

III.2.8.2 Palladium-Catalyzed Alkynylation with Alkynylmetals and Alkynyl Electrophiles

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A. INTRODUCTION AND GENERAL DISCUSSION

A.i. Scope of the Pd-Catalyzed Alkynylation with Respect to Metal Counteractions

As discussed in **Sect. III.2.8.1**, the Sonogashira alkyne synthesis^{[1],[2]} and related Heck-type alkynylation^[3] using terminal alkynes as reagents collectively offer widely applicable and generally satisfactory procedures for Pd-catalyzed alkynylation. Even so, various limitations and difficulties associated with the Sonogashira and related reactions have also been noted, as detailed later.

There are a group of Pd-catalyzed cross-coupling reactions that are also generally satisfactory, and their overall scope, especially that with alkynylzincs, appears to be considerably broader than that of the Sonogashira alkyne synthesis. Highly satisfactory Pd-catalyzed alkynylation with discrete alkynylmetals was developed during the course of a systematic investigation of the scope of Pd-catalyzed cross-coupling with respect to metal counteractions.^[4] To this end, a series of 1-heptynylmetals containing a wide variety of metals including Li, Mg, Zn, Hg, B, Al, Si, Sn, and Zr were reacted with *o*-tolyl iodide in the presence of a Pd catalyst. *o*-Tolyl iodide was chosen to probe both regiospecificity and possible steric influences, but no regioisomerization was observed.

As shown in **Table 1**, a wide variety of metal counteractions have been shown to participate in this reaction. Under the same reaction conditions, alkynylmetals containing Zn exhibit the highest reactivity (Entry 6), which is followed by those of Mg (Entries 4 and 5), Al (Entries 12–14), and Sn (Entries 16 and 17). Although the product yield observed with 1-heptynymagnesium bromide was modest (49%), alkynylmagnesium reagents have since been shown to be very satisfactory in many cases.^{[5],[6]}

The reaction of 1-heptynyltributyltin represents one of the prototypical examples of the Pd-catalyzed cross-coupling reactions of organotins and the first of the Pd-catalyzed alkynylation with alkynyltins. The 1-heptynylboron derivative generated by the treatment of 1-heptynyllithium with (*n*-Bu)₃B is relatively unreactive at room temperature (Entry 10), but it reacts readily under reflux (THF) to give the desired product in 92% yield (Entry 11). This reaction represents the first example of the Pd-catalyzed reaction of

TABLE 1. Effects of Counteranions in the Pd-Catalyzed Reaction of 1-Heptynylmetals with *o*-Tolyl Iodide^[4]

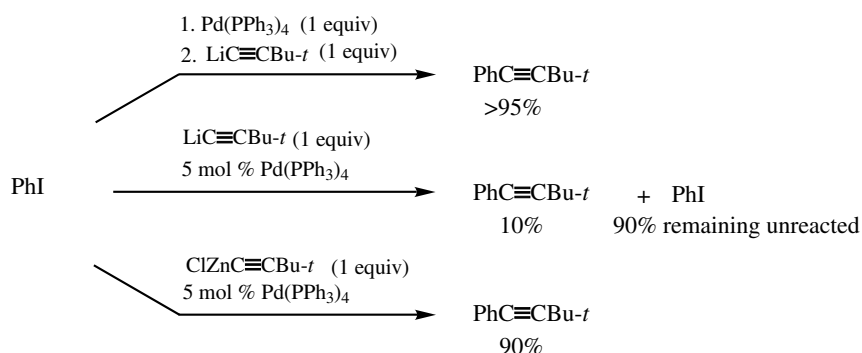
$$n\text{-PentC}\equiv\text{CM} + o\text{-TolI} \xrightarrow[\text{THF}]{\text{cat. PdL}_n} n\text{-PentC}\equiv\text{CTol-}o$$

Entry	M of <i>n</i> -PentC≡CM	Reaction Conditions ^a		Product Yield (%)	Residual <i>o</i> -TolI (%)
		Temperature (°C)	Time (h)		
1	Li	22	1	Trace	88
2	Li	22	24	30	80
3	Na(NaOMe)	Reflux	24	58	41
4	MgBr	22	1	29	55
5	MgBr	22	24	49	33
6	ZnCl	22	1	91	8
7	ZnCl	22	3	88	2
8	HgCl	22	1	Trace	92
9	HgCl	Reflux	6	Trace	88
10	BBu ₃ Li	22	3	10	76
11	BBu ₃ Li	Reflux	1	92	5
12	AlBu ₃ Li	22	3	4	80
13	AlBu ₃ Li	Reflux	1	38	10
14	AlBu ₂	22	3	49	46
15	SiMe ₃	Reflux	1	Trace	94
16	SnBu ₃	22	1	75	14
17	SnBu ₃	22	6	83	6
18	ZrCp ₂ Cl	Reflux	3	0	80

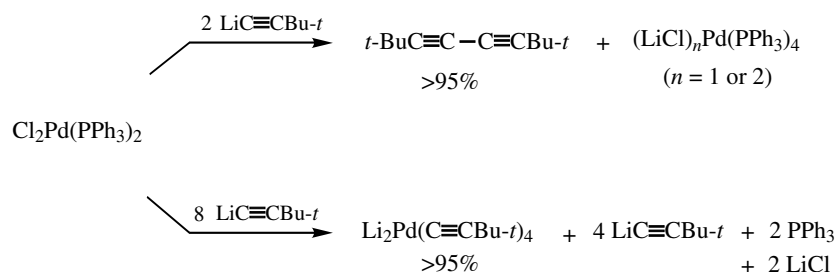
^aIn all cases except Entry 3, 5 mol % of Cl₂Pd(PPh₃)₂ treated with 10 mol % of *i*-Bu₂AlH was used as the catalyst. In Entry 3, 5 mol % of Pd(PPh₃)₄ was used as the catalyst, and the reaction was run as reported inassar.^[7]

organoboron compounds. It is striking that three metals most widely used in Pd-catalyzed cross-coupling today—Zn, B, and Sn—led to the highest product yields despite major differences in their intrinsic reactivities.

