K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, and P. Bertinato, *J. Am. Chem. Soc.*, **1993**, 115, 4419.
- [242] K. C. Nicolaou, A. D. Piscopio, P. Bertinato, T. K. Chakraborty, N. Minowa, and K. Koide, *Chem. Eur. J.*, **1995**, 1, 318.
- [243] F. Yokokawa, Y. Hamada, and T. Shiori, *Tetrahedron Lett.*, **1993**, 34, 6559.
- [244] N. Tanimoto, S. W. Gerritz, A. Sawabe, T. Noda, S. A. Filla, and S. Masamune, *Angew. Chem. Int. Ed. Engl.*, **1994**, 33, 673.
- [245] A. G. M. Barrett, J. J. Edmunds, J. A. Hendrix, K. Horita, and C. J. Parkinson, *J. Chem. Soc. Chem. Commun.*, **1992**, 1238.
- [246] S. D. Burke, A. D. Piscopio, M. E. Kort, M. A. Matulenko, M. H. Parker, D. M. Armistead, and K. Shankaran, *J. Org. Chem.*, **1994**, 59, 332.
- [247] K. C. Nicolaou, J. Xu, F. Murphy, S. Barluenga, O. Baudoin, H. Wei, D. L. F. Gray, and T. Ohshima, *Angew. Chem. Int. Ed. Engl.*, **1999**, 38, 2447.
- [248] B. Domínguez, B. Iglesias, and A. R. de Lera, *Tetrahedron*, **1999**, 55, 15071.
- [249] A. G. M. Barrett, A. J. Bennett, S. Menzer, M. L. Smith, A. J. P. White, and D. J. Williams, *J. Org. Chem.*, **1999**, 64, 162.

- [250] A. M. García, J. L. Mascareñas, L. Castedo, and A. Mouriño, *Tetrahedron Lett.*, **1995**, 36, 5413.
- [251] P. A. Wender and M. L. Snapper, *Tetrahedron Lett.*, **1987**, 28, 2221.
- [252] D. W. Hart, T. F. Blackburn, and J. Schwartz, *J. Am. Chem. Soc.*, **1975**, 97, 679.
- [253] J. S. Panek and T. Hu, *J. Org. Chem.*, **1997**, 62, 4912.
- [254] K. E. Drouet and E. A. Theodorakis, *J. Am. Chem. Soc.*, **1999**, 121, 456.
- [255] J. S. Panek and T. Hu, *J. Org. Chem.*, **1997**, 62, 4914.
- [256] A. Pimm, P. Kocienski, and S. D. A. Street, *Synlett*, **1992**, 886.
- [257] J. A. Soderquist and G. León-Colón, *Tetrahedron Lett.*, **1991**, 32, 43.
- [258] E. J. Corey and H. Kigoshi, *Tetrahedron Lett.*, **1991**, 32, 5025.
- [259] E. Negishi, M. Ay, and T. Sugihara, *Tetrahedron*, **1993**, 49, 5471.
- [260] E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **1967**, 89, 4245.
- [261] B. Jousseume and J. G. Duboudin, *J. Organomet. Chem.*, **1975**, 91, C1.
- [262] J. G. Duboudin and B. Jousseume, *J. Organomet. Chem.*, **1979**, 168, 1.
- [263] S. Ma, F. Liu, and E. Negishi, *Tetrahedron Lett.*, **1997**, 38, 3829.
- [264] E. Piers and Y.-F. Lu, *J. Org. Chem.*, **1988**, 53, 926.
- [265] E. Piers and T. Wong, *J. Org. Chem.*, **1993**, 58, 3609.
- [266] V. Farina, S. Kapadia, B. Krishnan, C. Wang, and L. S. Liebeskind, *J. Org. Chem.*, **1994**, 59, 5905.
- [267] G. Shi, X. Huang, and F. Hong, *J. Org. Chem.*, **1996**, 61, 3200.
- [268] M. Pour and E. Negishi, *Tetrahedron Lett.*, **1997**, 38, 525.
- [269] F. Tellier, R. Sauvêtre, and J. F. Normant, *J. Organomet. Chem.*, **1986**, 303, 309.
- [270] F. Tellier, R. Sauvêtre, and J. F. Normant, *J. Organomet. Chem.*, **1989**, 364, 17.
- [271] J. Ichikawa, C. Ikeura, and T. Minami, *Synlett*, **1992**, 739.
- [272] R. Hara, Y. Nishihara, P. D. Landré, and T. Takahashi, *Tetrahedron Lett.*, **1997**, 38, 447.