Despite its high intrinsic reactivity toward a wide variety of compounds including organic halides, the reaction of 1-heptynyllithium leads to a very low yield of the desired product (Entries 1 and 2). Although equilibrium mixtures of terminal alkynes and sodium alkoxides were reported to produce arylalkynes in good yields,^[7] alkynylmetals containing alkali metals appear to be generally inferior to several other metals, one of the general problems being their low chemoselectivity. The unexpectedly low reactivity of alkynyllithiums appears to stem from their intrinsically high chemical reactivity leading to catalyst poisoning. Under stoichiometric conditions, alkynyllithiums are at least as reactive and effective as the corresponding alkynylzincs. And yet, under catalytic conditions, they are ineffective^[8] (**Scheme 1**). There are indications that Pd catalysts are irreversibly transformed into inert complexes by the action of alkynyllithiums. Thus, for example, treatment of Cl₂Pd(PPh₃)₂ with an excess of LiC≡CBu-*t* produces Li₂Pd(C≡CBu-*t*)₄, which is catalytically inactive (**Scheme 2**).^[8]



Scheme 1



Scheme 2

Finally, Hg (Entries 8 and 9), Si (Entry 15), and Zr (Entry 18) appear to be essentially ineffective probably for different reasons. In short, the counteraction survey reported in 1978^[4] clearly indicated that, besides Cu used in the Sonogashira reaction (Sect. III.2.8.1), Zn, Mg, B, Al, and Sn showed promising results. Those alkynylmetals that contain Zn, B, Al, and Sn are usually generated from alkynylmagnesium derivatives or alkynyllithiums. So, in cases where alkynylmagnesium reagents are very satisfactory, there would be no need for any of the other metals. In reality, however, there are a number of limitations associated with alkynylmagnesium derivatives. In such cases, Zn, B, Al, and Sn may then be considered. In view of the relative ease of generation, low cost, and the highest intrinsic reactivity observed, Zn should be considered first among them. On the other hand, the usefulness of Al appears to be more limited than the other three metals. The lower intrinsic reactivities and significantly higher costs of B and Sn compounds as compared with alkynylzincs would have to be offset by some distinct advantages that B or Sn might offer. The generally high toxicity associated with organotin is another factor in the selection of a suitable counteraction. In some cases, however, the high intrinsic reactivity of alkynylzincs has some undesirable effects, and Sn has been shown to be superior to Zn, as discussed later.

Despite the initial promising results observed with alkynylboron derivatives,^[4] B had not been used further as the metal component of alkynylmetals until recently.^{[9]–[11]} In view of various factors including intrinsic reactivity and cost, it would be desirable to justify the use of B with some distinct advantages that B might offer.

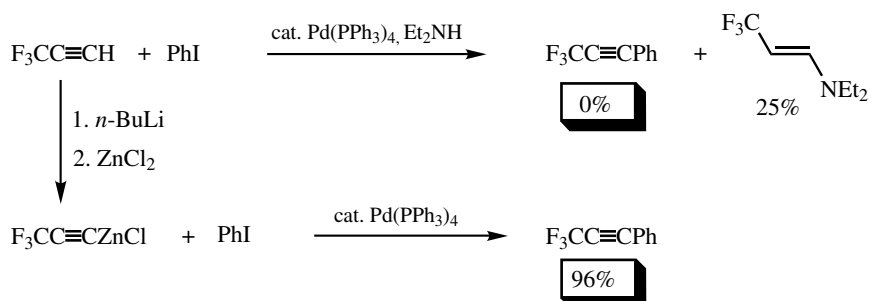
A.ii. Sonogashira Alkyne Synthesis versus Pd-Catalyzed Alkynylation with Preformed Alkynylmetals

Since Pd-catalyzed alkynylation with preformed alkynylmetals is generally somewhat more involved than the Sonogashira alkynylation, the use of the former protocol has to be duly justified. The following differences between the two protocols are worth noting.

A.ii.a. Synthesis of Terminal Alkynes. The synthesis of terminal alkynes by the Sonogashira reaction using acetylene itself is known not to produce the desired product in satisfactory yields,^{[1],[2],[6]} disubstitution at both ends of acetylene being the major side reaction. Consequently, a three-step alternative involving (i) protection of one end of acetylene, usually in the form of trimethylsilylacetylene, (ii) cross-coupling, and (iii) deprotection is generally employed. On the other hand, the synthesis of terminal alkynes from acetylene without its protection and deprotection was achieved using ethynylzinc chlorides and bromides as early as 1977.^[12] The required ethynylzinc haldies can readily be generated *in situ* from commercially available $\text{HC}\equiv\text{CMgX}$ ($\text{X}=\text{Br}$ or Cl). In fact, ethynylmagnesium halides themselves have been shown to be as satisfactory as any other alkynylmetals in many cases.^[6] So, it is advisable to consider first the use of $\text{HC}\equiv\text{CMgX}$ for Pd-catalyzed ethynylation. In cases where they are unsatisfactory, however, ethynylzinc halides should prove to be superior alternatives in most cases, as detailed below. Puzzlingly, ethynylboron derivatives have failed to give the desired terminal alkynes.^[6] Some side reactions, such as 1,2-migration, may be suspected.

A.ii.b. Electronic and Steric Impedance in the Sonogashira Alkyne Synthesis. There have been ample indications that terminal alkynes containing electron-withdrawing substituents either fail or are sluggish to undergo the Sonogashira alkynylation. Those that essentially fail to undergo the reaction include $\text{F}_3\text{CC}\equiv\text{CH}$ ^[13] and $\text{EtOCC}\equiv\text{CH}$.^[14] A striking difference between the Sonogashira and Negishi protocols is shown in **Scheme 3**.^[13]

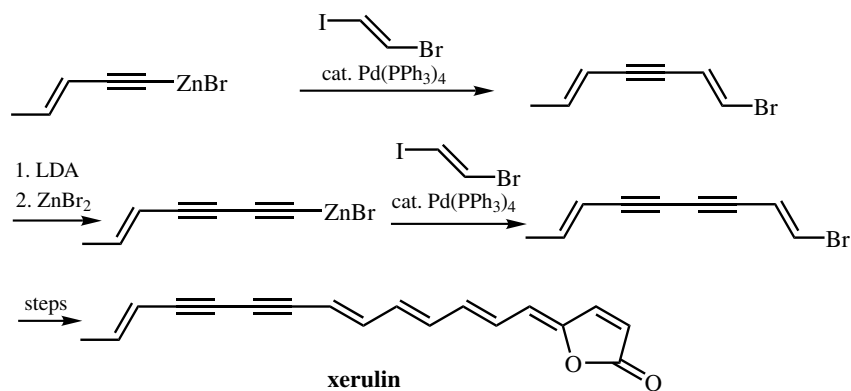
Although rigorous comparisons of steric and other electronic effects on the Sonogashira and Negishi alkyne syntheses are essentially unknown, a detailed investigation of the electronic and steric effects for comparing Mg, Zn, and Sn has clearly established that the Zn protocol not only is compatible with both electron-withdrawing and electron-donating substituents but also best tolerates steric hindrance, as detailed below.^[6]



Scheme 3

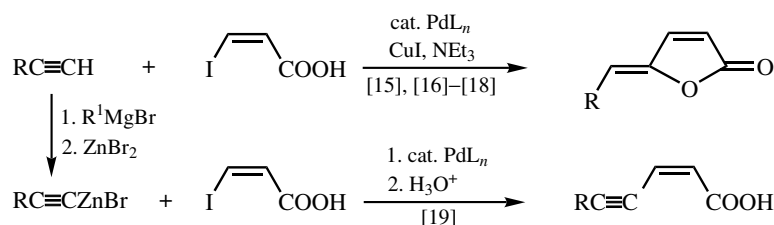
A.ii.c. Other Limitations and Difficulties Associated with the Sonogashira Alkyne Synthesis. Other limitations and difficulties observed with the Sonogashira alkyne synthesis include (i) alkyne dimerization, which appears to be induced by radicals, and (ii) addition of amines to alkynes as exemplified in **Scheme 3**.^[13]

A.ii.d. Comparison of Operational Simplicity. As mentioned earlier, the Sonogashira protocol is operationally somewhat simpler than the use of preformed alkynylmetals. This indeed is the main reason for considering first the Sonogashira protocol in cases where it is very satisfactory. When the starting terminal alkynes are prepared via alkynylmetal intermediates, however, the direct use of alkynylmetals would be more convenient, as demonstrated in a recent synthesis of xerulin^[15] (**Scheme 4**).



Scheme 4

A.ii.e. Distinct Reaction Paths for the Sonogashira Reaction and the Negishi Alkyne Synthesis. The Sonogashira and Negishi protocols can follow two distinct reaction paths to give much different products. For example, the reaction of terminal alkynes with (*Z*)- β -iodoacrylic acid under Sonogashira conditions leads to the formation of (*Z*)- γ -alkylidenebutenolides via a cross-coupling–lactonization tandem process.^{[15]–[18]} On the other hand, the corresponding reaction of alkynylzinc bromides provides the cross-coupling products without inducing lactonization^[19] (**Scheme 5**).



Scheme 5

B. Pd-CATALYZED ALKYNYLATION WITH ALKYNYLMETALS CONTAINING Mg, Zn, AND Al

B.i. Alkynylaluminums

Alkynylmetals containing Mg, Zn, and Al have been shown to be effective among those containing relatively electropositive metals.^[4] However, alkynylaluminum derivatives have rarely been used.^{[4],[20],[21]} Enol phosphates derived from ketones readily react with $\text{PhC}\equiv\text{CAI}(\text{Et})_2$ and $n\text{-BuC}\equiv\text{CAI}(\text{Et})_2$ in the presence of 1 mol % of $\text{Pd}(\text{PPh}_3)_4$ in 57–83% yields.^{[20],[21]} As the use of organoaluminums is somewhat more involved than those containing Mg or even Zn, it should be reserved for those cases in which the use of Al leads to more favorable results than other more convenient options.

B.ii. Synthesis of Terminal Alkynes with Ethynylmetals Containing Mg and Zn

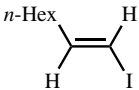
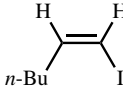
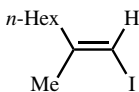
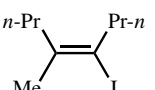
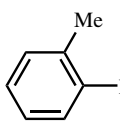
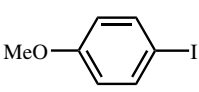
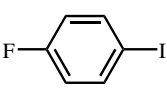
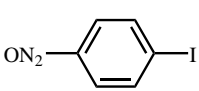
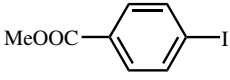
Because of the highest reactivity and the seemingly broadest scope that alkynylzincs display, they have been most extensively investigated and used among preformed alkynylmetals. With respect to ethynylation to produce terminal alkynes, a detailed comparison of Mg, Zn, and Sn was made.^{[6],[22],[23]} The results summarized in **Table 2** indicate that all three metals are satisfactory in less demanding cases but that the lower catalytic reactivity of Mg and Sn as well as a significantly higher tendency of Mg to undergo disubstitution are clearly seen in sterically and electronically more demanding cases. Even so, the direct use of commercially available and economical $\text{HC}\equiv\text{CMgX}$ ($\text{X} = \text{Cl}$ or Br) should be considered, when they are effective, while the use of more expensive and toxic Sn reagents should be reserved for those cases where neither Mg nor Zn is effective for chemoselectivity or other reasons.

B.iii. Scope of Pd-Catalyzed Alkynylation with Alkynylmetals Containing Mg and Zn with Respect to the Alkynyl Groups and Organic Electrophiles

Some additional representative examples of Pd-catalyzed alkynylation with alkynylmetals containing Mg and Zn are summarized in **Table 3**.^{[5],[24]–[39]} The results indicate that the scope of the reaction with respect to the alkynyl groups is indeed very broad. In addition to the parent ethynyl group (**Sect. B.ii.**) and electron-withdrawing carbon groups (**Scheme 3**), a wide variety of other carbon groups including alkyl, alkenyl, aryl, and alkynyl (**Scheme 4**) groups of various steric and electronic requirements can be accommodated. Heteroatom groups containing Si (Entries 9–13), N (Entry 14), and O (Entry 15) can also be accommodated.

The scope with respect to organic electrophiles has been largely limited to alkenyl, aryl, and acyl derivatives containing I, Br, $\text{OPO}(\text{OPh})_2$,^{[20],[21]} and OSO_2CF_3 .^[27] In the cases of acyl derivatives, acyl chlorides have mostly been used.^[24] Alkynylation of alkyl electrophiles including allyl, propargyl, and benzyl derivatives is usually better accomplished by some known methods involving Li, Mg, and Cu. Moreover, Pd catalysis appears to be largely ineffective in most of these cases. The Pd-catalyzed reaction of alkynylmetals containing Mg and Zn with alkynyl iodides and bromides proceeds readily but leads to the mixtures of the desired conjugated diynes and the two possible homodimers^[40] except in some favorable combinations. For strictly “pair-selective” synthesis of unsymmetrically substituted conjugated diynes by Pd-catalyzed cross-coupling, an alternate approach involving Pd-catalyzed alkynyl–alkenyl coupling with 1,2-dihaloethylene discussed in **Sect. III.2.14.2** and later in this section should be considered.

TABLE 2. Comparison of Metal Counteranions in the Direct Synthesis of Terminal Alkynes by Pd-Catalyzed Ethynylation with Ethynylmetals Containing Mg, Zn, and Sn

$\text{HC}\equiv\text{CM} + \text{RI} \xrightarrow[\text{THF}]{5\% \text{ Pd(PPh}_3)_4} \text{HC}\equiv\text{CR}$						
RI	M ^a	Time ^b (h)	Product Yield ^c (%)		Residual	
			HC≡CR	RC≡CR	RI ^c (%)	Reference
	MgBr	1	95	<i>d</i>	<i>d</i>	[6]
	ZnBr	1	96	<i>d</i>	<i>d</i>	
	SnBu ₃	6	95	<i>d</i>	<i>d</i>	
	ZnCl	<i>d</i>	83 (65)	<i>d</i>	<i>d</i>	[12]
	MgBr	1	94	<i>d</i>	<i>d</i>	[6]
	ZnBr	1	94	<i>d</i>	<i>d</i>	
	MgBr	24 ^e	82	<i>d</i>	<i>d</i>	[6]
	ZnBr	3 ^e	95	<i>d</i>	<i>d</i>	
	ZnCl	3	71	<i>d</i>	<i>d</i>	[22]
	MgBr	1	95	<i>d</i>	0	[6]
	ZnBr	1	95	<i>d</i>	0	
	MgBr	1	97 (72)	<i>d</i>	0	[6]
	ZnBr	1	94	<i>d</i>	0	
	MgBr	12	0	<i>d</i>	<i>d</i>	[6]
	ZnBr	3	93 (89)	<i>d</i>	0	
	ZnBr	1	92 (86)	<i>d</i>	0	[6]

(Continued)

TABLE 2. (Continued)

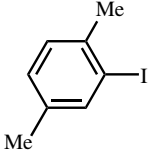
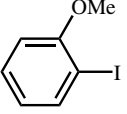
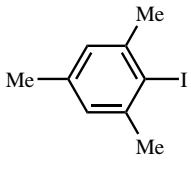
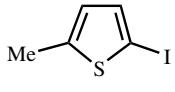
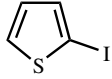
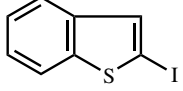
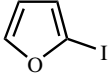
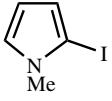
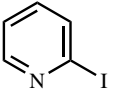
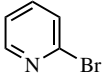
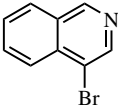
RI	M ^a	Time ^b (h)	Product Yield ^c (%)		Residual	Reference
			HC≡CR	RC≡CR	RI ^c (%)	
	MgBr	48	60 (56)	24	14	[6]
	ZnBr	3	92 (85)	4	0	
	SnBu ₃	24	73	6	15	
	MgBr	20	51	36	<i>d</i>	[6]
	ZnBr	2	77	Trace	<i>d</i>	
	MgBr	48 ^f	28	12	66	[6]
	MgBr	24 ^g	1	<i>d</i>	95	
	ZnBr	18 ^g	74 (68)	10	<i>d</i>	
	SnBu ₃	72 ^g	36	8	52	
	MgBr	<i>d</i>	35	24	<i>d</i>	[23]
	ZnBr	<i>d</i>	87	0	0	
	ZnBr	1	85 (71)	<i>d</i>	<i>d</i>	[23]
	ZnBr	1	92 (71)	<i>d</i>	<i>d</i>	[23]
	ZnBr	1	92	<i>d</i>	<i>d</i>	[23]
	ZnBr	4	76	<i>d</i>	<i>d</i>	[23]
	ZnBr	5 ^g	70	<2	<i>d</i>	[23]

TABLE 2. (Continued)

RI	M ^a	Time ^b (h)	Product Yield ^c (%)		Residual RI ^c (%)	Reference
			HC≡CR	RC≡CR		
	ZnBr	24 ^g	21	44	<i>d</i>	[23]
	ZnBr	24 ^g	62 (58)	24	<i>d</i>	[23]

^a HC≡CZnBr and HC≡CSnBu₃ were generated *in situ* from the treatment of HC≡CMgBr with ZnBr₂ and ClSnBu₃, respectively. HC≡CZnCl was generated by the treatment of HC≡CLi with ZnCl₂.

^b Unless otherwise mentioned, the reaction temperature was 22 °C.

^c GLC or NMR yield. The numbers in parentheses are isolated yields.

^d Not observed or detected.

^e At 50 °C in DMF.

^f At 60 °C in DMF.

^g At 50–60 °C in THF-DMF.

The effects of the structure and substituents of alkenyl and aryl groups have been delineated,^{[6],[12],[22],[23]} and some results are summarized in **Table 2** in the context of ethynylation. In addition, the results shown in **Table 3** indicate that alkenyl halides containing a wide variety of heteroatom substituents, such as β -silyl (Entry 6) and β -halo substituents (Entries 5, 7, 9, 10, and 14) (**Sect. III.2.14.2**), fluorinated alkenyl (Entry 3), and γ -oxy-substituted alkenyl, can be accommodated.

B.iv. Pd-Catalyzed Alkynyl–Alkenyl Coupling Route to Conjugated Diynes as a Strictly “Pair-Selective” Alternative to the Cadiot–Chodkiewicz Reaction

The Pd-catalyzed reaction of (*E*)-3-penten-1-ynylzinc bromide with (*E*)-bromoiodoethene followed by treatment with LDA shown in **Scheme 4**^[15] provides a selective and convenient route to the desired terminal diyne, which can be further converted to unsymmetrically substituted conjugated diynes. This and its modifications with (*E*)-chloroiodoethene provide synthetic equivalents or alternatives to the Cadiot–Chodkiewicz reaction.^[41] As shown in **Scheme 6**, both the Cadiot–Chodkiewicz protocol and the Negishi coupling protocol^[42] require three steps from one terminal alkyne, one ethyne, and a suitable electrophile, such as organic halides. In the former, the second terminal alkyne may be prepared either from ethyne and a suitable electrophile or by its alternative. One of the two alkynes must then be converted to the corresponding 1-bromo- or 1-iodoalkyne prior to the crucial Cu-catalyzed cross-coupling. In the latter protocol, ethyne is converted first to either bromoiodoethene or chloroiodoethene. This is then cross-coupled with an alkynyl-metal containing Zn, Mg, or another suitable metal generated *in situ*. In the third step, the haloalkyne prepared above is treated with a base to produce the corresponding 1-metallo-1,3-diyne, which can then be converted to variously substituted conjugated diynes (**Scheme 6**). Some representative results are summarized in **Scheme 7**.

TABLE 3. Pd-Catalyzed Cross-Coupling of Aryl and Alkenyl Electrophiles with Alkynylmetals Containing Mg and Zn



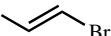
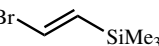
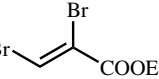
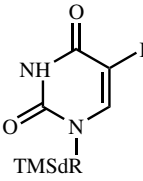
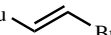
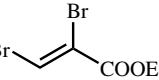
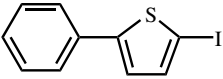
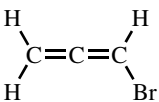
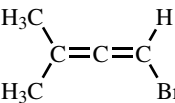
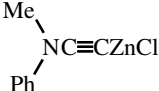
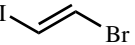
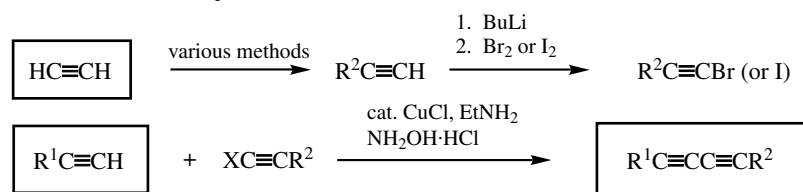
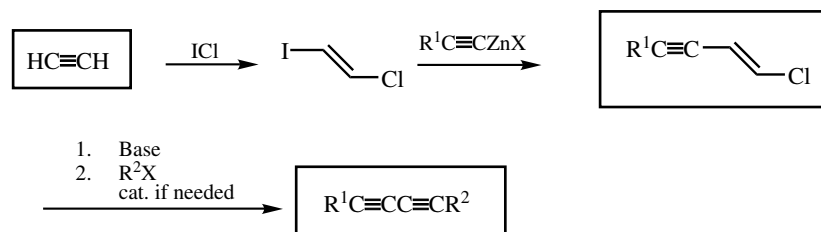
Entry	Alkynylmetal	Aryl, Alkenyl, or Acyl Electrophile ^a	Pd Catalyst ^b	Product Yield (%)	Reference
1	H ₃ CC≡CMgCl	C ₆ H ₁₃ 	A	83	[5]
2	C ₅ H ₁₁ C≡CZnCl	Me—C(=O)—Cl	A	81	[24]
3	HexC≡CZnCl		A	62	[25],[26]
4	H ₃ COH ₂ CC≡CZnCl	Ph—OSO ₂ CF ₃	A	67	[27]
5	PhC≡CZnCl	Br  Br	A	42	[28],[29]
6	PhC≡CZnCl	Br  SiMe ₃	A	88	[30],[31]
7	PhC≡CZnCl	Br  COOEt	A	64	[32]
8	PhC≡CZnCl		B	95	[33]
9	Me ₃ SiC≡CZnCl	Bu  Br	A	77	[34]
10	Me ₃ SiC≡CZnCl	Br  COOEt	A	91	[35]
11	Me ₃ SiC≡CMgBr		A	89	[36]

TABLE 3. (Continued)

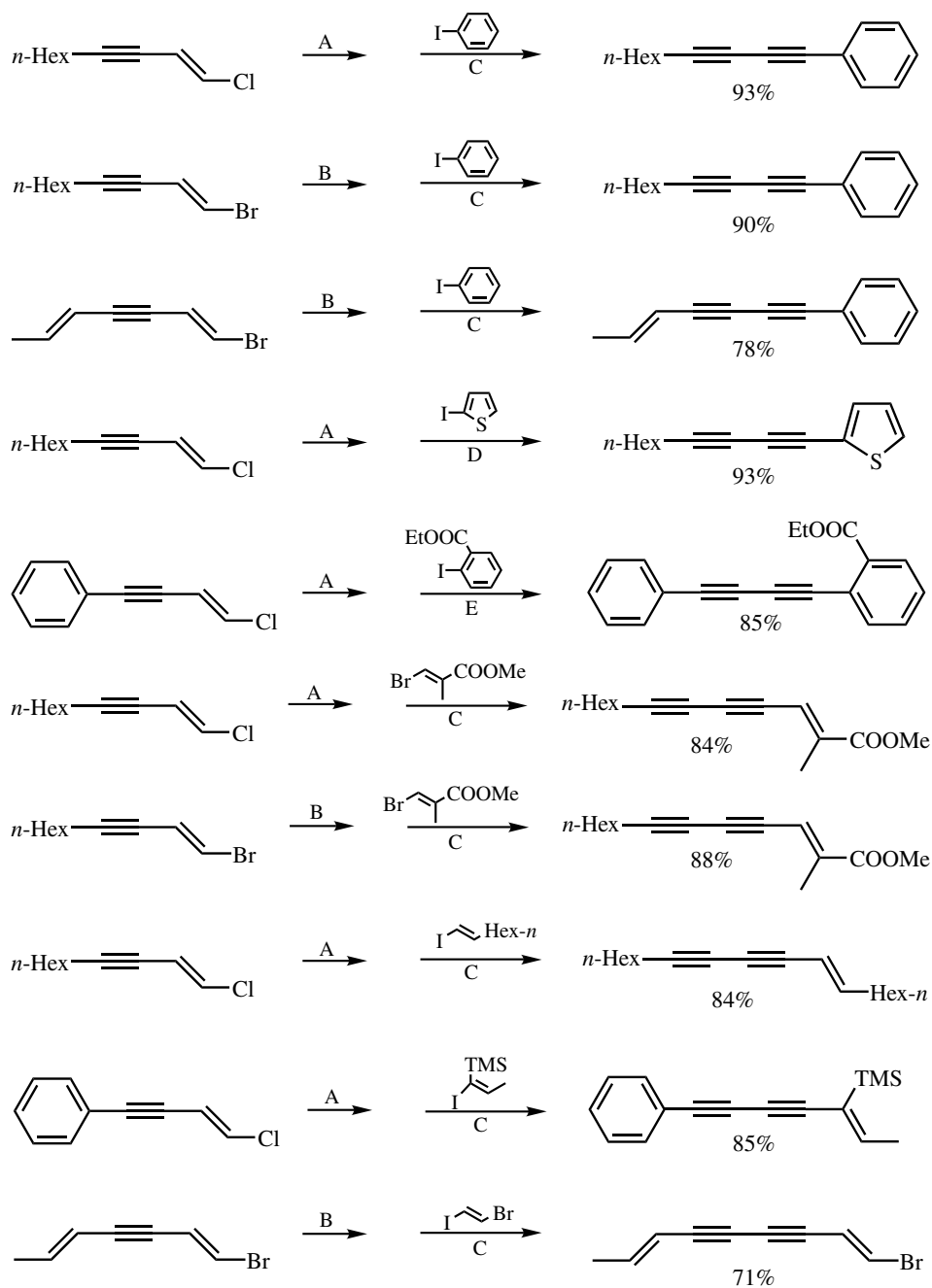
Entry	Alkynylmetal	Aryl, Alkenyl, or Acyl Electrophile ^a	Pd Catalyst ^b	Product Yield (%)	Reference
12	Me ₃ SiC≡CZnCl		A	90	[37]
13	Me ₃ SiC≡CZnCl		A	80	[37]
14	 NC≡CZnCl		A	48	[38]
15	EtOC≡CZnCl	PhI	B	65	[39]

^aTMSdR = *O*-bis(trimethylsilyl)deoxyribose.^bA = Pd(PPh₃)₄; B = Cl₂Pd(PPh₃)₂.

Although the relative merits and demerits of the two protocols are not yet very clear, the Cadiot–Chodkiewicz reaction has often been plagued with difficulties, such as cross-homo scrambling leading to the formation of symmetrical diynes and low product yields. The reaction does not appear to be suited for the synthesis of terminal 1,3-diynes either. The currently available data indicate that the Pd-catalyzed protocol does not generally suffer from these difficulties. Thus, essentially all cases examined to date have exhibited very high cross/homo selectivity and high product yields. Furthermore, 1,3-diynes are

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

Scheme 6



A: (1) 2 *n*-BuLi, $-30\text{ }^\circ\text{C}$; (2) dry ZnBr_2 . B: (1) 2.2 LDA, $-78\text{ }^\circ\text{C}$; (2) dry ZnBr_2 . C: 2% $\text{Pd}(\text{PPh}_3)_4$, $0\text{--}24\text{ }^\circ\text{C}$, 1 h. D: Same as C except that the reaction time was 2 h. E: Same as C except that the reaction was run overnight.

Scheme 7

produced as the key intermediates in all cases. The Pd-catalyzed protocol indeed promises to be more selective and more general than the conventional Cadiot–Chodkiewicz protocol. At the least, the Pd-catalyzed protocol should provide a potentially valuable route to conjugated diynes in some of those cases where the Cadiot–Chodkiewicz reaction is unsatisfactory, such as the synthesis of terminal 1,3-diynes.

Since the synthesis of haloenynes involves β -haloethenyl iodides, a detailed discussion of this part of the Pd-catalyzed protocol is presented in **Sect. III.2.14.2**. In this section, the Pd-catalyzed reaction of 1,3-diynylmetals generated *in situ* with organic halides and related electrophiles is presented.

As discussed in **Sect. III.2.14.2**, the requisite haloenynes can, in principle, be prepared by the Pd-catalyzed monoalkynylation of any of the six 1,2-dihaloethenes containing Cl, Br, and/or I. Indeed, four of them, that is, $\text{ClCH}=\text{CHCl}$, $\text{BrCH}=\text{CHBr}$, $\text{ClCH}=\text{CHI}$, and $\text{BrCH}=\text{CHI}$, have been used for this purpose. As can be expected, (*E*)- $\text{ClCH}=\text{CHI}$, readily preparable by treating acetylene with commercially available ICl , provides a combination of the highest reactivity and selectivity in terms of mono/di substitution ratio. (*E*)-Bromoiodoethene, preparable by the reaction of acetylene with IBr ,^[15] is also generally satisfactory. Although $\text{ClCH}=\text{CHCl}$ ^[43] offers an advantage of being less expensive than $\text{ClCH}=\text{CHI}$ or $\text{BrCH}=\text{CHI}$, this advantage seems more than offset by some disadvantages, such as the need for a large excess (typically five fold^[43]) of $\text{ClCH}=\text{CHCl}$ and its inherently lower reactivity. Although the use of (*Z*)- $\text{ClCH}=\text{CHCl}$ was reported to be advantageous in that the β -elimination of the chloroenyne intermediates is more facile than their *E* isomers,^[44] the latter intermediates are, nonetheless, generally quite satisfactory provided that NaNH_2 , LDA, *n*-BuLi (for chlorides but not for bromides), and their suitable alternatives are used.

Unsymmetrically disubstituted conjugated diynes containing alkyl, aryl, and alkenyl groups have been prepared by the double Pd-catalyzed cross-coupling protocol in a highly “pair-selective” manner and in high yields, as indicated by the results summarized in **Scheme 7**.^[45] In fact, no symmetrically disubstituted diyne is detected in any of the cases shown in **Scheme 7**. The chloro- and bromoenynes used in **Scheme 7** are preparable by the Pd-catalyzed reaction of the corresponding alkynylzincs with $\text{ClCH}=\text{CHI}$ and $\text{BrCH}=\text{CHI}$, respectively, in 70–90% yields (**Sect. III.2.14.2**).

C. Pd-CATALYZED ALKYNYLATION WITH ALKYNYL TINS

As discussed in **Sect. A.i**, Sn and B among relatively electronegative metals have displayed relatively high reactivities in the original metal counteraction screening.^[4] Alkynyltins, but not alkynylborons, have since been widely used, as indicated by the results summarized in **Table 4**. However, the relatively high costs and toxicity coupled with relatively low intrinsic reactivity associated with alkynyltins render the Sn-based method generally less attractive than the Sonogashira reaction and those involving Mg and Zn. Nonetheless, the intrinsically high chemoselectivity of alkynyltins will find some cases where Sn is superior to the alternatives mentioned above. One eloquent example is the cyclic carbopalladation–cross-coupling tandem reaction in which alkynyltins are distinctly superior to alkynylzincs because of their low reactivity. Whereas highly reactive alkynylzinc reagents give mostly uncyclized direct cross-coupling products, the opposite is true with Sn ^[46] (**Scheme 8**). This tandem process has

TABLE 4. Pd-Catalyzed Cross-Coupling of Aryl and Alkenyl Electrophiles with Alkynylmetals Containing Sn and B

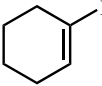
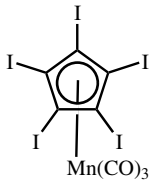
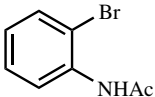
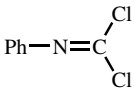
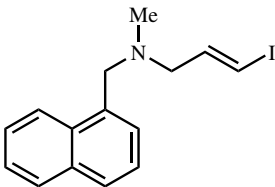
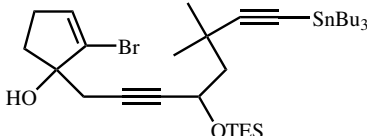
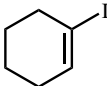
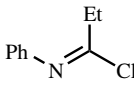
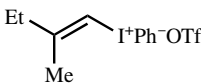
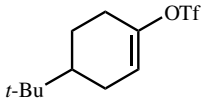
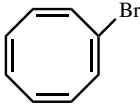
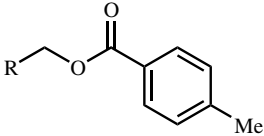
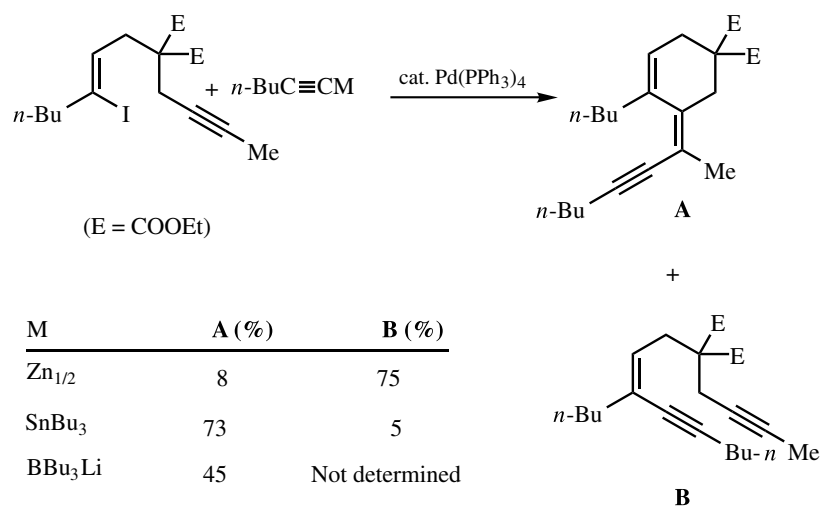
Entry	Alkynylmetal	Aryl or Alkenyl Electrophile	Pd Catalyst ^a	Product Yield (%)	Reference
1	HC≡CSnMe ₃		A	90	[50]
2	MeC≡CSnMe ₃		B	38	[51]
3	<i>n</i> -PrC≡CSnBu ₃		A	76	[52]
4	BuC≡CSnBu ₃		C	70	[53],[54]
5	<i>t</i> -BuC≡CSnBu ₃		B	87	[55]
6		A	72	[56]	
7	PhC≡CSnMe ₃		A	90	[50]
8	PhC≡CSnBu ₃		C	68	[57]
9	PhC≡CSnBu ₃		D	64	[58]

TABLE 4. (Continued)

Entry	Alkynylmetal	Aryl or Alkenyl Electrophile	Pd Catalyst ^b	Product Yield (%)	Reference
10	$\text{Me}_3\text{SiC}\equiv\text{CSnMe}_3$		A	90	[59]
11	$\text{EtOC}\equiv\text{CSnBu}_3$	PhI	C	60	[60]
12	$\text{Bu}_3\text{SnC}\equiv\text{CSnBu}_3$		E	45	[61]
13	$n\text{-BuC}\equiv\text{CB(OPr-}i\text{)}_2$	 R = Polystyrene resin	F	91	[11]

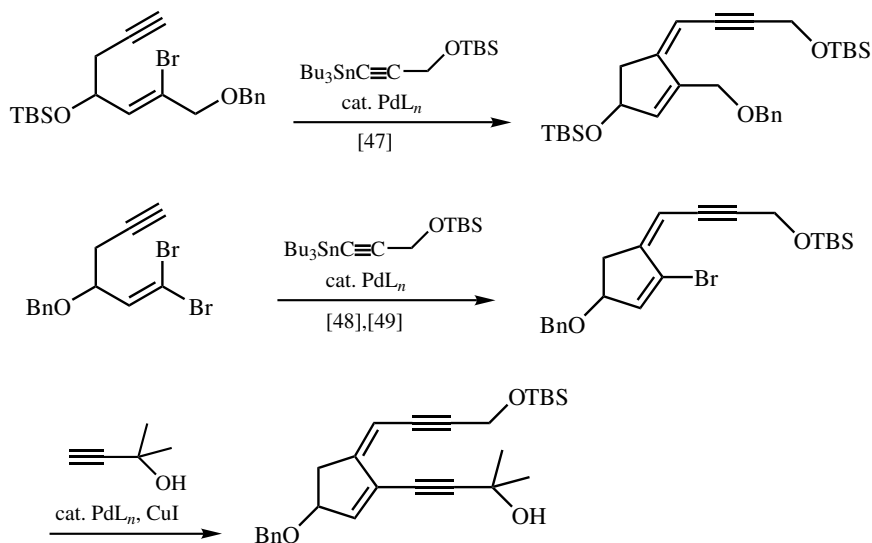
^aA = $\text{Pd}(\text{PPh}_3)_4$; B = $\text{Cl}_2\text{Pd}(\text{MeCN})_2$; C = $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$; D = $\text{ClPd}(\text{PPh}_3)_2\text{Bn} + \text{CuI}$; E = $\text{Pd}_2(\text{dba})_3$; F = $\text{Cl}_2\text{Pd}(\text{dppf})$.



Scheme 8

been ingeniously applied to the synthesis of a critical component of the neocarzinostatin chromophore^{[47]–[49]} (Scheme 9).

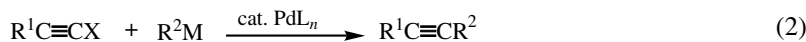
In most of the other cases, the relative merits and demerits of the alkynylation reactions relative to those of the others including the Sonogashira reaction and the alkynylmetal reactions with Mg and Zn are unclear.



Scheme 9

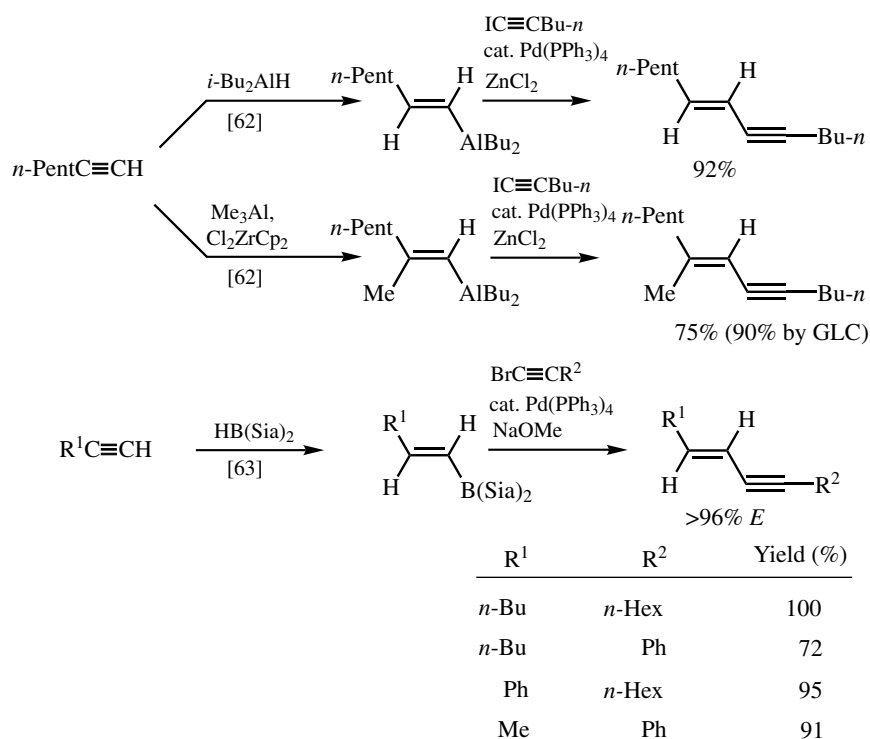
D. Pd-CATALYZED ALKYNYLATION OF HALOALKYNES

In comparing the two contrasting protocols shown in **Scheme 10**, one notes that the protocol represented by Eq. 2 is generally more involved than that shown by Eq. 1, unless the organometallic reagent in Eq. 2 is more readily available than the corresponding organic electrophiles used in Eq. 1. Alkenyl- and alkylmetals generated *in situ* by hydrometallation, carbometallation, and other addition reactions of alkynes and alkenes, respectively, are some representative examples of such organometals. Another aspect to be noted regarding Eq. 2 is that the reagent combination in Eq. 2 is generally more prone to metal-halogen and related exchange processes leading to cross-homo scrambling, since more highly electronegative alkynyl groups strongly prefer to be bonded to metals rather than to halogens. Presumably for these two reasons, the protocol represented by Eq. 2 has not been extensively investigated.



Scheme 10

The reaction of alkenylalanes and alkenylzirconium derivatives with 1-iodoalkynes doubly catalyzed with a Pd-phosphine complex and ZnCl_2 ^[62] appears to be the first example of this protocol. A related alkenylboron reaction was published shortly thereafter.^[63] Some additional examples involving Cu, Zn,^[64] and Sn^[65] are also known. These results are shown in **Scheme 11**.



Scheme 11

E. SUMMARY

1. Pd-Catalyzed alkynylation with alkynylmetals can be achieved with a wide variety of metals. Alkynylzincs display the highest intrinsic reactivity and the currently broadest scope.

2. In less demanding cases where various metals and protocols are comparably satisfactory, the inherent operational simplicity and economy should favor the Sonogashira reaction and the alkynylmagnesium reaction. In many more demanding cases where these reactions show some difficulties, the organozinc reaction should be considered.

3. The relatively low reactivity, high cost, and toxicity are some of the concerns associated with Sn, even though the low intrinsic reactivity and high chemoselectivity make Sn a metal of choice in some cases.

4. Although promising, alkynylaluminums and alkylborons have not been extensively used, and their unique advantages, if any, are essentially unknown.

5. For a variety of different reasons, other metals tested in Pd-catalyzed alkynylation including Li, Hg, Si, and Zr appear to be unsatisfactory at least in a comparative sense.

6. Pd-catalyzed alkynylation with 1-haloalkynes has not been extensively investigated. In cases where organometals are readily obtainable via hydrometallation or carbometallation, Pd-catalyzed alkenyl-alkynyl coupling may prove to be more advantageous than the corresponding reaction of alkynylmetals with alkenyl halides.

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